Organometallic Reactions Development, Mechanistic Studies and Synthetic Applications

Dam, Johan Hygum; Madsen, Robert

Publication date:
2009

Document Version
Publisher's PDF, also known as Version of record

Organometallic Reactions: Development, Mechanistic Studies and Synthetic Applications

PhD Dissertation

By

Johan Hygum Dam
May 2009

Department of Chemistry
Technical University of Denmark

Organometallic Reactions: Development, Mechanistic Studies and Synthetic Applications

PhD Dissertation

By

Johan Hygum Dam
May 2009

Department of Chemistry
Technical University of Denmark

Acknowledgements

Having difficulties writing this section I joked around with my fellow PhD-students and friends that I would thank only myself. Undertaking and coming through a great feat a PhD represents – great job, Johan. But in doing so I would inherently have to thank some of those, who were there to shape the beginning of a professional career in chemistry. First, I'd thank the late Ebbe Kelstrup, who originally caught my interest for organic chemistry with the basics of organic chemistry. Also, I would like to thank my supervisor Professor Robert Madsen. In our first meetings he presented two synthetic problems of which I could only work on one for my master thesis. I chose the challenge of synthesizing pancratistatin for its obvious complexity. In overcoming this challenge, I learned a lot of chemistry, becoming a much more skilled chemist. Thank you, Robert. Special appreciation goes to Professor Phil Baran, who let me into his lab at Scripps and work alongside a bunch of extraordinary chemists. That really was an eye-opener and developed my skills further than imagined. Thanks to Team Palau'amine: Dr. Ian Young, Dr. Dan O'Malley, Ian Seiple and Dr. Junichiro Yamaguchi for showing me the meaning of perseverance and those good times in pacific-side lab playing up the atrium.

During my time at DTU I had the pleasure of sharing lab with Thomas Jensen. Over the years we've had a lot of discussions about chemistry in general. We did not only discuss the ongoing projects in our hoods, but also Evans', Fukuyama's and Baran's dazzling mechanisms. Along a multitude of different workbooks, ASAPs, EarlyViews and 'Reaction of the Day' – especially with Dr. Lars Ulrik Nordstrøm. Also, I would like to thank Dr. Peter Fristrup for a nice collaboration and help in general – especially with the mechanistic studies. It wasn't chemistry all the time in building 201. We also enjoyed the frequent table tennis match in the basement – a thing I also became much better at during the years in building 201. All in all much learned overall, guys – thanks.

I appreciate Thomas Jensen, Dr. Lars Ulrik Nordstrøm, Dr. Rune Monrad and Professor Robert Madsen proofreading parts of my dissertation. Furthermore, The Technical University of Denmark, Center for Sustainable and Green Chemistry, Jørgen Esmers Mindelegat, Civilingeniør Poul V. Andersens Fond, Krista & Viggo Petersens Fond, Ingeniør Alexander Haynmann Fond, Rudolph Als Fondet, Otto Mønsteds Fond, Knud Højgaards Fond, Augustinus Fonden and Oticon Fonden are gratefully acknowledged for financial support.

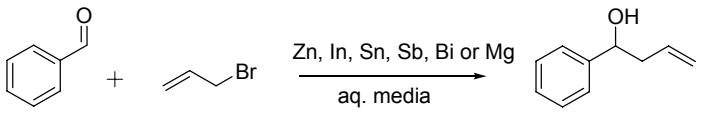
Last but not least: Showing a friend around the lab he suddenly said: "You have one of the most peculiar jobs in Denmark…". To Trine, my friends and family – thanks for your patience and your attempts to understand some organic chemistry and my interest for that realm.

Johan Hygum Dam
Kgs. Lyngby, May 2009

Abstract

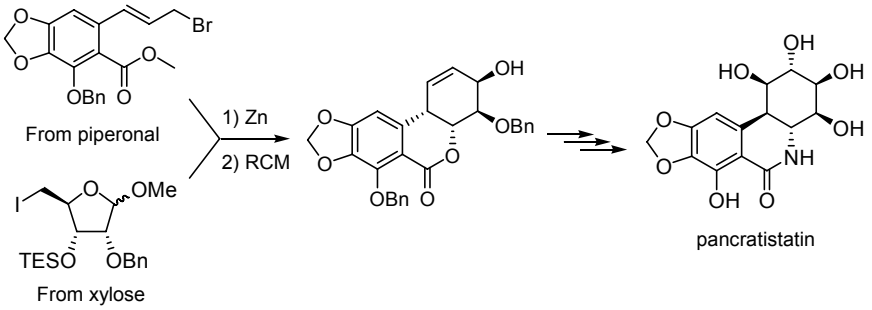
The present dissertation describes the research performed at the Technical University of Denmark and The Scripps Research Institute in the period March 2006 – May 2009. The four different topics are not interlinked and can be read independently of each other.

The first project describes a mechanistic study of the Barbier allylation of benzaldehydes with six different metals (Zn, In, Sb, Sn, Bi and Mg) in aqueous media. The mechanism of the allylation was investigated by means of Hammett plots and the secondary deuterium kinetic isotope effect. It was found that all metals except magnesium form a discrete allylmetal species and the rate-determining step is the polar addition to the carbonyl. For magnesium data indicates that the selectivity-determining step is generation of the radical anion of the benzaldehyde.



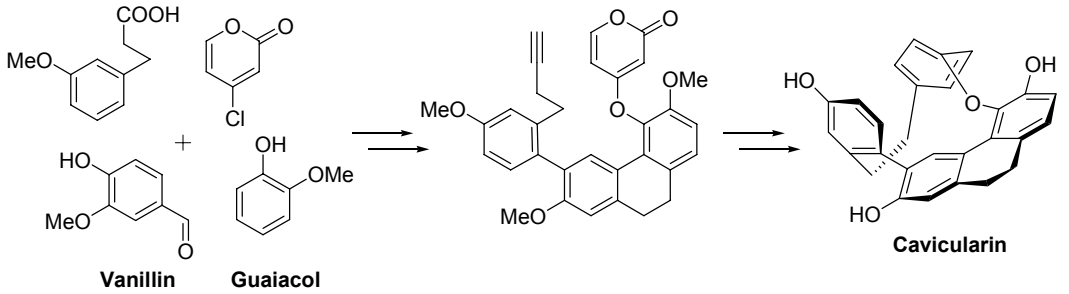
Project I: Mechanistic study of the Barbier allylation.

The second project discusses a concise and enantiopure total synthesis of (+)-pancratistatin from renewable resources by means of methodology developed in the Madsen group. The key step comprises a one-pot zinc-mediated fragmentation of a functionalized carbohydrate and consecutive allylation.



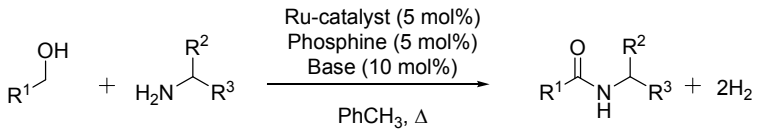
Project II: Total synthesis of pancratistatin.

The third project was performed in the laboratories of Professor Phil Baran and consisted of the successful total synthesis of the cyclophane cavicularin, which contains a bent aromatic moiety. The pivotal step in the synthesis embodied a pyrone-alkyne Diels-Alder cycloaddition with CO_2-extrusion to deliver the bent aromatic residue.



Project III: Total synthesis of cavicularin.

The fourth project involved further development of the conditions previously discovered in the Madsen group for the direct coupling of alcohols and amines to amides under dihydrogen liberation. The goal was to synthesize isolatable ruthenium catalysts and two 18-electron complexes capable of performing the reaction in excellent yields were prepared and characterized. Furthermore, it was found that several metathesis catalysts were found to be effective in the amidation.

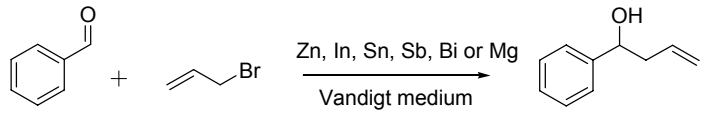


Project IV: Preparation of a isolatable Ru-catalyst for coupling of alcohols and amines.

Resumé

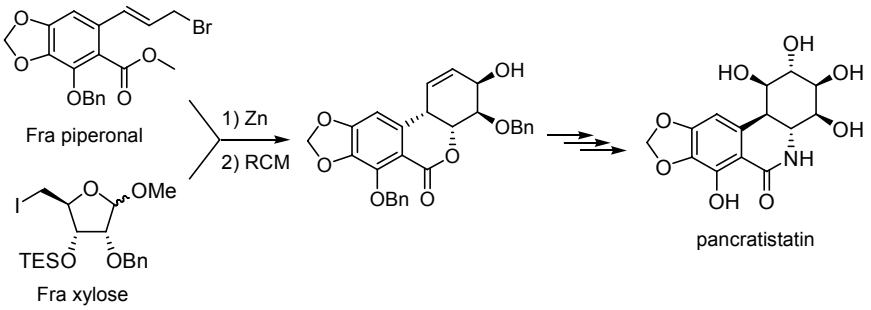
Nærværende ph.d.-afhandling beskriver den forskning, der er udført på Danmarks Tekniske Universitet i tidsrummet marts 2006 – maj 2009. De fire forskellige emner er ikke forbundne og kan læses hver for sig.

Det første projekt omhandler et mekanistisk studium af Barbier allylering af benzaldehyder med seks forskellige metaller (Zn, In, Sb, Sn, Bi og Mg). Mekanismen blev undersøgt ved hjælp af Hammett plots og den sekundære deuterium kinetiske isotop effekt. Det blev fundet, at alle metaller på nær magnesium danner en diskret allylmetal specie, og at det hastigheds-bestemmende trin er den polære addition til carbonylen. For magnesium indikerer data, at det selektivitets-bestemmende trin er dannelsen af den radikale anion fra benzaldehydet.



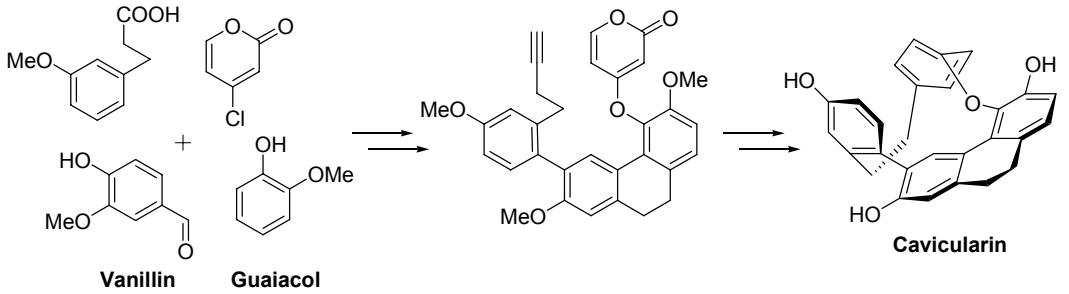
Projekt I: Mekanistisk studium af Barbier allylering.

Det andet projekt beskriver en kort totalsyntese af (+)-pancratistatin fra fornybare udgangsstoffer ved hjælp af en i gruppen udviklet metode. Nøgletrinnet bestod af en one-pot zink-medieret fragmentering af et funktionaliseret kulhydrat og efterfølgende allylering.



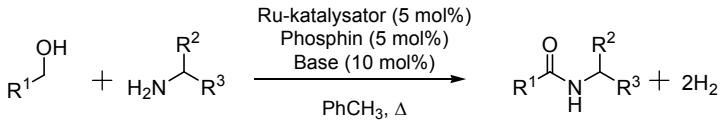
Projekt II: Total syntese af pancratistatin.

Det tredje projekt blev udført in professor Phil Barans laboratorier og bestod i en succesfuld totalsyntese af cyclophanen cavicularin, der indeholder en bøjet aromatisk ring. Det afgørende trin i syntesen omfattede en pyron-alkyn Diels-Alder cykloaddition med frigørelse af CO_2 til dannelse af den bøjede aromatiske ring.



Projekt III: Total syntese af cavicularin.

Det fjerde projekt drejede sig om videreudvikling af de i gruppen fundne betingelser for den direkte kobling af alkoholer og aminer til amider under frigørelse af dihydrogen. Videreudviklingen bestod i fremstilling af en isolerbar katalysator baseret på ruthenium. To 18-elektrons ruthenium-komplekser, der katalyserede reaktionen til udmærkede udbytter, blev fremstillet og karakteriseret. Desuden blev det opdaget, at adskillige metatese katalysatorer er effektive katalysatorer i koblingen.



Projekt IV: Fremstilling af isolerbar Ru-katalysator til kobling af alkoholer og aminer.

Abbreviations & Acronyms

)))	Sonication
Ac	Acetyl
AIBN	2,2′-Azobis(2-methylpropionitrile)
Anh	Anhydrous
APCI	Atmospheric pressure chemical ionization
aq.	Aqueous
BHT	2,6-Di-*tert*-butyl-4-methylphenol
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
Bn	Benzyl
br	Broad (NMR)
brsm	Based on recovered starting material
Bu	Butyl
c	Concentration
COD	1,5-Cyclooctadiene
COSY	Correlation spectroscopy
Cy	Cyclohexyl
Cyp	Cyclopentyl
d	Doublet (NMR)
d.r.	Diastereomeric ratio
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCB	*o*-Dichlorobenzene
DCC	*N,N*'-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DCVC	Dry column vacuum chromatography
DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone
DMA	*N,N*-Dimethylacetamide
DMAP	4-(Dimethylamino)-pyridine
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
DQF-COSY	Double quantum filtered correlation spectroscopy
EI	Electron ionization
ESI	Electrospray ionization
Et	Ethyl
Eq.	Equation
Equiv.	Equivalent(s)
FAB	Fast atom bombardment
GC	Gas chromatography
GCMS	Gas chromatography mass spectrometry
h	Hour(s)
HMBC	Heteronuclear multiple quantum coherence
HMPA	Hexamethylphosphoramide
HOBt	1-Hydroxybenzotriazole
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence

i	Iso
ICy	1,3-Dicyclohexylimidazol-2-ylidene
I^{i}Pr	1,3-Di-*iso*-propylimidazol-2-ylidene
IMe	1,3-Dimethylimidazol-2-ylidene
IMes	1,3-Dimesitylimidazol-2-ylidene
Imid	Imidazole
IR	Infrared spectroscopy
I^{t}Bu	1,3-Di-*tert*-butylimidazol-2-ylidene
KHMDS	Potassium bis(trimethylsilyl)amide
LAH	Lithium aluminum hydride
LCMS	Liquid chromatography mass spectrometry
LDA	Lithium diisopropylamide
LiHMDS	Lihium bis(trimethylsilyl)amide
Lindlar cat.	$Pd/CaCO_3$, lead-poisoned
LRMS	Low resolution mass spectrometry
m	*Meta*
m	Multiplet (NMR)
M	Molar
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
Mes	Mesityl
MOM	Methoxymethyl
Mp	Melting point
MS	Mass spectrometry
Ms	Mesyl; Methanesulfonyl
MW	Microwave
n	Normal
NBS	*N*-Bromosuccinamide
NHC	*N*-Heterocyclic carbene
NMO	*N*-Methylmorpholine-*N*-Oxide
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser effect
NOESY	Nuclear Overhauser enhancement spectroscopy
o	*Ortho*
p	*Para*
PCC	Pyridinium chlorochromate
Pent	Pentyl
Ph	Phenyl
Piv	Pivaloyl
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
PMB	*p*-Methoxybenzyl
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
Py	Pyridine
q	Quartet (NMR)
Q	Quantitative
RCM	Ring closing metathesis
Red Al	Sodium bis(2-methoxyethoxy)aluminum hydride
R_f	Retention Factor
rt	Room temperature

s	Singlet (NMR)
SDKIE	Secondary deuterium kinetic isotope effect
t	Triplet (NMR)
t	Tertiary
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBS	*tert*-Butyldimethylsilyl
TC	Thiophene-2-carboxylate
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
tert	Tertiary
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-Tetramethylethylenediamine
TMS	Trimethylsilyl
TOF	Time of flight
Tol	Toluene
Trop	5-H-dibenzo[a,d]cyclohepten-5-yl
Ts	*p*-Toluenesulfonyl; Tosyl
TS	Transition state
TTMSS	Tris(trimethylsilyl)silane
Vitride	Sodium bis(2-methoxyethoxy)aluminum hydride

Table of Contents

1 Mechanistic Investigation of the Barbier-Allylation

1.1 Introduction

In 1899, Barbier reported a one-pot coupling reaction between a carbonyl compound and an alkyl halide mediated by magnesium metal.[1] His student V. Grignard turned the reaction into a two-step protocol by preforming the organometallic reagent.[2] At the time the latter became the preferred method of the two, despite the major requisite of strict exclusion of moisture from the reaction media.[3] Not until 1977, where Killinger *et al*.[4] described the zinc-mediated allylation of carbonyl compounds in alcohols, were major progress made, in particular with the more reactive allyl halides.[5-7] Nowadays, in contrast to the Grignard reaction, the one-pot Barbier reaction often performs much better in terms of simplicity and yield, when it is carried out in the presence of water as a (co)solvent.[7] Additionally, by employing the Barbier reaction, instead of the Grignard protocol, a tedious protection-deprotection sequence can be avoided, contributing to much enhanced synthetic efficiency. Moreover, a range of different metals are known to mediate the reaction in aqueous media, including zinc, indium, tin, antimony, bismuth, magnesium and manganese.[4, 8-14]

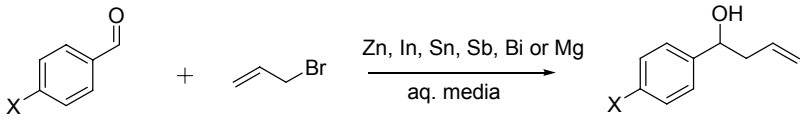
In the literature, it has been speculated whether the mechanism of the Barbier reaction in aqueous media follows a radical pathway or goes through a discrete allylmetal species. For zinc and tin in aprotic media, the Barbier reaction is known to proceed through a direct polar addition,[15, 16] whereas allylmagnesium bromide reacts by a single electron transfer process.[17] In 2005 Chang *et al.* provided a computational study showing that allylzinc, -indium, -tin, -antimony and -bismuth species are more prone to allylate a carbonyl compound than being hydrolyzed by water.[18] On the other hand, allylmagnesium bromide was predicted to be more reactive toward hydrolysis. Secondary deuterium kinetic isotope effects (SDKIE) indicate that the mechanism is highly dependent on the metal applied.[17, 19, 20] For zinc, indium and tin an inverse SDKIE was obtained indicating a rate-determining, polar addition to the carbonyl substrate. Contrary, a normal SDKIE was obtained for the allylation with magnesium and antimony suggesting single electron transfer processes. Additional experimental support comes from NMR studies, which show that indium, tin and antimony react with allyl bromide in water to form allyl metal intermediates.[21-24]

In the Madsen group we have on several occasions applied the Barbier reaction with zinc and indium as the key steps in total syntheses.[25-30] The reactions have provided good yields, but occasionally the diastereomeric outcome have varied. For the different metals there are still a

number of unanswered questions with regard to the nature of the allyl metal species or single electron transfer processes. Therefore, we decided to perform a more systematic study of the mechanism for the Barbier allylation in aqueous media. By means of competitive Hammett studies and indirectly measured secondary deuterium kinetic isotope effects we anticipated to address the nature various metal species with regard to zinc, indium, antimony, tin, bismuth and magnesium.

1.2 Initial Optimization of the Allylation Conditions

Optimal reaction conditions for the zinc allylation were quickly found to correspond to those found by Pétrier and Luche.[9] The highest yield of the homoallylic alcohols from benzaldehydes was obtained in a 1:1 mixture of THF and aqueous ammonium chloride, scheme 1.1. This mixture formed a two-phase system consisting of an aqueous THF phase and a saturated ammonium chloride phase. It was shown by GC that the aldehydes and the allylbromide were present in the THF phase, while no compounds could be detected in the ammonium chloride phase. The yields of the homoallylic alcohols were lower when the reactions were performed in a THF/water mixture, and this did not change by using ultrasound.



Scheme 1.1: General scheme for allylation of benzaldehydes.

On the other hand, with indium, tin, and bismuth the THF-water mixture proved to give the best results. All three metals reacted significantly slower than zinc and it was necessary to heat the reactions with tin and bismuth to 60 ºC. Both the tin and the bismuth allylation were about 40 min. to initiate and then quickly reacted to provide the homoallylalcohol. With indium the reaction rate could be dramatically increased by the addition of an equimolar amount of HCl. This did, however, result in pronounced formation of by-products – especially with electron-rich benzaldehydes. This additive was therefore abandoned. Over time the indium-powder clothed together, which might have slowed the reaction further, but the clumps still seemed able to react. Antimony and magnesium resulted in a slower reaction than all the other metals. With antimony it was necessary to use a solvent system of THF and 0.5 M hydrochloric acid.[23] Furthermore, antimony had to be prepared from antimony(III) chloride and sodium borohydride[31] in order to

give a good conversion while commercially available antimony powder reacted more sluggishly. By this activation procedure the amount of antimony could be reduced along with the reaction time, while conversion was maintained. We were not able to reduce the amount of antimony to the nearby equimolar level as Butsugan *et al.*[32] It has previously been reported that antimony and bismuth can be activated by potassium fluoride for the allylation of aldehydes,[33,14] but in our hands this procedure did not provide a more reactive metal. For the competitive studies we wanted to avoid a secondary metal functioning as a co-catalyst, *i.e.* generation of zero-valent antimony by *in situ* reduction of $SbCl_3$ with iron or aluminum[34, 35] – in this regard we decided to keep the system of activated antimony.

Magnesium proved even more troublesome and we were unable to reproduce the original conditions with allyliodide in either a THF-water mixture or in a 0.1 M ammonium chloride solution.[13, 36] In our hands these reactions did not go to completion and mainly led to pinacol coupling and reduction of the aldehyde even with a variety of different magnesium sources.[37, 38] Other solvent mixtures were investigated and it was found that 0.1 M ammonium chloride in either ethanol or DMF gave full conversion and fewer by-products. The best results were obtained in a 4:1 mixture of DMF and 0.1 M ammonium chloride.

1.3 Hammett Studies of the Allylation

The Hammett studies were performed as a series of competition experiments, where the reaction progress was determined by measuring the disappearance of aldehyde using naphthalene as internal standard. This method is valid when the starting materials are converted cleanly into the desired product. If the reactions are of first order in aldehydes, the concentrations of the aldehydes will follow eq. 1.1, where subscript '0' denotes the initial concentration, X is the concentration of the *para*-substituted aldehyde and H is the concentration of benzaldehyde at the same conversion. Plotting $\ln(H_0/H)$ against $\ln(X_0/X)$ gives a gradient equal to the relative rate constant, $k_{rel} = k_X / k_H$.

$$\ln(\frac{X_0}{X}) = k_{rel} \ln(\frac{H_0}{H}) \qquad (1.1)$$

We then plot $\log(k_{rel})$ versus σ in the standard Hammett plot to obtain the reactivity parameter ρ as the slope and also to check the correlation against different types of σ-values.

The competition experiments were carried out with 1 equiv. of benzaldehyde, 1 equiv. of one of the six different *para*-substituted benzaldehydes, 1–2 equiv. of allylbromide and 1–2 equiv. of the metal. Zinc was the first metal to be investigated and the experiments were performed by adding zinc in portions of approximately 0.1 equiv. because the reaction was otherwise too fast to be adequately monitored. The reaction was also highly exothermic and led to extensive formation of by-products if the temperature was not maintained at room temperature. It was not possible to extend the Hammett plot to include the *para*-nitrobenzaldehyde or *para*-dimethylamino-benzaldehyde since these aldehydes with strongly electron-withdrawing or –donating substituents were resistant to the allylation conditions.

Table 1.1: Yields for the allylations in Scheme 1.1.

Entry		Yield[a] (in %) with					
		Zn[b]	In[c]	Sn[c]	Sb[d]	Bi[c]	Mg[e]
1	-CN	99 (94[f])	90	94	93	98	-
2	-COOMe	98 (93[f])	87 (99[g])	82 (85[g])	95	83 (88[g])	25 (26[g])
3	$-CF_3$	99 (91[f])	98	99	66 (90[g])	94	60 (65[g])
4	-Cl	96 (90[f])	75 (80[g])	95	87 (92[g])	84 (92[g])	60 (62[g])
5	-H	96 (92[f])	92	94	69	88	49[f]
6	-Me	99 (95[f])	75 (81[g])	82 (93[g])	50 (83[g])	71 (84[g])	14 (79[g])
7	-^{t}Bu	99 (92[f])	56 (81[g])	-	-	63 (82[g])	-
8	-OMe	76 (82[f])	-	18 (41[g])	-	37 (72[g])	-
9	-OBu	83 (90[f])	-	-	-	-	-

[a] Yields determined by GC. [b] Performed in 1:1 THF:saturated aqueous NH_4Cl with acid-washed zinc. [c] Performed in 1:1 THF:H_2O. [d] Performed in 7:3 THF:0.5 M HCl with antimony metal prepared from reduction of $SbCl_3$ with $NaBH_4$. [e] Performed with allyliodide in 4:1 DMF:0.1 M NH_4Cl. [f] Isolated yield. [g] Yield based on converted aldehyde.

In all cases, the correlation coefficient was better than 0.99, when $\ln(X_0/X)$ was plotted against $\ln(H_0/H)$ (Figure 1.1).

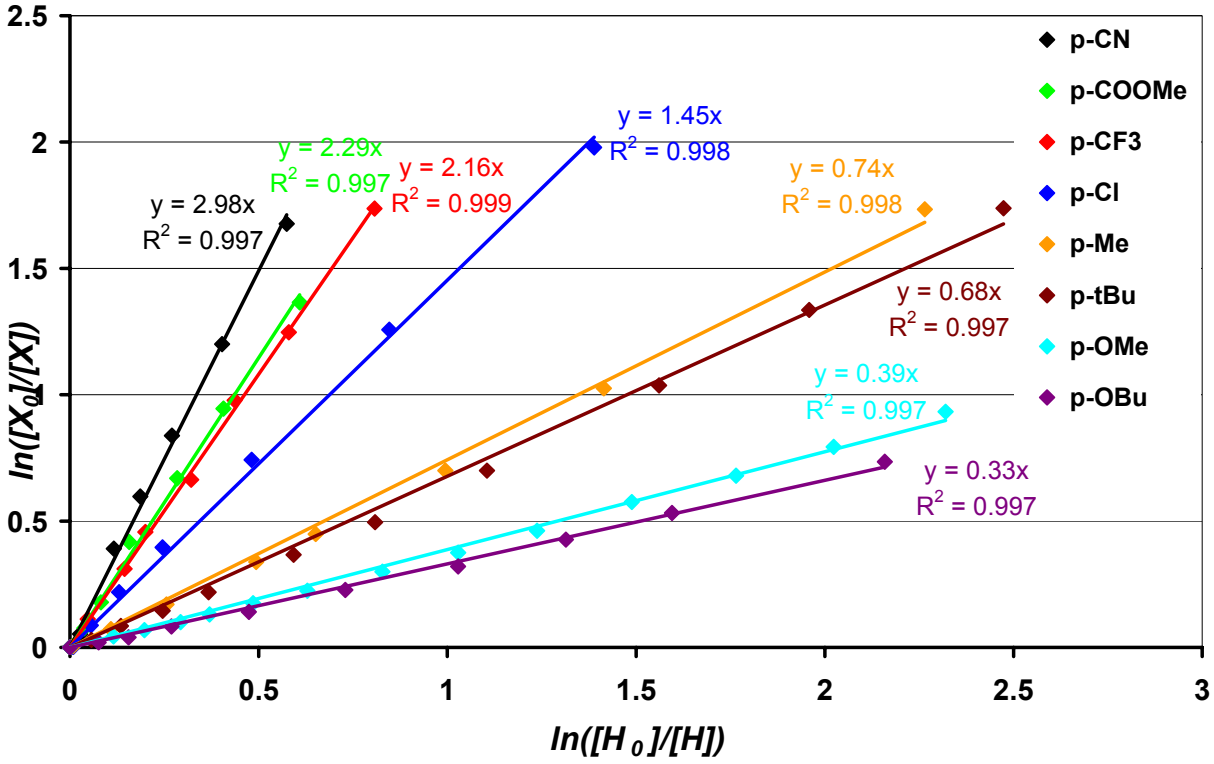


Figure 1.1: Kinetic data for the competitive zinc allylation.

The obtained k_{rel} values are used to construct the Hammett plot in figure 1.2. When applying the "regular" σ–values a plot with a small positive slope was obtained for the electron-withdrawing substituent (right hand side). However, this line could not be extended to include the electron-donating substituents, where a significantly steeper line was obtained. Surprisingly, we found a linear correlation when using σ^+–values, in spite of the fact that these values were originally developed for reactions in which a cation is developed.[39] Although the fit to the σ^+–values usually implies the involvement of a cation, the slope of the line is positive for both sets of σ–values, indicating that a small negative charge is being developed at the benzylic position, thus suggesting that the use of σ^+–values should be avoided. The methoxy– and butoxy–substituents caused the reaction to proceed slower than would be expected from the standard σ–values, which suggests that for these substituents there could be a change of rate-determining step.[40] In any case, the poor correlation with the $\sigma^\bullet$–values suggests that a radical intermediate is not involved in the allylation reaction.

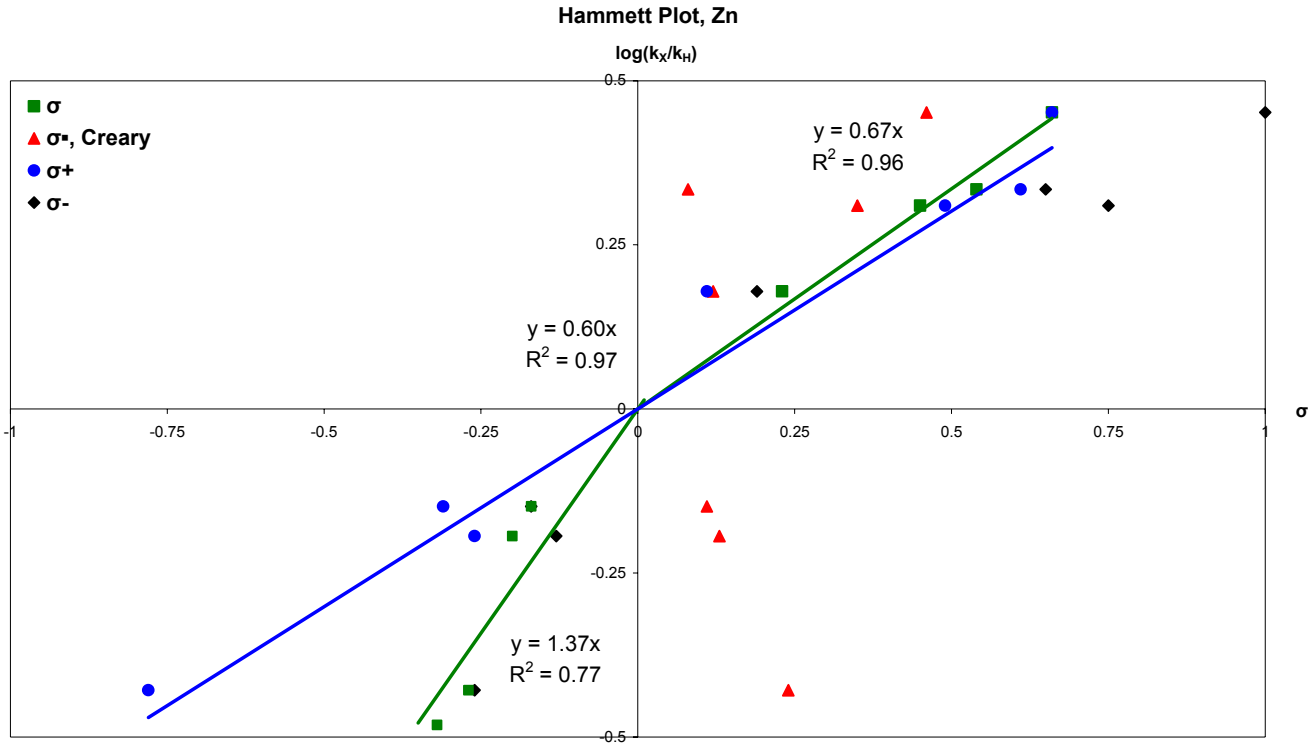


Figure 1.2: Hammett plot for the zinc-mediated allylation. σ–values were obtained from Hansch *et al*.[41]

The method applied for the zinc allylation was also used in the competitive allylations with indium, tin, antimony, bismuth, and magnesium, *i.e.* the disappearance of the starting material was monitored during the progress of the reaction. Compared to the zinc allylation these reactions were all slower and required several hours to reach full conversion. As a result, it was not necessary to add the metals in portions and the entire portion of metal was therefore added at the beginning of each experiment. For tin and bismuth the reaction took 1-4 h to initiate, and then went to completion in 3-4 h.

The kinetic data and the full Hammett plots have been included in the experimental section. For the four metals indium, tin, antimony, and bismuth a good correlation is obtained using ordinary σ–values, although the methoxy-substituent again deviates from the straight line (Figure 1.3). The slopes of the lines are positive with a slightly larger ρ–value than previously observed with zinc, indicating a larger build-up of negative charge in the selectivity-determining step (selection between which aldehyde to react with). The reactions with magnesium only led to the desired allylation products for the *para*-substituents Me, Cl, CF_3, and COOMe, and only in the former three cases in reasonable GC yields (Table 1.1). The Hammett plot for magnesium

indicates build-up of a significant negative charge in the benzylic position and clearly distinguishes this metal from the other five which are all very similar.

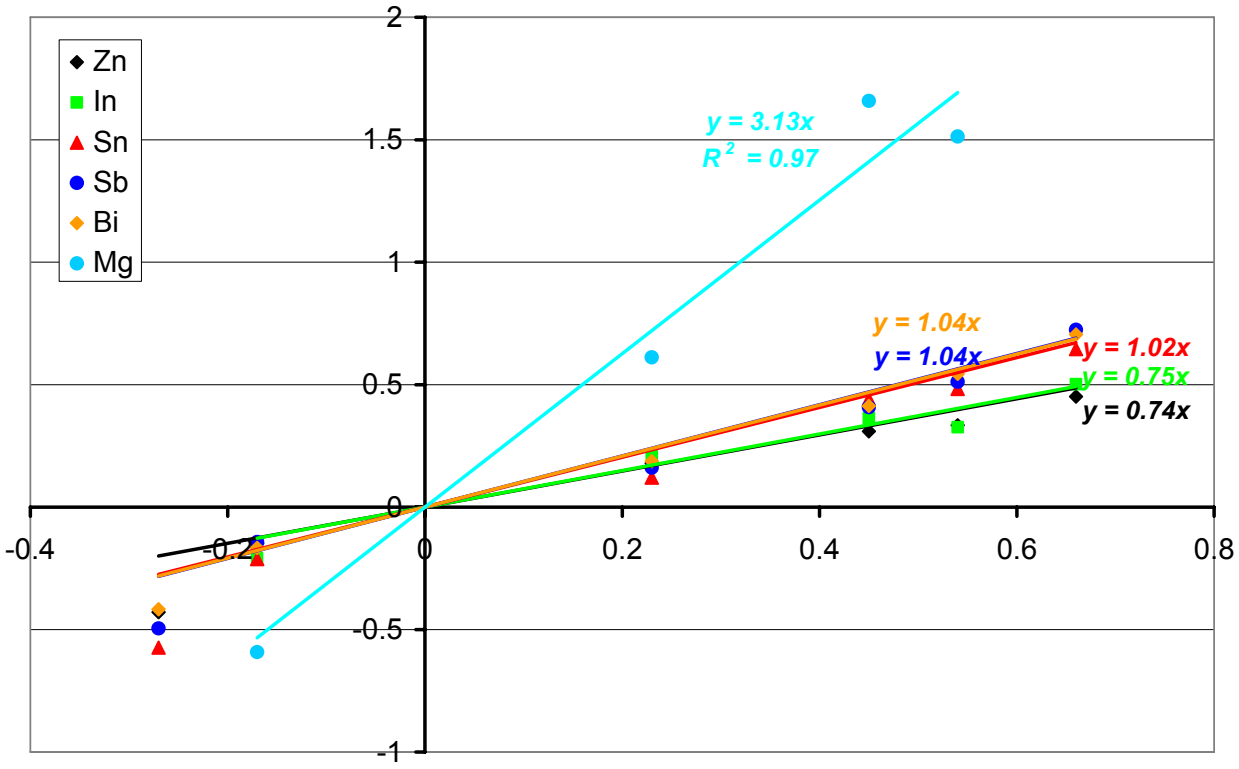


Figure 1.3: The Hammett plots for the allylations with zinc, indium, tin, antimony, bismuth, and magnesium.

The similarity between the first five metals is somewhat surprising when the differences in reaction conditions are taken into account, but gives a strong indication that a common mechanism is operating. The relatively small slope of the lines indicates that only a partial negative charge is built up in the transition state, which is what would be expected from a closed, six-membered transition state. For magnesium the significantly larger slope indicates that a significant negative charge is present in the selectivity-determining step. This would be expected, for instance, if the generation of a radical anion in the benzylic position is the selectivity-determining step as suggested earlier, which is then followed by a fast allylation reaction.[13] This mechanism is supported by two earlier Hammett studies where substituted benzophenones were reacted with *t*-butylmagnesium chloride,[41] and allylmagnesium bromide,[42] respectively. When *t*-butylmagnesium chloride was employed, a Hammett ρ–value of 3.0 was found, which is similar to the result in this study and in line with the formation of a radical anion by electron transfer from the Grignard reagent. On the contrary, when preformed allylmagnesium chloride was used, the reaction rate was completely unaffected by the nature of the *para*-substituents, which gave a slope of zero in the Hammett plot.[43] The results obtained for

magnesium indicate that under Barbier conditions the radical anion of benzaldehyde is generated first, as indicated by the high ρ–value, and that the following allylation is neither rate- nor selectivity-determining *i.e.* the ease of formation is determined by the stability of the radical from a given aldehyde.

1.4 Secondary Deuterium Kinetic Isotope Effect

To add further mechanistic support to the closed, six-membered transition state a study of the secondary deuterium kinetic isotope effect (SDKIE) was undertaken. The polar addition of a nucleophile to the aldehyde carbonyl involves a transition state with an additional bond. The addition will increase the bending frequencies and result in a greater lowering of the zero point energy upon deuterium substitution ($sp^2 \rightarrow sp^3$). In turn this leads to an inverse SDKIE. The formation of a radical ketyl anion will posses looser bonds than the starting aldehyde and will result in a normal SDKIE. Hence, an inverse SDKIE ($k_H/k_D < 1$) is a strong indication of a polar addition as the rate-determining step, whereas a normal SDKIE ($k_H/k_D > 1$) would be compatible with the formation of a radical species.[17, 19, 20]

By means of two separate competition experiments the relative rate of allylation of benzaldehyde and *d*-benzaldehyde could be determined relative to *p*-tolualdehyde. The comparison of the rates was carried out indirectly since standard GC is unable to differentiate between *d*-benzaldehyde and benzaldehyde. With zinc the SDKIE was determined to be as large as 0.83, which suggests a relatively "late" TS. With tin, antimony and bismuth almost equally large values were determined (k_H/k_D = 0.85 (Sn), 0.75 (Sb), and 0.85 (Bi), respectively), whereas the use of indium resulted in only a minor effect (k_H/k_D = 0.95) suggesting that a much "earlier" TS is operating for this metal. In a related study by Lucas *et al.*[20] a significantly lower SDKIE was found for indium (k_H/k_D = 0.82), and due to the obvious disagreement we decided to also perform a *direct* determination of the SDKIE for indium with GC-MS. Using selected ion monitoring (SIM) for the molecular ions of both benzaldehyde and *d*-benzaldehyde (*m/z* = 106 and 107, respectively) it was possible to quantify the disappearance of these aldehydes relative to the molecular ion of the internal standard (naphthalene, *m/z* = 128). This experiment gave a SDKIE of 0.92, which corroborates the slightly higher value (0.95) obtained in the indirect competition experiment. Also for antimony there are significant differences in the SDKIE determined here (0.75) and the one reported earlier by Lucas *et al.* (1.07). However, in their case a 2 M potassium fluoride solution was used as solvent, whereas we have used a 0.5 M solution of hydrochloric acid, which may significantly alter the pathway of the reaction. In contrast to the

other five metals the use of magnesium resulted in a normal SDKIE. The exact value was 1.04 which is very close to the value obtained by Lucas *et al.* (1.06).[20] The finding of a normal SDKIE for magnesium can be taken as an indication that a radical anion forms in the selectivity-determining step, in sharp contrast to all the previously investigated metals where the SDKIE below unity clearly indicates that C-C bond formation is rate-limiting.

1.5 Conclusion

The Barbier allylation of a series of *para*-substituted benzaldehydes with allylbromide in the presence of Zn, In, Sn, Sb, Bi, and Mg was investigated using competition experiments under aqueous conditions. For the first five metals linear Hammett plots were obtained with "regular" σ−values and therefore radicals did not seem to be involved in the rate-determining step. Also, for Zn, In, Sn, Sb, and Bi an inverse secondary kinetic isotope effect was found (k_H/k_D = 0.75-0.95), which is compatible with the formation of a discrete organometallic species prior to polar allylation *via* a closed six-membered transition state. With Mg a significantly larger build-up of negative charge from the Hammet correlation along with a small normal secondary deuterium kinetic isotope effect (k_H/k_D = 1.06) indicates that the selectivity-determining step is generation of the radical anion of benzaldehyde.

1.6 Experimental Section

General procedures

THF was distilled from Na/benzophenone under nitrogen, while DMF and CH_2Cl_2 were dried over 3 Å and 4 Å molecular sieves, respectively. Solvents used for chromatography were of HPLC grade. Zinc dust (8.0 g, 122 mmol, Fluka 00618, ≥ 99.0%) was activated by stirring with 2 M HCl (150 mL) for 10 min, then filtered and washed successively with water (75 mL), methanol (75 mL) and ether (75 mL) and dried with a heatgun under high vacuum for 10 min to leave a fine, light grey powder. Antimony was prepared by a revised procedure[31]: $SbCl_3$ (2.32 g, 10.2 mmol) was suspended in water (50 mL) and stirred with $NaBH_4$ (1.15 g, 30.4 mmol) under argon for 5 min. The precipitated metal was isolated by filtration and washed successively with water (50 mL), methanol (50 mL) and ether (50 mL) and dried with a heatgun under high vacuum for 10 min to leave a fine black powder. Indium powder (Aldrich 264032, -100 mesh, 99.99%), tin powder (Aldrich 265632, -325 mesh, 99.8%), bismuth powder (Aldrich 26562, -100 mesh, 99.5%) and magnesium powder (Strem 931298, 99%) were used as received. *p*-Tolualdehyde and *p*-anisaldehyde were purified by fractional distillation before use.

Thin layer chromatography was performed on aluminum plates coated with silica gel 60. Visualization was done by UV-radiation and/or charring with a heatgun after dipping in a solution of cerium(IV)sulfate (2.5 g) and ammonium molybdate (6.25 g) in 10% aqueous sulfuric acid (250 mL). Flash chromatography was performed with Matrex 60 Å silica gel (35-70 μm). NMR spectroscopy was performed on a Varian Mercury 300 MHz, Unity Inova 500 MHz or a Bruker AC-200 spectrometer. Signal positions were measured relative to the signals of residual $CHCl_3$ (δ_H = 7.26 ppm)/ $CDCl_3$ (δ_C = 77.0 ppm) or DMSO (2.50 ppm)/ DMSO-*d6* (39.4 ppm) as the internal standards. IR spectra were obtained for thin films on AgCl plates or KBr pellets on a Perkin-Elmer 1600 FTIR or as neat compounds on a Bruker Alpha-P FT-IR spectrophotometer. Mass spectrometry was obtained with a Shimadzu GCMS-QP5000. HRMS was obtained from the Department of Chemistry, University of Copenhagen or Department of Physics and Chemistry, University of Southern Denmark. Microanalyses were obtained from the Microanalytical Laboratory, University of Vienna, Austria. Sonication was performed on either a 1210 or a 2210 Branson cleaning bath (~47 KHz) with 1-2 vol% liquid detergent for reproducibility. All KHMDS- and butyllithium-solutions were titrated according to literature procedures to a sharp blue endpoint.[44, 45]

For the Hammett studies: Reaction progress was monitored by taking out samples of 100 μL and diluting with 0.9 mL of THF. Excess metal powder was removed by centrifugation. All

samples were stored at 5 ºC immediately after being taken out. Analysis was performed by gas chromatography on a Shimadzu GC-2010 equipped with a 30 m × 0.25 mm × 0.25 μm Supelco Equity-1 capillary column. Retention times for all compounds are shown below. The homoallylic alcohols were prepared according to the general procedure for the competitive zinc allylation. The corresponding pinacols were prepared as a mixture of isomers according to a literature procedure.[46]

The secondary kinetic isotope effect (SDKIE) was determined for each metal by a competition experiment using *d*-benzaldehyde and *p*-tolualdehyde, thus allowing straightforward separation by GC. The SDKIE could then be determined by comparison to the value determined in the competition experiment with *p*-tolualdehyde and benzaldehyde.

General procedure for competitive zinc allylation used for the Hammett plot

Benzaldehyde (0.5 mmol), the *p*-substituted benzaldehyde (0.5 mmol) and naphthalene (0.25 mmol) were dissolved in anhydrous THF (5.0 mL). A sample was taken out for analysis and allylbromide (173 μL, 2.0 mmol) was added. Another sample was taken out for analysis and saturated aqueous NH_4Cl (5.0 mL) was added. Portions of activated zinc dust (~ 13 mg, 0.2 mmol) were added at 5 min intervals on a water bath at rt until 2 equivalents of zinc was reached. Before each addition of zinc the vigorous stirring was discontinued and a sample was taken out for analysis.

General procedure for indium allylation used for the Hammett plot

Benzaldehyde (0.5 mmol), the *p*-substituted benzaldehyde (0.5 mmol) and naphthalene (0.25 mmol) were dissolved in THF (7.0 mL) and deionized H_2O (3.0 mL) at rt. A sample was taken out for analysis and allylbromide (130 μL, 1.5 mmol) was added. Another sample was taken out for analysis and indium powder (172 mg, 1.5 mmol) was added. Samples were then taken out every 20-30 min until the reaction had gone to completion (~5 h).

General procedure for tin allylation used for the Hammett plot

Benzaldehyde (0.5 mmol), the *p*-substituted benzaldehyde (0.5 mmol) and naphthalene (0.25 mmol) were dissolved in THF (7.0 mL) and deionized H_2O (3.0 mL) in a two-necked flask fitted with a reflux condenser. A sample was taken out for analysis and allylbromide (173 μL, 2.0 mmol) was added. Another sample was taken out for analysis followed by addition of tin powder (119 mg, 1.0 mmol) and heating the suspension in an oil bath to 60 ºC. After

approximately 40 min where the allylation initiated samples were taken out at the following intervals: 30, 5, 2×2.5, 5×2, 2×3, 4, 2×5, 8, 12, 2×15, and 2×30 min.

General procedure for antimony allylation used for the Hammett plot

Benzaldehyde (0.5 mmol), the *p*-substituted benzaldehyde (0.5 mmol) and naphthalene (0.25 mmol) were dissolved in THF (7.0 mL) and 0.5 M aqueous HCl (3.0 mL) at rt. A sample was taken out for analysis and allylbromide (216 μL, 2.5 mmol) was added. Another sample was taken out for analysis and activated antimony powder (244 mg, 2.0 mmol) was added. Samples were then taken out every hour until the reaction had gone to completion (~12-16 h). The reaction was run under an argon atmosphere.

General procedure for bismuth allylation used for the Hammett plot

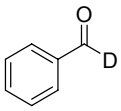
Benzaldehyde (0.5 mmol), the *p*-substituted benzaldehyde (0.5 mmol) and naphthalene (0.25 mmol) were dissolved in THF (5.0 mL) and deionized H_2O (5.0 mL) in a two-necked flask fitted with a reflux condenser. A sample was taken out for analysis and allylbromide (173 μL, 2.0 mmol) was added. Another sample was taken out for analysis followed by addition of bismuth powder (418 mg, 2.0 mmol) and heating the suspension in an oil bath to 60 ºC. After approximately 40 min where the allylation initiated samples were taken out at the following intervals: 30, 5, 2×2.5, 5×2, 2×3, 4, 2×5, 8, 12, 2×15, and 2×30 min.

General procedure for competitive magnesium allylation used for the Hammett plot

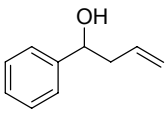
Benzaldehyde (0.5 mmol), the *p*-substituted benzaldehyde (0.5 mmol) and naphthalene (0.25 mmol) were dissolved in DMF (8.0 mL). A sample was taken out for analysis and allylbromide (457 μL, 5.0 mmol) was added. Another sample was taken out for analysis and 0.1 M aqueous NH_4Cl (2.0 mL) was added. Magnesium powder (486 mg, 20 mmol) was then added and the slurry was stirred at rt. Samples were drawn at regular time intervals and filtered through a small plug of cotton, which was washed with 0.8 mL of DMF. The samples were analyzed immediately by GC using a 15 m × 0.10 mm × 0.10 μm Supelco Equity-1 capillary column (FastGC). The temperature program was 100 ºC (hold 5 min) and then a ramp (20 ºC /min) to 300 ºC.

General procedure for the preparation of the corresponding pinacols

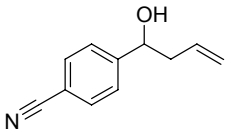
Benzaldehyde (5 mmol) was dissolved in methanol (10 mL) and aluminum powder (0.27 g, 10 mmol) was added followed by KOH (2.53 g, 45 mmol). After 10 min where the vigorous reaction had subsided, the slurry was filtered and 50 mL of H_2O was added. Extraction with 3 × 50 mL of ethyl acetate, drying with Na_2SO_4 and concentration *in vacuo* left a white, crude solid of the mixed pinacols in quantitative yield.



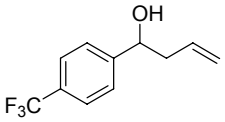
$LiAlD_4$ (1.02 g, 24.3 mmol) was added to 50.0 mL of THF in a three-necked flask fitted with a reflux-condenser and a drying-tube ($CaCl_2$). The suspension was refluxed for 15 min., before dropwise addition of benzoic acid (1.20 g, 9.83 mmol in 10.0 mL THF) by syringe. The slurry was refluxed for 1 h after the full addition at which point it was quenched with aq. $NaHCO_3$. The slurry was filtered through a pad of Celite and washed with 100 mL of Et_2O. The phases were separated and the aqueous phase was neutralized with 6 M aq. HCl. The combined organic phases were dried with $MgSO_4$, filtered and evaporated *in vacuo*. Yield (0.993 g, 95 %). The alcohol (0.720 g, 6.54 mmol) was dissolved in 40.0 mL of anhydrous CH_2Cl_2 under Ar and cooled to -40 ºC, where NEt_3 (3.6 mL, 26.1 mmol) and anhydrous DMSO (4.2 mL) were added. Then, a pre-mixed solution of SO_3·py (3.12 g, 19.6 mmol) in anhydrous DMSO (12.5 mL) was added by syringe. The solution was allowed to warm to rt, where 100 mL of CH_2Cl_2 was added and washed with 150 mL of sat. aq. $CuSO_4$ and 3 x 100 mL of 2 M HCl. The organic phase was dried with $MgSO_4$, filtered and concentrated *in vacuo* without heating. The residue was purified by flash chromatography in 1→5 % Et_2O in pentane to yield 0.494 g of the aldehyde (71 %).[47, 48] ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.86-7.91 (m, 2H), 7.60-7.66 (m, 1H), 7.50-7.56 (m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 191.9 (t, J = 26.4, 1*C), 136.3 (t, J = 3.6, 1*C), 134.3 (s, 1*C), 129.6 (s, 2*C), 128.9 (s, 2*C). HRMS (ESI-TOF) $[M+H]^+$: calcd 108.0553, found 108.0554.



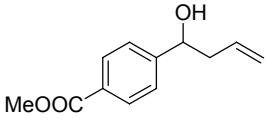
R_f = 0.47, 3:7 EtOAc:Heptane (v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.10 (s, 1H), 2.49-2.60 (m, 2H), 4.74 (dd, 1H, J = 5.5, 7.4 Hz), 5.12-5.21 (m, 2H), 5.82 (tdd, 1H, J = 7.1, 10.2, 17.1 Hz), 7.25-7.43 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 43.7, 73.2, 118.2, 125.7, 127.4, 128.3, 134.4, 143.8. IR (neat, cm^{-1}): br 3383, 3029, 2906, 1950, 1641, 1493, 1455, 1314, 1198, 1046, 916. MS *m/z*: 148. Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.85; H, 8.29.



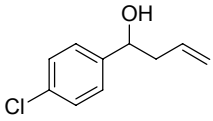
R_f = 0.30, 3:7 EtOAc:Heptane (v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.33-2.55 (m, 2H), 2.59 (bs, 1H), 4.77 (dd, 1H, *J* = 5.0, 7.8 Hz), 5.09-5.19 (m, 2H), 5.68-5.82 (m, 1H), 7.42-7.48 (m, 2H), 7.57-7.62 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 43.6, 72.2, 110.8, 118.8, 119.2, 126.4, 132.1, 133.3, 149.2. IR (neat, cm^{-1}): br 3460, 3076, 2907, 2228, 1641, 1608, 1504, 1414, 1055, 921, 843. MS *m/z*: 173. Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.02; H, 6.44; N, 7.94.



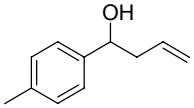
R_f = 0.47, 3:7 EtOAc:Heptane (v/v). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.19 (bs, 1H), 2.39-2.59 (m, 2H), 4.79 (dd, 1H, *J* = 4.8, 7.9 Hz), 5.14-5.22 (m, 2H), 5.71-5.86 (m, 1H), 7.44 (m, 2H), 7.57-7.63 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 43.9, 72.5, 119.5, 124.1 (q, *J* = 272.0 Hz), 125.3 (q, *J* = 3.8 Hz), 126.0, 129.6 (q, *J* = 32.3 Hz), 133.6, 147.7. IR (neat, cm^{-1}): br 3380, 3079, 2910, 1928, 1643, 1621, 1416, 1327, 1168, 1124, 1070. MS *m/z*: 216. Anal. Calcd for $C_{11}H_{11}F_3O$: C, 61.11; H, 5.13. Found: C, 60.92; H, 5.14.



R_f = 0.33, 3:7 EtOAc:Heptane (v/v). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.39-2.53 (m, 2H), 2.89 (bs, 1H), 3.86 (s, 3H), 4.74 (dd, 1H, *J* = 5.5, 7.5 Hz), 5.06-5.14 (m, 2H), 5.66-5.82 (m, 1H), 7.34-7.39 (m, 2H), 7.92-7.97 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 43.6, 52.0, 72.9, 118.6, 125.6, 128.9, 129.5, 133.8, 149.0, 166.9. IR(neat, cm^{-1}): br 3475, 3075, 2951, 1938, 1721, 1641, 1611, 1436, 1286, 1110. MS (ESP+) for $C_{22}H_{26}O_3$ $[M+Na]^+$: 229.1. Found: 229.1. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.69; H, 6.95.

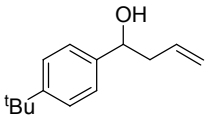


R_f = 0.43, 3:7 EtOAc:Heptane (v/v). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35-2.53 (m, 2H), 2.40 (s, 1H), 4.66 (dd, 1H, *J* = 5.5, 7.4 Hz), 5.09-5.18 (m, 2H), 5.75 (tdd, 1H, *J* = 7.1, 9.7, 17.2 Hz), 7.22-7.33 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 43.7, 72.5, 118.7, 127.1, 128.4, 133.0, 133.9, 142.2. IR (neat, cm^{-1}): br 3373, 3078, 2907, 1901, 1641, 1597, 1493, 1411, 1091, 1014. MS *m/z*: 182. Anal. Calcd for $C_{10}H_{11}ClO$: C, 65.76; H, 6.07; Cl, 19.41. Found: C, 65.71; H, 6.17; Cl, 19.27.

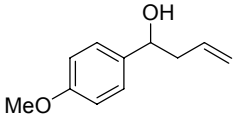


R_f = 0.47, 3:7 EtOAc:Heptane (v/v). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.08 (s, 1H), 2.36 (s, 3H), 2.48-2.56 (m, 2H), 4.70 (t, 1H, *J* = 6.5 Hz), 5.12-5.21 (m, 2H), 5.82 (tdd, 1H, *J* = 7.1, 10.2, 17.2 Hz), 7.15-7.21 (m, 2H), 7.23-7.30 (m, 2H). ^{13}C NMR (75

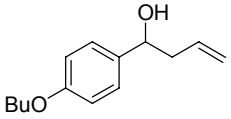
MHz, $CDCl_3$, δ): 21.1, 43.7, 73.1, 118.1, 125.7, 129.0, 135.6, 137.1, 140.9. IR (neat, cm^{-1}): br 3383, 3077, 2922, 1904, 1640, 1514, 1435, 1307, 1198, 1044, 915, 816. MS *m/z*: 162. Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.52; H, 8.91.



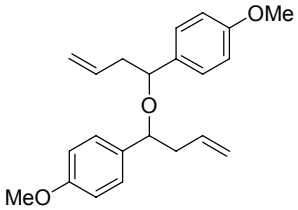
R_f = 0.43, 3:7 EtOAc:Heptane (v/v). ^1H NMR (300 MHz, $CDCl_3$): δ 1.33 (s, 9H), 2.13 (s, 1H), 2.46-2.57 (m, 2H), 4.66-4.73 (m, 1H), 5.13-5.22 (m, 2H), 5.83 (tdd, 1H, *J* = 5.1, 10.1, 17.3 Hz), 7.26-7.42 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 31.3, 34.5, 43.6, 73.1, 118.1, 125.3, 125.5, 134.7, 140.8, 150.4. IR (neat, cm^{-1}): br 3362, 3076, 2964, 1641, 1509, 1410, 1363, 1269, 1109, 1051, 914, 835. MS *m/z*: 204. Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.20; H, 9.85.



R_f = 0.33, 3:7 EtOAc:Heptane (v/v). ^1H NMR (300 MHz, $CDCl_3$): δ 2.24 (s, 1H), 2.46-2.52 (m, 2H), 3.80 (s, 3H), 4.66 (t, 1H, *J* = 6.6 Hz), 5.09-5.18 (m, 2H), 5.79 (tdd, 1H, *J* = 7.1, 10.2, 17.2 Hz), 6.85-6.91 (m, 2H), 7.24-7.31 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 43.6, 55.2, 72.9, 113.6, 118.1, 127.0, 134.6, 136.0, 158.9. IR (neat, cm^{-1}): br 3404, 3075, 2934, 2836, 1612, 1514, 1464, 1302, 1250, 1177, 1038. MS *m/z*: 178. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.98; H, 8.02.



R_f = 0.38, 3:7 EtOAc:Heptane (v/v). ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (t, 3H, *J* = 7.4 Hz), 1.43-1.56 (m, 2H), 1.71-1.82 (m, 2H), 2.11 (bs, 1H), 2.46-2.52 (m, 2H), 3.95 (t, 2H, *J* = 6.5 Hz), 4.66 (t, 1H, *J* = 6.5 Hz), 5.09-5.19 (m, 2H), 5.79 (tdd, 1H, *J* = 7.1, 10.1, 17.2 Hz), 6.84-6.91 (m, 2H), 7.23-7.29 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 13.8, 19.2, 31.3, 43.7, 67.6, 73.0, 114.3, 118.1, 127.0, 134.6, 135.8, 158.5. IR (neat, cm^{-1}): br 3385, 3075, 2961, 1707, 1617, 1507, 1246, 1173, 1035, 917, 833. MS *m/z*: 220. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.07; H, 9.14.



R_f = 0.47, 3:7 EtOAc:Heptane (v/v). ^1H NMR (300 MHz, $CDCl_3$): δ 2.26-2.42 (m, 2H), 2.47-2.65 (m, 2H), 3.83 (s, 6H), 4.03-4.09 (m, 2H), 4.89-5.00 (m, 4H), 5.59-5.75 (m, 2H), 6.86 (m, 4H), 7.14 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 43.1, 55.5, 77.7, 113.9, 116.8, 128.6, 134.3, 135.4, 159.3. IR (neat, cm^{-1}): 3072, 2933, 2834, 1610, 1513, 1302, 1249, 1170, 1073. HRMS (ESP+) for $C_{22}H_{26}O_3$ $[M+Na]^+$: 361.1780. Found: 361.1777.

General method for GC-analysis (Method A):

Temperature (°C)	Hold Time (min.)
100.0	12.0 (ramp 20)
200.0	10.0 (ramp 20)
300.0	5.0

Retention times for reaction components (Method A):

	Aldehyde	Benzylalcohol	Pinacols (*dl*/ *meso*)	Homoallyl
-CN	11.40	16.08	-	18.13
$-CF_3$	3.80	6.47	21.67/ 22.09	13.70
-COOMe	15.47	17.29	-	19.44
-Cl	8.48	12.46	30.34/ 30.57	18.81
-H	4.01	5.15	22.04/ 21.06	12.51
$-^tBu$	14.88	15.56	31.98/ 32.16	18.00
-OMe	12.98	13.94	31.16/ 31.35	17.18
-OBu	17.73	17.86	-	20.37

Method for *p*-Tolualdehyde GC-analysis (Method B):

Temperature (°C)	Hold Time (min.)
120.0	10.0 (ramp 20)
200.0	10.0 (ramp 20)
300.0	5.0

Retention times for reaction components (Method B):

	Aldehyde	Benzylalcohol	Pinacols (*dl*/ *meso*)	Homoallyl
-H	3.10	3.52	18.72/ 17.73	6.84
-Me	4.18	4.72	23.02/ 23.58	10.38

Table A: Data for the competition experiments with zinc.

X	k_X/k_H	R^2	$\log(k_X/k_H)$	σ	σ▪, Creary	σ+	σ-
t-Bu	0.68	0.997	0.167491	-0.2	0.13	-0.26	-0.13
OMe	0.39	0.997	0.408935	-0.27	0.24	-0.78	-0.26
Me	0.74	0.998	0.130768	-0.17	0.11	-0.31	-0.17
Cl	1.45	0.998	-0.16137	0.23	0.12	0.11	0.19
COOMe	2.29	0.997	-0.35984	0.45	0.35	0.49	0.75
CF3	2.16	0.999	-0.33445	0.54	0.08	0.61	0.65
CN	2.98	0.997	-0.47422	0.66	0.46	0.66	1

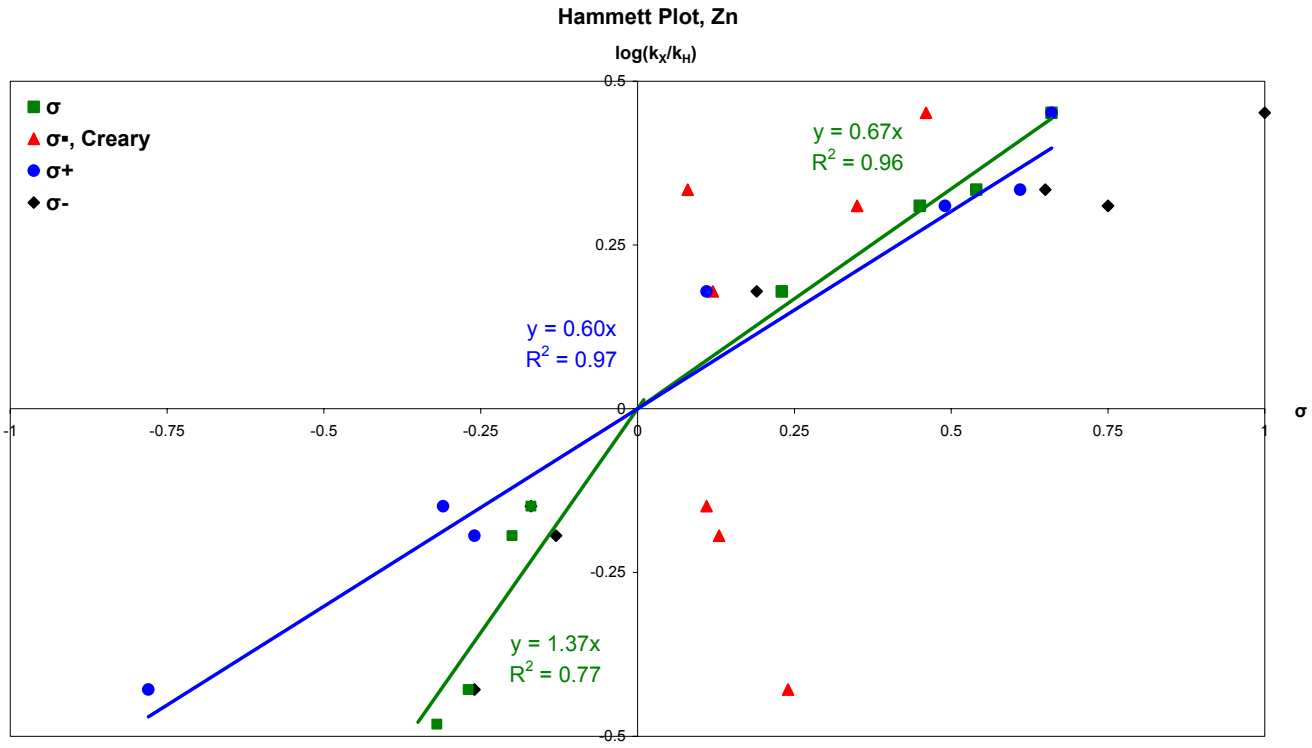


Figure A: Hammett plot for the allylation with zinc.

Table B: Data for the competition experiments with indium.

X	k_X/k_H	R^2	$\log(k_X/k_H)$	σ	σ▪, Creary	σ+	σ-
Me	0.62	0.999	-0.20761	-0.17	0.11	-0.31	-0.17
Cl	1.62	0.997	0.209515	0.23	0.12	0.11	0.19
COOMe	2.31	0.991	0.363612	0.45	0.35	0.49	0.75
CN	3.18	0.988	0.502427	0.66	0.46	0.66	1
t-Bu	0.58	0.999	-0.23657	-0.2	0.13	-0.26	-0.13
CF3	2.12	0.995	0.326336	0.54	0.08	0.61	0.65
Me	0.62	0.999	-0.20761	-0.17	0.11	-0.31	-0.17

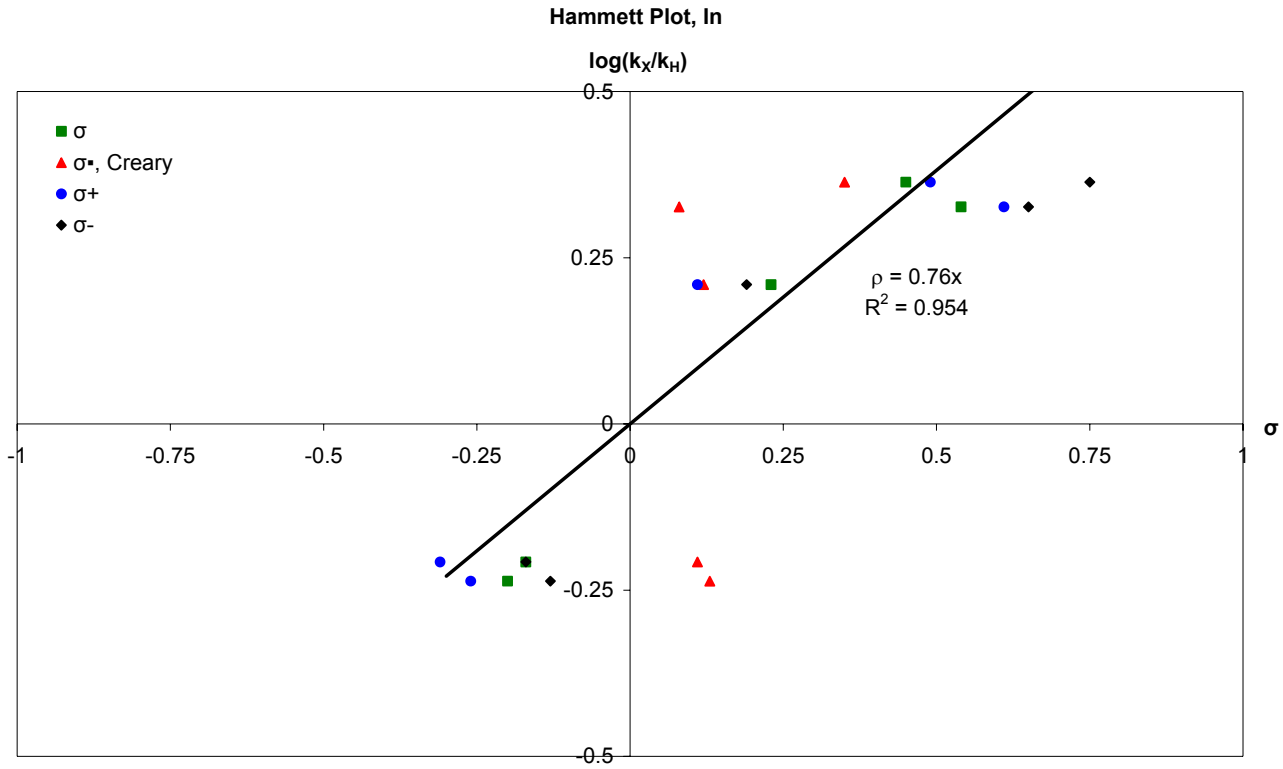


Figure B: Hammett plot for the allylation with indium.

Table C: Data for the competition experiments with tin.

X	k_X/k_H	R^2	$\log(k_X/k_H)$	σ	σ▪, Creary	σ+	σ-
OMe	0.267	0.997	-0.57349	-0.27	0.24	-0.78	-0.26
Me	0.614	0.999	-0.21183	-0.17	0.11	-0.31	-0.17
Cl	1.32	0.998	0.120574	0.23	0.12	0.11	0.19
COOMe	2.76	0.995	0.440909	0.45	0.35	0.49	0.75
CF3	3.04	0.997	0.482874	0.54	0.08	0.61	0.65
CN	4.42	0.999	0.645422	0.66	0.46	0.66	1

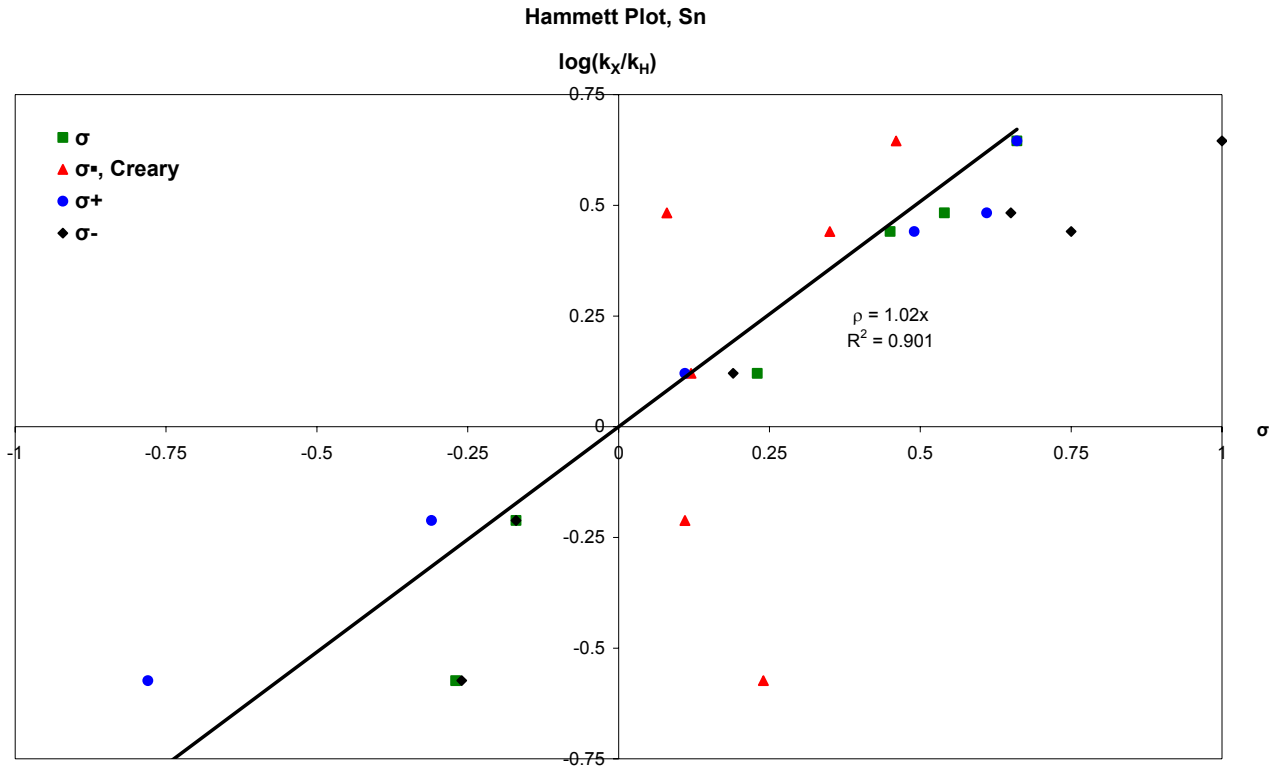


Figure C: Hammett plot for the allylation with tin.

Table D: Data for the competition experiments with antimony.

X	k_X/k_H	R^2	$\log(k_X/k_H)$	σ	σ▪, Creary	σ+	σ-
OMe	0.32	0.987	-0.49485	-0.27	0.24	-0.78	-0.26
Me	0.72	0.999	-0.14267	-0.17	0.11	-0.31	-0.17
Cl	1.45	0.997	0.161368	0.23	0.12	0.11	0.19
COOMe	2.56	0.991	0.40824	0.45	0.35	0.49	0.75
CN	5.3	0.988	0.724276	0.66	0.46	0.66	1
CF3	3.25	0.995	0.511883	0.54	0.08	0.61	0.65

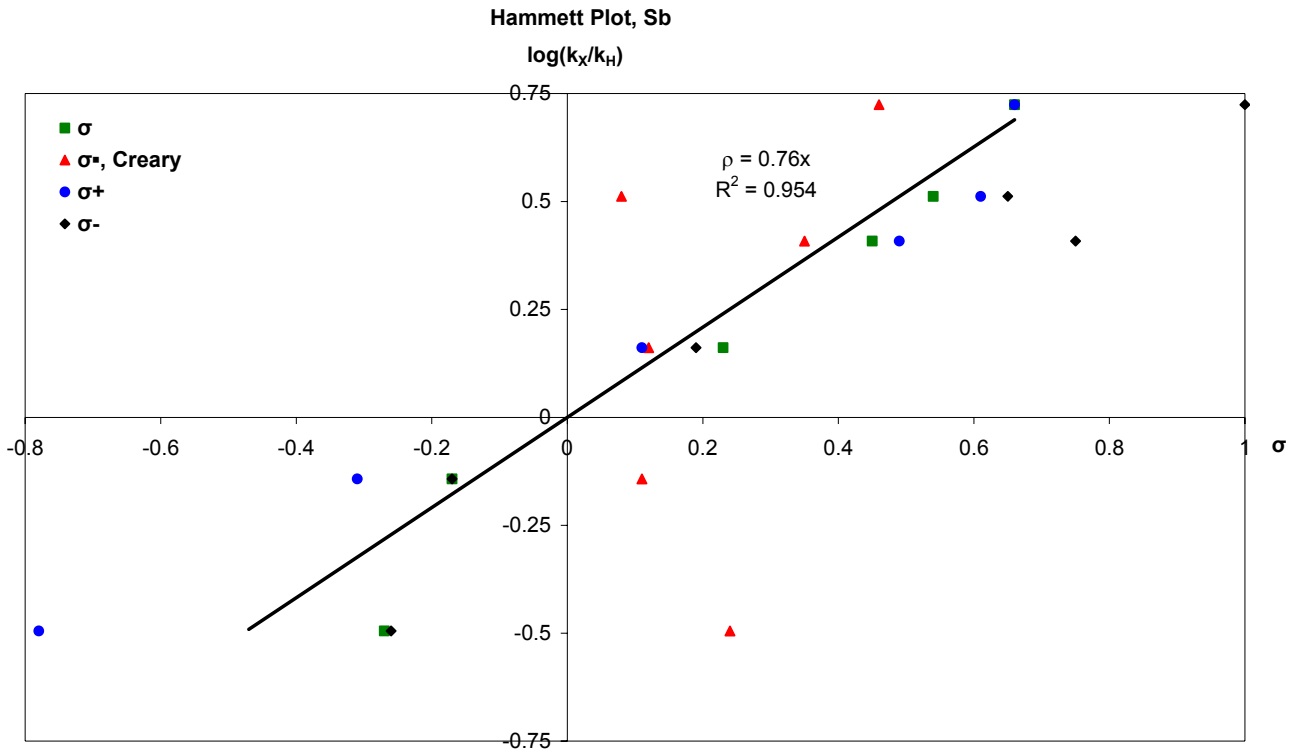


Figure D: Hammett plot for the allylation with antimony.

Table E: Data for the competition experiments with bismuth.

X	k_X/k_H	R^2	$\log(k_X/k_H)$	σ	σ▪, Creary	σ+	σ-
OMe	0.383	0.997	-0.4168	-0.27	0.24	-0.78	-0.26
Me	0.682	0.999	-0.16622	-0.17	0.11	-0.31	-0.17
Cl	1.54	0.995	0.187521	0.23	0.12	0.11	0.19
COOMe	2.59	0.998	0.4133	0.45	0.35	0.49	0.75
CF3	3.5	0.993	0.544068	0.54	0.08	0.61	0.65
CN	5.07	0.996	0.705008	0.66	0.46	0.66	1
t-Bu	0.723	0.999	-0.14086	-0.2	0.13	-0.26	-0.13

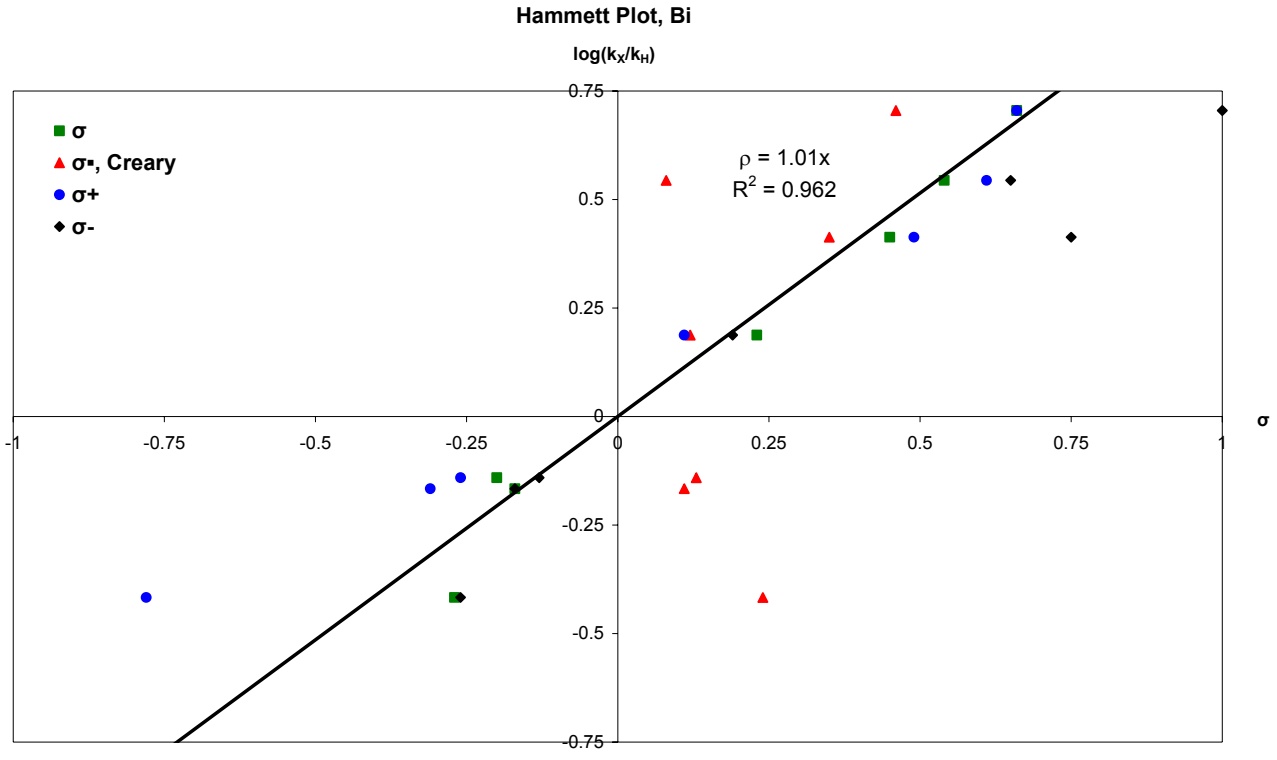


Figure E: Hammett plot for the allylation with bismuth.

Table F: Data for the competition experiments with magnesium.

X	k_X/k_H	R^2	$\log(k_X/k_H)$	σ	σ▪, Creary	σ+	σ-
Me	0.256	0.999	-0.59176	-0.17	0.11	-0.31	-0.17
Cl	4.09	0.995	0.611723	0.23	0.12	0.11	0.19
COOMe	45.6	0.998	1.658965	0.45	0.35	0.49	0.75
CF3	32.6	0.993	1.513218	0.54	0.08	0.61	0.65

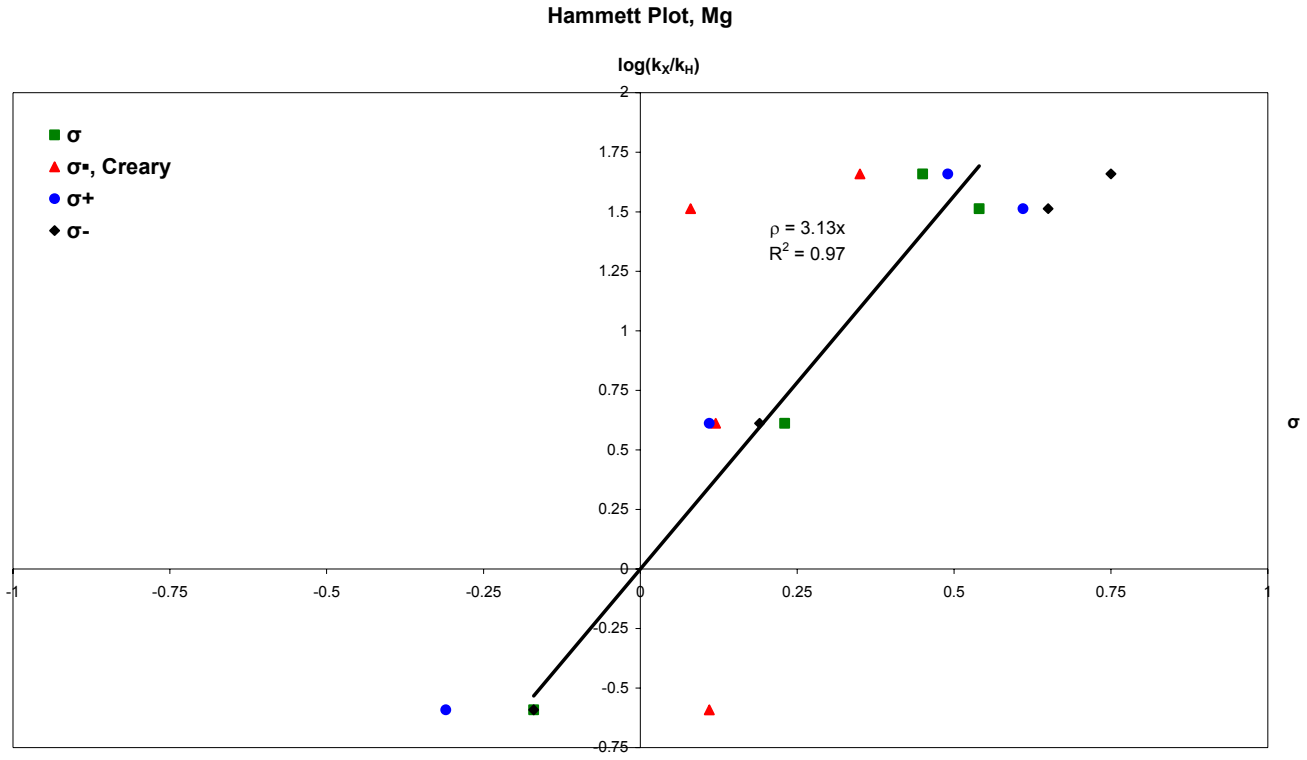
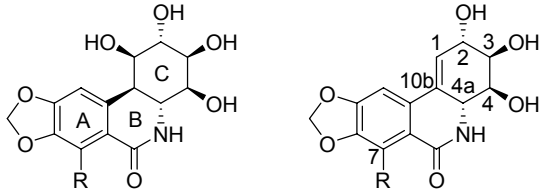


Figure F: Hammett plot for the allylation with magnesium.

2 Pancratistatin – An Overview

2.1 Introduction

Since the isolation of pancratistatin from the roots of the tropical spider lily *Pancratium Littorale* in 1984 by Pettit *et al.*, it has received a large amount of attention from the organic synthetic community.[49-54] This is in part due to the promising activity against a variety of different cancer cell lines, vira and parasites, but also because of the low bioavailability of 0.039 % based on dry plant material.[50, 55-57]



2.1 Pancratistatin, R = OH Narciclasine, R = OH
2.2 7-Deoxypancratistatin, R = H Lycoricidine, R = H

Figure 2.1: Structure of (+)-pancratistatin and related alkaloids from the *Amaryllidaceae* plant family.

Furthermore, the structure of pancratistatin offers a great synthetic challenge with its six continuous stereocenters and a highly electron-rich pentasubstituted aromatic moiety.

Several other compounds with similar activity and scarce availability have been isolated, but pancratistatin remains one of the more active compounds of the more than 100 isolated compounds from various *Amaryllidaceae* species.[58] In this connection a multitude of studies concerning the pharmacophore of pancratistatin have been reported.[52] The issue of its very low solubility in water (53 μg/mL) has been solved by installing a phosphate-residue on either the phenolic position or by generating a cyclic phosphate with the two C-ring cis-hydroxyl groups, which raises the solubility to 20 mg/mL.[59] The high activity of pancratistatin is hard to retain in unnatural and truncated analogues – even the phosphate functionalized analogues exhibit slightly lower activity.[59] It seems that at least 2-3 hydroxyls on the C-ring, the full phenanthridone ring-system along with the trans-relationship between the B and C-rings are not necessary for retaining high activity. As such even the dioxolane and the phenol-residue cannot be removed without loss of activity. Also the amide linkage in the B-ring is of importance. Removing the lactam-oxygen or replacing the lactam for a lactone lowers the cytotoxicity more than 10-fold in comparison to its natural congener.[52, 55, 60] However, simpler constituents than those shown in figure 2.1 have been isolated from natural sources and tested for activity. Pettit *et al.* found 1-deoxypancratistatin and 1,7-dideoxypancratistatin to be equally potent as pancratistatin itself when tested against a minipanel of human cancer cell lines, and at present

they comprise the minimum pharmacophore.[61-63] The development of this pharmacophore has come a long way despite the fact that the exact mechanism on a cellular level is unknown. McLachlan *et al.* suggest that pancratistatin induces apoptosis selectively in cancer cells.[64] More importantly, Kekre *et al*. have shown that pancratistatin does not harm healthy cells, which in turn could open up for efficient and non-toxic chemotherapy.[65, 66]

In regard to the synthesis of pancratistatin and its congeners many ingenious total syntheses have been reported.[52] The first synthesis was accomplished in 1989 by Danishefsky and Lee yielding racemic pancratistatin over 26 steps in less than 0.2 % yield. (See table 2.1). Not until 1995 was the first enantioselective synthesis achieved by Hudlicky *et al.* in one of the shortest feats still in a 2 % overall yield over 14 steps. Since then eight total syntheses, including two formal ones and a semi-synthetic, have been reported spanning from 0.4 % to 7.4 % yield over 10 to 22 steps.[67-76]

In the following section each published total synthesis of pancratistatin will be discussed shortly with focus on the key steps that have enabled the full synthesis.

Table 2.1: Overview of the existing total syntheses of pancratistatin.

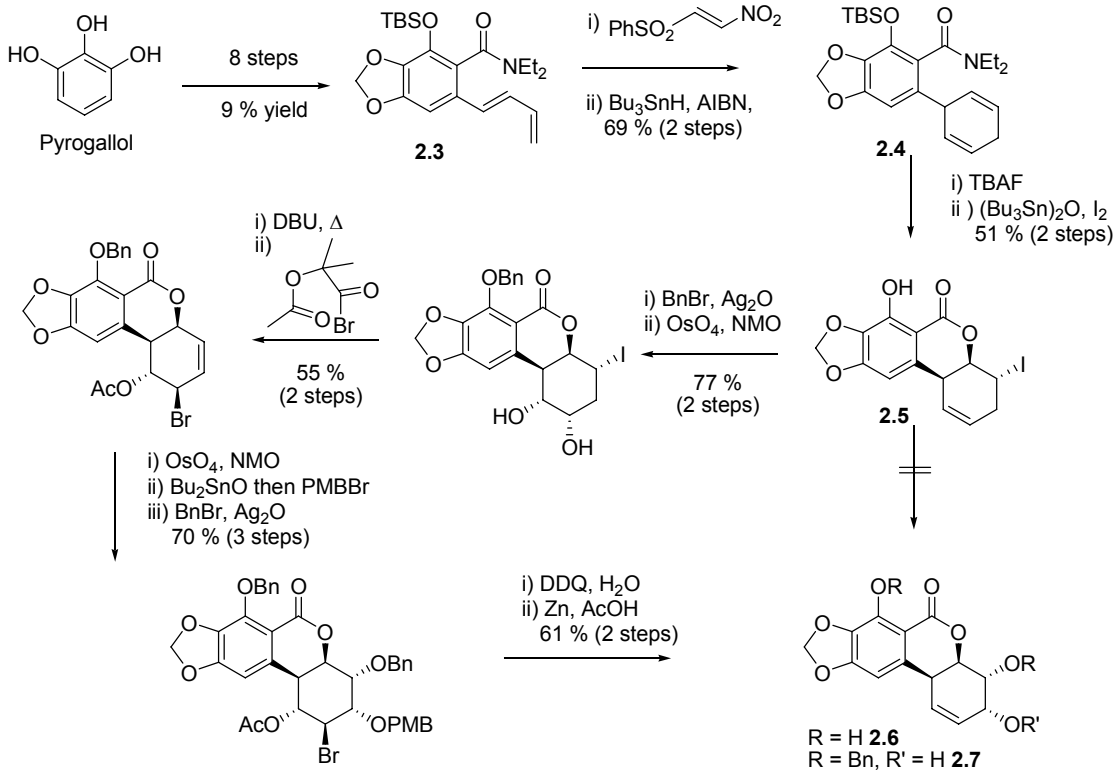
Synthesized by	Publication year	Total steps	Starting material	Comments
Danishefsky & Lee[67]	1989	26	Pyrogallol	Racemic, < 0.2 % yield, linear.
Hudlicky & Co-workers[58, 68]	1995	14	Bromobenzene & piperonylic acid	Enantioselective, 2 % yield, convergent.
Trost & Pulley[69]	1995	17	Benzoquinone & *o*-vanillin	Enantioselective, 7.4 % yield, convergent.
Haseltine & Co-workers[70]	1997	22[a]	Anthrone, benzoquinone & piperonol	Formal synthesis, 4.7 % yield[a], convergent.
Magnus & Sebhat[71, 77]	1998	22	*o*-Vanillin & 1,4-cyclohexanedione monoethylene acetal	Enantioselective, 1.2 % yield, convergent.
Rigby, Maharoof & Mateo[72]	2000	22	2,3-dihydroxybenzaldehyde & 3-cyclohexene-1-carboxylic acid	Enantioselective, < 0.4 % yield, convergent.
Pettit, Melody & Herald[73]	2001	10	Narciclasine	Semi synthetic, 3.6 % yield.
Kim & Co-workers[74, 78]	2002	21	Methyl gallate & 5-bromo-3-methoxysalicylaldehyde	Racemic (2.1 % yield) + formal enantioselective, both linear.
Li, Wu & Zhou[75]	2006	12	Pinitol & 2,3-dihydroxybenzaldehyde	Enantioselective, 2.2 % yield, convergent.
Crich & Krishnamurthy[76]	2006	~10[b]	Resorcinol	Formal synthesis[b], linear.
Dam & Madsen[c]	2009	15	Piperonal & D-xylose	Enantioselective, 7.1 % yield, convergent.

a) 5 steps short. **b**) 14 steps short. **c**) This dissertation.

2.2 Danishefsky & Lee's Approach

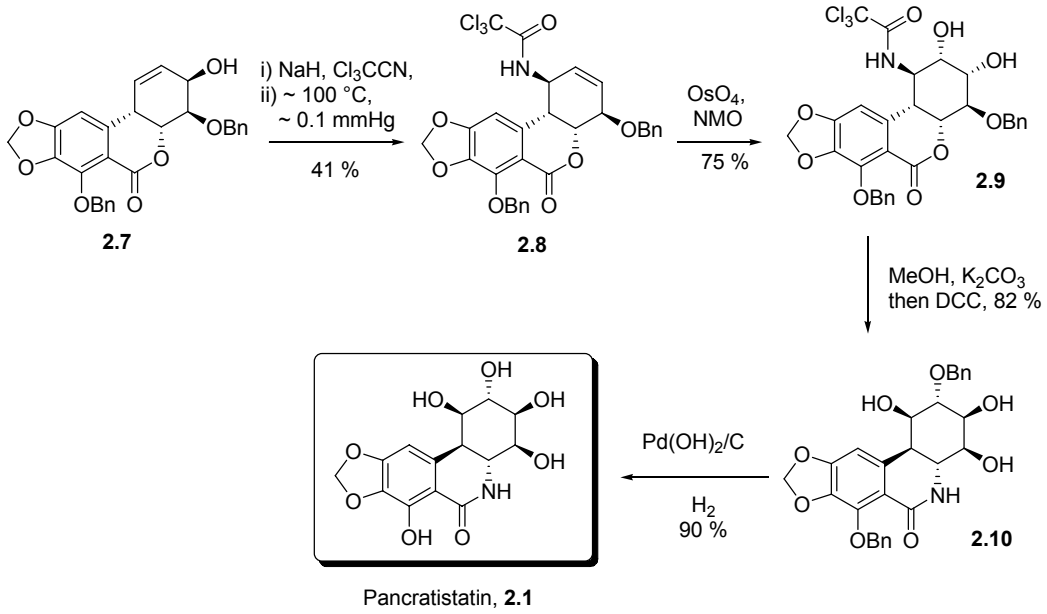
In the Danishefsky and Lee total synthesis from 1989 pyrogallol served as the starting material for the linear synthesis.[67] (Scheme 2.1). After a rather low-yielding sequence to produce diene **2.3** for the Diels-Alder reaction, the C-ring and the fully functionalized A-ring were formed. Attempts to halolactonize onto cyclohexene **2.4** failed due to steric repulsion between the silyl ether and an intermediate iminium ion. Removal of the TBS-group provided a free phenol that performed sluggishly in the lactonization. Increasing the nucleophilicity of the amide functionality by stannylation of the phenol produced the desired lactone **2.5** in a moderate 67 % yield. Unfortunately, all attempts to generate the conjugated diene from **2.5** by treatment

with base yielded a fully aromatized C-ring. A rather lengthy deroute, containing a series of dihydroxylations and a Moffatt transposition, gave rise to the mono-protected diol **2.7** – the Danishefsky lactone.[79, 80] The transposition with 2-acetoxyisobutyryl bromide afforded a mixture of two isomers in a ratio of 63:25 in favor of the desired product.



Scheme 2.1: Danishefsky and Lee's approach.

With the lactone **2.7** in hand focus was turned to completing the synthesis based on the lactone to lactam reorganization (**2.9** to **2.10**) in accordance with previously published accounts by Ohta *et al.* and Paulsen and Stubbe, scheme 2.2.[81, 82] The elegant endgame started out with an Overman rearrangement,[83, 84] which was accomplished under interesting conditions: It was most efficiently achieved under pyrolysis-like conditions, *i.e.* the imidate was heated to ~100 ºC at ~0.1 mmHg for 1.2 h to provide the rearranged product **2.8** in acceptable 56 % yield (from the imidate). Next followed the dihydroxylation of **2.8** from the concave face of the bicyclic system. It was found that the lactamization to produce **2.10** would not take place in refluxing methanol and K_2CO_3 – instead Danishefsky and Lee speculated that an amino acid was formed, and by treatment with DCC the lactam was produced in good yield.

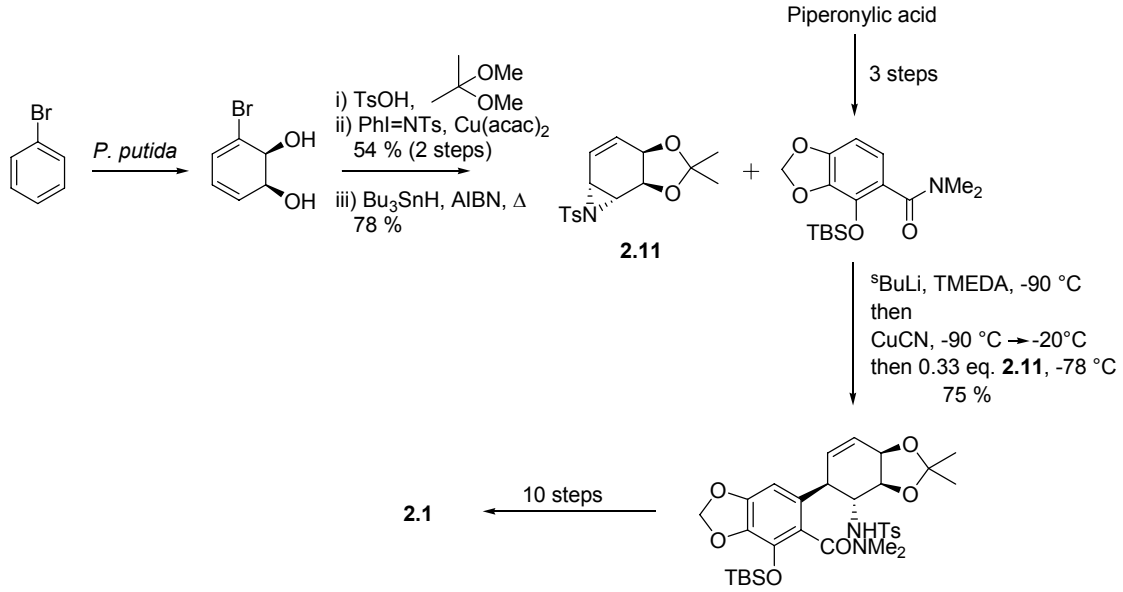


Scheme 2.2: End-game in Danishefsky and Lee's approach.

Global deprotection delivered pancratistatin in 26 steps and an overall yield of less than 0.2 %.

2.3 Hudlicky & Co-workers' Approach

The total synthesis by Hudlicky and co-workers took off by elaborating the pancratistatin C-ring (scheme 2.3).[58, 68] The enantiodiscriminating step was the first transformation in the synthesis and involved a whole cell oxidation of bromobenzene with *Pseudomonas Putida* 39/D. Key to the synthesis was the selective 1,2-addition of a nucleophile to C-10b (pancratistatin numbering) on a functionalized vinylaziridine **2.11** from the concave face of the system. This transformation was best done by a higher order cuprate-addition to afford aziridine opening, where other cuprates and Grignard reagents afforded 1,4-addition from the convex face.

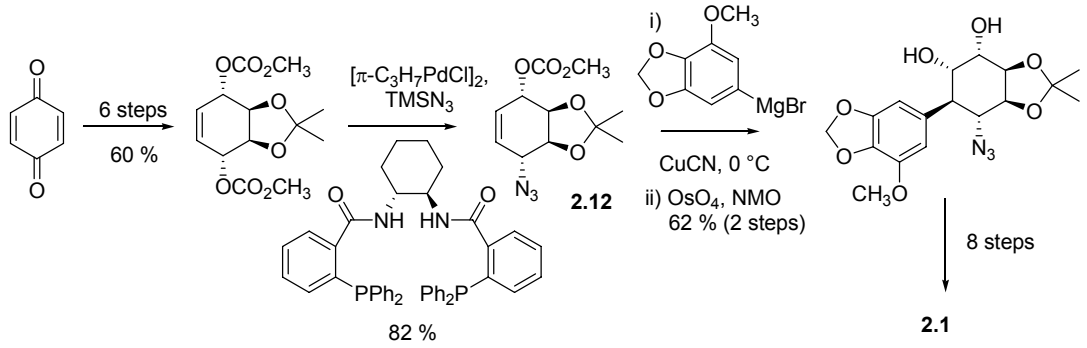


Scheme 2.3: Hudlicky & Co-workers' approach.

After some protection group interchange and C-ring manipulation the total synthesis was completed in a total of 14 steps in a 2 % overall yield.

2.4 Trost & Pulley's Approach

Within the same year as Hudlicky and co-workers' account, the second asymmetric total synthesis appeared.[69] (Scheme 2.4). Like in Hudlicky's approach, the enantioselectivity was determined early in the synthesis by a palladium-catalyzed desymmetrization with a chiral ligand. Again, the pivotal issue was the stereocontrolled S_n2'-addition to form the A- to C-ring connection. Trost and Pulley found that a one-pot addition of a low-order cuprate from the concave face of **2.12** would yield the desired product. It was immediately dihydroxylated due to purification difficulties.

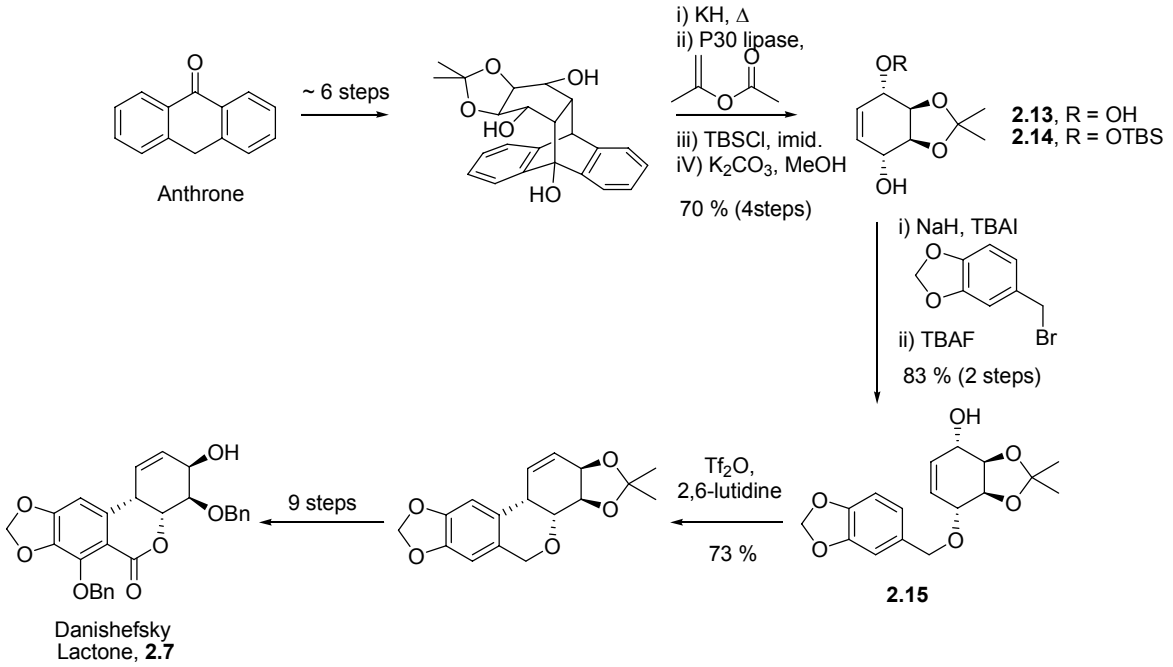


Scheme 2.4: Trost & Pulley's approach.

This formed a similar intermediate as in the Hudlicky approach, and pancratistatin was synthesized in another eight steps in a 7.4 % overall yield.

2.5 Haseltine & Co-workers' Approach

Haseltine *et al.* saw that a similar conduritol (**2.12** and **2.13**) as in Trost and Pulley's synthesis could be synthesized in a different manner.[70] By employing a published protocol utilizing a Diels-Alder cycloaddition between the potassium salt of anthrone and benzoquinone they were able to obtain a protected conduritol. Retro Diels-Alder with KH released the functionalized product and one enzymatic acetylation generated the conduritol **2.13** selectively after some protecting group manipulations. An enzymatic acetylation was applied to differentiate between the two alcohols ultimately leading to an asymmetric synthesis.

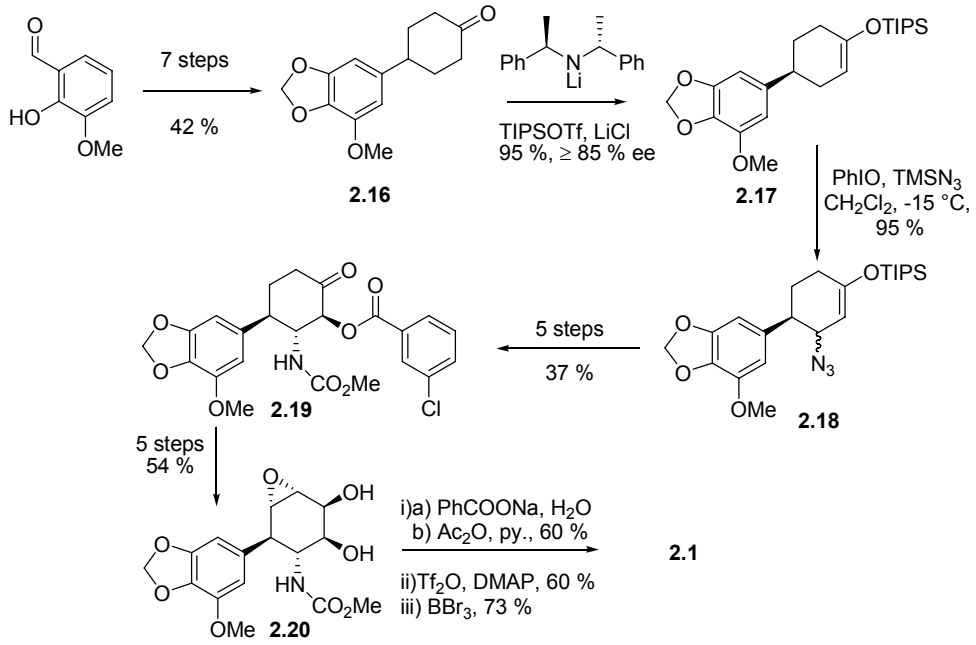


Scheme 2.5: Haseltine & Co-workers' approach.

Simple ether formation generated compound **2.15** containing the A- and C-ring. Haseltine *et al.* quickly found that having the pentasubstituted A-ring only led to a low yield of the desired product when treated with triflic anhydride and base. Instead, they were able to form the B-ring in good yield without the phenolic residue in the 7-position. The phenolic oxygen was installed by a late stage lateral metallation. They concluded the formal synthesis by synthesizing the Danishefsky intermediate **2.7** in another 9 steps – 5 steps short of a total synthesis.

2.6 Magnus & Sebhat's Approach

In the total synthesis by Magnus and Sebhat treatment of a prochiral cyclohexanone **2.16** with a chiral lithium amide was key to synthesize an enantiomerically enriched silyl enolate **2.17** in excellent yield.[71, 77]



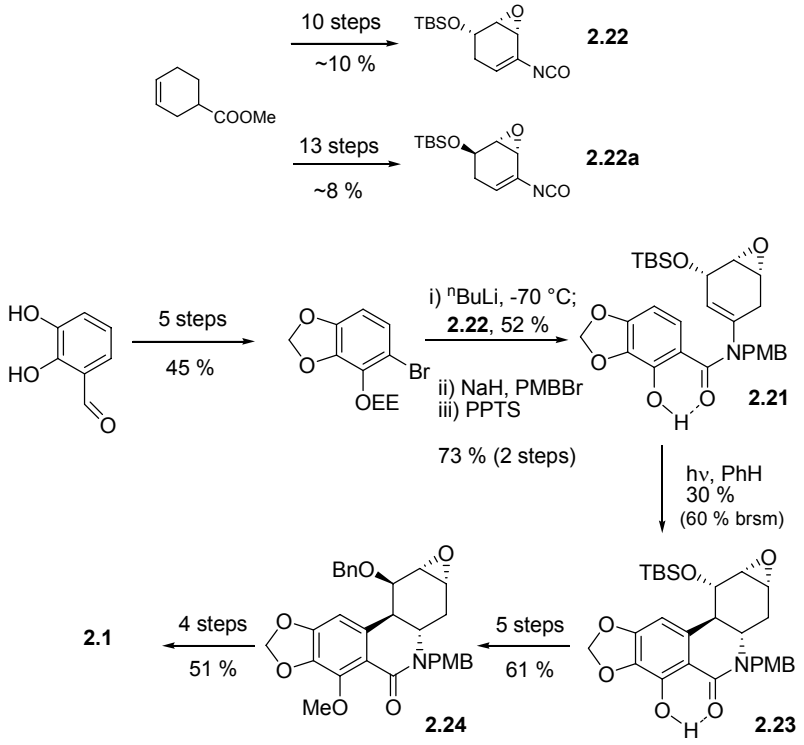
Scheme 2.6: Magnus & Sebhat's approach.

Subsequent treatment with iodosyl benzene and trimethylsilyl azide installed the allylic azide as a 3.5:1 mixture of diastereoisomers in favor of the desired trans isomer. A lengthy sequence was necessary to set up the stereocenters on the C-ring and make the proper B-ring connectivity. It took Magnus and Sebhat five steps to introduce the new stereocenter in **2.19** and protect the amine. Another five steps were required to install the epoxide of **2.20** and reduce the ketone selectively. The synthesis was completed in four steps from **2.20**, where the B-ring was secured by a Bischler-Napieralski reaction with Tf_2O, providing (+)-pancratistain in a longest linear sequence of 22 steps and a 1.2 % overall yield.

2.7 Rigby, Maharoof & Mateo's Approach

In the Rigby, Maharoof and Mateo total synthesis, the pivotal issue was a hydrogen bond-controlled aryl enamide photocyclization.[72] (Scheme 2.7). It was soon realized that without protection of the nitrogen in **2.21**, the photocyclization yielded an undesired regioisomer. The isocyanate **2.22a** was originally thought to have the proper setting for the C-ring

functionalization. Instead, it generated the wrong trans relationship between the B and C-ring during photocyclization to **2.23**. The requisite enamide precursor **2.22** was synthesized in 10 steps including an enzymatic resolution. This is three steps shorter than for **2.22a**, but necessitated inversion of a stereocenter on the C-ring of **2.23** through an unpleasant deprotection, oxidation-reduction and reprotection sequence to give **2.24**.

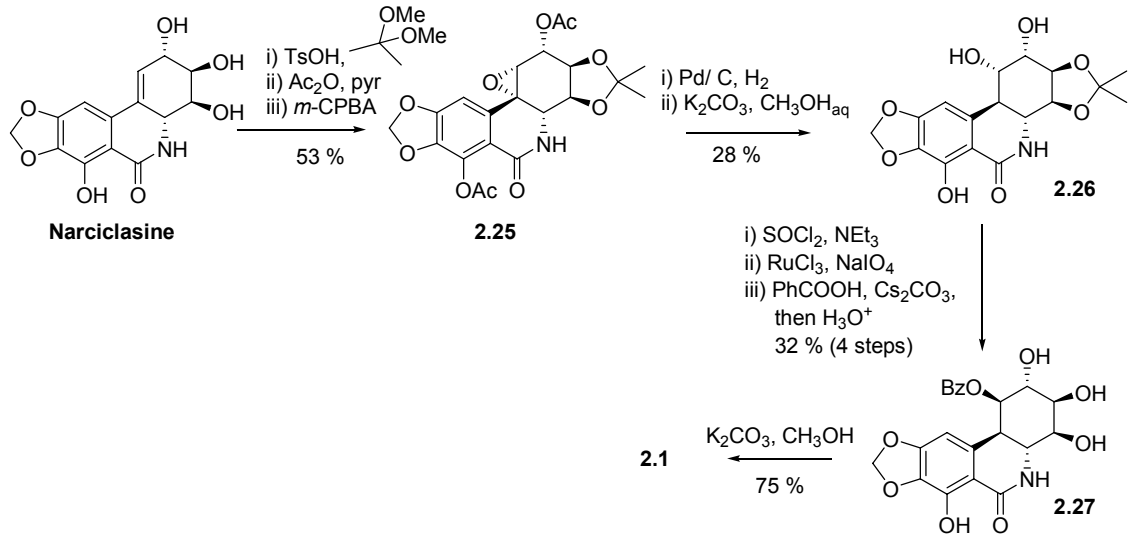


Scheme 2.7: Rigby, Maharoof & Mateo's approach.

Attempts to improve the yield of the photocyclization by switching to a solvent with less light absorbance failed, and unreacted enamide **2.21** was recycled. With the full phenanthridone system completed, the C-ring was elaborated in another four steps to give pancratistatin in a 0.35 % overall yield.

2.8 Pettit, Melody & Herald's Approach

While pancratistatin is scarce in plant material, narciclasine is much more abundant (up to 200 mg/ Kg wet plant material). Pettit, Melody and Herald reported a transformation of narciclasine into pancratistatin in an effort to make the latter more abundant, scheme 2.8.[73]

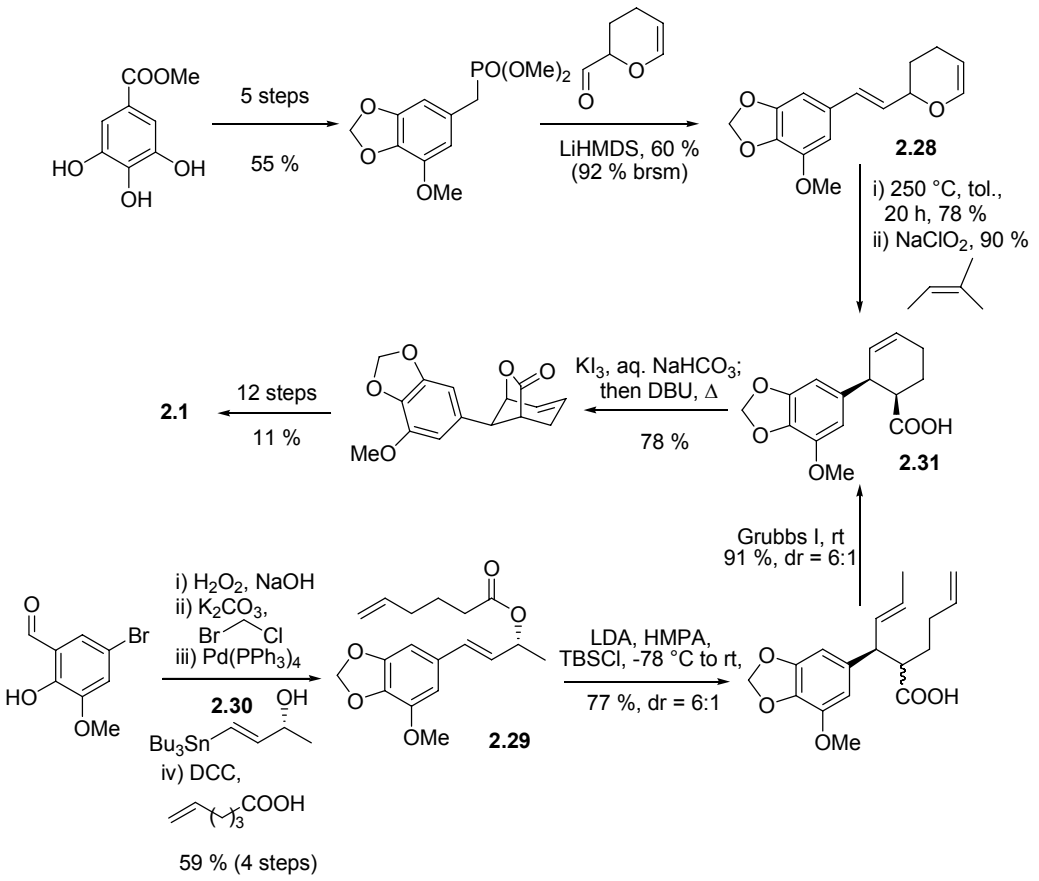


Scheme 2.8: Pettit, Melody & Herald's approach.

After global protection of narciclasine a low-yielding epoxidation followed to yield **2.25**. The epoxide was opened by hydrogenation and successive saponification of the esters generated **2.26**. Only 28 % of the desired product **2.26** was isolated with another 48 % combined yield of three other isomeric compounds. Transforming the diol **2.26** into a cyclic sulfate suffered from difficulties in oxidizing the sulfite epimers and hence a superstoichiometric amount of periodate was applied leading to a low yield. Although Pettit, Herald and Melody only required a ten-step procedure to synthesize pancratistatin, a number of low-yielding steps were involved giving an overall yield of only 3.6 %. Interestingly, all their compounds from narciclasine were screened for biological activity and compound **2.27** was found to possess increased activity compared to both narciclasine and pancratistatin.

2.9 Kim & Co-workers' Approaches

In the Kim and co-workers' first approach[74, 78] the highlight of the synthesis encompassed a Claisen rearrangement of **2.28** to afford the unfunctionalized C-ring in good yield (Scheme 2.9). The reaction was performed at 250 ºC because the reaction had to go through a boat-like transition state. The remaining stereocenters and the B-ring was completed in another 14 steps to yield pancratistatin in 2.1 % overall yield.

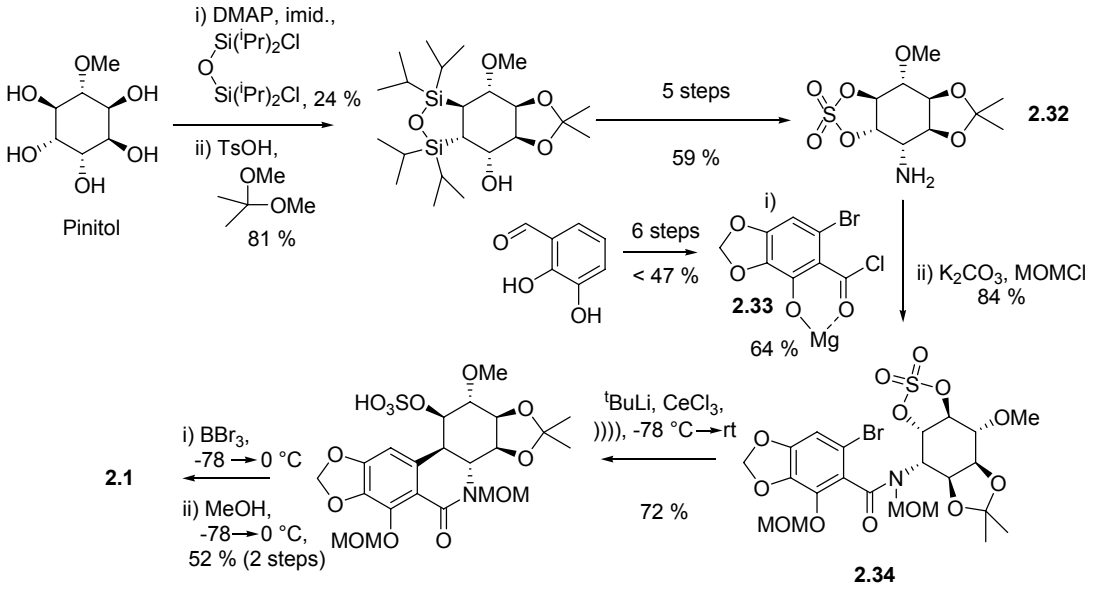


Scheme 2.9: Kim & Co-workers' approaches.

The second approach involved an enantioselective Ireland-Claisen rearrangement of **2.29**, where the stereogenic information from the enzymatically available alcohol **2.30** was transferred into two stereocenters under very mild conditions. Two diastereoisomers were formed, but first separated after ring-closing metathesis and iodolactonization, where the undesired isomer did not react. Fortunately, the desired isomer **2.31** was the major product from the rearrangement of **2.29**. Although their enantioselective route was shorter, Kim *et al.* did not complete the synthesis to produce pancratistatin enantioselectively.

2.10 Li, Wu & Zhou's Approach

The total synthesis by Li, Wu and Zhou represents the shortest route to date.[75] The synthesis started from the rather expensive pinitol containing five of the six stereocenters in pancratistatin (Scheme 2.10). They were only able to protect pinitol in a very low yield eventually affording one fragment, **2.32**, for further coupling to their activated acid chloride, **2.33**.

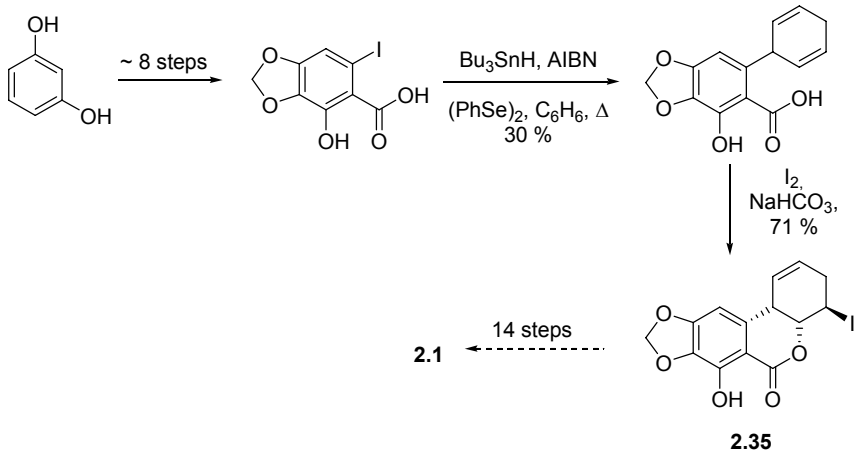


Scheme 2.10: Li, Wu & Zhou's approach.

After some experimentation, it was found that transmetallation to afford a softer cerium-nucleophile would lead to the desired opening of the cyclic sulfate of **2.34** and set the last stereocenter required for the pancratistatin configuration. By applying sonication, they achieved full conversion and shortened the reaction time. After careful global deprotection in two steps, pancratistatin was synthesized in 2.2 % overall yield over 12 steps.

2.11 Crich & Krishnamurthy's Approach

As part of a method development program about dearomatizing benzene Crich and Krishnamurthy produced compound **2.35**, which is an intermediate in the synthesis by Lee and Danishefsky (Scheme 2.11).[76] The synthesis was not completed as it required additional 14 steps to yield racemic pancratistatin and therefore represents a formal synthesis.



Scheme 2.11: Crich & Krishnamurthy's approach.

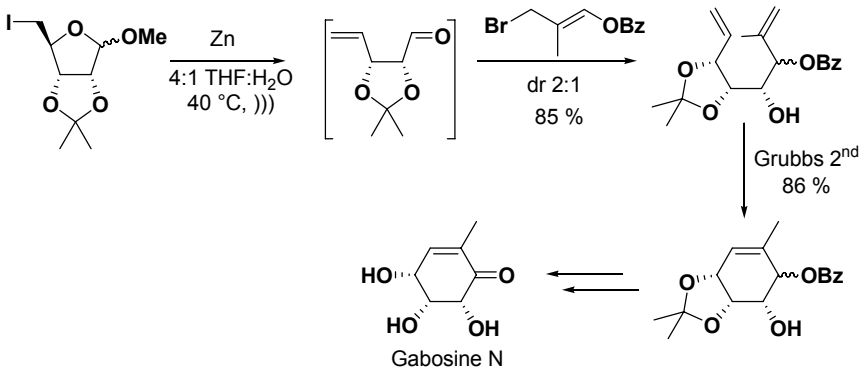
Crich and Krishnamurthy were only able to cut about three steps off the original synthesis. Because of the low yield in the radical dearomatization and the issue of the required Moffat transposition – see scheme 2.1 – from intermediate **2.35** the synthesis does not really address the original problem with regard to improved availability and synthetic efficiency.

3 Total Synthesis of (+)-Pancratistatin

3.1 Introduction

Carbohydrates are densely functionalized compounds and are as such an interesting renewable starting material for chemical synthesis. Madsen *et al.* have in a series of studies reported the successful application of carbohydrates as chiral pool starting materials for total synthesis.[25, 26, 28-30, 85, 86]

In this connection a sequence for converting a properly functionalized carbohydrate into a cyclohexene with retention of the absolute stereochemistry has been developed in the group. In this sequence it is not only some of the stereocenters that are set, but the carbocyclic framework is also formed. The method comprises a fragmentation of a carbohydrate to provide an enal that contains two new handles for further manipulations, an alkene and an aldehyde. By reaction with the proper allylating reagent a new stereocenter can be created along with chain elongation. Ring closing metathesis will form the carbocyclic framework. An example of the sequence is shown in scheme 3.1.[30]



Scheme 3.1: Example of the one-pot fragmentation-allylation reaction.

In connection to the allylation study in chapter 1 it was decided to undertake the enantioselective synthesis of (+)-pancratistatin along the lines of the previous synthesis in the group of 7-deoxypancratistain.[28] In this synthesis the fragmentation-allylation sequence produced an advanced intermediate eventually leading to 7-deoxypancratistatin.[28] With improved knowledge of the mechanism behind the Barbier-allylation the hope was to improve the overall yield. The methodology would additionally be pushed to the limit because of the increased steric bulk and large electron density in the allylating reagent.

3.2 Retrosynthetic Analysis

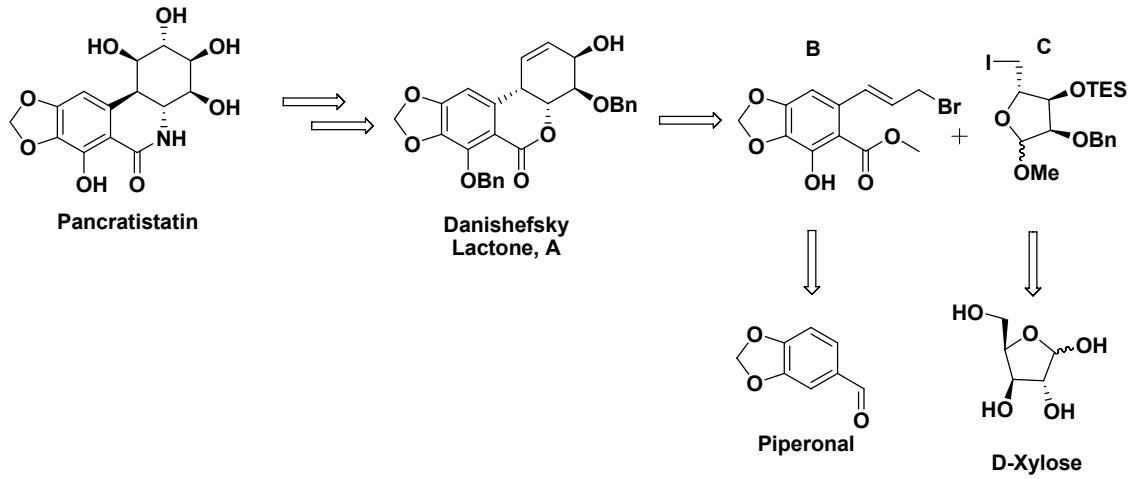
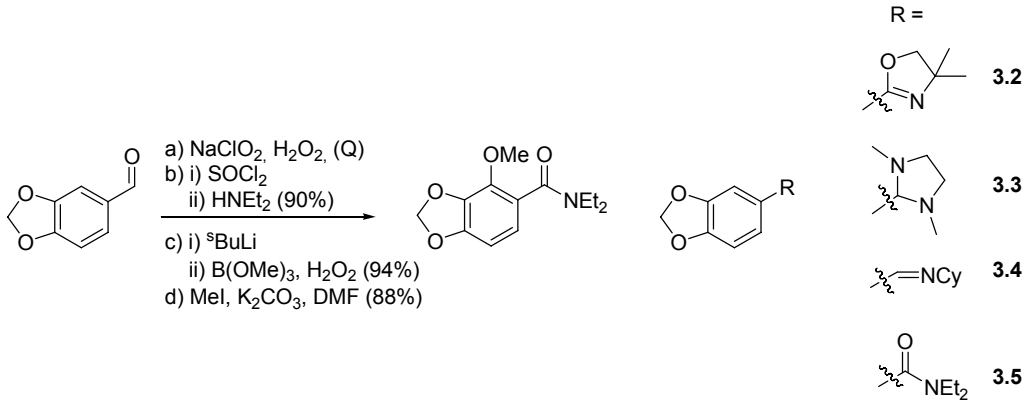


Figure 3.1: Retrosynthetic analysis for the synthesis of (+)-pancratistatin.

The strategy was to intercept the synthesis of Danishefsky and Lee by synthesizing the allylic alcohol, **A**, an intermediate in their pioneering synthesis.[67] This alcohol was envisioned to be synthesized from the allylating reagent **B** and the ω-iodoribofuranoside **C** by means of the fragmentation-allylation protocol earlier applied in the Madsen group.[25, 28-30, 87] The absolute stereochemistry of the alcohol **A** would originate from the functionalized carbohydrate **C** with ribo-configuration. In order to differentially protect the two alcohols in the furanoside, this substrate was generated from D-xylose by a procedure previously utilized in the synthesis of 7-deoxypancratistatin. The allylating reagent **B** could arise from commercially available piperonal or the carboxylic acid equivalent, piperonylic acid.

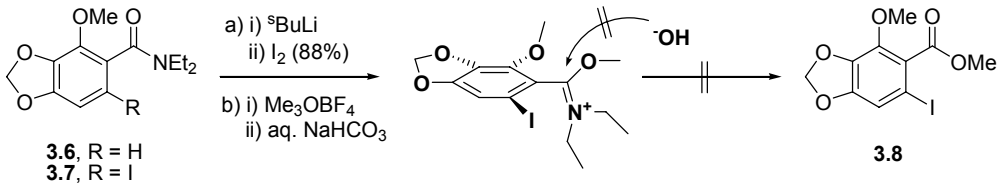
3.3 Synthesis of the Allyl Bromide

The work towards the allylating reagent was inspired by the work of PhD Anders Håkansson *et al.* in their total synthesis of 7-deoxypancratistatin.[28] While their tetrasubstituted allylating reagent was accessible in six steps, the synthesis of the pentasubstituted allylating reagent **3.1** to provide pancratistatin was a bit steppier. Although piperonylic acid is commercially available it was chosen to start the synthesis with piperonal in course of the much higher price of the acid and the ease by which the aldehyde was oxidized under Pinnick conditions.[88] In order to obtain synthetically useful yields, a tertiary amide (**3.5**) was implemented as directing group to install the phenol required for the full substitution pattern in pancratistatin. Substantially lower yields were obtained, when an oxazole **3.2** (8%), a 1,3-dimethylimidazolidine **3.3** (33%) or the *N*-cyclohexylimine **3.4** (69%) were used as directing groups.[89]



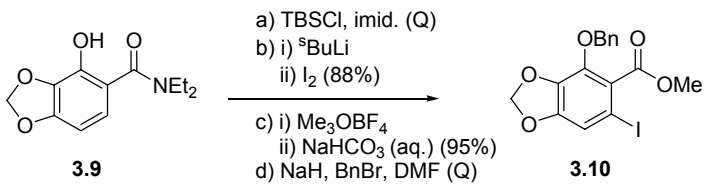
Scheme 3.2: Installation of the phenolic residue with different directing groups.

Early studies toward the desired allylating reagent showed that regioselective bromination was troublesome. Thus electrophilic bromination with Br_2 on the system containing the required phenolic residue to eventually provide the full pentacyclic system for pancratistatin went in low yield to the wrong regioisomer. *Directed ortho metalation* of the amide **3.6** and quench with iodine provided useful yields of the substrate **3.7** for the Heck cross-coupling, but first the amide had to be manipulated. In accordance with Keck *et al.* conversion of the tertiary amide to the methyl ester **3.8** with Meerwein's reagent was low-yielding, when both ortho positions next to the amide are blocked by permanent substituents.[90, 91]



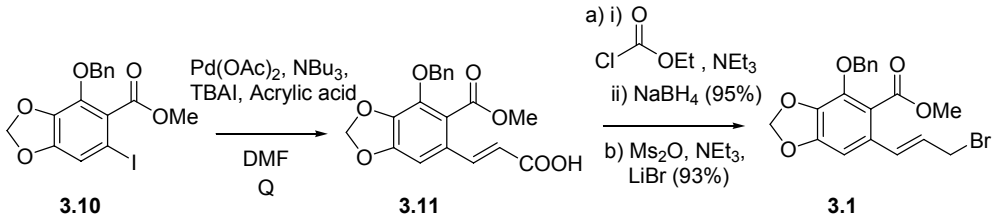
Scheme 3.3: **Attempted conversion of the tertiary amide.**

Furthermore all attempts to deprotect the methyl ether **3.7** were met with failure under a range of standard conditions (*e.g.* LiI, LiCl and NaCN in DMF, propanethiolate, thiophenolate and BBr_3) due to simultaneous removal of the dioxolane. Further optimization of this conversion proved unsuccessful and focus was turned to applying the protocol reported by Keck *et al.*



Scheme 3.4: Successful conversion of the amide to the methyl ester.

Therefore the phenol **3.9** was quantitatively TBS-protected, the iodide was installed in excellent yield and the tertiary amide was then converted to the methyl ester without event. It was chosen to protect the phenol as the corresponding benzyl derivative **3.10** since the synthesis eventually would intercept the total synthesis by Danishefsky and Lee and the formal synthesis by Doyle *et al.*[67, 70] Initially the Heck cross-coupling conditions earlier applied in the group was utilized, but only provided the desired product (**3.11**) in moderate yield. It is known that addition of phosphines can suppress cross-coupling, when the substrate is an aryl iodide.[92] Under Jeffery conditions the addition of phosphines is not required and the coupling was performed under these conditions in quantitative yield, only dropping slightly on a 11 g-scale.[93]

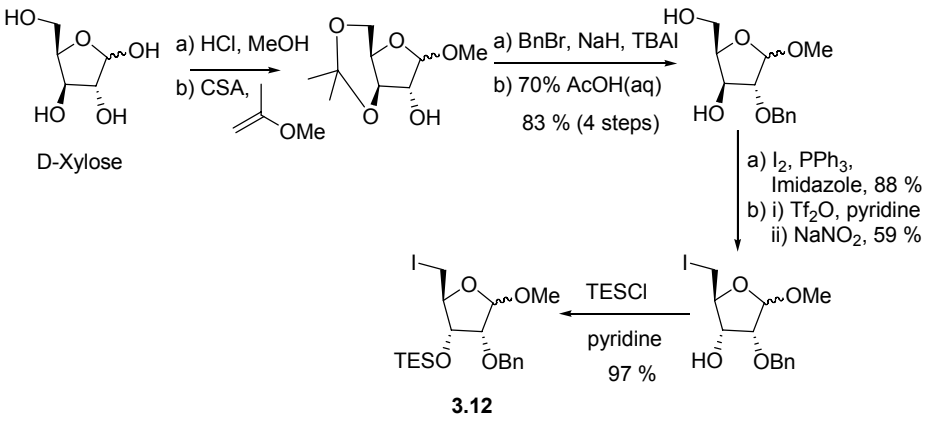


Scheme 3.5: Preparation of the allylating reagent.

Subsequent reduction of the carboxylic acid without affecting the ester was carried out *via* the carbonic anhydride. A one-pot displacement of the primary alcohol was accomplished using methanesulfonic anhydride and LiBr. Hydrobromic acid was utilized in the work-up to avoid the formation of the primary chloride. The allylating reagent **3.1** was now available in multigram quantities in nine steps from commercially available piperonylic acid. The reagent is fully stable up to seven months at ambient temperature, but decomposes rapidly on dry silica gel.

3.4 Synthesis of the ω-Iodoribofuranoside

The carbohydrate coupling partner **3.12** was synthesized uneventfully in similar yields as Håkansson *et al*.[28]



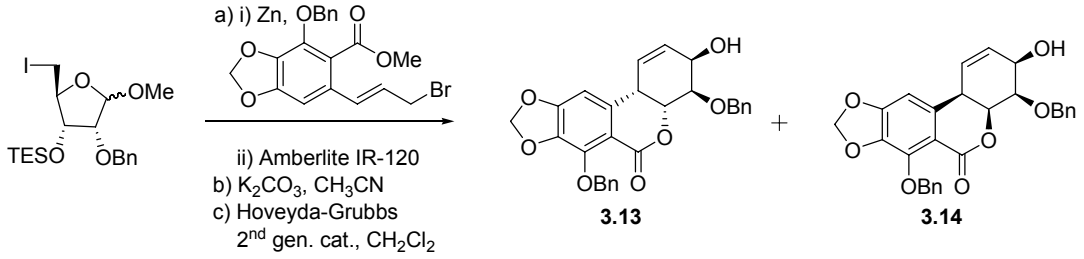
Scheme 3.6: Synthesis of the ω-iodoribofuranoside.

3.5 Synthesis of the Danishefsky Lactone

With both the iodosugar **3.12** and the allylating reagent **3.1** in hand attention turned to the fragmentation-allylation-metathesis sequence. Initially, conditions applied by our group in the synthesis of 7-deoxypancratistatin were low-yielding.[28, 87] The use of activated zinc-powder was found to be a necessary precaution since the Vasella-type reductive fragmentation otherwise would be slow to initiate.[94, 95] When Zn* was applied the fragmentation was smooth and full conversion to the corresponding enal was achieved within 1-2 h without racemization. It was also quickly realized that the compounds were reluctant to lactonize and consequently produced an inseparable mixture of two diastereoisomers. This obstacle was overcome by basic lactonization in refluxing CH_3CN and after RCM the two isomers **3.13** and **3.14** could be separated by flash chromatography. The Hoveyda-Grubbs 2nd generation catalyst was found better than Grubbs 2nd generation catalyst in terms of purification of the product. Although the yield was comparable to the yield in the synthesis of 7-deoxypancratistatin the diastereomeric ratio was somewhat poorer. Efforts to improve this ratio included allylation conditions earlier investigated by us.[96] Stepwise fragmentation and allylation with tin and indium did not provide any product and allylation in aqueous NH_4Cl with zinc only led to minor diastereomeric excess in low yields. Changing the H_2O:THF-ratio from 1:3 to 1:9 did indeed improve the ratio to 5:1 in favor of the desired product, but still not in synthetically useful yields. The most successful conditions were found to correspond to the Jaworsky and Gilman conditions to minimize Wurtz coupling.[97-99] These conditions included large excess of metal, high dilution of reagents and

slow addition of the allylating reagent. Hence the excess of the more inaccessible allylating reagent could be lowered to 1.5 equiv. from 3 equiv. by Håkansson *et al*.[28] In this work higher yields were obtained with Jaworsky conditions and when simultaneous fragmentation and allylation in 1:3 H_2O:THF during sonication and slow, continuous addition of the allylating reagent were applied. Although this procedure suffered from poor diastereomeric excess the good yield provided material to finish the synthesis. Reproducible yields were obtained on a routinely basis when 1-2 vol % of a liquid detergent was added to the sonication bath for better dispersion of the ultrasound.

Table 3.1: One-pot fragmentation, allylation and ring-closing metathesis.



Entry	Metal	Method	dr (3.13:3.14)	Yield (%)	Comment
1	Sn	A	-	0	
2	In	A	-	0	
3	Zn	B (NH_4Cl)	1.3:1 to 1.7:1	24-27	
4	Zn	C	1.5:1	14	40 % H_2O in THF
5	Zn	C	5:1	22	10 % H_2O in THF
6	Zn	C	1.5:1	38	25 % H_2O in dioxane
7	Zn	C	1.1:1	67	25 % H_2O in THF

Method A: The carbohydrate was fragmented with Zn under sonication, filtered through Celite and redissolved in THF: H_2O. The allylating reagent and the metal were added and the slurry was stirred (without sonication) for several hours. In the case of Sn the slurry was heated to 60 ºC in accordance with previous work.[96]

Method B: The carbohydrate was fragmented with Zn under sonication – after complete fragmentation sat. aq. NH_4Cl was added and the allylating reagent was added slowly by syringe plunger under vigorous stirring (without sonication).

Method C: The carbohydrate was fragmented with Zn under sonication while the allylating reagent was added by syringe plunger over 5 h.

The diastereomeric outcome of the allylation can be rationalized from the Felkin-Anh model and the Cram chelate model.[100-103] Earlier Paquette and Mitzel reported minor erosion of the diastereoselectivity in the allylation of α-oxygenated aldehydes with indium when water was present and sonication was applied.[104] Therefore chelation control must still be applicable. If the chelate model should yield the two observed diastereomers the transition state involves a high-energy boat conformation in both cases, figure 3.2, eq. A and B. This seems unlikely. Evans *et al*. have shown that under non-chelating conditions anti-α,β-bisalkoxy aldehydes yield products with an anti-relationship with regard to the newly formed stereocenter and the α-alkoxy substituent with high selectivity.[105] In accordance with this and applying the polar Felkin-Anh model the unwanted isomer **3.14** (setting the α-benzyloxy-substituent perpendicular to the π-face of the carbonyl) is favored, figure 3.2, eq. C.

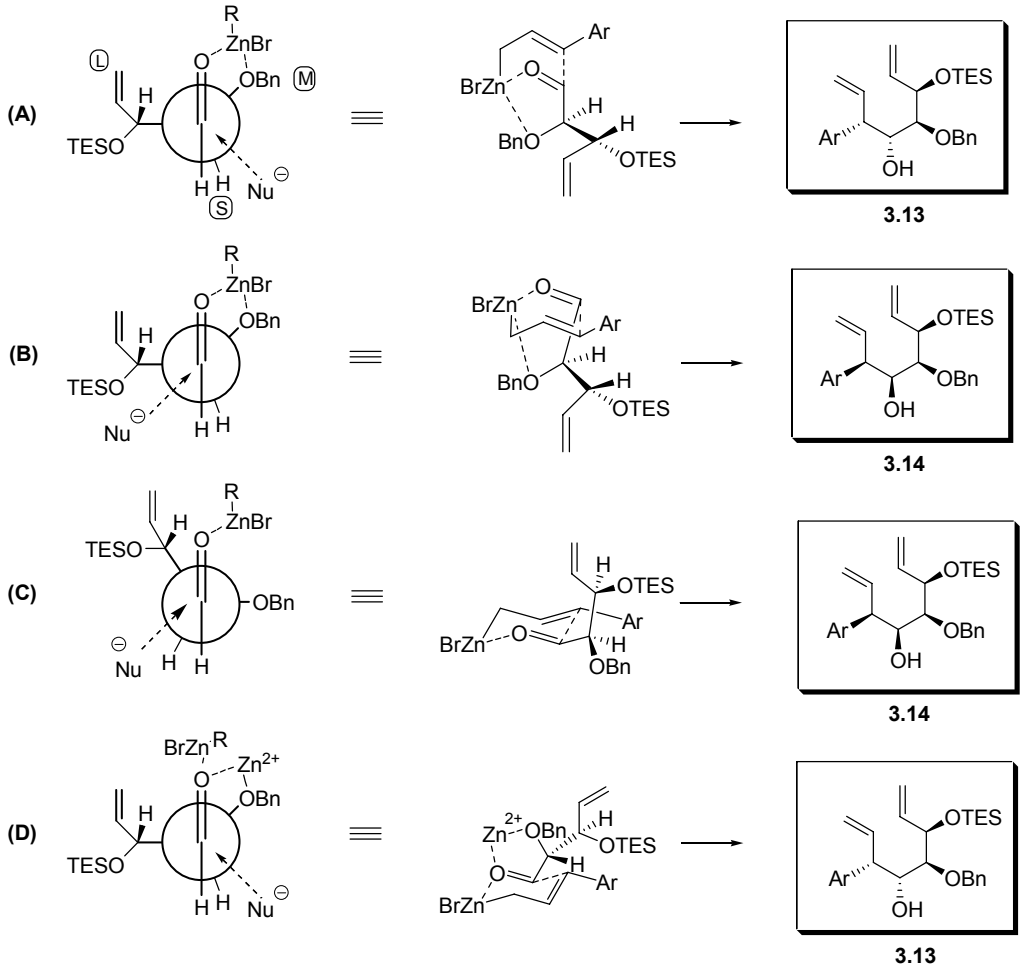


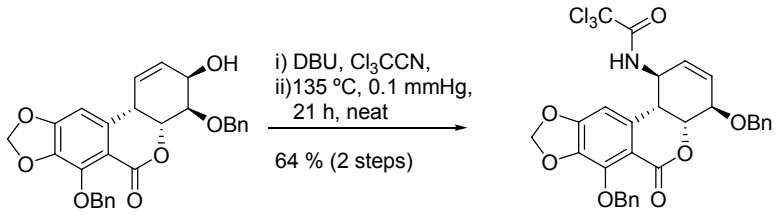
Figure 3.2: Projections and transitions states applied to explain the diastereomeric outcome. L> M> S.

As zinc was also used for the fragmentation of the aldehyde and the allylating reagent is added slowly there should be a large excess of Zn^{2+} present. By employing chelation between Zn^{2+} and

the aldehyde and the α-alkoxy-substituent the substrate would be locked in a 5-membered ring rendering attack possible only from the anti-Felkin face, figure 3.2, eq. D. This yields the desired isomer **3.13**. Also uncoordinated zinc (to the α-benzyloxy-substituent) in a six-membered transition state in a chair-conformation seems more likely. The two reasonable explanations clarifies, why the two products are formed in a nearly 1:1 ratio.

3.6 Toward Pancratistatin

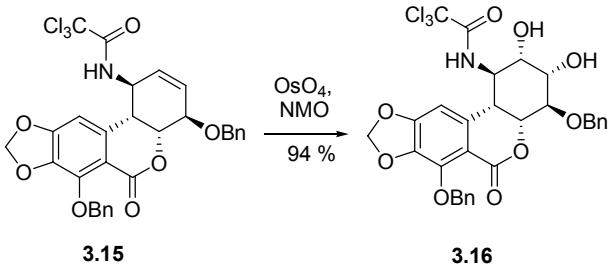
The attention was now focused on replicating the end game toward pancratistatin by Danishefsky and Lee. The Overman rearrangement to **3.15** was to be performed. By applying the conditions optimized by Håkansson *et al.*[28] the imidate of **3.13** was cleanly formed keeping the temperature below -20 ºC in the presence of DBU. Above -20 ºC extensive and fast decomposition was observed.



3.13 **3.15**

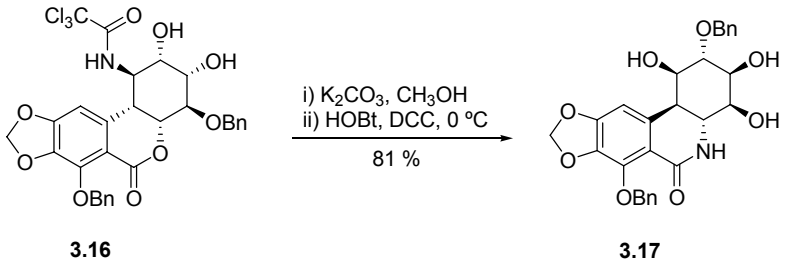
Scheme 3.7: Imidate formation and Overman rearrangement.

Interestingly, the imidate proved completely stable under the conditions used by Danishefsky and Lee, *i.e.* no conversion was observed when the imidate was heated to 100 ºC for 1 h under high vacuum (~ 0.1 mmHg). Danishefsky and Lee reported that the rearrangement was worked up after 1.2 h. In accordance with earlier work in our group higher temperature was required and increasing the temperature to 135 ºC and the reaction time to 21 h did bring about the rearrangement in good yield - 64 % of **3.15** over two steps in comparison to 42 % by Danishefsky and Lee. Following the Overman rearrangement came the dihydroxylation. As expected the reaction required a rather high catalyst loading to achieve a reasonable reaction rate as it was to take place from the concave side of the bicyclic system. Reaction times of up to 24 days with a catalyst loading of 10 % were observed.



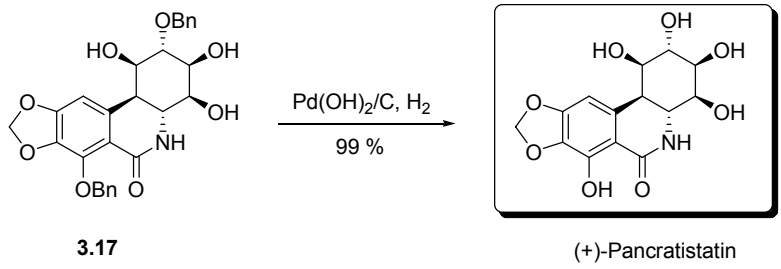
Scheme 3.8: Dihydroxylation on the concave face.

The next step toward pancratistatin was the methanolysis of the lactone and the amide in **3.16** with subsequent lactamization to afford the bisbenzylprotected pancratistatin, **3.17**. Direct conversion of the lactone to the lactam has been achieved in refluxing methanol with K_2CO_3 on similar systems by Paulsen and Stubbe, Ohta and Kimoto, Keck *et al.*, and Håkansson *et al*.[28, 81, 82, 106]



Scheme 3.9: Lactone to lactam reorganization.

In accordance with Danishefsky and Lee the lactone to lactam reorganization was not observed even on prolonged reflux. Instead further activation was required and accomplished by Danishefsky and Lee by the addition of DCC as it was speculated that an amino acid was formed. The exact nature of the intermediate remains obscure. In our hands simple addition of DCC or DIC did not perform in comparable yields. Only by adding HOBt as a standard peptide coupling additive were good yields of **3.17** achieved.



Scheme 3.10: Deprotection to yield (+)-pancratistatin.

The final debenzylation was accomplished uneventfully using Pearlman's catalyst and H_2 to provide pancratistatin with physical data in agreement with literature.[67, 73, 107] At this point a discrepancy between our synthesized material and reported data in regard to published ^{13}NMR-data. By careful 2D-NMR analysis (DQF-COSY, NOESY, gHMBC and gHSQC) it was realized that several groups has missassigned a single carbon-atom.[71, 72, 74, 75] Our analysis showed that the signal from carbon 10b was located under the DMSO-*d6* septet.

In connection to the previously synthesized natural products in the Madsen group, acting as glucosidase inhibitors,[25, 29] we decided to test whether pancratistatin and 7-deoxypancratistatin possess any capacity for enzyme inhibition, when tested against almond α-mannosidase, almond β-glucosidase and baker's yeast α-glucosidase. Interestingly, 7-deoxypancratistatin showed moderate inhibition of almond β-glucosidase (K_i = 2.8 × 10^{-5} M), while the parent molecule showed no inhibition of the three enzymes.

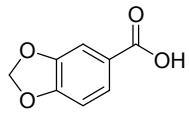
3.7 Conclusion

An enantioselective total synthesis of (+)-pancratistatin has been achieved in 15 steps from the carbohydrate D-xylose bearing the chiral information to provide pancratistatin in an overall 7.1 % yield. The longest linear sequence consists of 17 steps from commercially available piperonylic acid and supplies pancratistatin in an overall 7.0 % yield. The highlight of the synthesis consists of a tandem zinc-mediated reductive fragmentation and allylation of a ribofuranoside with ensuing lactonization and ring closing metathesis to intercept the first total synthesis of pancratistatin by Danishefsky and Lee.

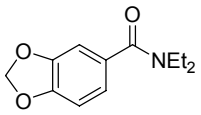
3.8 Experimental Section

General procedures

See section **1.6**

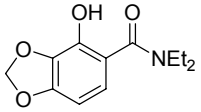


A solution of $NaClO_2$ (48.0 g, 0.425 mol) in H_2O (400 mL) was added dropwise to a stirred solution of piperonal (45.04 g, 0.300 mol) in MeCN (300 mL) containing NaH_2PO_4 (9.6 g, 0.080 mol) in 120 mL of H_2O and 30 mL of 35 % H_2O_2. The solution temperature was kept below 15 ºC by an ice-bath. After full addition the ice-bath was removed and the solution was stirred for another 2 h. Another 2.4 g of NaH_2PO_4 (0.020 mol) and 8.0 mL of 35 % H_2O_2 were added along with 12.1 g of $NaClO_2$ (0.134 mol) in H_2O (60 mL). After 1 h another 4.0 g of $NaClO_2$ (0.044 mol) was added and the slurry was stirred for 2 h, where it was quenched with 3.0 g of Na_2SO_3. Then 20 mL of 37 % aq. HCl was added and the slurry was filtered. The filtrate was extracted with 400 mL and 200 mL of EtOAc. The combined organic phases were dried with $MgSO_4$, filtered and evaporated to a white solid. Yield 50.0 g (Q). R_f = 0.58, 1:1:0.02 EtOAc:Heptane:Acetic Acid (v/v). Mp = 225-227 ºC. IR (KBr) ν 2918, 2560, 1671, 1617, 1452, 1298, 1260, 1113, 1036 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-*d6*): δ 12.77 (bs, 1H), 7.54 (dd, *J* = 1.7, 8.1, 1H), 7.36 (d, *J* = 1.6, 1H), 6.99 (d, *J* = 8.1, 1H), 6.12 (s, 2H). ^{13}C-NMR (75 MHz, DMSO-*d6*): δ 166.6, 151.1, 147.4, 124.9, 124.6, 108.8, 108.0, 101.9. Anal. Cald. for $C_8H_6O_4$: C, 57.84; H, 3.64; Found C, 57.78; H, 3.73.

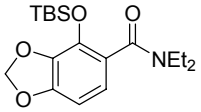


Piperonylic acid (74.5 g, 0.446 mol) was suspended in $SOCl_2$ (325 mL, 4.46 mol) in a 1 L flask with a reflux condenser. The suspension was heated to reflux for 1½ h on a heating mantle and the released SO_2 and HCl were passed into a beaker with water. It was cooled to rt and the excess $SOCl_2$ was removed under reduced pressure. Then 300 mL of CH_2Cl_2 was added and the flask was placed on an ice-bath and mounted a reflux condenser. The diethylamine (185.2 mL, 1.78 mol) was added dropwise through the condenser and residues washed down with 50 mL of CH_2Cl_2. The slurry was stirred under Ar overnight and then washed with 3 x 1 L of 2 M aq. HCl. The organic phase was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography in 30-50 % EtOAc in heptane to yield **3.5**: 88.6 g (90 %). R_f = 0.25, 1:1 EtOAc:Heptane (v/v). Mp = 65-66 ºC. IR (KBr) ν 2983, 2944, 2903, 1610, 1465, 1438, 1291, 1241, 1036 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.78-6.88 (m, 3H), 5.97 (s, 2H), 3.37 (bs, 4H), 1.16 (bs, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 170.6, 148.2, 147.4, 130.9, 120.4, 108.1, 107.3,

101.2, 43.2 (br), 40.1 (br), 13.8 (br). Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33; Found C, 65.50; H, 6.77; N, 6.28.

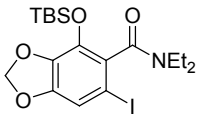


The amide **3.5** (40.0 g, 0.181 mol) was dissolved in THF (500 mL) in a 1 L 3-necked flask fitted with a reflux-condenser, an addition funnel and a thermometer. The solution was added 30.0 mL of anhydrous TMEDA (0.199 mol) and the mixture was cooled to -78 ºC. ^{s}BuLi (140 mL, 1.42 M in cyclohexane, 0.199 mol) was added dropwise from the addition funnel, the temperature not exceeding -72 ºC. The deeply bordeaux solution was stirred for 1 h at -78 ºC after full addition, where dry $B(OMe)_3$ (24.3 mL, 0.217 mol) was added and the solution warmed to 0 ºC on an ice-bath. Then acetic acid (16.8 mL, 0.293 mol) was added followed by slow addition of H_2O_2 (35 %, 42 mL, 0.488 mol). The solution stirred overnight at ambient temperature and was concentrated *in vacuo*. The slurry was redissolved in 600 mL of CH_2Cl_2 and washed with 1 L of 10 % $Na_2S_2O_3$. The aqueous phase was run through a pad of Celite and extracted with another 2 x 400 mL of CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered and evaporated *in vacuo*: The residue was purified by DCVC in 20-30 % EtOAc in heptane to yield of **3.9**: 40.5 g (94 %). R_f = 0.30, 1:1 EtOAc:Heptane (v/v). Mp = 59-60.5 ºC. IR (KBr) ν 2983, 2657, 1639, 1583, 1503, 1457, 1075, 1033, 801 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 10.06 (s, 1H), 6.85 (d, *J* = 8.3, 1H), 6.40 (d, *J* = 8.3, 1H), 6.01 (s, 2H), 3.51 (q, *J* = 7.1, 4H), 1.26 (t, *J* = 7.1). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 171.1, 150.7, 143.6, 135.2, 121.6, 114.2, 101.9, 99.6, 42.3, 13.3. Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90; Found C, 60.87; H, 6.31; N, 5.89. MS $[M+Na]^+$: calcd 260.0899, found 260.1371.

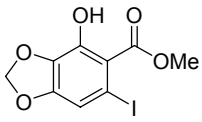


The phenol **3.9** (10.0 g, 42.2 mmol) was dissolved in CH_2Cl_2 (210 mL) and imidazole (5.74 g, 84.3 mmol) was added followed by TBSCl (7.04 g, 46.7 mmol). The slurry was stirred overnight and run through a pad of Celite, which was washed with 30 mL of CH_2Cl_2, The organic phase was washed with 100 mL of sat. aq. $NaHCO_3$ and 250 mL of H_2O, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The yellow oil was purified by DCVC in ½ L 5%, ½ L 10% and ½ L 50 % EtOAc in heptane to yield 14.8 g of an oil, which solidifies on standing (Q). R_f = 0.47, 1:1 EtOAc:Heptane (v/v). Mp = 65 ºC. IR (KBr) ν 2928, 2856, 1638, 1617, 1479, 1280, 1249, 1073, 1035, 865, 838 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.68 (d, *J* = 8.0, 1H), 6.50 (d, *J* = 8.0, 1H), 5.88-5.97 (m, 2H), 3.51(m, 2H), 3.03-3.34 (m, 2H), 1.22 (t, *J* = 7.2, 3H), 1.01 (t, *J* = 7.1, 3H), 0.94 (s, 9H), 0.21 (s, 3H), 0.18 (s,

3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 168.4, 148.9, 136.8, 135.3, 125.5, 120.7, 102.5, 100.9, 42.9, 39.3, 25.6, 18.2, 14.0, 13.2, -4.5. Anal. Calcd. for $C_{18}H_{29}NO_4Si$: C, 61.50; H, 8.32; N, 3.98; Found C, 61.69; H, 8.20; N, 4.11. MS $[2M+Na]^+$: calcd 725.3629, found 725.3617.

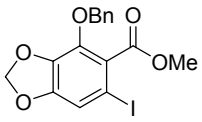


N,N-Diethyl-4-(*tert*-butyldimethylsiloxy)-benzo[1,3]dioxole-5-carboxamide (1.00 g, 2.85 mmol) was dissolved in THF (14.0 mL) and TMEDA (0.47 mL, 3.13 mmol) was added. The solution was cooled to -78 ºC and ^{s}BuLi (2.30 mL, 1.36 M in cyclohexane, 3.13 mmol) was added dropwise. The solution was stirred 2 h at -78 ºC after full addition at which point it had become yellow. Then I_2 (0.870 g in 3.4 mL THF) was added dropwise and the cooling bath was removed. The solution warmed up to rt after full addition, where it was poured into 100 mL of H_2O and 50 mL of sat. aq. $Na_2S_2O_3$ was added. Extraction with 3 x 50 mL of EtOAc. The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography in 15 % EtOAc in heptane to yield 1.20 g (88 %). R_f = 0.47, 3:7 EtOAc:Heptane (v/v). Mp = 66-67 ºC. IR (KBr) ν 2932, 2860, 1624, 1465, 1410, 1287, 1266, 1094, 1037, 874, 841 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.92 (s, 1H), 5.95 (d, *J* = 1.4, 1H), 5.92 (d, *J* = 1.4, 1H), 3.78-3.92 (m, 1H), 3.08-3.25 (m, 3H), 1.26 (t, *J* = 7.1, 3H), 1.11 (t, *J* = 7.2, 3H), 0.93 (s, 9H), 0.22 (s, 3H), 0.18 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 167.4, 149.3, 137.5, 135.9, 130.5, 112.5, 101.4, 82.2, 43.0, 39.3, 25.5, 18.2, 13.8, 12.6, -4.2, -4.7. Anal. Calcd. for $C_{18}H_{28}INO_4Si$: C, 45.28; H, 5.91; N, 2.93; Found C, 45.46; H, 5.87; N, 2.84. MS $[2M+Na]^+$: calcd 977.1562, found 977.1856.

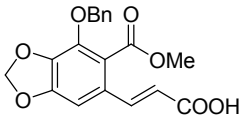


N,N-Diethyl-4-(*tert*-butyldimethylsiloxy)-6-iodo-benzo[1,3]dioxole-5-carboxamide (12.30 g, 25.8 mmol) was dissolved in CH_3CN (129 mL) and Na_2HPO_4 (5.49 g, 38.7 mmol) and Me_3OBF_4 (11.44 g, 77.3 mmol) were added in one portion. The suspension was stirred for 3½ h and slowly added 161 mL of sat. aq. $NaHCO_3$ from addition funnel under vigorous stirring followed by solid $NaHCO_3$ (10.82 g, 128.8 mmol). The slurry was stirred at ambient temperature for 15 h, poured into 500 mL of H_2O and extracted with 3 x 200 mL of EtOAc. The combined organic phases were dried with $MgSO_4$, filtered and evaporated *in vacuo*. The residue was dissolved in 100 mL of CH_2Cl_2 and run through a short column of silica (packed in CH_2Cl_2) and the solvent was evaporated to yield 7.867 g (95 %) of the ester. R_f = 0.30, 3:7 EtOAc:Heptane (v/v). Mp = 159-160 ºC. IR (KBr) ν 3006, 2947, 1666, 1503, 1490, 1340, 1301, 1194, 1081, 1036, 986 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 11.00 (s,

1H), 7.19 (s, 1H), 6.07 (s,2H), 3.96 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 168.7, 152.6, 146.8, 135.6, 115.4, 112.4, 102.9, 84.6, 51.9. Anal. Calcd. for $C_9H_7IO_5$: C, 33.56; H, 2.19; Found C, 33.43; H, 2.13. HRMS $[M+Na]^+$: calcd 344.9230, found 344.9232.

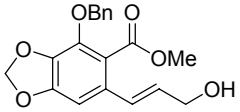


Methyl 4-hydroxy-6-iodo-benzo[1,3]dioxole-5-carboxylate (19.0 g, 59.0 mmol) was dissolved in DMF (500 mL) and cooled to 0 ºC. Then NaH (4.0 g, 55-65 % in mineral oil, 88.5 mmol) was added in small portions and the suspension was stirred for 20 min. followed by addition of BnBr (14.0 mL, 118 mmol). The solution stirred at ambient temperature overnight, quenched with H_2O and poured into 500 mL of Et_2O, which was washed with 4 x 1 L of H_2O. The combined aqueous phases were extracted with 2 x 500 mL of Et_2O and the organic phases were combined and coevaporated *in vacuo* with toluene. The residue was purified by DCVC in 10 % EtOAc in heptane to yield **3.10**: 24.3 g (Q). R_f = 0.42, 3:7 EtOAc:Heptane (v/v). Mp = 106-107 ºC. IR (KBr) ν 3029, 2948, 2912, 1727, 1617, 1466, 1374, 1346, 1271, 1134, 1088, 1037 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.28-7.39(m, 5H), 6.96(s, 1H), 5.97(s, 2H), 5.24(s, 2H), 3.87(s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 167.4, 150.7, 139.9, 137.4, 136.4, 128.4, 128.2, 127.9, 127.8, 113.4, 101.9, 81.0, 74.3, 52.7. Anal. Calcd. for $C_{16}H_{13}IO_5$: C, 46.62; H, 3.18; Found C, 46.48; H, 3.11. MS $[M+Na]^+$: calcd 434.9705, found 434.9466.

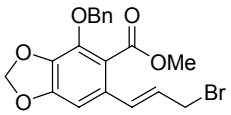


The iodide **3.10** (1.00 g, 2.43 mmol) was dissolved in DMF (10 mL) and degassed by sonication. Then NBu_3 (2.9 mL, 12.1 mmol), acrylic acid (0.50 mL 7.28 mmol), Bu_4NI (0.896 g, 2.43 mmol) and $Pd(OAc)_2$ (11.0 mg, 49 µmol, 2 mol%) were added successively. The solution was heated to 100 ºC for 2½ h and then poured into 100 mL of 1 M HCl and 50 mL of EtOAc. The flask was washed with 50 mL of EtOAc. Further extraction with 2 x 100 mL of EtOAc was performed. The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography in 50 % EtOAc in heptane with 1 % AcOH to yield 0.861 g of **3.11** as a white solid (Q). R_f = 0.21, 1:1:0.01 EtOAc:Heptane:AcOH (v/v). Mp = 185-187 ºC. IR (KBr) ν 3300-2700, 2675, 1731, 1680, 1628, 1602, 1480, 1430, 1381, 1290, 1265, 1217, 1088, 1034 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.67 (d, *J* = 15.8, 1H), 7.29-7.43 (m, 5H), 6.86 (s, 1H), 6.26 (d, *J* = 15.7, 1H), 6.04 (s, 2H), 5.25 (s, 2H), 3.89 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 171.6, 166.7, 150.5, 142.9, 139.4, 138.7, 136.4, 128.3, 128.1, 127.8, 127.0, 123.7, 118.4, 102.0, 100.7,

74.2, 52.6. Anal. Calcd. for $C_{19}H_{16}O_7$: C, 64.04; H, 4.53; Found C, 63.83; H, 4.62. HRMS (ESP+) $[M+H]^+$: calcd 357.0974, found 357.0980.

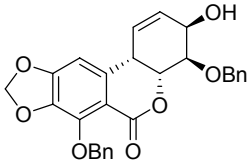


The carboxylic acid **3.11** (9.369 g, 26.3 mmol) was dissolved in THF (98 mL) and cooled to -6 ºC, where NEt_3 (4.8 mL, 34.2 mmol) was added. Then ethyl chloroformate (3.0 mL, 31.6 mmol) was added dropwise and the slurry was stirred for 2 h at -5 to -2 ºC. The slurry was filtered and the solid residue was washed with 120 mL of THF. To this solution was added 16 mL of H_2O and it was cooled to 0 ºC, where $NaBH_4$ (34.2 mL 2 M in triglyme, 68.4 mmol) was added dropwise not exceeding 1 ºC. The solution was stirred for 2½ h at 0 ºC. The reaction was quenched with 55 mL of 1 M HCl and the THF was removed *in vacuo*. The residue was poured into 95 mL of 1 M HCl and extracted with 400 mL of toluene. The aqueous phase was extracted with another 200 mL of toluene. The combined organic phases were washed 4 x 500 mL of H_2O and the organic phase was evaporated *in vacuo* to yield 8.579 g of the allyl alcohol (95 %). R_f = 0.20, 1:1 EtOAc:Heptane (v/v). Mp = 88 ºC. IR (KBr) ν 3400-3100, 3008, 2896, 2850, 1727, 1611, 1483, 1472, 1428, 1375, 1292, 1247, 1142, 1079, 1031 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.29-7.42 (m, 5H), 6.74 (s, 1H), 6.51 (dt, *J* = 1.5, 15.6, 1H), 6.19 (dt, *J* = 5.6, 15.7, 1H), 5.97 (s, 2H), 5.23 (s, 2H), 4.25 (dd, *J* = 1.1, 5.6, 2H), 3.83 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 167.8, 150.3, 139.2, 136.8, 136.2, 130.5, 129.9, 128.3, 128.1, 127.8, 127.0, 120.8, 101.6, 100.2, 74.1, 63.5, 52.4. Anal. Calcd. for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30; Found C, 66.29; H, 5.21. HRMS (ESP+) $[M+H]^+$: calcd 343.1176, found 343.1163.

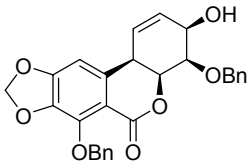


Methyl 4-(benzyloxy)-6-((E)-3-hydroxyprop-1-enyl)-benzo[1,3]dioxole-5-carboxylate (2.716 g, 7.93 mmol) was dissolved in THF (30.0 mL), and NEt_3 (1.8 mL, 12.9 mmol) and LiBr (2.02 g, 23.3 mmol) were added. The solution was cooled to -40 ºC and Ms_2O (2.08 g, 11.9 mmol) was added. The suspension warmed to rt – the cooling bath was removed at -10 ºC. The reaction was quenched with 50 mL of 4.8 % HBr and 50 mL of EtOAc was added followed by phase separation. The aqueous layer was extracted with another 3 x 30 mL of EtOAc after phase-separation. The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The slightly yellow oil was purified by flash chromatography in 25 % EtOAc in heptane to yield 2.973 g of **3.1** as a white solid, which is unstable on dry SiO_2 (93 %). R_f = 0.58, 1:1 EtOAc:Heptane (v/v). Mp = 69.5-71 ºC. IR (KBr) ν 3026, 2968, 2894, 1722, 1607, 1497, 1477, 1380, 1290, 1259, 1195, 1146, 1095,

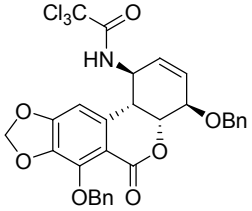
1030 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.28-7.40 (m, 5H), 6.76 (s, 1H), 6.56 (d, *J* = 15.4, 1H), 6.24 (dt, *J* = 7.8, 15.4, 1H), 5.98 (s, 2H), 5.24 (s, 2H), 4.09 (dd, *J* = 0.9, 7.8, 2H), 3.85 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 167.4, 150.4, 139.3, 136.8, 136.7, 130.4, 128.9, 128.4, 128.1, 127.8, 126.8, 121.2, 101.7, 100.3, 74.1, 52.4, 33.0. Anal. Calcd. for $C_{19}H_{17}BrO_5$: C, 56.31; H, 4.23; Found C, 56.10; H, 4.13. MS (ESP+) $[M+H]^+$: calcd 405.0338, found 405.0362.



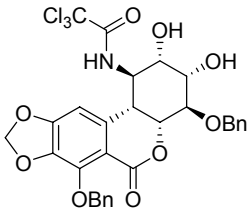
The iodide **3.12** (1.0036 g, 2.10 mmol) was dissolved in anh. THF (30 mL) in a 100 mL conical flask and water (10 mL) was added. After addition of Zn* (1.371 g, 21.0 mmol) the slurry was sonicated from 22 to 45 ºC, while the allylating reagent **3.1** (1.271 g, 3.14 mmol) in anh. THF (10 mL) was added by syringe plunger over 5 h. After full addition the mixture was sonicated for another 2 h and filtered through a pad of Celite, which was washed with 3 x 20 mL of EtOAc. Then 50 mL of 20 % NH_4Cl was added and the aqueous phase was extracted with another 3 x 20 mL of EtOAc. The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was redissolved in MeOH (50 mL) and stirred with Amberlite IR-120 overnight. It was filtered and the beads were washed with acetone and the filtrate was concentrated *in vacuo* with toluene (2 x 10 mL). This residue was dissolved in anh. CH_3CN (25 mL), K_2CO_3 (1.037 g, 7.50 mmol) was added and the mixture was refluxed for 1½ h. The slurry was diluted with CH_2Cl_2 (30 mL) and poured into 100 mL of 20 % NH_4Cl after cooling. Extraction with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The final residue was dissolved in anh. CH_2Cl_2 (25 mL), degassed by sonication and Ar-purge and Hoveyda-Grubbs 2nd gen. catalyst (37.7 mg, 60.2 μmol) was added. The solution was refluxed for 1½ h under Ar after which it was concentrated *in vacuo* and purified by flash chromatography in 40-60 % EtOAc in heptane with a 5 % interval-gradient to yield 345 mg (35 %) of the desired **3.13** and 318 mg (32 %) of **3.14** as white foams, combined yield (67 %). R_f = 0.24, 1:1 EtOAc:Heptane (v/v), IR (KBr) ν 3600-3170, 3026, 2913, 1718, 1610, 1472, 1369 1262, 1184, 1118, 1046, 933, 733, 697 cm^{-1}. $[\alpha]_D^{23}$ - 113.6 (*c* 1.07, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.27-7.56 (m , 10H), 6.50 (s, 1H), 6.04 (d, *J* = 1.1, 1H), 5.99 (d, *J* = 1.1, 1H), 5.71-5.76 (m, 1H), 5.44-5.48 (m, 1H), 5.34 (d, *J* = 11.4, 1H), 5.29 (d, *J* = 11.3, 1H), 4.69-4.76 (m, 3H), 4.51-4.56 (m, 1H), 4.09-4.15 (m, 1H), 3.53-3.57 (m, 1H), 2.45 (d, *J* = 11.0, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 160.2, 153.3, 143.9, 138.9, 138.0, 137.2, 136.7, 129.8, 128.7, 128.3, 128.0, 125.8, 111.5, 102.5, 102.0, 74.8, 74.5, 74.1, 73.9, 64.7, 35.4. HRMS calcd. for $C_{28}H_{24}NaO_7$ $[M+Na]^+$: calcd 495.1415, found 495.1414.



3.14: R_f = 0.08, 1:1 EtOAc: Heptane (v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.24-7.55 (m, 10H), 6.46 (s, 1H), 6.01-6.08 (m, 1H), 6.01(d, *J* = 1.2, 1H), 5.97 (d, *J* = 1.2, 1H), 5.44 (d, *J* = 9.9, 1H), 5.29 (s, 2H), 4.89 (d, *J* = 12.0, 1H), 4.83-4.86 (m, 1H), 4.67 (d, *J* = 12.0, 1H), 4.39 (m, 1H), 3.66 (dd, *J* = 1.6, 5.2, 1H), 3.36 (br s, 1H), 2.99 (d, *J* = 10.1, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 159.6, 153.3, 143.8, 138.0, 137.9, 137.7, 136.7, 129.5, 128.4, 128.2, 127.9, 127.8, 127.7, 124.8, 111.3, 102.0, 101.9, 75.6, 74.3, 74.1, 69.9, 63.2, 40.0. HRMS calcd. for $C_{28}H_{24}NaO_7$ $[M+Na]^+$: calcd 495.1415, found 495.1409.

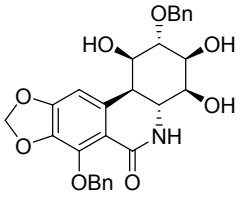


The alcohol **3.13** (0.2912 g, 0.616 mmol) was dissolved in anh. CH_2Cl_2 (5.0 mL) under Ar and cooled to -42 ºC, where Cl_3CCN (0.31 mL, 3.09 mmol) was added followed by dropwise addition of DBU (0.15 mL, 1.00 mmol). The solution warmed to -20 ºC where it was quenched with 30 mL of 20 % NH_4Cl. After phase-separation the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography in 20 % EtOAc in heptane to yield 0.3729 g (98 %) of a white foam. The imidate (0.2563 g, 0.416 mmol) was heated neat to 135 ºC in an oil bath under high vacuum (~ 0.1 mmHg) for 21 h. The vacuum was released and the black tar was dissolved in toluene after cooling and purified by flash chromatography in 20 % EtOAc in heptane to yield 166.9 mg (65 %) of **3.15** as a white solid. (64 % - two steps). R_f = 0.46, 1:1 EtOAc:Heptane (v/v). Decomposes > 145 ºC (lit. 186-187 ºC). IR (neat) ν 3307, 3031, 2909, 2872, 1701, 1615, 1478, 1305, 1264, 1246, 1088, 1053, 818 cm^{-1}. $[\alpha]_D^{21}$ -30.0 (*c* 1.0, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.28-7.55 (m, 10H), 6.80 (d, *J* = 9.2, 1H), 6.44 (s, 1H), 6.03 (m, 1H), 6.00 (d, *J* =1.4, 1H), 5.93 (d, *J* = 1.3, 1H), 5.88 (dd, *J* = 1.6, 10.2, 1H), 5.38 (d, *J* = 11.4, 1H), 5.32 (d, *J* = 11.3, 1H), 4.64-4.69 (m, 2H), 4.62 (d, *J* =11.7, 1H), 4.42-4.48 (m, 1H), 4.06-4.10 (m, 1H), 3.04 (dd, *J* = 2.4, 9.9, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 161.4, 160.8, 152.8, 144.6, 138.5, 137.9, 137.2, 136.7, 130.8, 128.6, 128.3, 128.1, 128.0, 127.8, 126.5, 111.1, 103.2, 102.1, 92.3, 75.4, 74.5, 72.2, 70.7, 50.2, 38.9. HRMS calcd. for $C_{30}H_{24}Cl_3NNaO_7$ $[M+Na]^+$: calcd 638.0511, found 638.0486.

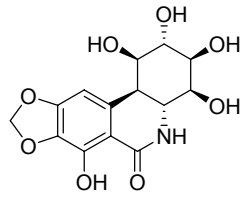


The alkene **3.15** (163.3 mg, 0.265 mmol) was dissolved in THF (2.65 mL) followed by addition of NMO (68.0 mg, 0.581 mmol), H_2O (0.2 mL) and OsO_4 (18.4 mg, 72.4 μmol). The solution was stirred in a sealed flask for 123 h at rt and then poured into 20 mL of 10 % Na_2SO_3 and 5 mL of

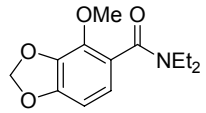
EtOAc. Extraction with EtOAc (3 x 10 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo.* The residue was purified by flash chromatography in 2-4 % CH_3OH in CH_2Cl_2 to yield the white solid **3.16** (161.7 mg, 94 %). R_f = 0.10, 1:1 EtOAc:Heptane (v/v). Mp = 201-202 ºC (lit. 202-206 ºC). IR (KBr) ν 3600-3150, 3025, 2923, 1713, 1701, 1610, 1472, 1374, 1297, 1256, 1092 cm^{-1}. $[\alpha]_D^{21}$ + 30.0 (*c* 1.0, DMSO). ^{1}H-NMR (500 MHz, $CDCl_3$ + 2 drops CD_3OD): δ 7.24-7.48 (m, 10H), 6.43 (s, 1H), 5.96 (d, *J* = 1.1, 1H), 5.85 (d, *J* = 1.0, 1H), 5.32 (d, *J* = 11.4, 1H), 5.26 (d, *J* = 11.4, 1H), 4.64 (d, *J* = 11.7, 1H), 4.55-4.59 (m, 2H), 4.22-4.25 (m, 1H), 4.14 (dd, *J* = 3.1, 10.7, 1H), 4.02 (t, *J* = 2.7, 1H), 3.97 (t, *J* = 11.1, 1H), 3.34 (dd, *J* = 2.7, 11.4, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$+ 2 drops CD_3OD): δ 162.7, 161.0, 152.9, 143.9, 138.2, 137.0, 136.8, 136.6, 128.4, 128.2, 128.0, 127.9, 127.8, 127.6, 110.7, 104.2, 102.0, 92.5, 76.3, 75.8, 74.4, 72.7, 70.7, 69.1, 52.0, 39.5. HRMS calcd. for $C_{30}H_{26}Cl_3NNaO_9$ $[M+Na]^+$: calcd 672.0565, found 672.0540.



The lactone **3.16** (112.2 mg, 0.172 mmol) and K_2CO_3 (239.2 mg, 1.731 mmol) were suspended in 7.0 mL of anh. 5:2 CH_3OH:CH_2Cl_2 and refluxed under Ar overnight. The suspension was carefully neutralized with Amberlite IR-120 after cooling. The beads were filtered off, washed with 1:1 CH_3OH:CH_2Cl_2 and the solvent was removed *in vacuo*. The residue was redissolved in 8.0 mL of CH_2Cl_2, HOBt (55.5 mg, 0.411 mmol) was added and the mixture cooled to -5 ºC under Ar. Then DCC (43.2 mg, 0.209 mmol) was added and the solution stirred for 5 min. before the cooling bath was removed and it warmed to rt over 1 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography in 1-4 % CH_3OH in CH_2Cl_2 in 1 % intervals to afford 71.0 mg of **3.17** as a white solid (81 %). R_f = 0.4, 1:19 MeOH: CH_2Cl_2 (v/v). Mp = 93-94 ºC (lit. 98-100 ºC). IR (neat) ν 3500-3200, 2904, 1644, 1612, 1475, 1453, 1366, 1335, 1285, 1218, 1069, 1030, 730 cm^{-1}. $[\alpha]_D^{21}$ + 52.0 (*c* 1.0, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.23-7.54 (m, 10H), 6.66 (s, 1H), 5.95 (d, *J* = 1.5, 1H), 5.94 (d, *J* = 1.5, 1H), 5.27 (d, *J* = 11.2, 1H), 5.23 (d, *J* = 11.3, 1H), 4.98 (br s, 1H), 4.64 (d, *J* = 11.8, 1H), 4.59 (d, *J* = 11.8, 1H), 4.45 (br s, 1H), 4.25 (br s, 1H), 4.05 (t, *J* = 3.0, 1H), 3.99 (m, 2H), 3.82 (dd, *J* = 10.1, 13.0, 1H), 3.10 (d, *J* = 13.1, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 165.4, 152.0, 143.1, 137.6, 137.5, 136.9, 136.5, 128.5, 128.4, 128.3, 128.0, 127.9, 127.5, 116.2, 101.7, 101.1, 76.7, 74.9, 72.4, 71.4, 71.0, 67.6, 49.9, 41.5. HRMS calcd. for $C_{28}H_{27}NNaO_8$ $[M+Na]^+$: calcd 528.1630, found 528.1621.

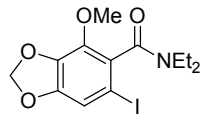


Pancratistatin: The dibenzylether **3.17** (34.2 mg, 67.7 µmol) was dissolved in 2.0 mL of EtOAc, $Pd(OH)_2/C$ (104 mg) was added and the mixture was degassed. The suspension was stirred, while bubbling through H_2 for 2 h – 1.0 mL of EtOAc was added after 1½ h and stirred for another 2 h under an H_2-atmosphere. It was filtered through a small plug of Celite, which was washed with 40 % CH_3OH in CH_2Cl_2. The solvent was removed *in vacuo* to afford 22.0 mg of an off-white solid (99 %). R_f = 0.24, 1:9 MeOH:CH_2Cl_2 (v/v). Decomposes > 250 ºC. IR (neat) ν 3348, 2926, 1671, 1615, 1597, 1462, 1416, 1347, 1296, 1228, 1082, 1065, 1036, 876 cm^{-1}. $[\alpha]_D^{21}$ + 37 (*c* 1.0, DMSO). ^{1}H-NMR (500 MHz, DMSO-*d6*): δ 13.06 (s, 1H), 7.50 (s, 1H), 6.49 (s, 1H), 6.06 (s, 1H), 6.04 (s, 1H), 5.36 (d, *J* = 4.0, 1H), 5.08 (d, *J* = 5.8, 1H), 5.05 (d, *J* = 6.1, 1H), 4.83 (d, *J* = 7.5, 1H), 4.28 (m, 1H), 3.97 (m, 1H), 3.85 (m, 1H), 3.67-3.74 (m, 2H), 2.97 (br d, *J* =11.8, 1H). ^{13}C-NMR (75 MHz, DMSO-*d6*): δ 169.4, 152.0, 145.3, 135.6, 131.6, 107.4, 101.7, 97.6, 73.2, 70.1, 69.9, 68.4, 50.4, 39.5. HRMS calcd. for $C_{14}H_{16}NO_8$ $[M+H]^+$: calcd 326.0870, found 326.0864. Pancratistatin can be recovered unchanged from DMSO by distilling off the DMSO at reduced pressure (< 10 mbar) into a Heckmann device at 100 ºC (oil bath). Pancratistatin is precipitated from the residue by dilution with CH_2Cl_2 and shortly sonicated. It is then purified and isolated by repeating circles of centrifuging, decanting and wash with CH_2Cl_2.



Compound previously prepared by Khaldi *et al.*[108]

Slightly yellow solid, Mp = 58-59 ºC. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.66 (d, *J* = 8.0, 1H), 6.52 (d, *J* = 8.0, 1H), 5.94 (s, 2H), 3.97 (s, 3H), 3.39-3.65 (br m, 2H), 3.17 (q, *J* = 7.1, 2H), 1.21 (t, *J* = 7.1, 3H), 1.03 (t, *J* = 7.1, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): 168.0, 149.5, 139.6, 136.2, 124.1, 120.3, 102.9, 101.0, 59.9, 42.8, 38.8, 13.9, 12.7. IR (neat) ν 2977, 2938, 1608, 1425, 1284, 1254, 1221, 1068, 1038 cm^{-1}. GC-MS $[M]^+$: 251.1.



Slightly yellow solid, Mp = 83-84 ºC. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.94 (s, 1H), 5.96 (d, *J* = 1.4, 1H), 5.94 (d, *J* = 1.4, 1H), 3.96 (s, 3H), 3.72-3.85 (m, 1H), 3.26-3.40 (m, 1H), 3.15 (q, *J* = 7.2, 2H), 1.25 (t, *J* = 7.2, 3H), 1.10 (t, *J* = 7.2, 3H).^{13}C-NMR (75 MHz, $CDCl_3$): δ 167.3, 150.0, 140.2, 137.9, 129.1, 113.0, 101.6, 82.1, 60.1, 42.7, 38.7, 13.7, 12.3. IR (neat) ν 2980, 2939, 1608, 1425, 1279, 1250, 1221, 1101, 1034 cm^{-1}.

4 Total Synthesis of Cavicularin

4.1 Introduction

Cyclophanes have been known for a long time and are often found in Nature.[109, 110] (A cyclophane consists of at least one aromatic system in which two non-adjacent positions are connected by another ring-system). Only rarely has Nature provided examples of these cyclophanes in which an aromatic ring is bent and the aromaticity is retained.[111] Bisbibenzyl compounds - like cavicularin - are often build up from two units of lunularin, which can be combined in several ways to yield an array of structurally different motifs (figure 4.1).[112] The cyclophane cavicularin comprises the structurally more intriguing representative within the class because the macrocyclic core contains a bent aromatic moiety.[113] The high strain derived from the cyclic array increases the atropisomerism around the biaryl axis and guarantees the configurational stability. Hence, the compound exhibits planar and axial chirality, which is not derived from a stereogenic isolated moiety like an asymmetric carbon-atom. The isolation of enantiopure (+)-cavicularin demonstrates that a biosynthetic route toward the compound must exist.

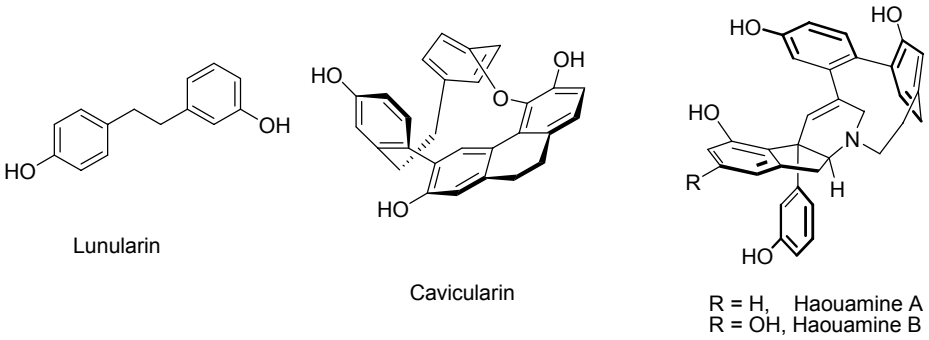
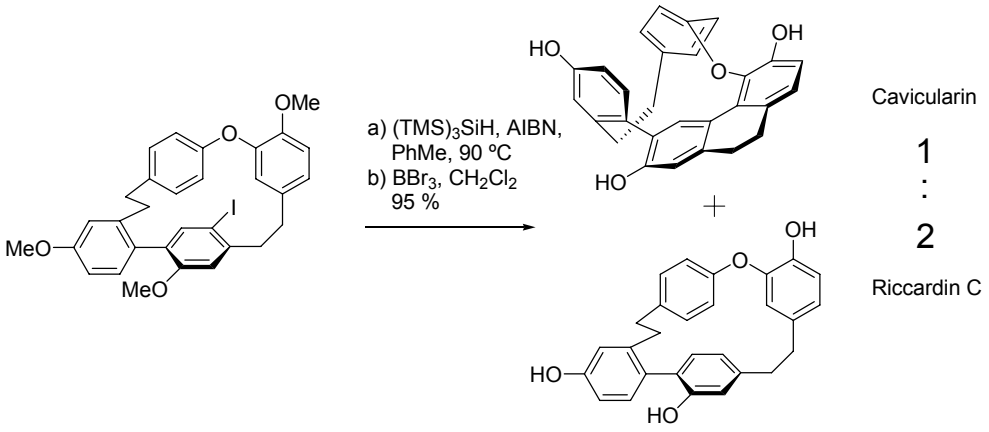


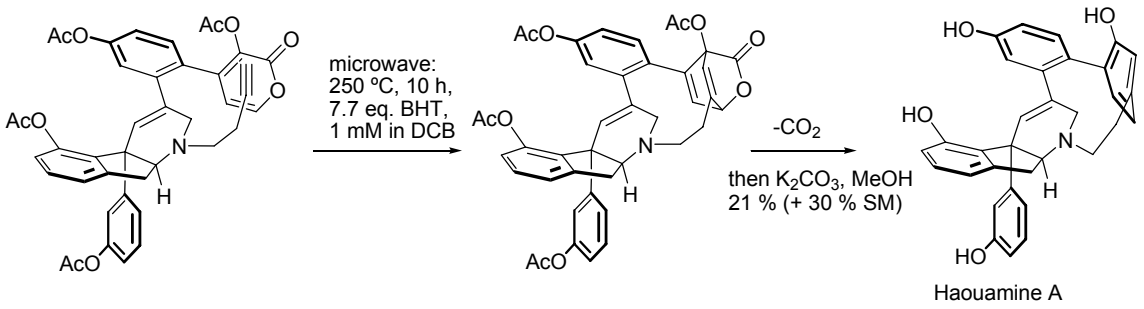
Figure 4.1: Strained para-cyclophanes and lunularin

Indeed, cavicularin and the haouamines could only be isolated because of their inherent lack of reactivity elsewhere in the molecules. The strained aromatic ring in cavicularin is bent 15º out of plane, while the haouamines are bent approximately 27º out of plane.[113, 114] In 2005 Harrowven, Woodcock and Howes were the first to complete the synthesis of racemic cavicularin and thereby also presenting the first example of a synthetic route to a bent para-cyclophane (scheme 4.1). Harrowven *et al.* completed the synthesis by a macrocyclic, radical ring contraction – presumably this represents a biomimetic approach to the natural compound.[113, 115, 116]



Scheme 4.1: Endgame toward cavicularin by Harrowven, Woodcock and Howes.

In 2006, Baran and Burns completed the synthesis of the other example of a bent aromatic para-cyclophane, haouamine A.[117] In their studies toward haouamine A, several standard approaches completely failed to furnish the target. Eventually, a pyrone-alkyne Diels-Alder with extrusion of CO_2 was successfully implemented although in low yield (scheme 4.2).



Scheme 4.2: Endgame toward haouamine A by Burns and Baran.

The low yield was ascribed to decomposition under the prolonged heating at 250 ºC because of the electron-rich moieties in the molecule, especially the indeno-tetrahydropyridine ring system (a similar approach to haouamine B possessing an additional phenol failed). In the ongoing studies to improve this critical macrocyclization, the synthesis of cavicularin was perceived as a suitable testing ground for improving the reaction due to its similarity to the haouamines, *i.e.* phenolic appendages, but without the tetrahydropyridine.

4.2 Retrosynthetic Analysis

The synthesis of cavicularin was undertaken with the requirement that the bent aromatic ring should be produced in a similar manner as haouamine A – a pyrone-alkyne Diels-Alder cyclization with CO_2-extrusion and cycloreversion leading to a bend aromatic moiety.

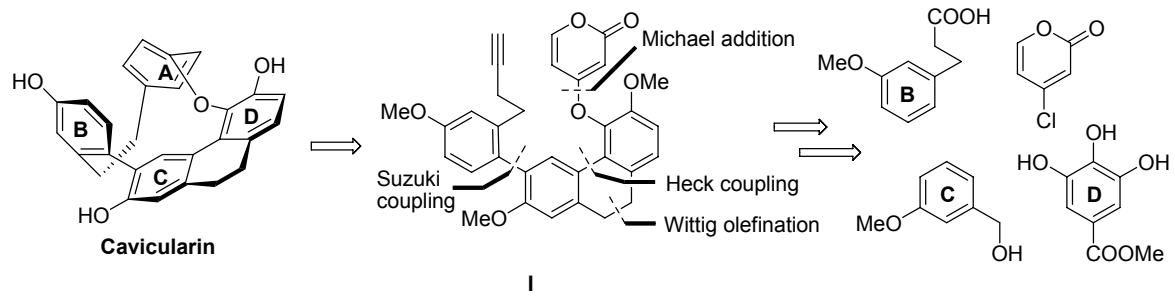
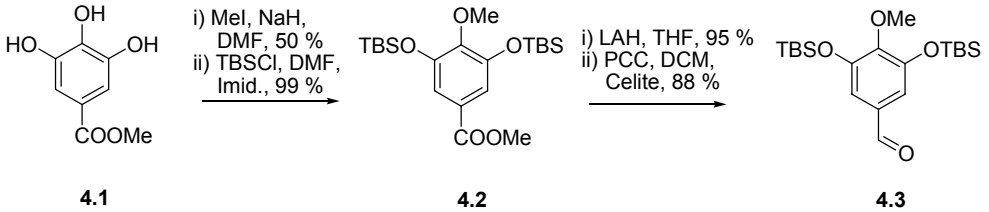


Figure 4.2: Retrosynthetic analysis of cavicularin

The precursor **I** for this cyclization was planned to arise from a Michael addition of a phenol from ring D to the pyrone and connecting the alkyne residue by means of a Suzuki cross coupling between ring B and C. In turn this leaves a dihydrophenanthrene, which was envisioned to be assembled by a Wittig olefination to obtain the two-carbon link between the aromatic rings between ring C and D. The aryl-aryl bond (C to D) in the phenanthrene could arise from a Heck-type direct arylation between an aromatic bromide and the other aromatic ring.

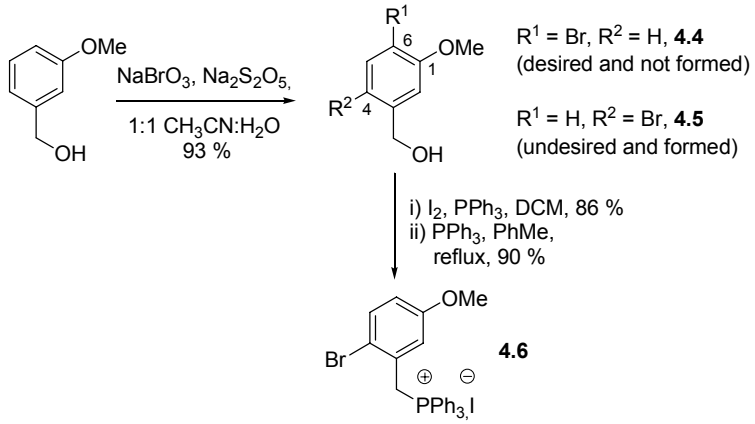
4.3 Results & Discussion

The first task was to synthesize the substrates for the Wittig coupling. The aldehyde coupling partner for the Wittig olefination was easily produced according to a literature procedure (scheme 4.3) from methyl gallate, **4.1**.[118] Differentiated protection of the most acidic phenol first, protection of the two other phenols followed by full reduction of the ester and finally oxidation to an aldehyde delivered the carbonyl coupling partner **4.3**.



Scheme 4.3: Synthesis of the Wittig coupling partner.

It was attempted to synthesize the desired phosphonium salt **4.4** in three steps employing bromination conditions, which would override the propensity to halogenate the 4-position by normal electrophilic aromatic substitution, scheme 4.4.



Scheme 4.4: Attempted synthesis of the Wittig coupling partner, 4.4.

The bromination could be performed regioselectively by a reported procedure: *in situ* reduction of sodium bromate to hypobromous acid would enable coordination to the ring oxygen and subsequently deliver the bromide *ortho* to the methoxy-group (scheme 4.4).[119, 120] Later in the synthetic work, it became apparent that this bromination did not brominate the 6-position as confirmed by X-ray crystallography (Figure 4.3).

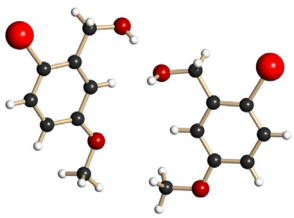
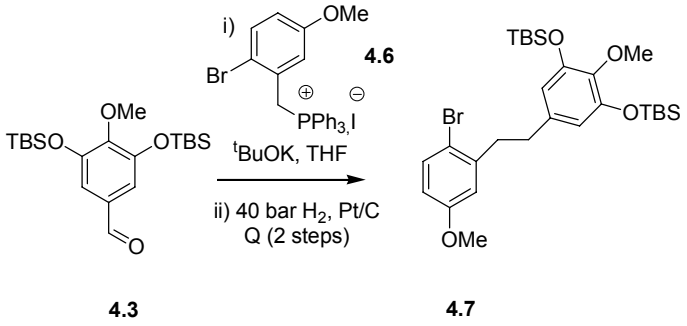


Figure 4.3: X-ray structure of the product from the bromination, compound 4.5.

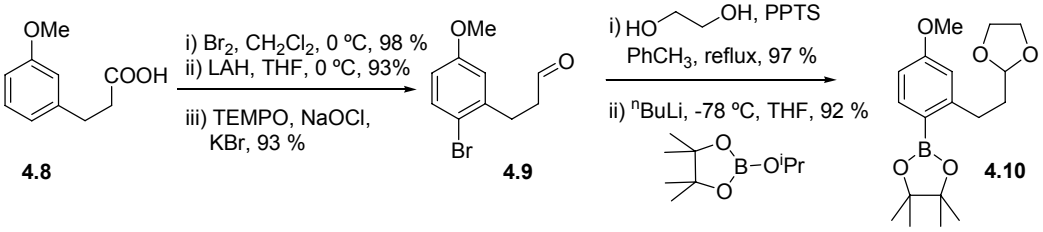
At this stage it was not realized that the regioselectivity was wrong, and the synthesis was carried on with the faulty bromination. **The structures will nevertheless from now on be presented in their actual form rather than their desired one.**

Iodination under Garegg conditions followed by reaction with triphenylphosphine delivered the phosphonium salt **4.6** (scheme 4.4).[121] The Wittig reaction[122, 123] was conducted under standard conditions producing a 1:1 mixture of *E* and *Z* stilbenes (scheme 4.5). Initial studies on the reduction of these alkenes with palladium led to extensive dehalogenation. Fortunately, Pt/C proved to be a suitable catalyst for the hydrogenation under moderate pressures and produced the arylhalide **4.7** for the Suzuki cross coupling quantitatively.



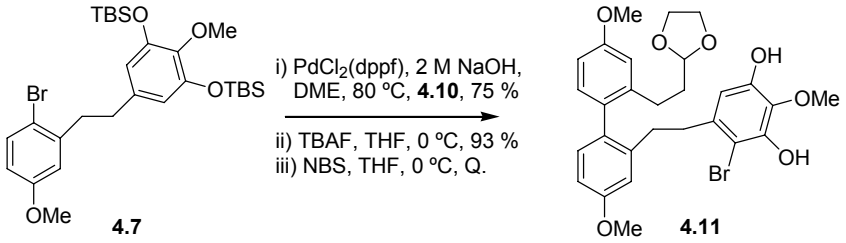
Scheme 4.5: Synthesis of the arylbromide.

A sequence to the boron-containing coupling partner **4.10** was developed for the Suzuki cross coupling, scheme 4.6.[124, 125] 3-(3-Methoxyphenyl)propanoic acid was brominated exclusively in the 4-position. The aldehyde **4.9** - obtained by full reduction of the carboxylic acid followed by TEMPO-mediated oxidation with bleach - was protected as its ethylene glycol acetal. After halogen-lithium exchange at low temperature and borolane quench, the boronic ester **4.10** was produced in excellent yield.



Scheme 4.6: Synthesis of the boronic ester.

Although this protocol was a bit lengthy for accessing the coupling substrate **4.10**, the sequence did not require chromatographic purification in any of the five steps. With both multigram quantities of the boronic ester **4.10** and the aryl bromide **4.7** in hand the stage was set for the Suzuki cross coupling, scheme 4.7.

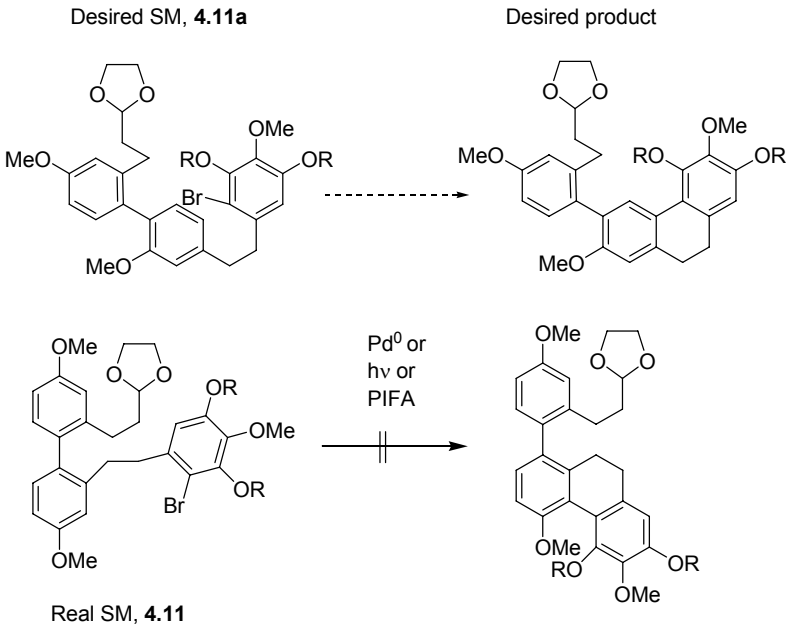


Scheme 4.7: Synthesis of the substrate for intramolecular Heck-type direct arylation.

Optimal conditions for the cross coupling was found to include $PdCl_2$(dppf) as the pre-catalyst in combination with a 1:1.3:1.3 ratio between arylbromide, boronic ester and aqueous base in ethereal solvent. Desilylation with TBAF and regioselective bromination of the electron-rich biphenol was achieved without event. In contrast to the ease by which compound **4.11** was synthesized, performing the direct arylation with a multitude of different conditions for Heck-type couplings only resulted in failure *i.e*. debromination and decomposition (scheme 4.8).[126] The TBS-, Ac- and Piv-protected derivatives of **4.11** also failed to undergo the direct arylation.

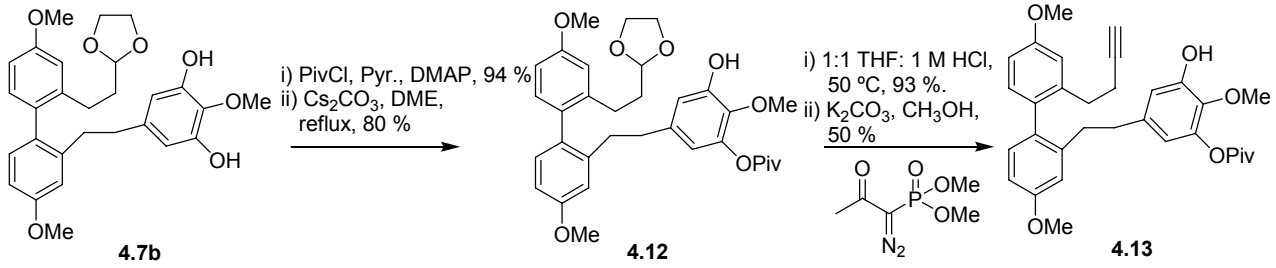
Due to the electron-richness of the aromatic rings (ring C and D) it was tried to induce the formation of the aryl-aryl bond by photochemical means *i.e*. the Witkop coupling (hν, epichlorohydrin, LiOAc),[127, 128] however this approach also failed.

Finally, it was attempted to construct the ring C to D aryl-aryl bond with hypervalent iodine *i.e*. PIFA. After the failure of this approach the synthesis was carried on without having installed the aryl-aryl bond. The aim was now to install the ring C to D bond at a late stage. If the desired connectivity had been present in **4.11** (shown in compound **4.11a**, scheme 4.8), the transformation might have been successful. Although it was realized that any metal-based catalyst would have to β-eliminate a hydrogen-atom positioned *trans* to the metal after insertion into the aromatic ring of **4.11a**, such eliminations are known in the literature at elevated temperatures.[126, 129]



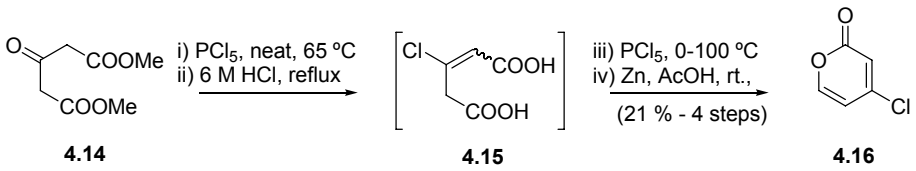
Scheme 4.8: Failed approaches for installing the aryl-aryl phenanthrene bond, R = H-, Ac-, TBS-, Piv-.

The attention was then turned to the differentiation of the two phenol moieties (scheme 4.9). It proved impossible to monoprotect compound **4.7b** in synthetically useful yields. Instead, a two-step sequence was employed in which **4.7b** was protected as the diester and subsequently mono-deprotected with Cs_2CO_3.[130] The acetal was removed under standard conditions, and the aldehyde was homologated to the alkyne **4.13** with the Ohira-Bestmann reagent.[131] The relatively poor yield for this transformation can be ascribed to partial acetylation by the reagent used and partial deprotection of the pivaloyl ester.



Scheme 4.9: Monoprotection and Seyferth-Gilbert homologation using the Ohira-Bestmann modification.

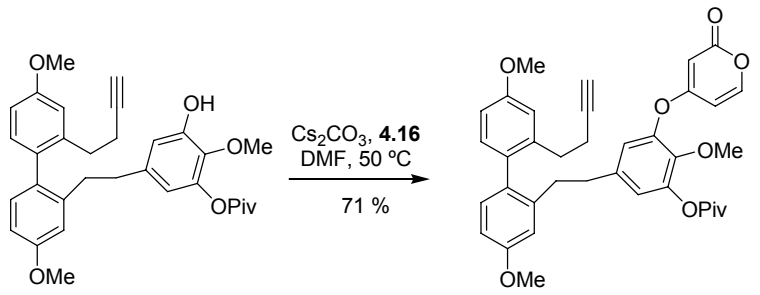
Now the stage was set for the Michael addition to the pyrone **4.16**, which had to be synthesized in four steps, scheme 4.10. Conversion of ketone **4.14** into the vinyl chloride and hydrolysis of the methyl esters gave **4.15**, which was cyclized to the 4,6-chloropyrone and final dechlorination with zinc dust under acidic conditions yielded the desired 4-chloropyrone, **4.16**.[132]



4.14 **4.15** **4.16**

Scheme 4.10: Synthesis of the 4-chloropyrone, 4.16.

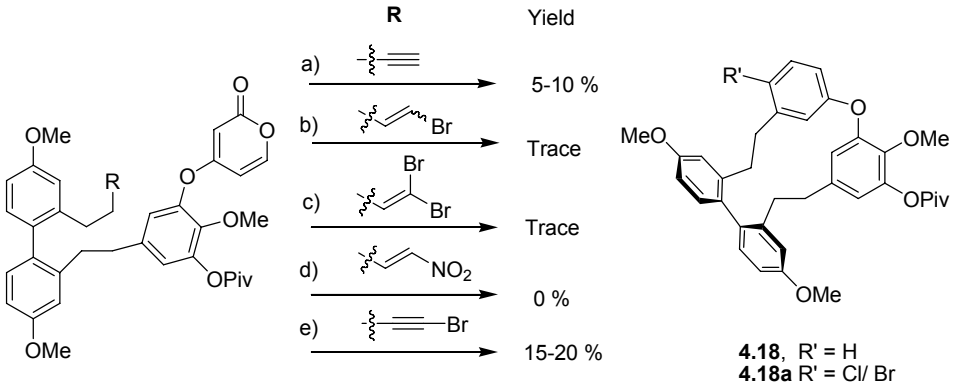
With gram quantities of the pyrone in hand, the Michael addition was accomplished in good yield finally delivering **4.18** for the intramolecular pyrone-alkyne Diels-Alder (scheme 4.11).[133]



4.13 **4.17**

Scheme 4.11: Michael addition to the pyrone.

The first attempt to perform the macrocyclization of **4.17** utilized the optimized conditions for the successful route to haouamine A, scheme 4.12.[117] This led to an initially satisfactory yield of 5-10 % as a mixture of two inseparable compounds. However, although this result was promising, the reaction turned out to be troublesome to improve.



4.18, R' = H
4.18a R' = Cl/ Br

Scheme 4.12: Approaches to synthesize the macrocycle.

General conditions: MW: 200-250 ºC, 10-15 h, < 20 mM in *o*-DCB.

Pyrones do not undergo Diels-Alder reactions readily but require rather forcing conditions.[132, 134] Efforts to improve the yield from the simple alkyne **4.17** included Lewis acid activation of the pyrone ($ScOTf_3$, $BF_3{\cdot}Et_2O$), which led to further decomposition. Transition metal catalysis (Ph_3PAuCl, $PtCl_2$, CuTC)[135, 136] induced cyclization of the alkyne to ring B or full decomposition. It was found that the addition of the radical scavenger BHT had no positive effect on the outcome of the reaction. Eventually, it was thought that further functionalization of the dienophile could bring about an mprovement. Different vinyl bromide derivatives did not lead to any product (scheme 4.12b and c). In the cyclization with the vinyl nitro-group (scheme 4.12d), a good yield (51 %) of a product was isolated, but it turned out that the nitro moiety had reacted as the diene. End-capping the alkyne as a bromide did however improve the yield to some extent (scheme 4.12e). The obtained product **4.18a** was submitted for X-ray crystallography, figure 4.4.

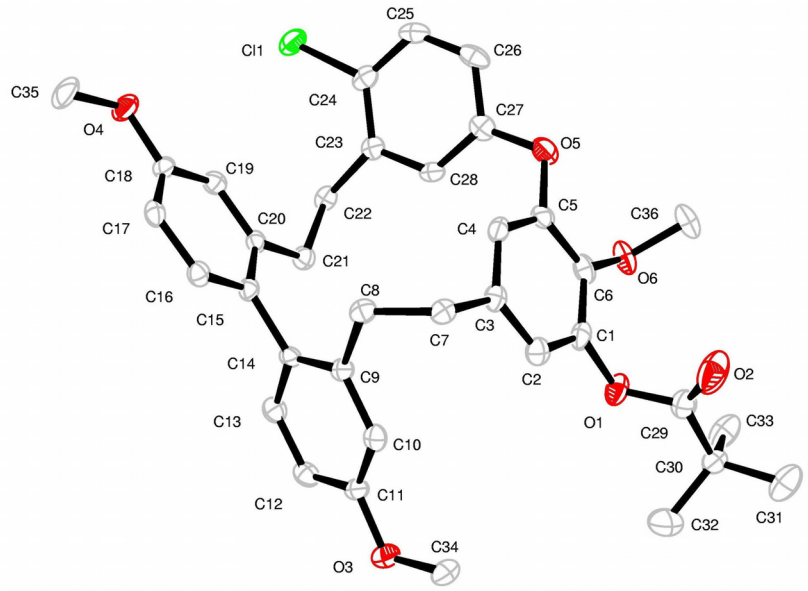
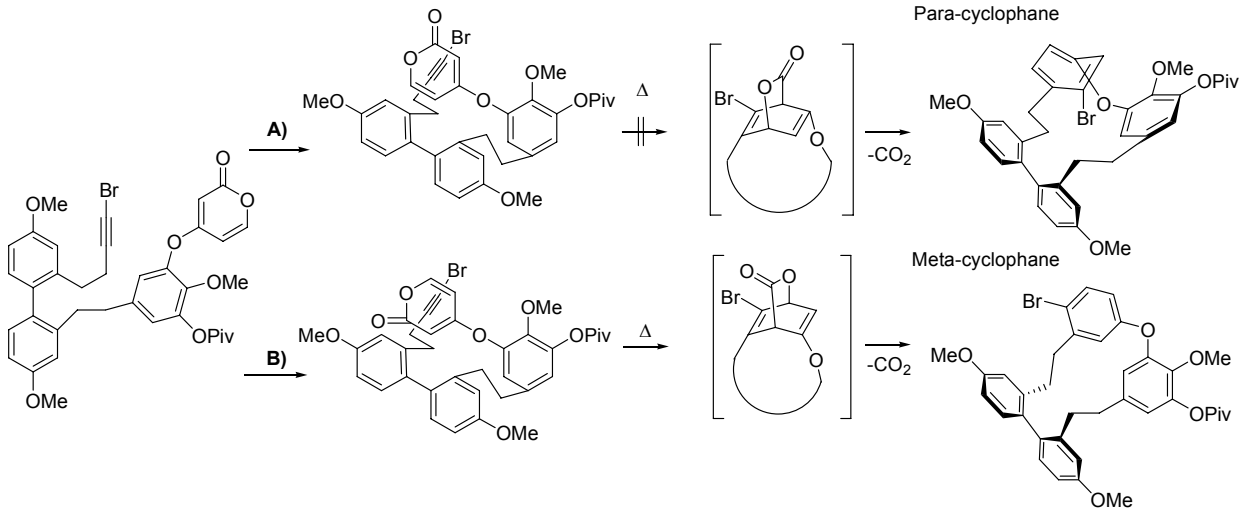


Figure 4.4: X-ray structure of the obtained product from the Diels-Alder reaction, 4.18a. See compound 4.18a in scheme 4.12 for printed structure.

Upon inspection on the received structure in figure 4.4 several issues can be addressed. First of all, there is a meta-relationship between C23 and C27, where a para-relationship is required. This can be explained by a simple attack of alkyne on the wrong side of the pyrone (scheme 4.13, path B). Apparently, the meta-cyclophane is much lower in energy and hence the only isolated product.



Scheme 4.13: Modes of macrocyclization.

Second, the connectivity around the C9-C14 aromatic ring is wrong (see figure 4.4 for numbering). The two-carbon tether (C8) should be attached to C10 and the C11 methoxy group should be attached to C13. This flaw was quickly traced back to wrong regioselectivity in the bromination step, scheme 4.4 and figure 4.3. Instead of the desired bromination of the 6-position, the 4-position was exclusively brominated as confirmed by single crystal X-ray analysis of the product from the reaction, figure 4.3. This suggests an erroneous claim of a formal total syntheses of Isoplagiochin C and D by Speicher *et al*. since they applied the bromination method depicted in scheme 4.4.[119, 137] Speicher *et al*. have reported NMR-data for compound **4.4**, which match those found in this study for compound **4.5**. Furthermore, they do not complete the total synthesis and only report 1D-NMR data with several unresolved signals.

Third, the C24-halide was found to consist of a 7:3 ratio between compounds having a chlorine-atom and a bromine-atom in this position, presumably by radical interchange with the solvent at the elevated temperatures. This was of no consequence since the halide had to be hydrogenated off in the endgame. Due to the complete breakdown of the applied approach, another strategy was devised in order to complete the synthesis.

4.4 Retrosynthetic Analysis – 2nd Strategy

It was anticipated that cavicularin could be successfully assembled by the same disconnections as in the previous strategy, but that the order of he bond formations had to be changed, figure 4.5

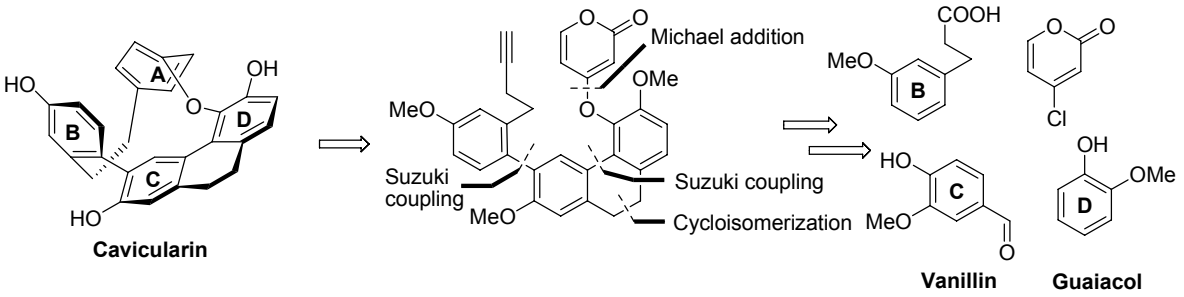
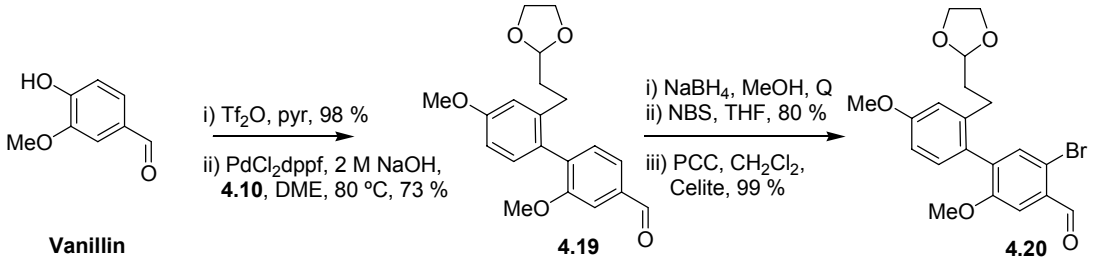


Figure 4.5: 2nd retrosynthetic analysis toward cavicularin.

The idea in the 2nd strategy was to install the aryl-aryl bond between ring C to D and ring B to C before the Diels-Alder macrocyclization. This would entail the correct connectivity and augment the chance of a successful Diels-Alder reaction since the alkyne inevitably approaches the pyrone *via* rotation around the aryl-aryl bond between ring B and C.

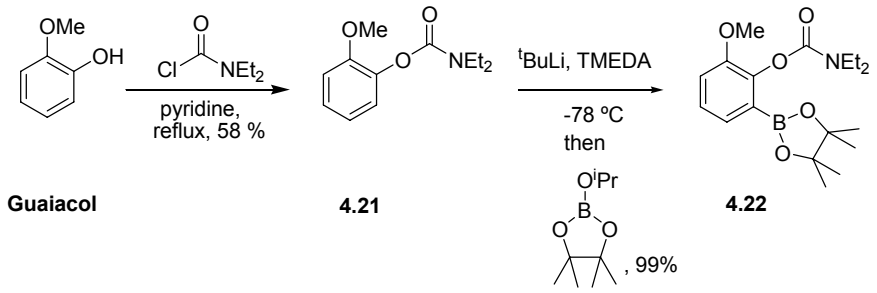
4.5 Results & Discussion – 2nd Strategy

The boronic ester **4.10** from section 4.3 could be reapplied and successfully cross coupled with vanillin triflate under similar conditions as achieved previously (scheme 4.14).



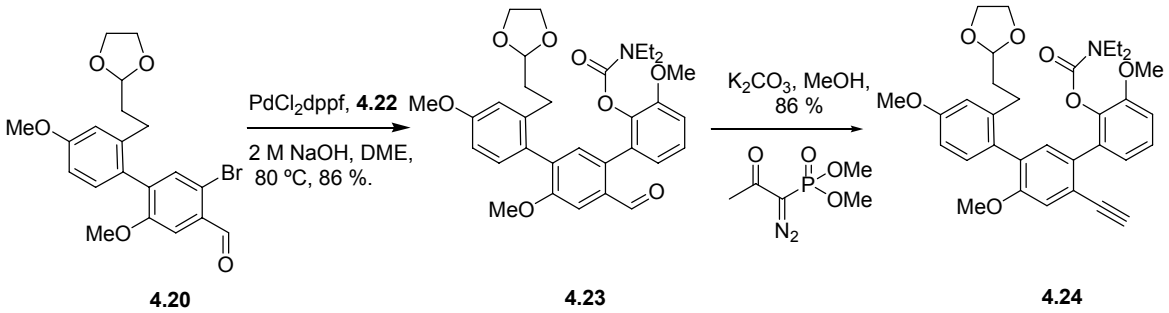
Scheme 4.14: Suzuki cross coupling and functionalization to enable further coupling.

Unfortunately, it quickly proved impossible to perform a clean regioselective bromination in the desired position of **4.19** without increasing the electron density of the aromatic system. The aldehyde was therefore reduced and the bromination was then performed in good yield. Reoxidation to the aldehyde with PCC furnished the substrate **4.20** for further elaboration by another Suzuki cross coupling with boronic ester **4.22**, which was synthesized in two steps (scheme 4.15). The phenol of guaiacol was converted into a strong ortho-directing group, followed by regioselective ortholithiation and quench with the borolane.



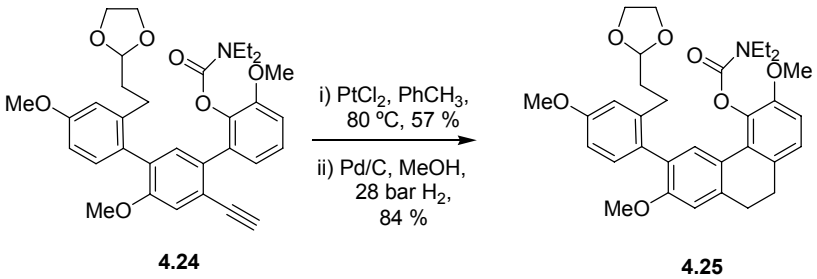
Scheme 4.15: Preparation of borolane 4.22.

The following Suzuki cross coupling of **4.20** and **4.22** was accomplished without event, and the aldehyde was one-carbon homologated to the alkyne with the Ohira-Bestmann reagent providing the precursor for the cycloisomerization, **4.24** (scheme 4.16).[131]



Scheme 4.16: 2nd Suzuki cross coupling and side-chain homologation.

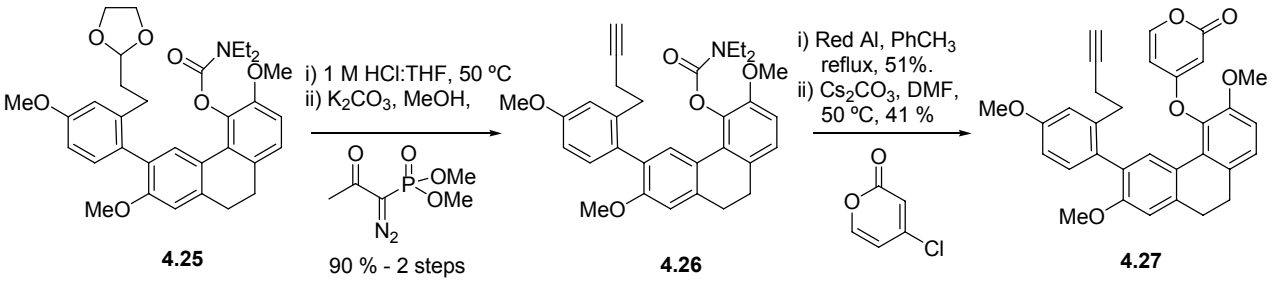
The attention was turned toward the synthesis of the dihydrophenanthrene system (scheme 4.17). Mamane and Fürstner recently showed the type of cyclization in scheme 4.17 to be very effective in providing a phenanthrene with different transition metals.[136, 138]



Scheme 4.17: Cycloisomerization to and reduction of the phenanthrene.

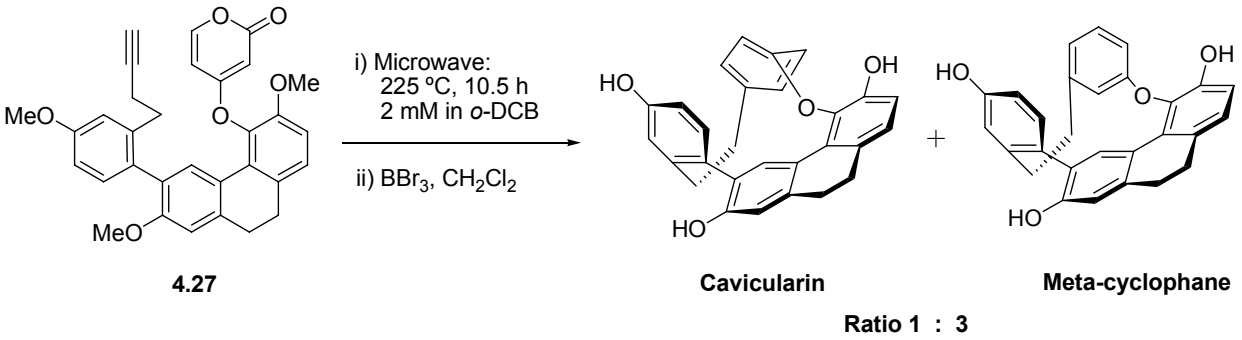
While $AuCl_3$ and $PdCl_2$ did produce the desired phenanthrene, decomposition of the starting material was fast and only led to a low yield – especially at elevated temperatures. On the other hand, treating the alkyne with $PtCl_2$ resulted in minor decomposition of both alkyne and

phenanthrene. The relatively low yield of 57 % was due to formation of a by-product, whose structure was not elucidated, but seemed to involve the acetal. After some experimentation, conditions were found, which were capable of reducing the phenanthrene in good yield to give the 4,5-dihydrophenanthrene **4.25**.[139]



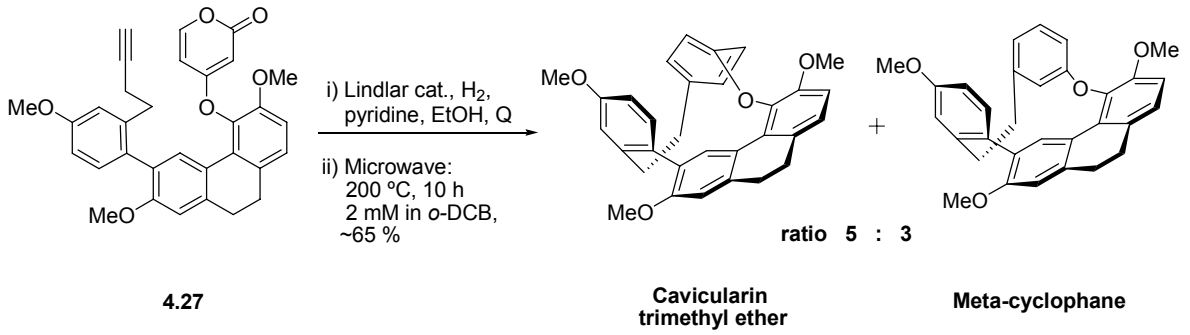
Scheme 4.18: Synthesis of the substrate for the intramolecular Diels-Alder.

The experience gained from the first strategy showed that the pyrone should be installed after conversion of the aldehyde into the alkyne, because of the high sensitivity of the pyrone toward nucleophiles. Therefore, the aldehyde was liberated and homologation to the alkyne **4.26** was performed under the previously utilized conditions (scheme 4.18). Removal of the carbamate from **4.26** turned out to be unexpectedly difficult. It showed complete resistance toward a series of strong reducing agents during prolonged heating. Hence, $LiAlH_4$, superhydride and $LiAlH(OMe)_3$ all failed to produce the unprotected phenol. Furthermore, a variety of hydroxides, alkoxides and Me_3OBF_4 followed by hydrolysis also failed.[90] Some deprotection was observed with anhydrous KOH by the procedure described by Gassmann *et al*., but this also led to isomerization of the alkyne to a mixture of different alkenes.[140] Eventually Red Al gave rise to the desired phenol, although in a somewhat low yield. The only observed by-product was identified as the dihydrophenanthrene, where the carbamate moiety had been removed on the aryl-side to ring D. The ensuing Michael addition to pyrone **4.16** furnished the Diels-Alder substrate **4.27** although in low yield, because the reaction was stopped prematurely and the starting material was recovered.



Scheme 4.19: The intramolecular Diels-Alder with CO_2-extrusion.

Investigations into the Diels-Alder reaction was then undertaken (scheme 4.19). Again the optimized conditions from the synthesis of haouamine A was tried first.[117] The reaction quantitatively produced a single product as judged by TLC, but NMR analysis revealed a 1:3 ratio between two compounds. Global deprotection did not furnish any separation of the two compounds, but NMR analysis did showed characteristic signals corresponding to the previously reported peaks for cavicularin.[113, 115] The major isomer was assumed to be the meta-cyclophane. Attempts to separate the compounds by HPLC was not performed due to time-constraints. Instead, the attention was focused on shifting the ratio between the two products. All attempts to cyclize **4.27** in another solvent (DMA, sulfolane, triglyme, neat, BMIMCl) than *o*-dichlorobenzene led to pronounced decomposition and multiple products. Addition of the radical scavenger BHT, a Lewis acid ($Eu(hfc)_3$) or citric acid,[141-143] as well as transition metal catalysis (CuTC)[135] or end-capping the alkyne with bromine[144] did not result in an improved ratio. The last attempt to improve the ratio involved reduction of the alkyne **4.27** under Lindlar conditions to the alkene and then subjecting this product to prolonged microwave irradiation (scheme 4.20).



Scheme 4.20: The improved intramolecular Diels-Alder with CO_2-extrusion.

This modification translated into a ~65% yield of a mixture between the two compounds in a 5:3 ratio, the major component being the desired trimethyl ether of cavicularin. Presumably, the

compounds are oxidized in air during work-up leading to the aromatic moieties. A third compound was isolated in ~35% yield and corresponded to the remaining unoxidized dienes.

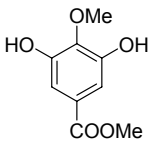
4.6 Conclusion

The naturally occurring paracyclophane cavicularin has been synthesized by using an intramolecular pyrone-alkene Diels-Alder reaction with concomitant liberation of CO_2. The synthesis was completed by 19 ensuing steps. The project is ongoing in Professor Phil Baran's laboratory and current focus is on shortening the synthesis and performing the synthesis enantioselectively.

4.7 Experimental Section

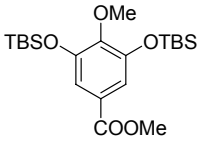
General Procedures.

All reactions were carried out under a nitrogen or an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran, triethylamine, dichloromethane, methanol, dimethylformamide, dimethoxyethane and benzene were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to spectroscopically (^{1}H-NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel 60 F_{254}-plates using UV light as visualizing agent and charring after staining with either *p*-anisaldehyde in ethanol/aqueous H_2SO_4/CH_3COOH or 5:2 phosphormolybdic acid: Cerium(IV)sulfate in aqueous H_2SO_4. Preparative TLC was performed on 0.25 mm or 0.50 mm Merck silica gel 60 Å F_{254}-plates in the noted solvent. Flash chromatography was performed with Merck Geduran 60 Å silica gel (40-63 μm) in the stated solvent. Alkyllithiums were titrated before each use according to Burchat *et al.*[44] Microwave experiments were performed on a Biotage Initiator. NMR spectra were recorded on either a Bruker DRX-600 with a cryoprobe, AMX-400 or a Varian Inova-400 and calibrated using residual solvent as an internal reference: $CHCl_3$ (7.26) and $CDCl_3$ (77.0), acetone (2.09), toluene (quintuplet, 2.09). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, br = broad. Coupling constants are given in hertz. IR spectra were recorded on a Perkin-Elmer Spectrum BX FTIR spectrometer. Melting points are uncorrected and were recorded on a Fisher-Johns 12-144 melting point apparatus. High resolution mass spectra were recorded on an Agilent Mass spectrometer using ESI-TOF or a ThermoFinnigan Mass spectrometer using FAB or EI. Low resolution mass spectra were recorded on an Agilent LCMS (ESI or APCI-ionization). X-ray crystallography was performed at UCSD by Dr. Antonio DiPasquale, Department of Chemistry and Biochemistry, Small Molecule X-ray Crystallography Facility.

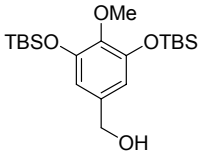


Methyl gallate (10.0 g, 54.3 mmol) was dissolved in DMF (109 mL) under Ar and cooled to 0 ºC. Then NaH (2.17 g, 60 % in mineral oil, 54.3 mmol) was added and the slurry was stirred for 30 min at 0 ºC and CH_3I (3.6 mL, 57.8 mmol) was added dropwise. The cooling bath was removed and the suspension stirred overnight at rt. It was then poured into ether (200 mL), which was washed with water (1.0 L). The aqueous layer was extracted with 2 x 200 and 2 x 150 mL of ether. The combined organic phases were washed with

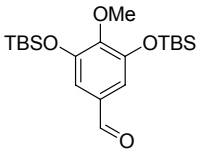
200 mL of water, dried with $MgSO_4$, filtered and evaporated *in vacuo*. The solid residue was purified by flash chromatography in 30-40 % EtOAc in hexanes. Yield of **4.1a**: 5.40 g (50 %). R_f = 0.28, 3:2 Hexanes:EtOAc (v/v). White solid, mp = 143-144 ºC (Lit. 147-148 ºC)[118]. ^{1}H-NMR (400 MHz, acetone-*d*6): δ 8.32 (br s, 2H), 7.09 (s, 2H), 3.87 (s, 3H), 3.81 (s, 3H). ^{13}C-NMR (100.5 MHz, acetone-*d*6): δ 166.3, 150.5, 137.7, 125.8, 109.1, 60.0, 51.5. IR(film) ν 3050-3650 2953, 1698, 1596, 1523, 1436, 1351, 1241, 1164, 1056, 1001 cm^{-1}. LCMS $[M+H]^+$: 199.



The diol **4.1a** (5.40 g, 27.3 mmol) was dissolved in 80 mL of DMF under Ar and 6.51 g of imidazole (95.6 mmol) and 12.3 g of TBSCl (81.8 mmol) were added. The solution was stirred at rt for 2 h. It was poured into 600 mL of water and extracted with 3 x 150 mL of ether. The combined organic phases were dried with $MgSO_4$, filtered and evaporated *in vacuo*. Purification by flash chromatography in 3 % EtOAc in hexanes. Yield of **4.2**: 11.48 g (99 %).[118] Colorless oil - 9:1 Hexanes:EtOAc (v/v), R_f = 0.53. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.19 (s, 2H), 3.86 (s, 3H), 3.77 (s, 3H), 1.01 (s, 18H), 0.19 (s, 12H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 166.6, 149.6, 147.3, 125.1, 116.1, 60.0, 52.0, 25.7, 18.3, -4.7. IR(film) ν 2954, 2932, 2860, 1726, 1578, 1492, 1427, 1353, 1252, 1223, 1090, 1014 cm^{-1}. LCMS $[M+Na]^+$: 449.

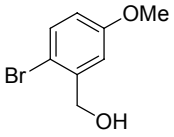


The ester **4.2** (11.48 g, 26.9 mmol) was dissolved in THF (135 mL) under Ar and cooled to 0 ºC, where 1.5 g of LAH (39.5 mmol) was added in portions. After full addition the cooling bath was removed and the slurry was stirred for 1 h. It was cooled to 0 ºC and quenched by slow addition of water (1.5 mL), 10 % NaOH (3.0 mL) and water (4.5 mL). The cooling bath was removed and the suspension was allowed to warm to rt, where it was dried with $MgSO_4$. The white salts were filtered off and the organic phase was evaporated *in vacuo*. Yield of **4.2a**: 10.19 g (95 %).[118] Colorless oil - 9:1 Hexanes:EtOAc (v/v), R_f = 0.25. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.51 (s, 2H), 4.51 (s, 2H), 3.71 (s, 2H), 1.00 (s, 18H), 0.17 (s, 12H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 149.8, 142.3, 136.2, 113.2, 65.1, 59.9, 25.7, 18.3, -4.7. IR(film) ν 2931, 1578, 1495, 1472, 1463, 1433, 1346, 1252, 1228, 1090, 1006 cm^{-1}.

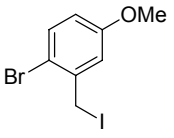


The alcohol **4.2a** (9.88 g, 24.8 mmol) was dissolved in CH_2Cl_2 (125 mL). Then PCC (10.68 g, 49.6 mmol) and Celite (11 g) were added. The slurry was stirred for 1 h and filtered. The dark organic phase was concentrated *in vacuo* and

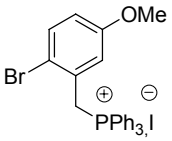
purified by flash chromatography in CH_2Cl_2. Yield of **4.3**: 8.60 g (88 %). White Solid, mp = 71-72 ºC (Lit. 75-77 ºC).[118] 9:1 Hexanes:EtOAc (v/v), R_f = 0.53. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 7.03 (s, 2H), 3.81 (s, 3H), 1.02 (s, 18H), 0.20 (s, 12H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 191.1, 150.4, 148.8, 131.8, 115.9, 60.1, 25.7, 18.3, -4.7. IR(film) ν 2955, 2931, 2858, 1697, 1576, 1489, 1440, 1389, 1346, 1259, 1215, 1090, 1007 cm^{-1}. HRMS $[M+H]^+$: calcd 397.2225, found 397.2236.



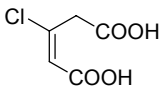
3-Methoxybenzyl alcohol (10.00 g, 72.38 mmol) was dissolved in 1:1 CH_3CN:H_2O (500 mL) and $NaBrO_3$ (19.15 g, 126.9 mmol) and $Na_2S_2O_5$ (13.83 g, 72.8 mmol) were added. The solution was stirred for 1 h and quenched with sat. aq. $Na_2S_2O_3$ (50 mL). The aqueous phase was extracted with 3 x 100 mL of ether after phase separation. The combined organic phases were dried with $MgSO_4$ and evaporated *in vacuo*. Yield of **4.5**: 14.62 g (93 %). White solid, mp = 42 ºC. 4:1 Hexanes:EtOAc (v/v), R_f = 0.23. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.7 Hz, 1H), 7.04 (d, *J* = 2.9 Hz, 1H), 6.69 (dd, *J* = 3.0, 8.7, 1H), 4.68 (s, 2H), 3.79 (s, 3H), 2.28 (br s, 1H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 159.1, 140.7, 133.0, 114.5, 114.0, 112.3, 64.7, 55.4. IR(film) ν 3000-3650, 2899, 2837, 1595, 1575, 1471, 1420, 1296, 1272, 1241, 1161, 1051, 1014 cm^{-1}. LCMS $[M+Na]^+$: 239.



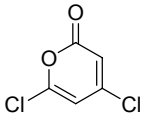
The benzyl alcohol **4.5** (19.42 g, 89.47 mmol) was dissolved in CH_2Cl_2 (500 mL) and cooled to -3 ºC, where imidazole (8.53 g, 0.125 mol) and PPh_3 (30.44 g, 0.116 mol) were added. After complete dissolution of the phosphine, the I_2 (30.70 g, 0.121 mol) was added in portions keeping the temperature below 10 ºC. After complete addition the cooling was removed and the slurry stirred for 1.5 h under Ar. It was then passed through a pad of silica, which was washed with 3 x 100 mL of ether. The organic phase was quenched with sat. aq. $Na_2S_2O_3$ (600 mL). The aqueous phase was extracted with 2 x 100 mL of ether after phase separation. The combined organic phases were dried with $MgSO_4$, filtered and evaporated *in vacuo*. Yield of **4.5a**: 24.99 g (86 %). The compound disproportionates to eliminate I_2 on prolonged storage in solution and solid state at rt. White solid, mp = 79-80 ºC. 4:1 Hexanes:EtOAc (v/v), R_f = 0.60. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.8, 1H), 6.96 (d, *J* = 2.8, 1H), 6.70 (dd, *J* = 2.8, 8.7, 1H), 4.49 (s, 2H), 3.79 (s, 3H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 159.1, 139.1, 134.0, 115.7, 114.4, 55.5, 5.9. IR(film) ν 2938, 2840, 1596, 1571, 1474, 1411, 1296, 1282, 1250, 1153, 1012 cm^{-1}. GCMS $[M]^+$: 326.



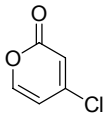
The iodide **4.5a** (25.87 g, 79.12 mmol) was dissolved in toluene (158 mL) and PPh_3 (20.76 g, 79.15 mmol) was added. The suspension was refluxed for 4 h under Ar. After cooling, it was filtered and the salt was washed with 3 x 100 mL of ether. Yield of **4.6**: 41.97 g (90 %).



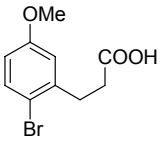
Prepared according to Afarinkia *et al*.[132] ^{1}H-NMR (400 MHz, Acetone-*d*6): δ (7:3 E:Z) 8.18 (br s, 2H), 6.38 & 6.28 (s, 1H), 4.12 (s, 2H).



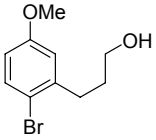
Prepared according to Afarinkia *et al*.[132] Pale yellow solid, mp = 41-42 ºC (Lit. 43-44 ºC[132]). CH_2Cl_2, R_f = 0.76. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.30 (s, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 158.4, 152.1, 150.4, 111.1, 106.6. IR(film) ν 3089, 1758, 1617, 1598, 1524, 1374, 1288, 1166, 1084, 1057, 823 cm^{-1}.



Prepared according to Afarinkia *et al*.[132] White needles, mp = 57-58 ºC (Lit. 59 ºC[132]). CH_2Cl_2, R_f = 0.51. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.44 (dd, *J* = 0.8, 5.6, 1H), 6.40 (dd, *J* = 0.8, 2.0, 1H), 6.28 (dd, *J* = 2.0, 5.6, 1H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 160.0, 151.2, 150.7, 114.6, 108.8. IR(film) ν 3078, 1720, 1612, 1535, 1413, 1240, 1170, 1039, 864, 824, 780, 689 cm^{-1}.

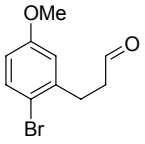


The 3-(3-methoxyphenyl)propionic acid (10.00 g, 55.5 mmol) was dissolved in CH_2Cl_2 (140 mL) and cooled to 0 ºC, where Br_2 (2.9 mL, 56.6 mmol) was added dropwise over 10 min. After 15 min. the solution was poured into 200 mL of water and extracted with 2 x 50 mL of CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered and evaporated *in vacuo*. Yield of **4.8a**: 14.10 g (98 %). White Solid, mp = 80-81 ºC (Lit. 81-83 ºC)[145]. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.8, 1H), 6.82 (d, *J* = 3.0, 1H), 6.66 (dd, *J* = 3.0, 8.8), 3.78 (s, 3H), 3.03 (t, *J* = 7.8, 2H), 2.71 (t, *J* = 7.8, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 179.0, 159.0, 140.3, 133.4, 116.1, 114.7, 113.8, 55.4, 33.8, 31.2. IR(film) ν 2936, 1706, 1595, 1572, 1472, 1413, 1241, 1162, 1057, 1023, 802 cm^{-1}. LCMS $[M+K]^+$: 297.

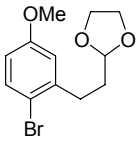


LAH (3.1 g, 81.7 mmol) was suspended in THF (252 mL) at 0 ºC under Ar. The acid **4.8a** (14.10 g, 54.4 mmol) in THF (20 mL) was added dropwise. (Flask rinsed with 3 x 7 mL of THF and added successively). The cooling bath was

removed and the suspension warmed to rt over 2 h. It was then recooled to 0 ºC and quenched by slow addition of H_2O (3.1 mL), 10 % NaOH (6.2 mL) and H_2O (9.3 mL). The cooling bath was removed and the slurry was dried with $MgSO_4$ at rt. The white salts were filtered off and the solvent was evaporated *in vacuo*. Yield of **4.8b**: 12.34 g (93 %). Colorless oil - 3:2 Hexanes:EtOAc (v/v), R_f = 0.38. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.7, 1H), 6.79 (d, *J* = 3.1, 1H), 6.62 (dd, *J* = 3.1, 8.7, 1H), 3.76 (s, 3H), 3.69 (t, *J* = 6.4, 2H), 2.75-2.82 (m, 2H), 2.00 (s, 1H), 1.84-1.92 (m, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 158.9, 142.0, 133.2, 116.0, 114.8, 113.1, 62.0, 55.3, 32.6, 32.5. IR(film) ν 3050-3600, 2952, 2836, 1596, 1571, 1474, 1275, 1241, 1161, 1053, 1013 cm^{-1}. LCMS $[M+Na]^+$: 267.

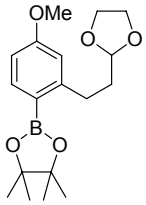


Solution 1: The alcohol **4.8b** (11.46 g, 46.76 mmol) was dissolved in CH_2Cl_2 (117 mL) and the mixture was cooled to 0 ºC. **Solution 2**: Aqueous $NaHCO_3$ (7.0 g in 70 mL of H_2O) was mixed with 70 mL of 0.83 M NaOCl (58.1 mmol). Solution 2 was cooled to 12 ºC and added to solution 1 after addition of TEMPO (77.5 mg, 0.5 mmol). Then KBr (557 mg, 4.68 mmol) was added and the biphasic system was stirred vigorously for 1 h. It was quenched sat. aq. $Na_2S_2O_3$ (20 mL). The phases were separated and the aqueous phase was extracted with 2 x 100 mL of CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered and evaporated *in vacuo*. Yield of **4.9**: 10.58 g (93 %). Colorless oil - 4:1 Hexanes:EtOAc (v/v), R_f = 0.35. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.82 (t, *J* = 1.3, 1H), 7.40 (d, *J* = 8.8, 1H), 6.79 (d, *J* = 3.0, 1H), 6.64 (dd, *J* = 3.0, 8.8, 1H), 3.77 (s, 1H), 3.01 (t, *J* = 7.6, 2H), 2.76-2.81 (m, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 200.9, 159.0, 140.6, 133.4, 116.2, 114.5, 113.6, 55.4, 43.6, 28.8. IR(film) ν 2832, 2722, 1720, 1595, 1572, 1474, 1406, 1277, 1242, 1162, 1058, 1013 cm^{-1}.

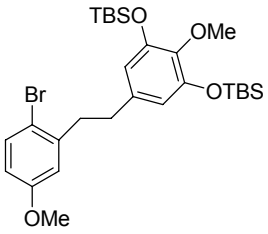


The aldehyde **4.9** (11.42 g, 46.98 mmol) was dissolved in toluene (59 mL), and ethylene glycol (3.0 mL, 53.65 mmol) and 593 mg of PPTS (2.36 mmol) were added. The solution was refluxed for 3 h and then poured into 400 mL of H_2O and 100 mL of EtOAc. The organic phase was washed with 2 x 200 mL of H_2O, dried with $MgSO_4$, filtered and evaporated *in vacuo*. Yield of **4.9a**: 13.07 g (97 %). Pale yellow oil - 4:1 Hexanes:EtOAc (v/v), R_f = 0.35. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.7 1H), 6.80 (d, *J* = 3.1, 1H), 6.62 (dd, *J* = 3.1, 8.7, 1H), 4.93 (t, *J* = 4.6, 1H), 3.96-4.03 (m, 2H), 3.86-3.92 (m, 2H), 3.76 (s, 3H), 2.79-2.85 (m, 2H), 1.94-2.01 (m, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 158.9, 141.8, 133.2, 115.9, 114.8, 113.3, 103.7, 64.9, 55.4, 33.6, 30.8. IR(film) ν 2955, 2881,

1596, 1572, 1474, 1413, 1280, 1240, 1138, 1033, 1013 cm^{-1}. HRMS $[M+Na]^+$: calcd 309.0097, found 309.0098.

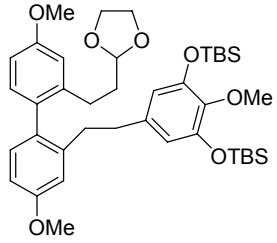


The bromide **4.9a** (11.46 g, 39.91 mmol) was dissolved in THF (200 mL) under Ar and cooled to -78 ºC. Then n-BuLi (43.68 mmol, 2.08 M in hexanes, 21 mL) was added dropwise. After full addition the slurry was stirred for 30 min. before the addition of 11.0 mL of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (53.92 mmol). The cooling bath was removed and the solution was allowed to warm to rt, where it was quenched with H_2O (500 mL) and extracted with 3 x 100 mL of CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered and evaporated *in vacuo*. Yield of **4.10**: 12.20 g (92 %). Colorless oil - 4:1 Hexanes:EtOAc (v/v), $R_f = 0.32$. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.2, 1H), 6.76 (d, *J* = 2.4, 1H), 6.72 (dd, *J* = 2.5, 8.2, 1H), 4.91 (t, *J* = 5.0, 1H), 3.94-4.01 (m, 2H), 3.84-3.92 (m, 2H), 3.80 (s, 3H), 2.97-3.03 (m, 2H), 1.89-1.95 (m, 2H), 1.33 (s, 12H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 161.7, 151.1, 138.1, 115.0, 110.5, 104.4, 83.1, 64.8, 55.0, 37.0, 30.7, 24.8. IR(film) ν 2976, 2884, 1600, 1566, 1380, 1347, 1316, 1231, 1144, 1126 cm^{-1}. HRMS $[M+Na]^+$: calcd 357.1844, found 357.1842.

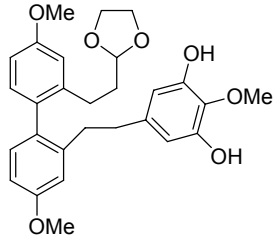


The phosphonium salt **4.6** (13.67 g, 23.20 mmol) was suspended in THF (116 mL) under Ar and cooled to 0 ºC. Then 2.22 g of ^{t}BuOK (19.78 mmol) was added and the suspension stirred for 1 h. The aldehyde **4.3** (7.08 g, 17.85 mmol) in THF (15 mL) was added – the flask was rinsed with 3 x 3 mL of THF. The cooling bath was removed and the slurry stirred overnight. The suspension was run through a pad of silica, which was washed with 5 x 50 mL of 1 % EtOAc in hexanes. The solvent was removed *in vacuo* and the residue flash chromatographed on a short column in 1 % EtOAc in hexanes. Yield: 10.35 g as a 1:1 mixture of E:Z stilbenes (Q). The stilbenes (2.00 g, 3.45 mmol) were dissolved in EtOAc (15 mL), 5 % Pt/C (2.1 g) was added and the mixture stirred vigorously under a 42 bar H_2-atmosphere for 3 h. The slurry was filtered through a pad of Celite and the solvent was removed *in vacuo*. Yield of **4.7**: 2.00 g (Q). Colorless oil - 4:1 Hexanes:EtOAc (v/v), $R_f = 0.78$. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.7, 1H), 6.67 (d, *J* = 3.0, 1H), 6.62 (dd, *J* = 3.1, 8.7, 1H), 6.35 (s, 2H), 3.73 (s, 3H), 3.70 (s, 3H), 2.83 (ddd, *J* = 7.1, 10.1, 15.9, 4H), 1.01 (s, 18H), 0.16 (s, 12H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 158.8, 149.5, 141.8, 141.1, 136.5, 133.2, 116.2, 114.8, 113.3,

59.9, 55.3, 38.5, 35.6, 25.8, 18.3, -4.7. IR(film) ν 2953, 2930, 2857, 1576, 1491, 1472, 1432, 1356, 1250, 1226, 1087, 1016, 832, 784 cm^{-1}.

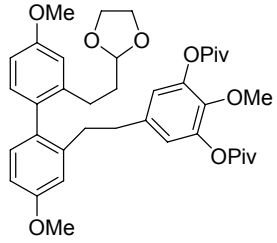


The bromide **4.7** (2.773 g, 4.767 mmol) and borolane **4.10** (2.07 g, 6.19 mmol) were dissolved in dioxane (24 mL) and degassed by sonication under Ar-purging. Then 2 M NaOH (3.1 mL, 6.2 mmol) and 175 mg of $PdCl_2$(dppf) (0.239 mmol, 5 mol %) were added. The solution was heated to 80 ºC, where it was stirred for 5 h. The dark solution was poured into 200 mL of H_2O and extracted with 3 x 100 mL of CH_2Cl_2. The combined organic phases were washed with brine (400 mL), dried with $MgSO_4$, filtered and the solvent was removed *in vacuo*. Purification by flash chromatography in 10 % EtOAc in hexanes. Yield of **4.7a**: 2.539 g (75 %). White solid, mp = 93 ºC. 4:1 Hexanes:EtOAc (v/v), R_f = 0.40. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.02 (d, *J* = 8.3, 1H), 6.99 (d, *J* = 8.3, 1H), 6.85 (d, *J* = 2.6, 1H), 6.80 (d, *J* = 2.6, 1H), 6.77 (d, *J* = 2.56 , 1H), 6.75 (d, *J* = 2.6, 1H), 6.08 (s, 2H), 4.70 (t, *J* = 4.9, 1H), 3.85-3.90 (m, 2H), 3.83 (s, 6H), 3.75 (m, 2H), 3.66 (s, 3H), 2.38-2.62 (m, 6H), 1.73-1.82 (m, 2H), 0.98 (s, 18H), 0.12 (s, 12H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 158.8, 158.7, 149.3, 141.3, 141.1, 140.8, 137.0, 132.9, 131.3, 114.5, 114.2, 111.0, 110.9, 103.9, 64.7, 59.9, 55.2, 55.1, 37.1, 36.1, 34.8, 28.1, 25.7, 18.3, -4.7. IR(film) ν 2952, 2931, 2890, 2857, 1605, 1576, 1484, 1431, 1355, 1231, 1085, 1052, 1004, 831 cm^{-1}.

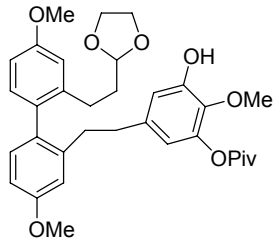


The disilylether **4.7a** (3.23 g, 4.56 mmol) was dissolved in THF (45 mL) under Ar and cooled to 0 ºC. Then 1 M TBAF (18 mL) was added and the cooling bath was removed. The solution darkened as it stirred for 3 h, where it was extracted from 30 % NH_4Cl with 1 x 100 and 2 x 50 mL of EtOAc. The combined organic phases were dried with $MgSO_4$, filtered and evaporated *in vacuo*. Purification by flash chromatography in 40-50 % EtOAc in hexanes. Yield of **4.7b**: 2.03 g (93 %). Slightly pink foam. 3:2 Hexanes:EtOAc (v/v), R_f = 0.15. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.01 (d, *J* = 8.2, 1H), 6.99 (d, *J* = 8.3, 1H), 6.86 (d, *J* = 2.6, 1H), 6.80 (d, *J* = 2.6, 1H), 6.74-6.79 (m, 2H), 6.11 (s, 2H), 5.45 (br s, 2H), 4.72 (t, *J* = 4.9, 1H), 3.88-3.91 (m, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.77-3.80 (m, 2H), 2.39-2.65 (m, 6H), 1.72-1.82 (m, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 158.7, 158.6, 148.6, 141.0, 138.6, 132.9, 132.7, 131.3, 131.2, 114.3, 111.0, 110.9, 107.9, 103.9, 64.7, 61.0, 55.2, 36.4, 35.1, 34.6, 28.0. IR(film)

ν 3150-3600, 2936, 2836, 1604, 1526, 1508, 1483, 1458, 1346, 1278, 1231, 1163, 1136, 1048, 1001 cm^{-1}. HRMS $[M+Na]^+$: calcd 503.2046, found 503.2042.

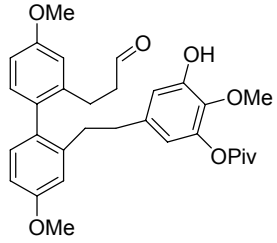


The diol **4.7b** (1.660 g, 3.45 mmol) was dissolved in CH_2Cl_2 (14 mL) under Ar and pyridine (4.2 mL, 51.8 mmol), PivCl (4.3 mL, 34.5 mmol) and DMAP (89 mg, 0.69 mmol) were added. The solution was stirred at rt for 18 h, quenched with 20 % NH_4Cl (200 mL) and extracted with 3 x 50 mL of CH_2Cl_2. The combined organic phases were washed with sat. aq. $NaHCO_3$ (100 mL), dried with $MgSO_4$, filtered and evaporated *in vacuo*. Purification by flash chromatography in 20-25 % acetone in hexanes to yield 2.11 g of diester **4.7c** (94%). White solid, mp = 126 ºC. 3:2 Hexanes:EtOAc (v/v), R_f = 0.58. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.03 (dd, *J* = 0.7, 7.9, 1H), 6.99 (d, *J* = 8.3, 1H), 6.85 (d, *J* = 2.6, 1H), 6.75-6.80 (m, 3H), 6.46 (s, 2H), 4.70 (t, *J* = 4.9, 1H), 3.86-3.90 (m, 2H), 3.83 (s, 3H), 3.82 (s, 2H), 3.75-3.79 (m, 2H), 3.69 (s, 3H), 2.37-2.67 (m, 6H), 1.73-1.82 (m, 2H), 1.36 (s, 9H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 176.3, 158.8, 158.7, 144.5, 142.0, 141.1, 140.9, 137.7, 132.9, 132.8, 131.3, 120.3, 114.3, 114.2, 111.3, 110..9, 103.8, 64.7, 61.2, 55.2, 55.1, 39.0, 36.6, 35.5, 34.7, 28.0, 27.1. IR(film) ν 2974, 1757, 1606, 1576, 1502, 1482, 1278, 1235, 1106, 1039 cm^{-1}.

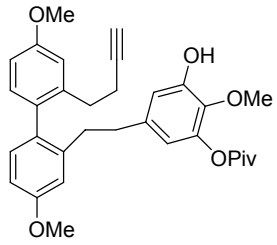


The diester **4.7c** (1.598 g, 2.46 mmol) was dissolved in DME (25 mL) and 1.601 g of Cs_2CO_3 (4.93 mmol) was added. The suspension was refluxed under Ar for 16 h, where more DME (10 mL) was added. The suspension was further refluxed for 27 h. After cooling to rt the slurry was poured into 100 mL of CH_2Cl_2 and washed with 20 % NH_4Cl (200 mL). The aqueous phase was extracted with 3 x 50 mL of CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by flash chromatography in 30 % acetone in hexanes. Yield of **4.12**: 1.109 g (80 %) (brsm 94 %). White solid, mp = 72-75 ºC. 3:2 Hexanes:EtOAc (v/v), R_f = 0.33. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.02 (d, *J* = 8.3, 1H), 6.98 (d, *J* = 8.3, 1H), 6.86 (d, *J* = 2.7, 1H), 6.80 (d, *J* = 2.6, 1H), 6.78 (dd, *J* = 1.2, 2.7, 1H), 6.76 (dd, *J* = 1.1, 2.7, 1H), 6.40 (d, *J* = 2.0, 1H), 6.17 (d, *J* = 2.0, 1H), 5.68 (br s, 1H), 4.71 (t, *J* = 4.9, 1H), 3.86-3.91 (m, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.75-3.79 (m, 2H), 2.38-2.66 (m, 6H), 1.74-1.81 (m, 2H), 1.37 (s, 9H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 176.3, 158.8, 158.7, 149.3, 143.4, 141.1, 141.0, 138.4, 137.0, 132.9, 131.3, 114.4, 114.3, 113.0, 111.1, 111.0,

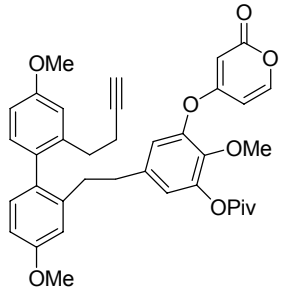
103.9, 64.7 61.4, 55.2, 39.0, 36.7, 35.4, 34.7, 28.0, 27.1. IR(film) ν 3200-3600, 2958, 1753, 1605, 1483, 1278, 1233, 1119, 1043, 1001 cm^{-1}.



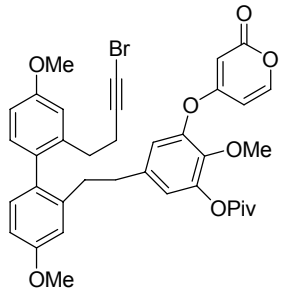
The acetal **4.12** (0.3747 g, 0.665 mmol) was dissolved in THF (9 mL), 1 M HCl (4.5 mL) was added and the mixture was stirred overnight at 50 ºC. The solution was extracted from sat. aq. NH_4Cl with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered and evaporated *in vacuo*. Purification by flash chromatography in 40 % EtOAc in hexanes. Yield of **4.12a**: 0.3201 g (93 %). Colorless oil - 3:2 Hexanes:EtOAc (v/v), R_f = 0.37. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.61 (t, *J* = 1.4, 1H), 6.98-7.04 (m, 2H), 6.75-6.84 (m, 4H), 6.41 (d, *J* = 2.0, 1H), 6.17 (d, *J* = 2.0, 1H), 5.79 (br s, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.75 (s, 3H), 2.48 (m, 8H), 1.38 (s, 9H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 201.6, 176.3, 158.9, 149.3, 143.4, 141.0, 139.8, 138.2, 137.0, 132.8, 132.5, 131.5, 131.2, 114.4, 113.0, 111.3, 111.2, 61.4, 55.2, 44.6, 39.0, 36.8, 35.4, 27.1, 26.0. IR(film) ν 3200-3600, 2965, 2831, 1752, 1719, 1605, 1482, 1458, 1277, 1233, 1165, 1117, 1042, 1002 cm^{-1}.



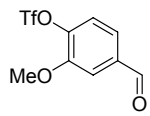
The aldehyde **4.12a** (0.1069 g, 0.205 mmol) was dissolved in MeOH (2.5 mL), K_2CO_3 (68.1 mg, 0.493 mmol) and 50.0 mg of the Ohira-Bestmann reagent (0.260 mmol) in 0.2 mL of MeOH were added. The suspension was stirred for 2½ h at rt, where 2 drops of the Ohira-Bestmann reagent was added. The mixture was stirred for another 2 h. The reaction was diluted with 10 mL of Et_2O, quenched with sat. aq. NH_4Cl and extracted with 2 x 10 mL of Et_2O. The combined organic phases were dried with $MgSO_4$, filtered and evaporated *in vacuo*. Purification by flash chromatography in 25 % EtOAc in hexanes. Yield of **4.13**: 53.1 mg (50 %). White solid, mp = 116-118 ºC. 3:2 Hexanes:EtOAc (v/v), R_f = 0.51. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.03 (d, *J* = 8.3, 1H), 7.00 (d, *J* = 8.3, 1H), 6.91 (d, *J* = 2.3), 6.77-6.83 (m, 3H), 6.42 (d, *J* = 2.0, 1H), 6.17 (d, *J* = 2.0, 1H), 5.58 (br s, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.76 (s, 3H), 2.50-2.65 (m, 6H), 2.24-2.30 (m, 2H), 1.91 (t, *J* = 2.6, 1H9, 1.40 (s, 9H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 176.6, 159.0, 158.9, 149.5, 143.6, 141.3, 140.0, 138.6, 137.2, 133.0, 132.9, 131.6, 131.5, 114.8, 114.7, 114.6, 113.2, 111.5, 111.4, 84.1, 69.1, 61.7, 55.4, 39.3, 37.0, 35.6, 32.6, 27.4, 19.7. IR(film) ν 3200-3600, 2959, 2937, 2835, 1752, 1605, 1506, 1482, 1459, 1278, 1233, 1162, 1117, 1044, 1002 cm^{-1}.



The phenol **4.13** (58.2 mg, 0.113 mmol) and 29.4 mg of pyrone **4.16** (0.225 mmol) were dissolved in DMF (2.3 mL), 40.9 mg of Cs_2CO_3 (0.126 mmol) was added and the mixture was stirred in a 50 ºC oil bath for 1½ h. The solution was cooled < 10 ºC and diluted with 10 mL of Et_2O, 4 % brine (50 mL) was added and the mixture was extracted with 2 x 10 mL of Et_2O. The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography in 25 % EtOAc in hexanes. Yield of **4.17**: 48.8 mg (71 %). Pale yellow oil. 3:2 Hexanes:EtOAc (v/v), R_f = 0.37. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.45 (d, *J* = 5.9, 1H), 7.04 (dd, *J* = 1.3, 7.4, 1H), 6.98 (d, *J* = 8.3, 1H), 6.90 (d, *J* = 2.6, 1H), 6.78-6.81 (m, 3H), 6.55 (d, *J* = 2.0, 1H), 6.45 (d, *J* = 2.0, 1H), 6.12 (dd, *J* = 2.4, 5.9, 1H), 5.36 (d, *J* = 2.4, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.69 (s, 3H), 2.50-2.69 (m, 6H), 2.25-2.29 (m, 6H), 1.89 (t, *J* = 2.6, 1H), 1.36 (s, 9H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 176.6, 168.9 163.8, 159.1, 159.0, 152.5, 145.2, 142.2, 140.7, 140.0, 138.6, 132.9, 132.8, 131.6, 121.5, 119.9, 114.8, 111.6, 111.5, 102.4, 94.5, 84.0, 69.1, 61.4, 55.5, 55.4, 39.3, 36.6, 35.6, 32.6, 27.3, 19.7. IR(film) ν 3290, 2959, 2936, 2836, 1753, 1726, 1641, 1606, 1561, 1482, 1432, 1326, 1278, 1234, 1199, 1162, 1110, 1056, 1037, 1002 cm^{-1}. LCMS $[M+Na]^+$: 633. HRMS $[M+H]^+$: calcd 611.2639, found 611.2645.

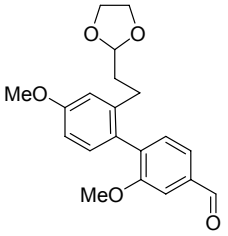


The alkyne **4.17** (91.4 mg, 0.150 mmol) was dissolved in acetone (2.0 mL), 3.1 mg of $AgNO_3$ (18.2 μmol) and 31.2 mg of NBS (0.175 mmol) were added. The solution was stirred for 1½ h and concentrated *in vacuo*. Purification by flash chromatography in 30 % EtOAc in hexanes. Yield of **4.17a**: 86.9 mg (84 %). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.45 (dd, *J* = 0.6, 5.9, 1H), 7.03 (d, *J* = 8.8, 1H), 6.98 (d, *J* = 8.3, 1H), 6.86 (d, *J* = 2.6, 1H), 6.80 (d, *J* = 2.9, 1H), 6.77-6.79 (m, 3H), 6.55 (d, *J* = 2.1, 1H), 6.44 (d, *J* = 2.1, 1H), 6.13 (dd, *J* = 2.4, 5.9, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.69 (s, 3H), 2.47-2.66 (m, 6H), 2.28 (t, *J* = 7.3, 2H), 1.36 (s, 9H).

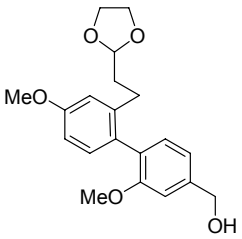


Vanillin (0.740 g, 4.86 mmol) was dissolved in CH_2Cl_2 (6.0 mL), and 1.5 mL of pyridine was added. The mixture was cooled to 0 ºC, and 0.9 mL of Tf_2O (5.35 mmol) in CH_2Cl_2 (3.0 mL) was added. After full addition the cooling bath was removed and the solution was allowed to warm to rt over 1 h. The solution was quenched with 20 % NH_4Cl and extracted three times with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$,

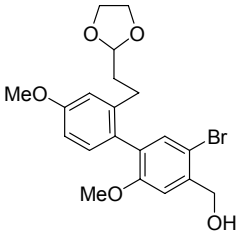
filtered and concentrated *in vacuo* to yield 1.351 g (98 %) of vanillin triflate, which was used immediately.[146] Pale yellow oil. 3:2 Hexanes:EtOAc (v/v), R_f = 0.41. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 7.56 (d, *J* = 1.8, 1H), 7.50 (dd, *J* = 1.8, 8.2, 1H), 7.40 (d, *J* = 8.2, 1H), 3.99 (s, 3H).



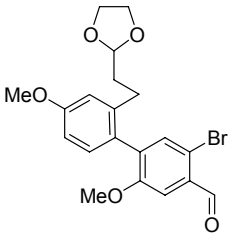
The triflate of vanillin (3.150 g, 11.08 mmol) and the boronic ester **4.10** (4.30 g, 12.87 mmol) were dissolved in DME (55 mL), and the solution was degassed by sonication. Then 2 M NaOH (12.0 mL) was added, followed by 343 mg of $PdCl_2$dppf (0.469 mmol). The dark solution was placed in an 80 ºC oil bath and stirred for 1 h. The black solution was poured into 100 mL of CH_2Cl_2 after cooling and washed with 8 % NH_4Cl (500 mL). The aqueous phase was extracted with 4 x 50 mL of CH_2Cl_2. The combined organic phases were washed with 12 % NaCl (300 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography in 25-30 % EtOAc in hexanes. Yield of **4.19**: 2.769 g (73 %). Pale yellow oil. 3:2 Hexanes:EtOAc (v/v), R_f = 0.38. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 7.50 (dd, *J* = 1.3, 7.5, 1H), 7.45-7.47 (m, 1H), 7.31 (d, *J* = 7.5, 1H), 7.07 (d, *J* = 8.4, 1H), 6.87 (d, *J* = 2.5, 1H), 6.81 (dd, *J* = 2.6, 1H), 4.71 (t, *J* = 4.8, 1H), 3.84-3.89 (m, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.74-3.79 (m, 2H), 2.48-2.58 (m, 2H), 1.75-1.85 (m, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 191.9, 159.4, 157.5, 141.4, 137.3, 136.9, 132.1, 130.9, 129.5, 124.2, 114.3, 111.3, 108.9, 103.9, 64.8, 55.6, 55.2, 34.7, 27.9.



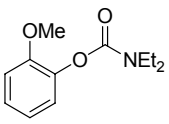
The aldehyde **4.19** (0.840 g, 2.45 mmol) was dissolved in MeOH (25 mL), and $NaBH_4$ (0.141 g, 3.73 mmol) was added. The solution was stirred for 1 h and then concentrated in vacuo. The residue was dissolved in EtOAc (50 mL) and washed with 100 mL of 20 % NH_4Cl. The aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Yield of **4.19a**: 0.845 g (Q). Colorless oil. 3:2 Hexanes:EtOAc (v/v), R_f = 0.10. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 7.5, 1H), 7.06 (d, *J* = 8.4, 1H), 6.95-6.99 (m, 2H), 6.86 (d, *J* = 2.6, 1H), 6.79 (dd, *J* = 2.7, 8.4, 1H), 4.74 (s, 2H), 4.72 (t, *J* = 4.9, 1H), 3.87-3.89 (m, 2H), 3.83 (s, 3H), 3.76 (s, 3H), 3.76-3.78 (m, 2H), 2.50-2.59 (m, 2H), 1.76-1.84 (m, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 158.9, 157.2, 141.6, 141.4, 131.6, 131.3, 130.5, 129.6, 118.8, 114.2, 111.1, 109.2, 104.1, 65.4, 64.8, 55.4, 55.2, 34.6, 28.0.



The alcohol **4.19a** (0.7908 g, 2.296 mmol) was dissolved in THF (46 mL) under N_2 and the flask was wrapped in tin foil. Then 0.452 g of NBS (2.540 mmol) was added in one portion and the solution stirred for 1 h at rt, where it was quenched with 10 mL of sat. aq. $Na_2S_2O_3$. The solution was concentrated *in vacuo* and the residue was taken up in EtOAc (50 mL), and washed with 100 mL of 10 % NH_4Cl. The aqueous phase was extracted with 4 x 25 mL of CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography in 40 % EtOAc in hexanes. Yield of **4.19b**: 0.7725 g (80 %). Colorless oil. 3:2 Hexanes:EtOAc (v/v), R_f = 0.16. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.30 (s, 1H), 7.14 (s, 1H), 7.04 (d, *J* = 8.4, 1H), 6.86 (d, *J* = 2.6, 1H), 6.78 (dd, *J* = 2.7, 8.4, 1H), 4.72-4.76 (m, 3H), 3.86-3.90 (m, 2H), 3.81 (s, 3H), 3.74-3.78 (m, 2H), 3.75 (s, 3H), 3.00 (br s, 1H), 2.50-2.60 (m, 2H), 1.79-1.88 (m, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 159.0, 156.3, 141.4, 139.6, 134.5, 131.1, 130.9, 128.9, 114.0, 111.7, 111.0, 110.7, 103.7, 64.6, 64.5, 55.5, 55.0, 34.4, 27.6.

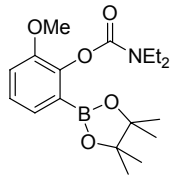


The alcohol **4.19b** (0.6287 g, 1.485 mmol) was dissolved in CH_2Cl_2 (8.0 mL), and 0.650 g of PCC (3.02 mmol) and 0.75 g of Celite were added. The slurry was stirred for 3 h at rt, where it was filtered through a pad of Celite, which was rinsed thoroughly with CH_2Cl_2. The filtrate was concentrated *in vacuo* and the residue was run through a short column with 20 % EtOAc in hexanes. Yield of **4.20**: 0.6165 g (99 %). 2:3 Hexanes:EtOAc (v/v), R_f = 0.73. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.34 (s, 1H), 7.47 (s, 1H), 7.42 (s, 1H), 7.05 (d, *J* = 8.4, 1H), 6.86 (d, *J* = 2.6), 6.81 (dd, *J* = 2.6, 8.4, 1H), 4.73 (t, *J* = 4.7, 1H), 3.87-3.91 (m, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 3.76-3.81 (m, 2H), 2.47-2.57 (m, 2H), 1.79-1.86 (m, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 191.7, 159.7, 156.7, 141.4, 138.7, 136.2, 132.9, 130.8, 128.1, 118.1, 114.4, 111.4, 110.5, 103.7, 64.8, 55.9, 55.2, 34.6, 27.7.

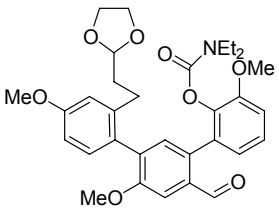


Guaiacol (10.0 g, 80.6 mmol) was dissolved in pyridine (322 mL), and 10.8 mL of carbamoyl chloride (84.6 mmol) was added. The solution was refluxed for 6 h and then concentrated *in vacuo*. The residue was taken up in 200 mL of Et_2O, washed with 200 mL of 20 % NH_4Cl. The aqueous phase was extracted with 4 x 50 mL of Et_2O. The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography in 20 % EtOAc in hexanes. Yield of **4.21**: 10.5 g (58 %).

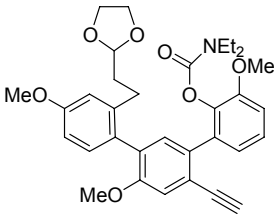
3:2 Hexanes:EtOAc (v/v), R_f = 0.51. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.06-7.26 (m, 2H), 6.88-6.96 (m, 2H), 3.82 (s, 3H), 3.35-3.50 (m, 4H), 1.17-1.31 (m, 6H).



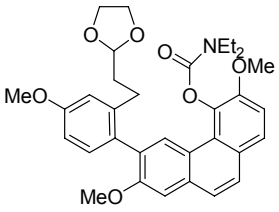
^{t}BuLi (5.0 mL, 1.15 M in pentane, 5.75 mmol) was added dropwise to THF (27 mL) at -78 ºC. Then 0.7 mL of TMEDA (4.67 mmol) was added, followed by 1.00 g of carbamate **4.21** (4.48 mmol) in THF (20 mL). After full addition the yellow solution was stirred for 1 h, where 6.1 mL of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.72 mmol) was added. The mixture warmed to rt in the cooling bath overnight. The solution was transferred to a separatory funnel with 100 mL of CH_2Cl_2 and washed with 300 mL of 13 % NH_4Cl. The aqueous phase was extracted with 4 x 50 mL of CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered and evaporated *in vacuo*. Yield of **4.22**: 1.55 g (99 %). 3:2 Hexanes:EtOAc (v/v), R_f = 0.44. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.33 (dd, *J* = 1.6, 7.5, 1H), 7.14 (dd, *J* = 7.4, 8.1, 1H), 7.03 (dd, *J* = 1.5, 8.2), 3.81 (s, 3H), 3.50 (br q, *J* = 6.9, 13.8, 2H), 3.39 (br q, *J* = 6.5, 13.7, 2H), 1.28-1.34 (m, 15H), 1.20 (br t, *J* = 7.0, 3H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 154.2, 151.7, 145.2, 127.2, 125.5, 115.3, 83.4, 56.1, 42.0, 41.7, 24.8, 14.0, 13.4. IR(film) ν 2976, 2937, 1718, 1577, 1465, 1417, 1355, 1320, 1271, 1160, 1051 cm^{-1}.



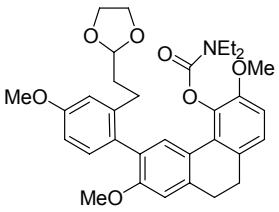
The bromide **4.20** (0.548 g, 1.30 mmol) and the boronic ester **4.22** (0.548 g, 1.56 mmol) were dissolved in DME (6.5 mL) and the mixture was degassed by N_2-purge during sonication. Then 0.80 mL of 2 M NaOH and 48.2 mg of $PdCl_2$dppf (65.9 μmol) were added and the dark solution was stirred in an 80 ºC oil bath for 2 h. After cooling the solution was transferred to a separatory funnel with 50 mL of CH_2Cl_2 and washed with 100 mL of 18 % NaCl. The aqueous phase was extracted with 3 x 25 mL of CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography in 40 % EtOAc in hexanes. Yield of **4.23**: 0.630 g (86 %). 2:3 Hexanes:EtOAc (v/v), R_f = 0.43. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 7.54 (s, 1H), 7.18-7.23 (m, 2H), 7.05 (br d, *J* = 8.2, 1H), 7.00 (dd, *J* = 1.4, 8.3, 1H), 6.91 (br d, *J* = 6.5, 1H), 6.85 (d, *J* = 2.6, 1H), 6.76 (dd, *J* = 2.6, 8.4, 1H), 4.73 (t, *J* = 4.8, 1H), 3.85 (s, 3H), 3.84-3.87 (m, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 3.73-3.77 (m, 2H), 3.15-3.26 (br m, 4H), 2.46-2.64 (br m, 2H), 1.77-1.91 (br m, 2H), 0.90-1.07 (br m, 6H). LCMS: $[M+H]^+$: 564. $[M+Na]^+$: 586.



The aldehyde **4.23** (1.360 g, 2.413 mmol) was dissolved in MeOH (24 mL), 0.669 g of K_2CO_3 (4.840 mmol) and 0.715 g of Ohira-Bestmann's reagent (3.72 mmol) were added – the flask was rinsed with 1.0 mL of MeOH. The suspension was stirred at rt for 2 h under N_2, where it was diluted with 100 mL of Et_2O and poured into 300 mL of 12 % NaCl. The aqueous phase was extracted with 3 x 50 mL of Et_2O. The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography in 40-60 % EtOAc in hexanes. Yield of **4.24**: 1.1473 g (86 %). White solid. 2:3 Hexanes:EtOAc (v/v), R_f = 0.48. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.16-7.21 (m, 2H), 7.13 (s, 1H), 7.03-7.07 (m, 2H), 6.95 (dd, *J* = 1.5, 8.2, 1H), 6.84 (d, *J* = 2.6, 1H), 6.75 (dd, *J* = 2.7, 8.4, 1H), 4.75 (t, *J* = 4.8, 1H), 3.86-3.90 (m, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.77 (s, 3H), 3.75-3.79 (m, 2H), 3.19-3.36 (m, 4H), 3.50-3.62 (m, 2H), 3.03 (s, 1H), 1.78-1.90 (m, 2H), 0.97-1.09 (m, 6H). ^{13}C-NMR (100.5 MHz, $CDCl_3$): δ 158.9, 155.6, 153.4, 152.0, 141.4, 138.3, 134.4, 133.1, 132.8, 131.1, 130.9, 129.6, 124.9, 123.1, 121.1, 114.5, 113.9, 111.5, 111.0, 103.9, 82.9, 79.6, 64.6, 56.0, 55.4, 55.0, 41.9, 41.8, 34.5, 27.4, 13.8, 13.2.

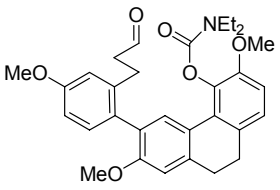


The alkyne **4.24** (1.0212 g, 1.825 mmol) and 48.6 mg of $PtCl_2$ (0.183 mmol) were dissolved in toluene (9.0 mL) and stirred under N_2 at 80 ºC for 2½ h. The brown suspension was concentrated *in vacuo* to ¼ of the volume and purified by flash chromatography in 45 % EtOAc in hexanes. Yield of **4.24a**: 0.5846 g (57 %). White foam. 2:3 Hexanes:EtOAc (v/v), R_f = 0.41. ^{1}H-NMR (400 MHz, *d*6-acetone): δ 8.87-8.95 (m 1H), 7.81 (d, *J* = 8.8, 1H), 7.73 (d, *J* = 8.9, 1H), 7.66 (d, *J* = 7.66, 1H), 7.48 (s, 1H), 7.43 (d, *J* = 8.8, 1H), 7.09-7.20 (m, 1H), 6.92 (d, *J* = 2.4, 1H), 6.85 (dd, *J* = 2.7, 8.3, 1H), 4.59 (t, *J* = 4.8, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 3.85 (s, 3H), 3.66-3.75 (m 2H), 3.56-3.65 (m, 2H), 3.13-3.47 (m, 4H), 2.47-2.65 (m, 2H), 1.65-1.80 (m, 2H), 0.95-1.15 (m, 6H). LRMS: $[M+H]^+$: 560. $[M+Na]^+$: 582.

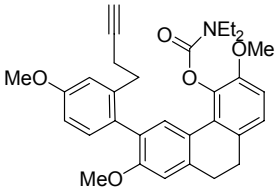


The phenanthrene **4.24a** (0.610 g, 1.090 mmol) was dissolved in MeOH (12.0 mL), 640 mg of 10 % Pd/C was added, and the mixture was stirred under a 28 bar H_2-atmosphere for 21 h. The slurry was filtered, concentrated *in vacuo* and purified by flash chromatography in 40 % EtOAc in hexanes. Yield of **4.25**: 511 mg (84 %). Colorless oil. 2:3 Hexanes:EtOAc (v/v), R_f = 0.45. ^{1}H-NMR (400 MHz, acetone- *d*6): δ 7.72 (s, 1H), 7.08 (d, *J* = 8.3, 1H), 7.03 (d, *J* = 8.2,

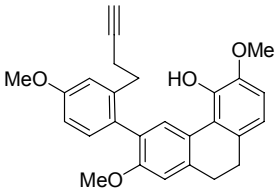
1H), 6.98 (s, 1H), 6.88 (d, *J* = 8.3, 1H), 6.86 (d, *J* = 2.7, 1H), 6.80 (dd, *J* = 2.6, 8.3, 1H), 4.66 (t, *J* = 4.7, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H), 3.67-3.84 (m, 4H), 3.09-3.55 (m, 4H), 2.73-2.85 (m, 4H), 2.48-2.60 (m, 2H), 1.68-1.80 (m, 2H), 0.93-1.12 (m, 6H). LRMS: $[M+Na]^+$: 584.



The acetal **4.25** (0.4345 g, 0.7736 mmol) was dissolved in MeOH (10.5 mL), 1 M HCl (5.5 mL) was added and the solution was stirred at 50 ºC overnight. The reaction was poured into 100 mL of 20 % NH_4Cl and extracted with 4 x 50 mL of CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford a quantitative yield of **4.25a**, 0.399 g. 2:3 Hexanes:EtOAc (v/v), R_f = 0.45. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.63 (s, 1H), 7.70 (s, 1H), 7.05 (d, *J* = 8.2, 1H), 7.07-7.10 (m, 1H), 6.81 (s, 1H), 6.75-6.79 (m, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.77 (s, 3H), 3.12-3.51 (m, 4H), 2.68-2.89 (m, 6H), 2.47-2.61 (m, 2H), 0.93-1.14 (m, 6H).

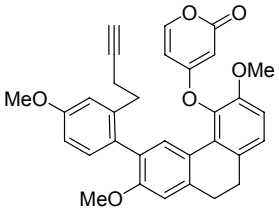


The aldehyde **4.25a** (0.395 g, 0.763 mmol) was dissolved in MeOH (8.0 mL), 214 mg of K_2CO_3 (1.55 mmol) and 211 mg of the Ohira-Bestmann reagent (1.10 mmol) were added – the flask was rinsed with 0.5 mL of MeOH. The suspension was stirred overnight and diluted with 50 mL of Et_2O and washed with 100 mL of H_2O. The aqueous phase was extracted with 2 x 50 and 2 x 25 mL of Et_2O. The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography in 40 % EtOAc in hexanes. Yield of **4.26**: 0.354 g (90 %). 3:2 Hexanes:EtOAc (v/v), R_f = 0.35. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.08 (d, *J* = 8.4, 1H), 7.05 (d, *J* = 8.2, 1H), 6.90 (d, *J* = 2.6, 1H), 6.81 (s, 1H), 6.76-6.80 (m, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.08-3.55 (m, 4H), 2.76-2.90 (m, 4H), 2.62-2.73 (m, 2H), 2.31 (dt, *J* = 2.5, 7.5, 2H), 1.92 (t, *J* = 2.6, 1H), 0.96-1.11 (m, 6H). LCMS $[M+H]^+$: 514.

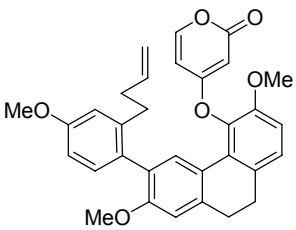


The carbamate **4.26** (0.1913 g, 0.373 mmol) was dissolved in benzene (10.0 mL), and 1.2 mL of Vitride (65 % in toluene) was added. The solution was heated to reflux under N_2. After 6 h an additional 0.6 mL of Vitride was added, and the mixture refluxed for another 4 h. The dark solution was quenched with 1.2 mL of 2 M NaOH after cooling, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography in 20 % EtOAc in

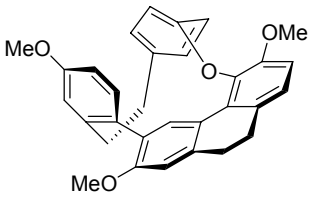
hexanes. Yield og **4.26a**: 79 mg (51 %). 3:2 Hexanes:EtOAc (v/v), R_f = 0.55. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.18 (d, *J* = 8.4, 1H), 6.92 (d, *J* = 2.7, 1H), 6.83 (dd, *J* = 2.7, 8.4, 1H), 6.82 (s, 1H), 6.74 (d, *J* = 8.1, 1H), 6.70 (d, *J* = 8.1, 1H), 6.13 (br s, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 2.79-2.89 (m, 4H), 2.75 (t, *J* = 7.8, 2H), 2.33-2.40 (m, 2H), 1.91 (t, *J* = 2.6, 1H). LCMS $[M+Na]^+$: 437.



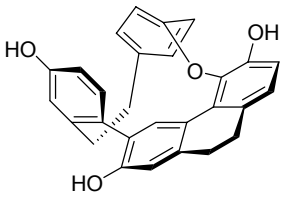
The phenol **4.26a** (6.0 mg, 14.5 μmol), Cs_2CO_3 (10.1 mg, 31 μmol) and pyrone **4.16** (22.0 mg, 0.169 mmol) were dissolved in DMF (2.0 mL) and stirred at 50 ºC for 24 h and then 80 ºC for 5 h. The solvent was removed *in vacuo* and the residue was purified by prep. TLC in 40 % EtOAc in hexanes. Yield of **4.27**: 3.0 mg (41 %). White solid, mp = 175-177 ºC. 3:2 Hexanes:EtOAc (v/v), R_f = 0.25. ^{1}H-NMR (400 MHz, toluene- *d*8): δ 8.03 (s, 1H), 7.06 (d, *J* = 8.4, 1H), 6.89 (d, *J* = 2.7, 1H), 6.84 (d, *J* = 8.3, 1H), 6.70 (dd, *J* = 2.7, 8.4, 1H), 6.54 (dd, *J* = 0.7, 5.9, 1H), 6.46 (s, 1H), 6.37 (d, *J* = 8.3, 1H), 5.60 (dd, *J* = 2.4, 5.9, 1H), 5.29 (dd, *J* = 0.7, 2.4, 1H), 3.41 (s, 3H), 3.25 (s, 3H), 3.21 (s, 3H), 2.67-2.80 (m, 2H), 2.49-2.58 (m, 4H), 2.19 (dt, *J* = 2.6, 7.8, 2H), 1.65 (t, *J* = 2.6, 1H). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.38 (d, *J* = 5.8, 1H), 7.15 (d, *J* = 8.3, 1H), 6.97 (d, *J* = 8.3, 1H), 6.89 (d, *J* = 2.6, 1H), 6.78-6.84 (m, 3H), 6.16 (dd, *J* = 2.3, 5.8, 1H), 5.14 (d, *J* = 2.3, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 2.83 (br s, 4H), 2.62 (t, *J* = 7.8, 2H), 2.18-2.24 (m, 2H), 1.26 (t, *J* = 7.1, 1H). IR(film) ν 3275, 2938, 2836, 1722, 1640, 1603, 1558, 1511, 1494, 1436, 1397, 1326, 1282, 1236, 1200, 1159, 1101, 1042 cm^{-1}. HRMS $[M+H]^+$: calcd 509.1959, found 509.1960, HRMS $[M+Na]^+$: calcd 531.1778, found 531.1780.



The alkyne **4.27** (5.3 mg,10.4 μmol) was dissolved in EtOH, 1 drop of pyridine and 1.8 mg of Lindlar's catalyst were added and the mixture was stirred under H_2 for ½ h. Purification by prep. TLC in 60 % EtOAc in hexanes after filtration through a small plug of Celite to yield **4.27a** quantitatively. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.35 (d, *J* = 5.9, 1H), 7.14 (d, *J* = 8.3, 1H), 6.98 (d, *J* = 8.3, 1H), 6.79-6.83 (m, 3H), 6.77 (dd, *J* = 2.7, 8.3, 1H), 6.14 (dd, *J* = 2.4, 5.8, 1H), 5.60-5.70 (m, 1H), 5.15 (d, *J* = 2.4, 1H), 4.81-4.86 (m, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H), 2.80-2.87 (m, 4H), 2.43-2.48 (m, 2H), 2.07-2.15 (m, 2H).



The alkene **4.27a** (5.5 mg, 10.8 µmol) was dissolved in *o*-DCB (5.5 mL) and heated to 200 ºC for 10 h under microwave irradiation. The solvent was removed *in vacuo* and the residue was purified by prep. TLC in 10 % EtOAc in hexanes to yield 3.2 mg of a mixture of two compounds in a ratio of 5:3 in favor of cavicularin trimethyl ether.



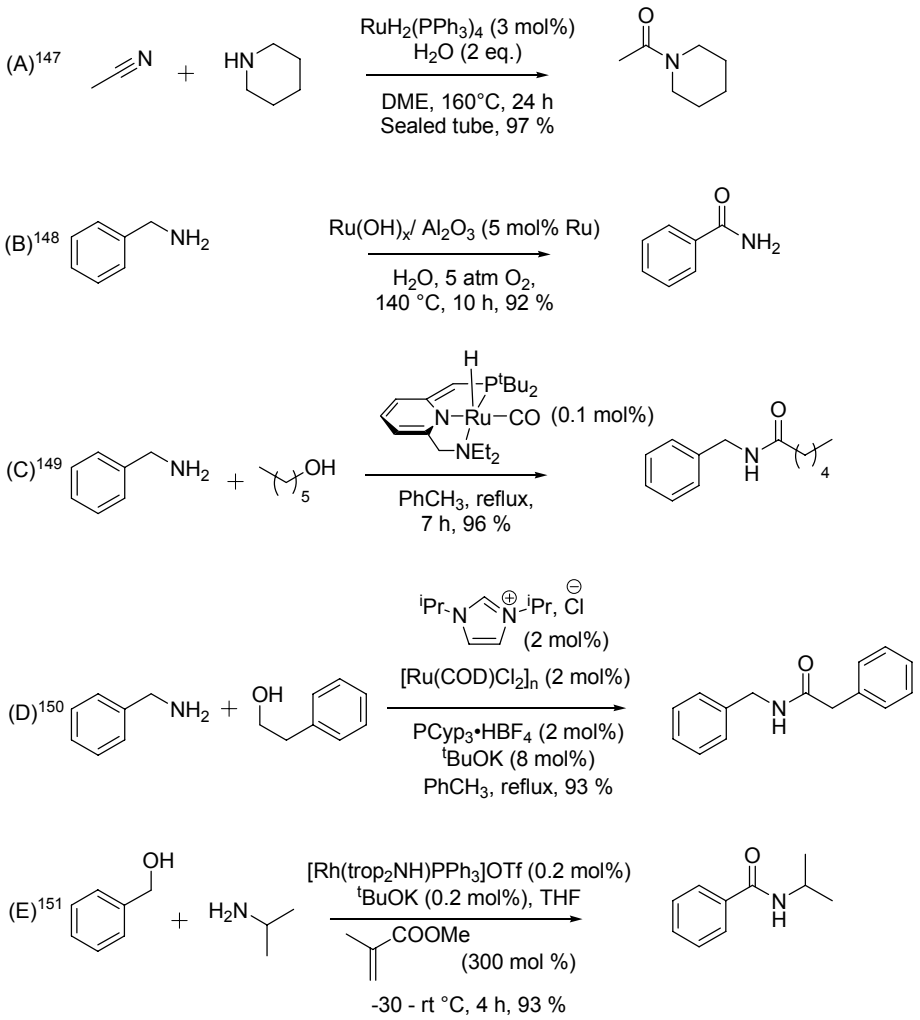
Cavicularin: The alkyne **4.27** (3.0 mg, 5.90 µmol) was dissolved in *o*-DCB (3.0 mL) and heated to 225 ºC for 10.5 h under microwave irradiation. The solvent was removed *in vacuo* and the residue was purified by prep. TLC in 10 % EtOAc in hexanes. This residue was dissolved in 0.2 mL of CH_2Cl_2, and BBr_3 (50 µmol, 50 µL, 1 M in CH_2Cl_2) was added. The solution was stirred for 3 h at rt and quenched with MeOH. The mixture was concentrated *in vacuo* several times with MeOH. The solids were purified by prep. TLC in 40 % EtOAc in hexanes to yield a mixture of two compounds.

^{1}H-NMR showed signals characteristic with those reported earlier for cavicularin.[113, 115]

5 Ruthenium-catalyzed Amidation

5.1 Introduction

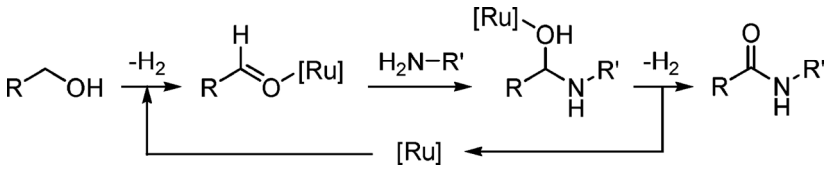
Traditionally, the generation of an amide relies extensively on the reaction between an activated carboxylic acid and an amine. This constitutes a strategy that often produces a stoichiometric amount of unfortuitous by-products. In recent years catalytic approaches that do not produce harmful by-products have appeared. Remarkably different systems all based on a variety of transition metal catalysts have been developed (scheme 5.1).[147-151]



Scheme 5.1: Transition metal-based amidation protocols.

A simple catalytic system for the conversion of alcohols and amines into amides with a ruthenium catalyst by H_2-liberation was recently developed in the Madsen group, scheme 5.1, eq. D.[150] Although, the reaction provided a diverse array of amides under standard conditions with commercially available reagents and in that sense performed excellently, the mechanism

was poorly understood. Nordstrøm *et al.* suggested a tentative mechanism based on the initial findings (scheme 5.2).[150] It was shown that the reaction does not go through an imine or ester, but rather through a hemiaminal intermediate with overall liberation of two equivalents of dihydrogen. On the other hand, the exact role and nature of the catalyst remains ambiguous, since the catalytically active species was generated *in situ*.

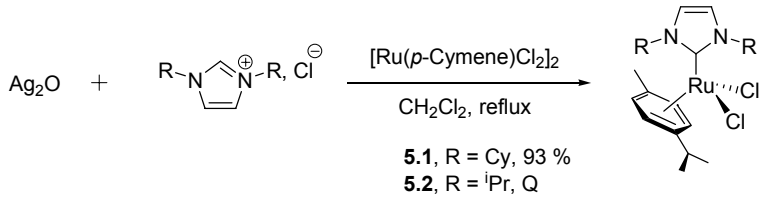


Scheme 5.2: Suggested mechanism according to Nordstrøm *et al.*

Milstein *et al.* had earlier on reported the same transformation with a fully preformed catalyst, scheme 5.1, eq. C.[149] This catalyst did not involve an NHC-ligand, but instead a PNN-pincer ligand. It was clear from Milstein *et al*.'s report that the PNN-pincer was participating in the reaction by an aromatization/dearomatization-shift. In connection to this it was unclear to us whether the NHC-ligand was involved in the catalytic cycle in a similar manner, *i.e.* C-H-activation of the ligand by ruthenium. Multiple reports have shown that ruthenium is able to activate a C-H-bond on its NHC-ligand.[152] In order to gain some insight into the mechanism *viz.* the nature of the catalytic active species and the rate-determining step, we set out to synthesize a pre-catalyst containing an NHC-ligand that would perform equally well as the previously reported system. The idea was to install the proper NHC-ligand on the ruthenium metal-center, isolate the complex and test it in the amidation reaction. When a suitable catalyst was obtained an actual mechanistic study could then be initiated.

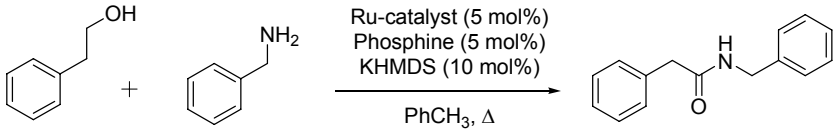
5.2 Results & Discussion

It was anticipated that the simplest route to a pre-catalyst was to generate the NHC-ligand in the presence of $[Ru(COD)Cl_2]_n$ and isolate the formed catalyst. Therefore, the first thing attempted was to install an NHC-ligand on $[Ru(COD)Cl_2]_n$ by different modes of carbene-addition or -transfer. It was quickly realized that a ruthenium-complex containing both an NHC-ligand and a COD-ligand was too sensitive to be isolated and applied in the amidation reaction without applying glove-box or Schlenk techniques. Furthermore, addition of an NHC-ligand to $Ru(PPh_3)_3Cl_2$ and $Ru(PPh_3)_3HCl$ according to Whittlesey *et al.* in order to obtain a pre-catalyst with both a phosphine and an NHC-ligand (*i.e.* fully elaborated pre-catalyst) failed due to purification difficulties.[152] Instead, we turned to a more stable ligand, *i.e.* an 18-electron complex with the cymene ligand. The cymene ligand was envisioned to depart from ruthenium at elevated temperature (85 ºC) and generate the same catalytically active species, although separate addition of a phosphine ligand would be required.[153] One-pot silver-carbene formation and NHC-transfer to ruthenium afforded the desired complex in excellent yield after flash chromatography (scheme 5.3).[154]



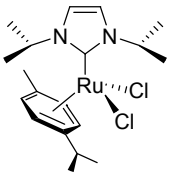
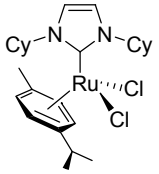
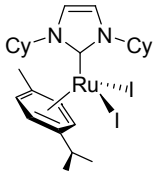
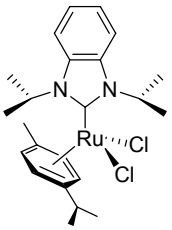
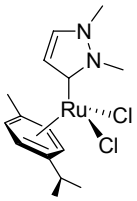
Scheme 5.3: Synthesis of an amidation pre-catalyst

The catalysts **5.1** and **5.2** proved to be equally efficient at producing the amide from 2-phenylethanol and benzylamine as the *in situ* generated catalyst from $[Ru(COD)Cl_2]_n$ (scheme 5.4 and table 5.1). This alcohol and amine were chosen as the standard test substrates for the amidation like the previous study in the group.[150] The 3-hour conversion of starting material into the desired amide was taken as a measure of how well different catalysts performed compared to each other. The yield (GC-yield obtained by comparison to an internal standard) at no further conversion is also shown (after 20-24 h).



Scheme 5.4: Benchmark amidation reaction for this study.

Table 5.1: Performance of different catalysts. GC-yields after 3/ 20+ h.

Entry		PCy_3	$PCyp_3 \cdot HBF_4$	$PCyp_3$	Without phosphine
1	$[Ru(COD)Cl_2]_n$	56/ 89[A]	92[B]	98[B]	-
2		65/ 95	19/ 61	53/ 100	55/ 70
3		61/ 97	30/ 70	56/ 91	38/ 57
4		*In situ*: 56/ 90 22/ 50	-	*In situ*: 63/ 87	-
5		0 / 5	-	-	-
6		25/ 45	-	-	-

A) With ICy, this work. **B**) Reaction performed with I^iPr, isolated yield, ref. 150.

Table 5.1 shows that both the NHC-ligands ICy and I^iPr (entry 2 & 3) perform equally well as the initial system depicted in scheme 5.1D, which provided the amide in 56 and 89 % yield after 3 and 20+ h respectively (entry 1). In our hands the use of either PCy_3 or $PCyp_3$ proved superior to the more stable salt $PCyp_3 \cdot HBF_4$. With the NHC-ligand installed on the ruthenium as little as 10 mol% base could be used at a 5 mol% catalyst loading. The strong base KHMDS (in toluene) was the base of choice since it gave consistent yields, although ^{t}BuOK usually performed well too. Interestingly, with KHMDS the solution was homogenous at all times during the reaction.

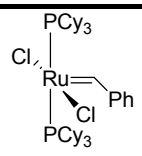
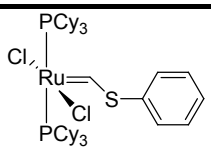
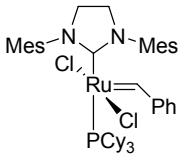
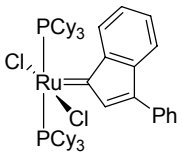
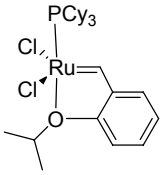
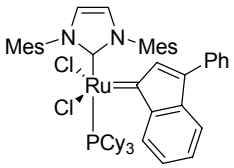
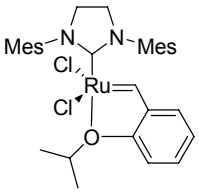
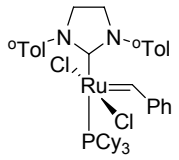
It was tried to alter different parts of the catalyst in order to improve the system. Exchange of the chlorides bonded to the ruthenium with iodides did not bring about any improvement (compare entry 3 & 4). By transferring the carbene to [Ru(*p*-cymene)I_2]$_2$ in analogy to scheme 5.3 two compounds – a red and yellow band by preparative thin layer chromatography – were isolated. The yellow band-compound showed identical ^{1}H-NMR shifts and elemental analysis as the corresponding chloride catalyst, entry 3. The red band diiodide catalyst (entry 4) did not work as well as the dichloride catalyst **5.1** in the amidation reaction. Running the reaction by *in situ* generation of the catalyst from [Ru(*p*-cymene)I_2]$_2$ and ICyHCl showed similar reactivity to that of catalyst **5.1**.

Early studies taught us that saturated NHC-ligands performed poorly.[150] An NHC-ligand where the backbone was fused to an aromatic system could provide a different reactivity (entry 5, table 5.1), since the NHC-ligand is still unsaturated, but the electrons are now less available. Indeed, such a modification altered the reactivity to generate an almost completely inactive catalyst. In turn it was envisioned that reducing the sterics around the ruthenium center would enhance the reactivity. An abnormal carbene as shown in entry 6 was chosen as a suitable testing ground. The complex was synthesized in analogy to scheme 5.2 according to the methods described by Peris *et al.*[155] As it turned out the catalyst only provided conversion to the desired amide to some extent. The lower degree of reactivity could not only be ascribed to less steric demand on the metal center, but also enhanced σ-donation from the ligand.[155, 156] Returning to the ICy-catalyst **5.1** and changing the solvent to dioxane or heptane (because of their boiling points) did not affect the course of the reaction. Furthermore, addition of 10 mol% of MsOH quenched the reaction completely as did silver triflate (10 mol%). Addition of up to 10 mol% of LiCl or omitting the phosphine only showed minor inhibition of the reaction progress, which eventually provided the amide.

At this point attention was directed toward the report by Grubbs *et al.* which stated that applying an H_2-atmosphere after ring closing metathesis with Grubbs 1st gen. catalyst would generate the effective hydrogenation catalyst RuHCl(H_2)(PCy_3)$_2$.[157] They showed that the benzylidene ligand for starting the RCM had been hydrogenated off. This allowed for the synthesis of a fully elaborated pre-catalyst (with a phosphine and an NHC-ligand) for the amidation reaction that would produce the proper catalytic species, because the H_2 formed in the reaction would remove the benzylidene. Indeed, it was found that simply applying Grubbs 1st without any NHC-ligand under standard conditions provided the amide in 71 % yield after ~20 h. Upon addition of ICyHCl or I^{i}PrHCl the amidation had taken place in 76 % yield after 3 h and

affording the amide quantitatively overnight. A screening of different metathesis catalysts was carried out to answer whether these would supply us with a ready-to-use catalyst, table 5.2**.**

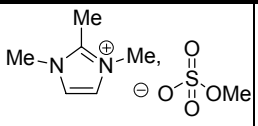
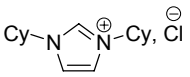
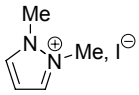
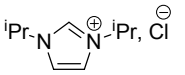
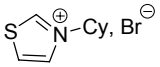
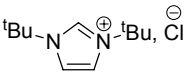
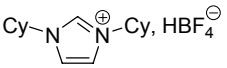
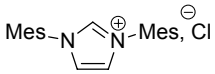
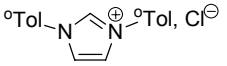
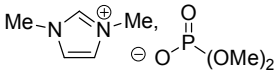
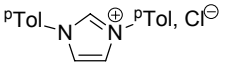
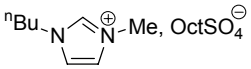
Table 5.2: Screening of metathesis catalysts' performance in the amidation. Loading: 5 mol%.

Entry		Yield (3/ 20+ h)	Entry		Yield (3/ 20+ h)
1	 Grubbs 1st	48/ 71 76/ 96[A]	5		9/ 15 34/ 78[A]
2	 Grubbs 2nd	29/ 49	6	 Neolyst M1	25/ 42 67/ 100[A]
3	 Hoveyda-Grubbs 1st	41/ 60 84/ 100[A]	7	 catMETium® IMesPCy	45/ 69
4	 Hoveyda-Grubbs 2nd	48/ 65 41/ 58[B]	8	 Grubbs 3rd	63/ 92

A) With 5 mol% ICy generated *in situ.* **B**) 5 mol% PCy_3 added.

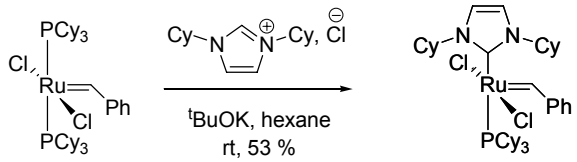
From table 5.2 it is seen that no metathesis catalyst on its own brings any improvement. The newer generation metathesis catalyst (entry 8) did however show comparable reactivity to the complexes containing the cymene ligand, catalysts **5.1** and **5.2**. This was surprising since it contained an NHC-ligand with a saturated backbone. By generating ICy *in situ* with the catalysts without any NHC-ligand (entry 1, 3 and 6) very effective amidation catalysts were formed. Delighted by this finding a small screening of other NHC-ligands was undertaken (table 5.3) with the conditions from scheme 5.4.

Table 5.3: Screening of NHC-ligands for amidation with Grubbs 1st.

Entry		Yield (3/ 20+ h)	Entry		Yield (3/ 20+ h)
1	None	48/ 71	8		37/ 55
2		76/ 96	9		30/ 50
3		76/ 100	10		5/ 7
4		23/ 53	11		72/ 100
5		44/ 71	12		36/ 65
6		65/ 91	13		41/ 65
7		27/ 75			

In accordance with previous findings by Nordstrøm, Vogt and Madsen I^{t}Bu and IMes (table 5.3, entry 4 and 5) did not perform well in the reaction. On the other hand, IMe (entry 6) performed much better showing that the *N*-methyl substitutions work well.[150] In connection to this the increased σ-donation of abnormal NHC-ligands (entry 8 and 9) must decrease their reactivity. Grubbs and Vougioukalakis had earlier on synthesized a range of effective thiazol-2-ylidene substituted metathesis catalysts, which displayed increased heat stability.[158] Inspired by this the *N*-cyclohexyl thiazolium salt (entry 10) was synthesized in two steps and applied to the amidation reaction only to find that the salt quenched the reaction. Most likely the thiazol-2-ylidene dimerizes readily when deprotonated as reported by Arduengo *et al.*[159] and the silver-carbene transfer procedure applied by Grubbs and Vougioukalakis was unsuccessfully employed both *in situ* with Grubbs 1st and with [Ru(*p*-cymene)Cl_2]$_2$. The commercially available ICyHBF_4 (entry 11) was included in the screening to establish that this type of counter ion had little influence on the reaction progress. Surprised by the efficiency of the Grubbs 3rd (Table 5.2, entry 8) both I^{o}TolHCl and I^{p}TolHCl were synthesized and applied with Grubbs 1st. Unfortunately, it provided a reactivity similar to that of IMes (entry 5) and the catMETium-catalyst (entry 7, table 5.2) although the sterics should be somewhat different, and as a result further NHC-screening was abandoned at this point.

On the basis of the findings in table 5.2 and 5.3 the synthesis of the known Grubbs 2nd-analoque, **5.3**, was undertaken (scheme 5.5).[160, 161] Following the original procedure reported by Herrmann *et al.* the isolated solid proved inferior in the amidation reaction.[161] They noted that low temperature was required in order to achieve the mono-carbene complex in THF. Only by applying the conditions reported by Nolan *et al.* were we able to produce a capable complex showing similar efficiency as the *in situ* generated system: 74 % yield in 3 h and 97 % overnight.[162, 163]



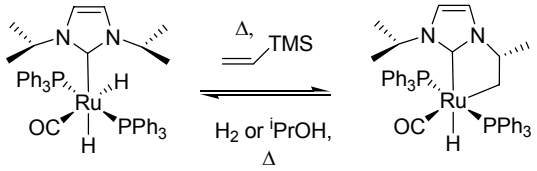
5.3

Scheme 5.5: Synthesis of the more effective amidation pre-catalyst according to Nolan *et al.*

With the most capable and easy to isolate pre-catalyst yet in hand it was tested whether it was able to provide amides from more demanding substrates *i.e.* anilines and secondary amines. It was quickly found that the amide from aniline and 2-phenylethanol in both mesitylene, toluene or under neat conditions afforded the desired amide in only 26 % yield. A substantial amount of alcohol had been turned into the analogous ester. This did not represent an improvement compared to the *in situ* generated catalyst from Nordstrøm *et al.*[150] On the other hand, catalyst **5.3** produced the desired tertiary amide from 2-phenylethanol and *N*-benzylmethylamine in toluene in 65 % isolated yield. Excited by this, the original conditions with the I^{i}Pr-ligand and $[Ru(COD)Cl_2]_n$ in toluene were applied to confirm the improvement.[150] Surprisingly, 70 % amide was isolated, which is in contrast to the reported 40 %. Presumably, the difference in yield is a result of different isolation procedures. Originally, the amide was isolated by flash chromatography, but the amides are hard to develop with a range of different stains and furthermore possess low UV-absorption when dilute. Hence, some amount of the product may have been lost. In this work the amide was isolated by preparative TLC. Overall the system is capable of producing tertiary amides in contrast to Milstein's catalyst, which however handles anilines much better.[149]

5.3 Mechanistic Considerations

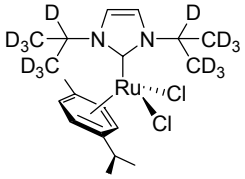
In 2007 Burling *et al.* showed that heating ruthenium-complex **5.4** in the presence of a dihydrogen acceptor resulted in reversible C-H-activation of the NHC-side chains (scheme 5.6).[164] They verified the structure of complex **5.5** by X-ray crystallography. The activation was reversed by the introduction of dihydrogen or an alcohol. Also, strong base (KHMDS or ^{t}BuOK) will abstract a proton from the NHC-ligand and lead to C-H-activation.[165]



5.4 **5.5**

Scheme 5.6: C-H-activation in a ruthenium-complex with I^{i}Pr.

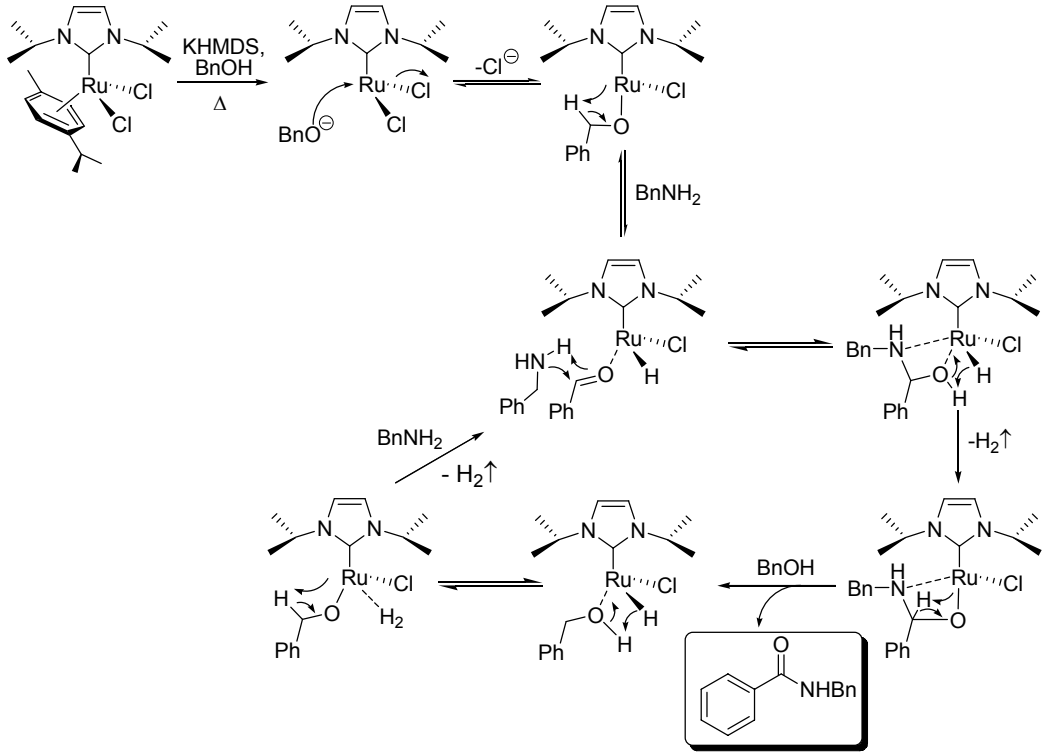
Chatwin *et al.* have reported that hydrogen-transfer from an alcohol or an amine to a Ru-hydride and ensuing elimination of dihydrogen is kinetically and thermodynamically feasible.[166] In view of these reports, initial studies toward a mechanistic understanding were begun. In order to elucidate whether ruthenium performs C-H-activation on the NHC-ligand a deutorated analogue of catalyst **5.2** was synthesized, scheme 5.7.



Scheme 5.7: Deutorated analogue of catalyst 5.2.

The reaction was run on a 2 mmol scale as depicted in scheme 5.4 with a catalyst loading of 10 mol% to achieve a reasonable distribution between the possible gases. In assuring not to obtain a false positive the gas sample was taken before the reaction had gone to completion and therefore before the idle catalyst would perform C-H-activation in its last turn-over. By employing selected ion monitoring on the liberated gases (H_2/ H-D) we were able to demonstrate the formation of H-D by C-H-activation. The two gases were found to be present in a ratio of H_2:H-D 50:1. Although KHMDS can abstract deuterium directly from the catalyst it cannot deliver the deuterium back to the catalyst and deuterium abstracted in this fashion would not appear in the gas. If KHMDS deprotonates the alcohol, this alkoxide would presumably abstract deuterium from the catalyst to a minor extent, based of the strength of the alkoxide as a base. In any case,

the presence of D_2 was found negligible. These pathways are therefore not dominating in releasing deuterium in the gas. Hence, the presence of H-D suggests that the catalyst is able to perform C-H-activation somewhere in the catalytic cycle, but the relatively small amount of deuterium imply that C-H-activation is not a major pathway. Based on this a tentative mechanism for the amidation reaction is proposed, scheme 5.8.



Scheme 5.8: Tentative mechanism for the amidation.

The catalytic cycle is initiated upon heating the ruthenium-complex **5.2**, which leads to loss of the cymene ligand. An alkoxide coordinates to the metal and is in turn oxidized to the aldehyde. In this fashion a ruthenium-hydride is generated and the cycle is entered. At this point a previously coordinated amine attacks the aldehyde to form a hemiaminal, neither the aldehyde nor the hemiaminal leaves the coordination-sphere of the metal at any point as shown by Nordstrøm *et al*.[150] Hydrogen transfer from the hemiaminal produces a molecule of dihydrogen and H_2 is liberated.[166, 167] The amide is produced by β-hydride elimination of the hemiaminal. Another alcohol coordinates to the metal and by hydrogen-transfer a molecule of dihydrogen is produced and liberated. The catalytic cycle is reentered by β-hydride elimination of the alcohol to form an aldehyde and ruthenium-hydride. It is improbable that a ruthenacycle formed by C-H-activation persists through the whole catalytic cycle in the presence of alcohols and amines at

elevated temperatures. Rather - according to scheme 5.6 - it represents a stabilized source of catalyst capable of producing a coordinatively unsaturated complex. The driving force of the productive catalytic cycle is the irreversible liberation of dihydrogen along with the formation of the unreactive amide. In accordance to the mechanism for ruthenium catalyzed transfer-hydrogenation with BINAP, ruthenium remains in the same oxidation state (II) throughout the catalytic cycle.[168, 169] As depicted by the screening (table 5.3) the substituent on the NHC-ligand matters, *i.e*. only a certain extent of steric bulk is tolerated. At some point during the cycle additional electron-density or bulk is needed and hence the addition of PCy_3 is necessary. Most likely the phosphine is responsible for stabilizing the catalyst resting state.

5.4 Conclusion

Two isolatable catalysts – [$RuCl_2$(*p*-cymene)I^iPr] and [$RuCl_2$(*p*-cymene)ICy] – have been prepared and proven to be equally active as the original system employing the *in situ* generated catalyst from $[Ru(COD)Cl_2]_n$ and I^iPrHCl. Furthermore, it was discovered that an array of different metathesis catalysts are able to perform the amidation under the conditions developed in the Madsen group. Especially, the 1st generation catalysts with ICy- or I^iPr-ligands proved very effective in the transformation. Also, a second generation metathesis catalyst **5.3** has been synthesized and found to be performing very well in the reaction. By means of deuterium-labeling, data suggests that C-H-activation of the ruthenium NHC-ligand is not a major pathway and a tentative catalytic cycle is suggested.

5.5 Experimental Section

General procedures

See section **1.6**

The reactions were analyzed by GC using a 15 m x 0.10 mm x 0.10 µm Supelco Equity-1 capillary column with the following retention times:

Benzylamine:	**2-Phenylethanol:**	**Dodecane:**	**N-Benzyl-2-phenylacetamide:**
4.09 min.	4.63 min.	5.11 min.	7.72 min.

GC-program for Ru-catalyzed amidation:

Temperature (°C)	**Hold Time (min.)**
50.0	2.0 (ramp 40)
300.0	5.0

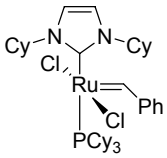
General Procedure for the Ru-catalyzed Amidation with Grubbs I

Grubbs I (25 µmol, 5 mol%), ICyHCl (25 µmol, 5 mol%), the amine (0.5 mmol) and the alcohol (0.5 mmol) were mixed in a Schlenk flask and three cycles of high vacuum/Ar-backfill were performed. A cold finger was mounted and 1.0 mL of anhydrous and degassed toluene was added followed by KHMDS (in toluene, 75 µmol, 15 mol%). The solution was heated to reflux for 20-24 h under a positive flow of Ar. The reaction could then be purified directly by flash chromatography in 20-50% EtOAc in pentane.

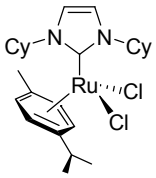
General Procedure for the Ru-catalyzed Amidation with Complex 5.1

The complex **5.1** (25 µmol, 5 mol%), PCy_3 (25 µmol, 5 mol%), the amine (0.5 mmol) and the alcohol (0.5 mmol) were mixed in a Schlenk flask and three cycles of high vacuum/Ar-backfill were performed. A cold finger was mounted and 1.0 mL of anhydrous and degassed toluene was added followed by KHMDS (in toluene, 75 µmol, 15 mol%). The solution was heated to reflux for 20-24 h under a positive flow of Ar. The reaction could then be purified directly by flash chromatography in 20-50% EtOAc in pentane.

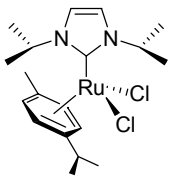
General Procedure for Installing an NHC-ligand on [Ru(*p*-Cymene)Cl_2]$_2$ exemplified with ICyHCl: ICyHCl (200.2 mg, 0.75 mmol) and Ag_2O (86.1 mg, 0.37 mmol) were suspended in 7.0 mL of dry and degassed CH_2Cl_2 under Ar and refluxed for 1 h in a Schlenk flask with a reflux condenser. Then [Ru(*p*-Cymene)Cl_2]$_2$ (226.0 mg, 0.37 mmol) in 3.0 mL of anhydrous, degassed CH_2Cl_2 was added and the solution was refluxed for 1 h and concentrated *in vacuo*. The residue was filtered through a short column of SiO_2 in 10 % ^{i}PrOH in CH_2Cl_2. Yield 0.3684 g (93%) of a red-orange solid.



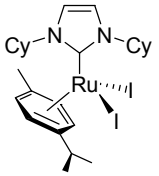
Prepared according to Nolan *et al.*[162] ICyHCl (56.1 mg, 0.209 mmol), ^{t}BuOK (36.0 mg, 0.320 mmol) and Grubbs I (164 mg, 0.20 mmol) were suspended in 5.0 mL of anhydrous, degassed hexane in a dry Schlenk flask and stirred under Ar at rt overnight. The slurry was Schlenk-filtered and the solid residue was washed with 2 x 5 mL of degassed H_2O and 2 x 5 mL of anhydrous, degassed hexane. The green solid was dried under high vacuum. Yield 81.0 mg (53 %).[160, 161]



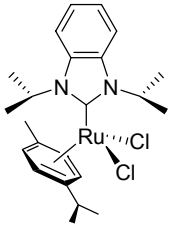
Yield: 93 % as a red-orange solid.[170] R_f = 0.64, 9:1 CH_2Cl_2:^{i}PrOH (v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.14-2.44 (m, 20H), 1.36 (d, *J* = 6.9, 6H), 2.13 (s, 3H), 2.84 (m, 1H), 4.84 (m, 2H), 5.14 (d, *J* = 6.0, 2H), 5.46 (d, *J* = 6.0, 2H), 7.04 (s, 2H). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 18.8, 23.1, 25.3, 25.4, 26.0, 31.2, 35.4, 35.8, 59.3, 83.6, 85.3, 97.3, 105.1, 119.3, 171.4. IR (neat) ν 3091, 2957, 2921, 2848, 1466, 1455, 1446, 1418, 1380, 1290, 1276, 1232, 1190, 897, 747, 697 cm^{-1}. MS [M-Cl]$^{+}$: calcd 503.1762, found 503.1456. Anal. Calcd for $C_{25}H_{38}Cl_2N_2Ru$: C, 55.75; H, 7.11; N, 5.20. Found: C, 55.14; H, 6.84; N, 5.16.



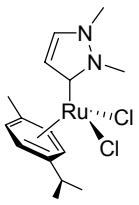
Yield: Q as a red-orange solid.[171] R_f = 0.64, 9:1 CH_2Cl_2:^{i}PrOH (v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.31 (d, *J* = 6.9, 6H), 1.44 (br d, *J* = 6.2, 12H), 2.08 (s, 3H), 2.92 (m, 1H), 5.15 (d, *J* = 6.0, 2H), 5.31 (m, 2H), 5.47 (d, *J* = 6.0, 2H), 7.07 (s, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 18.6, 22.8, 25.0, 30.8, 52.0, 83.4, 85.1, 97.1, 106.4, 118.9, 171.1. IR (neat) ν 3152, 3099, 3077, 2958, 2930, 2870, 1473, 1412, 1391, 1369, 1297, 1265, 1213, 1133, 856, 770, 700 cm^{-1}. MS [M-Cl]$^{+}$: calcd 423.1136, found 423.0657. Anal. Calcd for $C_{19}H_{30}Cl_2N_2Ru$: C, 49.78; H, 6.60; N, 6.11. Found: C, 49.84; H, 6.44; N, 6.05.



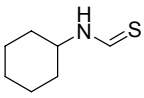
Purified by prep. TLC in 10 % acetone in CH_2Cl_2. Combined yield: 56 % Red band: R_f = 0.89, 9:1 CH_2Cl_2:^{i}PrOH (v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.20-2.46 (m, 20H), 1.35 (d, *J* = 6.9, 6H), 1.97 (s, 3H), 3.31 (m, 1H), 5.03 (d, *J* = 5.9, 2H), 5.14 (m, 2H), 5.80 (d, *J* = 5.9, 2H), 7.10 (s, 2H). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 20.0, 23.4, 24.7, 25.3, 26.1, 31.4, 35.3, 35.8, 61.8, 80.5, 88.1, 100.4, 107.3, 119.9, 167.7. IR (neat) ν 2924, 2853, 1439, 1371 1284, 1224, 1189, 995, 908, 725 cm^{-1}. Anal. Calcd for $C_{25}H_{38}I_2N_2Ru$: C, 41.62; H, 5.31; N, 3.88. Found: C, 42.50; H, 5.67; N, 3.78.



Yield: Q as a dark red solid. R_f = 0.22, 9:1 CH_2Cl_2:^{i}PrOH (v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.38 (d, *J* = 6.9, 6H), 1.69 (d, *J* = 7.2, 6H), 1.75 (d, 6.8, 6H), 2.12 (s, 3H), 2.97 (m, 1H), 5.23 (d, *J* = 6.1, 2H), 5.61 (d, *J* = 6.1, 2H), 5.80 (m, 2H), 7.20 (dd, *J* = 3.2, 6.2, 2H), 7.66 (dd, *J* = 3.2, 6.2, 2H). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 18.6, 22.3, 22.6, 22.9, 31.0, 53.7, 83.5, 86.6, 97.4, 106.8, 112.9, 121.8, 134.2, 187.5. IR (neat) ν 2963, 2935, 2875, 1478, 1344, 1285, 1093, 764 cm^{-1}. Anal. Calcd for $C_{23}H_{32}Cl_2N_2Ru$: C, 54.33; H, 6.34; 5.51. Found: C, 53.42; H, 6.01; N, 5.41.

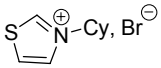


Yield: 36 % of an orange solid.[155] R_f = 0.64, 9:1 CH_2Cl_2:^{i}PrOH (v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.18 (d, *J* = 6.9, 6H), 2.06 (s, 3H), 2.70 (m, 1H), 3.80 (s, 3H), 4.00 (s, 3H), 5.08 (d, *J* = 5.9, 2H), 5.23 (d, *J* = 5.9, 2H), 6.46 (d, *J* = 2.8, 1H), 7.34 (d, *J* = 2.8, 1H). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 18.4, 22.3, 30.5, 37.3, 37.5, 83.9, 84.2, 99.1, 104.3, 116.6, 132.8, 179.7. IR (neat) ν 2957, 2923, 2870, 1523, 1480, 1430, 1383, 1358, 1274, 923, 785, 723 cm^{-1}. Anal. Calcd for $C_{15}H_{22}Cl_2N_2Ru$: C, 44.78; H, 5.51; N, 6.96. Found: C, 43.78; H, 5.23; N, 6.44.

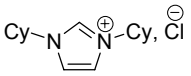


Cyclohexylformamide (5.0 g, 39.3 mmol) was dissolved in 40 mL of anhydrous benzene and P_4S_{10} (4.4 g, 9.9 mmol) was added. The slurry was refluxed under Ar for 1 h, where acetone (30 mL) was added and the slurry was cooled to 0 ºC. The cooling bath was removed after addition of 25 mL of 5.3 M aq. K_2CO_3 and the suspension was stirred for 1½ h. It was diluted further with water and extracted several times with EtOAc. The combined organic phases were washed with dilute aq. K_2CO_3, brine and finally dried with $MgSO_4$. The solvent was removed *in vacuo* and the residue was distilled under high vacuum (~1 mmHg) at 115-125 ºC to yield 3.4 g of an orange liquid (60 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ Two

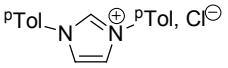
rotamers in ratio 1:2.25; 1.12-2.13 (m, 20H) Major rotamer: 4.49 (m, 1H), 9.33 (s, 1H). Minor rotamer: 3.47 (m, 1H), 9.19 (s, 1H). GC-MS $[M]^+$: 143.1.



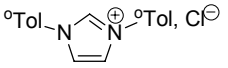
The cyclohexylthioformamide (1.334 g, 9.38 mmol) was dissolved in 8.0 mL of toluene and 5.5 mL of THF. Bromoacetaldehyde diethyl acetal (3.0 mL, 19.9 mmol) and 15 drops of 96 % H_2SO_4 were added and the solution was stirred at rt for 87 h. The salt was filtered off and the mother liquor was concentrated *in vacuo*, redissolved in CH_2Cl_2 and precipitated by addition of Et_2O and EtOAc. The solids were combined and purified by flash chromatography in 25 % EtOH in CH_2Cl_2 to yield a white solid. Yield 1.23 g (53 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.27-2.35 (m, 10H), 5.05 (m, 1H), 8.43 (dd, *J* = 2.4, 3.7, 1H), 8.65 (dd, *J* = 1.4, 3.8, 1H), 11.24 (dd, *J* = 1.5, 2.3, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 24.3, 25.0, 33.6, 66.2, 127.3, 135.1, 158.9. HRMS calcd. for $C_9H_{14}NS$ $[M\text{-}Br]^+$: 168.0842, found 168.0844.



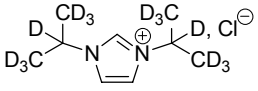
Prepared according to Mistryukov.[172] ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.15-2.32 (m, 20H), 4.52 (tt, *J* = 3.9, 11.9, 2H), 7.37 (s, 1H), 7.38 (s, 1H), 10.88 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 24.5, 24.8, 33.5, 59.7, 119.3, 136.1.



Prepared according to Arduengo.[173] ^{1}H-NMR (300 MHz, CD_3OD): δ 10.00 (s, 1H), 8.24 (s, 2H), 7.71 (d, *J* = 8.5, 4H), 7.50 (d, *J* = 8.5, 4H), 2.47 (s, 6H).

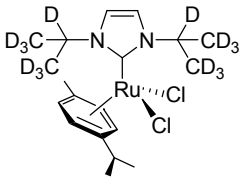


Prepared according to Delaude *et al.*[174] ^{1}H-NMR (500 MHz, DMSO-*d*6): δ 9.95 (s, 1H), 8.36 (s, 2H), 7.48-7.71 (m, 8H), 2.34 (m, 6H). ^{13}C-NMR (75 MHz, DMSO-*d*6): δ 17.1, 124.0, 126.7, 127.3, 130.7, 131.6, 133.4, 134.0, 137.7.

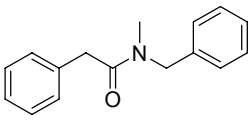


Prepared according to Arduengo.[173] Paraformaldehyde (0.172 g, 5.73 mmol) was suspended in 2.0 mL of toluene, and isopropyl-*d*7-amine (0.48 mL, 5.62 mmol, >98 atom % D from Isotec) was added. The mixture was gently heated with a heatgun to give a clear solution with a gummy, white precipitate. Cooled to 0 ºC and another portion of isopropyl-*d*7-amine (0.48 mL, 5.62 mmol, >98 atom % D from Isotec) was added along with 6 M aq. HCl (0.95 mL, 5.70 mmol) keeping T < 10 ºC. The cooling bath was removed and the solution warmed to rt over 30 min. Then aq. glyoxal (40 %, 0.65 mL, 5.69 mmol) was added and the suspension was stirred vigorously for 1 h. Water was removed azeotropically with toluene and a dean-stark trap. Toluene was removed *in vacuo* and the

residue crystallized under high vacuum overnight. Yield 1.11 g (97 %). ^{1}H-NMR (300 MHz, CD_3OD): δ 7.76 (s, 2H), 9.14 (s, 1H).



Silver oxide (164.0 mg, 0.71 mmol) and the imidazolium salt I^{i}PrHCl-*d*14 (304.0 mg, 1.5 mmol) were suspended in 8.0 mL of CH_2Cl_2 under Ar and refluxed for 2 h. Then [Ru(*p*-cymene)Cl_2]$_2$ (306 mg, 0.5 mmol) was added in one portion and the suspension was refluxed for another 1 h. The reaction was concentrated *in vacuo* and purified by flash chromatography in 10 % ^{i}PrOH in CH_2Cl_2. Yield: 0.429 g (90 %) as a red-orange solid.[171] R_f = 0.64, 9:1 CH_2Cl_2:^{i}PrOH (v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.32 (d, *J* = 6.9, 6H), 2.09 (s, 3H), 2.93 (m, 1H), 5.16 (d, *J* = 5.8, 2H), 5.48 (d, *J* = 5.8, 2H), 7.07 (s, 2H). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 18.6, 22.8, 24.0 (m), 30.8, 51.8 (t), 83.3, 85.2, 97.2, 106.5, 119.0, 171.1. IR (neat) ν 3032, 2964, 2930, 2874, 1467, 1416, 1348, 1294, 1261, 1202, 1050, 859, 719, 684 cm^{-1}.



Procedure 1: The complex **5.3** (19.4 mg, 25 μmol, 5 mol%), *N*-benzyl-*N*-methylamine (65 μL, 0.5 mmol) and 2-phenylethanol (60 μL, 0.5 mmol) were mixed in a Schlenk flask and three cycles of high vacuum/Ar-backfill were performed. A cold finger was mounted and 1.0 mL of anhydrous and degassed toluene was added followed by 0.17 mL of 0.44 M KHMDS (in toluene, 75 μmol, 15 mol%). The solution was heated to reflux for 20-24 h under a positive flow of Ar and concentrated *in vacuo*. It was then redissolved in CH_2Cl_2 and purified by prep. TLC in 40 % EtOAc in heptane. Yield of the tertiary amide: 77.7 mg (65 %). **Procedure 2**: [Ru(COD)Cl_2]$_n$ (7.0 mg, 25 μmol, 5 mol%), PCy_3 (7.0 mg, 25 μmol, 5 mol%), ^{t}BuOK (8.5 mg, 75 μmol, 15 mol%), I^{i}PrHCl (4.7 mg, 25 μmol, 5 mol%), *N*-benzyl-*N*-methylamine (65 μL, 0.5 mmol) and 2-phenylethanol (60 μL, 0.5 mmol) were mixed in a Schlenk flask and three cycles of high vacuum/Ar-backfill were performed. A cold finger was mounted and 1.0 mL of anhydrous and degassed toluene was added. The solution was heated to reflux for 20-24 h under a positive flow of Ar and concentrated *in vacuo*. It was then redissolved in CH_2Cl_2 and purified by prep. TLC in 40 % EtOAc in heptane. Yield of the tertiary amide: 83.8 mg (70 %). Two rotamers were present in ratio of 1:1.5 by ^{1}H-NMR (300 MHz, $CDCl_3$): δ major rotamer 7.20-7.39 (m, 9H), 7.07-7.11 (m, 1H), 4.61 (s, 2H), 3.79 (s, 2H), 2.95 (s, 3H), minor rotamer 7.20-7.39 (m, 9H), 7.07-7.11 (m, 1H), 4.52 (s, 2H), 3.76 (s, 2H), 2.90 (s, 3H).

Procedure for amidation with deutorated analogue of catalyst 5.2:

Catalyst **5.2-*d14*** (94.5 mg, 0.2 mmol, 10 mol%), PCy_3 (56.1 mg, 0.2 mmol, 10 mol%), benzylamine (218 μL, 2.0 mmol), 2-phenylethanol (240 μL, 2.0 mmol) and dodecane (180 μL, 0.8 mmol) were mixed in a Schlenk flask and three cycles of high vacuum/Ar-backfill were performed. A cold finger was mounted and 4.0 mL of anhydrous and degassed toluene was added followed by 1.27 mL of 0.47 M KHMDS (in toluene, 0.6 mmol, 15 mol%). The reaction was monitored by measuring the evolution of dihydrogen. The Schlenk flask was connected to the top of a burette filled with water. The bottom of the burette was further connected to a water reservoir. The solution was heated to reflux for 20-24 h at which point the GC-yield was 84 %. After 1 h and 4 h a sample of gas (1.0 mL) was taken out with a gas-tight syringe and the ratio between H_2:H-D was measured to 51:1 and 44:1 by selected ion monitoring, respectively.

6 References

1. Barbier, P., *C. R. Acad. Sci.* **1899**, *128*, 110-111.

2. Grignard, V., *C. R. Acad. Sci.* **1900**, *130*, 1322-1124.

3. Richey, H. G., Jr., *Grignard Reagents – New Developments* **2000**, *Wiley*, (New York).

4. Killinger, T. A.; Boughton, N. A.; Runge, T. A.; Wolinsky, J. J., *J. Organomet. Chem.* **1977**, *124*, 131-134.

5. Blomberg, C., *The Barbier Reaction and Related One-Step Processes* **1993**, *Springer*, (Berlin).

6. Li, C.-J., *Tetrahedron* **1996**, *52*, 5643-5668.

7. Li, C.-J., *Chem. Rev.* **2005**, *105*, 3095-3165.

8. Nokami, J.; Otera, J.; Sudo, T.; Okawara, R., *Organometallics* **1983**, *2*, 191-193.

9. Petriér, C.; Luche, J. L., *J. Org. Chem.* **1985**, *50*, 910-912.

10. Li, C.-J.; Chan, T. H., *Tetrahedron Lett.* **1991**, *32*, 7017-7020.

11. Wada, M.; Ohki, H.; Akiba, K.-Y., *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1738-1747.

12. Li, C.-J.; Meng, Y.; Yi, X.-H.; Ma, J.; Chan, T.-H., *J. Org. Chem.* **1998**, *63*, 7498-7504.

13. Zhang, W.-Z.; Li, C.-J., *J. Org. Chem.* **1999**, *64*, 3230-3236.

14. Li, L.-H.; Chan, T.-H., *Tetrahedron Lett.* **2000**, *41*, 5009-5012.

15. Yamataka, H.; Nishikawa, K., *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2145-2150.

16. Yamataka, H.; Nishikawa, K.; Hanafusa, T., *Bull. Chem. Soc. Jpn.* **1994**, *67*, 242-245.

17. Gajewski, J. J.; Bocian, W.; Harris, N. J.; Olson, L. P.; Gajewski, J. P., *J. Am. Chem. Soc.* **1999**, *121*, 326-334.

18. Chung, L. W.; Chan, T.-H.; Wu, Y.-D., *Organometallics* **2005**, *24*, 1598-1607.

19. Gajewski, J. J.; Bocian, W.; Brichford, N. L.; Henderson, J. L., *J. Org. Chem.* **2002**, *67*, 4236-4240.

20. Lucas, P.; Gajewski, J. J.; Chan, T.-H., *Can. J. Anal. Sci. Spectr.* **2003**, *48*, 1-6.

21. Chan, T.-H.; Yang, Y., *J. Am. Chem. Soc.* **1999**, *121*, 3228-3229.

22. Chan, T.-H.; Yang, Y.; Li, C.-J., *J. Org. Chem.* **1999**, *64*, 4452-4455.

23. Li, L.-H.; Chan, T.-H., *Can. J. Chem.* **2001**, *79*, 1536-1540.

24. Miao, W.; Chung, L. W.; Wu, Y.-D.; Chan, T.-H., *J. Am. Chem. Soc.* **2004**, *126*, 13326-13334.

25. Skaanderup, P. R.; Madsen, R., *J. Org. Chem.* **2003**, *68*, 2115-2122.

26. Keinicke, L.; Madsen, R., *Org. Biomol. Chem.* **2005**, *3*, 4124-4128.

27. Palmelund, A.; Madsen, R., *J. Org. Chem.* **2005**, *70*, 8248-8251.

28. Håkansson, A. E.; Palmelund, A.; Holm, H.; Madsen, R., *Chem. Eur. J.* **2006**, *12*, 3243-3253.

29. Hansen, F. G.; Bundgaard, E.; Madsen, R., *J. Org. Chem.* **2005**, *70*, 10139-10142.

30. Monrad, R. N.; Fanefjord, M.; Hansen, F. G.; Jensen, N. M. E.; Madsen, R., *Eur. J. Org. Chem.* **2009**, 396-402.

31. Ren, P.-D.; Jin, Q.-H.; Yao, Z.-P., *Synth. Commun.* **1997**, *27*, 2761-2767.

32. Butsugan, Y.; Ito, H.; Araki, S., *Tetrahedron Lett.* **1987**, *28*, 3707-3708.

33. Smith, K.; Lock, S.; El-Hiti, G. A.; Wada, M.; Miyoshi, N., *Org. Biomol. Chem.* **2004**, *2*, 935-938.

34. Wang, W.-B.; Shi, L.-L.; Xu, R.-H.; Huang, Y.-Z., *J. Chem. Soc. Perkin Trans. 1* **1990**, 424-425.

35. Wang, W.-B.; Shi, L.-L.; Huang, Y.-Z., *Tetrahedron* **1990**, *46*, 3315-3320.

36. Li, C.-J.; Zhang, W.-C., *J. Am. Chem. Soc.* **1998**, *120*, 9102-9103.

37. Zhang, W.-C.; Li, C.-J., *J. Chem. Soc. Perkin Trans. 1* **1998**, 3131-3132.

38. Toma, Š.; Mečarová, M., *Green Chemistry* **1999**, *1*, 257-259.

39. Brown, H. C.; Okamoto, Y., *J. Org. Chem.* **1958**, *23*, 4979-4987.

40. Schreck, J. O., *J. Chem. Educ.* **1971**, *48*, 103-107.

41. Hansch, C.; Leo, A.; Taft, R. W., *Chem. Rev.* **1991**, *91*, 165-195.

42. Holm, T.; Crossland, I., *Acta Chem. Scand.* **1971**, *25*, 59-69.

43. Yamataka, H.; Matsuyama, T.; Hanafusa, T., *J. Am. Chem. Soc.* **1989**, *111*, 4912-4918.

44. Burchat, A. F.; Chong, J. M.; Nielsen, N., *J. Organomet. Chem.* **1997**, *542*, 281-283.

45. Duhamel, L.; Plaquevent, J.-C., *J. Organomet. Chem.* **1993**, *448*, 1-3.

46. Khurana, J. M.; Sehgal, A., *J. Chem. Soc., Chem. Commun.* **1994**, 571.

47. Cygon, P.; Bondock, S.; Griesbeck, A. G., *J. Am. Chem. Soc.* **2003**, *125*, 9016-9017.

48. Leshecheva, I. F.; Torocheshnikov, V. N.; Sergeyev, N. M.; Chertkov, V. A.; Khlopkov, V. N., *J. Magn. Reson.* **1991**, *94*, 1-8.

49. Pettit, G. R.; Gaddamiddi, V.; Cragg, G. M.; Herald, D. L.; Sagawa, Y., *J. Chem. Soc. Chem. Commun.* **1984**, 1693-1694.

50. Pettit, G. R.; Gaddamiddi, V.; Herald, D. L.; Singh, S. B.; Cragg, G. M.; Schmidt, J. M., *J. Nat. Prod.* **1986**, *49*, 995-1002.

51. Rinner, U.; Hudlicky, T., *Synlett* **2005**, 365-387.

52. Kornienko, A.; Evidente, A., *Chem. Rev.* **2008**, *108*, 1982-2014.

53. Manpadi, M.; Kornienko, A., *Org. Prep. Proc. Int.* **2008**, *40*, 107-161.

54. Chapleur, Y.; Chrétien, F.; Ahmed, S. I.; Khaldi, M., *Curr. Org. Syn.* **2006**, *3*, 341-378.

55. Rinner, U.; Hillebrenner, H. L.; Adams, D. R.; Hudlicky, T.; Pettit, G. R., *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2911-2915.

56. Quarzane-Amara, M.; Franetich, J.-F.; Mazier, D.; Pettit, G. R.; Meijer, L.; Doerig, C.; Desportes-Livage, I., *Antimicrob. Agents Chemother.* **2001**, *45*, 3409-3415.

57. Lithikwitayawuid, K.; Angerhofer, C. K.; Chai, H.; Pezzuto, J. M.; Cordell, G. A., *J. Nat. Prod.* **1993**, *56*, 1331-1338.

58. Hudlicky, T.; Tian, X.; Königsberger, K.; Maurya, R.; Rouden, J.; Fan, B., *J. Am. Chem. Soc.* **1996**, *118*, 10752-10765.

59. Pettit, G. R.; Melody, N.; Herald, D. L., *J. Nat. Prod.* **2004**, *67*, 322-327.

60. Phung, A. N.; Zannetti, M. T.; Whited, G.; Fessner, W.-D., *Angew. Chem. Int. Ed.* **2003**, *42*, 4821-4824.

61. Pettit, G. R.; Melody, N., *J. Nat. Prod.* **2005**, *68*, 207-211.

62. McNulty, J.; Mao, J.; Gibe, R.; Mo, R.; Wolf, S.; Pettit, G. R.; Herald, D. L.; Boyd, M. R., *Bioorg. Med. Chem. Lett.* **2001**, *11*, 169-172.

63. McNulty, J.; Larichev, V.; Pandey, S., *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5315-5318.

64. McLachlan, A.; Kekre, N.; McNulty, J.; Pandey, S., *Apoptosis* **2005**, *10*, 619-630.

65. Kekre, N.; Griffin, C.; McNulty, J.; Pandey, S., *Cancer Chemother. Pharmacol.* **2005**, *56*, 29-38.

66. Pandey, S.; Kekre, N.; Naderi, J.; McNulty, J., *Artif. Cells, Blood Substitutes, Biotechnol.* **2005**, *33*, 279-295.

67. Danishefsky, S.; Lee, J. Y., *J. Am. Chem. Soc.* **1989**, *111*, 4829-4837.

68. Tian, X.; Hudlicky, T.; Königsberger, K., *J. Am. Chem. Soc.* **1995**, *117*, 3643-3644.

69. Trost, B. M.; Pulley, S. R., *J. Am. Chem. Soc.* **1995**, *117*, 10143-10144.

70. Doyle, T. J.; Hendrix, M.; VanDerveer, D.; Javanmard, S.; Haseltine, J., *Tetrahedron* **1997**, *53*, 11153-11170.

71. Magnus, P.; Sebhat, I. K., *Tetrahedron* **1998**, *54*, 15509-15524.

72. Rigby, J. H.; Maharoof, U. S. M.; Mateo, M. E., *J. Am. Chem. Soc.* **2000**, *122*, 6624-6628.

73. Pettit, G. R.; Melody, N.; Herald, D. L., *J. Org. Chem.* **2001**, *66*, 2583-2587.

74. Kim, S.; Ko, H.; Kim, E.; Kim, D., *Org. Lett.* **2002**, *4*, 1343-1345.

75. Li, M.; Wu, A.; Zhou, P., *Tetrahedron Lett.* **2006**, *47*, 3707-3710.

76. Crich, D.; Krishnamurthy, V., *Tetrahedron* **2006**, *62*, 6830-6840.

77. Magnus, P.; Sebhat, I. K., *J. Am. Chem. Soc.* **1998**, *120*, 5341-5342.

78. Ko, H.; Kim, E.; Park, J. E.; Kim, D.; Kim, S., *J. Org. Chem.* **2004**, *69*, 112-121.

79. Greenberg, S.; Moffatt, J. G., *J. Am. Chem. Soc.* **1973**, *95*, 4016-4025.

80. Russell, A. F.; Greenberg, S.; Moffatt, J. G., *J. Am. Chem. Soc.* **1973**, *95*, 4025-4030.

81. Ohta, S.; Kimoto, S., *Chem. Pharm. Bull.* **1976**, *24*, 2977-2984.

82. Stubbe, M.; Paulsen, H., *Tetrahedron Lett.* **1982**, *23*, 3171-3174.

83. Overman, L. E., *J. Am. Chem. Soc.* **1974**, *96*, 597-599.

84. Overman, L. E., *Acc. Chem. Res.* **1980**, *13*, 218-224.

85. Madsen, R., *Eur. J. Org. Chem.* **2007**, 399-415.

86. Lauritsen, A.; Madsen, R., *Org. Biomol. Chem.* **2006**, *4*, 2898-2905.

87. Hyldtoft, L.; Madsen, R., *J. Am. Chem. Soc.* **2000**, *122*, 8444-8452.

88. Dalcanale, E., *J. Org. Chem.* **1986**, *51*, 567-569.

89. Dam, J. H., *Master Thesis* **2005**, *Technical University of Denmark*, (Denmark).

90. Keck, G. E.; McLaws, M. D.; Wager, T. T., *Tetrahedron* **2000**, *56*, 9875-9883.

91. Keck, G. E.; Wager, T. T.; Rodriguez, J. F. D., *J. Am. Chem. Soc.* **1999**, *121*, 5176-5190.

92. Hegedus, L. S., *Transition Metals in the Synthesis of Complex Organic Molecuels 2nd Ed.* **1999**, *University Science Books*, (Sausalito).

93. Jeffery, T., *Tetrahedron* **1996**, *52*, 10113-10130.

94. Bernet, B.; Vasella, A., *Helv. Chim. Acta.* **1979**, *62*, 1990-2016, 2400-1241 & 2411-2431.

95. Henon, E.; Bercier, A.; Plantier-Royon, R.; Harakat, D.; Portella, C., *J. Org. Chem.* **2007**, *72*, 2271-2278.

96. Dam, J. H.; Fristrup, P.; Madsen, R., *J. Org. Chem.* **2008**, *73*, 3228-3235.

97. Jaworsky, W., *Berichte* **1909**, *42*, 435-438.

98. Gilman, H.; McGlumphy, J. H., *Bull. soc. chim.* **1928**, *43*, 1322-1328.

99. Henze, H. R.; Allen, B. B.; Leslie, W. B., *J. Org. Chem.* **1942**, *4*, 326-335.

100. Anh, N. T., *Top. Curr. Chem.* **1980**, *88*, 145-162.

101. Chérest, M.; Felkin, H.; Prudent, N., *Tetrahedron Lett.* **1968**, *9*, 2199-2204.

102. Chérest, M.; Felkin, H., *Tetrahedron Lett.* **1968**, *9*, 2205-2208.

103. Cram, D. J.; Elhafez, F. A. A., *J. Am. Chem. Soc.* **1952**, *74*, 5828-5835.

104. Paquette, L. A.; Mitzel, T. M., *J. Am. Chem. Soc.* **1996**, *118*, 1931-1937.

105. Evans, D. A.; Cee, V. J.; Siska, S. J., *J. Am. Chem. Soc.* **2006**, *128*, 9433-9441.

106. Keck, G. E.; McHardy, S. F.; Murry, J. A., *J. Am. Chem. Soc.* **1995**, *117*, 7289-7290.

107. Pearlman, W. M., *Tetrahedron Lett.* **1967**, *17*, 1663-1664.

108. Khaldi, M.; Chrétien, F.; Chapleur, Y., *Bull. Soc. Chim. Fr.* **1996**, *133*, 7-13.

109. Cram, D. J.; Cram, J. M., *Acc. Chem. Res.* **1971**, *4*, 204-213.

110. Brown, C. J.; Farthing, A. C., *Nature* **1949**, *164*, 915-916.

111. Bickelhaupt, F., *Pure & Appl. Chem.* **1990**, *62*, 373-382.

112. Asakawain, Y., *Progress in the Chemistry of Organic Natural Products* **1995**, *Springer*, (New York).

113. Toyota, M.; Yoshida, T.; Kan, Y.; Takaoka, S.; Asakawa, Y., *Tetrahedron Lett.* **1996**, *37*, 4745-4748.

114. Garrido, L.; Zubia, E.; Ortega, M. J.; Salva, J., *J. Org. Chem.* **2003**, *68*, 293-299.

115. Harrowven, D. C.; Woodcock, T.; Howes, P. D., *Angew. Chem. Int. Ed.* **2005**, *44*, 3899-3901.

116. Burns, N. Z.; Baran, P. S., *Angew. Chem. Int. Ed.* **2008**, *47*, 205-208.

117. Baran, P. S.; Burns, N. Z., *J. Am. Chem. Soc.* **2006**, *128*, 3908-3909.

118. Node, M.; Kodama, S.; Hamashima, Y.; Katoh, T.; Nishede, K.; Kajimoto, T., *Chem. Pharm. Bull.* **2006**, *54*, 1662-1679.

119. Speicher, A.; Backes, T.; Grosse, S., *Tetrahedron* **2005**, *61*, 11692-11696.

120. Viroopakshappa, J.; Jagannadham, V., *Indian J. Chem., Section A* **2004**, *43*, 532-534.

121. Garegg, P. J.; Samuelsson, B., *J. Chem. Soc. Perkin Trans. 1* **1980**, 2866-2869.

122. Wittig, G.; Schollkopf, U., *Chem. Ber.* **1954**, *97*, 1318-1330.

123. Wittig, G.; Haag, W., *Chem. Ber.* **1955**, *88*, 1654-1666.

124. Miyaura, N.; Suzuki, A., *J. Chem. Soc. Chem. Commun.* **1979**, 866-867.

125. Miyaura, N.; Yamada, K.; Suzuki, A., *Tetrahedron Lett.* **1979**, *20*, 3437-3440.

126. Alberico, D.; Scott, M. E.; Lautens, M., *Chem. Rev.* **2007**, *107*, 174-238.

127. Yonemitsu, O.; Cerutti, P.; Witkop, B., *J. Am. Chem. Soc.* **1966**, *88*, 3941-3945.

128. Li, J.; Jeong, S.; Esser, L.; Harran, P. G., *Angew. Chem. Int. Ed.* **2001**, *40*, 4765-4769.

129. McIntosh, M. C.; Weinreb, S. M., *J. Org. Chem.* **1993**, *58*, 4823-4832.

130. Zaugg, H. E., *J. Org. Chem.* **1976**, *41*, 3419-3421.

131. Pietruszka, J.; Witt, A., *Synthesis* **2006**, *24*, 4266-4268.

132. Afarinkia, K.; Bearpark, M. J.; Ndibwami, A., *J. Org. Chem.* **2003**, *68*, 7158-7166.

133. Rele, D.; Trivedi, G. K., *J. Sci. Ind. Res.* **1993**, *52*, 13-28.

134. Afarinkia, K.; Bearpark, M. J.; Ndibwami, A., *J. Org. Chem.* **2005**, *70*, 1122-1133.

135. Fürstner, A.; Stimson, C. C., *Angew. Chem. Int. Ed.* **2007**, *46*, 8845-8849.

136. Mamane, V.; Hannen, P.; Fürstner, A., *Chem. Eur. J.* **2004**, *10*, 4556-4575.

137. Eicher, T.; Fey, S.; Puhl, W.; Büchel, E.; Speicher, A., *Eur. J. Org. Chem.* **1998**, 877-888.

138. Mamane, V.; Fürstner, A., *J. Org. Chem.* **2002**, *67*, 6264-6267.

139. Fu, P. P.; Harvey, R. G., *Tetrahedron Lett.* **1977**, *5*, 415-418.

140. Gassmann, P. G.; Hodgson, P. K. G.; Balchunis, R. J., *J. Am. Chem. Soc.* **1976**, *98*, 1275-1276.

141. Carbaugh, A. D.; Vosburg, W.; Scherer, T. J.; Castillo, C. E.; Christianson, M. A.; Kostarellas, J.; Gosai, S. J.; Leonard, M. S., *ARKIVOC* **2007**, *xii*, 43-54.

142. Markó, I. E.; Evans, G. R.; Declercq, J.-P., *Tetrahedron* **1994**, *50*, 4557-4574.

143. Bläser, E.; Kolar, P.; Fenske, D.; Goesmann, H.; Waldmann, H., *Eur. J. Org. Chem.* **1999**, 329-333.

144. Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R., *Angew. Chem. Int. Ed.* **1984**, *23*, 727-729.

145. Meyer, M. D.; DeBernardis, J. F.; Hancock, A. A., *J. Med. Chem.* **1994**, *37*, 105-112.

146. Dowd, C. S.; Herrick-Davis, K.; Egan, C.; DuPre, A.; Smith, C.; Teitler, M.; Glennon, R. A., *J. Med. Chem.* **2000**, *43*, 3074-3084.

147. Murahashi, S.-I.; Naota, T.; Saito, E., *J. Am. Chem. Soc.* **1986**, *108*, 7846-7847.

148. Kim, J. W.; Yamaguchi, K.; Mizuno, N., *Angew. Chem. Int. Ed.* **2008**, *47*, 9249-9251.

149. Gunanathan, C.; Ben-David, Y.; Milstein, D., *Science* **2007**, *317*, 790-792.

150. Nordstrøm, L. U.; Vogt, H.; Madsen, R., *J. Am. Chem. Soc.* **2008**, *130*, 17672-17673.

151. Zweifel, T.; Naubron, J.-V.; Grützmacher, H., *Angew. Chem. Int. Ed.* **2009**, *48*, 559-563.

152. Burling, S.; Kociok-Köhn, G.; Mahan, M. F.; Whittlesey, M. K.; Williams, J. M. J., *Organometallics* **2005**, *24*, 5868-5878.

153. Delaude, L.; Delfosse, S.; Richel, A.; Demonceau, A.; Noels, A. F., *Chem. Commun.* **2003**, 1526-1527.

154. Wang, H. M. J.; Lin, I. J. B., *Organometallics* **1998**, *17*, 972-975.

155. Prades, A.; Viciano, M.; Sanaú, M.; Peris, E., *Organometallics* **2008**, *27*, 4254-4259.

156. Chianese, A. R.; Kovacevic, A.; Zeglis, B. M.; Faller, J. W.; Crabtree, R. H., *Organometallics* **2004**, *23*, 2461-2468.

157. Louie, J.; Bielawski, C. W.; Grubbs, R. H., *J. Am. Chem. Soc.* **2001**, *123*, 11312-11313.

158. Vougioukalakis, G. C.; Grubbs, R. H., *J. Am. Chem. Soc.* **2008**, *130*, 2230-2245.

159. Arduengo, A. J. I.; Göerlich, J. R.; Marshall, W. J., *Liebigs Ann./Recl.* **1997**, 365-374.

160. Weskamp, T.; Kohl, F. J.; Hieringer, W.; Gleich, D.; Herrmann, W. A., *Angew. Chem. Int. Ed.* **1999**, *38*, 2416-2419.

161. Weskamp, T.; Kohl, F. J.; Herrmann, W. A., *J. Organomet. Chem.* **1999**, *582*, 362-365.

162. Jafarpour, L.; Nolan, S. P., *Organometallics* **2000**, *19*, 2055-2057.

163. Jafarpour, L.; Hillier, A. C.; Nolan, S. P., *Organometallics* **2002**, *21*, 442-444.

164. Burling, S.; Paine, B. M.; Nama, D.; Brown, V. S.; Mahon, M. F.; Prior, T. J.; Pregosin, P. S.; Whittlesey, M. K.; Williams, J. M. J., *J. Am. Chem. Soc.* **2007**, *129*, 1987-1995.

165. Jonas, L.; Häller, L.; Page, M. J.; Macgregor, S. A.; Mahon, M. F.; Whittlesey, M. K., *J. Am. Chem. Soc.* **2009**, *131*, 4604-4605.

166. Chatwin, S. L.; Davidson, M. G.; Doherty, C.; Donald, S. M.; Jazzar, R. F. R.; Macgregor, S. A.; McIntyre, G. J.; Mahon, M. F.; Whittlesey, M. K., *Organometallics* **2006**, *25*, 99-100.

167. Samec, J. S. M.; Bäckvall, J.-E.; Andersson, P. G.; Brandt, P., *Chem. Soc. Rev.* **2006**, *35*, 237-248.

168. Ohta, T.; Takaya, H.; Noyori, R., *Tetrahedron Lett.* **1990**, *31*, 7189-7192.

169. Ashby, M. T.; Halpern, J., *J. Am. Chem. Soc.* **1991**, *113*, 589-594.

170. Herrmann, W. A.; Köcher, C.; Gooβen, L. J.; Artus, G. R. J., *Chem. Eur. J.* **1996**, *2*, 1627-1636.

171. Jafarpour, L.; Huang, J.; Stevens, E. D.; Nolan, S. P., *Organometallics* **1999**, *18*, 3760-3763.

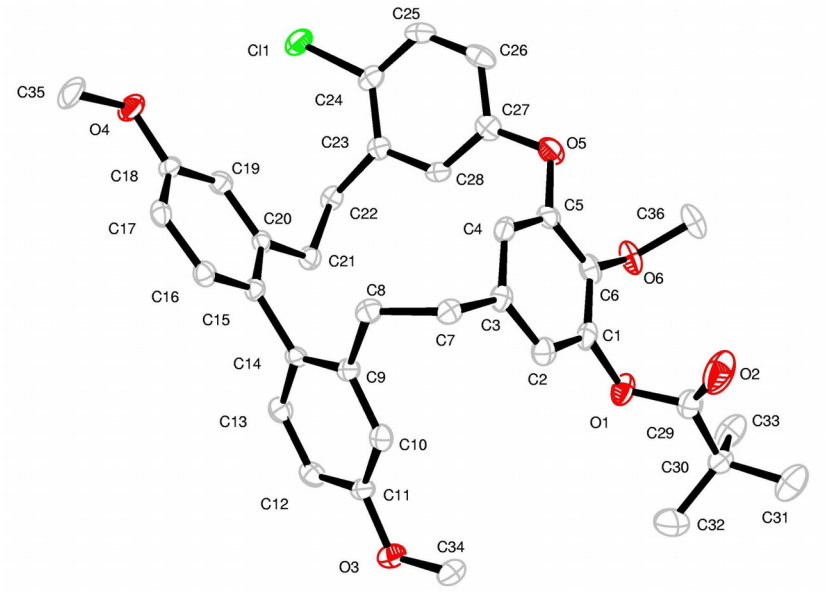
172. Mistryukov, E. A., *Mendeleev Commun.* **2006**, *16*, 258-259.

173. Arduengo, A. J.; III, **1991**, *U.S. Patent 5077414*.

174. Delaude, L.; Szypa, M.; Demonceau, A.; Noels, A. F., *Adv. Synth. Catal.* **2002**, *344*, 749-756.

7 Appendix

7.1 X-ray Crystal Structure



A colorless block 0.45 x 0.14 x 0.07 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 60 seconds per frame using a scan width of 1.0°. Data collection was 98.7% complete to 25.00° in θ. A total of 12636 reflections were collected covering the indices, -13<=*h*<=13, -14<=*k*<=14, -15<=*l*<=15. 5563 reflections were found to be symmetry independent, with an R_{int} of 0.0591. Indexing and unit cell refinement indicated a primitive, triclinic lattice. The space group was found to be P-1 (No. 2). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SIR-2004) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97.

Table 7.1: Crystal data and structure refinement for baran45.

X-ray ID	baran45	
Sample/notebook ID	188A-D	
Empirical formula	C36 H37 Br0.29 Cl0.71 O6	
Formula weight	614.04	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.8243(24) Å	α= 105.447(3)°.
	b = 12.2121(26) Å	β= 113.778(3)°.
	c = 13.1784(28) Å	γ = 90.441(3)°.
Volume	1523.4(6) $Å^3$	
Z	2	
Density (calculated)	1.339 Mg/m^3	
Absorption coefficient	0.528 mm^{-1}	
F(000)	646.5	
Crystal size	0.45 x 0.14 x 0.07 mm^3	
Crystal color/habit	colorless block	
Theta range for data collection	1.74 to 25.49°.	
Index ranges	-13<=h<=13, -14<=k<=14, -15<=l<=15	
Reflections collected	12636	
Independent reflections	5563 [R(int) = 0.0591]	
Completeness to theta = 25.00°	98.7 %	
Absorption correction	Analytical	
Max. and min. transmission	0.9472 and 0.7193	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5563 / 0 / 395	
Goodness-of-fit on F^2	1.048	
Final R indices [I>2sigma(I)]	R1 = 0.0619, wR2 = 0.0910	
R indices (all data)	R1 = 0.1183, wR2 = 0.1057	
Largest diff. peak and hole	0.295 and -0.259 $e.Å^{-3}$	

Table 7.2: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for baran45. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	2190(3)	-3350(3)	-1951(3)	24(1)
C(2)	1170(3)	-2734(3)	-2454(3)	23(1)
C(3)	636(3)	-1996(3)	-1782(3)	20(1)
C(4)	1153(3)	-1886(3)	-603(3)	22(1)
C(5)	2183(3)	-2504(3)	-106(3)	22(1)
C(6)	2715(3)	-3256(3)	-772(3)	23(1)
C(7)	-474(3)	-1291(2)	-2276(3)	21(1)
C(8)	51(3)	-14(3)	-1908(3)	21(1)
C(9)	1081(3)	299(3)	-2326(3)	18(1)
C(10)	1035(3)	-352(3)	-3401(3)	21(1)
C(11)	1965(3)	-73(3)	-3800(3)	20(1)
C(12)	2959(3)	863(3)	-3140(3)	23(1)
C(13)	3012(3)	1512(3)	-2086(3)	23(1)
C(14)	2075(3)	1253(3)	-1666(3)	18(1)
C(15)	2101(3)	2049(3)	-567(3)	18(1)
C(16)	1055(3)	2722(2)	-638(3)	20(1)
C(17)	1019(3)	3516(3)	317(3)	21(1)
C(18)	2062(3)	3634(3)	1401(3)	20(1)
C(19)	3112(3)	2952(3)	1499(3)	20(1)
C(20)	3162(3)	2171(2)	542(3)	18(1)
C(21)	4370(3)	1503(3)	662(3)	21(1)
C(22)	5206(3)	1353(3)	1867(3)	21(1)
C(23)	4466(3)	588(3)	2240(3)	19(1)
C(24)	4448(3)	859(3)	3333(3)	23(1)
C(25)	3857(3)	74(3)	3658(3)	25(1)
C(26)	3288(3)	-1005(3)	2910(3)	26(1)
C(27)	3268(3)	-1283(3)	1809(3)	23(1)
C(28)	3842(3)	-501(3)	1480(3)	20(1)
C(29)	2258(4)	-5134(3)	-3176(3)	27(1)
C(30)	3038(4)	-5751(3)	-3844(3)	28(1)
C(31)	2242(4)	-6929(3)	-4579(3)	40(1)
C(32)	3195(5)	-5063(3)	-4604(4)	64(1)

C(33)	4453(4)	-5872(3)	-2963(3)	39(1)
C(34)	1048(3)	-1704(3)	-5494(3)	31(1)
C(35)	1188(4)	5178(3)	2327(3)	38(1)
C(36)	3280(4)	-4839(3)	-69(3)	35(1)
O(1)	2803(2)	-4017(2)	-2622(2)	29(1)
O(2)	1304(3)	-5543(2)	-3095(3)	55(1)
O(3)	1969(2)	-663(2)	-4844(2)	26(1)
O(4)	2165(2)	4388(2)	2415(2)	30(1)
O(5)	2695(2)	-2384(2)	1080(2)	28(1)
O(6)	3756(2)	-3865(2)	-301(2)	30(1)
Cl(1)	5233(1)	2243(1)	4405(1)	31(1)
Br(1)	5233(1)	2243(1)	4405(1)	31(1)

Table 7.3: Bond lengths [Å] and angles [°] for baran45.

C(1)-C(2)	1.383(4)	C(18)-O(4)	1.368(3)
C(1)-C(6)	1.395(4)	C(18)-C(19)	1.399(4)
C(1)-O(1)	1.409(4)	C(19)-C(20)	1.385(4)
C(2)-C(3)	1.387(4)	C(19)-H(19)	0.9500
C(2)-H(2)	0.9500	C(20)-C(21)	1.522(4)
C(3)-C(4)	1.389(4)	C(21)-C(22)	1.541(4)
C(3)-C(7)	1.514(4)	C(21)-H(21A)	0.9900
C(4)-C(5)	1.389(4)	C(21)-H(21B)	0.9900
C(4)-H(4)	0.9500	C(22)-C(23)	1.518(4)
C(5)-C(6)	1.391(4)	C(22)-H(22A)	0.9900
C(5)-O(5)	1.396(4)	C(22)-H(22B)	0.9900
C(6)-O(6)	1.379(3)	C(23)-C(24)	1.399(4)
C(7)-C(8)	1.534(4)	C(23)-C(28)	1.399(4)
C(7)-H(7A)	0.9900	C(24)-C(25)	1.393(4)
C(7)-H(7B)	0.9900	C(24)-Cl(1)	1.819(3)
C(8)-C(9)	1.514(4)	C(25)-C(26)	1.375(4)
C(8)-H(8A)	0.9900	C(25)-H(25)	0.9500
C(8)-H(8B)	0.9900	C(26)-C(27)	1.392(4)
C(9)-C(14)	1.400(4)	C(26)-H(26)	0.9500
C(9)-C(10)	1.408(4)	C(27)-C(28)	1.383(4)
C(10)-C(11)	1.388(4)	C(27)-O(5)	1.391(4)
C(10)-H(10)	0.9500	C(28)-H(28)	0.9500
C(11)-O(3)	1.374(3)	C(29)-O(2)	1.198(4)
C(11)-C(12)	1.384(4)	C(29)-O(1)	1.361(4)
C(12)-C(13)	1.382(4)	C(29)-C(30)	1.521(5)
C(12)-H(12)	0.9500	C(30)-C(31)	1.522(5)
C(13)-C(14)	1.405(4)	C(30)-C(32)	1.524(5)
C(13)-H(13)	0.9500	C(30)-C(33)	1.541(4)
C(14)-C(15)	1.503(4)	C(31)-H(31A)	0.9800
C(15)-C(16)	1.392(4)	C(31)-H(31B)	0.9800
C(15)-C(20)	1.416(4)	C(31)-H(31C)	0.9800
C(16)-C(17)	1.384(4)	C(32)-H(32A)	0.9800
C(16)-H(16)	0.9500	C(32)-H(32B)	0.9800
C(17)-C(18)	1.387(4)	C(32)-H(32C)	0.9800
C(17)-H(17)	0.9500	C(33)-H(33A)	0.9800

C(33)-H(33B)	0.9800	H(7A)-C(7)-H(7B)	107.8
C(33)-H(33C)	0.9800	C(9)-C(8)-C(7)	116.5(3)
C(34)-O(3)	1.434(4)	C(9)-C(8)-H(8A)	108.2
C(34)-H(34A)	0.9800	C(7)-C(8)-H(8A)	108.2
C(34)-H(34B)	0.9800	C(9)-C(8)-H(8B)	108.2
C(34)-H(34C)	0.9800	C(7)-C(8)-H(8B)	108.2
C(35)-O(4)	1.428(3)	H(8A)-C(8)-H(8B)	107.3
C(35)-H(35A)	0.9800	C(14)-C(9)-C(10)	118.8(3)
C(35)-H(35B)	0.9800	C(14)-C(9)-C(8)	120.7(3)
C(35)-H(35C)	0.9800	C(10)-C(9)-C(8)	120.4(3)
C(36)-O(6)	1.445(4)	C(11)-C(10)-C(9)	121.2(3)
C(36)-H(36A)	0.9800	C(11)-C(10)-H(10)	119.4
C(36)-H(36B)	0.9800	C(9)-C(10)-H(10)	119.4
C(36)-H(36C)	0.9800	O(3)-C(11)-C(12)	115.9(3)
C(2)-C(1)-C(6)	122.0(3)	O(3)-C(11)-C(10)	124.2(3)
C(2)-C(1)-O(1)	119.3(3)	C(12)-C(11)-C(10)	120.0(3)
C(6)-C(1)-O(1)	118.4(3)	C(13)-C(12)-C(11)	119.4(3)
C(1)-C(2)-C(3)	120.1(3)	C(13)-C(12)-H(12)	120.3
C(1)-C(2)-H(2)	120.0	C(11)-C(12)-H(12)	120.3
C(3)-C(2)-H(2)	120.0	C(12)-C(13)-C(14)	121.7(3)
C(2)-C(3)-C(4)	118.8(3)	C(12)-C(13)-H(13)	119.1
C(2)-C(3)-C(7)	122.7(3)	C(14)-C(13)-H(13)	119.1
C(4)-C(3)-C(7)	118.5(3)	C(9)-C(14)-C(13)	118.9(3)
C(5)-C(4)-C(3)	120.7(3)	C(9)-C(14)-C(15)	121.6(3)
C(5)-C(4)-H(4)	119.6	C(13)-C(14)-C(15)	119.4(3)
C(3)-C(4)-H(4)	119.6	C(16)-C(15)-C(20)	118.0(3)
C(4)-C(5)-C(6)	121.1(3)	C(16)-C(15)-C(14)	118.8(3)
C(4)-C(5)-O(5)	120.2(3)	C(20)-C(15)-C(14)	123.1(3)
C(6)-C(5)-O(5)	118.7(3)	C(17)-C(16)-C(15)	123.2(3)
O(6)-C(6)-C(5)	122.5(3)	C(17)-C(16)-H(16)	118.4
O(6)-C(6)-C(1)	120.1(3)	C(15)-C(16)-H(16)	118.4
C(5)-C(6)-C(1)	117.3(3)	C(16)-C(17)-C(18)	118.5(3)
C(3)-C(7)-C(8)	112.7(3)	C(16)-C(17)-H(17)	120.7
C(3)-C(7)-H(7A)	109.0	C(18)-C(17)-H(17)	120.7
C(8)-C(7)-H(7A)	109.0	O(4)-C(18)-C(17)	124.9(3)
C(3)-C(7)-H(7B)	109.0	O(4)-C(18)-C(19)	115.7(3)
C(8)-C(7)-H(7B)	109.0	C(17)-C(18)-C(19)	119.4(3)

C(20)-C(19)-C(18)	122.1(3)	O(2)-C(29)-C(30)	126.8(3)
C(20)-C(19)-H(19)	119.0	O(1)-C(29)-C(30)	111.2(3)
C(18)-C(19)-H(19)	119.0	C(29)-C(30)-C(31)	107.7(3)
C(19)-C(20)-C(15)	118.7(3)	C(29)-C(30)-C(32)	109.8(3)
C(19)-C(20)-C(21)	121.0(3)	C(31)-C(30)-C(32)	110.9(3)
C(15)-C(20)-C(21)	120.2(3)	C(29)-C(30)-C(33)	108.3(3)
C(20)-C(21)-C(22)	116.6(3)	C(31)-C(30)-C(33)	110.2(3)
C(20)-C(21)-H(21A)	108.2	C(32)-C(30)-C(33)	109.9(3)
C(22)-C(21)-H(21A)	108.2	C(30)-C(31)-H(31A)	109.5
C(20)-C(21)-H(21B)	108.2	C(30)-C(31)-H(31B)	109.5
C(22)-C(21)-H(21B)	108.2	H(31A)-C(31)-H(31B)	109.5
H(21A)-C(21)-H(21B)	107.3	C(30)-C(31)-H(31C)	109.5
C(23)-C(22)-C(21)	114.9(3)	H(31A)-C(31)-H(31C)	109.5
C(23)-C(22)-H(22A)	108.5	H(31B)-C(31)-H(31C)	109.5
C(21)-C(22)-H(22A)	108.5	C(30)-C(32)-H(32A)	109.5
C(23)-C(22)-H(22B)	108.5	C(30)-C(32)-H(32B)	109.5
C(21)-C(22)-H(22B)	108.5	H(32A)-C(32)-H(32B)	109.5
H(22A)-C(22)-H(22B)	107.5	C(30)-C(32)-H(32C)	109.5
C(24)-C(23)-C(28)	116.9(3)	H(32A)-C(32)-H(32C)	109.5
C(24)-C(23)-C(22)	124.4(3)	H(32B)-C(32)-H(32C)	109.5
C(28)-C(23)-C(22)	118.5(3)	C(30)-C(33)-H(33A)	109.5
C(25)-C(24)-C(23)	121.5(3)	C(30)-C(33)-H(33B)	109.5
C(25)-C(24)-Cl(1)	117.2(3)	H(33A)-C(33)-H(33B)	109.5
C(23)-C(24)-Cl(1)	121.3(3)	C(30)-C(33)-H(33C)	109.5
C(26)-C(25)-C(24)	120.6(3)	H(33A)-C(33)-H(33C)	109.5
C(26)-C(25)-H(25)	119.7	H(33B)-C(33)-H(33C)	109.5
C(24)-C(25)-H(25)	119.7	O(3)-C(34)-H(34A)	109.5
C(25)-C(26)-C(27)	118.7(3)	O(3)-C(34)-H(34B)	109.5
C(25)-C(26)-H(26)	120.6	H(34A)-C(34)-H(34B)	109.5
C(27)-C(26)-H(26)	120.6	O(3)-C(34)-H(34C)	109.5
C(28)-C(27)-O(5)	122.1(3)	H(34A)-C(34)-H(34C)	109.5
C(28)-C(27)-C(26)	120.7(3)	H(34B)-C(34)-H(34C)	109.5
O(5)-C(27)-C(26)	117.2(3)	O(4)-C(35)-H(35A)	109.5
C(27)-C(28)-C(23)	121.5(3)	O(4)-C(35)-H(35B)	109.5
C(27)-C(28)-H(28)	119.3	H(35A)-C(35)-H(35B)	109.5
C(23)-C(28)-H(28)	119.3	O(4)-C(35)-H(35C)	109.5
O(2)-C(29)-O(1)	121.9(3)	H(35A)-C(35)-H(35C)	109.5

H(35B)-C(35)-H(35C)	109.5
O(6)-C(36)-H(36A)	109.5
O(6)-C(36)-H(36B)	109.5
H(36A)-C(36)-H(36B)	109.5
O(6)-C(36)-H(36C)	109.5
H(36A)-C(36)-H(36C)	109.5
H(36B)-C(36)-H(36C)	109.5
C(29)-O(1)-C(1)	117.1(3)
C(11)-O(3)-C(34)	117.3(3)
C(18)-O(4)-C(35)	116.9(2)
C(27)-O(5)-C(5)	115.4(2)
C(6)-O(6)-C(36)	112.1(2)

Table 7.4: Anisotropic displacement parameters ($Å^2 x\ 10^3$) for baran45. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	24(2)	14(2)	34(2)	2(2)	15(2)	-1(2)
C(2)	19(2)	21(2)	24(2)	4(2)	6(2)	-2(2)
C(3)	16(2)	17(2)	26(2)	4(2)	8(2)	-2(1)
C(4)	24(2)	15(2)	28(2)	2(2)	16(2)	1(2)
C(5)	25(2)	20(2)	22(2)	7(2)	11(2)	-4(2)
C(6)	16(2)	20(2)	32(2)	13(2)	8(2)	2(2)
C(7)	18(2)	22(2)	21(2)	4(2)	8(2)	1(2)
C(8)	17(2)	24(2)	23(2)	6(2)	11(2)	6(2)
C(9)	16(2)	21(2)	19(2)	8(2)	8(2)	9(2)
C(10)	16(2)	20(2)	24(2)	8(2)	6(2)	5(1)
C(11)	21(2)	24(2)	17(2)	9(2)	9(2)	12(2)
C(12)	21(2)	28(2)	28(2)	14(2)	14(2)	7(2)
C(13)	21(2)	23(2)	25(2)	10(2)	9(2)	5(2)
C(14)	21(2)	20(2)	16(2)	10(2)	8(2)	9(2)
C(15)	19(2)	14(2)	22(2)	4(2)	10(2)	1(1)
C(16)	19(2)	18(2)	20(2)	6(2)	6(2)	0(1)
C(17)	20(2)	17(2)	30(2)	10(2)	13(2)	6(1)
C(18)	26(2)	17(2)	23(2)	4(2)	16(2)	3(2)
C(19)	20(2)	21(2)	19(2)	7(2)	7(2)	1(2)
C(20)	19(2)	15(2)	21(2)	7(2)	10(2)	2(1)
C(21)	22(2)	20(2)	24(2)	7(2)	11(2)	5(2)
C(22)	16(2)	20(2)	21(2)	3(2)	5(2)	4(1)
C(23)	14(2)	23(2)	21(2)	9(2)	6(2)	10(2)
C(24)	19(2)	26(2)	21(2)	6(2)	7(2)	10(2)
C(25)	23(2)	39(2)	19(2)	12(2)	11(2)	12(2)
C(26)	18(2)	41(2)	29(2)	22(2)	12(2)	7(2)
C(27)	18(2)	27(2)	25(2)	11(2)	7(2)	5(2)
C(28)	21(2)	26(2)	16(2)	6(2)	9(2)	6(2)
C(29)	26(2)	24(2)	28(2)	6(2)	9(2)	2(2)
C(30)	36(2)	24(2)	23(2)	5(2)	13(2)	6(2)
C(31)	30(2)	35(2)	35(2)	-3(2)	4(2)	9(2)
C(32)	117(4)	49(3)	52(3)	21(2)	59(3)	26(3)
C(33)	29(2)	35(2)	40(2)	-6(2)	12(2)	0(2)

C(34)	40(2)	27(2)	26(2)	3(2)	18(2)	8(2)
C(35)	50(3)	32(2)	33(2)	7(2)	20(2)	27(2)
C(36)	36(2)	28(2)	45(2)	24(2)	14(2)	3(2)
O(1)	30(1)	19(1)	41(2)	2(1)	20(1)	5(1)
O(2)	55(2)	33(2)	79(2)	-10(2)	46(2)	-12(1)
O(3)	28(1)	29(1)	22(1)	5(1)	14(1)	5(1)
O(4)	39(2)	27(1)	24(1)	5(1)	16(1)	16(1)
O(5)	32(1)	27(1)	26(1)	13(1)	10(1)	0(1)
O(6)	26(1)	23(1)	47(2)	21(1)	15(1)	6(1)
Cl(1)	38(1)	29(1)	21(1)	3(1)	11(1)	13(1)
Br(1)	38(1)	29(1)	21(1)	3(1)	11(1)	13(1)

Table 7.5: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for baran45.

	x	y	z	U(eq)
H(2)	834	-2816	-3260	28
H(4)	797	-1384	-133	26
H(7A)	-1198	-1382	-2016	25
H(7B)	-883	-1588	-3134	25
H(8A)	-741	401	-2192	25
H(8B)	466	269	-1050	25
H(10)	354	-994	-3861	25
H(12)	3599	1057	-3409	28
H(13)	3700	2149	-1633	27
H(16)	331	2632	-1378	24
H(17)	295	3970	232	25
H(19)	3814	3026	2246	24
H(21A)	4990	1893	446	26
H(21B)	4029	733	92	26
H(22A)	6043	1030	1869	25
H(22B)	5489	2118	2450	25
H(25)	3847	285	4402	31
H(26)	2915	-1550	3142	32
H(28)	3813	-708	722	24
H(31A)	2116	-7341	-4077	59
H(31B)	2746	-7361	-4990	59
H(31C)	1350	-6842	-5144	59
H(32A)	2294	-4943	-5126	95
H(32B)	3656	-5483	-5063	95
H(32C)	3736	-4319	-4112	95
H(33A)	4952	-5109	-2488	59
H(33B)	4961	-6288	-3379	59
H(33C)	4345	-6295	-2462	59
H(34A)	1240	-2237	-5026	46
H(34B)	1165	-2053	-6206	46
H(34C)	109	-1535	-5696	46
H(35A)	1227	5623	1820	57

H(35B)	1392	5698	3100	57
H(35C)	274	4756	2002	57
H(36A)	2944	-4572	531	52
H(36B)	4033	-5284	201	52
H(36C)	2542	-5323	-780	52

7.2 Publications

Dam, J.H.; Madsen, R., **Convergent Synthesis of Pancratistatin from Piperonal and Xylose**, *J. Org. Chem*. **2009**, submitted.

Dam, J.H.; Fristrup, P.; Madsen, R., **Combined Experimental and Theoretical Mechanistic Investigation of the Barbier Allylation in Aqueous Media**, *J. Org. Chem*. **2008**, *73*, 3228-3235.

Book-chapter:

Dam, J.H.; Taarning, E.; Jensen, T.; Madsen, R., **Industriel Organisk Kemi**, *Nye Kemiske Horisonter*, DTU, **2007**, 88-112.