The Dissertation Committee for Shawn Thomas Blumberg Certifies that this is the approved version of the following dissertation:

Synthetic Studies Towards the Total Synthesis of Cortistatin A Synthesis of the Pentacyclic Core of Citreamicin μ and GA-ring Model Studies

Committee:

Stephen F. Martin, Supervisor

Michael J. Krische

Eric V. Anslyn

Carlton G. Willson

Sean M. Kerwin

Synthetic Studies Towards the Total Synthesis of Cortistatin A, Synthesis of the Pentacyclic Core of Citreamicin μ and GA-ring Model Studies

by

Shawn Thomas Blumberg, B. S.; M.S.

Dissertation

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Dedication

To my wife Katie, my partner in crime.

Acknowledgements

Though I may be the one receiving the degree, I owe all my success up to this point to the kind, dynamic, amazing and, most of all, weird people I have met over the years.

First and foremost, I would like to thank Dr. Steven Martin for taking me under his wing and teaching me the art and science of total synthesis. As a Lab 4 member I must thank Bob Fu, Noah Benjamin, Zhiguo Bian, Bo Cheng, Jingyue Yang Chris Marvin and Tim Hodges for their camaraderie and mentorship. I would especially like to thank Noah Benjamin for making Lab 4 an inspiring place to work, and I hope not the only place where reaction mechanisms and Miley Cyrus are talked about with equal seriousness and vigor. And finally, Caleb — I'm thankful for you always being there to discuss my latest chemistry conundrum and for your friendship.

Before I came to graduate school, I worked at Synthetech in Albany, Oregon. I thank Charles Wells and Sameer Athamneh for being my first mentors in Synthetic Organic Chemistry; Sameer, for teaching me techniques I use to this day and Charles who taught me the importance of epistemology in chemistry. I'd also like to thank Jessie Anderson for being a friend and my "hands" when I could not use mine. I'd like to also thank my friends Benji Horning, Nathan Collett and Aaron Sather for not only their friendship, but also for helping me develop my passion for chemistry. Finally, I would like to recognize Michal Haley, Darren Johnson and Gautam Bhattacharyya for believing in me when I didn't believe in myself.

Of course, I could not have done any of this without my wife, Katie Bingham, for her support and putting up with me for all these years. I'd also like to thank Andrew Molder for being a friend and "leaving your phone" in Katie's car so I'd get a second date.

Synthetic Studies Towards the Total Synthesis of Cortistatin A, Synthesis of the Pentacyclic Core of Citreamicin μ and GA-ring Model Studies

Shawn Thomas Blumberg, Ph.D.

The University of Texas at Austin, 2016

Supervisor: Stephen F. Martin

The route to the key bicyclic intermediate was streamlined to eight steps in 16% yield, using a TMSI promoted coupling of a furan and an enone. Additionally, methodology for the selective ozonolysis of the bicyclic intermediate was developed *via* ozone titration. Work on the dihydroxylation step led to the discovery and development of a new *p*H-neutral Sharpless-style asymmetric dihydroxylation.

The synthesis of pentacyclic core of citreamicin μ was accomplished in 12 steps. New methodologies were developed, including: an ortho- selective bromination of a vanillin derivative and the use of 4-(Phenylazo)diphenylamine (PDA) as an internal indicator for the acetylide coupling. The usefulness of PDA led to its development as a general all-purpose indicator for the titration of strong bases, Lewis acids and reducing agents. The discovery of $(n\text{-Bu})_4\text{NOAc}$ as a privileged additive led to the development of new methods for the synthesis of isocoumarins and new methodology for the condensation of amino acids using $LiMe_4$ was developed.

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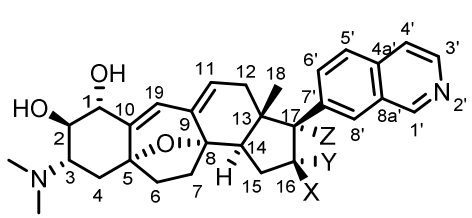
CHAPTER 1: SYNTHETIC STUDIES TOWARD THE SYNTHESIS OF CORTISTATIN A (1.1)

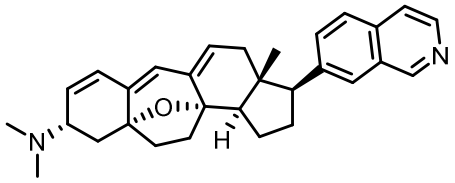
1.1: Isolation and Biological Activity

Cortistatins A, B, C and D (**1.1**-**1.4**) were isolated from the marine sponge *corticum simplex* by Kobayashi *et al* in 2006,[1] followed by cortisatins E-L in 2007 (Figure 1.1).[2,3] All members of the cortistatin family feature an unusual 9-(10→19)-*abeo*-androstane steroidal structure featuring an oxabicyclo-[3.2.1]-octene core. Cortistatins A-D (**1.1**-**1.4**) and J-L (**1.5**, **1.8**, **1.9**) feature a β-isoquinoline at C17 while, cortistatins E-H (**1.6**, **1.7**, **1.10**, **1.11**) have an alkyl-pyridine or piperidine substitution.

All members of the cortistatin family possess anti-angiogenic activity against human umbilical vein endothelial (HUVEC) cells, and cortistatin A (**1.1**) is the most potent member with an IC_{50} of 1.8 nM. In general, cortistatins A-D (**1.1**-**1.4**) and J-L (**1.5**, **1.8**, **1.9**) are much more biologically active than cortistatins E-H (**1.6**, **1.7**, **1.10**, **1.11**) (Figure 1.1) Cortistatin A (**1.1**) also exhibited impressive selectivity by showing little to no toxicity towards normal human dermal fibroblast (NHDF), KB epidermoid carcinoma cells (KB3-1), human chronic myelogenous leukemia cells (K562), and murine neuroblastoma cells (Neuro2A). Cortistatins E-H (**1.6**, **1.7**, **1.10**, **1.11**), which have differing substitution at C17, showed significantly less activity, suggesting that the isoquinoline ring is important for activity.

Figure 1.1: Members of the cortistatin family and their IC_{50} values against HUVEC





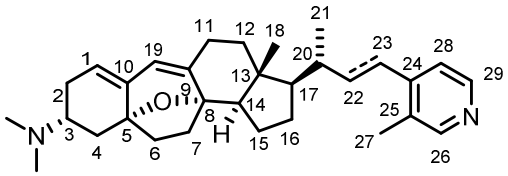
1.5: (Cortistatin J, 8 nM; 46 nM[31])

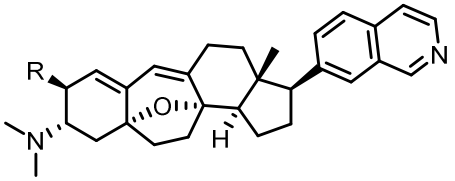
1.1: X = H, Y = H, Z = H (Cortistatin A, 1.8 nM; 2.1 nM[31])

1.2: X = OH, Y = H, Z = H (Cortistatin B, 1100 nM)

1.3: X = Y = O, Z = H (Cortistatin C 19 nM)

1.4; X = Y = O, Z = OH (Cortistatin D, 150 nM)



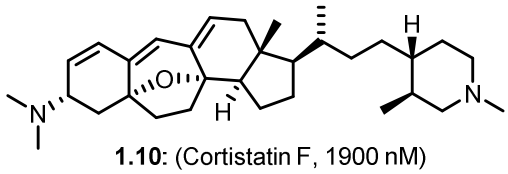


1.6: $\Delta^{22,23}$ (Cortistatin G, 800 nM)

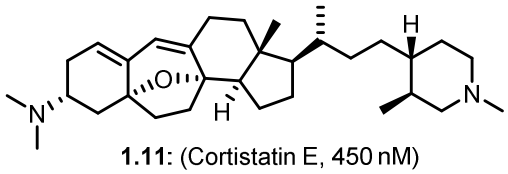
1.7: (Cortistatin H, 350 nM)

1.8: R = H (Cortistatin K, 40 nM, 112 nM[31])

1.9: R = OH (Cortistatin L, 23 nM, 32 nM[31])



1.10: (Cortistatin F, 1900 nM)



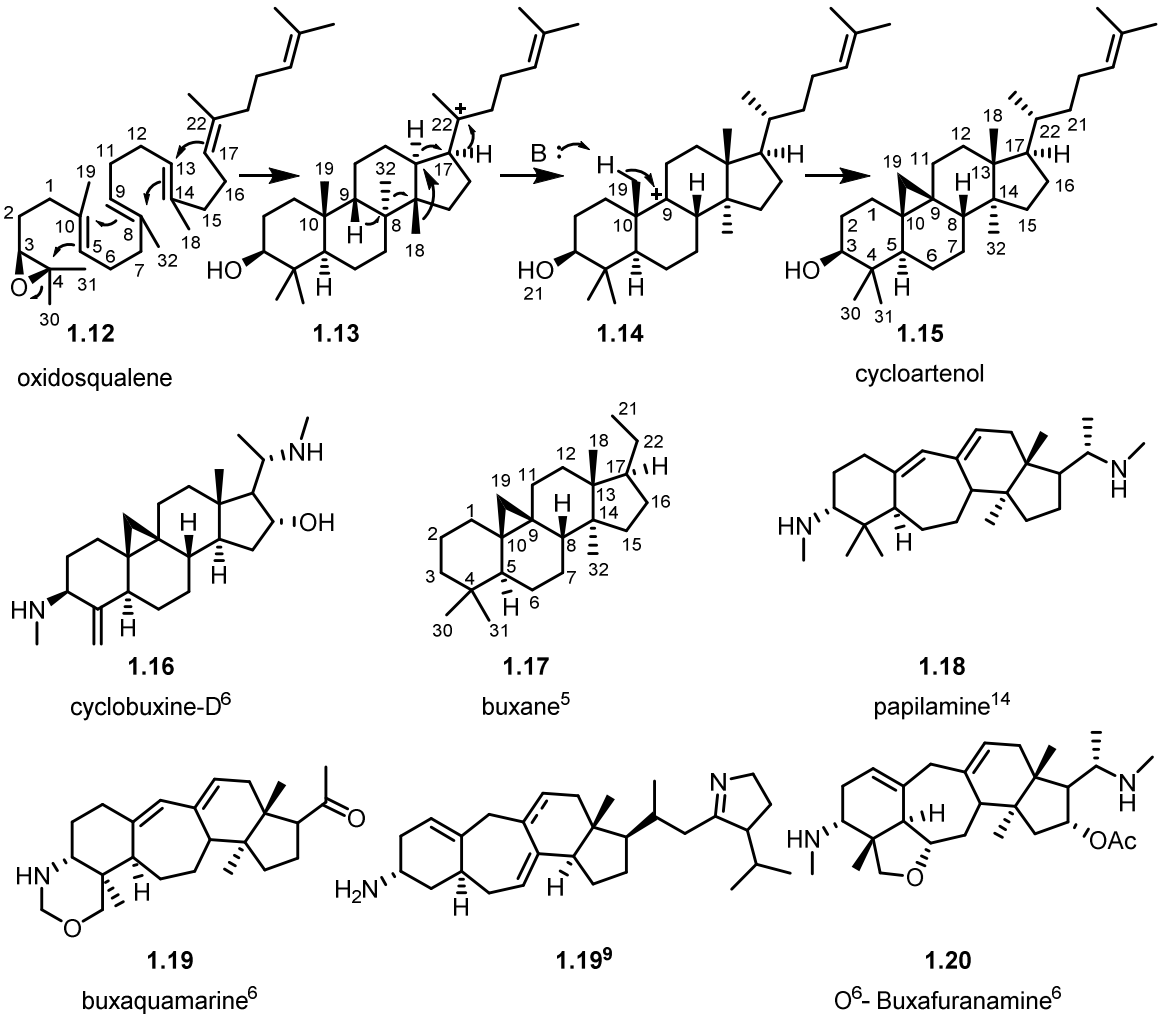
1.11: (Cortistatin E, 450 nM)

1.2: Biosynthetic hypothesis

Though the biosynthetic origin of the cortistatins in not known, information may be gleaned from a collection of structurally similar 9-(10→19)-*abeo*-pregnane alkaloids isolated from the *Buxaceae* family of plants (Figure 1.2).[5-16] Interestingly, alongside the 9-(10→19)-*abeo*-pregnane alkaloids, compounds such as cyclobuxine-D (**1.16**) were also isolated, suggesting that the 9(10→19) *abeo*-pregnane skeleton might originate from a cyclopropylcarbinyl rearrangement of a cyclopropane ring.[6] A key intermediate of plant sterol synthesis is cycloartenol (**1.15**) which is formed from oxido squalene (**1.12**) (Scheme 1.2).[17-20] The cyclopropane ring in cycloartenol (**1.15**) is thought to form during the cationic cyclization cascade *via* base promoted cyclization of the C19 methyl group onto the carbocation at C9. The

Buxus alkaloids may be formed either directly downstream of cycloartenol or by selective oxidation of C9 followed by base promoted cyclization as in **1.14→1.15**.

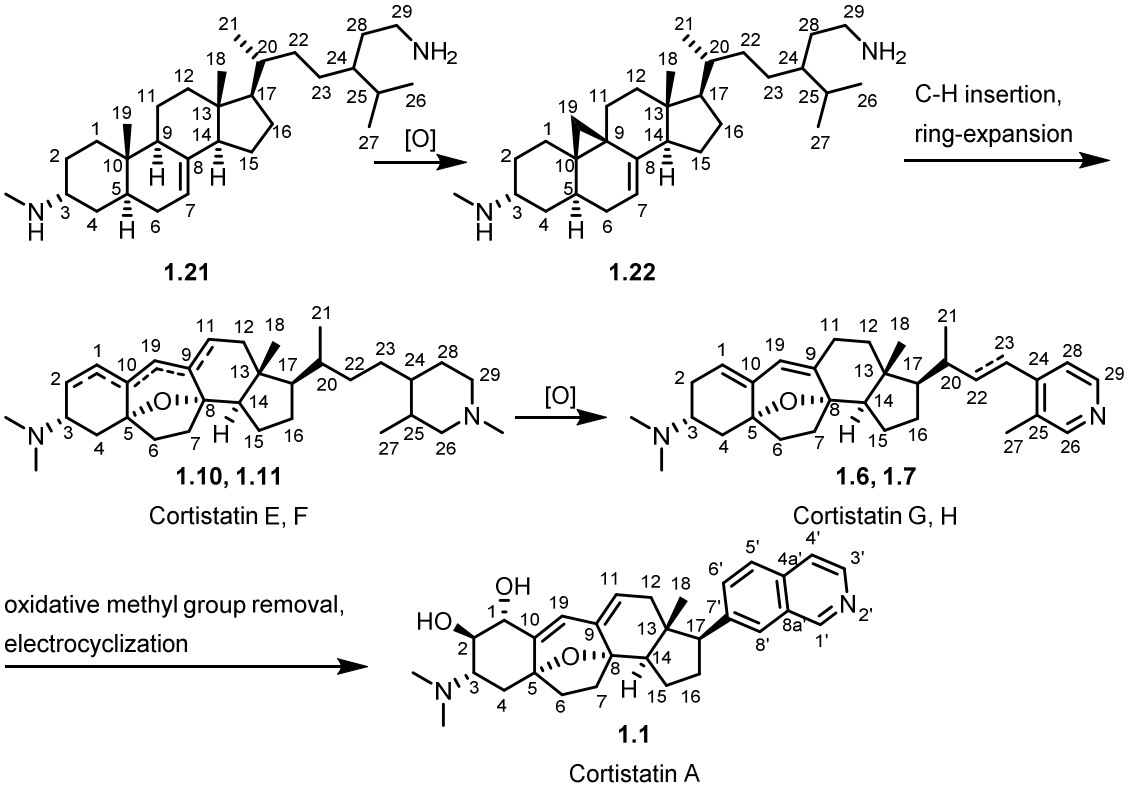
Figure 1.2: Known biosynthesis of cycloartenol and Buxane alkaloids



Due to the similar skeletons of the Buxus alkaloids and the fact that alkaloids such as **1.19** have been isolated in *Corticum simplex*, Kobayashi hypothesized that the cortistatins might be formed from a precursor such as **1.21** (Scheme 1.1).[2] Allylic oxidation of **1.21**, followed by base promoted cyclization as in **1.14→1.15** (Figure 1.2) gives cyclopropanated intermediate **1.22**. The 9-(10→19)-*abeo*-androstane structure in the cortistatins may come via an analogous cyclopropylcarbinyl rearrangement. The fact that cortisatins E-H (**1.6**, **1.7**, **1.10**, **1.11**) are

generally in lower oxidation states than cortistatins A-D (**1.1**-**1.4**) and J-L (**1.5**, **1.8**, **1.9**), Kobayashi hypothesized that the alkyl-piperidine substituent in cortistatins E (**1.10**) and F (**1.11**) may be biosynthetic precursors of the pyridine in cortistatins G (**1.6**) and H (**1.7**) and ultimately the source of the isoquinoline in cortistatins A-D (**1.1**-**1.4**). The C26 methyl group of alkaloid **1.21** may be oxidized to the piperidine in cortistatins E (**1.10**) and F (**1.11**) (note the alternate C23 cyclization in natural product **1.19**). Further oxidation of the piperidine ring to the pyridine ring gives cortistatins G (**1.6**) and H (**1.7**). Subsequent oxidative removal of the methyl group and electrocyclization to form cortistatins A-D (**1.1**-**1.4**) and J-L (**1.5**, **1.8**, **1.9**).[21-25]

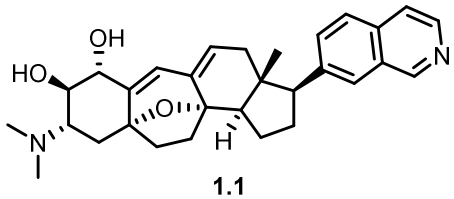
Scheme 1.1: Kobayashi's biosynthetic proposal[2]



1.3: Previous syntheses

Due to the combination of its unusual steroidal core and its impressive biological activity, cortistatin A (**1.1**) has attracted significant interest in the synthetic community. As of 2016, there have been five total syntheses,[26-32] four formal syntheses[34-37] and 11 synthetic studies towards the core[38-55] (Figure 1.4). Additionally, these has been numerous syntheses of medicinally relevant analogues.[56-61] Cortistatins J (**1.5**), K (**1.8**) and L (**1.9**) have also been synthesized, usually *via* a common intermediate *en route* to cortistatin A (**1.1**), with the exemption of Funk's synthesis of cortistatin J in 2011.[33] For sake of brevity, only the total and formal syntheses of cortistatin A (**1.1**) will be discussed.

Figure 1.3: Summary of the synthetic work towards cortistatin A (**1.1**), J (**1.5**), K (**1.8**) and L (**1.9**)



1.1

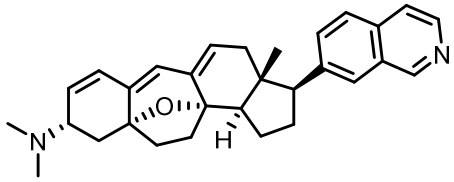
Cortistatin A

Total synthesis:

Baran[26,27]	2008, 15 steps, 2.10%
Nicolaou[28,29]	2008, 31 steps, 0.01%
Shair[30]	2008, 25 steps, 0.14%
Myers[31]	2010, 28 steps, 0.10%
Hirama[32]	2011, 25 steps, 0.79%

Formal synthesis:

Hirama[34]	2009, 27 steps, 0.27%
Sarpong[35]	2010, 37 steps, 0.18%
Yang[36]	2011, 31 steps, 0.02%
Chiu[37]	2015, 24 steps, 3.58%



1.5

Cortistatin J

Total synthesis:

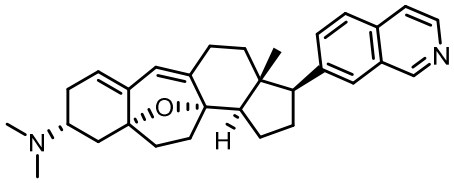
Nicolaou[29]	2009, 33 steps, 0.001%
Myers[31]	2010, 21 steps, 0.42%
Hirama[34]	2011, 25 steps, 0.87%
Funk[33]	2011, 20 steps, 3.42%

Formal synthesis:

Yang[36]	2011, 25 steps, 5.99%
Chiu[37]	2015, 22 steps, 4.92%

Approaches to the core:

Corey[48]	2008, 7 steps, 39.70%
Gung[47]	2008, 9 steps, 5.70%
Kobayashi[43]	2008, 22 steps, 3.40%
Magnus[49]	2009, 9 steps, 30.00%
Sorensen[50]	2009, 17 steps, 5.70%
Danishefsky[40-42]	2009, 9 steps, 2.60%
Stoltz[54]	2010, 13 steps, 3.04%
Zhai[46]	2010, 12 steps, 9.19%
Kobayashi[44]	2011, 29 steps, 0.36%
Danishefsky[39]	2011, 26 steps, 0.12%
Kobayashi[45]	2011, 18 steps, 5.47%



1.8

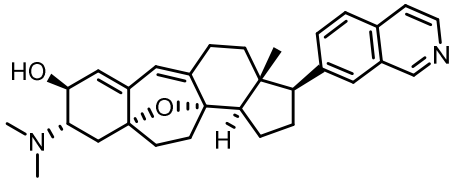
Cortistatin K

Total synthesis:

Myers[31] 2010, 24 steps, 0.32% yield

Formal synthesis:

Yang[36] 2011, 27 steps, 4.65%



1.9

Cortistatin L

Total synthesis:

Myers[31] 2010, 24 steps, 0.37% yield

Formal synthesis:

Yang[36] 2011, 27 steps, 5.26%

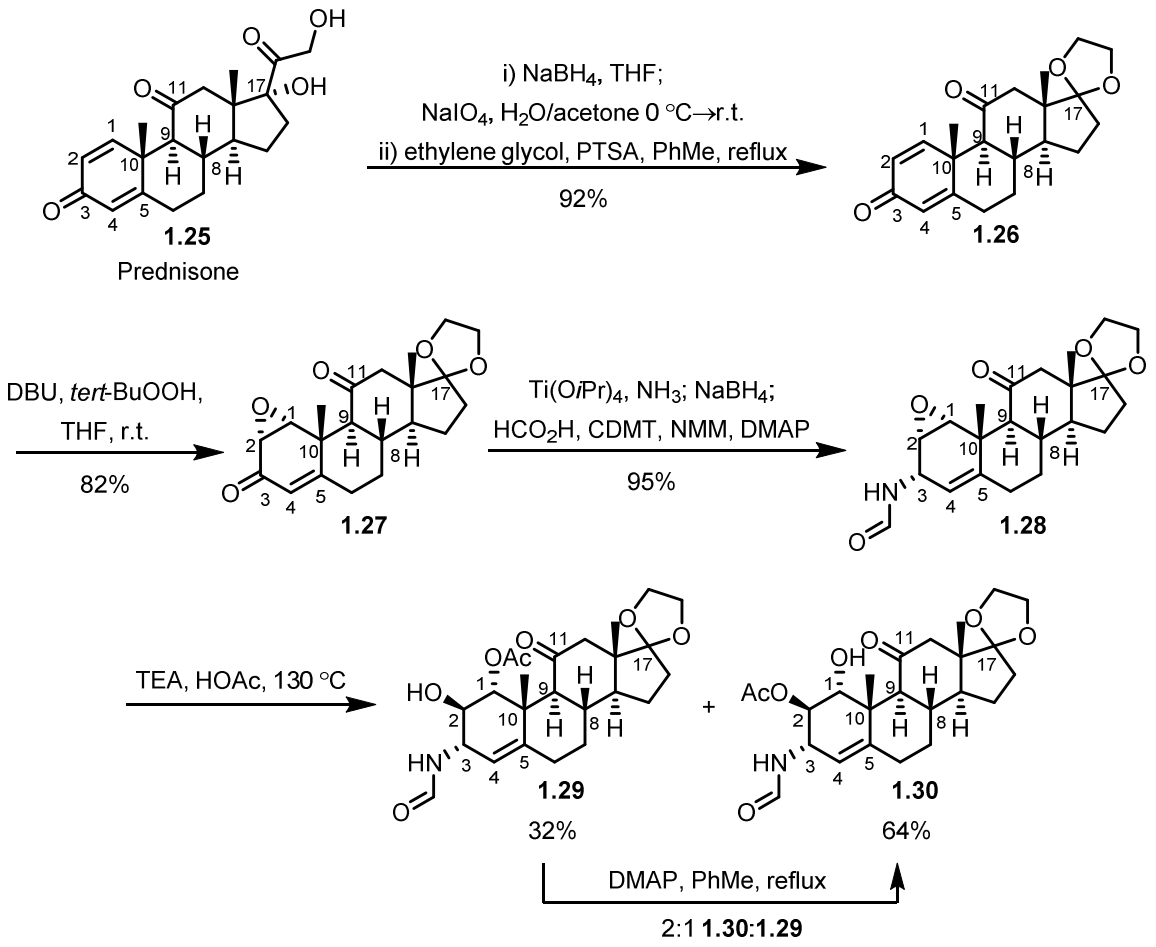
1.3.1: BARAN'S TOTAL SYNTHESIS

Only two years after Kobayashi published the isolation of cortistatin A (**1.1**) in 2006, Baran completed the first total synthesis in 2008,[26] which was followed by an improved scalable

route in 2011.[27] Baran's synthetic strategy was inspired by the historical precedent of using abundantly available steroidal precursors such as diosgenin and cholesterol as starting materials for the synthesis of cortisone and progesterone, as well as Kobayashi's intriguing biosynthetic proposal.

Baran's synthesis began with prednisone (**1.25**), which was selectively reduced at C20 and oxidatively cleaved to the ketone under Johnson-Lemieux[74] conditions (OsO_4, $NaIO_4$). Protection of the resulting ketone as the dioxolane gave intermediate **1.26** (Scheme 1.3). Nucleophilic epoxidation of the less substituted double bond with *t*-butylhydroperoxide and 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) lead to α-epoxy enone **1.27**. This offered an improvement over previously reported procedures utilizing dimethyldioxirane (DMDO). The epoxide proved to be acid and base sensitive, with a tendency for the C11 ketone to cyclize onto the C1 position of the epoxide to form a dihydrofuran. The first generation conditions for the reductive amination/formylation sequence reported in 2008 used $NH_4OAc/NaBH_3CN$ for the reductive amination and ethylformate for the formylation to provide **1.28** in 73% yield. The improved procedure in the second generation synthesis used the mild Lewis acid $Ti(O\textit{i}Pr)_4$ to form the imine with ammonia, followed by reductive workup with $NaBH_4$. Coupling of formic acid with 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), *n*-methylmorpholine (NMM) and N,N-dimethylaminopyridine (DMAP) furnished **1.28** in 95% yield. Initially, opening the epoxide with tetrabutylammonium acetate (TBAA) occurred exclusively at C1 but in only 48% yield. To improve the yield, Baran discovered that opening the epoxide with triethylamine (Et_3N) and acetic acid (AcOH) gave an equilibrium mixture (2:1) of **1.30** and **1.29** in a combined 96% yield. The undesired isomer **1.29** could be recycled to the desired isomer by resubjection to the reaction conditions.

Scheme 1.3: Synthesis of intermediate **1.30** from Prednisone **1.25**

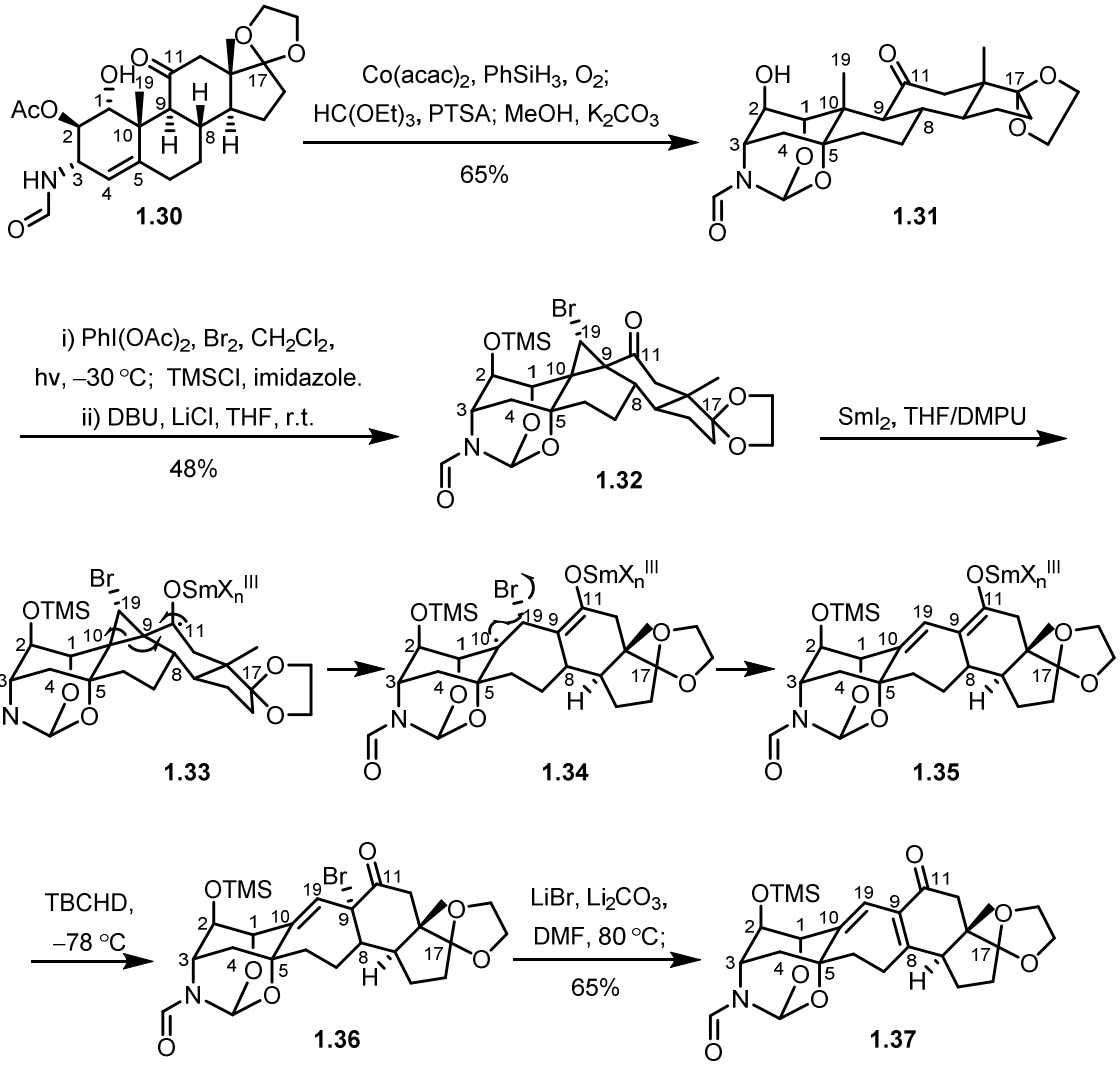


Hydration of the C4-C5 olefin in intermediate **1.30** under Mukaiyama[70] conditions ($Co(acac)_2$, $PhSiH_3$, O_2) provided the axial C5 alcohol. Protection of the C1, C5 alcohol and the C3 formamide as the orthoimide followed by removal of the C2 acetate furnished key cyclization precursor **1.31** (Scheme 1.4). The axial alcohol was used to selectively di-brominate the C19 methyl group under Suarez-like ($PhI(OAc)_2$, I_2)[85] conditions. Protection of the C2 hydroxyl group *in situ* before the intramolecular enolate alkylation was necessary to prevent the alcohol from cyclizing onto the dibrominated C19 methyl group. Traditional Suarez conditions favored the O-alkylated product exclusively. Intramolecular alkylation of the brominated methyl group with DBU gave key bromo-cyclopropane **1.32**.

Reductive fragmentation of **1.32** with SmI_2 led to a radical cyclopropylcarbinyl rearrangement (**1.33** → **1.35**) to give the extended enolate **1.35**, which was subsequently

quenched with tetrabromocyclohexadiene (TBCHD) to provide the expanded α-bromo ketone **1.36**. The bromide was then eliminated with Li_2CO_3 to give diene **1.37**. During model studies of the ring expansion, if the C19 methyl group was only mono-brominated, Baran was unable to form the C10-C19 double bond after oxidation of the samarium enolate.

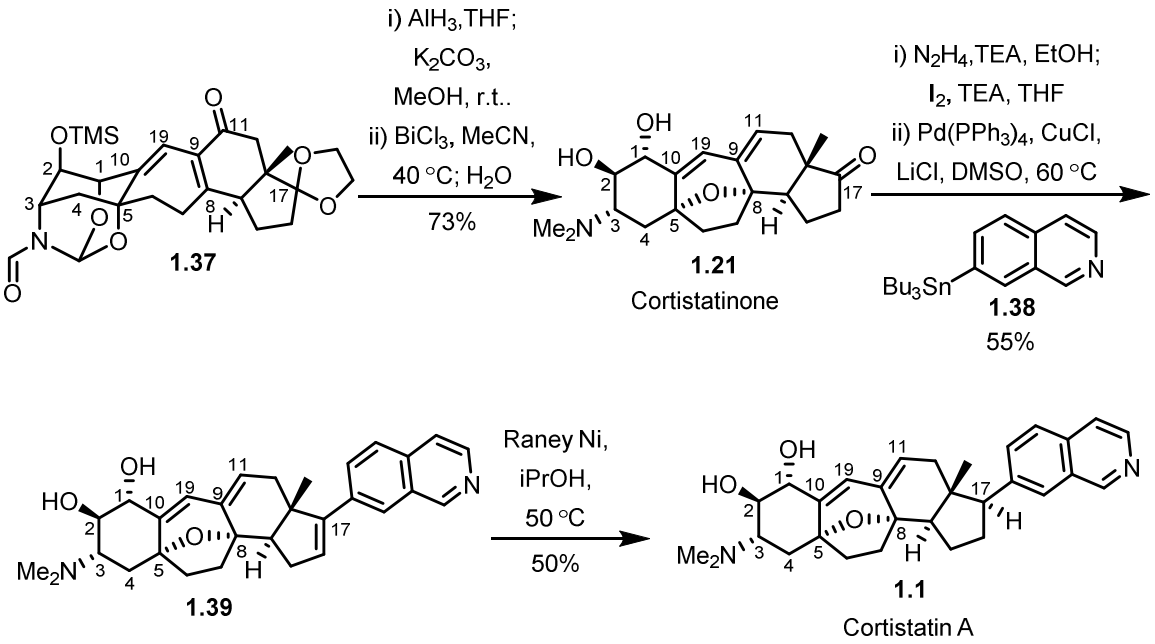
Scheme 1.4: Baran's key biomimetic ring expansion



Reduction of orthoimide **1.37** with AlH_3 proceeded to give the dimethylamino moiety at C3 and resulted in the concomitant reduction of the C11 ketone in one step (Scheme 1.5). Closure of the oxabicyclo [3.2.1] octene core initially proceeded stepwise *via* the acetylation of all the free hydroxyl groups followed by ionization of the C11 acetate with $MgBr_2 \bullet Et_2O$ and di-*t*-

butyl pyridine (DTBP) as a proton sponge to give key intermediate cortistatinone **1.21** in 65% yield for the three step sequence. The 2011 publication demonstrated a more streamlined procedure, both ionizing the alcohol directly using $BiCl_3$ as the Lewis acid as well as deprotecting the dioxolane acetal in 62% yield in only one step. Installation of the isoquinoline moiety began with transforming the ketone to the vinyl iodide *via* the Barton procedure (H_2NNH_2, I_2, base),[65] followed by a Stille coupling with the stannyl isoquinoline **1.38** provided the C16-C17 dehydro intermediate **1.39** (Scheme 1.5). Reducing the C16-C17 double bond proved challenging. Reductants such as Pd/C or diimide gave over-reduction or low yield. Ultimately, Raney-Ni gave clean reduction to give cortistatin A (**1.1**) in 50% yield. Barans's synthesis of cortistatin A (**1.1**) was completed in just 15 steps from prednisone (**1.25**) and in 2.1% yield.

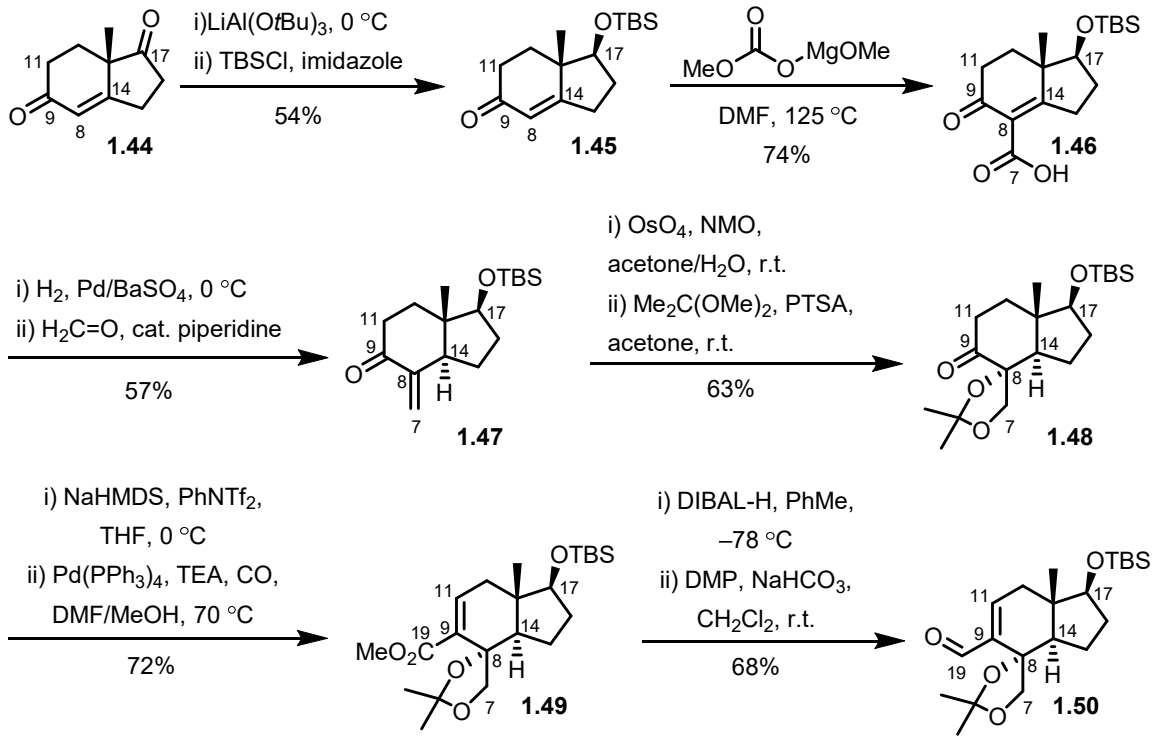
Scheme 1.5: Baran's completion of Cortistatin A (**1.1**)



1.3.2: NICOLAOU'S TOTAL SYNTHESIS

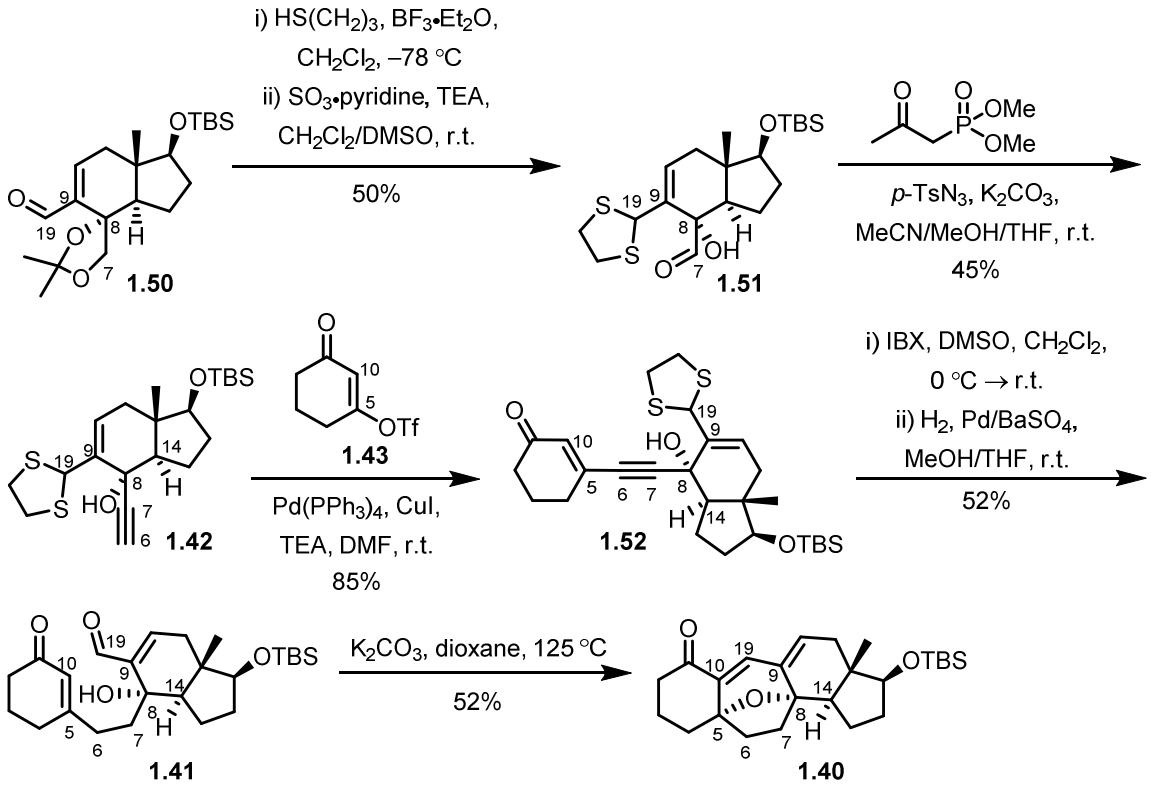
Nicolaou published his total synthesis of cortistatin A (**1.1**) in 2008[28] and followed up with a full paper in 2009[29] where he also synthesized cortistatin J and examined the biological activity of several intermediates. Using the previously reported synthesis of **1.47** by Danishefsky, the Hajos-Parrish ketone (**1.44**) was reduced diastereoselectively and the resulting alcohol protected as the TBS ether to furnish **1.47** (Scheme 1.7). The enone was then α-carboxylated with methylmagnesium carbonate (MMC) to provide dienone **1.46**. The double bond was reduced using Rosenmund's catalyst ($Pd/BaSO_4$) followed by a piperidine catalyzed aldol/decarboxylation sequence with formaldehyde to give the exo-methylene compound **1.47**. The exo-methylene group was diastereoselectively dihydroxylated under Upjohn conditions (OsO_4, NMO)[63] and protected as an acetonide to give **1.48**. Conversion of the ketone to the vinyl triflate with NaHMDS and McMurray's reagent ($PhNTf_2$)[84] followed by methoxycarbonylation provided **1.49**. Reduction of the ester with diisobutylaluminum hydride (DIBAL-H) followed by reoxidation with Dess-martin periodinane (DMP) gave **1.50**.

Scheme 1.7: Synthesis of intermediate **1.50** from Hajos-Parrish ketone (**1.44**)



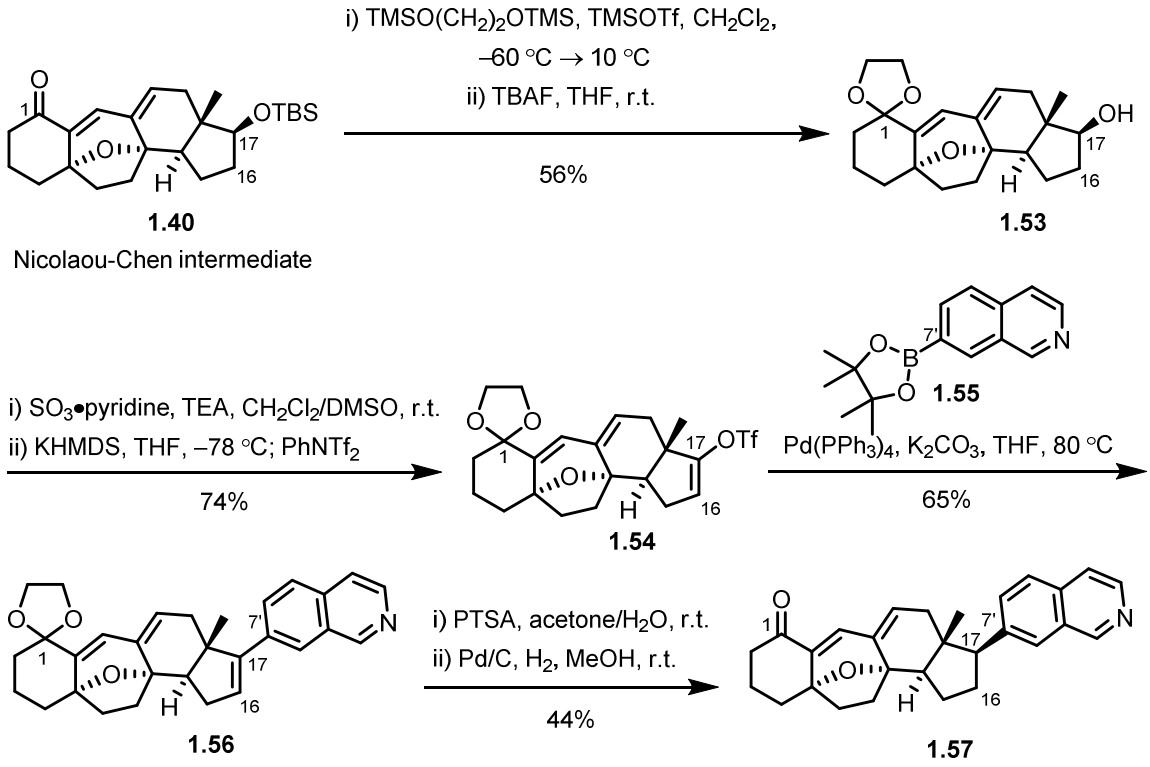
Protection of the aldehyde in **1.50** with BF_3•Et_2O and 1,2-dithioethane resulted in concomitant removal of the dioxolane ketal to unmask the diol. Oxidation of the primary alcohol to α-hydroxy aldehyde under Parikh-Doering conditions (SO_3•Pyridine, DMSO)[64] gave **1.51** (Scheme 1.8). Conversion of the aldehyde to the acetylene with the Ohira-Bestmann[76] reagent (made *in situ* with dimethyl-2-oxopropylphosphonate and tosyl azide) then gave the CD ring fragment **1.42**. Sonogashira coupling of **1.42** with β-keto vinyl triflate **1.43** gave yne-enone **1.52**. Oxidative deprotection of the dithiolane with 2-iodoxybenzoic acid (IBX) followed by reduction of the C6-C7 alkyne to the alkane was accomplished with Rosenmund's catalyst to give **1.46**. Ultimately, the key oxy-Michael/ aldol cascade proceeded cleanly with K_2CO_3 in dioxane to give the Nicolaou-Chen intermediate **1.40**.

Scheme 1.8: Synthesis of the Nicolaou-Chen intermediate (**1.40**)



Installation of the isoquinoline ring was achieved by a similar sequence to Baran's endgame. Protection of the ketone under Noyori's conditions (TMSOTf, 1,2 disiloxyethane)[77] as the dioxolane and subsequent deprotection of the TBS ether to alcohol gave **1.53** (Scheme 1.9). Parikh-Doering oxidation of the alcohol to the ketone, followed by conversion to the vinyl triflate with NaHMDS and McMurray's reagent provided **1.54**. Suzuki coupling of the borate ester **1.55** with vinyl triflate **1.54** furnished the C16-C17 dehydro intermediate **1.56**. Hydrolysis of the dioxolane followed by selective reduction of the C16-C17 double bond with Pd/C installed the isoquinoline with the desired β-stereochemistry. Curiously, while Nicolaou does not report any difficulty with this reaction, Pd/C catalyzed hydrogenation failed for Baran.

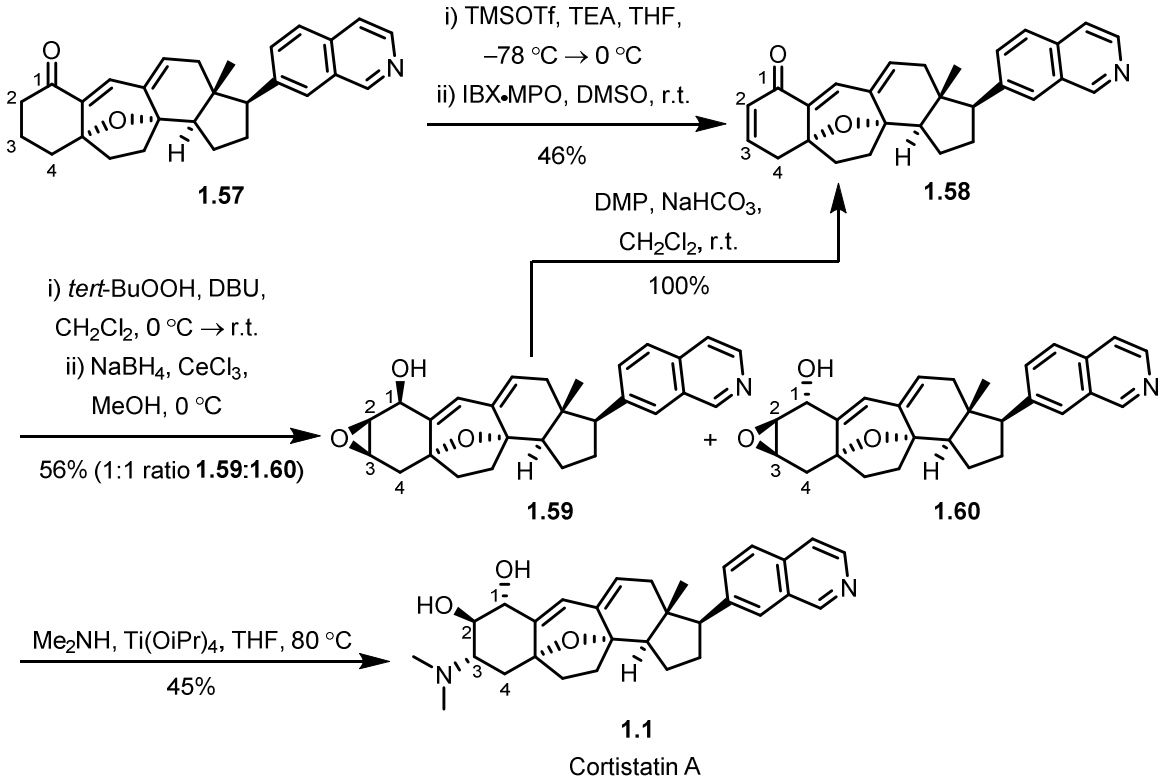
Scheme 1.9: Installation of the Isoquinoline



Installation of the C2 α-hydroxy and C3 β-dimethylamino groups took considerable development. Conversion of the ketone to the silyl enol ether followed by a Saegusa oxidation failed to provide the enone **1.58**. Ultimately, IBX•MPO (MPO = *p*-methoxypyridine N-oxide)[75] was successful in forming **1.58** (Scheme 1.10). The conjugate addition of nitrogen nucleophiles was initially investigated for the installation of the C3 dimethylamino group, but this resulted in the undesired addition to the β-face. Taking advantage of the observed facial selectivity, the enone **1.58** was epoxidized under nucleophilic conditions to provide the β-epoxide, setting up the future *trans* relationship between C2 and C3. After screening multiple reductants, the only conditions that gave decent yield of **1.60** were Luche conditions ($NaBH_4$, $CeCl_3$•$7H_2O$, MeOH),[69] giving a mixture of diastereomers **1.59** and **1.60** (1:1 dr, 80% combined yield). Undesired diastereomer **1.59** can be recycled by re-oxidation with DMP, but in his 2009 paper, Nicolaou uses **1.59** as an intermediate toward the synthesis of cortistatin J. Lewis acid-catalyzed opening of the epoxide to synthesize cortistatin A (**1.1**) proved to be poorly selective, giving a

mixture of C3 and C2 attack (1.26:1 ratio C3:C2 attack, 83% combined yield). Protecting the alcohol at C1 with TBS disfavored attack of the epoxide at C2 (4:1 C3:C2) but proceeded to add two extra steps to the synthesis.

Scheme 1.10: Nicolaou's completion of Cortistatin A (**1.1**)

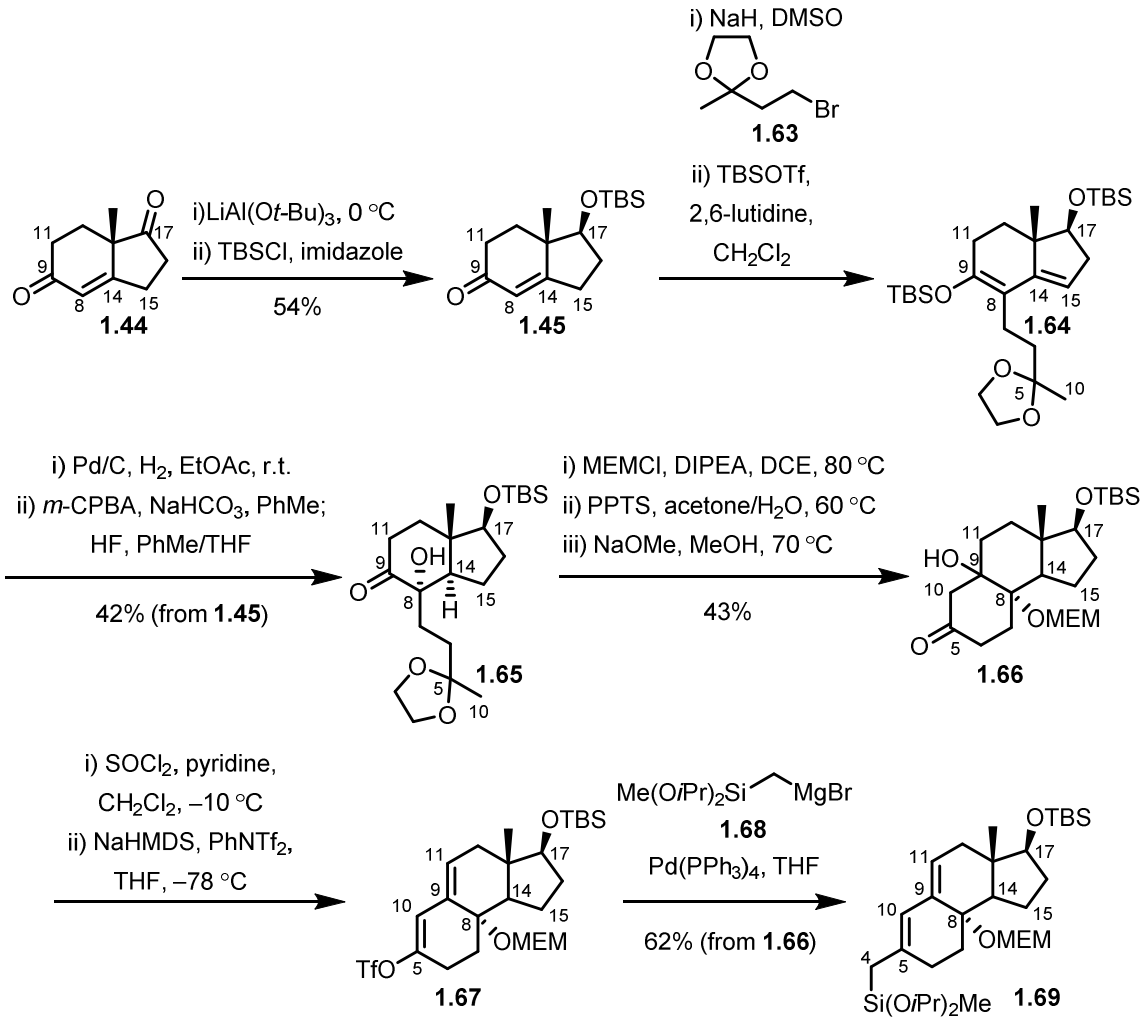


With one of the highest step counts and the lowest yield (30 steps (from Hajos-Parrish ketone (**1.44**)) and 0.009% yield), Nicolaou's synthetic strategy leaves room for improvement. Of the 31 steps from Hajos-Parrish ketone (**1.44**), eight are protection/deprotection steps and 13 are oxidation state adjustments. Several intermediates such as **1.57** (7 nM GI_{50} against HUVEC's), **1.58** (8 nM), and **1.59** (8 nM) showed equipotency to cortistatin A (**1.1**), revealing that the isoquinoline seems to be important for activity, while the substituents on the A ring are somewhat less consequential.

1.3.3: SHAIR'S TOTAL SYNTHESIS

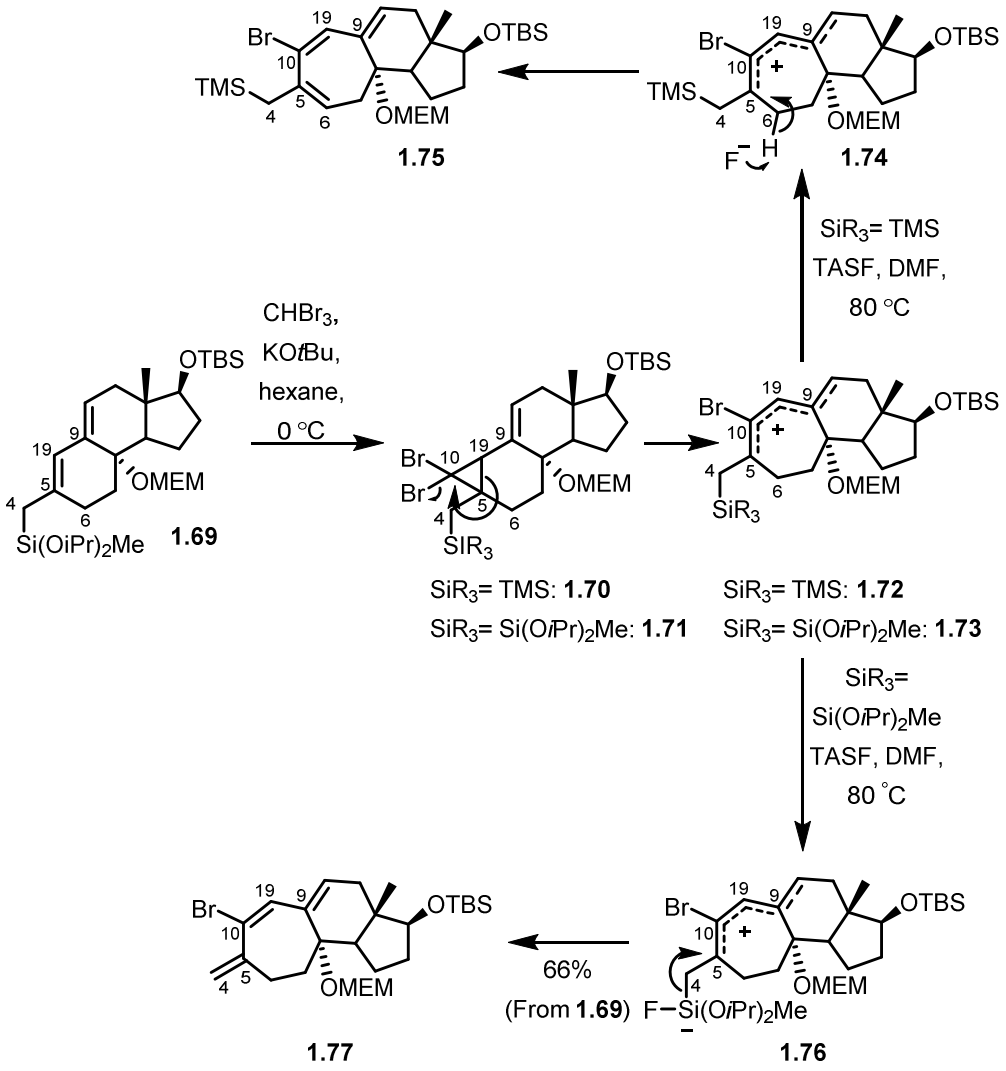
In 2008,[30] Shair published his approach to cortistatin A (**1.1**). Like Baran, Shair envisioned cortistatin to come from a late stage installation of the isoquinoline ring from cortistatinone **1.21** (Scheme 1.11). Hajos-Parrish ketone **1.44** was diastereoselectively reduced and subsequently protected as the TBS ether to furnish **1.45** (Scheme 1.12). α-Alkylation of the enone moiety under Molander's[82] conditions with bromodioxolane **1.63** and formation of the extended silyl enol ether gave **1.64**. Selective reduction of the C14-C15 double bond followed by a Rubottom[71] oxidation provided the Robinson annulation precursor **1.65**. Protection of the alcohol as the methoxyethoxymethyl ether (MEM) followed by deprotection of the ketone set up the formation of the B-ring via an intramolecular aldol to give BCD ring intermediate **1.66**. Elimination of the alcohol with $SOCl_2$ to form the enone followed by conversion to the vinyl triflate with NaHMDS and McMurray's reagent provided **1.67**. Kumada coupling with the silyl reagent **1.68** provided key allyl silyl compound **1.69**.

Scheme 1.12: Shair's synthesis of intermediate **1.69** from Hajos-Parrish ketone **1.44**



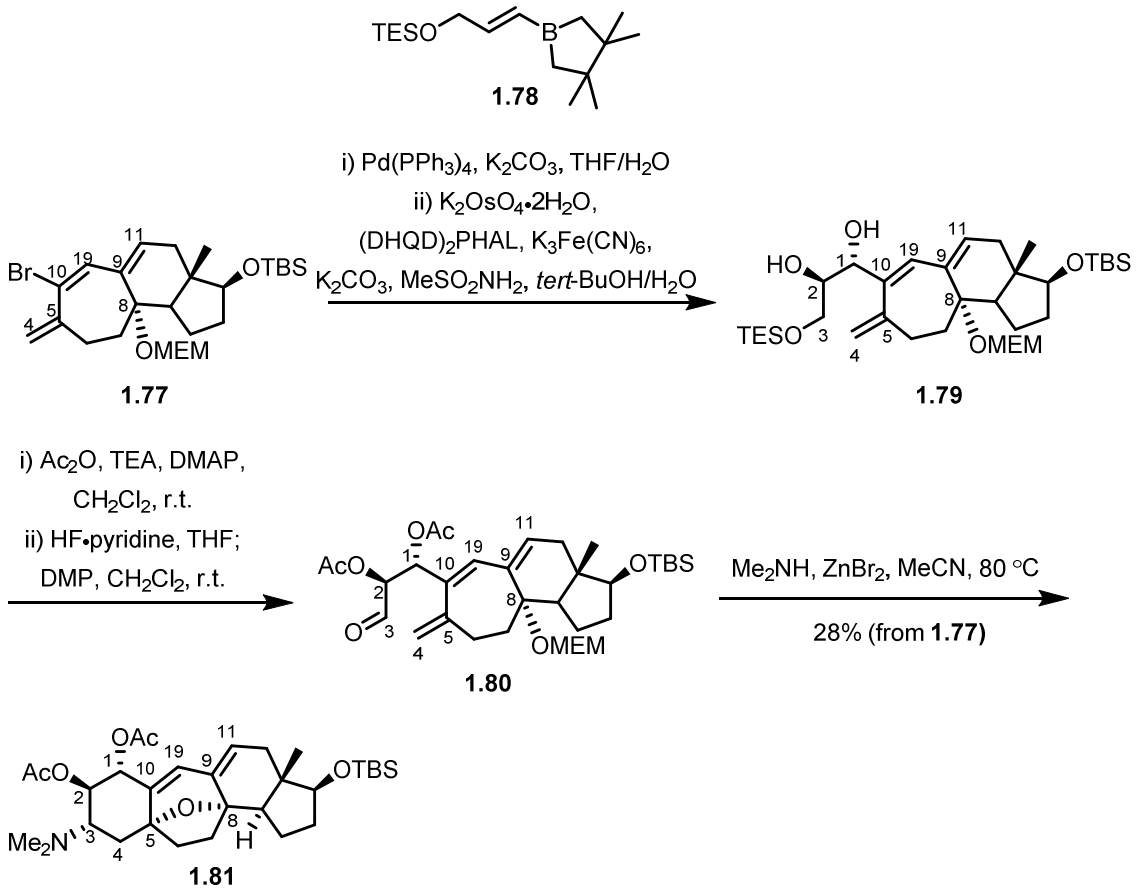
Allyl siloxane **1.69** then underwent a cyclopropanation with dibromo carbene to give **1.71** (Scheme 1.13). The key siloxy-directed cyclopropylcarbinyl rearrangement required proper choice of the silicon group. When TMS was used instead of the siloxane at C4, the ring expansion favored deprotonation by fluoride at C6, rather than elimination of the TMS group to provide the endocyclic olefin **1.75**. The enhanced Lewis acidity of the siloxane favors the formation of the "ate" complex **1.76** with fluoride anion which eliminates to the exocyclic olefin in **1.77**.

Scheme 1.13: Shair's key siloxy-directed ring expansion



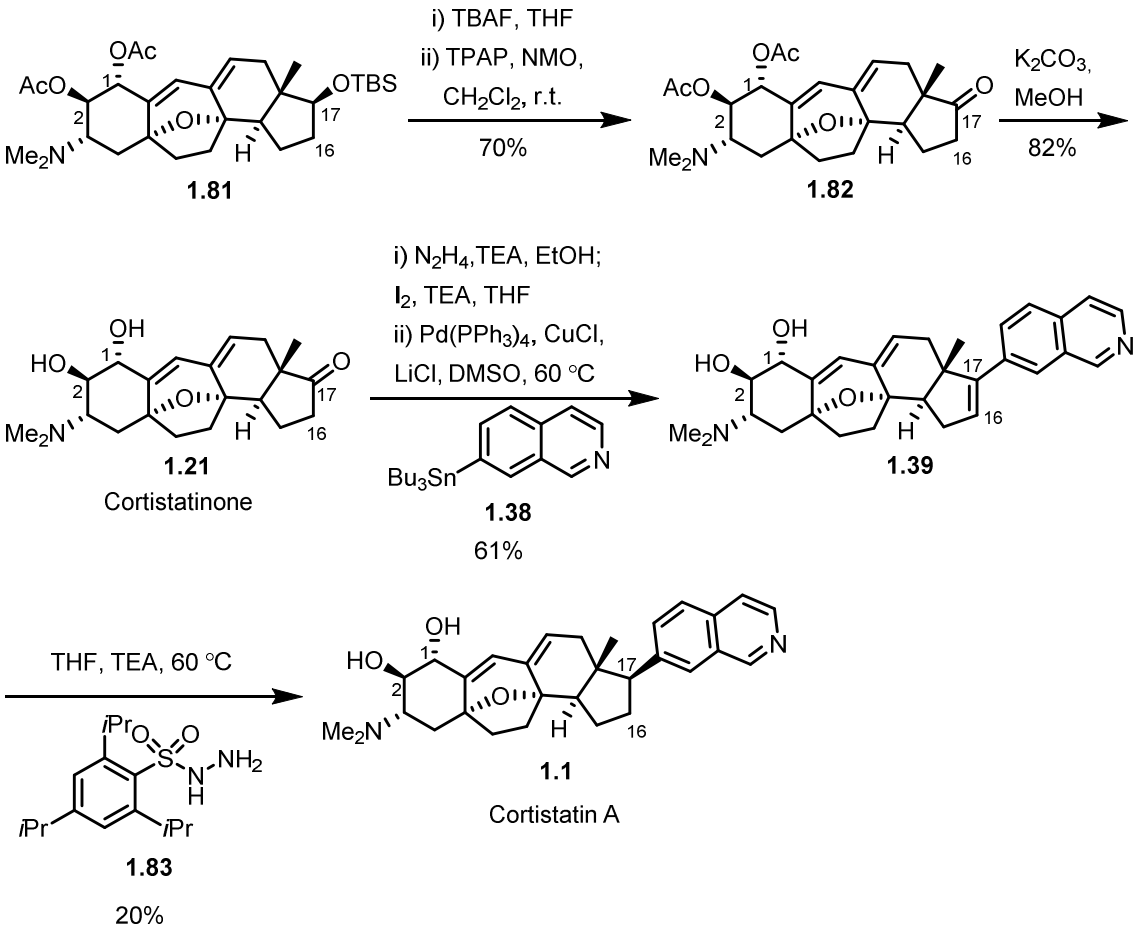
Suzuki coupling of **1.77** with vinyl boronate **1.78** followed by Sharpless asymmetric dihydroxylation provided triol **1.79**. Deprotection of the TES ether to the primary alcohol, followed by selective oxidation gave key transannular aza-Prins precursor **1.80** (Scheme 1.14). Ultimately, the aza-Prins reaction proceeded with excellent diastereocontrol, along with concomitant removal of the MEM protecting group to give **1.81**.

Scheme 1.14: Shair's key transannular aza-Prins



Completion of Shair's total synthesis mirrors the endgame of Baran, even intercepting cortistatinone **1.21** as an intermediate (Scheme 1.15). Deprotection of the TBS group to the alcohol, followed by a Ley oxidation (TPAP, NMO)[68] provided ketone **1.82**. Deprotection of the acetyl groups with K_2CO_3 and MeOH gave cortistatinone **1.21**. Conversion of the ketone to vinyl iodide under Barton's conditions followed by Stille coupling gave C16-C17 dehydro compound **1.39**. Selective reduction of the double bond proved challenging for Shair, reporting that only diimide reduced the C16-C17 double bond to give cortistatin A (**1.1**) in 25 steps and 0.0078% yield from Hajos-Parrish ketone **1.44**.

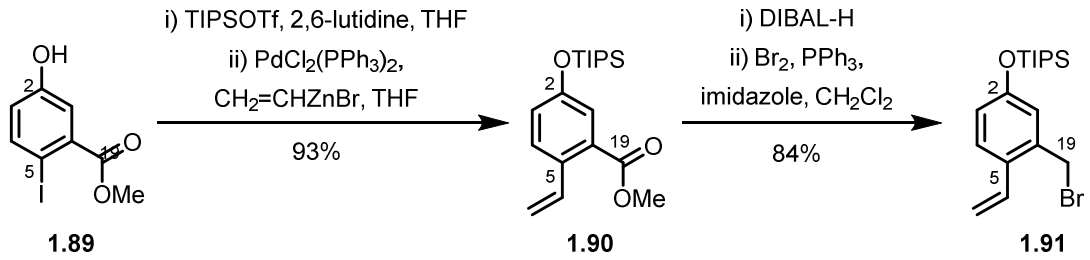
Scheme 1.15: Shair's completion of cortistatin A (**1.1**)



1.3.4: MYERS'S TOTAL SYNTHESIS

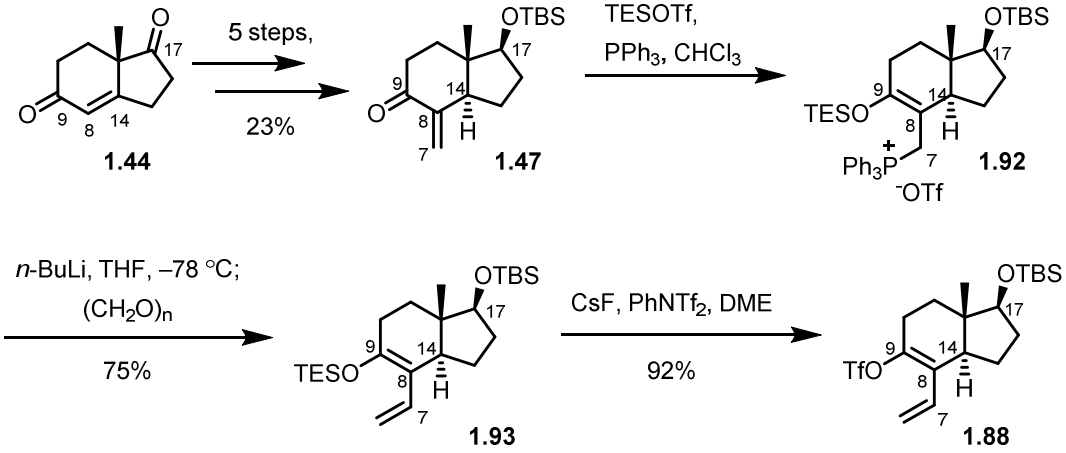
Myers goal in his 2010[31] publication was to develop a highly divergent synthesis from a common intermediate **1.85** (later intercepted by Yang) (Scheme 1.16). Myers managed to not only synthesize cortistatin A (**1.1**) and J but also K, L and other analogues for testing. Synthesis of key coupling partner **1.87** began with iodo phenol **1.89** (Scheme 1.17). Protection of the phenol as the triisopropyl silylether (TIPS) followed by a Negishi coupling with vinylzinc bromide gave carbomethoxy styrene **1.90**. The ester was reduced to the benzyl alcohol and then converted to the benzyl bromide **1.87** under Appel-like conditions using bromo triphenylphosphonium bromide.

Scheme 1.17: Synthesis of benzylic coupling partner **1.87**



Synthesis of the divinyl triflate **1.88** proceeded via TESOTf mediated conjugate addition of triphenylphosphine to enone **1.47** to provide an intermediate phosphonium salt **1.92** that was then used in a Wittig olefination with formaldehyde to furnish the TES dienol ether **1.93** (Scheme 1.18). Formation of the vinyl triflate under Corey's conditions (CsF, $PhNTf_2$)[79] provided **1.88**.

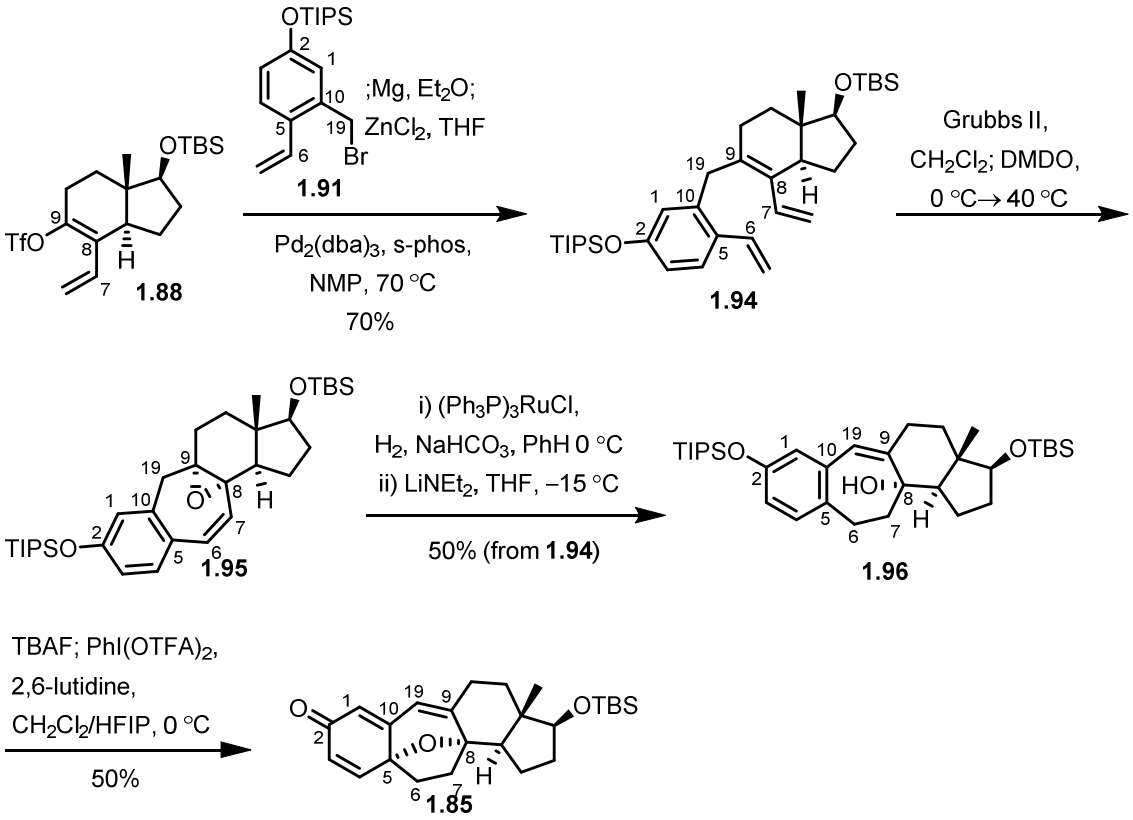
Scheme 1.18: Synthesis of vinyl triflate **1.88** from Hajos-Parrish ketone **1.44**



Conversion of the benzyl bromide **1.91** into the organozinc reagent took significant experimentation. Direct insertion of zinc under Knochel's conditions failed.[78] Formation of the Grignard reagent was sensitive to temperature and solvent and was plagued by Wurtz coupling as a side reaction. Only by etching the magnesium surface with ethylene dibromide to form magnesium with a great deal of surface area, was Myers able to form the benzylic Grignard reagent in good yield. Transmetalation of the Grignard reagent to the organozinc reagent with $ZnCl_2$ followed by Negishi coupling with vinyl triflate **1.88** provided **1.94** in 70% yield (Scheme

1.19). Initially, Myers tried to close the B ring *via* RCM and then selectively reduce the C6-C7 double bond, but he was unable to do so. Fortuitously, Myers found that the C8-C9 double bond reacted selectively with dimethyldioxirane (DMDO) to provide the epoxide **1.95** as a single diastereomer. Hydrogenation of the C6-C7 olefin with Wilkinson's catalyst and $NaHCO_3$ as an acid scavenger, followed by selective elimination of the epoxide at C19 gave allyl alcohol **1.96**. Phenolic oxidation with bis-trifluoroacetyl iodosylbenzene (PIFA) proceeded in 50% yield to give the intermediate **1.85**.

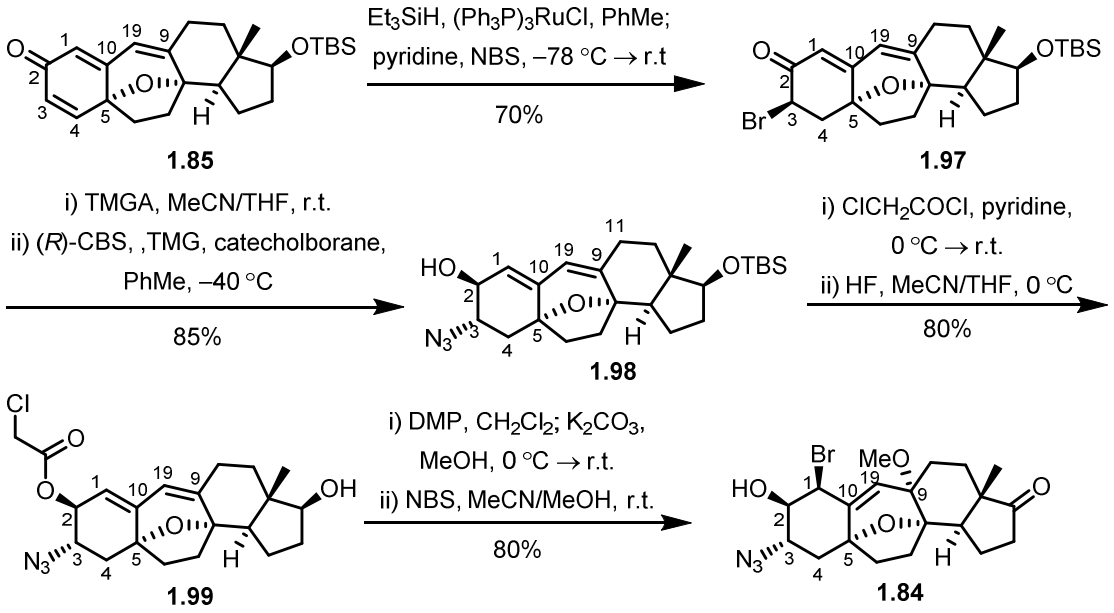
Scheme 1.19: Synthesis of the Myers-Flyer intermediate (**1.85**)



Conjugate reduction of the C3-C4 double bond in **1.85** with triethylsilane and Wilkinson's catalyst followed by bromination of the silyl enol ether gave the bromo-ketone **1.97** with the desired β-stereochemistry (Scheme 1.20). The inclusion of pyridine to complex the Wilkinson's catalyst proved to be essential for good diastereoselectivity. Displacement of the C3 bromide with tetramethylguanidinium azide (TMGA) followed by a diastereoselective reduction

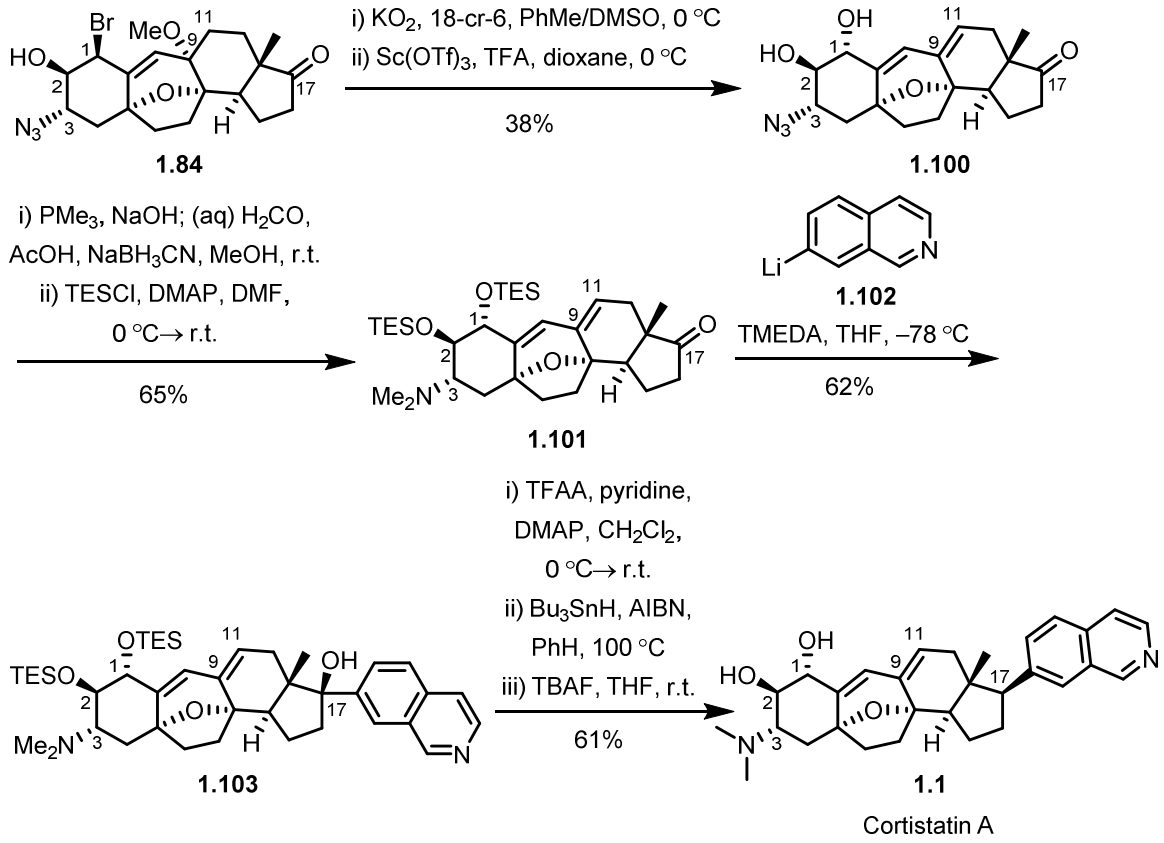
of the enone with the Corey-Bakshi-Shibata (CBS) catalyst provided key intermediate **1.98**. Protection of the alcohol moiety of **1.98** with chloroacetyl chloride followed by deprotection of the alcohol on the D ring gave **1.99**. The C17 alcohol was then oxidized with DMP to the ketone and exposure to NBS in MeCN/MeOH led to selective bromination at C1 and methanol capture at C9 to furnish intermediate **1.84**.

Scheme 1.20: Synthesis of intermediate **1.84**



Nucleophilic displacement of the bromide group in **1.84** with KO_2 followed by Lewis acid-mediated elimination of the methyl ether to form the C9-C11 double bond gave **1.100** (Scheme 1.21). Staudinger[73] reduction of the azide moiety followed by in situ reductive amination installed the C3 dimethylamino group. Protection of the C1 and C2 alcohols as the TES ethers provided **1.101**. Cognizant of the difficulties in reducing the C16-C17 double bond, Myers was inspired by the work of Hirama, who developed an alternate procedure for installing the isoquinoline ring (see Scheme 1.25 and 1.26 **1.53→1.123**). Addition of the lithiated isoquinoline **1.102** to the ketone **1.101** in the presence of tetramethylethylenediamine (TMEDA) gave **1.103**, followed by the Jang[80,81] modification of the Barton deoxygenation gave cortistatin A (**1.1**) in 28 steps and in 0.105% yield from Hajos-Parrish ketone **1.44**.

Scheme 1.21: Myers's completion of Cortistatin A (**1.1**)

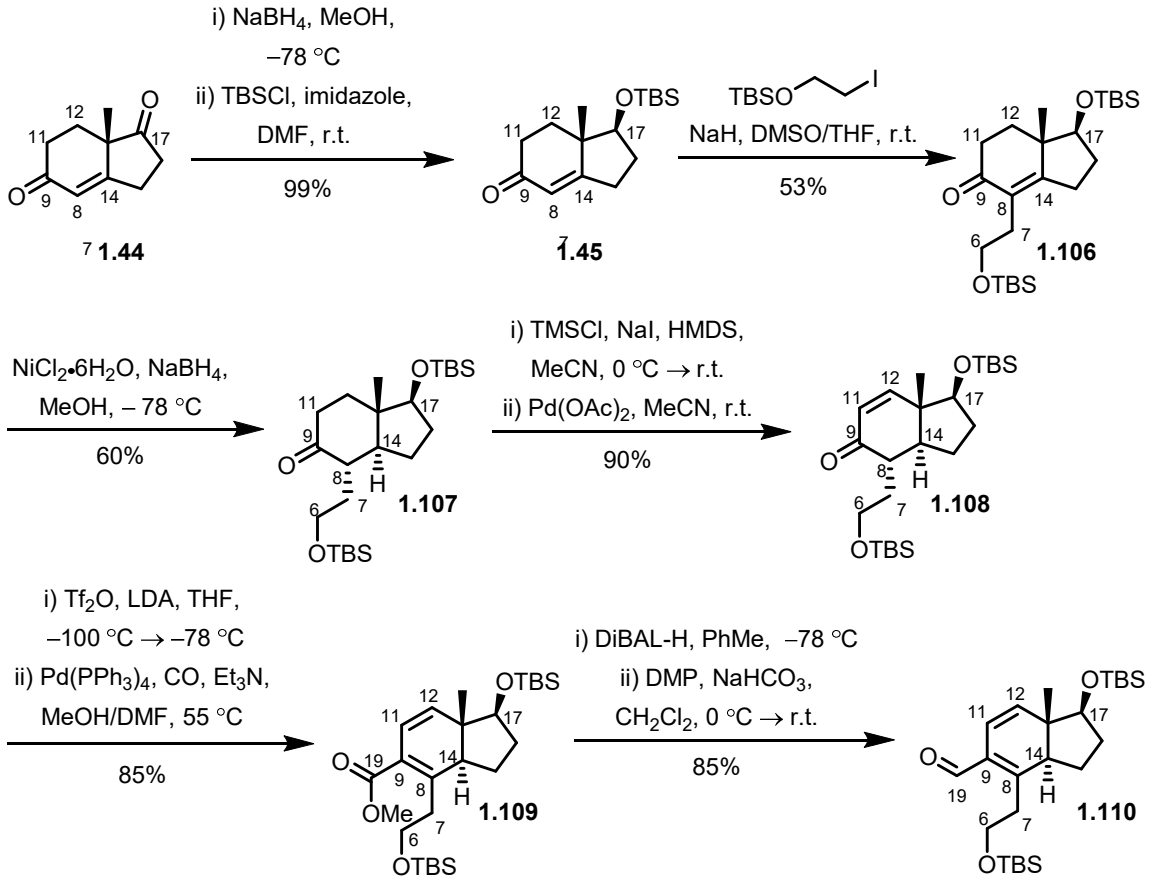


1.3.5: HIRAMA'S TOTAL SYNTHESIS

Hirama published his progress to the core of cortistatin A (1.1) (**1.1**) in 2008[53] followed by a formal synthesis in 2009[34] where he intercepted the Nicolaou-Chen intermediate **1.40**, and a total in 2011.[32] Hajos-Parrish ketone (**1.44**) was reduced and protected to give **1.45** (Scheme 1.23). The enone was alkylated at C8 under Molander's[82] conditions with TBS protected 2-iodoethanol to provide enone **1.106**. Reduction of the C9-C14 double bond in enone **1.106** turned out to be poorly diastereoselective. Reduction with Pd/C-H_2 favored addition of hydrogen to the β-face by 2.4:1. Nickel boride at –78 °C managed to reverse the selectivity to 1:4 in favor addition to the α-face to furnish ketone **1.107**. Conversion of the ketone in **1.107** to the silyl enol ether under thermodynamic conditions, followed by a Saegusa[72] oxidation provided enone **1.108** with the C11-C12 double bond. Deprotonation of **1.108** with LDA followed by quenching with triflic anhydride (Tf_2O) gave a vinyl triflate that was subsequently methoxycarbonylated to give

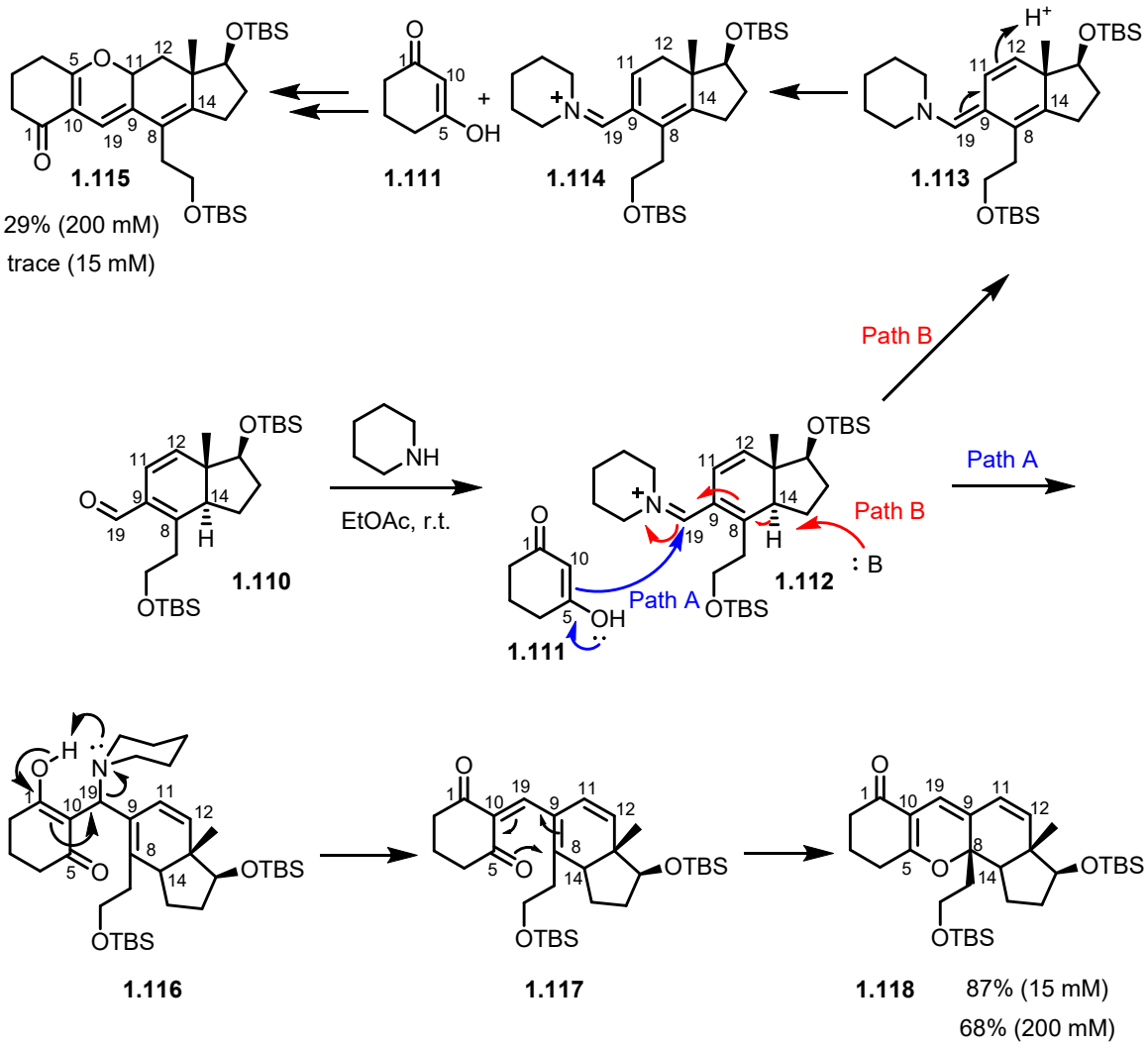
ester **1.109**. Reduction of the ester with DIBAL-H followed by oxidation to the aldehyde with DMP furnished **1.110**.

Scheme 1.23: Hirama's Synthesis of intermediate **1.110** from Hajos-Parrish ketone **1.44**



The piperidine catalyzed Knoevenagel/electrocyclic cyclization of **1.110** with 1,3-cyclohexadione and aldehyde **1.110** initially proceeded in 68% yield, forming significant amounts of byproduct **1.115**, which was thought to be formed via tautomerization of the iminium intermediate **1.112** (Scheme 1.24). Fortunately dilution from 200 mM to 15 mM favored formation of the desired **1.118** in 87% yield.

Scheme 1.24: Hirama's key piperidine catalyzed Knoevenagel/electrocyclization

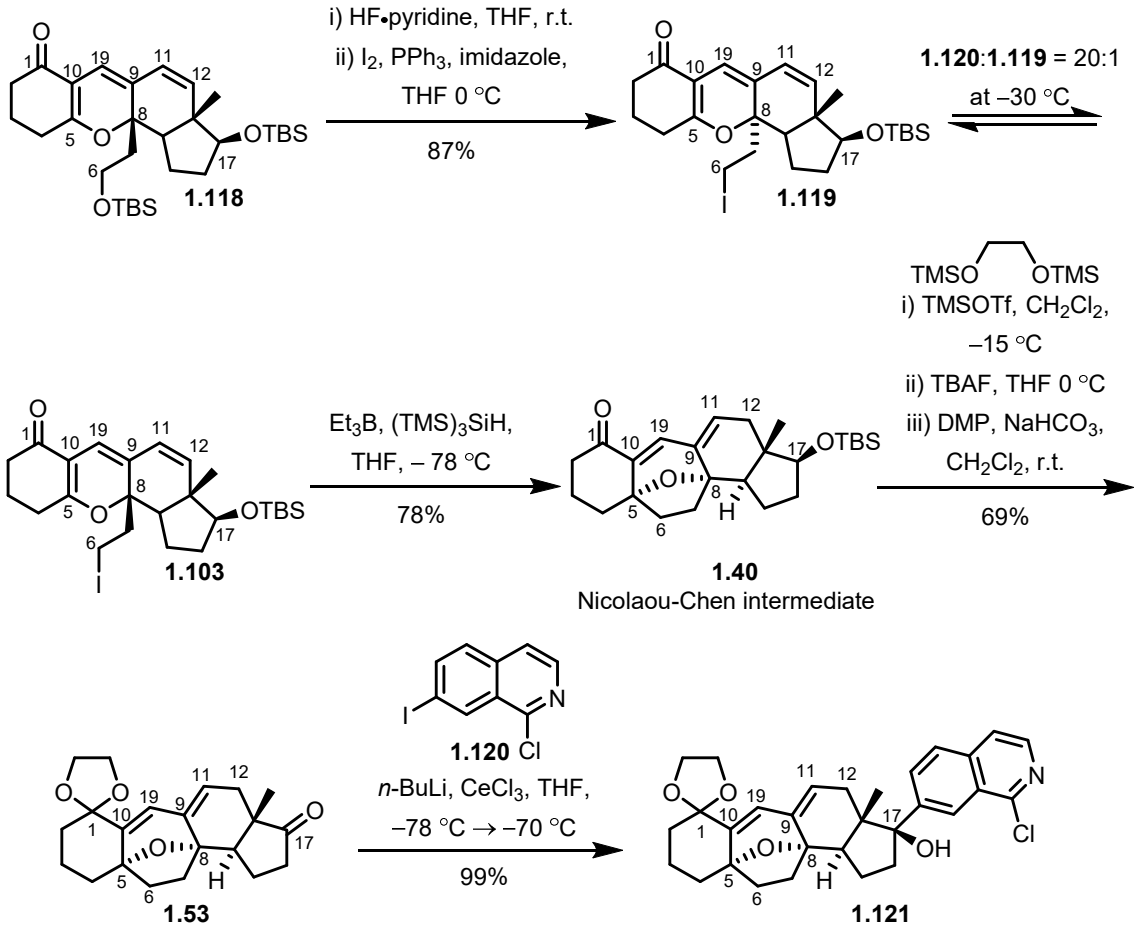


Selective deprotection of the primary TBS ether with HF•Pyridine, followed by iodination gave **1.103** (Scheme 1.25). Interestingly, Hirama observed epimerization at C8 due to reversible electrocyclization at room temperature. Hirama found that cooling to low temperatures favored the desired β-diastereomer and thus used a low temperature radical initiator (Et_3B, O_2) to cyclize **1.103** to the Nicolaou-Chen intermediate **1.40** as a single diastereomer.

In 2011, Hirama continued his work, applying his isoquinoline addition methodology and improving the endgame. Protection of the ketone of **1.40** as the dioxolane under Noyori's conditions followed by deprotection and oxidation of the C17 hydroxyl group provided **1.53**.

Addition of the organocerate **1.120** to ketone **1.53** gave **1.121** as a mixture (1.8:1) β:α of epimers at C17. The chlorine substitution was necessary due to addition of *n*-BuLi into the isoquinoline.

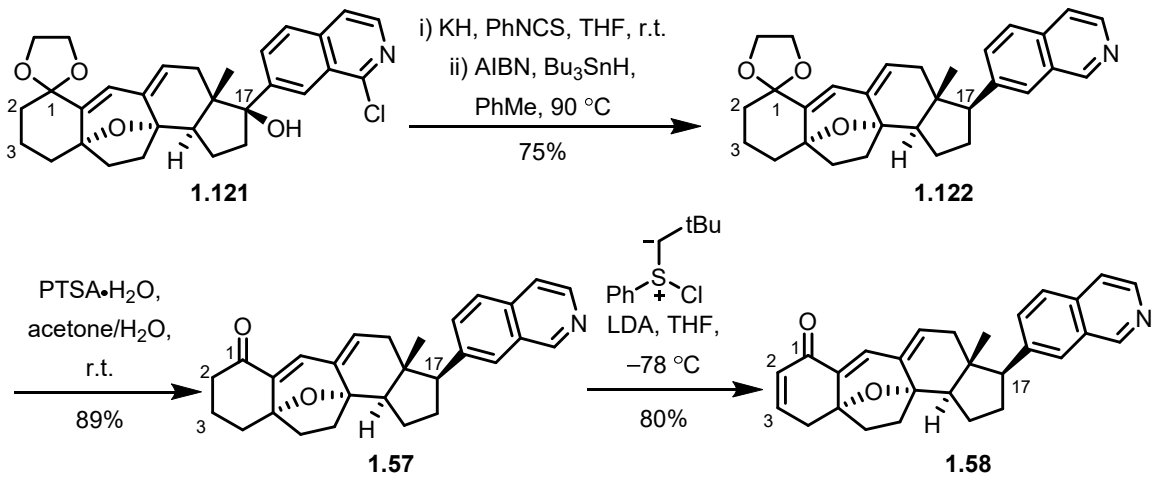
Scheme 1.25: Synthesis of Nicolaou-Chen intermediate **1.40** and endgame improvement



Formation of the tertiary thiohydroxamate ester followed by Barton[66,67] deoxygenation furnished **1.122** as a single diastereomer (Scheme 1.26). Hydrogen was added selectively to the α-face regardless of the stereochemistry of the C17 thiohydroxamate ester. Hirama's method of installing the isoquinoline offers significant improvements over the methods of Baran and Nicolaou (73% yield over three steps vs. 27% over three steps). Deprotection of the dioxolane

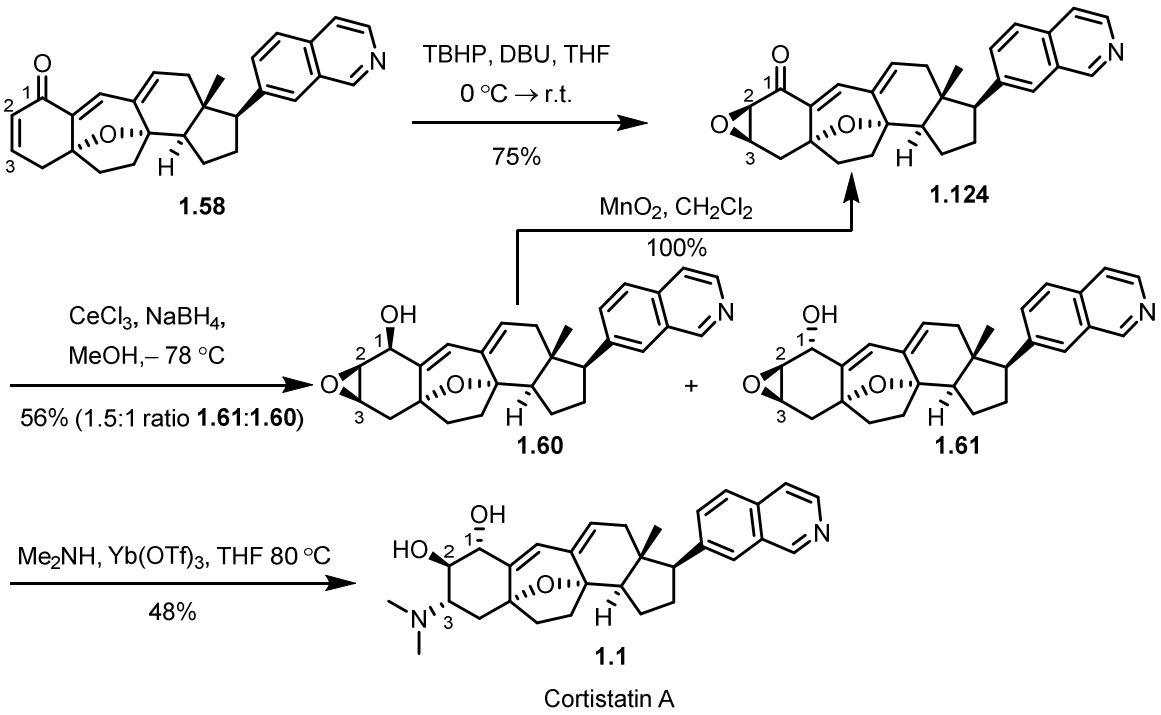
and oxidation with Mukaiyama's reagent[83] to give enone **1.58** also offers an improvement over Nicolaou IBX•MPO sequence (80% vs. 46%).

Scheme 1.26: Synthesis of Nicolaou-Chen intermediate **1.58** and endgame improvement



Like Nicolaou, Hirama attempted to add nitrogen nucleophiles to the enone in **1.58** to install the dimethylamino group. He was able to successfully add dimethylamine or $TMSN_3$ into the enone with the requisite stereochemistry at C3, but was unable to oxidize the α-position of the ketone. Following, the failure to add nucleophiles to the enone, Hirama decided to follow Nicolaou's endgame and epoxidized the enone to give **1.124**. He found that by cooling the reaction mixture to –78 °C during the Luche reduction improved the diastereomeric ratio from 1:1 to 1.5:1 in favor of the desired **1.61** (Scheme 1.27). Finally, opening the epoxide with dimethylamine using $Yb(OTf)_3$ as a Lewis acid instead of $Ti(OiPr)_4$ offered slight improvement in the regioselectivity (2.3:1 vs. 1.3:1) to provide cortistatin A (**1.1**) in 25 steps in 1.01% yield (27 steps for the formal, 0.34%).

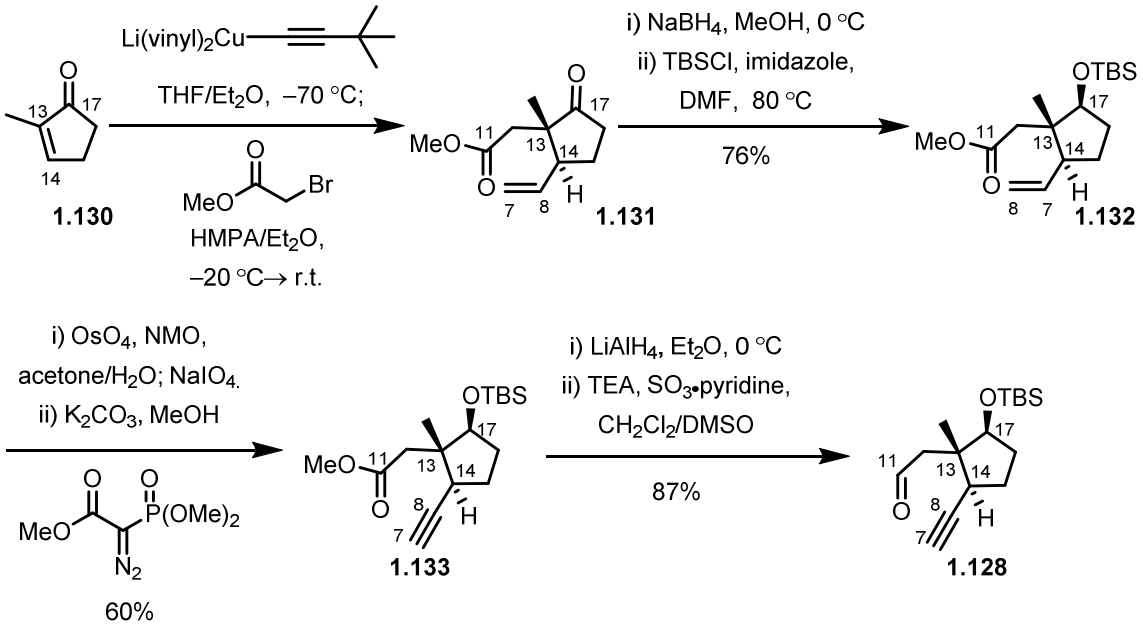
Scheme 1.27: Hirama's completion of Cortistatin A (**1.1**)



1.3.6: SARPONG'S FORMAL SYNTHESIS

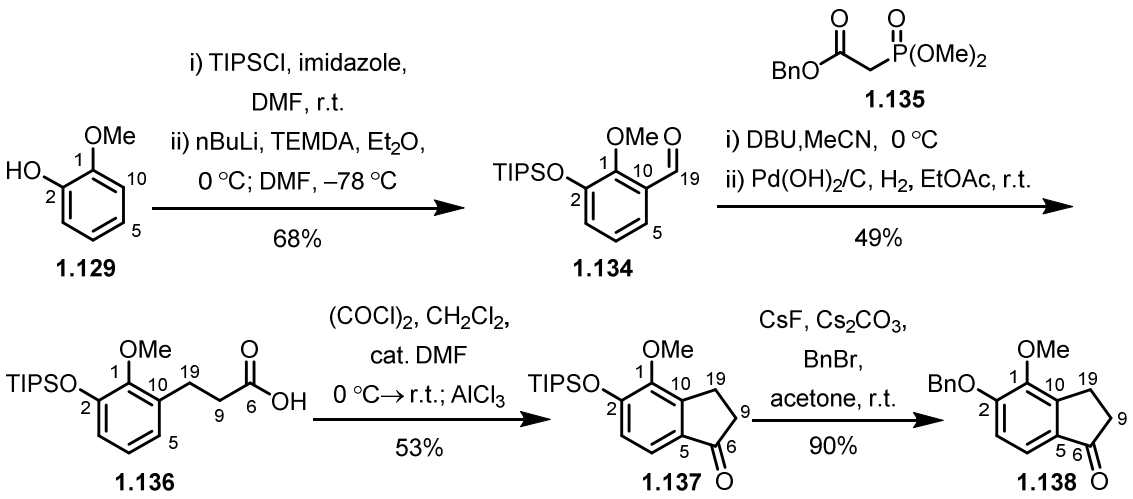
Sarpong published a model study in 2008[52] and a formal synthesis of cortistatin A in 2010.[35] The synthesis began with conjugate addition of vinyllithium into 2-methylcyclopentenone **1.130**, followed by alkylation with bromomethyl acetate to provide **1.131** (Scheme 1.29). Diastereoselective reduction, of **1.131** followed by protection as the TBS ether gave ester **1.132**. Oxidative cleavage of the vinyl group under Johnson-Lemieux[74] conditions followed by conversion to the alkyne with the Ohira-Bestmann provided **1.133**. Reduction of the ester with $LiAlH_4$, followed by Parikh-Doering oxidation gave coupling partner **1.128**.

Scheme 1.29: Sarpong's synthesis of coupling partner **1.128**



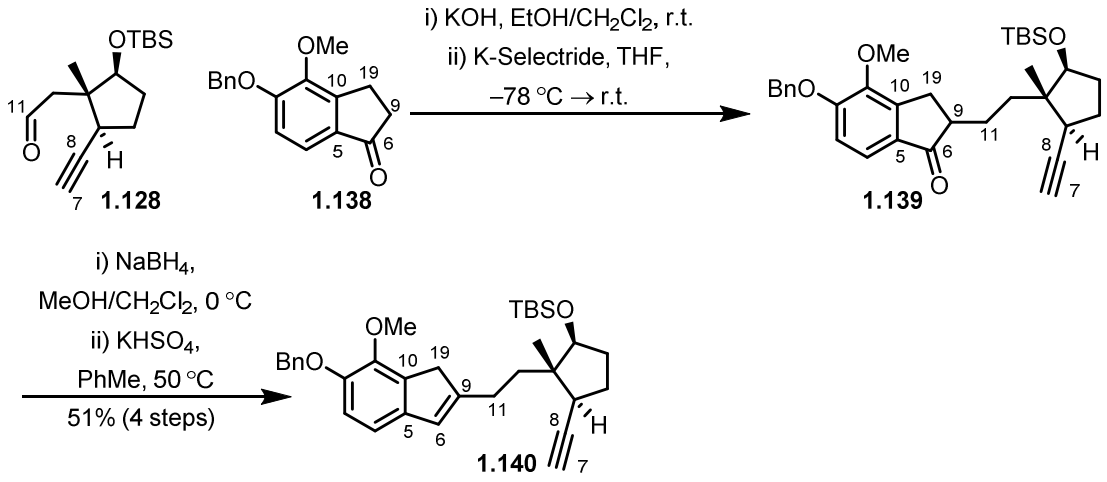
Synthesis of the indanone coupling partner **1.138** began with protection of guaiacol **1.129** as the TIPS ether, followed by ortho-lithiation and quenching with DMF to give aldehyde **1.134** (Scheme 1.30). Horner-Wadsworth-Emmons olefination of the aldehyde with phosphonate ester **1.135** resulted in a benzyl cinnamate ester that was subsequently reduced and debenzylated with Pearlman's catalyst ($Pd(OH)_2/C$) to furnish **1.136**. Conversion of **1.136** to the acetyl chloride followed by intramolecular Friedel-Crafts furnished indanone **1.137**. The TIPS ether was exchanged for the benzyl group to provide indanone **1.138** due to concerns with its stability in the presence of several Lewis acidic steps later in the synthesis.

Scheme 1.30: Synthesis of indanone **1.138**



Indanone **1.138** and aldehyde **1.128** were coupled via aldol condensation and the resulting double bond in the enone was reduced with K-Selectride to provide **1.139** (Scheme 1.31). Indanone **1.139** was reduced to the corresponding alcohol followed by acid catalyzed elimination to furnish indene **1.140**.

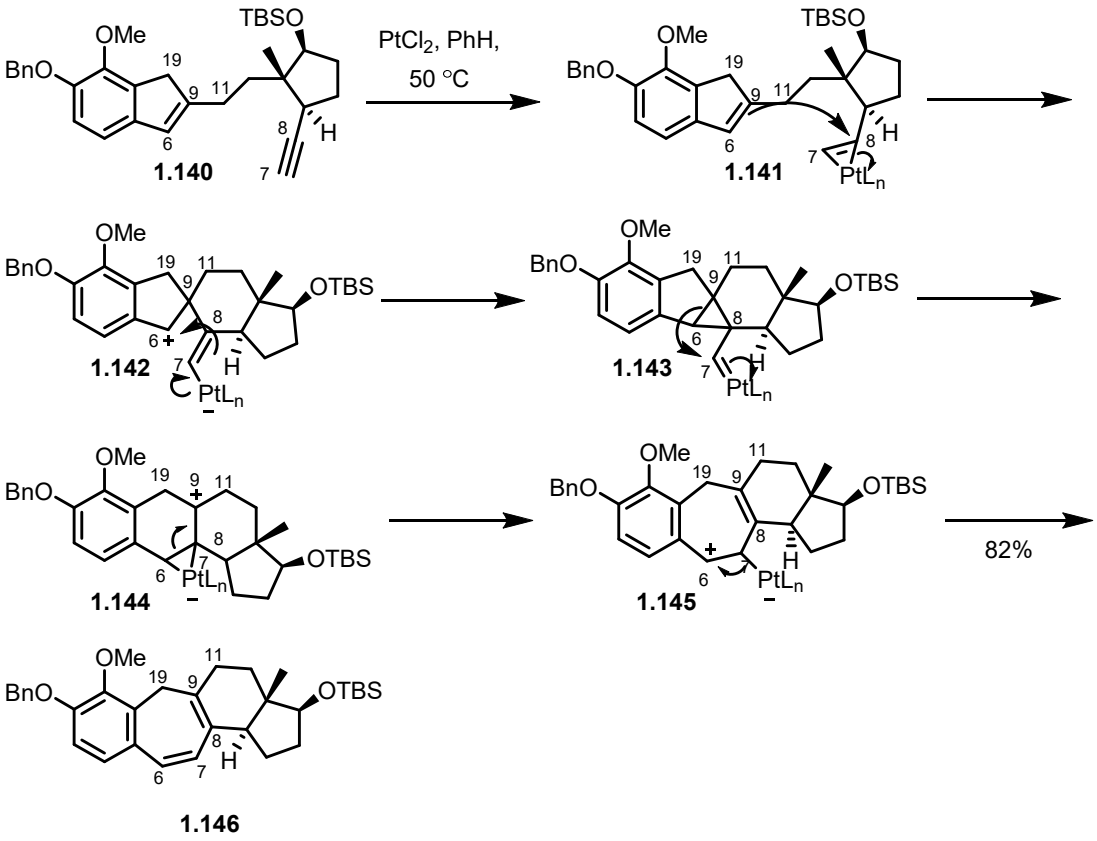
Scheme 1.31: Synthesis of key cycloisomerization precursor **1.140**



Several carbophilic Lewis acids were screened for the key cycloisomerization step, and $PtCl_2$ was found to convert indene **1.140** cleanly to the **1.146** in 82% yield (Scheme 1.32). The unusual transformation is thought to start with activation of the alkyne via the carbophilic Lewis

acid to provide **1.141**. Attack of the alkyne-metal complex (**1.141** → **1.143**) by the indene is thought to form a transient pentacyclic metal carbenoid **1.143**, which rearranges to the desired product **1.146**.

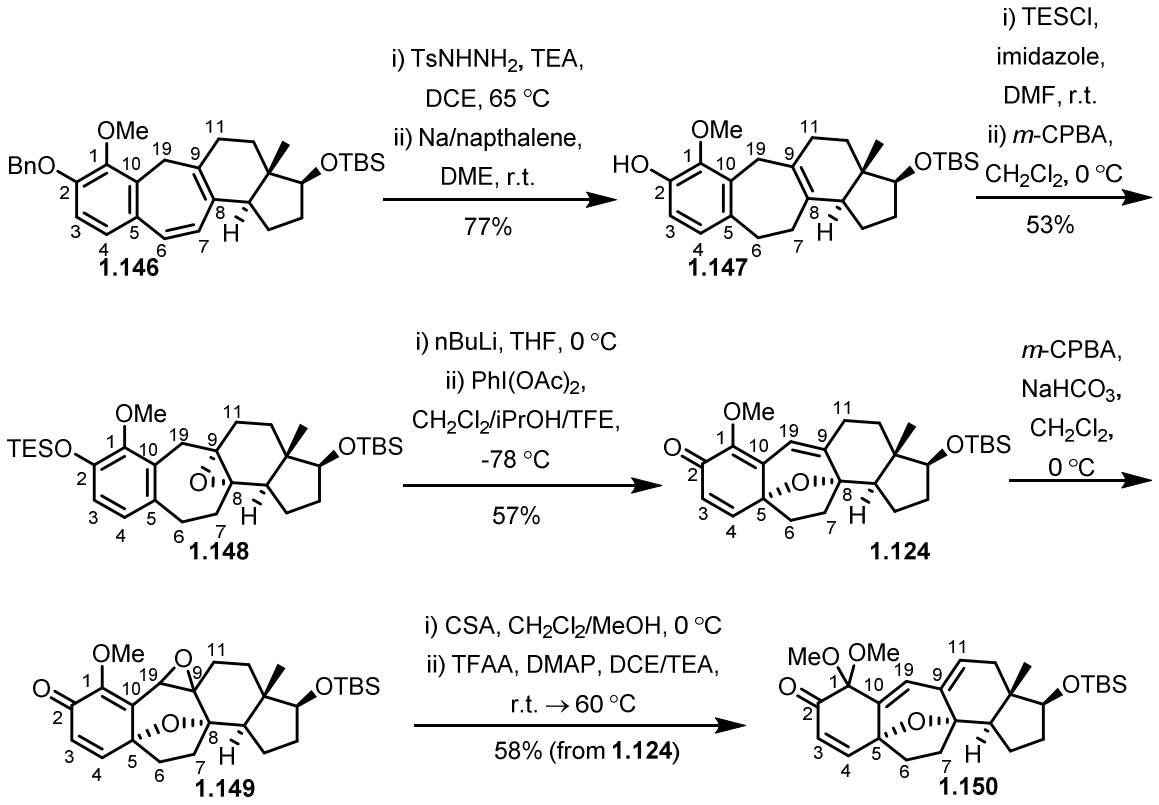
Scheme 1.32: Sarpong's key cycloisomerization



Selective reduction of the C6-C7 double bond with diimide followed by reductive removal of the benzyl group with Na/naphthalene furnished tetracycle **1.147** (Scheme 1.33). Protection of the phenol as the TES ether allowed for diastereoselective epoxidation to deliver **1.148**. Selective elimination of the epoxide at C19 with n-BuLi occurred with concomitant removal of the TES group to set up the key oxidative arene cyclization. Methanol, as the solvent, was too nucleophilic and led to solvent incorporation into the aromatic ring. The non-nucleophilic but acidic alcohol trifluoroethanol (TFE) furnished the desired product **1.124** but numerous other side products were also formed. Optimum conditions were found by using an alcohol co-solvent in addition to TFE. The C9-C11 double bond was installed by first

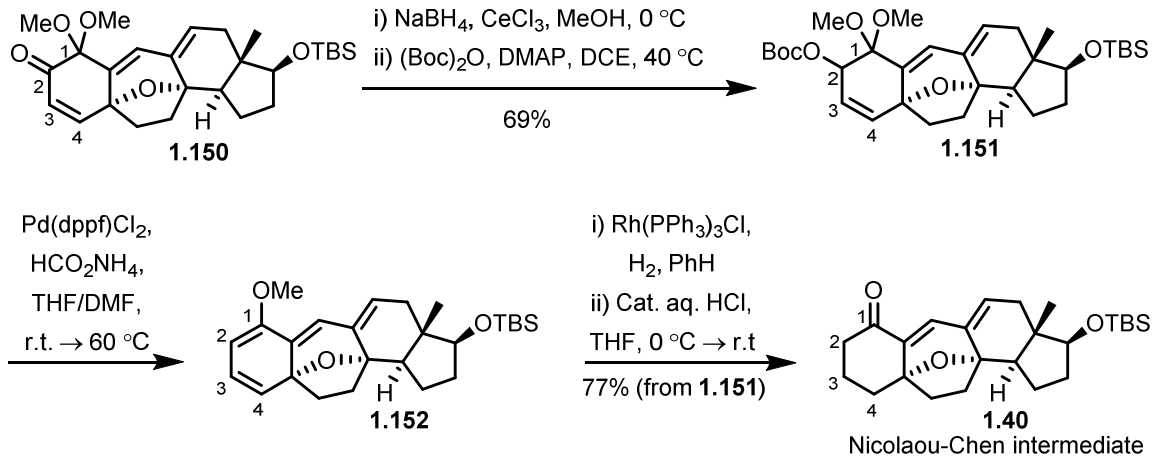
epoxidation of the C19-C9 double bond to provide the epoxide **1.149**. Acid catalyzed ring opening with CSA followed by elimination of the resulting C9 alcohol gave enone **1.150**.

Scheme 1.33: Sarpong's key oxidative arene cyclization



Reducing the enone **1.150** to intercept the Nicolaou-Chen intermediate **1.40** proved challenging (Scheme 1.34). The transformation was achieved by first reducing the enone under Luche conditions, followed by conversion of the allyl alcohol into the allylic carbonate **1.151**. Transfer-hydrogenation of the π-allyl cation intermediate furnished the divinyl ether **1.152**. Reduction of the C3-C4 double bond with Wilkinson's catalyst, followed by acid catalyzed deprotection provided the Nicolaou-Chen intermediate **1.40**, completing a formal synthesis of cortistatin A (**1.1**) in 35 steps and 0.18% yield.

Scheme 1.34: Sarpong's formal synthesis of Cortistatin A (**1.1**) via the Nicolaou-Chen intermediate **1.40**

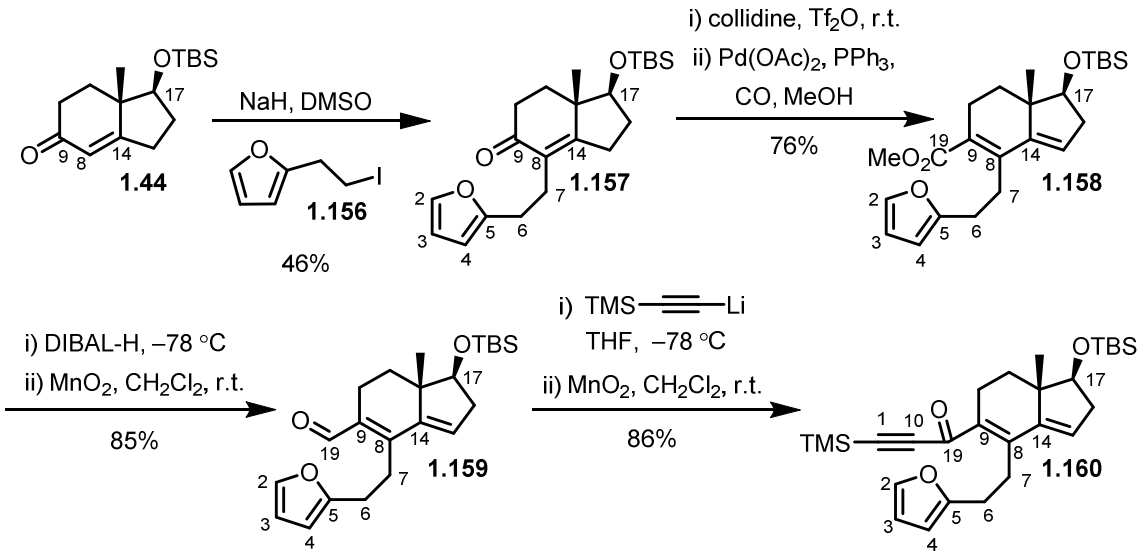


Like Danishefsky and Myers, Sarpong saw an oxidative arene cyclization from **1.125** to **1.124** as the key step toward the formation of the oxabicyclo-[3.2.1]-octene core (Scheme 1.28). The arene oxidation precursor was planned to come from indene **1.126** via Sarpong's novel cycloisomerization methodology, which he developed for the synthesis of the icetexanes.[62] Indene **1.126** was envisaged come from the coupling of aldehyde **1.128** and indanone **1.127**, which was planned to come from the simple starting materials of guaiacol **1.129** and 2-methyl-cyclopenenone **1.130**.

1.3.7: YANG'S FORMAL SYNTHESIS

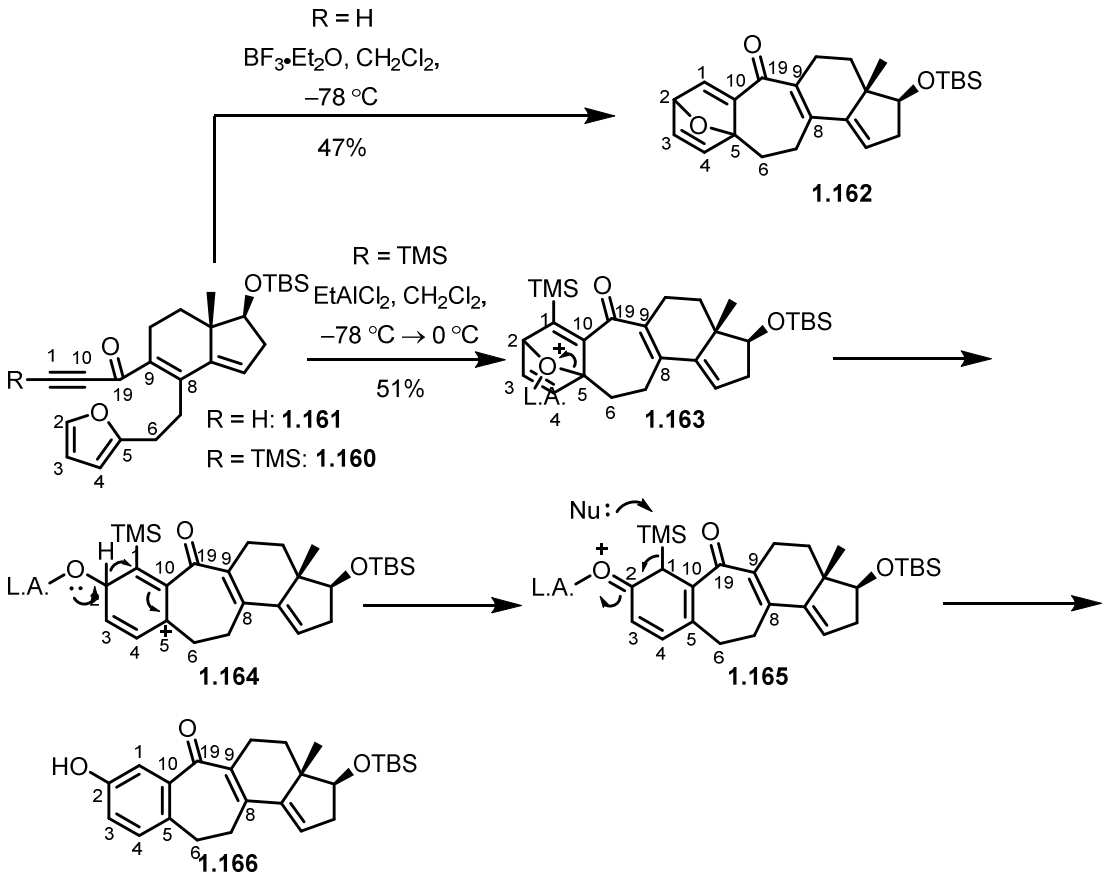
Yang published model studies in 2009[51] and a formal in 2011,[36] where he intercepted the Myers-Flyer intermediate **1.85**. Alkylation of Hajos-Parrish ketone (**1.44**) at C8 with furan **1.156** under Molander's conditions furnished the enone **1.157** (Scheme 1.36).[82] Yang reports the low yield is due to the propensity of **1.156** to eliminate to the vinyl furan under basic conditions. Conversion of the enone to the extended vinyl triflate with collidine and triflic anhydride followed by methoxycarbonylation gave the ester **1.158**. Reduction of the ester with DIBAL-H followed by oxidation to the aldehyde with MnO_2 furnished enal **1.159**. Addition of TMS lithium acetylide, followed by reoxidation with MnO_2 provided **1.160**.

Scheme 1.36: Yang's synthesis of Diels-Alder intermediate **1.160**



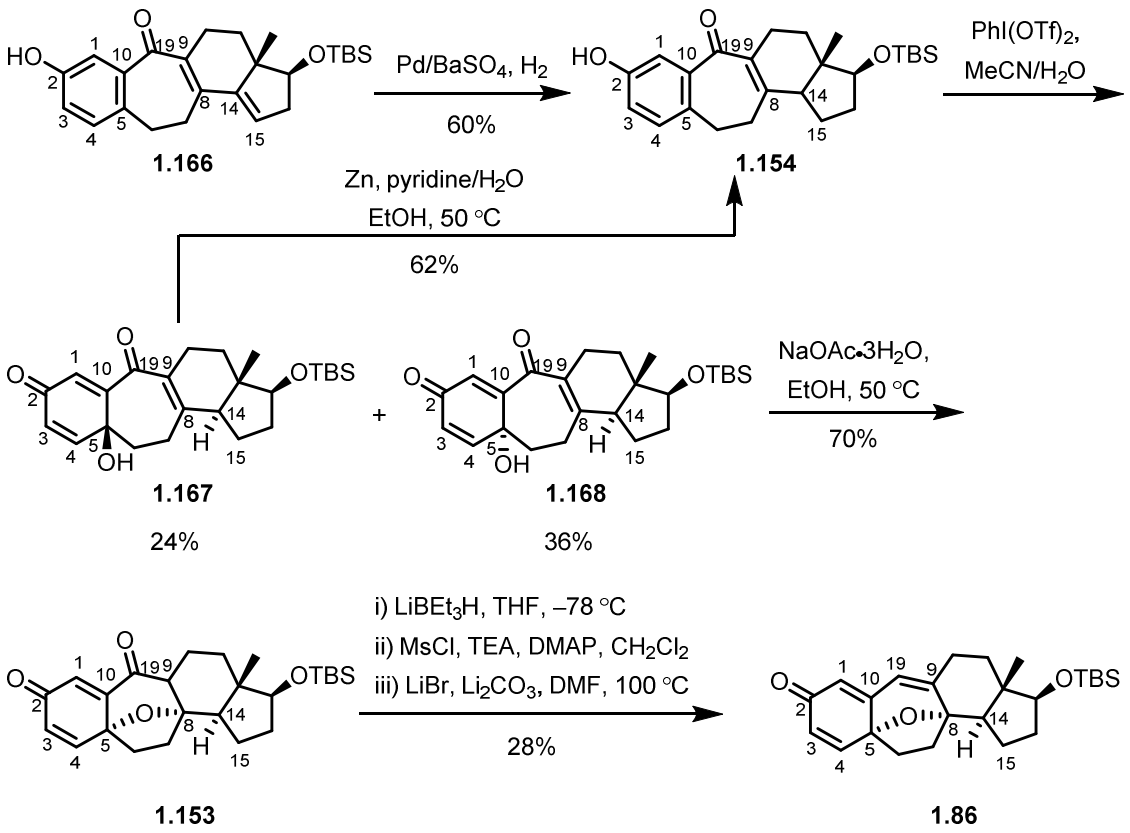
Unlike the model system studies, which spontaneously cyclized after the oxidation to the ynone, **1.160** did not cyclize (Scheme 1.37). A Lewis acid screen showed that $EtAlCl_2$ was an excellent Lewis acid for promoting the IMDA, which was accompanied by aromatization and TMS removal to give **1.166**. When the TMS group was deprotected before the Diels-Alder reaction, the reaction either stalled at the cycloadduct **1.162** or became mixtures of the cycloadduct **1.162** and the aromatized product **1.166**. Reasons for this difference are not clear, but may be due to the stabilizing effect of the TMS group on cationic intermediate **1.164**. A 1,2 hydride shift then gives the α-TMS oxonium intermediate **1.165** which is subsequently enolized with concomitant removal of the TMS group to form **1.166**.

Scheme 1.37: Yang's key intramolecular Diels-Alder (IMDA)



With the tetracycle **1.166** in hand, selective reduction of the C8-C9 double bond was achieved with Rosenmund's catalyst to provide **1.154** (Scheme 1.38). Arene oxidation with phenyliodo-bis-trifluoroacetate (PIFA) in the presence of water gave a mixture (1.5:1) of diastereomers of α and β-hydroxyl intermediates **1.167** and **1.168**. The undesired β-hydroxyl intermediate **1.167** could be recycled back to **1.154** by treatment with Zn metal in pyridine/H_2O. Cyclization of the hydroxyl compound **1.168** with NaOAc furnished the core **1.153**. Finally selective reduction of the C19 carbonyl over the C2 carbonyl was achieved with $LiEt_3BH$. Elimination of the alcohol with MsCl and Li_2CO_3, successfully intercepted the Myers intermediate **1.86** of cortistatin A (**1.1**), thereby completing a formal synthesis in 31 steps and 0.024% yield.

Scheme 1.38: Formal synthesis of Cortistatin A (**1.1**) *via* the Myers-Flyer intermediate **1.86**

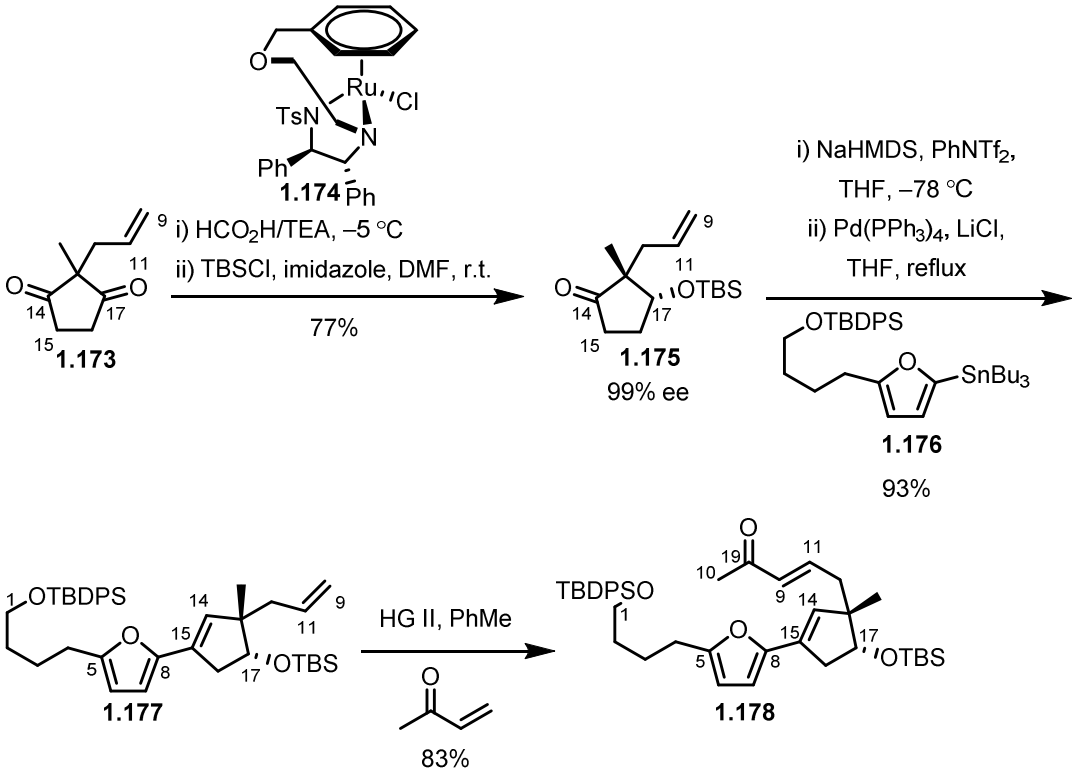


1.3.8: CHIU'S FORMAL SYNTHESIS

Chiu published a route to the core of cortistatin A (1.1) in 2011[38] and finished a formal in 2015.[37] Chiu sought to intercept Nicolaou's synthesis utilizing Hirama's improvements via intermediate **1.59**. Enantioselective reduction of the commercial dienone **1.173** via transfer hydrogenation with the R,R-Ts-Deneb catalyst **1.174**, proceeded in excellent enantioselectivity (>99% ee) and diastereoselectivity (4.6:1 dr) (Scheme 1.40). This offered an improvement over her 2011 communication[38] that used the CBS catalyst and gave comparable enantiomeric excess but also over-reduced to the diol (~12%). Protection of the alcohol as the TBS ether provided ketone **1.175**. Conversion of the ketone moiety to a vinyl triflate with NaHMDS and McMurray's reagent,[84] followed by Stille coupling of the vinyl triflate with furan **1.176** furnished cyclopentene **1.177**. This also offered an improvement over the 2011 communication

in that direct addition of the lithio-furan gave poor conversion (50%) and returned material. Cross metathesis of **1.117** with methyl acrylate then gave enone **1.178**.

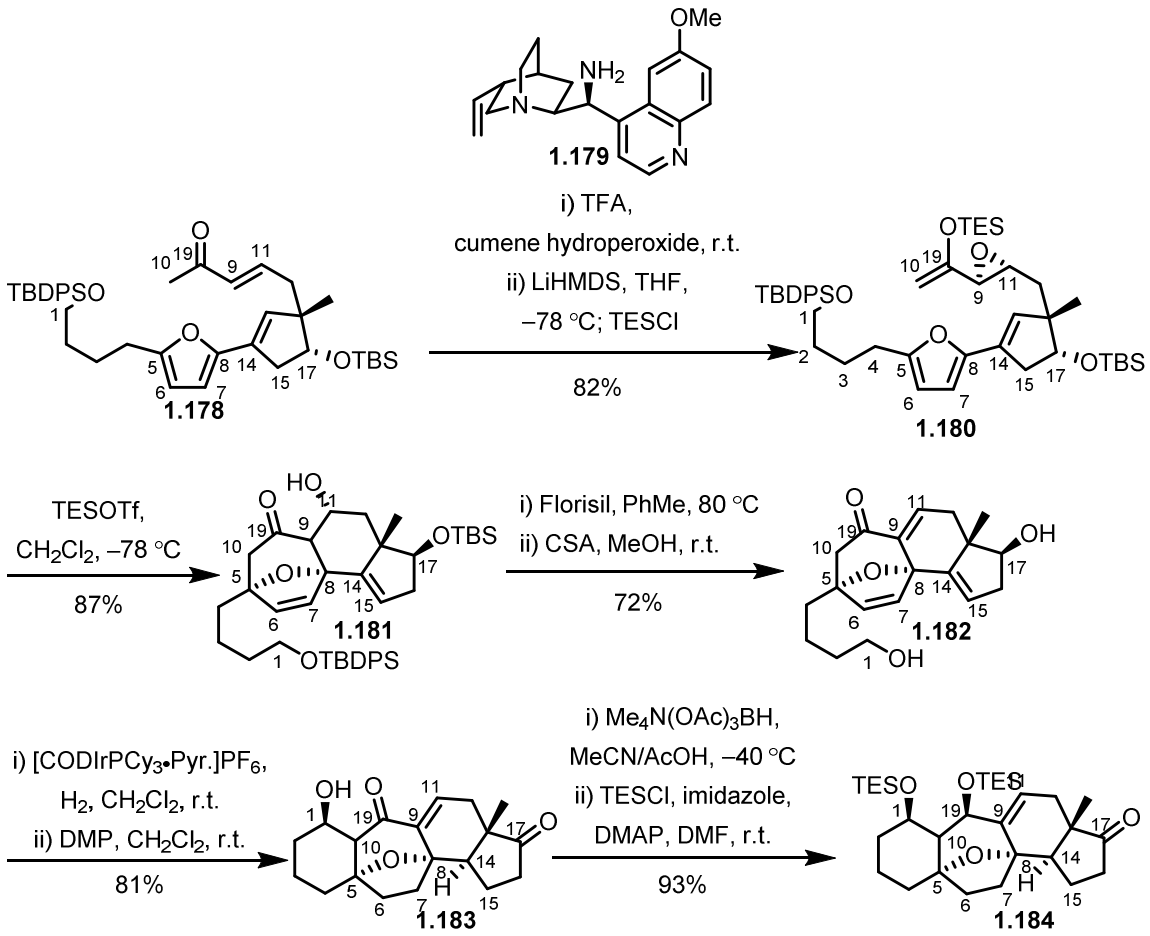
Scheme 1.40: Synthesis of [3+4] cyclization precursor **1.178**



Asymmetric nucleophilic epoxidation of enone **1.178** under Deng's conditions,[86] followed by conversion of the ketone to the silyl enol ether gave **1.180** (Scheme 1.41). Treatment of **1.180** with TESOTf triggered the key [3+4] cycloaddition to furnish **1.181** as a single diastereomer. Elimination of the alcohol with florisil, followed by deprotection of the silyl groups with camphorsulfonic acid (CSA) gave **1.182**. Diastereoselective reduction of the C14-C15 double bond in cyclopentene **1.182** proved problematic. Pd/C-H_2 delivered hydrogen to the undesired β-face and over-reduction. Fortunately, directed reduction with Crabtree's catalyst provided clean addition of hydrogen form the α-face of the C14-C15 double bond as well as fortuitous reduction of the C6-C7 double bond. Oxidation of the C17 alcohol with DMP then triggered a spontaneous intramolecular aldol reaction to provide **1.183** as a single diastereomer.

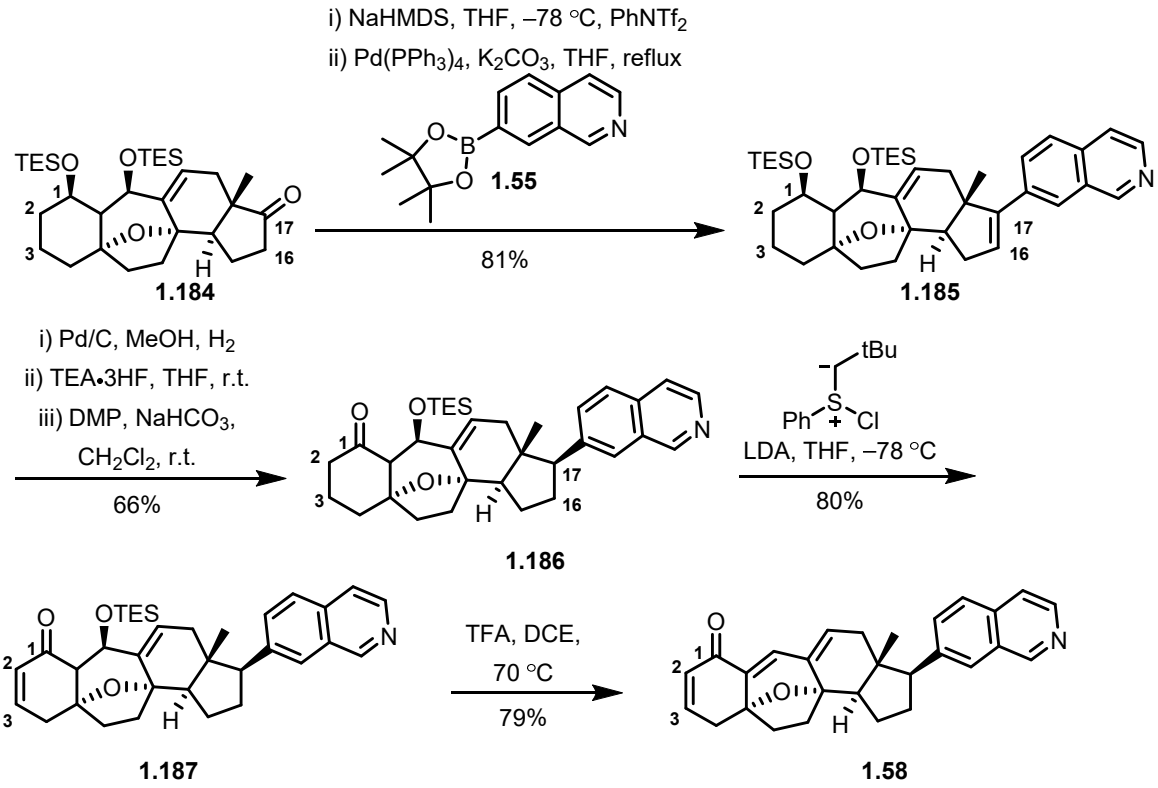
Directed reduction of **1.183** with $Me_4NBH(OAc)_3$ gave the desired selectivity, and protection of the alcohol as the TES ether then gave **1.184** as a single diastereomer.

Scheme 1.41: Chiu's key [3+4] cycloaddition



Ketone **1.184** was converted to the vinyl triflate with NaHMDS and McMurray's reagent followed by Suzuki coupling with isoquinoline-borate ester **1.55** to give **1.185** (Scheme 1.42). Despite numerous reports of the C16-C17 double bond reduction being problematic, Pd/C-H_2 furnished the desired reduction in good yield. Selective deprotection of the C1 alcohol and oxidation to the ketone with DMP furnished **1.86**. Conversion of the ketone **1.186** to enone **1.187** was accomplished with LDA and Mukaiyama's reagent. Elimination of the C19 alcohol with trifluoroacetic acid (TFA) provided the intermediate **1.58**, which intercepted the Hiyama and Nicolaou total synthesis of cortistatin A (1.1) (**1.1**) in 24 steps and 2.03% yield.

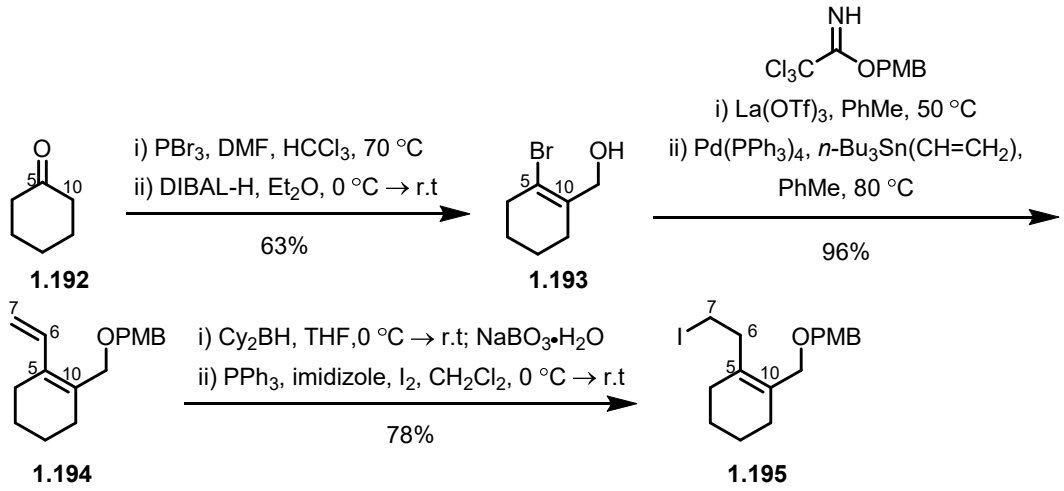
Scheme 1.42: Chiu's formal synthesis of cortistatin A (1.1) via the intermediate **1.58**



1.3.9: STOLTZ'S SYNTHESIS OF THE ABCD CORE WITH ENE-YNE METATHESIS

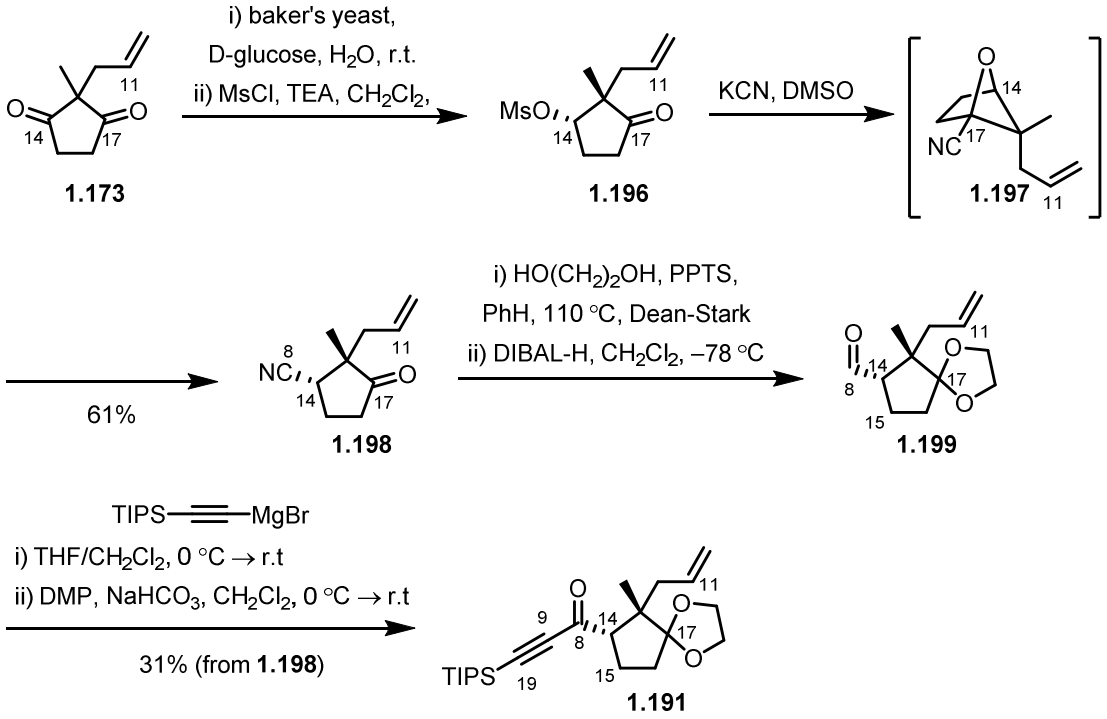
Concurrently with the studies in the Martin group, the Stoltz group published a model study toward the core of cortistatin A (**1.1**) in 2010,[54] utilizing a similar strategy of an ene-yne metathesis to close up the ABC and D rings in a single step. Cyclohexanone **1.192** was converted to β-bromo enal in a Vilsmeier-like reaction followed by reduction to give the allyl alcohol **1.193** (Scheme 1.44). The alcohol was protected as the *para*-methoxybenzyl (PMB) ether with 4-methoxybenzyl trichloroacetimidate and catalytic $La(OTf)_3$, followed by a Stille coupling to furnish vinyl compound **1.194**. Hydroboration/oxidation of **1.194** followed by conversion to the alkyl iodide then provided coupling partner precursor **1.195**.

Scheme 1.44: Synthesis of A-ring fragment **1.195**



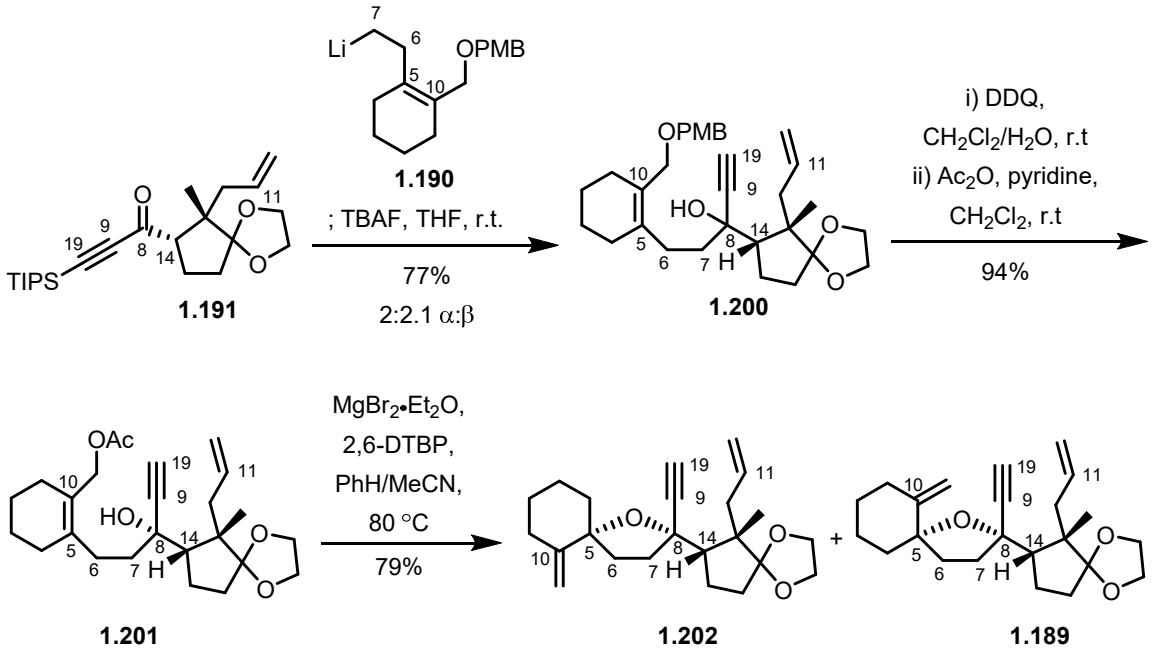
Synthesis of the D ring coupling partner began with desymmetrization of cyclopentadione **1.173** by enzymatic reduction with baker's yeast. Activation of the alcohol as the methanesulfonyl ester **1.196** allowed for displacement with cyanide (Scheme 1.45). Strangely, the reaction proceeded with retention of stereochemistry at C14, presumably through an intermediate such as **1.197**. Despite having the wrong stereochemistry at C14, the synthesis was continued by protecting the ketone was protected as the dioxolane and reducing the nitrile with DIBAL-H to provide the aldehyde **1.198**. A TIPS protected alkynyl magnesium bromide was then added into the aldehyde and the resulting alcohol was oxidized with MnO_2 to provide the ynone **1.191**.

Scheme 1.45: Synthesis of D-ring fragment **1.191**



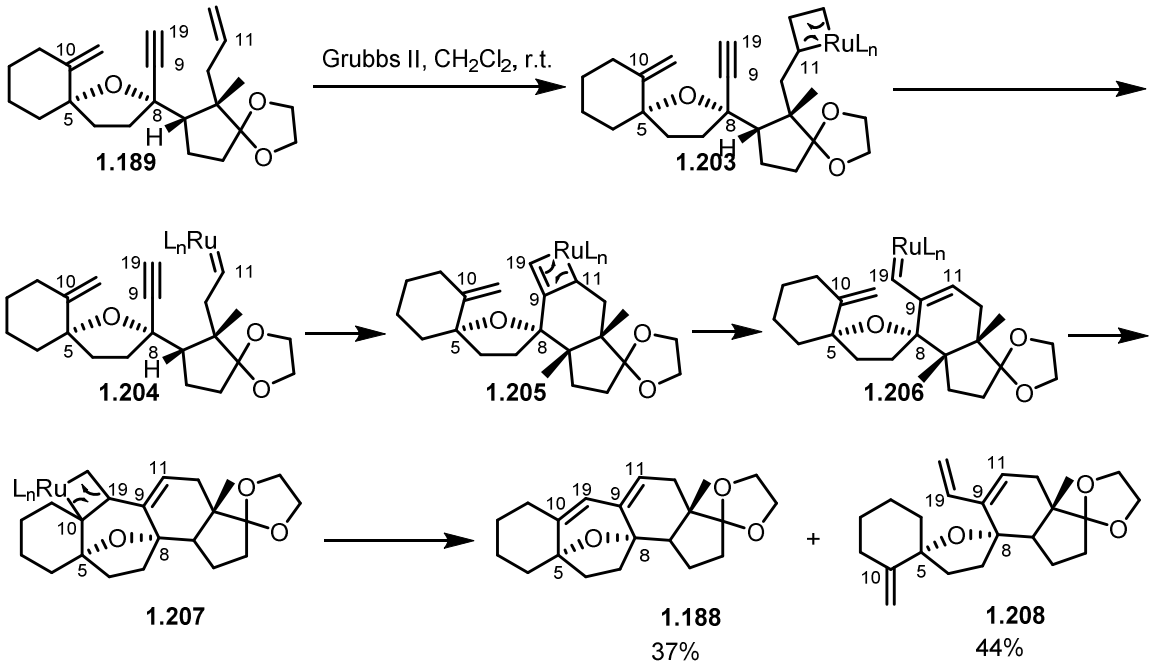
The alkyl lithium reagent **1.190**, was added into ynone **1.191** to give **1.200** as a ratio (2.2:1) of α and β-epimers in 77% combined yield (Scheme 1.46). After isolation of the desired α-epimer, the PMB group was removed, and the primary alcohol was acylated to give **1.201**. Allyl acetate **1.201** was then ionized with $MgBr_2 \bullet Et_2O$ with ditert butylpyridine (DTBP) as an acid scavenger to give **1.202** and **1.189** as mixture (1:1) of diastereomers. The diastereomers were inseparable, so the mixture was taken on through subsequent steps.

Scheme 1.46: Synthesis of key ene-yne metathesis precursor **1.189**



Even though the mixture of **1.202** and **1.189** was subjected to the reaction mixture, the key ene-yne metathesis impressively furnished the tetracyclic compound **1.188** in 36% yield (74% based on theoretically pure **1.189**) along with undesired compound **1.208** in 44% yield (88% based on theoretically pure **202**). Stoltz's route provides a simplified core of cortistatin A (1.1) in 13 steps and 2.1% yield.

Scheme 1.46: Stoltz's key ene-yne metathesis



1.4: Prior art in the Martin group

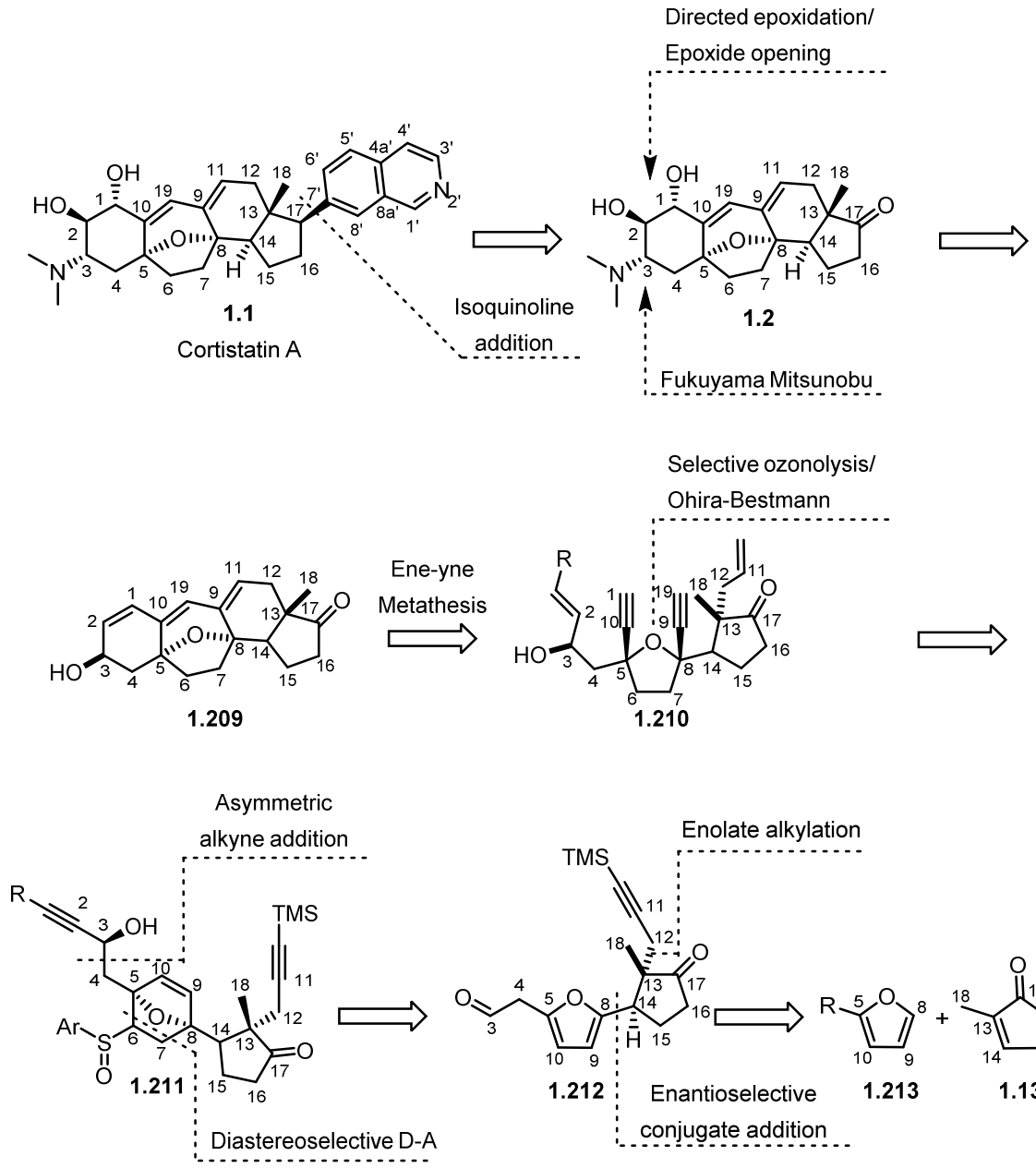
1.4.1: FIRST GENERATION SYNTHETIC PLAN

The approach the Martin group adopted for the synthesis of cortistatin A (**1.1**) begins with a late stage addition of isoquinoline to cortistatinone **1.2** in a similar strategy to Hiyama (Scheme 1.47, see Section **1.3.5**).[34,32] The α-stereochemistry of the C1 (cortistatin numbering) hydroxyl group was envisioned as arising from a regioselective opening of a β-epoxide with acetate ion. Strategic use of the Mitsunobu methodology developed by Fukuyama,[89] allows for the displacement of the C3 alcohol with inversion of stereochemistry to install the C3 dimethylamino group. The β-stereochemistry of the C3 alcohol can be used to direct the epoxidation to the desired face from **1.209**. In the key step, the plan called for forming all four rings in **1.209** by an ene-yne metathesis from **1.210**. The olefins at C2 and C11 would then come from a reduction with Lindlar's catalyst from the corresponding alkynes. The alkynes at C9 and C10 would be formed by treatment the bis-aldehyde produced by selective ozonolysis of the

bicyclic intermediate **1.211** with the Ohira-Bestmann reagent. The stereochemistry in **1.211** would arise from the diastereoselective intermolecular Diels-Alder reaction of furan **1.212** with a chiral sulfoxide. The stereochemistry at the C3 alcohol would be set by an enantioselective alkyne addition on aldehyde.[90-94] The stereochemistry at C14 can come from an enantioselective conjugate addition of furan **1.213** into enone **1.130**, followed by a diastereoselective alkylation.

At the outset of this work in 2009, no one had utilized ene-yne metathesis as a strategy toward cortistatin A (**1.1**). Although Stoltz later applied this strategy towards the synthesis of a core-like structure in 2010, the stereochemistry at C14 was incorrect and thus a successful application of ene-yne metathesis towards the total synthesis of cortistatin A (**1.1**) had yet to be accomplished. An additional challenge to the synthetic plan was the lack of enantioselective methods to add heteroaromatic moieties to enones. There were also few reports of intermolecular enantioselective and diastereoselective Diels-Alder reactions on furans with chiral sulfoxides. Synthetic methodologies would have to be developed to overcome these challenges.

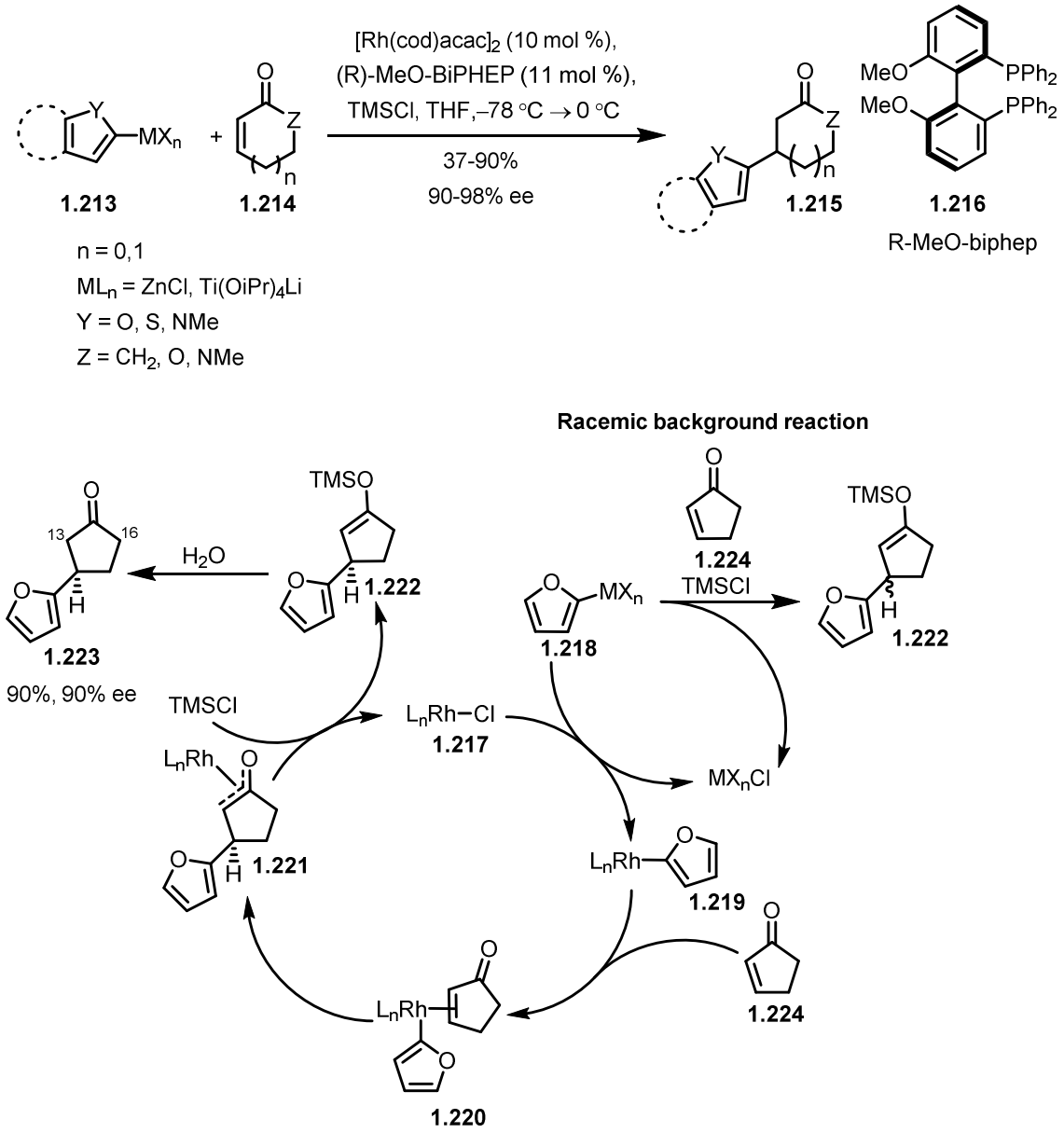
Scheme 1.47: 1st generation Martin group retro-synthetic strategy



In 2009, Dr. Anna Smith developed the synthetic methodology for the enantioselective addition of heteroaryl-zincs and titanates to a variety of enones using a Rh(I) precatalyst, the ligand MeO-biphep, and TMSCl (Scheme 1.48).[95] Generally, the enantioselectivities were better with the titanates due to a significant background reaction with the organo-zinc reagents that lead to racemic products. Mechanistically, the Rh(I) species **1.217** is presumed to be the active catalyst (Scheme 1.48). Transmetalation of the heteroaryl-metal species **1.218** then gives **1.219**,

which then undergoes a 1,4-addition with cyclopentenone **1.224** to give the rhodium enolate **1.221**. The rhodium enolate then reacts with TMSCl to regenerate the catalyst and release the product as the silyl enol ether **1.222**. Upon workup, the ketone **1.223** was isolated in 90% yield and 90% enantiomeric excess (absolute stereochemistry unknown).

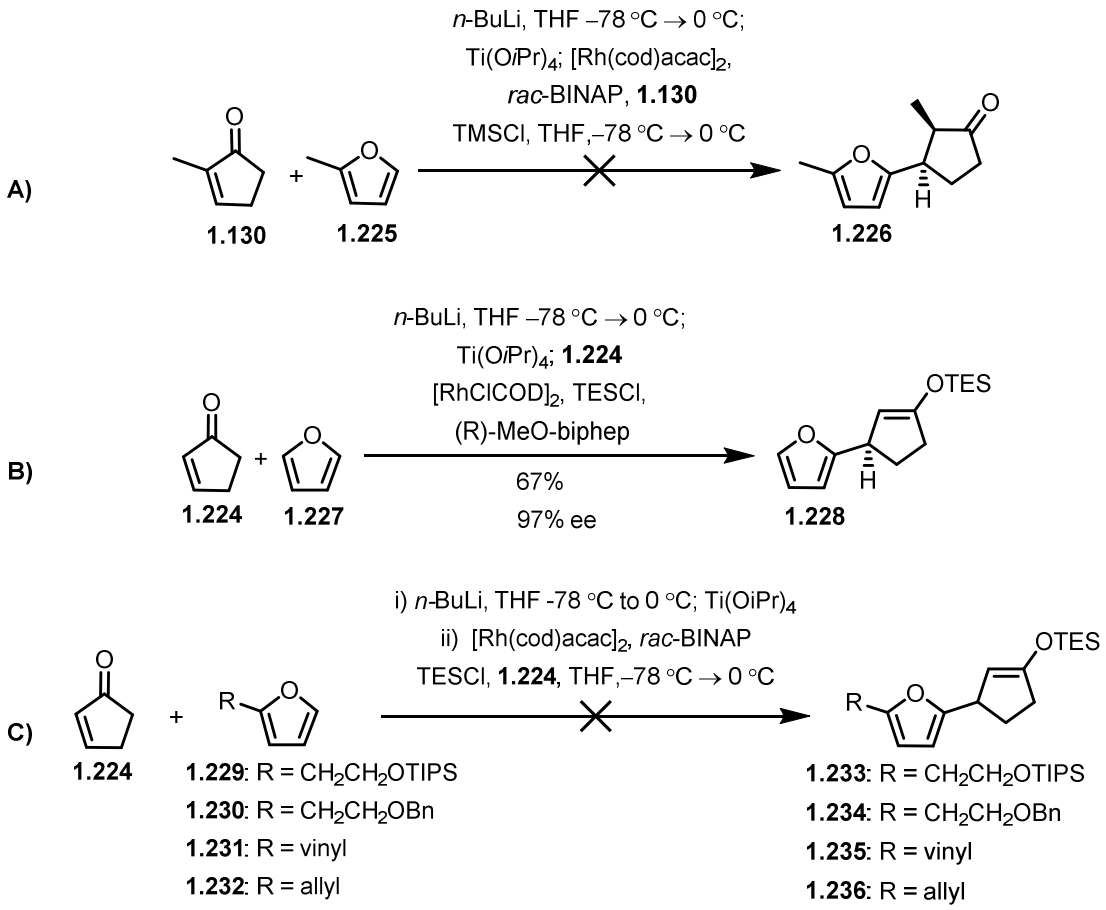
Scheme 1.48: Dr Anna Smith's enantioselective conjugate addition methodology



Disappointingly, attempts to add furan **1.225** to cyclopentenone **1.130** to install the C13 methyl group gave no desired product **1.226** (Figure 1.4, **A**). Based on the proposed mechanism, it is possible that α-substitution on the enone causes unfavorable steric interactions in complex **1.220** (Scheme 1.48). Conceivably, the C13 methyl group could be installed *via* alkylation of ketone **1.223**, but substituents in the β-position are poor directors of enolate geometry (selectivities range from 1:1 to 7:1 favoring formation of the enolate on the same side of the β-

substituent).[96] Fortunately, because the reaction produces the silyl enol ether with the desired regiochemistry, the reaction was modified to isolate the TES enol ether by substituting TESCl in place of TMSCl (Figure 1.4, **B**). Unfortunately, attempts to isolate the silyl enol ether from the conjugate addition of 2-substituted furans (with the exception of 2-methyl furan **1.225**) were unsuccessful (Figure 1.4, **C**). Lithiation of vinyl **1.231** or 2-allylfuran **1.232** in the 5-position lead to complex mixtures while the 5-titanates of furans **1.229** and **1.230** were unreactive under the reaction conditions.

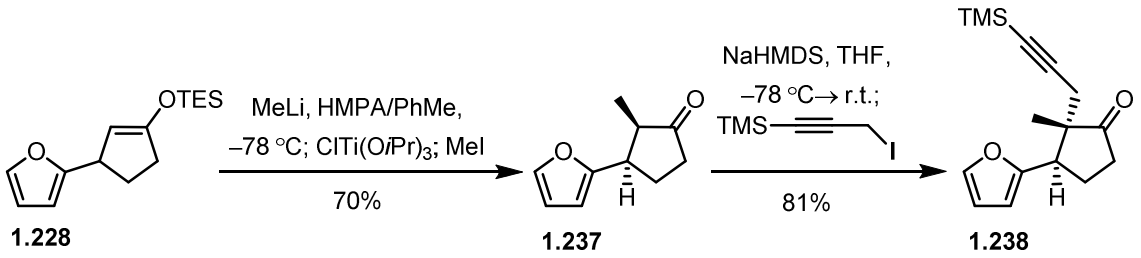
Figure 1.4: Conjugate addition of substituted furans with cyclopentenones **1.130** and **1.224**



The inability 5-substituted furans other than 5-methylfuran to participate in the conjugate addition necessitated the functionalization of the 5-position of **1.223** after methylation. Initial attempts at methylating silyl enol ether **1.228** gave either ketone **1.223**, polyalkylated material, or complex mixtures (Scheme 1.49). After screening unmasking agents (CsF, TBAT and MeLi), solvents (MeCN, CH_2Cl_2, THF, PhMe, THF, HMPA) and other additives (Et_3N, NaH, DIPEA, $TiCl(OiPr)_3$,[100] Dr. Smith found that unmasking the enolate with MeLi in toluene, followed by transmetalation with $TiCl(OiPr)_3$, and alkylating with MeI provided ketone **1.237** as a single diastereomer in 70% yield (Assigned as trans isomer based on ^{1}H-NMR shift of the methyl peak: 1.13, see also Chapter 2, Scheme 2.6 and discussion). The metal additive suppresses polyalkylation but reduces the reactivity of the enolate, so the inclusion of HMPA as a co-solvent

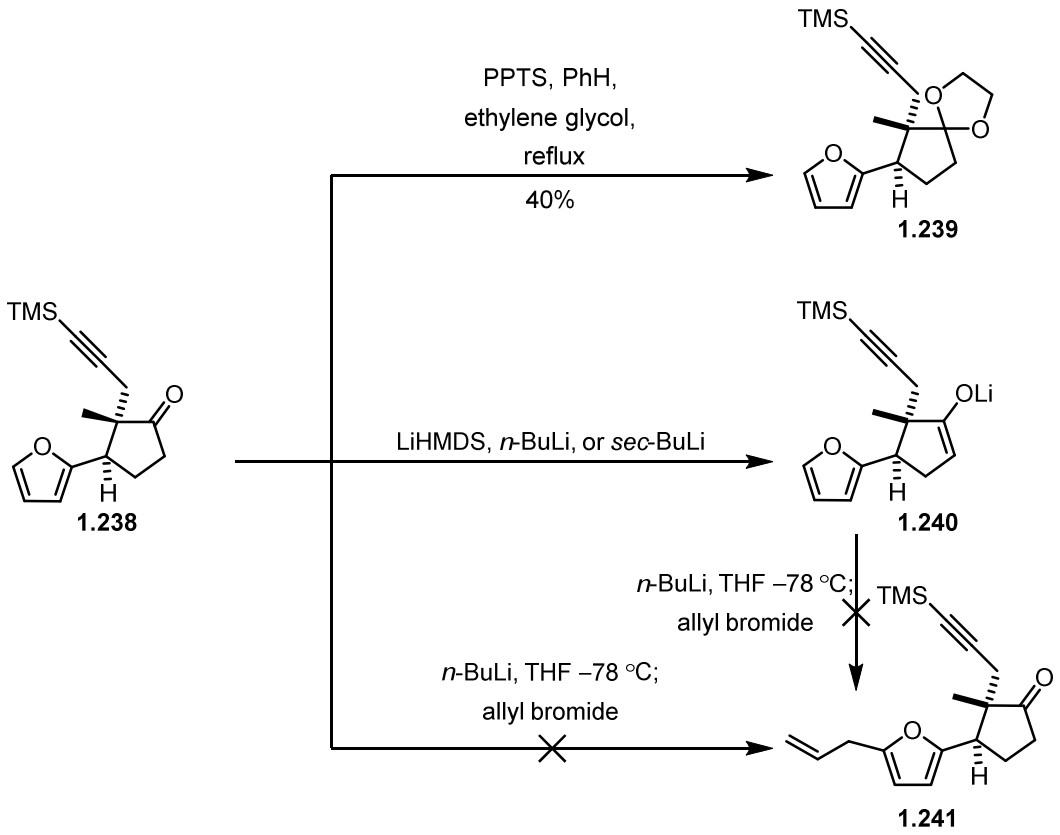
was essential to promote sufficient reactivity. Alkylation of **1.237** also proved problematic. Several bases and solvents were screened for the generation of the thermodynamic enolate and subsequent alkylation with TMS-propargyl iodide. Fortunately, adding NaHMDS to the ketone **1.237** at –78 ºC, followed by warming to room temperature and alkylation with TMS-propargyl iodide provided the ketone **1.238** in 81% yield as a single diastereomer (relative stereochemistry assigned based on crystal structure of downstream intermediate, see Chapter 2, Figure 2.2).

Scheme 1.49: Synthesis of ketone **1.238**



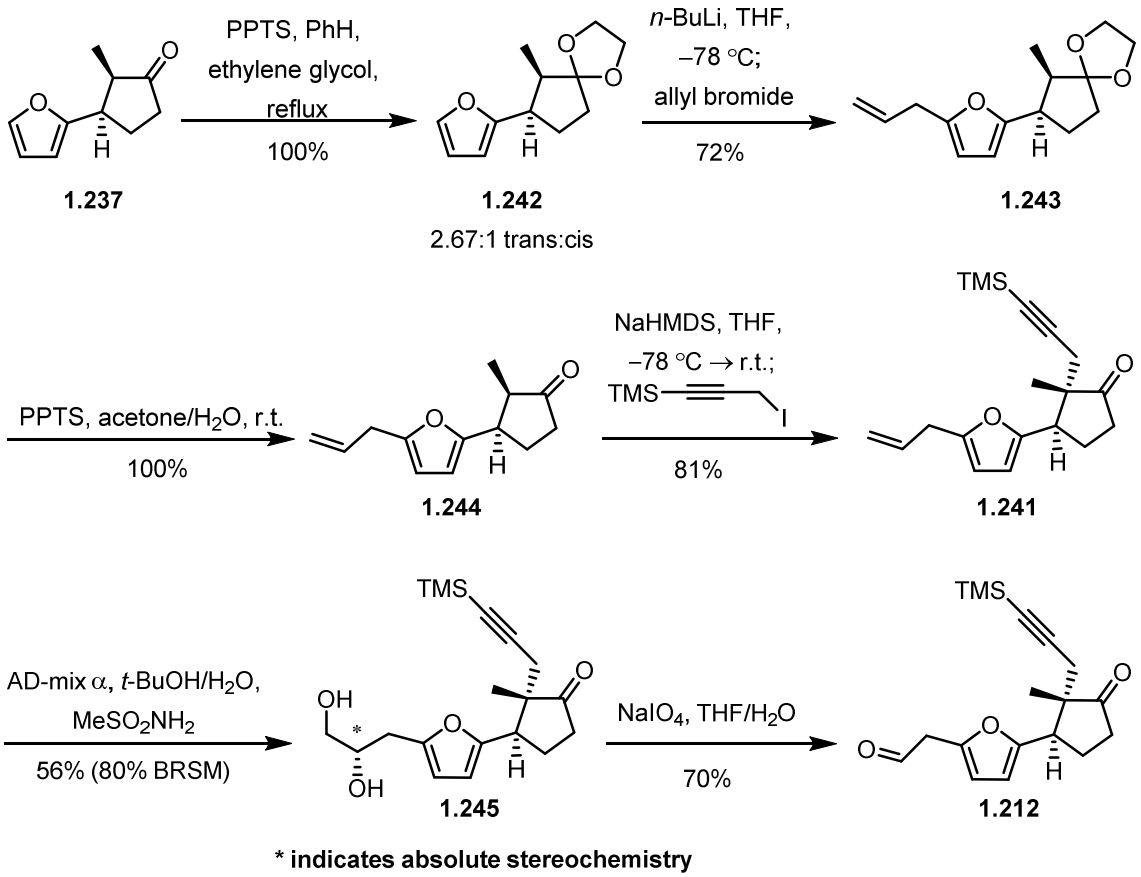
Attempts to metalate the 5-position of furan **1.238** directly or to protect the ketone as the enolate *in situ* led to complex mixtures of products (Scheme 2.4). The ketone was protected as the dioxolane **1.239**, but extended reaction times and low yields of this protection made this route unattractive. Due to the poor yield of the conversion of **1.238** to **1.239**, the sequence was modified to protect the ketone before the alkylation with the propargyl iodide (Scheme 1.51).

Scheme 1.50: 1st Attempt of the synthesis of ketone **1.241**



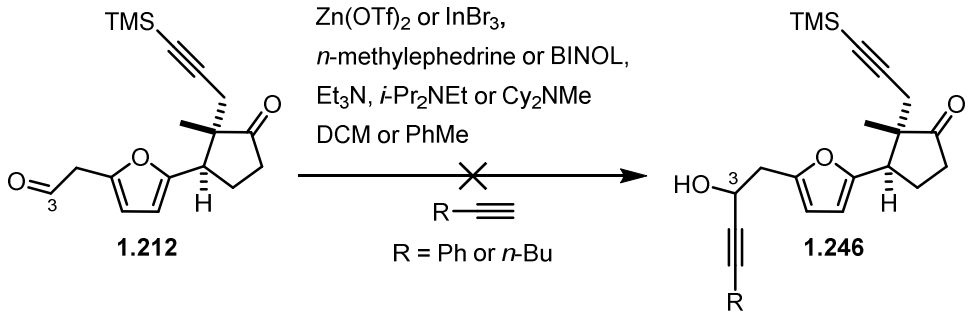
Protection of **1.237** as the dioxolane **1.242** proceeded in quantitative yield (Scheme 1.51). Lithiation of furan **1.242** at the 2-position and quenching with allylbromide then gave 2-allylfuran **1.243**, which was subsequently hydrolyzed to furnish ketone **1.244**. Formation of the thermodynamic enolate of **1.244** with NaHMDS and alkylation with propargyl iodide gave key intermediate **1.241** in 81% yield. Attempts to determine the relative stereochemistry of **1.241** by crystallization of the phenylhydrazone or by NOE were inconclusive (relative stereochemistry determined later by crystal structure, see Chapter 2, Figure 2.2). Attempts to oxidatively cleave the allyl group with ozone, Johnson-Lemieux conditions (OsO_4, $NaIO_4$), or "purple benzene" (*n*-Bu_4NMnO_4) all led to complex mixtures. However, a two step procedure of dihydroxylation with AD-mix α followed by cleavage with $NaIO_4$ gave aldehyde **1.212** in 39% yield after two steps.

Scheme 1.51: Synthesis of aldehyde **1.212**



Several attempts to use Carreira's[90-93] or Shibasaki's[94] enantioselective alkyne addition methodology met with little success (Equation 1.1). Varying the Lewis acid, ligand, or the base led to decomposition of aldehyde **1.212**. The aldehyde **1.212** was very sensitive to the Lewis acids used in the reaction, and in the presence of base, it polymerized very readily, making this strategy unattractive.

Equation 1.1: Failure of enantioselective alkyne addition with aldehyde **1.212**



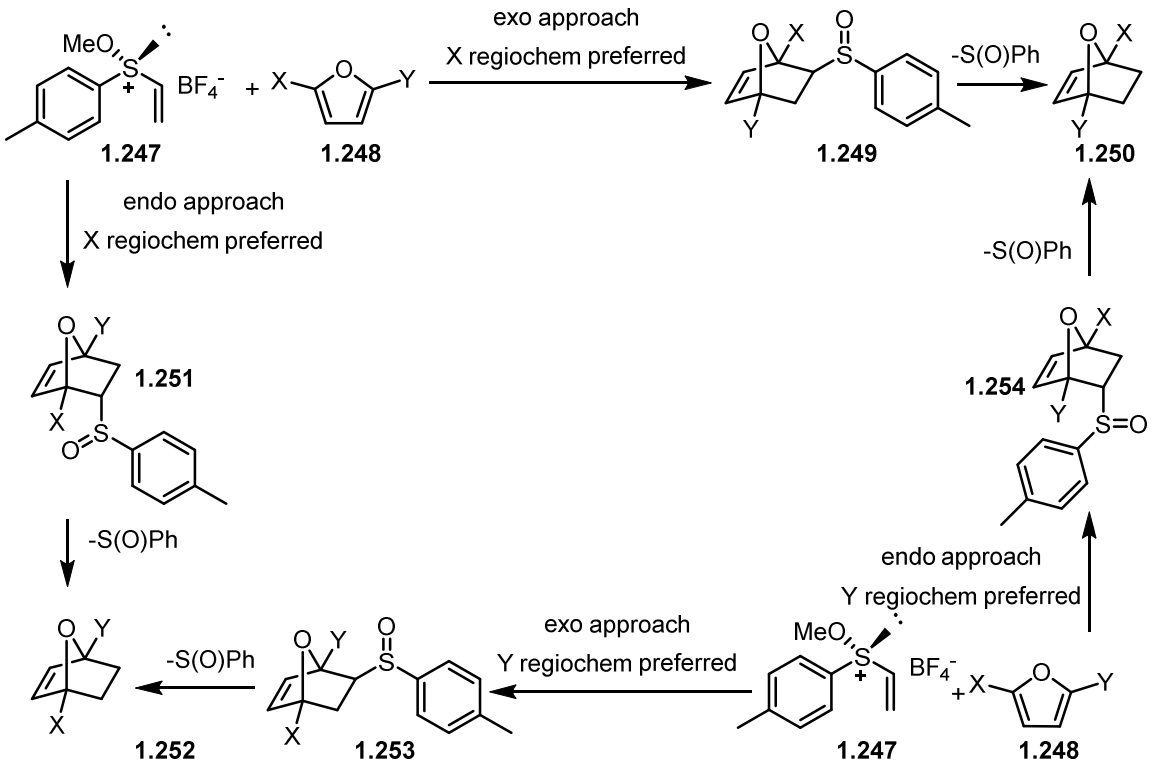
While an alternate strategy to set the C3 stereocenter was being devised, work on the enantioselective intermolecular Diels-Alder reaction was underway. Generally speaking, the reaction was thought to take place with the furan as the diene and an enantiopure sulfoxide acting as the dienophile. Method development would be needed as there were only a few examples of enantioselective intermolecular Diels-Alder reaction reactions of vinyl equivalents.

1.4.2: DIELS-ALDER REACTION CYCLIZATION OF ENANTIOPURE VINYL SULFONATES WITH FURANS

The Martin group strategy for setting the stereochemistry at C5 and C8 was inspired by the work of Kagan, who used enantiopure *O*-methylsulfoxonium tetrafluoroborates **1.247** as dienophiles in diastereoselective intermolecular Diels-Alder reaction with furans.[102] Before using *O*-methylsulfoxonium tetrafluoroborates **1.247** as a formal source of chiral ethylene, certain obstacles have to be addressed. Consider furan **1.248** with alkyl substitution in the 2- and 5-positions (Figure 1.5). Assuming 100% diastereomeric excess an exo-selective Diels-Alder reaction with the preferred regiochemistry being with the sulfoxide on the same side as "X" would provide the Diels-Alder adduct **1.249**, which after desulfurization would provide **1.250**. An endo-selective Diels-Alder reaction with the preferred regiochemistry being with the sulfoxide on the same side as "Y" would provide the Diels-Alder adduct **2.47**, which after desulfurization would provide the same product **1.250** as the exo-X selective Diels-Alder. Hence,

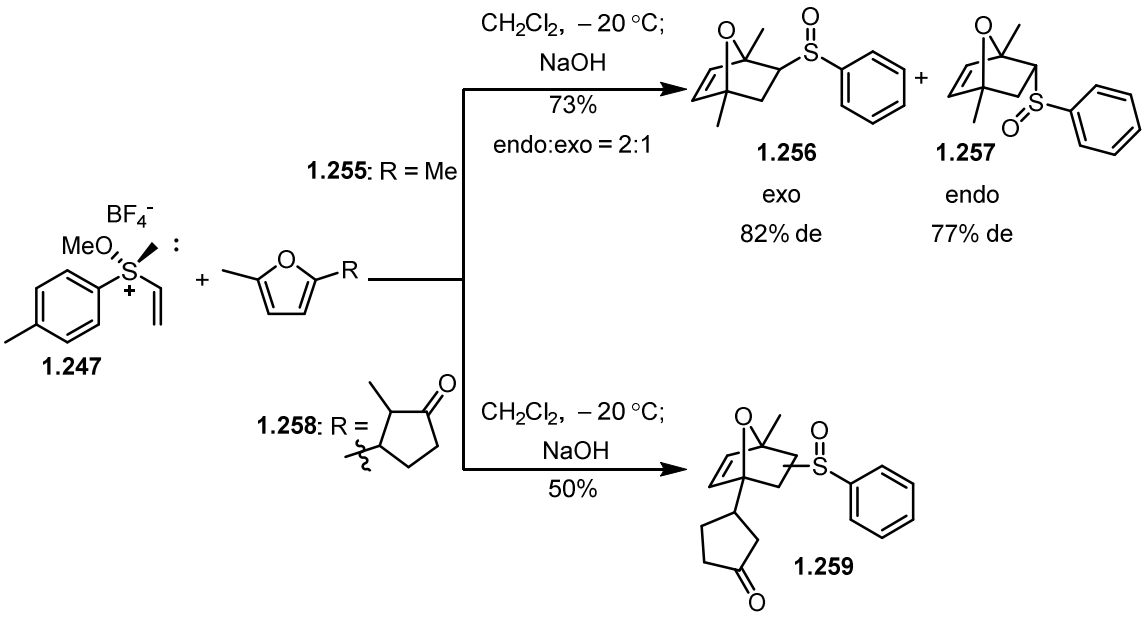
in order for the Diels-Alder reaction strategy to work, it must be enantioselective, endo/exo selective, and regioselective.

Figure 1.5: Regiochemical and stereochemical issues with Diels-Alder reaction



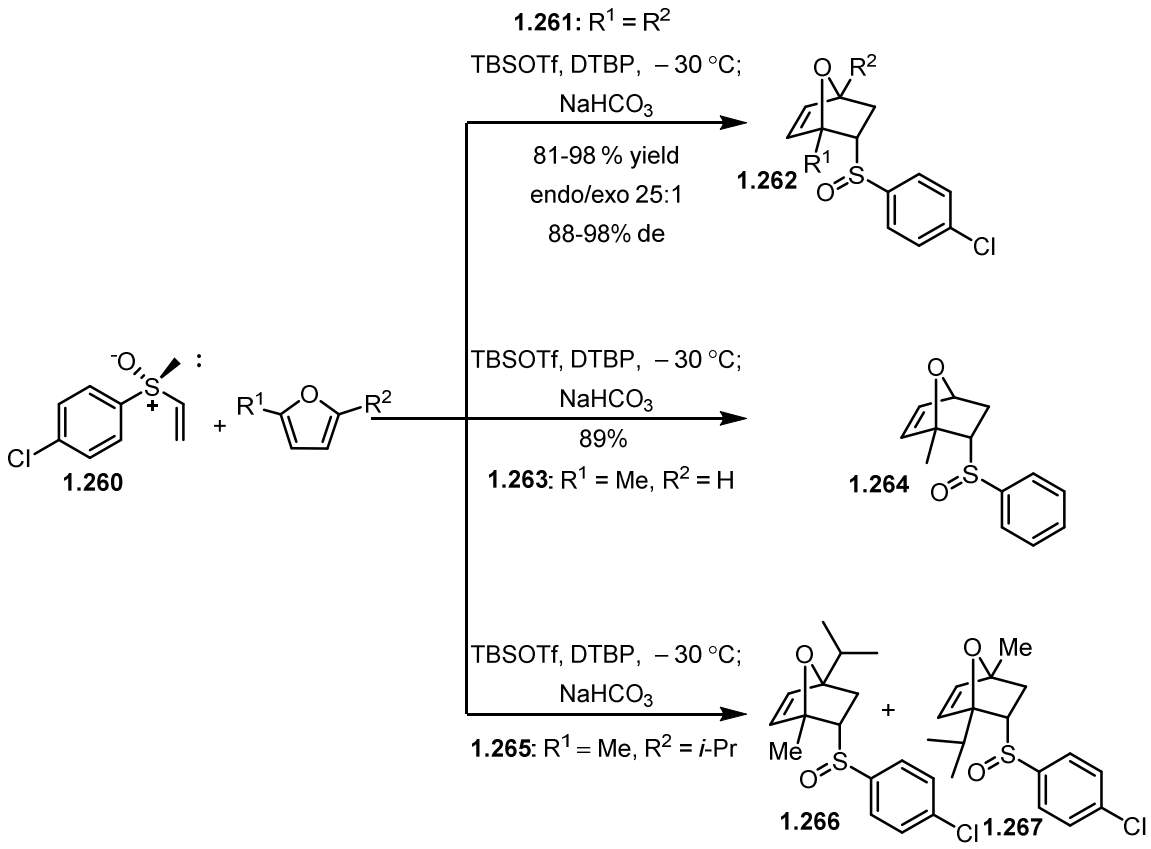
To investigate these issues, Dr. Smith applied Kagan's methodology to 2,5-dimethylfuran **1.255**, which provided the adducts **1.256** and **1.257** (1:2 exo:endo, 82% de, 77%) in 73% combined yield (Scheme 1.52). When furan **1.258** was subjected to Kagan's conditions, the adduct **1.259** was isolated, but as a mixture of stereoisomers and regioisomers, indicating that Kagan's methodology would not be useful for the synthesis of cortistatin A (**1.1**).

Scheme 1.52: Attempted use of Kagan's diastereoselective Diels-Alder reaction methodology



Using this problem as a platform for methodological development, Dr. Noah Benjamin investigated the diastereoselective Diels-Alder reaction of furans with enantiopure sulfoxides (Scheme 1.53).[103] After screening several sulfoxides and Lewis acids, the combination of sulfoxide **1.260** and TBSOTf with furans **1.261** or **1.263** gave Diels-Alder reaction adducts **1.262** and **1.264** in excellent diastereoselectivity and yields. Use of 2,6-di-*tert*-butylpyridine (DTBP) was essential to achieve high yields because the furans were very sensitive to traces of triflic acid. The use of Lewis acid and low temperatures made the exo/endo selectivity very good, but unfortunately, unless the furan was electronically biased as in the case of **1.263**, the regioselectivity between two different alkyl groups was poor.[88]

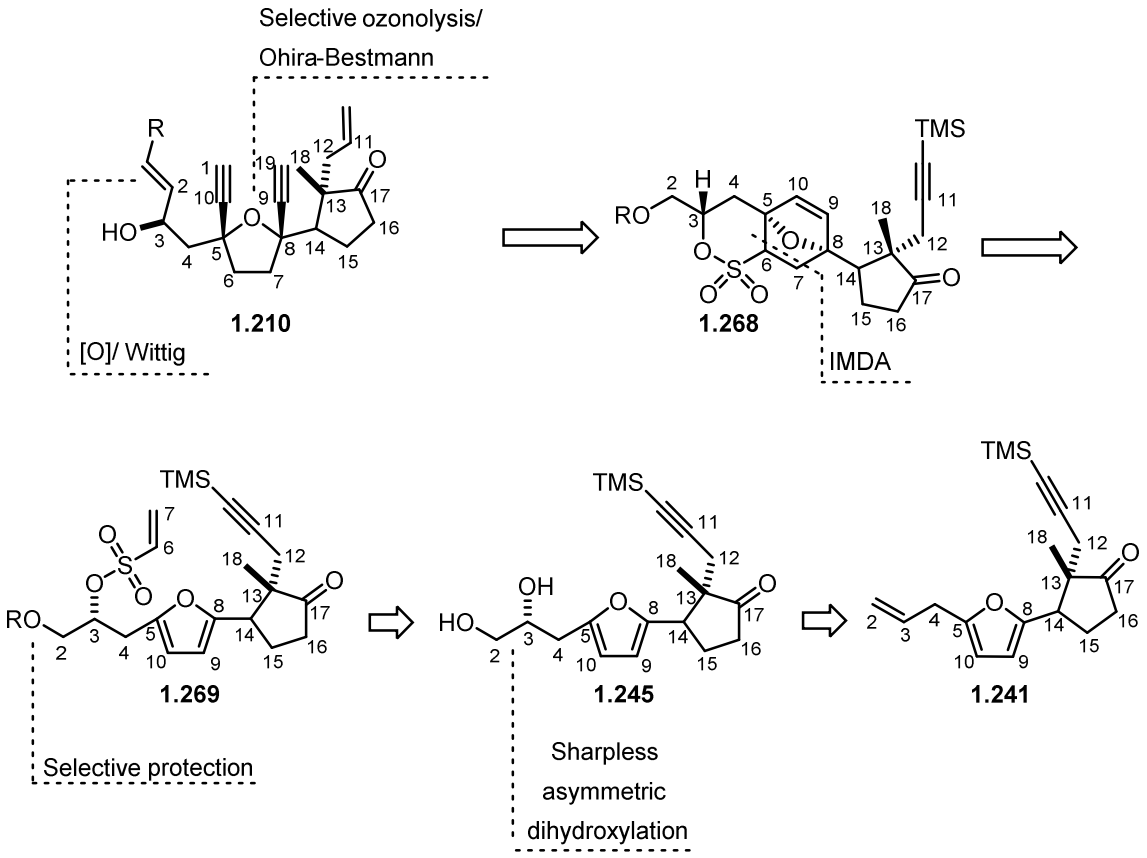
Scheme 1.53: Dr. Noah Benjamin's improved diastereoselective Diels-Alder reaction



1.4.3: SECOND GENERATION SYNTHETIC PLAN

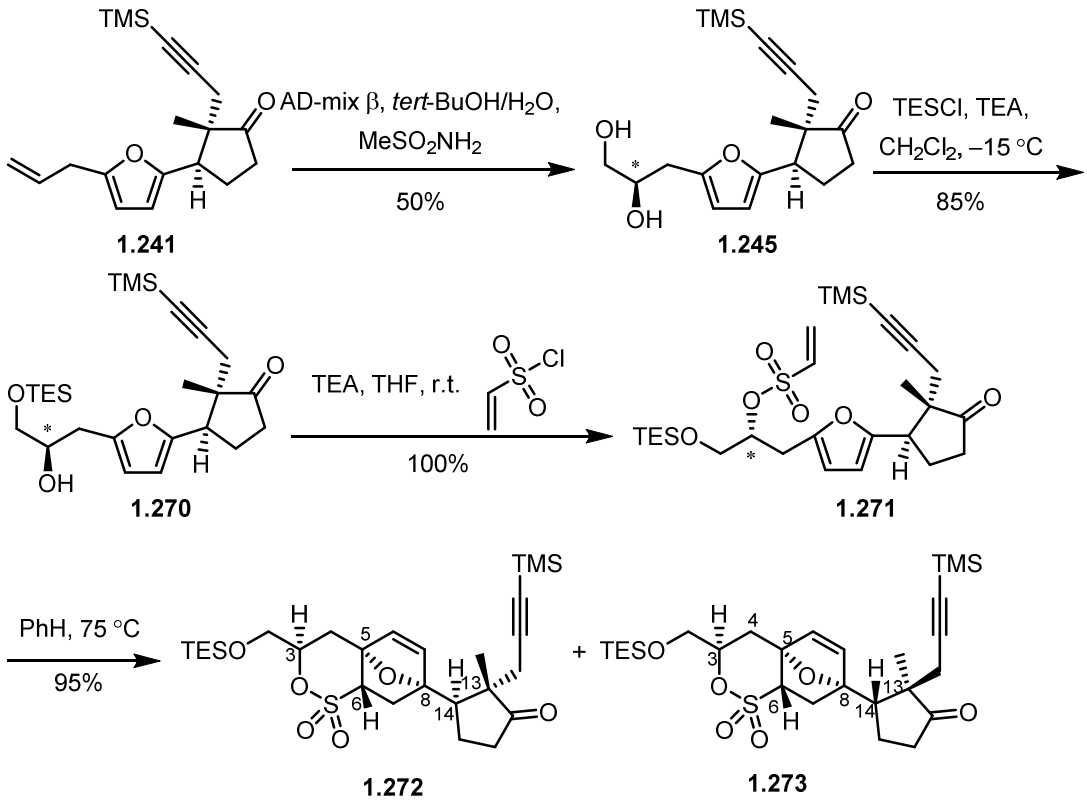
Due to the failure of the enantioselective alkyne addition on aldehyde **1.212** and the inability of the enantioselective Diels-Alder reaction to give good regioselectivity, the retrosynthetic strategy was revised (Scheme 1.54). Instead of an intermolecular Diels-Alder reaction, an intramolecular Diels-Alder reaction (IMDA) of vinyl sulfonate **1.269** would enforce the desired regioselectivity. The IMDA of vinyl sulfonates and furans has been studied by Metz and used in the synthesis of eriolanin and pamamycin.[104-113] The facial selectivity would then be directed by the stereochemistry of the alcohol at C3 in diol **1.245**, which would be set by a Sharpless enantioselective dihydroxylation from ketone **1.241**.

Scheme 1.54: 2nd Generation Martin group retro-synthetic strategy utilizing an IMDA



After determining that AD-mix β would give the desired stereochemistry at C3 (cortistatin numbering), ketone **1.241** was subjected to the dihydroxylation conditions (Scheme 1.55). Unfortunately, the reaction was very sluggish, providing only a 50% yield of **1.245** after four days at room temperature. Selective protection of the primary C2 alcohol over the C3 alcohol as the TES ether provided **1.270**. Conversion of the C3 alcohol of **1.270** to the sulfonate proceeded quantitatively, and heating in benzene then gave the Diels-Alder reaction adducts **1.272** and **1.273** as a mixture (1:1) of diastereomers in 95% yield (stereochemistry assigned based on a crystal structure of an analogue of **1.272**, see Chapter 2, Figure 2.2). Attempts to isolate a crystal of the Diels-Alder reaction adducts **1.272** or **1.273**, was unsuccessful, so the relative stereochemistry remained unknown.

Scheme 1.53: Synthesis of Diels-Alder reaction intermediate **1.272** and **1.273**



*** indicates absolute stereochemistry**

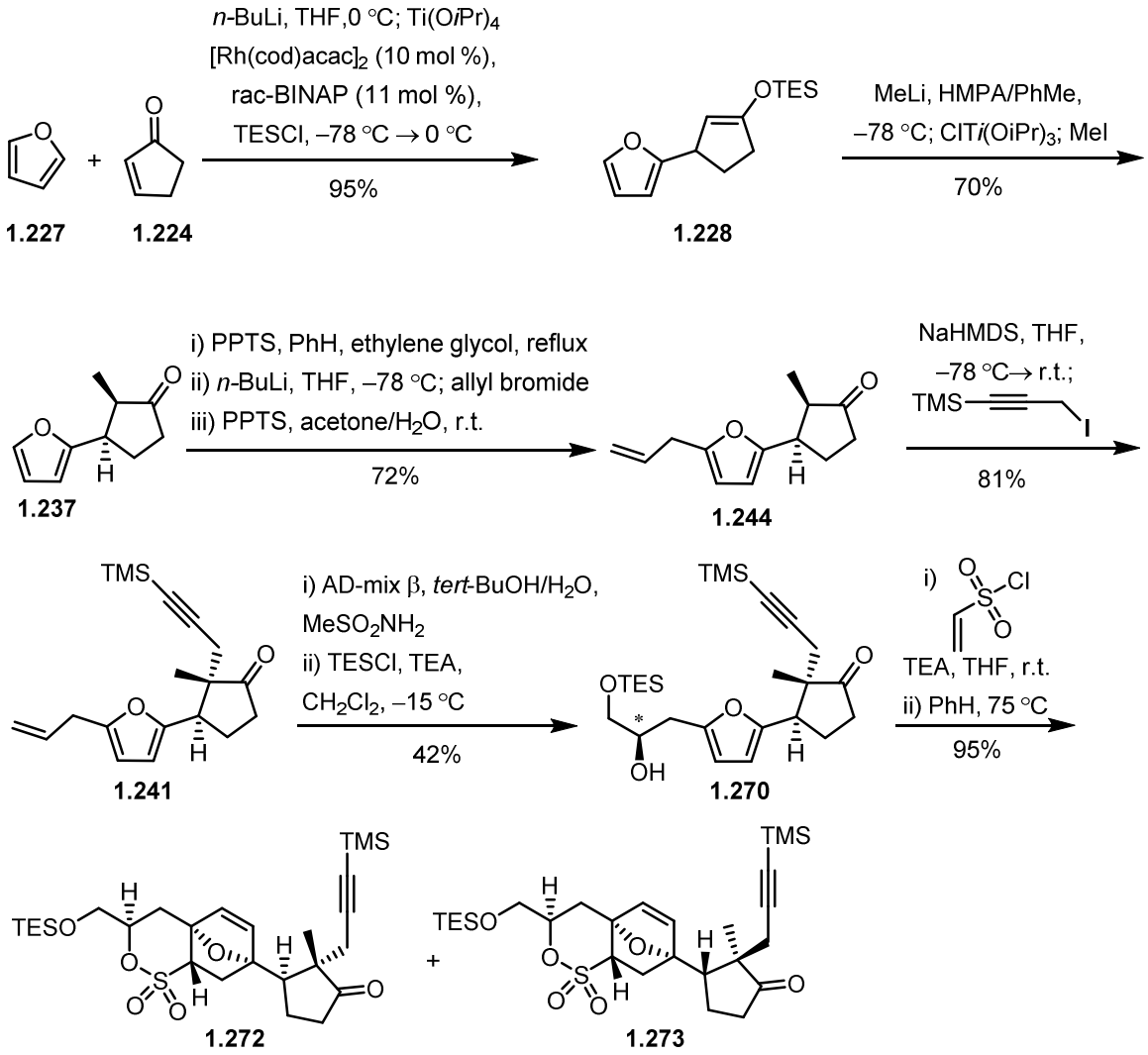
1.4.4: SUMMARY

An enantioselective method for the conjugate addition of furans to enones was developed, as well as an enantioselective Diels-Alder reaction of furans with enantiopure sulfoxides. Though the enantioselective Diels-Alder reaction methodology did not contribute the forward synthesis, the IMDA of vinyl sulfate **1.271** provided the important precursor **1.272** and **1.273** in 10 steps and 16% yield (Scheme 1.56).

Despite this promising result, major obstacles remained when we took over the project: the relative stereochemistry between the groups at C13 and C14 in ketone **1.241** and groups at C8 and C14 in the Diels-Alder reaction adducts **1.272** and **1.273** were unverified; the enantiopurity of the Diels-Alder adducts after the dihydroxylation was unknown and which of the isolated diastereomers (**1.272** or **1.273**) contained the relative stereochemistry required to

pursue the total synthesis of cortistatin A (**1.1**) (Note: at the time, the relative stereochemistries of **1.272** and **1.273** had not been determined).

Scheme 1.56: Synthetic summary towards Diels-Alder reaction adduct **1.272** and **1.273**



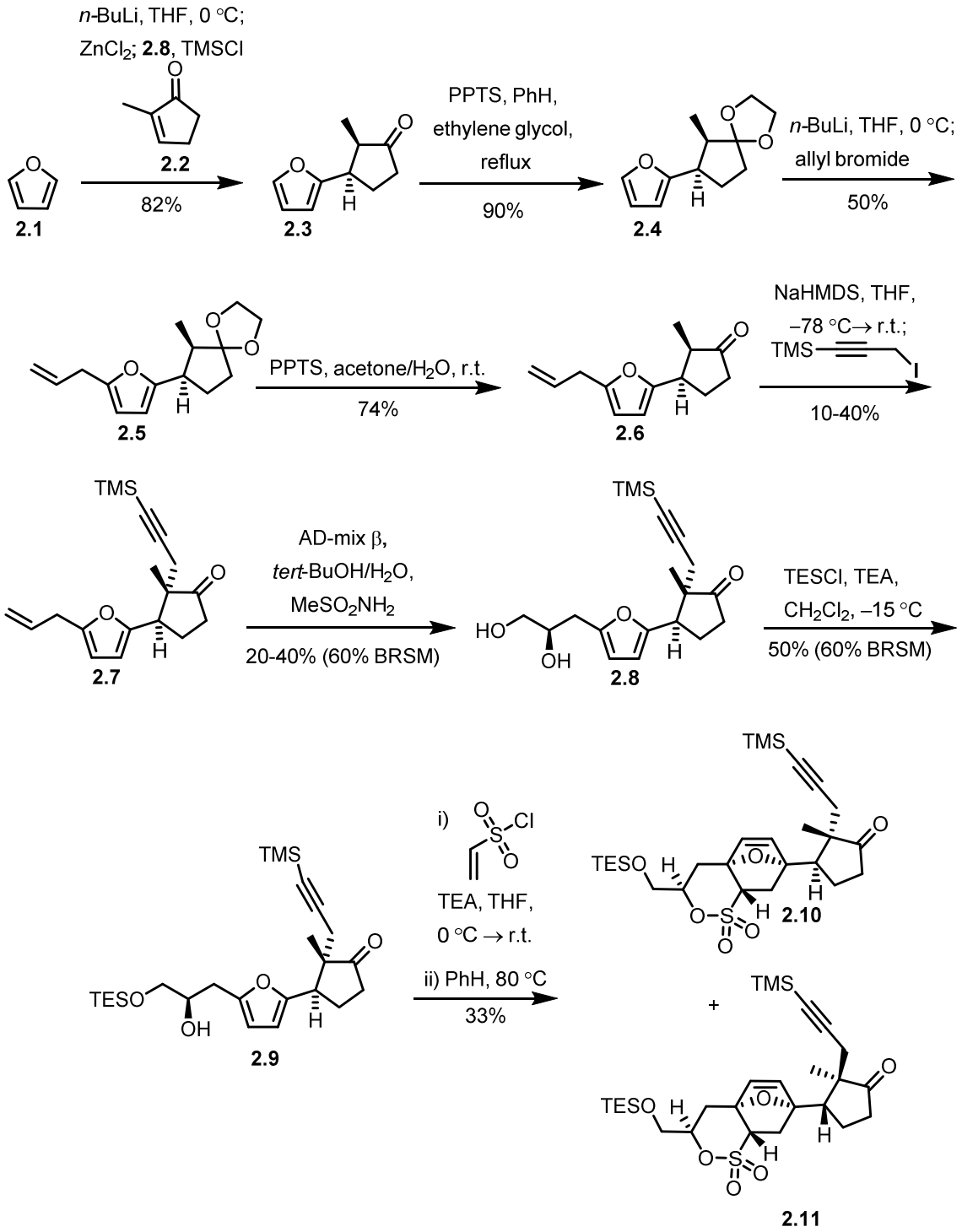
CHAPTER 2: CURRENT SYNTHETIC WORK TOWARD CORTISTATIN A IN THE MARTIN GROUP

2.1: First generation synthesis towards the Diels-Alder adduct

2.1.1: CONFIRMATION OF THE RELATIVE STEREOCHEMISTRY

The confirmation of which, if any, of the Diels-Alder reaction adducts **2.10** and **2.11** contained the requisite stereochemistry required for cortistatin A (see Chapter 1, Figure 1.1) was tantamount for the continuation of the project. Due to the cost of Rh (I) salts, the conjugate addition of furan **2.1** into enone **2.2** was adapted to use Knochel's[114] conditions, which make use of organo-zinc reagents to give ketone **2.3** in as a mixture of diastereomers (1:0.6 trans:cis) in 82% yield, which was subsequently protected as the acetal **2.4** (Scheme 2.1, see also Scheme 1.56 for comparison). Problems were encountered in reproducing several of yields in the later steps on scale. For example, alkylation of ketone **2.6** furnished low yields (10-40%) of **2. 7** compared to the 81% yield reported by Dr. Smith, and the vinyl sulfonate formation from **2.9** and subsequent Diels-Alder reaction sequence only furnished the desired mixture of adducts **2.10** and **2.11** in 30% yield. Despite the unexpected low yields of several of the steps, enough material was made to investigate the Diels-Alder reaction in detail and obtain crystals of **2.10** or **2.11** suitable for X-ray analysis.

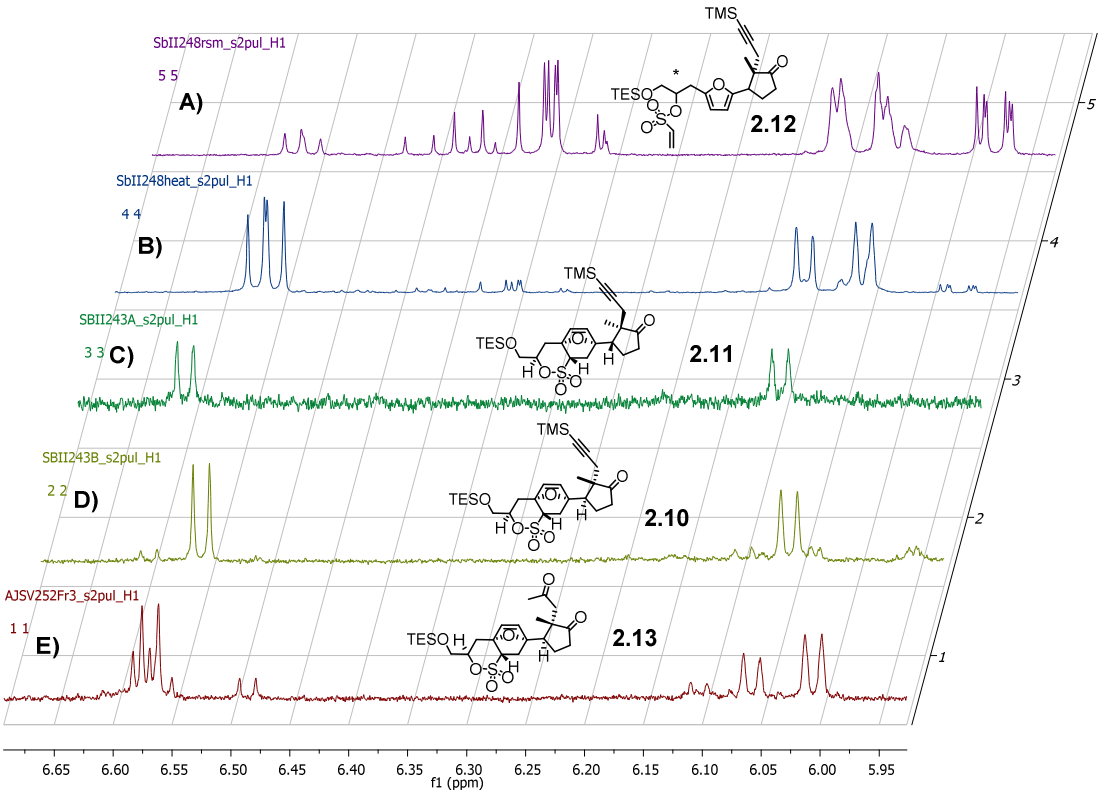
Scheme 2.1: Synthesis of Diels-Alder reaction adducts **2.10** and **2.11**



Heating the vinyl sulfonate ester **2.12** (Figure 2.1, **A**) in benzene for 24 h produces **2.10** and **2.11** (Figure 2.1, **B**), which were separable by chromatography. Diastereomer **2.11** (Figure

2.1, **C**) had characteristic doublets at 6.60 ppm and 6.10 ppm and diastereomer **2.10** (Figure 2.1, **D**) had characteristic doublets at 6.55 ppm and 6.05 ppm, which match the values obtained by Dr. Smith. Despite numerous attempts to crystallize **2.10** or **2.11**, no crystals could be grown. A sample of **2.10** originally synthesized by Dr. Smith was found, but the product had partially degraded to a more polar product by TLC (Rf = 0.2 in 3:1 EtOAc/Hexanes compared to an Rf of 0.5 for either Diels-Alder reaction adduct, Figure 2.1, **E**).

Figure 2.1: ^{1}H NMR traces of the vinyl sulfonate ester **2.12**, Diels-Alder reaction adducts **2.11** and **2.10** and by-product **2.13**

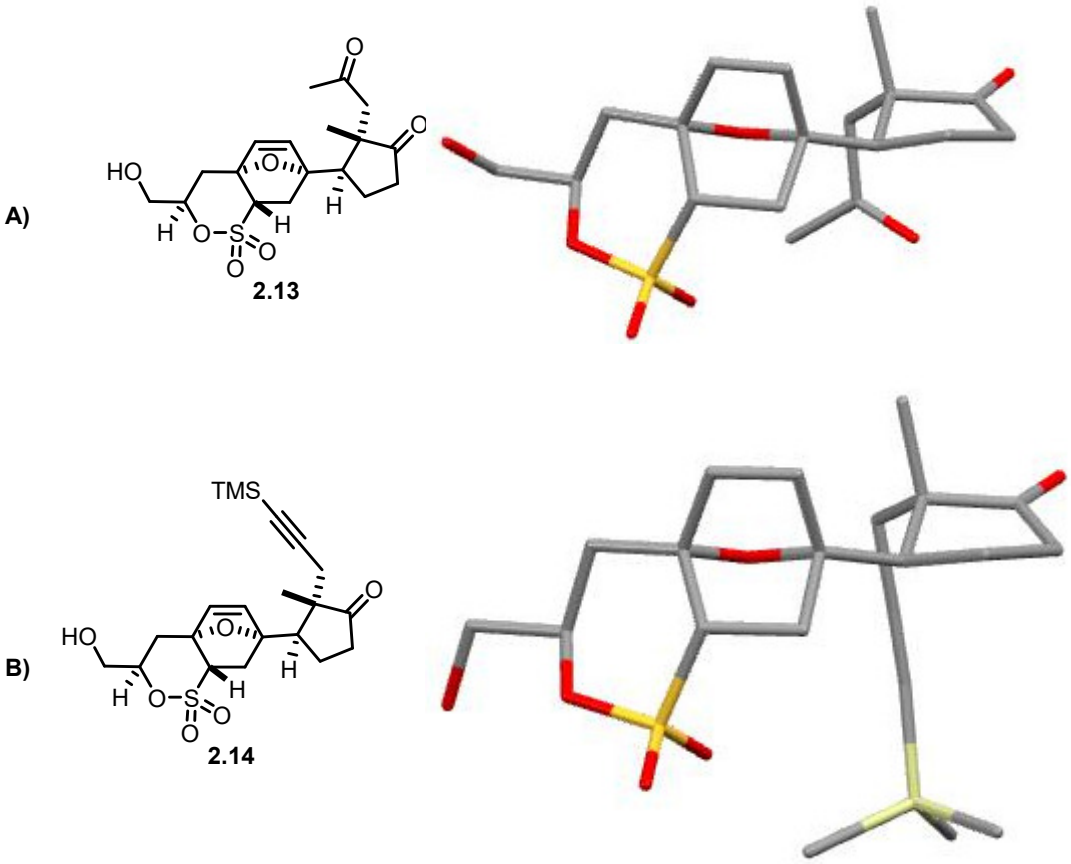


a) ^{1}H NMR of a (1:1) mixture of vinyl sulfonate diastereomers **2.12**; b) ^{1}H NMR of a (1:1) mixture of vinyl sulfonates diastereomers **2.12** after heating at 80 °C for 24h; c) ^{1}H NMR of **2.11**; d) ^{1}H NMR of **2.10**; e) ^{1}H NMR of partially degraded sample of **2.10** from Dr. Smith

Although no crystals of x-ray quality were able to be grown from a sample from either **2.10** or **2.11**, the purified sample from Dr. Smith (originally thought to be a derivative of **2.10**) crystallized nicely. X-ray analysis gave structure **2.13** (Figure 2.2, **A**). Although the relative stereochemistry was correct, it appeared that over six months in the freezer, the alkyne moiety had amazingly hydrated to the ketone. A sample of **2.10** was re-purified and unexpectedly, the TES group was lost giving **2.14**. Fortuitously, while the TES protected compound was not crystalline, the deprotected compound **2.14** crystallized, and x-ray analysis that confirmed the origin of ketone **2.13** was alkyne **2.10** (Figure 2.2, **B**). This confirmed that the relative stereochemistry between the furan and methyl group of **2. 7** after the propargylation is in the

desired trans relationship, and it also confirms that diastereomer **2.10** has the requisite stereochemistry required for cortistatin A (**2.1**).

Figure 2.2: Crystal structure of hydrated alkyne by-product **2.13** and desired product **2.14**



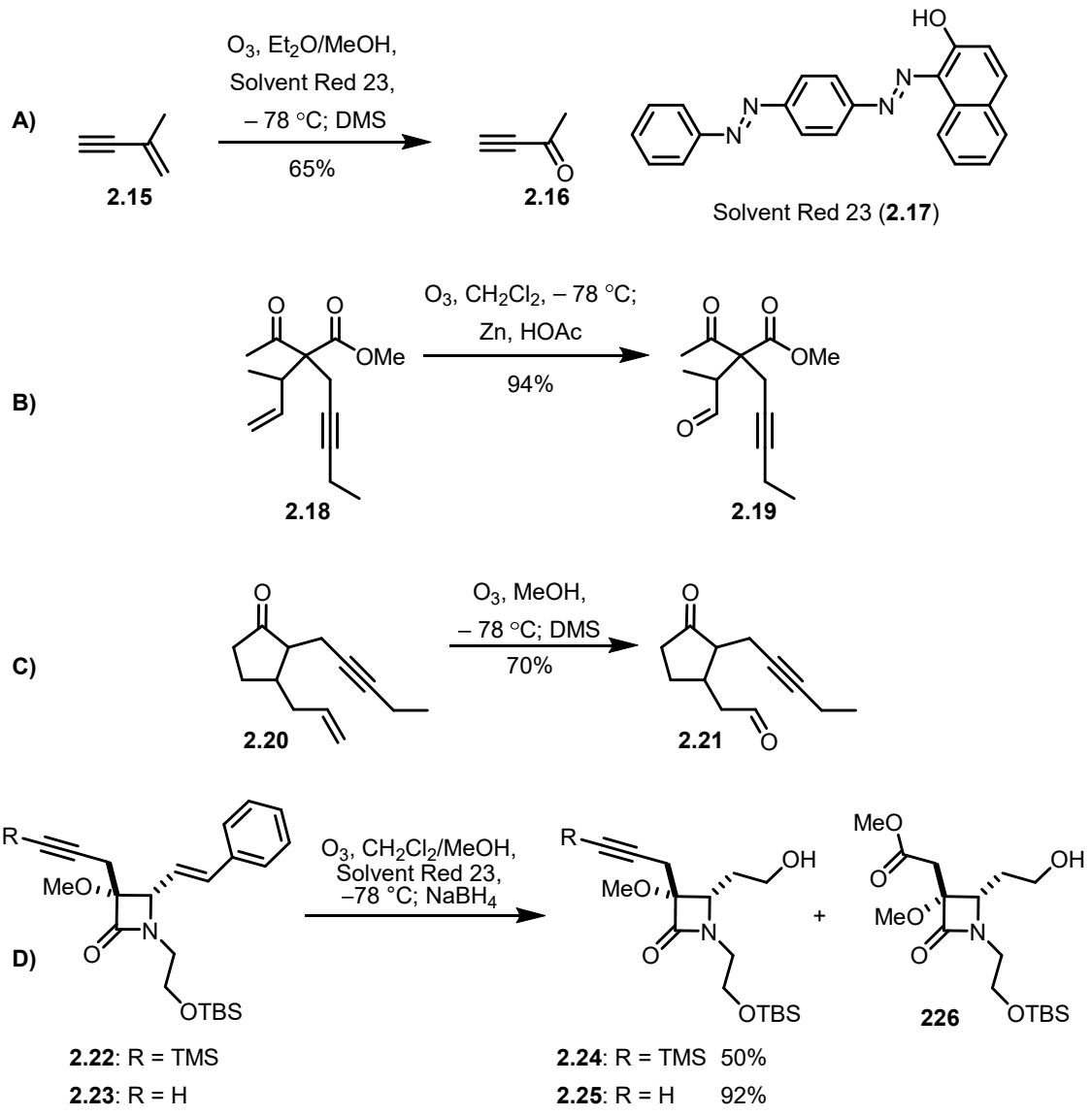
a) Crystal structure grown from purified degraded sample originally synthesized by Dr. Smith; b) Crystal structure grown of deprotected **2.14**

2.1.2: ATTEMPTS TO OZONOLYZE THE DIELS-ALDER REACTION ADDUCT 2.10

Ozonolysis was first demonstrated to be selective for alkenes over alkynes by Mc curry Jr. in the synthesis of cis-jasmone (Figure 2.3, **B**).[115] Krause also leveraged this selectivity in his synthesis of the epi-jasmones (Figure 2.3, **C**).[116] Alkynes can react with ozone to produce 1,2-diketones, anhydrides, and peroxy acids if no other reactive groups are present, making control of ozone equivalents important.[117-120] Veysoglu tested the rates of ozonolysis of various

functional groups and found a set of azo dyes that will react with ozone to de-color after the desired functional group has reacted but before the undesired one has.[121] He found that solvent red 23 **2.17** was ideal for use as an indicator in selective ozonolysis of alkenes over alkynes (Figure 2.3, **A**). That alkenes are more reactive than alkynes, however, is not always the case. When Banfi tried to ozonolyze **2.22** he recovered varying amounts of the alkyne cleavage product **2.26** even in the presence of solvent red 23 (Figure 2.3, **D**).[122] Subjecting the TMS-deprotected alkyne **2.23** to the same conditions gave the desired **2.25** in 92% yield, indicating that the TMS group may play a role in the diminished selectivity between the alkene and the alkyne.

Figure 2.3: Examples of selective ozonolysis of alkenes over alkynes

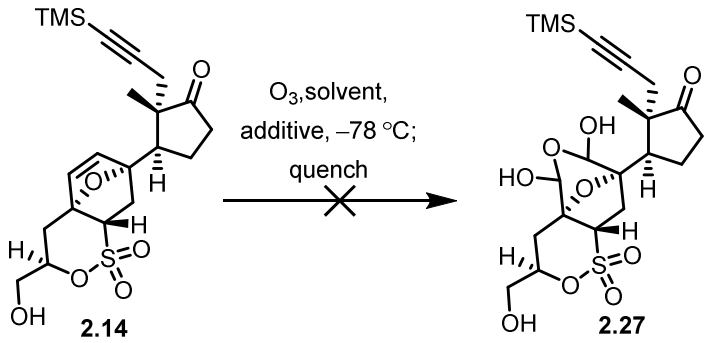


a) Selective ozonolysis by Veysoglu (1980), using solvent red 23 as an internal indicator;[121] b) Selective ozonolysis by McCurry Jr (1974) for the synthesis of *cis*-Jasmone;[115] c) Selective ozonolysis by Krause (2001), for the synthesis of epijasmonates;[116] d) Selective ozonolysis by Banfi (2002), for the synthesis of intramolecularly activated lactenediynes and example of TMS-alkyne cleavage.[122]

Multiple attempts were made to ozonolyze both the desired diastereomer **2.10** and the undesired diastereomer **2.11**, with no identifiable products being isolated (Equation 2.1). Use of solvent red 23 **2.17** to monitor the consumption of starting material provided no endpoint to the

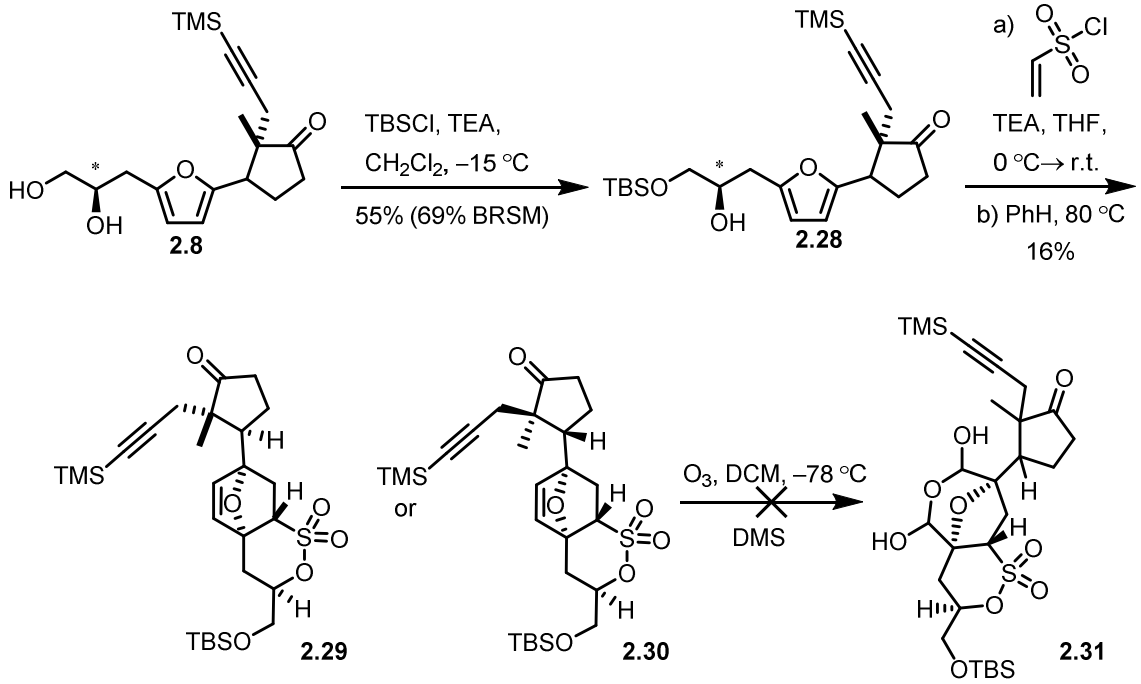
ozonolysis of the alkene over the alkyne. Use of different solvents, additives and reductive workups offered no improvements.

Equation 2.1: Attempted ozonolysis Diels-Alder reaction adduct **2.14**



When bringing up more material, the TES group was exchanged for the more robust TBS group to avoid deprotection during purification. Fortunately, use of TBSCl instead of TESCl in the conditions developed previously by Dr. Smith, gave selective protection of the primary alcohol (Scheme 2.2). Vinyl sulfonate formation followed by Diels-Alder reaction cyclization was again low yielding. Unfortunately, ozonolysis of either Diels-Alder reaction adduct **2.29** or **2.30** under the conditions tried previously on **2.14** gave no identifiable products.

Scheme 2.2: Synthesis of Diels-Alder reaction adduct **2.29** and **2.30** and attempted ozonolysis

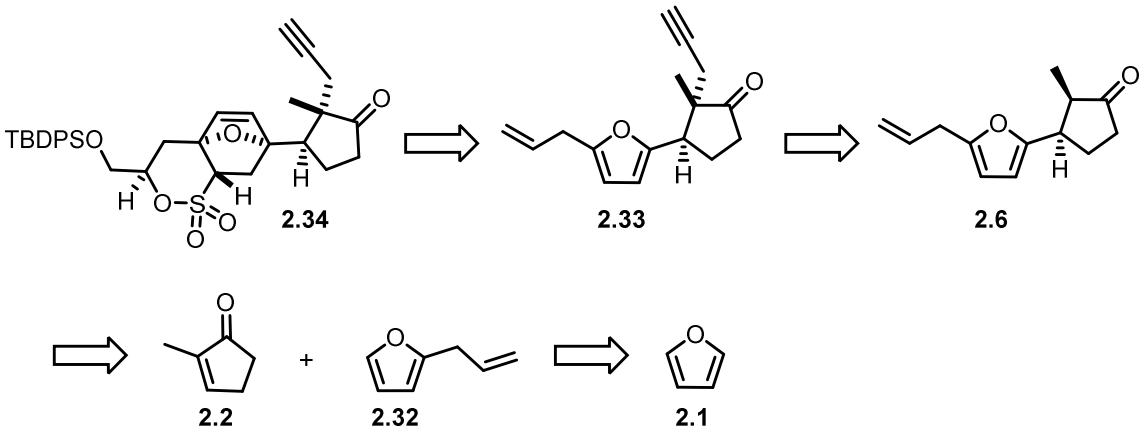


*** Indicates Absolute Stereochemistry**

Although no products were isolated from the ozonolysis of **2.29**, **2.30** or **2.14**, Banfi's observation that TMS-substituted alkynes may react with ozone at similar rate to alkenes suggests that removal of the TMS group prior to ozonolysis may be beneficial to the reaction (see Figure 2.3, **D**). Attempts to remove the TMS group in **2.10** or **2.11** with TBAF or K_2CO_3 in MeOH led to complex mixtures of unidentifiable products. Therefore, the forward synthesis was redesigned to remove the TMS group after the alkylation of ketone **2.6** (Scheme 2.3). Additionally, the conjugate addition of 2-allylfuran **2.32** into enone **2.2** was reinvestigated to reduce overall step count. The more robust TBDPS protecting group of the primary alcohol would be used instead of the TES or TBS group to avoid any hydrolysis during the Diels-Alder

reaction or purification and will also provide a chromophore will allow the easy development of an HPLC method to determine the enantioselectivity of the dihydroxylation.

Scheme 2.3: Modification of route

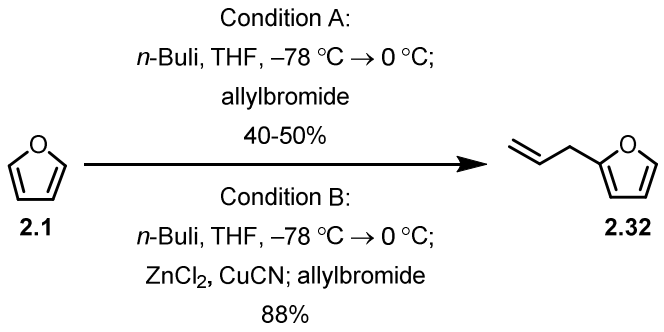


2.2.3: 2nd generation synthesis toward the Diels-Alder adduct

2.2.1: SYNTHESIS OF KETONE 2.6

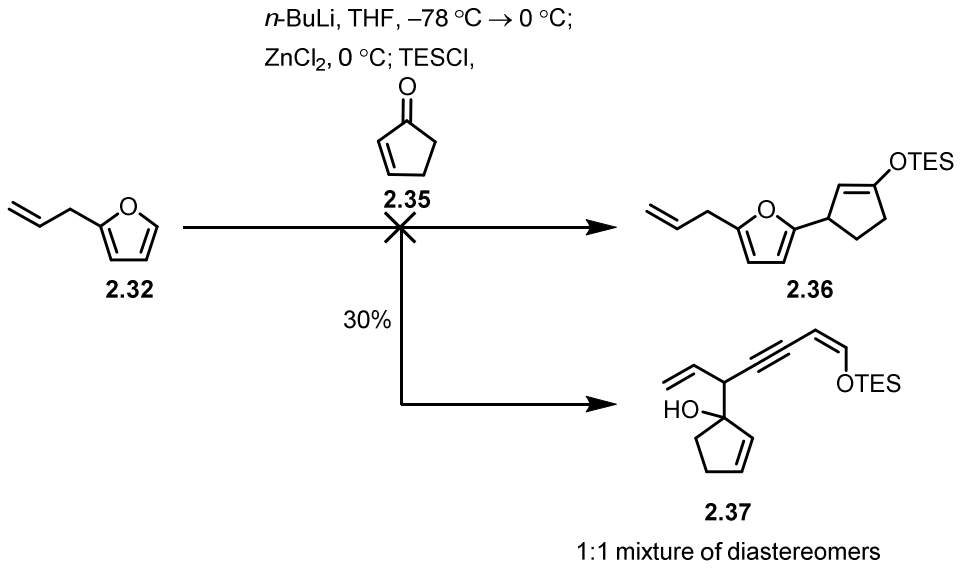
Lithiation of furan **2.1** in the 2-position followed by alkylation with allyl bromide provided 2-allylfuran **2.32** in only 40-50% yields (Equation 2.2, Condition A). Subjection of 2-allylfuran to the reaction conditions revealed that it was unstable to *n*-BuLi. The pK_a of the benzylic-type protons of similar compounds such as benzyl furan are 30, while the aromatic protons in the 2-position of furan have a pK_a of 36, so the product is more acidic than the starting material. To solve this problem, the 2-furyllithium species was transmetalated to a 2-furylzinc reagent with $ZnCl_2$ to attenuate the basicity of the furyl anion. Although the 2-furylzinc species was unreactive toward allylbromide, addition of a catalytic amount of CuCN provided 2-allylfuran **2.32** in 88% yield (Equation 2.2, Condition B).

Equation 2.2: Synthesis of 2-allylfuran **2.32**



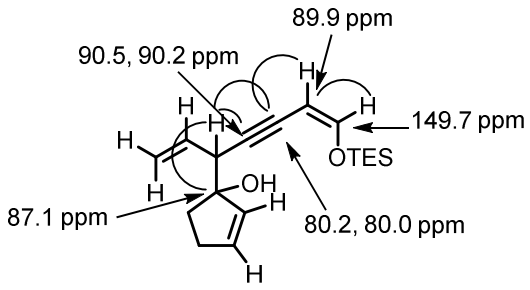
Several attempts were made to lithiate 2-allylfuran **2.32** at the 5-position but they all gave complex mixtures (Scheme 2.4). Thinking that the acidity of the benzylic position might be responsible for the unwanted side reactions, 2-allylfuran **2.32** was added into two equivalents of *n*-BuLi in an attempt to generate the dianion. The presumed dianion was then transmetalated to the organo zinc reagent using fused zinc chloride, which was added to cyclopentenone **2.35** in the presence of TESCl. A single compound was isolated as a mixture of diastereomers (1:1). The compound seemed to incorporate the cyclopentanone and TES group, so it initially seemed to be a 1,2-adduct of 2-allylfuran **2.32** and cyclopentenone **2.35**. After collecting 1D and 2D NMR spectra however, the structure of the isolated compound has been tentatively assigned as being the ring opened product **2.37**.

Scheme 2.4: Attempted 5-Lithiation of 2-allylfuran **2.32**



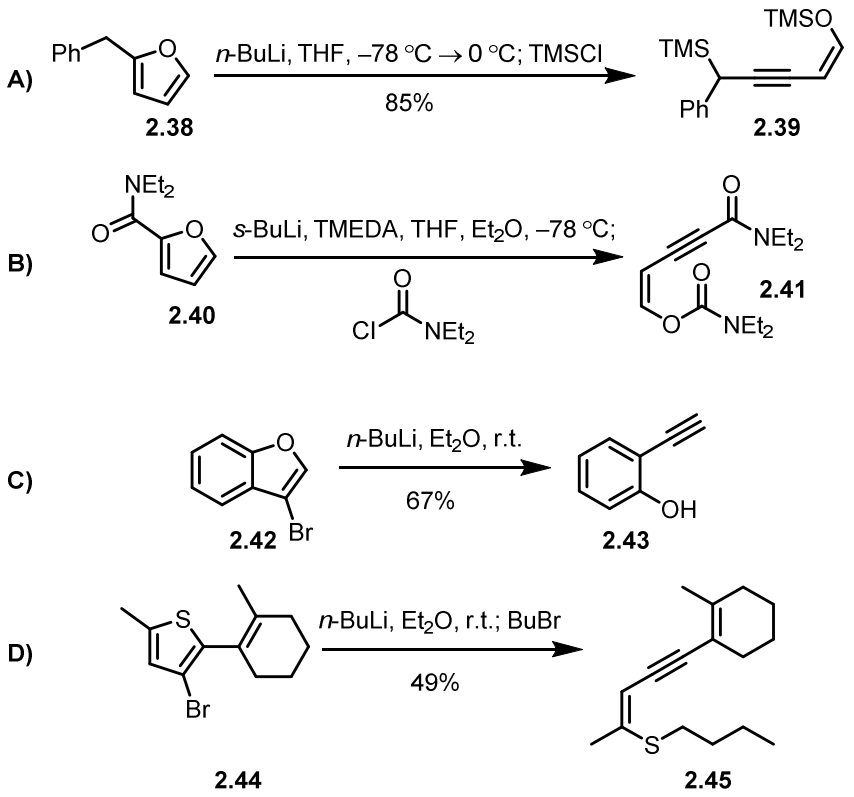
The IR spectrum of this product showed no peaks consistent with a carbonyl group and instead displayed a very strong OH stretch along with an alkyne stretch. Additionally, the presence of only nine carbon peaks between 150 ppm and 120 ppm was low compared to the expected 16 carbons (eight if both diastereomers overlapped perfectly) (Figure 2.4). Especially telling was that there was only a single carbon peak at 149.7 ppm, indicating that there was only one sp^2 hybridized carbon attached to an oxygen atom instead of the expected two to four if the furan was still intact. Additionally the carbon spectrum contained seven carbons between 90 ppm and 80 ppm indicative of alkynes and/or quaternary carbons attached to a oxygen atom.

Figure 2.4: Spectroscopic evidence of by-product **2.37**



Rearrangements of this type are unusual but not unprecedented. In 1979, Kuwajima discovered that exposure of benzyl furan **2.38** to excess *n*-BuLi facilitated a rearrangement, which after quenching with TMSCl, provided the enyne **2.39** in 85% yield (Figure 2.5, **A**).[123] Similar fragmentations are also seen with other heterocycles such as the side reaction reported by Snieckus in 1985 (Figure 2.5, **B**),[124] the lithium-halogen exchange of 3-bromobenzofuran **2.42** reported by Gilman in 1948 (Figure 2.5, **C**)[125] and the lithium-halogen exchange of 3-bromothiophene reported by Gronowitz in 1984 (Figure 2.5, **D**).[126]

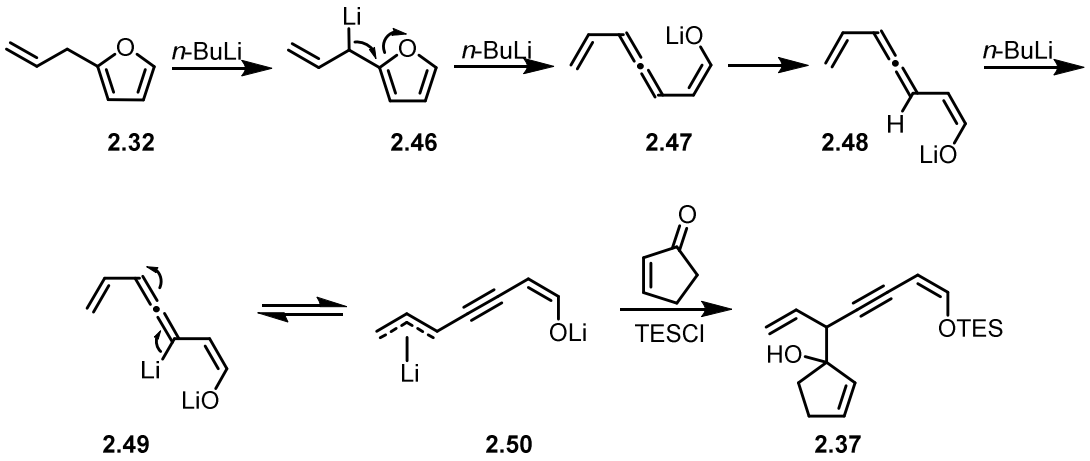
Figure 2.5: Anionic fragmentations of 2- and 3-lithioheterocycles



a)Example from Kuwajima[123] (1979); b) example from Snieckus[124] (1985); c) example from Gilman[125] (1948); d) example from Gronowitz[126] (1984)

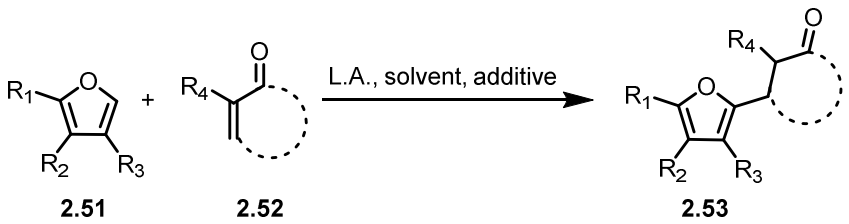
Based on the work of Kuwajima,[123] the first step in the formation of **2.37** is most likely deprotonation of the allylic position to give allylic anion **2.46**, followed by elimination to the allene-enolate **2.47** (Scheme 2.5). The oxygen atom in **2.47** might direct a second deprotonation of the allenic proton to give dianion **2.49**, which is in equilibrium with the enyne **2.50**. The ratio of the allene and enyne forms is determined by the stabilizing ability of the group in the 2-position of furan. Transmetalation with $ZnCl_2$ followed by 1,2-addition to with cyclopentenone and formation of the TES enol ether and the allyl anion subsequently adds in a 1,2 fashion to the cyclopentenone.

Scheme 2.5: Putative mechanism of formation of **2.37**



Since lithiation of 2-allylfuran **2.32** facilitates rearrangement to the enyne, acidic methods for the direct coupling with enone **2.2** may be more successful. Several Lewis and Bronsted acids are known to facilitate the Friedel-Crafts alkylation between enones and furans (Table 2.1). Transition metals such as palladium (entries 9 and 11), gold (entries 3 and 8) and vanadium (entry 7) give good yields with both cyclic and acyclic enones, but these catalysis are expensive. Of particular interest was the method of Dujardin (entry 4) and Kraus (entry 1) for their mild conditions and inexpensive reagents.[127-129] The method developed by Kraus was particularly interesting because it allows for the direct isolation of the silyl enol ether, which could be useful for the planned enolate alkylation later in the synthesis.[127]

Table 2.1: Friedel-Crafts reactions between furans and enones



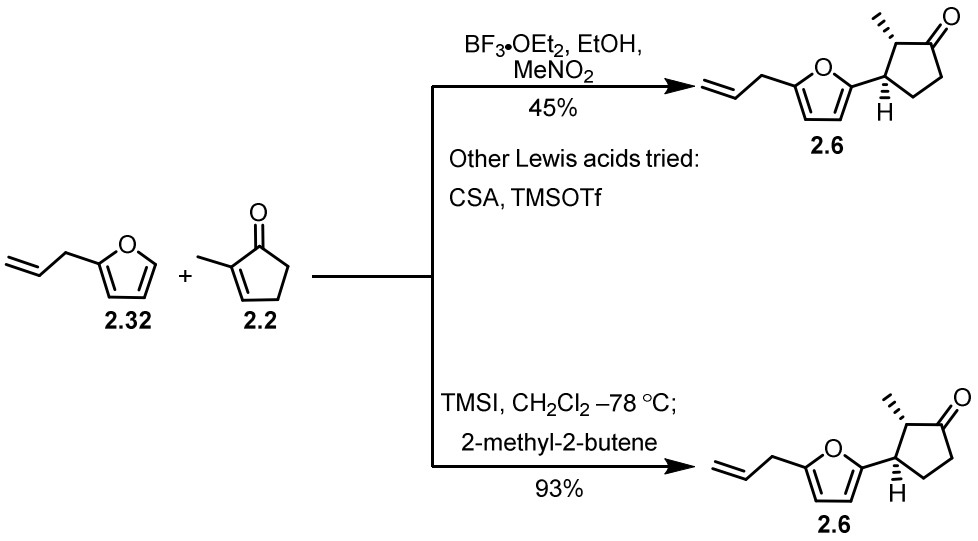
2.51 **2.52** **2.53**

reference	L.A.	Cond.	Additive	yield
Kraus[127]	TMSI	CH_2Cl_2, -78 °C	2-methyl-2-butene	67-92%
Deshpande[132]	$Cu(OTf)_2$	CH_2Cl_2, r.t.	N/A	53-77%
Dyker[133]	$AuCl_3$	MeCN, r.t.	N/A	80-90%
Dujardin[128,129]	BF_3•Et_2O	$MeNO_2$, 0 °C	EtOH	59-75%
Zefirou[134]	H_2SO_4	neat, 30-60 °C	Hydroquinone	59-75%
Vassilikogiannakis[135]	AcOH	AcOH/H_2O, 140 °C	Hydroquinone	75-90%
Chen[136]	$VO(OTf)_2$	CH_2Cl_2, r.t.	N/A	90-98%
Aguilar[137,138]	[Au]	MeCN, r.t.	AgOTf	60-84%
Bao[139]	$PdCl_2$	MeOH, r.t.	N/A	42-98%
Hoffmann[140]	$AlCl_3$	PhH, r.t.	N/A	37-43%
Roy[141]	$PdCl_2(MeCN)_2$	MeCN, r.t.	$SnCl_2$	50-90%

The mild conditions developed by Dujardin were tried first because the Magnus group used this procedure in their synthesis of the core of cortistatin A (Scheme 2.6).[128,129] Reaction of 2-allylfuran **2.32** with enone **2.2** in the presence of BF_3•OEt_2 provided ketone **2.6** in 45% yield. Altering reaction times, temperatures, or use of the protic acid CSA in place of BF_3•OEt_2 did not improve the yield. The modest yields provided by the Dujardin conditions prompted the investigation of the methodology developed by Kraus. Strict adherence to the Kraus conditions afforded the ketone **2.6** as a mixture of diastereomers (7.5:1 trans:cis) in 50-60% yield. After optimization, the ketone **2.6** was synthesized in 93% yield on gram scale. The key variables

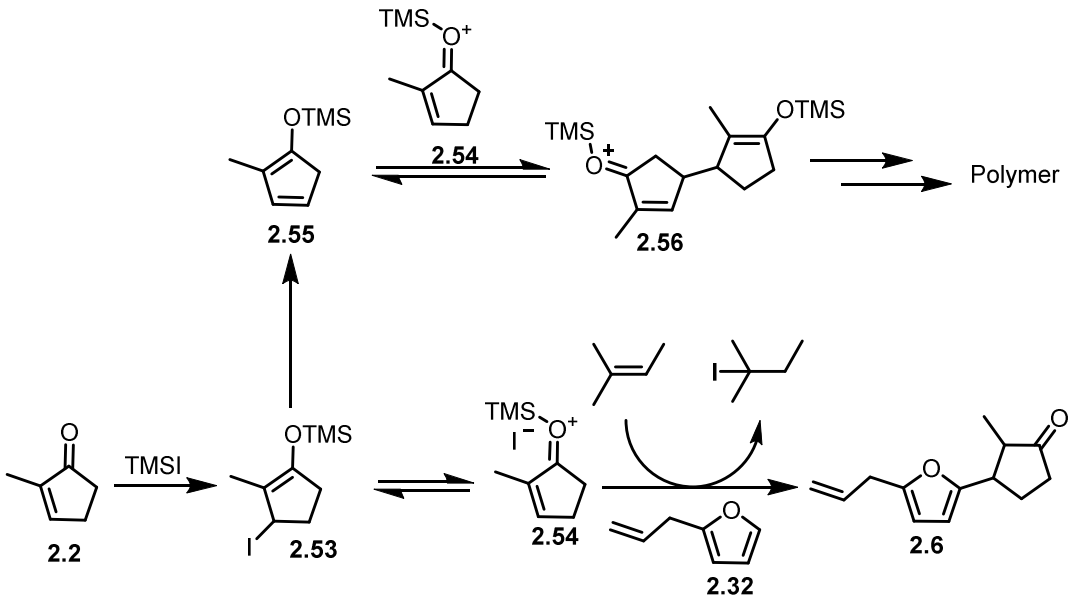
were: the time of incubation of the enone **2.2** with TMSI, the time stirred at –78 °C, and rapid addition of both 2-methyl-2-butene and 2-allylfuran in succession. Including 2-methyl-2-butene during the incubation of TMSI with the enone **2.2** resulted in lower yields. In the ^{1}H-NMR spectrum, the methyl peak shift of the major isomer is at 1.13 ppm while the minor isomer is at 0.86 ppm. Due to similar observations of the shielding effect of arenes on cis-methyl groups in 3,4-disubstituted cyclopentanes,[143-146] the major isomer of ketone **2.6** is tentatively assigned as trans.

Scheme 2.6: Lewis acid promoted coupling of 2-allylfuran **2.32** and enone **2.2**



2-Methyl-2-butene acted as a non-basic sponge for the hydroiodic acid produced as a byproduct during the reaction. Use of other bases led to rapid polymerization (Scheme 2.7). Even the presence of chloride ion in the form of tetrabutylammonium chloride (TBAC) or TMSCl proved too basic and caused polymerization. Presumably, TMSI and the enone react to form the β-iodo-silyl enol ether **2.53**. This intermediate is in equilibrium with oxonium species **2.54**, which, while being an excellent Friedel-Crafts partner, is very acidic. Deprotonation forms the highly reactive cyclopentadiene **2.55** that can then polymerize *via* multiple pathways.

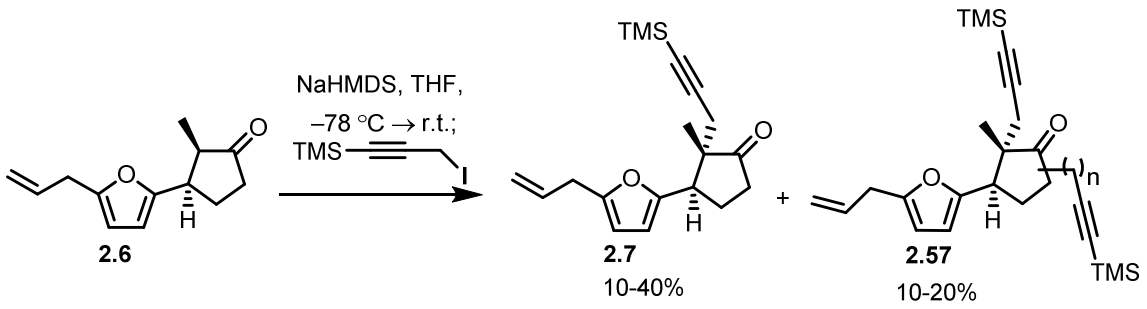
Scheme 2.7: Products identified in the presence of base during TMSI coupling



2.2.2: INVESTIGATION OF THE ENOLATE ALKYLATION OF 2.6

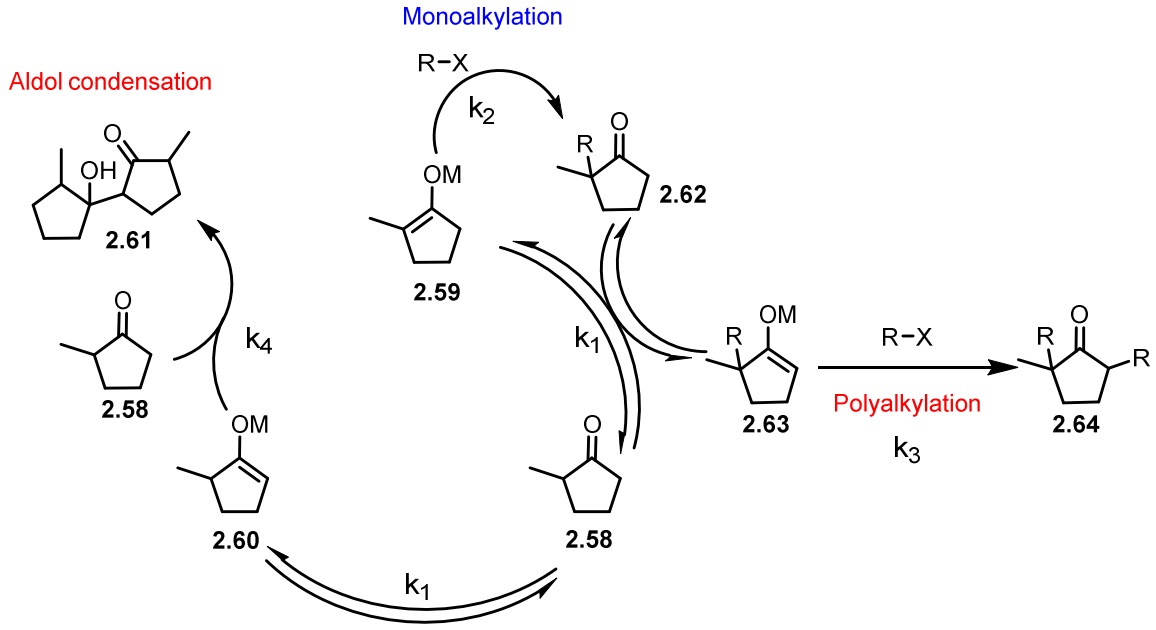
With access to multiple grams of the ketone **2.6**, the next problem to be solved was α-alkylation. The conditions developed by Dr. Anna Smith utilized substoichiometric amounts of NaHMDS in THF to allow the less substituted kinetic enolates equilibrate to the more substituted thermodynamic enolates before alkylating with TMS propargyl iodide. On scale up, however, alkylation of ketone **2.6** under the same conditions consistently afforded low (10-40%) yields of ketone **2.7** (Equation 2.3). Analysis of the reaction mixture revealed that a significant portion of the mixture contained poly-alkylated products represented as compound **2.57**.

Equation 2.3: Initial enolate alkylation of ketone **2.6**



There are two primary side reactions that occur during enolate alkylations involving cyclopentanones: polyalkylation and aldol condensation (Scheme 2.8). Under equilibrating conditions, aldol condensation (**2.59** → **2.61**) is in direct competition with proton exchange (**2.58** → **2.59/2.60**). Polyalkylation occurs because the rate of alkylation is slower than the proton exchange between ketone and enolate. In 1965, House suggested that the reason polyalkylation is such a problem is because the enolate becomes less aggregated and more reactive as substitution increases around the ketone.[147-152, 154] This hypothesis is supported by the work of Streitwieser, who found that dialkylation of tetralone is 1.8 times as fast as monoalkylation.[147]

Scheme 2.8: Side-reactions during the alkylations of ketones

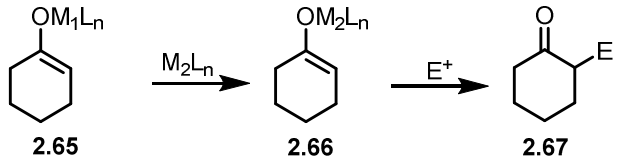


k_1 = rate of proton exchange between enolate and ketone; k_2 = rate of monoalkylation; k_3 = rate of dialkylation; k_4 = rate of aldol condensation; $k_1 > k_3 > k_2 > k_4$

One strategy to limit the amount of polyalkylation is by adding Lewis acids to the enolate before adding the alkylating agent (Table 2.2). The Lewis acids are thought to reduce the basicity of the enolate, thereby preventing proton exchange between the alkylated product and the unreacted enolate. Several Lewis acids that have been shown to accomplish this, which includes: $ZnMe_2$,[100] $TiCl(OiPr)_3$,[100] $MnCl_2$•2LiCl,[97,98,101] $AlEt_3$[99] and Bu_3SnCl[99] (Table 2.2). The Lewis acids $ZnMe_2$ and $TiCl(OiPr)_3$ are unattractive because of the requirement of HMPA as a co-solvent to enhance reactivity, large excesses of alkylating agent and prolonged cryogenic conditions (–78 ºC) (Table 2.2, entries 1,2). Conditions utilizing Bu_3SnCl and $AlEt_3$ are milder 0 ºC *vs* –78 ºC), but still require HMPA as a co-solvent (Table 1.2, entries 3,4). Manganese dichloride, which was independently developed by Reetz and Cahiez, only requires stoichiometric amounts of the alkylating agent and uses DMSO or DMPU as cosolvents so it was chosen as the Lewis acid to suppress polyalkylation (Table 2.2, entry 5). At first, the NaHMDS/THF conditions were used in conjunction with $MnCl_2$•2LiCl ($MnCl_2$ source soluble in THF), but no improvement was noted. Since most of the examples using Lewis acids to suppress

polyalkylation use the lithium enolate, it was theorized that the sodium enolate might make the resultant complex too basic to suppress polyalkylation. Accordingly, conditions were sought for the generation of the thermodynamic lithium enolate.

Table 2.2: Lewis acids to suppress poly-alkylation



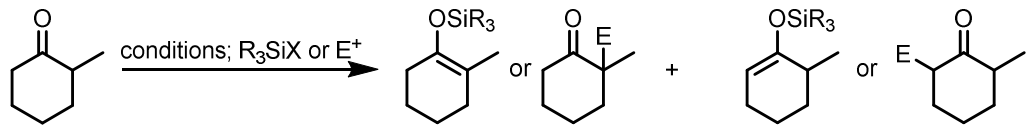
2.65 **2.66** **2.67**

M_1 = Li, Na, K

Reference	**Additive**	**E^+**	**conditions**	**yield**
Noyori[100]	$ZnMe_2$	MeI	THF/HMPA, -78 °C, 10h	94%
Noyori[100]	$ClTi(OiPr)_3$	MeI	THF/HMPA, -78 °C, 10h	94%
Tardella[99]	Bu_3SnCl	MeI	DME, 0 °C, 1h	93%
Tardella[99]	$AlEt_3$	MeI	DME/HMPA, 0 °C, 48h	94%
Reetz/Cahiez[97,98,101]	$MnCl_2$	MeI	THF/DMSO, r.t., 2h	93%

There are several methods to form thermodynamic enolates,[153-164] but many of them involve the use of sodium, potassium or magnesium bases that may make the Lewis acid complexes reactive towards electrophiles (Table 2.3). The only example with lithium enolates is Yamamoto's use of aluminum tris(2,6-diphenylphenoxide) (ATPH) and lithium diisopropylamide (LDA) (Table 1.3, entry 6).[159] Unfortunately, ketone **2.6** proved to be a uniquely frustrating substrate. Exposure of **2.6** to stronger bases than lithium hexamethyldisilazane (LiHMDS) (such as LDA or dimsyl anion) resulted in the formation of unidentifiable by-products, most likely related to the proclivity of 2-allylfuran to rearrange under basic conditions (see Scheme 2. 4)

Table 2.3: Methods for the generation of the thermodynamic enolate



2.68 **2.69** **2.70** **2.71** **2.72**

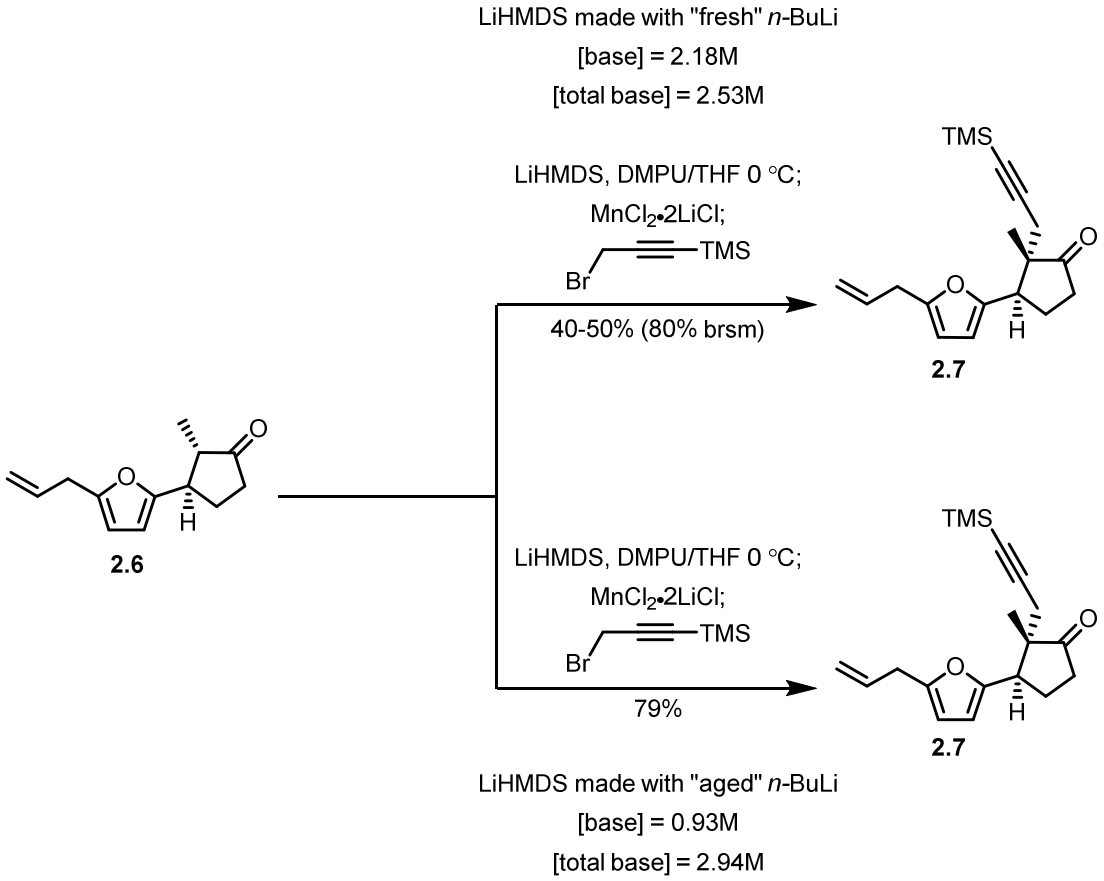
reference	base	additive	Cond.	E^+	T:K[a]
Stork[161]	NaH	N/A	DME, reflux	TMSCl	73:27
Brown[162]	KH	N/A	THF, r.t.	TMSCl	67:33
Krafft[160]	(*i*-Pr)$_2$NMgBr	Et_3N	Et_2O/HMPA, r.t.	TMSCl	97:3
Bordeau[158]	(2-pyr)$_2$Mg	N/A	-50 °C, THF	MeI, TMSCl	95:5
Negishi[157]	KH	BEt_3	THF, r.t.	MeI, TMSCl	93:7
Yamamoto[159]	LDA	ATPH	-78 °C, THF	MeI	100:0
Turner[164]	KH	N/A	THF/HMPA, -78 °C → r.t.	TBSCl	98:2
Krafft[163]	$FeCl_3$/MeMgBr	Et_3N	Et_2O/HMPA, r.t.	TMSCl	93:7

a) Ratio of T (Thermodynamic) (products **2.128** or **2.129**) to K (Kinetic) (products **2.130** or **2.131**)

To develop conditions to generate the thermodynamic lithium enolate, ketone **2.6** was added to a sub-stoichiometric amount of LiHMDS in THF at 0 °C. 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU) was then added, and the mixture was stirred at 0 °C. Aliquots were quenched with TESCl and analyzed by ^{1}H NMR to determine the ratio of thermodynamic to kinetic silyl enol ethers. These initial experiments revealed that equilibrium was established after four h. Transmetallation of the lithium enolate after the four h incubation with $MnCl_2$•2LiCl and subsequent alkylation with TMS-propargyl bromide gave ketone **2.7** in 79% yield (Scheme 2.9). Unfortunately, these results were difficult to reproduce. When the batch of *n*-BuLi that was initially used to generate LiHMDS ran out, use of a fresh bottle resulted in incomplete conversion of the starting material. Titration of similarly "aged" and fresh *n*-BuLi revealed that the "aged" *n*-BuLi contained less *n*-BuLi than the fresh bottle (0.93M vs 2.18M) but contained more basic species overall (2.94M vs 2.53M). The basic species are most likely a

mixture of LiH from β-hydride elimination, LiOH from traces of water and *n*-BuOLi from the reaction of *n*-BuLi with oxygen.

Scheme 2.9: Initial use of $MnCl_2$•2LiCl in suppression of polyalkylation

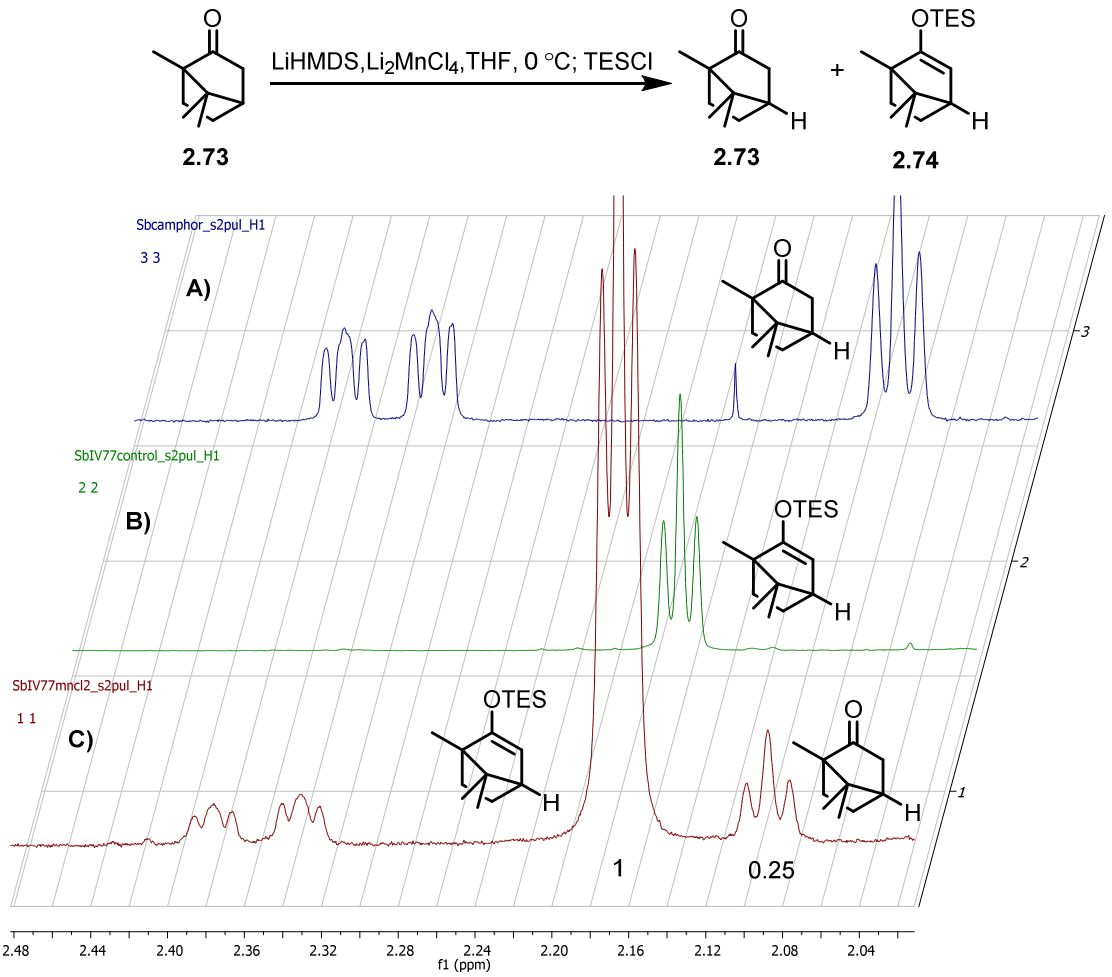


The success of the alkylation of **2.6** with the aged *n*-BuLi may be due to the presence of the extra base, which quenches quenching adventitious proton sources contained within the reaction mixture. Rigorous drying of the glassware, purification of ketone **2.6** via Kügelrohr distillation and/or use of internal indicators to ensure proper stoichiometry of base was attained had no effect on the reaction. That none of these interventions had any effect on the reaction course led to the conclusion that the source of the adventitious proton source was the $MnCl_2$•2LiCl. Unfortunately, rigorous drying of $MnCl_2$ by heating at elevated temperatures under vacuum for extended periods of time did not improve conversion of the starting material. Other

drying procedures such as, refluxing $SOCl_2$,[165-166] or slurrying the solution of $MnCl_2$•2LiCl over 4 Å molecular sieves also had no beneficial effect.[167]

A second tactic to remove adventitious proton sources from the $MnCl_2$•2LiCl solution would be to add an amount of base equivalent to the amount of proton sources contained within the $MnCl_2$•2LiCl solution. In order for this strategy to succeed, the exact amount of proton sources would have to be determined. Initial attempts to assay the solution of $MnCl_2$•2LiCl was complicated by the fact that most colorimetric indicators had no endpoint in the presence of $MnCl_2$•2LiCl, and the addition of organometallics, such as *n*-BuLi, caused a purple-violet precipitate to form, presumably a Mn^0 species. To circumvent this problem, a method was devised by generating the camphor enolate and quenching with the $MnCl_2$•2LiCl solution, followed by TESCl and analyzing the relative ratios of camphor and silyl enol ether. Fortunately, the bridgehead proton for camphor **2.73** (Figure 2.6, **A**) and the silyl enol ether **2.74** proton (Figure 2.6, **B**) were distinct and did not overlap in the ^1H NMR spectrum, allowing the ratio of protonated and deprotonated ketone to be assessed easily. The assay revealed that protic impurity contaminants were present in 25 mol % (Figure 2.6, **C**).

Figure 2.6: Titration of $MnCl_2$•2LiCl with camphor **2.73**

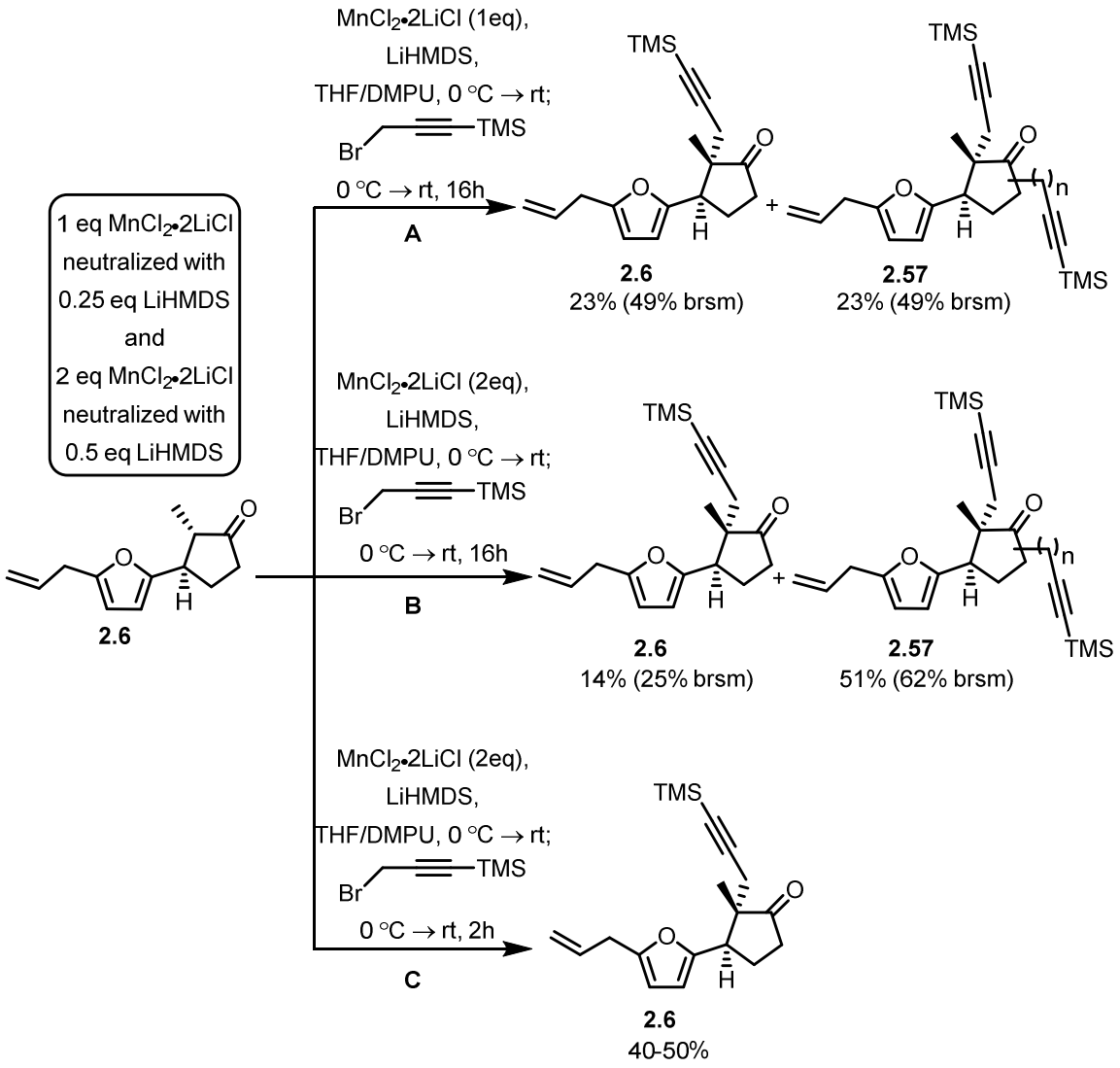


a) NMR of camphor; b) NMR of camphor + LiHMDS (1eq) and quenched with TESCl; c) NMR of camphor + LiHMDS (1eq), followed by $MnCl_2$•2LiCl (1eq) and quenched with TESCl

Alkylation of **2.6** with one equivalent of $MnCl_2$•2LiCl neutralized with 0.25 equivalents of LiHMDS gave polyalkylation products **2.57** in equal amounts to the desired product **2.7** (23% of **2.7** and 23% **2.57**) (Scheme 2.10, **A**). Use of two equivalents of $MnCl_2$•2LiCl neutralized with 0.5 equivalents of LiHMDS gave more polyalkylation products **2.57** than the desired product **2.7** (14% of **2.7** and 51% **2.57**) (Scheme 2.10, **B**). Fortunately, limiting the reaction time to two h as opposed to 16 h eliminated this problem, and the ketone **2.7** was reproducibly isolated in 40-50% yield (Scheme 2.10, **C**). Basic species present in the neutralized $MnCl_2$•2LiCl must be able to deprotonate the ketone during prolonged reaction times. Analysis of the reaction mixture revealed very little polyalkylation, but a significant amount of baseline material was observed by

thin layer chromatography (TLC). Attempts to isolate this baseline material revealed a mixture of unidentifiable products. Analysis of the material by IR showed a carbonyl stretch of 1713 cm^{-1}, shifted from where the cyclopentanone carbonyl stretch appears at 1741 cm^{-1} and more indicative of enones. Analysis of the material by LCMS showed several peaks, the most prominent being *m/z* = 413 and 443. The mass at 413 may be of the aldol dimer + sodium, and although the origin of the mass at 443 in not clear, it is significantly higher than the 204, which is the mass of the starting material. These facts seem to indicate that the missing mass is due to aldol condensation during the enolate equilibration.

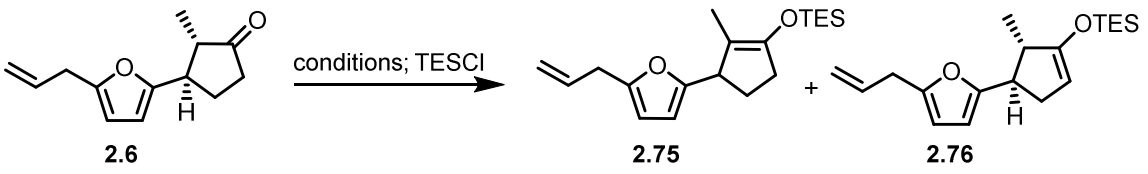
Scheme 2.10: Alkylation of **2.6** with $MnCl_2$•2LiCl neutralized with LiHMDS



The fact that there was such a big difference between using the bottle of aged and fresh *n*-BuLi in the initial $MnCl_2$•2LiCl alkylation could also mean that the enolate equilibration was also affected by the quality of the *n*-BuLi. The sediments present in the aged *n*-BuLi are most likely composed of lithium hydroxide, lithium hydride and lithium *n*-butoxide (*n*-BuOLi). Previous experiments showed that lithium hydride did not affect the deprotonation of ketone **2.6**, so *n*-BuOLi was identified as the contaminant most likely to affect the reaction. To better understand the role of *n*-BuOLi, ketone **2.6** was deprotonated with LiHMDS under a variety of conditions and then quenched with TESCl to analyze the formation of the thermodynamic

enolate through the formation of silyl enol ethers **2.75** and **2.76** (Table 2.4). Addition of ketone **2.4** to LiHMDS made from fresh *n*-BuLi gave the kinetic enolate almost exclusively (Table 2.4, entry 1). Interestingly, repeating the same experiment with aged *n*-BuLi reduced the ratio of **2.76**: **2.75** from 19:1 to 12:1 (Table 2.4, entry 2). Addition of LiHMDS to a mixture of *n*-BuOH and ketone also drastically eroded the selectivity, even at –78 °C, from 19:1 to 3.8-5.2:1 (Table 2.4, entries 3-5). Interestingly, *n*-BuOLi made *in situ* with *n*-BuLi was strong enough to deprotonate the ketone (~67% by crude NMR) and gave a 1:1.1 ratio of **2.76**:**2.75** (Table 2.4, entry 6). Adding LiHMDS to a mixture of the ketone **2.6** and *n*-BuOH at 0 °C gave almost quantitative thermodynamic enolate but only showed ~60% deprotonation by crude ^{1}H-NMR and was contaminated with aldol products.

Table 2.4: Examination of the kinetic and thermodynamic lithium enolates



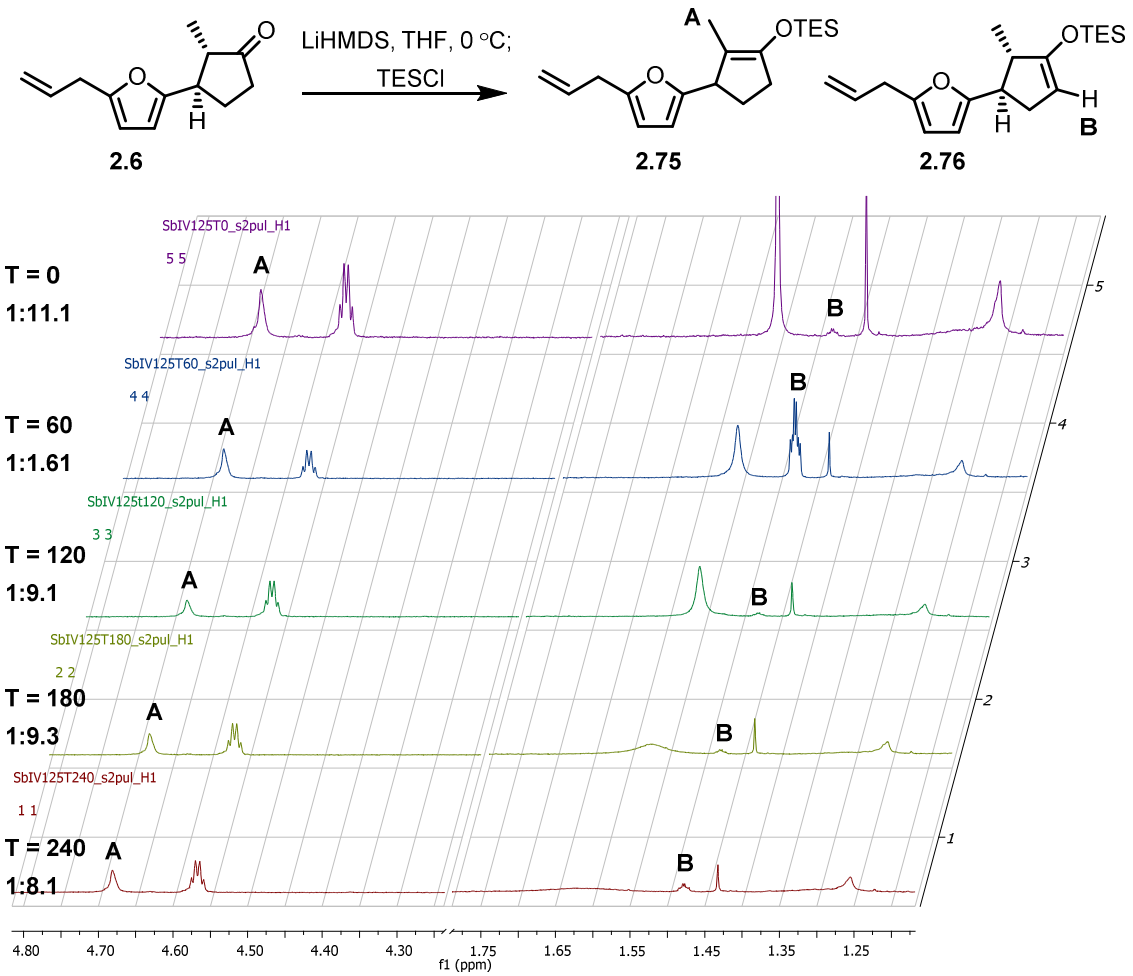
2.6 **2.75** **2.76**

base	eq	Additive	eq	solvent	T°	t (min)	2.75:2.76
LiHMDS[a,d]	0.95	N/A	N/A	THF	0 °C	10	1:19
LiHMDS[a,e]	0.95	N/A	N/A	THF	0 °C	10	1:12
LiHMDS[b,d]	2	*n*-BuOH	1	THF	-78 °C	10	1:4.6
LiHMDS[b,d]	2	*n*-BuOH	1	THF/DMPU	-78 °C	10	1:3.8
LiHMDS[c,d]	2	*n*-BuOH	1	THF	-78 °C	10	1:5.2
n-BuOLi[a,d]	1	N/A	N/A	THF	0 °C	10	1.1:1[f]
LiHMDS[c,d]	0.95	*n*-BuOH	0.1	THF	0 °C	60	20:1[g]

a) add starting material to base in one portion; b) add base to starting material dropwise; c) add base to starting material in one portion; d) base made with "fresh" n-BuLi; e) base made with "aged" n-BuLi; f) ~67% deprotonation; g) ~60% deprotonation

The equilibration behavior of the enolates was observed in more detail by adding 0.9 eq LiHMDS to ketone **2.6** and quenching aliquots with TESCl. The ratios of **2.76** (methyl peak labeled **A** in Figure 2.7) and **2.75** (alkenyl proton labeled **B** in Figure 2.7) were analyzed by ^{1}H-NMR. Initially the ratio starts at 1:11.1 (**2.76**: **2.75**), which is consistent with the results in Table 1.4. After one hour the enolate ratio increases to 1.61:1 (**2.76**: **2.75**). Interestingly, the thermodynamic silyl enol ether peak **B** seems to disappear and recede into the baseline as time progressed. This seemed to correlate with increased amounts of the baseline material by TLC. The most likely explanation for these results and the lower yields with the neutralized $MnCl_2$•2LiCl is that aldol reactions are taking place before the enolates **2.76** and **2.75** have reached equilibrium. These results indicate that generation of the thermodynamic enolate *via* incubation with substoichiometric base to the ketone will result in large amounts of aldol reactions and that the original success of the reaction (see Scheme 2.9) could be due to enolate equilibration after the addition of $MnCl_2$•2LiCl.

Figure 2.7: Examination of the kinetic and thermodynamic enolates as a function of time

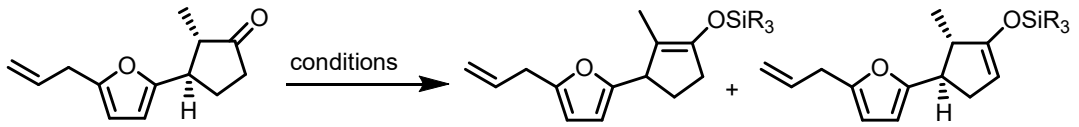


At T = 0 min, **2.76**:**2.75** is 1:11.1; At T = 60 min; 1: 1.61; At T = 120 min; 1:9.1; At T = 180 min; 1:9.3; At T = 240 min; 1:8.1

To circumvent the aldol problem, the generation of the thermodynamic enolate by isolating the silyl enol ether and unmasking using an alkyllithium reagent was investigated. Use of strongly basic conditions to form the silyl enol ether, such as Krafft's conditions (Table 2.3, entry 1) polymerized the starting material.[163] Turner's conditions (see Table 2.3) reduced polymerization, providing the TBS ether **2.78** in 85% yield, but the omission of HMPA resulted in a drop in selectivity for the thermodynamic silyl enol ether (3.3:1 ratio of **2.78**:**2.80**).[164] Soft enolization conditions for the formation of the silyl enol ether are known to be mild and selective for the more substituted isomer, but the choice of base proved to be key for isolating the silyl enol ether **2.77** in high yields. Bases such as K_2CO_3, Et_3N and DBU provided selective formation

of the thermodynamic silyl enol ether **2.77**, but also significant amounts polymerized material were formed (Table 1.5). Other bases such as 2,6-lutidine and pyridine gave incomplete conversions. Only HMDS furnished silyl enol ether **2.77** in high yields.

Table 2.5: Synthesis of thermodynamic silyl enol ether **2.77** or **2.78**



2.6 **2.77: R_3Si = TMS** **2.78: R_3Si = TBS** **2.79: R_3Si = TMS** **2.80: R_3Si = TBS**

SiR_3X	base	solvent	temp	t (h)	T:K[a]	yield
TESCl	$MeMgBr/FeCl_3$	Et_2O/HMPA	r.t.	2	N/A	N/A
TBSCl	KH	THF	–78 °C→ 0 °C	1	3.3:1	85%
TMSCl/KI	Et_3N	MeCN	reflux	2	20:1	N/A
TESCl/TBAI	K_2CO_3	MeCN	r.t.	1	3.7:1	N/A
TMSCl/NaI	HMDS	CH_2Cl_2/MeCN	r.t.	2	20:1	79%

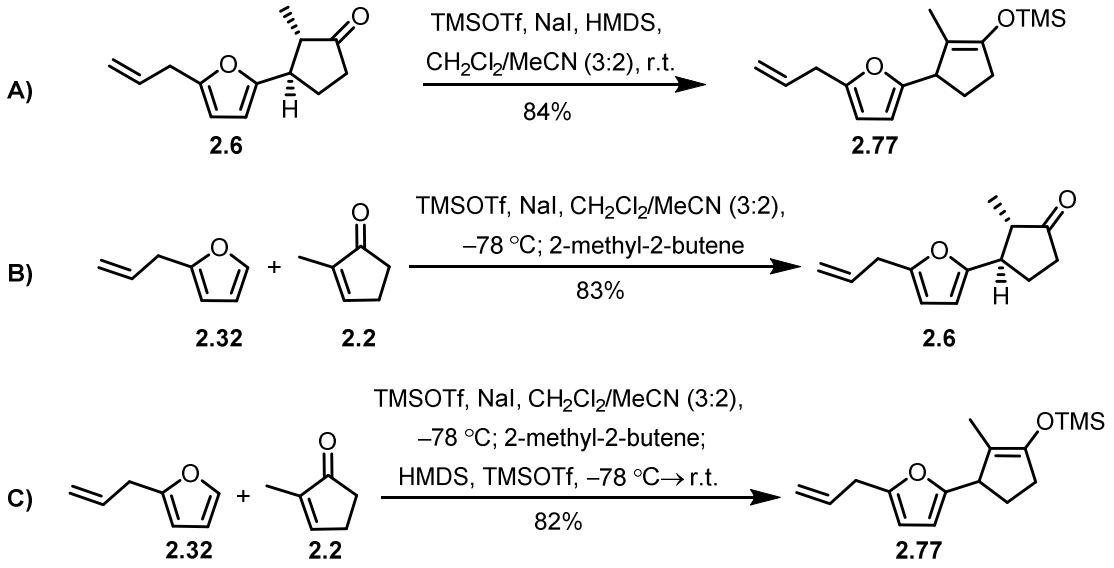
a) T = more substituted isomer, K = less substituted isomer

Having identified conditions for the generation of silyl enol ether **2.77** in high yield and selectivity, it was reasoned that it may be possible to isolate the silyl enol ether **2.77** directly from the Kraus reaction between 2-allylfuran **2.32** and enone **2.8**. Previously, attempts to generate TMSI *in situ* utilizing a Finklestein-like reaction between TMSCl and NaI in MeCN led to polymerization of the enone due to the basicity of the chloride counterion relative to the acidic species in the reaction mixture (see Scheme 2.7). The use of a R_3SiX source with a non-basic counterion may facilitate the Kraus reaction to allow the isolation of the silyl enol ether **2.77**. TMSOTf seemed an excellent substitution for TMSCl because the OTf counterion is almost inert.

To test whether TMSOTf delivers silyl enol ether **2.77**, the ketone **2.6** was subjected to the same conditions used previously except TMSOTf was used in place of TMSCl (Figure 2.8, **A**). Gratifyingly, the silyl enol ether **2.77** was isolated in 83% yield and with the same selectivity

as the conditions developed with TMSCl/NaI (Table 1.5, entry 5). After a determining that the maximum amount of MeCN in CH_2Cl_2 that stays liquid at –78 ºC to be 3:2, 2-allylfuran **2.32** and enone **2.8** were subjected to the modified Kraus conditions using TMSOTf/NaI in place of TMSI to provide the ketone **2.6** in 83% yield (Figure 2.8, **B**). The Kraus alkylation with TMSOTf/NaI in CH_2Cl_2/MeCN was significantly faster than with TMSI in CH_2Cl_2, taking only two h at –78 ºC compared to the eight h using TMSI in CH_2Cl_2. Initial attempts to isolate the silyl enol ether **2.77** from the Kraus reaction by quenching with HMDS led to substantial amounts of ketone **2.6**. Although 2-methyl-2-butene functions as an HI sponge during the reaction, it remains possible that HI may protonate the silyl enol ether to generate the ketone. To fully convert the reaction mixture to the silyl enol ether, an additional one equivalent of TMSOTf was added to the reaction mixture after the HMDS quench, and the mixture was stirred for an additional one h at room temperature (Figure 2.8, **C**). Gratifyingly, the silyl enol ether **2.77** was then obtained in 83% yield.

Figure 2.8: Modification of Kraus reaction using TMSOTf/NaI to isolate either ketone **2.6** or silyl enol ether **2.77**



a) Synthesis of silyl enol ether **2.77** from ketone **2.6**. b) Synthesis of ketone **2.6** from 2-allyl furan **2.32** and enone **2.8** utilizing modified Kraus alkylation conditions. c) Synthesis of silyl enol ether **2.77** from 2-allyl furan **2.32** and enone **2.8** utilizing modified Kraus alkylation conditions and HMDS quench.

Unfortunately, the TMS silyl enol ether **2.77** was unstable to the enolate unmasking conditions using alkyllithium reagents. Recalling that *n*-BuLi led to the rearrangement of 2-allylfuran **2.32** to the enyne **2.37**, it was hypothesized that the 2-allylfuran moiety in **2.32** may be decomposing via similar pathways (see Scheme 2. 4). The base sensitivity of silyl enol ether **2.77** led to the exploration of other nucleophiles that are not as basic as alkyllithiums. Potassium *tert*-butoxide *(tert*-BuOK) is known to cleave silyl enol ethers to their potassium enolates, so alkoxides such as *n*-BuOLi, LiNMe(OMe), Li-imidazole and LiOTMS were investigated to unmask the silyl enol ether **2.77** by assessing the recovery of ketone **2.6** (Table 1.6).[259-262] Use of *n*-BuOLi in THF at 0 ºC furnished the ketone **2.6**, but only in 65% yield. The addition of DMPU to the reaction mixture, which was the co-solvent required for alkylation with $MnCl_2$•2LiCl, decreased the yield to 50%. Gratifyingly, it was found that cooling the reaction mixture to –78 ºC, *n*-BuOLi furnished the ketone **2.6** in 90% yield. Other nucleophiles such as LiOTMS and LiNMe(OMe) proved inferior to *n*-BuOLi. Li-imidazole, however, deprotected the silyl enol ether **2.77** in near quantitative yield. Ultimately, *n*-BuOLi was chosen as the regent for the enolate unmasking due to the ease of purification of *n*-BuOH and the ability to inject *n*-BuOH into the reaction flask without compromising the mixture to air and/or water.

Table 2.6: Identification of conditions to unmask enolate from silyl enol ether **2.77**

2.77: R_3Si = TMS
2.78: R_3Si = TBS

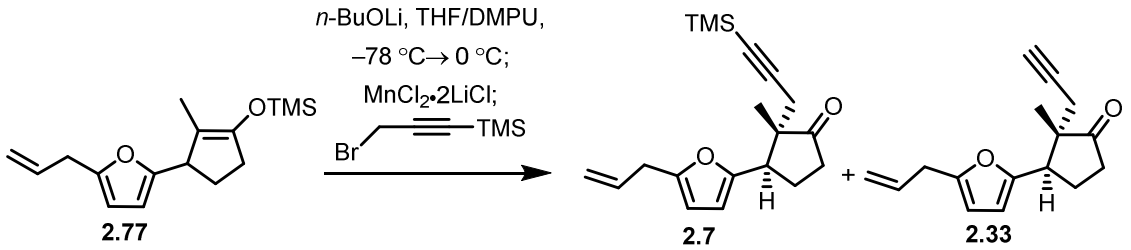
2.6

SiR_3	**RLi**	**solvent**	**temp**	**T (min)**	**yield**
TMS	*n*-BuLi	THF	–78 °C	10	decomp
TBS	*n*-BuOLi[a]	THF	0 °C → rt	960	71% (rsm)
TMS	*n*-BuOLi[a]	THF/DMPU	0 °C	60	50%
TMS	*n*-BuOLi[a]	THF	0 °C	60	65%
TMS	*n*-BuOLi[a]	THF/DMPU	–78 °C → 0 °C	30	90%
TMS	LiNMe(OMe)[b]	THF/DMPU	–78 °C → rt	16 h	54%
TMS	TMSOLi	THF/DMPU	–78 °C → 0 °C	2 h	59%
TMS	Li-imid.[c]	THF/DMPU	–78 °C → 0 °C	30	99%

a) Made *in situ* by adding *n*-BuLi to a mixture of *n*-BuOH in THF with triphenylmethane (Ph_3CH) as an internal indicator; b) Made *in situ* by adding *n*-BuLi to a mixture of MeNHOMe•HCl in THF with triphenylmethane (Ph_3CH) as an internal indicator; c) Made *in situ* by adding *n*-BuLi to a mixture of imidazole in THF with triphenylmethane (Ph_3CH) as an internal indicator

Unfortunately, unmasking the silyl enol ether **2.77** with *n*-BuOLi in THF/DMPU, followed by transmetalation with neutralized $MnCl_2$•2LiCl and alkylating with TMS-propargyl bromide furnished mixtures of the desired alkylated product **2.7** along with the TMS-deprotected product **2.33** and starting material as an inseparable mixture (Equation 2.4). Efforts to minimize formation of the deprotected compound **2.37** or push the reaction to completion by controlling temperature or stoichiometry only had a small effect on product distributions.

Equation 2.4: Alkylation of **2.77** via silyl enol ether unmasking with lithium alkoxide



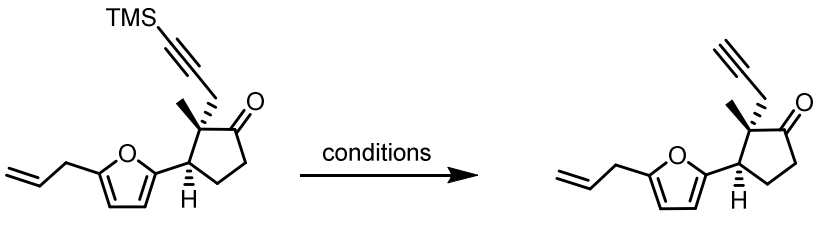
Optimal conditions required to generate the thermodynamic enolate remains challenging, though it is clear that allowing the enolate to equilibrate for an extended period of time results in a significant amount of aldol condensation. A successful strategy requires rapid generation of the thermodynamic enolate. The evidence gathered thus far seems to indicate that adding base to the ketone at 0 °C and/or the presence of alkoxides favors the generation of the thermodynamic enolate, but more development would be needed to suppress the aldol reactions. $MnCl_2$•2LiCl proved to be an effective additive for the suppression of polyalkylation, but protic impurities contained within, caused incomplete conversion of the starting material. The amount of adventitious proton sources was determined by using camphor and neutralization with LiHMDS before transmetalation prevents the enolate from being quenched and improved the yield, but yields of alkylated product **2.7** will remain between 40-50% until a proper method for the generation of the thermodynamic enolate is developed.

2.2.3: IMPROVEMENT OF THE FORWARD SYNTHESIS TO DIELS-ALDER REACTION ADDUCTS 2.34 AND 2.89

Despite the difficulties with the enolate alkylation, enough material was made to push forward. Deprotection of the TMS group in **2.7** under standard conditions (K_2CO_3/MeOH) provided the ketone **2.33** in 0–65% yield (Table 2.7, entry 1,2). Resubjection of the product **2.33** to the reaction conditions revealed that the ketone slowly decomposes to unidentifiable products, presumably via aldol condensation (see Scheme 2.19 and discussion). To avoid aldol condensation, acidic or buffered methods to remove the TMS group were investigated. Interestingly, reactions that were too acidic, such as pyridine•HF resulted in no removal of the

TMS group (Table 2.7, entry 6). Only TBAF buffered with acetic acid gave the desired product **2.33** in good yield.

Table 2.7: TMS Deprotection of **2.7**



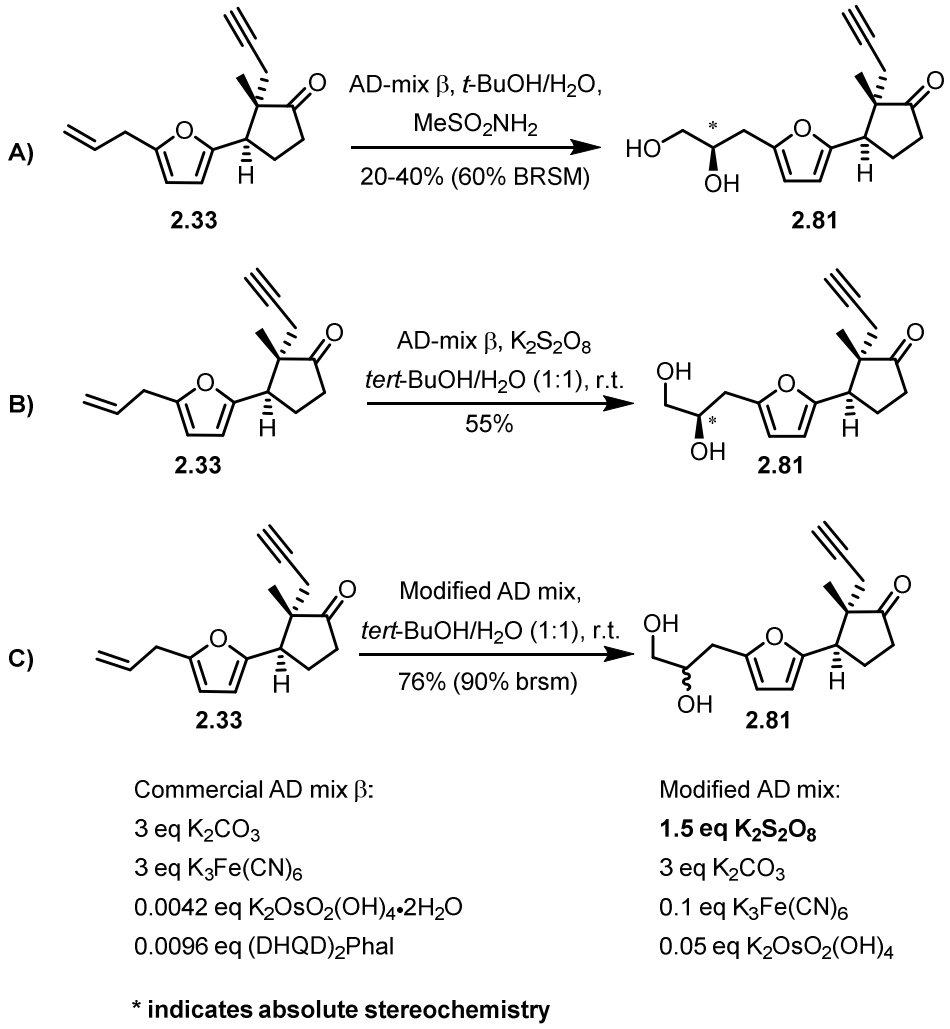
2.7 **2.33**

Reagent	**solvent**	**temperature**	**time**	**yield**
K_2CO_3	MeOH	R.T	24 hrs	30–65%
K_2CO_3	MeOH	Reflux	3 hrs	0%
TBAF/NH_4Cl	THF	R.T.	3 hrs	33%
TBAF/AcOH	THF	R.T.	24 hrs	76%
TBAF/AcOH	THF	Reflux	3 hrs	91%
Pyridine•HF	THF	R.T.	24 hrs	N/R

The conditions for the dihydroxylation of **2.33** were previously established by Dr. Smith and used AD-mix β, which gave low yields of diol **2.81** and required up to four days and additives known to accelerate the reaction such as methanesulfonamide[263] and tetrabutylammonium acetate[264] had little effect on the yield or the reaction time (Figure 2.9, **A**). By stirring ketone **2.33** in *tert*-BuOH/H_2O with only K_2CO_3, in the absence of AD-mix, it was determined that at least some of the low yield is due to base-catalyzed aldol condensation reactions. An extensive literature search revealed the work by Bittman, who found that supplementing the commercial AD-mix with potassium persulfate ($K_2S_2O_8$) greatly enhanced the yield.[172] Supplementing the AD-mix β with $K_2S_2O_8$ (1:1 w/w to AD-mix) to the dihydroxylation of **2.33** with AD-mix increased the yield of diol **2.81** to 55% (Figure 2.9, **B**). Commercial AD-mix only contains 0.002 mol% of the pre-catalyst $K_2OsO_2(OH)$, which may contribute to the long reaction times and low yields so a "custom" batch of AD-mix was formulated by pulverizing $K_2S_2O_8$ with 0.1 equivalents $K_3Fe(CN)_6$, three equivalents K_2CO_3 and 0.05

equivalents $K_2OsO_2(OH)_4$ together using a mortar and pestle. Use of this "custom" AD-mix gave diol **2.81** as a mixture (1:1) of diastereomers in 76% yield (90% based on recovered starting material) after only 16 h (Figure 2.9, **C**), representing a major improvement over earlier protocols. Because no ligand was used, the mixture of diastereomers produced in the reaction are not enantioenriched.

Figure 2.9: Improvement of dihydroxylation with using $K_2S_2O_8$

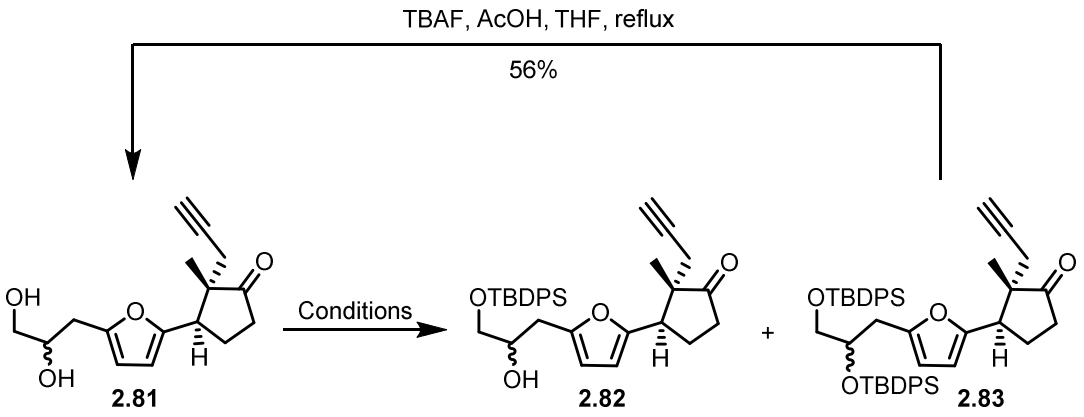


a) Dihydroxylation of **2.33** with AD-mix. b) Dihydroxylation of **2.33** with AD-mix, supplemented with $K_2S_2O_8$. c) Dihydroxylation of **2.33** with "custom" AD-mix containing no ligand.

The next task involved developing conditions for the selective TBDPS protection of the primary alcohol. While the selective TES protection of diol **2.36** (see Scheme 2.9), developed by Dr. Smith, used TESCl and Et_3N in CH_2Cl_2 and was complete within two h, the selective TBDPS

protection did not go to completion, even after stirring overnight (Table 2.8, entry 1). Use of imidazole as the base and DMF as the solvent increased the reaction rate but caused a significant amount of the bis-TBDPS protected diol **2.83** to be formed (Table 2.8, entry 2). To inhibit the second TBDPS protection, the reaction was cooled to – 40 ºC in a mixture (1:3) of DMF and CH_2Cl_2, and although some of the bis-protected alcohol by-product **2.83** was still seen, the major product **2.82** was isolated in 74% yield (Table 2.8, entry 3). The bis-protected alcohol by-product **2.83** could be recycled back to the diol **2.81** using the TBAF/AcOH conditions developed for the TMS deprotection of **2.7**.

Table 2.8: Selective protection of diol **2.82**

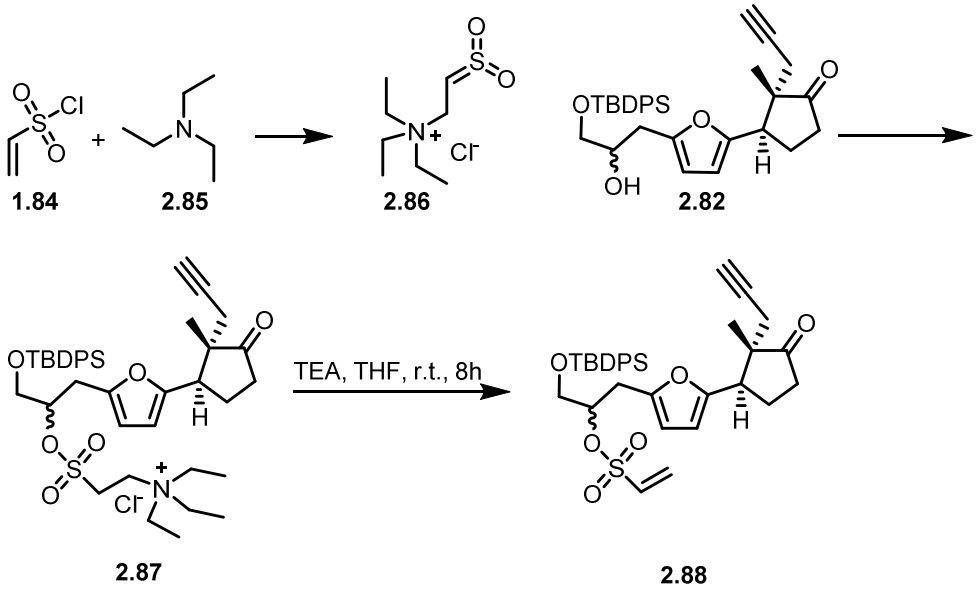


Solvent	base	temp	T (h)	Yield 2.82	Yield 2.83
CH_2Cl_2	Et_3N	0 °C	6	42% (93% brsm)	0%
DMF	imidazole	r.t.	2	24%	52%
CH_2Cl_2/DMF (3:1)	imidazole	–40 °C	6	74%	32%

Previously, the yields for the vinyl sulfonate formation were irreproducible and low yielding (10–40%) (see Scheme 2.1). Upon addition of vinylsulfonyl chloride to a mixture of alcohol **2.82** and triethylamine, a white precipitate formed. When this precipitate was isolated and analyzed by LCMS, it was found that the substance had a mass of 706 (positive ESI), corresponding to the mass of the vinyl sulfonate plus triethylamine. The current hypothesis for

structure of this species is the triethylamine adduct **2.87** (Scheme 2.11). It was initially thought that the reason for the low yield was that the desired product **2.88** formed rapidly, but after prolonged stirring, the excess Et_3N reacted with the product to form adduct **2.87**. Screening less nucleophilic bases such as *N*-methyl imidazole and 2,6-lutidine, however, revealed that ammonium adducts analogous to **2.87** were formed in each case. Closer examination of the reaction with triethylamine showed that adduct **2.87** will slowly produce **2.88** in the presence of Et_3N over eight h. The fact that prolonged stirring with excess Et_3N forms the desired compound **2.88** and not **2.87** suggests that the mechanism for the formation of **2.88** might actually go though the sulfene-like intermediate **2.86**, which rapidly reacts with alcohol **2.82** to form the ammonium salt **2.87**. The vinyl sulfonate was prone to elimination and other side reactions so it was telescoped directly into the Diels-Alder reaction.

Scheme 2.11: Vinyl sulfonate formation

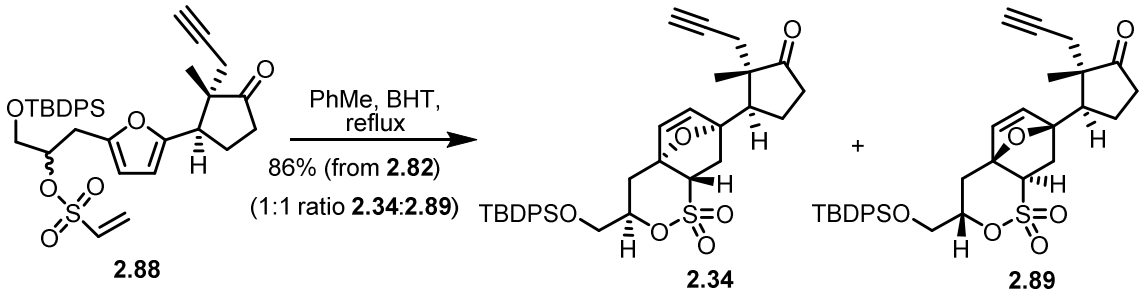


1.84 **2.85** **2.86** **2.82** **2.87** **2.88**

Heating the vinyl sulfonate **2.88** in PhMe delivered the Diels-Alder adducts **2.89** and **2.34**, but the starting material always remained. Heating the Diels-Alder adduct **2.89** produced mixtures of **2.89** and the vinyl sulfonate **2.88**, leading to the conclusion that the product and the starting material were in equilibrium under the reaction conditions, an observation corroborated

by Metz who developed the vinyl sulfonate/furan IMDA methodology.[109] Fortunately, the reaction was pushed to completion serendipitously by adding silica to the reaction in an effort to quickly purify the reaction mixture by column (Equation 2.5). Strangely, adding the silica to the solution of **2.88** in toluene and heating had no effect. The effect was only seen when enough silica was added to the reaction while hot that the solvent was completely absorbed. Diels-Alder reaction reactions are known to be accelerated by being adsorbed on silica,[193] and perhaps adding enough silica mimicked adsorption, and shifted the vinyl sulfonate/Diels-Alder reaction adduct equilibrium by functioning as a Lewis acid. Further improvements were seen when butylated hydroxytoluene (BHT) was added to the reaction mixture, presumably preventing detrimental radical side reactions. Using these modifications, both the vinyl sulfonate formation and the Diels-Alder reaction were optimized and **2.89** and **2.34** were isolated as a mixture (1:1) of diastereomers in 86% yield.

Equation 2.5: Optimization of Diels-Alder reaction adduct formation



2.2.4: INVESTIGATION OF ENANTIOSELECTIVE AND NEUTRAL DIHYDROXYLATION

After the synthesis of the Diels-Alder reaction adducts **2.89** and **2.34** was streamlined, the investigation returned to the enantioselective dihydroxylation of **2.33**. The "custom" conditions (see Figure 2.9, **C**) used no ligand, so both the Diels-Alder adducts **2.89** and **2.34** were racemic. Adding a ligand should render the dihydroxylation enantioselective, and several ligands are available, the most common being $(DHQD)_2PHAL$ **2.91** (Figure 2.10).[177] A review of the literature, however, revealed that $(DHQD)_2PHAL$ **2.91** is a poor ligand for dihydroxylation of

allyl aromatic substrates. Generally speaking, $(DHQD)_2PHAL$ **2.91** and $(DHQD)_2DPP$[182] **2.92** are best used for aromatic substrates where the double bond is attached to an arene ring (Table 2.9). $(DHQD)_2PYR$[181] **2.95** is best suited for substrates containing significant steric encumbrance at the α-position, whereas $(DHQD)_2AQN$[175] **2.93** is best for aliphatic substrates. Other ligands such as (DHQD)IND[177] **2.90** and Corey's ligand[176] **2.94** are useful for the dihydroxylation of *cis*-olefins and trisubstituted cyclic aliphatic olefins respectively. Because the ligand $(DHQD)_2AQN$ **2.93** is known to work well with allylbenzene, we began our investigation of the enantioselective dihydroxylation using this ligand.

Figure 2.10: Common ligands for the Sharpless enantioselective dihydroxylation

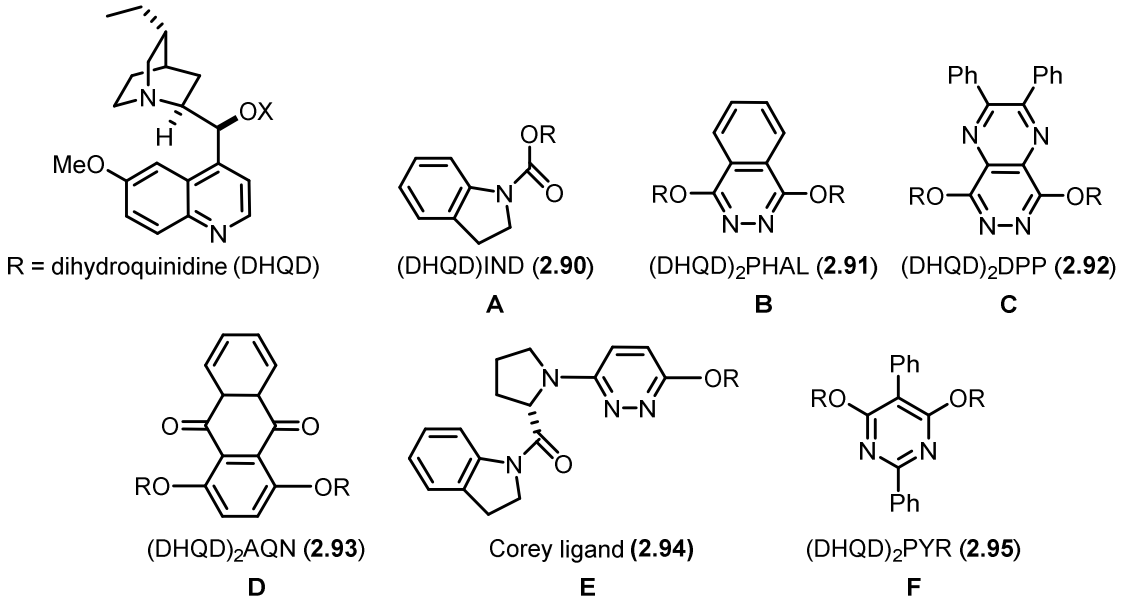


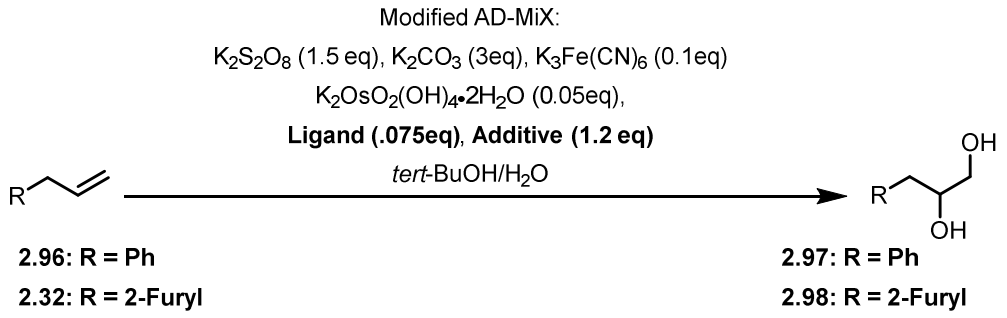
Table 2.9: Ligand choice for differing olefin classes[177]

Olefin-Class	1º	2º (1,1)	2º (cis)	2º (trans)	3º	4º
Aromatic/ Acyclic	B C	B C	A	C B	B C, D	F B
Aromatic/ Cyclic	N/A	N/A	F, C, D	N/A	B, C, D	F, B
Aliphatic/ Acyclic	D	D	A	D	B, C, D	F, B[a]
Aliphatic/ Cyclic	N/A	N/A			E	F, B[a]
Branched/ Acyclic	F	B, F				
Branched/ Cyclic	N/A	B, F				

a) low ee

Two questions need to be answered before attempting the enantioselective dihydroxylation of **2.33**: Does the use of $K_2S_2O_8$ in place of $K_3Fe(CN)_6$ effect the enantioselectivity, and is the 2-allylfuran moiety in **2.33** a suitable substrate? To answer these questions, 2-allylfuran **2.32** and allylbenzene **2.96** were chosen as model substrates. A custom batch of AD-mix was formulated by pulverizing $K_2S_2O_8$, 0.1 equivalents $K_3Fe(CN)_6$, three equivalents K_2CO_3, 0.075 equivalents of $(DHQD)_2PHAL$ **2.91** and 0.05 equivalents $K_2OsO_2(OH)_4$ together using a mortar and pestle. Dihydroxylation of allylbenzene using this mixture gave the dihydroxy compound **2.97** in 74% yield and 42% ee, matching the literature results of 74% and 44% ee (Table 2.10, entry 1). Subjection of 2-allylfuran **2.32** to these conditions also provided diol **2.98** with low enantioselectivity (30% ee) (Table 2.10, entry 4). Gratifyingly, use of $(DHQD)_2AQN$ **2.93** gave enhanced enantiomeric excess for both allylbenzene and 2-allylfuran (75% and 84% ee; Table 2.10, entries 3,6). Additives such as phenylboronic acid ($PhB(OH)_2$) are known to accelerate the reaction and protect the diol *in situ*, but these additives did not enhance the enantioselectivity (Table 2.10, entries 2,5).[190,191]

Table 2.10: Model studies on enantioselective dihydroxylation

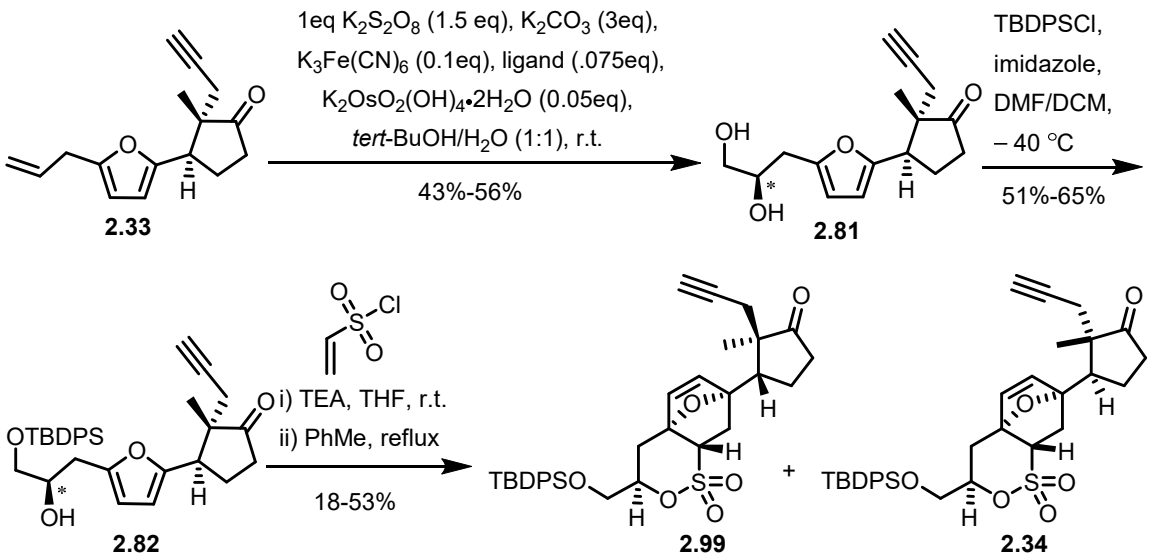


R	Ligand	Additive	yield	ee	Lit.[175]
Ph: **2.96**	$(DHQD)_2Phal$	N/A	74%	42%	44%
Ph: **2.96**	$(DHQD)_2Phal$	$PhB(OH)_2$	71%	42%	N/A
Ph: **2.96**	$(DHQD)_2AQN$	N/A	74%	75%	78%
2-Furyl: **2.32**	$(DHQD)_2Phal$	N/A	49%	30%	N/A
2-Furyl: **2.32**	$(DHQD)_2Phal$	$PhB(OH)_2$	34%	25%	N/A
2-Furyl: **2.32**	$(DHQD)_2AQN$	N/A	67%	84%	N/A

With the improved enantioselectivity for the dihydroxylation of 2-allylfuran confirmed using $(DHQD)_2AQN$ (**2.93**) as the ligand, we attempted to apply the reaction to the real system. In that event, the ligands $(DHQD)_2PHAL$ (**2.91**), $(DHQD)_2AQN$ (**2.93**) and Corey's ligand **2.94** were chosen, and **2.33** was dihydroxylated under the same conditions used for 2-allylfuran **2.32**. Enantioenriched diol **2.81** was thus obtained in slightly lower yields compared to the conditions that used no ligand (see Figure 2.9, **C**) (Scheme 2.12). Selective protection of the primary hydroxy group moiety in **2.81** furnished alcohol **2.82**, which was then converted to the vinyl sulfonate and cyclized to furnish diastereomers **2.34** and **2.99** (1:1-2.4:1 ratios) (Table 2.10). Unexpectedly, $(DHQD)_2PHAL$ (**2.91**) provided almost no enantioselectivity or diastereoselectivity (Table 2.10, entry 1), and use of $(DHQD)_2AQN$ (**2.93**) only gave slight improvement, affording **2.89** (5% ee) and **2.34** (11% ee). Use of Corey's ligand **2.94** gave the highest enantioselectivities of **2.89** (18% ee) and **2.34** (14% ee), but these values are still well

below the enantioselectivities demonstrated with 2-allylfuran **2.32**. Precisely how the cyclopentanone moiety negatively affects the enantioselective dihydroxylation is not clear. It is known that branching in close proximity to the olefin can affect the enantioselectivity of the dihydroxylation reaction, and it stands to reason that the α-disubstituted cyclopentenone moiety in substrate **2.33** might interfere with the subtle CH-π and π-π interactions required for facial discrimination of the terminal olefin. More work needs to be done to investigate the remote influence of the cyclopentanone moiety and whether new ligands would be needed for enantioselective discrimination of the two faces of the olefin.

Scheme 2.12: Synthesis of enantioenriched Diels-Alder reaction adducts **2.34** and **2.99**



*** indicates absolute stereochemistry**

Table 2.10

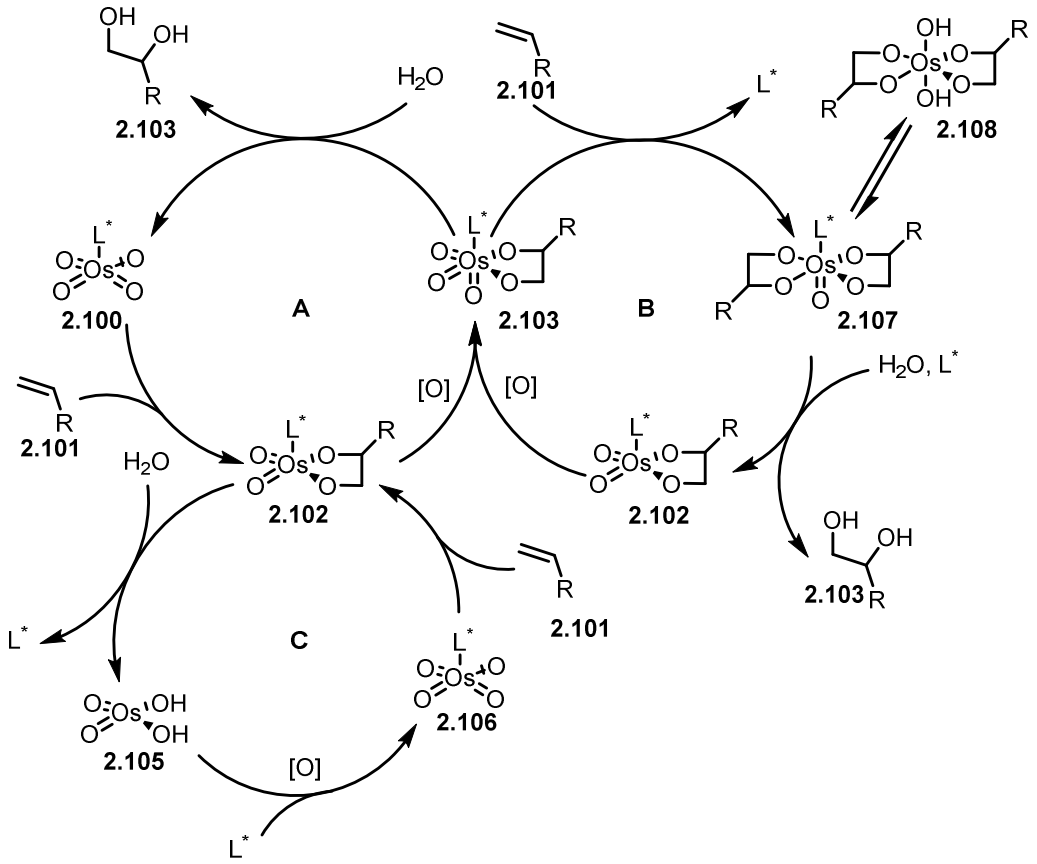
Ligand	2.99 ee[a]	2.34 ee[a]	Ratio 2.99:2.34[b]
$(DHQD)_2PHAL$	1%	7%	1:1
$(DHQD)_2AQN$	5%	11%	1:1
Corey	18%	14%	2.41:1

a) ee was determined by HPLC using chiralcel OD-H; b) ratios determined by the separation of the diastereomers by column chromatography

Despite the disappointing results of the enantioselective dihydroxylation of **2.33**, the impressive effect of $K_2S_2O_8$ on the dihydroxylation warranted further study. A problem encountered during the dihydroxylation of ketone **2.33** was the tendency to decompose under the basic conditions (see also Table 2.4 and section **2.2.2**). Although Sharpless reports that the reaction conditions can be buffered with sodium bicarbonate ($NaHCO_3$),[192] the reaction shuts down if $NaHCO_3$ is used as the sole base.[177] Osmium catalyzed dihydroxylations are known under almost neutral and even acidic conditions,[173] so reasons for the reaction shutting down at lower pH are not due to problems with the hydrolysis of the osmate ester (Figure 2.11). This observation along with the rate acceleration seen by using $K_2S_2O_8$ as the stoichiometric oxidant led us to propose the following: Cyanide ion produced by $K_4Fe(CN)_6$ is the reason for inability for the Sharpless dihydroxylation to function at lower pH, and acceleration seen by using $K_2S_2O_8$ is due to the lower concentration of cyanide ion present in the reaction mixture. Corollary to these proposals is that the pH of the reaction mixture could be dropped without a significant amount of cyanide present.

Though slightly basic or neutral dihydroxylation conditions, such as the Upjohn-like conditions (OsO_4, NMO) (Figure 2.11, Catalytic cycle **A**) are known, they often suffer from slow reaction rates and inferior enantioselectivities when a ligand is used compared to the Sharpless conditions (Figure 2.13, Catalytic cycle **C**). The reason is because of the so-called "second catalytic cycle" (Figure 2.11, catalytic cycle **B**) which occurs when the oxidant is in the same phase as the osmium catalyst.[169,177] Therefore a slightly basic or neutral Sharpless-type dihydroxylation would be as mild as the Upjohn dihydroxylation without the sacrifice of enantioselectivity.

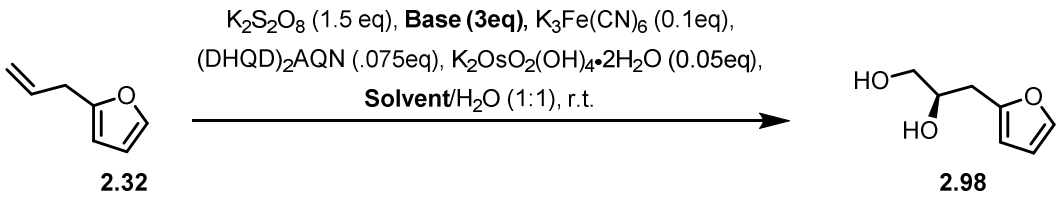
Figure 2.11: Osmium catalytic dihydroxylation cycles



a) Homogeneous oxidant catalytic cycle; b) Low enantioselectivity catalytic cycle; c) Heterogeneous oxidant catalytic cycle which results in high ee

Gratifyingly, the dihydroxylation of 2-allylfuran **2.32** using Na_2HPO_4 instead of K_2CO_3 as the base provided diol **2.98** with comparable enantioselectivities but only 26% yield due to poor conversion (Table 2.11, entries 1,2). A quick solvent screen revealed that *tert*-BuOH, is the best solvent for high enantioselectivity and yield.

Table 2.11: Study of the effect of solvent on Enantioselective dihydroxylation with Na_2HPO_4



2.32 **2.98**

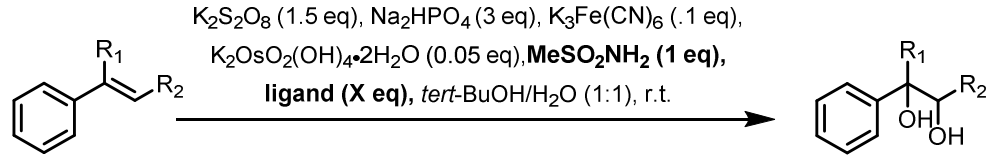
Base	**Solvent**	**yield**	**ee**
$NaHCO_3$	*tert*-BuOH	26%	N/A
Na_2HPO_4	*tert*-BuOH	26%	71%
Na_2HPO_4	CH_2Cl_2	N/A	58%
Na_2HPO_4	PhMe	N/A	27%
Na_2HPO_4	MeCN	N/A	41%

In an effort to improve the yield, several additives that are known to enhance the rate of osmium catalyzed dihydroxylation were screened (Table 2.12). Of the additives tried, only quinuclidine[171] and methanesulfonamide[170,177] provided a significant rate enhancement. Though methanesulfonamide is known to accelerate the rate of osmium catalyzed dihydroxylation by acting as a phase transfer catalyst between the hydroxide ion in the aqueous layer and the osmate ester in the organic layer,[170] recent evidence shows that it can also act as a general Lewis acid to facilitate hydrolysis of the osmate ester.[170]

With methanesulfonamide and quinuclidine identified as general additives to accelerate the dihydroxylation, styrene, α-methyl styrene and phenylcyclohexene were chosen as model substrates to test these conditions. The conditions using quinuclidine as the ligand provided the diols **2.112-4** in 67-99% yields (Table 2.12, entries 2,4,6). Substituting $(DHQD)_2PHAL$ (**2.91**) quinuclidine for gave the diols in slightly lower yields compared to quinuclidine (61-80%) and comparable enantioselectivities to those reported in the literature (Table 2.12, entries 1,3,5). It is

interesting that switching from the racemic dihydroxylation to the enantioselective variant provided the diols in lower yields when the opposite is true normally.[171]

Table 2.12: Optimization of modified dihydroxylation conditions



2.109: R_1 = H, R_2 = H
2.110: R_1 = Me, R_2 = H
2.111: R_1 = $(CH_2)_4$, R_2 = $(CH_2)_4$

2.112: R_1 = H, R_2 = H
2.113: R_1 = Me, R_2 = H
2.114: R_1 = $(CH_2)_4$, R_2 = $(CH_2)_4$

R_1	R_2	Ligand	eq	yield	ee	Lit[263]
H	H	$(DHQD)_2PHAL$	0.075	80%	97%	97%
H	H	Quinuclidine	0.3	99%	N/A	N/A
Me	H	$(DHQD)_2PHAL$	0.075	72%	90%	94%
Me	H	Quinuclidine	0.3	89%	N/A	N/A
$=R_2=(CH_2)_4$	$=R_1=(CH_2)_4$	$(DHQD)_2PHAL$	0.075	61%	94%	99%
$=R_2=(CH_2)_4$	$=R_1=(CH_2)_4$	Quinuclidine	0.3	67%	N/A	N/A[a]

a) 0.2 eq $K_3Fe(CN)_6$ was used

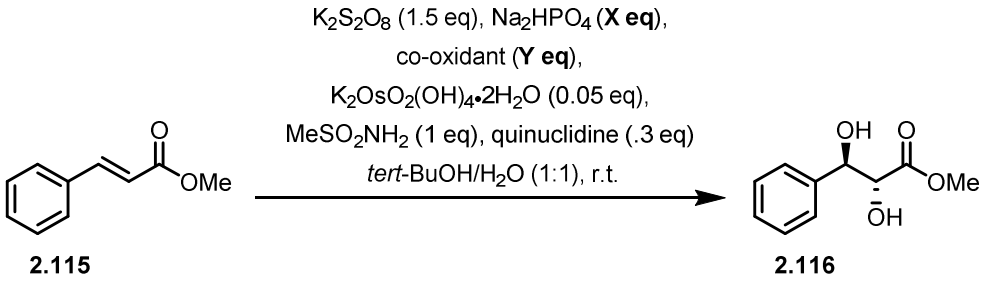
Following the hypothesis that the presence of cyanide ion impedes catalytic turnover, it may be possible to improve the reaction rate by replacing $K_3Fe(CN)_6$ altogether. Therefore, several catalytic co-oxidants were examined as possible replacements for $K_3Fe(CN)_6$ (Table 2.14).[174-189] Interestingly, only $NaIO_4$, $KBrO_3$, and $NaClO_2$ afforded any product when used as co-catalyst. Further investigation revealed that $NaIO_4$ and $KBrO_3$ function as catalytic co-oxidants with $K_2S_2O_8$, but $NaClO_2$ only acted stoichiometrically.

Methyl cinnamate **2.115**, which gave only 66% yield under the conditions used in Table 2.13 (see table 2.13, entry 2), was dihydroxylated using $NaIO_4$ and $KBrO_3$ as catalytic co-oxidants. The use of $KBrO_3$ gave a low yield of the diol **2.116** due to the large degree of oxidative cleavage resulting in benzaldehyde (Table 2.13, entry 5). The oxidant $NaIO_4$, gave

comparable yields of diol to $K_3Fe(CN)_6$ (Table 2.13, entry 6). Further optimization of the stoichiometry of the co-oxidant and base showed that using $NaIO_4$ (0.2 eq) with Na_2HPO_4 (3 eq) provided the diol **2.116** in 87% yield while $K_3Fe(CN)_6$ (0.2 eq) with Na_2HPO_4 (4 eq) provided the diol **2.116** in 91% yield.

That the diol **2.116** can be isolated in good yields is surprising. Under very similar conditions, the Johnson-Lemieux oxidation ($NaIO_4$, OsO_4) cleaves olefins to the corresponding ketones and aldehydes. The pH during a Johnson-Lemieux oxidation was found to be 5.7, compared to a pH of 8.5 for the dihydroxylation conditions. Dropping the pH of the modified dihydroxylation using $NaIO_4$ as the catalytic co-oxidant by adding phosphoric acid resulted in an increase in benzaldehyde formation but raising the pH by adding K_2CO_3 caused the reaction to shut down. There is thus a critical pH range where $NaIO_4$ acts as a catalytic co-oxidant but does not facilitate the oxidative cleavage of the diol.

Table 2.13: Further optimization of neutral dihydroxylation



2.115 **2.116**

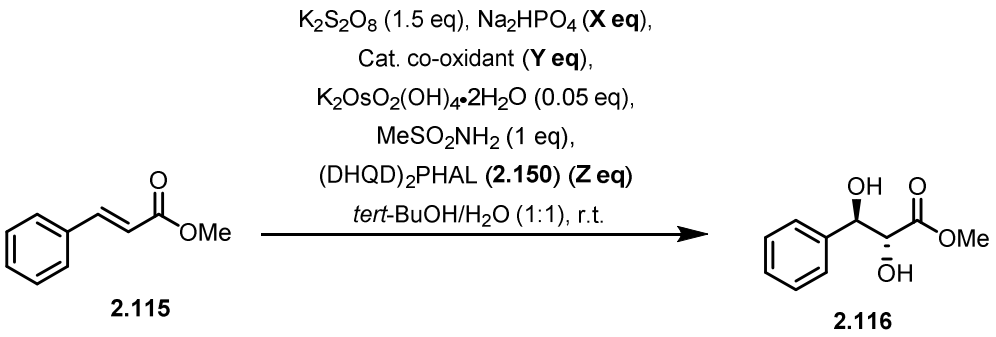
Catalytic co-oxidants screened:

$K_3Fe(CN)_6$, $NaClO_2$, Na_2MoO_4, $NiSO_4$, $KMnO_4$, **$KBrO_3$, $NaIO_4$,** $Ce(SO_4)_2$, $MnSO_4.H_2O$, $CuSO_4$, CAN, Na_2WO_4 .$2H_2O$

Co-oxidant	**Y**	**X**	**yield**
$K_3Fe(CN)_6$	0	3	N/R
$K_3Fe(CN)_6$	0.1	3	66%
$K_3Fe(CN)_6$	0.2	3	70%
$K_3Fe(CN)_6$	0.2	4	91%
$KBrO_3$	0.1	3	17%
$NaIO_4$	0.1	3	63%
$NaIO_4$	0.2	3	87%
$NaIO_4$	0.1	4	66%
$NaIO_4$	0.1	3 eq K_2CO_3	2%

Use of $NaIO_4$ as the catalytic co-oxidant in the enantioselective dihydroxylation of **2.115** using $(DHQD)_2PHAL$ (**2.91**) gave enantioselectivities comparable to the literature but in only 68% yield compared to 87% yield obtained using quinuclidine (Table 2.14). Use of $K_3Fe(CN)_6$ with $(DHQD)_2PHAL$ (**2.91**) led to a similar drop in yield. Interestingly, use of 0.3 eq of $(DHQD)_2PHAL$ (**2.91**) in the dihydroxylation reduced the yield from 68% to 51%.

Table 2.14: Enantioselective optimized dihydroxylation



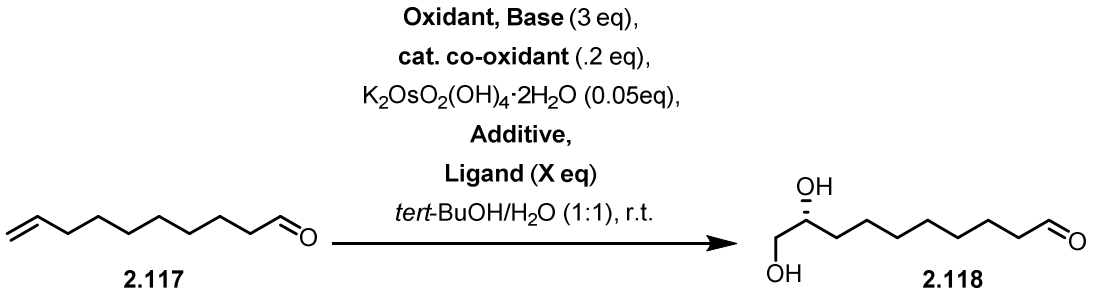
2.115 **2.116**

X	Co-Oxidant	Y	Z	yield	ee	Lit
3	$NaIO_4$	0.1	0.075	68%	96%	97%[263]
4	$K_3Fe(CN)_6$	0.2	0.075	68%	N/A	N/A
4	$K_3Fe(CN)_6$	0.1	0.3	51%	N/A	N/A

To demonstrate the potential utility of these mild dihydroxylation conditions, 9-decenal **2.117** was chosen as a challenge substrate, due to the base sensitivity of the aldehyde moiety. As expected, dihydroxylation of **2.117** using AD-mix β with or without $NaHCO_3$ as a buffer provided diol **2.118** in 33% and 51% yields (Table 2.15, entry 1,2). Use of the optimized conditions with quinuclidine as the ligand and either $NaIO_4$ or $K_3Fe(CN)_6$, as the catalytic co-oxidant, however, initially gave similar results to the AD-mix β (Table 2.15, entry 3-9). Though the aldehyde **2.117** was stable under the mildly basic reaction conditions, it slowly decomposed over time. Using four eq Na_2HPO_4 with quinuclidine $K_3Fe(CN)_6$ provided the optimum compromise between reaction rate and pH, delivering the diol **2.118** in 82% yield (Table 2.15, entry 9). Due to the significant rate acceleration seen when the ligand $(DHQD)_2Phal$ (**2.91**) is used, only three equivalents of base was needed to achieve a 71% yield (Table 2.15, entry 10). Strangely, the choice of catalytic co-oxidant during the enantioselective dihydroxylation had a big impact on the yield. Use of $K_3Fe(CN)_6$ provided the diol **2.118** in 34-49% whereas, while

$NaIO_4$ gave the diol **2.118** in 71% yield. Interestingly, $MeSO_2NH_2$ had a slight detrimental effect on the yield overall, and minimal rate acceleration was seen. (Table 2.15, entries 3,4 and 10,12).

Table 2.15: Enantioselective optimized dihydroxylation on aldehyde **2.117**



2.117 **2.118**

Oxidant[a]	Base	Co-Oxidant	Ligand	X	Yield	ee
AD-Mix β	N/A	N/A	N/A	N/A	33%[b]	
AD-Mix β	N/A	N/A	N/A	N/A	51%[b,c]	
$K_2S_2O_8$	Na_2HPO_4	$NaIO_4$	quinuclidine	0.3	40%[b]	N/A
$K_2S_2O_8$	Na_2HPO_4	$NaIO_4$	quinuclidine	0.3	45%	N/A
$K_2S_2O_8$	Na_2HPO_4	$K_3Fe(CN)_6$	N/A	N/A	45%[d]	N/A
$K_2S_2O_8$	Na_2HPO_4	$K_3Fe(CN)_6$	quinuclidine	0.3	51%	N/A
$K_2S_2O_8$	K_2CO_3	$K_3Fe(CN)_6$	N/A	N/A	63%[d]	N/A
$K_2S_2O_8$	K_2CO_3	$K_3Fe(CN)_6$	N/A	N/A	66%[c,d]	N/A
$K_2S_2O_8$	Na_2HPO_4	$K_3Fe(CN)_6$	quinuclidine	0.3	82%[e]	N/A
$K_2S_2O_8$	Na_2HPO_4	$K_3Fe(CN)_6$	$(DHQD)_2PHAL$	0.075	49%	
$K_2S_2O_8$	Na_2HPO_4	$NaIO_4$	$(DHQD)_2PHAL$	0.75	71%	
$K_2S_2O_8$	Na_2HPO_4	$K_3Fe(CN)_6$	$(DHQD)_2PHAL$	0.075	34%[b]	

a) 1.5 eq $K_2S_2O_8$ was used or 1.4 g/mmol substrate AD-mix b) $MeSO_2NH_2$ was added. c) 3 eq $NaHCO_3$ was added. d) Only 0.1 eq $K_3Fe(CN)_6$ was used. e) 4 eq of Na_2HPO_4 was used

The reasons for the differences in yield between the dihydroxylation with quinuclidine and $(DHQD)_2PHAL$ (**2.91**) are not yet clear. The fact that when more $(DHQD)_2PHAL$ (**2.91**) is added, the yield drops further and more oxidative cleavage is seen seems to indicate that $(DHQD)_2PHAL$ (**2.91**) is affecting the reaction in a way that is detrimental. A sample of the organic layer tested positive for oxidants with a starch-iodine test strip. Isolation of the ligand

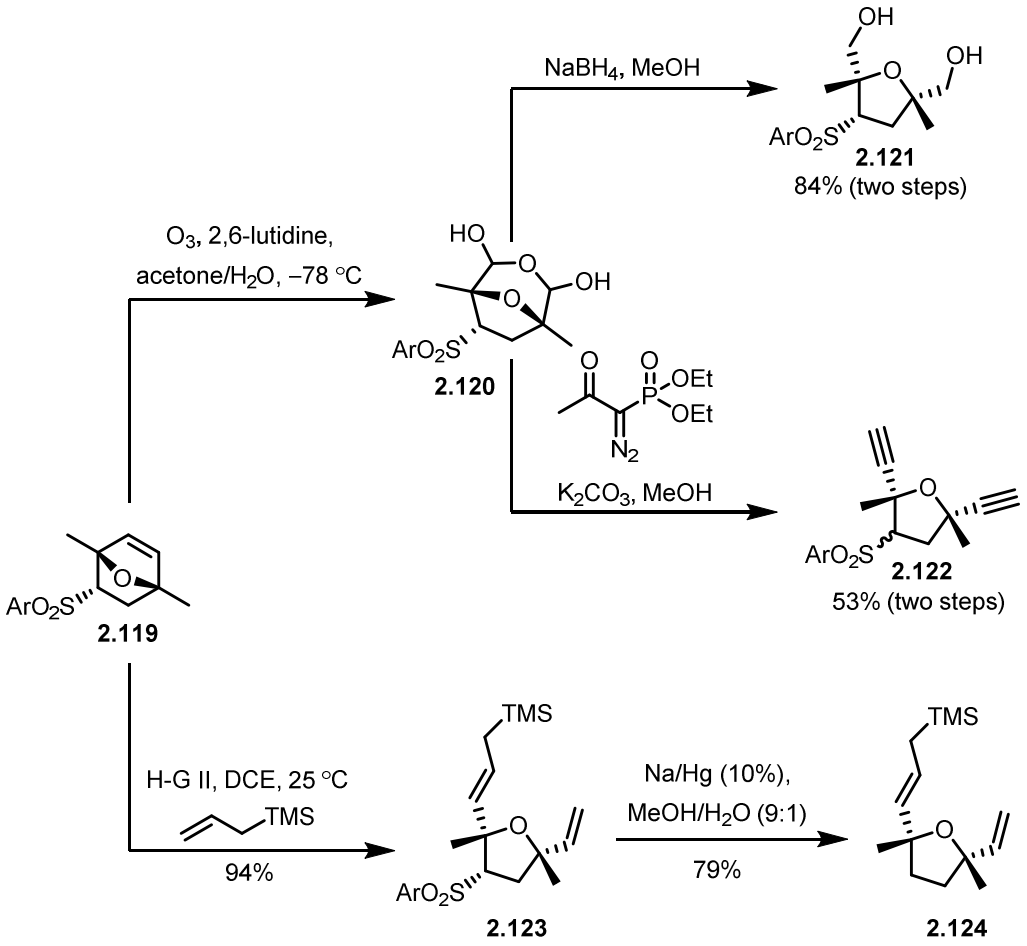
after the reaction revealed that none of the ligand had been oxidized, so the organic-soluble oxidizing species remains elusive.[188] The ligand $(DHQD)_2PHAL$ (**2.91**) is more lipophilic than quinuclidine and might act as a phase transfer agent for some oxidizing species in the reaction that facilitates the oxidative cleavage, but more research is needed to elucidate this pathway.

Though more work needs to be done to enhance the yield in the enantioselective dihydroxylation, The optimized conditions (0.2 eq $K_3Fe(CN)_6$ or $NaIO_4$, 3 eq Na_2HPO_4, $MeSO_2NH_2$) with quinuclidine provided excellent yields (67-98%) of a variety of diols and use of $(DHQD)_2PHAL$ (**2.91**) gave enantioselectivities comparable to those found in the literature and may be a useful alternative to NMO in enantioselective dihydroxylations. The dihydroxylation was even demonstrated on the aldehyde **2.117**, which is extremely base sensitive. The ability to use $NaIO_4$ as a catalytic co-oxidant with comparable efficiency to $K_3Fe(CN)_6$ was a surprising discovery, and fact that dropping the pH results in more oxidative cleavage products suggests that it may be possible to develop a new Johnson-Lemieux protocol that is catalytic in $NaIO_4$ and uses $K_2S_2O_8$ as the terminal oxidant.

2.2.5: ELABORATION OF DIELS-ALDER REACTION INTERMEDIATE 2.34

Although the methodology for the intermolecular Diels-Alder reaction between the enantiopure aryl, vinyl-sulfoxides with furans developed by Dr. Noah Benjamin was not applicable for the synthesis of cortistatin A, his work to elaborate the core served as a model system for the later steps in the synthesis (Scheme 2.13).[88,103] He found that ozonolysis of **2.119** using a mixture of acetone/water (95:5) in the presence of 2,6-lutidine gave optimum yields of the cleavage product **2.120**, which was transformed to the bis-alkyne **2.122** using the Ohira-Bestmann reagent. Additionally, he found that the oxa-bicyclic ring in **2.119** underwent a regioselective ring-opening metathesis with a variety of alkenes to give products such as **2.123**, which can be desulfurized to tetrahydrofuran **2.124**.

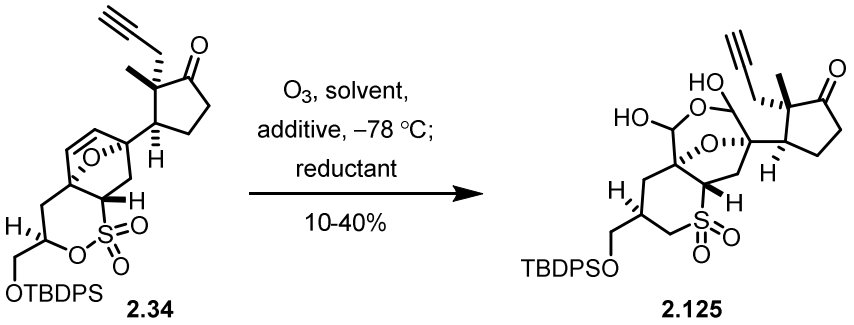
Scheme 2.13: Dr. Noah Benjamin's elaboration of oxa bicyclic intermediate **2.119**



Use of Dr. Benjamin's conditions (acetone/H_2O (95:5),[198] –78 ºC, 2,6 lutidine) for the ozonolysis of Diels-Alder reaction adduct **2.34** gave small amounts of desired product **2.125**, which stands in contrast to the ozonolysis of the TMS-protected alkyne **2.14** utilizing the same conditions (see Scheme 2.2 and Equation 2.1) (Equation 2.6). Other solvents, amine oxide additives and reductive quenches were screened, but the original conditions proved superior.[103] Following the reaction by TLC showed that the main issue was control of reaction time. Stopping the reaction after ca. 50% conversion returned primarily product and starting material, indicating that the loss in yields is due to over-oxidation of the product. Use of color indicators to monitor the consumption of the olefin was not helpful because the dyes de-colored either before

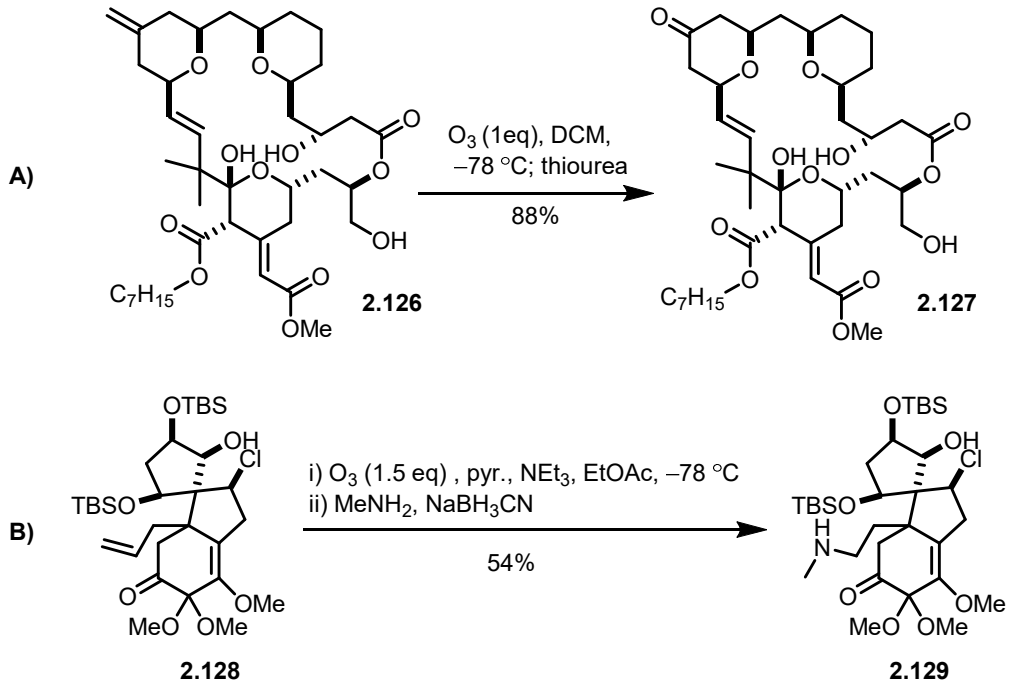
2.34 reacted or after the **2.34** had been consumed by ozone. Even using 1-hexyne as a sacrificial olefin to prevent over-oxidation had no impact on the yield.

Equation 2.6: Ozonolysis of Diels-Alder reaction intermediate **2.34**



Control of ozone stoichiometry is of critical importance for the success of this selective ozonolysis. Though previous examples (see Figure 2.1) reported that alkynes were unaffected by the presence of excess ozone, careful monitoring of the reaction revealed that consumption of the product commenced quickly after the starting material was ozonolyzed. A possible solution to this dilemma was found in the total synthesis of bryostatin by Wender, and the synthesis of acutumine by Castle (Figure 2.12),[197,201] both of which report selective ozonolysis of very complex intermediates with multiple double bonds. They were able to determine the concentration of a saturated solution of ozone by removing aliquots and adding to a solution of styrene. The ozone solution was added until the styrene had been consumed by TLC. By knowing the concentration ozone dissolved in the organic solvent both Wender and Castle were able to control the stoichiometry between ozone and the olefin without risking oxidation of other olefins in the molecule.

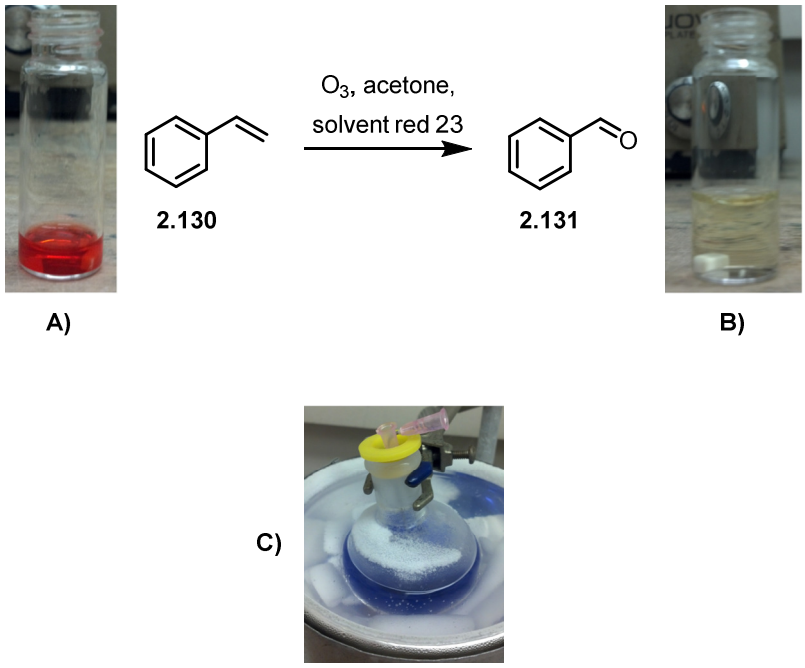
Figure 2.12: Examples of Ozone titration



a) Wender's ozone titration in his synthesis of bryostatin Analogues; b) Castles's ozone titration in his synthesis of acutumine

In trying to replicate the titration procedure, several obstacles arose: Monitoring the consumption of styrene by TLC proved tedious and inaccurate, and the stability of ozone in acetone/H_2O (95:5) was unknown. The addition of solvent red 23 (**2.17**) to styrene, however, allowed for a quick and accurate colorimetric titration of the ozone solutions (Figure 2.13 **A** → **B**).To test the stability of ozone in acetone/H_2O (95:5), a saturated solution of ozone in acetone was kept at –78 ^{o}C, and the titre was checked every 30 min for three h; there was no appreciable reduction in the concentration of ozone.

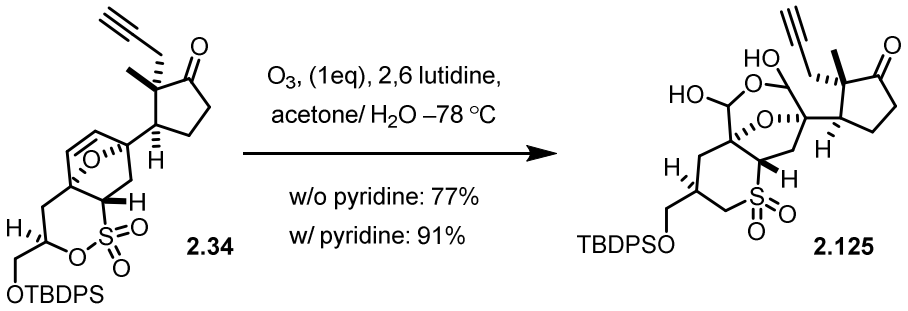
Figure 2.13: Successful application of ozone titration to the ozonolysis of styrene



a) Solution of styrene and solvent red 23 (**2.17**) in acetone; b) Solution of styrene and solvent red 23 (**2.17**) in acetone after ozone has been added to the endpoint; c) Solution of ozone in acetone at -78 ^{o}C

Ozone was bubbled through acetone at –78 ºC until saturated and and aliquots were removed and added to a 0.1 M solution of styrene with solvent red 23 as an indicator until the red color disappeared. After determining the concentration, a volume equal to one equivalent of ozone in acetone was added to **2.34** in acetone/H_2O (95:5) in the presence of 2,6 lutidine at –78 ºC *via* a jacketed addition funnel that had been cooled to –78 ºC. Gratifyingly, aldehyde hydrate **2.125** was isolated in 77% yield (Equation 2.7). Pyridine is known to give enhanced selectivity in ozonolysis,[195,199,200,202,204] the inclusion of which provided **2.125** in 92% yield.

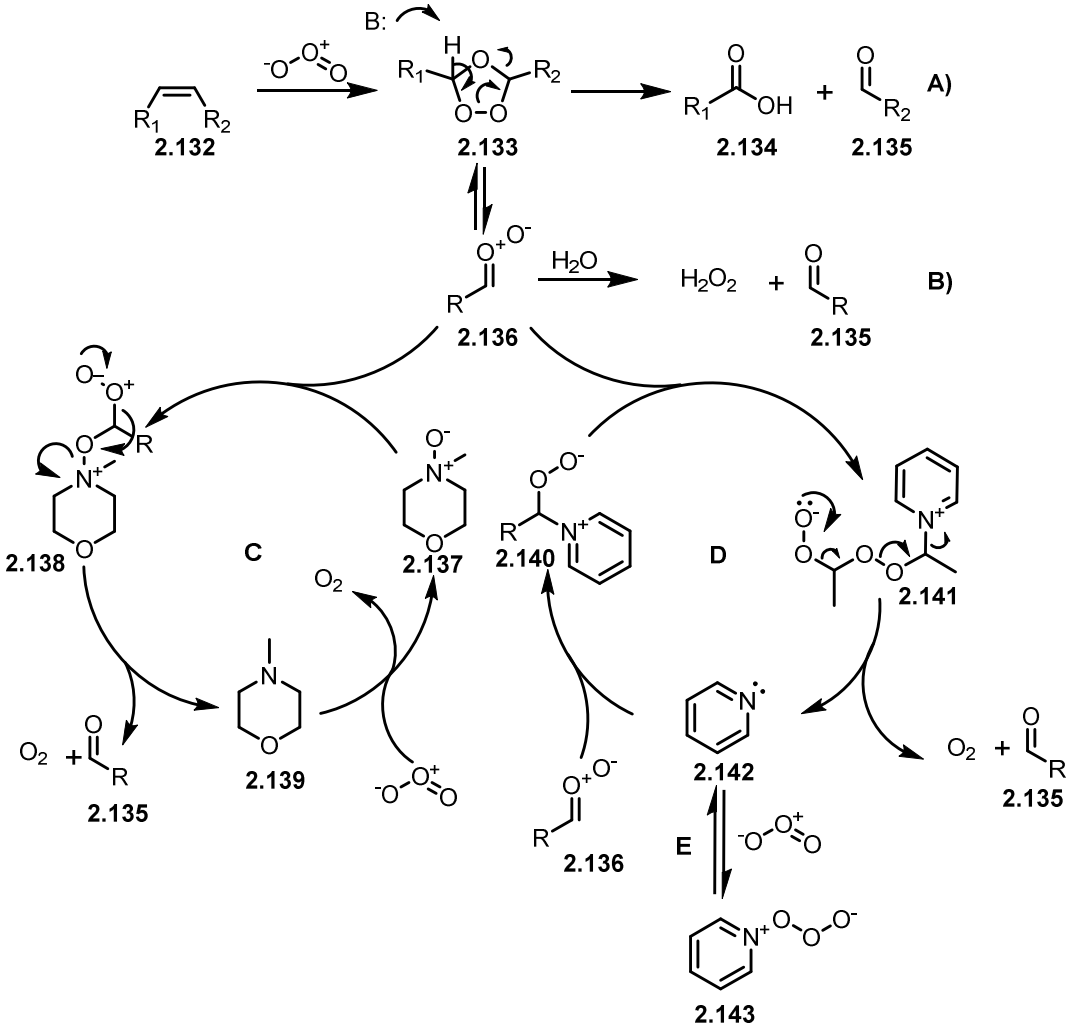
Equation 2.7: Successful application of ozone titration in the ozonolysis of **2.34**



2.34 **2.125**

The role of amines and other additives in ozonolysis is summarized in Figure 2.16. Basic amines can react with molozonide **2.133** to give an aldehyde **2.135** and a carboxylic acid **2.134** (Figure 2.14, pathway **A**).[194] When the molozonide collapses to the carbonyl oxide **2.136**, several mechanistic pathways are available for the production of an aldehyde depending on the additive used. In the presence of water, the carbonyl oxide **2.136** is intercepted to form the peroxy hemiacetal, which collapses to provide the aldehyde **2.135** and hydrogen peroxide (Figure 2.14, pathway **B**).[198] In the presence of non-basic amines or amine oxides, the carbonyl oxide **2.136** is intercepted to give an intermediate such as **2.198** (Figure 2.16, pathway **C**).[196] Breakdown of **2.198** releases the aldehyde **2.135**, amine **2.199** and singlet oxygen as the by-products. Pyridine however, has a unique effect on the reaction course (Figure 2.14, pathway **D**).[203] In addition to forming complexes with ozone (Figure 2.14, pathway **E**), pyridine is thought to intercept the carbonyl oxide **2.136** to form **2.140**. Pyridinium **2.140** then intercepts another carbonyl oxide **2.136** to form **2.141**, which collapses to release oxygen and the carbonyl compound **2.135**.

Figure 2.14: Roles of amine, amine-oxides, water and pyridine in ozonolysis

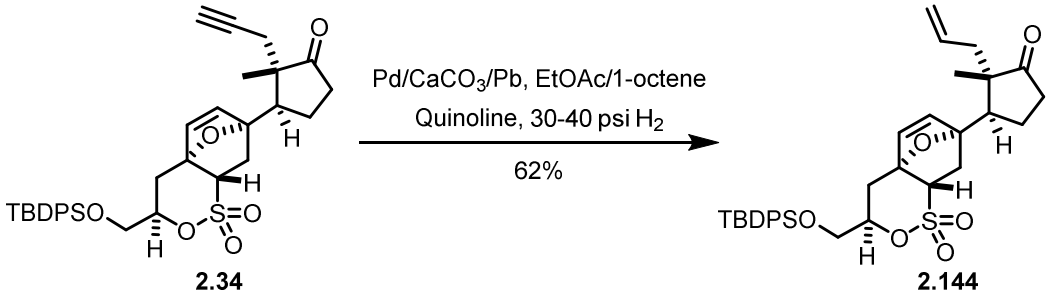


a) Decomposition pathway of secondary ozonides in the presence of strong bases; b) hydrolysis of carbonyl oxide in presence of water; c) Pathway in presence of amine oxides; d) Pathway in presence of pyridine; e) equilibrium of pyridine and ozone to form complex

Due to the fact that the ozonolyzed product **2.125** exists as a mixture of aldehyde hydrate diastereomers, the Diels-Alder reaction adduct **2.34** was used as a model system to determine the best conditions for partial reduction of the alkyne. Lindlar's catalyst ($Pd/CaCO_3$ poisoned with lead) is well known to facilitate the partial reduction of alkynes,[205-208] but hydrogenation of **2.34** under a balloon of hydrogen and quinoline gave no reaction. P2-nickel boride,[210,211] which is also known to reduce alkynes to alkenes, also gave no reaction. Hydrogenation of **2.34** with Lindlar's catalyst under a higher pressure of hydrogen (30-40 psi) reduced the alkyne, however, the ^{1}H-

NMR spectrum of the reaction showed a complex mixture of products and a lack of olefin protons, indicating over-reduction had occurred. In order to combat over-reduction of the olefin, 1-octene was added as a co-solvent to serve as a sacrificial olefin to protect against over reduction.[209] Thus, hydrogenation of **2.34** with Lindlar's catalyst and quinoline in 1:1 EtOAc/1-octene at of 30-40 psi H_2 cleanly gave **2.144** in 62% yield (Equation 2.8).

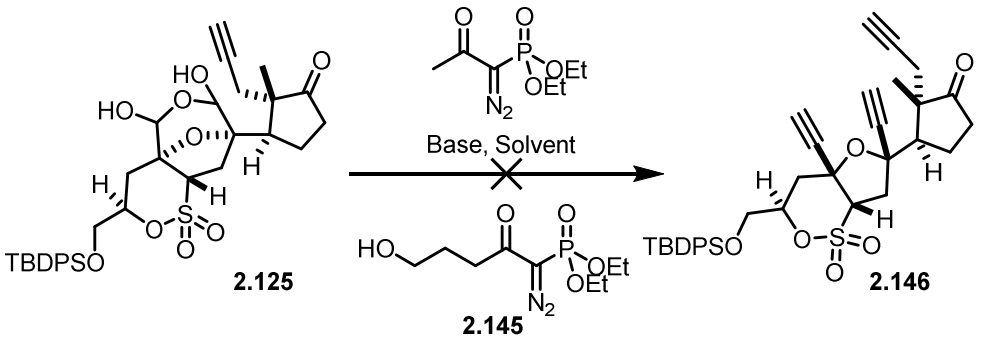
Equation 2.8: Successful partial reduction of alkyne moiety in Diels-Alder adduct **2.34**



2.34 **2.144**

With conditions for the hydrogenation of the alkyne to the alkene developed, work to investigate the transformation of the ozonolysis product **2.125** to the bis- alkyne was initiated. Despite considerable effort, all attempts to convert **2.125** into the bis-alkyne **2.146** were unsuccessful (Equation 2.9). Only trace amounts of product were isolated after reaction of **2.146** with the Ohira-Bestmann reagent in the presence of K_2CO_3 in MeOH. Changing the base to Cs_2CO_3, which is known to accelerate the reaction and reduce by-products, offered no improvement.[214] The methoxide present in the reaction mixture, which is necessary to transform the Ohira-Bestmann reagent into the Seyferth-Gilbert[212,213] reagent *in situ*, may be incompatible with the several base sensitive functionalities present in **2.125**. Zhang developed reagent **2.145**, which does not require methanol to transform into the (diazomethyl)phosphonate and thus may be used in any solvent.[215] Unfortunately, despite extensive screening of solvents and bases with reagent **2.145** only complex mixtures were observed.

Equation 2.9: Attempted conversion of bis-aldehyde hydrate **2.125** to bis-alkyne **2.146**



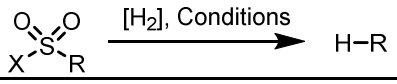
The failure to convert the ozonolysis product **2.125** to the bis-alkyne **2.146** using both protic and aprotic conditions was attributed to the base sensitivity of the sultone moiety. Sulfonate esters are powerful alkylating agents and may interact with nucleophiles either at carbon or at sulfur. Additionally, the α-position is potentially acidic enough to deprotonate under mild basic conditions causing β-elimination of the oxo-bicycle or other side-reactions. Therefore, removing the sultone before the Ohira-Bestmann homologation could potentially suppress these undesired side reactions.

2.2.6: ATTEMPTED DESULFURIZATION OF 2.34

Many other methods exist to reductively cleave carbon- sulfur bond, as well as the one developed by Dr. Benjamin. The methods generally fall into two categories: single electron transfer agents (Table 2.16, entries 1-8) and hydrogenolysis (Table 2.16, entries 9-15). Hydrogenolysis is most commonly effected with homogeneous or heterogeneous nickel and is probably the most widely used method for desulfurization. Depending on the method, the reactivity of the nickel can be modified to suit the system. Raney-nickel (Mozingo) is the most active nickel based desulfurization agent.[226] Caubere has pioneered the development of the Ni Containing Complex Reducing Agents (NiCRA,s) in an effort to develop milder, more consistent reductant than Raney-Nickel.[224,225,230] Nickel-boride is the least active of the heterogeneous nickel reducing agents.[227] Although in some instances compounds can be desulfurized in the presence olefins by de-activating the catalyst *via* refluxing in acetone,[257,258] re-activated catalysts

have, thus far, not been shown to reduce sulfonate esters which precludes use with the Diels-Alder reaction adduct **2.34**.[238,239] Fortunately, single electron reducing agents also offer some flexibility. The reactivity of single election reductant can be modulated by the choice of metal (Na,[216,220] Mg,[217,222] Al[218] or SmI_2[221]) and the use of protic additives.[220,] Further modulation of the reactivity can be done by adding transition metal additives such as titanium to generate low valent metal species that can aid in the reduction.[222,234,235]

Table 2.16: Compilation of desulfurization Methods



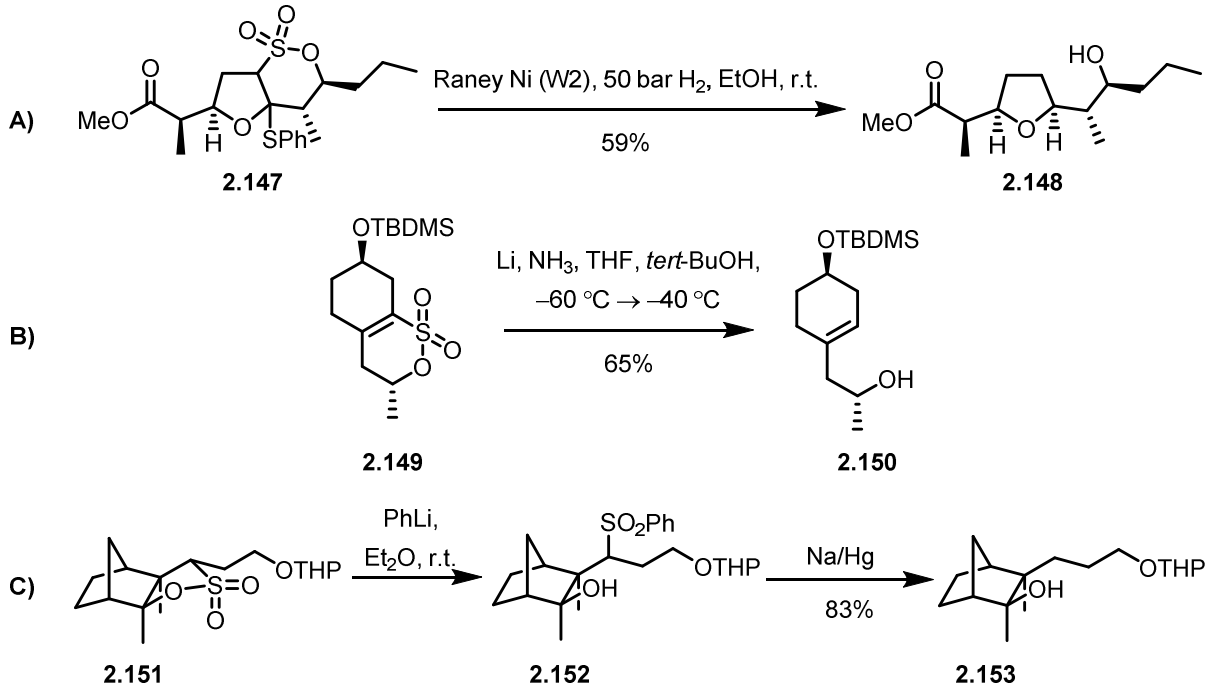
Refrence	X	reagent	additive	conditions	yield
Trost[216]	Ar	Na/Hg	Na_2HPO_4	MeOH, 0 °C	49-93%
Lee/Pak[217]	Ar	Mg/$HgCl_2$	Na_2HPO_4	EtOH, rt	98-100%
Corey[218]	Ar	Al	$HgCl_2$	THF, rt[a]	70-98%
Carpino[219]	Ar	Mg	N/A	MeOH, 50 °C	68-91%
Suh[220]	Alk	Na/Hg	$B(OH)_3$	MeOH, rt	87%
Kunzer[221]	Ar	SmI_2	HMPA	THF, rt	50-91%
Pathak[222]	Alk	Mg	$NiBr_2$	MeOH, rt	44-75%
Zhang[223]	Alk	$TiCl_4$/Zn	N/A	THF, rt	74-92%
Caubere[224,225]	Ar/Alk	NaH/$Ni(OAc)_2$	*t*-AmONa	THF, 65 °C	60-100%
Mozingo[226]	Ar	Raney-Ni[b]	N/A	EtOH, reflux	65-80%
Back[227]	Ar	$NiCl_2$/$NaBH_4$	N/A	MeOH, rt	0-14%
Luh[228]	Ar	Cp_2Ni/$LiAlH_4$	N/A	THF, rt	38-63%
Luh[229]	Ar/Alk	$NiBr_2$•DME/$LiAlH_4$	Ph_3P	THF, rt	55-92%
Caubere[230]	Ar	NaH/$Ni(OAc)_2$	NMHPNa[c]	THF, 65 °C	60-100%
Park[231]	Ar	iPrMgBr	Dppf•$NiCl_2$	Et_2O, reflux	31-95%
Wolinsky[232,233]	RO	$LiAlH_4$ or AlH_3	N/A	Et_2O, reflux	0-45%
Okamoto[234]	R_2N	Mg/$Ti(OiPr)_4$	TMSCl	THF, 50 °C	29-94%
Nayak[235]	RO	Li	$TiCl_3$	THF, rt	32-91%
DuBois[236]	Cl	Zn	$Cu(OAc)_2$	AcOH, rt	55%

a) Mixture of solvent and water; b) W2 Raney nickel; c) NMHPNa is n-Methyl 3-Hydroxy piperidine sodium salt

Compared to sulfones, the reductive desulfurization of sultones or sulfonate esters is an underdeveloped area of chemistry. The same reagents for reductive desulfurization of sulfones

also apply to sulfonate esters: aluminum hydrides (Table 2.17, entry 16), single electron transfer (SET) reduction (Table 2.17, entry 17,18,19, Figure 2.15, **B**),[112] Raney nickel (Figure 2.15, **A**) but the conditions are noticeably harsher and lower yielding than for the sulfones.[108] One interesting procedure, however, is a two step protocol devised by Wolinsky for his synthesis of β-santalol (Figure 2.15, **C**).[237] To circumvent the low yielding one-step reduction of the sultone, it was first converted to a sulfone that was subsequently removed with Na/Hg.

Figure 2.15: Literature examples of reductive desulfurization with sultones

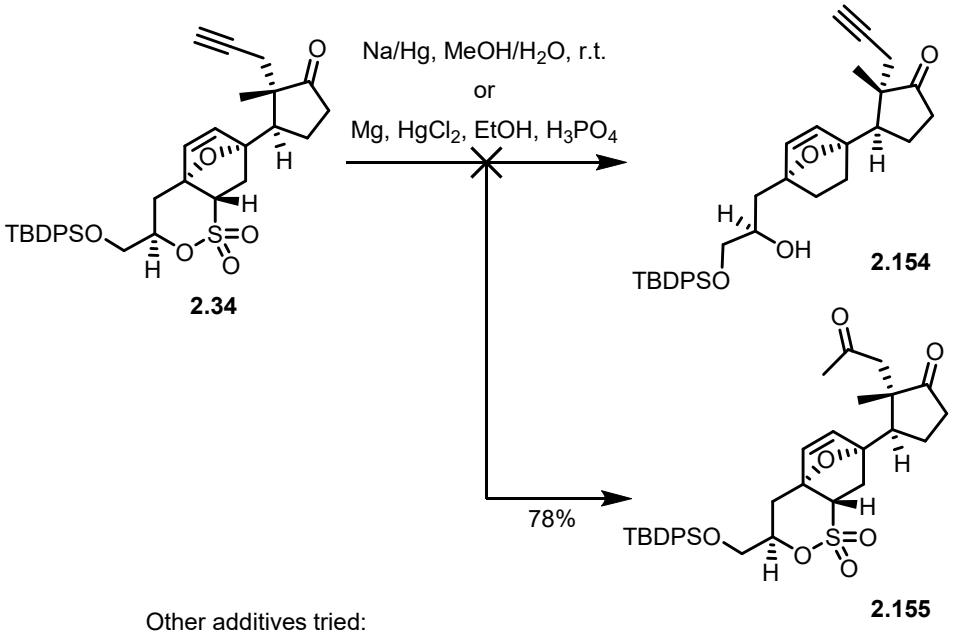


a) Desulfurization of sultone **2.147** by Metz in the synthesis of methyl nonactate;[108] b) Desulfurization of sultone **2.148** by Metz in his study of reductive desulfurization of sultones;[112] c) Desulfurization of sultone **2.151** by Wolinsky in the synthesis of β-santalol.[237]

As mentioned earlier, the olefins present in **2.34** preclude use of aluminum hydrides and hydrogenolysis methods for reductive desulfurization due to the robustness of sulfonate esters compared to sulfones and other sulfur containing groups so SET strategies were investigated first. Subjection of **2.34** to SET reduction conditions using either Na/Hg or Mg/Hg as the

reducing agent did not produce any of the desired product **2.154** (Scheme 1.24). Addition of $Ti(OiPr)_4$, $NiBr_2$ or $CeCl_3$ as additives to the SET reduction provided multiple products that could not be identified. Protic additives seemed to provide cleaner mixtures of products, and several that were screened include $B(OiPr)_3$ (for anhydrous $B(OH)_3$, TMSCl (for anhydrous HCl), H_2O, BHT, Na_2HPO_4, citric acid, phosphoric acid and TFA. Of the protic additives, only phosphoric acid in conjunction with Mg/Hg gave a single product, which was determined to be **2.155** in 78% yield.

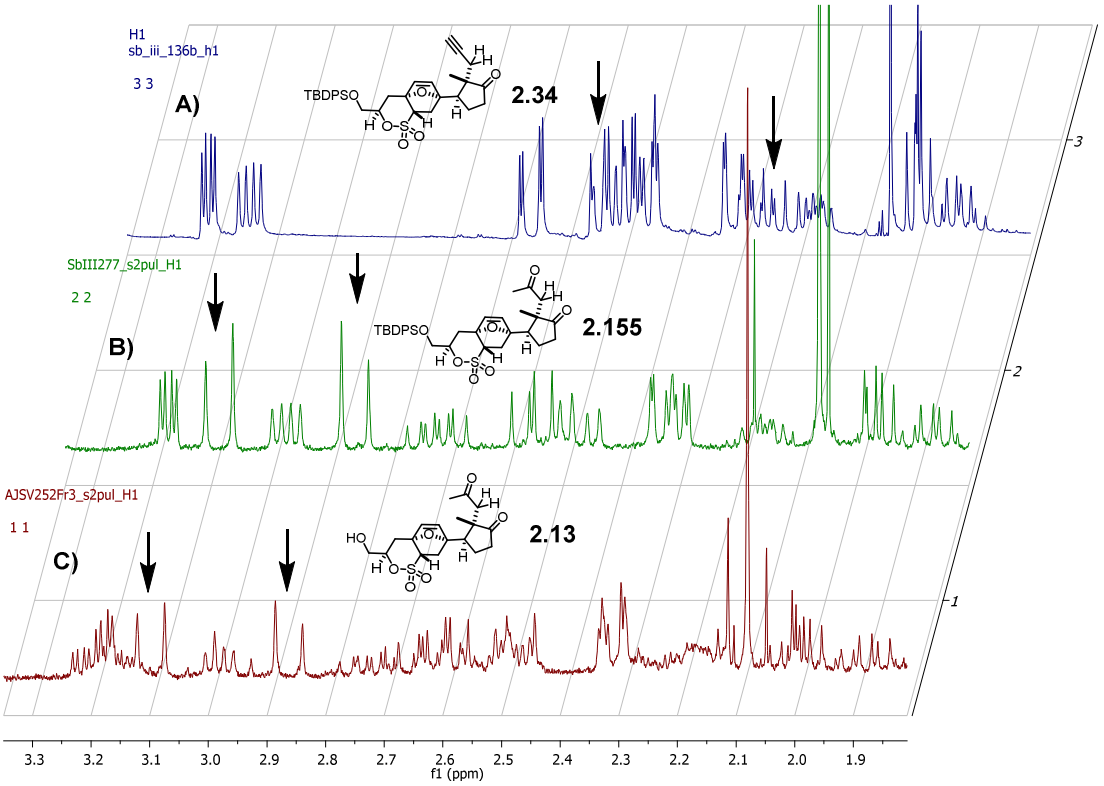
Scheme 2.14: Attempted reductive desulfurization of **2.34** with Na/Hg or Mg/Hg



The alkyne hydration product **2.155** was assigned based on its mass of 622 ($M+H_2O$) and the similarity of its ^1H NMR spectra to that of **2.72**, the structure of which was confirmed by X-ray crystallography (Figure 2.16). The key diagnostic peaks in the ^1H-NMR spectra that distinguishes **2.34** from **2.155** and **2.13** are the diastereotopic protons next to the alkyne (Figure 2.16, **A** for **2.34**, **B** for **2.155** and **C** for **2.13**). In the starting material, both protons appear as a

doublet of doublets at 2.49 and 2.26 ppm because they are being split by each other and the alkyne sp-proton. The peaks representing the protons in by-product **2.155** and **2.72** have shifted downfield to 3.08 and 2.85 ppm, respectively, and appear as doublet, indicating that the alkyne splitting has been lost.

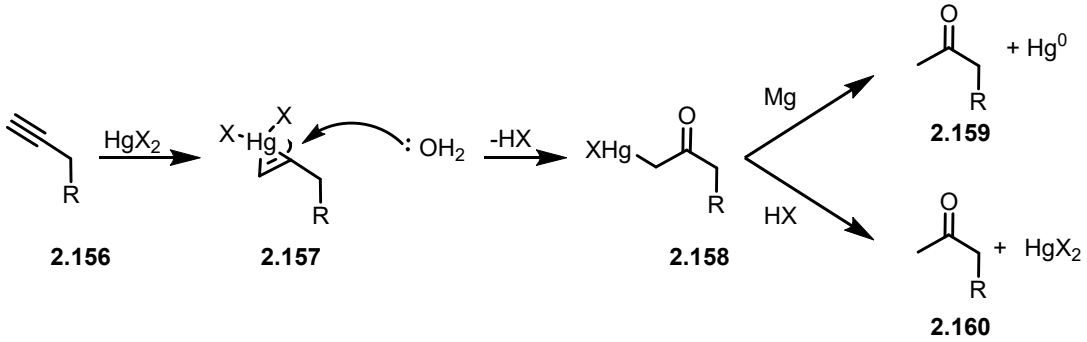
Figure 2.16: Proton NMR of Diels-Alder reaction adduct and alkyne hydrated products



a) ^{1}H NMR of starting material **2.34**; b) ^{1}H NMR of **2.155**; c) ^{1}H NMR of decomposition product **2.72**

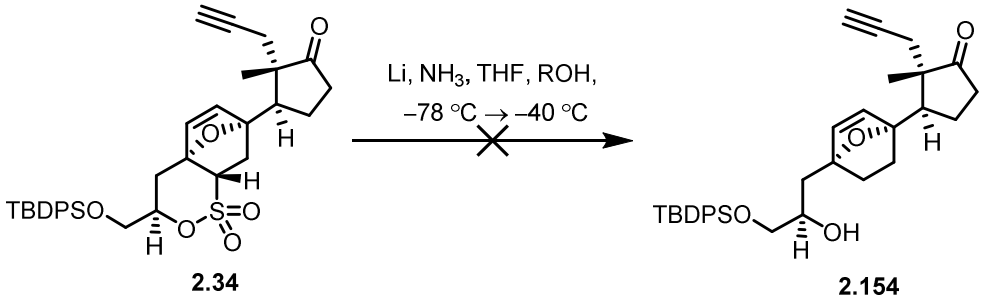
The exact pathway for forming **2.155** has not been elucidated; however trace amounts of Hg^{II} from the $HgCl_2$ added to the reaction mixture could have participated in an oxymercuration reaction to give the α-keto-organomercury compound **2.158** (Scheme 2.15). Mercury compound **2.158** could then be reduced by the Mg^{o} to the enolate and protonated by MeOH to give the ketone compound and Hg^{0}. Alternatively, protic additives may protonate the Hg-C bond to generate the ketone and the Hg^{II} species.

Scheme 2.15: Putative mechanism for the formation of byproduct **2.155**



The fact that none of the milder SET conditions showed any evidence for the desired reduction led to the investigation of the Birch reduction, which has been shown to desulfurized similar substrates (see Figure 2.15 **B**). Disappointingly, addition of a solution of **2.34** in THF to a cooled solution of lithium in ammonia resulted in complex mixtures with no identifiable products (Equation 10). Isolation of the crude reaction mixture showed additional Csp_2-H peaks in addition to those already present in the ^{1}H-NMR, indicating that the arene groups on the TBDPS protecting group might have been reduced in addition to other side reactions. The addition of alcohols to modulate the reduction potential of the reaction mixture only produced more complicated ^{1}H NMR spectra.

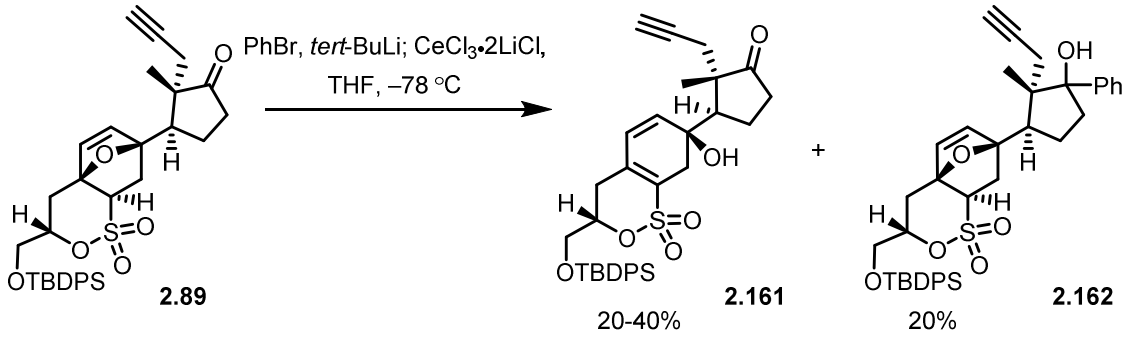
Equation 2.10: Attempted Birch reduction of **2.34**



The inability to desulfurized the Diels-Alder adduct **2.34** via single electron transfer methods led to the investigation of the two step procedure developed by Wolinsky (see Figure

2.17, **C**).[237] There are relatively few examples of cleaving sulfate esters with organometallics reagents and most studies on the addition of nucleophiles to sulfate esters involve phenyl sulfonates and not alkyl sulfonates.[238-248] A variety of phenyl nucleophiles were screened in order to convert the sulfate ester to the phenylsulfone. Exposure of **2.89** to phenylzinc chloride resulted in no reaction, and the addition of phenyllithium, with and without LiHMDS to protect the ketone *in situ*, generated unidentifiable products. Organocerium reagents are known to have reduced basicity and enhanced nucleophilicity, and reaction of the phenyl organocerium reagent with **2.89** gave a mixture of products that were determined to be the 1,2-adduct **2.162** and the ring-opened product **2.161** (Equation 2.11).[167] Use of phenylmagnesium bromide to make the organocerium compound provided a reagent that was far less reactive than the reagent made with the phenyllithium. Interestingly, use of mesityllithium to generate the organocerium reagent resulted in no formation of 1,2-adduct **2.162**, and only the ring opened product **2.161** was isolated.

Equation 2.11: Attempted conversion of sultone to sulfone

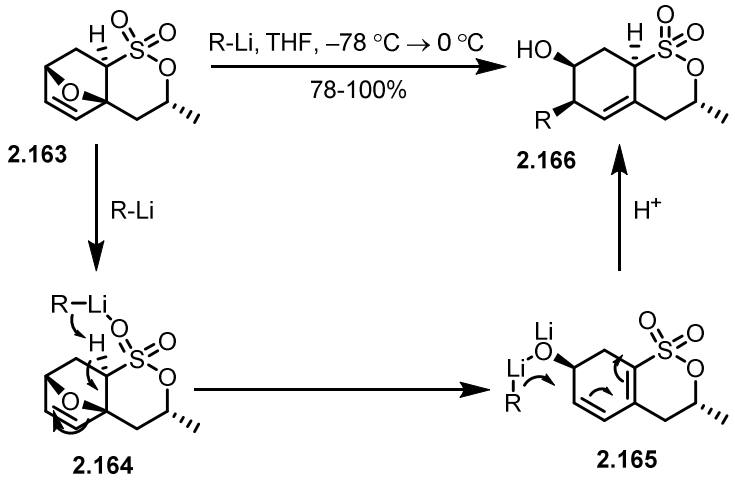


Other conditions tried:
PhBr, *n*-BuLi, $ZnCl_2$,THF, –78 °C; NR
PhBr, *n*-BuLi, THF, –78 °C; complex mixture
LiHMDS; PhBr, *n*-BuLi, $ZnCl_2$,THF, –78 °C; NR
PhMgBr, $CeCl_3$•2LiCl, THF, –78 °C; NR

Evidence for the structure **2.161** are as follows: The mass of the product was 587 which is indicative of no additional phenyl group and matches the molecular weight of the starting material minus water suggesting an ionizable alcohol. The ^{1}H-NMR chemical shifts of the olefinic protons have shifted from 6.57 and 6.09 ppm in **2.89** to 6.18 and 5.91 ppm and the coupling constants of the olefinic protons have also changed (5.5 → 10.0 Hz). Coupling constants of 5-6 Hz are typical for norbornenes and cyclopentenes whereas a coupling constant of 10 Hz is more indicative of a cyclohexene.[251-255] The ^{13}C-NMR shows that the olefinic carbon peaks have also shifted upfield (141.6, 135.9 → 138.6, 125.11 ppm). There are a total of 12 sp^2 carbons between 140 and 120 ppm but 8 of these carbons belong to the diastereotopic phenyl groups of the TBDPS group. Of the four carbons remaining, two are the olefinic protons leaving two extra quaternary olefinic carbons. Additionally, the bridgehead carbon atoms of the oxo-norbornene in the starting material are characteristic at 90.6 and 87.7 ppm, but there are no carbons in this region in the spectrum of **2.161**.

The probable mechanism for the formation of **2.161** is likely deprotonation of the sultone at the α-position, followed by elimination to form the cyclohexadiene moiety. The tendency for these systems to eliminate in this fashion was leveraged by Metz in his synthesis of nonactate and pamamycin.[107-111,256] Metz found that treatment of the oxabicycle **2.163** with organometallic agents facilitated the ring opening and 1,6-conjugate addition into the extended vinyl sulfonate ester (Scheme 2.16).

Scheme 2.16: Metz ring-opening/1,6 conjugate addition cascade



In correspondence with Dr. Metz, he revealed that the discovery of this reaction was the result of his initial attempts to desufurize the sultone and that removing the sulfur without ring opening is still an unsolved problem.

Dear Mr. Blumberg,

Desulfurization of a furan-derived sultone without breaking the oxygen bridge is an unsolved problem as far as I know. About 20 years ago when we worked on the synthesis of nonactic acid, we tried a lot of conditions but we could never avoid the beta-elimination with ring-opening. During this work, we actually discovered the Red-Al domino elimination/alkoxide-directed hydride addition that turned out to be quite helpful later. This also led us to the idea of doing similar chemistry with organolithium reagents, which was developed into key steps for the nactic [sic] acid and pamamycin [sic] syntheses eventually.
Even if the intended addition of an arylmetal species to the delta-sultone with formation of a hydroxyl sulfone would work (earlier we added phenyllithium to a cyclopentadiene-derived delta-sultone to isolate about 20% of the desired sulfone), the subsequent desulfurization might be rather tricky again.
I do not know your target, but maybe you can also utilize an elimination reaction with ring-opening just as we did for our 2,5-disubstituted THF targets.

All the best,
Peter Metz

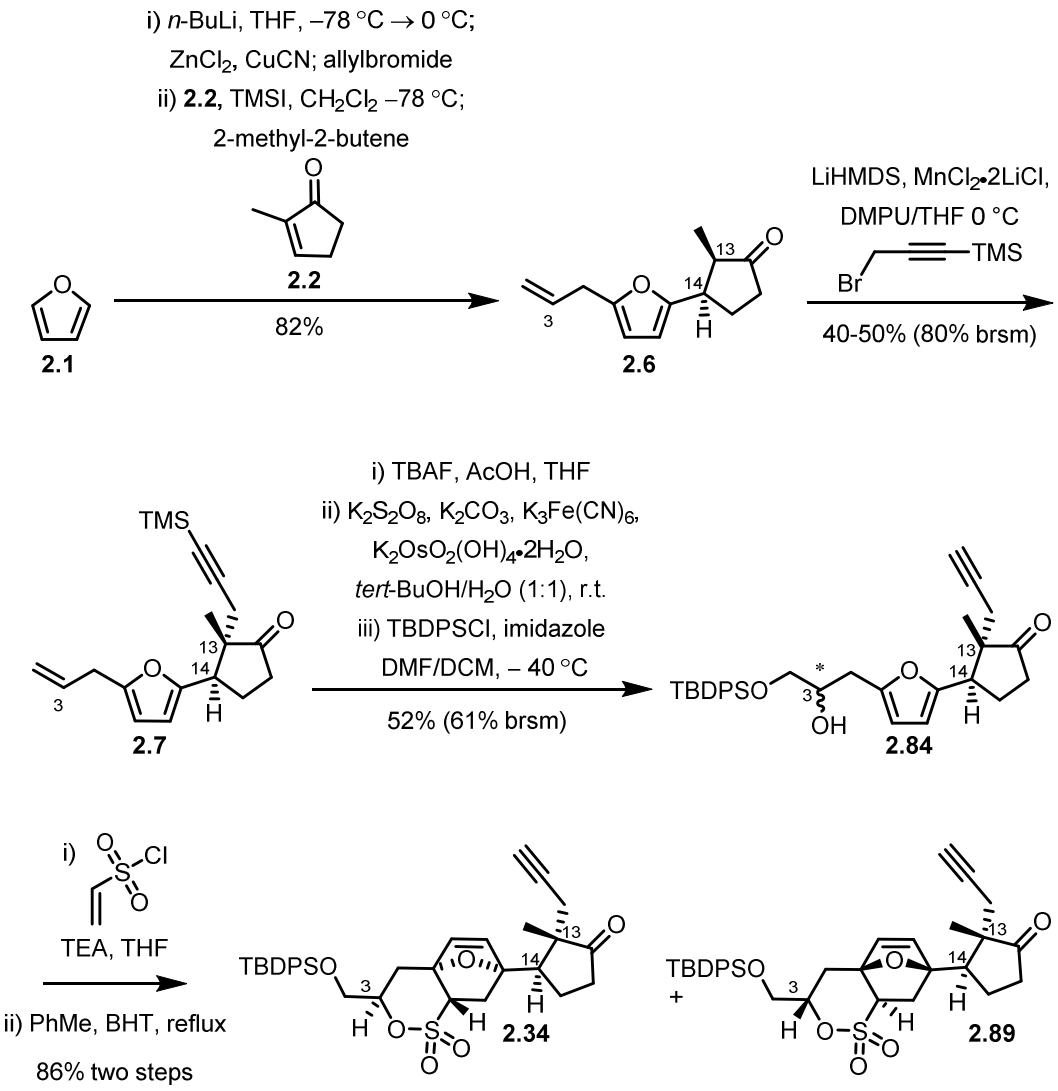
Unfortunately, due to the inability of removing the sulfur from Diels-Alder reaction adduct **2.34** or transform the ozonolysis product **2.125** into the bis-alkyne **2.146**, the project was not pursued further. The key problems seem to stem from the base sensitivity of the sultone which severely limits the synthetic transformations compatible with the system. The Wolinsky-like strategy of transforming the sultone into the phenyl sulfone seems unlikely to work as even organocerium reagents are basic enough to deprotonate the oxa-bicyclic ring, followed by ring opening to **2.161**.

2.2.7: SUMMARY

In summary, a crystal of x-ray quality was grown of **2.14**, confirming that the relative stereochemistry of the C13 propargyl group and the C14 furan as trans and confirming diastereomers **2.10** and **2.34** as having the desired stereochemistry required for cortistatin A. A two-step scaleable route to ketone **2.6** was established, shortening the sequence by three steps

using cost effective protocols by utilizing the Kraus alkylation (Scheme 2.17). Although a repeatable alkylation of ketone **2.6** proved difficult, insights into the generation of thermodynamic lithium enolates were gained, namely, that the addition of base to the ketone rather than incubation with substoichiometric base proved superior for the generation of the thermodynamic enolate. The dihydroxylation of ketone **2.33** was initially sluggish and low yielding, but an improved procedure was developed using potassium persulfate ($K_2S_2O_8$) as the stoichiometric oxidant which improved yields of diol **2.81** and improved reaction rates. Successful formation of the vinyl sulfonate in was found to be contingent on the elimination of polar ammonium salt **2.87** with excess base and subsequent Diels-Alder reaction furnished **2.34** and **2.89** in 86% yield.

Scheme 2.17: An improved, scaleable route to Diels-Alder adducts **2.34** and **2.89**

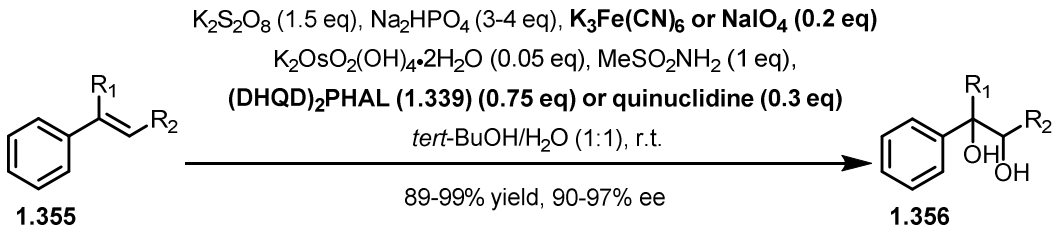


*** Indicates absolute stereochemistry**

The Sharpless asymmetric dihydroxylation can be used with a variety of olefins but the high pH (10-11.2) of the reactions conditions precludes use with base sensitive functionalities. Accordingly, a very mild (pH 8-9) Sharpless-style dihydroxylation was developed using

potassium persulfate ($K_2S_2O_8$) as the stoichiometric oxidant, hydrogen phosphate (Na_2HPO_4) as the base and either Potassium ferricyanide ($K_3Fe(CN)_6$) or sodium periodate ($NaIO_4$) as the catalytic co-oxidant (Equation 2.12). Use of quinuclidine as the ligand provided racemic diols in excellent yield, while use of $(DHQD)_2PHAL$ (**2.91**) generated the diols with enantioselectivities almost identical to those reported in the literature. These conditions were demonstrated to work even in the presence of base sensitive functionalities such as aldehydes and will be of use for the greater synthetic community.

Equation 2.12: Racemic and enantioselective Upjohn-like dihydroxylation conditions



1.355

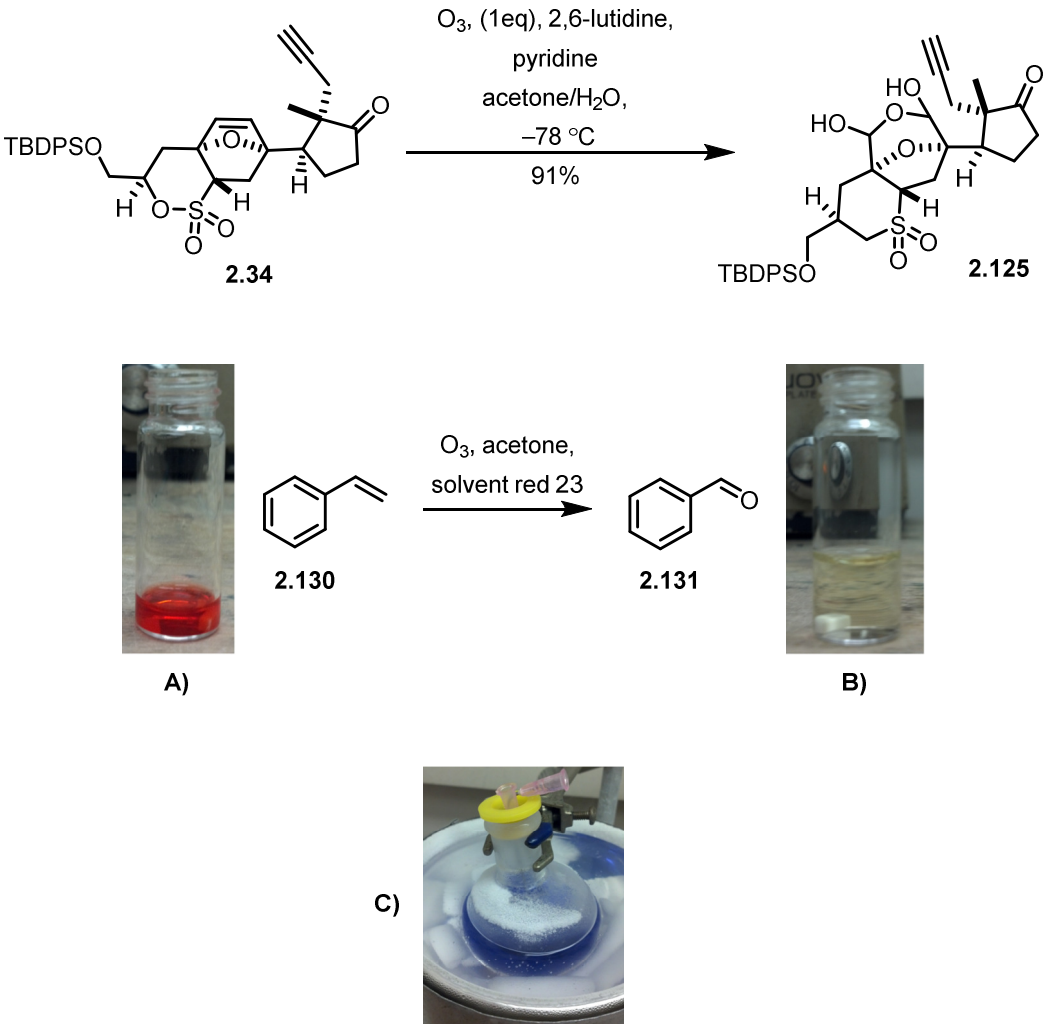
1.356

2.109: R_1 = H, R_2 = H
2.110: R_1 = Me, R_2 = H
2.111: R_1 = $(CH_2)_4$, R_2 = $(CH_2)_4$
2.115: R_1 = H, R_2 = CO_2Me

2.112: R_1 = H, R_2 = H
2.113: R_1 = Me, R_2 = H
2.114: R_1 = $(CH_2)_4$, R_2 = $(CH_2)_4$
2.116: R_1 = H, R_2 = CO_2Me

The selective ozonolysis of the Diels-Alder reaction adduct **2.34** was initially low yielding, owing to the difficulty in controlling the amount of ozone the substrate is exposed too. To control the ozone equivalents, a colorimetric titration was developed using Sudan III as an indicator and styrene as the consumption. The titration was utilized to add 1 equivalent of an ozone solution in acetone to a mixture of **2.34** in acetone/H_2O (95:5) and 2,6-lutidine at –78 ºC to provide the aldehyde hydrate **2.125** in 77% yield (Figure 2.17). The addition of pyridine further improved the yield of **2.125** to 92% yield.

Figure 2.17: Selective ozonolysis of the Diels-Alder reaction adduct **2.34**



CHAPTER 3: THE CITREAMICINS AND OTHER POLYCYCLIC XANTHONE NATURAL PRODUCTS

3.1: Isolation and Biological Activity

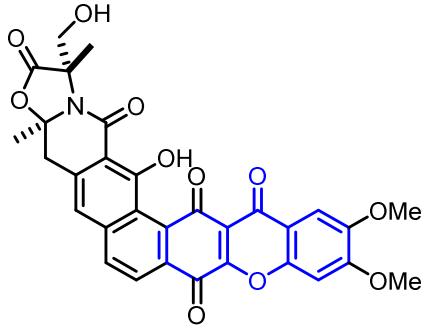
Citreamicin α **3.5** was isolated from a culture of *Micromonospora citrea* taken from Lake Manyara in Tanzania, Africa in 1989 by Lechevalier.[265] The structure was miss-characterized and originally called LL-E19085α before being correctly assigned to the structure shown in Figure 2.1 by Carter in 1990.[266] Citreamicins β (**3.6**), γ (**3.7**), ζ (**3.8**) and η (**3.2**) were also isolated and characterized by Carter in that same paper. In 2008, citreamicins δ (**3.9**) and ε (**3.3**) were isolated from a culture of *Streptomyces vinaceus* by Moek.[267] Neocitreamicins I (**3.10**) and II (**3.11**) were isolated in 2008 form a sandy soil sample collected in Falmouth, Massachusetts by Moore.[268] Citreamicin ε (**3.3**) and its epimer at C25 Citreamicin B (**3.4**), were isolated form a culture of *Streptomyces caelestes* taken from the coastal waters of the Red Sea in 2013 by Qian.[269]

The distinguishing characteristic of the citreamicins is the dihydrooxazolo-[3,2-b]-isoquinolinone moiety (the GAB rings), which is unique to this class of natural products and contains an (S)-α-methylserine. The hydroxyl group at C29 can be acylated with a variety of carboxylic acids. The other point of diversification is in the F ring. In paticular of the citreamicins contain substitution at C11 and C12 (citreamicins α, β, γ, ζ, and η) whereas citreamicins ε, B, and neocitreamicins I and II have substitution at C10 and C11. Interestingly, neocitreamicin II is the only glycosylated member of the citreamicin family isolated thus far.

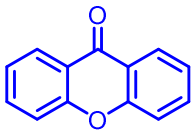
All known citreamicins have shown potent antibiotic activity against several gram-positive strains. Most notably, citreamicin η (**3.2**) exhibits a median inhibitory concentration (MIC) of 26 nM,[266] whereas citreamicins δ and ε have shown MIC values of 101 nM – 3.4 μM against multidrug-resistant *Staphylococcus aureus* (MDRSA) and vancomycin-resistant *Enterococcus faecalis* (VRE).[267] In 2013, Qian demonstrated that citreamicins ε and B displayed potent cytotoxic activity against HeLa and Hep62 cells in the 30-100 nM range.[269] Further

studies revealed that they induced HeLa cell apoptosis *via* CAS-3 dependent pathways and that the hydroquinone analogues increase reactive oxygen species generation (ROS) by 40% while the quinones increase ROS generation by 20%.[269]

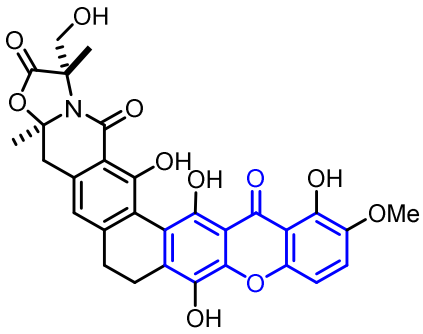
Figure 3.1: Isolated members of the citreamicin family



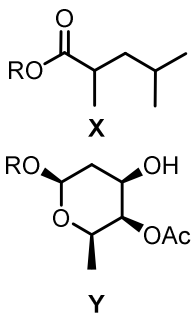
3.2
Citreamicin η[265,266]
MIC 26 nM



3.1
Xanthone

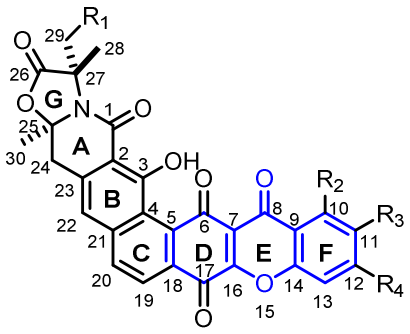


3.3: Citreamicin ε (202-842 nM)[267,268]
3.4: Citreamicin B (epi C_{25})[268]



X

Y

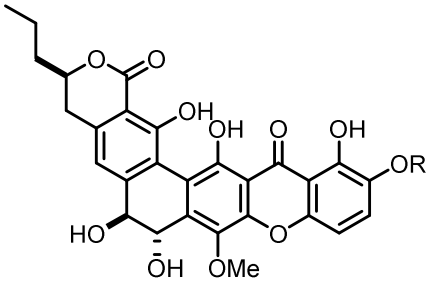


3.5: R_1= O(CO)*i*Bu, R_2= H, R_3= OMe, R_4= OMe, (Citreamicin α)[265,266]
3.6: R_1= O(CO)*i*Pr, R_2= H, R_3= OMe, R_4= OMe, (Citreamicin β)[265,266]
3.7: R_1= OAc, R_2= H, R_3= OMe, R_4= OMe, (Citreamicin γ)[265,266]
3.8: R_1= O(CO)*i*Bu, R_2= H, R_3= OH, R_4= OMe, (Citreamicin ζ)[265,266]
3.9: R_1= OH, R_2= OH, R_3= OMe, R_4= H, (Citreamicin δ, MIC 101 nM - 3.4 μM)[267]
3.10: R_1= X, R_2= H, R_3= OH, R_4= H, (Neocitreamicin I, MIC 92 nM - 764 nM)[268]
3.11: R_1= X, R_2= H, R_3= Y, R_4= H, (Neocitreamicin II, MIC 92 nM - 1.5 μM)[268]

The citreamicins belong to a class of type II polyketides called polycyclic xanthones and are characterized by an angularly fused hexacyclic structure, with the xanthone moiety comprising the D, E and F rings (Figure 2.2, Table 2.1). Though the citreamicins are the only members that feature the dihydrooxazolo-[3,2-b]- isoquinolinone moiety, the cervinomycins[270-272] (**3.17**-**3.19**) (Figure 2.2, Table 2.1, entry 3) and the kigamicins (**3.20**)[273,274] (Figure 2.3, Table 2.1, entry 10) feature a similar tetrahydrooxazolo-[3,2-b]-isoquinolinone moiety. Despite being isolated from different organisms and from different parts of the world, the compounds display a surprising degree of structural similarity. The A and F rings are the most diverse, with the A ring

being either 2-pyridone-based, or lactone-based as seen with FD-594 (**3.13**)[275,276] and IB-00208 (**3.14**)[277] (Figure 2.2, Table 2.1, entries 9, 11). The F ring can be aromatic, mono-unsaturated or bis-unsaturated and can have substitution at all positions on the ring. The D and E rings display the most consistency: The E ring remains the same, and the D ring is either a hydroquinone derivative or a quinone. One interesting feature of some members of this class is the methylenedioxy ring that spans C17 and C19 and is found in the kigamicins (**3.20**), xantholipin (**3.16**),[278] actinoplanone (**3.26**),[279] albofungin (**3.27**)[280] and lysolipin (**3.15**)[281] (Figure 2.2, 2.3, Table 2.1, entries 10, 12, 4, 1 and 2). Simaomicin (**3.22**) is the only member to have this bridge span C22 and C24 (Figure 2.3, Table 2.1, entry 6).[281] Virtually all members of this family possess nanomolar activity against several bacterial strains and cancer cell lines.

Figure 3.2: Polycyclic xanthone natural products

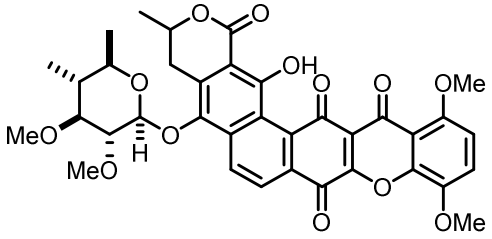


3.13

FD-594[275,276]

IC_{50} 106 nM - 1.1 μM HeLa

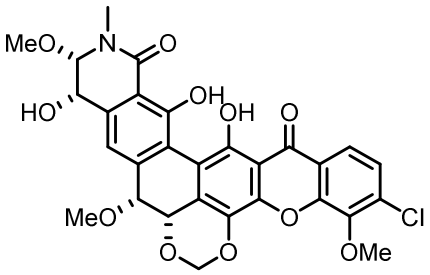
R = Gycosides



3.14

IB-00208[277]

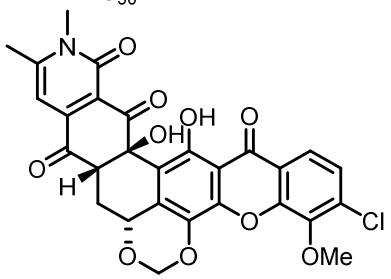
IC_{50} 1 nM



3.15

lysolipin[281]

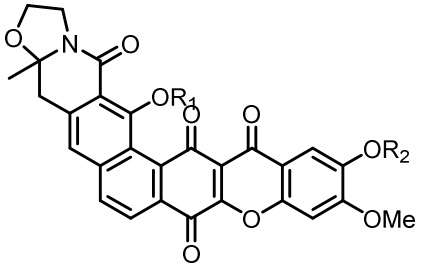
MIC 4 - 836 nM

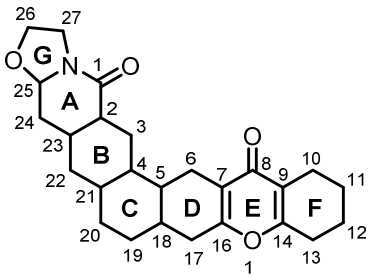


3.16

xantholipin[278]

IC_{50} 27 nM





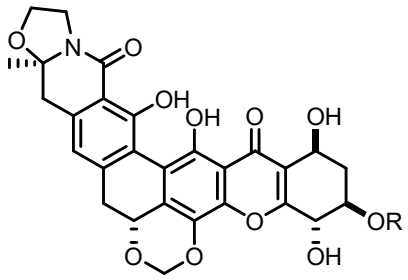
3.12

3.17: R_1 = H, R_2 = Me (Cervinomycin A_2, MIC 12 nM - 23 μM)[270]

3.18: R_1 = H, R_2 = H (167-A, MIC 78 - 332 nM)[271]

3.19: R_1 = Me, R_2 = H (167-B, MIC 78 - 332 nM)[271]

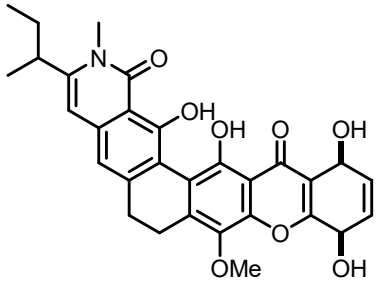
Figure 3.3: Polycyclic xanthone natural products continued



3.20

kigamicins (R = glycosides)[273,274]

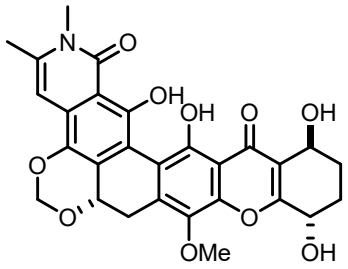
MIC 38 - 586 nM



3.21

Sch 56036[285]

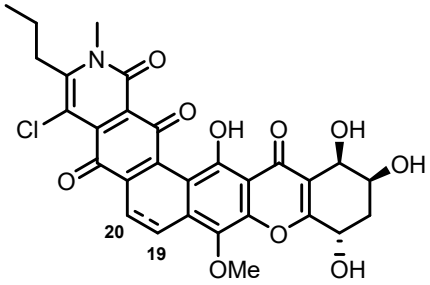
MIC 33 - 66 nM



3.22

simaomicin α[282]

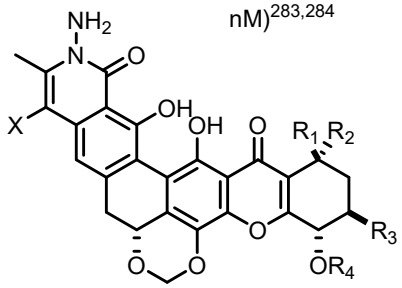
MIC 112 nM



3.23: $\Delta^{19,20}$ (Kibdelone A, 1.6 - 5 nM)[283,284]

3.24: (Kibdelone B, 1.6 - 5 nM)[283,284]

3.25: Dihydro, Kibdelone C, 1.6 - 5 nM)[283,284]



3.26: X = Cl, R_1 = OMe, R_2 = H, R_3 = OH, R_4 = H (actinoplanone A, IC_{50} 0.072 nM)[279]

3.27: X = H, R_1 = H, R_2 = OH, R_3 = H, R_4 = Me (albofungin)[280]

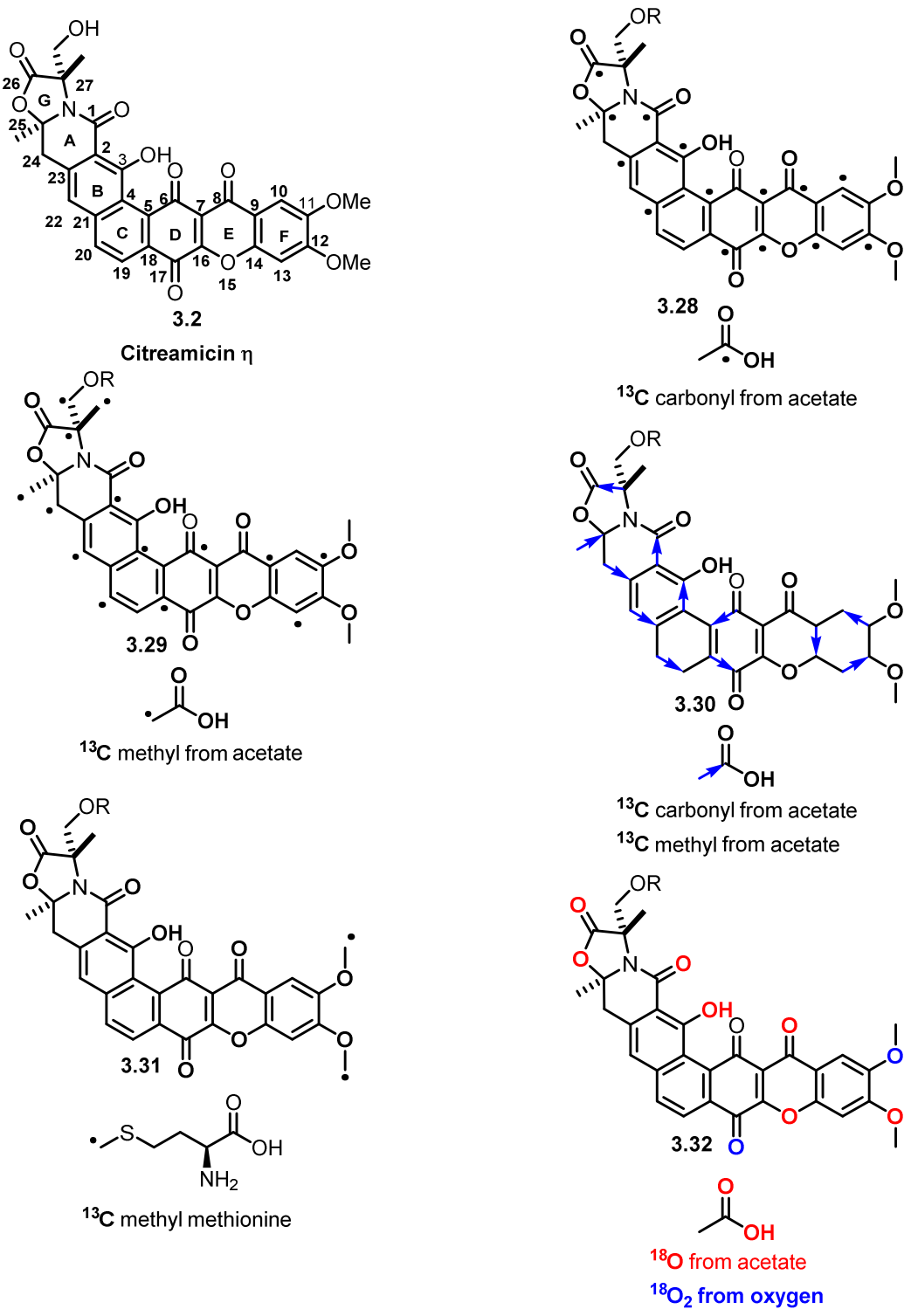
Table 3.1: Chronological list of polycyclic xanthone natural products

Name	Compound	Isolated	Location	Strain
Gureuich[280]	albofungin	1972		
Zahner[281]	lysolipin	1975		*Streptomyces violaceoniger*
Omura[270,272]	cervinomycin	1982	Soil, Saiwai-cho, Chiba city, Japan	*Streptomyces cervinus*
Nishino[279]	actinoplanone	1988	Forest soil in Okinawa prefecture, Japan	*Actinoplanes sp.*
Carter[266]	citreamicin	1990	Lake Manyara in Tanzania, Africa	*Micromonospora citrea*
Kantor[282]	simaomicin	1990	Soil, San Simao, Brazil	*Actinomadura madure*
Katrukha[271]	167-A,B	1993	Soil, Bulgaria	*Amylcocata autotrophica*
Chu[285]	Sch-56036	1998	Tarlac on Philippine island	*Actinoplanes sp.*
Mizoue[275,276]	FD-594	1998	Soil, Urawa city, Saitama prefecture, Japan	*Streptomyces sp.*
Kunimoto[273,274]	kigamicin	2003	City of Tuba, Mie prefecture, Japan	*Amicolatopsis sp.*
Romero[277]	IB-00208	2003	Northern coast of Spain	*Actinomadura sp.*
Terui[278]	xantholipin	2003	Soil, Shandong province, China	*Streptomyces sp.*
Capon[283,284]	Kibdelone	2007	Timber wool shed near port Augusta Australia	*Kibdelosporagium sp.*
Moek[267]	citreamicin δ	2008		*streptomyces vinaceus*
Moore[268]	neocitreamicin	2008	Sandy soil, Falmouth, Massachusetts	
Qian[269]	citreamicin B	2013	Coast, Red Sea	*streptomyces caelestes*

3.2: Biosynthetic Studies of the Citreamicins

In 1991, Carter fed a culture of *Micromonospora citrea* ^{13}C enriched acetates and isolated citreamicin to see where the ^{13}C atoms were incorporated (Figure 2.4).[289] Feeding acetate enriched in ^{13}C at the carbonyl showed incorporation all around the molecule, confirming that citreamicin is a type II polyketide (Figure 2.4, **3.28**). This feeding experiment revealed that the "amino acid" moiety that comprises the G ring is in fact acetate based. Strangely, this experiment revealed incorporation at C7, C8 and C16, which would not be expected unless some rearrangement had taken place. Feeding the bacterial culture acetate enriched in ^{13}C at the methyl group showed no incorporation at those positions, confirming the previous result. Interestingly this experiment also revealed that the origin of both the geminal groups at C27 are the methyl groups of acetate (Figure 2.4, **3.29**). Radiolabeled methionine revealed that the methyl groups on C11 and C12 are most likely introduced *via S*-adenosyl methionine (SAM) (Figure 2.4, **3.31**).[289] Feeding the bacterial culture acetate enriched in ^{18}O or under an ^{18}O atmosphere revealed that, as expected, most oxygen atoms originate from acetate, however, the oxygen atoms at C11 and C17 come from molecular oxygen (Figure 2.4, **3.32**). This stands in contrast to the feeding experiments done on lysolipin (**3.15**), which determined that the isoquinolone ring may come from an amino acid and that both of the oxygen atoms in the xanthone moiety come from molecular oxygen.[287,289, 290] These feeding studies reveal that despite the structural similarity between the polycyclic xanthone natural products, there exists a great deal of variation in the biosynthesis.

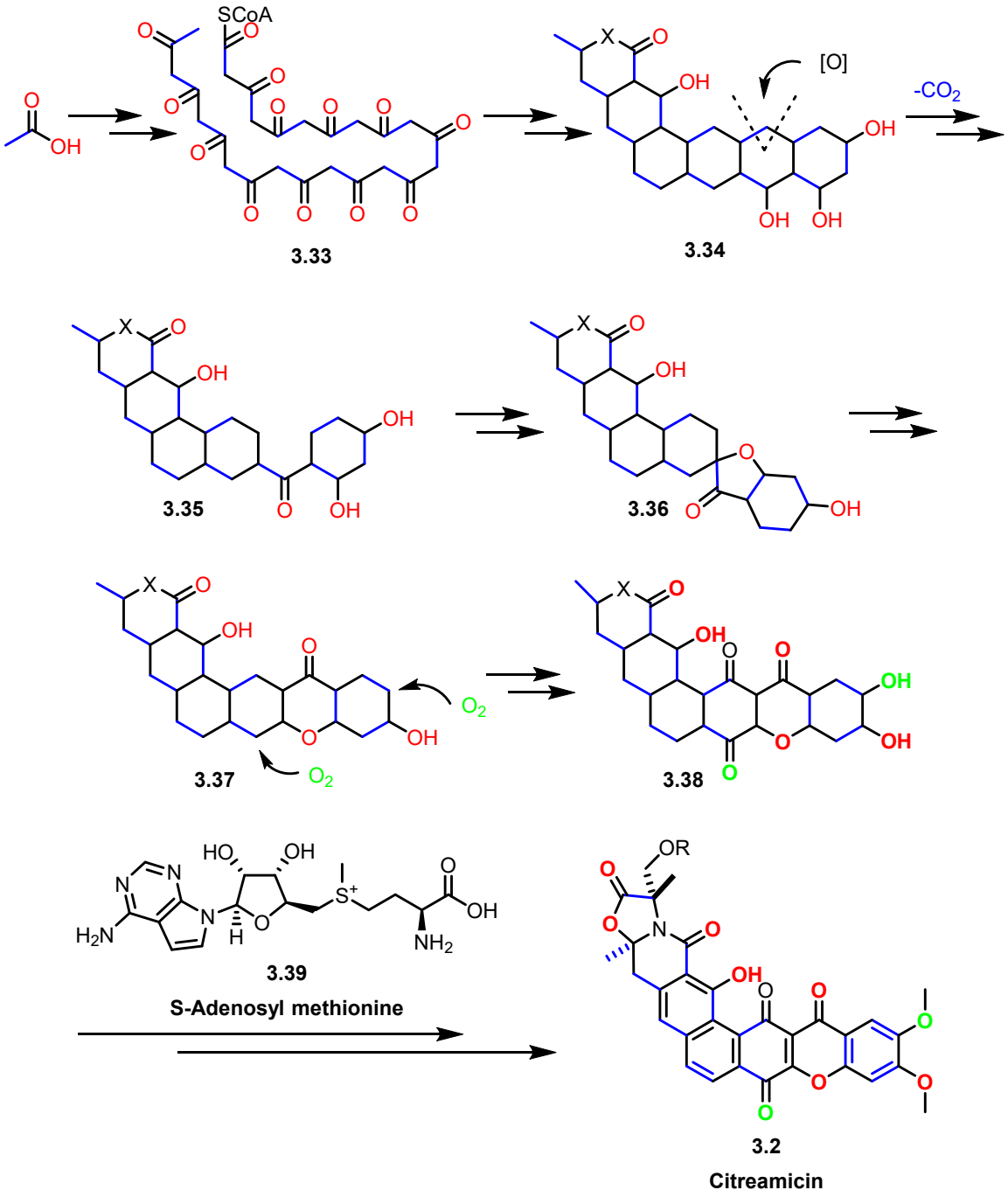
Figure 3.4: ^{13}C and ^{18}O labeled feeding studies on the biosynthesis of citreamicin



These results led Carter and Pearce to propose the following putative biosynthetic sequence (Scheme **3.1**).[289] Acetates are coupled together by polyketide synthase to form **3.33**,

and the chain then cyclizes to form a structure like **3.34**. One of the carbon atoms is oxidatively excised to give a compound like **3.35**. Intermediate **3.35** then cyclizes to the spirocycle **3.36**, which rearranges to **3.37**. The exact order of events is not certain, but at some point, the compound is oxidized at C17 and C12 by oxygenase enzymes to form a structure like **3.38**. The oxygen atoms are then methylated by SAM and acetates condensed onto C27 to form the G ring of citreamicin **3.2**.

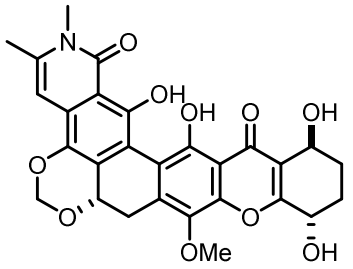
Scheme 3.1: Carter and Pearce's biosynthetic proposal for the citreamicins[289]



3.3: Previous synthesis of polycyclic xanthone natural products

The impressive biological activity and the challenging densely-functionalized hexacyclic core of the polycyclic xanthone natural products caught the attention of the Martin group that culminated in the synthesis of IB-00208 (**3.14**) aglycon (Figure 2.5).[345,346] The total syntheses of cervinomycin (**3.17**),[291,300,304] kibdelones A (**3.23**) and C (**3.25**),[307,314,317] simaomicin α (**3.22**),[318] and FD-594 (**3.13**)[323] have been reported by other groups as well as synthetic studies toward lysolipin (**3.15**)[329-332] and Sch-56036[333] (Figure 2.5, 2.6). As of 2016, no syntheses of citreamicin, xantholipin (**3.16**), albofungin (**3.27**), kigamicins (**3.20**), or actinoplanone (**3.26**) have been reported.

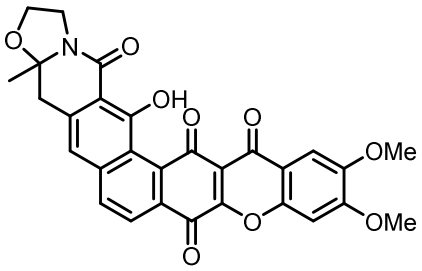
Figure 3.5: Summary of the synthetic work towards polycyclic xanthone natural products



3.5

Simaomicin α

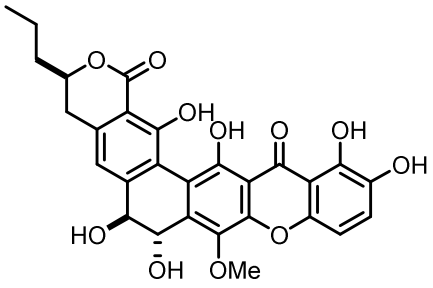
Ready 2013: 26 steps LLS, 36 steps total, 6.8%[318]



3.17

Cervinomycin A_2

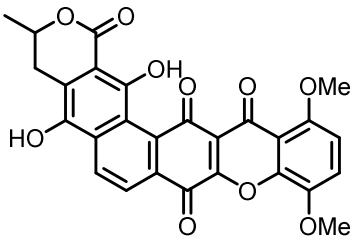
Kelly 1989	11 steps LLS	17 steps total, 6.5%[291]
Rao 1991		26 steps total, 2.4%[300]
Mehta 1994	19 steps LLS	22 steps total, 2.8%[304]



3.13

FD-594 (aglycone)

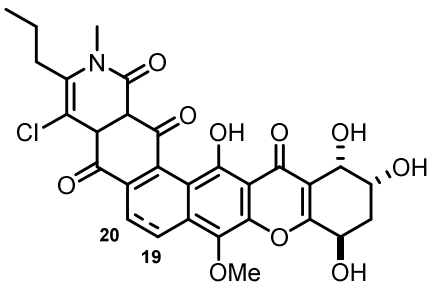
Susuki 2009: 33 steps LLS, 45 steps total, 10.7%[323]



3.14

IB-00208 (aglycone)

Martin 2015: 22 steps LLS, 29 steps total, 1.3%[345,346]



3.23, 3.25

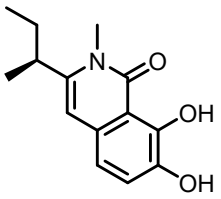
Kibdelone A Δ^{19}, B

Ready 2011	Kibdelone C: 21 steps LLS, 33 steps total, 1.02%[307]
Porco Jr. 2011	Kibdelone C: 18 steps LLS, 33 steps total, 1.4%[314]
Porco Jr. 2013	Kibdelone A: 15 steps LLS, 25 steps total, 0.8%[317]

In addition to the total syntheses, studies on the synthesis of the AB rings in Sch-56036 (**3.21**)[333] and the BCD rings of lysolipin (**3.15**)[329-332] have also been accomplished (Figure 2.6).

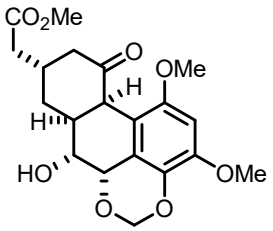
Though TMC-66 (**3.40**) is not in the polycyclic xanthone family of natural products, the synthesis of the G ring is informative.

Figure 3.6: Summary of approaches to the core or other relevant synthetic work towards polycyclic xanthone natural products



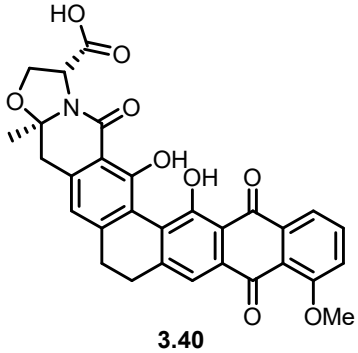
3.238

Barrett 2005 (AB core) 8 steps LLC, 11 steps total 35%[333]



3.231

Duthaler 1985 (BCD core): 21 steps,2.5%[329-332]



3.40

TMC-66

Hosokawa 2007: 9 steps LLC, 12 steps total 21.2%[326]

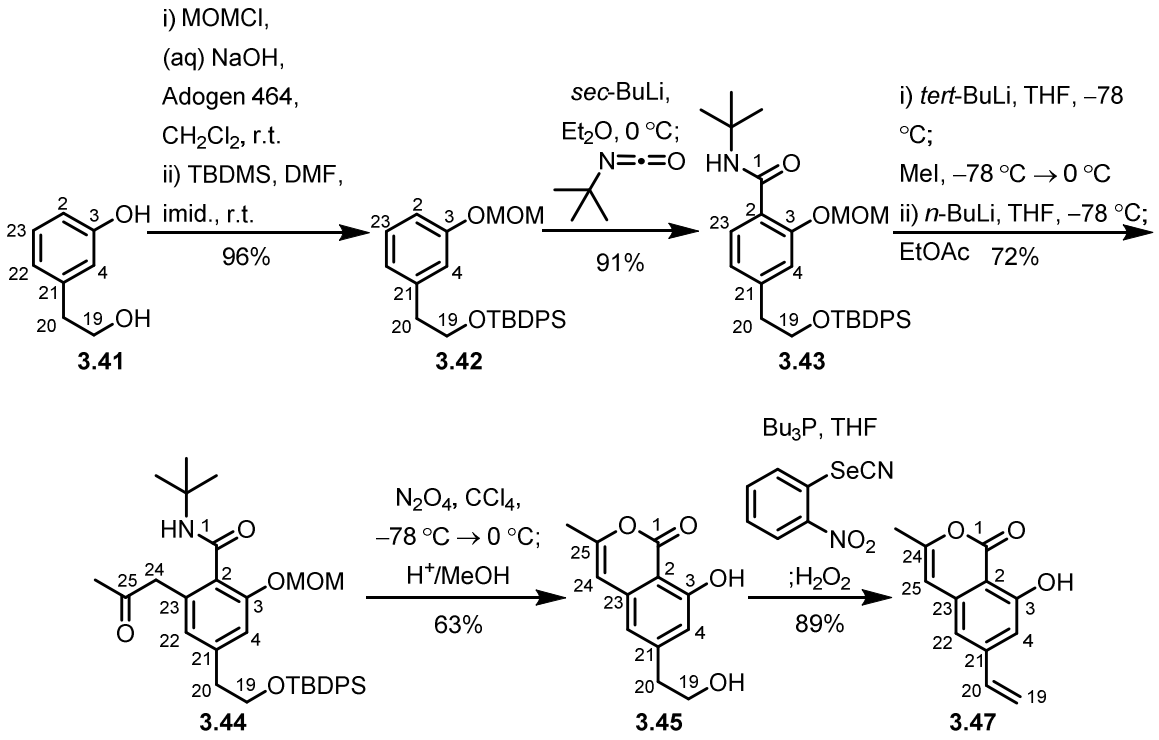
3.3.1: CERVINOMYCIN, KELLY

Cervinomycin (**3.17**) is the polycyclic xanthone natural product that shares the most similarity to citreamicin, the only difference being the tetrahydrooxazolo-[3,2-b]- isoquinolinone moiety in the G-ring. Cervinomycin (**3.17**) was the first member of the polycyclic xanthones to succumb to total synthesis by Kelly in 1989.[291] Kelly's key strategy involved joining the GAB and DEF ring fragments together *via* a Heck coupling, followed by an electrocyclization to form the C ring.

The triple ortholithiation sequence from **3.41** to **3.44** was originally developed by Kelly in 1988 for the synthesis of fredericamycin A.[292] Protection of alkoxy-phenol **3.41**, as the *tert*-

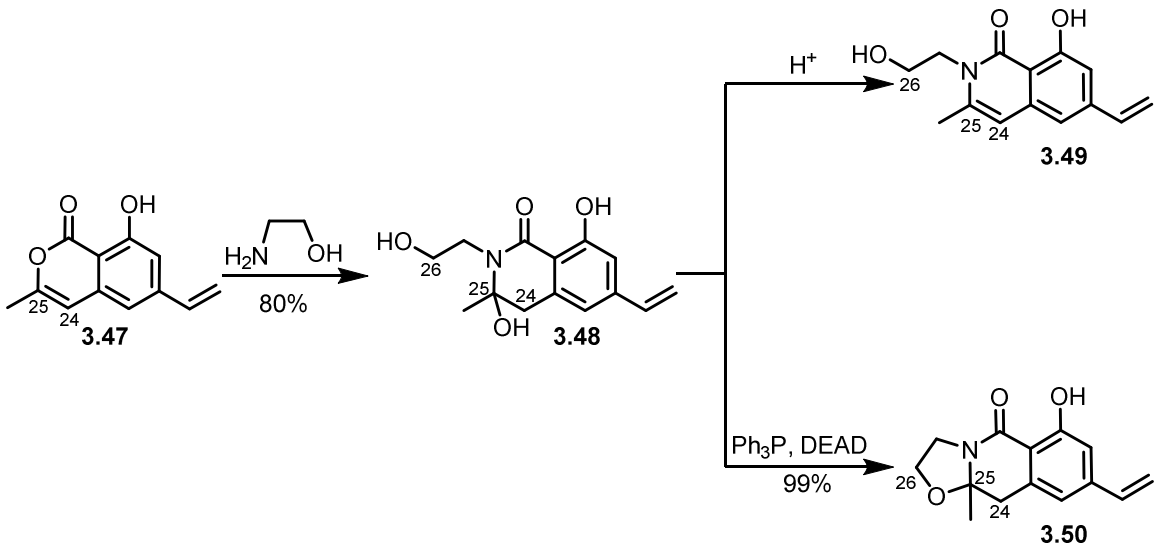
butyldiphenylsilyl (TBDPS) and MOM ether respectively furnished **3.42** (Scheme 3.2). Ortho-lithiation of compound **3.42** under kinetic conditions occurred selectively at C2, and quenching with *tert*-butyl isocyanate gave the *tert*-butyl amide **3.43**. The selectivity (C2 vs. C4) of the ortho-lithiation of meta-substituted MOM-ethers is determined by the chelating or electron withdrawing ability of the group at C21.[293-295] The *tert*-butyl amide moiety in **3.43** directed the next two subsequent lithiations, first at C23, which was methylated with methyl iodide, then at the methyl group to form the benzyl anion, which was quenched with ethyl acetate to give the aryl acetone **3.44**. The *tert*-butylamide was converted to an *N*-alkyl-*N*-nitroso amide by treatment with dinitrogen tetroxide (N_2O_4), which fragments to release nitrogen gas and form the *tert*-butyl ester.[269-268] The *tert*-butyl ester, MOM group and the TBDPS group were all removed with acidic methanol, and subsequent cyclization gave isocoumarin **3.45**. Finally, Grieco elimination (ArSeCN, Bu_3P; H_2O_2) delivers styrene coupling partner **3.47**.[299]

Scheme 3.2: Synthesis of isocoumarin **3.47** from **3.41**



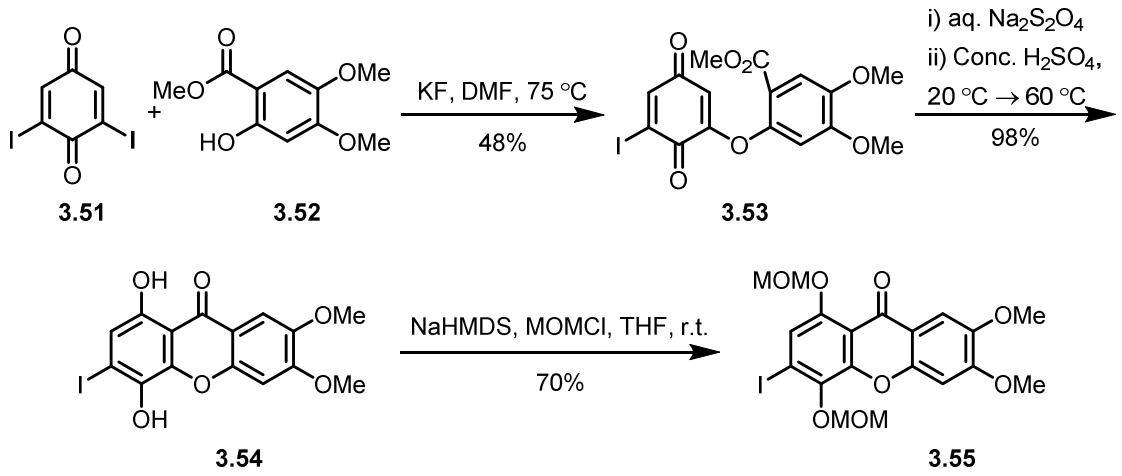
Transformation of the isocoumarin **3.47** to the tetrahydrooxazolo-[3,2-b]- isoquinolinone **2.50** was not straightforward (Scheme 3.3). Condensation of **3.47** with ethanolamine under reflux, or under acidic conditions failed to provide the desired product, instead leading to the isoquinolone **3.49**. Rather than make the alcohol at C26 the nucleophile, Kelly utilized the tertiary alcohol at C25 as the nucleophile in a Mitsunobu reaction to give the desired isoquinolone **3.50** in excellent yield.

Scheme 3.3: Synthesis of GAB ring fragment **3.50**



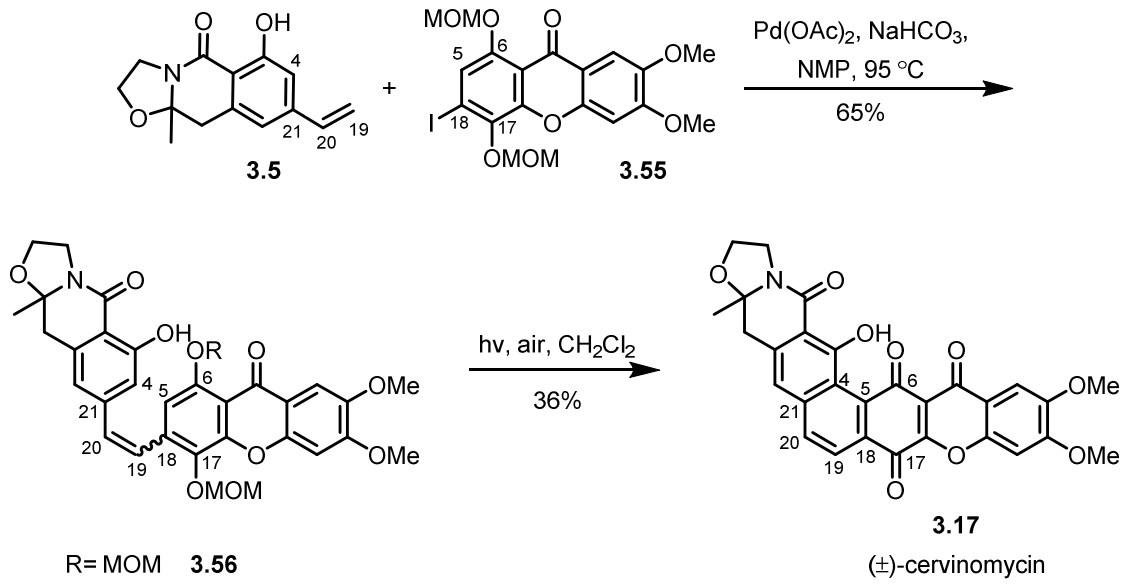
The synthesis of the xanthone coupling partner began with a conjugate addition of phenol **3.52** to bis-iodo quinone **3.51** to furnish quinone **3.53** (Scheme 3.4). The quinone moiety was reduced to the hydroquinone with sodium bisulfite and subsequent Friedel-Crafts cyclization with sulfuric acid provided the xanthone **3.54**. The xanthone was then protected as the bis-MOM ether with NaHMDS to give **3.55**.

Scheme 3.4: Synthesis of xanthone fragment **3.55**



Heck coupling of fragment **3.55** and styrene **3.50** gave the key step precursor **3.56** as a mixture of double bond isomers (Scheme 3.5). Oxidative photo-electrocyclization of **3.56** resulted in concomitant deprotection of both MOM groups and gave cervinomycin (**3.17**) in only 11 steps and in 6.5% overall yield from **3.41**.

Scheme 3.5: Kelly's completion of (±)-cervinomycin (**3.17**)



Kelly's landmark synthesis remains the shortest of the total synthesis of the cervinomycin (**3.17**) and also the shortest synthesis of any member of the polycyclic xanthone family. This is attributed to the strategic use of protecting groups and minimal redox manipulations. The synthesis features the first use of a photo-electrocyclization to close the C ring after joining the GAB (**3.5**) and DEF (**3.55**) fragments together. Kelly also utilized an interesting "umpolung" strategy to close the G ring by using Mitsunobu conditions to turn the pendant alcohol of ethanolamine in **3.48** from a nucleophile to and electrophile, avoiding the formation of the isoquinolone byproduct **3.49**.

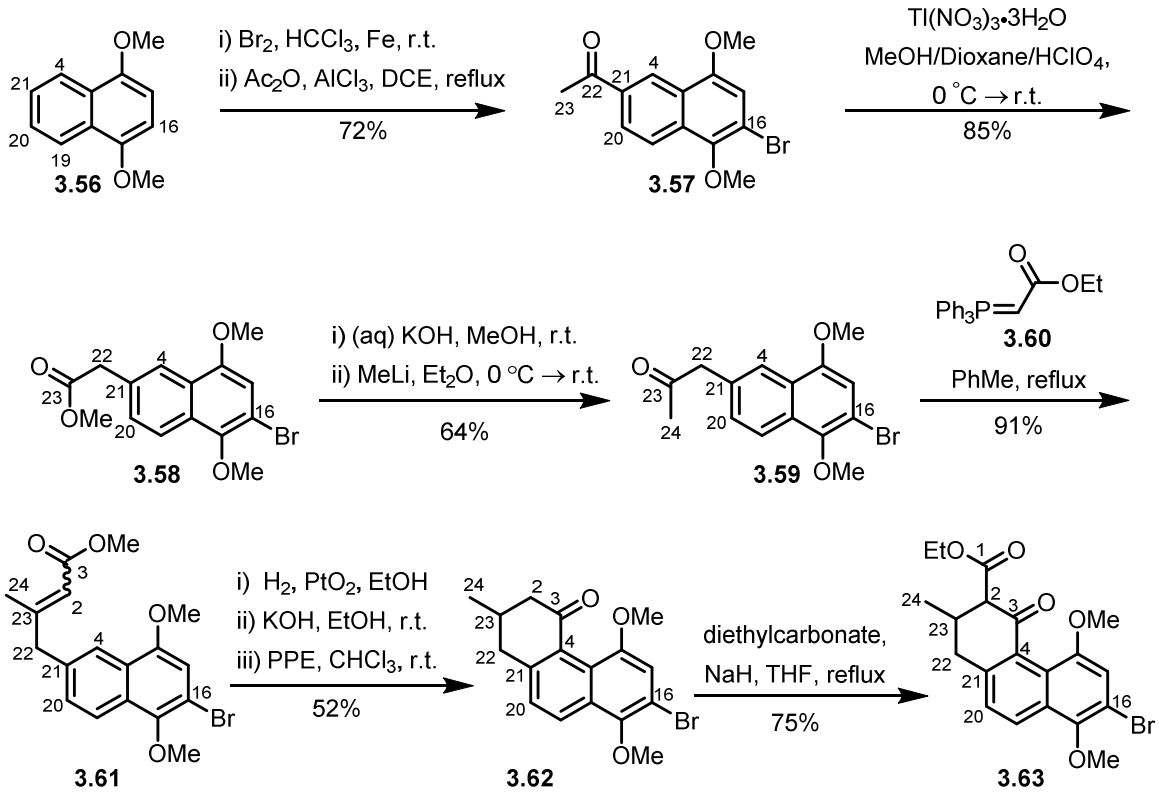
3.3.2: CERVINOMYCIN, RAO

Rao published his synthetic studies towards the GABC rings of cervinomycin (**3.17**) in 1988,[301] when he completed the synthesis of the tetrahydrooxazolo-[3,2-b]- isoquinolinone moiety, and in 1991 he published a total synthesis.[300,302]

The di-methoxy naphthalene **3.56** was brominated and selectively acylated at C21 under conditions reported by Zollinger to give the aceto-napthalene compound **3.57** (Scheme 3.5).[303] The acetyl moiety was oxidatively isomerized with $Tl(NO_3)_3$ to the aryl acetate **3.58**, which was then hydrolyzed and converted to the ketone **3.59** by reaction with methyllithium. Olefination of

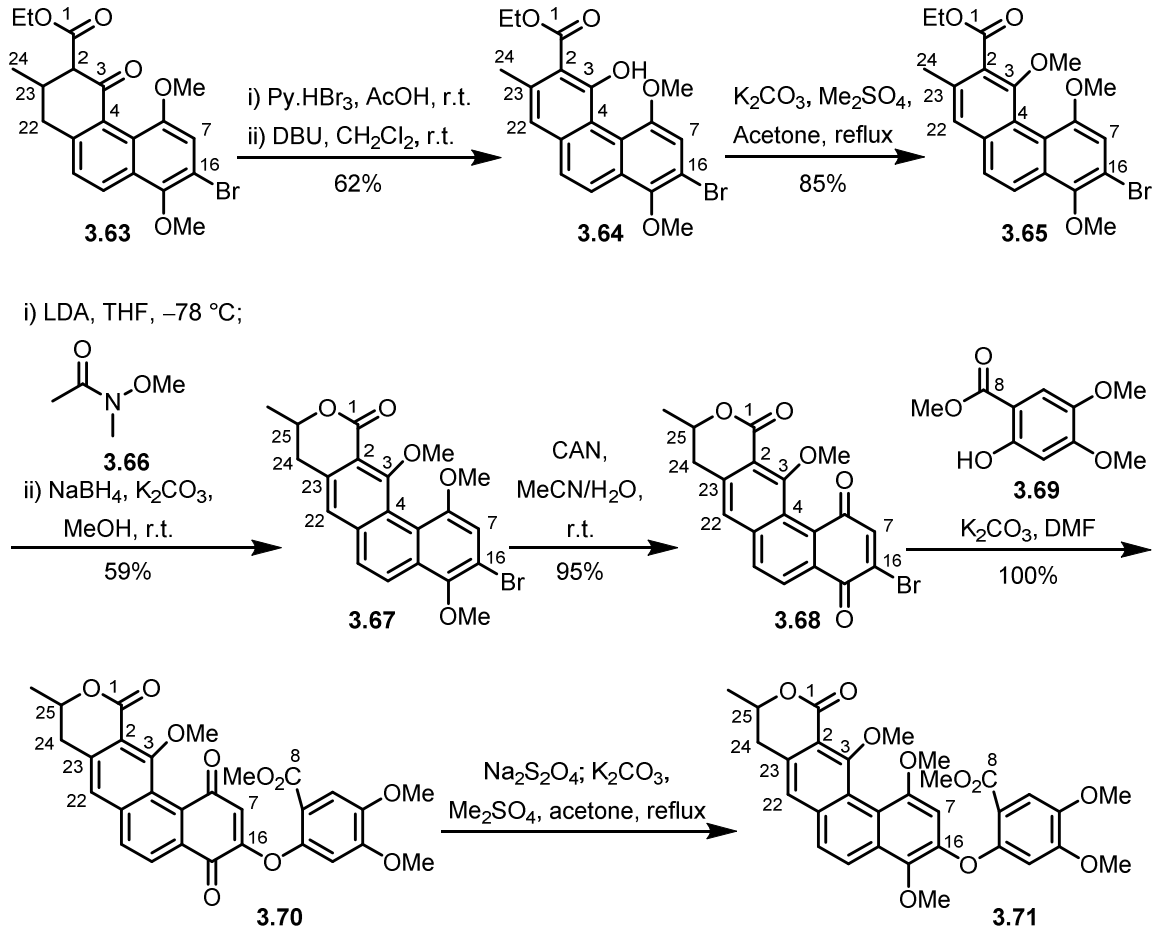
the ketone moiety in **3.59** with the phosphonium salt **3.60** provided **3.61** as an inconsequential mixture of olefin isomers that was hydrogenated with Adams catalyst (PtO_2). The ester was hydrolyzed to the acid and Friedel-Crafts cyclization with polyphosphoric ester (PPE) provided tricyclic compound **3.62**. Claisen condensation of compound **3.62** with diethylcarbonate furnished the BCD ring fragment **3.63**.

Scheme 3.5: Synthesis of the BCD ring fragment **3.63** from napthalene **3.56**



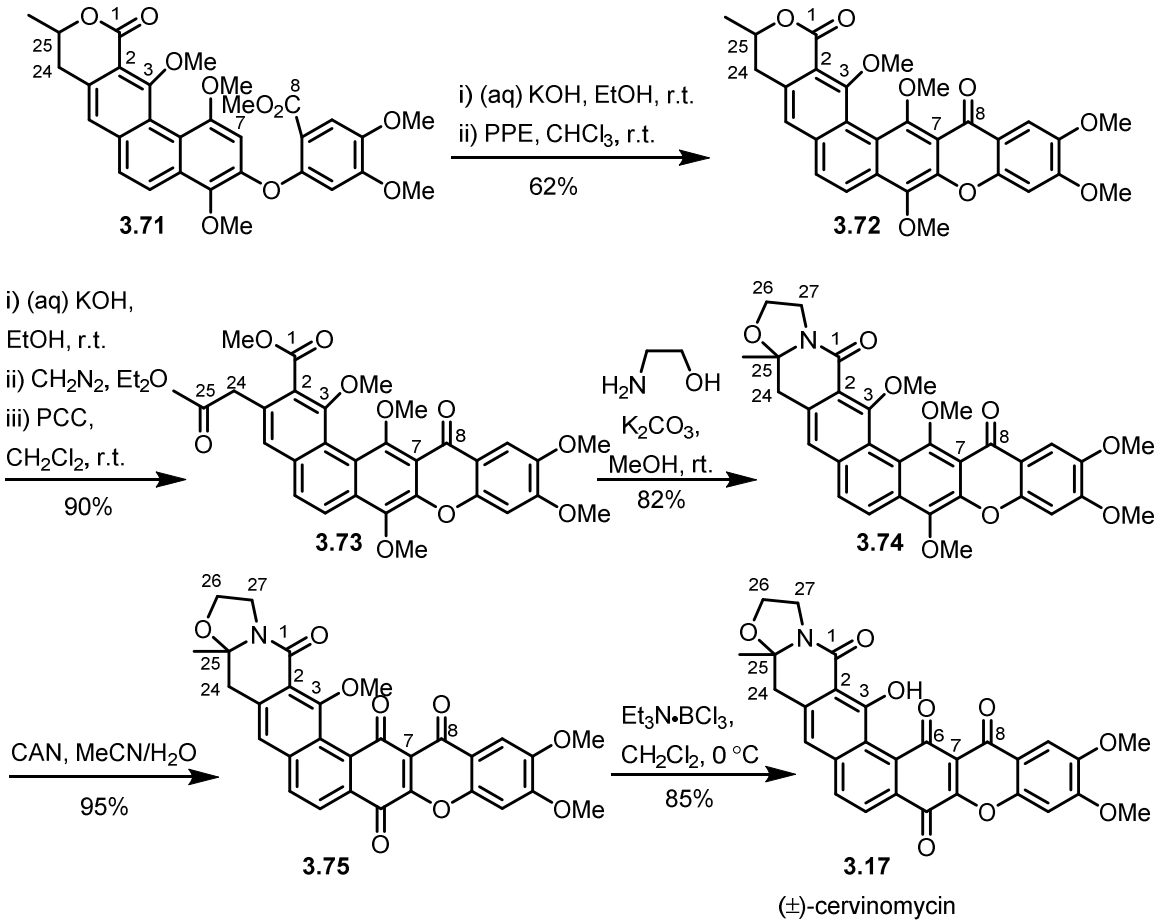
The malonate **3.63** was brominated at C2 with pyridinium hydrogen perbromide ($Pyr{\bullet}HBr_3$) (Scheme 3.6). Treatment of the resulting α-bromo compound with DBU formed the phenol **3.64**, which was protected as the methyl ether **3.65**. Deprotonation at the benzyl position, followed by quenching with the Weinreb amide **3.66** gave a homo phthalate that was reduced to the lactone **3.67**. The hydroquinone methyl ether in **3.68** was then unmasked with CAN and coupled to phenol **3.69** *via* an addition-elimination to furnish **3.70**. The quinone was then reduced and reprotected as the bis-methyl ether **3.71**.

Scheme 3.6: Synthesis of the ABCDF ring fragment **3.71**



The ester moiety in **3.71** was hydrolyzed and cyclized to the xanthone with polyphosphate ester (PPE) to provide the core compound **3.72** (Scheme 3.7). The lactone was hydrolyzed and the C25 alcohol was oxidized to provide the aryl-acetone compound **3.73**. Condensation of **3.73** with ethanolamine formed the tetrahydrooxazolo-[3,2-b]- isoquinolinone **3.74**, which was prone to aromatization to form an isoquinolone in the presence of acid, heat and even silica (see Figure 3.7). Deprotection of the hydroquinone methyl ether with CAN provided cervinomycin monomethyl ether **3.75**, and deprotection of the C3 methoxy group with BCl_3•Et_3N gave cervinomycin (**3.17**) in 25 steps from **3.56** and 2.4% overall yield.

Scheme 3.7: Rao's completion of (±)-cervinomycin (**3.17**)

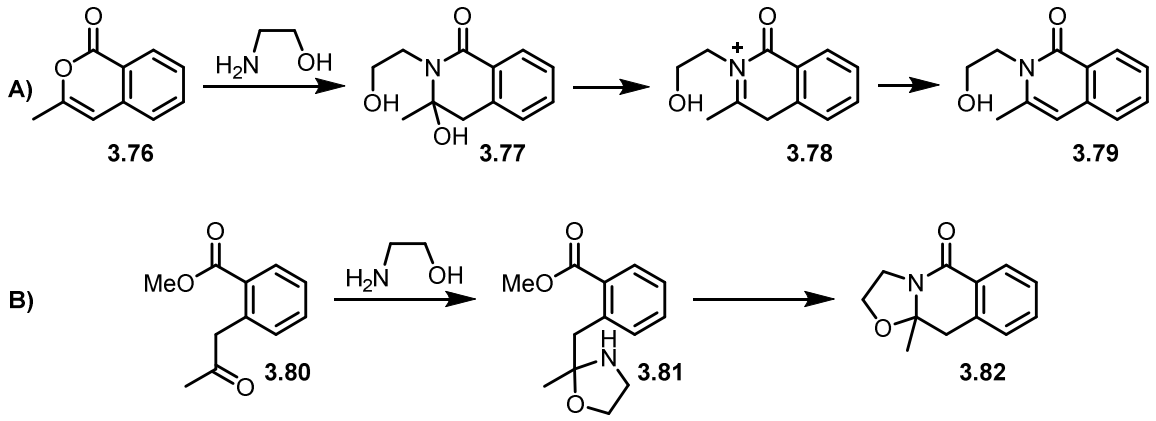


Although no new methodology was developed in Rao's synthesis of cervinomycin (**3.17**), he did establish important conditional tolerances for late-stage oxidations of the hydroquinone and for the tetrahydrooxazolo-[3,2-b]-isoquinolinone moiety, Namely, compound **3.75** was stable to oxidation with CAN and selective demethylation using BCl_3•Et_3N. The high step count is a result of seven protection/deprotection steps and six redox adjustments, which together, make up half of the total step count.

The initial plan was to condense ethanolamine onto the isocoumarin counterpart to give **3.73** (see Scheme 3.6, **3.73** → **3.74**). Condensation in methanol at room temperature led to the desired product in nearly quantitative yield. Condensation of ethanolamine with the aryl-acetone **3.73** in refluxing methanol or from the analogous isocoumarin, however, led to the byproduct analogous to **3.79**. Rao's hypothesis for the observed difference stems from a mechanistic

difference between the condensation of ethanolamine on the isocoumarin and the aryl-acetone (Figure 3.7). Condensation of ethanolamine onto the homo-phthalate **3.80** led to the *N*,*O*-ketal **3.81**, which subsequently cyclizes onto the ester to form the GAB ring compound **3.82** with minimal formation of the isoquinolone **3.79** (Figure 3.7, **B**). Addition of ethanolamine into the isocoumarin leads to the N,O-hemiaminal **3.77** *via* the *N*-acyliminium ion **3.78**, which is very acidic and can either cyclize to form **3.82** or be deprotonated to form the isoquinolone **3.79** (Figure 3.7, **A**).

Figure 3.7: Mechanistic differences between isocoumarin and aryl-acetone condensation

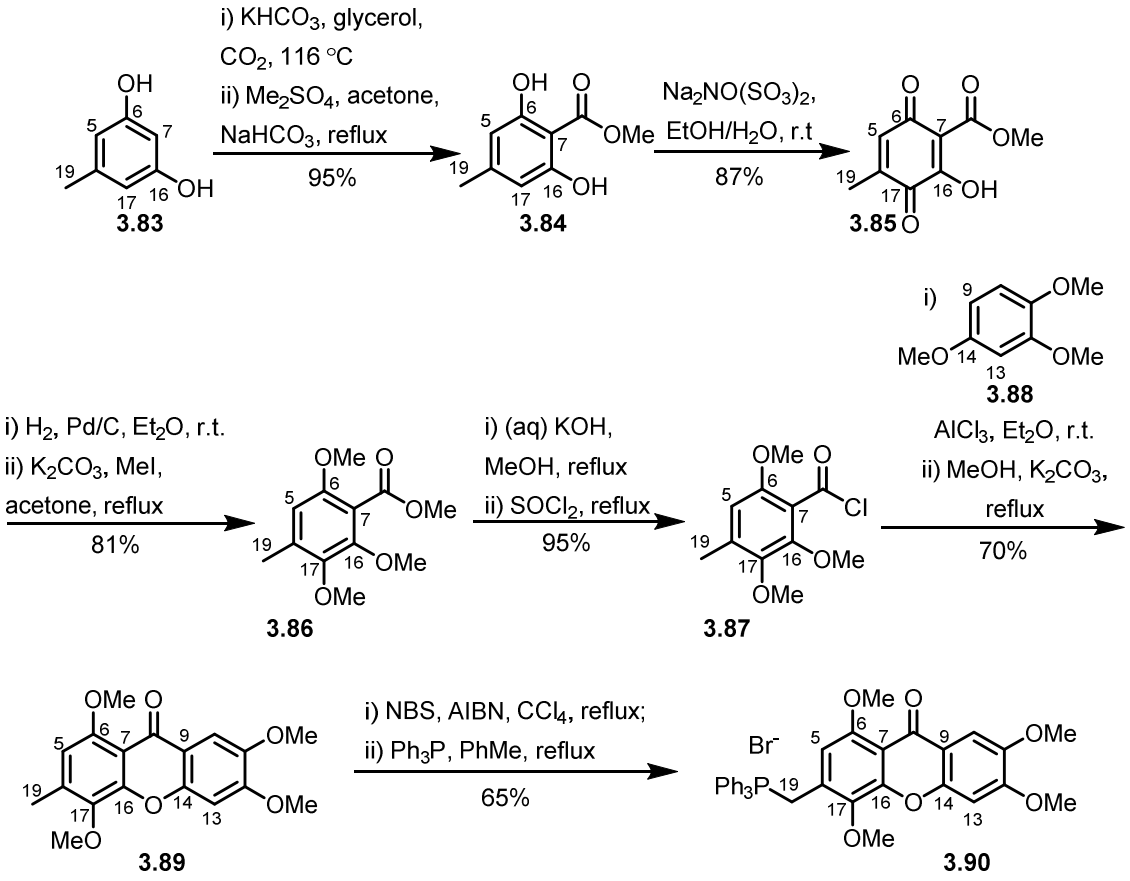


3.3.3: CERVINOMYCIN METHYL ETHER, MEHTA

In 1991,[304,305] Mehta published his approach to cervinomycin (**3.17**) methyl ether, beginning with the known ester **3.86**, which was synthesized in a five step sequence from orcinol (**3.83**) (Scheme 3.8).[306] Kolbe-Schmitt carboxylation of orcinol (**3.83**) followed by methylation gave ester **3.84**. Oxidation of ester **3.84** with Fremy's salt ($Na_2NO(SO_3)_2$) then furnished quinone **3.85**. Reduction of the quinone to the hydroquinone and subsequent protection as the dimethyl ether gave **3.86**. The ester moiety was hydrolyzed and transformed to the acyl chloride **3.87**, which was then coupled to 1,2,5-trihydroxy benzene **3.88** *via* a Friedel-Craft reaction to form a mixture of C14 hydroxyl and methoxy compounds. Cyclization of the mixture gave the xanthone **3.89** and returned C14 methoxy compound, which could be demethylated and resubjected to the

reaction conditions. Radical bromination of the C19 methyl group and displacement with triphenylphosphine gave Wittig precursor **3.90**.

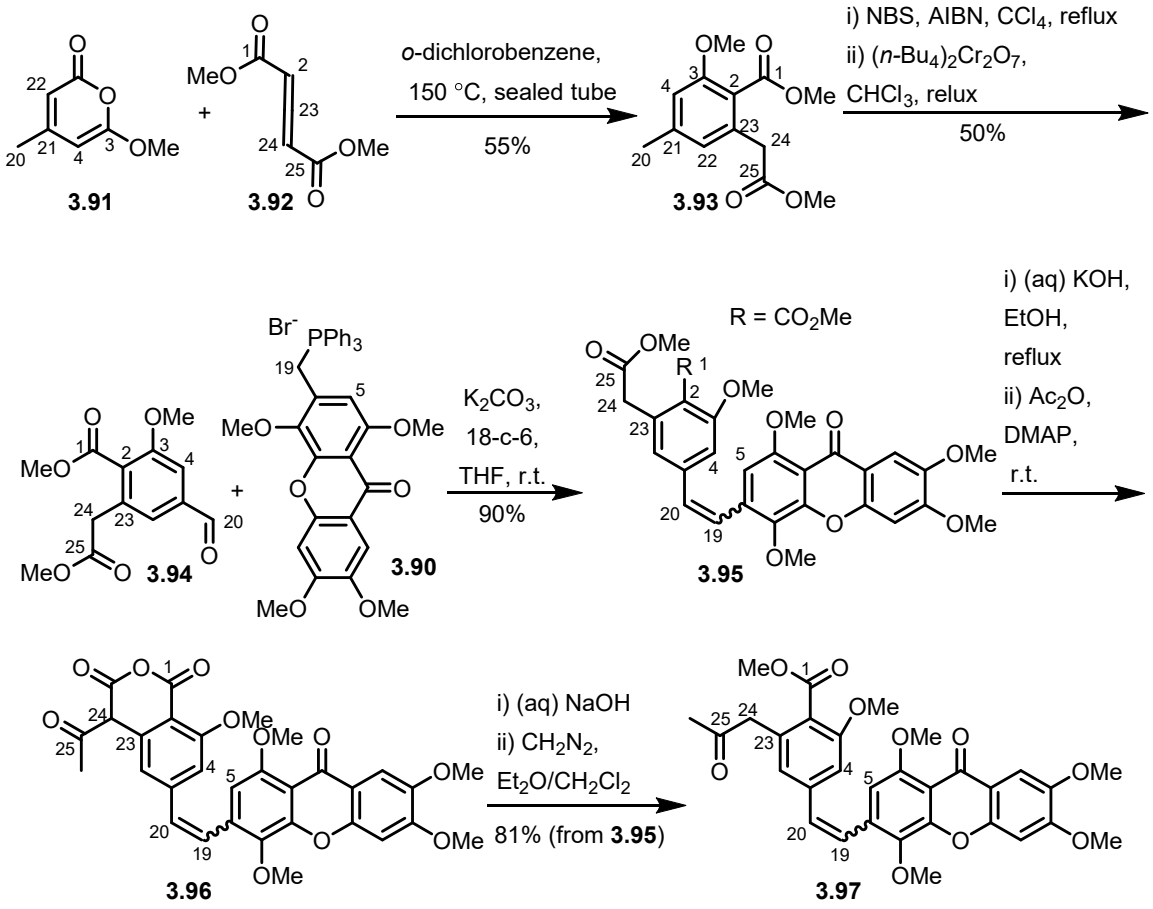
Scheme 3.8: Mehta's synthesis of xanthone coupling fragment **3.90**



The B ring fragment was synthesized *via* a Diels-Alder reaction of pyrone **3.91** and allene **3.92** to give the homo phthalate ester **3.93** (Scheme 3.9). Radical bromination of the C20 methyl group of **3.93**, followed by oxidation of the benzyl bromide to the aldehyde with tetrabutylammonium dichromate ($(n\text{-}Bu_4N)_2Cr_2O_7$) furnished **3.94**. Initial attempts to condense ethanolamine onto **3.93** to form the G ring before oxidation with($(n\text{-}Bu_4N)_2Cr_2O_7$) or radical bromination led to undesired oxidation of the C20 methyl group and/or decomposition of the sensitive tetrahydrooxazolo-[3,2-b]-isoquinolinone ring system. The aldehyde **2.94** was coupled to phosphonium salt **3.90** to give BDEF fragment **3.95** as a mixture of cis and trans double bond isomers, with trans predominating (ratio not reported). Hydrolysis of the ester moiety and a

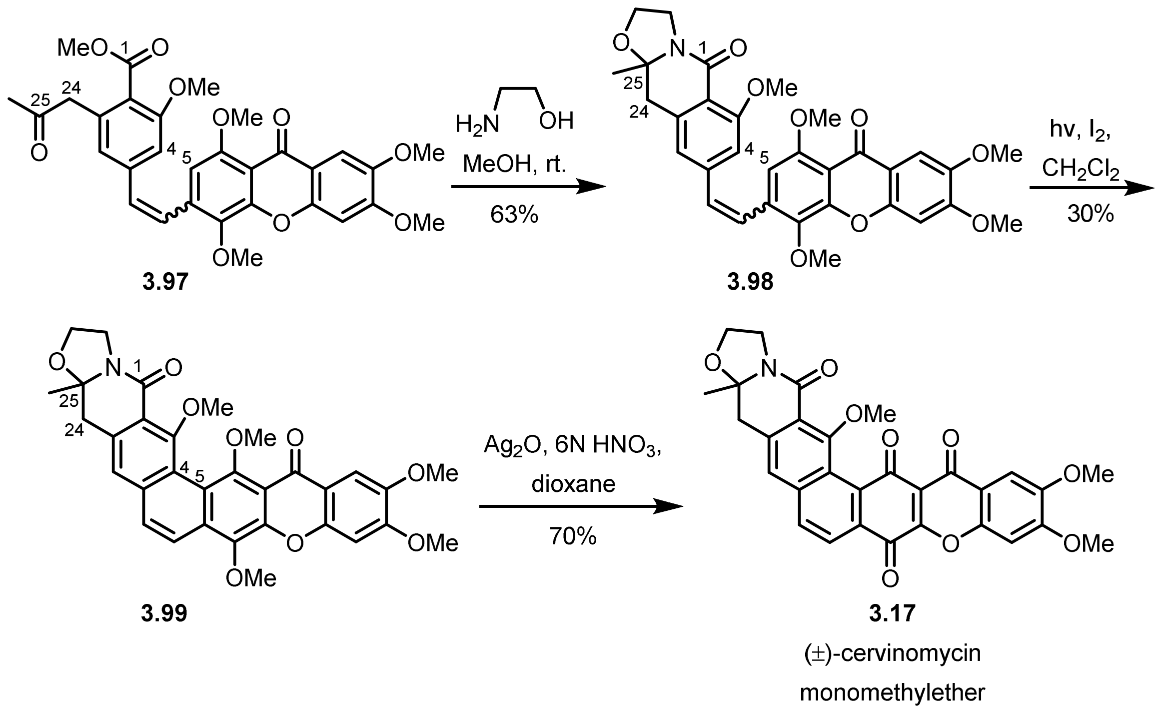
Dakin-West condensation with acetic anhydride gave cyclic anhydride **3.96**. Base induced hydrolysis of the anhydride led to decarboxylation of the malonate moiety to provide the keto-acid, which was esterified with diazomethane to give **3.97**.

Scheme 3.9: Synthesis of aldehyde coupling fragment **3.94** and key Wittig Olefination



Condensation of the keto-ester **3.97** with ethanolamine gave the GABDEF ring compound **3.98** (Scheme 3.10). Interestingly, Mehta reported difficulties in condensing ethanolamine with the isocoumarin, giving him almost exclusive byproduct formation. Photo-electrocyclization gave the cervinomycin trimethylether **3.99**, which was oxidatively deprotected with silver oxide and catalytic nitric acid to give cervinomycin (**3.17**) in 19 steps in 2.8% yield.

Scheme 3.10: Mehta's completion of (±)-cervinomycin (**3.17**)



No new methodology was developed for the synthesis and the photo-electrocyclization key step is almost identical to the one used by Kelly. Of the 19 steps, four were protecting group manipulations and three were redox adjustments. It is interesting that in Kelly's case, photocyclization resulted in oxidation of the hydroquinone to the quinone in addition to the cyclization, while in Mehta's case, only cyclization occurred. This may be due to the removal of the MOM groups under the reaction conditions to the hydroquinone in Kelly's case, while the methyl ethers are too robust to be oxidized or hydrolyzed under the reaction conditions. The final deprotection conditions are intriguing as they reveal that the G ring, which has been demonstrated to be acid sensitive, can tolerate Lewis acids strong enough to remove alkyl groups in the final product.

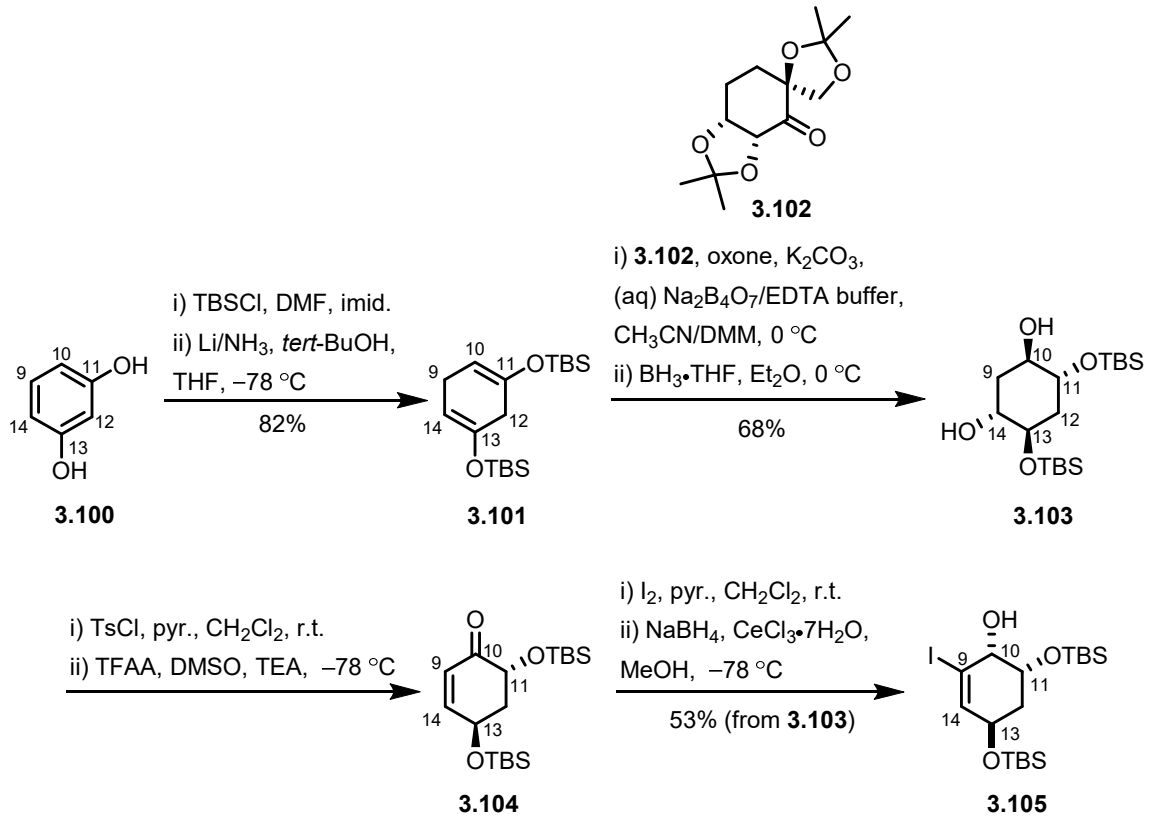
3.3.4: (–)-Kibdelone C, Ready

(+)-Kibdelone C (**3.25**), together with (–)-kibdelone A (**3.23**) and B (**3.24**) were isolated from a timber wool shed near Port Augusta, Australia by the Capon group in 2007.[283] All three kibdelones have nanomolar activity against a number of cancer cell lines. Interestingly,

kibdelones A, B, and C exist as a 3:2:1 equilibrium mixture of redox isomers upon standing in MeOH.[283,284] In 2011 Ready published his total synthesis of (–)-kibdelone C, helping to confirm the absolute stereochemistry of the natural compound as (+)-kibdelone C (**3.25**).[307]

To synthesize the F ring, Ready relied on Myers's asymmetric α-hydroxylation methodology using Shi's catalyst **3.102** on the bis-silyl enolether **3.101** (Scheme 3.11).[308] Reduction of the resulting bis-epoxide *in situ* gave the C2-symmetric tetrol **3.103**. Selective tosylation of the less-hindered, axial C14 alcohol, followed by Swern oxidation of the C10 alcohol, resulted in concomitant elimination of the tosylate to give enone **3.104**. Iodination of the enone at C9, followed by Luche reduction then gave F ring coupling partner **3.105**.[69]

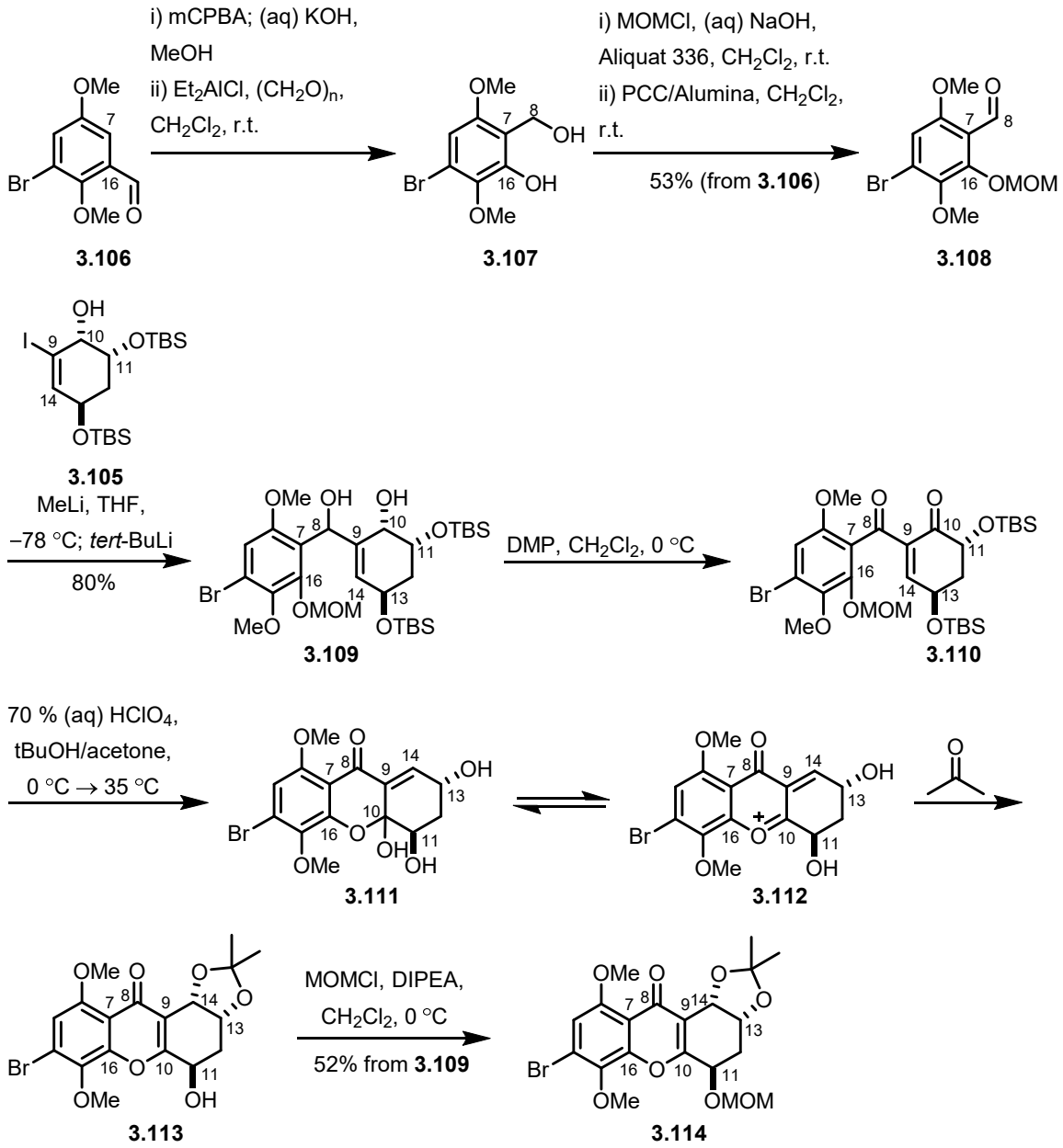
Scheme 3.11: Synthesis of F ring fragment **3.105**



Synthesis of the D ring coupling partner started with Dakin oxidation of the aldehyde **3.106** followed by ortho-selective Friedel-Crafts to give benzyl alcohol **3.107** (Scheme 3.12). MOM protection of the phenol, followed by oxidation of the benzyl alcohol to the aldehyde gave

the D ring coupling partner **3.108**. Lithium-halogen exchange of the F ring fragment **3.105** by first deprotonating with methyllithium, which undergoes exchange slowly, followed by treatment with *tert*-BuLi, and by adding the aldehyde **3.108** gave benzyl alcohol **3.109**. Oxidation of both the C8 and C10 alcohols with dess martin periodinane (DMP) furnished the α,β-unsaturated malonate **3.110**. Exposure of **3.110** to $HClO_4$ in *tert*-BuOH/acetone deprotected the MOM and TBS ethers and facilitated condensation of the phenol onto the C10 ketone to give **3.111**, which was in equilibrium with oxonium **3.122** under the reaction conditions. Acetone condensed onto the C13 alcohol of **3.112** to form the hemi-ketal, which cyclized onto C14 to deliver the tetrahydro xanthone **3.113**. The inclusion of *tert*-BuOH in the deprotection/cyclization step was important to suppress the liberated formaldehyde (from the MOM group) from cyclizing onto the C14 and C13 alcohols. Acetone was necessary to obtain the compound as a single diastereomer because condensation onto the C13 alcohol in **3.112** ensured that the trajectory of the attack by the oxygen atom onto the C14 is from the top face.

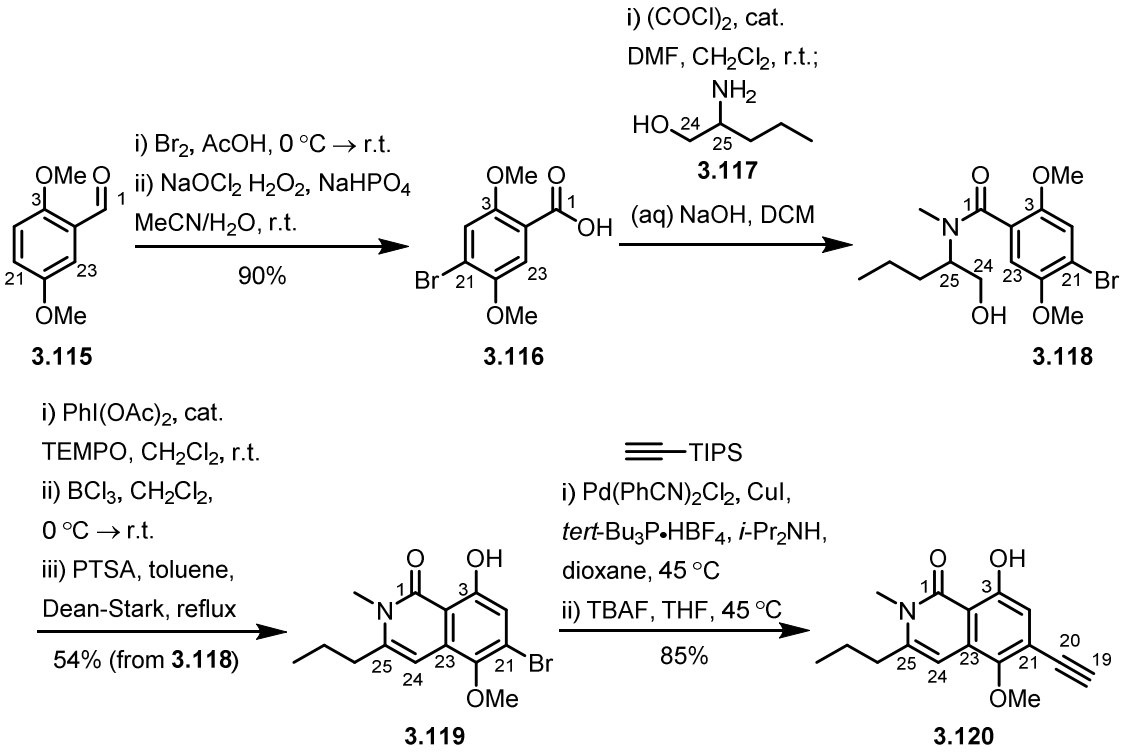
Scheme 3.12: Synthesis of tetrahydro xanthone ring fragment **3.114**



Synthesis of the AB ring fragment began with bromination of aldehyde **3.115**, followed by Pinnick[309,310] oxidation give **3.116** (Scheme 3.13). Activation of the acid as the acid chloride followed by coupling with amine **3.117** gave amide **3.118**. Ley[68] oxidation of the alcohol to the aldehyde set up a Pomeranz-Fritsch like cyclization. Several Lewis acids were screened to affect the cyclization and the removal of the C3 methoxy group, however, only BCl_3 provided the desired product while BBr_3 removed both methyl groups. Acid-catalyzed dehydration of the

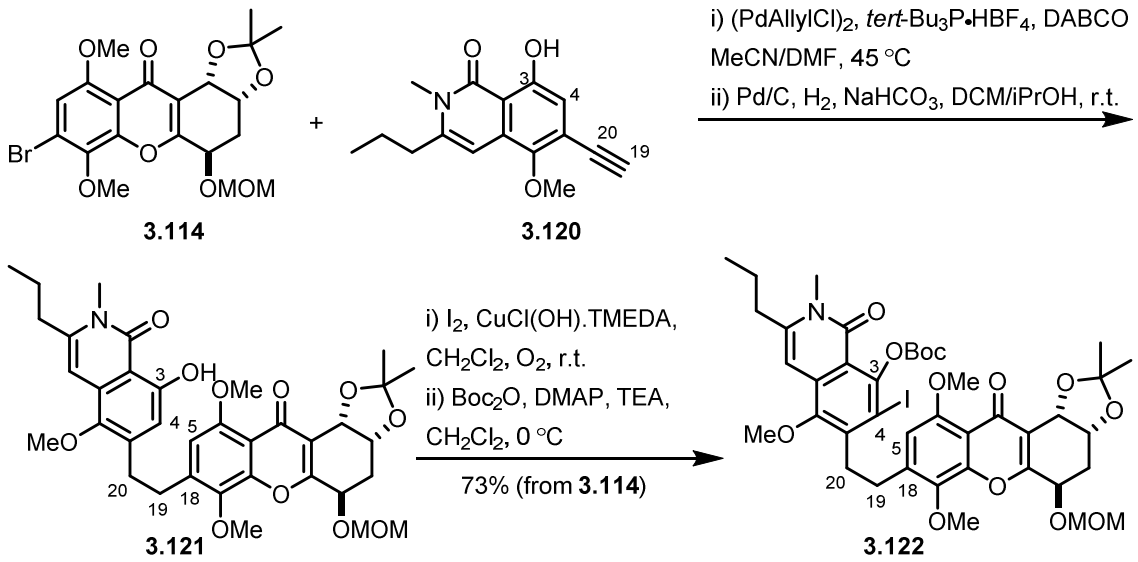
resulting alcohol gave isoquinolone **3.119**, and Sonagashira coupling with TIPS-protected acetylene followed by TBAF deprotection gave AB ring coupling partner **3.120**.

Scheme 3.13: Synthesis of the AB ring fragment **3.120**



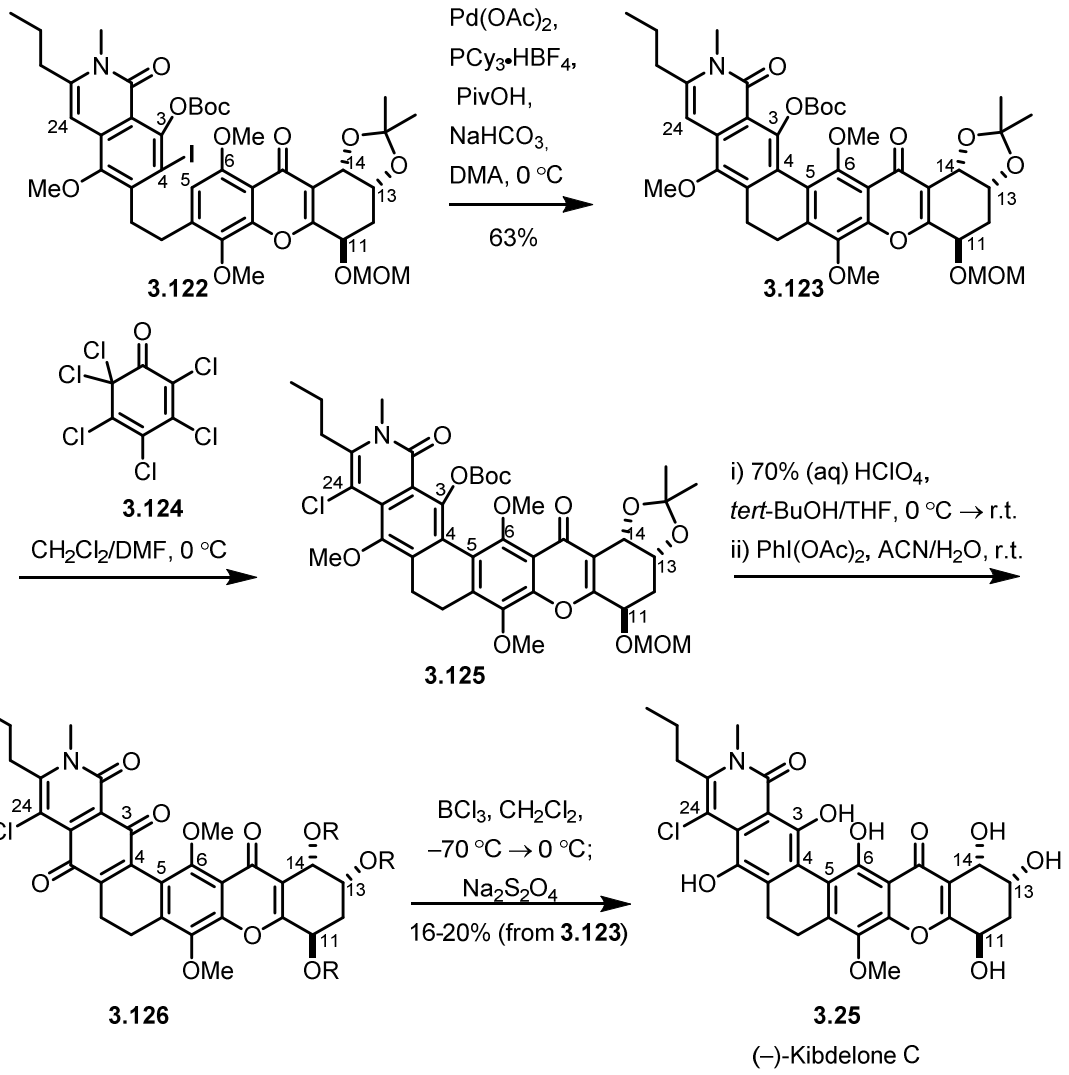
Sonagashira coupling of AB ring fragment **3.120** and DEF ring fragment **3.114** under Soheili's conditions provided the coupled product in 77% yield,[311] which after reduction of the alkyne then gave the ABDEF ring compound **3.121** (Scheme 3.14). Copper free conditions were necessary to achieve high yields due to competitive copper-mediated oxidative dimerization of the AB ring fragment. The ortho-iodination was discovered serendipitously while initially trying to form the C4-C5 biaryl bond via oxidation with Koga's reagent (CuCl(OH)•TMEDA in the presence of iodine. Boc protection then gave **3.122**.

Scheme 3.14: Coupling of AB ring fragment **3.120** to DEF ring fragment **3.114**



The iodination at C4 allowed the biaryl coupling to form the hexacyclic compound **3.123** (Scheme 3.15). Critical for the success of the reaction was protection of the phenol as the Boc carbonate because other protecting groups were unstable to the reaction conditions or gave low yields of **3.123**. Cyclization of the free phenol analogue of **3.122** was very sluggish and resulted in significant amount of de-iodinated material. Chlorination of the isoquinolone at C24 with hexachlorocyclohexadienone **3.124** delivered **3.125** in good yields, but purification led to numerous byproducts stemming from hydration at C25. Global deprotection of the MOM group, acetone ketal, and the Boc group led to a mixture of MOM protected compounds at C11, formaldehyde cyclized product between the C13 and C14 alcohols, and fully deprotected compound. Subjection of the mixture to phenyliodine(III)diacetate (PIDA) furnished the quinone **3.126** as a mixture of compounds, which were fully deprotected with BCl_3 with concomitant demethylation of the C6 methoxy group. Reductive workup with $Na_2S_2O_4$ delivered (–)-kibdelone C (**3.25**) in 21 steps in 1.0% yield.

Scheme 3.15: Ready's completion of (–)-kibdelone C (**3.25**)



The new methodology developed for the total synthesis involves the serendipitous discovery of Koga's reagent (CuCl(OH)•(TMEDA) to facilitate an ortho iodination reaction and subsequent C-H arylation to form the C ring. Although the general strategy for the synthesis of the tetrahydroxanthone unit was originally developed by Nicolaou in 2008 for the synthesis of diversonol and blennolide C,[312] Ready's use of acetone to control the diastereoselectivity at C14 was a useful modification.

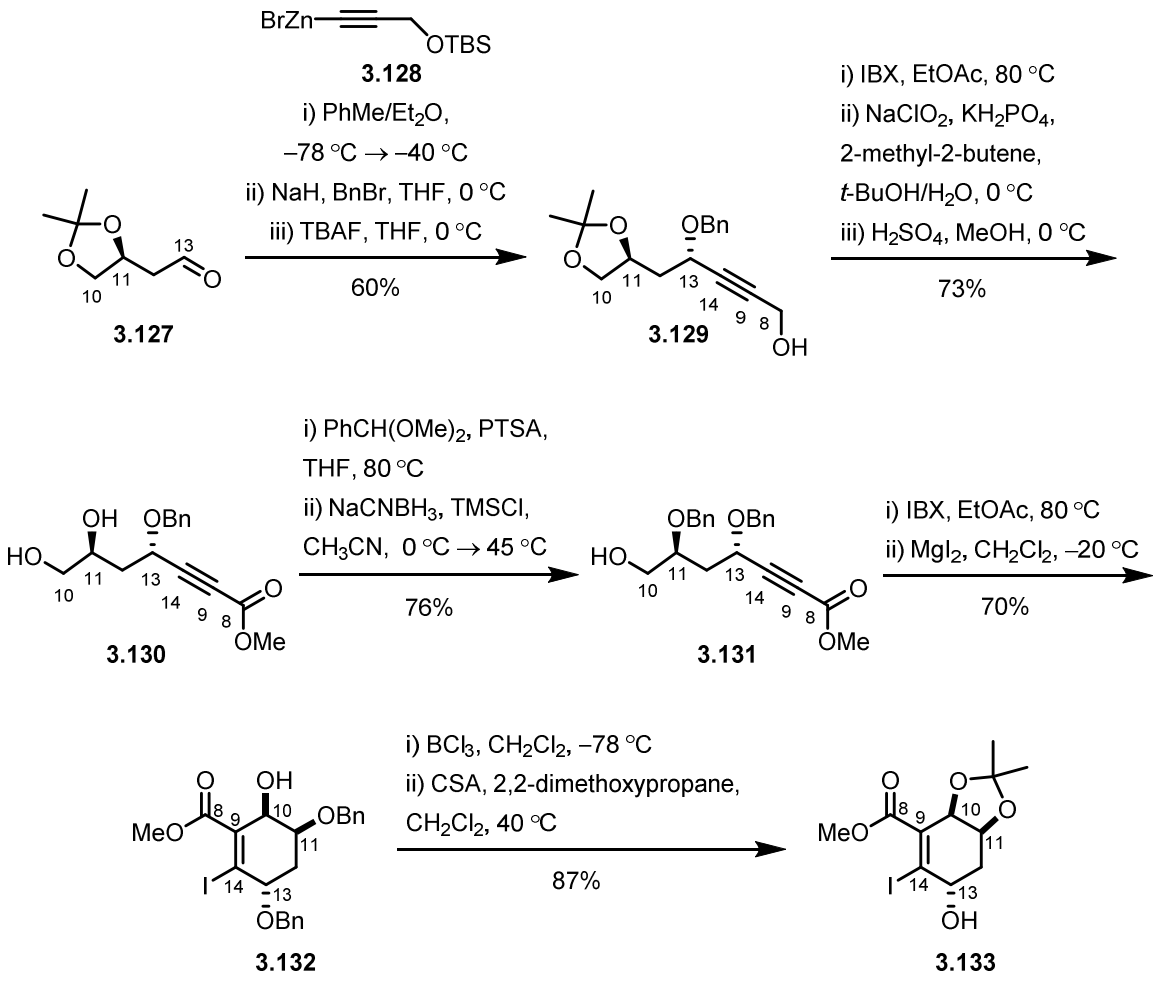
The highly convergent nature of the synthesis manages to mask the 33 total steps. The excessive number of oxidation steps , and six protecting group manipulations accounts for half of the total step count. Additionally, in order to synthesize the natural (+)- kibdelone C (**3.25**), one would need to use the enantiomer of the Shi's catalyst derived from D-fructose, and this requires 10 steps to synthesize.

3.3.5: (+)-KIBDELONE C, PORCO JR.

Porco Jr. published his first synthetic studies toward (+)-kibdelone C (**3.25**) in 2011 when he established the methodology requisite for the fragment couplings as well as biological testing of several intermediates,[313] followed by a total synthesis later in 2011, wherein he confirms the absolute stereochemistry as (+)-kibdelone C.[314]

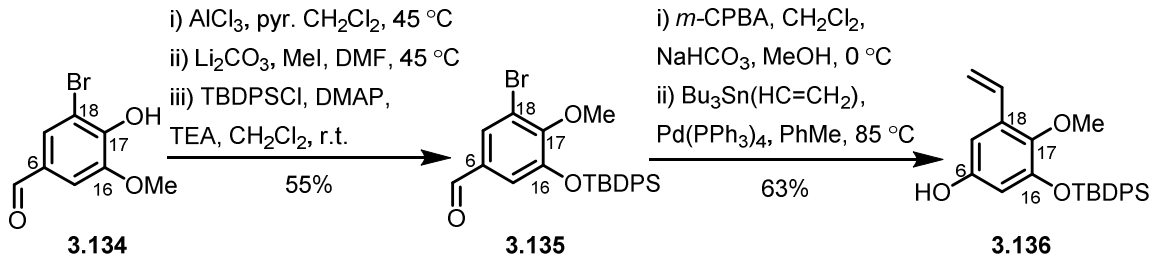
Synthesis of what would become the F-ring in (+)-kibdelone C began with a chelation-controlled addition of the alkynyl zinc reagent **3.128** into aldehyde **3.127** (Scheme 3.16). Protection of the resulting C13 alcohol as the benzyl ether, followed by deprotection of the TBS-protected propargyl alcohol with TBAF gave **3.129**. Oxidation of the propargyl alcohol with IBX, followed by Pinnick oxidation and acid-catalyzed esterification proceeded with concomitant acetal deprotection to give diol **3.130**. Protection of the diol moiety in **3.130** as the benzaldehyde acetal, followed by a reductive ring-opening gave **3.131**. Oxidation of the C10 alcohol to the aldehyde with IBX, followed by MgI_2 catalyzed cyclization gave β-iodoenone **3.132**. Several Lewis acids were screened for the *O*-benzyl deprotection but, only BCl_3 gave clean deprotection. Re-protection of the C10 and C11 alcohols as the acetone ketal gave **3.133**.

Scheme 3.16: Synthesis of F ring fragment **3.133**



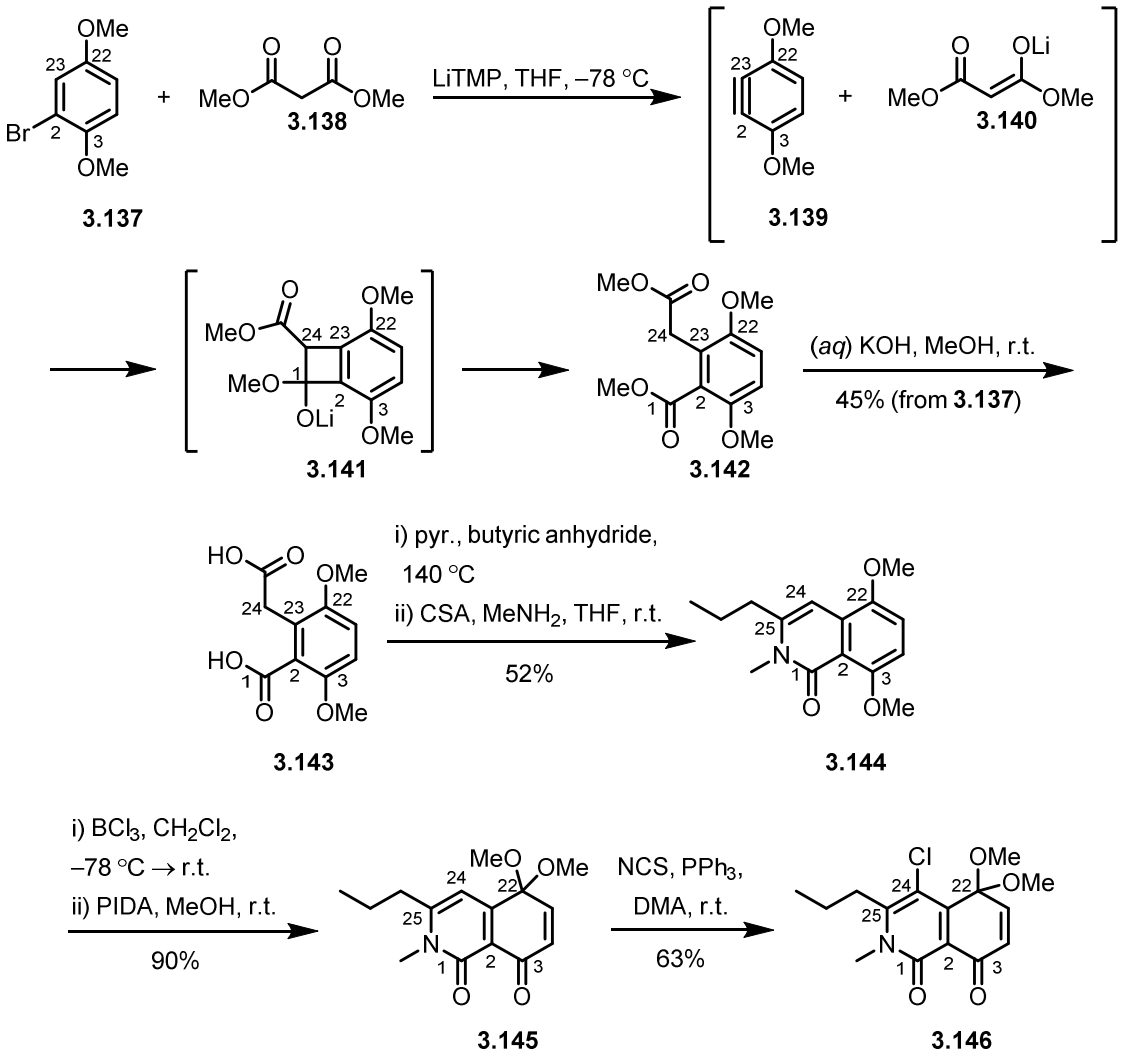
Synthesis of the D ring fragment began with demethylation of aldehyde **3.134** with $AlCl_3$ (Scheme 3.17). Selective methylation of the more acidic C17 phenol, followed by protection of the C16 phenol as the *tert*-butyldiphenylsilyl (TBDPS) ether afforded **3.135**. Dakin oxidation of the aldehyde followed by Stille coupling with vinyltributyltin gave the D ring fragment **3.136**.

Scheme 3.17: Synthesis of D ring fragment **3.136**



Synthesis of the AB ring fragment began with *ortho*-lithiation of the bromo-arene **3.137** at C23 with LiTMP in the presence of dimethyl malonate (Scheme 3.17). The *o*-lithiated bromoarene undergoes an elimination reaction to form benzyne **3.139** that then undergoes a [2+2] cyclization reaction with the enolate of diethyl malonate **3.140** to form the benzo cyclobutane intermediate **3.141**, which then underwent a retro-Claisen to give, the homo phthalate **3.142**. Hydrolysis of the esters with aqueous KOH followed by a Dakin-West condensation with butyric anhydride formed an isocoumarin compound that was subsequently condensed with methylamine to form isoquinolone **3.144**. Selective demethylation of the C3 methoxy with BCl_3, and PIDA oxidation to the quinone mono acetal provided **3.145**. Finally, triphenylphosphine catalyzed chlorination of the ring gave the AB ring precursor **3.146**.

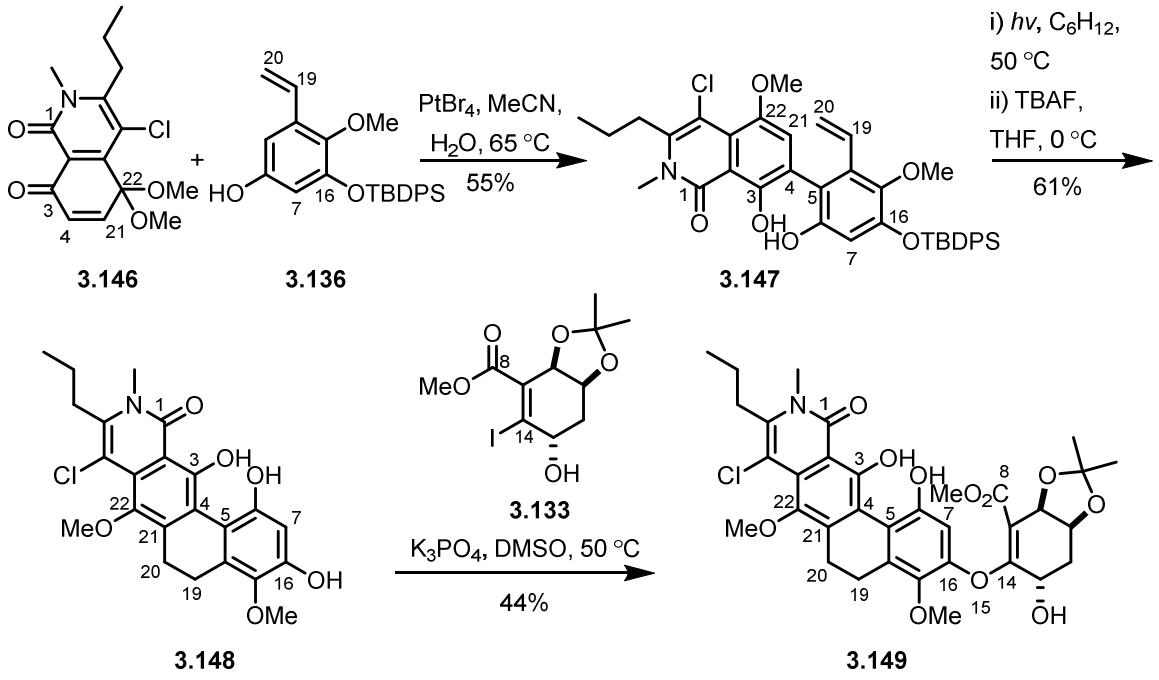
Scheme 3.17: Synthesis of AB ring fragment **3.146**



Initially, Porco attempted a cationic Lewis acid catalyzed [4+2] reaction between styrene **3.136** and quininone acetal **3.146** but he found that only small amounts of the conjugate addition product **3.147** were formed (Scheme 3.18). Optimization of the reaction lead to the identification of $PtBr_4$ as the optimal Lewis acid for the addition. The right amount of water was critical for the isolation of **3.147** in high yields Screening different quantities of water in the reaction revealed that 10 mol% water (2:1 ratio of water to catalyst) maximized the yield, indicating that the active catalyst may be $PtBr_4 \bullet 2H_2O$. Photo-electrocyclization of the compound **3.147**, followed by deprotection of the TBDPS group with TBAF gave ABCD ring fragment **3.148**. Attempts to

cyclize **3.147** in the presence of oxygen to afford kibdelone A (**3.23**) did not provide any $\Delta^{19,20}$-oxidized product (not shown). Conjugate addition of the ABCD ring fragment into the F ring fragment took significant optimization. The reaction was unsuccessful using benzyl protected alcohol **3.132**: Porco speculated that C13 benzyl alcohol was providing steric and/or electronic constraints on the attack of the phenolate anion onto the C14 carbon of the F ring fragment. Fortunately, the allylic alcohol did give some of the desired product **3.149**, but in low yields. Several bases and solvent were screened, finding that potassium phosphate (K_3PO_4) in DMSO followed by quenching with potassium bisulfate ($KHSO_4$) gave the best results.

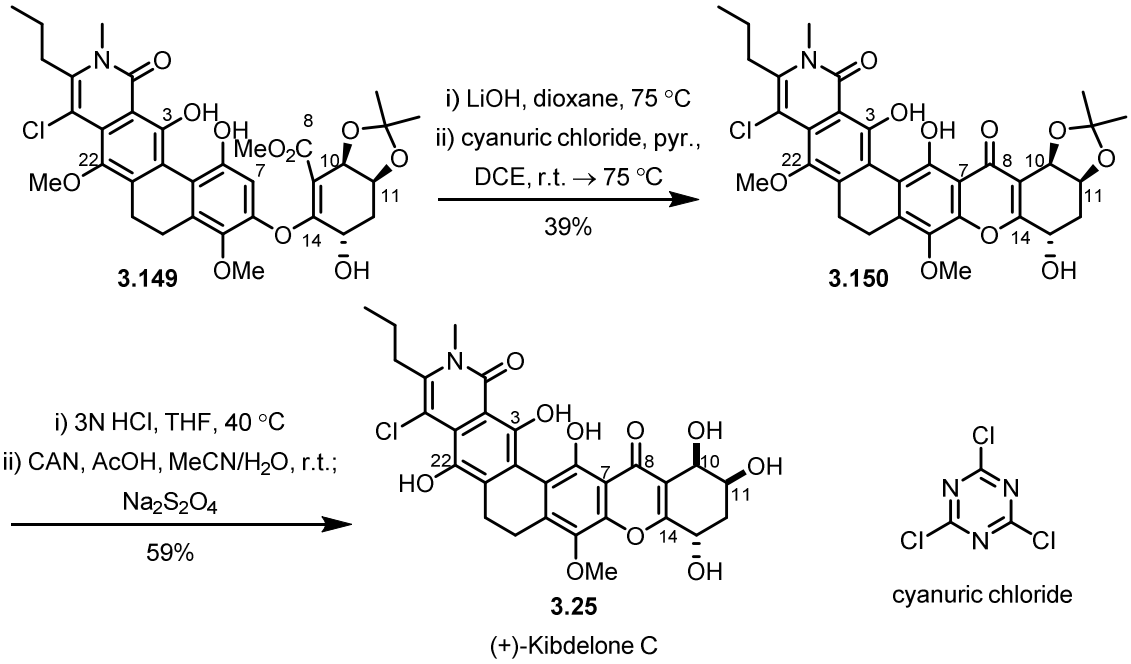
Scheme 3.18: Coupling of AB ring fragment **3.146**, D ring fragment **3.136** and F ring fragment **3.133**



Due to the acid sensitivity of **3.149**, neutral conditions were needed for the Friedel-Crafts cyclization to form the xanthone (Scheme 3.19). After much experimentation, Porco found that hydrolysis of the ester, and activation of the resulting acid with cyanuric chloride induced the requisite Friedel-Crafts reaction to furnish **3.150**. Deprotection of the C10-C11 acetal, followed by selective oxidative demethylation of the B ring, followed by reductive workup with $Na_2S_2O_4$

furnished kibdeleone C in 1.4% yield over 17 steps. Key to the selective oxidative demethylation was the inclusion of acetic acid to obviate B and D ring oxidation.

Scheme 3.19: Porco's completion of (+)-kibdelone C (**3.25**)



New methodology developed for the synthesis included the conjugate addition of the phenol **3.136** to the quinone mono acetal **3.146** and the use of cyanuric chloride for the intramolecular Friedel-Crafts reaction under relatively neutral conditions. Additionally, the use of the photo-electrocyclization to form the C ring *via* C20-C21 closure, as opposed to the C19-C20 photo-electrocyclization seen in the syntheses of cervinomycin (**3.17**), offers a novel disconnect towards polycyclic xanthones. Porco's highly convergent synthesis managed to mask a total step count of 32, which is about the same as Ready's total step count of 33 steps. The synthesis could be improved by reducing the amount of protection/deprotection steps (eight total) and finding a quicker synthesis of the F ring fragment **3.133**, which takes 12 steps to synthesize.

Porco tested several derivatives of intermediate **3.148** for biological activity in an NCI 60-cell screen and found that while most exhibited some cytotoxic activity (GI_{50} 4.5-10μM), they were less potent and less selective when compared to kibdelone C (**3.25**) which displayed 100-

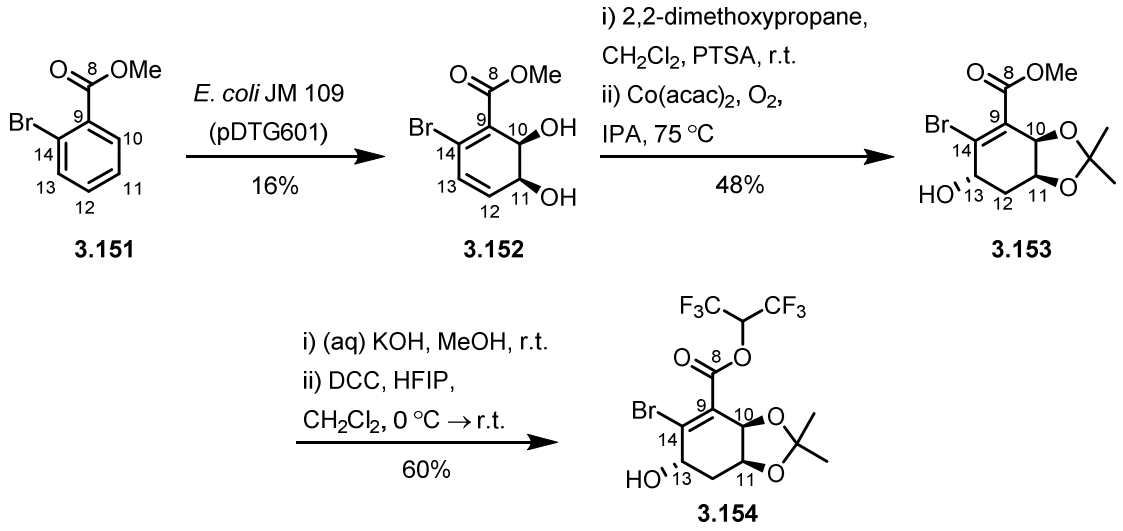
fold selectivity between the most and least sensitive cell lines and a GI_{50} of 2.4 nM, indicating that the F ring plays an important role in the activity and selectivity.

3.3.5: (+)-KIBDELONE A, PORCO JR.

In 2013, Porco published a synthesis of (+)-kibdelone A (**3.23**).[317] Working with Hudlicky, they developed an improved route to the F ring fragment using the microbial oxidation developed by Hudlicky.[315]

Oxidation of the bromomethyl benzoate **3.151** with an JM109 *E. coli* strain (pDTG601A), which was engineered to over-express toluene dioxygenase, yielded a mixture of C10/C11 and C12/C13 dihydroxylated compounds in a 3.5:1 ratio (23% combined yield) (Scheme 3.20). Pure compound **3.152** could be separated from the C12/C13 dihydroxy compound by chromatography in 16% yield. Interestingly, the iodobenzoate gave a ratio of C10/C11 and C12/C13 (1:4) dihydroxylated compounds, yielding the analogous iodo compound of **3.152** in 3.5% yield. The reason for the selectivity switch is due to what is known as Boyd's rule,[316] which states that the largest group directs the enzymatic dihydroxylation. The larger size of the iodine directed the oxidation at C12/C13. Protection of the diol as the acetal, and Mukaiyama hydration of the olefin at C13 gave acetonide **3.153**. The selectivity is due to the cobalt hydride species formed in the reaction preferring to add hydrogen at C12 to form the most stable radical at C13. The stereochemistry is due to the cobalt preferring the convex face of the molecule. Hydrolysis of the methyl ester and DCC mediated esterification with hexafluoroisopropanol (HFIP) gave the activated ester **3.154**.

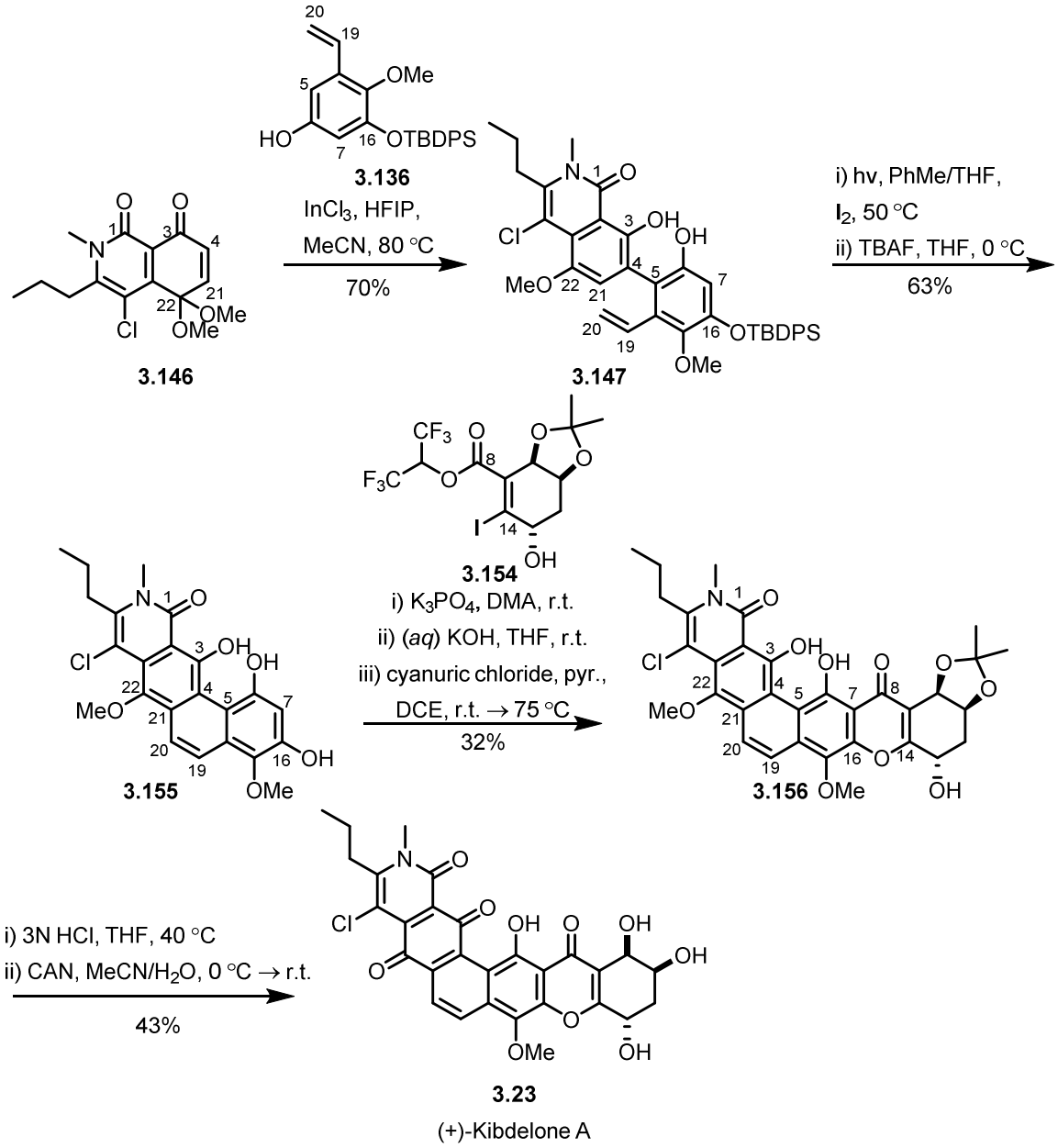
Scheme 3.20: Hudlucky's improved synthesis of F ring fragment **3.154**



3.151 **3.152** **3.153** **3.154**

The Friedel-Crafts reaction of phenol **3.136** and the quinone mono acetal **3.146** was optimized by using $InCl_3$ and solvent mixture of hexafluoroisopropanol (HFIP) and MeCN to give **3.147** in of 70% yield (increased from 54% with $PtBr_4$) (Scheme 3.21). Initially, photo-electrocyclization of **3.147** with iodine under similar conditions to those Kelly[291] *et al* and Mehta[304] *et al* used (see Schemes 3.5 and 3.10), allowed for the oxidation of the C19-C20 carbon atoms to give the fully aromatic analogue **3.155** in low yields (38%). The inclusion of THF as a co-solvent allowed for higher yields (73%) of the tetracyclic compound, most likely because THF scavenges the HI produced as a byproduct of the reduction of iodine. Deprotection of the TBDPS group with TBAF then gave **3.155**. Coupling of the phenol moiety in **3.155** with the activated ester **3.154** gave an improved yield of 53% vs. 44% for the previous iteration. Hydrolysis of the ester, and cyanuric chloride-mediated Friedel-Crafts reaction gave the **3.156**. Hydrolysis of the acetal and oxidation of the B ring with CAN under the same conditions used for kibdelone C (**3.25**), strangely gave mixtures of B and D ring oxidized products. Fortunately, omission of the acid form the CAN oxidation gave (+)-kibdelone A (**3.23**) in only 15 steps and in 0.8% yield. Compound **3.156** was found to be equipotent to (+)-kibdelone A (**3.23**) in a NCI 60 cell panel, with a mean GI_{50} of 3.2 nM.

Scheme 3.21: Coupling of AB ring fragment **3.146**, D ring fragment **3.136** and F ring fragment **3.154** and completion of (+)-Kibdelone A



Additionally, Porco improved on several of the steps developed for the synthesis of (+)-kibdelone C (**3.25**). The conjugate addition of the phenol into the quinone mono acetal **3.146** from 54% yield to 70% yield by using $InCl_3$ as the Lewis acid and HFIP as the solvent. His modification of the conditions for the oxidative electrocyclization by the inclusion of THF as an HI scavenger offered an improvement over Kelly's and Mehta's reported conditions (30-40%

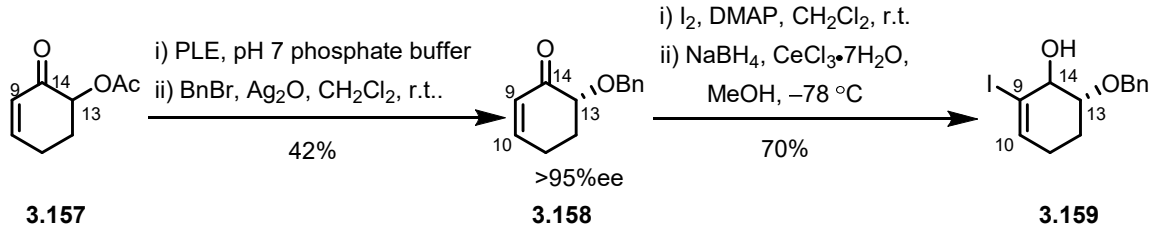
yield vs. 73% yield). Most notably, using Hudlicky's synthesis of the F ring reduced the overall step count by seven steps to a total of 25.

3.3.6:(–) -SIMAOMICIN A, READY

(+)-Simaomicin α was isolated in San Simao, Brazil by Kantor in 1990,[282] where it was determined to be a potent anticoccicidal agent. Tomoda and co-workers found that while simaomicin α (**3.22**) α had little cytotoxic activity, it synergized with the DNA-damaging agent bleomycin so that together they have 0.6 nM activity.[320] In 2013, ready published his total synthesis of (–)-Simaomicin α.[318]

Ready's synthesis began with an enzymatic resolution of α-acetoxy enone **3.157** with pig liver esterase (PLE), followed by protection of the hydroxy group as the benzyl ether to give **3.158** (Scheme 3.22). Iodination of the enone with iodine and DMAP, followed by a Luche reduction gave the F ring fragment **3.159**.

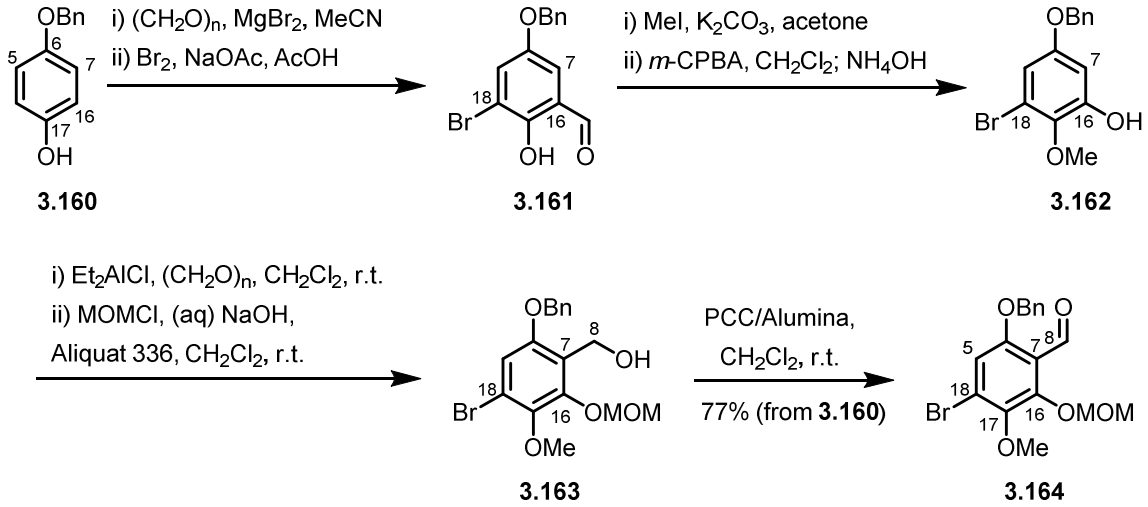
Scheme 3.22: Synthesis of F ring fragment **3.159**



3.157 **3.158** **3.159**

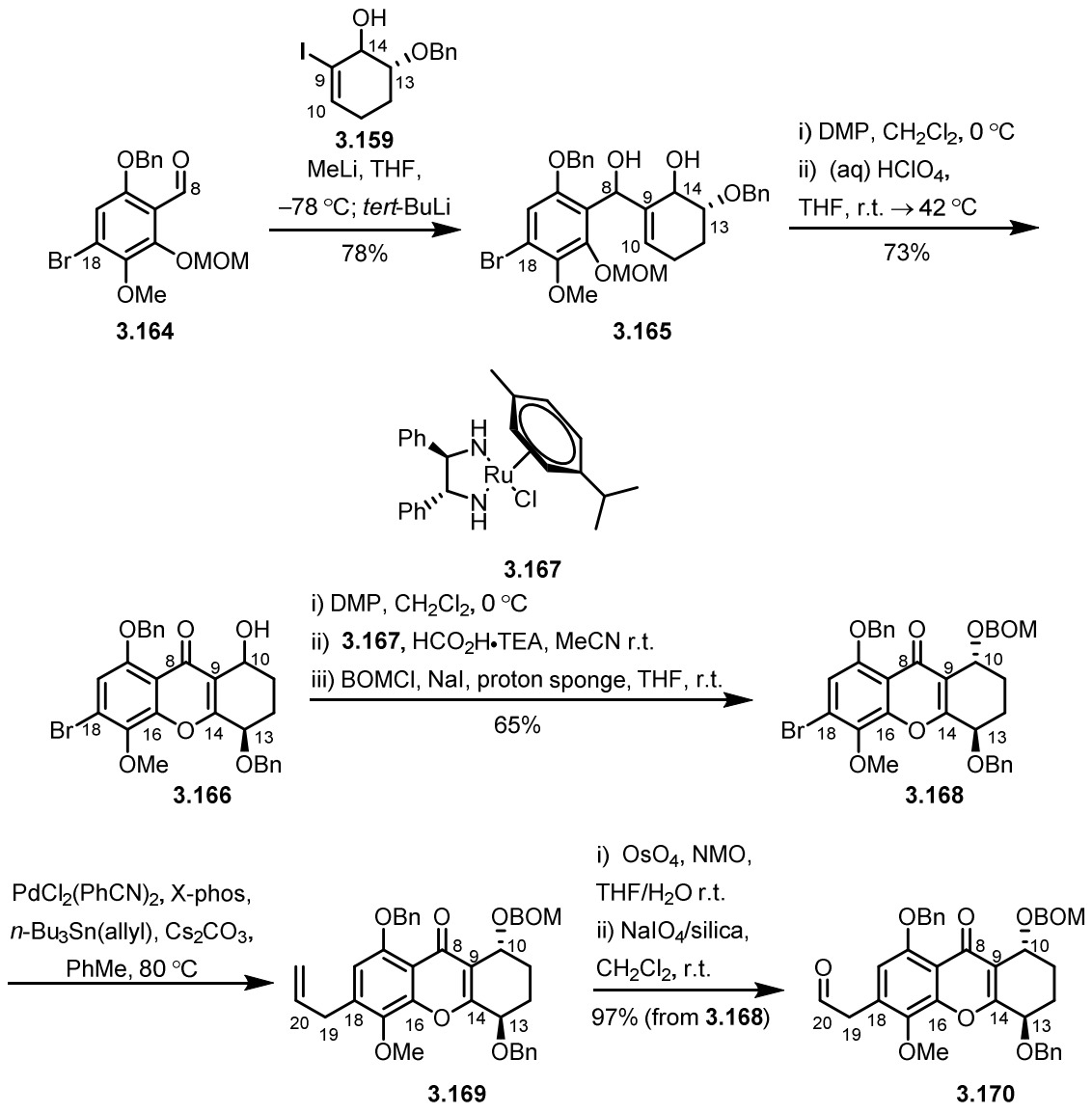
ortho-Formylation of the mono-benzylated hydroquinone **3.160** fortuitously gave salicylaldehyde, the result of the benzyl alcohol undergoing an Oppenauer oxidation under the reaction conditions (Scheme 3.23). *ortho*-Bromination of the phenol provided **3.161**. Protection of the phenol as the methyl ether and a Dakin oxidation gave phenol **3.162**. A second ortho-formylation followed by protection methylation of the phenol furnished the benzyl alcohol **3.163**. Finally, PCC oxidation of the benzyl alcohol provided the E ring fragment **3.164**.

Scheme 3.23: Synthesis of D ring fragment **3.164**



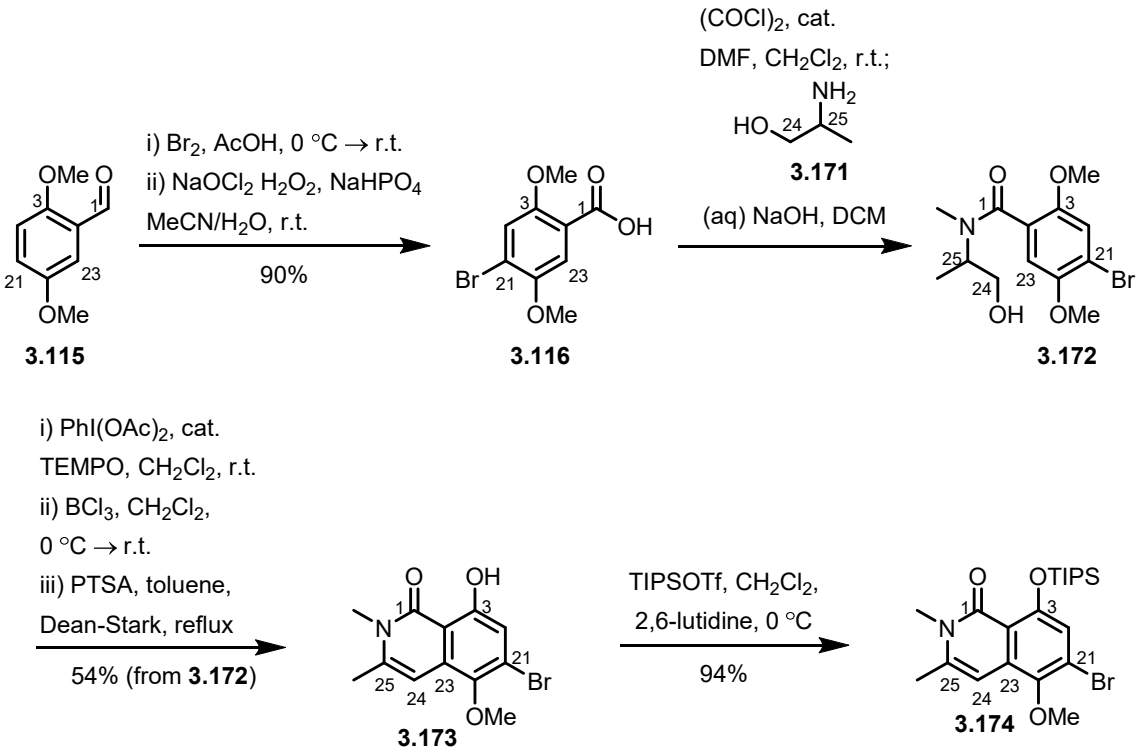
Coupling of the F ring fragment **3.159** and the E ring fragment **3.164** utilized the same methodology for the synthesis of kibdelone C (**3.25**) to give **3.165** (Scheme 3.24). Oxidation of the benzyl alcohol to the ketone with DMP, followed by acid catalyzed cyclization occurred to provide **3.166** as a mixture of epimers at C14. Oxidation of the C14 alcohol, followed by an enantioselective reduction with Noyori's catalyst **3.167** and protection of the resulting alcohol as the BOM ether furnished **3.168** as a single diastereomer.[321] Coupling of the aryl bromide at C18 with allyl-tributyltin provided **3.169**. Initial attempts to oxidatively cleave the olefin under Johnson-Lemieux conditions led only to the aryl aldehyde, but a two-step procedure gave the desired aldehyde **3.170** in 97% yield.

Scheme 3.24: Synthesis of DEF ring fragment **3.170**



Bromination of aldehyde **3.115** at C21, followed by Pinnick oxidation gave carboxylic acid **3.116** (Scheme 3.25). Conversion of the acid to the acid chloride, followed by condensation with amine **3.171** gave amide **3.172**. Ley oxidation of the alcohol to the aldehyde followed by a Pomerantz-Fritsch reaction gave isoquinolone **3.173**, which was protected as the TIPS ether **3.174**.

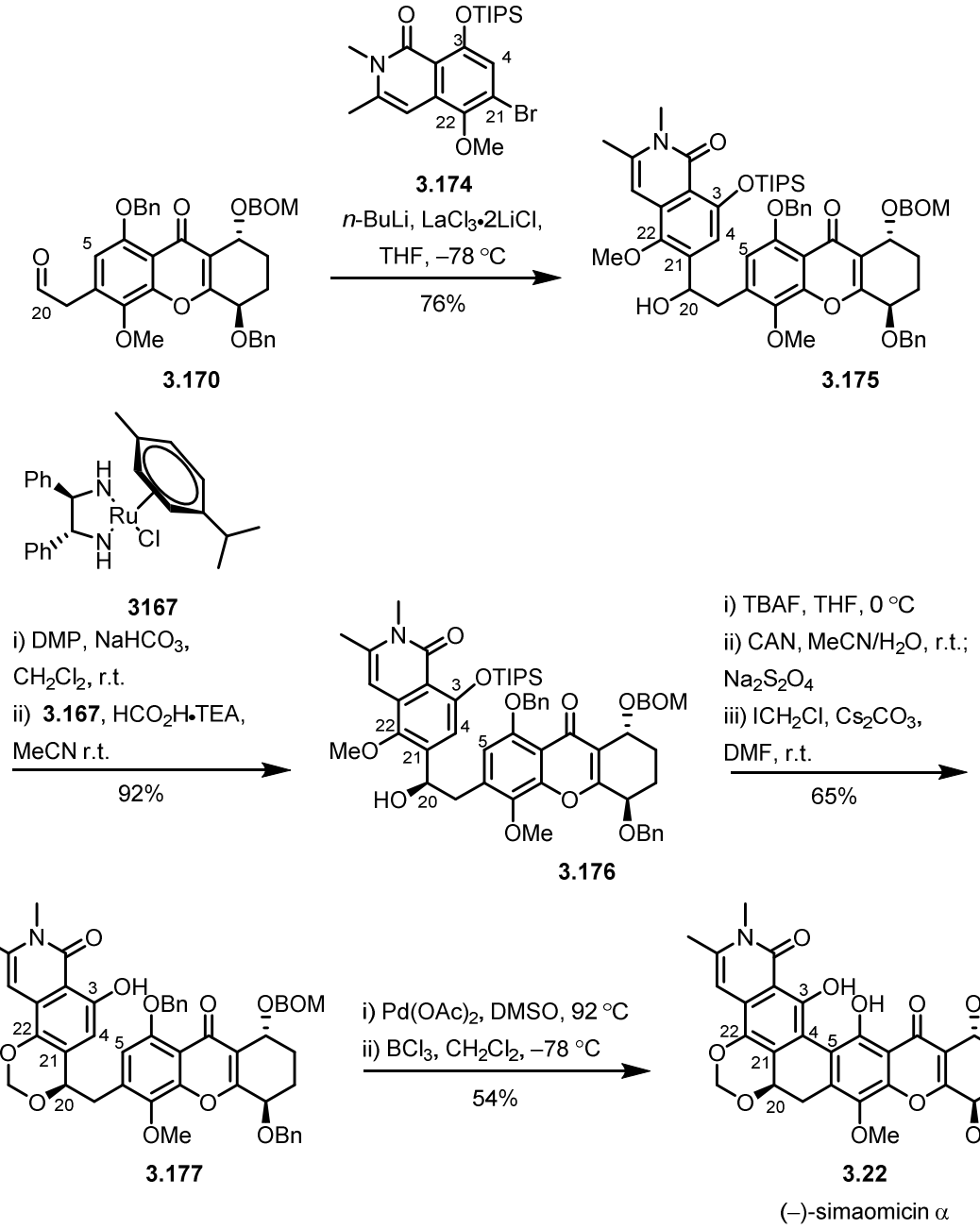
Scheme 3.25: Synthesis of AB ring fragment **3.174**



Several Lewis acids were screened for the addition of the organolithium of **3.174** to the aldehyde **3.170** to give **3.175**, $LaCl_3$•2LiCl delivered **3.175** in 76% yield.[167] Oxidation of the resulting alcohol to the ketone, followed by reduction with Noyori catalyst set the stereochemistry at C20 in **3.176**. Removal of the TIPS group with TBAF provided the monomethyl hydroquinone with was oxidized to the C3/C22 quinone with CAN, which after a reductive workup with $Na_2S_2O_4$ and subsequent alkylation with ICH_2Cl and Cs_2CO_3 provided **3.177**. Use of a alkylating more active alkylating agent (eg. CH_2I_2), for alkylation step led to polymerization of the hydroquinone, while weaker bases or alkylating agents led to low yields of **3.177**. Heating **3.177** with $Pd(OAc)_2$ in DMSO resulted in an oxidative bi-aryl coupling to form the C4-C5 bond, which after treatment with excess BCl_3 delivered (–)-simaomicin α in 25 steps and in 6.8% yield. Comparison of the optical rotations of (–)-simaomicin α and a sample of the natural product revealed that (–)-simaomicin α had the opposite rotation of the natural product in

a similar magnitude, indicating the actual natural product is (+)-simaomicin α (**3.22**) with the opposite configuration.

Scheme 3.26: Ready's completion of simaomicin α (**3.22**)



The absolute stereochemistry of (+)-simaomicin α (**3.22**) was not known until Ready published his synthesis of (–)-simaomicin α which had the opposite rotation of the natural

compound.[282] Interestingly, the unnatural (–)-simaomicin α demonstrated similar activity (IC_{50} 13-87 nM, anti-cancer; MIC 280 nM, antibacterial), to the natural (+)-simaomicin α when tested against colon cancer cell lines (HCT116) lung cancer (H460, H1819) and *Bacillus subtilis*.

Ready's synthesis of (–)-simaomicin α represents the first synthesis of the methylene dioxy sub-class of polycyclic xanthone natural products that include the kigamicins (**3.20**), xantholipin (**3.16**), actinoplanone (**3.26**), albofungin (**3.27**) and lysolipin (**3.15**). Experiments on the oxidative bi-aryl coupling done in model systems for (–)-simaomicin α, indicated that the methylene dioxy ring has a beneficial effect for the cyclization, which may explain why such a strategy failed when applied to the synthesis of kibdelone C (**3.25**). The weaknesses of this synthesis, however, are the excessive number of oxidations and reductions (12 total) and six protecting group manipulations accounting for over half of the total step count of 32. Additionally, the lack of stereocontrol for the cyclization to form the tetrahydroxanthone and the addition into the aldehyde necessitated the oxidation and use of Noyori's catalyst for an asymmetric reduction to set stereocenters at C20 and C10.

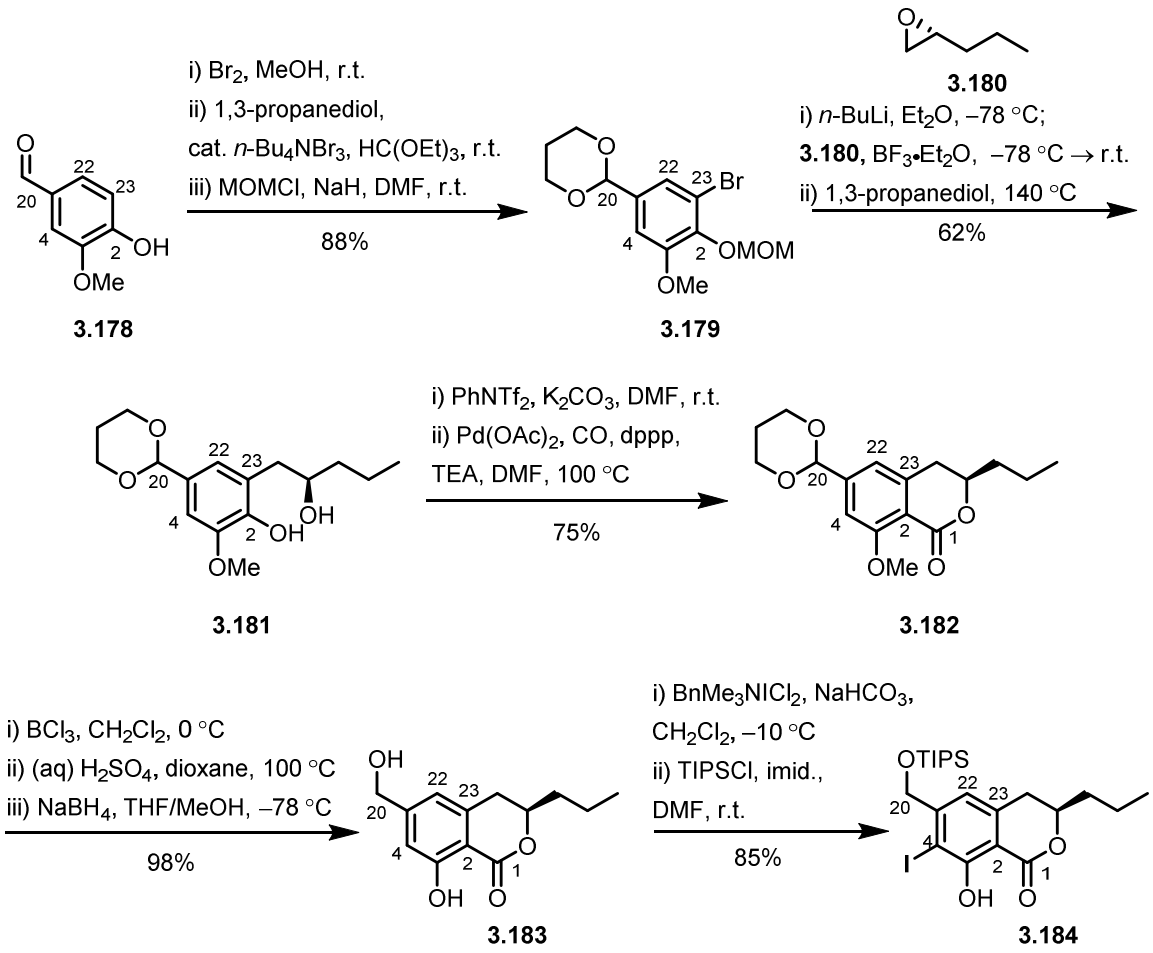
3.3.7: FD-594 AGLYCON, SUZUKI

FD-594 was isolated in 1998 in Urawa city, Saitama prefecture Japan by Mizoue.[275] In 2008, Suziki developed a general methodology to synthesize xanthones using an intramolecular nucleophilic aromatic substitution (S_nAr)[322] reaction and he completed a total synthesis of FD-594 aglycon (**3.202**) in 2009.[323]

Suzuki's synthesis of FD-594 aglycon (**3.202**) began with bromination of isovanillin (**3.178**) at C23, followed by protection of the aldehyde as the acetal (Scheme 3.27). Protection of the phenol as the MOM ether then gave **3.179**. Lithium-halogen exchange of the aryl bromide, followed by addition of epoxide **3.180** led to an alkylated intermediate, and selective deprotection of the MOM ether under Miyake's neutral conditions then gave **3.181**.[324] Triflation of the phenol with McMurray's reagent, followed by intramolecular alkoxy carbonylation gave the lactone **3.182**. Selective demethylation of **3.182**, followed by deprotection of the acetal and

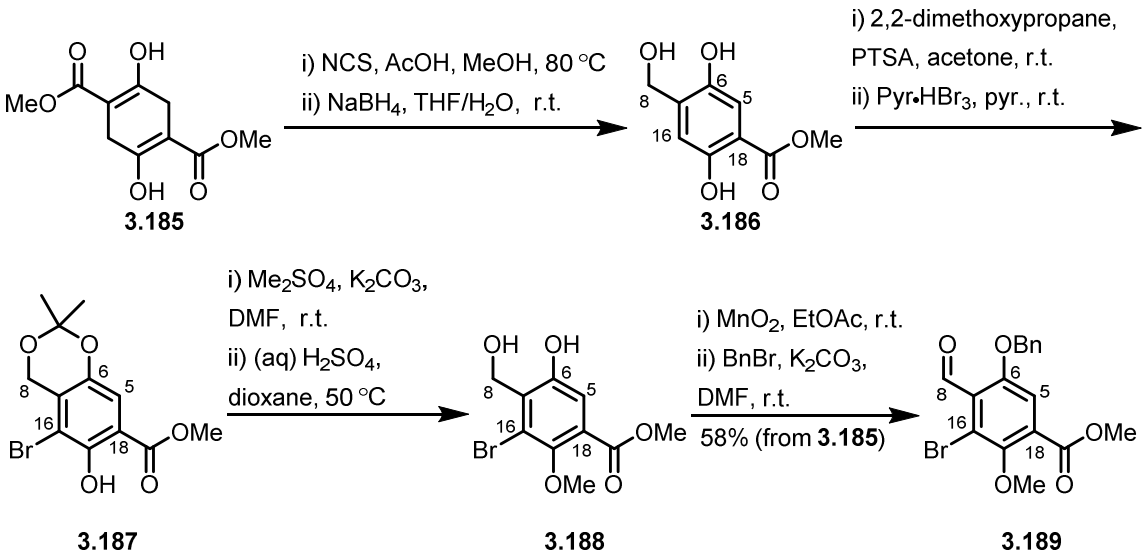
reduction with $NaBH_4$ gave benzyl alcohol **3.183**. *ortho*-Selective iodination of the phenol with $BnNMe_3ICl_2$, followed by TIPS protection of the benzyl alcohol gave iodo-phenol **3.184**.

Scheme 3.27: Synthesis of AB ring fragment **3.184**



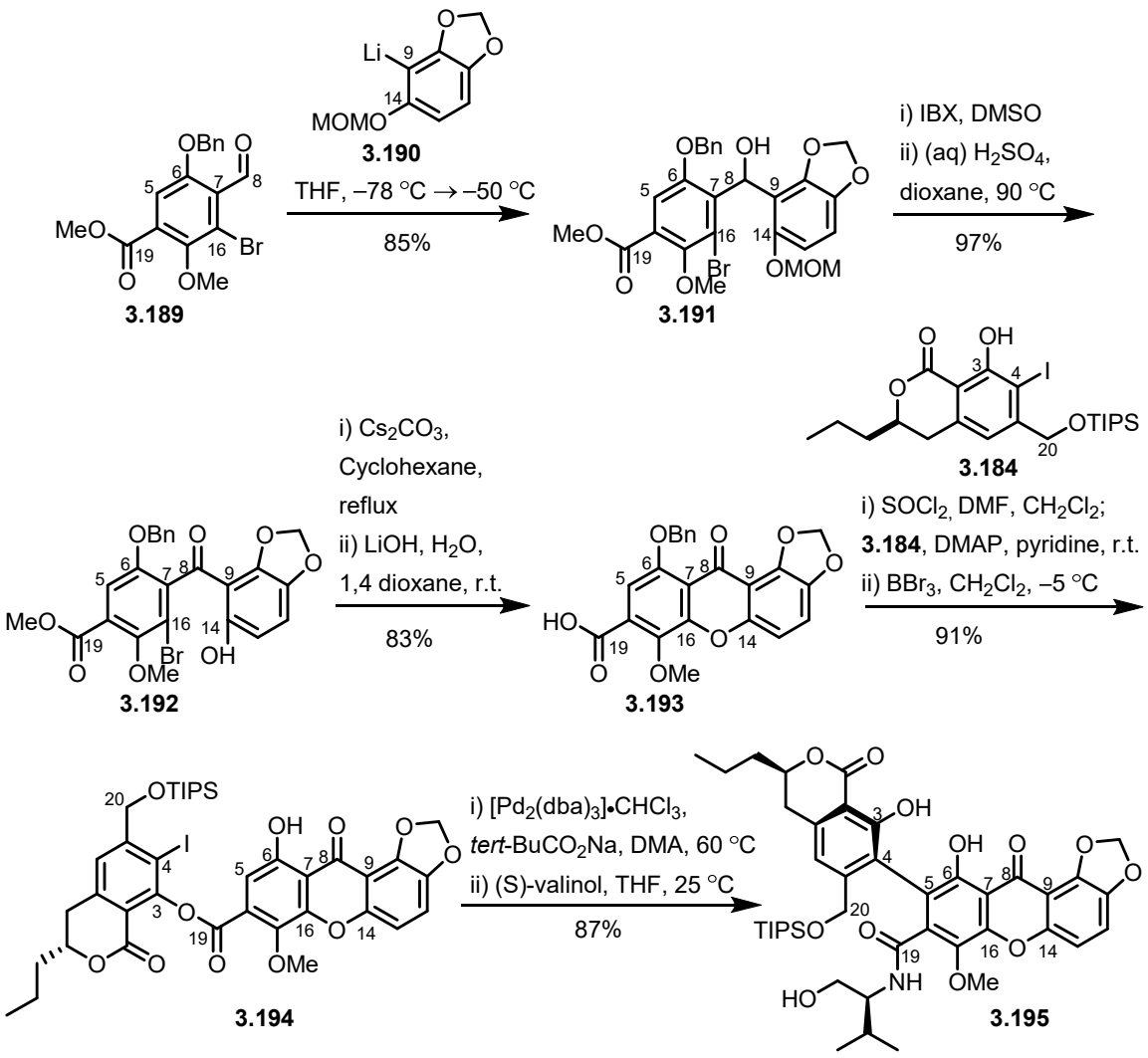
Synthesis of the D ring fragment began with bis-malonate **3.185** (Scheme 3.28). Oxidation to the bis-salicylic acid with *N*-Chlorosuccinimide (NCS), followed by mono-reduction with $NaBH_4$ gave benzyl alcohol **3.186**. Protection of the benzyl alcohol and the phenol as an acetonide, followed by selective bromination at C16 with pyridinium hydroperbromide ($Pyr{\bullet}HBr_3$) gave **3.187**. *O*-Methylation of the phenol, followed by deprotection of the acetal then gave benzyl alcohol **3.188**. Benzylic oxidation to the aldehyde with MnO_2, followed by protection of the phenol as the benzyl ether then gave **3.189**.

Scheme 3.28: Synthesis of D ring fragment **3.189**



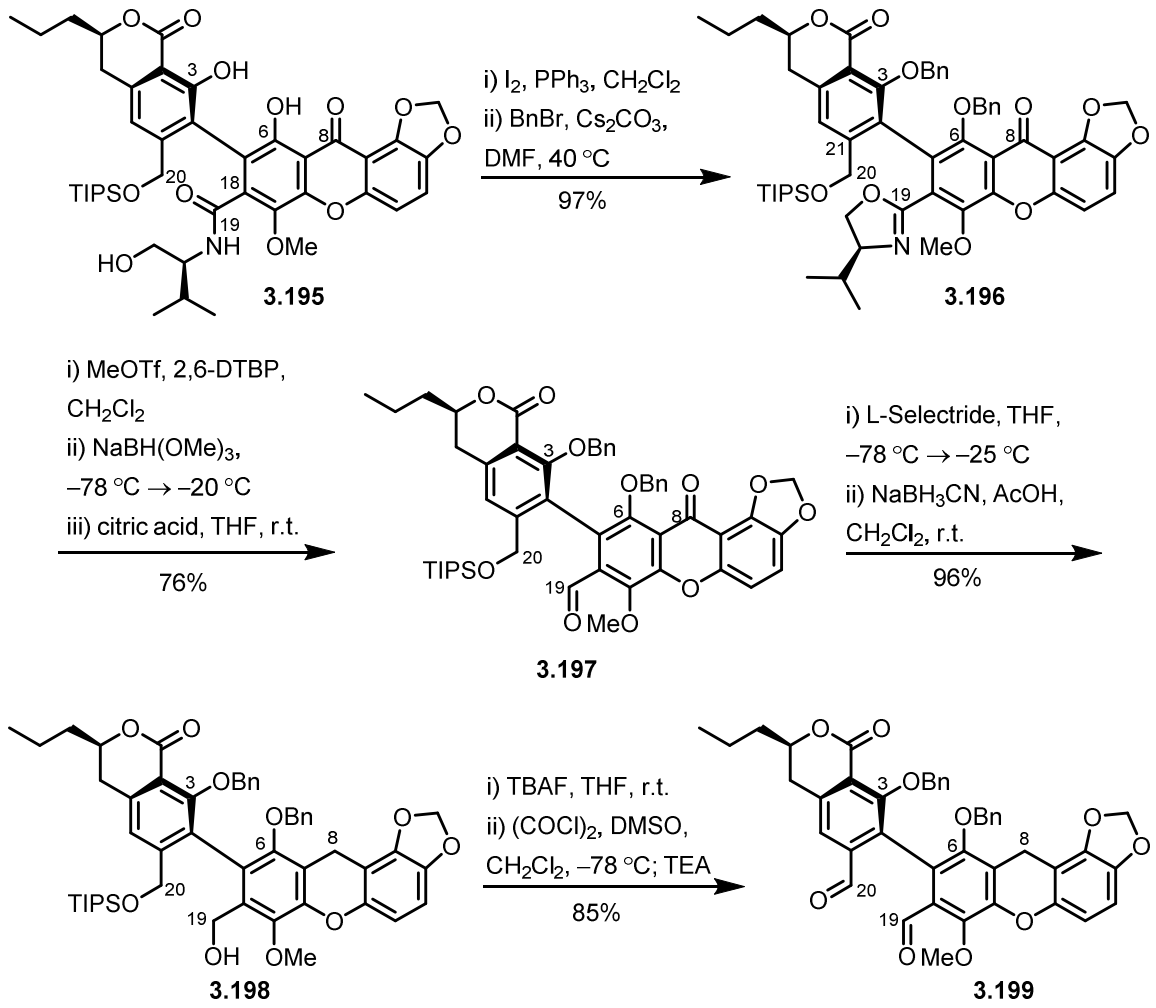
Addition of ortho-lithiated compound **3.190** into aldehyde **3.189** gave benzyl alcohol **3.191** (Scheme 3.29). Oxidation of the benzyl alcohol **3.191** with IBX, followed by deprotection of the MOM group with aqueous sulfuric acid gave **3.192**. Initial synthetic studies on the cyclization of **3.192** to form a xanthone found that the phenoxide can attack at C16 or C6. The selectivity was highly dependent on the solvent, with polar protic solvents favoring cyclization at C6 and polar aprotic solvents preferring to cyclize at C16. Accordingly, use of MeOH with Cs_2CO_3 as the base gave a mixture (1:1) of cyclization at C16 and C6. Switching the solvent to DMF gave a slight improvement (3:1, C16:C6), but cyclohexane was identified as the optimum solvent, furnishing the xanthone moiety in 84% yield and 23:1 selectivity. Saponification of the ester gave **3.193**. Activation of the acid as the acid chloride and esterification with the AB ring fragment **3.189**, followed by debenzylation with BBr_3 furnished **3.194**. Palladium catalyzed intramolecular aryl coupling at C5 set up the Bringmann diastereoselective lactone opening.[325] Opening the lactone with valinol to set the axial chirality was solvent dependant. Fortunately, THF provided **3.195** in 14:1 diastereoselectivity.

Scheme 3.29: Synthesis of ABDEF ring fragment **3.195**



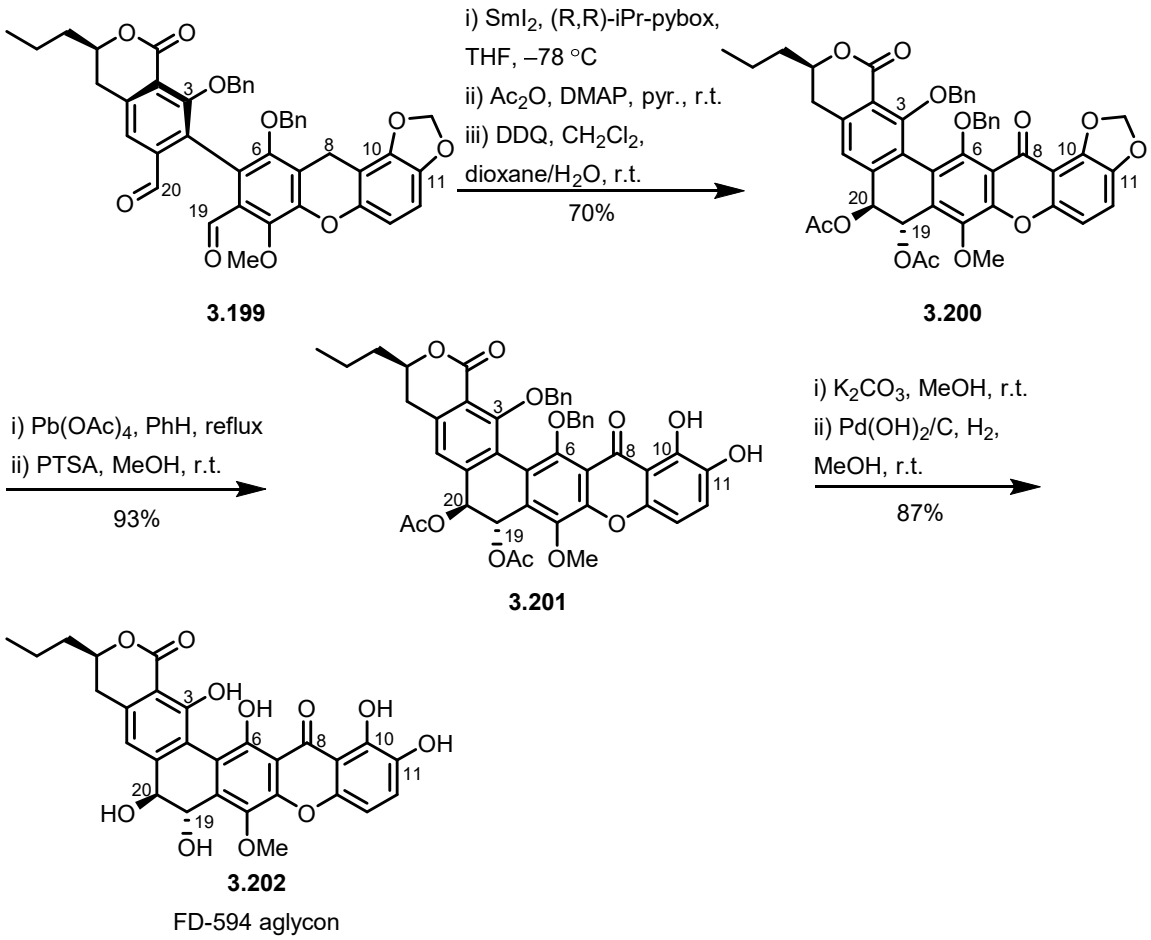
Cyclization of the valinol moiety in **3.195** to an oxazoline, followed by benzyl protection of the C3 and C6 phenols gave **3.196** (Scheme 3.30). Methylation of the oxazoline, followed by reduction with $NaBH(OMe)_3$ and hydrolysis gave the aldehyde **3.197**. The C20 alcohol was oxidized to the aldehyde, but many attempts to induce the pinacol coupling were unsuccessful. Accordingly, the xanthone and the aldehyde were reduced with L-Selectride and the C8 alcohol was removed with acetic acid and $NaBH_3CN$ to give the xanthene **3.198**. Deprotection of the TIPS group, followed by global Swern oxidation gave **3.199**.

Scheme 3.30: Synthesis of pinicol coupling precursor **3.199**



Initial attempts to induce the samarium mediated pinacol coupling provided the diol with poor diastereoselectivity (3.5:1) in 68% combined yield (Scheme 3.31). Addition of the crown ether 24-c-8 improved the diastereoselectivity to 8.2:1 in 74% combined yield. Addition of (R,R)-iPr-pybox led to a slight decrease in diastereoselectivity (7.1:1) but increased the overall yield to 81%. Protection of the alcohols as acetates, followed by benzylic oxidation with dichlorodicyanoquinone (DDQ) gave xanthone **3.200**. Oxidative deprotection of the methylenedioxy group with $Pb(OAc)_4$, and hydrolysis gave catechol **3.201**. Removal of the acetate groups and hydrogenolysis of the benzyl groups gave FD-594 aglycon (**3.202**) in 33 steps (longest linear sequence) and in 10.7% yield.

Scheme 3.31: Suzuki's completion of FD-594 aglycon (**3.202**)



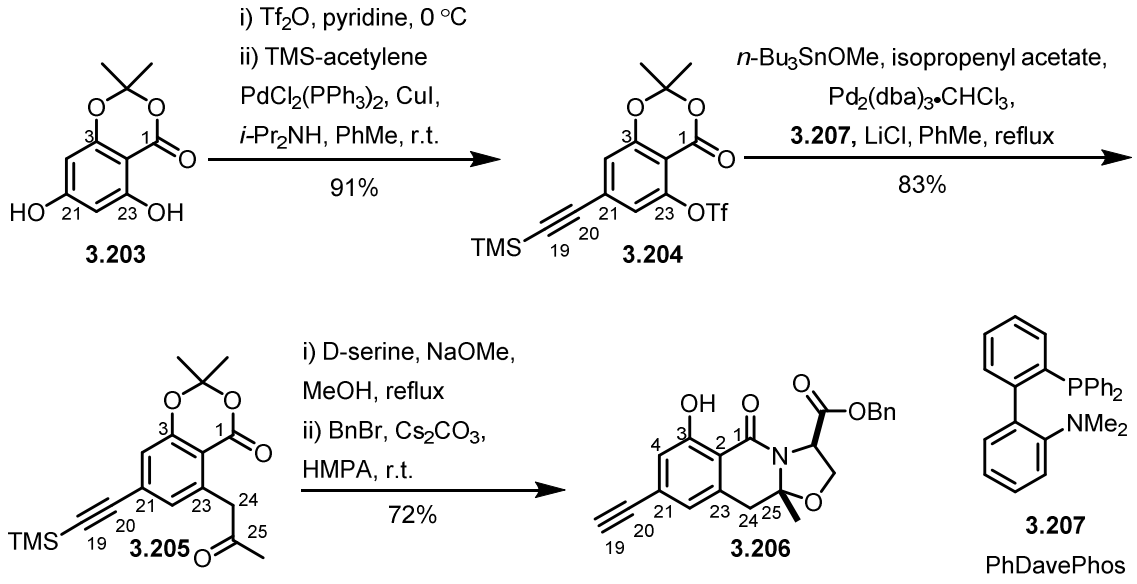
Suzuki developed several new methodologies towards the synthesis of FD-594 aglycon (**3.202**). Developing the conditions for the intramolecular nucleophilic aromatic substitution (S_nAr) reaction *via* displacement of the C16 bromide rather than the C6 benzyloxy group was critical for the formation of the xanthone with the right regiochemistry. Suzuki also demonstrated that axial chirality can be used to direct the stereochemistry of the C19 and C20 alcohols during the pinacol coupling of the bis-aldehyde **3.199**, and the addition of ligands improved the diastereoselectivity. The main weakness of Suzuki's synthesis, despite the high yield, is the high step count. The total step count is 45 steps is due to the overuse of protecting groups (16 steps) and great deal of redox manipulations (13 steps).

3.3.8: TMC-66, HOSOKAWA/TATSUTA

TMC-66 was isolated in 1999 by the Tanabe/Seikaku group and shows activity toward inhibition of endothelin converting enzyme (ECE) with an IC_{50} of 2.9 μM.[327] Hosokawa/Tatsuta published their short total synthesis of TMC-66 in 2007.[326]

The Hosokawa/Tatsuta synthesis of TMC-66 began with bis-triflation of the phenol **3.203** and selective Sonagashira coupling with TMS-acetylene at C21 gave the aryl-acetylene **3.204** (Scheme 3.32). A modified Migita coupling (isopropenylacetate, Bu_3SnOMe, P(*o*-tol)$_3$) in the presence of LiCl and the Buchwald ligand **3.207** provided the homo phthalate **3.205**.[328] Condensation of **3.205** with serine formed the G ring, with concomitant deprotection of the TMS group. Benzyl protection of the carboxylic acid furnished the GAB ring coupling partner **3.206** with the cis relationship between the C25 methyl group and the ester of the G ring.

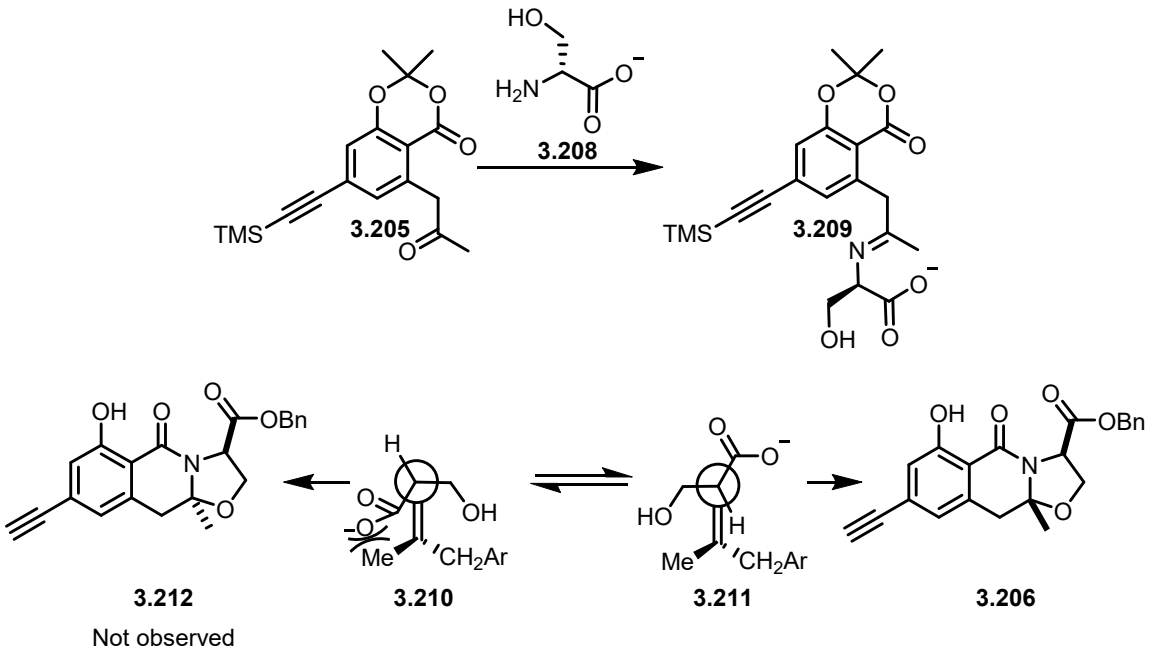
Scheme 3.32: Synthesis of GAB ring fragment **3.206**



The stereochemical outcome of the cyclization of serine onto **3.205** can be rationalized by an analysis of conformational preferences. The most stable conformer **3.211**, the hydrogen is eclipsing the imine to minimize $A^{1,3}$ strain from either the carboxylate or the alkoxymethyene groups. Cyclization of the alcohol moiety and condensation onto the ester gives the desired GAB

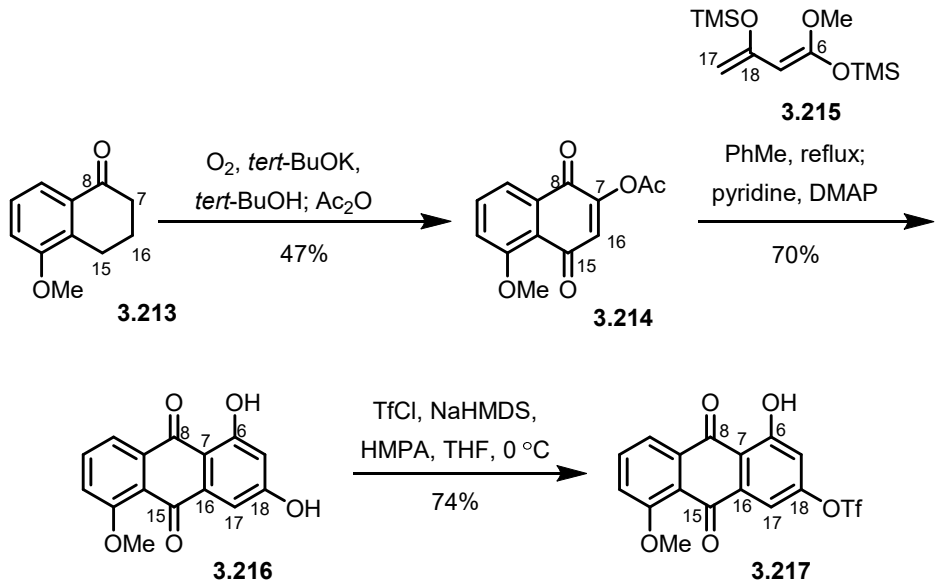
ring fragment **3.206** with cis stereochemistry. The other conformer **3.210** is too high in energy, having serious $A^{1,3}$ like interactions between the carboxylate and the alcohol group, so none of the GAB ring fragment **3.212** is seen with the undesired trans geometry.

Scheme 3.33: Stereochemical rationale for the serine condensation



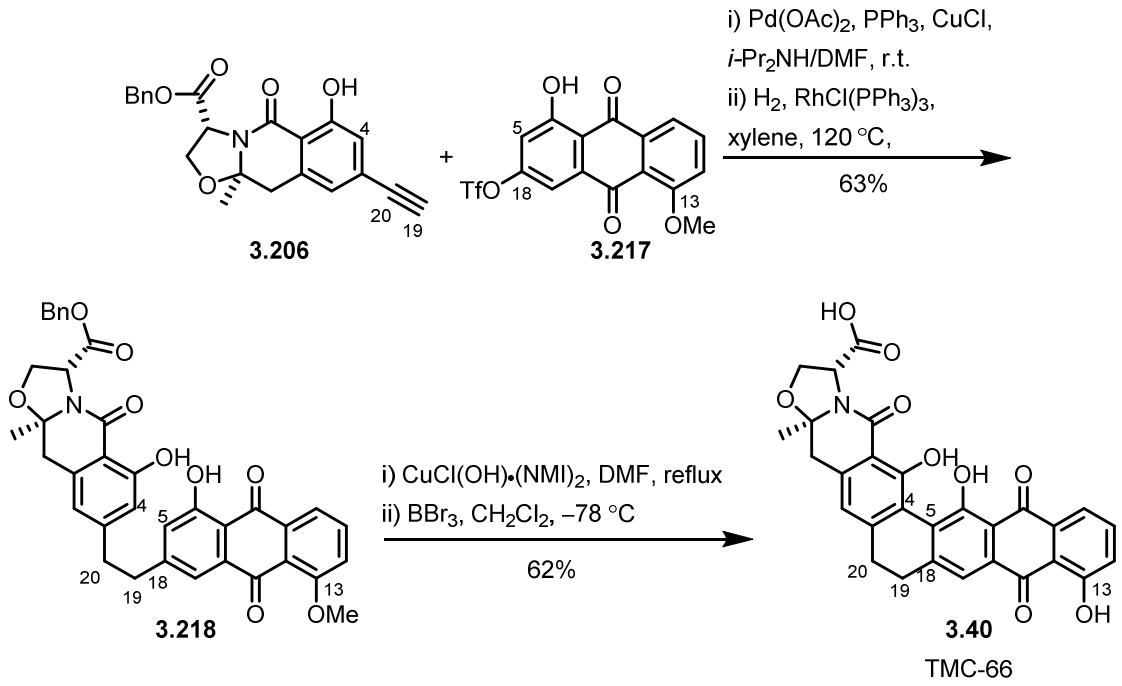
Synthesis of the DEF ring fragment began with oxidation of the tetralone **3.213**, followed by reaction with acetic anhydride quench to give the quinone **3.214** (Scheme 3.34). A Diels-Alder reaction between the quinone **3.214** and the silyl enol ether **3.215** gave the anthraquinone **3.216**. Presumably, the acetate at C7 makes the carbon at C16 more electrophilic, which favors bond formation at the more electron rich C17 carbon atom of the diene. Selective triflation of the less acidic C18 phenol over the more acidic C6 phenol was accomplished *via* formation of the dianion and reaction with TfCl to form **3.217**.

Scheme 3.34: Synthesis of DEF ring fragment **3.217**



Sonagashira coupling of the alkyne **3.206** and the triflate **3.217**, followed by hydrogenation with Wilkinson's catalyst provided **3.218** (Scheme 3.35). Of several oxidants screened for the oxidative intramolecular bi-aryl coupling, only Koga's reagent (CuCl(OH)•(TMEDA)) gave the desired product, but in only 20% yield. By screening ligands for the Cu^{II} oxidant, Hosokawa and Tatsuta found that use of N-methylimidazole (NMI) to form $CuCl(OH)•(NMI)_2$ was the ideal reagent for this transformation. Finally, deprotection of the benzyl group and the C13 methoxy group with BBr_3 gave TMC-66 in only nine steps from **3.203** and in 21% yield.

Scheme 3.35: Hosokawa/Tatsuta's completion of TMC-66 **2.40**



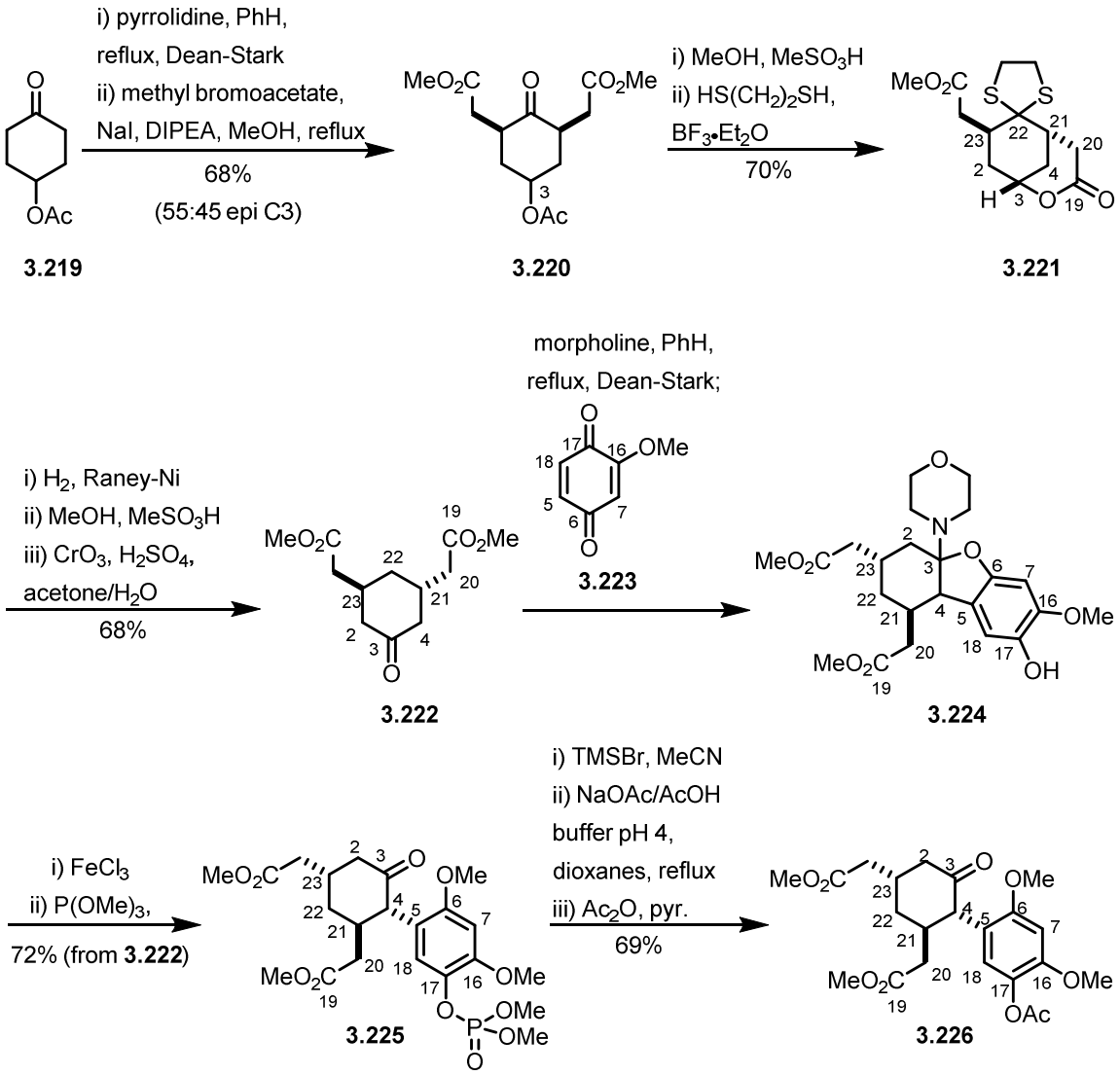
At only 9 steps, 12 steps total, the synthesis of TMC-66 is highly efficient. Hosokawa/Tatsuta's modification of the Migata coupling may prove useful for the formation of the A rings of other polycyclic xanthone natural products such which contain a methyl group at C25 (citreamicin numbering). Additionally, the stereochemical outcome of the condensation of D-serine **3.208** onto the ketone **3.205** is instructive for the synthesis of the citreamicins. Although Hosokawa's and Tatsuta's synthesis of TMC-66 is not directly related to the study of polycyclic xanthone natural products, several aspects of the synthesis and structure are informative. Of particular interest is the construction of the G ring using an amino acid and the use of the Migata procedure to synthesize the homo phthalate ester onto which the amino acid cyclizes.

3.3.9: SYNTHETIC STUDIES TOWARD LYSOLIPIN I, DUTHALER

Duthaler published three synthetic studies directed toward the core of lysolipin (**3.19**) in 1984[329-331] and a final account of his synthesis of the BCD ring core in 1985.[332] The pyrolidine enamine of ketone **3.219** was bis-alkylated methyl bromoacetate to form ketone **3.220** as a

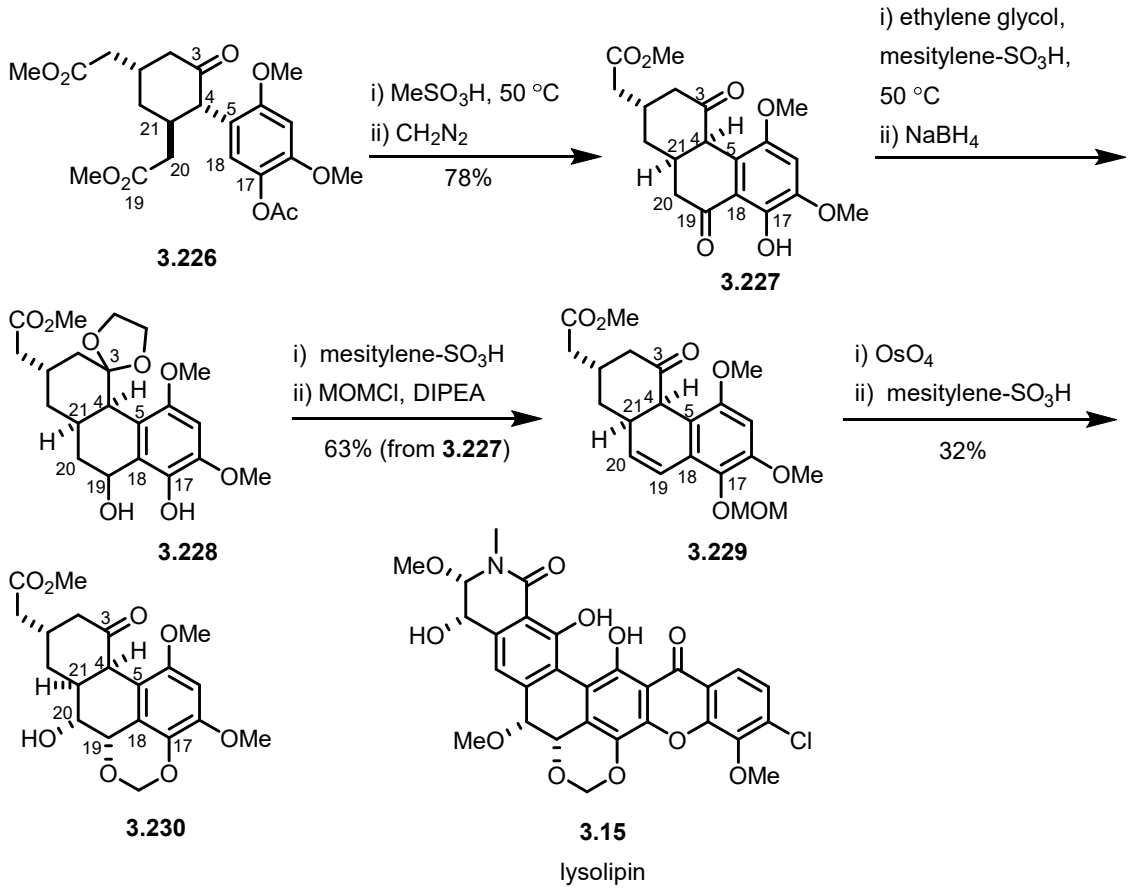
mixture (55:45) of C3 epimers (Scheme 3.36). Exposure of **3.220** to $MeSO_3H$ in MeOH removed the C3 acetate and, after epimerization at C21, enabled the lactonization between the C3 alcohol and the C19 ester. Protection of the ketone as the dithiolane provided **3.221**. Reductive desulfurization with Raney-nickel followed by trans-esterification and oxidation of the C3 alcohol gave **3.222**. Formation of the morpholine-enamine of **3.222**, followed by the addition of the quinone **3.223** resulted in the selective conjugate addition at the C5 carbon of the quinone to form the *N*,*O*-acetal **3.224**. Oxidation of **3.224** with $FeCl_3$ regenerated both the quinone and the ketone, and subsequent regioselective reductive methylation of the C17 phenol with $P(OMe)_3$ furnished hydroquinone **3.225**. The selectivity of the reduction may be due to the C16 methoxy group, which donates electron density into the C6 carbonyl and hence deactivates it toward nucleophilic attack by $P(OMe)_3$. Selective deprotection of the phosphate with TMSBr, followed by hydrolysis with buffered aqueous dioxanes, and acetylation with acetic anhydride gave **3.226**.

Scheme 3.36: Synthesis of the BD ring fragment **3.226**



Heating **3.226** in neat $MeSO_3H$ promoted hydrolysis of both esters, epimerization at C4, and an intramolecular Friedel-Crafts reaction to form an intermediate that was re-esterified with diazomethane to give **3.227** (Scheme 3.37). Protection of the C3 ketone as the dioxolane, followed by reduction of the C9 ketone gave benzyl alcohol **3.228**. Dehydration of the C9 alcohol, followed by protection of the C17 phenol gave **3.229**. Osmium-mediated dihydroxylation from the convex face, followed by acid catalyzed trans-acetalization with the MOM group gave the BCD ring core **3.230** in 21 steps and 2.5% yield.

Scheme 3.37: Duthaler's completion of synthetic studies toward BCD ring fragment **3.230** towards lysolipin **3.15**

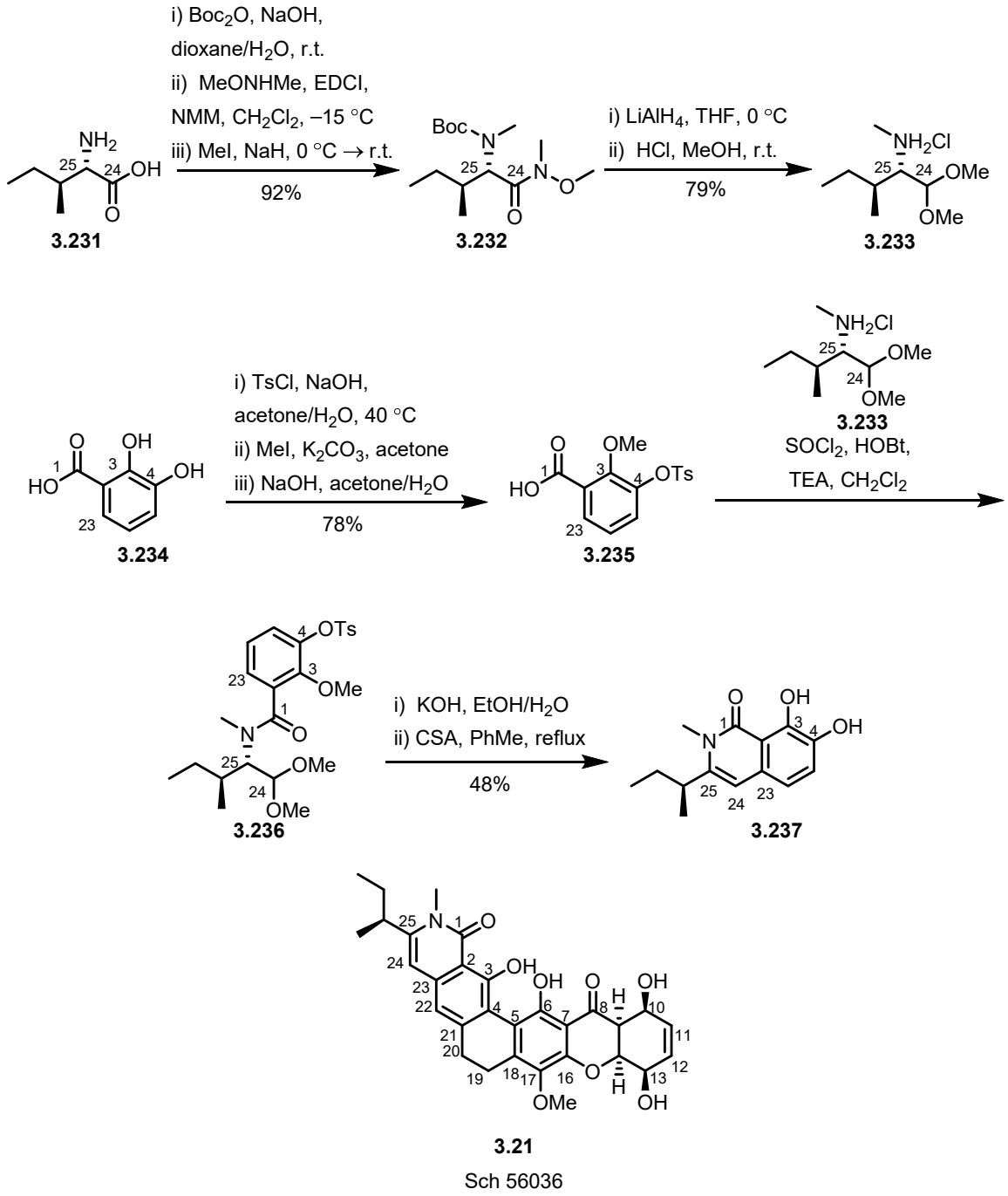


Although 21 steps approaches the step count characteristic of the total syntheses described earlier, Duthaler did develop some interesting methodology. The enamine mediated addition of ketones to quinones to trap out the *N*,*O*-acetal is an interesting way to prevent further side-reactions. Additionally, the regioselective reductive methylation with $P(OMe)_3$ methodology to provide the mono-methyl hydroquinones may prove useful for the synthesis of other polycyclic xanthones such as the kibdelones. The use of the proximal MOM group to form the methylenedioxy ring in the lysolipin core is an intriguing alternative to the method developed by Ready in the synthesis of simoamicin α (**3.22**) (see Scheme 3.26).

3.3.10: SYNTHETIC STUDIES TOWARD SCH-56036, BARRETT

In 2005, Barrett synthesized the AB rings of Sch-56036.[333] The synthesis of the amine fragment began with the Boc protection of isoleucine **3.231**, followed by EDCI mediated coupling with *N*,*O*-dimethylhydroxylamine and *N*-methylation of the Boc-protected amine gave **3.232** (Scheme 3.38). Reduction of the amide with $LiAlH_4$, followed by protection of the aldehyde as the acetal gave **3.233**. The aromatic fragment began with the selective tosylation of the benzoic acid **3.234** at the C4 position, followed by bis-methylation of both the phenol and the carboxylic acid. Saponification of the ester provided **3.235**, which was transformed into the acid chloride with $SOCl_2$ and coupled with the amine fragment **3.233** to provide **3.236**. Deprotection of the tosyl group in **3.236** with KOH and treatment with camphorsulfonic acid (CSA) promoted the cyclization with concomitant *O*-demethylation to furnish isoquinolone **3.237** in eight steps from isoleucine and 35% yield.

Scheme 3.38: Barrett's synthetic study of the AB ring of Sch-56036 (**2.21**)



At eight steps and 35% yield, Barrett's synthesis of the GA ring fragment **3.237** is competitive with the methods developed by Ready (eight steps, 41% yield for kibdelone and seven steps, 56% yield for simaomicin α (**3.22**)), Porco (seven steps, 13% yield for kibdelone), Suzuki (12 steps, 34% yield), and Kelly (seven steps, 35% yield). Barett's synthesis also

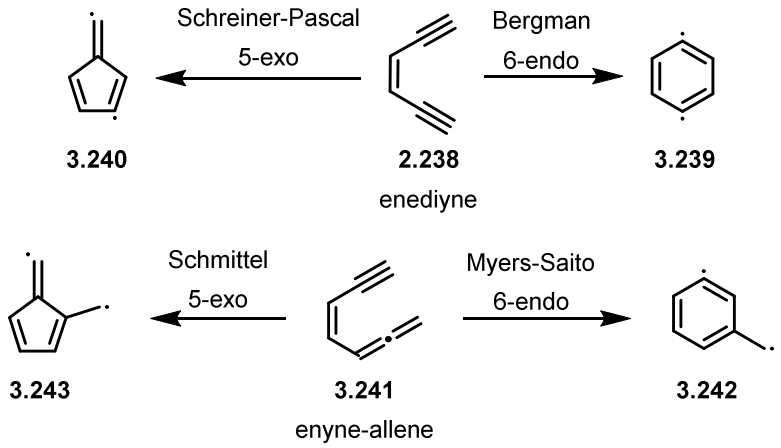
demonstrates the utility of the Pomeranz-Fritsch cyclization for the synthesis of the AB rings with chiral centers.

3.5: Prior art in the Martin group towards polycyclic xanthone natural products

3.5.1: THE MOORE REARRANGEMENT

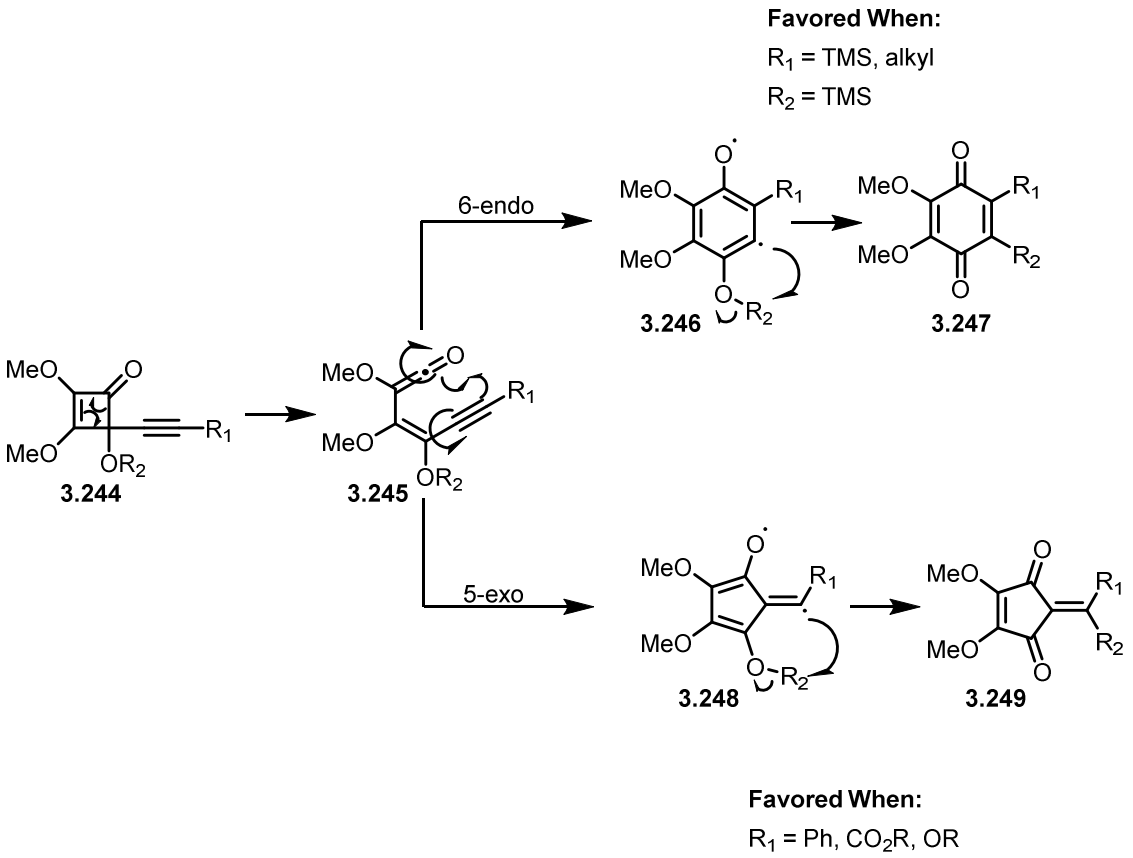
The rearrangement of 4-alkynylcyclobutenones to quinones was discovered by Moore in 1985.[334-339,438] It is part of a fascinating class of reactions involving enediynes **3.238** or eneyne-allenes **3.241** known as the cycloaromatization reactions (Figure 2.7).[436,440] Enediynes **3.238** can undergo a Bergman cyclization (6-endo) to produce a *p*-benzyne diradical **3.239** or a Schreiner-Pascal cyclization (5-exo) to produce the fulvene diradical **3.240**. Like enediynes **3.238**, eneyne-allenes **3.241** can also undergo a Myers-Saito cyclization (6-endo) to produce a toluene diradical **3.242** or a Schmittel cyclization (5-exo) to produce the fulvene diradical **3.243**. The Moore rearrangement can be considered a heteroatom variant of the Myers-Saito cyclization.[436,440]

Figure 3.7: Parent cycloaromatization reactions



The mechanism of the Moore rearrangement begins with the electrocyclic ring opening of the cyclobutanol **3.244** to the ene-yne-ketene (Scheme 3.39).[338] The ketene can cyclize in a 6-endo radical fashion to produce the diradical intermediate **3.246**, which can then undergo an intramolecular radical transfer with the R_2 group on oxygen to produce the quinone **3.247**. The alternate 5-exo cyclization can also occur to produce the fulvene diradical **3.248**, which also undergoes an intramolecular group transfer to form the cyclopentadione **3.249**. The preference for 5-exo *vs* 6-endo cyclization is dependant primarily on the substitution of the alkyne (R_1) and secondarily on the substitution of the alcohol group (R_2).[338] Groups that stabilize radicals such as alkoxy, phenyl or carbonyls favor the 5-exo mode of cyclization over 6-endo. To a lesser extent, TMS substituted alcohols favor the 6-endo mode of cyclization, but if the group at R_1 is too strongly radical stabilizing, any ability of the TMS group to direct is overridden.

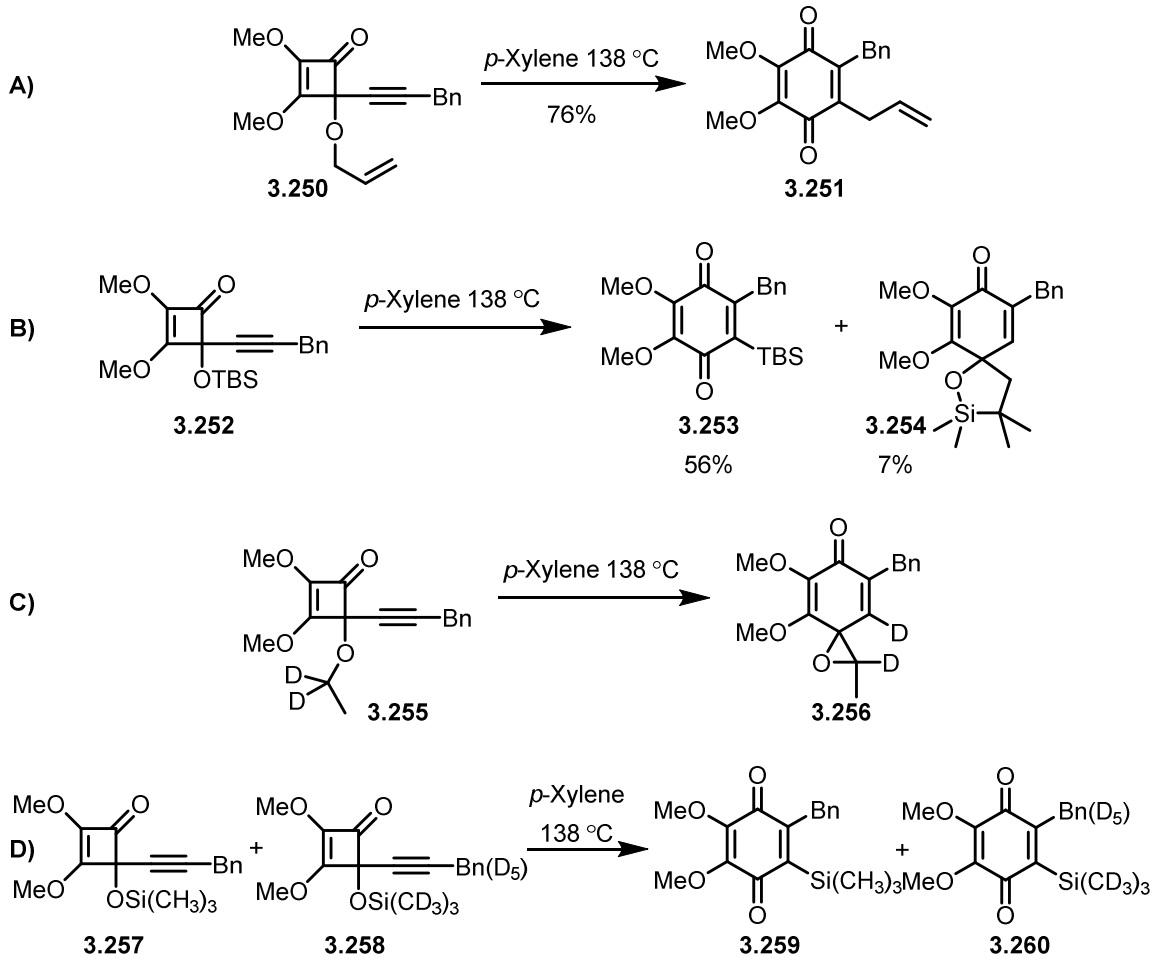
Scheme 3.39: Mechanism of the Moore rearrangement



Evidence for the radical mechanism in the Moore rearrangement can be seen in the byproducts of several examples (Figure 3.8).[338] Heating either cyclobutanone **3.250** or **3.252** resulted in the major product arising from the O→C group migration to provide quinones **3.251** and **3.253** (Figure 3.8, **A, B**). A minor product isolated from heating the OTBS protected cyclobutanol **3.252**, however, was **3.254** 7%, which arises from an intramolecular C-H abstraction of the putative diradical intermediate (Figure 3.8, **B**).[338] Heating the deuterium enriched *O*-alkyl compound **3.255** resulted in the epoxide **3.256** with exclusive deuterium incorporation. (Figure 3.8, **C**).[338] This result indicates that the C-H abstraction by the radical intermediate is most likely intramolecular. Further evidence for the intramolecular rather than intermolecular O→C group migration comes from a radical crossover experiment in which

heating **3.257** and **3.258** produced the products **3.259** and **3.260** with deuterium scrambling (Figure 3.8, **D**).[338]

Figure 3.8: Evidence for radical mechanism in Moore rearrangement



A) Example of allyl group migration during Moore rearrangement. B) Example of C-H abstraction of an adjacent group, followed by recombination. C) Example of preferred C-D abstraction over C-H abstraction. D) Radical crossover experiment indicating that intramolecular and not intermolecular radical transfer occurs.

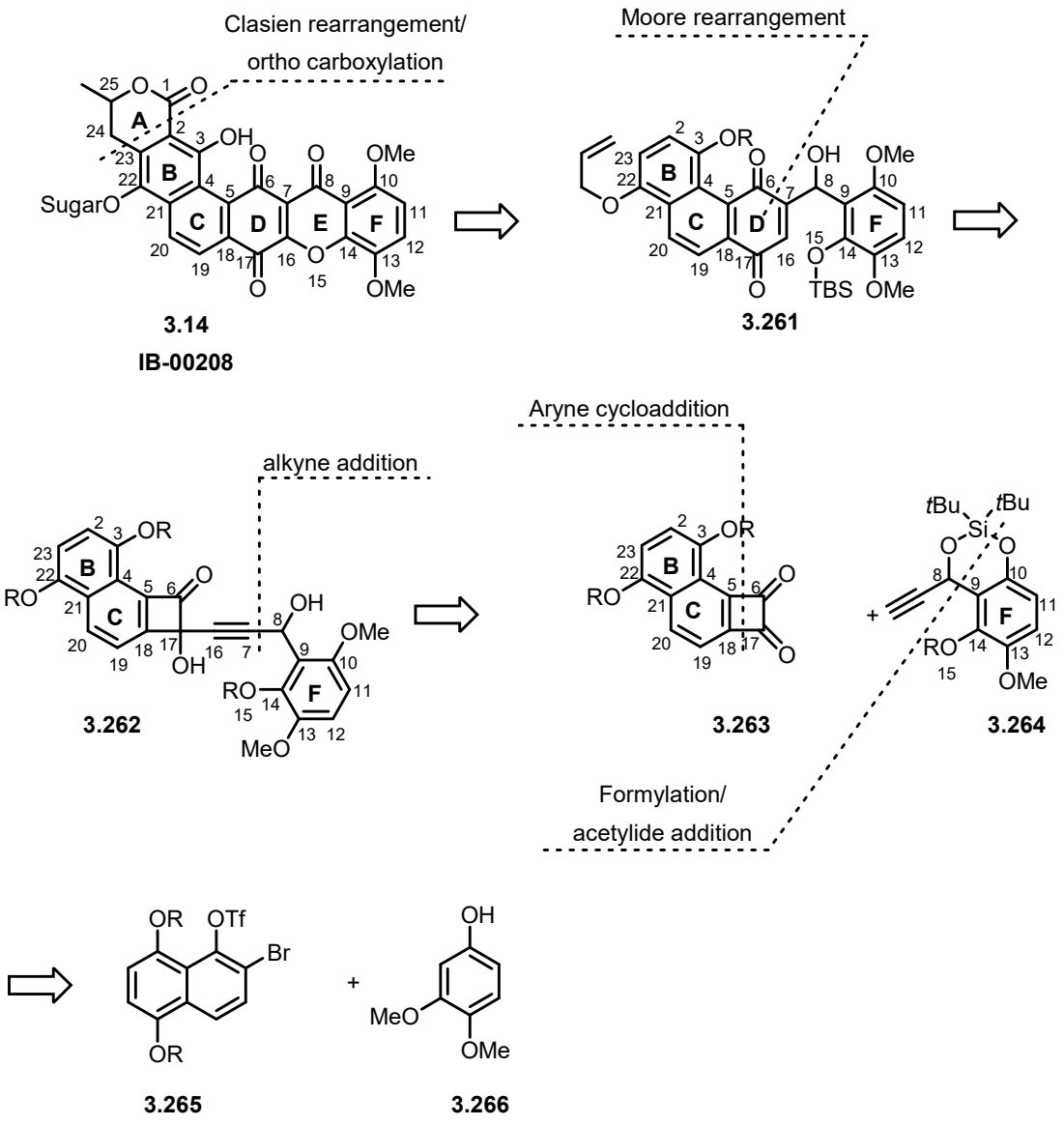
3.5.2: MARTIN GROUP TOTAL SYNTHESIS OF IB-00208 AGLYCONE

3.5.2.1: First generation approach toward IB-00208

The first generation approach of the Martin group toward the polycyclic xanthone IB-00208 (**3.14**) was developed by Dr. Mans in 2006.[340] The A ring was thought to come from a late-stage functionalization of **3.261** at C2 (citreamicin numbering) *via* Friedel-Crafts acylation or an bromination/alkoxycarbonylation sequence (Scheme 3.40). A Claisen rearrangement of the

phenolic allyl group moiety at C22 to C23 followed by a Wacker oxidation and an enantioselective reduction of the resulting ketone will provide access to either enantiomer of the IB-00208 (**3.14**) aglycone, (absolute stereochemistry unknown). A late-stage glycosylation of the less hindered C22 phenol would then provide IB-00208 (**3.14**). The D and E rings of **3.261** were thought to come from a Moore-like rearrangement from alkyne **3.262** (see Figure 3.9). The alkyne **3.262** was thought to come from the union of alkyne **3.264** and naphtho-cyclobutanone **3.263**, which would be derived from an aryne cycloaddition with an enol ether.

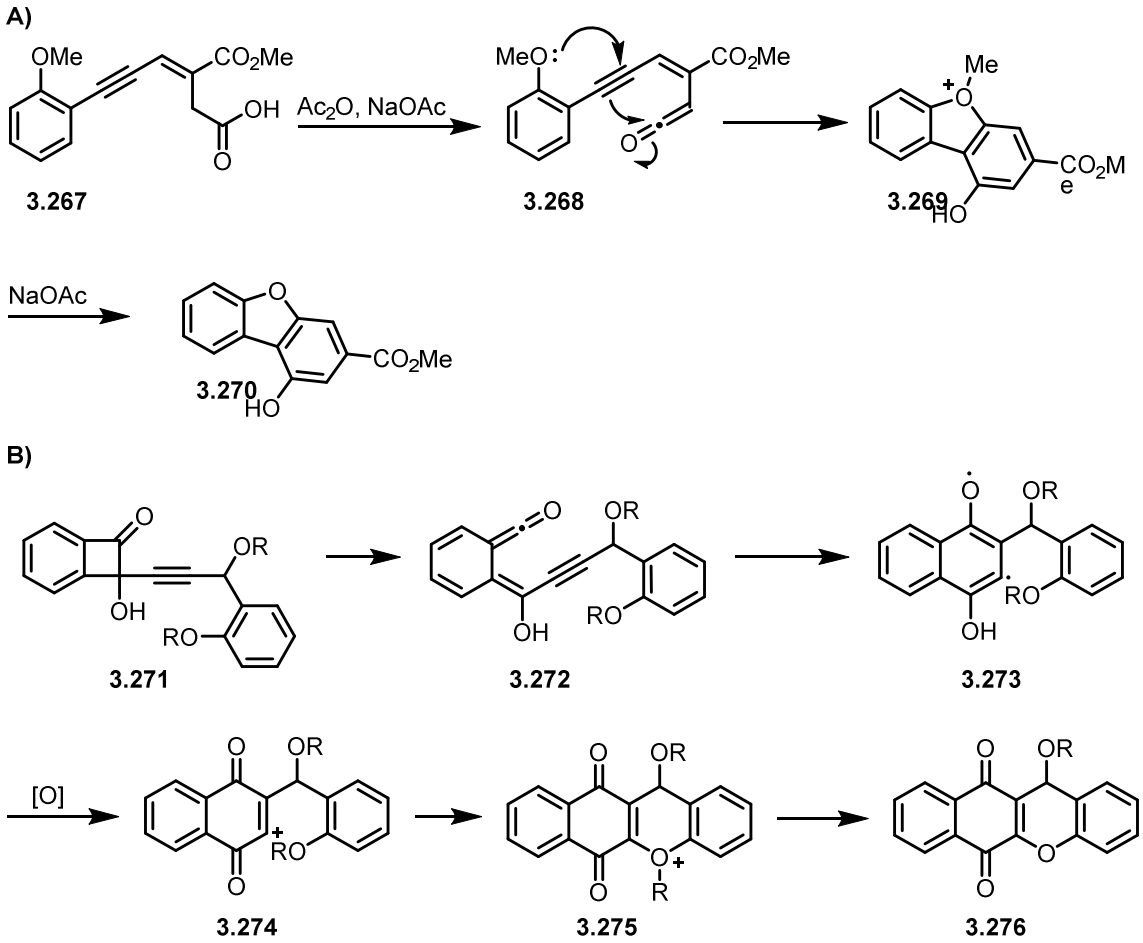
Scheme 3.40: First generation retro-synthesis for IB-00208 (**3.14**)



The key Moore-like rearrangement, was inspired by a benzannulation reaction reported by Fuganti in 2003 (Figure 3.9, **A**).[341,342] Heating **3.267** in a mixture of Ac_2O and NaOAc initiated a cascade in which the neighboring methoxy ether attacks the incipient carbocation to form the oxonium **3.269**, which is subsequently de-methylated to provide the benzofuran **3.270**. In an analogous fashion, heating the benzocyclobutanone **3.271** will lead to a Moore rearrangement to produce the diradical intermediate **3.273** (Figure 3.9, **B**). Oxidation of the radical intermediate would generate the quinone cation **3.274**, which would capture the

neighboring aryl ether to produce a similar oxonium intermediate **3.275**, subsequent demethylation of which should produce **3.276**

Figure 3.9: Fuganti's benzannulation cascade and proposed oxidative Moore rearrangement



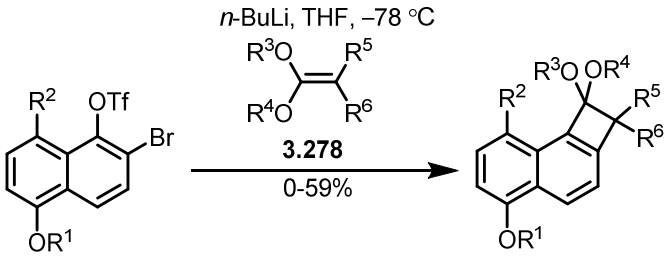
a) Fuganti's benzannulation. b) Proposed oxidative Moore rearrangement.

3.5.2.2: Strategies toward the synthesis of the naphthocyclobutanone fragment

Formation of the naphthyne *via* metal-halogen exchange with substrates such as **3.277** and subsequent 2+2 cycloaddition with a variety of enol ethers **3.278** did provide some of naphthocyclobutanone **3.279**, but only if the enol ether lacked substitution at R^6 and/or R^5 (Equation 3. 1). When substitution was present at both R^6 and R^5, no desired product was formed

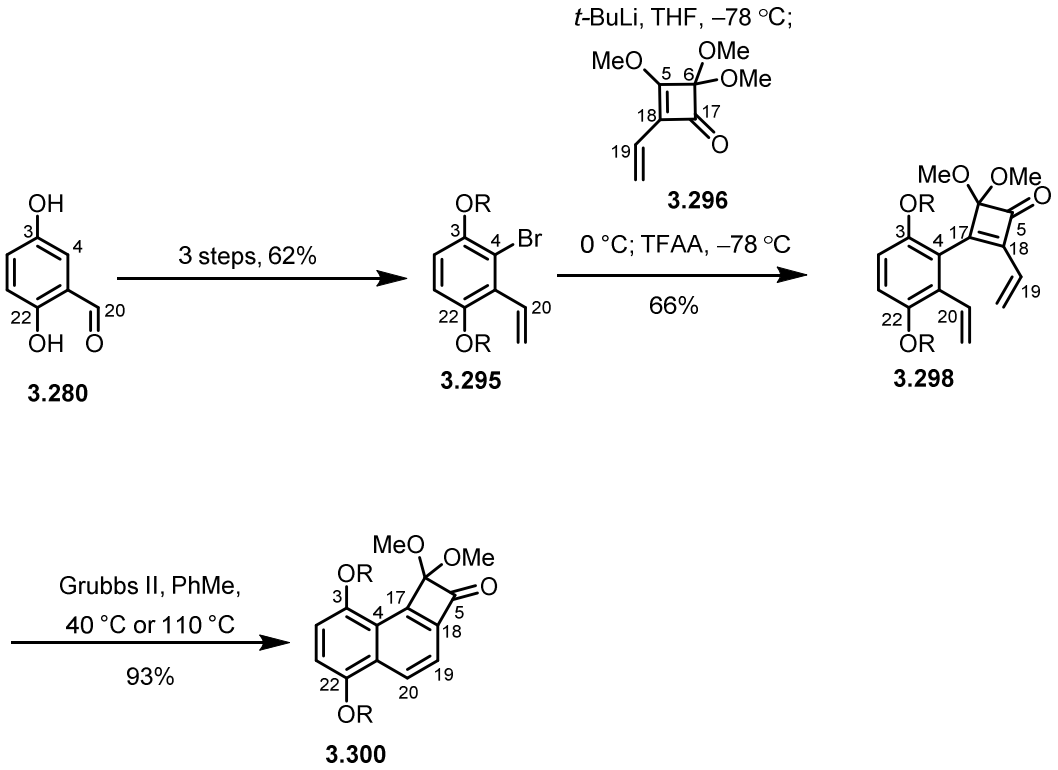
and thus the aryne cycloaddition strategy toward the naphthocyclobutanone fragment was deemed non-productive.

Equation 3.1: Unsuccessful Aryne route to naphthocyclobutanone fragment **3.263**



To overcome the limitations of the aryne chemistry, Dr. Mans developed a novel route towards the naphthocyclobutanone fragment **3.291**, which involved forming the arene *via* ring closing metathesis (RCM) (Scheme 3.41). Metal halogen exchange of the bromo-styrene **3.281** with *tert*-BuLi followed by reaction with the known vinyl squarate **3.282** furnished the squarate adduct **3.283** in 66% yield. Attempts to improve the yield with additives such as $CeCl_3$ or tetramethylethylenediamine (TMEDA) or varying the temperature did not improve the yield of **3.283**. Ring closing metathesis (RCM) then provided the desired naphthocyclobutanone **3.284**.

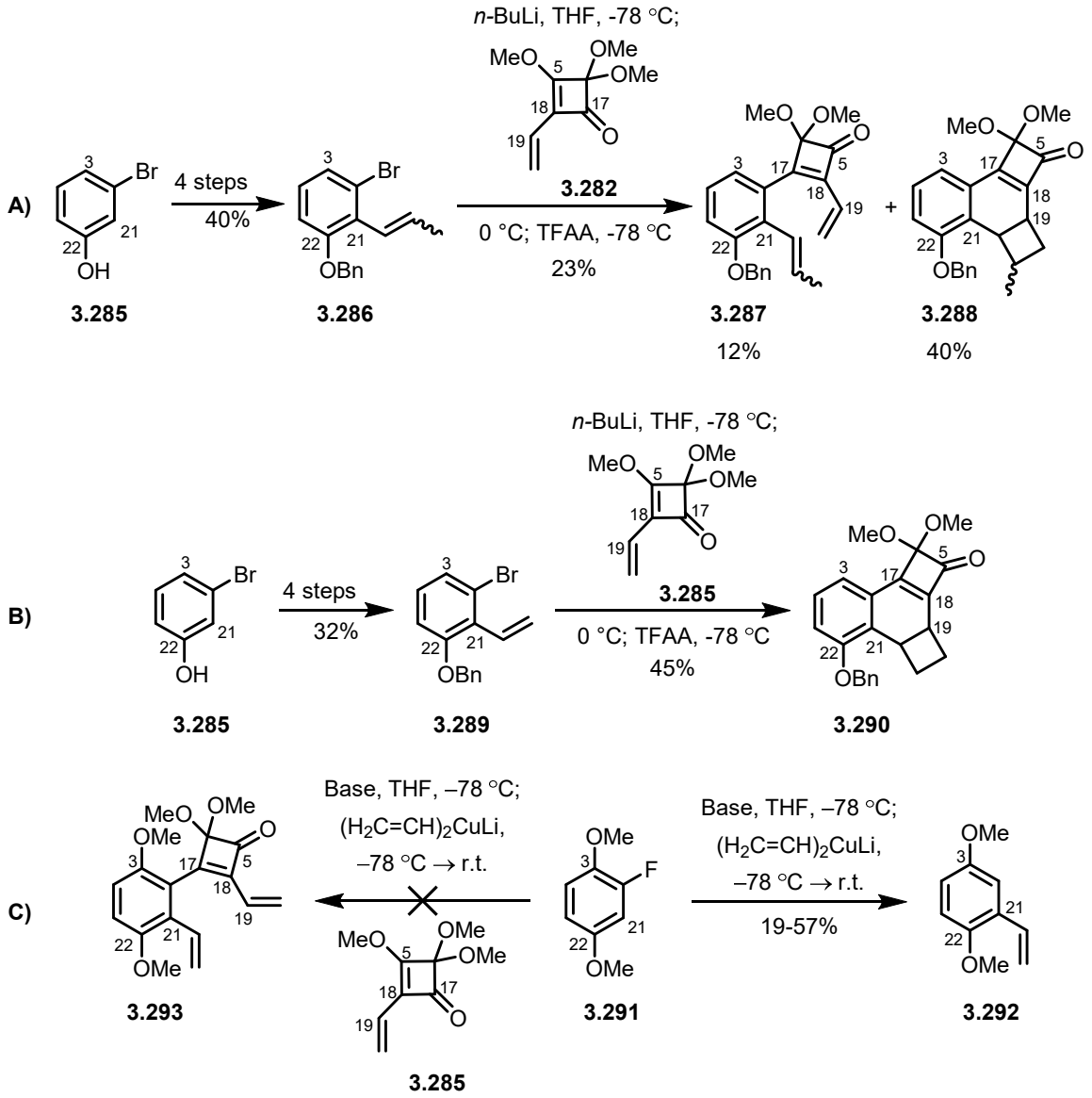
Scheme 3.41: Successful naphthocyclobutanone route *via* squarate addition and RCM



The moderate yields of the squarate addition prompted Dr. Mans and later Dr. Knueppel to investigate other methods of coupling the styrenes and vinyl squarate **3.282**. Hypothesizing that having substitution at C21 and C3 made the aryllithium too hindered to react with **3.282**, Dr. Mans investigated less substituted styrenes in the squarate addition. Metal-halogen exchange of either the bromostyrene **3.286** or **3.289**, and subsequent addition of the vinyl squarate **3.282** did provided only 12% of the desired adduct **3.287** (Figure 3.10, **A**, **B**). The major products were **3.288** and **3.290**, the result of an 8-π and subsequent 6-π electrocyclic ring closure (Figure 3.10, **A**,**B**). The reason why the electrocyclic ring-closed products are seen when bromostyrenes **3.286** and **3.289** are used and not when **3.294** or **3.280** were used is attributed to the $A^{1,3}$ strain associated with bringing the squarate moiety into the same plane as the arene ring in the former example and not in the latter. Later, Dr. Knueppel also attempted to improve the squarate addition by adapting a three-component coupling developed by Barett in his total synthesis of

ent-clavilactone B (Figure 3.10, **C**).[343] The methodology added Grignard reagents into arynes, generated from the ortholithiation of the arylfluoride, to generate a new aryl Grignard reagent. Although the vinyl arene **3.292** was furnished from the reaction of the aryne generated from **3.291** and lithium divinyl cuprate in 19-57% yield, the addition of squarate **3.282** provided no detectable amounts of the desired adduct **3.293**.

Figure 3.10: Unsuccessful attempts to add vinyl squarate to aryllithiums



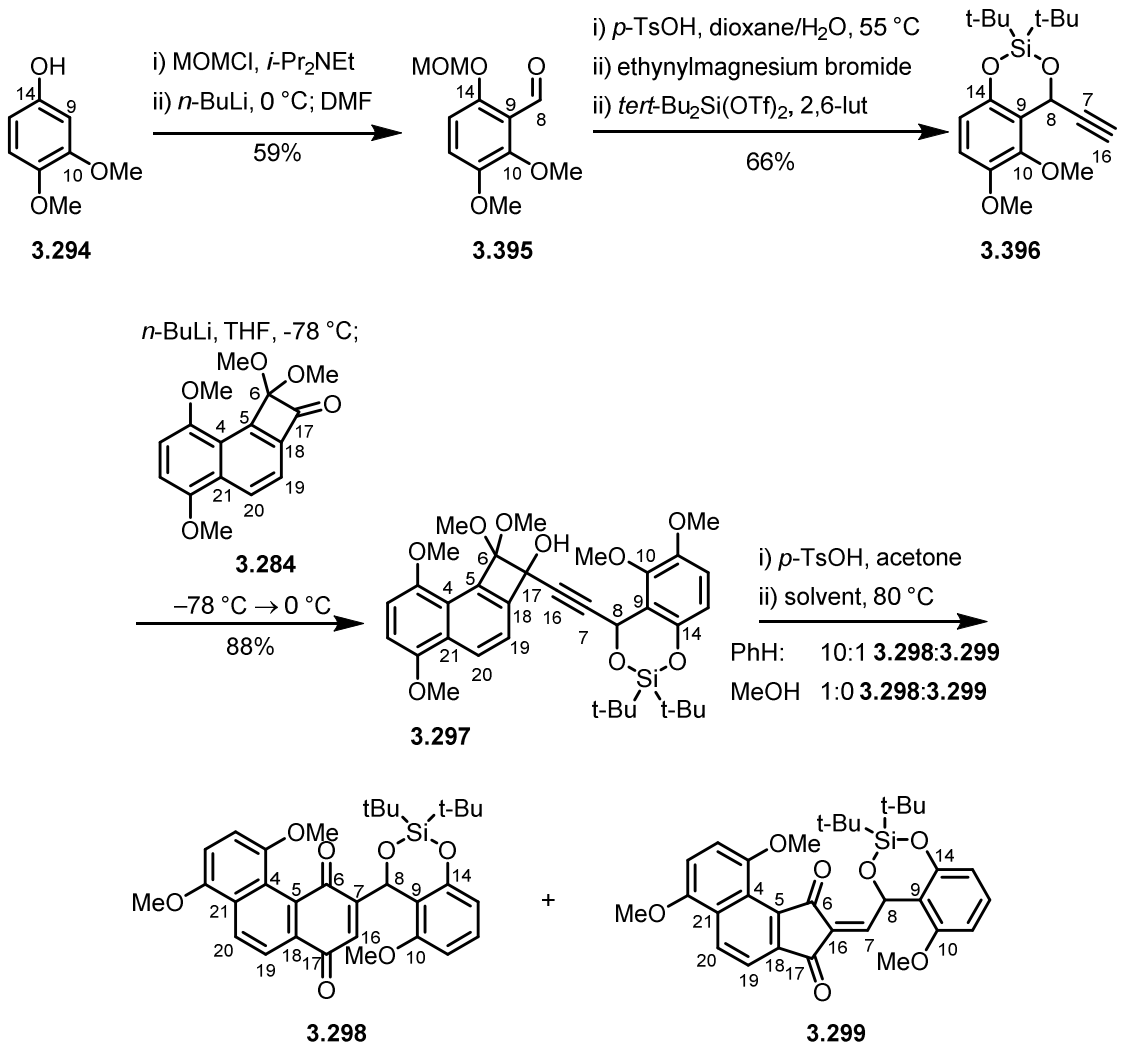
a) Attempted coupling of vinyl squarate **3.282** with bromostyrene **3.291**. b) Attempted coupling of vinyl squarate **3.282** with bromostyrene **3.289**. c) Attempted use of Barett's methodology by Dr. Knueppel toward the naphthocyclobutanone fragment.[343]

3.5.2.3: Evaluation of oxidative Moore rearrangement

With a reliable route to the naphthocyclobutanone **3.284** established, synthesis of the F ring coupling fragment commenced. MOM protection and subsequent ortho-lithiation of arene

3.294, followed by reaction with DMF furnished the aldehyde **3.295** (Scheme 3.42). Hydrolysis of the MOM ether and addition of ethynylmagnesium bromide provided a propargyl alcohol, which was protected as the cyclic silyl ether **3.296**. Deprotonation of **3.296** and addition into the naphthocyclobutanone **3.284** provided the propargyl alcohol **3.297** as a mixture (1:1) of diastereomers. Before embarking on the oxidative cascade to form the xanthone, the Moore rearrangement was investigated as a benchmark. Hydrolysis of the acetal with *p*-toluenesulfonic acid (PTSA) in acetone, followed by heating at 80 °C in degassed benzene provided a mixture (10:1) of the 6-endo product **3.298** and the 5-exo product **3.299**. Care was needed during purification after the hydrolysis of **3.297** as the Moore rearrangement initiated at surprisingly low temperatures. Interestingly, heating the hydrolyzed **3.297** in methanol provided a mixture (1:0) of **3.298** and **3.299**.

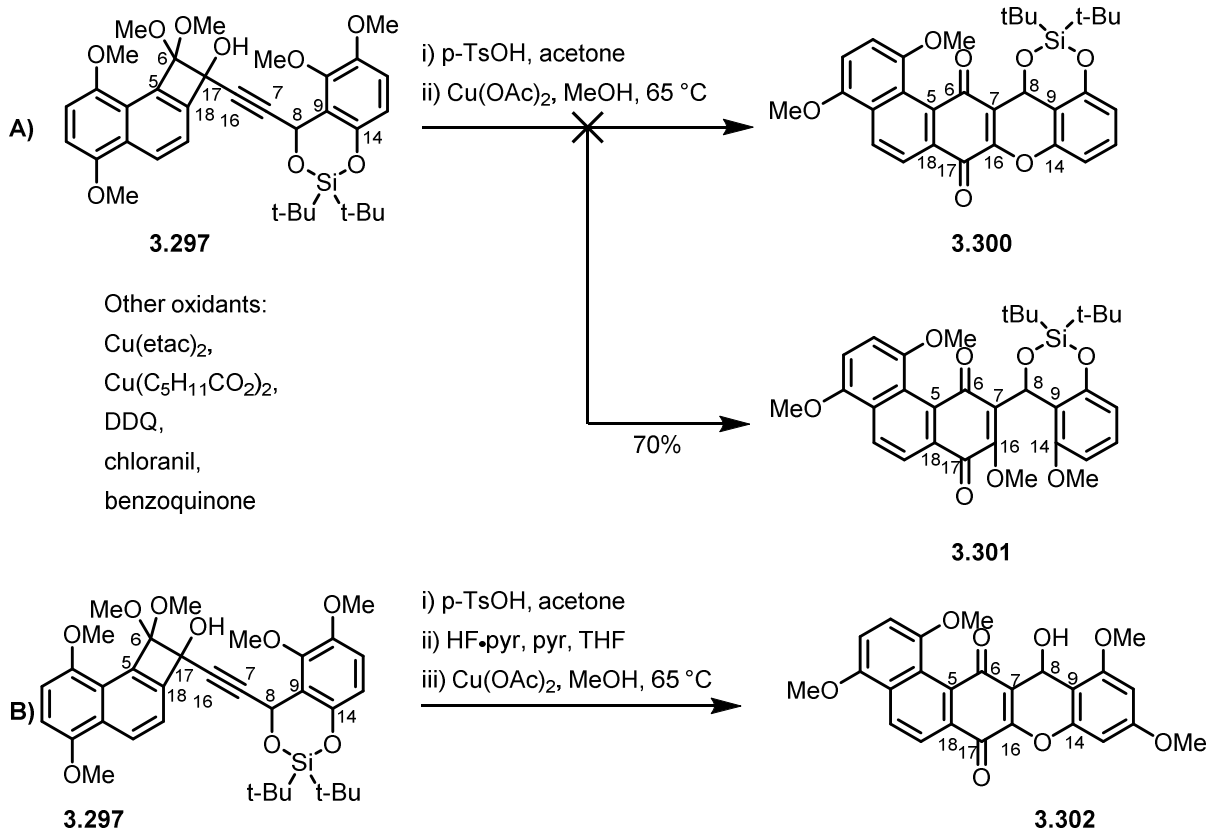
Scheme 3.42: Acetylide coupling and Moore rearrangement investigation



With **3.297** established as a substrate for the Moore rearrangement, the oxidative cascade was investigated. Hydrolysis of the acetal moiety in **3.297** and subsequent heating in methanol with copper acetate did not produce the desired cyclization product **3.300**, but instead gave **3.301** (tentative assignment), the result of methanol intercepting the putative quinone cation intermediate (Figure 3.11, **A**). A variety of protic (H_2O, *tert*-BuOH, *i*-PrOH, F_3CCH_2OH, AcOH), polar aprotic (acetone, DMF, MeCN) and organic (THF, hexanes, glyme) solvents were screened with copper-based and quinone based oxidants but most reactions produced

unidentified side-products. Interestingly, Dr. Mans reported that when benzoquinone was used as an additive, the main product detected was an adduct between benzoquinone and the desired product **3.300**. In the hopes that the cyclic silyl ether moiety was interfering with the capture of the phenol oxygen atom, **3.297** was deprotected with HF•pyr, and the derived phenol was subjected to the same reaction conditions used previously, but no desired product was identified (Figure 3.11, **B**). The failure of the Fuganti-inspired oxidative Moore concluded Dr. Mans contributions toward the synthesis of IB-00208 (**3.14**)

Figure 3.11: Attempted oxidative Moore rearrangement

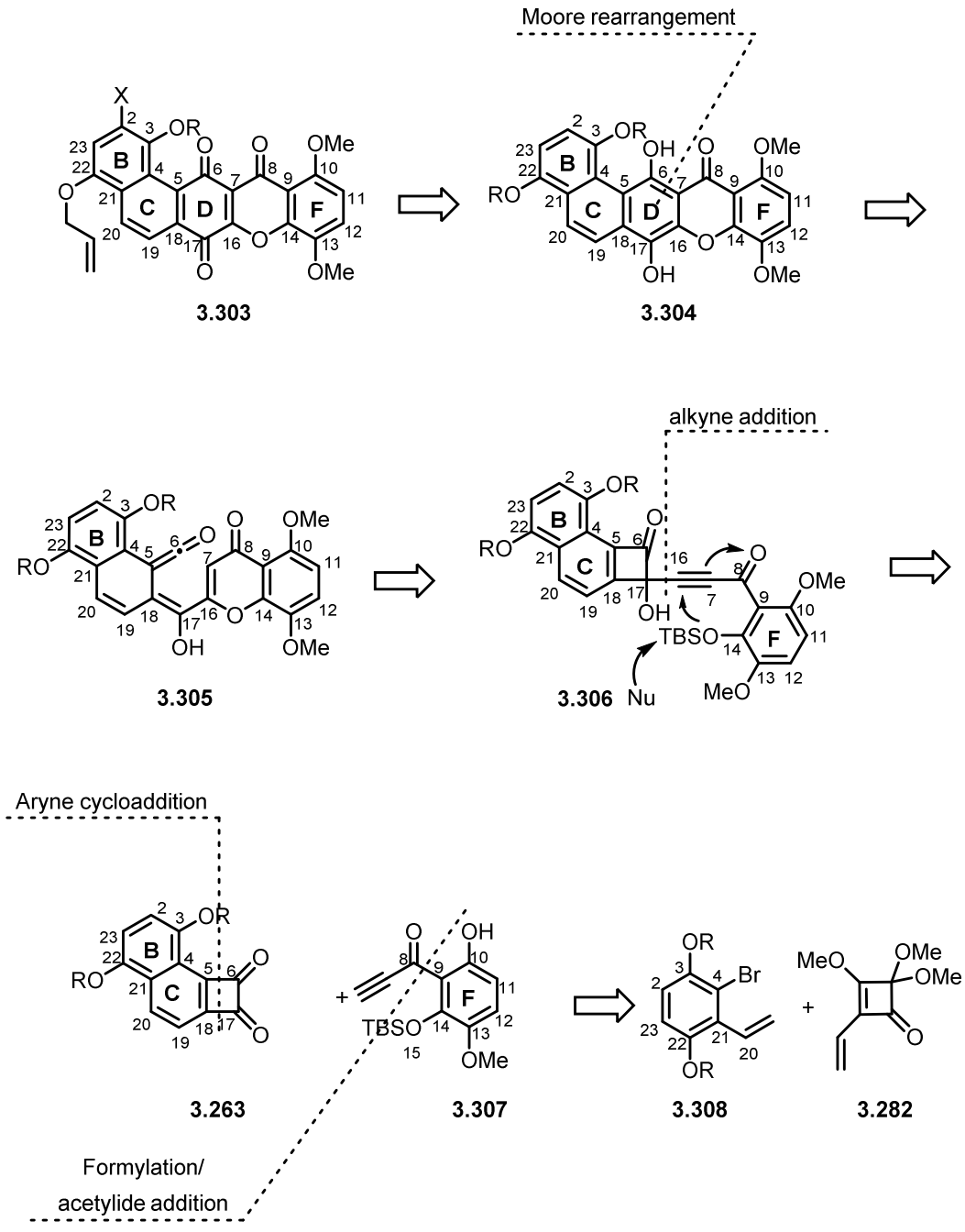


3.5.2.4: Second generation synthetic strategy toward IB-00208

Dr. Knueppel re-imagined the route to the pentacyclic core **3.303**.[344] Instead of the Fuganti-like Moore rearrangement, he envisioned a cyclization cascade from ynone **3.306**

(Scheme 3.43). Removal of the TBS group on the C14 phenol would result in an intramolecular conjugate addition of the phenol moiety to form the xanthone, which upon heating should open up to the ketene intermediate **3.305** prior to a 6-π electrocyclic ring closure to form the hydroquinone **3.304**. Oxidation of the hydroquinone and subsequent functionalization at C2 would provide the pentacyclic core **3.303** which would follow a similar sequence toward IB-00208 (**3.14**). The ynone **3.306** was thought to come from the addition of **3.307** to the naphthocyclobutanone **3.263**, which can be prepared with the previously established strategy.

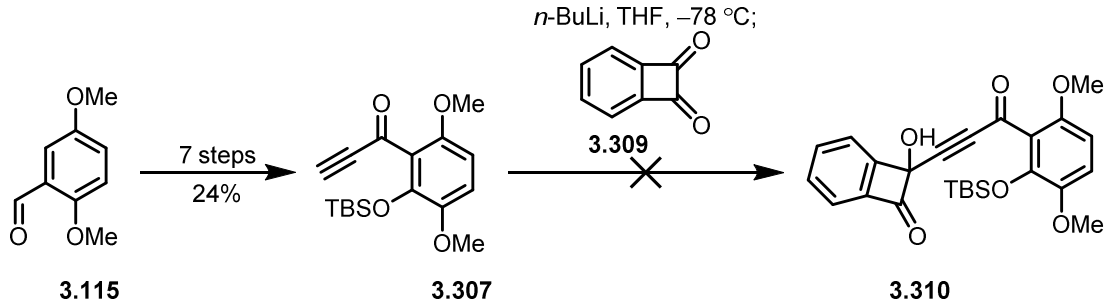
Scheme 3.43: Second generation retro-synthesis for IB-00208 (**3.14**) as envisioned by Dr. Knueppel



3.5.2.5: Model study

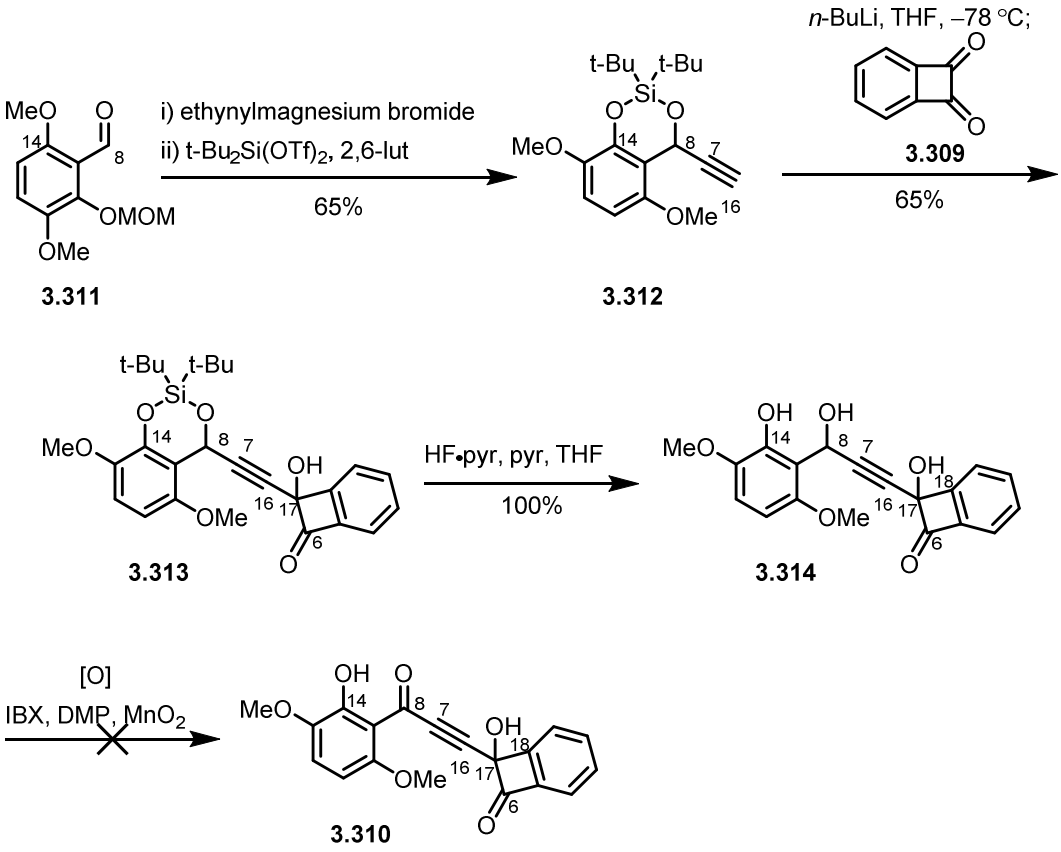
Model studies were initiated to investigate the chemistry involved in the addition of ynones to cyclobutanones and to evaluate the conjugate addition/electrocyclization cascade. Unfortunately, attempted coupling between the ynone **3.307** and the benzocyclobutadione **3.309** provided no desirable product **3.310**, even in the presence of $CeCl_3$ or 12-c-4 (Scheme 3.44). Deprotonation of **3.307** and quenching with MeI of benzaldehyde revealed that although the ynone was being deprotonated, the anion was not reacting with **3.309**.

Scheme 3.44: Attempted acetylide coupling between **3.307** and **3.309**



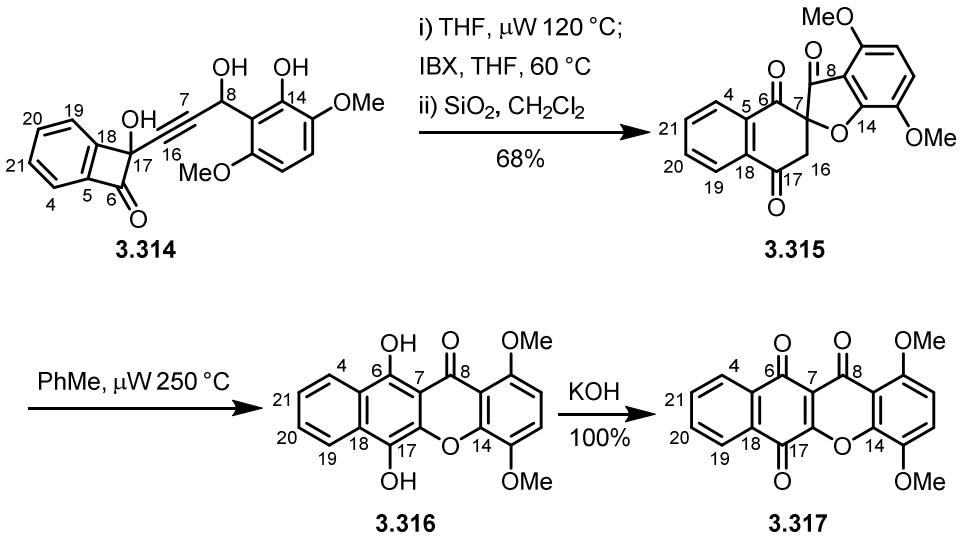
The failure to add the ynone **3.307** into **3.309** prompted the investigation of adding the propargyl alcohol into the benzocyclobutadione **3.309** first, then oxidize to the ynone **3.310**. Addition of ethynylmagnesium bromide to aldehyde **3.328** (prepared in three steps from **3.311** in 40% yield) formed the MOM-deprotected propargyl alcohol, which was protected as the cyclic silyl ether **3.312** (Scheme 3.45). Deprotonation of **3.312** and addition to the benzocyclobutadione **3.309** provided the adduct **3.313** in 65% yield. Deprotection of the cyclic silyl acetal with HF•Py provided the propargyl alcohol **3.314**. Several conditions were screened in order to oxidize the propargyl alcohol **3.314** to the ynone **3.310**, but only complex mixtures were obtained so this strategy was abandoned in favor of initiating the Moore cyclization before the oxidation of the benzyl alcohol.

Scheme 3.45: Successful acetylide coupling between **3.312** and **3.309** and attempted oxidation of **3.314**



Gratifyingly, the Moore rearrangement of **3.314** proceeded upon heating in THF, and subsequent oxidation of the benzyl alcohol with IBX delivered the quinone, which upon treatment with silica, unexpectedly resulted in the spontaneous cyclization to the spirocycle **3.315** in 68% yield from **3.314** (Scheme 3.46). Microwave heating the spirocycle in toluene gave mixtures of the desired quinone **3.317** and the hydroquinone **3.316**. Air and Ag_2O were evaluated to convert the hydroquinone **3.316** to **3.317** but it was found that a basic KOH workup after the toluene reaction delivered the tetracyclic core **3.317** directly in quantitative yield.

Scheme 3.46: Successful synthesis of tetracyclic core model system

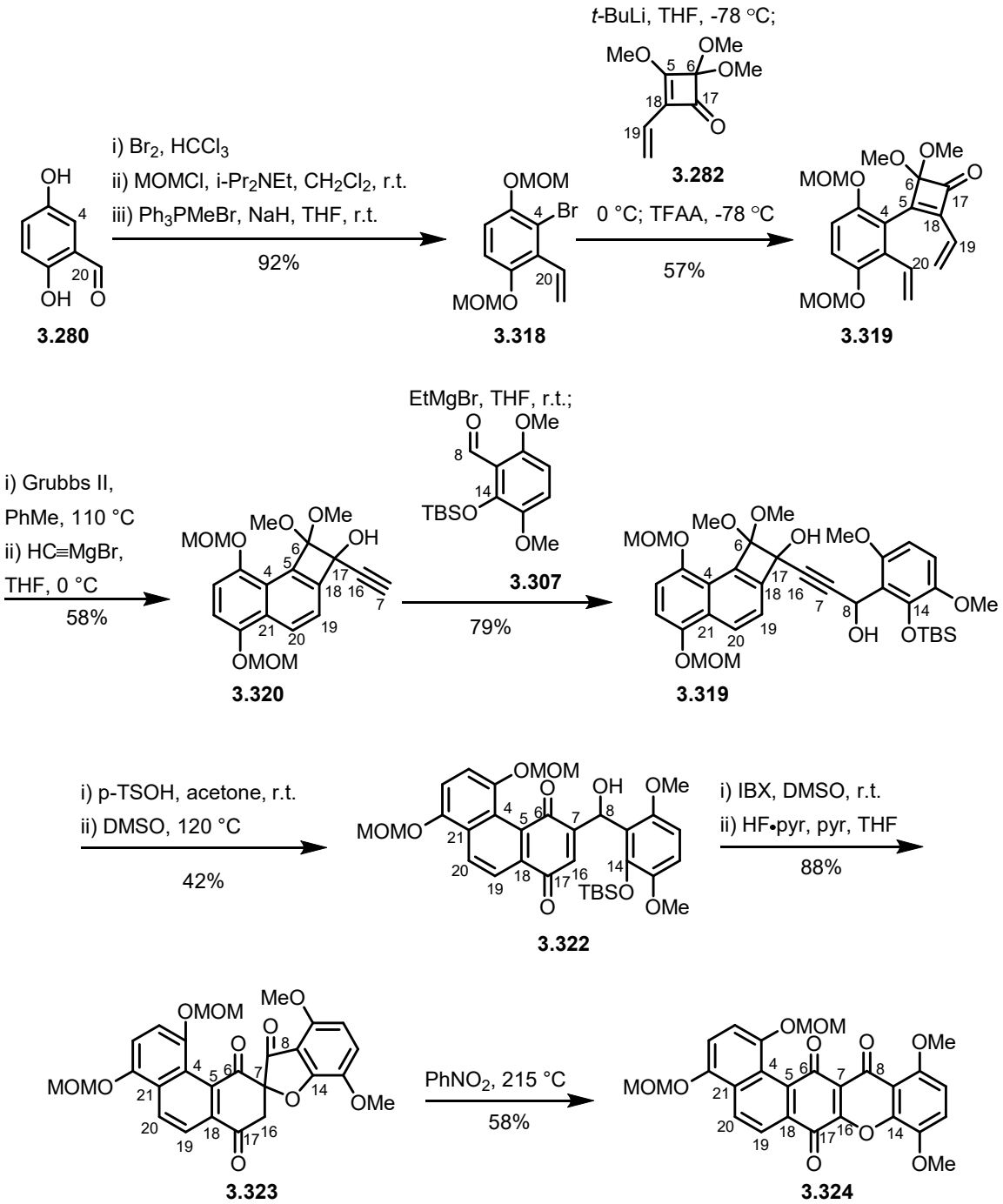


3.5.2.6: Synthesis of the pentacyclic core

Once the groundwork had been established in the model system, work began on the pentacyclic core. Bromination of the commercially available aldehyde **3.280** occurred selectively at C4 (Scheme 3.47). Protection of both phenols as the MOM ethers and Wittig olefination provided the bromostyrene **3.318** in 92% yield. Metal-halogen exchange of the bromostyrene **3.318** with *tert*-BuLi, followed by the addition of vinyl squarate **3.282** provided **3.319** in 57% yield. Ring closing metathesis (RCM) and addition of ethynylmagnesium bromide provided **3.320**. Double deprotonation of the propargyl alcohol **3.320** followed by quenching with the aldehyde **3.307** (see Scheme 3.51) provided the coupled product **3.321** in 79% yield. Initial experiments with adding acetylide **3.312** into the napthocyclobutanone provided none of **3.321**. Hydrolysis of the C6 acetal, followed by Moore rearrangement under the conditions used in the model system provided only trace amounts of the quinone **3.322**. A solvent screen found that PhMe, THF, PhCl, MeCN and DMF were all poor solvents for the Moore cyclization. Only degassed DMSO, which had been stored over 4Å molecular sieves provided the product **3.322** in 42% yield. Oxidation of **3.322** with IBX and subsequent deprotection provided the spirocycle

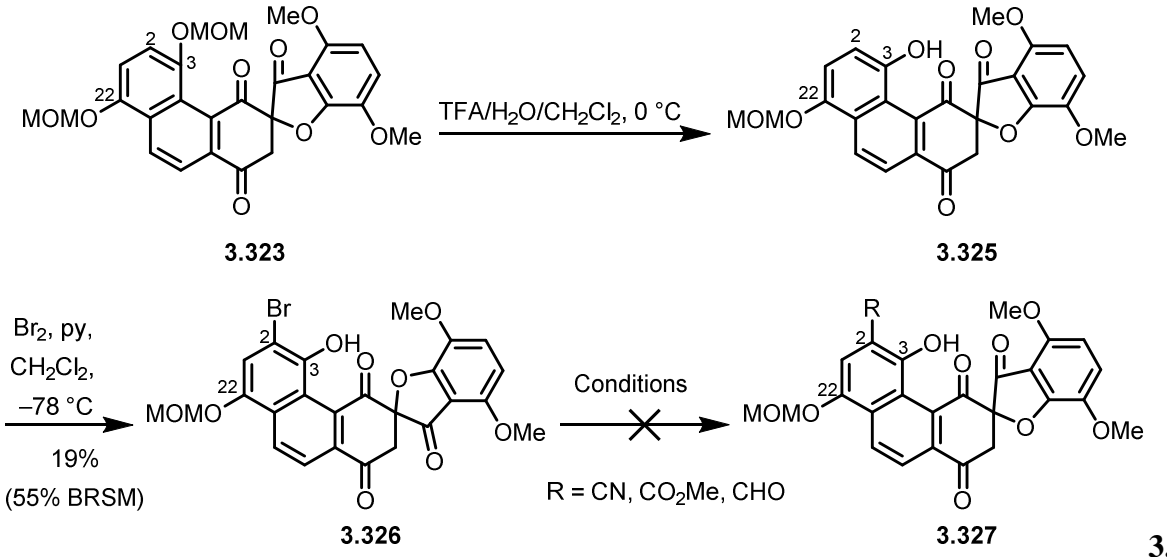
3.323, but attempts to use the conditions developed in the model system to generate the pentacyclic core **3.324** failed. Fortunately, use of $PhNO_2$ as the solvent furnished **3.324** in 58% yield.

Scheme 3.47: Synthesis of pentacyclic core of IB-00208 (**3.14**)



Attempts to deprotect both of the MOM ethers in **3.324** with TFA/H_2O resulted in complex mixtures. Fortunately, selective deprotection of the C3 MOM group of the spirocycle **3.323** was accomplished with TFA/H_2O, but attempted removal of the second MOM group gave complex mixtures (Scheme 3.48). Numerous bromination conditions were tried (NBS/i-Pr_2NH, $PyHBr_3$, NBS, Br_2, $CuBr_2$ and Br_2•1,4-dioxane) but only a slow addition of Br_2 to a mixture of **3.325** in pyridine/CH_2Cl_2 provided **3.326** in 19% yield, the major byproduct being the C22 MOM-deprotected product. Unfortunately, attempts to affect the alkoxy carbonylation, formylation or the Rosenmund-von Braun reaction of **3.326** to provide either the carbomethoxy-, formyl- or cyano- groups at C2 all led to complex mixtures.

Scheme 3.48: Attempted functionalization of the B ring

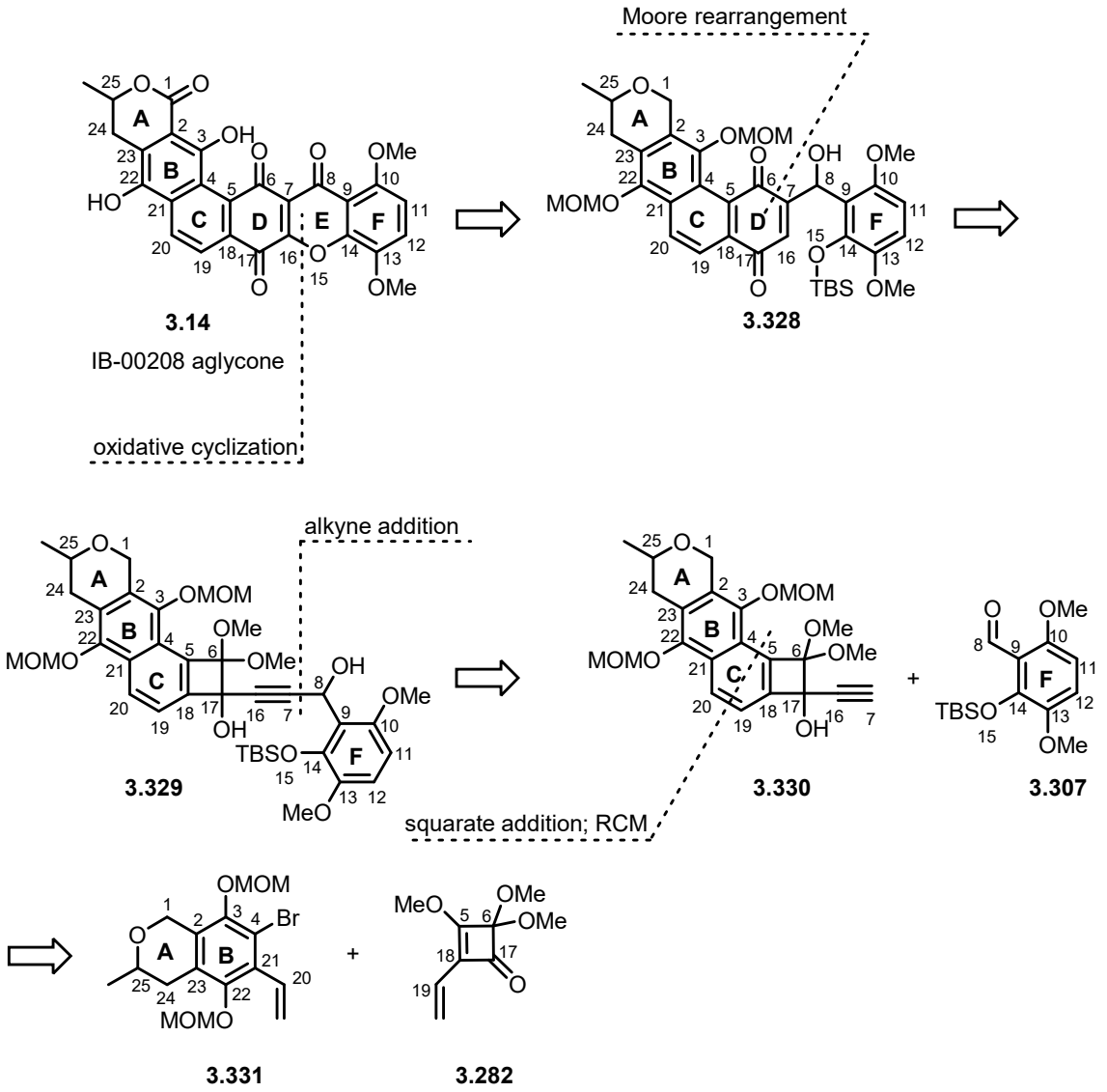


3.5.2.7: Successful strategy towards IB-00208 aglycone

The inability to functionalize the B ring in **3.325** led to a redesign of the synthesis. Dr. Knueppel envisaged that the A ring moiety could be appended to the quinone **3.328**, which would be prepared from the alkyne **3.329** *via* the Moore rearrangement (Scheme 3.49). The alkyne **3.329** would be formed from the union of the aldehyde **3.307** and propargyl alcohol **3.330**, which ultimately would come from the coupling of the bromostyrene **3.331** and the vinyl

squarate **3.282**. The utilization of this strategy culminated in the total synthesis of IB-00208 (**3.14**) aglycone **3.14** in 2015 through the combined efforts of Dr. Knueppel, Dr. Cheng and Dr. Yang.[345, 346]

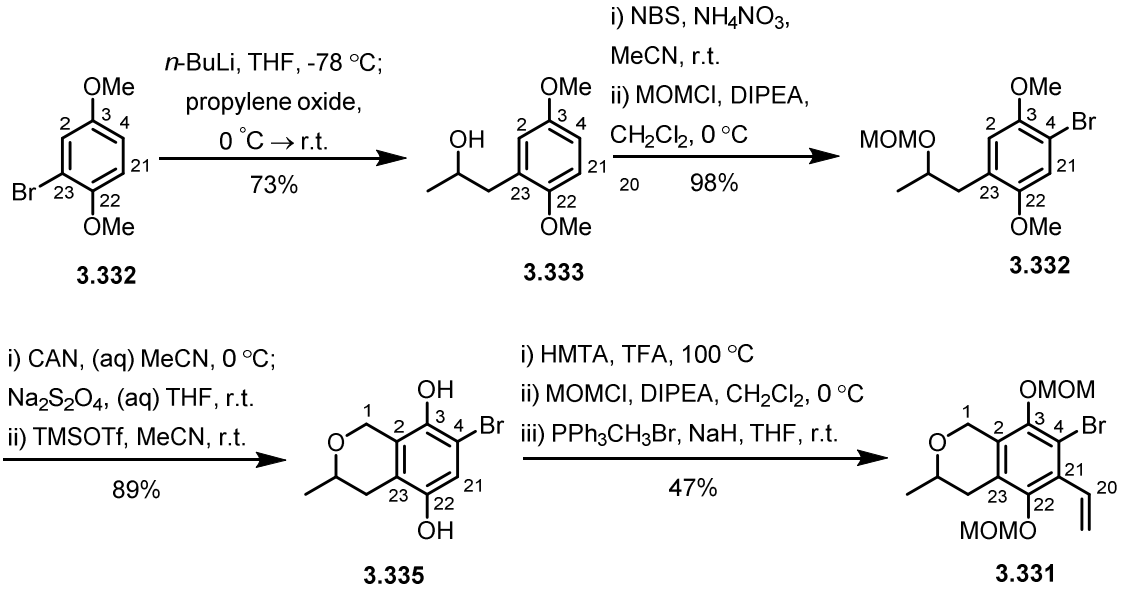
Scheme 3.49: Martin group's synthesis of IB-00208 (**3.14**) aglycone



Lithium-halogen exchange of the bromo arene **3.332**, followed by alkylation with propylene oxide provided alcohol **3.333** (Scheme 3.50). Bromination of **3.333** under Tanemura conditions (NBS, cat. NH_4NO_3) proceeded regioselectively at C4, and protection of the alcohol as the MOM ether furnished **3.334**.[347] Oxidative-demethylation of the arene to the quinone with

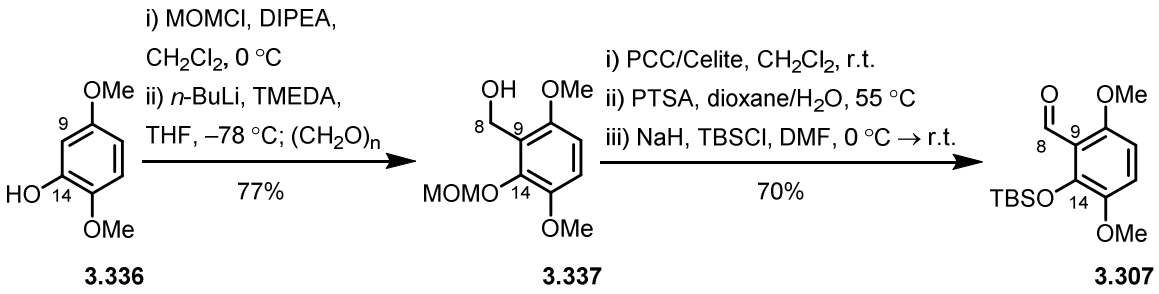
CAN, followed by a reductive workup with sodium dithionite ($Na_2S_2O_4$) provided the hydroquinone, which was subsequently cyclized to isochroman **3.335** *via* a TMSOTf catalyzed oxy-Pictet-Spengler cyclization with the MOM group. Attempts to initiate the oxy-Pictet-Spengler from the hydroquinone dimethyl ether **3.334** led to lower yields and competitive oxidation at C1 during the CAN oxidation. Duff formylation of **3.335** with hexamethylenetetramine (HMTA) in neat trifluoroacetic acid, followed by bis-MOM protection and Wittig olefination provided the key bromostyrene **3.331**.[348]

Scheme 3.50: Synthesis of AB ring fragment **3.331**



Synthesis of the F ring coupling partner began with protection of the phenol **3.336** as the MOM ether (Scheme 3.51). MOM-directed ortho-lithiation at C9, followed by quenching with paraformaldehyde furnished benzyl alcohol **3.337**. Oxidation of the benzyl alcohol with PCC/celite, followed by hydrolysis of the MOM ether and protection of the phenol as the TBS ether provided the F ring coupling partner **3.307**.

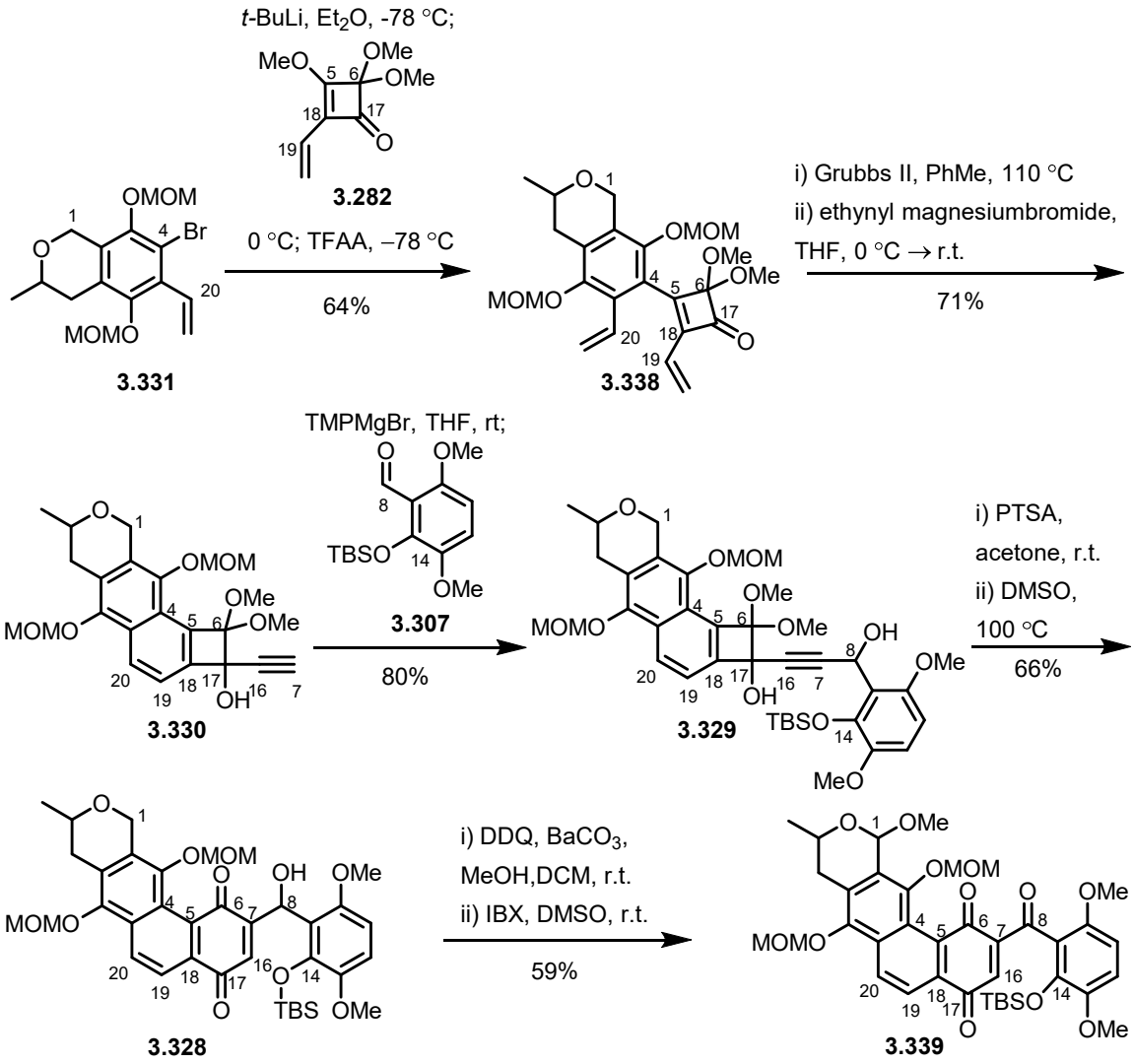
Scheme 3.51: Synthesis of F ring fragment **3.307**



Lithium-halogen exchange of the bromo-styrene **3.331** and addition into the vinyl squarate **3.282** provided **3.338** (Scheme 3.52). RCM with Grubbs II catalyst, followed by addition of ethynylmagnesium bromide to the C17 ketone furnished **3.330**. Attempts to add ethynylmagnesium bromide into aldehyde **3.307**, followed by double-deprotonation and addition into the benzocyclobutanone were unsuccessful, perhaps because of the steric bulk of both the nucleophile and the electrophile. Double-deprotonation the propargyl alcohol **3.330** with EtMgBr afforded the desired compound **3.329** in 83% yield, but these results were not reproducible, owing perhaps to adventitious proton sources. Adding super-stoichiometric quantities of base to consume the proton sources led to addition products of the aldehyde. Fortunately, tetramethylpiperidine magnesiumbromide (TMPMgBr) was sufficiently sterically hindered that it did not add into the aldehyde. Hence, adding TMPMgBr to a solution of **3.330** and **3.307** gave the bis-propargyl alcohol **3.329** in 80% yield. Deprotection of the acetal to the ketone and heating in dilute DMSO initiated the Moore rearrangement to give quinone **3.328**. Oxidation of the C1 carbon atom was very sensitive to the electronics of the aromatic core. Formation of the xanthone moiety or the C8 carbonyl group prior to oxidation with DDQ resulted in no reaction, while deprotection of the C14 TBS ether to the phenol and oxidation with DDQ led to complex mixtures. Benzylic oxidation proceeded from intermediate **3.328** with DDQ in CH_2Cl_2/H_2O to provide the C1 hemiacetal, but attempts to oxidize the C8 alcohol resulted complex mixtures. Modifying the DDQ oxidation by adding MeOH and $BaCO_3$ allowed for the

isolation of the C1 methoxy acetal, which enabled the oxidation of the C8 alcohol with IBX in DMSO to provide **3.339**.

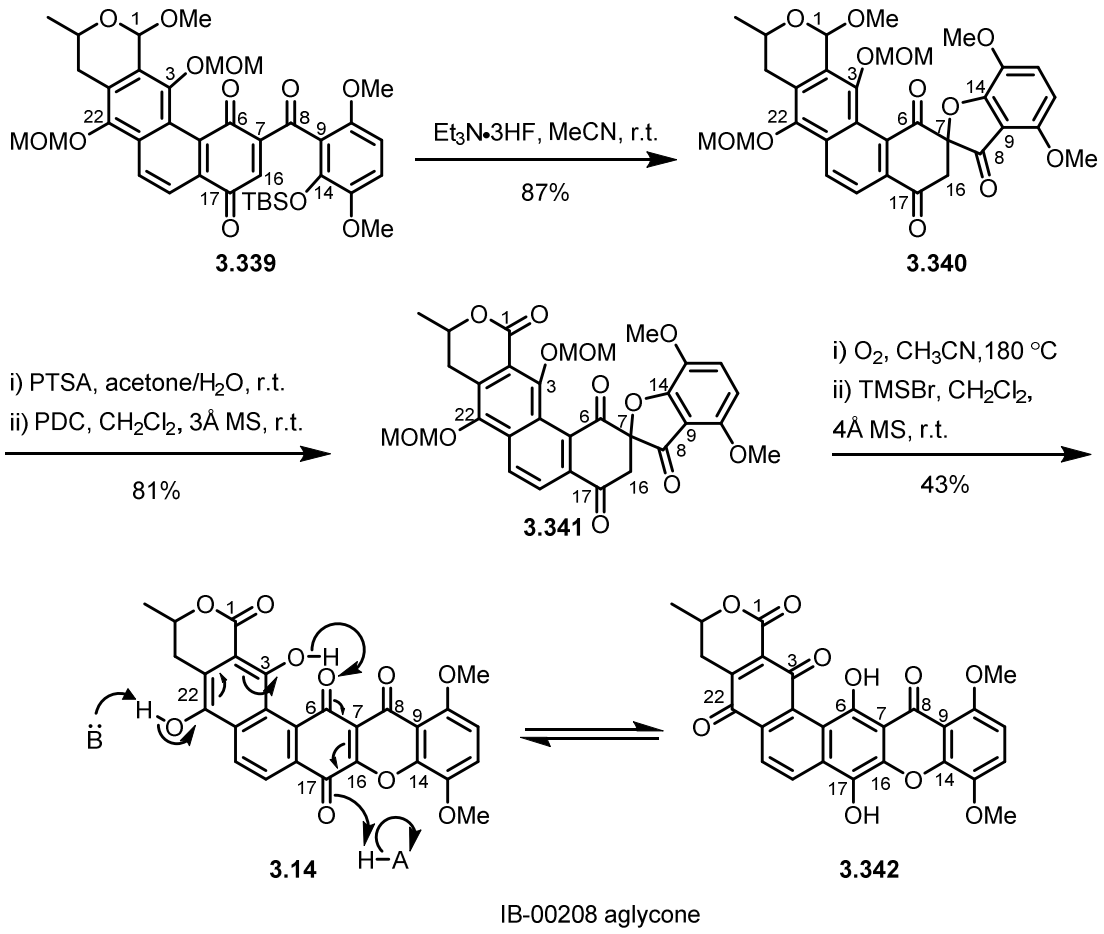
Scheme 3.52: Synthesis of ABCDF ring fragment **3.339**



Deprotection of the TBS moiety in **3.339** with $Et_3N \bullet 3HF$ and cyclization at C7 formed the spirocycle **3.340** (Scheme 3.53). Deprotection of the acetal moiety at C1, followed by oxidation with pyridinium dichromate (PDC) provided the lactone **3.341**. Heating **3.341** in MeCN in a microwave under an atmosphere of oxygen led to the bis-MOM protected core of IB-00208 (**3.14**). Deprotection of the MOM groups with TMSBr led to an equilibrating mixture (2:1) of redox tautomers **3.14** and **3.342** in 22 steps from **3.332** and in 1.3% overall yield. Both

the Ready group and the Porco group also noted similar redox tautomerization in the kibdelones when one of the hydroquinones was not protected.

Scheme 3.53: Martin's completion of IB-00208 (**3.14**) aglycon



The synthesis of IB-00208 (**3.14**) provided valuable lessons for the application of the Martin group strategy toward other polycyclic xanthone natural products. Although the synthesis of the napthocyclobutanone fragment was accomplished by the addition of the lithiostyrene into the vinyl squarate **3.282**, the reaction was sensitive to the substituents on the arene ring, and the yields only ranged from 50-60%. The coupling of the napthocyclobutanone fragment and the F ring fragment was also temperamental, perhaps because of adventitious proton sources and/or sterics effects. The outcomes of the Moore rearrangement of the adducts **3.319**, **3.314** and **3.297** were dependant on the solvent, providing the 6-endo and 5-exo cyclization products in varying

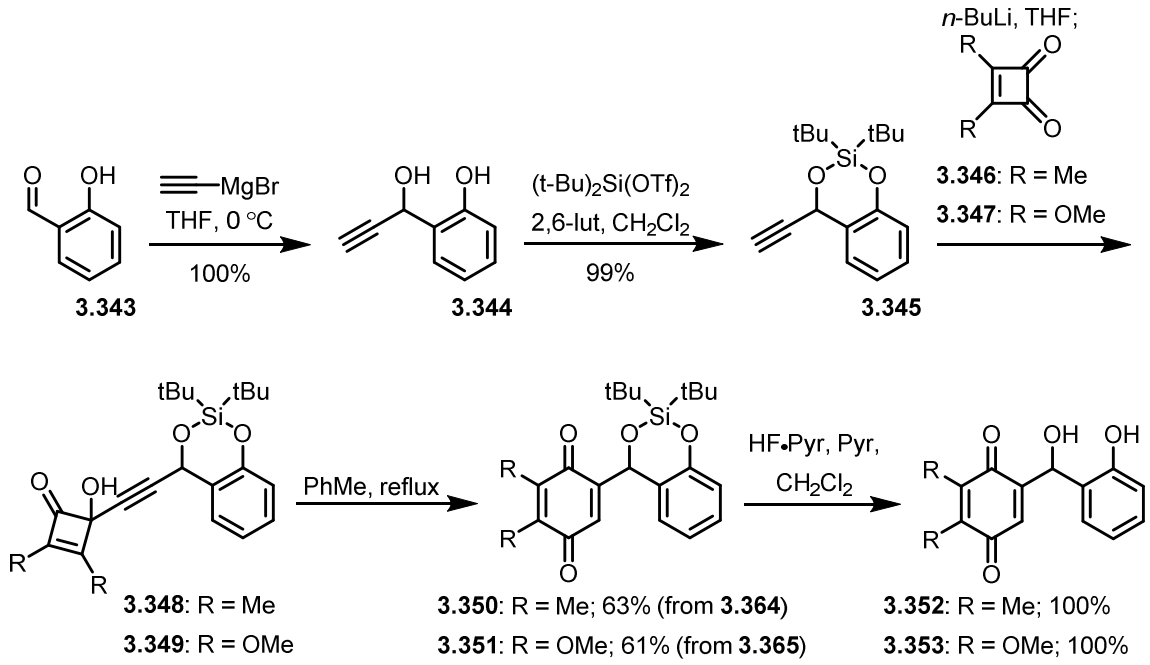
amounts (Scheme 3.47, 3.45 and 3.42). The late stage oxidation at C1 proved also proved to be dependent on the electronics of the aromatic ring, with even the remote C8 carbonyl affecting the outcome of the reaction. Future applications of this strategy toward other polycyclic xanthone natural products would need to investigate different strategies towards the synthesis of the G or A rings. Currently, the A ring is synthesized in the beginning, appended to styrene **3.331** and oxidation of the benzylic carbon furnishes the lactone moiety in IB-00208 (**3.14**). Though this strategy was successful for IB-00208 (**3.14**), other polycyclic xanthone natural products such as cervinomycin (**3.17**), kigamicins (**3.20**) and citreamicin have an additional G ring and the A ring are more densely functionalized and thus would make it difficult to build a suitable A and G ring precursor in the beginning, which would be stable to the strong base chemistry encountered during the synthesis.

3.5.3: WORK BY DR. NICHOLS TOWARD TRICYCLIC XANTHONES

The utilization of the Moore rearrangement toward the synthesis of xanthone natural products was more broadly explored by Dr. Alex Nichols who developed a general approach to 1,4-diogygenated xanthones that was applied to a synthesis of dulcisxanthone C.[349,350] The first approach xanthones utilized the coupling of the cyclic silyl ether protected propargyl alcohol derivative **3.345**, first reported by Dr. Mans (see Scheme 3.42), and the squarate **3.346** or **3.347**.

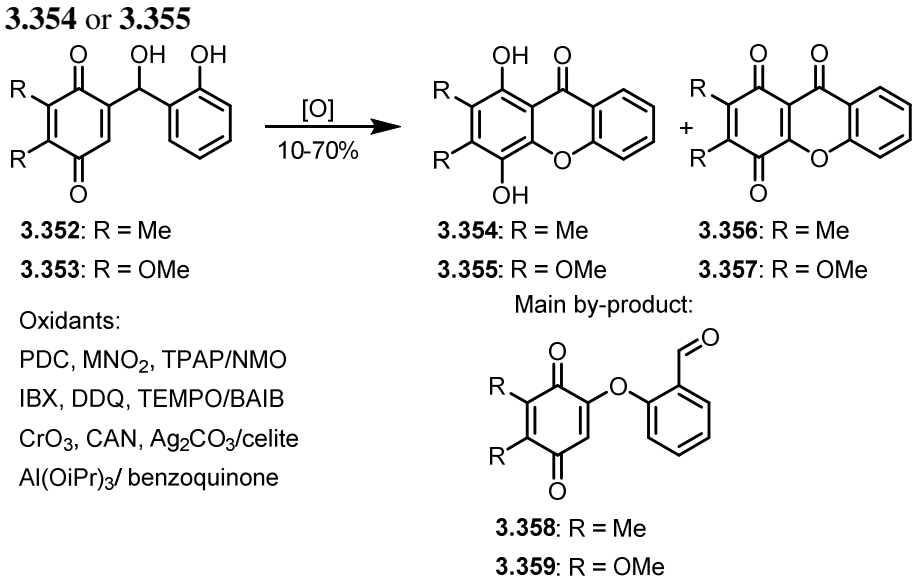
Addition of ethynyl magnesiumbromide to salicylaldehyde (**3.343**) furnished propargyl alcohol **3.344** (Scheme 3.54), and protection of both the alcohol and the phenol moieties provided the cyclic silyl ether **3.345**. Deprotonation of the acetylene moiety and addition of the subsequent anion to either the squarate **3.346** or **3.347**, gave the cyclobutanols **3.348** or **3.349**, which provided the quinones **3.350** and/or **3.351** upon heating in toluene. Removal of the cyclic silyl protecting group with HF•Pyr provided the phenols **3.352** and/or **3.353**.

Scheme 3.54: Dr. Alex Nichols's first generation approach



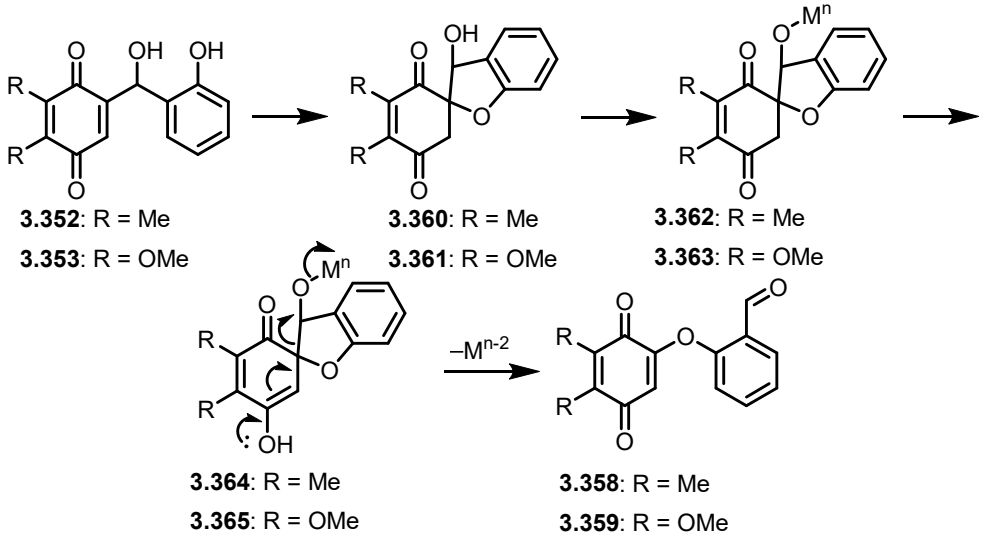
Several oxidants were screened to oxidize the benzylic alcohol in **3.352** or **3.353** to the ketone, which was thought to cyclize to the xanthone **3.354** or **3.355** under the reaction conditions (Equation 3.2). Though Dr. Nichols was able to isolate the desired products, the yields varied from 10% to 70% along with the byproducts **3.358** or **3.359** and the quinones **3.356** or **3.357**. Dr. Knueppel also had difficulty in oxidizing compounds such as **3.352** or **3.353** (see Scheme 3.45).[344] Subjection of the xanthone **3.354** or **3.355** to Jones oxidation conditions only returned 10% of the xanthone along with a substantial amount of degradation products, suggesting that the product was unstable to the reaction conditions.

Equation 3.2: Dr. Alex Nichols's attempted cyclization of **3.352** or **3.353** to the xanthone



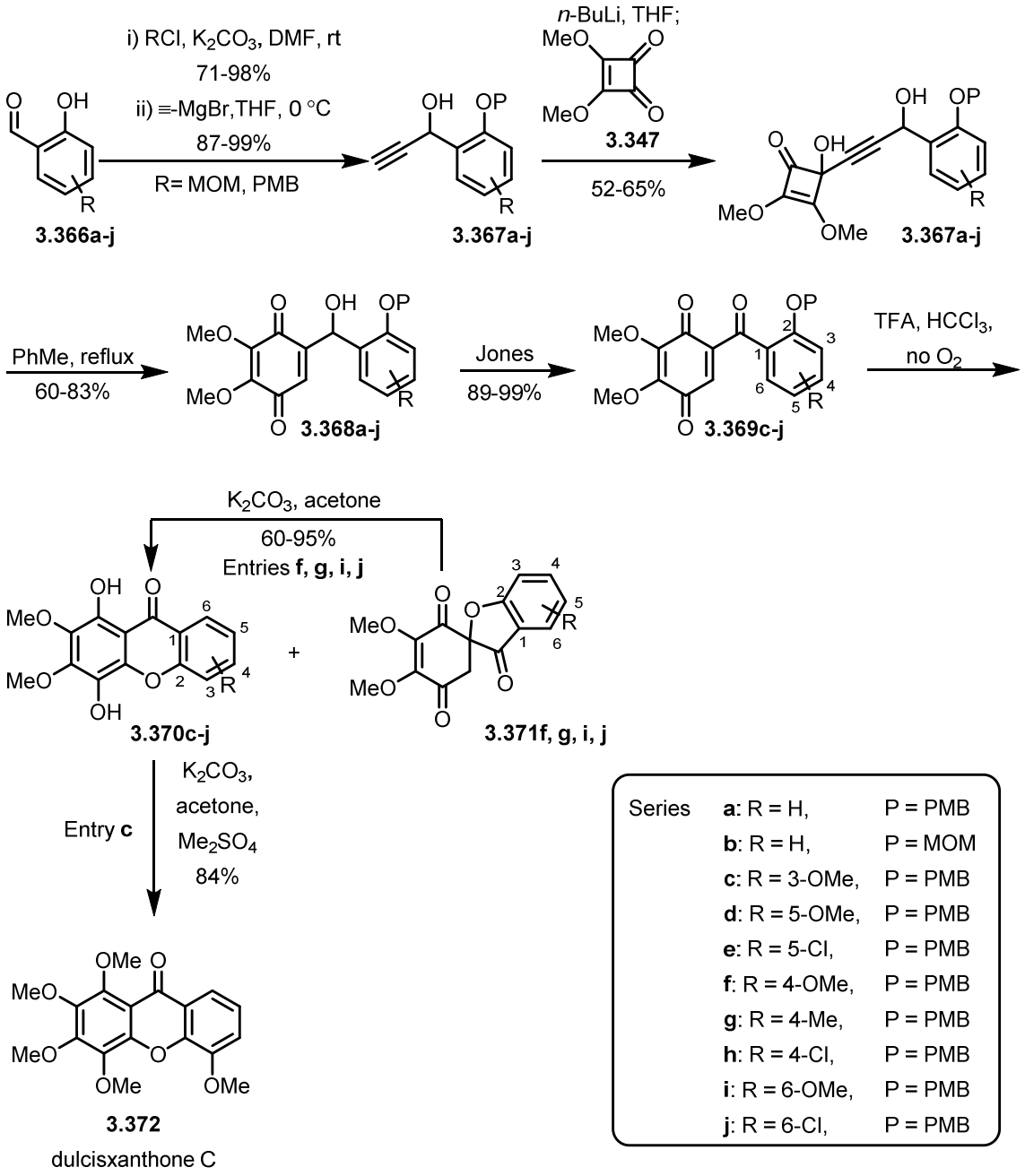
The byproducts **3.358** and/or **3.359** were proposed to be formed by first cyclizing to the spirocycle **3.360** or **3.361** (Scheme 3.55). Coordination of the oxidant to the alcohol forms complex **3.362** or **3.363**, which upon enolization to **3.364** or **3.365** facilitates an oxidative fragmentation to the byproduct **3.358** or **3.359**.

Scheme 3.55: Dr. Alex Nichols's mechanistic proposal for the formation of **3.358** or **3.359**



To overcome this problem, both MOM and PMB protecting were investigated as protecting groups for the phenol (Scheme 3.56). Addition of ethynyl magnesium bromide to PMB or MOM protected salicylaldehydes **3.366a-j** furnished propargyl alcohols **3.367a-j**. Double-deprotonation of these propargyl alcohols and addition into the squarate **3.347** gave the cyclobutanols **3.367a-j**, which after heating in toluene provided quinone **3.368a-j**. Gratifyingly, Jones oxidation cleanly provided the ketones **3.369a-j** in 88-99% yield, other oxidants such as PCC or PDC required longer reaction times and provided the ketone in lower yields. While the MOM protected derivative of **3.369a** required harsh conditions to deprotect and produced mixtures of products, the PMB group was cleanly removed in the presence of TFA to provide either the xanthones **3.370c,d,e** and **3.370h** or the spirocycles **3.371f,g,i** and **3.371j**. The exclusion of oxygen and light was key for the isolation of the xanthones in high yield, which paradoxically resulted in the reduction of the quinone to the hydroquinone. Fortunately, the spirocycles **3.371f,g,i** and **3.371j** can be converted to the xanthones **3.370f,g,i** and **3.370j** in the presence of K_2CO_3 and acetone. Finally, by alkylation of **3.370c** with K_2CO_3 and Me_2SO_4, Dr. Nichols was able to synthesize dulcisxanthone c (**3.372**) in seven steps and in 22% overall yield.

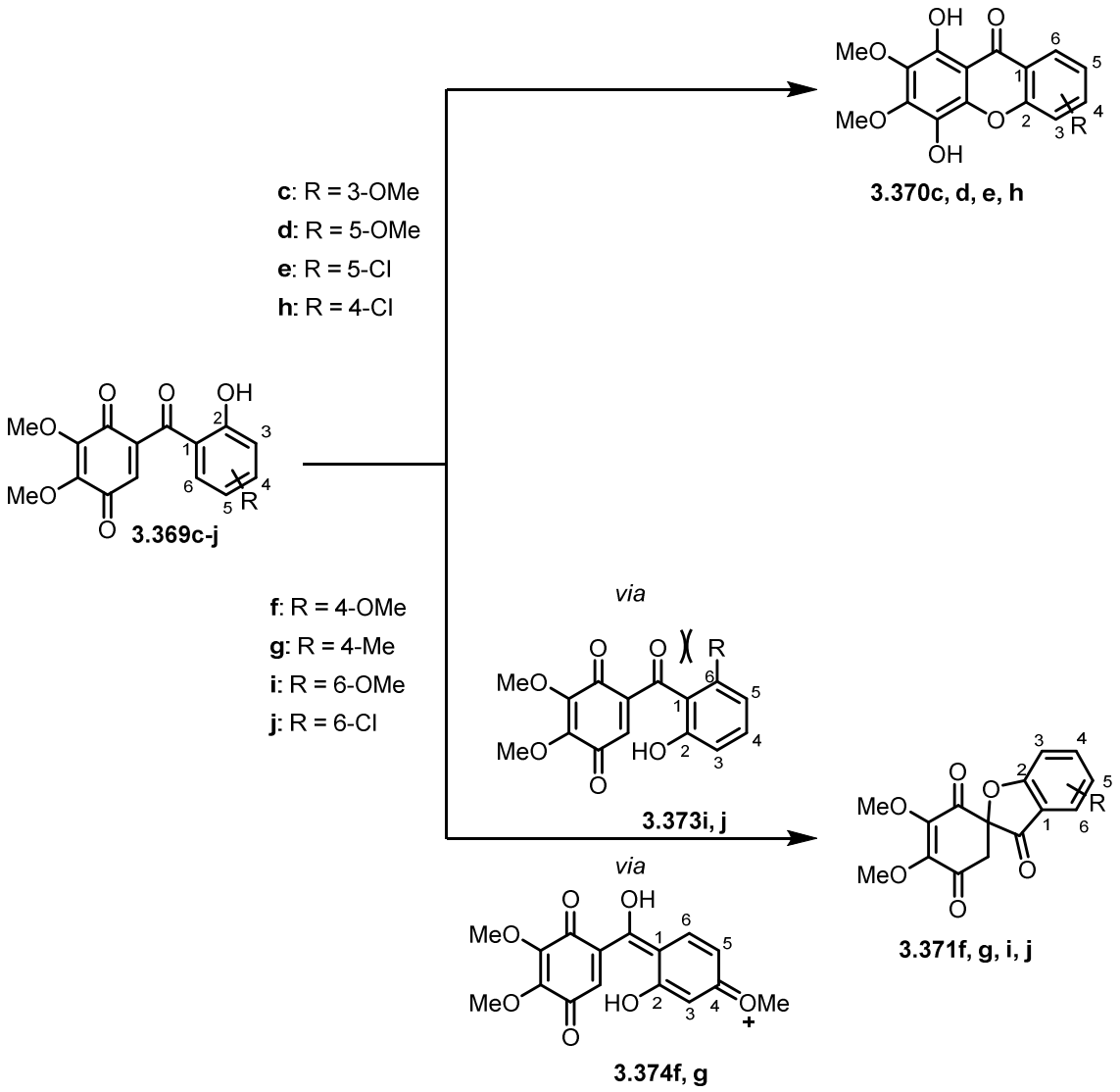
Scheme 3.56: Dr. Alex Nichols's second generation synthesis of xanthones



The substituents on the aromatic ring determined the product ratios between xanthone or spirocycle formation. While substituents at the 3- and 5-positions had little effect, producing only the xanthones **3.370c,d,e** and **3.370h**. Substituents at the 6-position and electron donating substituents at the 4-position favored the spirocycles **3.371f,g** (Scheme 3.57). The electron-

donating groups at C4 are thought to deactivate the carbonyl through resonance (Shown in structure **3.374**), which reduces the electrophilicity of the ketone and hence bias between the α- and β-positions of the quinone toward nucleophilic attack. Substituents at C6 are thought to favor the spirocycle because of the steric interactions between the substituent and the ketone that are encountered when cyclizing on the β-carbon, shown in **3.373**.

Scheme 3.57: Rational for spirocycle formation

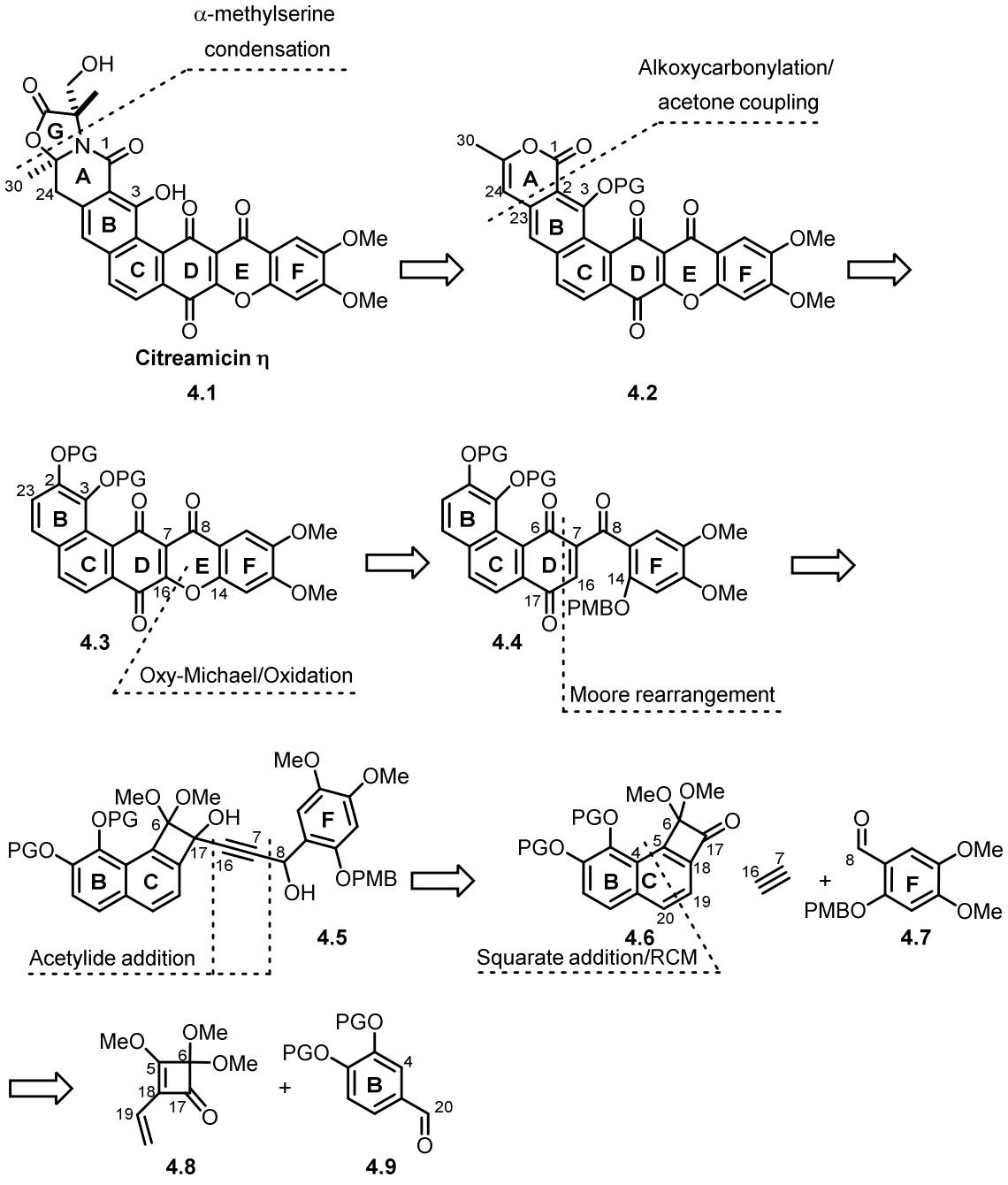


CHAPTER 4: SYNTHESIS OF THE CORE OF CITREAMICIN η AND GA-RING MODEL STUDIES

4.1 Synthetic strategy towards citreamicin η

The synthetic strategy developed in the Martin group for the synthesis of citreamicin η (**4.1**) was inspired by the work of Dr. Knueppel in his second-generation investigation towards the synthesis of IB-00208 (see Chapter 3, Section **3.5.2**).[344,345] An additional challenge presented by citreamicin η (**4.1**) is the presence of the GAB-rings, which comprise a dihydro-5H-oxazolo[3,2-b]isoquinoline-2,5(3H)-dione moiety, the chemistry of which has yet to be explored. Strategically, the stereochemistry in the G-ring was planned to come from a late-stage condensation of the amino acid derivative α-methyl serine onto the isocoumarin **4.2**, which can be formed from palladium-catalyzed couplings from the pentacyclic compound **4.3** (Scheme 4.1). New methodology must be developed for the transformation of **4.3** to citreamicin η (**4.1**). The E-ring in **4.3** can come from the quinone **4.4** in a cyclization cascade than is inspired by the work of Dr. Nichols (see Chapter 3, Scheme 3.56).[349-351] In a similar sequence seen in the synthesis of IB-00208, quinone **4.4** could be formed from a Moore rearrangement of the acetylide **4.5** which can be made from the union of acetylene, cyclobutanone **4.6** and the aldehyde fragment **4.7**. Finally, the benzocyclobutanone **4.6** can be synthesized from the addition of vanillin derivative **4.9** and vinyl squarate **4.8**.

Scheme 4.1: Martin group retro-synthesis towards the citreamicin η (**4.1**)

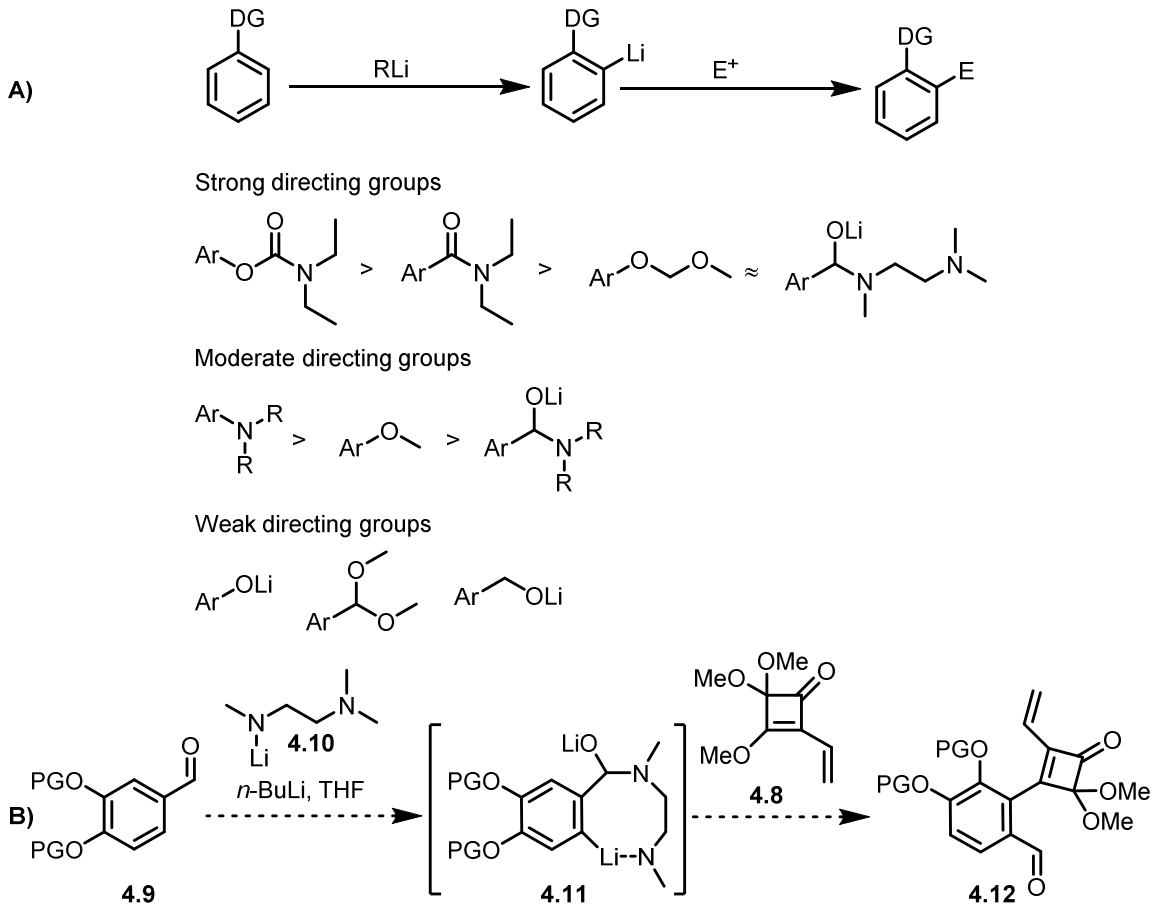


4.2: Synthesis of the BC-ring coupling fragment

4.2.1: ATTEMPTED USE OF COMINS *ORTHO*-METALATION

The two common methods used to generate aryllithium reagents are lithium-halogen exchange and directed *ortho*-lithiation (DOM). A variety of directing groups (DG) can be used for DOM, with amides and carbamates being among the most effective (Figure 4.1, **A**).[352-354] Comins discovered that the combination of lithium amide of the *N,N,N'*-trimethylethylenediamine (LTMDA) **4.10** and aryl aldehydes produces a tetrahedral intermediate **4.11** *in situ* that can function as a powerful DG for *ortho*-lithiation (Figure 4.1, **B**).[355-359] The use of Comins' methodology could then allow for the direct addition of the arene **4.9** without use of a bromo-arene as an intermediate.

Figure 4.1: Directed *ortho*-metalation and planned use of Comins LTMDA **4.10**

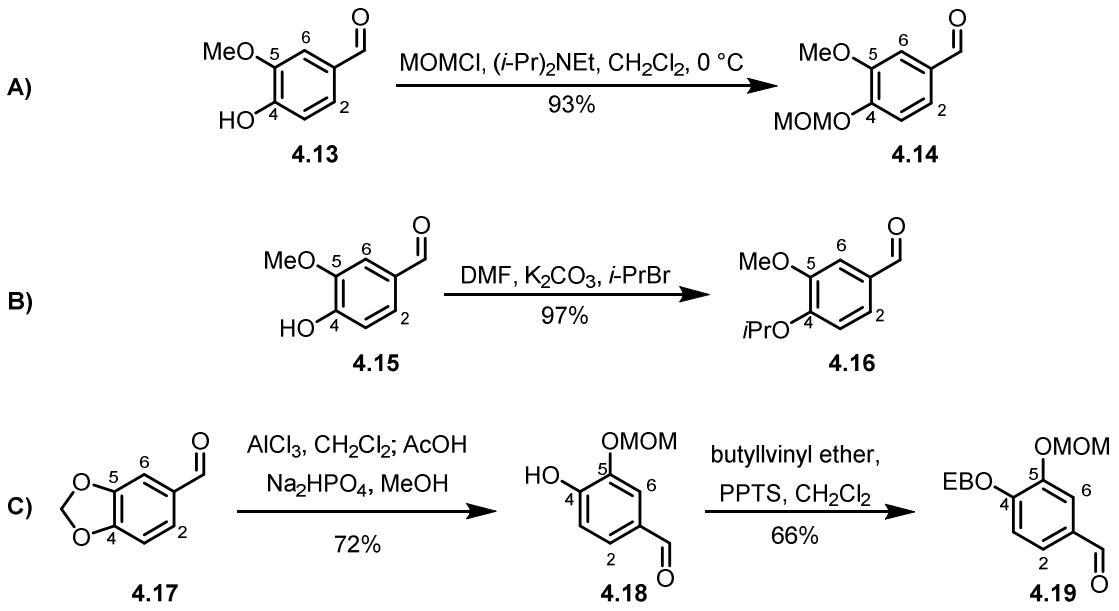


a) Directed *ortho*-metalation (DOM) and relative directing group (DG) efficacies. B) Proposed use of Comins' *ortho*-lithiation of vanillin derivative **4.9**.

The strongly basic conditions of DOM limits the types of protecting groups available for the protection of the C4 and C5 hydroxyl groups on the arene **4.9**. An additional problem is that the two protecting groups at C4 and C5 must be orthogonal and not affect *ortho*-lithiation selectivity (C2 vs C6). The three orthogonally protected vanillin derivatives were synthesized to evaluate compatibility with the DOM conditions: the C4 MOM group can be hydrolyzed selectively in **4.14** (Figure 4.2, **A**), the C4 isopropyl group in **4.16** can be selectively removed with Lewis acids (Figure 4.2, **B**),[360] and the C4 ethoxybutyl (EB) group should hydrolyze faster than the C5 MOM group in **4.19** (Figure 4.2, **C**). The differentially protected vanillin derivative

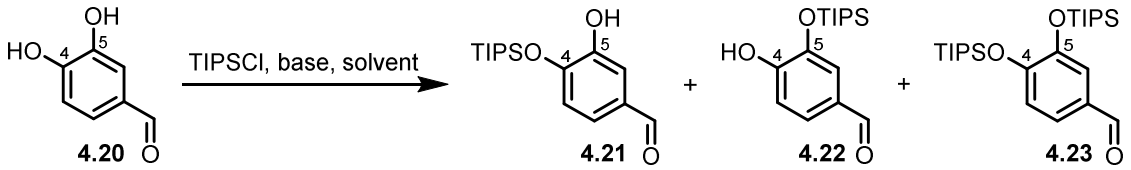
4.18 was synthesized from piperonal (**4.17**) *via* a procedure originally developed by Dr. Alex Nichols.[349]

Figure 4.2: Synthesis of protected vanillin derivatives



The C4 phenol protected TIPS-protected vanillin derivative **4.21** was synthesized, but C5 phenol protected compound **4.22** was also formed. (Table 4.1). Attempts to favor **4.21** over **4.22** by changing solvents and bases did not alter the product ratios from ~2:1 of **4.21**:**4.22**. Use of polar solvents, such as DMF produced a significant amount of bis-TIPS protected phenol **4.23**.

Table 4.1: Attempted selective synthesis of TIPS vanillin derivative

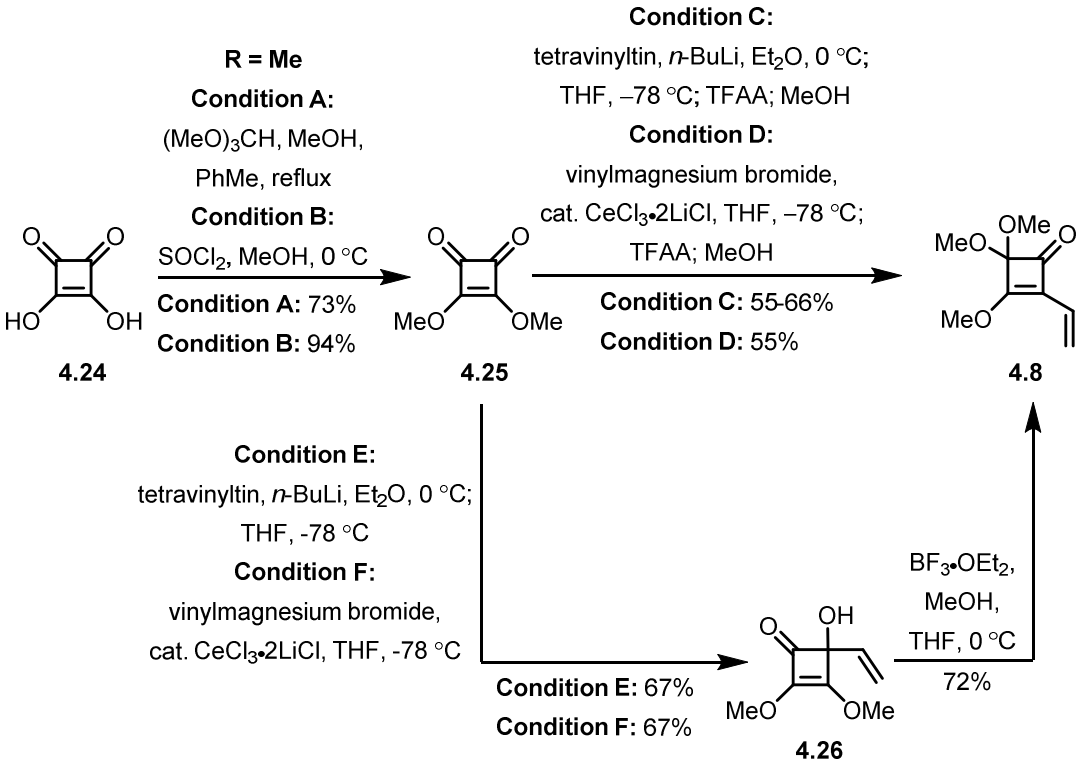


Base	Solvent	Yield 4.21	Yield 4.22	Yield 4.23
2,6-lutidine	THF	61	34	0
2,6-lutidine	CH_2Cl_2	59	33	0
2,6-lutidine	MeCN	24	18	0
2,6-lutidine	PhMe	64	36	0
2,6-lutidine	DMF	36	20	10
Et_3N	DMF	34	20	23
$(i\text{-Pr})_2NEt$	DMF	21	12	25
imidazole	DMF	35	12	10

With the protected vanillin derivatives **4.14**, **4.16** and **4.19** in hand, the synthesis of vinyl squarate **4.8** commenced with the conversion of squaric acid **4.24** to dimethyl squarate **4.25**. The literature procedures for the synthesis of dimethyl squarate **4.25** require long reaction times, so an alternate procedure using anhydrous HCl in MeOH was investigated (Scheme 4.3, Condition **A**).[361,362] Gratifyingly, dimethyl squarate **4.25** was synthesized in 94% yield at room temperature in under 2 h using this method (Scheme 4.3, Condition **B**). Transformation of **4.25** onto **4.8** was performed *via* a one-pot procedure developed by Moore, which required the use of vinyl lithium (made *in situ* from tetravinyltin and *n*-BuLi) (Scheme 4.3, Condition **C**).[361] Unfortunately, synthesis of large amounts of the vinyl squarate **4.8** was hampered by the moderate yields (55 – 66%) and the requirement of large amounts of tetravinyltin. An alternate procedure was devised to circumvent the use of large amounts of tetravinyltin by using vinylmagnesium bromide and a catalytic amount of $CeCl_3$•2LiCl (Scheme 4.3, Condition **D**). The yields were comparable to the vinyllithium method, but the vinylmagnesium bromide had to be made fresh and the synthesis of anhydrous $CeCl_3$•2LiCl proved tedious. The two step procedure using either of the two methods

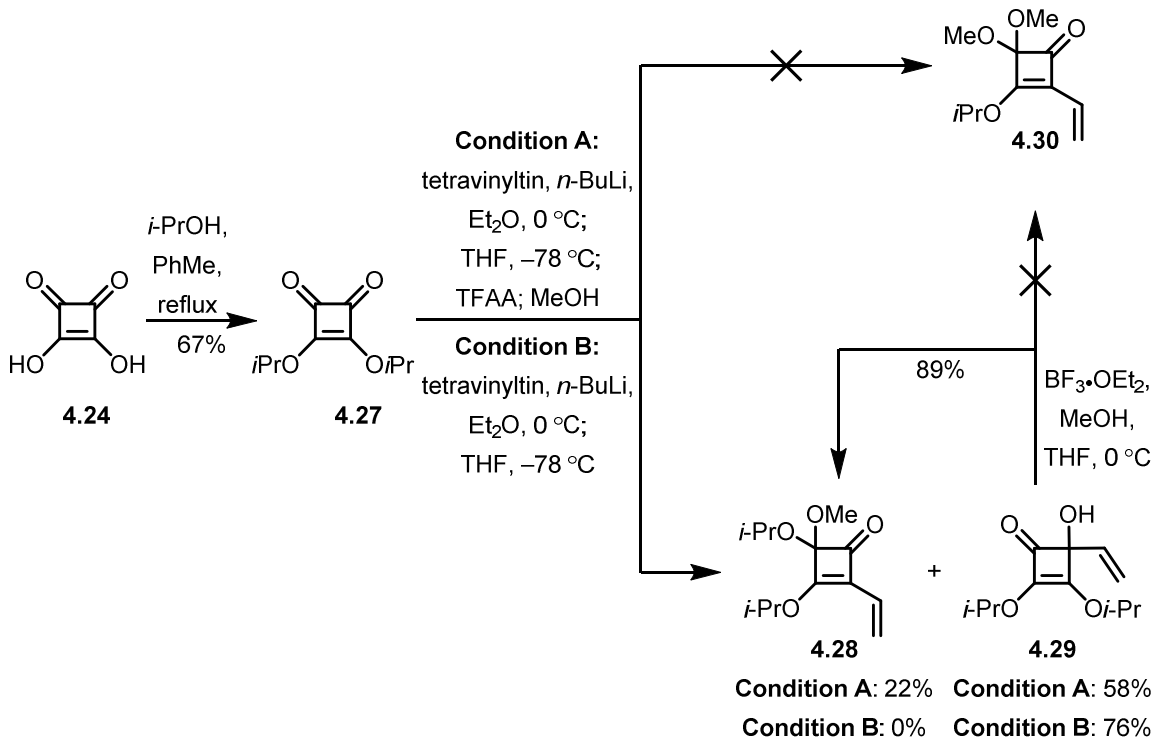
to produce the adduct **4.26** followed by ionization offered no improvements over the one-pot procedure (Scheme 4.3, Condition **E,F**).[337]

Scheme 4.2: Synthesis of vinyl squarate **4.8**



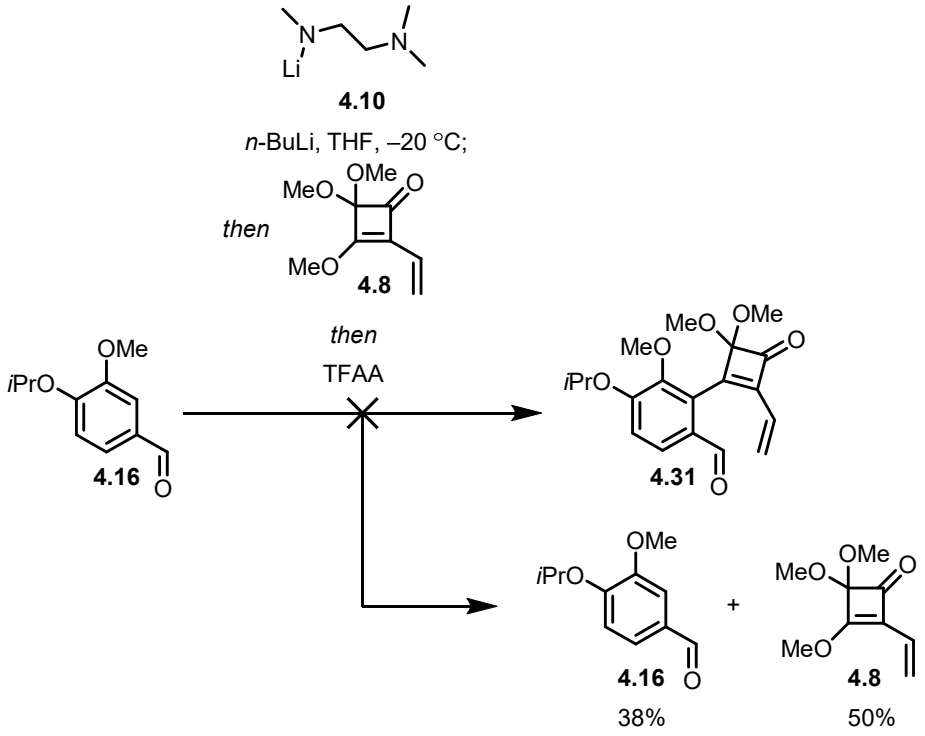
An additional complication that was encountered was that the dimethyl squarate **4.25** hydrolyzed and the vinyl squarate **4.8** would decompose in the freezer after 1 – 2 weeks. This prompted the investigation of the diisopropyl squarate **4.27**, which was reported by Liebeskind to be more stable.[363] Subjection of the isopropyl squarate **4.27** to the one-pot procedure for the vinyl squarate **4.8**, however, provided a mixture of the mixed acetal **4.28** and the vinyl adduct **4.29** instead of the desired **4.30** (Scheme 4.4, Condition A). The two step procedure exclusively provided the mixed acetal **4.28** instead of the desired **4.30** (Scheme 4.4, Condition B).

Scheme 4.3: Attempted synthesis of isopropyl squarate **4.30**



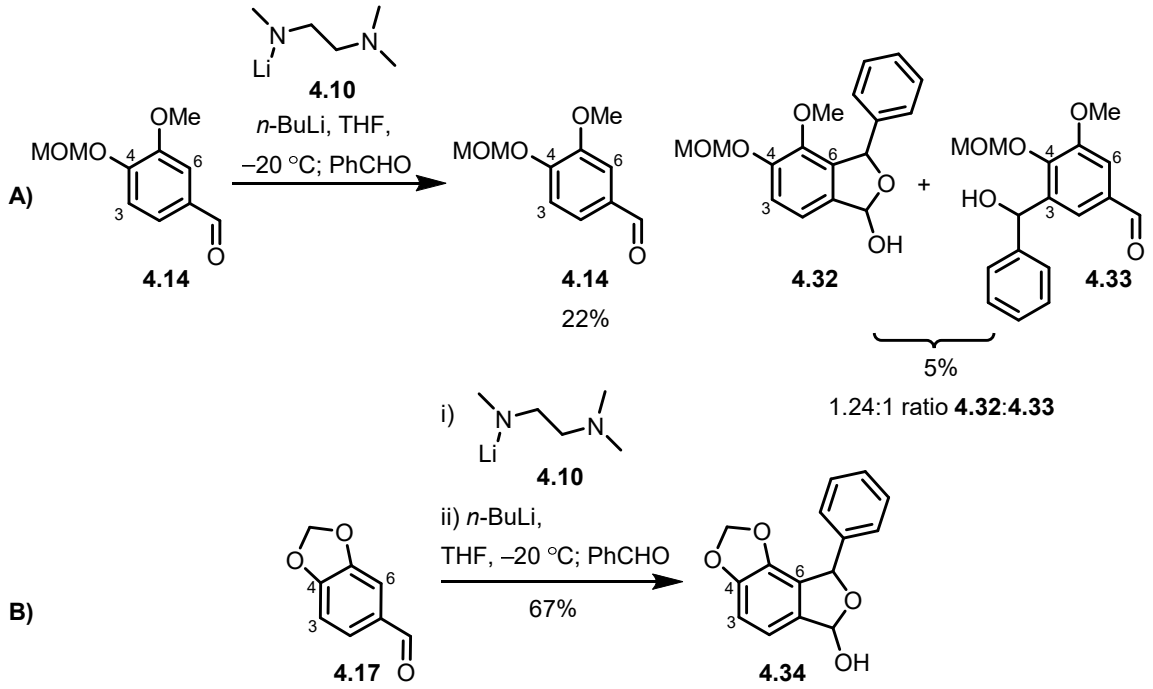
Several attempts were made to effect the *ortho*-lithiation of **4.16** utilizing Comins' methodology, followed by addition of vinyl squarate **4.8**; however, only starting material and vinyl squarate **4.8** were recovered (Scheme 4.4). Prolonged stirring after the addition of vinyl squarate **4.8** only resulted in a complex mixture of products.

Scheme 4.4: Attempted Comins *ortho*-lithiation/squarate addition



To assess whether the appropriate aryllithium was being formed, MOM protected vanillin derivative **4.14** and piperonal (**4.17**) were subjected to the reaction conditions used for the *ortho*-lithiation of **4.16**, followed by quenching with benzaldehyde as a model electrophile. Interestingly, the *ortho*-lithiation of vanillin derivative **4.14** resulted in a mixture of C3 and C6 benzaldehyde adducts **4.32** and **4.33** (1.2:1) (Figure 4.3, **A**). It is likely that the MOM group is a competitive directing group with the lithium-*N,O*-acetal generated from the addition of LTMDA to the aldehyde moiety. *ortho*-lithiation of piperonal (**4.17**), however, did give the desired product **4.34** in 67% yield (Figure 4.3, **B**). This result suggests that the MOM and EB protected derivative **4.19** and **4.14** will be poor substrates in the Comins *ortho*-lithiation due to competitive C6 and C3 lithiation.

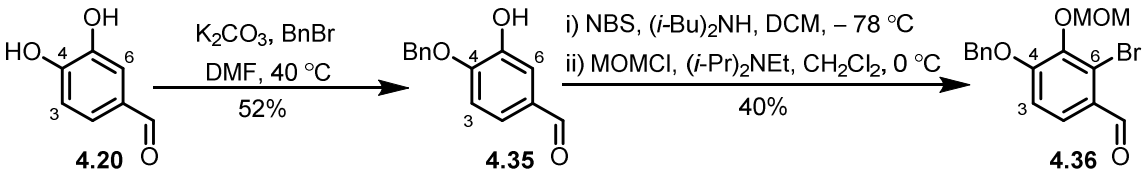
Figure 4.3: Comins *ortho*-lithiation of **4.14** and piperonal (**4.17**)



a) Attempted Comins *ortho*-lithiation of **4.14** resulting in a mixture of C6 and C3 alkylated products. b) Comins *ortho*-lithiation of piperonal delivering only the C6 alkylated product **4.10**.

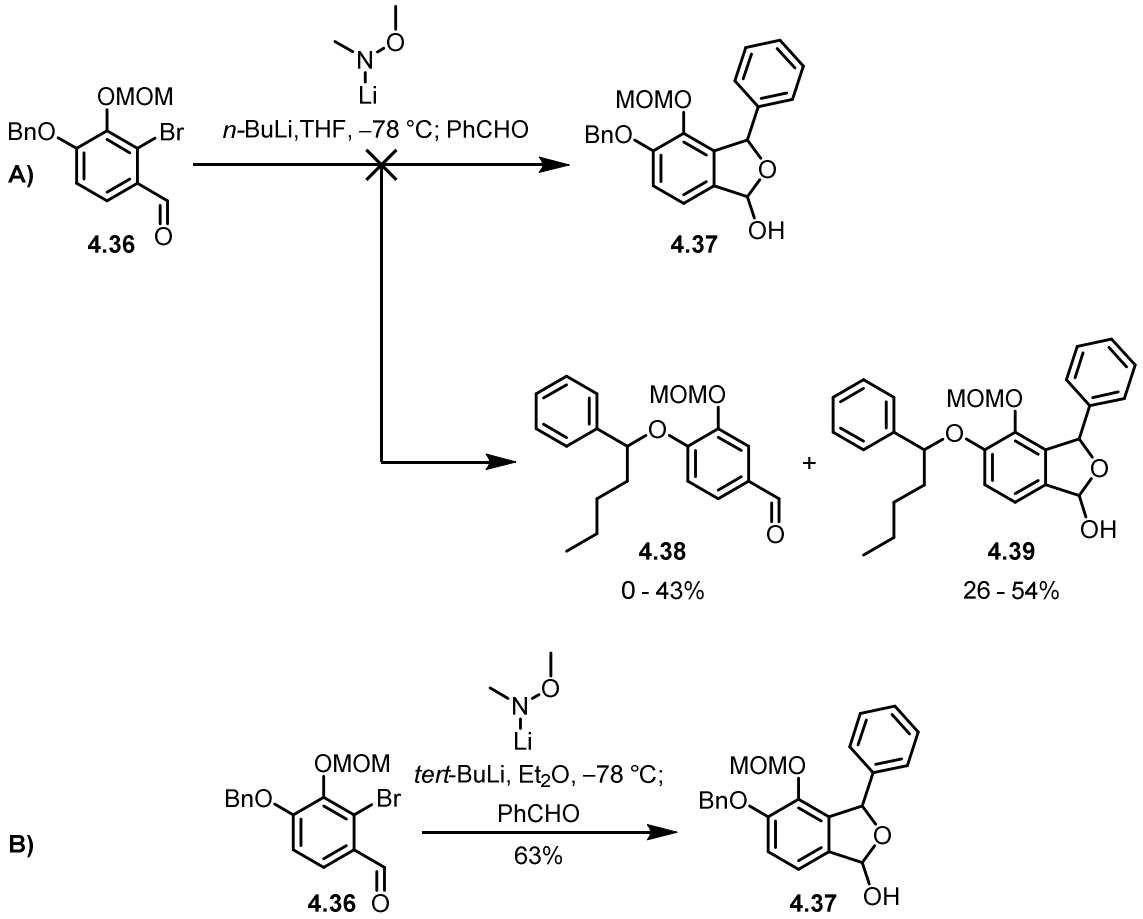
Due to the harsh conditions of the *ortho*-lithiation (excess *n*-BuLi, THF, –20 °C to 0 °C), and the ability of MOM protecting groups to compete with the LTMDA to direct *ortho*-lithiation, metal-halogen exchange was investigated using lithium *N,O*-dimethyl amine as an *in situ* protecting agent for the aldehyde. Preparation of differentially protected 4,5-dihydroxybenzaldehyde derivative **4.36** was accomplished in three steps (Scheme 4.5). Selective alkylation of 4,5-dihydroxybenzaldehyde with benzyl bromide in the presence of K_2CO_3 provided the 4-benzylated compound **4.35**. *Ortho*-selective bromination utilizing Fujisaki's procedure provided **4.36** (5:1 *ortho*:*para*).[364]

Scheme 4.5: Synthesis of *ortho*-lithiation probe **4.36**



Utilizing lithium *N,O*-dimethylamine as an *in situ* protecting agent, aldehyde **4.36** was subjected to metal-halogen exchange with *n*-BuLi followed by quenching with benzaldehyde as the model electrophile (Figure 4.4, **A**). Surprisingly, a mixture of butylated products **4.38** and **4.39** were recovered in varying amounts depending on the solvent, temperature, and number of equivalents of *n*-BuLi. The structure of **4.39** was confirmed by oxidizing the lactol to the lactone (see experimental). Use of *tert*-BuLi in place of *n*-BuLi only delivered the expected lactol **4.37** in 63% yield (Figure 4.4, **B**).

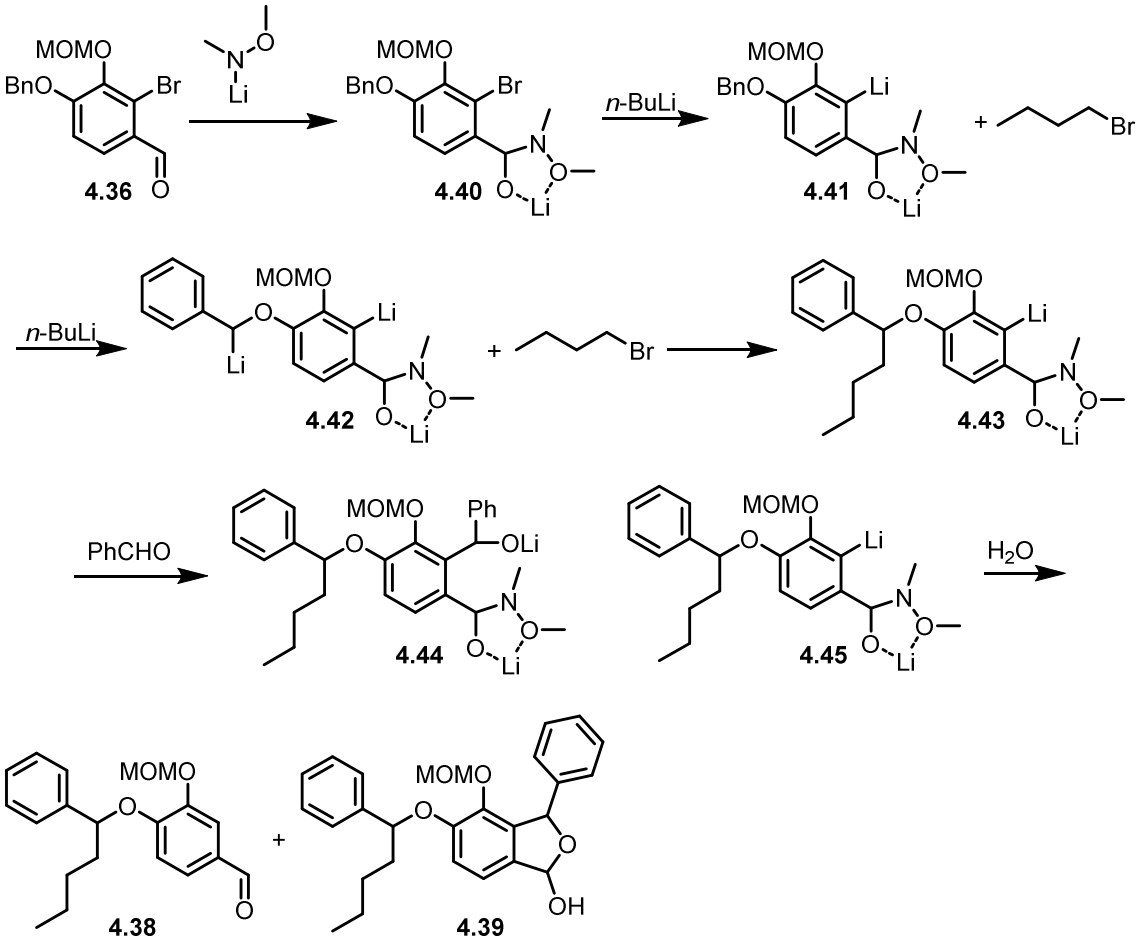
Figure 4.4: Attempted *in situ* protection/*ortho*-lithiation of aldehyde **4.36**



a) *In situ* protection of the aldehyde **4.36** with lithium N,O dimethyl amide and subsequent metal-halogen exchange with *n*-BuLi resulting in butylated products **4.38** and **4.39**. b) *In situ* protection of the aldehyde **4.36** with lithium N,O dimethyl amide and subsequent metal-halogen exchange with *tert*-BuLi resulting in aldehyde adduct **4.37**.

The putative mechanisms for the formation of **4.38** and **4.39** both involve the intermediacy of a benzyl anion (Scheme 4.6). Addition of the *N,O*-dimethylamide into aldehyde **4.36** produces the complex **4.40**, which after lithium-bromine exchange, gave the aryllithium **4.41** and butylbromide. A second equivalent of *n*-BuLi deprotonated the benzyl group to produce tri-anion **4.42**, which reacts with the butylbromide to give **4.43**; addition of benzaldehyde that produced a mixture of **4.38** and **4.39**.

Scheme 4.6: Proposed mechanism for the formation of **4.38** and **4.39**

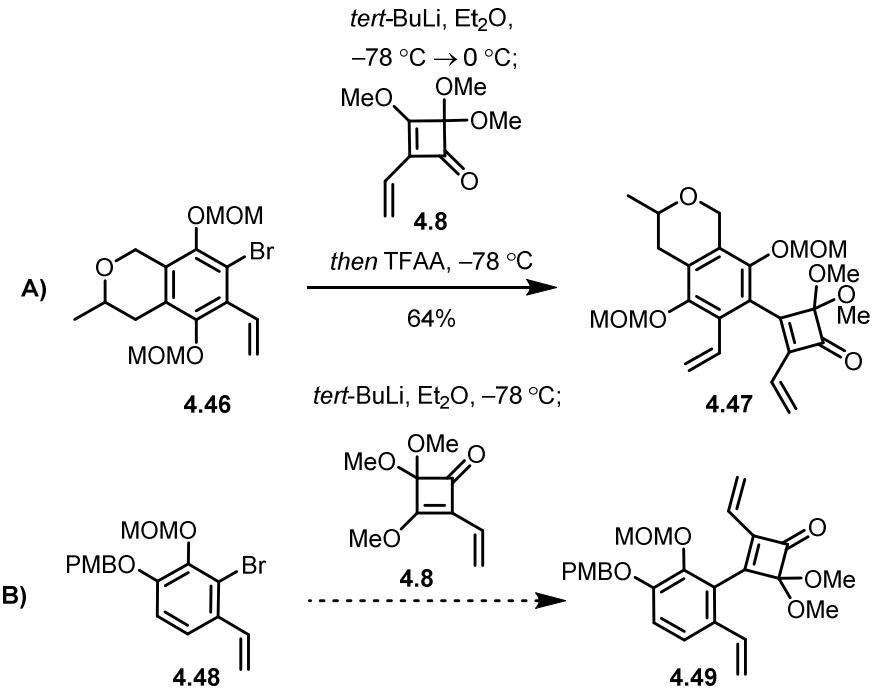


4.2.2: SQUARATE ADDITION *VIA* LITHIUM-HALOGEN EXCHANGE

4.2.2.1: Selective bromination

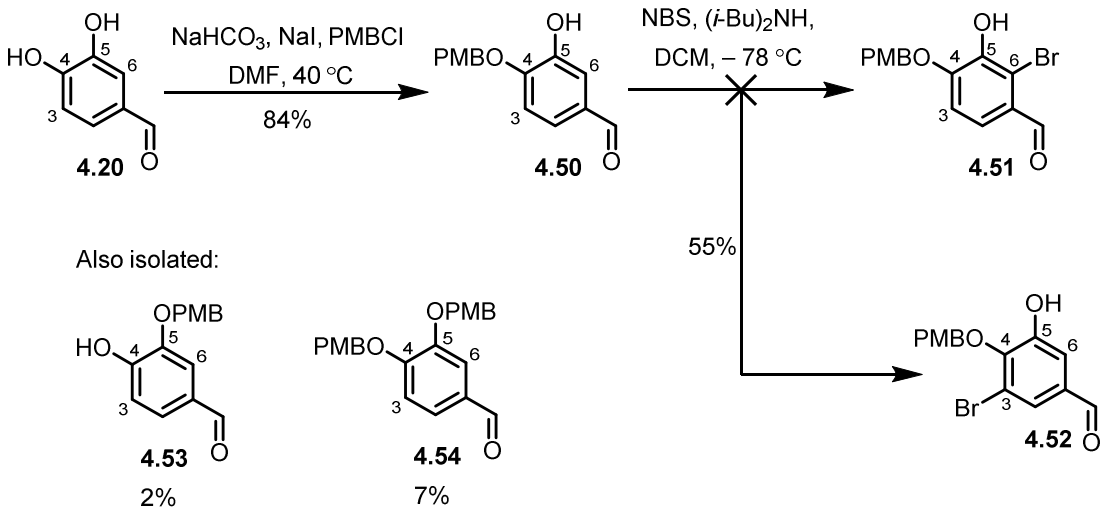
The failure of the Comins *ortho*-lithiation strategy for the synthesis of **4.12** was attributed to the lack of orthogonal protecting groups that are stable under the strongly basic reaction conditions. Thus, the strategy developed for the synthesis of IB-00208 (not shown) was revisited (Figure 4.5, **A**). The orthogonally protected vanillic derivative **4.48** was chosen instead of the benzyl protected compound **4.36** due to the diversity of conditions available to remove the PMB group as compared to the benzyl group (Figure 4.5, **B**).[556-587]

Figure 4.5: Revised synthetic plan toward benzocyclobutanone **4.6**



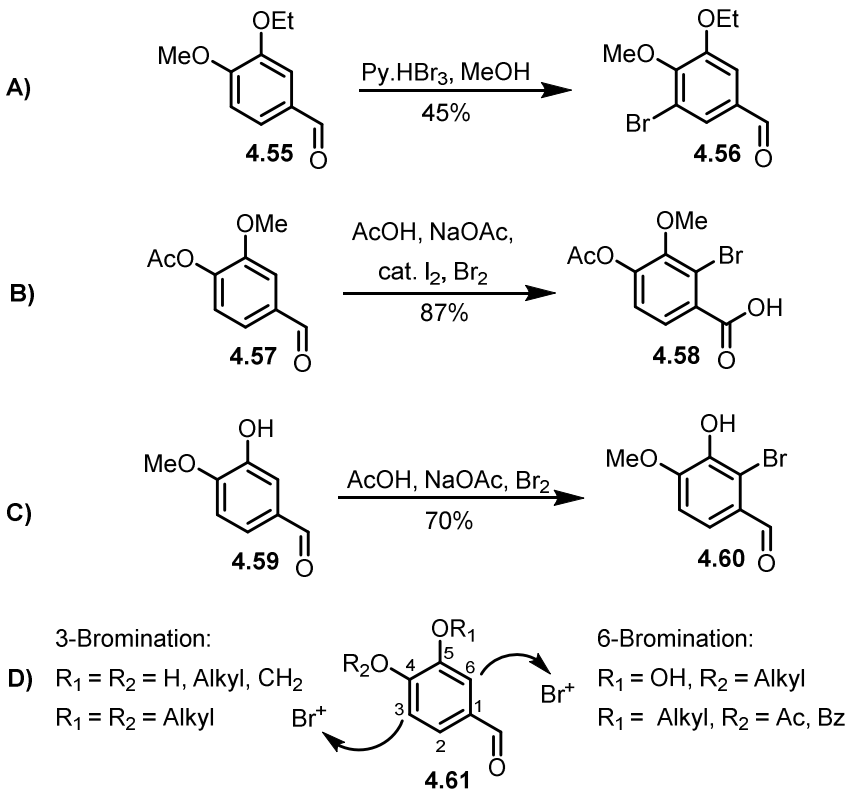
The first route to **4.48** involved selective alkylation of **4.20** with PMBCl in the presence of $NaHCO_3$ and NaI to provide **4.50** in 84% yield on 20 g scales (Scheme 4.7).[377] The undesired C5 alkylated product **4.53** and the bis- PMB protected compound **4.57** were only isolated in 2% and 7% yield respectively. Unexpectedly, *ortho*-bromination of **4.50** under the same conditions used for the benzyl protected analogue **4.35** (see Scheme 4.5) delivered the C3-brominated product **4.52** instead of the expected C6-brominated product **4.51**.

Scheme 4.7: Unexpected C3-bromination of PMB-protected vanillin derivative **4.52**



The fact that bromination at C3 of **4.50**, was favored even in the presence of amines that promote *ortho*-bromination, is unusual. In cases where both the substituents in the 4- and 5-positions are both alkyl or hydroxyl, bromination occurs in the 3-position (Figure 4.6, **A**).[371,372] Bromination at the 6-position can be favored if the substituent in the 4-position is deactivating or if the C5-phenol is unprotected (Figure 4.6, **B**,**C**).[374-376]

Figure 4.6: Selectivity in the bromination of vanillin derivatives

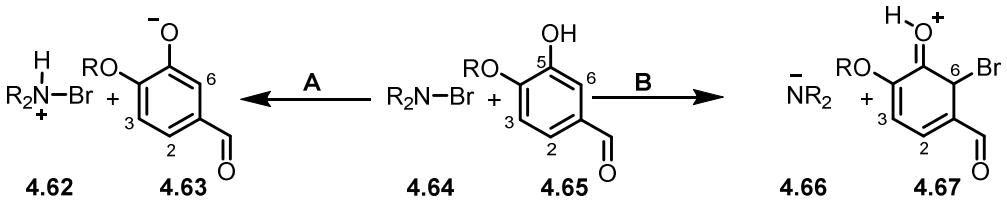


a) Example of bromination in the 3-position when both groups are alkyl from Sarma.[371] b) Example of bromination in the 6-position when the C4 group is an acyl group from Raiford.[374] c) Example of bromination in the 6-position when the C5 group is an OH group from Hazlet.[376] d) Generalized selectivity preferences for bromination of vanillin derivatives.

There are two known methods to effect the selective *ortho*-bromination of phenols: The method developed by Pearson in 1967 utilizes *tert*-$BuNH_2$ and bromine, whereas the method developed by Fujisaki in 1993 utilizes catalytic 2°-amines with NBS.[364,365] The combination of amine and bromine source is thought to generate an *N*-bromoamine intermediate **4.64** that favors *ortho*- rather than *para*-bromination (Figure 4.7). The fact that bromination of **4.50** under Fujisaki's conditions failed to provide the *ortho*-brominated product **4.51** presents a unique challenge of reversing the selectivity change induced by the PMB group. Two pathways were considered to provide insight to this problem. If bromination precedes deprotonation, one would expect the selectivity to be lower (Figure 4.7, Pathway **B**) than if deprotonation precedes bromination (Figure 4.7, Pathway **A**) because one would expect the phenoxide **4.63** to be more reactive at the 2- and 6-postions towards electrophilic reactions relative to the 2- and 6-postions

in **4.65** The reactivity of the 3-positions in **4.63** and **4.65** would be expected to be similar. Basic amines should favor pathway **A** over pathway **B** and hence be more selective for the bromination in the 6-position.

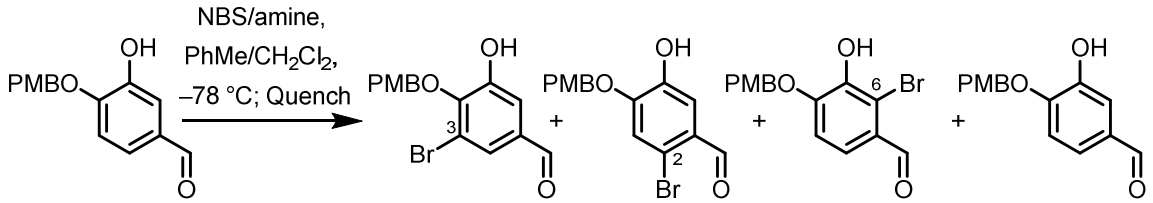
Figure 4.7: Hypothetical effect of amine basicity on bromination selectivity



Based on the proposed hypothesis, four amines were chosen with increasing p*K*a values: *tert*-$BuNH_2$ (p*K*a~10.6), (*i*-Bu)$_2$NH (p*K*a~11), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (p*K*a~12) and tetramethylguanidine (TMG) (p*K*a~14). These were screened with Br_2, 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCO) and NBS as sources of [Br^+].[366] NBS was quickly identified as the brominating reagent of choice due to the ease of handling and intermediate reactivity relative to Br_2 and TBCO. Solvent appeared to have a profound effect on the product ratios: the selectivity was the lowest in CH_2Cl_2 and increased with added toluene. Starting with a 2:3 ratio of PhMe/CH_2Cl_2, **4.50** was brominated with NBS with each of the four amines and the relative ratios of the 2-, 3- and 6-brominated products **4.52**, **4.68** and **4.51** were determined by ^{1}H-NMR (Table 4.2, entries 1 – 4). As expected, selectivities increased with the increasing p*K*a of the amine, with TMG providing >20:1 selectivity for the 6-brominated product **4.51**. Amines are known in the literature to catalyze the halogenation of alkenes in the presence of halogenating agents,[367-371] but this is the first instance of *N*-bromoTMG being used in the selective bromination of an aromatic ring.[367] On scale, however, the bromination of **4.50** with NBS and TMG delivered the product **4.51** in only 30 – 40% yields, and the reaction rarely went to completion. Simply adding more NBS to the reaction caused the formation of polybrominated compounds. Increasing the ratio of toluene in the mixed solvent system allowed the reaction to go to completion with a slight excess of NBS, but upon warming, polybrominated compounds

were formed. To drive the reaction to completion while avoiding over-bromination, reductive quenches to neutralize any active brominating agents in the reaction mixture were examined. Of the several quenching agents examined [butylated hydroxytoluene (BHT), sodium thiosulfate, hydroquinone, and thiourea], BHT proved the most effective. Repeating the selectivity experiment with the four amines still showed that TMG offered the highest selectivity. (Table 4.2, entries 5 – 9). Additional problems were encountered on scale-up: The yields ranged from 40 – 60%, and the selectivity between the 3- and 6-brominated products varied significantly. Interestingly, when stirring the NBS and TMG together at 0 ºC on scale, a white precipitate formed. Analysis of the solids with starch-iodine test strips revealed that was an active oxidizing agent and addition of these solids to **4.50** produced amounts of **4.51** and **4.52**.

Table 4.2: Effect of amine and solvent on bromination regioselectivity. Ratios determined by crude NMR



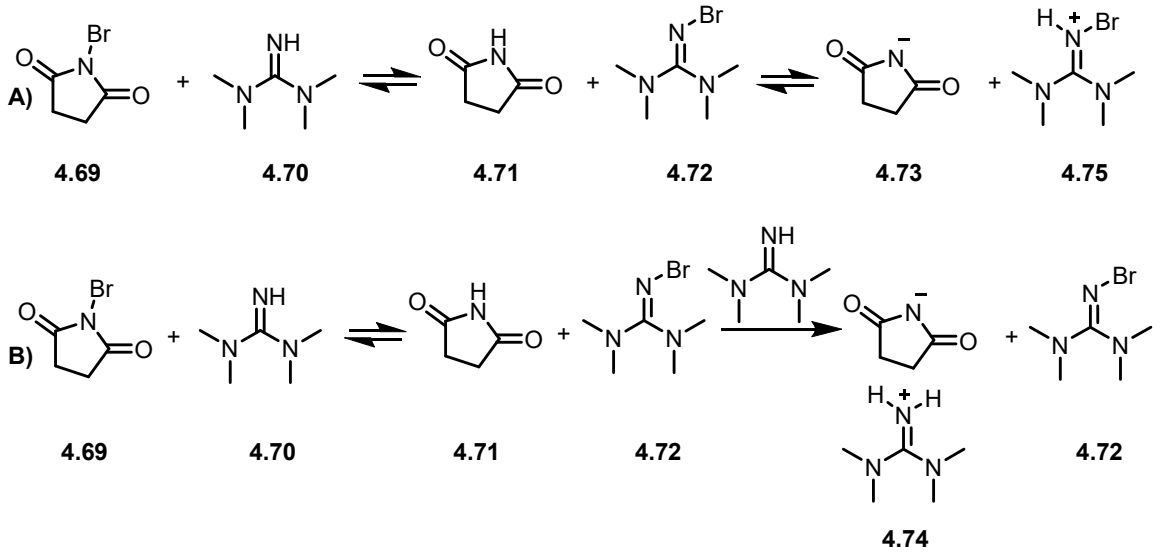
4.50 **4.52** **4.68** **4.51** **4.50**

Amine	**NBS:amine**	**PhMe:CH_2Cl_2**	**quench**	**4.52**	**4.68**	**4.51**	**4.50**
tert-$BuNH_2$	1:1	2:3	N/A	1	0	3.75	0.87
(i-Bu)$_2$NH	1:1	2:3	N/A	1	2.5	11.5	0
DBU	1:1	2:3	N/A	1	3	13.5	0
TMG	1:1	2:3	N/A	1	2	21.5	0
tert-$BuNH_2$	1.2:1.3	5:1	BHT	1	1.33	7.33	1.33
(i-Bu)$_2$NH	1.2:1.3	5:1	BHT	1	1	3.75	6.25
DBU	1.2:1.3	5:1	BHT	1	1	6	1.17
TMG[a]	1.2:1.3	5:1	BHT	1	0	11	0

a) 40 – 60% yield on scale, 1:1 – 5:1 ratios of 3- and 6-brominated products **4.52** and **4.51**

The discovery that the white precipitate contained active brominating reagent suggested that it may be a mixture of succinimide (**4.71**) and *N*-bromo TMG **4.72** (Figure 4.8, **A**). The salt (**4.73** + **4.75**) may be detrimental to the reaction due to its insolubility under the reaction conditions and may not be as selective of a brominating agent as *N*-bromo TMG **4.72** because it would not form any of phenolate. Changing the stoichiometry from 1.2:1.3 NBS:TMG to 1:2 may shift the equilibrium away from (**4.73** + **4.75**) towards the *N*-bromo TMG **4.72**, which may be beneficial to selectivity and solubility (Figure 4.8, **B**).

Figure 4.8: Formation of *N*-bromoTMG **4.72** with one and two equivalents of TMG **4.70**

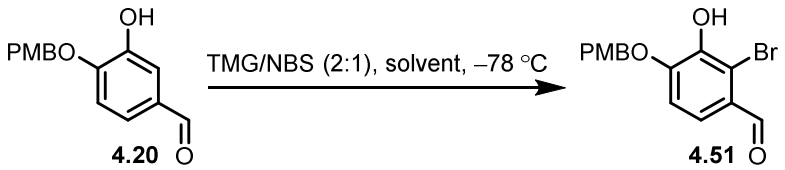


a) Possible incomplete formation of *N*-bromoTMG **4.72** when NBS/TMG ratio is 1:1. b) Possible complete formation of *N*-bromoTMG **4.72** when NBS/TMG ratio is 1:2.

Gratifyingly, changing the stoichiometry from 1.2:1.3 to 1:2 gave >20:1 selectivity for the 6-brominated derivative **4.51** in a variety of solvents and no reductive quench was necessary (Table 4.3, entries 1 – 4). Up to this point, the reactions had been run relatively dilute (0.0125 M) and hence large volumes would be required to synthesis significant quantities of **4.51**. Accordingly, the concentration of the reaction was varied from 0.00625 M to 0.1 M to determine the effect of concentration of the yields of **4.51** (Table 4.3, entries 5 – 9). Gratifyingly, the yield

increased with higher concentrations and on scale, the selectivities and yields stayed the same, and multiple grams of the brominated vanillin derivative **4.51** were synthesized in 83% yield.

Table 4.3: Bromination of **4.50** using 2:1 TMG:NBS



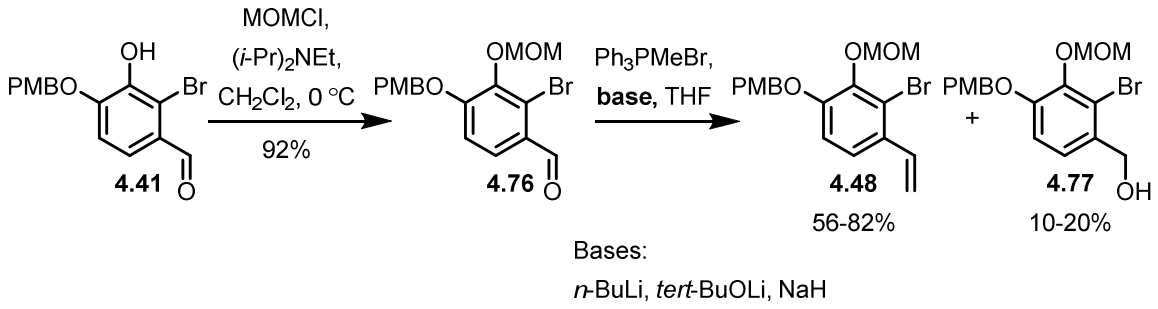
Solvent	Concentration (M)	Yield (%)	Ratio (4.51:4.52)
CH_2Cl_2/PhMe (5:1)	0.0125	39%	>20:1
PhMe	0.0125	44 – 62%	>20:1
CH_2Cl_2/MeCN (3:2)	0.0125	52%	>20:1
THF	0.0125	26%	>20:1
CH_2Cl_2	0.00625	18%	N/A
CH_2Cl_2	0.0125	39%	>20:1
CH_2Cl_2	0.025	61%	N/A
CH_2Cl_2	0.05	78%	N/A
CH_2Cl_2	0.1	84% (83%)[a]	N/A

a) Performed on gram scale

4.2.2.2: MOM protection and Wittig olefination

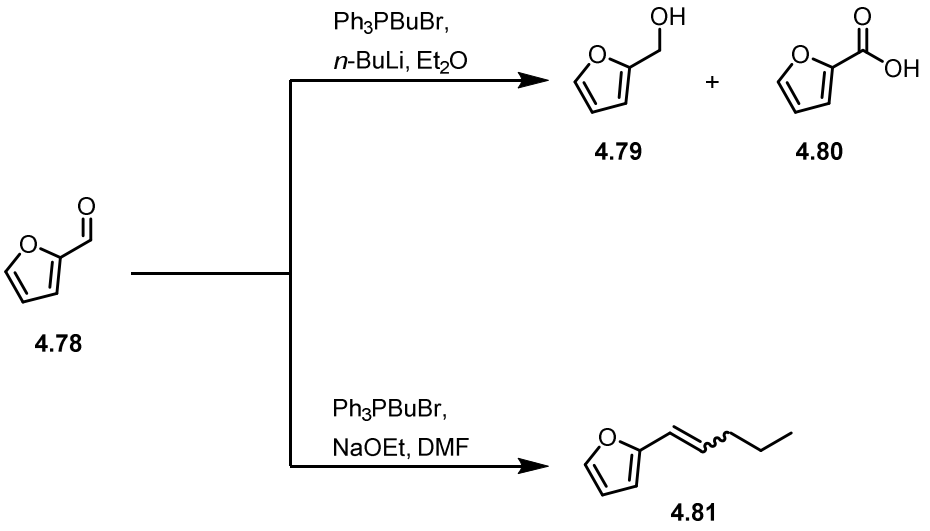
With access to multigram quantities of the bromoarene **4.51**, work was initiated toward the synthesis of styrene **4.48** (Scheme 4.8). MOM protection with diisopropylethylamine (DIPEA) and MOMCl gave the protected aldehyde **4.76** in 92% yield (Scheme 4.8). The initial conditions (NaH/Ph_3PMeBr) for the Wittig olefination provided styrene **4.48** in variable yields. The major byproduct of the reaction was the benzyl alcohol **4.77**, presumably arising either from reduction of the aldehyde by the base or a competing Cannizzaro reaction. Generation of the ylide with *n*-BuLi or *tert*-BuOLi did not reduce the amounts of the benzyl alcohol **4.77**.

Scheme 4.8: MOM protection of **4.51** and Wittig olefination



Curiously, there are few reports of Cannizzaro reactions occurring during Wittig olefinations. The only example found was the observation of Gupta in 1968 who found that reaction of 2-furaldehyde (**4.78**) with the ylide generated from butyltriphenylphosphonium bromide and *n*-BuLi in Et_2O produced a mixture of Cannizzaro products **4.79** and **4.80**.[379] If the same reaction was carried out in DMF and the ylide generated from butyltriphenylphosphonium bromide and NaOEt, the desired product **4.81** was major product (yield not reported) and only 7% of the Cannizzaro products **4.79** and **4.80** were detected.

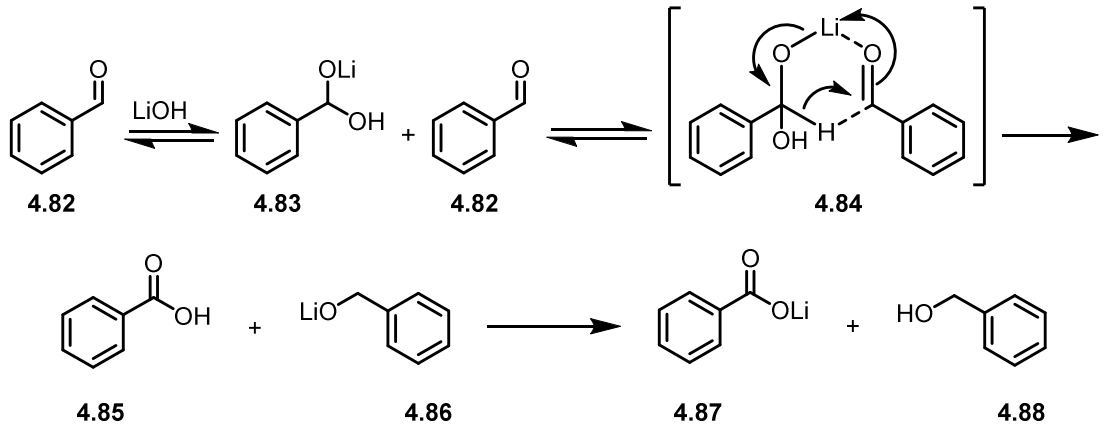
Scheme 4.9: Gupta's observation of Cannizzaro side-reactions during Wittig olefination



The benzyl alcohol **4.77** is most likely formed *via* the Cannizzaro reaction between aldehyde **4.76** and trace amounts of lithium hydroxide present in the reaction mixture. The lithium hydroxide adduct **4.83** can then react with another equivalent of aldehyde **4.82** to form

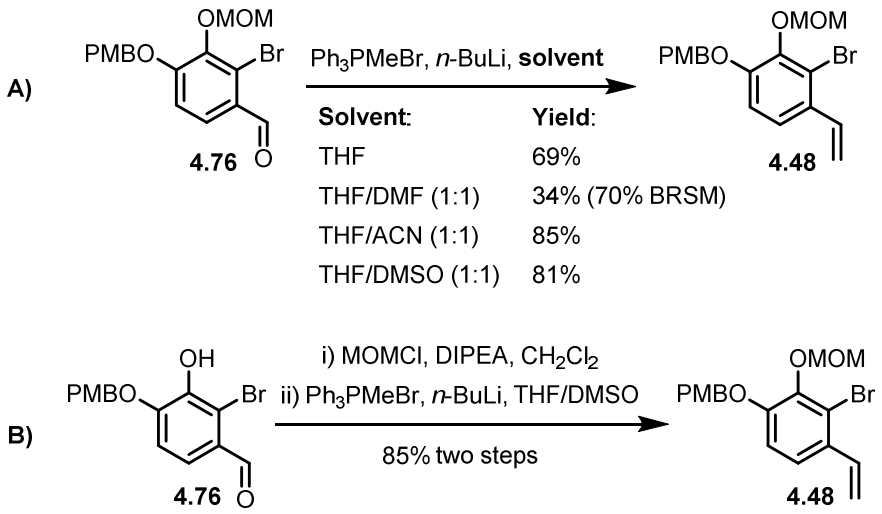
4.84, which can undergo a hydride transfer to form the benzyl-alkoxide **4.86** and benzoic acid **4.85** (Scheme 4.10). The benzoic acid is immediately deprotonated under the basic reaction conditions, which drives the reaction forward. The addition of polar aprotic solvents may coordinate the lithium counterion that is required to bind the aldehyde and form the highly ordered transition state needed for the hydride transfer in **4.84** and disfavor the formation of benzyl alcohol **4.77**, which is supported by Gupta's observation because the use of polar aprotic solvent DMF and the less Lewis acidic sodium base suppressed Cannizzaro side reaction.

Scheme 4.10: Putative mechanism for the formation of benzyl alcohol **4.77**



Several polar aprotic cosolvents such as DMF, MeCN and DMSO were screened in their ability to suppress the formation of **4.77** and increase the yield (Figure 4.9, **A**). Gratifyingly, MeCN and DMSO reduced the amount of **4.77** formed and provided styrene **4.48** in 85% and 81% yields respectively. Due to the relative cost of MeCN, DMSO was used as the co-solvent on scale. Telescoping the sequence from the phenol **4.51** and utilizing the optimized conditions provided multiple grams of the styrene **4.48** in 85% yield (Figure 4.9, **B**).

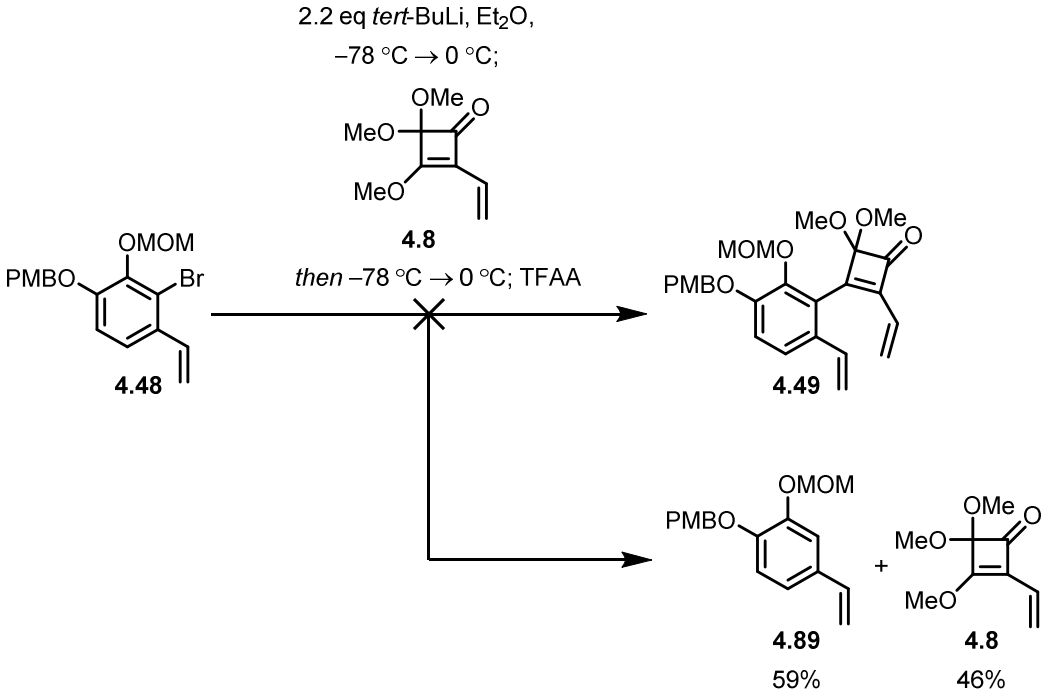
Figure 4.9: Solvent screen to reduce benzyl alcohol **4.77** byproduct



4.2.2.3: Squarate addition

With a robust and scaleable route for the synthesis of the bromostyrene **4.48** established, work began on the lithium-halogen exchange and subsequent coupling with the vinyl squarate **4.8**. Unfortunately, lithium-halogen exchange of the bromostyrene **4.48** and addition of the vinyl squarate **4.8** only gave returned squarate and the debrominated styrene **4.89** as the major products. Sadly, this result stands in contrast to the work done previously in the Martin group (see section **3.5.2**, Scheme 3.52, 3.41).

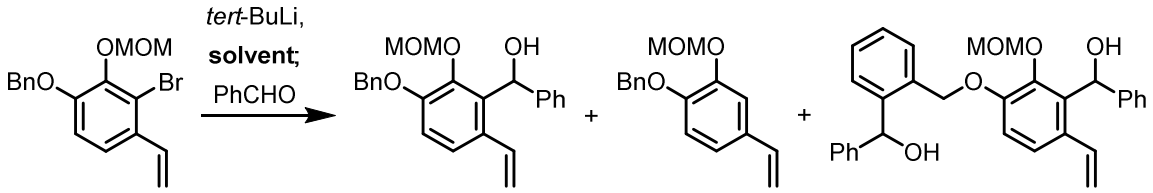
Scheme 4.11: Attempted squarate addition between **4.48** and **4.8**



The generation of the organolithium species was analyzed by lithium-halogen exchange of **4.90**, which was made *via* Wittig olefination from **4.36**, with *tert*-BuLi and quenching with benzaldehyde as a model electrophile. These experiments revealed that along with the expected adduct **4.91**, the debrominated styrene **4.92** and the bis-adduct **4.93** which was confirmed by oxidizing to the bis-ketone, (see experimental), were the primary side-products, and the cause of the mass imbalance (Table 4.2). Presumably, **4.92** was formed *via* the protonation of the aryllithium intermediate, but whether the proton source was internal or external was not clear. Several proton sponges in which their conjugate acids would not protonate the aryllithium intermediate, such as LiH, NaH and mesityllithium were added to the reaction mixture prior to metal-halogen exchange with *tert*-BuLi to rule out external proton sources as the origin of **4.92**. Sodium hydride provided a small yield improvement of the adduct **4.91** but large amounts of debrominated product **4.92** seemed to suggest that the primary source of protons was internal. A solvent screen revealed that nonpolar solvents such as toluene produced more of the debrominated byproduct **4.92** and less of the bis-adduct **4.93** while the opposite was true in more

polar solvents such as THF. Accordingly, it was found that a mixture (3:1) of ether and toluene provided **4.91** in 76% yield and minimized the formation of **4.92** and **4.93** (for an explanation of these effects, see figure 4.10).

Table 4.2: Solvent screen optimization for metal-halogen exchange



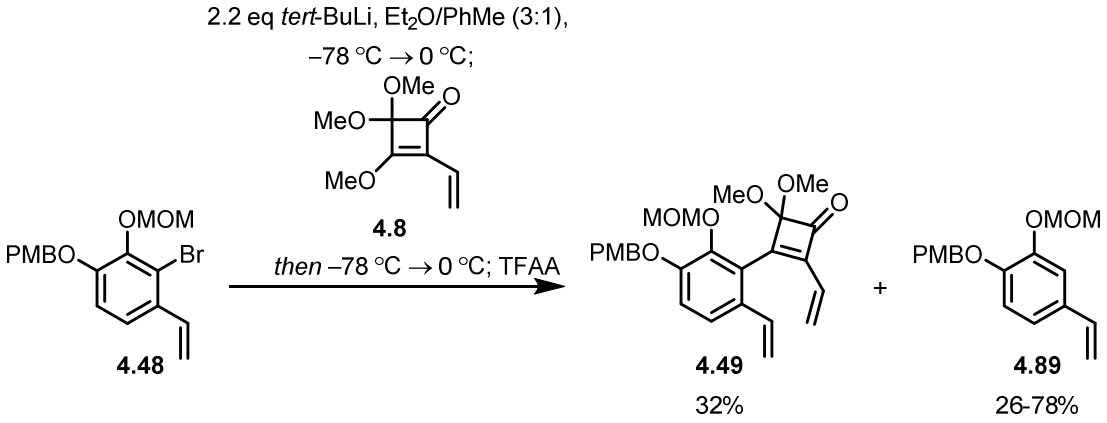
4.90 **4.91** **4.92** **4.93**

Solvent	**T**	**4.91**	**4.92**	**4.93**
Et_2O	–78 °C	59%	N/A	7%
THF	–78 °C	54%	N/A	9%
PhMe	–78 °C	67%	32%	N/A
Et_2O	–100 °C	50%	22%	N/A
THF/Et_2O/pentane[a]	–78 °C	45%	N/A	30%
MTBE	–78 °C	32%	N/A	N/A
PhMe/Hexane[b]	–78 °C	48%	N/A	N/A
Et_2O/PhMe[c]	–78 °C	76%	N/A	N/A

a) 4:4:1 ratio of THF/Et_2O/pentane. b) 1:1 ratio of PhMe/Hexane. c) 3:1 ratio of Et_2O/PhMe

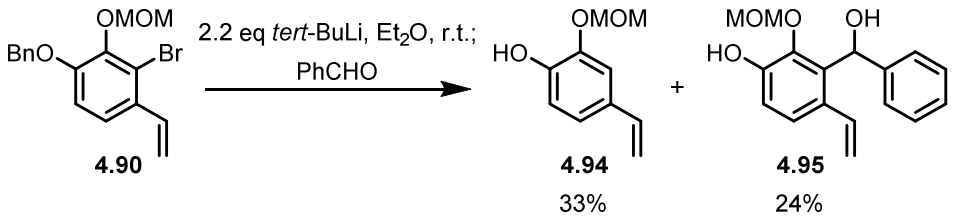
Use of the optimized conditions for the metal-halogen exchange of **4.48**, followed by reaction with the vinyl squarate **4.8** provided the desired adduct **4.49** in 32%, but 26 – 78% of the debrominated material **4.89** was also formed (Equation 4.1).

Equation 4.1: Successful squarate addition



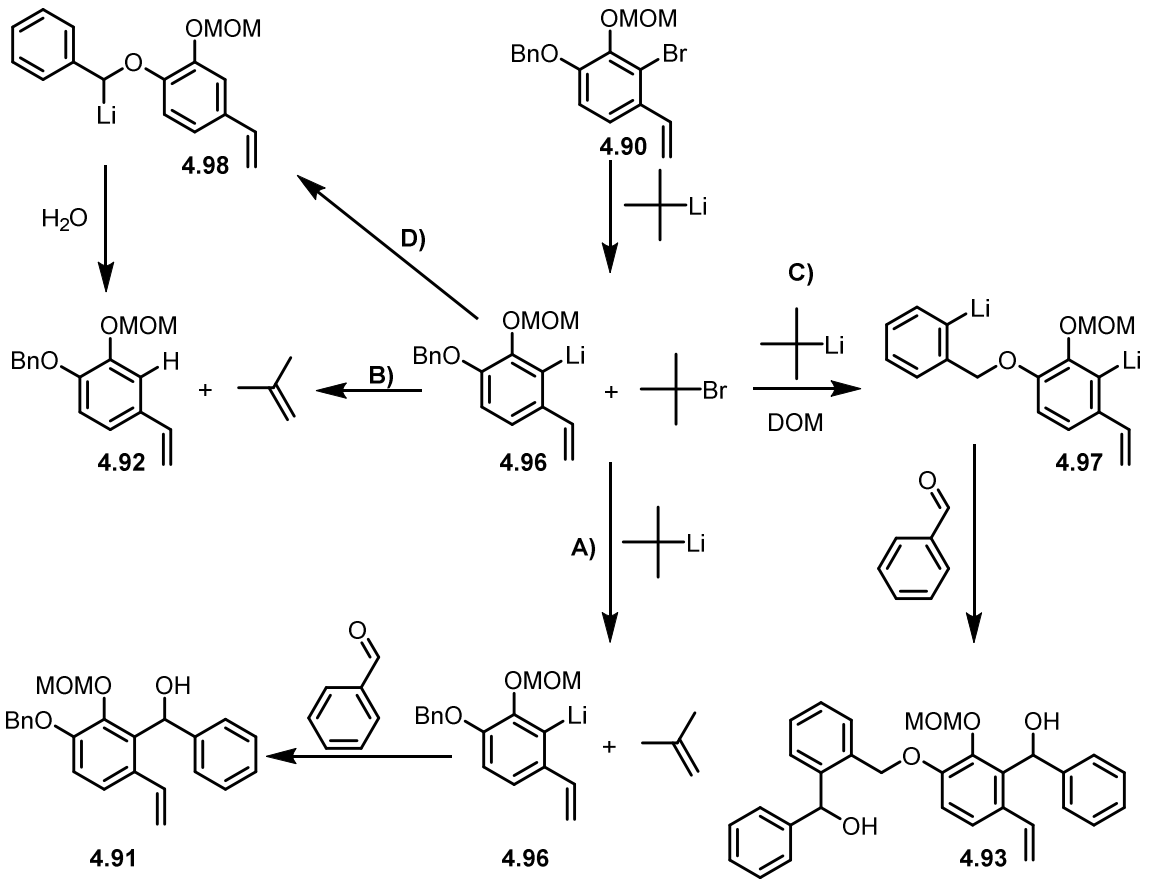
The presence of large amounts of **4.89**, despite using NaH as a "proton sponge" suggests that there is another internal proton source besides *tert*-butyl bromide. The butylated byproducts isolated during the lithium-halogen exchange with the *in situ* protected aldehyde **4.36** suggests that the protons in the benzylic position may be the source of the debrominated product **4.89** (see Figure 4.4). To investigate this possibility, the organolithium reagent was generated from **4.90** with *tert*-BuLi in Et_2O and stirred at room temperature for 2 h and then quenched with benzaldehyde (Equation 4.2). The main products were **4.94** and **4.95**. The formation of **4.94** and **4.95** are indicative of benzylic deprotonation during the reaction conditions. The benzylic anion must have reacted with oxygen to produce transient hemi-acetals, which collapsed to the phenoxide and benzaldehyde to give **4.94** and **4.95**.

Equation 4.2: Evidence for benzylic deprotonation during lithium-halogen exchange



The combined observations seen in the solvent screen and the benzylic deprotonation experiment reveals a surprising amount of side-reactions occur during the metal-halogen exchange of **4.90**. Metal-halogen exchange with *tert*-BuLi produces the aryllithium intermediate **4.96** and *tert*-BuBr. In the desired pathway, a second equivalent of *tert*-BuLi deprotonates the *tert*-BuBr to form isobutylene, and reaction with benzaldehyde produces **4.91** (Figure 4.10, pathway **A**). If the solvent is too non-polar, the aryllithium reagent competes with *tert*-BuLi in the elimination of *tert*-BuBr to from the de-brominated product **4.92** (Figure 4.10, pathway **B**). If the solvent is too polar, the MOM group directs a second equivalent of *tert*-BuLi to deprotonate the aromatic ring of the benzyl group to form **4.93** after quenching with benzaldehyde (Figure 4.10, pathway **C**). The organolithium **4.96** is unstable, and if the reaction temperature increases or too much time elapses, it will disproportionate to the benzyl anion **4.98**, which will provide the debrominated product **4.92** after workup (Figure 4.10, pathway **D**).

Figure 4.10: Putative mechanism for the formation of **4.91**, **4.92** and **4.93**

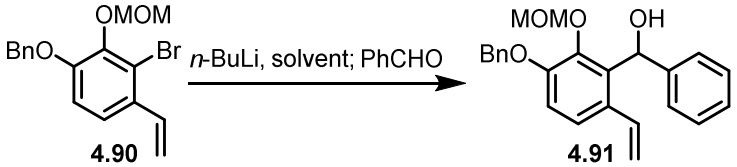


a) Desired pathway to provide the expected adduct **4.91**. b) Reaction of the aryl lithium with *tert*-BuBr to produce the debrominated product **4.92**, which is favored when the reaction solvent is non-polar. c) MOM-directed *ortho*-metalation (DOM) of the benzyl group to produce the dianion **4.97**, which produced **4.93** upon quenching with benzaldehyde. Favored in polar solvents. d) Disproportionation of the aryl lithium **4.96** to form benzyl anion **4.98**, which upon protonation produces the deprotonated byproduct **4.92**.

More aggregated organolithium reagents are less basic and should disfavor the benzylic deprotonation pathway to form **4.92**. The degree of aggregation of the organolithium reagent is often a function of the coordinating ability of the solvent: coordinating solvents favor less aggregated states, while non-coordinating solvents favor more aggregated states. Accordingly, conditions were developed to generate the aryllithium in a non-coordinating solvent such as toluene to favor the more highly aggregated species, thus disfavoring the undesirable benzylic deprotonation pathway. Using *n*-BuLi in place of *tert*-BuLi should suppress any **4.92** formed by the reaction of the aryllithium with *tert*-BuBr. Several solvent mixtures of toluene were screened

to optimize the amount of the benzaldehyde adduct **4.91** (Table 4.3).[380] Interestingly, toluene with no added co-solvent gave the best yield of **4.91** (Table 4.3, Entry 4). The metal-halogen exchange was slower in toluene and did not go to completion at –78 ºC, but warming to 0 ºC provided complete conversion. Gratifyingly, very little of the debrominated byproduct **4.92** was seen, even at 0 ºC (Table 4.3, Entry 5).

Table 4.3: Solvent screen in toluene



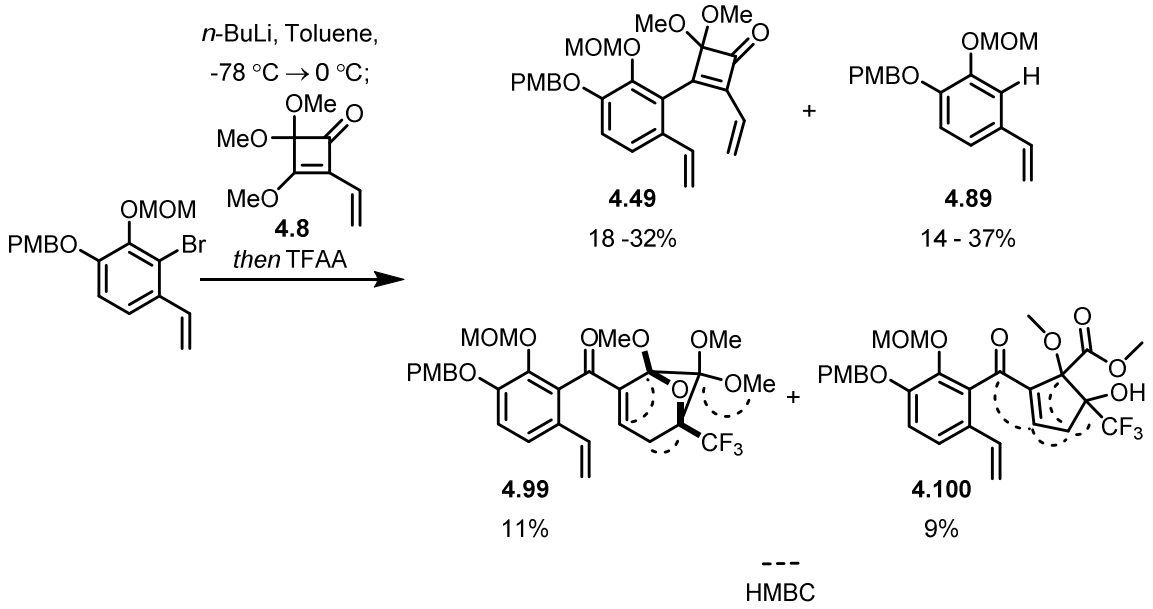
4.90 **4.91**

Solvent	**Temp (ºC)**	**Yield**
PhMe/THF (2:1)	–78	50%
PhMe/THF (9:1)	–78	55%
PhMe/THF (99:1)	–78	32%
PhMe	–78	54%
PhMe	–78 → 0	76%

Although application of the optimized conditions in toluene provided the desired product, the yields of **4.49** were only 18 – 32% (Equation 4.3). The product was accompanied with the debrominated compound **4.89**, together with the compounds tentatively assigned to be **4.99** and **4.100**, each as single diastereomers in 11% and 9% yields, respectively. The structures of **4.99** and **4.100** were assigned after full characterization by both 1D- and 2D-NMR (key HMBC correlations shown). Evidence for structure **4.100** was the presence of two carbonyl carbon atoms in the ^{13}C-NMR at 192 ppm and 167 ppm indicating ketone and an ester functional groups; only four methoxy groups, and the presence of a quartet at 124 ppm (J = 284 Hz), which is characteristic of a CF_3 carbon atom. Evidence for structure **4.99** was the presence of only one carbonyl carbon atom at 192 ppm, the presence of five methoxy groups and the presence of three acetal carbons at 99 ppm, 97 ppm and 120 ppm. The resonance at 99 ppm belonged to the carbon

atom of the MOM group (determined by HMBC, not shown) while two of the five methoxy groups were coupled to the acetal carbon at 120 ppm, and the other acetal was coupled to the olefin proton.

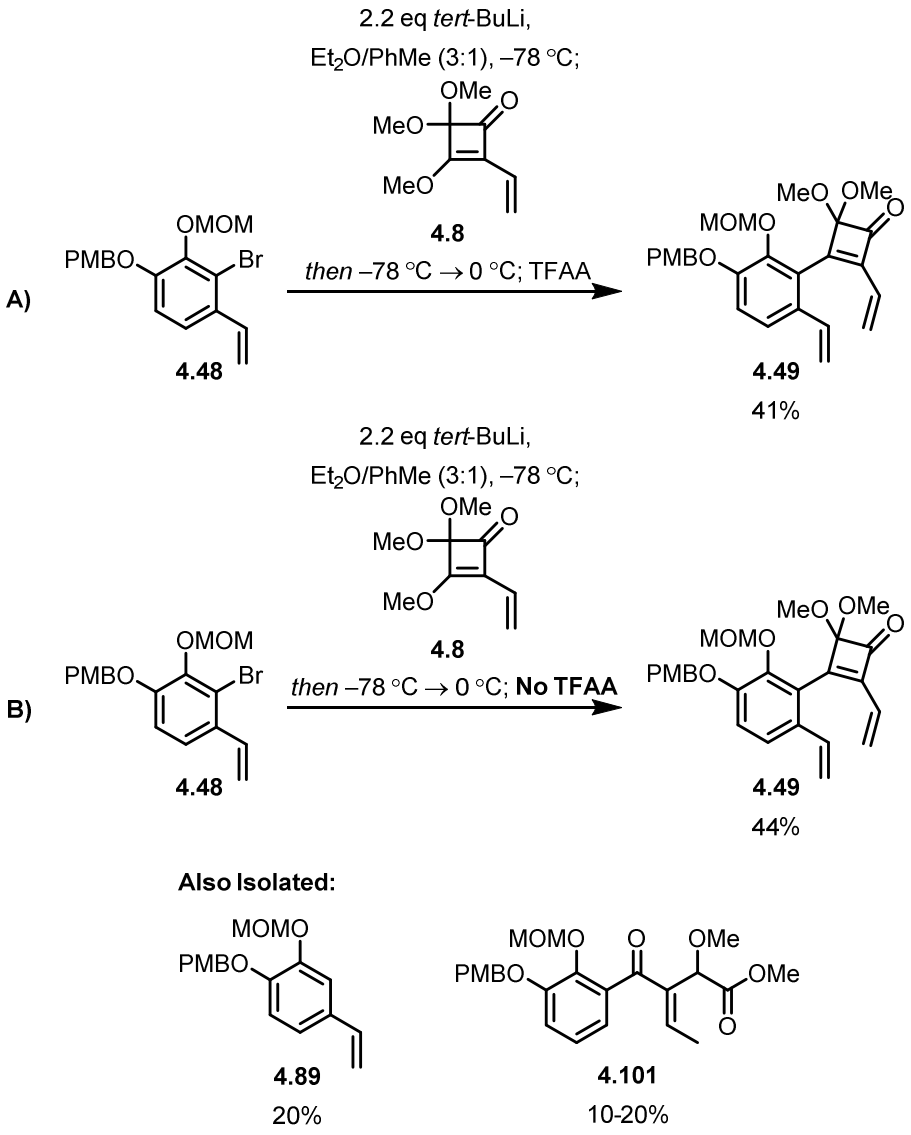
Equation 4.3: Attempted squarate addition in toluene



It is unclear if performing the metal-halogen exchange in toluene and subsequent addition of the vinyl squarate **4.8** had a role in the formation of **4.99** and **4.100**, thus the previously optimized conditions were reinvestigated in order to maximize the yields of **4.49**. Instead of warming the aryllithium to 0 °C before adding the squarate **4.8**, the squarate **4.8** was added at –78 °C, and the cooling bath was replace with an ice/water bath to rapidly warm the reaction mixture to 0 °C. Gratifyingly, use of this modification provided, after TFAA quench, the desired adduct **4.49** in 41% yield (Figure 4.11, **A**). Shockingly, the omission of TFAA also provided **4.49** in 44% yield, indicating that the TFAA quench is not necessary to produce **4.49** (Figure 4.11, **B**). In addition to the expected debrominated product **4.89**, which was isolated in 20% yield, analysis of the reaction mixtures revealed that most of the "missing" mass in the reaction was going to a single byproduct, which after full characterization by 1D- and 2D-NMR was

tentatively determined to be **4.101** as a mixture (3.7:1) of olefin isomers in 10 – 20% yields. Evidence for the structure of **4.101** was presence of two carbonyl carbons at 196/194 ppm and 171 ppm, indicative of a ketone and an ester; and the presence of two olefinic carbon atoms, (1) at 151 ppm, which was coupled to proton at 6.68 ppm (q, J = 7.3 Hz) *via* HSQC, and (2) at 139 ppm, which was coupled to no protons via HSQC. Additionally, the proton 6.68 ppm (q, J = 7.3 Hz) is coupled to the methyl group at 1.96 ppm (d, J = 7.3 Hz).

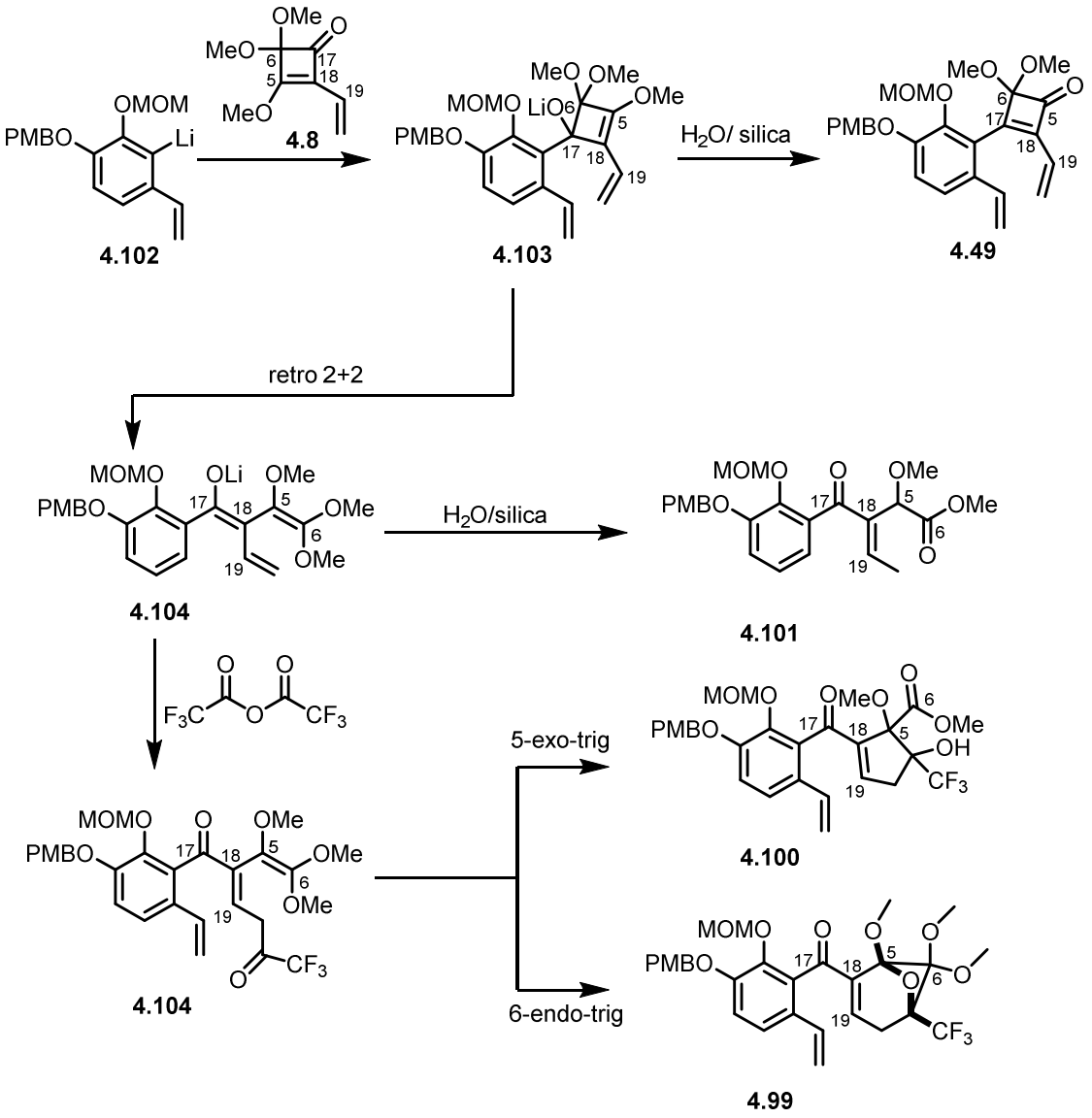
Figure 4.11: Squarate addition and isolation of byproduct **4.101**



a) Addition of vinyl squarate **4.8** at –78 °C, followed by warming to 0 °C with TFAA quench. b) Addition of vinyl squarate **4.8** at –78 °C, followed by warming to 0 °C, no TFAA quench. Discovery of byproduct **4.101**.

The byproducts **4.99**, **4.100** and **4.101** may be related through a common intermediate. Addition of the organolithium **4.102** to vinyl squarate **4.8** produces the alkoxide **4.103**, which upon workup and exposure to silica delivers the desired product **4.49**. The alkoxide intermediate **4.103**, however, can undergo an electrocyclic ring opening to produce the vinylogous enolate **4.104**.[381] In the presence of TFAA, the extended enolate undergoes a Claisen condensation to produce the trifluoro-ketone intermediate **4.105**. The electrophilicity of the trifluoro-ketone moiety causes both a 5-exo cyclization from C5 to form the **4.100** and a 6-endo cyclization from C6 to form **4.99**. In the absence of TFAA, the vinylogous enolate is simply protonated to produce **4.101**.

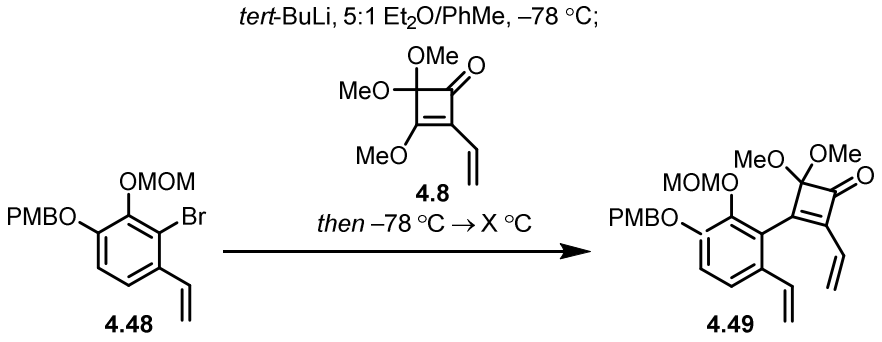
Scheme 4.12: Putative mechanism for the formation of **4.99**, **4.100** and **4.101**



Although oxy-anions are known to accelerate the electrocyclic ring opening,[381] there may be a minimum temperature at which the reaction takes place. Lithium-halogen exchange of the styrene **4.48**, followed by quenching with the vinyl squarate **4.8** and warming to temperature intervals between –78 ºC and 0 ºC revealed that the minimum temperature with which the electrocyclic ring opening occurs is – 40 ºC (Table 4.4). Surprisingly, keeping the temperature at –78 ºC, lead to a decrease in the yield of **4.49** (Table 4.4, Entry 2). Adding the squarate at –78 ºC and replacing the cooling bath with a dry ice/ethanol/glycol bath (1:9) to rapidly raise the

temperature to –20 ºC provided the desired product **4.49** in 68% yield (Table 4.4, Entry 3). Unfortunately the yield decreased from 68% on a 100 mg scale to 40% on a gram scale, perhaps because at larger scales, the rate at which the internal temperature rises is much slower than on smaller scales (Table 4.4, Entries 3,5,6).

Table 4.4: Temperature screen for squarate addition

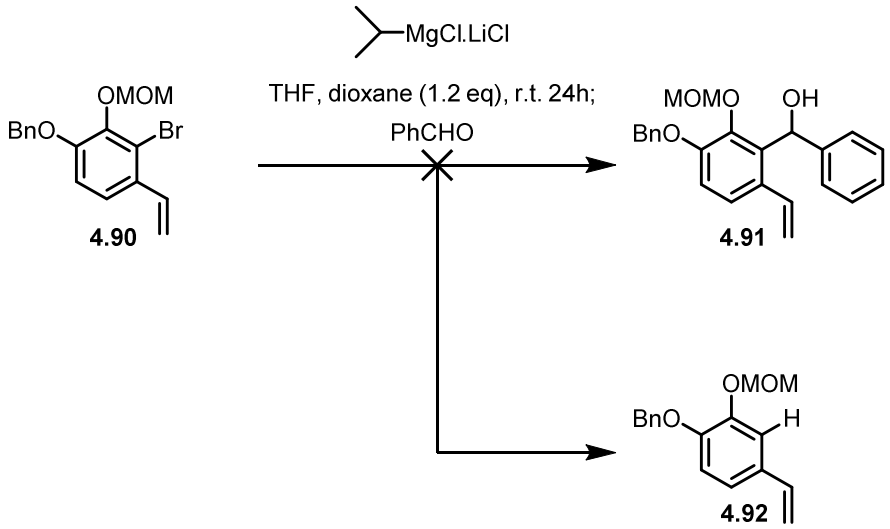


X ºC	Scale (mg)	Yield
0	500	45 – 55%
–78	100	43%
–20	100	68%
–40	500	53%
–20	500	61%
–20	1000	40%

4.2.2.4: Attempted magnesium-halogen exchange

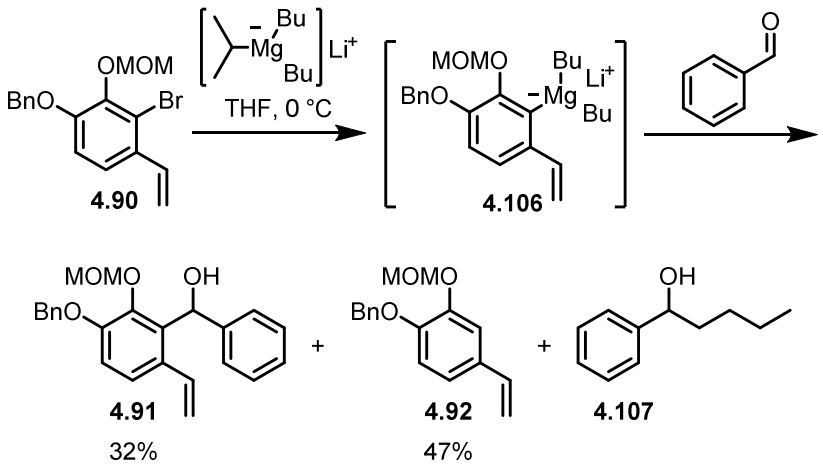
The difficulty encountered with the addition of the aryllithium into the vinyl squarate **4.8** prompted the investigation of the use of organomagnesium reagents, which are known to be less basic than their lithium counterparts. The magnesium-halogen exchange of **4.90** was attempted with *i*-PrMgBr•LiCl in THF with and without added dioxane, which was known to accelerate the reaction.[382-386] Even with dioxane, the magnesium-halogen exchange was sluggish, and after 24 h and quenching with benzaldehyde, only debrominated material **4.92** was isolated (Scheme 4.13). The formation of **4.92** under these conditions is most likely due to the elimination of *i*-PrBr, which is produced after the magnesium-halogen between **4.90** and *i*-PrMgBr•LiCl.

Scheme 4.13: Attempted magnesium-halogen exchange with *i*-PrMgBr•LiCl



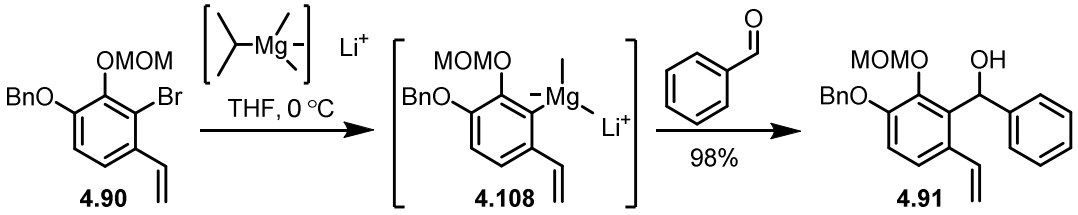
Magnesium ate complexes are known to be more reactive than monoalkyl- and dialkylmagnesium compounds, and in 2001, Oshima demonstrated that magnesium ate complexes can be used in magnesium halogen exchange of a variety of arenes, even at –78 ºC.[387,389] Generation of [*i*-PrMgBu$_2$]Li by adding two equivalents of *n*-BuLi to *i*-PrMgBr in THF, followed by addition of bromostyrene **4.90** presumably generated the ate-complex **4.106** (Scheme 4.14). Unfortunately, quenching with benzaldehyde produced a mixture of the desired compound **4.91**, debrominated compound **4.92**, and the butylated compound **4.107**.

Scheme 4.14: Attempted magnesium-ate-halogen exchange with **4.90**



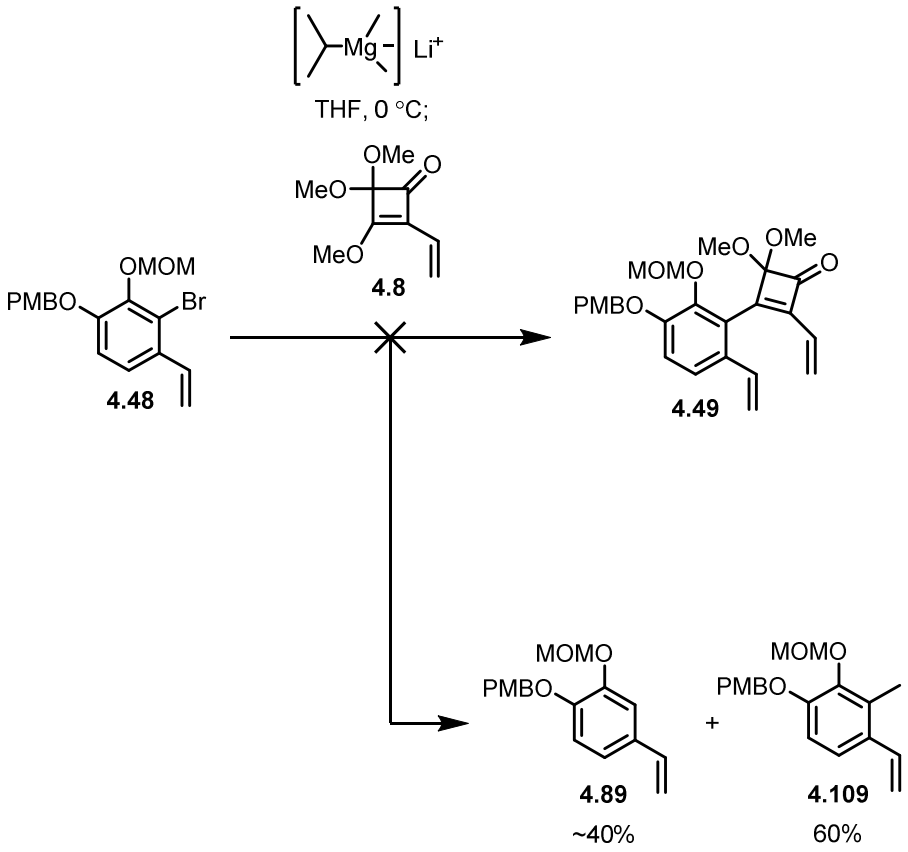
It is clear from these results that all three groups in the magnesium ate complex **4.106** can be transferred to an electrophile. To overcome this problem, MeLi was used instead of *n*-BuLi to generate the alternate ate complex [*i*-PrMgMe$_2$]Li (Scheme 4.15). Methyl groups are known to have low migratory aptitude with similar organometallics and thus can be thought of as "dummy ligands". [387,389] Gratifyingly, quenching with benzaldehyde furnished the desired adduct **4.91** in 98% yield.

Scheme 4.15: Successful magnesium-ate-halogen exchange with **4.90**



Unfortunately, generation of the magnesium ate complex **4.108** under the same conditions used previously and quenching with the vinyl squarate **4.8**, produced the methylated compound **4.109** in 60% yield and debrominated compound **4.89**. The formation of **4.109** can be explained by the reaction of [*i*-PrMgMe$_2$]Li and **4.48** to produce methylbromide rather than the expected *i*-PrBr. The reaction of the arylmagnesium-ate complex with methyl bromide must be faster than the reaction with vinyl squarate **4.8**.

Scheme 4.16: Attempted squarate addition with magnesium-ate complex



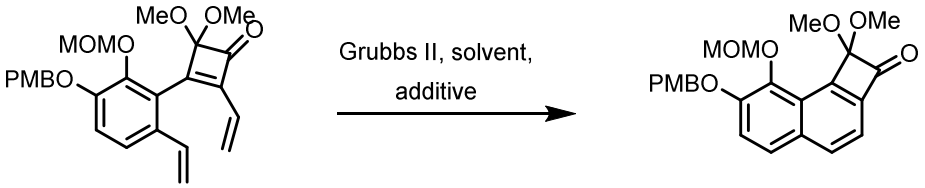
Previous work done in the Martin group encountered difficulties with the metal-halogen exchange of bromostyrenes and subsequent addition to vinyl squarate **4.8**. The bromostyrene **4.48** turned out to be a uniquely frustrating substrate in this reaction. However, after optimization, the yields of **4.49** are now equal to those obtained by Dr. Mans and Dr. Knueppel (61 – 68%, Chapter 3, Scheme 3.41, 3.45). Key to this optimization was the discovery that the intermediate aryllithium reagent **4.102** is unstable and will disproportionate to the benzyl anion **4.98** and that the intermediate vinyl squarate adduct **4.103** will undergo an anion-accelerated electrocyclic ring opening reaction at temperatures above – 40 °C (Scheme 4.12).

4.2.3: RING CLOSING METATHESIS (RCM)

Despite the moderate yields for the squarate addition, enough material was pushed through to explore the downstream chemistry. Subjection of **4.49** to the RCM conditions developed previously in the group provided the BC-ring fragment **4.110** in 60% yield, while use

of dichloroethylene (DCE) as the solvent offered no improvements (Table 4.5, Entry 1,2).[390-393] The presence of baseline material by TLC prompted the addition of BHT to the reaction mixture to suppress any possible radical side reactions.[394] Although BHT seemed to slow the reaction, the yield did not change, and the overall mass balance was improved (Table 4.5, Entry 3). Heating slightly longer and quenching with DMSO (to sequester Ru salts) provided the BC-ring fragment **4.110** in 78% yield (Table 4.5, Entry 4).[395]

Table 4.5: RCM of squarate adduct **4.49**



4.49 **4.110**

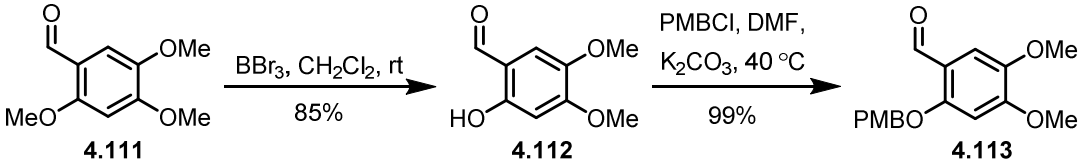
Solvent	T	Additive	Quench	Yield
PhMe	120 °C	N/A	N/A	60%
DCE	90 °C	N/A	N/A	58%
DCE	90 °C	BHT	N/A	57% (77% brsm)
DCE	90 °C	BHT	DMSO[a]	78% (91% brsm)

a) DMSO sequesters Ru salts.

4.3: Acetylide addition

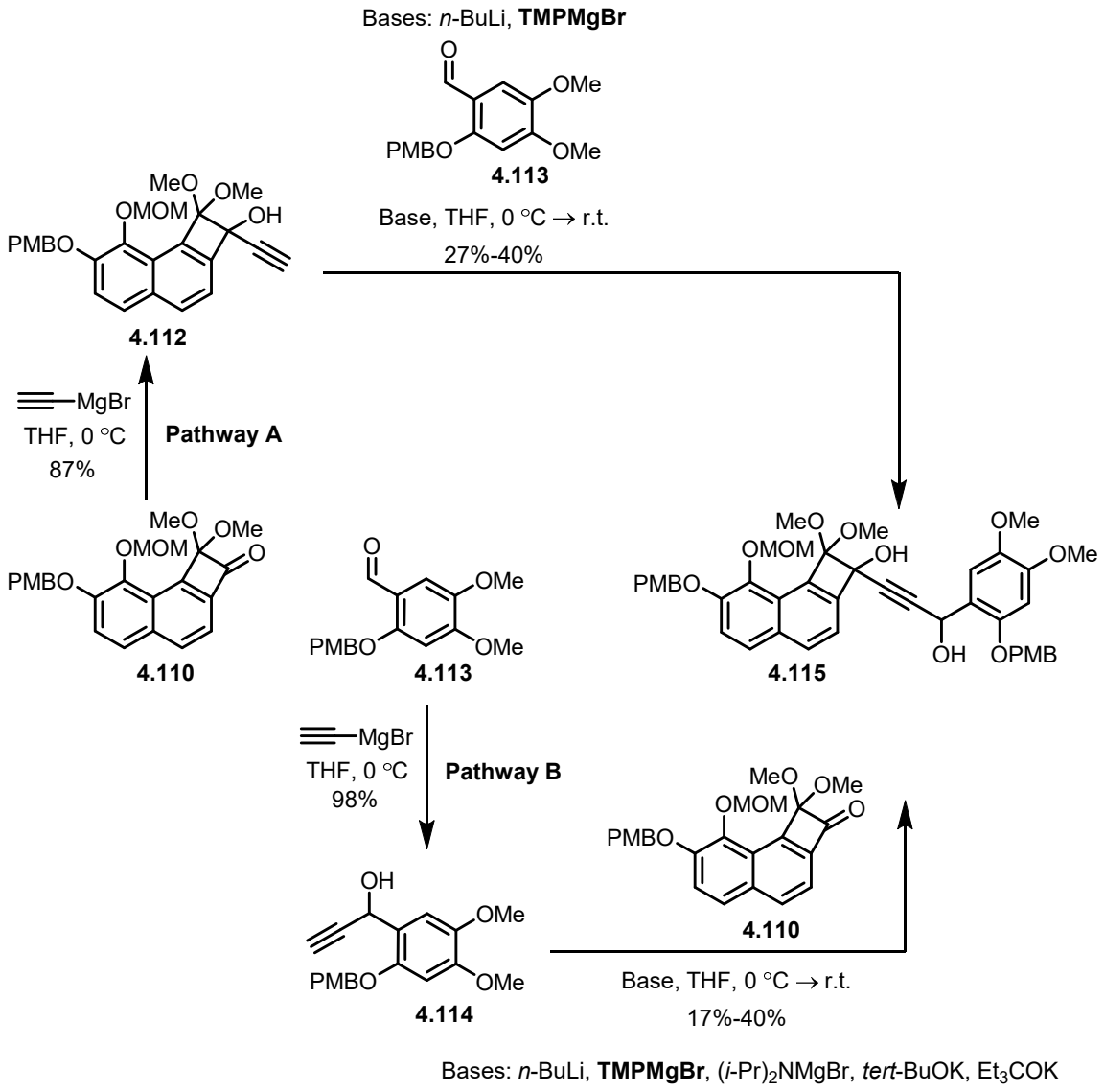
Synthesis of the F-ring fragment **4.113** began with demethylation of the aldehyde **4.111** using freshly distilled BBr_3, which was key for clean demethylation with minimal byproducts (Scheme 4.17).[396] PMB protection of the resulting phenol provided **4.113** in 99% yield.

Scheme 4.17: Synthesis of F-ring aldehyde **4.113**



Two sequences are possible for the generation of **4.115**, the precursor for the Moore rearrangement. Ethynyl magnesium bromide could be added to **4.110** followed by coupling with aldehyde **4.113** (Figure 4.13, Pathway **A**) or ethynyl magnesium bromide could be added to aldehyde **4.113** followed by coupling with **4.110** (Figure 4.13, Pathway **B**).[345, 346] Previous difficulties with adding **4.114** to **4.110** (Pathway **B**) prompted the investigation of adding **4.113** to **4.112** first (Pathway **A**). Several bases, solvents and additives were screened in an effort to prepare **4.115**. Bromomagnesium 2,2,6,6-tetramethylpiperidide (TMPMgBr) was shown to be highly effective for the similar coupling in the synthesis of IB-00208 (see Chapter 3, Scheme 3.52), but use of this base only provided **4.115** in 35% yield. Prolonged stirring with TMPMgBr or with other bases only produced multiple unidentifiable byproducts and did not increase yield. Interestingly, the coupling of **4.114** to **4.110** (Pathway **B**) using TMPMgBr also provided **4.115** in 40% yield.

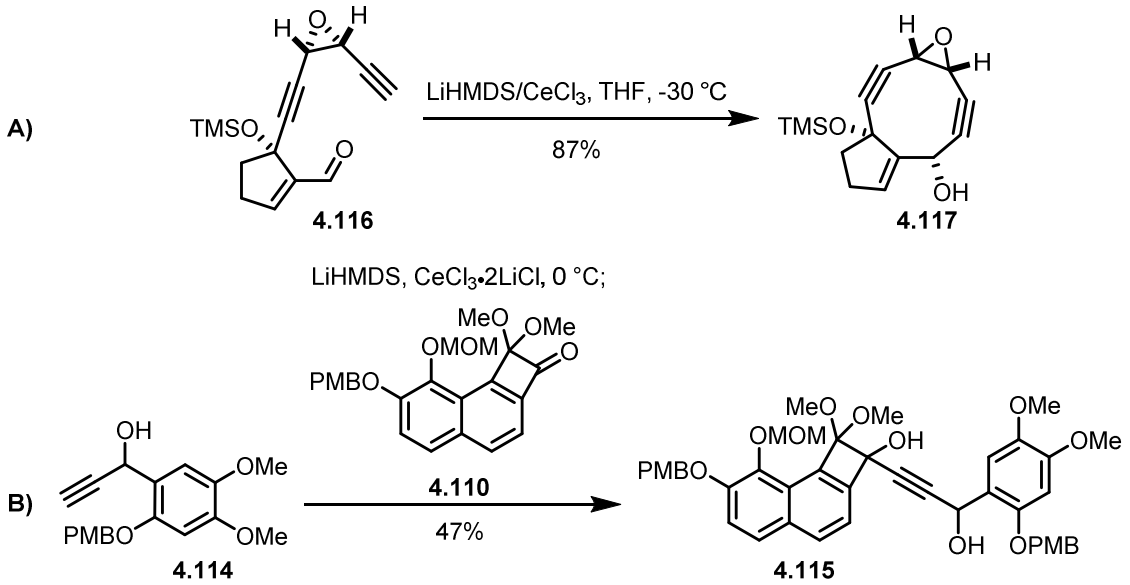
Figure 4.13: Coupling of the BC-ring fragment **4.110** and F-ring fragment **4.113**



A review of the literature for methods to couple aldehydes and alkynes lead to an intriguing example in Myers' synthesis of the core of neocarzinostatin.[397] The intramolecular coupling of the aldehyde and alkyne moieties in **4.116** proved troublesome due to the sensitivity of **4.116** to both basic and acidic conditions (Figure 4.14, **A**). To address these issues, Myers found that adding **4.116** to a pre-mixed solution of LiHMDS and anhydrous $CeCl_3$, formed the

cyclized product **4.117** in 87% yield. To replicate this procedure, **4.114** was added to a pre-mixed solution of LiHMDS and anhydrous $CeCl_3$•2LiCl, followed by **4.110** to provide **4.115** in 47% yield (Figure 4.14, **B**).

Figure 4.14: Myers's LiHMDS/$CeCl_3$ mediated coupling of acetylides and aldehydes



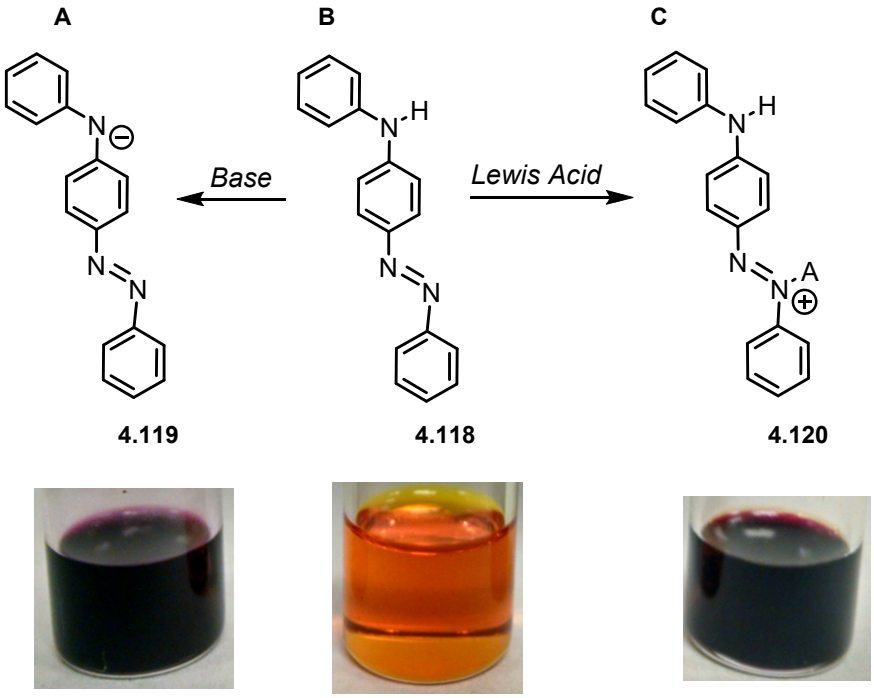
a) Myers's LiHMDS/$CeCl_3$ mediated intramolecular coupling of **4.116** toward neocarzinostatin.[397] b) Application of LiHMDS/$CeCl_3$ toward the intermolecular coupling of **4.114** and **4.110**.

This result prompted the investigation of organocerates because they are known to have enhanced nucleophilicity and reduced basicity. However, the use of anhydrous $CeCl_3$•2LiCl with LiHMDS or other amide bases did not offer any improvements.[167] The ideal method would be to quantitatively generate the cerium acetylide *in situ*. However, this poses a problem: As seen with $MnCl_2$•2LiCl (see Chapter 2, Figure 2.6), salts such as $CeCl_3$•2LiCl will contain adventitious proton sources which will consume any base used to generate the acetylide anion. Usually these problems can be solved by the addition of excess base, but only if the electrophile is either in excess or not a limiting reagent, which is presently the case. Ideally, an internal indicator would be used to measure the quantity of *n*-BuLi needed for acetylide formation, but the indicator must maintain a brightly colored endpoint in the presence of Lewis acids such as $CeCl_3$.

Serendipitously, such an indicator was discovered in 4-(phenylazo)diphenylamine (PDA) (**4.118**), which was originally used for the titration of TMPMgBr.[398] PDA was found to turn deep

purple once deprotonated even in the presence of $CeCl_3$, and it can form highly colored complexes even in the presence of a variety of Lewis acids and solvents (Figure 4.15).

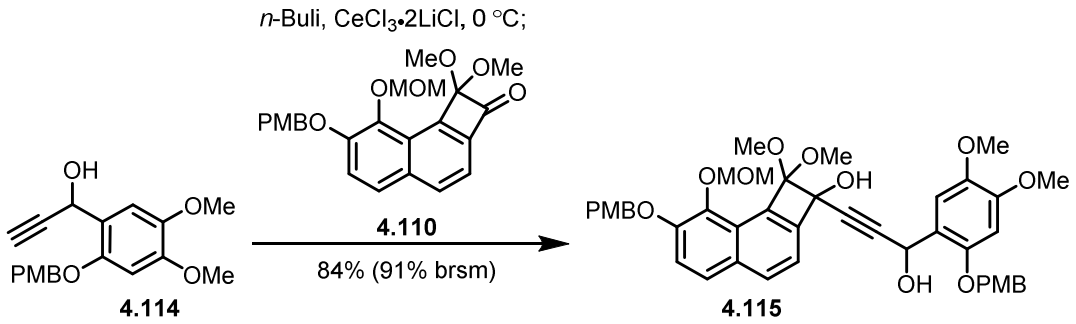
Figure 4.15: Discovery of PDA color change for acids and bases



a) Color of PDA after deprotonation. b) Color of PDA. c) Color of PDA after protonation or complexation with a Lewis acid.

To utilize PDA as an internal indicator for the quantitative deprotonation of **4.114**, the relative p*K*a values of the indicator, the alcohol and the acetylide needed to be determined. The addition of *n*-BuLi to a solution of freshly distilled propargyl alcohol and PDA revealed that the colored endpoint appeared after the addition of one equivalent of *n*-BuLi. This means that the p*K*a of PDA is greater than the alcohol proton, but less than the acetylide proton, thus to use PDA as an internal indication to generate the acetylide anion, additional equivalent of *n*-BuLi would be needed after the endpoint was seen. Gratifyingly, adding *n*-BuLi to a mixture of **4.114**, $CeCl_3$•2LiCl and PDA until a vivid purple endpoint was seen, followed by adding another equivalent of *n*-BuLi and **4.110** provided the adduct **4.115** in 84% yield (Equation 4.4).

Equation 4.4: Successful alkyne addition utilizing $CeCl_3$•2LiCl and PDA as an internal indicator



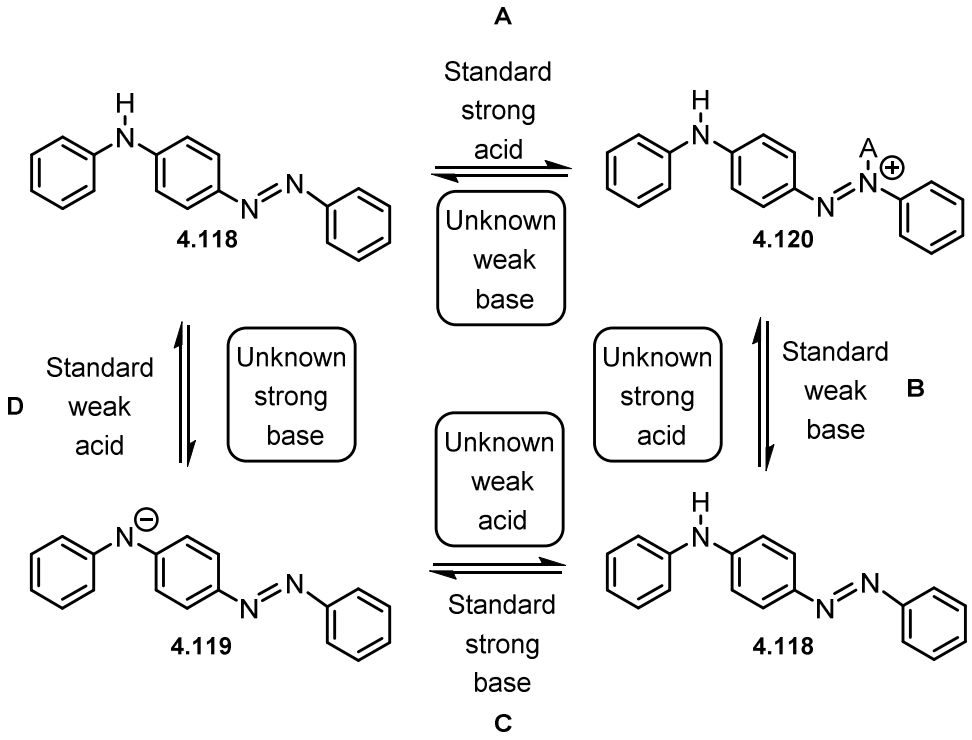
4.4: Use of PDA for the titration of bases, Lewis acids and reducing agents

4.4.1: TITRATION OF BASES

The success of the acetylide addition using PDA **4.118** as an internal indicator led to the investigation of PDA **4.118** as an general-purpose, indicator to titrate a variety of reagents.[399] While there are numerous techniques for determining the concentrations of strongly basic carbanions such as alkyllithium and Grignard reagents, reliable methods for titrating weaker bases, such as amide anions, are lacking.[400, 409,417] Furthermore, there are few reliable methods available for titrating solutions of common Lewis acids.[425-427]

The general strategy for using PDA to titrate bases and acids is outlined in Figure 4.16. Bases with conjugate acids have a pK_a greater than PDA can be titrated with an acid having a pK_a less than PDA (Figure 4.16, **4.118** → **4.119**). Alternatively, acids having a pK_a less than that of PDA can be titrated using a base that has a conjugate acid with a pK_a greater than PDA (Figure 4.16, **4.118** → **4.120**). By selecting the right standard acids and/or bases, a general method to titrate unknown acids and/or bases that have a pK_a above and below the pK_a of PDA could be developed.

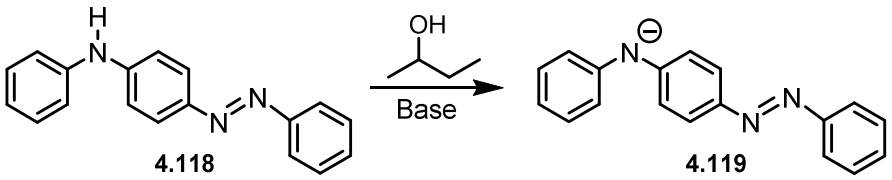
Figure 4.16: Use of PDA to titrate a variety of acids and bases



a) **4.118** → **4.120**: titration of an unknown weak base. b) **4.120** → **4.118**: titration of an unknown strong acid. c) **4.118** → **4.119**: titration of an unknown weak acid. d) **4.118** → **4.119**: titration of an unknown strong base.

To examine the feasibility and scope of using PDA as an indicator for the titration of bases, the concentration of a series of bases commonly encountered in a synthetic laboratory was determined using *sec*-butanol as the standard acid. The results thus obtained were compared to the concentrations obtained using other reported methods (Table 4.6). PDA is equally effective as known methods in determining the concentrations of *n*-BuLi, EtMgBr, $(i\text{-Pr})_2$NMgBr, *tert*-BuLi, *n*-BuZnX·MgX_2·LiX, and HC≡CMgBr. Endpoints for the various titrations were dramatic and ranged from bright red with magnesium bases to deep purple with potassium bases. In the case of HC≡CMgBr, it was necessary to add DMPU as a cosolvent to improve the rate of the color change (Table 4.5, Entry 6).

Table 4.6: Titration of bases with PDA



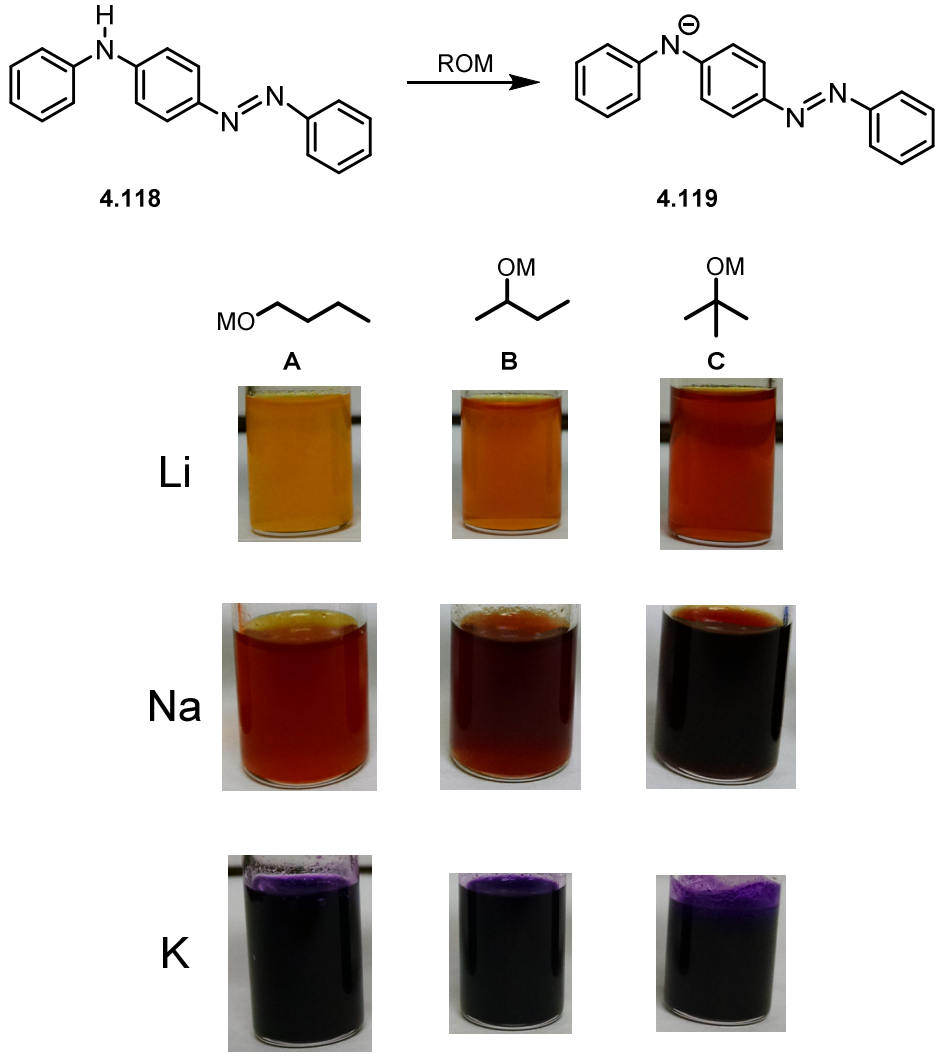
4.118 4.119

		Standard Methods[g]			PDA[g]		Total Base[f]
Base	(M)	Ind	H^+	(M)[j]	H^+	(M)[j]	
EtMgBr	1	1,10-Phen[d]	*s*-BuOH	1.07±0.01	*s*-BuOH[k]	1.06 ± 0.04	1.13
$(iPr)_2NMgBr$[a]	0.83	1,10-Phen[d]	*s*-BuOH	0.68±0.03	*s*-BuOH[k]	0.64 ± 0.04	0.86
n-BuLi	2.5	1,10-Phen[d]	*s*-BuOH	2.11±0.11	*s*-BuOH	2.10 ± 0.10	2.33
tert-BuLi	2	*n*-piv-toluidine[c]	N/A	1.61	*s*-BuOH[i,k]	1.64 ± 0.10	3.29
n-BuZnX[b]	0.5	I_2/LiCl[e]	N/A	0.27±0.01	*s*-BuOH[k]	0.25 ± 0.04	0.47
HC≡CMgBr	0.5	1,10-Phen[d]	*s*-BuOH	0.55±0.03	*s*-BuOH[h,k]	0.55 ± 0.02	0.55

[a]Made by refluxing (*i*-Pr)$_2$NH and EtMgBr in THF for 24 h. [b]Made *in situ* from Mg in THF with fused $ZnCl_2$, LiCl and *n*-BuBr (ref 421). [c]Added *tert*-BuLi to a solution of *n*-pivaloyl toluidine in THF at 0 °C until a yellow endpoint was observed (ref 405). [d]1,10-Phenanthroline was pre-activated with 1 drop *n*-BuLi, and *sec*-butanol was used as the proton source (ref 410, 416). [e]Used a solution of I_2 in 0.5 M LiCl in anhydrous THF (ref 418). [f]Calculations for total base were done by adding to deionized water and titrating with HCl that had been standardized with potassium hydrogen phthalate (KHP) using phenolphthalein as the indicator (ref 424). [g]Unless otherwise indicated, all titrations were done in anhydrous THF at 0 °C. [h]DMPU was added as a cosolvent to make color change more distinct. [i]Anhydrous Et_2O was used as the solvent. [j]Each titration was done in triplicate and confidence intervals set to 95%. [k]Endpoint was red.

In initial experiments to titrate NaHMDS with *sec*-butanol and PDA, no endpoint was observed. Surprisingly, sodium *2*-butoxide, which is produced during the titration, was found to deprotonate PDA. This finding prompted a brief inquiry of counterion effects with alkoxides. The lithium, sodium and potassium conjugate bases of *n*-BuOH, *sec*-BuOH and *tert*-BuOH were added to a solution of PDA in THF in order to determine which alkoxides can deprotonate PDA (Figure 4.17). These experiments showed that the lithium alkoxides do not deprotonate PDA in THF, but sodium and potassium alkoxides do.

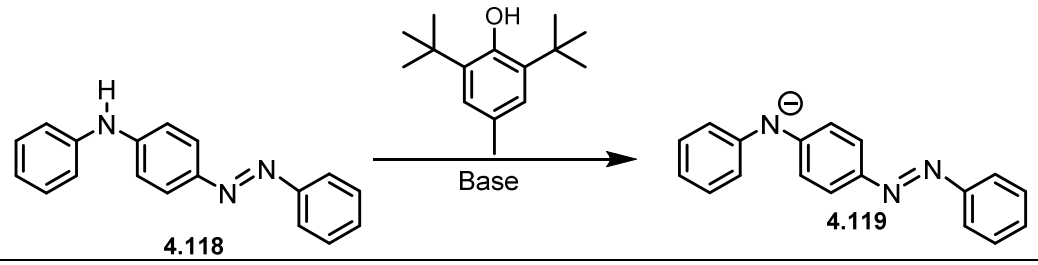
Figure 4.17: Effect of cation on alkoxides in the presence of PDA



With the knowledge that sodium and potassium alkoxides can deprotonate PDA, a different standard weak acid was sought with a p*K*a which is slightly lower than *sec*-butanol (p*K*a = 30.3 in DMSO).[422] Fortunately butylated hydroxytoluene (BHT) was found to fit this need (p*K*a = 16.8 in DMSO).[423] Gratifyingly, use of BHT instead of *sec*-butanol in the titration of NaHMDS gave titers that were comparable to the ones obtained when using 1,10-phenanthroline as the indicator (Table 4.7, Entry 1). The observation that potassium alkoxides can deprotonate PDA suggested that it might be possible to develop a procedure to titrate *tert*-BuOK utilizing BHT as the standard acid. As expected, PDA can also be used for the titration of *tert*-BuOK (Table 4.7, Entry 2). However, because there are no standard procedures titrating

potassium alkoxides, the question accuracy remains. KOH, the most likely basic contaminant in *tert*-BuOK, was added to a variety of organic solvents in order to determine if KOH can deprotonate PDA. KOH was found to not deprotonate PDA in every solvent screened except for DMSO. Even adding *tert*-BuOK to wet THF to generate reactive microcrystalline KOH did not deprotonate PDA. These results support that the titer for *tert*-BuOK with PDA and BHT is accurate, so PDA is the first indicator that has been reported to directly titrate solutions of *tert*-BuOK.

Table 4.7: Use of BHT to titrate NaHMDS and *tert*-BuOK



4.118 4.119

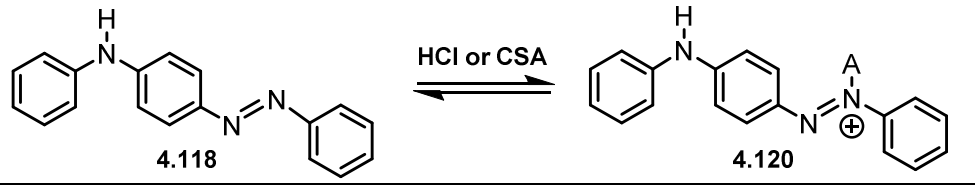
		Standard Methods			PDA[c]		Total Base[b]
Base	(M)	Ind	H^+	(M)	H^+	(M)[d]	
NaHMDS	2	1,10-Phen[a]	*s*-BuOH	1.87 ± 0.09	BHT	1.83 ± 0.12	2.18
tert-BuOK	1	N/A	N/A	N/A	BHT	0.71 ± 0.02	0.92

[a]1,10-Phenanthroline was pre-activated with 1 drop *n*-BuLi, and *sec*-butanol was used as the proton source. [b]Calculations for total base were done by quenching into deionized water and titrating with HCl that had been standardized with potassium hydrogen phthalate (KHP) using phenolphthalein as the indicator (ref 424). [c]Unless otherwise indicated, all titrations were done in anhydrous THF at 0 °C. [d]Each titration was done in triplicate and confidence intervals set to 95%.

Although PDA was shown to be an effective indicator for titrating strong bases such as *n*-BuLi, weaker bases such as $ZnMe_2$ and *n*-BuZnCl•LiCl do not deprotonate PDA. However, we resoned that it might be possible to titrate these bases by using a standard strong acid. The endpoint would occur when the base is consumed and the acid protonates PDA. A solution of NaOH was titrated with a standardized solution of HCl, and PDA proved just as effective as phenolphthalein as an indicator (Table 4.7, Entry 1). With the proof of principal established, the

titration of $ZnMe_2$ and *n*-BuZnCl•LiCl was attempted using CSA as an anhydrous standard acid (Table 4.7, Entries 2, 3). Unfortunately, the values obtained with PDA seemed to be closer to the values obtained when $ZnMe_2$ or *n*-BuZnCl•LiCl were quenched into water and titrated with HCl rather than the values obtained with iodometric titration. This suggests that protic strong acids may not be the best choice for determining the concentration of active weakly basic organometallic reagents.

Table 4.7: Attempted titration of weak bases



4.118 4.120

		Standard Methods[e]			PDA[e]		Total Base[d]
Base	(M)	Ind	H^+	(M)[g]	H^+	(M)[g]	
NaOH[a]	1	Phenolphthalein	HCl	0.95 ± 0.06	HCl[f]	0.96 ± 0.02	N/A
n-BuZnCl[b]	0.5	I_2/LiCl[c]	N/A	0.24 ± 0.02	CSA	0.50 ± 0.02	0.47
Me_2Zn	1.2	I_2/LiCl[c]	N/A	1.20 ± 0.21	CSA	1.31 ± 0.10	1.38

[a]Standardized with potassium hydrogen phthalate (KHP). [b]Made by adding *n*-BuLi to fused $ZnCl_2$. [c]Used a solution of I_2 in 0.5 M LiCl in anhydrous THF. [d]Calculations for total base were done by quenching into deionized water and titrating with HCl that had been standardized with potassium hydrogen phthalate (KHP) using phenolphthalein as the indicator (ref 424). [e]Unless otherwise indicated, all titrations were done in anhydrous THF at 0 °C (ref 418). [f]Titration done in MeOH/H_2O. [g]Each titration was done in triplicate and confidence intervals set to 95%.

4.4.2: TITRATION OF LEWIS ACIDS

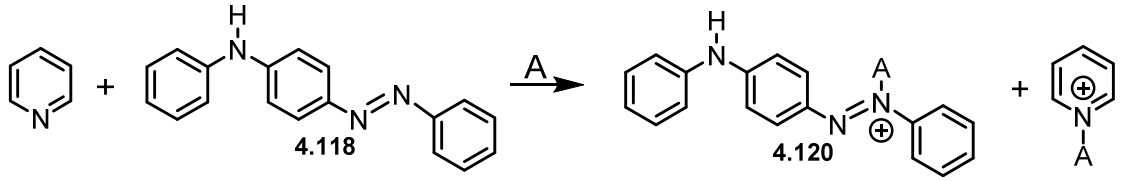
Methods for titrating Lewis acids have been surprisingly neglected. Indeed, there are only two general procedures that are frequently used to determine the concentration of solutions of Lewis acids. The first of these involves titrating the protic acid that is released upon quenching the Lewis acid in water using a standard base and phenolphthalein as the indicator. Although this method works in some cases, a number of Lewis acids, such as $MgBr_2$•Et_2O, do not produce an equivalent of acid when they are quenched with water. The second common procedure to determine concentrations of Lewis acids involves complexometric titration with ethylenediamine tetraacetic acid (EDTA).[425] Such titrations are performed by adding a standard solution of EDTA

to an aqueous solution of the Lewis acid containing an indicator that forms a colored complex with the metal ion. The endpoint is reached when the color disappears. The drawback of this method is that the total metal ion concentration may not accurately reflect the amount of active Lewis acid in solution owing to adventitious moisture. Hence, there is a need for better methods to determine the concentrations of common solutions of Lewis acids.

As outlined in Figure 4.16, pyridine was chosen as the standard weak base in the titration of Lewis acids using PDA as an indicator. The concentrations of $AlMe_3$ and *i*-Bu_2AlH that were determined using pyridine and PDA as the indicator gave titers comparable to those obtained using standard procedures (Table 4.8, entries 5,6).[426,427] The concentration of Me_2AlCl determined with PDA was in good agreement with the value obtained by quenching into water and the titration of the protic acid (Table 4.8, entry 1). The titers that were determined for 9-borobicyclononane bromide (9-BBN-Br), $TiCl_4$, and $MgBr_2$•Et_2O were roughly twice that obtained using standard methods (Table 4.8, entries 2 – 4). This may be due to complexes such as **4.122**, which is in equilibrium with **4.123**, that can form upon combination of Lewis acids and pyridine (Scheme 4.18).[428] The reaction of **4.122** or **4.123** with a second equivalent of Lewis base forms **4.124** before the violet endpoint is observed. Similar reactions may be envisioned for $TiCl_4$ and $MgBr_2$•Et_2O. When this 1:2 stoichiometry is taken into consideration, titration of these Lewis acids with pyridine using PDA as an indicator gave titers comparable to those obtained by titrating the Brønsted acid released upon reaction of the Lewis acid with water or by complexometric titration with EDTA using eriochrome black t as the indicator (Table 4.8, entries 4 – 6).[425] The concentrations of 9-BBN-Br determined by hydrolysis and $MgBr_2$•Et_2O determined using a EDTA titration were slightly different from the values determined with PDA (Table 4.8, entries 5,6). Although the reasons for these discrepancies are currently unknown, some possible causes may be postulated. For example, the borinic acid formed upon hydrolysis of 9-BBN-Br with water might consume hydroxide ion, thereby resulting in underestimating the Lewis acid concentration.[429] Supporting this hypothesis, titration of the acid released upon reaction of 9-BBN with methanol and triethylamine using PDA as an indicator also gave a titer

of 1.18 ± 0.24 M, a result very similar to that obtained with PDA and pyridine. That the concentration of $MgBr_2•Et_2O$ determined by titration with EDTA was somewhat higher than the one determined with PDA might arise because complexometric titration measures the total concentration of magnesium ions, not just $MgBr_2•Et_2O$. Hence, complexometric titration may overestimate the Lewis acid concentration.

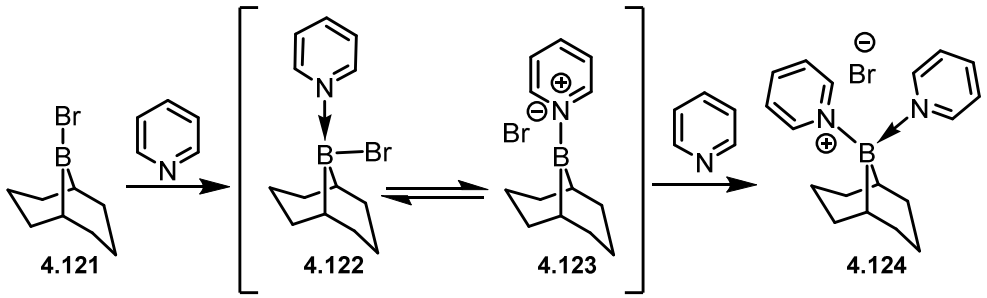
Table 4.8: Use of PDA to titrate Lewis acids



		Standard Methods			PDA[a]	
Acid	(M)	Ind	base	(M)[b]	H^+	(M)[b]
Et_2AlCl	1	Phenolphthalein[d]	NaOH	0.77 ± 0.37	pyridine	0.87 ± 0.06
9-BBN-Br	1	Phenolphthalein[d]	NaOH	1.01 ± 0.07	pyridine	1.18 ± 0.24[f]
$TiCl_4$	1	Phenolphthalein[d]	NaOH	0.93±0.23[g]	pyridine	0.96 ± 0.10[f]
$MgBr_2•Et_2O$[h]	0.86	Eriochrome black t[e]	EDTA	1.08 ± 0.03	pyridine	0.83 ± 0.11[f]
$AlMe_3$	1	Phenazine[c]	pyridine	0.72 ± 0.07	pyridine	0.79 ± 0.03
iBu_2AlH	1	Phenazine[c]	pyridine	0.83 ± 0.03	pyridine	0.83 ± 0.03

[a]Unless otherwise indicated, all reactions were run at room temperature in anhydrous DCM. [b]Each titration was done in triplicate and confidence intervals set to 95%. [c]Anhydrous toluene was used as the solvent (ref 426, 427). [d]Calculations were done by quenching into deionized water and titrating with NaOH that had been standardized with potassium hydrogen phthalate (ref 424). [e]EDTA was standardized with $Zn(OAc)_2•2H_2O$ and Eriochrome black t (ref 425). [f]Molarity calculated using 1:2 stoichiometry of Lewis acid to pyridine (see text for discussion). [g]Molarity calculated using 4:1 stoichiometry of NaOH to Lewis acid. [h]Prepared from Mg and ethylene dibromide in anhydrous Et_2O then adding benzene until the biphasic $MgBr_2•OEt_2$ mixture becomes homogeneous.

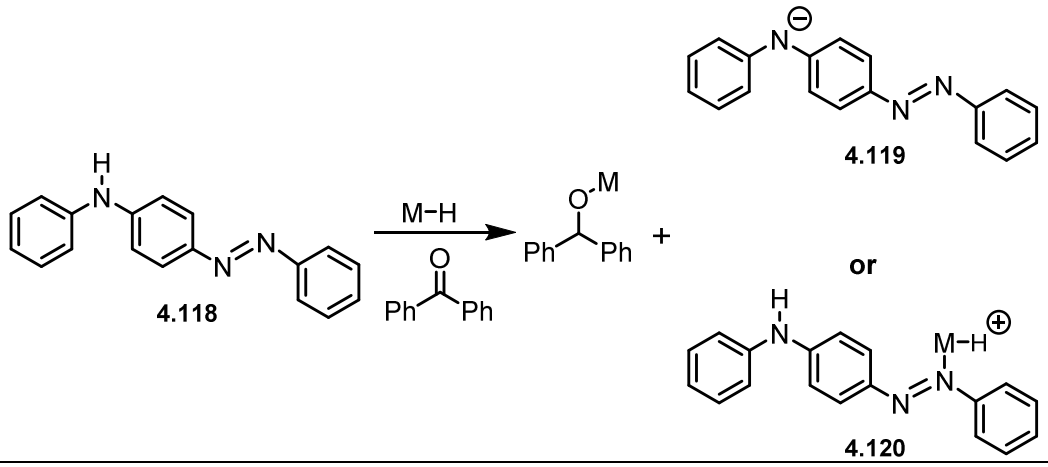
Scheme 4.18: Example of Lewis acid coordinating multiple equivalents of base



4.4.3: TITRATION OF REDUCING AGENTS

Metal hydride reducing reagents are frequently employed in synthesis, and many of the indicators that have been used to titrate bases have been also used to titrate $LiAlH_4$ and other reducing agents.[430-432] Benzophenone was found to be a convenient agent to determine the titer of some reducing agents using PDA as an indicator. Benzophenone reacts with the reducing agent to form a species that does not induce a change in the color of the indicator. Once all of the benzophenone is consumed, the reducing agent will either deprotonate the indicator to form a colored complex or form a colored Lewis acid/base pair depending upon the acidic or basic character of the reducing agent. The use of this method to determine the concentration of several reducing agents was compared to a commonly-used procedure in which reduction of fluorenone, which is yellow, leads to a colorless solution (Table 4.9). The titers of $LiAlH_4$ and $LiB(sia)_3H$ were determined using PDA as an indicator, and the values thus obtained compare well to those found with fluorenone (Table 4.9, entries 2,3). However, the titer of *i*-Bu_2AlH, which is Lewis acidic in nature, with PDA differs from that obtained using the fluorenone method (Table 4.9, entry 1). Notably, the titer of this solution of *i*-Bu_2AlH using benzophenone and PDA is within experimental error to that determined using pyridine and either PDA or phenazine (Table 4.8, entry 7). This observation suggests that the value obtained with fluorenone may overestimate the concentration.

Table 4.9: Use of PDA to titrate reducing agents



		Fluorenone[a]	PDA	
Red agent	(M)	(M)[e]	Hydride acceptor	(M)[e]
iBu_2AlH	1	1.02± 0.1	benzophenone	0.84 ± 0.06[b]
$LiAlH_4$	1	0.99 ± 0.15[d]	benzophenone	1.02 ± 0.18[c,d]
$LiB(sia)_3H$	1	1.06[f]	benzophenone	1.04 ± 0.09[c]

[a]Unless otherwise indicated, all titrations were done in anhydrous THF at room temperature (ref 430). [b]Titration was done in anhydrous CH_2Cl_2 at room temperature. [c]Titration was performed in anhydrous Et_2O at room temperature. [d]Molarity calculated using 4:1 stoichiometry of benzophenone to reducing agent. [e]Unless otherwise indicated, each titration was done in triplicate and confidence intervals set to 95%. [f]Titration was only done once due to unexpected color change.

In summary, PDA is a convenient, colorimetric indicator that can be easily used to directly determine the concentrations of a variety of strong carbon- and nitrogen-centered bases in the presence of a number of counterions, including Li, Na, K, Mg, and sometimes Zn. Additionally, we found that PDA could be used as an indicator to titrate *tert*-BuOK without interference from KOH or other basic impurities. Although the titration of weaker bases such as $ZnMe_2$ and *n*-BuZnCl•LiCl with CSA and PDA give results that reflect the total base content, it is possible that by prudent selection of the standard acid or base, it may be possible to determine the concentration of many reactive reagents commonly used in synthetic organic chemistry. PDA was also shown to be an effective indicator for titrating a number of Lewis acids using pyridine as a standard base. Finally, the concentrations of hydride reducing agents can be determined using benzophenone and PDA. Currently, however, the limitations of using PDA as an indicator include; (1) The titrations of weakly basic organometallic agents; (2) Hydride reducing agents

which are neither basic enough to deprotonate PDA nor acidic enough to protonate PDA, and (3) Weak Lewis acids which do not complex PDA to produce a colored complex.

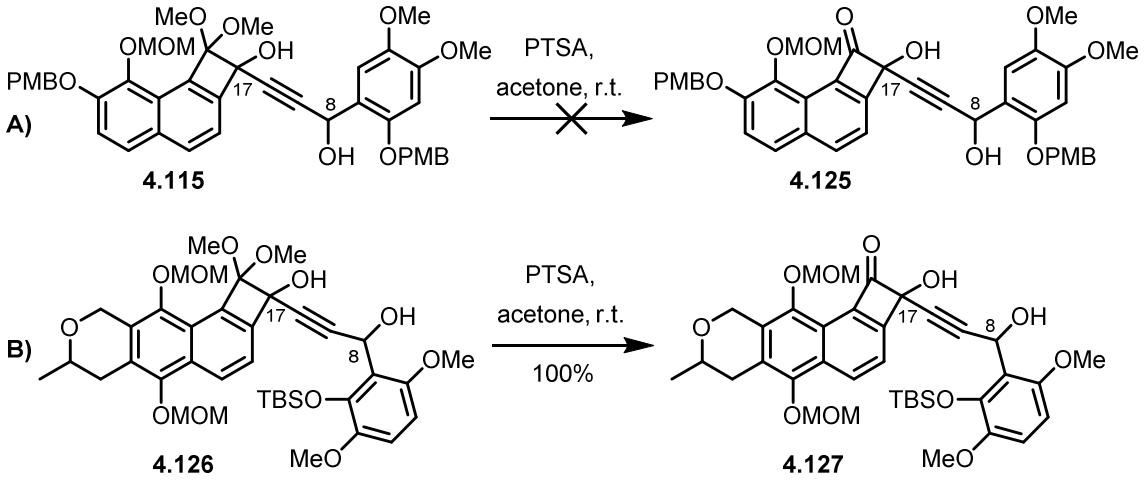
4.5 Hydrolysis of acetal and Moore rearrangement

4.5.1: HYDROLYSIS OF ACETAL 4.115

4.5.1.1: Hydrolysis of PMB protected F-ring fragment

The utilization of PDA as an internal indicator enabled the synthesis of multiple grams of the acetal **4.115**, and our focus was directed to effecting the hydrolysis of the **4.115** and subsequent Moore rearrangement. Hydrolysis of the acetal moiety in **4.115** using the same conditions used in the synthesis of IB-00208 (Figure 4.18, **B**) (see also Chapter 3, Schemes 3.42 and 3.52) produced only complex mixtures (Figure 4.18, **A**).

Figure 4.18: Hydrolysis of **4.115** and hydrolysis of **4.126** in the synthesis of IB-00208

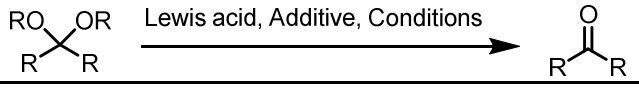


a) Attempted hydrolysis of acetal **4.115**. b) Successful hydrolysis of **4.126** using the same conditions

Both compound **4.115** and compound **4.126** contain several acid sensitive moieties such as the MOM and PMB protecting groups as well as the benzyl alcohol groups at C8 and C17. However, only **4.115** contains PMB groups, so they were initially thought to be the culprit. A survey of the literature for methods that hydrolyze acetals in the presence of benzyl alcohols or PMB groups (Table 4.10) revealed that lanthanide triflates (Table 4.10, entries 2,5 and 9) and

acid-doped silica (Table 4.10, entries 2,5 and 9) are highly effective Lewis acids for this purpose.[433-458]

Table 4.10: Lewis acid mediated hydrolysis of Acetal

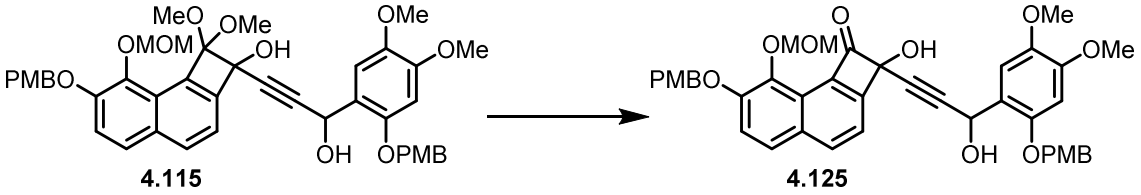


Ref	LA	Additive	Conditions	Yield
Conia[433]	silica	oxalic acid	CH_2Cl_2, rt	77 – 98%
Yadav[436]	$CeCl_3$	NaI	MeCN, reflux	81 – 92%
Yadav[437]	I_2		MeCN, rt	90 – 95%
Fujioka[438-447]	R_3SiOTf	R_3N	CH_2Cl_2, 0 ºC	74 – 92%
Fujioka[448-452]	TESOTf	P(*o*-tol)$_3$	CH_2Cl_2, 0 ºC	80 – 95%
Procopio[453]	$Ce(OTf)_3$		$MeNO_2$, rt	25 – 99%
Hu[454]	I_2		acetone, rt	93 – 98%
Gregg[455]	$In(OTf)_3$		acetone, rt	32 – 94%
Li[456]	TFA		$HCCl_3$, rt	90 – 100%
Procopio[457]	$Er(OTf)_3$		$MeNO_2$, rt	68 – 99%
Hou[458]	Ph_3PHBr		CH_2Cl_2, 50 ºC	61 – 90%

Several Lewis and Brønsted acids were screened to hydrolyze **4.115** to **4.125**, but all conditions produced complex mixtures except oxalic acid-doped silica, where the desired product was detected by LCMS in trace amounts (Equation 4.5). Developed by Conia in 1978,[433] acid-doped hydrated silica is prepared by adding either oxalic acid (0.25 mmol/g silica) or sulfuric acid (for harder to hydrolyze acetals) and water (0.1 mL/g silica) to a rapidly stirred slurry of silica in CH_2Cl_2. Conceivably, any acid could be doped onto the silica and in order to develop a milder hydrolysis of **4.115**. Hence, a series of Brønsted acids were screened according to their p*K*a values. Strong acids such as PTSA and HCl produced multiple products, while weaker acids such as acetic acid did not promote any reaction. Fortunately phosphoric acid and fumaric acid produced a single product, but the reaction times were considerably longer with

fumaric acid. Screening the solvent revealed an interesting trend: The reaction was fastest in nonpolar solvents CH_2Cl_2 and PhMe, while more polar solvents slowed the reaction down considerably. This observation is consistent with the need for the substrate to adsorb to the silica in order to hydrolyze.

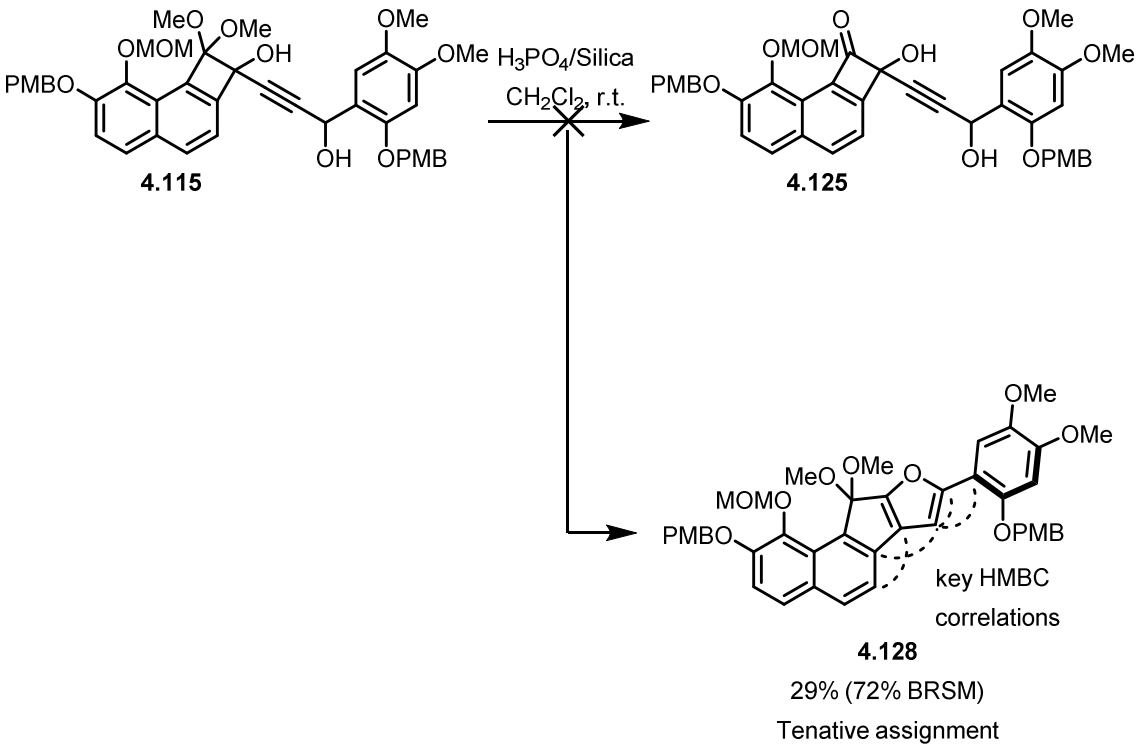
Equation 4.5: Hydrolysis screen



Oxalic acid/Silica	Acid/Silica:	pKa	Solvent:
$Ce(OTf)_3$	PTSA	-2.6	**CH_2Cl_2**
$In(OTf)_3$	HCl	-2.2	PhMe
TFA	oxalic acid	1.2	MeCN
acetic Acid	fumaric acid	3	acetone
	phosphoric acid	**2.1**	$MeNO_2$
	m-nitrobenzoic acid	2.4	
	acetic acid	4.8	

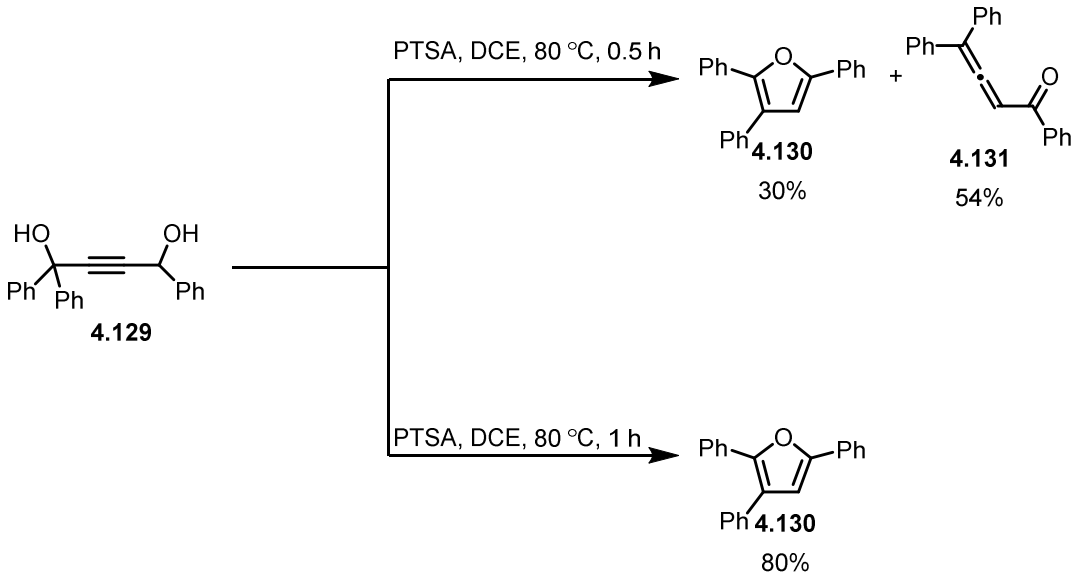
With the hydrolysis of **4.115** optimized using H_3PO_4/silica in CH_2Cl_2, the reaction was scaled up. A single product was produced, but the NMR spectra did not match that expected for **4.124**. After analyzing the ^{1}H-NMR, ^{13}C-NMR, HSQC, and HMBC spectra, the product of the reaction was assigned as being **4.128**, present as a mixture of rotamers (key HMBC correlations shown) (Scheme 4.19). Furthermore, the mass of **4.128** is 734, which is the same mass of the starting material less water. There were no carbonyl carbon atoms present in the ^{13}C-NMR, and the presence of two new Csp_2-O carbon atoms with an HMBC correlation to the proton attached to a carbon at 94 ppm is indicative of an enol ether moiety.

Scheme 4.19: Unexpected formation of **4.128** during hydrolysis of **4.115**



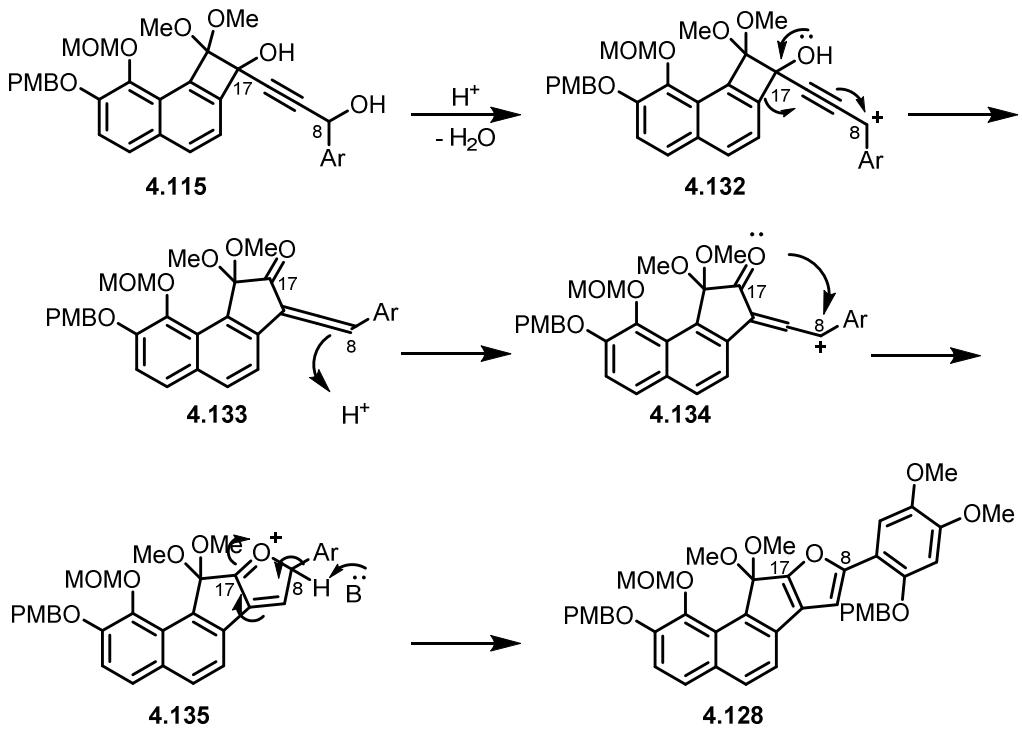
Examples of but-2-yne-1,4-diols rearranging to furans are known.[459,460] Particularly relevant is the work by Chan,[460] who found that heating but-2-yne-1,4-diol **4.129** in dichloroethane (DCE) with PTSA produced mixtures of the allene **4.131** and furan **4.130** when the reaction was stopped after only 30 minutes, but furan **4.130** was formed as the sole product after one hour (Scheme 4.20).

Scheme 4.20: Precedence for the rearrangement of but-2-yne-1,4-diols to furans



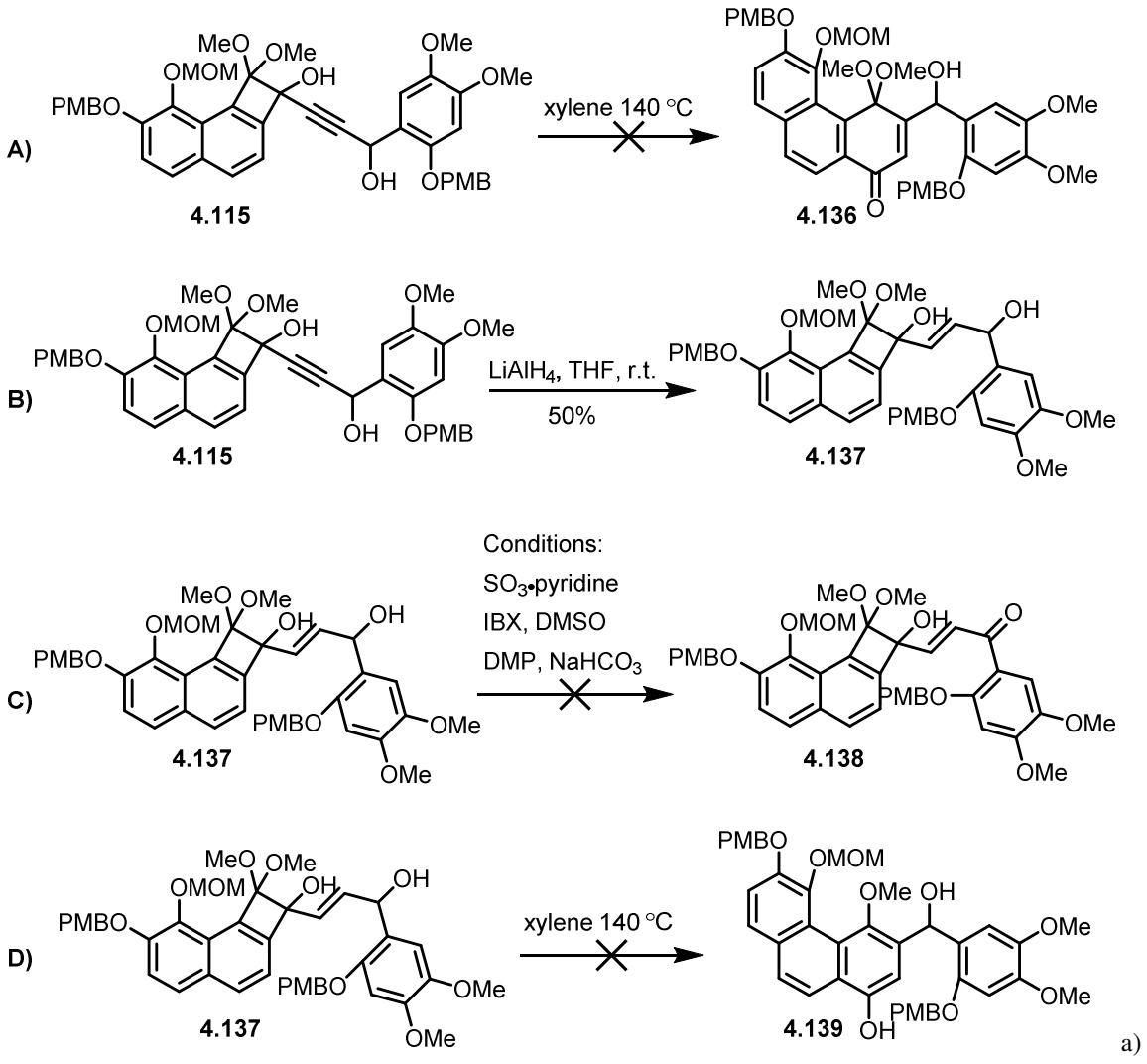
The putative mechanism for the formation of **4.128** is shown in Scheme **4.21**. The rearrangement starts by ionization of the C8 alcohol to the benzyl cation **4.132**, followed by a semipinacol-like rearrangement that results in the ring-expansion of the cyclobutanone and migration of the aryl ring to produce the allene **4.133**. Protonation of the allene produces the carbocation **4.134** that is intercepted by the carbonyl oxygen atom to form the oxonium ion **4.135**, deprotonation of which produces **4.128**.

Scheme 4.21: Putative Mechanism for the formation of **4.128**



The acid sensitivity of the C8 benzyl alcohol in **4.115** led to the investigation of other routes to circumvent the need to hydrolyze the acetal. Suzuki used a Moore-like rearrangement of benzocylobutanone acetals to produce hydroquinones in his syntheses of TAN-1085 and other natural products.[461-468] This strategy is attractive because it would circumvent the need to hydrolyze **4.115** to **4.125**. Unfortunately, attempts to rearrange **4.115** to the quinone acetal **4.136** by heating in toluene led to complex mixtures (Figure 4.19, **A**). Reducing the acetylene to the trans alkene with $LiAlH_4$ provided a compound with a mass consistent with **4.137** by LCMS in 50% yield (Figure 4.19, **B**).[469] Attempts to oxidize the benzyl alcohol to the ketone **4.138** or heating to produce the hydroquinone **4.139** led to complex mixtures (Figure 4.19, **C**, **D**).

Figure 4.19: Attempted alternate Moore-like rearrangements

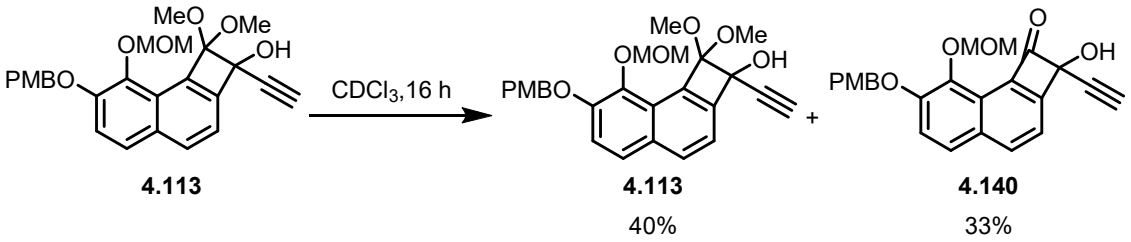


Attempted Moore cyclization from acetal **4.115**. b) Reduction of alkyne **4.115** to alkene **4.137** with $LiAlH_4$. c) Attempted oxidation of benzylic alcohol to the ketone **4.138**. d) Attempted cyclization of alkene **4.137** to monomethylhydroquinone **4.139**.

Serendipitously, compound **4.113** was left overnight in an NMR tube during characterization, whereupon returning the next day, two products were seen by TLC. Purification of the mixture provided **4.113** and **4.140** in 40% and 33% yields, respectively (Equation 4.6). Compound **4.140** was clearly formed upon the hydrolysis of **4.113** due to the trace acid in $CDCl_3$ as evidenced by the fact that there were only two methyl peaks present in the ^{1}H-NMR spectrum. This result further implicated the C8-benzyl alcohol as the acid sensitive moiety of **4.115** and not

the PMB or acetal groups. The question remained: Why was the hydrolysis of **4.126** successful but the hydrolysis of **4.115** unsuccessful?

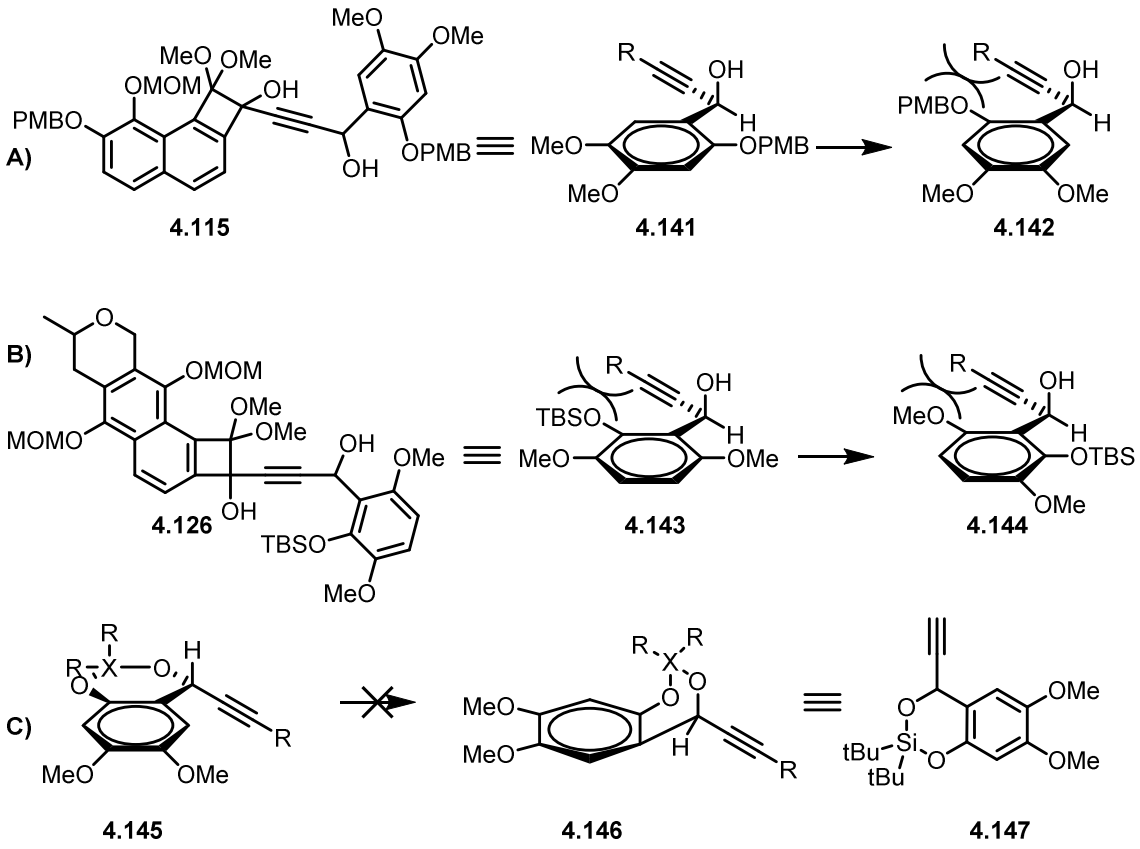
Equation 4.6: Serendipitous hydrolysis of **4.113** to **4.140** in $CDCl_3$



4.5.1.2: Design, synthesis and utilization of an acid stable F-ring fragment

The striking differences between hydrolysis outcomes can be explained by an in-depth analysis of mechanism. In order for a benzyl alcohol moiety to ionize, two things must occur: First, the alcohol must be activated *via* protonation. Second, the plane of the aromatic ring must rotate until perpendicular to the activated alcohol so that the π-system can donate into the O-C σ^*-orbital in order to break the bond (Figure 4.20, **A**). Compound **4.126**, because it contains substitution in both *ortho*-positions, will always suffer $A^{1,3}$ strain if the arene ring is perpendicular to the incipient oxonium ion (Figure 4.20, **B**). Compound **4.115**, however, has one $A^{1,3}$ interaction but it can rotate 180º so there is no steric penalty (Figure 4.20, **A**). In order to disfavor the rotation of the arene ring without the aid of $A^{1,3}$ strain, a new protecting group scheme was devised (Figure 4.20, **C**). Tethering both the propargyl alcohol and the phenol together in **4.145** would force the arene to adopt a high energy boat-like orientation in order for the arene to be perpendicular to the O-C σ^*-orbital (**4.146**). Additionally if the groups labeled R are sufficiently bulky, the boat like conformation would also have significant steric congestion. Looking to previous work by Dr. Mans, Dr. Knueppel and Dr. Nichols, the cyclic silyl ether **4.147** was identified as an ideal candidate for this purpose (see Chapter 3, sections 3.42, 3.45, and 3.54).

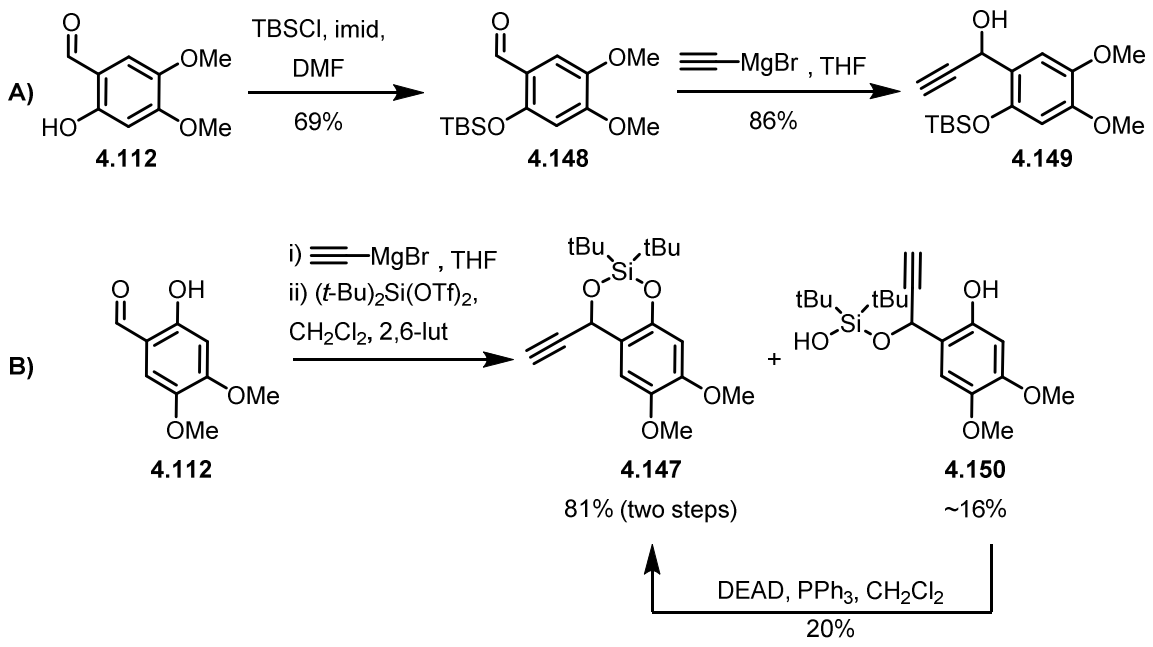
Figure 4.20: Putative hypothesis of the difference between the hydrolysis of **4.115** and **4.126**



a) Hydrolysis of **4.115**, only one $A^{1,3}$ interaction in **4.141**. b) Hydrolysis of **4.126**, two $A^{1,3}$ interaction are present in **4.143** and **4.144**. c) Cyclic derivative **4.145** would have to adopt the boat-like conformation **4.146** to ionize.

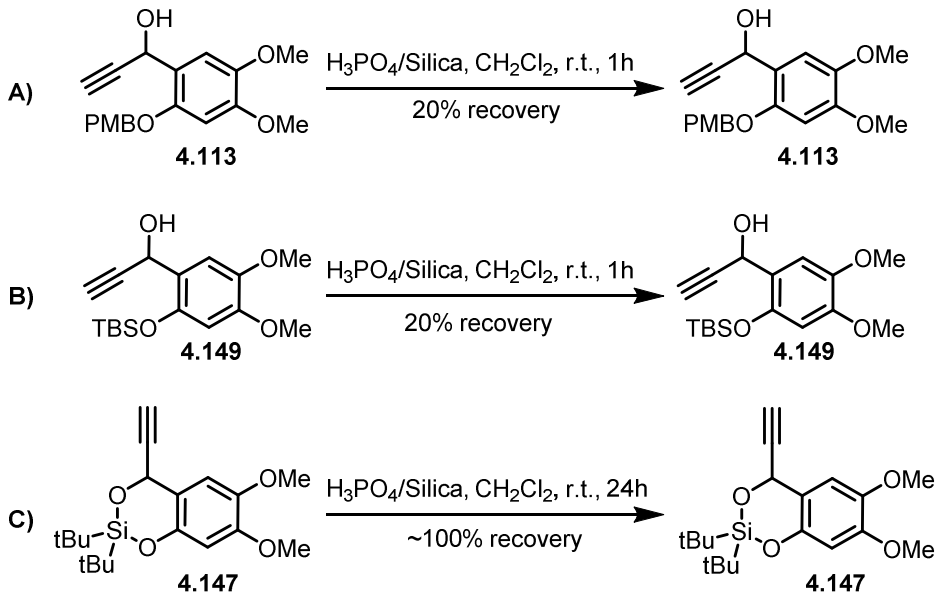
As a direct comparison to the fragment **4.126**, the TBS ether analogue of **4.147** was synthesized in two steps from the aldehyde **4.112** (Figure 4.21, **A**). The synthesis of the cyclic silyl ether **4.147**, however, was hampered by the extreme sensitivity of the intermediate acetylide adduct (not shown), which suffered rapid decomposition with acid, heat, prolonged exposure to silica gel and even the trace acid in $CDCl_3$. Initial attempts form **4.147** from the crude material without purification resulted in large amounts of the hydrolyzed compound **4.150**. Although **4.150** could be transformed into the desired product **4.147** under Mitsunobu conditions,[470,471] the yields were only 20%. Fortunately, purification of the crude acetylide with a quick silica plug and concentration of the eluent under reduce pressure without heat, sufficiently purified the material without decomposition. Thus, the subsequent protection as the cyclic silyl ether furnished **4.147** in 82% yield.

Figure 4.21: Synthesis of F-ring coupling partner **4.147** and **4.149**



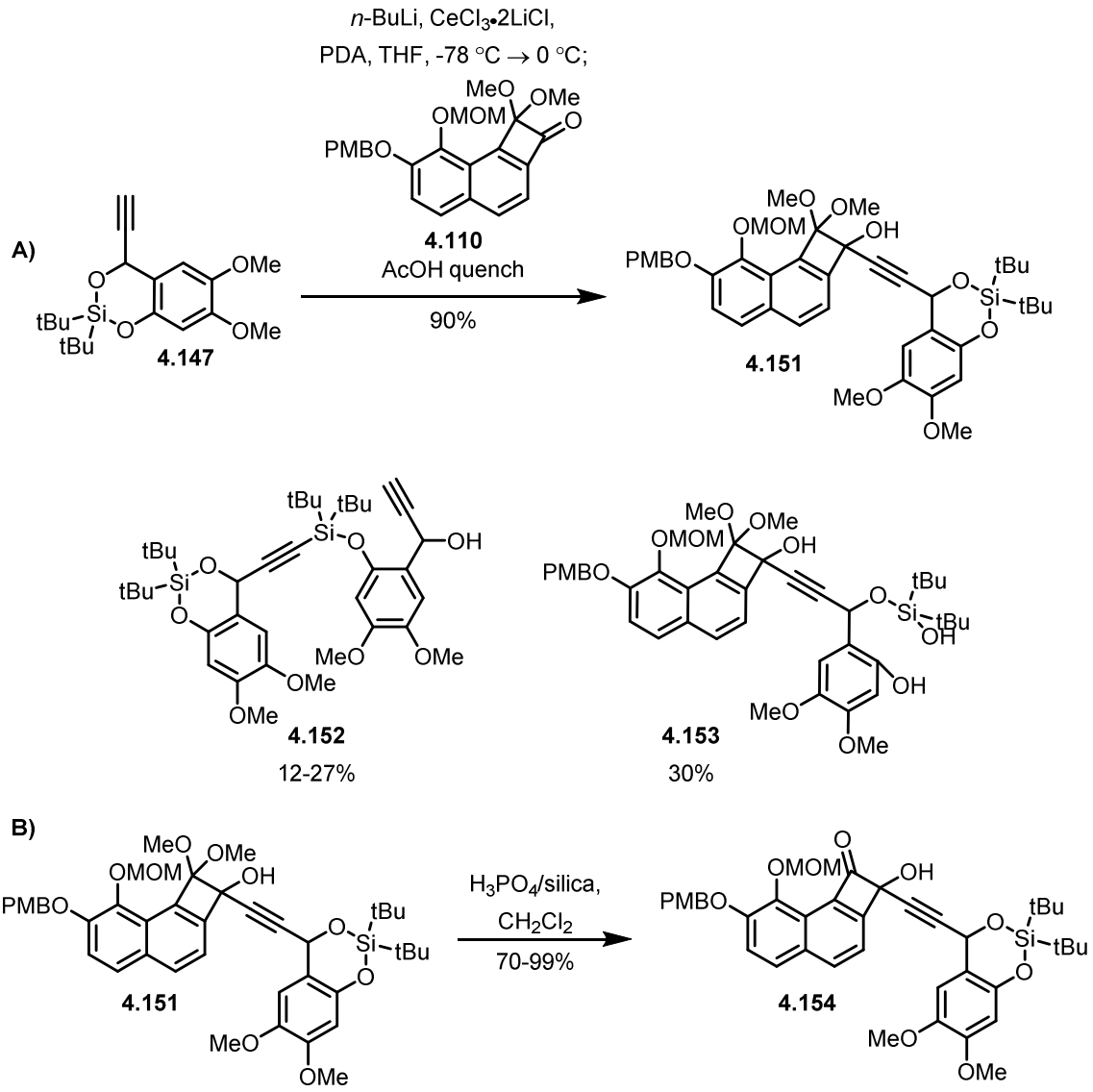
The three F-ring fragments **4.113**, **4.149** and **4.147** were subjected to the hydrolysis conditions developed previously (H_3PO_4/silica) (Figure 4.22). Unsurprisingly, F-ring fragment **4.113** decomposed under the reaction conditions (Figure 4.22, **A**). The TBS ether analogue **4.149** also decomposed when exposed to the H_3PO_4/silica hydrolysis conditions (Figure 4.22, **B**). Subjection of the cyclic silyl enol ether **4.147** to the reaction conditions produced no noticeable decomposition, even after 24 hours, and **4.147** was recovered in quantitative yield (Figure 4.22, **C**). Nearly quantitative recovery was seen.

Figure 4.22: Stability test of F-ring fragments **4.113**, **4.147** and **4.149** to acetal hydrolysis conditions



The addition of *n*-BuLi to a mixture of **4.147**, $CeCl_2$•2LiCl and PDA until a purple endpoint was seen, whereupon another equivalent of *n*-BuLi and **4.110** were added to provide **4.151**, which was contaminated with the ring-opened compound **4.152** and the dimer **4.152** (Figure 4.23). Dr. Alex Nichols encountered similar problems with ring opening during the coupling of cyclic silyl ethers such as **4.147**, but he was able to suppress the hydrolysis products by quenching the reaction with acetic acid instead of water or sodium bicarbonate.[349] Presumably, the cyclic silyl ether moiety is susceptible to cleavage by the hydroxide ion that is formed when the reaction is quenched with water or aqueous sodium bicarbonate solutions. The acetic acid quench allowed for the synthesis of **4.151** in 90% yield on multigram scale which after hydrolysis of the acetal moiety with H_3PO_4/silica provided **4.154** in 70 – 99% yield (Figure 4.23, **A**, **B**).

Figure 4.23: Adaption of alkyne addition toward the coupling of **4.147** and **4.110** and subsequent acetal hydrolysis



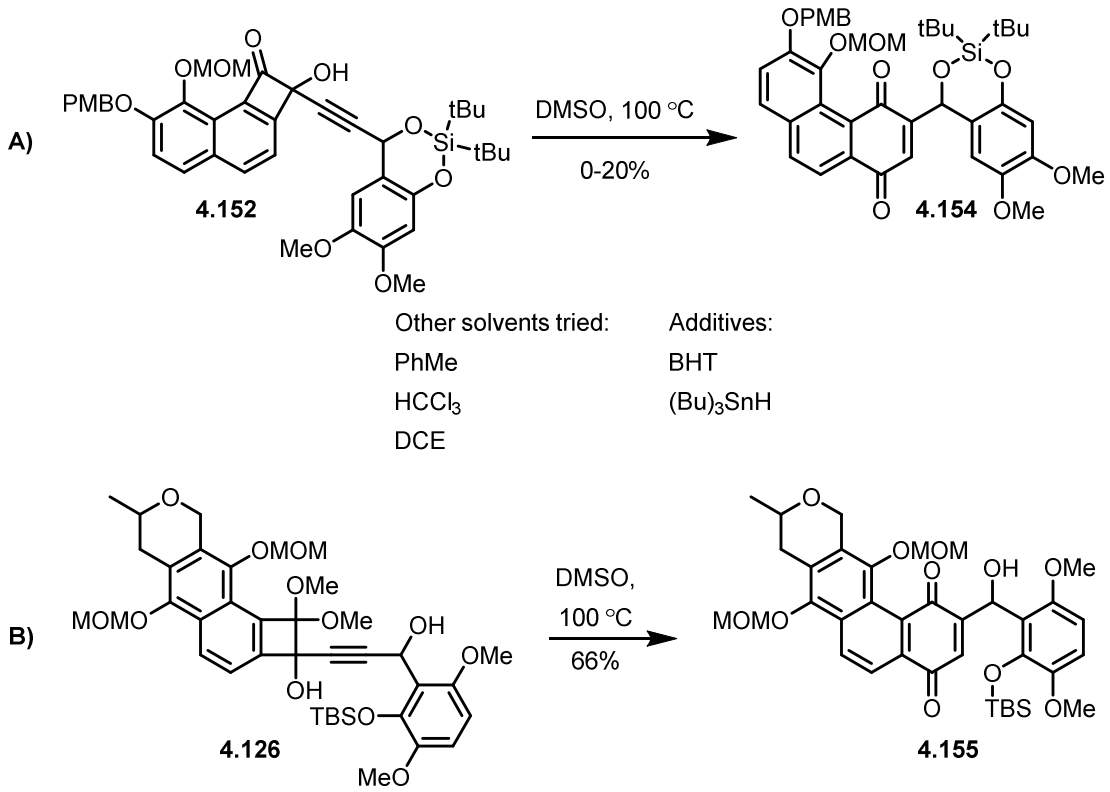
4.5.2: MOORE REARRANGEMENT

4.5.2.1: Optimization of Moore rearrangement

Attempts to initiate the Moore cyclization of **4.154** by heating in DMSO produced only trace amounts of desired product **4.154** (Scheme 4.25, **A**). This observation stands in contrast to the result obtained upon heating **4.126** in DMSO to produce **4.155** in 66% yield (Scheme 4.25, **B**). Changing the concentration, temperature or using other solvents also did not improve yields.

The Moore rearrangement has been shown to go through a radical mechanism, and radical side-reactions may be responsible for the low yield. Unfortunately, use of BHT or Bu_3SnH as radical inhibitors had little effect on the reaction outcome.

Figure 4.25: Initial screen for Moore rearrangement

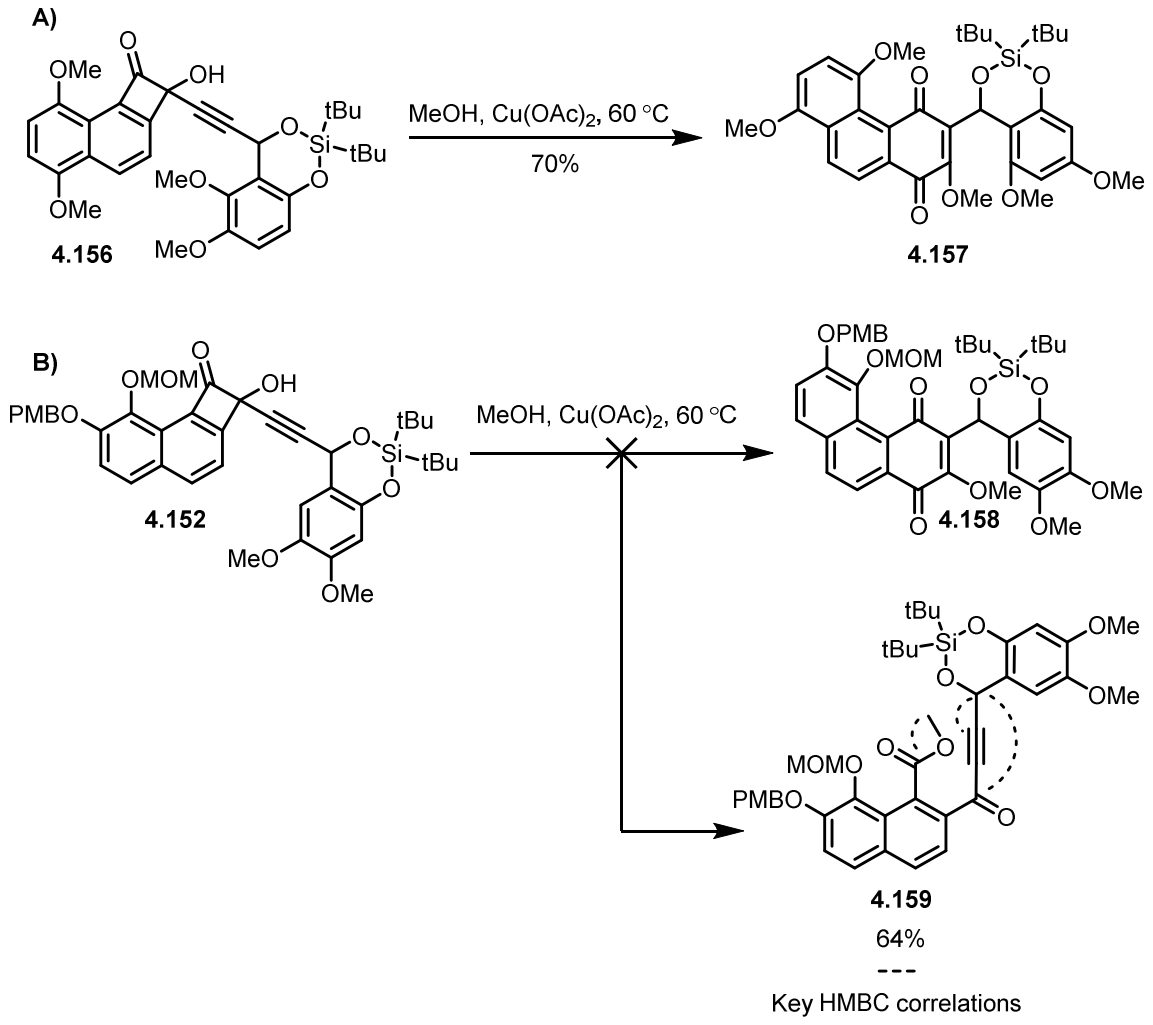


a) Attempted Moore rearrangement of **4.154**. b) Moore rearrangement of **4.126** in the synthesis of IB-00208 aglycone.

The initial failure of the Moore rearrangement led to the re-investigation of the $Cu(OAc)_2$ mediated transformation of **4.156** to **4.157** discovered by Dr. Mans (Figure 4.25, **A** see also Chapter 3, Figure 3.11). An intermediate such as **4.157** could potentially be elaborated to the core of citreamicin *via* displacement of the methoxy group by the neighboring phenoxide. Accordingly, subjection of **4.154** to Dr. Mans's conditions produced a single product in 64% yield. After characterization of the compound by 1D- and 2D-NMR spectroscopy, the product of the reaction was determined to be **4.159**, not the desired **4.158** (key HMBC correlations shown). Evidence for the structure of **4.159** came from the fact that the methyl group was only correlated

to one carbonyl carbon atom at 170 ppm, and there were two carbon peaks (the alkyne carbon atoms) that were correlated to the benzylic proton.

Figure 4.7: Example of an oxidative Moore rearrangement from Dr. Mans and attempted oxidative Moore rearrangement of **4.154**

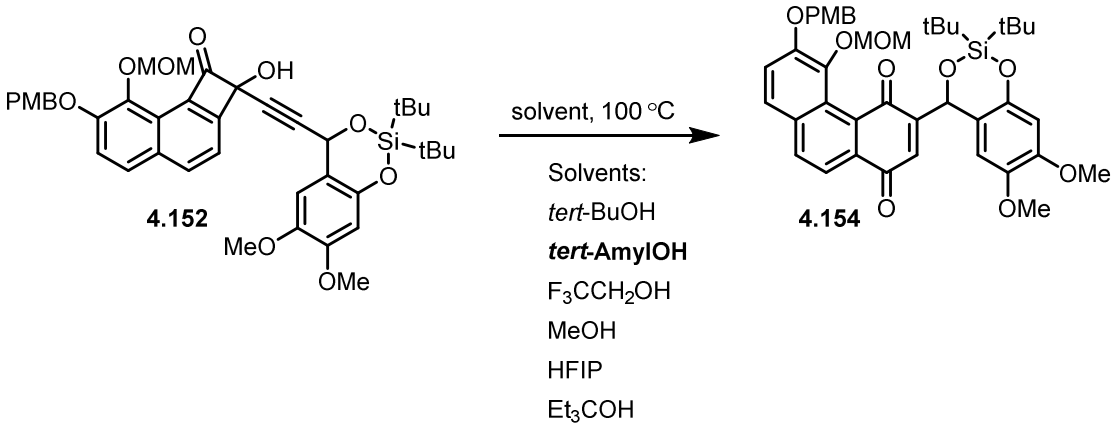


a) Example of an oxidative Moore rearrangement from Dr. Mans (see Chapter 3, Scheme 3.11). b) Attempted oxidative Moore rearrangement of **4.154** resulting in **4.159**.

Previous work in the Martin group showed that the yield of Moore cyclizations are solvent dependent (see Chapter 3, Scheme 3.42 and 3.47). In particular, Dr. Mans demonstrated that performing the Moore cyclization in MeOH gave exclusive formation of the quinone. Considering that the byproduct **4.159** arises from the interception of the ketene intermediate with

methanol, a solvent screen was done with protic solvents of decreasing nucleophilicity. Most of the solvents produced complex mixtures of products, but *tert*-amyl alcohol seemed to produce two major products cleanly (Equation 4.7).

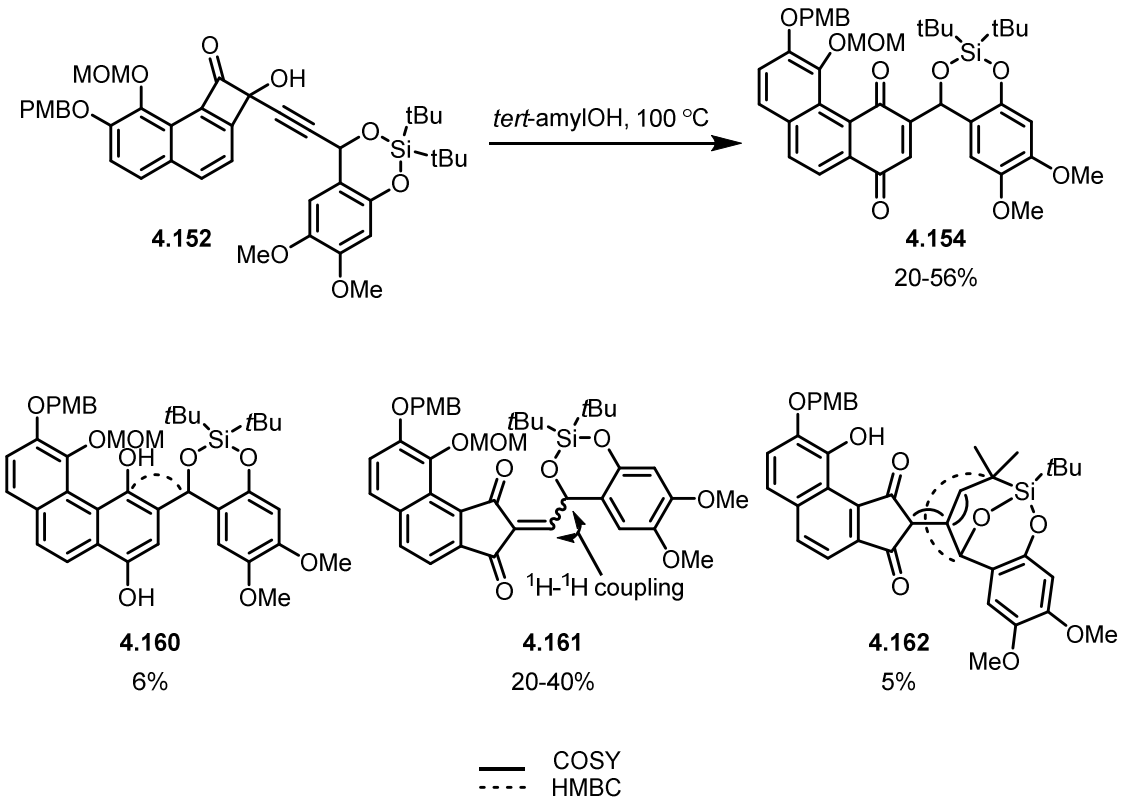
Equation 4.7: Solvent screen for the Moore rearrangement of **4.152**



A brief optimization of the reaction parameters found that dry *tert*-amylOH (482 ppm H_2O) provided cleaner reactions than wet *tert*-amylOH (5373 ppm H_2O). Heating **4.154** in *tert*-amylOH provided the desired quinone **4.154** in 20 – 56% yields, along with the 5-exo-cyclized product **4.161** as a mixture (1.5:1) of olefin isomers in nearly equal amounts (20 – 40%) (Equation 4.8). Attempts to alter the ratio of **4.154** to **4.161** by varying temperature or by using additives, such as radical inhibitors, had little effect on the ratio of **4.154** to **4.161**. Further analysis of the reaction mixture revealed that besides the 5-exo-cyclized product **4.161**, the hydroquinone **4.160** and, surprisingly, the C-H insertion product **4.162** as mixture (1.1:1) of diastereomers. Evidence for the 5-exo-cyclized product **4.161** was the coupling between the benzylic proton (7.05/7.01 ppm, d, J = 9.5/9.4 Hz) and the olefin proton (7.19/7.14 ppm, d, J = 9.5/9.4 Hz), while the evidence for the hydroquinone **4.161** was the lack of carbonyl carbon atoms, the presence two extra Csp_2-O carbon atoms at 140 and 150 ppm and the HMBC correlation between the benzylic proton and the carbon atom at 150 ppm. The structure of **4.162** was determined after 1D- and 2D-NMR characterization (key HMBC correlations shown). Further evidence for **4.162** can be seen in that the carbonyl carbon atoms are at 206 ppm and 198

ppm, which is downfield compared to the carbonyl carbon atoms of **4.161**, which appear at 190/189 ppm and 188/187 ppm.

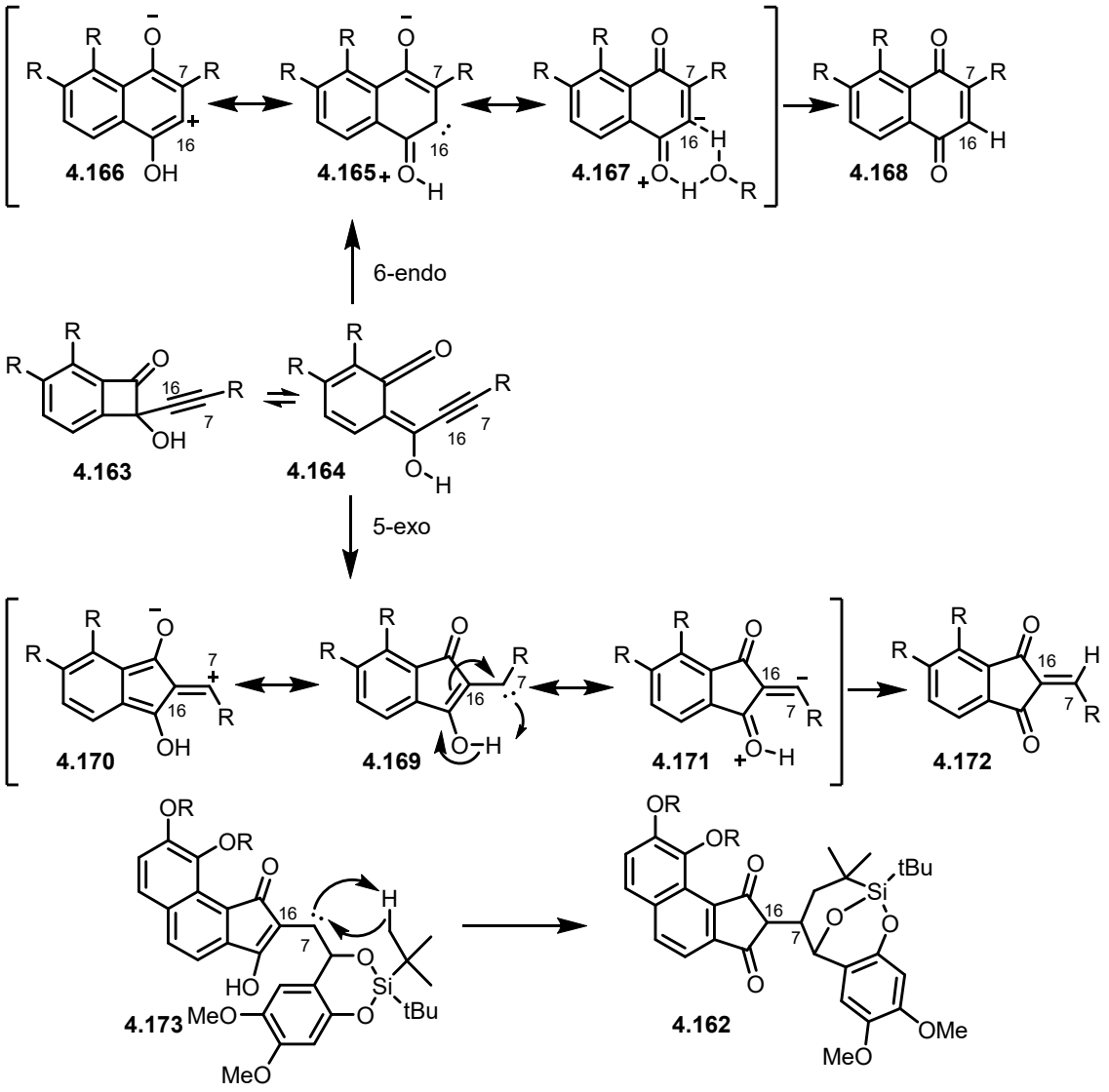
Equation 4.8: Successful Moore rearrangement in *tert*-amylOH



The isolation of **4.162** suggests that the Moore rearrangement may go through an ionic mechanism. For example, heating the benzocyclobutanone **4.163** produces the ketene intermediate **4.164**, which can undergo an ionic 6-endo cyclization to produce **4.165** that has carbene-like character at C16 (Scheme 4.22). Protonation at the C16 carbon atom of **4.165** then gives **4.168**. Alternatively, the 5-exo cyclization of **4.164** would produce **4.169**, which also has carbene-like character at C7. Protonation of **4.169** would provide the 5-exo product **4.172**. The carbene intermediate **4.169** may be a major resonance contributor because the C-H insertion onto the *tert*-butyl group of the cyclic silyl ether occurs to form **4.162**. In 2002, Engles analyzed the Moore rearrangement computationally and found that the carbene **4.169** may be a major

resonance contributor in the 5-exo cyclization.[472] The isolation of **4.162** represents direct evidence that the Moore rearrangement may proceed though a carbene-like mechanism.

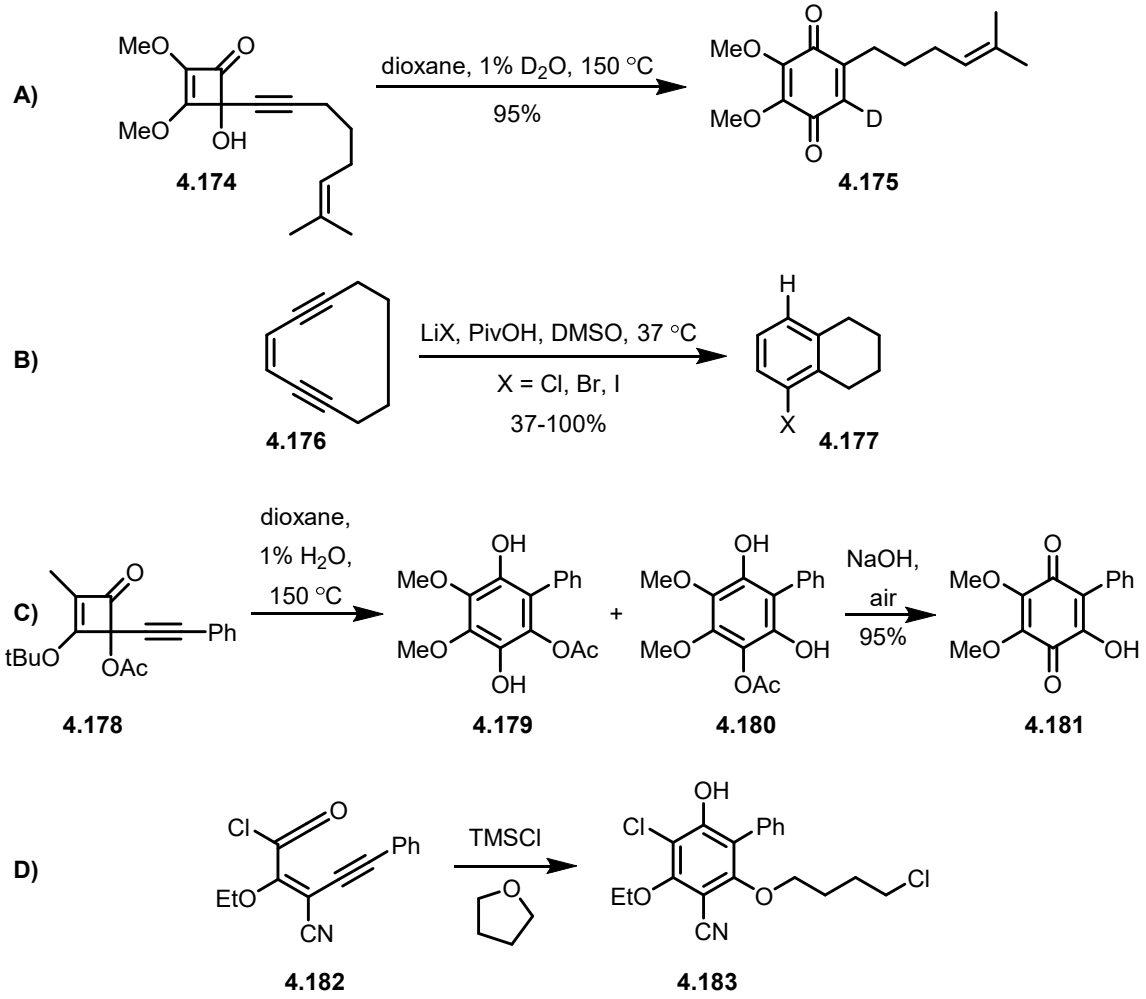
Scheme 4.22: Putative Mechanism for the formation of **4.154**, **4.161** and **4.162**



The switch from radical to ionic mechanisms in cycloaromatization reactions has been observed previously.[473-481] For example in 2015, Harrowven found that heating squarate **4.174** in dioxane with trace amounts of D_2O produced the deuterated compound **4.175** (Scheme 4.26, **A**).[473] O'Connor found that exposure of the ene-diyne **4.176** to lithium-halides and pivalic acid in polar aprotic solvent, gave **4.177** *via* a formal HX insertion across the putative ionic *p*-

benzyne intermediate (Scheme 4.26, **B**).[477] Evidence for the electrophilic character of the same carbon atom can be seen in another example from Harrowven, who found that heating the squarate **4.178** produced a mixture of **4.179** and **4.180**, which upon hydrolysis and oxidation produced the quinone **4.181** (Scheme 4.26, **C**).[473] Products **4.179** and **4.180** can come from electrophilic attack of the acetate ion onto a carbene intermediate similar to **4.169**. Finally, Moore observed the incorporation of THF during the rearrangement of the ketene **4.182**, indicating that the Moore rearrangement may have alternate mechanisms available (Scheme 4.26, **D**).[478]

Figure 4.26: Examples of ionic mechanism in Moore rearrangement

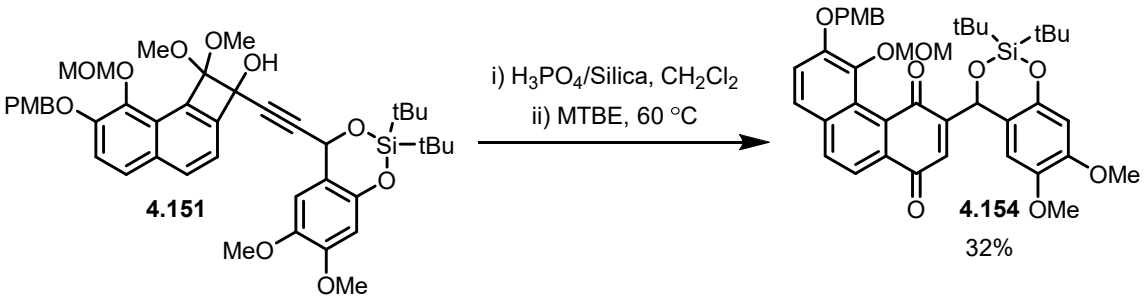


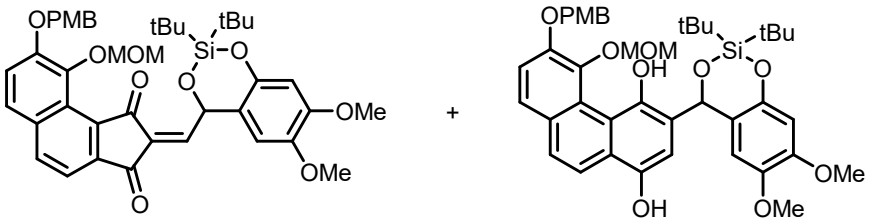
a) Deuterium incorporation during Moore cyclization suggestive of ionic mechanism from Harrowven, 2015.[473] b) Incorporation of "HX" during Bergmann cyclization suggests ionic mechanism example from O'Connor, 2007.[477] c) Intramolecular attack by acetate on ionic intermediate example from Harrowven, 2015.[473] d) Nucleophilic attack of THF on ionic intermediate in Moore cyclization example from Moore, 1986.[478]

Harrowven reported that heating squarates such as **4.174** in dioxanes with 1% H_2O, gave a mixture (1:1) of the 6-endo and 5-exo products.[473] These results seem to be consistent with the results of the Moore rearrangement of **4.154** in *tert*-amylOH. Owing to the radical/zwitterionic dichotomy of the Moore rearrangement, it may be possible to favor the desired **4.154** over **4.161** by changing the solvent. Previous results in the Martin group have also shown a strong dependence of the Moore rearrangement on the solvent (see Chapter 3, Scheme 3.42, 3.47). A comprehensive solvent and temperature screen was done to see if any other solvent would furnish **4.154** cleanly, but initial attempts to initiate the Moore rearrangement of **4.154** in a

variety of solvents gave complex mixtures. Degassing the solvent thoroughly, however, was key to obtaining the desired product **4.154** in non-protic solvents. The solvent screen in de-gassed solvent found that ethereal solvents and methyl-*tert*-butylether (MTBE) in particular provided the product **4.154** cleanly (Figure 4.27). Lower temperatures also seemed to produce less of the hydroquinone byproduct **4.160**, and the reaction was found to proceed at temperatures as low as 60 ºC. Scaling up the Moore rearrangement in MTBE did favor the desired product **4.154** over the 5-exo product **4.161**, but only in a 3:2 ratio in a combined yield of 53%.

Figure 4.27: Moore rearrangement using MTBE as a solvent





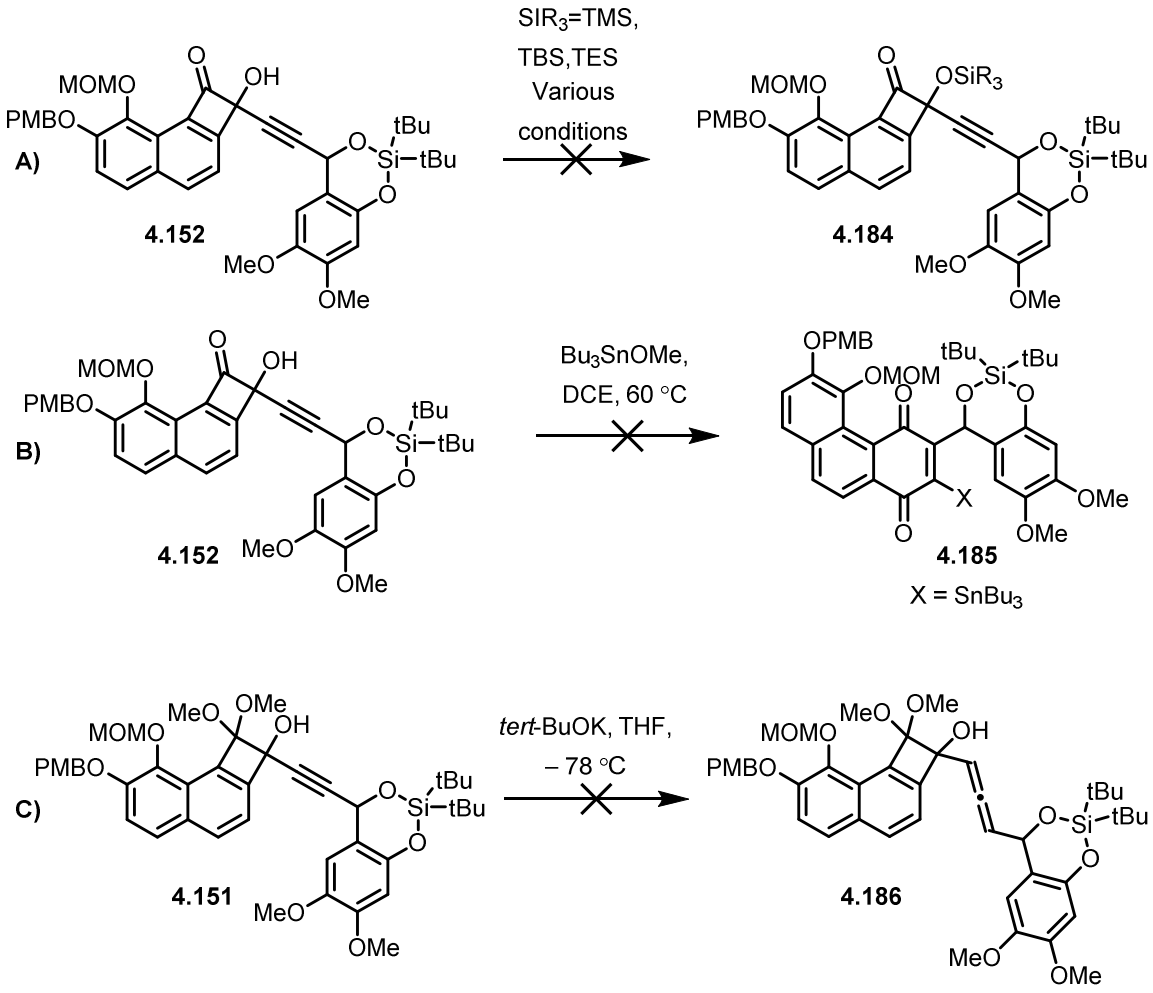
Temp	solvents	
100 °C	$BrCCl_3$	THF
80 °C	1,4-CHD	**MTBE**
60 °C	PhMe	Dibutyl ether
40 °C	DMSO	Dioxanes
rt	ACN	CPME
	CPME	
	DCE	

4.5.2.2: Attempts to improve 6-endo/5-exo product ratios

The low selectivity between the 6-endo and 5-exo cyclization modes in the Moore rearrangement is perplexing. Dr. Mans was able to achieve a 10:1 selectivity between the 6-endo

and 5-exo products utilizing very similar starting materials (see Chapter 3, Scheme 3.42). Likewise, none of the 5-exo product was reported during the Moore cyclization of **4.126** or in any of the substrates used by Dr. Nichols (see Chapter 3, Scheme 3.54). The substitution of the alcohol can modulate the selectivity between the 6-endo and 5-exo products (see Chapter 3, Scheme 3.39).[338] Attempts to substitute the alcohol moiety of **4.152** with TBS, TES or a TMS group only led to complex mixtures (Figure 4.28, **A**). Attempts to use Libeskind's Bu_3SnOMe modified Moore rearrangement, which exchanges the proton of the alcohol with a tributyltin moiety in situ, led to unidentifiable products (Figure 4.28, **B**).[485,486] Attempts to isomerize the propargyl group to the allene, to initiate a 6π-electrocyclization only returned starting material (Figure 4.28, **C**).[482-484]

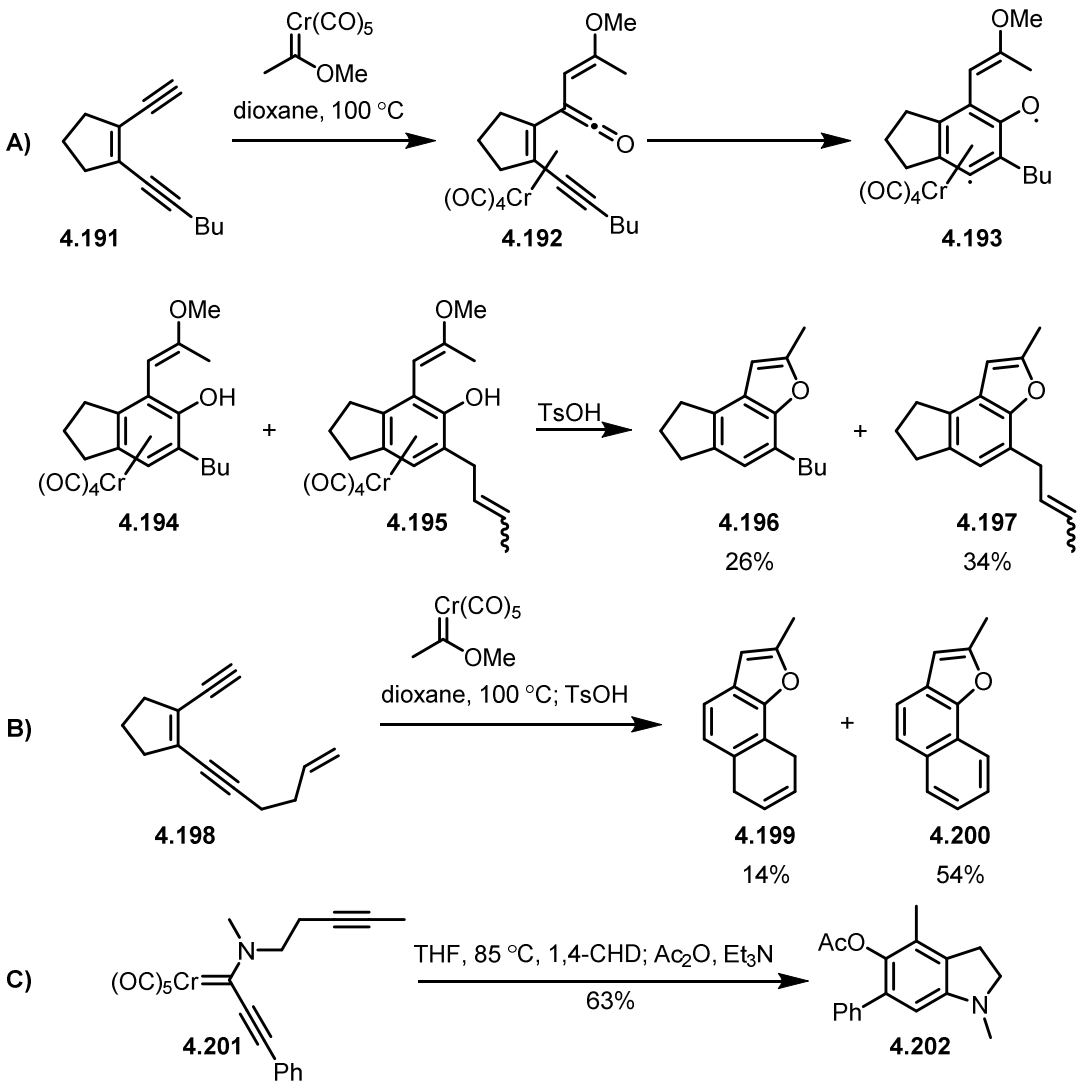
Figure 4.28: Attempts to alter 6-endo to 5-exo product ratio



a) Attempted silyl protection of **4.154**. b) Attempted isomerization to the allene **4.185** with *tert*-BuOK.[483] c) Attempted use of Libeskind's Bu_3SnOMe modified Moore rearrangement, to form **4.186**.[485,486]

Another possible route to affect the ratio of the 6-endo and 5-exo products could be the use of transition metal catalysts, which are known to affect outcomes of pericyclic reactions.[487-523] In fact, several examples of chromium-mediated Moore rearrangements are known (Figure 4.29).[492-500] The reaction of chromium Fischer carbenes with alkynes such as **4.187** leads to the η-6 chromium ketene complex **4.188**, which cyclizes in an analogous manner to the Moore rearrangement (Figure 4.29, **A**).[492] The coordination of a metal to an intermediate such as **4.188** could theoretically "template" the reaction to favor the 6-endo or 5-exo products.[488-490]

Figure 4.29: Examples of Chromium-mediated Moore rearrangement

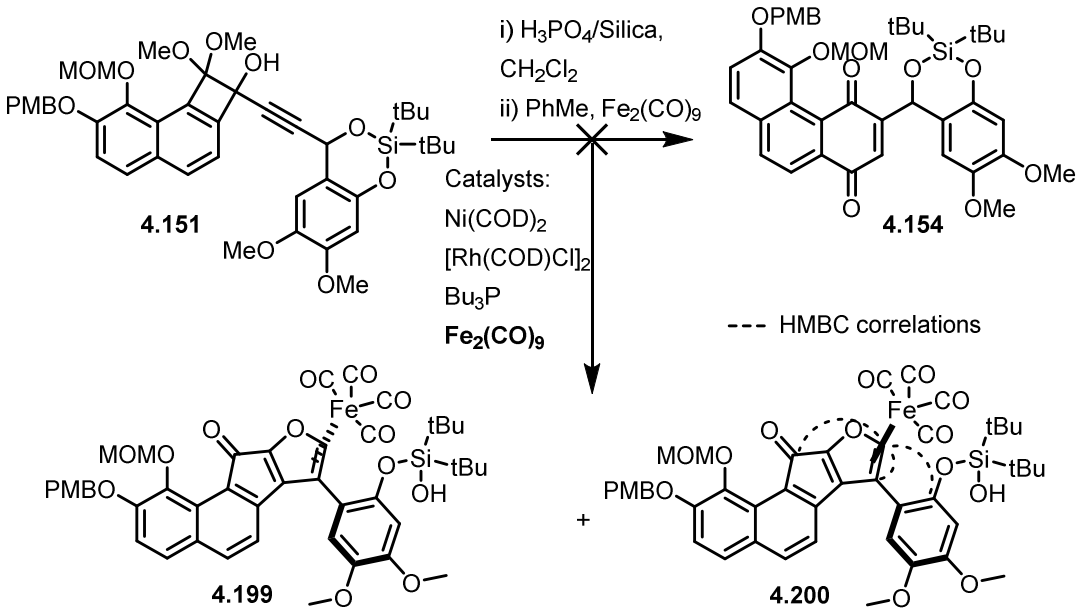


A) Example in 2008 by Herndon and Wang of a Moore-like rearrangement initiated by a chromium Fischer carbene which results proximal alkyl C-H abstraction.[492] B) Example in 2008 by Herndon and Wang of a Moore-like rearrangement initiated by a chromium Fischer carbene which results olefin cyclization.[469] C) Wulff's Moore-like rearrangement of Fischer carbine to form indoline in 1996.[493]

A review of the literature for catalysts that can catalyze the ring opening of cyclobutanones revealed that Fe,[501-508] Ni,[509-513] Co,[514,515] Rh,[517-519] Ru[516] and even phosphines[520-523] have been used. Accordingly, $Fe_2(CO)_9$, $Ni(COD)_2$, $[Rh(COD)Cl]_2$ and tributylphosphine were chosen for the initial screen. Previously, the Moore rearrangement of **4.154** was shown to occur at only 60 ºC, so the catalyst screen was done at room temperature. All catalysts produced complex mixtures except $Fe_2(CO)_9$, which furnished two distinct products at room temperature.

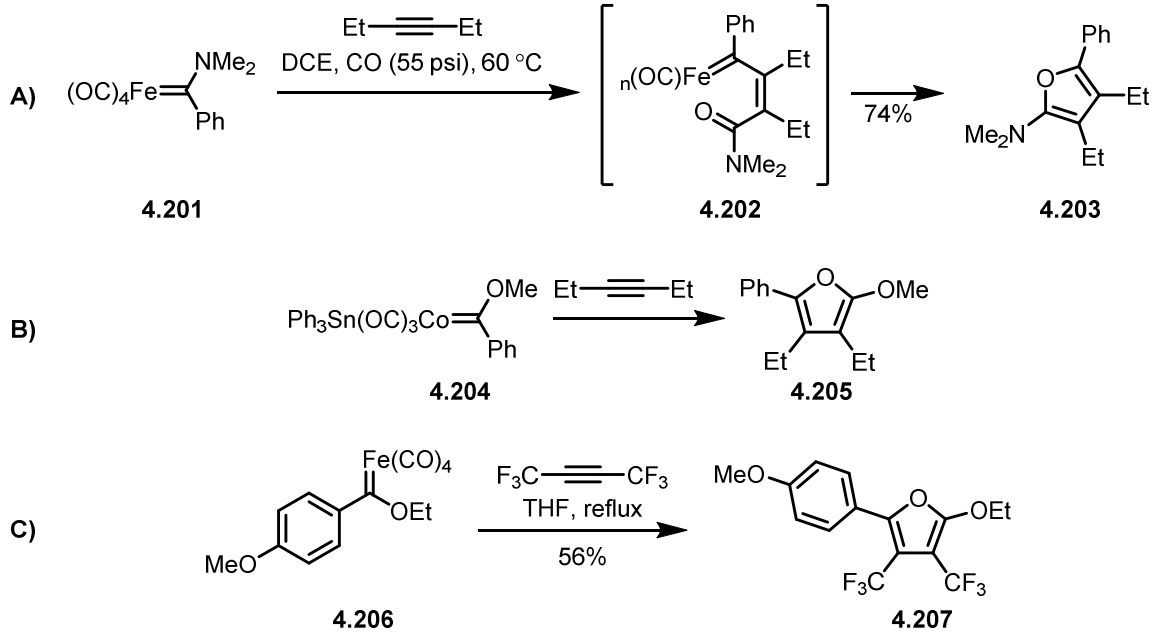
Scaling up this reaction and isolation of the two products revealed that neither the desired 6-endo product **4.154**, nor the 5-exo product was formed. After intensive NMR studies, the tentative assignments of the two compounds are **4.199** and **4.200** (key HMBC correlations shown). Evidence for the structure of **4.200** is the presence of two new Csp_2-O carbons atoms at 159 ppm and 139 ppm, an *m/z* of 917 (M + Na) indicating that the product has added the mass of ($Fe(CO)_4$), two carbonyl carbons atoms in ^{13}C-NMR spectrum at 171 ppm and 208 ppm and three carbonyl IR stretches at 2061 cm^{-1}, 2005 cm^{-1} and 1784 cm^{-1}.

Figure 4.30: Attempted metal mediated Moore rearrangement



Iron, cobalt and electrophilic Fischer carbene complexes are to produce furans in the presence of alkynes (Figure 4.31, **A**, **B**, **C**).[524-526] Coordination of the alkyne to the Fischer carbene complex **4.201** is thought to form the electrophilic carbene intermediate **4.202** (Figure 4.31 **A**). Attack of the carbene by the carbonyl produces an oxonium ion, which aromatizes to form the furan **4.203**. The formation of **4.199** and **4.200** may proceed though a similar intermediate to **4.202**, although the exact mechanism the formation of these byproducts is unclear.

Figure 4.31: Examples of furan formation with Fischer carbenes



a) Example of furan formation with Fe^0 Fischer carbene **4.201** from Semmelhack (1986).[525] b) Example of furan formation with Co^1 Fischer carbene **4.205** from O'Connor (1993).[515] c) Example of furan formation with Fe^0 Fischer carbene **4.206** from Schnatter (2009).[524]

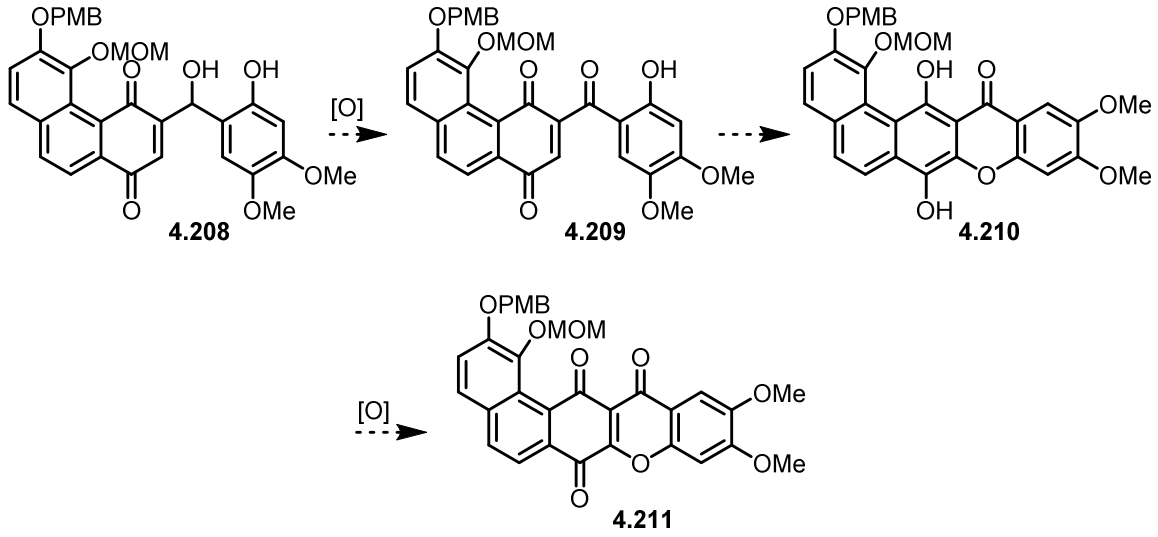
4.5.2.3: Summary

The Moore rearrangement is a complex reaction. It seems that by using *tert*-amylOH as the solvent, the reaction mechanism may switch from radical to ionic thus, forming **4.154** and **4.161** in equal amounts. The intermediates of the Moore rearrangement may also have carbene-like character, as evidenced by the formation of the byproduct **4.162**. Using MTBE as the solvent improved the ratio between **4.154** and **4.161** from 1:1 to 1.5:1 and eliminated the formation of **4.162**. At this point, it is not clear why such a significant amount of the unwanted 5-exo product **4.161** was isolated in the reaction. Dr. Mans only observed the 5-exo product in ~10% yield and others members in the Martin group did not report any of the 5-exo product (see Chapter 3, Schemes 3.42, and 3.54). Both **4.158** and **4.154** (Figure 4.25) have similar substitution on the arene ring and differ only in the position of the alkoxy groups and the protecting groups. Although the Moore rearrangement of **4.154** provided mixtures of **4.161** and the desired **4.154**, the procedure in MTBE was scaleable and several grams of **4.154** were obtained.

4.6: Formation of the xanthone core

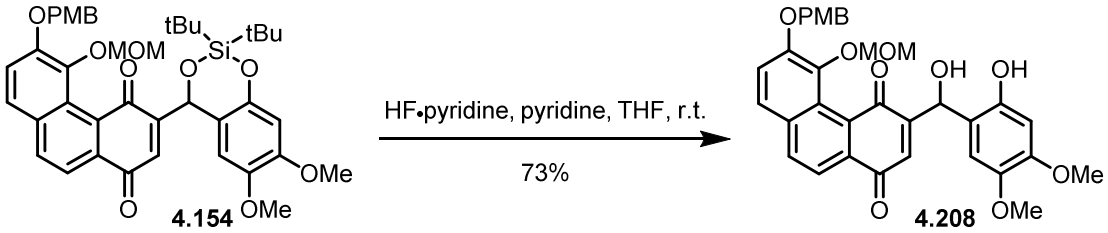
With ample quantities of **4.154** in hand, we explored the cyclization to the xanthone core as outlined in Scheme 4.23. Oxidation of the benzylic alcohol in **4.208** to **4.209** should enable cyclization to the hydroquinone **4.210** and, after further oxidation, provide the xanthone core **4.211**. Unfortunately, both Dr. Nichols and Dr. Knueppel attempted similar cyclizations with numerous oxidants without success (See Chapter 3, Scheme 3.45 and Equation 3.2).

Scheme 4.23: Planned cyclization of **4.208** to xanthone **4.211**



Removal of the silyl ether from the quinone **4.154** using HF•Pyridine buffered with additional pyridine provided the benzyl alcohol **4.208**, which was thermally and acid labile.

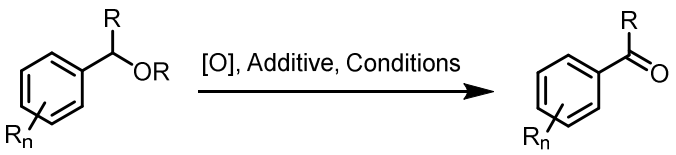
Equation 4.9: Deprotection of the cyclic silyl ether



Two different types of oxidations are needed to effect the transformation of **4.208** to **4.211**: An oxidation of the benzylic alcohol in **4.208** to the ketone **4.209** and an oxidation of the

hydroquinone **4.210** to the quinone **4.211** (see Scheme 4.23). A survey of the literature for methods to oxidize benzyl alcohols and hydroquinones to quinones revealed several possibilities (Table 4.12).[526-546] NO_x[530] ($NaNO_2$,[527,528,538] *tert*-BuONO[535,536,539]), Co,[526] Cu,[531,533,546] Fe[531] and V[532] salts are known to oxidize hydroquinones to quinones, whereas the nitroxyl oxidants (TEMPO, *N*-hydroxyphthalimide (NHPI), 5-F-AZADO, AcNH-TEMPO) can oxidize the alcohols to ketones. Of the reagents listed in Table 4.12, only DDQ and MnO_2 are precedented to perform both types of oxidations without other co-oxidants.[545,560]

Table 4.12: Oxidation of benzylic alcohols



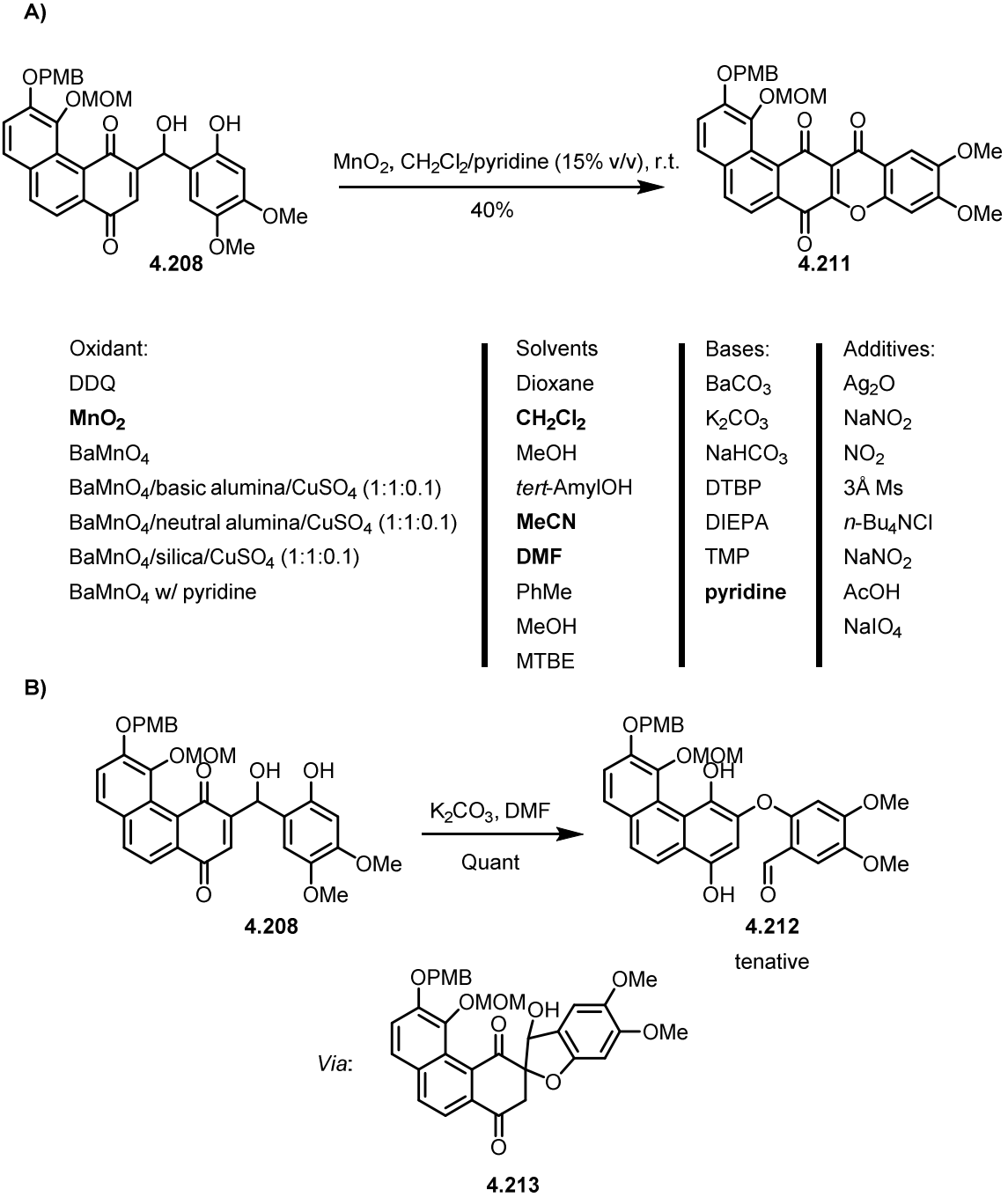
Ref	Oxidant	Additive	Conditions	Yield
Karimi[526]	Co(II)	NHPI[a]	O_2, MeCN, rt	82 – 95%
Iwabuchi[527,528]	5-F-AZADO[b]	$NaNO_2$	AcOH, O_2, rt	71 – 99%
Toofan[529]	BPCP[c]	N/A	PhH, reflux	60 – 95%
Ishii[530]	NO_x	NHPI[a]	MeCN, 60 ºC	10 – 84%
Sparfel[531]	Fe(II), Cu(I)	N/A	MeOH, O_2	34 – 95%
Bora[532]	*tert*-BuOOH	$V(O)SO_4$	MeCN/H_2O, rt	70 – 96%
Ji[533]	$Cu(OAc)_2$	TEMPO[d]	MeCN/H_2O, rt	82 – 96%
Sekar[534]	DABCO[e]-CuCl	TEMPO[d]	PhMe, O_2, 100 ºC	20 – 98%
Hu[535]	*tert*-BuONO	TEMPO[d]	DCE, O_2, 80 ºC	93 – 97%
Hu/Mo[536]	*tert*-BuONO	DDQ[f]	DCE, O_2, 80 ºC	95 – 99%
Stahl[537]	AcNH-TEMPO[d]	HNO_3/HCl	MeCN/H_2O, O_2, 45 ºC	43 – 98%
Gao[538]	DDQ[f]	$NaNO_2$	DCM/AcOH, O_2, rt	17 – 97%
Jahn[539]	TEMPO[d]	*tert*-BuONO[g]	CH_2Cl_2, reflux	60 – 99%
Golchoubian[540]	H_2O_2	Mn(II)	Neat, rt	90 – 97%
Lou[451]	MnO_2/Alumina	N/A	CH_2Cl_2, reflux	87 – 96%
Gritter[542]	MnO_2	N/A	PhH, rt	100%
Bunce[543]	MnO_2	N/A		74 – 97%
Trudell[544]	H_5IO_6	CrO_3	MeCN/CH_2Cl_2, - 78 ºC	52 – 93%
Adler[545]	DDQ[f]	N/A	Dioxane, rt	14 – 93%
Maumy[546]	Me_3NO	$CuCl_2$	MeCN, 60 ºC	40 – 100%

a) *N*-Hydroxyphthalimide (NHPI). b) 2-Azaadamantane-*N*-oxyl (AZADO). c) 2,2'-Bipyridylchromium (BPCP). d) (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO). e) 1,4-Diazabicyclo[2.2.2]octane (DABCO). f) 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). g) BF_3•OEt_2 also added.

DDQ, MnO_2 and $BaMnO_4$ were screened with a variety of bases and solvents to transform **4.208** to **4.211**. $BaMnO_4$, even on a variety of solid supports, proved too strong an oxidant and afforded intractable mixtures. Oxidation of **4.208** with DDQ was fastest in non-polar

solvents and slowest in polar aprotic solvents; however, even after identifying CH_2Cl_2 as the optimum solvent and K_2CO_3 as the optimum base, **4.211** was isolated in only 8 – 18% yield. Co-oxidants such as AcOH/$NaNO_2$ (to produce NO_x) or Ag_2O had a detrimental effect on the reaction. Oxidations of **4.208** with MnO_2 were much cleaner than those with DDQ, so MnO_2 was chosen for further study. A key observation was that the yields of **4.211** were lower when the starting material was incubated with K_2CO_3 before the addition of MnO_2. Stirring **4.208** in DMF with K_2CO_3 resulted in the quantitative conversion to new compound with an identical mass to the starting material by LCMS analysis. Based on similar byproducts isolated by Dr. Nichols, the identity of this compound is proposed to be **4.212** (Figure 4.31, **B** See also Chapter 3, Equation 3.2). Surprisingly, the transformation of **4.208** to **4.211** with MnO_2 proceeded without any base present. Re-screening the solvents revealed that polar aprotic solvents provided **4.211** in the highest yield, with DMF and MeCN providing **4.211** in 40% yield. Curiously, the presence of molecular sieves in the reaction caused the yield of **4.211** to drop significantly. The molecular sieves could sequester water, which is known to affect the oxidizing potential of MnO_2 by occupying active sites on the manganese surface.[554] This observation suggested that perhaps the MnO_2 was too active and that by "poisioning" the MnO_2, the yields might improve. Accordingly, oxidation of **4.208** with MnO_2 in CH_2Cl_2 poisoned with pyridine gave comparable yields (40%) of **4.211** to those obtained in DMF and MeCN (Figure 4.31, **A**).

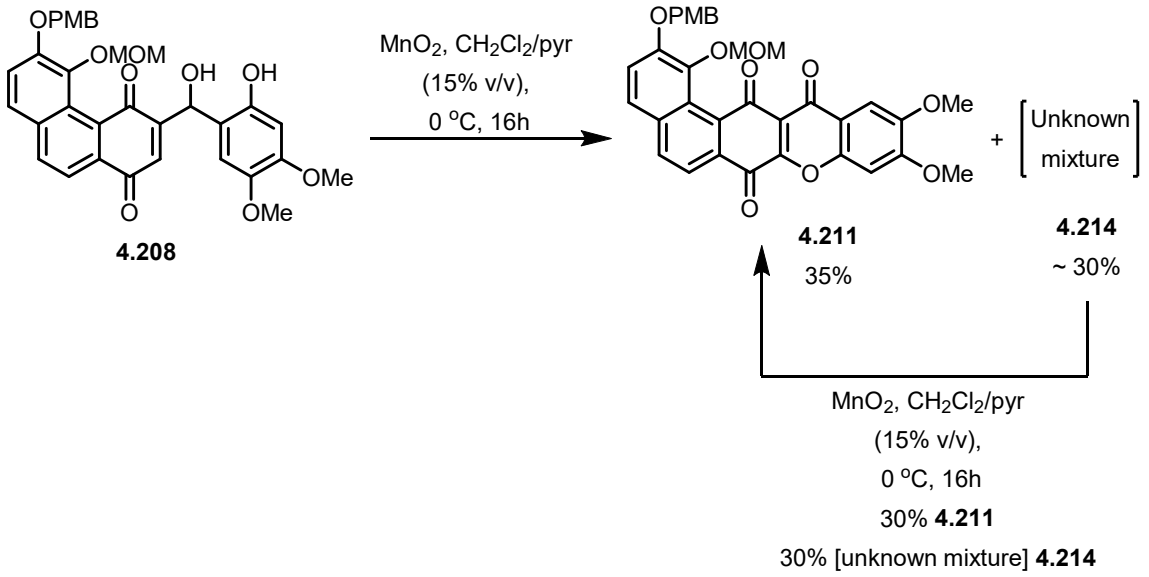
Figure 4.31: Cyclization of **4.208** to **4.211**



Subjecting the product **4.211** to the reaction conditions (MnO_2 in CH_2Cl_2/pyridine) resulted in 80% recovery of the product, suggesting that the product is stable under the reaction conditions and that the yield loss is due to side-reactions occurring during the oxidation of the intermediates such as **4.208** or **4.210** (Figure 4.32, **A**). Analysis of the crude reaction mixtures by

LCMS shows peaks with *m/z* of 1189, 1303 and 1827 amu, which are well above the mass of **4.211** and may indicate that oxidative dimerization is occurring. The mechanism of MnO_2 oxidation of benzylic alcohols is thought to involve benzylic radicals, which may be exceptionally stable and facilitate the desorption and oxidative polymerization. Therefore we reasoned that cooling the reaction might favor the subsequent oxidation without diffusion into the solvent. Accordingly, oxidizing **4.208** with MnO_2 in CH_2Cl_2/pyridine at 0 °C provided the desired product **4.211** in 35% yield and the isolation of several other products by TLC (**4.214**) (Figure 4.32, **B**). Analysis of these products by LCMS indicated that they might be partially oxidized intermediates, presumably a mixture of **4.209** and **4.210**. Resubjection to the reaction conditions provided **4.211** in ~30% yield with another 30% of the recovered intermediates. Unfortunately, prolonged stirring at 0 °C for 48 h did not improve conversion. The overall yield after "two cycles" of the reaction, though not ideal, is 50%, which is sufficient to explore the chemistry of the later steps.

Figure 4.32: Stability test of **4.211** to reaction conditions and MnO_2 oxidation at 0 °C



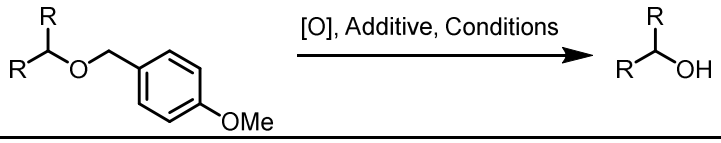
Currently, the conversion of **4.208** to **4.211** is not optimized. The tendency of the starting material **4.208** to rearrange under basic and acidic conditions continues to make this transformation difficult. Additionally, the phenol moiety is electron rich and presumably undergoes several unwanted side reactions such as oxidative dimerization and/or radical polymerization which results in the low yields. Similar difficulties with this transformation were encountered by other members in the Martin group (see Chapter 3, Schemes 3.45 and Equation 3.2). The discovery that "poisoning" MnO_2 with polar aprotic solvents such as DMF or pyridine and that the product is stable to these conditions suggests that this reaction can be optimized. In order optimize this reaction, it may be useful to explore of MnO_2-stable radical inhibitors such as TEMPO to suppress radical side-reactions during the oxidation of **4.208**, or use catalytic co-oxidants such as I_2 to increase conversion when performing the oxidation at 0 °C.

4.7: Selective removal of the PMB group

4.7.1: ATTEMPTED PMB GROUP REMOVAL BY OXIDATION

PMB was originally chosen as the protecting group because it can be removed *via* oxidation, hydrogenolysis, or ionization with Lewis acids. Removal of the PMB group by oxidation would provide the most orthoganality because the MOM group could be labile to Lewis acids, and the quinone moiety would be reduced during hydrogenolysis. A comprehensive literature search revealed that DDQ, CAN, and Ph_3CBF_4 are the most common oxidants used to remove the PMB group (Table 4.13).[556-565]

Table 4.13: Summary of methods for the oxidative removal of PMB

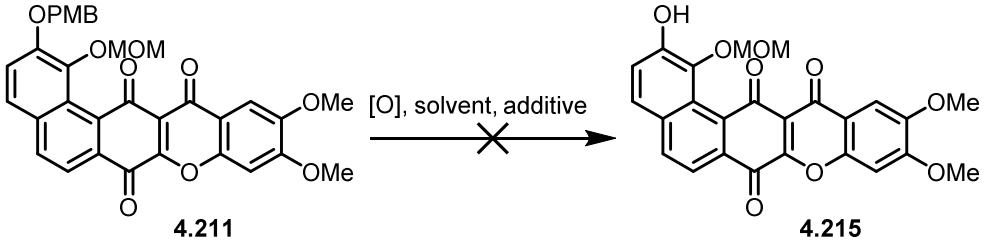


Ref	[O]	Additive	Conditions	Yield
Magnusson[556]	DDQ	KX/18-cr-6	PhMe, 80 ºC	33 – 92%
Shen/Hu[557]	DDQ	tBuONO	O_2, PhCl, 100 ºC	81 – 99%
Chandrasekhar[558]	$FeCl_3$	DDQ	CH_2Cl_2/H_2O, rt	62 – 94%
Sharma[559]	$Mn(OAc)_3$	DDQ	CH_2Cl_2, rt	61 – 90%
Floreancis[560]	MnO_2/PbO_2	DDQ	$MeNO_2$, 2,6-Cl_2-Py	70 – 92%
Katoh[561]	PIFA	tBuCHO	CH_2Cl_2, rt	30 – 94%
Cossy[562]	PCC		CH_2Cl_2, reflux	35 – 90%
Barton[563]	Ph_3CBF_4		CH_2Cl_2, rt	70 – 90%
Yonemitsu[564]	DDQ		CH_2Cl_2/H_2O, rt	60 – 95%
Samuelsson[565]	CAN		$MeCN/H_2O$, rt	8 – 89%

However, attempts to remove the PMB group in **4.211** with DDQ, Ph_3CBF_4 or CAN led to complex mixtures. Despite screening several solvents and additives to mitigate potential acid-catalyzed side reactions, the only observable product was *p*-anisaldehyde **4.216** (Equation 4.11). The fact that *p*-anisaldehyde was detected indicated that the PMB group was removed successfully, but the product **4.215** may be unstable to the reaction conditions. Analysis of crude

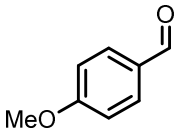
reaction mixtures by LCMS showed several compounds were produced in the reaction with masses between 1100 and 1400 amu, indicating oxidative polymerization.

Equation 4.11: Attempted oxidative PMB deprotection



4.211 **4.215**

Only detectable product:

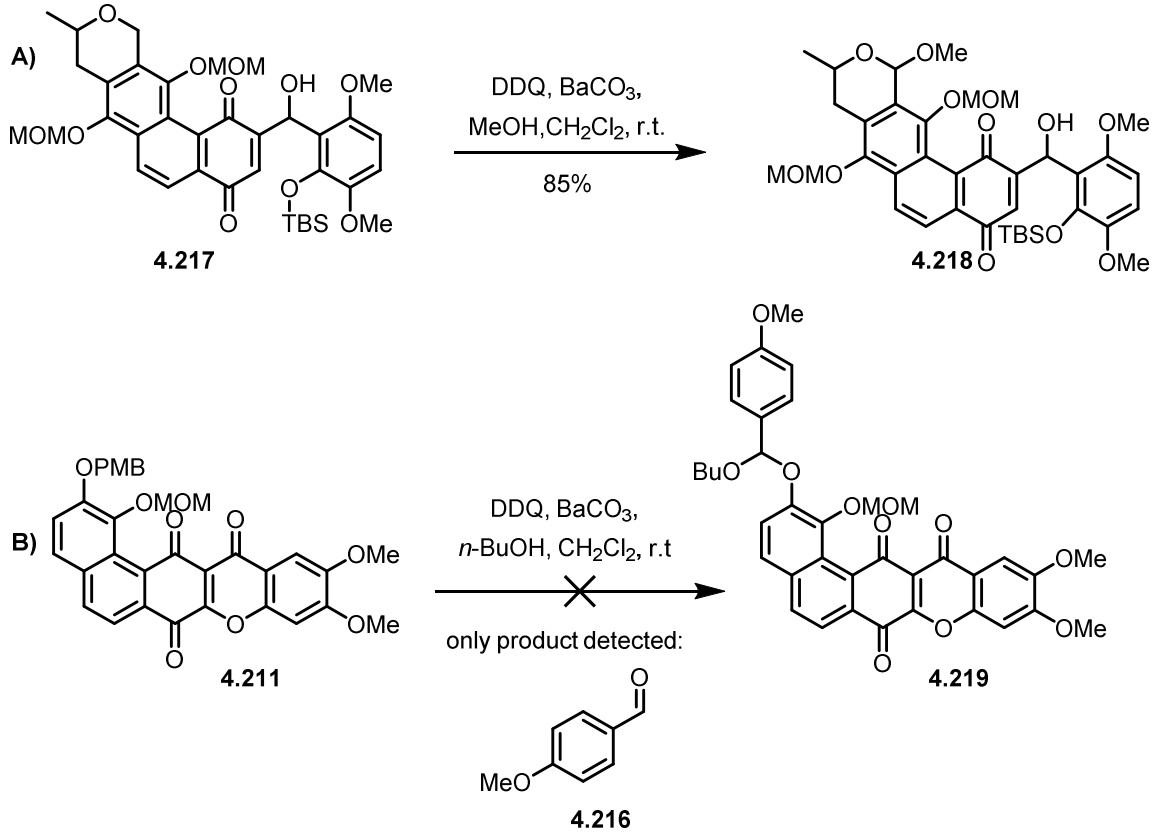


4.216

[O]	Solvent	Additives
DDQ	CH_2Cl_2	Na_2HPO_4
CAN	MeCN	1,3,5 Trimethoxy benzene
Ph_3CBF_4	DCM/H_2O	
	MeCN/H_2O	

An intermediate in the oxidation of the PMB group is a benzyl cation, which if intercepted by an alcohol, would form an acetal. This tactic was utilized by Dr. Yang who oxidized the C1 carbon atom in **4.217** with DDQ in the presence of MeOH and $BaCO_3$ to give the methoxy acetal **4.218** (Figure 4.34, **A**).[345,346, 566, 567] Unfortunately, subjection of **4.211** to these conditions except using *n*-BuOH as the alcohol, provided none of the desired product **4.219**; only *p*-anisaldehyde **4.216** was detected (Figure 4.33, **B**). The reasons for the failure to remove the PMB group via oxidation are not clear. Analysis of the reaction mixtures by LCMS showed multiple masses in the range between 1100 and 1400 amu. The fact that *p*-anisaldehyde was detected could mean that there was still sufficient water in the reaction intercept the oxonium intermediate after oxidation of the PMB group. The addition of desiccants such as molecular sieves to the reaction mixture may assist in forming **4.218**, but the removal of the PMB group by oxidation was abandoned in lieu of investigating simpler methods.

Figure 4.33: Attempted oxidation of the PMB group to the acetal



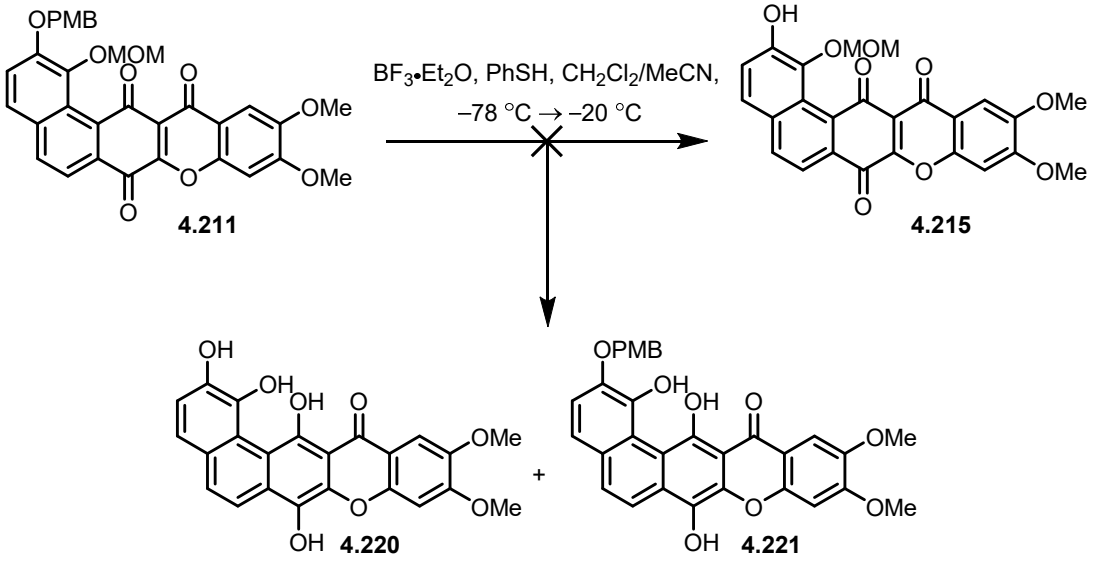
a) Example of successful DDQ benzylic oxidation to acetal from Martin groups' synthesis of IB-00208.[344, 345] b) Failure to adapt PMB oxidation to acetal with **4.211**.

4.7.2: PMB GROUP REMOVAL BY LEWIS ACIDS OR REDUCTION

4.7.2.1: Attempted PMB group removal with Lewis acids

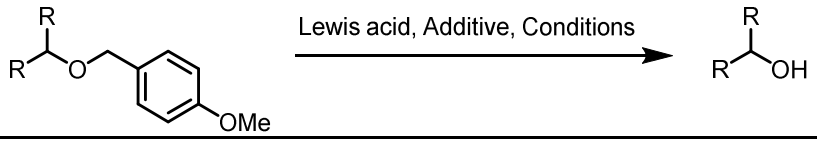
The instability of **4.215** to the reaction conditions used for the oxidative removal of the PMB group in **4.211** led to the investigation of Lewis acids for the deprotection. Unfortunately, subjection of **4.211** to conditions developed by Dr. Nichols gave a mixture of products that were determined to be the reduced MOM-deprotected compound **4.221** and the reduced bis-deprotected compound **4.220** by LCMS.[349] Compound **4.220** could potentially be elaborated to citreamicin after reoxidation to the quinone, but the lack of high yielding methods to oxidize the hydroquinones in this system and selectivity required to oxidize the *para*-hydroquinone over the *ortho*-hydroquinone moieties in **4.220** made this route difficult, and thus not pursued.

Figure 4.34: Attempted selective ionization of PMB group in **4.211**



The oxonium ion formed from the ionization of the PMB group should be more stable than the corresponding oxonium ion formed from ionization of a MOM acetal, so selective removal of a PMB group should be possible. Yet, to date, there are no methods that remove the PMB group with Lewis acids selectively over the MOM group. A survey of the literature revealed numerous Lewis acids that are capable of removing the PMB group that are available to use to develop a selective PMB deprotection over a MOM group.[568-587]

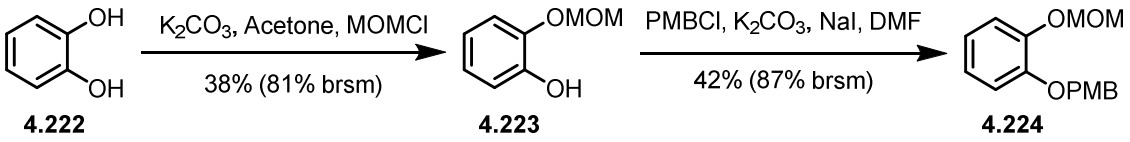
Table 4.14: Lewis acid mediated deprotection of PMB



Ref	LA	Additive	Conditions	Yield
Jung[568]	ClO_2SNCO		CH_2Cl_2, –78 ºC	72 – 88%
Hou[569]	Ph_3PHBr		MeCN, reflux	54 – 97%
Ilangolvan[570]	$Cl_2(CO)_2$		DCE, rt	46 – 89%
Iwasaki[571]	$MgBr_2•OEt_2$	DMS	CH_2Cl_2, rt	35 – 90%
Yadav[572]	CBr_4		MeOH, reflux	70 – 92%
Sawama/Sajiki[573]	$FeCl_3$		CH_2Cl_2, rt	53 – 98%
Ilangolvan[574]	$POCl_3$		DCE, rt	65 – 95%
Srikrishna[575]	$BF_3•OEt_2$	$NaCNBH_3$	THF, reflux	65 – 98%
Ploypradith[576]	Amberlyst-15		PhMe, 110 ºC	70 – 95%
Ozaki[577]	$TMSCl/SnCl_2$	anisole	CH_2Cl_2, rt	78 – 96%
Holmes[578]	$BCl_3•DMS$	HNO_3/HCl	CH_2Cl_2, rt	16– 100%
Kahne[579]	TFA		CH_2Cl_2, rt	84 – 99%
Sauve[580]	$SnCl_2/AlCl_3$	EtSH	CH_2Cl_2, rt	76 – 91%
Tokuyama[581]	BCl_3	$(Me)_5PhH$	CH_2Cl_2, –78 ºC	91 – 94%
Jung[582]	TfOH	$1,3\text{-}(MeO)_2Ar$	CH_2Cl_2, 0 ºC	79 – 94%
Codee[583]	HCl		HFIP, 0 ºC	48 – 90%
Sharma[584]	$ZnCl_4$		MeCN, rt	67 – 92%
Pale/Blanc[585]	$AgPF_6$	$1,3,5\text{-}(MeO)_3Ar$	CH_2Cl_2, 40 ºC	72– 100%
Marcantoni[586]	$CeCl_3$	NaI	MeCN, reflux	49 – 97%
Nino[587]	$Ce(OTf)_3$		$MeNO_2$, 60 ºC	30 – 99%

A simple model system **4.224** was chosen to evaluate the selective deprotection of PMB in the presence of a MOM group. Catechol (**4.222**) was treated with MOMCl in the presence of K_2CO_3 in acetone to provide **4.223**,[588] and subsequent PMB protection provided the **4.224**.

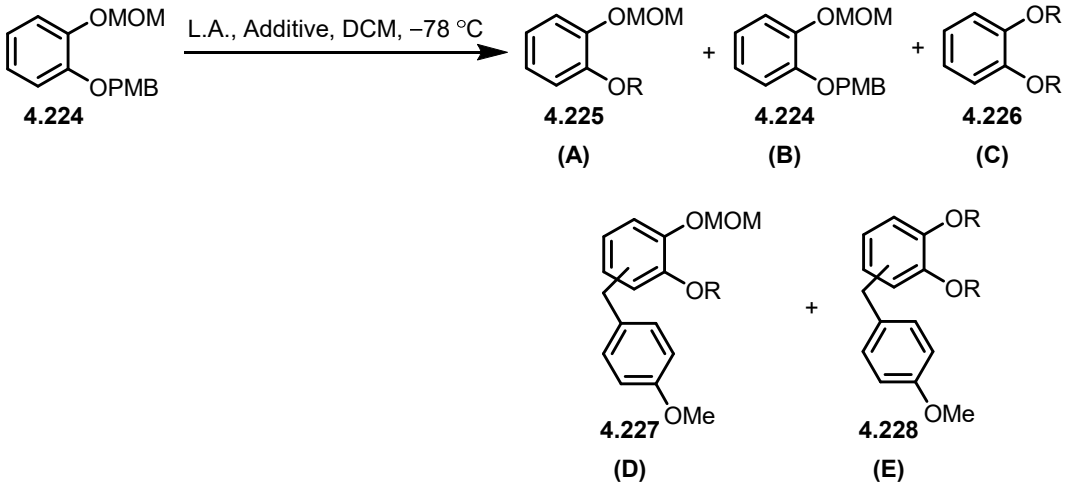
Scheme 4.24: Synthesis of selective PMB deprotection model system



4.222 **4.223** **4.224**

Several Lewis acids were added to a solution of the model compound **4.224** in CH_2Cl_2 at –78 ºC and the reactions, were stirred for 30 minutes and quenched. The crude reaction mixtures were analyzed by GCMS. The strong Lewis acids $SnCl_4$, BBr_3 and BCl_3 produced mixtures of **4.225** (R = H) and unidentified Lewis acid adducts, indicating that the PMB group may indeed be selectively removed (Table 4.15, entries 2,3,5). Reaction of **4.224** with TMSI provided **4.225** (R = TMS) as the major product, but catechol **4.227** was also isolated, indicating that TMSI can deprotect MOM groups even at –78 ºC (Table 4.15, entries 4). Et_2AlCl, however, produced only PMB deprotected product **4.225** and the PMB alkylated product **4.227**, with no evidence of MOM removal (Table 4.15, entries 1). Screening several additives to capture the PMB cation did not satisfactorily reduce the amount of the alkylated product **4.227** (Table 4.15, entries 6, 7, 8). Et_2AlCl seems to be a Lewis acid which promotes the selective ionization of the PMB group over the MOM group and a more thorough screen of cation sponges and/or solvents may reduce the amounts of the PMB alkylated products such as **4.227**. However, the selective removal of the PMB group in **4.211** using Et_2AlCl needed to be demonstrated before such optimization occurs.

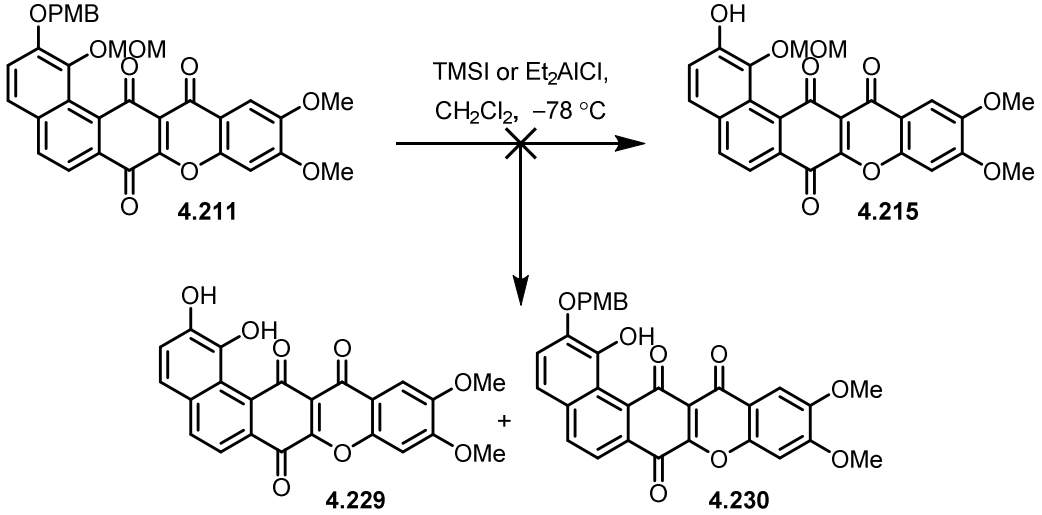
Table 4.15: Selective PMB deprotection Lewis acid screen



LA	Additive	R	A	B	C	D	E	other
Et_2AlCl	N/A	H	1.04	1	0	3.3	0	0
BCl_3	N/A	H	0	1	0	0	0	1.81
BBr_3	N/A	H	0.97	1	0	0	0	2.18
TMSI	N/A	TMS	2.30	0	1	0	0	0
$SnCl_4$	N/A	H	0	0	0	0	0	1
Et_2AlCl	allylTMS	H	1	0	0	4.70	0	0
Et_2AlCl	TES-H	H	1	0	0	4.08	0	1.63
Et_2AlCl	$AlMe_3$	H	1	0	0	7.01	0	2.16

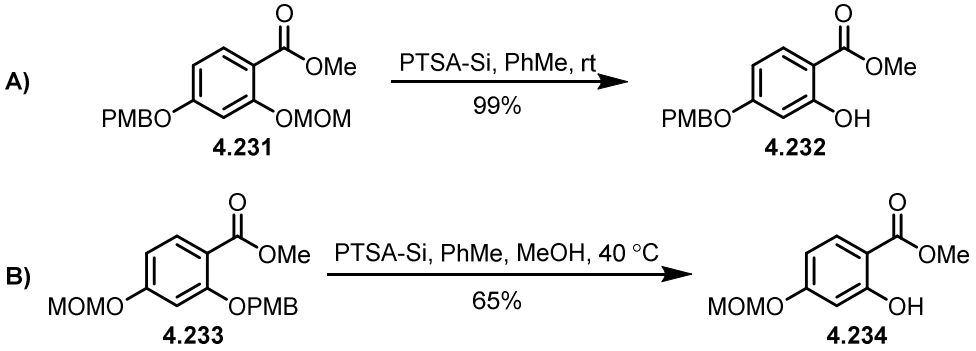
Unfortunately, use of either TMSI or Et_2AlCl for the selective removal of the PMB group in **4.211** produced mixtures of MOM-deprotected compound **4.230** and bis-deprotected compound **4.229** (Figure 4.35, see also Figure 4.34).

Figure 4.35: Unsuccessful use of TMSI or Et_2AlCl in PMB deprotection



The only literature example of selective removal of PMB group over a MOM group involved a directing effect of adjacent carbonyl group.[589] Keith found that selective PMB or MOM group deprotection can be governed by the groups proximity to the carbonyl group (Figure 4.36).[589] This result suggests that the MOM group is selectively removed because of a chelation effect of the C6-carbonyl group in **4.211**. Hence, selective removal of the PMB group under acidic conditions appears fatally flawed.

Figure 4.36: Keith's selective removal of MOM or PMB

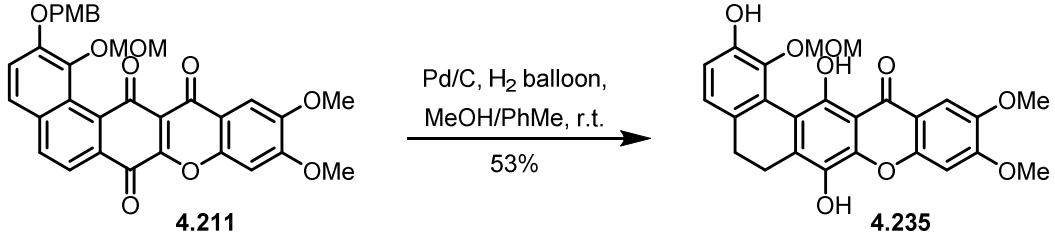


a) Example of carbonyl-assisted deprotection using a silica resin immobilized sulfonic acid (PTSA-Si) which favors MOM over PMB deprotection from Keith.[589] b) Example of carbonyl-assisted deprotection which favors PMB over MOM deprotection from Keith.[589]

4.7.2.2: Successful hydrogenolysis of PMB group

Because our ability to selectively remove the PMB group from **4.211** under both Lewis acid and oxidative conditions, the reductive removal of the PMB was investigated. In the event, hydrogenolysis of **4.211** with Pd/C in PhMe/MeOH under a balloon of hydrogen gas provided **4.235** in 53% yield (Equation 4.12). The reduction of the C19-C20 double bond was unexpected, but also intriguing as citreamicin ε, Sch-56036 and the kibdelones all lack this double bond (See Chapter 3, Figures 3.1, and 3.3).

Equation 4.12: Successful removal of the PMB group with hydrogenolysis



4.7.2.3: Summary

The hydrogenolysis of the PMB group is currently unoptimized and thus higher yields of **4.235** may be achieved by investigating solvents, catalyst loadings and hydrogen pressure. To

advance **4.236** to citreamicin, the hydroquinone moiety and the C19-C20 bond need to be installed.

4.8: GA-ring synthesis Model Studies

4.8.1: PROPOSAL AND MODEL SYNTHESIS

With the route to the core of citreamicin established, it was necessary to develop the methodology for the synthesis of the G- and A-rings. A significant portion of the structural variety in the polycyclic xanthone natural products is in the G-ring. Thus, a method that diverges from a common core could potentially access all the different members of the family. The general plan is outlined in Scheme 4.25. *ortho*-Bromination of the phenol of **4.236** and subsequent triflation would produce **4.237**, which would be the key divergent intermediate. Alkoxycarbonylation and palladium catalyzed ketone coupling would produce the isocoumarin **4.238**, which can be condensed with amines to form either isoquinolones such as **4.239** or dihydrooxazolo-[3,2-b]-isoquinolinones which are found in cervinomycin and citreamicin (Figure 4.38). By varying the ketone and the amine components, one could conceivably synthesize any member of the polycyclic xanthone natural products.

Scheme 4.25: Plan for the late stage G- and A-ring synthesis

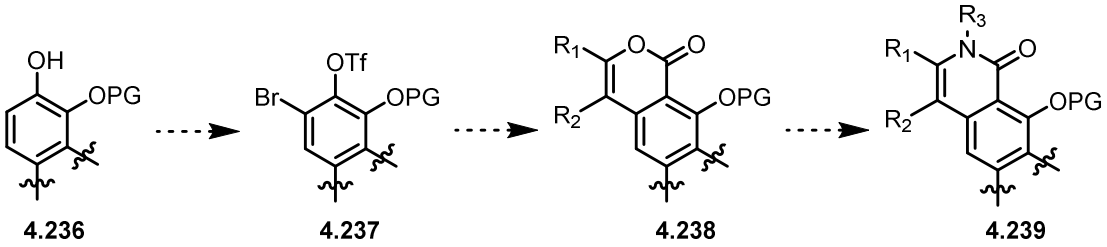
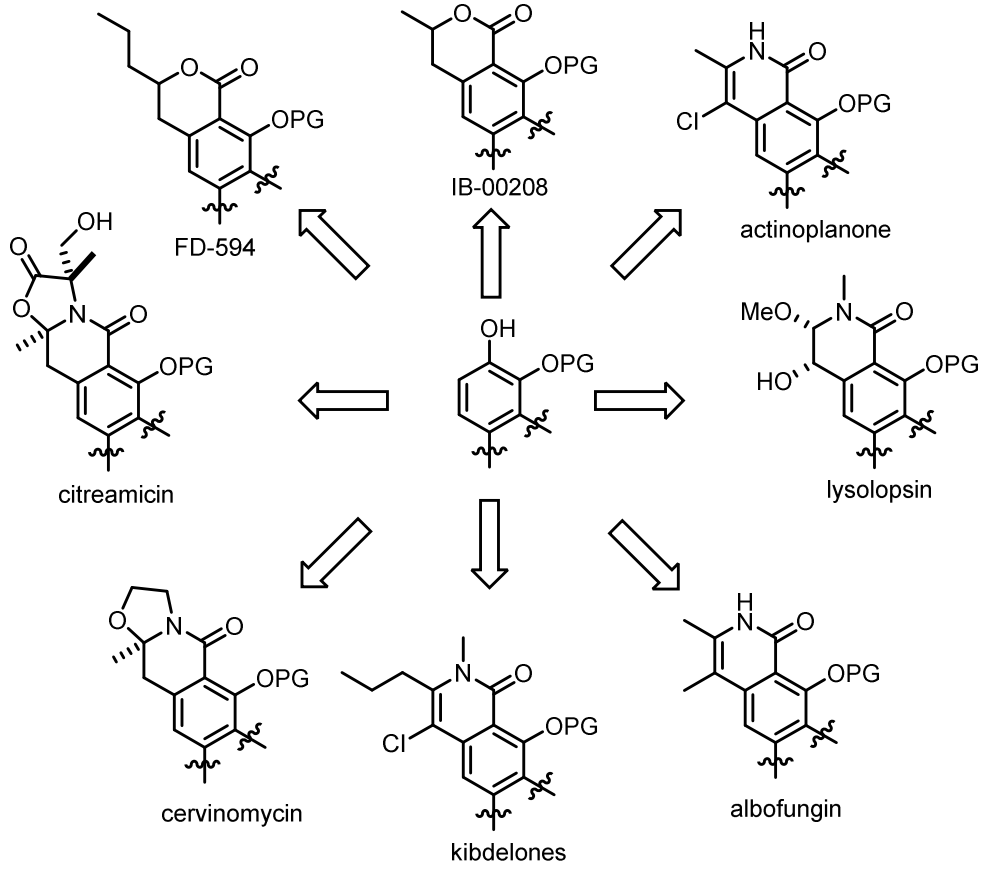
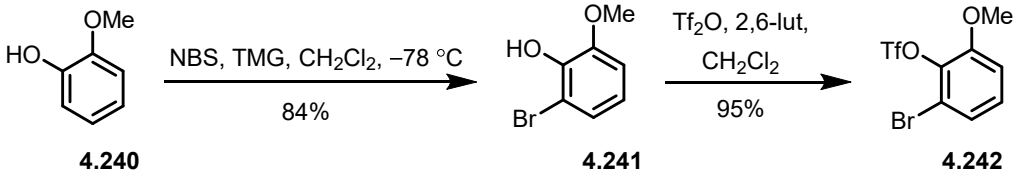


Figure 4.38: Plan for the late stage G- and A-ring synthesis



There are no known syntheses of isocoumarins like **4.238** (Scheme 4.25), so we selected the model system **4.242** to develop the key reactions. Guaiacol (**4.240**) was brominated using NBS/TMG to provide **4.241** in 84% yield (Scheme 4.26, see also Table 4.3). Triflation of the phenol group with triflic anhydride then provided **4.242** in 95% yield.

Scheme 4.26: Synthesis of model system



4.8.2: DEVELOPMENT OF THE ALKOXYCARBONYLATION

The alkoxycarbonylation of **4.242** to produce the ester **4.243** was done under standard conditions (Et_3N, DMSO/MeOH, $Pd(OAc)_2$) using dppf as the ligand, and the reactions were analyzed by GCMS to determine product ratios (Table 4.39, entry 1).[590] Unfortunately, the standard conditions resulted in poor conversion of **4.242**. Prolonged stirring or the use of K_2CO_3 under higher pressure (50 psi), only served to marginally improve conversions and produced the hydrolyzed product **4.241** (Table 4.39, entries 2, 3). The initial experiments revealed two major problems in the alkoxycarbonylation of **4.242**; (1) Poor conversion of the starting material **4.242** to **4.243** and (2) the hydrolysis of **4.242**. To solve these problems, several ligands were screened to improve conversion along with bases with p*K*a's less than Et_3N to produce less hydroxide (Table 4.39, entries 4 – 8). The ligand screen revealed that dppp was superior to other ligands and all bases tested provided none of the hydrolyzed material **4.241**. Most of the reaction showed poor conversion of **4.242** to **4.243** with the exception of sodium acetate, which dramatically increased the yield (Table 4.39, entries 6). However, this result was not reproducable so other conditions were investigated.

Figure 4.39: Initial attempt to alkoxycarbonylate **4.242**

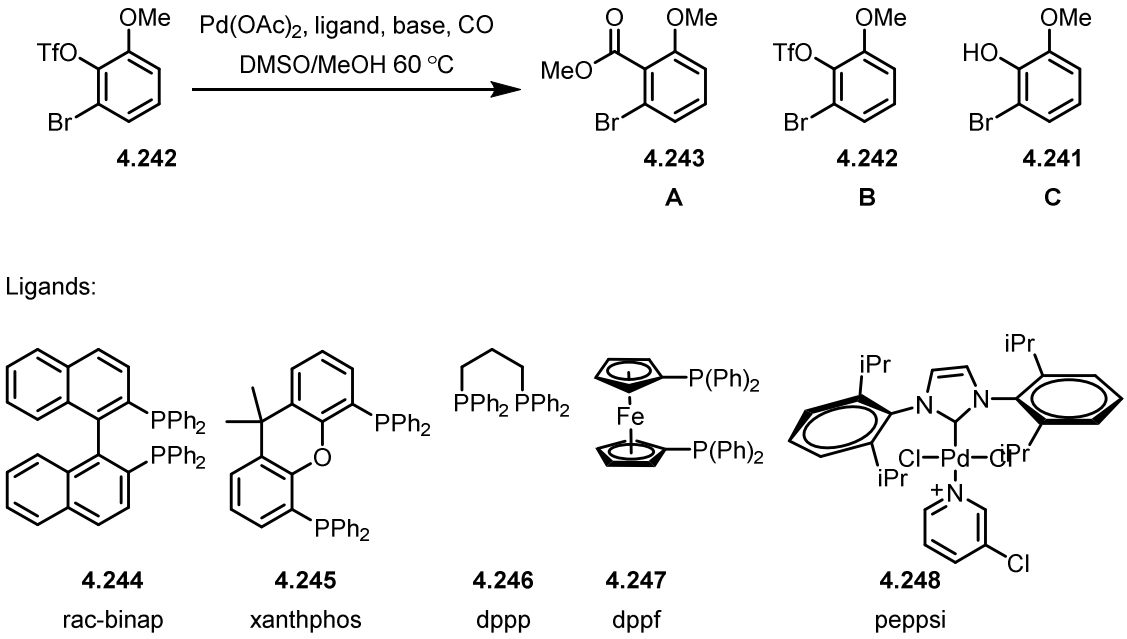


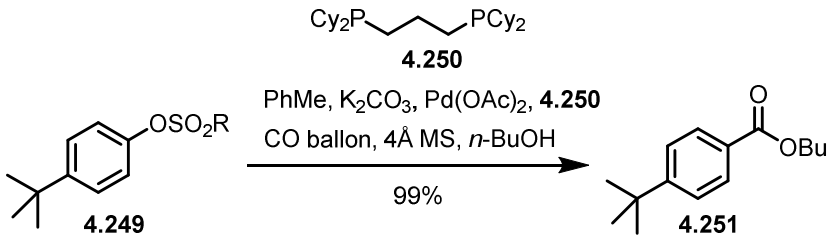
Table 4.16: Initial attempt to alkoxycarbonylate **4.242**: product ratios by GCMS

Ligand	**CO**	**Base**	**A**	**B**	**C**
dppf	Balloon	Et_3N	1	3.1	0
dppf[a]	Balloon	Et_3N	1	1.9	2.6
dppf	50psi	K_2CO_3	0	1	1.4
dppp	50psi	Na_2HPO_4	0	1	0
dppp	50psi	NMM	1	2.5	0
dppp	50psi	NaOAc	4.5	1	0
dppp	50psi	DTBP	1	4.2	0
dppp	50psi	NaH_2PO_4	0	1	0

a) reaction stirred for 24 h

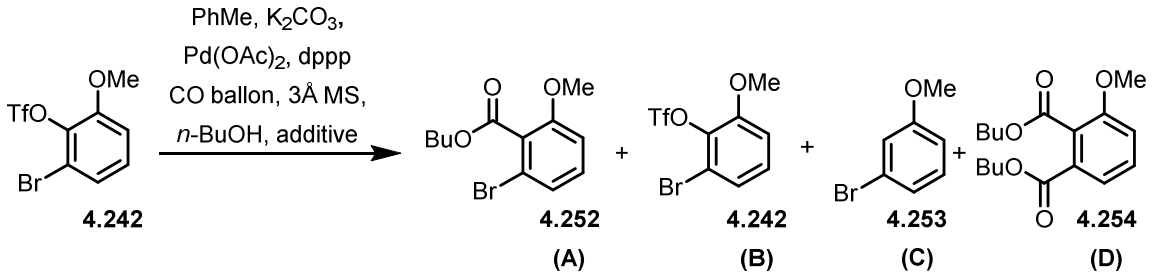
A review of the literature on alkoxycarbonylations of aryl sulfonate esters revealed many conditions,[590-593] but few insights into the problems of conversion or suppression of hydrolysis. One intriguing example from Buchwald in the alkoxycarbonylation of aryl-mesylate and tosylates mentions hydrolysis of the reactants as a problem.[594] Buchwald found that the hydrolysis of aryl mesylates and tosylates was minimized in non-polar solvents such as toluene and that the inclusion of molecular sieves improved conversion and increased yields.

Equation 4.13: Buchwald's alkoxycarbonylation of aryl-mesylate and tosylates



Adapting Buchwald's conditions to the alkoxy carbonylation of **4.242** suppressed hydrolysis, but poor conversion remained and the phthalate **4.244** and the reduced compound **4.243** were detected by GCMS: (Table 4.17). Several bases and temperatures were screened, but little improvement in conversion was seen (Table 4.17, entries 1 – 4). Recalling the interesting effect of acetate in the previous example, a soluble source of acetate was added to the reaction mixture (*n*-Bu_4NOAc), and a significant improvement in conversion was seen (Table 4.17, entry 5).

Table 4.17: Alkoxycarbonylation of **4.242** using modified Buchwald conditions: Product ratios by GCMS

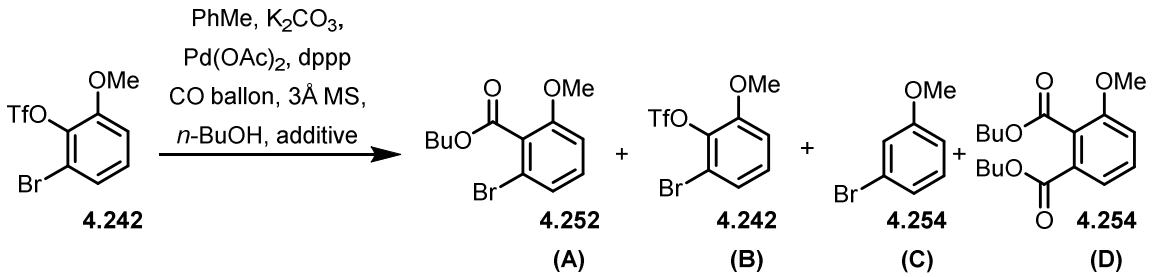


Ligand	Base	T	Additive	A[a]	B[a]	C[a]	D[a]
dppp	K_2CO_3	70 ºC	N/A	2.7	33.2	1.4	1
dppp	Cs_2CO_3	70 ºC	N/A	1.2	1.1	0.5	1
dppp	K_3PO_4	70 ºC	N/A	2.8	22.3	1.5	1
dppp	K_2CO_3	100 ºC	N/A	1.6	21.0	1.8	1
dppp	K_2CO_3	70 ºC	(*n*-Bu)$_4$NOAc	3.0	4.6	0.2	1

a) Ratios of **4.252**, **4.242**, **4.253** and **4.254** were determined by GCMS

Scaling up the reaction allowed for the isolation of the desired product **4.252** in 76% yield, but the phthalate compound **4.244** was also formed in 19% yield (Table 4.18, entry 1). Evidence that acetate ion is critical for the success of the reaction was found in two experiments. Omission of *n*-Bu_4NOAc provided **4.252** in only 9% yield, and using *n*-Bu_4NCl instead of *n*-Bu_4NOAc gave no **4.252** (Table 4.18, entries 3,4). Stronger bases such as K_3PO_3 provided lower yields of **4.252** (Table 4.18, entry 2). Use of only 0.2 equivalents of *n*-Bu_4NOAc still provided the desired product **4.252**, but in only 67% yield, and the reaction took 24 h to go to completion (Table 4.18, entry 5).

Table 4.18: Alkoxycarbonylation of **4.242** 500 mg to 1 g scale, isolated yields

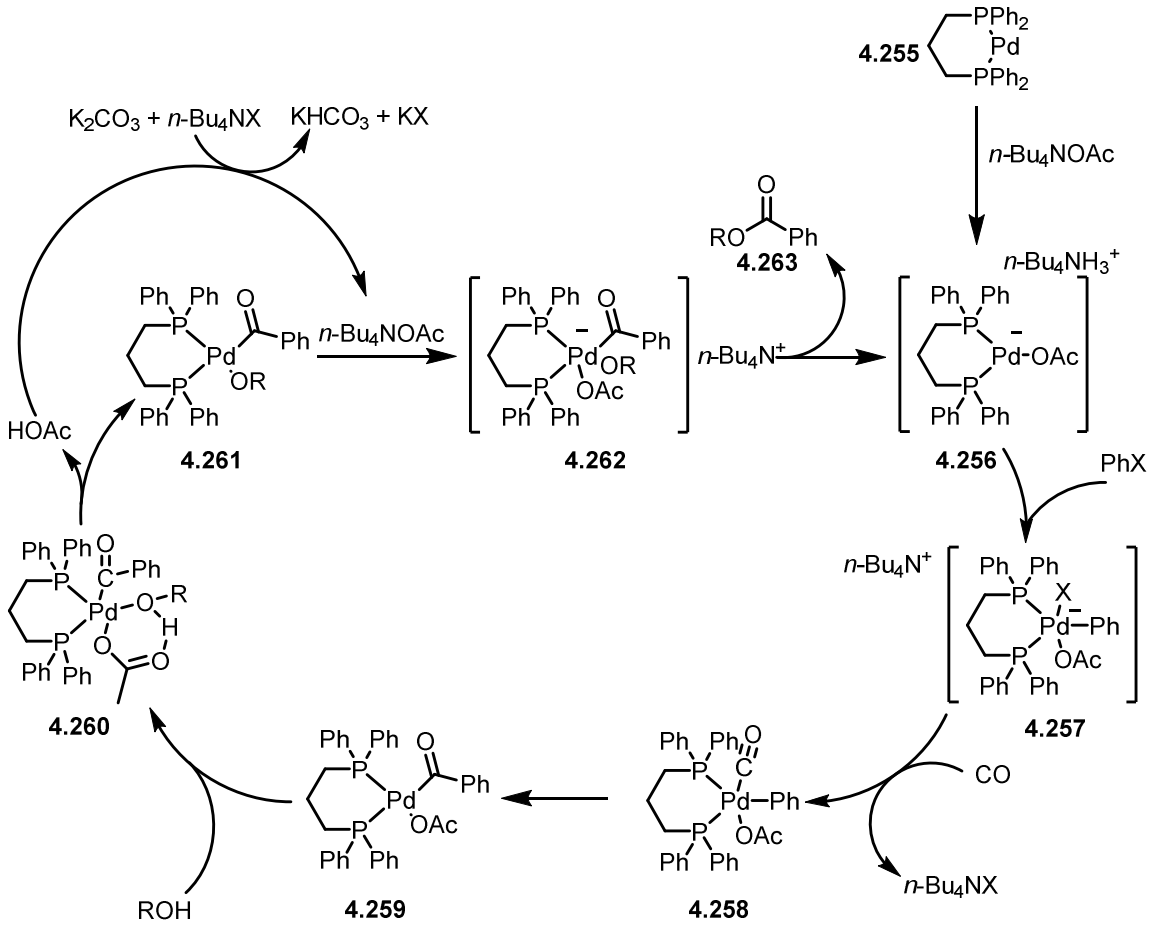


Ligand	Base	T	Additive	A	B	C	D
dppp	K_2CO_3	70 ºC	$(n\text{-Bu})_4NOAc$	76%	~5%	0%	19%
dppp	K_3PO_4	70 ºC	$(n\text{-Bu})_4NOAc$	45%	35%	0%	0%
dppp	K_2CO_3	70 ºC	N/A	9%	57%	0%	0%
dppp	K_2CO_3	70 ºC	$(n\text{-Bu})_4NCl$	0%	0%	0%	0%
dppp	K_2CO_3	70 ºC	$(n\text{-Bu})_4NOAc$[a]	67%	~5%	0%	11%

a) 0.2 equivalents used

Based on the work of Amatore on the mechanisms of Pd catalysis, and others on the mechanism of mechanism of alkoxycarbonylation,[595-579] the putative role of n-Bu_4NOAc is depicted in Scheme 4.27.[598] The Pd^0 species **4.255** reacts with n-Bu_4NOAc to form the anionic species **4.256**. Anionic species **4.256** oxidatively inserts with the aryl triflate to form **4.257**. Ligand association of carbon monoxide and de-complexation of n-Bu_4NX provides neutral complex **4.258**. α-Migratory insertion of carbon monoxide followed by coordination of the alcohol gives complex **4.259**. Mechanistic studies on alkoxy carbonylation of arenes have shown that the rate limiting step is attack of the alkoxide on the palladium species **4.259**.[595-579] The significant rate enhancement seen in the presence of n-Bu_4NOAc may be due to an general base-assisted deprotonation of the alcohol in **4.260** to form **4.261**, which after coordination of acetate to form the anionic complex **4.262** can then facilitate reductive elimination to give **4.256** and the desired product **4.263**.

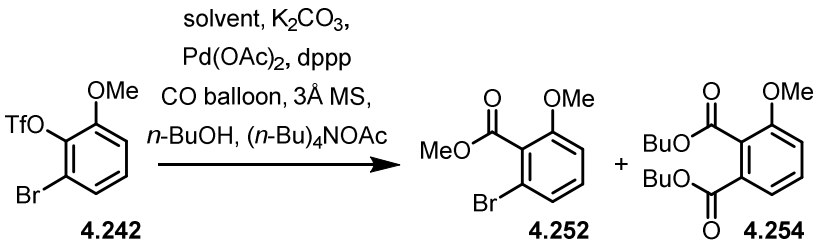
Scheme 4.27: Proposed mechanistic role of *n*-Bu_4NOAc in the alkoxy carbonylation of **4.242**



The palladium-ate complex **4.256** may favor oxidative insertion into the more polarized C_{sp2}-OTf bond over the less polarized C_{sp2}-Br bond, and hence may disfavor the formation of phthalate **4.244**. However, the proportion of the ionic ate-complex **4.256** in the reaction mixture would be expected to be smaller in non-polar solvents and larger in polar aprotic solvents. Thus, the reaction would also be expected to be more selective for the desired product **4.252** in polar

aprotic solvents. To test this hypothesis, several solvents with differing polarity were screened in the alkoxycarbonylation of **4.242** and the ratios of the desired product **4.252** and the phthalate **4.244** were measured by GCMS (Equation 4.14). The selectivity for **4.252** was highest in polar aprotic solvents and lowest in non-polar solvents, the highest selectivity being in DMSO and MeCN, supporting the hypothesis that the ate-complex favors oxidative insertion at the triflate rather than the bromide.

Equation 4.14: Effect of solvent on the ratios of **4.252** and **4.244** during alkoxycarbonylation

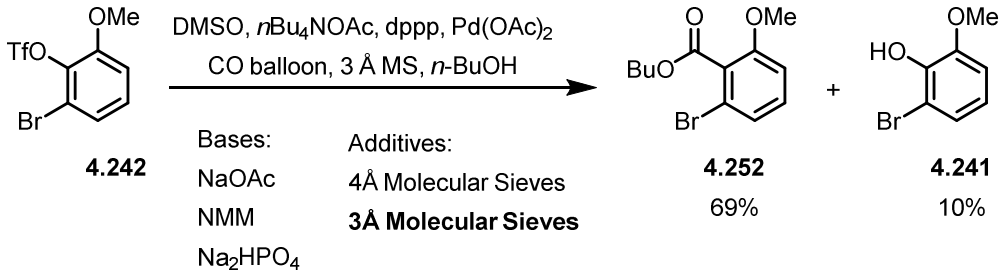


Solvent:	Ratio A:B
DMSO	8.4:1
MeCN	8.6:1
DMF	7.2:1
Glyme	5.9:1
THF	3.1:1
dioxane	3.2:1
anisole	3.1:1
PhMe	4.6:1

Using DMSO as a solvent, however, reintroduced the hydrolysis issues seen earlier. Several bases were screened in addition to *n*-Bu_4NOAc in order to suppress hydrolysis, but no improvement was observed. Minimization of **4.241** came from increasing the amount of molecular sieves (1.5 mg/mg vs. 0.5 mg/mg in toluene) and using *n*-Bu_4NOAc (2 eq) as the sole base. Interestingly, there was a significant difference between 4 Å molecular sieves and 3 Å molecular sieves, with 3 Å molecular sieves providing higher conversions and fewer byproducts than 4 Å molecular sieves. The reaction was scaled up, and the desired product **4.252** was isolated in 69% yield, which is comparable to the conditions using toluene; however the

hydrolysis product **4.241** was still seen in 10% yield. Although the yields for the alkoxycarbonylation of **4.242** to **4.252** were about the same in toluene or DMSO, the conditions in toluene were chosen to move forward due to the ease of purification.

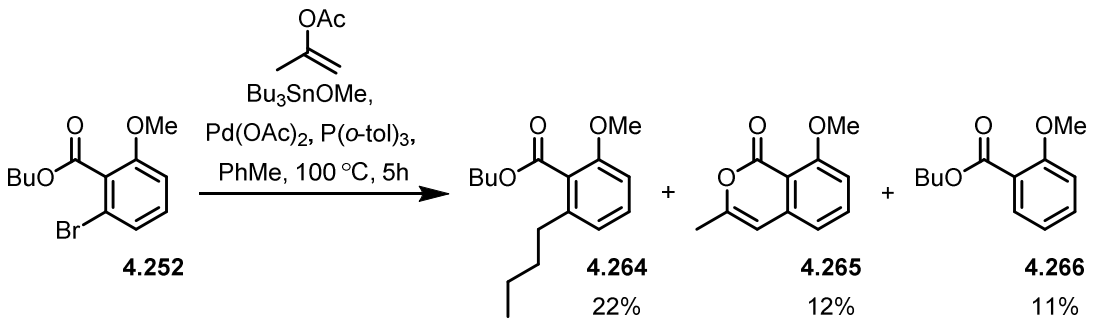
Equation 4.15: Reaction optimization of alkoxycarbonylation in DMSO



4.8.3: DEVELOPMENT OF A PALLADIUM-CATALYZED KETONE COUPLING TOWARDS ISOCOUMARINS

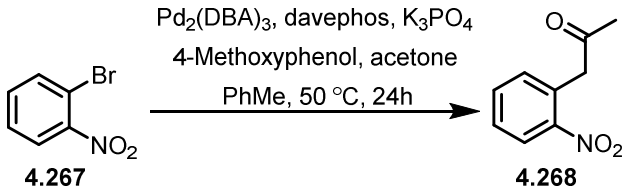
With the conditions for the alkoxycarbonylation developed, the coupling to form the isocoumarin **4.265** was investigated next. Based on the work of Hosokawa/Tatsuta in the synthesis of TMC-66, the Migita procedure seemed ideal due to the mild conditions (see Chapter 3, Scheme 3.32).[499] Unfortunately, this procedure produced mixtures of the butylated product **4.264**, the debrominated product **4.266**, along with the desired isocoumarin **4.265** (Equation 4.16).

Equation 4.16: Attempted Migita coupling with **4.252**



The low yield and presence of the butylated byproduct **4.264** led to the abandonment of the Migata procedure in favor of a method that utilizes acetone directly. A literature search revealed that the coupling of arenes to acetone suffers from two problems: (1) Polyarylation because the product is more acidic than the starting material, and (2) the proclivity of acetone to polymerize under the basic reaction conditions.[600-602] Several methods exist that can accomplish this transformation, but the ligands required were complicated and not commercially available and thus undesirable. Fortunately Buchwald developed a procedure for coupling acetone with of *ortho*-nitro arenes in his synthesis of substituted indoles. Inclusion of 4-methoxyphenol as a putative proton shuttle was key for the success of the reaction (Equation 4.17).[603]

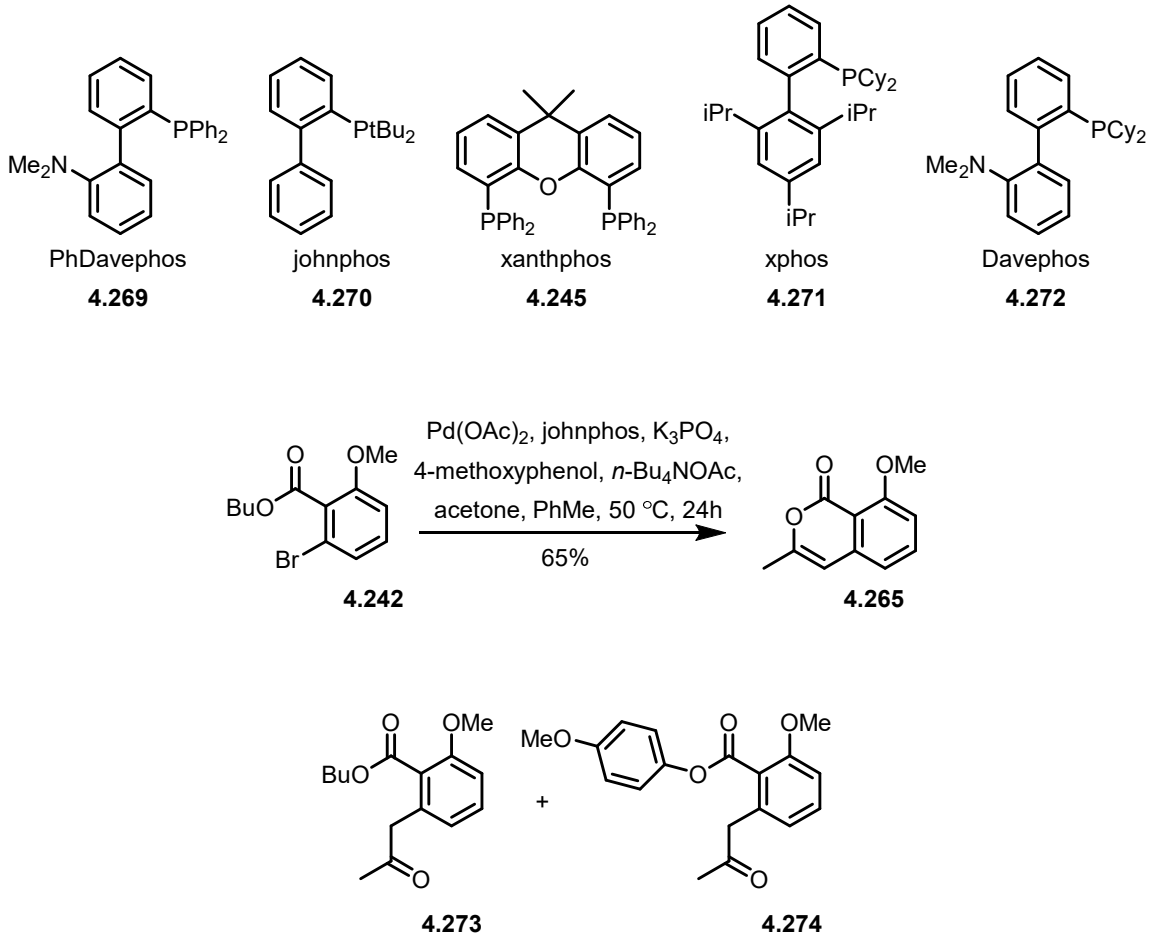
Equation 4.17: Buchwald's acetone coupling of *ortho*-nitro arenes



Several ligands and palladium sources were screened in an attempt to adapt Buchwald's coupling conditions for the synthesis of isocoumarin **4.265**, and the results were analyzed by GCMS. The screen identified johnphos **4.271** as the ligand that provided the highest conversion of **4.243** to **4.265** and $Pd_2(dba)_3$•$HCCl_3$ as the optimal palladium source (Figure 4.40). Initial attempts to scale up the reaction, however, only provided **4.265** in low yields. The dramatic effects seen in the alkoxycarbonylation reaction of **4.242** in the presence of *n*-Bu_4NOAc was

attributed to an assisted deprotonation of the alcohol by acetate. Accordingly, *n*-Bu_4NOAc was added to the reaction mixture with the expectation that it would facilitate formation of the acetone enolate. Gratifyingly, the addition of *n*-Bu_4NOAc to the reaction mixture produced the isocoumarin **4.265** in 65% yield (Figure 4.40). Inspection of the reaction mixture by GCMS also revealed compounds having masses consistent with **4.273** and **4.274**, which may be intermediates in the reaction. Currently, this reaction is unoptimized and future work to convert the intermediates **4.273** and/or **4.274** to the desired product **4.265** or whether 4-methoxyphenol is necessary in addition to *n*-Bu_4NOAc.

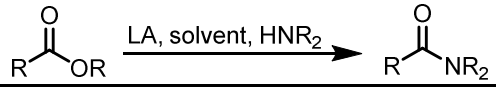
Figure 4.40: Development of acetone coupling to provide isocoumarin **4.265**



4.8.4: Development of the amine condensation

With the methodology established for both the alkoxycarbonylation and the acetone arylation, the coupling of amines with the isocoumarin **4.265** to form dihydrooxazolo-[3,2-b]-isoquinolinones was investigated. A literature search for reagents capable of transforming esters directly into amides revealed a number of Lewis acids (Table 4.19).[604-621] However, citreamicin requires the condensation of an amino acid, and in order to develop methods that can accommodate any of the polycyclic xanthone natural products the method would need to work for amino acids as well as aliphatic amines. There are few methods that are applicable to condensing amino acids with esters, and these include use of $CpTaCl_4$ and $AlMe_3$, the latter of which was reported previously in the Martin group.[616] (Table 4.19, entries 2,11).

Table 4.19: Summary of methods to transform esters to amides

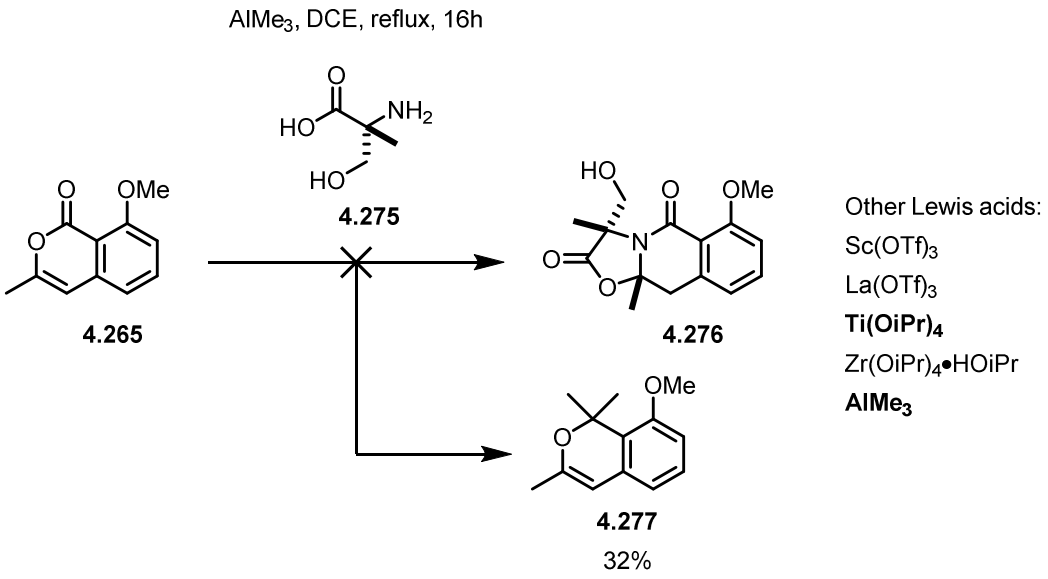


Reference	LA	conditions	Yield
Roskamp[604-606]	$Sn(HMDS)_2$	–40 ºC→ rt	30 – 94%
Goldman/Kohn[607]	$CpTaCl_4$	–14 ºC→ rt	60 – 98%
Lasne[608]	PrMgBr	70 ºC	30 – 70%
Helquist[609]	$Ti(OiPr)_4$	DCE, reflux	35 – 93%
Gellman/Stahl[610]	$Sc(OTf)_3$, $Ti(NMe_2)_4$	PhMe, 90 ºC	2 – 99%
Proco Jr.[611]	$Ti(OiPr)_4$, $Zr(OtBu)_4$[a]	PhMe, 100 ºC	50 – 98%
Morimoto/Ohshima[612]	$La(OTf)_3$	Rt → 70 ºC	80 – 99%
Guarna[613]	$LiNTf_2$	$HCCl_3$, 70 ºC	12 – 99%
Ranu[614]	InI_3	110 ºC	83 – 93%
Huang[615]	DIBAL-H	THF, rt	28 – 95%
Martin[616]	$AlMe_3$	DCE, reflux	31 – 77%
Weinreb[617,618]	$AlMe_3$	PhH, 50 ºC → reflux	31 – 100%
Roussi[619,620]	MAO[b]	Rt-100 ºC	10 – 97%
Yoon[621]	$NaAlEt_2H_2$	PhMe, reflux	88 – 96%

a) HOBt is an additive. b). MAO = methyl aluminum oxide

Several Lewis acids were screened for their ability to promote the coupling of α-methyl serine[622-626] **4.275** with the isocoumarin **4.265**, but only $AlMe_3$ and $Ti(OiPr)_4$ produced any products (Scheme 4.27). The reaction with $AlMe_3$ produced **4.277**, which resulted from $AlMe_3$ coordinating the carbonyl group, delivering a methyl group and subsequent ionization of the resulting benzyl alcohol.[627,628]

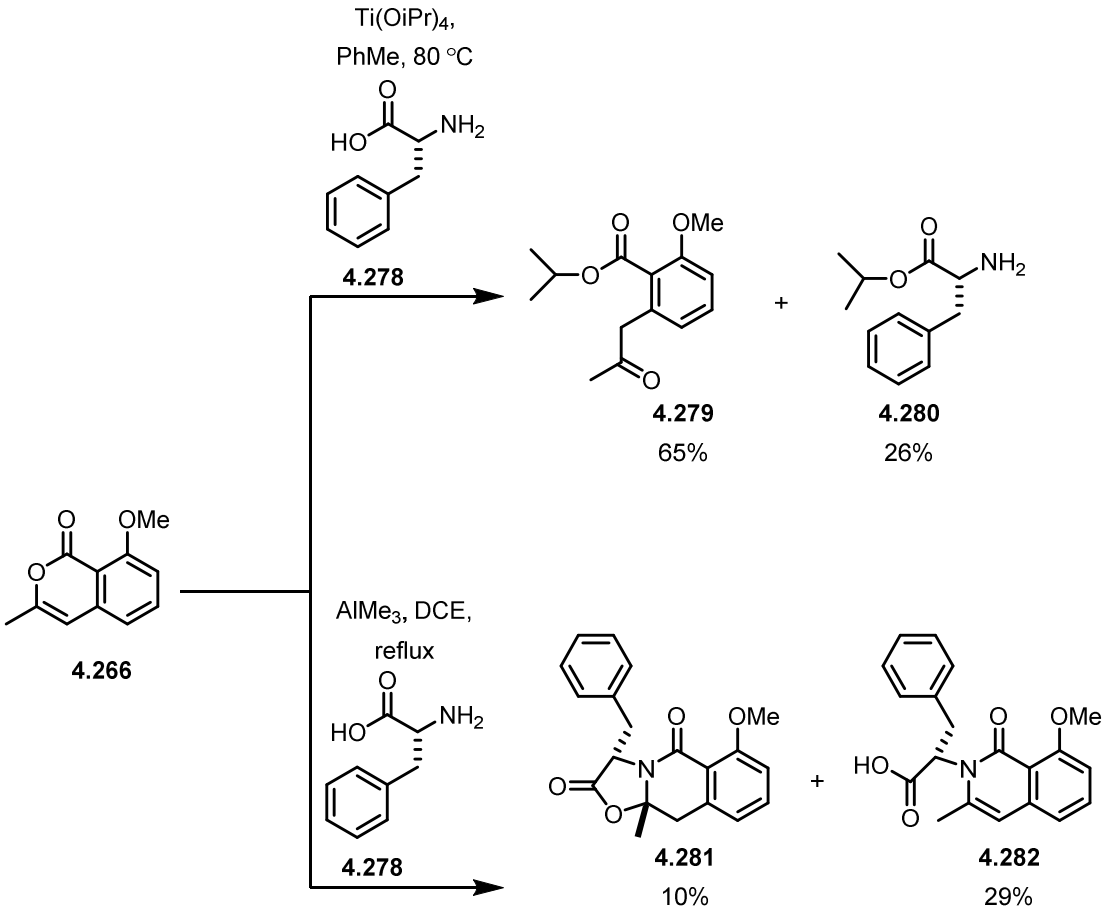
Scheme 4.28: Attempted coupling of α-Methyl serine **4.275** with the isocoumarin **4.265**



The isolation of **4.278** indicated that free $AlMe_3$ may methylate ionizable carbonyls during the reaction. To analyze these reactions in more detail without the burden of synthesizing large amounts of α-methyl serine (**4.275**), L-phenylalanine was used as a model amino acid. Accordingly, $Ti(OiPr)_4$ and $AlMe_3$ were re-tested in their capacity to couple amino acids to isocoumarins (Scheme 4.29). While $Ti(OiPr)_4$ only produced the ring opened product **4.279** and

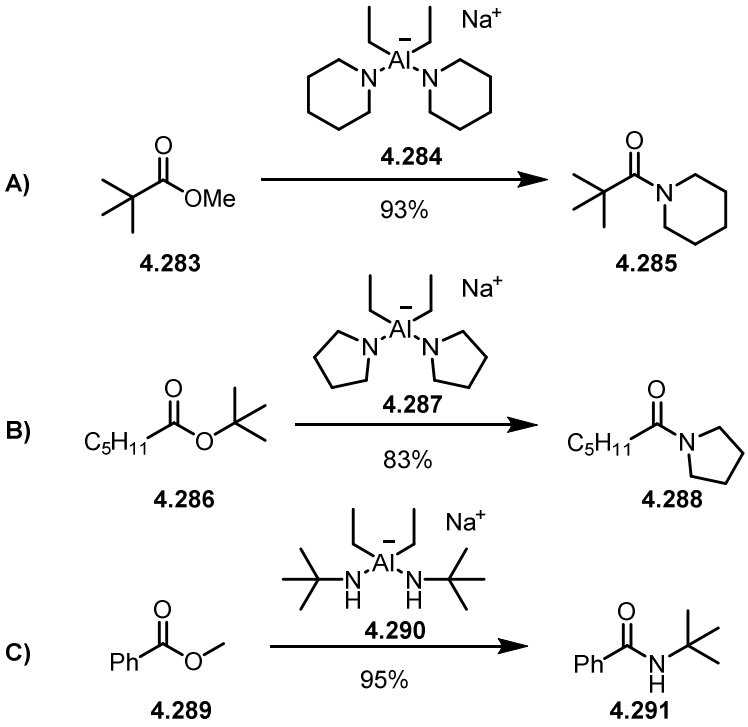
the isopropyl ester **4.280**, $AlMe_3$ produced the desired product **4.281**, along with the isoquinolone **4.282**, in 10% and 30% yields, respectively.

Scheme 4.29: Coupling of L-phenylalanine and isocoumarin **4.265**



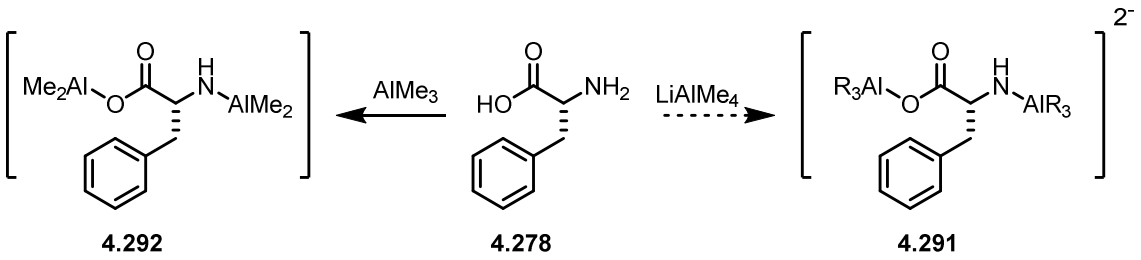
Review of the relevant literature revealed the work of Yoon (see Table 4.19, entry 14), who used aluminum ate complexes to effect the transformation of esters to amides (Figure 4.41).[621] A particularly attractive feature of the aluminum-ate complexes **4.284**, **4.287** or **4.290** was their ability to form amides with sterically hindered amines (Figure 4.41, **C**) and esters (Figure 4.41, **A**,**B**), as will be necessary when using α-methyl serine **4.275**.

Figure 4.41: Yoon's use of aluminum amide ate-complexes for the transformation of esters to amides



Yoon made his aluminum-ate complexes *in situ* by heating $Li[Et_2AlH_2]$ and the amine under reflux. Because $Li[Et_2AlH_2]$ is no longer commercially available, we hypothesized that the combination of $AlMe_3$ and MeLi, which are readily available, would produce $LiAlMe_4$ which may be used to affect similar transformations. The combination of $LiAlMe_4$ and phenylalanine **4.278** would aluminum-ate complex **4.291**, which is similar to those in Yoon's chemistry (Figure 4.42). The amido-aluminum ate complex **4.291** should also be more nucleophilic than the complexes **4.294** produced by reaction with $AlMe_3$.

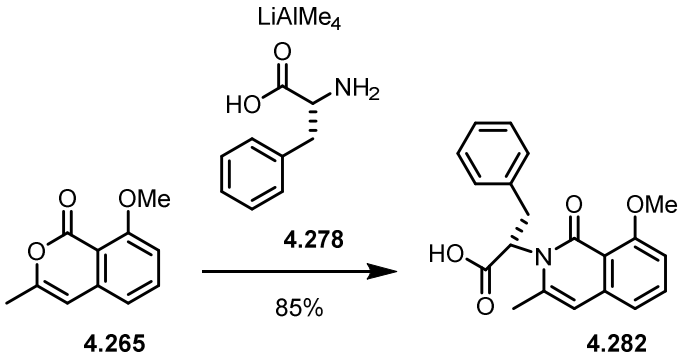
Figure 4.42: Formation of aluminum-ate complex with amino acid



4.292 **4.278** **4.291**

Refluxing L-phenylalanine **4.278** with $LiAlMe_4$, which was generated *in situ* from $AlMe_3$ and MeLi, in a mixture of THF and toluene, followed by the addition of the isocoumarin **4.265** provided the isoquinolone **4.282** in 85% yield; though none of the desired cyclized product **4.281** was observed.

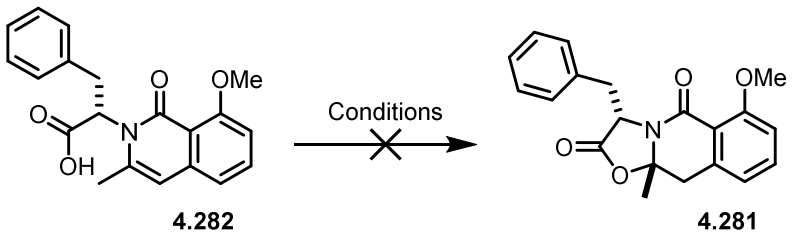
Equation 4.18: Successful coupling of phenylalanine and isocoumarin **4.265**



4.265 **4.282**

The fact that some of the tri-cyclic product **4.281** was formed from the coupling of phenylalanine **4.278** with isocoumarin **4.265** in the presence of $AlMe_3$ and not $LiAlMe_4$ may suggest that the cyclization of **4.282** to **4.281** may proceed in the presence of Lewis acids. Accordingly, several Brønsted and Lewis acids were screened in order to affect this transformation (Equation 4.19). Although traces of the tricyclic compound **4.281** were seen in some instances, the isoquinolone **4.282** remained the major product in every case.

Equation 4.19: Attempted conversion of **4.282** to **4.281** with Brønsted and Lewis acids

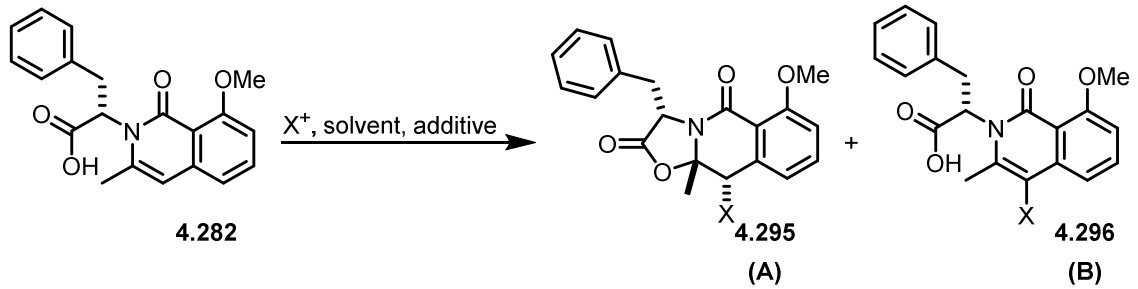


4.282 **4.281**

Lewis acids:	Bronsted acids:
$Hg(OTf)_2$	AcOH
$Ph_3PAuCl/AgOTf$	H_2SO_4
AgOTf	HCl
$Cu(OTf)_2$	H_3PO_4
$Pd(OTf)_2$	oxalic acid
	formic acid
	TfOH

Since the cyclization of **4.282** to **4.281** was unsuccessful with Lewis or Brønsted acids, halolactonization or oxy-mercuration followed by reduction was evaluated as a strategy (Table 4.20). Several halolactonization conditions were tried using $Ph_3P{=}S$ as a promoter, but the halogenated isoquinolone **4.296** (**B**) was the major product in each case.[632] Oxy-mercuration of **4.282**, followed by reduction with $NaBH_4$ only gave returned starting material (Table 4.20, entries 4,5). Examination of the reaction mixture before the reduction revealed that the isoquinolone B (X = HgX) was being formed exclusively. However, addition of $NaBH_4$ provided only starting material **4.282**. The only reaction to produce the desired product **4.295** was the iodolactonization conditions, but observation of the reaction mixture showed that the iodoisoquinolone **4.296** was produced rapidly, followed by a slower conversion to **4.295** in 29% yield (Table 4.20, entries 6,7).

Table 4.20: Attempted halolactonization of **4.282**



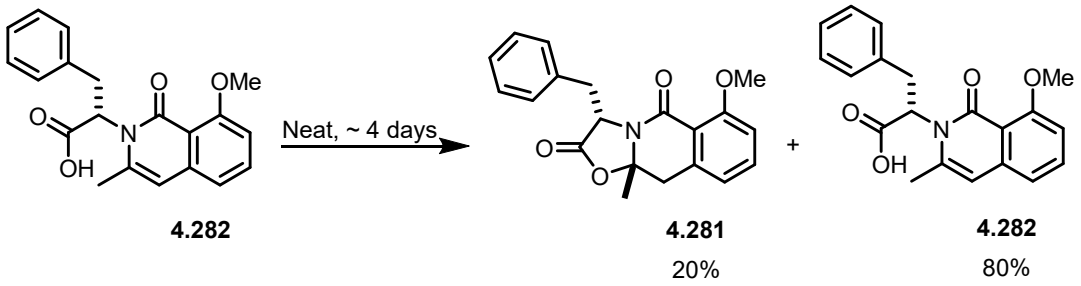
4.282 **4.295** (A) **4.296** (B)

X^+	Oxidant	Conditions	Additive	A	B	RSM
Br	NBS	CH_2Cl_2, –78 ºC→ r.t.	TMG	N/A	N/A	0%
Br	NBS	CH_2Cl_2, r.t.	Ph_3P=S	0%	~100%	0%
Br	NBS	CH_2Cl_2, r.t.	Ph_3P=S	0%	90%	0%
Hg	$Hg(TFA)_2$	MeOH, r.t.; $NaBH_4$	N/A	0%	0%	~100%
Hg	$Hg(TFA)_2$	MeOH, r.t.; $NaBH_4$	N/A	0%	0%	~100%
I	NIS	CH_2Cl_2, r.t.	Ph_3P=S	22%	0%	0%
I	NIS	CH_2Cl_2, –78 ºC→r.t.	Ph_3P=S	0%	17%	0%

a) $K_2CO_3$was added to the reaction mixture

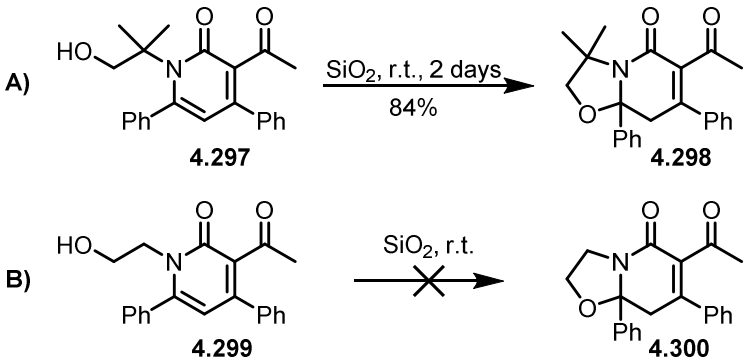
Serendipitously, the ring closure was realized by leaving a sample of isoquinolone **4.282** on the bench top for several days. Isoquinolone **4.282**, which is normally a viscous oil, seemed to solidify over time. Examination of the solid material showed that it contained some of the desired product **4.281**. Purification of the mixture provided **4.281** in 20% yield as a single diastereomer, along with 80% of the isoquinolone **4.282** (Equation 4.20).

Equation 4.20: Successful cyclization of isoquinolone **4.282**



Aside from the syntheses of cervinomycin (see Chapter 3, Sections **3.3.1**, **3.3.2** and **3.3.3**), there is little precedence for the formation of tetrahydro-5H-oxazolo[3,2-b]isoquinolin-5-one and dihydro-5H-oxazolo[3,2-b]isoquinoline-2,5(3H)-dione ring systems. Kelly, Mehta and Rao found that the cyclization of the isoquinolone to the tetrahydro-5H-oxazolo[3,2-b]isoquinolin-5-one ring system was unproductive for the formation of the G-ring, so the success of the transformation of **4.282** to **4.281** is unique. A result from Toda suggests that the substitution on the chain may favor the closed form *via* a Thorpe-Ingold effect (Figure 4.43).[629] The bis-methylated derivative **4.297** was cyclized to **4.298** upon standing, but the unsubstituted derivative **4.299** did not. Fortunately, this has beneficial implications for the synthesis of citreamicin because the bulky nature of the α-methyl serine **4.275** should favor the closed form.

Figure 4.43: Toda's example of Thorpe-Ingold assisted cyclization onto a quinolone

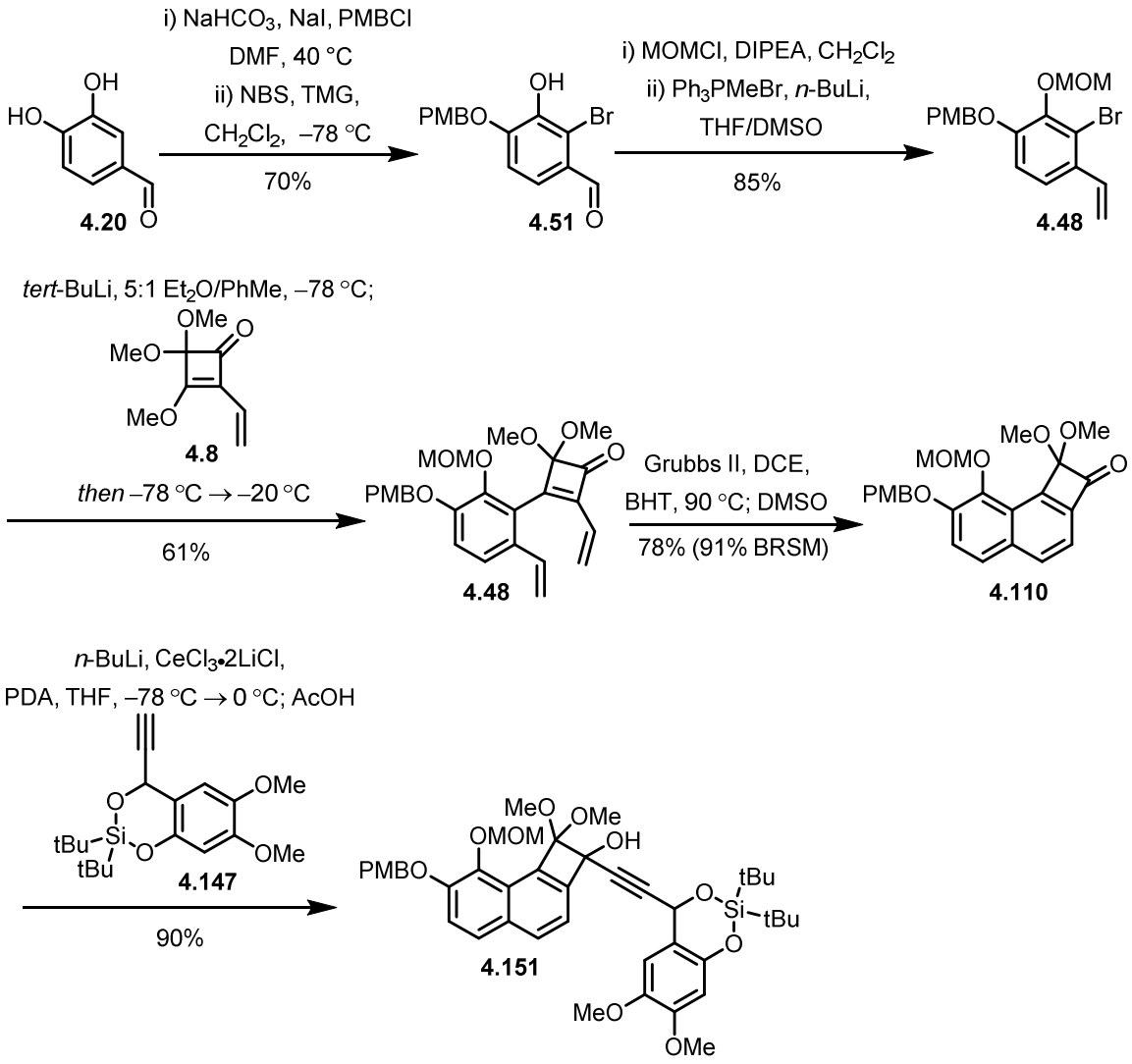


a) Potential example of Thorpe-Ingold assisted cyclization from Tohda.[629] b) Lack of cyclization without gem dimethyl substituents from Tohda.[629]

4.9: Summary

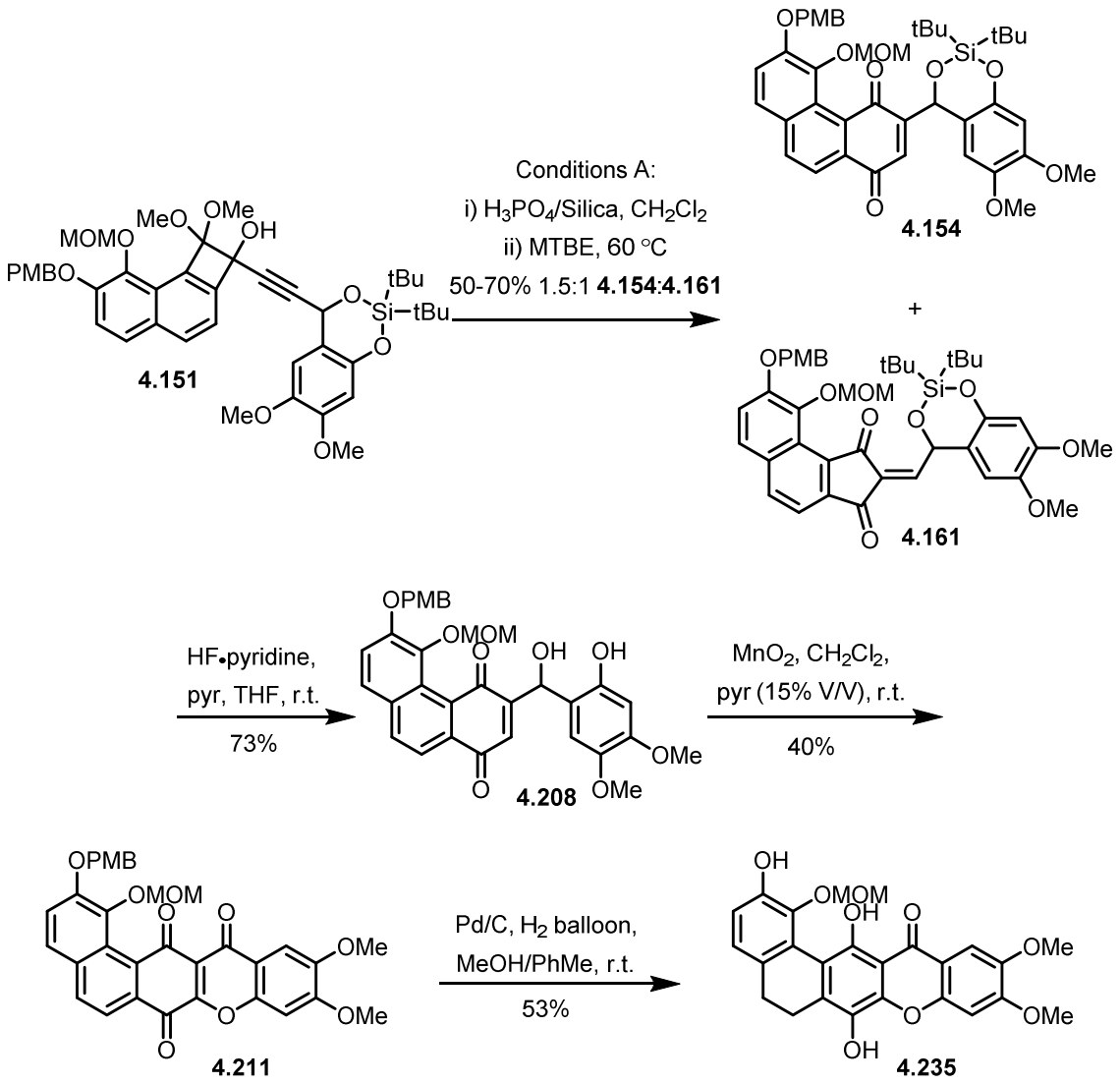
In summary, a short 12-step route to the pentacyclic core of citreamicin was developed. During the course of these efforts, new methodology for the regioselective bromination of PMB protected vanillins utilizing TMG and NBS was developed. Other technical advances include: (1) suppression of Cannizzaro side-reactions during the Wittig olefination of **4.76** by using DMSO as a cosolvent (Scheme 4.30); (2) metal-halogen exchange of styrene **4.48** and the subsequent squarate addition was optimized to avoid competitive *ortho*-lithiation, benzylic deprotonation and electrocyclic ring-opening side reactions (Scheme 4.30); and (3) the acetylide addition of **4.147** to **4.110** was improved with use of $CeCl_3$•2LiCl and PDA as an internal indicator (Scheme 4.30).

Scheme 4.30: Summary of the synthesis of acetylide intermediate **4.151**



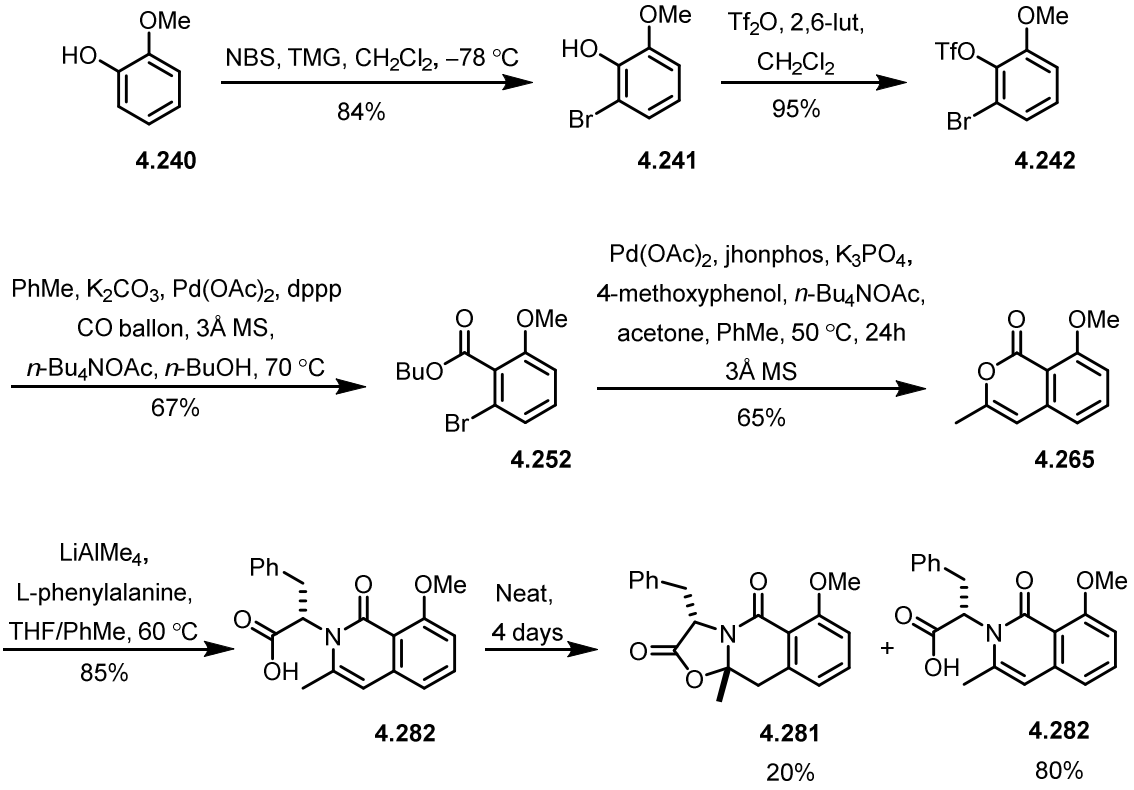
Use of the cyclic silyl protecting group **4.147** as the F-ring coupling partner was critical for the success of acetal hydrolysis and subsequent Moore rearrangement (Scheme 4.31). The Moore rearrangement was found to be a complicated reaction. In *tert*-amyl alcohol, the reaction produced a mixture (1:1) of **4.154** to **4.161**, while use of MTBE as the solvent provided at a mixture (1.5:1) of **4.154** to **4.161**. MnO_2 was found to be the best oxidant for the transformation of **4.208** to **4.211** where the use of polar aprotic solvents or bases provided the best yield of **4.211**. The PMB group was removed *via* hydrogenolysis as opposed to oxidative removal or Ionization *via* Lewis Acids.

Scheme 4.31: Summary of the synthesis of **4.235**



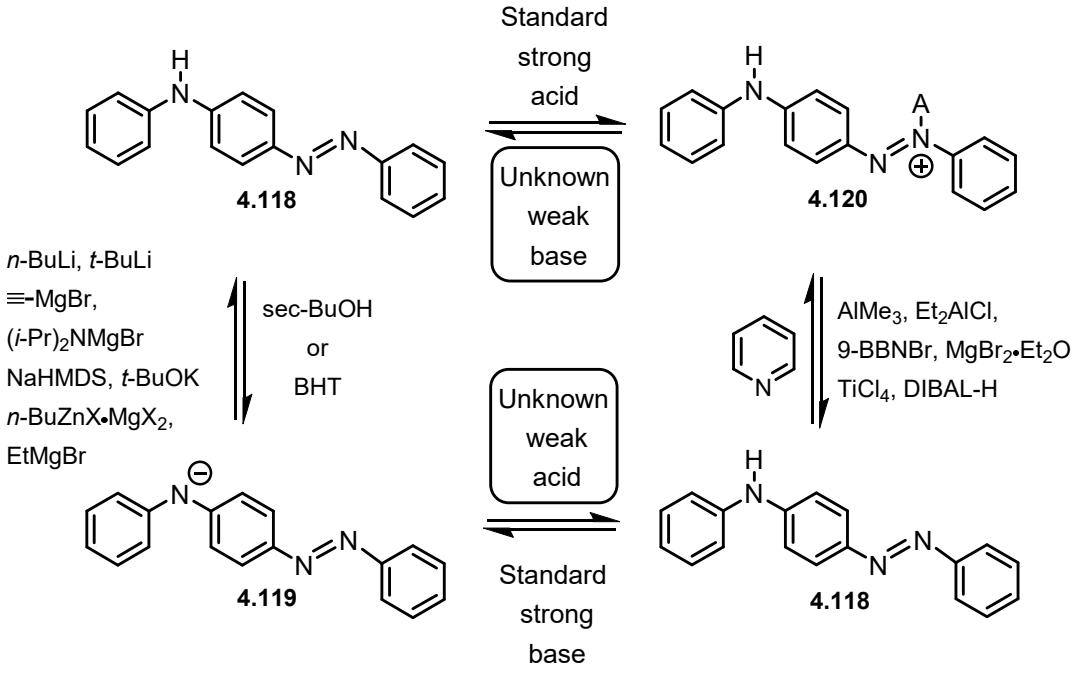
The downstream chemistry or the synthesis of the GA-rings in citreamicin was developed model system (Scheme 4.32). The addition of *n*-Bu_4NOAc was found to be critical for high conversions of both the alkoxycarbonylation of **4.242** and the subsequent coupling with acetone. A new procedure for the direct coupling of amino acids to isocoumarins to provide isoquinolines was developed using an in situ ate-complex generated from $LiAlMe_4$ and the isoquinolone was found to from tricyclic product **4.281** upon standing.

Scheme 4.32: Synthetic summary of the GA-ring fragment



4-(Phenylazo)diphenylamine (PDA) (**4.118**) was found to be a convenient, colorimetric indicator that can be easily used to directly determine the concentrations of a variety of strong carbon- and nitrogen-centered bases in the presence of a number of counterions, including Li, Na, K, Mg, and sometimes Zn (Figure 4.44).[394] PDA can also be used as an indicator to titrate *tert*-BuOK without interference from KOH or other basic impurities. PDA was also shown to be an effective indicator for titrating a number of Lewis acids using pyridine as a standard base as well as determining the concentrations of hydride reducing agents with benzophenone.

Figure 4.44: Summary of titrations with PDA



Chapter 5: Experimental Section

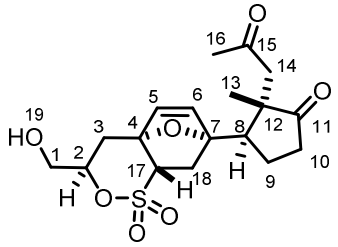
5.1: General Experimental

Unless otherwise noted, solvents and reagents were used without purification. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried by passage through two columns of activated neutral alumina. Methanol (CH_3OH), acetonitrile (CH_3CN), and *N,N*-dimethylformamide (DMF) were dried by passage through two columns of activated molecular sieves. Toluene was dried by sequential passage through a column of activated neutral alumina followed by a column of Q5 reactant.[635] Methylene chloride (CH_2Cl_2), benzene, triethylamine (Et_3N), diisopropylethylamine (DIPEA) and 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU) were distilled from calcium hydride prior to use. Dimethyl sulfoxide (DMSO), and *tert*-amyl alcohol were stored over 4Å molecular sieves for 48 h prior to use. All solvents were determined to contain less than 50 ppm H_2O by Karl Fischer coulometric moisture analysis. All reactions were performed in flame-dried glassware under argon or nitrogen unless otherwise indicated. Volatile solvents were removed under reduced pressure using a Buchi rotary evaporator. Reaction mixtures were degassed by putting the reaction vessel under vacuum until the solvent effervesced, and backfilling with nitrogen (3 x). Infrared (IR) spectra were obtained using a FT IR 1600 spectrophotometer using sodium chloride plates and reported as wave numbers. Low resolution chemical ionization mass spectra were obtained with a TSQ-70 instrument. High resolution measurements were made with a VG Analytical ZAB2-E instrument. Thin layer chromatography (TLC) was performed on glass-backed precoated silica gel plates (0.25 mm thick with 60 F254) and were visualized using one or both of the following manners: UV light (254 nm) and staining with basic aqueous $KMnO_4$ or Cerium ammonium molybdate (CAM). Flash flash chromatography was performed according to Still's procedure using ICN Silitech 32-67 D 60A silica gel.[636] ^1H nuclear magnetic resonance (NMR) spectra were obtained at either 600, 500, or 400 MHz as indicated as solutions in $CDCl_3$ with 0.05% v/v tetramethylsilane (TMS) unless indicated otherwise. ^{13}C-NMR were obtained at either 125, 100

or 75 MHz as shown in the indicated deuterated solvent. Chemical shifts are reported in parts per million (ppm, δ), and referenced to TMS, and coupling constants are reported in Hertz (Hz). Spectral splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; quint, quintuplet; sex, sextet; sept, septuplet; m, multiplet; comp, overlapping multiplets of magnetically nonequivalent protons; br, broad; and app, apparent.

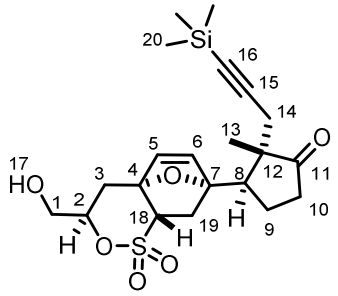
5.2: EXPERIMENTAL PROCEDURES

5.2.1: Cortistatin



2.13

3-(Hydroxymethyl)-1,1-dioxido-3,4,8,8a-tetrahydro-7H-4a,7-epoxybenzo[c][1,2]oxathiin-7-yl)-2-methyl-2-(2-oxopropyl)cyclopentan-1-one (**2.13**). (SB-II-86). A sample of AJS-252Fr2 was crystallized *via* vapor diffusion from EtOAc and pentanes. (see section **5.1** for crystal structure).

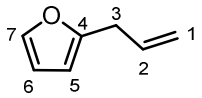


2.14

3-(Hydroxymethyl)-1,1-dioxido-3,4,8,8a-tetrahydro-7H-4a,7-epoxybenzo[c][1,2]oxathiin-7-yl)-2-methyl-2-(3-(trimethylsilyl)prop-2-yn-1-yl)cyclopentan-1-one (**2.14**). (SB-II-243B). Isolated after purification of **2.10** by flash chromatography (20% IPA/hexanes) to provide 4 mg of **2.14**. Crystals were grown by slow evaporation from ethyl

acetate, pentane, and chloroform (see section **5.2** for crystal structure); ^{1}H-NMR (400 MHz) δ 6.57 (d, *J* = 5.6 Hz, 1 H), 6.06 (d, *J* = 5.6 Hz, 1 H), 4.94 (dddd, *J* = 2.0, 2.8, 4.4, 12.4 Hz, 1 H), 4.00 (bd, *J* = 12.8 Hz, 1 H), 3.79 (bd, *J* = 12.8 Hz, 1 H), 3.22 (dd, *J* = 3.2, 8.0 Hz, 1 H), 3.14 (dd, *J* = 6.4, 13.2 Hz, 1H), 2.65 (dd, *J* = 2.4, 16.4 Hz, 1 H), 2.62 (dd, *J* = 3.2, 12.4 Hz, 1 H), 2.48 (m, 1 H), 2.44 (m, 1 H), 2.33-2.15 (comp, 4 H), 2.01 (dd, *J* = 8.0, 12.4 Hz, 1 H), 2.00 (t, *J* = 2.8 Hz, 1 H), 1.92 (ddd, *J* = 7.6, 11.6, 23.2 Hz, 1 H), 1.64 (bs, 1 H), 1.02 (s, 3 H)

NMR assignments: ^{1}H-NMR (400 MHz) δ 6.57 (d, *J* = 5.6 Hz, 1 H, C6-H), 6.06 (d, *J* = 5.6 Hz, 1 H, C5-H), 4.94 (dddd, *J* = 2.0, 2.8, 4.4, 12.4 Hz, 1 H, C2-H), 4.00 (bd, *J* = 12.8 Hz, 1 H, C1-H), 3.79 (bd, *J* = 12.8 Hz, 1 H, C1-H), 3.22 (dd, *J* = 3.2, 8.0 Hz, 1 H, C18-H), 3.14 (dd, *J* = 6.4, 13.2 Hz, 1H, C8-H), 2.65 (dd, *J* = 2.4, 16.4 Hz, 1 H, C10-H), 2.62 (dd, *J* = 3.2, 12.4 Hz, 1 H, C3-H), 2.48 (m, 1 H, C10-H), 2.44 (m, 1 H, C19-H), 2.33-2.15 (comp, 4 H, C3-H, C9-H, C14-H), 2.01 (dd, *J* = 8.0, 12.4 Hz, 1 H, C19-H), 2.00 (t, *J* = 2.8 Hz, 1 H, C16-H), 1.92 (ddd, *J* = 7.6, 11.6, 23.2 Hz, 1 H, C9-H), 1.64 (bs, 1 H, O17-H), 1.02 (s, 3 H, C13-H).

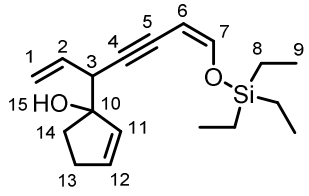


2.32

2-Allylfuran (2.32). (SB-IV-175). Furan **2.1** (freshly distilled from KOH, 10.4 mL, 144 mmol) was dissolved in anhydrous THF (100 mL), cooled to –78 °C, and degassed. A solution of *n*-BuLi (2.18 M, 72.5 mL, 158.0 mmol) in hexanes was added *via* a pressure equalizing addition funnel, and the reaction mixture was warmed to 0 °C and stirred for 2 h. The mixture was transferred *via* cannula to a flask containing freshly fused $ZnCl_2$ (21.5 g, 158.1 mmol) and CuCN (643 mg, 7.2 mmol) in anhydrous THF (140 mL) at 0 °C, and the mixture was stirred for 10 min. Freshly distilled allylbromide (21.2 g, 15.2 mL, 176 mmol) was then added over 15 min, and the mixture was stirred for an additional 15 min. Cold aqueous 1 M HCl (100 mL) was added and the mixture was extracted with Et_2O (2 x 100 mL). The organic layer was washed with cold

aqueous 1 M HCl (1 x 100 mL), concentrated NH_4OH (1 x 100 mL), and H_2O (1 x 100 mL). The organic layer was dried (Na_2SO_4), and purified by fractional distillation using a heated jacketed column (7.5 mm x 13 mm) packed with glass helices. The temperature of both the heating bath and column jacket was slowly increased (bath: 40 °C → 100 °C, jacket: 40 °C → 80 °C) and the pressure was slowly decreaced (760 torr → 40 torr) to isolate two fractions of **2.32** as a solution in THF/hexanes; Fraction 1: (bath temperature: 100 °C, jacket temperature: 80 °C, pressure: 450 torr → 300 torr), Fraction 2: (bath temperature: 100 °C, jacket temperature: 80 °C, 300 torr → 40 torr). The concentration of **2.32** in both fractions was determined by ^{1}H-NMR using a known amount of mesitylene as an internal standard; Fraction 1: (2.53 M, 12.0 mL, 30.36 mmol, 21%), Fraction 2: (7.06 M, 13.7 mL, 96.72 mmol, 67%) (88% combined yield); ^{1}H-NMR (500 MHz) δ 7.31 (m, 1 H), 6.28 (ddd, *J* = 0.5, 2.5, 4 Hz, 1 H) 6.02 (m, 1 H) 5.98-5.88 (m, 1 H) 5.17-5.09 (comp, 2 H) 3.39 (dd, *J* = 1.5, 8.5 Hz, 2 H); ^{13}C-NMR (500 MHz) δ 153.8, 141.2, 133.9, 116.8, 110.2, 105.4, 32.6; HRMS (CI) *m/z* calc for $C_7H_7O^+$ (M–H), 107.0497; found, 107.0496.

NMR assignments: ^{1}H-NMR (500 MHz) δ 7.31 (m, 1 H, C-7H), 6.28 (ddd, *J* = 0.5, 2.5, 4 Hz, 1 H, C6-H) 6.02 (m, 1 H, C5-H) 5.98-5.88 (m, 1 H, C2-H) 5.17-5.09 (comp, 2 H, C1-H) 3.39 (dd, *J* = 1.5, 8.5 Hz, 2 H, C3-H); ^{13}C-NMR (500 MHz) δ 153.8 (C4), 141.2 (C7), 133.9 (C2), 116.8 C1), 110.2 (C6), 105.4 (C5), 32.6 (C3).



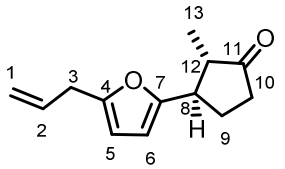
2.37

(*Z*)-1-(7-((Triethylsilyl)oxy)hepta-1,6-dien-4-yn-3-yl)cyclopent-2-en-1-ol (2.37). (SB-I-237B). A solution of anhydrous 2-allylfuran (**2.32**) in THF (1.8 M, 1.80 mL, 3.24 mmol) was added to a solution of *n*-BuLi in hexanes (1.86 M, 1.74 mL, 3.24 mmol) in THF (10 mL) at –78 °C. The mixture was stirred for 30 min, whereupon it was transferred *via* cannula to a flask

containing a solution of freshly fused $ZnCl_2$ (0.54 g, 4.05 mmol) in THF (20 mL) at –78 °C. The mixture was stirred for an additional 30 min before transferring *via* cannula to a flask containing a solution of cyclopentenone (0.13 g, 0.13 mL, 1.62 mmol) and TESCl (0.36 g, 0.41 mL, 2.43 mmol) in THF (10 mL) at –78 °C. The mixture was stirred for 5 h at –78 °C and warmed to room temperature over 16 h, whereupon H_2O (1 x 10 mL) was added. The reaction mixture was extracted with Et_2O (2 x 10 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure. The crude material was purified by flash chromatography eluting with a gradient of Et_2O/hexanes (1:20 → 3:20) to provide 119 mg (30%) of **2.37** as a clear oil: ^{1}H-NMR (500 MHz) δ 6.51 (d, *J* = 4.2 Hz, 1H), 6.50 (d, *J* = 4.1 Hz, 1 H), 5.93 (ddd, *J* = 2.3, 2.3, 5.6 Hz, 1 H), 5.90 (ddd, *J* = 2.3, 2.3, 5.7 Hz, 1 H), 5.83 (ddd, *J* = 5.8, 5.8, 10.1 Hz, 1 H), 5.79 (ddd, *J* = 7.0, 7.0, 12.7 Hz, 1 H), 5.75-5.73 (comp, 2 H), 5.44 (dt, *J* = 1.6, 17.0 Hz, 1 H), 5.35 (dt, *J* = 1.5, 17.0 Hz, 1 H), 5.17 (dt, *J* = 1.6, 9.9 Hz, 1 H), 5.15 (dt, *J* = 1.6, 9.3 Hz, 1 H), 4.63 (dd, *J* = 1.8, 5.9 Hz, 1 H), 4.62 (dd, *J* = 1.9, 5.9 Hz, 1 H), 3.45 (dd, *J* = 1.4, 6.0 Hz, 1 H), 3.41 (dd, *J* = 1.0, 7.1 Hz, 1 H), 2.51-2.44 (comp, 2H), 2.29-2.22 (comp, 2 H), 2.21-2.12 (comp, 2H), 1.86 (ddd, *J* = 4.6, 8.5, 13.4 Hz, 1 H), 1.80 (ddd, *J* = 4.4, 8.8, 13.5 Hz, 1H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.94 (t, *J* = 7.9 Hz, 9 H), 0.67 (q, *J* = 8.0 Hz, 6 H), 0.56 (q, *J* = 8.0 Hz, 6 H); ^{13}C-NMR (125 MHz) δ 149.7, 135.1, 134.7, 134.2, 134.1, 133.9, 133.8, 117.85, 117.80, 90.5, 90.2, 89.9, 87.10, 87.07, 80.2, 80.0, 47.8, 47.5, 35.5, 34.8, 31.7, 31.5, 6.5, 6.3, 5.8, 4.4; IR (film) 3400 (O-H), 2957 (C-H), 2914 (C-H), 2879 (C-H), 1621, 1262, 1098, 1006; LCMS (ESI+APCI); found, 287.4 (M–H_2O).

NMR assignments: ^{1}H-NMR (500 MHz) δ 6.51 (d, *J* = 4.2 Hz, 1H, C7-H), 6.50 (d, *J* = 4.1 Hz, 1 H, C7-H), 5.93 (ddd, *J* = 2.3, 2.3, 5.6 Hz, 1 H, C11-H), 5.90 (ddd, *J* = 2.3, 2.3, 5.7 Hz, 1 H, C11-H), 5.83 (ddd, *J* = 5.8, 5.8, 10.1 Hz, 1 H, C2-H), 5.79 (ddd, *J* = 7.0, 7.0, 12.7 Hz, 1 H, C2-H), 5.75-5.73 (comp, 2 H, C12-H), 5.44 (dt, *J* = 1.6, 17.0 Hz, 1 H, C1-H), 5.35 (dt, *J* = 1.5, 17.0 Hz, 1 H, C1-H), 5.17 (dt, *J* = 1.6, 9.9 Hz, 1 H, C1-H), 5.15 (dt, *J* = 1.6, 9.3 Hz, 1 H, C1-H), 4.63 (dd, *J* = 1.8, 5.9 Hz, 1 H, C6-H), 4.62 (dd, *J* = 1.9, 5.9 Hz, 1 H, C6-H), 3.45 (dd, *J* = 1.4, 6.0 Hz, 1 H, C3-H), 3.41 (dd, *J* = 1.0, 7.1 Hz, 1 H, C3-H), 2.51-2.44 (comp, 2H, C13-H), 2.29-2.22

(comp, 2 H, C13-H), 2.21-2.12 (comp, 2H, C14-H), 1.86 (ddd, *J* = 4.6, 8.5, 13.4 Hz, 1 H, C14-H), 1.80 (ddd, *J* = 4.4, 8.8, 13.5 Hz, 1H, C14-H), 0.97 (t, *J* = 8.0 Hz, 9H, C9-H), 0.94 (t, *J* = 7.9 Hz, 9 H, C9-H), 0.67 (q, *J* = 8.0 Hz, 6 H, C8-H), 0.56 (q, *J* = 8.0 Hz, 6 H, C8-H); ^{13}C-NMR (125 MHz) δ 149.7 (C7), 135.1 (C11), 134.7 (C11), 134.2 (C2), 134.1 (C2), 133.9 (C12), 133.8 (C12), 117.85 (C1), 117.80 (C1), 90.5 (C4), 90.2 (C4), 89.9 (C6), 87.10 (C10), 87.07 (C10), 80.2 (C5), 80.0 (C5), 47.8 (C3), 47.5 (C3), 35.5 (C14), 34.8 (C14), 31.7 (C13), 31.5 (C13), 6.5 (C9), 6.3 (C9), 5.8 (C8), 4.4 (C8).



2.6

3-(5-Allylfuran-2-yl)-2-methylcyclopentanone (**2.6**). **From TMSI:** (SB-III-98). 2-Methyl-2-cyclopenten-1-one (**2.2**) (1.02 mL, 10.4 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL) and cooled to –78 °C. Freshly distilled TMSI (2.28 g, 1.62 mL, 11.4 mmol) was added and the mixture was stirred for 45 min. A solution of 2-allylfuran (**2.32**) in THF (9.35 M, 1.67 mL, 15.6 mmol) and 2-methyl-2-butene (1.47 g, 2.2 mL, 20.8 mmol) was added, and the reaction was stirred for 6 h at –78 °C. Triethylamine (Et_3N) (2.9 mL, 20.8 mmol) was added, followed by MeOH (20 mL), and the reaction mixture was warmed to room temperature and stirred for an additional 16 h before concentrating under reduced pressure. The crude residue was purified by flash chromatography eluting with a gradient of Et_2O/ hexanes (1:20 → 1:5) to provide 1.98 g (93%) of **2.6** as a mixture (7.5:1 Trans:Cis) of diastereomers (clear oil).

From TMSOTf and NaI: (SB-V-52). Neat TMSOTf (1.03 mL, 5.72 mmol) was added to a solution of NaI (935 mg, 6.24 mmol) in MeCN (10 mL) at room temperature. The mixture

was stirred for 5 min before CH_2Cl_2 (15 mL) was added and the mixture was cooled to –78 °C. Methyl-2-cyclopenten-1-one (**2.2**) (500 mg, 511 µL, 10.4 mmol) was added and the mixture was stirred for 30 min before adding a solution of 2-allylfuran (**2.32**) in THF (7.1 M, 1.1 mL, 7.8 mmol) and 2-methyl-2-butene (0.73 g, 1.1 mL, 10.4 mmol). The reaction was stirred for 2 h at –78 °C before adding Et_3N (1.05 g, 1.45 mL, 10.4 mmol) and MeOH (2.1 mL) and warming to room temperature. The reaction was concentrated under reduced pressure and the crude oil was purified by flash chromatography eluting with a gradient of Et_2O/ hexanes (1:20 → 1:5) to provide 887 mg (83%) of **2.6** as a mixture (7.5:1 Trans:Cis) of diastereomers (clear oil).

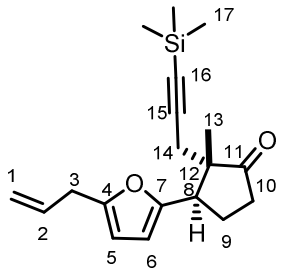
Trans isomer; ^{1}H-NMR (400 MHz) δ 6.00 (d, *J* = 3.2 Hz, 1 H), 5.95 (d, *J* = 2.8 Hz, 1 H), 5.93 (dddd, *J* = 6.4, 6.4, 10.0, 16.8 Hz, 1H), 5.13 (dddd, *J* = 1.6, 1.6, 1.6, 16.8 Hz, 1 H), 5.11 (dq, *J* = 1.6, 9.9 Hz, 1 H), 3.37 (dd, *J* = 1.2, 6.4 Hz, 2 H), 2.88 (td, *J* = 6.0, 11.6 Hz, 1 H), 2.49 (m, 1H), 2.35-2.17 (comp, 3 H), 2.00 (dddd, *J* = 7.2, 9.6, 10.8, 10.8 Hz, 1 H), 1.13 (d, *J* = 7.2 Hz, 3 H); ^{13}C-NMR (100 MHz) δ 219.4, 154.8, 152.8, 133.9, 116.8, 105.9, 105.5, 49.4, 43.6, 37.2, 32.6, 26.6, 12.8.

NMR assignments: ^{1}H-NMR (400 MHz) δ 6.00 (d, *J* = 3.2 Hz, 1 H, C6-H), 5.95 (d, *J* = 2.8 Hz, 1 H, C5-H), 5.93 (dddd, *J* = 6.4, 6.4, 10.0, 16.8 Hz, 1H, C2-H), 5.13 (dddd, *J* = 1.6, 1.6, 1.6, 16.8 Hz, 1 H, C1-H), 5.11 (dq, *J* = 1.6, 9.9 Hz, 1 H, C1-H), 3.37 (dd, *J* = 1.2, 6.4 Hz, 2 H, C3-H), 2.88 (td, *J* = 6.0, 11.6 Hz, 1 H, C8-H), 2.49 (m, 1H, C10-H), 2.35-2.17 (comp, 3 H, C9-H, C10-H), 2.00 (dddd, *J* = 7.2, 9.6, 10.8, 10.8 Hz, 1 H, C12-H), 1.13 (d, *J* = 7.2 Hz, 3 H, C13-H); ^{13}C-NMR (100 MHz) δ 219.4 (C11), 154.2 (C7), 152.9 (C4), 133.9 (C2), 116.7 (C1), 106.8 (C6), 105.7 (C5), 47.6 (C12), 39.8 (C8), 36.1 (C10), 32.5 (C3), 25.5 (C9), 10.7 (C13).

Cis isomer: (SB-II-250B); ^{1}H-NMR (400 MHz) δ 6.00 (d, *J* = 3.2 Hz, 1 H), 5.95 (d, *J* = 2.8 Hz, 1 H), 5.89 (dddd, *J* = 6.4, 6.4, 10.4, 16.8 Hz, 1H), 5.13-5.07 (comp, 2 H), 3.31 (dd, *J* = 1.2, 6.8 Hz, 2 H), 2.52-1.95 (comp, 6 H), 0.86 (d, *J* = 7.2 Hz, 3 H); ^{13}C-NMR (100 MHz) δ 220.2, 154.2, 152.9, 133.9, 116.7, 106.8, 105.7, 47.6, 39.8, 36.1, 32.5, 25.5, 10.7.

NMR assignments: ^{1}H-NMR (400 MHz) δ 6.00 (d, *J* = 3.2 Hz, 1 H, C6-H), 5.95 (d, *J* = 2.8 Hz, 1 H, C5-H), 5.89 (dddd, *J* = 6.4, 6.4, 10.4, 16.8 Hz, 1H, C2-H), 5.13-5.07 (comp, 2 H,

C1-H), 3.31 (dd, *J* = 1.2, 6.8 Hz, 2 H, C3-H), 2.52-1.95 (comp, 6 H, C8-H, C9-H, C10-H, C12-H), 0.86 (d, *J* = 7.2 Hz, 3 H, C13-H); ^{13}C-NMR (100 MHz) δ 220.2 (C11), 154.8 (C7), 152.8 (C4), 133.9 (C2), 116.8 (C1), 105.9 (C6), 105.5 (C5), 49.4 (C12), 43.8 (C8), 37.2 (C10), 32.6 (C3), 26.6 (C9), 12.8 (C13).

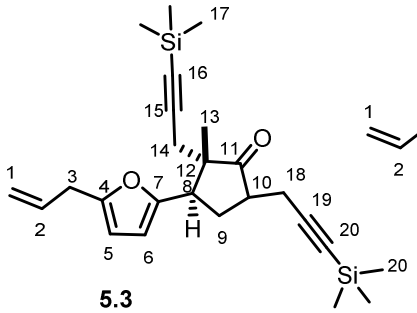


2.7

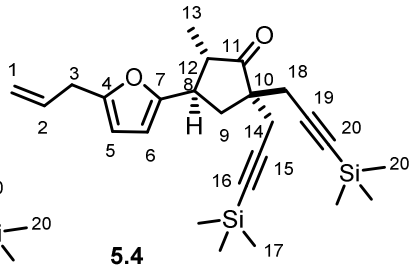
3-(5-Allylfuran-2-yl)-2-methyl-2-(3-(trimethylsilyl)prop-2-ynyl)cyclopentanone (**2.7**). (SB-III-131). Triphenylmethane (30 mg, 12 mmol) and HMDS (376 mg, 488 µL, 2.32 mmol) were dissolved in anhydrous THF (7.5 mL) and cooled to 0 °C. *n*-BuLi was added until the solution turned a red color that persisted for at least one minute. Ketone **2.6** (500 mg, 2.44 mmol) was added, followed by DMPU (freshly distilled from CaH_2, 7.5 mL) and the solution was stirred for 4 h at 0 °C. 3-Bromoprop-1-ynyl)trimethylsilane (1.7 g, 7.32 mmol)[630] was added at 0 °C and stirred for an additional 1 h before adding a 25% (w/v) aqueous sodium bisulfate solution (10 mL). The mixture was extracted with EtOAc (3 x 20 mL), and the combined organic extracts were washed with 13% (w/v) aqueous brine solution (4 x 10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of Et_2O/ hexanes (1:20 → 1:5) to provide 603 mg (79%) of **2.7** as a pale yellow oil: ^{1}H-NMR (400 MHz) δ 6.02 (d, *J* = 3.2 Hz, 1 H), 5.94 (d, *J* = 3.2 Hz, 1 H), 5.90 (dddd, *J* = 6.8, 6.8, 10.4, 16.8 Hz, 1 H), 5.11 (dddd, *J* = 1.6, 1.6, 1.6, 17.2 Hz, 1 H), 5.09 (dddd, *J* = 1.2, 1.2, 1.2, 9.2 Hz, 1 H) 3.71 (dd, *J* = 6.0, 11.2 Hz, 1 H) 3.35 (d, *J* = 7.2, Hz, 2 H) 2.56 (d, *J* = 16.4 Hz,

1 H) 2.52 (m, 1 H), 2.36 (d, *J* = 16.8 Hz, 1 H), 2.41-2.18 (comp, 3 H), 0.70 (s, 3 H), 0.12 (s, 9 H); ^{13}C-NMR (100 MHz) δ 219.8, 153.43, 153.12, 134.1, 116.8, 107.3, 106.0, 103.7, 87.4, 52.4, 42.4, 37.8, 32.7, 27.6, 22.9, 18.5, 0.2.

NMR assignments: ^{1}H-NMR (400 MHz) δ 6.02 (d, *J* = 3.2 Hz, 1 H, C6-H), 5.94 (d, *J* = 3.2 Hz, 1 H, C5-H), 5.90 (dddd, *J* = 6.8, 6.8, 10.4, 16.8 Hz, 1 H, C2-H), 5.11 (dddd, *J* = 1.6, 1.6, 1.6, 17.2 Hz, 1 H, C1-H), 5.09 (dddd, *J* = 1.2, 1.2, 1.2, 9.2 Hz, 1 H, C1-H) 3.71 (dd, *J* = 6.0, 11.2 Hz, 1 H, C8-H) 3.35 (d, *J* = 7.2, Hz, 2 H, C3-H) 2.56 (d, *J* = 16.4 Hz, 1 H, C14-H) 2.52 (m, 1 H, C10-H), 2.36 (d, *J* = 16.8 Hz, 1 H, C14-H), 2.41-2.18 (comp, 3 H, C9-H, C10-H), 0.70 (s, 3 H, C13-H), 0.12 (s, 9 H, C17-H); ^{13}C-NMR (100 MHz) δ 219.8 (C11), 153.43 (C7), 153.12 (C4), 134.1 (C2), 116.8 (C1), 107.3 (C6), 106.0 (C5), 103.7 (C16), 87.4 (C15), 52.4 (C12), 42.4 (C8), 37.8 (C14), 32.7 (C3), 27.6 (C10), 22.9 (C9), 18.5 (C13), 0.2 (C17).



5.3

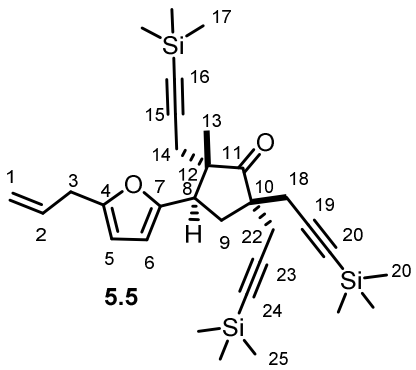


5.4

3-(5-Allylfuran-2-yl)-2-methyl-2,5-bis(3-(trimethylsilyl)prop-2-yn-1-yl)cyclopentan-1-one and **4-(5-Allylfuran-2-yl)-5-methyl-2,2-bis(3-(trimethylsilyl)prop-2-yn-1-yl)cyclopentan-1-one**. (SB-III-93D). Isolated from the reaction of ketone **2.6** with (3-bromoprop-1-ynyl)trimethylsilane. Isolated as a mixture as an 0.8:1 ratio of inseparable isomers *via* flash chromatography, eluting with a gradient of PhMe/hexanes (2:5 → 4:5) to provide 39 mg (4%) of the named compounds as a clear oil: ^{1}H-NMR (400 MHz) δ 6.06 (d, *J* = 3.2 Hz, 0.8 H), 6.03 (d, *J* = 2.8 Hz, 1 H), 5.99-5.85 (comp, 3.6 H), 5.15-5.09 (comp, 3.6 H), 3.70 (m, 1 H), 3.36 (m, 3.6 H), 3.16 (m, 0.8H), 2.63-2.16 (comp, 12.6 H), 1.11 (d, *J* = 6.8 Hz, 2.4 H), 0.67 (s, 3

H), 0.15 (s, 9 H), 0.14 (s, 9 H), 0.13 (s, 7.2 H), 0.12 (s, 7.2 H); ^{13}C-NMR (100 MHz) δ 219.7, 219.4, 218.2, 154.7, 153.9, 153.22, 153.18, 153.14, 134.10, 134.06, 116.95, 116.87, 107.5, 107.4, 106.13, 106.06, 106.0, 104.3, 104.1, 103.72, 103.67, 103.0, 102.7, 88.1, 87.7, 87.5, 87.4, 86.7, 86.3, 53.3, 52.4, 51.6, 50.4, 48.4, 45.3, 40.8, 40.3, 36.1, 32.83, 32.27, 28.45, 28.38, 28.1, 27.9, 27.6, 20.5, 19.9, 18.8, 18.1, 12.2, 0.3, 0.1, 0.2, 0.14, 0.09; HRMS (CI) *m/z* found for $C_{25}H_{37}O_2Si_2^+$ (M+H), 425.

NMR assignments: ^{1}H-NMR (400 MHz) (10,10 dialkylated) δ 6.03 (d, *J* = 2.8 Hz, 1 H, C6-H), 5.99-5.85 (comp, 3.6 H, C2-H, C5-H), 5.15-5.09 (comp, 3.6 H, C1-H), 3.70 (m, 1 H, C8-H), 3.36 (m, 3.6 H, C3-H), 2.63-2.16 (comp, 12.6 H, C9-H, C10-H, C14-H, C18-H), 0.67 (s, 3 H, C13-H), 0.15 (s, 9 H, C17-H or C21-H), 0.14 (s, 9 H, C17-H or C21-H); (10,12 dialkylated) 6.06 (d, *J* = 3.2 Hz, 0.8 H, C6-H), 5.99-5.85 (comp, 3.6 H, C2-H, C5-H), 5.15-5.09 (comp, 3.6 H, C1-H), 3.36 (m, 3.6 H, C3-H), 3.16 (m, 0.8H, C8-H), 2.63-2.16 (comp, 12.6 H, C9-H, C10-H, C14-H, C18-H), 1.11 (d, *J* = 6.8 Hz, 2.4 H, C13-H), 0.13 (s, 7.2 H, C17-H or C21-H), 0.12 (s, 7.2 H, C17-H or C21-H); ^{13}C-NMR (100 MHz) (10,10 dialkylated, major diastereomer) δ 219.4 (C11), 153.9 (C7), 153.22 (C4), 134.10 (C2), 116.95 (C1), 107.4 (C6), 106.06 (C5), 103.72 (C16), 103.0 (C20), 87.7 (C19), 87.5 (C15), 51.6 (C12), 50.4 (C10), 48.4 (C8), 32.27 (C3), 27.6 (C18), 19.9 (C9), 18.1 (C13), 0.3 (C17), 0.2 (C21), (10,10 dialkylated, minor diastereomer) δ 219.7 (C11), 153.9 (C7), 153.18 (C4), 134.10 (C2), 116.95 (C1), 107.5 (C6), 106.13 (C5), 104.3 (C20), 103.67 (C16), 87.4 (C15), 86.3 (C19), 53.3 (C12), 45.3 (C10), 40.3 (C8), 32.27 (C3), 28.38 (C14), 19.9 (C9), 18.8 (C13), 0.3 (C17), 0.2 (C21), (10,12 dialkylated) δ 218.2 (C11), 154.7 (C7), 153.14 (C4), 134.06 (C2), 116.87 (C1), 107.4 (C6),106.0 (C5), 104.1 (C16), 102.7 (C20), 88.1 (C15), 86.7 (C19), 52.4 (C10), 48.4 (C12), 36.1 (C8), 32.83 (C3), 28.1 (C14), 27.9 (C18), 20.5 (C9), 12.2 (C13), 0.14 (C17), 0.09 (C21).

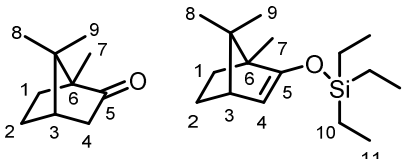


5.5

3-(5-Allylfuran-2-yl)-2-methyl-2,5,5-tris(3-(trimethylsilyl)prop-2-yn-1-yl)cyclopentan-1-one. (SB-III-93C). By-product isolated from the reaction of ketone **2.6** with (3-bromoprop-1-ynyl)trimethylsilane. Purified *via* flash chromatography, eluting with a gradient of PhMe/hexanes (2:5 → 4:5) to provide 41 mg (3%) of the named compound as a clear oil: ^{1}H-NMR (400 MHz) δ 6.09 (d, *J* = 3.2 Hz, 1 H), 5.97 (d, *J* = 2.8 Hz, 1 H), 5.93 (dddd, *J* = 6.8, 6.8, 10.4, 16.8 Hz, 1 H), 5.13 (dddd, *J* = 1.6, 1.6, 1.6, 16.4 Hz, 1 H), 5.109 (dddd, *J* = 1.2, 1.2, 1.2, 10.0 Hz, 1 H), 3.77 (dd, *J* = 6.4, 12.8 Hz, 1H), 3.37 (d, *J* = 7.2, Hz, 2 H), 2.71 (d, *J* = 16.8 Hz, 1 H), 2.70 (d, *J* = 17.2 Hz, 1 H), 2.64 (d, *J* = 16.8 Hz, 1 H), 2.61 (t, *J* = 13.2 Hz, 1 H), 2.61 (d, *J* = 16.8 Hz, 1 H), 2.40 (d, *J* = 16.8 Hz, 1 H), 2.34 (dd, *J* = 6.4, 13.2 Hz, 1 H), 2.05 (d, *J* = 17.6 Hz, 1 H), 0.74 (s, 3 H), 0.15 (s, 9 H), 0.13 (s, 9 H), 0.11 (s, 9 H); ^{13}C-NMR (100 MHz) δ 219.9, 153.3, 153.0, 134.1, 116.9, 107.5, 106.1, 104.5, 104.2, 101.5, 88.4, 87.6, 87.4, 53.4, 51.8, 38.6, 32.8, 30.6, 27.7, 26.0, 25.1, 18.2, 0.2, 0.11, 0.06; HRMS (CI) *m/z* found for $C_{31}H_{47}O_2Si_3^+$ (M+H), 534.

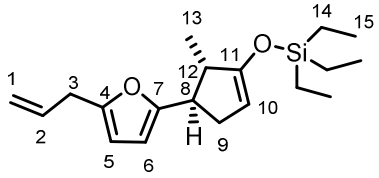
NMR assignments: ^{1}H-NMR (400 MHz) δ 6.09 (d, *J* = 3.2 Hz, 1 H, C6-H), 5.97 (d, *J* = 2.8 Hz, 1 H, C5-H), 5.93 (dddd, *J* = 6.8, 6.8, 10.4, 16.8 Hz, 1 H, C2-H), 5.13 (dddd, *J* = 1.6, 1.6, 1.6, 16.4 Hz, 1 H, C1-H), 5.109 (dddd, *J* = 1.2, 1.2, 1.2, 10.0 Hz, 1 H, C1-H), 3.77 (dd, *J* = 6.4, 12.8 Hz, 1H, C8-H), 3.37 (d, *J* = 7.2, Hz, 2 H, C3-H), 2.71 (d, *J* = 16.8 Hz, 1 H, C18-H), 2.70 (d, *J* = 17.2 Hz, 1 H, C22-H), 2.64 (d, *J* = 16.8 Hz, 1 H, C18-H), 2.61 (t, *J* = 13.2 Hz, 1 H, C9-H), 2.61 (d, *J* = 16.8 Hz, 1 H, C14-H), 2.40 (d, *J* = 16.8 Hz, 1 H, C14-H), 2.34 (dd, *J* = 6.4, 13.2 Hz, 1 H, C9-H), 2.05 (d, *J* = 17.6 Hz, 1 H, C22-H), 0.74 (s, 3 H, C13-H), 0.15 (s, 9 H, C17-H, C21-H or C25-H), 0.13 (s, 9 H, C17-H, C21-H or C25-H), 0.11 (s, 9 H, C17-H, C21-H or C25-H); ^{13}C-

NMR (100 MHz) δ 219.9 (C11), 153.3 (C7), 153.0 (C4), 134.1 (C2), 116.9 (C1), 107.5 (C6), 106.1 (C5), 104.5 (C16), 104.2 (C24), 101.5 (C20), 88.4 (C15), 87.6 (C23), 87.4 (C19), 53.4 (C12), 51.8 (C10), 38.6 (C8), 32.8 (C3), 30.6 (C14), 27.7 (C22), 26.0 (C18), 25.1 (C9), 18.2 (C13), 0.2 (C17), 0.11 (C25), 0.06 (C21).



2.73 **2.74**

Procedure to assay water content in $MnCl_2$•2LiCl solution using camphor (2.73): (SB-IV-71,72); Triphenylmethane (2 mg, 0.008 mmol) and HMDS (28 µL, 21 mg, 0.131 mmol) were dissolved in anhydrous THF (0.25 mL) and cooled to 0 °C. *n*-BuLi (1.56 M) was added until the solution turned a red color that persisted for at least one minute. A solution of camphor **2.73** (20 mg, 0.131 mmol) in anhydrous THF (0.25 mL) was added and the solution was stirred for 30 min, followed by adding a solution of $MnCl_2$•2LiCl (0.32 mL, 0.408 M, 0.131 mmol). The solution was stirred for 5 min before adding TESCl (freshly distilled from CaH_2, 44 mg, 66 µL, 0.293 mmol). The mixture was stirred for an additional 30 min, whereupon the solvent was removed reduced pressure. The residue was re-dissolved in pentanes, filtered through Celite, concentrated under reduced pressure, and the residue was analyzed by ^{1}H-NMR (400 MHz). Ratio of the C3 proton in camphor **2.73** 2.08 (t, *J* = 4.4 Hz, 1 H) to the C3 proton in the silyl enol ether **2.74** 2.17 (t, *J* = 3.6 Hz, 0.25 H) was 1:0.25, indicating a proton content of 25 mol %.

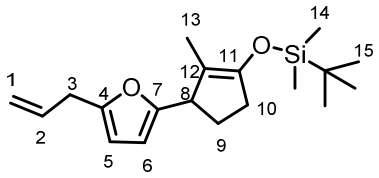


2.76

4-(5-Allylfuran-2-yl)-5-methylcyclopent-1-en-1-yl)oxy)triethylsilane (**2.76**). (SB-III-295). Triphenylmethane (3 mg, 0.007 mmol) was dissolved in anhydrous THF (0.5 mL) and cooled to 0 °C. Hexamethyldisilazide (HMDS) (24 mg, 31 µL, 0.146 mmol) was added, followed by *n*-BuLi (ca. 1.56 M, 93 µL, 0.146 mmol) until the reaction mixture turned red. Ketone **2.6** (30

mg, 0.146 mmol) was added and the reaction mixture was stirred for 30 min before adding TESCl (freshly distilled from CaH_2, 26 mg, 29 μL, 0.175 mmol) and stirring for an additional 30 min. The reaction mixture was diluted with pentanes and filtered through Celite. The organic was concentrated to an oil to get **2.76**: ^{1}H-NMR (400 MHz) δ 5.93-5.84 (comp, 3 H), 5.10-5.02 (comp, 2 H), 4.51 (dd, *J* = 2.0, 4.0 Hz, 1 H), 3.30 (d, *J* = 6.4 Hz, 2 H), 2.86 (q, *J* = 8.4 Hz, 1 H), 2.47 (ddt, *J* = 2.0, 8.8, 14.8 Hz, 1 H), 2.31 (ddt, *J* = 2.0, 8.0, 14.8 Hz, 1 H), 1.07 (d, *J* = 6.8 Hz, 3 H), 0.93 (t, *J* = 8.0 Hz, 9 H), 0.64 (q, *J* = 7.6 Hz, 6 H).

NMR assignments: ^{1}H-NMR (400 MHz) δ 5.93-5.84 (comp, 3 H, C2-H, C5-H, C6-H), 5.10-5.02 (comp, 2 H, C1-H), 4.51 (dd, *J* = 2.0, 4.0 Hz, 1 H, C10-H), 3.30 (d, *J* = 6.4 Hz, 2 H, C3-H), 2.86 (q, *J* = 8.4 Hz, 1 H, C12-H), 2.47 (ddt, *J* = 2.0, 8.8, 14.8 Hz, 1 H, C9-H), 2.31 (ddt, *J* = 2.0, 8.0, 14.8 Hz, 1 H, C9-H), 1.07 (d, *J* = 6.8 Hz, 3 H, C13-H), 0.93 (t, *J* = 8.0 Hz, 9 H, C15-H), 0.64 (q, *J* = 7.6 Hz, 6 H, C14-H).

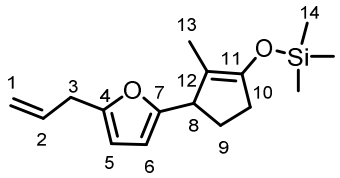


2.78

((3-(5-Allylfuran-2-yl)-2-methylcyclopent-1-en-1-yl)oxy)(*tert*-butyl)dimethylsilane (**2.78**). (SB-IV-178). A slurry of KH (139 mg, 0.976 mmol) in THF (0.5 mL) was cooled to –78 °C. A solution of ketone **2.6** (50 mg, 0.244 mmol) and TBSCl (96 mg, 0.634 mmol) in THF (0.5 mL) were added to the reaction at –78 °C. The reaction mixture was stirred for 1 h and then warmed to room temperature. The reaction was diluted with hexanes and the mixture was filtered through Celite. The filtrate was concentrated under reduced pressure and the crude oil was redissolved in hexanes and purified via silica plug eluting with 1% Et_3N in hexanes to provide 66 mg (85%) of **2.78** as a clear oil: ^{1}H-NMR (400 MHz) δ 5.93 (dddd, *J* = 6.4, 6.4, 10.0, 16.8 Hz, 1 H), 5.89 (d, *J* = 3.6 Hz, 1 H), 5.86 (d, *J* = 3.2 Hz, 1 H), 5.11 (dq, *J* = 1.6, 15.6 Hz, 1 H), 5.08 (dq,

J = 1.2, 8.0 Hz, 1 H), 3.62 (m, 1H), 3.34 (app dd, *J* = 1.2, 6.8 Hz, 2 H), 2.42 (m, 1 H), 2.27 (m, 1 H), 2.17 (dddd, *J* = 5.6, 8.8, 8.8 12.4 Hz, 1 H), 1.87 (dddd, *J* = 4.0, 4.0, 8.8, 12.4 Hz, 1H), 1.47 (td, *J* = 0.8, 2.0 Hz, 3 H), 0.95 (s, 9 H), 0.14 (s, 6 H).

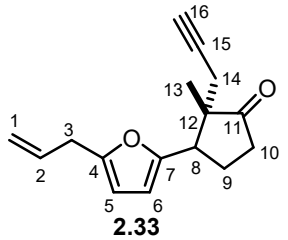
NMR assignments: ^{1}H-NMR (400 MHz) δ 5.93 (dddd, *J* = 6.4, 6.4, 10.0, 16.8 Hz, 1 H, C2-H), 5.89 (d, *J* = 3.6 Hz, 1 H, C6-H), 5.86 (d, *J* = 3.2 Hz, 1 H, C5-H), 5.11 (dq, *J* = 1.6, 15.6 Hz, 1 H, C1-H), 5.08 (dq, *J* = 1.2, 8.0 Hz, 1 H, C1-H), 3.62 (m, 1H, C8-H), 3.34 (app dd, *J* = 1.2, 6.8 Hz, 2 H, C3-H), 2.42 (m, 1 H, C9-H or C10-H), 2.27 (m, 1 H, C9-H or C10-H), 2.17 (dddd, *J* = 5.6, 8.8, 8.8 12.4 Hz, 1 H, C9-H or C10-H), 1.87 (dddd, *J* = 4.0, 4.0, 8.8, 12.4 Hz, 1H, C9-H or C10-H), 1.47 (td, *J* = 0.8, 2.0 Hz, 3 H, C13-H), 0.95 (s, 9 H, C15-H), 0.14 (s, 6 H, C14-H).



((3-(5-Allylfuran-2-yl)-2-methylcyclopent-1-en-1-yl)oxy)trimethylsilane (**2.77**). **From ketone 2.6**: (SB-IV-235). Neat TMSOTf (325 mg, 265 µL, 1.46 mmol) was added to a solution of NaI (265 mg, 1.51 mmol) in MeCN (2 mL) at room temperature. The mixture was stirred for 5 min, and CH_2Cl_2 (3 mL), HMDS (317 mg, 412 µL, 1.95 mmol), and ketone **2.6** (100 mg, 0.49 mmol) were added sequentially. The mixture was stirred at room temperature for 24 h and then diluted with hexanes (50 mL). The reaction mixture was filtered through a silica plug (deactivated with Et_3N), and the plug was washed once with hexanes (10 mL). The combined organic filtrates were concentrated under reduced pressure to provide 113 mg (84%) **2.77** as a clear oil.

From Methyl-2-cyclopenten-1-one (**2.2**): (SB-IV-255); Neat TMSOTf (254 mg, 207 µL, 1.14 mmol) was added to a solution of NaI (187 mg, 1.25 mmol) in MeCN (2 mL) at room temperature. The mixture was stirred for 5 min before CH_2Cl_2 (3 mL) was added and the mixture

was cooled to –78 °C. Methyl-2-cyclopenten-1-one (**2.2**) (100 mg, 102 µL, 1.04 mmol) was added, and the mixture was stirred for 30 min before adding a solution of 2-allylfuran (**2.32**) in THF (7.1 M, 221 µL, 1.56 mmol) and 2-methyl-2-butene (180 mg, 270 µL, 2.08 mmol). The reaction was stirred for 2 h at –78 °C, whereupon HMDS (507 mg, 658 µL, 3.12 mmol) was added, and the reaction was warmed to room temperature. A second aliquot of TMSOTf (115 mg, 94 µL, 0.52 mmol) was added, and the reaction was stirred for an additional 2 h before adding MeOH (67 mg, 85 µL, 2.08 mmol). The mixture was diluted with hexanes (50 mL) and filtered through a silica plug (deactivated with Et_3N) and eluted with hexanes with 1% Et_3N. The combined organic layers were concentrated under reduced pressure to provide 235 mg (82%) **2.77** as a clear oil.

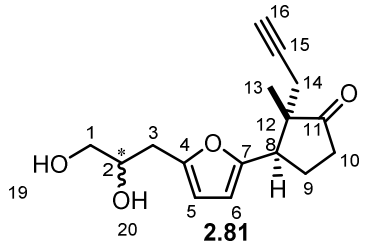


2.33

3-(5-Allylfuran-2-yl)-2-methyl-2-(prop-2-ynyl)cyclopentanone (**2.33**). (SB-III-100). A solution of **2.7** (270 mg, 0.86 mmol), AcOH (98 µL, 1.72mmol), and TBAF (450 mg, 1.72 mmol) in anhydrous THF (2.7 mL) and the reaction was refluxed for 2 h. The solution was cooled to room temperature before the solvent was removed under reduced pressure and the crude material was purified by flash chromatography eluting with a gradient of Et_2O/hexanes (1:20 → 1:5) to yield 189 mg (91%) of **2.33** as a pale yellow oil: ^{1}H-NMR (500 MHz) δ 6.04 (d, *J* = 3.0 Hz, 1 H), 5.95 (d, *J* = 3.0 Hz, 1 H), 5.91 (dddd, *J* = 6.5, 6.5, 10.1, 16.2 Hz, 1H), 5.13-5.09 (comp, 2 H), 3.71 (dd, *J* = 5.8, 12.1 Hz, 1 H), 3.35 (d, *J* = 6.4 Hz, 2 H) 2.59-2.50 (comp, 2 H) 2.37-2.24 (comp, 3 H) 2.17-2.08 (m, 1 H) 2.0 (t, *J* = 2.6 Hz, 1 H), 0.72 (s, 3 H); ^{13}C-NMR

(125 MHz) δ 219.5, 153.0, 133.9, 116.7, 107.2, 105.8, 80.9, 70.6, 52.1, 42.2, 37.2, 32.5, 25.7, 22.5, 18.2.

NMR assignments: ^{1}H-NMR (500 MHz) δ 6.04 (d, *J* = 3.0 Hz, 1 H, C6-H), 5.95 (d, *J* = 3.0 Hz, 1 H, C5-H), 5.91 (dddd, *J* = 6.5, 6.5, 10.1, 16.2 Hz, 1H, C2-H), 5.13-5.09 (comp, 2 H, C1-H), 3.71 (dd, *J* = 5.8, 12.1 Hz, 1 H, C8-H), 3.35 (d, *J* = 6.4 Hz, 2 H, C3-H) 2.59-2.50 (comp, 2 H, C10-H, C14-H) 2.37-2.24 (comp, 3 H, C9-H, C10-H, C14-H) 2.17-2.08 (m, 1 H, C9-H) 2.0 (t, *J* = 2.6 Hz, 1 H, C16-H), 0.72 (s, 3 H, C13-H); ^{13}C-NMR (125 MHz) δ 219.5 (C11), 153.0 (C4, C7), 133.9 (C2), 116.7 (C1), 107.2 (C6), 105.8 (C5), 80.9 (C15), 70.6 (C16), 52.1 (C12), 42.2 (C8), 37.2 (C14), 32.5 (C3), 25.7 (C10), 22.5 (C9), 18.2 (C13).



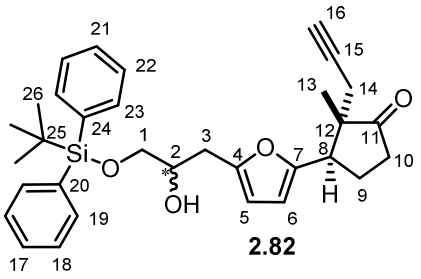
2.81

* Indicates absolute stereochemistry

(2S)-3-(5-(2,3-Dihydroxypropyl)furan-2-yl)-2-methyl-2-(prop-2-ynyl)cyclopentanone (**2.81**). (SB-III-117). K_2CO_3, (250 mg, 1.81 mmol), $K_3Fe(CN)_6$ (20 mg, 0.06 mmol), $K_2OsO_2(OH)_4$•$2H_2O$ (11 mg, 0.03 mmol) and $K_2S_2O_8$ (243 mg, 0.9 mmol) were added to a flask, followed by H_2O (3 mL). A solution of **2.33** (146 mg, 0.6 mmol) in *tert*-BuOH (3 mL) was added to the vigorously stirred mixture, and stirring at room temperature was continued for 24 h, whereupon a solution of saturated aqueous $Na_2S_2O_3$ (1 mL) was added. The mixture was extracted with EtOAc (3 x 10 mL), and the the combined organic extracts were washed with 13% aqueous brine solution (4 x 5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:2 → 1:0) to provide 126 mg (76%) of **2.81** as a mixture (1:1) of diastereomers

(clear oil). δ 6.08 (app s, 2 H), 4.01 (m, 1 H), 3.74-3.70 (comp, 2 H), 3.62 (m, 1 H), 2.82 (app d, *J* = 6.4 Hz, 2 H), 2.59 (app dt, *J* = 2.4, 16.4 Hz, 1 H), 2.54 (m, 1 H), 2.37-2.24 (comp, 3 H), 2.18-2.06 (m, 1 H), 2.01 (app t, *J* = 2.8 Hz, 1 H), 0.73 (s, 3 H).

NMR assignments: δ 6.08 (app s, 2 H, C5-H, C6-H), 4.01 (m, 1 H, C2-H), 3.74-3.70 (comp, 2 H, C1-H), 3.62 (m, 1 H, C8-H), 2.82 (app d, *J* = 6.4 Hz, 2 H, C3-H), 2.59 (app dt, *J* = 2.4, 16.4 Hz, 1 H, C9-H), 2.54 (m, 1 H, C14-H), 2.37-2.24 (comp, 3 H, C9-H, C10-H, C14-H), 2.18-2.06 (m, 1 H, C10-H), 2.01 (app t, *J* = 2.8 Hz, 1 H, C16-H), 0.73 (s, 3 H, C13-H).



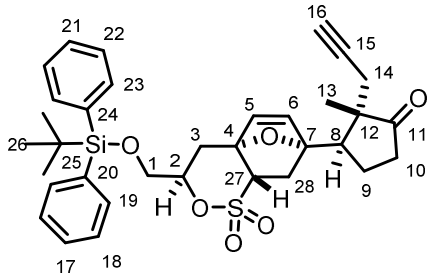
2.82

* Indicates absolute stereochemistry

3-(5-(3-(*tert*-Butyldiphenylsilyloxy)-2-hydroxypropyl)furan-2-yl)-2-methyl-2-(prop-2-ynyl)cyclopentanone (**2.82**). (SB-III-124). Diol **2.81** (126 mg, 0.46 mmol) and imidazole (37 mg, 0.55 mmol) were dissolved in anhydrous DMF (2 mL) and CH_2Cl_2 (0.7 mL), and the solution was cooled to –50 °C. TBDPSCl (137 mg, 130 μL, 0.5 mmol) was added, and the reaction was stirred for 6 h at –50 °C, whereupon a saturated aqueous $NaHCO_3$ solution (2 mL) was added. The mixture was extracted with EtOAc (3 x 5 mL), and the combined organic extracts were then washed with 13% aqueous brine solution (4 x 3 mL), dried (Na_2SO_4), filtered, concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of Et_2O/hexanes (1:5 → 1:2) to provide 175 mg (75%) of **2.82** as a mixture (1:1) of diastereomers (clear oil): ^{1}H-NMR (500 MHz) δ 7.66-7.63 (comp, 4 H), 7.45-7.36 (comp, 6 H), 6.02-6.01 (app m, 1 H), 5.98 (app t, 1 H), 4.02-3.97 (app m, 1 H), 3.71-3.64 (app m, 2 H), 3.60-3.56 (app m, 1 H), 2.84-2.76 (app m, 2 H), 2.54-2.47 (app m, 2 H), 2.30-2.18 (app m, 3 H), 2.11-2.04 (app m, 1 H), 1.96 (app q, 1 H), 1.07 (bs, 9 H), 0.63 (app d, 3 H); ^{13}C-NMR (125

MHz) δ 219.4, 153.1, 151.4, 151.4, 135.5, 135.5, 133.1, 133.0, 129.9, 127.8, 107.4, 107.3, 80.9, 70.7, 67.1, 52.1, 42.2, 37.2, 32.1, 32.1, 26.9, 25.7, 22.5, 19.3, 18.3.

NMR assignments: δ 7.66-7.63 (comp, 4 H, C19-H, C23-H), 7.45-7.36 (comp, 6 H, C17-H, C18-H, C21-H, C22-H), 6.02-6.01 (app m, 1 H, C6-H), 5.98 (app t, 1 H, C5-H), 4.02-3.97 (app m, 1 H, C2-H), 3.71-3.64 (app m, 2 H, C1-H), 3.60-3.56 (app m, 1 H, C1-H), 2.84-2.76 (app m, 2 H, C3-H), 2.54-2.47 (app m, 2 H, C9-H, C14-H), 2.30-2.18 (app m, 3 H, C9-H, C10-H, C14-H), 2.11-2.04 (app m, 1 H, C10-H), 1.96 (app q, 1 H, C16-H), 1.07 (bs, 9 H, C26-H), 0.63 (app d, 3 H, C13-H); ^{13}C-NMR (125 MHz) δ 219.4 (C11), 153.1 (C7), 151.4 (C4), 151.4 (C4), 135.5 (C19, C23), 135.5 (C19, C23), 133.1 (C20, C24), 133.0 (C20, C24), 129.9 (C17, C21), 127.8 (C18, C22), 107.4 (C6), 107.3 (C5), 80.9 (C15), 70.7 (C16), 67.1 (C1), 52.1 (C12), 42.2 (C8), 37.2 (C14), 32.1 (C3), 32.1 (C3), 26.9 (C26), 25.7 (C10), 22.5 (C9), 19.3 (C13), 18.3 (C25).



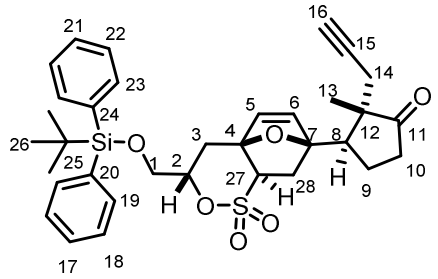
2.34

(((*tert*-Butyldiphenylsilyl)oxy)methyl)-1,1-dioxido-3,4,8,8a-tetrahydro-7H-4a,7-epoxybenzo[c][1,2]oxathiin-7-yl)-2-methyl-2-(prop-2-yn-1-yl)cyclopentan-1-one (2.34). (SB-III-137). Alcohol **2.34** (96 mg, 0.19 mmol) and Et_3N (45 mg, 62 µL, 0.47 mmol) was dissolved in anhydrous THF (2 mL) and cooled to 0 °C. Vinylsulfonyl chloride (28 mg, 20 µL, 0.22 mmol)[631] was added and the mixture was stirred for 8 h. The mixture was cooled to 0 °C and Et_3N (42µL, 0.32 mmol) followed by vinylsulfonyl chloride (18 mg, 13µL, 0.14 mmol). The mixture was stirred for 16 h, whereupon 1 M HCl (1 mL) was added. The mixture was extracted with Et_2O (3 x 5 mL), and the combined organic extracts were washed with 1 M HCl (1 x 5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was re-

dissolved in toluene (3 mL), filtered, and the filtrate was heated to 75 °C for 16 h. Silica gel (3 g) was added at 75 °C, and the reaction was cooled to room temperature before removing the solvent under reduced pressure. The crude material was purified by flash chromatography eluting with EtOAc/hexanes (1:4) to provide 48 mg (43%) of **2.34** and 49 mg (44%) of **2.89** as an off white solid: ^{1}H-NMR (500 MHz) δ 7.69-7.66 (comp, 4 H), 7.47-7.39 (comp, 6 H), 6.55 (d, *J* = 5.5 Hz, 1 H), 6.04 (d, *J* = 5.5 Hz, 1 H), 4.90 (dddd, *J* = 2.0, 4.0, 4.0, 12.0 Hz, 1 H), 3.92 (dd, *J* = 4.0, 12.0 Hz, 1 H), 3.84 (dd, *J* = 4.5, 11.5 Hz, 1H), 3.20 (dd, *J* = 3.5, 8.0 Hz, 1H), 3.13 (dd, *J* = 6.5, 12.5 Hz, 1 H), 2.65 (dd, *J* = 2.5, 17.0 Hz, 1H), 2.531 (dd, *J* = 12.0, 15.5 Hz, 1 H), 2.526 (dd, *J* = 8.0, 17.5 Hz, 1 H), 2.47 (dd, *J* = 2.5, 14.5 Hz, 1 H), 2.44 (dd, *J* = 3.5, 12.0 Hz, 1 H), 2.31 (dd, *J* = 1.5, 15.5 Hz, 1 H), 2.26 (dd, *J* = 7.0, 19.0 Hz, 1 H), 2.12 (ddd, *J* = 6.5, 9.0, 12.0 Hz, 1 H), 1.99 (dd, *J* = 8.0, 12.5 Hz, 1 H), 1.99 (m, 1 H), 1.92 (dddd, *J* = 9.0, 12.5, 12.5, 12.5 Hz, 1 H), 1.09 (s, 9 H), 1.02 (s, 3 H); ^{13}C-NMR (125 MHz) δ219.5, 141.7, 135.6, 135.6, 134.5, 132.7, 132.6, 129.9, 127.8, 91.2, 88.1, 80.9, 80.3, 71.2, 64.8, 58.9, 51.0, 44.3, 37.0, 33.8, 29.4, 27.0, 26.8, 21.9, 19.3, 18.8; IR (film) 2960 (C-H), 2932 (C-H), 2858 (C-H), 1741 (C=O), 1365 (S=O), 1172 (S=O), 1112 (S=O)cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{34}H_{40}O_6SSi^+$ (M+Na), 627.2207; found, 627.2211.

NMR assignments: ^{1}H-NMR (500 MHz) δ 7.69-7.66 (comp, 4 H, C19-H, C23-H), 7.47-7.39 (comp, 6 H, C17-H, C18-H, C21-H, C22-H), 6.55 (d, *J* = 5.5 Hz, 1 H, C6-H), 6.04 (d, *J* = 5.5 Hz, 1 H, C5-H), 4.90 (dddd, *J* = 2.0, 4.0, 4.0, 12.0 Hz, 1 H, C2-H), 3.92 (dd, *J* = 4.0, 12.0 Hz, 1 H, C1-H), 3.84 (dd, *J* = 4.5, 11.5 Hz, 1H, C1-H), 3.20 (dd, *J* = 3.5, 8.0 Hz, 1H, C27-H), 3.13 (dd, *J* = 6.5, 12.5 Hz, 1 H, C8-H), 2.65 (dd, *J* = 2.5, 17.0 Hz, 1H, C10-H), 2.531 (dd, *J* = 12.0, 15.5 Hz, 1 H, C3-H), 2.526 (dd, *J* = 8.0, 17.5 Hz, 1 H, C14-H), 2.47 (dd, *J* = 2.5, 14.5 Hz, 1 H, C10-H), 2.44 (dd, *J* = 3.5, 12.0 Hz, 1 H, C28-H), 2.31 (dd, *J* = 1.5, 15.5 Hz, 1 H, C3-H), 2.26 (dd, *J* = 7.0, 19.0 Hz, 1 H, C14-H), 2.12 (ddd, *J* = 6.5, 9.0, 12.0 Hz, 1 H, C9-H), 1.99 (dd, *J* = 8.0, 12.5 Hz, 1 H, C28-H), 1.99 (m, 1 H, C16-H), 1.92 (dddd, *J* = 9.0, 12.5, 12.5, 12.5 Hz, 1 H, C9-H), 1.09 (s, 9 H, C26-H), 1.02 (s, 3 H, C13-H); ^{13}C-NMR (125 MHz) δ219.5 (C11), 141.7 (C6), 135.6 (C19), 135.6 (C23), 134.5 (C5), 132.7 (C20), 132.6 (C24), 129.9 (C18, C22), 127.8

(C17, C21), 91.2 (C7), 88.1 (C4), 80.9 (C15), 80.3 (C2), 71.2 (C16), 64.8 (C1), 58.9 (C27), 51.0 (C12), 44.3 (C8), 37.0 (C14), 33.8 (C28), 29.4 (C3), 27.0 (C10), 26.8 (C26), 21.9 (C9), 19.3 (C25), 18.8 (C13).

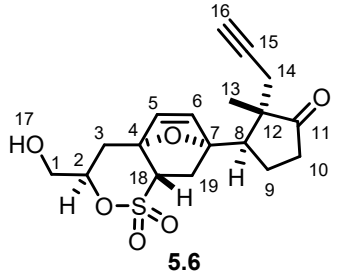


2.89

(((*tert*-Butyldiphenylsilyl)oxy)methyl)-1,1-dioxido-3,4,8,8a-tetrahydro-7H-4a,7-epoxybenzo[c][1,2]oxathiin-7-yl)-2-methyl-2-(prop-2-yn-1-yl)cyclopentan-1-one (**2.89**). (SB-III-137): ^{1}H-NMR (500 MHz) δ7.68-7.65 (comp, 4 H), 7.46-7.39 (comp, 6 H), 6.57 (d, *J* = 5.5 Hz, 1H), 6.09 (d, *J* = 5.5 Hz, 1H), 4.93 (dddd, *J* = 2.0, 4.0, 4.0, 12.0 Hz, 1 H), 3.91 (dd, *J* = 3.5, 11.5 Hz, 1 H), 3.84 (dd, *J* = 4.5, 11.5 Hz, 1 H), 3.18 (dd, *J* = 3.5, 8.0 Hz, 1 H), 3.15 (dd, *J* = 6.0, 11.5 Hz, 1 H), 2.76 (dd, *J* = 2.5, 17.0 Hz, 1 H), 2.59 (dd, *J* = 3.0, 12.0 Hz, 1 H), 2.53 (dd, *J* = 9.5, 12.5 Hz, 1 H), 2.50 (m, 1 H), 2.32-2.28 (comp, 3H), 2.21 (dd, *J* = 9.0, 19.0 Hz, 1 H), 2.08 (m, 1 H), 2.06 (t, *J* = 2.5 Hz, 1 H), 1.85 (dd, *J* = 8.0, 12.5 Hz, 1H), 1.08 (s, 9H), 0.98 (s, 3 H); ^{13}C-NMR (125 MHz) δ219.5, 141.6, 135.9, 135.6, 135.5, 132.7, 132.6, 129.9, 127.8, 90.6, 87.7, 80.5, 80.5, 71.9, 64.8, 58.5, 51.7, 43.1, 36.3, 32.6, 29.3, 26.8, 26.6, 20.3, 19.6, 19.3.

NMR assignments: ^{1}H-NMR (500 MHz) δ 7.68-7.65 (comp, 4 H, C19-H, C23-H), 7.46-7.39 (comp, 6 H, C17-H, C18-H, C21-H, C22-H), 6.57 (d, *J* = 5.5 Hz, 1H, C6-H), 6.09 (d, *J* = 5.5 Hz, 1H, C5-H), 4.93 (dddd, *J* = 2.0, 4.0, 4.0, 12.0 Hz, 1 H, C2-H), 3.91 (dd, *J* = 3.5, 11.5 Hz, 1 H, C1-H), 3.84 (dd, *J* = 4.5, 11.5 Hz, 1 H, C1-H), 3.18 (dd, *J* = 3.5, 8.0 Hz, 1 H, C27-H), 3.15 (dd, *J* = 6.0, 11.5 Hz, 1 H, C8-H), 2.76 (dd, *J* = 2.5, 17.0 Hz, 1 H, C10-H), 2.59 (dd, *J* = 3.0, 12.0 Hz, 1 H, C28-H), 2.53 (dd, *J* = 9.5, 12.5 Hz, 1 H, C3-H), 2.50 (m, 1 H, C14-H), 2.32-2.28 (comp, 3H, C9-H, C3-H), 2.21 (dd, *J* = 9.0, 19.0 Hz, 1 H, C14-H), 2.08 (m, 1 H, C10-H), 2.06 (t, *J* = 2.5 Hz, 1 H, C16-H), 1.85 (dd, *J* = 8.0, 12.5 Hz, 1H, C28-H), 1.08 (s, 9H, C26-H), 0.98 (s, 3

H, C13-H); ^{13}C-NMR (125 MHz) δ219.5 (C11), 141.6 (C6), 135.9 (C5), 135.6 (C19), 135.5 (C23), 132.7 (C20), 132.6 (C24), 129.9 (C18, C22), 127.8 (C17, C21), 90.6 (C7), 87.7 (C4), 80.5 (C15), 80.5 (C2), 71.9 (C16), 64.8 (C1), 58.5 (C27), 51.7 (C12), 43.1 (C8), 36.3 (C14), 32.6 (C28), 29.3 (C3), 26.8 (C26), 26.6 (C9), 20.3 (C10), 19.6 (C25), 19.3 (C13).



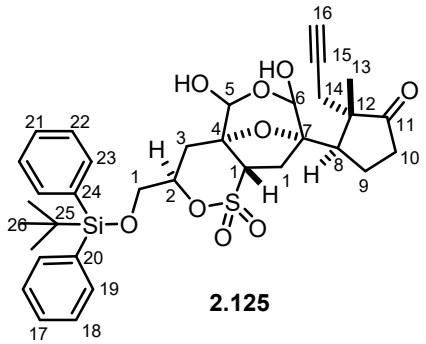
5.6

3-(Hydroxymethyl)-1,1-dioxido-3,4,8,8a-tetrahydro-7H-4a,7-epoxybenzo[c][1,2]oxathiin-7-yl)-2-methyl-2-(prop-2-yn-1-yl)cyclopentan-1-one. (SB-III-271C). Isolated after leaving a sample of **2.34** on the bench-top. The material was purified by flash chromatography eluting with EtOAc/hexanes (1:4) to provide 13 mg of the named compound: ^{1}H-NMR (400 MHz) δ 6.55 (d, *J* = 5.6 Hz, 1 H), 6.06 (d, *J* = 5.6 Hz, 1 H), 4.94 (m, 1 H), 4.00 (m, 1 H), 3.78 (m, 1 H), 3.21 (dd, *J* = 3.2, 8.0 Hz, 1 H), 3.15 (dd, *J* = 5.6, 12.4 Hz, 1 H), 2.67 (d, *J* = 16.8 Hz, 1 H), 2.60 (dd, *J* = 12.4, 15.2 Hz, 1 H), 2.59-2.44 (comp, 2 H), 2.47 (d, *J* = 17.2 Hz, 1 H), 2.30 (dd, *J* = 1.6, 15.2 Hz, 1 H), 2.27-2.15 (comp, 2 H), 2.00 (dd, *J* = 8.0, 12.4 Hz, 1 H), 1.89 (m, 1 H), 1.01 (s, 3 H), 0.12 (s, 9 H).

NMR assignments: ^{1}H-NMR (400 MHz) δ 6.55 (d, *J* = 5.6 Hz, 1 H, C6-H), 6.06 (d, *J* = 5.6 Hz, 1 H, C5-H), 4.94 (m, 1 H, C2-H), 4.00 (m, 1 H, C1-H), 3.78 (m, 1 H, C1-H), 3.21 (dd, *J* = 3.2, 8.0 Hz, 1 H, C18-H), 3.15 (dd, *J* = 5.6, 12.4 Hz, 1 H, C8-H), 2.67 (d, *J* = 16.8 Hz, 1 H, C14-H), 2.60 (dd, *J* = 12.4, 15.2 Hz, 1 H, C3-H), 2.59-2.44 (comp, 2 H, C10-H, C19-H), 2.47 (d, *J* = 17.2 Hz, 1 H, C14-H), 2.30 (dd, *J* = 1.6, 15.2 Hz, 1 H, C3-H), 2.27-2.15 (comp, 2 H, C9-H, C10-H), 2.00 (dd, *J* = 8.0, 12.4 Hz, 1 H, C19-H), 1.89 (m, 1 H, C9-H), 1.01 (s, 3 H, C13-H), 0.12 (s, 9 H, C20-H).

Ozone Titration procedure:

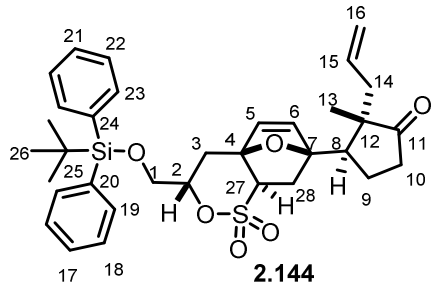
A 0.1 M stock solution of styrene in acetone with Sudan III indicator was prepared by dissolving styrene (575 µL, 5 mmol) and Sudan III (5 mg, 0.014 mmol) in 50 mL acetone. Acetone (80 mL) in a 100 mL round-bottom flask fitted with a stir-bar, was cooled to –78 °C and ozone was bubbled through for 5-6 min until the solution was a deep blue color. Aliquots (1 mL) were then removed from the ozone solution with a disposable polypropylene syringe and were added to the 0.1 M styrene stock solution (2 mL) at room temperature until the red color of the Sudan III disappeared and the solution turned colorless. The molarity of the ozone solution was calculated using the volume of ozone added and 1:1 molar ratio of ozone to styrene consumed.



2.125

3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-5,7-dihydroxy-1,1-dioxidotetrahydro-2H,5H-4a,8-epoxythiopyrano[3,2-c]oxepin-8(7H)-yl)-2-methyl-2-(prop-2-yn-1-yl)cyclopentan-1-one (**2.125**). (SB-III–203). **2.34** (15 mg, 0.025 mmol), pyridine (2 mg, 2 µL, 0.025 mmol) and 2,6-lutidine (13 mg, 14 µL, 0.124 mmol) was dissolved in acetone/H_2O (9:1, 2 mL). The mixture was cooled to –78 °C, and a solution of ozone in acetone (0.28 M, 0.89 mL, 0.025mmol) was added to a jacketed pressure equalizing addition funnel that was pre-cooled to –78 °C. The ozone solution was added over 1 min, and the reaction mixture was warmed to room temperature. The solvent was removed under reduced pressure, and the aqueous layer was extracted with EtOAc (3 x 1 mL). The combined organic extracts were washed with cold 1 M HCl (2 x 1 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to provide 15 mg (92%) of **2.135**. HRMS (ESI) *m/z* calc for $C_{34}H_{39}O_8SiS^+$ (M–H_2O), 635.2135; found,

635.2141; (SB-III-130): When a sample of **2.125** was reduced with $NaBH_4$ in MeOH, a product was isolated with $M+3H_2$ which is indicative of the reduction of three carbonyl groups. HRMS (ESI) *m/z* calc for $NaC_{34}H_{44}O_8SSi+$ (M+Na), 663.2418; found, 663.2419.

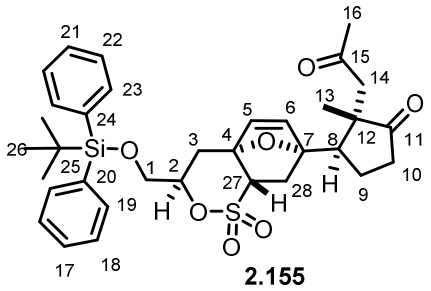


2.144

2-Allyl-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1,1-dioxido-3,4,8,8a-tetrahydro-7H-4a,7-epoxybenzo[c][1,2]oxathiin-7-yl)-2-methylcyclopentan-1-one (**2.144**). (SB-III-189). Lindlar's catalyst (26 mg), quinoline (57 mg, 52 µL, 0.44 mmol) was added to a solution of **2.89** (27 mg, 0.45 mmol) in a mixture of EtOAc/1-octene (1:1, 0.6 ml). The mixture was purged with N_2 then H_2 (30 psi) was introduced and the reaction was shaken in a par-hydrogenator at room temperature for 6 h. The mixture was filtered through Celite, the solvent was removed under reduced pressure to provide 11 mg (62%) of **2.144**: ^{1}H-NMR (400 MHz) δ 7.69-7.66 (comp, 4 H), 7.45-7.38 (comp, 6 H), 6.54 (d, *J* = 5.6 Hz, 1 H), 6.08 (d, *J* = 5.6 Hz, 1 H), 5.60 (dddd, *J* = 6.0, 9.2, 10.4, 16.4 Hz, 1 H), 5.15-5.08 (comp, 2 H), 4.92 (dtd, *J* = 2.0, 4.0, 8.0 Hz, 1 H), 3.92 (dd, *J* = 3.6, 11.6 Hz, 1 H), 3.18 (dd, *J* = 2.8, 7.6 Hz, 1 H), 2.76 (dd, *J* = 6.0, 10.4 Hz, 1 H), 2.62 (ddt, *J* = 1.2, 6.0, 14.4 Hz, 1 H), 2.55-2.44 (comp, 2 H), 2.53 (d, *J* = 12.4 Hz, 1 H), 2.50 (d, *J* = 12.0 Hz, 1 H), 2.30 (dd, *J* = 2.0, 15.2 Hz, 1 H), 2.22-2.08 (comp, 3 H), 1.83 (dd, *J* = 8.0, 12.4 Hz, 1 H), 1.08 (s, 9 H), 1.01 (s, 3 H).

NMR assignments: ^{1}H-NMR (400 MHz) δ 7.69-7.66 (comp, 4 H, C19-H, C23-H), 7.45-7.38 (comp, 6 H, C17-H, C18-H, C21-H, C22-H), 6.54 (d, *J* = 5.6 Hz, 1 H), 6.08 (d, *J* = 5.6 Hz, 1 H, C5-H), 5.60 (dddd, *J* = 6.0, 9.2, 10.4, 16.4 Hz, 1 H, C15-H), 5.15-5.08 (comp, 2 H, C16-H), 4.92 (dtd, *J* = 2.0, 4.0, 8.0 Hz, 1 H, C2-H), 3.92 (dd, *J* = 3.6, 11.6 Hz, 1 H, C1-H), 3.18 (dd, *J* = 2.8, 7.6 Hz, 1 H, C1-H), 2.76 (dd, *J* = 6.0, 10.4 Hz, 1 H, C27-H), 2.62 (ddt, *J* = 1.2, 6.0, 14.4 Hz,

1 H, C8-H), 2.55-2.44 (comp, 2 H, C3-H, C10-H), 2.53 (d, *J* = 12.4 Hz, 1 H, C14-H), 2.50 (d, *J* = 12.0 Hz, 1 H, C14-H), 2.30 (dd, *J* = 2.0, 15.2 Hz, 1 H, C3-H), 2.22-2.08 (comp, 3 H, C9-H, C28-H), 1.83 (dd, *J* = 8.0, 12.4 Hz, 1 H, C28-H), 1.08 (s, 9 H, C26-H), 1.01 (s, 3 H, C13-H).

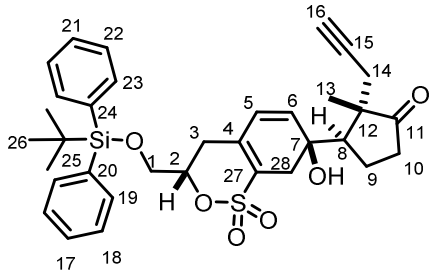


2.155

(((*tert*-Butyldiphenylsilyl)oxy)methyl)-1,1-dioxido-3,4,8,8a-tetrahydro-7H-4a,7-epoxybenzo[c][1,2]oxathiin-7-yl)-2-methyl-2-(2-oxopropyl)cyclopentan-1-one (**2.155**). (SB-III-279). Magnesium turnings (4.6 mg, 0.189 mmol) and $HgCl_2$ (1.7 mg, 0.006 mmol) were added to a round-bottom flask. EtOH (0.5 mL) was added, and the mixture was cooled to 0 °C and stirred for 10 min before adding H_3PO_4 (10 μL, 0.172 mmol). The mixture was stirred for 5 min before adding a solution of **2.34** (5 mg, 0.0063 mmol) in EtOH (0.5 mL). The mixture was stirred for 1 h, whereupon a saturated aqueous NH_4Cl solution (0.5 mL) was added. The mixture was filtered through Celite, washed with EtOAc (3 x 1 mL), and the layers were separated. The aqueous layers were extracted with EtOAc (3 x 1 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:4 → 1:2) to provide 4 mg (78%) of **2.155**: ^{1}H-NMR (400 MHz) δ 7.69-7.65 (comp, 4 H), 7.48-7.39 (comp, 6 H), 6.54 (d, *J* = 5.6 Hz, 1 H), 6.00 (d, *J* = 5.6 Hz, 1H), 4.86 (dtd, *J* = 2.0, 4.4, 8.0 Hz, 1 H), 3.94 (dd, *J* = 4.0, 11.6 Hz, 1 H), 3.84 (dd, *J* = 4.4, 12.0 Hz, 1 H), 3.17 (dd, *J* = 3.2, 7.6 Hz, 1 H), 3.08 (d, *J* = 18.4 Hz, 1 H), 2.97 (dd, *J* = 6.8, 12.8 Hz, 1 H), 2.85 (d, *J* = 18.4 Hz, 1 H), 2.71 (ddd, *J* = 9.6, 12.0, 18.8 Hz, 1 H), 2.55 (dd, *J* = 12.0, 15.6 Hz, 1 H), 2.47 (dd, *J* = 8.0, 18.4 Hz, 1 H), 2.33 (dd, *J* = 2.0, 14.8 Hz, 1 H), 2.30 (dd, *J* = 3.2, 11.2 Hz, 1 H), 2.15 (m, 1 H), 2.06 (s, 3 H), 1.96

(dd, *J* = 7.6, 12.0 Hz, 1 H), 1.86 (qd, *J* = 8.4, 12.4 Hz, 1 H), 1.09 (s, 9 H), 0.96 (s, 3H); IR (film) 3291 (O-H), 2961 (C-H), 2932 (C-H), 2859 (C-H), 1741 (C=O), 1365, 1173, 1140, 1113 cm^{-1}; HRMS (ESI); found, 645.2 (M+Na); HRMS (CI); found, 623.5 (M+H).

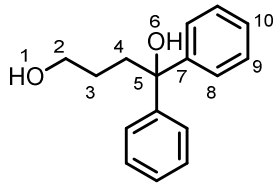
NMR assignments: ^{1}H-NMR (400 MHz) δ 7.69-7.65 (comp, 4 H, C19-H, C23-H), 7.48-7.39 (comp, 6 H, C17-H, C18-H, C21-H, C22-H), 6.54 (d, *J* = 5.6 Hz, 1 H, C6-H), 6.00 (d, *J* = 5.6 Hz, 1H, C5-H), 4.86 (dtd, *J* = 2.0, 4.4, 8.0 Hz, 1 H, C2-H), 3.94 (dd, *J* = 4.0, 11.6 Hz, 1 H, C1-H), 3.84 (dd, *J* = 4.4, 12.0 Hz, 1 H, C1-H), 3.17 (dd, *J* = 3.2, 7.6 Hz, 1 H, C27-H), 3.08 (d, *J* = 18.4 Hz, 1 H, C14-H), 2.97 (dd, *J* = 6.8, 12.8 Hz, 1 H, C8-H), 2.85 (d, *J* = 18.4 Hz, 1 H, C14-H), 2.71 (ddd, *J* = 9.6, 12.0, 18.8 Hz, 1 H, C10-H), 2.55 (dd, *J* = 12.0, 15.6 Hz, 1 H, C3-H), 2.47 (dd, *J* = 8.0, 18.4 Hz, 1 H, C10-H), 2.33 (dd, *J* = 2.0, 14.8 Hz, 1 H, C3-H), 2.30 (dd, *J* = 3.2, 11.2 Hz, 1 H, C28-H), 2.15 (m, 1 H, C9-H), 2.06 (s, 3 H, C16-H), 1.96 (dd, *J* = 7.6, 12.0 Hz, 1 H, C28-H), 1.86 (qd, *J* = 8.4, 12.4 Hz, 1 H, C9-H), 1.09 (s, 9 H, C26-H), 0.96 (s, 3H, C13-H).



3-(((*Tert*-butyldiphenylsilyl)oxy)methyl)-7-hydroxy-1,1-dioxido-3,4,7,8-tetrahydrobenzo[c][1,2]oxathiin-7-yl)-2-methyl-2-(prop-2-yn-1-yl)cyclopentan-1-one (**2.161**). (SB-IV-49C). *n*-BuLi (1.56 M, 0.31 mL, 0.49 mmol) was added to a solution of bromobenzene (80 mg, 53 μL, 0.51 mmol) in THF (1 mL) at –78 °C. The mixture was stirred for 45 min before adding a solution of $CeCl_3$•2LiCl (0.19 M, 1.9 mL, 0.36 mmol).[167] The mixture was stirred for an additional 30 min before adding **2.89** (11 mg, 0.018 mmol) as a solution in THF (1 mL). The mixture was stirred for 1 h at –78 °C before adding a saturated aqueous NH_4Cl solution (1 mL) and extracting with EtOAc. The combined organic extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure and the crude residue was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:2) to provide 3 mg (27%)

of **2.161** and 3 mg (24%) of **2.161**: ^{1}H-NMR (400 MHz) δ 7.68-7.64 (comp, 4 H), 7.49-7.36 (comp, 6 H), 6.18 (d, *J* = 10.0 Hz, 1 H), 5.91 (d, *J* = 10.0 Hz, 1H), 4.99 (dq, *J* = 4.4, 8.3 Hz, 1H), 3.88 (app t, *J* = 2.4 Hz, 1 H), 3.87 (dd, *J* = 2.8, 4.4 Hz, 1 H), 3.04 (dd, *J* = 2.4, 16.8 Hz, 1 H), 2.94 (dd, *J* = 6.0, 12.8 Hz, 1 H), 2.86 (dt, *J* = 2.8,16.8 Hz, 1 H), 2.83 (dt, *J* = 3.2, 18.8 Hz, 1 H), 2.73 (ddd, *J* = 2.2, 3.4, 16.8 Hz, 1 H), 2.66 (dd, *J* = 2.8, 16.8 Hz, 1 H), 2.48 (dd, *J* = 6.0, 12.8 Hz, 1 H), 2.35 (dd, *J* = 2.8, 16.8 Hz, 1 H), 2.24-2.16 (comp, 2 H), 1.91 (t, *J* = 4.0 Hz, 1 H), 1.87 (ddd, *J* = 2.4, 6.4, 14.6 Hz, 1 H), 1.08 (s, 3 H), 1.07 (s, 9 H); ^{13}C-NMR (150 MHz) δ 219.6, 138.6, 135.6, 135.5, 134.9, 132.5, 132.4, 130.04, 130.03, 128.1, 127.0, 125.1, 81.0, 80.6, 71.6, 64.5, 51.2, 46.8, 36.6, 32.8, 28.9, 28.2, 26.7, 21.0, 19.6, 19.5; IR (film) 3389 (O-H), 2925 (C-H), 2854 (C-H), 1734 (C=O), 1493, 1448 (S=O), 1343, 1261, 1176, 1112, 1053, 973 cm^{-1}; LRMS (APCI); found, 587.2 $(M–H_2O)^+$.

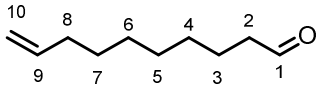
NMR assignments: ^{1}H-NMR (400 MHz) δ 7.68-7.64 (comp, 4 H, C19-H, C23-H), 7.49-7.36 (comp, 6 H, C17-H, C18-H, C21-H, C22-H), 6.18 (d, *J* = 10.0 Hz, 1 H, C6-H), 5.91 (d, *J* = 10.0 Hz, 1H, C5-H), 4.99 (dq, *J* = 4.4, 8.3 Hz, 1H, C2-H), 3.88 (app t, *J* = 2.4 Hz, 1 H, C1-H), 3.87 (dd, *J* = 2.8, 4.4 Hz, 1 H, C1-H), 3.04 (dd, *J* = 2.4, 16.8 Hz, 1 H, C28-H), 2.94 (dd, *J* = 6.0, 12.8 Hz, 1 H, C10-H), 2.86 (dt, *J* = 2.8,16.8 Hz, 1 H, C3-H), 2.83 (dt, *J* = 3.2, 18.8 Hz, 1 H, C3-H), 2.73 (ddd, *J* = 2.2, 3.4, 16.8 Hz, 1 H, C8-H), 2.66 (dd, *J* = 2.8, 16.8 Hz, 1 H, C28-H), 2.48 (dd, *J* = 6.0, 12.8 Hz, 1 H, C14-H), 2.35 (dd, *J* = 2.8, 16.8 Hz, 1 H, C14-H), 2.24-2.16 (comp, 2 H, C9-H), 1.91 (t, *J* = 4.0 Hz, 1 H, C16-H), 1.87 (ddd, *J* = 2.4, 6.4, 14.6 Hz, 1 H, C10-H), 1.08 (s, 3 H, C13-H), 1.07 (s, 9 H, C26-H); ^{13}C-NMR (150 MHz) δ 219.6 (C11), 138.6 (C6), 135.6 (C19 or C23), 135.5 (C19 or C23), 134.9 (C4), 132.5 (C20 or C24), 132.4 (C20 or C24), 130.04 (C18 or C22), 130.03 (C18 or C22), 128.1 (C17, C21), 127.0 (C27), 125.1 (C5), 81.0 (C15), 80.6 (C2), 71.6 (C16), 64.5 (C1), 51.2 (C12), 46.8 (C12), 36.6 (C8), 32.8 (C14), 28.9 (C10), 28.2 (C3), 26.7 (C26), 21.0 (C9), 19.6 (C13), 19.5 (C25).



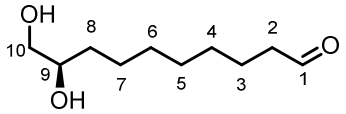
5.7

1,1-Diphenylbutane-1,4-diol. (SB-IV-49C). Isolated from the reaction of with **2.89** with phenylcerium. Purified *via* flash chromatography, eluting with a gradient of EtOAc/hexanes (1:10 → 1:2): ^{1}H-NMR (500 MHz) δ 7.43 (dd, *J* = 1.3, 8.5 Hz, 4 H), 7.31 (t, *J* = 7.4 Hz, 4 H), 7.22 (tt, *J* = 1.2, 6.8 Hz, 2 H), 3.68 (t, *J* = 6.0 Hz, 2 H), 2.43 (app. t, *J* = 7.3 Hz, 2 H), 1.66 (bs, 2 H), 1.60 (m, 2 H); ^{13}C-NMR (125 MHz) δ 147.1, 128.2, 126.8, 126.1, 77.9, 63.2, 38.9, 27.2.

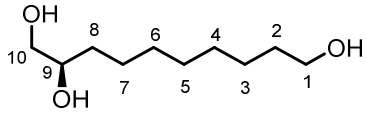
NMR assignments: ^{1}H-NMR (500 MHz) δ 7.43 (dd, *J* = 1.3, 8.5 Hz, 4 H, C8-H), 7.31 (t, *J* = 7.4 Hz, 4 H, C9-H), 7.22 (tt, *J* = 1.2, 6.8 Hz, 2 H, C10-H), 3.68 (t, *J* = 6.0 Hz, 2 H, C2-H), 2.43 (app. t, *J* = 7.3 Hz, 2 H, C4-H), 1.66 (bs, 2 H, O1-H, O6-H), 1.60 (m, 2 H, C3-H); ^{13}C-NMR (125 MHz) δ 147.1 (C7), 128.2 (C9), 126.8 (C10), 126.1 (C8), 77.9 (C5), 63.2 (C2), 38.9 (C4), 27.2 (C3).



Dec-9-enal (**2.117**). (SB-VIII–104). Pyridinium chlorochromate (PCC) (830 mg, 3.84 mmol) was added to a slurry of basic alumina (3.84 g) in CH_2Cl_2 (6 mL) and stirred at room temperature for 2 h. Dec-9-en-1-ol (300 mg, 363 μL, 1.92 mmol) was added, and the mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through a silica plug and eluted with a mixture of EtOAc/hexanes (1:3, 50 mL). The solvent was removed under reduced pressure to provide 288 mg (97%) of **2.117**, which was taken on to the next step without further purification.



(R)-9,10-Dihydroxydecanal (**2.118**). (SB-VIII–106). Water (3.1 mL) was added to a solid mixture of $K_2S_2O_8$ (252 mg, 0.932 mmol), Na_2HPO_4 (264 mg, 1.863 mmol), $NaIO_4$ (26 mg, 0.124 mmol) and $K_2OsO_2(OH)_4 \bullet 2H_2O$ (11 mg, 0.031 mmol) at room temperature and stirred for 5 min. $(DHQD)_2Phal$ (36 mg, 0.046 mmol) was added, followed by *tert*-BuOH (3.1 mL) and **2.117** (96 mg, 0.621 mmol) and the reaction was stirred at room temperature for 4 h whereupon a saturated aqueous $Na_2S_2O_3$ solution (1 mL) was added. The mixture was salted with NaCl and extracted with acetone (3 x 5 mL) and the combined organic extracts were then dried (Na_2SO_4), filtered, concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with a gradient of acetone/hexanes (3:10 → 1:2) to provide 83 mg (71%) of **2.118** as a white solid (stereochemistry assigned based on generalized model).



(*R*)-Decane-1,2,10-triol. (SB-VIII-107). $NaBH_4$ (78 mg, 2.07 mmol) was added to a solution of **2.118** (78 mg, 0.413 mmol) in MeOH (5 mL) at room temperature. The reaction was stirred for 4 h before adding AcOH (~0.1 mL) and concentrating the reaction mixture under reduced pressure. The crude residue was purified by flash chromatography eluting with a gradient of acetone/hexanes (1:2 → 3:4) to provide 54 mg (69%) of the named compound as a white solid: mp 53-55 °C; ^{1}H-NMR (CD_3OD, 500 MHz) δ 3.58-3.54 (m, 1 H), 3.54 (t, J = 6.5 Hz, 2 H), 3.54 (dd, J = 4.5, 11.0 Hz, 1 H), 4.41 (dd, J = 6.5, 11.0 Hz, 1 H), 1.56-1.46 (comp, 4 H), 1.39-1.30 (comp, 10 H); ^{13}C-NMR (CD_3OD, 125 MHz) δ 73.3, 67.4, 63.0, 34.4, 33.7, 30.8, 30.7, 30.5, 36.9, 26.7; IR (film) 3373 (O-H), 2924 (C-H), 2851 (C-H), 1644, 1466, 1073 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{10}H_{22}O_3^+$ (M+Na), 213.1461; found, 213.1471.

NMR assignments: ^{1}H-NMR (CD_3OD, 500 MHz) δ 3.58-3.54 (m, 1 H, C9-H), 3.54 (t, J = 6.5 Hz, 2 H, C1-H), 3.54 (dd, J = 4.5, 11.0 Hz, 1 H, C10-H), 4.41 (dd, J = 6.5, 11.0 Hz, 1 H, C10-H), 1.56-1.46 (comp, 4 H, C2-H, C8-H), 1.39-1.30 (comp, 10 H, C3-H, C4 C7-H-H, C5-H,

C6-H); ^{13}C-NMR (CD_3OD, 125 MHz) δ 73.3 (C9), 67.4 (C10), 63.0 (C1), 34.4 (C8), 33.7 (C2), 30.8 (C7), 30.7 (C3), 30.5 (C6), 36.9 (C4), 26.7 (C5).

Dihydroxylation procedure A.

Water (5 mL/mmol substrate) was added to a solid mixture of $K_2S_2O_8$ (1.5 eq), Na_2HPO_4 (3 eq), $NaIO_4$ (0.2 eq), $MeSO_2NH_2$ (1 eq) and $K_2OsO_2(OH)_4$•$2H_2O$ (0.05 eq) at room temperature and stirred for 5 min. Quinuclidine (0.3 eq) was added, followed by *tert*-BuOH (5 mL/mmol substrate) and the olefin (1 eq) and the reaction was stirred at room temperature until olefin was consumed (as judged by TLC) whereupon a solution of saturated aqueous $Na_2S_2O_3$ was added. The mixture was extracted with CH_2Cl_2 (3 x 5 mL/mmol substrate) and the combined organic extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure. The crude residue was purified by flash chromatography to provide the pure diol.

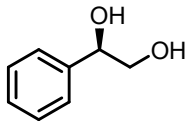
Dihydroxylation procedure B.

Water (5 mL/mmol substrate) was added to a solid mixture of $K_2S_2O_8$ (1.5 eq), Na_2HPO_4 (3 eq or 4 eq), $K_3Fe(CN)_6$ (0.2 eq), $MeSO_2NH_2$ (1 eq) and $K_2OsO_2(OH)_4$•$2H_2O$ (0.05 eq) at room temperature and stirred for 5 min. Quinuclidine (0.3 eq) is then added, followed by *tert*-BuOH (5 mL/mmol substrate) and the olefin (1 eq) and the reaction was stirred at room temperature until olefin was consumed (as judged by TLC) whereupon a solution of saturated aqueous $Na_2S_2O_3$ was added. The mixture was extracted with CH_2Cl_2 (3 x 5 mL/mmol substrate) and the combined organic extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure. The crude residue was purified by flash chromatography to provide the pure diol.

Dihydroxylation procedure C.

Water (5 mL/mmol substrate) was added to a solid mixture of $K_2S_2O_8$ (1.5 eq), Na_2HPO_4 (3 eq or 4 eq), $NaIO_4$ (0.2 eq) or $K_3Fe(CN)_6$ (0.2 eq), $MeSO_2NH_2$ (1 eq) and $K_2OsO_2(OH)_4$•$2H_2O$ (0.05 eq) at room temperature and stirred for 5 min. $(DHQD)_2Phal$ (0.075 eq) was added, followed by *tert*-BuOH (5 mL/mmol substrate) and the olefin (1 eq) and the

reaction was stirred at room temperature until olefin was consumed (as judged by TLC) whereupon a solution of saturated aqueous $Na_2S_2O_3$ was added. The mixture was extracted with CH_2Cl_2 (3 x 5 mL/mmol substrate) and the combined organic extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure. The crude residue was purified by flash chromatography to provide the pure diol.

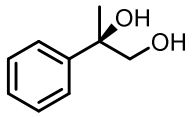


2.112

(R)-1-phenylethane-1,2-diol. (SB-V-178/189).

Compound **2.112** was prepared according to the general procedure B. The crude residue was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:3 → 1:0) to provide 16 mg (99%) of **2.112** as a white solid.

Compound **2.112** was prepared according to the general procedure C. The crude residue was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:3 → 1:0) to provide 11 mg (80%) of **2.112** as a white solid.Enantiomeric excess was determined to be 97% *via* chiral HPLC using a chiralcel OD-H column and eluting with a mixture of IPA/hexanes (2%) at a rate of 1 mL/min. Enantiomer A: rt = 52 min, Enantiomer B: rt = 56 min.



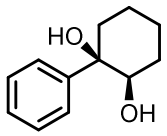
2.113

(R)-2-phenylpropane-1,2-diol. (SB-V-153).

Compound **2.113** was prepared according to the general procedure B. The crude residue was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:3 → 1:0) to provide 52 mg (89%) of **2.113** as a white solid.

Compound **2.113** was prepared according to the general procedure C. The crude residue was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:3 → 1:0) to

provide 11 mg (72%) of **2.113** as a white solid. Enantiomeric excess was determined to be 90% *via* chiral HPLC using a chiralcel OJ-H column and eluting with a mixture of IPA/hexanes (10%) at a rate of 1 mL/min. Enantiomer A: rt = 14 min, Enantiomer B: rt = 18 min.

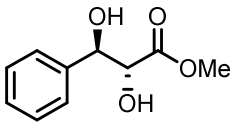


2.114

(1R,2R)-1-phenylcyclohexane-1,2-diol. (SB-V-169/SB-VIII-99).

Compound **2.114** was prepared according to the general procedure B. The crude residue was purified by flash chromatography eluting with a gradient of acetone/hexanes (1:9 → 1:3) to provide 41 mg (67%) of **2.114** as a white solid.

Compound **2.114** was prepared according to the general procedure B. The crude residue was purified by flash chromatography eluting with a gradient of acetone/hexanes (1:9 → 1:3) to provide 11 mg (57%) of **2.114** as a white solid. Enantiomeric excess was determined to be 94% *via* chiral HPLC using a chiralcel OJ-H column and eluting with a mixture of IPA/hexanes (8%) at a rate of 1 mL/min. Enantiomer A: rt = 11 min, Enantiomer B: rt = 13 min.



2.116

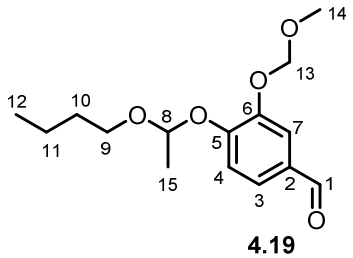
methyl (2R,3R)-2,3-dihydroxy-3-phenylpropanoate. (SB-V-197/202).

Compound **2.116** was prepared according to the general procedure B. The crude residue was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:3 → 1:0) to provide 89 mg (91%) **2.116** as a white solid.

Compound **2.116** was prepared according to the general procedure C. The crude residue was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:3 → 1:0) to provide 67 mg (68%) **2.116** as a white solid. Enantiomeric excess was determined to be 96% *via*

chiral HPLC using a chiralcel OD-H column and eluting with a mixture of IPA/hexanes (5%) at a rate of 1 mL/min. Enantiomer A: rt = 26 min, Enantiomer B: rt = 30 min.

5.2.2: Citreamicin

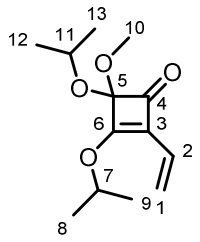


4.19

4-(*n*-Butoxyethoxy)-3-(methoxymethoxy)benzaldehyde (**4.19**). (SB-IV-301). *n*-Butyl vinyl ether (41 mg, 53 µL, 0.411 mmol) was added to a solution of **4.18** (50 mg, 0.274 mmol) and pyridinium *para*-toluenesulfonate (PPTS) (7 mg, 0.027) in CH_2Cl_2 (0.5 mL) at room temperature. The mixture was stirred for 16 h before adding a solution of saturated aqueous $NaHCO_3$ (1 mL). The mixture was extracted with CH_2Cl_2 (3 x 1 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:4) to provide 3 mg (72%) of **4.19**: ^{1}H-NMR (400 MHz) δ 9.87 (s, 1 H), 7.66 (d, *J* = 2.0 Hz, 1 H), 7.51 (dd, *J* = 2.0, 8.4 Hz, 1 H), 7.24 (d, *J* = 8.4 Hz, 1 H), 5.53 (q, *J* = 5.2 Hz, 1 H), 5.28 (d, *J* = 6.8 Hz, 1 H), 5.25 (d, *J* = 6.8 Hz, 1 H), 3.75 (dt, *J* = 6.4, 9.6 Hz, 1 H), 3.53 (s, 3 H), 3.50 (dt, *J* = 6.8, 9.8 Hz, 1 H), 1.57 (d, *J* = 5.2 Hz, 31 H), 1.56 (m, 2 H), 1.35 (sex, *J* = 7.6 Hz, 2 H), 0.89 (t, *J* = 7.6 Hz, 1 H).

NMR assignments: ^{1}H-NMR (400 MHz) δ 9.87 (s, 1 H, C1-H), 7.66 (d, *J* = 2.0 Hz, 1 H, C7-H), 7.51 (dd, *J* = 2.0, 8.4 Hz, 1 H, C3-H), 7.24 (d, *J* = 8.4 Hz, 1 H, C4-H), 5.53 (q, *J* = 5.2 Hz, 1 H, C8-H), 5.28 (d, *J* = 6.8 Hz, 1 H, C14-H), 5.25 (d, *J* = 6.8 Hz, 1 H, C14-H), 3.75 (dt, *J* = 6.4, 9.6 Hz, 1 H, C9-H), 3.53 (s, 3 H, C15-H), 3.50 (dt, *J* = 6.8, 9.8 Hz, 1 H, C9-H), 1.57 (d, *J* =

5.2 Hz, 31 H, C16-H), 1.56 (m, 2 H, C10-H), 1.35 (sex, *J* = 7.6 Hz, 2 H, C11-H), 0.89 (t, *J* = 7.6 Hz, 1 H, C12-H).



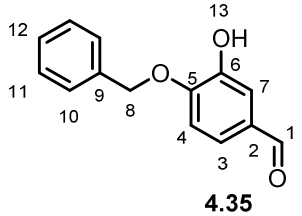
4.28

3,4-Diisopropoxy-4-methoxy-2-vinylcyclobut-2-en-1-one (**4.28**). (SB-VI-99). A solution of diisopropyl squarate **4.27** (580 mg, 2.93 mmol) in THF (20 mL) was cooled to – 78 °C, then degassed. In a separate flask, a solution of tetravinyl stannane (200 mg, 160 µL, 0.88 mmol) in Et_2O (3 mL) was cooled to – 78 °C, then degassed. A solution of *n*-BuLi (1.56 M, 2.06 mL, 3.22 mmol) was added to the tetravinyl stannane solution at – 78 °C. The reaction mixture was warmed to 0 °C and stirred for 20 min before adding to the solution of diisopropyl squarate **4.27** at – 78 °C. The reaction mixture was stirred for 2 h at – 78 °C, whereupon a solution of saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was extracted with EtOAc (3 x 10 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:2) to provide 501 mg (76%) of **4.29**.

A solution of **4.29** (250 mg, 1.1 mmol) and MeOH (0.70 g, 0.89 mL, 22.0 mmol) in THF (11 mL) was cooled to 0 °C. $BF_3.OEt_2$ (184 mg, 0.16 mL, 1.32 mmol) was added and the reaction mixture was stirred at 0 °C for 2 h whereupon a solution of saturated aqueous $NaHCO_3$ solution (5 mL) was added. The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:2) to provide 140 mg (53%) of **4.28**: ^{1}H-NMR (600 MHz) δ 6.14 (dd, *J* = 11.1, 17.6 Hz, 1 H), 6.00 (dd, *J* = 1.9, 17.6 Hz, 1 H), 5.41 (dd, *J* = 1.9, 11.1 Hz, 1 H), 4.96 (sep, *J* = 6.2, 1 H), 4.22 (sep, *J* = 6.2, 1 H), 3.50 (s, 3 H), 1.45 (d, *J* = 6.2 Hz, 3 H), 1.43 (d, *J* =

6.2 Hz, 3 H), 1.24 (d, *J* = 6.2 Hz, 3 H), 1.20 (d, *J* = 6.2 Hz, 3 H); ^{13}C-NMR (150 MHz) δ 189.9, 179.8, 126.7, 121.95, 121.87, 113.4, 78.0, 68.9, 53.3, 23.3, 23.5, 22.56, 22.52; IR (film) 2979 (C-H), 2937 (C-H), 2877, 2836, 1759 (C=O), 1643, 1605, 1584, 1425, 1374, 1324, 1256, 1181, 1078, 994 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{13}H_{20}O_4^+$ (M+Na), 263.1254; found, 263.1252.

NMR assignments: ^{1}H-NMR (600 MHz) δ 6.14 (dd, *J* = 11.1, 17.6 Hz, 1 H, C2-H), 6.00 (dd, *J* = 1.9, 17.6 Hz, 1 H, C1-H), 5.41 (dd, *J* = 1.9, 11.1 Hz, 1 H, C1-H), 4.96 (sep, *J* = 6.2, 1 H, C7-H), 4.22 (sep, *J* = 6.2, 1 H, C11-H), 3.50 (s, 3 H, C10-H), 1.45 (d, *J* = 6.2 Hz, 3 H, C12-H or C13-H), 1.43 (d, *J* = 6.2 Hz, 3 H, C12-H or C13-H), 1.24 (d, *J* = 6.2 Hz, 3 H, C8-H or C9-H), 1.20 (d, *J* = 6.2 Hz, 3 H, C8-H or C9-H); ^{13}C-NMR (150 MHz) δ 189.9 (C4), 179.8 (C6), 126.7 (C3), 121.9 (C1), 121.9 (C2), 113.4 (C5), 78.0 (C7), 68.9 (C11), 53.3 (C10), 23.3 (C8 or C9), 23.5 (C8 or C9), 22.6 (C12 or C13), 22.5 (C12 or C13).

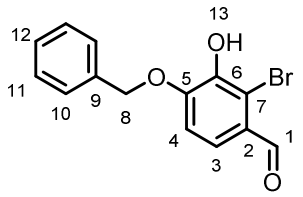


4.35

4-(Benzyloxy)-3-hydroxy benzaldehyde (**4.35**). (SB-IV-267). A mixture of 4,5-dihydroxybenzaldehyde (**4.20**) (5.0 g, 36.2 mmol) and K_2CO_3 (5.0 g, 36.2 mmol) in DMF (20 mL) was heated at 60 °C for 4 h. The mixture was cooled to room temperature and benzyl bromide (7.7 g, 5.4 mL, 45.2 mmol) was added, and the mixture was stirred 16 h whereupon a solution of saturated aqueous NH_4Cl (10 mL) and H_2O (10 mL) was added. The mixture was extracted with toluene (3 x 20 mL), and the combined organic extracts were washed with 13% aqueous brine solution (4 x 3 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was crystallized by dissolving in hot toluene (20 mL) to provide 3.4 g (35%) of **4.35** as a tan solid: mp 115-120 °C. Hexanes (20 mL) were added to the mother liquors and the mixture was heated until the solids were dissolved. Upon cooling to room temperature, another 0.9 g (11%) of **4.35** (46% total) was isolated as a tan solid: ^{1}H-NMR (400 MHz) δ 9.84 (s, 1 H), 7.46 (d, *J* = 2.0 Hz, 1 H), 7.44-7.40 (comp, 6 H), 7.04 (d, *J* = 8.0 Hz, 1 H), 5.82 (s, 1 H),

5.21 (s, 2 H); ^{13}C-NMR (100 MHz) δ 191.0, 150.9, 146.3, 135.2, 130.8, 128.9, 128.8, 127.9, 124.3, 114.4, 111.5, 71.3; IR (film) 3217 (OH), 2871 (CH), 1675 (C=O), 1606, 1582, 1512, 1455, 1345, 1281, 1117, 1016 cm^{-1}; HRMS (ESI) *m/z* calc for $C_{14}H_{11}O_3^-$, 227.0714; found, 227.0716.

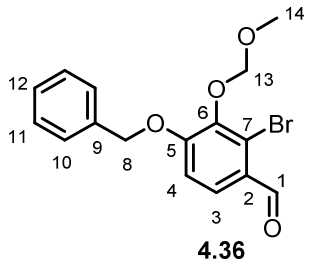
NMR assignments: ^{1}H-NMR (400 MHz) δ 9.84 (s, 1 H, C1-H), 7.46 (d, *J* = 2.0 Hz, 1 H, C7-H), 7.44-7.40 (comp, 6 H, C3-H, C10-H, C11-H, C12-H), 7.04 (d, *J* = 8.0 Hz, 1 H, C4-H), 5.82 (s, 1 H, C13-H), 5.21 (s, 2 H, C8-H); ^{13}C-NMR (100 MHz) 191.0 (C1), 150.9 (C5), 146.3 (C6), 135.2 (C9), 130.8 (C2), 128.9 (C11), 128.8 (C12), 127.9 (C10), 124.3 (C3), 114.4 (C7), 111.5 (C4), 71.3 (C8).



4-(Benzyloxy)-2-bromo-3-hydroxy benzaldehyde. (SB-VI-34). A solution of aldehyde **4.35** (2.93 g, 12.84 mmol) in CH_2Cl_2 (108 mL) and toluene (667 mL) was cooled to –78 °C. A separate flask containing a slurry of NBS (2.74g, 15.41 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 °C and tetramethylguanidine (TMG) (1.92 g, 2.09 mL, 16.69 mmol) was added dropwise. The slurry was stirred for 5 min (or until homogeneous) before being added to the solution of **4.35** at –78 °C. The reaction mixture was stirred at –78 °C for 2 h whereupon butylatedhydroxytoluene (BHT) (0.85g, 3.85 mmol) was added, the bath was removed, and the reaction was warmed to room temperature over 2 h. The mixture was washed with saturated aqueous NH_4Cl (1 x 100 mL), deionized H_2O (1 x 100 mL), dried (Na_2SO_4). The combined organic extracts were then filtered through a silica plug (500 mL). The combined organic extracts were discarded, and the plug was eluted with 1:1 EtOAc/hexanes (1 x 1 L) and the eluent was concentrated under reduced pressure to provide 2.56 g (65%) of the crude named compound as an orange to brown solid. The crude was recrystallized in IPA (49 mL) to provide 2.46 g (62%) of the pure titled

compound as an off-white solid: mp 118-120 °C; ^{1}H-NMR (400 MHz) δ 10.25 (s, 1 H), 7.53 (d, *J* = 8.6 Hz, 1 H), 7.43-7.40 (comp, 5 H), 6.98 (d, *J* = 8.6 Hz, 1 H), 6.21 (s, 1 H), 5.22 (s, 2 H); ^{13}C-NMR (100 MHz) 190.9, 150.8, 143.4, 134.9, 128.9, 128.9, 127.8, 127.4, 122.5, 113.1, 110.6, 71.6; HRMS (ESI) *m/z* calc for $C_{14}H_{10}BrO_3^-$, 304.9819; found, 304.982; *m/z* calc for $C_{14}H_{10}BrO_3^-$, 306.9800; found, 306.9802.

NMR assignments: ^{1}H-NMR (400 MHz) δ 10.25 (s, C1-H), 7.53 (d, *J* = 8.6 Hz, C3-H), 7.43-7.40 (comp, C10-H, C11-H, C12-H), 6.98 (d, *J* = 8.6, C4-H), 6.21 (s, C13-H), 5.22 (s, C8-H); ^{13}C-NMR (100 MHz) 190.9 (C1), 150.8 (C5), 143.4 (C6), 134.9 (C9), 128.9 (C2), 128.9 (C11), 127.8 (C12), 127.4 (C10), 122.5 (C3), 113.1 (C7), 110.6 (C4), 71.6 (C8).

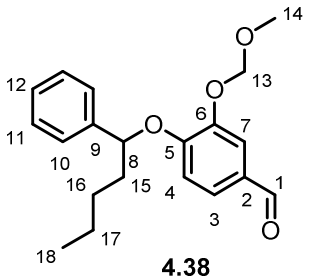


4.36

4-(Benzyloxy)-2-bromo-3-(methoxymethoxy)benzaldehyde (**4.36**). (SB-V-194). A solution of 4-(benzyloxy)-2-bromo-3-hydroxybenzaldehyde (1.36 g, 4.43 mmol) and diisopropylethylamine (DIPEA) (0.69 g, 0.93 mL, 5.32 mmol) in CH_2Cl_2 (27 mL) was cooled to 0 °C. Chloromethylmethylether (MOMCl)[633] (0.53 g, 0.50 mL, 6.64 mmol) was added, and the reaction mixture was warmed to room temperature and stirred for 2 h whereupon a solution of saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was extracted with EtOAc (3 x 5 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil solidified slowly upon standing to provide **4.36** as a waxy white solid: mp 54-56 °C; ^{1}H-NMR (400 MHz) δ 10.26 (s, 1 H), 7.70 (d, *J* = 8.8 Hz, 1 H), 7.43-7.33 (comp, 5 H), 7.01 (d, *J* = 8.8 Hz, 1 H), 5.21 (s, 2 H), 5.17 (s, 2 H), 3.59 (s, 3 H); ^{13}C-NMR (100 MHz) 190.0, 157.3, 143.7, 135.3, 128.8, 128.5, 127.7, 127.5, 126.4, 123.3, 112.2, 98.9, 71.2, 58.2; IR (film) 2935 (CH), 1682 (C=O), 1579, 1482, 1378, 1298, 1275, 1254, 1214, 1158 cm^{-1};

HRMS (ESI) *m/z* calc for $NaC_{16}H_{15}BrO_4^+$ (M+Na), 373.0046; found, 373.0054; *m/z* calc for $NaC_{17}H_{17}BrO_3^+$ (M+Na), 375.0027; found, 375.0037.

NMR assignments: ^{1}H-NMR (400 MHz) δ 10.26 (s, 1 H, C1-H), 7.70 (d, *J* = 8.8 Hz, 1 H, C3-H), 7.43-7.33 (comp, 5 H, C10-H, C11-H, C12-H), 7.01 (d, *J* = 8.8 Hz, 1 H, C4-H), 5.21 (s, 2 H, C8-H), 5.17 (s, 2 H, C13-H), 3.59 (s, 3 H, C14-H); ^{13}C-NMR (100 MHz) 190.0 (C1), 157.3 (C5), 143.7 (C6), 135.3 (C9), 128.8 (C2), 128.5 (C11), 127.7 (C12), 127.5 (C10), 126.4 (C3), 123.3 (C7), 112.2 (C4), 98.9 (C13), 71.6 (C8), 58.2 (C14).

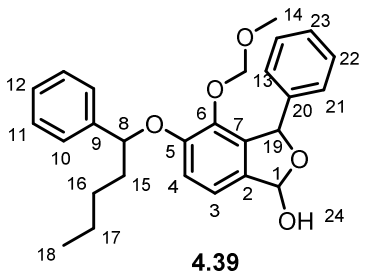


4.38

3-(Methoxymethoxy)-4-((1-phenylpentyl)oxy)benzaldehyde (**4.38**). (SB-IV-282). A solution of *n*-BuLi (2.5 M, ca. 0.35 mL, 0.880 mmol) was added to a slurry of triphenylmethane (Ph_3C-H) (2 mg, 0.007 mmol), and *N,O*-dimethylhydroxylamine hydrochloride (42 mg, 0.426 mmol) in THF (1 mL) at 0 °C until the solution turned a persistent red color (5 min). The solution was added to a slurry of **4.36** (50 mg, 0.142 mmol) and NaH (60 % dispersion in mineral oil, ca. 4 mg, 0.071 mmol) in THF (1 mL) at 0 °C, and the mixture was stirred for 30 min. In a separate flask, a solution of *n*-BuLi (2.5 M, 0.14 mL, 0.312 mmol) in hexanes was added to THF (0.5 mL) at –78 °C. The reaction mixture containing **4.36** was added to the *n*-BuLi and stirred for 1 h before adding benzyl bromide (49 mg, 34 μL, 0.286 mmol) and warming to 0 °C. The reaction was stirred for 10 min, whereupon a solution of saturated aqueous $NaHCO_3$ (1 mL) was added. The mixture was extracted with EtOAc (3 x 1 mL) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:5) to

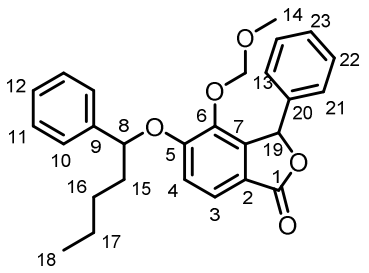
provide 11 mg (24%) of **4.38** as an oil and 19 mg (49%) of **4.92**: ^{1}H-NMR (400 MHz) δ 9.77 (s, 1 H), 7.59 (d, *J* = 2.0 Hz, 1 H), 7.34-7.32 (comp, 6 H), 6.81 (d, *J* = 8.4 Hz, 1 H), 5.30 (app dd, *J* = 1.2, 6.4 Hz, 2 H), 5.19 (dd, *J* = 5.2, 7.2 Hz, 1 H), 3.57 (s, 3 H), 2.11 (dddd, *J* = 4.8, 8.0, 10.0, 18.8 Hz, 1 H), 1.89 (ddt, *J* = 5.2, 5.2, 10.4, 14.0 Hz, 1 H), 1.52 (dtdd, *J* = 3.2, 5.6, 11.2, 11.2, 12.4 Hz, 1 H), 1.43-1.32 (comp, 3 H), 0.90 (t, *J* = 7.6 Hz, 3 H); ^{13}C-NMR (100 MHz) δ 190.7, 154.4, 147.3, 141.3, 129.9, 128.7, 127.8, 126.2, 125.8, 116.8, 114.7, 95.5, 81.6, 56.4, 38.3, 27.9, 22.5, 14.0; IR (film) 2954 (C-H), 2930 (C-H), 2858 (C-H), 1687 (C=O), 1595, 1504, 1263, 1155, 1127, 1078, 997 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{20}H_{24}O_4^+$ (M+Na), 351.1567; found, 351.1571.

NMR assignments: ^{1}H-NMR (400 MHz) δ 9.77 (s, 1 H, C1-H), 7.59 (d, *J* = 2.0 Hz, 1 H, C7-H), 7.34-7.32 (comp, 6 H, C3-H, C10-H, C11-H, C12-H), 6.81 (d, *J* = 8.4 Hz, 1 H, C4-H), 5.30 (app dd, *J* = 1.2, 6.4 Hz, 2 H, C13-H), 5.19 (dd, *J* = 5.2, 7.2 Hz, 1 H, C8-H), 3.57 (s, 3 H, C14-H), 2.11 (dddd, *J* = 4.8, 8.0, 10.0, 18.8 Hz, 1 H, C15-H), 1.89 (ddt, *J* = 5.2, 5.2, 10.4, 14.0 Hz, 1 H, C15-H), 1.52 (dtdd, *J* = 3.2, 5.6, 11.2, 11.2, 12.4 Hz, 1 H, C16-H), 1.43-1.32 (comp, 3 H, C16-H, C17-H), 0.90 (t, *J* = 7.6 Hz, 3 H, C18-H); ^{13}C-NMR (100 MHz) δ 190.7 (C1), 154.4 (C5), 147.3 (C6), 141.3 (C9), 129.9 (C2), 128.7 (C11), 127.8 (C12), 126.2 (C3), 125.8 (C10), 116.8 (C7), 114.7 (C14), 95.5 (C13), 81.6 (C8), 56.4 (C14), 38.3 (C15), 27.9 (C16), 22.5 (C17), 14.0 (C18).



4.39

4-(Methoxymethoxy)-3-phenyl-5-((1-phenylpentyl)oxy)-1,3-dihydroisobenzofuran-1-ol (**4.39**). (SB-IV-278). A solution of *n*-BuLi (2.5 M, ca. 0.35 mL, 0.880 mmol) was added to a slurry of triphenylmethane (Ph_3C-H) (2 mg, 0.007 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (17 mg, 0.170 mmol) in THF (1 mL) at 0 °C until the solution turned a persistent red color (5 min). The solution was added to a slurry of **4.36** (50 mg, 0.142 mmol) and NaH (60 % dispersion in mineral oil, ca. 4 mg, 0.071 mmol) in THF (1 mL) at 0 °C and the mixture was stirred for 30 min. In a separate flask, a solution of *n*-BuLi (2.5 M, 0.14 mL, 0.312 mmol) in hexanes was added to THF (0.5 mL) cooled to –78 °C. The reaction mixture containing **4.36** was added to the *n*-BuLi and stirred for 1 h before adding benzaldehyde (21 µL, 23 mg, 0.213 mmol) and warming to 0 °C. The reaction was stirred for 10 min whereupon a solution of saturated aqueous $NaHCO_3$ (1 mL) was added. The mixture was extracted with EtOAc (3 x 1 mL) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:4 → 1:2) to provide 33 mg (53%) of **4.39** as a mixture of diastereomers.

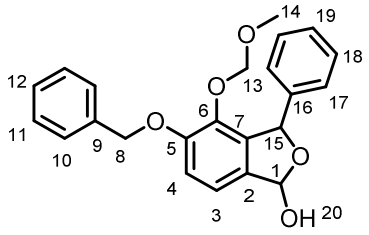


4-(Methoxymethoxy)-3-phenyl-5-((1-phenylpentyl)oxy)isobenzofuran-1(3H)-one.

(SB-IV-280B). Pyridinium chlorochromate (PCC) (44 mg, 0.200 mmol) was added to a solution of **4.39** (33 mg, 0.076 mmol) in CH_2Cl_2 (0.5 mL) at room temperature. The reaction mixture was stirred for 1 h before adding silica (~ 200 mg), and removing the solvent under reduced pressure and the crude material was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:4) to provide 26 mg (79%) of the titled compound as a mixture (1:1) of diastereomers: ^{1}H-NMR (400 MHz) δ 7.50 (d, *J* = 8.4 Hz, 1 H), 7.49 (d, *J* = 8.4 Hz, 1 H), 7.37-7.25 (comp, 20 H), 6.92 (d, *J* = 8.4 Hz, 1 H), 6.91 (d, *J* = 8.4 Hz, 1 H), 6.41 (s, 1 H), 6.39 (s, 1 H), 5.20 (app q, *J* = 7.2 Hz, 2 H), 5.11 (d, *J* = 5.6 Hz, 1 H), 5.00 (d, *J* = 5.6 Hz, 1 H), 4.85 (d, *J* = 5.6 Hz, 1 H), 4.83 (d, *J* = 5.6 Hz, 1 H), 3.33 (s, 3 H), 3.29 (s, 3 H), 2.09-2.00 (comp, 2 H), 1.98-1.82 (comp, 2 H), 1.49-1.39 (comp, 2 H), 1.38-1.29 (comp, 6 H), 0.88 (t, *J* = 6.8 Hz, 3 H) 0.87 (t, *J* = 7.2 Hz, 3 H); ^{13}C-NMR (100 MHz) δ 169.8, 155.8, 155.6, 142.52, 142.49, 140.6, 140.5, 140.4, 136.1, 129.3, 128.8, 128.7, 128.1, 128.0, 127.9, 127.8, 125.90, 125.88, 121.95. 121.86, 119.23, 119.21, 117.0, 116.8, 98.3, 98.1, 82.0, 81.8, 81.3, 57.22, 57.16, 38.2, 38.1, 27.7, 27.6, 22.5, 22.4, 13.9; IR (film) 2932 (C-H), 1764 (C=O), 1491, 1458, 1338, 1251, 1271, 1159, 1076, 1049, 1002, 954 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{27}H_{28}O_5^+$ (M+Na), 455.1829; found, 455.1835.

NMR assignments: ^{1}H-NMR (400 MHz) δ 7.50 (d, *J* = 8.4 Hz, 1 H, C3-H), 7.49 (d, *J* = 8.4 Hz, 1 H, C3-H), 7.37-7.25 (comp, 20 H, C10-H, C11-H, C12-H, C21-H, C22-H, C23-H), 6.92 (d, *J* = 8.4 Hz, 1 H, C4-H), 6.91 (d, *J* = 8.4 Hz, 1 H, C4-H), 6.41 (s, 1 H, C19-H), 6.39 (s, 1 H, C19-H), 5.20 (app q, *J* = 7.2 Hz, 2 H, C8-H), 5.11 (d, *J* = 5.6 Hz, 1 H, C13-H), 5.00 (d, *J* = 5.6 Hz, 1 H, C13-H), 4.85 (d, *J* = 5.6 Hz, 1 H, C13-H), 4.83 (d, *J* = 5.6 Hz, 1 H, C13-H), 3.33 (s,

3 H, C14-H), 3.29 (s, 3 H, C14-H), 2.09-2.00 (comp, 2 H, C15-H), 1.98-1.82 (comp, 2 H, C15-H), 1.49-1.39 (comp, 2 H, C16- H), 1.38-1.29 (comp, 6 H, C16-H, C17-H), 0.88 (t, J = 6.8 Hz, 3 H, C18-H) 0.87 (t, J = 7.2 Hz, 3 H, C18-H); ^{13}C-NMR (100 MHz) δ 169.8 (C1), 155.8 (C5), 155.6 (C5), 142.52 (C6), 142.49 (C6), 140.6 (C9), 140.5 (C7), 140.4 (C7), 136.1 (C9), 129.3 (C20), 128.8 (C22), 128.7 (C22), 128.1 (C11), 128.0 (C11), 127.9 (C12 or C23), 127.8 (C12 or C23), 125.90 (C10 or C21), 125.88 (C10 or C21), 121.95 (C2). 121.86 (C2), 119.23 (C3), 119.21 (C3), 117.0 (C4), 116.8 (C4), 98.3 (C13), 98.1 (C13), 82.0 (C19), 81.8 (C19), 81.3 (C8), 57.22 (C14), 57.16 (C14), 38.2 (C15), 38.1 (C15), 27.7 (C16), 27.6 (C16), 22.5 (C17), 22.4 (C17), 13.9 (C18).

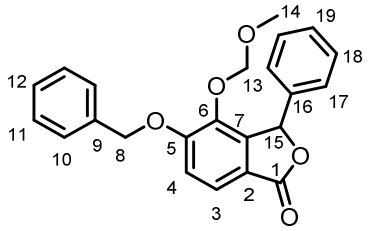


4.37

5-(Benzyloxy)-4-(methoxymethoxy)-3-phenyl-1,3-dihydroisobenzofuran-1-ol (**4.37**). (SB-V-21). A solution of *n*-BuLi (2.5 M, ca. 0.14 mL, 0.341 mmol) was added to a slurry of triphenylmethane (Ph_3C-H) (2 mg, 0.007 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (17 mg, 0.170 mmol) in THF (1 mL) at 0 °C until the solution turns a persistent (5 min) red color. The solution was added to a slurry of **4.36** (50 mg, 0.142 mmol) and NaH (60 % dispersion in mineral oil, ca. 4 mg, 0.071 mmol) in THF (1 mL) at 0 °C and the mixture was stirred for 30 min before cooling to –78 °C. A solution of *tert*-BuLi (1.41 M, 0.22 mL, 0.312 mmol) in pentanes was added, and the mixture stirred for five min before adding benzaldehyde (21 µL, 23 mg, 0.213 mmol) and warming to 0 °C. The reaction was stirred for 10 min whereupon a solution of saturated aqueous $NaHCO_3$ (1 mL) was added. The mixture was extracted with EtOAc (3 x 1 mL) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:2) to provide 34 mg (63%)

of **4.37** as a mixture of diastereomers: ^{1}H-NMR (400 MHz) δ 7.43-7.27 (comp, 20 H), 7.15 (d, *J* = 8.0 Hz, 1 H), 7.148 (d, *J* = 8.4 Hz, 1 H), 7.03 (d, *J* = 8.4 Hz, 1 H), 7.02 (d, *J* = 8.0 Hz, 1 H), 6.60 (s, 1 H), 6.45 (s, 1 H), 6.42 (d, *J* = 2.0, 1 H), 6.20 (s, 1 H), 5.08 (app s, 4 H), 4.94 (d, *J* = 4.0 Hz, 1 H), 4.93 (d, *J* = 4.0 Hz, 1 H), 4.68 (d, *J* = 4.0 Hz, 1 H), 4.67 (d, *J* = 4.0 Hz, 1 H), 3.23 (s, 3 H), 3.22 (s, 3 H).

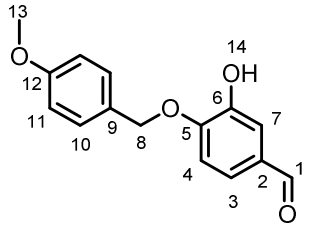
NMR assignments: ^{1}H-NMR (400 MHz) δ 7.43-7.27 (comp, 20 H, C10-H, C11-H, C12-H, C17-H, C18-H, C19-H), 7.15 (d, *J* = 8.0 Hz, 1 H, C3-H), 7.148 (d, *J* = 8.4 Hz, 1 H, C3-H), 7.03 (d, *J* = 8.4 Hz, 1 H, C4-H), 7.02 (d, *J* = 8.0 Hz, 1 H, C4-H), 6.60 (s, 1 H, C15-H), 6.45 (s, 1 H, C1- H), 6.42 (d, *J* = 2.0, 1 H, C1-H), 6.20 (s, 1 H, C15-H), 5.08 (app s, 4 H, C8-H), 4.94 (d, *J* = 4.0 Hz, 1 H, C13-H), 4.93 (d, *J* = 4.0 Hz, 1 H, C13-H), 4.68 (d, *J* = 4.0 Hz, 1 H, C13-H), 4.67 (d, *J* = 4.0 Hz, 1 H, C13-H), 3.23 (s, 3 H, C14-H), 3.22 (s, 3 H, C14-H).



5-(Benzyloxy)-4-(methoxymethoxy)-3-phenylisobenzofuran-1(3H)-one. (SB-V-23). Pyridinium chlorochromate (PCC) (44 mg, 0.691 mmol) was added to a solution of **4.37** (34 mg, 0.090 mmol) in CH_2Cl_2 (0.5 mL) at room temperature. The reaction mixture was stirred for 2 h whereupon silica was added and the residual solvent was removed under reduced pressure. The crude material was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:2) to provide 22 mg (65%) of the titled compound as a clear oil: ^{1}H-NMR (500 MHz) δ 7.69 (d, *J* = 8.4 Hz, 1 H), 7.41-7.38 (comp, 4 H), 7.36-7.35 (comp, 4 H), 7.29-7.26 (comp, 2 H), 7.19 (d, *J* = 8.4, 1 H), 6.42 (s, 1 H), 5.17 (s, 2 H), 4.96 (d, *J* = 5.7 Hz, 1 H), 4.78 (d, *J* = 5.7 Hz, 1 H), 3.20 (s, 3 H); ^{13}C-NMR (125 MHz) δ 169.8, 156.2, 142.3, 140.5, 136.0, 135.5, 129.3, 128.76, 128.75, 128.5, 127.8, 127.5, 122.1, 119.8, 115.7, 98.1, 81.4, 71.4, 57.2; IR (film) 3034

(C-H), 2936 (C-H), 1765 (C=O), 1613, 1495, 1456, 1385, 1339, 1279, 1200, 1160, 1076, 1002, 949 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{23}H_{20}O_5$ (M+Na), 399.1203; found, 399.1207.

NMR assignments: ^{1}H-NMR (500 MHz) δ 7.69 (d, *J* = 8.4 Hz, 1 H, C3-H), 7.41-7.38 (comp, 4 H, C11-H, C18-H), 7.36-7.35 (comp, 4 H, C10-H, C17-H), 7.29-7.26 (comp, 2 H, C12-H, C19-H), 7.19 (d, *J* = 8.4, 1 H, C4-H), 6.42 (s, 1 H, C15-H), 5.17 (s, 2 H, C8-H), 4.96 (d, *J* = 5.7 Hz, 1 H, C13-H), 4.78 (d, *J* = 5.7 Hz, 1 H, C13-H), 3.20 (s, 3 H, C14-H); ^{13}C-NMR (125 MHz) δ 169.8 (C1), 156.2 (C5), 142.3 (C6), 140.5 (C16), 136.0 (C9), 135.5 (C7), 129.3 (C19), 128.76 (C11 or C18), 128.75 (C11 or C18), 128.5 (C12), 127.8 (C17), 127.5 (C10), 122.1 (C2), 119.8 (C3), 115.7 (C4), 98.1 (C13), 81.4 (C15), 71.4 (C8), 57.2 (C14).

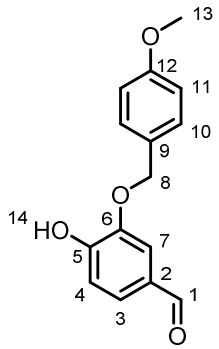


4.50

3-Hydroxy-4-((4-methoxybenzyl)oxy) benzaldehyde (**4.50**). (SB-V-297). A mixture of 4,5-dihydroxybenzaldehyde **4.20** (10.0 g, 65.6 mmol), $NaHCO_3$ (8.2 g, 98.4 mmol) and sodium iodide (NaI) (3.0 g, 19.6 mmol) in anhydrous DMF (40 mL) was heated at 40 °C for 2 h. Para methoxybenzyl chloride (PMBCl)[634] (20.6 g, 17.8 mL, 131.2 mmol) was added and then stirred at 40 °C for an additional 24 h whereupon the reaction was cooled to room temperature and H_2O (80 mL) was added. The mixture was extracted with EtOAc (3 x 30 mL) and the combined organic extracts were then washed with 13% aqueous brine solution (4 x 10 mL), and the combined organic extracts were dried (Na_2SO_4). Hexanes (50 mL) was added and the combined organic extracts were filtered through a silica plug and eleted with 2:1 EtOAc/Hexanes (1 x 300 mL) and the combined organic layers were concentrated under reduced pressure. The crude material was crystallized from toluene (40 mL) to yield 13.4g (79%) pure **4.50** as a white solid: mp 117-120 °C.

The mother liquors were washed with a 5% NaOH solution (3 x 60 mL) and the combined organic extracts were discarded. The aqueous layer was neutralized with saturated aqueous NH_4Cl and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The solids were purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:4 $\rightarrow$ 1:2) to provide 3.4 g (20%) more **4.50** as an off-white solid (99% total): ^{1}H-NMR (400 MHz) δ 9.83 (s, 1 H), 7.52 (d, *J* = 2.0 Hz, 1 H), 7.44 (dd, *J* = 2.0, 8.0 Hz, 1 H), 7.36 (d, *J* = 8.8, 2 H), 7.05 (d, *J* = 8.0 Hz, 1 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 5.10 (s, 2 H), 3.84 (s, 3 H); ^{13}C-NMR (100 MHz) δ 191.0, 160.0, 151.1, 146.3, 130.7, 129.8, 127.2, 124.3, 114.3, 114.2, 111.5, 71.1, 55.3; IR (film) 3213 (OH), 1668 (C=O), 1612, 1504, 1274, 1128 cm^{-1}; HRMS (ESI) *m/z* calc for $C_{15}H_{14}O_4^-$, 257.0819; found, 257.0826.

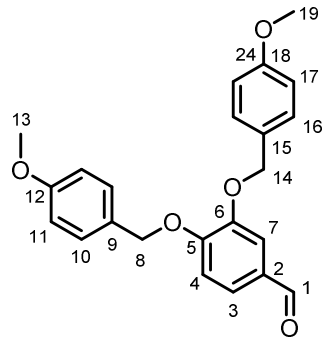
NMR assignments: ^{1}H-NMR (400 MHz) δ 9.83 (s, 1 H, C1-H), 7.52 (d, *J* = 2.0 Hz, 1 H, C7- H), 7.44 (dd, *J* = 2.0, 8.0 Hz, 1 H, C3- H), 7.36 (d, *J* = 8.8, 2 H, C10- H), 7.05 (d, *J* = 8.0 Hz, 1 H, C4- H), 6.95 (d, *J* = 8.8 Hz, 2 H, C11- H), 5.10 (s, 2 H, C8- H), 3.84 (s, 3 H, C13- H); ^{13}C-NMR (100 MHz) δ 191.0 (C1), 160.0 (C12), 151.1 (C5), 146.3 (C6), 130.7 (C2), 129.8 (C10), 127.2 (C9), 124.3 (C3), 114.3 (C7), 114.2 (C11), 111.5 (C4), 71.1 (C8), 55.3 (C13).



4.53

4-Hydroxy-3-((4-methoxybenzyl)oxy) benzaldehyde (**4.53**) (SB-V-83/94/95). The mother liquors from the PMB protection of **4.50** were purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:5 → 1:2) to provide 3.0 g of crude oily solid. The solid was dissolved in toluene (10 mL) and extracted with 2 M NaOH solution (3 x 5 mL). The aqueous layer was neutralized with 1 M HCl solution and extracted with toluene (3 x 10 mL). The combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure and the crude was purified by flash chromatography eluting with EtOAc/hexanes (2:5) buffered with 1% Et_3N to provide 175 mg **4.53** (2%) as a white solid: mp 125-127 °C; ^{1}H-NMR (400 MHz) δ 9.85 (s, 1 H), 7.45 (d, *J* = 2.0 Hz, 1 H), 7.42 (dd, *J* = 2.0, 8.0 Hz, 1 H), 7.36 (d, *J* = 8.8 Hz, 2 H), 7.06 (d, *J* = 8.0 Hz, 1 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 5.77 (bs, 1 H), 5.13 (s, 2 H), 3.84 (s, 3 H); ^{13}C-NMR (100 MHz) δ 191.0, 160.0, 151.0, 146.3, 130.7, 129.8, 127.2, 124.3, 114.3, 114.2, 111.4, 71.1, 55.3; HRMS (ESI) *m/z* calc for $NaC_{15}H_{14}O_4^+$ (M+Na), 281.0784; found, 281.0783.

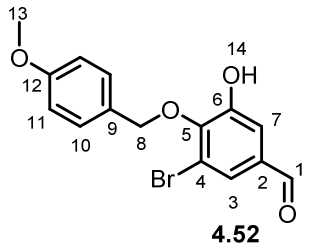
NMR assignments: ^{1}H-NMR (400 MHz) δ 9.85 (s, 1 H, C1- H), 7.45 (d, *J* = 2.0 Hz, 1 H, C7- H), 7.42 (dd, *J* = 2.0, 8.0 Hz, 1 H, C3- H), 7.36 (d, *J* = 8.8 Hz, 2 H, C10-H), 7.06 (d, *J* = 8.0 Hz, 1 H, C4-H), 6.95 (d, *J* = 8.8 Hz, 2 H, C11-H), 5.77 (bs, 1 H, OH), 5.13 (s, 2 H, C8-H), 3.84 (s, 3 H, C13-H); ^{13}C-NMR (100 MHz) δ 191.0 (C1), 160.0 (C12), 151.0 (C5), 146.3 (C6), 130.7 (C2), 129.8 (C10), 127.2 (C9), 124.3 (C3), 114.3 (C7), 114.2 (C11), 111.4 (C4), 71.1 (C8), 55.3 (C13).



4.54

3,4-Bis((4-methoxybenzyl)oxy)benzaldehyde (**4.54**) (SB-V-83/94/95). The combined organic extracts from the PMB protection of **4.50** were dried (Na_2SO_4), filtered, and concentrated under reduced pressure and the crude was purified by flash chromatography eluting with EtOAc/hexanes (2:5) buffered with 1%Et_3N to provide 840 mg (7%) of **4.54** as a waxy solid: mp 57-60 °C; ^{1}H-NMR (400 MHz) δ 9.81 (s, 1 H), 7.48 (m, 1 H), 7.42-7.34 (comp, 5 H), 7.02 (dd, *J* = 2.8, 8.0 Hz, 1 H), 6.91-6.81 (comp, 4 H), 5.17 (d, *J* = 2.0 Hz, 2 H), 5.13 (d, *J* = 2.0 Hz, 2 H), 3.82 (comp, 6 H); ^{13}C-NMR (100 MHz) δ 190.9, 159.5, 159.4, 154.4, 149.2, 136.2, 129.1, 128.8, 128.6, 128.2, 126.6, 114.0, 113.9, 113.2, 112.6, 70.8, 70.7, 55.3; IR (film) 3206 (OH), 1669 (C=O), 1612, 1517, 1505, 1274, 1250, 1206, 1178, 1128 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{23}H_{22}O_5^+$ (M+Na), 401.1359; found, 401.1359.

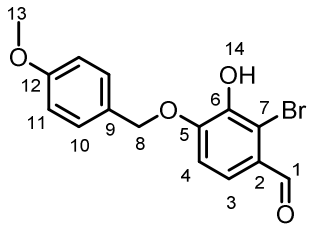
NMR assignments: ^{1}H-NMR (400 MHz) δ 9.81 (s, 1 H, C1-H), 7.48 (m, 1 H, C7-H), 7.42-7.34 (comp, 5 H, C4-H, C10-H, C16-H), 7.02 (dd, *J* = 2.8, 8.0 Hz, 1 H, C3-H), 6.91-6.81 (comp, 4 H, C11-H, C17-H), 5.17 (d, *J* = 2.0 Hz, 2 H, C8-H), 5.13 (d, *J* = 2.0 Hz, 2 H, C14-H), 3.82 (comp, 6 H, C13-H, C19-H); ^{13}C-NMR (100 MHz) δ 190.9 (C1), 159.5 (C12), 159.4 C18), 154.4 (C5), 149.2 (C6), 136.2 (C2), 129.1 (C10), 128.8 (C16), 128.6 (C9), 128.2 (C10), 126.6 (C3), 114.0 (C11), 113.9 (C17), 113.2 (C7), 112.6 (C4), 70.8 (C8), 70.7 (C14), 55.3 (C13, C19).



4.52

3-Bromo-5-hydroxy-4-((4-methoxybenzyl)oxy)benzaldehyde (**4.52**) (SB-V-87). A solution of NBS in CH_2Cl_2 (0.1 M, 14.4 mL, 1.45 mmol) was added over 1.5 h to a slurry of aldehyde **4.50** (248 mg, 0.96 mmol) and diisobutylamine (24 mg, 33 μL, 0.19 mmol) in CH_2Cl_2 (4 mL) at – 78 °C. The reaction was stirred for 30 min, whereupon a solution of saturated aqueous $Na_2S_2O_3$ (2 mL) was added, and the reaction was warmed to room temperature over 2 h. The mixture was extracted with CH_2Cl_2 (1 x 2 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:4) to provide 167 mg (55%) of **4.52** as a yellow solid: mp 147-149 °C; ^{1}H-NMR (400 MHz) δ 9.77 (s, 1 H), 7.65 (d, *J* = 1.5 Hz, 1 H), 7.45 (d, *J* = 1.5 Hz, 1 H), 7.35 (d, *J* = 8.8 Hz, 2 H), 6.94 (d, *J* = 8.8 Hz, 2 H), 6.60 (bs, 1 H), 5.12 (s, 2 H), 3.83 (s, 3 H); ^{13}C-NMR (100 MHz) δ 189.6, 160.1, 149.1, 146.8, 130.2, 130.0, 129.9, 126.9, 114.3, 109.4, 108.2, 71.6, 55.3; IR (film) 3223 (OH), 1673 (C=O), 1515, 1426, 1290, 1254, 1150 cm^{-1}; HRMS (ESI) *m/z* calc for $C_{15}H_{12}BrO_4^-$, 334.9924; found, 334.9934.

NMR assignments: ^{1}H-NMR (400 MHz) δ 9.77 (s, 1 H, C1-H), 7.65 (d, *J* = 1.5 Hz, 1 H, C7-H), 7.45 (d, *J* = 1.5 Hz, 1 H, C3-H), 7.35 (d, *J* = 8.8 Hz, 2 H, C10-H), 6.94 (d, *J* = 8.8 Hz, 2 H, C11-H), 6.60 (bs, 1 H, O-H), 5.12 (s, 2 H, C8-H), 3.83 (s, 3 H, C13-H); ^{13}C-NMR (100 MHz) δ 189.6 (C1), 160.1 (C12), 149.1 (C5), 146.8 (C6), 130.2 (C2), 130.0 (C10), 129.9 (C3), 126.9 (C9), 114.3 (C11), 109.4 (C7), 108.2 (C4), 71.6 (C8), 55.3 (C13).

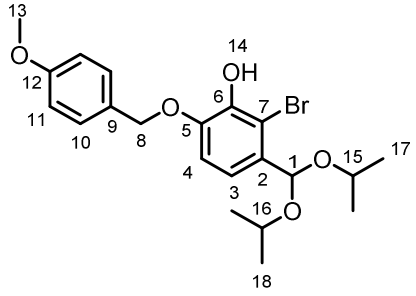


4.51

2-Bromo-3-hydroxy-4-((4-methoxybenzyl)oxy) benzaldehyde (**4.51**). (SB-VII-68). Aldehyde **4.50** (3.73 g, 14.44 mmol) was slurried in CH_2Cl_2 (144 mL) and cooled to – 78 °C. In a separate flask, TMG (3.32 g, 3.62 mL, 28.88 mmol) was added to a slurry of NBS (2.57 g, 14.44 mmol) in CH_2Cl_2 (43 mL) at 0 °C. The mixture was stirred until it became homogenous (~ 5 min), whereupon it was added in one portion to the aldehyde slurry at – 78 °C. The reaction mixture was stirred for 30 min at – 78 °C, whereupon AcOH (0.87 g, 0.83 mL, 28.88 mmol) was added and the reaction was warmed to room temperature. The mixture was filtered through a silica plug (300 mL) eluting with EtOAc/Hexane (1:1, 1 x 1.5 L). The eluent was concentrated under reduced pressure to provide 4.05 g (83%) **4.51** as a white to light yellow solid: mp 154-156 °C (IPA). The crude material can be purified by flash chromatography eluting with a gradient of acetone/hexanes with 1% Et_3N (7:13 $\rightarrow$ 7:3) but in most cases the material was sufficiently pure for the next step; ^{1}H-NMR (400 MHz) δ 10.26 (s, 1 H), 7.55 (d, *J* = 8.2 Hz, 1 H), 7.35 (d, *J* = 8.8 Hz, 2 H), 6.99 (d, *J* = 8.2 Hz, 1 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 6.13 (s, 1 H), 5.17 (s, 2 H), 3.84 (s, 3 H); ^{13}C-NMR (100 MHz) δ 190.9, 160.1, 150.8, 143.5, 129.8, 127.3, 126.8, 122.5, 114.3, 113.0, 110.6, 71.5, 55.4; IR (film) 3388 (OH), 2927 (C-H) 1680 (C=O), 1588, 1516, 1487, 1464, 1282, 1251, 1176, 1130 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{15}H_{13}BrO_4^+$ (M+Na), 358.9889; found, 358.9010.

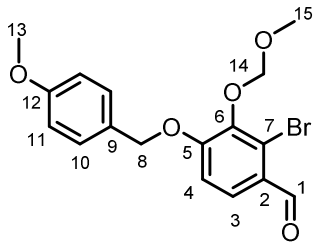
NMR assignments: ^{1}H-NMR (400 MHz) δ 10.26 (s, 1 H, C1-H), 7.55 (d, *J* = 8.2 Hz, 1 H, C3-H), 7.35 (d, *J* = 8.8 Hz, 2 H, C10-2), 6.99 (d, *J* = 8.2 Hz, 1 H, C4-H), 6.95 (d, *J* = 8.8 Hz, 2 H, C11-H), 6.13 (s, 1 H, O-H), 5.17 (s, 2 H, C8-H), 3.84 (s, 3 H, C13-H); ^{13}C-NMR (100

MHz) δ 190.9 (C1), 160.1 (C12), 150.8 (C5), 143.5 (C6), 129.8 (C2), 127.3 (C10), 126.8 (C9), 122.5 (C3), 114.3 (C7), 113.0 (C11), 110.6 (C4), 71.5 (C8), 55.4 (C13).



2-Bromo-3-(diisopropoxymethyl)-6-((4-methoxybenzyl)oxy)phenol. (SB-VI-63B). By-product isolated from the crystallization of **4.51** in IPA. Purified *via* flash chromatography eluting with a gradient of acetone/hexanes (1:5 → 2:5) buffered with 1% Et_3N to isolate 105 mg of the named compound as a clear oil; ^{1}H-NMR (400 MHz) δ 7.33 (d, *J* = 8.8 Hz, 2 H), 7.21 (d, *J* = 8.8 Hz, 1 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 6.91 (d, *J* = 8.8 Hz, 1 H), 5.75 (s, 1 H), 5.06 (s, 2 H), 3.88 (sept, *J* = 6.4 Hz, 2 H), 3.83 (s, 3H), 1.21 (d, *J* = 6.0 Hz, 6 H), 1.18 (d, *J* = 6.0 Hz, 6 H); ^{13}C-NMR (100 MHz) δ 159.8, 156.1, 143.0, 132.6, 129.6, 127.9, 119.1, 114.1, 111.1, 109.3, 98.4, 71.4, 68.7, 55.3, 22.9, 22.5; LCMS (APCI): 381 (M–C_3H_8O).

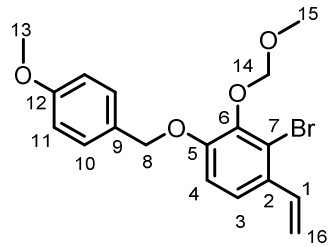
NMR assignments: ^{1}H-NMR (400 MHz) δ 7.33 (d, *J* = 8.8 Hz, 2 H, C10-H), 7.21 (d, *J* = 8.8 Hz, 1 H, C3-H), 6.92 (d, *J* = 8.8 Hz, 2 H, C11-H), 6.91 (d, *J* = 8.8 Hz, 1 H, C4-H), 5.75 (s, 1 H, C1-H), 5.06 (s, 2 H, C8-H), 3.88 (sept, *J* = 6.4 Hz, 2 H, C15-H, C16-H), 3.83 (s, 3H, C13-H), 1.21 (d, *J* = 6.0 Hz, 6 H, C17-H or C18-H), 1.18 (d, *J* = 6.0 Hz, 6 H, C17-H or C18-H); ^{13}C-NMR (100 MHz) δ 159.8 (C12), 156.1 (C5), 143.0 (C6), 132.6 (C10), 129.6 (C2), 127.9 (C9), 119.1 (C3), 114.1 (C7), 111.1 (C11), 109.3 (C4), 98.4 (C1), 71.4 (C8), 68.7 (C15, C16), 55.3 (C13), 22.9 (C17 or C18), 22.5 (C17 or C18).



4.76

2-Bromo-4-((4-methoxybenzyl)oxy)-3-(methoxymethoxy) benzaldehyde (**4.76**). (SB-VII-70). A solution of the crude aldehyde **4.51** (6.76 g, 20.05 mmol) and diisopropylethylamine (DIPEA) (3.89 g, 5.25 mL, 30.07 mmol) in CH_2Cl_2 (140 mL) was cooled to 0 °C. Chloromethyl methyl ether (MOMCl)[633] (1.18 M, 25.5 mL, 30.07 mmol) was added, and the cooling bath was removed. The solution was stirred at room temperature for 3 h, whereupon a solution of saturated aqueous $NaHCO_3$ (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 20 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide crude **4.76** as a white solid: mp 88-90 °C. The crude material can be purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:20 → 1:3) but in most cases the material was sufficiently pure for the next step; ^{1}H-NMR (400 MHz) δ 10.27 (s, 1 H), 7.72 (d, *J* = 8.6 Hz, 1 H), 7.34 (d, *J* = 8.6 Hz, 2 H), 7.02 (d, *J* = 8.6 Hz, 1 H), 6.92 (d, *J* = 8.6 Hz, 2 H), 5.19 (s, 2 H), 5.11 (s, 2 H), 3.82 (s, 3 H), 3.58 (s, 3 H); ^{13}C-NMR (100 MHz) δ 191.0, 159.8, 157.4, 143.6, 129.4, 127.5, 127.2, 126.4, 123.2, 114.1, 112.2, 98.8, 71.0, 58.1, 55.3; IR (film) 2968 (C-H), 1674 (C=O), 1515, 1382, 1250, 931 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{17}H_{17}BrO_5^+$ (M+Na), 403.0152; found, 403.0147.

NMR assignments: ^{1}H-NMR (400 MHz) δ 10.27 (s, 1 H, C1-H), 7.72 (d, *J* = 8.6 Hz, 1 H, C3-H), 7.34 (d, *J* = 8.6 Hz, 2 H, C10-H), 7.02 (d, *J* = 8.6 Hz, 1 H, C4-H), 6.92 (d, *J* = 8.6 Hz, 2 H, C11-H), 5.19 (s, 2 H, C8-H), 5.11 (s, 2 H, C14-H), 3.82 (s, 3 H, C13-H), 3.58 (s, 3 H, C15-H); ^{13}C-NMR (100 MHz) δ 191.0 (C1), 159.8 (C12), 157.4 (C5), 143.6 (C6), 129.4 (C10), 127.5 (C2), 127.2 (C9), 126.4 (C3), 123.2 (C7), 114.1 (C11), 112.2 (C4), 98.8 (C14), 71.0 (C8), 58.1 (C13), 55.3 (C15).



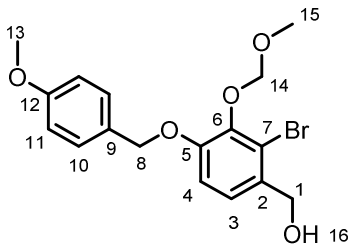
4.48

2-Bromo-4-((4-methoxybenzyl)oxy)-3-(methoxymethoxy)-1-vinylbenzene (**4.48**). **Procedure using *tert*-BuOLi**: (SB-V-196): A slurry of methyltriphenylphosphonium bromide (Ph_3PMeBr) (2.86 g, 8.01 mmol) and crude **4.76** in a mixture of anhydrous THF (18 mL) and DMSO (ppm $H_2O \leq 600$, 18 mL) was cooled to 0 °C and degassed. In a separate flask, a solution of *tert*-BuOLi in THF (9 mL) was prepared by adding *n*-BuLi (ca. 1.44 M, 7.4 mL, 10.7 mmol) to a solution of *tert*-BuOH (freshly distilled over CaH_2, 0.79 g, 1.02 mL, 10.68 mmol) and triphenylmethane (Ph_3C-H) (66 mg, 0.27 mmol) in THF (9 mL) until a red endpoint was observed. The solution of *tert*-BuOLi was added to the flask containing Ph_3PMeBr and **4.76** at 0 °C, and the stirring was continued for 30 min, whereupon a solution of saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was extracted with EtOAc (3 x 10 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:20 → 1:4) to provide 1.72 g (85%) of **4.48** as a waxy white solid.

Procedure using *n*-BuLi: (SB-VI-70): THF (35 mL) was added to a round bottom flask containing. A slurry of methyltriphenylphosphonium bromide (Ph_3PMeBr) (14.12 g, 40.10 mmol) was cooled to 0 °C, and degassed. A solution of *n*-BuLi in hexanes (1.61 M, 25 mL, 40.10 mmol) was slowly added over 10 min. The mixture was stirred for an additional 5 min whereupon DMSO (70 mL) was added followed by a solution of the crude **4.76** in THF (35 mL). The reaction was stirred for 10 min before a solution of saturated aqueous $NaHCO_3$ (50 mL) and water (100 mL) was added. The mixture was extracted with EtOAc (3 x 100 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:20 → 1:4) to provide 6.51 g (86%

from **4.51**) of **4.48** as a white waxy solid: mp 41-43 °C; ^{1}H-NMR (400 MHz) δ 7.34 (d, *J* = 8.8 Hz, 2 H), 7.26 (d, *J* = 8.8 Hz, 1 H), 7.02 (dd, *J* = 11.2, 17.2 Hz, 1 H), 6.90 (comp, 3 H), 5.56 (dd, *J* = 1.2, 17.2 Hz, 1 H), 5.25 (dd, *J* = 1.2, 11.2 Hz, 1 H), 5.17 (s, 2 H), 5.03 (s, 2 H) 3.82 (s, 3 H), 3.59 (s, 3 H); ^{13}C-NMR (100 MHz) δ 159.8, 151.8, 143.7, 135.7, 131.7, 129.3, 128.3, 121.9, 119.6, 115.2, 114.0, 113.2, 98.7, 71.0, 58.1, 55.3; IR (film) 2934 (C-H) 2835, 1614, 1587, 1515, 1484, 1465, 1382, 1287, 1251, 1214, 1174, 1159, 1033, 985 cm^{-1}; HRMS (CI) *m/z* calc for $C_{18}H_{19}BrO_4^+$, 377.0388; found, 377.0391.

NMR assignments: ^{1}H-NMR (400 MHz) δ 7.34 (d, *J* = 8.8 Hz, 2 H, C10-H), 7.26 (d, *J* = 8.8 Hz, 1 H, C3-H), 7.02 (dd, *J* = 11.2, 17.2 Hz, 1 H, C1-H), 6.90 (comp, 3 H, C4-H, C11-H), 5.56 (dd, *J* = 1.2, 17.2 Hz, 1 H, C16-H), 5.25 (dd, *J* = 1.2, 11.2 Hz, 1 H, C16-H), 5.17 (s, 2 H, C8-H), 5.03 (s, 2 H, C14-H) 3.82 (s, 3 H, C13-H), 3.59 (s, 3 H, C15-H); ^{13}C-NMR (100 MHz) δ 159.8 (C12), 151.8 (C5), 143.7 (C6), 135.7 (C1), 131.7 (C2), 129.3 (C10), 128.3 (C9), 121.9 (C16), 119.6 (C7), 115.2 (C3), 114.0 (C11), 113.2 (C4), 98.7 (C14), 71.0 (C8), 58.1 (C13), 55.3 (C16).

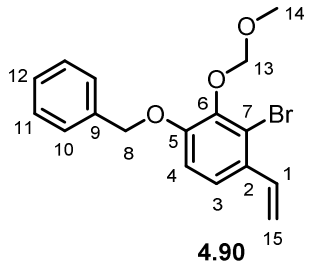


4.77

(2-Bromo-4-((4-methoxybenzyl)oxy)-3-(methoxymethoxy)phenyl) methanol (**4.77**) (SB-V-138). Isolated from the Wittig olefination of **4.76**. Purified *via* flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 3:4) to provide 142 mg (17%) of **4.77** as a clear oil: ^{1}H-NMR (400 MHz) δ 7.33 (d, *J* = 8.8 Hz, 2 H), 7. 15 (d, *J* = 8.4 Hz, 1 H), 6.93 (d, *J* = 8.4 Hz, 1 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 5.18 (s, 2 H), 5.02 (s, 2 H), 4.70 (d, *J* = 6.4 Hz, 2 H), 3.80 (s, 3 H), 3.57 (s, 3 H), 1.98 (t, *J* = 6.4 Hz, 1 H); ^{13}C-NMR (100 MHz) δ 159.5, 151.7, 143.7, 133.3, 129.3, 128.3, 124.1, 118.5, 114.0, 113.0, 98.7, 70.9, 65.0, 58.0, 55.3; IR (neat) 3431

(OH), 2935 (C-H), 1613, 1592, 1516, 1485, 1466, 1382, 1252, 1213, 1175, 1159, 1003 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{17}H_{19}BrO_5^+$ (M+Na), 405.0308; found, 405.0310.

NMR assignments: ^{1}H-NMR (400 MHz) δ 7.33 (d, *J* = 8.8 Hz, 2 H, C10-H), 7. 15 (d, *J* = 8.4 Hz, 1 H, C3- H), 6.93 (d, *J* = 8.4 Hz, 1 H, C4-H), 6.90 (d, *J* = 8.8 Hz, 2 H, C11-H), 5.18 (s, 2 H, C8-H), 5.02 (s, 2 H, C14-H), 4.70 (d, *J* = 6.4 Hz, 2 H, C1-H), 3.80 (s, 3 H, C13-H), 3.57 (s, 3 H, C15-H), 1.98 (t, *J* = 6.4 Hz, 1 H, OH); ^{13}C-NMR (100 MHz) δ 159.5 (C12), 151.7 (C5), 143.7 (C6), 133.3 (C9), 129.3 (C10), 128.3 (C7), 124.1 (C3), 118.5 (C2), 114.0 (C11), 113.0 (C4), 98.7 (C14), 70.9 (C8), 65.0 (C1), 58.0 (C15), 55.3 (C13).

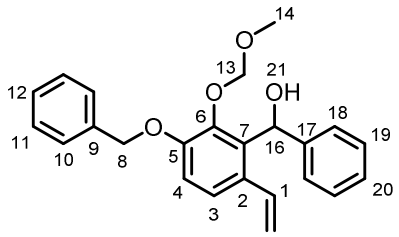


4.90

1-(Benzyloxy)-3-bromo-2-(methoxymethoxy)-4-vinylbenzene (**4.90**). (SB-V-194). A slurry of methyltriphenylphosphonium bromide (Ph_3PMeBr) (2.40 g, 6.64 mmol) and crude **4.36** in anhydrous THF (14 mL) and DMSO (ppm $H_2O \leq 600$, 14 ML) was cooled to 0 °C and degassed. In a separate flask, a solution of *tert*-BuOLi in THF was prepared by adding *n*-BuLi (*ca*. 1.90 M, 4.66 mL, 8.86 mmol) to a solution of *tert*-BuOH (freshly distilled over CaH_2, 0.66 g, 0.85 mL, 8.86 mmol) and triphenylmethane (Ph_3C-H) (54 mg, 0.22 mmol) in THF (14 mL) until a red endpoint was observed. The solution of *tert*-BuOLi was added to the flask containing methyltriphenylphosphonium bromide and crude **4.36** at 0 °C, and the mixture was stirred for 30 min. A solution of saturated aqueous $NaHCO_3$ solution (10 mL) was then added, and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, concentrated under reduced pressure, and the crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:20 → 1:4) to provide 1.45 g (94%)

of **4.90** as a clear oil: ^{1}H-NMR (400 MHz) δ 7.43-7.33 (comp, 5 H), 7.26 (d, *J* = 8.6 Hz, 1 H), 7.02 (dd, *J* = 11.0, 17.4 Hz, 1 H), 6.90 (d, *J* = 8.6 Hz, 1 H), 5.56 (d, *J* = 17.4 Hz, 1 H), 5.25 (d, *J* = 11.0 Hz, 1 H), 5.20 (s, 2 H), 5.11 (s, 2 H), 3.60 (s, 3 H); ^{13}C-NMR (100 MHz) δ 151.7, 143.7, 136.3, 135.7, 131.8, 128.6, 128.2, 127.4, 121.9, 119.7, 115.2, 113.2, 98.8, 71.1, 58.1; IR (film) 2924 (CH), 1588, 1484, 1382, 1289, 1262, 1160 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{17}H_{17}BrO_3^+$ (M+Na), 371.0253; found, 371.0260; *m/z* calc for $NaC_{17}H_{17}BrO_3^+$ (M+Na), 373.0235; found, 373.0241.

NMR assignments: ^{1}H-NMR (400 MHz) δ 7.43-7.33 (comp, 5 H, C12-H, C11-H, C10-H), 7.26 (d, *J* = 8.6 Hz, 1 H, C3-H), 7.02 (dd, *J* = 11.0, 17.4 Hz, 1 H, C1-H), 6.90 (d, *J* = 8.6 Hz, 1 H, C4-H), 5.56 (d, *J* = 17.4 Hz, 1 H, C15-H), 5.25 (d, *J* = 11.0 Hz, 1 H, C15-H), 5.20 (s, 2 H, C8-H), 5.11 (s, 2 H, C13-H), 3.60 (s, 3 H, C14-H); ^{13}C-NMR (100 MHz) δ 151.7 (C5), 143.7 (C6), 136.3 (C9), 135.7 (C1), 131.8 (C2), 128.6 (C11), 128.2 (C12), 127.4 (C10), 121.9 (C15), 119.7 (C7), 115.2 (C3), 113.2 (C4), 98.8 (C13), 71.1 (C8), 58.1 (C14).



4.91

(3-(Benzyloxy)-2-(methoxymethoxy)-6-vinylphenyl)(phenyl)methanol (**4.91**). (SB-VI-48).

Using *tert*-BuLi: Styrene **4.90** (100 mg, 0.29 mmol) was dissolved in toluene (2 mL), concentrated under reduced pressure (3 x) and put under vacuum for 2 h. Toluene (2 mL) and Et_2O (9 mL) was added, followed by NaH (60 % dispersion in mineral oil, ca. 2 mg, 0.06 mmol), and the slurry was stirred for 15 min. The reaction mixture was cooled to – 78 °C, and degassed. A solution of *tert*-BuLi in pentanes (1.60 M, 0.39 mL, 0.63 mmol) was added dropwise over the course of 1 min and then stirred for an additional 1 min before adding benzaldehyde (freshly distilled from CaH_2, 125 mg, 120 µL, 1.14 mmol). The reaction was stirred for 10 min whereupon a solution of saturated aqueous $NaHCO_3$ (1 mL) was added, and the reaction was warmed to room temperature. The mixture was extracted with EtOAc (3 x 2 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:4) to provide 36 mg (85%) of **4.91** as a clear oil.

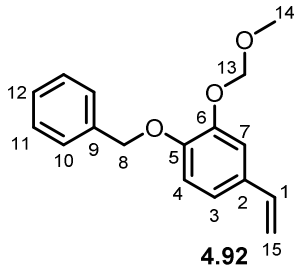
Using *n*-BuLi: (SB-V-212): Styrene **4.90** (50 mg, 0.143 mmol) was dissolved in toluene (2 mL), concentrated under reduced pressure (3 x) and put under vacuum for 2 h. Toluene (2 mL) was added and the reaction mixture was cooled to – 78 °C and degassed. A solution of *n*-BuLi in hexanes (1.87 M, 0.10 mL, 0.186 mmol) was added at – 78 °C, and stiring continued for 30 min before warming to 0 °C and stirring for an additional 1 h. Benzaldehyde (freshly distilled from CaH_2, 29 mg, 28 µL, 0.286 mmol) was then added, and the reaction was stirred for 10 min before adding a solution of saturated aqueous $NaHCO_3$ (1 mL) and warming to room temperature. The mixture was extracted with EtOAc (3 x 2 mL) and the combined organic

extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:4) to provide 36 mg (69%) of **4.91** as a clear oil.

Using Li[*i*-PrMgMe$_2$] (SB-VI-216): Styrene **4.90** (50 mg, 0.143 mmol) was dissolved in toluene (2 mL), concentrated under reduced pressure (3 x) and put under vacuum for 2 h. THF (1 mL) was added, followed by NaH (60 % dispersion in mineral oil, ca. 1 mg, 0.03 mmol) and the slurry was stirred for 15 min. In a separate flask, THF (2 mL) was added and the solvent was cooled to – 78 °C and degassed. The solvent was warmed to 0 °C and a solution of *i*-PrMgBr•LiCl in THF (1.36 M, 0.13 mL, 0.172 mmol) was added, followed by a solution of MeLi in Et_2O (1.56 M, 0.22 mL, 0.343 mmol) and the reaction mixture was stirred for 10 min at 0 °C. The solution of styrene **4.90** in THF was added to the flask containing Li[*i*-PrMgMe$_2$], and the mixture was stirred for 30 min before adding benzaldehyde (freshly distilled from CaH_2, 60 mg, 58 μL, 0.573 mmol) and stirring for an additional 10 min. A solution of saturated aqueous $NaHCO_3$ (1 mL) was then added, and the mixture was warmed to room temperature. The mixture was extracted with EtOAc (3 x 2 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:4) to provide 36 mg (98%) of **4.91** as a clear oil. ^{1}H-NMR (400 MHz) δ 7.41-7.18 (comp, 11 H), 6.94 (d, *J* = 8.4 Hz, 1 H), 6.90 (dd, *J* = 10.8, 17.2 Hz, 1 H), 6.30 (d, *J* = 9.2 Hz, 1 H), 5.47 (dd, *J* = 1.2, 17.2 Hz, 1 H), 5.14 (dd, *J* = 1.6, 11.2 Hz, 1 H), 5.07 (d, *J* = 1.6 Hz, 2 H), 5.03 (d, *J* = 5.4 Hz, 1 H), 4.78 (d, *J* = 5.4 Hz, 1 H), 4.02 (d, *J* = 9.2 Hz, 1 H), 3.31 (s, 3 H); ^{13}C-NMR (100 MHz) δ 150.8, 144.5, 144.3, 136.5, 135.1, 134.5, 131.4, 128.6, 128.1, 128.0, 127.5, 126.6, 125.5, 123.1, 115.9, 113.5, 99.2, 70.8, 69.7, 57.6; IR (film) 3459 (OH), 3085, 3062, 3030, 2938 (CH), 1597, 1487, 1452, 1382, 1283, 1189, 1157, 1062, 995 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{24}H_{24}O_4^+$ (M+Na), 399.1567; found, 399.1576.

NMR assignments: ^{1}H-NMR (400 MHz) δ 7.41-7.18 (comp, 11 H, C3-H, C10-H, C11-H, C12-H,C18-H, C19-H, C20-H), 6.94 (d, *J* = 8.4 Hz, 1 H, C4-H), 6.90 (dd, *J* = 10.8, 17.2 Hz, 1

H, C1-H), 6.30 (d, *J* = 9.2 Hz, 1 H, C16-H), 5.47 (dd, *J* = 1.2, 17.2 Hz, 1 H, C15- H), 5.14 (dd, *J* = 1.6, 11.2 Hz, 1 H, C15- H), 5.07 (d, *J* = 1.6 Hz, 2 H, C8-H), 5.03 (d, *J* = 5.4 Hz, 1 H, C13-H), 4.78 (d, *J* = 5.4 Hz, 1 H, C13-H), 4.02 (d, *J* = 9.2 Hz, 1 H, O-H), 3.31 (s, 3 H, C14- H); ^{13}C-NMR (100 MHz) δ 150.8 (C5), 144.5 (C6), 144.3 (C1), 136.5 (C17), 135.1 (C9), 134.5 (C2), 131.4 (C15), 128.6 (C11), 128.1 (C12), 128.0 (C4), 127.5 (C19), 126.6 (C20), 125.5 (C18), 123.1 (C3), 115.9 (C7), 113.5 (C4), 99.2 (C13), 70.8 (C16), 69.7 (C8), 57.6 (C14).

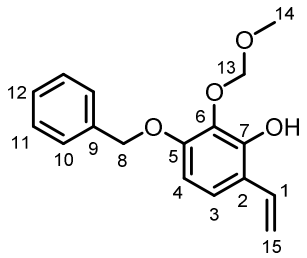


4.92

1-(Benzyloxy)-2-(methoxymethoxy)-4-vinylbenzene (**4.92**). (SB-V-28A). By-product isolated as a result of the metal-halogen exchange of **4.90**. Purified *via* flash chromatography eluting with a gradient of EtOAc/hexanes (1:20 → 1:10) to provide 15 mg (14%) of **4.92** as a clear oil ^{1}H-NMR (400 MHz) δ 7.43-7.30 (comp, 5 H), 7.23 (d, *J* = 2.0 Hz, 1 H), 6.97 (dd, *J* = 2.0, 8.4 Hz, 1 H), 6.86 (d, *J* = 8.4 Hz, 1 H), 6.61 (dd, *J* = 11.2, 17.6 Hz, 1 H), 5.60 (d, *J* = 17.6 Hz, 1 H), 5.24 (s, 2 H), 5.16 (s, 2 H), 5.14 (d, *J* = 11.2 Hz, 1 H), 3.53 (s, 3 H); ^{13}C-NMR (125 MHz) δ 149.0, 147.1, 137.1, 132.2, 131.4, 128.5, 127.9, 127.2, 120.9, 115.0, 114.3, 112.3, 95.8, 71.0, 56.3; IR (film) 3034 (C-H), 2931 (C-H), 1603, 1579, 1511, 1455, 1430, 1391, 1262, 1226, 1155, 1131, 1078 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{17}H_{18}O_3^+$ (M+Na), 293.1148; found, 293.1152.

NMR assignments: ^{1}H-NMR (400 MHz) δ 7.43-7.30 (comp, 5 H, C10-H, C11-H, C12-H), 7.23 (d, *J* = 2.0 Hz, 1 H, C7-H), 6.97 (dd, *J* = 2.0, 8.4 Hz, 1 H, C3-H), 6.86 (d, *J* = 8.4 Hz, 1 H, C4-H), 6.61 (dd, *J* = 11.2, 17.6 Hz, 1 H, C1-H), 5.60 (d, *J* = 17.6 Hz, 1 H, C15-H), 5.24 (s, 2 H, C8-H), 5.16 (s, 2 H, C13-H), 5.14 (d, *J* = 11.2 Hz, 1 H, C15-H), 3.53 (s, 3 H, C14-H); ^{13}C-

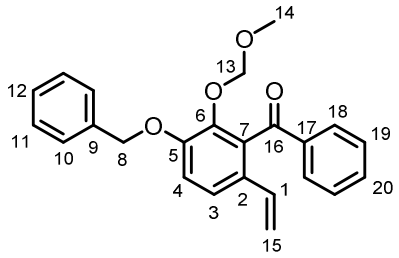
NMR (125 MHz) δ 149.0 (C5), 147.1 (C6), 137.1 (C9), 132.2 (C1), 131.4 (C2), 128.5 (C10), 127.9 (C12), 127.2 (C11), 120.9 (C3), 115.0 (C7), 114.3 (C4), 112.3 (C15), 95.8 (C13), 71.0 (C8), 56.3 (C14).



3-(Benzyloxy)-2-(methoxymethoxy)-6-vinylphenol. (SB-VII-82). Styrene **4.90** (50 mg, 0.143 mmol) was dissolved in toluene (2 mL), concentrated under reduced pressure (3 x) and put under vacuum for 2 h. THF (1 mL) was added, followed by NaH (60 % dispersion in mineral oil) (ca. 1 mg, 0.03 mmol) and the slurry was stirred for 15 min. In a separate flask, THF (1 mL) was added and the solvent was cooled to – 78 °C and degassed. The solvent was warmed to 0 °C and a solution of *i*-PrMgBr•LiCl in THF (1.43 M, 0.11 mL, 0.157 mmol) was added, followed by a solution of MeLi in Et_2O (1.47 M , 0.21 mL, 0.315 mmol) and the mixture was stirred for 10 min at 0 °C. The solution of styrene **4.90** in THF was added to the flask containing Li[*i*-$PrMgMe_2$], and the reaction mixture was stirred for 30 min before the solution was aerated with a balloon of oxygen for 10 min. A solution of saturated aqueous $NaHCO_3$ (1 mL) was then added, and the mixture was warmed to room temperature and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure, and the crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:4) to provide 20 mg (49%) of the named compound: ^{1}H-NMR (400 MHz) δ 7.42-7.31 (comp, 5 H), 7.12 (d, *J* = 8.8 Hz, 1 H), 6.91 (dd, *J* = 11.2, 17.6 Hz, 1 H), 6.73 (s, 1 H), 6.51 (d, *J* = 8.8 Hz, 1 H), 5.70 (dd, *J* = 1.2, 17.6 Hz, 1 H), 5.20 (dd, *J* = 1.2, 11.2 Hz, 1

H), 5.13 (s, 2 H), 5.10 (s, 2 H), 3.54 (s, 3 H); ^{13}C-NMR (125 MHz) δ 150.7, 147.8, 136.8, 134.0, 131.1, 128.6, 128.1, 127.4, 122.1, 119.0, 113.1, 105.4, 99.6, 70.8, 57.6; IR (film) 3373 (O-H), 2910 (C-H), 1612, 1509, 1455, 1317, 1291, 1239, 1223, 1154, 1093, 1073, 999 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{17}H_{18}O_4^+$ (M+Na), 309.1097; found, 309.1098.

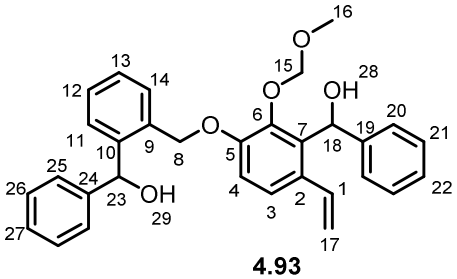
NMR assignments: ^{1}H-NMR (400 MHz) δ 7.42-7.31 (comp, 5 H, C10-H, C11-H, C12-H), 7.12 (d, *J* = 8.8 Hz, 1 H, C3-H), 6.91 (dd, *J* = 11.2, 17.6 Hz, 1 H, C1-H), 6.73 (s, 1 H, O-H), 6.51 (d, *J* = 8.8 Hz, 1 H, C4-H), 5.70 (dd, *J* = 1.2, 17.6 Hz, 1 H, C15-H), 5.20 (dd, *J* = 1.2, 11.2 Hz, 1 H, C15-H), 5.13 (s, 2 H, C8-H), 5.10 (s, 2 H, C13-H), 3.54 (s, 3 H, C15-H); ^{13}C-NMR (125 MHz) δ 150.7 (C5), 147.8 (C7), 136.8 (C9), 134.0 (C6), 131.1 (C1), 128.6 (C11), 128.1 (C12), 127.4 (C10), 122.1 (C15), 119.0 (C2), 113.1 (C3), 105.4 (C4), 99.6 (C13), 70.8 (C8), 57.6 (C14).



(3-(Benzyloxy)-2-(methoxymethoxy)-6-vinylphenyl)(phenyl)methanone (SB-V-89). Pyridinium chlorochromate (PCC) (149 mg, 0.691 mmol) was added to a solution of **4.91** (130 mg, 0.345 mmol) in CH_2Cl_2 (2 mL) at room temperature. The mixture was stirred for 2 h, whereupon silica was added and the residual solvent was removed under reduced pressure. The crude material was purified by flash chromatography eluting with EtOAc/hexanes (1:10) to provide 81 mg (67%) of the named compound as a clear oil: ^{1}H-NMR (500 MHz) δ 7.84 (app. d, *J* = 8.5, 2 H), 7.56 (app. t, *J* = 7.3, 1 H), 7.45-7.32 (comp, 8 H), 7.04 (d, *J* = 8.5, 1 H), 6.41 (dd, *J* = 11.0, 17.3, 1 H), 5.56 (dd, *J* = 0.8, 17.3, 1 H), 5.14 (s, 2 H), 5.07 (dd, *J* = 0.8, 11.0, 1 H), 5.03 (s, 2 H), 3.16 (s, 3 H); ^{13}C-NMR (125 MHz) δ 196.7, 150.7, 142.7, 137.5, 136.4, 134.2, 133.6, 132.8, 129.7, 129.2, 128.64, 128.59, 128.2, 127.5, 121.6, 115.2, 115.0, 98.8, 71.0, 57.3; IR

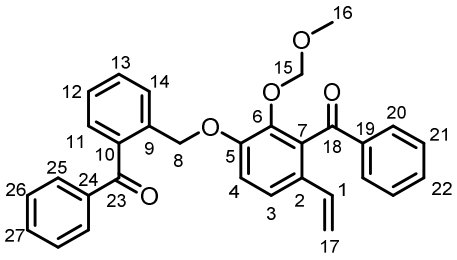
(film) 2926 (C-H), 1673 (C=O), 1596, 1483, 1451, 1315, 1273, 1213, 1160, 1059, 994 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{24}H_{22}O_4^+$ (M+Na), 397.1410; found, 397.1416.

NMR assignments: ^{1}H-NMR (500 MHz) δ 7.84 (app. d, *J* = 8.5, 2 H, C18-H), 7.56 (app. t, *J* = 7.3, 1 H, C20-H), 7.45-7.32 (comp, 8 H, C3-H, C10-H, C11-H, C12-H, C19-H), 7.04 (d, *J* = 8.5, 1 H, C4-H), 6.41 (dd, *J* = 11.0, 17.3, 1 H, C1-H), 5.56 (dd, *J* = 0.8, 17.3, 1 H, C15-H), 5.14 (s, 2 H, C8-H), 5.07 (dd, *J* = 0.8, 11.0, 1 H, C15-H), 5.03 (s, 2 H, C13-H), 3.16 (s, 3 H, C14-H); ^{13}C-NMR (125 MHz) δ 196.7 (C16), 150.7 (C5), 142.7 (C6), 137.5 (C17), 136.4 (C1), 134.2 (C9), 133.6 (C2), 132.8 (C20), 129.7 (C18), 129.2 (C15), 128.64 (C19), 128.59 (C11), 128.2 (C12), 127.5 (C10), 121.6 (C7) 115.2 (C3), 115.0 (C4), 98.8 (C13), 71.0 (C8), 57.3 (C14).



4.93

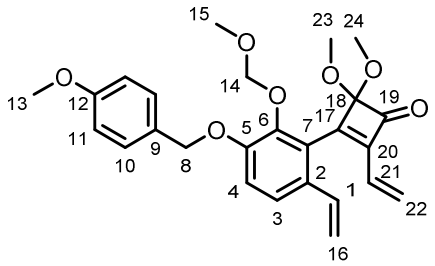
(2-((3-(Hydroxy(phenyl)methyl)-2-(methoxymethoxy)-4-vinylphenoxy)methyl)phenyl)(phenyl)methanol (**4.93**). (SB-V-88B). By-product isolated as a consequence of DOM on the benzyl group during metal-halogen exchange of **4.90**. Purified *via* flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:4) to provide 22 mg (32%) of **4.93** as a clear oil.



(2-**((3-Benzoyl-2-(methoxymethoxy)-4-vinylphenoxy)methyl)phenyl)(phenyl)methanone**. (SB-V-88). Pyridinium chlorochromate (PCC) (40 mg, 0.185 mmol) was added to a solution of **4.93** (22 mg, 0.046 mmol) in CH_2Cl_2 (1

mL) at room temperature. The mixture was stirred for 2 h, whereupon silica was added and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:4) to provide 7 mg (32%) of the named compound as a clear yellow oil: ^{1}H-NMR (400 MHz) δ 7.81 (app. d, *J* = 8.0 Hz, 4 H), 7.74 (d, *J* = 7.6 Hz, 1 H), 7.61-7.52 (comp, 3 H), 7.48-7.38 (comp, 6 H), 7.29 (d, *J* = 8.4 Hz, 1 H), 6.96 (d, *J* = 8.4 Hz, 1 H), 6.38 (dd, *J* = 10.8, 17.2 Hz, 1 H), 5.53 (d, *J* = 17.2 Hz, 1 H), 5.32 (s, 2 H), 5.05 (d, *J* = 10.8 Hz, 1 H), 4.94 (s, 2 H), 3.13 (s, 3 H); LCMS (APCI) found 497.

NMR assignments: ^{1}H-NMR (400 MHz) δ 7.81 (app. d, *J* = 8.0 Hz, 4 H, C20-H, C25-H), 7.74 (d, *J* = 7.6 Hz, 1 H, C11-H), 7.61-7.52 (comp, 3 H, C12-H, C22-H, C27-H), 7.48-7.38 (comp, 6 H, C13-H, C14-H, C21-H, C26-H), 7.29 (d, *J* = 8.4 Hz, 1 H, C4-H), 6.96 (d, *J* = 8.4 Hz, 1 H, C3-H), 6.38 (dd, *J* = 10.8, 17.2 Hz, 1 H, C1-H), 5.53 (d, *J* = 17.2 Hz, 1 H, C17-H), 5.32 (s, 2 H, C8-H), 5.05 (d, *J* = 10.8 Hz, 1 H, C17-H), 4.94 (s, 2 H, C15-H), 3.13 (s, 3 H, C16-H).

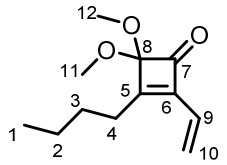


4,4-Dimethoxy-3-(3-((4-methoxybenzyl)oxy)-2-(methoxymethoxy)-6-vinylphenyl)-2-vinylcyclobut-2-en-1-one (**4.49**). (SB-VI-173). A round bottom flask containing **4.90** (500 mg, 1.32 mmol) was dissolved in toluene (2 mL) and concentrated under reduced pressure (2 x) and put under vacuum for 2 h. Separately, 3,4,4-trimethoxy-2-vinylcyclobut-2-en-1-one (**4.8**) was freshly purified *via* flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:2) and put under vacuum for 2 h. Toluene (9 mL), Et_2O (44 mL) and NaH (60 % dispersion in mineral oil, 16 mg, 0.26 mmol) was added to the flask containing **4.90**, and the mixture was

stirred for 10 min before cooling to – 78 °C. The reaction vessel was put under vacuum until the solvent effervesced, and backfilled with nitrogen (4 x). A solution of *tert*-BuLi in pentanes (1.85 M, 1.64 mL, 3.03 mmol) was added dropwise to the mixture at – 78 °C and stirring was continued for an additional 5 min before adding a solution of **4.8** in Et_2O (2 mL) that had been slurried over NaH (60 % dispersion in mineral oil, 8 mg, 0.13 mmol) for at least 5 min. The reaction mixture was warmed to –20 °C and stirred for an additional 15 min, whereupon a solution of saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was extracted with EtOAc (3 x 10 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:4) to provide 364 mg (61%) of **4.90** as a yellow oil that slowly turns into a solid upon standing: mp 75-77 °C; ^{1}H-NMR (600 MHz) δ 7.37 (d, *J* = 8.6 Hz, 1 H), 7.34 (d, *J* = 8.8 Hz, 2 H), 7.02 (d, *J* = 8.6 Hz, 1 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 6.77 (dd, *J* = 10.8, 17.6 Hz, 1 H), 6.16 (dd, *J* = 2.8, 17.6 Hz, 1 H), 6.08 (dd, *J* = 10.4, 18.0 Hz, 1 H) 5.60 (dd, *J* = 1.2, 17.6 Hz, 1 H), 5.56 (dd, *J* = 2.8, 10.4 Hz, 1 H), 5.18 (dd, *J* = 1.2, 10.8 Hz, 1 H), 5.06 (s, 2 H), 5.04 (s, 2 H) 3.81 (s, 3 H), 3.47 (s, 6 H), 3.38 (s, 3 H); ^{13}C-NMR (150 MHz) δ 191.1, 170.9, 159.6, 152.8, 151.1, 142.5, 134.2, 129.3, 129.3, 128.4, 126.0, 125.8, 124.1, 121.3, 116.7, 115.1, 114.5, 114.0, 99.0, 70.7, 57.3, 55.3, 52.7; IR (film) 2945 (C-H), 1765 (C=O), 1515, 1465, 1251, 1028, 992 cm^{-1}; HRMS (CI) *m/z* calc for $C_{26}H_{28}O_7^+$ (M^+), 452.1835; found, 452.1837.

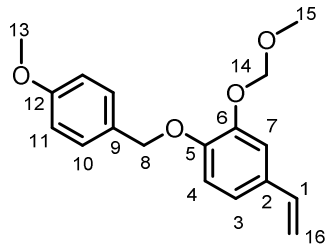
NMR assignments: ^{1}H-NMR (600 MHz) δ 7.37 (d, *J* = 8.6 Hz, 1 H, C3-H), 7.34 (d, *J* = 8.8 Hz, 2 H, C10-H), 7.02 (d, *J* = 8.6 Hz, 1 H, C4-H), 6.90 (d, *J* = 8.8 Hz, 2 H, C11-H), 6.77 (dd, *J* = 10.8, 17.6 Hz, 1 H, C1-H), 6.16 (dd, *J* = 2.8, 17.6 Hz, 1 H, C22-H), 6.08 (dd, *J* = 10.4, 18.0 Hz, 1 H, C21-H) 5.60 (dd, *J* = 1.2, 17.6 Hz, 1 H, C16-H), 5.56 (dd, *J* = 2.8, 10.4 Hz, 1 H, C22-H), 5.18 (dd, *J* = 1.2, 10.8 Hz, 1 H, C16-H), 5.06 (s, 2 H, C8-H), 5.04 (s, 2 H, C14-H) 3.81 (s, 3 H, C13-H), 3.47 (s, 6 H, C23-H, C24-H), 3.38 (s, 3 H, C15-H); ^{13}C-NMR (150 MHz) δ 191.1 (C19), 170.9 (C17), 159.6 (C12), 152.8 (C20), 151.1 (C5), 142.5 (C6), 134.2 (C1), 129.3 (C11),

129.3 (C2), 128.4 (C9), 126.0 (C22), 125.8 (C7), 124.1 (C21), 121.3 (C3), 116.7 (C18), 115.1 (C4), 114.5 (C16), 114.0 (C10), 99.0 (C14), 70.7 (C8), 57.3 (C15), 55.3 (C13), 52.7 (C23, C24).



3-Butyl-4,4-dimethoxy-2-vinylcyclobut-2-en-1-one. (SB-IV-270A). By-product isolated from the reaction of **4.90** with **4.8**. Purified *via* flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:5) to provide 4 mg (10%) of the named compound. ^{1}H-NMR (400 MHz) δ 6.17 (dd, *J* = 11.2, 17.6 Hz, 1 H), 6.00 (dd, *J* = 2.0, 17.6 Hz, 1 H), 5.43 (dd, *J* = 2.0, 11.2 Hz, 1 H), 4.41 (t, *J* = 6.4 Hz, 2 H), 3.53 (s, 6 H), 1.79 (quint, *J* = 6.4 Hz, 2 H), 1.48 (sex, *J* = 7.6 Hz, 2 H) 0.98 (t, *J* = 7.6 Hz, 3 H).

NMR assignments: ^{1}H-NMR (400 MHz) δ 6.17 (dd, *J* = 11.2, 17.6 Hz, 1 H, C9-H), 6.00 (dd, *J* = 2.0, 17.6 Hz, 1 H, C10-H), 5.43 (dd, *J* = 2.0, 11.2 Hz, 1 H, C10-H), 4.41 (t, *J* = 6.4 Hz, 2 H, C4-H), 3.53 (s, 6 H, C11-H, C12-H), 1.79 (quint, *J* = 6.4 Hz, 2 H, C3-H), 1.48 (sex, *J* = 7.6 Hz, 2 H, C2-H) 0.98 (t, *J* = 7.6 Hz, 3 H, C1-H).

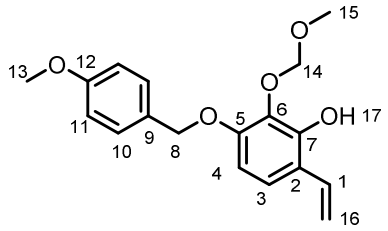


4.89

1-((4-Methoxybenzyl)oxy)-2-(methoxymethoxy)-4-vinylbenzene (**4.89**). (SB-V-184). By-product isolated from the reaction of **4.90** with **4.8**. Purified *via* flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:4) to provide 51 mg of **4.89** as a white waxy solid: mp 55-58 °C; ^{1}H-NMR (400 MHz) δ 7.34 (d, *J* = 8.8 Hz, 2 H), 7.22 (d, *J* = 2.2 Hz, 1 H), 6.97

(dd, *J* = 2.2, 8.4 Hz, 1 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 6.86 (d, *J* = 8.4 Hz, 1 H), 6.61 (dd, *J* = 10.8, 17.6 Hz, 1 H), 5.59 (dd, *J* = 0.8, 17.6 Hz, 1 H), 5.22 (s, 2 H), 5.13 (dd, *J* = 0.8, 10.8 Hz, 1 H), 5.01 (s, 2 H), 3.79 (s, 3 H), 3.51 (s, 3 H); ^{13}C-NMR (100 MHz) δ 159.3, 149.0, 147.1, 136.2, 131.3, 129.0, 129.0, 120.9, 115.0, 114.4, 113.9, 112.2, 95.7, 70.8, 56.3, 55.3; IR (film) 2916 (C-H), 1514, 1251, 1223, 1177, 1156, 1127, 1084, 1029 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{18}H_{20}O_4^+$ (M+Na), 323.1254; found, 323.1261.

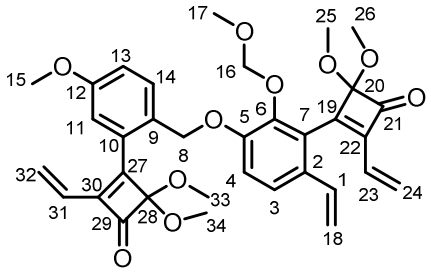
NMR assignments: ^{1}H-NMR (400 MHz) δ 7.34 (d, *J* = 8.8 Hz, 2 H, C10-H), 7.22 (d, *J* = 2.2 Hz, 1 H, C7-H), 6.97 (dd, *J* = 2.2, 8.4 Hz, 1 H, C3-H), 6.89 (d, *J* = 8.8 Hz, 2 H, C11-H), 6.86 (d, *J* = 8.4 Hz, 1 H, C4-H), 6.61 (dd, *J* = 10.8, 17.6 Hz, 1 H, C1-H), 5.59 (dd, *J* = 0.8, 17.6 Hz, 1 H, C16-H), 5.22 (s, 2 H, C8-H), 5.13 (dd, *J* = 0.8, 10.8 Hz, 1 H, C16-H), 5.01 (s, 2 H, C14-H), 3.79 (s, 3 H, C13-H), 3.51 (s, 3 H, C15-H); ^{13}C-NMR (100 MHz) δ 159.3 (C12), 149.0 (C5), 147.1 (C6), 136.2 (C1), 131.3 (C16), 129.0 (C9), 129.0 (C10), 120.9 (C2), 115.0 (C3), 114.4 (C7), 113.9 (C11), 112.2 (C4), 95.7 (C14), 70.8 C8), 56.3 (C15), 55.3 (C13).



3-((4-Methoxybenzyl)oxy)-2-(methoxymethoxy)-6-vinylphenol. (SB-V-120C2). By-product isolated from the reaction of **4.90** with **4.8**. Isolated *via* flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:4) to provide 5 mg (12%) of the named compound as a white solid; ^{1}H-NMR (400 MHz) δ 7.34 (d, *J* = 8.8 Hz, 2 H), 7.13 (d, *J* = 8.4 Hz, 1 H), 6.91 (d, *J* = 8.8 Hz, 2 H), 6.91 (dd, *J* = 11.2, 18.0 Hz, 1 H), 6.69 (s, 1 H), 6.52 (d, *J* = 8.8 Hz, 1 H), 5.70 (dd, *J* = 1.6, 18.0 Hz, 1 H), 5.20 (dd, *J* = 1.6, 11.2 Hz, 1 H), 5.11 (s, 2 H), 5.02 (s, 2 H), 3.82 (s, 3 H), 3.53 (s, 3 H); LCMS (APCI); found, 285 $(M–CH_3O)^+$.

NMR assignments: ^{1}H-NMR (400 MHz) δ 7.34 (d, *J* = 8.8 Hz, 2 H, C10-H), 7.13 (d, *J* = 8.4 Hz, 1 H, C3-H), 6.91 (d, *J* = 8.8 Hz, 2 H, C11-H), 6.91 (dd, *J* = 11.2, 18.0 Hz, 1 H, C1-H),

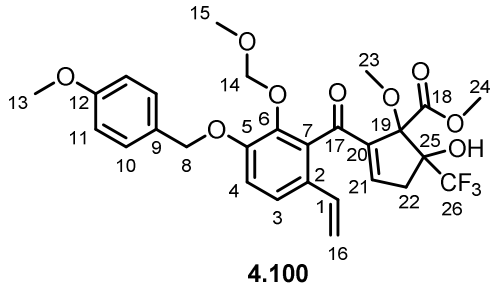
6.69 (s, 1 H, O17-H), 6.52 (d, *J* = 8.8 Hz, 1 H, C4-H), 5.70 (dd, *J* = 1.6, 18.0 Hz, 1 H, C16-H), 5.20 (dd, *J* = 1.6, 11.2 Hz, 1 H, C16-H), 5.11 (s, 2 H, C8-H), 5.02 (s, 2 H, C14-H), 3.82 (s, 3 H, C13-H), 3.53 (s, 3 H, C14-H).



3-(2-((3-(4,4-Dimethoxy-3-oxo-2-vinylcyclobut-1-en-1-yl)-2-(methoxymethoxy)-4-vinylphenoxy)methyl)-5-methoxyphenyl)-4,4-dimethoxy-2-vinylcyclobut-2-en-1-one. (SB-VII-252C). By-product isolated from the reaction of **4.90** with **4.8**. Purified *via* flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:4) to provide 523 mg (8%) of the named compound as a yellow oil which crystallizes in the freezer; ^{1}H-NMR (500 MHz) δ 7.57 (d, *J* = 9.0 Hz, 1 H), 7.35 (d, *J* = 8.5 Hz, 1 H), 7.11 (d, *J* = 3.0 Hz, 1 H), 7.00 (dd, *J* = 3.0, 9.0 Hz, 1 H), 6.95 (d, *J* = 8.5 Hz, 1 H), 6.75 (dd, *J* = 11.0, 17.5 Hz, 1 H), 6.35-6.24 (comp, 2 H), 6.15-6.02 (comp, 2 H), 5.63-5.52 (comp, 3 H), 5.15 (dd, *J* = 1.0, 11.0 Hz, 1 H), 5.08 (s, 2 H), 5.00 (s, 2 H), 3.83 (s, 3 H), 3.441 (s, 6 H), 3.438 (s, 6 H), 3.34 (s, 3 H); ^{13}C-NMR (125 MHz) δ 191.5, 190.9, 170.8, 170.1, 159.4, 152.7, 151.0, 150.2, 142.3, 134.1, 131.37, 131.36, 129.3, 127.4, 126.5, 125.9, 125.7, 124.0, 123.5, 121.3, 116.8, 116.7, 116.3, 114.9, 114.5, 113.6, 98.9, 68.3, 57.2, 55.4, 53.3, 52.5; IR (film) 2944 (C-H), 2838 (C-H), 1768 (C=O), 1605, 1505, 1470, 1335, 1256, 993 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{34}H_{36}O_{10}^{+}$ (M+Na), 627.2201; found, 627.2201.

NMR assignments: ^{1}H-NMR (500 MHz) δ 7.57 (d, *J* = 9.0 Hz, 1 H, C14-H), 7.35 (d, *J* = 8.5 Hz, 1 H, C3-H), 7.11 (d, *J* = 3.0 Hz, 1 H, C11-H), 7.00 (dd, *J* = 3.0, 9.0 Hz, 1 H, C13-H),

6.95 (d, *J* = 8.5 Hz, 1 H, C4-H), 6.75 (dd, *J* = 11.0, 17.5 Hz, 1 H, C1-H), 6.35-6.24 (comp, 2 H, C31-H, C32-H), 6.15-6.02 (comp, 2 H, C23-H, C24-H), 5.63-5.52 (comp, 3 H, C18-H, C24-H, C32-H), 5.15 (dd, *J* = 1.0, 11.0 Hz, 1 H, C18-H), 5.08 (s, 2 H, C8-H), 5.00 (s, 2 H, C16-H), 3.83 (s, 3 H, C17-H), 3.441 (s, 6 H, C25-H, C26-H or C33-H, C34-H), 3.438 (s, 6 H, C25-H, C26-H or C33-H, C34-H), 3.34 (s, 3 H, C15-H); ^{13}C-NMR (125 MHz) δ 191.5 (C29), 190.9 (C21), 170.8 (C27), 170.1 (C19), 159.4 (C12), 152.7 (C5), 151.0 (C30), 150.2 (C22), 142.3 (C6), 134.1 (C1), 131.37 (C10), 131.36 (C14), 129.3 (C9), 127.4 (C32), 126.5 (C2), 125.9 (C24), 125.7 (C7), 124.0 (C23), 123.5 (C31), 121.3 (C3), 116.8 (C28), 116.7 (C20), 116.3 (C13), 114.9 (C4), 114.5 (C18), 113.6 (C11), 98.9 (C16), 68.3 (C8), 57.2 (C15), 55.4 (C17), 53.3 (C25, C26 or C33, C34), 52.5 (C25, C26 or C33, C34).

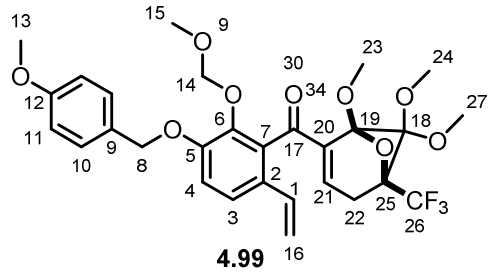


4.100

Methyl 5-hydroxy-1-methoxy-2-(3-((4-methoxybenzyl)oxy)-2-(methoxymethoxy)-6-vinylbenzoyl)-5-(trifluoromethyl)cyclopent-2-ene-1-carboxylate (**4.100**). (SB-V-216E). By-product isolated from the reaction of **4.90** with **4.8** when TFAA was included. Purified *via* flash chromatography eluting with acetone/hexanes (1:4) to provide 54 mg (9%) of **4.100**: ^{1}H-NMR (500 MHz) δ 7.34 (d, *J* = 8.6 Hz, 2 H), 7.31 (d, *J* = 8.6 Hz, 1 H), 7.03 (d, *J* = 8.6 Hz, 1 H), 6.90 (d, *J* = 8.6 Hz, 2 H), 6.67 (t, *J* = 2.7, 1 H), 6.51 (dd, *J* = 11.0, 17.3 Hz, 1 H), 5.59 (d, *J* = 17.3, 1 H), 5.18 (d, *J* = 11.0, 1 H), 5.07 (d, *J* = 5.1, 1 H), 5.04 (s, 2 H), 5.04 (d, *J* = 5.1, 1 H), 4.46 (s, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.68 (s, 3 H), 3.36 (s, 3 H), 3.00 (dd, *J* = 3.2, 19.5 Hz, 1 H), 2.75 (dd, *J* = 2.2, 19.5 Hz, 1 H); ^{13}C-NMR (125 MHz) δ 192.8, 167.5, 159.7, 153.0, 150.6, 144.1, 142.3, 133.0, 132.4, 129.4, 129.3, 129.1, 128.2, 124.2 (q, *J* = 284 Hz), 121.2, 115.2, 115.2, 114.0, 99.2, 86.8, 84.9 (q, *J* = 29 Hz), 70.9, 57.8, 56.2, 55.3, 52.7, 40.6; IR (film) 3462 (O-H), 2954 (C-H), 2840 (C-H), 1756 (C=O), 1668 (C=O), 1614, 1596, 1516, 1484, 1467, 1380, 1250,

1173, 1113, 1033, 993 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{28}H_{29}O_9^+$ (M+Na), 589.1656; found, 589.1658.

NMR assignments: ^{1}H-NMR (500 MHz) δ 7.34 (d, *J* = 8.6 Hz, 2 H, C10-H), 7.31 (d, *J* = 8.6 Hz, 1 H, C3-H), 7.03 (d, *J* = 8.6 Hz, 1 H, C4-H), 6.90 (d, *J* = 8.6 Hz, 2 H, C11-H), 6.67 (t, *J* = 2.7, 1 H, C21-H), 6.51 (dd, *J* = 11.0, 17.3 Hz, 1 H, C1-H), 5.59 (d, *J* = 17.3, 1 H, C16-H), 5.18 (d, *J* = 11.0, 1 H, C16-H), 5.07 (d, *J* = 5.1, 1 H, C14-H), 5.04 (s, 2 H, C8-H), 5.04 (d, *J* = 5.1, 1 H, C14-H), 4.46 (s, 1 H, O-H), 3.81 (s, 3 H, C24-H), 3.80 (s, 3 H, C13-H), 3.68 (s, 3 H, C23-H), 3.36 (s, 3 H, C15-H), 3.00 (dd, *J* = 3.2, 19.5 Hz, 1 H, C22-H), 2.75 (dd, *J* = 2.2, 19.5 Hz, 1 H, C22-H); ^{13}C-NMR (125 MHz) δ 192.8 (C17), 167.5 (C18), 159.7 (C12), 153.0 (C12), 150.6 (C21), 144.1 (C5), 142.3 (C20), 133.0 (C6), 132.4 (C2), 129.4 (C1), 129.3 (C10), 129.1 (C7), 128.2 (C9), 124.2 (C26), 121.2 (C3), 115.2 (C4), 115.2 (C16), 114.0 (C11), 99.2 (C14), 86.8 (C19), 84.9 (C25), 70.9 (C8), 57.8 (C15), 56.2 (C23) 55.3 (C24), 52.7 (C13), 40.6 (C22).

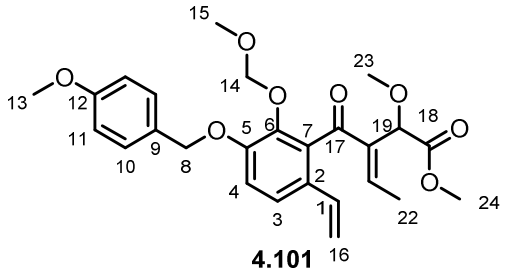


4.99

(3-((4-Methoxybenzyl)oxy)-2-(methoxymethoxy)-6-vinylphenyl)((1R,5S)-1,7,7-trimethoxy-5-(trifluoromethyl)-6-oxabicyclo[3.1.1]hept-2-en-2-yl)methanone (**4.99**). (SB-V-216D). By-product isolated from the reaction of **4.90** with **4.8** when TFAA was included. Purified *via* flash chromatography eluting with acetone/hexanes (1:4) to provide 67 mg (11%) of **4.99**. Further purified *via* prep TLC eluting with a gradient of Et_2O/CH_2Cl_2/hexanes (1:3:40 → 1:3:10) to provide 12 mg (40%) of **4.99**: ^{1}H-NMR (500 MHz) δ 7.35 (d, *J* = 8.8 Hz, 3 H), 7.03 (d, *J* = 8.5 Hz, 1 H), 6.91 (d, *J* = 8.8 Hz, 2 H), 6.62 (m, 1 H) 6.59 (bs, 1 H), 5.63 (d, *J* = 17.3 Hz, 1 H), 5.17 (d, *J* = 11.7 Hz, 1 H), 5.11 (bd, *J* = 4.4 Hz, 1 H), 5.05 (s, 1 H), 5.01 (bd, *J* = 4.4 Hz, 1 H), 3.82 (s, 3 H), 3.59 (s, 3 H), 3.41 (s, 3 H), 3.37 (s, 3 H), 3.35 (s, 3 H), 2.95 (dd, *J* = 2.4, 20.5 Hz, 1 H), 2.22 (dd, *J* = 2.9, 20.2 Hz, 1 H); ^{13}C-NMR (125 MHz) δ 192.3, 159.7, 152.0, 150.6,

142.0, 141.5, 134.0, 132.6, 129.4, 128.8, 128.2, 123.4 (q, *J* = 279 Hz), 120.9, 119.8, 114.8, 114.0, 99.3, 96.6, 84.0 (bm), 70.9, 58.0, 55.3, 54.3, 51.7, 50.2; IR (film) 2952 (C-H), 2850 (C-H), 1671 (C=O), 1614, 1516, 1484, 1467, 1283, 1251, 1172, 1083, 1033, 993 cm^{-1}; HRMS (ESI) *m/z* found, 581.

NMR assignments: ^{1}H-NMR (500 MHz) δ 7.35 (d, *J* = 8.8 Hz, 3 H, C3-H, C10-H), 7.03 (d, *J* = 8.5 Hz, 1 H, C4-H), 6.91 (d, *J* = 8.8 Hz, 2 H, C11-H), 6.62 (m, 1 H, C1-H) 6.59 (bs, 1 H, C21-H), 5.63 (d, *J* = 17.3 Hz, 1 H, C16-H), 5.17 (d, *J* = 11.7 Hz, 1 H, C16-H), 5.11 (bd, *J* = 4.4 Hz, 1 H, C14-H), 5.05 (s, 1 H, C8-H), 5.01 (bd, *J* = 4.4 Hz, 1 H, C14-H), 3.82 (s, 3 H, C13-H), 3.59 (s, 3 H, C27-H), 3.41 (s, 3 H, C23-H), 3.37 (s, 3 H, C15-H), 3.35 (s, 3 H, C24-H), 2.95 (dd, *J* = 2.4, 20.5 Hz, 1 H, C22-H), 2.22 (dd, *J* = 2.9, 20.2 Hz, 1 H, C22-H); ^{13}C-NMR (125 MHz) δ 192.3 (C17), 159.7 (C12), 152.0 (C21), 150.6 (C5), 142.0 (C6), 141.5 (C7), 134.0 (C20), 132.6 (C1), 129.4 (C10), 128.8 (C2), 128.2 (C9), 123.4 (C26), 120.9 (C3), 119.8 (C18), 114.8 (C4, C16), 114.0 (C11), 99.3 (C14), 96.6 (C19), 84.0 (C25), 70.9 (C8), 58.0 (C15), 55.3 (C13), 54.3 (C23), 51.7 (C27), 50.2 (C24).



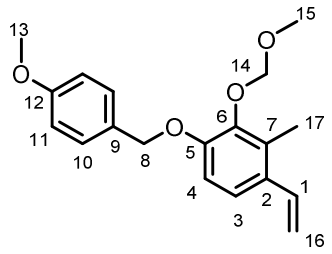
4.101

Methyl-2-methoxy-3-(3-((4-methoxybenzyl)oxy)-2-(methoxymethoxy)-6-vinylbenzoyl)pent-3-enoate (**4.101**). (SB-VI-107C). Isolated from the reaction of **4.90** with **4.8** when TFAA was not included. Purified *via* flash chromatography eluting with a gradient of EtOAc/hexanes (1:4 → 2:5) to provide 59 mg (10%) of **4.101** as a yellow oil; ^{1}H-NMR (600 MHz) δ (Major isomer) 7.34 (d, *J* = 8.8 Hz, 2 H), 7.29 (d, *J* = 8.6 Hz, 1 H), 6.99 (d, *J* = 8.6 Hz, 1 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 6.68 (q, *J* = 7.3, 1 H), 6.42 (dd, *J* = 11.0, 17.4 Hz, 1 H), 5.56 (d, *J* =

17.4 Hz, 1 H), 5.23 (bs, 1 H), 5.13 (d, *J* = 11.0 Hz, 1 H), 5.05-5.02 (comp, 4 H), 3.81 (s, 3 H), 3.77 (s, 3 H), 3.47 (s, 3 H), 3.37 (s, 3 H), 1.96 (d, *J* = 2.3 Hz, 3 H); (Minor isomer) 7.34 (d, *J* = 8.8 Hz, 2 H), 7.29 (d, *J* = 8.6 Hz, 1 H), 7.00 (d, *J* = 8.6 Hz, 1 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 6.68 (q, *J* = 9.6, 1 H), 6.52 (dd, *J* = 11.0, 17.4 Hz, 1 H), 5.56 (d, *J* = 17.4 Hz, 1 H), 5.23 (bs, 1 H), 5.15 (d, *J* = 11.0 Hz, 1 H), 5.05-5.02 (comp, 4 H), 3.81 (s, 3 H), 3.75 (s, 3 H), 3.39 (s, 3 H), 3.38 (s, 3 H), 1.59 (d, *J* = 7.3 Hz, 3 H); ^{13}C-NMR (150 MHz) δ (Major isomer) 196.1, 171.1, 159.6, 151.3, 150.8, 142.3, 139.2, 133.4, 132.7, 129.3, 129.3, 128.3, 121.2, 114.7, 114.6, 114.0, 99.1, 73.4, 70.8, 57.6, 57.6, 55.3, 52.1, 15.4; (Minor isomer) 194.9, 171.2, 159.6, 151.0, 143.8, 142.2, 139.2, 137.2, 136.1, 129.3, 129.0 128.3, 121.8, 115.3, 115.0, 114.0, 99.0, 79.1, 70.9, 57.8, 57.6, 55.3, 52.1, 15.0; IR (neat) 2951 (C-H), 2836 (C-H), 1754 (C=O), 1661 (C=O), 1642, 1614, 1595, 1516, 1483, 1467, 1382, 1292, 1252, 1214, 1195, 1176, 1115, 1033, 992 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{26}H_{30}O_8^+$ (M+Na), 493.1833; found, 493.1831.

NMR assignments: ^{1}H-NMR (600 MHz) δ (Major isomer) 7.34 (d, *J* = 8.8 Hz, 2 H, C10-H), 7.29 (d, *J* = 8.6 Hz, 1 H, C3-H), 6.99 (d, *J* = 8.6 Hz, 1 H, C4-H), 6.90 (d, *J* = 8.8 Hz, 2 H, C11-H), 6.68 (q, *J* = 7.3, 1 H, C21-H), 6.42 (dd, *J* = 11.0, 17.4 Hz, 1 H, C1-H), 5.56 (d, *J* = 17.4 Hz, 1 H, C16-H), 5.23 (bs, 1 H, C19-H), 5.13 (d, *J* = 11.0 Hz, 1 H, C16-H), 5.05-5.02 (comp, 4 H, C8-H, C14-H), 3.81 (s, 3 H, C23-H), 3.77 (s, 3 H, C13-H), 3.47 (s, 3 H, C24-H), 3.37 (s, 3 H, C15-H), 1.96 (d, *J* = 2.3 Hz, 3 H, C22-H); (Minor isomer) 7.34 (d, *J* = 8.8 Hz, 2 H, C10-H), 7.29 (d, *J* = 8.6 Hz, 1 H, C3-H), 7.00 (d, *J* = 8.6 Hz, 1 H, C4-H), 6.90 (d, *J* = 8.8 Hz, 2 H, C11-H), 6.68 (q, *J* = 9.6, 1 H, C21-H), 6.52 (dd, *J* = 11.0, 17.4 Hz, 1 H, C1-H), 5.56 (d, *J* = 17.4 Hz, 1 H, C16-H), 5.23 (bs, 1 H, C19-H), 5.15 (d, *J* = 11.0 Hz, 1 H, C16-H), 5.05-5.02 (comp, 4 H, C8-H, C14-H), 3.81 (s, 3 H, C23-H), 3.75 (s, 3 H, C13-H), 3.39 (s, 3 H, C24-H), 3.38 (s, 3 H, C15-H), 1.59 (d, *J* = 7.3 Hz, 3 H, C22-H); ^{13}C-NMR (150 MHz) δ (Major isomer) 196.1 (C17), 171.1 (C18), 159.6 (C12), 151.3 (C5), 150.8 (C21), 142.3 (C6), 139.2 (C20), 133.4 (C2), 132.7 (C1), 129.3 (C10), 129.3 (C7), 128.3 (C9), 121.2 (C3), 114.7 (C4), 114.6 (C16), 114.0 (C11), 99.1 (C14), 73.4 (C19), 70.8 (C8), 57.6 (C24), 57.6 (C15), 55.3 , 52.1 (C13), 15.4 (C22); (Minor isomer) 194.9 (C17), 171.2 (C18), 159.6 (C12), 151.0 (C5), 143.8 (C21), 142.2

(C6), 139.2 (C20), 137.2 (C2), 136.1 (C1), 129.3 (C10), 129.0 (C7), 128.3(C9), 121.8 (C3), 115.3 (C16), 115.0 (C4), 114.0 (C11), 99.0 (C14), 79.1 (C19), 70.9 (C8), 57.8 (C15), 57.6 (C24), 55.3 (C23), 52.1 (C13), 15.0 (C22).

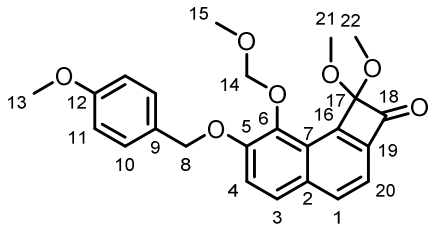


4.109

1-((4-Methoxybenzyl)oxy)-2-(methoxymethoxy)-3-methyl-4-vinylbenzene (**4.109**). (SB-VI-226). Styrene **4.90** (161 mg, 0.425 mmol) was dissolved in toluene (2 mL), concentrated under reduced pressure (3 x) and put under vacuum for 2 h. THF (2 mL) was added, followed by NaH (60 % dispersion in mineral oil) (~1 mg, 0.03 mmol) and the slurry was stirred for 15min. In a separate flask, THF (6 mL) was added and the solvent was cooled to – 78 °C and the reaction vessel was degassed. The solvent was warmed to 0 °C and a solution of *i*-PrMgBr•LiCl in THF (1.36 M, 0.34 mL, 0.467 mmol) was added, followed by a solution of MeLi in Et_2O (1.56 M, 0.60 mL, 0.935 mmol) at 0 °C and the mixture was stirred for 10 min. The solution of Styrene **4.90** in THF was added to the flask containing Li[*i*-PrMgMe_2], and the reaction mixture was stirred for 30 min before adding squarate **4.8** (120 mg, 0.637 mmol) and the reaction was stirred for an additional 15 min whereupon a solution of saturated aqueous $NaHCO_3$ (1 mL) was added, and the mixture was warmed to room temperature. The mixture was extracted with EtOAc (3 x 5 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:2) to provide 95 mg (71%) of **4.109** as a white solid: mp 48-50 °C; ^{1}H-NMR (600 MHz) δ 7.34 (d, *J* = 8.8 Hz, 2 H), 7.19 (d, *J* = 8.5 Hz, 1 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 6.87 (dd, *J* = 10.9, 17.4 Hz, 1 H), 6.81 (d, *J* = 8.5 Hz, 1 H), 5.51 (dd, *J* = 1.5, 17.4 Hz, 1 H), 5.20 (dd, *J* = 1.5, 10.9 Hz, 1 H), 5.08 (s, 2 H), 5.01 (s, 2 H), 3.81 (s, 3 H), 3.53 (s, 3 H), 2.32 (s, 3 H); ^{13}C-NMR (150 MHz) δ 159.4, 150.9, 144.6, 134.7, 131.2, 130.2,

129.1, 129.0, 121.4, 114.1, 113.9, 111.5, 98.9, 70.5, 57.5, 55.3, 12.6; IR (film) 2937 (C-H), 1614, 1517, 1488, 1462, 1380, 1293, 1250, 1159, 1044, 977 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{19}H_{22}O_4^+$ (M+Na), 337.1410; found, 337.1407.

NMR assignments: ^{1}H-NMR (600 MHz) δ 7.34 (d, *J* = 8.8 Hz, 2 H, C10-H), 7.19 (d, *J* = 8.5 Hz, 1 H, C3-H), 6.90 (d, *J* = 8.8 Hz, 2 H, C11-H), 6.87 (dd, *J* = 10.9, 17.4 Hz, 1 H, C1-H), 6.81 (d, *J* = 8.5 Hz, 1 H, C4-H), 5.51 (dd, *J* = 1.5, 17.4 Hz, 1 H, C16-H), 5.20 (dd, *J* = 1.5, 10.9 Hz, 1 H, C16-H), 5.08 (s, 2 H, C8-H), 5.01 (s, 2 H, C14-H), 3.81 (s, 3 H, C13-H), 3.53 (s, 3 H, C15-H), 2.32 (s, 3 H, C17-H); ^{13}C-NMR (150 MHz) δ 159.4 (C12), 150.9 (C5), 144.6 (C6), 134.7 (C1), 131.2 (C2), 130.2 (C7), 129.1 (C10), 129.0 (C16), 121.4 (C9), 114.1 (C3), 113.9 (C11), 111.5 (C4), 98.9 (C14), 70.5 (C8), 57.5 (C13), 55.3 (C15), 12.6 (C17).

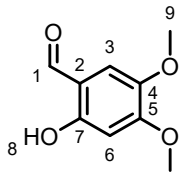


4.110

1,1-Dimethoxy-7-((4-methoxybenzyl)oxy)-8-(methoxymethoxy)cyclobuta[a]naphthalen-2(1H)-one (**4.110**). (SB-VI-177). A solution of **4.49** (1.14 g, 2.513 mmol), Grubbs II (149 mg, 0.176 mmol) and BHT (111 mg, 0.502 mmol) in dichloroethylene (DCE) was put under vacuum until the solvent effervesced, and the flask was backfilled with nitrogen (3 x). The reaction was then heated under reflux for 8 h. The reaction mixture was cooled to room temperature, DMSO (0.564 g, 0.62 mL, 8.795 mmol) was added, and the mixture was stirred for 16 h at room temperature. The solvent was removed under reduced pressure, and the crude material was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:2) to provide 836 mg (78%) of **4.110** as a brown to green

solid: mp 83-85 °C and 214 mg (13%) **4.49** (91% brsm); ^{1}H-NMR (500 MHz) δ 7.90 (d, *J* = 8.4 Hz, 1 H), 7.70 (d, *J* = 8.8 Hz, 1 H), 7.51 (d, *J* = 8.8 Hz, 1 H), 7.41 (d, *J* = 8.8 Hz, 2 H), 7.36 (d, *J* = 8.4 Hz, 1 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 5.35 (s, 2 H), 5.20 (s, 2 H), 3.82 (s, 3 H), 3.57 (comp, 9 H); ^{13}C-NMR (125 MHz) δ 193.2, 160.3, 159.6, 150.4, 147.5, 140.6, 133.8, 132.7, 129.4, 128.4, 125.8, 125.2, 120.1, 118.2, 114.7, 114.0, 99.6, 71.7, 57.7, 55.3, 53.7; IR (film) 2942 (C-H), 2836, 1760 (C=O), 1614, 1584, 1515, 1462, 1334, 1251, 1174, 1108, 1033, 937 cm^{-1}; HRMS (CI) *m/z* calc for $C_{24}H_{25}O_7^+$ (M+), 425.1600; found, 425.1596.

NMR assignments: ^{1}H-NMR (500 MHz) δ 7.90 (d, *J* = 8.4 Hz, 1 H, C3-H), 7.70 (d, *J* = 8.8 Hz, 1 H, C20-H), 7.51 (d, *J* = 8.8 Hz, 1 H, C1-H), 7.41 (d, *J* = 8.8 Hz, 2 H, C10-H), 7.36 (d, *J* = 8.4 Hz, 1 H, C4-H), 6.92 (d, *J* = 8.8 Hz, 2 H, C11-H), 5.35 (s, 2 H, C8-H), 5.20 (s, 2 H, C14-H), 3.82 (s, 3 H, C13-H), 3.57 (comp, 9 H, C15, C21, C22-H); ^{13}C-NMR (125 MHz) δ 193.2 (C18), 160.3 (C16), 159.6 (C12), 150.4 (C19), 147.5 (C5), 140.6 (C6), 133.8 (C20), 132.7 (C2), 129.4 (C11), 128.4 (C9), 125.8 (C1), 125.2 (C7), 120.1 (C3), 118.2 (C4), 114.7 (C17), 114.0 (C10), 99.6 (C14), 71.7 (C8), 57.7 (C15), 55.3 (C13), 53.7 (C21, C22).

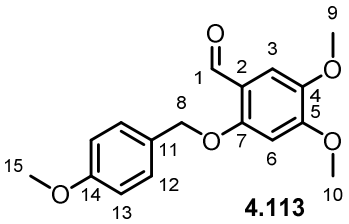


4.112

2-Hydroxy-4,5-dimethoxy benzaldehyde (**4.112**). (SB-VI–200). A solution of 2,4,5-trimethoxybenzaldehyde **4.111** (3.3 g, 16.78 mmol) in CH_2Cl_2 (84 mL) was cooled to 0 °C. BBr_3 (freshly distilled from CaH_2, 4.59 g, 1.74 mL, 18.45 mmol) was added, and the mixture was warmed to room temperature and stirred for 24 h. H_2O (20 mL) was added, and stirring was continued for an additional 10 min. The mixture was extracted with CH_2Cl_2 (2 x 20 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide 2.60 g (85%) crude **4.112** as a dark green solid: mp 104-106 °C (MeOH). The crude material can be purified by flash chromatography eluting with a gradient of

acetone/hexanes (1:3 → 1:1), but in most cases the material is sufficiently pure for the next step; ^{1}H-NMR (400 MHz) δ 11.41 (s, 1 H), 9.71 (s, 1 H), 6.91 (s, 1 H), 6.48 (s, 1 H), 3.94 (s, 3 H), 3.89 (s, 3 H); ^{13}C-NMR (100 MHz) δ 194.0, 159.3, 152.2, 142.9, 113.1, 112.8, 100.1, 56.4, 56.3; IR (film) 2838 (C-H), 1625 (C=O), 1506, 1475, 1443, 1369, 1339, 1280, 1251, 1198, 1147, 998 cm^{-1}; LRMS (CI) *m/z* found, 183.

NMR assignments: ^{1}H-NMR (400 MHz) δ 11.41 (s, 1 H, C1-H), 9.71 (s, 1 H, O-H), 6.91 (s, 1 H, C3-H), 6.48 (s, 1 H, C6-H), 3.94 (s, 3 H, C10-H), 3.89 (s, 3 H, C9-H); ^{13}C-NMR (100 MHz) δ 194.0 (C1), 159.3 (C7), 152.2 (C5), 142.9 (C4), 113.1 (C3), 112.8 (C2), 100.1 (C6), 56.4 (C10), 56.3 (C9).

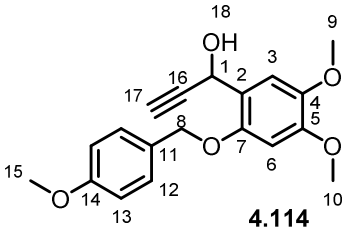


4.113

4,5-Dimethoxy-2-((4-methoxybenzyl)oxy)benzaldehyde (**4.113**). (SB-VI-75). A mixture of crude aldehyde **4.112** (0.50 g, 2.74 mmol), K_2CO_3 (0.76 g, 5.48 mmol) and NaI (0.12 g, 0.82 mmol) in DMF (1.7 mL) was heated at 40 °C for 2 h. Paramethoxybenzyl chloride (PMBCl)[634] (0.64 g, 0.56 mL, 4.12 mmol) was then added, and stirring continued at 40 °C for 24 h. H_2O (10 mL) was then added, and the reaction was cooled to room temperature. The mixture was extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic extracts were washed with 5% NaOH solution (1 x 10 mL), 13% aqueous brine solution (4 x 3 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:4 → 1:2) to provide 820 mg (99%) **4.113** as a white solid: mp (IPA) 98-99 °C; ^{1}H-NMR (500 MHz) δ 10.34 (s, 1 H), 7.35 (d, *J* = 8.8 Hz, 2 H), 7.32 (s, 1 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 6.56 (s, 1 H), 5.10 (s, 2 H), 3.93 (s, 3 H), 3.88 (s, 3 H), 3.83 (s, 3 H); ^{13}C-NMR (125 MHz) δ 188.1, 159.8, 157.8, 155.6, 144.0, 129.2, 128.1, 118.2, 114.2, 108.8, 98.1, 71.7, 56.2, 55.3; IR (film) 2958 (C-H), 2937 (C-H), 2837, 1655 (C=O), 1606, 1468,

1454, 1276, 1216, 1127, 1037, 1021, 915 cm^{-1}; HRMS (CI) *m/z* calc for $C_{17}H_{18}O_5^+$ (M+), 302.1154; found, 302.1159.

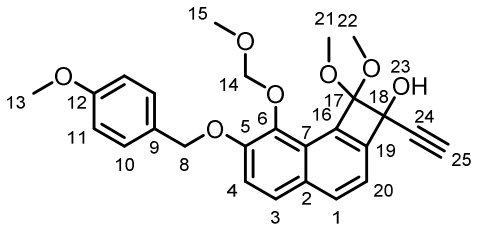
NMR assignments: ^{1}H-NMR (500 MHz) δ 10.34 (s, 1 H, C1-H), 7.35 (d, *J* = 8.8 Hz, 2 H, C12-H), 7.32 (s, 1 H, C3-H), 6.93 (d, *J* = 8.8 Hz, 2 H, C13-H), 6.56 (s, 1 H, C6-H), 5.10 (s, 2 H, C8-H), 3.93 (s, 3 H, C10-H), 3.88 (s, 3 H, C9-H), 3.83 (s, 3 H, C15-H); ^{13}C-NMR (125 MHz) δ 188.1 (C1), 159.8 (C7), 157.8 (C5), 155.6 (C14), 144.0 (C4), 129.2 (C12), 128.1 (C11), 118.2 (C2), 114.2 (C13), 108.8 (C3), 98.1 (C6), 71.7 (C8), 56.2 (C10, C15), 55.3 (C9).



4.114

1-(4,5-Dimethoxy-2-((4-methoxybenzyl)oxy)phenyl)prop-2-yn-1-ol (**4.114**). (SB-VI-70). A solution of aldehyde **4.113** (354 mg, 1.17 mmol) in THF (7 mL) was degassed. A solution of ethynyl magnesium bromide (0.5 M, 5.8 mL, 2.93 mmol) in THF was added and the reaction mixture was stirred for 2 h at 5 °C, whereupon a solution of saturated aqueous $NaHCO_3$ (1 mL) was added. The mixture was extracted with EtOAc (3 x 2 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with EtOAc/hexanes (1:2) to provide 375 mg (98%) of **4.114** as a waxy solid: ^{1}H-NMR (600 MHz) δ 7.36 (d, *J* = 8.8 Hz, 2 H), 7.13 (s, 1 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 6.60 (s, 1 H), 5.68 (dd, *J* = 2.4, 6 Hz, 1 H), 5.05 (dd, *J* = 4, 10.6 Hz, 2 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.82 (s, 3 H), 2.79 (d, *J* = 6 Hz, 1 H), 2.62 (d, *J* = 2.4 Hz, 1 H); ^{13}C-NMR (150 MHz) δ 159.6, 150.1, 149.7, 143.5, 129.1, 128.7, 120.8, 114.1, 111.5, 99.5, 83.6, 73.9, 71.7, 66.3, 56.5, 56.2, 55.3; IR (film) 3469 (O-H), 3282, 3001, 2936 (C-H), 2836 (C-H), 1612, 1515, 1464, 1405, 1383, 1304, 1249, 1209, 1175, 1114, 1019, 941 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{19}H_{20}O_5^+$ (M+Na), 351.1203; found, 351.1200.

NMR assignments: ^{1}H-NMR (600 MHz) δ 7.36 (d, *J* = 8.8 Hz, 2 H, C12-H), 7.13 (s, 1 H, C3-H), 6.92 (d, *J* = 8.8 Hz, 2 H, C13-H), 6.60 (s, 1 H, C6-H), 5.68 (dd, *J* = 2.4, 6 Hz, 1 H, C1-H), 5.05 (dd, *J* = 4, 10.6 Hz, 2 H, C8-H), 3.87 (s, 3 H, C10-H), 3.86 (s, 3 H, C9-H), 3.82 (s, 3 H, C15-H), 2.79 (d, *J* = 6 Hz, 1 H, O-H), 2.62 (d, *J* = 2.4 Hz, 1 H, C17-H); ^{13}C-NMR (150 MHz) δ 159.6 (C14), 150.1 (C7), 149.7 (C5), 143.5 (C4), 129.1 (C12), 128.7 , 120.8 (C3), 114.1 (C13), 111.5 (C2), 99.5 (C6), 83.6 (C16), 73.9 (C17), 71.7 (C8), 66.3 (C1), 56.5 (C15 or C10), 56.2 (C15 or C10), 55.3 (C9).

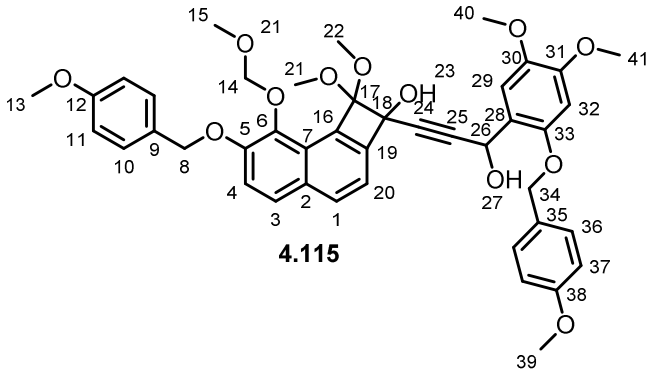


4.112

22-Ethynyl-1,1-dimethoxy-7-((4-methoxybenzyl)oxy)-8-(methoxymethoxy)-1,2-dihydrocyclobuta[a]naphthalen-2-ol (**4.112**). (SB-VI-76). A round bottom flask containing **4.110** (162 mg, 0.381 mmol) was put under vacuum for 2 h. THF (1.6 mL) was added, and the reaction mixture was degassed. The mixture was warmed to 0 °C, and a solution of ethynyl magnesium bromide (0.5 M, 4.3 mL, 2.14 mmol) in THF was added. The reaction mixture was stirred for 2 h at 5 °C, whereupon a solution of saturated aqueous $NaHCO_3$ (1 mL) was added. The mixture was extracted with EtOAc (3 x 2 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with EtOAc/hexanes (1:4) to provide 149 mg (87%) of **4.112** as a brown to orange solid: mp 95-100 °C; ^{1}H-NMR (500 MHz) δ 7.84 (d, *J* = 8.2 Hz, 1 H), 7.61 (d, *J* = 9.2 Hz, 1 H), 7.40 (d, *J* = 8.2 Hz, 1 H), 7.39 (d, *J* = 8.6 Hz, 2 H), 7.32 (d, *J* = 9.2 Hz, 1 H), 6.90 (d, *J* = 8.6 Hz, 2 H) 5.33 (d, *J* = 5.4 Hz, 1 H), 5.20 (d, *J* = 11.6 Hz, 1 H), 5.16 (d, *J* = 11.6 Hz, 1 H), 5.13 (d, *J* = 5.4 Hz, 1 H) 3.81 (s, 3 H), 3.67 (s, 3 H), 3.66 (s, 3 H), 3.55 (s, 3 H), 2.70 (s, 1 H);

^{13}C-NMR (150 MHz) δ 159.5, 150.1, 146.0, 138.7, 136.8, 132.7, 131.1, 129.4, 128.8, 126.3, 126.2, 116.9, 116.7, 113.9, 107.4, 99.9, 81.8, 77.4, 75.5, 71.6, 57.6, 55.27, 53.2, 52.0; IR (film) 3494 (O-H), 3286 (O-H), 2942 (C-H), 2838 (C-H), 1614, 1594, 1515, 1463, 1336, 1251, 1176, 1154, 1118, 1078, 1031, 948 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{26}H_{26}O_7^+$ (M+Na), 473.1571; found, 473.1562.

NMR assignments: ^{1}H-NMR (500 MHz) δ 7.84 (d, *J* = 8.2 Hz, 1 H, C20-H), 7.61 (d, *J* = 9.2 Hz, 1 H, C3-H), 7.40 (d, *J* = 8.2 Hz, 1 H, C1-H), 7.39 (d, *J* = 8.6 Hz, 2 H, C10-H), 7.32 (d, *J* = 9.2 Hz, 1 H, C4-H), 6.90 (d, *J* = 8.6 Hz, 2 H, C11-H) 5.33 (d, *J* = 5.4 Hz, 1 H, C8-H), 5.20 (d, *J* = 11.6 Hz, 1 H, C14-H), 5.16 (d, *J* = 11.6 Hz, 1 H, C14-H), 5.13 (d, *J* = 5.4 Hz, 1 H, C8-H) 3.81 (s, 3 H, C13-H), 3.67 (s, 3 H, C21-H), 3.66 (s, 3 H, C22-H), 3.55 (s, 3 H, C15-H), 2.70 (s, 1 H, C25-H); ^{13}C-NMR (150 MHz) δ 159.5 (C12), 150.1 (C6), 146.0 (C5), 138.7 (C16), 136.8 (C19), 132.7 (C20), 131.1 (C2), 129.4 (C10), 128.8 (C9), 126.3 (C1), 126.2 (C7), 116.9 (C7), 116.7 (C3), 113.9 (C11), 107.4 (C17), 99.9 (C14), 81.8 (C24), 77.4 (C18), 75.5 (C25), 71.6 (C8), 57.6 (C15), 55.27 (C13), 53.2 (C21), 52.0 (C22).



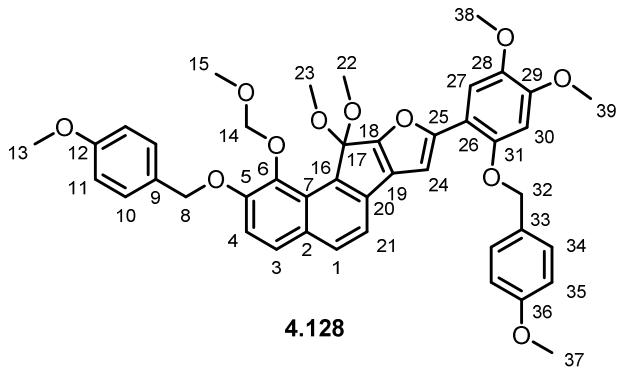
4.115

2-(3-(4,5-Dimethoxy-2-((4-methoxybenzyl)oxy)phenyl)-3-hydroxyprop-1-yn-1-yl)-1,1-dimethoxy-7-((4-methoxybenzyl)oxy)-8-(methoxymethoxy)-1,2-dihydrocyclobuta[a]naphthalen-2-ol (**4.115**). (SB-VI-150). A solution of **4.112** (143 mg, 0.337 mmol) in toluene (2 mL) was concentrated under reduced pressure (3 x), put under vacuum for 2 h and dissolved in THF (2.7 mL). A separate roundbottomed flask containing **4.114** (221 mg, 0.674 mmol) was dissolved in toluene (2 mL), concentrated under reduced pressure (3 x) and put under vacuum for 2 h. 4-(Phenylazo)diphenylamine (PDA) (**4.118**) (5 mg, 0.017 mmol) was added to the flask containing **4.114**, followed by a solution of $CeCl_3$•2LiCl in THF (0.33 M, 4.1 mL, 1.35 mmol)[167], and the reaction mixture was cooled to – 78 °C and degassed. The cooling bath was removed, and the mixture was warmed to 0 °C, whereupon a solution of *n*-BuLi in hexanes was added until the reaction mixture turned a persistent purple color (1.21 M, ca. 1.5 mL, 1.81 mmol). After the purple endpoint had been seen, an additional ammount of *n*-BuLi in hexanes (1.21 M, 0.56 mL, 0.67 mmol) was added, and the reaction mixture was stirred for 10 min at 0 °C. The solution of **4.112** in THF (1 mL) was slurried over NaH (60 % dispersion in mineral oil, ca. 6 mg, 0.150 mmol) before adding to the reaction mixture containing **4.114**, and stirring was continued for 1 h at 0 °C. A solution of saturated aqueous $NaHCO_3$ (5 mL) was then added and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:2 → 3:4) to provide 212 mg (84%) of **4.115** and 10 mg (7%) of **4.112** (91% brsm): ^{1}H-NMR (600 MHz) δ 7.81 (d, *J* = 8.6 Hz, 1 H), 7.78 (d, *J* = 8.6 Hz, 1 H), 7.60 (d, *J* =

6.9 Hz, 1 H), 7.58 (d, *J* = 6.9 Hz, 1 H), 7.40-7.35 (Comp, 6 H), 7.30 (d, *J* = 9.0 Hz, 2 H), 7.27 (d, *J* = 8.8 Hz, 2 H), 7.24 (d, *J* = 8.8 Hz, 2 H), 7.084 (s, 1 H), 7.07 (s, 1 H), 6.55 (s, 1 H), 6.53 (s, 1 H) 5.74 (app. d, 2 H), 5.29 (d, *J* = 5.3 Hz, 1 H), 5.25 (d, *J* = 5.3 Hz, 1 H), 5.16 (app qd, 4 H), 5.09 (d, *J* = 5.3 Hz, 1 H), 5.04 (d, *J* = 5.3 Hz, 1 H), 4.96 (app qd, 4 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.80 (s, 6 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.72 (s, 3 H), 3.67 (s, 3 H), 3.64 (s, 3 H), 3.63 (s, 3 H), 3.58 (s, 3 H), 3.53 (s, 3 H), 3.52 (app. d, 6 H); ^{13}C-NMR (150 MHz) δ 159.5, 159.4, 150.3, 150.1, 150.0, 149.5, 149.4, 146.3, 143.4, 138.7, 136.7, 132.6, 131.0, 129.4, 129.2, 128.8, 128.7, 126.3, 126.2, 121.4, 117.2, 117.1, 116.6, 114.0, 113.9, 111.8, 111.6, 107.6, 99.8, 99.7, 87.1, 83.9, 83.7, 77.6, 71.8, 71.6, 60.9, 60.6, 57.6, 56.3, 56.2, 56.1, 55.3, 55.2, 53.2, 51.9, 51.8; IR (film) 3466 (O-H), 2939 (C-H), 2838 (C-H), 2251 (C≡C), 1728, 1613, 1515, 1463, 1405, 1382, 1303, 1251, 1209, 1113, 1032, 912 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{43}H_{44}O_{12}^{+}$ (M+Na), 775.2725; found, 775.2722.

NMR assignments: ^{1}H-NMR (600 MHz) δ 7.81 (d, *J* = 8.6 Hz, 1 H, C20-H), 7.78 (d, *J* = 8.6 Hz, 1 H, C20-H), 7.60 (d, *J* = 6.9 Hz, 1 H, C3-H), 7.58 (d, *J* = 6.9 Hz, 1 H, C3-H), 7.40-7.35 (Comp, 6 H, C10-H,C1-H), 7.30 (d, *J* = 9.0 Hz, 2 H, C4-H), 7.27 (d, *J* = 8.8 Hz, 2 H, C36-H), 7.24 (d, *J* = 8.8 Hz, 2 H, C36-H), 7.08 (s, 1 H, C29-H), 7.07 (s, 1 H, C29-H), 6.55 (s, 1 H, C32-H), 6.53 (s, 1 H, C32-H) 5.74 (app. d, 2 H, C26-H), 5.29 (d, *J* = 5.3 Hz, 1 H, C8-H), 5.25 (d, *J* = 5.3 Hz, 1 H, C8-H), 5.16 (app qd, 4 H, C14-H), 5.09 (d, *J* = 5.3 Hz, 1 H, C8-H), 5.04 (d, *J* = 5.3 Hz, 1 H, C8-H), 4.96 (app qd, 4 H, C34-H), 3.82 (s, 3 H, C40-H), 3.81 (s, 3 H, C41-H), 3.80 (s, 6 H, C13-H), 3.74 (s, 3 H, C40-H), 3.73 (s, 3 H, C41-H), 3.72 (s, 3 H, C39-H), 3.67 (s, 3 H, C39-H), 3.64 (s, 3 H, C21-H or C22-H), 3.63 (s, 3 H, C21-H or C22-H), 3.58 (s, 3 H, C21-H or C22-H), 3.53 (s, 3 H, C21-H or C22-H), 3.52 (app. d, 6 H, C15-H); ^{13}C-NMR (150 MHz) δ 159.5 (C12), 159.4 (C38), 150.3 (C33), 150.1 (C33, C6), 150.0 (C6), 149.5 (C31), 149.4 (C31), 146.3 (C5), 143.4 (C30), 138.7 (C16), 136.7 (C19), 132.6 (C20), 131.0 (C2), 129.4 (C10), 129.2 (C36), 128.8 (C9, C35), 128.7 (C35), 126.3 (C1), 126.2 (C7), 121.4 (C29), 117.2 (C4), 117.1 (C4), 116.6 (C3), 114.0 (C11), 113.9 (C11, C37), 111.8 (C28), 111.6 (C28), 107.6 (C17), 99.8 (C14), 99.7 (C32), 87.1 (C24), 83.9 (C25), 83.7 (C25), 77.6 (C18), 71.8 (C8), 71.6 (C34), 60.9 (C26),

60.6 (C26), 57.6 (C15), 56.3 (C39 or C11), 56.2 (C39 or C11), 56.1 (C39 or C11), 55.3 (C13), 55.2 (C40), 53.2 (C21 or C22), 51.9(C21 or C22), 51. 8 (C21 or C22).



4.128

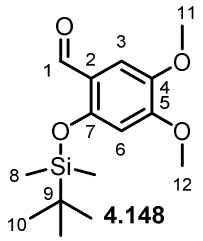
8-(4,5-Dimethoxy-2-((4-methoxybenzyl)oxy)phenyl)-10,10-dimethoxy-2-((4-methoxybenzyl)oxy)-1-(methoxymethoxy)-10H-benzo[4,5]indeno[2,1-b]furan (**4.128**). (SB-VI-170). A batch of Phosphoric acid-doped SiO_2 was prepared by the addition of neat 85% Phosphoric acid (29 µL, 49 mg, 0.5 mmol) to a slurry of silica (2.0 g) in CH_2Cl_2 (5 mL). Water (50 µL) was added and the slurry was stirred vigorously for 1 h. The solvent was removed under reduced pressure until the silica became a free-flowing powder. A portion of the Phosphoric acid-doped SiO_2 (111 mg) was added to a solution of **4.115** (169 mg, 0.222 mmol) in CH_2Cl_2 (2.7 mL) at room temperature. The reaction mixture was stirred for 30 min whereupon triethylamine (Et_3N) (72 mg, 0.1 mL, 0.7165 mmol) was added and the mixture was filtered through Celite and washed with CH_2Cl_2 (1 x 5 mL). The combined organic extracts were concentrated under reduced pressure and the crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:4 → 3:4) to provide 46 mg (29%) of **4.128** and 72 mg (43%) of **4.115**.

^{1}H-NMR (600 MHz) δ 7.79 (d, *J* = 8.5 Hz, 0.5 H), 7.77 (d, *J* = 8.5 Hz, 0.5 H), 7.58 (d, *J* = 8.8 Hz, 1 H), 7.42-7.40 (comp, 4.5 H), 7.38-7.35 (comp, 4.5 H), 7.34 (d, *J* = 8.8 Hz, 0.5 H), 7.33 (d, *J* = 8.8 Hz, 0.5 H), 7.22 (s, 0.5 H), 7.20 (s, 0.5 H), 6.94 (d, *J* = 8.5 Hz, 1 H), 6.91-6.90

(comp, 3 H), 6.68 (s, 0.5 H) 6.62 (s, 0.5 H), 6.55 (s, 0.5 H), 6.54 (s, 0.5 H), 5.25 (app d, 2 H), 5.17 (s, 2 H), 5.02 (app d., 2 H), 4.00 (s, 1.5 H), 3.94 (s, 1.5 H), 3.87 (s, 1.5 H), 3.86 (s, 1.5 H), 3.83 (s, 1.5 H), 3.81 (s, 4.5 H), 3.57 (s, 1.5 H), 3.56 (s, 1.5 H), 3.44 (s, 3 H), 3.43 (s, 3 H); ^{13}C-NMR 159.5, 153.2, 153.0, 150.6, 150.6, 150.5, 150.1, 149.4, 144.2, 144.2, 140.5, 140.5, 135.8, 135.5, 134.4, 133.9, 132.2, 132.1, 131.1, 131.0, 129.4, 129.3, 129.2, 129.1, 129.0, 129.0, 128.8, 128.8, 128.3, 127.6, 127.4, 127.4, 127.3, 125.6, 125.5, 125.3, 125.3, 118.6, 118.6, 117.1, 117.0, 117.0, 114.0, 113.9, 116.6, 110.4, 109.9, 100.1, 99.6, 99.1, 94.1, 93.6, 72.2, 71.7, 71.6, 71.6, 60.4, 57.6, 56.5, 56.2, 56.1, 55.3, 55.3, 51.8, 51.8; IR (film) 2938 (C-H), 2836 (C-H), 2252, 2044, 1612, 1586, 1516, 1462, 1404, 1288, 1251, 1211, 1175, 1127, 1101, 1032, 919 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{43}H_{42}O_{11}^{+}$ (M+Na), 757.2619; found, 757.2615.

NMR assignments: ^{1}H-NMR (600 MHz) δ 7.79 (d, *J* = 8.5 Hz, 0.5 H, C1-H), 7.77 (d, *J* = 8.5 Hz, 0.5 H, C1-H), 7.58 (d, *J* = 8.8 Hz, 1 H, C4-H), 7.42-7.40 (comp, 4.5 H, C10-H, C34-H, C21-H), 7.38-7.35 (comp, 4.5 H, C10-H, C34-H, C21-H), 7.34 (d, *J* = 8.8 Hz, 0.5 H, C3-H), 7.33 (d, *J* = 8.8 Hz, 0.5 H, C3-H), 7.22 (s, 0.5 H, C27-H), 7.20 (s, 0.5 H, C27-H), 6.94 (d, *J* = 8.5 Hz, 1 H, C11-H, C35-H), 6.91-6.90 (comp, 3 H, C11-H, C35-H), 6.68 (s, 0.5 H, C24-H) 6.62 (s, 0.5 H, C24-H), 6.55 (s, 0.5 H, C30-H), 6.54 (s, 0.5 H, C30-H), 5.25 (app d, 2 H, C14-H), 5.17 (s, 2 H, C8-H), 5.02 (app d., 2 H, C32-H), 4.00 (s, 1.5 H, C39-H), 3.94 (s, 1.5 H, C39-H), 3.87 (s, 1.5 H, C38-H), 3.86 (s, 1.5 H, C38-H), 3.83 (s, 1.5 H, C13-H, C37-H), 3.81 (s, 4.5 H, C13-H, C37-H), 3.57 (s, 1.5 H, C15-H), 3.56 (s, 1.5 H, C15-H), 3.44 (s, 3 H, C22-H, C23-H), 3.43 (s, 3 H, C22-H, C23-H); ^{13}C-NMR 159.5 (C12, C36), 153.2 (C25), 153.0 (C25), 150.6 (C5), 150.6 (C31), 150.5 (C5), 150.1 (C31), 149.4 (C28), 144.2 (C29), 144.2 (C29), 140.5 (C6), 140.5 (C6), 135.8 (C20), 135.5 (C20), 134.4 (C16), 133.9 (C16), 132.2 (C1), 132.1 (C1), 131.1 (C2), 131.0 (C2), 129.4 (C9), 129.3 (C33), 129.2 (C33), 129.1 (C34), 129.0 (C34), 129.0 (C21), 128.8 (C21), 128.8 (C10), 128.3 (C10), 127.6 (C18), 127.4 (C17), 127.4 (C18), 127.3 (C17), 125.6 (C7), 125.5 (C7), 125.3 (C4), 125.3 (C4), 118.6 (C26), 118.6 (C26), 117.1 (C3), 117.0 (C3), 117.0 (C19), 114.0 (C11, C35), 113.9 (C11, C35), 116.6 (C19), 110.4 (C27), 109.9 (C27), 100.1 (C30), 99.6 (C30), 99.1 (C14), 94.1 (C24), 93.6 (C24), 72.2 (C32), 71.7 (C32), 71.6 (C8), 71.6 (C8),

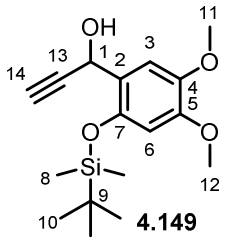
60.4 (C38), 57.6 (C15), 56.5 (C39), 56.2 (C39), 56.1 (C38), 55.3 (C13, C37), 55.3 (C13, C37), 51.8 (C22, C23), 51.8 (C22, C23).



4.148

2-((*tert*-Butyldimethylsilyl)oxy)-4,5-dimethoxybenzaldehyde (**4.148**). (SB-VI-181). TBSCl (166 mg, 1.098 mmol) was added to a solution of **4.112** (100 mg, 0.549 mmol) and imidazole (75 mg, 1.098 mmol) in DMF (0.5 mL) at room temperature. The mixture was stirred for 1 h, whereupon a solution of saturated aqueous $NaHCO_3$ (1 mL) was added. The mixture was extracted with EtOAc (3 x 2 mL) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with acetone/hexanes (1:10) to provide 112 mg (69%) of **4.148** as a waxy white solid: mp 64-65 °C; ^{1}H-NMR (500 MHz) δ 10.25 (s, 1 H), 7.25 (s, 1 H), 6.33 (s, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 1.01 (s, 9 H), 0.24 (s, 6 H); ^{13}C-NMR (125 MHz) δ 188.3, 155.5, 155.2, 144.3, 119.7, 108.2, 103.5, 56.1, 56.0, 25.6, 18.3, -4.4; IR (film) 2951 (C-H), 2836 (C-H), 1754 (C=O), 1661 (C=O), 1642, 1614, 1595, 1516, 1483, 1467, 1382, 1292, 1252, 1214, 1195, 1176, 1115, 1033, 992 cm^{-1}; HRMS (CI) *m/z* calc for $C_{15}H_{25}O_4Si^+$ (M+), 297.1522; found, 297.1527.

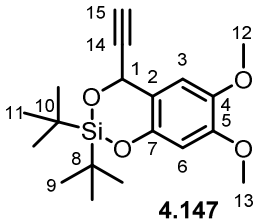
NMR assignments: ^{1}H-NMR (500 MHz) δ 10.25 (s, 1 H, C1-H), 7.25 (s, 1 H, C3-H), 6.33 (s, 1 H, C6-H), 3.88 (s, 3 H, C12-H), 3.86 (s, 3 H, C11-H), 1.01 (s, 9 H, C10-H), 0.24 (s, 6 H, C8-H); ^{13}C-NMR (125 MHz) δ 188.3 (C1), 155.5 (C7) 155.2 (C5), 144.3 (C4), 119.7 (C2), 108.2 (C3), 103.5 (C6), 56.1 (C12), 56.0 (C11), 25.6 (C10), 18.3 (C9), -4.4 (C8).



4.149

1-(2-((*tert*-Butyldimethylsilyl)oxy)-4,5-dimethoxyphenyl)prop-2-yn-1-ol (**4.149**). (SB-VI-189). A solution of aldehyde **4.148** (110 mg, 0.371 mmol) in THF (1.1 mL) was cooled to – 78 °C and reaction vessel was degassed. A solution of ethynyl magnesiumbromide (0.5 M, 0.9 mL, 0.445 mmol) was then added at – 78 °C, and the mixture was warmed to room temperature, and stirred for an additional 30 min. A solution of saturated aqueous $NaHCO_3$ (2 mL) was then added, and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure, and the crude oil was purified by flash chromatography eluting with acetone/hexanes (1:4) to provide 103 mg (86%) of **4.149**: ^{1}H-NMR (500 MHz) δ 7.12 (s, 1 H), 6.38 (s, 1 H), 5.67 (d, *J* = 2.0 Hz, 1 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 2.62 (bs, 1 H), 2.57 (d, *J* = 2.0 Hz, 1 H), 1.01 (s, 9 H), 0.25 (s, 3 H), 0.24 (s, 3 H); ^{13}C-NMR (125 MHz) δ 149.6, 146.6, 143.7, 121.9, 111.1, 103.8, 83.7, 73.8, 59.6, 56.3, 55.9, 25.7, 18.1, -4.1, -4.2; IR (neat) 3493 (O-H), 3288 (O-H), 2932 (C-H), 2858 (C-H), 2253 (C≡C), 2114 (C≡C), 1611, 1514, 1469, 1404, 1322, 1204, 1117, 1012, 945, 1252, 1214, 1195, 1176, 1115, 1033, 992 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{17}H_{26}O_4Si^+$ (M+Na), 345.1493; found, 345.1494.

NMR assignments: ^{1}H-NMR (500 MHz) δ 7.12 (s, 1 H, C3-H), 6.38 (s, 1 H, C6-H), 5.67 (d, *J* = 2.0 Hz, 1 H, C1-H), 3.84 (s, 3 H, C12-H), 3.80 (s, 3 H, C11-H), 2.62 (bs, 1 H, O-H), 2.57 (d, *J* = 2.0 Hz, 1 H, C14-H), 1.01 (s, 9 H, C10-H), 0.25 (s, 3 H, C8-H), 0.24 (s, 3 H, C8-H); ^{13}C-NMR (125 MHz) δ 149.6 (C5), 146.6 (C7), 143.7 (C4), 121.9 (C3), 111.1 (C2), 103.8 (C6), 83.7 (C13), 73.8 (C14), 59.6 (C1), 56.3 (C12), 55.9 (C11), 25.7 (C10), 18.1 (C9), –4.1 (C8), –4.2 (C8).



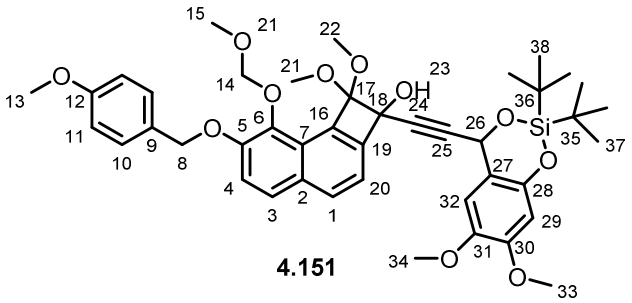
4.147

2,2-Di-*tert*-butyl-4-ethynyl-6,7-dimethoxy-4H-benzo[d][1,3,2]dioxasiline (**4.147**). (SB-VI-277). A solution of aldehyde **4.122** (1.56 mg, 8.57 mmol) in THF (16 mL) was cooled to – 78 °C, the reaction vessel was degassed, and a solution of ethynyl magnesium bromide (0.5 M, 42.8 mL, 21.41 mmol) was added at – 78 °C. The cooling bath was removed, and the reaction mixture was warmed to room temperature and stirred for 1 h, whereupon a solution of dilute NH_4Cl (10 mL) was added. The mixture was extracted with EtOAc (3 x 10 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by silica plug eluting with 1:1 mixture acetone/hexanes (500 mL) to provide 1.44 g of the acetylide adduct as a brown solid which used directly in the next step.

A solution the acetylide adduct (1.44 g, 6.92 mmol) and 2,6-lutidine (1.85 g, 2.0 mL, 17.3 mmol) in CH_2Cl_2 (18 mL) was cooled to – 40 °C, (*tert*-Bu)$_2$Si(OTf)$_2$ (3.65 g, 2.7 mL, 8.30 mmol) was added, and the reaction mixture was warmed to 0 °C and stirred for 4 h. Saturated aqueous $NaHCO_3$ (5 mL) was added, and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:20 → 1:10) to provide 1.98 mg (82%) of **4.147** as a waxy white solid: mp 78-80 °C; ^{1}H-NMR (500 MHz) δ 6.82 (s, 1 H), 6.49 (s, 1 H), 5.84 (dd, *J* = 0.7, 2.3 Hz, 1 H), 3.85 (s, 1 H), 3.83 (s, 3 H), 2.66 (d, *J* = 2.3 Hz, 1 H), 1.06 (s, 9 H), 1.03 (s, 9 H); ^{13}C-NMR (125 MHz) δ 149.8, 147.1, 143.2, 116.5, 109.8, 103.6, 83.1, 74.1, 64.5, 56.4, 55.9, 26.9, 26.9, 21.5, 20.9; IR (film) 3287 2936 (C-H), 2896 (C-H), 2860, 2120, 1616, 1512, 1471, 1471, 1450, 1405, 1364,

1326, 1291, 1264, 1218, 1200, 1195, 1175, 1126, 1084, 1012, 940 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{19}H_{28}O_4Si^+$ (M+Na), 371.1649; found, 371.1652.

NMR assignments: ^{1}H-NMR (500 MHz) δ 6.82 (s, 1 H, C3-H), 6.49 (s, 1 H, C6-H), 5.84 (dd, *J* = 0.7, 2.3 Hz, 1 H, C1-H), 3.85 (s, 1 H, C13-H), 3.83 (s, 3 H, C12-H), 2.66 (d, *J* = 2.3 Hz, 1 H, C15-H), 1.06 (s, 9 H, C11-H or C9-H), 1.03 (s, 9 H, C11-H or C9-H); ^{13}C-NMR (125 MHz) δ 149.8 (C5), 147.1 (C7), 143.2 (C4), 116.5 (C3), 109.8 (C2), 103.6 (C6), 83.1 (C14), 74.1 (C15), 64.5 (C1), 56.4 (C13), 55.9 (C12), 26.9 (C9 or C11), 26.9 (C9 or C11), 21.5 (C8 or C10), 20.9 (C8 or C10).



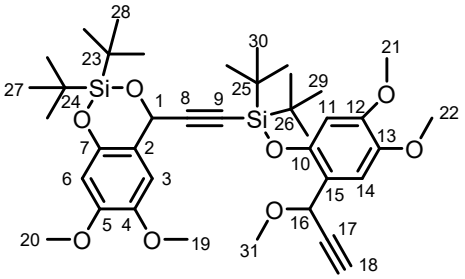
4.151

2-((2,2-Di-*tert*-butyl-6,7-dimethoxy-4H-benzo[d][1,3,2]dioxasilin-4-yl)ethynyl)-1,1-dimethoxy-7-((4-methoxybenzyl)oxy)-8-(methoxymethoxy)-1,2-dihydrocyclobuta[a]naphthalen-2-ol (**4.151**). (SB-VI-243). A solution of **4.112** (100 mg, 0.236 mmol) in toluene (2 mL) was concentrated under reduced pressure (1 x), put under vacuum for 2 h, and dissolved in THF (1 mL). A separate round bottomed flask containing **4.147** (164 mg, 0.471 mmol) was dissolved in toluene (2 mL), concentrated under reduced pressure (1 x), and put under vacuum for 2 h. 4-(Phenylazo)diphenylamine (PDA) (**4.118**) (3 mg, 0.012 mmol), and a solution of $CeCl_3$•2LiCl in THF (0.33 M, 1.43 mL, 0.471 mmol)[167] was added to the flask containing **4.147** and the mixture was cooled to – 78 °C and the reaction vessel was degassed. A solution of *n*-BuLi in hexanes was added until the reaction mixture turned a persistent purple color. After the purple endpoint had been seen, an additional ammount of *n*-BuLi in hexanes (2.27 M, 0.21 mL, 0.471 mmol) was added, the cooling bath was removed, and the reaction mixture was warmed to 0 °C. The solution of **4.112** was in THF (1 mL) was slurried

over NaH (60 % dispersion in mineral oil, ca. 6 mg, 0.15 mmol) before adding to the reaction mixture containing **4.147**, and stirring continued for an additional 1 h. AcOH (0.13 mL, 136 mg, 2.36 mmol) and de-ionized H_2O (5 mL) were then added, and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:4 → 1:2) to provide 145 mg (79%) of **4.151**; ^{1}H-NMR (600 MHz) δ 7.81 (d, *J* = 8.3 Hz, 2 H), 7.60 (d, *J* = 8.9 Hz, 2 H), 7.41 (d, *J* = 8.3 Hz, 1 H), 7.40 (d, *J* = 8.3 Hz, 1 H), 7.39 (d, *J* = 8.8 Hz, 4 H), 7.31 (d, *J* = 9.0 Hz, 2 H), 6.90 (d, *J* = 9.7 Hz, 4 H), 6.78 (s, 1 H), 6.69 (s, 1 H), 6.44 (s, 1 H), 6.43 (s, 1 H), 5.89 (d, *J* = 6.4 Hz, 2 H), 5.31 (dd, *J* = 5.3, 6.8 Hz, 2 H), 5.18 (dq, *J* = 2.4, 11.4 Hz, 4 H), 5.10 (dd, *J* = 5.3, 8.3 Hz, 2 H), 3.82 (s, 3 H), 3.81 (s, 6 H), 3.67 (s, 3 H), 3.66 (s, 3 H), 3.65 (s, 3 H), 3.61 (s, 3 H), 3.56 (s, 3 H), 3.53 (s, 3 H), 3.52 (s, 3 H), 3.51 (s, 3 H), 3.50 (s, 3 H), 1.51 (s, 9 H), 1.03 (s, 9 H), 0.96 (s, 9 H), 0.90 (s, 9 H); ^{13}C-NMR (150 MHz) δ 159.5, 150.1, 150.0, 149.5, 149.4, 147.0, 146.3, 143.0, 142.9, 138.7, 136.8, 136.7, 132.5, 131.0, 129.4, 128.8, 128.7, 126.3, 126.2, 117.1, 117.0, 116.6, 113.9, 109.9, 109.8, 107.6, 107.5, 103.4, 99.8, 86.7, 83.8, 77.5, 71.6, 64.8, 57.6, 56.1, 55.9, 55.3, 53.2, 51.9, 51.8, 26.9, 21.5, 21.0, 20.8; IR (film) 3498 (O-H), 2937 (C-H), 2860 (C-H), 2353 (C≡C), 1732, 1615, 1594, 1513, 1464, 1405, 1337, 1252, 1200, 1175, 1121, 1080, 1035, 1012, 938 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{19}H_{28}O_4Si^+$ (M+Na), 795.3171; found, 795.3163.

NMR assignments: ^{1}H-NMR (600 MHz) δ 7.81 (d, *J* = 8.3 Hz, 2 H, C20-H), 7.60 (d, *J* = 8.9 Hz, 2 H, C3-H), 7.41 (d, *J* = 8.3 Hz, 1 H, C1-H), 7.40 (d, *J* = 8.3 Hz, 1 H, C1-H), 7.39 (d, *J* = 8.8 Hz, 4 H, C10-H), 7.31 (d, *J* = 9.0 Hz, 2 H, C4-H), 6.90 (d, *J* = 9.7 Hz, 4 H, C11-H), 6.78 (s, 1 H, C29-H), 6.69 (s, 1 H, C29-H), 6.44 (s, 1 H, C32-H), 6.43 (s, 1 H, C32-H), 5.89 (d, *J* = 6.4 Hz, 2 H, C26-H), 5.31 (dd, *J* = 5.3, 6.8 Hz, 2 H, C14-H), 5.18 (dq, *J* = 2.4, 11.4 Hz, 4 H, C8-H), 5.10 (dd, *J* = 5.3, 8.3 Hz, 2 H, C14-H), 3.82 (s, 3 H, C33-H), 3.81 (s, 6 H, C33-H, C34-H), 3.67 (s, 3 H, C34-H), 3.66 (s, 3 H, C13-H), 3.65 (s, 3 H, C13-H), 3.61 (s, 3 H, C21-H or C22-H), 3.56 (s, 3 H, C21-H or C22-H), 3.53 (s, 3 H, C21-H or C22-H), 3.52 (s, 3 H, C21-H or C22-H), 3.51 (s, 3 H, C15-H), 3.50 (s, 3 H, C15-H), 1.51 (s, 9 H, C36-H or C37-H), 1.03 (s, 9 H, C36-H or C37-H),

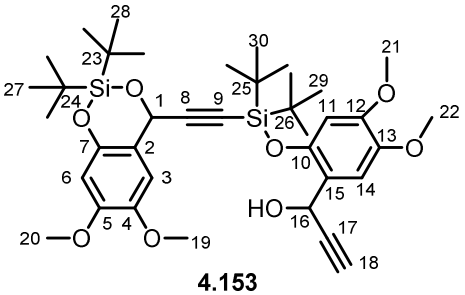
0.96 (s, 9 H, C36-H or C37-H), 0.90 (s, 9 H, C36-H or C37-H); ^{13}C-NMR (150 MHz) δ 159.5 (C12), 150.1 (C30), 150.0 (C30), 149.5 (C6), 149.4 (C6), 147.0 (C28), 146.3 (C5), 143.0 (C31), 142.9 (C31), 138.7 (C16), 136.8 (C19), 136.7 (C19), 132.5 (C20), 131.0 (C2), 129.4 (C10), 128.8 (C9), 128.7 (C9), 126.3 (C1), 126.2 (C1), 117.1 (C4), 117.0 (C4), 116.6 (C32), 113.9 (C11), 109.9 (C27), 109.8 (C27), 107.6 (C17), 107.5 (C17), 103.4 (C29), 99.8 (C14), 86.7 (C24), 83.8 (C25), 77.5 (C18), 71.6 (C8), 64.8 (C26), 57.6 (C15), 56.1 (C33), 55.9 (C33), 55.3 (C13), 53.2 (C21 or C22), 51.9 (C21 or C22), 51.8 (C21 or C22), 26.9 (C37 or C38), 21.5 (C35 or C36), 21.0 (C35 or C36), 20.8 (C35 or C36).



2,2-Di-*tert*-butyl-4-((di-*tert*-butyl(4,5-dimethoxy-2-(1-methoxyprop-2-yn-1-yl)phenoxy)silyl)ethynyl)-6,7-dimethoxy-4H-benzo[d][1,3,2]dioxasiline. (SB-VII-295A). Isolated from the hydrolysis of **4.151** when contaminated with **4.153**. Purified *via* flash chromatography eluting with a gradient of acetone/hexanes (1:10 → 3:10) to provide 96 mg (the named compound); ^{1}H-NMR (600 MHz) δ 7.20 (s, 2 H), 7.06 (s, 2 H), 6.81 (s, 2 H), 6.47 (s, 2 H), 5.94 (s, 2 H), 5.39 (app. t, *J* = 1.8 Hz, 2 H), 3.833 (s, 6 H), 3.832 (s, 6 H), 3.70 (s, 6 H), 3.69 (s, 6 H), 3.40 (s, 3 H), 3.39 (s, 3 H), 2.54 (dd, *J* = 1.2, 2.4 Hz, 2 H), 1.121 (s, 9 H), 1.118 (s, 9 H), 1.104 (s, 9 H), 1.101 (s, 9 H), 1.06 (s, 18 H), 0.98 (s, 18 H); ^{13}C-NMR (150 MHz) δ 149.7, 149.5, 147.45, 147.44, 146.9, 143.4, 143.2, 118.5, 115.8, 110.81, 110.79, 109.3, 108.35, 108.34, 103.6, 102.93, 102.92, 85.60, 85.59, 82.1, 74.49, 74.48, 66.76, 66.75, 65.1, 56.23, 56.22, 56.14, 56.11, 55.9, 55.7, 27.38, 27.36, 27.30, 27.28, 26.8, 26.7, 21.4, 21.1, 21.04, 21.02, 20.96; IR (film) 3307, 2934 (C-H), 2255 (C≡C), 2174 (C≡C), 1614, 1505, 1470, 1404, 1364, 1327, 1262,

1213, 1124, 1077, 1014, 912 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{39}H_{58}O_8Si_2^+$ (M+Na), 733.3562; found, 733.3562.

NMR assignments: ^{1}H-NMR (600 MHz) δ 7.20 (s, 2 H, C14-H), 7.06 (s, 2 H, C11-H), 6.81 (s, 2 H, C3-H), 6.47 (s, 2 H, C6-H), 5.94 (s, 2 H, C2-H), 5.39 (app. t, *J* = 1.8 Hz, 2 H, C16-H), 3.833 (s, 6 H, C19-H or C21-H), 3.832 (s, 6 H, C19-H or C21-H), 3.70 (s, 6 H, C20-H), 3.69 (s, 6 H, C22-H), 3.40 (s, 3 H, C31-H), 3.39 (s, 3 H, C31-H), 2.54 (dd, *J* = 1.2, 2.4 Hz, 2 H, C18-H), 1.121 (s, 9 H, C29-H or C30-H), 1.118 (s, 9 H, C29-H or C30-H), 1.104 (s, 9 H, C29-H or C30-H), 1.101 (s, 9 H, C29-H or C30-H), 1.06 (s, 18 H, C27-H or C28-H), 0.98 (s, 18 H, C27-H or C28-H); ^{13}C-NMR (150 MHz) δ 149.7 (C4), 149.5 (C13), 147.45 (C10), 147.44 (C10), 146.9 (C7), 143.4 (C12), 143.2 (C5), 118.5 (C15), 115.8 (C2), 110.81 (C11), 110.79 (C11), 109.3 (C3), 108.35 (C8), 108.34 (C8), 103.6 (C6), 102.93 (C14), 102.92 (C14), 85.60 (C9), 85.59 (C9), 82.1 (C18), 74.49 (C17), 74.48 (C17), 66.76 (C16), 66.75 (C16), 65.1 (C1), 56.23 (C19, C20, C21 or C22), 56.22 (C19, C20, C21 or C22), 56.14 (C19, C20, C21 or C22), 56.11 (C31), 55.9 (C19, C20, C21 or C22), 55.7 (C19, C20, C21 or C22), 27.38 (C29 or C30), 27.36, 27.30 (C29 or C30), 27.28 (C29 or C30), 26.8 (C27 or C28), 26.7 (C27 or C28), 21.4 (C23 or C24), 21.1 (C25 or C26), 21.04 (C25 or C26), 21.02 (C25 or C26), 20.96 (C23 or C24).

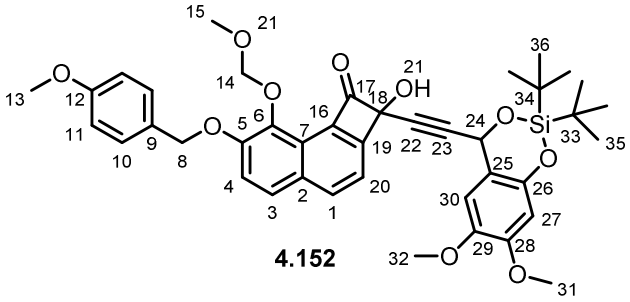


4.153

1-(2-((Di-*tert*-butyl((2,2-di-*tert*-butyl-6,7-dimethoxy-4H-benzo[d][1,3,2]dioxasilin-4-yl)ethynyl)silyl)oxy)-4,5-dimethoxyphenyl)prop-2-yn-1-ol (**4.153**). (SB-VIII-52A). By-product isolated from the reaction of **4.110** with **4.147.** Purified *via* flash chromatography eluting with a gradient of EtOAc/hexanes (1:4 → 1:2) to provide 90 mg (**4.153**); ^{1}H-NMR (500 MHz) δ 7.22 (s, 2 H), 7.15 (s, 2 H), 6.84 (s, 2 H), 6.51 (s, 2 H), 5.98 (s, 2 H), 5.82 (bs, 2 H), 3.869 (s, 6

H), 3.867 (s, 6 H), 3.74 (s, 6 H), 3.73 (s, 6 H), 2.60 (d, *J* = 2.0 Hz, 2 H), 1.17 (s, 9 H), 1.13 (s, 9 H), 1.09 (s, 9 H), 1.02 (s, 9 H); ^{13}C-NMR (125 MHz) δ 149.8, 149.5, 147.1, 146.9, 143.5, 143.3, 120.6, 115.8, 110.4, 109.3, 108.5, 103.6, 103.3, 85.5, 83.7, 73.9, 65.1, 59.3, 56.3, 56.2, 55.9, 55.8, 27.44, 27.41, 26.9, 26.8, 21.5, 21.2, 21.04, 20.99; IR (film) 3498 (O-H), 3309, 2935 (C-H), 2860, 1614, 1512, 1469, 1449, 1405, 1261, 1204, 1122, 1087, 1013 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{38}H_{56}O_8Si_2^+$ (M+Na), 719.3406; found, 719.3407.

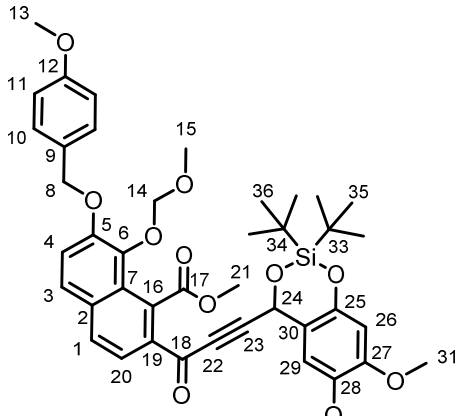
NMR assignments: ^{1}H-NMR (500 MHz) δ 7.22 (s, 2 H, C14-H), 7.15 (s, 2 H, C10-H), 6.84 (s, 2 H, C3-H), 6.51 (s, 2 H, C6-H), 5.98 (s, 2 H, C1-H), 5.82 (bs, 2 H, C16-H), 3.869 (s, 6 H, C19-H, C20-H, C21-H or C22-H), 3.867 (s, 6 H, C19-H, C20-H, C21-H or C22-H), 3.74 (s, 6 H, C19-H, C20-H, C21-H or C22-H), 3.73 (s, 6 H, C19-H, C20-H, C21-H or C22-H), 2.60 (d, *J* = 2.0 Hz, 2 H, C18-H), 1.17 (s, 9 H, C27-H, C28-H, C29-H or C30-H), 1.13 (s, 9 H, C27-H, C28-H, C29-H or C30-H), 1.09 (s, 9 H, C27-H, C28-H, C29-H or C30-H), 1.02 (s, 9 H, C27-H, C28-H, C29-H or C30-H); ^{13}C-NMR (125 MHz) δ 149.8 (C4), 149.5 (C13), 147.1 (C10), 146.9 (C7), 143.5 (C12), 143.3 (C5), 120.6 (C15), 115.8 (C2), 110.4 (C11), 109.3 (C3), 108.5 (C8), 103.6 (C6), 103.3 (C14), 85.5 (C9), 83.7 (C18), 73.9 (C17), 65.1 (C1), 59.3 (C16), 56.3 (C19, C20, C21 or C22), 56.2 (C19, C20, C21 or C22), 55.9 (C19, C20, C21 or C22), 55.8 (C19, C20, C21 or C22), 27.44 (C29, or C30), 27.41 (C29, or C30), 26.9 (C27, or C28), 26.8 (C27, or C28), 21.5 (C23, or C24), 21.2 (C25, or C26), 21.04 (C25, or C26), 20.99 (C23, or C24).



4.152

2-((2,2-Di-*tert*-butyl-6,7-dimethoxy-4H-benzo[d][1,3,2]dioxasilin-4-yl)ethynyl)-2-hydroxy-7-((4-methoxybenzyl)oxy)-8-(methoxymethoxy)cyclobuta[a]naphthalen-1(2H)-one (**4.152**). (SB-VII-38). H_3PO_4 (85%, 7 mg, 4 µL, 0.0697 mmol) and H_2O (28 mg, 28 µL, 1.2546 mmol) was added to a slurry of silica (280 mg) in CH_2Cl_2 (2.1 mL). The mixture was stirred vigorously for 1 h, whereupon **4.151** (54 mg, 0.0697 mmol), and CH_2Cl_2 (1 mL) were added and the mixture was stirred for an additional 1 h. Et_3N (35 mg, 49 µL, 0.3485 mmol) was then added, and the mixture was filtered through a silica plug (~10 mL). The plug was eluted with EtOAc/hexanes (1:1, 1 x 100 mL) and the eluant was concentrated under reduced pressure (bath temp 30 °C) to provide 48 mg (95%) of **4.152** as an orange oil. The material was unstable, and so it was used directly in the next step withut further purification: ^{1}H-NMR (600 MHz) δ 8.04 (d, *J* = 8.3 Hz, 1 H), 8.03 (d, *J* = 8.5 Hz, 1 H), 7.66 (d, *J* = 9.0 Hz, 1 H), 7.65 (d, *J* = 9.0 Hz, 1 H), 7.63 (d, *J* = 8.2 Hz, 1 H), 7.61 (d, *J* = 8.2 Hz, 1 H), 7.41-7.37 (comp, 6 H), 6.91 (d, *J* = 8.7 Hz, 4 H), 6.72 (s, 1 H), 6.68 (s, 1 H), 6.46 (s, 1 H), 6.44 (s, 1 H), 5.90 (d, *J* = 0.7 Hz, 1 H), 5.87 (d, *J* = 0.7 Hz, 1 H), 5.40-5.36 (m, 4 H), 5.20 (d, *J* = 3.2 Hz, 4 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 3.81 (s, 6 H), 3.75 (s, 3 H), 3.73 (s, 3 H), 3.54 (s, 3 H), 3.52 (s, 3 H), 1.04 (s, 9 H), 1.03 (s, 9 H), 0.99 (s, 9 H), 0.97 (s, 9 H); ^{13}C-NMR (150 MHz) δ 182.9, 160.4, 160.3, 159.6, 151.6, 149.8, 149.7, 147.0, 146.9, 143.2, 142.1, 140.4, 138.6, 130.9, 129.3, 128.3, 126.1, 124.1, 118.1, 116.6, 116.4, 116.3, 114.0, 109.5, 103.6, 103.5, 99.6, 99.5, 90.0, 89.9, 85.5, 82.2, 82.1, 71.5, 64.7, 57.7, 56.3, 56.2, 56.0, 55.9, 55.3, 27.0, 26.9, 26.8, 21.5, 20.8; IR (neat) 3435 (O-H), 2935 (C-H), 2860 (C-H), 1765 (C=O), 1615, 1587, 1512, 1465, 1406, 1336, 1251, 1216, 1200, 1175, 1120, 1080, 1034, 941 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{41}H_{46}O_{10}Si^+$ (M+Na), 749.2752; found, 749.2739.

NMR assignments: ^{1}H-NMR (600 MHz) δ 8.04 (d, *J* = 8.3 Hz, 1 H, (C20-H), 8.03 (d, *J* = 8.5 Hz, 1 H, C20-H), 7.66 (d, *J* = 9.0 Hz, 1 H, C3-H), 7.65 (d, *J* = 9.0 Hz, 1 H, C3-H), 7.63 (d, *J* = 8.2 Hz, 1 H, C1-H), 7.61 (d, *J* = 8.2 Hz, 1 H, C1-H), 7.41-7.37 (comp, 6 H, C10-H, C4-H), 6.91 (d, *J* = 8.7 Hz, 4 H, C11-H), 6.72 (s, 1 H, C27-H), 6.68 (s, 1 H, C27-H), 6.46 (s, 1 H, C30-H), 6.44 (s, 1 H, C30-H), 5.90 (d, *J* = 0.7 Hz, 1 H, C24-H), 5.87 (d, *J* = 0.7 Hz, 1 H, C24-H), 5.40-5.36 (m, 4 H, C14-H), 5.20 (d, *J* = 3.2 Hz, 4 H, C8-H), 3.84 (s, 3 H, C31-H), 3.82 (s, 3 H, C31-H), 3.81 (s, 6 H, C32-H), 3.75 (s, 3 H, C13-H), 3.73 (s, 3 H, C13-H), 3.54 (s, 3 H, C15-H), 3.52 (s, 3 H, C15-H), 1.04 (s, 9 H, C35-H or C36-H), 1.03 (s, 9 H, C35-H or C36-H), 0.99 (s, 9 H, C35-H or C36-H), 0.97 (s, 9 H, C35-H or C36-H); ^{13}C-NMR (150 MHz) δ 182.9 (C17), 160.4 (C19), 160.3 (C19), 159.6 (C12), 151.6 (C6), 149.8 (C28), 149.7 (C28), 147.0 (C26), 146.9 (C26), 143.2 (C29), 142.1 (C5), 140.4 (C20), 138.6 (C16), 130.9 (C2), 129.3 (C10), 128.3 (C9), 126.1 (C7), 124.1 (C1), 118.1 (C4), 116.6 (C3), 116.4 (C30), 116.3 (C30), 114.0 (C11), 109.5 (C25), 103.6 (C27), 103.5 (C27), 99.6 (C14), 99.5 (C14), 90.0 (C22), 89.9 (C22), 85.5 (C23), 82.2 (C18), 82.1 (C18), 71.5 (C8), 64.7 (C24), 57.7 (C15), 56.3 (C31), 56.2 (C31), 56.0 (C32), 55.9 (C32), 55.3 (C13), 27.0 (C35 or C36), 26.9 (C35 or C36), 26.8 (C35 or C36), 21.5 (C33 or C34), 20.8 (C33 or C34).

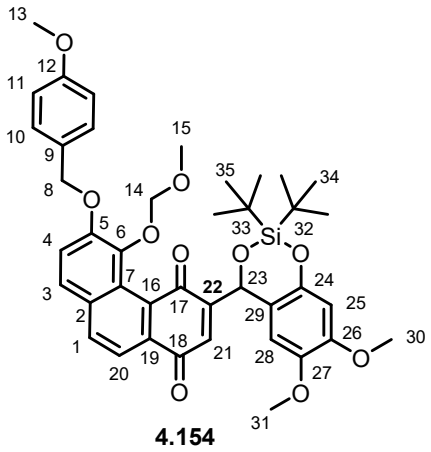


4.159

Methyl 2-(3-(2,2-di-*tert*-butyl-6,7-dimethoxy-4H-benzo[d][1,3,2]dioxasilin-4-yl)propioloyl)-7-((4-methoxybenzyl)oxy)-8-(methoxymethoxy)-1-naphthoate (**4.159**) (SB-VI-235). A solution of **4.152** (52 mg, 0.072 mmol) and $Cu(OAc)_2 \bullet H_2O$ (57 mg, 0.286 mmol) in MeOH (3.6 mL) was heated to 70 °C in a sealed tube for 45 min. The reaction mixture was cooled to room temperature and then diluted with Et_2O (5 mL), washed with de-ionized H_2O (2 x 5 mL) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure and the crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (7:20 → 1:2) to provide 33 mg (63%) of **4.159**: ^{1}H-NMR (600 MHz) δ 8.14 (d, *J* = 8.6 Hz, 1 H), 7.86 (d, *J* = 8.7 Hz, 1 H), 7.61 (d, *J* = 9.1 Hz, 1 H), 7.57 (d, *J* = 9.0 Hz, 1 H), 7.38 (d, *J* = 8.7 Hz, 2 H), 6.91 (d, *J* = 8.7 Hz, 2 H), 6.78 (s, 1 H), 6.52 (s, 1 H), 6.11 (s, 1 H), 5.15 (s, 4 H), 4.04 (s, 3 H), 3.87 (s, 3 H), 3.82 (s, 3 H), 3.82 (s, 3 H), 3.46 (s, 3 H), 1.08 (s, 9 H), 1.03 (s, 9 H); ^{13}C-NMR (150 MHz) δ 176.8, 170.0, 159.7, 150.1, 149.2, 147.1, 143.5, 140.1, 132.4, 131.1, 130.6, 129.6, 129.3, 128.4, 126.1, 125.2, 124.4, 120.0, 114.5, 114.0, 109.2, 103.8, 98.8, 93.6, 83.7, 71.8, 64.9, 57.9, 56.4, 56.0, 55.3, 52.7, 26.9, 26.8, 21.6, 20.9; IR (film) 2935 (C-H), 2860 (C-H), 2175 (C≡C), 1733 (C=O), 1656, 1613, 1513, 1444, 1405, 1367, 1333, 1250, 1213, 1152, 1014, 908 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{42}H_{48}O_{11}Si^+$ (M+Na), 779.2858; found, 779.2840.

NMR assignments: ^{1}H-NMR (600 MHz) δ 8.14 (d, *J* = 8.6 Hz, 1 H, C20-H), 7.86 (d, *J* = 8.7 Hz, 1 H, C1-H), 7.61 (d, *J* = 9.1 Hz, 1 H, C3-H), 7.57 (d, *J* = 9.0 Hz, 1 H, C4-H), 7.38 (d, *J* =

8.7 Hz, 2 H, C10-H), 6.91 (d, *J* = 8.7 Hz, 2 H, C11-H), 6.78 (s, 1 H, C30-H), 6.52 (s, 1 H, C27-H), 6.11 (s, 1 H, C24-H), 5.15 (s, 4 H, C8-H, C14-H), 4.04 (s, 3 H, C21-H), 3.87 (s, 3 H, C31-H), 3.82 (s, 3 H, C32-H), 3.82 (s, 3 H, C13-H), 3.46 (s, 3 H, C15-H), 1.08 (s, 9 H, C36-H or C35-H), 1.03 (s, 9 H, C36-H or C35-H); ^{13}C-NMR (150 MHz) δ 176.8 (C18), 170.0 (C17), 159.7 (C12), 150.1 (C28), 149.2 (C5), 147.1 (C26), 143.5 (C29), 140.1 (C6), 132.4 (C2), 131.1 (C16), 130.6 (C19), 129.6 (C10), 129.3 (C1), 128.4 (C9), 126.1 (C7), 125.2 (C20), 124.4 (C3), 120.0 (C4), 114.5 (C25), 114.0 (C11), 109.2 (C30), 103.8 (C27), 98.8 (C14), 93.6 (C22), 83.7 (C23), 71.8 (C8), 64.9 (C24), 57.9 (C15), 56.4 (C32), 56.0 (C31), 55.3 (C13), 52.7 (C21), 26.9 (C35 or C36), 26.8 (C35 or C36), 21.6 (C33 or C34), 20.9 (C33 or C34).



4.154

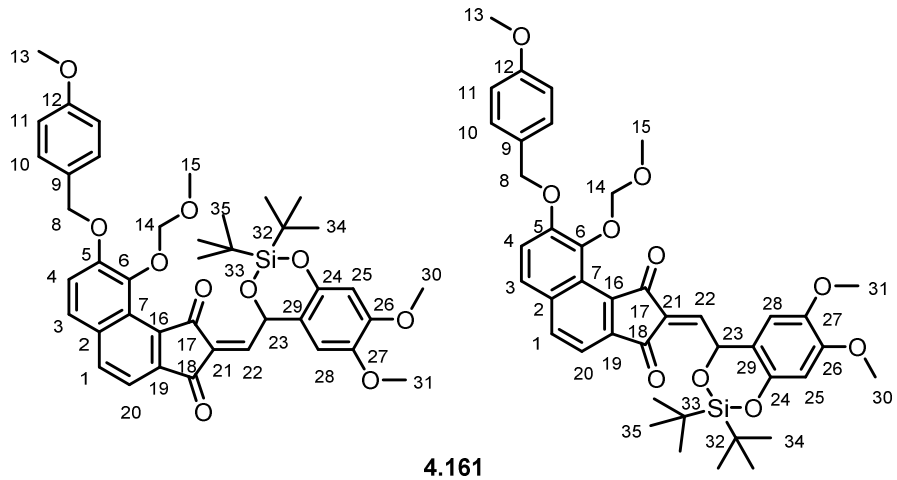
3-(2,2-Di-*tert*-butyl-6,7-dimethoxy-4H-benzo[d][1,3,2]dioxasilin-4-yl)-6-((4-methoxybenzyl)oxy)-5-(methoxymethoxy)phenanthrene-1,4-dione (**4.154**). (SB-VII-43).

Method A: A solution of crude **4.152** (35 mg, 0.0472 mmol) in *tert*-amyl alcohol (ppm $H_2O \leq 500$, 10 mL) was heated to 100 °C for 30 min. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure and the crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (3:20 → 1:2) to provide 10 mg (29%) of **4.154** as a red solid and 15 mg (43%) of **4.161**.

Method B: A solution of crude **4.152** (35 mg, 0.0472 mmol) in MTBE (14 mL) was heated to 60 °C for 1 h. The reaction mixture was cooled to room temperature, the solvent was

removed under reduced pressure and the crude oil was purified by flash chromatography eluting with a gradient of acetone/hexanes (1:10 → 3:10) to provide 61 mg (37%) of **4.154** as a red solid and 48 mg (29%) of **4.161**: ^{1}H-NMR (600 MHz) δ 8.00 (d, *J* = 8.5 Hz, 1 H), 7.97 (d, *J* = 8.5 Hz, 1 H), 7.63 (d, *J* = 8.9 Hz, 1 H), 7.48 (d, *J* = 8.9 Hz, 1 H), 7.40 (d, *J* = 8.7 Hz, 2 H), 6.91 (d, *J* = 8.7 Hz, 2 H), 6.73 (s, 1 H), 6.56 (s, 1 H), 6.47 (s, 1 H), 6.37 (s, 1 H), 5.29-5.16 (comp, 4 H), 3.87 (s, 3 H), 3.81 (s, 3 H), 3.66 (s, 3 H), 3.31 (s, 3 H), 1.09 (s, 9 H), 1.02 (s, 9 H); ^{13}C-NMR (150 MHz) δ 186.9, 185.4, 159.6, 154.8, 150.9, 149.8, 148.3, 143.3, 142.8, 133.6, 133.1, 133.0, 132.9, 132.0, 129.4, 128.5, 125.3, 125.0, 120.1, 119.6, 117.8, 114.0, 110.6, 103.7, 98.9, 71.9, 69.4, 57.6, 56.5, 56.0, 55.3, 27.1, 27.1, 21.9, 20.8; IR (film) 2934 (C-H), 2859 (C-H), 1662 (C=O), 1614, 1588, 1513, 1448, 1407, 1336, 1299, 1251, 1199, 1135, 1058, 919 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{41}H_{46}O_{10}Si^{+}$ (M+Na), 749.2752; found, 749.2747.

NMR assignments: ^{1}H-NMR (600 MHz) δ 8.00 (d, *J* = 8.5 Hz, 1 H, C1-H), 7.97 (d, *J* = 8.5 Hz, 1 H, C20-H), 7.63 (d, *J* = 8.9 Hz, 1 H, C3-H), 7.48 (d, *J* = 8.9 Hz, 1 H, C4-H), 7.40 (d, *J* = 8.7 Hz, 2 H, C10-H), 6.91 (d, *J* = 8.7 Hz, 2 H, C11-H), 6.73 (s, 1 H, C21-H), 6.56 (s, 1 H, C25-H), 6.47 (s, 1 H, C23-H), 6.37 (s, 1 H, C28-H), 5.29-5.16 (comp, 4 H, C8-H, C14-H), 3.87 (s, 3 H, C30-H), 3.81 (s, 3 H, C13-H), 3.66 (s, 3 H, C31-H), 3.31 (s, 3 H, C15-H), 1.09 (s, 9 H, C35-H or C35-H), 1.02 (s, 9 H, C35-H or C35-H); ^{13}C-NMR (150 MHz) δ 186.9 (C17), 185.4 (C18), 159.6 (C12), 154.8 (C22), 150.9 (C5), 149.8 (C26), 148.3 (C25), 143.3 (C27), 142.8 (C6), 133.6 (C1), 133.1 (C16), 133.0 (C19), 132.9 (C20), 132.0 (C21), 129.4 (C10), 128.5 (C9), 125.3 (C2), 125.0 (C3), 120.1 (C4), 119.6 (C7), 117.8 (C29), 114.0 (C11), 110.6 (C28), 103.7 (C25), 98.9 (C14), 71.9 (C8), 69.4 (C23), 57.6 (C15), 56.5 (C31), 56.0 (C30), 55.3 (C13), 27.1 (C34 or C35), 27.1 (C34 or C35), 21.9 (C32 or C33), 20.8 (C32 or C33).

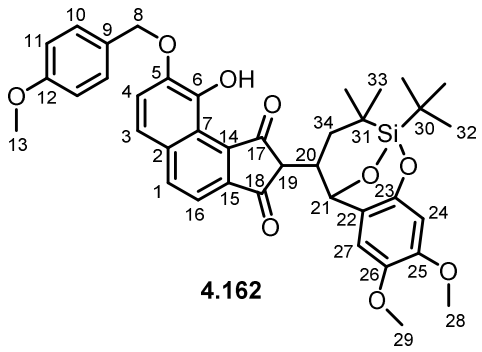


4.161

(Z)-2-((2,2-Di-*tert*-butyl-6,7-dimethoxy-4H-benzo[d][1,3,2]dioxasilin-4-yl)methylene)-8-((4-methoxybenzyl)oxy)-9-(methoxymethoxy)-1H-cyclopenta[a]naphthalene-1,3(2H)-dione and (E)-2-((2,2-Di-*tert*-butyl-6,7-dimethoxy-4H-benzo[d][1,3,2]dioxasilin-4-yl)methylene)-8-((4-methoxybenzyl)oxy)-9-(methoxymethoxy)-1H-cyclopenta[a]naphthalene-1,3(2H)-dione (**4.161**). (SB-VI-252). Isolated from the rearrangement of **4.152** to **4.154**. Purified *via* flash chromatography eluting with a gradient of EtOAc/hexanes (3:20 → 1:2): ^{1}H-NMR (600 MHz) δ (major isomer) 8.18 (d, *J* = 8.2 Hz, 1 H), 7.88 (d, *J* = 8.2 Hz, 1 H), 7.73 (d, *J* = 8.9 Hz, 1 H), 7.55 (d, *J* = 8.9 Hz, 1 H), 7.41 (d, *J* = 8.7 Hz, 2 H), 7.19 (d, *J* = 9.5 Hz, 1 H), 7.01 (d, *J* = 9.5 Hz, 1 H), 6.91 (d, *J* = 8.7 Hz, 2 H), 6.53 (s, 1 H), 6.52 (s, 1 H), 5.30-5.22 (comp, 4 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.67 (s, 3 H), 3.49 (s, 3 H), 1.11 (s, 9 H), 1.09 (s, 9 H); (minor isomer) 8.17 (d, *J* = 8.2 Hz, 1 H), 7.86 (d, *J* = 8.2 Hz, 1 H), 7.74 (d, *J* = 8.9 Hz, 1 H), 7.54 (d, *J* = 8.9 Hz, 1 H), 7.42 (d, *J* = 8.7 Hz, 2 H), 7.14 (d, *J* = 9.5 Hz, 1 H), 7.05 (d, *J* = 9.5 Hz, 1 H), 6.92 (d, *J* = 8.7 Hz, 2 H), 6.58 (s, 1 H), 6.53 (s, 1 H), 5.30-5.22 (comp, 4 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.64 (s, 3 H), 3.48 (s, 3 H), 1.11 (s, 9 H), 1.09 (s, 9 H); ^{13}C-NMR (150 MHz) δ (major isomer) 190.1, 186.6, 159.6, 152.5, 149.9, 147.8, 146.5, 145.3, 143.4, 142.9, 137.9, 133.8, 130.0, 129.4, 128.3, 126.2, 125.0, 119.7, 116.4, 116.1, 114.0, 109.8, 104.0, 99.9, 71.7, 68.5, 57.9, 56.5, 56.0, 55.3, 27.2, 27.0, 21.9, 20.3; (minor isomer) 189.2, 188.0, 159.6, 152.3, 149.9, 147.8, 145.8, 144.0, 143.4, 143.1, 137.9, 137.8, 130.1, 129.4, 129.3, 126.2, 124.7, 119.8, 116.4, 115.8, 114.0, 110.1, 103.9, 99.8, 71.7, 68.3, 57.9, 56.5, 56.0, 55.3, 27.2,

27.0, 21.9, 20.3; IR (film) 2934 (C-H), 2860 (C-H), 1731 (C=O), 1694 (C=O), 1613, 1586, 1513, 1454, 1405, 1250, 1219, 1200, 1155, 1072, 928 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{41}H_{46}O_{10}Si^{+}$ (M+Na), 749.2752; found, 749.2740.

NMR assignments: ^{1}H-NMR (600 MHz) δ (major isomer) 8.18 (d, *J* = 8.2 Hz, 1 H, C1-H), 7.88 (d, *J* = 8.2 Hz, 1 H, C20-H), 7.73 (d, *J* = 8.9 Hz, 1 H, C4-H), 7.55 (d, *J* = 8.9 Hz, 1 H, C3-H), 7.41 (d, *J* = 8.7 Hz, 2 H, C10-H), 7.19 (d, *J* = 9.5 Hz, 1 H, C22-H), 7.01 (d, *J* = 9.5 Hz, 1 H, C23-H), 6.91 (d, *J* = 8.7 Hz, 2 H, C11-H), 6.53 (s, 1 H, C25-H), 6.52 (s, 1 H, C28-H), 5.30-5.22 (comp, 4 H, C8-H, C14-H), 3.85 (s, 3 H, C30-H), 3.82 (s, 3 H, C13-H), 3.67 (s, 3 H, C31-H), 3.49 (s, 3 H, C15-H), 1.11 (s, 9 H, C34-H or C25-H), 1.09 (s, 9 H, C34-H or C35-H); (minor isomer) 8.17 (d, *J* = 8.2 Hz, 1 H, C1-H), 7.86 (d, *J* = 8.2 Hz, 1 H, C20-H), 7.74 (d, *J* = 8.9 Hz, 1 H, C4-H), 7.54 (d, *J* = 8.9 Hz, 1 H, C3-H), 7.42 (d, *J* = 8.7 Hz, 2 H, C10-H), 7.14 (d, *J* = 9.5 Hz, 1 H, C22-H), 7.05 (d, *J* = 9.5 Hz, 1 H, C23-H), 6.92 (d, *J* = 8.7 Hz, 2 H, C11-H), 6.58 (s, 1 H, C25-H), 6.53 (s, 1 H, C28-H), 5.30-5.22 (comp, 4 H, C8-H, C14-H), 3.85 (s, 3 H, C30-H), 3.82 (s, 3 H, C13-H), 3.64 (s, 3 H, C31-H), 3.48 (s, 3 H, C15-H), 1.11 (s, 9 H, C34-H or C25-H), 1.09 (s, 9 H, C34-H or C25-H); ^{13}C-NMR (150 MHz) δ (major isomer) 190.1 (C18), 186.6 (C17), 159.6 (C12), 152.5 (C5), 149.9 (C6), 147.8 (C21), 146.5 (C22), 145.3 (C24), 143.4 (C26), 142.9 (C27), 137.9 (C1), 133.8 (C2), 130.0 (C29), 129.4 (C10), 128.3 (C19), 126.2 (C4), 125.0 (C16), 119.7 (C3), 116.4 (C20), 116.1 (C7), 114.0 (C11), 109.8 (C28), 104.0 (C25), 99.9 (C14), 71.7 (C8), 68.5 (C23), 57.9 (C15), 56.5 (C31), 56.0 (C13), 55.3 (C30), 27.2 (C32 or C33), 27.0 (C32 or C33), 21.9 (C34 or C35), 20.3 (C34 or C35); (minor isomer) 189.2 (C18), 188.0 (C17), 159.6 (C12), 152.3 (C5), 149.9 (C6), 147.8 (C21), 145.8 (C22), 144.0 (C24), 143.4 (C26), 143.1 (C27), 137.9 (C1), 137.8 (C2), 130.1 (C29), 129.4 (C10), 129.3 (C19), 126.2 (C4), 124.7 (C16), 119.8 (C3), 116.4 (C20), 115.8 (C7), 114.0 (C11), 110.1 (C25), 103.9 (C28), 99.8 (C14), 71.7 (C8), 68.3 (C23), 57.9 (C15), 56.5 (C31), 56.0 (C13), 55.3 (C30), 27.2 (C32 or C33), 27.0 (C32 or C33), 21.9 (C34 or C35), 20.3 (C34 or C35).

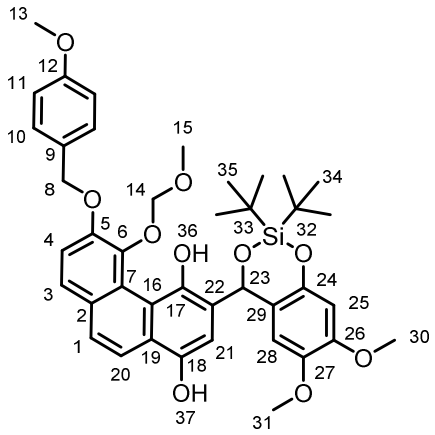


4.162

2-(2-(*Tert*-butyl)-8,9-dimethoxy-3,3-dimethyl-3,4,5,6-tetrahydro-2H-2,6-epoxybenzo[g][1,2]oxasilocin-5-yl)-9-hydroxy-8-((4-methoxybenzyl)oxy)-1H-cyclopenta[a]naphthalene-1,3(2H)-dione (**4.162**). (SB-VII-276B3). Isolated as a mixture (1:1) of diastereomers from the rearrangement of **4.152** to **4.154**. Purified *via* flash chromatography eluting with a gradient of EtOAc/hexanes (3:20 → 1:2): ^{1}H-NMR (600 MHz) δ 12.11 (s, 1 H), 8.163 (d, *J* = 9.0 Hz, 0.5 H), 8.161 (d, *J* = 8.4 Hz, 0.5 H), 7.73 (d, *J* = 8.4 Hz, 0.5 H), 7.69 (d, *J* = 8.4 Hz, 0.5 H), 7.49 (d, *J* = 8.4 Hz, 0.5 H), 7.48 (d, *J* = 8.4 Hz, 0.5 H), 7.44-7.40 (comp, 3 H), 6.894 (d, *J* = 8.4 Hz, 1 H), 6.890 (d, *J* = 9.0 Hz, 1 H), 6.52 (s, 0.5 H), 6.51 (s, 0.5 H), 6.37 (s, 0.5 H), 6.35 (s, 0.5 H), 5.70 (d, *J* = 3.6 Hz, 0.5 H), 5.67 (d, *J* = 3.6 Hz, 0.5 H), 5.274 (s, 1 H), 5.269 (s, 1 H), 3.840 (s, 1.5 H), 3.837 (s, 1.5 H), 3.79 (s, 3 H), 3.75 (s, 1.5 H), 3.72 (s, 1.5 H), 3.63 (d, *J* = 8.4 Hz, 0.5 H), 3.61 (d, *J* = 5.6 Hz, 0.5 H), 2.34 (comp, 1 H), 1.94 (comp, 1 H), 1.35 (comp, 1 H), 1.32 (s, 3 H), 1.11 (s, 9 H), 1.07 (s, 3 H); ^{13}C-NMR (150 MHz) δ 206.2, 206.0, 198.5, 198.2, 159.50, 159.48, 149.5, 147.66, 147.65, 146.59, 146.54, 145.2, 145.1, 144.9, 144.6, 142.74, 142.72, 140.2, 140.1, 139.6, 139.0, 133.4, 133.3, 129.2, 128.9, 128.8, 121.3, 120.75, 120.71, 120.25, 120.20, 119.9, 119.8, 115.7, 115.6, 114.04, 114.00, 109.63, 109.62, 103.41, 103.39, 74.43, 74.39, 71.7, 71.6, 56.7, 56.6, 55.9, 55.3, 52.7, 52.4, 44.9, 44.8, 38.4, 38.3, 26.2, 26.1, 26.0, 25.90, 23.0, 18.95, 18.94; IR (film) 2936 (C-H), 2861 (C-H), 1727 (C=O), 1671 (C=O), 1615, 1588, 1514, 1466, 1449, 1413, 1271, 1251, 1222, 1198, 1174, 1125, 1033, 1014, 912 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{39}H_{42}O_9Si$+ (M+Na), 705.2490; found, 705.2488.

NMR assignments: ^{1}H-NMR (600 MHz) δ 12.11 (s, 1 H, O-H), 8.163 (d, *J* = 9.0 Hz, 0.5 H, C1-H), 8.161 (d, *J* = 8.4 Hz, 0.5 H, C1-H), 7.73 (d, *J* = 8.4 Hz, 0.5 H, C16-H), 7.69 (d, *J* = 8.4

Hz, 0.5 H, C16-H), 7.49 (d, *J* = 8.4 Hz, 0.5 H, C3-H), 7.48 (d, *J* = 8.4 Hz, 0.5 H, C3-H), 7.44-7.40 (comp, 3 H, C4-H, C10-H), 6.894 (d, *J* = 8.4 Hz, 1 H, C11-H), 6.890 (d, *J* = 9.0 Hz, 1 H, C11-H), 6.52 (s, 0.5 H, C27-H), 6.51 (s, 0.5 H, C27-H), 6.37 (s, 0.5 H, C24-H), 6.35 (s, 0.5 H, C24-H), 5.70 (d, *J* = 3.6 Hz, 0.5 H, C21-H), 5.67 (d, *J* = 3.6 Hz, 0.5 H, C21-H), 5.274 (s, 1 H, C8-H), 5.269 (s, 1 H, C8-H), 3.840 (s, 1.5 H, C28-H), 3.837 (s, 1.5 H, C28-H), 3.79 (s, 3 H, C13-H), 3.75 (s, 1.5 H, C29-H), 3.72 (s, 1.5 H, C29-H), 3.63 (d, *J* = 8.4 Hz, 0.5 H, C19-H), 3.61 (d, *J* = 5.6 Hz, 0.5 H, C19-H), 2.34 (comp, 1 H, C20-H), 1.94 (comp, 1 H, C34-H), 1.35 (comp, 1 H, C34-H), 1.32 (s, 3 H, C33-H), 1.11 (s, 9 H, C18-H), 1.07 (s, 3 H, C33-H); ^{13}C-NMR (150 MHz) δ 206.2 (C17), 206.0 (C17), 198.5 (C18), 198.2 (C18), 159.50 (C12), 159.48 (C12), 149.5 (C25), 147.66 (C23), 147.65 (C23), 146.59 (C5), 146.54 (C5), 145.2 (C6), 145.1 (C6), 144.9 (C2), 144.6 (C2), 142.74 (C26), 142.72 (C26), 140.2 (C1), 140.1 (C1), 139.6 (C14), 139.0 (C14), 133.4 (C15), 133.3 (C15), 129.2 (C10), 128.9 (C9), 128.8 (C9), 121.3 (C3), 120.75 (C3), 120.71 (C4), 120.25 (C4), 120.20 (C4), 119.9 (C22), 119.8 (C22), 115.7 (C16), 115.6 (C16), 114.04 (C16), 114.00 (C16), 109.63 (C11), 109.62 (C11), 103.41 (C24), 103.39 (C24), 74.43 (C27), 74.39 (C27), 71.7 (C8), 71.6 (C8), 56.7 (C29), 56.6 (C29), 55.9 (C28), 55.3 (C13), 52.7 (C19), 52.4 (C19), 44.9 (C20), 44.8 (C20), 38.4 (C34), 38.3 (C34), 26.2 (C33), 26.1 (C33), 26.0 (C33), 25.90 (C32, C33), 23.0 (C31), 18.95 (C30), 18.94 (C30).

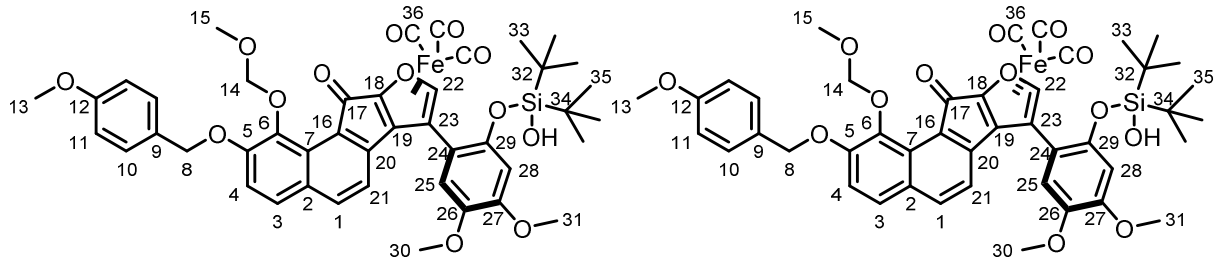


4.160

3-(2,2-Di-*tert*-butyl-6,7-dimethoxy-4H-benzo[d][1,3,2]dioxasilin-4-yl)-6-((4-methoxybenzyl)oxy)-5-(methoxymethoxy)phenanthrene-1,4-diol (**4.160**). (SB-VII-276B2). Isolated from the rearrangement of **4.152** to **4.154**. Purified *via* flash chromatography eluting with a gradient of EtOAc/hexanes (3:20 → 1:2): ^{1}H-NMR (500 MHz) δ 9.79 (s, 1 H), 8.03 (d, *J* = 9.0 Hz, 1 H), 7.68 (d, *J* = 9.0 Hz, 1 H), 7.57 (d, *J* = 9.5 Hz, 1 H), 7.41 (comp, 3 H), 7.16 (s, 1 H), 6.94-6.92 (comp, 3 H), 6.58 (s, 1 H), 5.98 (s, 1 H), 5.23 (d, *J* = 11.5 Hz, 1 H), 5.18 (d, *J* = 11.5 Hz, 1 H), 5.08 (d, *J* = 6.0 Hz, 1 H), 4.98 (d, *J* = 6.0 Hz, 1 H), 3.86 (s, 3 H), 3.83 (s, 3 H), 3.45 (s, 3 H), 3.32 (s, 3 H), 1.18 (s, 9 H), 1.07 (s, 9 H); ^{13}C-NMR (125 MHz) δ 159.6, 150.3, 149.3, 148.8, 145.7, 144.6, 142.7, 140.4, 129.3, 128.6, 128.5, 125.9, 125.7, 125.5, 124.5, 124.0, 121.5, 119.5, 119.0, 115.1, 114.0, 112.6, 111.6, 103.4, 100.9, 71.8, 69.8, 58.4, 56.6, 55.9, 55.3, 27.4, 27.2, 21.8, 21.3; IR (film) 3443 (O-H), 2936 (C-H), 3209 (O-H), 2935 (C-H), 2859 (C-H), 1703, 1662, 1614, 1513, 1468, 1450, 1405, 1364, 1336, 1251, 1200, 1174, 1123, 1039, 1013, 907 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{41}H_{46}O_{10}Si^{+}$ (M+Na), 749.2752; found, 749.2755.

NMR assignments: ^{1}H-NMR (500 MHz) δ 9.79 (s, 1 H, O36-H), 8.03 (d, *J* = 9.0 Hz, 1 H, C20-H), 7.68 (d, *J* = 9.0 Hz, 1 H, C3-H), 7.57 (d, *J* = 9.5 Hz, 1 H, C1-H), 7.41 (comp, 3 H, C4-H, C10-H), 7.16 (s, 1 H, C21-H), 6.94-6.92 (comp, 3 H, C11-H, C23-H), 6.58 (s, 1 H, C28-H), 5.98 (s, 1 H, C25-H), 5.23 (d, *J* = 11.5 Hz, 1 H, C8-H), 5.18 (d, *J* = 11.5 Hz, 1 H, C8-H), 5.08 (d, *J* = 6.0 Hz, 1 H, C14-H), 4.98 (d, *J* = 6.0 Hz, 1 H, C14-H), 3.86 (s, 3 H, C30-H), 3.83 (s, 3 H, C13-H), 3.45 (s, 3 H, C31-H), 3.32 (s, 3 H, C15-H), 1.18 (s, 9 H, C34-H or C35-H), 1.07 (s,

9 H, C34-H or C35-H); ^{13}C-NMR (125 MHz) δ 159.6 (C12), 150.3 (C5), 149.3 (C26), 148.8 (C24), 145.7 (C17), 144.6 (C18), 142.7 (C27), 140.4 (C6), 129.3 (C10), 128.6 (C9), 128.5 (C22), 125.9 (C1), 125.7 (C3), 125.5 (C7), 124.5 (C2), 124.0 (C19), 121.5 (C29), 119.5 (C20), 119.0 (C16), 115.1 (C4), 114.0 (C11), 112.6 (C21), 111.6 (C25), 103.4 (C28), 100.9 (C14), 71.8 (C8), 69.8 (C23), 58.4 (C15), 56.6 (C31), 55.9 (C30), 55.3 (C13), 27.4 (C34 or C35), 27.2 (C34 or C35), 21.8 (C32 or C33), 21.3 (C32 or C33).



4.199/4.200

(**4.199/4.200**). (SB-VII-278A and SB-VII-278B). 85% H_3PO_4 (2 μL, 3 mg, 0.0325 mmol) was added to a slurry of silica (129 mg) in CH_2Cl_2 (1 mL) followed by H_2O (13 μL) and the slurry was stirred vigorously for 1 h. **4.151** (25 mg, 0.0325 mmol) was added, and the reaction mixture was stirred for 1 h whereupon Et_3N (16 mg, 22 μL, 0.161 mmol) was added and the slurry was filtered through a silica plug. The plug was eluted with EtOAc/hexanes (1:1, 1 x 10 mL) and the eluent was concentrated under reduced pressure (bath temp 30 °C) to provide the crude **4.152** as a orange oil.

The crude **4.152** was dissolved in C_6D_6 (~ 1 mL) followed by $Fe_2(CO)_9$ (9 mg, 0.244 mmol) and the reaction mixture was sonicated for 2 h. The reaction was monitored by ^{1}H-NMR and the fraction was determined to be complete after 24 h at room temperature. The mixture was concentrated under reduced pressure (bath temp 30 °C) and the crude oil was purified by flash chromatography eluting with a gradient of acetone/hexanes (1:10 → 1:2) to provide a mixture of **4.199** and **4.200** (~100%).

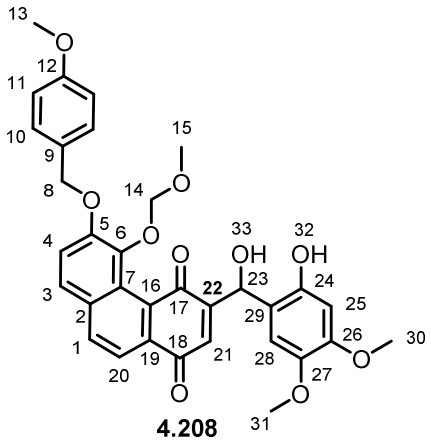
Compound A: ^{1}H-NMR (500 MHz) δ 8.74 (s, 1 H), 8.64 (s, 1 H), 7.45 (d, *J* = 8.5 Hz, 2 H), 7.36 (d, *J* = 8.5 Hz, 1 H), 7.31 (d, *J* = 9.0 Hz, 2 H), 7.25 (d, *J* = 9.0 Hz, 1 H), 7.21 (d, *J* = 9.5 Hz, 1 H), 6.96 (d, *J* = 8.5 Hz, 2 H), 6.61 (s, 1 H), 5.72 (d, *J* = 5.0 Hz, 1 H), 5.49 (d, *J* = 5.0 Hz, 1 H), 5.19 (s, 2 H), 3.99 (s, 3 H), 3.96 (s, 3 H), 3.86 (s, 3 H), 3.54 (s, 3 H), 1.26 (s, 9 H), 1.06 (s, 9 H); ^{13}C-NMR (125 MHz) δ 208.4, 166.5, 159.7, 157.4, 155.2, 154.3, 151.0, 143.9, 142.8, 142.1, 129.4, 129.3, 128.9, 128.7, 128.5, 128.2, 124.8, 120.0, 118.8, 117.2, 116.2, 114.1, 112.3, 110.4, 105.3, 104.4, 98.1, 71.4, 58.2, 56.2, 56.1, 53.3, 27.6, 27.5, 21.01, 20.62; IR (film) 3396 (O-H), 2935 (C-H), 2859 (C-H), 2062 (C=O), 2006 (C=O), 1614, 1559, 1511, 1467, 1406, 1386, 1334, 1284, 1251, 1217, 1175, 1087, 1012, 917 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{45}H_{46}FeO_{14}Si^{+}$ (M+Na), 915.1945; found, 915.1950.

NMR assignments: ^{1}H-NMR (500 MHz) δ 8.74 (s, 1 H, C25-H), 8.64 (s, 1 H, C22-H), 7.45 (d, *J* = 8.5 Hz, 2 H, C10-H), 7.36 (d, *J* = 8.5 Hz, 1 H, C3-H), 7.31 (d, *J* = 9.0 Hz, 2 H, C4-H), 7.25 (d, *J* = 9.0 Hz, 1 H, C21-H), 7.21 (d, *J* = 9.5 Hz, 1 H, C1-H), 6.96 (d, *J* = 8.5 Hz, 2 H, C11-H), 6.61 (s, 1 H, C28-H), 5.72 (d, *J* = 5.0 Hz, 1 H, C14-H), 5.49 (d, *J* = 5.0 Hz, 1 H, C14-H), 5.19 (s, 2 H, C8-H), 3.99 (s, 3 H, C30-H), 3.96 (s, 3 H, C31-H), 3.86 (s, 3 H, C13-H), 3.54 (s, 3 H, C15-H), 1.26 (s, 9 H, C33-H or C35-H), 1.06 (s, 9 H, C33-H or C35-H); ^{13}C-NMR (125 MHz) δ 208.4 (C36), 166.5 (C17), 159.7 (C12), 157.4 (C18), 155.2 (C27), 154.3 (C29), 151.0 (C5), 143.9 (C26), 142.8 (C6), 142.1 (C22), 129.4 (C10), 129.3 (C16), 128.9 (C20), 128.7 (C2), 128.5 (C21), 128.2 (C9), 124.8 (C3), 120.0 (C1), 118.8 (C19), 117.2 (C24), 116.2 (C4), 114.1 (C11), 112.3 (C25), 110.4 (C23), 105.3 (C7), 104.4 (C28), 98.1 (C14), 71.4 (C8), 58.2 (C15), 56.2 (C30), 56.1 (C31), 53.3 (C13), 27.6 (C33 or C35), 27.5 (C33 or C35), 21.01 (C32 or C34), 20.62 (C32 or C34).

Compound B: ^{1}H-NMR (500 MHz) δ 8.62 (s, 1 H), 8.56 (s, 1 H), 7.44 (d, *J* = 9.0 Hz, 2 H), 7.36 (d, *J* = 8.5 Hz, 1 H), 7.32 (d, *J* = 8.5 Hz, 1 H), 7.23 (app. d, *J* = 2.0 Hz, 2 H), 6.95 (d, *J* = 8.5 Hz, 2 H), 6.88 (s, 1 H), 5.68 (d, *J* = 5.0 Hz, 1 H), 5.48 (d, *J* = 5.0 Hz, 1 H), 5.19 (s, 2 H), 4.14 (s, 3 H), 3.93 (s, 3 H), 3.84 (s, 3 H), 3.56 (s, 3 H), 1.13 (s, 9 H), 1.12 (s, 9 H); ^{13}C-NMR (125 MHz) δ 208.3, 171.0, 159.6, 159.3, 154.5, 154.3, 151.0, 145.2, 143.3, 138.9, 129.6, 129.4,

129.3, 129.1, 128.9, 128.1, 124.8, 119.3, 116.9, 116.0, 114.0, 113.9, 113.4, 110.0, 103.0, 98.4, 71.4, 58.2, 52.4, 56.0, 55.2, 27.4, 27.3, 20.84, 20.82; IR (film) 3492 (O-H), 2936 (C-H), 2860 (C-H), 2061 (C=O), 2005 (C=O), 1784, 1644, 1597, 1561, 1512, 1468, 1406, 1373, 1349, 1312, 1276, 1251, 1217, 1175, 1156, 1099, 1036, 1004, 964 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{45}H_{46}FeO_{14}Si^{+}$ (M+Na), 915.1945; found, 915.1931.

NMR assignments: ^{1}H-NMR (500 MHz) δ 8.62 (s, 1 H, C25-H), 8.56 (s, 1 H, C22-H), 7.44 (d, *J* = 9.0 Hz, 2 H, C10-H), 7.36 (d, *J* = 8.5 Hz, 1 H, C3-H), 7.32 (d, *J* = 8.5 Hz, 1 H, C4-H), 7.23 (app. d, *J* = 2.0 Hz, 2 H, C21-H, C1-H), 6.95 (d, *J* = 8.5 Hz, 2 H, C11-H), 6.88 (s, 1 H, C28-H), 5.68 (d, *J* = 5.0 Hz, 1 H, C14-H), 5.48 (d, *J* = 5.0 Hz, 1 H, C14-H), 5.19 (s, 2 H, C8-H), 4.14 (s, 3 H, C30-H), 3.93 (s, 3 H, C31-H), 3.84 (s, 3 H, C13-H), 3.56 (s, 3 H, C15-H), 1.13 (s, 9 H, C33-H or C35-H), 1.12 (s, 9 H, C33-H or C35-H); ^{13}C-NMR (125 MHz) δ 208.3 (C36), 171.0 (C17), 159.6 (C12), 159.3 (C18), 154.5 (C27), 154.3 (C29), 151.1 (C5), 145.2 (C26), 143.3 (C6), 138.9 , 129.6 (C16), 129.4 (C10, C1), 129.3 (C20), 129.1 (C21), 128.9 (C2), 128.1 (C), 124.8 (C3), 119.3 (C4), 116.9 (C24), 116.0 (C19), 114.0 (C11), 113.9 (C7), 113.4 (C25), 110.0 (C23), 103.0 (C28), 98.4 (C14), 71.4 (C8), 58.2 (C15), 52.4 (C30), 56.0 (C31), 55.2 C13), 27.4 (C33 or C35), 27.3 (C33 or C35), 20.84 (C32 or C34), 20.82 (C32 or C34).

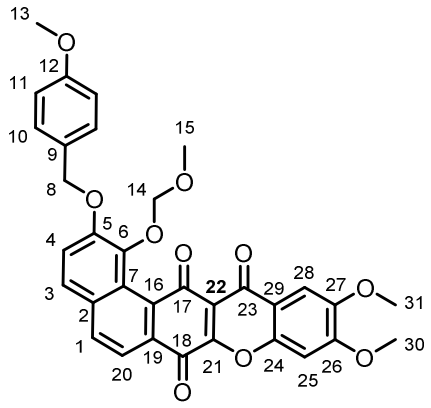


4.208

3-(Hydroxy(2-hydroxy-4,5-dimethoxyphenyl)methyl)-6-((4-methoxybenzyl)oxy)-5-(methoxymethoxy)phenanthrene-1,4-dione (**4.208**). (SB-VII-30B). One drop of HF•Pyridine was added to a solution of **4.154** (41 mg, 0.0565 mmol) and pyridine (49 mg, 50 µL, 0.621 mmol) in THF (2 mL), and the reaction was stirred for 30 min. The mixture was diluted with EtOAc (5 mL), and washed with NH_4Cl (1 x 2 mL) and de-ionized H_2O (1 x 2 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure and the crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:2 → 3:4) to provide 24 mg (72%) of **4.208** as a red solid: ^{1}H-NMR (600 MHz) δ 7.97 (d, *J* = 8.5 Hz, 1 H), 7.90 (d, *J* = 8.5 Hz, 1 H), 7.68 (bs, 1 H), 7.63 (d, *J* = 8.9 Hz, 1 H), 7.47 (d, *J* = 8.9 Hz, 1 H), 7.39 (d, *J* = 8.7 Hz, 2 H), 6.93 (d, *J* = 8.7 Hz, 2 H), 6.67 (s, 1 H), 6.55 (s, 1 H), 6.47 (d, *J* = 1.6 Hz, 1 H), 6.17 (bs, 1 H), 5.19 (s, 2 H), 5.13 (d, *J* = 4.8 Hz, 1 H), 5.19 (d, *J* = 4.8 Hz, 1 H), 4.40 (bs, 1 H), 3.86 (s, 3 H), 3.82 (s, 3 H), 3.82 (s, 3 H), 3.19 (s, 3 H); ^{13}C-NMR (150 MHz) δ 188.8, 185.0, 159.7, 152.7, 150.9, 150.3, 150.0, 143.0, 141.4, 133.8, 133.2, 132.9, 132.7, 130.0, 129.4, 128.3, 125.3, 125.1, 119.6, 114.1, 114.0, 113.6, 111.2, 102.4, 98.2, 71.7, 70.3, 57.6, 56.6, 56.0, 55.3; IR (film) 3431 (O-H), 2933 (C-H), 2837 (C-H), 1659 (C=O), 1614, 1588, 1514, 1449, 1335, 1302, 1250, 1197, 1137, 1112, 1055, 1035, 916 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{33}H_{39}O_{10}^+$ (M+Na), 609.1731; found, 609.1722.

NMR assignments: ^{1}H-NMR (600 MHz) δ 7.97 (d, *J* = 8.5 Hz, 1 H, C1-H), 7.90 (d, *J* = 8.5 Hz, 1 H, C20-H), 7.68 (bs, 1 H, O32-H), 7.63 (d, *J* = 8.9 Hz, 1 H, C3-H), 7.47 (d, *J* = 8.9 Hz,

1 H, C4-H), 7.39 (d, *J* = 8.7 Hz, 2 H, C10-H), 6.93 (d, *J* = 8.7 Hz, 2 H, C11-H), 6.67 (s, 1 H, C21-H), 6.55 (s, 1 H, C25-H), 6.47 (d, *J* = 1.6 Hz, 1 H, C23-H), 6.17 (bs, 1 H, C28-H), 5.19 (s, 2 H, C8-H), 5.13 (d, *J* = 4.8 Hz, 1 H, C14-H), 5.19 (d, *J* = 4.8 Hz, 1 H, C14-H), 4.40 (bs, 1 H, O33-H), 3.86 (s, 3 H, C30-H), 3.82 (s, 3 H, C13-H), 3.82 (s, 3 H, C31-H), 3.19 (s, 3 H, C15-H); ^{13}C-NMR (150 MHz) δ 188.8 (C17), 185.0 (C18), 159.7 (C12), 152.7 (C22), 150.9 (C5), 150.3 (C24), 150.0 (C26), 143.0 (C6), 141.4 (C27), 133.8 (C1), 133.2 (C16), 132.9 (C19), 132.7 (C20), 130.0 (C21), 129.4 (C10), 128.3 (C9), 125.3 (C2), 125.1 (C3), 119.6 (C7), 114.1 (C11), 114.0 (C4), 113.6 (C29), 111.2 (C28), 102.4 (C25), 98.2 (C14), 71.7 (C8), 70.3 (C23), 57.6 (C15), 56.6 (C31), 56.0 (C30), 55.3 (C13).

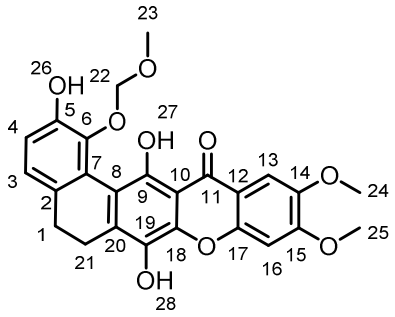


4.210

10,11-Dimethoxy-2-((4-methoxybenzyl)oxy)-1-(methoxymethoxy)-13H-naphtho[1,2-b]xanthene-7,13,14-trione (**4.210**). (SB-VII-79). Activated manganese dioxide (MnO_2) (445 mg, 5.11 mmol) was added to a solution of **4.208** (20 mg, 0.341 mmol) in CH_2Cl_2 (2 mL) and pyridine (0.3 mL) at 0 °C. The reaction mixture was stirred for 48 h at 0 °C and then filtered through a silica plug, eluting with a mixture (1:1) of acetone/hexanes (20 mL). The combined filtrates were concentrated under reduced pressure, and purified by flash chromatography eluting

with a gradient of acetone/hexanes (7:20 → 1:2) to provide 7 mg (35%) of **4.210** as an orange solid and 6 mg (~30%) of a mixture of partially oxidized compounds. The partially oxidized compounds can be resubjected to the reaction mixture to provide another 3 mg (15%) of **4.210** and 3 mg (~15%) of the partially oxidized compounds: ^{1}H-NMR (500 MHz) δ 8.04 (d, *J* = 8.5 Hz, 1 H), 7.99 (d, *J* = 8.5 Hz, 1 H), 7.65 (s, 1 H), 7.61 (d, *J* = 9.1 Hz, 1 H), 7.50 (d, *J* = 9.0 Hz, 1 H), 7.42 (d, *J* = 8.8 Hz, 2 H), 7.15 (s, 1 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 5.26 (s, 2 H), 5.23 (s, 2 H), 4.03 (s, 3 H), 4.01 (s, 3 H), 3.82 (s, 3 H), 3.44 (s, 3 H); ^{13}C-NMR (125 MHz) δ 182.1, 179.1, 172.6, 159.6, 155.6, 153.8, 151.2, 150.6, 148.8, 143.7, 135.2, 133.7, 133.3, 130.4, 129.4, 128.5, 125.2, 124.7, 121.6, 121.0, 119.8, 119.1, 114.0, 105.1, 100.6, 99.2, 77.1, 57.8, 56.8, 56.5, 55.3; IR (film) 2928 (C-H), 1688 (C=O), 1641, 1620, 1600, 1512, 1467, 1450, 1428, 1402, 1334, 1272, 1249, 1175, 1126, 1081, 1048, 992 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{33}H_{26}O_{10}^{+}$ (M+Na), 605.1418; found, 605.1410.

NMR assignments: ^{1}H-NMR (500 MHz) δ 8.04 (d, *J* = 8.5 Hz, 1 H, C20-H), 7.99 (d, *J* = 8.5 Hz, 1 H, C1-H), 7.65 (s, 1 H, C28-H), 7.61 (d, *J* = 9.1 Hz, 1 H, C3-H), 7.50 (d, *J* = 9.0 Hz, 1 H, C4-H), 7.42 (d, *J* = 8.8 Hz, 2 H, C10-H), 7.15 (s, 1 H, C25-H), 6.92 (d, *J* = 8.8 Hz, 2 H, C11-H), 5.26 (s, 2 H, C14-H), 5.23 (s, 2 H, C8-H), 4.03 (s, 3 H, C30-H), 4.01 (s, 3 H, C31-H), 3.82 (s, 3 H, C13-H), 3.44 (s, 3 H, C15-H); ^{13}C-NMR (125 MHz) δ 182.1 (C17), 179.1 (C18), 172.6 (C23), 159.6 (C12), 155.6 (C26), 153.8 (C21), 151.2 (C24), 150.6 (C5), 148.8 (C27), 143.7 (C6), 135.2 (C16), 133.7 (C2), 133.3 (C1), 130.4 (C19), 129.4 (C10), 128.5 (C9), 125.2 (C7), 124.7 (C3), 121.6 (C4), 121.0 (C22), 119.8 (C29), 119.1 (C20), 114.0 (C11), 105.1 (C28), 100.6 (C25), 99.2 (C14), 77.1 (C8), 57.8 (C15), 56.8 (C30), 56.5 (C31), 55.3 (C13).

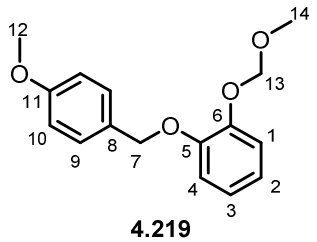


4.237

2,7,14-Trihydroxy-10,11-dimethoxy-1-(methoxymethoxy)-5,6-dihydro-13H-naphtho[1,2-b]xanthen-13-one (**4.237**). (SB-VIII-78). Pd/C (ca. 1-2 mg) was added to a solution of **4.210** (7 mg, 0.12 mmol) in a mixture (1:1) of MeOH/PhMe (1 mL). The reaction mixture was sparged with a balloon of H_2 for 5 min then stirred at room temperature for 24 h under a hydrogen atmosphere. The reaction mixture was filtered through a silica plug, eluting with a mixture (1:1) acetone/hexanes (5 mL). The solution was concentrated under reduced pressure and the crude material was purified by flash chromatography eluting with a gradient of acetone/hexanes (7:20 → 1:2) to provide 3 mg (53%) of **4.237** as yellow solid: ^{1}H-NMR (500 MHz) δ 13.06 (s, 1 H), 8.25 (s, 1 H), 6.98 (d, *J* = 8.5 Hz, 1 H), 6.944 (s, 1 H), 6.941 (d, *J* = 8.0 Hz, 1 H), 5.39 (bs, 1 H), 5.29 (bs, 2 H), 4.07 (s, 3 H), 4.03 (s, 3 H), 3.62 (s, 3 H), 1.57 (bs, 4 H); ^{13}C-NMR (125 MHz) δ 180.9, 156.1, 151.9, 151.3, 148.1, 147.2, 143.9, 142.9, 136.5, 131.9, 131.5, 124.6, 123.4, 115.8, 114.8, 113.4, 106.8, 104.7, 99.7, 99.3, 57.0, 56.6, 56.4, 29.2, 23.9; IR (film) 3396 (O-H), 2955 (C-H), 1644 (C=O), 1615, 1588, 1509, 1479, 1453, 1434, 1382, 1361, 1299, 1277, 1237, 1211, 1175, 1147, 1115, 1073, 1030, 1003, 988 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{25}H_{22}O_9^+$ (M+Na), 489.1156; found, 489.1154.

NMR assignments: ^{1}H-NMR (500 MHz) δ 13.06 (s, 1 H, O27-H), 8.25 (s, 1 H, O26-H), 6.98 (d, *J* = 8.5 Hz, 1 H, C13-H), 6.944 (s, 1 H, C4-H), 6.941 (d, *J* = 8.0 Hz, 1 H, C16-H), 5.39 (bs, 1 H, O28-H), 5.29 (bs, 2 H, C22-H), 4.07 (s, 3 H, C25-H), 4.03 (s, 3 H, C24-H), 3.62 (s, 3 H, C23-H), 1.57 (bs, 4 H, C1-H, C21-H); ^{13}C-NMR (125 MHz) δ 180.9 (C11), 156.1 (C15), 151.9 (C17), 151.3 (C5), 148.1 (C14), 147.2 (C9), 143.9 (C6), 142.9 (C18), 136.5 (C19), 131.9 (C10),

131.5 (C12), 124.6 (C7), 123.4 (C4), 115.8 (C3), 114.8 (C8), 113.4 (C20), 106.8 (C2), 104.7 (C13), 99.7 (C22), 99.3 (C16), 57.0 (C23), 56.6 (C25), 56.4 (C24), 29.2 (C21), 23.9 (C1).



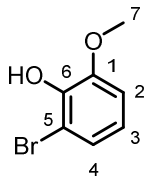
4.219

1-((4-Methoxybenzyl)oxy)-2-(methoxymethoxy)benzene (**4.219**). (SB-VIII-40/SB-VIII-38). 2-(Methoxymethoxy)phenol (**4.224**) was prepared according to known literature procedures.[588] K_2CO_3 (5.6 g, 40.9 mmol) was added to a solution of catechol (**4.223**) (3.0 g, 27.2 mmol) in anhydrous acetone (90 mL) at room temperature and stirred for 20 min before adding a solution of MOMCl[633] (1.18 M, 24.2 mL, 28.6 mmol) in methyl hexanoate. The reaction mixture was stirred for 8 h at room temperature and then filtered through Celite. The solution was concentrated under reduced pressure and crude material was purified by flash chromatography eluting with a gradient of acetone/hexanes (3:20 → 1:4) to provide 2.8 g (38%) of 2-(methoxymethoxy)phenol (**4.224**) as a white waxy solid.

2-(Methoxymethoxy)phenol (**4.224**) (1.6 g, 10.4 mmol), K_2CO_3 (2.1 g, 15.6 mmol) and sodium iodide (NaI) (0.47 g, 3.1 mmol) in anhydrous DMF (42 mL) was heated at 40 °C for 1 h. para-methoxybenzyl chloride (PMBCl)[634] (3.2 g, 2.8 mL, 20.8 mmol) was added, and the mixture was stirred at 40 °C for an additional 24 h, whereupon the reaction was cooled to room temperature and H_2O (80 mL) was added. The mixture was extracted with EtOAc (3 x 30 mL), and the combined organic extracts were washed with 13% aqueous brine solution (4 x 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was purified by flash chromatography eluting with a gradient of acetone/hexanes (1:50 → 1:4) buffered with 1% Et_3N to provide 1.2 g (42%) of **4.219** as white solid: mp 64-66 °C; ^{1}H-NMR (400 MHz) δ 7.30 (d, *J* = 8.4 Hz, 2 H), 7.14 (d, *J* = 8.4 Hz, 1 H), 6.87-6.94 (comp, 4 H), 5.21 (s, 2 H), 5.08 (s, 2 H), 3.81 (s, 3 H), 3.51 (s, 3 H); ^{13}C-NMR (100 MHz) δ 159.3, 149.2, 147.0, 129.2, 128.9, 122.7,

121.4, 117.7, 114.7, 113.9, 95.7, 70.8, 56.2, 55.3; IR (film) 2917 (C-H), 1613, 1515, 1455, 1379, 1302, 1247, 1153, 1118, 1077, 995 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{16}H_{18}O_4^+$ (M+Na), 297.1097; found, 297.1095.

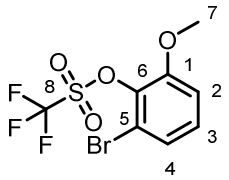
NMR assignments: ^{1}H-NMR (400 MHz) δ 7.30 (d, *J* = 8.4 Hz, 2 H, C9-H), 7.14 (d, *J* = 8.4 Hz, 1 H, C4-H), 6.87-6.94 (comp, 4 H, C1-H, C2-H, C3-H, C10-H), 5.21 (s, 2 H, C13-H), 5.08 (s, 2 H, C7-H), 3.81 (s, 3 H, C12-H), 3.51 (s, 3 H, C14-H); ^{13}C-NMR (100 MHz) δ 159.3 (C11), 149.2 (C6), 147.0 (C5), 129.2 (C8), 128.9 (C9), 122.7 (C3), 121.4 (C2), 117.7 (C1), 114.7 (C4), 113.9 (C10), 95.7 (C13), 70.8 (C7), 56.2 (C14), 55.3 (C12).



4.243

2-Bromo-6-methoxyphenol (**4.243**). (SB-VII-76). Guiacol (**4.242**) (2.0 g, 16.11 mmol) was dissolved in CH_2Cl_2 (160 mL) and cooled to – 78 °C. In a separate flask, TMG (4.45 g, 4.85 mL, 38.66 mmol) was added to a slurry of NBS (3.44 g, 19.33 mmol) in CH_2Cl_2 (43 mL) at 0 °C. The mixture was stirred until it became homogenous (~5 min), then it was added to the solution contining guiacol (**4.242**) at – 78 °C over 10 min. The reaction mixture was stirred for 30 min at – 78 °C whereupon AcOH (1.1 mL, 1.15 g, 19.33 mmol) was added, and the reaction was warmed to room temperature. The mixture was washed with H_2O (1 x 100 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of acetone/hexanes (1:4 → 1:2) buffered with 1% Et_3N to provide 2.74 g (84%) of **4.234** as a white solid: mp 49-53 °C; ^{1}H-NMR (600 MHz) δ 7.09 (dd, *J* = 1.4, 8.1 Hz, 1 H), 6.81 (dd, *J* = 1.4, 8.1 Hz, 1 H), 6.74 (t, *J* = 8.1 Hz, 1 H), 3.90 (s, 3 H); ^{13}C-NMR (150 MHz) δ 147.4, 143.2, 124.8, 120.7, 109.9, 108.4, 56.3; IR (film) 3409 (O-H), 2953 (C-H), 2848 (C-H), 1601, 1490, 1471, 1442, 1354, 1287, 1263, 1234, 1201, 1147, 1072, 1027 cm^{-1}; HRMS (CI) *m/z* calc for $C_7H_7O_2Br^+$ (M+), 201.9629; found, 201.9632.

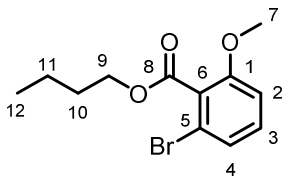
NMR assignments: ^{1}H-NMR (600 MHz) δ ^{1}H-NMR (600 MHz) δ 7.09 (dd, *J* = 1.4, 8.1 Hz, 1 H, C4-H), 6.81 (dd, *J* = 1.4, 8.1 Hz, 1 H, C2-H), 6.74 (t, *J* = 8.1 Hz, 1 H, C3-H), 3.90 (s, 3 H, C7-H); ^{13}C-NMR (150 MHz) δ 147.4 (C1), 143.2 (C6), 124.8 (C4), 120.7 (C3), 109.9 (C2), 108.4 (C5), 56.3 (C7).



4.244

2-Bromo-6-methoxyphenyl trifluoromethanesulfonate (**4.244**). (SB-VII-73). A solution of phenol **4.243** (4.38 g, 21.57 mmol) and pyridine (3.41 g, 3.47 mL, 43.14 mmol) in CH_2Cl_2 (120 mL) was cooled to 0 °C. Neat triflic anhydride (Tf_2O) (7.31 g, 4.35 mL, 25.88 mmol) was added, and the reaction mixture was stirred for 1 h. H_2O (100 mL) was added, and the layers were separated. The organic layer was washed with aqueous $CuSO_4$ (1 M, 1 x 100 mL) dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with EtOAc/hexanes (1:10) to provide 6.83 g (94%) of **4.244** as a clear oil: ^{1}H-NMR (600 MHz) δ 7.22 (dd, *J* = 1.5, 8.2 Hz, 1 H), 7.18 (t, *J* = 8.2 Hz, 1 H), 6.97 (dd, *J* = 2.5, 8.2 Hz, 1 H), 3.91 (s, 3 H); ^{13}C-NMR (150 MHz) δ 152.6, 137.0, 129.3, 125.3, 118.6 (q, *J* = 321 Hz), 116.9, 112.0, 56.4; IR (film) 1595, 1475, 1300, 1282, 1210, 1136, 1036, 883 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_8H_6BrF_3O_4S^+$ (M+Na), 356.9014; found, 356.9026.

NMR assignments: ^{1}H-NMR (600 MHz) δ 7.22 (dd, *J* = 1.5, 8.2 Hz, 1 H, C2-H), 7.18 (t, *J* = 8.2 Hz, 1 H, C3-H), 6.97 (dd, *J* = 2.5, 8.2 Hz, 1 H, C4-H), 3.91 (s, 3 H, C7-H); ^{13}C-NMR (150 MHz) δ 152.6 (C1), 137.0 (C6), 129.3 (C4), 125.3 (C3), 118.6 (C8), 116.9 (C5), 112.0 (C2), 56.4 (C7).



4.264

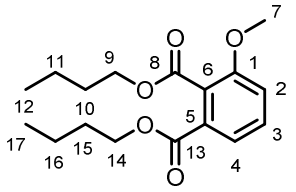
Butyl 2-bromo-6-methoxybenzoate (**4.264**). (SB-VII-148). $Pd(OAc)_2$ (75 mg, 0.33 mmol), 1,3-bis(diphenylphosphino)propane (DPPP) (270 mg, 0.65 mmol), K_2CO_3 (1.81 g, 13.08 mmol) and tetrabutylammonium acetate (TBAA) (1.97 g, 6.54 mmol) were weighed in a glove-box and added to a flame dried round bottomed flask. Pulverized 3 Å molecular sieves (1.1 g) were added, and the flask was put under vacuum and backfilled with N_2 (3 x). Toluene (20 mL) was added and the reaction mixture was stirred for 10 min before adding **4.244** (2.19 g, 6.54 mmol) and *n*-BuOH (1.46 g, 1.80 mL, 19.61 mmol). The reaction mixture was heated to 70 °C for 16 h. The mixture was cooled to room temperature and filtered through a silica plug. The plug was washed with 1:1 EtOAc/hexanes (200 mL), and the combined eluant was concentrated and purified by flash chromatography eluting with a gradient of CH_2Cl_2/hexanes (1:4 → 3:4) to provide 1.26 g (67%) of **4.264** as a clear oil.

Procedure using DMSO as the solvent (SB-VII-211):

$Pd(OAc)_2$ (34 mg, 0.149 mmol), 1,3-bis(diphenylphosphino)propane (DPPP) (123 mg, 0.298 mmol), and tetrabutylammonium acetate (TBAA) (900 mg, 2.98 mmol) were weighed in a glove-box, and added to a flame dried round bottomed flask. Pulverized 3 Å molecular sieves (1.5 g) were added and the flask was put under vacuum and backfilled with N_2 (3 x). Degassed DMSO (20 mL) was added, and the reaction mixture was stirred for 10 min before adding **4.224** (500 mg, 1.49 mmol) and *n*-BuOH (0.33 g, 0.41 mL, 4.47 mmol). The mixture was heated to 70 °C for 16 h. The mixture was cooled to room temperature and filtered through a silica plug. The plug was washed with 1:1 EtOAc/hexanes (1 x 100 mL), and the combined eluant was washed with H_2O (1 x 50 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure and the crude oil was purified by flash chromatography eluting with a gradient of CH_2Cl_2/hexanes (1:4 → 3:4) to provide 272 mg (69%) of **4.264** as a clear oil.

^{1}H-NMR (500 MHz) δ 7.18 (dd, *J* = 8.1, 8.0 Hz, 1 H), 7.13 (dd, *J* = 1.0, 8.3 Hz, 1 H), 6.85 (dd, *J* = 1.0, 8.0 Hz, 1 H), 4.36 (t, *J* = 6.6 Hz, 2 H), 3.81 (s, 3 H), 1.74 (quin, *J* = 6.6 Hz, 2 H), 1.47 (sex, *J* = 7.6 Hz, 2 H), 0.96 (t, *J* = 7.3 Hz, 3 H); ^{13}C-NMR (125 MHz) δ 166.3, 157.2, 131.1, 126.4, 124.5, 119.7, 110.0, 65.6, 56.1, 30.6, 19.1, 13.7; IR (film) 2960 (C-H), 2873 (C-H), 1731 (C=O), 1591, 1573, 1464, 1433, 1267, 1187, 1157, 1107, 1066, 1035, 839 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{12}H_{15}BrO_3^+$ (M+Na), 309.0097; found, 309.0102.

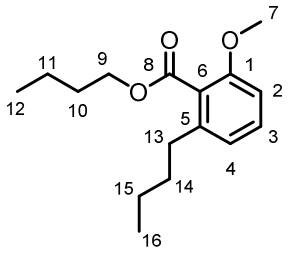
NMR assignments: ^{1}H-NMR (500 MHz) δ 7.18 (dd, *J* = 8.1, 8.0 Hz, 1 H, C3-H), 7.13 (dd, *J* = 1.0, 8.3 Hz, 1 H, C4-H), 6.85 (dd, *J* = 1.0, 8.0 Hz, 1 H, C2-H), 4.36 (t, *J* = 6.6 Hz, 2 H, C9-H), 3.81 (s, 3 H, C7-H), 1.74 (quin, *J* = 6.6 Hz, 2 H, C10-H), 1.47 (sex, *J* = 7.6 Hz, 2 H, C11-H), 0.96 (t, *J* = 7.3 Hz, 3 H, C12-H); ^{13}C-NMR (125 MHz) δ 166.3 (C8), 157.2 (C1), 131.1 (C3), 126.4 (C5), 124.5 (C4), 119.7 (C6), 110.0 (C2), 65.6 (C9), 56.1 (C7), 30.6 (C10), 19.1 (C11), 13.7 (C12).



4.266

Dibutyl 3-methoxyphthalate (**4.266**). (SB-VII-130C2). Isolated as a byproduct from the reaction mixture. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:4) to provide 229 mg (11%) of **4.266** as a clear oil: ^{1}H-NMR (500 MHz) δ 5.79 (d, *J* = 7.8 Hz, 1 H), 7.40 (dd, *J* = 7.8, 8.3 Hz, 1 H), 7.11 (d, *J* = 8.3 Hz, 1 H), 4.36 (t, *J* = 6.6 Hz, 2 H), 4.28 (t, *J* = 6.8 Hz, 2 H), 3.85 (s, 3 H), 1.76-1.68 (comp, 4 H), 1.49-1.40 (comp, 4 H), 0.96 (app t, *J* = 7.6 Hz, 6 H); ^{13}C-NMR (125 MHz) δ 167.5, 165.3, 156.4, 130.0, 129.0, 125.7, 121.9, 115.3, 65.4, 65.3, 56.2, 30.6, 30.5, 19.13, 19.10, 13.7; IR (film) 2961 (C-H), 2874 (C-H), 1729 (C=O), 1592, 1470, 1439, 1384, 1279, 1186, 1160, 1113, 1068, 756 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{17}H_{24}O_5^+$ (M+Na), 331.1516; found, 331.1517.

NMR assignments: ^{1}H-NMR (500 MHz) δ 5.79 (d, *J* = 7.8 Hz, 1 H, C4-H), 7.40 (dd, *J* = 7.8, 8.3 Hz, 1 H, C3-H), 7.11 (d, *J* = 8.3 Hz, 1 H, C2-H), 4.36 (t, *J* = 6.6 Hz, 2 H, C9-H or C14-H), 4.28 (t, *J* = 6.8 Hz, 2 H, C9-H or C14-H), 3.85 (s, 3 H, C7-H), 1.76-1.68 (comp, 4 H, C10-H, C15-H), 1.49-1.40 (comp, 4 H, C11-H, C16-H), 0.96 (app t, *J* = 7.6 Hz, 6 H, C12-H, C17-H); ^{13}C-NMR (125 MHz) δ 167.5 (C8), 165.3 (C13), 156.4 (C1), 130.0 (C3), 129.0 (C5), 125.7 (C6), 121.9 (C4), 115.3 (2), 65.4 (C9 or C14), 65.3 (C9 or C14), 56.2 (C7), 30.6 (C10 or C15), 30.5 (C10 or C15), 19.13 (C11 or C16), 19.10 (C11 or C16), 13.7 (C12, C17).

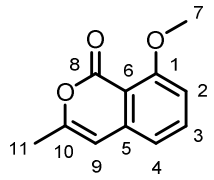


4.276

Butyl 2-butyl-6-methoxybenzoate (**4.276**). (SB-VII-140). Isolated as a byproduct from the reaction mixture. The crude oil was purified by flash chromatography eluting with EtOAc/hexanes (1:4) to provide 10 mg (22%) of **4.276** as a clear oil: ^{1}H-NMR (500 MHz) δ 7.52 (dd, *J* = 7.8, 8.3 Hz, 1 H), 6.81 (dd, *J* = 0.5, 7.3 Hz, 1 H), 6.75 (dd, *J* = 0.5, 8.3 Hz, 1 H), 5.23 (sex, *J* = 7.3 Hz, 2 H), 4.33 (t, *J* = 6.6 Hz, 2 H), 3.81 (s, 3 H), 2.56 (dd, *J* = 7.8, 8.1 Hz, 2 H), 1.73 (quin, *J* = 6.6 Hz, 2 H), 1.57 (m, 2 H), 1.46 (sex, *J* = 7.6 Hz, 2 H), 0.96 (t, *J* = 7.3 Hz, 3 H), 0.91 (t, *J* = 7.3 Hz, 3 H); ^{13}C-NMR (125 MHz) δ 168.6, 156.2, 141.2, 130.0, 123.9, 121.5, 108.4, 65.0, 55.8, 33.4, 33.1, 30.2, 22.6, 19.1, 13.9, 13.6; IR (film) 2958 (C-H), 2931 (C-H), 2872 (C-H), 1729 (C=O), 1585, 1470, 1379, 1271, 1113, 1076 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{16}H_{24}O_3^+$ (M+Na), 287.1618; found, 287.1612.

NMR assignments: ^{1}H-NMR (500 MHz) δ 7.52 (dd, *J* = 7.8, 8.3 Hz, 1 H, C3-H), 6.81 (dd, *J* = 0.5, 7.3 Hz, 1 H, C4-H), 6.75 (dd, *J* = 0.5, 8.3 Hz, 1 H, C2-H), 5.23 (sex, *J* = 7.3 Hz, 2 H, C15-H), 4.33 (t, *J* = 6.6 Hz, 2 H, C9-H), 3.81 (s, 3 H, C7-H), 2.56 (dd, *J* = 7.8, 8.1 Hz, 2 H,

C10-H), 1.73 (quin, *J* = 6.6 Hz, 2 H, C13-H), 1.57 (m, 2 H, C14-H), 1.46 (sex, *J* = 7.6 Hz, 2 H, C11-H), 0.96 (t, *J* = 7.3 Hz, 3 H, C12-H), 0.91 (t, *J* = 7.3 Hz, 3 H, C16-H); ^{13}C-NMR (125 MHz) δ 168.6 (C8), 156.2 (C1), 141.2 (C5), 130.0 (C3), 123.9 (C6), 121.5 (C4), 108.4 (C2), 65.0 (C9), 55.8 (C7), 33.4 (C13), 33.1 (C14), 30.2 (C10), 22.6 (C15), 19.1 (C11), 13.9 (C16), 13.6 (C12).

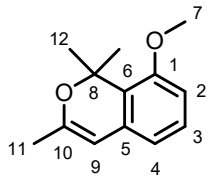


4.277

8-Methoxy-3-methyl-1H-isochromen-1-one (**4.277**). (SB-VII-178). $Pd_2(DBA)_3$•$HCCl_3$ (45 mg, 0.043 mmol), (2-biphenyl)di-*tert*-butylphosphine (52 mg, 0.174 mmol), K_3PO_4 (923 mg, 4.35 mmol), *para*-methoxyphenol (43 mg, 0.348 mmol) and tetrabutylammonium acetate (TBAA) (525 mg, 1.74 mmol) were weighed in a glove-box and added to a flame dried round bottomed flask. Pulverized 3 Å molecular sieves (250 mg) was added and the flask was put under vacuum and backfilled with N_2 (3 x). Toluene (5 mL) was added, and the reaction mixture was stirred for 10 min before adding a degassed solution of **4.294** (2.19 g, 6.54 mmol) in toluene (4 mL) and acetone (freshly distilled from CaH_2, 0.61 g, 0.77 mL, 10.44 mmol) and the mixture was heated to 60 °C for 16 h. The mixture was then cooled to room temperature, and filtered through a silica plug. The plug was washed with 3:1 EtOAc/hexanes (100 mL) and the combined eluant was concentrated and purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:4 → 1:2) to provide 197 mg (59%) of **4.277** as a brown solid: ^{1}H-NMR (600 MHz) δ 7.57 (dd, *J* = 7.77, 7.78 Hz, 1 H), 6.89 (d, *J* = 8.3 Hz, 1 H), 6.86 (d, *J* = 7.77 Hz, 1 H), 6.15 (app d, *J* = 1 Hz, 1 H), 3.99 (s, 3 H), 2.23 (d, *J* = 1 Hz, 3 H); ^{13}C-NMR (150 MHz) δ 161.6, 159.8, 155.1, 140.7, 135.7, 117.0, 109.3, 108.0, 103.6, 56.3, 19.5; IR (film) 3436, 1729 (C=O), 1666, 1599, 1571, 1478, 1434, 1319, 1282, 1262, 1163, 1089, 1039, 980 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{11}H_{10}O_3^+$ (M+Na), 213.0522; found, 213.0523.

NMR assignments: ^{1}H-NMR (600 MHz) δ 7.57 (dd, *J* = 7.77, 7.78 Hz, 1 H, C3-H), 6.89 (d, *J* = 8.3 Hz, 1 H, C2-H), 6.86 (d, *J* = 7.77 Hz, 1 H, C4-H), 6.15 (app d, *J* = 1 Hz, 1 H, C9-H),

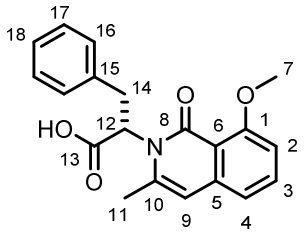
3.99 (s, 3 H, C7-H), 2.23 (d, *J* = 1 Hz, 3 H, C11-H); ^{13}C-NMR (150 MHz) δ 161.6 (C8), 159.8 (C1), 155.1 (C10), 140.7 (C5), 135.7 (C3), 117.0 (C4), 109.3 (C2), 108.0 (C6), 103.6 (C9), 56.3 (C7), 19.5 (C11).



4.290

8-8-Methoxy-1,1,3-trimethyl-1H-isochromene (**4.290**). (SB-VII–200). Isolated by-product from the reaction mixture. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:5 → 11:20) to provide 17 mg (32%) of **4.290** as a brown solid: ^{1}H-NMR (600 MHz) δ 7.07 (dd, *J* = 7.6, 8.3 Hz, 1 H), 6.65 (dd, *J* = 0.9, 8.3 Hz, 1 H), 6.49 (dd, *J* = 1.0, 7.5 Hz, 1 H), 5.51 (d, *J* = 0.9 Hz, 1 H), 3.78 (s, 3 H), 1.86 (d, *J* = 0.9 Hz, 3 H), 1.66 (s, 6 H); ^{13}C-NMR (150 MHz) δ 155.2, 151.9, 132.6, 128.1, 122.6, 116.3, 109.3, 99.1, 79.1, 55.3, 27.7, 20.3; IR (film) 2924 (C-H), 1669, 1574, 1471, 1377, 1356, 1267, 1160, 1135, 1090, 1063, 1021, 985 cm^{-1}; HRMS (CI) *m/z* calc for $C_{13}H_{16}O_2^+$ (M+), 204.1150; found, 204.1154.

NMR assignments: ^{1}H-NMR (600 MHz) δ 7.07 (dd, *J* = 7.6, 8.3 Hz, 1 H, C3-H), 6.65 (dd, *J* = 0.9, 8.3 Hz, 1 H, C4-H), 6.49 (dd, *J* = 1.0, 7.5 Hz, 1 H, C2-H), 5.51 (d, *J* = 0.9 Hz, 1 H, C9-H), 3.78 (s, 3 H, C7-H), 1.86 (d, *J* = 0.9 Hz, 3 H, C11-H), 1.66 (s, 6 H, C12-H); ^{13}C-NMR (150 MHz) δ 155.2 (C1), 151.9 (C10), 132.6 (C5), 128.1 (C6), 122.6 (C3), 116.3 (C4), 109.3 (C2), 99.1 (C9), 79.1 (C8), 55.3 (C7), 27.7 (C12), 20.3 (C11).

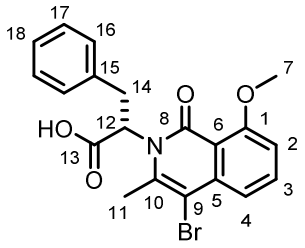


4.295

(S)-2-(8-Methoxy-3-methyl-1-oxoisoquinolin-2(1H)-yl)-3-phenylpropanoic acid (**4.295**). (SB-VII-212). A solution of $AlMe_3$ (2 M, 3.44 mL, 6.89 mmol) in toluene was added to THF (10 mL), followed by a solution of MeLi (1.26 M, 5.5 mL, 6.89 mmol) in Et_2O. The mixture was stirred for 10 min before adding to a degassed flask containg solid L-phenylalanine (487 mg, 2.95 mmol). The mixture was stirred for 10 min before heating to 50 °C and heating for an additional 30 min or until the mixture became homogeneous. A solution of **4.277** (187 mg, 0.98 mmol) in toluene (10 mL) was then added and the mixture was stirred for 1 h at 50 °C, whereupon the reaction was cooled to room temperature and poured into cold 1 M HCl (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of MeCN/$HCCl_3$ (1:20 → 1:10) buffered with 2% AcOH to provide 262 mg (79%) of **4.295** as a yellow oil: ^{1}H-NMR (600 MHz) δ 7.50 (m, 1 H), 7.16 (comp, 3 H), 7.01 (m, 2 H), 6.92 (m, 1 H), 6.85 (m, 1 H), 6.09 (app d, 1 H), 4.65 (m, 1 H), 3.98 (app d, 3 H), 3.67-3.60 (comp, 2 H), 2.64 (s, 3 H); ^{13}C-NMR (150 MHz) δ 175.9, 161.8, 160.9, 140.1, 140.0, 138.3, 133.4, 129.5, 128.6, 126.7, 117.5, 113.8, 107.3, 106.6, 61.3, 56.0, 34.4, 20.8; IR (film) 3443 (O-H), 2924 (C-H), 1730 (C=O), 1653 (C=O), 1602, 1561, 1481, 1455, 1399, 1335, 1296, 1267, 1212, 1180, 1154, 1115, 1084, 1065 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{20}H_{19}NO_4^+$ (M+Na), 360.1206; found, 360.1208.

NMR assignments: ^{1}H-NMR (600 MHz) δ 7.50 (m, 1 H, C3-H), 7.16 (comp, 3 H, C17-H, C18-H), 7.01 (m, 2 H, C16-H), 6.92 (m, 1 H, C4-H), 6.85 (m, 1 H, C2-H), 6.09 (app d, 1 H, C9-H), 4.65 (m, 1 H, C12-H), 3.98 (app d, 3 H, C7-H), 3.67-3.60 (comp, 2 H, C14-H), 2.64 (s, 3

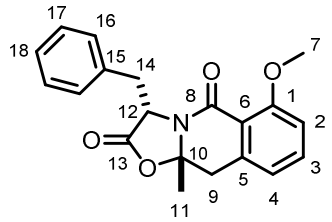
H, C11-H); ^{13}C-NMR (150 MHz) δ 175.9 (C13), 161.8 (C8), 160.9 (C1), 140.1 (C10), 140.0 (C15), 138.3 (C5), 133.4 (C3), 129.5 (C16), 128.6 (C17) 126.7 (C18), 117.5 (C4), 113.8 (C6), 107.3 (C2), 106.6 (C9), 61.3 (C12), 56.0 (C7), 34.4 (C14), 20.8 (C11).



(S)-2-(4-Bromo-8-methoxy-3-methyl-1-oxoisoquinolin-2(1H)-yl)-3-phenylpropanoic acid. (SB-VII-227). *N*-Bromosuccinimide (NBS) (9 mg, 0.049 mmol) was added to a slurry of **4.295** (16 mg, 0.044 mmol), Ph_3P=S (1 mg, 0.004 mmol) and $NaHCO_4$ (6 mg, 0.67 mmol) in THF (0.5 mL) at room temperature. The reaction mixture was stirred for 5 h whereupon a solution of saturated aqueous $Na_2S_2O_8$ (0.5 mL) was added followed by cold 1 M HCl (0.5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (1 mL) and the organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was purified by preparative TLC (10% MeCN/$HCCl_3$ w/ 2% AcOH) to provide 16 mg (90%) of the named compound as a white solid: ^{1}H-NMR (600 MHz) δ 8.91 (bs, 1 H), 7.64 (t, *J* = 8.2 Hz, 1 H), 7.56 (d, *J* = 8.2 Hz, 1 H), 7.27-7.19 (comp, 3 H), 7.02 (m, 2 H), 6.97 (d, *J* = 8.2 Hz, 1 H), 4.80 (bd, *J* = 6.5 Hz, 1 H), 4.00 (s, 3 H), 3.72-3.57 (comp, 2 H), 1.26 (s, 3 H); ^{13}C-NMR (150 MHz) δ 175.8, 161.1, 160.6, 139.3, 138.4, 138.0, 134.1, 129.4, 128.7, 126.9, 118.6, 113.8, 108.7, 102.5, 62.6, 56.4, 34.6, 21.4; IR (film) 3474 (O-H), 3211 (C-H), 1776, 1712 (C=O), 1645, 1599, 1430, 1356, 1295, 1265, 1244, 1183 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{20}H_{18}BrNO_4^+$ (M+Na), 438.0311; found, 438.0308.

NMR assignments: ^{1}H-NMR (600 MHz) δ 8.91 (bs, 1 H, O-H), 7.64 (t, *J* = 8.2 Hz, 1 H, C3-H), 7.56 (d, *J* = 8.2 Hz, 1 H, C4-H), 7.27-7.19 (comp, 3 H, C17-H, C18-H), 7.02 (m, 2 H, C16-H), 6.97 (d, *J* = 8.2 Hz, 1 H, C2-H), 4.80 (bd, *J* = 6.5 Hz, 1 H, C12-H), 4.00 (s, 3 H, C7-H),

3.72-3.57 (comp, 2 H, C14-H), 1.26 (s, 3 H, C11-H); ^{13}C-NMR (150 MHz) δ 175.8 (C13), 161.1 (C8), 160.6 (C1), 139.3 (C10), 138.4 (C15), 138.0 (C5), 134.1 (C3), 129.4 (C16), 128.7 (C17), 126.9 (C18), 118.6 (C4), 113.8 (C6), 108.7 (C2), 102.5 (C9), 62.6 (C12), 56.4 (C7), 34.6 (C14), 21.4 (C11).



4.294

(3S,10aS)-3-Benzyl-6-methoxy-10a-methyl-10,10a-dihydro-5H-oxazolo[3,2-b]isoquinoline-2,5(3H)-dione (**4.294**). (SB-VII–207A). Isolated from a sample of **4.295** which was left on the bench at room temperature for ~ 1 week. Purified via preparative TLC (50% EtOAc/hexanes) to provide 9 mg (10%) of **4.294** as a white solid: ^{1}H-NMR (600 MHz) δ 7.40 (dd, *J* = 7.5, 8.5 Hz, 1 H), 7.27-7.20 (comp, 5 H), 6.96 (d, *J* = 8.6 Hz, 1 H), 6.76 (d, *J* = 7.4 Hz, 1 H), 4.97 (dd, *J* = 2.6, 6.4 Hz, 1 H), 3.95 (s, 3 H), 3.52 (dd, *J* = 6.4, 13.9 Hz, 1 H), 3.42 (dd, *J* = 2.6, 13.9 Hz, 1 H), 3.16 (d, *J* = 14.6 Hz, 1 H), 3.05 (d, *J* = 14.7 Hz, 1 H), 0.53 (d, *J* = 1.0 Hz, 3 H); ^{13}C-NMR (150 MHz) δ 171.3, 161.0, 159.9, 136.3, 136.0, 133.7, 130.5, 128.6, 127.3, 120.2, 116.5, 111.9, 94.2, 69.6, 58.0, 56.3, 53.8, 24.6; IR (film) 3436, 1729 (C=O), 1666 (C=O), 1599, 1571, 1478, 1434, 1319, 1282, 1262, 1163, 1089, 1039, 980 cm^{-1}; HRMS (CI) *m/z* calc for $C_{20}H_{19}NO_4^+$ (M+), 337.1314; found, 337.131.

NMR assignments: ^{1}H-NMR (600 MHz) δ 7.40 (dd, *J* = 7.5, 8.5 Hz, 1 H, C3-H), 7.27-7.20 (comp, 5 H, C16-H, C17-H, C18-H), 6.96 (d, *J* = 8.6 Hz, 1 H, C4-H), 6.76 (d, *J* = 7.4 Hz, 1 H, C2-H), 4.97 (dd, *J* = 2.6, 6.4 Hz, 1 H, C12-H), 3.95 (s, 3 H, C7-H), 3.52 (dd, *J* = 6.4, 13.9 Hz, 1 H, C14-H), 3.42 (dd, *J* = 2.6, 13.9 Hz, 1 H, C14-H), 3.16 (d, *J* = 14.6 Hz, 1 H, C9-H), 3.05 (d, *J* = 14.7 Hz, 1 H, C9-H), 0.53 (d, *J* = 1.0 Hz, 3 H, C11-H); ^{13}C-NMR (150 MHz) δ 171.3 (C13), 161.0 (C8), 159.9 (C1), 136.3 (C15), 136.0 (C5), 133.7 (C3), 130.5 (C17), 128.6 (C16), 127.3

(C18), 120.2 (C4), 116.5 (C6), 111.9 (C2), 94.2 (C10), 69.6 (C12), 58.0 (C9), 56.3 (C14), 53.8 (C7), 24.6 (C11).

General procedure for titrating strong bases.

To a solution of 4-(Phenylazo)diphenylamine (PDA) (**4.118**) (0.02–0.05 mmol) in Anhydrous THF (3 mL) was added 2-butanol or BHT (~1 mmol). A solution of the base is then added at room temperature until the colored endpoint is reached. The titre is calculated using a 1:1 molar ratio with the proton source.

General procedure for titrating Lewis acids.

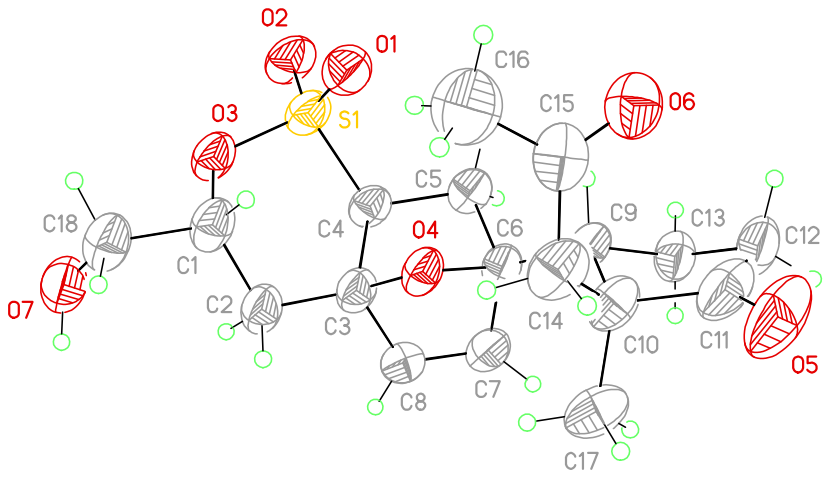
To a solution of 4-(Phenylazo)diphenylamine (PDA) (**4.118**) (0.02–0.05 mmol) in anhydrous CH_2Cl_2 (3 mL) was added pyridine (1 eq). A solution of the Lewis acid is then added at room temperature until the colored endpoint is reached. The titre is calculated using either a 1:1 molar ratio of Lewis acid to pyridine for the weaker Lewis acids such as AlR_3,AlR_2H or R_2AlX or a 1:2 molar ratio of Lewis acid to pyridine for the stronger Lewis acids such as R_2BX or MX_n.

General procedure for titrating hydride reducing agents.

To a solution of 4-(Phenylazo)diphenylamine (PDA) (**4.118**) (0.02–0.05 mmol) in anhydrous ether or CH_2Cl_2 (3 mL) was added benzophenone (1 eq). A solution of the reducing agent is then added at room temperature until the colored endpoint is reached. The titre is calculated using a 1:N molar ratio of benzophenone to active hydride in the reducing agent, where N is the number of hydride equivalents.

5.2.3: Crystallography

Figure 5.1 View of **2.13** showing the atom labeling scheme.



Displacement ellipsoids are scaled to the 50% probability level.

X-ray Experimental for $C_{18}H_{24}O_7S$: Crystals grew as colorless plates by slow vapor diffusion from ethylacetate and pentanes. The data crystal was cut from a larger crystal and had approximate dimensions; 0.20 x 0.20 x 0.06 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKa radiation (l = 0.71073Å). A total of 340 frames of data were collected using w-scans with a scan range of 1.3° and a counting time of 186 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection, and structure refinement are listed in Table 1. Data reduction were performed using DENZO-SMN.[637] The structure was solved by direct methods using SIR97[638] and refined by full-matrix least-squares on F^2 with

anisotropic displacement parameters for the non-H atoms using SHELXL-97.[639] Structure analysis was aided by use of the programs PLATON98[640] and WinGX.[641] The hydrogen atoms calculated in idealized position with Uiso set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(s(F_o))^2 + (0.0494*P)^2 + (1.6931*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_W(F^2)$ refined to 0.148, with R(F) equal to 0.0609 and a goodness of fit, S, = 1.07. Definitions used for calculating R(F), $R_W(F^2)$ and the goodness of fit, S, are given below.[636] The data were checked for secondary extinction but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[637] All figures were generated using SHELXTL/PC.[638] Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

Table 5.1. Crystal data and structure refinement for **2.13**.

Empirical formula	**C18 H24 O7 S**	
Formula weight	384.43	
Temperature	153(2) K	
Wavelength	0.71075 Å	
Crystal system	Monoclinic	
Space group	P21/n	
Unit cell dimensions	a = 8.4314 Å	α= 90°
	b = 9.5852 Å	β= 90.343(3)°
	c = 23.175(2) Å	γ = 90°
Volume	1872.9(4) $Å^3$	
Z	4	
Density (calculated)	1.363 Mg/m^3	

Absorption coefficient	0.210 mm^{-1}
F	816
Crystal size	0.20 x 0.20 x 0.06 mm
Theta range for data collection	3.22 to 25.00°.
Index ranges	-9<=h<=10,-11<=k<=11, - 27<=l<=27
Reflections collected	10495
Independent reflections	3274 [R(int) = 0.0665]
Completeness to theta = 25.00°	99.6 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3274 / 0 / 238
Goodness-of-fit on F^2	1.069
Final R indices [I>2sigma(I)]	R1 = 0.0609, wR2 = 0.1207
R indices (all data)	R1 = 0.1268, wR2 = 0.1479
Largest diff. peak and hole	0.212 and -0.279 e.$Å^{-3}$

Table 5.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **2.13**.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S1	3886(1)	7716(1)	9658(1)	49(1)
O1	3470(3)	6581(3)	9289(1)	57(1)
O2	3201(3)	7768(3)	10219(1)	61(1)
O3	3391(3)	9135(3)	9364(1)	51(1)
O4	6804(2)	7288(2)	8798(1)	44(1)
O5	9840(4)	3046(4)	7798(2)	105(1)
O6	6012(3)	3055(3)	8226(1)	68(1)
O7	3429(3)	11858(3)	8834(1)	65(1)
C1	4035(4)	9365(4)	8781(2)	51(1)
C2	5785(4)	9669(4)	8843(2)	51(1)
C3	6694(4)	8536(4)	9138(1)	45(1)
C4	5978(4)	7909(4)	9709(1)	42(1)
C5	6818(4)	6485(4)	9741(1)	45(1)
C6	7847(4)	6503(4)	9178(1)	42(1)
C7	9127(4)	7589(4)	9304(1)	48(1)
C8	8426(4)	8808(4)	9289(2)	51(1)
C9	8191(4)	5088(4)	8930(1)	43(1)
C10	8656(4)	5009(4)	8286(2)	55(1)
C11	9469(5)	3581(5)	8251(2)	73(1)
C12	9773(5)	3033(4)	8856(2)	69(1)
C13	9513(4)	4288(4)	9246(2)	52(1)

C14	7248(4)	5120(5)	7864(2)	62(1)
C15	5854(5)	4196(5)	7992(2)	61(1)
C16	4241(6)	4736(6)	7845(3)	109(2)
C17	9908(5)	6102(5)	8124(2)	71(1)
C18	3102(5)	10592(4)	8536(2)	58(1)

Table 5.3 Bond lengths [Å] and angles [°] for **2.13**.

S1-O1	**1.426(3)**	**H2A-C2-H2B**	**107.7**
S1-O2	1.427(2)	O4-C3-C2	112.9(3)
S1-O3	1.576(3)	O4-C3-C8	101.8(3)
S1-C4	1.776(3)	C2-C3-C8	118.0(3)
O3-C1	1.475(4)	O4-C3-C4	99.8(3)
O4-C3	1.436(4)	C2-C3-C4	117.6(3)
O4-C6	1.452(4)	C8-C3-C4	104.1(3)
O5-C11	1.210(5)	C5-C4-C3	101.6(2)
O6-C15	1.229(5)	C5-C4-S1	111.5(2)
O7-C18	1.422(4)	C3-C4-S1	111.7(2)
O7-H7O	0.84	C5-C4-H4	110.6
C1-C2	1.510(5)	C3-C4-H4	110.6
C1-C18	1.523(5)	S1-C4-H4	110.6
C1-H1	1.00	C4-C5-C6	101.9(3)
C2-C3	1.493(5)	C4-C5-H5A	111.4
C2-H2A	0.99	C6-C5-H5A	111.4
C2-H2B	0.99	C4-C5-H5B	111.4

C3-C8	1.523(5)	C6-C5-H5B	111.4
C3-C4	1.576(5)	H5A-C5-H5B	109.3
C4-C5	1.540(5)	O4-C6-C9	110.7(3)
C4-H4	1.0000	O4-C6-C7	100.8(3)
C5-C6	1.571(4)	C9-C6-C7	123.4(3)
C5-H5A	0.99	O4-C6-C5	100.0(2)
C5-H5B	0.99	C9-C6-C5	114.6(3)
C6-C9	1.502(5)	C7-C6-C5	104.0(3)
C6-C7	1.526(5)	C8-C7-C6	106.6(3)
C7-C8	1.310(5)	C8-C7-H7	126.7
C7-H7	0.95	C6-C7-H7	126.7
C8-H8	0.95	C7-C8-C3	106.6(3)
C9-C13	1.535(5)	C7-C8-H8	126.7
C9-C10	1.547(5)	C3-C8-H8	126.7
C9-H9	1.0000	C6-C9-C13	114.2(3)
C10-C11	1.533(6)	C6-C9-C10	117.7(3)
C10-C17	1.535(5)	C13-C9-C10	104.4(3)
C10-C14	1.538(5)	C6-C9-H9	106.6
C11-C12	1.516(6)	C13-C9-H9	106.6
C12-C13	1.522(5)	C10-C9-H9	106.6
C12-H12A	0.99	C11-C10-C17	106.7(3)
C12-H12B	0.99	C11-C10-C14	111.8(3)
C13-H13A	0.99	C17-C10-C14	109.1(3)
C13-H13B	0.99	C11-C10-C9	102.2(3)
C14-C15	1.502(6)	C17-C10-C9	112.4(3)
C14-H14A	0.99	C14-C10-C9	114.3(3)
C14-H14B	0.99	O5-C11-C12	127.7(4)

C15-C16	1.492(6)	O5-C11-C10	122.8(5)
C16-H16A	0.98	C12-C11-C10	109.5(3)
C16-H16B	0.98	C11-C12-C13	104.6(3)
C16-H16C	0.98	C11-C12-H12A	110.8
C17-H17A	0.98	C13-C12-H12A	110.8
C17-H17B	0.98	C11-C12-H12B	110.8
C17-H17C	0.98	C13-C12-H12B	110.8
C18-H18A	0.99	H12A-C12-H12B	108.9
C18-H18B	0.99	C12-C13-C9	102.6(3)
O1-S1-O2	118.31	C12-C13-H13A	111.3
O1-S1-O3	109.61	C9-C13-H13A	111.3
O2-S1-O3	104.78	C12-C13-H13B	111.3
O1-S1-C4	111.12	C9-C13-H13B	111.3
O2-S1-C4	110.05	H13A-C13-H13B	109.2
O3-S1-C4	101.45	C15-C14-C10	115.8(3)
C1-O3-S1	115.2(2)	C15-C14-H14A	108.3
C3-O4-C6	98.0(2)	C10-C14-H14A	108.3
C18-O7-H7O	109.5	C15-C14-H14B	108.3
O3-C1-C2	107.9(3)	C10-C14-H14B	108.3
O3-C1-C18	105.4(3)	H14A-C14-H14B	107.4
C2-C1-C18	112.8(3)	O6-C15-C16	120.4(4)
O3-C1-H1	110.2	O6-C15-C14	122.0(4)
C2-C1-H1	110.2	C16-C15-C14	117.6(4)
C18-C1-H1	110.2	C15-C16-H16A	109.5
C3-C2-C1	113.7(3)	C15-C16-H16B	109.5
C3-C2-H2A	108.8	H16A-C16-H16B	109.5
C1-C2-H2A	108.8	C15-C16-H16C	109.5

C3-C2-H2B	108.8	H16A-C16-H16C	109.5
C1-C2-H2B	108.8	H16B-C16-H16C	109.5

Table 5.4 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **2.13**.

The anisotropic displacement factor exponent takes the form: -2p2[h2 a*2U11 + ... + 2 h k a* b* U12]

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	40(1)	62(1)	46(1)	3(1)	8(1)	6(1)
O1	49(2)	57(2)	65(2)	-4(1)	-1(1)	1(1)
O2	52(2)	82(2)	48(2)	8(1)	19(1)	8(1)
O3	43(1)	65(2)	46(2)	5(1)	11(1)	13(1)
O4	40(1)	58(2)	34(1)	5(1)	4(1)	14(1)
O5	77(2)	129(3)	108(3)	-60(2)	18(2)	20(2)
O6	66(2)	70(2)	67(2)	-8(2)	-9(1)	8(2)
O7	57(2)	69(2)	68(2)	5(2)	4(1)	17(1)
C1	49(2)	66(3)	39(2)	1(2)	5(2)	17(2)
C2	49(2)	59(3)	46(2)	8(2)	11(2)	18(2)
C3	42(2)	49(2)	43(2)	0(2)	9(2)	10(2)
C4	39(2)	53(2)	34(2)	2(2)	5(2)	4(2)
C5	43(2)	58(2)	34(2)	2(2)	1(2)	6(2)
C6	39(2)	49(2)	38(2)	3(2)	2(2)	9(2)
C7	38(2)	59(3)	47(2)	4(2)	4(2)	5(2)
C8	43(2)	52(3)	58(2)	7(2)	10(2)	2(2)
C9	36(2)	53(2)	41(2)	0(2)	3(2)	8(2)
C10	49(2)	70(3)	47(2)	-13(2)	9(2)	8(2)
C11	50(2)	86(3)	83(3)	-31(3)	12(2)	5(2)
C12	48(2)	61(3)	99(3)	-8(3)	1(2)	18(2)
C13	46(2)	51(2)	61(2)	-1(2)	-3(2)	11(2)

C14	62(3)	86(3)	38(2)	-4(2)	8(2)	8(2)
C15	69(3)	66(3)	48(2)	-10(2)	-8(2)	13(2)
C16	75(3)	112(5)	140(5)	40(4)	-33(3)	9(3)
C17	65(3)	95(4)	54(3)	-6(2)	25(2)	0(2)
C18	54(2)	70(3)	50(2)	-3(2)	1(2)	16(2)

Table 5.5 Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **2.13**.

	x	y	z	U(eq)
H7O	4126	12308	8656	97
H1	3866	8517	8537	62
H2A	6236	9817	8454	62
H2B	5921	10545	9063	62
H4	6271	8499	10049	51
H5A	6045	5707	9735	54
H5B	7490	6410	10091	54
H7	10218	7414	9379	58
H8	8906	9689	9359	61
H9	7201	4524	8973	52
H12A	10871	2678	8894	83
H12B	9024	2273	8950	83
H13A	10488	4859	9280	63
H13B	9172	3996	9636	63
H14A	6877	6100	7859	74
H14B	7631	4898	7471	74
H16A	3477	3966	7852	164
H16B	4255	5153	7459	164
H16C	3932	5444	8128	164
H17A	10261	5938	7727	106
H17B	10816	6027	8388	106

H17C	9446	7037	8153	106
H18A	3369	10709	8124	70
H18B	1954	10387	8561	70

Table 5.6 Torsion angles [°] for **2.13**.

O1-S1-O3-C1	**-55.1(3)**	**C5-C6-C7-C8**	**-71.9(3)**
O2-S1-O3-C1	177.0(2)	C6-C7-C8-C3	-1.5(4)
C4-S1-O3-C1	62.5(3)	O4-C3-C8-C7	-29.4(4)
S1-O3-C1-C2	-72.3(3)	C2-C3-C8-C7	-153.5(3)
S1-O3-C1-C18	166.9(2)	C4-C3-C8-C7	74.0(3)
O3-C1-C2-C3	58.0(4)	O4-C6-C9-C13	169.6(3)
C18-C1-C2-C3	174.0(3)	C7-C6-C9-C13	50.3(4)
C6-O4-C3-C2	174.9(3)	C5-C6-C9-C13	-78.2(4)
C6-O4-C3-C8	47.4(3)	O4-C6-C9-C10	46.7(4)
C6-O4-C3-C4	-59.4(3)	C7-C6-C9-C10	-72.6(4)
C1-C2-C3-O4	69.0(4)	C5-C6-C9-C10	158.9(3)
C1-C2-C3-C8	-172.6(3)	C6-C9-C10-C11	160.4(3)
C1-C2-C3-C4	-46.4(4)	C13-C9-C10-C11	32.7(4)
O4-C3-C4-C5	36.4(3)	C6-C9-C10-C17	46.4(4)
C2-C3-C4-C5	158.8(3)	C13-C9-C10-C17	-81.3(4)
C8-C3-C4-C5	-68.5(3)	C6-C9-C10-C14	-78.6(4)
O4-C3-C4-S1	-82.5(3)	C13-C9-C10-C14	153.7(3)
C2-C3-C4-S1	39.8(4)	C17-C10-C11-O5	-71.1(5)
C8-C3-C4-S1	172.6(2)	C14-C10-C11-O5	48.1(5)

O1-S1-C4-C5	-39.7(3)	C9-C10-C11-O5	170.7(4)
O2-S1-C4-C5	93.3(2)	C17-C10-C11-C12	106.3(4)
O3-S1-C4-C5	-156.2(2)	C14-C10-C11-C12	-134.5(3)
O1-S1-C4-C3	73.1(3)	C9-C10-C11-C12	-11.8(4)
O2-S1-C4-C3	-153.9(2)	O5-C11-C12-C13	163.7(4)
O3-S1-C4-C3	-43.3(3)	C10-C11-C12-C13	-13.6(4)
C3-C4-C5-C6	-1.3(3)	C11-C12-C13-C9	33.6(4)
S1-C4-C5-C6	117.7(2)	C6-C9-C13-C12	-171.7(3)
C3-O4-C6-C9	179.8(3)	C10-C9-C13-C12	-41.8(4)
C3-O4-C6-C7	-48.0(3)	C11-C10-C14-C15	66.9(4)
C3-O4-C6-C5	58.6(3)	C17-C10-C14-C15	-175.3(3)
C4-C5-C6-O4	-33.7(3)	C9-C10-C14-C15	-48.5(5)
C4-C5-C6-C9	-152.1(3)	C10-C14-C15-O6	-30.9(5)
C4-C5-C6-C7	70.3(3)	C10-C14-C15-C16	146.6(4)
O4-C6-C7-C8	31.4(3)	O3-C1-C18-O7	67.1(4)
C9-C6-C7-C8	155.2(3)	C2-C1-C18-O7	–50.3(4)

Table 5.7 Hydrogen bonds for **2.13** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O7-H7O...O6#1	0.84	2.01	2.843(4)	170

Symmetry transformations used to generate equivalent atoms: #1 x,y+1,z

Figure 5.2 View of molecule 1 of **2.14** showing the atom labeling scheme.

Displacement ellipsoids are scaled to the 50% probability level.

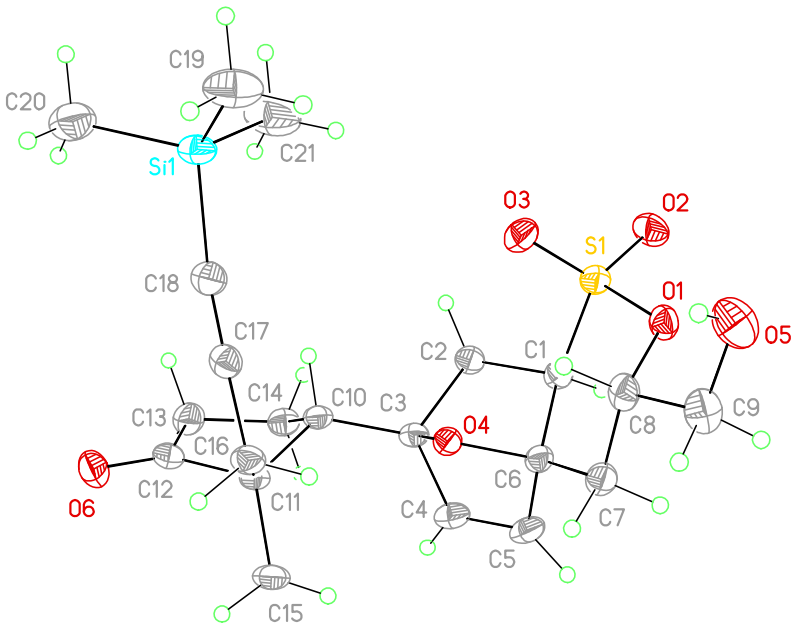
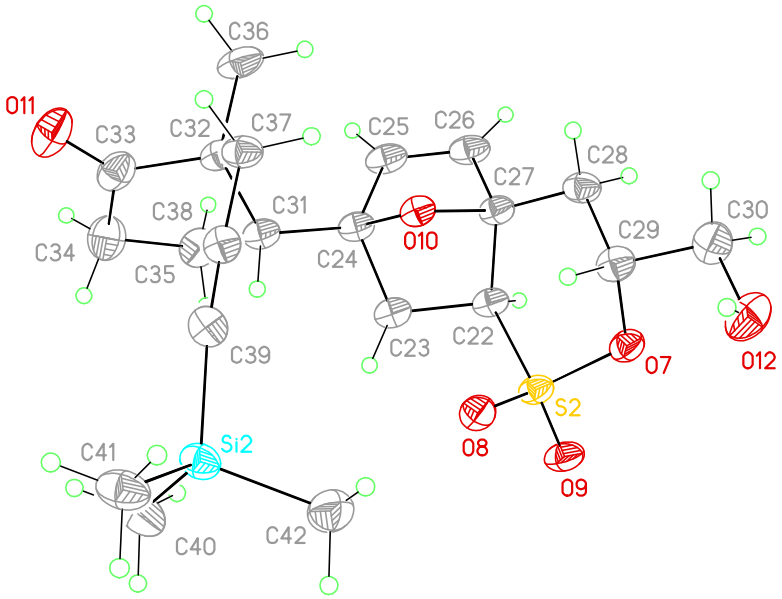
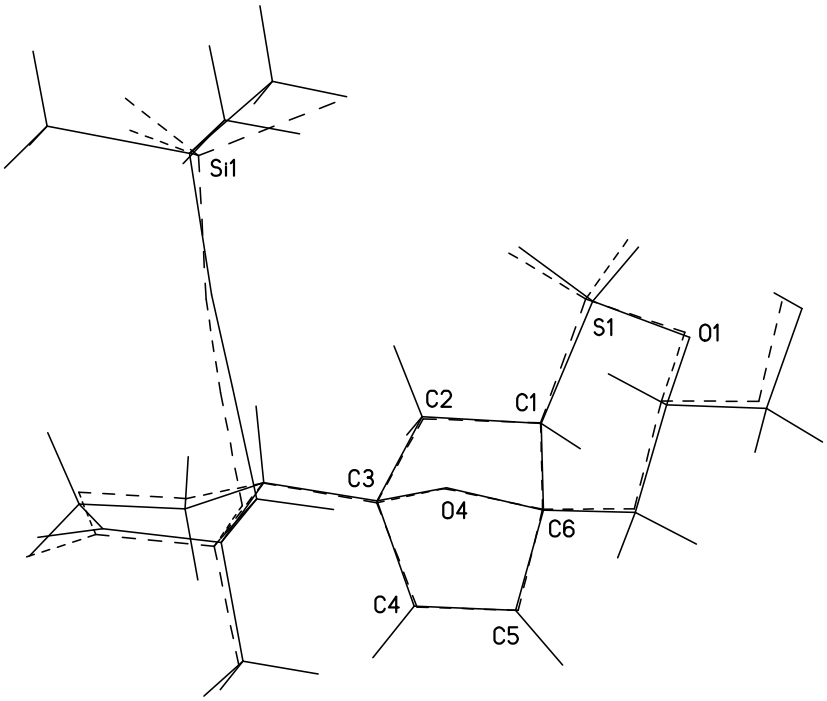


Figure 5.3 View of molecule 2 of **2.14** showing the atom labeling scheme.

Displacement ellipsoids are scaled to the 50% probability level.

Figure 5.4 View of the fit by least-squares of selected atoms of molecule 2 (dashed lines) onto the equivalent atoms of molecule 1 (solid lines). The coordinates of molecule 2 were inverted prior to the fit. Atoms of molecule 1 used in the fit are labeled.





X-ray Experimental for $C_{21}H_{30}SSiO_6$: Crystals grew as colorless prisms by slow evaporation from ethyl acetate, pentane and chloroform. The data crystal was cut from a larger crystal and had approximate dimensions; 0.36 x 0.26 x 0.17 mm. The data were collected on a Rigaku AFC12 diffractometer with a Saturn 724+ CCD using a graphite monochromator with MoKα radiation (λ = 0.71073Å). A total of 1398 frames of data were collected using ω-scans with a scan range of 0.5° and a counting time of 10 seconds per frame. The data were collected at 100 K using a Rigaku XStream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using the Rigaku Americas Corporation's Crystal Clear version 1.40.[637] The structure was solved by direct methods using SIR97[638] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[639] Structure analysis was

aided by use of the programs PLATON98[640] and WinGX.[641] The hydrogen atoms were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0564*P)^2 + (1.3034*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.134, with R(F) equal to 0.0487 and a goodness of fit, S, = 1.06. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below.[636] The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[637] All figures were generated using SHELXTL/PC.[638] Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

Table 5.8 Crystal data and structure refinement for **2.14**.

Empirical formula	**C21 H30 O6 S Si**	
Formula weight	438.60	
Temperature	100(2) K	
Wavelength	0.71075 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 11.8357 Å	α= 96.830(2)°.
	b = 12.829(2) Å	β= 98.351(2)°.
	c = 17.194(2) Å	γ = 115.442(3)°.

Volume	2284.0(5) $Å^3$
Z	4
Density (calculated)	1.275 Mg/m^3
Absorption coefficient	0.227 mm^{-1}
F	936
Crystal size	0.36 x 0.26 x 0.17 mm
Theta range for data collection	3.09 to 27.48°.
Index ranges	-15<=h<=15,-16<=k<=16,-22<=l<=22
Reflections collected	36450
Independent reflections	10405 [R(int) = 0.0752]
Completeness to theta = 27.48°	99.2 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00 and 0.809
Refinement method	Full-matrix least-squares on F^2

Data / restraints / parameters	10405 / 0 / 533
Goodness-of-fit on F^2	1.060
Final R indices [I>2sigma(I)]	R1 = 0.0487, wR2 = 0.1283
R indices (all data)	R1 = 0.0567, wR2 = 0.1338
Largest diff. peak and hole	0.651 and -0.370 e.$Å^{-3}$

Table 5.9 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **2.14**.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S1	8781(1)	4254(1)	6266(1)	23(1)
Si1	8017(1)	8061(1)	4594(1)	25(1)
O1	7938(1)	3763(1)	6891(1)	23(1)
O2	9996(1)	4327(1)	6601(1)	32(1)
O3	8718(1)	5291(1)	6094(1)	30(1)
O4	6226(1)	3265(1)	4827(1)	19(1)
O5	6729(2)	4280(2)	8059(1)	39(1)
O6	4856(1)	4602(1)	2152(1)	34(1)
C1	8000(2)	3069(2)	5416(1)	21(1)
C2	8210(2)	3498(2)	4622(1)	22(1)
C3	6795(2)	3087(2)	4167(1)	19(1)
C4	6206(2)	1745(2)	3959(1)	25(1)
C5	6046(2)	1392(2)	4641(1)	25(1)
C6	6491(2)	2496(2)	5282(1)	20(1)
C7	5909(2)	2385(2)	6006(1)	23(1)

C8	6574(2)	3485(2)	6663(1)	23(1)
C9	6068(2)	3298(2)	7417(1)	30(1)
C10	6667(2)	3795(2)	3549(1)	19(1)
C11	5322(2)	3683(2)	3232(1)	21(1)
C12	5520(2)	4208(2)	2483(1)	25(1)
C13	6656(2)	4160(2)	2213(1)	29(1)
C14	7108(2)	3523(2)	2783(1)	24(1)
C15	4273(2)	2402(2)	2946(1)	27(1)
C16	4865(2)	4355(2)	3809(1)	24(1)
C17	5790(2)	5605(2)	4070(1)	23(1)
C18	6613(2)	6608(2)	4261(1)	26(1)
C19	7931(2)	8798(2)	5558(2)	45(1)
C20	8012(2)	8942(2)	3804(2)	44(1)
C21	9447(2)	7790(2)	4693(2)	51(1)
S2	12202(1)	9169(1)	2553(1)	24(1)
Si2	9273(1)	11913(1)	1764(1)	27(1)
O7	13328(1)	9317(1)	2112(1)	26(1)
O8	11758(1)	10007(1)	2389(1)	28(1)
O9	12689(1)	9176(1)	3365(1)	32(1)

O10	10053(1)	7994(1)	894(1)	22(1)
O11	5363(2)	7717(2)	-230(1)	43(1)
O12	15104(2)	10927(1)	1309(1)	42(1)
C22	11014(2)	7721(2)	2073(1)	23(1)
C23	9664(2)	7552(2)	2132(1)	26(1)
C24	8995(2)	7270(2)	1223(1)	23(1)
C25	8841(2)	6041(2)	906(1)	28(1)
C26	9999(2)	6179(2)	867(1)	29(1)
C27	10891(2)	7493(2)	1140(1)	24(1)
C28	12108(2)	7993(2)	836(1)	27(1)
C29	13016(2)	9264(2)	1240(1)	27(1)
C30	14273(2)	9721(2)	971(1)	36(1)
C31	7917(2)	7607(2)	1080(1)	25(1)
C32	7354(2)	7598(2)	212(1)	26(1)
C33	6046(2)	7540(2)	280(1)	33(1)
C34	5741(2)	7227(2)	1065(2)	39(1)
C35	6744(2)	6852(2)	1405(1)	33(1)
C36	7070(2)	6481(2)	-394(1)	38(1)
C37	8158(2)	8691(2)	-114(1)	27(1)

C38	8467(2)	9800(2)	424(1)	25(1)
C39	8739(2)	10678(2)	910(1)	27(1)
C40	8278(3)	11318(2)	2498(2)	42(1)
C41	9054(2)	13148(2)	1423(1)	35(1)
C42	10992(2)	12402(2)	2206(2)	44(1)

Table 5.10 Bond lengths [Å] and angles [°] for **2.14**.

S1-O3	**1.4273**	**C36-H36A**	**0.98**
S1-O2	1.4283	C36-H36B	0.98
S1-O1	1.5749	C36-H36C	0.98
S1-C1	1.7810	C37-C38	1.468(3)
Si1-C18	1.836(2)	C37-H37A	0.99
Si1-C19	1.846(2)	C37-H37B	0.99
Si1-C21	1.858(2)	C38-C39	1.206(3)
Si1-C20	1.868(3)	C40-H40A	0.98
O1-C8	1.474(2)	C40-H40B	0.98
O4-C6	1.435(2)	C40-H40C	0.98
O4-C3	1.443(2)	C41-H41A	0.98

O5-C9	1.411(3)	C41-H41B	0.98
O5-H5	0.84	C41-H41C	0.98
O6-C12	1.215(2)	C42-H42A	0.98
C1-C2	1.545(2)	C42-H42B	0.98
C1-C6	1.580(2)	C42-H42C	0.98
C1-H1	1	O3-S1-O2	119.16(9)
C2-C3	1.567(2)	O3-S1-O1	109.60(8)
C2-H2A	0.99	O2-S1-O1	104.29(8)
C2-H2B	0.99	O3-S1-C1	111.17(9)
C3-C10	1.510(2)	O2-S1-C1	109.20(9)
C3-C4	1.527(2)	O1-S1-C1	101.81(8)
C4-C5	1.315(3)	C18-Si1-C19	109.40
C4-H4	0.95	C18-Si1-C21	106.31
C5-C6	1.523(3)	C19-Si1-C21	111.88
C5-H5A	0.95	C18-Si1-C20	108.18
C6-C7	1.502(3)	C19-Si1-C20	110.69
C7-C8	1.515(3)	C21-Si1-C20	110.22
C7-H7A	0.99	C8-O1-S1	116.56
C7-H7B	0.99	C6-O4-C3	97.59

C8-C9	1.508(3)	C9-O5-H5	109.5
C8-H8	1	C2-C1-C6	101.41
C9-H9A	0.99	C2-C1-S1	111.96
C9-H9B	0.99	C6-C1-S1	112.32
C10-C14	1.540(3)	C2-C1-H1	110.3
C10-C11	1.545(2)	C6-C1-H1	110.3
C10-H10	1	S1-C1-H1	110.3
C11-C12	1.525(3)	C1-C2-C3	101.32
C11-C15	1.537(2)	C1-C2-H2A	111.5
C11-C16	1.540(3)	C3-C2-H2A	111.5
C12-C13	1.509(3)	C1-C2-H2B	111.5
C13-C14	1.526(3)	C3-C2-H2B	111.5
C13-H13A	0.99	H2A-C2-H2B	109.3
C13-H13B	0.99	O4-C3-C10	111.32
C14-H14A	0.99	O4-C3-C4	101.41
C14-H14B	0.99	C10-C3-C4	121.77
C15-H15A	0.98	O4-C3-C2	100.78
C15-H15B	0.98	C10-C3-C2	114.17
C15-H15C	0.98	C4-C3-C2	104.73

C16-C17	1.466(3)	C5-C4-C3	105.81
C16-H16A	0.99	C5-C4-H4	127.1
C16-H16B	0.99	C3-C4-H4	127.1
C17-C18	1.201(3)	C4-C5-C6	106.54
C19-H19A	0.98	C4-C5-H5A	126.7
C19-H19B	0.98	C6-C5-H5A	126.7
C19-H19C	0.98	O4-C6-C7	112.03
C20-H20A	0.98	O4-C6-C5	101.87
C20-H20B	0.98	C7-C6-C5	118.28
C20-H20C	0.98	O4-C6-C1	100.62
C21-H21A	0.98	C7-C6-C1	118.35
C21-H21B	0.98	C5-C6-C1	103.08
C21-H21C	0.98	C6-C7-C8	113.58
S2-O8	1.4230	C6-C7-H7A	108.8
S2-O9	1.4277	C8-C7-H7A	108.8
S2-O7	1.5808	C6-C7-H7B	108.8
S2-C22	1.7789	C8-C7-H7B	108.8
Si2-C39	1.840(2)	H7A-C7-H7B	107.7
Si2-C41	1.857(2)	O1-C8-C9	105.70

Si2-C42	1.858(3)	O1-C8-C7	108.11
Si2-C40	1.858(2)	C9-C8-C7	112.21
O7-C29	1.477(2)	O1-C8-H8	110.2
O10-C27	1.437(2)	C9-C8-H8	110.2
O10-C24	1.444(2)	C7-C8-H8	110.2
O11-C33	1.214(3)	O5-C9-C8	113.57
O12-C30	1.419(3)	O5-C9-H9A	108.9
O12-H12	0.84	C8-C9-H9A	108.9
C22-C23	1.538(3)	O5-C9-H9B	108.9
C22-C27	1.569(3)	C8-C9-H9B	108.9
C22-H22	1	H9A-C9-H9B	107.7
C23-C24	1.568(3)	C3-C10-C14	113.48
C23-H23A	0.99	C3-C10-C11	117.72
C23-H23B	0.99	C14-C10-C11	104.11
C24-C31	1.510(3)	C3-C10-H10	107
C24-C25	1.528(3)	C14-C10-H10	107
C25-C26	1.317(3)	C11-C10-H10	107
C25-H25	0.95	C12-C11-C15	106.55
C26-C27	1.522(3)	C12-C11-C16	110.89

C26-H26	0.95	C15-C11-C16	109.00
C27-C28	1.505(3)	C12-C11-C10	100.96
C28-C29	1.518(3)	C15-C11-C10	113.65
C28-H28A	0.99	C16-C11-C10	115.22
C28-H28B	0.99	O6-C12-C13	125.11
C29-C30	1.511(3)	O6-C12-C11	124.94
C29-H29	1	C13-C12-C11	109.95
C30-H30A	0.99	C12-C13-C14	105.26
C30-H30B	0.99	C12-C13-H13A	110.7
C31-C32	1.540(3)	C14-C13-H13A	110.7
C31-C35	1.542(3)	C12-C13-H13B	110.7
C31-H31	1	C14-C13-H13B	110.7
C32-C33	1.540(3)	H13A-C13-H13B	108.8
C32-C36	1.543(3)	C13-C14-C10	102.86
C32-C37	1.544(3)	C13-C14-H14A	111.2
C33-C34	1.502(3)	C10-C14-H14A	111.2
C34-C35	1.529(3)	C13-C14-H14B	111.2
C34-H34A	0.99	C10-C14-H14B	111.2
C34-H34B	0.99	H14A-C14-H14B	109.1

C35-H35A	0.99	C11-C15-H15A	109.5	
C35-H35B	0.99			

Table 5.11 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **2.14**.

The anisotropic displacement factor exponent takes the form: -2p2[h2 a*2U11 + ... + 2 h k a* b* U12]

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	18(1)	22(1)	25(1)	7(1)	3(1)	7(1)
Si1	20(1)	20(1)	31(1)	-2(1)	3(1)	8(1)
O1	21(1)	28(1)	24(1)	9(1)	4(1)	13(1)
O2	17(1)	38(1)	34(1)	9(1)	1(1)	8(1)
O3	37(1)	20(1)	31(1)	7(1)	6(1)	11(1)
O4	15(1)	19(1)	23(1)	6(1)	5(1)	8(1)
O5	41(1)	50(1)	29(1)	2(1)	7(1)	25(1)
O6	36(1)	32(1)	28(1)	5(1)	-6(1)	16(1)
C1	17(1)	20(1)	27(1)	7(1)	5(1)	9(1)
C2	16(1)	24(1)	25(1)	6(1)	5(1)	8(1)
C3	14(1)	16(1)	22(1)	3(1)	4(1)	5(1)
C4	21(1)	17(1)	33(1)	1(1)	6(1)	6(1)
C5	22(1)	16(1)	37(1)	7(1)	8(1)	6(1)

C6	16(1)	18(1)	26(1)	8(1)	4(1)	8(1)
C7	18(1)	26(1)	28(1)	10(1)	7(1)	10(1)
C8	21(1)	29(1)	28(1)	11(1)	7(1)	16(1)
C9	30(1)	40(1)	28(1)	10(1)	10(1)	20(1)
C10	15(1)	15(1)	23(1)	3(1)	3(1)	4(1)
C11	16(1)	16(1)	26(1)	3(1)	1(1)	4(1)
C12	25(1)	18(1)	24(1)	0(1)	-4(1)	4(1)
C13	31(1)	28(1)	24(1)	8(1)	7(1)	10(1)
C14	21(1)	23(1)	26(1)	5(1)	7(1)	7(1)
C15	17(1)	19(1)	37(1)	1(1)	0(1)	3(1)
C16	16(1)	21(1)	32(1)	4(1)	3(1)	8(1)
C17	22(1)	24(1)	25(1)	3(1)	3(1)	13(1)
C18	24(1)	24(1)	30(1)	2(1)	3(1)	13(1)
C19	39(1)	37(1)	44(1)	-8(1)	11(1)	7(1)
C20	41(1)	34(1)	44(1)	9(1)	7(1)	5(1)
C21	25(1)	43(1)	75(2)	-10(1)	0(1)	16(1)
S2	28(1)	19(1)	23(1)	1(1)	-1(1)	12(1)

Si2	35(1)	23(1)	26(1)	5(1)	7(1)	16(1)
O7	27(1)	25(1)	25(1)	3(1)	-1(1)	13(1)
O8	29(1)	19(1)	34(1)	3(1)	1(1)	12(1)
O9	39(1)	30(1)	22(1)	-1(1)	-4(1)	17(1)
O10	27(1)	18(1)	21(1)	6(1)	2(1)	10(1)
O11	35(1)	41(1)	48(1)	11(1)	-6(1)	16(1)
O12	32(1)	38(1)	41(1)	10(1)	1(1)	6(1)
C22	31(1)	16(1)	21(1)	4(1)	0(1)	11(1)
C23	31(1)	20(1)	22(1)	6(1)	3(1)	9(1)
C24	29(1)	16(1)	22(1)	4(1)	3(1)	7(1)
C25	38(1)	16(1)	24(1)	3(1)	0(1)	9(1)
C26	40(1)	18(1)	25(1)	1(1)	0(1)	13(1)
C27	30(1)	18(1)	23(1)	2(1)	0(1)	13(1)
C28	35(1)	24(1)	23(1)	2(1)	3(1)	16(1)
C29	33(1)	25(1)	25(1)	6(1)	2(1)	15(1)
C30	32(1)	36(1)	38(1)	7(1)	6(1)	15(1)
C31	30(1)	19(1)	22(1)	4(1)	3(1)	8(1)

C32	31(1)	21(1)	22(1)	2(1)	-1(1)	11(1)
C33	29(1)	23(1)	38(1)	3(1)	-2(1)	8(1)
C34	32(1)	39(1)	46(1)	13(1)	10(1)	14(1)
C35	33(1)	30(1)	36(1)	12(1)	9(1)	11(1)
C36	49(1)	28(1)	27(1)	-5(1)	-9(1)	18(1)
C37	37(1)	25(1)	20(1)	5(1)	4(1)	17(1)
C38	28(1)	23(1)	25(1)	10(1)	6(1)	13(1)
C39	31(1)	24(1)	30(1)	10(1)	10(1)	13(1)
C40	65(2)	43(1)	40(1)	20(1)	26(1)	36(1)
C41	55(1)	28(1)	28(1)	6(1)	9(1)	23(1)
C42	41(1)	38(1)	46(1)	-5(1)	-2(1)	20(1)

Table 5.12 Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **2.14**.

	x	y	z	U(eq)
H5	6388	4733	8037	59
H1	8301	2457	5470	25
H2A	8636	3117	4325	26
H2B	8722	4365	4717	26
H4	5998	1263	3444	30
H5A	5717	602	4718	30
H7A	5939	1716	6226	28
H7B	4996	2201	5839	28
H8	6489	4157	6469	28
H9A	5150	3112	7297	36
H9B	6128	2608	7586	36
H10	7239	4644	3799	23
H13A	7344	4965	2249	35
H13B	6403	3721	1651	35

H14A	8051	3835	2889	29
H14B	6700	2664	2564	29
H15A	3483	2392	2669	41
H15B	4111	2027	3410	41
H15C	4555	1970	2576	41
H16A	4031	4286	3538	28
H16B	4732	3990	4286	28
H19A	7141	8885	5489	68
H19B	8674	9578	5733	68
H19C	7932	8322	5963	68
H20A	8008	8515	3291	67
H20B	8781	9706	3957	67
H20C	7246	9067	3751	67
H21A	9445	7338	5114	76
H21B	10226	8545	4834	76
H21C	9423	7343	4181	76
H12	14918	11348	1029	62

H22	11198	7120	2309	28
H23A	9691	8278	2425	31
H23B	9228	6890	2397	31
H25	8067	5324	765	34
H26	10230	5577	701	35
H28A	11886	7945	251	32
H28B	12555	7504	922	32
H29	12594	9776	1134	33
H30A	14714	9246	1121	43
H30B	14093	9612	379	43
H31	8264	8433	1386	30
H34A	4865	6573	979	47
H34B	5806	7915	1432	47
H35A	6451	6000	1211	40
H35B	6941	7028	2000	40
H36A	6553	5780	-196	56
H36B	7879	6480	-457	56

H36C	6598	6475	-914	56
H37A	8965	8675	-188	32
H37B	7677	8657	-646	32
H40A	7377	11076	2261	63
H40B	8562	11928	2984	63
H40C	8371	10635	2637	63
H41A	9551	13408	1013	53
H41B	9353	13805	1881	53
H41C	8144	12882	1195	53
H42A	11114	11721	2316	65
H42B	11258	12979	2708	65
H42C	11512	12764	1828	65

Table 5.13 Torsion angles [°] for **2.14**.

O3-S1-O1-C8	**57.03**	**O8-S2-O7-C29**	**-54.08**
O2-S1-O1-C8	-174.33	O9-S2-O7-C29	176.52
C1-S1-O1-C8	-60.75	C22-S2-O7-C29	62.44

O3-S1-C1-C2	37.10	O8-S2-C22-C23	-40.31
O2-S1-C1-C2	-96.38	O9-S2-C22-C23	93.11
O1-S1-C1-C2	153.76	O7-S2-C22-C23	-156.40
O3-S1-C1-C6	-76.24	O8-S2-C22-C27	72.82
O2-S1-C1-C6	150.28	O9-S2-C22-C27	-153.75
O1-S1-C1-C6	40.41	O7-S2-C22-C27	-43.26
C6-C1-C2-C3	-0.62	C27-C22-C23-C24	-0.65
S1-C1-C2-C3	-120.57	S2-C22-C23-C24	118.90
C6-O4-C3-C10	179.55	C27-O10-C24-C31	178.53
C6-O4-C3-C4	48.60	C27-O10-C24-C25	-48.93
C6-O4-C3-C2	-59.01	C27-O10-C24-C23	57.99
C1-C2-C3-O4	35.46	C22-C23-C24-O10	-34.22
C1-C2-C3-C10	154.87	C22-C23-C24-C31	-153.16
C1-C2-C3-C4	-69.51	C22-C23-C24-C25	70.29
O4-C3-C4-C5	-32.01	O10-C24-C25-C26	31.96
C10-C3-C4-C5	-156.15	C31-C24-C25-C26	156.56
C2-C3-C4-C5	72.49	C23-C24-C25-C26	-72.57

C3-C4-C5-C6	1.7(2)	C24-C25-C26-C27	-1.2(2)
C3-O4-C6-C7	-175.06	C24-O10-C27-C28	175.72
C3-O4-C6-C5	-47.66	C24-O10-C27-C26	48.44
C3-O4-C6-C1	58.28	C24-O10-C27-C22	-58.23
C4-C5-C6-O4	29.42	C25-C26-C27-O10	-30.1(2)
C4-C5-C6-C7	152.67	C25-C26-C27-C28	-153.87
C4-C5-C6-C1	-74.59	C25-C26-C27-C22	74.12
C2-C1-C6-O4	-34.58	C23-C22-C27-O10	35.48
S1-C1-C6-O4	85.11	S2-C22-C27-O10	-83.40
C2-C1-C6-C7	-156.91	C23-C22-C27-C28	158.19
S1-C1-C6-C7	-37.22	S2-C22-C27-C28	39.3(2)
C2-C1-C6-C5	70.40	C23-C22-C27-C26	-69.55
S1-C1-C6-C5	-169.91	S2-C22-C27-C26	171.57
O4-C6-C7-C8	-71.64	O10-C27-C28-C29	70.5(2)
C5-C6-C7-C8	170.35	C26-C27-C28-C29	-171.35
C1-C6-C7-C8	44.7(2)	C22-C27-C28-C29	-45.8(2)
S1-O1-C8-C9	-167.88	S2-O7-C29-C30	166.04

S1-O1-C8-C7	71.79	S2-O7-C29-C28	-72.61
C6-C7-C8-O1	-57.14	C27-C28-C29-O7	58.2(2)
C6-C7-C8-C9	-173.31	C27-C28-C29-C30	175.75
O1-C8-C9-O5	58.2(2)	O7-C29-C30-O12	-65.0(2)
C7-C8-C9-O5	175.81	C28-C29-C30-O12	176.64
O4-C3-C10-C14	-172.91	O10-C24-C31-C32	55.5(2)
C4-C3-C10-C14	-53.5(2)	C25-C24-C31-C32	-64.5(2)
C2-C3-C10-C14	73.80	C23-C24-C31-C32	168.52
O4-C3-C10-C11	-51.0(2)	O10-C24-C31-C35	179.04
C4-C3-C10-C11	68.4(2)	C25-C24-C31-C35	59.0(2)
C2-C3-C10-C11	-164.29	C23-C24-C31-C35	-68.0(2)
C3-C10-C11-C12	-164.28	C24-C31-C32-C33	160.65
C14-C10-C11-C12	-37.68	C35-C31-C32-C33	32.68
C3-C10-C11-C15	–50.6(2)	C24-C31-C32-C36	46.4(2)
C14-C10-C11-C15	75.99	C35-C31-C32-C36	-81.6(2)
C3-C10-C11-C16	76.2(2)	C24-C31-C32-C37	-79.4(2)
C14-C10-C11-C16	-157.21	C35-C31-C32-C37	152.62

C15-C11-C12-O6	82.0(2)	C31-C32-C33-O11	166.7(2)
C16-C11-C12-O6	-36.5(2)	C36-C32-C33-O11	-73.8(2)
C10-C11-C12-O6	-159.06	C37-C32-C33-O11	44.2(3)
C15-C11-C12-C13	-97.69	C31-C32-C33-C34	-13.5(2)
C16-C11-C12-C13	143.83	C36-C32-C33-C34	105.90
C10-C11-C12-C13	21.25	C37-C32-C33-C34	-136.08
O6-C12-C13-C14	-176.33	O11-C33-C34-C35	168.8(2)
C11-C12-C13-C14	3.4(2)	C32-C33-C34-C35	-11.0(2)
C12-C13-C14-C10	-26.81	C33-C34-C35-C31	31.0(2)
C3-C10-C14-C13	169.95	C24-C31-C35-C34	-170.93
C11-C10-C14-C13	40.74	C32-C31-C35-C34	-40.2(2)
C12-C11-C16-C17	-59.7(2)	C33-C32-C37-C38	62.8(2)
C15-C11-C16-C17	-176.67	C31-C32-C37-C38	-52.0(2)
C10-C11-C16-C17	54.2(2)	C36-C32-C37-C38	179.58

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