THE TOTAL SYNTHESIS OF ALTERNARIC ACID
AND PROGRESS TOWARD THE SYNTHESIS OF SUBGLUTINOL

Rebecca A.D. Cuellar

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Approved By:

Jeffrey S. Johnson

Michael T. Crimmins

Marcey L. Waters

Michel R. Gagné

Cynthia K. Schauer

ABSTRACT

REBECCA A. D. CUELLAR: The Total Synthesis of Alternaric Acid and Progress
Toward the Synthesis of Subglutinol
(Under the direction of James P. Morken and Jeffrey S. Johnson)

The Oshima-Utimoto reaction coupling an allylic alcohol and butyl vinyl ether is utilized to construct the furan ring of the natural product subglutinol B. Methodology for the diastereoselective substitution of furans is also reported.

Methodology utilizing silylglyoxylates as latent acyl anions for use in stereoselective multicomponent reactions is developed in the form of addition of carbon nucleophiles followed by an intermolecular aldol reaction. This methodology was then applied towards the total synthesis of alternaric acid.

Dedicated to Matt and my parents.

ACKNOWLEDGEMENTS

I would first like to thank my advisor, Dr. Jeffrey S. Johnson, not only for his guidance and support, but for giving an orphaned chemist a home and a chance to continue. I would also like to thank my previous advisor, Dr. James P. Morken, for helping me begin my graduate career and for always finding an obscure paper when I thought I'd exhausted my options. I need to thank the past and present members of the Morken and Johnson groups for welcoming me and for making Carolina a great place to do chemistry. My list of thanks would not be complete without naming names: Heather Burks, Nate Fuller, Jeremy Morgan, Stéphane Trudeau, Mary Robert Garrett, Matthew Campbell, and Steve Greszler for making me want to be a better chemist.

Most of all, I'd like to thank my family and friends. First and foremost, I need to thank my husband Matt, without whom these past five years may have stomped out my sunny disposition. I have also been blessed with the most supportive family, especially my parents, Ramiro and Judy; they have been cheering on my scientific endeavors from when I was in my first Science Fair. You've taught me to never give up and that no dream is too distant. My appreciation also extends to the many friendships I've formed and maintained during my time at UNC. Your camaraderie, understanding, and support have known no bounds.

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2D NMR	two-dimensional nuclear magnetic resonance spectroscopy
Å	angstrom
Ac	acetate
acac	acetylacetonate
APCI	atmospheric pressure chemical ionization
aq.	aqueous
brine	saturated sodium chloride solution in water
n-BuLi	*n*-butyllithium
t-BuLi	*t*-butyllithium
^{13}C NMR	carbon nuclear magnetic resonance spectroscopy
CSA	camphorsulfonic acid
dba	dibenzylideneacetone
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DIBAL	diisobutylaluminum hydride
DIEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppf	bis(diphenylphosphino)ferrocene

d.r.	diastereomeric ratio
EDCI	*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide
ee	enantiomeric excess
eq.	equation
equiv.	equivalents
ESI	electrospray ionization
Et$_3$N	triethylamine
EtOAc	ethyl acetate
Fm	fluorenylmethyl
h	hours
H$_2$O$_2$	hydrogen peroxide
HMDS	hexamethyldisilazane
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
HPLC	high performance liquid chromatography
HRFABMS	high resolution fast atom bombardment mass spectrometry
IR	infrared spectroscopy
LDA	lithium diisopropylamide
MeCN	acetonitrile
MeOH	methanol
min	minutes
MLR	mixed lymphocyte reaction
MsCl	methanesulfonyl chloride
NA	not available

nc	not calculated
ND	not determined
NR	no reaction
NMO	*N*-methylmorpholine-*N*-oxide
[O]	oxidation
*p*ABSA	*para*-acetamidobenzenesulfonyl azide
PCC	pyridinium chlorochromate
pyr	pyridine
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
TBSOTf	*t*-butyldimethylsilyl trifluoromethansulfonate
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
TP	thymocyte proliferation
TPAP	tetrapropylammonium perruthenate
TsOH	*para*-toluenesulfonic acid monohydrate
UPLC	ultra high performance liquid chromatography

CHAPTER I

PROGRESS TOWARD THE SYNTHESIS OF SUBGLUTINOL

A. The Immune System and Transplantation Therapeutics

The immune system performs a variety of functions in the human body, most notably warding off foreign entities such as bacteria and viruses that may result in infection.[1] To facilitate this process, the body must first recognize Self (what actually belongs in the body, such as our own organs) versus Non-Self (what does not belong in the body, such as infectious bacteria). Cell surface proteins, called the major and minor histocompatability complex (MHC and mHC, respectively), allow the immune system to accomplish this task. Other than recognizing foreign bacteria and viruses, the most renowned exploitation of the MHC is its use in blood-typing. As is the case with DNA, each person has an MHC that is unique to them on each of their organs, including on their blood cells. However, the MHC can be grouped into categories of similar nature, for instance people with blood type A have similar type A antigens (markers) on their blood cells. The body will be more likely to recognize a transplanted organ or blood as its own (Self) if it has similar MHC on its cell surfaces. Thus the most successful type of organ and tissue transplantation is called an autograft, that is, the donor and the recipient are the same person. Unfortunately, autologous transplants are rarely possible for cases other than skin grafts and blood transfusions. In spring 2006, the United Network for Organ

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[1] Goldsby, R.A.; Kindt, T.J.; Osborne, B.A.; Kuby, J. *Immunology*. 4th Edition. New York: W.H. Freeman & Company, 2000.

Sharing—the United States organ donor/acceptor matching service organization—had nearly 99,000 people in need of an allograft transplant (from one person to another).[2] Even when the MHC between donor and acceptor is well matched between two individuals, physicians will put the recipient on immunosuppressive therapy. This is to ensure that even if an immune response is generated, it will be greatly diminished, giving the grafted organ and, more importantly the patient, the greatest chance for compatible survival. In addition to transplantation therapeutics, there are other times in which suppressing the immune system becomes desirable, such as in the cases of autoimmune disorders like rheumatoid arthritis or diabetes, where the body has begun to attack its own organs with detrimental consequences.

Currently, there are two major medications that are used to invoke immunosuppression in transplant patients: cyclosporin A (CsA) and FK-506. Both compounds have been used for decades to ward off the response of the immune system in recent organ and tissue recipients. Unfortunately, these drugs have lifetime limit dosages due to their cytotoxicity, making a strong case for development of non-cytotoxic alternative therapeutics for immunosuppression.

B. The Isolation and Characterization of the Subglutinols

In 1995, Jon Clardy and coworkers isolated two novel immunosuppressive compounds, now known as subglutinol A (**1.1)** and B (**1.2**), from a culture broth of the endophytic fungus *Fusarium subglutinans* found on the perennial twining vine

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[2] The United Network for Organ Sharing. 09 April 2008. <http://www.unos.org>

Tripterygium wildfordii (Figure 1.1).[3] The compounds were equally potent in both the mixed lymphocyte reaction (MLR) and the thymocyte (TP) assays, suggesting that the configuration at the C12 stereocenter is inconsequential with regard to their immunosuppressive capabilities and their ability to bind to the biological target. For comparison, CsA is approximately equipotent in the MLR and 10^4 times more potent in the TP assay.   One important attribute of these diterpene pyrones is the fact that they were determined to be non-cytotoxic in all examined cell lines, rendering them attractive targets for further study.

Figure 1.1. The Subglutinols

Subglutinol A (**1.1**): 12 *S*
Subglutinol B (**1.2**): 12 *R*
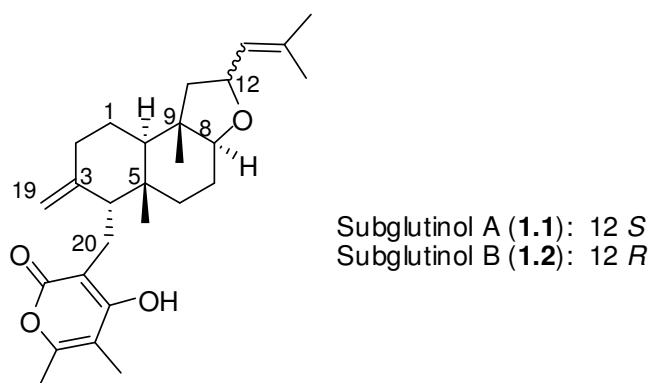
The molecular formula of both compounds was determined to be $C_{27}H_{38}O_4$ by HRFABMS, requiring nine degrees of unsaturation in its structure. Examination of the nearly identical ^1H and ^{13}C NMR of the two compounds and IR data, as well as extensive 2D NMR experiments, revealed the tentative structure as shown in Figure 1.1, differing only at the C12 stereocenter. Upon completion of the NMR studies, a single crystal X-ray analysis of subglutinol B confirmed the structure of the subglutinols, including the enol tautomerism of the α-pyrone (Figure 1.2).

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[3] Lee, J.C.; Lobkovsky, E.; Pliam, N.B.; Strobel, G.; Clardy, J. *J. Org. Chem.* **1995**, *60*, 7076-7077.

Figure 1.2. Crystal Structure of Subglutinol B
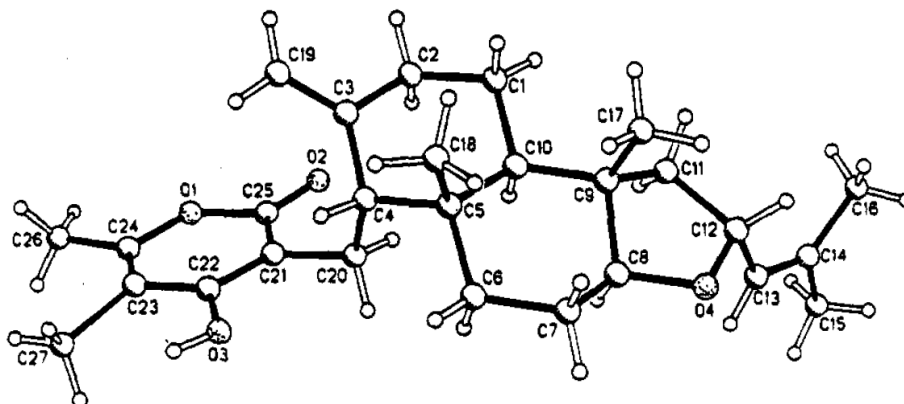
C. Related Diterpenoid Natural Products

A number of compounds with structures analogous to that of the subglutinols have also been isolated and characterized (Figure 1.2). Although to date no other group has completed the total synthesis of subglutinol, syntheses of natural products with strikingly similar architectures have been reported. In particular, sesquicillin[4] and candelalide A[5] have succumbed to total synthesis at the hands of the Danishefsky[6] and Katoh[7] labs, respectively. Sesquicillin, candelalide A, and the subglutinols all contain a methyl substituted *trans*-fused decalin ring system with an *exo*-methylene substituent and a pyrone moiety both on the *A* ring. In subglutinol and sesquicillin, the pyrone exists as the α-isomer, whereas in candelalide A this pyrone is present as the γ-pyrone methyl ether.

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[4] Engel, B.; Erkel, G.; Anke, T.; Sterner, O. *J. Antibiot.* **1998**, *51*, 518-521.

[5] Singh, S. B.; Zink, D. L.; Dombrowski, A. W.; Dezeny, G.; Bills, G. F.; Felix, J. P.; Slaughter, R. S.; Goetz, M. A. *Org. Lett.* **2001**, *3*, 247-250.

[6] Zhang, F.; Danishefsky, S.J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1434-1437.

[7] Watanabe, K.; Iwasaki, K.; Abe, T.; Inoue, M.; Ohkubo, K.; Suzuki, T.; Katoh, T. *Org. Lett.* **2005**, *7*, 3745-3748.

The *C*-ring is expanded from a tetrahydrofuran to a dihydropyran ring in candelalide A and is found in its open state as a homoprenyl group and acetate in sesquicillin. In addition, the oxygen and methyl groups are of a *trans* relationship in the closed isomers of the *C*-ring.

Figure 1.3. Diterpenoid Natural Products

Subglutinol A (**1.1**): 12 *S*
Subglutinol B (**1.2**): 12 *R*

Candelalide A (**1.3**)
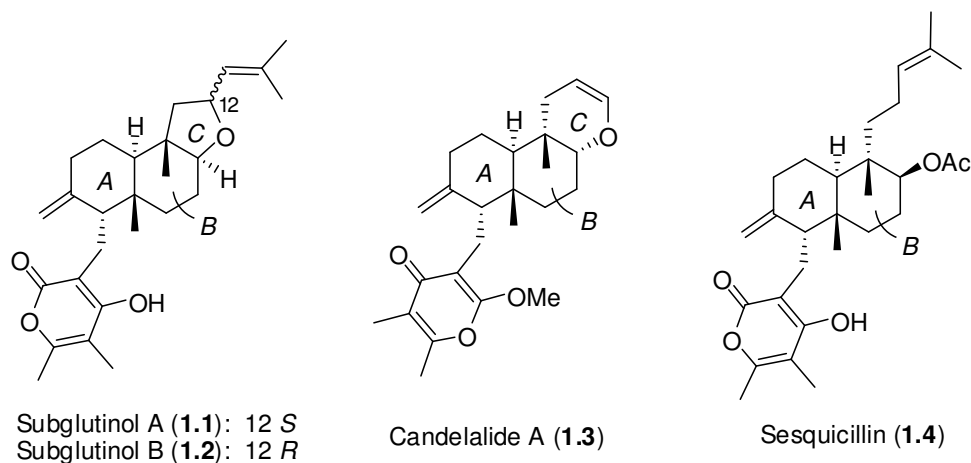
Sesquicillin (**1.4**)

C.1. Sesquicillin and Its Total Synthesis

Sesquicillin, isolated from a fermentation broth of *Acremonium* sp., was discovered through investigation for new glucocorticoid antagonists.[4] In 2004, the Danishefsky lab reported the first total synthesis of sesquicillin.[6] Their strategy began with the acetal protected variant of known (+)-5-methyl-Wieland-Miescher ketone **1.5** (Scheme 1), reported in 1987 by Hagiwara and Uda.[8] To that they appended the homoprenyl side chain and manipulated the *A*-ring carbon chain, revealing compound **1.6** as the precursor for their crucial Eschenmoser Claisen rearrangement. After the successful rearrangement, Zhang and Danishefsky introduced in a stepwise manner an ester-diketone branched chain (**1.7**). Upon DBU-promoted enol lactonization to the requisite pyrone, sesquicillin was isolated in 3.1% overall yield.

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[8] Hagiwara, H.; Uda, H. *J. Chem. Soc.* **1987**, 1351-1353.

Scheme 1.1. Danishefsky's Synthesis of Sesquicillin

Sesquicillin (**1.4**)

1.5

1.6

1.7
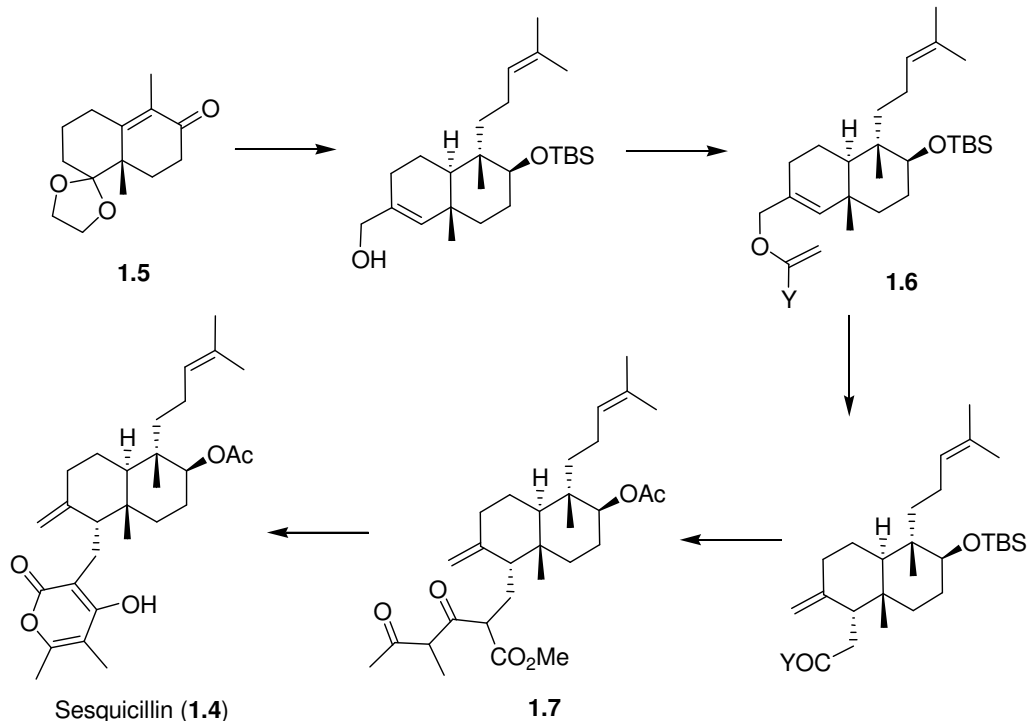
C.2. Candelalide A and Its Total Synthesis

In 2001, Merck researchers isolated candelalide A from a culture broth of *Sesquicillium candelabrum*.[5]   Not only is candelalide similar in composition to the subglutinols, it is also potentially similar in its biological properties. Candelalide A has been shown to be a potent inhibitor of the voltage-gated potassium channel Kv1.3. Blockage of Kv1.3 is known to cause a depolarization in human T cells, which disallows Ca^{2+} from entering the cell and thus prevents T cell proliferation, the final result being an abated immune response.

While we were working on our synthesis of subglutinol, the Katoh group published the total synthesis of candelalide A.[7]   Their synthesis supported our idea that the completed pyrone moiety could be appended to the remainder of the molecule rather than stepwise construction and cyclization as was seen in the sesquicillin synthesis. Katoh's

synthesis of candelalide A began with protection and allylation of the same ketone that Zhang and Danishefsky used (Scheme 1.2). Also in a manner similar to Danishefsky, Katoh's group formed their desired sigmatropic rearrangement substrate. A [2,3]-Wittig rearrangement of **1.8** gave way to coupling partner **1.9**. In an unprecendented fashion, a sterically congested coupling with lithio-pyrone **1.10** was successfully completed to afford candelalide A.

Scheme 1.2. Katoh's Synthesis of Candelalide A

Candelalide A (**1.3**)
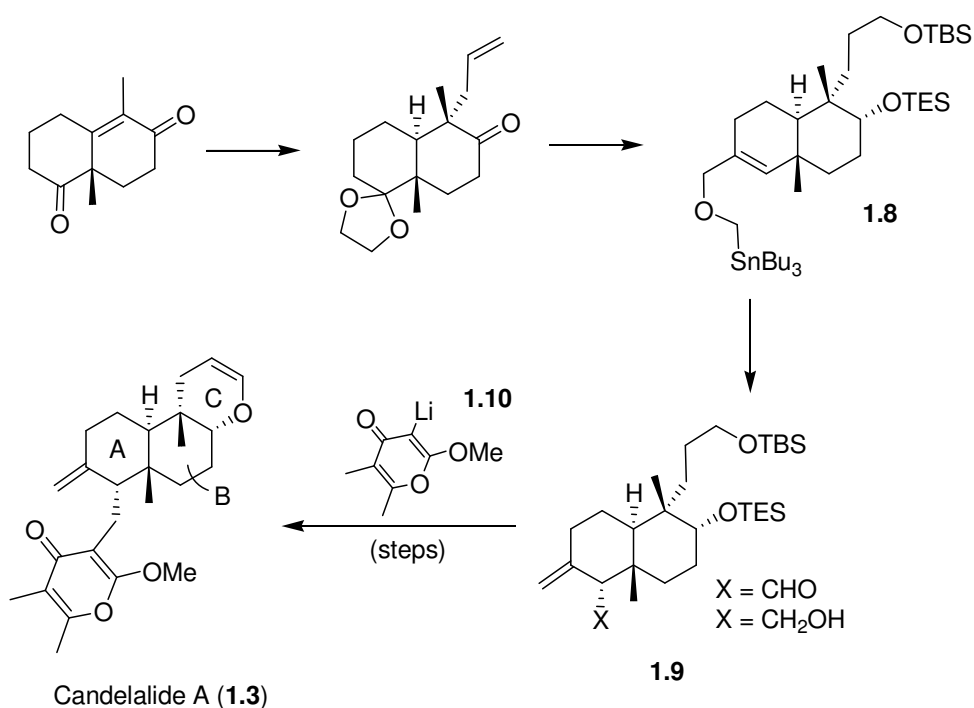
D. Results and Discussion

D.1. Retrosynthesis of Subglutinol Utilizing the Oshima-Utimoto Reaction

In 1987, Oshima and Utimoto published on the formation of substituted tetrahydrofurans from allylic alcohols and vinyl ethers in the presence of palladium(II)

acetate (Scheme 1.3, equation 1).[9] In 2004, the Morken group re-examined this reaction in an attempt to acquire diastereoenriched products (Scheme 1.3, equation 2).[10] By ^{1}H NMR analysis, the product appeared to be a nearly 1:1 mixture of diastereomers. However, lactone formation by Jones oxidation showed that the 1:1 d.r. was not entirely representative of the stereochemistry of the product. The offending stereocenter was actually the butoxy site, and the products were in fact diastereoenriched for the *trans*-2,3 product.

Scheme 1.3. The Oshima-Utimoto Reaction and a Diastereoselective Variant
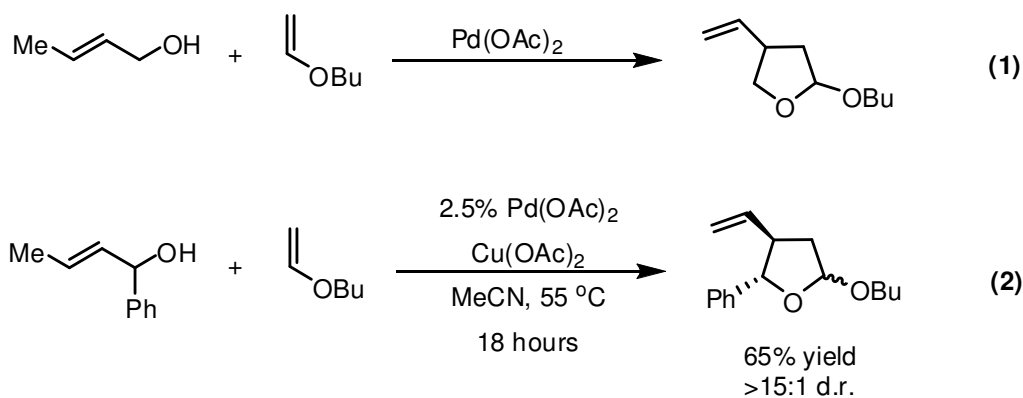
The mechanism for the Oshima-Utimoto reaction begins with addition of butyl vinyl ether to palladium(II) acetate with concomitant loss of an acetate (Scheme 1.4). The oxygen of the allylic alcohol then adds to carbon, quenching the oxocarbenium. Carbopalladation of the tethered alkene --both *cis* and *trans* are tolerated-- most likely goes through a chair-like transition state, effecting the observed 2,3-*trans* configuration of the product. The catalyst is then released from the product by β-hydride elimination, and, following reoxidation, reenters the catalytic cycle. Subglutinol, with its *trans*-fused

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[9] (a) Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 809. (b) Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2050.

[10] Evans, M. A.; Morken, J. P. *Org. Lett.* **2005**; *7*, 3367-3370.

2,3-disubstituted furan, seemed an ideal target to utilize and further study this diastereoselective Oshima-Utimoto variant.

Scheme 1.4. The Mechanism for the Oshima-Utimoto Reaction
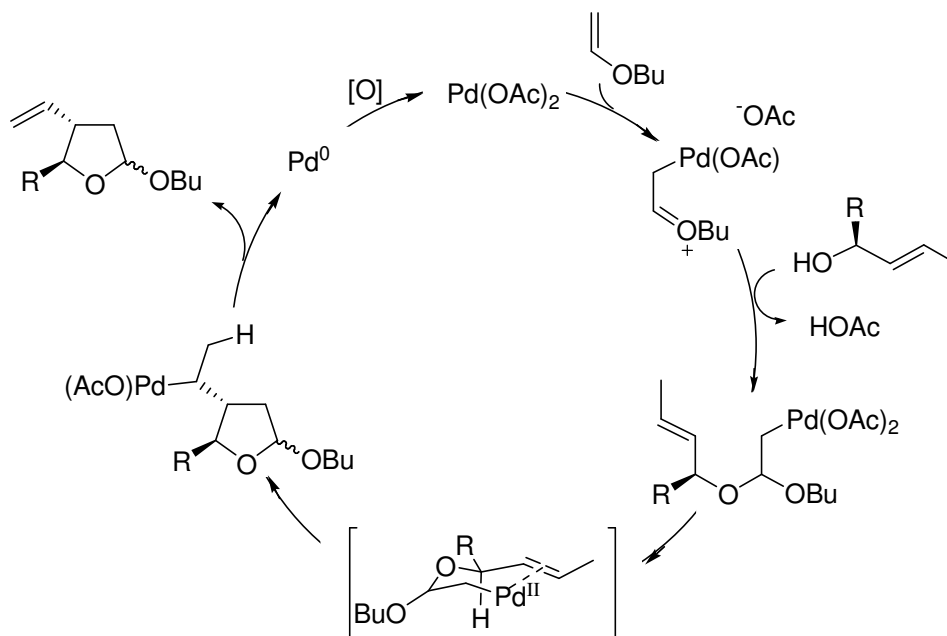
Building around the Oshima reaction, the remainder of the retrosynthesis was put in place (Scheme 1.5). The first disconnection was made at the pyrone, as in the candelalide synthesis, and an elimination was proposed to reveal the *exo*-methylene on ring *A*. In addition, a Lewis-acid assisted methallylation of the furan – with subsequent migration of the alkene – would be the final elaboration to reach subglutinol. To make the core **1.11**, we envisioned the *A* ring as coming from an intermolecular Diels-Alder, the diene of which would arise from intramolecular ene-yne metathesis of substrate **1.12**. The ene-yne compound was seen as coming from selective conversion of the mono-substituted terminal alkene of the Oshima product **1.13** to the terminal alkyne. The key Oshima reaction would occur between butyl vinyl ether and allylic alcohol **1.14**, which would be formed from addition of the Grignard of 2-bromo-2-butene to aldehyde **1.15**.

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Scheme 1.5. Retrosynthesis of Subglutinol
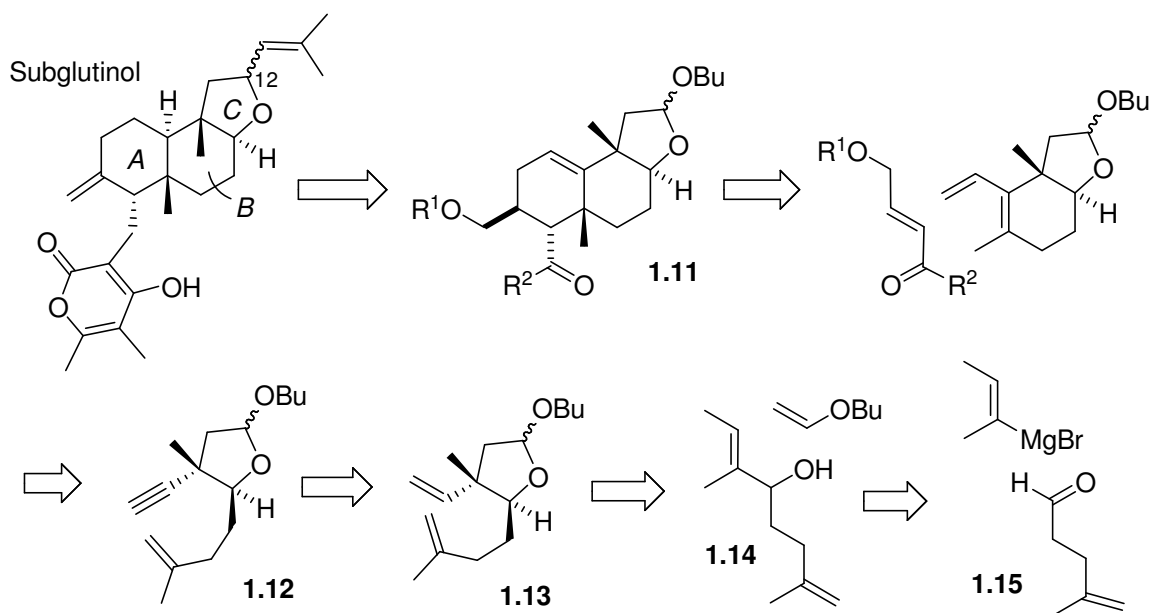
D.2. Studies Toward the Lewis-Acid Mediated Substitution of the Furan Ring

While beginning to synthesize the Oshima substrate for subglutinol, simpler Oshima starting materials (**1.16-1.21,** Scheme 1.6*)* were also being generated from commercially available aldehydes and nucleophiles. Under Oshima conditions,[10] these allylic alcohols were then cyclized with butyl vinyl ether to generate tetrahydrofurans **1.16a-1.21a** (Scheme 1.6). The butoxy substituted Oshima products were then to be used to conduct model studies on allylation of the ring via the oxocarbenium ion produced from exposure to a Lewis acid in the presence of allylsilane. Similar substitutions have been performed on oxasilacyclopentane acetal (Scheme 1.7, equation 3) and tetrahydrofuran acetals (equation 4) by Woerpel, and that methodology was used as a starting point in this endeavor.[11] Our main questions in this research were whether or not this could be

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[11] (a) Shaw, J. T.; Woerpel, *K. A. J. Org. Chem.* **1997**, *62, 6706-6707.* (b) Shaw, J. T.; Woerpel, K. A. *Tetrahedron* **1997**, *53,* 16597-16606. (c) Shaw, J.T.; Woerpel K.A. *Tetrahedron* **1999**, *55,* 8747-8756.

accomplished with alkoxy as the lesser leaving group, if this reaction could be made

diastereoselective, and whether or not it could be catalytic in Lewis acid.

Scheme 1.6. Synthesis of Allylic Alcohols and Use in the Oshima Reaction

R^1, R^2, R^3 = Me, Me, H (**1.16**)
= Bu, Me, H (**1.17**)
= H, H, H   (**1.18**)
= Cy, H, H   (**1.19**)
= Bu, H, Me (**1.20**)
= Bu, H, H   (**1.21**)

R^1, R^2, R^3 = Me, Me, H (**1.16a**)
= Bu, Me, H (**1.17a**)
= H, H, H   (**1.18a**)
= Cy, H, H   (**1.19a**)
= Bu, H, Me (**1.20a**)
= Bu, H, H   (**1.21a**)
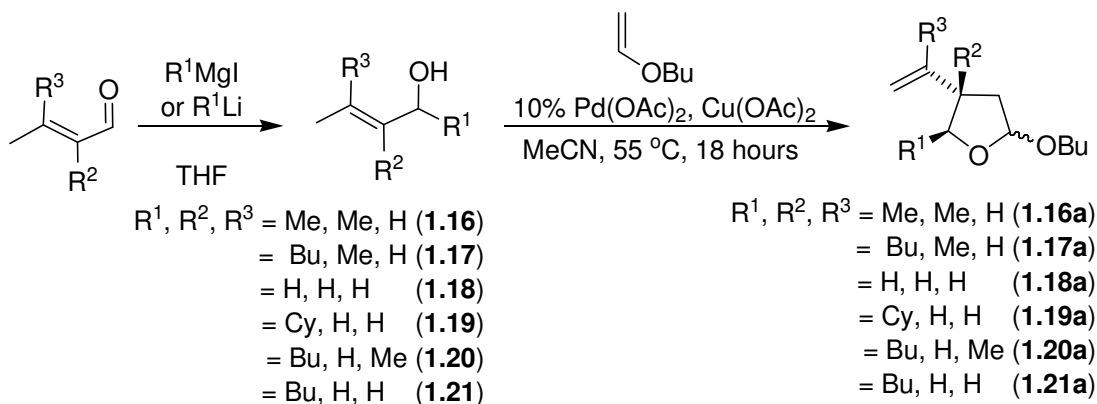
Scheme 1.7. Woerpel's Lewis-Acid Mediated Substition of 5-Membered Acetals

93%

92 : 8 diastereoselectivity

(3)

93%

63 : 36 diastereoselectivity

(4)
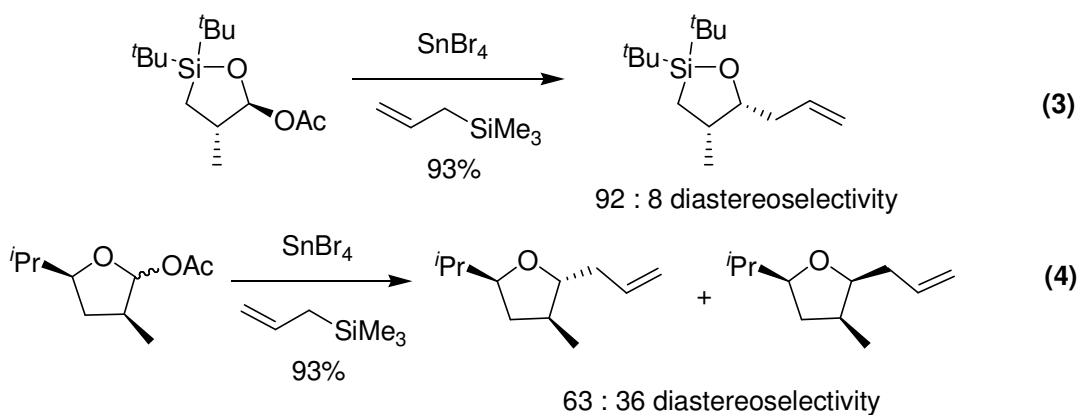
Several substrates were studied using allyltrimethylsilane and a variety of Lewis acids

to determine what, if any, effect was observed on the resulting diastereoselectivity.[12]

First methyl and butyl substituted tetrahydrofurans **1.16a** and **1.17a** were subjected to

varying equivalents of Lewis acid and allyltrimethylsilane at -78 °C and room

temperature (Table 1.1). The main finding was that the reaction could be performed with

1.5 equivalents of silane and could be made catalytic in Lewis acid, needing only 20 mole

[12] Duenes, R.A.; Morken, J.P. *Synlett* **2007**, *4*, 587-590.

percent. After stirring in CH_2Cl_2 for three hours, products could be isolated in 54-69% yield, irrespective of temperature. In addition, ^1H NMR revealed that the allylation products (**1.16b** and **1.17b**) were diastereoenriched and could be isolated as a >20:1 mixture of diastereomers.

Table 1.1. Optimization of Allylation Reaction Conditions

R^1 = Me (**1.16a**)
   = Bu (**1.17a**)

R^1 = Me (**1.16b**)
   = Bu (**1.17b**)
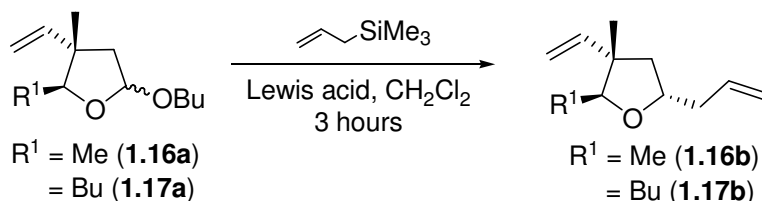
Entry	R^1	Lewis Acid (LA)	Equiv. LA	Equiv. silane	Temp. (°C)	d.r.	Yield (%)
1	Me	Y(OTf)$_3$	1.2	4.0	-78	>20:1	66
2	Bu	SnBr$_4$	2.0	2.0	-78	>20:1	52
3	Bu	BF$_3$•OEt$_2$	2.0	2.0	-78	>20:1	69
4	Bu	SnBr$_4$	0.2	1.5	25	>20:1	67
5	Bu	BF$_3$•OEt$_2$	0.2	1.5	25	>20:1	52

The next step was examining the scope of the reaction with respect to the furan substitution (Table 1.2). For furan **1.17a** with the butyl chain and quaternary center, the Lewis acids examined were BF$_3$•OEt$_2$, Sc(OTf)$_3$, SnCl$_4$, SnBr$_4$, TiCl$_4$, Y(OTf)$_3$, and YF$_3$ (entries 1-7). The yields and diastereoselectivies of **1.17b** were consistent across the survey (54-69%, >20:1 d.r.), with the exception being yttrium trifluoride for which there was complete recovery of starting material. For ease of weighing, handling, and addition, Sc(OTf)$_3$ was used in the substitution of the other furans. Allylated **1.16b** was isolated in 52% yield with a decrease in diastereoselectivity to 5.8:1 (entry 8). When the substitution reaction was performed on a furan with only vinyl and butoxy substituents (**1.18a**), the allylation proceeded in 53% yield with 4.6:1 diastereoselectivity (entry 9).

Interestingly, when no quaternary center was present (furans **1.19a**, **1.20a**, and **1.21a**) the opposite diastereomer was produced in approximately 1:3 ratio (entries 10-12).

Table 1.2. Allylation of Substituted Furans

R^1, R^2, R^3 = Me, Me, H (**1.16a**)
= Bu, Me, H (**1.17a**)
= H, H, H (**1.18a**)
= Cy, H, H (**1.19a**)
= Bu, H, Me (**1.20a**)
= Bu, H, H (**1.21a**)

R^1, R^2, R^3 = Me, Me, H (**1.16b**)
= Bu, Me, H (**1.17b**)
= H, H, H (**1.18b**)
= Cy, H, H (**1.19b**)
= Bu, H, Me (**1.20b**)
= Bu, H, H (**1.21b**)
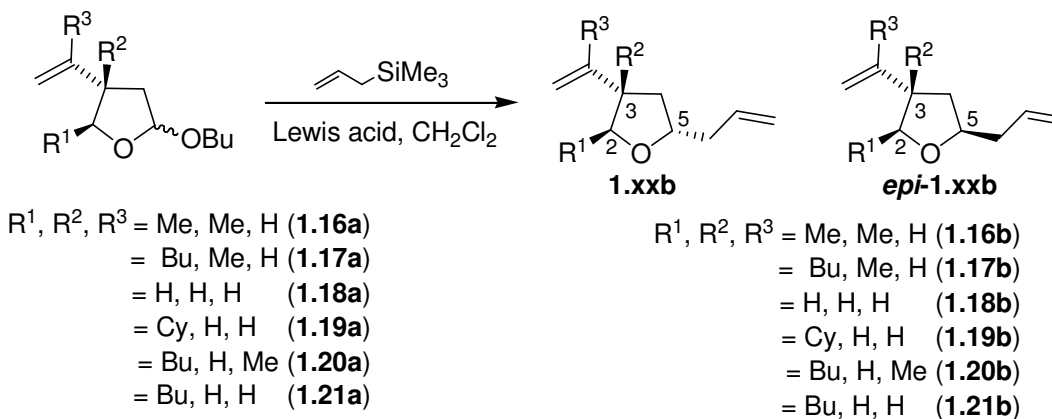
Entry	Furan	Lewis Acid (LA)	1.xxb:*epi*-1.xxb	Yield (%)
1	**1.17a**	SnCl$_4$	>20 : 1	56
2	**1.17a**	BF$_3$•OEt$_2$	>20 : 1	54
3	**1.17a**	SnBr$_4$	>20 : 1	68
4	**1.17a**	Sc(OTf)$_3$	>20 : 1	61
5	**1.17a**	Y(OTf)$_3$	>20 : 1	60
6	**1.17a**	YF$_3$	-	0
7	**1.17a**	TiCl$_4$	>20 : 1	69
8	**1.16a**	Sc(OTf)$_3$	5.8 : 1	52
9	**1.18a**	Sc(OTf)$_3$	4.6 : 1	53
10	**1.19a**	Sc(OTf)$_3$	1 : 2.5	58
11	**1.20a**	Sc(OTf)$_3$	1 : 3.0	56
12	**1.21a**	Sc(OTf)$_3$	1 : 3.4	62

Using the NOESY data for each of the products, the dominant diastereomer for substrates with the quaternary center was determined to be the 3,5-*cis* diastereomer. Allylation of furans with equivalent non-vinyl substituents at the 2 and 3 positions generated the 3,5-*cis* diastereomer (**1.16b** and **1.18b**), albeit in decreased selectivity. When the substrate lacked the quaternary center and did not have equivalent non-vinyl groups at positions 2 and 3, the selectivity flipped to favor the 3,5-*trans* diastereomer

(entries 10 and 12). The *trans* selectivity was also observed when the vinyl group had an α-methyl group branching off of it (entry 11).

Additionally, a more applicable system for the subglutinol allylation was examined. This case utilized methallyltrimethylsilane and tetrahydrofuran **1.17a**, as the alkene could be internalized to mimic subglutinol. In 65% yield, an 11.9:1 mixture of diastereomers was isolated, having the configuration of that of subglutinol B with 3,5-*cis* selectivity as determined by NOESY analysis (Scheme 1.8).

Scheme 1.8. Model System for Subglutinol Methallylation

1.17a

20% Sc(OTf)$_3$
CH$_2$Cl$_2$
3 hours

1.17c

65% yield
11.9 : 1 d.r.
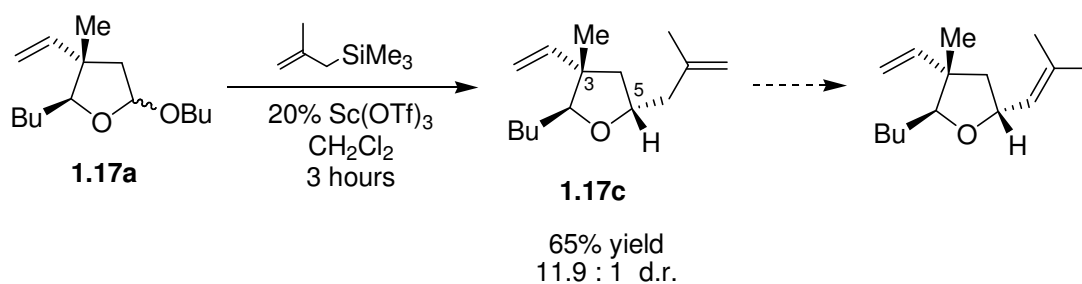
A model for the selectivity has been created as seen in Figure 1.4, and is rooted with a steric argument. The top face of the intermediate oxocarbenium is largely blocked by the methyl of the quaternary center and the butyl side chain, lending a bias for the nucleophilic attack from the less hindered bottom face. When the methyl group is not present on the vinyl substituted 3 position of the furan, that bias is abated and instead nucleophilic attack is possible on the top face, albeit with a decreased preference. As for furan **1.19a** in which a cyclohexyl group extends to the top side, the argument can be made that the chair is pointed away from the area of attack allowing for a percentage of substrate to be approached from the top face.

Figure 1.4. Model for Selectivity of Allylation
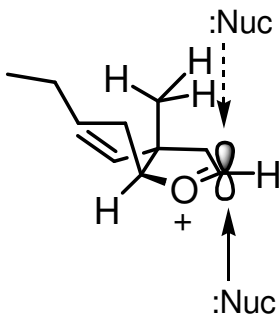
D.3. Initial Attempts Toward the Oshima Substrate

Preliminary endeavors concerning the synthesis of the Grignard addition partner involved the oxidation of an alcohol to the requisite aldehyde **1.15** (Scheme 1.9). Beginning with 4-*oxo*-1-pentanol, a methylene Wittig was performed in 47% yield.[13] Surprisingly, the next step, the oxidation of alcohol **1.22**, was problematic regardless of the conditions employed. Oxidations using Swern conditions, TPAP/NMO, pyridine-SO$_3$, Dess-Martin periodinane, and PCC all resulted in intractable mixtures that at most yielded 15% product that rapidly decomposed. The most probable scenario is that the product was being formed with most or all of the conditions, but once formed, it then reacted either with remaining starting material or itself *in situ*.

Scheme 1.9. Attempted Formation of Aldehyde 1.15
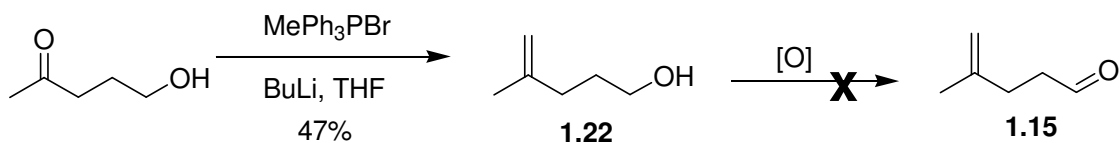
[13] Padwa, A.; Kulkarni, Y. S.; Zhang, Z. *J. Org. Chem.* **1990**, *55*, 4144-4153.

Citing stability of the product as the issue, the next focus was on swapping the roles of the Grignard partner and aldehyde. Thus rather than using 2-bromo-2-butene as the Grignard starting material and aldehyde **1.15**, tiglic aldehyde and an appropriate vinyl halide would be used. To this end, 3-methyl-3-buten-1-ol was converted to bromide **1.23** via mesylation and exchange with lithium bromide (Scheme 1.10).[14] Attempted halogenation with PBr_3 gave very little product and use of PPh_3/Br_2, PPh_3/I_2, or PPh_3/CBr_4 effected only decomposition of product on attemped distillation.[15] Use of bromide **1.23** in a Grignard reaction with tiglic aldehyde generated the desired Oshima precursor **1.14**. Upon subjection of this allylic alcohol to butyl vinyl ether and catalytic palladium(II) acetate in acetonitrile with benzoquinone as the reoxidant and acetic acid as an additive, the desired furan **1.13** was obtained in 49% yield.[16]

Scheme 1.10. First Synthesis and Utilization of Oshima Substrate
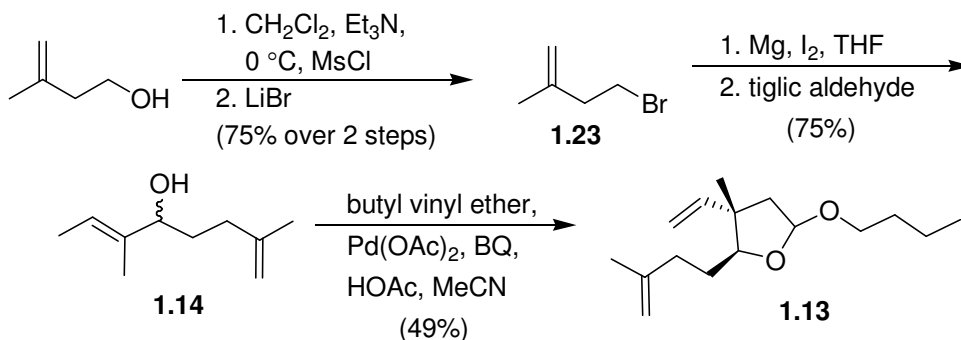
The attempts at making the bromide, however, were less than reproducible so a new manner of producing **1.14** was devised that was reliant on the Johnson ortho-ester Claisen reaction (Scheme 1.11). First 2-methyl-2-propen-1-ol was subjected to catalytic

[14] Leach, A. G.; Wang, R.; Wohlhieter, G. E.; Khan, S. I.; Jung, M. E.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 4271-4278.

[15] Yong, K. H.; Lotoski, J. A.; Chong, J. M. *J. Org. Chem.* **2001**, *66*, 8248-8251.

[16] Trudeau, S.; Morken, J.P. *Org. Lett.* **2005**, *7*, 5465-5468.

propionic acid and excess triethyl orthoacetate to effect the rearrangement to ester **1.24**,[17] which was hydrolyzed to the acid using lithium hydroxide. The crude acid was then converted to the Weinreb's amide **1.25** in using EDCI, triethylamine, and catalytic DMAP.[18] Attempts to generate the amide directly from the ester using Weinreb's amine salt and either iPrMgCl or Me$_3$Al were met with disappointing yields of approximately thirty percent.[19] Conversion of the acid to the acid chloride proved unachievable as did conversion of the ester to aldehyde **1.15** via LAH reduction/Swern oxidation, supporting our previous claims of aldehyde instability. Upon attempting to displace the amide functionality with the lithium of 2-bromo-2-butene, no desired product was obtained. However, if the Grignard was used, the ketone was obtained in a cumulative 26% yield from commercially available 2-methyl-2-propenol. A mixture of *cis* and *trans* 2-bromo-2-butene was used for cost-effectiveness, because, as stated above, both alkene configurations are tolerated in the Oshima reaction. Following Luche reduction in 74% yield, allylic alcohol **1.14** was isolated. Notably, once the details have been enumerated, the entire synthesis can be made enantiopure by utilizing a stereoselective CBS reduction at this stage.[20] New conditions for the Oshima reaction were examined following a report by Hosokawa in which a new system of catalytic palladium(II) acetate with substoichiometric copper(II) acetate and catechol are used with oxygen as the

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[17] Clarke, P.A.; Grist, M.; Ebden, M.; Wilson, C.; Blake, A.J. *Tetrahedron* **2005**, *61*, 353-363.

[18] Evans, D.A.; Tregay, S.W.; Burgey, C.S.; Paras, N.A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936-7943.

[19] Williams, J.M.; Jobson, R.B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E.J.J. *Tetrahedron Lett.* **1995**, *36*, 5461-5464.

[20] Corey, E.J.; Bakshi, R.K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553.

stoichiometric reoxidant.[21] The yield of the Oshima reaction with the new conditions was

72 percent.

Scheme 1.11. Ortho-Ester Claisen Route
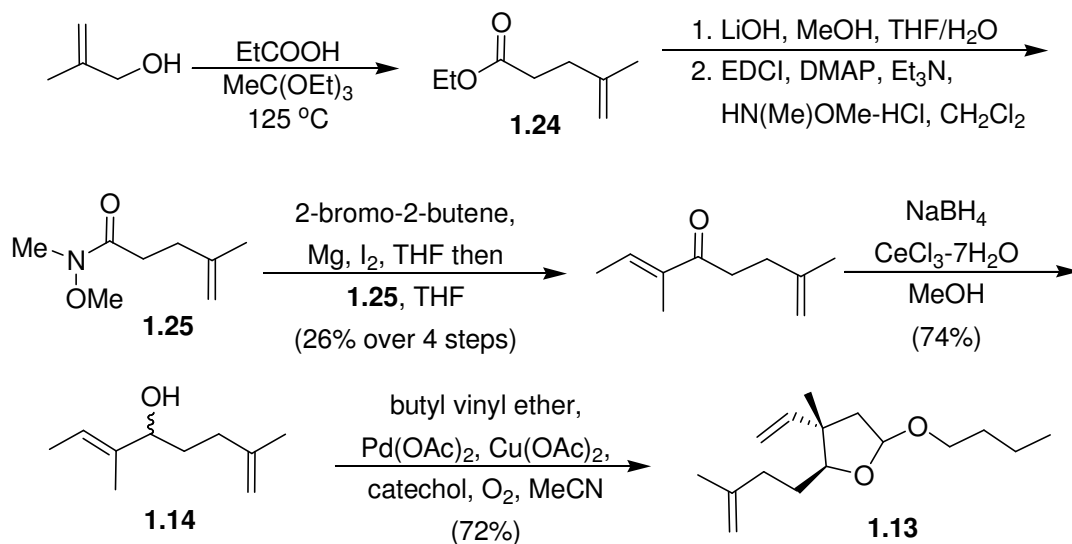
D.4. Efforts to Form the Ene-Yne Precursor

Upon synthesis of the Oshima product **1.13**, many attempts were made to convert it

into the desired ene-yne **1.12** for the metathesis reaction (Scheme 1.12). The original

goal was to perform a Wacker oxidation[22] on the mono-substituted alkene to form the

methyl ketone. The methyl ketone could in turn be converted into the alkyne,[23] however,

all endeavors to this end using varying Wacker conditions were met with no sign of the

sought after methyl ketone. Upon realization that the Wacker would not be a viable

method for transforming the alkene, we attempted to employ our group's diboration

[21] Minami, K.; Kawamura, Y.; Koga, K.; Hosokawa, T. *Org. Lett.* **2005**, *7*, 5689-5692.

[22] (a) Januszkiewicz, K.; Alper, H. *Tetrahedron Lett.* **1983**, *24*, 5159. (b) Kulkarni, M.G.; Pendharkar, D.S. *Tetrahedron* **1997**, *53*, 3167.

[23] Negishi, E.; King, A.O.; Klima, W.L.; Patterson, W.; Silveira, A. *J. Org. Chem.* **1980**, *45*, 2526.

methodology.[24]   This diboration had been successfully applied to a similar system consisting of a monosubstituted alkene with an α–quaternary center. Diboration followed by alkaline oxidation with H_2O_2 should have resulted in diol formation selectively at the monosubstituted alkene site, which could then be cleaved to the aldehyde necessary to form the desired alkyne **1.12**. However, upon subjecting the Oshima product to the diboration conditions, we recovered only starting material.

Scheme 1.12. Unsuccessful Attempts to Obtain Alkyne for Ene-Yne Metathesis
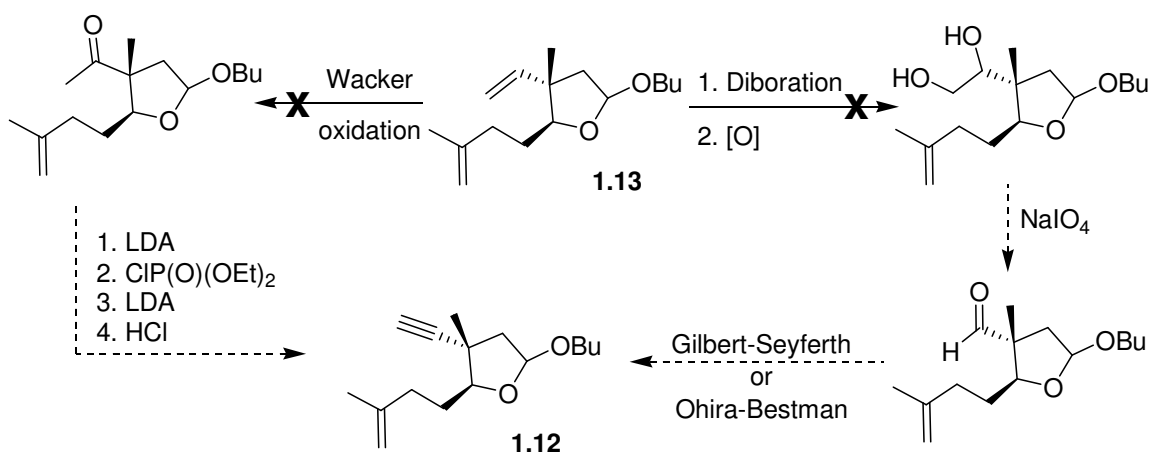
D.5. First Generation Intramolecular Diels-Alder Route

After exerting much energy and time into selectively transforming the monosubstituted alkene into an alkyne, the idea of ene-yne metathesis followed by intermolecular Diels-Alder to form our decalin system was abandoned. Instead, we entertained the idea of an *intra*molecular Diels-Alder that would form both six-membered rings with the desired *trans*-fused ring junction. To this end, we wanted to create a diene from either of the alkenes, as long as it was selective. Depending on which alkene was converted to the diene, after subsequent Diels-Alder cyclization, we would end up with

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[24] Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003,** *125*, 8702-8703.

an alkene at either C1-C2 or C3-C4 (Scheme 1.13). We had hoped that we could preferentially form diene **1.26** because we could better envision a plan to establish the *exo*-methylene and append the necessary pyrone (Scheme 1.2).

Scheme 1.13. Proposed Intramolecular Diels-Alder Reactions
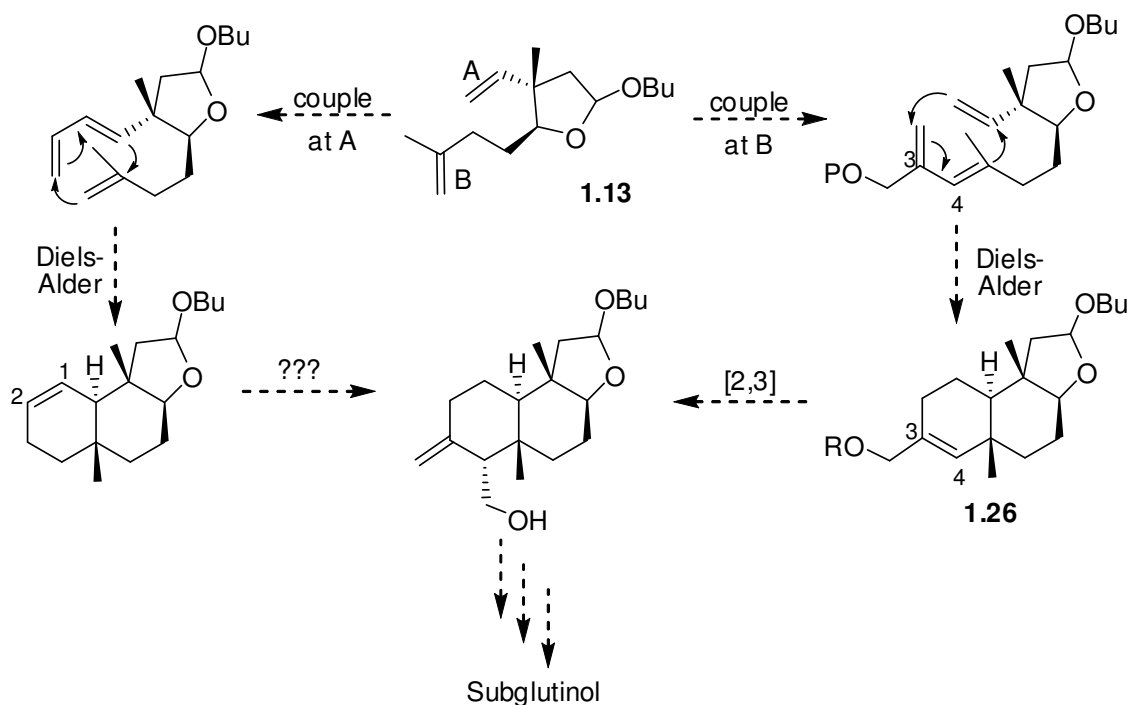
Multiple reactions were undertaken to form a diene from Oshima product **1.13**. Direct coupling using a vinyl bromide and palladium was attempted on both the Oshima substrate and the tetrahydrofuran, both of which showed no reaction (Scheme 1.14, eq. 5).[25] Dihydroxylation was also attempted, not knowing which, if either, alkene might be favored.[26] However, yet again only starting material was recovered (Scheme 1.14, eq. 6).

[25] Speare, D.M.; Fleming, S.M.; Beckett, M.N.; Li, J.-J.; Bugg, T.D.H. *Org. and Biomol. Chem.* **2004**, *2*, 2942-2950.

[26] Kolb, H.C.; VanNieuwenhze, M.S.; Sharpless, K.B. *Chem. Rev.* **1994**, *94*, 2483-547.

Scheme 1.14. Attempted Conversion of 1.13 to Diels-Alder Substrate
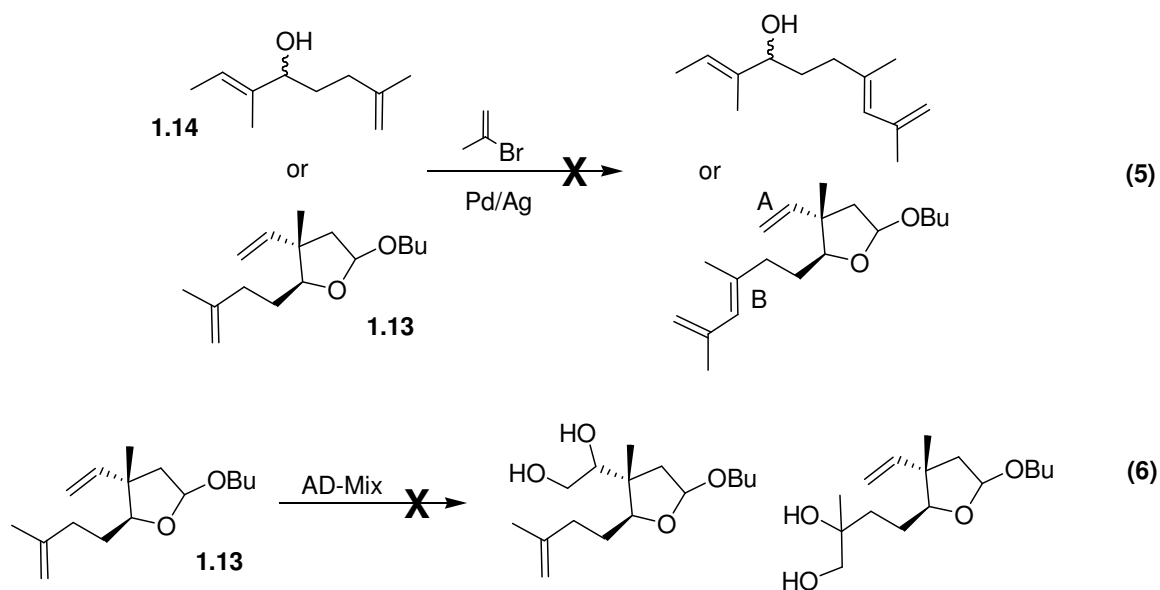
Finally after subjecting the seemingly unreactive furan **1.13** to mCPBA, not only did a reaction occur, but it was selective for the more desirable disubstituted alkene (B) forming epoxide **1.27** in 42% yield, 78% based on recovered starting material (Scheme 1.15). From here, the desire was to open the epoxide and then eliminate the alcohol to reveal the necessary diene. Despite repeated attempts using the Grignard and the organolithium[27] of 2-bromopropene, starting material was recovered each time. This route too was discarded in lieu of making a different substrate for the Oshima reaction that could then be more readily converted into the desired diene.

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[27] Hodgson, D.M.; Fleming, M.J.; Stanway, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 12250-12251.

Scheme 1.15. Epoxidation of 1.13 and Attempted Diene Formation
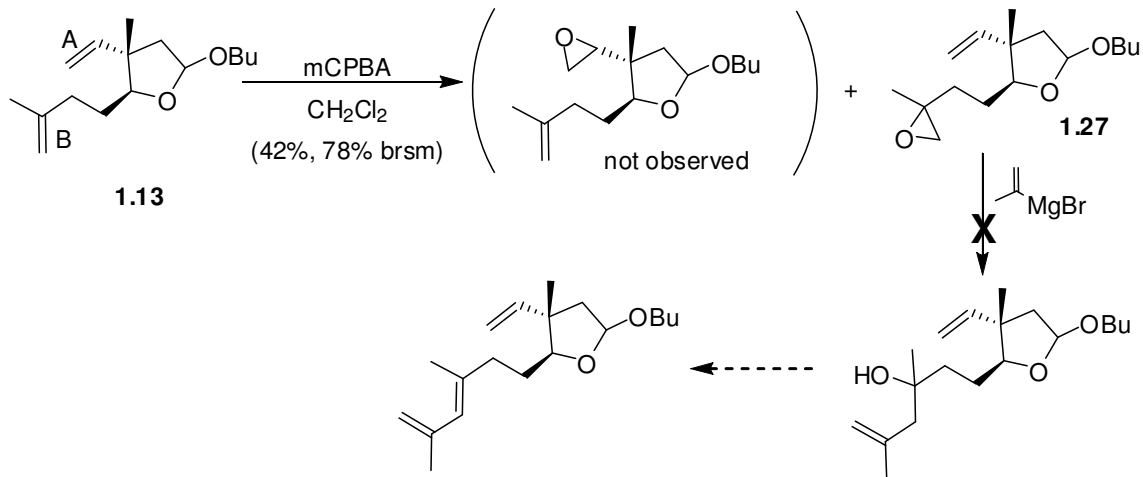
D.6. Second Generation Intramolecular Diels-Alder Route

Still aspiring to have the Oshima generated vinyl group as our dienophile for the intramolecular Diels-Alder, we set out to create a substrate that could better lend itself to generation of the crucial diene. With this aim in hand we created a new synthetic route (Scheme 1.16). First we monoprotected 1,4-butanediol,[28] followed by oxidation of the free alcohol to the aldehyde in nearly quantitative yield. Using aldehyde **1.28** and 2-bromo-2-butene in a Grignard reaction, our Oshima substrate **1.29** was obtained in 99% yield over two steps. Employing the Hosokawa conditions,[21] tetrahydrofuran **1.30** was isolated in 61% yield. The sidechain was then deprotected and the free alcohol oxidized to aldehyde **1.31**, preparing the substrate for an alkynylation reaction. The Gilbert-Seyferth[29] and Ohira-Bestman[30] reagents were both utilized in the alkynylation reaction;

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[28] Abdel-Baky, S.; Giese, R.W. *J. Org. Chem.* **1986**, *51*, 3390-3391.

[29] (a) Brown, D. G.; Velthuisen, E. J.; Commerford, J. R.; Brisbois, R. G.; Hoye, T. H. *J. Org. Chem.* **1996**, *61*, 2540-2541. (b) Flamme, E.M.; Roush, W.R. *Org. Lett.* **2005**, *7*, 1411-1414.

[30] (a) Curphey, T.J. *Org. Prep. Proc. Intl.* **1981**, *13,* 112-115. (b) Marshall, J. A.; Schaaf, G. M. *J. Org. Chem.* **2003**, *68*, 7428-7432.

however, the Ohira-Bestman reagent showed a marked increase in yield (28 versus 86%) most likely due to the milder anion generating conditions (K_2CO_3/MeOH versus KO^{t}Bu). Alkyne **1.32** was to be the substrate for a regio- and stereoselective carbometallation, which, after exchange with iodine, we saw as the prospective coupling partner (**1.33**) to form the requisite diene for the Diels-Alder.[31] The carbometallation/exchange reaction, however, did not go as planned using either the methylcupration[32] or the methylzirconation[33] methodologies. It has been reported that when the alkyl group to be transferred is a simple methyl, the reactions tend to be more problematic.[34] Thus, after multiple attempts and varying conditions, we backtracked yet again in our proposed synthetic route.

[31] Schlosser, M. *Organometallics in Synthesis*. Hoboken, New Jersey: John Wiley & Sons, Inc., 1995.

[32] (a) Gardette, M.; Alexakis, A.; Normant, J.F. *Tetrahedron* **1985**, *41*, 5887-5899. (b) Marfat, P.; McGuirk, R.; Helquist, P. *J. Org. Chem.* **1979**, *44*, 3888-3901. (c) Iyer, R.S.; Helquist, P. *Org. Synth.* **1986**, *64*, 1-9.

[33] (a) Van Horn, D.E.; Negishi, E. *J. Am. Chem. Soc.* **1978**, *100*, 2252-2254. (b) Negishi, E.; Okukado, N.; King, A.O.; Van Horn, D.E.; Spiegel, B. *J. Am. Chem. Soc.* **1978**, *100*, 2254-2256. (c) Hanessian, S.; Ma, J.; Wang, W. *J. Am. Chem. Soc.* **2001**, *123*, 10200-10206.

[34] Baker, R.; Billington, D.C.; Ekanayake, N. *J. Chem. Soc., Perkin Trans. I.* **1983**, 1387.

Scheme 1.16. New Proposed Synthesis of Intramolecular Diels-Alder Substrate
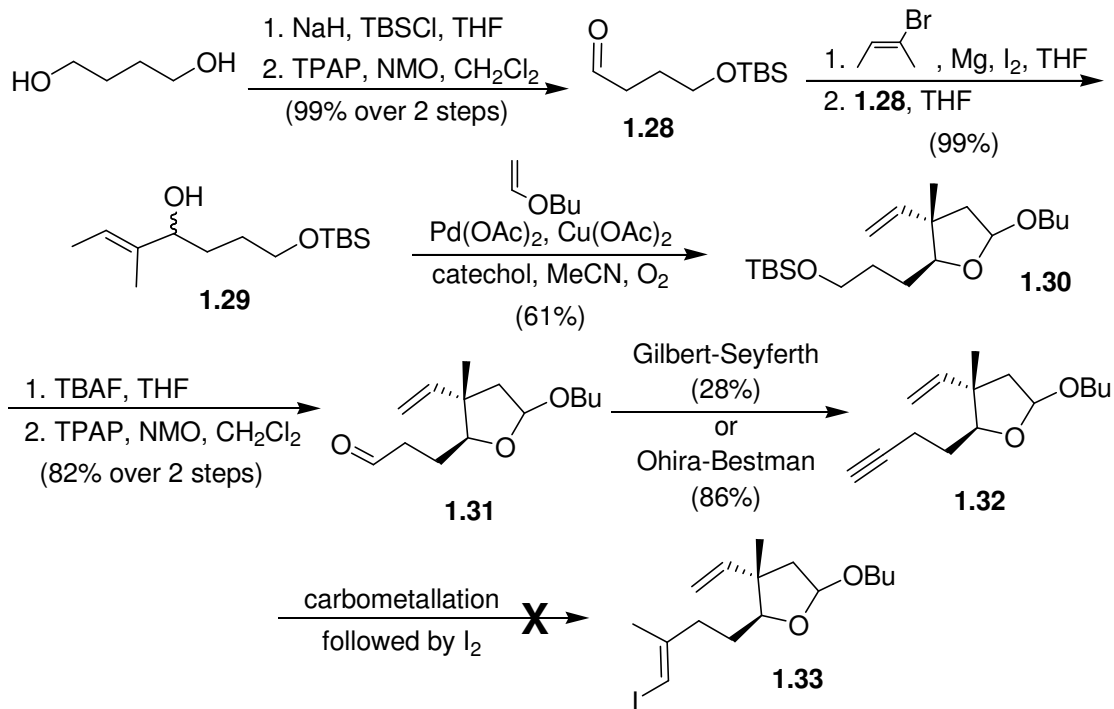
D.7. Utilization of a Vinyl Iodide Surrogate

Two possibilities to circumvent the late stage *cis*-selective formation of the vinyl iodide would be having either the diene already in place prior to the Oshima reaction or having a masked vinyl iodide. In the total synthesis of formamicin, Roush and coworkers successfully used a vinyl silane as a surrogate for their desired vinyl iodide (Scheme 1.17).[35] Beginning with a retro-Brook rearrangement of TMS-ether **1.34** (made from protection of 2-propen-1-ol) they set the stage to do an Ireland-Claisen reaction to yield the vinyl silane. Later on in the synthetic sequence, they subjected the silane to NIS to reveal their desired vinyl iodide.

[35] Powell, N.A.; Roush, W.R. *Org. Lett.* **2001**, *3*, 453-456.

Scheme 1.17. Roush's Synthesis of Vinyl Silane as Vinyl Iodide Surrogate
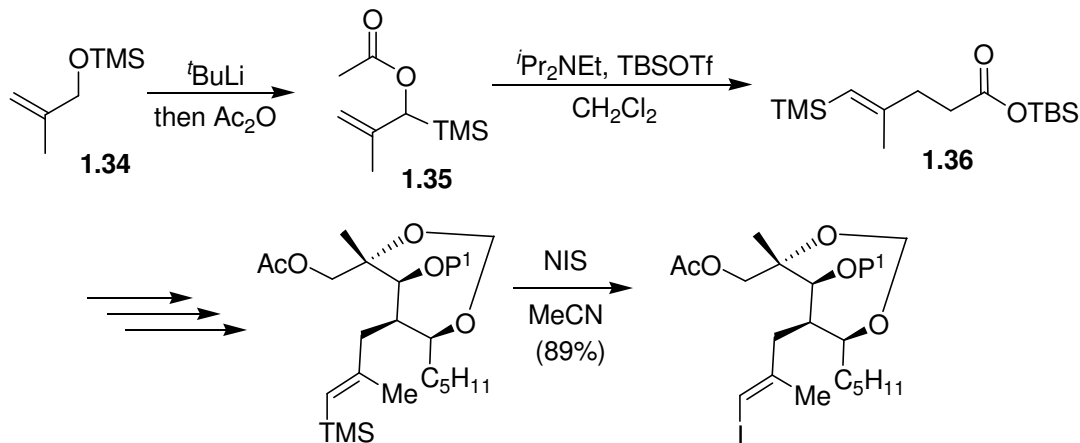
Following Roush's lead, ester **1.35** was synthesized in two steps from 2-propen-1-ol

(Scheme 1.18). In the next step, rather than stirring at room temperature for 3 days in the

presence of TBSOTf, we chose to run the reaction at 50 °C, enabling us to acquire TBS-

ester **1.36** in 24 hours. DIBAL reduction of the ester[36] afforded alcohol **1.37** in 96%

yield, which was reoxidized to the aldehyde using TPAP/NMO. Initially there were

problems with achieving a consistent yield much higher than 45% on the oxidation using

TPAP/NMO or Swern conditions, but the problem was believed to be volatility of the

product. Once the workup of the TPAP/NMO reaction was modified, yields improved,

albeit slightly. Aldehyde **1.38** was used as a solution from the oxidation reaction in a

Grignard reaction with 2-bromo-2-butene to yield the Oshima substrate **1.39** in 94%

yield. The Oshima reaction, using Hosokawa's conditions,[21] could be carried out in 58%

yield to provide furan **1.40**. All that remained was revealing the vinyl iodide and

coupling to procure the Diels-Alder substrate.

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[36] White, J.D.; Amedio, Jr., J.C. *J. Org. Chem.* **1989**, *54*, 736-738.

Scheme 1.18. Final Attempted Synthesis of Diels-Alder Coupling Precursor
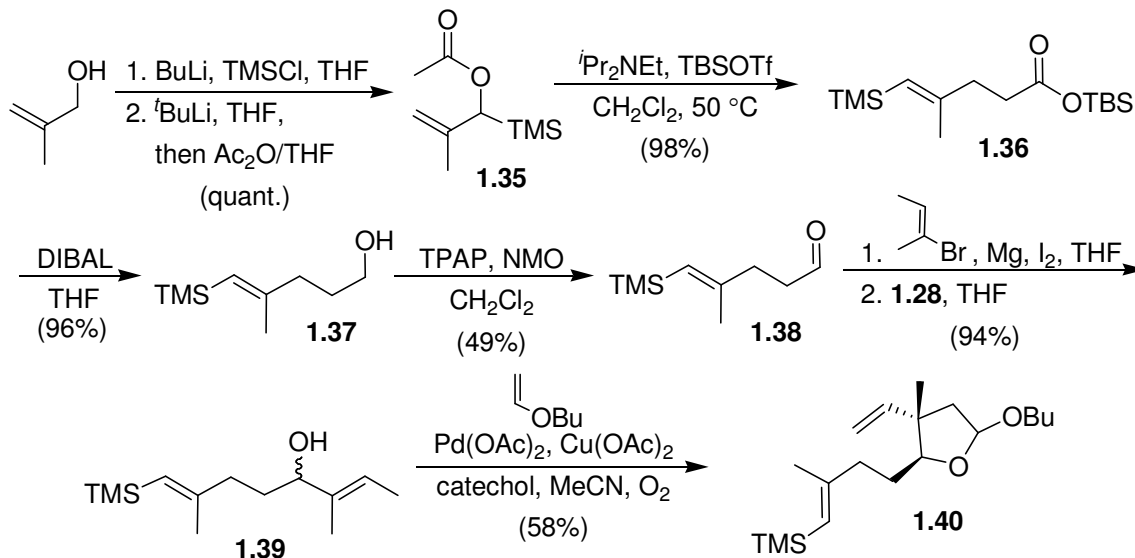
Using NIS as the iodinating agent[37] on vinyl silane **1.40**, vinyl iodide **1.33** was still unstable. Before attempting to use NBS as a brominating agent, more material had to be made, but the synthesis of the aldehyde **1.38** was too cumbersome due to volatility. Despite altering the workup and purification conditions, yields continued to suffer. Attempting to oxidize alcohol **1.37** to the acid, and then converting to the Weinreb's amide were met with loss of the TMS group.

D.8. Revisiting the Alkyne as an Intramolecular Diels-Alder Precursor

At this point, we envisioned a new path to the Diels-Alder substrate using alkynyl ketones to form Z-vinyl stannanes (Scheme 1.19).[38] First alkyne **1.32** was methallylated (**1.41**) using our new methodology to minimize the mixture of diastereomers (7:1 after

[37] Durham, T.B.; Blanchard, N.; Savall, B.M.; Powell, N.A.; Roush, W.R. *J. Am. Chem. Soc.* **2004**, *126*, 9307-9317.

[38] Lautens, M.; Zhang, C.H.; Goh, B.J.; Crudden, C.M.; Johnson, M.J.A. *J. Org. Chem.* **1994**, *59*, 6208-6222.

methallylation). The alkyne was then deprotonated using butyllithium and added into Weinreb amide **1.42**, yielding the desired alkynyl ketone **1.43**. Upon subjecting the alkynyl ketone to Pd(PPh$_3$)$_4$ and hexamethylditin in refluxing THF, the appropriate conversion to the Z-vinyl stannane seemed to be complete, as supported by presence of a new vinyl peak in the ^{1}H NMR spectrum. The next step was a methylene Wittig on the ketone, however, the reaction was only attempted once and the starting material was unreactive. Due to the extremely small scale, the activation of the MePPh$_3$Br may have been insufficient. Following a successful Wittig reaction, exchanging the tin for a methyl group would have provided the desired Diels-Alder substrate.

Scheme 1.19. Revisiting the Intramolecular Diels-Alder Substrate
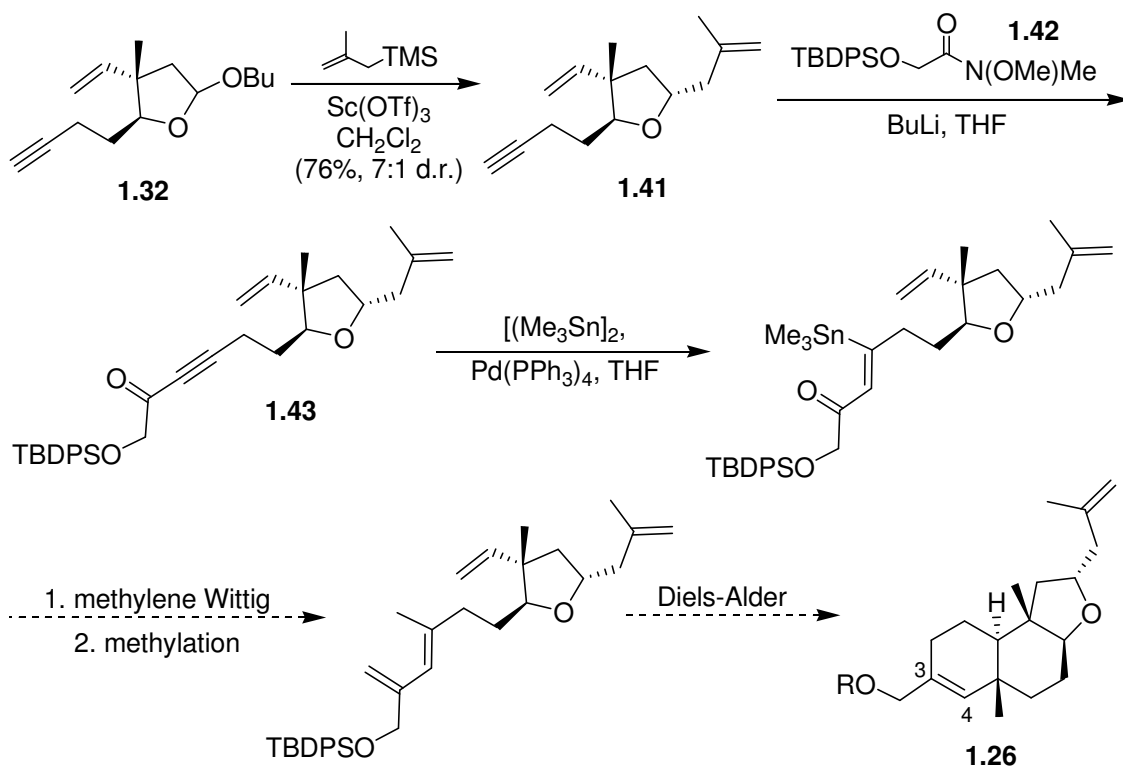
D.9. Synthesis of Pyrone

Prior to the publication of the candelalide synthesis, our plan had been to link the entire pre-formed pyrone unit to the remainder of the molecule via a substitution reaction. When the candelalide work was published, their efforts bolstered our belief that this was in fact a viable route. The most prevalent synthesis of pyrone **1.44** takes advantage of the propensity for C_3O_2 (carbon suboxide) to form heterocycles in the presence of appropriate nucleophiles (Scheme 1.20).[39] Indeed, this was an option we had entertained; however, upon further study we decided there must be a more straightforward synthesis. Extreme conditions such as heating to several hundred degrees and condensing and distilling through a series of lines are necessary to generate carbon suboxide (also called dicarbonyl methane and dioxallene).[40] This, coupled with the facts that C_3O_2 is a gas at room temperature and a ferocious lachrymator, led us to seek a different means by which to construct the α-pyrone.

Scheme 1.20. Formation of α-Pyrone from Carbon Suboxide
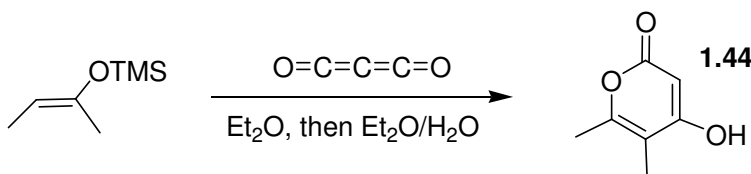
The first attempts at making the pyrone centered around enolizing butanone and trapping with TMS chloride. In spite of numerous attempts to enolize solely at the more substituted ethyl group using LDA, LiHMDS, and KHMDS as well as simple

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[39] Bonsignore, L.; Cabiddu, S.; Loy, G.; Secci, D. *Heterocycles* **1989**, *29*, 913-919.

[40] Paquette, L.A. *Encyclopedia of Organic Reagents*. Hoboken, New Jersey: John Wiley & Sons, Inc., 1995.

triethylamine, and even forming TMSI *in situ*[41] only mixtures of the silyl enol ethers were garnered. Additionally, as a means to the protected enol, a three step procedure consisting of Luche reduction of 3-buten-2-one, protection of the resultant alcohol using imidazole and TMSCl, followed by alkene migration using iridium[42] was attempted unsuccessfully (Scheme 1.21). Subjection of a portion of the 50:50 mixture of silyl enol ethers to $POCl_3$ and malonic acid at elevated temperatures in hope of eliciting a cyclization event was met with failure. Mixing butanone itself with $POCl_3$, to determine if any of the enol tautomer would cyclize was also fruitless.[43]

Scheme 1.21. Attempted Synthesis of Silyl Enol Ether
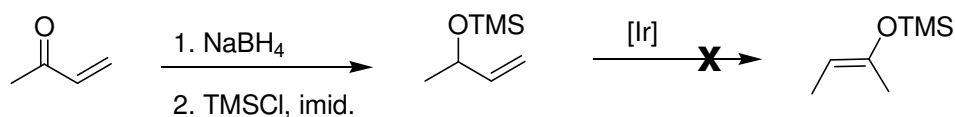
Finally, after several attempts at making the pyrone, an article was discovered from 1980[44] that made the exact pyrone we were seeking, and we were able to repeat their results (Scheme 1.22). Beginning from 3-methylpentane-2,4-dione, ester **1.45** could be formed in 81% yield by exposure to dimethyl carbonate with a mixture of LiHMDS and HMDS in THF. After stirring in pH 9.2 buffer for 16 hours, desired pyrone **1.44** was isolated in 55% yield.

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[41] Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2075-2088.

[42] Ohmura, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **1999**, *18*, 413-416.

[43] Stadlbauer, W.; Badawey, E.-S.; Hojas, G.; Roschger, P.; Kappe, T. *Molecules* **2001**, *6*, 338-352.

[44] Barrett, A.G.M.; Morris, T.M.; Barton, D.H.R. *J. Chem. Soc., Perkin Trans. I.* **1980**, 2272.

Scheme 1.22. Synthesis of Pyrone 1.44
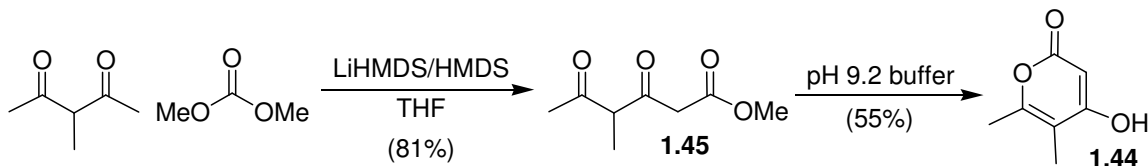
D.10. Proposed Completion of Synthesis and SAR study

Upon completion of the total synthesis, an SAR study has been proposed to access a number of different compounds that have structures similar to subglutinol. Our proposed mechanism of immunosuppression is blockage of the Kv1.3 ion channel as was observed with candelalide (*vida supra*). The hope is to confirm this via patch-clamp testing for cell voltage changes as well as the TP and MLR assays for immunosuppression quantification to determine which portions of the subglutinol structure are responsible for its activity.

E. Conclusion

The Oshima-Utimoto reaction has been employed to diastereoselectively access complex tetrahydrofurans that have been further functionalized using newly developed allylation and methallylation methodologies. In addition, several routes have been examined for the total synthesis of subglutinol, though, to-date the synthetic natural product remains elusive.

F. EXPERIMENTAL PROCEDURES

General. Infrared spectra were recorded on a Nicolet Magna 560 spectrometer, v_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^{1}H NMR spectra were recorded on a Varian Gemini (300 MHz) and Bruker (400 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane ith the solvent resonance as the internal standard (CDCl$_3$: 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, br = broad, and m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR were recorded on a Bruker 400 spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (CDCl$_3$: 77.0 ppm).

Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on Sigma silica gel 60 (SiO$_2$, 230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60 plates. Visualization was achieved with exposure to iodine fumes, UV light (254 nm), phosphomolybdic acid in ethanol followed by heating, or potassium permanganate in ethanol/water followed by heating. Analytical gas-liquid chromatography (GC) was performed on a Hewlett-Packard 6890 Series chromatograph equipped with a split mode capillary injection system, the indicated chiral GC column, a flame ionization detector and using helium as the carrier gas. Analytical supercritical fluid chromatography (SFC) was performed on a Berger SFC using methanol as the modifier with the indicated chiral column.

All reactions were conducted in oven or flame-dried glassware under an inert atmosphere of dry nitrogen or argon, unless otherwise noted. Tetrahydrofuran was distilled from sodium and benzophenone. Acetonitrile and triethylamine were distilled from calcium hydride. Dichloromethane and diethyl ether were passed through an alumina column prior to use in a reaction. All other reagents were purchased from Acros, Aldrich, or Strem chemical companies.
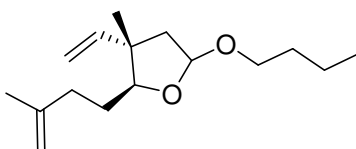
5-butoxy-3-methyl-2-(3-methyl-3-butenyl)-3-vinyltetrahydrofuran (1.13): Method A [benzoquinone as reoxidant]: To a vial containing 100 mg (0.648 mmol) of allylic alcohol **1.14** was added 1 mL of MeCN and 0.17 mL (1.30 mmol) of butyl vinyl ether. Next, 43 mg (0.19 mmol) of Pd(OAc)$_2$, 119 mg (1.1 mmol) of benzoquinone, and 0.02 mL (0.32 mmol) of HOAc was added simultaneously. The reaction was allowed to stir at room temperature for 16 hours. The black solution was then extracted three times with 4 mL of hexanes and filtered through cotton before concentrating. The crude product was purified by column chromatography using 95:5 hexanes: ethyl acetate, to afford 80 mg (49%) of the desired furan product as a clear, light yellow oil. **Method B (O$_2$ as reoxidant):** To a vial containing 100 mg (0.648 mmol) of allylic alcohol **1.14** was added 1 mL of MeCN and 0.34 mL (2.59 mmol) of butyl vinyl ether. Next, 15 mg (0.07 mmol) of Pd(OAc)$_2$, 12 mg (0.07 mmol) of Cu(OAc)$_2$, and 14 mg (0.13 mmol) of catechol was added simultaneously and the solution turned dark brown. The vial was fitted with a cap that had an inlaid septum before introducing a balloon filled with oxygen via a 10 cm, 18

gauge needle. The oxygen was allowed to bubble through the solution by adding a vent needle (26 gauge), and the whole apparatus was left stirring for 16 hours at room temperature. The black solution was then extracted three times with 4 mL of hexanes and filtered through cotton before concentrating. The crude product was purified by column chromatography using 95:5 hexanes: ethyl acetate, to afford 117 mg (72%) of the desired furan product as a clear, light yellow oil. R_f (80:20 hexanes:ethyl acetate): 0.71. ^{1}H NMR: δ 5.79 (dd, J = 17.4, 10.8 Hz, 1H), 5.10 (t, J = 4.3 Hz, 1H), 5.05-5.00 (m, 2H), 4.67 (d, J = 7.9 Hz, 2H), 3.72-3.68 (m, 2H), 3.41-3.35 (m, 1H), 1.98 (dd, J = 12.6, 4.4 Hz, 1H), 1.87 (dd, J = 13.5, 4.2 Hz, 1H), 1.69 (s, 3H), 1.62-1.12 (m, 8H), 0.97(s, 3H), 0.90 (t, J = 1.4 Hz, 3H). ^{13}C NMR: δ 145.4, 143.2, 113.1, 109.8, 102.5, 82.7, 67.6, 47.8, 47.1, 35.1, 31.8, 26.7, 22.3, 19.2, 18.0, 13.7.
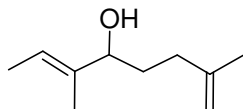
3,7-dimethylocta-2,7-dien-4-ol (1.14): Method A (via Grignard): Magnesium (0.89 g, 36.4 mmol) was flame-dried in a dry flask equipped with an addition funnel and stir bar. A crystal of iodine was added and the flask evacuated and backfilled with nitrogen. A solution of 5.15 g (34.55 mmol) of bromide **1.22** in 185 mL of THF was slowing dripped into the flask. The yellow solution was stirred overnight, consuming most of the magnesium. Next a solution of 2.23 mL (23.0 mmol) of tiglic aldehyde in 25 mL of THF was slowly dripped into the Grignard solution. The reaction was stirred at room temperature for 3 hours before quenching with 150 mL of water and 20 mL of 1 M HCl. The mixture was extracted three times with 150 mL of Et_2O, and the combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. A silica gel

column eluted with 90:10 hexanes: ethyl acetate afforded 2.63 g (75%) of a dark yellow oil. **Method B (via Grignard):** To a dry flask was added 2.16 g of magnesium, which was then flame-dried under vacuum. A crystal of iodine was added and the vessel evacuated and backfilled with nitrogen. A solution of 8.88 mL (86.9 mmol) of 2-bromo-2-butene (mixture of *cis* and *trans*) and 150 mL of THF was added slowly to the stirring magnesium. After stirring until the magnesium was consumed (2-3 hours), a solution of 6.83 g amide (43.4 mmol) of **1.25** in 60 mL of THF was added dropwise to the stirring Grignard. The reaction was allowed to stir for 3 hours at room temperature before quenching with saturated aqueous NH_4Cl. After extracting three times with 200 mL of Et_2O, the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash column chromatography using 85:15 hexanes:ethyl acetate as the eluent. The desired alcohol was isolated as 3.91 g (59%) of a light yellow oil. **Method C (via reduction of ketone):** To a flask equipped with stir bar was added 6.68 g (43.9 mmol) of 3,7-dimethylocta-2,7-dien-4-one (**SI-1.2**), 160 mL of MeOH, and 16.3 g (43.9 mmol) of $CeCl_3 \cdot 7H_2O$. The reaction was stirred until the [Ce] was completely dissolved, and then 1.66 g (43.9 mmol) of $NaBH_4$ was slowly added. The reaction was stirred at room temperature for 2 hours and then quenched with H_2O. The pH was adjusted to 7 with 1 M HCl. After extracting three times with 100 mL of EtOAc, the combined organics were dried over Na_2SO_4, filtered, and concentrated. A gradient column (95:5 → 80:20 hexanes: ethyl acetate) was used to purify the compound, providing 5.00 g (74%) of Oshima precursor as a clear, light yellow oil. R_f (80:20 hexanes:ethyl acetate): 0.35. ^{1}H NMR: δ 5.42 (q, *J* = 7.2 Hz, 1H), 4.71 (d, *J* = 6.5 Hz, 2H), 3.94 (t, *J* = 7.2 Hz, 1H), 2.08-1.91 (m, 2H), 1.82 (br s, 1H), 1.73 (s, 3H), 1.68-1.60

(m, 2H), 1.59 (d, J = 8.5 Hz, 3H), 1.58 (s, 3H). ^{13}C NMR: δ 145.5, 137.6, 120.7, 109.7, 77.4, 33.6, 32.3, 22.1, 12.6, 10.4.

Representative Procedure for Synthesis of Allylic Alcohols (1.16-1.21): To a flame-dried flask was added 40 mL of THF and 7.5 mL (12 mmol) of methyllithium (1.6 M in Et$_2$O). The solution was chilled to 0 ℃ and 0.96 mL (10 mmol) of tiglic aldehyde was added dropwise via syringe while stirring. The ice bath was removed and the yellow solution allowed to stir for 3 hours at room temperature before carefully adding saturated aqueous NH$_4$Cl to quench. The biphasic mixture was extracted three times with 30 mL of Et$_2$O and the combined organics were washed with brine, dried over MgSO$_4$, filtered, and concentrated. The clear, colorless oil (900 mg, 90%) was pure enough to use in the subsequent Oshima reaction. R_f (80:20 hexanes:ethyl acetate): 0.26.
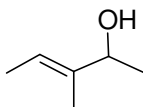
3-methyl-3-penten-2-ol (1.16): ^{1}H NMR: δ 5.44 (q, J = 6.6 Hz, 1H), 4.16 (q, J = 6.4 Hz, 1H), 1.58 (s, 3H), 1.56 (d, J = 7.6 Hz, 3H), 1.40 (br s, 1H), 1.20 (d, J = 6.4 Hz, 3H). ^{13}C NMR: δ 139.2, 119.2, 73.4, 21.5, 13.0, 11.1.
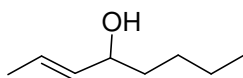
3-methyl-2-octen-4-ol (1.17): Made using n-butyllithium and tiglic aldehyde. ^{1}H NMR: δ 5.45 (q, J = 6.6 Hz, 1H), 3.97 (t, J = 6.8 Hz, 1H), 1.60 (d, J = 10.0 Hz, 3H), 1.59 (s, 3H), 1.55-1.48 (m, 2H), 1.38 (br s, 1H), 1.34-1.28 (m, 4H), 0.89 (t, J = 7.2 Hz, 3H).

2-buten-1-ol (1.18): Commercially available 2-butene-1-ol (crotyl alcohol) was used.
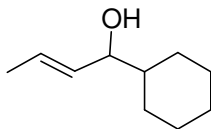
1-cyclohexylbut-2-en-1-ol (1.19): Made using cyclohexylmagnesium chloride and crotonaldehyde. ^{1}H NMR: δ 5.61 (dq, *J* = 14.9, 6.3 Hz, 1H), 5.47 (dd, *J* = 15.2, 7.5 Hz, 1H), 3.73 (q, *J* = 5.9 Hz, 1H), 1.88-1.72 (m, 1H), 1.69 (d, *J* = 6.4 Hz, 3H), 1.73-1.63 (m, 4H), 1.52 (br s, 1H), 1.40-1.39 (m, 1H), 1.27-1.08 (m, 3H), 1.00-0.88 (m, 2H). ^{13}C NMR: δ 133.0, 127.6, 68.2, 43.4, 29.0, 29.2, 26.7, 25.8, 25.6, 17.9.

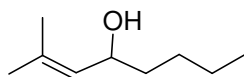

2-methyloct-2-en-4-ol (1.20): Made using *n*-butyllithium and 3-methyl-2-buten-1-al. ^{1}H NMR: δ 5.13 (d, *J* = 6.2 Hz, 1H), 4.30 (q, *J* = 4.7 Hz, 1H), 1.69 (s, 3H), 1.66 (s, 3H), 1.61-1.52 (m, 2H), 1.45-1.23 (m, 4H), 0.89 (t, *J* = 3.2 Hz, 3H). ^{13}C NMR: δ 128.1, 68.9, 37.5, 27.4, 25.5, 22.3, 18.0, 13.9, 13.8.
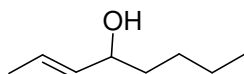
2-octen-4-ol (1.21): Made using *n*-butyllithium and crotonaldehyde. ^{1}H NMR: δ 5.65 (dq, *J* = 15.3, 6.4 Hz, 1H), 5.48 (dd, *J* = 16.8, 7.1 Hz, 1H), 4.02 (q, *J* = 6.8 Hz, 1H), 1.69 (d, *J* = 4.8 Hz, 3H), 1.66 (d, *J* = 1.7 Hz, 1H), 1.57-1.42 (m, 2H), 1.35-1.23 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H).

Representative Procedure for Oshima-Utimoto reaction of Allylic Alcohols and Butyl Vinyl Ether (1.16a-1.16b): In a dry flask 1.08 g (7.55 mmol) of 3-methyl-2-octen-4-ol was mixed with 7.5 mL of MeCN followed by addition of 1.96 mL (15.11 mmol) of butyl vinyl ether. Next, a mixture of 170 mg of Pd(OAc)$_2$ and 3.43 g of

Cu(OAc)$_2$ was added. The brown suspension was stirred for 16 hours at 55 ºC before cooling to room temperature and extracting with a 3:1 mixture of hexanes:diethyl ether. The dark yellow solution was concentrated to a viscous brown oil and purified via flash column chromatography, eluting with 95:5 hexanes:ethyl acetate. A light yellow oil (1.0 g, 55%) was isolated as the desired product. R_f (80:20 hexanes:ethyl acetate): 0.79.
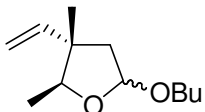
5-butoxy-2,3-dimethyl-3-vinyltetrahydrofuran (1.16a): ^{1}H NMR: δ 5.94 (dd, *J* = 17.2, 10.9 Hz, 1H), 5.12 (dd, *J* = 5.8, 4.5 Hz, 1H), 5.06-4.98 (m, 2H), 3.91 (q, *J* = 6.4 Hz, 1H), 3.75-3.69 (m, 1H), 3.42-3.33 (m, 1H), 2.01 (dd, *J* = 13.5, 5.9 Hz, 1H), 1.91 (dd, *J* = 13.5, 4.0 Hz, 1H), 1.61-1.50 (m, 2H), 1.40-1.32 (m, 2H), 1.20 (d, *J* = 6.4 Hz, 3H), 1.11 (s, 3H), 1.05 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR: δ 143.2, 113.3, 102.9, 79.2, 68.0, 47.6, 47.4, 31.8, 19.3, 17.9, 13.8, 13.3. IR (neat): 2957 (m), 2924 (s), 2843 (m), 1507 (m), 1447 (w), 1361 (w), 1225 (w), 1073 (w). HRMS (ESI): Calculated for C$_{12}$H$_{22}$O$_2$ [M+Na]$^+$: 221.152. Found [M+Na]$^+$: 221.151.
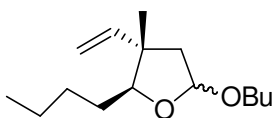
5-butoxy-2-butyl-3-methyl-3-vinyltetrahydrofuran (1.17a): ^{1}H NMR: δ 5.81 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.12 (dd, *J* = 5.8, 4.4 Hz, 1H), 5.05-5.00 (m, 2H), 3.74-3.69 (m, 2H), 3.41-3.38 (m, 1H), 1.98 (dd, *J* = 13.6, 5.8 Hz, 1H), 1.87 (dd, *J* = 13.6, 4.2 Hz, 1H), 1.59-1.42 (m, 4H), 1.40-1.24 (m, 6H), 0.96 (s, 3H), 0.91 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR: δ 143.5, 113.1, 102.7, 83.5, 67.7, 48.0, 47.3, 31.9, 29.5, 28.4, 22.8, 19.3, 18.2, 14.1, 13.9. HRMS (ESI): Calculated for C$_{15}$H$_{28}$O$_2$ [M+Na]$^+$: 263.199. Found [M+Na]$^+$: 263.199.
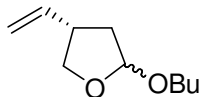
2-butoxy-4-vinyltetrahydrofuran (1.18a): ^{1}H NMR: δ 5.81 (ddd, *J* = 17.1, 9.4, 8.5 Hz, 1H), 5.13 (dd, *J* = 5.5, 2.9 Hz, 1H), 5.08-4.97(m, 2H), 3.95 (t, *J* = 7.9 Hz, 1H), 3.71-3.64 (m, 1H), 3.56 (t, *J* = 8.6 Hz, 1H), 3.44-3.35 (m, 1H), 2.82 (m, 1H), 2.30 (ddd, *J* = 13.4, 8.7, 5.5 Hz, 1H), 1.68 (ddd, *J* = 17.1, 7.4, 3.7 Hz, 1H), 1.59-1.50 (m ,2H), 1.43-1.32 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR: δ 139.0, 115.3, 104.4, 70.9, 67.3, 43.1, 39.2, 31.7, 19.2, 13.6. IR (neat): 3071 (w), 2957 (s), 2935 (s), 2865 (s), 1643 (w), 1350 (m), 1100 (s), 1002 (s), 915 (m).
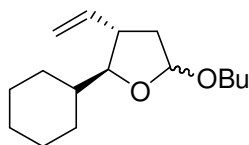
5-butoxy-2-cyclohexyl-3-vinyltetrahydrofuran (1.19a): ^{1}H NMR: δ 5.82 (ddd, *J* = 17.1, 9.1, 9.0 Hz, 1H), 5.05 (dd, *J* = 5.3, 2.1 Hz, 1H), 5.02-4.91 (m, 2H), 3.67-3.64 (m, 1H), 3.43-3.32 (m, 2H), 3.54 (m, 1H), 2.25 (ddd, *J* = 13.4, 9.0, 5.3 Hz, 1H), 1.77-1.61 (m, 6H), 1.60-1.41 (m, 2H), 1.40-1.31 (m, 2H), 1.27-1.01 (m, 6H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR: δ 141.2, 114.8, 112.9, 88.9, 67.0, 45.1, 40.2, 31.6, 29.1, 28.4, 26.6, 26.4, 19.3, 13.8. IR (neat): 3082 (w), 2919 (s), 2848 (s), 2658 (w), 1643 (m), 1447 (m), 1387 (m), 1100 (s). HRMS (ESI): Calculated for $C_{16}H_{28}O_2$ [M+Na][+]: 275.199. Found [M+Na][+]: 275.203.
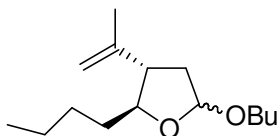
5-butoxy-2-butyl-3-(prop-1-en-2-yl)tetrahydrofuran (1.20a): ^{1}H NMR: δ 5.06 (dd, *J* = 17.0, 5.2 Hz, 1H), 4.78 (d, *J* = 3.7, 1H), 4.77 (d, *J* = 4.3 Hz, 1H), 3.86-3.79 (m, 1H),

3.69 (dt, J = 9.7, 6.7 Hz, 1H), 3.42-3.30 (m, 1H), 2.42-2.25 (m, 1H), 2.06-1.92 (m, 2H), 1.73 (s, 3H), 1.66-1.20 (m, 10H), 0.92 (t, J = 7.3 Hz, 3H), 0.88 (t, J = 6.7 Hz, 3H).
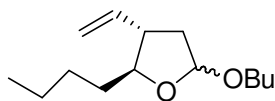
5-butoxy-2-butyl-3-vinyltetrahydrofuran (1.21a): ^{1}H NMR: δ 5.71 (ddd, J = 17.1, 9.4, 8.4 Hz, 1H), 5.07-5.02 (m, 1H), 5.01-4.92 (m, 2H), 3.66 (t, J = 6.7 Hz, 1H), 3.63 (t, J = 6.7 Hz, 1H), 3.33 (dt, J = 9.6, 6.5 Hz, 1H), 2.33-2.24 (m, 1H), 1.69-1.21 (m, 12H), 0.87 (t, J = 7.7 Hz, 6H). ^{13}C NMR: δ 139.1, 115.6, 103.3, 81.2, 67.2, 49.4, 39.9, 33.2, 31.9, 28.5, 22.7, 19.3, 14.0, 13.8.

Representative Procedure for Allylation and Methallylation of Substituted Furans (Table 1.3): To a flame-dried vial equipped with stir bar was added 72 mg (0.30 mmol) of furan **1.17a** and 1.2 mL of dichloromethane. Next 70 μl (0.45 mmol) of allyltrimethylsilane was added, followed by 26 mg (0.06 mmol) of SnBr$_4$, upon doing so the pale yellow solution began to slowly turn dark reddish brown. The vial was capped and the solution allowed to stir for 3 hours at room temperature, at which time saturated aqueous NaHCO$_3$ was added. The reaction was stirred for 5 minutes before extracting 3 times with dichloromethane. The combined organics were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography using 99:1 CH$_2$Cl$_2$: MeOH, providing 42 mg (67%) of 5-allyl-2-butyl-3-methyl-3-vinyltetrahydrofuran (**1.17b)** as a yellow oil in a >20:1 *syn*:*anti* ratio of diastereomers. R_f (80:20 hexanes:ethyl acetate): 0.81.
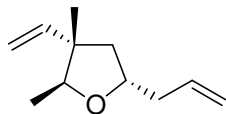
5-allyl-2,3-dimethyl-3-vinyltetrahydrofuran (1.16b): ^{1}H NMR: δ 5.82-5.70 (m, 2H), 5.10-5.00 (m, 4H), 4.13 (m, 1H), 3.73 (q, *J* = 6.4 Hz, 1H), 2.29 (m, 2H), 1.79 (dd, *J* = 12.4, 6.4 Hz, 1H), 1.68 (dd, *J* = 12.5, 9.6 Hz, 1H), 1.04 (d, *J* = 8.4 Hz, 3H), 1.00 (s, 3H). ^{13}C NMR: δ 153.4, 144.6, 127.0, 123.1, 90.5, 86.26, 57.9, 56.1, 51.2, 27.2, 24.2. IR (neat): 3076 (w), 2968 (m), 2924 (m), 2865 (m), 1730 (s), 1638 (m), 1442 (m), 1371 (s), 1241 (s), 1116 (m), 1089 (m), 1019 (m), 910 (m). LRMS (ESI) Calculated for $C_{11}H_{18}O$ (M+H)$^+$: 167.13. Found (M+H)$^+$: 167.2.
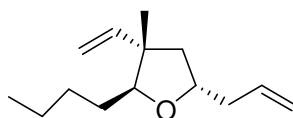
5-allyl-2-butyl-3-methyl-3-vinyltetrahydrofuran (1.17b): ^{1}H NMR: δ 5.80-5.73 (m, 2H), 5.11-5.01 (m, 4H), 4.13 (dq, *J* = 9.2, 6.3 Hz, 1H), 3.54 (dd, *J* = 8.0, 4.1 Hz, 1H), 2.37 (m, 1H), 2.24 (m, 1H), 1.78 (dd, *J* = 12.4, 6.4 Hz, 1H), 1.67 (dd, *J* = 12.4, 9.3 Hz, 1H), 1.32 (m, 6H), 1.02 (s, 3H), 0.89 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR: δ 143.8, 134.6, 116.7, 112.6, 84.7, 75.8, 47.5, 46.0, 40.7, 29.2, 29.0, 22.5, 6.9, 3.6. IR (neat): 3071 (m), 2962 (s), 2930 (s), 2865 (s), 1632 (m), 1469 (m), 1377 (m), 1100 (m), 1073 (m), 997 (m), 919 (s), 845 (w), 666 (w). LRMS (ESI) Calculated for $C_{14}H_{24}O$ (M+H)$^+$: 209.2. Found (M+H)$^+$: 209.2.
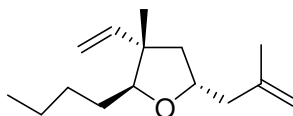
2-butyl-3-methyl-5-(2-methylallyl)-3-vinyltetrahydrofuran (1.17c): ^{1}H NMR: δ 5.77 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.07-5.00 (m, 2H), 4.75 (dd, *J* = 18.9, 1.8 Hz, 2H), 4.22 (m,

1H), 3.54 (dd, J = 8.2, 4.0 Hz, 1H), 2.37 (dd, J = 13.6, 6.5 Hz, 1H), 2.12 (dd, J = 13.6, 6.7 Hz, 1H), 1.80 (dd, J = 12.5, 6.4 Hz, 1H), 1.76 (s, 3H), 1.63 (dd, J = 12.5, 9.1 Hz, 1H), 1.37-1.25 (m, 6H), 1.02 (s, 3H), 0.88 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 144.1, 143.0, 112.8, 112.2, 84.6, 75.5, 47.7, 46.9, 45.0, 29.6, 29.3, 23.1, 22.9, 17.3, 14.0. IR (neat): 3071 (w), 2962 (s), 2930 (s), 2870 (m), 1735 (w), 1638 (m), 1453 (m), 1377 (m), 1111 (m), 1040 (m), 997 (m), 910 (m), 888 (m). LRMS (ESI) Calculated for $C_{15}H_{26}O$ (M+H)$^+$: 223.20. Found (M+H)$^+$: 223.2.
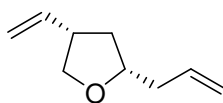
2-allyl-4-vinyltetrahydrofuran (1.18b): ^{1}H NMR: δ 5.82-5.64 (m, 2H), 5.08-4.99 (m, 2H), 4.96 (dd, J = 12.1, 1.7 Hz, 2H), 4.12-3.94 (m, 2H), 3.39 (t, J = 11.9, 1H), 2.89-2.78 (m, 1H), 2.34-2.13 (m, 2H), 1.76 (t, J = 7.9 Hz, 2H). ^{13}C NMR: δ 138.8, 134.6, 116.7, 114.8, 78.0, 72.6, 42.9, 40.1, 37.0. IR (neat): 2946 (s), 2848 (m), 1648 (m), 1458 (w), 1371 (w), 1089 (w), 910 (w). LRMS (ESI) Calculated for $C_9H_{14}O$ (2M + Na)$^+$: 299.2. Found (2M + Na)$^+$: 299.2.
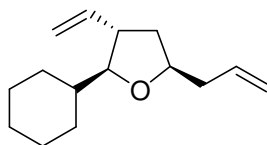
5-allyl-2-cyclohexyl-3-vinyltetrahydrofuran (1.19b): ^{1}H NMR: δ 5.85-5.68 (m, 2H), 5.22-5.00 (m, 2H), 4.96 (dd, J = 12.1, 1.8 Hz, 2H), 3.95 (m, 1H), 3.37 (dd, J = 8.2, 4.0 Hz, 1H), 2.72-2.57 (m, 1H), 2.43-2.30 (m, 1H), 2.35-2.14 (m, 1H), 2.83-1.60 (m, 7H), 1.50-1.39 (m, 1H), 1.27-1.03 (m, 5H). ^{13}C NMR: δ 140.5, 134.9, 116.7, 114.5, 88.2, 77.8, 45.4, 41.8, 40.4, 38.2, 29.8, 28.6, 26.6, 26.2, 26.1. IR (neat): 3076 (w), 2919 (s),

2859 (s), 1643 (m), 1447 (m), 1371 (w), 1084 (m), 975 (m), 915 (m). LRMS (ESI)

Calculated for $C_{15}H_{24}O$ (M+H)$^+$: 221.1. Found (M+H)$^+$: 221.1.
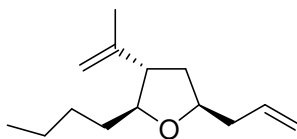
5-allyl-2-butyl-3-(prop-1-en-2-yl)tetrahydrofuran (1.20b): ^{1}H NMR: δ 5.86-5.78 (m,

1H), 5.08 (d, J = 18.7 Hz, 1H), 5.05 (d, J = 10.2 Hz, 1H), 4.76 (s, 2H), 3.98 (m, 1H), 3.67

(m, 1H), 2.41 (m, 2H), 2.24 (m, 1H), 1.92 (dt, J = 12.6, 5.2 Hz, 1H), 1.79-1.72 (m, 1H),

1.72 (s, 3H), 1.58-1.28 (m, 6H), 0.89 (t, J = 7.0 Hz, 3H). ^{13}C NMR: δ 145.0, 134.7,

116.6, 111.3, 82.1, 77.3, 51.4, 40.6, 36.3, 34.4, 28.2, 22.7, 20.0, 13.9. IR (neat): 3082

(w), 2957 (s), 2930 (s), 2859 (m), 1632 (m), 1453 (m), 1377 (m), 1095 (m), 997 (m), 915

(m), 888 (m). LRMS (ESI) Calculated for $C_{14}H_{24}O$ (M+H)$^+$: 209.2. Found (M+H)$^+$:

209.1.
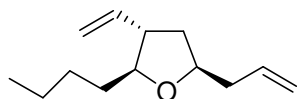
5-allyl-2-butyl-3-vinyltetrahydrofuran (1.21b): ^{1}H NMR (C_6D_6): δ 5.90-5.79 (m, 1H),

5.59-5.49 (m, 1H), 5.08-4.95 (m, 1H), 4.91 (dd, J = 16.2, 2.1 Hz, 2H), 3.93-3.87 (m, 1H),

3.42 (dt, J = 11.9, 3.8 Hz, 1H), 2.35-2.21 (m, 2H), 2.20-2.09 (m, 1H), 1.69-1.23 (m, 8H),

0.88 (t, J = 7.8, 3H). ^{13}C NMR: δ 139.4, 135.0, 116.8, 115.3, 84.0, 77.2, 48.7, 40.6,

37.5, 33.7, 28.3, 22.7, 13.8. IR (neat): 3082 (w), 2952 (s), 2930 (s), 2859 (m), 1648 (m),

1464 (m), 1377 (w), 1127 (m), 1078 (m), 986 (m), 910 (s), 666 (w). LRMS (ESI)

Calculated for $C_{13}H_{22}O$ (M+H)$^+$: 195.1. Found (M+H)$^+$: 195.1.

$$\text{(structure: 4-methylpent-4-en-1-ol with OH)}$$
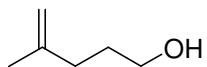
4-methylpent-4-en-1-ol (1.22): In a flame dried flask with a dry stir bar, methyl triphenylphosphonium bromide (41 g, 115 mmol) was dried with stirring under vacuum at 65 ºC for 4 hours before dissolving in 300 mL of THF. Next 78.2 mL of a 1.6 M solution of BuLi in hexanes was added, followed by 9.6 mL (94 mmol) of 3-acetyl-1-propanol. The mixture was stirred at room temperature for 4 hours before filtering through celite and removing the solvent under reduced pressure. Water (200 mL) was added to the residue and it was extracted three times with 150 mL of Et_2O. The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified via column chromatography using 90:10 hexanes:ethyl acetate as the eluent, yielding 4.48 g (47%) of a yellow oil as the product. R_f (80:20 hexanes:ethyl acetate): 0.12. ^{1}H NMR: δ 4.79 (d, J = 3.7 Hz, 2H), 3.77 (t, J = 4.7 Hz, 2H), 2.32 (t, J = 5.4 Hz, 2H), 2.02-1.92 (m, 5H). ^{13}C NMR: δ 149.4, 109.1, 66.8, 35.4, 27.6, 18.8.

$$\text{(structure: 3-methylbut-3-enyl methanesulfonate with OMs)}$$
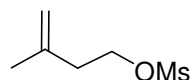
3-methylbut-3-enyl methanesulfonate (SI-1): To a flame-dried 2-neck flask equipped with stir bar and addition funnel, was added 20.0 mL (198 mmol) of 3-methyl-3-buten-1-ol and 400 mL of CH_2Cl_2. The solution was chilled to 0 ºC and 42.0 mL (301 mmol) of Et_3N was added. A solution of 23.2 mL (300 mmol) of MsCl and 100 mL of CH_2Cl_2 was mixed in the addition funnel and then added dropwise at 0 ºC. The solution was allowed to warm to room temperature and stirred for 1 hour. The reaction was quenched with 300 mL of saturated aqueous NH_4Cl and separated. The organic layer was washed twice with

100 mL of saturated aqueous NH_4Cl, followed by brine. The aqueous layers were extracted with CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude mesylate (a brownish green oil) was used immediately in the subsequent bromination reaction. ^1H NMR: δ 4.81 (d, $J = 31.6$ Hz, 2H), 4.29 (t, $J = 6.8$ Hz, 2H), 2.98 (s, 3H), 2.43 (t, $J = 6.8$ Hz, 2H), 1.75 (s, 3H).
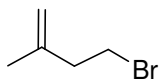
4-bromo-2-methylbut-1-ene (1.23): Unpurified **SI-1.1** was dissolved in 250 mL of THF and 34.0 g (391 mmol) of LiBr was added in one portion. The reaction was stirred at 65 °C for 12 hours and the reaction turned greenish-brown. Upon cooling, 300 mL of H_2O was added, and the organic layer was washed with brine before drying over Na_2SO_4. After filtering and concentrating, the crude brownish oil (19.7 g, 67% from 3-methyl-3-buten-1-ol) was used without further purification. R_f (80:20 hexanes:ethyl acetate): 0.64. ^1H NMR: δ 4.71 (d, $J = 38.7$ Hz, 2H), 3.48 (t, $J = 7.2$ Hz, 2H), 2.59 (t, $J = 7.2$ Hz, 2H), 1.64 (s, 3H).
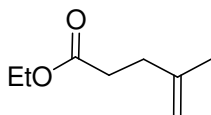
ethyl 4-methylpent-4-enoate (1.24): To a flame-dried flask was added 14 mL (166 mmol) of 2-methyl-2-propen-1-ol, 6 mL of propionic acid, and 280 mL of triethyl orthoacetate. The flask was fitted with a Claisen distillation adapter and heated to 130 °C for 7 hours. After cooling to room temperature, 400 mL of 3 M HCl was added slowly and stirred for 30 minutes (caution: very exothermic!). The solution was extracted three times with 300 mL of Et_2O and the combined organics were washed with 500 mL of saturated aqueous $NaHCO_3$ followed by brine. The organics were dried over $MgSO_4$,

filtered, and concentrated to reveal a clear, colorless oil with a pungently sweet odor. The crude ester was used in the next reaction without further purification. ^{1}H NMR: δ 4.52 (d, J = 22.7 Hz, 2H), 3.90 (q, J = 7.6 Hz, 2H), 2.10 (t, J = 8.7 Hz, 2H), 1.98 (t, J = 8.3 Hz, 2H), 1.35 (s, 3H), 0.83 (t, J = 7.6 Hz, 3H). ^{13}C NMR: δ 173.2, 144.0, 110.1, 60.0, 32.3, 32.2, 22.1, 13.8.
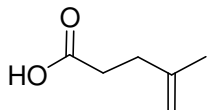
4-methylpent-4-enoic acid (S1-2): To crude ester **1.24** was added 200 mL of THF, 75 mL of H$_2$O, 75 mL of MeOH, and 11.84 g (282 mmol) of LiOH-H$_2$O. The mixture was stirred overnight at room temperature and then diluted with saturated aqueous NaHCO$_3$. The solution was acidified to pH 2 using 1 M HCl and then extracted three times with 150 mL of Et$_2$O. The combined organics were washed with 300 mL of H$_2$O, then 300 mL of brine before drying over MgSO$_4$, filtering, and concentrating. The acid was used in the next step without further purification. ^{1}H NMR: δ 4.69 (d, J = 21.7 Hz, 2H), 2.47 (t, J = 8.5 Hz, 2H), 2.30 (t, J = 8.5 Hz, 2H), 1.71 (s, 3H).
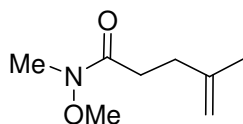
***N*-methoxy-*N*,4-dimethylpent-4-enamide (1.25):** The crude carboxylic acid was dissolved in 600 mL of CH$_2$Cl$_2$ before adding 47.7 g (249 mmol) of EDCI, 34.7 mL (249 mmol) of Et$_3$N, 24.3 g (249 mmol) of *N,O*-hydroxylamine hydrochloride, and 4.06 g (33.2 mmol) of DMAP. The solution was stirred under nitrogen for 2 hours before quenching with brine. The mixture was extracted three times with 250 mL of CH$_2$Cl$_2$ and the combined organics washed with 5% HCl then brine. The organics were dried

over Na$_2$SO$_4$, filtered, and concentrated, revealing the Weinreb's amide product as a clear, colorless oil. No further purification was needed for the next step. R_f (80:20 hexanes:ethyl acetate): 0.10. ^{1}H NMR: δ 4.68 (d, J = 4.8 Hz, 2H), 3.66 (s, 3H), 3.14 (s, 3H), 2.53 (t, J = 7.3 Hz, 2H), 2.30 (t, J = 8.7 Hz, 2H), 1.72 (s, 3H). ^{13}C NMR: δ 173.1, 144.9, 109.2, 67.7, 32.0, 25.3, 22.4, 18.9.
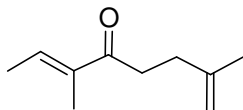
3,7-dimethylocta-2,7-dien-4-one (SI-1.2): In a dry flask equipped with stir bar and addition funnel, 8.27 g (340 mmol) of magnesium was flame-dried under vacuum. A solution of 33.96 mL (332 mmol) of 2-bromo-2-butene and 400 mL of THF was slowly added to the magnesium at 0 ℃ via the addition funnel, rinsing with 20 mL of THF (caution: very exothermic!). The solution was allowed to warm to room temperature and stirred for 1 hour before chilling to 0 ℃. A solution of crude amide **1.25** and 100 mL of THF was added to the reaction slowly via the additional funnel, rinsing with 10 mL of THF. The solution was warmed to room temperature and stirred for 3 hours. Upon quenching with saturated aqueous NH$_4$Cl and extracting three times with 300 mL of Et$_2$O, the combined organics were washed with brine, dried over MgSO$_4$, filtered and concentrated. The crude ketone was purified via column chromatography using 95:5 hexanes:ethyl acetate, producing 6.68 g of a clear, yellow oil as the desired product (a mixture of *E* and *Z* isomers) in 26% yield from 2-methyl-2-propen-1-ol. R_f (80:20 hexanes:ethyl acetate): 0.55. ^{1}H NMR: δ 6.71 (q, J = 7.4 Hz, 1H), 4.70 (d, J = 24.5 Hz, 2H), 2.46 (t, J = 8.3 Hz, 2H), 1.95 (t, J = 8.3 Hz, 2H), 1.47 (d, J = 7.4 Hz, 3H), 1.38 (s,

3H), 1.34 (s, 3H). ^{13}C NMR: δ 201.1, 144.9, 138.1, 137.8, 109.7, 35.0, 32.1, 22.3, 14.3, 10.6.
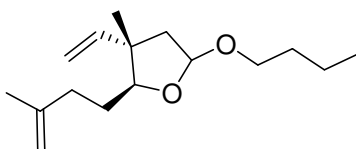
5-butoxy-3-methyl-2-(2-(2-methyloxiran-2-yl)ethyl)-3-vinyltetrahydrofuran (1.27): To a dry vial with stir bar was added 70 mg (0.28 mmol) of furan **1.13** and 1 mL of CH$_2$Cl$_2$, followed by 47 mg (0.28 mmol) of dry *m*CPBA. The solution was stirred overnight at room temperature before adding water and extracting three times with 5 mL of CH$_2$Cl$_2$. The combined organics were dried over Na$_2$SO$_4$ and concentrated. A flash chromatography column (95:5 hexanes:ethyl acetate) was used to purify the crude epoxide, revealing 31 mg (42%, 78% brsm) of a clear, colorless oil. R_f (80:20 hexanes:ethyl acetate): 0.17. ^{1}H NMR: δ 5.80 (dd, J = 17.4, 10.8 Hz, 1H), 5.10 (t, J = 4.2 Hz, 1H), 5.08-5.01 (m, 2H), 3.68 (m, 2H), 3.42-3.36 (m, 1H), 2.65-2.62 (m, 1H), 2.60-2.57 (m, 1H), 2.00 (dd, J = 12.1, 4.6 Hz, 1H), 1.89 (dd, J = 12.1, 4.2 Hz, 1H), 1.60-1.33 (m, 8H), 1.30 (s, 3H), 0.98 (s, 3H), 0.91 (t, J = 1.5 Hz, 3H). ^{13}C NMR: δ 143.0, 113.0, 112.4, 82.9, 67.6, 56.8, 53.4, 47.9, 34.0, 31.7, 24.1, 21.1, 20.9, 19.2, 18.1, 13.8. HRMS (ESI): Calculated for C$_{16}$H$_{28}$O$_3$ [M+Na]$^+$: 291.194. Found [M+Na]$^+$: 291.194.
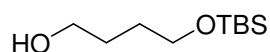
4-(*tert*-butyldimethylsiloxy)butan-1-ol[25] **(SI-1.3):** In a glovebox, to a dry flask was added 4.8 g (200 mmol) of NaH and 250 mL of THF. The flask was sealed with a septum and removed from the glovebox. To the stirring suspension was added 17.7 mL (200 mmol) of 1,4-butanediol. An extremely thick white precipitate formed as the reaction was allowed to stir for 45 minutes at room temperature. After that time, 30.2 g

(200 mmol) of TBSCl was added swiftly. The precipitate broke up and the solution was allowed to stir 45 more minutes at room temperature. The solution was quenched with 10% K_2CO_3 and extracted three times with 200 mL of Et_2O. The combined organics were washed with brine and dried over $MgSO_4$ before filtering and concentrating. No further purification was performed before oxidizing in the next step. R_f (80:20 hexanes:ethyl acetate): 0.28. ^{1}H NMR: δ 3.68-3.61 (m, 2H), 2.55 (br s, 1H), 1.68-1.62 (m, 4H), 0.88 (s, 9H), 0.07 (s, 6H). ^{13}C NMR: δ 63.3, 62.7, 30.2, 29.9, 26.0, 18.1, -5.4.
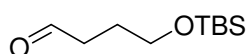
4-(*tert*-butyldimethylsilyloxy)butanal (1.28): The crude monoprotected butanediol (**SI-1.3**) was then mixed with 300 mL of CH_2Cl_2 and 20 g of powdered 4 Å molecular sieves. The stirring solution was chilled to 0 ºC before slowly adding a combination of 1.05 g (3.0 mmol) of TPAP and 35.2 g (300 mmol) of NMO. The solution was stirred to room temperature for 3 hours. At that time, the molecular sieves were filtered off through a cotton plug and rinsed with CH_2Cl_2. The filtrate was concentrated before running through a thick silica plug using 95:5 hexanes:ethyl acetate to remove the remaining ruthenium. A clear, light yellow oil (40.2 g, 99%) was isolated. R_f (80:20 hexanes:ethyl acetate): 0.55. ^{1}H NMR: δ 9.78 (t, J = 1.8 Hz, 1H), 3.65 (t, J = 5.9 Hz, 2H), 2.50 (dt, J = 7.2, 1.8 Hz, 2H), 1.82 (qu, J = 5.1 Hz, 2H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR: δ 202.4, 61.9, 40.6, 25.8, 25.3, 18.1, -5.6. HRMS (ESI): Calculated for $C_{10}H_{22}O_2Si$ [2M+Na][+]: 427.268, [3M+Na][+]: 629.406. Found [2M+Na][+]: 427.260 and [3M+Na][+]: 629.398.
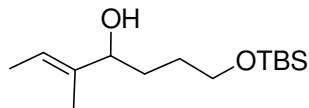
7-(*tert*-butyldimethylsilyloxy)-3-methyl2-hepten-4-ol (1.29): To a dry flask with stir bar and addition funnel was added 190 mg (7.81 mmol) of magnesium, which was in turn flame-dried under vacuum. A crystal of iodine was added and the flask evacuated and backfilled with nitrogen. A solution of 0.76 mL (7.41 mmol) of 2-bromo-2-butene and 15 mL of THF was added slowly to the magnesium via the addition funnel (*caution*: very exothermic!). After approximately 3 hours, when most of the magnesium had been consumed, a solution of 1 g (4.94 mmol) of aldehyde **1.28** in 10 mL of THF was slowly added to the stirring Grignard solution. After the addition was complete, the reaction was allowed to stir for 3 hours before quenching carefully with saturated aqueous NH_4Cl. The mixture was then extracted three times with 30 mL of Et_2O, and the combined organics were washed with brine and dried over $MgSO_4$ before concentrating. The crude residue was pushed through a silica plug using 85:15 hexanes:ethyl acetate, revealing 1.26 g (99%) of a clear, colorless oil. R_f (80:20 hexanes:ethyl acetate): 0.36. ^{1}H NMR: δ 5.33 (q, J = 8.1 Hz, 1H), 3.70-3.62 (m, 3H), 1.71-1.67 (m, 3H), 1.65-1.55 (m, 7H), 0.92 (s, 9H), 0.08 (s, 6H). ^{13}C NMR: δ 137.4, 121.2, 68.9, 63.0, 32.0, 29.1, 25.5, 18.1, 17.3, 12.8, -5.7. IR (neat): 3408 (br m), 2957 (s), 2924 (s), 2886 (m), 2859 (s), 1719 (m), 1469 (m), 1377 (w), 1252 (s), 1100 (s), 1002 (m), 845 (s), 774 (s). HRMS (ESI) Calculated for $C_{14}H_{30}O_2Si$ [M+Na]$^+$: 281.191. Found [M+Na]$^+$: 281.191.
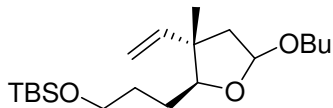
5-butoxy-3-methyl-3-vinyltetrahydrofuran-2-ylpropoxy(*tert*-butyl)dimethylsilane

(1.30): To a vial containing a stir bar and 1.23 g (4.76 mmol) of allylic alcohol **1.29** was added 10 mL of MeCN before adding 2.46 mL (19.0 mmol) of butyl vinyl ether. Palladium(II) acetate (107 mg, 0.48mmol), 86 mg (0.48 mmol) of Cu(OAc)$_2$, and 105 mg (0.95 mmol) of catechol were weighed together and simultaneously added to the starting material solution which immediately turned very dark brown in color. The vial was fitted with a cap that has an inlaid septum before introducing a balloon filled with oxygen via a 10 cm, 18 gauge needle. The oxygen was allowed to bubble through the solution by adding a vent needle (26 gauge), and the whole apparatus was left stirring for 16 hours at room temperature. After that time, the solution was extracted three times with 15 mL of hexanes. The combined extractions were filtered through cotton before concentrating. The crude residue was purified via column chromatography (95:5 hexanes:ethyl acetate), revealing 1.29 g (76%) of a clear, yellow oil as a mixture of diastereomers of the furan product. R_f (80:20 hexanes:ethyl acetate): 0.69. ^{1}H NMR: δ 5.81 (dd, J = 17.4, 10.8 Hz, 1H), 5.11 (dd, J = 4.5, 4.4 Hz, 1H), 5.06-5.01 (m, 2H), 3.74-3.55 (m, 4H), 3.43-3.37 (m, 1H), 2.00 (dd, J = 13.5, 5.8 Hz, 1H), 1.89 (dd, J = 13.5, 4.3 Hz, 1H), 1.76-1.34 (m, 8H), 0.97 (s, 3H), 0.92 (t, J = 7.4 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H). ^{13}C NMR: δ 143.5, 113.2, 102.7, 83.3, 67.8, 63.0, 48.0, 47.4, 31.9, 30.5, 25.9, 25.0, 19.4, 18.3, 18.2, 13.8, -5.3. IR (neat): 3076 (w), 2968 (s), 2930 (s), 2859 (s), 1638 (w), 1469 (m), 1382 (m), 1257 (s), 1100 (s), 1002 (s), 915 (m), 826 (s), 774 (s). HRMS (ESI): Calculated for C$_{20}$H$_{40}$O$_3$Si [M+Na]$^+$: 379.264. Found [M+Na]$^+$: 379.270.
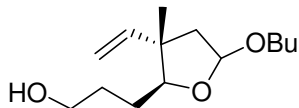
5-butoxy-3-methyl-3-vinyltetrahydrofuran-2-yl-propanol (SI-1.4): In a dry flask with stir bar was mixed 732 mg (2.05 mmol) of furan **1.30** and 8 mL of THF. The vessel was purged with N_2 and 2.46 mL (2.46 mmol) of TBAF (1 M in THF) was added slowly. The solution was stirred 2 hours at room temperature, over which time it turned dark greenish yellow. Brine was added and the mixture was extracted three times with 10 mL of Et_2O. The combined organics were dried over $MgSO_4$ before filtering and concentrating. A flash chromatography column (70:30 hexanes:ethyl acetate) was used to purify the residue, yielding 363 mg (73%) of a clear, yellow oil as a mixture of diastereomers of the desired product. R_f (80:20 hexanes:ethyl acetate): 0.14. ^{1}H NMR: δ 5.79 (dd, J = 17.7, 10.6 Hz, 1H), 5.13 (t, J = 5.3 Hz, 1H), 5.07-5.00 (m, 2H), 3.75-3.62 (m, 4H), 3.42-3.33 (m, 1H), 2.51 (br s, 1H), 2.01 (dd, J = 13.6, 5.8 Hz, 1H), 1.89 (dd, J = 13.6, 4.5 Hz, 1H), 1.72-1.65 (m, 2H), 1.58-1.47 (m, 4H), 1.44-1.33 (m, 2H), 1.15 (s, 3H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C NMR: δ 144.4, 113.6, 103.3, 83.7, 68.0, 62.9, 47.7, 46.3, 31.8, 30.8, 27.5, 19.4, 18.5, 13.8. IR (neat): 3408 (br m), 3082 (w), 2962 (s), 2930 (s), 2870 (s), 1643 (w), 1458 (m), 1371 (m), 1095 (s), 1057 (s), 1002 (s), 915 (m). HRMS (ESI): Calculated for $C_{14}H_{26}O_3$ [M+Na]$^+$: 265.178. Found [M+Na]$^+$: 265.177.
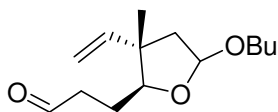
5-butoxy-3-methyl-3-vinyltetrahydrofuran-2-yl-propanal (1.31): In a dry vial was mixed 150 mg of powdered 4 Å molecular sieves, 4 mL of CH_2Cl_2, 262 mg (2.24 mmol) of NMO, and 8 mg (0.02 mmol) of TPAP. A solution of 362 mg of **S1-2** in 2 mL of

CH$_2$Cl$_2$ was added and the reaction stirred for 2 hours at room temperature. The molecular sieves were filtered off through a Büchner funnel and rinsed with CH$_2$Cl$_2$. The filtrate was concentrated and run through a thick silica plug using 95:5 hexanes:ethyl acetate to remove the ruthenium, yielding 290 mg (81%) of a clear, colorless oil as a mixture of diastereomers of the desired aldehyde. R_f (80:20 hexanes:ethyl acetate): 0.33. ^{1}H NMR: δ 5.81 (dd, J = 17.4 and 10.7 Hz, 1H), 5.12-5.01 (m, 3H), 3.72-3.63 (m, 2H), 3.41-3.33 (m, 1H), 2.66-2.59 (m, 1H), 2.54-2.47 (m, 1H), 2.02 (dd, J = 13.6, 5.8 Hz, 1H), 1.90 (dd, J = 13.6, 4.3 Hz, 1H), 1.71-1.66 (m, 2H), 1.60-1.51 (m, 2H), 1.41-1.32 (m, 2H), 1.00 (s, 3H), 0.92 (t, J = 7.4 Hz, 3H). ^{13}C NMR: δ 202.1, 142.9, 113.7, 102.7, 82.7, 67.9, 47.9, 47.3, 41.8, 31.8, 21.5, 19.3, 18.2, 13.8. IR (neat): 3087 (w), 2962 (s), 2924 (s), 2876 (m), 2707 (w), 1730 (m), 1643 (w), 1447 (w), 1328 (w), 1089 (m), 1094 (s), 915 (w). HRMS (ESI) Calculated for C$_{14}$H$_{24}$O$_3$ [M+Na]$^+$: 263.17 and [M+K]$^+$: 279.17. Found [M+Na]$^+$: 263.2 and [M+K]$^+$: 279.2.
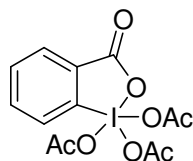
Dess-Martin periodinane: To a dry 3-neck, 1-L round bottom flask equipped with mechanical stirrer and a condenser, was added 51.7 g (310 mmol) of KBrO$_3$ and 479 (958 mmol) of H$_2$SO$_4$. A tube was fitted from the condenser to the back panel of the hood for ventilation of Br$_2$ that would form over the course of the reaction. The reaction was heated to 60 ºC, and through the open neck was added 51.2 g (206 mmol) of 2-iodobenzoic acid in small portions over 40 minutes. The sides of the flask were rinsed with 50 mL of H$_2$SO$_4$. By this time, the solution had turned orange and was evolving bromine gas. The mixture was stirred at 60 ºC for 2.5 hours before chilling in an ice-bath

and then filtering through a Büchner funnel, taking care to contain the bromine gas. (CAUTION: the solid is extrememly shock sensitive and should be handled with care). The solid was washed with 350 mL of cold H_2O, twice with 75 mL of cold absolute EtOH, and finally by another 350 mL portion of cold H_2O. The solid is a contact explosive and should not be allowed to completely dry. Using a rubber policeman, the white solid is scraped gently into a 2-neck, 500 mL flask for the next step. The flask is then flushed with nitrogen after adding a condenser. To the flask is added 191 mL of Ac_2O and 96 mL of HOAc. The reaction was slowly heated with stirring until the solid completely dissolved (approximately 80 ºC over 45 minutes) and a clear solution was obtained. Heating and stirring were stopped and the solution was allowed to sit at room temperature overnight, over which time white crystals should have precipitated out of solution. Upon no formation of crystals overnight, the cloudy solution was put in the refrigerator for 3 hours. The crystals that formed were then filtered off and washed with 500 mL of dry Et_2O before storing in a dark bottle. The bottle was put under high vacuum in a desiccator equipped with a cold trap to contain the acetic acid. After sufficient drying, yielding approximately 50 g Dess-Martin periodinane in 39% yield as a white solid. The slight HOAc odor should not effect oxidation reactions. The readily hydrolyzable crystals should be stored in a dark bottle in a desiccator in the freezer. (Dess, D.B.; Martin, J.C. *J. Org. Chem.* **1983**, *48*, 4155-4156.)
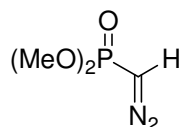
dimethyl diazomethylphosphonate (Gilbert-Seyferth reagent): In a dry flask, 2.0 mL (18.4 mmol) of dimethyl methylphosphonate was dissolved with 40 mL of THF and the

solution was chilled to -78 ºC. Dropwise was added 7.36 mL (18.4 mmol) of *n*-butyllithium (2.5 M in hexanes), and the reaction stirred for 30 minutes at -78 ºC. Quickly, 3.73 mL (27.6 mmol) of 2,2,2-trifluoroethyl trifluoroacetate was added and the reaction stirred for 15 minutes at -78 ºC. The reaction was warmed to room temperature and 100 mL of Et_2O and 100 mL of 1 M HCl were added. The biphasic mixture was extracted three times with 75 mL of Et_2O. The combined organics were washed with saturated aqueous $NaHCO_3$ followed by brine and then dried over $MgSO_4$, filtered, and concentrated. A yellow oil (4.39 g, 100%) was obtained and used without further purification. The crude oil (4.39 g, 18.4 mmol) was then dissolved in 40 mL of MeCN in a flask with stir bar and 3.97 g (16.5 mmol) of *p*ABSA was added. (Note: commercially available *p*ABSA can be used, but the yields are higher with freshly prepared *p*ABSA—see below) The reaction was chilled to 0 ºC and 2.29 mL (16.5 mmol) of Et_3N was slowly added. The solution was warmed to room temperature and stirred overnight. The solution was concentrated and should have revealed an orange/white slurry. However, upon adding ethyl acetate and re-concentrating, the orange-white slurry was obtained. Column chromatography, eluting with 100% EtOAc revealed 1.04 g (38%) of the desired yellow oil. R_f (80:20 hexanes:ethyl acetate): 0.24. **pABSA:** To a dry flask with stir bar is added 2.85 g (43.9 mmol) of NaN_3 and 500 mL of dry acetone. The solution is cooled to 0 ºC and 10.05 g (43 mmol) of *N*-acetylsulfanilyl chloride was added in portions. The reaction was stirred for 48 hours at room temperature, over which time a thick slurry formed. The slurry was filtered and the filtrate was concentrated to reveal beige crystals. ^{1}H NMR: δ 7.87 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 2H), 2.24 (s, 3H). ^{13}C NMR δ

168.9, 144.1, 132.3, 128.8, 119.3, 24.6. (Brown, D. G.; Velthuisen, E. J.; Commerford, J. R.; Brisbois, R. G.; Hoye, T. H. *J. Org. Chem.* **1996**, *61*, 2540-2541.)
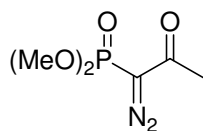
dimethyl 1-diazo-2-oxopropylphosphonate (Ohira-Bestman reagent): In a flask equipped with stir bar, 1.51 g (23.26 mmol) of NaN_3 was dissolved in 24 mL of H_2O and 6 mL of acetone. Next, a solution of 4.03 g (21.14 mmol) of TsCl in 8 mL of acetone was slowly added to the reaction and the syringe rinsed with 2 mL of acetone into the flask. After stirring overnight, the acetone was removed under reduced pressure and the remaining residue was dissolved in CH_2Cl_2. The biphasic mixture was washed three times with 30 mL of H_2O and the organic layer dried over Na_2SO_4, filtered, and concentrated to reveal crude tosyl azide in quantitative yield. R_f (80:20 hexanes:ethyl acetate): 0.36. In a glovebox, 512 mg (21.34 mmol) of NaH was added to a flask with stir bar. The flask was sealed and removed to the fume hood. Under a stream of N_2 was added 60 mL of toluene and 5 mL of THF. The slurry was chilled to 0 °C and stirred for 15 minutes before adding dropwise a solution of 2.7 mL (19.76 mmol) of dimethyl-(2-oxopropyl)-phosphonate in 20 mL of toluene. The solution was stirred 1 hour at 0 °C and then crude TsN_3 (4.17 g, 21.14 mmol) was added dropwise as a solution in 10 mL of toluene. The reaction was stirred for 2.5 hours at room temperature before filtering through silica and concentrating. Column chromatography (1:2 hexanes:ethyl acetate) revealed a clear yellow oil (3.83 g, 94%) as the desired product. (Curphey, T.J. *Org. Prep. Proc. Intl.* **1981**, *13,* 112-115.)
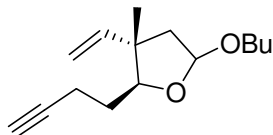
2-(3-butynyl)-5-butoxy-3-methyl-3-vinyltetrahydrofuran (1.32): To a dry vial with stir bar was added 80 mg (0.33 mmol) of **1.31**, 3 mL of dry MeOH, 77 mg (0.40 mmol) of Ohira-Bestman reagent, and 92 mg (0.67 mmol) of dry K_2CO_3. The cloudy mixture was stirred overnight, over which time the K_2CO_3 dissolved in the dark yellow solution. The solution was quenched with 5% $NaHCO_3$ and extracted three times with 5 mL of Et_2O. The combined organics were dried over $MgSO_4$, filtered and concentrated. The cloudy biphasic residue was redissolved in CH_2Cl_2 and dried over Na_2SO_4, filtered, and concentrated. To purify, the crude yellow oil was diluted with hexanes at which point a white precipitate formed and was filtered off through a thick plug of silica using hexanes. The filtrate was concentrated to 68 mg (87%) of a clear, light yellow oil as a mixture of diastereomers of the desired alkyne. R_f (80:20 hexanes:ethyl acetate): 0.67. ^{1}H NMR: δ 5.82 (dd, J = 17.2, 11.0 Hz, 1H), 5.11 (dd, J = 5.7, 4.4 Hz, 1H), 5.08-5.01 (m, 2H), 3.82 (dd, J = 8.8, 3.9 Hz, 1H), 3.72-3.67 (m, 1H), 3.43-3.35 (m, 1H), 2.31 (m, 2H), 2.01 (dd, J = 13.6, 5.8 Hz, 1H), 1.95-1.88 (m, 2H), 1.62-1.53 (m, 4H), 1.40-1.36 (m, 2H), 0.98 (s, 3H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR: δ 142.9, 113.3, 102.6, 84.0, 81.8, 68.1, 67.6, 47.9, 47.0, 31.7, 28.0, 19.3, 18.1, 16.4, 13.7. IR (neat): 2957 (s), 2924 (s), 2870 (m), 1442 (w), 1333 (w), 1084 (m), 1051 (w), 1013 (m), 910 (w). LRMS (APCI) Calculated for $C_{15}H_{24}O_2$ (M+H)$^+$: 237.18. Found (M+H)$^+$: 237.2.
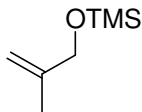
tert-butyldimethyl(2-methylallyloxy)silane (1.34): To a flame-dried flask was added 8 mL (95.1 mmol) of 2-methyl-2-propen-1-ol and 200 mL of THF. The solution was chilled to -78 ℃ and 41.84 mL (104.6 mmol) of butyllithium (2.5 M in hexanes) was added dropwise. The solution was stirred for 30 minutes at this temperature before adding a solution of 13.4 mL (104.6 mmol) of TMSCl and 12 mL of THF. The reaction was again stirred for 30 minutes at -78 ℃. The light yellow solution was used immediately in the following rearrangement. LRMS (ESI) Calculated for $C_9H_{18}O_2Si$ (M)$^+$: 186.11. Found (M)$^+$: 186.23.
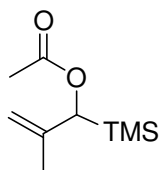
2-methyl-1-(trimethylsilyl)allyl acetate (1.35): At -78 ℃, 67 mL (114.1 mmol) of _tert_-butyllithium (1.7 M in pentane) was added slowly to the solution of **1.34** and the resulting dark yellow slurry was stirred for 10 minutes. The reaction was then allowed to warm to -40 ℃ and stirred for 3 hours while it became a solution before rapidly adding a solution of 12.7 mL (134.1 mmol) of Ac_2O and 12 mL of THF. The solution was then warmed to room temperature and quenched with water. Following extraction (three times with 200 mL of EtOAc), the organic layers were washed with water, then with saturated aqueous $NaHCO_3$, then brine. After drying over $MgSO_4$, the organics were filtered, and concentrated to reveal a dark reddish yellow oil that was used immediately in the next step.
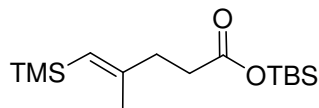
(*E*)-tert-butyldimethylsilyl 4-methyl-5-(trimethylsilyl)pent-4-enoate (1.36): In a dry flask with stir bar, crude ester **1.35** was mixed with 200 mL of CH_2Cl_2 and chilled to 0 ℃. Diisoproylethylamine (33.13 mL, 190 mmol) was added slowly. Next 28.4 mL (124 mmol) of TBSOTf was added and the reaction was stirred to room temperature. The solution was heated to reflux for 24 hours before cooling to 0 ℃ and carefully quenching with saturated aqueous $NaHCO_3$. The mixture was extracted three times with 200 mL of CH_2Cl_2. The combined organics were washed twice with 1 M $KHSO_4$ then brine, and dried over Na_2SO_4, filtered, and concentrated. A reddish orange oily solid (28.0 g, 98%) was obtained and used without further purification. MS (APCI+) Calculated for $C_{15}H_{32}O_2Si_2$ $(M+H)^+$: 300.2. Found $(M+H)^+$: 300.3.
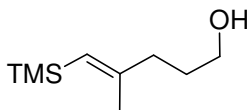
(*E*)-4-methyl-5-(trimethylsilyl)pent-4-en-1-ol (1.37): In a dry flask, 1.47 g (4.89 mmol) of crude silyl ester **1.36** was mixed with 10 mL of THF. The solution was chilled to 0 ℃ before slowly adding 9.78 mL (9.78 mmol) of diisobutylaluminum hydride (1.0 M in toluene). The reaction was stirred for 16 hours before quenching carefully with saturated aqueous potassium sodium tartrate (Rochelle's salt). The slurry was stirred at room temperature for an hour before extracting three times with 20 mL of EtOAc. The combined organics were dried over Na_2SO_4, filtered, and concentrated. A silica gel column was run using 70:30 hexanes:ethyl acetate, revealing 812 mg (96%) of a dark yellow oil. R_f (80:20 hexanes: ethyl acetate): 0.17.
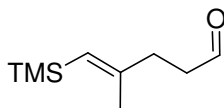
(*E*)-4-methyl-5-(trimethylsilyl)pent-4-enal (1.38): To a dry flask with stir bar was added 1.10 g (6.38 mmol) of alcohol **1.37**, 25 mL of CH_2Cl_2, and 1 g 4 Å molecular sieve beads. The solution was chilled to 0 ºC before slowly adding 1.12 g (9.57 mmol) of NMO and 34 mg (0.09 mmol) of TPAP. The black reaction was stirred at room temperature for 3 hours before filtering off the molecular sieves, washing with CH_2Cl_2. The dark brown solution was concentrated and then run through a thick silica plug using 90:10 hexanes:ethyl acetate to remove the ruthenium, yielding 536 mg (49%) of a bright yellow oil as the desired aldehyde. R_f (80:20 hexanes: ethyl acetate): 0.36.
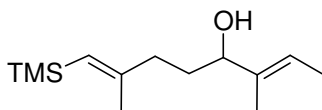
(2*E*,7*E*)-3,7-dimethyl-8-(trimethylsilyl)octa-2,7-dien-4-ol (1.39): To a flame-dried flask with stir bar was added 121 mg (4.96 mmol) of magnesium flakes, which was then flame-dried under vacuum. A crystal of iodine was added and the vessel evacuated and backfilled with nitrogen. A solution of 0.48 mL (4.72 mmol) of 2-bromo-2-butene (*cis* and *trans* mixture) in 10 mL of THF was added dropwise to the stirring magnesium. The reaction was allowed to stir at room temperature until the magnesium was nearly completely consumed (3 hours). Next a solution of 534 mg of **1.38** in 5 mL of THF was added dropwise to the Grignard solution. After stirring for 3 hours at room temperature, saturated aqueous NH_4Cl was added and the biphasic mixture was extracted three times with 20 mL of Et_2O. The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated. A silica gel column eluted with 95:5 hexanes:ethyl acetate

revealed 666 mg of a light yellow oil (94%). R_f (80:20 hexanes: ethyl acetate): 0.38. MS

(APCI+) Calculated for $C_{13}H_{26}OSi$ (M+H)$^+$: 226.18. Found (M+H)$^+$: 226.3.
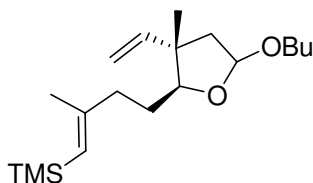
((*E*)-4-((2*S*,3*S*)-5-butoxy-3-methyl-3-vinyltetrahydrofuran-2-yl)-2-methylbut-1-

enyl)trimethylsilane (1.40): To a dry vial with stir bar was added 110 mg of allylic

alcohol **1.39**, 1 mL of MeCN, and 0.25 mL of butyl vinyl ether. In one addition,

palladium(II) acetate (11 mg, 0.049 mmol), copper(II) acetate (9 mg, 0.049 mmol), and

catechol (11 mg, 0.097 mmol) were added. The cap with inlaid septum was secured and

oxygen was bubbled through the solution from a balloon while stirring for 24 hours. At

this time, the dark brown solution was extracted with hexanes and filtered through a

cotton plug prior to concentrating. The crude product was run through a silica gel

column eluted with 95:5 hexanes:ethyl acetate, yielding 92 mg of a yellow oil (58%). R_f

(80:20 hexanes: ethyl acetate): 0.71. HRMS (ESI) Calculated for $C_{19}H_{36}O_2Si$ (M+Na)$^+$:

347.25. Found (M+Na)$^+$: 347.24.
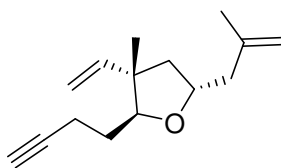
2-(3-butynyl)-3-methyl-5-(2-methylallyl)-3-vinyltetrahydrofuran (1.41): To a dry

vial with stir bar was added 233 mg (0.99 mmol) of alkyne **1.32**, 1 mL of CH_2Cl_2, and

0.26 mL (1.48 mmol) of methallyltrimethylsilane. Next 97 mg (0.20 mmol) of Sc(OTf)$_3$

was added, and the reaction began turning dark yellow. After stirring for 5 hours at room

temperature, the reaction was quenched with saturated aqueous NaHCO$_3$. The biphasic

mixture was allowed to stir for 10 minutes before extracting three times with 5 mL of CH$_2$Cl$_2$. The combined organics were dried over Na$_2$SO$_4$, filtered, and concentrated. After running through a silica column eluting with 99:1 CH$_2$Cl$_2$:MeOH, 170 mg (79%) of a clear, colorless oil as a 7:1 mixture of diastereomers of the desired furan. R_f (80:20 hexanes:ethyl acetate): 0.64. ^{1}H NMR δ 5.78 (dd, J = 17.4, 10.7 Hz, 1H), 5.08-5.03 (m, 2H), 4.75 (d, J = 19.7 Hz, 2H), 4.22 (m, 1H), 3.65 (dd, J = 6.7, 4.6 Hz, 1H), 2.40-2.31 (m, 2H), 2.27-2.16 (m, 1H), 2.12 (dd, J = 13.8, 6.34 Hz, 1H), 1.93 (s, 1H), 1.83 (dd, J = 12.5, 6.4 Hz, 1H), 1.76 (s, 3H), 1.68 (dd, J = 12.5, 9.05 Hz, 1H), 1.60-1.53 (m, 2H), 1.03 (s, 3H). ^{13}C NMR δ 143.3, 142.7, 113.1, 112.1, 84.1, 82.6, 75.5, 68.0, 47.4, 46.7, 44.7, 28.6, 22.9, 17.2, 16.1. IR (neat): 3310 (m), 3082 (w), 2957 (s), 2935 (s), 2865 (m), 1741 (w), 1632 (m), 1464 (m), 1371 (m), 1252 (w), 1149 (m), 1105 (m), 1057 (m), 915 (m), 888 (m), 617 (m). LRMS (APCI) Calculated for C$_{15}$H$_{22}$O [M+H]$^+$: 219.17. Found [M+H]$^+$: 219.2.
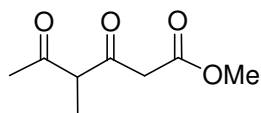
methyl 4-methyl-3,5-dioxohexanoate (1.45): In a dry flask was mixed 26.6 mL (26.6 mmol) of a 1 M solution of LiHMDS in hexane, 4.3 mL (20.6 mmol) of HMDS, and 20 mL of THF at -78 ℃. Next 1 mL (8.59 mmol) of 3-methylpentane-2,4-dione was added and the reaction stirred at room temperature for 4 hours. The solution was recooled to -78 ℃ and 0.8 mL (9.5 mmol) of dimethyl carbonate was added before allowing to stir to room temperature overnight. After quenching with 1 M HCl, it was extracted three times with 20 mL of EtOAc. The combined organics were dried over Na$_2$SO$_4$, filtered, and

concentrated, revealing an orange oily solid, which was used without further purification in the cyclization reaction.
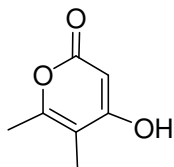
4-hydroxy-5,6-dimethyl-2*H*-pyran-2-one (1.44): 1.11 g of **1.45** and 50 mL of pH 9.2 buffer. The solution was stirred overnight at room temperature before acidifying with 1 M HCl and extracting three times with 25 mL of EtOAc. The extracts were dried over Na_2SO_4, filtered, and concentrated, revealing 491 mg (55%) of a yellow/orange solid as product after drying under high vacuum. ^{1}H NMR: δ 5.18 (s, 1H), 2.13 (s, 3H), 1.83 (s, 3H).

CHAPTER II

SILYLGLYOXYLATES AND
THE TOTAL SYNTHESIS OF ALTERNARIC ACID

A. Synthesis and Utilization of Silylglyoxylates

A.1. Background and Recent Advances

Tandem reactions and multicomponent couplings have long been a desirable goal for organic synthesis, as they quickly and efficiently fashion complex molecules from simpler starting materials.[1] The crucial determinant of success in such domino reactions, however, is the ability to control how and when the building blocks will react with one another. The solution to this challenge is also the benefit to domino reactions, that is, *in situ* formation of a reactant rather than pre-formation.

A common multicomponent reaction is Michael addition to a conjugated enone followed by trapping with an electrophile to yield a new vicinal disubstituted product (Scheme 2.1).[2] A similar, albeit more synthetically challenging, multicomponent reaction arises when the electrophilic carbon center and the nucleophilic carbon center are one and the same. Therefore, the *how* and the *when* of the individual steps become that much more important when all of the components are present in the reaction solution contemporaneously.

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[1] Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115-36.

[2] Suzuki, M.; Kawagishi, T.; Yanagisawa, A.; Suzuki, T.; Okamura, N.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1299-1312.

Scheme 2.1. Multicomponent Coupling with Nucleophilic/Electrophilic Carbon
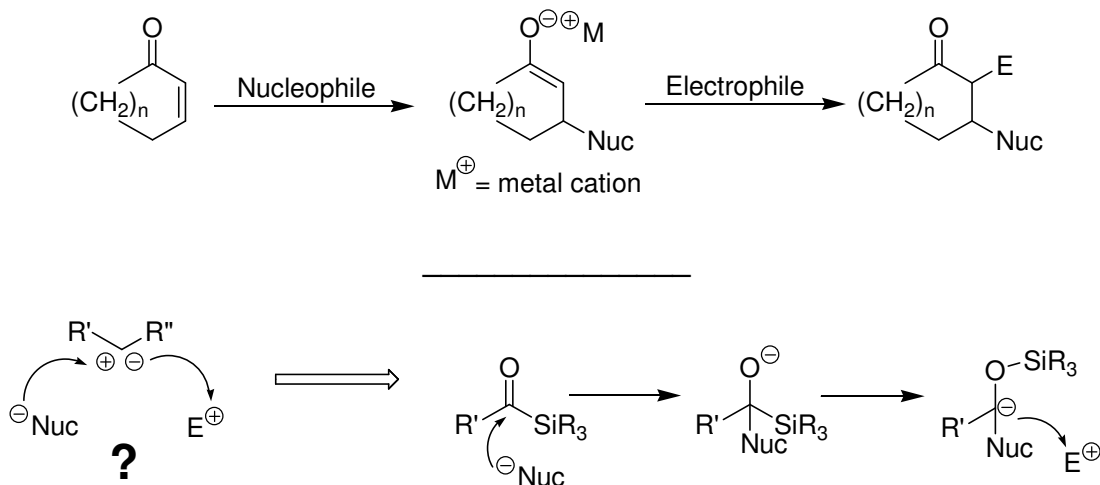
One solution to this conundrum comes in the form of acyl silanes (**2.1**, Scheme 2.2).[3] Nucleophilic addition to an acylsilane often prompts migration of the silyl group to the formed oxyanion, thus generating a carbanion at the addition center.[4] The driving force for this Brook rearrangement stems from the net energy difference between a carbon-silicon bond and an oxygen silicon bond.   The newly formed carbanion can then participate in an additional bond forming event with another electrophile.[5]   One such reaction developed by the Johnson lab is the catalytic tandem cyanation/Brook rearrangement/*C*-acylation reaction.[6]   In this case, an acylsilane (**2.1**) is subjected to a cyanoformate ester in the presence of catalytic metal cyanide and 18-crown-6. After a nucleophilic attack of cyanide on the acylsilane, the Brook rearrangement leaves a cyano-

[3] Moser, W. H. *Tetrahedron* **2001**, *57*, 2065-2084.

[4] Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77-84.

[5] (a) Kuwajima, I.; Kato, M. *Tetrahedron Lett.* **1980**, *21*, 623-626. (b) Takeda, K.; Ohnishi, Y. *Tetrahedron.Lett* **2000**, *41*, 4169-4172. (c) Reich, H. J.; Holtan, R. C.; Bolm, C. *J. Am. Chem. Soc.* **1990**, *112*, 5609-5617. (d) Degl'Innocenti, A.; Ricci, A.; Mordini, A.; Reginato, G.; Colotta, V. *Gazz. Chim. Ital.* **1987**, *117*, 645-648.

[6] (a) Linghu, X.; Nicewicz, D. A.; Johnson, J. S. *Org. Lett.* **2002**, *4*, 2957-2960. (b) Nicewicz, D. A.; Yates, C. M.; Johnson, J. S. *J. Org. Chem.* **2004**; *69,* 6548-6555.

stabilized carbanion (**2.2**). The carbanion then adds into the formate, expelling the product (**2.3**) and cyanide which re-enters the catalytic cycle.

Scheme 2.2.   Catalytic Cycle for Tandem Cyanation/ Brook rearrangement/ *C*-Acylation
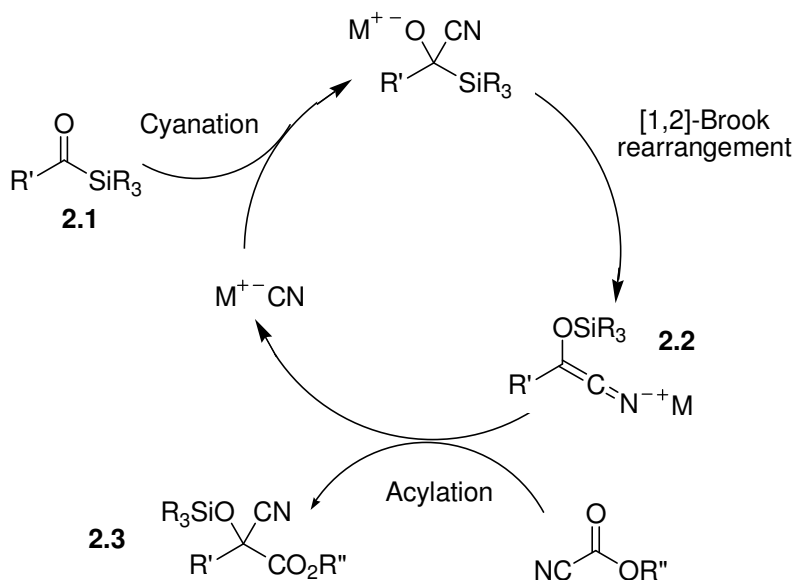
When an anion stabilizing group is already present in the acylsilane such as with a silylgloxylate, a wider array of nucleophiles that do not have to stabilize negative charge can be employed. Silylglyoxylates are formed with relative ease through a high-yielding three step sequence. First there is diazotization/deacylation of *tert*-butyl acetoacetate with *para*-acetamidobenzenelsulfonyl azide (*p*ABSA) in the presence of aqueous sodium hydroxide and tetrabutylammonium bromide as phase transfer agent. Following this, silylation with the silyl triflate of choice, and finally oxidation of the diazo site yield silylglyoxylate **2.4** as an extremely bright yellow oil (Scheme 2.3).

Scheme 2.3. Synthesis of Silylglyoxylate
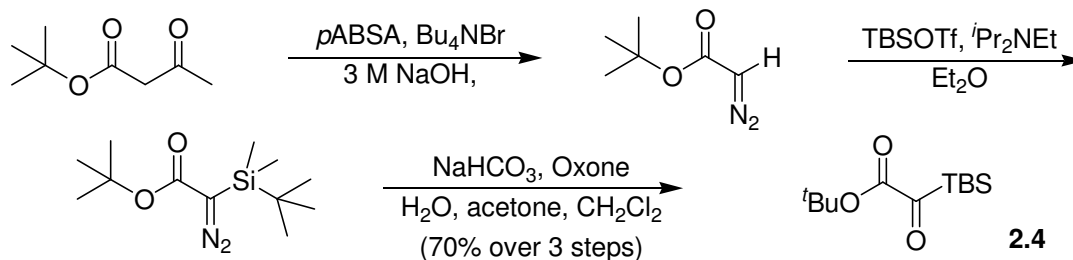
In one tandem reaction, silylglyoxylates (**2.5**) coupled with carbon-based nucleophiles can be used to form *in situ* latent anions (**2.6**) for use in subsequent nucleophilic additions yielding aldol products (**2.7**). Previously in our lab, this nuance was exploited to perform a tandem alkynylation/[1,2]-Brook rearrangement/aldol reaction in the presence of tertiary amine and Zn^{II} halide (Scheme 2.4).[7]

Scheme 2.4. Tandem Alkynylation/ Brook rearrangement/ Aldol reaction
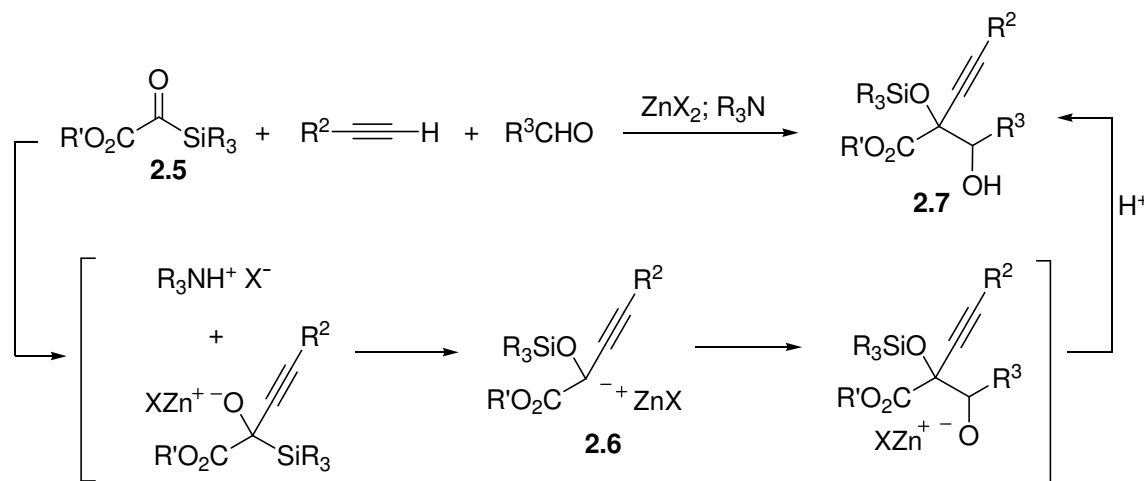
A central issue with the current research in this area is that it has yet to explore how the selectivity will be influenced when a chiral or unsaturated aldehyde is employed (e.g. using (*S*)-2-methylbutanal or tiglic aldehyde). However, one of the attractive features of silylgloxylates is the ability to make them chiral via an ester chiral auxiliary. It is

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[7] Nicewicz, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 6170-6171.

hypothesized that this modification might result in transfer of chirality to the desired products.

A.2. Nucleophile and Electrophile Scope for Tandem Alkenylation/ [1,2]-Brook Rearrangement/ Aldol Reaction

Initial studies in our lab performed by Xin Linghu involved vinylmagnesium bromide addition to *tert*-butyldimethylsilyl *tert*-butylglyoxylate **2.4**. In the presence of an aldehyde this sequence yields the desired tandem reaction culminating in aldol addition. A variety of aldehydes were examined, and the diastereomeric ratio of the products was determined (Table 2.1). If the reactions were run at -78 ℃ for thirty minutes and then quenched at that temperature, *anti* diols could be isolated in good yields and moderate diastereoselectivities (entries 6 and 7). However, if the reactions were allowed to warm to room temperature for thirty minutes after the -78 ℃ addition of Grignard, *syn* diols were isolated in diastereoselectivities of >95:5 and yields ranging from 72-76 percent (entries 1-5). The exception was phenylacetaldehyde which was isolated in an 80:20 diastereomeric ratio (entry 3). The aldehydes were all commercially available except chiral entry 4, which was readily synthesized by TEMPO oxidation of (*S*)-2-methyl-butanol (86%).

Table 2.1. Vinyl Grignard as Nucleophile in Silylglyoxylate Tandem Reaction

^{t}BuO... TBS, O, O ... $\diagup$MgBr, THF → ^{t}BuO, O, OH, R, TBSO, *syn*

2.4, TBS = Si^{t}BuMe$_2$
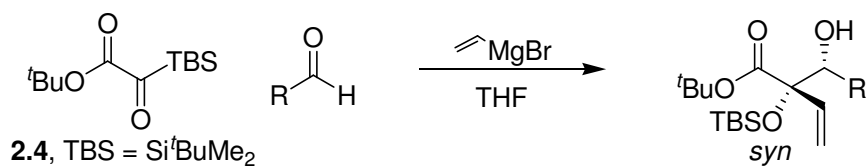
entry	R	temp.* (ºC)	yield (%)	*syn:anti*
1		25	76	>95:5
2		25	72	>95:5
3	Ph	25	75	80:20
4		25	74	>95:5
5	Ph	25	74	>95:5
6		-78	60	1:4
7		-78	86	1:10

*CH$_2$=CHMgBr added at -78 ºC, then reaction run at
indicated temperature for 30 minutes before quenching

After examining secondary electrophiles, we surveyed a variety of nucleophiles, using benzaldehyde or (*S*)-2-methylbutanal as the secondary electrophile (Table 2.2). In addition to vinyl Grignard studied above, allylmagnesium bromide, methylmagnesium bromide, butyllithium, cyclopropylmagnesium bromide, and phenylmagnesium bromide were examined. All were allowed to warm to room temperature for 30 minutes prior to quenching. With the exception of cyclopropylmagnesium bromide, all nucleophiles gave desired product in good yields. The diastereoselectivity for aryl and alkyl nucleophiles was significantly lower than with the vinyl and allyl Grignards. It is possible that the

addition of a vinyl group at the α-position could conceivably stabilize the resultant enolate. However, it is unknown why the phenyl ring did not serve a similar purpose yielding highly diastereoenriched product. In a related issue, the allyl nucleophile still showed high diastereoselectivity even though it cannot stabilize the intermediate enolate by resonance.

Table 2.2. Scope of Non-Vinyl Nucleophiles in Silylglyoxylate Tandem Reaction

2.4, TBS = Si^{t}BuMe$_2$
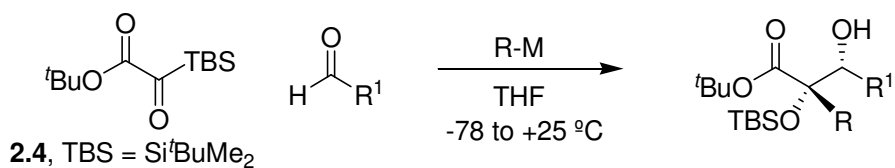
entry	R	R^1	yield (%)	d.r.
1	allyl-MgBr	(S)-CH(Me)Et	60	>95:5
2	MeMgBr	Ph	77	1:1
3	PhMgBr	Ph	82	4:1
4	BuLi	Ph	59	1:1
5	▷—MgBr	Ph	0	-

The key to the diastereocontrol with the vinyl nucleophiles is thought to be a reversible aldolization step. Under thermodynamic control, the aldehyde orients itself so as to minimize the steric interaction between its R^1 group and the *tert*-butoxy group of the glyoxylate yielding the *syn* diol as the major product, whereas under kinetic control, the major steric interaction that must be minimized is between the siloxy group and the R^1 group of the aldehyde yielding the *anti* diol as the major product (Figure 2.1). These

steric interactions were thought to be exploitable to increase the selectivities of the reaction by manipulating the functional group size on both the aldehyde and the silylglyoxylates.

Figure 2.1. Model for Diasterechemical Control
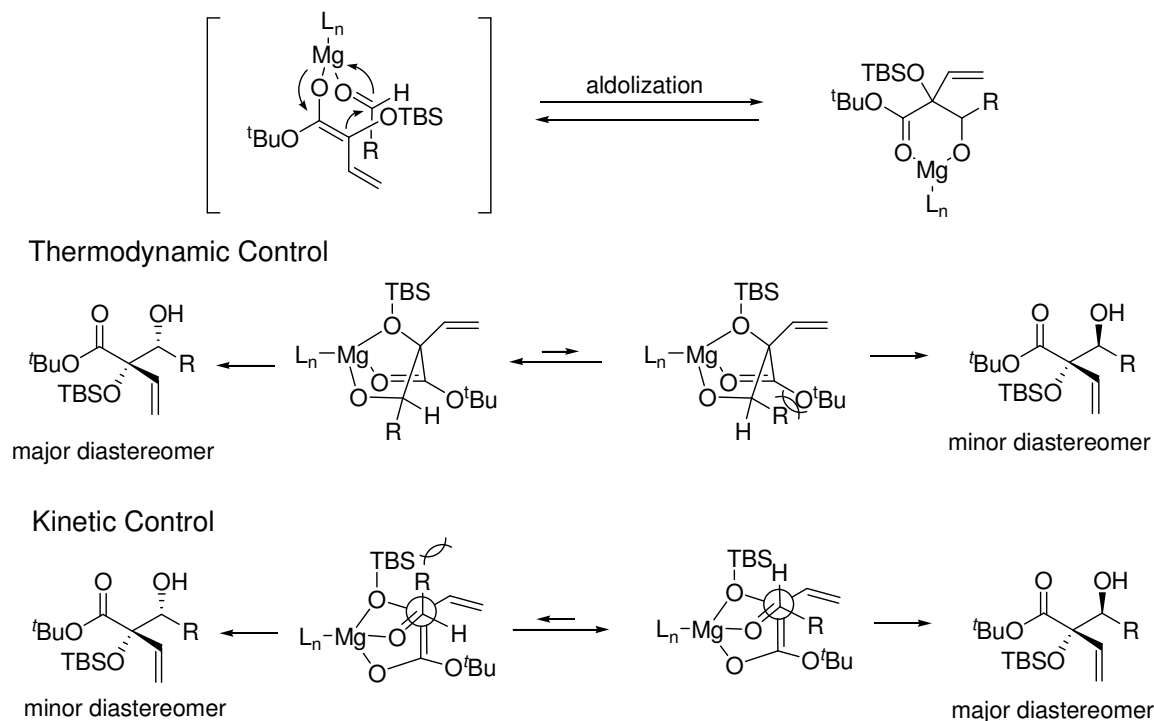
There were four main areas of exploration of this initial reaction for which we proposed to form α,β-dihydroxy, γ-chiral carbonyl compounds. Specifically we:

1) examined the induction of diastereoselectivity by making a chiral silylglyoxylate via the ester functionality;

2) examined induction of enantioselectivity via chiral ligands for magnesium;

3) assessed the potential for addition to unsaturated aldehydes followed by enantioselective hydroxyl-directed hydrogenation; and

4) utilized the aforementioned methodology in the synthesis of a relevant natural product.

B. Extant Syntheses of Alternaric Acid

A noteworthy feature of this methodology is its prospective usage in rapid construction of stereochemically dense bioactive natural products and therapeutics. As an exemplar of its promise, we proposed a concise synthesis of alternaric acid (Figure 2.2) from the three-component tandem alkenylation/Brook rearrangement/aldol reaction.

Figure 2.2. Alternaric Acid
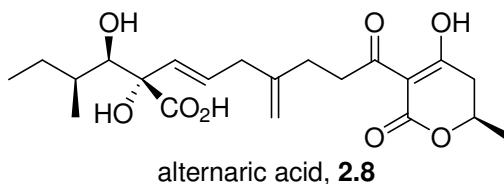
alternaric acid, **2.8**

Alternaric acid (**2.8**) was isolated by Brian and coworkers in 1949 as a metabolite from *Alternaria solani*, and was shown to exhibit antifungal as well as phytotoxic properties.[8] The synthesis of alternaric acid has been reported twice: first a 29 step total synthesis was published by Ichihara and coworkers in 1994, and then more efficiently an advanced intermediate was reached in an 11 step formal synthesis by Trost and coworkers in 1998.[9,10]

B.1. Ichihara's Total Synthesis

The Ichihara synthesis was noteworthy in that it unequivocally established the absolute stereochemistry of alternaric acid. Before proposing a retrosynthesis, they had to determine the configuration of the C10 and C11 stereocenters. By synthesizing the four diastereomers of the C9-14 fragment and comparing them to the degradation products of the natural sample they were able to determine it was the *syn* diol (Figure

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[8] Brian, P.W.; Curtis, P.J.; Hemming, H.G.; Unwin, C.H.;.Wright, J.M. *Nature,* **1949**, *164*, 534.

[9] Tabuchi, H.; Hamamoto, T.; Miki, S.; Tejima, T.; Ichihara, A. *J. Org. Chem.* **1994**, *59*, 4749-4759.

[10] Trost, B.M.; Probst, G.D.; Schoop, A. *J. Am. Chem. Soc.* **1998**, *120*, 9228-9236.

2.3). The C12 and C17 stereocenters were found to be 12-*S* and 17-*R* by analyzing the

optical rotations of the degradation products.

Figure 2.3. Degradation Studies of Alternaric Acid.

alternaric acid, **2.8**

(R)-(–)-methyl-3-hydroxybutyrate
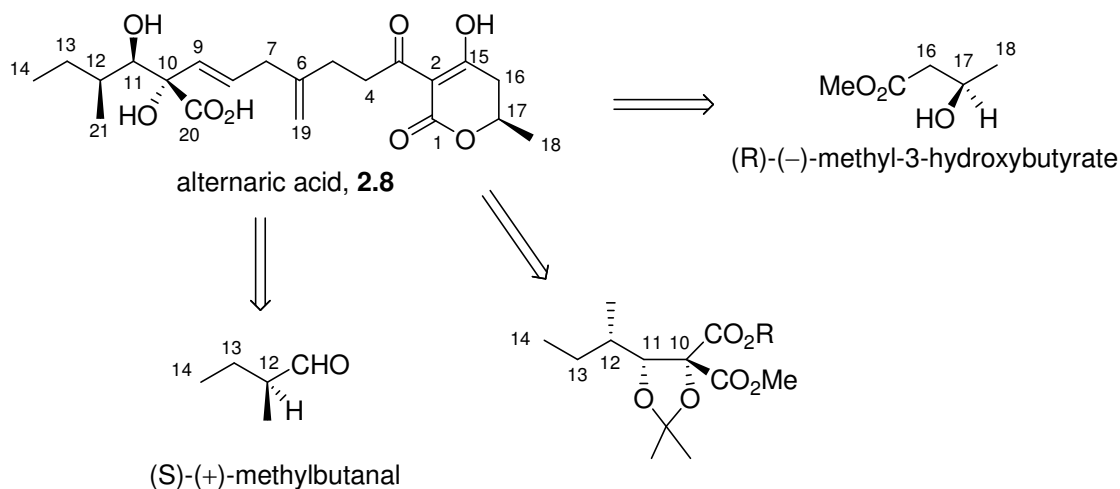
(S)-(+)-methylbutanal

The Ichihara retrosynthesis revealed three building blocks: aldehyde **2.9**,

phenylsulfone **2.10**, and β-keto-δ-valerolactone **2.11** (Figure 2.4). The C12 stereocenter

was pre-set from commercially available (*S*)-(-)-2-methylbutanol, and the C11

stereocenter was addressed by an aldol reaction yielding the desired product with a

selectivity of 64:36. Dihydroxylation installed their C10 stereocenter and poised the

fragment for oxidation to their proposed building block **2.9**. The aldehyde and

phenylsulfone were then joined by a demanding Julia olefination. The installation of the

lactone was accomplished by a novel one-pot construction of 3-acyl-4-hydroxy-5,6-

dihydro-2-pyrone from carboxylic acid **2.12** and lactone **2.11**. This Fries-type

rearrangement of the *O*-enol acyl group of β-keto-δ-valerolactone toward the α-position

of the δ-lactone was achieved using their methodology utilizing DCC and DMAP

(Scheme 2.5). Finally the methyl ester was hydrolyzed and the acetal removed to

generate alternaric acid in 29 steps and 0.003% overall yield.

Figure 2.4. Ichihara's Retrosynthesis of Alternaric Acid
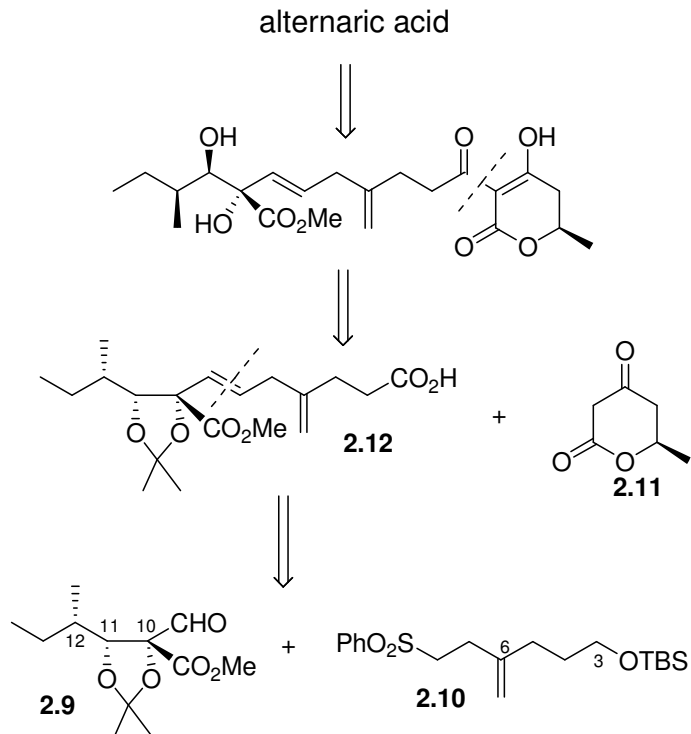
Scheme 2.5. Ichihara's Pyrone Installation via Fries-Type Rearrangement
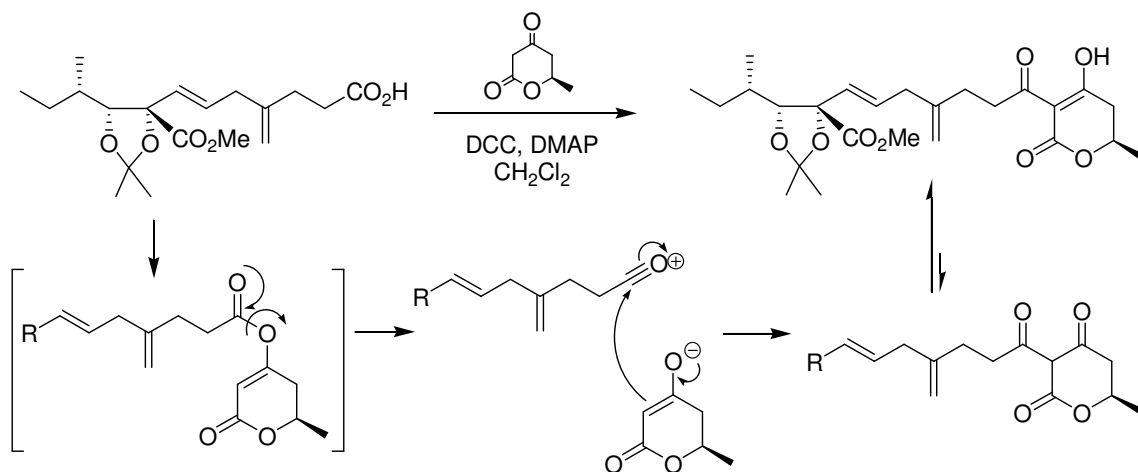
B.2. Trost's Formal Synthesis

The Trost synthesis, however, was far more efficient. Eyeing the 1,4-diene, composed of a terminal methylene and an (*E*)-1,2-disubstituted olefin, the researchers

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saw an opportunity to utilize their established Alder-ene methodology coupling a monosubstituted alkene and a terminal alkyne (Figure 2.5). In designing their synthesis, they invoked three retrosynthetic targets that were very similar to the Ichihara synthesis: pyrone **2.13**, alkene **2.14**, and alkyne **2.15** (Scheme 2.6). As the researchers note, the conciseness of their synthesis would stem directly from the number of steps to their proposed alkene. Ultimately, they constructed their crucial alkenyl coupling partner in eight steps from commercially available (*S*)-2-methylbutanol, installing the C10 and C11 stereocenters via asymmetric dihydroxylation.

Figure 2.5. Trost's Retrosynthesis for Formation of 1,4-Diene
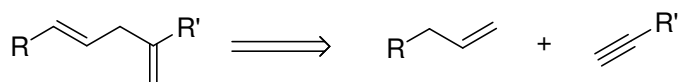
Scheme 2.6. Trost's Formal Synthesis Approach

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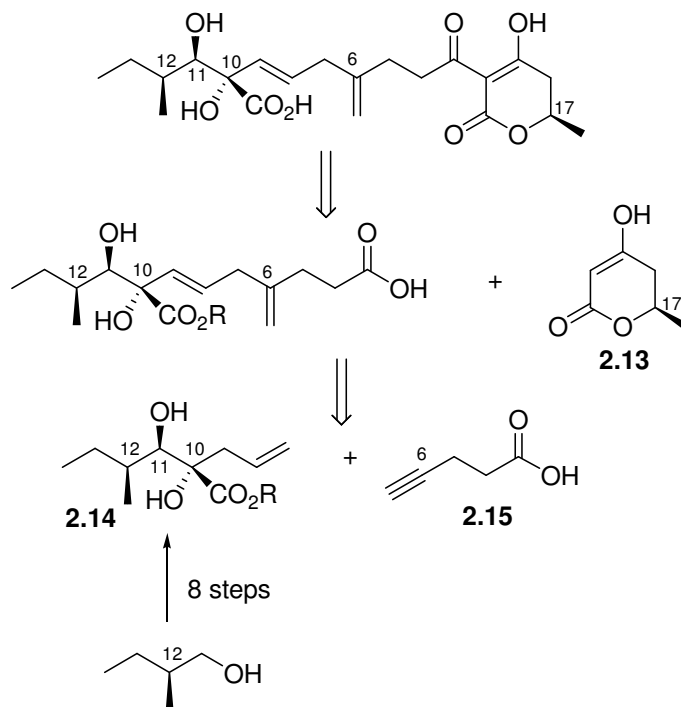
Trost's model studies of the Alder-ene using CpRu(COD)Cl proved to have significant turnover issues in the presence of substrates with free carboxylic acids and acyldihydropyrones, most likely due to their ability to generate good coordinating anions for the ruthenium. In light of this, the methyl ester of their alkene coupling partner was used. Further studies showed that both the free diol and acetonide-protected alkene coupling partner performed equally well in the coupling reaction. With their desire to access C3 as a free carboxylic acid for the pyrone coupling, model studies were also performed for the hydrolysis of the ester after the Alder-ene. It was discovered that the product with either a *tert*-butyl or methyl ester could not be converted to the corresponding carboxylic acid in appreciable yield. Their substrates showed sensitivity to acid and suffered from regioselectivity issues in the presence of nucleophilic bases. In light of this, they tried masking the acid of the alkyne as either the trimethylsilylethyl (SEM) or 9-fluorenylmethyl (Fm) esters. Both groups can be cleaved with a non-nucleophilic base, however, only the fluorenylmethyl ester participated in the ruthenium-catalyzed Alder-ene and consequently was used in their final sequence.

The optimization studies undertaken by the Trost group were aimed also at determining conditions to maximize the yield of the branched product (**2.16**), as a similar linearly-linked product (**2.17**) is possible depending on the regioselectivity of the reaction (Scheme 2.7). The mechanism initiates with an oxidative coupling of the alkene and alkyne, which can take one of two orientations depending on steric interference and coordination of the hydroxyls or esters. Following β-hydride elimination, a final reductive elimination releases the catalyst from coupled product possessing a 1,1- or 1,2-disubstituted alkene. After the Alder-ene reaction, they were able to access Ichihara's

advanced intermediate by forming the acetonide and removing the fluorenylmethyl group, completing their formal synthesis in 11 steps and 27% overall yield.

Scheme 2.7. Mechanistic Rationale of the Ru-Catalyzed Alder-Ene
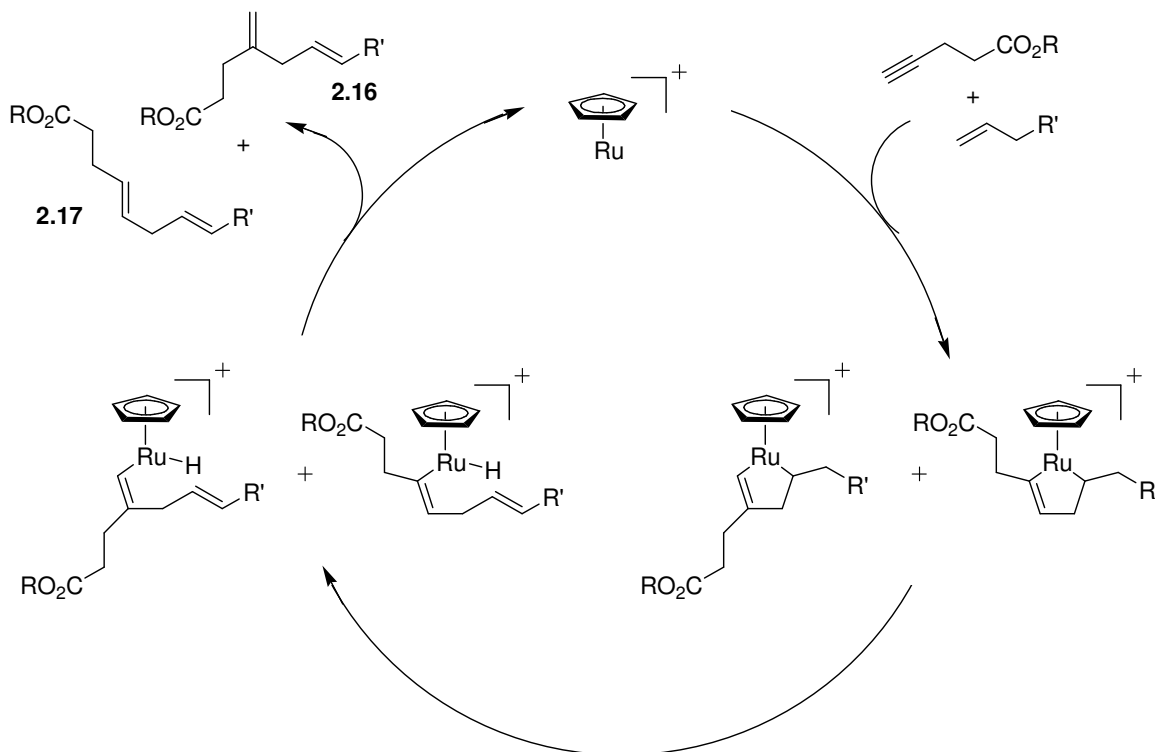
C. Results and Discussion

C.1. Chiral Ester Stereoinduction

In our methodology the ester functionality of the silylglyoxylate lends itself to use of a chiral auxiliary, which may then positively influence the diastereoselectivity of the reaction. Previously in the Johnson group, a chiral silylglyoxylate has been made utilizing 8-phenylmenthol (four known steps from pulegone) (Scheme 2.8).[11] The choice of 8-phenylmenthol (**2.18**) comes from its usage in the glyoxylate-ene reaction by the

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[11] Ort, O. *Org. Synth.* **1987**, *65*, 203-204.

Whitesell and Corey groups (Figure 2.6).[12,13] They examined several menthol derivatives and found that the 8-phenyl substituted auxiliary encouraged π-π stacking of the glyoxylate over the phenyl ring, thus successfully blocking the back face to impending nucleophilic attack.

Scheme 2.8. Synthesis of 8-Phenylmenthol
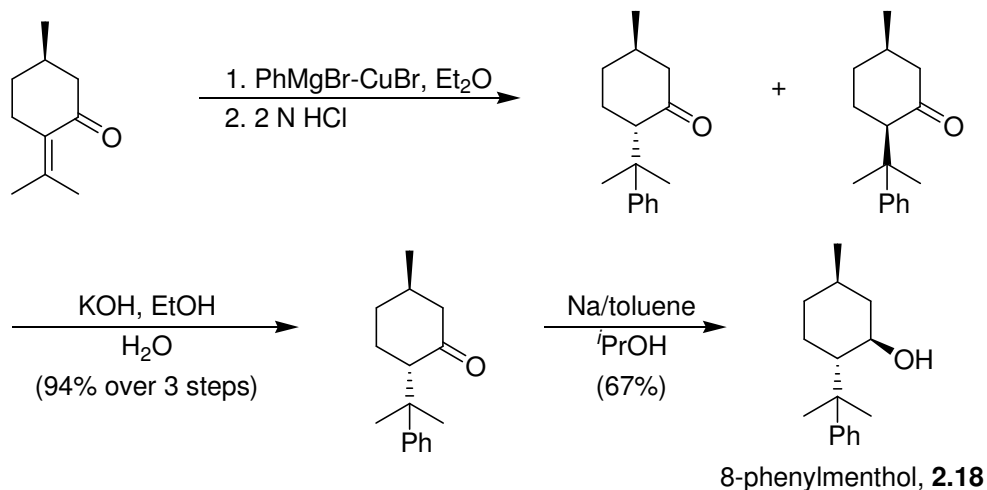
Figure 2.6. Model for Facial Selectivity with 8-Phenylmenthol
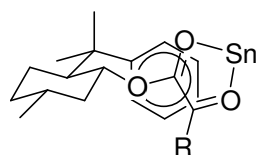
model for glyoxylate facial accessibility   model for enolate facial selectivity
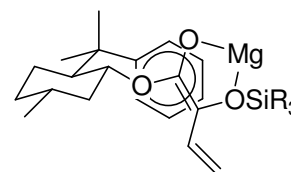
After synthesis of 8-phenylmenthol (**2.18**), the chiral silylglyoxylate can be accessed (Scheme 2.9). First, alkaline addition of the alcohol into diketene in the presence of a

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[12] Whitesell, J.K.; Lawrence, R.M.; Chen, H.-H. *J. Org. Chem.* **1986**, *51*, 4779-4784.

[13] Ensley, H.E.; Parnell, C.A.; Corey, E.J. *J. Org. Chem.* **1978**, *43*, 1610-12.

diazo transfer agent (*p*ABSA) yields the diazodicarbonyl.[14] Aqueous KOH then removes the acyl group allowing for silylation in a subsequent step, leaving only Oxone® oxidation to reveal the desired silylglyoxylate (**2.19**).[15] Similar syntheses were envisioned for other chiral silylglyoxylates from compounds such as diacetonide-protected fructose (**2.20**), valinol (**2.21**), and BOC-protected phenylalaninol (**2.22**) (Figure 2.7). The rationale for choosing these chiral esters stems from their previous utilization as chiral auxiliaries. D-Fructose diacetonide has been used to transfer chirality in enantioselective α-alkylation reactions, yielding chiral carboxylic acids after hydrolysis.[16] Valinol has been shown to induce chirality in highly *syn* selective aldol reactions after which it can be readily removed by mild saponification;[17] we foresaw phenylalaninol as possibly performing in a similar fashion.

Scheme 2.9. Synthesis of 8-Phenylmenthol TBS Silylglyoxylate
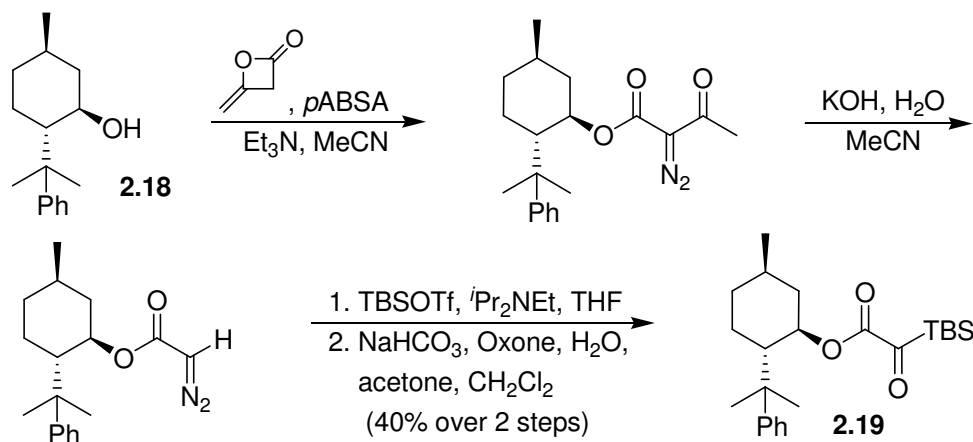
[14] Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K. L. *J. Am. Chem. Soc.* **1990,** *112*, 1906-1912.

[15] O'Bannon, P. E.; Dailey, W.P. *Tetrahedron* **1990**, *46*, 7341-7358.

[16] Yu, H.; Ballard, C.E.; Wang, B. *Tetrahedron Lett.* **2001**, *42*, 1835-1838.

[17] Ghosh, A.K.; Kim, J.-H. *Tetrahedron Lett.* **2002**, *43*, 5621-5624.

Figure 2.7. Proposed Chiral Silylglyoxylates

2.20, from fructose   **2.21**, from valine   **2.22**, from phenylalanine
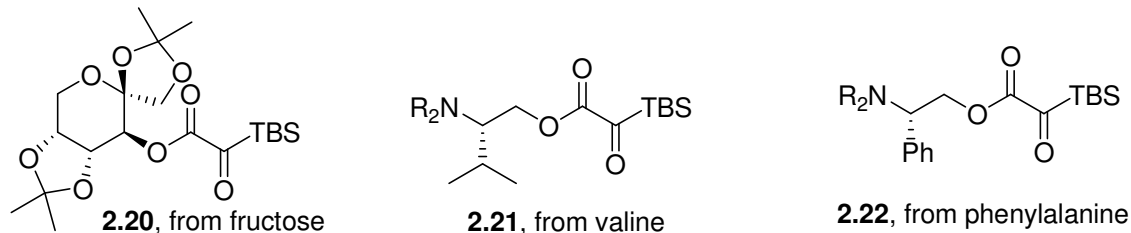
Although the desired product of the vinyl addition/aldol reaction using the 8-phenylmenthol silylglyoxylate was isolated and confirmed by mass spectrometry, the compound was extraordinarily impure and the diastereoselectivity was difficult to determine by NMR. As a means of differentiating the compounds, alkaline hydrolysis to the acid was tried, as was deprotection using TBAF at room temperature, reduction using LAH, and deprotection/hydrolysis using trifluoroacetic acid—all were unsuccessful, yielding intractable mixtures.

Our attempts at accessing coupled products from the other chiral silyl glyoxylates were obstructed, as even the production of the silylglyoxylates proved too problematic. The attempted syntheses were thwarted by the silylation step, with no desired product obtained. It was decided that as a matter of atom economy, the *t*-butyl/TBS silylglyoxylate would be used for all further transformations with attempts to otherwise render the reaction enantioselective.

C.2. Chiral Ligands for Magnesium

Perhaps even more attractive than internal chirality induction in this circumstance is control by an external chiral source, precluding the need for later auxiliary removal. Internal chirality transfer would also mean that the original *tert*-butyldimethylsilyl *tert*-butylglyoxylate (**2.4**, Scheme 2.3), could be employed. Thus, the search for chiral

ligands for magnesium focuses on less expensive, preferably commercially available materials. A few of the possible magnesium ligands that were examined included (-)-sparteine (**2.23**), 1,2-diaminocyclohexane (**2.24**), and pseudoephedrine (**2.25**) (Table 2.3), as they have previously been utilized in the formation of chiral Grignard and lithium reagents.[18] The ligand was pre-complexed with Grignard or lithium reagents by stirring in a non-coordinating solvent (such as CH_2Cl_2) prior to its addition to the silylglyoxylate/aldehyde solution. The diaminocyclohexane addition prevented a reaction altogether, and the pseudoephedrine and sparteine showed only a slight increase in diastereoselectivity (*d.r.* = 1.5:1 and <2.5:1, respectively). Additionally, the purification became more difficult when the reaction was run in the presence of sparteine.

Table 2.3. Chiral Magnesium Ligands
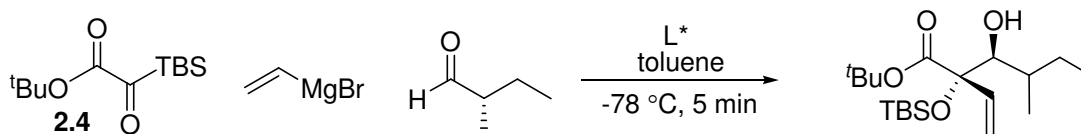
Ligand	Yield	Facial selectivity
trans-1,2-diaminocyclohexane, **2.24**	0	–
N-methyl-pseudoephedrine, **2.25**	46	1.5
(−)-sparteine, **2.23**	65	<2.5

[18] (a) Yamashita, Y.; Odashima, K.; Koga, K. *Tetrahedron Lett.* **1999**, *40*, 2803-2806. (b) Shintani, R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 1057-1059. (c) Yasuda, K.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1997**, *38*, 3531-3534.

C.3. Addition to Unsaturated Aldehydes with Hydroxyl-Directed Hydrogenation

As an alternative to rendering the aldol reaction facially selective with a chiral aldehyde, there was the possibility for later installation of the α-aldol stereocenter via hydroxyl directed hydrogenation (Scheme 2.10). The reaction proceeded as previously depicted except that tiglic aldehyde was used in the tandem addition/aldol reaction, yielding diene **2.26**. It was our hope that this case would circumvent any issues with differentiation between comparable substituents (e.g. using tiglic aldehyde rather than distinguishing between methyl and ethyl groups of the chiral saturated aldehyde). It should be noted that when this reaction was run in THF, the yields were a mere 27-39%. Several possibilities were examined to ameliorate this problem. Since there was loss of color on addition of the Grignard, we presumed that the initial addition to silylglyoxylate was not the issue. The possibility of hindered reactivity with tiglic aldehyde was addressed by a competition experiment. The tandem reaction was set up normally with one equivalent of silylglyoxylate and two equivalents of vinylmagnesium bromide, but there were two equivalents each of benzaldehyde and tiglic aldehydes as the secondary electrophiles. Upon quenching the reaction, it was found that the product distribution was 5.5:1 for incorporation of benzaldehyde and tiglic aldehydes, respectively, in 52% combined yield. Finally, a solvent screen was performed, revealing that THF was the issue. Although 2-Me-THF and Et$_2$O were approximately equally effective in the reaction (57-63% yield), CH$_2$Cl$_2$ was employed for all subsequent reactions with tiglic aldehydes (67% yield).

Scheme 2.10. Proposed Hydrogenation of Prochiral Aldol Products
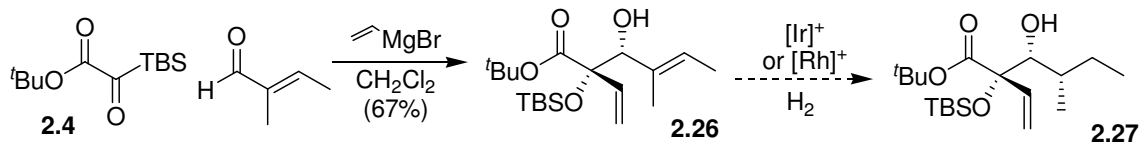
Following an hydroxyl-directed hydrogenation using either $Ir(COD)(py)(PCy_3)PF_6$ or

$[Rh(nbd)(DIPHOS-4)]BF_4$ as the catalyst, the desired product **2.27** was expected to be

obtained.[19] When using the iridium catalyst for four hours under an atmosphere of

hydrogen at room temperature, the reaction had gone to completion, and a sole product

was indeed obtained in 86% yield. However, ^{1}H NMR analysis of the isolated product

showed that both the mono- and tri-substituted alkenes were fully hydrogenated. When

the reaction time was reduced and the solution made more dilute, unfortunately, the

monosubstituted alkene was preferentially hydrogenated. When the less-reactive

rhodium catalyst was employed, starting material was recovered. Unfortunately, in light

of this, the reaction as such was abandoned and instead a differentiation of diastereomers

would have to be employed after the reaction with chiral aldehydes.

Table 2.4. Hydrogenation of Prochiral 2.26

Catalyst	Time	Yield	Product
$Ir(COD)py(PCy3)PF_6$	3 h	86	fully saturated
$Ir(COD)py(PCy3)PF_6$	1 h	nc	mostly mono, some tri
$(nbd)Rh(dppb)BF_4$	12 h	0	recovered sm

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[19] Evans, D.A.; Morrissey, M.M. *J. Am. Chem. Soc.* **1984**, *106*, 3866-3868.

C.4. Total Synthesis of Alternaric Acid

a. Retrosynthesis of Alternaric Acid

Our preliminary retrosynthesis made similar disconnections to that of the Trost group.[10] However, rather than ene-yne metathesis, we initially anticipated an alternative route that would utilize traditional alkene metathesis for synthesis of (*E*)-alkene **2.28** (Scheme 2.11). Using our aforementioned developed methodology we proposed the construction of our desired coupling partner **2.29** – complete with three contiguous stereocenters – via silylglyoxylate **2.4** in one step. In addition to attempting the tandem reaction with vinyl Grignard to reach alternaric acid, we proposed using allyl Grignard as a complementary approach to the natural product. Via the allyl product **2.30**, an Alder-ene coupling was anticipated akin to that in the Trost synthesis. The three-component coupling with the silylglyoxylate, allyl Grignard, and (*S*)-2-methylbutanal proceeded in nearly the same fashion as the vinyl equivalent, with product isolated in 60% yield (Scheme 2.11).

Scheme 2.11. Retrosyntheses Featuring Silylglyoxylate
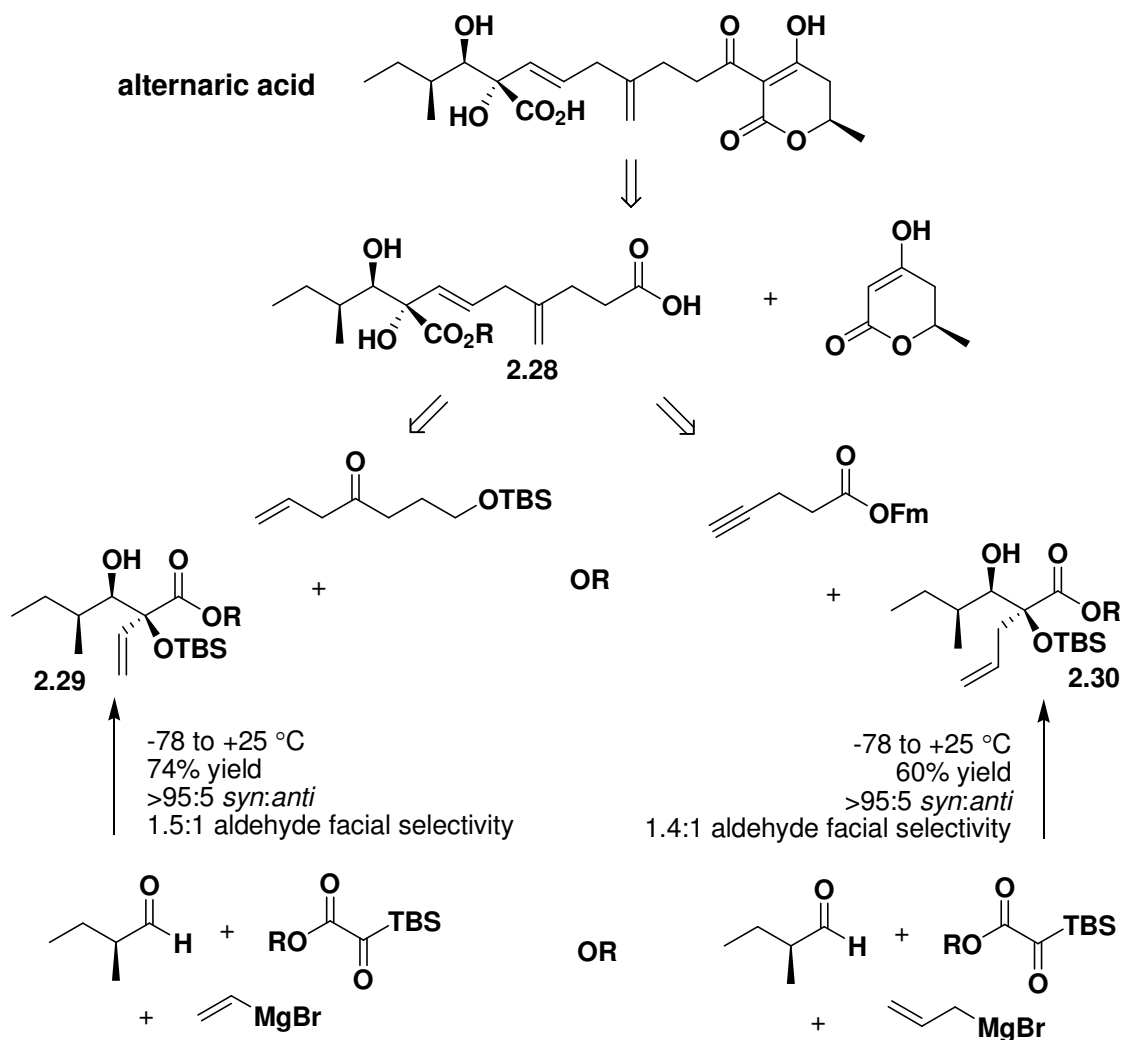
In a convergent approach, the alkene coupling partner and the pyrone were to be separately constructed with the pyrone assembly route taken from the Ichihara synthesis. Claisen condensation of (*R*)-methyl-3-hydroxybutanoate with *tert*-butylacetate (91%) was followed by lactonization with trifluoroacetic acid to access pyrone **2.31** in 87% yield (Scheme 2.12).[20]

Scheme 2.12. Synthesis of Pyrone
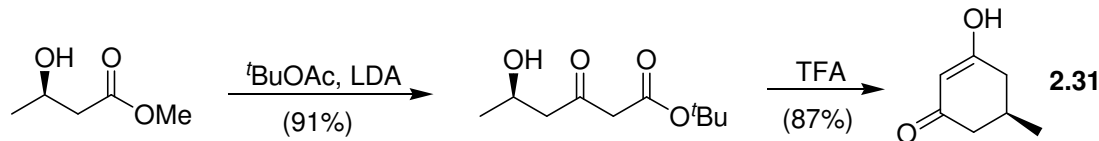
b. Coupling Partner Generation for Alkene Metathesis

Alkene **2.32** was originally envisioned to come from opening γ-butyrolactone to the Weinreb amide, followed by protection of the alcohol as the TBS ether, and finally allylation using a Grignard reagent (Scheme 2.13).[20] Grubbs' second generation catalyst was used in all olefin metatheses to avoid the known coordination issues with allylic alcohols with Grubbs' first generation catalyst.[19,21] Attempted cross metathesis with this substrate, however, resulted in a not-unforeseen migration of the alkene to the conjugated enone (Scheme 2.14). A pre-emptive olefination was sought to solve the problem, with the belief that the projected metathesis would occur preferentially at the monosubstituted alkene. The use of Tebbe[22] or Takai[23] olefination reagents or Wittig conditions to form the diene, however, were unsuccessful.

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[20] Fukuda, Y.-I.; Shindo, M.; Shishido, K. *Org. Lett.* **2003**, *5*, 749-751.

[21] Engelhardt, F. C.; Schmitt, M. J.; Taylor, R. E. *Org. Lett.* **2001**, *3*, 2209-2212.

[22] Tebbe, F.N.; Parshall, G.W.; Reddy, G.S. *J. Am. Chem. Soc.*, **1978**, *100*, 3611-3613.

[23] (a) Trotter, N.S.; Takahashi, S.; Nakata, T. *Org. Lett.*, **1999**, *1*, 957-959. (b) Hibino, J.-i.; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron. Lett.*, **1985**, *26*, 5579-5581.

Scheme 2.13. Synthesis of Initial Alkene Coupling Partner
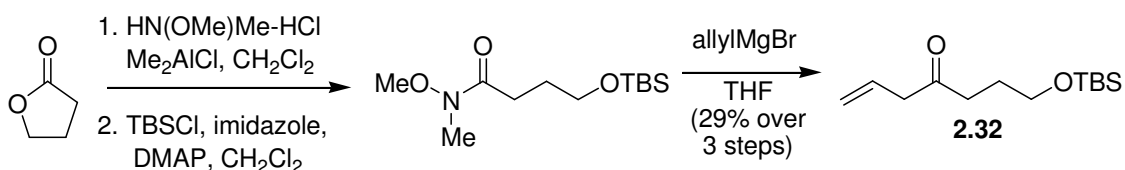
Scheme 2.14. Attempted Cross-Metathesis with β,γ-Unsaturated Enone
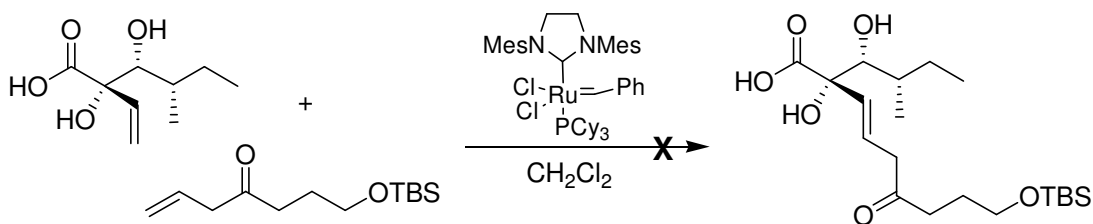
At that time, an alternative route to the diene was offered (Scheme 2.15). [24] First 4-pentyn-1-ol was TBS protected in quantitative yield. The protected alcohol was then subjected to stoichiometric indium and 8 equivalents of allyl bromide and heated to ebullition. After stirring for several hours, the desired 1,4-diene **2.33** could be isolated in excellent yield. Although Ranu and coworkers do not speculate as to the mechanism for their methodology, this researcher believes it to occur via a Grignard-esque pathway as the indium is fully consumed and protic sources shut down the reactivity. Rather than waiting until after the coupling to deprotect and oxidize, subjecting diene **2.33** to TBAF and then Jones' reagent gave the corresponding carboxylic acid **2.35**. Additionally, two further advanced coupling partners were made: the fluorenylmethyl ester **2.36** for an olefin metathesis analogous to the Alder-ene, and the acylpyrone diene **2.37** which would – in the event of a successful coupling – yield completed alternaric acid (Scheme 2.16).

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[24] Ranu, B.C.; Majee, A. *J. Chem. Soc., Chem. Comm.* **1997**, 1225.

Scheme 2.15. Synthesis of Alkene Coupling Partner from 4-Pentyn-1-ol
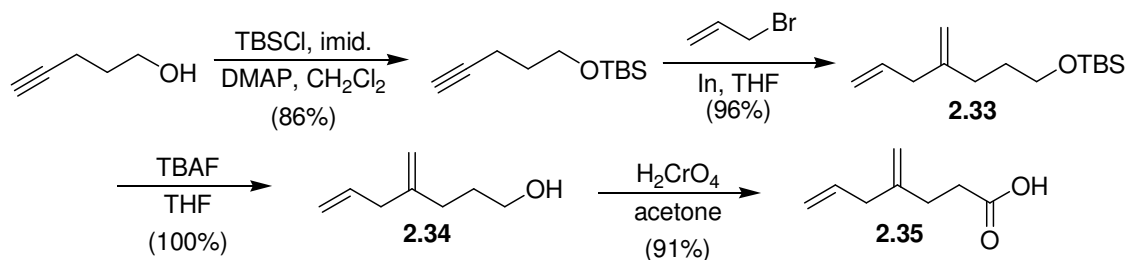
Scheme 2.16. DCC/DMAP Couplings to Two Additional Alkene Coupling Partners
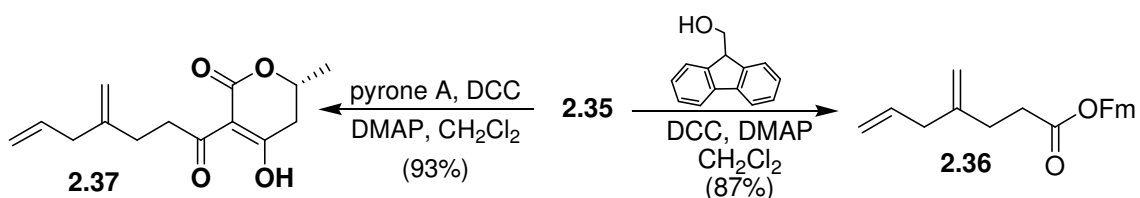
c. Coupling Partner Generation for Alder-Ene Metathesis

The coupling partner for the ene-yne metathesis was more straightforward (Scheme 2.17). Using Trost's approach,[10] commercially available 4-pentynoic acid was esterified in 78% yield (**2.38**) using 9-fluorenylmethanol (FmOH) in the presence of DCC/DMAP. The alkyne with the pyrone already attached (**2.39**) was made as well in hopes of a more succinct synthesis.

Scheme 2.17. Synthesis of Alder-Ene Coupling Partners
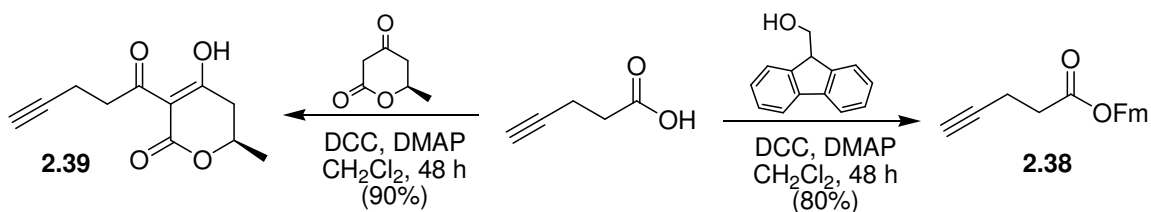
d. Olefin Cross-Metathesis

Initially the cross-metathesis was attempted with the TBS protected **2.29** and diene **2.33**. It was quickly ascertained that the steric bulk adjacent to the site of coupling may have been problematic, recovering only starting materials when the reactions were run at room temperature with Grubbs' II with degassed solvent. It should be noted that removal of the ^{t}Bu and TBS groups was no small feat. Initial attempts at cleaving the silyl ether with TBAF under conventional conditions at room temperature in THF resulted in loss of vinyl protons by ^{1}H NMR analysis. This problem could be remedied by running the deprotection in acetonitrile at -30 ºC for 24 hours (95% yield). The *tert*-butyl group could also be removed by subjecting the free diol to TFA in dichloromethane. Attempts at cross metathesis were made with all partners from category A with partners from category B. All were met with recovery of starting material and/or homocoupling of the diene fragment from category A (Figure 2.8).

Figure 2.8. Attempted Olefin Metathesis Coupling Partners

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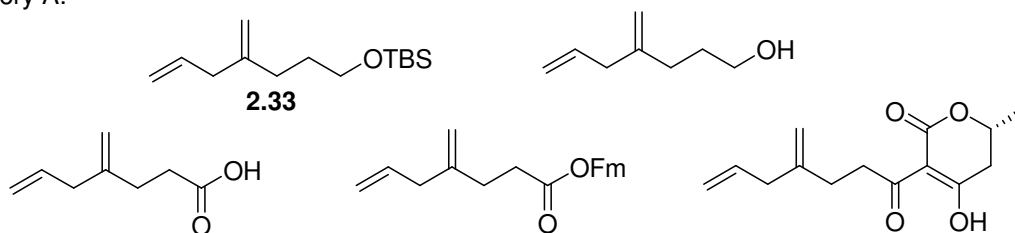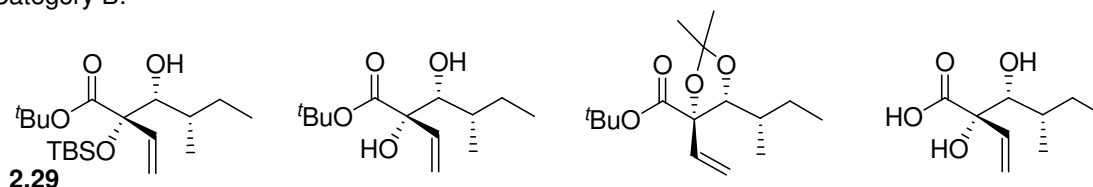
With concerns that the congested intermolecular metathesis would be unfavorable, a similar coupling partner was designed with hopes of an *intra*molecular metathesis by esterification at the secondary hydroxyl (Scheme 2.18). Rather than waiting until after the coupling to deprotect and oxidize, acid **2.35** was used with DCC/DMAP to form the ester at the free secondary hydroxyl group of deprotected tandem reaction product **2.40**. The esterification with the acid chloride and diol **2.40** was unsuccessful, but the esterification with the acid was repeatedly successful. The metathesis, on the other hand, proved cumbersome. A reaction did occur and the ^{1}H NMR spectrum was for the most part consistent with the desired cyclic product, except for additional vinyl proton signals present in the spectrum. Attempts to open the ester to determine if the metathesis was indeed successful were met with recovery of starting material. The most likely scenario is that the NMR represented a mixture of starting material as well as dimerized product at the terminus of the 1,4-diene. Additional attempts at intermolecular as well as intramolecular olefin metathesis were abandoned after test reactions with highly reactive simple allyl acetate were fruitless (Scheme 2.19), indicating the system was not amenable to this type of union.

Scheme 2.18. Esterification for Intramolecular Olefin Metathesis
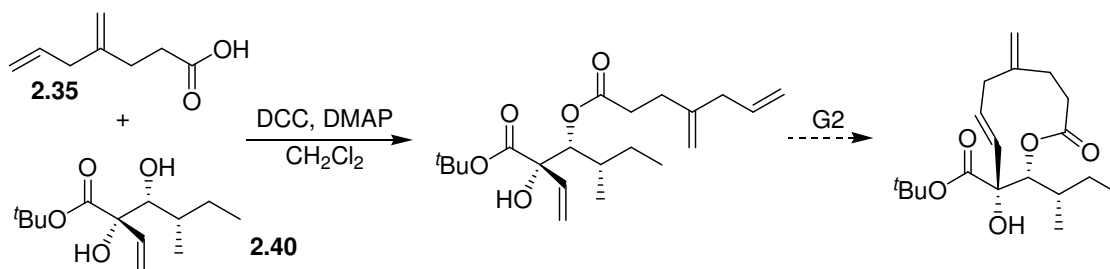
Scheme 2.19. Positive Control for Intermolecular Olefin Metathesis with 2.39
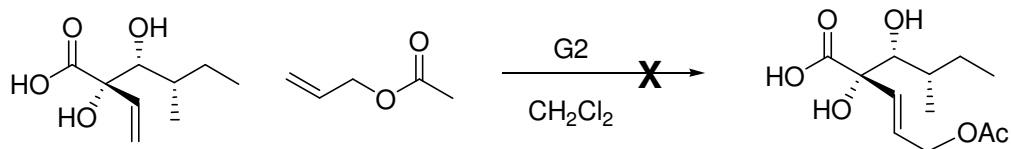
e. Alder-Ene Metathesis: Preparation and Execution

Initially ene-yne metathesis was also attempted with the TBS protected tertiary alcohol in place. As with the olefin metathesis, the steric bulk proved too problematic and removal of the *t*Bu and TBS groups were the focus of the next area of research (Scheme 2.20). As with the deprotection of the TBS group in our vinyl substrate with TBAF at room temperature, subjection of the allyl product **2.30** to TBAF resulted in loss of the vinyl protons by ^{1}H NMR analysis. Lowering the temperature to -30 ºC and running the reaction in acetonitrile, however, did not ameliorate this problem as it did with the vinyl substrate. Instead, alternative sources of fluoride were investigated. Usage of TBAT (tetrabutylammonium difluorotriphenylsilicate, an anhydrous TBAF derivative) showed no reaction and starting material was recovered. Use of HF-pyridine resulted in loss of vinyl protons again. Aqueous hydrofluoric acid was also utilized in an attempt to remove the TBS group. While successful in converting starting material to desired product, there were a couple of issues with this step: the yields ranged inexplicably from 20-80%, and there are obvious health and safety concerns with employing HF. One last fluoride source was examined (H_2SiF_6), and fortunately, it repeatedly performed well in our desired deprotection step. The free diol could be isolated in 72% yield, and the *t*-butyl group cleaved with TFA in up to 77% yield. Isolation of this dihydroxy carboxylic acid **2.41** from these conditions, however, proved slightly problematic. It was thought

that perhaps if the order of these two steps were reversed, the isolation may be more facile. Gratifyingly, exposure of the three-component coupling product **2.30** to 10 equivalents of TFA in CH_2Cl_2 removed both the *t*-butyl group and the TBS group, giving **2.41** in 99% yield (Scheme 2.21). This dihydroxy carboxylic acid was then carried on to further Alder-ene experiments.

Scheme 2.20 Deprotection of 2.30
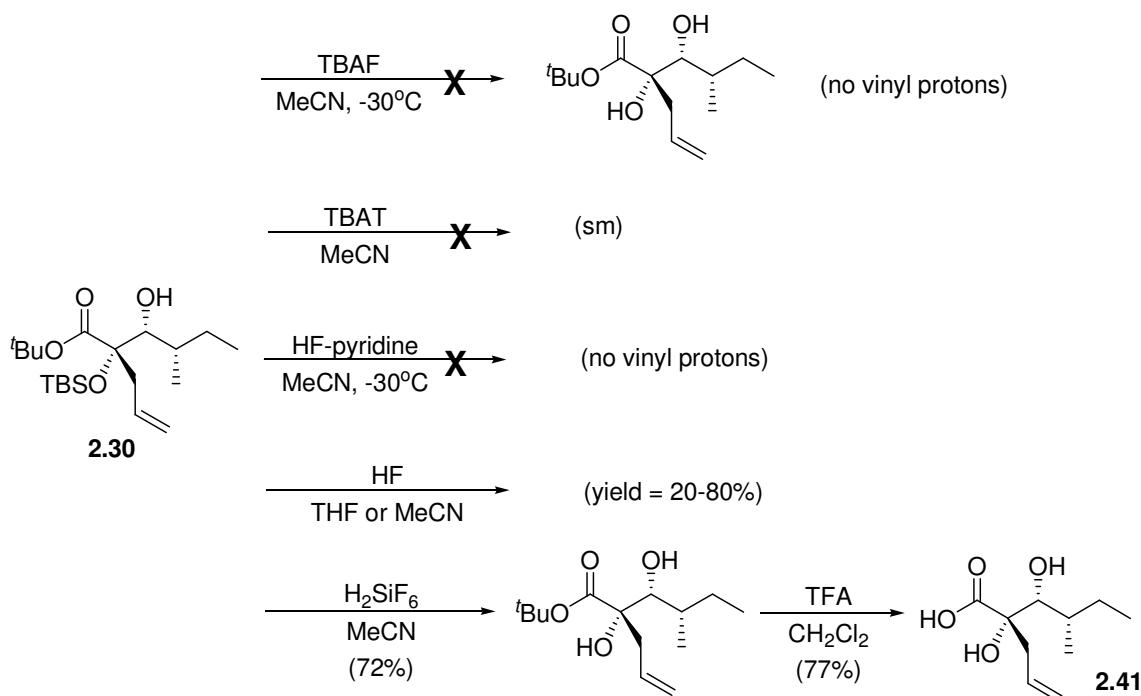
Scheme 2.21 Streamlined Deprotection of 2.30
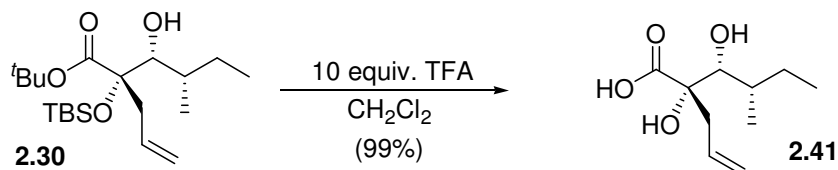
Only starting materials were recovered when the Alder-ene reactions were run at room temperature with fluorenylmethyl ester **2.38** in the presence of

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Cp*Ru(COD)Cl/NH$_4$PF$_6$. It should be noted that in the original Trost synthesis, CpRu(COD)Cl was used, not the commercially available pentamethylcyclopentadienyl (Cp*) derivative. The synthesis of simple CpRu(COD)Cl was attempted several times, to no avail. At the suggestion of members of the Trost lab,[25] the more active – and commercially available – CpRu(MeCN)$_3$PF$_6$ was obtained and used in subsequent reactions. Coupling of dihydroxy carboxylic acid **2.41** with an alkyne that already had the pyrone appended (**2.39**) resulted in halted conversions. The coupling of **2.41** and **2.38**, however, performed well in both acetone and methanol (Scheme 2.22). Both reactions were successful (yields = 80 and 83%, respectively), however the solubility of the fluorenylmethyl ester and the purification were much better with acetone as the reaction medium. The initial concern of regioselectivity of the branched over the linear product seemed to be a non-issue, with the branched isomer **2.42** being the sole product, as evidenced by the ^{1}H NMR signal of the 1,1-disubstituted alkene presenting as a doublet integrating for two protons at approximately 4.7 ppm.

Scheme 2.22. Alder-Ene of α,β-Dihydroxy Acid 2.41 with Alkyne 2.38
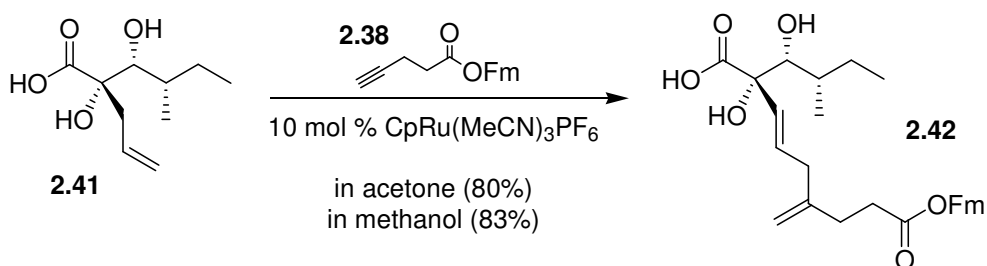
Although the issue of regioselectivity seemed to have resolved itself, upon attempting to repeat the Alder-ene, a new obstacle had arisen. The diol product was persistently formed as a 1:2 mixture of the free diol **2.42** and the acetonide **2.43** (Scheme 2.23). In an

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[25] McDougall, P.T. Personal communication.

attempt to shut down protic acetonide formation, 0.01 equivalents of 2,6-lutidine was added to the reaction, however, the desired coupling was also completely arrested. In hopes of still attaining the most direct synthetic route, it was decided to remove the acetonide from the product mixture. To this end, the acetonide was subjected to cleavage conditions by heating to 120 ℃ in EtOH : H_2O as in the Ichihara synthesis. After the deprotection, subjecting **2.42** to piperidine revealed the carboxylic acid necessary for the pyrone attachment. At this point it became abundantly clear that the extraordinary polarity of this dihydroxy dicarboxylic acid would preclude its purification by conventional means. Thus, rather than fully removing the acetonide from the Alder-ene product mixture, the alternative was explored in which the free diol was converted to the corresponding acetonide **2.43**. The Alder-ene reaction could be filtered through a silica plug using 98:2 CH_2Cl_2:MeOH to remove the more non-polar reaction components, and then flushed with 93:7 CH_2Cl_2:MeOH to push off the mixture of acetonide and free diol products. This mixture was then subjected to 2,2-dimethoxypropane, CSA, and acetone. After stirring overnight, the volatiles could be removed *in vacuo* and the remaining residue purified by column chromatography to reveal solely acetonide-protected Alder-ene product **2.43** in 60% yield from alkene **2.41** (Scheme 2.24).

Scheme 2.23. Mixture of Acetonide and Free Diol from Alder-Ene Reaction

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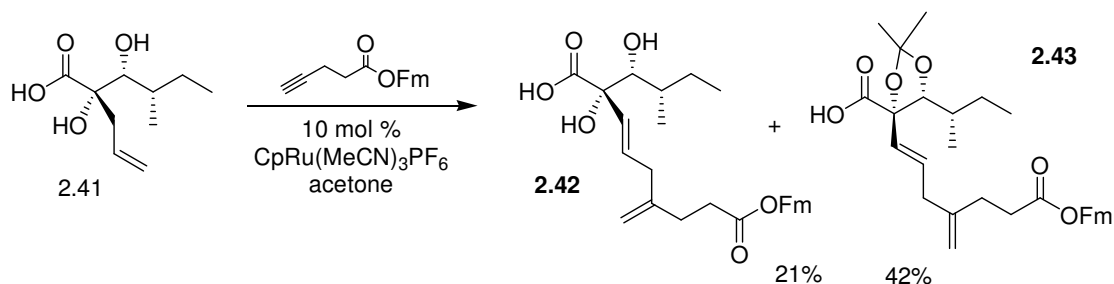
Scheme 2.24. Complete Conversion of Mixture of Alder-Ene Products to Acetonide
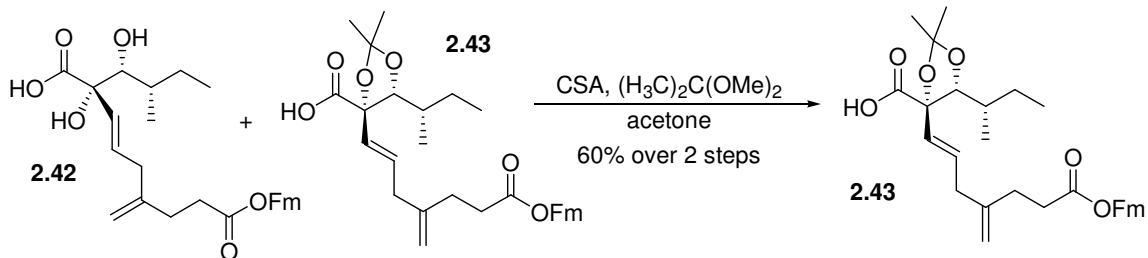
To ensure that we had indeed synthesized what we had purported, derivatization steps were invoked at this point to spectroscopically match two of Trost's known compounds (Scheme 2.25). First, the methyl ester **2.44** was formed in by exposing acetonide **2.43** to trimethylsilyldiazomethane, and indeed the ^{1}H NMR spectrum of the resultant ester was a match for Trost's compound. Additionally, a formal synthesis was completed by taking methyl ester **2.44** and removing the fluorenylmethyl group in the presence of piperidine. Matching the ^{1}H NMR spectrum of **2.45** to both Trost and Ichihara's intermediates confirmed that the desired compound had been synthesized.

Scheme 2.25. Derivatization of 2.43 and Completion of Formal Synthesis
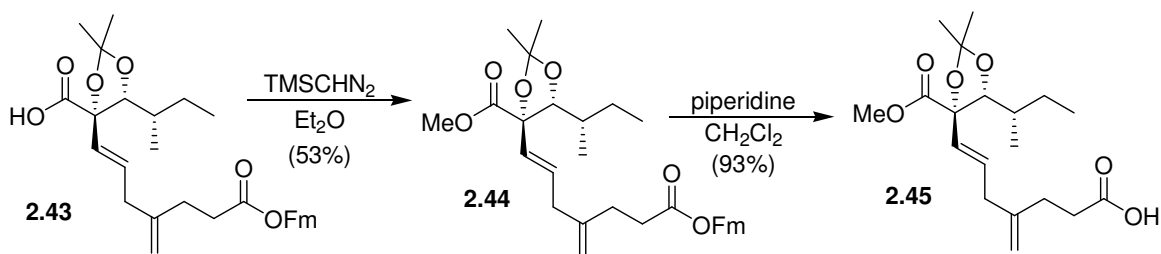
f. Appendage of Pyrone and Completion of Synthesis

To conclude the total synthesis, the pyrone needed to be put in place and the acetonide removed. Before the pyrone could be attached, the fluorenylmethyl group had to be removed. To accomplish this, ester **2.43** was subjected to piperidine, and the new

dicarboxylic acid could be obtained in 94% yield after acid-base extraction followed by filtration through a plug of silica (Scheme 2.26). Stirring the diacid **2.46** with DCC, DMAP, and pyrone **2.31** for 48 hours accomplished the desired addition and Fries rearrangement to reveal a single product (still as a mixture of diastereomers) in up to 69% yield. Although we believed that the reaction would occur preferentially at the less-sterically encumbered C3 carbonyl, a control experiment was performed to confirm this theory. Fluorenylmethyl ester **2.43** with its C20 free acid was subjected to the same pyrone appending conditions, and in fact, even after stirring for more than 48 hours, there was complete recovery of unreacted starting material.

Scheme 2.26. Removal of Fm and Installation of Pyrone
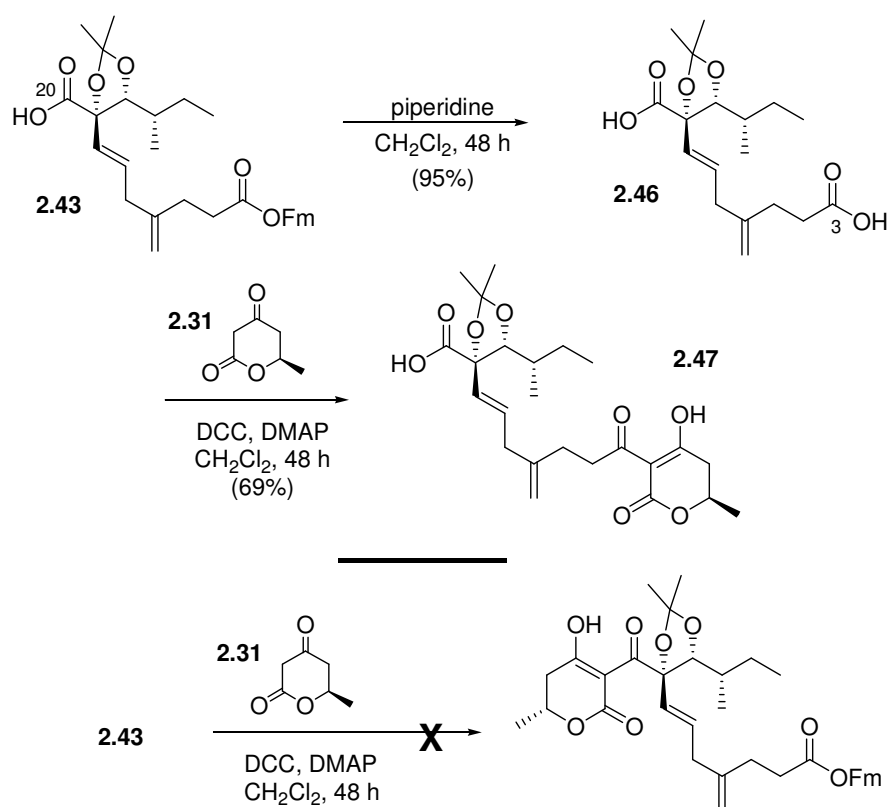
In a final step, the acetonide needed to be removed. However, conventional conditions would not accomplish this transformation, as explored in the Ichihara

synthesis. When they subjected their methyl ester acetonide to 1 N HCl, they were only able to isolate 21% of their desired deprotected material which was then to be subjected to hydrolysis. Due to this low yield, they instead decided to reverse the order of the hydrolysis and removal of the acetonide. They first removed the methyl ester with LiOH and then autoclaved the crude carboxylic acid in a 1:1 mixture of ethanol and water at 120 ºC for 1 hour. They successfully isolated alternaric acid in 52% yield over the two steps. However, important to the desired outcome, they noted, was the increased pressure and the presence of the free carboxylic acid.

We thought that perhaps a similar feat could be accomplished in a microwave reactor. Upon solubilizing the yellow oil of **2.47** in ethanol and water, the microwave tube was sealed and the vessel stirred at 120 ºC for 10 minutes at 300 watts (Scheme 2.27). The ^{1}H NMR spectrum was identical to the authentic sample in all respects except that the C4 protons were both present at δ 2.94 instead of one at δ 2.94 and one at δ 3.25. Ultra high performance liquid chromatography (UPLC) and mass spectral analysis identified the mass of our compound as that of alternaric acid, leading us to believe it may be a tautomer or diastereomer of alternaric acid. Although the ^{13}C NMR spectrum contained all of the correct peaks, the sample was not pure enough to irrefutably conclude that our synthesis was complete. On repeating the experiment, rather than simply extracting from water as we had previously, the extracts were washed with saturated aqueous NH_4Cl as in the Ichihara synthesis. It appears that the issue was resolved, supporting our belief that tautomerization at one of the other four possible sites was the likely culprit.

Scheme 2.26. Final Deprotection to Reveal Alternaric Acid
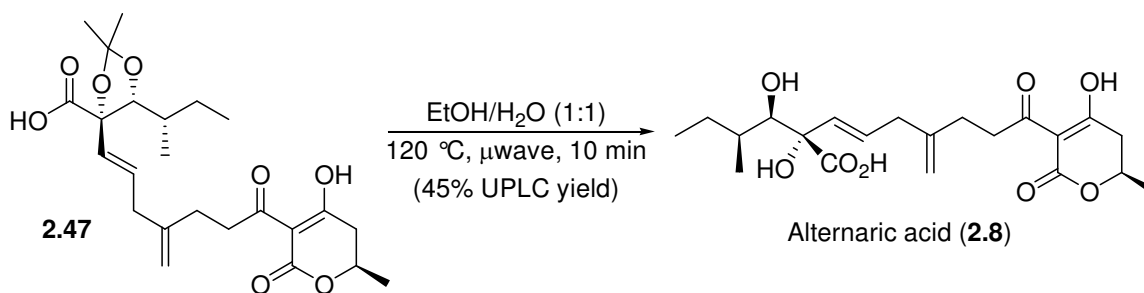
After determining the synthesis was correct, the diastereomers had to be resolved. UPLC conditions were established and the final UPLC yield on deprotection of the acetonide with diastereomeric separation was found to be 45 percent. Current efforts are underway to get isolation yields on pure synthetic alternaric acid.

D. Conclusion

Silylglyoxylates are useful implements for rapid construction of α,β-dihydroxy, γ-chiral carbonyl compounds. This research has examined a variety of carbon-based nucleophiles and aldehydes in a tandem addition/[1,2]-Brook rearrangement/aldol reaction. In addition, the tandem reaction has been used to generate a new synthesis of alternaric acid, completed in seven steps with an overall yield of 10% from silylglyoxylate.

E. EXPERIMENTAL PROCEDURES

General. Infrared spectra were recorded on a Nicolet Magna 560 spectrometer, υ_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^{1}H NMR spectra were recorded on a Varian Gemini (300 MHz) and Bruker (400 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane ith the solvent resonance as the internal standard (CDCl$_3$: 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, br = broad, and m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR were recorded on a Bruker 400 spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (CDCl$_3$: 77.0 ppm).

Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on Sigma silica gel 60 (SiO$_2$, 230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60 plates. Visualization was achieved with exposure to iodine fumes, UV light (254 nm), phosphomolybdic acid (PMA) in ethanol followed by heating, cerric ammonium nitrate (CAM) in water followed by heating, anisaldehyde stain followed by heating, or potassium permanganate in ethanol/water followed by heating. Analytical gas-liquid chromatography (GC) was performed on a Hewlett-Packard 6890 Series chromatograph equipped with a split mode capillary injection system, the indicated chiral GC column, a flame ionization detector and using helium as the carrier gas. High performance liquid chromatography (HPLC) was performed on a Varian PrepStar chromatograph with a Cyano 60A column or reverse phase on a Waters chromatograph with a Vydac C$_{18}$

semipreparative column. Ultra high performance liquid chromatography (UPLC) was performed on an Agilent Techologies 1200 Series chromatograph with a Zorbax Eclipse SB-C$_{18}$ analytical column. Elemental analyses were performed by Atlantic Microlab, Inc., of Norcross, Georgia.

All reactions were conducted in oven or flame-dried glassware under an inert atmosphere of dry nitrogen or argon, unless otherwise noted. Tetrahydrofuran was distilled from sodium and benzophenone or passed through an alumina column prior to use. Acetonitrile and triethylamine were distilled from calcium hydride. Dichloromethane, diethyl ether, toluene were passed through an alumina column prior to use in a reaction. All other reagents were purchased from Acros, Aldrich, or Strem chemical companies.
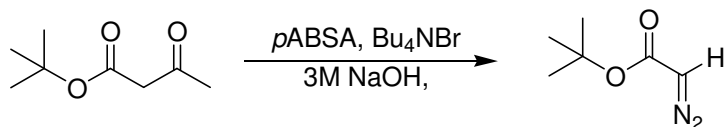
***tert*-butyl 2-diazoacetate (SI-2.1):** To a dry 250 ml flask with stir bar were added 12.61 g (52.5 mmol) of *p*ABSA (see Chapter 1 supporting information for preparation), 8.29 ml (50.0 mmol) of *tert*-butyl acetoacetate, 322 mg (1.0 mmol) of tetrabutylammonium bromide, and 105 ml of pentane. The suspension was stirred and chilled to 0ºC. Dropwise was added 55 ml of iced 3M NaOH, at which time the suspension turned to a dark orange/yellow biphasic solution. The reaction was stirred at room temperature overnight after which the solution was extracted three times with pentane. The combined organics were washed with water, then brine and finally dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to yield 3.77 g (53%) of a dark red oil. ^{1}H NMR

(400 MHz, CDCl$_3$) δ 4.61 (br s, 1H), 1.47, (s, 9H). (O'Bannon, P.E.; Dailey, W.P. *Tetrahedron* **1990**, 7341.)
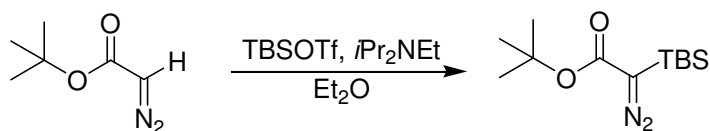
tert-butyl 2-(tert-butyldimethylsilyl)-2-diazoacetate (SI-2.2): To a dry flask was added 3.77 g (27.0 mmol) of **2.1**, 40 ml of Et$_2$O, and 5.57 ml (32.0 mmol) of iPr$_2$NEt. The flask was purged with argon and the solution was chilled to -30 ºC, at which time 7.35 ml (32.0 mmol) of TBSOTf was added slowly over 15 minutes. The suspension was stirred at -30 ºC for 45 minutes before stirring overnight at -20 ºC. The salts were then removed by filatration through cotton and the solution concentrated under vacuum to reveal 6.69 g (97%) of an orange oil. TLC (95:5 hexanes: EtOAc) R$_f$ 0.21. ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.47 (s, 9H), 0.94 (s, 9H), 0.21, (s, 6H).
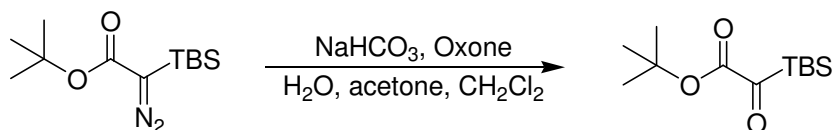
tert-butyl 2-(tert-butyldimethylsilyl)-2-oxoacetate (t-butyl/TBS silyl glyoxylate, 2.4): A 2-neck flask was charged with 17.53 g (209 mmol) of NaHCO$_3$, 50 ml of H$_2$O, and 35 ml of acetone. The suspension was cooled to 0 ºC, and 32.08 g Oxone® was added slowly in portions. A solution of 6.69 g (26.1 mmol) of **SI-2.2** in 45 ml of CH$_2$Cl$_2$ was added. The frothy suspension was stirred at 0 ºC until starting material was consumed (approx. 4.5 hours). Copious amounts of water were added and the organics extracted three times with 75 ml of CH$_2$Cl$_2$. The combined organics were dried over Na$_2$SO$_4$, filtered, and concentrated. After flash chromatography purification (99:1 Hex:EtOAc), 3.34 g (52%) of a bright yellow oil was obtained as product. TLC (95:5 hexanes: EtOAc)

R$_f$ 0.50. ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.56 (s, 9H), 0.97 (s, 9H), 0.27 (s, 6H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 233.0, 162.9, 83.7, 28.1, 26.6, 17.2, -6.5.
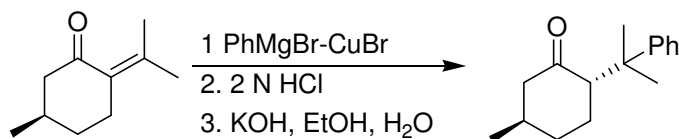
(2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexanone (SI-2.3) To a dry flask with stirbar was added 1.60 g (66 mmol, 2.2 equiv) of Mg. After flame-drying, a crystal of iodine was added and the vessel was purged with argon before adding a solution of 12 ml of bromobenzene (60 mmol, 2.0 equiv)/ 60 ml of Et$_2$O dropwise. The solution was stirred until the magnesium was consumed (~15 min.), putting on ice to calm the temperature. To a separate dry flask with an addition funnel was added 516 mg CuBr (3.6 mmo, 0.12 equiv) and 10 ml of Et$_2$O. The solution was chilled to -20 ℃ and the Grignard was added via cannula and stirred for 30 minutes. A solution of 4.91 ml of pulegone (30 mmol, 1.0 equiv) in 60 ml of Et$_2$O was added dropwise via the addition funnel. The reaction was stirred overnight at -20 ℃ and then poured into 100 ml of 2 M HCl at 0 ℃. After stirring for 20 minutes and then extracting with Et$_2$O, the organic layer was dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude mixture of diastereomers of the desired product [TLC (80:20 hexanes: EtOAc) R$_f$ 0.76-0.86] was then immediately subjected to epimerization conditions. A solution of 75 ml of EtOH, 8.96 g KOH, and 10 ml of H$_2$O was mixed and then added to the light green oil from the previous step. The solution was refluxed for 3 hours and then cooled and stirred overnight before concentrating. To the residue was added 150 ml of brine and then extracted with 4 x Et$_2$O. The combined organics were dried over MgSO$_4$, filtered, and concentrated. After flash chromatography (95:5 Hexanes:EtOAc followed by Et$_2$O),

a clear dark yellow oil was isolated as desired product in 94% yield (6.51 g) over 2 steps.

TLC (95:5 hexanes: EtOAc) R$_f$ 0.36. (White, et. al. *Org. Synth.* **1987**, *65*, 203-214.)
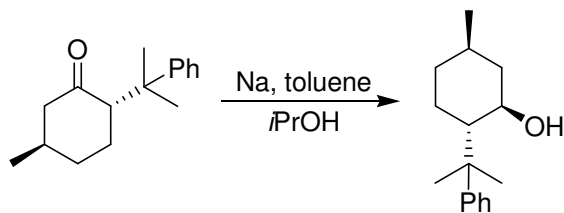
(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexanol (8-phenylmenthol, 2.18):

To a 2-neck, dry flask with condenser was added 45 ml of toluene and 2.11 g (91.9

mmol, 3.25 equiv) of freshly washed sodium. After purging with argon, **SI-2.3** was

added dropwise as a solution in 11 ml of *i*PrOH and the reaction refluxed overnight.

After cooling slowly to 0 ºC, the solution was poured carefully into iced brine and then

diluted with Et$_2$O. The biphasic mixture was separated and the aqueous layer was

extracted three times with Et$_2$O. The combined organics were washed with saturated

aqueous NH$_4$Cl then brine before drying over MgSO$_4$, filtering, and concentrating. The

residue was purified by flash chromatography (85:15 Hex:EtOAc) and 8-phenylmenthol

was isolated (4.40 g, 67% yield). TLC (95:5 hexanes: EtOAc) R$_f$ 0.14. ^{1}H NMR (300

MHz, CDCl$_3$) δ 7.43–7.17 (m, 5H), 3.52 (dt, *J* = 10.5and 4.0 Hz, 1H), 1.02-1.93 (m, 9H),

1.43 (s, 3H), 1.30 (s, 3H), 0.88 (d, *J* = 6.6 Hz, 3H).
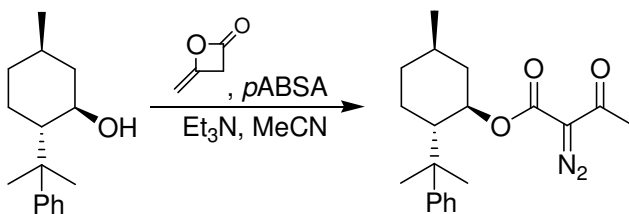
(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl   2-diazo-3-oxobutanoate

(SI-2.4): A dry 2-neck flask was equipped with condenser and stir bar before adding 7.26

g *p*ABSA (30.2 g, 1.6 equiv), 3.16 ml of Et$_3$N (22.7 mmol, 1.2 equiv), 4.39 g 8-

phenylmenthol (18.9 mmol, 1.0 equiv), and 5 ml of MeCN. The solution was brought to reflux and then a solution of freshly distilled diketene (3.18 ml, 37.8 mmol, 2.0 equiv) in 2 ml of MeCN was added dropwise. After the addition, the solution was cooled to room temperature and stirred overnight. Next, Et_2O and saturated aqueous NH_4Cl was added and the mixture was extracted three times with EtOAc. The combined organics were dried over Na_2SO_4, filtered, and concentrated and used without further purification. TLC (95:5 hexanes: EtOAc) R_f 0.29.
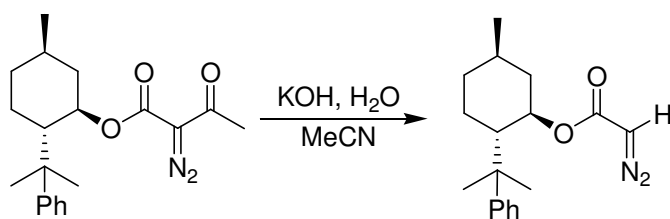
(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-(tert-butyldimethylsilyl)-2-diazoacetate (SI-2.5): Unpurified diazo compound **SI-2.4** was mixed with 35 ml of MeCN and a solution of 5.4 g KOH (94.47 mmol, 5 equiv) in 36 ml of H_2O. The solution was stirred overnight at room temperature before quenching with 3 M HCl. The mixture was separated and the aqueous layer was extracted three times with EtOAc. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude residue was carried on to the silylation step without further purification.
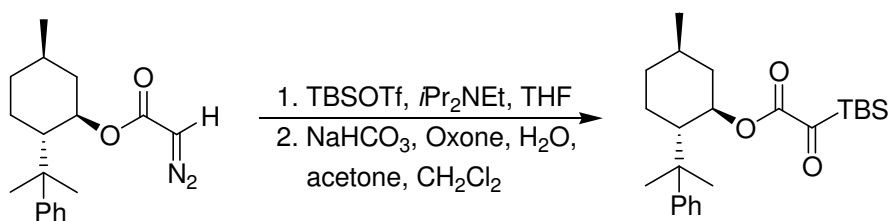
(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-(tert-butyldimethylsilyl)-2-oxoacetate (2.19): To a solution of unpurified diazoester **SI-2.5** in 40 ml of THF was added 3.95 ml of iPr$_2$Net (22.7 mmol, 1.2 equiv). The solution was chilled to -30 ℃ and

flushed with argon. Over 15 minutes, 5.21 ml of TBSOTf (22.7 mmol, 1.2 equiv) was added dropwise. The solution was stirred for 45 minutes at -30 ℃ before warming to -20 ℃ and stirring overnight. The salts were then filtered off through cotton and the filtrate was concentrated to an orange oil (**SI-2.6**) that was used without further purification in the subsequent oxidation. A 2-neck flask was equipped with a mechanical stirrer before adding 12.7 g NaHCO$_3$ (151 mmol, 8.0 equiv), 41 ml of H$_2$O, and 29 ml of acetone. The suspension was chilled to 0 ℃ and 23.23 g Oxone (37.9 mmol, 2.0 equiv) as added carefully in 3 portions. Next a solution of silyldiazoester **SI-2.6** in 38 ml of CH$_2$Cl$_2$ was added and the yellow biphasic mixture was stirred at 0 ℃ until starting material was consumed (~6 hours). Water (500 ml) was added and the aqueous layer was extracted three times with CH$_2$Cl$_2$. The combined organics were dried over MgSO$_4$, filtered, and concentrated. Flash chromatography (95:5 Pet. Ether: Et$_2$O) was used for purification. A bright yellow oil was isolated as desired product in 40% yield over 2 steps. ^{1}H NMR: δ 7.25-7.07 (m, 5H), 4.86 (dt, 1H, J = 10.8, 4.4 Hz), 2.05 (m, 1H), 1.89 (m, 1H), 1.58 (m, 1H), 1.44 (m, 1H), 1.29 (s, 3H), 1.24 (s, 3H), 1.08 (m, 1H), 0.91 (s, 9H), 0.86 (m, 2H), 0.85 (d, 3H, J = 10.8 Hz), 0.23 (s, 3H), 0.19 (s, 3H). (*Andrew Satterfield, unpublished results*)
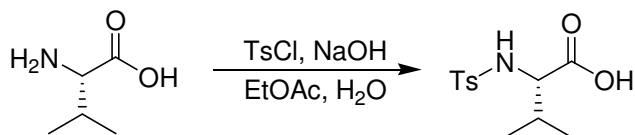

(**S**)-**3-Methyl-2-(toluene-4-sulfonamido)butyric acid (SI-2.7)**: To 4.59 g L-valine (39.2 mmol, 1.0 equiv) and 9.71 g of TsCl (50.9 mmol, 1.3 equiv) was added 78 ml of EtOAc, 20 ml of H$_2$O. Next a 2M NaOH solution (52.9 ml, 106 mmol, 2.7 equiv) was added dropwise. After stirring for an hour, the solution was extracted with Et$_2$O. The

aqueous layer was acidified to pH=1 with 6 M HCl and then extracted with Et$_2$O. The

combined organics were dried over MgSO$_4$, filtered, and concentrated to reveal 10.7 g of

a shiny white solid as the desired product in quantitative yield. TLC (95:5 Hex:EtOAc)

R_f 0.38. ^{1}H NMR δ 7.70 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 5.31 (d, J = 9.8 Hz,

1H), 3.75 (dd, J = 9.8, 4.7 Hz, 1H), 2.48 (s, 3H), 2.09 (m, 1H), 0.93 (d, J = 6.8, 3H), 0.85

(d, J = 6.8, 3H). (Ghosh, et. al. *Tetrahedron Lett.*, **2002**, *43*, 5621-5624. Craig, et. al.

Chem. Comm., **2005**, 3439-3441)
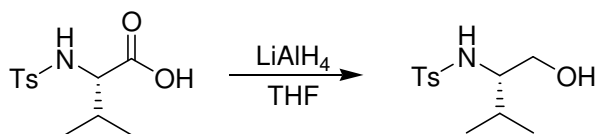
(*S*)-3-Methyl-2-(toluene-4-sulfonamido)butanol (SI-2.8): Protected amino acid **SI-2.7**

(10.6 g, 39.2 mmol, 1.0 equiv) was dissolved in 150 ml of THF and chilled to 0 ℃. Then

4.46 g (117 mmol, 3.0 equiv) LiAlH$_4$ was added carefully. The suspension was warmed

to room temperature and refluxed for 2 hours. The reaction as then diluted with 75 ml of

EtOAc and 100 ml of 50% w/v Rochelle's salt in H$_2$O was added. The mixture was

stirred until the layers separated and then extracted three times withEtOAc. The

combined organics were washed with brine and dried over Na$_2$SO$_4$, filtered, and

concentracted. The gray, oily solid was purified by flash chromatography (80:20

Hex:EtOAc → EtOAc) to reveal a clear, colorless oil as desired product (6.62 g, 66%

yield). TLC (95:5 Hex:EtOAc) R_f 0.05. ^{1}H NMR δ 7.78 (d, J = 8.0 Hz, 2H), 7.29 (d, J =

8.0 Hz, 2H), 5.24 (d, J = 8.0 Hz, 1H), 3.49-3.59 (m, 2H), 2.98-3.08 (m, 1H), 2.41 (s, 3H),

1.74-1.83 (m, 1H), 2.78 (d, J = 3.2 Hz, 6H). (Ghosh, et. al. *Tetrahedron Lett.* **2002**, *43*,

5621-5624. Craig, et. al. *Chem. Comm.* **2005**, 3439-3441)
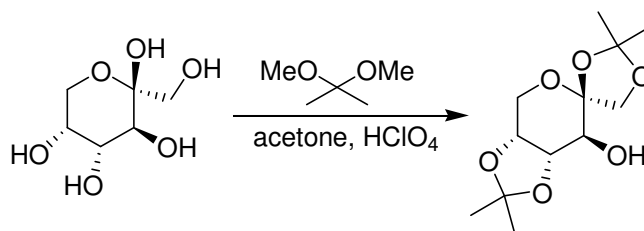
1,2:4,5-Di-*O*-isopropylidene-D-**erythro-2,3-hexodiuro-2,6-pyranose (SI-2.9)**:   To a

suspension of 5 g D-fructose in 100 ml of acetone was added 2.01 ml (16.37 mmol, 0.59

equiv) 2,2-dimethoxypropane. After chilling to 0 ºC, 1.17 ml of 70% $HClO_4$ was added

slowly and the mixture was stirred for 6 hours at 0 ºC. The solution was then neutralized

to pH=7-8 with concentrated NH_4OH (~10 drops) and allowed to stir 5 mintues before

concentrating. The residue was recrystallized with 4:1 hexanes:CH_2Cl_2 to reveal 2.95 g

(41% yield) of desired product as white needles. TLC (95:5 Hex:EtOAc) R_f 0.05. ^{1}H

NMR ☐ 4.22 (ddd, *J* = 5.7, 2.7, 0.9 Hz, 1H), 4.19 (d, *J* = 9.0 Hz, 1H), 4.13 (dd, *J* = 6.8,

5.7 Hz, 1H), 4.12 (dd, *J* = 13.2, 2.7 Hz, 1H), 4.01(dd, *J* = 13.2, 0.9 Hz, 1H), 3.98 (d, *J* =

9.0 Hz, 1H), 3.67 (dd, *J* = 8.1, 6.8 Hz, 1H), 1.99 (d, *J* = 8.1 Hz, 1H), 1.54 (s, 3H), 1.52 (s,

3H),1.44 (s, 3H), 1.37 (s, 3H) (Wang, et. al. *Tetrahedron Lett.*, **2001**, *42*, 1835-1838.

Shi, et. al. *J. Am. Chem. Soc.*, **1997**, *119*, 11224-11235.)
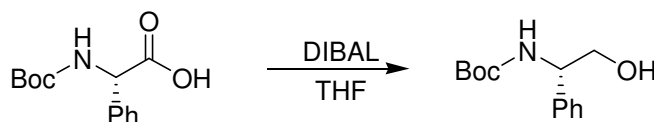
***tert*-butyl (*S*)-2-hydroxy-1-phenylethylcarbamate (SI-2.10)**:   *N*-Boc-phenylalanine (2

g, 7.54 mmol, 1.0 equiv) was dissolved in 20 ml of THF. The solution was chilled to 0

ºC and then 15.08 ml (15.08 mmol, 2.0 equiv) of DIBAL (1.0 M in hexane) was added

and the mixture was allowed to stir 14 hours at room temperature. A saturated solution of

Rochelle's salt (75 ml) was added and the emulsion was stirred at room temperature until

two distinct layers formed (~1 hour). The layers were separated and the aqueous layer

was extracted three times with EtOAc. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The residue was pushed through a plug of silica with 80:20 Hex:EtOAc to reveal a clear, colorless oil as desired product (853 mg, 45% yield). TLC (95:5 Hex:EtOAc; CAM visualization) R_f 0.12.
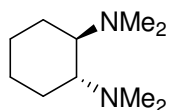
(±)-*trans*-N^1,N^1,N^2,N^2-tetramethylcyclohexane-1,2-diamine (2.24): To a flask with stir bar was added 1.59 g (6.0 mmol, 1.0 equiv) (±)-*trans*-1,2-diaminocyclohexane tartrate, Et_2O, and 50% $NaOH_{aq}$. The mixture was extracted three times with Et_2O and the combined organics were concentrated to reveal the diamine. The diamine was cooled to 0 ºC and 2.20 ml (42.0 mmol, 7.0 equiv) formic acid was added dropwise followed by 2.62 ml (37% w/v in H_2O, 33.22 mmol, 5.37 mmol) of formaldehyde. The solution was heated slowly to 80 ºC and stirred at that temperature for 24 hours. The reaction was then cooled to room temperature, acidified with 10% HCl, and extracted three times with Et_2O. The aqueous layer was cooled to <0 ºC and 50% aq. KOH was added dropwise to pH = 12, keeping the temperature below 15 ºC. The aqueous layer was again extracted wih 3 x Et_2O, and the combined organics were dried over $MgSO_4$, filtered, and concentrated. A clear yellow oil was isolated as desired product (527 mg, 52% yield).
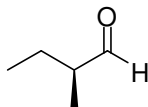

(*S*)-2-methylbutanal: To a flask was added 8.15 ml (75.0 mmol) of (*S*)-2-methyl-1-butanol, 469 mg (3.0 mmol) of TEMPO, and 25 ml of CH_2Cl_2. A solution of 893 mg (7.5 mmol) of KBr in 3.75 ml of H_2O was added. The solution was stirred 10 minutes at room

temperature and then cooled to -10 ºC. Next, a solution of 118 ml (82.5 mmol) of 0.7 M

NaOCl buffered with 1.4 g of $NaHCO_3$ was added dropwise, maintaining the temperature

below 10 ºC. The solution was then returned to room temperature and stirred an

additional 10 minutes before extracting 3x with CH_2Cl_2. The combined organics were

washed with 15 ml of 2 M HCl with 200 mg KI, followed by washing with 15 ml of 10%

$Na_2S_2O_3$, and finally washing with H_2O. The organics were dried over Na_2SO_4, filtered,

and concentrated. A thick silica plug was run using CH_2Cl_2 as eluent, followed by

distilling the solvent off to recover a clear, very pungent oil as the desired product (4.52

g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62(d, J = 2.0 Hz, 1H), 2.29 (m, 1H), 1.75 (m,

1H), 1.44 (m, 1H), 1.10 (d, J = 7.0 Hz, 3H), 0.96 (d, J = 7.5 Hz, 3H). ^{13}C NMR (400

MHz, $CDCl_3$) δ 205.2, 47.7, 23.5, 12.8, 11.3.

Procedure (A), Thermodynamic Conditions: A 25 ml flame-dried round-bottomed

flask equipped with a stirbar was charged with silylglyoxylate **1** (1.0 equiv) and a

carbonyl compound **3** (2.0 equiv) in 10 mL of THF. To the resulting solution at -78 °C

was added dropwise 1.0 M vinylmagnesium bromide solution in THF (2.0 equiv) under

Ar. Following addition of the Grignard reagent, the yellow color of silylglyoxylate

disappeared. The reaction was warmed to 25 °C for 30 min before it was quenched by

the addition of 5 mL of saturated aqueous NH_4Cl solution. The layers were separated and

the aqueous layer was extracted with Et_2O (2 X 10 mL). The combined organic layers

were washed with H_2O (15 mL), brine (15 mL), dried (Na_2SO_4), and concentrated *in*

*vacuo*. The crude material was purified by flash chromatography using the specified

solvent system.

Procedure (B), Kinetic Conditions: A 25 mL flame-dried round-bottomed flask equipped with a stirbar was charged with silylglyoxylate **1** (1.0 equiv) and a carbonyl compound **3** (2.0 equiv) in 10 mL of THF or toluene. To the resulting solution at -78 °C was added dropwise 1.0 M vinylmagnesium bromide solution in THF (2.0 equiv) under Ar (In the case of (-)-sparteine (2.0 equiv) was pre-mixed with vinylmagnesium bromide solution at 0 °C for 30 min). Following addition of the Grignard reagent, the yellow color of silylglyoxylate disappeared. The reaction was stirred at the same temperature for 5 min before it was quenched by the slow addition of 3 mL of saturated aqueous NH$_4$Cl solution or pre-cooled 1 mL of acetic acid in 3 mL of THF. The layers were separated and the aqueous layer was extracted with Et$_2$O (2 X 10 mL). The combined organic layers were washed with H$_2$O (15 mL), brine (15 mL), dried (Na$_2$SO$_4$), and concentrated *in vacuo*. The crude material was purified by flash chromatography using the specified solvent system. *(Xin Linghu, unpublished results)*
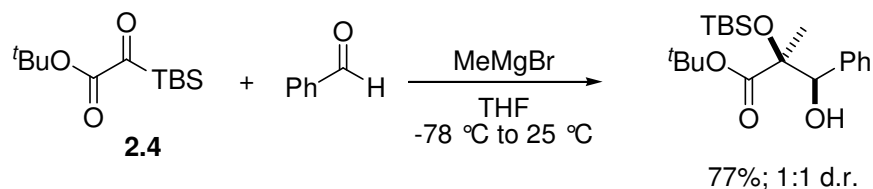
2-*tert*-Butyldimethylsilyloxy-3-hydroxyl-2-methyl-3-phenyl-propanoic acid *tert*-butyl ester (SI-2.11). The title compound was prepared according to Procedure **A** using 75 mg of silylglyoxylate **2.4** (0.31 mmol, 1.0 equiv), 62 μL of benzaldehyde (0.613 mmol, 2.0 equiv), and 0.20 ml of 3.0 M MeMgBr in Et$_2$O (0.613 mmol, 2.0 equiv) in 6 ml of THF. The crude material was purified by flash chromatography (95:5 hexanes: EtOAc) to furnish 87 mg (77%) of the pure clear, colorless oil as a 1.3:1 mixture of diastereomers. Analytical data: **IR** (thin film, cm^{-1}) 2979, 2954, 2931, 2894, 2858, 1744, 1493, 1472,

1455, 1393, 1370, 1289, 1254, 1173, 1121, 1048, 999, 891, 837, 810, 779; **¹H NMR** (400

MHz, CDCl₃) δ 7.41-7.28 (m, 5H), 4.68 (d, *J* = 6.8 Hz, 1H), 3.12 (d, *J* = 6.8 Hz, 1H),

1.34 (s, 9H), 1.24 (s, 3H), 0.96 (s, 9H), 0.17 (s, 3H), 0.03 (s, 3H); **¹³C NMR** (400 MHz,

CDCl₃) δ 172.5, 139.7, 128.1, 127.8, 127.5, 81.7, 80.5, 79.0, 27.8, 26.0, 22.5, 18.5, -2.79,

-2.96; **TLC** (95:5 hexanes: EtOAc) R$_f$ 0.13. LRMS (ESI+) Calculated for C$_{20}$H$_{34}$O$_4$Si

[M+NH$_4$]$^+$: 384.22.   Found [M+NH$_4$]$^+$: 384.3; [M+Na]$^+$: 389.3; [2M+H]$^+$: 733.5;

[2M+Na]$^+$: 755.5. **Anal.** Calcd. for C$_{20}$H$_{34}$O$_4$Si: C, 65.53; H, 9.35; Found: C, 65.24; H,

9.43.
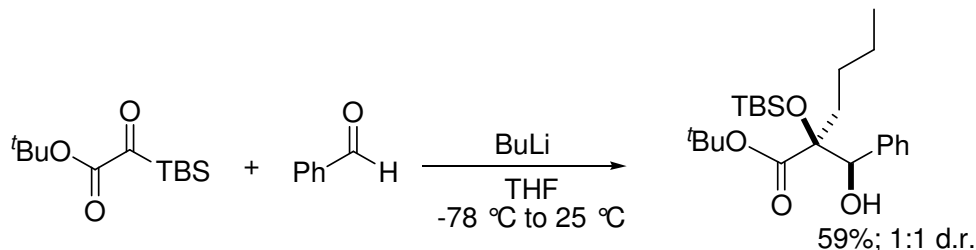
**2-*tert*-Butyldimethylsilyloxy-2-(hydroxy-phenylmethyl)-hexanoic   acid   *tert*-butyl

ester (SI-2.12).** The title compound was prepared according to Procedure **A** using 75 mg

of **1** (0.31 mmol, 1.0 equiv), 62 μl of benzaldehyde (0.613 mmol, 2.0 equiv), and 0.41 ml

of 1.5 M BuLi in hexane (0.613 mmol, 2.0 equiv) in 6 ml of THF. The crude material

was purified by flash chromatography (95:5 hexanes: EtOAc) to furnish 78 mg (62%) of

the pure clear, colorless oil as a 1.1:1 mixture of diastereomers. Analytical data: **IR** (thin

film, cm^{-1}) 2958, 2929, 2900, 2860, 1727, 1472, 1463, 1393, 1368, 1252, 1219, 1148,

1098, 1069, 874, 837; **¹H NMR** (400 MHz, CDCl₃) δ 7.40-7.34 (m, 2H), 7.30-7.25 (m,

3H), 4.74 (s, 1H), 3.34 (s, 1H), 1.59-1.43 (m, 2H), 1.36-1.23 (m, 2H), 1.07-0.87 (m, 2H),

1.40 (s, 9H), 0.89 (s, 9H), 0.82 (t, *J* = 7.4 Hz, 3H), 0.91 (s, 3H), -0,18 (s, 3H); **¹³C NMR**

(400 MHz, CDCl₃) δ 172.8, 140.1, 128.6, 127.8, 127.3, 82.1, 80.8, 80.6, 35.2, 27.8, 25.7,

25.36, 22.9, 18.2, 13.8, -4.7, -5.2 ; **TLC** (95:5 hexanes: EtOAc) R_f 0.23. LRMS (ESI+)

Calculated for $C_{23}H_{40}O_4Si$ [M+Na]$^+$: 431.27. Found [M+Na]$^+$: 431.3; [2M+Na]$^+$: 839.6.

Anal. Calcd. for $C_{23}H_{40}O_4Si$: C, 67.60; H, 9.87; Found: C, 67.88; H, 9.64.

^tBuO ... TBS (**2.4**) + Ph—CHO $\xrightarrow[\text{-78 °C to 25 °C}]{\text{PhMgBr}\atop\text{THF}}$ TBSO, Ph / ^tBuO ... Ph, OH 82%; 4:1 d.r.
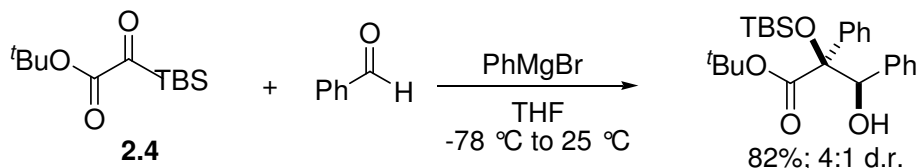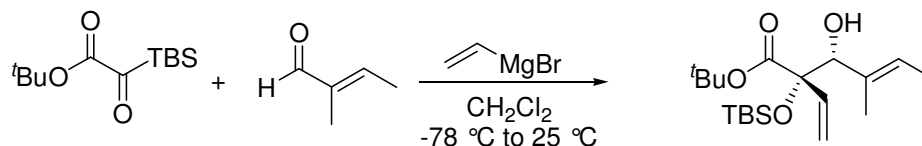
2-*tert*-Butyldimethylsilyloxy-3-hydroxy-2,3-diphenyl-propanoic acid *tert*-butyl ester

(SI-2.13). The title compound was prepared according to Procedure **A** using 75 mg of **1**

(0.31 mmol, 1.0 equiv), 62 µl of benzaldehyde (0.613 mmol, 2.0 equiv), and PhMgBr

(0.613 mmol, 2.0 equiv.; prepared from 64 µl PhBr and 15 mg Mg in 0.6 ml of THF) in 6

ml of THF. The crude material was purified by flash chromatography (95:5 hexanes:

EtOAc) to furnish 110 mg (83%) of the pure clear, colorless oil as a 4.5:1 mixture of

diastereomers. Analytical data: **IR** (thin film, cm^{-1}) 3060, 3029, 2954, 2927, 2900, 2883,

2854, 1742, 1706, 1661, 1495, 1472, 1449, 1393, 1370, 1318, 1277, 1254, 1158 (br),

1079, 1048, 970, 901, 837, 779; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.35-7.32 (m, 4H), 7.28-

7.25 (m, 6H), 5.31 (d, J = 9.0 Hz, 1H), 3.24 (d, J = 9.0 Hz, 1H), 1.53 (s, 9H), 0.94 (s,

9H), 0.13 (s, 3H), -0.04 (s, 3H) ; **^{13}C NMR** (400 MHz, CDCl$_3$) δ 171.9, 140.2, 139.1,

128.4, 128.1, 127.7, 127.2, 127.0, 126.7, 85.6, 83.5, 78.4, 28.0, 26.5, 19.4, -2.3, -

2.7; **TLC** (95:5 hexanes: EtOAc) R_f 0.19. LRMS (ESI+) Calculated for $C_{25}H_{36}O_4Si$

[M+Na]$^+$: 451.24.   Found [M+Na]$^+$: 451.3; [2M+Na]$^+$: 879.5.   **Anal.** Calcd. for

$C_{25}H_{36}O_4Si$: C, 70.05; H, 8.47; Found: C, 70.22; H, 8.55.

^{t}BuO ... TBS ... O ... O ... + ... H ... O ... MgBr ... CH$_2$Cl$_2$ ... -78 °C to 25 °C ... O ... OH ... ^{t}BuO ... TBSO

***tert*-butyl (*E*,2*S*,3*R*)-2-*tert*-butyldimethylsilyloxy-3-hydroxy-4-methyl-2-vinylhex-4-enoate (2.26)**: To a dry scintillation vial purged with argon was added 75 mg (0.307 mmol, 1.0 equiv) silylglyoxylate **2.4**, 60 µl (0.614 mmol, 2.0 equiv) tiglic aldehyde, and 6 ml of dichloromethane. The bright yellow solution was chilled to -78 °C and 0.61 ml (0.614 mmol, 2.0 equiv) vinylmagnesium bromide was added dropwise. Next the reaction was warmed to room temperature for 30 minutes, during which time the reaction lost its bright yellow color and after turning clear became a faintly dull yellow. The reaction was then quenched with 3 ml of saturated aqueous NH$_4$Cl and diluted with H$_2$O. The layers were separated and the aqueous layer was extracted three times with Et$_2$O. The combined organics were dried over MgSO$_4$, filtered, and concentrated. The yellow oil was purified by flash chromatography using 95:5 hexane:ethyl acetate to reveal a clear, colorless oil as the desired product (74 mg, 67%). TLC (95:5 Hex:EtOAc) R_f 0.83. **^{1}H NMR** (400 MHz, CDCl$_3$) δ 5.83, dd, *J* = 16.5 ad 10.3 Hz, 1H), 5.44 (q, *J* = 6.2 Hz, 1H), 5.34 (dd, *J* = 16.5, 1.0 Hz, 1H), 5.20 (dd, *J* = 10.3, 1.0 Hz, 1H), 4.19 (d, *J* = 6.6 Hz, 1H), 2.89 (d, *J* = 6.6 Hz, 1H), 1.60 (s, 3H), 1.58 (d, *J* = 6.2 Hz, 3H), 1.48 (s, 9H), 0.90 (s, 9H), 0.18 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (400 MHz, CDCl$_3$) δ 171.4, 138.2, 134.3, 124.6, 116.8, 84.2, 82.8, 82.4, 28.7, 26.9, 19.5, 13.4, 13.1, -1.8, -1.9.
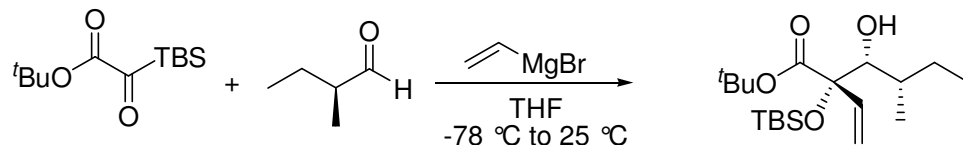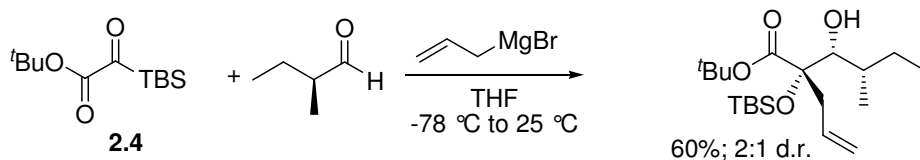
(2S,3R,4S)-*tert*-butyl 2-(*tert*-butyldimethylsilyl)oxy-3-hydroxy-4-methyl-2-vinyl hexanoate (2.29): To a dry scintillation vial purged with argon was added 100 mg (0.409 mmol) of silylglyoxylate **2.4**, 0.70 mg (0.818 mmol) of (*S*)-2-methylbutanal, and 8 ml of THF. The bright yellow solution was chilled to -78 ºC and 0.82 ml (0.818 mmol) of vinyl magnesiumbromide (1.0 M in THF) was added dropwise with concomitant loss of bright yellow color. The clear faintly yellow solution was warmed to room temperature and stirred for 30 minutes. At that time the dark yellow solution was quenched with 5 ml of saturated aqueous NH_4Cl and diluted with water. The layers were separated and the aqueous solution was extracted three times with Et_2O. The combine organics were dried over anhydrous $MgSO_4$, filtered, and concentrated. The yellow oil was purified by flash chromatography using 95:5 hexane:ethyl acetate to reveal a clear, colorless oil as the desired product (115 mg, 79%). Analytical data for major diastereomer of **2.29**: **IR** (thin film, cm^{-1}) 3583, 3490, 2963, 2930, 2858, 1747, 1472, 1393, 1369, 1253, 1155, 1138, 1057, 1005, 926, 839, 780; **^{1}H NMR** (300 MHz, CDCl$_3$) δ 5.95 (dd, *J* = 11.1, 17.4 Hz, 1H), 5.40 (dd, *J* = 1.2, 17.7 Hz, 1H), 5.21 (dd, *J* = 1.2, 10.8 Hz, 1H), 3.72 (dd, *J* = 3.0, 10.8 Hz, 1H), 2.41 (d, *J* = 10.8 Hz, 1H), 1.78-1.62 (m, 1H), 1.49 (s, 9H), 0.95-0.80 (m, 8H), 0.92 (s, 9H), 0.20 (s, 3H), 0.12 (s, 3H); **^{13}C NMR** (75 MHz, CDCl$_3$) δ 171.8, 138.4, 116.0, 83.9, 82.4, 80.7, 35.3, 28.6, 28.0, 26.4, 26.3, 24.0, 19.2, -2.2, -2.3; TLC (20:1 hexanes: EtOAc) R$_f$ 0.22. **Anal.** Calcd. for C$_{19}$H$_{38}$O$_4$Si: C, 63.64; H, 10.68. Found: C, 63.86; H, 10.74.
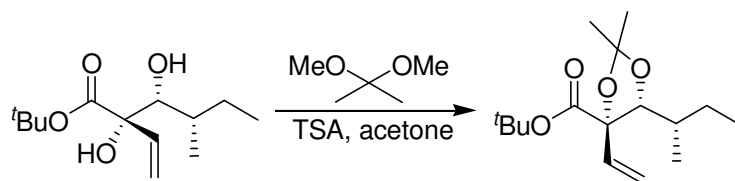
(4*S*,5*R*)-*tert*-butyl 5-*sec*-butyl-2,2-dimethyl-4-vinyl-1,3-dioxolane-4-carboxylate (SI-2.14): To a vial with stir bar was added 67 mg of **2.39** (0.274 mmol, 1.0 equiv) and 1.5 ml of acetone. Next 2.6 mg (0.14 mmol, 0.05 equiv) *p*-toluenesulfonic acid was added and the solution was allowed to stir overnight at room temperature. The solution was concentrated and immediately filtered through silica and concentrated before subjecting to flash chromatography (90:10 Hex:EtOAc) to reveal a clear, colorless oil as desired product (68 mg, 87%). TLC (95:5 Hex:EtOAc) R_f 0.40.

2-*tert*-Butyldimethylsilyloxy-3-hydroxy-4-methyl-2-propenyl-hexanoic acid *tert*-butyl ester (2.30). The title compound was prepared according to Procedure **A** using 100 mg of **2.4** (0.41 mmol, 1.0 equiv), 70 mg of (*S*)-2-methyl-butanal (0.82 mmol, 2.0 equiv), and 0.82 ml of 1.0 M allyl-MgBr in THF (0.82 mmol, 2.0 equiv) in 8 ml of THF. The crude material was purified by flash chromatography (95:5 hexanes: EtOAc) to furnish 104 mg (83%) of the pure clear, colorless oil as a 2.4:1 mixture of diastereomers. Analytical data: **IR** (thin film, cm^{-1}) 3080, 2964, 2933, 2906, 2885, 2860, 1744, 1700, 1642, 1472, 1463, 1393, 1370, 1252, 1138, 1050, 1005, 960, 916, 835, 779, 741; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 5.86–5.75 (m, 1H), 5.15-5.04 (m, 2H), 3.58 (d, *J* = 10.4 Hz, 1H), 2.69-2.60 (m, 1H), 2.52-2.39 (m, 2H), 2.49 (d, *J* = 10.4 Hz, 1H), 1,82-1.73 (m, 1H), 1.49 (s, 9H), 1.48-1.40 (m, 1H), 1.35-1.26 (m, 1H), 0.91, (t, *J* = 7.4 Hz, 3H), 0.88 (s, 9H),

0.84, (d, J = 6.9 Hz, 3H), 0.20 (s, 3H), 0.15 (s, 3H); ^{13}C **NMR** (400 MHz, CDCl$_3$)

δ 173.1, 133.0, 118.6, 82.4, 80.6, 78.4, 42.8, 34.6, 28.1, 26.3, 26.2, 19.0, 13.1, 11.9, -1.9,

-2.3; **TLC** (95:5 hexanes: EtOAc) R$_f$ 0.21. LRMS (ESI+) Calculated for C$_{20}$H$_{40}$O$_4$Si

[M+H]$^+$: 373.27.   Found [M+H]$^+$: 373.3; [M+Na]$^+$: 395.4; [2M+Na]$^+$: 767.5. **Anal.**

Calcd. for C$_{20}$H$_{40}$O$_4$Si: C, 64.47; H, 10.82; Found: C, 64.50; H, 10.97.
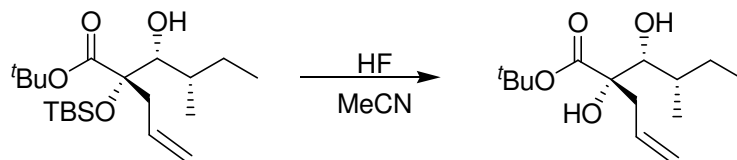

tert-butyl 2,3-dihydroxy-4-methyl-2-(2-propenyl)-hexanoate (SI-2.15): To plastic vial

with stir bar was added 220 mg (0.59 mmol, 1.0 equiv) **2.30** in 3 ml of MeCN. Next 2.3

ml of HF (49% in H$_2$O) was added, and the solution was stirred at room temperature for

15 hours. At that time the vial was put on ice and very carefully quenched with saturated

aqueous NaHCO$_3$. The aqueous layer was extracted three times with EtOAc, and the

combined organics were dried over MgSO$_4$, filtered, and concentrated. The residue was

purified by column chromatography (80:20 Hex:EtOAc) to reveal 78 mg of a yellow oil

as desired product (51% yield). TLC (80:20 Hex:EtOAc, CAM visualization) R$_f$ 0.04.
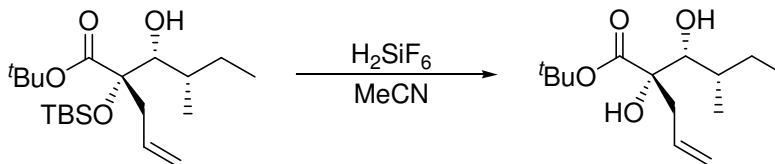
tert-butyl 2,3-dihydroxy-4-methyl-2-(2-propenyl)-hexanoate (SI-2.15): To a plastic

vial with stir bar was added 135 mg (0.362 mmol, 1.0 equiv) of **2.30**, in 1 ml of MeCN.

Next 0.11 ml of H$_2$SiF$_6$ (22 % in H$_2$O) was added, and the solution was stirred at room

temperature for 15 hours. At that time, brine was added and the aqueous layer was

extracted three times with EtOAc. The combined organics were dried over MgSO$_4$,

filtered, and concentrated. The residue was purified by running through a silica gel plug using 80:20 → 0:100 Hexanes : EtOAc. A clear, light yellow oil was obtained as desired product in 95% yield. TLC R_f (95:5 Hex:EtOAc, CAM visualization) 0.02.
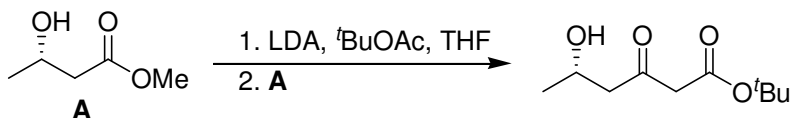
(*S*)-*tert*-butyl 5-hydroxy-3-oxohexanoate (SI-2.16): In a dry vial with stir bar was mixed 9.5 ml (67.95 mmol, 5.0 equiv) iPr$_2$NH and 65 ml of THF. The solution was chilled to 0 °C, and 36.3 ml of butyllithium (1.5 M in hexane, 54.40 mmol, 4.0 equiv) was added dropwise. The LDA was stirred for 15 minutes at 0 °C and then chilled to -78 °C before adding 7.3 ml (54.40 mmol, 4.0 equiv) of *t*-butylacetate. After stirring at -78 °C for 20 minutes, a solution of 1.5 ml (13.59 mmol, 1.0 equiv) of methyl-(*R*)-3-hydroxybutyrate in 8 ml of THF was added dropwise at -78 °C. The reaction was then stirred at -50 °C for 2 hours and then 15 minutes at -15 °C before quenching with iced H$_2$O and separating. The aqueous layer was extracted three times with Et$_2$O, acidified with 1 M HCl, and extracted again. The combined organics were dried over MgSO$_4$, filtered, and concentrated. The crude oil was purified by running through a silica gel plug using 80:20 Hex:EtOAc to reveal 2.49 g of a clear, faintly yellow oil as desired product (91% yield). TLC (80:20 Hex:EtOAc, anisaldehyde visualization) R_f 0.09. ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.25 (m, 1H), 3.38 (s, 2H), 2.93 (d, J = 3.3 Hz, 1H), 2.74 (dd, J = 17.7, 3.2 Hz, 1H), 2.63 (dd, J = 17.7 Hz, 8.6 Hz, 1H), 1.47 (s, 9H), 1.20 (d, J = 6.4 Hz, 3H). (Miyashita, et. al. *Org. Lett.*, **2005**, *7*, 2929-2932.)
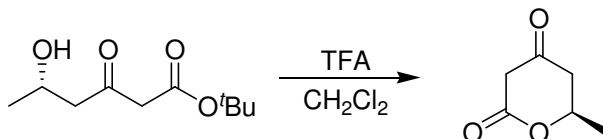
**(R)-dihydro-6-methyl-3H-pyran-2,4-dione** **(2.31)**: To a dry flask containing 1.00 g (4.94 mmol, 1.0 equiv) ester **SI-2.16** was added 28 ml of CH_2Cl_2 followed by 0.37 ml (4.94 mmol, 1.0 equiv) TFA at 10°C. The solution was stirred at room temperature for 24 hours before removing the solvent under vacuum. The residue was recrystallized from CH_2Cl_2/hexanes to reveal 438 mg (69% yield) fluffy, shiny, light yellow crystals. **¹H NMR** (400 MHz, CDCl₃) δ 4.83 (m, 1H), 3.62 (d, 1H, $J = 18.8$ Hz), 3.43 (d, 1H, $J = 18.8$ Hz), 2.74 (dd, 1H, $J = 18.4, 2.8$ Hz), 2.48 (dd, 1H, $J = 18.3, 11.3$ Hz), 1.55 (d, 3H, $J = 6.4$ Hz); **TLC** (80:20 hexanes: EtOAc, anisaldehyde) R_f 0.05. LRMS (ESI+) Calculated for $C_6H_8O_3$ [M+H]⁺: 128.05. Found [M+H]⁺: 129.1; [M+Na]⁺: 151.0; [2M+H]⁺: 257.2; [2M+Na]⁺: 279.1; [3M+H]⁺ : 385.3; [3M+Na]⁺: 407.2.
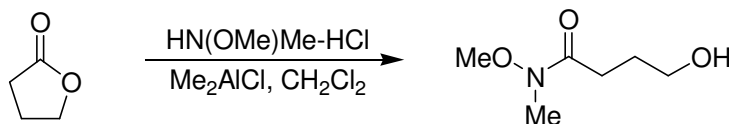
4-hydroxy-N-methoxy-N-methylbutanamide (SI-2.17): To a dry flask was added 2.15 g (22 mmol, 1.10 equiv) of N,O-dimethylhydroxylamine hydrochloride and 100 ml of CH_2Cl_2. After cooling to 0 ºC, 22 ml of Me₂AlCl (1.0 M in hexane, 22 mmol, 1.10 equiv) was added dropwise and the reaction stirred at 0 ºC for 1 hour. Next, 1.54 ml of γ–butyrolactone (20.0 mmol, 1.0 equiv) was added slowly and the solution stirred at room temperature overnight. The solution was extracted three times with CH_2Cl_2, and the combined organics were dried over Na_2SO_4, filtered, and concentrated. The product was used in the subsequent protection step without further purification (1.78 g, 61% yield).
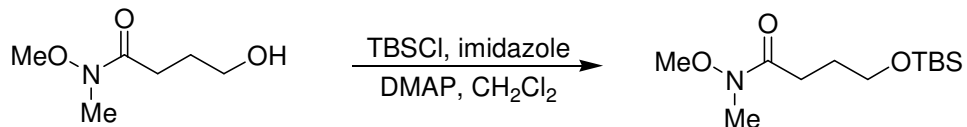
4-(*tert*-butyldimethylsiloxy)-*N*-methoxy-*N*-methylbutanamide (SI-2.18): To a dry flask with stir bar was added 1.78 g (12.09 mmol, 1.0 equiv) of alcohol **SI-2.17**, 50 ml of CH$_2$Cl$_2$, and 947 mg (13.90 mmol, 1.15 equiv) of imidazole. The solution was chilled to 0 °C and 1.91 g (12.69 mmol, 1.05 equiv) of TBSCl and 74 mg (0.60 mmol, 0.05 equiv) of DMAP was added. The reaction was stirred at room temperature for 15 hours before adding water and extracting three times with CH$_2$Cl$_2$. The combined organics were washed with brine, dried over MgSO$_4$, filtered, and concentrated. The crude clear, faintly yellow oil was used without further purification (3.01 g, 95% yield). ^{1}H NMR δ 3.69 (s, 3H), 3.66 (t, *J* = 6.0 Hz, 2H), 3.18 (s, 3H), 2.51 (t, *J* = 7.6 Hz, 2H), 1.82 (p, *J* = 6.9 Hz, 2H), 0.89 (s, 9H), 0.04 (s, 6H).
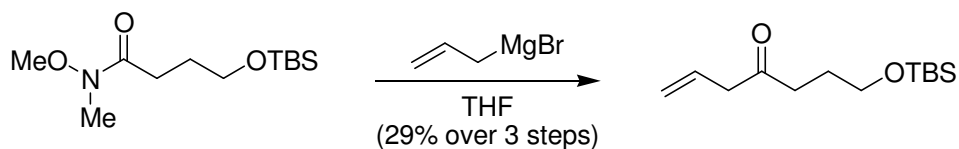
7-(*tert*-butoxydimethylsiloxy)hept-1-en-4-one (2.32): To a dry flask with stir bar was added 12.6 ml (1.0 M in Et$_2$O, 12.6 mmol, 1.1 equiv) of allylmagnesium bromide and 30 ml of THF. A solution of crude amide **SI-2.18** in 15 ml of THF was added dropwise. The clear yellow solution was allowed to stir 15 hours at room temperature before quenching with water and saturated aqueous NH$_4$Cl. The white biphasic mixture was extracted three times with Et$_2$O. The combined organics were dried over MgSO$_4$, filtered, and concentrated. The crude oil was purified by column chromatography (90:10 Hex:EtOAc) to reveal a clear, orange oil as desired product (861 mg, 29% yield over 3 steps). TLC (95:5 Hex:EtOAc, anisaldehyde visualization) R_f 0.15. ^{1}H NMR (400 MHz,

CDCl$_3$) δ 5.91 (m, 1H), 5.09-5.17 (m, 2H), 3.60 (t, J = 5.7 Hz, 2H), 3.18 (d, J = 6.5 Hz, 2H), 2.51 (t, 2H, J = 6.8 Hz, 2H), 1.77 (p, J = 6.2 Hz, 2H), 0.86 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 209.0, 131.2, 119.2, 62.4, 48.1, 38.9, 27.5, 26.3, 18.8, -4.7.
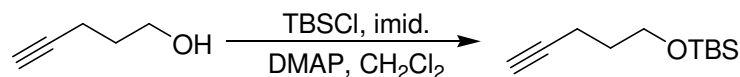
**tert-butyldimethyl(pent-4-ynyloxy)silane (SI-2.19)**:   To a dry vial under argon was added 0.25 ml (2.7 mmol) of 4-pentyn-1-ol and 11 ml of CH$_2$Cl$_2$. To this solution was added 0.43 g (2.84 mmol, 1.05 equiv) TBSCl, 0.21 g (3.11 mmol) of imidazole, and 16 mg (0.14 mmol) of DMAP.   The cream slurry was stirred for 16 hours at room temperature before quenching with water and extracting three times with CH$_2$Cl$_2$.   The combined organics were dried over Na$_2$SO$_4$, filered, and concentrated.   The residue was purified by flash chromatography using 90:10 hexanes:ethyl acetate.   A clear, colorless oil was isolated as the desired product (459 mg, 86%). TLC (95:5 Hex:EtOAc) R_f 0.53. ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.68 (t, J = 6.0 Hz, 2H), 2.25 (dt, J = 7.1, 2.6 Hz, 2H), 1.91 (t, J = 2.6 Hz, 1H), 1.70 (quintet, J = 6.4 Hz, 2H), 0.87 (s, 9H), 0.04 (s, 6H).
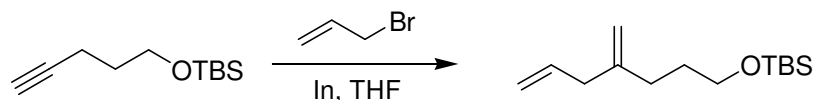
(4-methylenehept-6-enyloxy)(tert-butyl)dimethylsilane (2.33):   Under argon was mixed 2.00 g (10.08 mmol, 1.0 equiv) of **2.19** and 40 ml of THF. Next 7.0 ml (80.7 mmol) of allyl bromide was added. Indium shot (1.16 g, 10.08 mmol, 1.0 equiv) was freshly minced and added to the solution upon cutting. The reaction was heated with a heat gun until ebullition and then stirred at room temperature (indium was consumed after ~10 minutes) for 16 hours. Flash chromatography (90:10 hexanes:ethyl acetate)

was used to purify the residue to a clear, colorless oil (2.33 g, 96%). TLC (95:5 hexanes:ethyl acetate, CAM visualization) R_f 0.66.
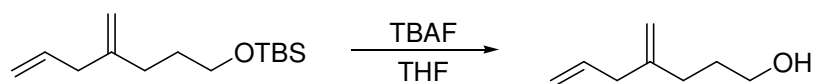
4-methylenehept-6-en-1-ol (2.34): To a vial with stir bar was added 115 mg of **2.33** (0.48 mmol, 1.0 equiv) and 5 ml of THF before adding 0.57 ml (1.0 M in THF, 0.57 mmol, 1.2 equiv) tetrabutylammonium fluoride dropwise. The yellow solution was stirred for 3 hours at room temperature before adding brine and extracting three times with EtOAc. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (90:10 Hex:EtOAc) to reveal 57 mg of a clear, faintly yellow oil as desired product in 97% yield. TLC (80:20 Hex:EtOAc) R_f 0.17. ^{1}H NMR δ 5.73-5.84 (m, 1H), 5.07 (m, 2H), 4.79 (d, J = 4.8 Hz, 2H), 3.67 (t, J = 5.4 Hz, 2H), 2.79 (d, J = 6.0 Hz, 2H), 2.08 (t, J = 7.4 Hz, 2H), 1.71 (p, J = 6.3 Hz, 2H), 1.50 (br s, 1H).
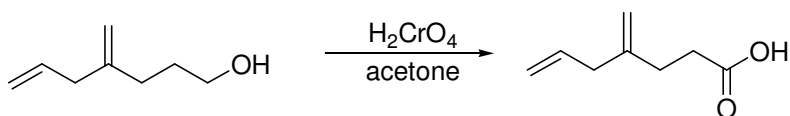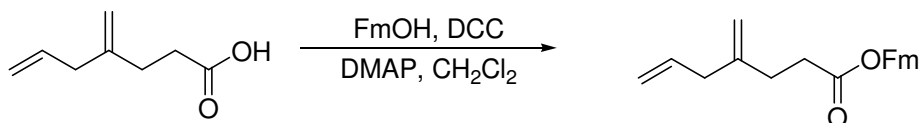

4-methylenehept-6-enoic acid (2.35): To a vial with stir bar was added 91 mg (0.72 mmol, 1.0 equiv) of **2.34** and 7.2 ml of acetone. The solution was cooled to 0 ºC and 0.45 ml (8 N, 3.6 mmol, 5.0 equiv) Jones' reagent was added dropwise and the reaction allowed to stir 1 hour at 0 ºC. At that time, water was added and the aqueous layer was extracted three times with Et_2O. The combined organics were washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 2 x Et_2O and then carefully acidified with 1 M HCl before extracting three times with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated. The clear colorless oil

required no further purification (92 mg, 91% yield).   TLC (80:20 Hex:EtOAc, anisaldehyde visualization) R_f 0.21. ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.30 (br s, 1H), 5.77 (m, 1H), 5.05 (m, 2H), 4.78 (d, J = 13.0 Hz, 2H), 2.75 (d, J = 6.8 Hz, 2H), 2.48 (t, J = 7.4 Hz, 2H), 2.32 (t, J = 7.4 Hz, 2H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 179.2, 145.9, 135.7, 116.3, 110.5, 40.8, 32.2, 30.2.
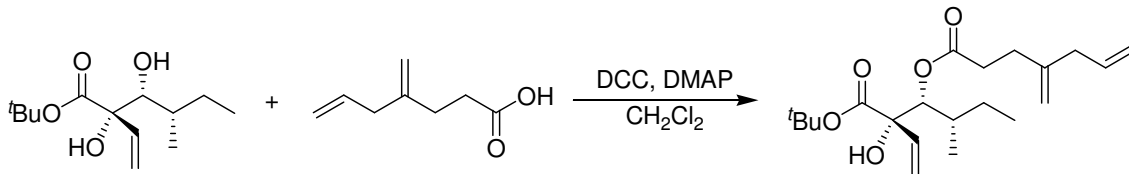

(9-fluorenylmethyl) 4-methylenehept-6-enoate (2.36): To a dry vial with stir bar was added 90 mg (0.642 mmol, 1.0 equiv) of acid **2.35** and 2.4 ml of CH$_2$Cl$_2$. Next 154 mg (0.783 mmol, 1.22 equiv) 9-fluorenylmethanol, 199 mg (0.963 mmol, 1.5 equiv) dicyclohexylcarbodiimide, and 8 mg (0.064 mmol, 0.10 equiv) 4-dimethylaminopyridine. After stirring for 14 hours at room temperature, the solid was filtered off, rinsing with CH$_2$Cl$_2$, and the filtrate concentrated.   The residue was purified by column chromatography (95:5 Hex:EtOAc) to reveal a yellow waxy solid as desired product (177 mg, 87% yield). TLC (80:20 Hex:EtOAc, anisaldehyde visualization) R_f 0.51. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.80 (d, J = 4.9 Hz, 2H), 7.63 (d, J = 4.9 Hz, 2H), 7.45 (d, J = 4.9 Hz, 2H), 7.34 (d, J = 4.9 Hz, 2H), 5.77-5.89 (m, 1H), 5.09-5.16 (m, 2H), 4.82 (d, J = 10.0 Hz, 2H), 4.41 (d, J = 4.7 Hz, 2H), 4.20 (t, J = 4.7 Hz, 1H), 2.79 (d, J = 4.5 Hz, 2H), 2.56 (t, J = 4.9 Hz, 2H), 2.35 (t, J = 4.9 Hz, 2H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 172.9, 146.4, 143.3, 141.0, 136.2, 136.1, 127.7, 126.9, 124.6, 124.5, 116.4, 110.0, 65.9, 46.8, 40.8, 32.3, 30.9.
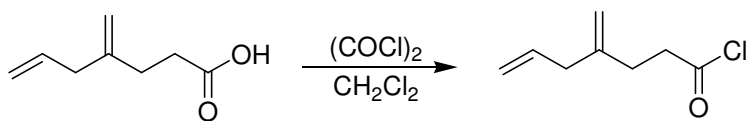
4-methylenehept-6-enoyl chloride (SI-2.20): A dry vial containing a stir bar and 200 mg (1.43 mmol, 1.0 equiv) of acid **2.35** 1 ml of CH$_2$Cl$_2$ was chilled to 0 ºC. Next 0.14 ml (1.64 mmol, 1.15 equiv) oxalyl chloride was added dropwise. The faintly pink solution was stirred at 0 ºC for 1 hour and then 1 hour at room temperature before concentrating. The sharp-smelling reddish oil was used in the subsequent step without further purification.

(3S,4R,5S)-3-(*tert*-butoxycarbonyl)-3-(*tert*-butyldimethylsiloxy)-5-methylhept-1-en-4-yl 4-methylenehept-6-enoate (SI-2.21): To a dry vial with stir bar was added 118 mg (0.483 mmol, 1.0 equiv) of diol **2.39**, 81 mg (0.579 mmol, 1.2 equiv) of acid **2.35**, and 2 ml of CH$_2$Cl$_2$, followed by 150 mg (0.725 mmol, 1.5 equiv) dicyclohexylcarbodiimide, and 89 mg (0.725 mmol, 1.5 equiv) 4-dimethylaminopyridine. A precipitate formed and the reaction was allowed to stir at room temperature for 12 hours. At that time, the solids were filtered off and the filtrate concentrated. The residue was purified by column chromatography (90:10 Hex:EtOAc) to reveal a yellow oil as desired product (101 mg, 57% yield). *note: when catalytic DMAP was used, the yield was only 29%.* TLC (80:20 Hex:EtOAc, CAM visualization) R_f 0.57. ^{13}C NMR (400 MHz, CDCl$_3$): δ 172.2, 172.0, 146.1, 135.8, 135.5, 116.4, 116.3, 110.5, 83.3, 80.6, 79.2, 40.9, 34.8, 32.4, 30.7, 27.6, 24.2, 14.3, 11.7.
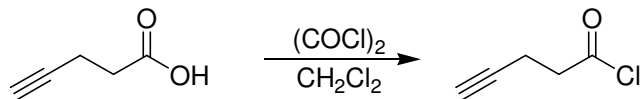
pent-4-ynoyl chloride (SI-2.22): To a dry vial with stir bar was added 687 mg (7.0 mmol, 1.0 equiv) 4-pentynoic acid and 20 ml of CH_2Cl_2, followed by 0.69 ml (8.05 mmol, 1.0 equiv) oxalyl chloride. The solution was allowed to stir for 12 hours at room temperature at which time it was concentrated to reveal a pungent clear, faintly yellow oil as desired product (771 mg, 95% yield). TLC (80:20 Hex:EtOAc, anisaldehyde visualization) R_f 0.31. ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.14 (t, J = 7.0 Hz, 2H), 2.57 (dt, J = 7.0, 2.7 Hz, 2H), 2.05 (t, J = 2.7 Hz, 1H).
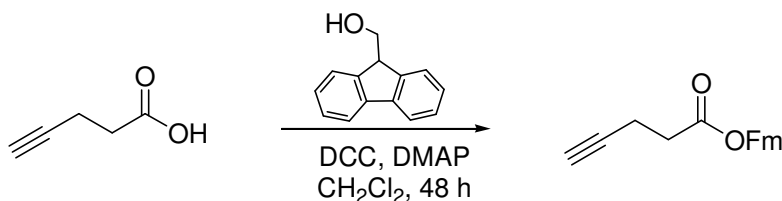
(9-fluorenylmethyl) pent-4-ynoate (2.38): To a dry flask was added 3 g (30.58 mmol, 1.0 equiv) 4-pentynoic acid and 120 ml of CH_2Cl_2 before adding 7.32 g (37.31 mmol, 1.22 equiv) 9-fluorenylmethanol, 9.46 g (45.87 mmol, 1.50 equiv) dicyclohexylcarbodiimide, and 374 mg (3.06 mmol, 0.10 equiv) 4-dimethylaminopyridine. A precipitate quickly formed and the reaction was allowed to stir for 16 hours at room temperature. At that time, the salts were filtered off, rinsing with CH_2Cl_2. The filtrate was concentrated and purified by flash chromatography (85:15 Hex:EtOAc) to reveal a light yellow opaque solid as desired product (6.60 g, 78%). TLC (80:20 Hex:EtOAc, PMA visualization) R_f 0.48. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.77 (d, J = 7.5 Hz, 2H), 7.61 (d, J = 7.5 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.32 (t, J = 7.5 Hz, 2H), 4.42 (d, J = 7.2 Hz, 2H), 4.23 (t, J = 7.2 Hz, 1H), 2.65 (t, J = 7.7 Hz, 2H), 2.52 (dt, J =

7.7, 2.6 Hz, 2H), 1.99 (t, J = 2.6 Hz, 1H). ^{13}C NMR δ 171.9, 144.0, 141.4, 127.9, 127.3, 125.1, 120.0, 82.4, 69.2, 66.7, 46.7, 33.3, 13.9.
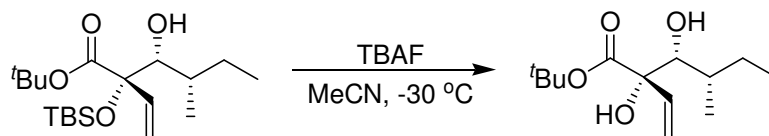
(2S,3R,4S)-*tert*-butyl 2,3-dihydroxy-4-methyl-2-vinylhexanoate (2.40): A solution was made of 120 mg (0.33 mmol) of **2.29** in 1.5 ml of MeCN in a dry vial with stir bar. The solution was chilled to -30 ºC, and 0.67 ml (0.67 mmol) of tetrabutylammonium fluoride (1.0 M in hexane) was added. The yellow solution was stirred for 24 hours at -30 ºC and then quenched with saturated aqueous NaHCO$_3$, and diluted with water. The layers were separated and extracted 3x with ethyl acetate. The combined organics were dried over MgSO$_4$, filtered, and concentrated. A silica plug was used to purify the compound by eluting with 80:20 hexanes:ethyl acetate to reveal a very faintly yellow, clear oil (68 mg, 85%). TLC (15:1 hexanes: EtOAc) R$_f$ 0.3. ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.89 (m, 1H), 5.55 (dd, J = 2.0, 17.2 Hz, 1H), 5.27 (dd, J = 2.0, 10.8 Hz, 1H), 3.90 (d, J = 7.6 Hz, 1H), 3.66 (s, 1H), 2.06 (dd, J = 11.4 Hz, 1H), 1.68-1.60 (m, 1H), 1.58-1.47 (m, 1H), 1.48 (s, 9H), 1.35-1.20 (m, 1H), 0.96 (d, J = 6.4 Hz, 1H), 0.94-0.84 (m, 6H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 173.5, 136.0, 115.1, 83.3, 81.3, 78.1, 36.1, 27.6, 22.6, 17.3, 11.5.
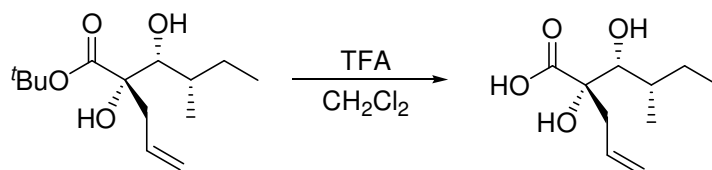
2,3-dihydroxy-4-methyl-2-(2-propenyl)-hexanoic acid (2.41). A dried scintillation vial with stir bar was charged with 175 mg of ester **SI-2.16** and 4 ml of CH$_2$Cl$_2$ under

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nitrogen. Next 0.35 ml of trifluoroacetic acid was added dropwise. The darkened solution was stirred at room temperature under nitrogen for 8 hours. The solution was concentrated under vacuum to an oily solid. The TFA was removed through a series of three alternating additions of hexanes/removal under vacuum. The tan colored solid was recrystallized from CH_2Cl_2/hexanes to reveal 83 mg (87%) of a shiny white solid. Analytical data: m.p. 162-167 °C. IR (thin film, cm^{-1}) 3102, 2550 (br), 1694, 1642, 1497, 1463, 1436, 1316, 1227, 1173, 1088, 1038, 988, 958, 916, 884; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.67 (br s, 1H), 5.74-5.67 (m, 1H), 5.14-5.08 (m, 2H), 3.91 (s, 1H), 2.40 (d, 2H, J = 7.3 Hz), 1.74-1.71 (m, 1H), 1.44-1.38 (m, 1H), 1.37-1.26 (m, 1H), 0.91 (d, 3H, J = 6.8 Hz), 0.89 (t, 3H, J = 7.2 Hz); ^{13}C NMR (400 MHz, CDCl$_3$) δ 178.0, 131.2, 120.0, 80.0, 78.8, 40.5, 35.0, 28.2, 12.7, 11.8; TLC (50:50 hexanes: EtOAc) R$_f$ 0.04-0.38. LRMS (ESI+) Calculated for $C_{10}H_{18}O_4$ [M+H]$^+$: 203.12. Found [M+H]$^+$: 203.1; [M+Na]$^+$: 225.1; [2M+H]$^+$: 405.4; [2M+Na]$^+$: 427.3.
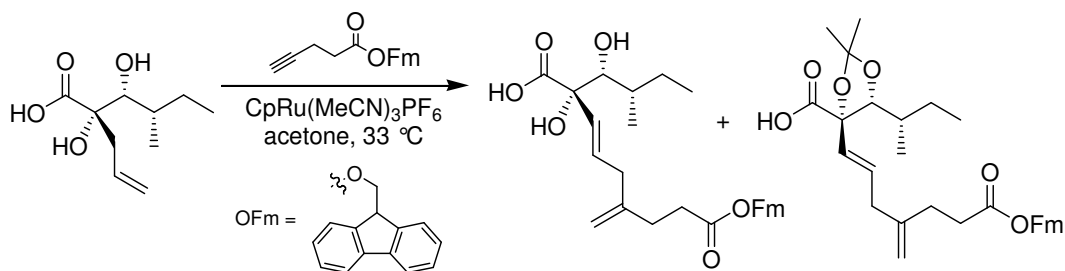
**(*E*)-8-(fluorenylmethoxycarbonyl)-2-(1-hydroxy-2-methylbutyl)-2-hydroxy-6-methyleneoct-3-enoic acid (2.42 + 2.43):** In a glove box, a dried scintillation vial with stir bar was charged with 480 mg of acid **2.41** (2.37 mmol, 1.04 equiv), 631 mg of fluorenylmethyl ester **2.38** (2.28 mmol, 1.0 equiv), and 3 ml of dry acetone. To the yellow solution was added 49 mg of tris(acetonitrile)cyclopentadienylruthenium hexafluorophosphate (0.228 mmol, 0.10 equiv), upon which the solution turned dark

brownish red. The vial was sealed with a threaded cap (with conical PTFE insert) and secured with electrical tape. The sealed vial was stirred at 33 ºC for 3 hours, at which time the solution had lightened to dark orange. The vial was cooled, and the solvent was removed under vacuum. The dark brown residue was run through a plug of silica with 99:1 CH$_2$Cl$_2$:MeOH until no more color eluted. At that time, the polarity of the eluent was increased (by gradients) to 90:10 until no more material eluted (as followed by TLC in 50:50 Hexanes:EtOAc). The ~2:1 mixture of acetonide and free diol (R$_f$ = 0.00 to 0.62) was carried on to the next step without further purification.
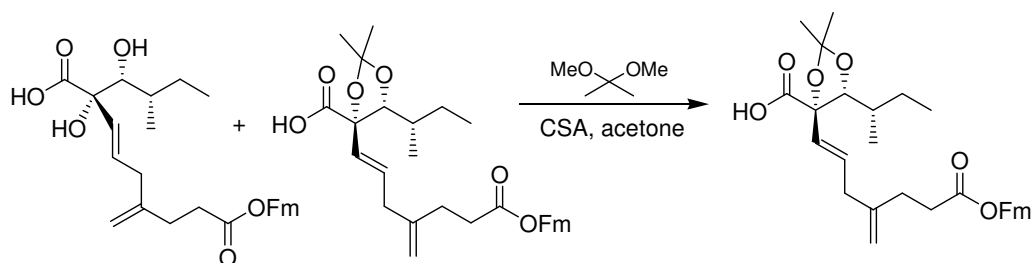
(4S,5R)-4-((E)-6-(fluorenylmethylcarbonyl)-4-methylenehex-1-enyl)-5-sec-butyl-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (2.43): The mixture of acetonide and free diol from the previous procedure was then dissolved in 38 ml of 2,2-dimethoxypropane and 38 ml of acetone. Next 226 mg camphorsulfonic acid (CSA) was added and the solution stirred at room temperature for 12 hours. At that time, the solvent was evaporated at reduced pressure. The resultant reddish-brown oil was immediately purified by flash chromatography (99:1 CH$_2$Cl$_2$: MeOH until the color eluted followed by 93:7 CH$_2$Cl$_2$:MeOH) to yield 735 mg of a clear, yellow oil as desired product (62% yield from **2.41**). Analytical data: IR (thin film, cm^{-1}) 3066, 3020, 2970, 2937, 2879, 1739, 1161, 1451, 1382, 1266, 1219, 1158, 1061, 980, 897, 739, 704; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.79 (d, 2H, J = 7.5 Hz), 7.61 (d, 2H, J = 7.4 Hz), 7.42 (d, 2H, J = 7.4 Hz), 7.34

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(d, 2H, *J* = 7.5 Hz), 6.02-5.91 (m, 1H), 5.87 (d, 1H, *J* = 15.4 Hz), 4.77 (br s, 2H), 4.41 (d, 2H, *J* = 7.0 Hz), 4.22 (t, 1H, *J* = 7.0 Hz), 3.78 (d, 1H, *J* = 7.6 Hz), 2.81 (d, 2H, *J* = 6.8 Hz), 2.56 (t, 2H, *J* = 7.4 Hz), 2.35 (t, 2H, *J* = 7.4 Hz), 1.84–1.67 (m, 2H), 1.63 (s, 3H), 1.45 (s, 3H), 1.24-1.11 (m, 1H), 0.97 (d, 3H, *J* = 6.4 Hz), 0.92 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (400 MHz, CDCl$_3$) δ 173.0, 173.0, 145.9, 143.8, 141.3, 129.7, 129.4, 127.8, 127.1, 125.0, 120.0, 111.0, 109.3, 89.2, 85.5, 66.3, 46.9, 39.0, 34.8, 34.6, 32.5, 30.8, 26.9, 25.3, 15.3, 11.0, ; TLC (50:50 Hex: EtOAc) R$_f$ 0.26-0.52. LRMS (ESI+) Calculated for C$_{32}$H$_{38}$O$_6$ [M+Na]$^+$: 541.27. Found [M+NH$_4$]$^+$: 536.3; [M+Na]$^+$: 541.3; [M+K]$^+$: 557.3.
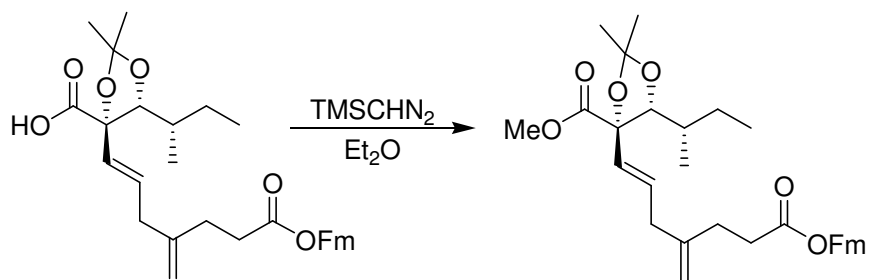

(4*S*,5*R*)-methyl 4-((*E*)-6-(fluorenylmethylycarbonyl)-4-methylenehex-1-enyl)-5-*sec*-butyl-2,2-dimethyl-1,3-dioxolane-4-carboxylate (2.44): To a dry vial containing 41 mg (0.079 mmol, 1.0 equiv) of **2.43** was added 1 ml of dry MeOH and dry Et$_2$O. Next 0.083 ml (0.166 mmol, 2.0 equiv) of TMSCHN$_2$ (2.0 M in Et$_2$O) was added dropwise with evolution of gas. The solution was allowed to stir overnight at room temperature before removing volatiles under vacuum. The residue was purified by running through a silica gel plug with 99:1 CH$_2$Cl$_2$:MeOH. A clear oil was isolated as desired product (23 mg, 53% yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.79 (d, 2H, *J* = 7.5 Hz), 7.61 (d, 2H, *J* = 7.5 Hz), 7.43 (t, 2H, *J* = 7.5 Hz), 7.34 (dt, 2H, *J* = 7.5, 1.0 Hz), 5.91 (m, 1H), 5.69 (d, 1H, *J* = 15.3 Hz), 4.81 (br s, 1H), 4.79 (br s, 1H), 4.41 (d, 2H, *J*= 7.3 Hz), 4.22 (d, 1H, *J* = 7.3 Hz), 4.14 (d, 1H, *J* = 7.7 Hz), 3.77 (s, 3H), 2.85 (d, 2H, *J* = 7.0 Hz), 2.56 (m, 2H), 2.35

(m, 2H), 1.67 (m, 2H), 1.58 (s, 3H), 1.46 (s, 3H), 1.15 (m, 1H), 0.99 (d, 3H, J = 6.6 Hz),

0.91 (t, 3H, J = 7.0 Hz). TLC (50:50 Hex:EtOAc, CAM visualization) R_f 0.83. LRMS

(ESI+) Calculated for $C_{33}H_{40}O_6$ [M+H]$^+$: 533.28.   Found [M+H]$^+$: 533.4; [M+Na]$^+$:

555.4; [M+K]$^+$: 571.4.
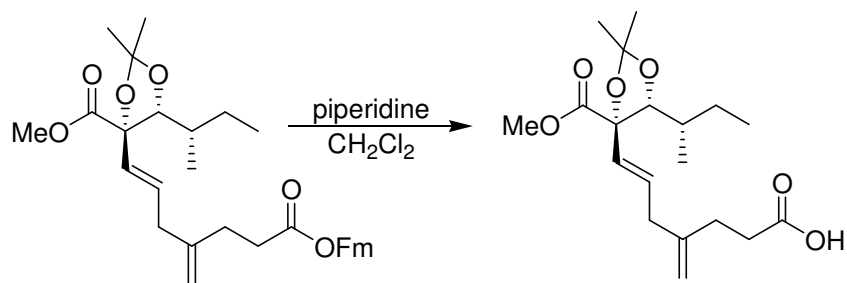
(*E*)-7-((4*S*,5*R*)-4-(methoxycarbonyl)-5-*sec*-butyl-2,2-dimethyl-1,3-dioxolan-4-yl)-4-

methylenehept-6-enoic acid (2.45): To a dry vial containing 12 mg (0.023 mmol, 1.0

equiv) of **2.44** was added 0.5 ml of CH_2Cl_2. Next 11 µl (0090 mmol, 4.0 equiv) of

piperidine was added. The solution was stirred for 48 hours at room temperature before

adding water. The aqueous layer was extracted two times with CH_2Cl_2 before acidifying

to pH=1 with 1 M HCl. The acidified aqueous layer was then extracted again three times

with EtOAc.   The ethyl acetate extractions were dried over $MgSO_4$, filtered, and

concentrated. The residue was filtered through a silica plug using 95:5 CH_2Cl_2 : MeOH.

A clear, yellow oil was isolated as desired product (7 mg, 92% yield). ^{1}H NMR (400

MHz, CDCl$_3$) δ 5.92 (m, 1H), 5.70 (d, 1H, J = 16.0 Hz), 4.83 (br s, 1H), 4.80 (br s, 1H),

4.14 (d, 1H, J = 7.8 Hz), 3.79 (s, 3H), 2.84 (d, 2H, J = 7.0 Hz), 2.54 (m, 2H), 2.37 (t, 2H,

J = 7.2 Hz), 1.63 (m, 1H), 1.53 (s, 3H), 1.49 (m, 1H), 1.46 (s, 3H), 1.14 (m, 1H), 0.98 (d,

3H, J = 6.6 Hz), 0.90 (t, 3H, J = 7.4 Hz). TLC (50:50 Hex: EtOAc, CAM visualization)

0.17-0.45.
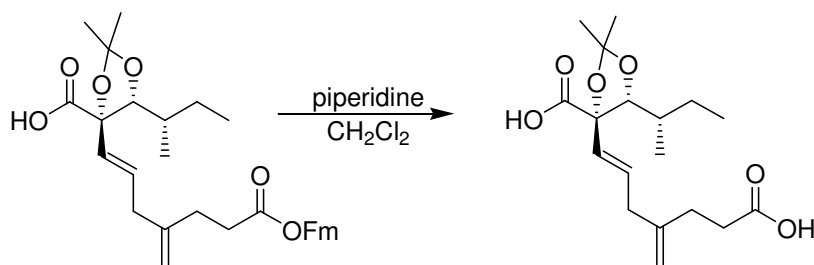
(4S,5R)-5-sec-butyl-4-((E)-6-carboxy-4-methylenehex-1-enyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (2.46): Acetonide **2.43** (200 mg, 0.386 mmol, 1.0 equiv) was diluted with 8 ml of CH_2Cl_2 and treated with 0.20 ml of piperidine. The solution was stirred for 48 hours and 3 ml of water added. The biphasic mixture was extracted with CH_2Cl_2 (containing mainly piperidine/Fm residue), and then the aqueous layer was acidified with 1 M HCl. The aqueous layer was then extracted 3 times with EtOAc before drying the combined organics over $MgSO_4$, filtering, and concentrating under reduced pressure. The residue was purified through a silica plug using 92:8 CH_2Cl_2:MeOH to isolate 125 mg (95% yield) of a dark yellow oil. Analytical data: IR (thin film, cm^{-1}) 2979, 2933, 2892, 1700, 1652, 1607, 1557, 1463, 1436, 1382, 1260, 1218, 1158, 1117, 1057, 982, 897, 739; ^1H NMR (400 MHz, $CDCl_3$) δ 10.80 (br s, 2H), 5.89 (dt, 1H, J = 15.2, 6.9 Hz), 5.67 (d, 1H, J = 15.2 Hz), 4.81 (br s, 1H), 4.78 (br s, 1H), 4.08 (d, 1H, J = 7.4 Hz), 2.81 (d, 2H, J = 6.8 Hz), 2.49 (t, 2H, J = 7.3 Hz), 2.32 (t, 2H, J = 7.3 Hz), 1.69-1.52 (m, 2H), 1.52 (s, 3H), 1.45 (s, 3H), 1.24-1.09 (m, 1H), 0.96 (d, 3H, J = 6.5 Hz), 0.88 (t, 3H, J = 7.4 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 179.4, 176.6, 145.6, 130.7, 127.1, 111.2, 109.4, 85.7, 84.9, 39.4, 35.1, 32.3, 30.3, 27.3, 26.0, 25.0, 15.4, 11.1; TLC(50:50 hexanes: EtOAc) R_f 0-0.21. LRMS (ESI-) Calculated for $C_{18}H_{28}O_6$ [M-H]⁻ : 339.19. Found [M-H]⁻ : 339.2; [M-2H]²⁻ : 169.1.
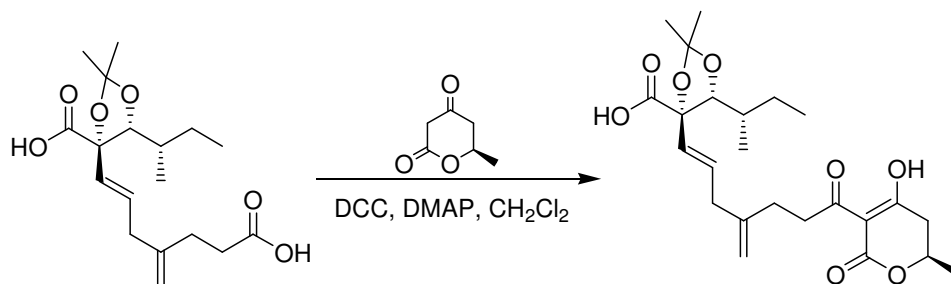
(4S,5R)-5-*sec*-butyl-4-((*E*)-6-((*R*)-5,6-dihydro-4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carboxy)-4-methylenehex-1-enyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (2.47): Dicarboxylic acid **2.46** (67 mg, 0.197 mmol, 1.0 equiv) was diluted with 1.9 ml of CH$_2$Cl$_2$ and treated with 31 mg (0.240 mmol, 1.22 equiv) of pyrone **2.31**, 61 mg (0.295 mmol, 1.5 equiv) DCC, and 12 mg (0.098 mmol, 0.10 equiv) DMAP. The yellow solution darkened and became cloudy and was allowed to stir for 48 hours to ensure complete Fries rearrangement. The precipitate was filtered off and the resultant clear yellow solution was concentrated under reduced vacuum. The dark yellow residue was purified via flash chromatography (99:1 to 97:3 CH$_2$Cl$_2$:MeOH) to yield a yellow oil as the desired product (61 mg, 69% yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.93 (m, 1H), 5.83 (d, 1H, *J* = 15.4 Hz), 4.80 (s, 1H), 4.76 (s, 1H), 4.52 (m, 1H), 3.76 (d, 1H, *J* = 7.6 Hz), 3.21 (m, 1H), 3.15 (m, 1H), 2.81 (d, 2H, *J* = 6.9 Hz), 2.64 (m, 2H), 2.36 (m, 2H), 1.71 (m, 1H), 1.61 (s, 3H), 1.45 (d, 3H, *J* = 6.3 Hz), 1.43 (s, 3H), 1.14 (m, 2H), 0.95 (d, 3H, *J* = 6.5 Hz), 0.90 (t, 3H, *J* = 7.3 Hz);). ^{13}C NMR (400 MHz, CDCl$_3$) δ 203.8, 194.4, 172.1, 164.2, 145.9, 139.8, 139.7, 111.9, 109.5, 103.1, 89.0, 85.7, 70.3, 46.9, 39.2, 37.1, 34.8, 30.8, 27.1, 25.0, 20.5, 15.4, 11.0; TLC (50:50 hexanes: EtOAc) R$_f$ 0.38. LRMS (ESI-) Calculated for C$_{24}$H$_{34}$O$_8$ [M-H]$^-$: 449.23. Found [M-H]$^-$: 449.2.
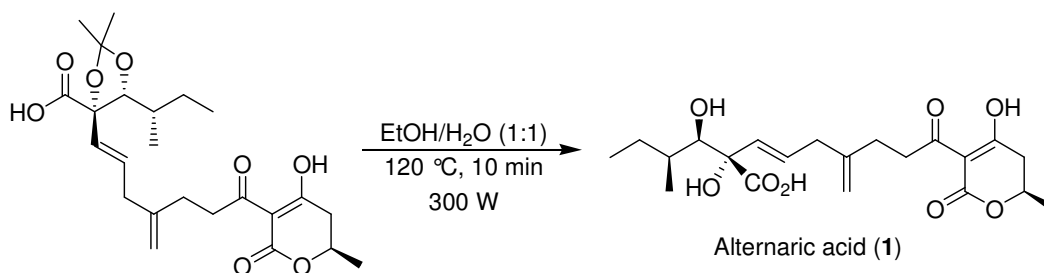
Alternaric acid (2.8): Acetonide **2.47** (62 mg, 0.137 mmol, 1.0 equiv) was diluted with 2.5 ml of EtOH and 2.5 ml of H_2O. The yellow solution was microwaved at 120 ºC (300 W) for 10 minutes. After cooling, the solution was extracted three times with EtOAc. The combined organics were washed with saturated aqueous NH_4Cl before drying over $MgSO_4$, filtering, and concentrating. The components of the residue were identified via UPLC to determine a yield of 45% for the desired diastereomer of alternaric acid. ^1H NMR (400 MHz, $CDCl_3$) δ 17.89 (br s, 1H), 5.99 (m, 1H), 5.72 (d, 1H, J = 15.0 Hz), 4.89 (br s, 1H), 4.83 (br s, 1H), 4.57 (m, 1H), 3.96 (br s, 1H), 3.25 (m, 1H), 2.98 (m, 1H), 2.84 (m, 1H), 2.67 (m, 2H), 2.42 (m, 1H), 2.31 (m, 1H), 1.82 (m, 1H), 1.47 (d, 3H, J = 6.0 Hz), 1.43 (m, 1H), 1.33 (m, 1H), 0.88 (m, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 203.8, 195.3, 176.4, 165.0, 145.3, 129.9, 129.6, 112.3, 102.8, 78.4, 70.8, 39.3, 38.9, 37.3, 35.0, 31.3, 31.0, 27.0, 20.6, 12.7, 11.8; TLC (50:50 hexanes: EtOAc) R_f 0.17. LRMS (ESI+) Calculated for $C_{21}H_{30}O_6$ [M-H]$^+$: 411.3. Found [M-H]$^+$: 411.3; [M-Na]$^+$ 433.3.

REFERENCES

Abdel-Baky, S.; Giese, R.W. *J. Org. Chem.* **1986**, *51*, 3390-3391.

Baker, R.; Billington, D.C.; Ekanayake, N. *J. Chem. Soc., Perkin Trans. I.* **1983**, 1387.

Barrett, A.G.M.; Morris, T.M.; Barton, D.H.R. *J. Chem. Soc., Perkin Trans. I.* **1980**, 2272.

Bonsignore, L.; Cabiddu, S.; Loy, G.; Secci, D. *Heterocycles* **1989**, *29*, 913-919.

Brian, P.W.; Curtis, P.J.; Hemming, H.G.; Unwin, C.H.; Wright, J.M. *Nature,* **1949**, *164*, 534.

Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77-84.

Brown, D. G.; Velthuisen, E. J.; Commerford, J. R.; Brisbois, R. G.; Hoye, T. H. *J. Org. Chem.* **1996**, *61*, 2540-2541.

Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2075-2088.

Clarke, P.A.; Grist, M.; Ebden, M.; Wilson, C.; Blake, A.J. *Tetrahedron* **2005**, *61*, 353-363.

Corey, E.J.; Bakshi, R.K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553.

Curphey, T.J. *Org. Prep. Proc. Intl.* **1981**, *13,* 112-115.

Degl'Innocenti, A.; Ricci, A.; Mordini, A.; Reginato, G.; Colotta, V. *Gazz. Chim. Ital.* **1987**, *117*, 645-648.

Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K. L. *J. Am. Chem. Soc.* **1990,** *112*, 1906-1912.

Duenes, R.A.; Morken, J.P. *Synlett* **2007**, *4*, 587-590.

Durham, T.B.; Blanchard, N.; Savall, B.M.; Powell, N.A.; Roush, W.R. *J. Am. Chem. Soc.* **2004**, *126*, 9307-9317.

Engel, B.; Erkel, G.; Anke, T.; Sterner, O. *J. Antibiot.* **1998**, *51*, 518-521.

Engelhardt, F. C.; Schmitt, M. J.; Taylor, R. E. *Org. Lett.* **2001**, *3*, 2209-2212.

Ensley, H.E.; Parnell, C.A.; Corey, E.J. *J. Org. Chem.* **1978**, *43*, 1610-12.

Evans, D.A.; Morrissey, M.M. *J. Am. Chem. Soc.* **1984**, *106*, 3866-3868.

Evans, D.A.; Tregay, S.W.; Burgey, C.S.; Paras, N.A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936-7943.

Evans, M. A.; Morken, J. P. *Org. Lett.* **2005**; *7*, 3367-3370.

Flamme, E.M.; Roush, W.R. *Org. Lett.* **2005**, *7*, 1411-1414.

Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2050.

Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 809.

Fukuda, Y.-I.; Shindo, M.; Shishido, K. *Org. Lett.* **2003**, *5*, 749-751.

Gardette, M.; Alexakis, A.; Normant, J.F. *Tetrahedron* **1985**, *41*, 5887-5899.

Ghosh, A.K.; Kim, J.-H. *Tetrahedron Lett.* **2002**, *43*, 5621-5624.

Goldsby, R.A.; Kindt, T.J.; Osborne, B.A.; Kuby, J. *Immunology*. 4th Edition. New York: W.H. Freeman & Company, 2000.

Hagiwara, H.; Uda, H. *J. Chem. Soc.* **1987**, 1351-1353.

Hanessian, S.; Ma, J.; Wang, W. *J. Am. Chem. Soc.* **2001**, *123*, 10200-10206.

Hibino, J.-i.; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron. Lett*., **1985**, *26*, 5579-5581.

Hodgson, D.M.; Fleming, M.J.; Stanway, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 12250-12251.

Iyer, R.S.; Helquist, P. *Org. Synth.* **1986**, *64*, 1-9.

Januszkiewicz, K.; Alper, H. *Tetrahedron Lett.* **1983**, *24*, 5159.

Kolb, H.C.; VanNieuwenhze, M.S.; Sharpless, K.B. *Chem. Rev.* **1994**, *94*, 2483-547.

Kulkarni, M.G.; Pendharkar, D.S. *Tetrahedron* **1997**, *53*, 3167.

Kuwajima, I.; Kato, M. *Tetrahedron Lett.* **1980**, *21*, 623-626.

Lautens, M.; Zhang, C.H.; Goh, B.J.; Crudden, C.M.; Johnson, M.J.A. *J. Org. Chem.* **1994**, *59*, 6208-6222.

Leach, A. G.; Wang, R.; Wohlhieter, G. E.; Khan, S. I.; Jung, M. E.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 4271-4278.

Lee, J.C.; Lobkovsky, E.; Pliam, N.B.; Strobel, G.; Clardy, J. *J. Org. Chem.* **1995**, *60*, 7076-7077.

Linghu, X.; Nicewicz, D. A.; Johnson, J. S. *Org. Lett.* **2002**, *4*, 2957-2960.

Marfat, P.; McGuirk, R.; Helquist, P. *J. Org. Chem.* **1979**, *44*, 3888-3901.

Marshall, J. A.; Schaaf, G. M. *J. Org. Chem.* **2003**, *68*, 7428-7432.

McDougall, P.T. Personal communication.

Minami, K.; Kawamura, Y.; Koga, K.; Hosokawa, T. *Org. Lett.* **2005**, *7*, 5689-5692.

Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003,** *125*, 8702-8703.

Moser, W. H. *Tetrahedron* **2001**, *57*, 2065-2084.

Negishi, E.; King, A.O.; Klima, W.L.; Patterson, W.; Silveira, A. *J. Org. Chem.* **1980**, *45*, 2526.

Negishi, E.; Okukado, N.; King, A.O.; Van Horn, D.E.; Spiegel, B. *J. Am. Chem. Soc.* **1978**, *100*, 2254-2256.

Nicewicz, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 6170-6171.

Nicewicz, D. A.; Yates, C. M.; Johnson, J. S. *J. Org. Chem.* **2004**; *69,* 6548-6555.

O'Bannon, P. E.; Dailey, W.P. *Tetrahedron* **1990**, *46*, 7341-7358.

Ohmura, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **1999**, *18*, 413-416.

Ort, O. *Org. Synth.* **1987**, *65*, 203-204.

Padwa, A.; Kulkarni, Y. S.; Zhang, Z. *J. Org. Chem.* **1990**, *55*, 4144-4153.

Paquette, L.A. *Encyclopedia of Organic Reagents*. Hoboken, New Jersey: John Wiley & Sons, Inc., 1995.

Powell, N.A.; Roush, W.R. *Org. Lett.* **2001**, *3*, 453-456.

Ranu, B.C.; Majee, A. *J. Chem. Soc., Chem. Comm.* **1997**, 1225.

Reich, H. J.; Holtan, R. C.; Bolm, C. *J. Am. Chem. Soc.* **1990**, *112*, 5609-5617.

Schlosser, M. *Organometallics in Synthesis*. Hoboken, New Jersey: John Wiley & Sons, Inc., 1995.

Shaw, J. T.; Woerpel, *K. A. J. Org. Chem.* **1997**, *62,* 6706-6707.

Shaw, J. T.; Woerpel, K. A. *Tetrahedron* **1997**, *53,* 16597-16606.

Shaw, J.T.; Woerpel K.A. *Tetrahedron* **1999**, *55*, 8747-8756.

Shintani, R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 1057-1059.

Singh, S. B.; Zink, D. L.; Dombrowski, A. W.; Dezeny, G.; Bills, G. F.; Felix, J. P.; Slaughter, R. S.; Goetz, M. A. *Org. Lett.* **2001**, *3*, 247-250.

Speare, D.M.; Fleming, S.M.; Beckett, M.N.; Li, J.-J.; Bugg, T.D.H. *Org. and Biomol. Chem.* **2004**, *2*, 2942-2950.

Stadlbauer, W.; Badawey, E.-S.; Hojas, G.; Roschger, P.; Kappe, T. *Molecules* **2001**, *6*, 338-352.

Suzuki, M.; Kawagishi, T.; Yanagisawa, A.; Suzuki, T.; Okamura, N.; Noyori, R. *Bull. Chem. Soc. Jpn*. **1988**, *61*, 1299-1312.

Tabuchi, H.; Hamamoto, T.; Miki, S.; Tejima, T.; Ichihara, A. *J. Org. Chem.* **1994**, *59*, 4749-4759.

Takeda, K.; Ohnishi, Y. *Tetrahedron Lett.* **2000**, *41*, 4169-4172.

Tebbe, F.N.; Parshall, G.W.; Reddy, G.S. *J. Am. Chem. Soc.***, 1978**, *100*, 3611-3613.

Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115-36.

Trost, B.M.; Probst, G.D.; Schoop, A. *J. Am. Chem. Soc.* **1998**, *120*, 9228-9236.

Trotter, N.S.; Takahashi, S.; Nakata, T. *Org. Lett.*, **1999**, *1*, 957-959.

Trudeau, S.; Morken, J.P. *Org. Lett.* **2005**, *7*, 5465-5468.

United Network for Organ Sharing. 09 April 2008. <http://www.unos.org>

Van Horn, D.E.; Negishi, E. *J. Am. Chem. Soc.* **1978**, *100*, 2252-2254.

Watanabe, K.; Iwasaki, K.; Abe, T.; Inoue, M.; Ohkubo, K.; Suzuki, T.; Katoh, T. *Org. Lett.* **2005**, *7*, 3745-3748.

White, J.D.; Amedio, Jr., J.C. *J. Org. Chem.* **1989**, *54*, 736-738.

Whitesell, J.K.; Lawrence, R.M.; Chen, H.-H. *J. Org. Chem.* **1986**, *51*, 4779-4784.

Williams, J.M.; Jobson, R.B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E.J.J. *Tetrahedron Lett.* **1995**, *36*, 5461-5464.

Yamashita, Y.; Odashima, K.; Koga, K. *Tetrahedron Lett.* **1999**, *40*, 2803-2806.

Yasuda, K.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1997**, *38*, 3531-3534.

Yong, K. H.; Lotoski, J. A.; Chong, J. M. *J. Org. Chem.* **2001**, *66*, 8248-8251.

Yu, H.; Ballard, C.E.; Wang, B. *Tetrahedron Lett.* **2001**, *42*, 1835-1838.

Zhang, F.; Danishefsky, S.J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1434-1437.