Total Synthesis of (+)-Ipalbidine and Synthetic Studies on (+)-Sorbicillactone A

by

JongMyoung Chea

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Department of Chemistry
University of Alberta

ABSTRACT

Chapter 1 describes the total synthesis of (+)-ipalbidine. The indolizidine core structure was formed by use of an unusual 6-*exo*-trigonal radical cyclization as a key step. I started from the chiral pool using L-proline and obtained ipalbidine with an ee of >99.6%.

Chapter 2 describes synthetic studies towards the total synthesis of sorbicillactone A. Most of the carbon skeleton of sorbicillactone A was assembled. However, the amination and methylation steps at C-3 remain to be accomplished. Several different approaches were explored to add stereoselectively the amino and methyl group at C-3. The most promising approach appears to be an unusual Claisen rearrangement that introduces two carbons at C-3 so constituted that they can be manipulated individually with one of them eventually being replaced by nitrogen.

DEDICATED TO

MY WIFE HYO JUNG,

MY DAUGHTER IRENE AND MY FAMILY

ACKNOWLEDGEMENTS

I would like to express my sincere thanks to my supervisor Dr. D. L. J. Clive for his advice, guidance, support as well as encouragement during my Ph.D. program and his assistant during the preparation of my thesis.

I also want to extend my thanks to all members of my research lab for their assistance, useful discussions and friendship.

I would like to offer my thanks to the support staff of the Department (IR, MS, NMR, elemental analysis laboratories, glass blowing, electronic, machine and chemical shops) for their constant support and valuable advice.

Finally, I would like to thank my wife for her infinite support, encouragement and her love during graduate studies.

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Chapter 1

Total synthesis of (+)-Ipalbidine

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LIST OF ABBREVIATIONS

Ac	acetyl
AIBN	azobisisobutyronitrile
Ar	aromatic ring
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	*n*-butyl
t-Bu	*tert*-butyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DIPEA	diisopropylethylamine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
EDCI	*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
FTIR	Fourier transform infrared spectroscopy
HATU	1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate
HPLC	high-performance liquid chromatography
IC_{50}	concentration that gives 50% inhibition of an enzyme

ImH	imidazole
LDA	lithium diisopropylamide
Ms	methanesulfonyl
NMO	*N*-methylmorpholine-*N*-oxide
Pmb	*p*-methoxybenzyl
pyr	pyridine
TBAF	tetrabutylammonium fluoride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

Chapter 1

Total Synthesis of (+)-Ipalbidine

1 INTRODUCTION

1.1 General

Indolizidine alkaloids are very popular synthetic targets; they have attractive bioactivities and the structures provide opportunities to develop new synthetic methods and strategies for nitrogen-heterocyclic ring analogues.

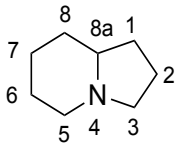
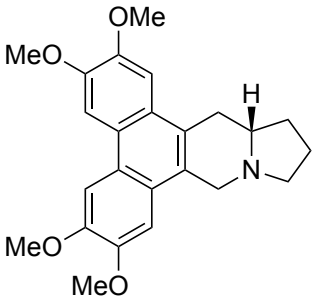
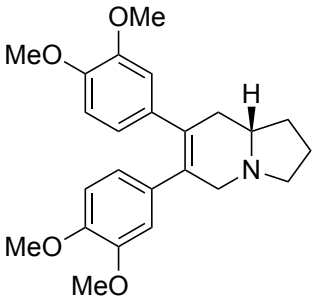


Figure 1. Skeleton of indolizidine

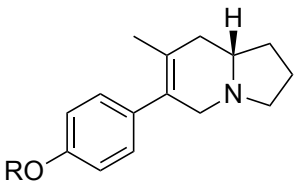
The basic skeleton of these alkaloids is the 1-azabicyclo[4.3.0]nonane system, as illustrated by the following examples of indolizidine alkaloids:



(+)-tylophorine (**1.1**)



(+)-septicine (**1.2**)



R = H; ipalbidine (**1.3**)
R = ! -D-glucosyl; ipalbine (**1.4**)

Scheme 1. Examples of Indolizidine alkaloids

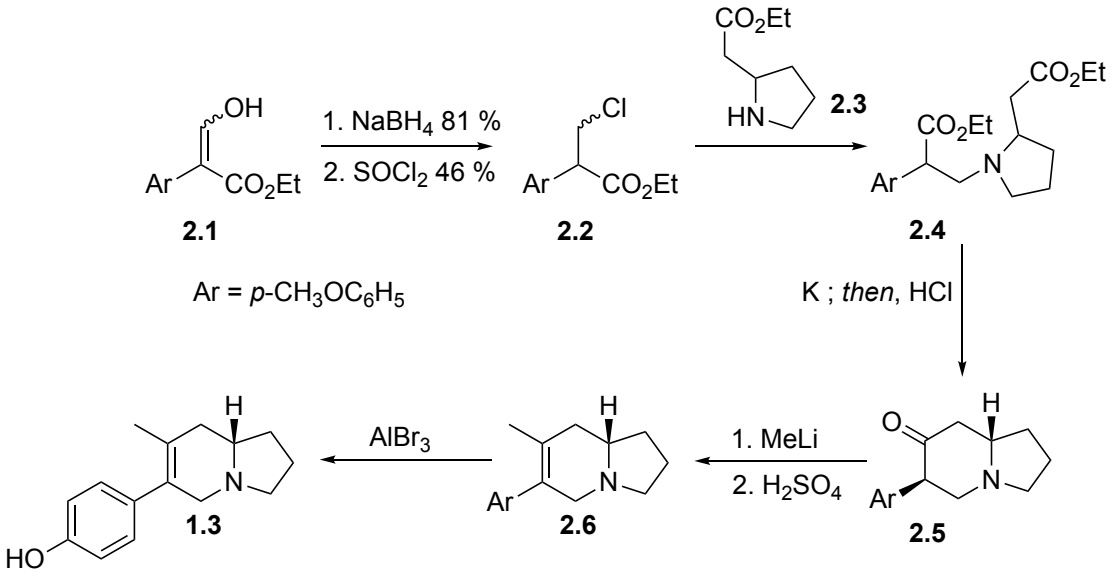
1.2 (+)-Ipalbidine

The hexahydroindolizine alkaloid ipalbine and the aglycone (+)-ipalbidine were each isolated many years ago from seeds of *Ipomoea alba* L.[1,2] and, subsequently, the aglycone was

also obtained from *Ipomoea hardwickii* Hemsl.[3] and *Ipomoea muricata*.[4] Ipalbidine is reported to be a non-addictive analgesic[5] in mice which is not antagonized by naloxone. It has anti-inflammatory properties,[6] exerts an inhibitory effect on the respiratory burst of leucocytes, and also scavenges oxygen free radicals.[7] It is likely that ipalbine from some sources is a mixture of β-D-glycosides of racemic ipalbidine.[8,9]

Ipalbidine is well known as a synthetic target for testing new synthetic methods and strategies. Our aim was to develop a method that would furnish the indolizidine core in optically pure form. Several groups have reported the total synthesis of racemic ipalbidine; however, only 5 groups have described[10,11,12,13,14] routes to optically active ipalbidine and of these, only two[12,13] measured the optical purity (96%[12] and 94%[13]) of the synthetic ipalbidine by HPLC. These syntheses of racemic and optically active ipalbidine will be described in the following sections, with the routes classified according to whether the product was racemic or optically active. In each section the work is treated chronologically.

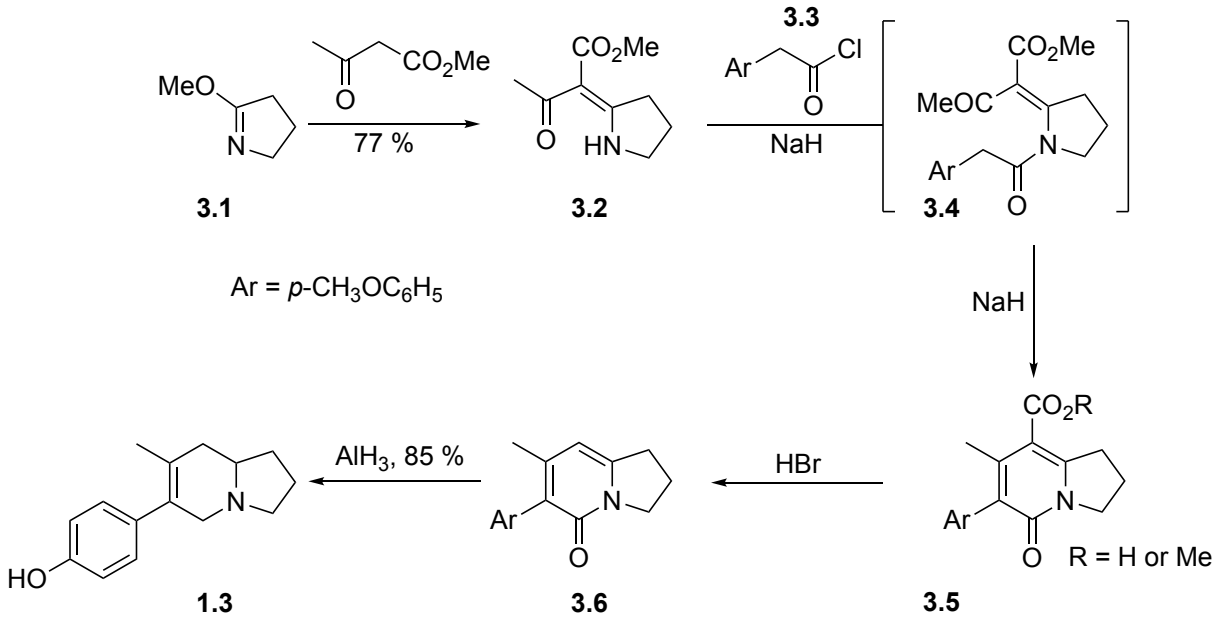
1.2.1 Total synthesis of racemic ipalbidine by Govindachari[15]



Scheme 2. Govindachari's total synthesis of racemic ipalbidine

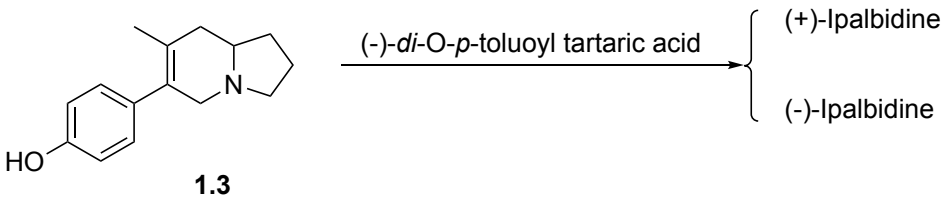
Govindachari[15] accomplished the first total synthesis of racemic ipalbidine. His approach started with 4-methoxyphenyl acetate which was treated with sodium and ethyl formate to provide the hydroxymethylene enol **2.1**. The aldehyde tautomer of this compound was reduced with sodium borohydride and treated with thionyl chloride to generate chloro compound **2.2**. The chlorine was replaced by the addition of the pyrrolidine derivative **2.3** to give the Dieckmann cyclization precursor **2.4**, which was cyclized by using potassium amide in liquid ammonia and decarboxylated to give the indolizidine **2.5**. The methyl group was installed by reaction with MeLi, and dehydration of the resulting tertiary alcohol was then carried out with sulfuric acid. Exposure to $AlBr_3$ removed the methyl group of the phenolic substituent, affording racemic ipalbidine **1.3**.

1.2.2 Total synthesis of racemic ipalbidine by Wick[8]



Scheme 3. Wick's total synthesis of racemic ipalbidine

In 1971, the Wick group described the total synthesis of racemic ipalbidine, and also obtained optically active ipalbidine by chemical resolution. 2-Methoxy-1-pyrroline (**3.1**) was used as a starting material and was reacted with methyl acetoacetate to generate enamine **3.2.** Reaction with acid chloride **3.6** in the presence of NaH provided **3.4** which was used *in situ* for the subsequent intramolecular condensation to form a 6-membered ring (**3.4**→**3.5**). This condensation was brought about by addition of a further equivalent of NaH. Decarboxylation with HBr, followed by demethylation with AlH_3, gave racemic ipalbidine **1.3**.

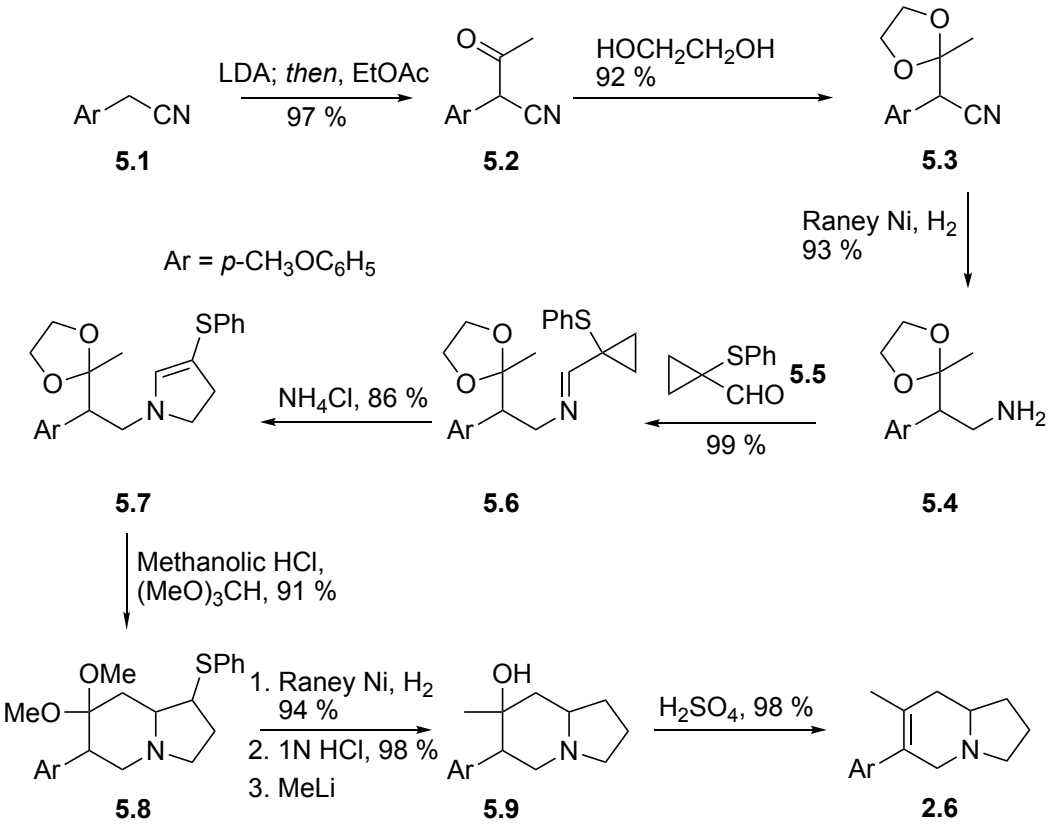


1.3

Scheme 4. Resolution of racemic ipalbidine with (-)-*di*-O-*p*-toluoyl tartaric acid

The resulting racemic ipalbidine was acetylated and resolved using (-)-di-*O*-*p*-toluoyl tartaric acid and and (+)-di-*O*-*p*-toluoyl tartaric acid. The optically pure bases were then released from individual diastereoisomers from. Crystallization of (–)-ipalbidine from a mixture of benzene and cyclohexane gave material that contained some of these solvents. Finally, solvent-free (–)-ipalbidine was obtained as a glass through bulb-to-bulb distillation under oil pump vacuum. The authors obtained the $[\alpha]^{25}_{D}$ values –237 (*c* 1, $CHCl_3$) and $[\alpha]^{25}_{D}$ –190.5 (*c* 1, MeOH) for (–)-ipalbidine.

1.2.3 Total synthesis of racemic ipalbidine by Stevens[16]

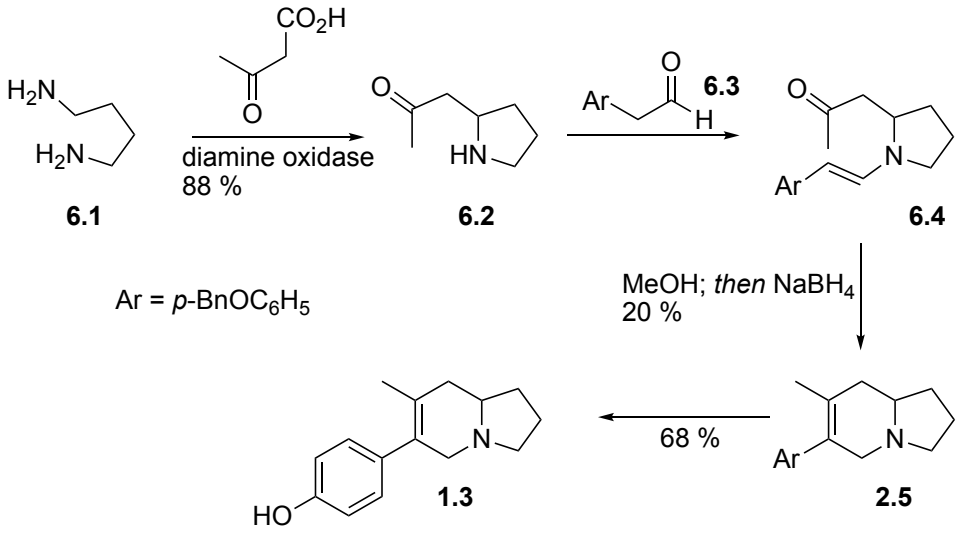


Scheme 5. Stevens's total synthesis of racemic ipalbidine

p-Methoxybenzyl cyanide (**5.1**) was reacted with ethyl acetate in the presence of LDA to give keto cyanide **5.2**. The carbonyl group was protected with ethylene glycol to obtain the ketal **5.3**, and then the nitrile was reduced by treatment with Raney Ni and hydrogen to give amine **5.4**. Condensation of the amine with cyclopropyl aldehyde **5.5** generated the imine **5.6**. Under acidic conditions rearrangement occurred to form the enamine intermediate **5.7**. The ketal was converted to the indolizidine core structure **5.8** by reaction with methanolic hydrogen chloride and trimethyl orthoformate. Raney Ni treatment removed the phenylthio substituent. The ketal group was removed to release the parent ketone which was then allowed to react with MeLi to furnish alcohol **5.9**. The olefin **2.6** was obtained on dehydration with sulfuric acid, and

demethylation of the phenolic substituent generated (±)-ipalbidine (**1.3**).

1.2.4 Total synthesis of racemic ipalbidine by Herbert[17,18]

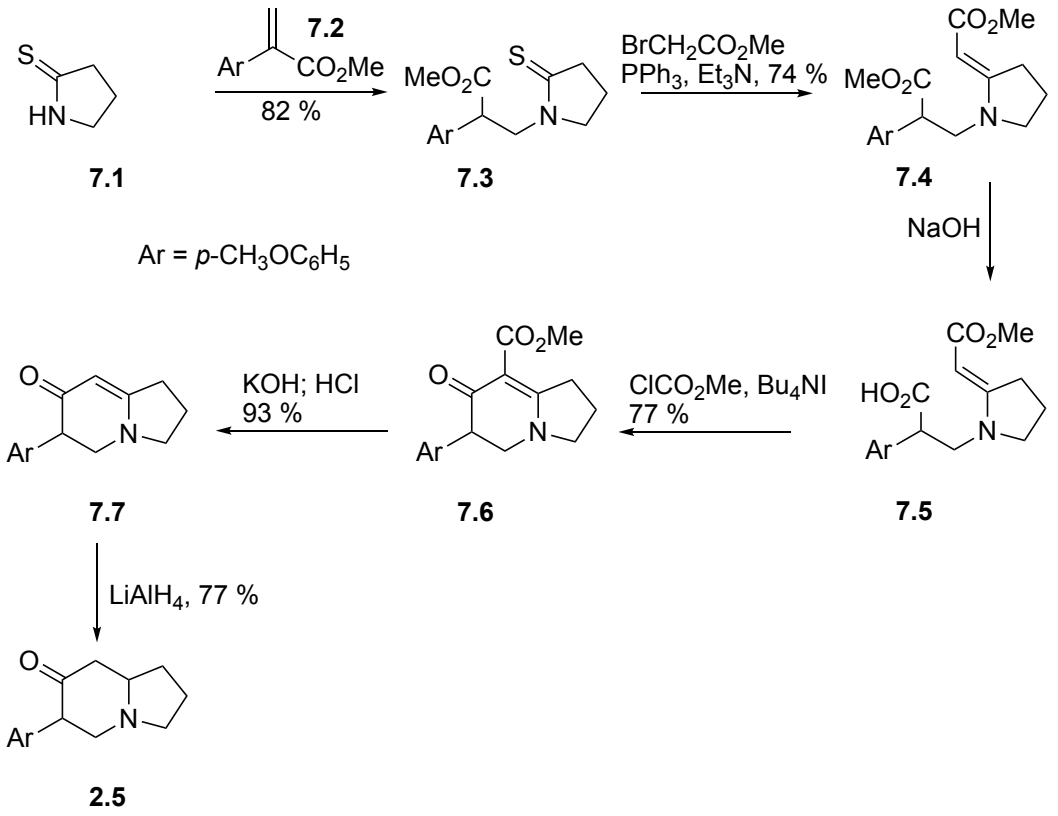


Scheme 6. Herbert's total synthesis of racemic ipalbidine

The Herbert group pursued a short and direct route to racemic ipalbidine based on cyclization of the enamine ketone **6.3** in MeOH as a key step.

Norhygine **6.2**, which was the starting material, was obtained by enzymatic oxidation of a mixture of **6.1** and acetoacetic acid. Compound **6.2** was reacted with aldehyde **6.3** to generate the enamine **6.4**. The subsequent cyclization occurred in MeOH and the intermediate imine was reduced by treatment with $NaBH_4$ to give *O*-benzyl ipalbidine (**2.5)**. Finally, debenzylation gave racemic ipalbidine (**1.3**).

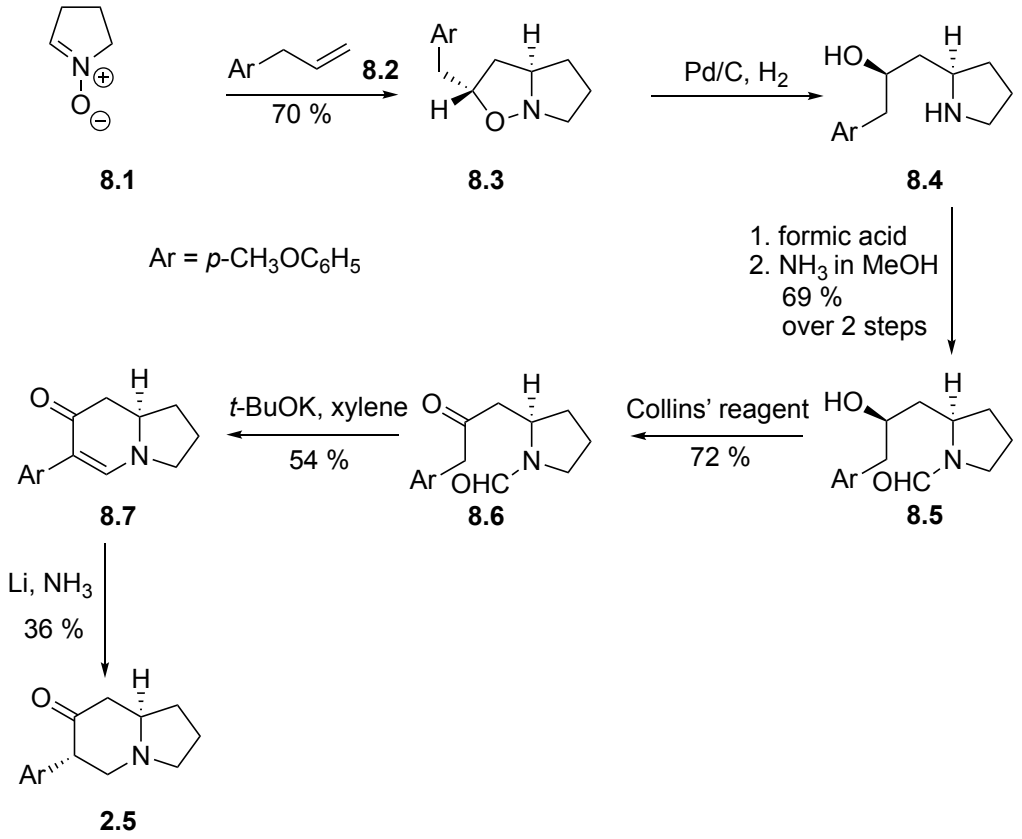
1.2.5 Formal synthesis of racemic ipalbidine by Howard[19]



Scheme 7. Howard's total synthesis of racemic ipalbidine

Howard's group employed the exocyclic vinylogous urethane **7.4** as a key intermediate to generate the bicyclic core structure. Thione **7.1** underwent a Michael addition to **7.2** give to thiolactam **7.3**. Then an Eschenmoser sulfide contraction was performed by reaction with methyl bromoacetate in the presence of triethylamine and triphenylphosphine to give **7.4**. The benzylic ester was hydrolyzed to carboxylic acid **7.5**. This acid was converted to a mixed anhydride and it underwent cyclization to the indolizidine core structure **7.6**. Hydrolysis of ester **7.6** was carried out with KOH, and decarboxylation then gave the conjugated ketone **7.7**. The olefin was removed by using $LiAlH_4$ to give the precursor (**2.5**) of ipalbidine, identical to material made by Govindachari[15] and converted into ipalbidine.

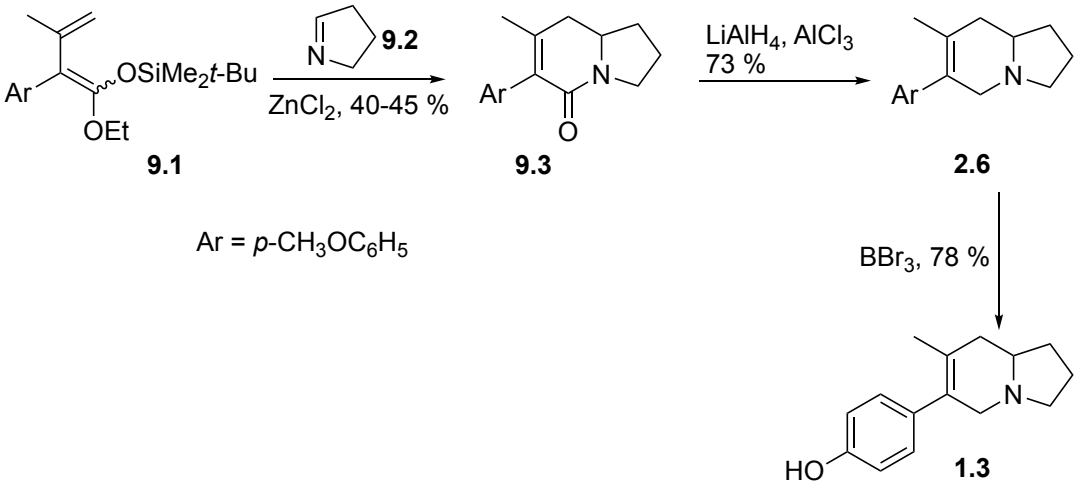
1.2.6 Formal synthesis of racemic ipalbidine by Kibayashi[20,21]



Scheme 8. Kibayashi's total synthesis of racemic ipalbidine

The Kibayashi group started with the nitrone **8.1** which underwent [3+2]-dipolar cycloaddition regioselectively and stereoselectively with the allyl aromatic **8.2** to give **8.3** as a single diastereomer. N-O bond cleavage on treatment with Pd/C gave amino alcohol **8.4**. The *N*-formyl alcohol **8.5** was then obtained by heating with formic acid and subsequently an aldol reaction performed under basic conditions led to **8.7**. The olefin was selectively reduced with lithium in liquid ammonia to provide a precursor compound (**2.5**) to ipalbidine. The precursor compound **2.5** has already been converted into racemic ipalbidine in two steps reported by the groups of Govindachari[15] and Stevens.[16]

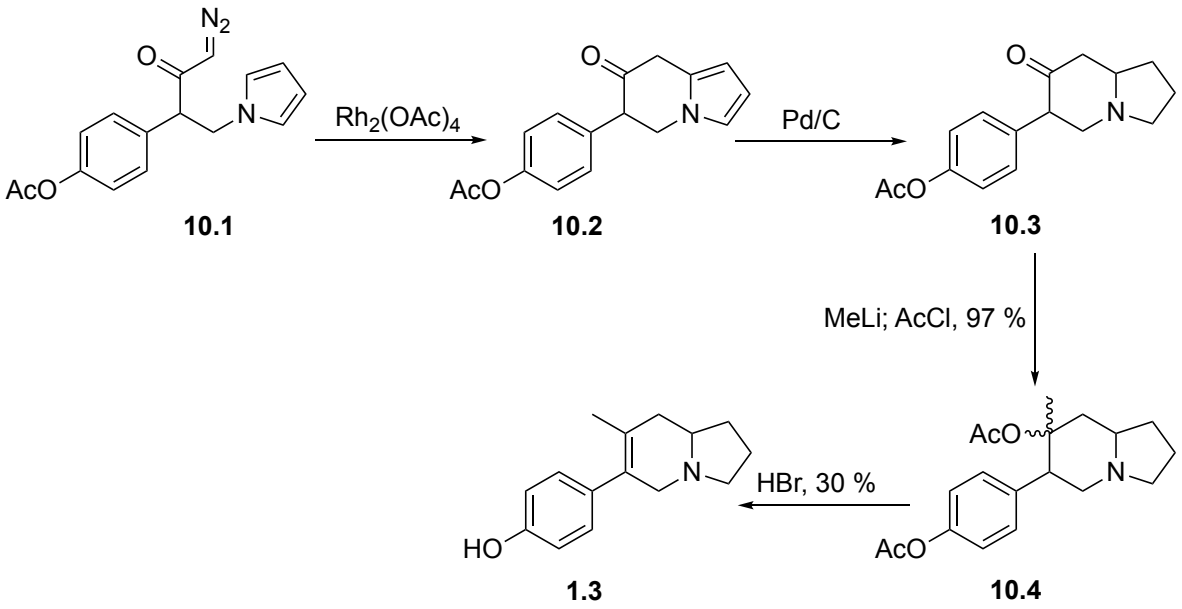
1.2.7 Total synthesis of racemic ipalbidine by Danishefsky[22]



Scheme 9. Danishefsky's total synthesis of racemic ipalbidine

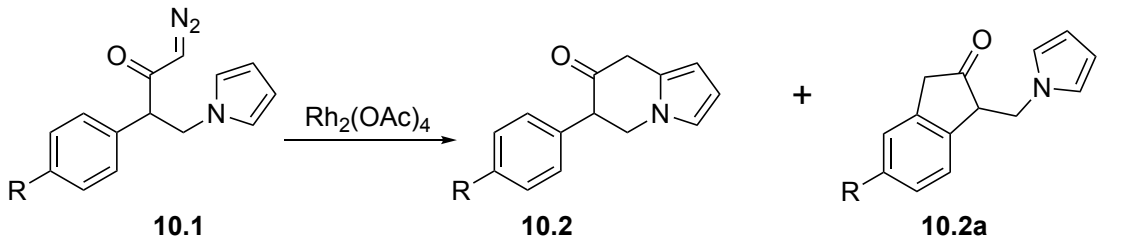
Danishefsky's group used a Lewis-acid catalyzed Diels-Alder reaction in a short route to racemic ipalbidine (**1.3**). Silylketene acetal **9.1** was reacted with aldimine **9.2** in the presence of $ZnCl_2$ to give the unsaturated lactam **8.2**. Reduction of the unsaturated lactam with $LiAlH_4$ and $AlCl_3$ and then demethylation by treatment with BBr_3 gave racemic ipalbidine. Although Danishefsky's method gave a low yield, it is a very convenient method.

1.2.8 Total synthesis of racemic ipalbidine by Jefford[23]



Scheme 10. Jefford's total synthesis of racemic ipalbidine

Jefford's group employed a diazoketone to generate the six-membered ring as a key step in the formation of the indolizidine core. Diazoketone **10.1** was treated with $Rh_2(OAc)_4$. This generated a carbenoid, which captured the pendant pyrrole ring to give the indolizidine core structure **10.2**. The authors found that a byproduct was formed by reaction of the carbenoid with the benzene ring. When the benzene ring carried an electron-donating group this undesired pathway was more prominent, but an electron-withdrawing group largely suppressed reaction with the benzene ring. Both an acetyl group and a nitro group are gave very largely the desired product. However, it was difficult to later replace the nitro group by a phenolic hydroxyl and so they used the acetyl group which gave a high yield in the carbenoid reaction and was easy to manipulate at a later stage.



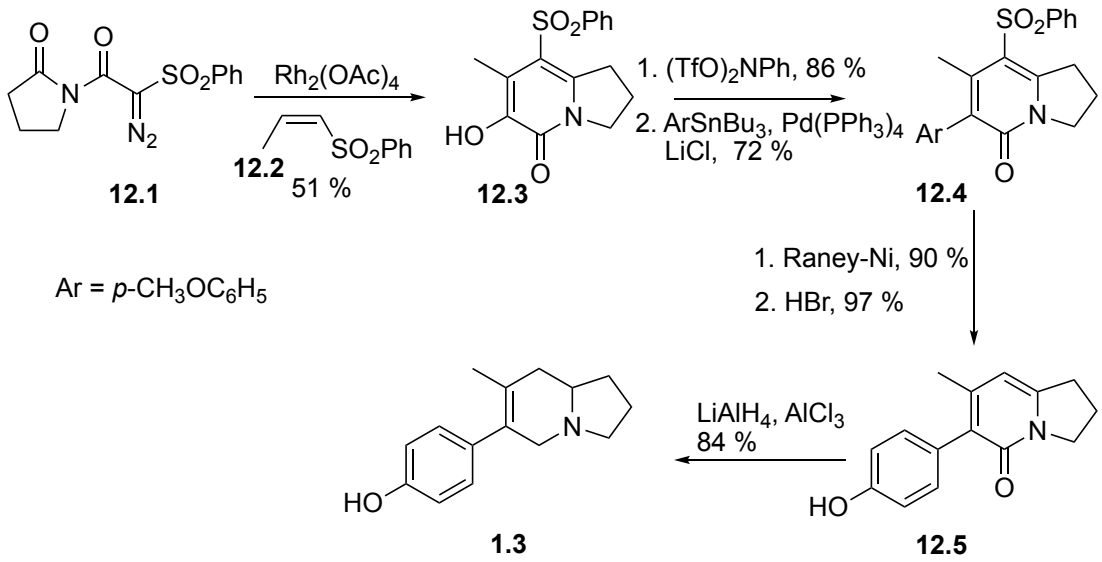
10.1 **10.2** **10.2a**

Substituent	*Ratio* (**10.2** : **10.2a**)	*Yield* **10.2** (**10.2a**) %
R = H	6 : 1	75 (51)
R = OMe	7 : 2	89
R = NO_2	>100 : 1	76 (76)
R = AcO	36 : 1	89 (82)
R = $PhCH_2O$	4 : 1	85

Scheme 11. Jefford's total synthesis of racemic ipalbidine

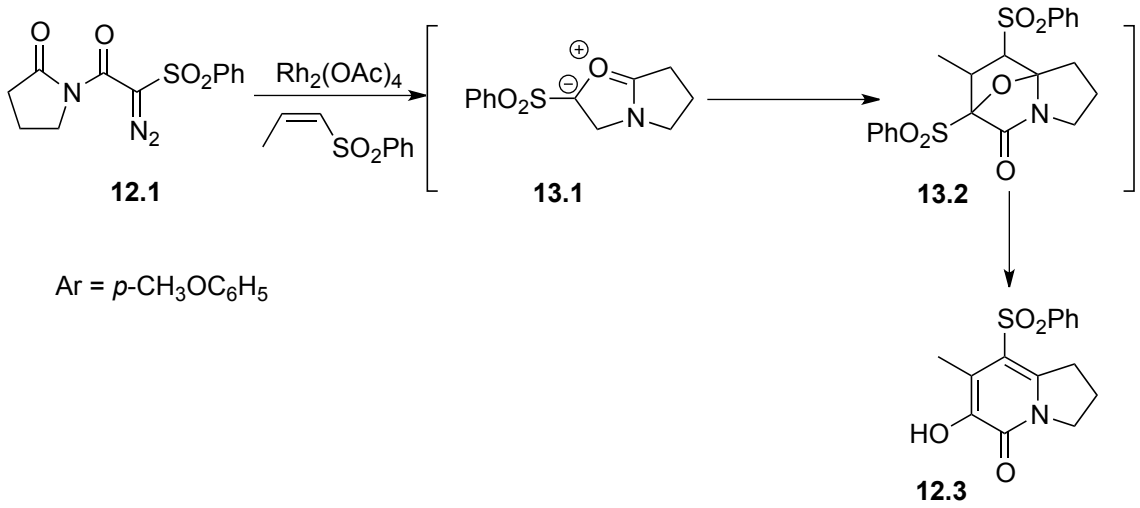
The double bonds of the pyrrole were selectively reduced on treatment with Pd/C and hydrogen to furnish indolizidine ketone **10.3**. MeLi was added to the ketone carbonyl and the resulting alcohol was trapped with acetyl chloride to provide **10.4**. The desired olefin was obtained on removal of the acetate group and deprotection of the phenolic oxygen, both being effected by treatment with hydrobromic acid, to give racemic ipalbidine.

1.2.9 Total synthesis of racemic ipalbidine by Padwa[24,25]



Scheme 12. Padwa's total synthesis of racemic ipalbidine

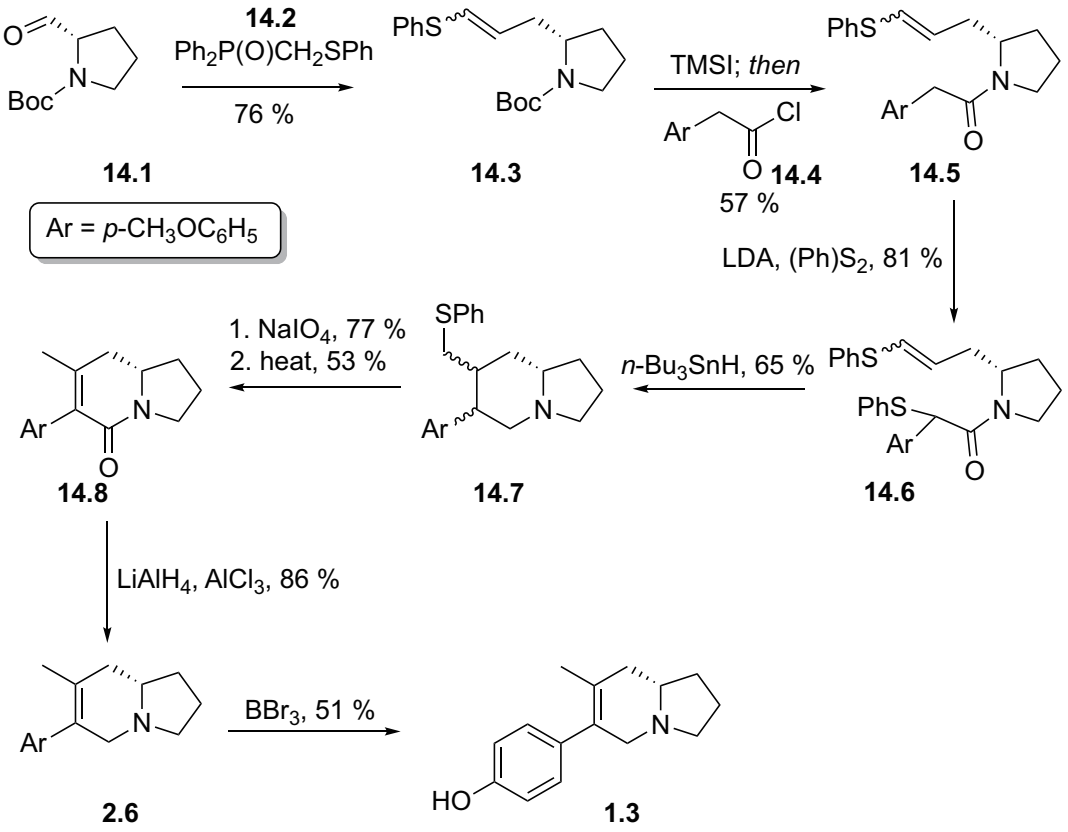
Padwa's group utilized a [3 + 2] cycloaddition as a key step. Diazoketone **12.1** was converted to the corresponding carbenoid with $Rh_2(OAc)_4$ and a [3 + 2] cycloaddition to vinyl sulfone **12.2** gave **12.3**. The mechanism for this transformation is shown in Scheme 13.



Scheme 13. Key step in Padwa's approach for the total synthesis of racemic ipalbidine

The intermediates **13.1** and **13.2** were not observed and **12.3** was obtained directly from the reaction. The hydroxyl of **12.3** was converted to a triflate, and then Stille coupling with $MeOC_6H_4SnBu_3$ and $Pd(PPh)_3$ provided **12.4**. The phenyl sulfone group was eliminated by using Raney-nickel and hydrogen, and demethylation occurred under acid conditions (**12.4**→**12.5**). Finally, the amide was reduced to an amine and one of the double bonds was selectively reduced on treatment with $LiAlH_4$ and $AlCl_3$ to give racemic ipalbidine.

1.2.10 Total synthesis of racemic ipalbidine by Ishibashi[26]



Scheme 14. Ishibashi's total synthesis of racemic ipalbidine

Ishibashi's group tried to obtain optically active ipalbidine by using material from the chiral pool and radical cyclization to generate the indolizidine core. They generated aldehyde

14.1 from L-proline as starting material.

A sulfur group was installed (**14.1**→**14.2**) by Wittig reaction with **14.2**. The Boc group was then removed and the free amine was acylated with acid chloride **14.4**. The resulting amide was then sulfenylated (**14.5**→**14.6**).

Radical cyclization occurred on treatment with tributyltin hydride and AIBN through a 6-*exo*-*trig* pathway to give the indolizidine core structure **14.7**. The sulfide was oxidized to the sulfoxide level on treatment with sodium periodate and heating of the sulfoxides generated the desired compound **14.8**. The amide group was reduced to an amine by using AlH_3, and demethylation with boron tribromide gave ipalbidine; unfortunately, the material was found to be racemic. The melting point of the product was similar to that of racemic ipalbidine. Ishibashi concluded that the stereochemistry was lost during the Wittig reaction. Although they did not get optically active ipalbidine, the attractive feature of their strategy is the fact that they started with material from the chiral pool.

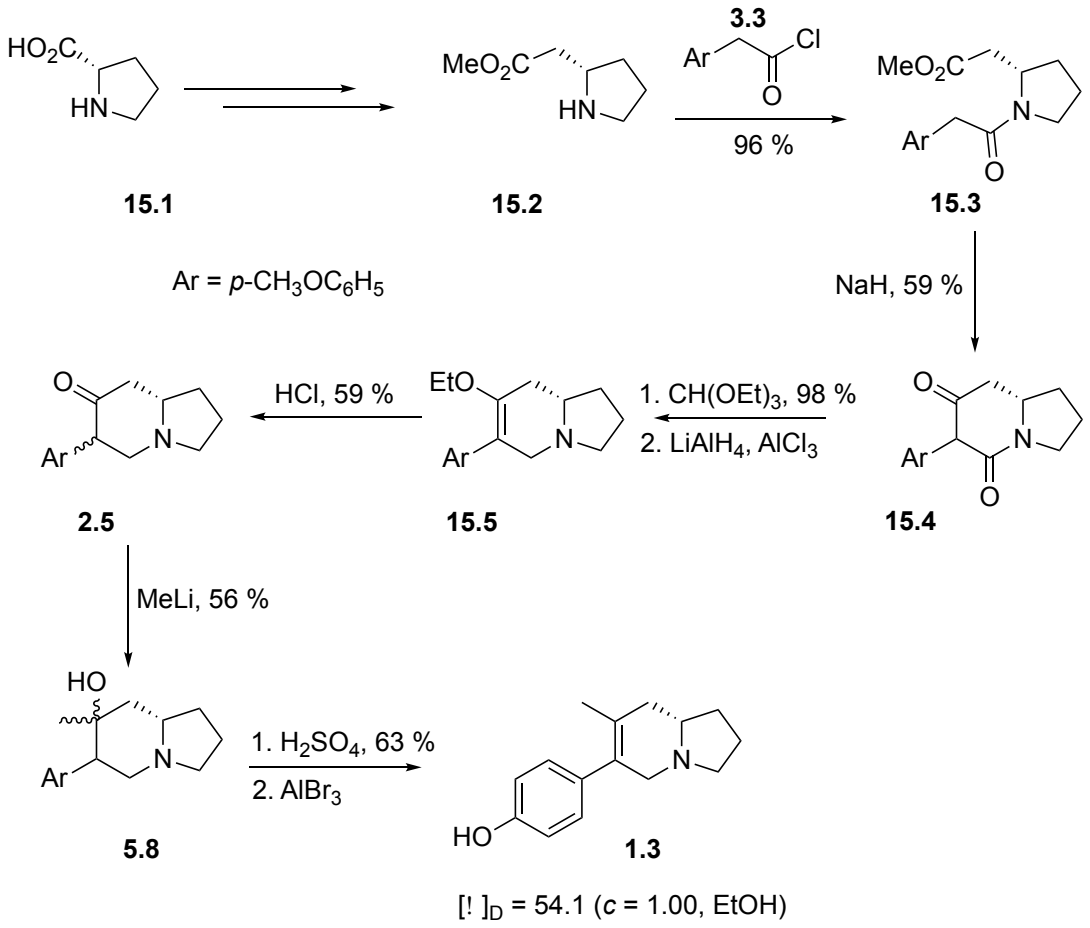
1.2.11 Conclusion: The total synthesis of racemic ipalbidine

Many different methods to generate the indolizidine core structure have been explored. Dieckmann cyclization, Diels-Alder reactions, [3 + 2]-dipolar cycloaddition and carbenoids have been used in key steps. The most promising method was from Ishibashi's group since a compound from the chiral pool was used. In subsequent work, this last method has been extended to achieve the total synthesis of optically active ipalbidine of high ee.

1.3 Total synthesis of optical active ipalbidine

Five groups have reported the total synthesis of optical active ipalbidine.

1.3.1 Total synthesis of optical active ipalbidine by Liu[10]

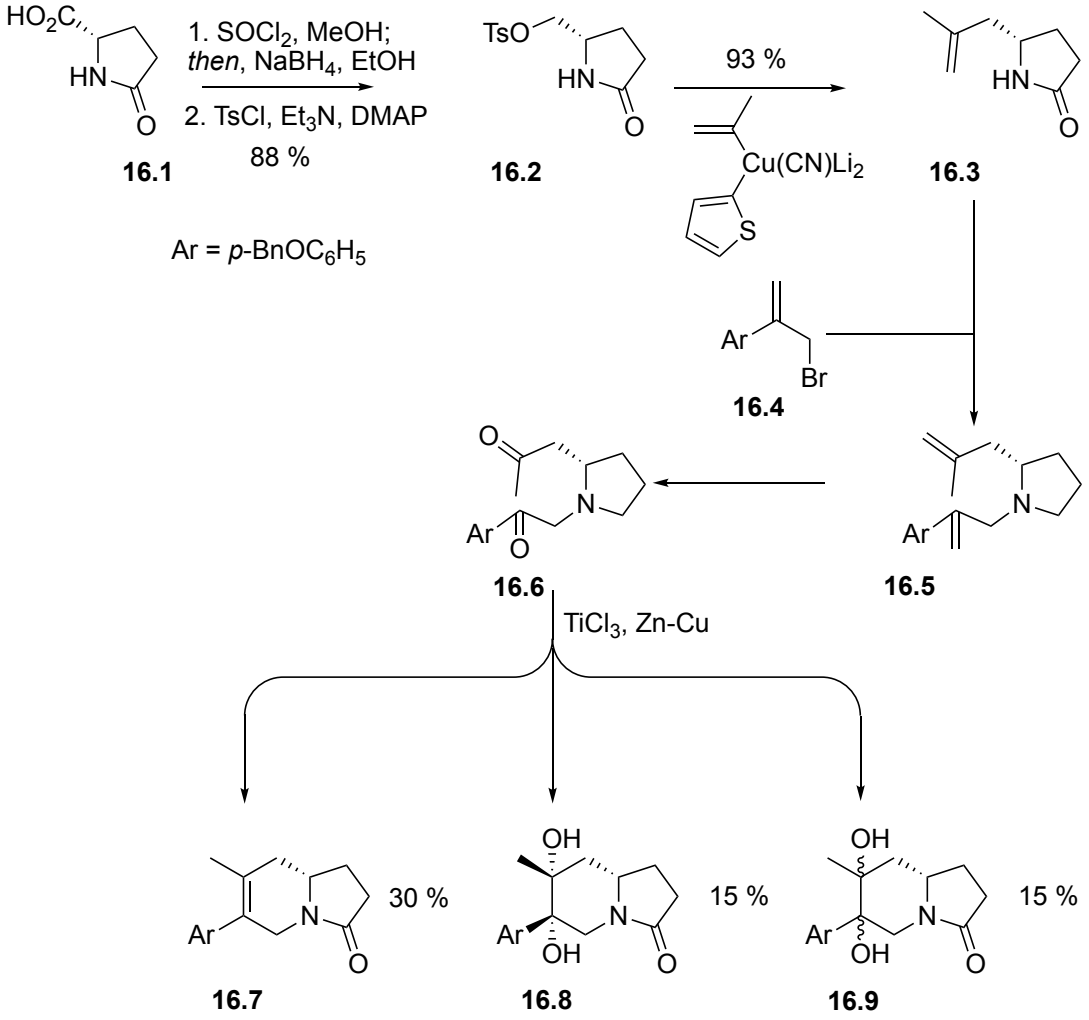


Scheme 15. Liu's total synthesis of optical active ipalbidine

Liu's group was the first to attempt the total synthesis of optical pure ipalbidine. L-Proline (**15.1**) was used as a starting material so as to set the stereogenic center. The carboxylic acid was converted to the homologated ester **15.2** and this was then acylated with **3.3** to generate **15.3**. Treatment with NaH effected cyclization to give the indolizidine core structure **15.4**. The ketone group was protected as an enol ether by reaction with triethyl orthoformate and the amide group was then reduced by using $LiAlH_4$ and $AlCl_3$ to yield **15.5**. The enol ether was hydrolyzed to ketone **2.5** under acidic conditions, and reaction with MeLi generated alcohols **5.8**. The olefin

was obtained on dehydration of the alcohols with acid, and demethylation by using $AlBr_3$ gave the desired optically active ipalbidine. The material had $[\alpha]_D$ +54.1 (*c* = 1.00, EtOH). Wick's group[8] reported $[\alpha]_D$ –90.5 (*c* = 1, MeOH) for the (–)-isomer and –237 (*c* = 1.00, $CHCl_3$). Consequently, racemization happened at some point under acidic or basic conditions.

1.3.2 Total synthesis of optical active ipalbidine by Honda[11]

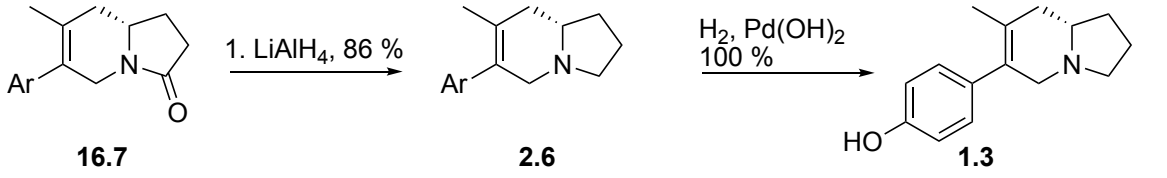


Scheme 16. Honda's approach to the total synthesis of optical active ipalbidine

Honda's group synthesized optical active ipalbidine by using a McMurry coupling as a

key step. They used L-pyroglutamic acid as the starting material. The carboxylic acid group was first converted to an ester and, subsequently, the ester group was reduced and the resulting alcohol was converted to tosylate **16.2**. The tosyloxy group was replaced by reaction with a freshly prepared propen-2-yl cuprate to generated **16.3**. The lactam was reacted with the aryl bromide **16.4** to give **16.5**. Attempts to perform ring closing metathesis with the Grubbs catalyst,[27] the Hoveyda catalyst[28] or the Schrock catalyst[29] all gave complex mixtures, and so the approach to produce the indolizidine structure was changed to one using McMurry coupling.

Diene **16.5** was converted to diketone **16.6**, the precursor compound for McMurry coupling, which was reacted with $TiCl_3$ and Zn-Cu to provide a mixture 3 major compounds.



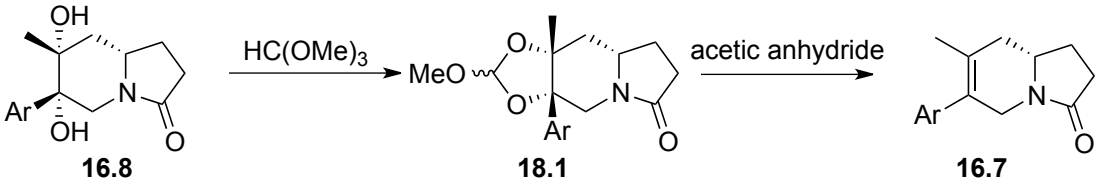
16.7 **2.6** **1.3**

Ar = *p*-$BnOC_6H_5$

$[\alpha]_D$ = 158.6 (*c* = 0.8, MeOH)
$[\alpha]_D$ = 189.4 (*c* = 1.0, $CHCl_3$)

Scheme 17. Honda's total synthesis of optical active ipalbidine

The carbonyl of the major compound was reduced with $LiAlH_4$ (Scheme 17) and the benzyl group was removed by hydrogenation over Pearlman's catalyst to give optical active ipalbidine.



16.8 **18.1** **16.7**

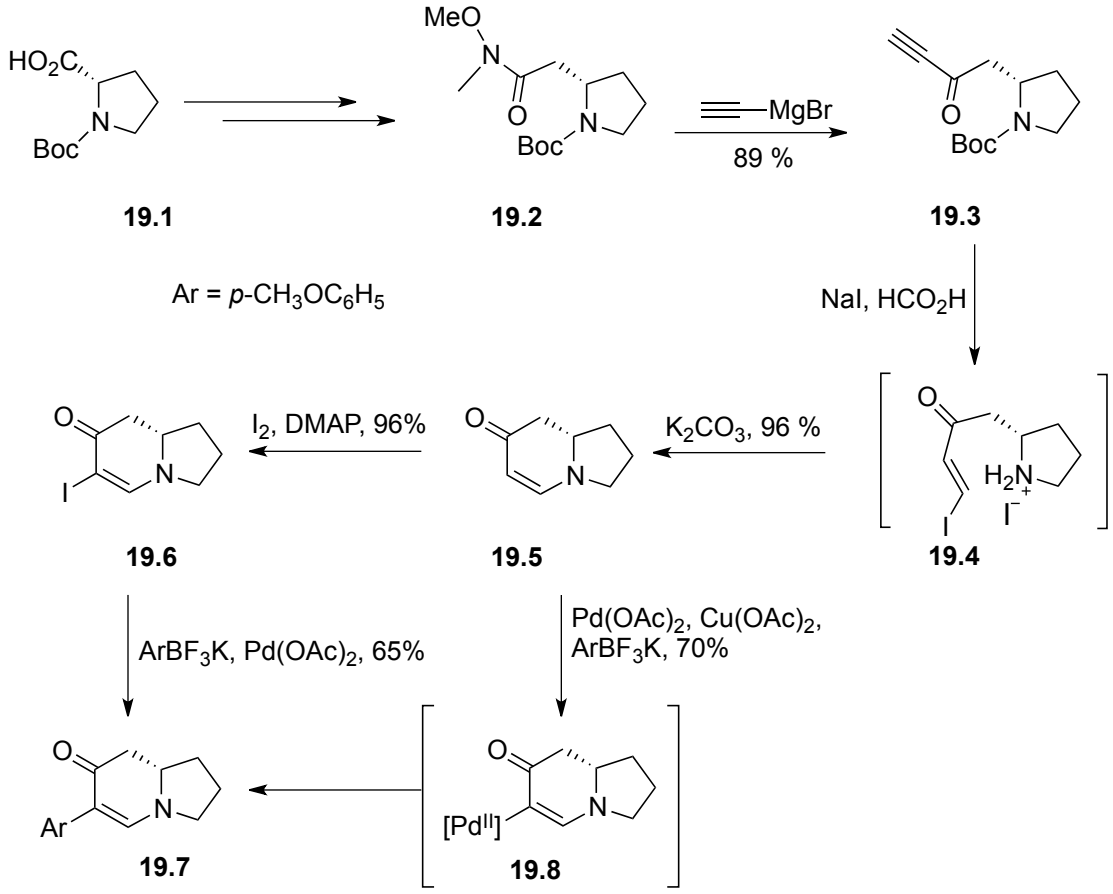
Ar = *p*-$BnOC_6H_5$

Scheme 18. Honda's total synthesis of optical active ipalbidine

The yield in the McMurry coupling was unsatisfactory and so the reaction was repeated but for a shorter time to get the diol **16.8** in 66% yield. The diol was protected by reaction with triethyl orthoformate to produce orthoesters **18.1**, and, on heating with acetic anhydride compound **16.7** was formed.

Honda group also measured the $[\alpha]_D$ value which was +158.6 (*c* = 0.8, MeOH) and +189.4 (*c* = 1.00, $CHCl_3$) in chloroform. These values do not match the values obtained by Wick[8] If the material was pure (the difficulty of removing[8] solvent must be kept in mind) racemization must have occurred, most likely at the stage of **16.6**—a β-amino ketone that could undergo a retro-Michael/Michael sequence.

1.3.3 Total synthesis of optically active ipalbidine by Georg[12]

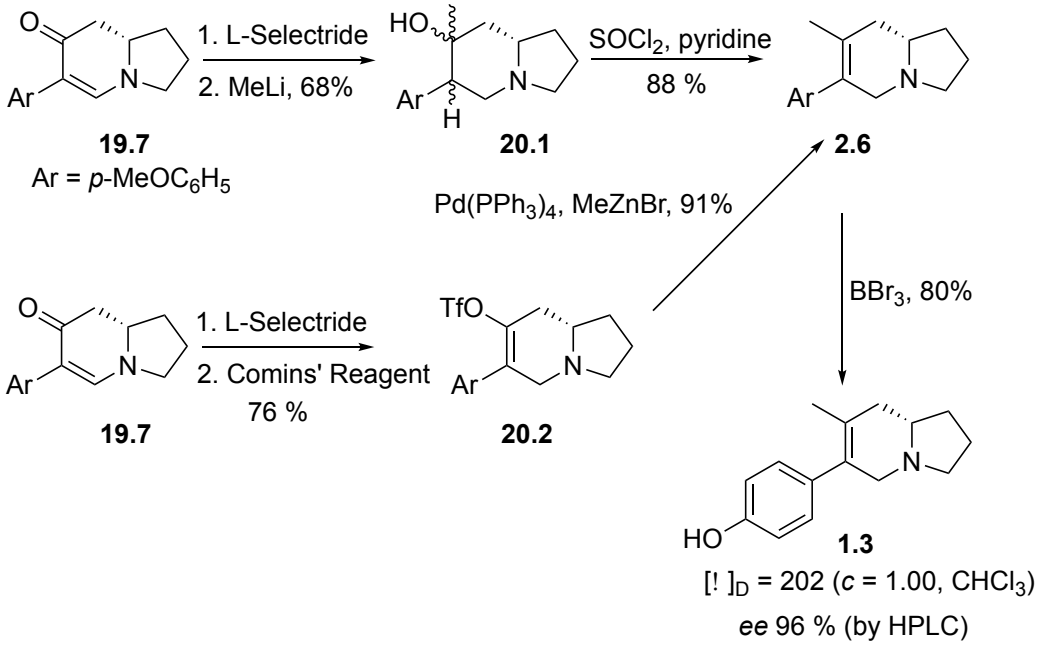


Scheme 19. Georg's total synthesis of optical active ipalbidine, initial steps

Georg's group has reported the total synthesis of optically active ipalbidine based on cross coupling and C-H activation with palladium and copper catalysts.[30]

N-Boc-L-proline **19.1** was converted to the homologated Weinreb amide **19.2** by using a Wolff rearrangement. Reaction with ethynylmagnesium bromide gave the desired ynone **19.3**. Treatment with formic acid removed the Boc group and addition of NaI/HCO_2H formed the vinyl intermediate **19.4**. The intermediate was treated with K_2CO_3 to generate the indolizidine core structure **19.5**. The aryl group was installed by using cross coupling. First of all, iodine was added at the α position of the enaminone in the presence of DMAP and molecular iodine to

give **19.6**. Subsequently, the aryl group was installed by using a Suzuki cross coupling to obtain **19.7**. However, during the course of the work, a shorter and more direct route to add the aryl unit was examined: C-H activation of **19.5** with $Pd(OAc)_2$ and $Cu(OAc)_2$ as the oxidant gave **19.7** in a better yield.

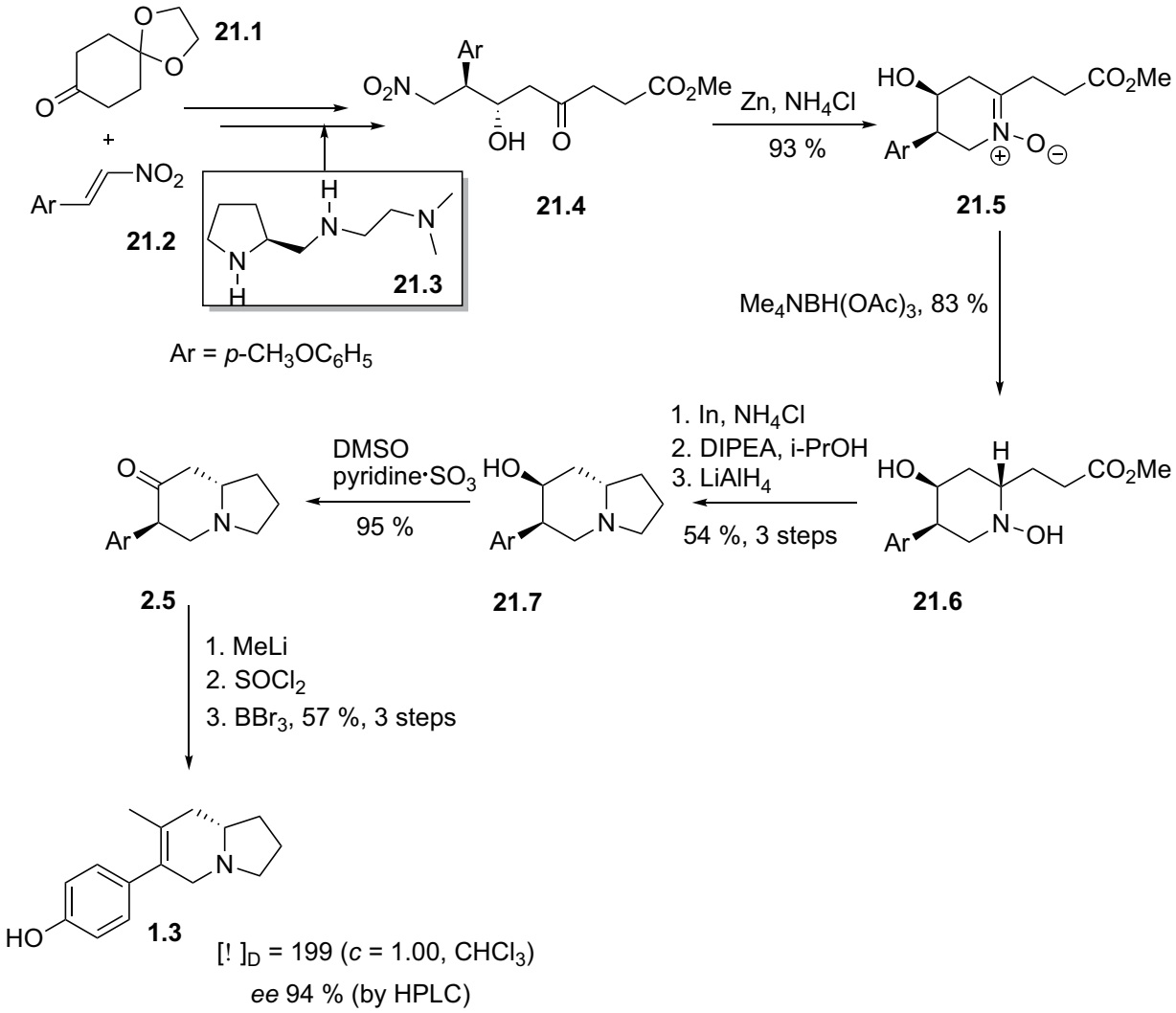


Scheme 20. Georg's total synthesis of optical active ipalbidine, final steps

With the aryl indolizidine in hand, the Georg group first reduced the double bond with L-Selectride and then the ketone was reacted with MeLi to give **20.1**. The olefin was then obtained on treatment of the tertiary alcohol with $SOCl_2$ and pyridine to generate *O*-methyl ipalbidine (**2.6**). In spite of the success of this route, the George group attempted to improve on it by using a cross coupling reaction. After L-Selectride reduction, the resulting enolate was trapped with Commins's reagent to provide triflate **20.2** which was a good substrate for the cross coupling. The triflate underwent cross coupling with MeZnBr to give **2.6**. Finally, demethylation was performed with BBr_3 to yield optically active ipalbidine. The compound had $[\alpha]_D$ +202 (*c* =

1.00, $CHCl_3$), which was numerically close to the literature value[8] of –233 (c = 1.00, $CHCl_3$) for the enantiomer. Chiral HPLC established that the enantiomeric excess was 96%. Consequently, there was only a small loss of stereochemical integrity from the starting proline.

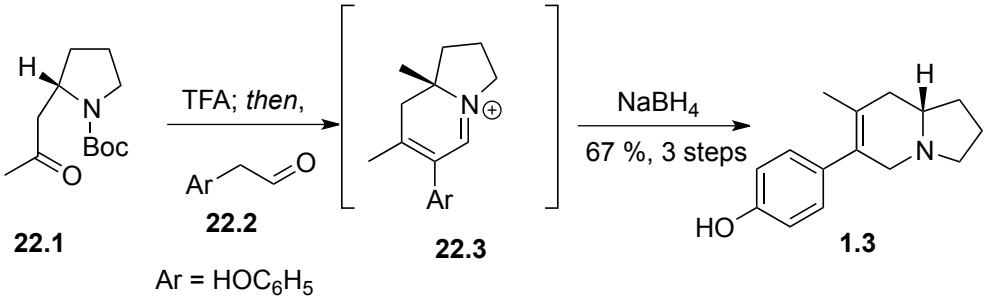
1.3.4 Total synthesis of optical active ipalbidine by Pansare[13]



Scheme 21. Pansare's total synthesis of optical active ipalbidine

Pansare's group published the total synthesis of optical active ipalbidine based on an organocatalytic Michael reaction. Ketal **21.1** and nitrostyrene **21.2** was reacted in the presence of organocatalyst **21.3** and gave the desire intermediate **21.4** with 92% *ee*. The nitro group was partially reduced with zinc to nitrone **21.5** which was stereoselectively reduced with tetramethylammonium triacetoxyborohydride to generate the secondary alcohol **21.6**. The reaction was stereoselective because of the directing effect of hydroxyl in **21.5**. Compound **21.6** was then reacted successively with indium (for N–O cleavage), DIPEA (for lactonization) and $LiAlH_4$ (for amide reduction) to give the hydroxy indolizidine **21.7**. The alcohol was oxidized by using the Parikh–Doering method to generate the advanced intermediate **2.5** for the synthesis of ipalbidine. Installation of the methyl group, dehydration with $SOCl_2$ and demethylation with the Lewis acid BBr_3 yielded optical active ipalbidine. The material had $[\alpha]_D$ +199 (*c* = 1.00, $CHCl_3$), which was a little different from the literature value[8] of –233 (*c* = 1.00, $CHCl_3$) for the enantiomer. Analysis by chiral HPLC showed that the enantiomeric excess was 94%.

1.3.5 Total synthesis of optical active ipalbidine by Hanessian[14]



Scheme 22. Hanessian's total synthesis of optical active ipalbidine

Recently, Hanessian's group reported the synthesis of ipalbidine by using an iminium ion-enamine cascade cyclization as a key step. They were able to develop the shortest route to

ipalbidine. The *N*-Boc ketone **20.1**, derived from L-proline, was treated with TFA to generate the free amine and directly reacted with aldehyde **22.2** to give the intermediate **20.2**. This iminium salt was reduced with $NaBH_4$ to provide ipalbidine. The route is very short and the synthetic ipalbidine had $[\alpha]_D$ +213.1 (*c* = 1.00, $CHCl_3$).

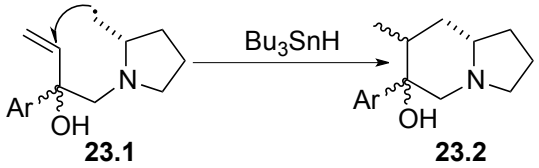
1.3.6 Conclusion: Total synthesis of optical active ipalbidine

Several group have accomplished the synthesis of optically active ipalbidine. All these groups used a starting material from the chiral pool, except for Pansare *et al*. In every case there appeared to be some loss of optical purity. Our aim was to synthesize the compound without compromising the enantiomeric purity of the starting material and this was achieved.

2.1 Results and Discussion

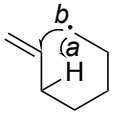
Our aim was to accomplish the total synthesis of optical pure ipalbidine based on 6-*exo-trig* radical cyclization as a key step to generate the desired indolizidine core (Scheme 23). We started from the chiral pool using L-proline and obtained ipalbidine with an ee of >99.6%.[31]

6-*Exo-trig* radical cyclization has not often been used while 5-*exo-trig* radical cyclization in common in total synthesis. One of the main reasons for this is that generally allylic hydrogen abstraction (Scheme 24, path *a*) competes[32] with ring closure (path *b*) and is faster than ring



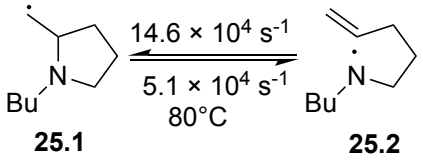
Scheme 23. Planned key radical pathway

closure. If the substituent on the distal end of the double bond is an electron-withdrawing or radical-stabilizing group,[33] the ring closure becomes faster than allylic hydrogen abstraction. However, in our case, allylic hydrogen abstraction cannot occur because there are no allylic hydrogens. Also, the geminal substitution (Thorpe-Ingold effect[34]) is expected to make radical cyclization easy in **23.1** and the ring closure may also be helped by the presence of the heteroatom[35] in the chain undergoing closure.



Scheme 24. Possible radical cyclization pathways

In our planned approach a β-amino radical is formed. It is known that radicals of type **23.1** can undergo ring opening (Scheme 23).[36,37] For radical **25.1** the rate constant at 80 °C for ring opening has been reported to be 5.1×10^4 s^{-1}, while for cyclization of the resulting aminyl radical **25.2** the rate constant is 14.6×10^4 s^{-1}. These rates were determined by Newcomb's radical reporter method.[36] If our planned cyclization is to work it would have to be faster than 5.1×10^4 s^{-1}.



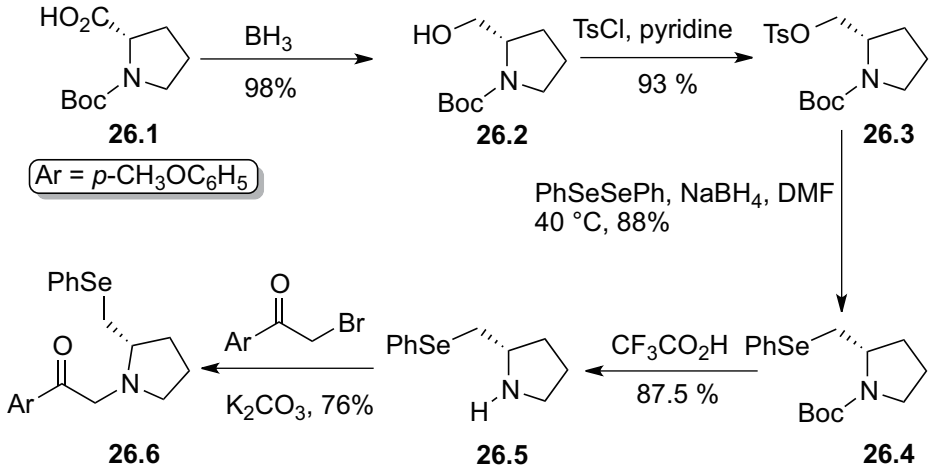
Scheme 25. Rates of cyclization and closure

While cyclizations of β-amino radicals have been reported,[35,38] we could not find any previous examples that the reversible ring opening would be possible to lose the optical purity of the starting materials. However, we could find references to cyclization of radicals β to nitrogen to generate optically active products using substrates in which the nitrogen is part of a *lactam*.[39,40] Our intended approach would benefit, as stated above, from the Thorpe-Ingold effect by virtue of the geminal substitution in the chain undergoing cyclization.

Our strategy for synthesizing ipalbidine without any loss of optical purity would utilize 6-*exo-trig* radical cyclization under conditions of low stannane concentration, so as to avoid premature reduction of the radical.

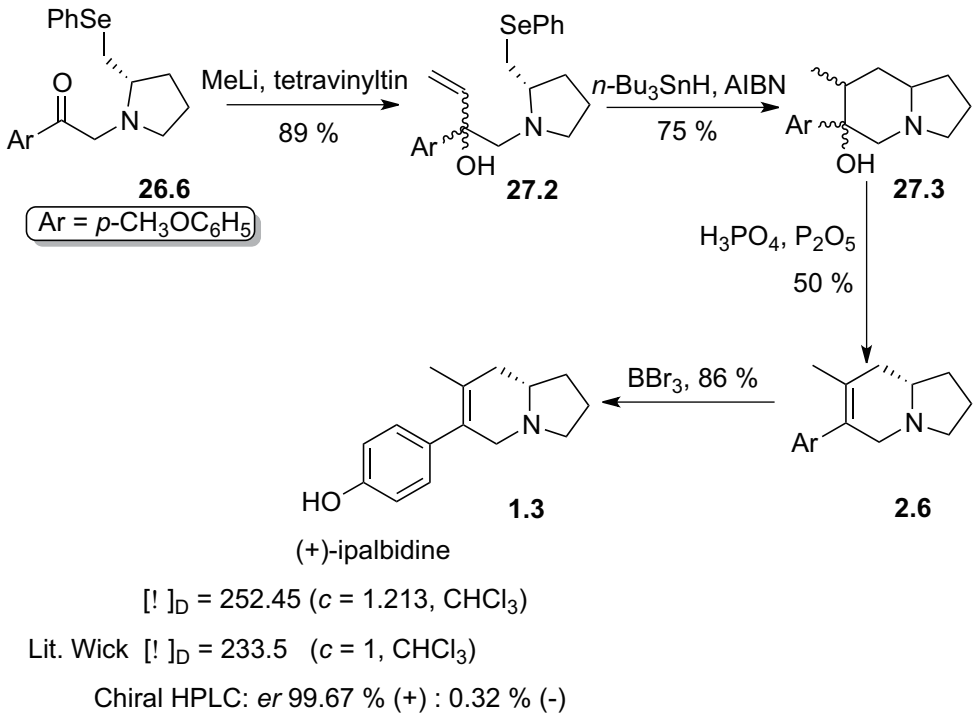
Commercially available *N*-Boc-proline (**26.1**) was used as a starting material, which is derived from the chiral pool. The carboxylic acid was reduced with $BH_3.SMe_2$[41] to give alcohol **26.2**. This was then converted to tosylate **26.3** by reaction with tosyl chloride in the presence of

pyridine.[41] The tosylate was reacted with phenyl selenide which was generated *in situ* from PhSeSePh and $NaBH_4$ in DMF to give the selenide **26.4**[42] in high yield. The Boc group was then removed upon treatment with TFA and the resulting free amine[43] was alkylated with 4-methoxyphenacyl bromide in the presence of K_2CO_3, the phenacyl bromide itself being made by a reported procedure.[44]



Scheme 26. Formation of keto selenide **26.7**

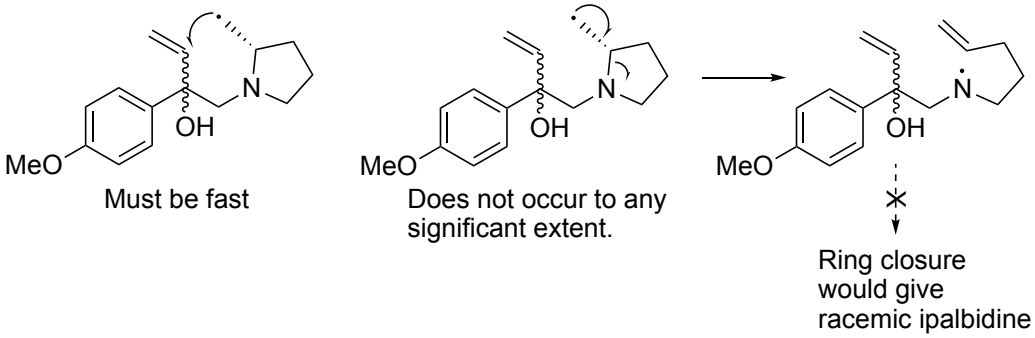
The next step was that ketone **26.7** was converted into the vinyl alcohols **27.2**. Vinylmagnesium bromide gave a poor yield but freshly-prepared vinyllithium generated *in situ* from tetravinyltin and MeLi[45] gave a high yield (89%). This step gave a 1:1 mixture of diastereoisomeric alcohols **27.2**.



Scheme 27. Final steps in ipalbidine synthesis

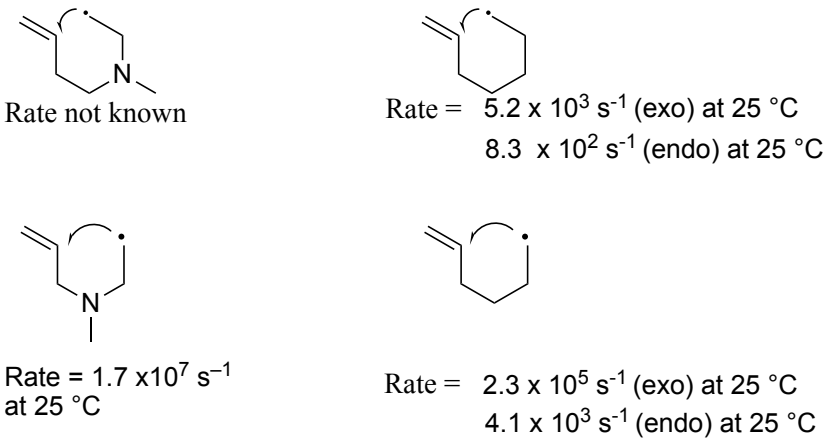
Radical cyclization was achieved by adding a toluene solution of Bu_3SnH and AIBN to a refluxing solution (PhMe) of **27.2** over several hours to afford the desired indolizidine core **27.3** as a mixture of stereoisomers. One of the isomers could be isolated by preparative layer chromatography over silica gel, using a 1:4 mixture of isopropanol and dichloromethane. The double bond was obtained on dehydration of the mixture of alcohol diastereomers by heating with a mixture of P_2O_5 and H_3PO_4[46] to produce *O*-methyl ipalbidine (**2.6**). Finally, demethylation with a Lewis acid at –78 °C to room temperature provided optical pure ipalbidine (**1.3**) and a bulb to bulb distillation to remove solvent gave material with $[\alpha]^{20}_{D}$ +252.45 (*c* = 1.213, $CHCl_3$). HPLC analysis showed that the compound had an *ee* of 99.3%. The starting amino acid had an *ee* of ≥99%.

Our results show that ring closure must be much faster than opening of the intermediate β-amino radical, if indeed any such opening takes place (Scheme 28). This accounts for the fact that the optical purity of the starting material was not lost during radical cyclization. Clearly, in suitable cases, β-amino radicals can be employed to obtain compounds with high *ee*, starting from material in the chiral pool. It should be born in mind, though, that our example probably benefits from the Thorpe-Ingold effect[34] and from the presence of a heteroatom in the ring being formed.



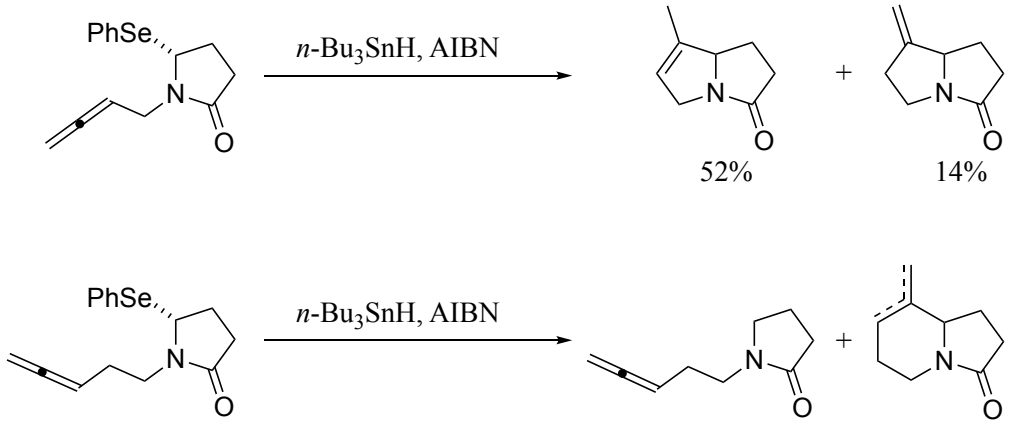
Scheme 28. Possible radical pathways

Our finding is remarkable because a 6-*exo*-*trigonal* radical closure is significantly slower than a 5-*exo*-*trig* closure (at 25 °C a 0.023-fold reduction in the case of hexenyl radicals[47]) and is rarely utilized; in contrast, 5-*exo*-*trig* cyclization is a very common process. The rate of ring closure of 3-azahex-6-enyl radicals has not been reported and so we cannot make a comparison with the rate of the related 5-exo closure,[35] as can be done in the all-carbon system.



Scheme 29. Rates of radical cyclization

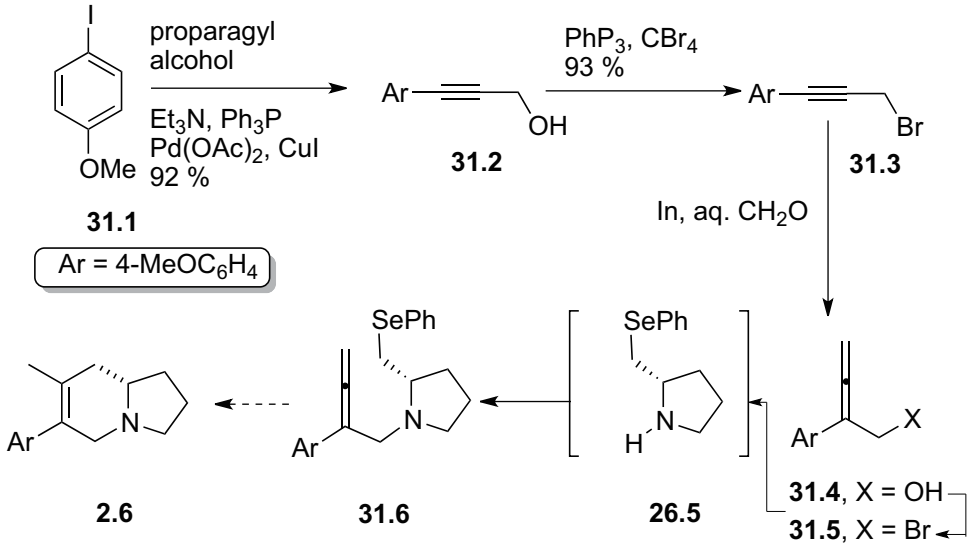
During this work, we attempted to pursue a shorter and more direct route by using radical cyclization onto an allene.[48] There are several examples of radical cyclization reported with allenes, as shown in Scheme 30.[48]



Scheme 30. Known examples of radical cyclization onto an allene

The required allenyl bromide **31.5** for our experiments was prepared by literature procedures reported for analogous compounds.[49,50] The propargyl alcohol **31.2** was made from **31.1** by Sonogashira cross coupling with $Pd(OAc)_2$ and CuI and the hydroxyl was converted into

a bromide (**31.2**→**31.3**). Subsequent treatment with indium and formalin gave allene alcohol **31.4**. This was reacted with Ph_3P and CBr_4 to give the desired allene bromide **31.5**. The allene bromide was used to alkylate **26.5** to provide a high yield of **31.6**. However, the radical cyclization did not occur using tributyltin hydride in either benzene or toluene. In all cases attempted radical ring closure using Bu_3SnH yielded complex mixtures. This was surprising as several examples of ring closures of alkyl radicals onto allenes have been reported,[48] and we do not know the reason for the lack of closure in our case.

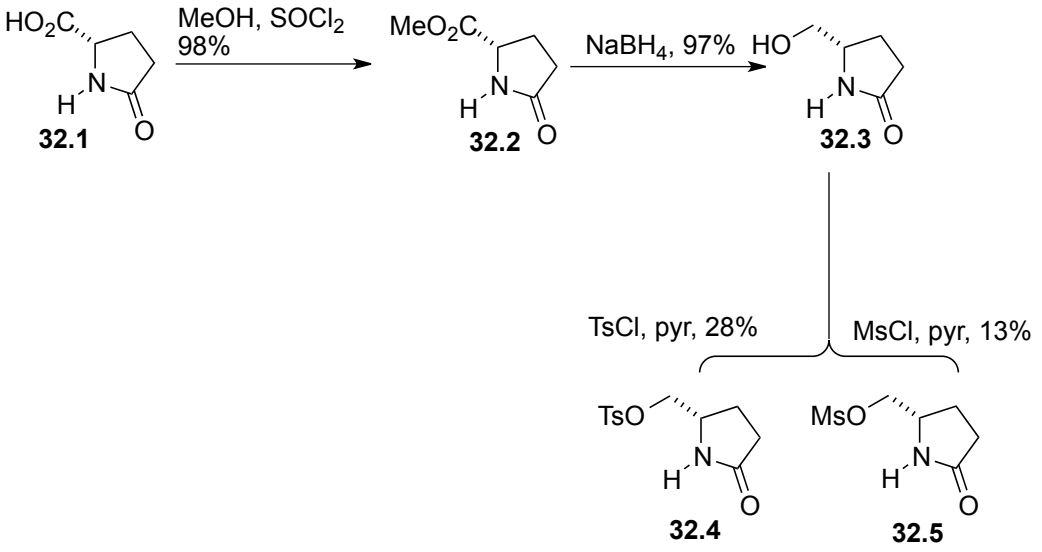


Scheme 31. Attempted route via an allene

We also attempted to develop another short route. To this end L-pyroglutamic acid **32.1** was esterified by treatment with $SOCl_2$ in MeOH to give ester **32.2** and the ester group was reduced with sodium borohydride to generate the alcohol **32.3**.[51]

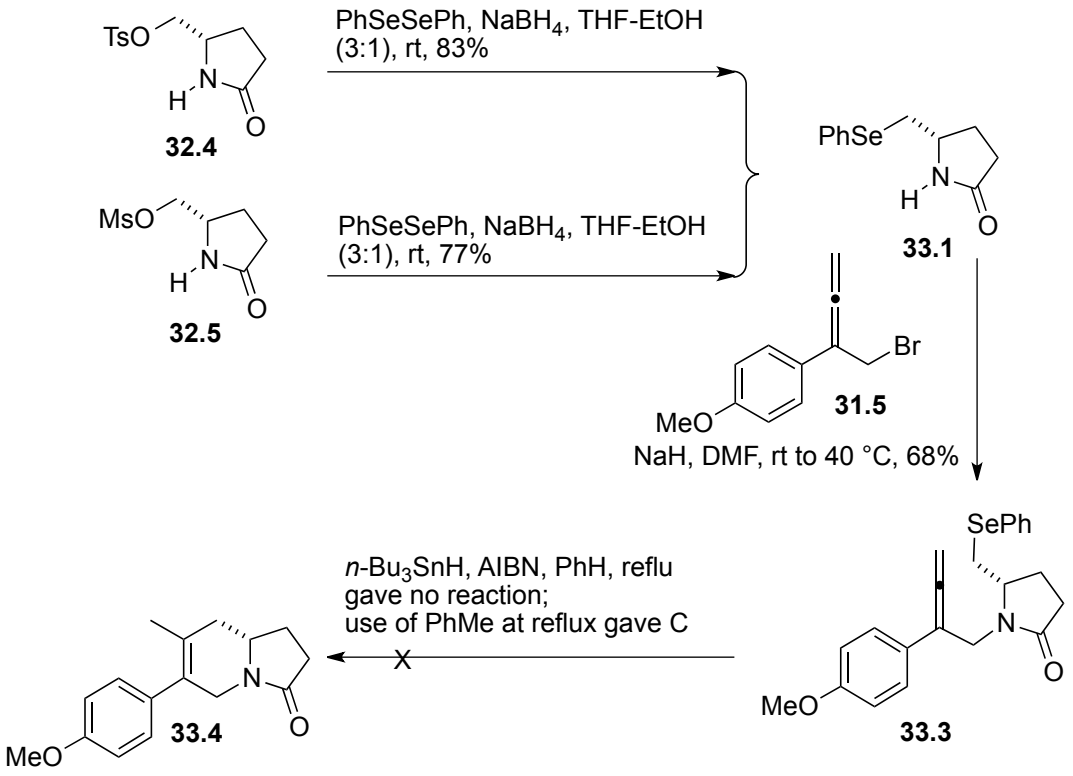
The hydroxy group of **32.3** was tosylated (**32.1**→**32.4**) on treatment with tosyl chloride and pyridine.[52] However, the reaction gave a low yield, so we attempted to use mesyl chloride, which is more reactive than tosyl chloride. Unfortunately, mesylation to form **31.5** also gave a

low yield (13%).[52]



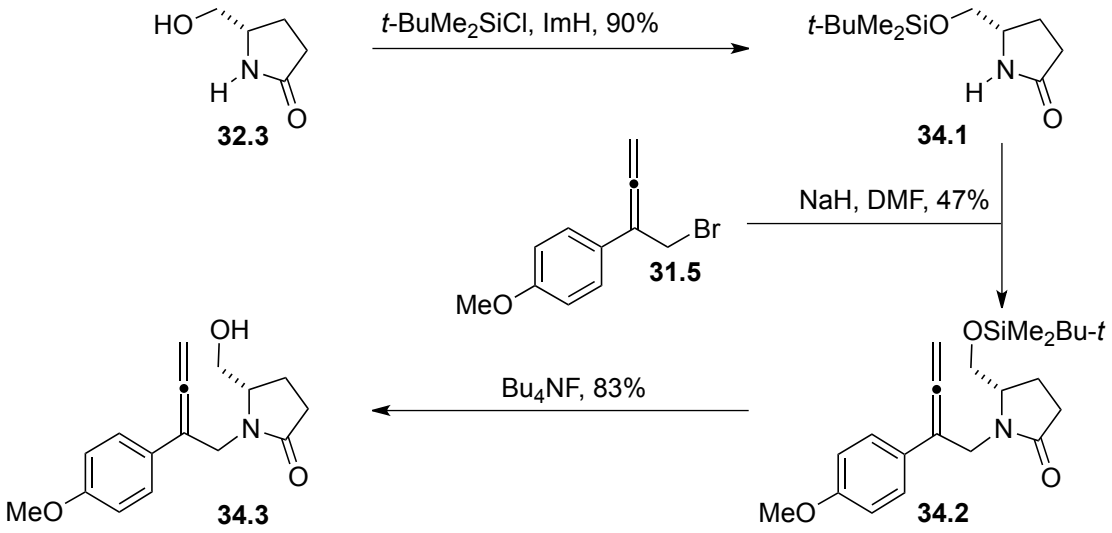
Scheme 32. Formation of **32.4** and **32.5**

The tosylate and mesylate were reacted individually with phenyl selenide anion generated *in situ* from PhSeSePh and $NaBH_4$ in THF-EtOH to give the selenide **33.1** in high yield.[52] The allene bromide **31.5** was used to alkylate **33.1** to provide a high yield of **33.3**. However, the radical cyclization did not take place, either in refluxing benzene or toluene. There was no reaction with tributyltin hydride in refluxing benzene, but a complex mixture was formed at the higher temperature of refluxing toluene.



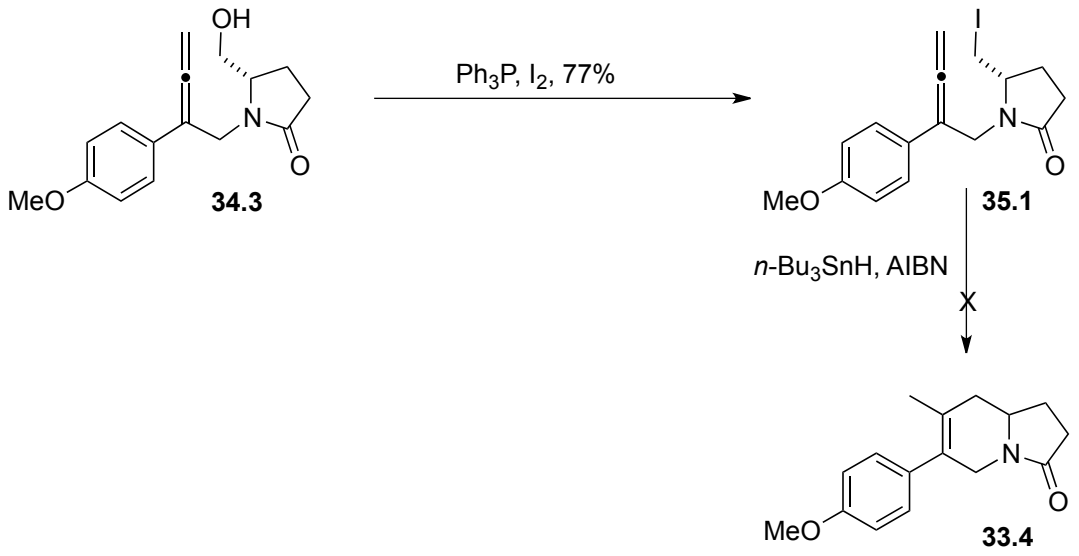
Scheme 33. Attempted allene-lactam route

Secondly, we tried to use an iodide instead of a phenyl selenide. The alcohol **32.3** was protected by treatment with *t*-butyldimethylsilyl chloride in the presence of imidazole to give silyl ether **34.1**[53] which was alkylated with bromide **31.5**. Subsequently, deprotection with Bu_4NF generated alcohol **34.3**.



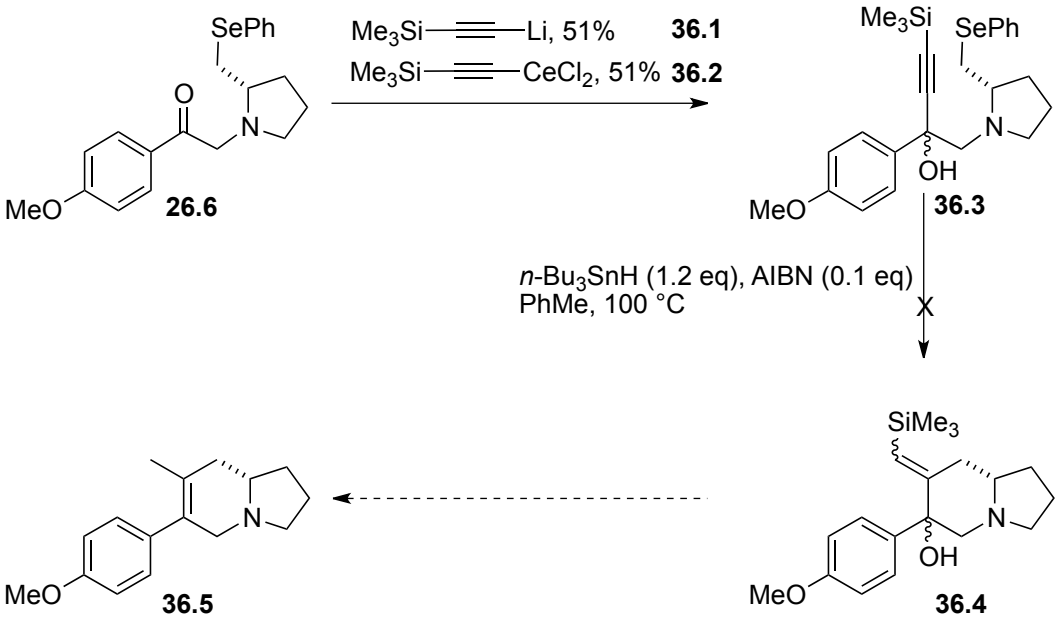
Scheme 34. Formation of allene alcohol **34.3**

The hydroxy group was replaced by iodine (**34.3**→**35.1**) by treatment with Ph_3P and iodine.[54] However, the desired radical cyclization did not occur under several different conditions: standard tributyltin hydride, zinc dust,[55a] Rieke zinc,[55b] and $Ru(bpy)_3(BF_4)_2$ and light.[55c]



Scheme 35. Attempted cyclization of iodo allene **35.1**

Lastly, we attempted to install an acetylene group on the ketone **26.7**. The ketone was treated with trimethylsilylacetylene anion **35.1**, which was generated *in situ* from trimethylsilylacetylene and MeLi in THF to give compound **35.3**. Because the yield was poor we decided to try the corresponding cerium salt.[56] Unfortunately, the cerium acetylide gave the same yield as lithium trimethylsilylacetylene. Once again, the radical cyclization was not successful, at least under our standard conditions (tributyltin hydride in toluene at 80 °C).



Scheme 36. Attempted cyclization onto a triple bond

If the radical cyclization had been successful, the plan was to remove the silyl group from **35.4** with TFA in the presence of $(TMS)_3SiH$ to give *O*-methyl ipalbidine by hydride reduction of an intermediate allylic carbocation. Unfortunately the failure of the cyclization prevented me from completing this short synthesis of optically pure ipalbidine.

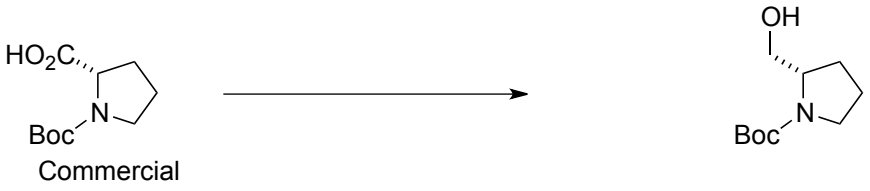
2.2 Conclusion: Total synthesis of optical active ipalbidine

Through a radical cyclization pathway, we have obtained (+)-ipalbidine with an *ee* 99.3% without any lose of stereochemistry from the starting L-proline. The potential interference by reversible opening of the intermediate β-amino radical did not occur and we observed a satisfactory 6-*exo*-*trig* cyclization. It is possible that the substitution pattern of the cyclization substrate and the presence of a heteroatom in the ring being formed contributed to the favorable outcome of this key step.

EXPERIMENTAL SECTION

General Procedures. Solvents used for chromatography were distilled before use. Commercial thin layer chromatography plates (silica gel, Merck 60F-254) were used. Silica gel for flash chromatography was Merck type 60 (230–400 mesh). Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. The symbols s, d, t and q used for ^{13}C NMR spectra indicate zero, one, two, or three attached hydrogens, respectively, the assignments being made from APT spectra. Solutions were evaporated under water pump vacuum and the residue was then kept under oil pump vacuum. High resolution electrospray mass spectrometric analyses were done with an orthogonal time of flight analyzer and electron ionization mass spectra were measured with a double-focusing sector mass spectrometer.

***tert*-Butyl (2*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (26.2).**[41]

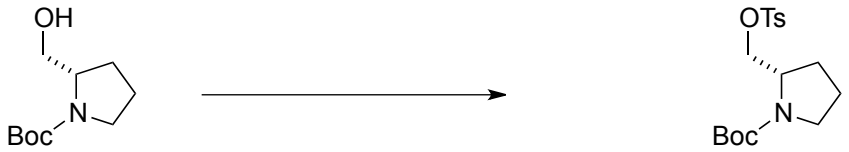


26.1 **26.2**

$BH_3.SMe_2$ (2 M in THF, 6 mL, 12 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *N*-Boc-L-proline (2.0 g, 9.2 mmol) in dry THF (20 mL). When gas evolution ceased the ice bath was removed and stirring was continued overnight. The solution was cooled to 0 °C and MeOH (0.3 mL) was added dropwise. The mixture was extracted with EtOAc, washed with brine, dried ($MgSO_4$) and evaporated to afford **26.2** (1.83 g, 98%) as a colorless oil that was used directly in the next step. The material had: FTIR (CH_2Cl_2 cast) 3430, 2974, 2932,

2878, 1695, 1672, 1406, 1171 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 9 H), 1.76–1.84 (m, 2 H), 1.97–2.04 (m, 1 H), 3.28–3.33 (m, 1 H), 3.42–3.44 (m, 1 H), 3.56–3.67 (m, 2 H), 3.80–4.02 (br, 2 H), 4.70–4.72 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.1 (t), 28.5 (q), 28.8 (s), 47.6 (t), 60.2 (d), 67.8 (t), 80.2 (t), 157.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{10}H_{19}NNaO_3$ (M + Na) 224.1257, found 224.1253.

***tert*-Butyl (2*S*)-2-{[(4-methylbenzenesulfonyl)oxy]methyl)pyrrolidine-1-carboxylate (26.3)**.[42]

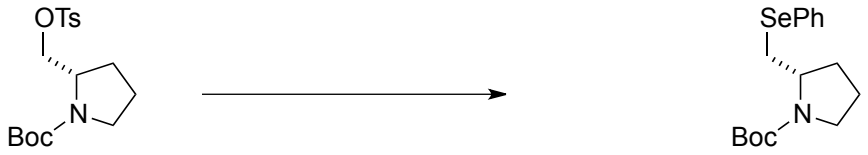


26.2 **26.3**

TsCl (0.84 g, 4.0 mmol) was added as a solid to a stirred solution of *N*-Boc-L-prolinol (**26.2**) (0.81 g, 4.0 mmol) in dry pyridine (0.8 mL). The mixture was stirred overnight at room temperature, diluted with EtOAc and washed with ice-cold hydrochloric acid (1 N, 27 mL). The organic extract was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 3:7 EtOAc-hexane, gave **26.3** (1.32 g, 93%) as a colorless oil: $[\alpha]^{20}_D$ –37.65 (*c* 1.07600, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2976, 2932, 1694, 1177 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.38–1.42 (m, 9 H), 1.80–2.00 (m, 4 H), 2.50 (s, 3 H), 3.29–3.35 (m, 2 H), 3.90–4.00 (m, 2 H), 4.10–4.12 (m, 1 H), 7.40 (br s, 2 H), 7.79 (d, *J* = 7.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.6 (q), 22.9 (t), 23.8 (t), 27.7 (t), 28.4 (q), 28.5 (t), 46.5 (t), 46.9 (t), 55.6 (d), 70.0 (s), 79.6 (t), 79.9 (t), 127.9 (d),

129.9 (d), 133.0 (s), 144.7 (s), 144.8 (s), 154.0 (s), 154.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{17}H_{25}NNaO_5S$ (M + Na) 378.1346, found 378.1342.

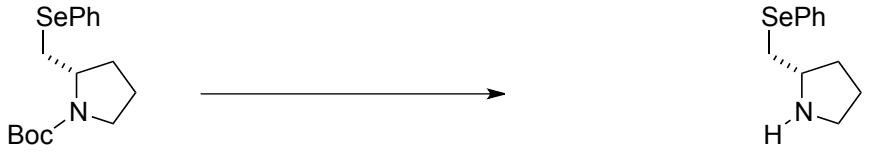
***tert*-Butyl (2*S*)-2-[(phenylselanyl)methyl]pyrrolidine-1-carboxylate (26.4)**.[42]



26.3 **26.4**

$NaBH_4$ (0.20 g, 5.6 mmol) was added to a stirred and warmed (40 °C) solution of PhSeSePh (0.87 g, 2.8 mmol) in dry DMF (8 mL). After 30 min a solution of **26.3** (1.54 g, 4.3 mmol) in DMF (8 mL) was added and stirring at 40 °C was continued overnight. The mixture was cooled, poured into water and extracted with Et_2O. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using increasing amounts of EtOAc in hexane from 5% EtOAc to 30% EtOAc in hexane, gave **26.4** (1.3 g, 88%) as a yellow oil: $[\alpha]^{20}_{D}$ –17.79 (*c* 1.07200, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3070, 2973, 2929, 1693, 1392 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) (rotamers) δ 1.30–1.40 (m, 9 H), 1.70–2.10 (m, 4 H), 2.92–2.96 (m, 1 H), 3.22–3.52 (m, 3 H), 3.97–4.11 (m, 1 H), 7.25–7.28 (m, 3 H), 7.55–7.56 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.8 (t), 23.7 (t), 28.6 (q), 30.4 (t), 30.9 (t), 31.1 (s), 31.9 (s), 46.7 (t), 47.2 (t), 57.1 (d), 79.2 (t), 79.6 (t), 126.5 (d), 127.0 (d), 129.1 (d), 129.9 (s), 130.5 (s), 131.8 (d), 132.9 (d), 154.3 (s), 154.4 (s); exact mass (electron impact) *m*/*z* calcd for $C_{16}H_{23}N^{80}SeO_2$ 341.0894, found 341.0896.

(2*S*)-2-[(Phenylselanyl)methyl]pyrrolidine (26.5).[43]



26.4 **26.5**

CF_3CO_2H (5.7 mL was added dropwise over 1 h to a stirred and cooled (0 °C) solution of **26.4** (0.57 g, 1.6 mmol) in CH_2Cl_2 (5.7 mL). After the addition stirring at 0 °C was continued for 4 h and then saturated aqueous $NaHCO_3$ was added dropwise until the pH of the solution was 8–9 (indicator paper). The organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 1:19 MeOH-CH_2Cl_2, gave material that was partitioned between Et_2O and 10%w/v aqueous NaOH. The organic extract was dried and evaporated to give **26.5** (0.36 g, 87%) as an amber oil: $[\alpha]^{20}_{D}$ +24.94 (*c* 1.496, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3052, 2960, 2869, 1679, 1478, 1437, 1400, 737 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.45–1.52 (m, 1 H), 1.75–1.91 (m, 2 H), 1.94–2.01 (m, 1 H), 2.92–2.96 (m, 2 H), 3.02–3.10 (m, 3 H), 3.35 (quintet, *J* = 6.9 Hz, 1 H), 7.23–7.29 (m, 3 H), 7.52–7.54 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.3 (t), 31.7 (t), 34.0 (t), 46.3 (t), 58.5 (d), 127.0 (d), 129.1 (d), 130.1 (s), 132.7 (d); exact mass (electrospray) *m*/*z* calcd for $C_{11}H_{16}N^{80}Se$ 242.0442 [M + H], found 240.0442.

2-Bromo-1-(4-methoxyphenyl)ethan-1-one (26.6).[44]

A solution of Br_2 (0.3 mL, 6.5 mmol) in $CHCl_3$ (10 mL) was added slowly to a stirred solution of *p*-methoxyacetophenone (1.0 g, 6.79 mmol) in $CHCl_3$ (10 mL). The mixture was then stirred overnight, diluted with Et_2O (10 mL) and washed with water. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using increasing amounts of EtOAc in hexane from 0% to 5% EtOAc in hexane, gave **26.6** (1.14 g, 73%) as a white solid: mp 69–70 °C; FTIR (CH_2Cl_2 cast) 3078, 3061, 3011, 2943, 2844, 1685, 1602, 1206 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.90 (s, 3 H), 4.41 (s, 2 H), 6.96–7.02 (m, 2 H), 7.97–8.04 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.7 (t), 55.6 (q), 114.1 (d), 127.0 (s), 131.4 (d), 164.2 (d), 190.0 (d); exact mass (electrospray) *m*/*z* calcd for $C_9H_9{}^{79}BrNaO_2$ (M + Na) 250.9678, found 250.9678.

1-(4-Methoxyphenyl)-2-[(2*S*)-2-[(phenylselanyl)methyl]pyrrolidin-1-yl]ethan-1-one (26.7).

K_2CO_3 (5.5 g, 4.0 mmol) was added to a stirred solution of amine **26.5** (580 mg, 2.40 mmol) in dry MeCN (17 mL), followed by bromide **26.6** (450 mg, 2.0 mmol) (N_2 atmosphere). Stirring at room temperature was continued for 3 h and then water was added. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 1:1 EtOAc-hexane, gave **26.7** (710 mg, 76%) as a tan-colored oil containing minor impurities (^{1}H NMR and ^{13}C NMR) [We obtained a pure sample of the corresponding racemic material; see Supporting Information for copies of the NMR spectra]. The compound is unstable and should be used within a day: $[\alpha]^{20}_{D}$ –18.66 (*c* 1.0200, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3055, 2925, 2853, 1712, 1601, 1256 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.70–1.90 (m, 3 H), 2.04–2.10 (m, 1 H), 2.43 (q, *J* = 9.1 Hz, 1 H), 2.90–2.97 (m, 1 H), 3.00–3.09 (m, 1 H), 3.13–3.18 (m, 1 H), 3.21–3.25 (m, 1 H), 3.87 (s, 3 H), 3.97 (AB q, *J* = 15.9, $\Delta\nu_{AB}$ = 235.7 Hz, 2 H), 6.91–6.95 (m, 2 H), 7.22–7.28 (m, 3 H), 7.47–7.51 (m, 2 H), 8.00–8.04 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.9 (t), 31.2 (t), 32.9 (t), 54.6 (t), 55.5 (d), 60.3 (t), 63.8 (q), 113.7 (d), 126.7 (d), 129.1 (s), 129.2 (d), 130.6 (d), 130.9 (s), 132.3 (d), 163.6 (s), 196.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{24}NO_2{}^{80}Se$ (M + H) 390.0968, found 390.0961.

2-(4-Methoxyphenyl)-1-[(2*S*)-2-[(phenylselanyl)methyl]pyrrolidin-1-yl]but-3-en-2-ol (27.2).

26.7 **27.2**

MeLi (1.6 M in Et_2O, 5.2 mL, 8.2 mmol) was added dropwise to a stirred and cooled (0 °C) solution of tetravinyltin (0.37 mL, 2.04 mmol) in Et_2O (40 mL).[45] Stirring was continued for 1 h and the solution was then cooled to -78 °C. A solution of ketone **26.7** (200 mg, 0.51 mmol) in Et_2O (10 mL) was added dropwise at -78 °C, the cold bath was left in place, but not recharged, and stirring was continued overnight. The mixture was cooled to 0 °C, quenched with water, and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 16 cm), using 1:1 EtOAc-hexane, gave **27.2** [190 mg, 89%, or 96% corrected for recovered **26.7** (15 mg)] as a pale yellow oil which was a mixture of isomers: FTIR (CH_2Cl_2 cast) 3418, 3070, 3056, 2953, 2834, 1610, 1510, 1248, 1199 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.55–1.85 (m, 4 H), 1.92–2.03 (m, 1 H), 2.35–2.40 (m, 1 H), 2.87–3.00 (m, 3 H), 3.05–3.08 (m, 0.5 H), 3.14–3.18 (m, 0.5 H), 3.30–3.42 (m, 1 H), 3.81–3.82 (two s, 3 H), 4.34–4.48 (two br s, 1 H), 5.11 (ddd, *J* = 1.4, 10.4, 20.4 Hz, 1 H), 5.26 (dd, *J* = 1.4, 16.9 Hz, 0.5 H), 5.48 (dd, *J* = 1.4, 17.1 Hz, 0.5 H), 6.10 (dd, *J* = 16.9, 10.4 Hz, 0.5 H), 6.24 (dd, *J* = 10.4, 16.9 Hz, 0.5 H), 6.86–6.89 (m, 2 H), 7.22–7.30 (m, 3 H), 7.38–7.42 (m, 2 H),

7.48–7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.7 (t), 23.8 (t), 30.2 (t), 30.5 (t), 33.81 (t), 33.89 (t), 55.2 (q), 56.0 (t), 56.9 (t), 65.0 (d), 65.3 (d), 65.7 (t), 66.6 (t), 74.0 (t), 112.9 (s), 113.2 (s), 113.4 (d), 113.6 (d), 126.2 (d), 126.7 (d), 126.8 (d), 126.9 (d), 129.0 (d), 129.1 (d), 130.4 (s), 132.67 (d), 132.70 (d), 132.74 (d), 137.62 (s), 137.68 (s), 143.5 (d), 144.5 (d), 158.3 (s), 158.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{22}H_{27}NO_2{}^{80}Se$ (M + H) 418.1280, found 418.1279.

(8a*S*)-6-(4-Methoxyphenyl)-7-methyloctahydroindolizin-6-ol (27.3).

27.2 **27.3**

A solution of Bu_3SnH (0.2 mL, 0.76 mmol) and AIBN (6 mg, 0.03 mmol) in PhMe (2 mL) was added via syringe pump over 8 h to a stirred and heated (110 °C) solution of **27.2** (mixture of isomers) (160 mg, 0.38 mmol). Stirring at 110 °C was continued for 2 h after the addition, and the solvent was then evaporated at room temp (waterpump vacuum). Flash chromatography of the residue over 10% KF on silica gel[57] (2 × 16 cm) using 1:19 MeOH-EtOAc) gave **27.3** [75 mg, 75% or 85.9% corrected for recovered **27.2** (20 mg)] as a light-brown oil which appeared to be a mixture of at least two isomers. Preparative tlc (20 x 20 x 0.215 mm), using 1:4 *i*-PrOH-CH_2Cl_2, allowed isolation of one isomer, which had: FTIR (CH_2Cl_2 cast) 3483, 2962, 2930, 2799, 1512, 1247 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.69 (d, *J* = 6.4 Hz, 3 H), 1.23–1.32 (m, 1 H), 1.42–1.50 (m, 1 H), 1.68–1.94 (m, 6 H), 1.95–2.06 (m, 1 H), 2.21 (q, *J* = 8.8

Hz, 1 H), 2.57 (AB q, J = 11.2, $\Delta\nu_{AB}$ = 223.8 Hz, 2 H), 2.96 (dt, J = 2.3, 8.5 Hz, 1 H), 3.47 (s, 1 H), 3.82 (s, 3 H), 6.87–6.91 (m, 2 H), 7.38–7.42 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.0 (q), 21.5 (t), 30.6 (t), 35.9 (t), 39.0 (d), 53.3 (t), 55.2 (q), 64.1 (d), 65.5 (t), 73.6 (s), 113.4 (d), 126.1 (d), 136.7 (s), 158.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{16}H_{24}NO_2$ (M + H) 262.1802, found 262.1804.

(8a*S*)-6-(4-Methoxyphenyl)-7-methyl-1,2,3,5,8,8a-hexahydroindolizine (2.6).

27.3 **2.6**

P_2O_5 (8.4 mg, 0.06 mmol) was added to a solution of **27.3** (42 mg, 0.16 mmol) in 85% H_3PO_4 (12.6 mL)[46] and the mixture was heated at 120 °C for 2 h, cooled, poured onto ice and basified to pH 12 with powdered KOH. The resulting mixture was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.1 × 15 cm), using 1:19 MeOH-EtOAc, gave **2.6** (20 mg, 50%) as a colorless oil containing trace impurities (^{1}H NMR): $[\alpha]^{20}_D$ +133.76 (*c* 0.676, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3033, 2956, 2930, 1511 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49–1.57 (m, 1 H), 1.61 (s, 3 H), 1.76–2.35 (m, 7 H), 2.91–2.95 (m, 1 H), 3.24 (dt, J = 8.3, 2.0 Hz, 1 H), 3.64 (d, J = 15.4 Hz, 1 H), 3.81 (s, 3 H), 6.86–6.89 (m, 2 H), 7.09–7.13 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.1 (q), 21.4 (t), 30.8 (t), 38.4 (t), 54.1 (t), 55.2 (q), 57.8 (t), 60.2 (d),

113.5 (d), 128.0 (s), 129.8 (d), 130.3 (s), 133.7 (s), 158.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{16}H_{22}NO$ (M + H) 244.1696, found 244.1696.

4-[(8a*S*)-7-Methyl-1,2,3,5,8,8a-hexahydroindolizin-6-yl]phenol [(+)-ipalbidine] (1.3).

2.6 **1.3**

BBr_3 (1 M in CH_2Cl_2, 0.24 mL) was added to a stirred and cooled (-78 °C) solution of **2.6** (20 mg, 0.08 mmol) in dry CH_2Cl_2 (1.0 mL).[12,13] The cold bath was left in place but not recharged and stirring was continued overnight. The mixture was cooled to 0 °C and quenched by addition of water. The mixture was stirred and saturated aqueous $NaHCO_3$ was added until all the dark gummy material dissolved. The mixture was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.1 × 15 cm), using 1:19 MeOH-CH_2Cl_2, gave **1.3** (16 mg, 86%) as a semi-solid: FTIR (CH_2Cl_2 cast) 3030, 2966, 2914, 2878, 2829, 2791, 1609, 1585, 1513, 1445, 1267 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.62 (s, 3 H), 1.64–1.68 (m, 1 H), 1.81–1.86 (m, 1 H), 1.98–2.11 (m, 2 H), 2.20–2.33 (m, 3 H), 2.40–2.49 (m, 1 H), 3.10 (d, *J* = 15.4 Hz, 1 H), 3.30 (dt, *J* = 1.5, 9.0 Hz, 1 H), 3.53 (d, *J* = 15.5 Hz), 6.79–6.82 (m, 2 H), 7.00–7.04 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.1 (q), 21.2 (t), 30.2 (t), 37.6 (t), 54.1 (t), 57.7 (t), 60.7 (d), 115.5 (d), 128.3 (s), 129.7 (d), 129.8 (s), 132.1 (s), 155.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{19}NO$ (M + H) 230.1539, found 230.1542. Kugelrohr distillation of a sample (140 °C, 0.005 mmHg) gave (+)-ipalbidine as a glass: $[\alpha]^{20}_D$ +252.45 (*c*

1.21300, $CHCl_3$) [Lit.[8] $[\alpha]^{25}_D$ +233.5 (*c* 1, $CHCl_3$)]. Chiral HPLC analysis [RegisPack CLA-1, 250 x 4.6 cm, hexane/ethanol (90/10) + 0.1% Et_2NH, 1 mL per min, wavelength 254 nm] established the ee as 99.3%. For comparison purposes racemic ipalbidine was made the same way as the optically active compound, starting with racemic proline.

I thank H. Fu for the Chiral HPLC measurement, Ted Szczerba (Regis Technologies, Inc) for first establishing chiral HPLC conditions.

2-(4-Methoxyphenyl)buta-2,3-dien-1-ol (31.4).[50]

31.3 **31.4**

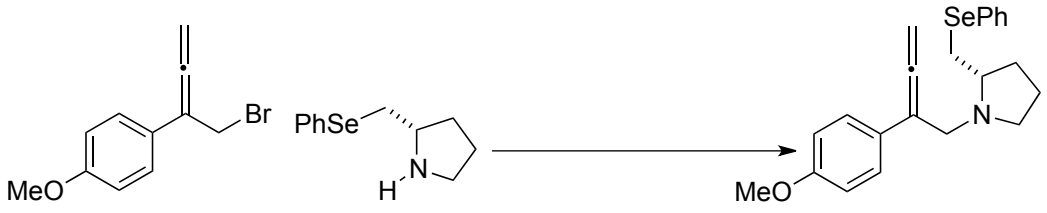
Formaldehyde (37% aqueous solution, 0.32 mL, 3.2 mmol) was added to a vigorously stirred solution of 1-(3-bromoprop-1-yl)-4-methoxybenzene[49] (**31.3**) (0.82 g, 3.6 mmol) in 1:1 THF-water (16.4 mL). Indium powder (0.62 g, 5.4 mmol) was added quickly and vigorous stirring was continued for 12 h. The mixture was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 16 cm), using a gradient of hexane to 5% CH_2Cl_2 in hexane, gave **31.4** (0.52 g, 82%) as a white solid: mp 65–67 °C; FTIR (CH_2Cl_2 cast) 3367, 3039, 2935, 1940 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.62 (t, *J* = 6.0, 1 H), 3.83 (s, 3 H), 4.55–4.57 (m, 2 H), 5.24 (t, *J* = 2.5, 2 H), 6.89–6.92 (m, 2 H), 7.35–7.39 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.3 (q), 61.7 (t), 80.3 (s), 105.6 (t), 114.2 (d), 126.0 (s), 127.3 (s), 158.9 (s), 207.2 (s); exact mass (electron impact) *m*/*z* calcd for $C_{11}H_{12}O_2$ 176.0837, found 176.0837.

1-(1-Bromobuta-2,3-dien-2-yl)-4-methoxybenzene (31.5).[49]

31.4 **31.5**

CBr_4 (2.74 g, 0.0081 mol) was added to a stirred solution of **31.4** (1.2 g, 0.0068 mol) and Ph_3P (2.14 g, 0.0081 mol) in CH_2Cl_2 (25 ml) and stirring was continued at room temperature for 6 h. Evaporation of solvent and flash chromatography of the residue over silica gel (2 × 16 cm), using 1:20 EtOAc-hexane, gave **31.5** (1.2 g, 73.8%) as a yellow solid: mp 41–45 °C: FTIR (CH_2Cl_2 cast) 3038, 2956, 1934, 1512, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.85 (s, 3 H), 4.43 (s, 2 H), 5.20 (s, 2 H), 6.92–6.94 (m, 2 H), 7.40–7.42 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 32.0 (t), 55.3 (q), 79.3 (t), 103.0 (s), 114.1 (s), 125.1 (d), 127.4 (d), 159.1 (s), 209.2 (s); exact mass (electron impact) *m*/*z* calcd for $C_{11}H_{11}O^{79}Br$ 237.9993, found 237.9995.

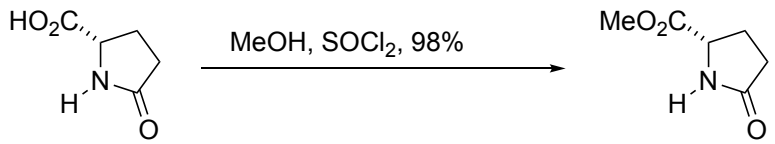
(2*S*)-1-[2-(4-Methoxyphenyl)buta-2,3-dien-1-yl]-2-[(phenylselanyl)methyl]pyrrolidine (31.6).



31.5 **26.5** **31.6**

K_2CO_3 (2.76 g, 20.0 mmol) was added to a stirred solution of amine **26.5** (300 mg, 1.2 mmol) in dry MeCN (8.6 mL) followed by bromide **31.5** (230 mg, 1.0 mmol) (N_2 atmosphere). Stirring at room temperature was continued for 3 h and then water was added. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 3:7 EtOAc-hexane, gave **31.6** (280 mg, 70%) as a yellow oil: FTIR (CH_2Cl_2 cast) 3056, 2963, 2832, 1940, 1510, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.66–1.76 (m, 3 H), 1.98–2.03 (m, 1 H), 2.30–2.37 (m, 1 H), 2.79–2.83 (m, 1 H), 2.99–3.04 (m, 1 H), 3.06–3.15 (m, 1 H), 3.15–3.19 (m, 1 H), 3.21–3.25 (br d, 1 H), 3.80 (s, 3 H), 3.82–3.86 (m, 1 H), 4.96–5.03 (m, 2 H), 6.85–6.88 (m, 2 H), 7.22–7.27 (m, 3 H), 7.46–7.51 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.6 (t), 31.3 (t), 33.3 (t), 54.4 (t), 55.3 (q), 55.6 (t), 63.7 (d), 102.5 (t), 113.8 (d), 126.5 (d), 127.68 (s), 127.71 (d), 129.0 (d), 131.2 (s), 132.4 (d), 158.6 (s), 209.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{22}H_{26}NO^{80}Se$ (M + H) 400.1174, found 400.1171.

Methyl (2*S*)-5-Oxopyrrolidine-2-carboxylate (32.2).[51]

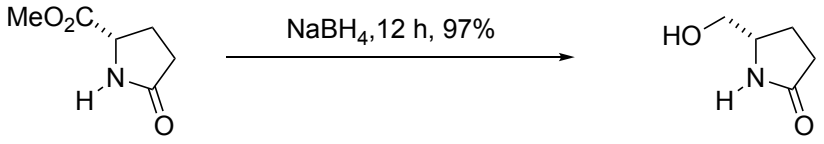


32.1 **32.2**

$SOCl_2$ (0.4 mL, 4.68 mmol) was added over 15 min to a stirred and cooled (–25 °C) solution of L-pyroglutamic acid (**32.1**) (0.55 g, 4.26 mmol) in MeOH (4.8 mL). The cold bath was removed and stirring was continued for 2 h. Evaporation of the solvent under water pump

vacuum and Kugelrohr distillation of the residue under oilpump vacuum gave **32.2** (0.6 g, 98%) as a colorless oil: bp 120 °C, 0.05 mmHg; FTIR ($CDCl_3$, cast) 3233, 2956, 1743, 1702, 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.50–2.53 (m, 1 H), 2.24–2.51 (m, 4 H), 4.28–4.31 (m, 1 H), 3.80 (s, 3 H), 6.76 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.8 (t), 29.2 (t), 52.6 (d), 55.4 (q), 172.4 (s), 178.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_6H_9NO_3$ $(M+H)^+$ 144.0653, found 144.0655.

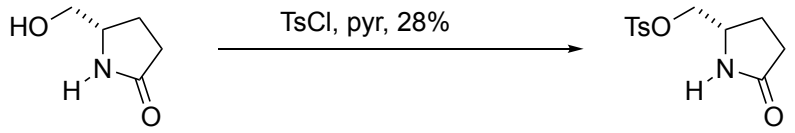
(5*S*)-5-(Hydroxymethyl)pyrrolidin-2-one (32.3).[51]



32.2 **32.3**

$NaBH_4$ (0.29 g, 7.7 mmol) was added to a stirred and cooled (0 °C) solution of **32.2** (1 g, 6.9 mmol) in EtOH (41 mL). The cold bath was left in place but not recharged and stirring was continued for 12 h. The mixture was cooled in an ice bath, acidified with concentrated hydrochloric acid and evaporated. Flash chromatography of the residue over silica gel (2 × 16 cm), using 5% MeOH–CH_2Cl_2, gave **32.3** (0.77 g, 97%) as pale yellow crystals: mp 86–88 °C; FTIR ($CDCl_3$, cast) 3280, 2931, 1684 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.79–1.86 (m, 1 H), 2.16–2.24 (m, 1 H), 2.35–2.40 (m, 2 H), 3.44–3.51 (m, 2 H), 3.69–3.72 (m, 1 H), 3.80–3.85 (m, 1 H), 7.12 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.6 (t), 30.2 (t), 56.4 (q), 66.0 (t), 179.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_5H_9NO_2$ $(M+H)^+$ 116.0706, found 116.0706.

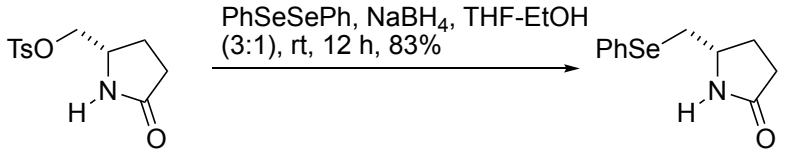
[(2*S*)-5-Oxopyrrolidin-2-yl]methyl 4-methylbenzene-1-sulfonate (32.4).



32.3 **32.4**

TsCl (0.18 g, 0.93 mmol) was added to a stirred solution of **32.3** (0.09 g, 0.78 mmol) in anhydrous pyridine (0.5 mL) and stirring was continued overnight. The reaction mixture was quenched with aqueous 1N hydrochloric acid and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 5% MeOH–CH_2Cl_2, gave **32.4** (0.06 g, 28%) as a white solid: mp 127–129 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.77–1.78 (m, 1 H), 2.21–2.32 (m, 3 H), 2.43 (s, 3 H), 3.88–3.91 (m, 2 H), 4.00–4.02 (m, 1 H), 6.74 (br s, 1 H), 7.35 (d, *J* = 8 Hz, 2 H), 7.77 (d, *J* = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.7 (q), 22.8 (t), 29.3 (t), 56.4 (d), 72.0 (t), 128.0 (d), 130.1 (d), 148.5 (s), 178.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_5H_9NO_2$ $(M+H)^+$ 116.0706, found 116.0706.

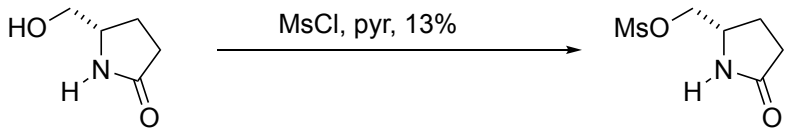
(5*S*)-5-[(Phenylselanyl)methyl]pyrrolidin-2-one (33.1).



32.4 **33.1**

$NaBH_4$ (0.02 g, 0.48 mmol) was added to a stirred solution of PhSeSePh (0.06 g, 0.48 mmol) in THF (3 mL) and then EtOH (1 mL) was added dropwise (N_2 atmosphere). A clear solution formed immediately and stirring was continued for 10 min. A solution of **32.4** (0.1 g, 0.37 mmol) in THF (1.1 mL) was added slowly via cannula, and stirring was continued overnight. The resulting mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 5% MeOH–CH_2Cl_2, gave **33.1** (0.08 g, 83%) as a colorless oil: FTIR ($CDCl_3$, cast) 3215, 3072, 2925, 1695 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.79–1.83 (m, 1 H), 2.22–2.44 (m, 3 H), 2.88–3.01 (m, 2 H), 3.01–3.82 (m, 1 H), 3.69–3.72 (m, 1 H), 6.51 (br s, 1 H), 7.27–7.30 (m, 3 H), 7.52–7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.4 (t), 30.3 (t), 34.3 (t), 54.0 (d), 127.7 (d), 128.6 (s), 128.4 (d), 133.6 (d), 177.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{11}H_{13}NO^{80}Se$ $(M+H)^+$ 256.0237, found 256.0235.

[(2*S*)-5-Oxopyrrolidin-2-yl]methyl methanesulfonate (32.5).[52]

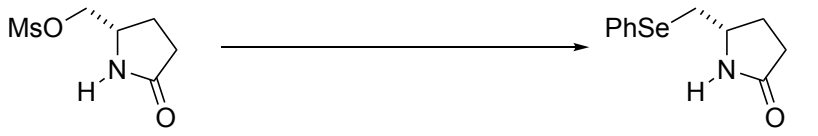


32.3 **32.5**

MsCl (0.5 mL, 6.6 mmol) and Et_3N (1.1 mL, 8.0 mmol) were added sequentially to a stirred and cooled (0 °C) suspension of **32.3** (0.51 g, 4.4 mmol) in CH_2Cl_2 (2.4 mL). Stirring at 0 °C was continued for 1.5 h. The reaction mixture was quenched with water and the aqueous

phase was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 10% MeOH–EtOAc, gave **32.5** (0.11 g, 13%) as a colorless oil: FTIR ($CDCl_3$, cast) 3232, 3020, 2935, 1697, 1352, 1173 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.88–1.91 (m, 1 H), 2.32–2.43 (m, 3 H), 3.10 (s, 3 H), 4.02–4.10 (m, 2 H), 4.27–4.30 (m, 1 H), 6.38 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.0 (t), 39.3 (t), 37.7 (d), 54.7 (q), 71.3 (t), 177.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_6H_{11}NO_4S$ $(M+H)^+$ 194.0482, found 194.0482.

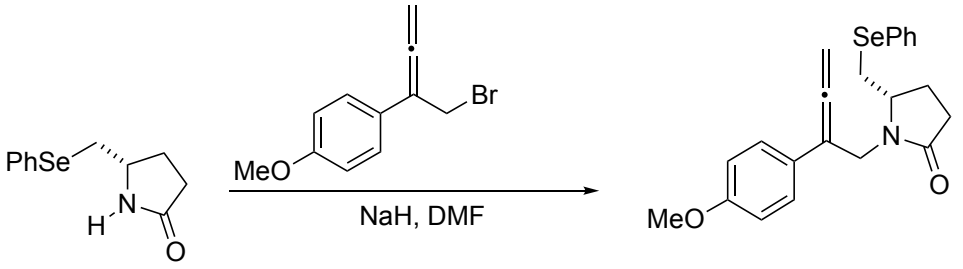
(5*S*)-5-[(Phenylselanyl)methyl]pyrrolidin-2-one (33.1).[52]



32.5 **33.1**

$NaBH_4$ (0.07 g, 1.9 mmol) was added to a stirred solution of PhSeSePh (0.25 g, 0.8 mmol) in THF (4 mL) and then EtOH (2 mL) was added dropwise (N_2 atmosphere). A clear solution formed immediately and stirring was continued for 10 min. A solution of **32.5** (0.29 g, 1.5 mmol) in THF (2 mL) was added slowly via cannula and stirring was continued overnight. The resulting mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 10% MeOH–CH_2Cl_2, gave **33.1** (0.32 g, 83%) as a colorless oil, identical with material described above.

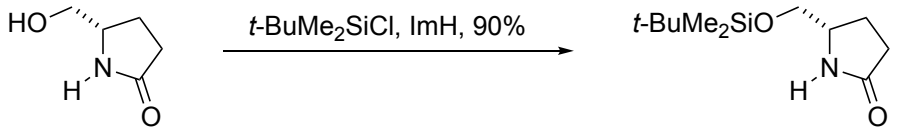
(5*S*)-1-[2-(4-Methoxyphenyl)buta-2,3-dien-1-yl]-5-[(phenylselanyl)methyl]pyrrolidin-2-one (33.3).



33.1 **33.3**

NaH (0.1 g, 2.4 mmol) was tipped into a stirred solution of **33.1** (0.52 g, 2.0 mmol) in dry DMF (6 mL) and, after ca 2 min, a solution of the allene bromide (0.52 g, 2.2 mmol) in dry DMF (6 mL) was added at a fast dropwise rate (N_2 atmosphere). Stirring was continued overnight and the resulting mixture was quenched with water and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 20% EtOAc–hexane, gave **33.3** (0.56 g, 68%) as a yellowish oil: FTIR ($CDCl_3$, cast) 3053, 2932, 2835, 1940, 1687, 1512, 1294 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.79–1.84 (m, 1 H), 2.08–2.13 (m, 1 H), 2.25–2.31 (m, 2 H), 2.46–2.52 (m, 1 H), 2.92 (dd, *J* = 12.7, 8.9 Hz, 1 H), 3.27 (dd, *J* = 12.4, 2.9 Hz, 1 H), 3.27–3.65 (m, 1 H), 3.76–3.80 (m, 1 H), 3.81 (s, 3 H), 3.89 (td, *J* = 14.9, 3.5 Hz, 1 H), 4.95–5.10 (m, 2 H), 6.84–6.87 (m, 2 H), 7.23–7.26 (m, 2 H), 7.29–7.32 (m, 3 H), 7.53–7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.1 (t), 30.1 (t), 31.7 (t), 40.7 (t), 55.3 (d), 56.7 (q), 100.8 (s), 114.1 (d), 126.3 (s), 127.3 (d), 127.6 (d), 129.2 (d), 129.3 (d), 133.6 (d), 162.5 (s), 174.9 (s), 208.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{22}H_{23}NO_2{}^{80}Se$ $(M+H)^+$ 414.0965, found 414.0967.

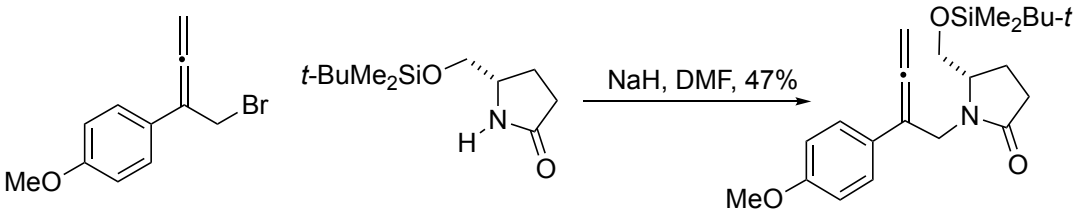
(5*S*)-{[(*tert*-Butydimethylsilyl)oxy]methyl}pyrrolin-2-one (34.1).[53]



32.3 **34.1**

t-$BuMe_2SiCl$ (1.3 g, 8.6 mmol) was added to a stirred solution of imidazole (0.73 g, 10 mmol) and **32.3** (0.83 mL, 7.2 mmol) in CH_2Cl_2 (8.6 mL) and stirring was continued for 4 h. The mixture was quenched with water and the organic phase was washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 5% MeOH in CH_2Cl_2, gave **34.1** (1.5 g, 90%) as a colorless oil: FTIR ($CDCl_3$, cast) 3207, 3102, 2954, 2929, 2895, 1703, 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.05 (s, 6 H), 0.88 (s, 9 H), 1.73–1.79 (m, 1 H), 2.13–2.20 (m, 1 H), 2.27–2.34 (m, 2 H), 3.44–3.60 (m, 1 H), 3.60–3.63 (m, 1 H), 3.72–3.76 (m, 1 H), 6.21 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –5.4 (q), 18.2 (s), 22.8 (t), 29.8 (t), 55.8 (d), 66.9 (t), 177.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{11}H_{23}NO_2Si$ $(M+H)^+$ 230.1569, found 230.1571.

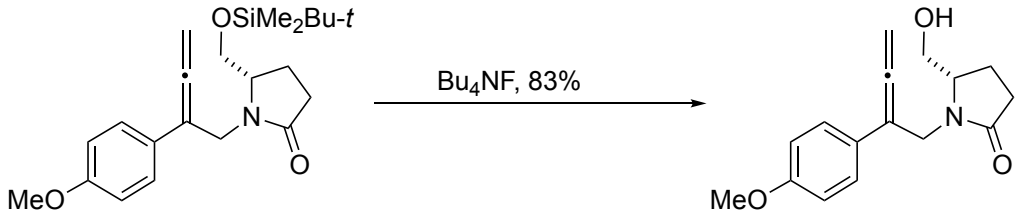
(5*S*)-5-{[(*tert*-Butydimethylsilyl)oxy]methyl}-1-[2-(4-methoxyphenyl)buta-2,3-dien-1-yl]pyrrolin-2-one (34.2).



31.5 **32.3** **34.2**

NaH (0.11 g, 2.76 mmol) was added to a stirred solution of **32.3** (0.5 g, 2.2 mmol) in dry DMF (15 mL) and after ca 2 min a solution of **31.5** (0.57 g, 2.3 mmol) in dry DMF (5 mL) was added at a fast dropwise rate (N_2 atmosphere). Stirring was continued overnight and the resulting mixture was quenched with water and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 30% EtOAc–hexane, gave **34.2** (0.4 g, 47%) as a colorless oil: FTIR ($CDCl_3$, cast) 2953, 2929, 2856, 1940, 1690, 1513, 1281 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.06 (s, 6 H), 0.89 (s, 9 H), 1.86–1.98 (m, 2 H), 2.25–2.30 (m, 1 H), 2.46–2.53 (m, 1 H), 3.61–3.66 (m, 2 H), 3.76–3.79 (m, 2 H), 3.83 (s, 3 H), 5.02 (td, J = 15, 4 Hz, 1 H), 5.12–5.18 (m, 2 H), 6.87–6.89 (m, 2 H), 7.34–7.36 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –5.4 (q), 18.2 (s), 21.3 (t), 25.8 (q), 30.6 (t), 40.7 (s), 55.3 (d), 58.1 (q), 62.8 (t), 79.0 (s), 101.1 (s), 114.1 (d), 125.7 (d), 127.3 (d), 158.9 (s), 175.4 (s), 208.8 (s); exact mass (electrospray) m/z calcd for $C_{22}H_{33}NO_3Si$ $(M+H)^+$ 388.2296, found 388.2302.

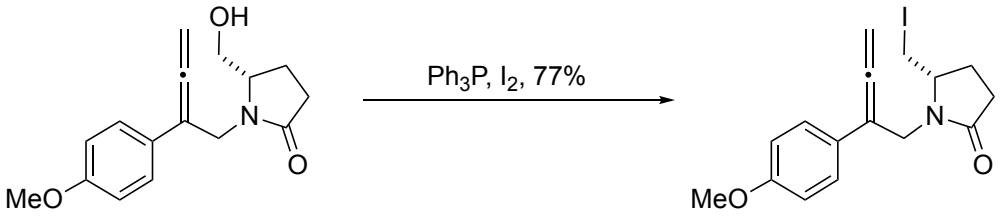
(5*S*)-5-(Hydoxymethyl}-1-[2-(4-methoxyphenyl)buta-2,3-dien-1-yl]pyrrolin-2-one (34.3).



34.2 **34.3**

TBAF (1.3 mL, 1.32 mmol) was added to a stirred solution of **34.2** (0.43 g, 1.1 mmol) in dry THF (10 mL) and stirring was continued overnight. The solvent was evaporated and the residue was dissolved into EtOAc (10 mL). The solution was washed with water, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 5% MeOH–CH_2Cl_2, gave **34.3** (0.25 g, 83%) as a reddish oil: FTIR ($CDCl_3$, cast) 3373, 3039, 2933, 2836, 1941, 1665, 1512, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.94–2.00 (m, 2 H), 2.23–2.31 (m, 1 H), 2.46–2.52 (m, 1 H), 3.05 (br s, 1 H), 3.55–3.66 (m, 2 H), 3.79 (s, 3 H), 3.90–3.99 (m, 2 H), 4.98 (td, J = 15, 4 Hz, 1 H), 5.16 (s, 1 H), 6.81–6.88 (m, 2 H), 7.23–7.34 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ20.9 (t), 30.7 (t), 41.0 (t), 55.3 (d), 58.8 (q), 62.2 (t), 79.3 (t), 101.1 (s), 114.2 (d), 125.5 (s), 127.3 (d), 159.0 (s), 176.1 (s), 208.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{16}H_{19}NO_3$ $(M+H)^+$ 274.1434, found 274.1438.

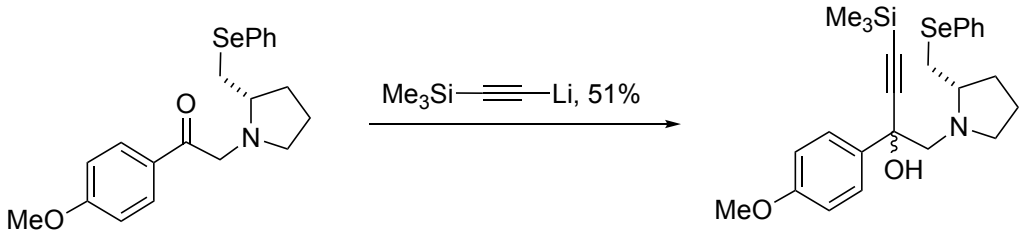
(5*S*)-5-(Iodomethyl}-1-[2-(4-methoxyphenyl)buta-2,3-dien-1-yl]pyrrolin-2-one (35.1).[54]



34.3 **35.1**

Imidazole (0.14 mL, 2.0 mmol), Ph_3P (0.38 g, 1.46 mmol) and I_2 (0.36 g, 1.4 mmol) were added sequentially to a stirred and cooled (0 °C) solution of **34.3** (0.15 g, 0.54 mmol) in dry THF (10 mL). Stirring was continued overnight and the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 30% EtOAc in hexane, gave **35.1** as a colorless oil: FTIR ($CDCl_3$, cast) 3036, 2999, 2955, 2933, 1939, 1686, 1512, 1414, 1247 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.74–1.78 (m, 1 H), 2.01–2.11 (m, 1 H), 2.27–2.34 (m, 1 H), 2.52–2.57 (m, 2 H), 3.34–3.42 (m, 2 H), 3.56–3.58 (m, 1 H), 3.71–3.74 (m, 1 H), 3.80 (s, 3 H), 5.01 (td, J = 15, 4 Hz, 1 H), 5.20 (s, 1 H), 6.86–6.90 (m, 2 H), 7.32–7.36 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ10.7 (t), 24.5 (t), 30.0 (t), 40.6 (t), 55.3 (d), 56.3 (q), 79.3 (t), 100.5 (s), 114.2 (d), 125.2 (s), 127.3 (d), 159.0 (s), 174.8 (s), 209.0 (s); exact mass (electrospray) *m/z* calcd for $C_{16}H_{18}NO_2{}^{129}I$ $(M+H)^+$ 384.0449, found 384.0455.

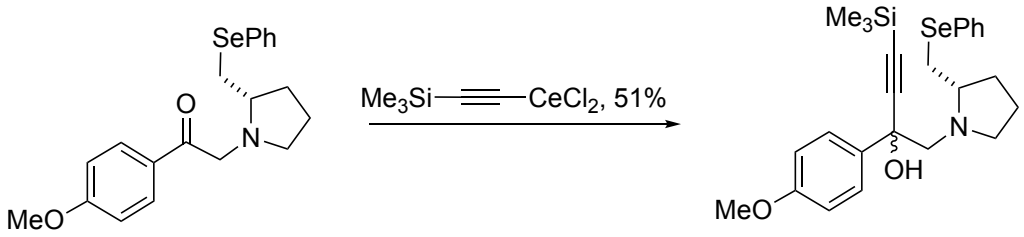
2-(4-Methoxyphenyl)-1-[(2*S*)-2-[(phenylselanyl)methyl]pyrrolidin-1-yl]-4-(trimethyl-silyl)but-3-yn-2-ol (36.3).



26.7 **36.3**

BuLi (2.5 M, 1.52 mL, 3.8 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of trimethylsilylacetylene (0.6 mL, 4.18 mmol) in THF (10 mL). After ca 30 min a solution of **26.7** (0.15 g, 0.38 mmol) in THF (2 mL) was added at a fast dropwise rate. The cold bath was left in place but not recharged and stirring was continued overnight. The resulting mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 5% EtOAc– hexane, gave **36.3** (0.08 g, 51%) as a yellow oil: FTIR ($CDCl_3$, cast) 3403, 3070, 2957, 2834, 2167, 1509, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.17 (s, 9 H), 1.62–1.71 (m, 3 H), 1.94–1.97 (m, 1 H), 2.25–2.30 (m, 1 H), 2.67–2.70 (m, 1 H), 2.89–3.05 (m, 3 H), 3.17–3.22 (m, 2 H), 3.83 (s, 3 H), 4.45 (br s, 1 H), 6.89 (d, J = 4 Hz, 2 H), 6.90–7.30 (m, 3 H), 7.51–7.54 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –0.04 (q), 23.9 (t), 30.5 (t), 33.8 (t), 55.3 (q), 56.4 (s), 65.2 (d), 68.9 (t), 70.5 (t), 89.2 (s), 108.7 (s), 113.4 (d), 126.7 (d), 129.1 (d), 130.5 (s), 132.6 (d), 136.2 (s), 158.9 (s); exact mass (electrospray) m/z calcd for $C_{25}H_{33}NO_2{}^{80}SeSi$ $(M+H)^+$ 488.1511, found 488.1519.

2-(4-Methoxyphenyl)-1-[(2*S*)-2-[(phenylselanyl)methyl]pyrrolidin-1-yl]-4-(trimethyl-silyl)but-3-yn-2-ol (36.3).



26.7 **36.3**

$CeCl_3.7H_2O$ (1.7 g, 4.6 mol) in a round bottomed flask closed with a bent adaptor with a tap connected to an oil pump was heated (oil bath) for 3 h at 130 °C (0.05 mmHg). The flask was allowed to cool and THF (8 mL) was added. The mixture was stirred vigorously for a few minutes and the suspension was sonicated overnight to obtain a fine suspension, which was then stirred and cooled to –78 °C.

BuLi (2.5 M, 1.52 mL, 3.8 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of trimethylsilylacetylene (0.6 mL, 4.18 mmol) in THF (10 mL). After ca 30 min the solution was transferred by cannula to the above stirred and cooled (–78 °C) suspension of $CeCl_3$. After an additional period of ca 30 min, a solution of **26.7** (0.15 g, 0.38 mol) in THF (2 mL) was added at a fast dropwise rate to the above organocerium reagent. The cold bath was left in place but not recharged and stirring was continued overnight. The resulting mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the

residue over silica gel (3 × 20 cm), using 5% EtOAc in hexane, gave **36.3** (0.08 g, 51%) as a yellow oil spectroscopically identical with material made from the lithium acetylide.

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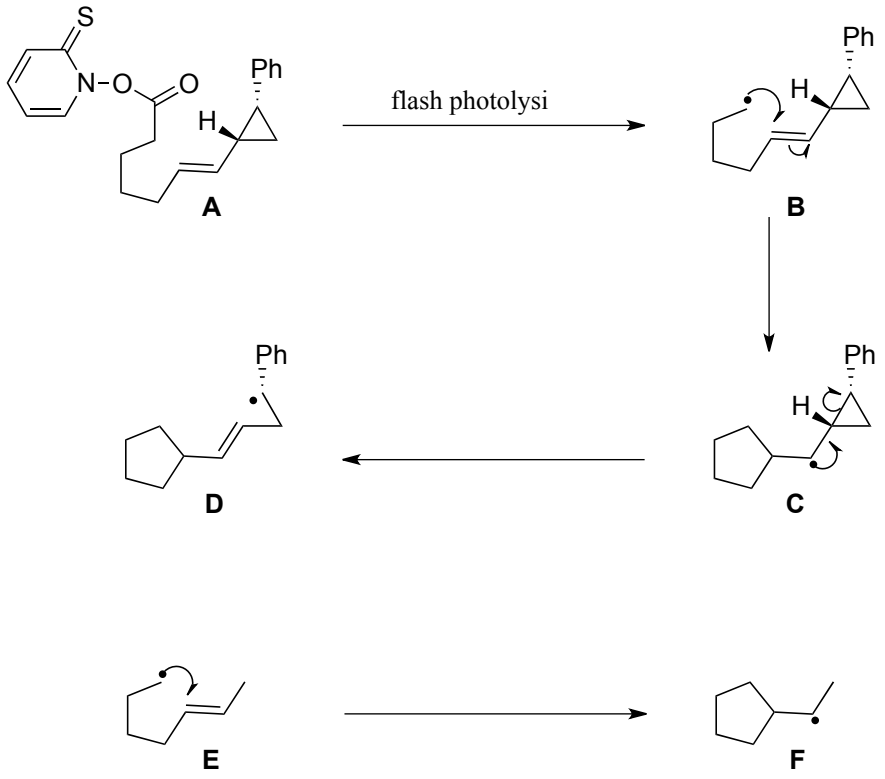
opening with a known rate constant of $>1 \times 10^{-11}$ sec^{-1} to generate radical **D**. Radical **D** can be detected by its UV spectrum and so its rate of formation can be measured. Therefore the much slower rate of cyclization of radical **B** can be calculated and is found to be 8.3×10^{-4} sec^{-1} at 25 °C. It has been established that the incorporation of the phenylcyclopropyl unit does not have an appreciable influence on the cyclization rate of corresponding radicals without the reporter unit. Hence the rate of cyclization of **E** (which cannot be detected by UV) can be assigned a value of 8.3×10^{-4} sec^{-1} at 25 °C.



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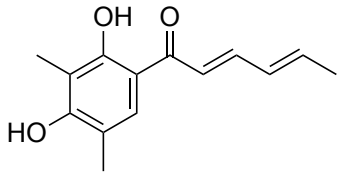
Chapter 2

Synthetic Studies on Sorbicillactone A

1. Introduction

1.1 Isolation of sorbicillinoids

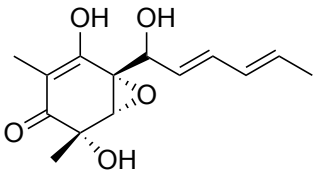
The sorbicillinoids were isolated by Cram and Tishler of Merck & Co. in 1948 from the fungus *Pencillium notatum*.[1] One of these compounds was named "Sorbicillin" (Scheme 1), and the structure was determined by a Japanese group.[2] Several years later, sorbicillin and several related compounds were isolated by Dreiding's group[3] from *Verticillium intertextum* and their structures were determined. For decades, many different groups have reported examples of the sobicillinoid family isolated from fungi. This family includes monomeric (Scheme 2), dimeric (Scheme 3) and trimeric members (Scheme 4), as well as vertinolides (Scheme 5) and nitrogen-containing sorbicillinoids (Scheme 6).[4]



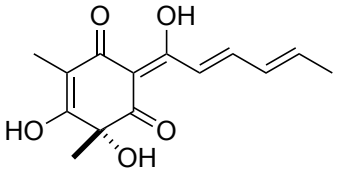
Scheme 1. Sorbicillin

1.2 Monomeric sorbicillinoids

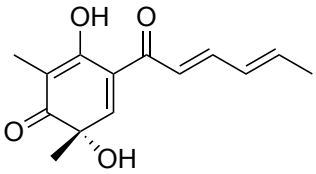
Crews's group[5] has reported the isolation of epoxysorbicillinol (**2.1**), which was isolated from the sponge *Trichoderma longibrachiatum*. They also isolated oxosorbicillinol (**2.2**). Dreiding's group proposed that oxosorbicillinol was formed biosynthetically through the intermediacy of **2.3**, but it was only after some 20 years that this compound (called sorbicillinol) was actually isolated, the work being done by Abe's group.[6]



epoxysorbicillinol (**2.1**)



oxosorbicillinol (**2.2**)

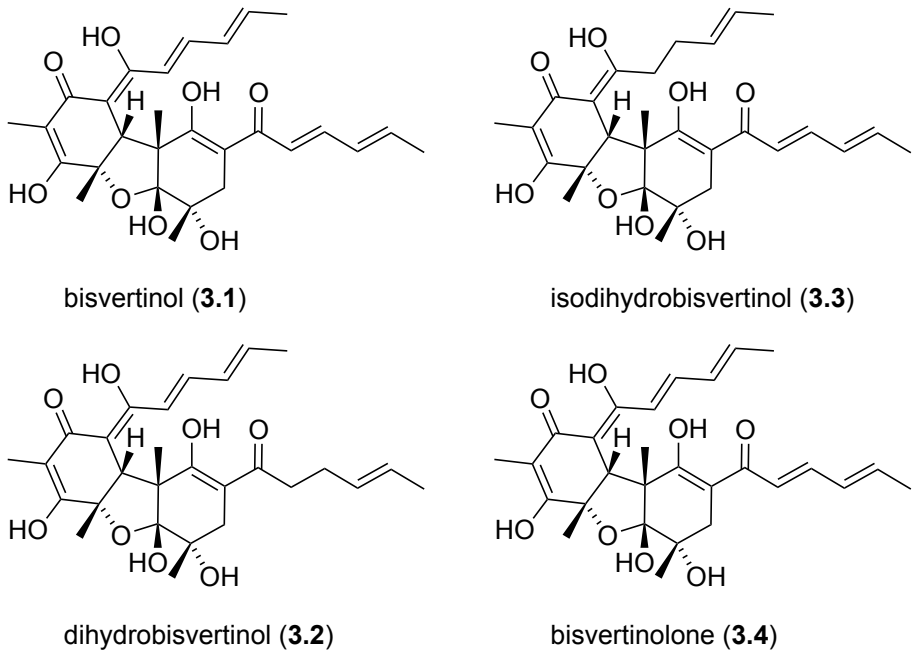


sorbicillinol (**2.3**)

Scheme 2. Monomeric sorbicillinoids

1.3 Dimeric sorbicillinoids

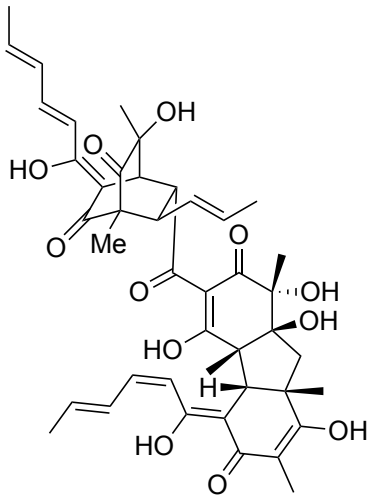
The bisvertinols are examples of dimeric sorbicillinoids having a [6.5.6]-tricyclic fused ring system. In early work, Dreiding's group[7] characterized bisvertinols which were isolated from *Verticillium intertextum*. These compounds were known as bisvertinol (**3.1)**, dihydrobisvertinol (**3.2**), isodihydrobisvertinol **(3.3)** and bisvertinolone (**3.4**). Many other groups have also isolated these compounds.



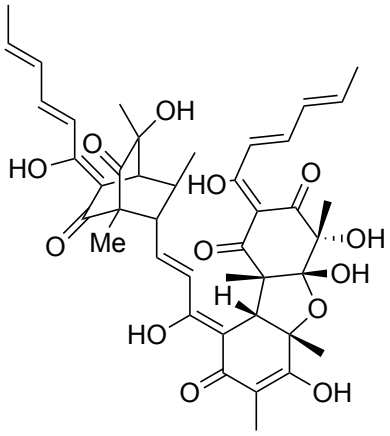
Scheme 3. Dimeric sorbicillinoids

1.4 Trimeric sorbicillinoids

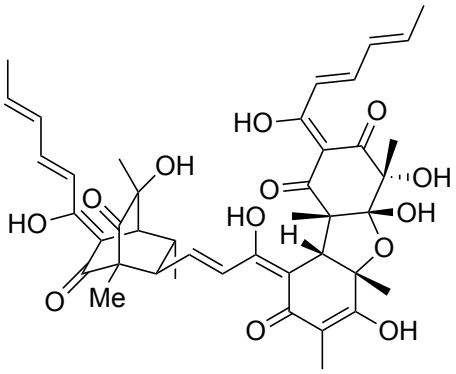
Since trisorbicillinone A (**4.1**) was isolated from the deep-sea fungus, *Phialocephala sp*. in 2007,[8] and also characterized, more examples of trisorbicillinones (e.g. **4.2**, **4.3**) were reported.[8,9] The biosynthesis of trisorbicillinone C was proposed and its bioactivities were reported.[8] The compound showed cytotoxicity against P388 and HL-60 cell lines with IC_{50} values of 9.10 and 3.14 μM, respectively.



trisorbicillinone A (**4.1**)



trisorbicillinone B (**4.2**)

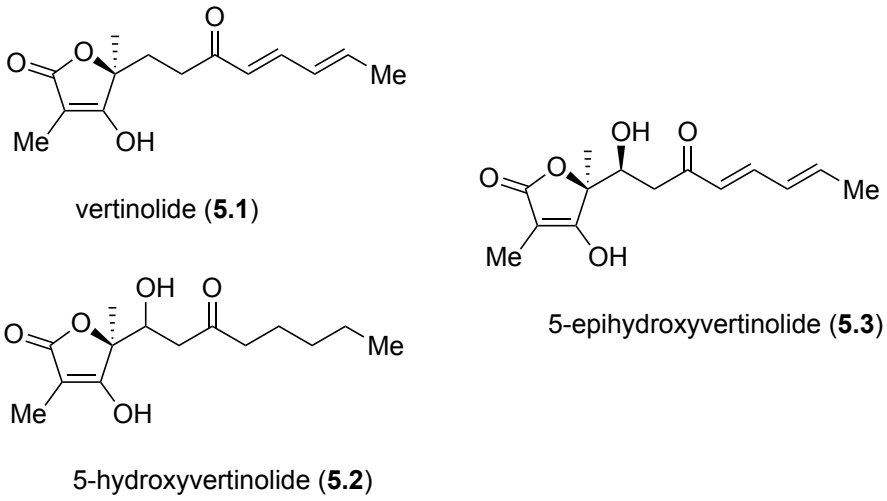


trisorbicillinone C (**4.3**)

Scheme 4. Sorbicillinoids

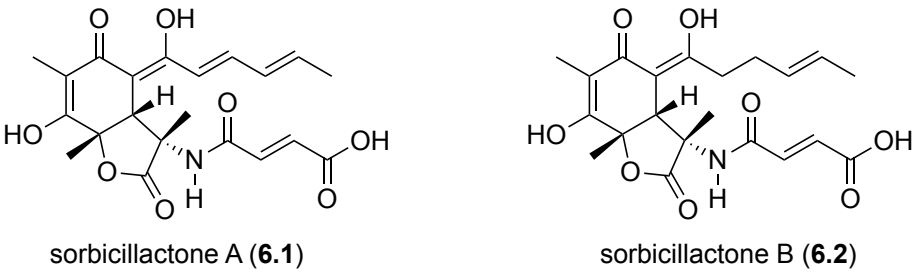
1.5 Vertinolides

Vertinolides are a part of the sorbicillinoid family. Since the initial work of Dreiding in 1981 other groups[10,11] have isolated these compounds and contributed to their structural assignment.



Scheme 5. Vertinolides

1.6 Nitrogen-containing sorbicillinoids



Scheme 6. Nitrogen-containing sorbicillinoids

The first isolation of sorbicillactones A (**6.1**) and B (**6.2**) was reported in 2005 by Bringmann's group.[12] Sorbicillactone A has strong biological activities, as described below. Nitrogen containing compounds are not common in the sorbicillinoid family[4] and only one group[13] has reported the total synthesis of sorbicillactone A (in racemic form). However, they did not accomplish the synthesis of optically pure sorbicillactone A and the racemic compound was slightly impure. My aim is to synthesize optically pure sorbicillactone A and I will describe later the approaches I have explored.

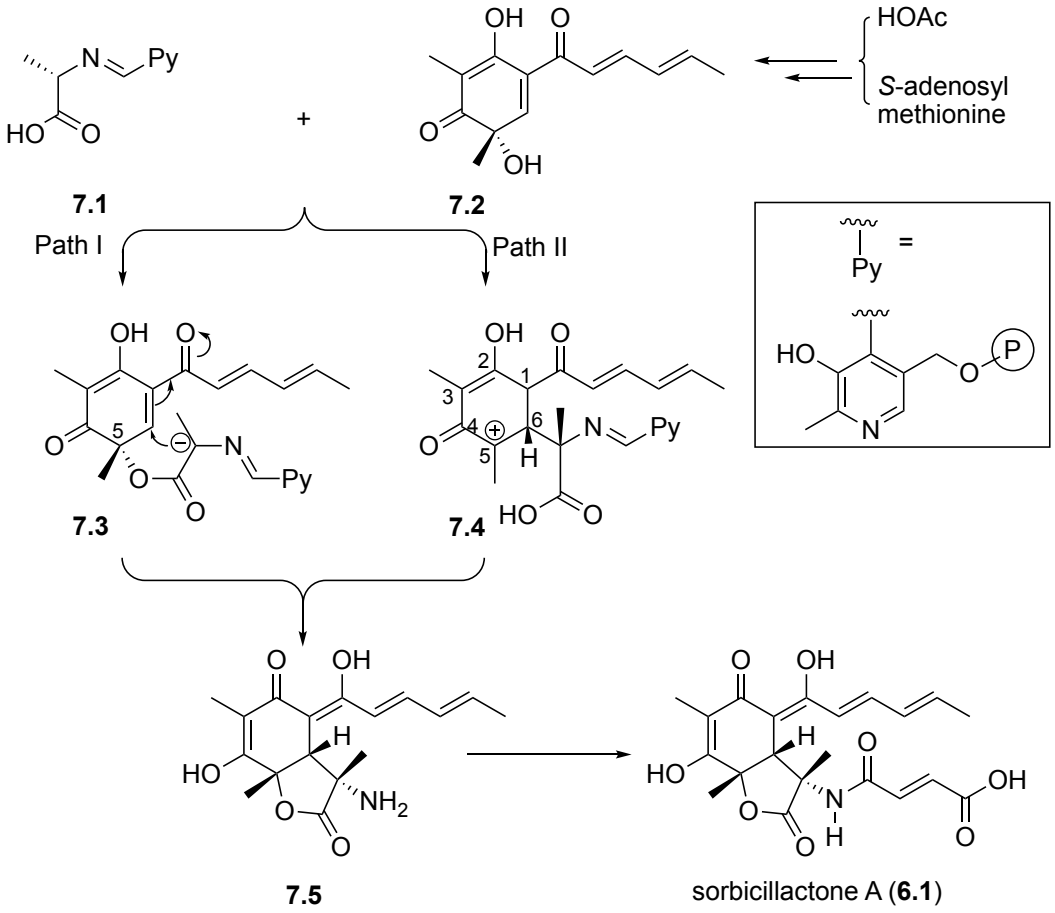
1.7 Biological properties of sorbicillactone A

Among the sorbicillinoid family of compounds, sorbicillactone A (**6.1**) and sorbicillactone B (**6.2**) have the most promising bioactivities.

Bringmann's group reported the biological properties of both sorbicillactone A (**6.1**) and sorbicillactone B (**6.2**).[14,15] Sorbicillactone A has cytotoxic and cytostatic activity against several cancer cell lines such as rat adrenal pheochromocytoma PC12 cells, human T lymphocytes H9 cells and human cervix carcinoma HeLa S3 cells. Most importantly, sorbicillactone A showed important activity against the murine leukemic lymphoblast L5178y cell line with an IC_{50} value of 2.2 μg/mL. Unfortunately, it has lower activity against other cell lines and the IC_{50} values were >10 μg/mL. In the case of sorbicillactone B, it was found to have a lower activity than sorbicillactone A against L5178y, PC13 and HeLa cells (IC_{50} >10 μg/mL).

In addition, sorbicillactone A (**6.1**) has high anti-HIV activity. In the concentration range of 0.3 to 3.0 mg/mL, sorbicillactone A was shown to protect human T lymphocytes (H9 cells) against the cytopathic effect of HIV-1, and it inhibited the expression of viral proteins. The effect of sorbicillactone A on the concentration of intracellular Ca^{2+} in primary neurons has also been examined. When neurons were incubated with L-glutamic acid or serotonin and Ca^{2+} there was a strong increase in the concentration of *intracellular* Ca^{2+}. However, pre-exposure of neurons to sorbicillactone A significantly suppressed the concentration of *intracelluar* Ca^{2+} in such experiments. As both L-glutamic acid and serotonin are important neurotransmitters, sorbicillactone A is a candidate of potential use in the study of neurochemistry. In summary, sorbicillactone A has selective anti-leukemic activities, antiviral and neuroprotective properties as well as anticancer activity. It is due to these diverse activities that sorbicillactone A is a potential lead structure in medicinal chemistry.[12]

1.8 Biosynthesis of sorbicillactone A



Scheme 7. Biosynthesis of sorbicillactone A

The sorbicillinoids are found in fungi of the penicillium family Bringmann's group[12] has proposed a biosynthetic route (Scheme 7) to sorbicillactone A (**6.1**) on the basis of labeling and feeding experiments. To start with, the sorbicillinol unit (**7.2** = **2.3**) is obtained via the reaction between acetate and *S*-adenosyl methionine. A Schiff base is generated from alanine with pyridoxal phosphate. The resulting imine carboxylic acid **7.1** reacts with the tertiary hydroxyl group of **7.2** to provide the intermediate imine ester **7.3**. After deprotonation of the α proton of the imine, cyclization occurs to give a bicyclic lactone through intramolecular Michael addition

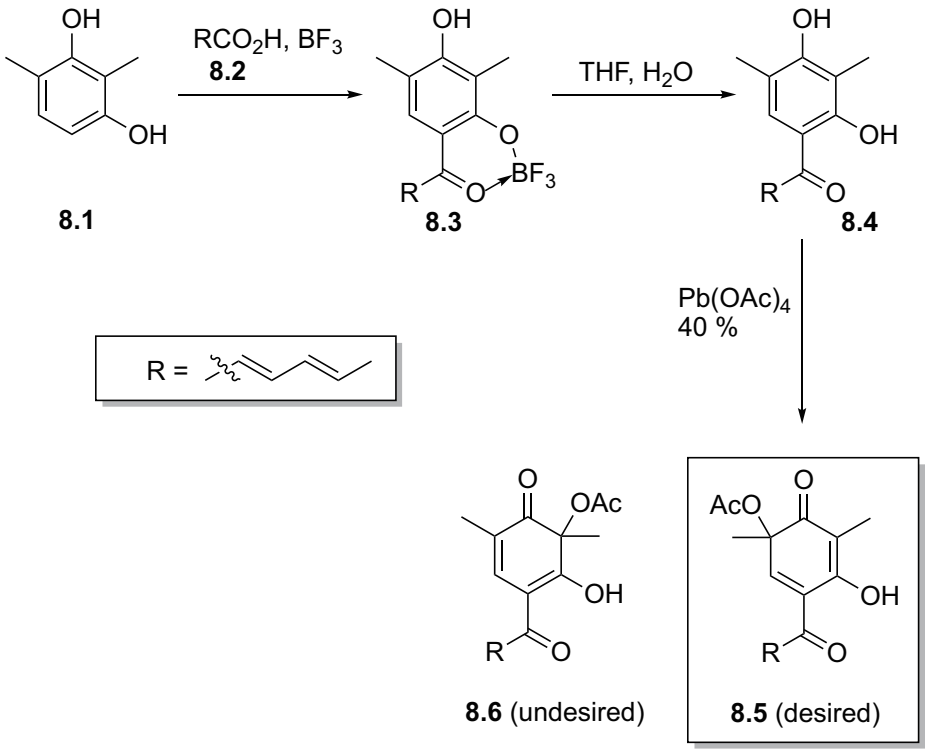
(Path I). The other route proposed was that Michael addition occurred first to generate the intermediate **7.4** and then cyclization takes place to give the bicyclic lactone (Path II) after generation of a carbocation at C-5. Of the two mechanisms, path I was regarded as a better route to generate the *cis*-fused ring system because the stereochemistry at C-5 is retained when the C,C-bond is formed since the stereochemistry of the hydroxyl is already established. However, in path II, the cyclization occurs after generating the carbocation, and then ring cyclization happens. When the carbocation is formed, the stereochemistry is lost at C-5. Finally, the bicyclic lactone amine **7.5** is acylated to yield sorbicillactone A (**6.1**). This argument in favor of path I is flimsy because **7.4** is also likely to cyclize to give *cis* ring fusion.

1.9 Attempted synthesis of sorbicillactone A and related compounds

1.9.1 Nicolaou's total synthesis of sorbicillinoids and analogues[16]

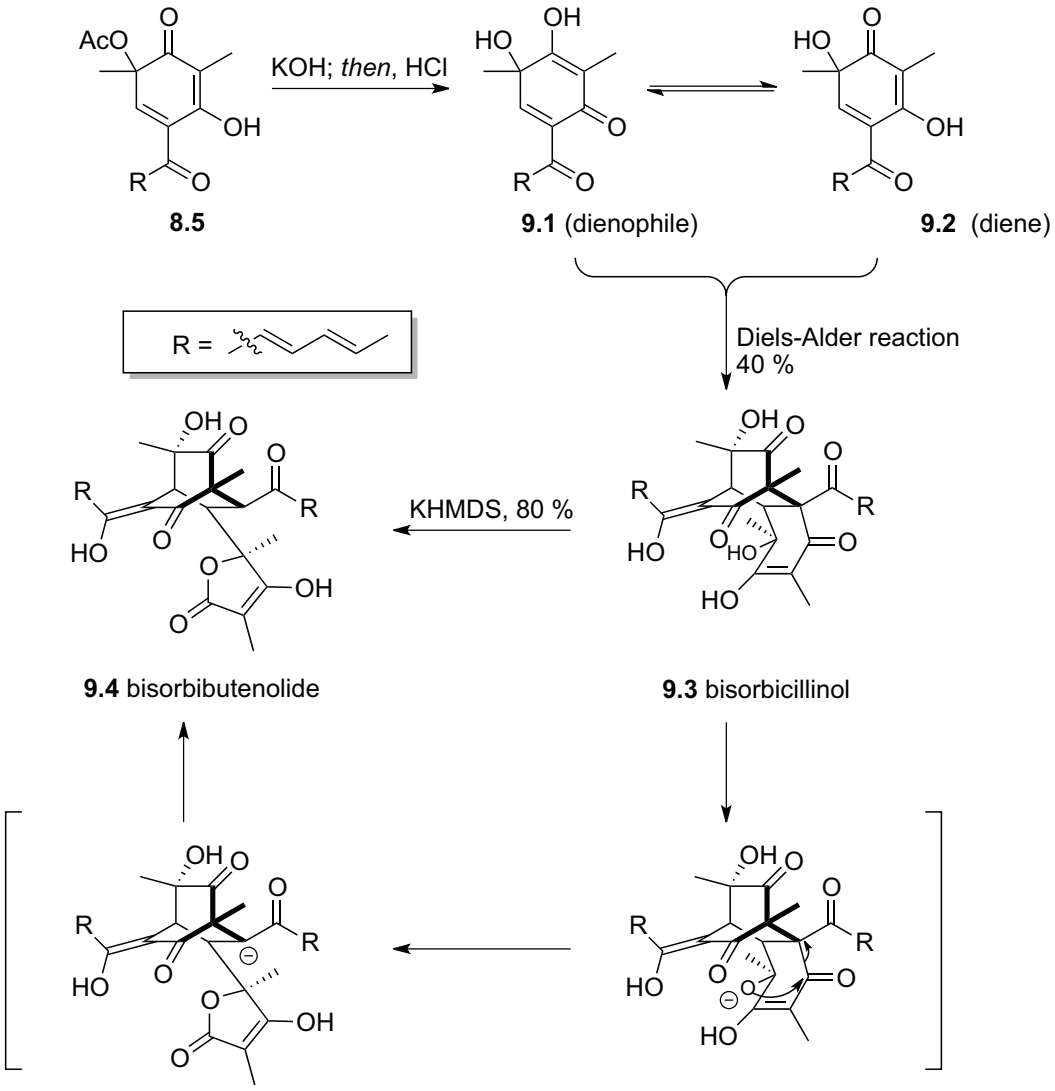
The bisorbicillinoids are very popular synthetic targets and they also have interesting biological activities. In 2000, Nicolaou's group reported the synthesis of bisorbicillinol (**9.3**), bisorbibutenolide (**9.4**) and analogues of the bisorbicilloids (see Scheme 9).

2,4-Dimethylresorcinol **8.1** (Scheme 8) was reacted with carboxylic acid **8.2** in the presence of BF_3 to generated the boron complex **8.3** by Friedel-Craft acylation. Subsequent quenching of the reaction mixture with aqueous THF as a



Scheme 8. Synthesis of acetate from resorcinol

cosolvent produced **8.4**. This compound was treated with lead tetraacetate and acetic acid to yield a 5:1 mixture of **8.5** and **8.6.** The isolated yield of the mixture was 40%. It was possible to isolate enantiomerically pure **8.5** by HPLC using a chiral column and the material was used in Nicolaou's synthesis of bisorbicillinol (**9.3**) and a number of analogs, the results being reported in 2000.



Scheme 9. Total synthesis of Bisorbicillinol (**9.3**) and Bisorbibutenolide (**9.4**)

The α-acetoxy diene **8.5** was treated with KOH to give dienophile **9.1** (Scheme 9) and diene **9.2** which provided the desired product (**9.3**) in 40% yield through a Diels-Alder reaction. NMR studies showed that the diene and dienophile are in rapid equilibrium. The optical rotation of the product **9.3** was $[\alpha]^{25}_{D}$ +171.5 (*c* 0.2, MeOH) which was reasonably close to the literature value of $[\alpha]^{25}_{D}$ +195.2 (*c* 0.2, MeOH). From this result, it was clear that the Diels-Alder reaction,

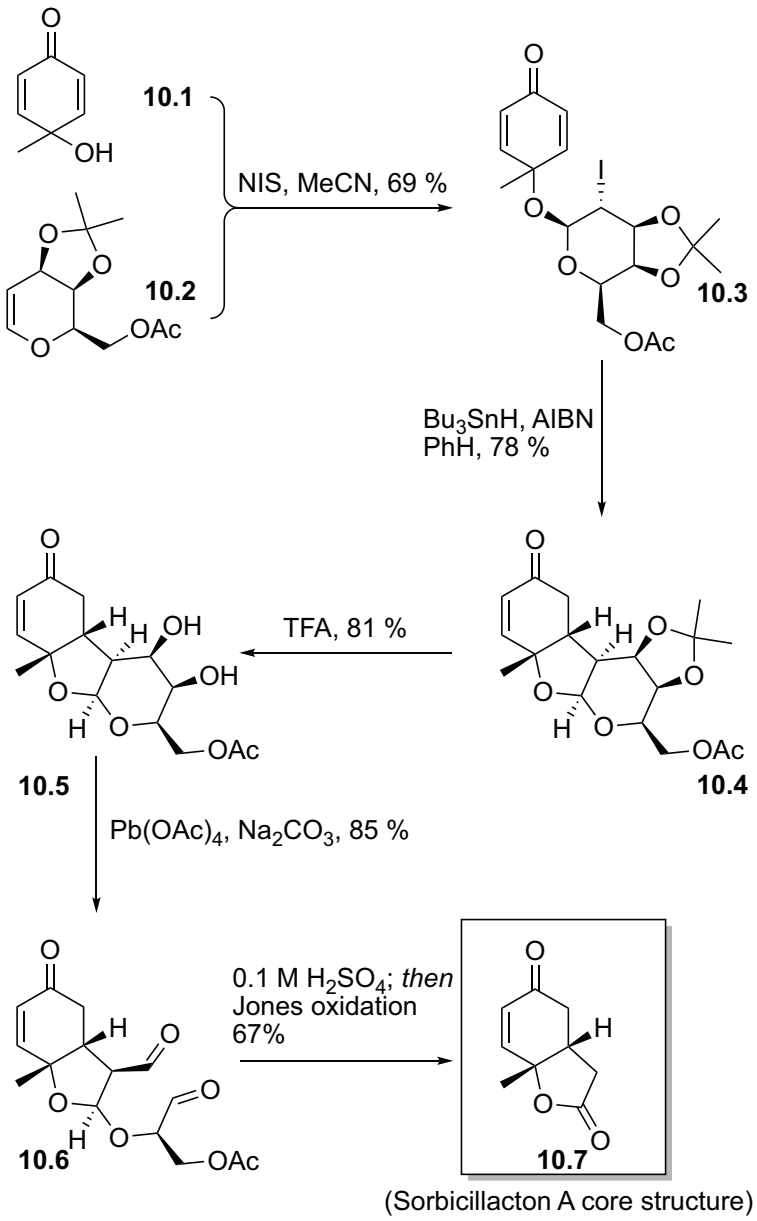
which generated the four stereogenic centers, was regio- and diastereoselective. Interestingly, the α-*acetoxy* diene **8.5** did not undergo the Diels Alder reaction.

Based on Abe's[17] proposal for the biosynthesis, bisorbicillinol **9.3** was then converted into bisorbibutenolide **9.4** in a biomimetic fashion. To this end, the Nicolaou group used an anionic rearrangement induced by KHMDS. After deprotonation of the tertiary alcohols in **9.3** rearrangement occurred to yield bisorbibutenolide **9.4.** This biomimetic route was used for the total synthesis of several other sorbicillinoids.

1.9.2 Clive's synthesis of the optically pure core structure of sobicillactone A[18]

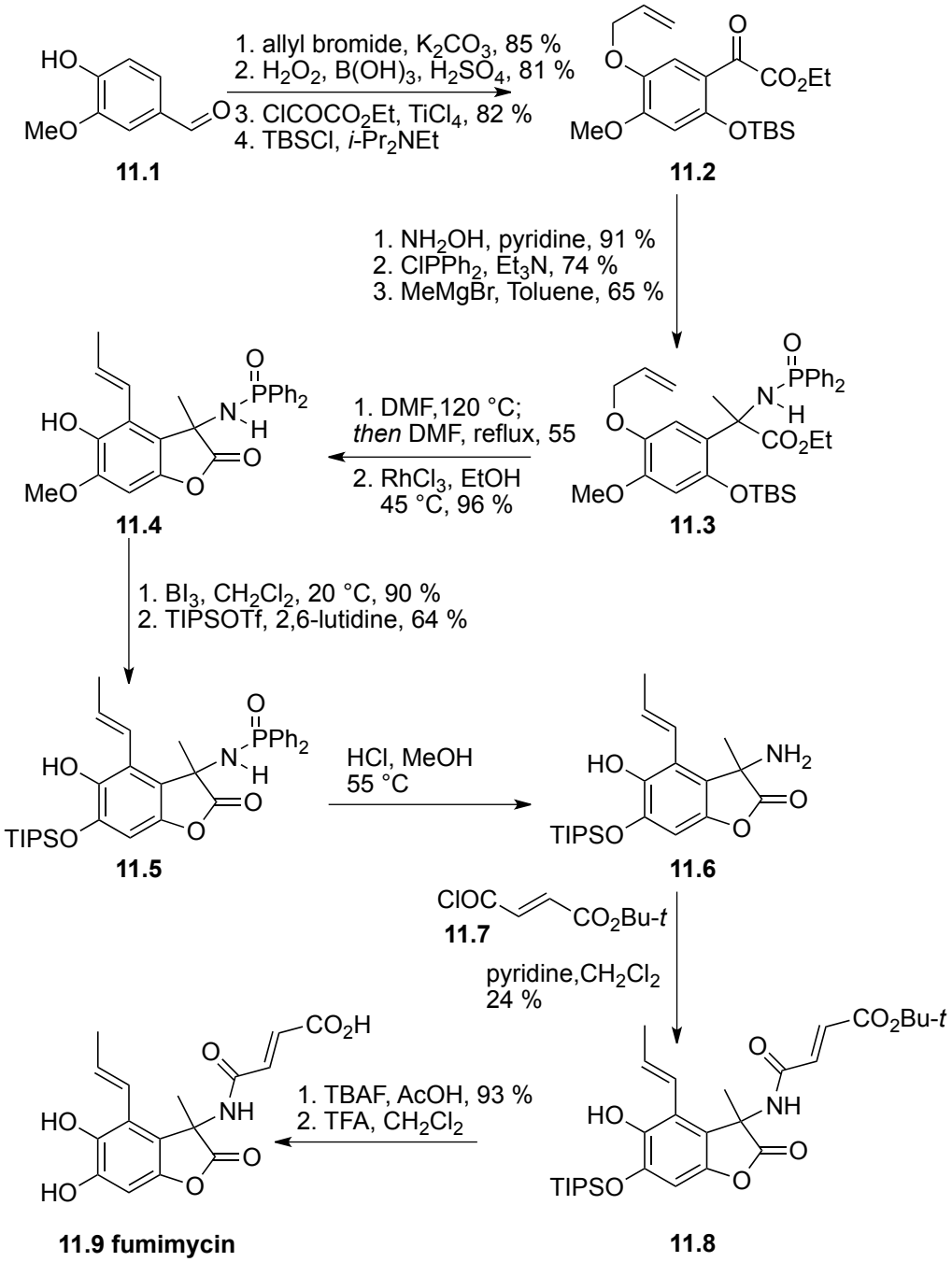
In 2010, Clive's group reported the synthesis of the optically pure lactone **10.7** by using a radical cyclization. The absolute configuration of the bicyclic lactone **10.7** is identical to that of the core structure of sorbicillactone A.

In the presence of NIS, the tertiary alcohol **10.1** was reacted with **10.2** to generate an iodoether **10.3**. This underwent radical cyclization in the presence of tributyltin hydride and AIBN to provide **10.4**. Subsequently, acid hydrolysis of **10.4**, using aqueous CF_3CO_2H, provided the diol **10.5** (81%). This step was followed by treatment with $Pb(OAc)_4$ to give dialdehyde **10.6** (85%). It was found that acid hydrolysis with 0.1 M H_2SO_4, followed by Jones oxidation of the resulting crude product, gave the lactone **10.7** in 65% yield over the two steps. This compound is the core of sorbicillactone A in correct optically pure form. This optically pure lactone should be a promising intermediate for the total synthesis of solbicillactone A.



Scheme 10. Construction of the optically pure core of sorbicillactone A

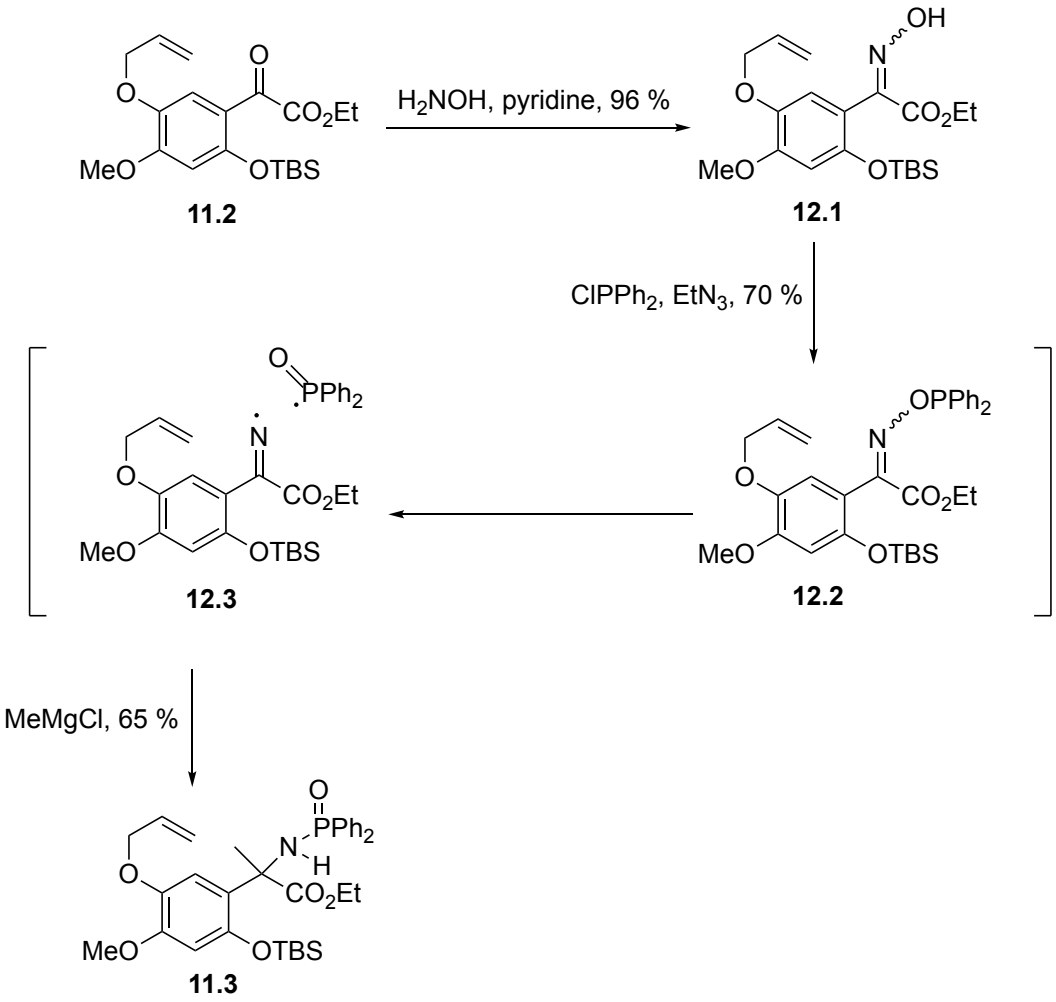
1.9.3 Brase's total synthesis of fumimycin[19]



Scheme 11. Total synthesis of fumimycin

Kim's group[20] reported the structure and biological activity of fumimycin in 2007, and Bräse's group completed the total synthesis of the compound in 2010.[19] Fumimycin has a similar lactone structure to sorbicillactone A. Both compounds have a quaternary center adjacent to the lactone carbonyl and the amino group is acylated in both compounds.

Vanillin **11.1** was used as the starting material which was allylated by treatment with allyl bromide in the presence of K_2CO_3. Then a Dakin oxidation was performed by using H_2O_2 and $B(OH)_3$. The resulting compound underwent Friedel-Crafts acylation with EtO_2CCOCl and $TiCl_4$ and the phenolic hydroxyl was protected through silylation to give ketone **11.2**. The ketone was converted to an oxime on reaction with NH_2OH and the oxime was further transformed to a diphenylphosphosphoroso imine. 1,2-Addition of MeMgBr to the imine yielded the (diphenylphosphoroso)amino compound **11.3** (see Scheme 12). A Claisen rearrangement was then used to introduce the three-carbon unit directly onto the benzene ring and isomerization of the terminal double bond of the resulting allyl pendant was achieved by the action of rhodium chloride. Under the high temperature conditions of the Claisen rearrangement the TBS group was lost and so lactone **11.4** was generated. The material was a 10:1 *trans*:*cis* isomer mixture and the desired *trans* compound was isolated by column chromatography over silica gel impregnated with $AgNO_3$.[21] Demethylation occurred on treatment with BI_3 to generate the *ortho* bis phenol. Selective mono silylation gave **11.5**. The (diphenylphosphoroso)amine **11.5** was hydrolyzed under acidic conditions in the presence of the silyl group to give the desired amine **11.6** as its hydrochloride salt. The free amine was acylated with acid chloride **11.7** to give **11.8**. Finally, cleavage of the silyl group with TBAF and hydrolysis of the ester using CF_3CO_2H provided fumimycin (**11.9**).

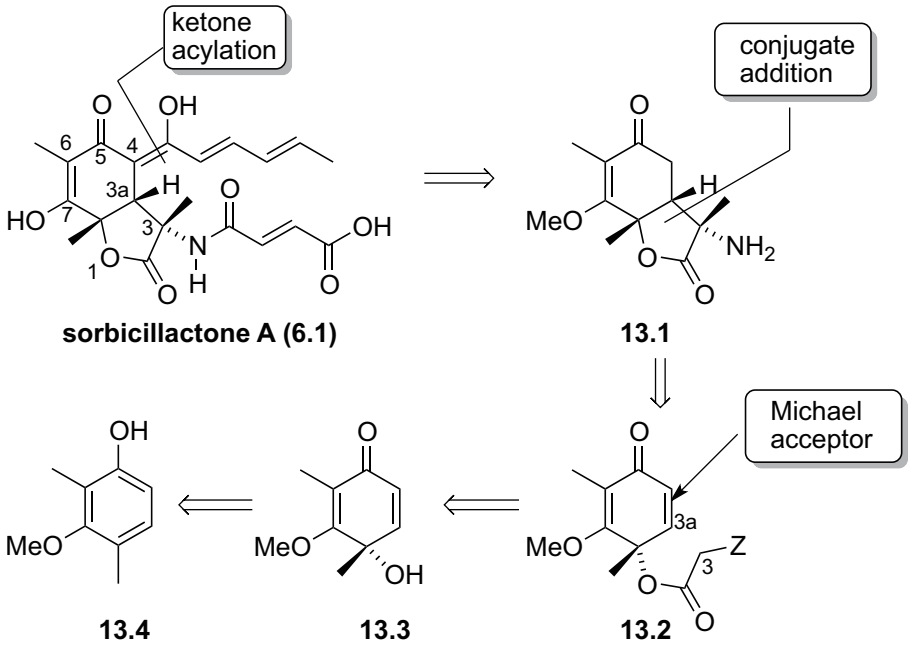


Scheme 12. Key step in the total synthesis of fumimycin

The key process in this synthesis is the installation of the amino group by using phosphorus chemistry. The N-$OPPh_2$ bond in **12.2** underwent homolytic cleavage to generate the two kinds of radical shown in **12.3**. One was a nitrogen-centered radical and the other was a phosphorus centered radical. Recombination of the two yielded a diphenylphosphoroso imine which reacted with methylmagnesium bromide.

1.9.4 Harned's total synthesis of racemic sorbicillactone A[13]

In 2011, Harned's group reported the first and only total synthesis of sorbicillactone A.



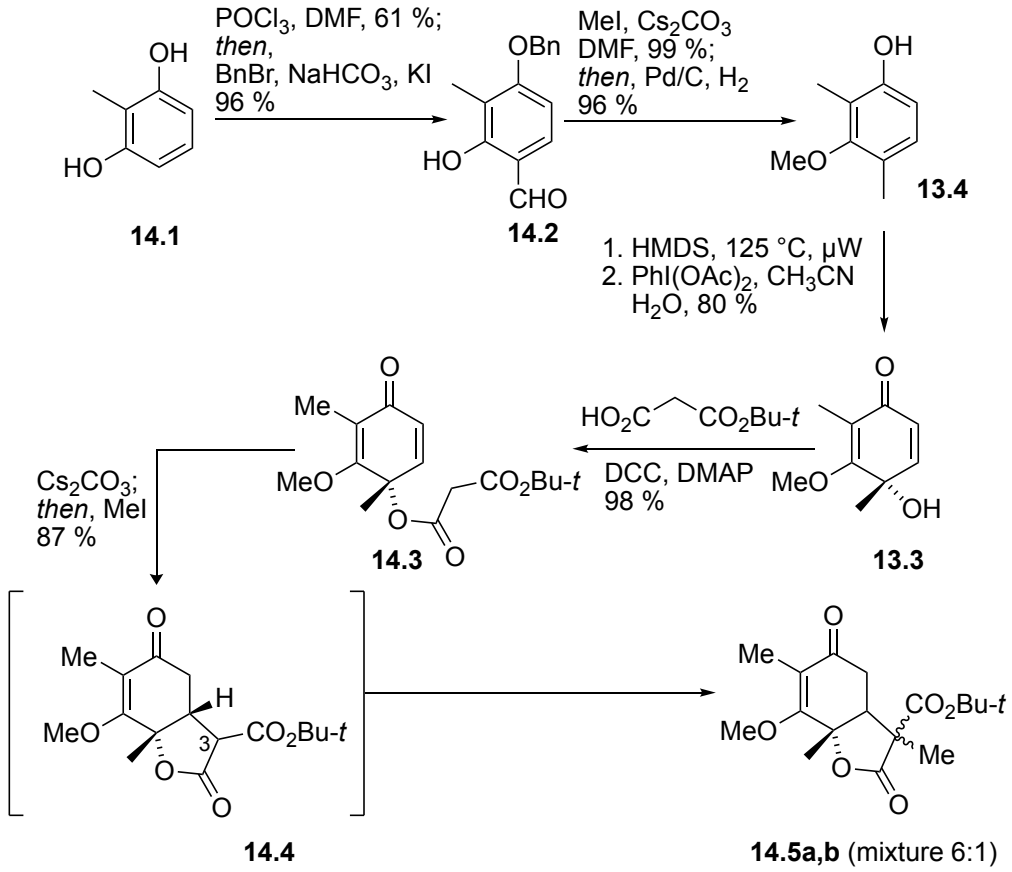
Scheme 13. Retrosynthesis of sorbicillactone A from Harned's group

To reach their synthetic target, they proposed the above retrosynthesis of sorbicillactone A. The key step was to construct the C-3–C-3a bond (see **13.2**) to give the bicyclic lactone **13.1** through Michael addition of **13.2,** where *Z* is an activating group to support a negative charge on the adjacent carbon (C-3). The alcohol **13.3** was to be obtained by oxidizing phenol **13.4**.

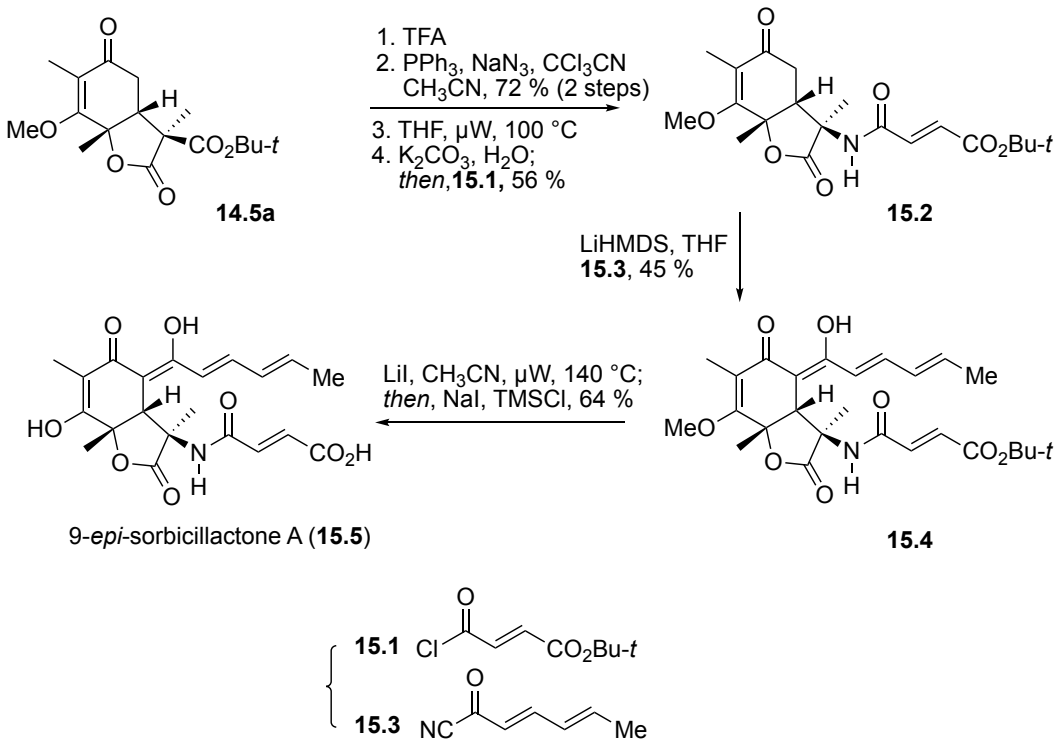
2-Methylresorcinol (**14.1**) was the starting material. First a formyl group was installed by using $POCl_3$ with DMF, and then selective benzylation of the less hindered hydroxyl and methylation of the other hydroxyl were carried out (Scheme 14). The aldehyde group was reduced by exhaustive hydrogenolysis to give **13.4**. Oxidation took place on treatment with $PhI(OAc)_2$ to give quinol **13.3** in high yield. The hydroxyl group was acylated by reaction with malonic acid *t*-butyl ester in the presence of DCC to generate dienone **14.3**. This dienone

underwent intramolecular Michael addition on treatment with Cs_2CO_3 to provide the desired core structure **14.4** of sorbicillactone A .

The resulting bicyclic lactone was alkylated with MeI to give **14.5a**,**b** as a 6:1 mixture of isomers.



Scheme 14. Synthesis of sorbicillactone A core structure

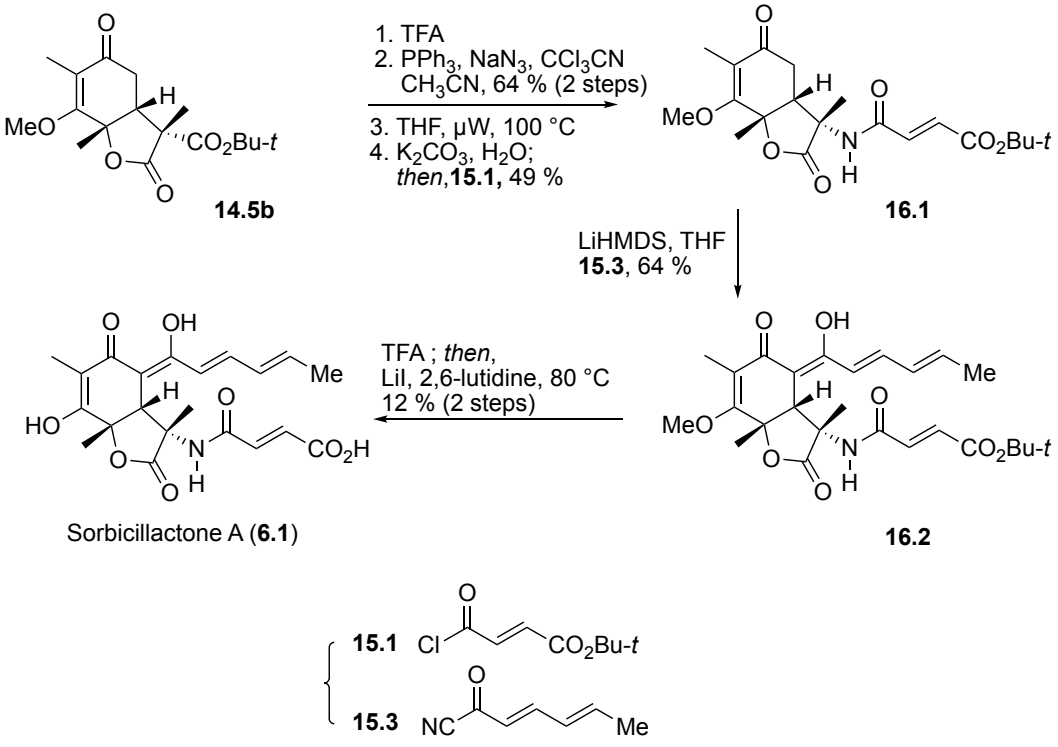


Scheme 15. Synthesis of 9-*epi*-sorbicillactone A

Unfortunately, the major isomer (**14.5a**) had the wrong stereochemistry α to the lactone carbonyl. However, by working on a large scale it was possible to get over 1 g of the desired diastereomeric compound **14.5b** (see Scheme 16). In addition, **14.5a** was used to practice the remaining steps leading to *epi*-sorbicillactone A (Scheme 15) and later similar methods were applied to obtain natural sorbicillactone A.

With **14.5a** in hand, the ester group was converted to an acyl azide (Scheme 15) and subsequently this underwent Curtius rearrangement. The resulting free amine was acylated with **15.1** to give amide **15.2**. The ketone was reacted with LiHMDS to generate an enolate which underwent acylation with **15.3** to provide **15.4**. Finally, demethylation with LiI, and deprotection of the *tert*-butyl ester was performed by using NaI and TMSCl to give 9-*epi*-sorbicillactone A (**15.5**). With this successful pathway established, the Harned group was able to use a very

similar sequence to complete the total synthesis of the desired natural sorbicillactone A. For reasons that are not understood the exact same sequence proved unsuitable when applied to compounds with the natural stereochemistry. Also, the final synthetic sorbicillactone A was not absolutely pure, as judged by the ^{1}H NMR spectrum.



Scheme 16. Completed total synthesis of sorbicillactone A

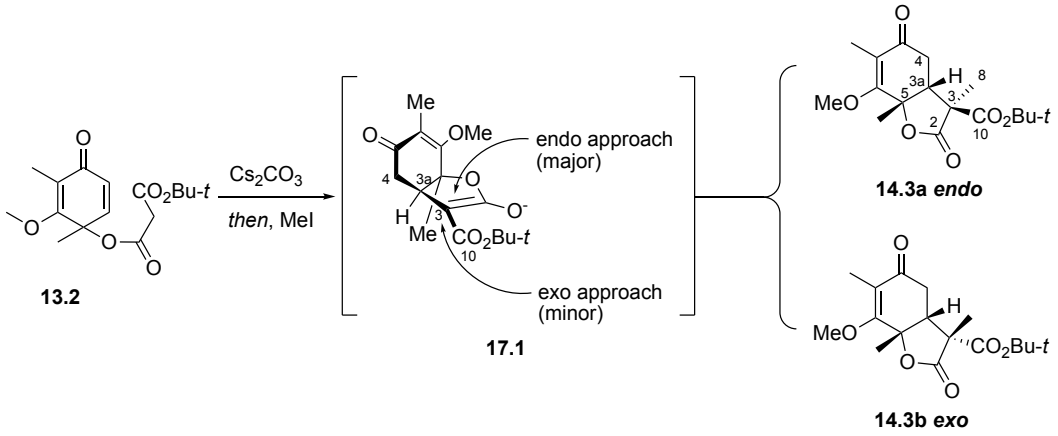
In the case of the desired diastereomeric intermediate **14.5b** (Scheme 16), the acyl azide was formed by using a Curtius rearrangement as in the *epi*-series. The free amine was converted to amide **16.1**, followed by aldol condensation to provide **16.2**. Finally, the ester group was deprotected to a carboxylic acid and subsequently the methyl group on the methoxy substituent was removed by using LiI and 2,6-lutidine to provide pure sorbicillactone A. This was the first and, so far, the only synthesis of sorbicillactone A. However, the total yield was very low. Our

aim is to generate optically pure sorbicillactone A in a stereocontrolled manner by using the optically pure bicyclic lactone made through the radical cyclisation of Scheme 10.

As indicated above, Harned's group found an interesting and unexpected stereochemical outcome when they tried to alkylated their bicyclic lactone.[13] They predicted that the alkylation of the bicyclic lactone **14.4** should occur by approach from the convex (*exo*) face, to generate the correct stereocenter at C-7. However, the major compound was **14.5a**.[22] This meant that when the electrophile (MeI) approached the intermediate anion, it must have approached the crowed concave (*endo*) face. This was unexpected because approach of an electrophile from the convex face of related bicyclic lactones is well-precedented.[23]

Harned's group has suggested an explanation for this unusual stereochemical outcome. They found that carbon-based electrophiles larger than methyl iodide were quite selective in approaching the convex (*exo*) face. On the other hand, alkylation with MeI occurred from the concave (*endo*) face of the bicyclic lactone system. To understand this unusual result, they performed computational studies. The results showed that the stereoselectivity is due to energy differences between a staggered transition state with less torsional strain and an avoidance of steric interactions. Computational studies showed the *endo* transition states were of lower energy than the *exo* transition states. The calculations show that when the electrophile approaches from the *endo* face, the dihedral angle between C-10–C-3 and C-3a–C-4 is ~ 75º, but when from the *exo* face the angle is only 15º. This compression of the dihedral angle creates a torsional strain and increases the energy of the *exo* transition state. Another reason was that the C-3a–C-3–C-8 bond angle in the *endo* transition state (~115º) is lager than in the *exo* transition state (~104º). The larger angle avoids excessive steric hindrance with the cyclohexenone ring as the methyl group approaches C-3. However, when the size of electrophile is bigger, severe steric

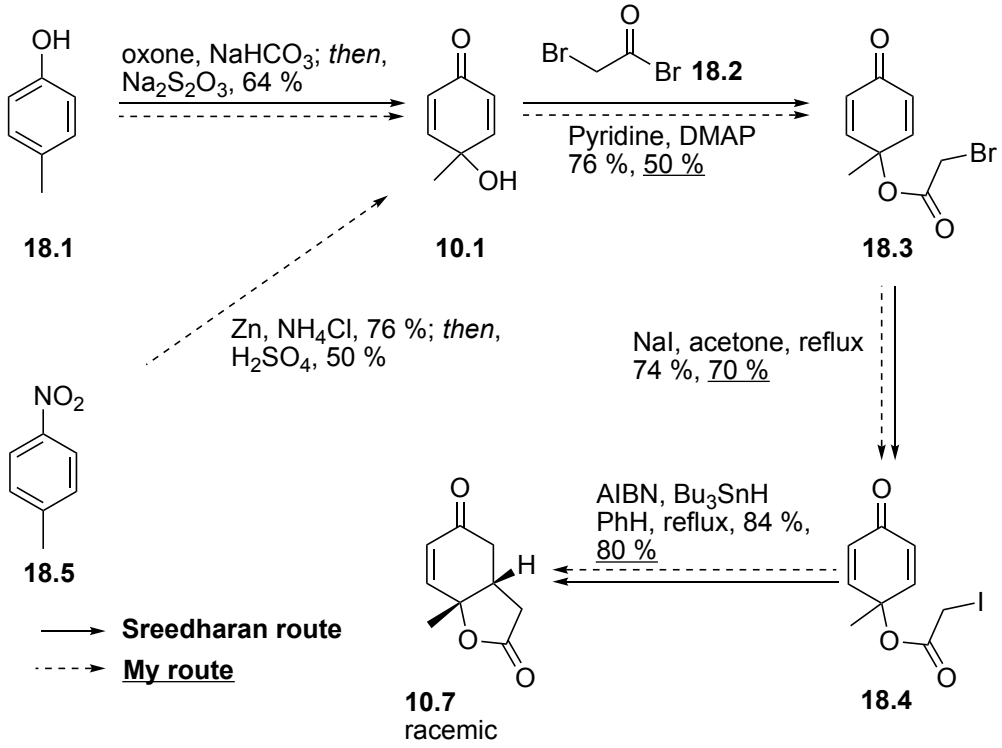
hindrance with the cyclohexenone ring is generated in an *endo* face approach. Therefore, in that case the reaction pathway is via an *exo* face approach.



Scheme 17. Harned's group explanation for unusual stereochemical outcome

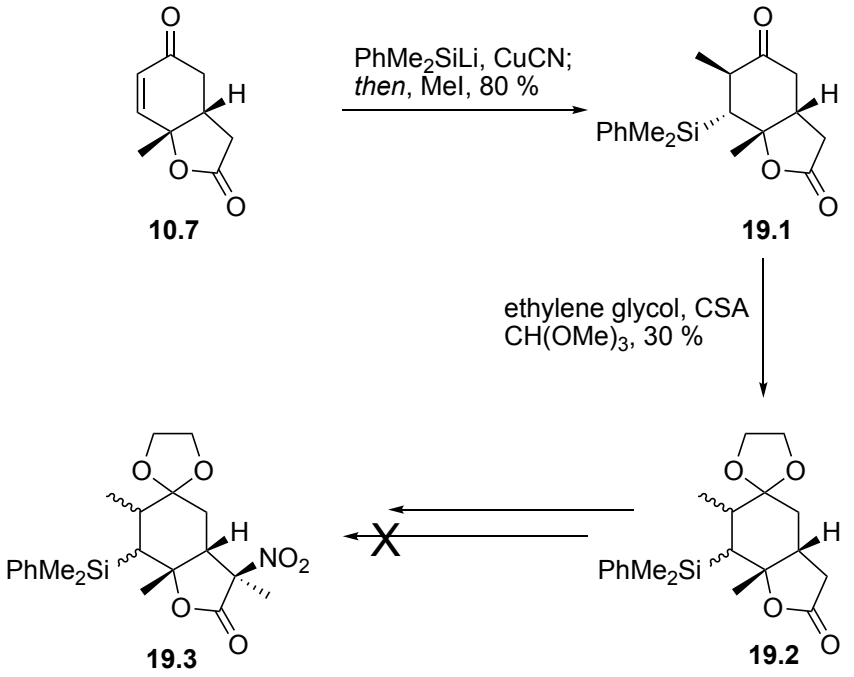
2. Results and Discussion

Our plan for the total synthesis of sorbicillactone A (**6.1**) involved starting from commercially available *p*-cresol (**18.1**), and much exploration of this plan was carried out by Dr. Dinesh Sreedharan.[24] The *p*-cresol was oxidized with Oxone in the presence of $NaHCO_3$, following a procedure described by Carreño and co-workers,[25] to generate cyclohexadienone **10.1**. The hydroxyl group of **10.1** was acylated by treatment with bromoacetyl bromide in the presence of pyridine to give acyl bromide **18.3**, and the bromide was converted to the corresponding iodide through a Finkelstein reaction with NaI to provide compound **18.4**, the precursor for a radical cyclization step. This cyclization was achieved by reaction with tributyltin hydride and AIBN to yield the racemic lactone **10.7**.



Scheme 18. Approach for synthesis of sorbicillactone A

First of all, Dr. Sreedharan prepared compound **19.1** (Scheme 19) by treating bicyclic lactone **10.7** with $PhMe_2SiLi$ and CuI and trapping the intermediate enolate with MeI. The ketone group was protected by treatment with ethylene glycol under acidic conditions to generate the ketal **19.2**. However, this approach was unsatisfactory. First, the preparation of cyclohexadienone **10.1** from *p*-cresol **18.1** was an unreliable procedure and the yield varied greatly. Secondly, when the ketone was protected, the yield was very low, as reported by Dr. Sreedharan and, on repeating this experiment, I found that the lactone ring opened. Thirdly, with the cyclic ketals **19.2** in hand, although only in very small quantities, it was impossible to install both the amino and methyl groups on the lactone ring. For these reasons, I tried to optimize and modify the route.



Scheme 19. Sreedharan's approach for synthesis of sorbicillactone A

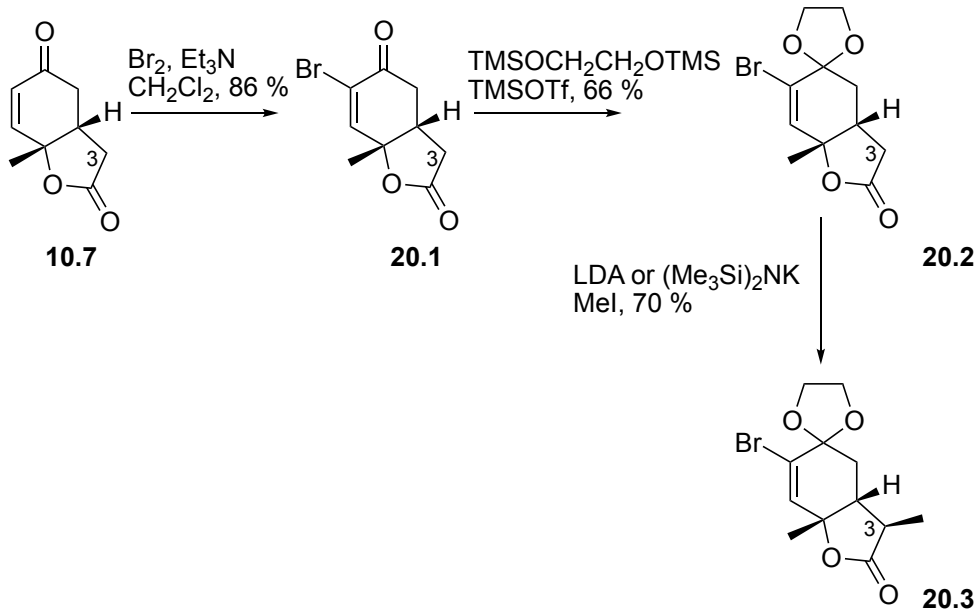
My own synthetic studies (see Scheme 18) towards sorbicillactone A began with *p*-nitrotoluene (**18.5**) which was reduced with Zn in the presence of NH_4Cl, to give

cyclohexadienone **10.1**.[26] This modified method gave an acceptable and reproducible yield (50%), provided the reaction mixture was continuously extracted with ether about 7 days). Acylation of the hydroxyl group of **10.1** with bromoacetyl bromide (**18.2)** produced **18.3**, which was then subjected to Finkelstein reaction with NaI to give **18.4**. The iodide **18.4** underwent radical cyclization under standard conditions, giving the cyclized product **10.7**, as reported by Dr. Sreedharan.

After synthesis of the bicyclic core **10.7**, Dr. Sreedharan studied the installation of the amino group on the lactone ring and, later, I continued these studies.

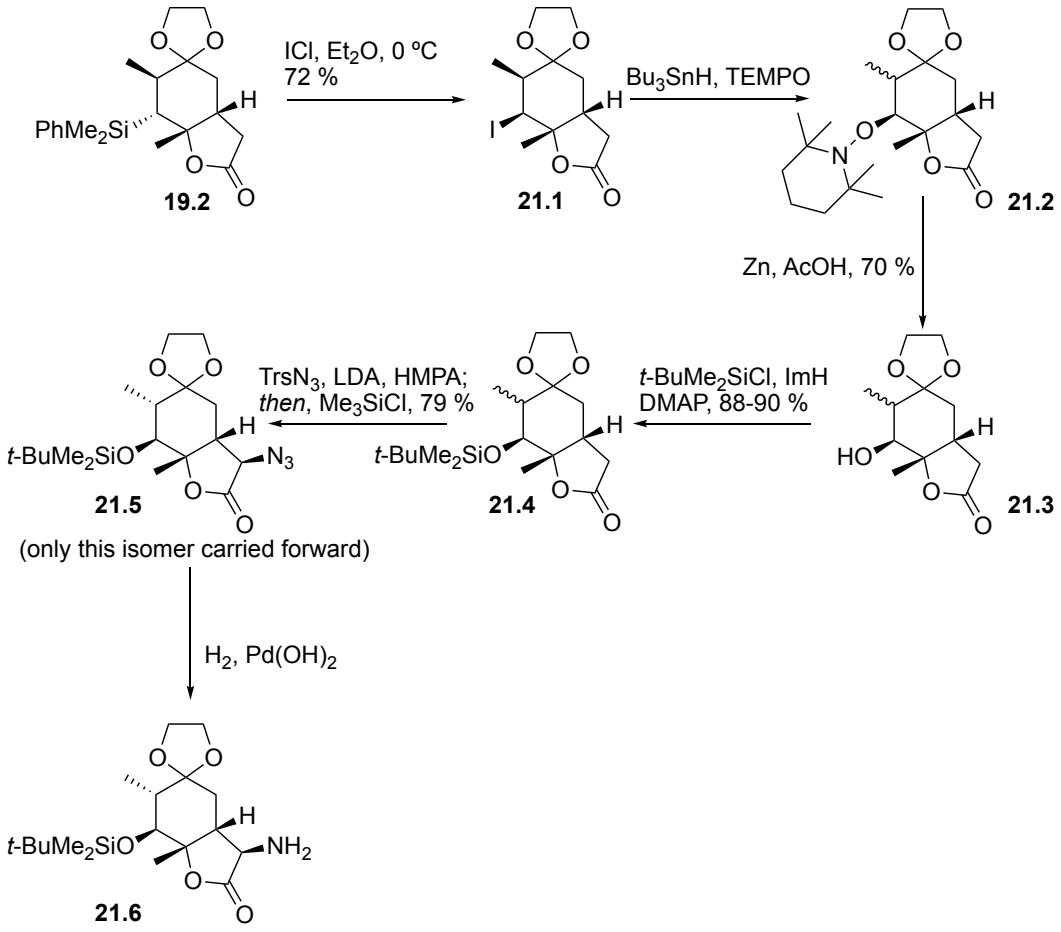
Initially, he attempted to install a methyl group at C-3 on the lactone ring. The first approach started with bromination of **10.7** by treatment with Br_2 and Et_3N, to give the bromo compound **20.1**. The ketone was protected as a ketal, using 1,2-bis(trimethylsiloxy)ethane in the presence of $Me_3SiOSO_2CF_3$. The desired methylated bicyclic lactone **20.3** was then obtained by standard methylation and the structure was confirmed by X-ray crystallographic analysis.

From the stereochemical outcome, in particular the orientation of the C-3 methyl group in **20.3** it was clear that the amino group should be installed before



Scheme 20. Sreedharan's approach

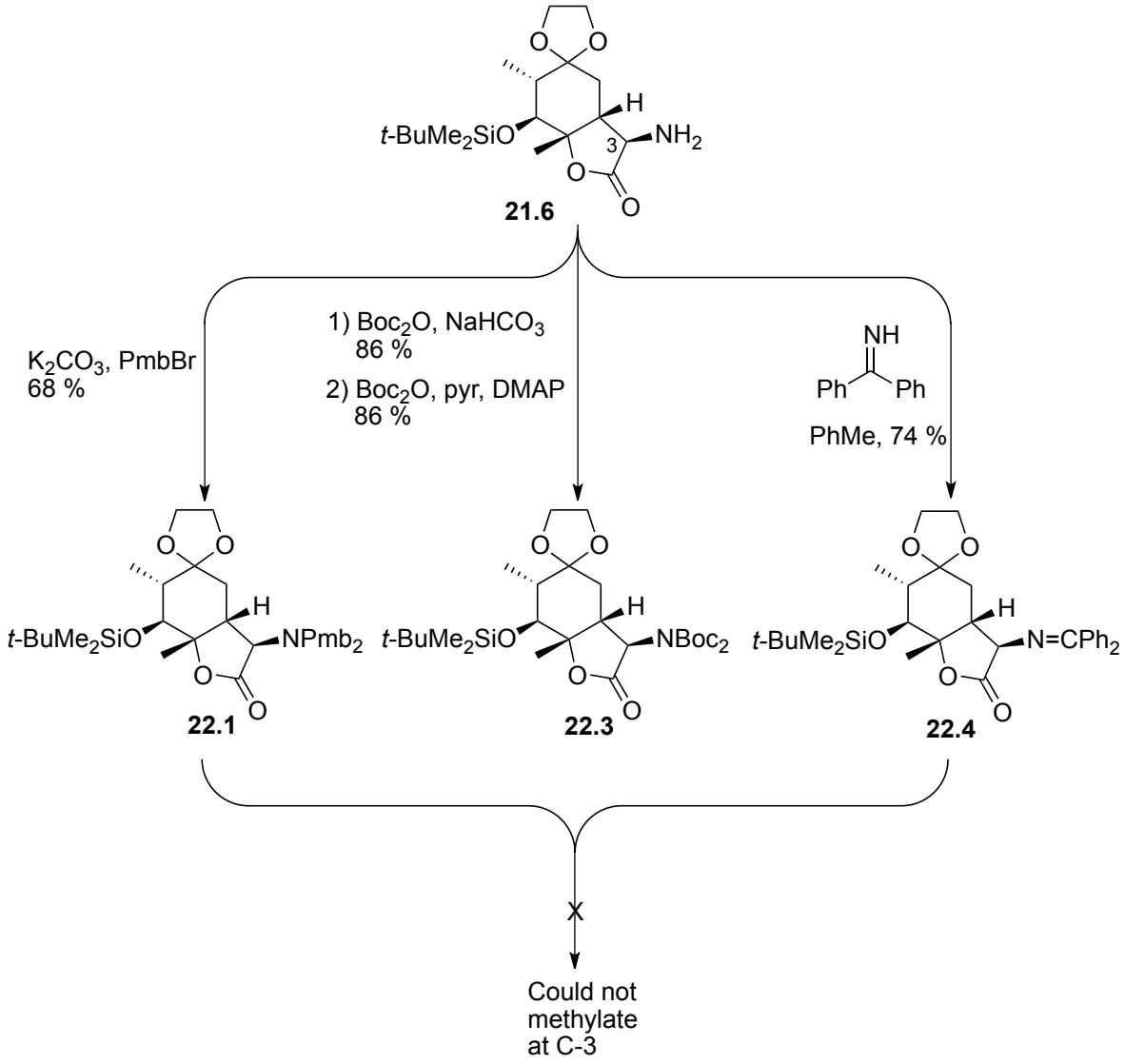
adding the methyl group. Accordingly, Sreedharan attempted to add the amino group at C-3. In his first approach (Scheme 21), he treated **19.2** with ICl and obtained the iodo lactone **21.1**. Bu_3SnH and TEMPO were added to give **21.2** and then the N-O bond was cleaved by using Zn in AcOH to generate the hydroxy lactone **21.3**. The hydroxy group was then protected by silylation (**21.3→21.4)**. Treatment with LDA and trisyl azide generated the azide **21.5**. Subsequently, the azide was reduced by hydrogenation on treatment with Pearlman's catalyst and H_2 to give the desired amine **21.6**.



Scheme 21. Sreedharan's approach to install the amine group at C-3

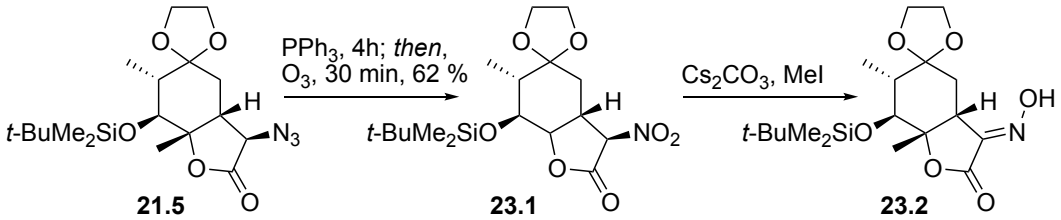
Protection of the nitrogen with two Pmb groups gave **22.1** (Scheme 22). However, attempts at methylation at C-3 were unsuccessful. His next approach was to protect the amine with two Boc groups. The first was added in the presence of $NaHCO_3$ and subsequently the second Boc group was installed in the presence of pyridine and a catalytic amount of DMAP to give doubly *N*-Boc protected amine **22.3**. This compound also could not be methylated at C-3.

In a third approach, the amine was protected as a benzophenone imine in order to increase the acidity of the hydrogen at C-3. Unfortunately, **22.4** was also resistant to methylation.



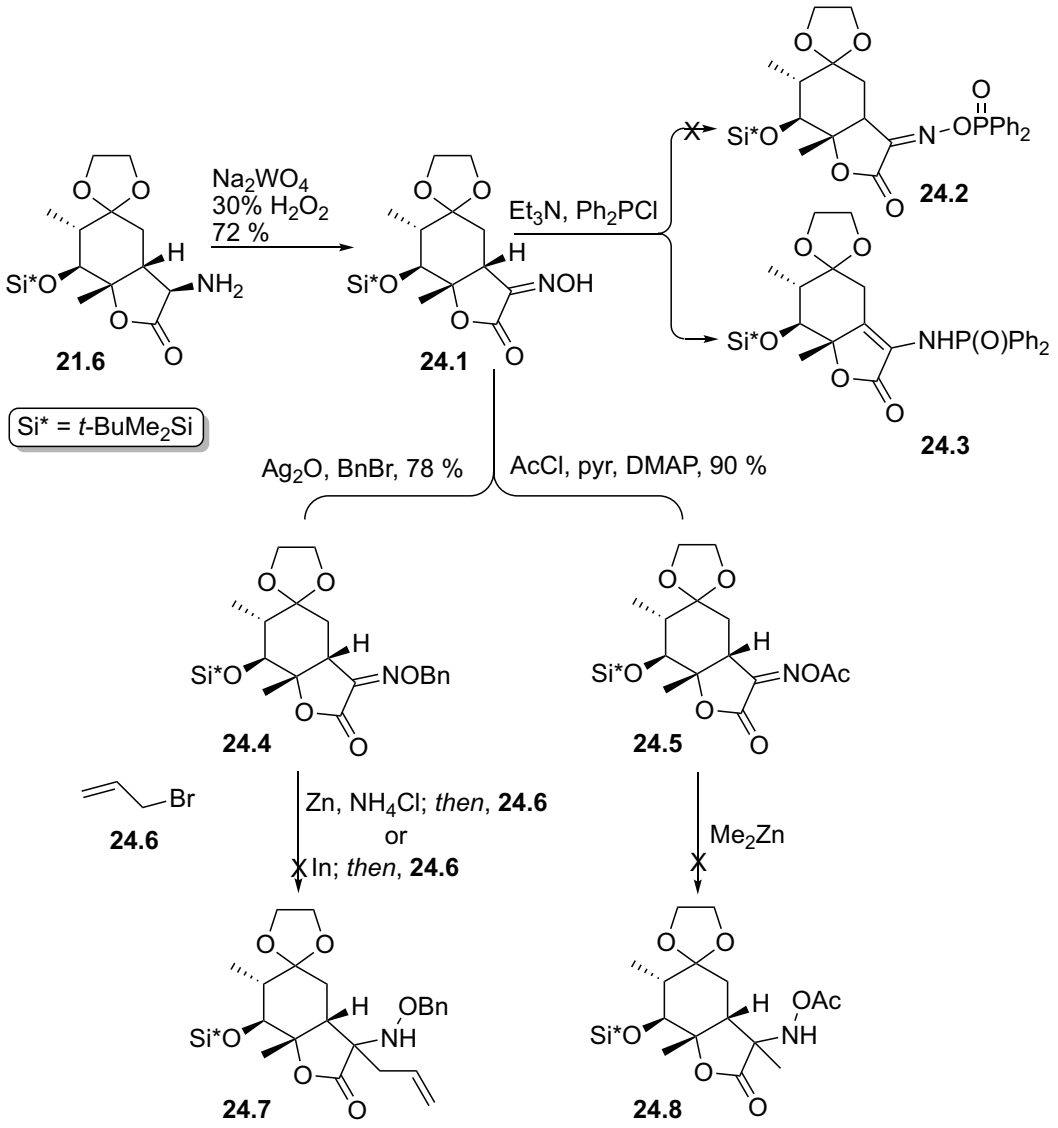
Scheme 22. Sreedharan's approach to install the methyl group at C-3

At this point Sreedharan tried to increase the acidity of the α-hydrogen at C-3 by installing a nitro group. First of all, the azide **21.5** was reacted with PPh_3 (Scheme 23) and subsequently treated with Ozone to generate the nitro



Scheme 23. Sreedharan's approach to install the methyl group at C-3

compound[27] **23.1**. In an attempt to methylate this compound it was treated with Cs_2CO_3 and MeI but surprisingly gave the oxime **23.2**.



Scheme 24. Oxime pathway

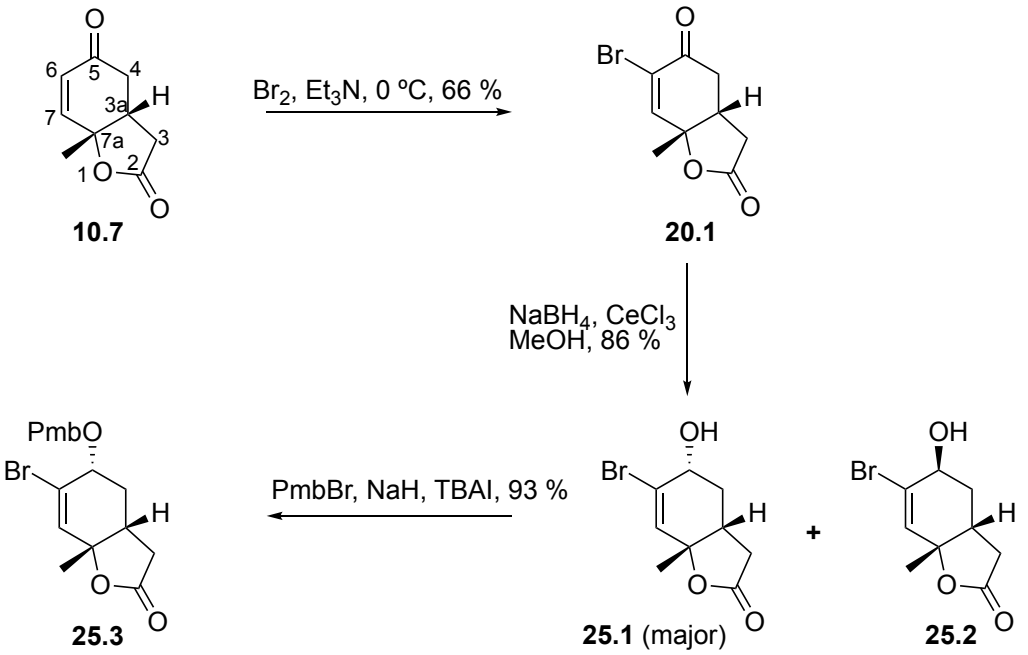
Since electrophilic methylation had failed, he attempted to use a nucleophilic method for alkylation. The amine **21.6** was reacted with Na_2WO_4 and 30% H_2O_2 to give oxime **24.1**.[28] The first aim was to convert oxime **24.1** into phosphinate **24.2** by treatment with Ph_2PCl and Et_3N. Unfortunately, the (diphenylphosphoroso)amino compound **24.3** was formed instead of the desired product. Next, he generated the benzyl oxime **24.4** by reaction with Ag_2O and BnBr and

treated the product with allylzinc[29] and allylindium reagents.[30] However, the desired product **24.7** was not formed.

Finally, the oxime **24.1** was converted into the *O*-acyl oxime **24.5** by using AcCl and a catalytic amount of DMAP in the presence of pyridine. Again, methylation experiments were unsuccessful.

Although the above studies generated what appear to be advanced intermediates some of the yields were very low and so alternative procedures had to be developed.

In my work, I first tried to repeat the bromination of **10.7** and ketalization of the ketone carbonyl (Scheme 20). Unfortunately, the reasonable yield (66%) reported by Sreedharan for very small scale ketalization, was not achievable on a synthetically useful scale and so I examined the possibility of protecting the ketone group by reduction. Luche reduction[31] of **10.7** gave a very low yield but the bromoketone **20.1**[32] (Scheme 20) was reduced smoothly to provide a mixture of alcohols **25.1** and **25.2** in a ratio of 1.4:1. I assume that the presence of the halogen made the carbonyl group more electron-deficient by induction and facilitated reduction. It was possible to isolate the isomers by column chromatography and the major alcohol **25.1** was used in the next step. The hydroxyl was protected with a Pmb group using NaH and PmbBr in the presence of Bu_4NI to give **25.3**.[33] This sequence gave good yields in manipulation of the ketone carbonyl.

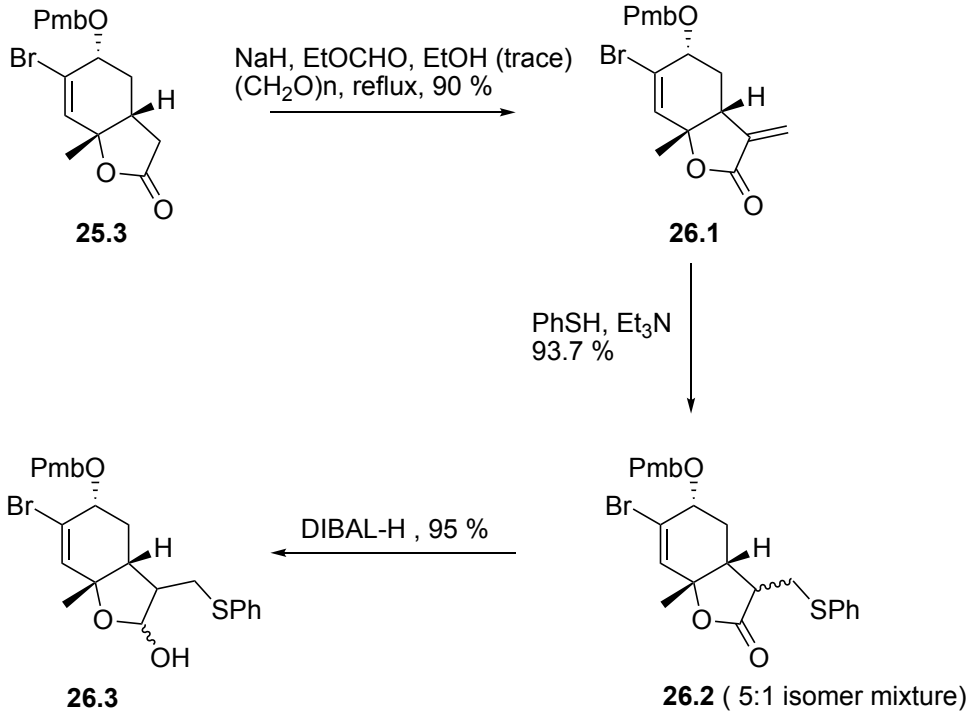


Scheme 25. Preparation of the protected bromo alcohol

The above sequence depends, of course, on the ability to introduce oxygen at C-7 and such a method was developed in this laboratory and is based on conjugate addition of a silicon unit, followed by Tamao-Fleming oxidation.[34]

I then attempted to attach an amino group at C-3 on the lactone ring. First, an exocyclic double bond was installed in two steps (Scheme 26). Reaction of **25.3** with NaH and a trace amount of EtOH, and treatment with ethyl formate and then with paraformaldehyde generated the unsaturated lactone **26.1**.[35] 1,4-Addition took place on exposure to PhSH in the presence of Et_3N to give **26.2**.[36] The resulting lactone isomer mixture (about 5:1 by ^1H NMR) was reduced with DIBAL-H to provide the lactols **26.3**. The material was an inseparable mixture of isomers and NMR measurements showed that only two isomers were present in a 1:1 ratio. Presumably, these are derived from the major parent lactone and so the isomers differ only in the stereochemistry at the hydroxyl-bearing carbon. The resulting lactols were treated with *p*-

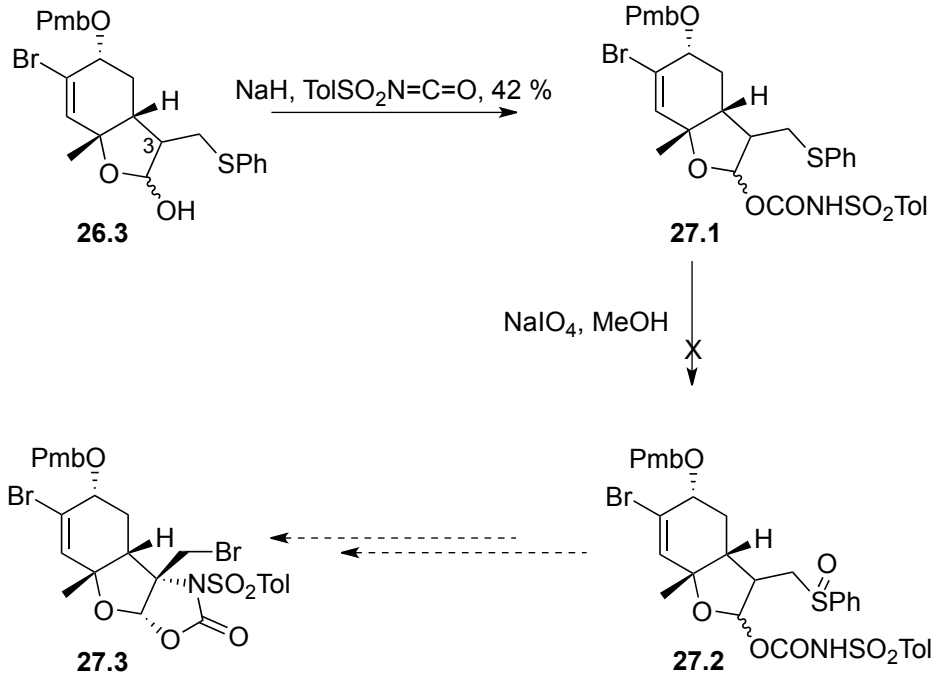
toluenesulfonyl isocyanate in the presence of NaH (Scheme 27) to give the sulfonamides **27.1** in low yield. One of the byproducts isolated showed OH and aldehyde CHO signals in the ^{1}H NMR spectrum, and so it seems that the lactol ring opened.



Scheme 26. Lactol sulfur series

From the sulfonamides, the plan was to generate sulfoxide **27.2** by oxidizing the sulfur with $NaIO_4$ so that a double bond could be generated at C-3 by heating the sulfoxides. The resulting compound should be amenable to stereoselective cyclization in the presence of a source of Br^+ to give compound **27.3** provided the sulfonamide substituent has the correct stereochemistry. Unfortunately, although we made the thioether **27.1**, we could not convert it into compound **27.2** beyond trace amounts, as judged by mass spectroscopy. What I assumed from the mass spectrum to be the desired sulfoxide was heated in the hope of generating a double

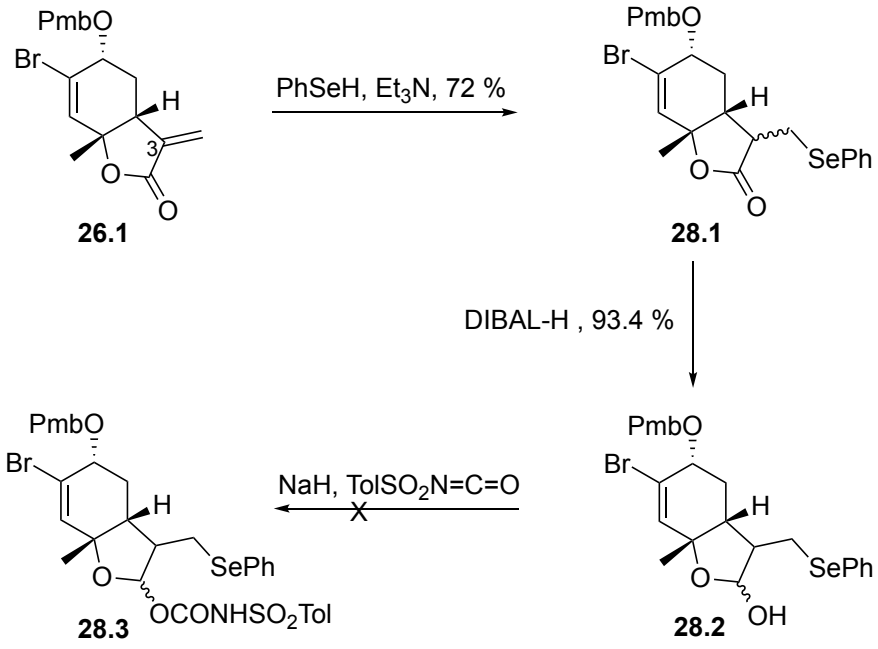
bond, but only a complex mixture was obtained. Therefore, we decided to use a seleno ether, as the PhSe group is much easier to remove to form an olefin.[37]



Scheme 27. *N*-Sulfonyl carbamate series

The synthetic route with selenium (Scheme 28) was modeled on that in the sulfur series. 1,4-Addition of PhSeH to **26.1** took place in the presence of Et_3N to give **28.1** as a 1.4:1 mixture of isomers. The resulting lactones were converted to lactols **28.2** by using DIBAL-H. Again the material was a mixture of two isomers that could not be separated. NMR analysis showed one of the isomers was the major product, the ratio of the two being 1.2:1. Unfortunately, we could not prepare crystals suitable for X-ray analysis and so we were unable to establish the stereochemistry. When the resulting inseparable alcohols were reacted with *p*-toluenesulfonyl isocyanate in the presence of NaH in the hope of generating the sulfonamides **28.3**, a complex mixture was obtained. I also examined *p*-$MeOC_6H_4N$=C=O, and $ClSO_2N$=C=O but they both

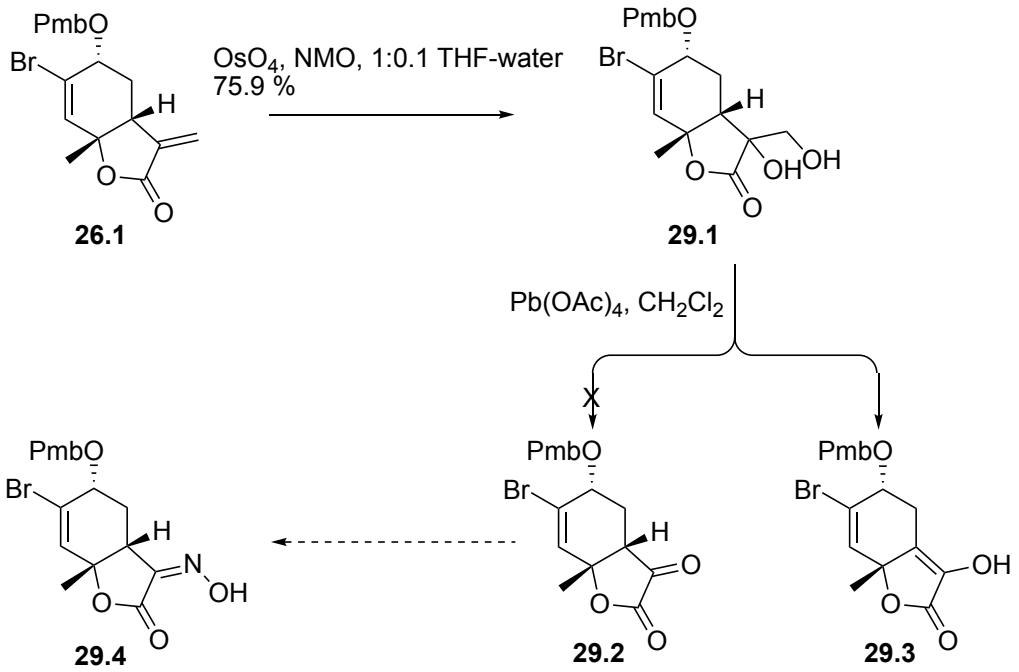
gave complex mixtures and the lactol ring was opened at the same time, as judged by the presence of a C**H**O signal in the ^{1}H NMR spectra.



Scheme 28. Lactol selenium series

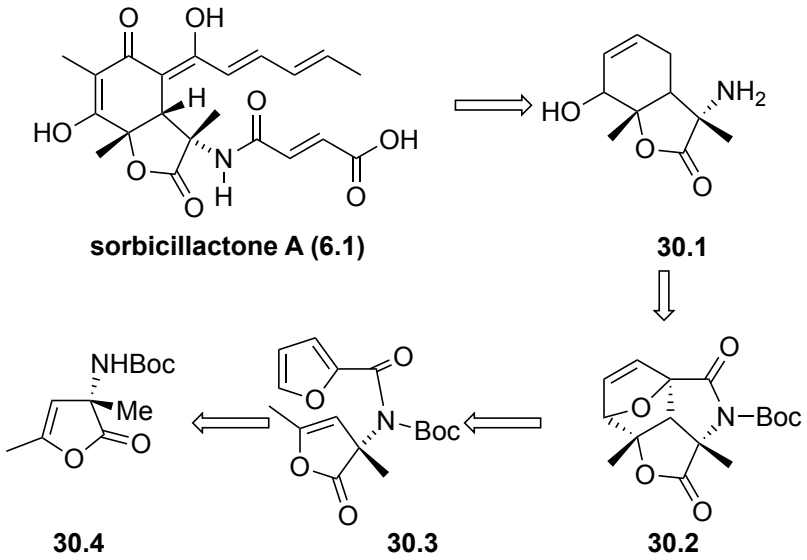
The next route I tried was to generate an oxime to explore in more detail than had previously been done the introduction of the methyl group.

To implement this approach, the unsaturated lactone **26.1** was converted into diol **29.1** by using OsO_4 in the presence of a catalytic amount of NMO (Scheme 29).[38] The diol was cleaved with lead tetraacetate. However, instead of the expected diketone **29.2** we obtained the corresponding enol **29.3**, as judged by the FTIR and ^{13}C NMR spectrum of the crude product. The plan had been to then generate oxime **29.4** for further studies on the introduction of the methyl group.



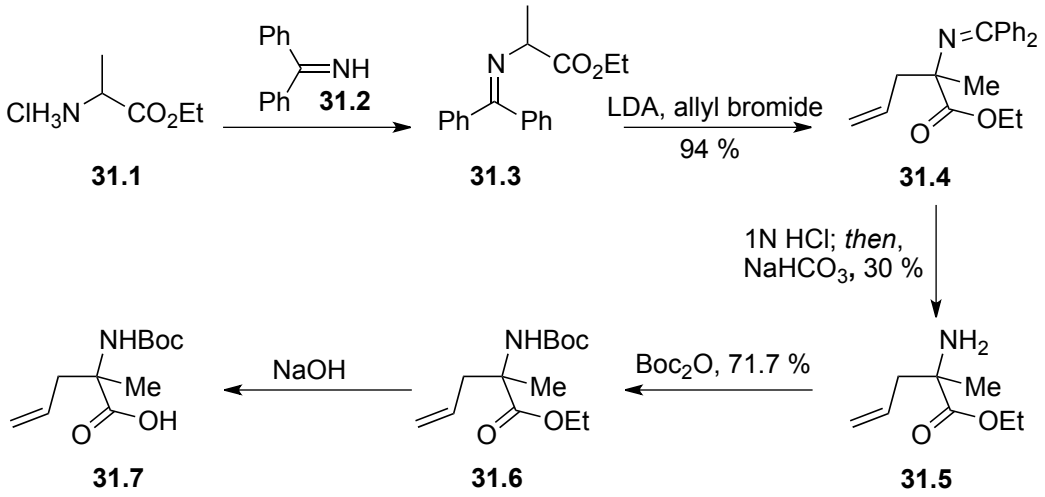
Scheme 29. Planned oxime route

From these observations it was clear that the route had to be changed as we had been unable to install both the amino and methyl groups at C-3. At this point we decide to explore the use of a Diels-Alder reaction to make sorbicillactone A.



Scheme 30. Retrosynthesis for sorbicillactone A via the Diels-Alder route

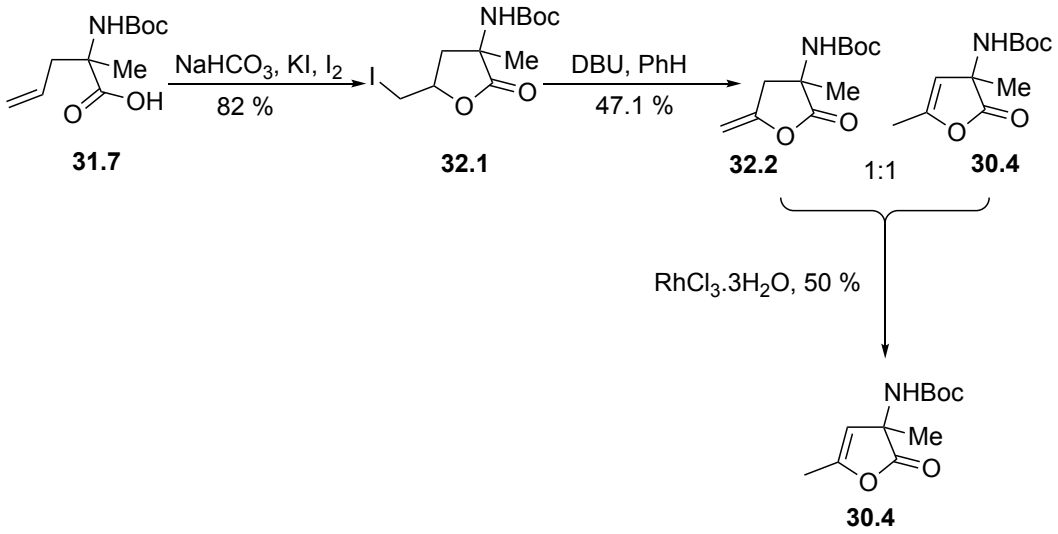
The specific plan was to use an intramolecular Diels-Alder reaction, a type of process well established in natural product synthesis.[39] For the present case the diene would be delivered from the same face as the amino group, as summarized in Scheme 30. This strategy seems to be ideal for constructing the sorbicillactone A core. First of all we would produce the unsaturated lactone **30.4** from allyl alanine, which has been prepared[40] in optically pure form, and then attach the furan unit which would undergo intramolecular Diels-Alder reaction to generate **30.2**. The resulting compound would be converted to **30.1** by removal of the Boc group and a ring opening step. There was also the possibility of using a furan that already carried the methyl group eventually attached to the six-membered ring of sorbicillactone A.



Scheme 31. Synthesis of amino acid derivative **21.7**

We used alanine ethyl ester hydrochloride (**31.1**) and condensed the compound with benzophenone imine (**31.2**) to give *N*-protected alanine ethyl ester **31.3** (Scheme 31).[41] The compound was reacted with LDA and subsequently treated with allyl bromide to provide *N*-protected allyl alanine ethyl ester **31.4**[42] in high yield. The nitrogen protecting group was

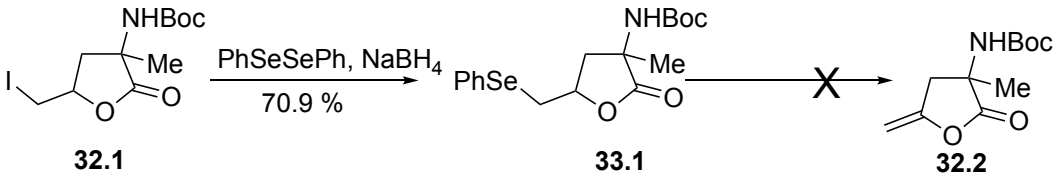
removed on treatment with 1N HCl to generate the free amine **31.5**.[41] The yield in this step was low because the free amine is surprisingly volatile. The free amino group was protected by reaction with Boc_2O to give *N*-Boc-allyl alanine ethyl ester **31.6**. Finally, the ester was hydrolyzed using NaOH to give *N*-Boc-allyl alanine **31.7**.[43] The individual compounds are known but this route is based on a literature procedure[43] that was reported for the *tert*-butyl ester.



31.7 **32.1** **32.2** **30.4** **30.4**

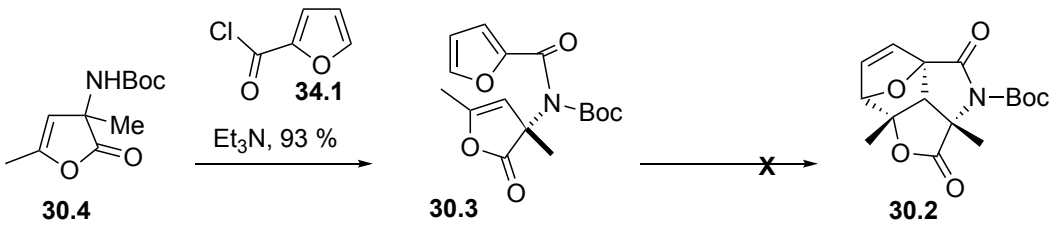
Scheme 32. Synthesis of amino lactone **30.4**

N-Boc-allyl alanine **31.7** was subjected to halolactonization by treatment with KI and I_2 under basic conditions ($NaHCO_3$) to give the iodo lactone **32.1**[44] as a single isomer of unestablished stereochemistry, and this was treated with DBU in refluxing benzene to produce a 1:1 mixture of the regioisomers **32.2** and **30.4**.[45] However, the reaction yield was low (47%). Isomerization of the exocyclic double bond with rhodium chloride gave the desired compound **30.4**.[46] This reaction was very clean, but again the yield was low (50%).



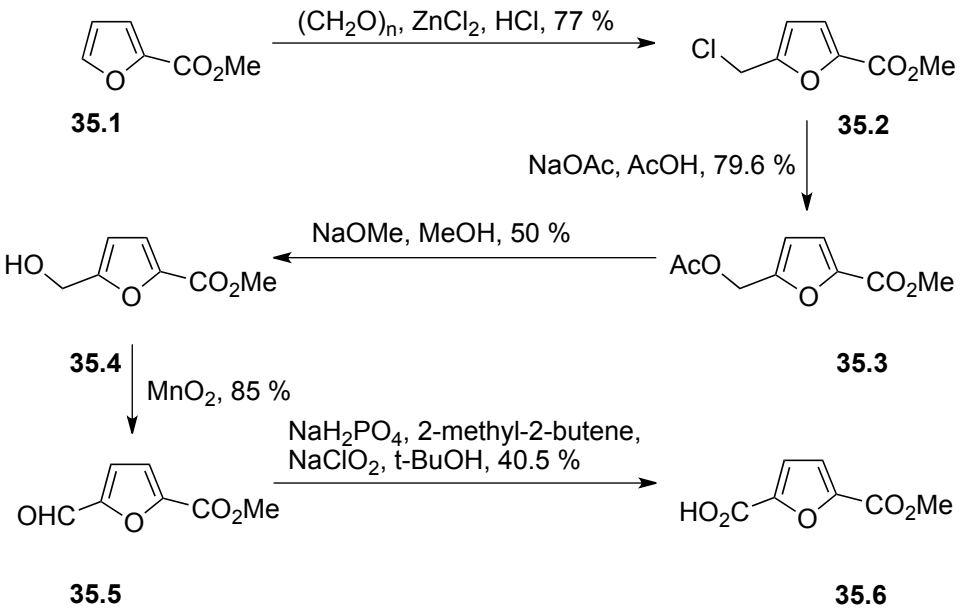
Scheme 33. Attempted synthesis of lactone **32.2**

Although we could make the iodo lactone **32.1** in a reasonable yield, the unsatisfactory yields in the next steps prompted examination of another route based on selenium. Iodo lactone **32.1** was reacted with PhSeNa (Scheme 33), which was generated from PhSeSePh and $NaBH_4$ *in situ,* to give the phenyl selenide **33.1**. Subsequently the selenium was oxidized with H_2O_2 or $NaIO_4$; however, the expected compound (**32.2**) was not produced as the appropriate ^1H signals for a methylidene group (4–5 ppm) were not detected and only a complex mixture was formed. Therefore, we decided to accept the low yield of the DBU method.



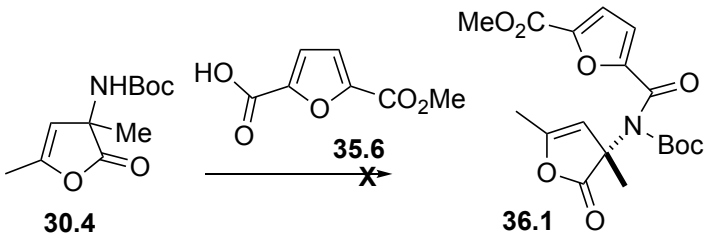
Scheme 34. Planned synthesis of sorbicillactone A by the Diels-Alder route

The unsaturated lactone **30.4** was acylated with 2-furoyl chloride (Scheme 34) in the presence of Et_3N to give **30.3**, the compound needed for Diels-Alder reaction. We tried the use of the high boiling solvents toluene and 1,2-dichlorobenzene and also the use of the Lewis acid $BF_3.OEt_2$. Unfortunately, the reaction did not work and most (ca 90%) of the starting material was recovered in each experiment. Therefore, we next examined a furan ring with an additional electron-withdrawing substituent.



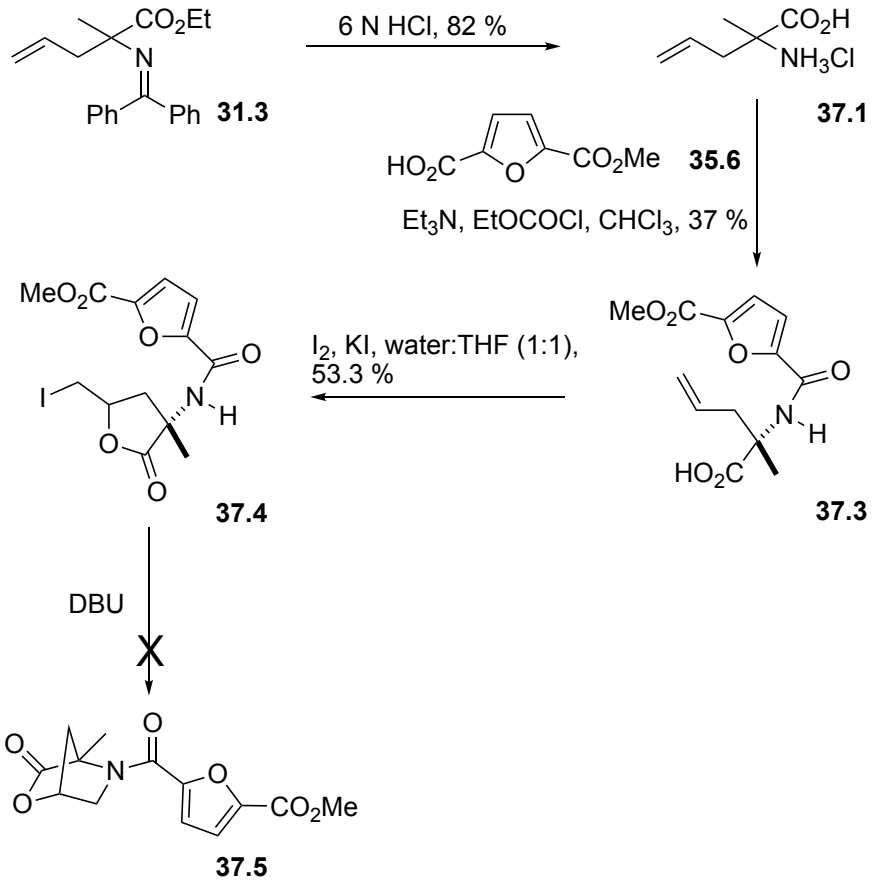
Scheme 35. Synthesis of furan **35.6**

2-Methyl furoate (**35.1**) was used as the staring material (Scheme 35) and this was treated with zinc chloride and hydrogen chloride to give the chloromethyl furoate **35.2**.[47] The chlorine was replaced by an acetoxy group on treatment with sodium acetate in acetic acid to produce **35.3**[47] and the acetoxy group was converted to a hydroxyl by reaction with sodium methoxide to provide compound **35.4**. The hydroxy group was treated with $KMnO_4$,[47] but this experiment produced a complex mixture. Therefore, we decided to oxidize the hydroxyl in a stepwise manner. Treatment of **35.4** with activated MnO_2 yielded aldehyde **35.5** and this was then oxidized by the Pinnick method[48] by treatment with $NaClO_2$ under acidic conditions to produce the desired carboxylic acid **35.6**.[47]



Scheme 36. Synthesis of sorbicillactone A

We then tried to acylate the unsaturated lactone **30.4** with the furoic acid **35.6**, but were unable to obtain the desired adduct **36.1**. Several coupling reagents such as EDCI and DCC with additives such as HOBT or HATU were tried and we also converted the acid to the acid chloride *in situ,* in the hope it would be a more powerful acylating reagent, but we could not effect the desired acylation. Therefore, we decided to install the furan group before formation of the lactone.



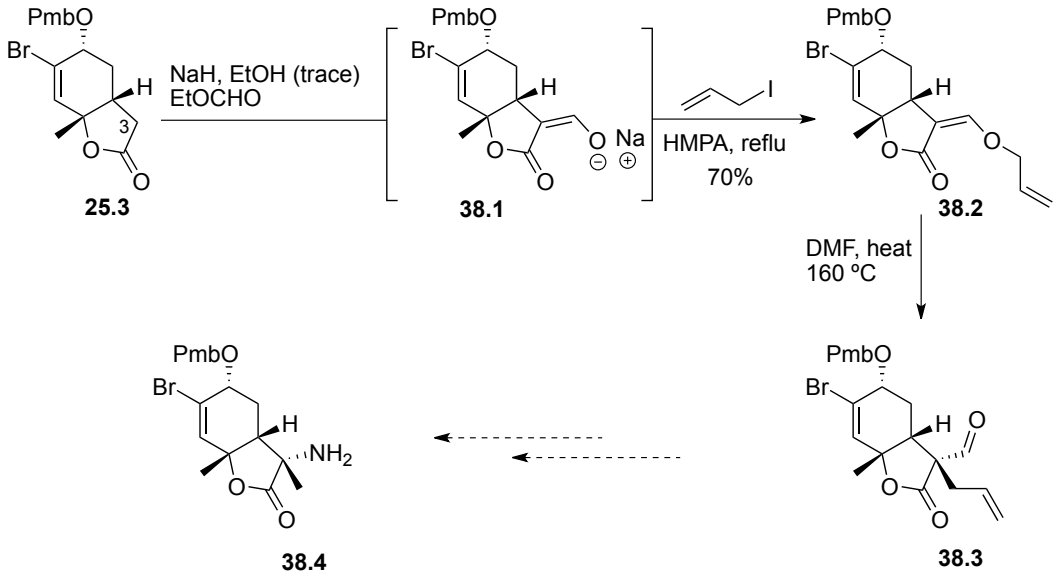
Scheme 37. Reaction of iodoamide **33.4** with DBU

The starting material was prepared (Scheme 37) by deprotection and hydrolysis of *N*-protected allylalanine **31.3** to generate the salt **37.1**.[49] This was acylated with **35.6** using the coupling reagent EDCI. The yield was only 10% and so we tried the mixed anhydride method (ethyl chloroformate in the presence of Et_3N),[50] which gave compound **37.3** in 37% yield. This compound underwent halolactonization with KI and I_2 to produce iodo lactone **37.4**. However, treatment with DBU did not give the desired product. The NMR spectra showed the product to be **37.5**; evidently, the secondary amide was deprotonated by DBU and the anion attacked the carbon carrying the iodine to give the undesired cyclized compound **37.5**.

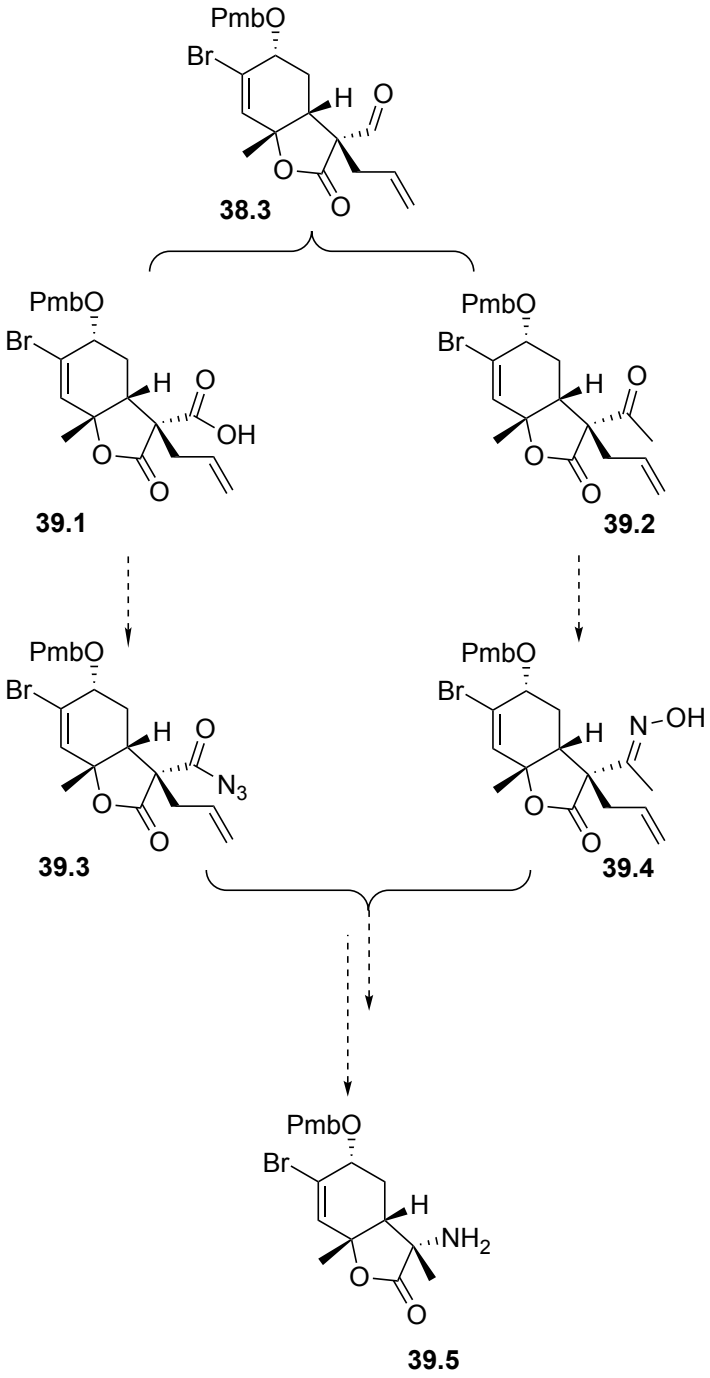
2.1 Current work toward the synthesis of sorbicillactone A

As the above experiments show, installation of the methyl and amino groups on the lactone ring have proven to be very challenging, and assembly of a precursor of a planned Diels-Alder approach was not achieved.

I am currently (June 2017) exploring several different approaches to add stereoselectively the amino and methyl group at C-3. Recently, I found the remarkable and welcome result that an unusual Claisen rearrangement can be used to introduce two different carbon units at C-3. The intermediate **38.1**, formed in the reaction of **25.3** with NaH and a trace amount of EtOH, was treated with allyl iodide and HMPA to generate the allyl ether **38.2** in 70% overall for the two steps. In my first experiments allyl bromide was used but the reaction is much less clean and the yield was lower. The stereochemistry of **38.2** is assigned on the basis of the chemical shift of the new vinyl proton by analogy with measurements made on simple analogs of γ-butyrolactone itself.[53] This vinyl proton has a chemical shift of 6.52 ppm, close to the value expected for the *Z*-isomer; the *E*-isomer would be expected to have a chemical shift of 7.27 ppm.[53] The ether **38.2** was converted thermally into **38.3** at 160 °C in high yield (Scheme 38). NOE measurements served to establish the indicated stereochemistry since no NOE was observed between the aldehyde proton and the adjacent ring fusion proton, but the latter showed an NOE to the methylene group of the allyl unit. That methylene also showed an NOE with the methyl group at C-7a. With the C-3 carbon now functionalized a number of standard modifications are available to convert the formyl group into an amino group and the ally unit into a methyl group.



Scheme 38. Claisen approach to sorbicillactone A



Scheme 39. Future work on the synthesis of sorbicillactone A

The first strategy for converting the formyl group into an amino group, will be to oxidize **38.3** to carboxylic acid **39.1** and then form the acyl azide **39.3**. This azide should undergo a

Curtius rearrangement. A second strategy is to convert the aldehyde to the methyl ketone **39.2**. The ketone group will be converted to the oxime **39.4** and then a Beckmann rearrangement should give the amino group (Scheme 39). Degradation of the allyl chain to a methyl group may be possible by isomerization of the double bond to the internal position, dihydroxylation and diol cleavage. Finally reduction of the resulting aldehyde will generate the desired methyl group.

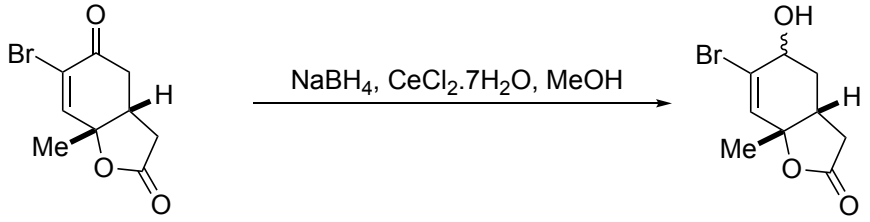
2.2 Conclusion

Much of the skeleton of sorbicillactone A has been obtained. However, we have found that installing the amino and methyl groups on the lactone ring is difficult. In addition, the bicyclic lactone ring seems to be fragile. The current approach involves installing two carbon units at C-3; one of them will be converted to an amino group and the other to a methyl group. In the Claisen rearrangement, one of the double bonds is initially conjugated with an electron-withdrawing group and an aldehyde is formed. This type of Claisen rearrangement is rare and a search of the REAXYS database for related examples retrieved only three publications,[54] all referring to acyclic compounds; there appear to be no previous examples where the electron-withdrawing group is a lactone carbonyl.

EXPERIMENTAL SECTION

General Procedures. Solvents used for chromatography were distilled before use. Commercial thin layer chromatography plates (silica gel, Merck 60F-254) were used. Silica gel for flash chromatography was Merck type 60 (230–400 mesh). Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. The symbols s, d, t and q used for ^{13}C NMR spectra indicate zero, one, two, or three attached hydrogens, respectively, the assignments being made from APT spectra. Solutions were evaporated under water pump vacuum and the residue was then kept under oil pump vacuum. High resolution electrospray mass spectrometric analyses were done with an orthogonal time of flight analyzer and electron ionization mass spectra were measured with a double-focusing sector mass spectrometer.

(3a*R*,7a*S*)-*rel*-6-Bromo-5-hydroxy-7a-methyl-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2-one (25.1).[31]



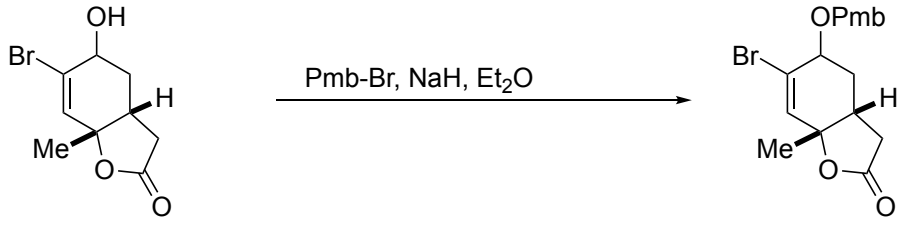
20.1 **25.1** (major)

$CeCl_3$ (0.86 g, 2.31 mmol) in MeOH (5.6 mL) was added to a stirred and cooled (–78 °C) solution of **20.1** (190 mg, 0.77 mmol) in CH_2Cl_2 (5 mL). Then, $NaBH_4$ (64 mg, 1.67 mmol) was added and stirring was continued at –78 °C for 1 hr. The reaction mixture was quenched with solid $NaHSO_3$ and stirring was continued for 30 min. Water was added and the organic layer

was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 × 15 cm), using 50% EtOAc-hexane, gave **25.1** (170 mg, 88%) as a white solid which was a 1.4:1 mixture of diastereomers. The major isomer had: FTIR ($CDCl_3$, cast) 3448, 3048, 2928, 1731, 1646, 1238 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.51 (s, 3 H), 2.10–2.15 (m, 2 H), 2.50–2.53 (m, 2 H), 2.70–2.15 (m, 2 H), 2.72 (dd, *J* = 18.5, 8.5 Hz, 1 H), 3.00 (dd, *J* = 17.8, 9.5 Hz, 1 H), 4.23 (t, *J* = 4.5, 3 H), 6.16 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.3 (q), 30.8 (t), 34.6 (t), 37.4 (q), 68.1 (d), 84.1 (s), 129.8 (s), 131.4 (d), 175.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_9H_{12}{}^{79}BrO_3$ $(M+H)^+$ 246.9964, found 246.9963.

The minor isomer had: FTIR ($CDCl_3$, cast) 3425, 2974, 2931, 1765, 1645, 1277 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.55 (s, 3 H), 1.98–2.13 (m, 2 H), 2.34–2.40 (m, 2 H), 2.66–2.71 (m, 1 H), 2.83 (dd, *J* = 17.5, 8.0 Hz, 1 H), 4.37–4.40 (m, 1 H), 6.20 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.8 (q), 32.5 (t), 34.1 (t), 36.4 (q), 67.8 (d), 83.6 (s), 130.2 (s), 131.7 (d), 174.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_9H_{12}{}^{79}BrO_3$ $(M+H)^+$ 246.9964, found 246.9961.

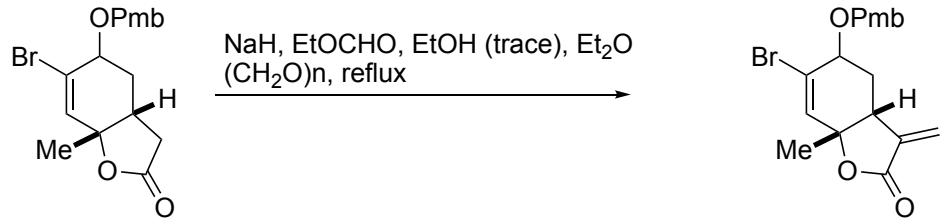
(3a*R*,7a*S*)-*rel*-6-Bromo-5-[(4-methoxy)methoxy]-7a-methyl-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2-one (25.3).



25.1 **25.3**

NaH (60 mg , 1.49 mmol) and Bu_4NI (55 mg, 0.15 mmol) were suspended in cooled and stirred (0 °C) THF (7 mL). A solution of *p*-methoxybenzyl bromide (0.3 mL, 1.56 mmol) and **25.1** (0.37 g, 1.49 mmol) in THF (9 mL) was added rapidly. The ice bath was left in place but not removed and stirring was continued overnight. The mixture was quenched with water and extracted with Et_2O. The organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.0 × 15 cm), using 30% EtOAc-hexane, gave **25.3** (540 mg, 98.6%) as a white solid: FTIR ($CDCl_3$, cast) 2933, 2863, 1773, 1612, 1514, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.49 (s, 3 H), 1.97 (dt, *J* = 15, 4.5 Hz, 1 H), 2.14–2.18 (m, 1 H), 2.50–2.51 (m, 1 H), 2.61 (dd, *J* = 8.5, 17.8 Hz, 1 H), 3.18 (dd, *J* = 10.5, 17.5 Hz, 1 H), 3.83 (s, 3 H), 4.0–4.02 (m, 1 H), 4.62–4.67 (m, 1 H), 6.2 (s, 1 H), 6.90–6.92 (m, 2 H), 7.30–7.31 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.2 (q), 28.0 (t), 34.2 (t), 37.4 (d), 55.3 (q), 72.9 (t), 74.6 (d), 84.1 (s), 113.9 (d), 126.7 (s), 129.5 (s), 129.6 (d), 132.3 (d), 159.5 (s), 175.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{17}H_{19}O_4{}^{79}BrNa$ $(M+Na)^+$ 389.0354, found 389.0539.

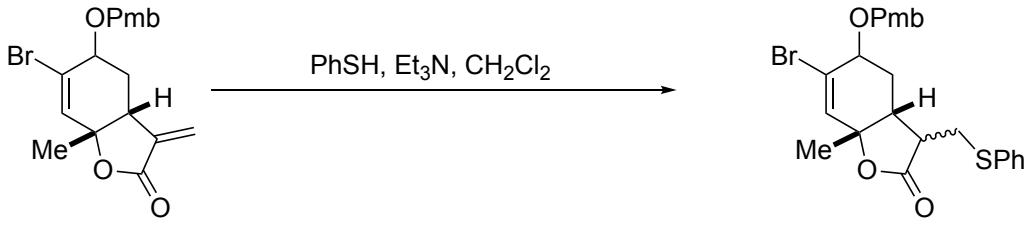
(3a*R*,7a*S*)-*rel*-6-Bromo-5-[(4-methoxy)methoxy]-7a-methyl-3-methylidene-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2-one (26.1).[35]



25.3 **26.1**

NaH (3 mg, 0.08 mmol) was covered with THF (2 mL) and then EtOH (0.48 μL) was added. When bubbling had stopped (ca 5 min) the **25.3** (30 mg, 0.08 mmol) was tipped in and the reaction flask was lowered into a preheated oil bath (ca 40 °C) and HCO_2Et (6 mL, 0.08 mmol) was injected. Stirring at reflux was continued for 1 h. A slurry of paraformaldehyde (36 mg, 1.15 mmol) and THF (4 mL) was added and refluxing was continued for 2 h. The mixture was cooled and quenched with aqueous K_2CO_3 (1 M) and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 15 cm), using 50% EtOAc-hexane, gave **26.1** (700 mg, 90%) as a colorless oil: FTIR ($CDCl_3$, cast) 2930, 2866, 1762, 1612, 1514, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.48 (s, 3 H), 2.13–2.19 (m, 2 H), 2.93–2.96 (m, 1 H), 3.83 (s, 3 H), 4.0–4.02 (m, 1 H), 4.59–4.64 (m, 2 H), 5.66 (d, *J* = 2 Hz, 1 H), 6.21–6.22(m, 1 H), 6.31 (d, *J* = 2 Hz, 1 H), 6.90–6.92 (m, 2 H), 7.28–7.32 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.8 (q), 30.1 (t), 42.1 (d), 55.3 (q), 72.2 (t), 73.7 (d), 81.3 (s), 113.9 (d), 123.1 (s), 129.1 (s), 129.6 (d), 132.1 (d), 138.4 (s), 159.5 (s), 168.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{18}H_{19}{}^{79}BrNaO_4$ $(M+Na)^+$ 401.0359, found 401.0354.

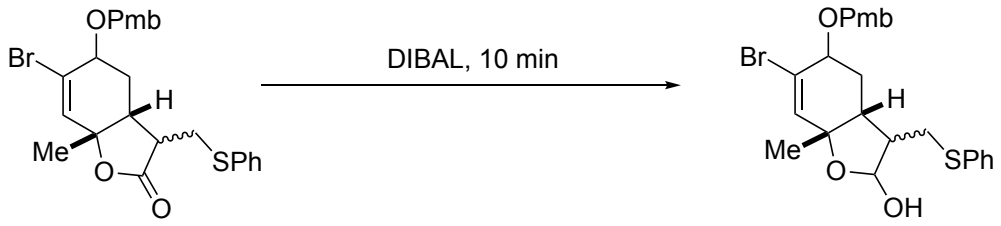
(3a*R*,7a*S*)-*rel*-6-Bromo-5-[(4-methoxy)methoxy]-7a-methyl-3-[(phenylsulfanyl)-methyl]-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2-one (26.2).[36]



26.1 **26.2**

PhSH (0.8 mL, 4.74 mmol) and Et_3N (1.0 mL, 4.74 mmol) were injected sequentially into a stirred solution of **26.1** (140 mg, 0.37 mmol) in CH_2Cl_2 (12 mL). Stirring at room temperature was continued overnight (N_2 atmosphere). The mixture was quenched with water and the aqueous phase was extracted with CH_2Cl_2 (1.5 × 15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.0 × 15 cm), using 20% EtOAc-hexane, gave **26.2** (170 mg, 93.7%) as a colorless oil: FTIR ($CDCl_3$, cast) 3058, 2933, 1773, 1612, 1513, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.41 (s, 3 H), 2.22–2.63 (m, 1 H), 2.48–2.53 (m, 1 H), 2.83 (dd, *J* = 12.8, 12 Hz, 1 H), 3.18–3.23 (m, 1 H), 3.53 (dd, *J* = 15.5, 4 Hz, 1 H), 3.83 (s, 3 H), 4.04–4.07 (m, 1 H), 4.54–4.70 (m, 2 H), 6.22 (d, *J* = 2 Hz, 1 H), 6.88–6.93 (m, 2 H), 7.28–7.32 (m, 3 H), 7.35–7.38 (m, 4 H), 7.41–7.43 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.8 (q), 28.3 (t), 29.3 (t), 39.9 (d), 43.7 (d), 55.3 (t), 72.0 (s), 74.0 (d), 81.2 (s), 113.9 (d), 127.2 (d), 129.1 (d), 129.5 (s), 129.9 (d), 130.3 (d), 132.7 (s), 134.4 (s), 159.5 (s), 174.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{24}H_{25}{}^{79}BrO_4S$ $(M+H)^+$ 488.0657, found 489.073.

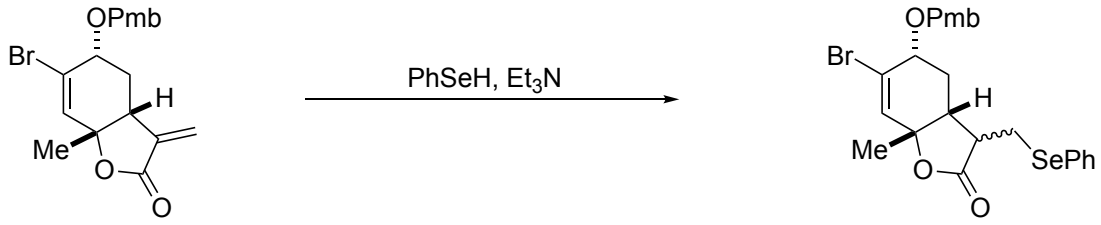
(3a*R*,7a*S*)-*rel*-6-Bromo-5-[(4-methoxy)methoxy]-7a-methyl-3-[(phenylsulfanyl)-methyl]-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2-ol (26.3).



26.2 **26.3**

DIBAL-H (1 M solution in hexane, 0.5 mL, 0.5 mmol) was added to a stirred and cooled (0 °C) solution of **26.2** (160 mg, 0.32 mmol) in CH_2Cl_2 (2 mL). Stirring was continued for 10 min. The mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 20 cm), using 30% EtOAc-hexane, gave **26.3** (150 mg, 95%) as a colorless oil: FTIR ($CDCl_3$, cast) 3249, 3064, 2926, 2850, 1642, 1513, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.22–1.40 (m, 3 H), 1.58–1.65 (m, 1 H), 2.11–2.32 (m, 2 H), 2.69–2.76 (m, 1 H), 2.77–3.21 (m, 1 H), 3.80 (s, 3 H), 3.90–4.01 (m, 1 H), 4.59–4.70 (m, 2 H), 5.23–5.40 (m, 1 H), 6.00–6.23 (m, 1 H), 6.84–6.92 (m, 2 H), 7.15–7.40 (m, 7 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.2 (q), 28.6 (t), 29.2 (q), 29.5 (t), 29.6 (t), 31.2 (t), 41.3 (d), 43.2 (d), 45.5 (d), 48.8 (d), 55.3 (q), 71.8 (d), 71.9 (d), 74.9 (d), 75.0 (d), 82.1 (s), 82.5 (s), 97.8 (d), 99.1 (d), 101.9 (d), 113.8 (d), 121.9 (s), 126.4 (d), 126.5 (d), 127.9 (s), 128.9 (s), 129.1 (d), 129.1 (d), 129.4 (d), 129.5 (d), 129.6 (d), 129.7 (d), 129.8 (s), 129.9 (s), 130.0 (s), 134.3 (d), 135.3 (d), 135.7 (s), 136.0 (d), 136.2 (s), 159.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{24}H_{27}{}^{79}BrNaO_4S$ $(M+Na)^+$ 513.0706, found 513.069.

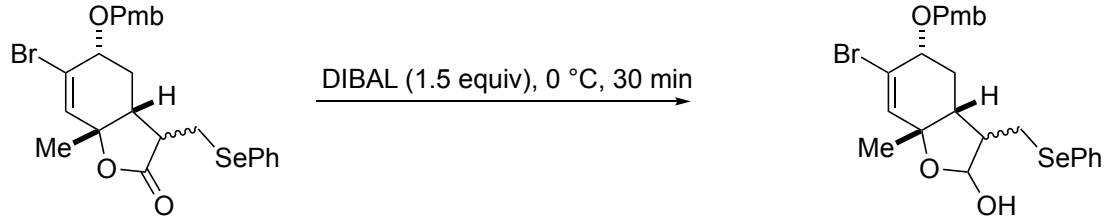
(3a*R*,7a*S*)-*rel*-6-Bromo-5-[(4-methoxy)methoxy]-7a-methyl-3-[(phenylselanyl)-methyl]-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2-one (28.1).[36]



26.1 **28.1**

PhSeH (0.2 mL, 1.88 mmol) and Et_3N (0.8 mL, 6.3 mmol) were injected sequentially into a stirred solution of **26.1** (120 mg, 0.31 mmol) in CH_2Cl_2 (9 mL). Stirring at room temperature was continued overnight (N_2 atmosphere). The mixture was quenched with water and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 20 cm), using 50% EtOAc-hexane, gave **28.1** (20 mg, 74%) as a colorless oil: FTIR ($CDCl_3$, cast) 3058, 2932, 2835, 1772, 1612, 1513, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.40–1.48 (m, 3 H), 1.85 (dt, *J* = 15.5, 4.5 Hz, 1 H), 2.12–2.23 (m, 1 H), 2.42–2.50 (m, 1 H), 2.80 (t, *J* = 13 Hz, 1 H), 3.15–3.31 (m, 2 H), 3.45 (dd, *J* = 13, 4 Hz, 1 H), 3.77–3.81 (m, 1 H), 3.83 (s, 3 H), 3.94–4.03 (m, 1 H), 4.55–4.67 (m, 2 H), 6.14–6.22 (m, 1 H), 6.88–6.93 (m, 2 H), 7.26–7.29 (m, 3 H), 7.32–7.36 (m, 2 H), 7.51–7.59 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.9 (d), 25.0 (q), 25.7 (q), 26.4 (t), 26.6 (t), 28.3 (t), 40.4 (d), 42.7 (d), 44.4 (d), 44.7 (d), 55.3 (q), 72.0 (d), 73.2 (d), 74.0 (d), 74.6 (d), 80.9 (s), 82.4 (s), 113.9 (d), 125.6 (s), 127.2 (d), 128.0 (d), 128.4 (s), 129.3 (d), 129.5 (d), 129.5 (d), 129.6 (s), 129.8 (d), 130.6 (s), 131.3 (d), 132.5 (d), 132.8 (d), 133.2 (s), 133.6 (d), 159.5 (s), 174.3 (s), 175.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{24}H_{25}{}^{79}BrNaO_4{}^{80}Se$ $(M+Na)^+$ 558.9983, found 558.9994.

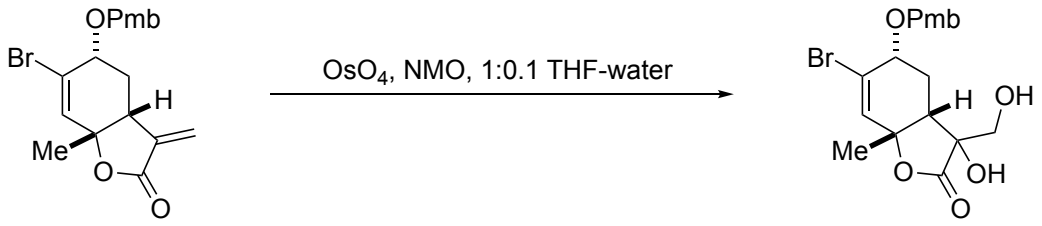
(3a*R*,7a*S*)-*rel*-6-Bromo-5-[(4-methoxy)methoxy]-7a-methyl-3-[(phenylselanyl)-methyl]-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2-ol (28.2).



28.1 **28.2**

DIBAL-H (1 M solution in hexane, 0.5 mL, 0.05 mmol) was added to a stirred and cooled (0 °C) solution of **28.1** (20 mg, 0.037 mmol) in CH_2Cl_2 (2 mL) (N_2 atmosphere). Stirring was continued for 30 min. The mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 20 cm), using 33% EtOAc-hexane, gave **28.2** (20 mg, 93.4%) as a colorless oil: FTIR ($CDCl_3$, cast) 3404, 3057, 2930, 2865, 2835, 1612, 1513, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.22–1.37 (m, 3 H), 1.55–1.62 (m, 1 H), 2.06–2.30 (m, 2 H), 2.70–3.00 (m, 2 H), 3.02 (br s, 1 H), 3.07–3.17 (m, 1 H), 3.82 (s, 3 H), 3.82–3.98 (m, 1 H), 4.55–4.68 (m, 2 H), 5.19–5.38 (m, 1 H), 6.16 (d, J = 40 Hz, 1 H), 6.20–6.91 (m, 2 H), 7.28–7.32 (m, 3 H), 7.32–7.36 (m, 2 H), 7.53–7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.1 (t), 24.4 (t), 28.2 (q), 28.7 (t), 29.1 (q), 29.5 (t), 41.9 (d), 43.7 (d), 46.4 (d), 49.6 (d), 55.3 (d), 71.2 (t), 71.9 (t), 74.9 (d), 75.0 (d), 81.9 (s), 82.5 (s), 99.4 (d), 102.3 (d), 113.8 (d), 127.0 (d), 127.3 (d), 127.4 (s), 128.0 (s), 129.2 (d), 129.3 (d), 129.5 (s), 129.5 (s), 129.6 (d), 129.8 (s), 129.9 (s), 130.0 (s), 133.0 (d), 133.1 (d), 134.4 (d), 135.3 (d), 159.4 (s); exact mass (electrospray) m/z calcd for $C_{24}H_{27}{}^{79}BrNaO_4{}^{80}Se$ $(M+Na)^+$ 560.9983, found 560.9994.

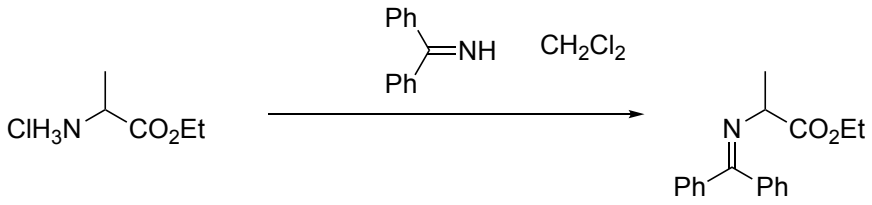
(3a*R*,7a*S*)-*rel*-6-Bromo-3-hydroxy-3-hydroxymethyl-5-[(4-methoxy)methoxy]-7a-methyl-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2-one (29.1).[38]



26.1 **29.1**

NMO (61 mg, 0.525 mmol) and OsO_4 (0.05 M in PhMe, 0.6 mL, 0.0316 mmol) were added to a stirred solution of **26.1** (0.06 g, 0.158 mmol) in a mixture of THF (0.1 mL) and water (1 mL). The mixture was stirred overnight and diluted with EtOAc. The organic layer was separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 × 20 cm), using 5% MeOH-CH_2Cl_2, gave **29.1** (50 mg, 75.9%) as a colorless oil: FTIR ($CDCl_3$, cast) 3279, 3002, 2931, 2832, 1756, 1513, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.63 (s, 3 H), 1.83–1.90 (m, 1 H), 2.11–2.19 (m, 1 H), 2.46–2.49 (m, 1 H), 3.46 (br s, 1 H), 3.71–3.75 (m, 1 H), 3.83 (s, 3 H), 4.00–4.03 (m, 2 H), 4.62–4.75 (m, 2 H), 6.25 (s, 1 H), 6.90–6.92 (m, 2 H), 7.33–7.34 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.8 (t), 27.8 (q), 29.7 (t), 45.8 (d), 55.3 (q), 63.2 (t), 73.2 (s), 73.2 (d), 82.2 (s), 114.0 (d), 128.8 (s), 129.5 (s), 129.9 (d), 132.6 (d), 159.7 (s), 176.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{18}H_{25}{}^{79}BrO_6N$ $(M+NH_4)^+$ 430.0866, found 430.086.

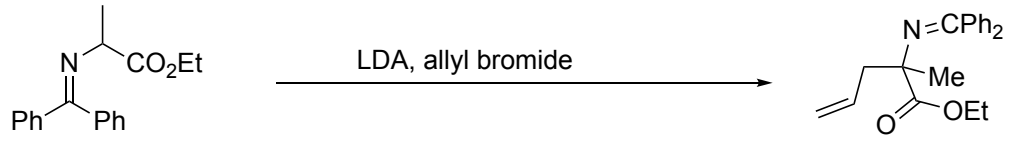
Ethyl 2-[(Diphenylmethylidene)amino]propanoate (31.3).[43]



31.1 **31.3**

Benzophenone imine (0.12 g, 0.65 mmol) was added to a stirred solution of **31.1** (0.1 g, 0.65 mmol) in CH_2Cl_2 (2 mL) and stirring was continued overnight. The mixture was quenched with water and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to afford the **31.3**, which was used directly in the next step: FTIR ($CDCl_3$, cast) 3.58, 2981, 2954, 1738, 1661, 1446, 1196 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.28 (t, J = 7 Hz, 3 H), 1.44 (d, J = 6.5 Hz, 3 H), 4.14–4.23 (m, 2 H), 7.20–7.67 (m, 10 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2 (q), 19.2 (q), 60.7 (d), 60.8 (d), 127.7 (d), 128.0 (d), 128.6 (d), 128.8 (d), 130.3 (d), 136.4 (s), 172.9 (s), 169.6 (s), 172.9 (s); exact mass (electrospray) m/z calcd for $C_{18}H_{19}NNaO_2$ $(M+Na)^+$ 281.1416, found 304.1308.

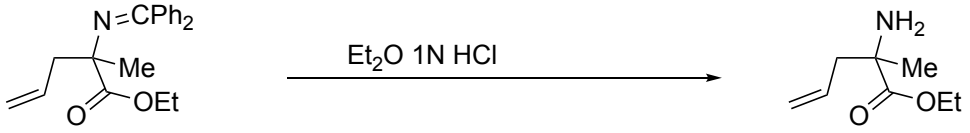
Ethyl 2-[(Diphenylmethylidene)amino]-2-methylpent-4-enoate (31.4).[42,43]



31.3 **31.4**

THF (20 mL) was added to *i*-Pr_2NH (6.8 mL, 0.048 mmol) and the stirred solution was cooled to at –78 °C (N_2 atmosphere). *n*-BuLi (2.5 M in hexane, 18 mL, 0.046 mmol) was added and stirring was continued for 40 min. A solution of **31.3** (5.7 g, 0.02 mol) in THF (8 mL) was added dropwise and stirring at –78 °C was continued for 40 min. Allyl bromide (4.1 mL, 0.048 mol) was added rapidly in one portion, the cold bath was left in place but not recharged and stirring was continued overnight. The resulting mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (15 × 15 cm), using 20% EtOAc-hexane, gave **31.4** (6.1 g, 94%) as a yellow oil: FTIR ($CDCl_3$, cast) 3061, 2980, 2937, 1731, 1629, 1445, 1277 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.12 (t, *J* = 7 Hz, 3 H), 1.42 (s, 3 H), 2.71–2.77 (m, 2 H), 3.63–3.75 (m, 2 H), 5.12–5.17 (m, 2 H), 5.90–5.97 (m, 1 H), 7.17–7.19 (m, 2 H), 7.31–7.40 (m, 6 H), 7.58–7.59 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9 (q), 24.2 (q), 47.6 (d), 60.3 (d), 66.3 (s), 118.3 (t), 127.7 (d), 128.0 (d), 128.3 (d), 128.5 (d), 128.6 (d), 130.0 (d), 133.8 (d), 137.2 (s), 141.1 (s), 166.7 (s), 174.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{21}H_{23}NO_2$ $(M+H)^+$ 321.1729, found 322.1802.

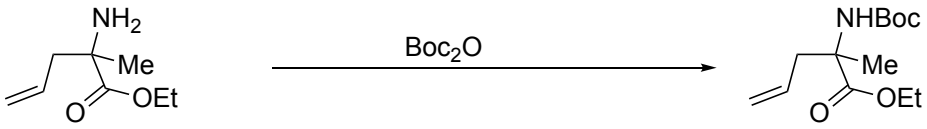
2-Amino-2-methylpent-4-enoate (31.5).[41]



31.4 **31.5**

Hydrochloric acid (1 N, 20 mL) was added to a stirred solution of **31.4** (3.2 g, 0.99 mol) in Et_2O (20 mL) and stirring was continued overnight. The organic layer was separated and the aqueous phase was basified with powder K_2CO_3 (to pH ~ 9) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. (water pump vacuum only) to afford **31.5**, which was used directly in the next step; FTIR ($CDCl_3$, cast) 3378, 2980, 1731, 1213, 1144 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.29 (t, J = 7 Hz, 3 H), 1.34 (s, 3 H), 1.70 (br s, 2 H), 2.27–2.31 (m, 1 H), 2.52–2.56 (m, 1 H), 4.15–4.21 (m, 2 H), 5.13–5.16 (m, 1 H), 5.70–5.78 (m, 2 H); exact mass (electrospray) m/z calcd for $C_{21}H_{23}NO_2$ $(M+H)^+$ 321.1729, found 322.1802.

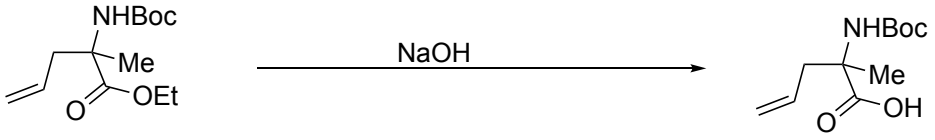
Ethyl 2-{[(*tert*-Butoxy)carbonyl]amino}-2-methylpent-4-enoate (31.6).[43]



31.5 **31.6**

Boc_2O (6.1 g, 0.0169 mmol) was added to a stirred solution of **31.5** (2.1 g, 0.013 mmol) in THF (200 mL) and stirring was continued overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel (15 × 20 cm), using 5% EtOAc-hexane, gave **31.6** (2.4 g, 71.7%) as a colorless oil: FTIR ($CDCl_3$, cast) 3430, 3371, 2980, 1718, 1497, 1173 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.30 (t, J = 7 Hz, 3 H), 1.45 (s, 9 H), 1.56 (s, 3 H), 2.59 (dd, J = 14, 7 Hz, 1 H), 2.76 (br, 1 H), 4.19–4.25 (m, 2 H), 5.12–5.15 (m, 2 H), 5.66–5.74 (m, 1 H); exact mass (electrospray) m/z calcd for $C_{13}H_{23}NO_4$ $(M+H)^+$ 257.1627, found 280.1519.

Ethyl 2-{[(*tert*-Butoxy)carbonyl]amino}-2-methylpent-4-enoic Acid (31.7).

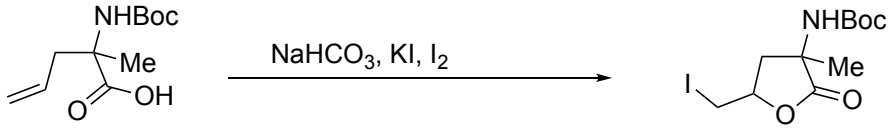


31.6 **31.7**

Aqueous NaOH (3 N, 25.4 mL) was added to a stirred solution of **31.6** (1.74 g, 6.76 mmol) in a mixture of THF (56 mL) and MeOH (56 mL). The mixture was heated at 80 °C overnight. The organic solvent was evaporated under (water pump, rotary evaporator) and the residue was extracted with CH_2Cl_2. The aqueous phase was acidified to pH ~ 1 with hydrochloric acid (1 N) and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated to give **31.7**, which was used without further purification: FTIR ($CDCl_3$, cast) 3430, 3371, 2980, 1718, 1497, 1173 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.45 (s, 9 H), 1.56 (s, 3 H), 2.66–2.69 (m, 2 H), 5.16–5.20 (m, 2 H), 5.71–5.78 (m, 1

H), 9.60 (br, 1 H); exact mass (electrospray) *m*/*z* calcd for $C_{11}H_{19}NO_4$ $(M–H)^-$ 229.1314, found 228.1.

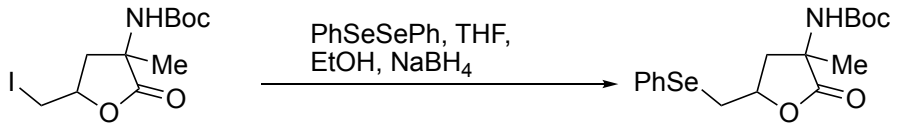
***tert*-Butyl *N*-[5-(Iodomethyl)-3-methyl-2-oxooxolan-3-yl]carbamate (32.1)**.[44]



31.7 **32.1**

A solution of **31.7** (0.25 g, 1.09 mmol) in aqueous $NaHCO_3$ (0.5 N, 7.3 mL) was added dropwise to a stirred solution of KI (1.08 g, 6.54 mmol) and I_2 (0.55 g, 2.18 mmol) in a mixture of THF (4 mL) and MeOH (4 mL). Stirring was continued overnight and the mixture was quenched with sufficient saturated aqueous $Na_2S_2O_5$ until the color was converted from dark brown to yellow. The resulting mixture was extracted with Et_2O and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 20 cm), using 20% EtOAc-hexane, gave **32.1** (0.32 g, 82.6%) as a white solid: FTIR ($CDCl_3$, cast) 3349, 2978, 2933, 1789, 1704, 1516, 1167 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.46 (s, 9 H), 1.49 (s, 3 H), 2.49–2.62 (m, 2 H), 3.33–3.52 (m, 2 H), 4.50–4.60 (m, 1 H), 5.02 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 5.55 (t), 23.02 (q), 28.32 (q), 41.46 (t), 57.90 (s), 80.67 (s), 154.27 (s), 176.52 (s) ; exact mass (electrospray) *m*/*z* calcd for $C_{11}H_{19}{}^{127}IO_4$ $(M+H)^+$ 356.0364, found 356.0353.

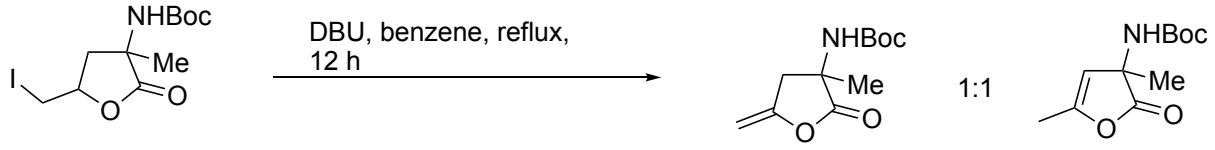
***tert*-Butyl *N*-{3-Methyl-2-oxo-5-[(phenylselanyl)methyl]oxolan-3-yl}carbamate (33.1)**.[51]



32.1 **33.1**

$NaBH_4$ (11 mg, 0.286 mmol) was added to a stirred and cooled (0 °C) solution of $(PhSe)_2$ (34 mg, 0.11 mmol) in THF (2 mL) (N_2 atmosphere). Then EtOH (1 mL) was added dropwise to produce a clear solution, and stirring was continued for 10 min. A solution of **32.1** (0.08 g, 0.22 mmol) in THF (1 mL) added dropwise, the cold bath was left in place, but not recharged, and stirring was continued overnight. The resulting mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 20 cm), using 33% EtOAc-hexane, gave **33.1** (60 mg, 70.9%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.44 (s, 9 H), 1.51 (s, 3 H), 2.47–2.60 (m, 2 H), 3.10–3.51 (m, 3 H), 4.50–4.54 (m, 1 H), 4.95–5.05 (m, 1H), 7.28–7.30 (m, 3 H), 7.54–7.57 (m, 2 H).

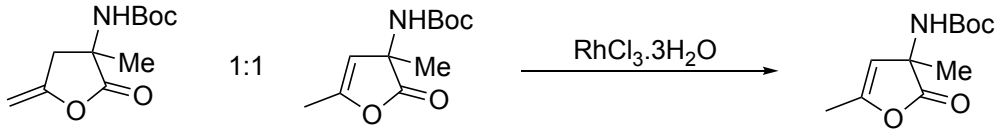
***tert*-Butyl *N*-(3-Methyl-5-methylidene-2-oxooxolan-3-yl)carbamate (32.2) and *tert*-Butyl *N*-(3,5-Dimethyl-2-oxo-2,3-dihydrofuran-3-yl)carbamate (30.4).**[45]



32.1 **32.2** **30.4**

DBU (0.76 mL, 5.52 mmol) was added to a stirred solution of **32.1** (0.3 g, 0.84 mmol) in PhH (15 mL) and the mixture was refluxed for 2 days at 80 °C. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 × 20 cm), using 30% EtOAc-hexane, gave **32.2** and **30.4** (90 mg, 47.1%) as a colorless oil which was a 1:1 mixture of isomers. The material had: FTIR ($CDCl_3$, cast) 3430, 2978, 2930, 1744, 1720, 1500, 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.41–1.46 (m, 18 H), 1.48–1.51 (m, 6 H), 2.03–2.04 (m, 2 H), 3.42 (br s, 1 H), 4.36–4.38 (m, 1 H), 4.81–4.82 (m, 1 H), 5.02 (br, 1 H), 5.20 (s, 1 H).

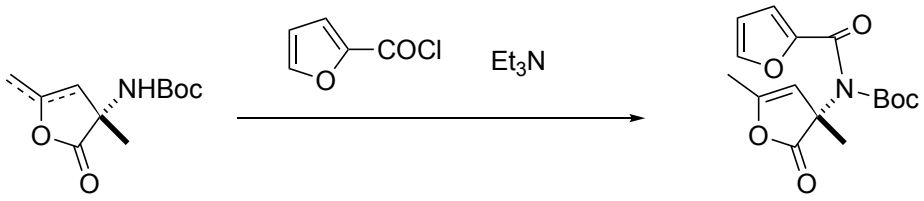
***tert*-Butyl *N*-(3,5-Dimethyl-2-oxo-2,3-dihydrofuran-3-yl)carbamate (30.4)**.[46]



32.2 **30.4** **30.4**

$RhCl_3.3H_2O$ (4 mg, 0.017 mmol), followed by water (1 mL) was added to a stirred solution of **32.2** and **30.4** (0.04 g, 0.17 mmol) in a mixture of EtOH (1 mL) and $CHCl_3$ (1 mL). The mixture was then stirred at 70 °C overnight, cooled and quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 20 cm), using 30% EtOAc-hexane, gave **30.4** (20 mg, 50%) as a colorless oil: FTIR ($CDCl_3$, cast) 3348, 3138, 2980, 2932, 1811, 1713, 1689, 1511, 1368, 1169 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.42 (s, 9 H), 1.50 (s, 3 H), 2.03 (s, 3 H), 4.94 (s, 1 H), 5.19 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.15 (q), 24.0 (q), 28.30 (q), 58.9 (s), 81.5 (s), 109.5 (d), 153.8 (s), 177.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{11}H_{17}NNaO_4$ $(M+Na)^+$ 227.1158, found 250.105.

***tert*-Butyl *N*-(3,5-Dimethyl-2-oxo-2,3-dihydrofuran-3-yl)-*N*-(furan-2-carbonyl)carbamate (30.3)**.

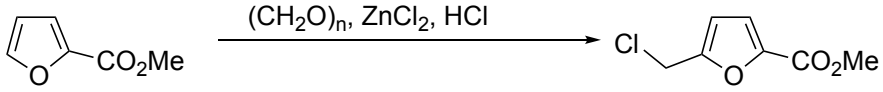


30.4 **30.3**

2-Furoyl chloride (0.59 μL, 0.6 mmol) was added to a stirred and cooled (0 °C) solution of **30.4** (70 mg, 0.3 mmol) in CH_2Cl_2 (2 mL). Et_3N (0.25 mL, 1.8 mmol) was added rapidly in one portion and stirring at room temperature was continued overnight. The mixture was

quenched with water and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 20 cm), using 50% EtOAc-hexane, gave **30.3** (90 mg, 93%) as a colorless oil: FTIR ($CDCl_3$, cast) 3142, 2981, 2917, 1798, 1725, 1466, 1270, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.43 (s, 9 H), 1.46 (s, 3 H), 2.04 (d, *J* = 1.5 Hz, 3 H), 5.20 (s, 1 H), 6.60 (dd, *J* = 3.3, 1.5 Hz, 1 H), 7.40 (dd, *J* = 3, 0.5 Hz, 1 H), 7.70 (dd, *J* = 3, 0.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 24.0 (q), 28.2 (q), 28.4 (s), 56.0 (s), 107.5 (d), 112.7 (d), 121.7 (d), 143.0 (s), 152.9 (s), 153.8 (s), 177.7 (s).

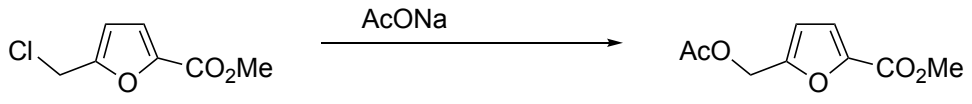
Methyl 5-(Chloromethyl)furan-2-carboxylate (35.2).[47]



35.1 **35.2**

HCl gas was bubbled for 2 h into a stirred slurry of **35.1** (9 mL, 0.084 mmol), $ZnCl_2$ (3.2 g, 0.023 mmol) and paraformaldehyde (3.65 g, 0.12 mol) in CH_2Cl_2 (40 mL) at room temperature. The mixture was poured onto ice and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (15 × 15 cm), using 10% EtOAc-hexane, gave **35.2** (11.3 g, 77%) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 3.92 (s, 3 H), 4.61 (s, 2 H), 6.51 (d, *J* = 3.5 Hz, 1 H), 7.15 (d, *J* = 3.5 Hz, 1 H).

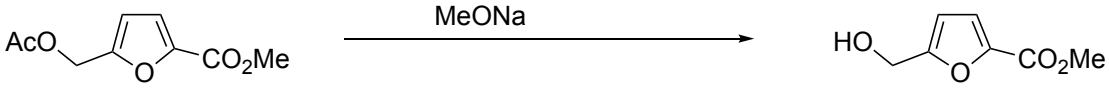
Methyl 5-[(Acetoxy)methyl]furan-2-carboxylate (35.3).[47]



35.2 **35.3**

AcONa (6.6 g, 0.08 mol) was added to a stirred solution of **35.2** (3.3 g, 0.019 mol) in a mixture of AcOH (13 mL) and Ac_2O (1.3 mL). The mixture was heated at 120 °C for 5 h, cooled to room temperature and diluted with Et_2O. The resulting suspension was neutralized with saturated aqueous Na_2CO_3 and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (15 × 25 cm), using 50% EtOAc-hexane, gave **35.3** (3 g, 79.6%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.10 (s, 3 H), 3.92 (s, 3 H), 5.10 (s, 2 H), 6.52 (d, J = 3.5 Hz, 1 H), 7.15 (d, J = 4.0 Hz, 1 H).

5-(Hydroxymethyl)furan-2-carboxylate (35.4).[47]

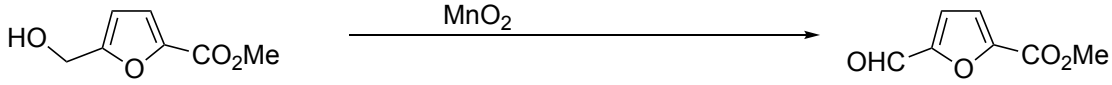


35.3 **35.4**

A solution of MeONa in MeOH [made from Na (391 mg) and MeOH (43 mL)] was added to a stirred solution of **35.3** (6.7 g, 0.033 mol) and stirring was continued overnight. The

yellow solution was passed through a column (3 × 30 cm) of cation ion-exchange resin (IRC-50) using MeOH. [The resin was added to aqueous NaOH solution (0.1 M). The mixture was swirled for a minute and the liquid was decanted. The resulting resin was swirled 3 times with water, the supernatant being decanted each time. Finally, dilute hydrochloric acid (0.1 N) was added, the mixture was swirled and the acid was decanted. The resin was washed three times as before with water and then poured into a chromatography column (3 × 30) and washed with MeOH. The above yellow solution was passed through the column, using MeOH.] The eluate was evaporated to give **35.4**, which was used without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.91 (s, 3 H), 4.70 (s, 2 H), 6.43 (d, J = 3.5 Hz, 1 H), 7.15 (d, J = 3.5 Hz, 1 H).

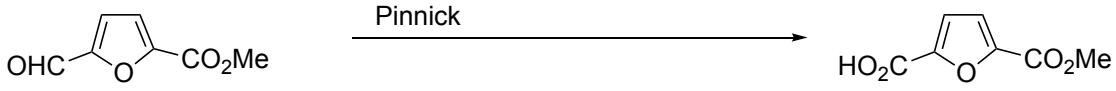
Methyl 5-Formylfuran-2-carboxylate (35.5).[52]



35.4 **35.5**

Commercial activated MnO_2 (11.1 g, 0.128 mmol) was added to a stirred solution of **35.4** (2.6 g, 0.016 mol) in CH_2Cl_2 (26 mL) and stirring was continued overnight, and the mixture was then filtered through a pad of Celite, using CH_2Cl_2 (20 mL) as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (15 × 25 cm), using 50% EtOAc-hexane, gave **35.5** (2.1 g, 85%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.98 (s, 3 H), 5.10 (s, 2 H), 7.28 (d, J = 4.5 Hz, 1 H), 9.83 (s, 1 H).

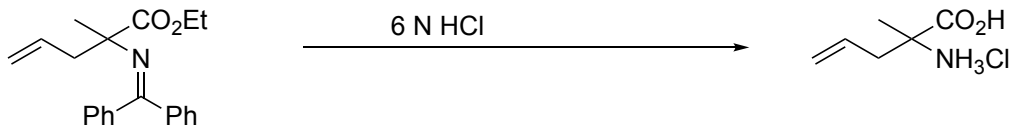
5-(Methoxycarbonyl)furan-2-carboxylic Acid (35.6).[48]



35.5 **35.6**

NaH_2PO_4 (104 mg, 0.87 mmol), 2-methyl-2-butene (0.46 mL, 4.35 mmol) and $NaClO_2$ (131 mg, 1.45 mmol) were added to a solution of **35.5** (90 mg, 0.58 mmol) in a mixture of *t*-BuOH (22 mL) and water (4 mL). Stirring was continued overnight at room temperature. The volatile materials were removed under reduced pressure (water pump, rotary evaporator, room temp.) and the residual liquid was extracted with CH_2Cl_2. Dilute hydrochloric acid (1 N) was added to the aqueous phase to adjust the pH to ~ 4) at which point the product crystallized. The solid was collected, washed with water and dried under vacuum to give **35.6** as a white solid (40 mg, 40.5%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.10 (s, 3 H), 8.52 (s, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.6 (q), 118.4 (d), 146.6 (s), 147.2 (s), 158.0 (s).

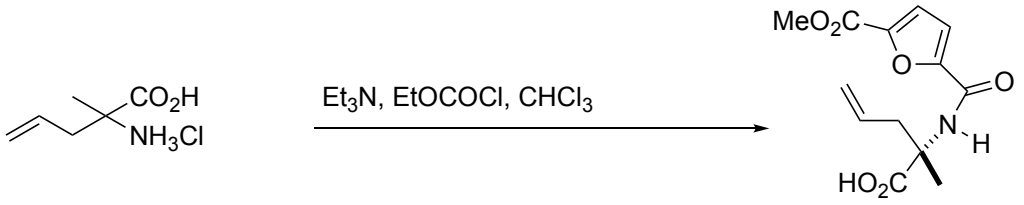
2-Amino-2-methylpent-4-enoic Acid Hydrochloride (37.1).[49]



31.3 **37.1**

Hydrochloric acid (6 N, 8 mL) was added to **31.3** (0.31 g, 0.97 mmol) and the mixture was refluxed (80 °C) overnight, cooled and extracted with CH_2Cl_2. The aqueous phase was evaporated under reduced pressure (oil pump vacuum, room temperature) to give **37.1** as a white solid, which was used without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.57 (s, 3 H), 2.46–2.8 (m, 2 H), 5.23–5.39 (m, 2 H), 5.78–5.82 (m, 1 H).

2-{[5-(Methoxycarbonyl)furan-2-yl]formamido}-2-methylpent-4-enoic Acid (37.3).[50]

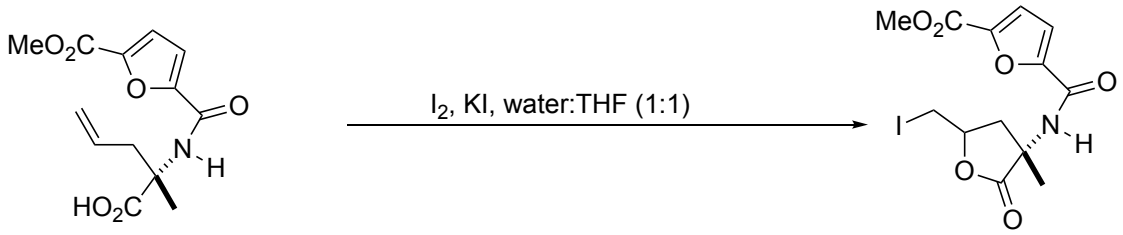


37.1 **37.3**

Et_3N (0.2 mL) was added to a stirred and cooled (0 °C) solution of **37.1** (200 mg, 0.50 mmol) with in a mixture of $CHCl_3$ (10 mL) and MeOH (1 mL). In another flask Et_3N (0.2 mL) was added to a stirred and cooled (0 °C) solution of 5-(methoxycarbonyl)furan-2-carboxylic acid (0.24 g, 1.43 mmol) in $CHCl_3$ (5 mL). EtOCOCl (0.12 mL, 1.27 mmol) was injected, followed by addition of the prepared solution of **37.1**. The resulting mixture was heated for 2 h at 50 °C, cooled and evaporated. Flash chromatography of the residue over silica gel (1.5 × 20 cm), using 33% EtOAc-hexane, gave **37.3** (0.15 g, 37%) as a colorless oil: FTIR ($CDCl_3$, cast) 3126, 2982, 2957, 2936, 1828, 1732, 1673, 1294 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.55 (s, 3 H), 2.53–2.70 (m, 2 H), 3.94 (s, 3 H), 5.13–5.22 (m, 2 H), 5.61–5.72 (m, 1 H), 7.15 (d, J = 3.6 Hz, 1 H), 7.30 (d,

J = 3.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.3 (q), 42.2 (t), 52.5 (q), 69.8 (t), 117.5 (d), 118.8 (d), 121.0 (s), 130.4 (d), 143.1 (s), 147.5 (s), 151.5 (s), 158.3 (s), 178.6 (s).

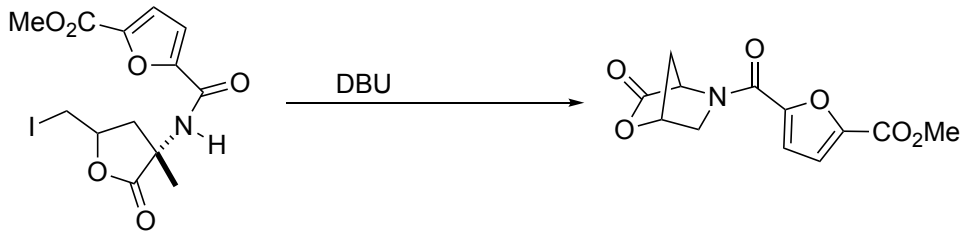
Methyl 5-{[5-(Iodomethyl)-3-methyl-2-oxooxolan-3-yl]carbamoyl}-furan-2-carboxylate (37.4).[44]



37.3 **37.4**

A solution of **37.3** (0.13 g, 0.46 mmol) in aqueous $NaHCO_3$ (0.5 N, 4 mL) was added dropwise to a stirred solution of KI (0.23 g, 0.38 mmol) and I_2 (0.12 g, 0.46 mmol) in a mixture of THF (4 mL) and MeOH (4 mL). Stirring was continued overnight and the mixture was quenched with sufficient saturated aqueous $Na_2S_2O_5$ until the color changed from dark brown to yellow. The resulting mixture was extracted with Et_2O and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 20 cm), using 50% EtOAc-hexane, gave **37.4** (0.1 g, 53.3%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.75 (s, 3 H), 2.05 (s, 3 H), 2.53–2.70 (m, 2 H), 3.36–3.57 (m, 2 H), 3.94 (s, 3 H), 4.61–4.67 (m, 1 H), 7.00–7.04 (m, 1 H), 7.18–7.20 (m, 1 H).

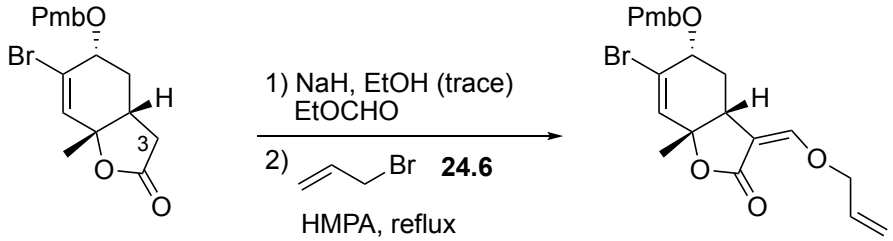
Methyl 5-{3-Oxo-2-oxa-5-azabicyclo[2.2.1]heptane-5-carbonyl}furan-2-carboxylate (37.5).[45]



37.4 **37.5**

DBU (0.3 mL, 1.94 mmol) was added to a stirred solution of **37.4** (0.12 g, 0.29 mmol) in PhH (12 mL) and the mixture was refluxed overnight at 80 °C. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 × 20 cm), using 50% EtOAc-hexane, gave the product (30 mg, 41.3%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.97 (s, 3 H), 2.20–2.73 (m, 2 H), 3.75–3.77 (m, 1 H), 3.93 (s, 3 H), 4.35–4.37 (m, 1 H), 5.07 (s, 1 H), 7.19–7.23 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.5 (q), 45.3 (t), 52.4 (q), 54.8 (t), 66.0 (s), 75.0 (d), 118.4 (d), 118.5 (d), 145.2 (s), 150.4 (s), 158.5 (s), 159.8 (s), 171.5 (s).

(3*Z*,3a*R*,5*R*,7a*S*)-*rel*-6-Bromo-5-[(4-methoxyphenyl)methoxy]-7a-methyl-3-[(prop-2-en-1-yloxy)methylidene]-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2-one (38.2).[35]



25.3 **38.2**

NaH (60%w/w in mineral oil, 6 mg, 0.16 mmol) was covered with THF (4 mL) and then EtOH (0.96 μL) was added. When bubbling had stopped (ca 5 min) **25.3** (60 mg, 0.16 mmol) was tipped in and the reaction flask was lowered into a preheated oil bath (ca 40 °C) and HCO_2Et (12 μL, 0.16 mmol) was injected. Stirring at reflux was continued for 1 h. HMPA (0.11 mL, 0.64 mmol) was added and refluxing was continued for 30 min. Then, allyl bromide (**24.6)** (55 μL, 0.64 mmol) was added and refluxing was continued for 2 h. The mixture was cooled and quenched with aqueous saturated NH_4Cl and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 × 15 cm), using 50% EtOAc-hexane, gave **38.2** (20 mg, 28%) as a colorless oil: FTIR ($CDCl_3$, cast) 2969, 2929, 2867, 1752, 1665, 1514, 1249, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.44 (s, 3 H), 2.05–2.17 (m, 2 H), 2.89–2.91 (m, 1 H), 3.82 (s, 3 H), 3.97 (t, J = 6 Hz, 1 H), 4.25 (dd, J = 18, 7.5 Hz, 1 H), 4.4 (dd, J = 18, 7.5 Hz, 1 H), 4.63 (AB q, J = 14, $\Delta\nu_{AB}$ = 235.7 Hz, 2 H), 5.25–5.32 (m, 2 H), 5.81–5.90 (m, 1 H), 6.16–6.17 (m, 1 H), 6.52–6.53 (m, 1 H), 6.88–6.91 (m, 2 H), 7.32–7.34 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.1 (q), 31.6 (t), 40.6 (d),

55.3 (d), 72.6 (t), 74.0 (q), 75.5 (t), 80.8 (s), 105.8 (t), 113.9 (d), 119.3 (s), 128.4 (s), 129.5 (d), 129.9 (s), 132.4 (d), 154.9 (d), 159.4 (s), 166.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{21}H_{23}{}^{79}BrNaO_5$ $(M+Na)^+$ 457.0621, found 457.0633.

Improved method

NaH (60%w/w in mineral oil, 4 mg, 0.081 mmol) was covered with THF (2 mL) and then EtOH (2 drops) was added. When bubbling had stopped (ca 5 min) **25.3** (30 mg, 0.081 mmol) was tipped in and the reaction flask was lowered into a preheated oil bath (ca 40 °C) and HCO_2Et (7 μL, 0.081 mmol) was injected. Stirring at reflux was continued for 2 h. HMPA (40 μL, 0.24 mmol) was added and refluxing was continued for 30 min. Then, allyl iodide (44 μL, 0.49 mmol) was added and refluxing was continued overnight. The mixture was cooled and quenched with water and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 × 15 cm), using 50% EtOAc-hexane, gave **38.2** (25 mg, 70%) as a colorless oil.

(3*R*,3a*R*,5*R*,7a*S*)-*rel*-6-Bromo-5-[(4-methoxyphenyl)methoxy]-7a-methyl-2-oxo-3-[(prop-2-en-1-yl)-2,3,3a,4,5,7a-hexahydro-1-benzofuran-3-carbaldehyde (38.3).

38.2 **38.3**

Compound **38.2** (20 mg, 0.046 mmol) was dissolved in dry DMF (2 mL) and the solution was refluxed overnight (oil bath at 160 °C). The resulting solution was cooled and diluted with EtOAc. The organic layer was transferred to a separatory funnel and washed with water (5 × 2 mL) (do not shake!). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 × 20 cm), using 30% EtOAc-hexane, gave **38.3** (20 mg, 99%) as a colorless oil: FTIR ($CDCl_3$, cast) 3076, 3007, 2928, 2868, 2838, 1773, 1719, 1514, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.55 (s, 3 H), 2.03–2.09 (m, 1 H), 2.19–2.28 (m, 1 H), 2.29–2.62 (m, 3 H), 3.84 (s, 3 H), 3.92–3.94 (m, 1 H), 4.53 (s, 2 H), 4.53–5.32 (m, 2 H), 5.74–5.80 (m, 1 H), 6.29 (s, 1 H), 6.90–6.92 (m, 2 H), 7.29–7.30 (m, 2 H), 9.56 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.5 (t), 27.6 (q), 38.6 (s), 42.4 (d), 55.3 (d), 61.6 (t), 72.3 (t), 76.7 (q), 81.9 (s), 113.8 (d), 121.2 (t), 127.5 (s), 128.8 (s), 130.0 (d), 131.5 (d), 133.7 (d), 159.6 (s), 173.6 (s), 196.3 (d); exact mass (electrospray) *m*/*z* calcd for $C_{21}H_{23}{}^{79}BrNaO_5$ $(M+Na)^+$ 457.0621, found 457.0619.

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