University of Alberta

Preparation of *para*-disubstituted benzenes, formation of optically pure cyclic amines by intramolecular conjugate displacement and total synthesis of marinopyrrole B

by

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DEDICATED TO

MY PARENTS AND MY HUSBAND XI HU

ABSTRACT

The first chapter of this thesis describes a method for making *para*-disubstituted benzenes. The process involves reaction of acetylides with aldehydes to give 1,4-diols, triple bond reduction and oxidation of the resulting 1,4-diols to 1,4-diketones. Treatment of the 1,4-diketones with vinylmagnesium bromide, followed by ring-closing metathesis and dehydration, affords *para*-disubstituted benzenes. The method was applied to the synthesis of C5-aryl carbohydrates.

The second chapter describes an intramolecular conjugate displacement (ICD) between a nitrogen nucleophile and a Morita-Baylis-Hillman acetate with a chiral auxiliary for making optically pure cyclic amines. Removal of the chiral auxiliary from the ICD products with DIBAL-H provides optically pure six- or seven-membered cyclic amines having a stereogenic center α to nitrogen.

The last chapter of this thesis describes the first total synthesis of the marine antibiotic alkaloid, marinopyrrole B, which shows very strong activity against methicillin-resistant *Staphylococcus aureus*. It is known that marinopyrrole B can not be made directly by bromination of marinopyrrole A, and so bromination of one pyrrole unit at an early stage was the basis of my successful route. The nitrogen of the brominated pyrrole was alkylated with a Michael acceptor having an allylic leaving group, and the product was then modified to construct the second pyrrole via a Paal-Knorr reaction. The nitrogen of the resulting 1,3'-bipyrrole was then protected, followed by addition of an

appropriate Grignard reagent, oxidation and deprotection reactions, to obtain a 1,3'-bipyrrole with two aromatic carbonyl groups. Finally, dichlorination and demethylation generated racemic marinopyrrole B.

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LIST OF ABBREVIATIONS

Ac	Acetyl
Ar	Aromatic ring
9-BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
brsm	Based on recovered starting materials
Bu	*n*-Butyl
^{t}Bu (or *t*-Bu or Bu^{t} or Bu-*t*)	*tert*-Butyl
CD	Circular dichroism
Cbz	Benzyloxycarbonyl
COSY	Correlation spectroscopy
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylidene acetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
$(DHQD)_2PHAL$	Hydroquinidine 1,4-phthalazinediyl diether
DIBAL-H	Diisobutylaluminum hydride
DMA	*N*,*N*-Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine

DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
ee	Enantiomeric excess
Et	Ethyl
EWG	Electron-withdrawing group
HMBC	Heteronuclear Multiple Bond Correlation
HPLC	High-performance liquid chromatography
HSQC	Heteronuclear Single Quantum Coherence
IBX	2-Iodoxybenzoic acid
IC_{50}	Concentration that gives 50% inhibition of an enzyme
ICD	Intramolecular conjugate displacement
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
LG	Leaving group
MBH	Morita-Baylis-Hillman
Me	Methyl
MIC	Minimum inhibitory concentration is the lowest concentration of a drug in μg/mL that inhibits the visible growth of a strain of bacteria
MIC_{50}	Minimum concentration of an antimicrobial

	agent which inhibits 50% of the bacteria being tested
MIC_{90}	Minimum concentration of an antimicrobial agent which inhibits 90% of the bacteria being tested
mp	Melting point
MRSA	Methicillin-resistant *Staphylococcus aureus*
MS	Molecular sieves
NBS	*N*-Bromosuccinimide
NCE	New chemical entity
NCS	*N*-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
NMO	*N*-Methylmorpholine-*N*-oxide
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
Nu	Nucleophile
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PCC	Pyridinium chlorochromate
Ph	Phenyl
PPTS	Pyridinium *p*-toluenesulfonate
i-Pr	Isopropyl
pyr	Pyridine
rr	Regioisomer ratio

rt	Room temperature
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
Ts	*p*-Toluenesulfonyl
TsOH	*p*-Toluenesulfonic acid

Chapter 1

Conversion of 1,4-Diketones into *para*-Disubstituted Benzenes

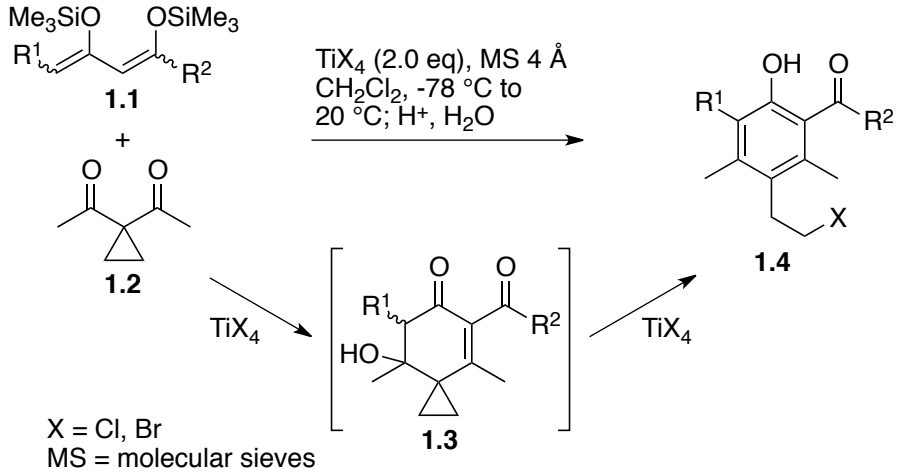
1. Introduction

1.1 General

Making aromatic rings has been studied by chemists for many years and a number of different methods for constructing aromatic rings, which can be used to *p*repare aromatic systems existing in natural products, have been developed.[1] Some of the recent methods for the preparation of aromatic rings will be described in this Introduction.[2-8]

1.2 Formation of aromatic rings via a formal [3+3] cyclization

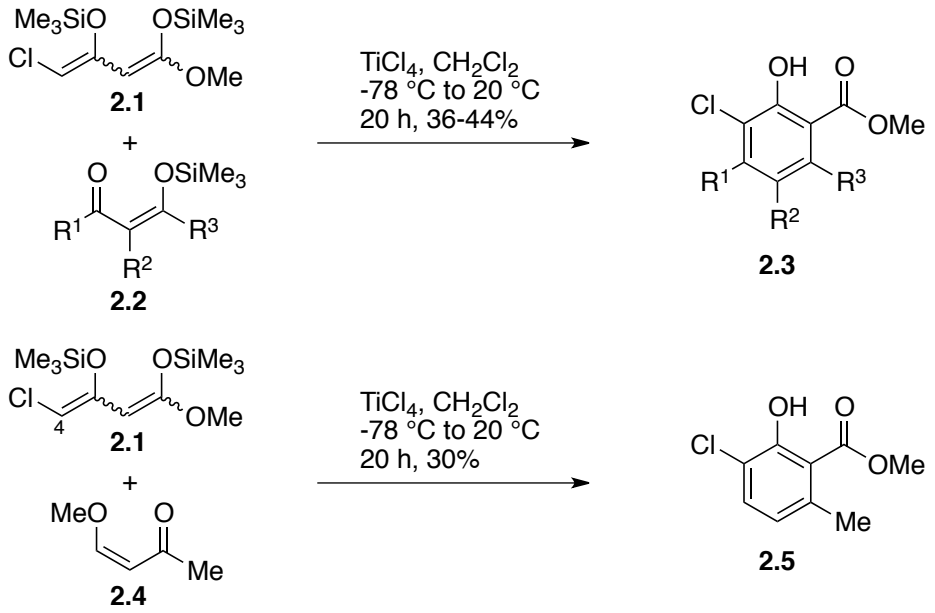
Langer and coworker found that when the silyl enol ether **1.1** and 1,1-diacetylcyclopropane (**1.2)** were treated with $TiCl_4$, the functionalized salicylic ester **1.4** was obtained in moderate to good (44–82%) yield.[2a] They proposed that the intermediate **1.3** was formed first, and then a $TiCl_4$-mediated homoallyl



Scheme 1

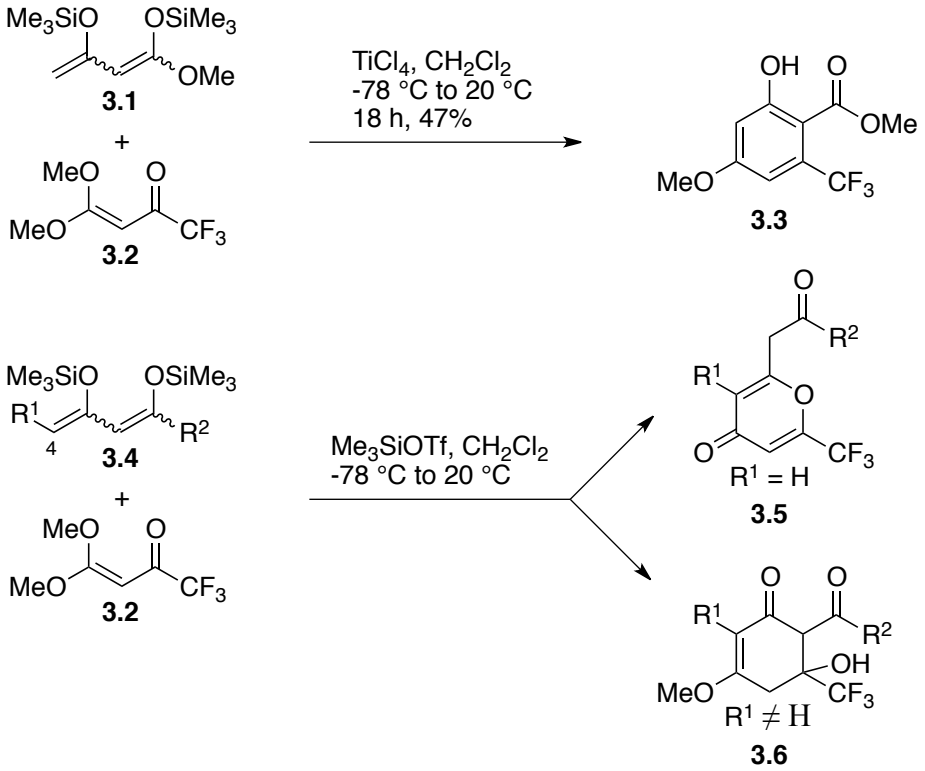
rearrangement, followed by elimination of water, generated the substituted benzene **1.4**. Intermediate **1.3** was isolated when only 0.5–0.7 equivalents of $TiCl_4$ was used. When $TiBr_4$ was used instead of $TiCl_4$, a similar result was observed.

When one carbonyl group of the 1,3-diketone component was silylated (Scheme 2), the formal [3+3] cyclization reaction also worked.[2b] In this case the use of high concentrations resulted in improved yields. The 3-chlorosalicylate **2.3** was formed via $TiCl_4$-mediated isomerization of **2.2**, followed by conjugate addition and cyclization reactions. When compound **2.4**, instead of the 1,3-diketone, was used in the reaction, the corresponding substituted phenol **2.5** was produced in 30% yield.[2b] Langer and coworkers proposed that this cyclization occurred via conjugate addition of C(4) of **2.1** onto **2.4**, followed by a Mukaiyama-aldol reaction.



Scheme 2

Langer and coworkers also found that the trifluoromethyl-substituted benzene **3.3** could be formed via the $TiCl_4$-mediated formal [3+3] cyclization.[2c] The yield of **3.3** was affected by the concentration of the reaction mixture, the temperature and the stoichiometry. The best result was obtained when the reaction mixture was slowly warmed from –78 °C to 20 °C, and highly concentrated solutions and 2 equivalents of **3.1** were used. Possibly, $TiCl_4$-mediated oxidative dimerization of the diene **3.1**[9] made 2 equivalents necessary.

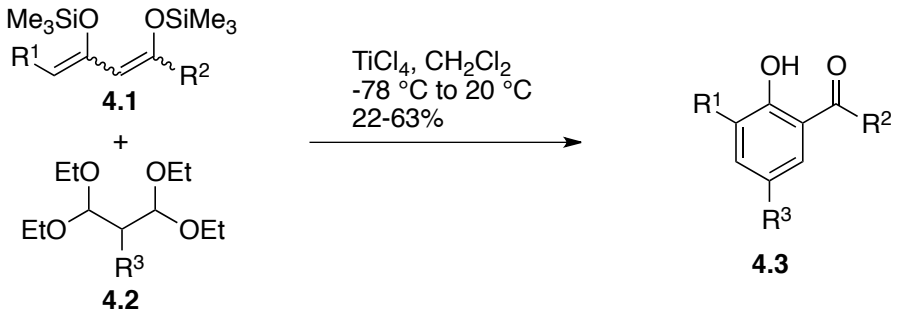


Scheme 3

When compounds **3.4** and **3.2** were treated with $Me_3SiOSO_2CF_3$ rather than $TiCl_4$, totally different products were obtained. When there was no

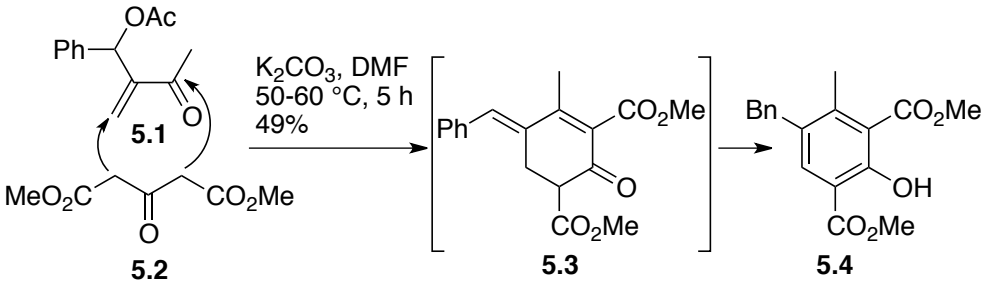
substituent on C(4) of **3.4**, the pyran-4-one **3.5** was produced. When C(4) of **3.4** carried an alkyl group or chlorine atom, the cyclohexenone **3.6** was generated because of steric hindrance due to the substituent at C(4) of **3.4**. In contrast to the $TiCl_4$-mediated cyclization, this $Me_3SiOSO_2CF_3$-mediated reaction gave highest yields when *dilute* solutions were used.

When 2-alkyl-1,1,3,3-tetraethoxypropanes **4.2** were subjected to the $TiCl_4$-mediated [3+3] cyclization reaction with 1,3-bis silyl enol ethers **4.1**, similar results were obtained.[2d]



Scheme 4

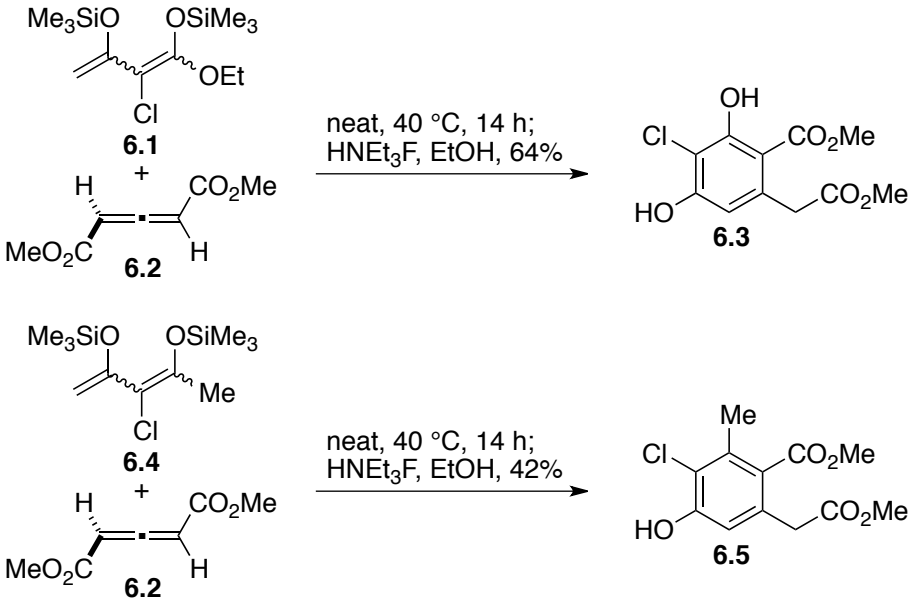
Kim and coworkers reported that highly substituted phenols could be prepared from Baylis-Hillman adducts via a [3+3] annulation reaction.[3a] One example is shown in Scheme 5. The Baylis-Hillman acetate **5.1** was treated with the 1,3-dinucleophilic compound **5.2** and K_2CO_3 to afford the substituted phenol derivative **5.4** via an S_N2' reaction, aldol condensation, keto-enol tautomerization and 1,3-H shift.



Scheme 5

1.3 Formation of aromatic rings via a [4+2] annulation strategy

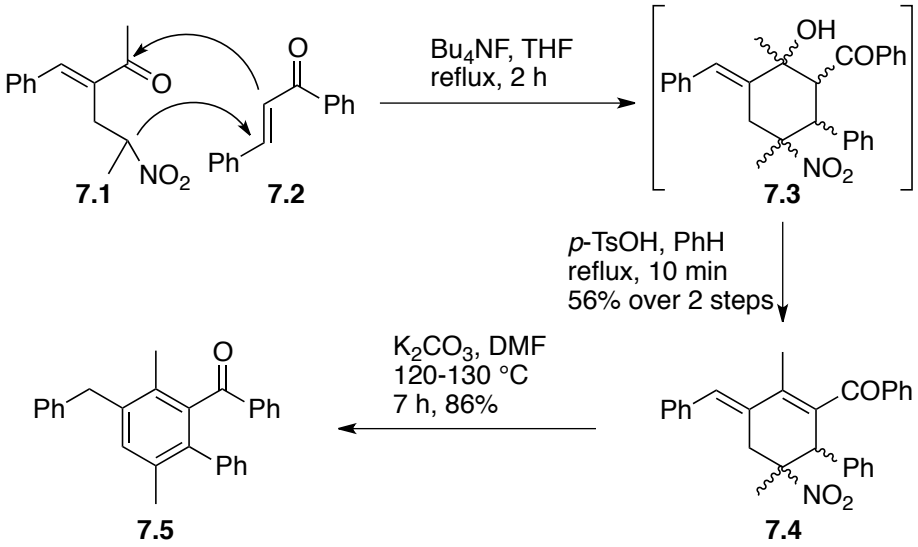
In addition to the $TiCl_4$-mediated [3+3] cyclization reaction, Langer and coworkers also reported a [4+2] cycloaddition and used it to form substituted phenols (Scheme 6).[2e] The [4+2] cyclization between diene **6.1** and allene **6.2** gave the regioselectively chlorinated phenol **6.3** in 64% yield. The product **6.5** was obtained via a similar process. This method provides a good way to prepare



Scheme 6

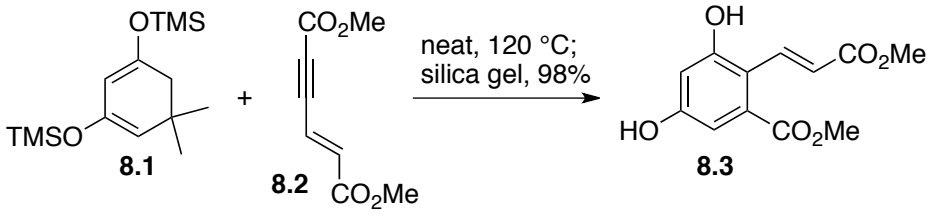
regioselectively chlorinated benzene derivatives which are not available by direct chlorination of the corresponding benzoate.

Kim and coworkers also synthesized in a regioselective manner some polysubstituted benzene derivatives via a [4+2] annulation strategy.[3b] Compound **7.1**, which was prepared from the corresponding Baylis-Hillman acetate and nitroethane, was used as starting material and treated with the *β*-substituted Michael acceptor **7.2** in the presence of Bu_4NF to afford the cyclic intermediate **7.3** in 80% yield as a mixture of diastereomers. Refluxing a mixture of **7.3** and *p*-TsOH in PhH gave **7.4** as a mixture of two isomers (*syn*/*anti*), confirming the structure of **7.3**. Finally, elimination of HNO_2 and isomerization of the *exo*-double bond generated the substituted benzene **7.5**.



Scheme 7

By heating a mixture of diene **8.1** and dienophile **8.2**, Danishefsky and coworkers synthesized the polysubstituted aromatic compound **8.3** as the only product via Diels-Alder reaction.[4] They found that the reaction proceeded under kinetic control, by monitoring the progress of the reaction at different temperatures by ^{1}H NMR spectroscopy. They also found that the cyclization occurred at the ynoate site of the dienophile, and the regioselectivity was controlled by the olefinic ester group. Computational studies on the four possible transition states for the reaction, led to predictions consistent with the experiment results, and also showed that acetylenes with two electron-withdrawing groups were more reactive in Diels-Alder reactions than ethylenes with two electron-withdrawing groups.

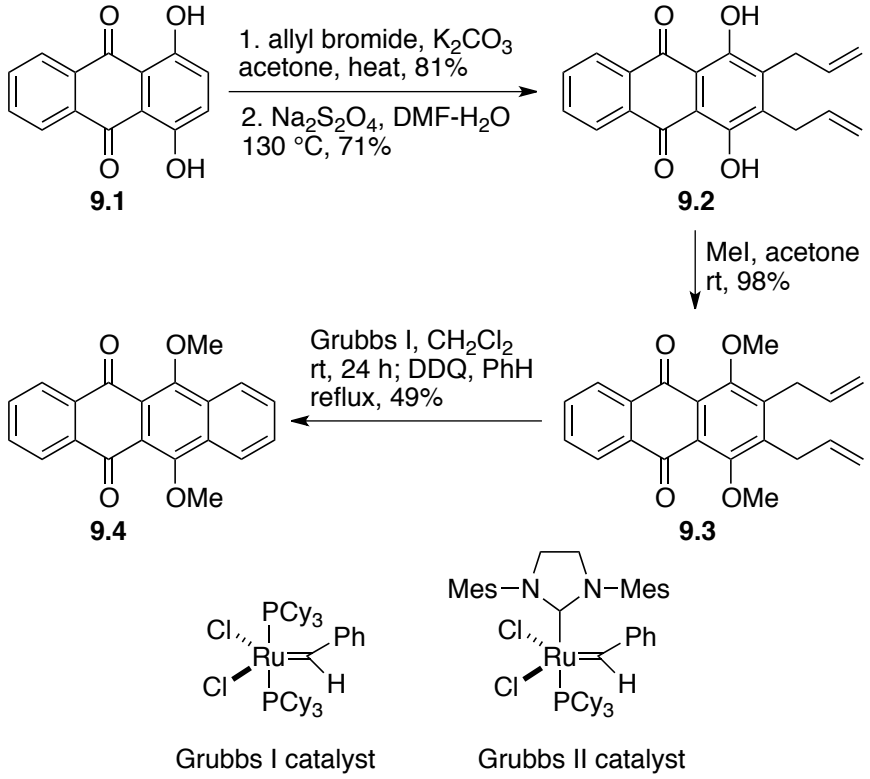


Scheme 8

1.4 Formation of aromatic rings via ring-closing metathesis

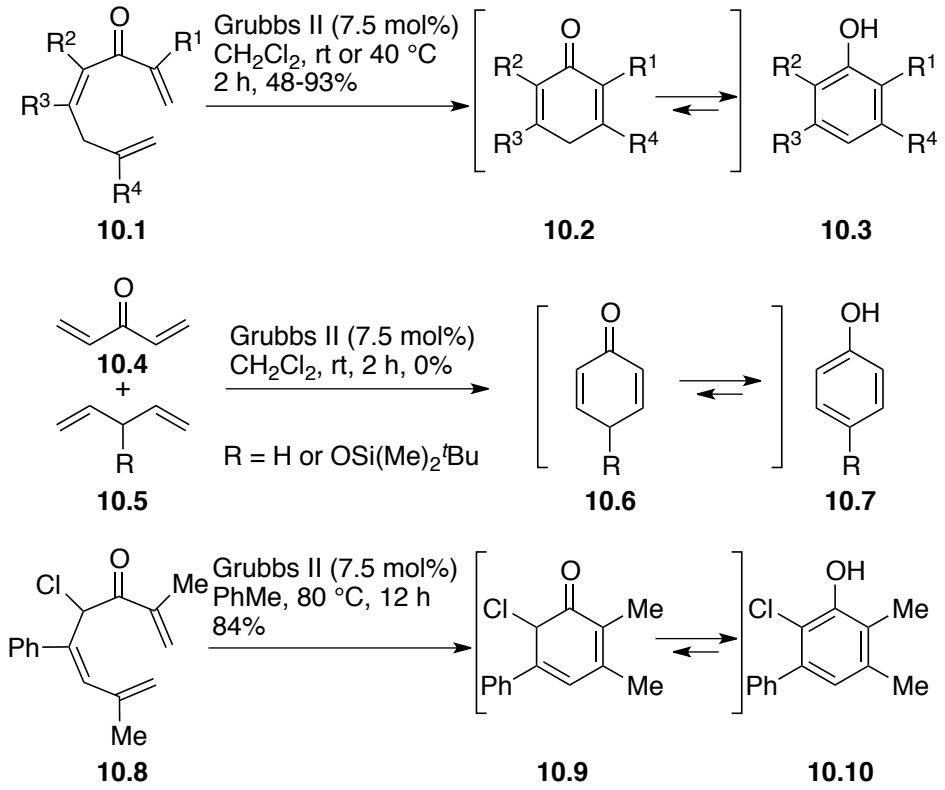
Kotha and coworker reported a methodology for benzannulation using ring-closing metathesis as a key step.[5a] *O*-Allylation of the *p*-benzenediol **9.1**, followed by double Claisen rearrangement, gave compound **9.2**. Attempts to apply the ring-closing metathesis reaction to **9.2** using Grubbs' catalysts (Grubbs I[10] and Grubbs II[11] catalysts) failed, probably due to coordination of the phenolic

OH groups with the catalyst. After protecting the OH groups by alkylation with MeI, the product **9.3** was subjected to ring-closing metathesis using Grubbs I catalyst,[10] and then DDQ oxidation generated the desired substituted benzene **9.4** in 49% yield over two steps.



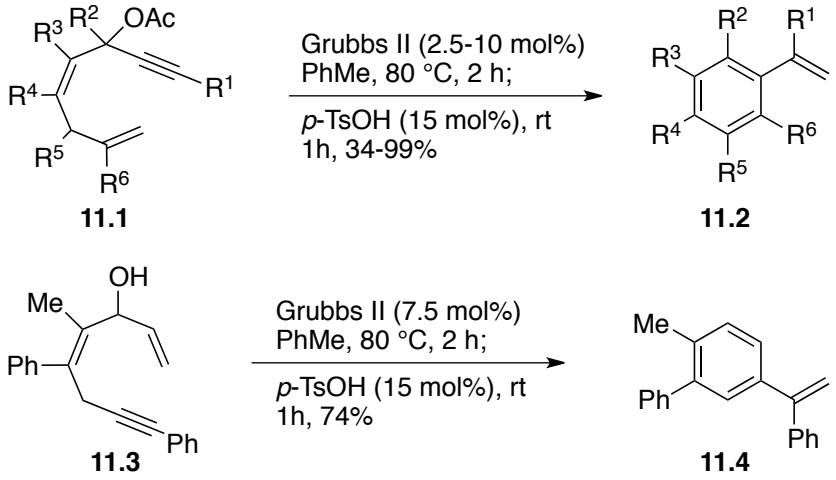
Scheme 9

Yoshida and coworker prepared a variety of substituted phenols **10.3** using ring-closing olefin metathesis.[5b] When compounds **10.4** and **10.5** were treated with Grubbs II catalyst,[11] none of the desired phenol was formed, probably due to oligomerization. Heating (80 °C) a mixture of **10.8** and Grubbs II catalyst[11] in PhMe gave the expected phenol derivative **10.10** in good yield.



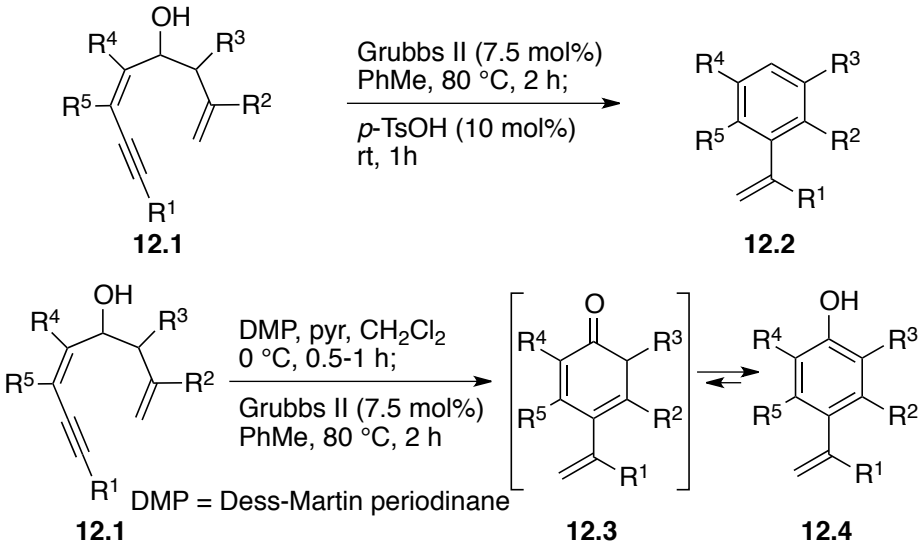
Scheme 10

Yoshida and coworkers also found that the substituted styrenes **11.2** could be produced by treating acyl-protected enyne substrates **11.1** with Grubbs II catalyst,[11] followed by dehydration under acidic conditions.[5c] When the substrate contained an OH group instead of an OAc group, the yield decreased dramatically to 9%, a large amount of the substrate being recovered from the ring-closing metathesis step. When a different type of enyne **11.3** was used under similar conditions, the expected styrene **11.4** was obtained in good yield (74%).



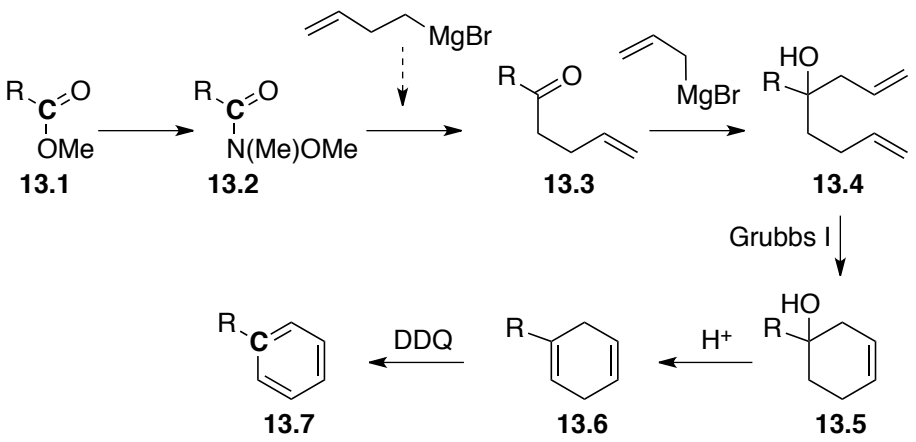
Scheme 11

In order to improve the synthesis of substituted styrenes, Yoshida and coworkers subjected compounds **12.1** to ring-closing metathesis without acyl protection of the hydroxyl group in **12.1**.[5d] A variety of substituted styrenes **12.2** were prepared under both nitrogen and ethylene atmospheres (29–90% yield under N_2, and 28–84% yield under C_2H_4). The results revealed that the yields were higher for reactions run under ethylene than under nitrogen in most cases. The OH group in **12.1** was then oxidized, and the resulting ketones were treated with Grubbs II catalyst[11] to give 4-vinylphenols **12.4** under both nitrogen and ethylene atmospheres, after tautomerization. It was found that reactions under ethylene provided the desired products in high yields in most cases.

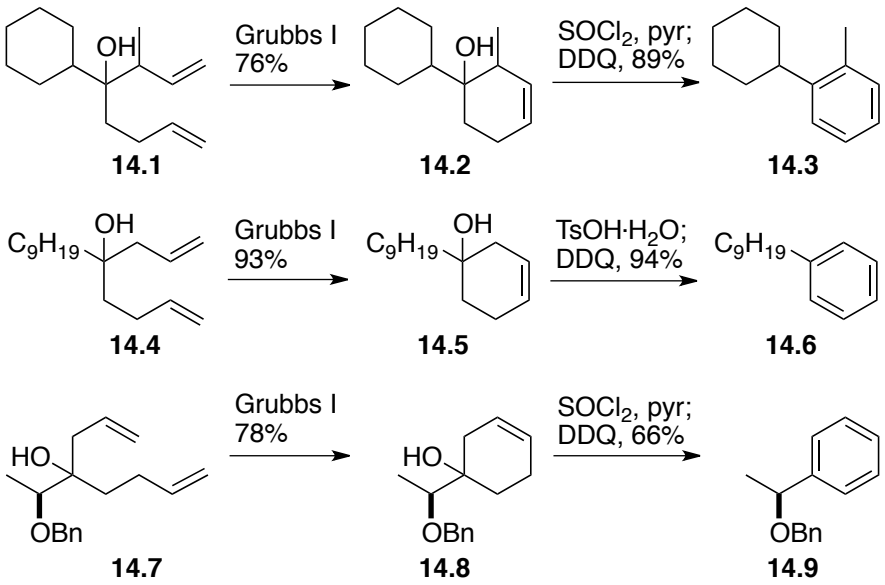


Scheme 12

Using ring-closing metathesis to make substituted benzenes was also studied in this laboratory.[6] The aim of the procedure was to convert an ester into a benzene ring in such a way that the carbonyl carbon of the ester is incorporated into the benzene ring. The principle of this unusual route for making benzenes is shown in Scheme 13. A variety of monosubstituted benzenes and a limited range of polysubstituted benzenes were produced by this process. In the ring-closing metathesis step, the six-membered rings were formed in 78–100% yield with Grubbs I catalyst[10] or Grubbs II catalyst.[11] Then, using TsOH or else $SOCl_2$ and pyridine, followed by dehydrogenation with DDQ gave the substituted benzenes in 66–94% yield. Some examples are listed in Scheme 14.



Scheme 13

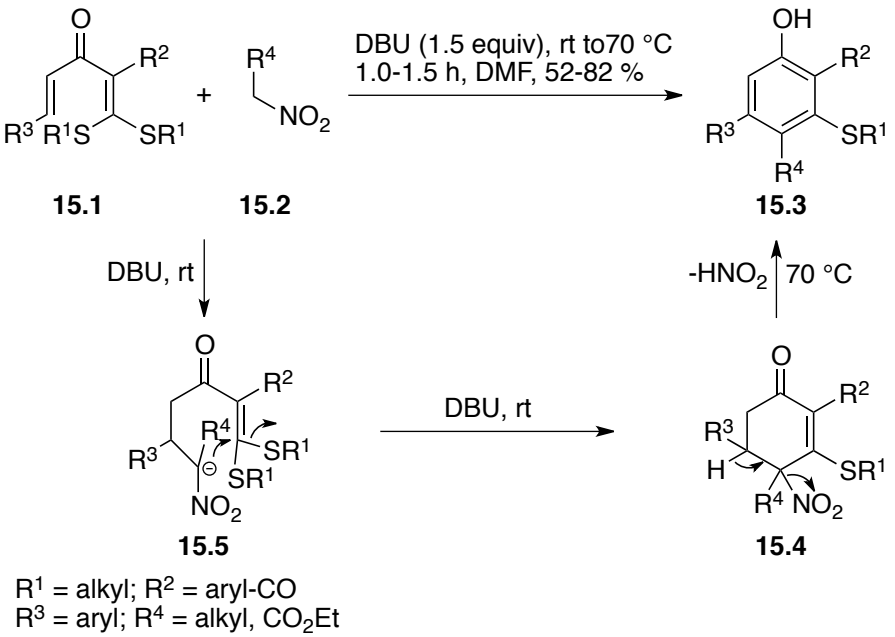


Scheme 14

1.5 Other methods for making aromatic rings

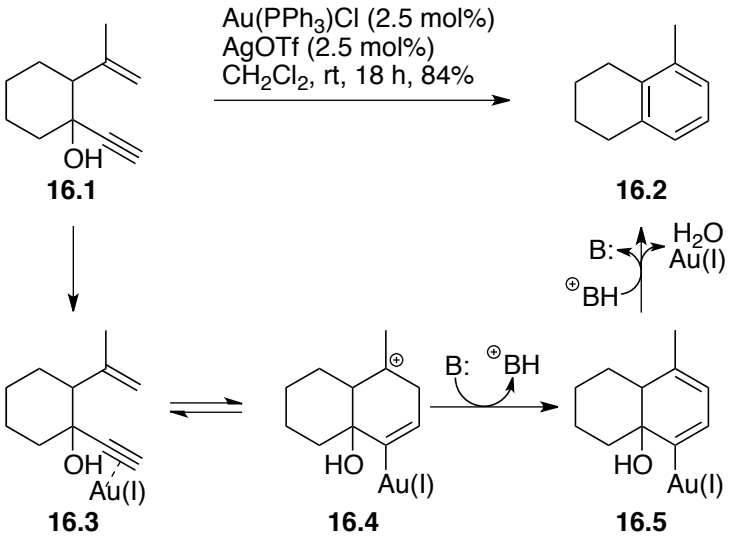
Dong and coworkers reported the synthesis of substituted phenols by [5+1] annulation.[7] α-Alkenoylketenedithioacetals **15.1** as the five-carbon 1,5-

bielectrophilic components and nitroalkanes **15.2** as the one-carbon nucleophiles in the presence of DBU generated the highly substituted phenols **15.3** in 52–82% yield. It was proposed that addition of the carbanions of **15.2** to the double bond bearing an aryl group in **15.1** occurs first. This step is followed by an intramolecular addition-elimination, to give cyclohexenones **15.4**. Finally, elimination of HNO_2 and tautomerization affords the products **15.3**.



Scheme 15

With gold catalysis, Barriault and coworker synthesized substituted tetrahydronaphthalenes.[8] They proposed that the formation of a Au(I) complex **16.3**, followed by 6-*endo-dig* cyclization gives intermediate **16.4**; deprotonation of **16.4**, followed by dehydration and protonolysis of **16.5**, then produces the substituted benzene **16.2** in 84% yield.

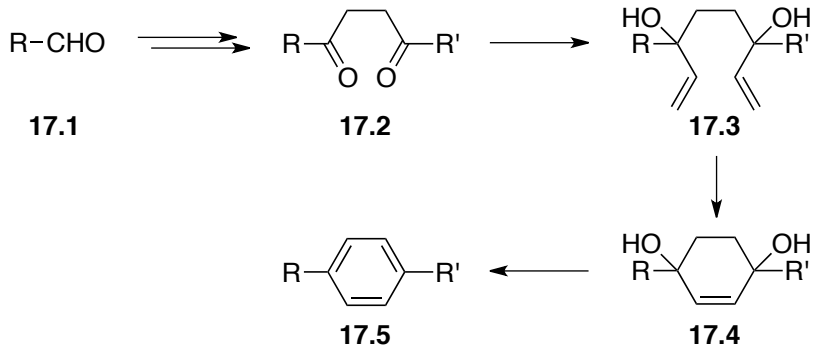

Au(PPh3)Cl (2.5 mol%)
AgOTf (2.5 mol%)
CH2Cl2, rt, 18 h, 84%
OH
16.1
16.2
B:
H2O
Au(I)
BH
OH
Au(I)
16.3
HO
Au(I)
16.4
B:
BH
HO
Au(I)
16.5

Scheme 16

2. Results and Discussion

2.1 Research objectives

As mentioned in the introduction to this chapter, conversion of esters into benzene rings that incorporate the ester carbonyl carbon has been developed in this laboratory.[6] To extend this methodology, a related procedure, conversion of aldehydes into *p*-substituted benzenes incorporating the original carbonyl carbon was explored (Scheme 17). In this approach, the intermediate 1,4-diketones **17.2** were treated with vinyllithium to give diols **17.3** which were then subjected to ring-closing metathesis so as to generate the six-membered rings **17.4**. Finally, double dehydration of **17.4** afforded the *p*-substituted benzenes **17.5**.

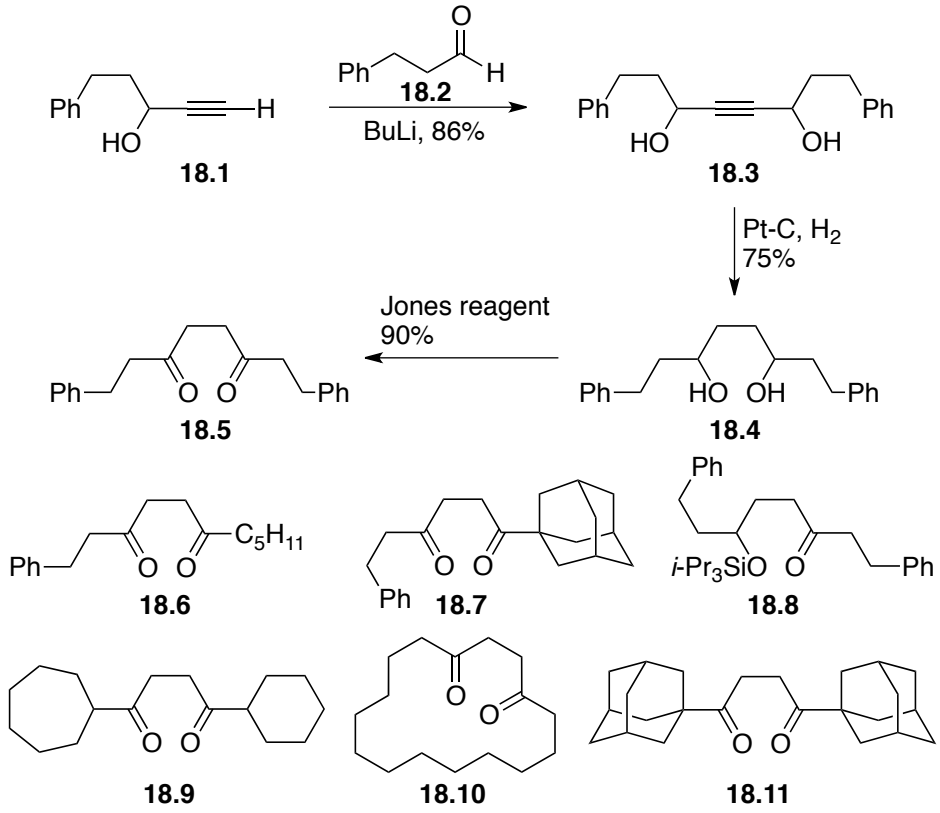


Scheme 17

2.2 Preparation of 1,4-diketones

Dr. Ziffle, a former member of this laboratory, had prepared the 1,4-diketones listed in Scheme 18. Treatment of acetylene **18.1** with aldehyde **18.2** and BuLi generated alkyne diol **18.3**, which was converted into diol **18.4** with Pt-

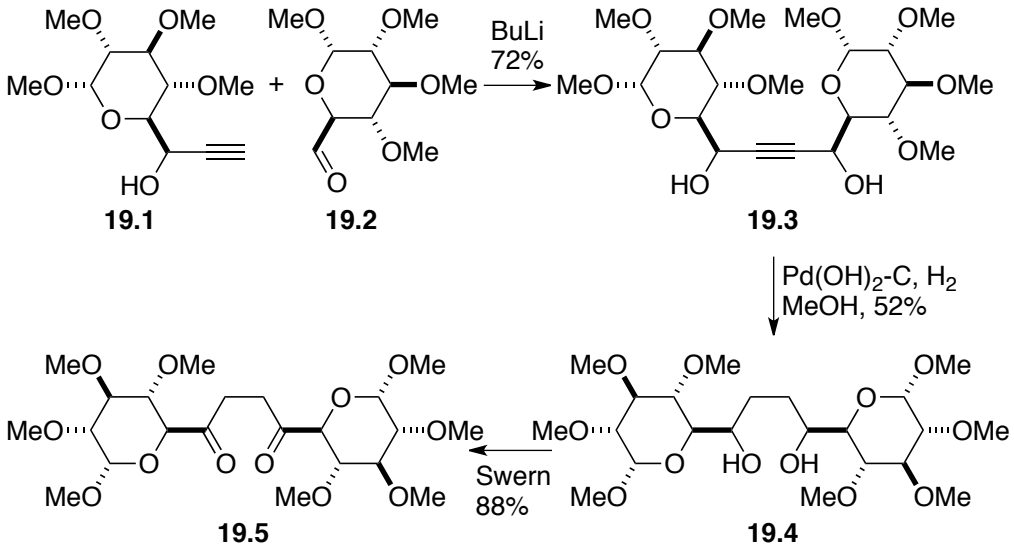
C and H_2. Jones oxidation of **18.4** afforded the 1,4-diketone **18.5** in 90% yield. Using similar methods, the other ketones shown in Scheme 18 were prepared.



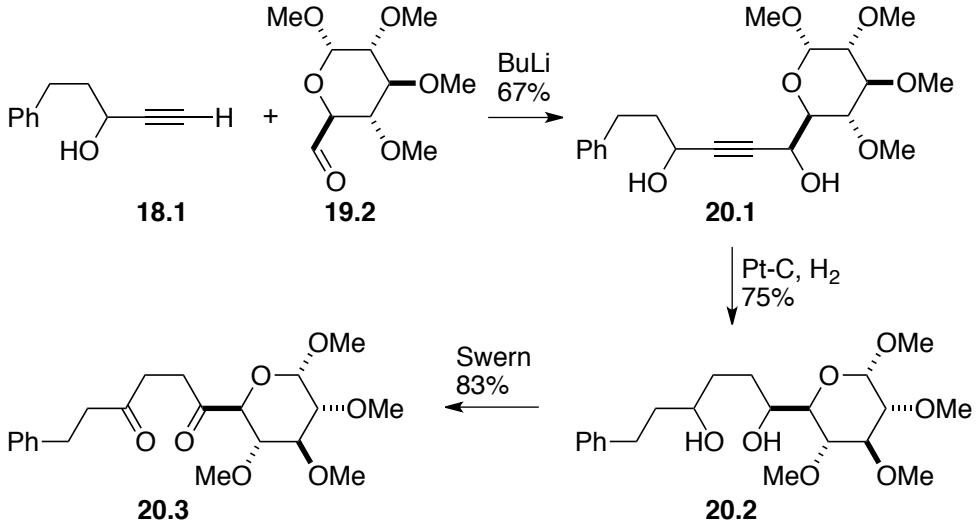
Scheme 18

To continue this project, acetylene **19.1** was used as the starting material and treated with BuLi and then aldehyde **19.2**[13] to give compound **19.3** in 72% yield. Hydrogenation of the triple bond over $Pd(OH)_2$-C afforded the desired diol **19.4** in 52% yield. For the oxidation of diol **19.4**, several methods were tried. Use of Jones reagent gave the diketone **19.5** in 57% yield as two diastereomers. With PCC the yield was improved to 73%, but the product was still a mixture of two diastereomers. When Swern oxidation was used, the desired 1,4-diketone

19.5 was produced in good yield (88%) as a single isomer as judged by the ^{1}H NMR and ^{13}C NMR spectra.



Scheme 19

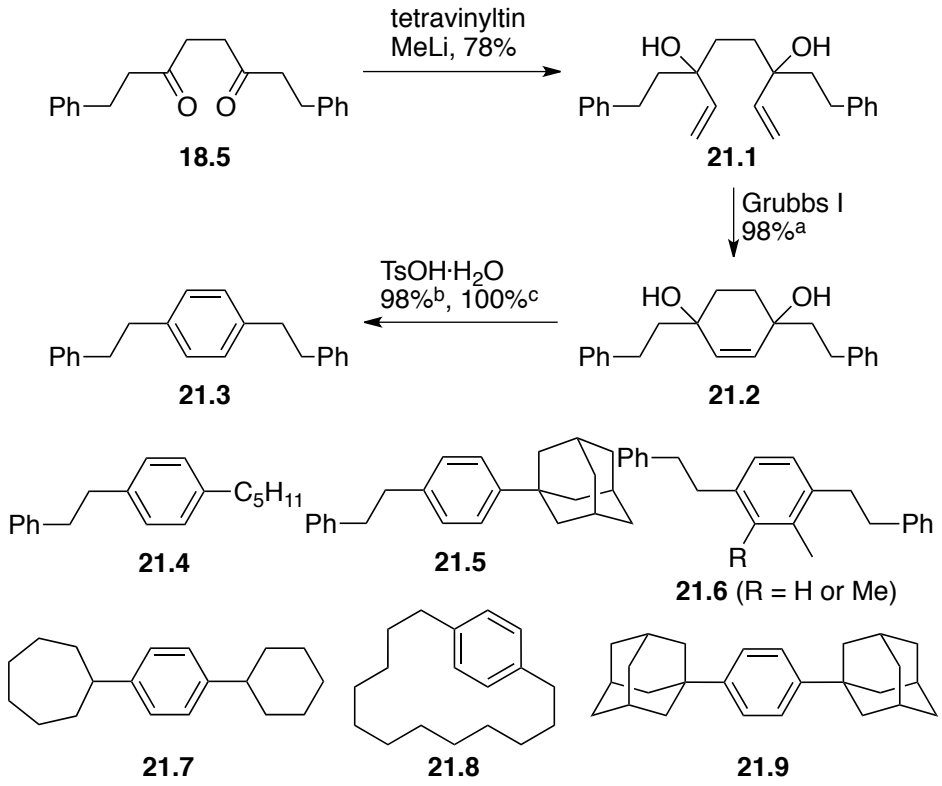


Scheme 20

Treatment of acetylene **18.1** with BuLi and aldehyde **19.2**[13] afforded the alkyne diol **20.1** in 67% yield (or 85% corrected for recovered **19.2**). Then hydrogenation, followed by Swern oxidation, generated the expected 1,4-diketone **20.3** as a single diastereomer.

2.3 Preparation of *para*-disubstituted benzenes

With the ketones (Scheme 18) in hand, Dr. Ziffle synthesized the corresponding substituted benzenes as shown in Scheme 21. The addition of vinyllithium (generated from tetravinyltin and MeLi) to diketone **18.5** formed the

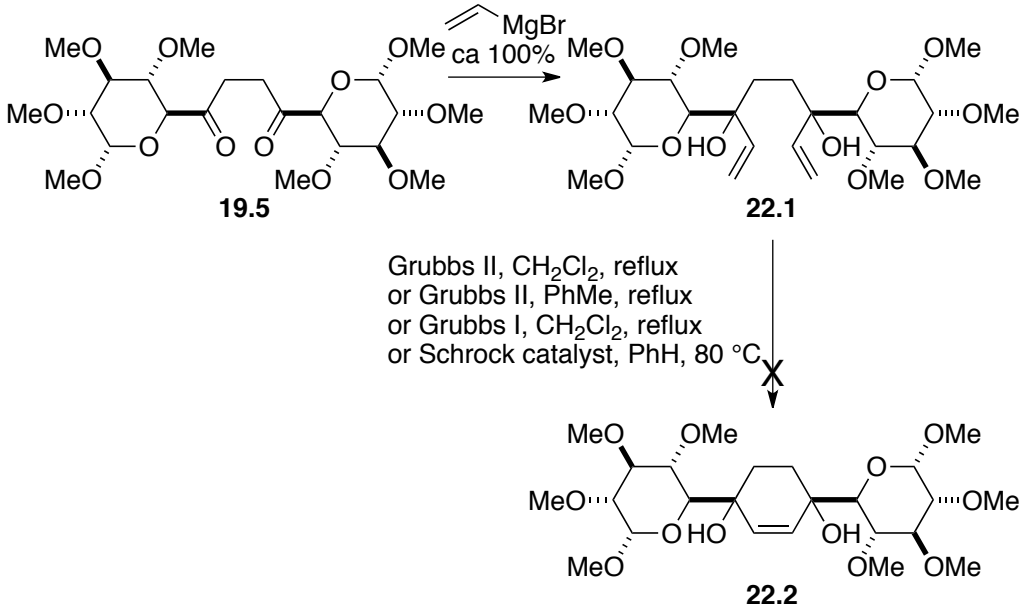


a = yield of less polar isomer 35%; yield of more polar isomer 62%
b = yield from more polar diol
c = yield from less polar diol

Scheme 21

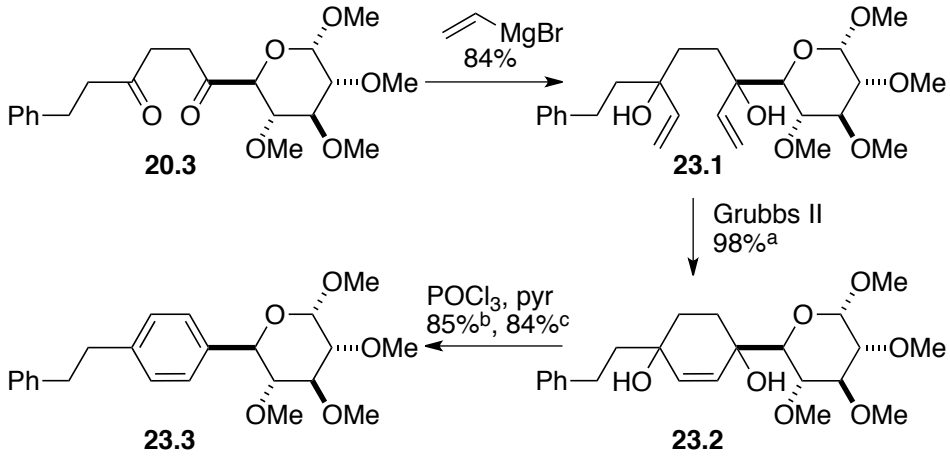
terminal diene **21.1** in good yield. Ring-closing metathesis of **21.1** provided two separable diastereomers of **21.2** in excellent yield. The individual diols were then dehydrated under acidic conditions to give the desired substituted benzene **21.3** in 100% and 98% yields, respectively. Several other substituted benzenes (these are shown in Scheme 21) were obtained in a similar way.

The present work expanded upon Dr. Ziffle's research and established that the installation of two vinyl groups on the 1,4-diketone **19.5** generated diols **22.1** in 100% yield as a mixture of diastereomers (^{13}C NMR) containing minor impurities (^{1}H NMR). These diols were then subjected to ring-closing metathesis, but no reaction occurred with Grubbs I,[10] Grubbs II[11] or Schrock[14] catalysts, and the diols were recovered. This was probably due to unfavorable steric or conformational factors or the presence of multiple coordination sites.



Scheme 22

With vinylmagnesium bromide, 1,4-diketone **20.3** was converted into diols **23.1** in 84% yield as a mixture of diastereomers. Ring-closing metathesis of **23.1** with the Grubbs II catalyst[11] formed the required cyclohexene diols **23.2** in excellent yield as two separable diastereomers. Treatment of the separated diols **23.2** with $POCl_3$ in ice-cold pyridine gave the desired *para*-disubstituted benzene **23.3** in good yield in both cases.



a: Yield of less polar isomer 29%; yield of more polar isomer 69%
b: Yield from less polar diol
c: Yield from more polar diol

Scheme 23

This route provides a method to make C5-aryl carbohydrates, which have previously been prepared by introduction of the aromatic unit followed by assembly of the pyranose ring[15] (often by Diels-Alder reaction with a Danishefsky diene[15a-c]) or addition of a carbanion to a dialdehydofuranose, followed by ring expansion to the pyranose system.[16,17] A number of carbohydrates bearing a C5-aryl unit have potentially important medicinal properties such as use for control of

diabetes[18] by inhibiting sodium-dependent glucose co-transporter type 2[19] and thereby increasing urinary excretion of glucose.

3. Conclusion

The route described above offers an approach to convert aldehydes into substituted benzenes incorporating the aldehyde carbonyl carbon. Application of this approach to carbohydrates appears to be convenient and may be useful in preparing medically important C-5 aryl pyranosides that can act as inhibitors of sodium glucose co-transporter type 2; such inhibitors are likely to be useful for treating diabetes.[18,19]

4. Experimental

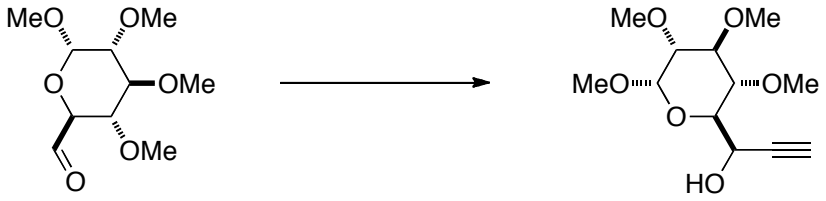
General Procedures. Unless otherwise specified, reactions were carried out under a slight static pressure of Ar or N_2 that had been purified by passage through a column (3.5 × 42 cm) of R-311 catalyst and then through a similar column of Drierite. Solvents for reactions were dried as described below. Glassware was dried in an oven (140 °C) overnight before use and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a light static pressure of Ar or N_2.

Solvents used for chromatography were distilled before use. Commercial thin layer chromatography plates (silica gel, Merck 60F-254 was 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. Dry THF and Et_2O were distilled from sodium and benzophenone ketyl. Dry MeCN, Et_3N and pyridine were distilled from CaH_2.

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 by from APT spectra.

Solutions were evaporated under water pump vacuum and the residue was then kept under oil pump vacuum.

Methyl 7,8-Dideoxy-2,3,4-tri-*O*-methyl- α-D-*gluco*-oct-7-ynopyranoside (19.1).

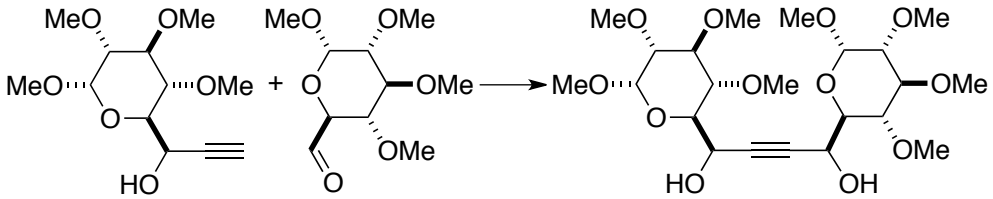


19.2 **19.1**

A solution of ethynylmagnesium bromide (0.5 M in THF, 15 mL, 7.5 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of crude 2,3,4-tri-*O*-methyl-α-D-*gluco*-hexodialdo-1,5-pyranoside[13] **19.2** (540.0 mg, 2.31 mmol) in THF (20 mL) (Ar atmosphere). The cold bath was left in place but not recharged, and stirring was continued for 18 h. The yellow solution was then quenched with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 1:1 EtOAc-hexanes, gave **19.1** (304.8 mg, 51%) as a light yellow oil which was a mixture of two diastereoisomers (^{13}C NMR): FTIR ($CHCl_3$, microscope) 3418, 3252, 2982, 2934, 2837, 2249, 2114, 1740, 1670, 1466, 1466 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.46–2.54 (m, 1 H), 2.65 (d, J = 10.5 Hz, 1 H), 3.17–3.26 (m, 1 H), 3.33 (dd, J = 9.2, 9.7 Hz, 1 H), 3.42–3.44 (m, 3 H), 3.51–3.72 (m, 11 H), 4.56–4.67 (m, 1 H), 4.86–4.88 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.1 (q), 55.3 (q), 59.1 (q), 60.6 (q), 60.8 (q), 60.9 (q), 61.3

(q), 62.4 (q), 71.8 (d), 71.9 (d), 73.1 (d), 74.8 (d), 79.3 (d), 81.0 (d), 81.8 (d), 82.7 (s), 83.4 (d), 83.6 (d), 97.55 (d), 97.59 (d); exact mass *m*/*z* calcd for $C_{12}H_{20}NaO_6$ (M + Na) 283.1152, found 283.1152.

1,4-Bis-[(2*R*,3*S*,4S,5*R*,6*S*)-tetrahydro-3,4,5,6-tetramethoxypyran-2-yl]-but-2-yne-1,4-diol (19.3).

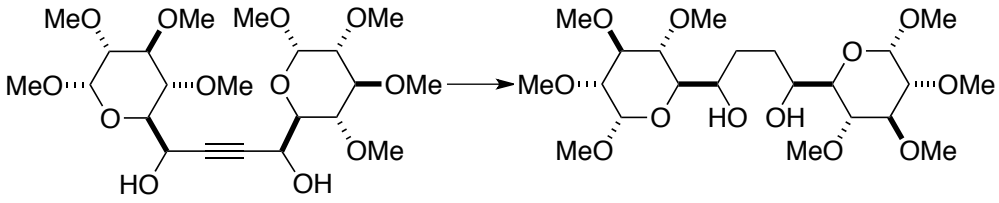


19.1 **19.2** **19.3**

BuLi (2.5 M in hexanes, 0.7 mL, 1.75 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **19.1** (228.0 mg, 0.877 mmol) in THF (8 mL). After 1.5 h, freshly prepared crude methyl 2,3,4-tri-*O*-methyl-α-D-glucohexodialdo-1,5-pyranoside[13] **19.2** (133.4 mg, 0.57 mmol) in THF (1 mL) was added dropwise. The cooling bath was left in place but not recharged, and stirring was continued for 40 h. The mixture was quenched with saturated aqueous NH_4Cl (8 mL) and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 1:1 EtOAc-hexanes and then 3:100 MeOH-EtOAc, gave **19.3** (174 mg, 61% or 72%, based on recovered starting material) as a white solid which was a mixture of diastereoisomers (^{13}C NMR):

FTIR ($CHCl_3$, microscope) 3433, 2934, 2836, 2249, 1466, 1446 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.63–2.75 (m, 2 H), 3.13–3.26 (m, 2 H), 3.28–3.46 (m, 8 H), 3.47–3.74 (m, 22 H), 4.59–4.69 (m, 2 H), 4.79–4.83 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.2 (q), 55.3 (q), 59.1 (q), 60.60 (q), 60.63 (q), 60.72 (q), 60.78 (q), 60.82 (q), 60.85 (q), 61.4 (q), 61.7 (q), 62.5 (q), 62.6 (q), 70.6 (d), 71.7 (d), 71.9 (d), 72.0 (d), 72.3 (d), 79.3 (d), 79.4 (d), 79.6 (d), 81.0 (d), 81.1 (d), 81.6 (d), 81.7 (d), 81.8 (d), 82.2 (s), 83.4 (d), 83.6 (d), 83.9 (s), 85.5 (s), 97.5 (d), 97.6 (d); exact mass *m*/*z* calcd for $C_{22}H_{38}NaO_{12}$ (M + Na) 517.2255, found 517.2259.

1,4-Bis-[(2*R*,3*S*,4*S*,5*R*,6*S*)-tetrahydro-3,4,5,6-tetramethoxypyran-2-yl]-butane-1,4-diol (19.4).

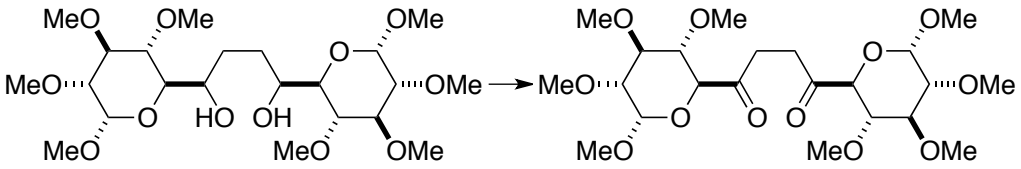


19.3 **19.4**

$Pd(OH)_2$-C (20% w/w, 23.0 mg) was added to a solution of **19.3** (58.4 mg, 0.118 mmol) in MeOH (1.5 mL), and the mixture was stirred under H_2 (balloon) for 2 h, and then filtered through Celite, using EtOAc as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.2 x 15 cm), using EtOAc and then 3:50 MeOH-EtOAc, gave **19.4** (35.2 mg, 60%) as a white solid which was a mixture of diastereoisomers (^{13}C NMR): FTIR ($CHCl_3$,

microscope) 3472, 2935, 2835, 2248, 1445, 1379 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.50–1.94 (m, 4 H), 2.38 (s, 1 H), 3.12–3.17 (m, 3 H), 3.26–3.31 (m, 2 H), 3.35–3.40 (m, 7 H), 3.46–3.53 (m, 9 H), 3.56–3.63 (m, 12 H), 3.80 (d, *J* = 3.0 Hz, 2 H), 4.72–4.80 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.1 (t), 30.5 (t), 32.0 (t), 55.2 (q), 55.3 (q), 58.9 (q), 59.0 (q), 60.2 (q), 60.7 (q), 60.8 (q), 69.2 (d), 69.4 (d), 71.1 (d), 71.6 (d), 72.2 (d), 72.5 (d), 73.2 (d), 79.5 (d), 81.7 (d), 82.0 (d), 82.6 (d), 83.6 (d), 83.8 (d), 97.3 (d), 97.6 (d); exact mass *m*/*z* calcd for $C_{22}H_{42}NaO_{12}$ (M + Na) 521.2568, found 521.2568.

1,4-Bis-[(2*S*,3*S*,4*S*,5*R*,6*S*)-tetrahydro-3,4,5,6-tetramethoxypyran-2-yl]-butane-1,4-dione (19.5).

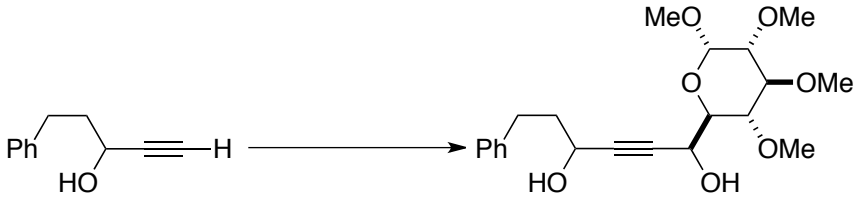


19.4 **19.5**

DMSO (0.04 mL, 0.564 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to a stirred and cooled (–78 °C) solution of $(COCl)_2$ (0.023 mL, 0.266 mmol) in CH_2Cl_2 (0.5 mL). After 15 min, a solution of **19.4** (50.0 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise and stirring at –78 °C was continued for 35 min. Then Et_3N (0.08 mL) was added dropwise, and stirring was continued at –78 °C for 5 min. The cooling bath was removed, stirring was continued for 25 min, and water (2 mL) was added. The organic layer was separated, dried ($MgSO_4$)

and evaporated. Flash chromatography of the residue over silica gel (1.2 x 15 cm), using 3:1 EtOAc-hexanes, gave **19.5** (47.6 mg, 96%) as a colorless oil: $[a]_D^{20}$ 132.8 (*c* 1.32, $CHCl_3$); FTIR ($CHCl_3$, cast microscope) 2935, 2836, 1726, 1466, 1446 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.79–2.87 (m, 2 H), 2.97–3.05 (m, 2 H), 3.21 (dd, *J* = 3.5, 9.5 Hz, 2 H), 3.28 (dd, *J* = 8.5, 10.0 Hz, 2 H), 3.44 (s, 6 H), 3.51–3.56 (m, 14 H), 3.62 (s, 6 H), 4.06 (d, *J* = 10.0 Hz, 2 H), 4.85 (d, *J* = 4.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.2 (t), 55.9 (q), 59.4 (q), 60.8 (q), 61.2 (q), 74.1 (d), 81.0 (d), 81.5 (d), 83.8 (d), 98.2 (d), 205.4 (s); exact mass *m*/*z* calcd for $C_{22}H_{38}NaO_{12}$ (M + Na) 517.2255, found 517.2265.

Methyl 7,8,10,11-Tetradeoxy-2,3,4-tris-*O*-methyl-11-phenyl-α-D-*gluco*-unedec-7-ynopyranoside (20.1).

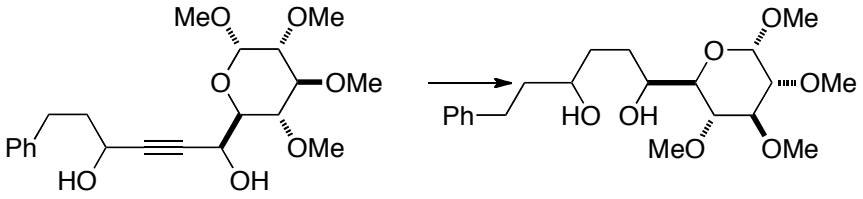


18.1 **20.1**

BuLi (2.5 M in hexanes, 1 mL, 2.5 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **18.1** (196.5 mg, 1.23 mmol) in THF (11 mL). After 1 h, a solution of freshly prepared crude methyl 2,3,4-tri-*O*-methyl-α-D-*gluco*-hexodialdo-1,5-pyranoside[13] **19.2** (161.2 mg, 0.69 mmol) in THF (2 mL) was added dropwise. The cooling bath was left in place but not recharged, and

stirring was continued for 23 h. The mixture was quenched with saturated aqueous NH_4Cl (8 mL) and extracted with EtOAc. The combined organic extracts were dried (MgSO4) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 3:1 EtOAc-hexanes, gave **20.1** (181.2 mg, 67% or 85%, based on recovered starting material) as an oil that was a mixture of diastereoisomers (^{13}C NMR): FTIR ($CHCl_3$, microscope) 3423, 3085, 3062, 3026, 2934, 2836, 2248, 1604, 1496, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.94–2.12 (m, 2 H), 2.19–2.32 (m, 1 H), 2.73–2.83 (m, 3 H), 3.18–3.26 (m, 1 H), 3.31–3.73 (m, 15 H), 4.39–4.46 (m, 1 H), 4.62–4.73 (m, 1 H), 4.85 (d, J = 3.2 Hz, 1 H), 7.17–7.22 (m, 3 H), 7.26–7.31 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.58 (t), 31.66 (t), 31.69 (t), 39.3 (t), 39.4 (t), 55.4 (q), 55.5 (q), 59.3 (q), 60.9 (q), 61.1 (q), 61.2 (q), 61.5 (q), 61.6 (q), 61.8 (q), 61.9 (q), 62.8 (q), 72.21 (d), 72.26 (d), 72.30 (d), 79.5 (d), 81.3 (d), 81.4 (d), 81.99 (d), 82.04 (d), 82.5 (s), 82.6 (s), 83.6 (d), 83.8 (d), 84.3 (s), 86.2 (s), 88.0 (s), 97.7 (d), 97.9 (d), 126.30 (d), 126.31 (d), 128.71 (d), 128.72 (d), 141.34 (s), 141.36 (s); exact mass m/z calcd for $C_{21}H_{30}NaO_7$ (M + Na) 417.1884, found 417.1891.

Methyl 7,8,10,11-Tetradeoxy-2,3,4-tris-*O*-methyl-11-phenyl-α-D-*gluco*-unedecanopyranoside (20.2).

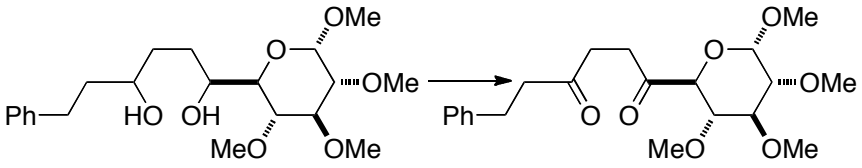


20.1 **20.2**

Pt-C (5% w/w, 14 mg) was added to a solution of **20.1** (35.9 mg, 0.091 mmol) in MeOH (1.5 mL), and the mixture was stirred under H_2 (balloon) for 1 h, and then filtered through Celite, using EtOAc as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.6 x 8 cm), using EtOAc-hexanes from 50% EtOAc to 100% EtOAc, gave **20.2** (27.3 mg, 75%) as an oil which was a mixture of diastereoisomers (^{13}C NMR): FTIR ($CHCl_3$, microscope) 3448, 3085, 3061, 3025, 2933, 2836, 1603, 1496, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.52–1.90 (m, 6 H), 2.42 (s, 1 H), 2.64–2.85 (m, 2 H), 3.14–3.20 (m, 2 H), 3.26–3.31 (m, 1 H), 3.36–3.69 (m, 15 H), 3.79 (s, 1 H), 4.78 (dd, *J* = 3.4, 15.4 Hz, 1 H), 7.16–7.21 (m, 3 H), 7.26–7.30 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.1 (t), 28.9 (t), 30.3 (t), 31.3 (t), 32.09 (t), 32.13 (t), 32.15 (t), 32.19 (t), 33.8 (t), 34.1 (t), 34.4 (t), 34.7 (t), 39.1 (t), 39.4 (t), 55.17 (q), 55.24 (q), 55.29 (q), 55.31 (q), 58.9 (q), 59.0 (q), 60.2 (q), 60.6 (q), 60.7 (q), 60.8 (q), 69.3 (d), 69.4 (d), 70.9 (d), 71.0 (d), 71.1 (d), 71.3 (d), 71.4 (d), 72.1 (d), 72.4 (d), 73.2 (d), 73.3 (d), 79.5 (d), 81.7 (d), 82.0 (d), 82.26 (d), 82.33 (d), 83.6 (d), 83.7

(d), 97.2 (d), 97.6 (d), 125.7 (d), 125.8 (d), 128.34 (d), 128.38 (d), 128.39 (d), 128.41 (d), 142.0 (s), 142.27 (s), 142.29 (s); exact mass *m*/*z* calcd for $C_{21}H_{34}NaO_7$ (M + Na) 421.2197, found 421.2199.

6-Phenyl-1-[(2*S*,3*S*,4*S*,5*R*,6*S*)-tetrahyro-3,4,5,6-tetramethoxypyran-2-yl]hexane-1,4-dione (20.3).

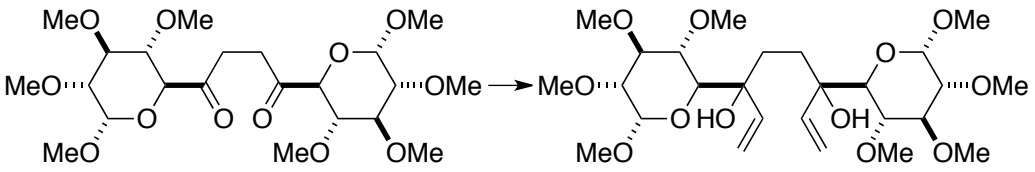


20.2 **20.3**

DMSO (0.09 mL, 1.27 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise to a stirred and cooled (–78 °C) solution of $(COCl)_2$ (0.06 mL, 0.694 mmol) in CH_2Cl_2 (1 mL). After 15 min, a solution of **20.2** (101.6 mg, 0.255 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise, and stirring at –78 °C was continued for 35 min. Then Et_3N (0.2 mL) was added dropwise, and stirring at –78 °C was continued for 5 min. The cooling bath was removed, and stirring was continued for 25 min. Water (2 mL) was added, and the organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 13 cm), using 1:1 EtOAc-hexanes, gave **20.3** (83.9 mg, 83%) as a colorless oil: $[a]_D^{20}$ 79.2 (*c* 1.35, $CHCl_3$); FTIR ($CHCl_3$, cast microscope) 3062, 3027, 2933, 2836, 1716, 1604, 1497, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.60–2.68 (m, 1 H), 2.72–2.85 (m, 4 H), 2.89–3.03 (m, 3 H), 3.20–3.31 (m, 2 H), 3.45–3.63 (m,

13 H), 4.06 (dd, *J* = 1.6, 10.0 Hz, 1 H), 4.87 (dd, *J* = 1.6, 3.2 Hz, 1 H), 7.17–7.21 (m, 3 H), 7.26–7.30 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.0 (t), 34.7 (t), 36.0 (t), 44.5 (t), 55.9 (q), 59.4 (q), 60.8 (q), 61.2 (q), 74.0 (d), 80.9 (d), 81.5 (d), 83.7 (d), 98.1 (d), 126.3 (d), 128.5 (d), 128.7 (d), 141.2 (s), 205.8 (s), 208.2 (s); exact mass *m*/*z* calcd for $C_{21}H_{30}NaO_7$ (M + Na) 417.1884, found 417.1879.

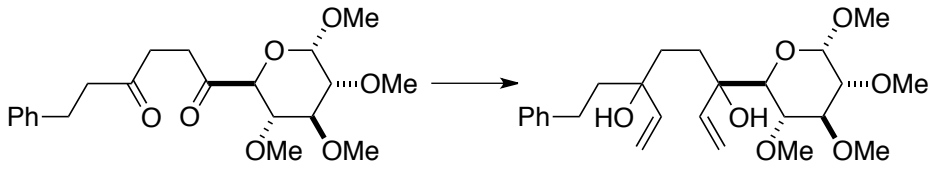
3,6-Bis-[(2*S*,3*S*,4*S*,5*R*,6*S*)-tetrahydro-3,4,5,6-tetramethoxypyran-2-yl]-octa-1,7-diene-3,6-diol (22.1).



19.5 **22.1**

Vinylmagnesium bromide (1.0 M in THF, 1.1 mL, 1.10 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **19.5** (55.7 mg, 0.11 mmol) in THF (1 mL). The cooling bath was left in place but not recharged and stirring was continued for 16 h. The mixture was then quenched with saturated aqueous NH_4Cl (1 mL) and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.2 x 15 cm), using 2:1 EtOAc-hexanes, gave **22.1** (63.0 mg, ca 100%) as a mixture of diastereoisomers (^{13}C NMR) that contained some impurities (^{1}H NMR). The NMR spectra were too complicated to be of diagnostic value: exact mass *m*/*z* calcd for $C_{26}H_{46}NaO_{12}$ (M + Na) 573.2881, 573.2880.

Methyl 7,8,10,11-Tetradeoxy-6,9-bis(ethenyl)-2,3,4-tris-*O*-methyl-11-phenyl-α-D-*gluco*-undecanopyranoside (23.1).

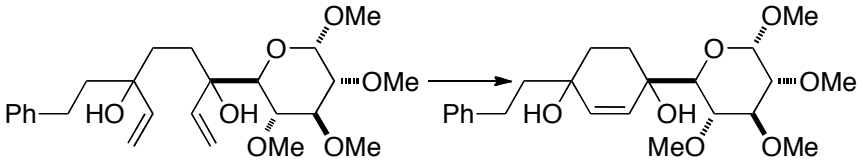


20.3 **23.1**

Vinylmagnesium bromide (1.0 M in THF, 1.89 mL, 1.89 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **20.3** (74.3 mg, 0.189 mmol) in THF (3 mL). The cooling bath was left in place but not recharged and stirring was continued for 7 h. The mixture was quenched with saturated aqueous NH_4Cl (3 mL) 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 x 13 cm), using 3:5 EtOAc-hexanes, gave **23.1** (62.7 mg, 84%) as a mixture of two diastereoisomers (^{13}C NMR): FTIR ($CHCl_3$, microscope) 3453, 3086, 3061, 3025, 2931, 2837,1717, 1640, 1604, 1559, 1540, 1497, 1453 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.56–1.92 (m, 6 H), 2.56 (s, 1 H), 2.60–2.77 (m, 2 H), 3.11–3.15 (m, 1 H), 3.25–3.29 (m, 1 H), 3.46 (s, 3 H), 3.51–3.59 (m, 8 H), 3.61 (s, 3 H), 4.47–4.63 (m, 1 H), 4.78 (d, J = 3.5 Hz, 1 H), 5.16–5.20 (m, 1 H), 5.28–5.36 (m, 2 H), 5.47–5.53 (m, 1 H), 5.78–5.95 (m, 2 H), 7.16–7.20 (m, 3 H), 7.26–7.29 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.07 (t), 30.09 (t), 31.3 (t), 33.4 (t), 33.5 (t), 43.2 (t), 43.7 (t), 55.7 (q), 55.8 (q), 59.0 (q), 60.03 (q), 60.05 (q), 60.7 (q), 72.0 (d), 72.6 (d), 74.6 (s), 74.8 (s), 76.9 (s), 77.0 (s), 81.7 (d), 81.8 (d), 82.1

(d), 84.0 (d), 97.37 (d), 97.44 (d), 113.0 (t), 113.2 (t), 115.0 (t), 115.5 (t), 125.55 (d), 125.63 (d), 128.29 (d), 128.34 (d), 128.39 (d), 140.0 (d), 140.4 (d), 142.8 (s), 143.0 (s), 143.8 (d), 143.9 (d); exact mass *m*/*z* calcd for $C_{25}H_{38}NaO_7$ (M + Na) 473.2510, found 473.2503.

1-(2-Phenethyl)-4-[(2*S*,3*S*,4*S*,5*R*,6*S*)-tetrahydro-3,4,5,6-tetramethoxy-pyran-2-yl]cyclohex-2-ene-1,4-diol (23.2).



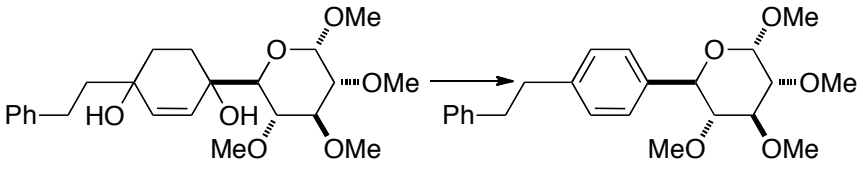
23.1 **23.2**

A solution of **23.1** (92.7 mg, 0.206 mmol) in CH_2Cl_2 (6 mL) was degassed for 30 min with a stream of Ar. Grubbs II catalyst[11] (26.2 mg, 0.03 mmol) was added and the Ar stream was continued for 15 min. The mixture was stirred and refluxed for 24 h under a static pressure of Ar and then cooled and evaporated. Flash chromatography of the residue over silica gel (1.5 x 13 cm), using first Et_2O and then EtOAc, gave **23.2** as a mixture of diastereoisomers [25.1 mg, 29% less polar diastereoisomer; 60.0 mg, 69% more polar diastereoisomer (98% overall)]: The less polar diastereoisomer (small impurity signals in the ^1H and ^{13}C NMR spectra) had: FTIR ($CHCl_3$, microscope) 3458, 3061, 3026, 2933, 2835, 2247, 1603, 1497, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.52 (d, *J* = 1.0 Hz, 1 H), 1.62 (s, 1 H), 1.71–2.01 (m, 4 H), 2.15 (t, *J* = 13.0 Hz, 1 H), 2.28 (t, *J* = 13.0 Hz,

1 H), 2.78–2.90 (m, 2 H), 3.25–3.28 (m, 1 H), 3.42 (t, J = 9.2 Hz, 1 H), 3.51–3.53 (m, 4 H), 3.60–3.71 (m, 10 H), 4.90 (d, J = 2.0 Hz, 1 H), 5.93 (s, 2 H), 7.25–7.30 (m, 3 H), 7.35–7.38 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.2 (t), 30.1 (t), 31.4 (t), 44.3 (t), 55.8 (q), 59.2 (q), 60.3 (q), 61.1 (q), 69.5 (s), 70.5 (s), 73.7 (d), 80.6 (d), 82.1 (d), 84.5 (d), 97.6 (d), 126.0 (d), 128.6 (d), 128.7 (d), 131.0 (d), 135.2 (d), 142.6 (s); exact mass m/z calcd for $C_{23}H_{34}NaO_7$ (M + Na) 445.2197, found 445.2192.

The more polar diastereoisomer had: FTIR ($CHCl_3$, microscope) 3441, 3061, 3026, 2934, 2835, 2248, 1603, 1497, 1453 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.74–2.07 (m, 7 H), 2.71–2.77 (m, 2 H), 3.16 (dd, J = 3.6, 9.6 Hz, 1 H), 3.28–3.34 (m, 2 H), 3.40 (s, 3 H), 3.50–3.56 (m, 5 H), 3.59 (s, 3 H), 3.62 (s, 3 H), 4.78 (d, J = 3.6 Hz, 1 H), 5.81 (AB q, J = 10.3 Hz, $\Delta\nu_{AB}$ = 7.4 Hz, 2 H), 7.15–7.20 (m, 3 H), 7.25–7.30 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.1 (t), 30.4 (t), 32.7 (t), 42.6 (t), 55.6 (q), 59.2 (q), 60.3 (q), 61.1 (q), 70.5 (s), 71.1 (s), 73.9 (d), 80.5 (d), 82.0 (d), 84.7 (d), 97.5 (d), 126.0 (d), 128.6 (d), 128.7 (d), 131.1 (d), 135.9 (d), 142.7 (s); exact mass m/z calcd for $C_{23}H_{34}NaO_7$ (M + Na) 445.2197, found 445.2195.

Methyl (*5R*)-*2*,3,4-Tri-*O*-methyl-5-*C*-[4-(2-phenethyl)phenyl]-α-D-*gluco*-pyranoside (23.3).



23.2 **23.3**

(a) $POCl_3$ (0.22 mL, 2.34 mmol) was added dropwise to a stirred and cooled (0 °C) solution of the less polar diastereoisomer of **23.2** (19.3 mg, 0.0457 mmol) in pyridine (0.86 mL) and stirring was continued for 4 h. The ice bath was left in place but not recharged, and stirring was continued for 7.5 h. Water (0.5 mL) was added and the mixture was extracted with Et_2O. The combined organic extracts were washed with 10% hydrochloric acid, saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.6 x 8 cm), using 3:10 EtOAc-hexanes, gave **23.3** (15 mg, 85%) as a thick oil: $[a]_D^{20}$ 92.06 (*c* 1.22, $CHCl_3$); FTIR ($CHCl_3$, microscope) 3060, 3027, 2980, 2931, 2858, 2832, 1604, 1516, 1496, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.95 (s, 4 H), 3.06 (s, 3 H), 3.12 (dd, *J* = 9.0, 9.8 Hz, 1 H), 3.37 (dd, *J* = 3.8, 9.4 Hz, 1 H), 3.45 (s, 3 H), 3.60 (s, 3 H), 3.63 (t, *J* = 9.2 Hz, 1 H), 3.67 (s, 3 H), 4.44 (d, *J* = 9.6 Hz, 1 H), 4.92 (d, *J* = 3.6 Hz, 1 H), 7.18–7.23 (m, 5 H), 7.26–7.31 (m, 2 H), 7.34–7.36 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.9 (t), 38.1 (t), 55.6 (q), 59.4 (q), 60.6 (q), 61.3 (q), 72.9 (d), 82.1 (d), 83.5 (d), 86.0 (d), 98.1 (d), 126.2 (d), 127.9 (d), 128.6 (d), 128.7 (d), 128.8 (d), 136.7 (s),

141.9 (s), 142.1 (s); exact mass *m*/*z* calcd for $C_{23}H_{30}NaO_5$ (M + Na) 409.1985, found 409.1984.

(b) $POCl_3$ (0.53 mL, 5.69 mmol) was added dropwise to a stirred and cooled (0 °C) solution of the more polar diastereoisomer of **23.2** (47.0 mg, 0.11 mmol) in pyridine (2 mL) and stirring was continued for 4 h. The ice bath was left in place but not recharged and stirring was continued for 7.5 h. Water (1 mL) was added and the mixture was extracted with Et_2O. The combined organic extracts were washed with 10% hydrochloric acid, saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 8 cm), using 3:10 EtOAc-hexanes, gave **23.3** (36.1 mg, 84%) as a thick oil.

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Chapter 2

Formation of Optically Pure Cyclic Amines by Intramolecular Conjugate Displacement

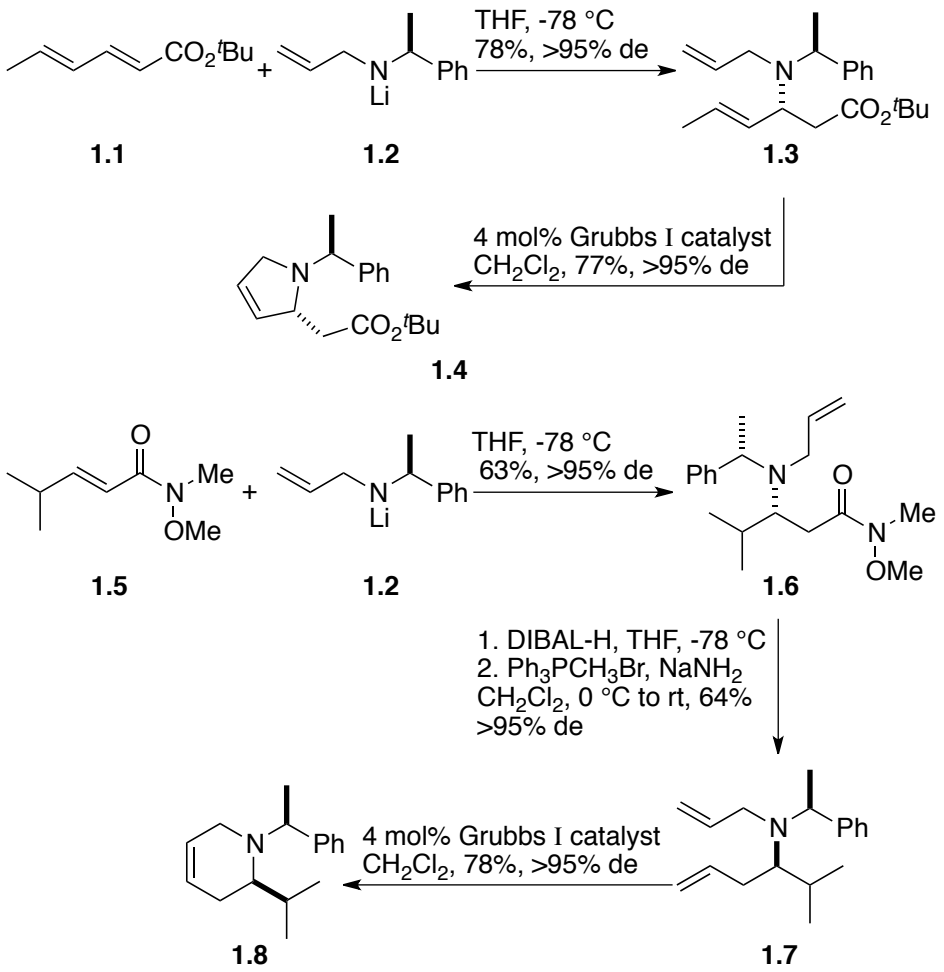
1. Introduction

1.1 General

In this chapter of my thesis, I will describe a new method for making optically pure cyclic amines with a stereogenic center α to nitrogen, and in the review section I will cover other prior ways of making such amines and will give the background to the methodology that I developed.

1.2 Existing methods of making cyclic amines with stereogenic centers α to nitrogen

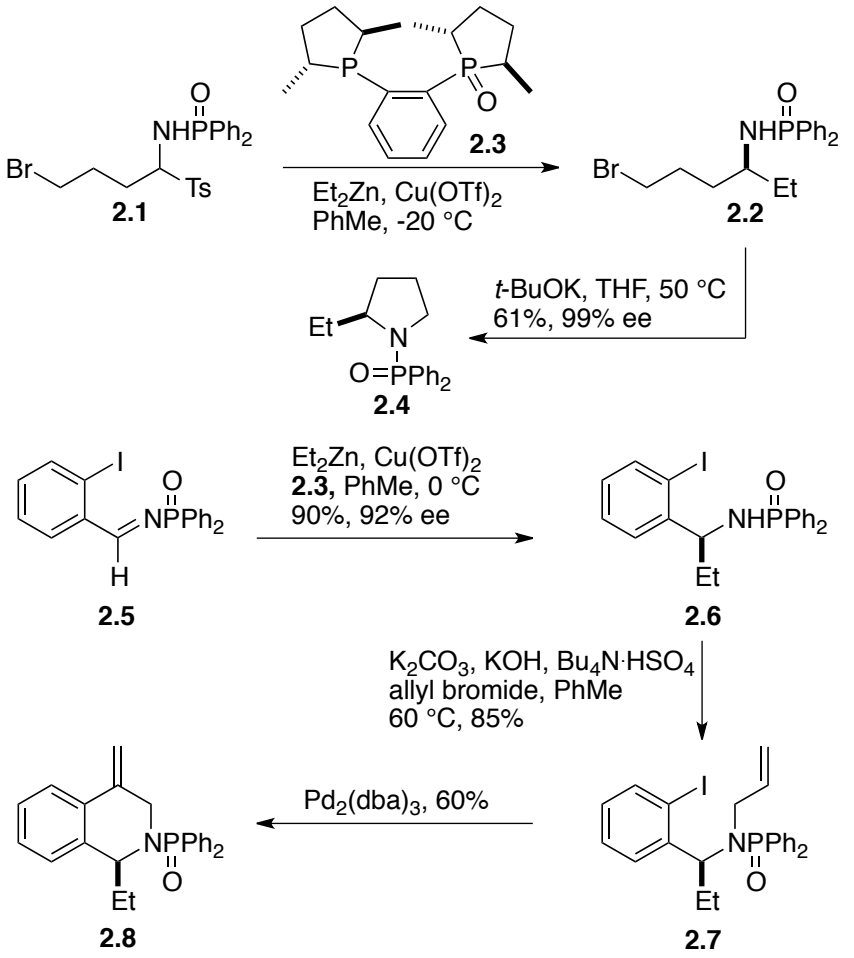
Davies and coworkers synthesized cyclic amines via sequential diastereoselective conjugate addition and ring closing metathesis.[1] Conjugate addition of lithium (*S*)-*N*-allyl-*N*-α-methylbenzylamide **1.2** to α,β-unsaturated ester **1.1** gave the homochiral diene **1.3** in >95% de, which was converted to the desired cyclic amine **1.4** as a single diastereomer via ring closing metathesis (Scheme 1). This result showed that no epimerization had occurred during the ring closing metathesis step. Having prepared the homochiral diene **1.3** via conjugate addition of **1.2** to an α,β-unsaturated ester, the α,β-unsaturated Weinreb amide **1.5 w**as used as the acceptor in this methodology. The desired **1.6** was obtained in >95% de. Reduction, Wittig reaction, and ring closing metathesis gave the cyclic amine **1.8** without compromising the diastereomeric excess.



Scheme 1

Charette and coworker reported the stereoselective synthesis of α-chiral cyclic amines via the asymmetric Cu-catalyzed addition of Et_2Zn to functionalized alkyl and aryl imines, followed by cyclization.[2] The brominated compound **2.1** was converted to **2.2** by catalytic asymmetric reaction with Et_2Zn. Without purification, crude **2.2** was treated with *t*-BuOK to give the functionalized cyclic amine **2.4** with excellent enantioselectivity. This enantioselective addition methodology was then applied to the aryl imine **2.5**, and the *N*-protected α-chiral amine **2.6** was produced with good enantioselectivity.

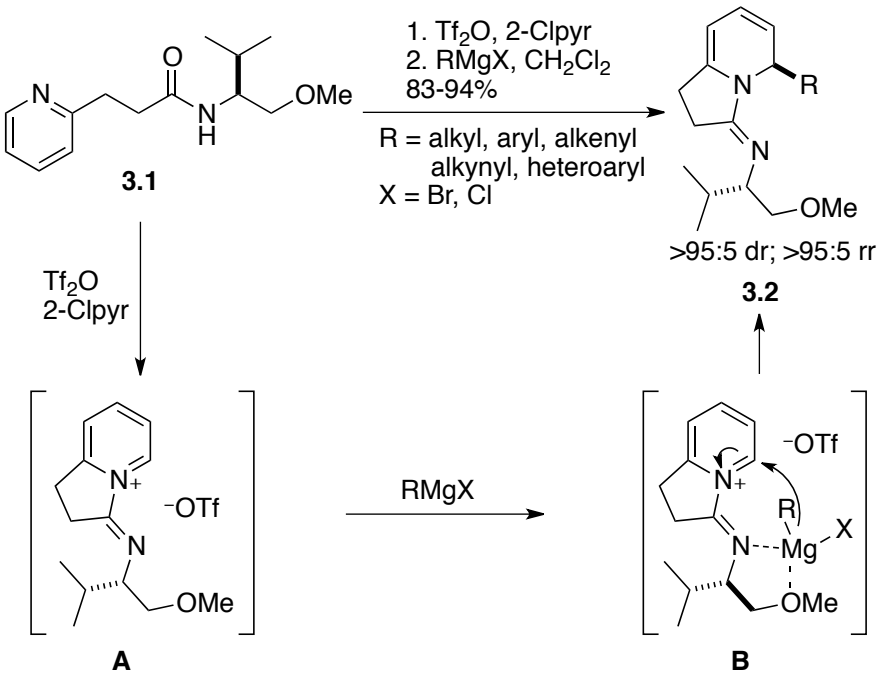
Reaction of **2.6** with allyl bromide, followed by Heck coupling, gave the cyclic amine **2.8**.



Scheme 2

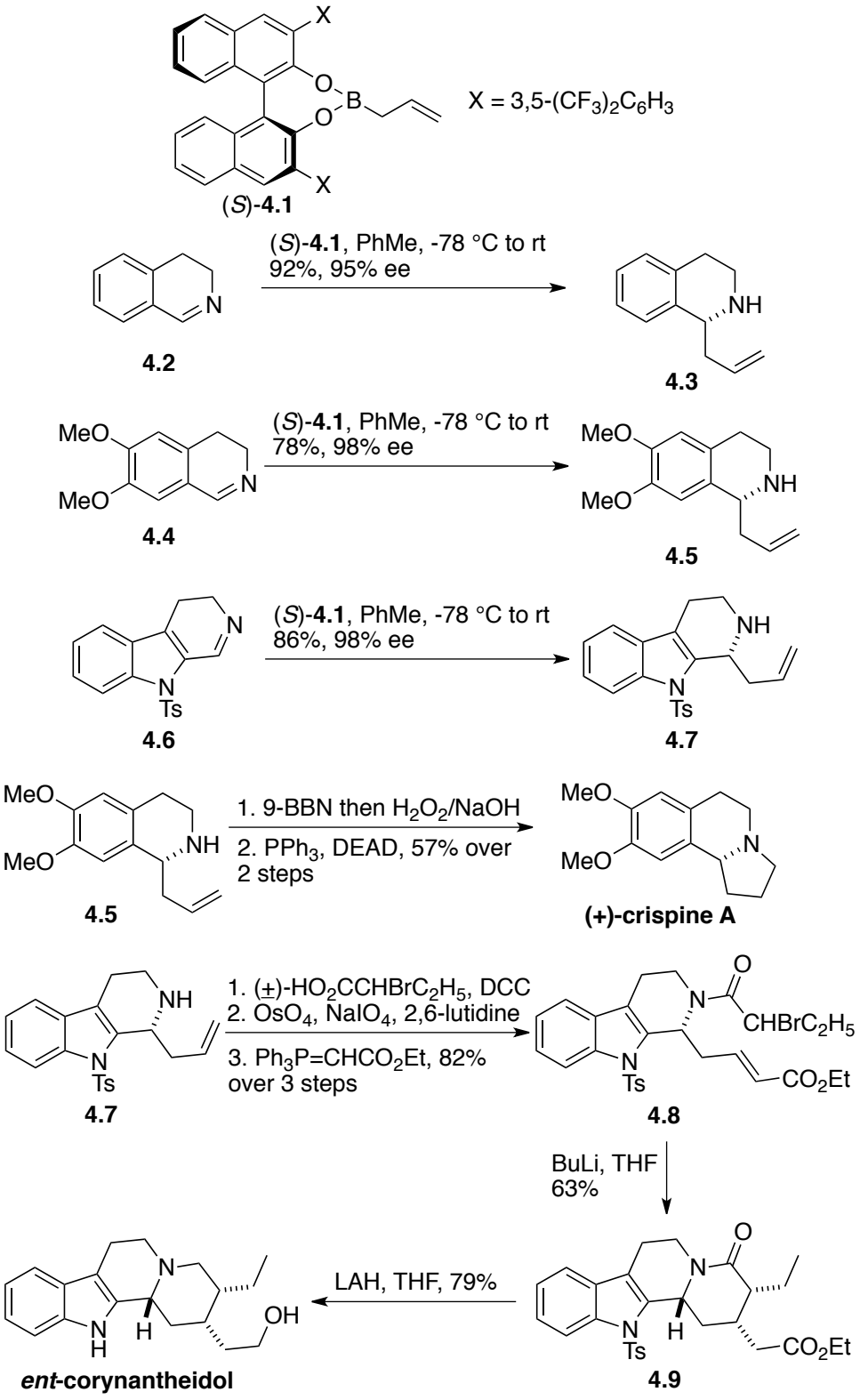
Charette and coworker also reported the stereoselective synthesis of cyclic amines via an intramolecular pyridine activation-asymmetric dearomatization reaction.[3] Amides **3.1** were treated with Tf_2O in the presence of 2-chloropyridine to produce the pyridinium salt **A** as a transient intermediate. With the chiral auxiliary on nitrogen, the addition of Grignard reagents to the pyridinium salt

induced the formation of bicyclic amines **3.2** as single regio- and diastereomers. The involvement of intermediate **B** accounts for the observed stereochemical outcome.



Scheme 3

By using the chiral boron compound (*S*)-**4.1**, Chong and coworker prepared a variety of α chiral cyclic amines via the asymmetric allylboration of cyclic imines.[4] Several examples are presented in Scheme 4. Some of the allylation products were used as intermediates for the synthesis of natural products. For instance, hydroboration of **4.5** with 9-BBN followed by an intramolecular Mitsunobu reaction produced the antitumor alkaloid (+)-crispine


X = 3,5-(CF3)2C6H3
(S)-4.1
(S)-4.1, PhMe, -78 °C to rt
92%, 95% ee
4.2
4.3
(S)-4.1, PhMe, -78 °C to rt
78%, 98% ee
4.4
4.5
(S)-4.1, PhMe, -78 °C to rt
86%, 98% ee
4.6
4.7
1. 9-BBN then H2O2/NaOH
2. PPh3, DEAD, 57% over 2 steps
4.5
(+)-crispine A
1. (±)-HO2CCHBrC2H5, DCC
2. OsO4, NaIO4, 2,6-lutidine
3. Ph3P=CHCO2Et, 82% over 3 steps
4.7
4.8
BuLi, THF
63%
LAH, THF, 79%
ent-corynantheidol
4.9

Scheme 4

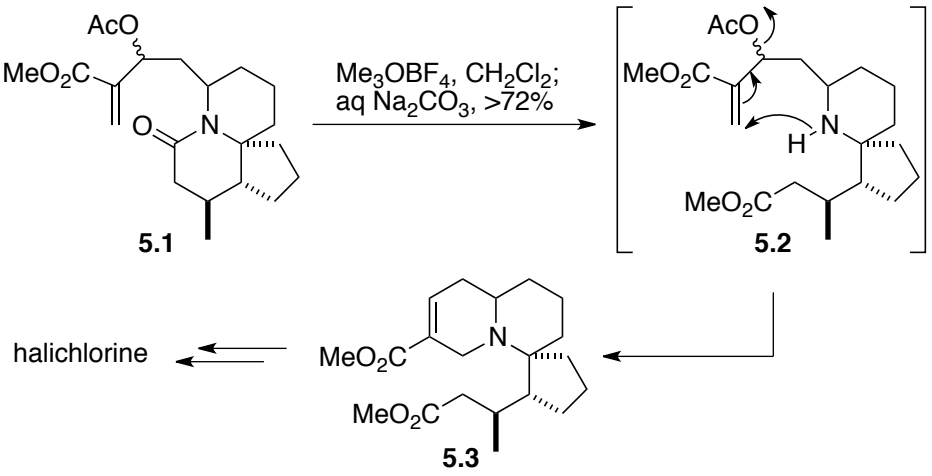
A. Treatment of the cyclic amine **4.7** with (±)-2-bromobutyric acid and DCC, followed by oxidation and Wittig reaction, gave α,β-unsaturated ester **4.8**. The addition of BuLi produced all-*cis* trisubstituted lactam **4.9**. Finally, reduction with $LiAlH_4$ completed the synthesis of the enantiomer of the alkaloid corynantheidol.

Several other methodologies, such as asymmetric hydrogenation of cyclic imines[5] and Diels-Alder cycloaddition of imines bearing a chiral auxiliary on nitrogen,[6] have also been applied to prepare the α chiral cyclic amines.

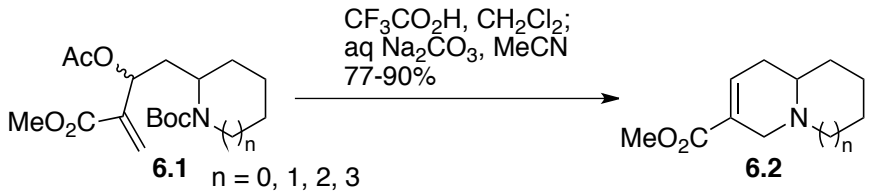
1.3 Intermolecular and intramolecular conjugate displacements

During the course of synthetic work conducted in this laboratory on the total synthesis of halichlorine,[7] the process summarized in Scheme 5 was carried out. This reaction is a combination of conjugate addition and S_N2' displacement and it was given the name "intramolecular conjugate displacement" (ICD for short). The accepting unit is a double bond carrying an electron-withdrawing group with an allylic leaving group. Such substructures had been known[8] to be much more reactive towards nucleophiles in *intermolecular* processes than related Michael acceptors lacking the allylic leaving group. However, the usefulness of an intramolecular version of this process was not widely appreciated and only a few examples for protein crosslinking[9] and for making macrocycles[10] had been reported. The example of Scheme 5 was found in this laboratory to present a generally useful process and many suitably protected amines, such as those listed in Scheme 6 were prepared.[7] Numerous examples of this process were studied in

this laboratory and the reaction was extended to all-carbon systems,[11] in which the nucleophile is a carbon atom. More recently, the use of sulfur as the nucleophile was also reported.[12] In this review, I will describe what is known about corresponding intermolecular reactions, and I will also give examples of ICD reactions — the intramolecular version.



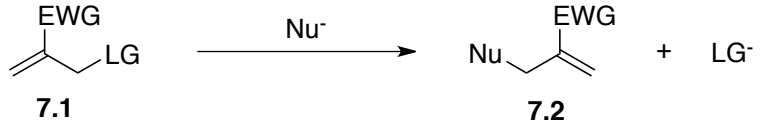
Scheme 5



Scheme 6

1.3.1 Intermolecular conjugate displacement with carbon nucleophiles and heteroatom nucleophiles

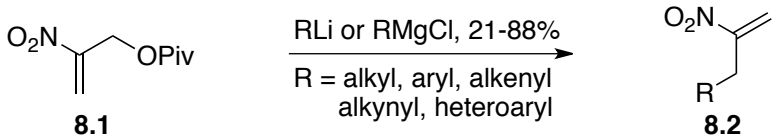
The generic intermolecular conjugate displacement, summarized in Scheme 7, involves a classical Michael addition and S_N2' displacement. Early examples of this type of reaction were reported by Seebach and coworkers.[8] They found that treatment of the nitroallyl pivaloate **8.1** with organolithiums or Grignard reagents produced the products **8.2**. From these results, they believed that the presence of the pivaloyloxy group enhanced the acceptor properties of the double bond. The product, which is a Michael acceptor, is clearly less reactive than the starting material. Seebach and coworkers also briefly discussed the mechanism of this process and excluded a one-electron transfer radical mechanism, since the *cis* geometry of the double bond is retained when *cis*-1-heptenyllithium was used as the reagent.



7.1 **7.2**

EWG: electron-withdrawing group
LG: leaving group
Nu: nucleophile

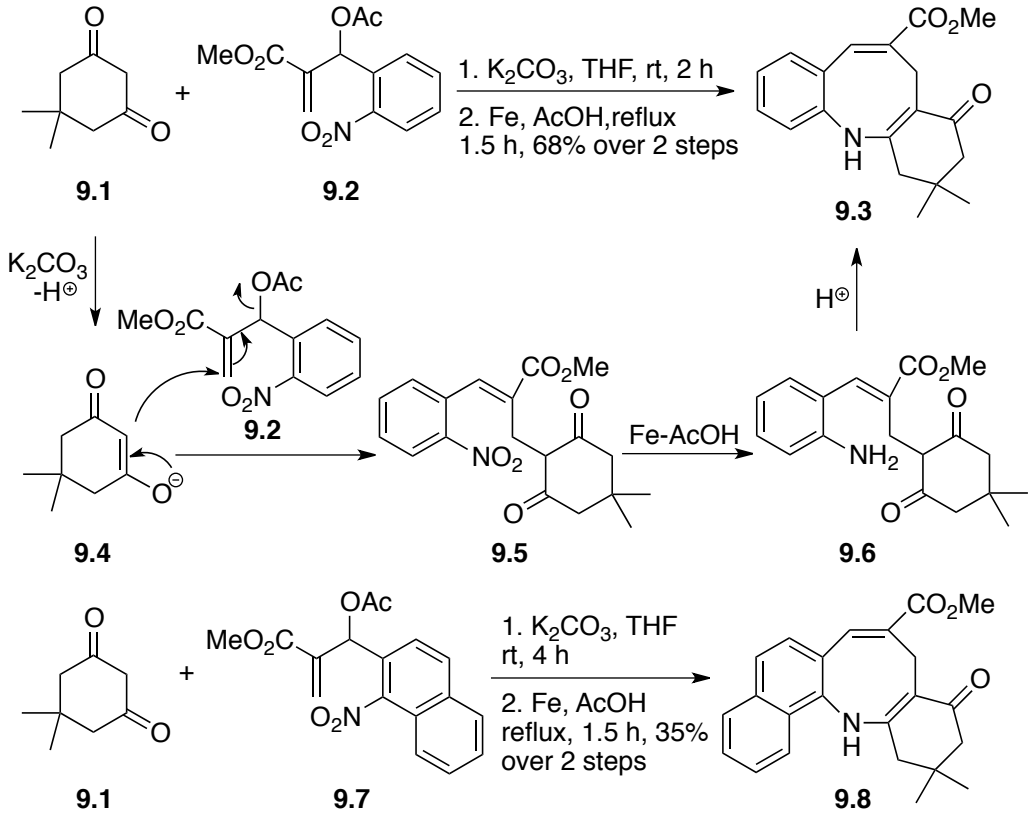
Scheme 7



8.1 **8.2**

Scheme 8

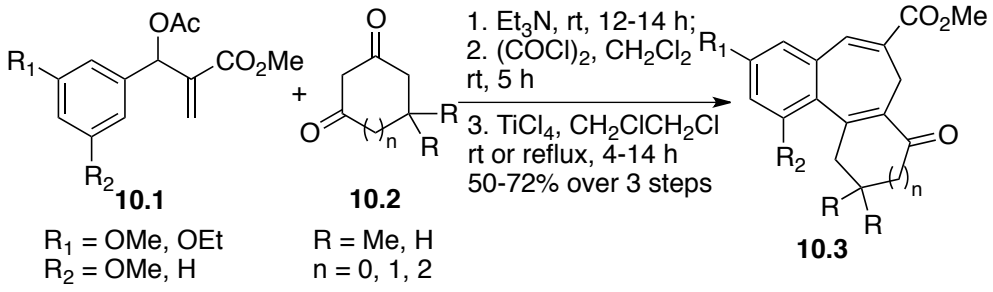
This type of S_N2' process has been studied by many groups. Both carbanions and heteroatoms such as nitrogen and phosphorus have been successfully used as nucleophiles. The starting materials were usually prepared by acetylation of Morita-Baylis-Hillman (MBH) alcohols. The most common nucleophilic carbanions used in this type of intermolecular reaction usually carry two electron-withdrawing groups, of which 1,3-dicarbonyl compounds are the most classic examples.[13] For instance, Basavaiah and coworker reported the synthesis of fused tri-/tetracyclic frameworks containing an azocine moiety using this intermolecular conjugate displacement as a key step (Scheme 9).[13a]



Scheme 9

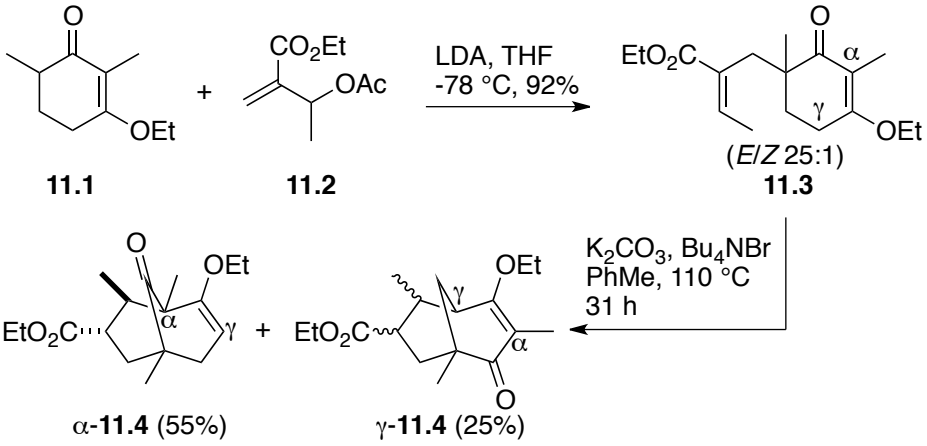
The 1,3-dicarbonyl compound **9.1** was used as the nucleophile in the presence of K_2CO_3 and gave the intermolecular conjugate displacement product **9.5** with the MBH acetate **9.2**. Reduction of the nitro group with Fe and AcOH produced compound **9.6**, which was then converted to **9.3** under acidic conditions. The tetracyclic structure **9.8** was prepared in a similar way.

More recently, Basavaiah and coworkers applied this methodology to the synthesis of angularly fused [6-7-5], [6-7-6] and [6-7-7] tricyclic structures.[13b] The intermolecular conjugate displacement occurred under mild basic conditions, and then formation of a vinyl chloride and intramolecular Friedel-Crafts (or Michael) reaction, gave the tricyclic compounds **10.3**.



Scheme 10

Takagi and coworkers used this S_N2' reaction to produce compound **11.3** from the enolate of **11.1** and allyl acetate **11.2**.[14] A subsequent intramolecular Michael addition gave the bicyclic compound α-**11.4** as the major compound and γ-**11.4** as the byproduct. This methodology was applied to assemble the core structure of plukenetione A.

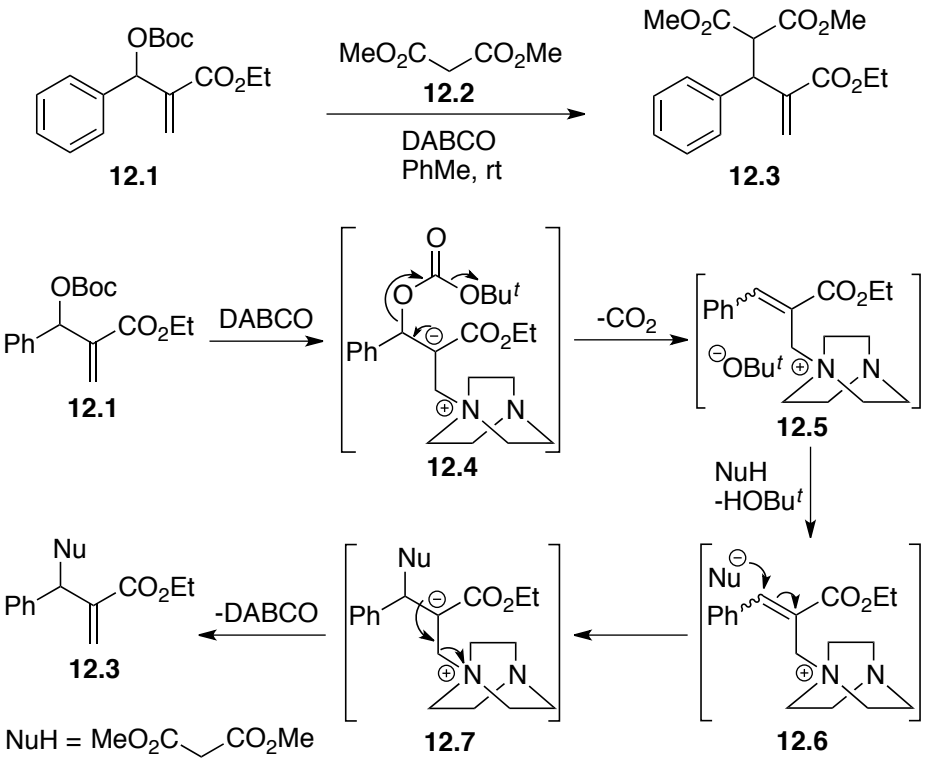


Scheme 11

Many research groups have been attracted by another type of intermolecular conjugate displacement that retains the regiochemistry of the double bond. This is achieve by two successive S_N2'-S_N2' processes that are initiated by a promoter, commonly a phosphine[15] or a tertiary amine.[13c,13d]

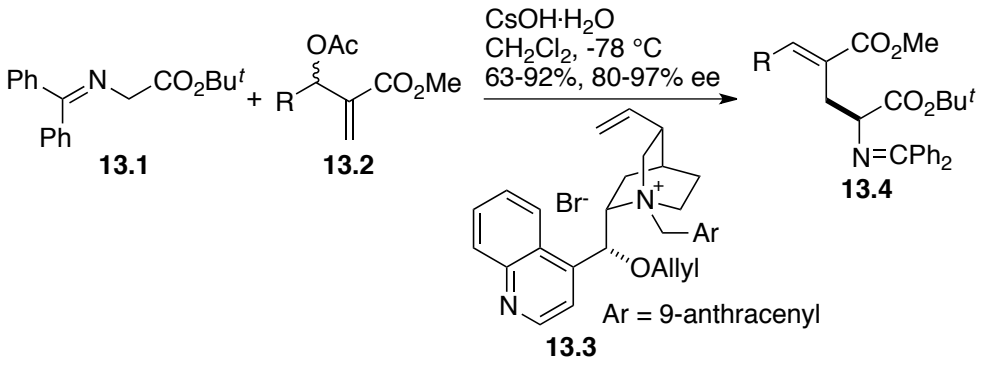
Lu and coworkers reported successive S_N2'-S_N2' reactions (i.e. intermolecular conjugate displacements), using DABCO as the promoter.[13c] They showed that it is important to choose a suitable nucleophile, leaving group and catalyst for a successful outcome. To avoid a direct nucleophilic displacement, a pronucleophile should be used at the beginning of the reaction. After the first S_N2' process, the pronucleophile should be deprotonated to generate a strong nucleophile, which can expel the promoter in the second S_N2' process. The OBoc group was chosen as the leaving group, as this can generate a *tert*-butoxide anion having the ability to produce a strong nucleophile from the pronucleophile. As shown in Scheme 12, a quaternary ammonium ion was formed first, followed by elimination of the *tert*-butyl carbonate anion. The pronucleophile (**12.2**) was

deprotonated by the *tert*-butoxide anion produced in situ to give a carbanion, which attacked the double bond of **12.6** to afford **12.3**.



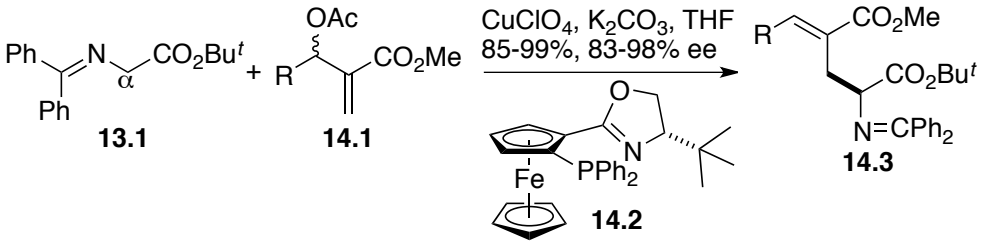
Scheme 12

By using a chiral phase-transfer catalyst, Ramachandran and coworkers reported an enantioselective intramolecular conjugate displacement.[16] In the presence of ammonium salt **13.3** and CsOH, the MBH acetates **13.2** reacted with the benzophenone imine of glycine *tert*-butyl ester (**13.1**) to afford 4-substituted glutamic acid derivatives **13.4** in 63-92% yield and 80-97% ee.



Scheme 13

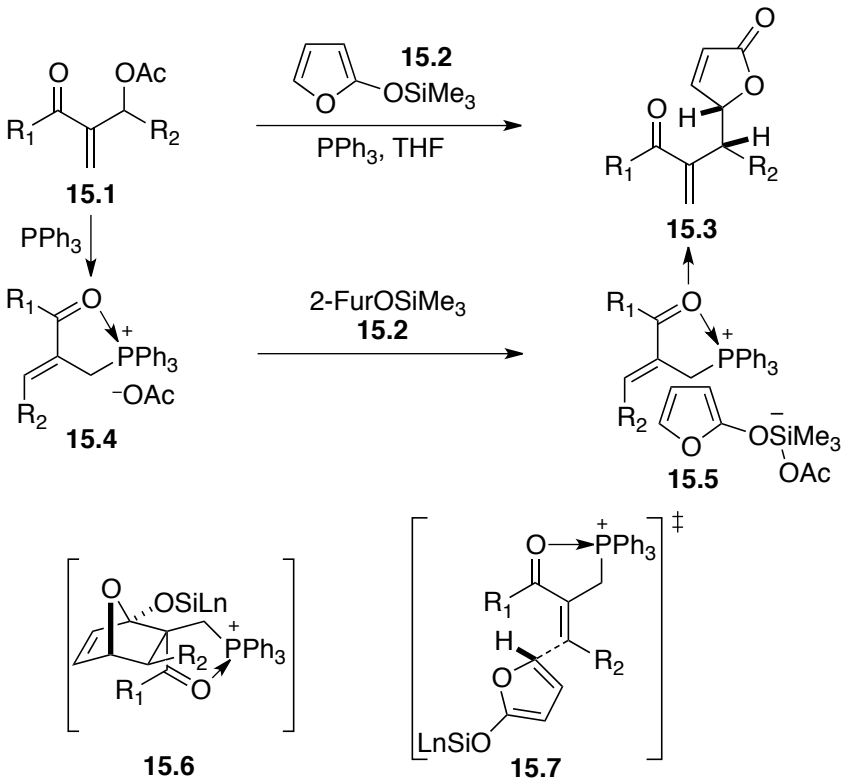
Using the same glycine ester **13.1**, Hou and coworkers also carried out an asymmetric synthesis of glutamic acid derivatives.[17] They used a copper salt and a chiral ferrocenyl ligand as the chiral environment (Scheme 14). When an α-substituted glycine ester was used, both the yield and ee were lowered, probably due to the steric hindrance at the α position of the glycine ester, but how the steric factors influence the outcome is not clear.



Scheme 14

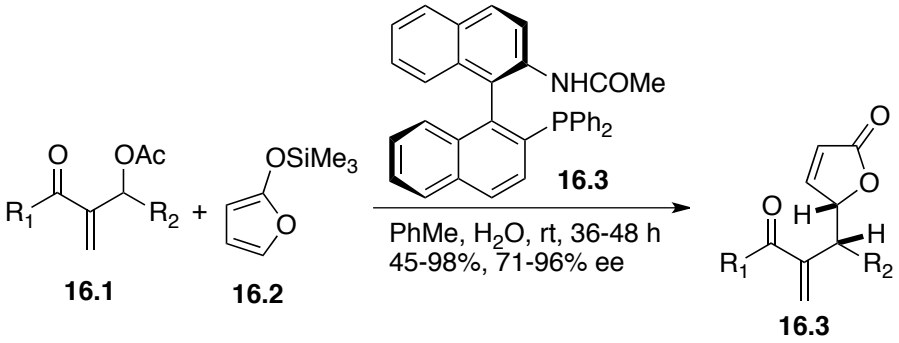
Krische and coworker used 2-trimethylsilyloxy furan **15.2** as the nucleophile and examined the reaction between **15.2** and MBH acetates **15.1**, using PPh_3 as the promoter to produce the products **15.3**.[15a] They proposed that

the electrophile-nucleophile ion pair intermediates **15.5** were generated. Most of the reactions afforded good yields (80%) with high regioselectivity and diastereoselectivity (*syn*/*anti*>20:1, *syn*/*anti* refer to the hydrogens indicated in **15.3**). The high diastereoselectivity was believed to be the result of formation of the Diels-Alder cycloadducts **15.6** as the intermediates, although reaction via an open transition state **15.7** was also possible. However, Krische and coworker emphasized that the intermediate phosphine adducts **15.4** as single enone geometrical isomers were essential for high diastereoselectivity, regardless of the reaction mechanism.



Scheme 15

Shi and coworkers also reported an S_N2'-S_N2' process, using the chiral phosphine **16.3** as the promoter.[15c] Most of the products were obtained in good to excellent yields and with high diastereoselectivity (Scheme 16). The stereochemistry of the products was rationalized using Krische's *endo* [4+2] cycloaddition mechanism.



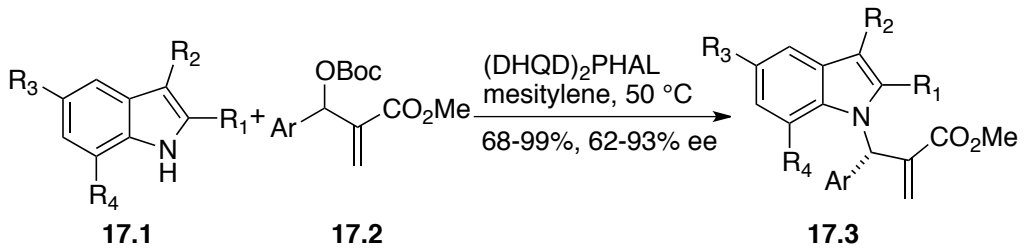
Scheme 16

Examples of other carbon nucleophiles, such as enamines,[18] indoles[19] and phenols[20] have also been studied.

Besides carbon nucleophiles, heteroatom nucleophiles (nitrogen[21] and oxygen.[22]) have been applied in this type of conjugate displacement reaction.

In contrast to alkylation at the indole C3 position using an MBH acetate and AgOTf,[23] Chen and coworkers developed the asymmetric *N*-alkylation of indoles using MBH carbonates (Scheme 17).[21f] As mentioned in connection with Scheme 12, the carbonate leaving group is crucial in this methodology. The indole nitrogen is not a good nucleophile, and so it needs to be deprotonated for the $(DHQD)_2PHAL$-promoted S_N2' reaction with the MBH adduct. However,

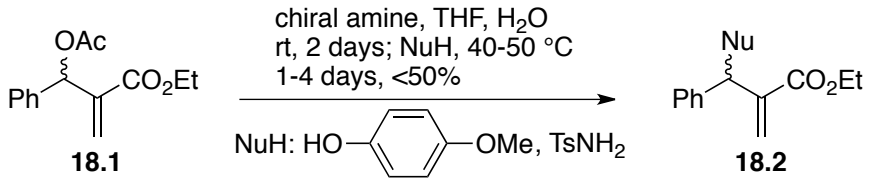
deprotonation of the indole nitrogen with an external base at the beginning of the reaction is unsatisfactory, since the nitrogen anion will compete with $(DHQD)_2PHAL$ in the first conjugate addition process. However, with OBoc as the leaving group, the *t*-butoxide anion will be expelled by the $(DHQD)_2PHAL$ and can then deprotonate the indole nitrogen.



17.1 **17.2** **17.3**

Scheme 17

Kim and coworkers reported that the use of acetate as the leaving group also works in this type of reaction, although the process is slower and the products were obtained in lower yields (Scheme 18).[21j]

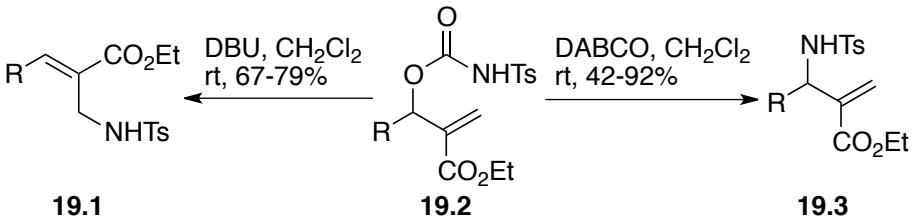


18.1 **18.2**

Scheme 18

Orena and coworkers found an interesting phenomenon in the regioselectivity of the conjugate displacement process: the basicity of the amine

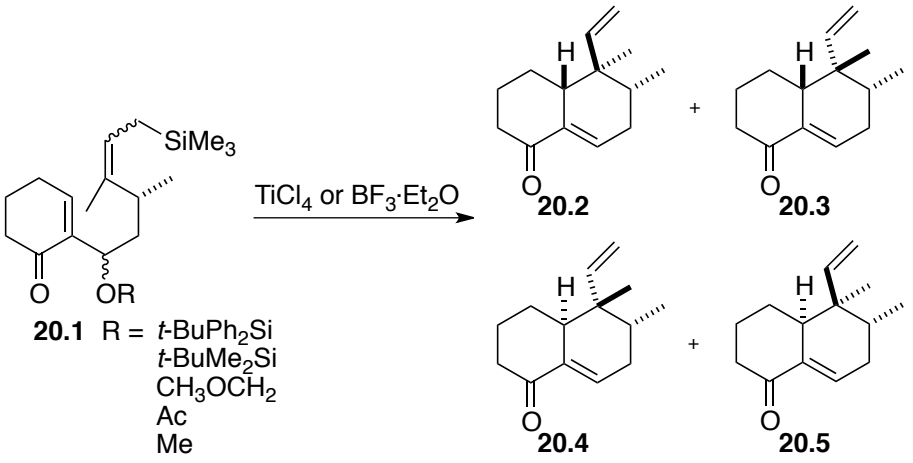
catalyst can affect the reaction pathway.[21i] Treatment of compound **19.2** with DBU, formed an anion on the nitrogen and then a [3,3]-sigmatropic rearrangement took place to give compound **19.1**. When DABCO was used instead of DBU, the S_N2'-S_N2' process occurred to generate **19.3**. These results were attributed to the different basicities of DBU and DABCO. The stronger base DBU deprotonated the NHTs group of the substrate first, and the weaker base DABCO acted as a nucleophile first. Another factor in this outcome is that DABCO is more nucleophilic than DBU.[24]



Scheme 19

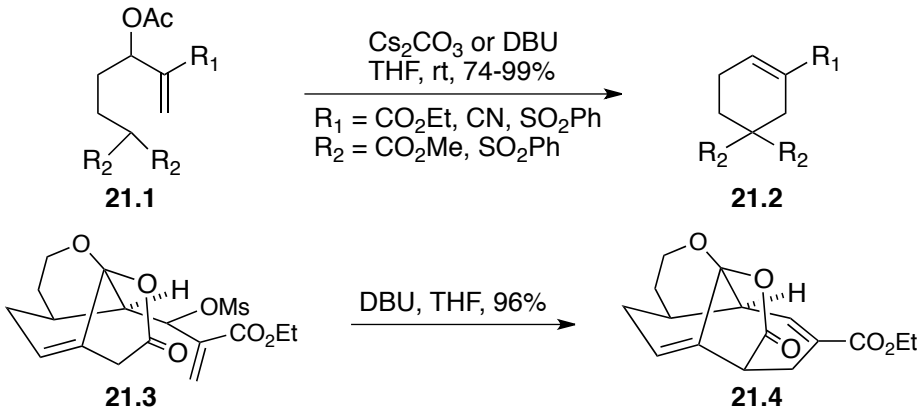
1.3.2 Intramolecular conjugate displacement with carbon nucleophiles and heteroatom nucleophiles

One example of intramolecular conjugate displacement (ICD) using a carbon nucleophile was reported by the Tokoroyama group.[25] Treatment of compounds **20.1** with a Lewis acid ($TiCl_4$ or $BF_3{\cdot}Et_2O$) resulted in several bicyclic products (Scheme 20). The diastereomeric outcome was complicated, and no simple correlation with the substrate configuration (*syn* or *anti*) was apparent. The results showed that diastereomer **20.2** is usually the major product in most cases.



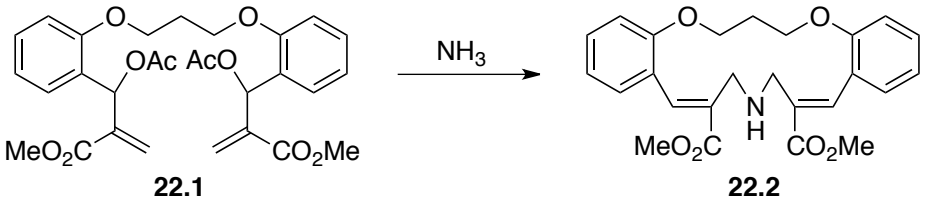
Scheme 20

Other members of this laboratory have developed the ICD process to construct many functionalized carbocycles.[11] In the presence of Cs_2CO_3 or DBU, five-, six- and seven-membered rings were prepared, and some examples are shown in Scheme 21. This method was then used to construct the core structure (**21.4**) of the natural products CP-225,917 and CP-263,114.



Scheme 21

Use of a nitrogen nucleophile for an ICD reaction was reported by the Foucaud group as one of the few prior examples reported before the work done in this laboratory.[10] The Foucaud group synthesized the macrocycle **22.2**, using ammonia as the nucleophile.

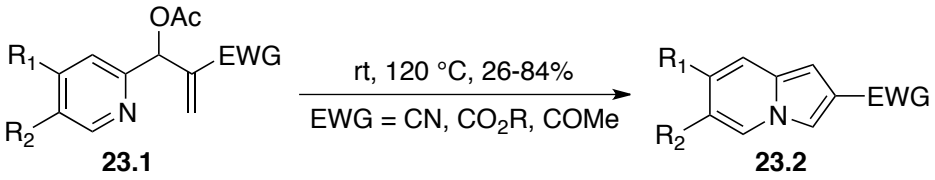


22.1 **22.2**

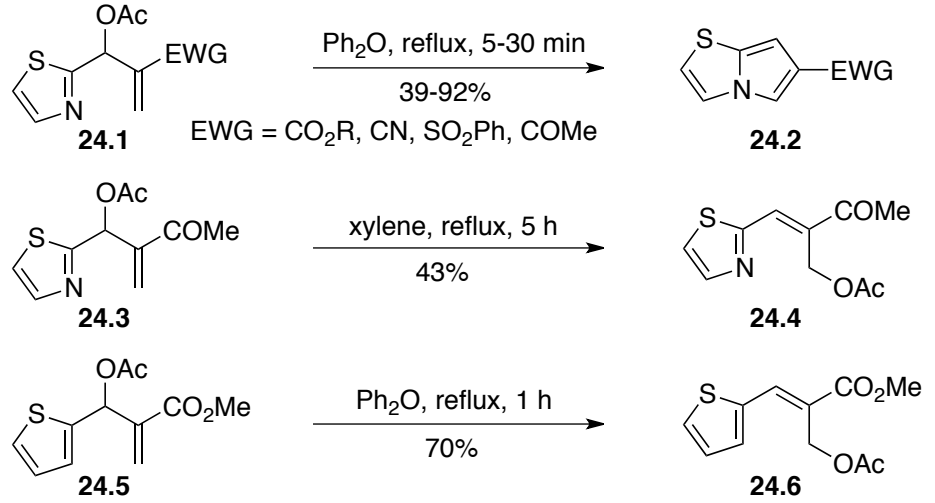
Scheme 22

Kaye and coworker prepared indolizines using the nitrogen of pyridine as the nucleophile.[26] They proposed that the compounds **23.1** were converted to the 2-substituted indolizines **23.2** via a nucleophilic addition-elimination sequence. However, this mechanism is disfavored by Baldwin's rules (5-*endo*-*trig* cyclizations are disfavored). The reaction probably involves a migration of the leaving group first, followed by a simple S_N2 process and migration of the double bond to give the cyclization product. Lee's group proved that migration occurred before the cyclization.[27] They found that when compounds **24.1** were stirred in refluxing Ph_2O (boiling point 258 °C) for a short time, the 6-substituted pyrrolo[2,1-*b*]thiazoles **24.2** were generated. When the methyl ketone **24.3** was heated in refluxing xylene (boiling pointing 137-140 °C) for 5 h, only acetate migration was observed instead of a cyclization product. Substrate **24.5**, lacking

the nucleophilic nitrogen, also gave only the migration product **24.6**, after being heated in refluxing Ph_2O for 1 h.

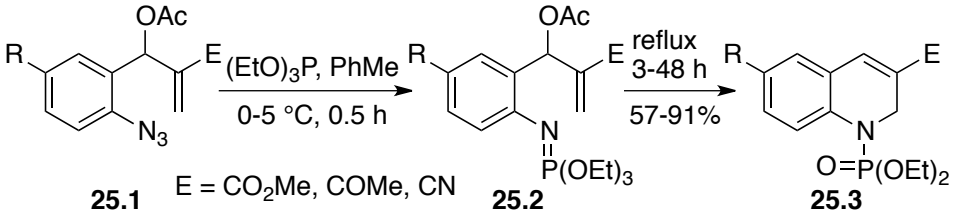


Scheme 23



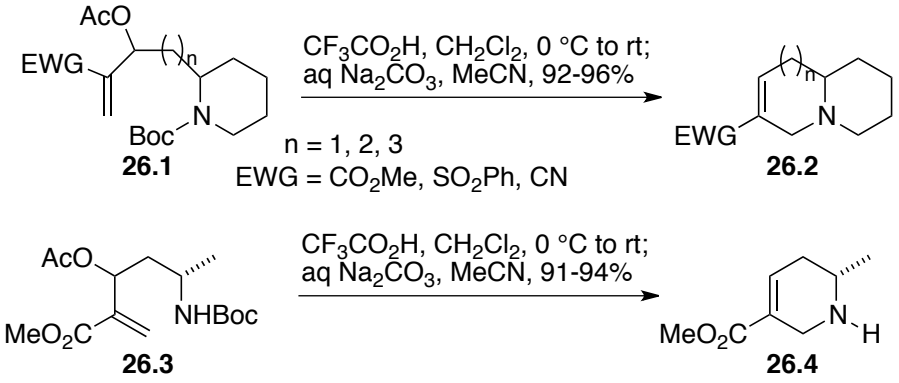
Scheme 24

Lee and coworkers also developed ICD reactions using iminophosphoranes as nucleophiles.[28] The azides **25.1** were first converted to the iminophosphoranes **25.2** via the Staudinger reaction, and then refluxing of the mixtures in PhMe generated the desired 1,2-dihydroquinoline derivatives **25.3** by sequential ICD reaction and Michaelis-Arbuzov rearrangement.



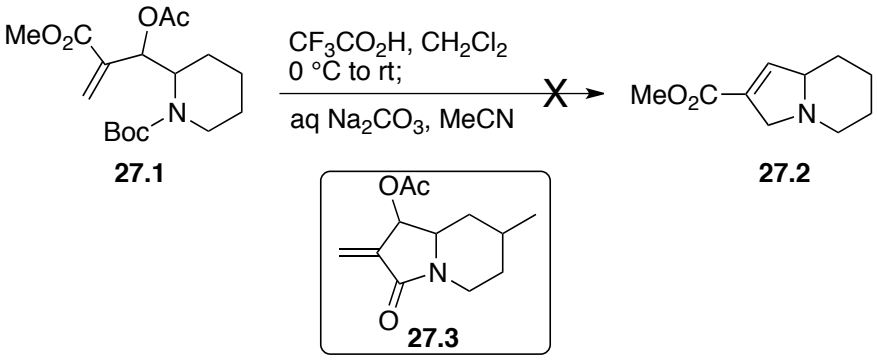
Scheme 25

Many examples of ICD reactions using nitrogen as the nucleophile were reported from this laboratory. Besides the previously mentioned process (Scheme 5) conducted on an intermediate in the synthesis of the marine alkaloid halichlorine and the cases shown in Scheme 6, more examples of monocyclic and bicyclic nitrogen-containing compounds were prepared in good yield (Scheme 26).[29] However, substrates having a substituent at the β position of α,β-unsaturated esters normally gave somewhat lower yields, probably due to steric hindrance.

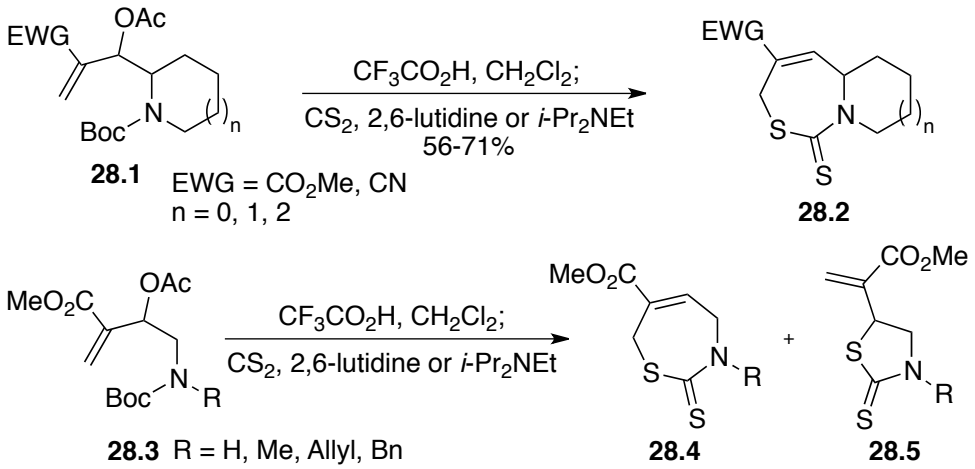


Scheme 26

Encouraged by the apparent facility of the first few ring closures, a formally disfavored 5-*endo-trig* cyclization, using compound **27.1**, was also tried.[29] The expected ICD reaction did not take place, and instead closure onto the methyl ester carbonyl occurred to produce the lactam **27.3**. This outcome indicated that amines of the type derived from **27.1** by removal of the Boc group do not undergo the ICD reaction. Consequently, if a neutral nucleophile X=Y could trap the free amine after removal of the Boc group, then a new anion $^{-}$X-Y-N would be formed and the anion would attack the double bond in an ICD process without violating Baldwin's rules.[12] Several neutral nucleophiles [PhNCO, PhNCS, SO_2, $BnN{=}CH_2$, $(Cl_3C)_2C{=}NBn$, CO_2, CS_2 and H_2NCN] were examined, and CS_2 was found to be a satisfactory choice. Some MBH acetates were treated with CF_3CO_2H, and then with CS_2 and base, and the desired bicyclic ICD products were obtained in 56-71% yield (Scheme 28). When acyclic substrates were subjected to the same conditions, a five-membered side product was also formed (see **28.5**).

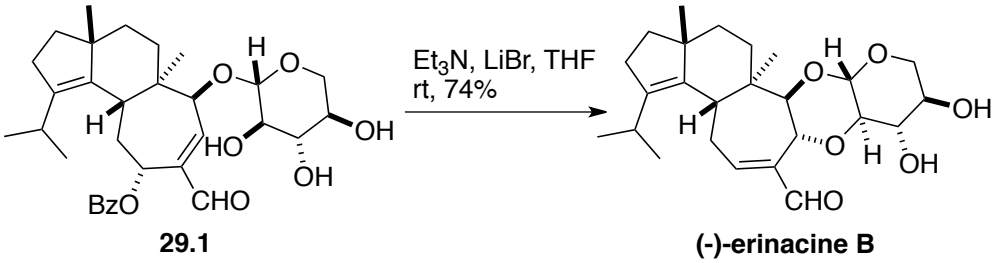


Scheme 27



Scheme 28

For oxygen nucleophiles, one example was reported by Nakada and coworkers.[22b] In the total synthesis of (-)-erinacine B, they found that treating the advanced intermediate **29.1** with Et_3N and LiBr produced the desired (-)-erinacine B as a single diastereomer in 74% yield. This process can be classified as an ICD reaction.

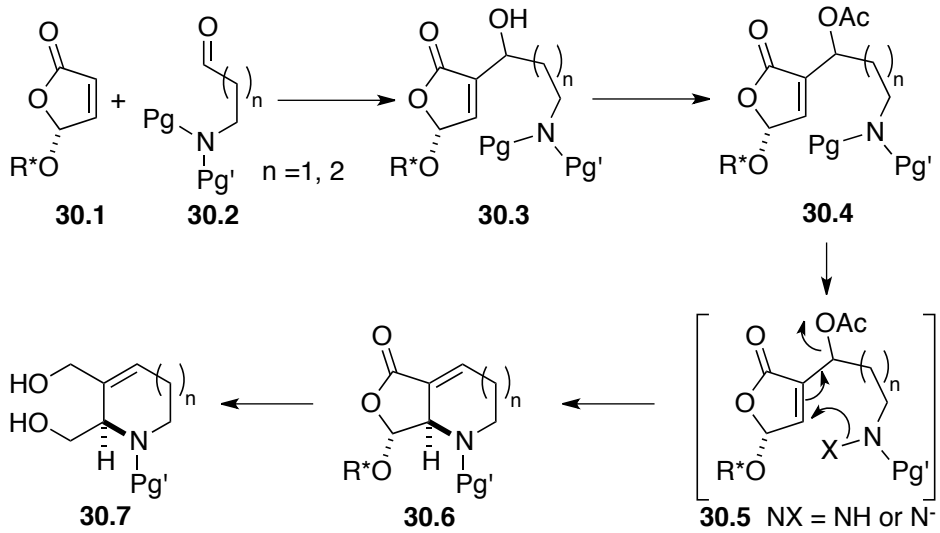


Scheme 29

2. Results and Discussion

2.1 Research objectives

After the ICD reaction had been successfully applied in the synthesis of halichlorine (Scheme 5), a series of bicyclic amines (Schemes 6 and 26) were prepared in this group. However, the stereochemistry of this ICD reaction was not studied, and my project was to develop an asymmetric version of the reaction shown in Scheme 5. The plan was to do this by placing a detachable chiral auxiliary R* on the acceptor double bond, as summarized in Scheme 30. For this purpose, the MBH acetates **30.4** would be prepared from lactone **30.1** and an *N*-protected β-amino- or γ-aminoaldehyde **30.2**, followed by acetylation. The ICD reaction would then generate a stereogenic center α to nitrogen (see **30.6**). Finally, removal of the chiral auxiliary by DIBAL-H reduction should afford the optically pure functionalized amine **30.7**.

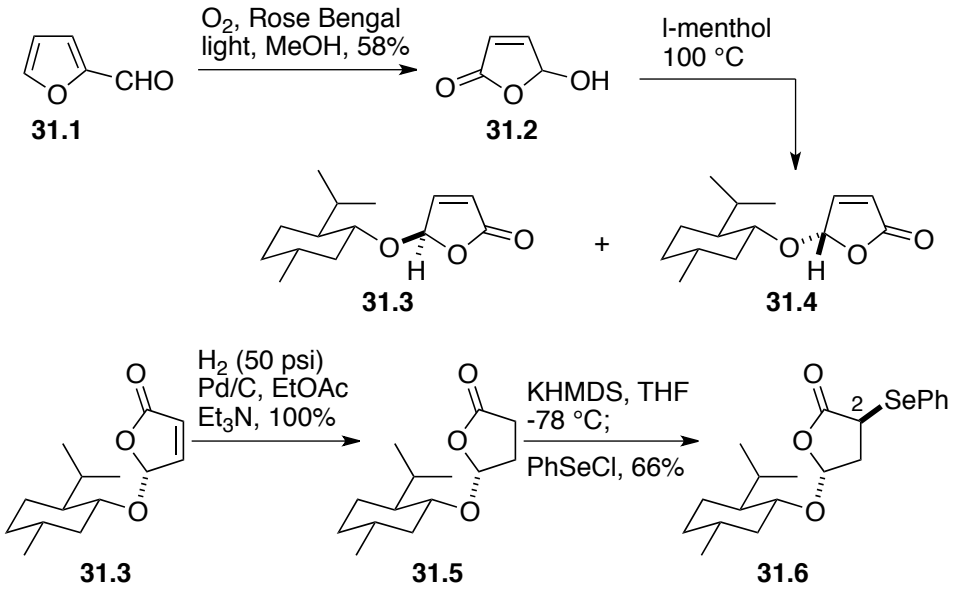


Scheme 30

2.2 Preparation of lactones corresponding to 30.1

The reaction of (–)-menthol with racemic lactone **31.2**, which can be prepared easily by photooxygenation of furfural (**31.1)** in MeOH, afforded epimeric derivatives **31.3** and **31.4**, which were readily separated.[30] Diastereomer **31.3** was used for coupling with a number of aldehydes. Alternatively, the selenide **31.6**, which was obtained via hydrogenation of **31.3**[31] (100%), followed by deprotonation and selenation with PhSeCl (66%), was used in the coupling reaction instead of lactone **31.3**.

The selenation reaction generated the 2*S* isomer **31.6** as the major product and the other C(2) epimer in 9% yield. The configuration of **31.6** was determined by X-ray analysis of the 2*R* isomer (Figure 1), which was prepared by deprotonation of **31.6** with LDA and reprotonation with aqueous NH_4Cl.



Scheme 31

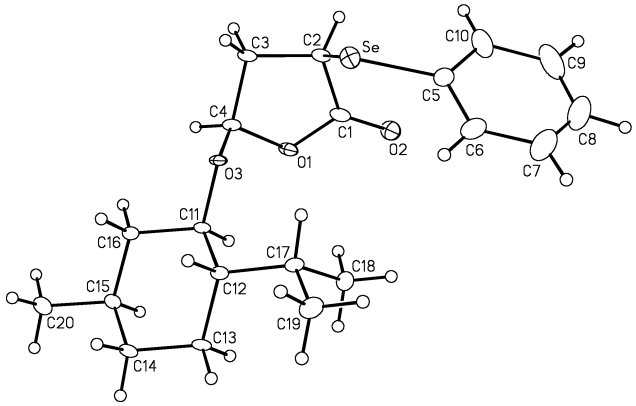
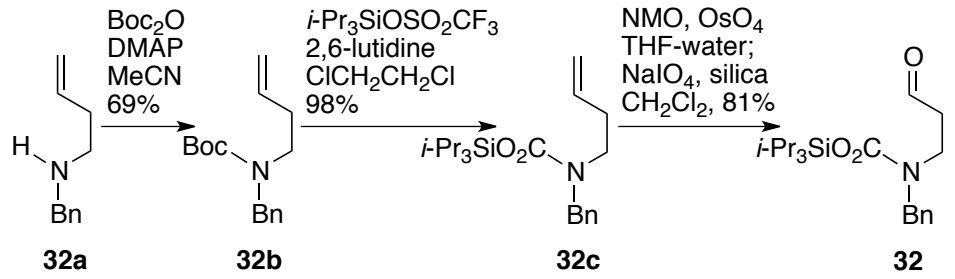


Figure 1. ORTEP diagram of 2*R* isomer of 31.5

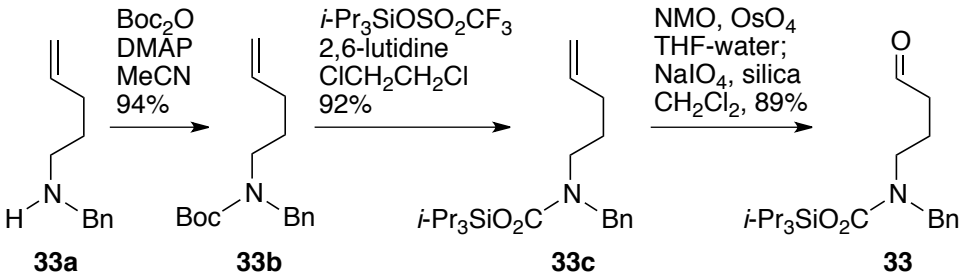
2.3 Preparation of amino aldehydes corresponding to 30.2

Two aliphatic amino aldehydes and five aromatic amino aldehydes were prepared for coupling with the lactone. The preparation of aldehyde **32** started with the known *N*-benzyl amine **32a**.[32] Treatment with Boc_2O and DMAP produced the *N*-Boc derivative **32b**,[32] which reacted with *i*-$Pr_3SiOSO_2CF_3$ in the presence of 2,6-lutidine to generate *O*-silyl carbamate **32c**.[33] Finally, several different methods were tried to make the desired aldehyde **32**: ozonolysis gave the aldehyde in 32% yield, while the yield with the Lemieux-Johnson oxidation was 79%. The best method was found to be the use of OsO_4 and NMO in aqueous THF, followed by reaction with $NaIO_4$/silica gel;[34] this procedure gave the aldehyde in 81% yield.



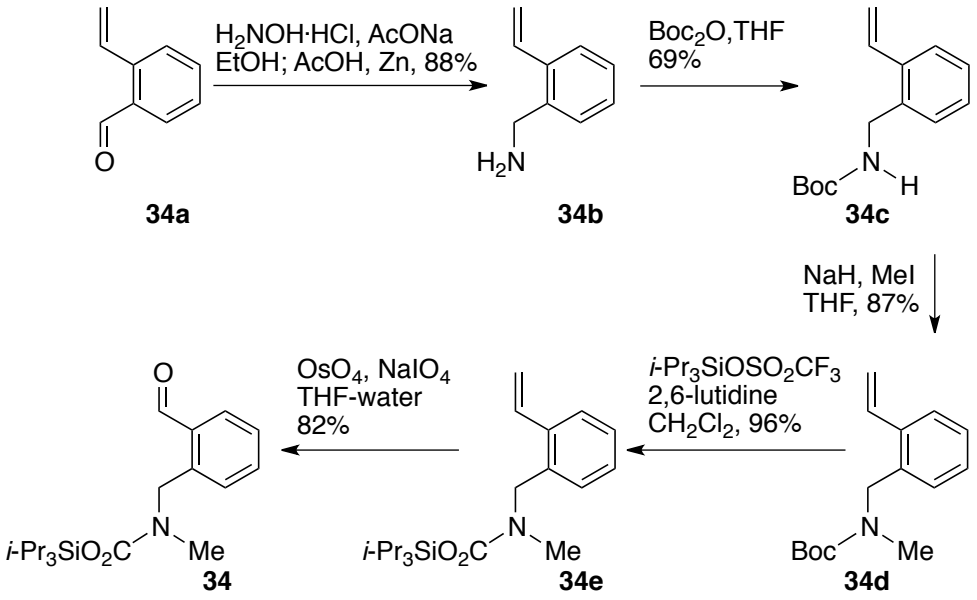
Scheme 32

Aldehyde **33** was prepared in a very similar way[35] (Scheme 33). The cleavage of the double bond was first done by ozonolysis, and aldehyde **33** was obtained in 70% yield. However, the use of OsO_4 and NMO in aqueous THF, followed by treatment with $NaIO_4$/silica gel, improved the yield to 89%.



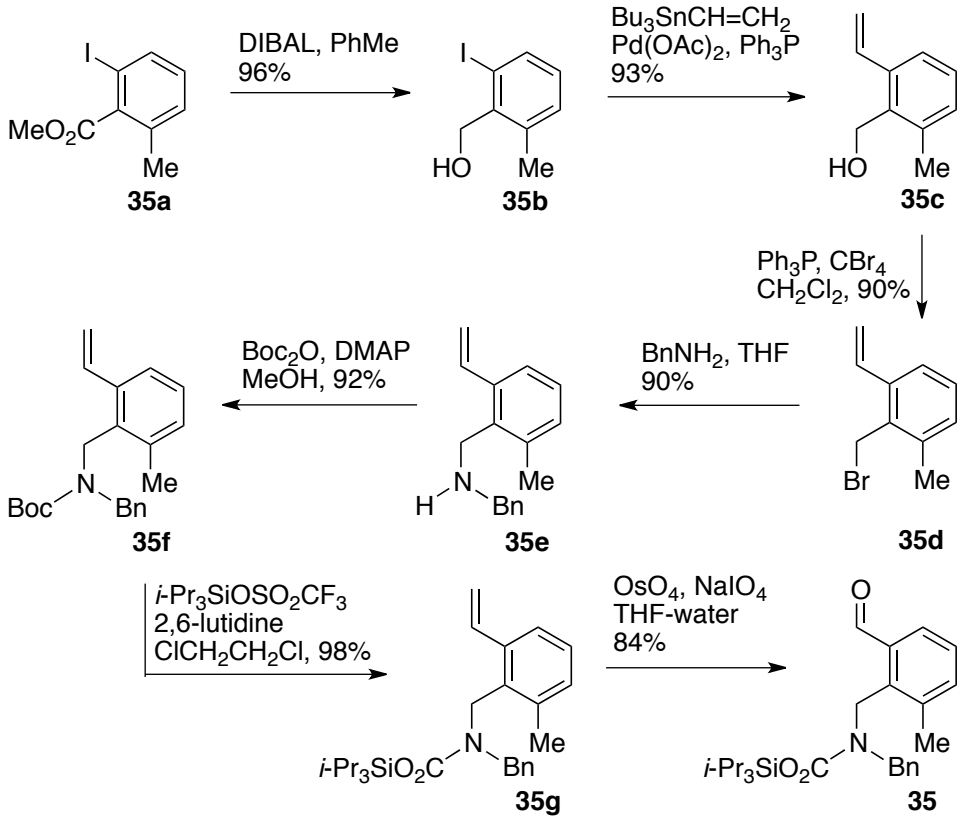
Scheme 33

Aromatic aldehyde **34** was prepared by the route summarized in Scheme 34: the starting *O*-vinylbenzaldehyde **34a** was treated with $H_2NOH{\cdot}HCl$ and AcONa, and then with Zn in AcOH,[36] followed by *N*-protection with Boc_2O[37] and *N*-methylation with NaH and MeI, to give compound **34d**. Treatment of **34d** with *i*-$Pr_3SiOSO_2CF_3$ and 2,6-lutidine, followed by double bond cleavage using the Lemieux-Johnson method, produced the desired aldehyde **34**.



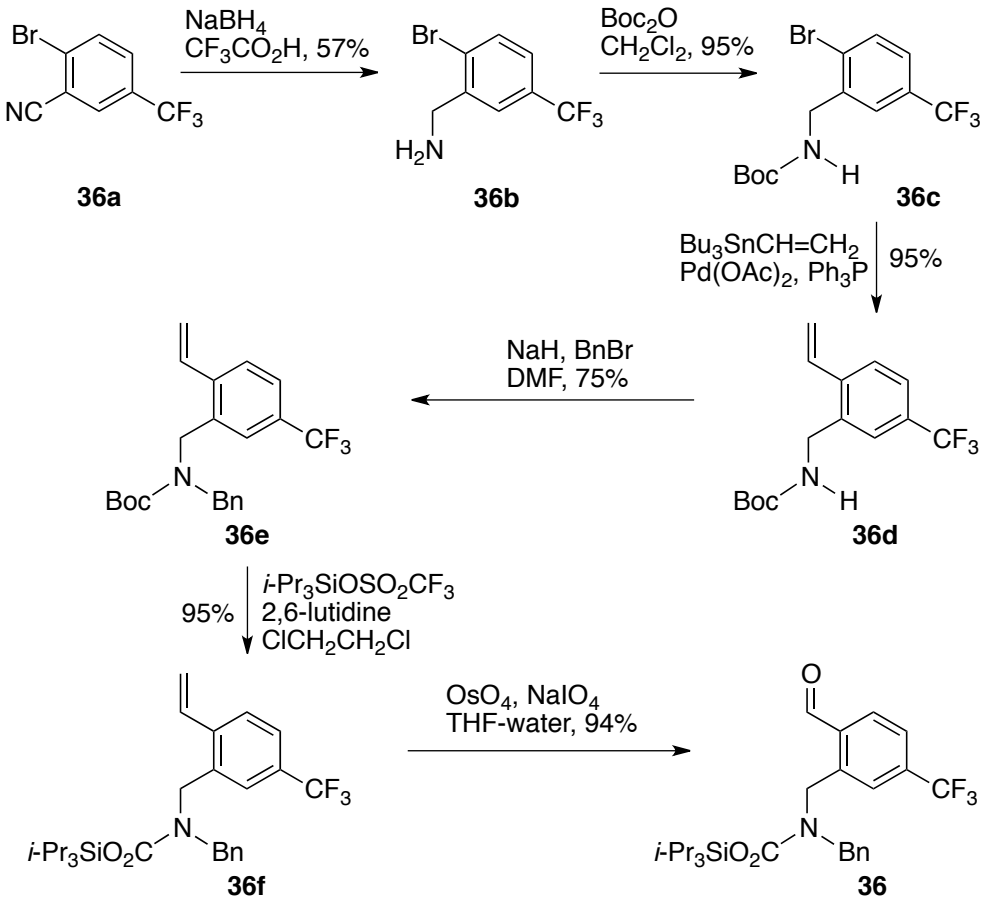
Scheme 34

The preparation of **35** began with reduction (DIBAL-H) of iodo ester **35a**, which is prepared from 2-methylbenzoic acid,[38] and Stille coupling with tributyl(vinyl)tin. Then, replacement of the hydroxyl by bromine, displacement with $BnNH_2$, *N*-protection with Boc_2O and DMAP, treatment with *i*-$Pr_3SiOSO_2CF_3$ and 2,6-lutidine, and double bond cleavage (Lemieux-Johnson), gave the methyl-substituted benzaldehyde **35**.



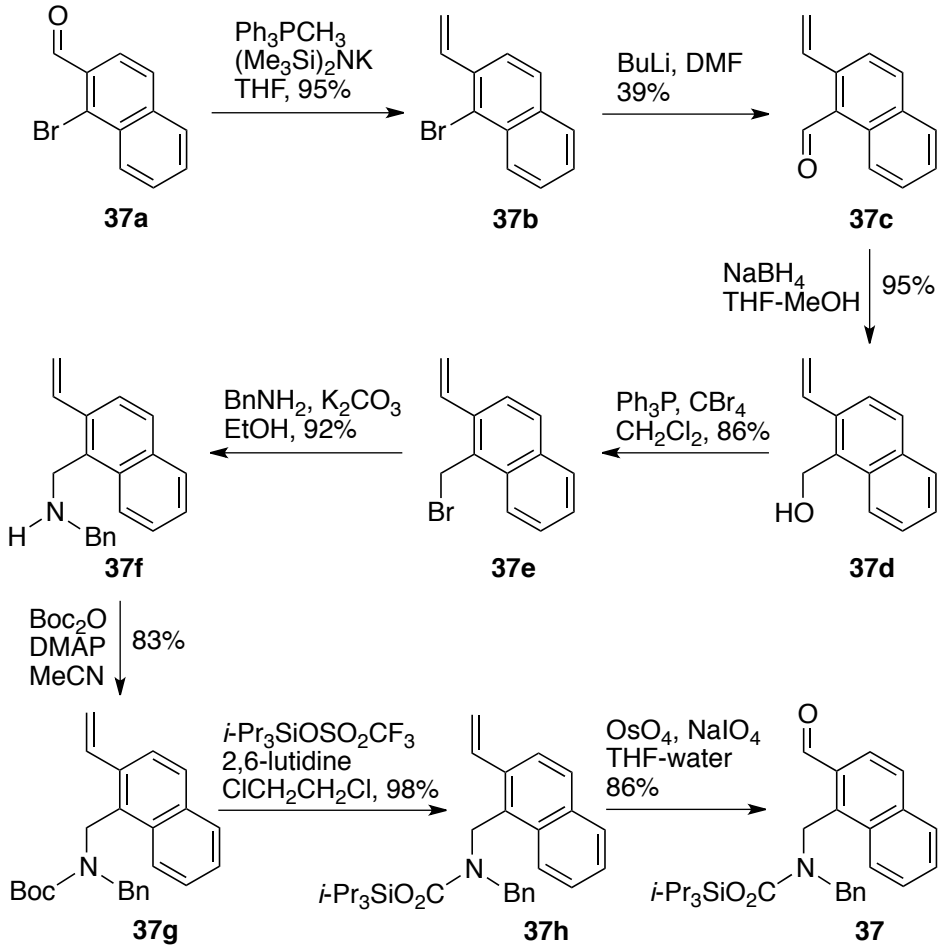
Scheme 35

The substituted aldehyde **36** was synthesized by the following route: Reduction of bromonitrile **36a** with $NaBH_4/CF_3CO_2H$,[39] followed by *N*-protection with Boc_2O and Stille coupling, generated **36d**, which was treated with BnBr[40] to give **36e**. Conversion to the triisopropylsilyl carbamate **36f** and double bond cleavage with OsO_4 and $NaIO_4$ then produced **36**. I had first applied the Stille reaction after *N*-benzylation, but the route shown in Scheme 36 is better, since some of the intermediates are easier to purify.



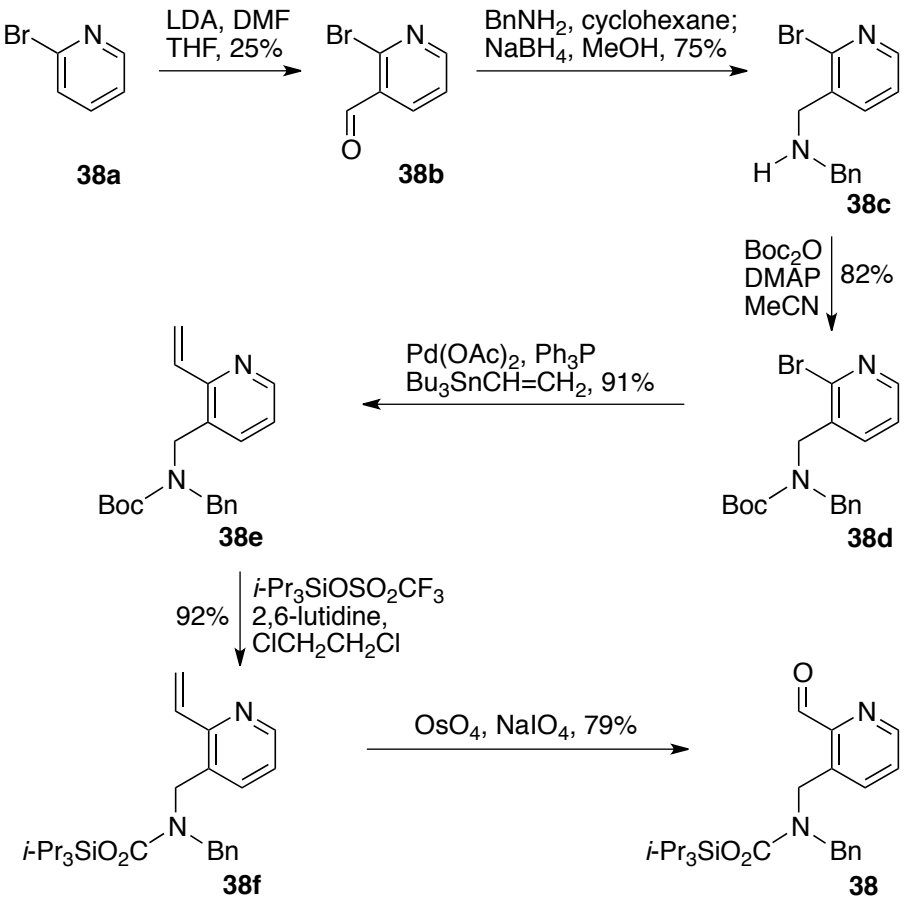
Scheme 36

The naphthalene aldehyde **37** was prepared from 1-bromonaphthalene-2-carbaldehyde (**37a**), which is readily available[41] from commercial 1-bromo-2-methylnaphthalene. Wittig reaction served to convert **37a** into the bromo olefin **37b**,[42] and then halogen/metal exchange, followed by quenching with DMF,[42] produced aldehyde **37c**. Reduction with $NaBH_4$, followed by Appel reaction and treatment with $BnNH_2$, gave the secondary amine **37f**. The remaining steps (from **37f** to **37**) followed the route used for the previous examples.



Scheme 37

The substituted pyridine aldehyde **38** was prepared by the route summarized in Scheme 38. Conversion of 2-bromopyridine to aldehyde **38b**,[43] followed by reductive amination,[44] gave secondary amine **38c**. From this point similar operations to those used earlier, provided aldehyde **38**.

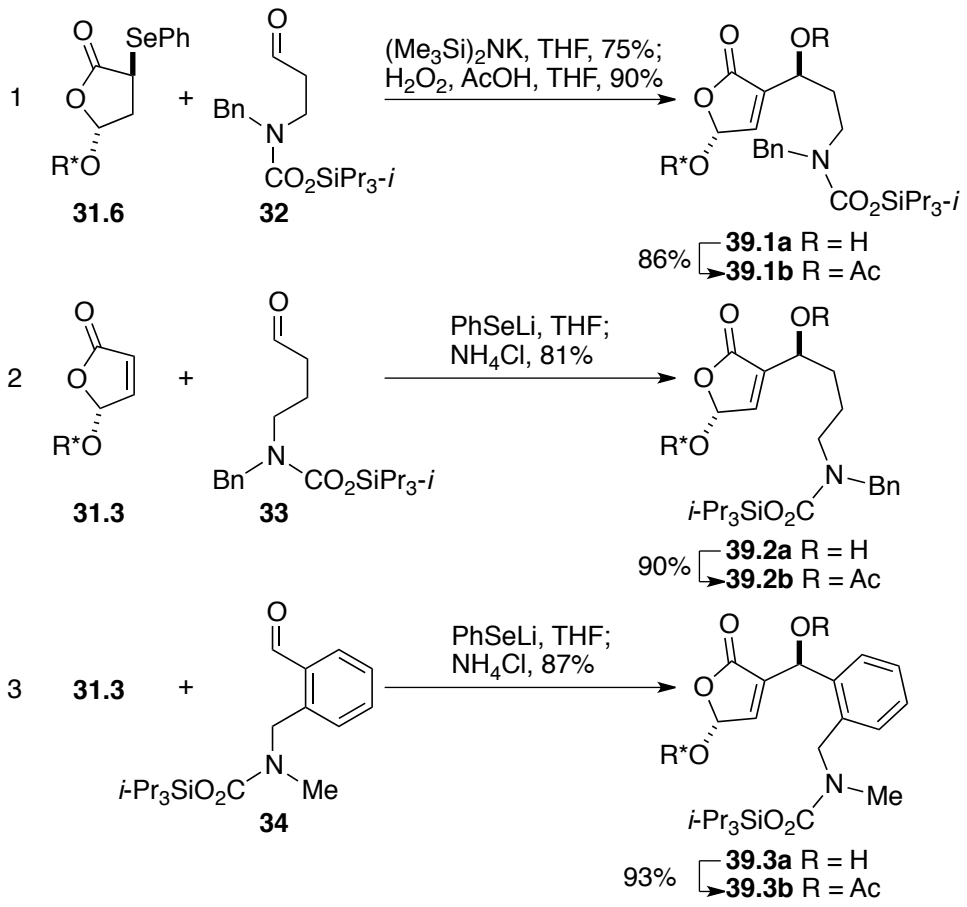


Scheme 38

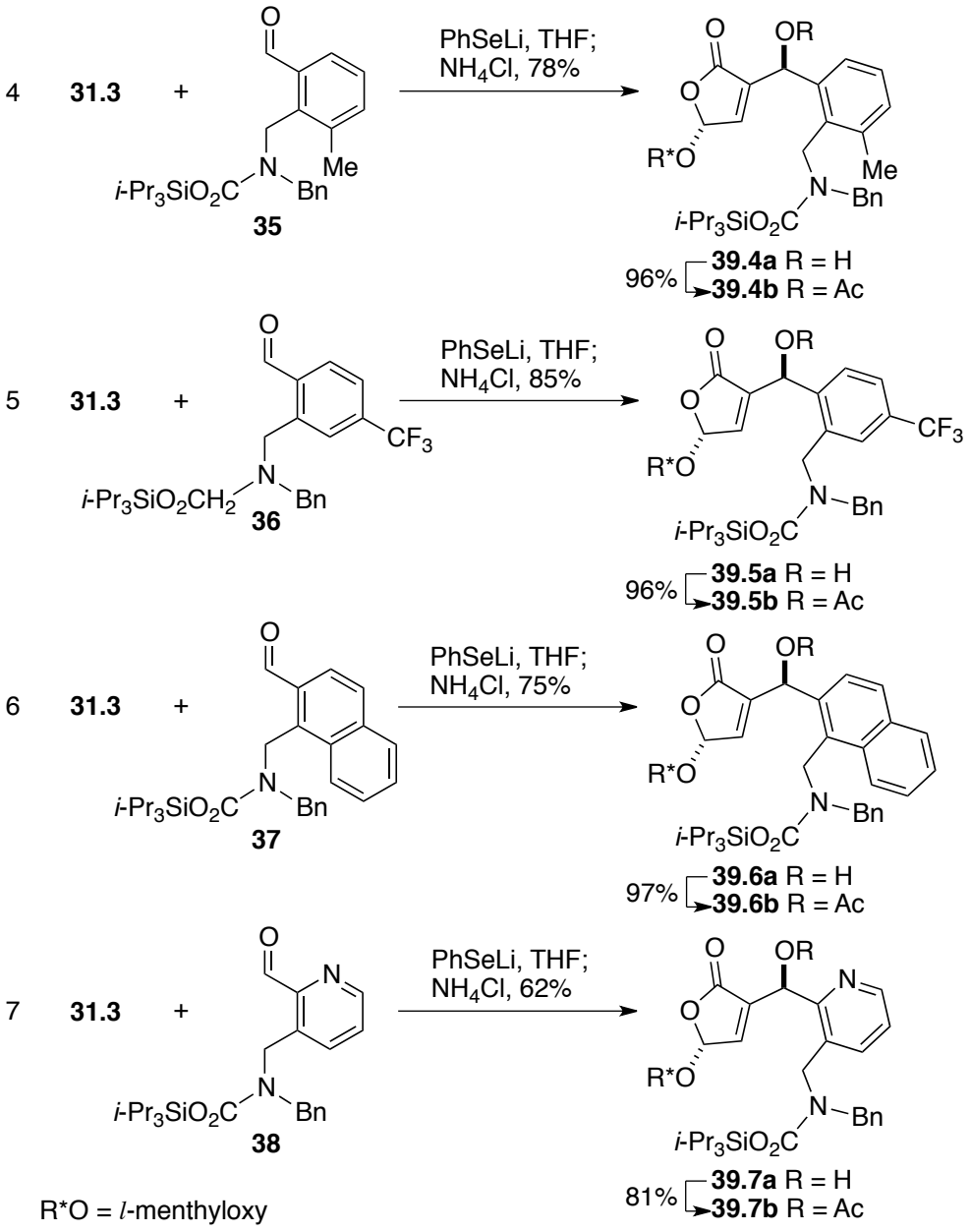
2.4 Coupling of the aldehydes with the chiral lactones

Aldehyde **32** was the first substrate examined for coupling with the optically pure lactone **31.3**, using PhSeLi as the nucleophilic catalyst. This version of the Morita-Baylis-Hillman reaction had been reported[45] to work well (high yield and high diastereoselectivity) with lactone **31.3** and a number of aldehydes such as PhCHO, *i*-PrCHO, *t*-BuCHO and cinamaldehyde. However, the reaction failed and both starting materials were recovered. I then tried to condense aldehyde **32** with lactone **31.6**: Deprotonation of **31.6** with LDA and addition of aldehyde **32** produced the desired hydroxy selenide as a mixture of

diastereomers in 60% yield. Later, I found that using $(Me_3Si)_2NK$ instead of LDA improved the yield to 75%. Oxidation with H_2O_2 gave the expected unsaturated alcohol **39.1a**, which is consistent with the normal regioselectivity observed for oxidation of β-hydroxy selenides.[46] The acetate **39.1b** was then obtained using AcCl, DMAP and pyridine. As expected, the 2*R* isomer of **31.6** behaved in the same way, as did mixtures of the two diastereomers.



Scheme 39



Scheme 39 (continued)

When aldehyde **33** was examined using the PhSeLi-catalyzed Baylis-Hillman reaction, the desired alcohol **39.2a** was produced in good yield (81%); the same method also worked well for aromatic aldehydes **34**-**38**. All these Baylis-Hillman reactions were conducted at –42 °C, and under these conditions

the required double bond was formed in situ without the need for an additional step (addition of BnBr[45]) to eliminate the PhSe group. For all the alcohols prepared by the Baylis-Hillman reaction, the stereochemistry at the hydroxy-bearing carbon was assumed to follow the uniform pattern observed for this type of Baylis-Hillman process.[45] I tried to crystallize four of the alcohols (**39.1a**, **39.2a**, **39.6a**, **39.7a**), but was successful only with **39.1a**, and single crystal X-ray analysis (Figure 2) established the indicated stereochemistry, which is consistent with the result observed before in a simpler case,[45] even though the condensation method for making **39.1a** was different from the Baylis-Hillman condensation method (PhSeLi) used for other examples.

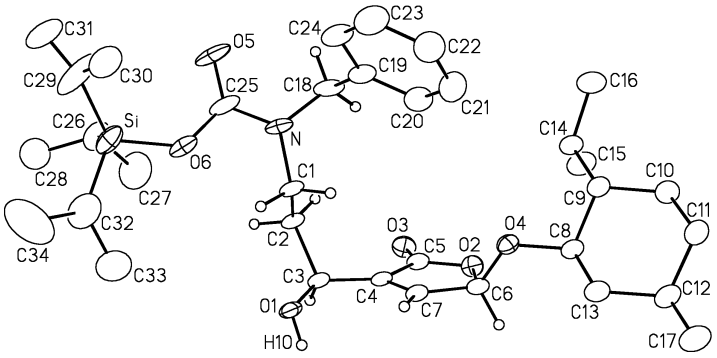


Figure 2. ORTEP diagram of 39.1a

The PhSeLi-mediated Baylis-Hillman condensation gave all the alcohols[45,47] (Scheme 39, entries 2-7) essentially (>99% de) as a single isomer, but the ^{1}H NMR spectra of alcohols and their acetates are complicated, so I had to prove if rotamers or diastereomers are present. For alcohols **39.1a**, **39.3a**, **39.4a**, **39.5a** and **39.6a**, the ^{13}C NMR showed that only a single isomer was obtained. In

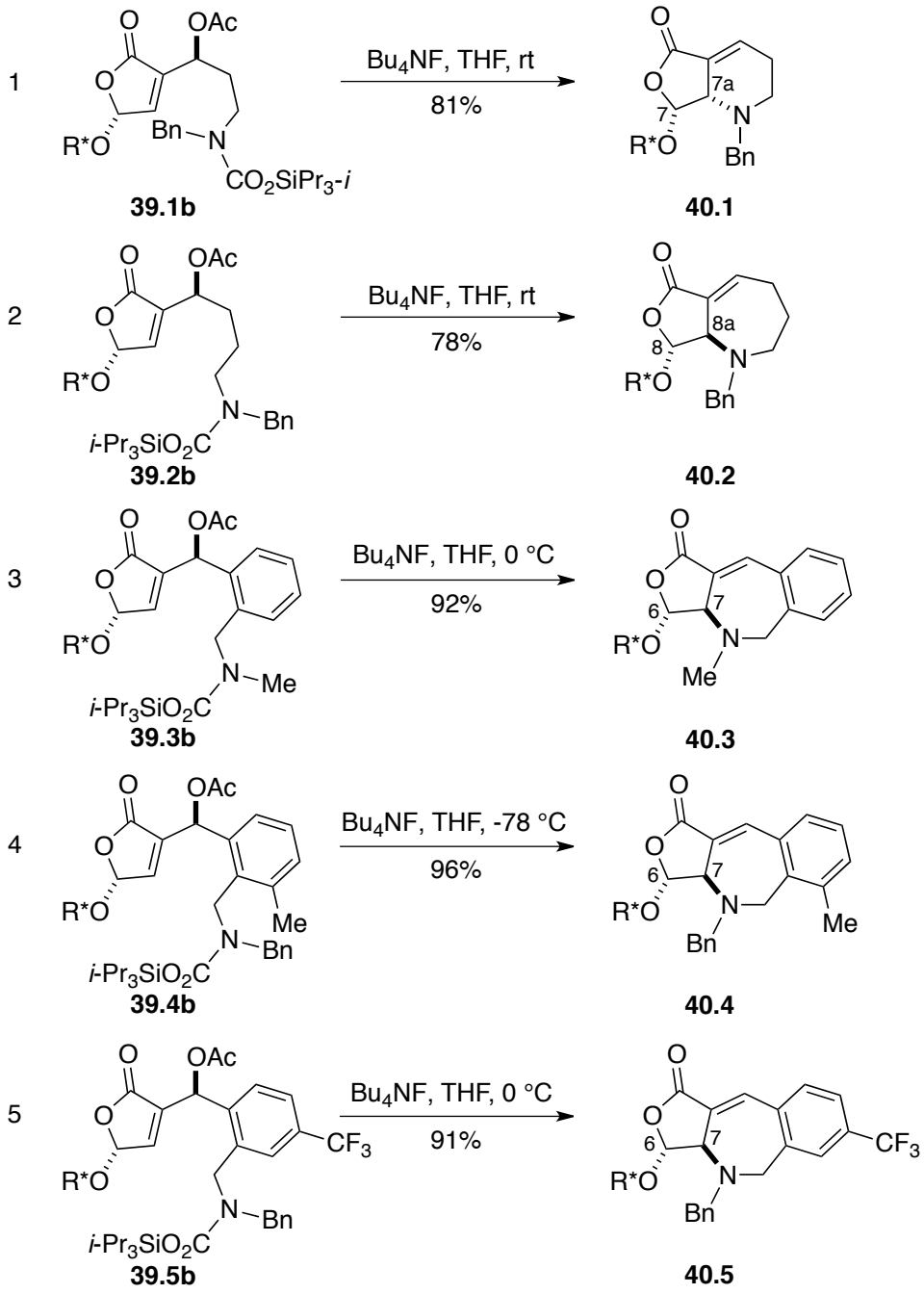
the case of acetate **39.2b** and alcohol **39.7a**, it was difficult to decide if rotamers or isomers were present from both ^{1}H NMR and ^{13}C NMR spectra. When the ^{1}H NMR spectrum of **39.2b** was run at a higher temperature (60 °C), signal coalescence was observed, which indicated that **39.2b** is a mixture of rotamers. Likewise, the ^{1}H NMR signals of **39.7a** coalesced at 60 °C, establishing the presence of rotamers.

2.5 Intramolecular conjugate displacement

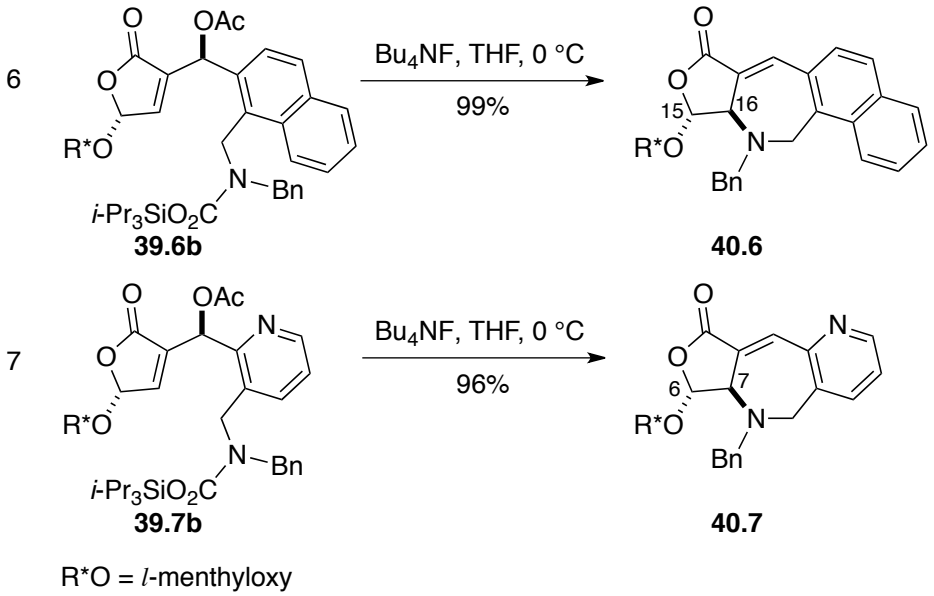
Treatment of acetate **39.1b** with Bu_4NF in THF gave the bicyclic compound **40.1** as a single isomer (^{1}H NMR and ^{13}C NMR) in 81% yield. The structure of **40.1** was established by IR, NMR and mass spectral data, and the stereochemistry was initially assumed to be as shown in Scheme 30 (see **30.6**, R*O and adjacent H *syn*). However, crystals of **40.1** were obtained at a later date, and surprisingly, single crystal X-ray analysis (Figure 3) showed that the R*O group and nitrogen were *syn*. The coupling constant $^{3}J_{7,7a}$ (see **40.1**) was 5.5 Hz. Before flash chromatography, the ^{1}H NMR spectrum of the crude product showed that a minor isomer (10:1) was also produced. This minor isomer ($^{3}J_{7,7a}$ = 6.0 Hz) was isolated and assumed to be different from **40.1** only at C(7a), but I was unable to obtain crystals to prove this assumption by X-ray analysis.

For making compound **40.2**, acetate **39.2b** was treated with Bu_4NF, and two diastereomers were always produced. The optimum conditions were to run the reaction at room temperature for 1 h. The two products were obtained in 78% combined yield and their ratio was 1:31 in favor of **40.2** ($^{3}J_{8,8a}$ = 2.5 Hz).

Preparative TLC was used to isolate the minor product, which was proved to be the C(8a) isomer, using COSY, ^{1}H NMR ($^{3}J_{8,8a}$ = 5.1 Hz) and ^{13}C NMR data.



Scheme 40



Scheme 40 (continued)

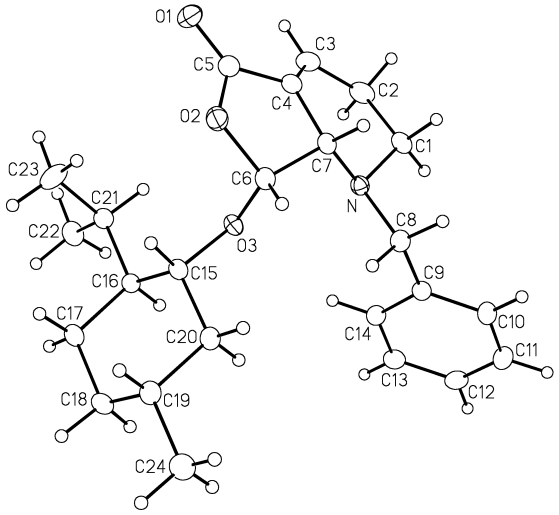


Figure 3. ORTEP diagram of 40.1

Acetate **39.3b** reacted smoothly with Bu_4NF in THF at 0 °C to give the tricyclic compound **40.3** as a single diastereomer ($^3J_{6,7}$ = 3.2 Hz) in 92% yield.

The choice of 0 °C was arbitrarily made to illustrate the mildness of the conditions required for the ICD process.

The cyclization reaction of **39.4b** showed a more complicated behavior than that of **39.3b**. When the reaction was conducted at −78 °C, the ^{1}H NMR spectrum of the isolated ICD product **40.4** ($^3J_{6,7}$ = 3.0 Hz) showed small signals which were assumed to represent the C(7) epimer of **40.4**, and the ratio of the products was 23:1 (combined yield 96%); when the reaction temperature was changed to 0 °C, the ratio was 9.6:1. Preparative TLC (silica, 1:1 hexanes/CH_2Cl_2) was then applied to separate the 23:1 mixture, and the desired **40.4** was isolated. However, the minor component could not be purified by preparative TLC.

Acetate **39.5b,** in which the benzene ring carries a trifluoromethyl group, was treated with Bu_4NF in THF at 0 °C to generate the expected heterocycle **40.5** ($^3J_{6,7}$ = 3.5 Hz) as a yellow solid in 91% yield. The structure and stereochemistry of the product were confirmed by single crystal X-ray analysis (Figure 4).

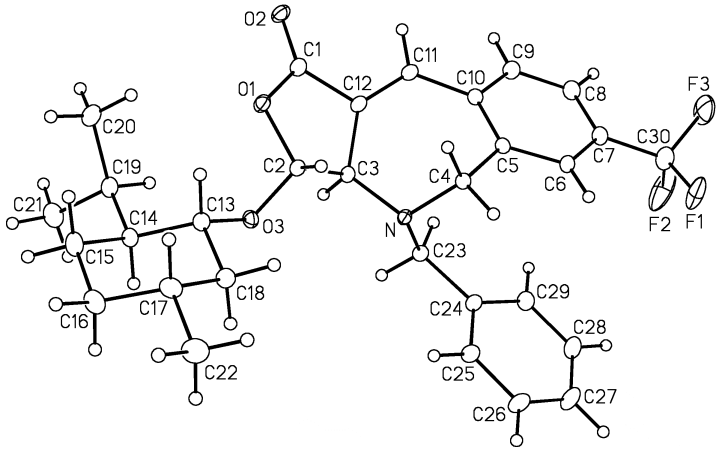


Figure 4. ORTEP diagram of 40.5

By using Bu_4NF, the naphthyl acetate **39.6b** gave the desired ICD product **40.6** ($^3J_{15,16}$ = 2.0 Hz) as a single diastereomer in very high yield (99%). The structure of **40.6** was also confirmed by single crystal X-ray diffraction (Figure 5).

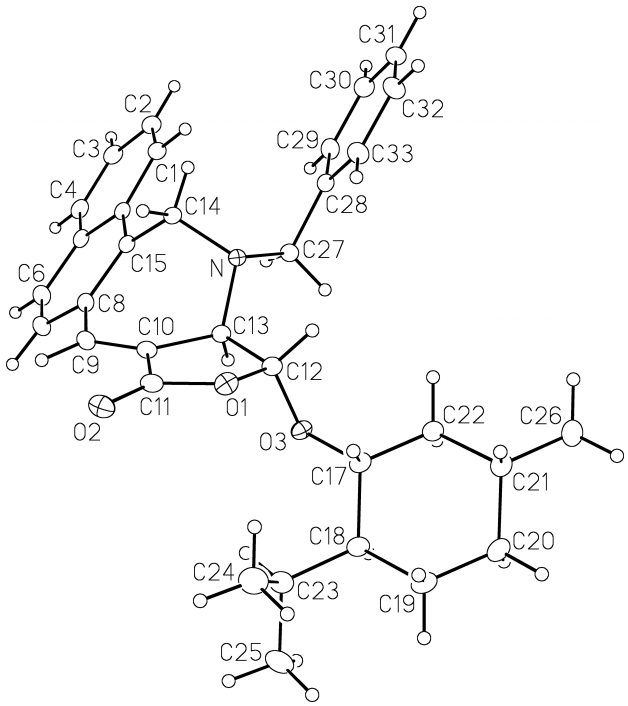


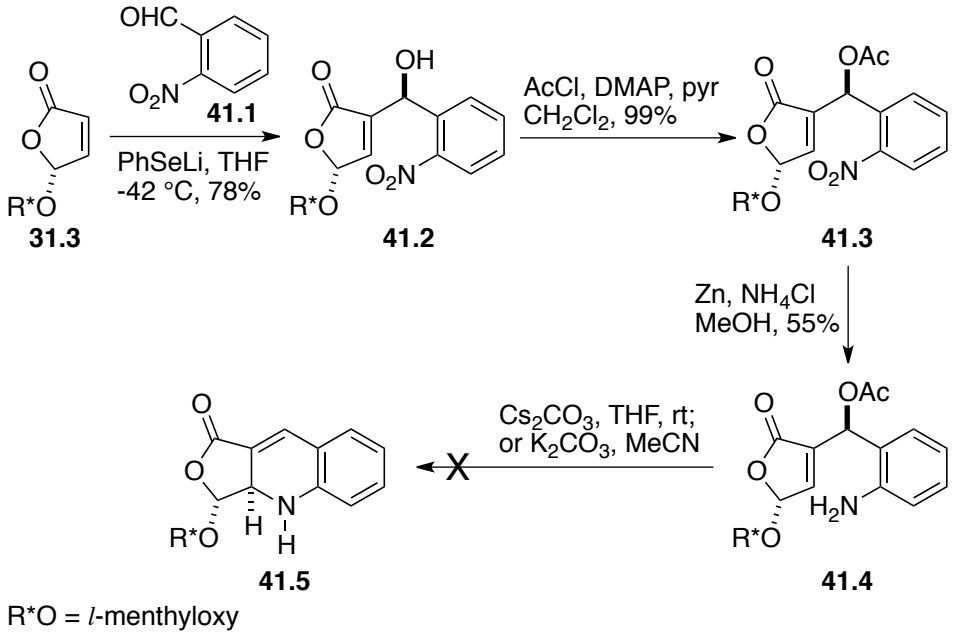
Figure 5. ORTEP diagram of 40.6

When acetate **39.7b** was subjected to the ICD process, the expected tricyclic compound **40.7** ($^3J_{6,7}$ = 3.5 Hz) was obtained as a single isomer in high yield (96%).

The stereochemistry of ICD products **40.2**, **40.3**, **40.4** and **40.7** was assigned by analogy with the stereochemistry of **40.5** and **40.6,** whose structures were established by X-ray analysis. All products except **40.1** have similar ^3J values for the R*OC**H**-C**H**N spin system.

In all cases except entry 1 in Scheme 40, the attack of nitrogen is *anti* to the menthyloxy group and *syn* to the acetate leaving group. The formation of compound **40.1** was from attack of nitrogen *syn* to the menthyloxy group and *anti* to the acetate leaving group. However, I have not established the reason for this stereochemical outcome.

In addition to the examples shown in Scheme 40, I also tried to make the tricyclic amine **41.5** using the ICD process. 2-Nitrobenzaldehyde (**41.1**) was used as the starting material and treated with **31.3** in the presence of PhSeLi to generate the desired Morita-Baylis-Hillman alcohol **41.2** in 78% yield. Alcohol **41.2** was then acetylated to give **41.3** (99% yield) which was reduced (Zn, NH_4Cl)[48] to phenylamine **41.4**. An attempt to obtain the ICD product failed, using Cs_2CO_3,

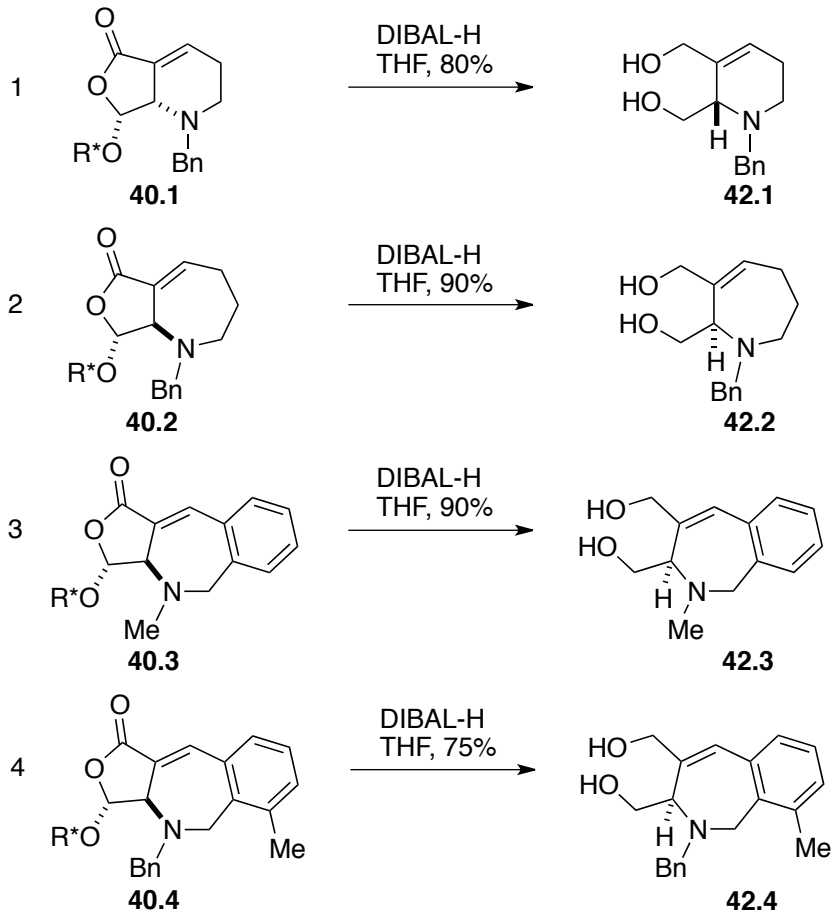


Scheme 41

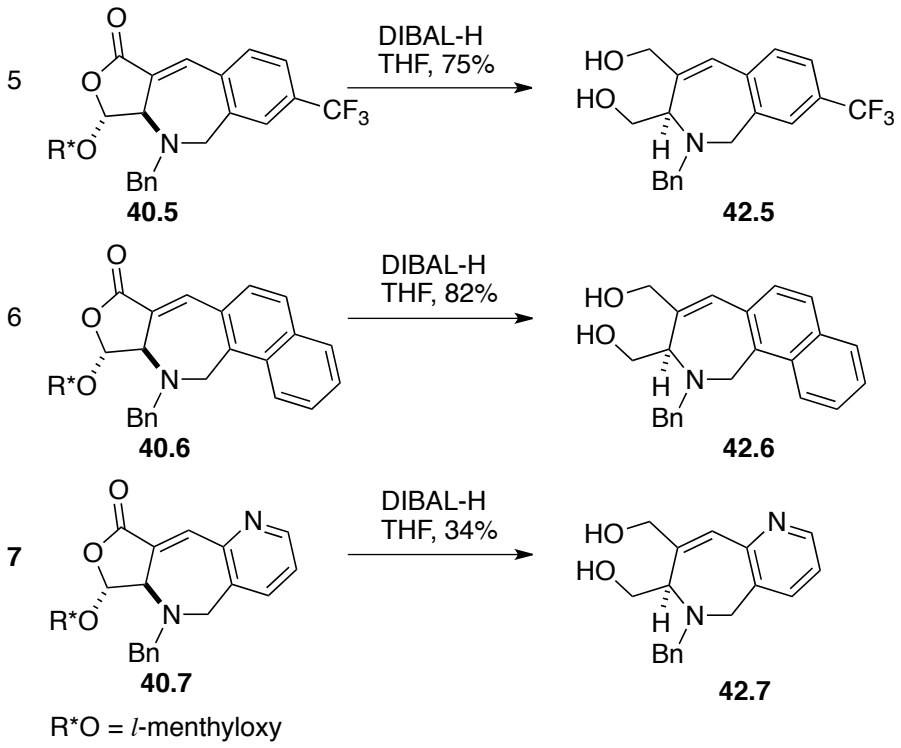
and the starting material was recovered. When K_2CO_3 was used *O*→*N* acetyl transfer occurred.

2.6 Reduction of the ICD products

The chiral auxiliary was removed using DIBAL-H, and most of the resulting optically pure cyclic amines were obtained in good yield (Scheme 42).



Scheme 42



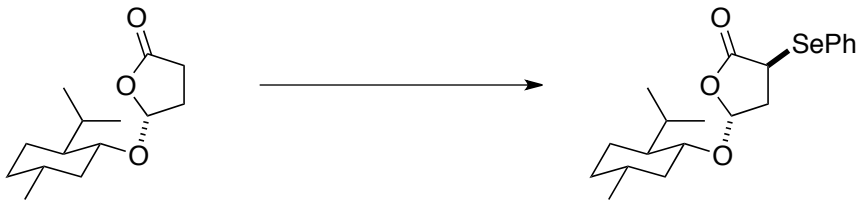
Scheme 42 (continued)

3. Conclusion

The PhSeLi-mediated Morita-Baylis-Hillman (MBH) condensation was successfully applied to prepare MBH alcohols carrying a chiral auxiliary. The derived acetates were made from the MBH alcohols and converted into six- or seven-membered heterocycles having a stereogenic center α to nitrogen via intramolecular conjugate displacement (ICD). Removal of the chiral auxiliary from the ICD products generated optically pure cyclic amines that are functionalized in a way that should permit further elaboration. It appears that the stereochemical outcome of the ICD process is controlled by stereoelectronic rather than steric factors.

4. Experimental

(3*S*,5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-3-(phenylselanyl)oxolan-2-one (31.6).



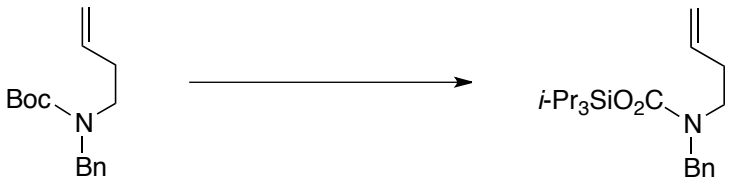
31.5 **31.6**

BuLi (2.5 M in hexane, 1.45 mL, 3.63 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.52 mL, 3.72 mmol) in THF (30 mL). After 30 min at –78 °C, **31.5** (860.0 mg, 3.58 mmol) in THF (4 mL) was added dropwise and stirring was continued for 70 min at –78 °C. PhSeCl (329.2 mg, 1.72 mmol) in THF (1 mL) was then added quickly to the reaction mixture by syringe. After 16 min, saturated aqueous NH_4Cl (20 mL) was added, and the mixture was extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 14 cm), using 1:20 Et_2O-hexanes, gave **31.6** (451.0 mg, 66%) as a light yellow oil: $[\alpha]_D^{20}$ –93.54 (*c* 1.04, $CHCl_3$); FTIR ($CHCl_3$, cast) 3057, 2954, 2924, 2869, 1774, 1578, 1477, 1455, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.75−1.05 (m, 12 H), 1.14−1.23 (m, 1 H), 1.26−1.40 (m, 1 H), 1.59−1.67 (m, 2 H), 1.95−2.07 (m, 2 H), 2.34−2.40 (m, 1 H), 2.46−2.52 (m, 1 H), 3.43−3.50 (m, 1 H), 4.09 (dd, *J* = 8.0, 8.4 Hz, 1 H), 5.45 (dd, *J* = 2.8, 5.6 Hz, 1 H), 7.30−7.40 (m,

3 H), 7.60−7.68 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.6 (q), 20.9 (q), 22.2 (q), 23.0 (t), 25.4 (d), 31.3 (d), 34.2 (t), 35.9 (d), 37.5 (t), 39.8 (t), 47.7 (d), 77.1 (d), 99.2 (d), 126.4 (s), 129.0 (d), 129.4 (d), 136.0 (d), 175.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{28}NaO_3Se$ (M + Na) 419.1096, found 419.1093.

In some runs, a small amount (ca 9%) of the C(2) epimer was also isolated: mp 105−108 °C; $[\alpha]_D^{20}$ –97.75 (*c* 1.04, $CHCl_3$); FTIR ($CHCl_3$, cast) 3073, 2991, 2947, 2917, 2866, 1779, 1745, 1577, 1478, 1452, 1439 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.80−1.07 (m, 12 H), 1.24−1.29 (m, 1 H), 1.37−1.44 (m, 1 H), 1.66−1.73 (m, 2 H), 2.09−2.14 (m, 1 H), 2.26−2.35 (m, 2 H), 2.89 (ddd, *J* = 5.5, 9.5, 14.5 Hz 1 H), 3.58 (dt, *J* = 4.0, 10.5 Hz, 1 H), 3.84 (dd, *J* = 4.0, 9.5 Hz, 1 H), 5.74 (dd, *J* = 2.0, 6.0 Hz, 1 H), 7.32−7.38 (m, 3 H), 7.72−7.75 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.5 (q), 21.1 (q), 22.3 (q), 22.8 (t), 25.1 (d), 31.4 (d), 34.3 (t), 35.2 (d), 37.2 (t), 39.6 (t), 47.7 (d), 99.0 (d), 128.5 (d), 129.1 (s), 129.3 (d), 134.8 (d), 176.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{28}NaO_3Se$ (M + Na) 419.1097, found 419.1096.

Tris(propan-2-yl)silyl *N*-benzyl-*N*-(but-3-en-1-yl)carbamate (32c).



32b **32c**

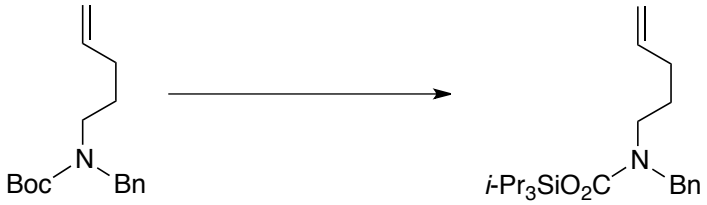
2,6-Lutidine (0.12 mL, 1.03 mmol) and *i*-$Pr_3SiOSO_2CF_3$ (0.24 mL, 0.89 mmol) were added successively to a stirred solution of **32b**[32] (130.2 mg, 0.50 mmol) in $ClCH_2CH_2Cl$ (10 mL). After 15 min, the mixture was lowered into a preheated oil bath set at 96 °C, and stirring was continued for 18 h. The mixture was cooled, evaporated and diluted with Et_2O (10 mL). The solution was washed with saturated aqueous NH_4Cl and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 18 cm), using 1:20 *t*-BuOMe-hexanes, gave **32c** (177.1 mg, 98%) as a colorless oil: FTIR ($CHCl_3$, cast) 3066, 3031, 2945, 2893, 2868, 1681, 1642, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.06–1.14 (m, 18 H), 1.24–1.42 (m, 3 H), 2.252.33 (m, 2 H), 3.26 (t, *J* = 7.5 Hz, 1 H), 3.33 (t, *J* = 7.5 Hz, 1 H), 4.52 (s, 2 H), 4.99−5.07 (m, 2 H), 5.68−5.81 (m, 1 H), 7.22−7.34 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.13 (d), 12.15 (d), 17.87 (q), 17.92 (q), 19.95 (q), 32.3 (t), 32.9 (t), 46.4 (t), 46.6 (t), 50.4 (t), 51.3 (t), 116.6 (s), 116.8 (s), 127.0 (d), 127.18 (d), 127.24 (d), 127.7 (d), 128.5 (d), 135.1 (d), 135.4 (d), 138.17 (s), 138.19 (s), 155.0 (s), 155.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{21}H_{35}NNaO_2Si$ (M + Na) 384.2329, found 384.2332.

Tris(propan-2-yl)silyl *N*-benzyl-*N*-(3-oxopropyl)carbamate (32).

32c **32**

N-Methylmorpholine-*N*-oxide (1.39 g, 11.87 mmol), followed by OsO_4 (tiny crystal, catalytic), was added to a stirred solution of **32c** (1.07 g, 2.97 mmol) in THF (15 mL) and water (15 mL). The flask was stoppered and covered with Al foil and the mixture was stirred for 3 h. The mixture was diluted with EtOAc, and washed with water and brine. The organic extract was dried ($MgSO_4$) and evaporated. The residue was dissolved in CH_2Cl_2 (30 mL), and $NaIO_4$-SiO_2 (18%w/w, 12.71 g, 10.69 mmol) was then added with stirring. After 30 min, no starting material was left (TLC control, silica gel, 3:20 EtOAc-hexanes). The mixture was filtered through Celite and evaporated. Flash chromatography of the residue over silica gel (3.8 x 18 cm), using 3:20 EtOAc-hexanes, gave **32** (0.85 g, 79%) as a light yellow oil: FTIR ($CHCl_3$, cast) 3065, 2946, 2893, 2868, 2726, 1725, 1679, 1606, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.06−1.11 (m, 18 H), 1.26−1.40 (m, 3 H), 2.65 (dt, J = 1.0, 7.0 Hz, 1 H), 2.69 (dt, J = 1.5, 7.0 Hz, 1 H), 3.51−3.57 (m, 2 H), 4.53 (d, J = 9.5 Hz, 2 H), 7.23−7.35 (m, 5 H), 9.72−9.75 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.1 (d), 17.8 (q), 17.9 (q), 40.7 (t), 41.1 (t), 42.8 (t), 43.4 (t), 50.9 (t), 51.9 (t), 127.1 (d), 127.4 (d), 127.5 (d), 127.9 (d), 128.7 (d), 137.8 (s), 137.9 (s), 155.0 (s), 155.2 (s), 200.2 (d), 200.8 (d); exact mass (electrospray) m/z calcd for $C_{20}H_{34}NO_3Si$ (M + H) 364.2303, found 364.2307.

Tris(propan-2-yl)silyl *N*-benzyl-*N*-(pent-4-en-1-yl)carbamate (33c).



33b **33c**

2,6-Lutidine (0.26 mL, 2.24 mmol) and *i*-$Pr_3SiOSO_2CF_3$ (0.60 mL, 2.23 mmol) were added successively to a stirred solution of **33b** (0.60 g, 2.18 mmol) in $ClCH_2CH_2Cl$ (30 mL). After 15 min, the mixture was lowered into a preheated oil bath set at 96 °C, and stirring was continued for 12 h. The mixture was cooled, evaporated and diluted with Et_2O (40 mL). The solution was washed with saturated aqueous NH_4Cl and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 18 cm), using 1:20 *t*-BuOMe-hexanes, gave **33c** (0.756 g, 92%) as a colorless oil: FTIR ($CHCl_3$, cast) 3066, 3031, 2945, 2867, 1680, 1642, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.06-1.14 (m, 18 H), 1.22−1.44 (m, 3 H), 1.58−1.70 (m, 2 H), 2.02 (quintet, J = 7.5 Hz, 2 H), 3.23 (dt, J = 19.2, 7.5 Hz, 2 H), 4.51 (s, 2 H), 4.93−5.03 (m, 2 H), 5.69−5.86 (m, 1 H), 7.22−7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.15 (d), 12.17 (d), 17.9 (q), 18.0 (q), 26.9 (t), 27.5 (t), 31.0 (t), 31.1 (t), 46.6 (t), 46.7 (t), 50.4 (t), 51.1 (t), 114.9 (s), 115.0 (s), 127.0 (d), 127.16 (d), 127.21 (d), 127.7 (d), 128.49 (d), 128.50 (d), 137.7 (d), 138.0 (d), 138.2 (s), 138.3 (s), 155.0 (s), 155.5 (s); exact

mass (electrospray) *m*/*z* calcd for $C_{22}H_{37}NNaO_2Si$ (M + Na) 398.2486, found 398.2488.

Tris(propan-2-yl)silyl *N*-benzyl-*N*-(4-oxobutyl)carbamate (33).

33c **33**

N-Methylmorpholine-*N*-oxide (590 mg, 5.04 mmol), followed by OsO_4 (1.0 M in PhMe, 0.1 mL, 0.1 mmol), was added to a stirred solution of **33c** (612.3 mg, 1.63 mmol) in THF (6 mL) and water (6 mL). The mixture was stirred for 45 min, during which time the solution turned dark brown. The mixture was diluted with EtOAc, and washed with water and brine. The organic extract was dried ($MgSO_4$) and evaporated. The residue was dissolved in CH_2Cl_2 (18 mL), and $NaIO_4$-SiO_2 (20.4%w/w, 6.16 g, 5.87 mmol) was then added with stirring. Stirring was continued for 20 min by which time all of the diol had reacted (TLC control, silica gel, 1:10 EtOAc-hexanes). The mixture was filtered through Celite, using CH_2Cl_2 as a rinse, and the filtrate was evaporated. Flash chromatography of the residue over silica gel (2.8 x 15 cm), using 1:10 EtOAc-hexanes, gave **33** (550 mg, 89%) as an oil: FTIR ($CHCl_3$, cast) 3065, 2945, 2893, 2868, 2720, 1727, 1678, 1606, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.06−1.12 (m, 18 H),

1.26−1.42 (m, 3 H), 1.80−1.90 (m, 2 H), 2.39 (dt, *J* = 1.2, 7.2 Hz) and 2.44 (dt, *J* = 1.2, 7.2 Hz, both signals together 2 H), 3.24 (t, *J* = 7.6 Hz) and 3.28 (t, *J* = 7.6 Hz, both signals together 2 H), 4.51 (s, 2 H), 7.22−7.34 (m, 5 H), 9.71−9.74 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.1 (d), 17.85 (q), 17.91 (q), 20.1 (t), 20.7 (t), 40.9 (t), 41.1 (t), 46.0 (t), 46.1 (t), 50.2 (t), 51.0 (t), 127.0 (d), 127.3 (d), 127.4 (d), 127.8 (d), 128.6 (d), 137.9 (s), 138.0 (s), 155.2 (s), 155.4 (s), 201.0 (d), 201.6 (d); exact mass (electrospray) *m*/*z* calcd for $C_{21}H_{35}NNaO_3Si$ (M + Na) 400.2278, found 400.2281.

tert-Butyl _N_-[(2-ethenylphenyl)methyl]-_N_-methylcarbamate (34d).

34c **34d**

NaH (60% in oil, 60.0 mg, 1.50 mmol) was added to a stirred solution of **34c** (153.3 mg, 0.66 mmol) in THF (6 mL). After 15 min, the mixture was cooled to 0 °C, and MeI (0.16 mL, 2.57 mmol) was added. The ice bath was left in place but not recharged and stirring was continued for 18 h. Water (4 mL) was added to destroy the excess of NaH and the mixture was 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 (1.8 x 14 cm),

using 1:20 EtOAc-hexanes, gave **34d** (140.6 mg, 87%) as a colorless oil: FTIR ($CHCl_3$, cast) 3064, 2976, 2931, 1696, 1628, 1603, 1572, 1481, 1453 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.49 (s, 9 H), 2.71 and 2.78 (two br s, 3 H), 4.54 (s, 2 H), 5.30 (d, *J* = 11.0 Hz, 1 H), 5.63 (d, *J* = 17.5 Hz, 1 H), 6.98 (s, 1 H), 7.15−7.16 (m, 1 H), 7.23−7.29 (m, 2 H), 7.49−7.51 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.4 (q), 33.4 (q), 49.6 (t), 50.1 (t), 79.6 (s), 116.0 (s), 126.1 (d), 127.5 (d), 127.8 (d), 128.6 (d), 134.2 (d), 134.8 (s), 137.2 (s), 155.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{21}NNaO_2$ (M + Na) 270.1465, found 270.1465.

Tris(propan-2-yl)silyl *N*-[(2-ethenylphenyl)methyl]-*N*-methyl-carbamate (34e).

34d **34e**

2,6-Lutidine (0.10 mL, 0.86 mmol) and *i*-$Pr_3SiOSO_2CF_3$ (0.20 mL, 0.72 mmol) were added successively to a stirred solution of **34d** (123.6 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) and stirring was continued for 9.5 h. The mixture was washed with saturated aqueous NH_4Cl and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 14 cm), using 1:20 Et_2O-hexanes, gave **34e** (167.8 mg, 96%) as a colorless oil: FTIR ($CHCl_3$, cast) 3064, 2945, 2892, 2868, 1682, 1559, 1465, 1421 cm^{-1}; ^1H NMR ($CDCl_3$, 400

MHz) δ 1.04−1.13 (m, 18 H), 1.28−1.40 (m, 3 H), 2.79 and 2.85 (two s, 3 H), 4.61 (s, 2 H), 5.30 (t, *J* = 10.4 Hz, 1 H), 5.64 (d, *J* = 17.2 Hz, 1 H), 6.94 (dd, *J* = 10.8, 17.2 Hz, 1 H) and 7.01 (dd, *J* = 10.8, 17.2 Hz, both signals together 1 H), 7.16−7.20 (m, 1 H), 7.23−7.28 (m, 2 H), 7.49−7.53 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.1 (d), 17.86 (q), 17.90 (q), 33.7 (q), 34.0 (q), 50.0 (t), 50.9 (t), 116.1 (s), 116.5 (s), 126.0 (d), 126.2 (d), 127.3 (d), 127.5 (d), 127.68 (d), 127.72 (d), 127.9 (d), 128.8 (d), 133.7 (d), 134.1 (d), 134.4 (s), 134.5 (s), 136.7 (s), 137.3 (s), 155.0 (s), 155.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{33}NNaO_2Si$ (M + Na) 370.2173, found 370.2172.

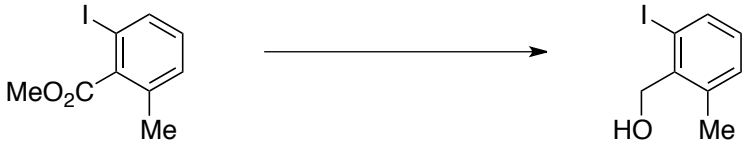
Tris(propan-2-yl)silyl *N*-[(2-formylphenyl)methyl]-*N*-methyl-carbamate (34).

34e **34**

OsO_4 (0.1 M in PhMe, 0.05 mL, 0.005 mmol) was added to a stirred solution of **34e** (157.5 mg, 0.45 mmol) in THF (4 mL) and water (1.5 mL). The mixture was stirred for 7 min, during which time the solution turned dark brown. $NaIO_4$ (301.1 mg, 1.41 mmol) was then added slowly and stirring was continued for 1.5 h. The mixture was filtered through Celite, using EtOAc as a rinse. The

filtrate was washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 14 cm), using 1:10 EtOAc-hexanes, gave **34** (129.3 mg, 82%) as a light yellow oil: FTIR ($CHCl_3$, cast) 3071, 2945, 2892, 2867, 2729, 1683, 1601, 1576, 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.95−1.11 (m, 18 H), 1.19−1.35 (m, 3 H), 2.94 and 2.99 (two s, 3 H), 4.96 (s, 2 H), 7.35 (d, *J* = 7.5 Hz, 1 H), 7.46 (q, *J* = 8.0 Hz, 1 H), 7.58 (q, *J* = 7.5 Hz, 1 H), 7.84 (d, *J* = 7.5 Hz, 1 H) 10.14 and 10.20 (two s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.0 (d), 12.1 (d), 17.7 (q), 17.9 (q), 35.0 (q), 35.3 (q), 49.8 (t), 51.4 (t), 126.4 (d), 127.3 (d), 127.5 (d), 127.8 (d), 133.3 (s), 133.5 (d), 133.9 (d), 134.0 (d), 135.1 (d), 140.1 (s), 140.5 (s), 155.29 (s), 155.33 (s), 193.0 (d), 193.4 (d); exact mass (electrospray) *m/z* calcd for $C_{19}H_{31}NNaO_3Si$ (M + Na) 372.1965, found 372.1962.

(2-Iodo-6-methylphenyl)methanol (35b).



35a **35b**

DIBAL-H (1.0 M in PhMe, 4.0 mL, 4.00 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **35a** (440.9 mg, 1.60 mmol) in PhMe (5 mL). Stirring at –78 °C was continued for 2.25 h, the cooling bath was removed, and stirring was continued for 15 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 to give **35b** as a white solid (96%): FTIR ($CHCl_3$, cast) 3280, 3053, 3009, 2967, 2934, 2732, 2618, 1588, 1555, 1480, 1445 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.77−1.80 (m, 1 H), 2.50 (s, 3 H), 4.84 (d, *J* = 6.5 Hz, 2 H), 6.88 (t, *J* = 7.5 Hz, 1 H), 7.17 (d, *J* = 7.5 Hz, 1 H), 7.70 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.5 (q), 67.1 (t), 101.7 (s), 129.9 (d), 131.0 (d), 137.6 (d), 139.2 (s), 140.5 (s); HRMS (EI) *m*/*z* calcd for C_8H_9IO 247.9698, found 247.9700.

(2-Ethenyl-6-methylphenyl)methanol (35c).

35b **35c**

Ph_3P (135.0 mg, 0.51 mmol) was added to a stirred solution of $Pd(OAc)_2$ (27.6 mg, 0.12 mmol) in PhMe (2.5 mL). The color of the mixture turned yellow after several minutes. Alcohol **35b** (297.6 mg, 1.20 mmol) and then a solution of tributyl(vinyl)tin (456.6 mg, 1.44 mmol) in PhMe (1.0 mL) were added. The solution was purged with a stream of Ar for 10 min and then heated to 110-120 °C for 15 h, during which time the solution turned black. The mixture was cooled and filtered through Celite, using MeOH as a rinse. Evaporation of the filtrate and flash chromatography of the resulting red residue over silica gel (2.8 x 14

cm), using 1:5 Et_2O-hexanes, gave **35c** (165.9 mg, 93%): FTIR ($CHCl_3$, cast) 3256, 3085, 3070, 3027, 2958, 2933, 2720, 2591, 1626, 1591, 1581, 1497, 1470 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.49 (t, *J* = 5.5 Hz, 1 H), 2.47 (s, 3 H), 4.80 (d, *J* = 5.5 Hz, 2 H), 5.39 (dd, *J* = 1.5, 11.0 Hz, 1 H), 5.69 (dd, *J* = 1.5, 17.0 Hz, 1 H), 7.15−7.25 (m, 3 H), 7.39 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.5 (q), 58.9 (t), 117.1 (t), 124.4 (d), 128.3 (d), 130.1 (d), 134.8 (d), 135.4 (s), 137.4 (s), 138.2 (s); HRMS (EI) *m*/*z* calcd for $C_{10}H_{12}O$ 148.0888, found 148.0886.

2-(Bromomethyl)-1-ethenyl-3-methylbenzene (35d).

35c **35d**

Ph_3P (394.6 mg, 1.49) was added to a stirred and cooled (0 °C) mixture of **35c** (183.7 mg, 1.24 mmol) and CBr_4 (479.6 mg, 1.49 mmol) in CH_2Cl_2 (6 mL). Stirring at 0 °C was continued for 50 min, at which point no starting material remained (TLC, silica, 1:20 EtOAc-hexanes). Evaporation of the mixture and flash chromatography of the residue over silica gel (2.8 x 14 cm), using hexanes, gave **35d** (236.0 mg, 90%) as a white solid: FTIR ($CHCl_3$, cast) 3085, 3067, 3028, 3008, 2978, 2950, 2912, 2868, 1628, 1581, 1472, 1462 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.47 (s, 3 H), 4.65 (s, 2 H), 5.48 (dd, *J* = 1.0, 11.0 Hz, 1 H), 5.75 (dd, *J* = 1.0, 17.0 Hz, 1 H), 7.12−7.18 (m, 2 H), 7.24 (t, *J* = 7.5 Hz, 1 H),

7.37 (d, *J* = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2 (q), 28.8 (t), 117.6 (t), 124.7 (d), 128.8 (d), 130.2 (d), 132.8 (s), 134.2 (d), 137.5 (s), 138.2 (s); HRMS (EI) *m*/*z* calcd for $C_{10}H_{11}Br$ 212.0024, found 212.0021.

Benzyl[(2-ethenyl-6-methylphenyl)methyl]amine (35e).

35d **35e**

$BnNH_2$ (0.2 mL, 1.79 mmol) was added to a stirred solution of **35d** (127.9 mg, 0.61 mmol) in THF (3 mL), and stirring was continued for 12 h. The mixture was then diluted with EtOAc, washed twice with aqueous NaOH (1 N) and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.4 x 14 cm), using 3:20 EtOAc-hexanes, gave **35e** (130.0 mg, 90%) as a yellow oil: FTIR ($CHCl_3$, cast) 3323, 3084, 3063, 3027, 2976, 2950, 2915, 2859, 1626, 1604, 1582, 1495, 1453 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.35 (s, 1 H), 2.37 (s, 3 H), 3.83 (s, 2 H), 3.90 (s, 2 H), 5.31 (dd, *J* = 1.5, 11.0 Hz, 1 H), 5.66 (dd, *J* = 1.5, 17.0 Hz, 1 H), 7.06 (dd, *J* = 11.0, 17.0 Hz, 1 H), 7.12 (d, *J* = 7.5 Hz, 1 H), 7.17 (t, *J* = 7.5 Hz, 1 H), 7.27−7.31 (m, 1 H), 7.35−7.41 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.5 (q), 46.7 (t), 54.1 (t), 116.2 (t), 124.0 (d), 127.0 (d), 127.3 (d), 128.2 (d), 128.3 (d), 130.0 (d), 135.2 (d), 135.7 (s), 137.2 (s), 137.9 (s),

140.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{17}H_{20}N$ (M + H) 238.1590, found 238.1591.

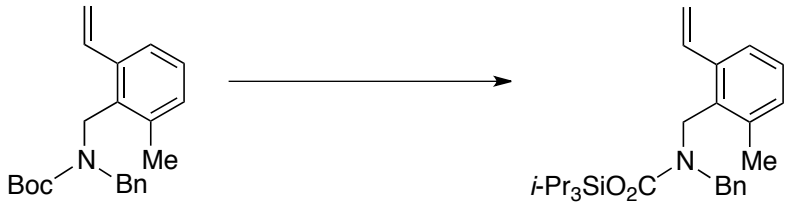
***tert*-Butyl *N*-benzyl-*N*-[(2-ethenyl-6-methylphenyl)methyl]carbamate (35f).**

35e **35f**

DMAP (126.7 mg, 1.03 mmol) and Boc_2O (226.3 mg, 1.03 mmol) were added successively to a stirred solution of **35e** (137.5 mg, 0.50 mmol) in MeCN (6 mL), and stirring was continued for 37 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.8 x 14 cm), using 1:20 Et_2O-hexanes, gave **35f** (158.9 mg, 92%) as a colorless oil: FTIR ($CHCl_3$, cast) 3087, 3065, 3030, 3006, 2976, 2930, 1693, 1626, 1605, 1581, 1540, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.53 (s, 9 H), 2.13 (s, 3 H), 4.15 (s, 2 H), 4.72 (s, 2 H), 5.20 (dd, *J* = 1.5, 11.0 Hz, 1 H), 5.55 (d, *J* = 17.5 Hz, 1 H), 6.87 (br s, 1 H), 7.06−7.09 (m, 3 H), 7.19−7.36 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.8 (q), 28.5 (q), 42.8 (t), 47.4 (t), 80.0 (s), 116.0 (t), 124.6 (d), 126.8 (d), 127.0 (d), 127.8 (d), 128.4 (d), 130.1 (d), 132.3 (s), 135.5 (d), 138.2 (s), 139.2 (s), 155.8 (s); exact

mass (electrospray) *m*/*z* calcd for $C_{22}H_{27}NNaO_2$ (M + Na) 360.1934, found 360.1937.

[Tris(propan-2-yl)silyl *N*-benzyl-*N*-[(2-ethenyl-6-methylphenyl)-methyl]carbamate (35g).



35f **35g**

2,6-Lutidine (0.10 mL, 0.86 mmol) and *i*-$Pr_3SiOSO_2CF_3$ (0.21 mL, 0.76 mmol) were added successively to a stirred solution of **35f** (147.1 mg, 0.44 mmol) in $ClCH_2CH_2Cl$ (5 mL). The mixture was lowered into a preheated oil bath set at 96 °C, and stirring was continued for 4 h. The mixture was then cooled, evaporated and diluted with Et_2O (10 mL). The solution was washed with saturated aqueous NH_4Cl and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 18 cm), using 1:25 Et_2O-hexanes, gave **35g** (186.6 mg, 98%) as a colorless oil: FTIR ($CHCl_3$, cast) 3087, 3065, 3030, 2945, 2893, 2867, 1677, 1606, 1581, 1550, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.07−1.20 (m, 18 H), 1.31−1.48 (m, 3 H), 2.05 and 2.08 (two s, 3 H), 4.19 (s, 2 H), 4.74 and 4.78 (two s, 2 H), 5.15 (d, *J* = 11.0 Hz, 1 H), 5.50−5.57 (m, 1 H), 6.78 (dd, *J* = 11.0, 17.0 Hz) and 6.85 (dd, *J* = 11.0, 17.5 Hz,

both signals together 1 H), 7.01−7.06 (m, 3 H), 7.17−7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.17 (d), 12.23 (d), 17.9 (q), 18.0 (q), 19.7 (q), 19.8 (q), 43.2 (t), 44.1 (t), 47.1 (t), 47.9 (t), 116.1 (t), 116.4 (t), 124.3 (d), 124.7 (d), 126.5 (d), 126.9 (d), 127.4 (d), 127.8 (d), 127.9 (d), 128.3 (d), 128.4 (d), 130.1 (d), 130.2 (d), 131.4 (s), 132.0 (s), 135.0 (d), 135.2 (d), 137.9 (s), 138.0 (s), 138.1 (s), 138.4 (s), 139.1 (s), 139.2 (s), 155.1 (s), 155.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{27}H_{40}NO_2Si$ (M + H) 438.2823, found 438.2820.

Tris(propan-2-yl)silyl *N*-benzyl-*N*-[(2-formyl-6-methylphenyl)-methyl]carbamate (35).

35g **35**

OsO_4 (0.1 M in PhMe, 0.05 mL, 0.005 mmol) was added to a stirred solution of **35g** (184.4 mg, 0.42 mmol) in THF (3 mL) and water (1 mL). The mixture was stirred for 8 min, during which time the solution turned dark brown. $NaIO_4$ (280.0 mg, 1.31 mmol) was then added slowly and stirring was continued for 50 min. The mixture was filtered through Celite, using EtOAc as a rinse. The filtrate was washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 14 cm), using 1:20 EtOAc-

hexanes, gave **35** (155.3 mg, 84%) as a light yellow oil: FTIR ($CHCl_3$, cast) 3066, 3031, 2946, 2892, 2867, 2728, 1676, 1591, 1552, 1496, 1465 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.09−1.20 (m, 18 H), 1.30−1.50 (m, 3 H), 2.24 (s, 3 H), 4.26 (s, 2 H), 5.10 (s, 2 H), 6.97−7.03 (m, 2 H), 7.24−7.29 (m, 3 H), 7.34−7.39 (m, 2 H), 7.71 (d, *J* = 7.0 Hz, 1 H), 9.94 and 10.07 (two s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.1 (d), 17.9 (q), 18.0 (q), 19.3 (q), 41.4 (t), 42.2 (t), 47.8 (t), 48.5 (t), 126.6 (d), 127.2 (d), 127.4 (d), 127.9 (d), 128.1 (d), 128.6 (d), 135.98 (d), 136.02 (s), 136.8 (s), 137.5 (s), 139.7 (s), 155.1 (s), 155.3 (s), 191.5 (s), 192.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{26}H_{38}NO_3Si$ (M + H) 440.2615, found 440.2615.

***tert*-Butyl *N*-{[2-bromo-5-(trifluoromethyl)phenyl]methyl}carbamate (36c).**

36b **36c**

Boc_2O (157.7 mg, 0.72 mmol) in CH_2Cl_2 (2 mL) was added to a stirred solution of **36b** (181.9 mg, 0.72 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 14 h and the solvent was then evaporated. Flash chromatography of the residue over silica gel (2.8 x 14 cm), using 1:20 EtOAc-hexanes, gave **36c** (242.1 mg, 95%) as a white solid: FTIR ($CHCl_3$, cast) 3296, 3062, 2986, 2936, 2817,

1678, 1646, 1603, 1582, 1518, 1475 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.48 (s, 9 H), 4.43 (d, *J* = 6.0 Hz, 2 H), 5.16 (s, 1 H), 7.40 (d, *J* = 7.5 Hz, 1 H), 7.62 (s, 1 H), 7.67 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.3 (q), 44.6 (t), 80.1 (s), 120.5 (s), 122.7 (s), 124.8 (s), 125.40 (d), 125.43 (d), 125.46 (d), 125.49 (d), 125.7 (d), 127.0 (s), 129.7 (s), 130.0 (s), 130.2 (s), 130.5 (s), 133.3 (d), 139.2 (s), 155.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{15}BrF_3NNaO_2$ (M + Na) 376.0130, found 376.0127.

***tert*-Butyl *N*-{[2-ethenyl-5-(trifluoromethyl)phenyl]methyl}carbamate (36d).**

36c **36d**

Ph_3P (110.0 mg, 0.42 mmol) was added to a stirred solution of $Pd(OAc)_2$ (22.0 mg, 0.096 mmol) in PhMe (5 mL). The color of the mixture turned yellow after several minutes. Bromide **36c** (340.8 mg, 0.96 mmol) and tributyl(vinyl)tin (351.0 mg, 1.11 mmol) were then added sequentially. The solution was purged with a stream of Ar for 5 min and then heated (Ar atmosphere) to 110-120 °C for 19 h, during which time the mixture turned black. The mixture was cooled and filtered through Celite, using MeOH as a rinse. Evaporation of the filtrate and

flash chromatography of the residue over silica gel (2.8 x 14 cm), using 1:20 EtOAc-hexanes, gave **36d** (275.8 mg, 95%) as a light yellow solid: FTIR ($CHCl_3$, cast) 3342, 2980, 2934, 1696, 1619, 1514, 1456 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.48 (s, 9 H), 4.44 (d, *J* = 4.0 Hz, 2 H), 4.87 (s, 1 H), 5.48 (d, *J* = 11.0 Hz, 1 H), 5.48 (d, *J* = 17.0 Hz, 1 H), 6.99 (dd, *J* = 11.0, 17.0 Hz, 1 H), 7.52−7.54 (m, 2 H), 7.60 (d, *J* = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.3 (q), 42.2 (t), 79.9 (s), 118.8 (t), 120.8 (s), 123.0 (s), 124.49 (d), 124.52 (d), 125.1 (d), 125.16 (d), 125.19 (s), 126.6 (d), 127.3 (s), 129.4 (s), 129.7 (s), 129.9 (s), 130.2 (s), 132.8 (d), 136.4 (s), 140.2 (s), 155.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{18}F_3NNaO_2$ (M + Na) 324.1182, found 324.1183.

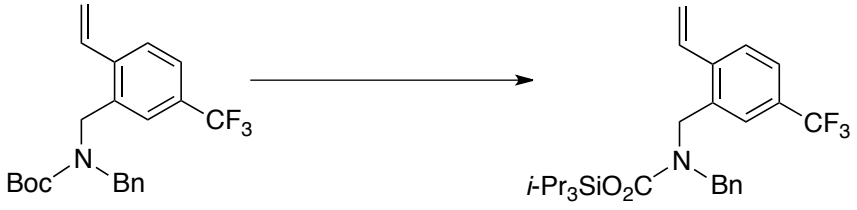
***tert*-Butyl *N*-benzyl-*N*-{[2-ethenyl-5-(trifluoromethyl)phenyl]methyl}-carbamate (36e).**

36d **36e**

A solution of **36d** (275.8 mg, 0.92 mmol) in DMF (2 mL) was added dropwise to a stirred suspension of NaH (60% in oil, 47.0 mg, 1.18 mmol) in DMF (7 mL). Stirring was continued for 30 min, and then BnBr (0.24 mL, 1.38 mmol) was added. Stirring was continued for 19.5 h, and the mixture was

quenched with hydrochloric acid (1 N) and extracted with Et_2O. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 14 cm), using 1:50 EtOAc-hexanes, gave **36e** (268.7 mg, 75%) as a colorless oil: FTIR ($CHCl_3$, cast) 3089, 3066, 3032, 2978, 2931, 1696, 1620, 1573, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.50 (s, 9 H), 4.31−4.55 (m, 4 H), 5.39 (dd, *J* = 1.0, 11.0 Hz, 1 H), 5.68 (dd, *J* = 1.0, 17.5 Hz, 1 H), 6.90 (s, 1 H), 7.17 (br s, 2 H), 7.25−7.38 (m, 4 H), 7.50 (d, *J* = 8.5 Hz, 1 H), 7.56 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.3 (q), 46.8 (t), 49.4 (t), 80.5 (s), 118.4 (t), 120.9 (s), 123.1 (s), 124.3 (d), 125.2 (s), 126.6 (d), 127.4 (d), 128.6 (d), 129.3 (s), 129.6 (s), 129.8 (s), 130.1 (s), 133.1 (d), 135.5 (s), 137.6 (s), 140.7 (s), 155.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{22}H_{24}F_3NNaO_2$ (M + Na) 414.1651, found 414.1654.

Tris(propan-2-yl)silyl *N*-benzyl-*N*-{[2-ethenyl-5-(trifluoromethyl)-phenyl]methyl}-carbamate (36f).



36e **36f**

2,6-Lutidine (0.14 mL, 1.20 mmol) and *i*-$Pr_3SiOSO_2CF_3$ (0.30 mL, 1.11 mmol) were added successively to a stirred solution of **36e** (236.9 mg, 0.61 mmol) in $ClCH_2CH_2Cl$ (6 mL). The mixture was lowered into a preheated oil bath set at 96 °C, and stirring was continued for 4 h. The mixture was cooled, evaporated and diluted with Et_2O (10 mL). The solution was washed with saturated aqueous NH_4Cl and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 18 cm), using 1:50 EtOAc-hexanes, gave **36f** (282.0 mg, 95%) as a colorless oil: FTIR ($CHCl_3$, cast) 3089, 3065, 3032, 2947, 2893, 2868, 1681, 1620, 1574, 1549, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.09−1.16 (m, 18 H), 1.34−1.44 (m, 3 H), 4.44−4.64 (m, 4 H), 5.42 (d, *J* = 11.0 Hz, 1 H), 5.70−5.76 (m, 1 H), 6.84 (dd, *J* = 11.0, 17.5 Hz) and 6.97 (dd, *J* = 11.0, 17.0 Hz, both signals together 1 H), 7.21 (d, *J* = 7.5 Hz, 1 H), 7.27−7.38 (m, 4 H), 7.43 (d, *J* = 12.0 Hz, 1 H), 7.54 (d, *J* = 7.5 Hz, 1 H), 7.58−7.63 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (because of the presence of rotamers, signal splitting by fluorine is ignored) δ 12.08 (d), 12.15 (d), 17.8 (q), 17.9 (q), 47.0 (t), 47.7 (t), 50.0 (t), 118.6 (t), 118.9 (t), 120.9 (s), 123.0 (s), 123.89 (d), 123.92 (d), 124.2 (d), 124.3 (d), 124.4 (d), 124.5 (d), 125.21 (d), 125.24 (d), 126.6 (d), 126.7 (d), 127.3 (d), 127.5 (d), 127.55 (d), 127.64 (d), 127.8 (d), 128.0 (d), 128.4 (d), 128.7 (d), 129.3 (s), 129.5 (s), 129.6 (s), 129.8 (s), 129.9 (s), 130.07 (s), 130.12 (s), 130.3 (s), 132.6 (d), 133.0 (d), 135.2 (s), 135.4 (s), 137.2 (s), 137.4 (s), 140.1 (s), 140.7 (s), 155.2 (s), 155.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{27}H_{36}F_3NNaO_2Si$ (M + Na) 514.2360, found 514.2359.

Tris(propan-2-yl)silyl *N*-benzyl-*N*-{[2-formyl-5-(trifluoromethyl)-phenyl]methyl}carbamate (36).

36f **36**

OsO_4 (0.1 M in PhMe, 0.05 mL, 0.005 mmol) was added to a stirred solution of **36f** (273.1 mg, 0.56 mmol) in THF (4.5 mL) and water (1.5 mL). The mixture was stirred for 8 min, during which time the solution turned dark brown. $NaIO_4$ (369.0 mg, 1.72 mmol) was then added slowly and stirring was continued for 1 h. The mixture was filtered through Celite, using EtOAc as a rinse. The filtrate was washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 14 cm), using 1:20 EtOAc-hexanes, gave **36** (257.1 mg, 94%) as a light yellow oil: FTIR ($CHCl_3$, cast) 3089, 3066, 3032, 2947, 2893, 2869, 2740, 1703, 1681, 1583, 1553, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.99−1.14 (m, 18 H), 1.25−1.42 (m, 3 H), 4.57 and 4.62 (two s, 2 H), 4.97 and 5.01 (two s, 2 H), 7.22−7.35 (m, 5 H), 7.63 (s, 1 H), 7.71 (t, J = 8.0 Hz, 1 H), 7.95 (d, J = 8.0 Hz, 1 H), 10.17 and 10.22 (two s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (because of the presence of rotamers, signal splitting by fluorine is ignored) δ 12.0 (d), 12.1 (d), 17.7 (q), 17.8 (q), 47.47 (t), 47.54 (t), 51.4 (t), 51.6 (t), 120.0 (s), 120.1 (s), 122.2 (s), 122.3 (s), 123.97 (d),

123.99 (d), 124.18 (d), 124.21 (d), 124.3 (d), 124.4 (d), 124.5 (s), 124.79 (d), 124.81 (d), 126.6 (s), 126.7 (s), 127.3 (d), 127.6 (d), 127.7 (d), 128.0 (d), 128.4 (d), 128.7 (d), 128.8 (d), 133.4 (d), 134.6 (d), 134.8 (s), 134.9 (s), 135.0 (s), 135.2 (s), 135.3 (s), 135.4 (s), 135.5 (s), 136.1 (s), 137.0 (s), 137.2 (s), 141.2 (s), 141.9 (s), 155.3 (s), 155.4 (s), 191.8 (d), 192.0 (d); exact mass (electrospray) *m*/*z* calcd for $C_{26}H_{34}F_3NNaO_3Si$ (M + Na) 516.2152, found 516.2151.

(2-Ethenylnaphthalen-1-yl)methanol (37d).

37c **37d**

$NaBH_4$ (138.5 mg, 3.65 mmol) was added to a solution of **37c**[42] (132.7 mg, 0.73 mmol) in THF (2 mL) and EtOH (2 mL) at room temperature. The mixture was stirred for 30 min and then quenched with cold water. The pH was adjusted to 5−6 and the solution was stirred for 15 min. The mixture was then extracted with Et_2O and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.4 x 14 cm), using 3:10 EtOAc-hexanes, gave **37d** (127.7 mg, 95%) as a white solid: FTIR ($CHCl_3$, cast) 3396, 3082, 3057, 2993, 2948, 2911, 1620, 1596, 1513, 1497 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.71 (s, 1 H), 5.19 (s, 2 H), 5.50 (dd, *J* = 1.0, 11.0

Hz, 1 H), 5.81 (dd, *J* = 1.0, 17.5 Hz, 1 H), 7.33 (dd, *J* = 11.0, 17.5 Hz, 1 H), 7.46−7.50 (m, 1 H), 7.54−7.75 (m, 1 H), 7.65 (d, *J* = 8.5 Hz, 1 H), 7.79 (d, *J* = 9.0 Hz, 1 H), 7.83 (d, *J* = 9.0 Hz, 1 H), 8.23 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 58.1 (t), 118.1 (t), 124.4 (d), 124.5 (d), 126.1 (d), 127.2 (d), 128.8 (d), 129.2 (d), 132.5 (s), 132.6 (s), 133.7 (s), 134.7 (d), 135.1 (s); HRMS (EI) *m*/*z* calcd for $C_{13}H_{12}O$ 184.0888, found 184.0885.

1-(Bromomethyl)-2-ethenylnaphthalene (37e).

37d **37e**

Ph_3P (156.2 mg, 0.59 mmol) and CBr_4 (195.7 mg, 0.59 mmol) were added successively to a stirred and cooled (0 °C) solution of **37d** (90.4 mg, 0.49 mmol) in CH_2Cl_2 (2.5 mL). After 1 h at 0 °C, the solvent was evaporated. Flash chromatography of the residue over silica gel (1.4 x 14 cm), using 1:50 EtOAc-hexanes, gave **37e** (104.5 mg, 86%) as a white solid: FTIR ($CHCl_3$, cast) 3085, 3057, 3020, 1618, 1595, 1564, 1512, 1470 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.07 (s, 2 H), 5.60 (dd, *J* = 1.0, 11.0 Hz, 1 H), 5.89 (dd, *J* = 1.0, 17.5 Hz, 1 H), 7.27 (dd, *J* = 11.0, 17.5 Hz, 1 H), 7.49−7.52 (m, 1 H), 7.60−7.63 (m, 2 H), 7.81 (d, *J* = 8.5 Hz, 1 H), 7.84 (d, *J* = 8.5 Hz, 1 H), 8.15 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.3 (t), 118.4 (t), 123.6 (d), 124.2 (d), 126.0 (d), 127.0 (d),

128.6 (d), 129.4 (s), 129.5 (d), 131.4 (s), 133.4 (s), 134.0 (d), 135.0 (s); HRMS (EI) *m*/*z* calcd for $C_{13}H_{11}Br$ 246.0044, found 246.0046.

Benzyl[(2-ethenylnaphthalen-1-yl)methyl]amine (37f).

37e **37f**

A solution of **37e** (147.3 mg, 0.60 mmol) and $BnNH_2$ (0.2 mL, 1.79 mmol) in THF (1.5 mL) was stirred at room temperature for 22 h and then diluted with EtOAc. The mixture was washed twice with aqueous NaOH (1 M) and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 14 cm), using 1:5 EtOAc-hexanes, gave **37f** (149.1 mg, 92%) as a yellow oil: FTIR ($CHCl_3$, cast) 3324, 3084, 3061, 3026, 2917, 2850, 1665, 1622, 1597, 1564, 1511, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.57 (s, 1 H), 3.98 (s, 2 H), 4.26 (s, 2 H), 5.43 (dd, *J* = 1.0, 11.0 Hz, 1 H), 5.80 (dd, *J* = 1.0, 17.5 Hz, 1 H), 7.22 (dd, *J* = 11.0, 17.0 Hz, 1 H), 7.29−7.32 (m, 1 H), 7.36−7.52 (m, 6 H), 7.66 (d, *J* = 8.5 Hz, 1 H), 7.75 (d, *J* = 9.0 Hz, 1 H), 7.81 (d, *J* = 8.0 Hz, 1 H), 8.06 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 45.3 (t), 54.2 (t), 116.9 (t), 123.9 (d), 124.3 (d), 125.6 (d), 126.6 (d), 127.1 (d), 128.0 (d), 128.35 (d), 128.43

(d), 128.5 (d), 132.6 (s), 132.7 (s), 133.5 (s), 134.4 (s), 134.8 (d), 140.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{20}N$ (M + H) 274.1590, found 274.1591.

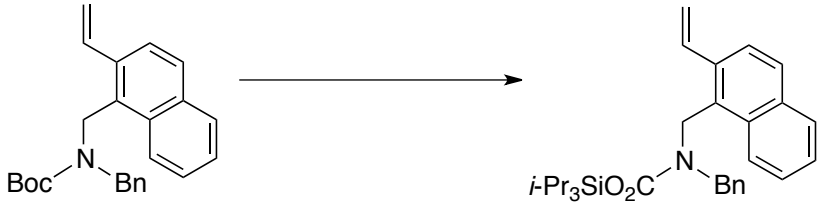
***tert*-Butyl *N*-benzyl-*N*-[(2-ethenylnaphthalen-1-yl)methyl]carbamate (37g).**

37f **37g**

DMAP (155.0 mg, 1.26 mmol) and Boc_2O (222.0 mg, 1.01 mmol) were added successively to a stirred solution of **37f** (137.5 mg, 0.50 mmol) in MeCN (5 mL). Stirring was continued for 24 h, and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.8 x 14 cm), using 1:20 Et_2O-hexanes, gave **37g** (155.6 mg, 83%) as a colorless oil: FTIR ($CHCl_3$, cast) 3087, 3062, 3031, 3007, 2975, 2931, 1689, 1622, 1605, 1511, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.40−1.80 (m, 9 H), 4.15 (s, 2 H), 5.19 (s, 2 H), 5.31 (d, *J* = 11.0 Hz, 1 H), 5.71 (d, *J* = 17.0 Hz, 1 H), 7.04 (d, *J* = 7.0 Hz, 3 H), 7.20−7.30 (m, 3 H), 7.48−7.54 (m, 2 H), 7.64 (d, *J* = 8.5 Hz, 1 H), 7.80 (d, *J* = 9.0 Hz, 1 H), 7.82−7.86 (m, 1 H), 8.20 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.5 (q), 41.5 (t), 47.6 (t), 80.2 (s), 117.3 (t), 124.0 (d), 124.8 (d), 125.8 (d), 126.7 (d), 126.8 (d), 126.9 (d), 127.0 (d), 128.3 (d), 128.5 (d), 128.7 (d), 132.9 (s), 133.4 (s), 134.8 (d),

136.2 (s), 138.5 (s), 155.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{25}H_{27}NNaO_2$ (M + Na) 396.1934, found 396.1937.

Tris(propan-2-yl)silyl *N*-benzyl-*N*-[(2-ethenylnaphthalen-1-yl)-methyl]carbamate (37h).



37g **37h**

2,6-Lutidine (0.036 mL, 0.31 mmol) and *i*-$Pr_3SiOSO_2CF_3$ (0.075 mL, 0.27 mmol) were added successively to a stirred solution of **37g** (57.1 mg, 0.15 mmol) in $ClCH_2CH_2Cl$ (2 mL) and stirring was continued for 24 h. The mixture was washed with saturated aqueous NH_4Cl and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.2 x 14 cm), using 1:25 Et_2O-hexanes, gave **37h** (71.0 mg, 98%) as a colorless oil: FTIR ($CHCl_3$, cast) 3087, 3063, 3033, 2945, 2892, 2867, 1674, 1623, 1606, 1560, 1511, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.11−1.30 (m, 18 H), 1.36−1.56 (m, 3 H), 4.22 (s, 2 H), 5.23−5.29 (m, 3 H), 5.66−5.72 (m, 1 H), 6.86−7.07 (m, 3 H), 7.21−7.29 (m, 3 H), 7.42−7.51 (m, 2 H), 7.62−7.65 (m, 1 H), 7.79−7.85 (m, 2 H), 8.11−8.23 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.2 (d), 12.3 (d), 17.9 (q), 18.1 (q), 42.0 (t), 43.0 (t), 47.4 (t), 48.2 (t), 117.4 (t), 123.9 (d), 124.1 (d), 124.3 (d), 125.0 (d),

125.8 (d), 125.9 (d), 126.5 (d), 126.6 (d), 126.8 (d), 127.3 (d), 128.2 (d), 128.3 (d), 128.4 (d), 128.5 (d), 128.7 (d), 128.8 (d), 129.3 (s), 132.8 (s), 132.9 (s), 133.3 (s), 134.5 (d), 134.6 (d), 136.2 (s), 137.9 (s), 138.0 (s), 155.2 (s), 155.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{30}H_{40}NO_2Si$ (M + H) 474.2823, found 474.2821.

Tris(propan-2-yl)silyl *N*-benzyl-*N*-[(2-formylnaphthalen-1-yl)methyl]-carbamate (37).

37g **37**

OsO_4 (0.1 M in PhMe, 0.05 mL, 0.005 mmol) was added to a stirred solution of **37g** (224.5 mg, 0.48 mmol) in THF (4 mL) and water (1.3 mL). The mixture was stirred for 7 min, during which time the solution turned dark brown. $NaIO_4$ (315.0 mg, 1.47 mmol) was then added slowly, and stirring was continued for 1.5 h. The mixture was filtered through Celite, using EtOAc as a rinse, and the filtrate was washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 14 cm), using 1:20 EtOAc-hexanes, gave **37** (193.7 mg, 86%) as a light yellow oil: FTIR ($CHCl_3$, cast) 3287, 3064, 2945, 2892, 2867, 1675, 1623, 1599, 1549, 1496 cm^{-1}; ^1H NMR

($CDCl_3$, 500 MHz) δ 1.10−1.29 (m, 18 H), 1.37−1.57 (m, 3 H), 4.21−4.24 (m, 2 H), 5.55 (s, 2 H), 6.94−7.01 (m, 2 H), 7.23−7.29 (m, 3 H), 7.58 (t, *J* = 7.5 Hz, 1 H), 7.65−7.67 (m, 1 H), 7.90−7.95 (m, 3 H), 8.34−8.43 (m, 1 H), 9.98 and 10.11 (two s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.2 (d), 12.3 (d), 17.7 (q), 17.9 (q), 18.1 (q), 39.7 (t), 40.7 (t), 47.7 (t), 48.6 (t), 123.4 (d), 123.57 (d), 123.64 (d), 125.3 (d), 126.0 (d), 126.6 (d), 127.2 (d), 127.4 (d), 127.5 (d), 128.7 (d), 128.8 (d), 128.9 (d), 129.3 (d), 129.39 (d), 129.42 (d), 132.4 (s), 133.3 (s), 133.5 (s), 136.1 (s), 136.6 (s), 137.0 (s), 137.1 (s), 137.2 (s), 155.1 (s), 155.3 (s), 190.4 (d), 190.9 (d); exact mass (electrospray) *m*/*z* calcd for $C_{29}H_{38}NO_3Si$ (M + H) 476.2615, found 476.2612.

***tert*-Butyl *N*-benzyl-N-[(2-bromopyridin-3-yl)methyl]carbamate (38d).**

38c **38d**

DMAP (54.6 mg, 0.44 mmol) and then Boc_2O (97.6 mg, 0.44 mmol) in MeCN (0.5 mL) were added successively to a stirred solution of **38c** (61.4 mg, 0.22 mmol) in MeCN (2.5 mL), and stirring was continued for 30 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.2 x 14 cm), using 1:5 EtOAc-hexanes, gave **38d** (70.4 mg, 84%) as a colorless oil: FTIR ($CHCl_3$, cast) 3031, 2976, 2930, 1697, 1605, 1578, 1561, 1496 cm^{-1}; ^1H NMR

($CDCl_3$, 500 MHz) δ 1.43 and 1.51 (two br s, 9 H), 4.41−4.53 (m, 4 H), 7.22−7.35 (m, 6 H), 7.43 and 7.54 (two s, 1 H), 8.26 (dd, *J* = 1.5, 4.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.4 (q), 49.1 (t), 49.4 (t), 50.5 (t), 50.9 (t), 80.7 (s), 123.0 (d), 127.6 (d), 128.1 (d), 128.7 (d), 134.6 (s), 134.7 (s), 135.9 (d), 136.9 (d), 137.4 (s), 137.5 (s), 142.4 (s), 142.8 (s), 148.5 (d), 155.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{18}H_{22}BrN_2O_2$ (M + H) 377.0859, found 377.0860.

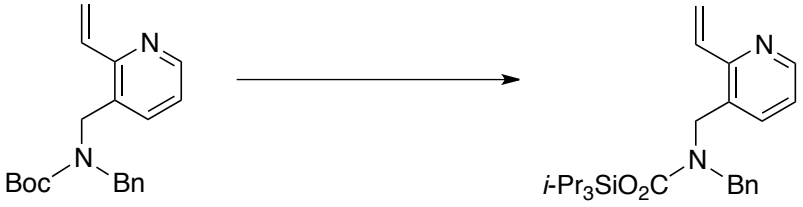
***tert*-Butyl *N*-benzyl-*N*-[(2-ethenylpyridin-3-yl)methyl]carbamate (38e).**

38d **38e**

Ph_3P (79.0 mg, 0.30 mmol) was added to a stirred solution of $Pd(OAc)_2$ (15.7 mg, 0.071 mmol) in PhMe (4 mL). The color of the mixture turned yellow after several minutes. Bromide **38d** (258.9 mg, 0.69 mmol) and tributyl(vinyl)tin (261.3 mg, 0.82 mmol) were then added sequentially. The solution was purged with a stream of Ar for 10 min and then heated (Ar atmosphere) to 110−120 °C for 18 h, during which time the solution turned black. The mixture was cooled and filtered through Celite, using MeOH as a rinse. Evaporation of the filtrate and flash chromatography of the red residue over silica gel (2.8 x 14 cm), using 1:5 EtOAc-hexanes, gave **38e** (203.9 mg, 91%) as a light yellow oil: FTIR

($CHCl_3$, cast) 3088, 3063, 3027, 2976, 2928, 2873, 1695, 1605, 1584, 1561, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.48 (s, 9 H), 4.29−4.53 (m, 4 H), 5.47 (dd, *J* = 2.0, 10.5 Hz, 1 H), 6.35 (dd, *J* = 2.0, 17.0 Hz, 1 H), 6.93 (br s, 1 H), 7.12−7.22 (m, 3 H), 7.24−7.33 (m, 3 H), 7.42 (d, *J* = 7.5 Hz, 1 H), 8.50 (dd, *J* = 1.5, 4.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.4 (q), 45.8 (t), 49.3 (t), 80.5 (s), 120.2 (t), 122.4 (d), 127.4 (d), 128.6 (d), 130.0 (s), 132.3 (d), 137.5 (s), 148.4 (d), 155.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{25}N_2O_2$ (M + H) 325.1911, found 325.1911.

Tris(propan-2-yl)silyl *N*-benzyl-*N*-[(2-ethenylpyridin-3-yl)methyl]-carbamate (38f).



38e **38f**

2,6-Lutidine (0.15 mL, 1.29 mmol) and *i*-$Pr_3SiOSO_2CF_3$ (0.31 mL, 1.13 mmol) were added successively to a stirred solution of **38e** (193.9 mg, 0.60 mmol) in $ClCH_2CH_2Cl$ (6.5 mL). After 15 min, the mixture was lowered into a preheated oil bath set at 96 °C, and stirring was continued for 4 h. The mixture was cooled, evaporated and diluted with Et_2O (10 mL). The solution was washed with saturated aqueous NH_4Cl and brine, dried ($MgSO_4$) and evaporated. Flash

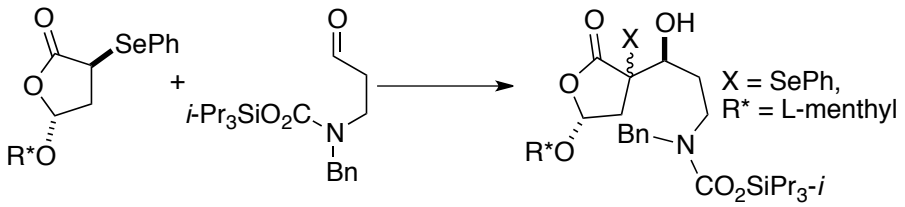
chromatography of the residue over silica gel (2.8 x 18 cm), using 1:5 *t*-BuOMe-hexanes, gave **38f** (232.8 mg, 92%) as a colorless oil: FTIR ($CHCl_3$, cast) 3063, 3028, 2945, 2892, 2867, 2726, 1680, 1606, 1584, 1561, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.05 (d, *J* = 7.5 Hz) and 1.09 (d, *J* = 7.5 Hz, both signals together 18 H), 1.29−1.39 (m, 3 H), 4.36−4.59 (m, 4 H), 5.47 (dd, *J* = 2.0, 11.0 Hz, 1 H), 6.33−6.40 (m, 1 H), 6.85 (dd, *J* = 10.5, 17.0 Hz) and 6.99 (dd, *J* = 11.0, 17.0 Hz, both signals together 1 H), 7.11−7.17 (m, 2 H), 7.21−7.34 (m, 4 H), 7.41−7.45 (m, 1 H), 8.49−8.52 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.05 (d), 12.11 (d), 17.8 (q), 17.9 (q), 46.1 (t), 46.7 (t), 49.6 (t), 49.7 (t), 120.4 (t), 120.5 (t), 122.4 (d), 122.5 (d), 127.1 (d), 127.4 (d), 127.5 (d), 128.0 (d), 128.7 (d), 129.6 (s), 129.7 (s), 131.8 (d), 132.4 (d), 135.0 (d), 136.9 (d), 137.1 (s), 137.3 (s), 148.2 (d), 148.5 (d), 153.0 (s), 153.8 (s), 155.2 (s), 155.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{25}H_{37}N_2O_2Si$ (M + H) 425.2619, found 425.2621.

Tris(propan-2-yl)silyl *N*-benzyl-*N*-[(2-formylpyridin-3-yl)methyl]-carbamate (38).

38f **38**

OsO_4 (0.1 M in PhMe, 0.1 mL, 0.01 mmol) was added to a stirred solution of **38f** (216.0 mg, 0.51 mmol) in THF (4.5 mL) and water (1.5 mL). The mixture was stirred for 7 min, during which time the solution turned dark brown. $NaIO_4$ (338.0 mg, 1.58 mmol) was then added slowly, and stirring was continued for 2 h. The mixture was filtered through Celite, using EtOAc as a rinse. The filtrate was washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 14 cm), using 3:20 EtOAc-hexanes, gave **38** (156.3 mg, 79%) as a light yellow oil: FTIR ($CHCl_3$, cast) 3063, 3028, 2945, 2892, 2867, 2726, 1680, 1606, 1584, 1561, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.98 (d, *J* = 7.5 Hz) and 1.11 (d, *J* = 7.5 Hz, both signals together 18 H), 1.21−1.40 (m, 3 H), 4.52 and 4.59 (two s, 2 H), 4.95 and 5.02 (two s, 2 H), 7.20−7.34 (m, 5 H), 7.44−7.48 (m, 1 H), 7.73 (d, *J* = 7.5 Hz) and 7.78 (d, *J* = 7.5 Hz, both signals together 1 H), 8.70 (t, *J* = 6.0 Hz, 1 H), 10.11 and 10.14 (two s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.0 (d), 12.1 (d), 17.7 (q), 17.9 (q), 46.6 (t), 47.5 (t), 51.5 (t), 52.0 (t), 126.91 (d), 126.95 (d), 127.3 (d), 127.5 (d), 127.7 (d), 128.0 (d), 128.6 (d), 128.7 (d), 134.7 (d), 135.6 (d), 136.2 (s), 136.7 (s), 137.19 (s), 137.23 (s), 148.2 (d), 148.3 (d), 149.1 (s), 149.4 (s), 155.5 (s), 155.6 (s), 195.5 (d), 195.6 (d); exact mass (electrospray) *m*/*z* calcd for $C_{24}H_{35}N_2O_3Si$ (M + H) 427.2411, found 427.2410.

Tris(propan-2-yl)silyl *N*-benzyl-*N*-{(3*S*)-3-hydroxy-3-[5-(5*R*)-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-3-(phenylselanyl)oxolan-3-yl]propyl}carbamate (pre-39.1a).

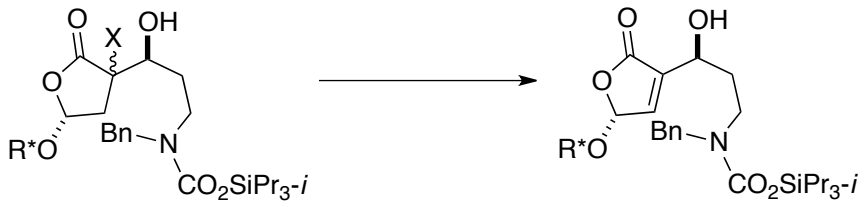


31.6 **32** **pre-39.1a**

Selenide **31.6** (91.7 mg, 0.23 mmol) in THF (0.5 mL) was added dropwise to a stirred and cooled (–78 °C) solution of $(Me_3Si)_2NK$ (0.5 M in PhMe, 0.48 mL, 0.24 mmol) in THF (4 mL). Stirring at –78 °C was continued for 70 min, and then **32** (88.9 mg, 0.25 mmol) in THF (0.5 mL) was added dropwise. Stirring at –78 °C was continued for 70 min. The mixture was then quenched with saturated aqueous NH_4Cl (5 mL) was extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 14 cm), using 3:25 EtOAc-hexanes, gave pre-**39.1a** (136.0 mg, 77%) as an oil: FTIR ($CHCl_3$, cast) 3386, 3061, 3031, 2950, 2927, 2868, 1772, 1677, 1650, 1607, 1579, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.72−1.14 (m, 30 H), 1.19−1.44 (m, 6 H), 1.55−1.69 (m, 2 H), 1.89−1.98 (m, 1 H), 2.04−2.17 (m, 1 H), 2.27−2.55 (m, 2 H), 2.82−3.03 (m, 1 H), 3.43−3.61 (m, 1 H), 3.66−3.87 (m, 3 H), 4.36−4.62 (m, 2 H), 5.64−5.73 (m, 1 H), 7.18−7.41 (m, 8 H), 7.55−7.77 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.0 (d), 12.1 (d), 12.2 (d), 15.5 (q),

17.80 (q), 17.82 (q), 18.0 (q), 21.1 (q), 22.2 (q), 22.3 (q), 22.8 (t), 24.9 (d), 29.6 (t), 31.4 (d), 34.3 (t), 34.4 (t), 35.5 (t), 39.6 (t), 42.3 (t), 47.7 (d), 47.8 (d), 50.3 (t), 50.4 (t), 68.0 (d), 77.1 (d), 97.7 (d), 126.5 (s), 127.0 (d), 127.5 (d), 128.6 (d), 128.7 (d), 128.98 (d), 129.03 (d), 129.20 (d), 129.24 (d), 134.8 (d), 137.27 (d), 137.30 (s), 137.9 (d), 156.7 (s), 176.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{40}H_{62}NO_6SeSi$ (M + H) 760.3506, found 760.3509.

Tris(propan-2-yl)silyl *N*-benzyl-*N*-{(3*S*)-3-hydroxy-3-[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydro-furan-3-yl]propyl}carbamate (39.1a).

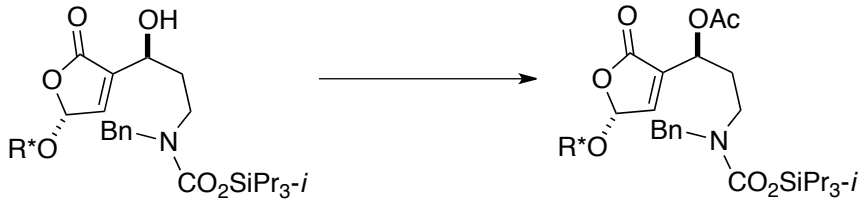


pre-39.1a **39.1a**

H_2O_2 (30%, 0.08 mL, 0.71 mmol) and AcOH (2 drops) were added to a stirred and cooled (0 °C) solution of pre-**39.1a** (82.4 mg, 0.11 mmol) in THF (2 mL). After 30 min, the ice bath was removed, and stirring was continued for 15 min. The mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.2 x 14 cm), using 3:20 EtOAc-hexanes, gave **39.1a** (60.0 mg, 90%) as a colorless oil that

became a solid after being covered with pentane and slow evaporation of the solvent: mp 103−105 °C; FTIR ($CHCl_3$, cast) 3416, 3089, 3065, 3031, 2950, 2927, 2868, 1769, 1677, 1652, 1587, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.79−1.13 (m, 30 H), 1.20−1.53 (m, 6 H), 1.64−1.68 (m, 2 H), 2.07−2.14 (m, 2 H), 2.19−2.23 (m, 1 H), 3.01−3.05 (m, 1 H), 3.63 (dt, *J* = 4.0, 10.4 Hz, 1 H), 3.86−3.93 (m, 1 H), 4.25 (d, *J* = 16.0 Hz, 1 H), 4.42−4.60 (m, 1 H), 4.82 (d, *J* = 16.0 Hz, 1 H), 4.98 (d, *J* = 3.6 Hz, 1 H), 5.99 (s, 1 H), 7.07 (s, 1 H), 7.23−7.36 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.0 (d), 15.8 (q), 17.8 (q), 20.8 (q), 22.2 (q), 23.2 (t), 25.3 (d), 31.5 (d), 33.8 (t), 34.2 (t), 40.5 (t), 42.2 (t), 47.7 (d), 50.7 (t), 63.5 (d), 79.1 (d), 99.3 (d), 127.1 (d), 127.5 (d), 128.7 (d), 137.1 (s), 140.2 (s), 143.5 (d), 157.0 (s), 170.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{34}H_{56}NO_6Si$ (M + H) 602.3871, found 602.3874. A sample was crystallized from petroleum ether (35-60 °C) for X-ray analysis.

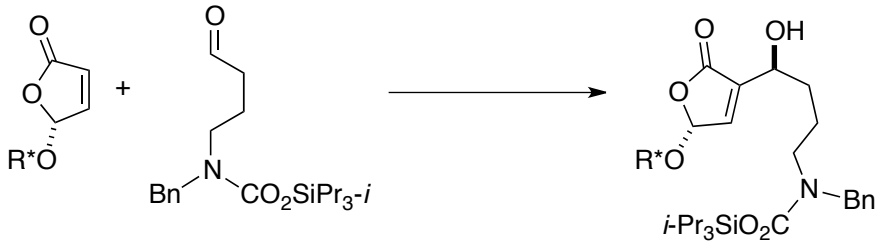
(1*S*)-3-[Benzyl({[tris(propan-2-yl)silyl]oxy}carbonyl)amino]-1-((5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydro-furan-3-yl]propyl acetate (39.1b).



39.1a **39.1b**

DMAP (4.7 mg, 0.039 mmol) was added to a stirred solution of **39.1a** (72.6 mg, 0.12 mmol) in CH_2Cl_2 (2 mL). The mixture was cooled to –78 °C, and AcCl (0.026 mL, 0.37 mmol) and pyridine (0.07 mL, 0.87 mmol) were added sequentially. The dry ice bath was replaced by an ice bath which was left in place but not recharged, and stirring was continued for 7.5 h. The mixture was quenched with hydrochloric acid (1 M, 2 mL) and water (4 mL), 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 (1.2 x 14 cm), using 3:20 EtOAc-hexanes, gave **39.1b** (66.9 mg, 86%) as a colorless oil: FTIR ($CHCl_3$, cast) 3089, 3066, 3031, 2949, 2868, 1771, 1679, 1606, 1587, 1559, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.79−1.12 (m, 29 H), 1.22−1.43 (m, 6 H), 1.64−1.69 (m, 2 H), 1.90−2.28 (m, 7 H), 3.20−3.46 (m, 2 H), 3.59−3.64 (m, 1 H), 4.41−4.57 (m, 2 H), 5.50−5.52 (m, 1 H), 5.96 (s, 1 H), 6.79−6.86 (m, 1 H), 7.20−7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.1 (d), 15.8 (q), 17.8 (q), 17.9 (q), 20.7 (q), 20.75 (q), 20.83 (q), 22.2 (q), 23.1 (t), 25.30 (d), 25.34 (d), 30.4 (t), 31.3 (t), 31.5 (d), 34.2 (t), 40.5 (t), 42.5 (t), 43.3(t), 47.7 (d), 50.4 (t), 50.8 (t), 66.4 (d), 66.9 (d), 79.3 (d), 79.5 (d), 98.88 (d), 98.91 (d), 127.1 (d), 127.3 (d), 127.4 (d), 127.9 (d), 128.6 (d), 136.6 (s), 137.7 (s), 137.8 (s), 143.83 (d), 143.85 (d), 144.37 (d), 144.39 (d), 154.9 (s), 155.2 (s), 168.5 (s), 168.8 (s), 169.5 (s), 169.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{36}H_{58}NO_7Si$ (M + H) 644.3977, found 644.3977.

Tris(propan-2-yl)silyl *N*-benzyl-*N*-{(4*S*)-4-hydroxy-4-[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydro-furan-3-yl]butyl}carbamate (39.2a).



31.3 **33** **39.2a**

BuLi (2.5 M in hexane, 0.115 mL, 0.29 mmol) was added dropwise to a stirred and cooled (–20 °C) solution of PhSeSePh (88.9 mg, 0.28 mmol) in THF (1 mL). After 10 min, the mixture was cooled to –42 °C (dry ice/MeCN), and a mixture of **31.3** (62.0 mg, 0.26 mmol) and **33** (146.7 mg, 0.39 mmol) in THF (1.5 mL) was added dropwise. Stirring at –42 °C was continued for 9 h. The mixture was then quenched with saturated aqueous NH_4Cl (3 mL) 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 (1.6 x 15 cm), using 1:5 EtOAc-hexanes, gave **39.2a** (130.6 mg, 81%) as a colorless oil: FTIR ($CHCl_3$, cast) 3440, 3089, 3065, 2948, 2868, 1767, 1673, 1559, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.79−1.12 (m, 29 H), 1.21−1.85 (m, 11 H), 2.07−2.14 (m, 2 H), 3.23−3.29 (m, 2 H), 3.42−3.49 (m, 1 H), 3.59−3.65 (m, 1 H), 3.96 (br s, 1 H), 4.41−4.57 (m, 3 H), 5.97 (s, 1 H), 6.83 and 6.93 (two s, 1 H), 7.21−7.34 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.1 (d), 15.7 (q), 15.8 (q), 17.7 (q), 17.8

(q), 17.9 (q), 20.9 (q), 22.2 (q), 23.1 (t), 23.2 (t), 23.7 (t), 24.1 (t), 25.3 (d), 31.4 (t), 31.5 (d), 32.5 (t), 34.2 (t), 40.4 (t), 46.1 (t), 46.6 (t), 47.7 (d), 50.1 (t), 50.9 (t), 66.4 (d), 67.0 (d), 79.1 (d), 79.3 (d), 99.2 (d), 127.0 (d), 127.26 (d), 127.31 (d), 127.8 (d), 128.5 (d), 128.6 (d), 137.8 (s), 138.1 (s), 139.8 (s), 140.5 (s), 142.9 (d), 143.2 (d), 155.5 (s), 155.8 (s), 170.39 (s), 170.42 (s); exact mass (electrospray) *m*/*z* calcd for $C_{35}H_{57}NNaO_6Si$ (M + Na) 638.3847, found 638.3847.

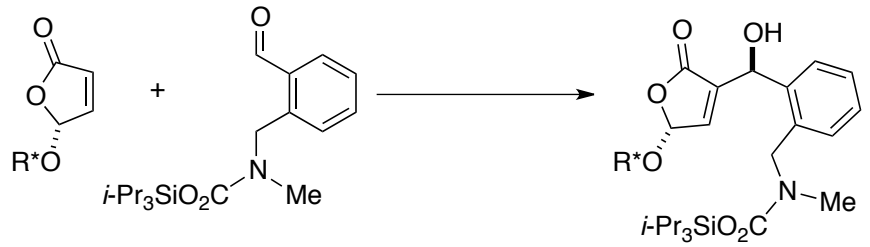
(1*S*)-4-[Benzyl({[tris(propan-2-yl)silyl]oxy}carbonyl)amino]-1-[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydro-furan-3-yl]butyl acetate (39.2b).

39.2a **39.2b**

DMAP (3.4 mg, 0.028 mmol) was added to a stirred solution of **39.2a** (87.4 mg, 0.14 mmol) in CH_2Cl_2 (2.5 mL). The mixture was then cooled to –78 °C, and AcCl (0.03 mL, 0.42 mmol) and pyridine (0.07 mL, 0.85 mmol) were added sequentially. The mixture was cooled in an ice bath which was left in place but not recharged, and stirring was continued for 7.5 h. The mixture was quenched with hydrochloric acid (1 M, 1 mL) and water (5 mL), 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 (1.2 x 14 cm), using 1:1 EtOAc-hexanes, gave **39.2b** (84.4 mg, 90%) as a colorless oil: FTIR ($CHCl_3$, cast) 3064, 3030, 2948, 2868, 1772, 1749, 1678, 1606, 1559, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.78−1.12 (m, 30 H), 1.23−1.44 (m, 5 H), 1.53−1.88 (m, 6 H), 2.06 and 2.07 (two s, 3 H), 2.09−2.12 (m, 2 H), 3.21 (t, *J* = 7.5 Hz) and 3.27 (t, *J* = 7.5 Hz, both signals together 2 H), 3.60−3.66 (m, 1 H), 4.44−4.52 (m, 2 H), 5.51−5.56 (m, 1 H), 5.96 (s, 1 H), 6.81 and 6.84 (two s, 1 H), 7.21−7.34 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.1 (d), 15.8 (q), 15.9 (q), 17.87 (q), 17.94 (q), 20.7 (q), 20.82 (q), 20.84 (q), 20.9 (q), 22.2 (q), 23.16 (t), 23.18 (t), 23.4 (t), 24.0 (t), 25.4 (d), 30.2 (t), 30.4 (t), 31.5 (d), 34.2 (t), 40.5 (t), 46.1 (t), 46.5 (t), 47.7 (d), 50.2 (t), 51.0 (t), 68.19 (d), 68.24 (d), 79.3 (d), 79.5 (d), 98.85 (d), 98.90 (d), 127.0 (d), 127.2 (d), 127.3 (d), 127.8 (d), 128.53 (d), 128.54 (d), 137.0 (s), 138.0 (s), 138.1 (s), 143.9 (d), 144.1 (d), 155.0 (s), 155.4 (s), 168.76 (s), 168.82 (s), 169.6 (s), 169.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{37}H_{59}NNaO_7Si$ (M + Na) 680.3953, found 680.3955.

Tris(propan-2-yl)silyl *N*-({2-[(*S*)-hydroxy[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydrofuran-3-yl]-methyl]phenyl}methyl)-*N*-methylcarbamate (39.3a).



31.3 **34** **39.3a**

BuLi (2.5 M in hexane, 0.22 mL, 0.55 mmol) was added dropwise to a stirred and cooled (–20 °C) solution of PhSeSePh (174.0 mg, 0.55 mmol) in THF (1.58 mL). After 10 min, a portion of the freshly prepared PhSeLi solution (0.6 mL) was added dropwise by syringe to a stirred and cooled (–42 °C) solution of **31.3** (42.6 mg, 0.18 mmol) and **34** (87.5 mg, 0.25 mmol) in THF (2 mL). Stirring at –42 °C (dry ice/MeCN) was continued for 9 h, and the mixture was quenched with saturated aqueous NH_4Cl (3 mL) 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 (1.2 x 15 cm), using 1:5 EtOAc-hexanes, gave **39.3a** (91.2 mg, 87%) as a colorless oil: FTIR ($CHCl_3$, cast) 3410, 3068, 2949, 2869, 2726, 1771, 1660, 1606, 1465 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.76−1.75 (m, 38 H), 2.09 (s, 2 H), 2.87−3.23 (m, 3 H), 3.62 (dt, J = 4.0, 10.5 Hz, 1 H), 4.24−4.81 (m, 2 H), 5.78−6.01 (m, 2 H), 6.65−6.97 (m, 1 H), 7.25−7.42 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.0 (d), 15.9 (q), 17.8 (q),

20.8 (q), 22.2 (q), 23.3 (t), 25.4 (d), 31.5 (d), 35.6 (q), 40.3 (t), 47.7 (d), 49.5 (t), 65.8 (d), 79.2 (d), 99.3 (d), 127.7 (d), 127.8 (d), 128.4 (d), 128.6 (d), 135.4 (s), 137.9 (s), 139.4 (s), 144.6 (d), 155.6 (s), 170.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{33}H_{53}NNaO_6Si$ (M + Na) 610.3534, found 610.3527.

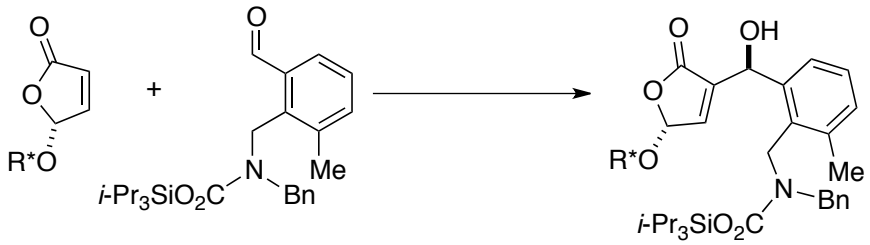
(*S*)-(2-{[Methyl({[tris(propan-2-yl)silyl]oxy}carbonyl)amino]methyl}-phenyl)-[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydrofuran-3-yl]methyl acetate (39.3b).

39.3a **39.3b**

DMAP (3.4 mg, 0.028 mmol) was added to a stirred solution of **39.3a** (199.5 mg, 0.34 mmol) in CH_2Cl_2 (9 mL). The mixture was then cooled to 0 °C, and AcCl (0.09 mL, 1.24 mmol) and pyridine (0.19 mL, 2.35 mmol) were added sequentially. The ice bath was left in place but not recharged, and stirring was continued for 5.5 h. The mixture was then quenched with hydrochloric acid (1 M, 3 mL) and water (6 mL), 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 (1.8 x 14 cm), using 3:20 EtOAc-hexanes, gave **39.3b** (199.3 mg, 93%) as a colorless oil: FTIR

($CHCl_3$, cast) 3069, 2949, 2928, 2895, 2868, 2725, 1775, 1749, 1680, 1606, 1583, 1553, 1465 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.74−1.43 (m, 35 H), 1.63−1.68 (m, 2 H), 2.01−2.10 (m, 5 H), 2.90 and 2.92 (two s, 3 H), 3.59−3.65 (m, 1 H), 4.71 and 4.79 (two s, 2 H), 6.01 (d, *J* = 6.0 Hz, 1 H), 6.73 and 6.78 (two s, 1 H), 6.89 (s, 1 H), 7.20−7.39 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.0 (d), 12.1 (d), 15.8 (q), 17.8 (q), 17.9 (q), 20.8 (q), 22.2 (q), 23.18 (t), 23.20 (t), 25.30 (d), 25.34 (d), 31.4 (d), 34.2 (t), 34.57 (q), 34.61 (q), 40.4 (t), 47.7 (d), 48.7 (t), 49.9 (t), 65.9 (d), 66.7 (d), 79.3 (d), 79.4 (d), 98.8 (d), 98.9 (d), 126.1 (d), 127.4 (d), 127.5 (d), 127.6 (d), 127.9 (d), 128.1 (d), 129.2 (d), 133.7 (s), 134.2 (s), 135.8 (s), 135.9 (s), 136.6 (s), 136.9 (s), 144.9 (d), 145.5 (d), 155.4 (s), 155.6 (s), 168.30 (s), 168.35 (s), 169.1 (s), 169.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{35}H_{55}NNaO_7Si$ (M + Na) 652.3640, found 652.3632.

Tris(propan-2-yl)silyl *N*-benzyl-*N*-({2-[(*S*)-hydroxy[(5*R*)-5-{[(1*S*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydro-furan-3-yl)methyl]-6-methylphenyl}methyl)-carbamate (39.4a).



31.1 **35** **39.4a**

BuLi (2.5 M in hexane, 0.28 mL, 0.70 mmol) was added dropwise to a stirred and cooled (–20 °C) solution of PhSeSePh (220.6 mg, 0.70 mmol) in THF (1.72 mL). After 10 min, a portion of the freshly prepared PhSeLi solution (1.0 mL) was added dropwise by syringe to a stirred and cooled (–42 °C) solution of **31.1** (75.0 mg, 0.32 mmol) and **35** (190.1 mg, 0.43 mmol) in THF (4 mL). Stirring was continued for 10 h at –42 °C (dry ice/MeCN). The mixture was then quenched with saturated aqueous NH_4Cl (3 mL) 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 (1.8 x 15 cm), using 3:20 EtOAc-hexanes, gave **39.4a** (167.4 mg, 78%) as a colorless oil: FTIR ($CHCl_3$, cast) 3431, 3066, 3032, 2951, 2927, 2868, 1773, 1674, 1607, 1552, 1496, 1462 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.79−1.46 (m, 35 H), 1.64−1.72 (m, 2 H), 2.06−2.14 (m, 2 H), 2.25−2.27 (m, 3 H), 3.43−3.63 (m, 2 H), 4.37−4.90 (m, 4 H), 5.43−5.66 (m, 1 H), 5.97 (s, 1 H), 6.62−6.90 (m, 1 H), 7.10−7.51 (m, 8 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.1 (d), 15.8 (q), 15.9 (q), 17.9 (q), 20.1 (q), 20.2 (q), 20.8 (q), 20.9 (q), 22.2 (q), 23.1 (t), 23.3 (t), 25.2 (d), 25.4 (d), 31.5 (d), 34.2 (t), 40.3 (t), 40.5 (t), 43.7 (t), 44.0 (t), 47.7 (d), 47.8 (d), 65.4 (d), 65.6 (d), 78.9 (d), 79.3 (d), 99.1 (d), 99.2 (d), 125.1 (d), 125.2 (d), 126.5 (d), 126.6 (d), 127.2 (d), 128.2 (d), 128.7 (d), 130.9 (d), 131.0 (d), 137.9 (s), 138.6 (s), 138.7 (s), 139.6 (s), 139.8 (s), 140.0 (s), 144.3 (d), 155.5 (s), 169.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{40}H_{60}NO_6Si$ (M + H) 678.4184, found 678.4185.

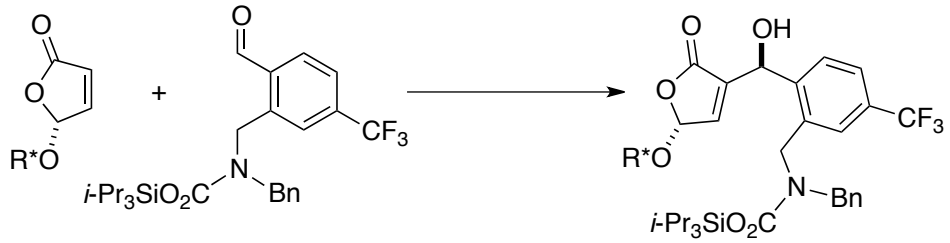
(*S*)-(2-{[Benzyl({[tris(propan-2-yl)silyl]oxy}carbonyl)amino]methyl}-3-methylphenyl)[(5*R*)-5-{[(1*S*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]-oxy}-2-oxo-2,5-dihydrofuran-3-yl]-methyl acetate (39.4b).

39.4a **39.4b**

DMAP (2.2 mg, 0.018 mmol) was added to a stirred solution of **39.4a** (62.2 mg, 0.092 mmol) in CH_2Cl_2 (1.5 mL). The mixture was then cooled to 0 °C, and AcCl (0.03 mL, 0.41 mmol) and pyridine (0.05 mL, 0.62 mmol) were added sequentially. The ice bath was left in place but not recharged, and stirring was continued for 40 min. The mixture was then quenched with hydrochloric acid (1 M, 2 mL) and water (3 mL), 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 (1.2 x 14 cm), using 1:10 EtOAc-hexanes, gave **39.4b** (64.0 mg, 96%) as a colorless oil: FTIR ($CHCl_3$, cast) 3066, 3032, 2950, 2868, 1778, 1753, 1676, 1606, 1555, 1496, 1459 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.80−1.46 (m, 35 H), 1.64−1.72 (m, 2 H), 2.02−2.18 (m, 8 H), 3.54−3.72 (m, 1 H), 4.14−4.44 (m, 2 H), 4.77−4.94 (m, 2 H), 5.77 and 5.94 (two s, 1 H), 6.70−6.85 (m, 2 H), 7.03−7.29 (m, 8 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.1 (d), 15.9 (q), 17.8 (q), 18.0 (q), 20.0 (q), 20.7 (q), 20.80

(q), 20.85 (q), 22.2 (q), 23.3 (t), 25.5 (d), 31.5 (d), 34.2 (t), 40.5 (t), 43.5 (t), 47.7 (d), 48.2 (t), 67.5 (d), 79.3 (d), 98.6 (d), 125.7 (d), 125.9 (d), 126.1 (d), 126.7 (d), 127.1 (d), 128.1 (d), 128.4 (d), 131.4 (d), 131.6 (d), 132.8 (s), 133.1 (s), 136.0 (s), 136.3 (s), 136.7 (s), 136.9 (s), 137.1 (s), 137.9 (s), 138.2 (s), 139.5 (s), 139.6 (s), 145.8 (d), 155.4 (s), 168.0 (s), 169.0 (s), 169.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{42}H_{61}NNaO_7Si$ (M + Na) 742.4110, found 742.4106.

Tris(propan-2-yl)silyl *N*-benzyl-*N*-({2-[(*S*)-hydroxy[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydrofuran-3-yl)methyl]-5-(trifluoromethyl)phenyl}methyl)carbamate (39.5a).

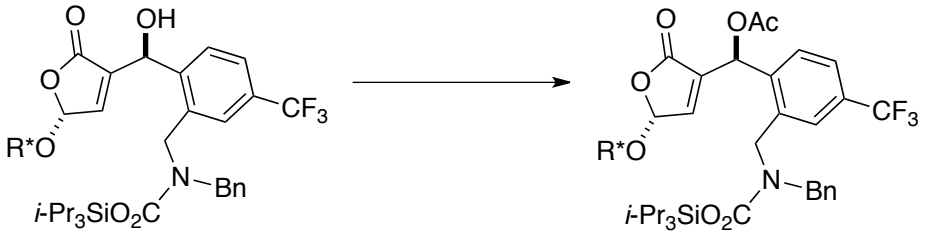


31.3 **36** **39.5a**

BuLi (2.5 M in hexane, 0.24 mL, 0.60 mmol) was added dropwise to a stirred and cooled (–20 °C) solution of PhSeSePh (189.1 mg, 0.60 mmol) in THF (0.96 mL). After 10 min, a portion of the freshly prepared PhSeLi solution (0.8 mL) was added dropwise by syringe to a stirred and cooled (–42 °C) solution of **31.3** (92.0 mg, 0.39 mmol) and **36** (257.1 mg, 0.52 mmol) in THF (4.5 mL). Stirring was continued for 8 h at –42 °C (dry ice/MeCN), and the mixture was quenched with saturated aqueous NH_4Cl (4 mL) 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 (2.8 x 15 cm), using 1:5 EtOAc-hexanes, gave **39.5a** (240.4 mg, 85%) as a colorless oil: FTIR ($CHCl_3$, cast) 3421, 3089, 3066, 3033, 2951, 2929, 2869, 1770, 1680, 1655, 1587, 1556, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.79−1.09 (m, 29 H), 1.22−1.47 (m, 5 H), 1.65−1.73 (m, 2 H), 2.11 (br s, 2 H), 3.32 (br s, 1 H), 3.60−3.68 (m, 1 H), 4.32−4.78 (m, 5 H), 5.67−6.02 (m, 2 H), 6.54 and 6.98 (two s, 1 H), 7.27−7.53 (m, 8 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (because of the presence of rotamers, signal splitting by fluorine is ignored) δ 12.0 (d), 16.0 (q), 17.8 (q), 20.8 (q), 22.2 (q), 23.3 (t), 25.5 (d), 31.5 (d), 34.2 (t), 40.4 (t), 47.0 (t), 47.7 (d), 52.2 (t), 65.4 (d), 79.5 (d), 99.5 (d), 120.6 (s), 122.8 (s), 124.5 (d), 124.90 (d), 124.94 (s), 125.0 (d), 127.1 (s), 127.5 (d), 127.8 (d), 128.1 (d), 128.9 (d), 130.6 (s), 130.8 (s), 131.1 (s), 136.6 (s), 137.1 (s), 138.6 (s), 141.6 (s), 144.5 (d), 145.0 (d), 155.6 (s), 169.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{40}H_{56}F_3NNaO_6Si$ (M + Na) 754.3721, found 754.3717.

(*S*)-(2-{[Benzyl({[tris(propan-2-yl)silyl]oxy}carbonyl)amino]methyl}-4-(trifluoromethyl)phenyl)[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)-cyclohexyl]oxy}-2-oxo-2,5-dihydro-furan-3-yl]methyl acetate (39.5b).

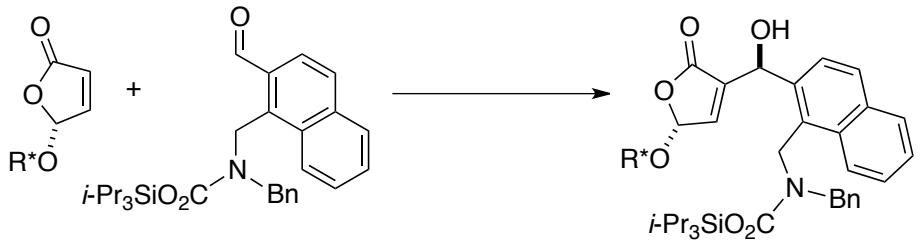


39.5a **39.5b**

DMAP (3.5 mg, 0.031 mmol) was added to a stirred solution of **39.5a** (240.0 mg, 0.33 mmol) in CH_2Cl_2 (4 mL). The mixture was then cooled to 0 °C, and AcCl (0.11 mL, 1.52 mmol) and pyridine (0.19 mL, 2.35 mmol) were added sequentially. The ice bath was left in place but not recharged, and stirring was continued for 50 min. The mixture was quenched with hydrochloric acid (1 M, 3 mL) and water (3 mL), 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 (2.8 x 14 cm), using 1:10 EtOAc-hexanes, gave **39.5b** (243.7 mg, 96%) as a colorless oil: FTIR ($CHCl_3$, cast) 3033, 2951, 2869, 1775, 1680, 1623, 1496, 1466 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.74−1.13 (m, 30 H), 1.20−1.42 (m, 5 H), 1.62−1.70 (m, 2 H), 2.00−2.09 (m, 5 H), 3.57−3.64 (m, 1 H), 4.46−4.58 (m, 2 H), 4.69−4.84 (m, 2 H), 5.97 (d, J = 10.0 Hz, 1 H), 6.60 and 6.69 (two s, 1 H), 6.85 and 6.91 (two s, 1 H), 7.22−7.35 (m, 5 H), 7.44−7.53 (m, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz)

(because of the presence of rotamers, signal splitting by fluorine is ignored) δ 12.0 (d), 12.1 (d), 15.8 (q), 17.7 (q), 17.8 (q), 20.57 (q), 20.62 (q), 20.8 (q), 22.2 (q), 23.2 (t), 24.7 (t), 25.4 (d), 31.5 (d), 34.2 (t), 36.6 (t), 40.4 (t), 46.6 (t), 47.5 (t), 47.7 (d), 50.8 (t), 51.0 (t), 65.2 (d), 66.1 (d), 79.5 (d), 79.6 (d), 98.9 (d), 99.0 (d), 122.65 (s), 122.70 (s), 123.1 (d), 124.2 (d), 124.3 (d), 124.8 (s), 124.9 (s), 127.0 (s), 127.48 (d), 127.54 (d), 128.2 (d), 128.4 (d), 128.6 (d), 128.7 (d), 130.82 (s), 130.85 (s), 131.08 (s), 131.11 (s), 131.3 (s), 131.4 (s), 131.60 (s), 131.63 (s), 135.7 (s), 136.1 (s), 137.0 (s), 137.2 (s), 137.3 (s), 137.38 (s), 137.43 (s), 137.6 (s), 138.1 (s), 145.2 (d), 145.9 (d), 155.5 (s), 155.6 (s), 168.0 (s), 168.8 (s), 169.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{42}H_{58}F_3NNaO_7Si$ (M + Na) 796.3827, found 796.3825.

Tris(propan-2-yl)silyl *N*-benzyl-*N*-({2-[(*S*)-hydroxy[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydro-furan-3-yl]methyl]naphthalen-1-yl}methyl)-carbamate (39.6a).

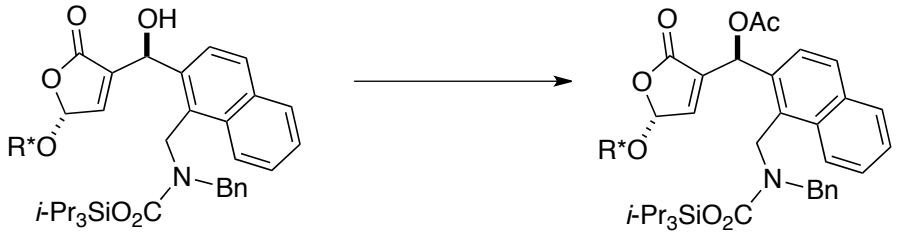


31.3 **37** **39.6a**

BuLi (2.5 M in hexane, 0.37 mL, 0.87 mmol) was added dropwise to a stirred and cooled (–20 °C) solution of PhSeSePh (274.0 mg, 0.87 mmol) in THF

(2.03 mL). After 10 min, a portion of the freshly prepared PhSeLi solution (0.8 mL) was added dropwise by syringe to a stirred and cooled (–42 °C) solution of **31.3** (64.8 mg, 0.27 mmol) and **37** (168.1 mg, 0.35 mmol) in THF (3 mL). Stirring was continued for 9 h at –42 °C (dry ice/MeCN), and the mixture was quenched with saturated aqueous NH_4Cl (3 mL) 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 (1.8 x 15 cm), using 3:20 EtOAc-hexanes, gave **39.6a** (145.0 mg, 75%) as a colorless oil: FTIR ($CHCl_3$, cast) 3434, 3061, 3033, 2950, 2928, 2868, 2726, 1770, 1671, 1605, 1553, 1513, 1496, 1461 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.77−1.68 (m, 37 H), 2.02−2.16 (m, 2 H), 3.21 (s, 1 H), 3.58−3.67 (m, 1 H), 4.09 (d, J = 16.5 Hz, 1 H), 4.61−4.78 (m, 1 H), 4.90−5.10 (m, 1 H), 5.39−5.48 (m, 1 H), 5.71 (s, 1 H), 5.94 (s, 1 H), 6.68 (s, 1 H), 6.99−7.17 (m, 2 H), 7.28−7.34 (m, 3 H), 7.50−7.54 (m, 3 H), 7.84−7.86 (m, 2 H), 8.21 (d, J = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.2 (d), 15.8 (q), 17.9 (q), 20.8 (q), 22.2 (q), 23.3 (t), 25.3 (d), 31.5 (d), 34.2 (t), 40.4 (t), 42.1 (t), 47.6 (d), 48.9 (t), 65.6 (d), 79.4 (d), 99.3 (d), 124.1 (d), 125.1 (d), 126.3 (d), 126.4 (d), 126.9 (d), 127.3 (d), 128.5 (d), 128.7 (d), 129.4 (d), 129.8 (s), 132.5 (s), 133.5 (s), 137.3 (s), 137.7 (s), 139.5 (s), 144.4 (d), 155.5 (s), 169.9 (s); exact mass (electrospray) m/z calcd for $C_{43}H_{59}NNaO_6Si$ (M + Na) 736.4004, found 736.4002.

(*S*)-(1-{[Benzyl({[tris(propan-2-yl)silyl]oxy}carbonyl)amino]methyl}-naphthalen-2-yl)[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]-oxy}-2-oxo-2,5-dihydrofuran-3-yl]methyl acetate (39.6b).

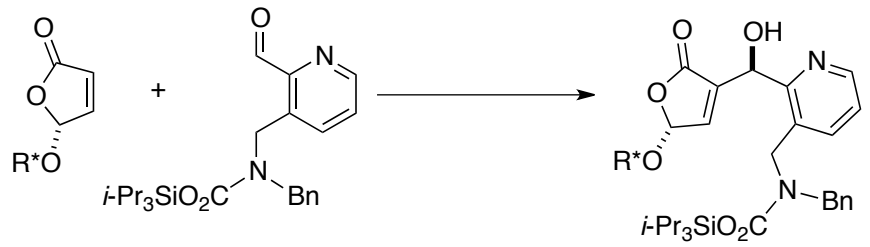


39.6a **39.6b**

DMAP (2.8 mg, 0.023 mmol) was added to a stirred solution of **39.6a** (129.8 mg, 0.18 mmol) in CH_2Cl_2 (2.5 mL). The mixture was then cooled to 0 °C, and AcCl (0.06 mL, 0.83 mmol) and pyridine (0.11 mL, 1.36 mmol) were added sequentially. The ice bath was left in place but not recharged, and stirring was continued for 1 h. The mixture was quenched with hydrochloric acid (1 M, 3 mL) and water (4 mL), 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 (1.4 x 14 cm), using 3:25 EtOAc-hexanes, gave **39.6b** (133.0 mg, 97%) as a colorless oil: FTIR ($CHCl_3$, cast) 3063, 3033, 2949, 2868, 2726, 1775, 1751, 1672, 1605, 1558, 1513, 1496, 1459 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.76−1.56 (m, 35 H), 1.66−1.70 (m, 2 H), 2.03−2.13 (m, 5 H), 3.64 (dt, J = 4.0, 10.5 Hz, 1 H), 4.27−4.41 (m, 2 H), 5.31−5.49 (m, 2 H), 5.96 (s, 1 H), 6.76−6.92 (m, 2 H), 7.04 (d, J = 7.0 Hz, 2 H), 7.10−7.22 (m, 3 H), 7.46−7.54 (m, 3 H), 7.83 (d, J = 9.0 Hz, 2 H), 8.21 and 8.30

(two d, J = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.2 (d), 12.3 (d), 15.9 (q), 17.8 (q), 18.1 (q), 20.7 (q), 20.9 (q), 22.2 (q), 23.3 (t), 25.4 (d), 31.5 (d), 34.2 (t), 40.5 (t), 42.8 (t), 47.7 (d), 48.4 (t), 67.4 (d), 79.4 (d), 98.7 (d), 124.2 (d), 125.6 (d), 125.9 (d), 126.6 (d), 126.7 (d), 127.0 (d), 128.3 (d), 128.4 (d), 129.3 (d), 131.6 (s), 132.8 (s), 133.6 (s), 133.7 (s), 136.8 (s), 137.8 (s), 145.9 (d), 155.6 (s), 168.0 (s), 169.1 (s); exact mass (electrospray) m/z calcd for $C_{45}H_{61}NNaO_7Si$ (M + Na) 778.4110, found 778.4103.

Tris(propan-2-yl)silyl *N*-benzyl-*N*-({2-[(*R*)-hydroxy[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydro-furan-3-yl]methyl]pyridin-3-yl}methyl)carbamate (39.7a).



31.3 **38** **39.7a**

BuLi (2.5 M in hexane, 0.21 mL, 0.525 mmol) was added dropwise to a stirred and cooled (–20 °C) solution of PhSeSePh (167.2 mg, 0.525 mmol) in THF (0.99 mL). After 10 min, a portion of the freshly prepared PhSeLi solution (0.4 mL) was added dropwise by syringe to a stirred and cooled (–42 °C) solution of **31.3** (40.5 mg, 0.17 mmol) and **38** (108.8 mg, 0.255 mmol) in THF (1.7 mL). Stirring was continued for 9 h at –42 °C (dry ice/MeCN). The mixture was

quenched with saturated aqueous NH_4Cl (3 mL) 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 (1.4 x 15 cm), using 3:10 EtOAc-hexanes, gave **39.7a** (70.0 mg, 62%) as a colorless oil: FTIR ($CHCl_3$, cast) 3412, 3089, 3064, 3031, 2949, 2928, 2868, 1770, 1680, 1606, 1579, 1496, 1465 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.75−1.44 (m, 34 H), 1.67 (t, J = 12.5 Hz, 2 H), 2.02−2.12 (m, 2 H), 3.60 (dt, J = 4.0, 10.5 Hz, 1 H), 4.38−4.65 (m, 4 H), 4.72−4.92 (m, 1 H), 5.49−5.66 (m, 1 H), 5.94 (s, 1 H), 6.80 and 6.89 (two s, 1 H), 7.21−7.37 (m, 6 H), 7.54−7.59 (m, 1 H), 8.49 (d, J = 4.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.0 (d), 12.1 (d), 15.78 (q), 15.83 (q), 17.9 (q), 20.9 (q), 22.2 (q), 23.1 (t), 23.2 (t), 25.3 (d), 31.5 (d), 34.2 (t), 40.6 (t), 45.6 (t), 46.2 (t), 47.7 (d), 50.7 (t), 51.1 (t), 64.3 (d), 64.9 (d), 79.0 (d), 79.4 (d), 99.19 (d), 99.24 (d), 123.4 (d), 127.2 (d), 127.3 (d), 127.7 (d), 128.1 (d), 128.2 (d), 128.75 (d), 128.78 (d), 130.8 (s), 130.9 (s), 135.1 (d), 136.5 (d), 137.0 (s), 137.2 (s), 139.0 (s), 139.2 (s), 145.1 (d), 145.3 (d), 147.2 (d), 147.4 (d), 154.7 (s), 155.3 (s), 155.5 (s), 155.6 (s), 169.5 (s); exact mass (electrospray) m/z calcd for $C_{38}H_{57}N_2O_6Si$ (M + H) 665.3980, found 665.3977.

(R)-(3-{[Benzyl({[tris(propan-2-yl)silyl]oxy}carbonyl)amino]methyl}-pyridin-2-yl)[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydrofuran-3-yl]methyl acetate (39.7b).

39.7a **39.7b**

DMAP (4.0 mg, 0.032 mmol) was added to a stirred solution of **39.7a** (65.8 mg, 0.099 mmol) in CH_2Cl_2 (1.5 mL). The mixture was then cooled to 0 °C, and AcCl (0.032 mL, 0.44 mmol) and pyridine (0.06 mL, 0.74 mmol) were added sequentially. The ice bath was left in place but not recharged, and stirring was continued for 40 min. The mixture was quenched with hydrochloric acid (1 M, 1 mL) and water (3 mL), 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 (1.2 x 14 cm), using 3:10 EtOAc-hexanes, gave **39.7b** (57.0 mg, 81%) as a colorless oil: FTIR ($CHCl_3$, cast) 3064, 3032, 2949, 2868, 1771, 1749, 1681, 1576, 1496, 1466 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.73−1.40 (m, 33 H), 1.57−1.68 (m, 2 H), 2.04−2.10 (m, 5 H), 2.16−2.17 (m, 2 H), 3.61 (dt, *J* = 4.5, 10.5 Hz, 1 H), 4.45−4.55 (m, 2 H), 4.72−4.86 (m, 2 H), 6.02 (d, *J* = 5.0 Hz, 1 H), 6.54 and 6.65 (two s, 1 H), 7.00 (d, *J* = 14.5 Hz, 1 H), 7.21−7.34 (m, 6 H), 7.52 (d, *J* = 8.0 Hz)

and 7.56 (d, *J* = 8.0 Hz, both signals together 1 H), 8.49 (d, J = 5.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.0 (d), 12.1 (d), 15.9 (q), 17.8 (q), 17.9 (q), 20.6 (q), 20.7 (q), 20.9 (q), 22.2 (q), 23.2 (t), 25.26 (d), 25.29 (d), 31.5 (d), 34.2 (t), 40.60 (t), 40.64 (t), 45.8 (t), 46.6 (t), 47.7 (d), 50.7 (t), 50.8 (t), 66.0 (d), 66.8 (d), 78.9 (d), 79.1 (d), 99.45 (d), 99.51 (d), 123.7 (d), 123.8 (d), 127.46 (d), 127.54 (d), 127.6 (d), 128.4 (d), 128.66 (d), 128.70 (d), 132.4 (s), 134.3 (d), 135.3 (s), 135.5 (s), 135.8 (d), 137.3 (s), 137.4 (s), 146.2 (d), 146.3 (d), 148.2 (d), 148.3 (d), 152.1 (s), 152.7 (s), 155.57 (s), 155.63 (s), 168.87 (s), 168.88 (s), 169.46 (s), 169.53 (s); exact mass (electrospray) *m*/*z* calcd for $C_{40}H_{58}N_2NaO_7Si$ (M + Na) 729.3905, found 729.3897.

(7*R*,7a*S*)-1-Benzyl-7-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohex-yl]oxy}-1*H*,2*H*,3*H*,5*H*,7*H*,7a*H*-furo[3,4-*b*]pyridin-5-one (40.1).

39.1b **40.1**

Bu_4NF (1.0 M in THF, 0.09 mL, 0.09 mmol) was added to a stirred solution of **39.1b** (39.0 mg, 0.059 mmol) in THF (4 mL). After 21 min, the mixture was quenched with saturated aqueous NH_4Cl (2 mL) and diluted with EtOAc (4 mL). The organic layer was washed with brine, dried ($MgSO_4$) and

evaporated. Flash chromatography of the residue over silica gel (1.0 x 14 cm), using 3:20 EtOAc-hexanes, gave **40.1** (28.7 mg, 81%) as white crystals: mp 123−124 °C; $[\alpha]_D^{20}$ –154.10 (*c* 1.07, $CHCl_3$); FTIR ($CHCl_3$, cast) 3062, 3029, 2954, 2922, 2869, 2804, 2759, 1774, 1694, 1636, 1603, 1495, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.81−0.90 (m, 10 H), 0.91−1.06 (m, 2 H), 1.37−1.44 (m, 2 H), 1.62−1.67 (m, 2 H), 2.00−2.07 (m, 2 H), 2.20−2.25 (m, 2 H), 2.44−2.52 (m, 1 H), 2.99 (dd, *J* = 6.5, 11.0 Hz, 1 H), 3.33 (d, *J* = 13.0 Hz, 1 H), 3.39−3.42 (m, 1 H), 3.61 (dt, *J* = 4.0, 11.0 Hz, 1 H), 3.99 (d, *J* = 13.0 Hz, 1 H), 5.78 (d, *J* = 5.5 Hz, 1 H), 6.90 (d, *J* = 3.0 Hz, 1 H), 7.27−7.36 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.5 (q), 20.8 (q), 22.2 (q), 23.1 (t), 25.1 (d), 26.4 (t), 31.5 (d), 34.3 (t), 39.8 (t), 47.4 (d), 47.7 (t), 59.1 (t), 62.2 (d), 77.1 (d), 99.0 (d), 127.2 (s), 127.6 (d), 128.4 (d), 129.7 (d), 135.8 (d), 136.5 (s), 167.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{24}H_{34}NO_3$ (M + H) 384.2533, found 384.2534.

In some experiments a small amount of the C(7a) epimer was isolated (10:1 ratio of major to minor products): $[\alpha]_D^{20}$ –116.93 (*c* 1.24, $CHCl_3$); FTIR ($CHCl_3$, cast) 2954, 2922, 2869, 2810, 1773, 1692, 1495, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.81−1.10 (m, 12 H), 1.29−1.35 (m, 1 H), 1.36−1.44 (m, 1 H), 1.64−1.71 (m, 2 H), 2.12−2.19 (m, 2 H), 2.23−2.32 (m, 2 H), 2.35−2.42 (m, 1 H), 2.93 (dd, *J* = 6.5, 12.0 Hz, 1 H), 3.32 (d, *J* = 13.5 Hz, 1 H), 3.38−3.42 (m, 1 H), 3.69 (dt, *J* = 4.0, 11.0 Hz, 1 H), 4.24 (d, *J* = 14 Hz, 1 H), 5.59 (d, *J* = 6 Hz, 1 H), 6.86 (q, *J* = 3.5 Hz, 1 H), 7.30−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.0 (q), 20.9 (q), 22.2 (q), 23.2 (t), 25.5 (d), 26.5 (t), 31.4 (d), 34.3 (t), 39.7 (t), 47.8 (t), 47.9 (d), 59.2 (t), 65.4 (d), 78.5 (d), 104.0 (d), 127.3 (d), 128.4 (d), 129.2

(d), 129.4 (s), 135.1 (d), 137.5 (s), 166.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{24}H_{34}NO_3$ (M + H) 384.2533, found 384.2528.

(8*R*,8a*R*)-1-Benzyl-8-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohex-yl]oxy}-1*H*,2*H*,3*H*,4*H*,6*H*,8*H*,8a*H*-furo[3,4-*b*]azepin-6-one (40.2).

39.2b **40.2**

Bu_4NF (1.0 M in THF, 0.059 mL, 0.059 mmol) was added to a stirred solution of **39.2b** (39.0 mg, 0.059 mmol) in THF (0.8 mL). After 2 min, the reaction mixture was quenched with saturated aqueous NH_4Cl (1 mL) and diluted with EtOAc (4 mL). The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 14 cm), using 3:25 EtOAc-hexanes, gave **40.2** (18.3 mg, 78%) as a light yellow oil: FTIR ($CHCl_3$, cast) 3086, 3061, 3028, 2952, 2926, 2869, 1764, 1678, 1603, 1495, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) isomer mixture δ 0.78−1.05 (m, 12 H), 1.21−1.26 (m, 1 H), 1.31−1.39 (m, 1 H), 1.49−1.53 (m, 1 H), 1.61−1.67 (m, 2 H), 1.80−1.87 (m, 1 H), 2.06−2.14 (m, 2 H), 2.36−2.48 (m, 1 H), 2.52−2.58 (m, 1 H), 2.81−2.86 (m, 1 H), 3.08−3.12 (m, 1 H), 3.41−3.47 (m, 1 H), 3.55−3.67 (m, 1 H), 3.73−3.93 (m, 1 H), 4.09 (d, *J* = 2.5 Hz, 1 H), 5.54−5.69 (m, 1 H), 7.13−7.39 (m,

6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.3 (q), 15.7 (q), 15.8 (q), 17.7 (q), 20.8 (t), 20.9 (q), 22.3 (q), 23.1 (t), 23.4 (t), 24.7 (t), 25.4 (d), 25.5 (d), 26.8 (t), 28.5 (t), 29.1 (t), 31.4 (d), 34.3 (t), 36.7 (t), 39.1 (t), 39.6 (t), 47.7 (d), 47.8 (d), 52.6 (t), 53.9 (t), 54.5 (t), 57.8 (t), 66.9 (d), 68.4 (d), 76.3 (d), 77.2 (d), 97.3 (d), 101.6 (d), 127.19 (d), 127.23 (d), 128.2 (d), 128.5 (d), 128.7 (s), 129.1 (d), 130.7 (s), 138.8 (s), 142.1 (d), 144.1 (d), 168.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{25}H_{36}NO_3$ (M + H) 398.2690, found 398.2687.

Data for the major isomer: $[\alpha]_D^{20}$ −94.57 (*c* 1.22, $CHCl_3$); FTIR ($CHCl_3$, cast) 3086, 3063, 3028, 2952, 2927, 2869, 1764, 1678, 1603, 1495, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.77−1.07 (m, 12 H), 1.25−1.30 (m, 1 H), 1.33−1.42 (m, 1 H), 1.51−1.58 (m, 1 H), 1.63−1.70 (m, 2 H), 1.83−1.90 (m, 1 H), 2.08−2.20 (m, 2 H), 2.44−2.51 (m, 1 H), 2.55−2.61 (m, 1 H), 2.83−2.89 (m, 1 H), 3.13 (ddd, *J* = 2.5, 5.5, 14.5 Hz, 1 H), 3.61 (dt, *J* = 4.0, 10.5 Hz, 1 H), 3.63 (AB q, *J* = 14.3 Hz, $\Delta\nu_{AB}$ = 143.0 Hz, 2 H), 4.12 (q, *J* = 2.5 Hz, 1 H), 5.57 (d, *J* = 2.5 Hz, 1 H), 7.27−7.30 (m, 2 H), 7.34−7.38 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.7 (q), 20.85 (t), 20.94 (q), 22.3 (q), 23.1 (t), 25.4 (d), 29.1 (t), 31.4 (d), 34.3 (t), 39.6 (t), 47.8 (d), 52.6 (t), 54.5 (t), 68.4 (d), 77.2 (d), 101.6 (d), 127.2 (d), 128.47 (d), 128.48 (d), 130.7 (s), 138.8 (s), 144.1 (d), 168.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{25}H_{36}NO_3$ (M + H) 398.2690, found 398.2691.

Data for the minor isomer: $[\alpha]_D^{20}$ −157.58 (*c* 0.99, $CHCl_3$); FTIR ($CHCl_3$, cast) 3061, 3026, 2952, 2923, 2868, 2801, 2732, 1770, 1684, 1603, 1494, 1452 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.77−1.09 (m, 12 H), 1.33−1.46 (m, 2 H), 1.64−1.81 (m, 4 H), 2.08−2.13 (m, 2 H), 2.27−2.35 (m, 1 H), 2.42 (ddd, *J* = 2.5,

8.8, 13.8 Hz, 1 H), 2.49−2.55 (m, 1 H), 3.14 (ddd, J = 2.5, 7.6, 13.6 Hz, 1 H), 3.67 (dt, J = 4.0, 10.8 Hz, 1 H), 3.70 (AB q, J = 13.3 Hz, $\Delta\nu_{AB}$ = 246.4 Hz, 2 H), 3.90−3.93 (m, 1 H), 5.72 (d, J = 5.0 Hz, 1 H), 7.16−7.19 (m, 1 H), 7.28−7.31 (m, 1 H), 7.34−7.37 (m, 2 H), 7.41−7.43 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.8 (q), 20.8 (q), 23.4 (t), 25.5 (d), 26.8 (t), 28.5 (t), 31.4 (d), 34.3 (t), 39.1 (t), 47.7 (d), 53.9 (t), 57.8 (t), 66.9 (d), 76.7 (d), 97.3 (d), 127.2 (d), 128.2 (d), 128.7 (s), 129.1 (d), 138.8 (s), 142.1 (d), 169.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{25}H_{36}NO_3$ (M + H) 398.2690, found 398.2692.

(6*R*,7*R*)-8-Methyl-6-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohex-yl]oxy}-5-oxa-8-azatricyclo[8.4.0.0^{3,7}]tetradeca-1(14),2,10,12-tetraen-4-one (40.3).

39.3b **40.3**

Bu_4NF (1.0 M in THF, 0.317 mL, 0.317 mmol) was added to a stirred and cooled (0 °C) solution of **39.3b** (199.3 mg, 0.317 mmol) in THF (4 mL). After 15 min, the mixture was quenched with saturated aqueous NH_4Cl (4 mL) and diluted with EtOAc (4 mL). The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.4 x 14

cm), using 1:5 EtOAc-hexanes, gave **40.3** (108.1 mg, 92%) as a light yellow oil: $[\alpha]_D^{20}$ 119.87 (*c* 1.12, $CHCl_3$); FTIR ($CHCl_3$, cast) 3064, 3017, 2953, 2924, 2870, 2852, 2794, 1763, 1657, 1600, 1568, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.77−1.06 (m, 12 H), 1.17−1.26 (m, 1 H), 1.35−1.44 (m, 1 H), 1.61−1.69 (m, 2 H), 2.06−2.18 (m, 2 H), 2.44 (s, 3 H), 3.21 (t, *J* = 3.2 Hz, 1 H), 3.61 (dt, *J* = 4.0, 10.4 Hz, 1 H), 3.80 (AB q, *J* = 15.2 Hz, $\Delta\nu_{AB}$ = 116.8 Hz, 2 H), 5.57 (d, *J* = 3.2 Hz, 1 H), 7.28−7.43 (m, 4 H), 7.73 (d, *J* = 2.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7 (q), 20.9 (q), 22.3 (q), 23.1 (t), 25.3 (d), 31.4 (d), 34.3 (t), 39.7 (t), 40.8 (q), 47.7 (d), 59.1 (t), 68.6 (d), 77.7 (d), 103.5 (d), 127.8 (d), 129.4 (d), 129.6 (s), 130.7 (d), 131.3 (d), 135.6 (s), 139.2 (s), 139.4 (d), 168.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{23}H_{32}NO_3$ (M + H) 370.2377, found 370.2379.

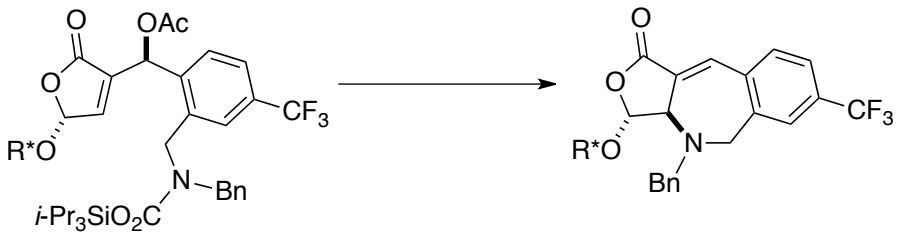
(6*R*,7*R*)-8-Benzyl-11-methyl-6-{[(1*S*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-5-oxa-8-azatricyclo[8.4.0.0^{3,7}]tetradeca-1(14),2,10,12-tetraen-4-one (40.4).

39.4b **40.4**

Bu_4NF (1.0 M in THF, 0.0385 mL, 0.0385 mmol) was added to a stirred and cooled (–78 °C) solution of **39.4b** (27.7 mg, 0.0385 mmol) in THF (0.8 mL).

After 15 min, the mixture was quenched with saturated aqueous NH_4Cl (3 mL) and diluted with EtOAc (4 mL). The organic phase was washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 14 cm), using 1:20 EtOAc-hexanes, gave **40.4** (17.0 mg, 96%) as a light pink foam: $[\alpha]_D^{20}$ 97.44 (*c* 1.07, $CHCl_3$); FTIR ($CHCl_3$, cast) 3063, 3028, 2954, 2924, 2869, 1763, 1661, 1586, 1495, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.76−1.06 (m, 12 H), 1.14−1.20 (m, 1 H), 1.34−1.40 (m, 1 H), 1.59−1.67 (m, 2 H), 2.02−2.12 (m, 2 H), 2.21 (s, 3 H), 3.40 (t, J = 3.0 Hz, 1 H), 3.61 (dt, J = 4.0, 10.5 Hz, 1 H), 3.76 (AB q, J = 15.0 Hz, $\Delta\nu_{AB}$ = 104.9 Hz, 2 H), 3.82 (AB q, J = 15.0 Hz, $\Delta\nu_{AB}$ = 41.4 Hz, 2 H), 5.65 (d, J = 3.0 Hz, 1 H), 7.15−7.48 (m, 8 H), 7.82 (d, J = 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.7 (q), 20.1 (q), 20.9 (q), 22.2 (q), 23.1 (t), 25.3 (d), 31.3 (d), 34.3 (t), 39.6 (t), 47.7 (d), 49.1 (t), 56.6 (t), 67.6 (d), 77.3 (d), 103.9 (d), 127.3 (d), 127.4 (d), 128.2 (d), 128.5 (d), 128.9 (d), 129.3 (s), 131.5 (d), 137.0 (s), 138.1 (s), 138.2 (s), 139.0 (s), 140.4 (d), 168.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{30}H_{38}NO_3$ (M + H) 460.2846, found 460.2846.

(6*R*,7*R*)-8-Benzyl-6-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]-oxy}-12-(trifluoromethyl)-5-oxa-8-azatricyclo[8.4.0.0^{3,7}]tetradeca-1(14),2,10,12-tetraen-4-one (40.5).

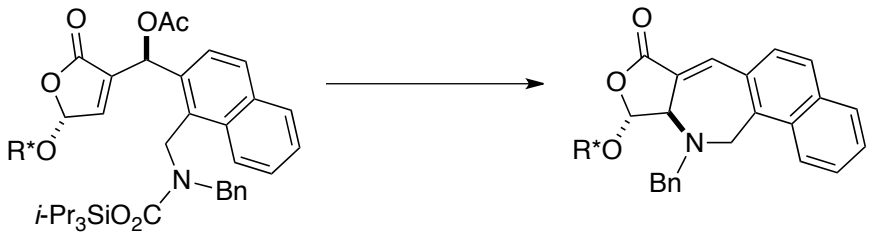


39.5b **40.5**

Bu_4NF (1.0 M in THF, 0.076 mL, 0.076 mmol) was added to a stirred and cooled (0 °C) solution of **39.5b** (58.9 mg, 0.076 mmol) in THF (1 mL). After 10 min, the mixture was quenched with saturated aqueous NH_4Cl (3 mL) and diluted with EtOAc (4 mL). The organic phase was washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 14 cm), using 1:20 EtOAc-hexanes, gave **40.5** (35.6 mg, 91%) as a white solid: 136−140 °C; $[\alpha]_D^{20}$ 159.11 (*c* 1.47, $CHCl_3$); FTIR ($CHCl_3$, cast) 3087, 3064, 3029, 2955, 2925, 2870, 1764, 1666, 1617, 1496, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.79−1.06 (m, 12 H), 1.16−1.22 (m, 1 H), 1.34−1.43 (m, 1 H), 1.61−1.69 (m, 2 H), 2.07−2.13 (m, 2 H), 3.52 (t, *J* = 3.5 Hz, 1 H), 3.61 (dt, *J* = 4.5, 11.0 Hz, 1 H), 3.72 (AB q, *J* = 15.0 Hz, $\Delta\nu_{AB}$ = 67.3 Hz, 2 H), 3.74 (AB q, *J* = 13.8 Hz, $\Delta\nu_{AB}$ = 27.5 Hz, 2 H), 5.69 (d, *J* = 3.5 Hz, 1 H), 7.32−7.42 (m, 6 H), 7.56 (d, *J* = 8.0 Hz, 1 H), 7.65 (dd, *J* = 1.5, 8.0 Hz, 1 H), 7.76 (d, *J* = 3.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.8 (q), 20.9 (q), 22.2 (q), 23.1 (t), 25.3 (d), 31.4

(d), 34.3 (t), 39.9 (t), 47.7 (d), 53.3 (t), 57.1 (t), 68.2 (d), 78.1 (d), 104.1 (d), 120.4 (s), 122.6 (s), 124.7 (d), 124.77 (d), 124.79 (d), 124.82 (d), 126.9 (s), 127.35 (d), 127.38 (d), 127.41 (d), 127.67 (d), 127.73 (d), 128.5 (d), 128.6 (d), 128.7 (d), 128.8 (d), 130.3 (s), 130.5 (s), 130.8 (s), 131.0 (s), 131.4 (d), 132.8 (s), 137.3 (d), 138.1 (s), 139.4 (s), 140.2 (s), 167.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{30}H_{35}F_3NO_3$ (M + H) 514.2564, found 514.2567.

(15*R*,16*R*)-17-Benzyl-15-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-14-oxa-17-azatetracyclo[8.8.0.0^{2,7}.0^{12,16}]octadeca-1,3,5,7,9,11-hexaen-13-one (40.6).



39.6b **40.6**

Bu_4NF (1.0 M in THF, 0.16 mL, 0.16 mmol) was added to a stirred and cooled (0 °C) solution of **39.6b** (120.0 mg, 0.16 mmol) in THF (2 mL). After 10 min, the mixture was quenched with saturated aqueous NH_4Cl (3 mL) and diluted with EtOAc (4 mL). The organic phase was washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.2 x 14 cm), using 3:50 EtOAc-hexanes, gave **40.6** (78.3 mg, 99%) as a light yellow solid: mp 183−184 °C; $[\alpha]_D^{20}$ 54.89 (*c* 0.98, $CHCl_3$); FTIR ($CHCl_3$, cast) 3057,

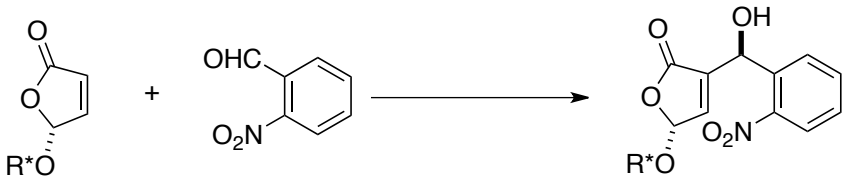
3026, 2954, 2924, 2869, 1763, 1658, 1618, 1596, 1559, 1511, 1495, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.74−1.17 (m, 13 H), 1.32−1.43 (m, 1 H), 1.61−1.67 (m, 2 H), 2.05−2.15 (m, 2 H), 3.20 (t, *J* = 2.0 Hz, 1 H), 3.64 (dt, *J* = 4.0, 10.5 Hz, 1 H), 3.84 (AB q, *J* = 15.0 Hz, $\Delta\nu_{AB}$ = 19.4 Hz, 2 H), 4.08 (AB q, *J* = 15.0 Hz, $\Delta\nu_{AB}$ = 276.1 Hz, 2 H), 5.73 (d, *J* = 2.0 Hz, 1 H), 7.41 (t, *J* = 7.0 Hz, 1 H), 7.48−7.59 (m, 7 H), 7.81 (d, *J* = 8.5 Hz, 1 H), 7.90 (t, *J* = 7.0 Hz, 2 H), 8.02 (d, *J* = 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.7 (q), 20.9 (q), 22.2 (q), 23.1 (t), 25.3 (d), 31.4 (d), 34.3 (t), 39.6 (t), 46.9 (t), 47.7 (d), 57.7 (t), 67.3 (d), 77.2 (d), 124.4 (d), 126.5 (d), 126.9 (d), 127.0 (d), 127.6 (d), 128.2 (d), 128.5 (d), 128.66 (d), 128.71 (d), 130.9 (s), 133.4 (s), 133.5 (s), 135.3 (s), 137.8 (s), 138.9 (s), 140.8 (d), 168.7 (s); exact mass (electrospray) *m/z* calcd for $C_{33}H_{38}NO_3$ (M + H) 496.2846, found 496.2843.

(6*R*,7*R*)-8-Benzyl-6-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]-oxy}-5-oxa-8,14-diazatricyclo[8.4.0.0^{3,7}]tetradeca-1(14),2,10,12-tetraen-4-one (40.7).

39.7b **40.7**

Bu_4NF (1.0 M in THF, 0.058 mL, 0.058 mmol) was added to a stirred and cooled (0 °C) solution of **39.7b** (41.2 mg, 0.058 mmol) in THF (1 mL). After 10 min, the mixture was quenched with saturated aqueous NH_4Cl (2 mL) and diluted with EtOAc (4 mL). The organic phase was washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.2 x 14 cm), using 2:5 EtOAc-hexanes, gave **40.7** (25.1 mg, 96%) as a light yellow solid: $[\alpha]_D^{20}$ 125.75 (*c* 1.22, $CHCl_3$); FTIR ($CHCl_3$, cast) 3029, 2954, 2925, 2869, 1764, 1670, 1604, 1566, 1496, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.78−1.05 (m, 12 H), 1.13−1.22 (m, 1 H), 1.34−1.43 (m, 1 H), 1.60−1.68 (m, 2 H), 2.06−2.13 (m, 2 H), 3.53 (t, *J* = 3.5 Hz, 1 H), 3.57−3.77 (m, 5 H), 5.68 (d, *J* = 3.5 Hz, 1 H), 7.21 (dd, *J* = 5.0, 8.0 Hz, 1 H), 7.29−7.44 (m, 6 H), 7.85 (d, *J* = 3.0 Hz, 1 H), 8.67 (dd, *J* = 1.5, 4.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.7 (q), 20.9 (q), 22.2 (q), 23.1 (t), 25.3 (d), 31.3 (d), 34.3 (t), 39.8 (t), 47.7 (d), 52.3 (t), 56.9 (t), 68.2 (d), 77.9 (d), 103.7 (d), 122.8 (d), 127.7 (d), 128.7 (d), 128.8 (d), 133.3 (s), 135.7 (s), 138.1 (d), 138.2 (s), 139.2 (d), 149.2 (d), 155.0 (s), 167.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{28}H_{35}N_2O_3$ (M + H) 447.2642, found 447.2641.

(5*R*)-3-[(*S*)-Hydroxy(2-nitrophenyl)methyl]-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-5*H*-furan-2-one (41.2).



31.3 **41.1** **41.2**

BuLi (2.5 M in hexane, 0.71 mL, 1.78 mmol) was added dropwise to a stirred and cooled (–20 °C) solution of PhSeSePh (559.4 mg, 1.78 mmol) in THF (12 mL). After 10 min, the mixture was cooled to –42 °C (dry ice/MeCN), and a mixture of **31.3** (409.4 mg, 1.72 mmol) and **41.1** (389.6 mg, 2.58 mmol) in THF (5 mL) was added dropwise. Stirring at –42 °C was continued for 9 h. The mixture was then quenched with saturated aqueous NH_4Cl (10 mL) 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 (2.8 x 20 cm), using 2:5 to 3:5 Et_2O-hexanes, gave **41.2** (526.8 mg, 78%) as a light yellow solid: FTIR ($CDCl_3$, cast) 3449, 3107, 3021, 2955, 2926, 2870, 1767, 1663, 1611, 1579, 1528, 1456 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.70−1.10 (m, 12 H), 1.20−1.30 (m, 1 H), 1.30−1.45 (m, 1 H), 1.55−1.80 (m, 2 H), 2.00−2.15 (m, 2 H), 3.62 (dt, *J* = 4.0, 10.0 Hz, 1 H), 3.84 (br s, 1 H), 6.02 (t, *J* = 1.2 Hz, 1 H), 6.19 (s, 1 H), 6.80−6.84 (m, 1 H), 7.48−7.54 (m, 1 H), 7.66−7.72 (m, 1 H), 7.77−7.84 (m, 1 H), 8.00−8.05 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ

15.9 (q), 20.8 (q), 22.2 (q), 23.3 (t), 25.4 (d), 31.4 (d), 34.2 (t), 40.4 (t), 47.7 (d), 64.7 (d), 79.3 (d), 99.4 (d), 125.0 (d), 129.0 (d), 129.2 (d), 134.0 (d), 135.1 (s), 137.7 (s), 145.1 (d), 147.8 (s), 170.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{21}H_{27}NNaO_6$ (M + Na) 412.1731, found 412.1726.

(*S*)-[(5*R*)-5-{[(1*R*,2*R*,5*S*)-5-Methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydrofuran-3-yl](2-nitrophenyl)methyl acetate (41.3).

41.2 **41.3**

DMAP (19.3 mg, 0.16 mmol) was added to a stirred solution of **41.2** (301.7 mg, 0.78 mmol) in CH_2Cl_2 (8 mL). The mixture was then cooled to –78 °C, and AcCl (0.17 mL, 2.35 mmol) and pyridine (0.38 mL, 4.70 mmol) were added sequentially. The reaction flask was transferred to an ice bath (0 °C) and stirring was continued for 8.5 h, the ice bath being left in place but not recharged. The mixture was then quenched with hydrochloric acid (1 M, 6 mL) and water (6 mL), 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 (1.8 x 20 cm), using 3:10 EtOAc-hexanes, gave **41.3** (331.6 mg, 99%) as a light pink solid: FTIR ($CHCl_3$, cast)

3090, 2956, 2926, 2871, 1775, 1670, 1653, 1612, 1581, 1530, 1457 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.74−1.06 (m, 12 H), 1.17−1.28 (m, 1 H), 1.32−1.45 (m, 1 H), 1.58−1.70 (m, 2 H), 2.00−2.12 (m, 2 H), 2.12−2.18 (m, 3 H), 3.61 (dt, *J* = 4.0, 10.8 Hz, 1 H), 6.01 (t, *J* = 1.2 Hz, 1 H), 6.90−6.94 (m, 1 H), 7.21 (s, 1 H), 7.49−7.55 (m, 1 H), 7.68 (dt, *J* = 1.2, 7.6 Hz, 1 H), 7.76 (dd, *J* = 1.2, 7.6 Hz, 1 H), 8.05 (dd, *J* = 1.2, 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.8 (q), 20.7 (q), 20.8 (q), 22.2 (q), 23.2 (t), 25.3 (d), 31.4 (d), 34.1 (t), 40.5 (t), 47.7 (d), 65.4 (d), 79.3 (d), 98.7 (d), 125.1 (d), 128.9 (d), 129.6 (d), 132.0 (s), 133.7 (d), 135.0 (s), 147.3 (d), 147.8 (s), 168.0 (s), 169.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{23}H_{29}NNaO_7$ (M + Na) 454.1836, found 454.1832.

(*S*)-(2-Aminophenyl)[(5*R*)-5-{[(1*R*,2*R*,5*S*)-5-methyl-2-(propan-2-yl)-cyclohexyl]oxy}-2-oxo-2,5-dihydrofuran-3-yl]methyl acetate (41.4).

41.3 **41.4**

Zinc dust (460.0 mg, 7.08 mmol) was added to a stirred mixture of **41.3** (34.0 mg, 0.079 mmol), NH_4Cl (70.2 mg, 1.31 mmol) and H_2O (0.53 mL) in MeOH (5 mL). After 3 min, the reaction mixture was filtered through a pad of silica gel, using CH_2Cl_2 as a rinse. The organic phase was separated, washed

twice with aqueous NaOH (1 M), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.2 x 15 cm), using 3:10 to 2:5 EtOAc-hexanes, gave **41.4** (17.4 mg, 55%) as a yellow oil: FTIR ($CHCl_3$, cast) 3377, 3032, 2956, 2926, 2870, 2253, 1767, 1634, 1606, 1586, 1498, 1458 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.72−1.04 (m, 12 H), 1.19−1.26 (m, 1 H), 1.33−1.44 (m, 1 H), 1.61−1.69 (m, 2 H), 2.00−2.16 (m, 5 H), 3.61 (dt, *J* = 4.5, 10.5 Hz, 1 H), 4.16 (s, 2 H), 6.01−6.04 (m, 1 H), 6.67−6.72 (m, 2 H), 6.74−6.79 (m, 1 H), 6.95−6.98 (m, 1 H), 7.11−7.16 (m, 1 H), 7.19 (dd, *J* = 1.5, 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.8 (q), 20.8 (q), 20.9 (q), 22.2 (q), 23.2 (t), 25.3 (d), 31.5 (d), 34.2 (t), 40.5 (t), 47.7 (d), 66.8 (d), 79.4 (d), 99.2 (d), 117.4 (d), 118.9 (d), 121.0 (s), 128.6 (d), 129.9 (d), 136.4 (s), 144.6 (d), 144.9 (s), 169.1 (s), 169.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{23}H_{32}NO_5$ (M + H) 402.2275, found 402.2279.

[(2*R*)-1-Benzyl-2-(hydroxymethyl)-1,2,5,6-tetrahydropyridin-3-yl] methanol (42.1).

40.1 **42.1**

DIBAL-H (1.0 M in PhMe, 1.60 mL, 1.60 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **40.1** (123.2 mg, 0.32 mmol) in THF (3 mL). Stirring at –78 °C was continued for 1 h, the cold bath being left in place but not recharged, and stirring was continued for 10 h. MeOH (0.5 mL) and saturated aqueous Rochelle's salt (ca. 5 mL) were then added sequentially. Stirring was continued for 2 h, and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.2 x 14 cm), using 1:20 MeOH-EtOAc, gave **42.1** (60.2 mg, 80%) as a light yellow oil: $[\alpha]_D^{20}$ –26.86 (*c* 1.13, $CHCl_3$); FTIR ($CHCl_3$, cast) 3360, 3085, 3062, 3028, 2923, 2873, 1592, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.88 (dd, *J* = 3.0, 18.0 Hz, 1 H), 2.26−2.32 (m, 1 H), 2.63 (ddd, *J* = 2.5, 5.0, 13.0 Hz, 1 H), 2.85−2.97 (m, 3 H), 3.21−3.23 (m, 1 H), 3.51 (dd, *J* = 8.5, 11.0 Hz, 1 H), 3.67−3.77 (m, 3 H), 4.00 (AB q, *J* = 12.5 Hz, $\Delta\nu_{AB}$ = 32.3 Hz, 2 H), 5.95 (s, 1 H), 7.25−7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.7 (t), 42.0 (t), 57.5 (t), 60.3 (d), 61.3 (t), 65.3 (t), 124.6 (d), 127.3 (d), 128.5 (d), 129.0 (d), 135.7 (s), 138.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{14}H_{20}NO_2$ (M + H) 234.1489, found 234.1490.

[(2*R*)-1-Benzyl-3-(hydroxymethyl)-2,5,6,7-tetrahydro-1*H*-azepin-2-yl]methanol (42.2).

40.2 **42.2**

DIBAL-H (1.0 M in PhMe, 0.66 mL, 0.66 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **40.2** (52.5 mg, 0.13 mmol) in THF (1.5 mL). Stirring at –78 °C was continued for 2 h, the cold bath being left in place but not recharged, and stirring was continued for 12 h. MeOH (0.3 mL) and saturated aqueous Rochelle's salt (ca. 5 mL) were then added sequentially. Stirring was continued for 3 h, and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.2 x 14 cm), using 3:100 MeOH-EtOAc, gave **42.2** (29.6 mg, 90%) as an oil: $[\alpha]_D^{20}$ –2.10 (*c* 1.00, $CHCl_3$); FTIR ($CHCl_3$, cast) 3363, 3086, 3061, 3028, 2926, 2848, 1559, 1522, 1452 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40−1.47 (m, 1 H), 1.74−1.86 (m, 2 H), 2.18−2.38 (m, 3 H), 2.97−3.03 (m, 1 H), 3.12−3.22 (m, 1 H), 3.46−3.57 (m, 2 H), 3.73−3.87 (m, 3 H), 3.93 (s, 2 H), 5.99 (t, *J* = 5.7 Hz, 1 H), 7.21−7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4 (t), 28.1 (t), 49.9 (t), 55.9 (t), 59.2 (t), 64.3 (d), 68.1 (t), 127.4 (d), 128.7 (d), 129.0 (d), 130.6 (d), 139.5 (s), 140.9

(s); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{22}NO_2$ (M + H) 248.1645, found 248.1648.

[(3*R*)-3-(Hydroxymethyl)-2-methyl-2,3-dihydro-1*H*-2-benzazepin-4-yl]methanol (42.3).

40.3 **42.3**

DIBAL-H (1.0 M in PhMe, 1.46 mL, 1.46 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **40.3** (108.1 mg, 0.29 mmol) in THF (3 mL). Stirring at –78 °C was continued for 1 h, the cold bath being left in place but not recharged, and stirring was continued for 6.5 h. MeOH (0.5 mL) and saturated aqueous Rochelle's salt (ca. 6 mL) were then added sequentially. Stirring was continued for 12 h, and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.2 x 14 cm), using 1:20 MeOH-EtOAc, gave **42.3** (58.0 mg, 90%) as a white solid: $[\alpha]_D^{20}$ 59.87 (*c* 1.18, $CHCl_3$); FTIR ($CHCl_3$, cast) 3349, 3059, 3018, 2928, 2878, 1665, 1600, 1577, 1559, 1541, 1491 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.29 (s, 3 H), 3.16 (s, 2 H), 3.43 (t, *J* = 10.0 Hz, 1 H), 3.51 (dd, *J* = 5.0, 9.5 Hz, 1 H), 3.78 (dd, *J*

= 5.0, 10.0 Hz, 1 H), 3.89 (AB q, J = 15.0 Hz, $\Delta\nu_{AB}$ = 229.7 Hz, 2 H), 4.19 (AB q, J = 13.0 Hz, $\Delta\nu_{AB}$ = 28.7 Hz, 2 H),, 6.63 (s, 1 H), 7.16−7.26 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4 (t), 41.5 (q), 54.1 (t), 62.2 (t), 67.3 (d), 67.4 (t), 127.27 (d), 127.30 (d), 128.8 (d), 129.2 (d), 131.0 (d), 135.3 (s), 137.9 (s), 140.8 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{18}NO_2$ (M + H) 220.1332, found 220.1332.

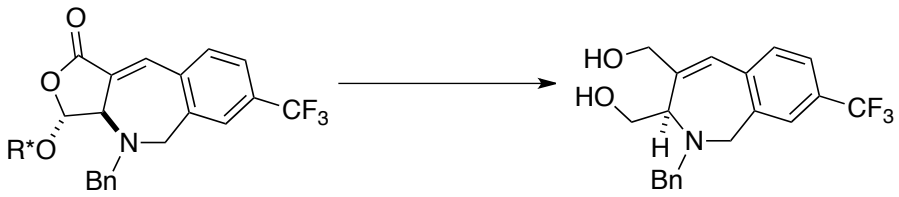
[(3-*R*)-2-Benzyl-3-(hydroxymethyl)-9-methyl-2,3-dihydro-1*H*-2-benz-azepin-4-yl]-methanol (42.4).

40.4 **42.4**

DIBAL-H (1.0 M in PhMe, 0.38 mL, 0.38 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **40.4** (35.2 mg, 0.077 mmol) in THF (1 mL). Stirring at –78 °C was continued for 2 h, the cold bath being left in place but not recharged, and stirring was continued for 5 h. MeOH (0.3 mL) and saturated aqueous Rochelle's salt (ca. 3 mL) were then added sequentially. Stirring was continued for 1.2 h, and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.2 x 14 cm),

using 1:1 EtOAc-hexanes, gave **42.4** (17.7 mg, 75%) as a light yellow solid: $[\alpha]_D^{20}$ 21.97 (*c* 0.83, $CHCl_3$); FTIR ($CHCl_3$, cast) 3384, 3062, 3028, 2922, 2858, 1733, 1671, 1585, 1495, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.93 (s, 3 H), 3.43 (t, *J* = 9.5 Hz, 1 H), 3.61 (s, 2 H), 3.72 (dd, *J* = 5.5, 9.5 Hz, 1 H), 3.77 (dd, *J* = 5.5, 10.0 Hz, 1 H), 3.87 (s, 2 H), 4.25 (AB q, *J* = 13.0 Hz, $\Delta\nu_{AB}$ = 30.3 Hz, 2 H), 6.71 (s, 1 H), 7.03 (dd, *J* = 1.5, 7.0 Hz, 1 H), 7.13−7.22 (m, 4 H), 7.26−7.35 (m, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.7 (q), 46.2 (t), 58.1 (t), 62.6 (t), 66.1 (d), 67.6 (t), 126.8 (d), 127.4 (d), 128.5 (d), 129.0 (d), 129.3 (d), 129.67 (d), 129.70 (d), 135.9 (s), 136.0 (s), 136.8 (s), 138.5 (s), 140.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{24}NO_2$ (M + H) 310.1802, found 310.1803.

[(3*R*)-2-Benzyl-3-(hydroxymethyl)-8-(trifluoromethyl)-2,3-dihydro-1*H*-2-benz-azepin-4-yl]methanol (42.5).

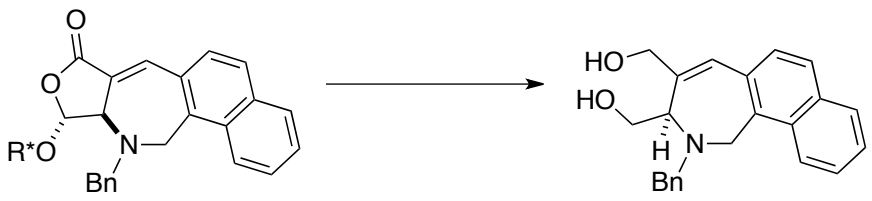


40.5 **42.5**

DIBAL-H (1.0 M in PhMe, 0.11 mL, 0.11 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **40.5** (11.3 mg, 0.022 mmol) in THF (0.6 mL). Stirring at –78 °C was continued for 1 h, the cold bath being left in place but not recharged, and stirring was continued for 7 h. MeOH (0.1 mL) and

saturated aqueous Rochelle's salt were then added sequentially. Stirring was continued overnight, and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.6 x 8 cm), using 2:1 EtOAc-hexanes, gave **42.5** (6.0 mg, 75%) as a light yellow solid: $[\alpha]_D^{20}$ 65.42 (*c* 1.35, $CHCl_3$); FTIR ($CHCl_3$, cast) 3375, 3087, 3064, 3030, 2922, 2855, 1650, 1616, 1495, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.50−3.58 (m, 3 H), 3.72−3.77 (m, 2 H), 3.87 (dd, *J* = 5.5, 11.0 Hz, 1 H), 4.20 (d, *J* = 15.5 Hz, 1 H), 4.24 (AB q, *J* = 13.5 Hz, $\Delta\nu_{AB}$ = 20.6 Hz, 2 H), 6.76 (s, 1 H), 7.15−7.22 (m, 3 H), 7.28−7.35 (m, 3 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.55 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 56.1 (t), 57.2 (t), 62.4 (t), 65.9 (d), 67.0 (t), 120.8 (s), 122.9 (s), 124.11 (d), 124.14 (d), 124.17 (d), 124.19 (d), 125.1 (s), 126.39 (d), 126.42 (d), 126.45 (d), 126.48 (d), 127.4 (d), 127.7 (d), 128.5 (d), 128.6 (d), 128.7 (s), 129.0 (s), 129.1 (d), 131.6 (d), 137.8 (s), 138.6 (s), 138.7 (s), 144.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{21}F_3NO_2$ (M + H) 364.1519, found 364.1514.

[(3*R*)-2-Benzyl-3-(hydroxymethyl)-1*H*,2*H*,3*H*-naphtho[1,2-*c*]azepin-4-yl]methanol (42.6).



40.6 **42.6**

DIBAL-H (1.0 M in PhMe, 0.79 mL, 0.79 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **40.6** (78.3 mg, 0.16 mmol) in THF (2 mL). Stirring at –78 °C was continued for 1 h, the cold bath being left in place but not recharged and stirring was continued overnight. MeOH (0.3 mL) and saturated aqueous Rochelle's salt (ca. 5 mL) were then added sequentially. Stirring was continued for 2.5 h, and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.2 x 14 cm), using 1:20 MeOH-Et_2O, gave **42.6** (45.0 mg, 82%) as a white solid: $[\alpha]_D^{20}$ –26.39 (*c* 0.91, $CHCl_3$); FTIR ($CHCl_3$, cast) 3367, 3079, 3063, 3024, 2983, 2964, 2946, 2918, 2894, 2874, 2843, 1598, 1511, 1493, 1453 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.05 (br s, 2 H), 3.56 (t, *J* = 9.5 Hz, 1 H), 3.65−3.75 (m, 4 H), 4.26−4.39 (m, 4 H), 6.89 (s, 1 H), 7.20−7.22 (m, 2 H), 7.29−7.31 (m, 3 H), 7.37−7.39 (m, 2 H), 7.44−7.47(m, 1 H), 7.71 (d, *J* = 8.5 Hz, 1 H), 7.77 (d, *J* = 8.5 Hz, 1 H), 7.83 (dd, *J* = 1.3, 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 46.3 (t), 59.1 (t), 62.9 (t), 65.8 (d), 67.6 (t), 123.4 (d), 125.7 (d), 126.4 (d), 127.4 (d), 127.5 (d), 128.3 (d), 128.49 (d), 128.53 (d), 129.1 (d), 129.7 (d), 132.1 (s), 132.7 (s), 133.5 (s), 133.7 (s), 138.7 (s), 142.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{23}H_{24}NO_2$ (M + H) 346.1802, found 346.1801.

[(7*R*)-6-Benzyl-7-(hydroxymethyl)-5*H*,6*H*,7*H*-pyrido[3,2-*c*]azepin-8-yl]methanol (42.7).

40.7 **42.7**

DIBAL-H (1.0 M in PhMe, 0.14 mL, 0.14 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **40.7** (12.1 mg, 0.027 mmol) in THF (0.6 mL). Stirring at –78 °C was continued for 3 h, the cold bath being left in place but not recharged, and stirring was continued for 4 h. MeOH (0.1 mL) and saturated aqueous Rochelle's salt (ca. 3 mL) were then added sequentially. Stirring was continued for 1 h, and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.6 x 8 cm), using 1:25 MeOH-EtOAc, gave **42.7** (2.7 mg, 34%) as a yellow solid: $[\alpha]_D^{20}$ 69.92 (*c* 1.15, $CHCl_3$); FTIR ($CHCl_3$, cast) 3346, 3062 3028, 2922, 2855, 1650, 1582, 1494, 1444 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.18 (s, 1 H), 3.35 (s, 1 H), 3.46−3.60 (m, 3 H), 3.66 (d, J = 16.0 Hz, 1 H), 3.82 (dd, J = 5.0, 9.5 Hz, 1 H), 3.89−3.94 (m, 1 H), 4.18 (d, J = 15.5 Hz, 1 H), 4.24 (AB q, J = 13.5 Hz, $\Delta\nu_{AB}$ = 19.1 Hz, 2 H), 7.02 (s, 1 H), 7.12 (dd, J = 5.0, 7.5 Hz, 1 H), 7.18 (d, J = 7.5 Hz, 2 H), 7.28−7.35 (m, 4 H), 8.57 (d, J = 5.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ

49.6 (t), 57.1 (t), 62.5 (t), 66.0 (d), 67.3 (t), 121.6 (d), 127.6 (d), 128.5 (d), 129.0 (d), 130.5 (d), 133.8 (s), 137.3 (d), 137.9 (s), 145.2 (s), 148.3 (d), 154.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{18}H_{21}N_2O_2$ (M + H) 297.1598, found 297.1597.

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Chapter 3

Total Synthesis of Racemic Marinopyrrole B

1. Introduction

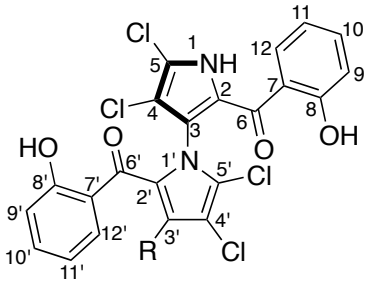
1.1 General

Historically, the majority of drugs have been discovered and developed from natural products, as well as their derivatives, metabolites and mimics.[1] In the past 20 years, over 50% of the small molecule new chemical entities (NCEs) introduced to the market were natural products or synthetic or semisynthetic natural product derivatives.[2]

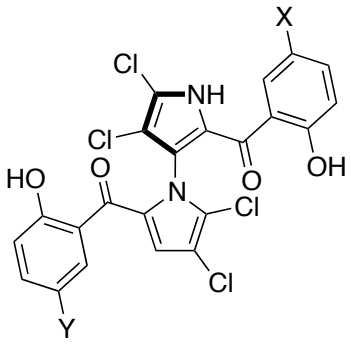
For over half a century, bacteria have been a source of structurally diverse and biologically active secondary metabolites.[3] Traditionally, the majority of bacteria that have been studied were obtained from soil habitats due to the limitation of the technologies, such as scuba diving, for collecting samples from marine habitats. Today, using deep water sampling tools instead of scuba diving, marine sediments have been collected and examined for new antibiotics.[4] With the improvement of the methods for collecting samples from the ocean and the development of analytical technologies, more and more chemists have been attracted to this field.

In 2008, Fenical and coworkers reported[5] that chemical studies of actinomycetes, which inhabit ocean sediments and include new species, have produced a growing number of unique, bioactive natural products.[6] By extracting actinomycete strain CNQ-418, which was obtained from a marine sediment sample, two compounds, (–)-marinopyrroles A (**1.1**) and B (**1.2**) were isolated. Both marinopyrrole A and B show significant activity against methicillin-resistant *Staphylococcus aureus* (MRSA) with MIC_{90} values of less than 1 μg/mL. In

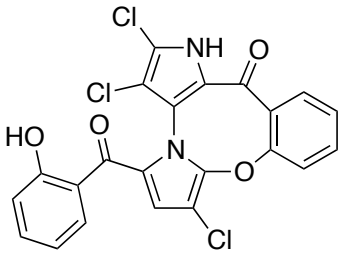
addition, both of also show interesting anticancer properties against a human colon cancer cell line (HCT-166) with IC_{50} values around 5 μg/mL.[5,7] Later on, four additional members of this family were also found (Scheme 1).[7]



(–)-marinopyrrole A (**1.1**), R = H
(–)-marinopyrrole B (**1.2**), R = Br



(–)-marinopyrrole C (**1.3**), X = Cl, Y = H
(–)-marinopyrrole D (**1.4**), X = H, Y = Cl
(–)-marinopyrrole E (**1.5**), X = H, Y = Br



(±)-marinopyrrole F (**1.6**)

Scheme 1

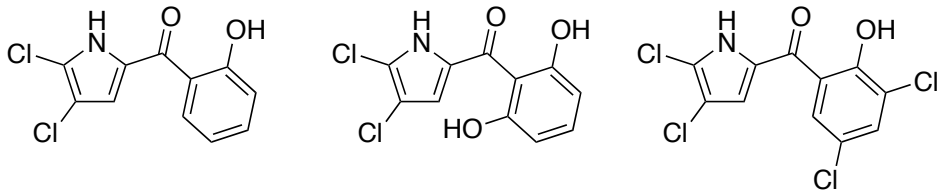
1.2 Isolation and structural elucidation of the marinopyrroles

Cultivation of the marine *Streptomyces* strain CNQ-418 in a seawater-based medium for 7 days with vigorous shaking, followed by solid phase extraction of the broth using Amberlite resin (XAD-16), filtration through cheesecloth, elution of the resin with acetone, and solvent removal under vacuum, afforded a gummy extract which was then subjected to fractionation on silica gel.[5]

Using C8 reverse phase HPLC, two prominent metabolites, marinopyrrole A and B, were isolated from a fraction. With the optimization of culturing conditions, another four members of this family were also isolated.[7]

In order to determine the structures of these metabolites, 1D and 2D NMR spectra of marinopyrrole A (**1.1**) were first collected. With COSY, HSQC and HMBC spectra, two independent benzoyl groups were identified. However, the central core of marinopyrrole A (**1.1**) was difficult to determine due to the lack of correlations in 2D NMR spectra. A number of derivatives of marinopyrrole A (**1.1**) were prepared in an attempt to produce suitable crystals for X-ray analysis. Both phenolic hydroxyl groups of **1.1** were esterified to give the corresponding *O*,*O*'-diacetate, *O*,*O*'-di-*p*-bromobezoate and *O*,*O*'-di-*p*-nitrobenzoates. *N*-Methylation of **1.1** with CH_2N_2 produced the corresponding *N*-methyl derivative. Unfortunately, none of these solid derivatives yielded crystals suitable for X-ray analysis. Fortunately, crystals of marinopyrrole B (**1.2**) were obtained by slow evaporation from PhMe, and X-ray analysis established the structure of **1.2** and its *M*-configuration. By comparing the NMR spectral data of **1.1** with those of **1.2**, the planar structure of **1.1** was assigned. The two marinopyrroles have similar optical rotations, suggesting marinopyrrole A also has the *M*-configuration. The structures of marinopyrroles **1.3**, **1.4** and **1.5** were also determined by their mass spectral data and comparison of their NMR and circular dichroism (CD) spectra with those of **1.2**. The structure of marinopyrrole F (**1.6**) was determined by X-ray analysis.

With the exception of marinopyrrole F (**1.6**), the marinopyrroles were isolated as single atropo-enantiomers, suggesting that the pyrrole-pyrrole coupling is an enzyme-catalyzed process.[5,7] Along with the marinopyrroles, a structural subunit of marinopyrrole A, monodeoxypyoluteorin (**2.1**) was also isolated from cultivation of actinomycete strain CNQ-418. The presence of mono-deoxypyoluteorin (**2.1**) suggests a route for the biosynthesis of marinopyrrole A. Pyoluteorin (**2.2**) and the related pyrrolomycins are known to have antibacterial activity.[8]



monodeoxypyoluteorin (**2.1**) pyoluteorin (**2.2**) pyrrolomycin C (**2.3**)

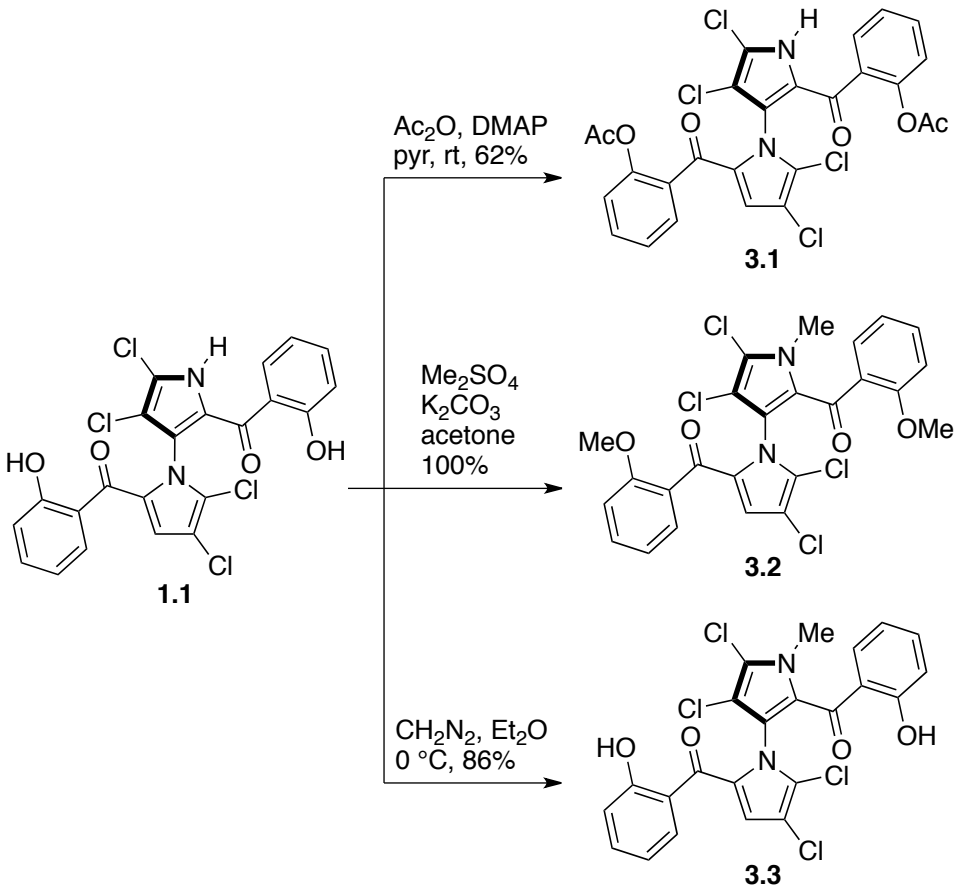
Scheme 2

Although marinopyrroles A−E (**1.1**−**1.5**) were obtained from actinomycete strain CNQ-418 as single atropo-enantiomers, racemization of the compounds occurs at elevated temperatures.[9] Both **1.1** and **1.2** can be racemized by heating them in PhMe at 120 °C for 20 h. Racemization of **1.3** needs a longer time and higher temperature (150 °C in $ClCH_2CH_2Cl$), and racemization **of 1.4** and **1.5** could not be accomplished even at 180 °C, due to the increase of the energy barrier to rotation along the C-N axis caused by halogens at C-11 and C-11'. Marinopyrrole F (**1.6**) was isolated as a racemate, presumably due to the significant decrease of the barrier for atropisomerism by the fused ether ring. To

confirm this explanation, a sample of enantioenriched **1.6**, collected using chiral HPLC, was stored in MeOH at room temperature; complete racemization was observed after 18 h.

1.3 Reactivity of the marinopyrroles

The marinopyrroles are the first reported natural products with a 1,3'-bipyrrole structure. This special subunit was assumed to probably have different reactivity from that of simpler pyrrole congeners,[6,7] and such turned out to be the case. In order to identify the reactivity patterns of the marinopyrroles, Fenical and



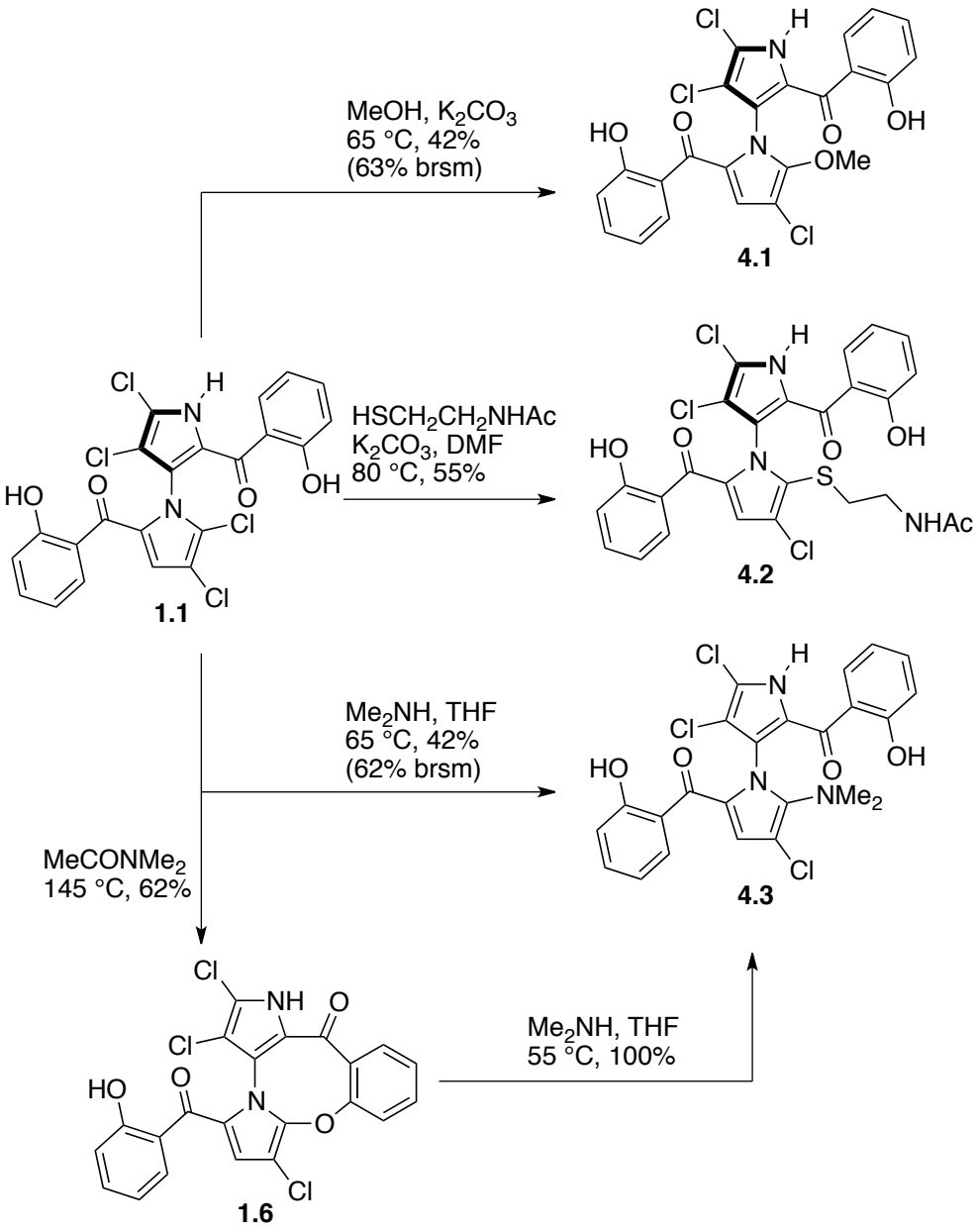
Scheme 3

coworkers carried out a number of simple reactions with marinoyrrole A, as summarized in Schemes 3−5.[7]

The phenolic hydroxyl groups of **1.1** were acetylated with Ac_2O to afford the diacetate **3.1**. With Me_2SO_4 and K_2CO_3, both phenolic hydroxyl groups and the pyrrole nitrogen were methylated (**3.2**). In the *N*-methylation with CH_2N_2 in Et_2O, only the pyrrole nitrogen reacted to give **3.3**; however, when MeOH was used as the solvent, the yield was lowered, possibly because intramolecular hydrogen bonding is disrupted by MeOH, making the phenolic hydroxyls more reactive.[7]

Because of the presence of the electron-withdrawing halogens, it was expected that the marinopyrroles would be electrophilic. Consequently, marinopyrrole A (**1.1**) was treated with several heteroatom-containing nucleophiles and the reaction results are shown in Scheme 4.[7] In all cases, the chlorine at C-5' was displaced by the nucleophile via an aromatic substitution reaction.[10]

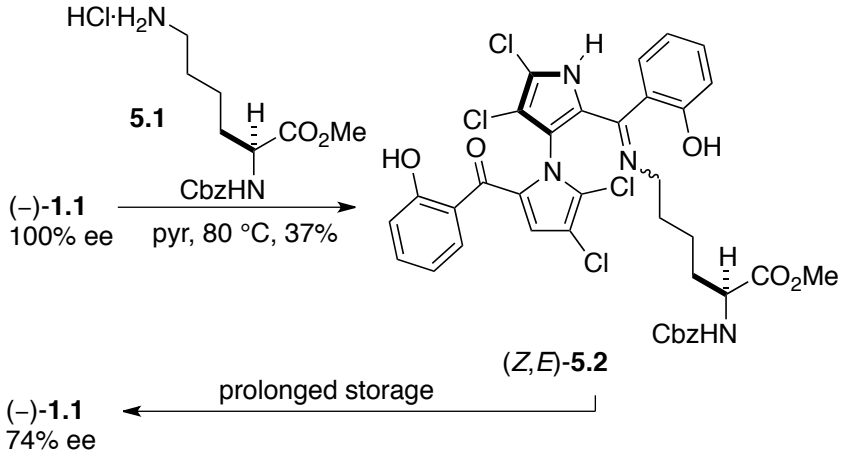
When **1.1** was heated at 145 °C in *N*,*N*-dimethylacetamide (DMA), **1.1** was converted into **1.6**, and treatment of **1.6** with Me_2NH gave compound **4.3** in quantitative yield. In contrast, monodeoxypyoluteorin and its derivatives do not undergo any nucleophilic aromatic substitution under similar conditions. Although these reactions occurred at temperatures below 100 °C, loss of optical purity was observed. Both **4.1** and **4.3** were obtained as racemates, and **4.2** was produced in 76% ee.



Scheme 4

Finally, **1.1** was treated with a primary amine **5.1** (a lysine derivative) at 80 °C in pyridine to generate the corresponding imine **5.2** as a mixture of two imine geometries. This result suggests that the mechanism by which marinopyrrole A (**1.1**) targets actin and results in its cytotoxicity in eukaryotic

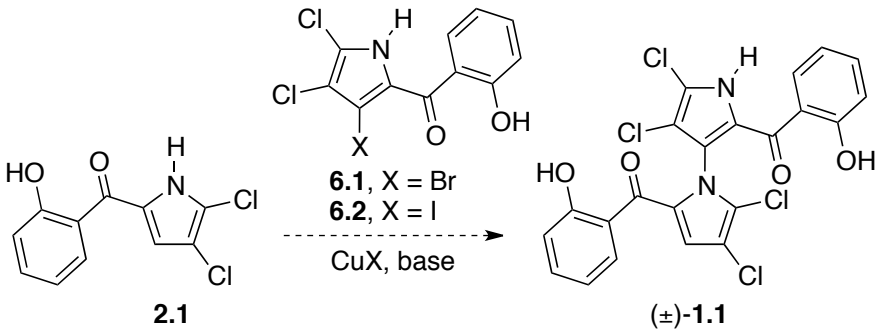
cells may involve imine formation.[11] During prolonged storage of imine **5.2**, marinopyrrole A (**1.1**) was obtained with degraded ee (74%).



Scheme 5

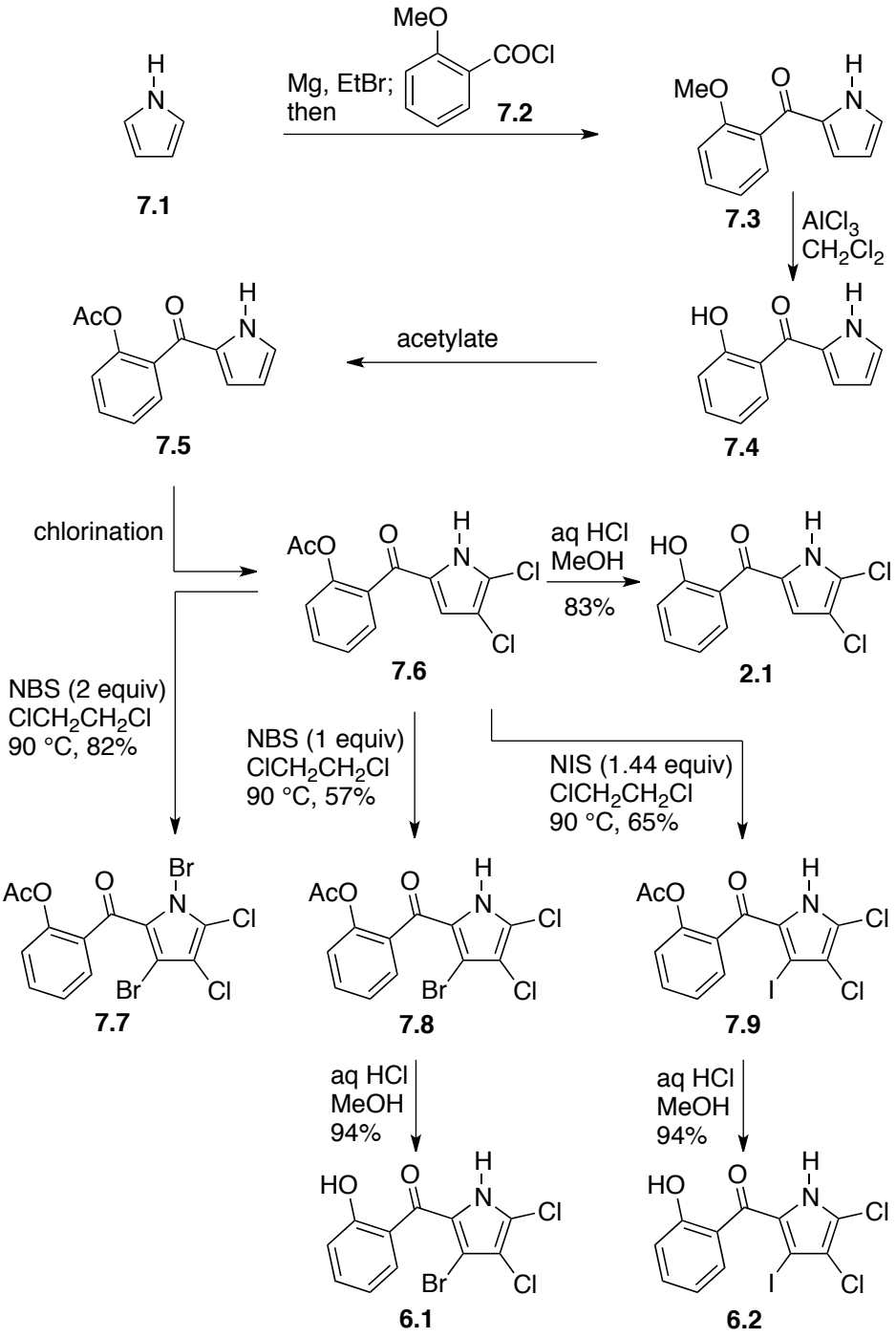
1.4 Early synthetic studies on the marinopyrroles by the Fenical group

A total synthesis of marinopyrrole A via Ullmann coupling was planned by Fenical and coworkers (Scheme 6).[7] Although Ullmann coupling has been used to prepare *N*-phenylazoles, the direct formation of *N*,*C*-linked bipyrroles via this coupling has not been reported.[12,13] The starting materials needed for the Ullmann coupling were prepared by the route shown in Scheme 7.



Scheme 6

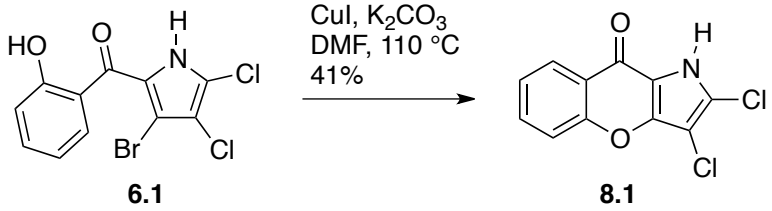
First, monodeoxypyoluteorin (**2.1**)[8g] was prepared, starting from pyrrole (**7.1)**, which was converted to compound **7.3** by acylation with 2-methoxybenzoyl chloride (**7.2**). Demethylation of **7.3** with $AlCl_3$, followed by acetylation and selective chlorination of the pyrrole, afforded *O*-acetyl monodeoxypyoluteorin (**7.6**). Finally, hydrolysis of acetate **7.6** under acidic conditions produced monodeoxypyoluteorin (**2.1**). Treatment of *O*-acetyl monodeoxypyoluteorin (**7.6**) with 1 equivalent of *N*-bromosuccinimide (NBS) gave **7.8** in 57% yield. However, when 2 equivalents of NBS were used, only the *N*-brominated compound **7.7** was obtained. Under acidic conditions, **7.8** was converted into the desired compound **6.1**. By using of *N*-iodosuccinimide (NIS) instead of NBS, compound **6.2** was generated in a similar way.



Scheme 7

Unfortunately, all attempts to couple 3-halopyrroles (**6.1**, **6.2**, **7.8** and **7.9**) with **2.1** or **7.6** via Ullmann reaction were unsuccessful. This might be due to

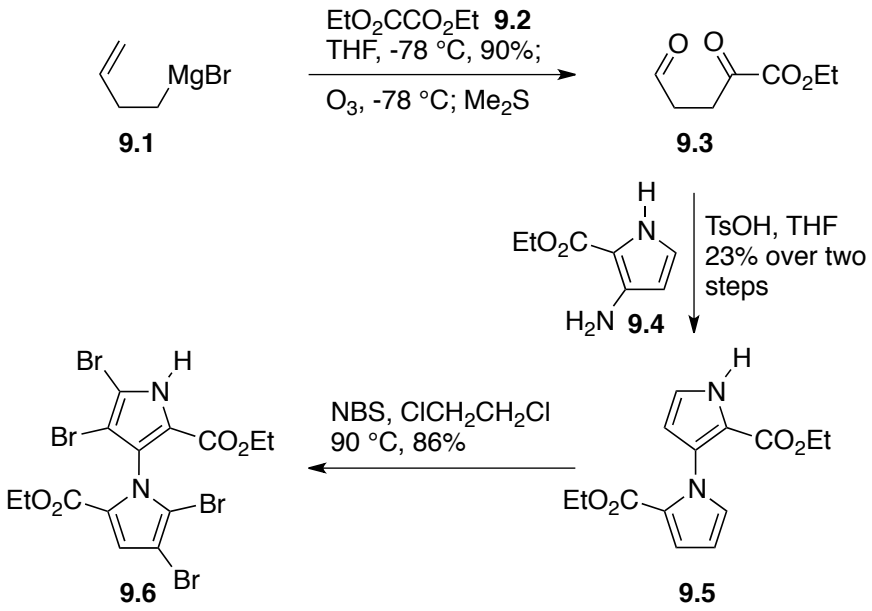
steric interactions between the four substituents *ortho* to the intended coupling site. Such steric effects had been reported in the literature and it is known that the difficulty of preparing substituted biaryl structures dramatically increases when two *ortho* substituents are present.[12a] Instead of intermolecular Ullmann coupling, the 3-halopyrroles could undergo an intramolecular coupling to form a 1*H*-chromeno[3,2-*b*]pyrrol-9-one (Scheme 8). Even **7.8** and **7.9** could form the chromene **8.1** after the acetyl group was removed under the coupling conditions.



6.1 **8.1**

Scheme 8

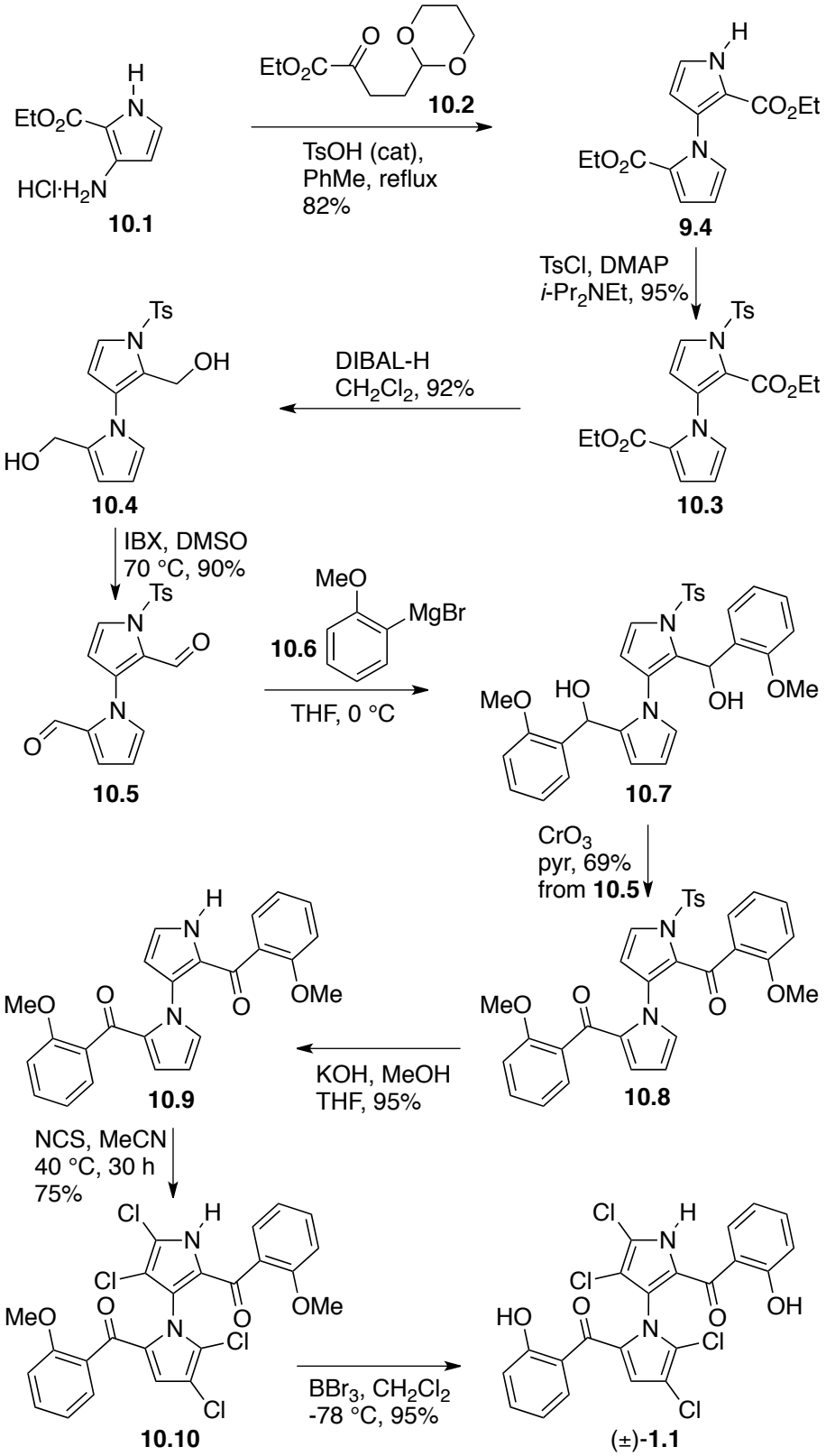
Although attempts to synthesize marinopyrrole A failed, Fenical and coworkers prepared the 1,3'-bipyrrole core of marinopyrroles via Paal-Knorr reaction (Scheme 9). Addition of Grignard reagent **9.1** to oxalate **9.2** at low temperature, followed by ozonolysis, gave the 1,4-dicarbonyl compound **9.3**. The Paal-Knorr reaction between **9.3** and **9.4**[14] formed the bipyrrole **9.5**. Tetrabromination of **9.5** with NBS produced the brominated bipyrrole **9.6**, while tetrachlorination of **9.5** with NCS was unsuccessful. The structure of **9.6** was confirmed by X-ray analysis.



Scheme 9

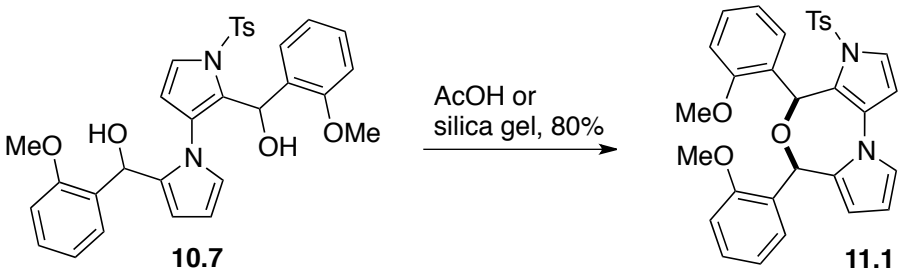
1.5 First total synthesis of (±)-Marinopyrrole A and its analogs

In early 2010, Li and coworkers reported the first total synthesis of racemic marinopyrrole A (**1.1**).[1] The 1,3'-bipyrrole **9.4** was first prepared via Paal-Knorr reaction between **10.1** and **10.2**. The nitrogen of the upper pyrrole unit in **9.4** was then protected by reaction with TsCl to afford **10.3**, which was reduced by DIBAL-H. Oxidation with IBX in DMSO, gave the dialdehyde **10.5** in good yield. Addition of Grignard reagent **10.6** to the dialdehyde provided the diol **10.7**, which could not be purified by flash chromatography due to its sensitivity to acid. When the diol **10.7** was exposed to the action of AcOH or silica gel, it was converted efficiently into the cyclic ether **11.1** (Scheme 11), whose structure was established by X-ray analysis. Therefore, the crude diol was directly oxidized by CrO_3 in pyridine to produce the diketone **10.8** in 69% yield over two steps . A small amount (10%) of cyclic ether **11.1** was formed as the


10.1
10.2
TsOH (cat),
PhMe, reflux
82%
9.4
TsCl, DMAP
i-Pr2NEt, 95%
10.3
DIBAL-H
CH2Cl2, 92%
10.4
IBX, DMSO
70 °C, 90%
10.5
10.6
THF, 0 °C
10.7
CrO3
pyr, 69%
from 10.5
10.8
KOH, MeOH
THF, 95%
10.9
NCS, MeCN
40 °C, 30 h
75%
10.10
BBr3, CH2Cl2
-78 °C, 95%
(±)-1.1

Scheme 10

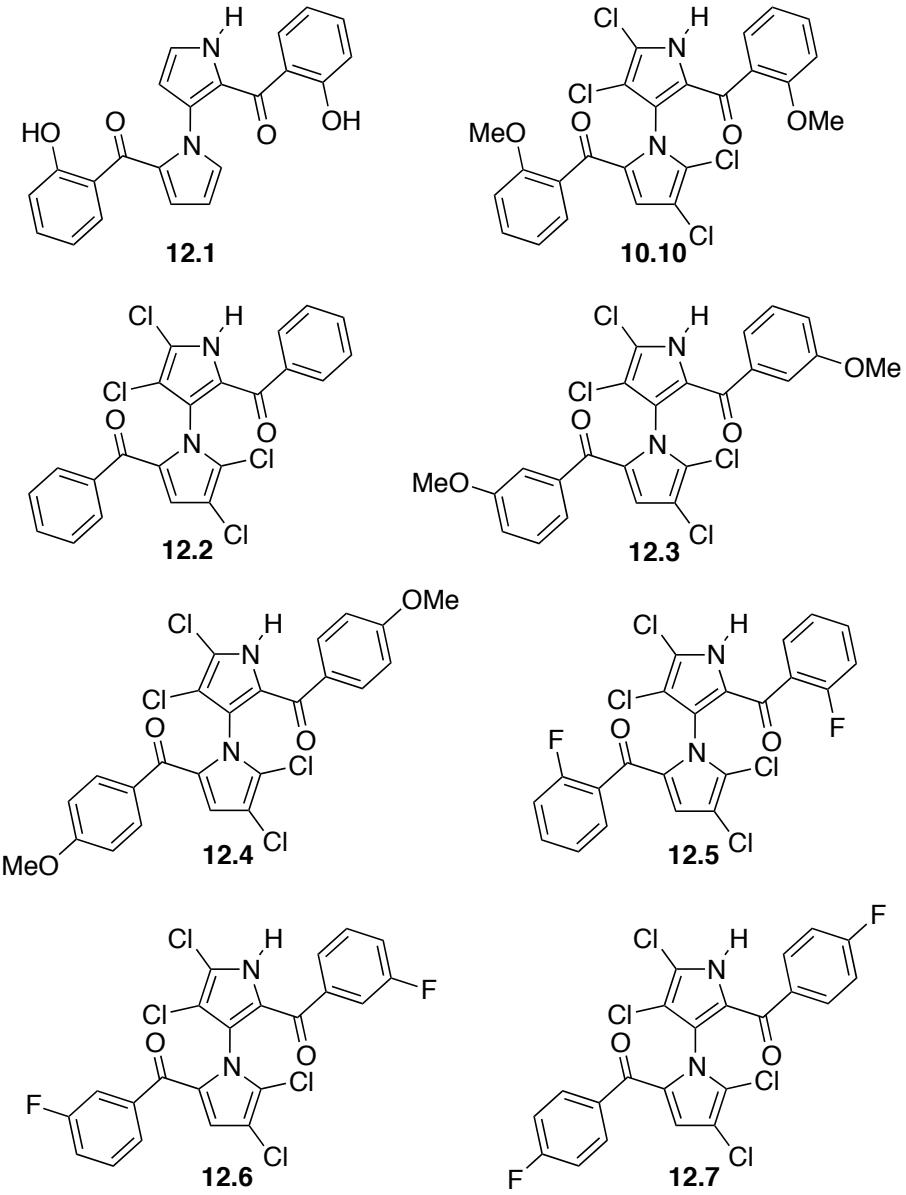
byproduct. Removal of the tosyl group under basic conditions gave **10.9**, which reacted with NCS to afford the tetrachlorinated bipyrrole **10.10**. Finally, demethylation of **10.10** with BBr_3 produced racemic marinopyrrole A (**1.1**) in excellent yield. Attempts to make marinopyrrole B from marinopyrrole A by reaction with NBS were unsuccessful, probably due to the electron-deficient properties of the lower pyrrole ring carrying three electron-withdrawing groups. This total synthesis of racemic marinopyrrole A was accomplished in 9 steps with an overall yield of 30%.



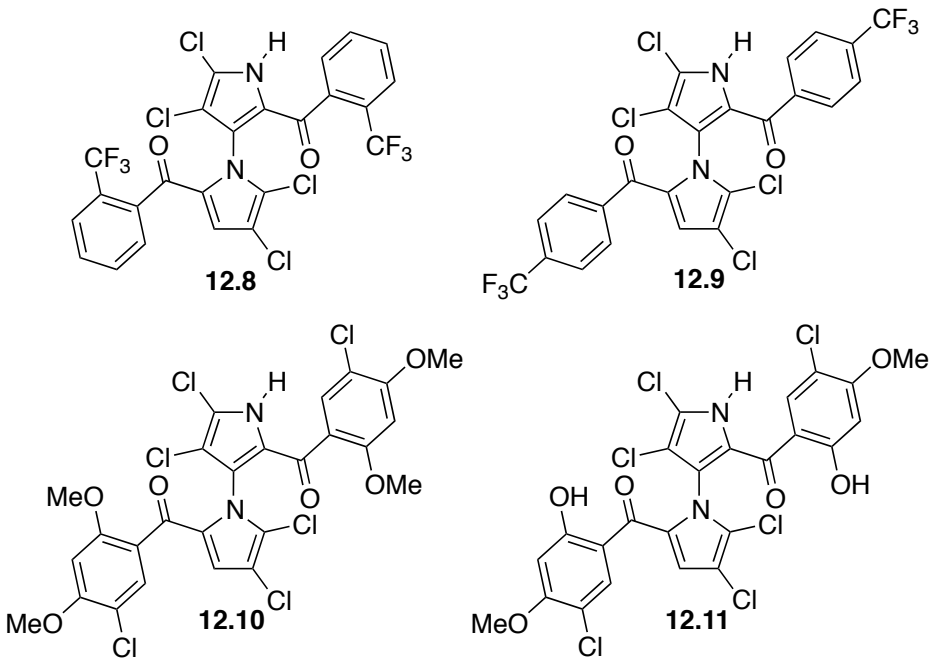
Scheme 11

The dialdehyde **10.5** was a key intermediate in the synthesis of analogs (Scheme 12) of marinopyrrole A.[1] Addition of appropriate Grignard reagents or organolithium reagents gave the corresponding alcohols, which were oxidized (CrO_3, pyridine), and then the tosyl group was removed. Chlorination with NCS afforded the analogs as racemates. Demethylation of **10.9** gave the non-halogenated analog (**12.1**) of marinopyrrole A. The additional chlorines on the benzene rings of **12.10** and **12.11** are the result of unintentional halogenation

during halogenation of the pyrrole rings. Phenol **12.11** was made by selective demethylation of **12.10** with BBr_3 in CH_2Cl_2.



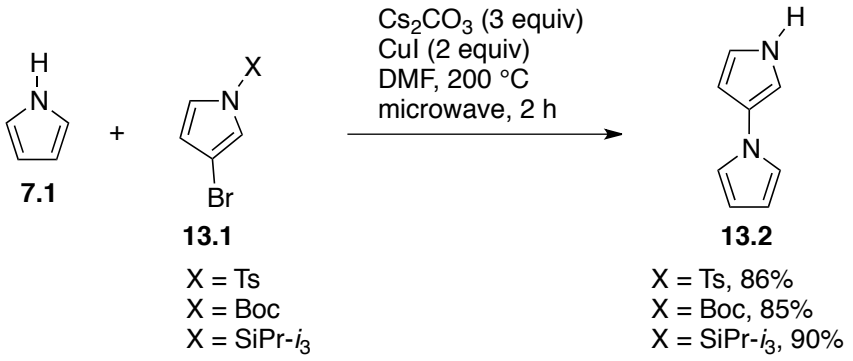
Scheme 12



Scheme 12 (continued)

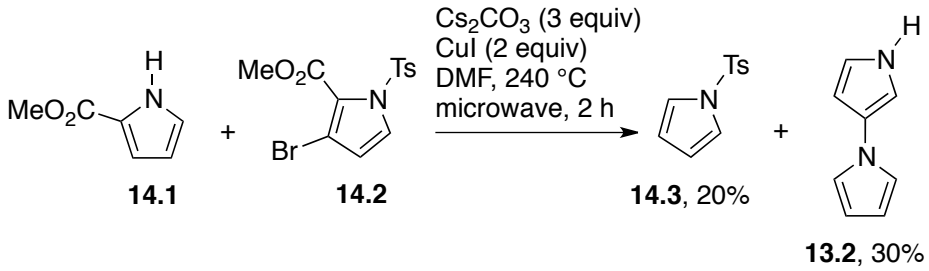
1.6 Second total synthesis of (±)-Marinopyrrole A

In late 2010, Sarli and coworker reported the second total synthesis of racemic marinopyrrole A.[15] Inspired by the assumption that the biosynthesis of the marinopyrroles probably involves an enzyme-mediated pyrrole-pyrrole coupling,[5] they planned to make the 1,3'-bipyrrole core via an Ullmann coupling reaction. In order to establish if a 1,3'-bipyrrole could be made by Ullman reaction, coupling of pyrrole (**7.1**) with *N*-protected 3-bromopyrrole **13.1** (X = Ts) was first examined. The desired coupling was observed to be accompanied by loss of the tosyl group under the optimized conditions (Scheme 13). Two other *N*-protecting groups (X = Boc and SiPr-i_3 in **13.1**) were also tested, and similar results were obtained.



Scheme 13

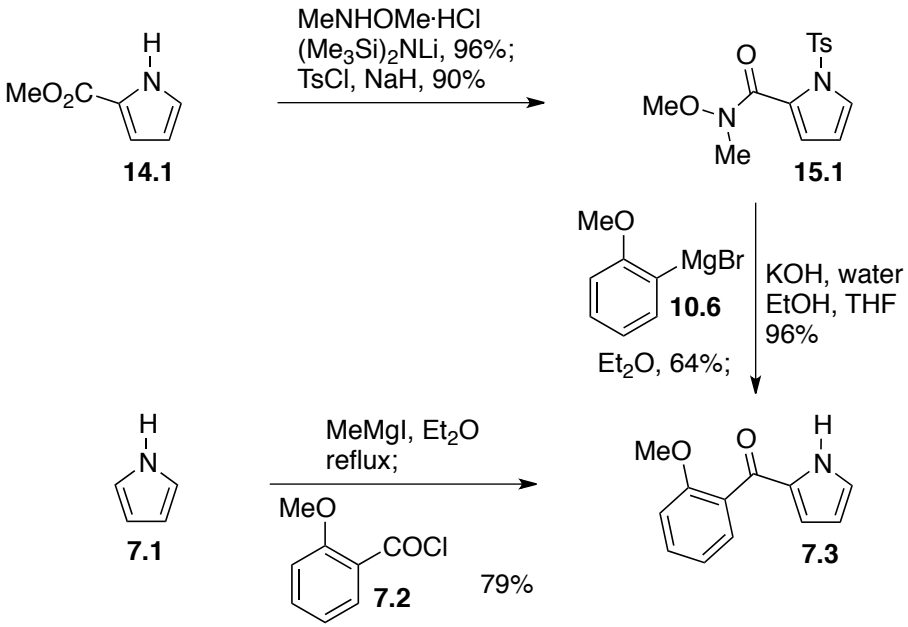
When pyrrole esters **14.1** and **14.2** were subjected to the optimized coupling conditions, a higher temperature was required (240 °C), and ester hydrolysis, decarboxylation and loss of the nitrogen protecting group occurred at the same time (Scheme 14). When **13.1** (X = Ts) instead of **14.2** was used in this reaction, the bipyrrole **13.2** was also produced.



Scheme 14

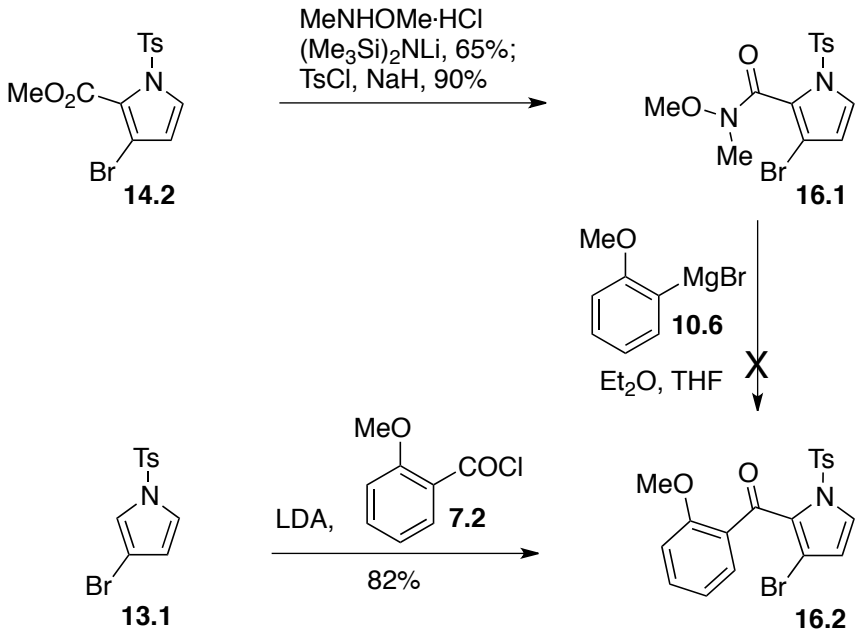
With the Ullmann conditions established, a substrate with an *ortho*-methoxyaryl group (**7.3**) was then prepared (Scheme 15). Pyrrole ester **14.1** was converted into the corresponding Weinreb amide, and the NH group of the pyrrole was protected by tosylation to give sulfonamide **15.1**. Treatment of **15.1** with

Grignard reagent **10.6**, followed by removal of the tosyl group, generated dechloropyoluteorin (**7.3**). Alternatively, **7.3** could be prepared by acylation of pyrrole (**7.1**) with 2-methoxybenzoyl chloride (**7.2**).



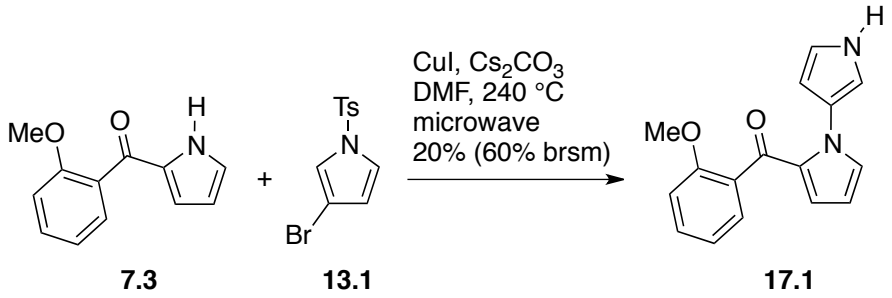
Scheme 15

Attempts to make compound **16.2** via the Weinreb amide route, using **14.2** as the starting material, was unsuccessful (Scheme 16). Fortunately, acylation of the *N*-protected pyrrole **13.1** (X = Ts) with 2-methoxybenzoyl chloride (**7.2**) gave **16.2** in 82% yield.



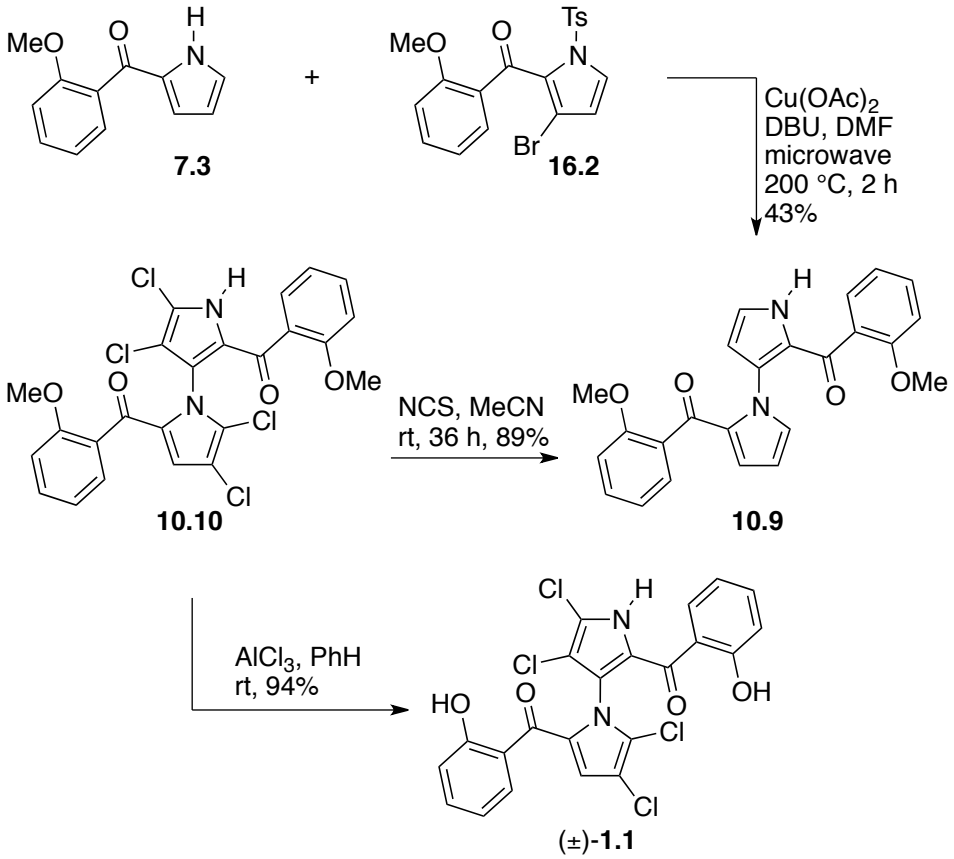
Scheme 16

Compound **7.3** was then subjected to Ullmann reaction with **13.1** (X = Ts) and the desired tosyl-bipyrrole **17.1** was obtained in 20% yield (60% based on recovered **7.3**). When coupling of **7.3** and **16.2** was examined under the previously optimized conditions, the desired bipyrrole **10.9** was produced in 24% yield. To improve the yield, the coupling was tested using different solvents, bases, catalysts, reaction temperatures and times, and it was found that the desired 1,3'-bipyrrole **10.9** could be isolated in 43% yield by using $Cu(OAc)_2$ and DBU in DMF. The resulting bipyrrole **10.9** was then chlorinated with NCS, and then demethylation with $AlCl_3$, afforded racemic marinopyrrole A. This total synthesis was accomplished in 6 steps and 22% overall yield.



7.3 **13.1** **17.1**

Scheme 17

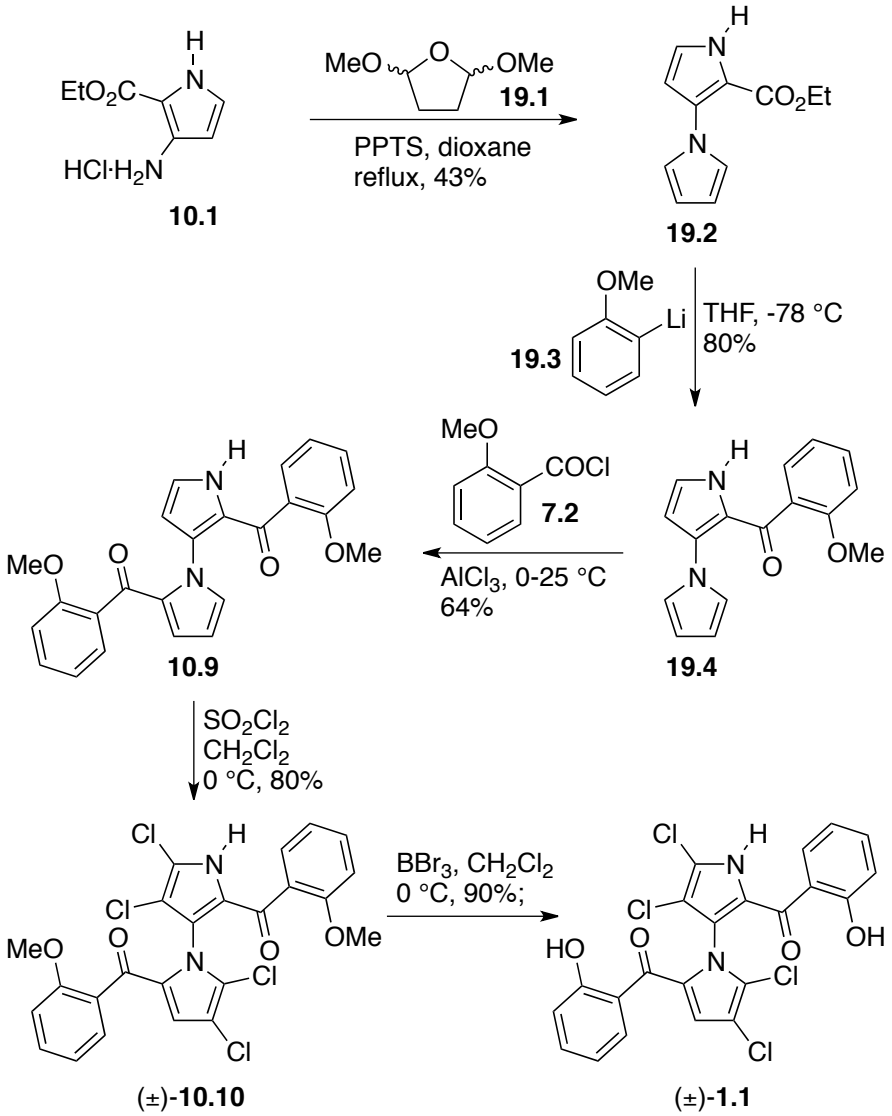


7.3 **16.2** **10.10** **10.9** (±)-**1.1**

Scheme 18

1.7 Third total synthesis of (±)-Marinopyrrole A and analogs

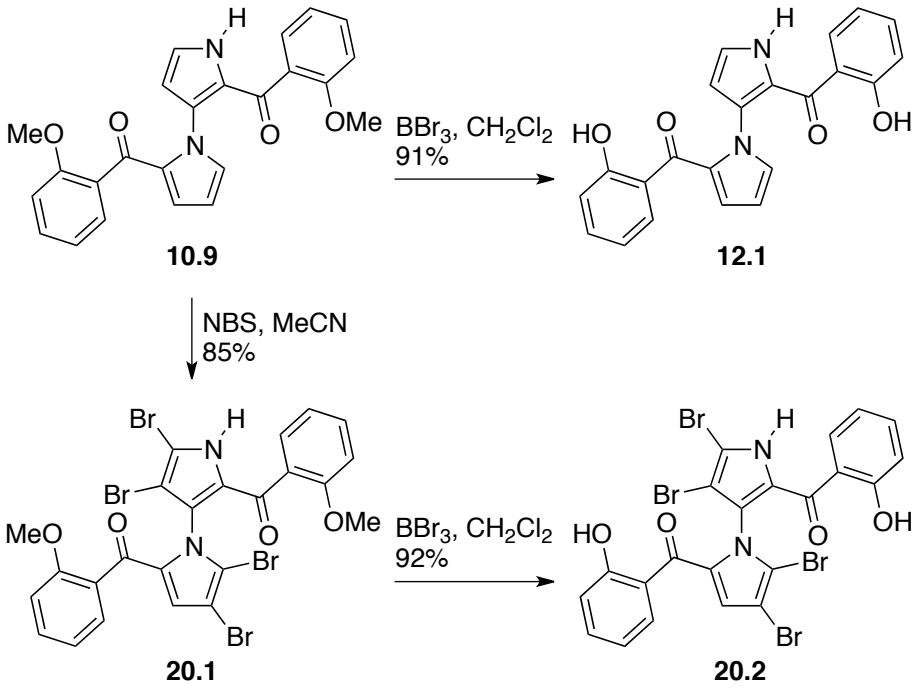
In 2011, Nicolaou and coworkers reported the third total synthesis of racemic marinopyrrole A.[16] Aminopyrrole hydrochloride **10.1** was used as the starting material and subjected to a Clauson-Kaas condensation with 2,5-dimethoxytetrahydrofuran **19.1** to afford the bipyrrole **19.2** in moderate yield. Monoaddition of *o*-methoxyphenyllithium (**19.3**) to **19.2** served to install the first



Scheme 19

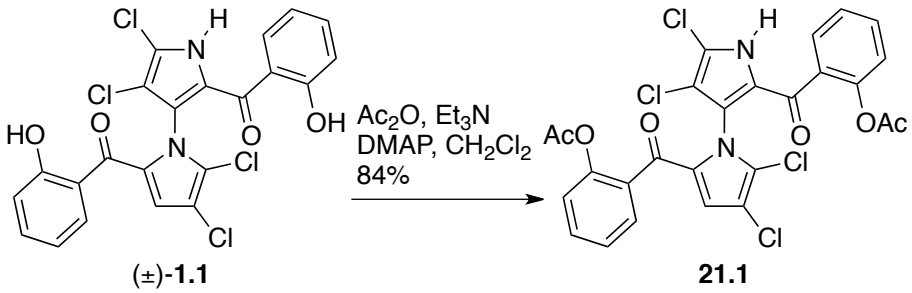
methoxyphenyl group, and Friedel-Crafts arylation with acid chloride **7.2** introduced the second methoxyphenyl group and gave 1,3'-bipyrrole **10.9** in 64% yield. Chlorination with SO_2Cl_2 and demethylation with BBr_3 produced racemic marinopyrrole A, which was resolved by chiral HPLC. The racemic marinopyrrole A was prepared in 5 steps and 16% overall yield from **10.1**.

Several analogs were also prepared by Nicolaou and coworkers.[16] Demethylation of compound **10.9** generated the the non-halogenated analog **12.1** which was previously prepared by Li's group. Tetrabromination of **10.9** with NBS, followed by demethylation with BBr_3, gave tetrabromomarinopyrrole **20.2**.



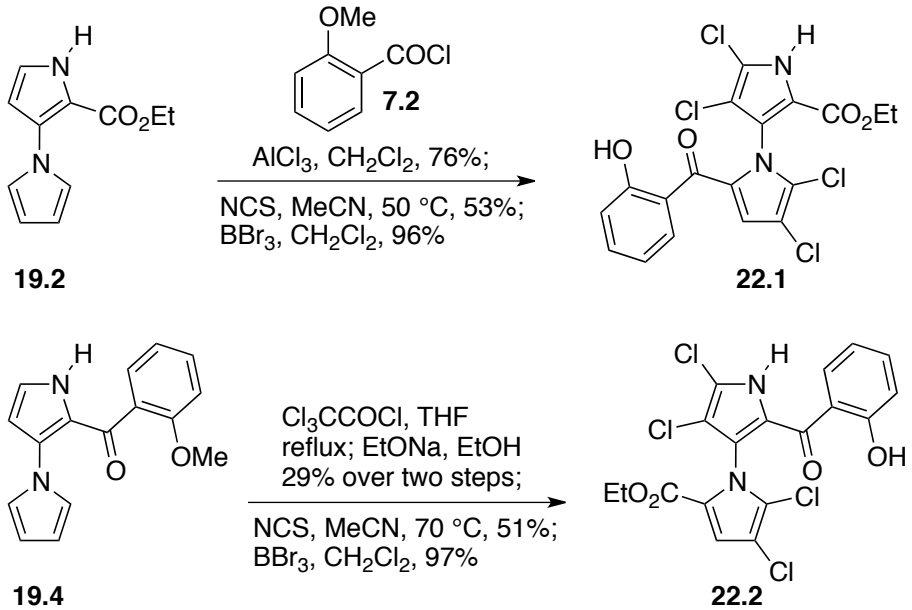
Scheme 20

Acetylation of the phenolic hydroxyl group of marinopyrrole A with acetic anhydride, Et_3N and catalytic DMAP furnished the diacetate **21.1** in good yield (Scheme 21).



Scheme 21

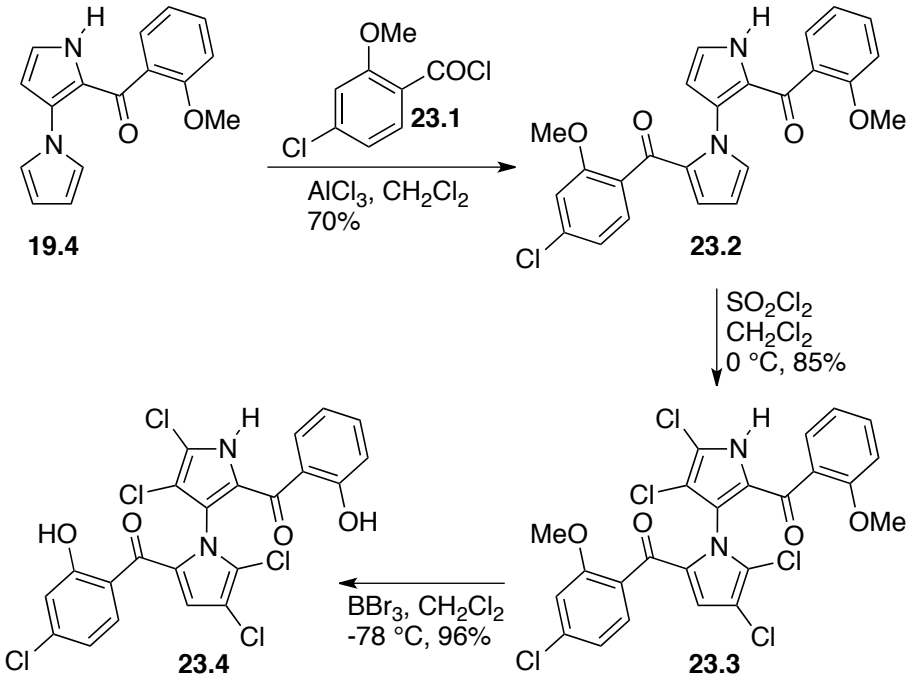
The bipyrrole **19.2** was subjected to Friedel-Crafts acylation (Scheme 22), followed by chlorination and demethylation, to give analog **22.1**. Similarly, compound **22.2** was prepared from **19.4** in 14% yield over 4 steps (Scheme 22).



Scheme 22

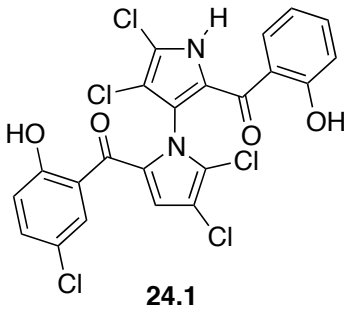
1.8 Synthesis of asymmetrical marinopyrrole analogs by the Li group

In 2012, Li and coworkers synthesized some asymmetrical marinopyrrole analogs.[17] Compound **19.4**, first prepared by the Nicolaou group, was treated with acid chloride **23.1** and $AlCl_3$ to give marinopyrrole precursor **23.2** in 70% yield. Tetrachlorination of **23.2** with SO_2Cl_2 formed **23.3** in 85% yield, which was then treated with BBr_3 to afford the asymmetrical marinopyrrole analog **23.4** in 96% yield.

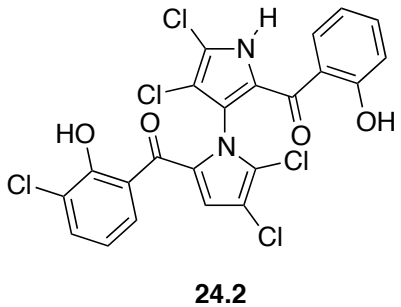


Scheme 23

Using suitable acid chlorides instead of **23.1**, and following the above synthetic route, the asymmetrical marinopyrrole analogs **24.1** and **24.2** were synthesized in 48% and 46% yield over 3 steps, respectively.



24.1



24.2

Scheme 24

1.9 Biological activity and mode of action of the marinopyrroles

The antibiotic activity of the marinopyrroles (Table 1), especially against methicillin-resistant *Staphylococcus aureus* (MRSA),[18] is an important property because the development of antibiotic resistance has generated a pressing need for new antibiotics.[4,17,19] Against methicillin-resistant *Staphylococcus aureus* (MRSA), the natural marinopyrroles A−C (**1.1**, **1.2** and **1.3**) showed minimum inhibitory concentrations (MIC_{90}) of less than 1 μg/mL.[5,7] Marinopyrrole F (**1.6**) and derivatives **4.2** and **4.3** were much less active against MRSA, showing that the C-5' chlorine substituent may play an important role in the mechanism of antibiotic action. The data for derivatives **3.1**, **3.2** and **3.3** (see Scheme 3) showed that replacement of the acidic hydrogens O**H** or N**H** resulted in reduced antimicrobial activity, suggesting the importance of hydrogen bonding in the mechanism of action. The fact that the methoxy compound **4.1** retains activity might indicate that the methoxy group can be displaced *in vivo*. Many of the MRSA-active marinopyrroles and derivatives also showed significant cytotoxicity against a human colon cancer cell line, HCT-116.[5,7] The results in Table 1 also

showed that both the natural marinopyrrole A [(–)-**1.1**] and the enantiomeric unnatural marinopyrrole A have similar activity.

The therapeutic window for the marinopyrroles (the IC_{50} values are not sufficiently greater than the MIC_{90} values, see Table 1) may be too narrow for treatment of bacterial infections in humans, but their use in cancer chemotherapy remains to be explored.[7]

Table 1. Biological activity of marinopyrroles and analogs[5,7]

Compound	MRSA[a] (MIC_{90}[b])	HCT-116[c] (IC_{50}[b])
(–)-**1.1 (marinopyrrole A)**	0.31	4.5
(+)-**1.1 (marinopyrrole A)**	0.16	4.8
(–)-**1.2 (marinopyrrole B)**	0.63	5.3
(–)-**1.3 (marinopyrrole C)**	0.16	0.21
(±)-**1.6 (marinopyrrole F)**	3.1	2.9
3.1	1.6	4.2
3.2	NSA	NSA
3.3	NSA	NSA
4.1 (racemic)	0.78	1.1
4.2 (76% ee)	6.3	7.2
4.3 (racemic)	1.6	4.4

[a]MRSA = methicillin-resistant *Staph. aureus*. [b]Units: μg/mL. Positive control: vancomycin (MIC_{90} = 0.20−0.39 μg/mL) and penicillin G (MIC_{90} = 6.3−12 μg/mL). [c]HTC-116 is a human colon cancer cell line. Positive control: etoposide (IC_{50} = 0.29−2.9 μg/mL). NSA = no significant activity (>8 μg/mL).

Nicolaou and coworkers tested the antibacterial activities of marinopyrrole A and analogs against TCH-1516, a strain representative of the current epidemic

clone of community-acquired MRSA.[19b] The results are shown in Table 2.[16]

Table 2. Biological activity of marinopyrrole A and analogs[16]

Compound	**Activity against MRSA TCH-1516**, MIC_{50} μg/mL
(±)-**1.1**	0.375-0.750
(+)-**1.1**	0.189
(–)-**1.1**	0.189
10.9 (racemic)	>96
10.10 (racemic)	>96
12.1 (racemic)	48
20.1 (racemic)	>96
20.2 (racemic)	0.75
21.1 (racemic)	0.375
22.1 (racemic)	3
22.2 (racemic)	1.5

As indicated in Table 2, (+)-**1.1** had the same activity as (–)-**1.1** (the natural configuration) against MRSA TCH-1516, and the synthetic racemic marinopyrrole A also exhibited high antibacterial activity. The tetrabrominated analog **20.2** had comparable activity to racemic marinopyrrole A, while the dehalogenated analog **12.1** was much less active, indicating the importance of halogens for antibacterial activity. Dimethylated marinopyrrole analogs **10.9**, **10.10** and **20.1** showed no activity, indicating that the free phenolic groups were necessary for activity. The less active analogs **22.1** and **22.2**, which only have one phenolic group, also showed the importance of phenolic groups. The tetrachlorinated bis-acetate **21.1** exhibited similar activities to racemic

marinopyrrole A, probably due to in situ hydrolysis within the cell. When these compounds were tested in the presence of 20% normal pooled human serum, the antibacterial activity was lost, presumably due to protein adsorption.

A recent detailed report[19b] indicated that marinopyrrole A was active against a wide range of MRSA strains (12 were tested) as well as against other Gram-positive organisms. The MIC values (0.188−1.5 μg/mL) were generally lower than for vancomycin (1−8 μg/mL) and linezolid (3 μg/mL). Marinopyrrole A was active against *H. influenzae* but inactive against the two other Gram-negative strains that were tested (*P. aeruginosa* and *E. coli*).[19b]

In the presence of human serum activity was lost, suggesting that marinopyrroles may be effective in vivo only for topical application and prodrug-like compounds may be needed for systemic applications.[16,19b] However, it may be possible to overcome the effect of serum by appropriate modification of the marinopyrrole structure and encouraging progress in this direction had already been made:[17] Analogs **23.4**, **24.1** and **24.2** were tested in this connection (Table 3).

Table 3. MIC (μM) of marinopyrrole derivatives against MRSA[17]

Compound	Todd-Hewitt broth	Todd-Hewitt broth + 20% serum
marinopyrrole A	0.74	94-188
23.3	>200	>200
23.4	0.19−0.39	12.5−25
24.1	1.56	>200
24.2	3.13	>200

The data in Table 3 show that not only is **23.4** more potent than marinopyrrole A but it is also much less sensitive to inactivation by human serum. Possibly, this results from the effect on the pK_a of the phenolic hydroxyl by the extra chlorine substituent.

A conclusion to be drawn from the preliminary publications[5,7] is that the marinopyrroles may contain a previously unknown pharmacophore of possible use in the design of new antibiotics.

One of the biological targets of marinopyrrole A was identified as actin in HCT-116 cancer cells by the method of acyl dye transfer.[11] In this approach a dye was attached to a natural product which then binds to the target protein and transfers the dye to the protein, releasing the natural product and leaving the protein labeled at the site of binding. This technique was applied[11] to marinopyrroles A and B (only data for marinopyrrole A was reported) for several reasons: they are available in mg/L quantities; they have an unknown mode of action; they are active in tumor cell lines (GI_{50} = 10 mM in HCT-116 cells, and 620 nM for marinopyrrole A; and 500 nM for marinopyrrole B in A549 breast cancer cells); they undergo acetylation without loss of activity (GI_{50} = 0.8 mM for *O*,*O*'-bis-acetyl marinopyrrole A in HCT-116 cells — an approximately 12-fold increase over that observed with marinopyrrole A or B). Application of the acyl dye transfer method allowed lysine-115 in actin to be identified as the likely target of marinopyrrole A.[11]

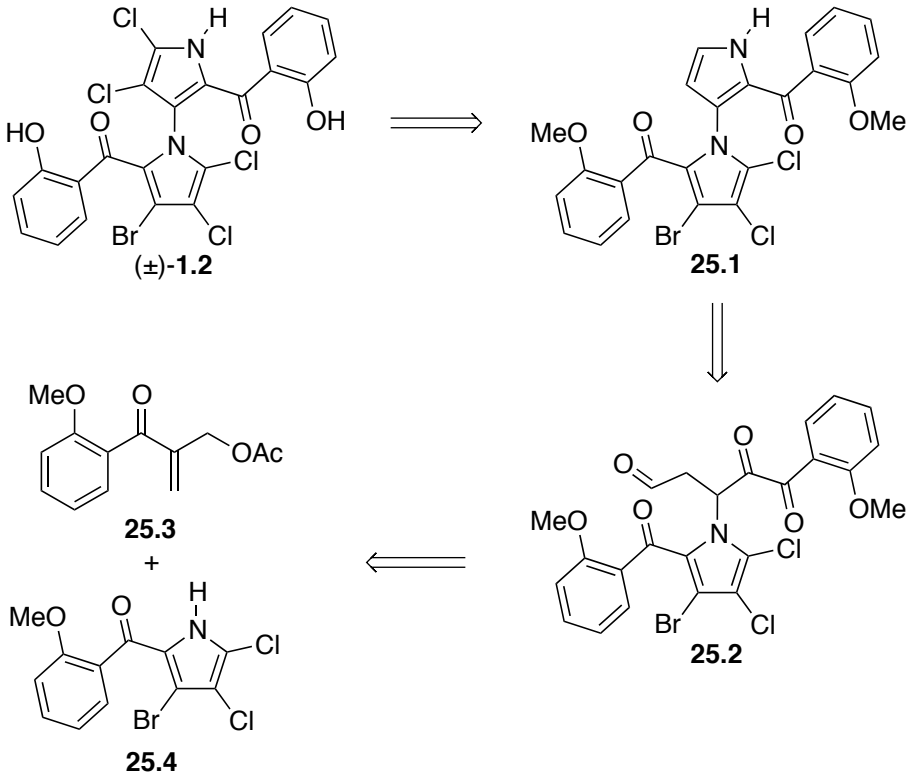
2. Results and Discussion

2.1 Research objective

Marinopyrroles A and B are two marine antibiotic natural products which are highly halogenated bispyrroles and show high activity against MRSA. Given the significance of the marinopyrroles as potential drug candidates, marinopyrrole A has been synthesized by several groups. However, all attempts to make marinopyrrole B were unsuccessful. Consequently, the main goal of this project was the synthesis of marinopyrrole B.

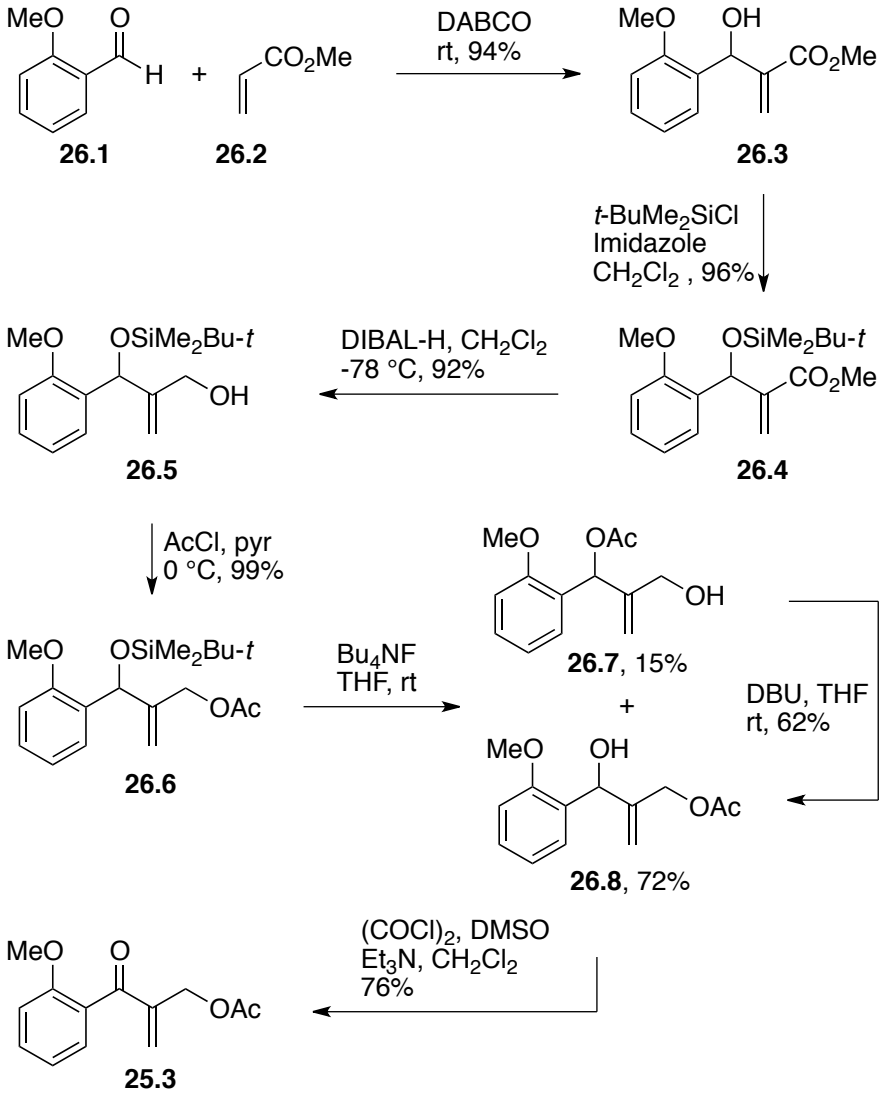
2.2 Synthetic studies on marinopyrrole B

Attempts by others to prepare marinopyrrole B by bromination of marinopyrrole A were unsuccessful.[1] This observation and prior experiments in this laboratory suggested that introducing bromine at the C-3' position at an early stage would be a promising approach. A retrosynthetic proposal was then developed along the following lines (Scheme 25): Compound **25.1** was chosen as a key intermediate which already has the bromine at C-3' and should be easily converted into marinopyrrole B via chlorination and demethylation reactions. Unlike other approaches, I decided to construct the second pyrrole ring onto the brominated first pyrrole via a Paal-Knorr reaction, which would require the keto aldehyde **25.2**. This keto aldehyde **25.2** should be available using an intermolecular conjugate displacement between **25.3** and **25.4**, followed by several standard functionality transformations.



Scheme 25

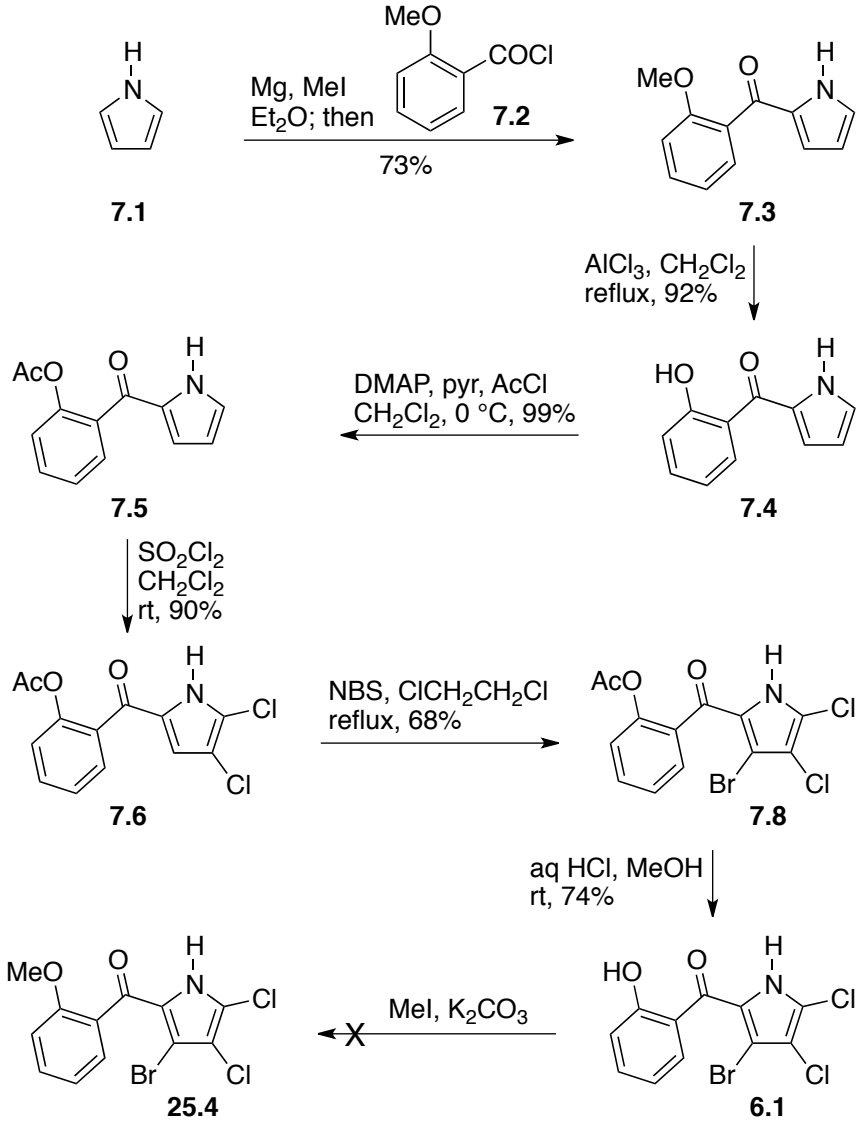
Compound **25.3** was prepared (Scheme 26) from *o*-anisaldehyde (**26.1**), which was converted into **26.3**[20] by Baylis-Hillman reaction with methyl acrylate (**26.2**). Protection of the hydroxyl group of **26.3** by reaction with *t*-$BuMe_2SiCl$, followed by reduction, gave alcohol **26.5**. Acetylation of **26.5** generated compound **26.6**, which was then treated with Bu_4NF to produce compounds **26.7** and **26.8** in 15% and 72% yield, respectively. By exposure to DBU, **26.7** could be converted into the desired compound **26.8** in 62% yield. When **26.8** was subjected to Swern oxidation, the desired allylic acetate **25.3** was obtained in good yield.



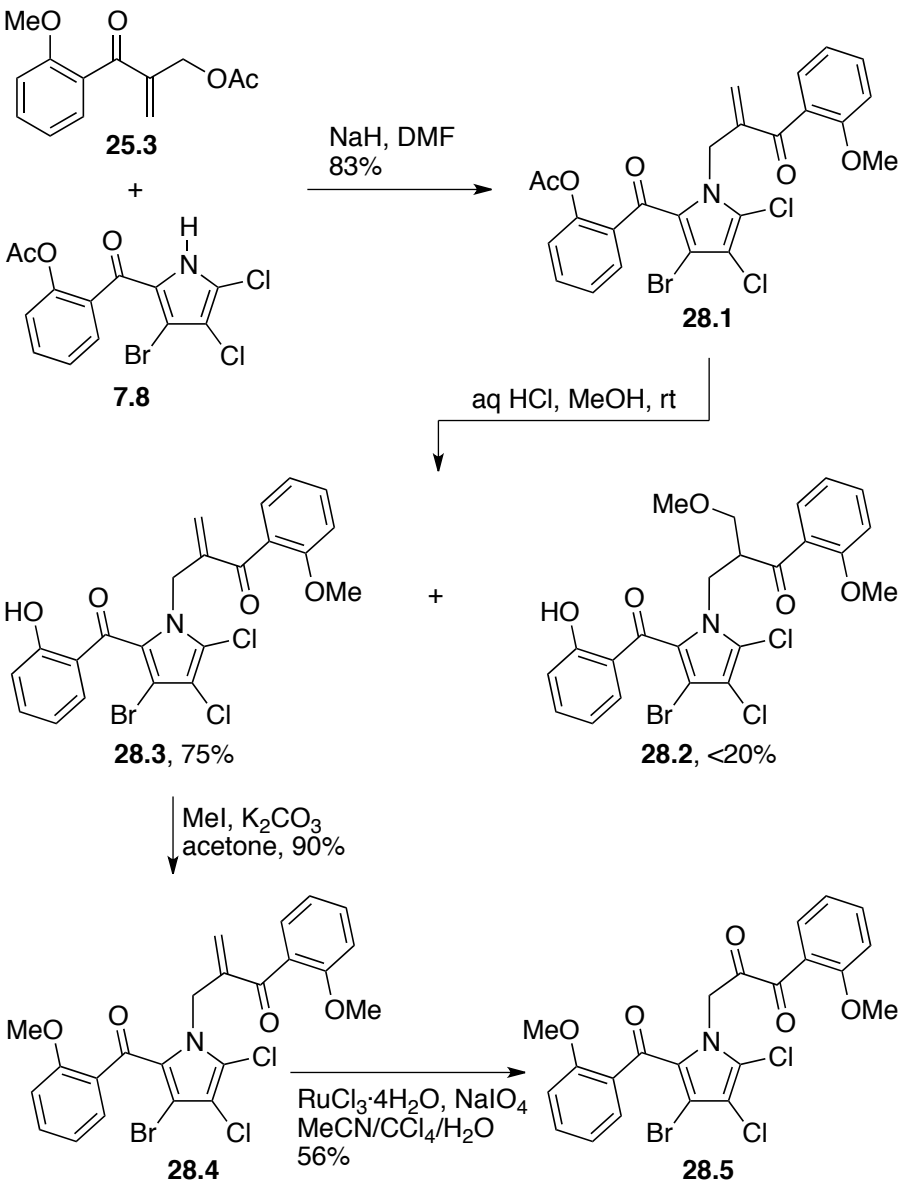
Scheme 26

The lower pyrrole subunit was synthesized by the route developed by the Fenical group (Scheme 27):[7] Friedel-Crafts acylation of pyrrole (**7.1**) with 2-methoxybenzoyl chloride (**7.2**) produced **7.3** in good yield.[15] An attempt to chlorinate **7.3** with NCS was unsuccessful, and only starting material was recovered. Consequently, the route was modified slightly. Demethylation of **7.3** furnished phenol **7.4**, which was acetylated to give pyrrole **7.5** in excellent yield.

Now, selective chlorination with SO_2Cl_2 and bromination with NBS afforded the desired halogenated pyrrole **7.8**, which was hydrolyzed under acidic conditions to give compound **6.1**. However, an attempt to make compound **25.4** was unsuccessful.



Scheme 27



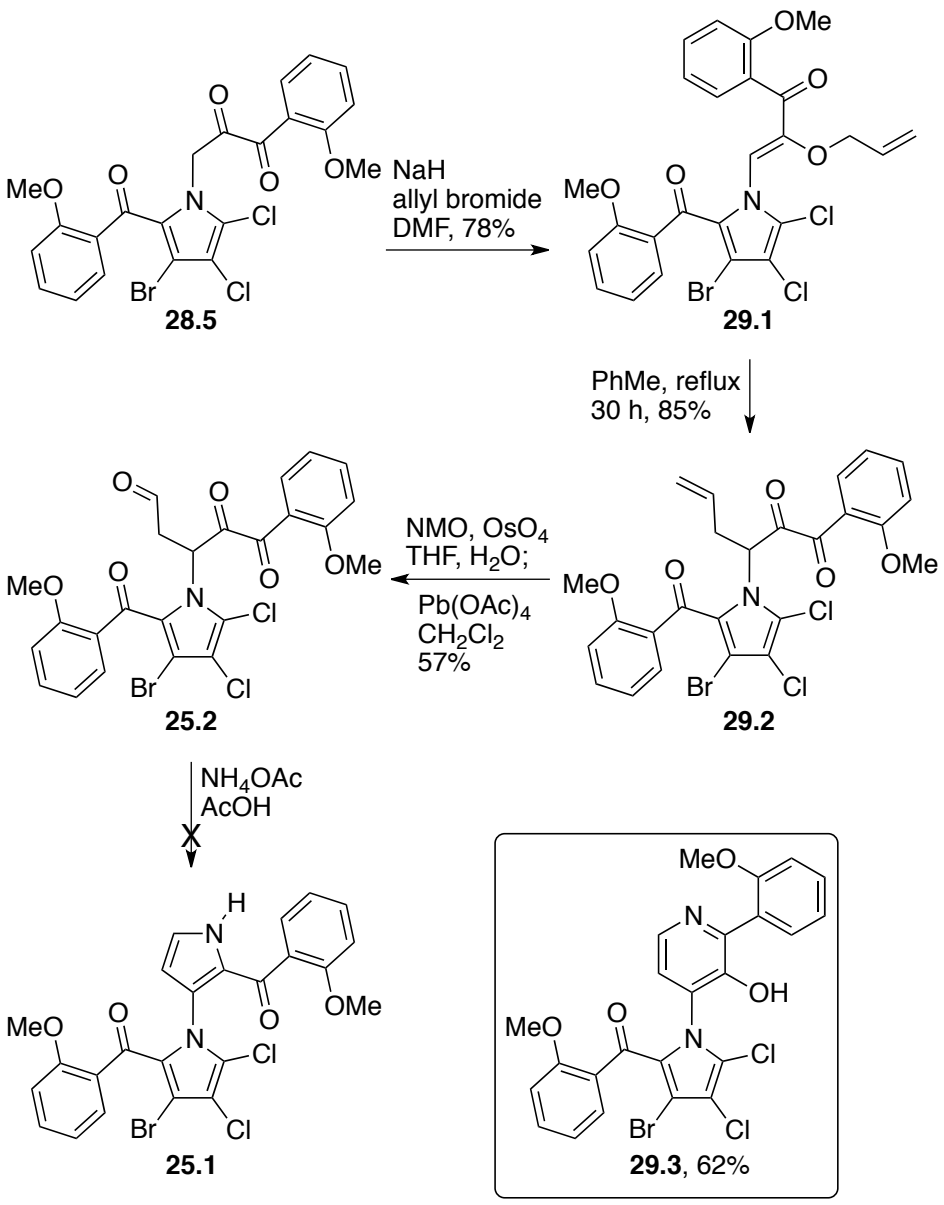
Scheme 28

Fortunately, it was found that the reaction between allylic acetate **25.3** and acetate **7.8** in the presence of NaH provided the desired intermolecular conjugate displacement adduct **28.1** in 83% yield. This process takes advantage of the fact that Michael acceptors carrying an allylic leaving group (these acceptors are usually derivatives of Baylis-Hillman alcohols), such as **25.3**, show enhanced

reactivity compared to related acceptors that lack the leaving group,[21,22] and so reaction stops after a single addition.

Hydrolysis of **28.1** under acidic conditions gave the desired phenol **28.3** as the major product and a byproduct **28.2** as the minor component.[7] Treatment of **28.3** with MeI and K_2CO_3 generated the phenolic methyl ether **28.4** in 90% yield. Finally, cleavage of the double bond with $RuCl_3$ and $NaIO_4$ produced the expected ketone **28.5** in 56% yield.[23]

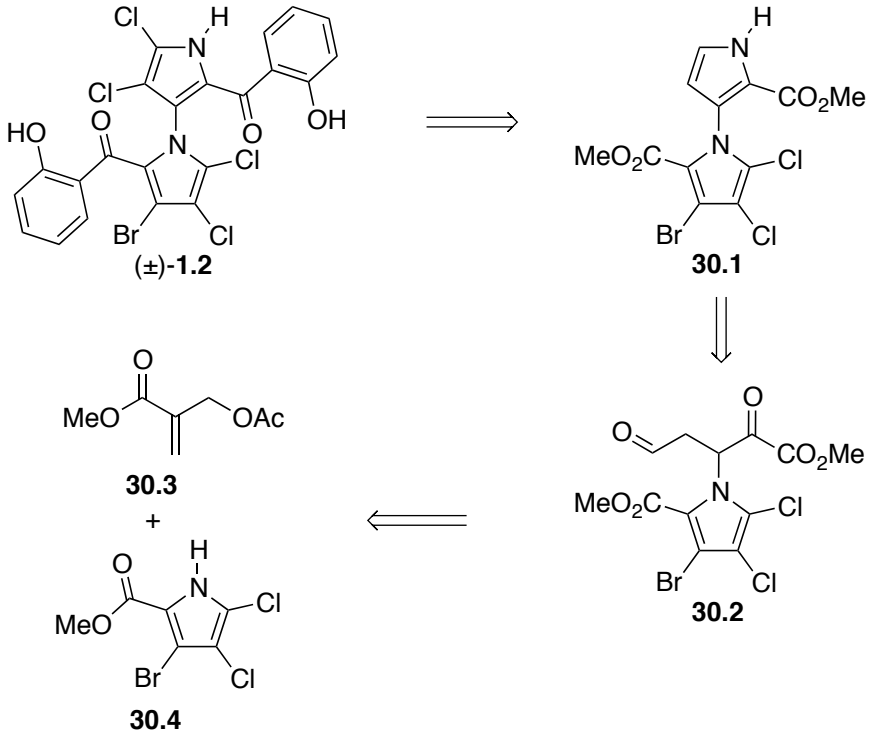
Alkylation of ketone **28.5** with allyl bromide did not give the expected *C*-allyl product, instead, the *O*-allyl enol ether **29.1** was formed in 78% yield. Fortunately, refluxing **29.1** in PhMe for 30 h gave the desired ketone **29.2** via Claisen rearrangement. Lemieux-Johnson oxidation and ozonolysis were then examined in order to cleave the double bond of **29.2**. However, none of desired aldehyde was obtained under these two conditions. Finally, it was found that using OsO_4 and *N*-methylmorpholine-*N*-oxide (NMO), followed by $Pb(OAc)_4$, afforded the desired aldehyde **25.2** in 57% yield. Treatment of **25.2** with NH_4OAc and AcOH[24] did not furnish the expected 1,3'-bipyrrole **25.1**, but gave the pyridine **29.3** instead. This behavior indicated that the carbonyl group adjacent to the *o*-methoxyphenyl unit was more reactive than the adjacent ketone. In order to circumvent this problem, use of an ester group instead of the *o*-methoxyphenyl carbonyl group was indicated.



Scheme 29

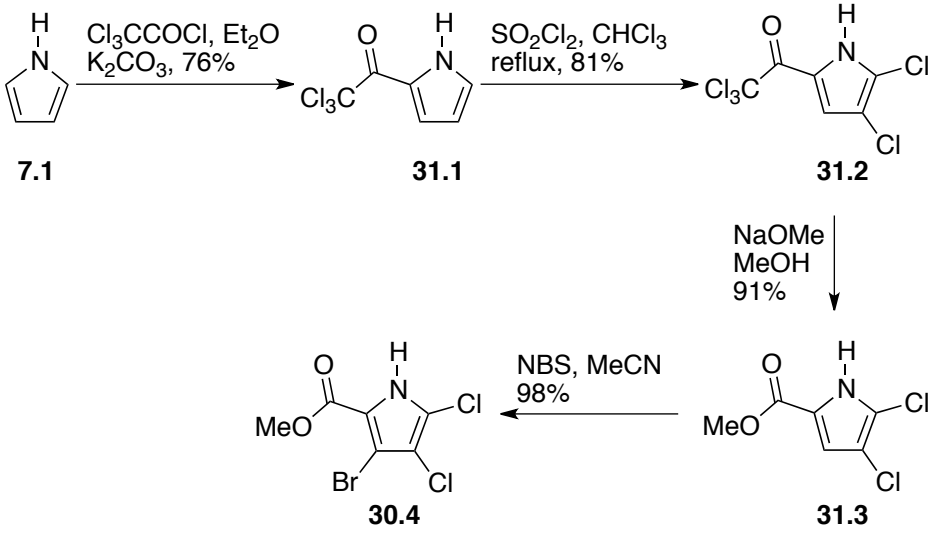
The new synthetic plan (Scheme 30) was to prepare 1,3'-bipyrrole **30.1** as a key intermediate, and the *o*-methoxyphenyl group would be installed after formation of the second pyrrole ring. 1,3'-Bipyrrole **30.1** should be accessible from **30.2** via a Paal-Knorr reaction. An intermolecular conjugate displacement between **30.3** and **30.4** should serve to alkylate the nitrogen atom of pyrrole **30.4**.

Subsequent oxidative cleavage of the double bond, alkylation and ozonolysis should then afford the desired aldehyde **30.2**.



Scheme 30

The bottom pyrrole unit **30.4** was prepared by the route developed by Dr. Fernandopulle, a former member of this group (Scheme 31): Pyrrole (**7.1**) was converted to trichloromethyl ketone **31.1** by using Cl_3CCOCl and a base.[25] Regioselective chlorination with SO_2Cl_2 yielded the dichlorinated pyrrole **31.2** in good yield.[26] The trichloromethyl ketone was then converted into the corresponding ester **31.3** by treatment with NaOMe in MeOH. Direct bromination at C-3, using NBS, afforded **30.4** in excellent yield.

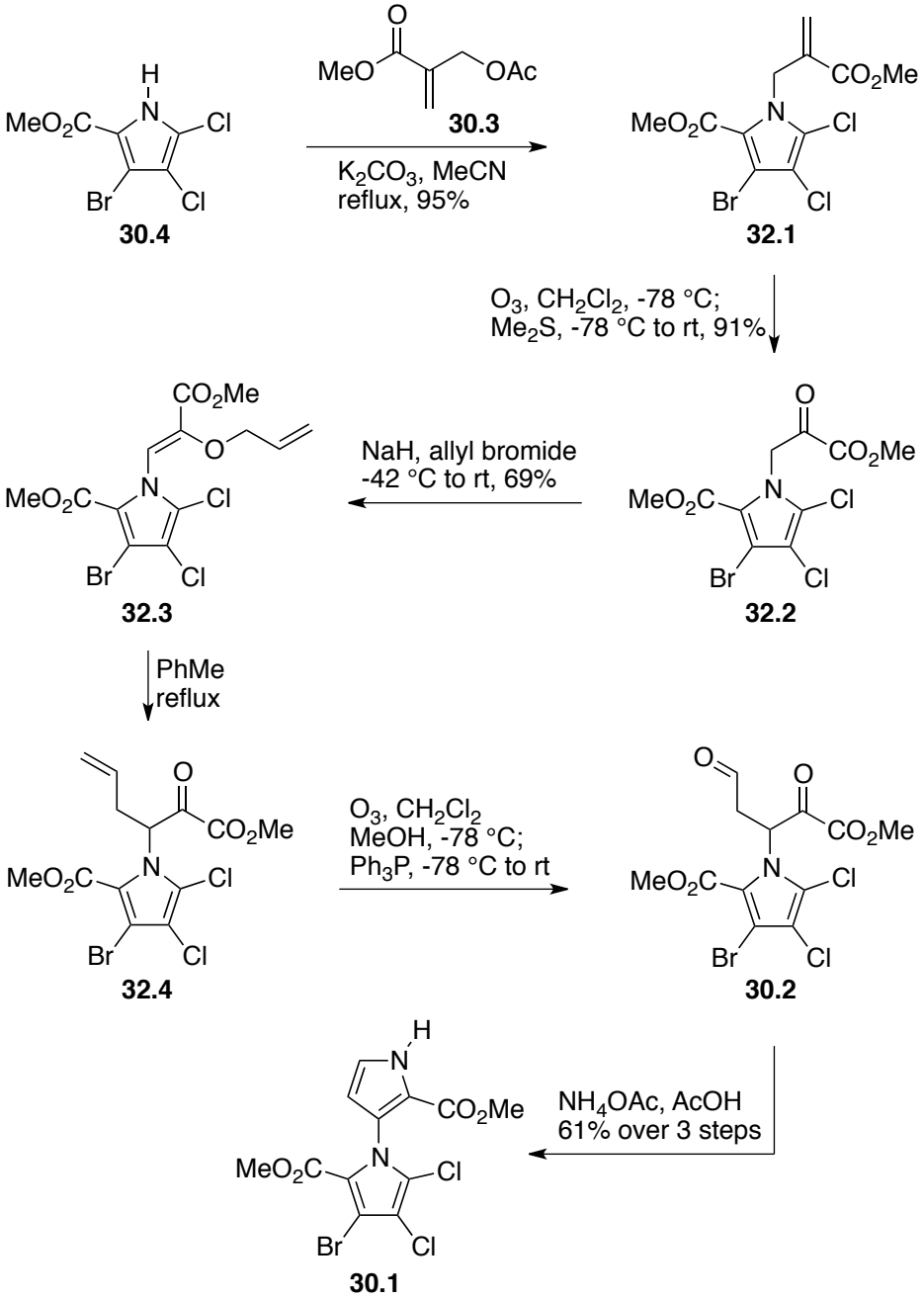


Scheme 31

The intermolecular conjugate displacement reaction of **30.4** with the allylic acetate **30.3**[27] in the presence of K_2CO_3 produced compound **32.1** in 95% yield (Scheme 32). Cleavage of the terminal double bond in **32.1** with $RuCl_3$ and $NaIO_4$ gave the keto ester **32.2** in 35% yield. When **32.1** was treated with ozone and then Me_2S, the yield of **32.2** was improved to 91%. Alkylation with allyl bromide afforded the expected *O*-allyl enol ether **32.3**, whose stereochemistry was established by single crystal X-ray analysis (Figure 1).

When **32.3** was heated in refluxing PhMe, the required α-alkyl ketone **32.4** was formed smoothly. The new terminal double bond in **32.4** was also cleaved by ozonolysis to provide aldehyde **30.2**, which could not be purified by flash chromatography due to its lability on silica gel. The crude aldehyde was directly treated with NH_4OAc and AcOH to afford the desired 1,3'-bipyrrole **30.1**,[24] whose structure was also confirmed by X-ray analysis (Figure 2). It was not necessary to purify **32.4**, and it was more convenient to use the crude

compound for the next step; in this way, pure **30.1** was obtained in 61% yield over 3 steps from **32.3**.



Scheme 32

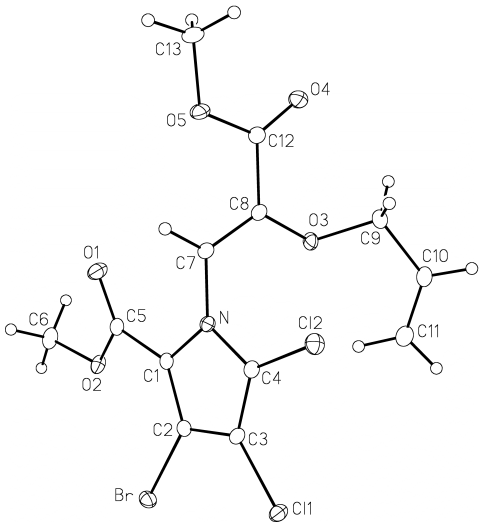


Figure 1. ORTEP diagram of 32.3

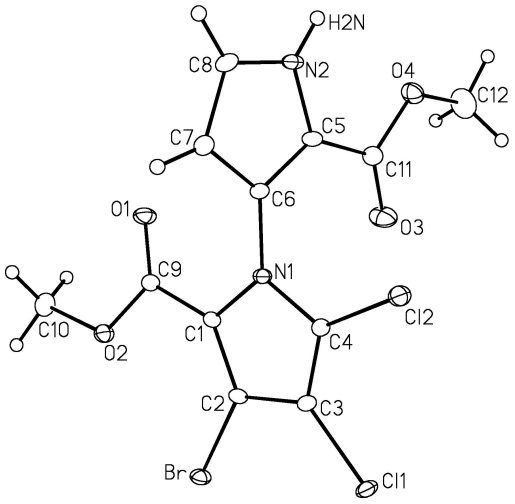
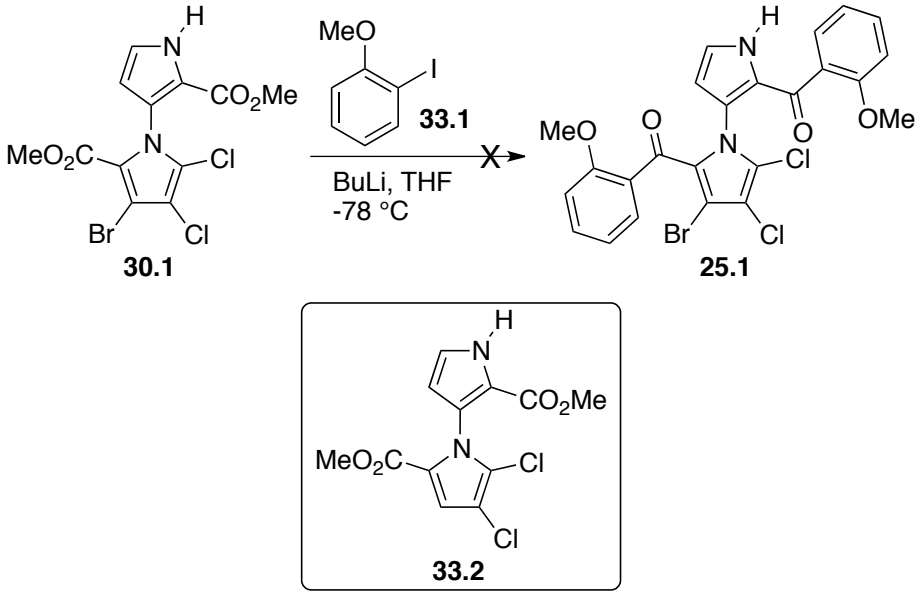


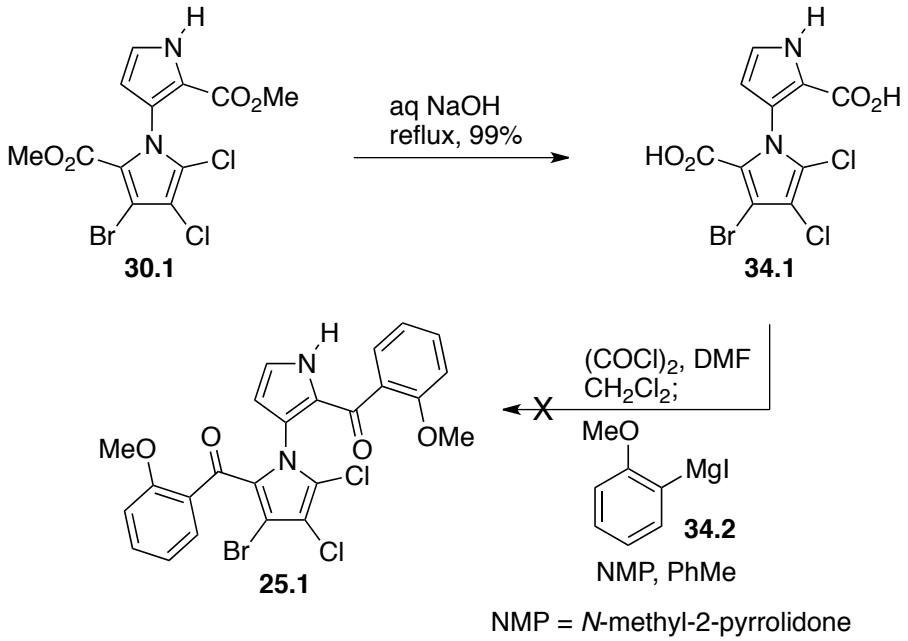
Figure 2. ORTEP diagram of 30.1

When **30.1** was treated with *o*-methoxyphenylmagnesium iodide or *o*-methoxyphenyllithium, prepared from 2-iodoanisole (**33.1**) and BuLi,[16] however, the expected compound **25.1** was not formed, and the dichlorinated 1,3'-bipyrrole

33.2 was formed (Scheme 33). This result was probably attributed to the low reactivity of the ester.

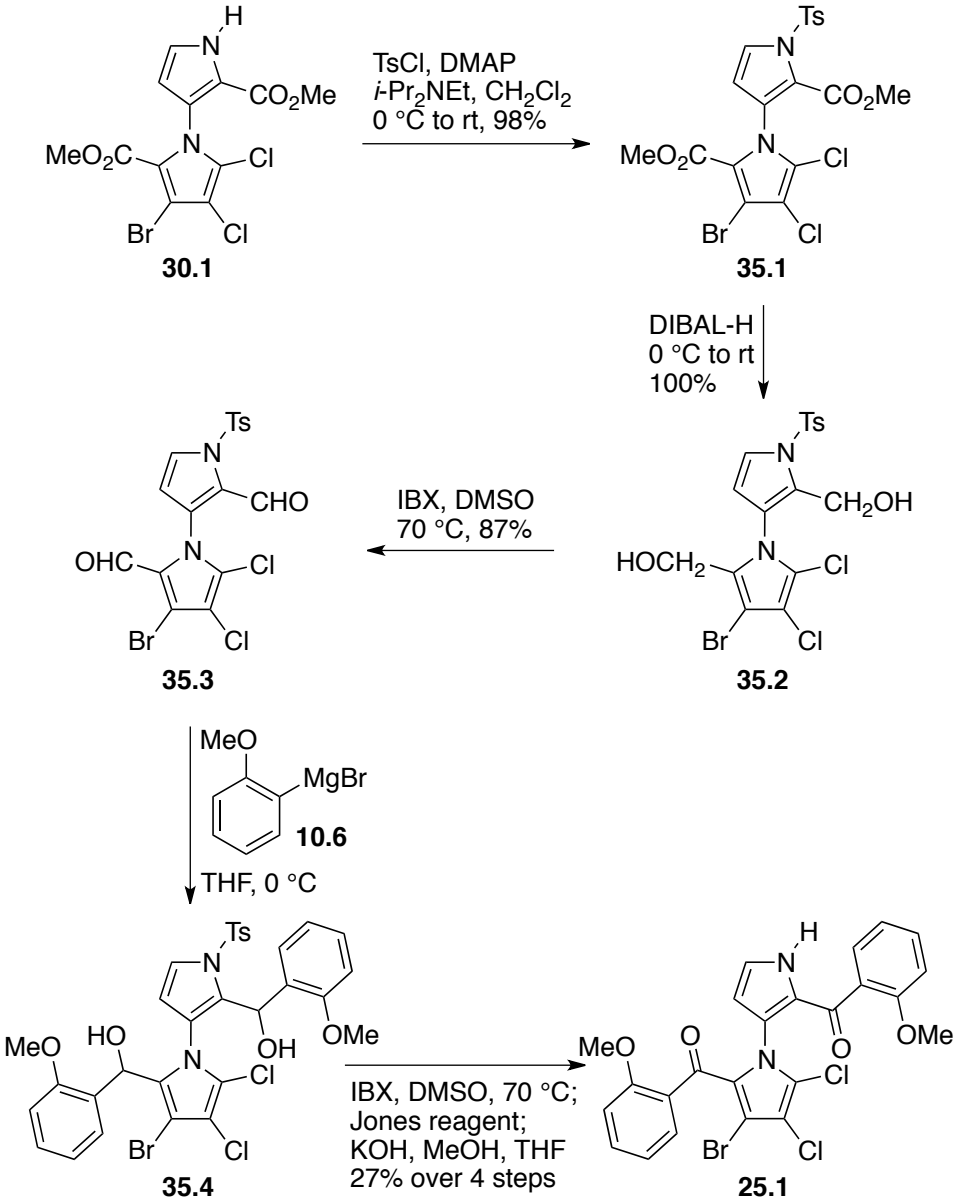


Scheme 33



Scheme 34

The reaction of *o*-methoxyphenylmagnesium iodide (**34.2**) with the bis-acid chloride derived from diacid **34.1** was also tested (Scheme 34);[28] unfortunately, none of the desired compound **25.1** was obtained.



Scheme 35

It seemed likely that the unprotected pyrrole in **30.1** might also retard the addition of Grignard reagent or organolithium reagent, and so the pyrrole nitrogen was protected by reaction with TsCl to give **35.1** in 98% yield (Scheme 35).[1] Reduction of the two ester groups of **35.1** with DIBAL-H gave the diol **35.2** in quantitative yield. For the oxidation step, Swern oxidation and MnO_2 were tried, but different monoaldehydes were obtained. When the diol was treated with TPAP, the desired dialdehyde **35.3** with a small amount of impurities was generated in 60% yield. Use of IBX[1] instead of TPAP gave the pure dialdehyde **35.3** in 87% yield.

With the dialdehyde **35.3** in hand, the Grignard reagent **10.6** was added at 0 °C. Fortunately, the installation of the two phenyl groups was successful in this case and the corresponding diol **35.4** was obtained as a mixture of diastereomers. The diols were then oxidized without purification, as I was concerned that they would be sensitive to silica gel.[29] Later I found that the diols could be chromatographed, but I did not go back to characterize them. However, crystals of the more polar diol were obtained, and X-ray analysis (Figure 3) showed that the two hydroxyl-bearing carbons have an *R*,*R* relative configuration. Different oxidation conditions were tried to oxidize the diols, and it was found that the two hydroxyl groups could not be oxidized at the same time. IBX (or Dess-Martin reagent and pyridine) oxidized one hydroxyl group, and then Jones reagent oxidized the other hydroxyl group. Direct use of Jones reagent did not give any of the desired product, and the diols were inert to $BaMnO_4$. The crude diketone

from the second oxidation was directly treated with KOH to afford the desired compound **25.1** in 27% yield over 4 steps.

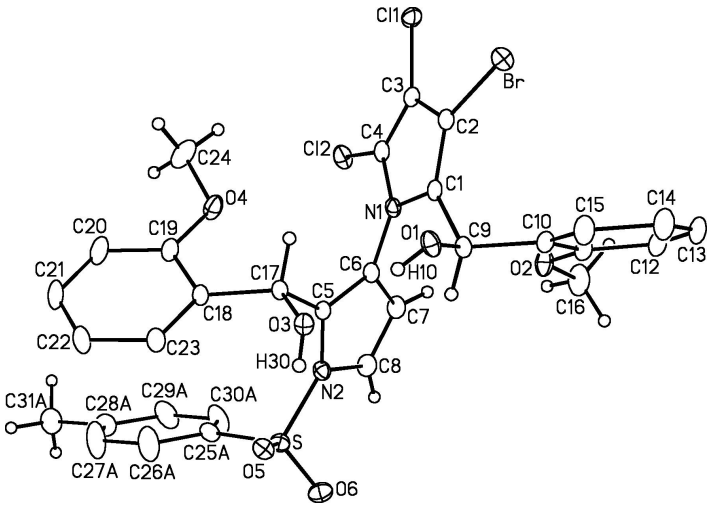
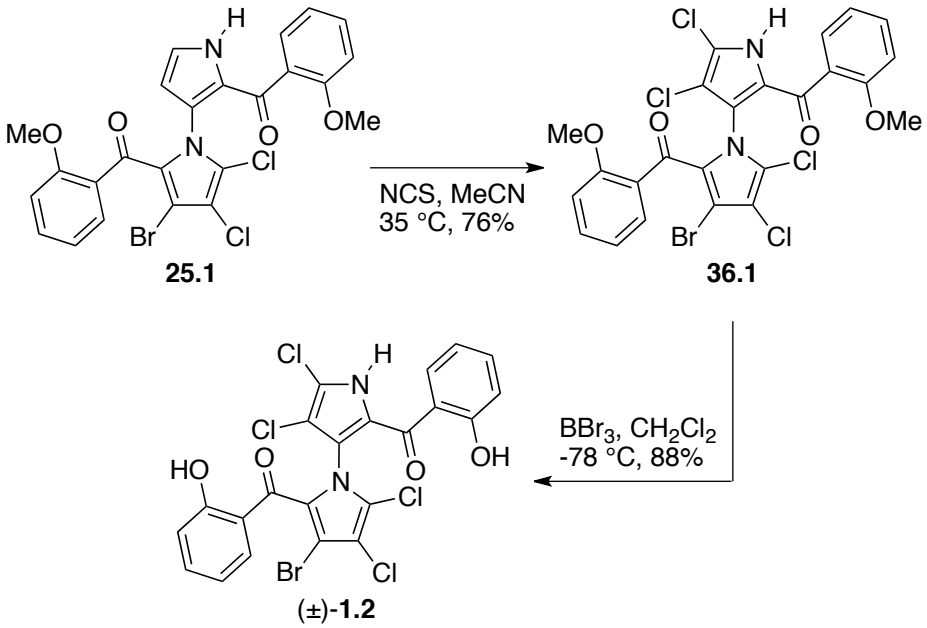


Figure 3. ORTEP diagram of the more polar 35.4

Dichlorination[1] of **25.1** with NCS (Scheme 36) gave the desired compound **36.1** in 76% yield, and demethylation[1] with BBr_3 completed the synthesis of racemic marinopyrrole B in 88% yield. Finally, crystallization of the compound from PhMe gave yellow crystals, and X-ray analysis confirmed the structure (Figure 4).



Scheme 36

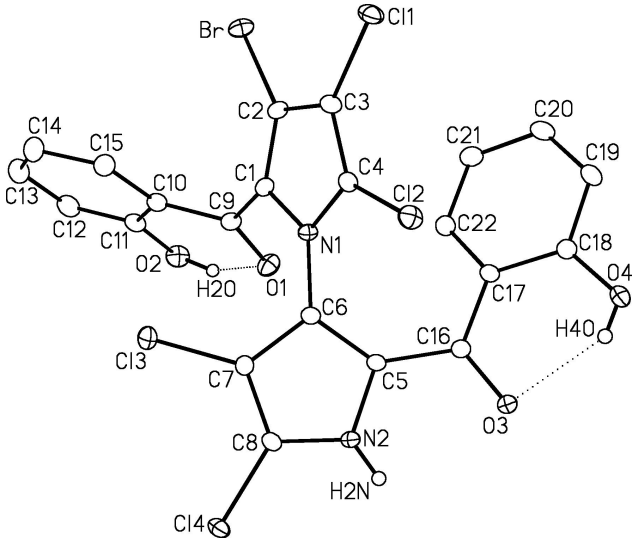


Figure 4. ORTEP diagram of (±)-1.2

3. Conclusion

The first total synthesis of marinopyrrole B was achieved by introducing bromine at a very early stage. The alkylation of **30.4** with the allylic acetate **30.3** was an important step to construct an appropriate carbon chain on the nitrogen so that the second pyrrole ring could be prepared via a Paal-Knorr reaction from the functionalized carbon chain. In future work it may be possible to modify the present rout so as to give access to analogs having differently substituted benzene rings. For example, the bromodichloro ester **30.4** would be a suitable substrate for DIBAL-H reduction to an aldehyde, which should react with a variety of Grignard reagents. The resulting pyrroles could then be subjected to the intermolecular conjugate displacement, leading, eventually to a 1,3'-bipyrrole carrying an ester group on the 2'-position. Such a compound should provide opportunities for installing a second benzene ring on the upper pyrrole.

4. Experimental

Methyl 2-{[(*tert*-butyldimethylsilyl)oxy](2-methoxyphenyl)methyl}-prop-2-enoate (26.4).

26.3 **26.4**

Imidazole (1.55 g, 22.54 mmol) and *t*-BuMe$_2$SiCl (2.08 g, 13.52 mmol) were added successively to a stirred solution of **26.3**[20] (2.00 g, 9.01 mmol) in CH_2Cl_2 (20 mL). Stirring was continued for 5 h, and the mixture was quenched with water and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.8 x 20 cm), using 3:50 EtOAc-hexanes, gave **26.4** (2.92 g, 96%) as a colorless oil: FTIR ($CDCl_3$, cast) 2998, 2954, 2930, 2895, 2857, 1727, 1632, 1601, 1590, 1491, 1464 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ –0.07 (s, 3 H), 0.10 (s, 3 H), 0.90 (s, 9 H), 3.72 (s, 3 H), 3.85 (s, 3 H), 5.85 (t, *J* = 2.0 Hz, 1 H), 6.09 (s, 1 H), 6.25−6.26 (m, 1 H), 6.87 (dd, *J* = 1.0, 8.0 Hz, 1 H), 6.95 (dt, *J* = 1.0, 7.5 Hz, 1 H), 7.23-7.27 (m, 1 H), 7.39 (dd, *J* = 2.0, 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –5.1 (q), –5.0 (q), 18.2 (s), 25.8 (q), 51.6 (q), 55.4 (q), 66.1 (d), 110.4 (d), 120.4 (d), 124.5 (t), 127.9 (d), 128.4 (d), 131.0 (s), 143.9 (s), 156.2 (s), 166.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{18}H_{28}NaO_4Si$ (M + Na) 359.1649, found 359.1650.

2-{[(*tert*-Butyldimethylsilyl)oxy](2-methoxyphenyl)methyl}prop-2-en-1-ol (26.5).

26.4 **26.5**

DIBAL-H (1.0 M in PhMe, 22.0 mL, 22.0 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **26.4** (2.92 g, 8.69 mmol) in CH_2Cl_2 (40 mL). Stirring at –78 °C was continued for 2.5 h, and MeOH (2.0 mL) was added. After the cooling bath was removed, a saturated aqueous solution of Rochelle's salt (ca. 100 mL) was added. Stirring was continued for 4 h, and the mixture was then extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.8 x 20 cm), using 1:10 to 3:25 EtOAc-hexanes, gave **26.5** (2.46 g, 92%) as a colorless oil: FTIR ($CDCl_3$, cast) 3374, 3078, 3035, 2999, 2956, 2930, 2886, 2857, 2710, 1654, 1601, 1589, 1490, 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ –0.06 (s, 3 H), 0.10 (s, 3 H), 0.93 (s, 9 H), 2.34 (br s, 1 H), 3.85 (s, 3 H), 3.98−4.02 (m, 1 H), 4.13 (d, J = 13.5 Hz, 1 H), 5.09−5.11 (m, 1 H), 5.21−5.22 (m, 1 H), 5.78 (s, 1 H), 6.87 (dd, J = 1.0, 8.0 Hz, 1 H), 6.98−7.02 (m, 1 H), 7.23−7.27 (m, 1 H), 7.52 (dd, J = 2.0, 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –5.2 (q), –5.0 (q), 18.2 (s), 25.8 (q), 55.4 (q), 63.8 (t), 70.2 (d), 110.3 (d), 111.6 (t), 120.8

(d), 127.5 (d), 128.3 (d), 131.1 (s), 149.6 (s), 155.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{17}H_{28}NaO_3Si$ (M + Na) 331.1700, found 331.1696.

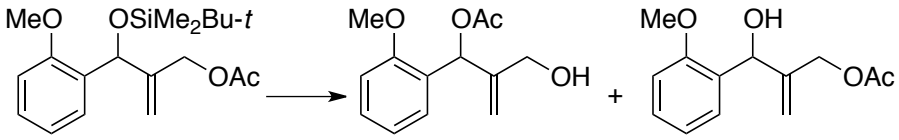
2-{[(*tert*-Butyldimethylsilyl)oxy](2-methoxyphenyl)methyl}prop-2-en-1-yl acetate (26.6).

26.5 **26.6**

Pyridine (1.30 mL, 16.09 mmol) and AcCl (0.93 mL, 12.83 mmol) were added successively to a stirred and cooled (0 °C) solution of **26.5** (2.00 g, 9.01 mmol) in CH_2Cl_2 (40 mL). After 40 min, the mixture was quenched with saturated aqueous $NaHCO_3$ and washed with saturated aqueous $CuSO_4$, water and brine. The organic solution was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.8 x 20 cm), using 3:50 EtOAc-hexanes, gave **26.6** (2.76 g, 99%) as a colorless oil: FTIR ($CDCl_3$, cast) 3078, 3034, 3000, 2956, 2930, 2887, 2857, 1745, 1656, 1601, 1589, 1490, 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ –0.10 (s, 3 H), 0.05 (s, 3 H), 0.89 (s, 9 H), 1.98 (s, 3 H), 3.80 (s, 3 H), 4.49 (AB q, J = 13.5 Hz, $\Delta\nu_{AB}$ = 9.6 Hz, 2 H), 5.11−5.12 (m, 1 H), 5.31−5.32 (m, 1 H), 5.69 (s, 1 H), 6.82 (dd, J = 1.0, 8.5 Hz, 1 H), 6.94 (dt, J = 1.0, 7.5 Hz, 1 H), 7.21 (ddd, J = 2.0, 7.3, 8.3 Hz, 1 H), 7.44 (dd, J = 2.0, 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –5.2 (q), –5.1 (q), 18.2 (s), 20.8 (q), 25.8 (q),

55.3 (q), 63.9 (t), 68.6 (d), 110.2 (d), 112.3 (t), 120.6 (d), 127.6 (d), 128.2 (d), 131.0 (s), 145.9 (s), 155.9 (s), 170.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{19}H_{30}NaO_4Si$ (M + Na) 373.1806, found 373.1806.

3-Hydroxy-1-(2-methoxyphenyl)-2-methylidenepropyl acetate (26.7) and 3-Hydroxy-3-(2-methoxyphenyl)-2-methylidenepropyl acetate (26.8).



26.6 **26.7** **26.8**

Bu_4NF (1.0 M in THF, 3.79 mL, 3.79 mmol) was added dropwise to a stirred solution of **26.6** (1.33 g, 3.79 mmol) in THF (40 mL). Stirring was continued for 3.5 h and the mixture was then quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 20 cm), using 3:20 to 3:10 EtOAc-hexanes, gave **26.8** (646.2 mg, 72%) as a colorless oil. Further development of the column, using 2:5 to 3:5 EtOAc-hexanes, gave **26.7** (135.0 mg, 15%) as a colorless oil. Compound **26.8**: FTIR ($CDCl_3$, cast) 3464, 3078, 3003, 2956, 2940, 2839, 1739, 1657, 1601, 1588, 1491, 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.04 (s, 3 H), 2.98 (s, 1 H), 3.84 (s, 3 H), 4.57 (AB q, J = 13.5 Hz, $\Delta\nu_{AB}$ = 37.7 Hz, 2 H), 5.25−5.26 (m, 1 H), 5.29−5.31 (m, 1 H), 5.52 (s, 1 H), 6.90 (dd, J = 1.0, 8.5 Hz, 1 H), 6.98 (dt, J = 1.0,

7.5 Hz, 1 H), 7.28 (ddd, *J* = 2.0, 7.5, 8.3 Hz, 1 H), 7.33 (dd, *J* = 1.5, 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.9 (q), 55.4 (q), 64.7 (t), 70.5 (d), 110.8 (d), 113.5 (t), 120.9 (d), 127.8 (d), 129.0 (d), 129.5 (s), 145.1 (s), 156.9 (s), 170.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{16}NaO_4$ (M + Na) 259.0941, found 259.0937.

Compound **26.7**: FTIR ($CDCl_3$, cast) 3444, 3005, 2938, 2840, 1739, 1657, 1602, 1589, 1493, 1464 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.13 (s, 3 H), 2.20 (br s, 1 H), 3.86 (s, 3 H), 4.11 (s, 2 H), 5.17 (t, *J* = 1.0 Hz, 1 H), 5.28 (t, *J* = 1.0 Hz, 1 H), 6.74 (s, 1 H), 6.91 (dd, *J* = 1.0, 8.5 Hz, 1 H), 6.99 (dt, *J* = 1.0, 7.5 Hz, 1 H), 7.31 (m, 1 H), 7.38 (dd, *J* = 1.5, 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.2 (q), 55.7 (q), 63.6 (t), 69.6 (d), 110.8 (d), 112.3 (t), 120.7 (d), 126.7 (s), 127.4 (d), 129.4 (d), 147.1 (s), 156.6 (s), 170.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{16}NaO_4$ (M + Na) 259.0941, found 259.0937.

3-Hydroxy-3-(2-methoxyphenyl)-2-methylidenepropyl acetate (26.8).

26.7 **26.8**

DBU (0.1 mL, 0.66 mmol) was added to a stirred solution of **26.7** (74.1 mg, 0.31 mmol) in THF (4 mL). After 3 days, water was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$)

and evaporated. Flash chromatography of the residue over silica gel (1.4 x 20 cm), using 1:10 to 1:5 EtOAc-hexanes, gave **26.8** (46.0 mg, 62%) as a colorless oil.

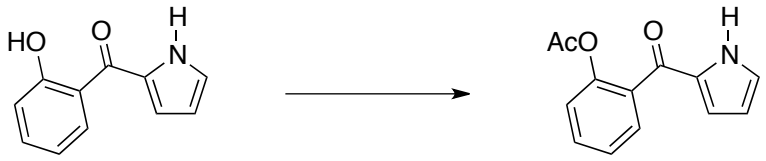
3-(2-Methoxyphenyl)-2-methylidene-3-oxopropyl acetate (25.3).

26.8 **25.3**

DMSO (0.77 mL, 10.86 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred and cooled (–78 °C) solution of $(COCl)_2$ (0.47 mL, 5.44 mmol) in CH_2Cl_2 (10 mL). After 15 min, a solution of **26.8** (629.0 mg, 2.67 mmol) in CH_2Cl_2 (10 mL) was added dropwise over ca. 10 min and stirring at –78 °C was continued for 45 min. Then Et_3N (1.20 mL) was added dropwise, and stirring was continued at –78 °C for 5 min. The cooling bath was removed, stirring was continued for 50 min, and water (10 mL) was added. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 20 cm), using 2:25 to 1:5 EtOAc-hexanes, gave **25.3** (473.8 mg, 76%) as a colorless oil: FTIR ($CDCl_3$, cast) 3075, 3005, 2946, 2940, 2840, 1745, 1664, 1599, 1582, 1489, 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.13 (s, 3 H), 3.83 (s, 3 H), 4.99 (t, J = 1.5 Hz, 2 H), 5.84 (d, J = 1.0 Hz, 1 H), 6.07 (dt, J = 0.5, 1.5 Hz,

1 H), 6.97 (d, *J* = 8.5 Hz, 1 H), 7.01 (dt, *J* = 1.0, 7.5 Hz, 1 H), 7.30 (dd, *J* = 1.5, 7.5 Hz, 1 H), 7.44 (ddd, *J* = 1.5, 7.5, 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.9 (q), 55.7 (q), 62.3 (t), 111.5 (d), 120.4 (d), 128.3 (s), 128.8 (t), 129.3 (d), 131.9 (d), 143.9 (s), 157.2 (s), 170.5 (s), 196.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{14}NaO_4$ (M + Na) 257.0784, found 257.0782.

2-[(1*H*-Pyrrol-2-yl)carbonyl]phenyl acetate (7.5).

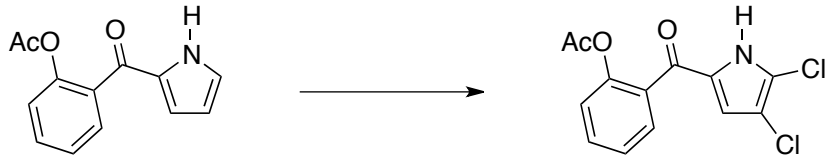


7.4 **7.5**

DMAP (45.0 mg, 0.37 mmol), pyridine (1.80 mL, 22.28 mmol) and AcCl (1.60 mL, 22.05 mmol) were successively added to a stirred and cooled (0 °C) solution of **7.4** (3.13 g, 16.74 mmol) in CH_2Cl_2 (60 mL). After 1 h, the reaction mixture was quenched with water and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.8 x 20 cm), using 3:10 to 2:5 EtOAc-hexanes, gave **7.5** (3.79 g, 99%) as a colorless oil: FTIR ($CDCl_3$, cast) 3293, 3137, 3077, 2934, 1767, 1625, 1606, 1575, 1543, 1483 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.19 (s, 3 H), 6.32 (dt, *J* = 4.0, 2.5 Hz, 1 H), 6.75−6.78 (m, 1 H), 7.18−7.21 (m, 1 H), 7.23 (dd, *J* = 1.0, 8.0 Hz, 1 H), 7.35 (dt, *J* = 1.0, 7.5 Hz, 1 H), 7.55 (ddd, *J* = 2.0, 7.5, 8.0 Hz, 1 H), 7.71 (dd, *J* = 2.0, 8.0 Hz, 1 H), 10.63 (br s, 1 H); ^{13}C NMR ($CDCl_3$,

125 MHz) δ 20.8 (q), 111.1 (d), 120.6 (d), 123.6 (d), 125.6 (d), 126.7 (d), 130.2 (d), 131.62 (s), 131.64 (s), 131.7 (d), 148.6 (s), 169.5 (s), 182.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{11}NNaO_3$ (M + Na) 252.0631, found 252.0630.

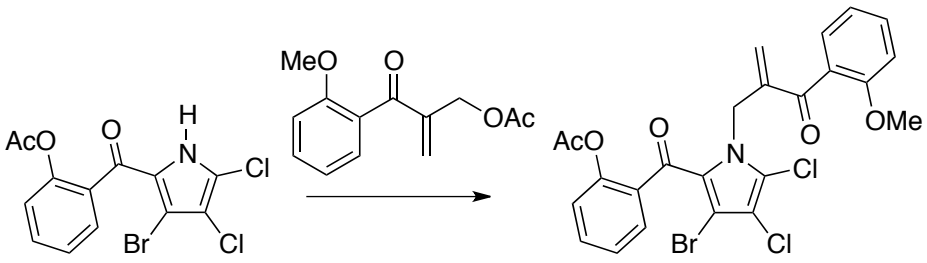
2-[(4,5-Dichloro-1*H*-pyrrol-2-yl)carbonyl]phenyl acetate (7.6).



7.5 **7.6**

SO_2Cl_2 (1.45 mL, 17.51 mmol) was added dropwise to a stirred solution of **7.5** (1.87 g, 8.15 mmol) in CH_2Cl_2 (40 mL) at room temperature. After 7 h, the solvent was evaporated. Flash chromatography of the residue over silica gel (3.8 x 20 cm), using 2:25 to 3:20 EtOAc-hexanes, gave **7.6** (2.20 g, 90%) as a white solid: mp 164−167 °C; FTIR ($CDCl_3$, cast) 3221, 3081, 2985, 2935, 2885, 2803, 2694, 2255, 1768, 1746, 1626, 1607, 1574, 1548, 1484 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.21 (s, 3 H), 6.66 (d, *J* = 3.0 Hz, 1 H), 7.20 (dd, *J* = 1.0, 8.5 Hz, 1 H), 7.33 (dt, *J* = 1.0, 7.5 Hz, 1 H), 7.55 (ddd, *J* = 1.5, 7.5, 8.0 Hz, 1 H), 7.62 (dd, *J* = 1.5, 8.0 Hz, 1 H), 10.15 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.9 (q), 112.3 (s), 119.0 (d), 122.0 (s), 123.6 (d), 125.7 (d), 128.5 (s), 129.9 (d), 130.1 (s), 132.4 (d), 148.6 (s), 169.3 (s), 181.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_9{}^{35}Cl_2NNaO_3$ (M + Na) 319.9852, found 319.9850.

2-({3-Bromo-4,5-dichloro-1-[3-(2-methoxyphenyl)-2-methylidene-3-oxopropyl]-1*H*-pyrrol-2-yl}carbonyl)phenyl acetate (28.1).

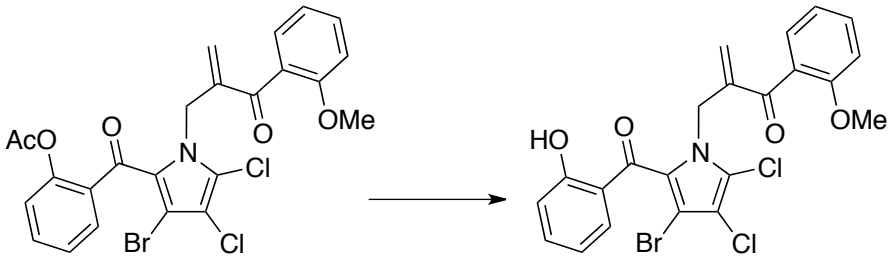


25.3 **7.8** **28.1**

NaH (60% in oil, 30.5 mg, 0.76 mmol) was added to a stirred solution of **25.3** (221.5 mg, 0.59 mmol) in DMF (5 mL). After 20 min, a solution of **7.8** (164.8 mg, 0.70 mmol) in DMF (6 mL) was added, and stirring was continued for 84 h. The mixture was quenched with 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 (2.8 x 20 cm), using 2:25 to 3:20 EtOAc-hexanes, gave **28.1** (267.1 mg, 83%) as a white foam: FTIR ($CDCl_3$, cast) 3074, 3007, 2942, 2838, 2254, 1768, 1645, 1600, 1580, 1486, 1448 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.19 (s, 3 H), 3.72 (s, 3 H), 5.40-5.42 (m, 2 H), 5.45 (t, *J* = 1.5 Hz, 1 H), 5.75 (t, *J* = 1.5 Hz, 1 H), 6.93 (d, *J* = 8.5 Hz, 1 H), 6.99 (dt, *J* = 1.0, 7.5 Hz, 1 H), 7.23 (dd, *J* = 1.0, 8.0 Hz, 1 H), 7.29−7.33 (m, 2 H), 7.43 (ddd, *J* = 1.5, 7.5, 8.3 Hz, 1 H), 7.53−7.59 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.8 (q), 47.0 (t), 55.5 (q), 106.2 (s), 111.4 (d), 113.4 (s), 120.3 (d),

123.5 (d), 123.6 (s), 125.9 (d), 127.4 (t), 128.0 (s), 128.1 (s), 129.4 (d), 130.9 (d), 131.2 (s), 132.1 (d), 132.8 (d), 144.4 (s), 149.0 (s), 157.3 (s), 169.1 (s), 182.9 (s), 196.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{24}H_{18}{}^{79}Br^{35}Cl_2NNaO_5$ (M + Na) 571.9638, found 571.9631.

2-({3-Bromo-4,5-dichloro-2-[(2-hydroxyphenyl)carbonyl]-1*H*-pyrrol-1-yl}methyl)-1-(2-methoxyphenyl)prop-2-en-1-one (28.3).

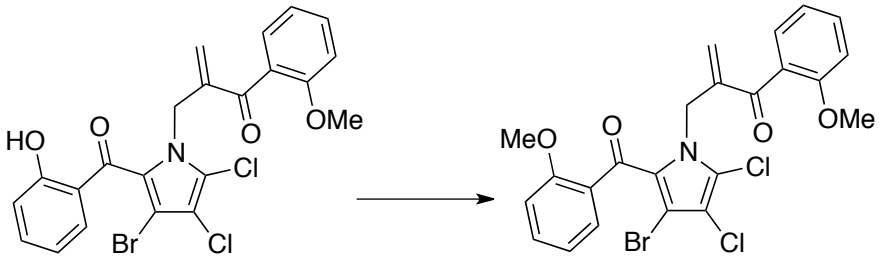


28.1 **28.3**

Concentrated hydrochloric acid (36.5-38%, 0.6 mL) was added dropwise to a stirred solution of **28.1** (552.8 mg, 1.00 mmol) in MeOH (11 mL). Stirring was continued for 6.5 h and the solvent was then evaporated. The residue was dissolved in Et_2O, and the solution was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 20 cm), using 1:50 to 1:20 EtOAc-hexanes, gave **28.3** (385.6 mg, 75%) as a yellow oil: FTIR ($CDCl_3$, cast) 3007, 2963, 2838, 2254, 1661, 1622, 1598, 1484 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.68 (s, 3 H), 5.21 (br s, 2 H), 5.51 (t, *J* = 1.5 Hz, 1 H), 5.74 (t, *J* = 1.5 Hz, 1 H), 6.90−6.98 (m, 3 H), 7.05−7.08 (m, 1 H), 7.21 (dd, *J* = 1.5, 7.5 Hz, 1 H),

7.42 (ddd, J = 2.0, 7.5, 8.5 Hz, 1 H), 7.52−7.56 (m, 1 H), 7.66−7.69 (m, 1 H), 11.5 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 46.6 (t), 55.4 (q), 102.9 (s), 111.4 (d), 112.8 (s), 118.2 (d), 119.2 (d), 119.3 (s), 120.4 (d), 121.5 (s), 127.71 (s), 127.73 (s), 128.3 (t), 129.3 (d), 132.2 (d), 134.3 (d), 137.1 (d), 144.0 (s), 157.2 (s), 162.8 (s), 189.8 (s), 195.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{22}H_{16}{}^{79}Br^{35}Cl_2NNaO_4$ (M + Na) 529.9532, found 529.9536.

2-({3-Bromo-4,5-dichloro-2-[(2-methoxyphenyl)carbonyl]-1*H*-pyrrol-1-yl}methyl)-1-(2-methoxyphenyl)prop-2-en-1-one (28.4).

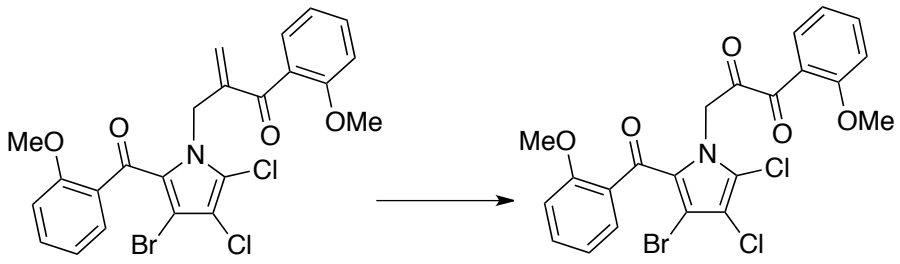


28.3 **28.4**

K_2CO_3 (131.8 mg, 0.94 mmol), followed by MeI (0.06 mL, 0.95 mmol), were added to a stirred solution of **28.3** (97.1 mg, 0.19 mmol) in dry acetone (3 mL). Stirring was continued for 22 h, and the mixture was then filtered through a pad of Celite, using Et_2O as a rinse. The filtrate was washed with water, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.4 x 20 cm), using 3:50 to 3:20 EtOAc-hexanes, gave **28.4** (90.1 mg, 90%) as a white solid: mp 142−145 °C; FTIR ($CDCl_3$, cast) 3074, 3006, 2943, 2838, 1661,

1635, 1599, 1582, 1488, 1463 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.76 (s, 3 H), 3.77 (s, 3 H), 5.46 (t, *J* = 1.5 Hz, 1 H), 5.51−5.54 (m, 2 H), 5.77 (t, *J* = 1.5 Hz, 1 H), 6.94 (d, *J* = 3.5 Hz, 1 H), 6.96 (d, *J* = 4.5 Hz, 1 H), 6.99 (dt, *J* = 1.0, 7.5 Hz, 1 H), 7.06 (dt, *J* = 1.0, 7.5 Hz, 1 H), 7.33 (dt, *J* = 2.0, 7.5 Hz, 1 H), 7.40 (dt, *J* = 2.0, 7.5 Hz, 1 H), 7.43 (ddd, *J* = 1.5, 7.5, 8.3 Hz, 1 H), 7.50 (ddd, *J* = 1.5, 7.5, 8.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 46.7 (t), 55.6 (q), 55.7 (q), 105.7 (s), 111.3 (d), 111.4 (d), 113.1 (s), 120.3 (d), 120.9 (d), 123.0 (s), 127.3 (t), 128.1 (s), 129.0 (s), 129.5 (d), 130.1 (d), 132.0 (d), 132.9 (d), 144.4 (s), 157.3 (s), 157.9 (s), 184.4 (s), 196.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{23}H_{18}{}^{79}Br^{35}Cl_2NNaO_4$ (M + Na) 543.9688, found 543.9686.

3-{3-Bromo-4,5-dichloro-2-[(2-methoxyphenyl)carbonyl]cyclopenta-2,4-dien-1-yl}-1-(2-methoxyphenyl)propane-1,2-dione (28.5).

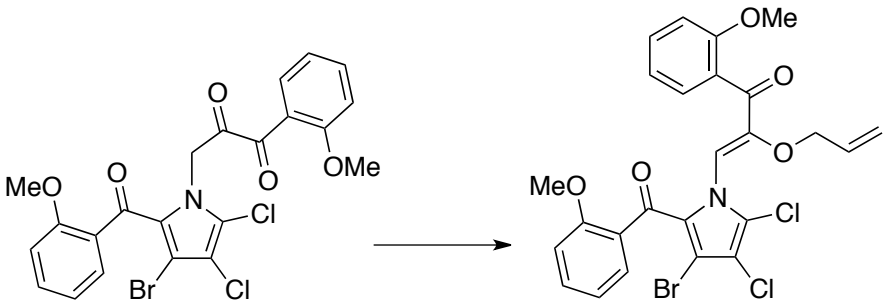


28.4 **28.5**

$NaIO_4$ (156.0 mg, 0.73 mmol) and $RuCl_3{\cdot}4H_2O$ (7.5 mg, 0.027 mmol) were added successively to a stirred solution of **28.4** (126.8 mg, 0.24 mmol) in a mixture of MeCN (0.9 mL), CCl_4 (0.9 mL) and water (1.4 mL). After 1.5 h, the

mixture changed to dark green-brown. At that time an additional quantity of $NaIO_4$ (60.0 mg, 0.28 mmol) was added, and stirring was continued for 1 h and CH_2Cl_2 (ca. 6 mL) and water (ca. 5 mL) were then added. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. All the combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.4 x 20 cm), using 3:50 to 3:25 EtOAc-hexanes, gave **28.5** (71.5 mg, 56%) as a light yellow solid: mp 110−113 °C; FTIR ($CDCl_3$, cast) 3076, 2945, 2840, 2253, 1734, 1662, 1634, 1599, 1582, 1487, 1465 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.77 (s, 3 H), 3.79 (s, 3 H), 5.96 (br s, 2 H), 6.96 (d, *J* = 6.0 Hz, 1 H), 6.97 (d, *J* = 6.0 Hz, 1 H), 7.04 (dt, *J* = 1.0, 7.5 Hz, 1 H), 7.10 (dt, *J* = 1.0, 7.5 Hz, 1 H), 7.40 (dd, *J* = 2.0, 7.5 Hz, 1 H), 7.49 (ddd, *J* = 2.0, 7.5, 8.5 Hz, 1 H), 7.59 (ddd, *J* = 2.0, 7.5, 8.5 Hz, 1 H), 7.80 (dd, *J* = 1.5, 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.9 (t), 55.8 (q), 55.9 (q), 107.0 (s), 111.4 (d), 111.9 (d), 113.7 (s), 120.8 (d), 121.3 (d), 123.0 (s), 123.6 (s), 128.8 (s), 129.1 (s), 129.9 (d), 130.8 (d), 132.8 (d), 136.2 (d), 157.9 (s), 160.2 (s), 185.1 (s), 192.8 (s), 193.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{22}H_{16}{}^{79}Br^{35}Cl_2NNaO_5$ (M + Na) 545.9481, found 545.9479.

(2*Z*)-3-{3-Bromo-4,5-dichloro-2-[(2-methoxyphenyl)carbonyl]-1*H*-pyrrol-1-yl}-1-(2-methoxyphenyl)-2-(prop-2-en-1-yloxy)prop-2-en-1-one (29.1).

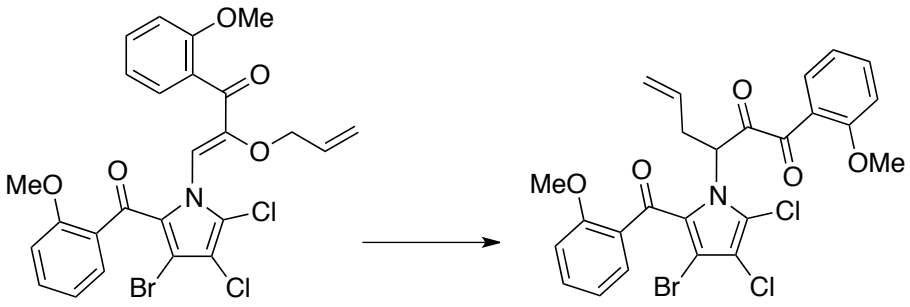


28.5 **29.1**

NaH (11.8 mg, 60% in oil, 0.30 mmol) was added to a stirred and cooled (–42 °C) solution of **28.5** (106.8 mg, 0.20 mmol) in DMF (4 mL). After 20 min, allyl bromide (0.025 mL, 0.29 mmol) was added, and stirring was continued for 1.5 h, during which time the temperature was allowed to rise slowly up to room temperature. Stirring was continued for 12 h. Saturated aqueous NH_4Cl was then added and the mixture was extracted with Et_2O. The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.4 x 20 cm), using 3:50 to 1:10 EtOAc-hexanes, gave **29.1** (90.1 mg, 78%) as a light yellow oil: FTIR ($CDCl_3$, cast) 3078, 3007, 2943, 2838, 1670, 1640, 1599, 1581, 1488, 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.75 (s, 3 H), 3.82 (s, 3 H), 4.43 (dt, *J* = 6.0, 1.0 Hz, 2 H), 5.11−5.15 (m, 2 H), 5.79 (ddt, *J* = 10.0, 17.5, 6.0 Hz, 1 H), 6.77 (s, 1 H), 6.92 (d, *J* = 8.0 Hz, 1 H), 6.95 (d, *J* = 8.5 Hz, 1 H), 7.01 (dt, *J* = 1.0, 7.5 Hz, 2 H), 7.38 (dd, *J* = 1.5, 7.5

Hz, 1 H), 7.44−7.49 (m, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.6 (q), 55.8 (q), 72.0 (t), 105.9 (s), 111.3 (d), 111.4 (d), 114.1 (s), 118.4 (t), 120.1 (d), 120.4 (d), 120.8 (d), 122.0 (s), 127.2 (s), 128.1 (s), 129.8 (s), 130.20 (d), 130.25 (d), 130.3 (d), 133.0 (d), 133.1 (d), 151.0 (s), 158.02 (s), 158.03 (s), 183.3 (s), 191.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{25}H_{20}{}^{79}Br^{35}Cl_2NNaO_5$ (M + Na) 585.9794, found 585.9791.

3-{3-Bromo-4,5-dichloro-2-[(2-methoxyphenyl)carbonyl]-1*H*-pyrrol-1-yl}-1-(2-methoxyphenyl)hex-5-ene-1,2-dione (29.2).

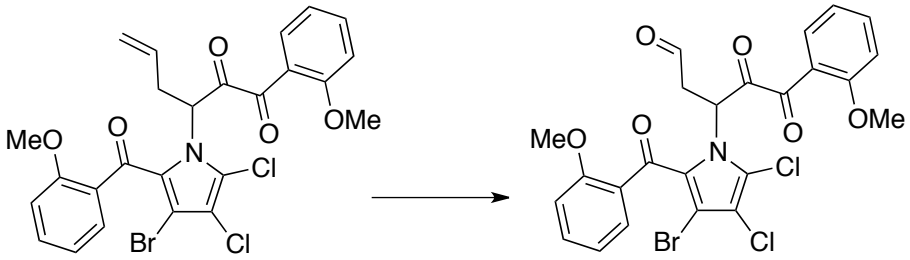


29.1 **29.2**

A solution of **29.1** (90.4 mg, 0.16 mmol) in PhMe (3 mL) was stirred and refluxed for 30 h and then cooled to room temperature and evaporated. Flash chromatography of the yellow residue over silica gel (1.4 x 20 cm), using 3:50 to 1:10 EtOAc-hexanes, gave **29.2** (76.4 mg, 85%) as a light yellow oil: FTIR ($CDCl_3$, cast) 3077, 3007, 2944, 2839, 1722, 1662, 1628, 1599, 1582, 1487, 1465 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.98 (br s, 1 H), 3.17 (br s, 1 H), 3.67 (s, 3 H), 3.73−3.86 (m, 4 H), 5.04-5.16 (m, 2 H), 5.75 (br s, 1 H), 6.88 (d, *J* = 8.0 Hz, 1

H), 6.94−7.00 (m, 2 H), 7.06 (t, J = 7.5 Hz, 1 H), 7.17 (br s, 1 H), 7.42−7.46 (m, 1 H), 7.53−7.57 (m, 1 H), 7.96 (br s, 1 H); I was unable to obtain a satisfactory ^{13}C NMR ($CDCl_3$, 125 MHz) spectrum (some carbon signals do not appear in the spectrum); exact mass (electrospray) m/z calcd for $C_{25}H_{20}{}^{79}Br^{35}Cl_2NNaO_5$ (M + Na) 585.9794, found 585.9783.

3-{3-Bromo-4,5-dichloro-2-[(2-methoxyphenyl)carbonyl]-1*H*-pyrrol-1-yl}-5-(2-methoxyphenyl)-4,5-dioxopentanal (25.2).

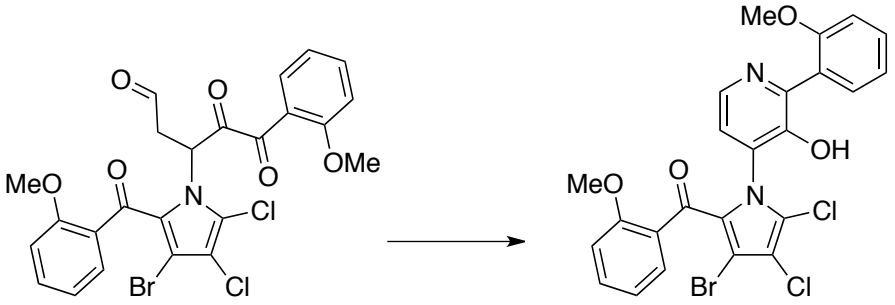


29.2 **25.2**

NMO (41.2 mg, 0.34 mmol) and OsO_4 (0.1 M in PhMe, 0.1 mL, 0.01 mmol) were added successively to a stirred solution of **29.2** (53.6 mg, 0.095 mmol) in a mixture of THF (1 mL) and water (1 mL). After 2 h, the reaction mixture was diluted with EtOAc, washed with water, dried ($MgSO_4$) and evaporated to give a yellow residue. A solution of $Pb(OAc)_4$ (54.8 mg, 0.12 mmol) in CH_2Cl_2 (0.5 mL) was added to a stirred solution of the yellow residue in CH_2Cl_2 (1.5 mL), and and stirring was continued for 15 min. The mixture was then filtered through a pad of silica gel, using EtOAc as a rinse. Evaporation of

the filtrate and flash chromatography of the residue over silica gel (1.2 x 15 cm), using 1:5 to 2:5 EtOAc-hexanes, gave **25.2** (30.7 mg, 57%) as a yellow oil: FTIR ($CDCl_3$, cast) 3077, 2944, 2840, 2733, 2254, 1725, 1660, 1632, 1599, 1582, 1486, 1465 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.11 (d, *J* = 16.3 Hz, 1 H), 3.60−4.00 (m, 7 H), 6.90 (d, *J* = 8.5 Hz, 1 H), 6.94−7.04 (m, 2 H), 7.07 (t, *J* = 7.5 Hz, 1 H), 7.23 (d, *J* = 7.0 Hz, 1 H), 7.45−7.50 (m, 1 H), 7.56−7.60 (m, 1 H), 7.88 (br s, 1 H), 9.88 (s, 1 H); I was unable to obtain a satisfactory ^{13}C NMR ($CDCl_3$, 125 MHz) spectrum (some carbon signals do not appear in the spectrum); exact mass (electrospray) *m*/*z* calcd for $C_{24}H_{18}{}^{79}Br^{35}Cl_2NNaO_6$ (M + Na) 587.9587, found 587.9587.

4-{3-Bromo-4,5-dichloro-2-[(2-methoxyphenyl)carbonyl]-1*H*-pyrrol-1-yl}-2-(2-methoxyphenyl)pyridin-3-ol (29.3).

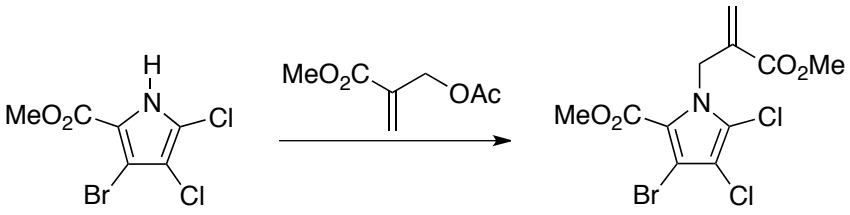


25.2 **29.3**

NH_4OAc (118.7 mg, 1.54 mmol) was added to a stirred solution of **25.2** (54.9 mg, 0.097 mmol) in AcOH (1 mL). After 1 h, water (ca. 3 mL) was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were

washed with saturated aqueous $NaHCO_3$ and water, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.2 x 15 cm), using 2:5 to 1:2 EtOAc-hexanes, gave **29.3** (33.0 mg, 62%) as a yellow oil: FTIR ($CDCl_3$, cast) 3246, 3076, 2942, 2838, 2251, 1726, 1646, 1600, 1489, 1463 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.79 (s, 3 H), 3.86 (s, 3 H), 6.87 (d, *J* = 8.5 Hz, 1 H), 6.93 (dt, *J* = 1.0, 7.5 Hz, 1 H), 7.05 (dd, *J* = 1.0, 8.5 Hz, 1 H), 7.17−7.23 (m, 2 H), 7.37−7.48 (m, 3 H), 7.57 (br s, 1 H), 7.75 (dd, *J* = 2.0, 8.0 Hz, 1 H), 8.38 (d, *J* = 5.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.9 (q), 57.0 (q), 105.4 (s), 111.3 (d), 112.4 (d), 114.1 (s), 120.5 (d), 121.7 (s), 122.6 (d), 123.0 (d), 126.8 (s), 127.88 (s), 127.89 (s), 130.5 (d), 130.7 (d), 130.8 (s), 133.0 (d), 133.3 (d), 133.7 (s), 142.2 (d), 146.7 (s), 147.0 (s), 155.0 (s), 158.1 (s), 183.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{24}H_{17}{}^{79}Br^{35}Cl_2N_2NaO_4$ (M + Na) 568.9641, found 568.9637.

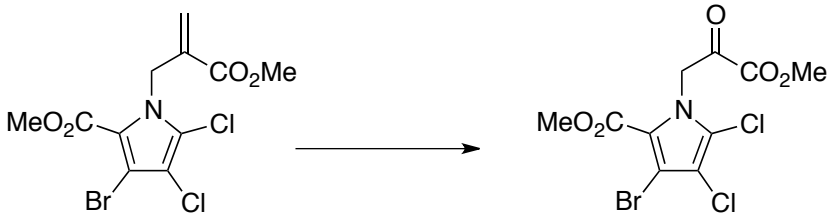
Methyl 3-bromo-4,5-dichloro-1-(3-methoxy-2-methylidene-3-oxo-propyl)-1*H*-pyrrole-2-carboxylate (32.1).



30.4 **30.3** **32.1**

A solution of **30.3** (321.3 mg, 1.98 mmol) in MeCN (5 mL) was added to a stirred suspension of **30.4** (337.3 mg, 1.24 mmol) and K_2CO_3 (690.0 mg, 4.94 mmol) in MeCN (20 mL). The mixture was refluxed for 42 h, then cooled, diluted with water and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 20 cm), using 1:50 to 3:50 EtOAc-hexanes, gave **32.1** (436.0 mg, 95%) as a white solid: mp 108−112 °C; FTIR ($CDCl_3$, cast) 3003, 2954, 2846, 1716, 1644, 1519, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) (mixture of rotamers) δ 3.81 (s, 3 H), 3.840 and 3.844 (two s, 3 H), 4.92−4.93 (m, 1 H), 5.29−5.31 (m, 2 H), 6.24 (t, J = 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (mixture of rotamers) δ 47.2 (t), 47.5 (t), 51.76 (q), 51.82 (q), 52.2 (q), 105.3 (s), 111.3 (s), 113.5 (s), 118.0 (s), 119.2 (s), 119.8 (s), 121.6 (s), 121.8 (s), 124.58 (t), 124.63 (t), 135.75 (s), 135.78 (s), 159.4 (s), 165.3 (s); exact mass (electrospray) m/z calcd for $C_{11}H_{10}{}^{79}Br^{35}Cl_2NNaO_4$ (M + Na) 391.9058, found 391.9062.

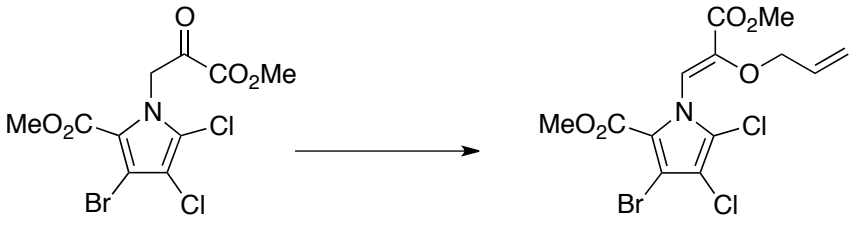
Methyl 3-bromo-4,5-dichloro-1-(3-methoxy-2,3-dioxopropyl)-1*H*-pyrrole-2-carboxylate (32.2).



32.1 **32.2**

A stream of ozonized oxygen was bubbled through a stirred and cooled (–78 °C) solution of **32.1** (1.17 g, 3.15 mmol) in CH_2Cl_2 (30 mL). After 18 min, the solution became blue. Then O_2 was allowed to bubble through the solution for 20 min to remove the excess of O_3. Me_2S (2.34 mL, 31.50 mmol) was then added, the cold bath was removed, and stirring was continued for 6.5 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3.8 x 20 cm), using 1:10 to 1:5 EtOAc-hexanes, gave **32.2** (1.07 g, 91%) as a white solid: mp 112−116 °C; FTIR ($CDCl_3$, cast) 3006, 2956, 2847, 1761, 1737, 1698, 1517, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.82−3.86 (m, 3 H), 3.96−4.00 (m, 3 H), 5.67 (s, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.0 (q), 53.5 (q), 53.6 (t), 105.9 (s), 113.9 (s), 119.5 (s), 122.0 (s), 159.7 (s), 160.1 (s), 185.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{10}H_8{}^{79}Br^{35}Cl_2NNaO_5$ (M + Na) 393.8858, found 393.8855.

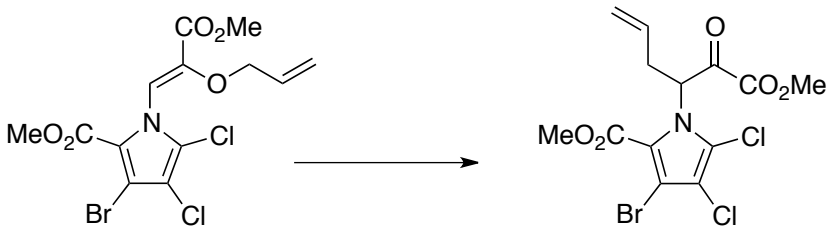
Methyl 3-bromo-4,5-dichloro-1-[(1*E*)-3-methoxy-3-oxo-2-(prop-2-en-1-yloxy)prop-1-en-1-yl]-1*H*-pyrrole-2-carboxylate (32.3).



32.2 **32.3**

NaH (115.3 mg, 60% in oil, 2.88 mmol) was added to a stirred and cooled (–42 °C) solution of **32.2** (808.1 mg, 2.17 mmol) in DMF (20 mL). After 20 min, allyl bromide (0.23 mL, 2.63 mmol) was added, and stirring was continued for 1.5 h, during which time the temperature was allowed to slowly reach room temperature. Stirring was continued for a further 6 h, water was then added and the mixture was extracted with Et_2O. The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 20 cm), using 1:25 to 1:10 EtOAc-hexanes, gave **32.3** (618.3 mg, 69%) as a white solid: mp 72−74 °C; FTIR ($CDCl_3$, cast) 3104, 3000, 2954, 1733, 1714, 1654, 1525, 1457 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.88 (s, 3 H), 3.90 (s, 3 H), 4.37 (ddd, *J* = 1.0, 1.5, 6.0 Hz, 2 H), 5.15−5.20 (m, 2 H), 5.72 (ddd, *J* = 6.0, 10.5, 17.0 Hz, 1 H), 7.30 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.9 (q), 52.7 (q), 73.1 (t), 105.8 (s), 114.5 (s), 119.1 (t), 119.5 (d), 121.2 (s), 121.3 (s), 132.4 (d), 143.3 (s), 159.2 (s), 162.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{12}{}^{79}Br^{35}Cl_2NNaO_5$ (M + Na) 433.9164, found 433.9168. A sample was crystallized from *i*-Pr_2O for X-ray analysis.

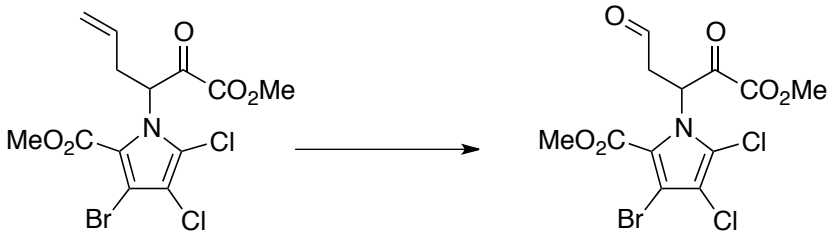
Methyl 3-bromo-4,5-dichloro-1-(1-methoxy-1,2-dioxohex-5-en-3-yl)-1*H*-pyrrole-2-carboxylate (32.4).



32.3 **32.4**

A solution of **32.3** (862.7 mg, 2.09 mmol) in PhMe (10.5 mL) was stirred and refluxed for 16 h and then cooled to room temperature. Evaporation of the solution gave **32.4** as a light yellow solid, which was used directly in the next step. In an earlier experiment, the solid was purified by flash chromatography over silica gel, using 1:25 to 1:10 EtOAc-hexanes to give pure **32.4**: mp 104−106 °C; FTIR ($CDCl_3$, cast) 3464, 3082, 3005, 2955, 2850 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.63 (dt, *J* = 15.0, 4.0 Hz, 1 H), 3.16-3.22 (m, 1 H), 3.81 (s, 3 H), 3.90 (s, 3 H), 4.99−5.05 (m, 2 H), 5.53−5.62 (m, 1 H), 5.85 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 34.7 (t), 52.1 (q), 53.2 (q), 64.0 (d), 106.8 (s), 114.3 (s), 119.1 (s), 119.9 (s), 131.5 (d), 160.2 (s), 161.2 (s), 186.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{12}{}^{79}Br^{35}Cl_2NNaO_5$ (M + Na) 433.9168, found 433.9161.

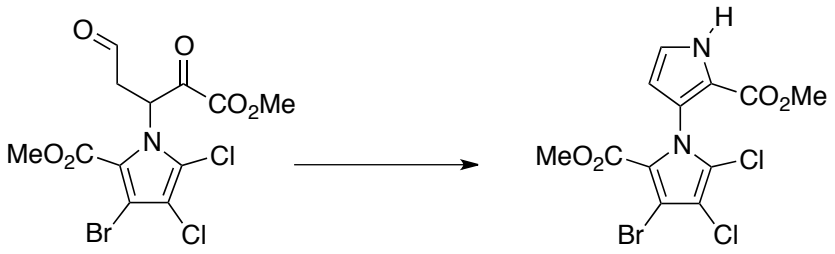
Methyl 3-bromo-4,5-dichloro-1-(1-methoxy-1,2,5-trioxopentan-3-yl)-1*H*-pyrrole-2-carboxylate (30.2).



32.4 **30.2**

The above crude ketoester **32.4** was dissolved in MeOH (10 mL) and CH_2Cl_2 (10 mL). A stream of ozonized oxygen was bubbled through the stirred and cooled (–78 °C) solution. After 12 min, the solution became blue and O_2 was then bubbled through the mixture for 15 min to remove the excess of ozone. Ph_3P (1.11 g, 4.19 mmol) was added, the cooling bath was left in place but not recharged, and stirring was continued for 14 h. Evaporation of the solution gave aldehyde **30.2** [^{1}H NMR ($CDCl_3$, 500 MHz) signal at δ 9.8] as a yellow residue, which was used directly in the next step.

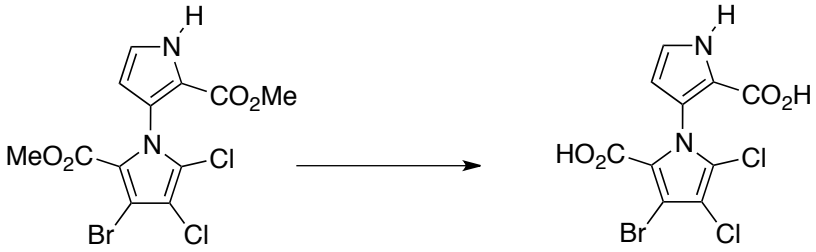
Methyl 3-bromo-4,5-dichloro-1-[2-(methoxycarbonyl)-1*H*-pyrrol-3-yl]-1*H*-pyrrole-2-carboxylate (30.1).



30.2 **30.1**

NH_4OAc (2.57 g, 33.3 mmol) was added to a stirred solution of the above crude ketoaldehyde **30.2** in AcOH (14 mL) and stirring was continued for 30 min. Saturated aqueous NH_4Cl was then added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 25 cm), using 1:10 to 3:10 EtOAc-hexanes, gave **30.1** (504.5 mg, 61% over three steps) as a light yellow solid: mp 188−190 °C; FTIR ($CDCl_3$, cast) 3309, 3141, 3004, 2953, 2847, 2256, 1707, 1581, 1523, 1504, 1445 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.73 (s, 3 H), 3.77 (s, 3 H), 6.29 (d, J = 3.0 Hz, 1 H), 6.98 (d, J = 3.0 Hz, 1 H), 9.53 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.6 (q), 51.9 (q), 105.3 (s), 110.9 (d), 113.5 (s), 118.2 (s), 121.2 (d), 121.8 (s), 122.8 (s), 125.6 (s), 159.2 (s), 159.8 (s); exact mass (electrospray) m/z calcd for $C_{12}H_9{}^{79}Br^{35}Cl_2N_2NaO_4$ (M + Na) 416.9015, found 416.9008. A sample was crystallized from $CHCl_3$ for X-ray analysis.

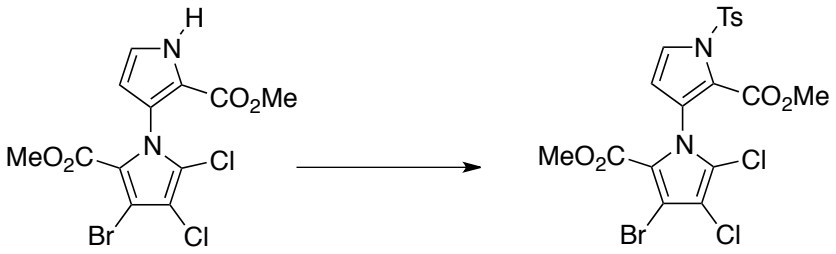
3-Bromo-1-(2-carboxy-1*H*-pyrrol-3-yl)-4,5-dichloro-1*H*-pyrrole-2-carboxylic acid (34.1).



30.1 **34.1**

A mixture of **30.1** (103.0 mg, 0.26 mmol) and 20% NaOH (6 mL) was stirred under reflux for 2.5 h. The mixture was cooled to 0 °C, acidified with hydrochloric acid (6 M), and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated to give **34.1** (94.8 mg, 99%) as a light brown solid: FTIR (neat) 3256, 3132, 1673, 1580, 1524, 1513, 1459 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 6.23 (t, J = 2.8 Hz, 1 H), 6.98 (d, J = 3.2 Hz, 1 H), 12.06 (s, 1 H), 12.65 (br s, 2 H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 108.3 (s), 115.2 (d), 116.4 (s), 123.5 (s), 126.3 (s), 126.6 (d), 128.1 (s), 130.1 (s), 164.1 (s), 165.5 (s); exact mass (electrospray) m/z calcd for $C_{10}H_4{}^{79}Br^{35}Cl_2N_2O_4$ (M – H) 364.8737, found 364.8738.

Methyl 3-bromo-4,5-dichloro-1-[2-(methoxycarbonyl)-1-[(4-methyl-benzene)sulfonyl]-1*H*-pyrrol-3-yl]-1*H*-pyrrole-2-carboxylate (35.1).

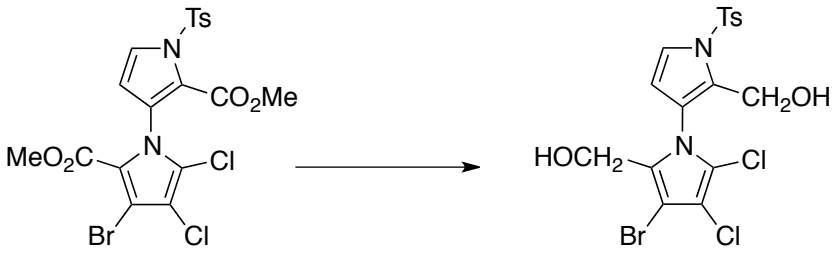


30.1 **35.1**

DMAP (286.5 mg, 2.32 mmol) and *i*-Pr_2NEt (0.41 mL, 2.35 mmol) were added to a stirred and cooled (0 °C) solution of **30.1** (463.8 mg, 1.16 mmol) in CH_2Cl_2 (12 mL). After 10 min, TsCl (886.5 mg, 4.65 mmol) was added. The ice bath was left in place but not recharged and stirring was continued for 24 h. The mixture was then 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 (2.8 x 20 cm), using 1:10 to 1:5 EtOAc-hexanes, gave **35.1** (631.6 mg, 98%) as a white solid: mp 165−167 °C; FTIR ($CDCl_3$, cast) 3157, 3130, 3036, 3002, 2954, 2921, 2850, 2257, 1926, 1724, 1595, 1569, 1530, 1448, 1422 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.44 (s, 3 H), 3.52 (s, 3 H), 3.62 (s, 3 H), 6.35 (d, J = 3.5 Hz, 1 H), 7.34−7.37 (m, 2 H), 7.75 (d, J = 3.5 Hz, 1 H), 7.85−7.87 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.8 (q), 51.6 (q), 52.2 (q), 105.8 (s), 111.4 (d), 113.9 (s), 121.2 (s), 121.7 (s), 122.4 (s), 126.3 (d), 128.0 (d), 129.6 (d), 130.9 (s), 135.6 (s), 145.5 (s), 157.8 (s), 158.5

(s); exact mass (electrospray) *m*/*z* calcd for $C_{19}H_{15}{}^{79}Br^{35}Cl_2N_2NaO_6S$ (M + Na) 570.9103, found 570.9096.

{3-Bromo-4,5-dichloro-1-[2-(hydroxymethyl)-1-[(4-methylbenzene)-sulfonyl]-1*H*-pyrrol-3-yl]-1*H*-pyrrol-2-yl}methanol (35.2).

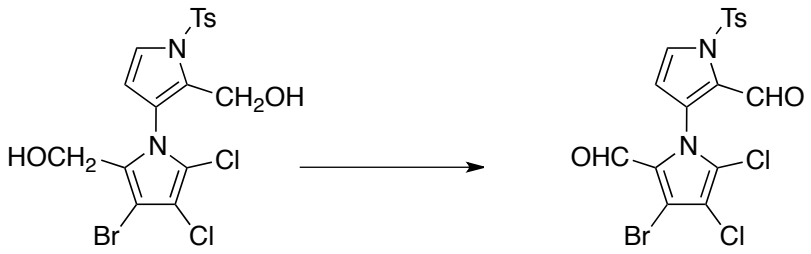


35.1 **35.2**

DIBAL-H (1.0 M in PhMe, 1.80 mL, 1.80 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **35.1** (184.2 mg, 0.33 mmol) in CH_2Cl_2 (4 mL). The cooling bath was removed and stirring was continued for 10.5 h. MeOH (0.5 mL) and saturated aqueous Rochelle's salt (ca 10 mL) were then added sequentially. Stirring was continued for 1 h, and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 20 cm), using 3:10 to 2:5 EtOAc-hexanes, gave **35.2** (169.7 mg, 100%) as a white solid: mp 95−98 °C; FTIR (neat) 3233, 3145, 3124, 2940, 2884, 2733, 1920, 1653, 1589, 1485, 1447 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.44 (s, 3 H), 3.21 (br s, 1 H), 3.49 (br s, 1 H), 4.08−4.14 (m, 2 H), 4.47 (d, *J* = 13.5 Hz, 1 H),

4.69 (d, J = 14.0 Hz, 1 H), 6.24 (d, J = 3.5 Hz, 1 H), 7.35−7.37 (m, 3 H), 7.81−7.84 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.7 (q), 52.2 (t), 54.5 (t), 98.8 (s), 111.3 (s), 111.4 (d), 116.1 (s), 122.3 (d), 123.4 (s), 127.2 (d), 130.3 (d), 131.8 (s), 131.9 (s), 135.3 (s), 146.1 (s); exact mass (electrospray) m/z calcd for $C_{17}H_{15}{}^{79}Br^{35}Cl_2N_2NaO_4S$ (M + Na) 514.9205, found 514.9202.

3-Bromo-4,5-dichloro-1-{2-formyl-1-[(4-methylbenzene)sulfonyl]-1*H*-pyrrol-3-yl}-1*H*-pyrrole-2-carbaldehyde (35.3).

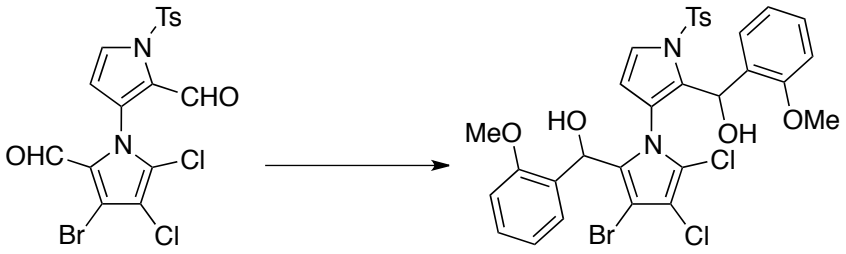


35.2 **35.3**

IBX (898.8 mg, 3.21 mmol) was added to a stirred solution **35.2** (239.7 mg, 0.49 mmol) in DMSO (10 mL). The mixture was heated to 70 °C for 15 h and then cooled to room temperature. The resulting suspension was filtered and water was added to the filtrate. The solution was then extracted with EtOAc and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 20 cm), using 1:10 to 1:5 EtOAc-hexanes, gave **35.3** (332.5 mg, 87%) as a white solid: mp 140−143 °C; FTIR ($CDCl_3$, cast) 3331, 3147, 3056, 2924, 2850, 2801, 2255, 1674, 1595, 1559,

1515, 1493, 1481, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.44 (s, 3 H), 6.40 (dd, *J* = 0.5, 3.0 Hz, 1 H), 7.36-7.39 (m, 2 H), 7.63 (d, *J* = 3.5 Hz, 1 H), 7.76-7.79 (m, 2 H), 9.43 (s, 1 H), 9.97 (d, *J* = 0.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.8 (q), 111.5 (s), 112.7 (d), 114.8 (s), 125.7 (s), 126.8 (d), 127.01 (s), 127.05 (s), 127.2 (d), 130.3 (s), 130.5 (d), 134.9 (s), 146.7 (s), 176.7 (d), 178.1 (d); exact mass (electrospray) *m*/*z* calcd for $C_{17}H_{11}{}^{79}Br^{35}Cl_2N_2NaO_4S$ (M + Na) 510.8992, found 510.8890.

(3-{3-Bromo-4,5-dichloro-2-[hydroxy(2-methoxyphenyl)methyl]-1*H*-pyrrol-1-yl}-1-[(4-methylbenzene)sulfonyl]-1*H*-pyrrol-2-yl)(2-methoxyphenyl)methanol (35.4).



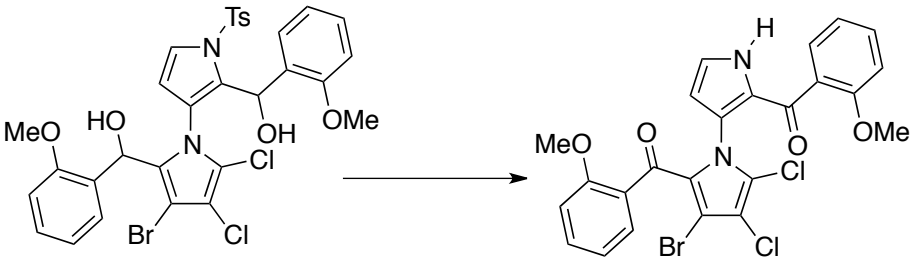
35.3 **35.4**

2-Methoxyphenylmagnesium bromide (1.0 M in THF, 3.13 mL, 3.13 mmol) was added to a stirred and cooled (0 °C) solution of **35.3** (153.6 mg, 0.31 mmol) in THF (3 mL), and stirring at 0 °C was continued for 4 h. The mixture was quenched with saturated aqueous Na_2SO_4 and extracted with EtOAc. The

combined organic extracts were dried ($MgSO_4$) and evaporated to give **35.4** as a yellow residue, which was used directly in the next step.

In a subsequent attempt to oxidize the diols **35.4**, one isomer was recovered and had: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.45 (s, 3 H), 2.88 (d, *J* = 7.5 Hz, 1 H), 3.40 (s, 3 H), 3.60 (d, *J* = 7.5 Hz, 1 H), 3.61 (s, 3 H), 5.35 (d, *J* = 5.5 Hz, 1 H), 5.64 (d, *J* = 3.5 Hz, 1 H), 6.17 (d, *J* = 7.0 Hz, 1 H), 6.58 (d, *J* = 8.5 Hz, 1 H), 6.74−6.77 (m, 1 H), 6.84−6.90 (m, 2 H), 7.15−7.26 (m, 3 H), 7.27−7.32 (m, 3 H), 7.40−7.43 (m, 1 H), 7.62−7.66 (m, 2 H); exact mass (electrospray) *m*/*z* calcd for $C_{31}H_{27}{}^{79}Br^{35}Cl_2N_2NaO_6S$ (M + Na) 727.0042, found 727.0027. A sample was crystallized from Et_2O for X-ray analysis.

3-Bromo-4,5-dichloro-2-[(2-methoxyphenyl)carbonyl]-1-{2-[(2-methoxyphenyl)carbonyl]-1*H*-pyrrol-3-yl}-1*H*-pyrrole (25.1).



35.4 **25.1**

DMSO (6 mL) was added to dissolve the above crude diols **35.4**, and IBX (263.3 mg, 0.94 mmol) was added to the solution. The mixture was stirred at 70 °C for 29 h and then cooled, quenched with water and extracted with EtOAc. The

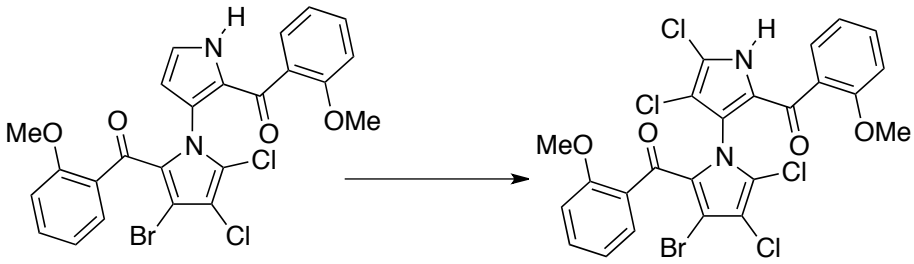
combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 20 cm), using 1:10 to 1:5 EtOAc-hexanes, gave the intermediate ketoalcohol(s) as a yellow oil. I was unable to obtain satisfactory NMR data: exact mass (electrospray) *m*/*z* calcd for $C_{31}H_{25}{}^{79}Br^{35}Cl_2N_2NaO_6S$ (M + Na) 724.9886, found 724.9882.

Jones reagent (7.0 M in acetone, 0.25 mL, 1.75 mmol) was added dropwise to a stirred and cooled (0 °C) solution of the ketoalcohol(s) in acetone (2 mL) and stirring at 0 °C was continued for 4 h. The mixture was quenched with MeOH (2 mL) and stirring was continued for 30 min, by which time the mixture had become dark green. The mixture was diluted with EtOAc and washed with water and brine, dried ($MgSO_4$) and evaporated to give the diketone as a yellow residue: exact mass (electrospray) *m*/*z* calcd for $C_{31}H_{23}{}^{79}Br^{35}Cl_2N_2NaO_6S$ (M + Na) 722.9729, found 722.9731.

MeOH (1.5 mL) and THF (1.5 mL) were then added to the diketone, followed by KOH (74.0 mg, 1.32 mmol). The mixture was stirred for 1 h at room temperature and then adjusted to pH 7.0 with hydrochloric acid (0.5 M). The neutralized mixture was extracted with EtOAc, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 20 cm), using 1:10 to 1:2 EtOAc-hexanes, gave **25.1** (46.0 mg, 27% over four steps) as a yellow oil: FTIR ($CDCl_3$, cast) 3283, 3077, 3004, 2942, 2838, 2249, 1714, 1634, 1599, 1581, 1556, 1489, 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.72 (s, 3 H), 3.78 (s, 3 H), 6.01 (t, *J* = 3.0 Hz, 1 H), 6.73 (dt, *J* = 1.0,

7.5 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 6.81 (d, *J* = 8.5 Hz, 1 H), 6.88 (t, *J* = 3.0 Hz, 1 H), 6.91 (dt, *J* = 1.0, 7.5 Hz, 1 H), 7.14 (dd, *J* = 1.5, 7.5 Hz, 1 H), 7.18 (dd, *J* = 2.0, 7.5 Hz, 1 H), 7.28 (ddd, *J* = 2.0, 7.5, 8.5 Hz, 1 H), 7.33 (ddd, *J* = 1.5, 7.5, 8.5 Hz, 1 H), 9.62 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.5 (q), 55.7 (q), 105.0 (s), 110.6 (d), 110.8 (d), 111.0 (d), 113.6 (s), 119.5 (d), 120.5 (d), 122.5 (s), 122.8 (d), 125.7 (s), 126.6 (s), 127.9 (s), 128.2 (d), 129.0 (s), 129.5 (d), 130.8 (s), 131.5 (d), 132.2 (d), 156.5 (s), 157.3 (s), 183.2 (s), 183.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{24}H_{17}{}^{79}Br^{35}Cl_2N_2NaO_4$ (M + Na) 568.9641, found 568.9636.

3-Bromo-4,5-dichloro-1-{4,5-dichloro-2-[(2-methoxyphenyl)carbonyl]-1*H*-pyrrol-3-yl}-2-[(2-methoxyphenyl)carbonyl]-1*H*-pyrrole (36.1).

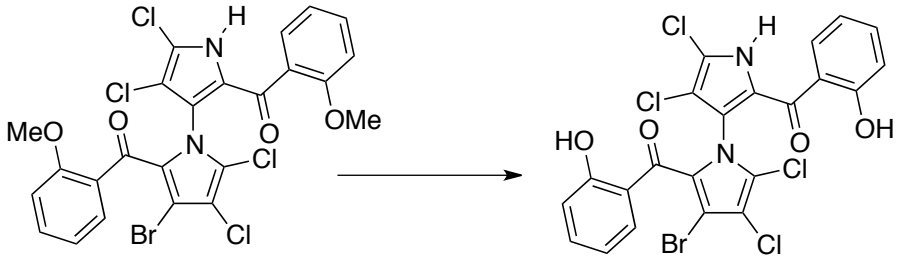


25.1 **36.1**

NCS (22.7 mg, 0.17 mmol) was added to a stirred solution of **25.1** (45.4 mg, 0.083 mmol) in MeCN (1 mL). The mixture was heated to 35 °C for 15.5 h, cooled to room temperature, quenched with water and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash

chromatography of the residue over silica gel (1.8 x 20 cm), using 1:10 to 2:5 EtOAc-hexanes, gave **36.1** (38.8 mg, 76%) as a yellow oil: FTIR ($CDCl_3$, cast) 3200, 3004, 2943, 2838, 2250, 1726, 1634, 1599, 1581, 1558, 1489, 1463 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.74 (s, 3 H), 3.77 (s, 3 H), 6.74 (dt, *J* = 1.0, 7.5 Hz, 1 H), 6.79 (d, *J* = 8.5 Hz, 1 H), 6.84 (d, *J* = 8.5 Hz, 1 H), 6.92 (dt, *J* = 1.0, 7.5 Hz, 1 H), 7.16 (dd, *J* = 1.5, 7.5 Hz, 1 H), 7.18 (dd, *J* = 1.5, 7.5 Hz, 1 H), 7.29 (ddd, *J* = 2.0, 7.5, 8.5 Hz, 1 H), 7.38 (ddd, *J* = 1.5, 7.5, 8.5 Hz, 1 H), 9.88 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.59 (q), 55.60 (q), 106.4 (s), 110.6 (d), 110.8 (s), 111.0 (d), 114.5 (s), 119.6 (d), 119.9 (s), 120.5 (d), 122.8 (s), 123.3 (s), 125.9 (s), 126.4 (s), 128.3 (s), 128.4 (d), 129.3 (d), 130.4 (s), 132.1 (d), 132.2 (d), 156.6 (s), 157.2 (s), 182.3 (s), 183.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{24}H_{15}{}^{79}Br^{35}Cl_4N_2NaO_4$ (M + Na) 636.8862, found 636.8861.

2-[(3-{3-Bromo-4,5-dichloro-2-[(2-hydroxyphenyl)carbonyl]-1*H*-pyrrol-1-yl}-4,5-dichloro-1*H*-pyrrol-2-yl)carbonyl]phenol, [(±)-marinopyrrole B].



36.1 (±)-**marinopyrrole B**

BBr_3 (1.0 M in CH_2Cl_2, 1.04 mL, 1.04 mmol) was added to a stirred and cooled (–78 °C) solution of **36.1** (64.1 mg, 0.104 mmol) in CH_2Cl_2 (1.5 mL). After 50 min at –78 °C, the mixture was quenched with MeOH, diluted with water and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 20 cm), using 1:20 to 3:20 EtOAc-hexanes, gave (±)-marinopyrrole B (54.0 mg, 88%) as a yellow solid: mp 199-201 °C; FTIR ($CDCl_3$, cast) 3232, 1622, 1592, 1483, 1452 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.58 (t, *J* = 2.5 Hz, 1 H), 6.86 (t, *J* = 2.5 Hz, 1 H), 6.97 (dd, *J* = 1.0, 8.5 Hz, 1 H), 7.00 (d, *J* = 8.5 Hz, 1 H), 7.40−7.44 (m, 2 H), 7.48−7.54 (m, 2 H), 9.96 (br s, 1 H), 10.36 (s, 1 H), 11.10 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 104.7 (s), 114.7 (s), 117.9 (d), 118.1 (d), 118.5 (s), 118.7 (d), 118.9 (s), 119.2 (d), 120.2 (s), 121.7 (s), 122.0 (s), 124.3 (s), 128.4 (s), 130.0 (d), 134.2 (d), 136.4 (d), 137.3 (d), 161.3 (s), 162.5 (s), 185.4 (s), 188.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{22}H_{10}{}^{79}Br^{35}Cl_4N_2O_4$ (M – H) 584.8584, found 584.8583. A sample was crystallized from PhMe for X-ray analysis.

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