UNIVERSITY OF ALBERTA

Synthesis of a Biologically Active Analog of the Angiotensin Converting Enzyme Inhibitor A58365A and Synthetic Studies on Indenones, Coleophomone B and Benesudon

by

Haikang Yang

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TO

my wife, Ni Yang,

my two daughters, Shuling and Nina Yang,

and my parents

ACKNOWLEDGMENTS

I would like to express my gratitude to my supervisor, Dr. D. L. J. Clive, for his constant support, encouragement and advice during the course of my Ph.D. program, and for his assistance during the preparation of this thesis.

I would also like to thank all the group members, past and present, for their useful discussions. In particular, I want to thank Dr. Don Coltart and Dr. Hua Cheng for their generous assistance during the initial stages of my laboratory work.

My thanks also go to the support staff of the Department of Chemistry, especially those in the NMR, MS, IR and X-ray crystallography laboratories, and the Chemical Stores.

Finally, I must give my very special thanks to my wife and my two lovely daughters for their constant support, encouragement and understanding.

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LIST OF ABBREVIATIONS

AIBN	2,2′-azobisisobutyronitrile
9-BBN	9-borabicyclo[3.3.1]nonane
Boc	*tert*-butoxycarbonyl
t-Bu	*tert*-butyl
cod	1,5-cyclooctadiene
mCPBA	*m*-chloroperoxybenzoic acid
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
EDCI	1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride
HBTU	*O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HMPA	hexamethylphosphoramide
HOBt	hydroxybenztriazole
IBX	2-iodoxybenzoic acid
KHMDS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiHDMS	lithium hexamethyldisilazide
LTMP	lithium tetramethylpiperidide
MOM	methoxymethyl
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide

NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
PCC	pyridinium chlorochromate
Pg	protecting group
Ph	phenyl
PPTS	pyridinium *p*-toluenesulfonate
Py	pyridine
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	*p*-toluenesulfonyl

CHAPTER 1

SYNTHESIS OF AN ANALOG OF ACE INHIBITOR A58365A

INTRODUCTION

Renin-Angiotensin system[1]

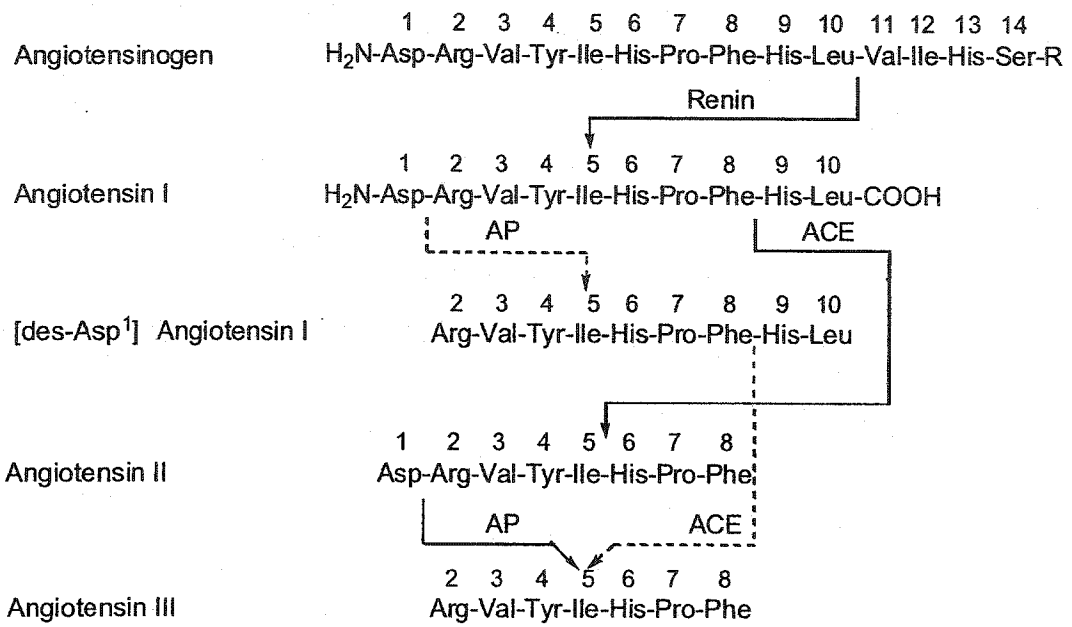
A pressor principle called renin exists in the crude saline extracts of kidney. This compound is an enzyme which produces persistent hypertension (elevated blood pressure) in humans and animals by constricting the renal arteries. The process occurs when renin acts on a plasma protein substrate called angiotensinogen to catalyze the formation of the actual pressor material, a peptide called angiotensin.

In the 1950s, Skeggs and Peart determined the amino acid composition and sequence of angiotensin. Two forms, a decapeptide (angiotensin I) and an octapeptide (angiotensin II) were recognized. Angiotensin II is formed from angiotensin I by enzymatic cleavage by another enzyme, termed angiotensin-converting enzyme (ACE). The octapeptide, angiotensin II, was shown to be more active, and its synthesis[2] in 1957 made the material available for intensive study.

The synthesis and degradation of the angiotensins is a complex process, which is outlined in Scheme 1. Briefly, the sequence is initiated when renin acts on angiotensinogen (the renin substrate) to release the decapeptide angiotensin I. This decapeptide has limited pharmacological activity, but it is cleaved by ACE to yield the highly active octapeptide angiotensin II. This, in turn, undergoes hydrolysis by an aminopeptidase (AP) to yield the heptapeptide angiotensin III, which is also pharmacologically active. Further cleavage yields peptides with little activity.

In an alternative and minor pathway, ACE and AP act in the opposite order such that the decapeptide angiotensin I, is hydrolyzed first to [des-Asp^1]angiotensin I which, like the parent compound, has limited pharmacological activity. The [des-Asp^1]angiotensin I is then cleaved by ACE to form the active angiotensin III.[2,3]

Scheme 1



AP = Aminopeptidase; ACE = Angiotensin-Converting Enzyme
Solid arrows indicate major pathway; Dashed arrowed indicated minor pathways

Many fatal diseases are related to excessive amounts of angiotensin II in the blood. The compound causes vasoconstriction and often has an indirect effect on the heart, such that cardiac output is lowered. Angiotensin II is the most potent pressor agent known – about 40 times more powerful than norepinephrine on a molar basis. It also causes kidney disease due to its indirect effects on renal tubular function. In addition, angiotensin influences urine formation through hemodynamic and intrarenal actions that interact in a complex way.

Angiotensin I has less than 1% of the intrinsic activity of angiotensin II. However, angiotensin III retains most of the activity of angiotensin II, although in most instances it is somewhat weaker.

Angiotensin II Antagonists and Angiotensin Converting Enzyme Inhibitors

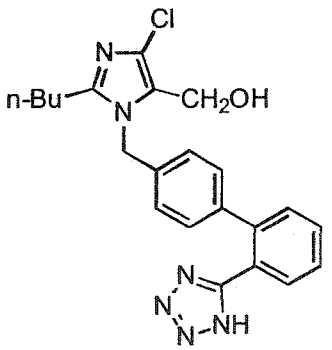
The renin-angiotensin system (RAS) plays an important

role in the control of renal function and blood pressure, and in the pathogenesis of some forms of hypertension. Consequently, much work has been focused on developing agents that can block the RAS in order to keep blood pressure within the proper range.

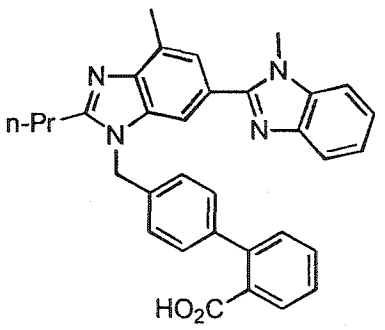
In the 1970s, two distinct classes of effective inhibitors of the RAS were identified: angiotensin II antagonists that block receptors for the peptide, and ACE inhibitors that slow the rate of formation of angiotensin II from its inactive precursor.

Useful angiotensin II antagonists are slightly modified analogs of the natural structure, in which agonist activity is profoundly attenuated by replacement of phenylalanine in position 8 with some other amino acid. The substances [Sar^1, Val^5, Ala^8] angiotensin (1-8) octapeptides, known as the Saralasin series, were introduced by Pals in 1971. Although angiotensin II analogs are highly specific antagonists, they also retain some agonist activity, which complicates interpretation of some of their effects.[4] However, direct blockade of the angiotensin II receptor (AT_1 receptor) has recently become feasible by the development of a series of orally active non-peptide antagonists for the AT_1 receptor. Losartan **2.1**

Scheme 2



2.1
Losartan, DUP 753



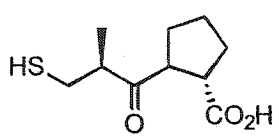
2.2
Telmisartan, BIBR 277

and Telmisartan **2.2**, shown in Scheme 2, have been found to be very powerful AT_1 antagonists.[5,6,7] These non-peptide antagonists are highly selective for the AT_1 receptor and, in contrast to the peptide-based antagonists that are angiotensin analogs, they do not show any partial agonism.

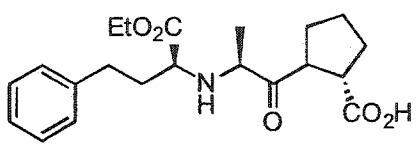
Angiotensin-converting Enzyme (ACE) inhibitors are also commonly used to inhibit the renin-angiotensin system (RAS).[1] The essential effect of ACE inhibitors on the RAS is to inhibit conversion of the relatively inactive angiotensin I into the active angiotensin II (or the conversion of [des-Asp^1]angiotensin I to angiotensin III). In this way they attenuate or abolish responses to angiotensin I. ACE inhibitors are highly specific drugs. They do not interact directly with other components of the RAS, including the receptor for the peptide. Also, research has shown that ACE inhibitors cause a greater decrease in blood pressure than does angiotensin II antagonism.

Captopril[8] (**3.1**, Scheme 3), the first orally active ACE inhibitor, has been marketed for the treatment of severe or drug-resistant hypertension since the 1980s. Unfortunately, it can cause some potentially hazardous side effects, possibly due to its sulfhydryl moiety.[9] Enalapril (**3.2**), a nonsulfhydryl-containing ACE inhibitor, is also used for treatment of hypertension. Enalapril is a prodrug that is not itself highly active; it must be hydrolyzed to its active parent dicarboxylic acid, Enalaprilate. Enalapril has been found to be more potent than captopril

Scheme 3



3.1
Captopril



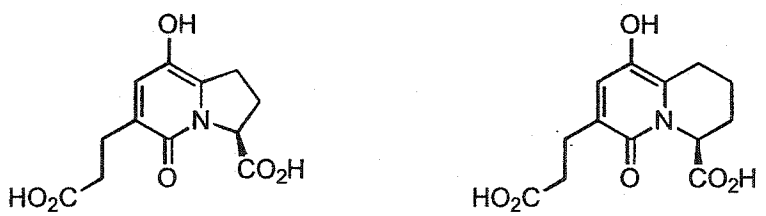
3.2
Enalapril

and to inhibit ACE for longer periods.[8,9,10]

(-)-A58365A and (-)-A58365B

(-)-A58365A and (-)-A58365B, two potent ACE inhibitors, were isolated from the fermentation broth of a soil bacterium *Streptomyces chromofuscus* NRRL 15089.[11,12,13] These two natural products possess homologous nitrogen-containing bicyclic structures shown in Scheme 4.

Scheme 4

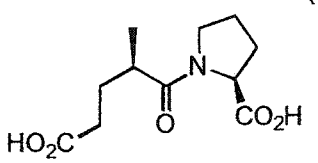


4.1

(-)-A58365A

4.2

(-)-A58365B



4.3

(-)-A58365A is, in fact, a naturally occurring, conformationally restricted analog of α-methylglutaryl-L-proline (**4.3**), which was important in the structure-activity relationship studies leading to the development of captopril.

The Nakatsukasa research group investigated[14] a biosynthetic pathway for the formation of (-)-A58365A and (-)-A58365B by *Streptomyces chromofuscus* NRRL 15098. Fermentation studies afforded an increase in the amount of the ACE inhibitor from less than 1 μg/mL to 20 μg/mL. L-Proline was the obligatory supplement for ACE inhibitor biosynthesis. Without L-proline, less than 1 μg/mL of both (-)-A58365A and (-)-A58365B was synthesized. D-Proline or L-hydroxyproline could be used instead of L-proline, but were not superior to L-proline. Greater amounts of (-)-

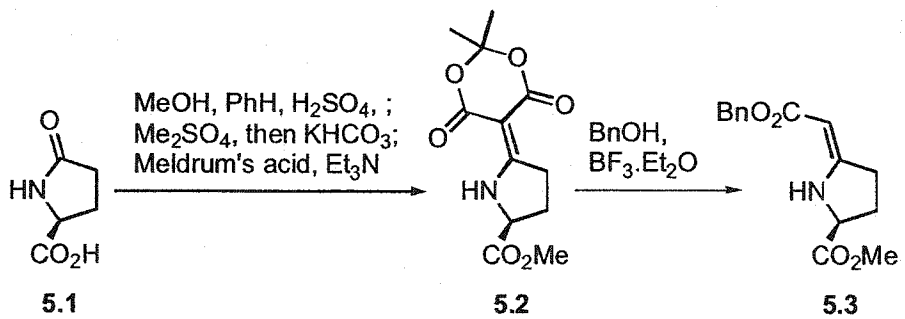
A58365A were synthesized when L-tyrosine was added to the medium with proline. Addition of lysine in combination with proline resulted in the fermentation process yielding greater amounts of (-)-A58365B. This suggested that (-)-A58365B synthesis is closely linked to that of (-)-A58365A. The studies also showed that (-)-A58365A is synthesized before its homolog (-)-A58365B.

Syntheses of A58365A and A58365B

Total Synthesis of (-)-A58365A by the Danishefsky Group

In 1989, Danishefsky and Fang reported[15] the first total synthesis of (-)-A58365A. The authors pointed out that their route to (-)-A58365A involves some low yielding steps. The synthesis was accomplished in eleven steps, starting from commercially available L-pyroglutamic acid (**5.1**), which was converted into vinylogous urethane **5.3** using a literature procedure (Scheme 5).

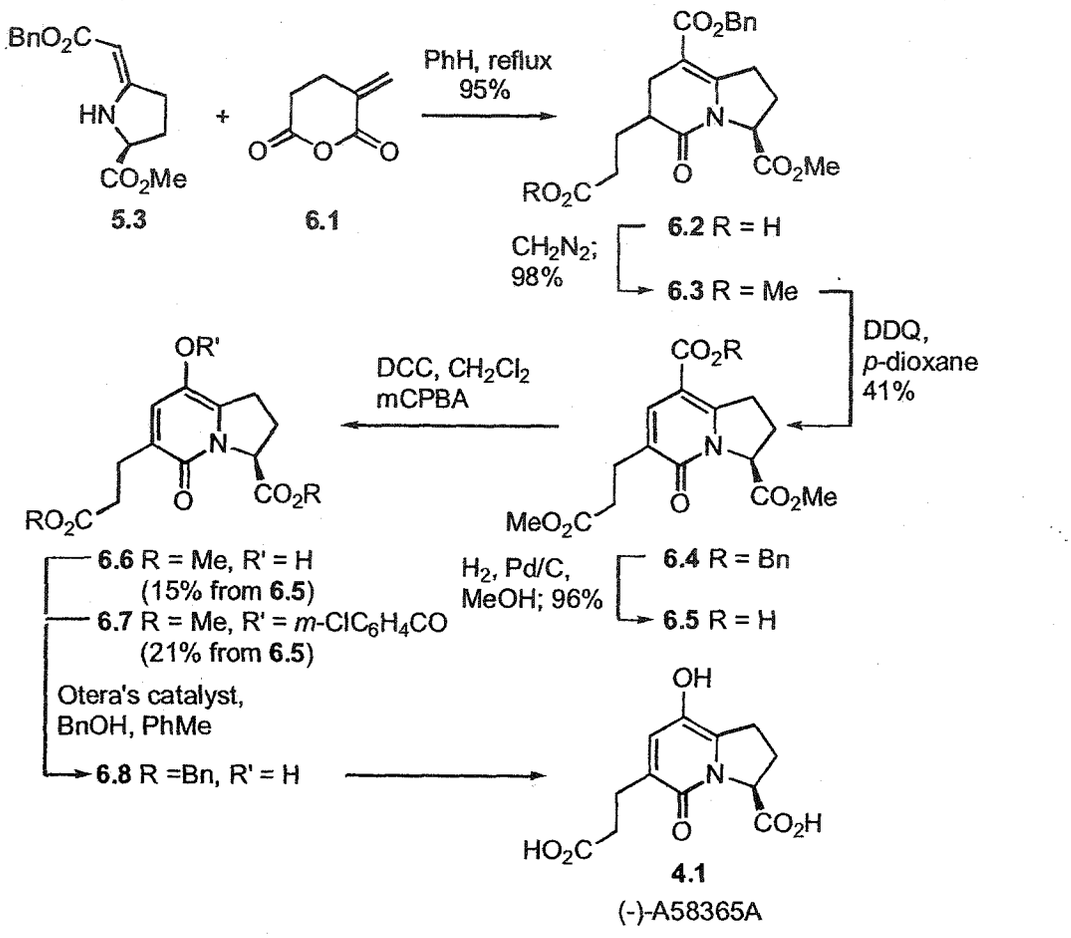
Scheme 5



5.1 **5.2** **5.3**

The annulation of **5.3** with α-methyleneglutaric anhydride (**6.1**) gave hexahydroindolizidine **6.2** (Scheme 6) in 95% yield. Esterification, following by DDQ oxidation, then generated pyridone **6.4**, which was subjected to hydrogenolysis to monocarboxylic acid **6.5**. Carboxy-inversion of **6.5** was effected by successive treatment with DCC and *m*-CPBA to provide A58365A-dimethyl ester (**6.6**) and

Scheme 6



A58365A-dimethyl ester *m*-chlorobenzoate **6.7**. Treatment of **6.6** and **6.7** with Otera's catalyst and BnOH gave dibenzyl ester **6.8**, which was made in order to facilitate purification. Finally, hydrogenolysis afforded optically pure (-)-A58365A.

Total Synthesis of (±)-A58365B and Formal Synthesis of (−)-A58365A by the Moeller Group[16]

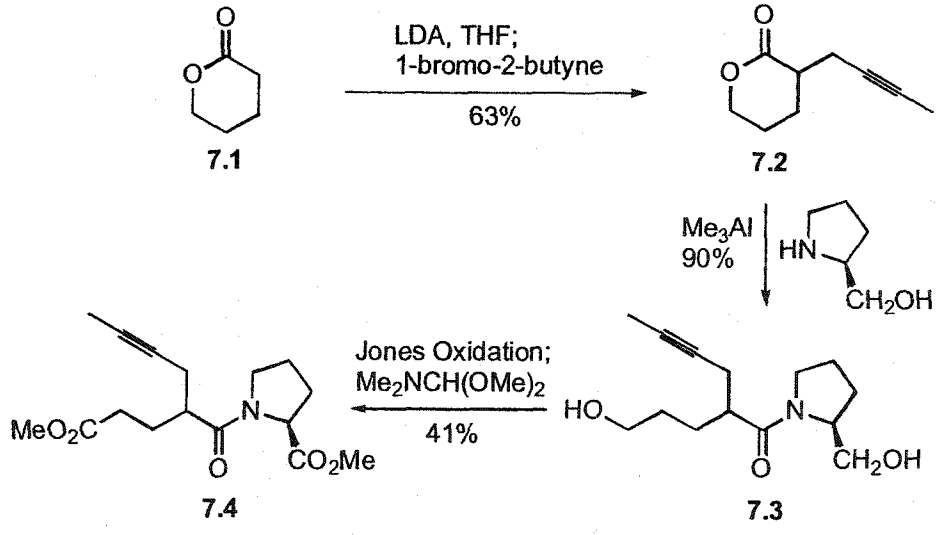
The first synthesis of (±)-A58365B and a formal synthesis of (-)-A58365A were achieved by Moeller and Wong, using an anodic amide oxidation-iminium ion cyclization strategy as a key transformation. An amide containing a nucleophile is selectively oxidized electrolytically at the position α to the nitrogen atom. Then a Lewis acid is used

to generate an iminium ion *in situ* and this is attacked by the nucleophile, giving a lactam. This oxidation-cyclization process was used to construct the bicyclic rings of A58365A and A58365B.

Formal Synthesis of (-)-A58365A

In the synthesis of (-)-A58365A, the electrolysis substrate **7.4** was prepared in four steps, as outlined in Scheme 7. Alkylation of δ-valerolactone (**7.1**) afforded lactone **7.2**, which was treated with (*S*)-(+)-2-pyrrolidinemethanol and Me_3Al to give compound **7.3** as a mixture of diastereomers. Jones oxidation, followed by esterification, then led to the required electrolysis substrate **7.4** in 41% yield.

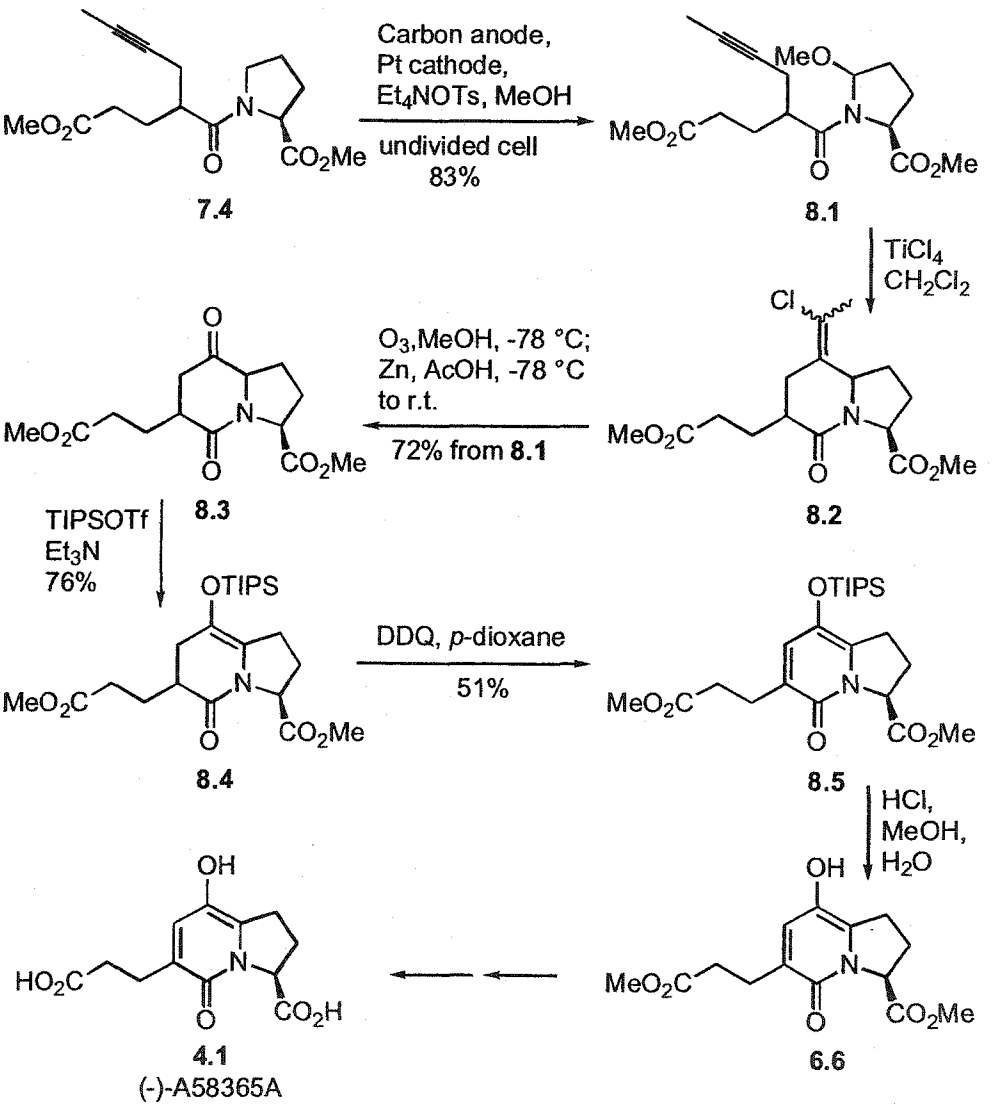
Scheme 7



The stage was now set for the key anodic amide oxidation and iminium ion cyclization (Scheme 8). Oxidation of **7.4** at a Pt cathode resulted in the methoxylated amide **8.1**, which underwent cyclization in the present of $TiCl_4$ to give the crude vinyl chlorides **8.2**. Immediate ozonolysis of **8.2** afforded ketone **8.3**, which was then converted into silyl enol ether **8.4**. Oxidation with DDQ, followed by deprotection of the triisopropylsilyloxy

group gave compound **6.6** with ca 92% ee. The modest ee indicated that epimerization at the original stereogenic center occurred during the synthesis, but the stage at which this took place was not established. The subsequent steps make the sequence converge with Danishefsky's route to (-)-A58365A.

Scheme 8

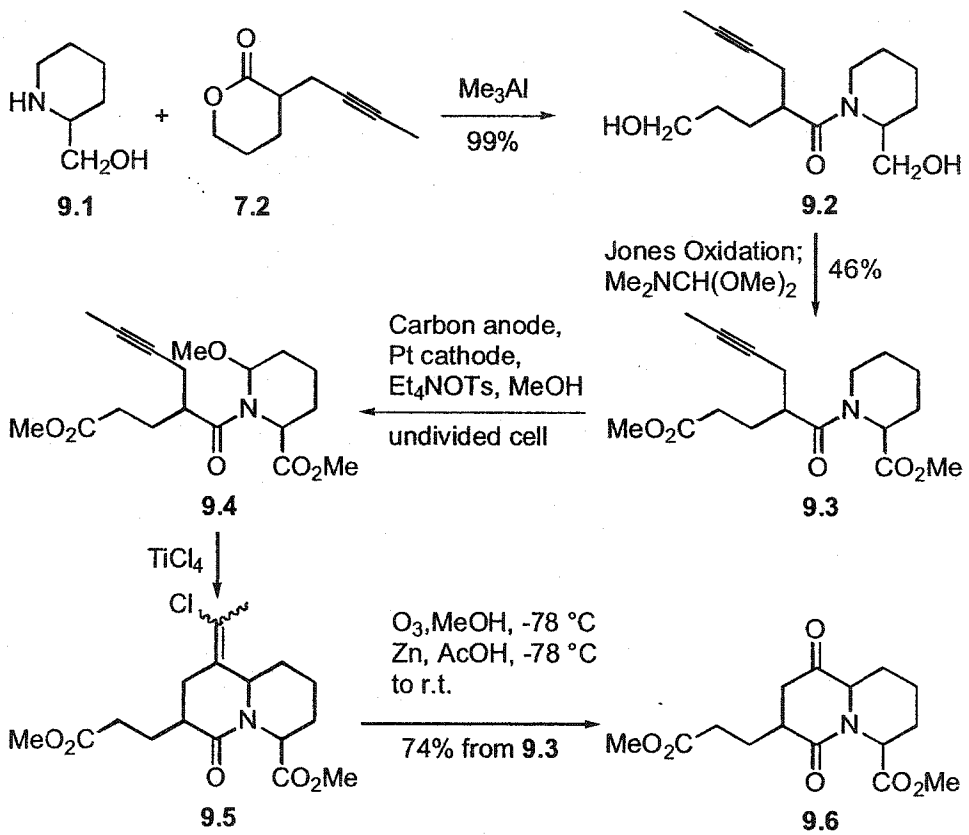


Total Synthesis of (±)-A58365B

The route to (-)-A58365A was modified for the synthesis of (±)-A58365B. The required substrate (**9.3**)

(Scheme 9) for the anodic amide oxidation was obtained using the same sequence as described above for the preparation of **7.4** (Scheme 7), except that the initial amine used was racemic 2-piperidinemethanol (**9.1**). The anodic amide oxidation, followed by titanium-induced cyclization and ozonolysis, afforded compound **9.6** in 74% yield over three steps.

Scheme 9

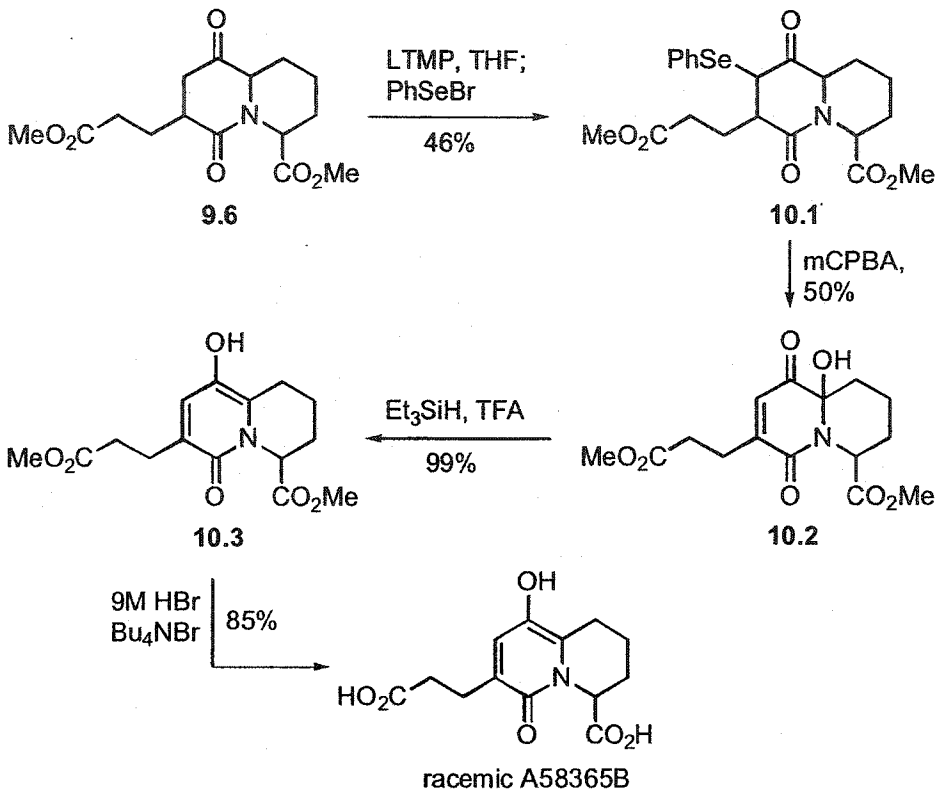


Selenenylation of **9.6**, followed by oxidation with *m*-CPBA, gave compound **10.2** (Scheme 10). Reduction with Et_3SiH and CF_3CO_2H led to formation of **10.3**, which was hydrolyzed to the desired product, (±)-A58365B, completing the first total synthesis of (±)-A58365B.

In the above syntheses there are some significant drawbacks: several steps gave low yields, the synthetic route was not completely general, and epimerization

occurred in the formal synthesis of (-)-A58365A.

Scheme 10



Total Synthesis of A58365B and A58365A by the Clive Group[17]

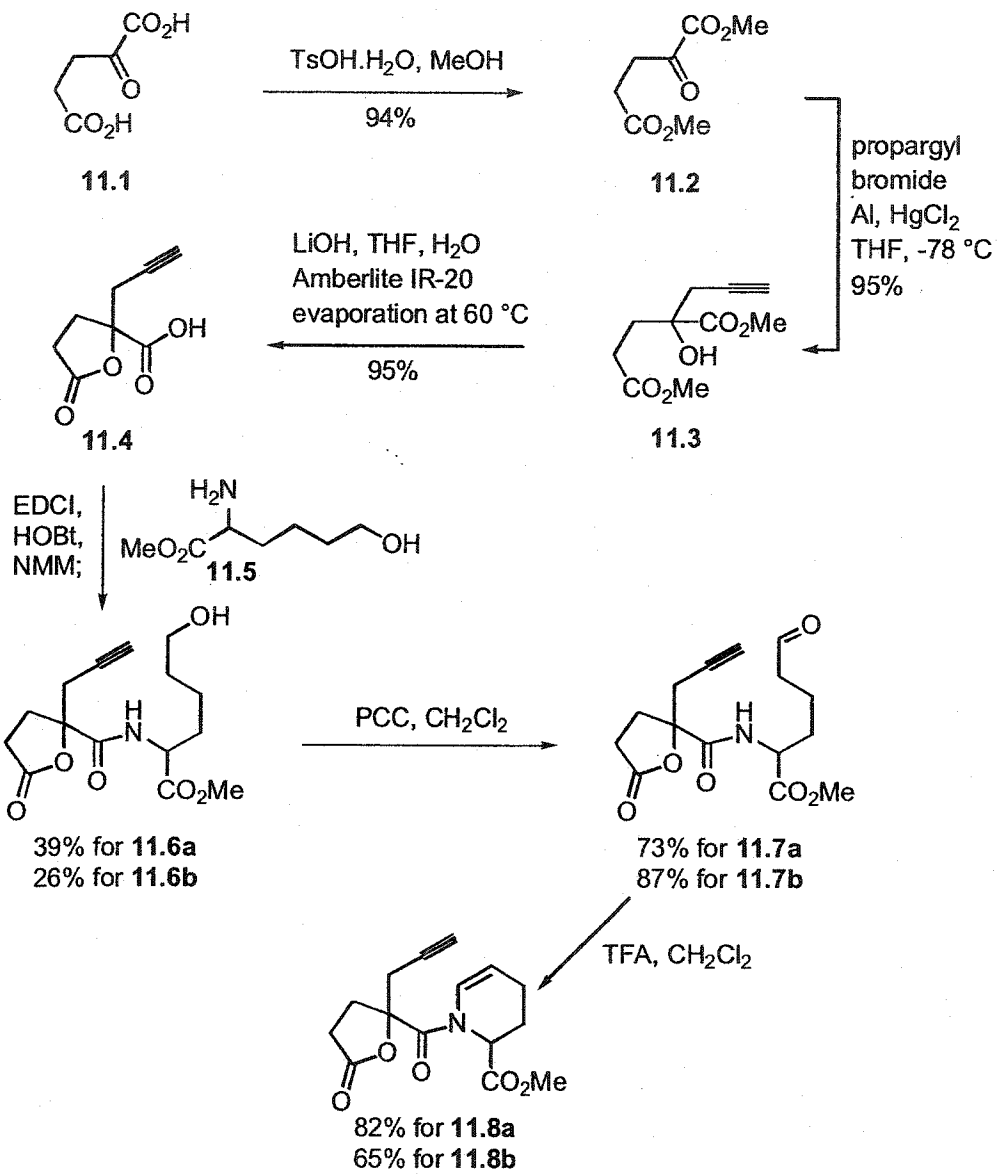
In order to efficiently construct the bicyclic pyridone rings of A58365A and A58365B, a general approach was developed in this laboratory. The strategy involves an enyne radical cyclization as a key step, subsequent cleavage of an exocyclic double bond with O_3, and opening of a spirolactone. This approach avoids the difficulties associated with attempts to selectively oxidize one ring of the bicyclic core structure.

Total Synthesis of (±)-A58365B

The general approach described above was first applied to the synthesis of (±)-A58365B. The radical cyclization substrate **11.8a,b** (Scheme 11) was synthesized from two

subunits, α-ketoglutaric acid **11.1** and ester **11.5**.

Scheme 11

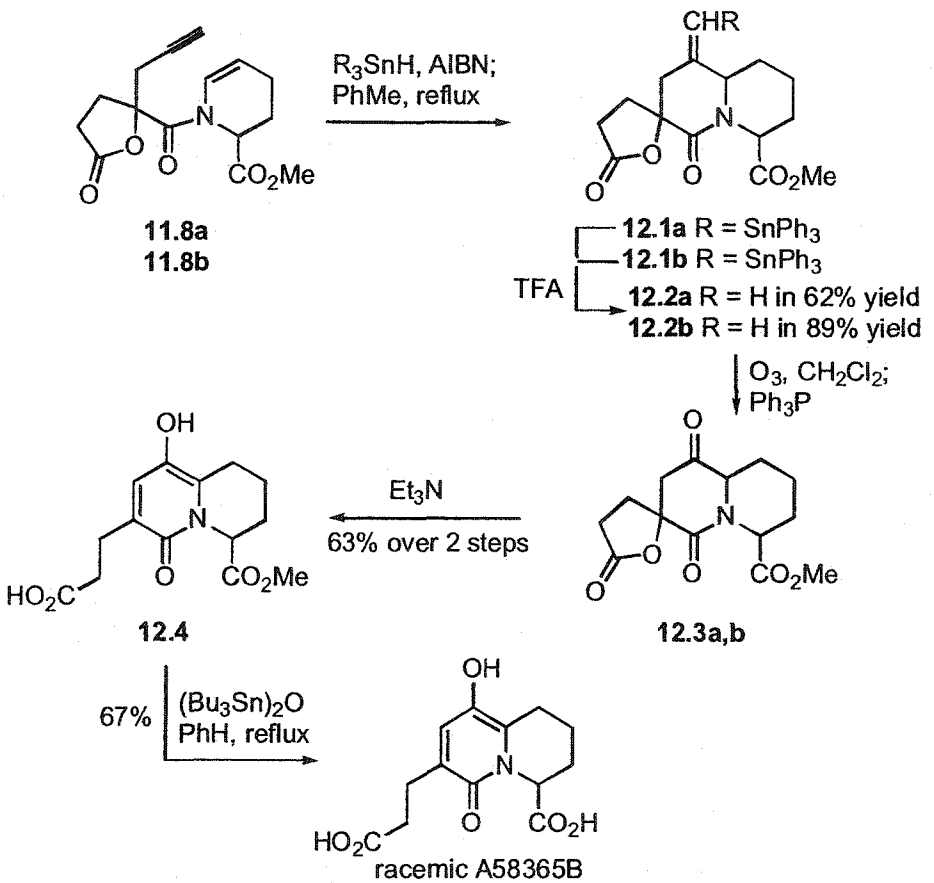


Methylation of **11.1**, followed by treatment with propargyl bromide and amalgamated aluminum, gave the desired product **11.3**. Ester hydrolysis, followed by ion-exchange chromatography and evaporation of the eluant, led to the formation of lactone acid **11.4**. This underwent coupling with **11.5** to afford the amides **11.6a** and **11.6b**, in 39% and 26% yield, respectively. PCC oxidation of the

individual amides, followed by acid catalyzed cyclization, resulted in the required substrates **11.8a,b** for the enyne radical cyclization.

Enyne radical cyclization occurred in the required manner, and protodestannylation with CF_3CO_2H gave compounds **12.2a,b** (Scheme 12). Ozonolysis and subsequent opening of the spirolactone with Et_3N generated acid **12.4** in 63% yield over two steps for each of the isomers. Finally, hydrolysis afforded (±)-A58365B.

Scheme 12

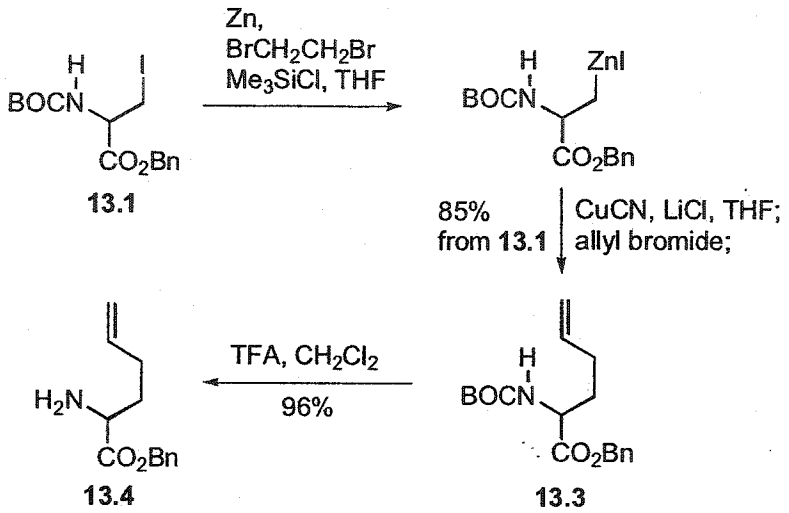


Total Syntheses of (±)-A58365A, (-)-A58365A, and (-)-A58365B

The route used above in the synthesis of (±)-A58365B was applied to (±)-A58365A, in a modified form. Two subunits **11.4** (Scheme 11) and **13.4** (Scheme 13) were required to construct the radical cyclization substrate

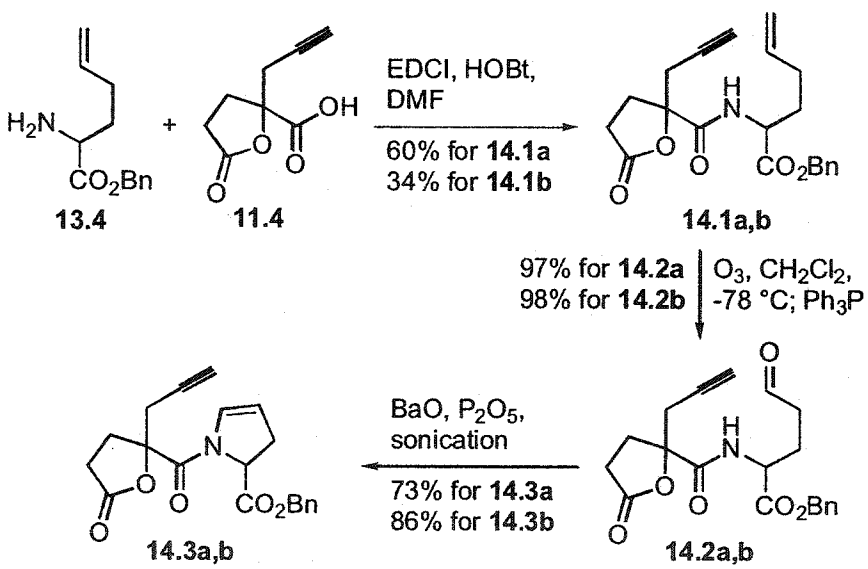
14.3a,b (Scheme 14).

Scheme 13



Allylation of iodide **13.1**[17c] and deprotection with CF_3CO_2H led to **13.4**, which was coupled with **11.4** to afford

Scheme 14

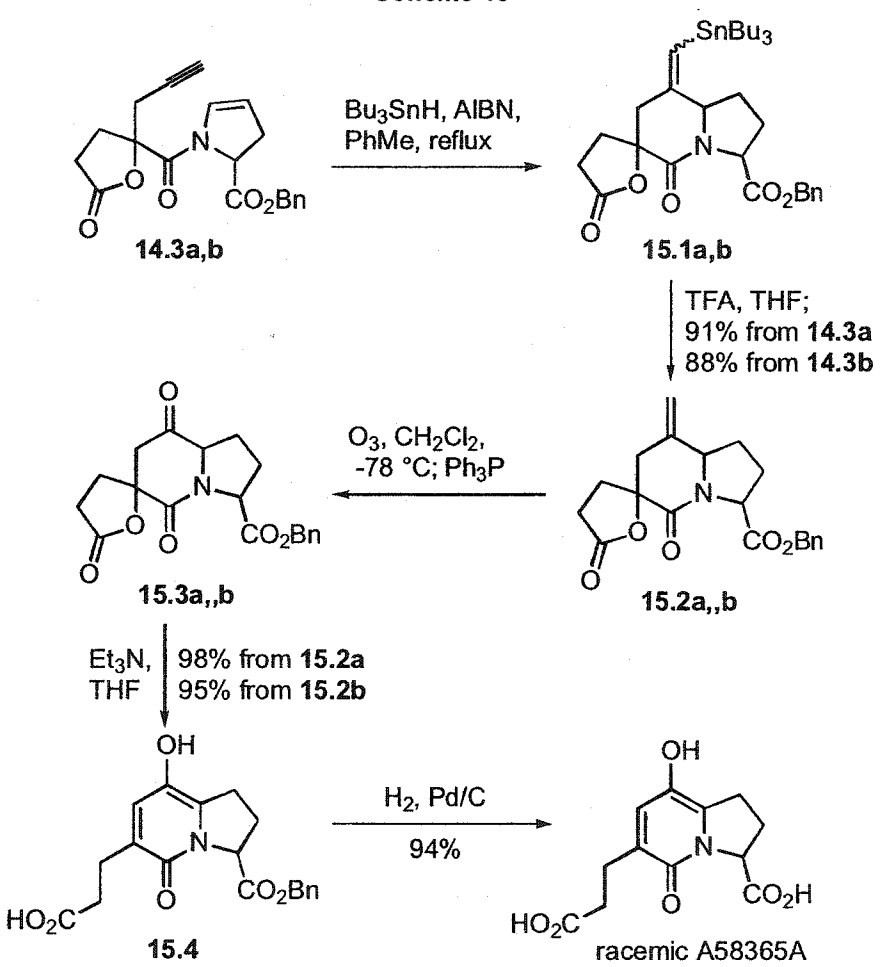


the two amides **14.1a** and **14.1b**, in 60% and 34% yields, respectively. Cleavage of the pendant double bond with O_3, followed by sonication with BaO and P_2O_5, then gave the required enamides **14.3a,b**.

The stage was now set for the enyne radical

cyclization. Separate treatment of **14.3a** and **14.3b** with Bu_3SnH and AIBN, and protodestannylation with CF_3CO_2H provided the desired compounds **15.2a,b** (Scheme 15). Once again, ozonolysis and spirolactone opening released the desired core structure, and hydrogenolysis then gave (±)-A58365A.

Scheme 15

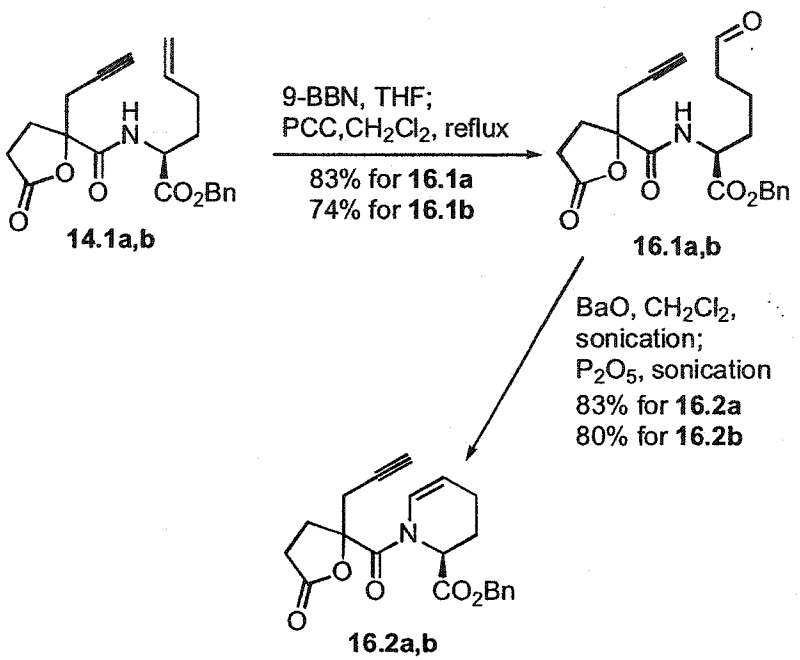


Optically pure (-)-A58365A was synthesized with an ee of 98.5%, using the same sequence, except that optically pure iodide **13.1**[17c] (Scheme 13) was used.

Based on the previous work leading to A58365A and (±)-A58365B in this laboratory, the synthesis of (-)-A58365B was also accomplished, commencing from the optically active intermediates **14.1a,b** (Scheme 14). Hydroboration with 9-

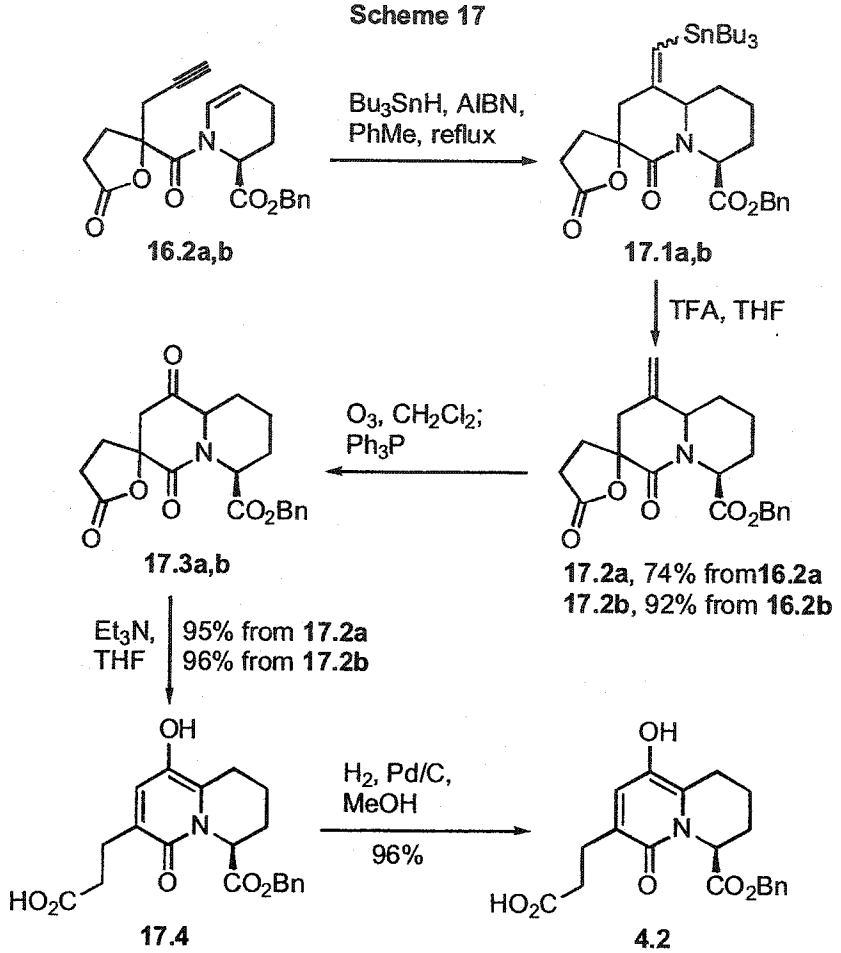
BBN occurred selectively at the double bond, and oxidation with PCC *in situ* afforded the desired aldehydes **16.1a,b** (Scheme 16). Sonication with BaO and P_2O_5 gave the enamides **16.2a,b** required for the enyne radical cyclization.

Scheme 16



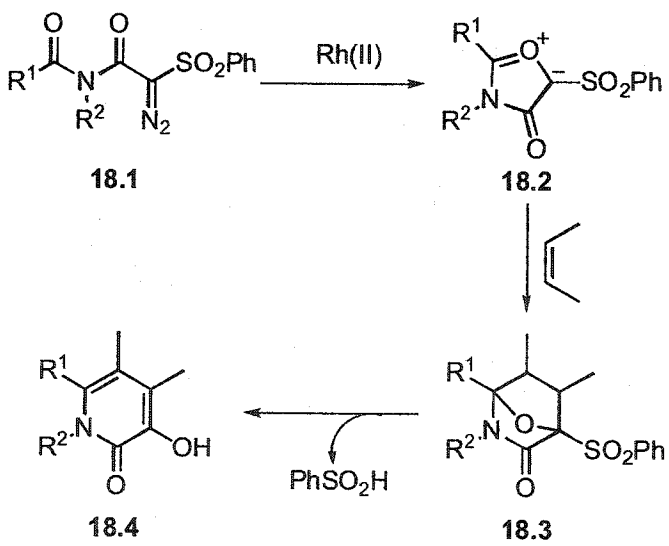
With compounds **16.2a,b** in hand, treatment with Bu_3SnH and AIBN, and protodestannylation with CF_3CO_2H led to the exocyclic olefins **17.2a,b** (Scheme 17). Cleavage of the double bond with O_3 and subsequent lactone opening with Et_3N furnished the benzyl ester **17.4**. Finally, deprotection was done by hydrogenolysis, thus completing the first synthesis of (-)-A58365B **4.2**. The material had an ee of 99%.

Scheme 17



Formal Synthesis of (-)-A58365A by the Padwa Group[18]

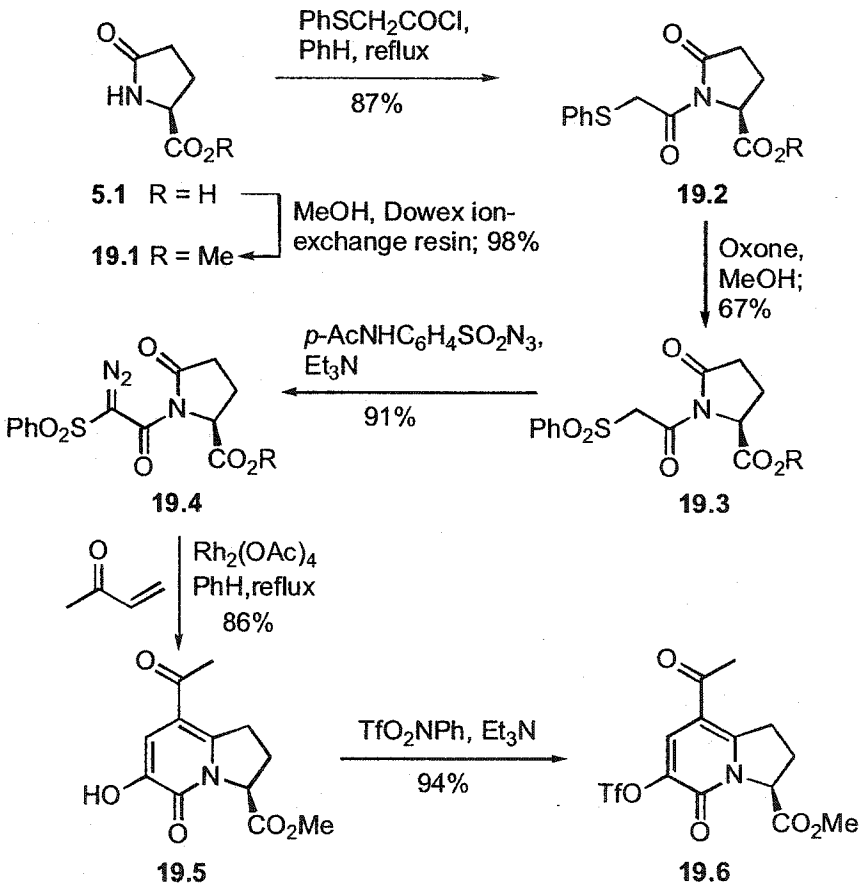
Scheme 18



The principle of the Padwa route is shown in Scheme 18. A [3+2] cycloaddition of phenylsulfonyl-substituted isomünchnone intermediate **18.2** was used as a key transformation in this formal synthesis. Once the cycloaddition occurs, the resulting adduct **18.3** spontaneously undergoes ring opening with loss of $PhSO_2H$ to generate the pyridone **18.4**.

The required isomünchnone precursor **19.4** (Scheme 19) for the [3+2]-cycloaddition was prepared from commercially

Scheme 19

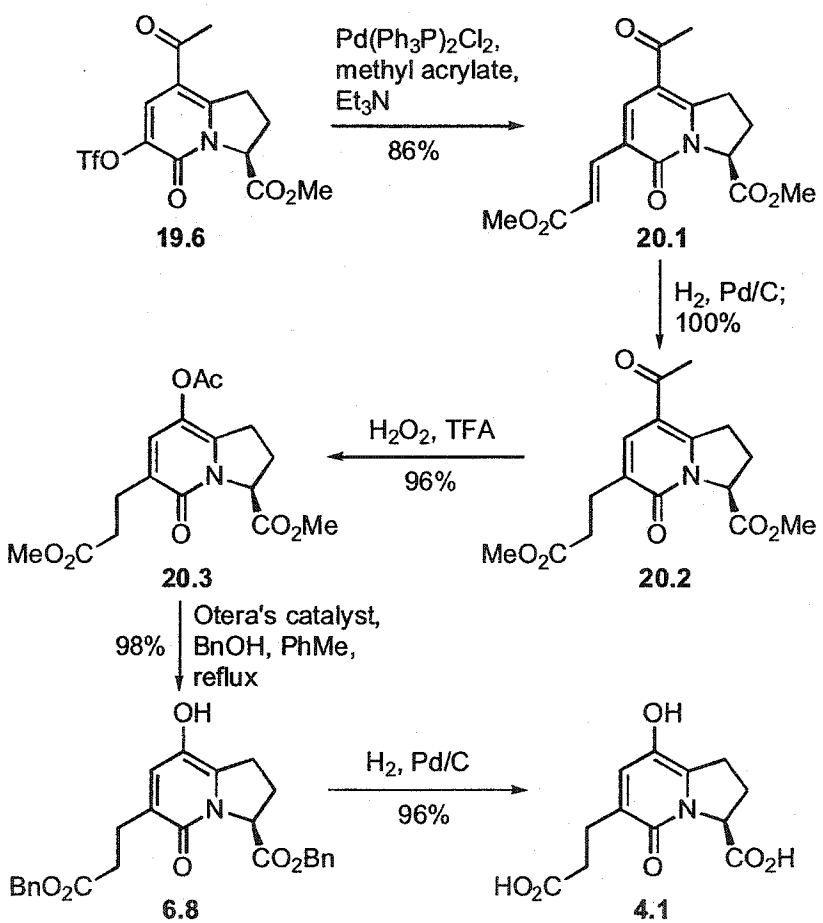


available L-pyroglutamic acid **5.1**. Esterification of **5.1**, followed by treatment with (phenylthio)acetyl chloride, gave compound **19.2**, which was oxidized with Oxone to sulfone **19.3**. Diazotization afforded the isomünchnone precursor **19.4**, and this was treated with $Rh_2(OAc)_4$ and

methyl vinyl ketone to furnish the desired pyridone **19.5**. The pyridone was then converted into the corresponding triflate **19.6**.

Heck reaction with methyl acrylate, followed by hydrogenation, gave pyridone **20.2** (Scheme 20). Baeyer-Villiger oxidation then led to acetate **20.3**, which was exposed to Otera's catalyst in the presence of BnOH to produce the known dibenzyl ester **6.8** (Scheme 6) that had been made by the Danishefsky group.

Scheme 20



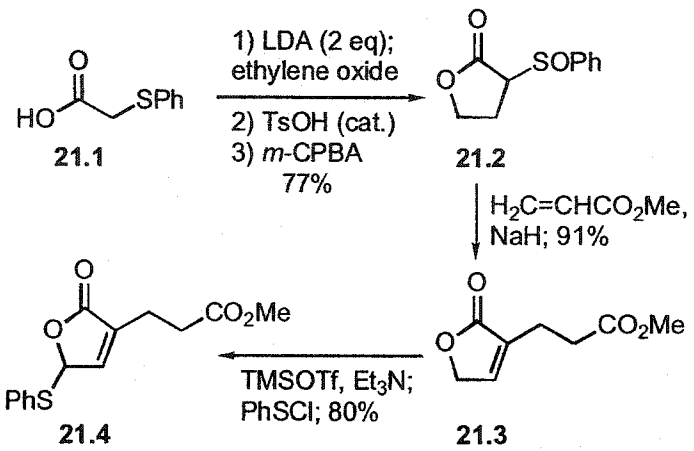
Total Synthesis of (-)-A58365A by the Martin Group[19]

Recently, a concise route to (-)-A58365A was reported by the Martin group. A vinylogous Mannich reaction and subsequent lactone-lactam rearrangement were employed as

the key transformations in the synthesis.

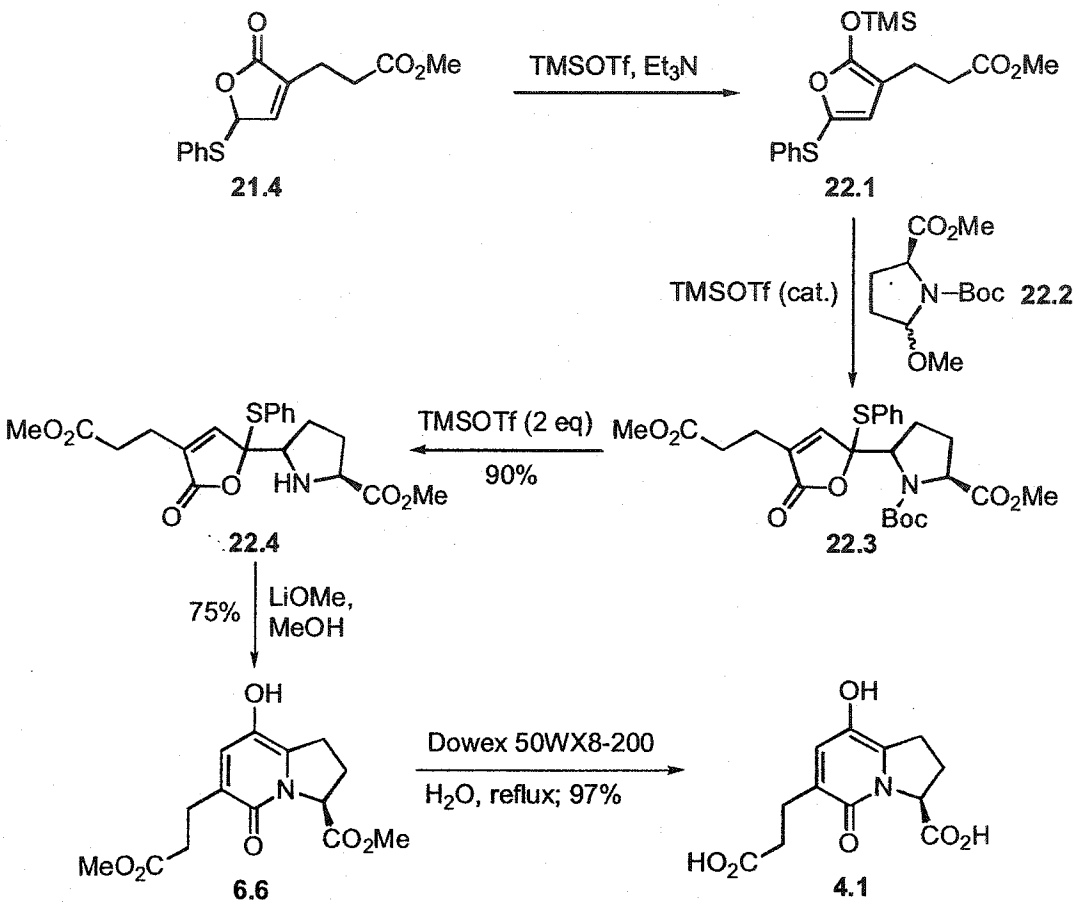
The synthesis was achieved commencing with commercially available (phenylthio)acetic acid **21.1** (Scheme 21), which was converted in three steps into the sulfoxide **21.2**. Michael addition to methyl acrylate and sulfoxide elimination gave the desired butenolide **21.3**. This was treated with $Me_3SiOSO_2CF_3$ in the presence of Et_3N, and then with freshly prepared PhSCl to afford compound **21.4**.

Scheme 21



The stage was now set for the key vinylogous Mannich reaction. Treatment of **21.4** with $Me_3SiOSO_2CF_3$ gave the intermediate silyloxyfuran **22.1** (Scheme 22), which was allowed to react with the known aminal **22.2** to furnish a mixture of adducts **22.3**. Without isolation, deprotection of nitrogen with excess $Me_3SiOSO_2CF_3$ afforded a mixture of isomers (**22.4**) in 90% yield overall from **21.4**. The lactone-lactam rearrangement was then done with MeOLi in MeOH to generate the known compound **6.6**[15] that had been made by the Danishefsky group. Direct transformation of **6.6** into (-)-A58365A **4.1** was completed by hydrolysis with Dowex ion-exchange resin.

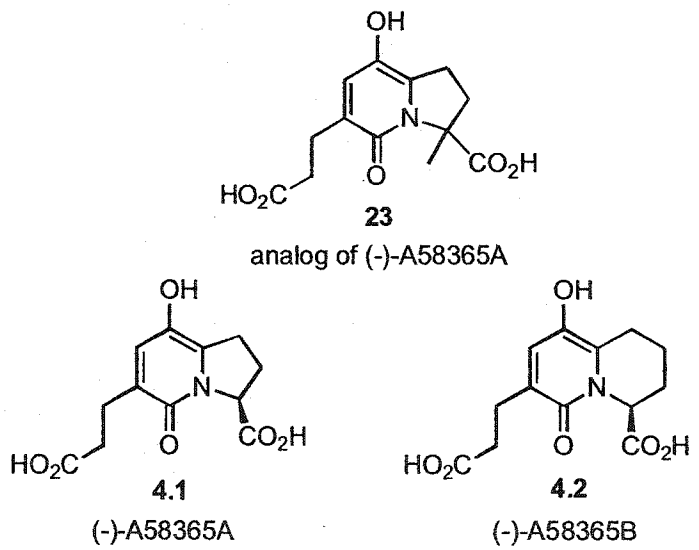
Scheme 22



RESULTS AND DISCUSSION

After A58635A and A58365B were made in racemic and optically pure form in our laboratory,[17] we were interested in whether a methyl-substituted analog[20] such as compound **23** (Scheme 23) could also be synthesized using our general approach. The substitution pattern of **23** might influence the biological activity by steric or hydrophobic effects, and/or by preventing reactions at the substituted position.[21] The additional methyl group might generate sufficient conformational bias in our precursors to impede some reactions, especially the enyne radical cyclization. Accordingly, we applied our general method to the preparation of **23**. As expected, some synthetic steps gave a little lower yield than in the corresponding unsubstituted case, but the racemic analog **23** was indeed found to be accessible by our general route, and it did show ACE inhibitory activity.

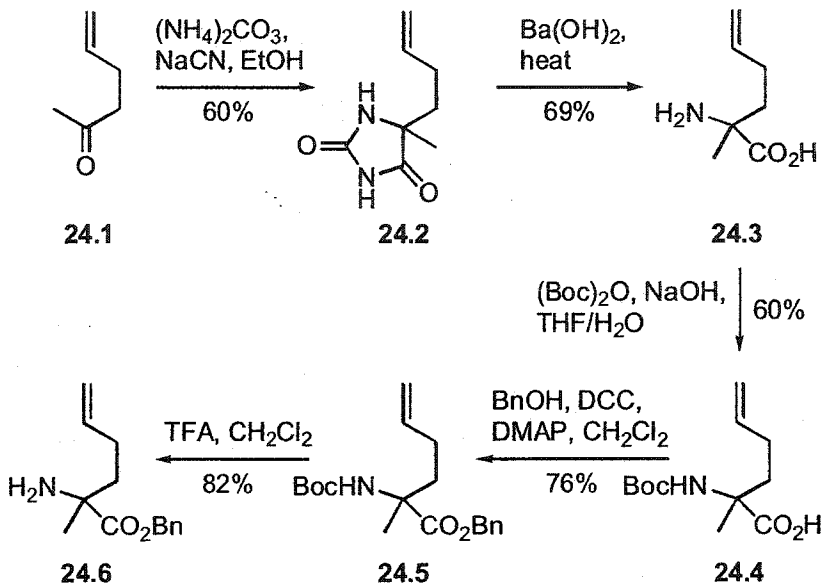
Scheme 23



To make **23** we needed two subunits – lactone acid **11.4**[17] and the amino ester **24.6** (Scheme 24). Treatment of allyl acetone **24.1**[22] with $(NH_4)_2CO_3$ and NaCN in EtOH gave hydantoin **24.2**.[23] This was hydrolyzed with $Ba(OH)_2$ in a

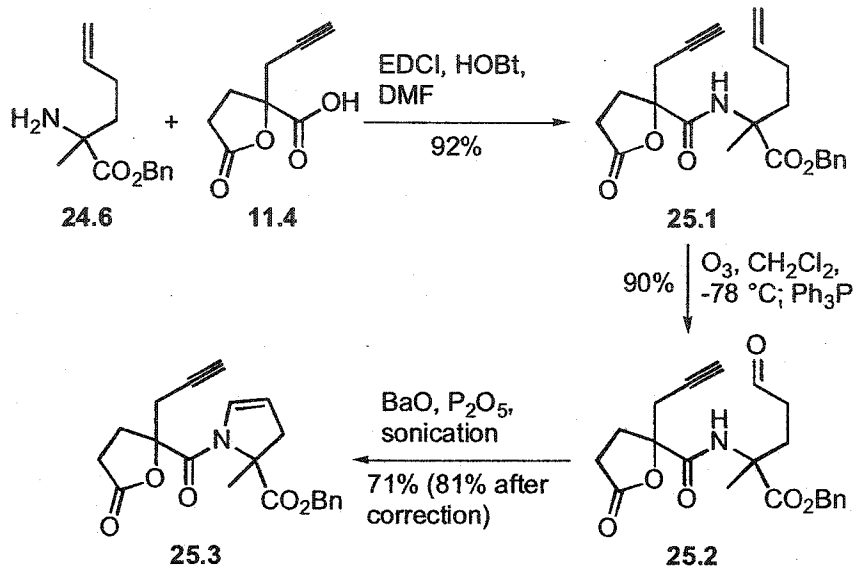
autoclave at 125 °C[24] to afford the known amino acid **24.3**.[23,25] Boc protection of nitrogen under standard conditions, followed by coupling with BnOH using DCC and DMAP, furnished the benzyl ester **24.5**. Then the Boc protecting group was removed by the action of CF_3CO_2H to afford amino acid ester **24.6** in 82% yield.

Scheme 24



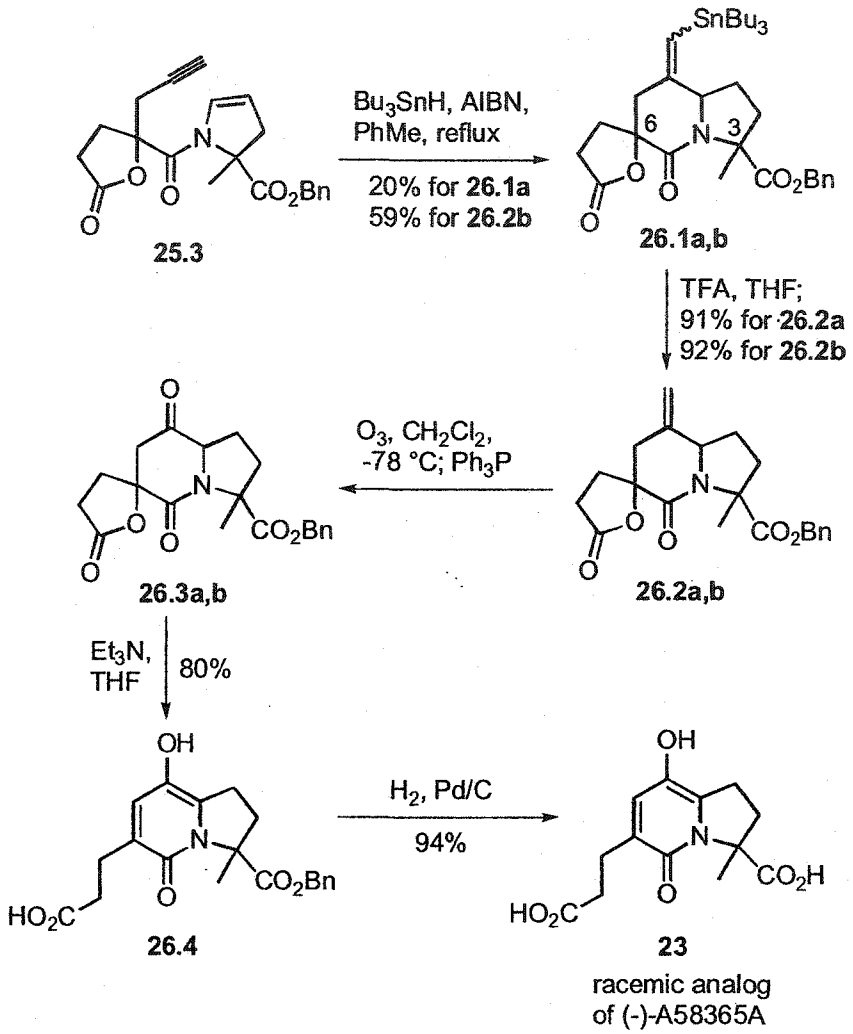
With **24.6** in hand, the next task was to acylate the nitrogen with lactone acid **11.4**. We wondered whether the methyl substituent would hinder the coupling reaction, but, to our delight, the reaction could be accomplished in high yield (92%) under the same conditions (EDCI, HOBt, CH_2Cl_2 and DMF) as used earlier with an unsubstituted amine. Compound **25.1** (Scheme 25) was obtained as an inseparable mixture of diastereoisomers. Ozonolysis served to cleave the double bond to give the amido aldehyde **25.2**, which was sonicated with BaO and P_2O_5 to generate the enamide **25.3** in 71% yield (81% based on recovered starting material). The enamide was, of course, a mixture of diastereoisomers.

Scheme 25



Once more, the stage was set for our crucial stannane addition to the terminal triple bond, followed by cyclization of the intermediate vinyl radical onto the double bond. In our previous syntheses of A58365A and A58365B, one diastereoisomer underwent cyclization more efficiently than the other. We were concerned that the same phenomenon might be observed again, and might be sufficiently severe to thwart the cyclization. However, the mixture of acetylenes **25.3** afforded the desired cyclized products **26.1a,b** (Scheme 26), and the diastereoisomers could be separated and isolated in yields of 20% and 59%, respectively. Obviously, the substituted methyl group does allow the radical cyclization to occur. Each of the isomers **26.1a** and **26.1b** was obtained with a single double bond geometry, which was not determined, so that the diastereoisomerism arises from the presence of two asymmetric centers at C(3) and C(6). Protodestannylation with CF_3CO_2H resulted in the olefins **26.2a** and **26.2b**. We knew from previous work in this laboratory that cleavage of the exocyclic double bond, followed by lactone ring opening, would convert each of the olefins **26.2a** and **26.2b** to the same compound **26.4**. Therefore, a mixture of both

Scheme 26



isomers **26.2a,b** was ozonized to give the ketonic products **26.3a,b**, which were difficult to separate from Ph_3PO, formed during workup of the ozonide with Ph_3P. The crude material was treated with Et_3N to cause the lactone ring opening, and **26.4** was then obtained in 80% yield overall. Finally, hydrogenolysis and subsequent purification by reverse-phase chromatography gave the racemic analog **23**. The compound was tested in another laboratory for ACE inhibitory activity, as described below.

ACE INHIBITORY ACTIVITY

The ACE inhibitory activity of **23** was measured (see

experimental section), using porcine kidney ACE. The IC_{50} of the A58365A analog **23** was found to be 491 nM – a value approximately double that of captopril **3.1** (IC_{50} = 280 nM), which was used as the standard. Thus, given the fact that our A58365A analog **23** is racemic, and assuming that one enantiomer is inactive, the pure (-)-enantiomer would have approximately the same inhibitory effect on ACE as captopril. We note that the IC_{50} found for captopril is approximately one order of magnitude greater than that normally reported.[9,26] However, the IC_{50} is system- and tissue-dependent and most IC_{50} values for captopril have determined using a rabbit lung ACE; in the current study a porcine kidney ACE was used. IC_{50} values for captopril on ACE from different species are known to be highly variable, ranging from 3 nM to 2100 nM, depending on the species.[27]

CONCLUSION

The preparation of **23** extends the generality of the route developed in this laboratory. The route has now been used to make not only the natural products (-)-A58365A (**4.1**) and (-)-A58365B (**4.2**),[17] but also the unnatural analog **23**.[28] The fact that racemic **23** is a powerful inhibitor of angiotensin converting enzyme – about half as potent as (optically pure) captopril (**3.1**) – shows that the structure of (-)-A58365A (**4.1**) can be modified in a chemically significant way (substitution α to nitrogen) with retention of *in vitro* biological activity, although we have not established whether each enantiomer of **23** is an ACE inhibitor.

EXPERIMENTAL

Unless stated to the contrary, the following conditions apply: Reactions were done under a slight static pressure of Ar or N_2 that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst[29] and then through a similar column of Drierite. Glassware was dried in an oven for at least 3 h before use (130 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar or N_2. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane and EtOAc used for chromatography was distilled before use.

Products were isolated from solution by evaporation under water-aspirator vacuum at, or below, room temperature, using a rotary evaporator.

Cannula transfers were done under slight pressure (Ar or N_2), not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F–254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid[30] or *p*-anisaldehyde,[31] followed by charring with a heat gun, or by examination of the untreated plate under UV light. 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, Et_2O, PhH, PhMe and dioxane were distilled from sodium and benzophenone ketyl. Dry CH_2Cl_2, $ClCH_2CH_2Cl$, Et_3N, *i*-Pr_2NEt, MeCN and pyridine were distilled from CaH_2. Dry MeOH and EtOH was distilled from $Mg(OEt)_2$. Acetone was distilled from K_2CO_3.

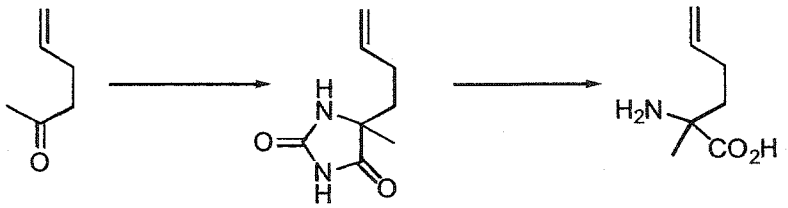
FT-IR measurements were recorded on a Nicolet 7000 FT-IR instrument and were made as casts from the specified solvent using potassium bromide plates.

^{1}H Nuclear magnetic resonance spectra (NMR) were recorded with Bruker AM spectrometers (at 300, 360, 400 MHz), or Varian INOVA spectrometers (at 300, 400, 500 MHz) in the specified deuterated solvent at 27.5 °C. ^{13}C NMR were recorded with Bruker AM spectrometers (at 75.5, 100.6 MHz) or Varian UNITY or INOVA spectrometers (at 100.6, 125.7 MHz) at 27.5 °C. The symbols s, d, t, and q used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively, which are assigned based on APT experiments. In cases where the number of signals is less than expected, we assume this is due to coincident chemical shifts.

Mass spectra were recorded with AEI Models MS-12, MS-50, MS-9 (modified), Kratos MS-50 (modified) or Micromass ZabSpec Hybrid Sector-TOF mass spectrometers.

Compounds isolated by flash chromatography were pure by TLC and, unless otherwise stated, also as judged by high field ^{1}H and ^{13}C NMR spectra.

2-Amino-2-methyl-5-hexenoic Acid (24.3).



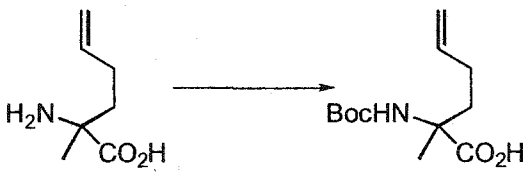
24.1 **24.2** **24.3**

Hydantoin **24.2** was prepared by method A of reference,[23] except that, after acidification of the final aqueous solution, residual EtOH was removed by evaporation, and the resulting slurry was filtered to afford the crude product, which was crystallized from water (60% yield).

A general literature procedure[24] was modified slightly and applied to the conversion of **24.2** into **24.3**. A mixture of **24.2** (8.43 g, 50.0 mmol), $Ba(OH)_2$ (80.0 g, 250 mmol) and water (175 mL) was heated and shaken for 24 h in an

autoclave at 125 °C. The mixture was allowed to cool to room temperature, transferred to a fume hood, stirred, and acidified slowly with 4 N H_2SO_4 (200 mL). The resulting suspension was heated at 100 °C for 1 h in a fume hood, cooled to room temperature, and filtered. The insoluble material was washed with water (200 mL). The filtrate was neutralized with concentrated NH_4OH to pH 6-7 (pH paper) and kept overnight in a refrigerator. As no crystals formed, the solution was evaporated to dryness, to afford a solid. This was taken up in a small amount of water (ca 5 mL) and chromatographed over BIO-RAD AG 50W-X8 resin (100-200 mesh) (5 x 25 cm), using 0.5 N NH_4OH, to obtain **24.3**[23] (4.94 g, 69%) as a solid.

2-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-methyl-5-hexenoic Acid (24.4).

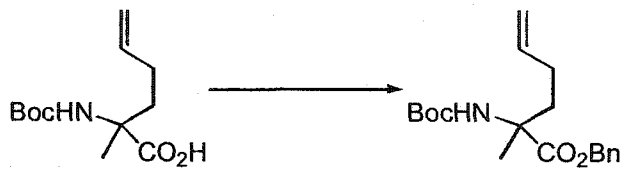


24.3 **24.4**

$(Boc)_2O$ (3.3 g, 15 mmol) in a 2:1 mixture (24 mL) of THF and water was added to a stirred and cooled (0 °C) solution of **24.3**[23,25] (1.44 g, 10.0 mmol) in 2:1 THF-water (15 mL) and 10% aqueous NaOH (4.1 mL) (pH of solution was 9). After 15 min the ice-water bath was removed and stirring was continued for 24 h. The solvent was evaporated and the residue was dissolved in EtOAc (15 mL) and acidified with 10% aqueous $KHSO_4$. The aqueous layer was extracted with EtOAc (2 x 15 mL), and the combined organic extracts were washed with water (2 x 25 mL) and brine (25 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 1:4 EtOAc-hexanes, gave **24.4** (1.47 g, 60%) as a colorless oil,

containing slight impurities (^{1}H NMR): FTIR (CH_2Cl_2, cast) 3500-2400, 1713, 1643 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.43 (s, 9 H), 1.55 (s, 3 H), 1.80-2.20 (m, 4 H), 4.90-5.10 (m, 2 H), 5.15-5.45 (br s, 1 H), 5.70-5.87 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 23.5 (q), 28.37 (q), 28.37 (t), 35.9 (t), 59.4 (s), 115.3 (t), 137.4 (d), 179.0 (s) (two signals not observed in this spectrum); exact mass (HR electrospray) *m/z* calcd for $C_{12}H_{21}NNaO_4$ (M + Na) 266.1368, found 266.1365.

Phenylmethyl 2-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-methyl-5-hexenoate (24.5).

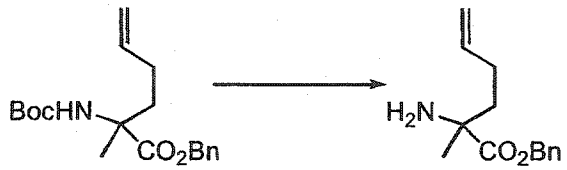


24.4 **24.5**

BnOH (0.732 g, 6.80 mmol) was added to a stirred mixture of **24.4** (1.47 g, 6.00 mmol), DCC (1.40 g, 6.80 mmol) and DMAP (0.073 g, 0.60 mmol) in dry CH_2Cl_2 (35 mL) (Ar atmosphere). Stirring was continued for 2 h, by which time a white precipitate had formed and all the starting material had reacted (TLC control, silica gel, 3:17 EtOAc-hexane). The mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (2.5 x 20 cm), using 3:17 EtOAc-hexane, gave **24.5** as a colorless oil (1.56 g, 76%): FTIR (CH_2Cl_2, cast) 1717 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 9 H), 1.56 (s, 3 H), 1.75-2.25 (m, 4 H), 4.87-4.95 (m, 2 H), 5.17 (AB q, $\Delta\nu_{AB}$ = 9.8 Hz, J = 12.3 Hz, 2 H) 5.19-5.33 (1 H), 5.66-5.78 (m, 1 H), 7.26-7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 23.5 (q), 28.3 (q), 28.4 (t), 36.1 (t), 59.4 (s) 67.2 (t), 79.5 (s), 115.1 (t), 128.2 (d), 128.4 (d), 128.6 (d), 135.6 (s), 137.5 (d), 154.2 (s), 174.2 (s); exact mass (HR electrospray) *m/z*

calcd for $C_{19}H_{27}NNaO_4$ (M + Na) 356.1838, found 356.1842.

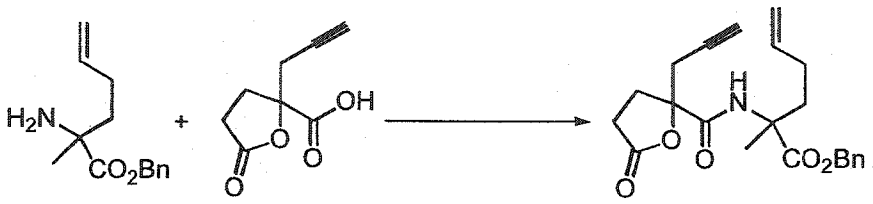
Phenylmethyl 2-Amino-2-methyl-5-hexenoate (24.6).



24.5 **24.6**

CF_3CO_2H (15 mL) was added over ca 10 min to a stirred and cooled (ice-water bath) solution of **24.5** (1.406 g, 4.220 mmol) in dry CH_2Cl_2 (25 mL). The cooling bath was removed and stirring was continued until all the starting material had been consumed (ca 1.5 h, TLC control, silica gel, 3:17 EtOAc-hexanes). The solution was evaporated, and the residue was dissolved in EtOAc (40 mL), washed with saturated aqueous $NaHCO_3$ (2 x 40 mL), water (2 x 40 mL) and brine (40 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 20 cm), using 10:1 EtOAc-hexanes, gave **24.6** (0.806 g, 82%) as a colorless oil: FTIR (CH_2Cl_2, cast) 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.35 (s, 3 H), 1.58-1.72 (m, including s at 1.63, 3 H in all), 1.78-1.99 (m, 2 H), 2.00-2.12 (m, 1 H), 4.89-5.01 (m, 2 H), 5.14 (AB q, $\Delta\nu_{AB}$ = 7.9 Hz, J = 12.3 Hz, 2 H), 5.75 (ddt, J = 17.2, 10.3, 6.6 Hz, 1 H), 7.26-7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 26.4 (q), 28.7 (t), 40.2 (t), 57.7 (s), 66.8 (t), 114.9 (t), 128.2 (d), 128.3 (d), 128.6 (d), 136.0 (s), 137.9 (d), 177.4 (s); exact mass (HR electrospray) *m/z* calcd for $C_{14}H_{19}NNaO_2$ (M + Na) 256.1313, found 256.1311.

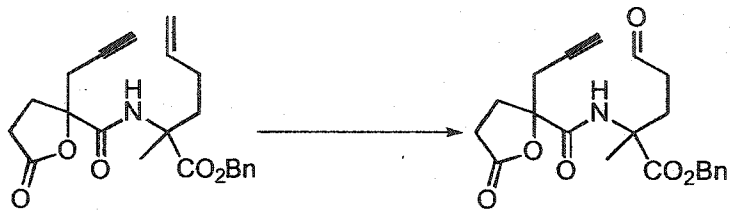
Phenylmethyl 2-Methyl-2-[[[tetrahydro-5-oxo-2-(2-propynyl)-2-furanyl]carbonyl]amino]-5-hexenoate (25.1).



24.6 **11.4** **25.1**

Lactone acid **11.4**[17] (0.5209 g, 3.100 mmol), 1-hydroxybenzotriazole (1.143 g, 8.460 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.622 g, 8.460 mmol) were added in that order to a stirred solution of **26.6** (0.6575 g, 2.820 mmol) in a mixture of dry CH_2Cl_2 (22 mL) and freshly distilled, dry DMF (5.5 mL, stored over 4 Å molecular sieves) (Ar atmosphere). Stirring at room temperature was continued for 24 h, and the mixture was washed with water (2 x 15 mL) and brine (15 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the resulting dark-purple oil over silica gel (2.5 x 20 cm), using 1:1 EtOAc-hexanes, gave **25.1** (0.9948 g, 92%) as a colorless oil, which was a mixture [ca 1.8:1 (^{1}H NMR)] of two diastereoisomers: FTIR (CH_2Cl_2, cast) 1792, 1728, 1681 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.57 and 1.61 (two s, 3 H in all), 1.79-2.10 (m, 4 H), 2.11-2.25 (m, 1 H), 2.30-2.52 (m, 3 H), 2.58-2.81 (m, 3 H), 4.90-5.00 (m, 2 H), 5.16 (AB q, $\Delta\nu_{AB}$ = 34 Hz, J = 12.2 Hz, 2 H), 5.63-5.76 (m, 1 H), 7.01 and 7.08 (two s, 1 H in all), 7.26-7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 22.6 (q), 23.0 (q), 28.3 (t), 28.3 (t), 28.4 (t), 29.6 (t), 29.7 (t), 35.2 (t), 36.1 (t), 60.0 (s), 60.1 (s), 67.5 (t), 72.3 (d), 77.1 (s), 85.3 (s), 115.6 (t), 115.8 (t), 128.5 (d), 128.6 (d), 128.6 (d), 135.3 (s), 136.8 (d), 137.0 (d), 169.9 (s), 173.0 (s), 175.0 (s); exact mass *m/z* calcd for $C_{22}H_{25}NO_5$ 383.1733, found 383.1728.

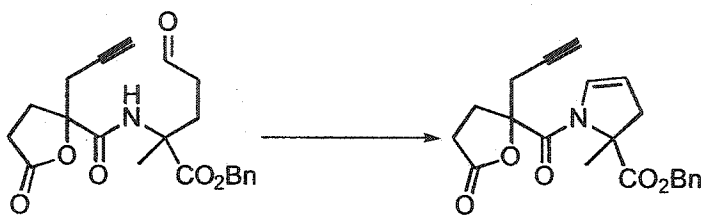
Phenylmethyl 2-Methyl-5-oxo-2-[[[tetrahydro-5-oxo-2-(2-propynyl)-2-furanyl]carbonyl]amino]-5-pentanoate (25.2).



25.1 **25.2**

An O_3-O_2 stream was passed through a stirred and cooled (-78 °C) solution of **25.1** (0.5450 g, 1.420 mmol) in dry CH_2Cl_2 (15 mL) for 10 min, by which time all the starting material had reacted (TLC control, silica gel, 1:1 EtOAc-hexane). (In some experiments, a trace of Sudan Red 7B was added to the original mixture before starting the O_3 stream.) The solution was purged with O_2 for 10 min, and then Ph_3P (0.7547 g, 2.880 mmol) was added. The cooling bath was removed and stirring was continued for 4 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 90:10 EtOAc-hexanes, gave **25.2** (0.4920 g, 90%) as a colorless oil, which was a mixture [ca 1.7:1 (^{1}H NMR)] of diastereoisomers: FTIR (CH_2Cl_2, cast) 1790, 1737, 1679 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.56-1.70 (s, 3 H), 1.90-2.95 (m, 11 H), 5.00-5.28 (m, 2 H), 7.05 and 7.20 (s, 1 H), 7.26-7.40 (m, 5 H), 9.65 and 9.66 (two s, 1 H in all); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 22.9 (q), 23.2 (q), 27.8 (t), 28.3 (t), 28.4 (t), 28.4 (t), 28.5 (t), 29.6 (t), 29.7 (t), 38.8 (t), 59.4 (s), 67.8 (t), 72.4 (d), 77.4 (s), 85.3 (s), 128.3 (d), 128.6 (d), 128.7 (d), 135.2 (s), 170.3 (s), 172.5 (s), 175.0 (s), 200.7 (d), 200.8 (d); exact mass *m/z* calcd for $C_{21}H_{23}NO_6$ 385.1525, found 385.1526.

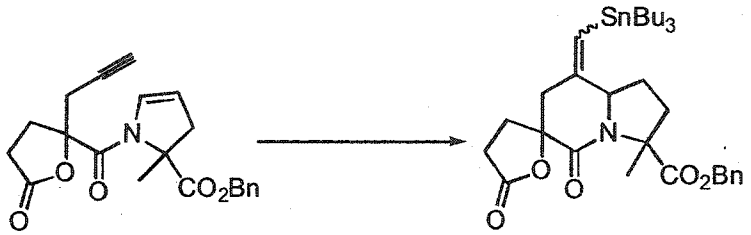
Phenylmethyl 2,3-Dihydro-3-methyl-1-[[tetrahydro-5-oxo-2-(2-propynyl)-2-furanyl]carbonyl]-1*H*-pyrrole-2-carboxylate (25.3).



25.2 **25.3**

BaO (0.6380 g, 4.170 mmol) was tipped into a solution of **25.2** (0.5340 g, 1.390 mmol) in dry CH_2Cl_2 (10 mL), contained in a round-bottomed flask fused onto a condenser (Ar atmosphere), and the suspension was sonicated (Branson, model B-12, 80 W) for 1 h. P_2O_5 (0.7333 g, 5.160 mmol) was then tipped into the flask, the system was re-sealed with a septum and flushed with Ar. Sonication was continued until no more aldehyde was consumed (ca 3 h, TLC control, silica gel, 1:1 EtOAc-hexane; some aldehyde did not react), and the suspension was then filtered. Evaporation of the filtrate, and flash chromatography of the orange residue over silica gel (2 x 20 cm), using 1:1 EtOAc-hexanes, gave **25.3** (0.3623 g, 71%, or 81% after correction for recovered starting material) as a colorless oil, which was a mixture of two diastereoisomers, whose ratio could not be determined from the ^1H NMR spectrum, due to peak overlap. The material had: FTIR (CH_2Cl_2, cast) 1793, 1762, 1646 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.67 (s, 3 H), 2.00-2.58 (m, 5 H), 2.60-2.76 (m, 2 H), 2.77-3.00 (m, 2 H), 4.95-5.35 (m, 3 H), 7.05-7.15 (m, 1 H), 7.26-7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 21.5 (q), 22.1 (q), 27.7 (t), 28.1 (t), 28.9 (t), 29.4 (t), 30.7 (t), 41.9 (t), 42.3 (t), 67.0 (t'), 67.1 (t), 68.0 (d), 68.5 (d), 72.6 (s), 72.7 (s), 86.0 (s), 86.4 (s), 109.8 (d), 109.9 (d), 128.3 (d), 128.4 (d), 128.4 (d), 128.6 (d), 128.7 (d), 135.6 (s), 165.3 (s), 171.9 (s), 175.0 (s), 175.3 (s); exact mass *m/z* calcd for $C_{21}H_{21}NO_5$ 367.1420, found 367.1417.

Phenylmethyl Octahydro-3′-methyl-5,5′-dioxo-8′-[(tributylstannyl)methylene]spiro[furan-2(3*H*),6′(5′*H*)-indolizine]-3′-carboxylic acid (26.1).



25.3 **26.1a,b**

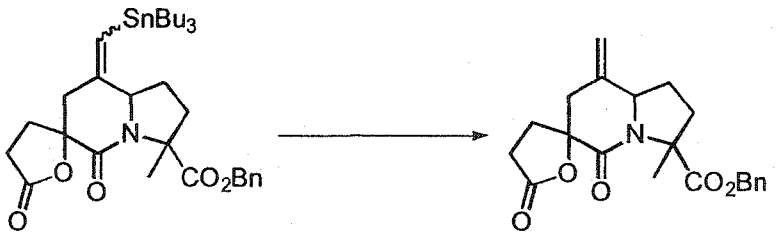
A solution of AIBN (8.8 mg, 0.057 mmol, 8.1 mM) and Bu_3SnH (0.20 mL, 0.75 mmol, 0.11 M) in dry PhMe (7.0 mL) was injected over ca 10 sec into a stirred and refluxing solution of **25.3** (0.124 g, 0.340 mmol) in PhMe (7 mL) (Ar atmosphere). Stirring at reflux was continued for 3 h. Another solution of AIBN (8.4 mg, 0.054 mmol, 15 mM) and Bu_3SnH (0.02 mL, 0.75 mmol, 0.22 M) in dry PhMe (3.5 ml) was then injected over ca 10 sec, and stirring and refluxing were continued until no starting material remained (ca 1.5 h, TLC control, silica gel, 30:70 EtOAc-hexanes). The mixture was cooled and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 3:7 EtOAc-hexanes, gave the faster-eluting diastereoisomer **26.1a** (0.0441 g, 20%) as a colorless oil containing slight impurities (^1H NMR), and the slower-eluting diastereoisomer **26.1b** (0.1321 g, 59%), also as a colorless oil.

The faster-eluting diastereoisomer **26.1a** had: FTIR (CH_2Cl_2, cast), 1788, 1742, 1667 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.80-1.06 (m, 15 H), 1.20-1.70 (m, 16 H), 1.79-2.01 (m, 3 H), 2.10-2.35 (m, 2 H), 2.40-2.58 (m, 1 H), 2.60-2.95 (m, 4 H), 4.50-4.70 (m, 1 H), 5.16 (AB q, $\Delta\nu_{AB}$ = 12.8 Hz, J = 12.3 Hz, 2 H) 5.83 (vinyl H, d, J = 1.5 Hz, 1 H, Sn satellite signals at 5.74 and 5.92), 7.26-7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) (two signals overlap in this spectrum) δ 10.3 (t), 13.7 (q), 21.1 (q), 27.3 (t), 28.8 (t), 29.2

(t), 29.8 (t), 30.5 (t), 36.9 (t), 44.0 (t), 64.7 (d), 66.0 (s), 67.2 (t), 83.7 (s), 125.3 (d), 128.2 (d), 128.6 (d), 135.8 (s), 147.8 (s), 166.1 (s), 172.9 (s), 175.9 (s); exact mass (HR electrospray) *m/z* calcd for $C_{33}H_{49}NNaO_5Sn$ (M + Na) 682.2530, found 682.2529.

The slower-eluting isomer **26.1b** had: FTIR (CH_2Cl_2, cast) 1786, 1742, 1659 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.80-1.06 (m, 15 H), 1.20-1.76 (m, 16 H), 1.78-2.01 (m, 2 H), 2.05-2.30 (m, 2 H), 2.32-2.56 (m, 3 H), 2.61-2.78 (m, 1 H), 2.85-2.95 (m, 1 H), 4.30-4.45 (m, 1 H), 5.12 (AB q, $\Delta\nu_{AB}$ = 48.9 Hz, J = 12.4 Hz, 2 H), 5.83 (vinyl H, d, J = 1.5 Hz, 1 H, Sn satellite signals at 5.74 and 5.92), 7.26-7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.5 (t), 13.7 (q), 23.0 (q), 27.3 (t), 28.5 (t), 29.1 (t), 29.9 (t), 31.1 (t), 37.6 (t), 43.9 (t), 64.2 (d), 66.2 (s), 67.1 (t), 82.9 (s), 126.8 (d), 128.2 (d), 128.4 (d), 128.6 (d), 135.7 (s), 146.3 (s), 166.6 (s), 172.7 (s), 176.3 (s); exact mass (HR electrospray) *m/z* calcd for $C_{33}H_{49}NNaO_5Sn$ (M + Na) 682.2530, found 682.2541.

Phenylmethyl Octahydro-3′-methyl-8′-methylene-5,5′-dioxospiro[furan-2(3*H*),6′(5′*H*)indolizine]-3′-carboxylate (26.2a) from less polar stannane.

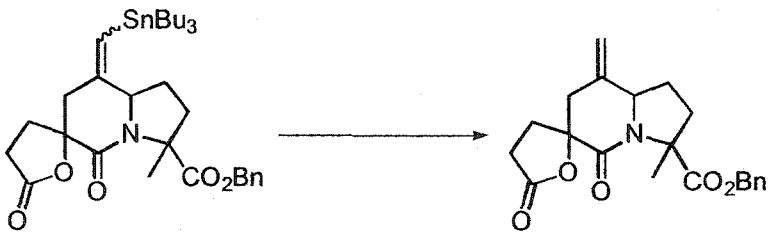


26.1a **26.2a**

Dry CF_3CO_2H (0.25 mL) was injected over a few seconds into a stirred solution of the chromatographically less polar stannane **26.1a** (0.038 g, 0.058 mmol) in THF (3 mL) (Ar, atmosphere). After ca 1 h no vinyl stannane could be detected (TLC control, silica gel 50:50 EtOAc-hexanes).

Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 20 cm), using 50:50 EtOAc-hexanes, gave **26.2a** (0.0195 g, 91%) as a colorless oil, which was a single isomer, different from that obtained by destannylation of the more polar stannane. Compound **26.2a** had: FTIR (CH_2Cl_2, cast) 1782, 1739, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.60 (s, 3 H), 1.80-2.05 (m, 3 H), 2.10-2.30 (m, 2 H), 2.45-2.57 (m, 1 H), 2.60-2.85 (m, 3 H), 2.98 (dd, J = 15.7, 1.2 Hz, 1 H), 4.47-4.57 (1 H), 5.04 (dq, J = 17, 1.9 Hz, 2 H), 5.15 (AB q, $\Delta\nu_{AB}$ = 15 Hz, J = 12.3 Hz, 2 H), 7.26-7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.0 (q), 28.6 (t), 29.0 (t) 30.9 (t), 37.0 (t), 42.0 (t), 62.7 (d), 66.7 (s), 67.2 (t), 83.2 (s), 111.6 (t), 128.2 (d), 128.6 (d), 135.7 (s), 139.7 (s), 166.4 (s), 172.8 (s), 175.9 (s); exact mass m/z calcd for $C_{21}H_{23}NO_5$ 369.1576, found 369.1571.

Phenylmethyl Octahydro-3'-methyl-8'-methylene-5,5'-dioxo-spiro[furan-2(3*H*),6'(5'*H*)indolizine]-3'-carboxylate (26.2b) from more polar stannane.

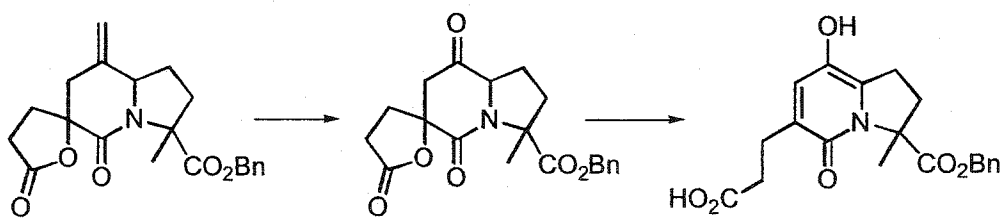


26.1b **26.2b**

Dry CF_3CO_2H (0.75 mL) was injected over a few seconds into a stirred solution of the chromatographically more polar stannane **26.1b** (0.098 g, 0.15 mmol) in THF (8 mL) (Ar atmosphere). After ca 1 h no vinyl stannane could be detected (TLC control, silica gel, 50:50 EtOAc-hexanes). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 20 cm), using 50:50 EtOAc-hexanes, gave **26.2b** (0.0505 g, 92%) as a colorless oil

which was a single isomer, different from that obtained by destannylation of the less polar stannane. Compound **26.2b** had: FTIR (CH_2Cl_2, cast) 1780, 1737, 1654 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.60-1.80 (m, including s at 1.70, 4 H in all), 1.82-2.02 (m, 2 H), 2.04-2.16 (m, 2 H), 2.18-2.40 (m, 3 H), 2.51-2.75 (m, 2 H), 2.93-3.05 (d, J = 14.0 Hz, 1 H), 4.26-4.36 (m, 1 H), 5.04 (br d, J = 13.0 Hz, 2 H), 5.12 (AB q, $\Delta\nu_{AB}$ = 46.7 Hz, J = 12.3, Hz, 2 H), 7.26-7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 23.0 (q), 28.3 (t), 28.8 (t), 31.7 (t), 37.7 (t), 42.3 (t), 62.1 (d), 65.9 (s), 67.2 (t), 82.6 (s), 112.8 (t), 128.2 (d), 128.4 (d), 128.6 (d), 135.7 (s), 138.5 (s), 167.0 (s), 172.5 (s), 176.5 (s); exact mass m/z calcd for $C_{21}H_{23}NO_5$ 369.1576, found 369.1579.

1,2,3,5-Tetrahydro-8-hydroxy-3-methyl-5-oxo-3-[(phenylmethoxy)carbonyl]-6-indolizinepropanoic Acid (26.4).



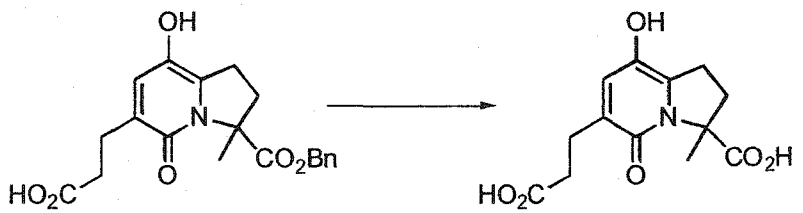
26.2a,b **26.3a,b** **26.4**

An O_3-O_2 stream was passed through a stirred and cooled (-78 °C) solution of **26.2a,b** (mixture of two diastereoisomers) (0.0805 g, 0.220 mmol) in dry CH_2Cl_2 (10 mL) for 5 min, by which time all the starting material had reacted (TLC control, silica gel, 1:1 EtOAc-hexane). (In some experiments, a trace of Sudan Red was added to the original mixture before starting the O_3 stream.) The solution was purged with O_2 for 10 min, and then Ph_3P (0.115 g, 0.440 mmol) was added. The cooling bath was removed and stirring was continued for 1.5 h. Evaporation of the solvent gave a light-yellow solid. The desired ketonic

product (**26.3**) could not be separated chromatographically from Ph_3PO, and so the crude mixture was used directly in the next step.

Dry Et_3N (1.0 mL, 7.2 mmol) was added to a stirred solution of the above crude ozonolysis product in dry THF (10 mL) (Ar atmosphere) and the mixture was stirred at 60 °C (oil bath) for 1.5 h, cooled and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 16:4:1 EtOAc-hexanes-AcOH, gave **26.4** (0.0650 g, 80%) as a white crystalline solid: mp = 191-193 °C; FTIR (microscope) 1746, 1714, 1536 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 1.68 (s, 3 H), 2.13-2.24 (m, 1 H), 2.35-2.60 (m, 3 H), 2.65-2.77 (m, 2 H), 3.03-3.15 (m, 2 H), 5.12 (s, 2 H), 7.17 (s, 1 H), 7.26-7.40 (m, 5 H); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 20.6 (q), 26.9 (t), 27.1 (t), 33.7 (t), 36.0 (t), 68.4 (s), 72.2 (t), 129.2 (d), 129.2 (d), 129.5 (d), 130.1 (s), 133.7 (s), 134.5 (d), 136.7 (s), 137.2 (s), 159.8 (s), 173.1 (s), 176.6 (s); exact mass *m/z* calcd for $C_{20}H_{21}NO_6$ 371.1369, found 371.1372.

3-Carboxy-1,2,3,5-tetrahydro-8-hydroxy-3-methyl-5-oxo-6-indolizinepropanoic Acid (23).



26.4 **23**

10% Pd/C (ca 10 mg) was added to a stirred solution of **26.4** (0.0356 g, 0.0960 mmol) in MeOH (15 mL). The reaction flask was flushed with H_2, and the mixture was stirred under H_2 (balloon) until all the starting material had been consumed (ca 30 min, TLC control, silica gel, 95:5 EtOAc-hexanes). The mixture was filtered through a sintered

glass frit (grade D). Evaporation of the filtrate gave a residue which was partitioned between 1% aqueous AcOH (10 mL) and $CHCl_3$ (5 mL). The aqueous layer was washed with $CHCl_3$ (2 x 5 mL), and evaporated. Chromatography of the residue over reverse phase C-18 silica gel (SiliCycle, Quebec City, 230-400 mesh) (1 x 15 cm), using 4:1 water-MeCN, gave **23** as a light-yellow partially crystalline mass (0.0271 g, 94%): mp = 156-159 °C; FTIR (microscope) 1713, 1536 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 1.68 (s, 3 H), 2.12-2.23 (m, 1 H), 2.44-2.61 (m, 3 H), 2.68-2.79 (m, 2 H), 3.01-3.14 (m, 2 H), 7.18 (s, 1 H); ^{13}C NMR (CD_3OD, 100.6 MHz) δ 21.2 (q), 26.8 (t), 27.1 (t), 33.9 (t), 36.6 (t), 73.1 (s), 130.2 (s), 134.1 (d), 134.3 (s), 136.8 (s), 160.0 (s), 176.3 (s), 176.9 (s); exact mass *m/z* calcd for $C_{13}H_{15}NO_6$ 281.0899, found 281.0894.

Measurement of ACE inhibitory activity

The ACE inhibitory activity of our A58365A analog **23** was measured by Dr. R. Lewanczuk (Division of Endocrinology and Metabolism, University of Alberta) using a slight modification of the method of Buttery and Stuart.[32] Porcine kidney ACE (Sigma, St. Louis, Mo, 7.8 mU in 0.1 mL of 80 nM borate buffer, pH 8.2) was incubated with a series of 8 concentrations (0 nM - 1000 nM) of the A58365A analog in borate buffer, giving a combined volume of 0.2 mL. The incubation was carried out at 37 °C for 10 min, after which time *N*-[3-(2-furyl)acryloyl]-L-phenylalanylglycylglycine (FAPGG, Sigma, St. Louis, Mo, 0.8 mL (final concentration 1 mM) was added, and the mixture was vortexed gently. After 5 min, the absorbance was measured at 340 nm. The reaction between ACE and FAPGG was monitored for 20 min in order to ensure linearity of response. Captopril (Sigma, St. Louis, Mo) was used as a standard. The effect of each drug concentration was measured in triplicate and the entire experiment was carried out twice. The data were processed using the logistic dose-response curve-fitting function of

Table Curve-2D (Jandel Scientific, San Rafael, Ca) to obtain IC_{50} values. These were 491 nM for A58365A analog **23**, and 280 nM for captopril, which was used as the standard.

The ACE-FAPGG reaction showed linearity of FAP formation from 5 to 20 min, and IC_{50} values from the two repeated experiments agreed within 3%. There was excellent curve-fit for the various concentrations of both the A58365A analog and captopril (R^2 value for the curve fit was $\geq$ 0.996 in all cases).

REFERENCES AND NOTES

1 *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 7th Ed.; Gilman, A. G.; Goodman, L. S.; Rall, T. W.; Murad, W. R., Eds; Macmillan: London, 1985; p 639.

2 Page, I. H.; Bumpuss, F. M. *Handbuch der Experimentellen Pharmakologie* **1974**, *37*.

3 Regoli, D. *Pharmacol. Rev.* **1974**, *26*, 69.

4 Streeten, D. H. P.; Anderson, G. H. In *Handbook of Hypertension, Angiotensin-Receptor Blocking Drugs*, Doyle, A. E., Ed.; Elsevier Science Publishers, **1984**, 5; p 246.

5 Carini, D. J.; Duncia, J. V. *J. Med. Chem.* **1991**, *34*, 2525.

6 Chang, R. S. L.; Lotti, V. *Mol. Pharmacol.* **1991**, *29*, 347.

7 Schambye, H. T.; Hjorth, S. A. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 7046.

8 Ferguson, R. K.; Vlasses, P. H. *J. Clin. Pharmacol.* **1982**, *22*, 281.

9 Cushman, D. W.; Ondetti, M. A. *Biochem.* **1977**, *16*, 5484.

10 Gross, D. M.; Sweet, C. S. *J. Pharmacol. Exp. Ther.* **1981**, *216*, 552.

11 Mynderse, J. S.; Samlaska, S. K.; Fukuda, D. S.; Du Bus, P. J. *J. Antibiot.* **1985**, *38*, 1003.

12 O'Connor, S.; Somers, P. *J. Antibiot.* **1985**, *38*, 993.

13 Hunt, A. H.; Mynderse, J. S.; Samlaska, S. K.; Fukuda, D. S.; Maciak, G. M. *J. Antibiot.* **1988**, *41*, 771.

14 Nakatsukasa, W. M.; Wilgus, R. M.; Thomas, D. D.; Mertz, F. P.; Boeck, L. V. D. *J. Antibiot.* **1985**, *38*, 997.

15 Fang, F. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1989**, *30*, 3621.

16 (a) Moeller, K. D.; Wong, P. L. *Bioorg. & Med. Chem. Lett.* **1992**, *2*, 739. (b) Wong, P. L.; Moeller, K. D. *J. Am. Chem. Soc.* **1993**,*115*, 11434.

17 (a) Clive, D. L. J.; Zhou, Y.; de Lima, D. P. *J. Chem. Soc., Chem. Commun.* **1996**, 1463. (b) Clive, D. L. J.; Coltart, D. M. *Tetrahedron Lett.* **1998**, *39*, 2519. (c) Clive, D. L. J.; Coltart, D. M.; Zhou, Y. *J. Org. Chem.* **1999**, *64*, 1447.

18 Straub, C. S.; Padawa, A. *Org. Lett.* **1999**, *1*, 83.

19 Reichelt, A.; Bur, S. K.; Martin, S. F. *Tetrahedron* **2002**, *58*, 6323.

20 Mynderse, J. S.; Fukuda, D. S.; Hunt, A. H. *J. Antibiot.* **1995**, *48*, 425.

21 Goodman, M.; Ro, S. In *Burger's Medicinal Chemistry and Drug Discovery*, 5th ed.; Wolff, M. E., Ed., Wiley, New York, 1995, , Vol. 1, p 803.

22 Schechter, M. S.; Green, N.; LaForge, F. B. *J. Am. Chem. Soc.* **1949**, *71*, 3165.

23 Goodson, L. H.; Honigberg, I. L.; Lehman, J. J.; Burton, W. H. *J. Org. Chem.* **1960**, *25*, 1920.

24 Obrecht, D.; Spiegler, C.; Schonholzer, P.; Muller, K. *Helv. Chim. Acta.* **1992**, *75*, 1666.

25 Ipatov, A. V. *Zh. Obsch. Khim.* **1941**, *11*, 605.

26 Ondetti, M. A.; Rubin, B.; Cushman, D. W. *Science* **1977**, *196*, 441.

27 Ibarra-Rubio, M. E.; Peña, J. C.; Pedraza-Chaverri, J. *Comp. Biochem. Physiol.* **1989**, *92B*, 399.

28 Clive, D. L. J.; Yang, H.; Lewanczuk, R. Z. *C. R. Acad. Sci. Paris, Chimie/Chemistry* **2001**, *4*, 505.

29 Supplied by Chemical Dynamics Corp., South Plainfield, N. J.

30 Phosphomolybdic acid (15 g) and $(NH_4)_4Ce(NO_3)_6$ (2.5 g) dissolved in a mixture of water (485 mL) and concentrated H_2SO_4 (15 mL).

31 *p*-Anisaldehyde (15 drops) was added to concentrated H_2SO_4 (6 mL) and EtOH (94 mL).

32 Buttery, J. E.; Stuart, S. *Clin. Chem.* **1993**, *39*, 312.

CHAPTER 2

A NEW SYNTHESIS OF INDENONES

INTRODUCTION

Indenones are useful intermediates in the synthesis of a variety of molecules, including the *C*-nor-*D*-homosteroid ring system,[1] photochromic indenone oxides,[2] 2,4- and 3,4-disubstituted 1-naphthols,[3] gibberellins,[4] indanones,[5] indenes,[6] and natural products such as coriandrin[7] and the kinamycins.[8] Indenones have also been used as estrogen binding receptors,[9] fermentation activators[10] and fungicides.[11]

Methods for Indenone Syntheses

Traditional Synthetic Methods

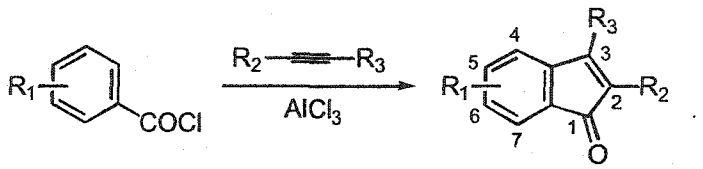
In traditional syntheses of indenones, there are two major approaches: $AlCl_3$-catalyzed addition of benzoyl chlorides to acetylenes[1b] and intramolecular Friedel-Crafts acylation of β-chloro-β-arylpropionyl chlorides, followed by β-elimination.[12] Indenones can also be prepared directly from indanones.[13]

(a) $AlCl_3$-catalyzed addition of benzoyl chlorides to acetylenes[1b]

In the 1970s, Martens and Hoornaert reported a synthetic route to selected indenones using $AlCl_3$-catalyzed addition of a series of methyl- or methoxy-substituted benzoyl chlorides to acetylenes (Scheme 1). The methyl substituent in the benzoyl chloride influences the course of indenone formation. A *meta*-methyl in the benzoyl chloride increases the amount of indenone formed (entries 3 and 4), whereas a *para*-methyl decreases the yield of indenone. No indenone was obtained in the addition of *p*-methylbenzoyl chloride or 2,4-dimethylbenzoyl chloride to 3-hexyne. When cyclization can take place *ortho* as well as *para* to the activating substituent, much more *para* cyclization occurs (entries 3, 7, 8). The reactivity of the methoxy-substituted benzoyl chlorides varied in the same manner as that of the methyl-substituted benzoyl

chlorides. No indenone was produced from *p*-methoxybenzoyl chloride and 3-hexyne. As shown in the Table, yields are sometimes very low, using this method.

Scheme 1



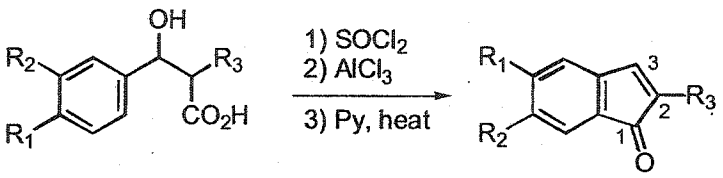
entry	R_1	R_2	R_3	yield (%)
1	H	Et	Et	63
2	7-Me	Et	Et	2
3	6-Me	Et	Et	22
	4-Me	Et	Et	
4	4,6-di(Me)	Et	Et	39
5	4,7-di(Me)	Et	Et	58
6	6,7-di(Me)	Et	Et	26
7	5,6-di(Me)	Et	Et	18
	4,5-di(Me)	Et	Et	
8	6-MeO	Et	Et	60
	4-MeO	Et	Et	
9	4,6-di(MeO)	Et	Et	60
10	4,6-di(MeO)	Ph	Ph	70
11	4,6-di(MeO)	Et	Ph	70
12	4,6-di(MeO)	H	Ph	50

(b) Intramolecular Friedel-Crafts acylation of β-chloro-β-arylpropionyl chlorides followed by β-elimination[12]

Indenones can be prepared by intramolecular Friedel-Crafts acylation of β-chloro-β-arylpropionyl chlorides, followed by β-elimination. This methodology was first reported by Floyd and Allen[12a] in 1970. Over 20 years later, an improved synthetic protocol was described by the Galatsis group[12b] (Scheme 2). This method does, however, have an obvious drawback, since only 2-substituted

indenones can be made in acceptable yields. For R_3 = H, indenones were obtained in poor yields or no indenone products were formed at all (entries 1-4).

Scheme 2



entry	R_1	R_2	R_3	yield (%)
1	H	H	H	5
2	Me	H	H	0
3	MeO	H	H	0
4	Me	MeO	H	15
5	H	H	Me	74
6	Me	H	Me	63
7	Me	MeO	Me	72
8	H	H	Et	79
9	H	H	Bn	40

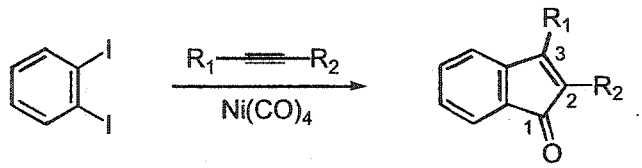
Transition Metal-Mediated Reactions

(a) $Ni(CO)_4$ mediated reaction of o-diiodobenzene with alkynes[14]

Liebeskind and South reported a synthesis of substituted indenones using the reaction of *o*-diiodobenzene with alkynes and $Ni(CO)_4$ (Scheme 3). In this methodology, unsymmetrical disubstituted alkynes (entries 4-7) gave both possible isomeric 2,3-disubstituted indenones. Although the reaction is not regiospecific, there appears to be a trend that the major isomer is that in which the bulkier alkyne substituent occupies the 2-position in the indenone. This trend is dominant with terminal alkynes (entries 8-10), which provided only 2-substituted indenones in moderate yields. However, electron-deficient alkynes ($MeC{\equiv}CCO_2Et$, $EtO_2CC{\equiv}CCO_2Et$) did not yield any indenones [in

cyclohexane at 120 °C in a sealed tube for 6 h with *o*-diiodobenzene (1.0 equiv), $Ni(CO)_4$ (1.5 equiv) and alkyne (1.5 equiv)].

Scheme 3



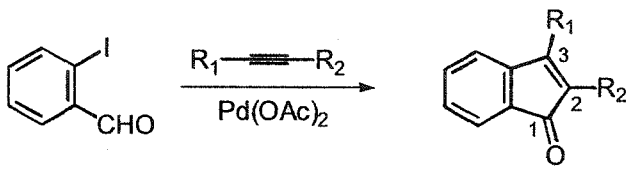
entry	R_1	R_2	yield (%)
1	Et	Et	89
2	Me	Me	77
3	Ph	Ph	51
4	Me	Et	39
	Et	Me	39
5	Me	*n*-Pr	42
	n-Pr	Me	42
6	Me	*t*-Bu	49
	t-Bu	Me	13
7	Me	Ph	30
	Ph	Me	37
8	H	*n*-Bu	52
9	H	*t*-Bu	53
10	H	*c*-Hex	50

(b) Palladium-catalyzed reaction of o-iodobenzaldehyde with internal alkynes[15]

Heck first reported the palladium-catalyzed formation of 2,3-diphenyl-1-indenone from *o*-iodobenzaldehyde and diphenylacetylene as a single example in 1989.[15a] Larock and Doty improved the reaction conditions for palladium-catalyzed synthesis of a wide variety of 2,3-disubstituted indenones[15b] (Scheme 4). This annulation process was highly regioselective for alkynes containing tertiary alkyl, trimethylsilyl, or other hindered groups, with the major

isomer having the more sterically demanding group at the 2-position of the indenone (entries 3-5). Less hindered alkynes produced a 1:1 mixture of regioisomers (entries 2 and 6). Electronic effects through aromatic rings appeared to be minimal (entry 6). Isomerization of the product was a problem with certain indenones bearing a primary alkyl group at the 3-position. The ease of isomerization has been attributed to indenone antiaromaticity. The rate of isomerization was dependent on the particular indenone being formed and different mechanisms were postulated for the isomerization, depending on the reaction conditions.

Scheme 4



entry	R_1	R_2	yield (%)
1	Ph	Ph	84
2	Me	Ph	31
	Ph	Me	31
3	Ph	CMe_3	81
4	Ph	$SiMe_3$	42
5	Ph	$C(CH_3)_2OH$	58
6	*p*-MeOPh	Ph	41
	Ph	*p*-MeOPh	41

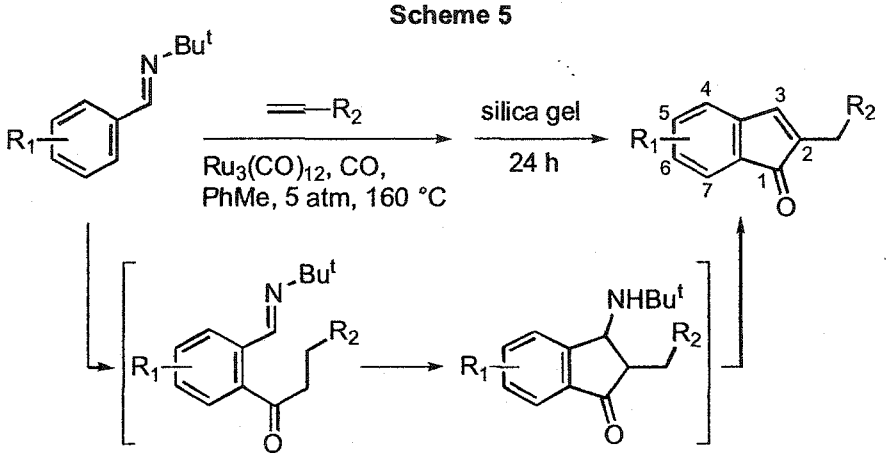
In addition, reaction of *o*-iodobenzene with 3-hexyne in the presence of $Pd(PPh_3)_4$ under CO gave 2,3-diethylindenone.[14] Several other 2,3-disubstituted indenones have been made from pregenerated palladium complexes.[16] However, neither of the above Pd-mediated approaches has been used very much to make 2,3-disubstituted indenones.

(c) $Ru_3(CO)_{12}$-catalyzed reaction of aromatic imines with CO

and olefins[17]

Murai reported a simple synthetic method for the preparation of 2-substituted indenones using $Ru_3(CO)_{12}$-catalyzed reaction of aromatic imines with CO and olefins. This process involved carbonylation at an *ortho* C-H bond in the aromatic imine to generate the keto imine intermediate. This then underwent intramolecular aldol-type cyclization to a five-membered ring intermediate in which elimination of *tert*-butylamine occurred smoothly to give the indenone on treatment with silica gel. The substitution pattern of

Scheme 5



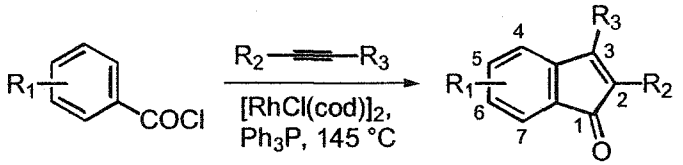
entry	R_1	R_2	yield (%)
1	4-Me	H	82
2	4-Me	*t*-Bu	41
3	4-Me	$SiMe_3$	64
4	4-MeO	H	85
5	4-CF_3	H	58
6	4-F	H	66
7	5-Me	H	69
8	5,6-cyclobutadiene	H	68

the olefins influenced the yield of indenone. More hindered olefins gave lower yields (entries 2 and 3) and some olefins (1-hexene, styrene and methyl acrylate) did not generate any indenone (not shown). Electronic effects

on the formation of indenones were obvious. The electron-donating groups (MeO and Me, entries 1 and 4) on the aromatic ring afforded indenones in high yields, whereas the electron-withdrawing group (CF_3, entry 5) resulted in a decrease in the yield of indenone. Regioselectivity of carbonylation was a problem with the aromatic amines bearing two *ortho* C-H bonds, although carbonylation could take place at a sterically less hindered *ortho* C-H bond to give indenones regioselectively (entries 7 and 8). As seen from the results, some 2-substituted indenones can be made in reasonable yield by this method but the reaction temperature needed is quite high (160 °C).

(d) Rhodium-catalyzed reactions

Scheme 6



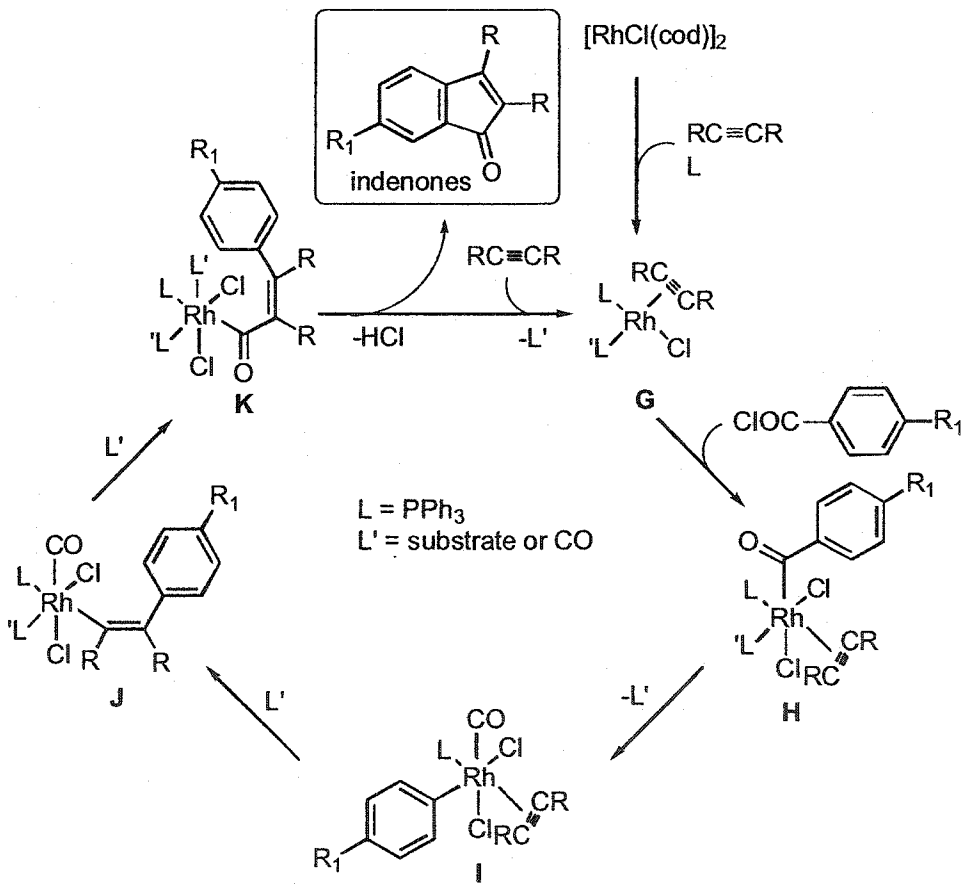
entry	R1	R_2	R_3	yield (%)
1	H	Pr	Pr	76
2	6-Cl (*p*-Cl in ArCOCl)	Pr	Pr	61
3	6-Me (*p*-Me in ArCOCl)	Pr	Pr	67
4	5-Me (*o*-Me in ArCOCl)	Pr	Pr	88
5	H	Et	Et	49
6	H	Ph	Ph	13
7	H	Ph	Et	13
	H	Et	Ph	13
8	H	Bu	Me	18
	H	Me	Bu	18
9	H	Ph	$SiMe_3$	18
	H	$SiMe_3$	Ph	6

In 1979, Hong[18] reported a synthetic approach to 2,3-

disubstituted indenones, especially 2,3-diphenylindenones, using $Rh_4(CO)_{12}$-catalyzed reaction of benzene, toluene, fluorobenzene or anisole with internal alkynes under CO at 220 °C. However, the yields were poor (10-20%).

$[RhCl(cod)]_2$-catalyzed reaction of aroyl chlorides with internal alkynes was reported by Miura[19] to produce 2,3-disubstituted indenones (Scheme 6). Some internal alkynes gave the corresponding indenones in moderate to low yields (entries 5-9). The regioselectivity was poor in reactions using unsymmetrical alkynes (entries 6-9). For $BuC{\equiv}CCO_2Et$, no indenone was obtained (not shown). Interestingly, the carbonyl moiety in the products was found to shift to the neighboring position in the starting aroyl chlorides (entries 2-4), as explained below.

Scheme 7

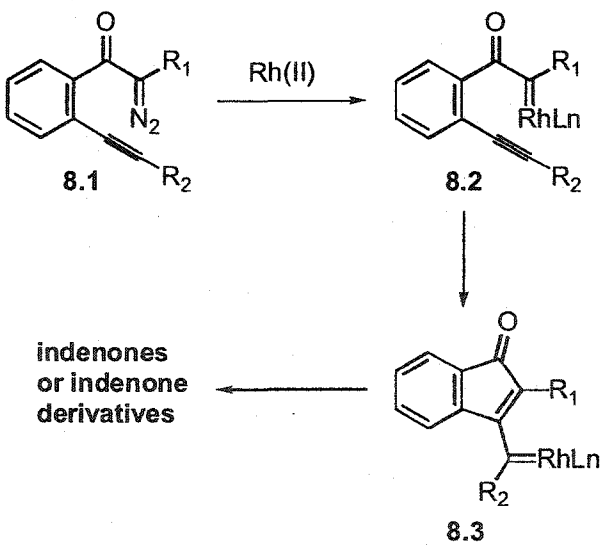


A plausible mechanism to account for the formation of

indenones was proposed and is shown in Scheme 7. The key intermediate leading to indenones might be the arylchlororhodium(III) species **I**, formed via complexes **G** and **H**. Arylrhodation in **I** followed by reinsertion of the CO coordinated to the metal center affords complex **K**. The subsequent cyclization, accompanied by regeneration of **G** and evolution of HCl, gives the indenone. The structure of the indenone (entry 4) might suggest that the final cyclization step of **K** to the final product was sterically controlled; steric hindrance by a methyl group on the benzene ring might be the major reason for the regioselective formation of the product.

In addition, Padwa reported a synthetic approach to indenones or indenone derivatives using Rh(II) carboxylate-catalyzed cyclization of *o*-alkynyl-substituted aryl diazo ketones.[20] Briefly, ketone **8.1** was treated with a catalytic amount of a Rh(II) carboxylate to produce the intermediate **8.3** (indenone-rhodium carbene complex), which could undergo a number of different reactions to give an indenone or an indenone derivative, depending on the nature of the two groups R_1 and R_2 (Scheme 8).

Scheme 8

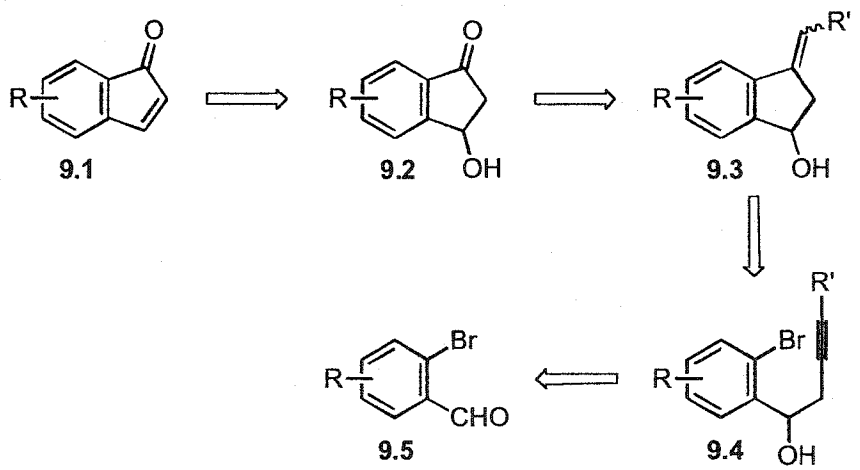


RESULTS AND DISCUSSION

The methods described above were used to make 2- and/or 3-substituted indenones. The synthesis of 2,3-disubstituted indenones has been widely studied. These methods have some drawbacks in terms of substrate limitations, yield or harshness of reaction conditions.

We were interested in indenones unsubstituted at the 2 and 3 positions, and wanted to develop a general route to such compounds, despite the fact that unsubstituted indenones are less stable than those with substituents.[12] From a retrosynthetic standpoint, the unsubstituted indenones **9.1** can be derived from homopropargylic alcohols **9.4** using radical cyclization onto the triple bond, followed by cleavage of the resulting exocyclic double bond and subsequent dehydration. Homopropargylic alcohols **9.4** can be prepared from *o*-bromobenzaldehydes **9.5** (Scheme 9).

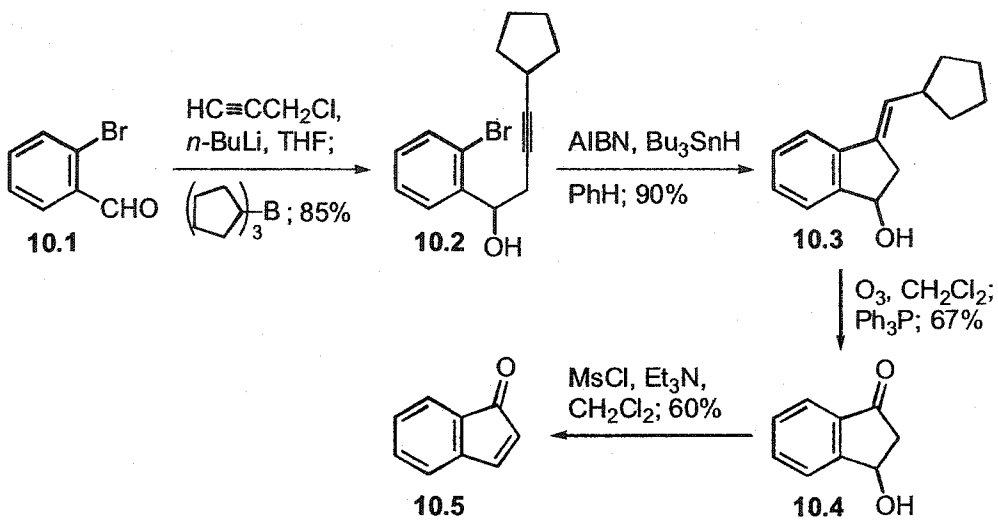
Scheme 9



In the first example we examined we used commercially available *o*-bromobenzaldehyde (**10.1**) as starting material. Following a literature procedure,[21] *o*-bromobenzaldehyde (**10.1**) was treated with a mixture of lithium chloropropargylide and tricyclopentylborane, to give alcohol **10.2** in 85% yield (Scheme 10). The mechanism for this transformation is illustrated in Scheme 11. Radical

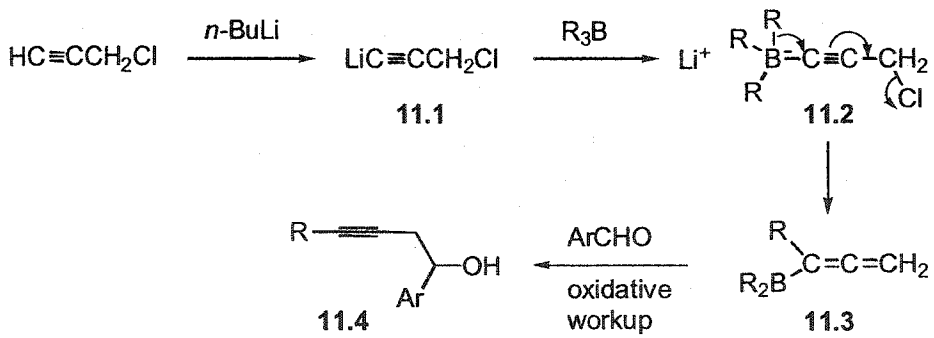
cyclization under standard conditions afforded homoallylic alcohol **10.3**, which was ozonized to the known β-hydroxyketone **10.4**.[22] Compound **10.3** was a single isomer, but we did not establish the double bond geometry. Finally, dehydration of **10.4** was achieved by treatment with MsCl in the presence of Et_3N, leading to the known indenone **10.5**[23] in 60% yield.

Scheme 10



The mechanism for the homopropargylic alcohol formation is as follows. Deprotonation of propargyl chloride with *n*-BuLi gives lithium chloropropargylide **11.1**,

Scheme 11

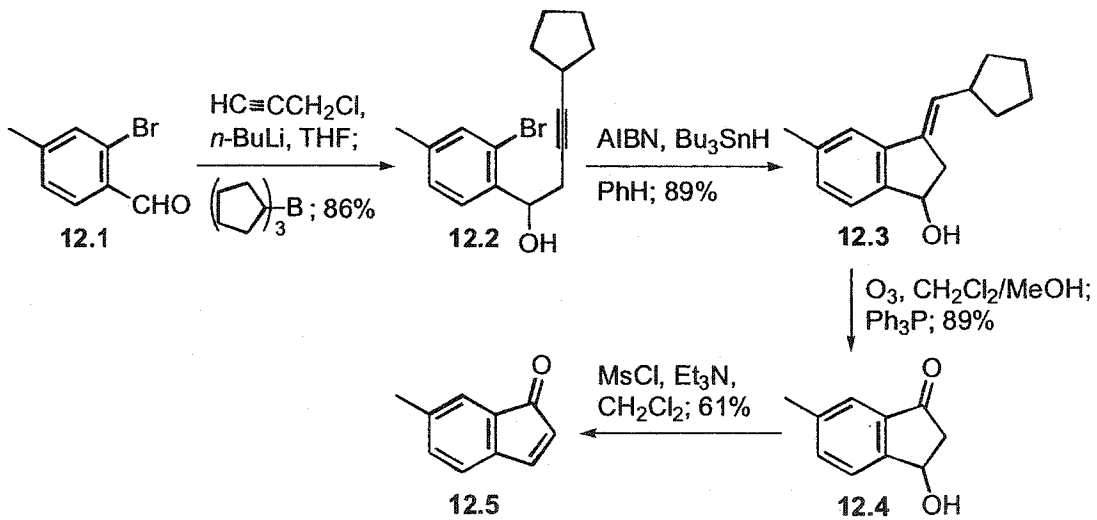


which is treated with a trialkylborane forming the ate complex **11.2**. Complex **11.2** undergoes a spontaneous

anionotropic rearrangement in which one R group migrates from boron to the adjacent carbon, concomitant with an electron-pair shift and loss of chloride, to provide the allenic borane **11.3**. Reaction of **11.3** with an aryl aldehyde leads to an allenic-propargylic rearrangement to give, after oxidative workup, the homopropargylic alcohol **11.4** (Scheme 11).

The second example, using 2-bromo-4-methyl benzaldehyde,[24] **12.1** as starting material worked well (Scheme 12), and again the radical cyclization afforded a single isomer of unestablished double bond geometry. In the ozonolysis step, use of the more polar MeOH as cosolvent increased the yield (89%) while reaction in CH_2Cl_2 gave 60%. The superiority of MeOH may be due to the increased solubility of the compounds involved or to the fact that the ozonolysis mechanism is different in a participating solvent.

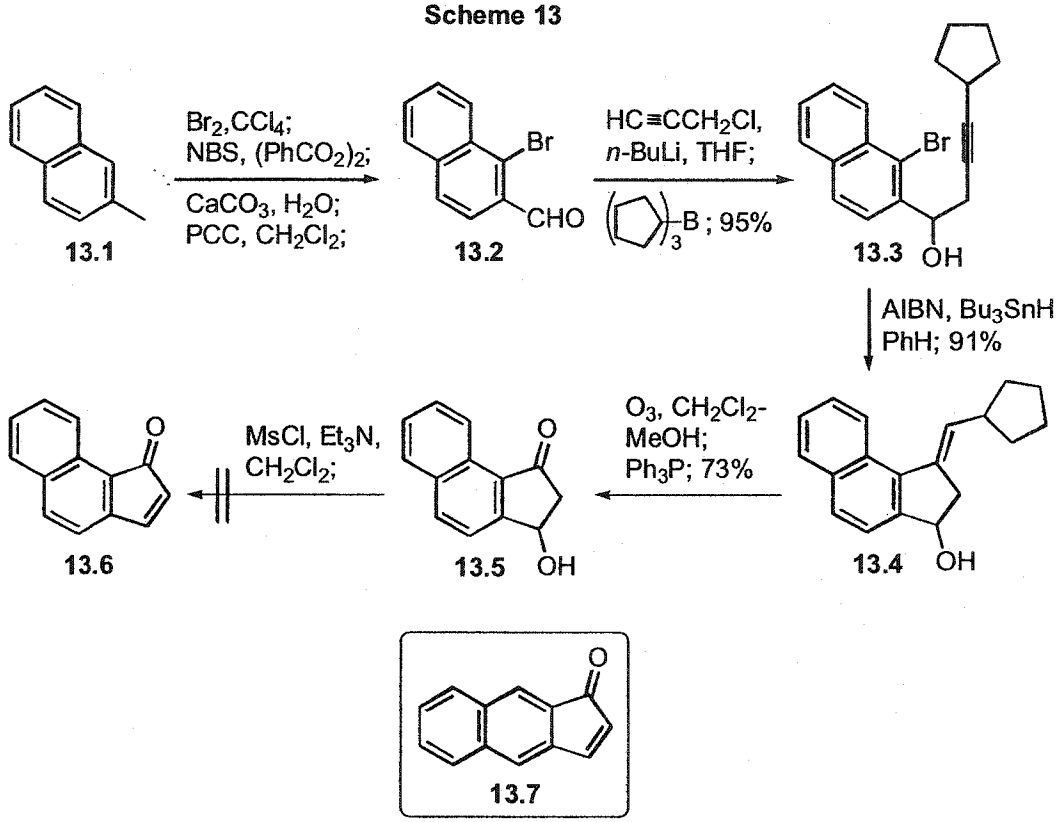
Scheme 12



Next, we examined our route to indenones using the *o*-bromonaphthaldehyde **13.2**, which was synthesized by a four-step literature procedure[25] from compound **13.1**. There were no problems with the first three steps in our route, giving **13.4** (a single isomer). Unfortunately, dehydration of **13.5**

with MsCl and Et_3N provided an unidentified product, and none of the desired indenone **13.6** was obtained. We wondered if indenone **13.6**, may have unusual properties that cause it to decompose. Interestingly, indenone **13.7**,[26] an isomer of **13.6**, is a known and stable compound, but no examples have been reported of angularly fused indenones corresponding to **13.6**, either with or without substituents on the naphthalene substructure.

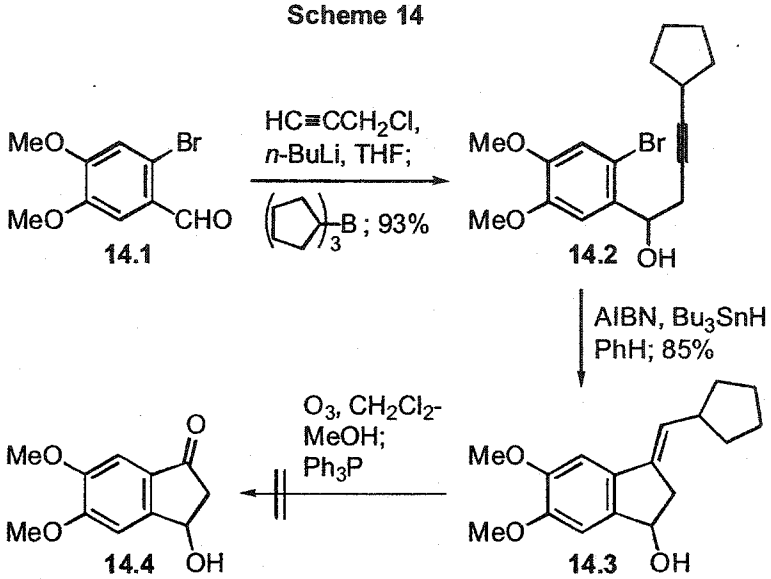
Scheme 13



We turned our attention to the next example, using the known *o*-bromobenzaldehyde **14.1**[27] as substrate. No problems were observed in the first two steps. However, ozonolysis did not work and none of the desired product **14.4** was formed. The electron-rich benzene ring in compound **14.3** (single isomer) was destroyed by O_3 and a complex mixture was produced. Although double bond cleavage could, in principle, be achieved using other oxidants, such as

$OsO_4/NaIO_4$, we decided to stop work on our indenone synthesis, as other research in the group, which had depended on the synthesis of an indenone, had been brought to a successful conclusion by using a new method to prepare indenols.[28]

Scheme 14



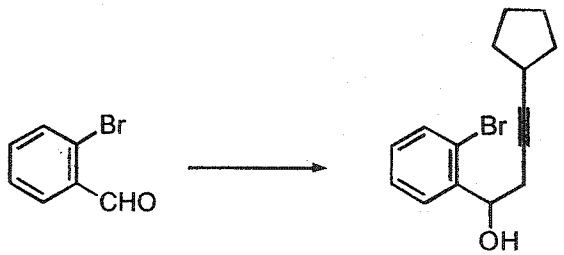
CONCLUSION

A synthetic method for making 2,3-unsubstituted indenones was developed. Although the method appeared not to be general, it worked well in some cases.

EXPERIMENTAL

The same general procedures were used as described in Chapter 1. In many ^1H NMR spectra, certain spin systems are described as AB quartets even though the value of $\Delta\nu/J$ is greater than 10. Strictly, such spectra should be described as AM systems.

1-(2-Bromophenyl)-4-cyclopentylbut-3-yn-1-ol (10.2).



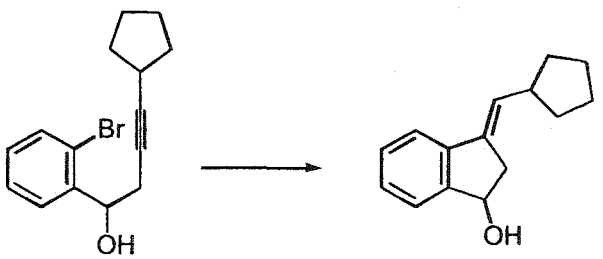
10.1 **10.2**

$BH_3 \cdot Me_2S$ (0.30 mL, 10.0-10.2 M in THF) was added dropwise to a stirred solution of cyclopentene (0.88 mL, 10 mmol) in THF (3 mL). The mixture was stirred at 42 °C for 3 h before being cooled to room temperature and added to a solution of lithium chloropropargylide in THF, which was prepared as follows.

n-BuLi (1.2 mL, 2.5 M in hexanes) was added dropwise to a stirred and cooled (-90 °C, nitroethane/liquid nitrogen) solution of propargyl chloride (0.22 mL, 3.0 mmol) in THF (5 mL). Stirring at -90 °C was continued for 15 min, and then the previously prepared solution of tricyclopentylborane in THF was added over 10 min at -90 °C. The mixture was transferred to an acetone-dry ice bath and stirred at -78 °C for 30 min. Then a solution of **10.1** (0.542 g, 2.93 mmol) in THF (0.5 mL) was added dropwise. The resulting mixture was stirred at -78 °C for 1 h. The cold bath was removed and stirring was continued for 30 min, by which time the mixture had attained room temperature. MeOH (2 mL), 3 N NaOH (1.2 mL) and 30% H_2O_2

(0.8 mL) were added. The resulting mixture was stirred at 50 °C for 1 h, cooled to room temperature, and extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 10% EtOAc-hexanes, gave **10.2** (0.732 g, 85%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3406, 3064, 2957, 2868 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.42-1.98 (m, 8 H), 2.49 (ddd, J = 16.8, 7.5, 2.1 Hz, 1 H), 2.54-2.67 (m, 2 H), 2.80 (ddd, J = 16.8, 4.1, 2.1 Hz, 1 H), 5.15 (dd, J = 7.5, 4.1 Hz, 1 H), 7.10-7.17 (m, 1 H), 7.30-7.37 (m, 1 H), 7.51 (dd, J = 8.1, 1.1 Hz, 1 H), 7.60 (dd, J = 8.1, 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 24.9 (t), 28.4 (t), 30.3 (d), 34.0 (t), 71.1 (d), 74.8 (s), 88.4 (s), 121.8 (s), 127.4 (d), 127.5 (d), 129.0 (d), 132.6 (d), 141.7 (s); exact mass m/z calcd for $C_{15}H_{17}{}^{81}BrO$ 294.0442 and $C_{15}H_{17}{}^{79}BrO$ 292.0463, found 294.0440 and 292.0461.

3-Cyclopentylmethyleneindan-1-ol (10.3).

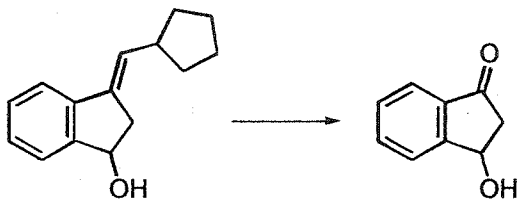


10.2 **10.3**

A solution of Bu_3SnH (0.44 mL, 1.6 mmol) and AIBN (27 mg, 0.16 mmol) in PhH (10 mL) was added by syringe pump over 10 h to a stirred and heated (85 °C) solution of **10.2** (0.396 g, 1.35 mmol) in PhH (40 mL). Stirring was continued for 2 h after the addition, and the mixture was allowed to cool to room temperature. Evaporation of solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 15% EtOAc-hexanes, gave **10.3** (0.26

g, 90%) as a white solid: mp 93-94 °C; FTIR (CH_2Cl_2, cast) 3308, 3069, 2950, 2865 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.22-1.98 (m, 9 H), 2.61 (dt, *J* = 16.7, 2.9 Hz, 1 H), 2.65-2.77 (m, 1 H), 3.17 (ddd, *J* = 16.7, 8.5, 2.2 Hz, 1 H), 5.27 (dd, *J* = 8.4, 3.3 Hz, 1 H), 5.95 (dt, *J* = 9.1, 2.4 Hz, 1 H), 7.20-7.52 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 25.4 (t), 33.5 (t), 39.4 (t), 40.7 (d), 73.7 (d), 120.0 (d), 125.1 (d), 126.9 (d), 127.9 (d), 128.8 (d), 136.7 (s), 141.1 (s), 146.1 (s); exact mass *m/z* calcd for $C_{15}H_{18}O$ 214.1358, found 214.1357.

3-Hydroxyindan-1-one (10.4).



10.3 **10.4**

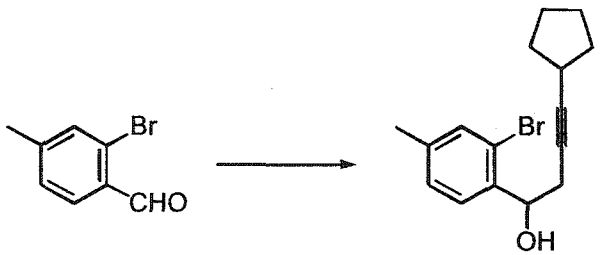
An O_3-O_2 stream was passed through a stirred and cooled (-78 °C) solution of **10.3** (0.12 g, 0.56 mmol) in dry CH_2Cl_2 (10 mL) for 5 min, by which time all the starting material had reacted (TLC control, silica gel, 1:1 EtOAc-hexane). The solution was purged with O_2 for 10 min, and then Ph_3P (0.37 g, 1.4 mmol) was added. The cooling bath was removed and stirring was continued for 3 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 20), using 50% EtOAc-hexanes, gave **10.4**[22] (55 mg, 67%) as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 2.41 (br s, 1 H), 2.63 (dd, *J* = 18.8, 2.8 Hz, 1 H), 3.13 (dd, *J* = 18.8, 6.7 Hz, 1 H), 5.45 (dd, *J* = 6.7, 2.8 Hz, 1 H), 7.42-7.60 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 40.2 (t), 68.6 (d), 123.3 (d), 125.9 (d), 129.5 (d), 135.3 (d), 136.4 (s), 155.1 (s), 203.2 (s).

Inden-1-one (10.5).

10.4 **10.5**

Et_3N (0.16 mL, 1.1 mmol), followed by MsCl (44 μL, 0.56 mmol), was added dropwise to a stirred and cooled (0 °C) solution of **10.4** (55 mg, 0.37 mmol) in Et_2O (3 mL). The mixture was stirred at 0 °C for 1 h. The cold bath was removed and stirring was continued for 1 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 20), using 10% EtOAc-hexanes, gave **10.5**[23] (29 mg, 60%) as a yellow oil, which was identified spectroscopically (^1H NMR) by comparison with published data.

1-(2-Bromo-4-methylphenyl)-4-cyclopentylbut-3-yn-1-ol (12.2).



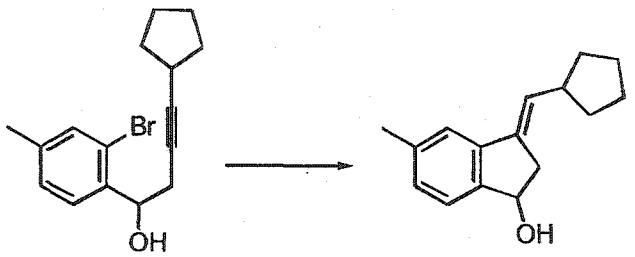
12.1 **12.2**

The same procedure used for **10.2** was followed.

$BH_3 \cdot Me_2S$ (0.30 mL, 10.0-10.2 M in THF) was added dropwise to a stirred solution of cyclopentene (0.88 mL, 10 mmol) in THF (3 mL). The mixture was stirred at 42 °C for 3 h before being cooled to room temperature and added to a solution of lithium chloropropargylide in THF, which was prepared as follows.

n-BuLi (1.2 mL, 2.5 M in hexanes) was added dropwise to a stirred and cooled (-90 °C, nitroethane/liquid nitrogen) solution of propargyl chloride (0.22 mL, 3.0 mmol) in THF (5 mL). Stirring at -90 °C was continued for 15 min, and then the previously prepared solution of tricyclopentylborane in THF was added over 10 min at -90 °C. The mixture was transferred to an acetone-dry ice bath and stirred at -78 °C for 30 min. Then a solution of **12.1**[24] (0.578 g, 2.90 mmol) in THF (0.5 mL) was added dropwise. The resulting mixture was stirred at -78 °C for 1 h. The cold bath was removed and stirring was continued for 30 min, by which time the mixture had attained room temperature. MeOH (2 mL), 3 N NaOH (1.2 mL) and 30% H_2O_2 (0.8 mL) were added. The resulting mixture was stirred at 50 °C for 1 h, cooled to room temperature, and extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 10% EtOAc-hexanes, gave **12.2** (0.769 g, 86%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3405, 2958, 2869 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.42-1.98 (m, 8 H), 2.31 (s, 3 H), 2.47 (ddd, *J* = 16.8, 7.6, 2.1 Hz, 1 H), 2.52-2.65 (m, 2 H), 2.76 (ddd, *J* = 16.8, 4.2, 2.1 Hz, 1 H), 5.11 (dd, *J* = 7.6, 4.1 Hz, 1 H), 7.14 (dd, *J* = 8.1, 0.8 Hz, 1 H), 7.34 (d, *J* = 0.8 Hz, 1 H), 7.46 (d, *J* = 8.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.7 (q), 24.9 (t), 28.5 (t), 30.3 (d), 34.0 (t), 70.9 (d), 75.0 (s), 88.3 (s), 121.6 (s), 127.1 (d), 128.3 (d), 133.0 (d), 138.6 (s), 139.1 (s); exact mass *m/z* calcd for $C_{16}H_{19}{}^{81}BrO$ 308.0599 and $C_{16}H_{19}{}^{79}BrO$ 306.0619, found 308.0510 and 306.0616.

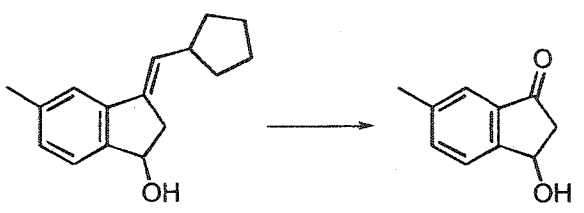
3-Cyclopentylmethylene-5-methylindan-1-ol (12.3).



12.2 **12.3**

A solution of Bu_3SnH (0.35 mL, 1.3 mmol) and AIBN (21 mg, 0.13 mmol) in PhH (8 mL) was added by syringe pump over 10 h to a stirred and heated (85 °C) solution of **12.2** (0.334 g, 1.09 mmol) in PhH (35 mL). Stirring was continued for 2 h after the addition, and the mixture was allowed to cool to room temperature. Evaporation of solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 15% EtOAc-hexanes, gave **12.3** (0.222 g, 89%) as a white solid: mp 109.5-110.5 °C; FTIR (CH_2Cl_2, cast) 3319, 2950, 2864 cm^{-1}; ^1H NMR (C_6D_6, 360 MHz) δ 1.20-1.95 (m, 9 H), 2.22 (s, 3 H), 2.50 (ddd, *J* = 16.8, 3.5, 2.3 Hz, 1 H), 2.58-2.73 (m, 1 H), 2.98 (ddd, *J* = 16.8, 8.6, 2.3 Hz, 1 H), 5.02-5.11 (m, 1 H), 5.96 (dt, *J* = 9.2, 2.4 Hz, 1 H), 6.98 (dd, *J* = 8.6, 0.8 Hz, 1 H), 7.28 (s, 1 H), 7.31 (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 20.8 (q), 25.4 (t), 33.5 (t), 39.8 (t), 40.7 (d), 73.0 (d), 120.4 (d), 124.9 (d), 125.5 (d), 128.9 (d), 137.6 (s), 137.9 (s), 141.3 (s), 144.4 (s); exact mass *m/z* calcd for $C_{16}H_{20}O$ 228.1514, found 228.1515.

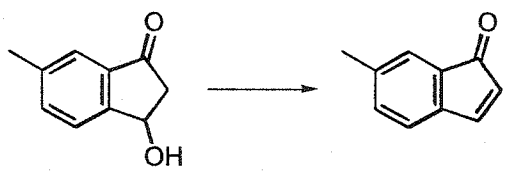
3-Hydroxy-6-methylindan-1-one (12.4).



12.3 **12.4**

An O_3-O_2 stream was passed through a stirred and cooled (-78 °C) solution of **12.3** (93.5 mg, 0.410 mmol) in a mixture of CH_2Cl_2 (10 mL) and MeOH (2 mL) for 5 min, by which time all the starting material had reacted (TLC control, silica gel, 1:1 EtOAc-hexane). The solution was purged with O_2 for 15 min, and then Ph_3P (0.27 g, 1.0 mmol) was added. The cooling bath was removed and stirring was continued for 3 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 20), using 50% EtOAc-hexanes, gave **12.4** (59.2 mg, 89%) as a white solid: mp 92-93 °C; FTIR (CH_2Cl_2, cast) 3400, 2921, 1698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.36 (br s, 1 H), 2.43 (s, 3 H), 2.61 (dd, J = 18.6, 2.7 Hz, 1 H), 3.11 (dd, J = 18.6, 6.8 Hz, 1 H), 5.40 (dd, J = 6.8, 2.7 Hz, 1 H), 7.48-7.62 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 21.1 (q), 47.5 (t), 68.4 (d), 123.2 (d), 125.5 (d), 136.5 (d), 136.6 (s), 139.8 (s), 152.6 (s), 203.3 (s); exact mass *m/z* calcd for $C_{10}H_{10}O_2$ 162.0681, found 160.0680.

6-Methylinden-1-one (12.5).

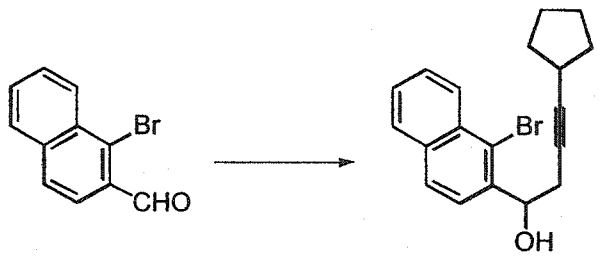


12.4 **12.5**

Et_3N (0.19 mL, 1.4 mmol), followed by MsCl (54 μL, 0.70 mmol), was added dropwise to a stirred and cooled (0 °C) solution of **12.4** (75 mg, 0.46 mmol) in Et_2O (3 mL). The mixture was stirred at 0 °C for 1 h. The cooling bath was removed and stirring was continued for 1 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 20), using 10% EtOAc-hexanes, gave **12.5** (41 mg, 61%) as a yellow solid: mp 34.5-35.5 °C; FTIR (CH_2Cl_2, cast) 2921, 1705 cm^{-1}; ^1H NMR (C_6D_6, 360 MHz) δ 1.92 (s, 3

H), 5.60 (d, J = 5.8 Hz, 1 H), 6.46 (d, J = 7.2 Hz, 1 H), 6.72 (d, J = 7.3 Hz, 1 H), 6.87 (d, J = 5.8 Hz, 1 H), 7.22 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.0 (q), 121.9 (d), 124.0 (d), 126.6 (d), 131.2 (s), 133.2 (d), 139.3 (s), 142.2 (s), 149.3 (d), 197.8 (s); exact mass *m/z* calcd for $C_{10}H_8O$ 144.0575, found 144.0574.

1-(1-Bromonaphthalen-2-yl)-4-cyclopentylbut-3-yn-1-ol (13.3).



13.2 **13.3**

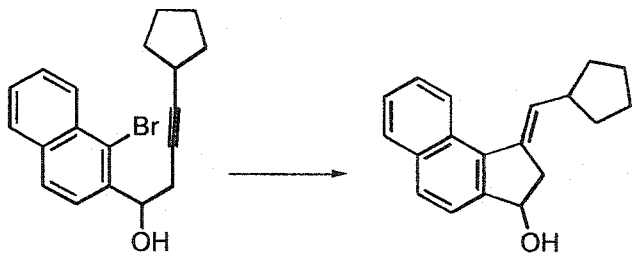
The same procedure used for **10.2** was followed.

$BH_3 \cdot Me_2S$ (0.30 mL, 10.0-10.2 M in THF) was added dropwise to a stirred solution of cyclopentene (0.88 mL, 10 mmol) in THF (3 mL). The mixture was stirred at 42 °C for 3 h before being cooled to room temperature and added to a solution of lithium chloropropargylide in THF, which was prepared as follows.

n-BuLi (1.2 mL, 2.5 M in hexanes) was added dropwise to a stirred and cooled (-90 °C, nitroethane/liquid nitrogen) solution of propargyl chloride (0.22 mL, 3.0 mmol) in THF (5 mL). Stirring at -90 °C was continued for 15 min, and then the previously prepared solution of tricyclopentylborane in THF was added over 10 min at -90 °C. The mixture was transferred to an acetone-dry ice bath and stirred at -78 °C for 30 min. Then a solution of **13.2**[25] (0.705 g, 3.00 mmol) in THF (0.5 mL) was added dropwise. The resulting mixture was stirred at -78 °C for 1 h. The cold bath was removed and stirring was continued for 30

min, by which time the mixture had attained room temperature. MeOH (2 mL), 3 N NaOH (1.2 mL) and 30% H_2O_2 (0.8 mL) were added. The resulting mixture was stirred at 50 °C for 1 h, cooled to room temperature, and extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 10% EtOAc-hexanes, gave **13.3** (0.979 g, 95%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3406, 3057, 2958, 2868 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.45-1.98 (m, 8 H), 2.55-2.67 (m, 2 H), 2.77 (s, 1 H), 2.80-2.90 (m, 1 H), 5.49 (dd, J = 7.1, 4.1 Hz, 1 H), 7.50-8.35 (m, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 24.9 (t), 28.4 (t), 30.3 (d), 34.0 (t), 72.0 (d), 74.9 (s), 88.4 (s), 121.7 (s), 124.3 (d), 126.6 (d), 127.3 (d), 127.4 (d), 127.9 (d), 128.2 (d), 131.1 (s), 134.2 (s), 139.8 (s); exact mass *m/z* calcd for $C_{19}H_{19}{}^{81}BrO$ 344.0599 and $C_{19}H_{19}{}^{79}BrO$ 342.0619, found 344.0597 and 342.0615.

1-Cyclopentylmethylene-2,3-dihydro-1*H*-cyclopenta[*a*]-naphthalen-3-ol (13.4).

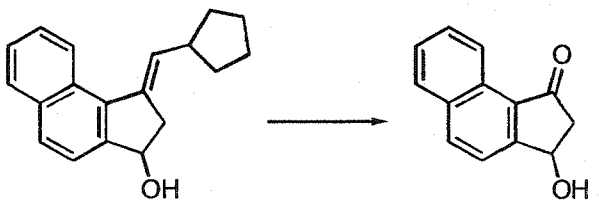


13.3 **13.4**

A solution of Bu_3SnH (0.88 mL, 3.3 mmol) and AIBN (54 mg, 0.33 mmol) in PhH (19 mL) was added by syringe pump over 10 h to a stirred and heated (85 °C) solution of **13.3** (0.964 g, 2.81 mmol) in PhH (100 mL). Stirring was continued for 2 h after the addition, and the mixture was allowed to cool to room temperature. Evaporation of

solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 15% EtOAc-hexanes, gave **13.4** (0.674 g, 91%) as a white solid: mp 88-89 °C; FTIR (CH_2Cl_2, cast) 3300, 3050, 2950, 2864 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 1.25-2.10 (m, 9 H), 2.55 (ddd, *J* = 15.6, 4.5, 2.5 Hz, 1 H), 2.63-2.80 (m, 1 H), 3.14 (ddd, *J* = 15.6, 7.2, 1.8 Hz, 1 H), 5.03-5.15 (m, 1 H), 6.48 (dt, *J* = 8.6, 2.2 Hz, 1 H), 7.30-7.80 (m, 4 H), 8.71 (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR (C_6D_6, 75.5 MHz) δ 25.7 (t), 25.8 (t), 34.0 (t), 34.1 (t), 41.7 (t), 41.9 (d), 73.4 (d), 123.1 (d), 125.0 (d), 125.7 (d), 126.9 (d), 129.1 (d), 129.5 (d), 129.7 (s), 130.8 (d), 135.0 (s), 135.7 (s), 138.7 (s), 146.1 (s); exact mass *m/z* calcd for $C_{19}H_{20}O$ 264.1514, found 264.1511.

3-Hydroxy-2,3-dihydrocyclopenta[*a*]naphthalen-1-one (13.5).

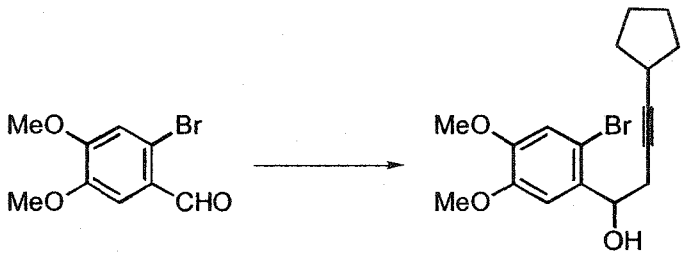


13.4 **13.5**

An O_3-O_2 stream was passed through a stirred and cooled (-78 °C) solution of **13.4** (0.357 g, 1.35 mmol) in a mixture of CH_2Cl_2 (20 mL) and MeOH (5 mL) for 5 min, by which time all the starting material had reacted (TLC control, silica gel, 1:1 EtOAc-hexane). The solution was purged with O_2 for 15 min, and then Ph_3P (0.889 g, 3.38 mmol) was added. The cooling bath was removed and stirring was continued for 3 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 25), using 50% EtOAc-hexanes, gave **13.5** (0.195 g, 73%) as a white solid: mp 129.5-131 °C; FTIR (CH_2Cl_2, cast) 3387, 3055, 2919, 1699, 1682 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.55 (br s, 1 H), 2.72

(dd, J = 18.5, 2.7 Hz, 1 H), 3.21 (dd, J = 18.5, 6.6 Hz, 1 H), 5.46 (dd, J = 6.5, 2.7 Hz, 1 H), 7.55-7.75 (m, 3 H), 7.89 (d, J = 8.2 Hz, 1 H), 8.10 (d, J = 8.2 Hz, 1 H), 9.07 (d, J = 8.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 47.7 (t), 68.3 (d), 122.4 (d), 124.7 (d), 127.4 (d), 128.2 (s), 128.6 (d), 129.3 (s), 130.7 (s), 133.6 (s), 136.5 (d), 157.3 (s), signal for carbonyl not observed; exact mass *m/z* calcd for $C_{13}H_{10}O_2$ 198.0681, found 198.0684.

1-(2-Bromo-4,5-dimethoxyphenyl)-4-cyclopentylbut-3-yn-1-ol (14.2).



14.1 **14.2**

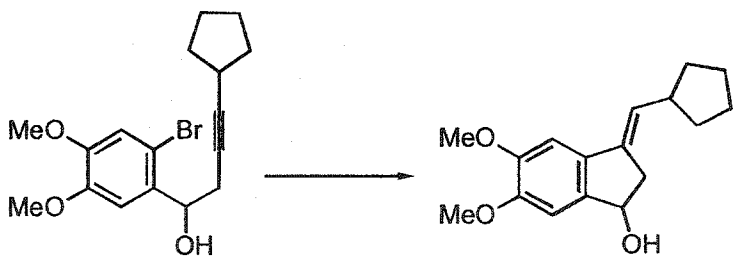
The same procedure used for **10.2** was followed.

$BH_3 \cdot Me_2S$ (0.30 mL, 10.0-10.2 M in THF) was added dropwise to a stirred solution of cyclopentene (0.88 mL, 10 mmol) in THF (3 mL). The mixture was stirred at 42 °C for 3 h before being cooled to room temperature and added to a solution of lithium chloropropargylide in THF, which was prepared as follows.

n-BuLi (1.2 mL, 2.5 M in hexanes) was added dropwise to a stirred and cooled (-90 °C, nitroethane/liquid nitrogen) solution of propargyl chloride (0.22 mL, 3.0 mmol) in THF (5 mL). Stirring at -90 °C was continued for 15 min, and then the previously prepared solution of tricyclopentylborane in THF was added over 10 min at -90 °C. The mixture was transferred to an acetone-dry ice bath and stirred at -78 °C for 30 min. Then a solution of **14.1**[27] (0.735 g, 3.00 mmol) in THF (0.5 mL) was added dropwise.

The resulting mixture was stirred at -78 °C for 1 h. The cold bath was removed and stirring was continued for 30 min, by which time the mixture had attained room temperature. MeOH (2 mL), 3 N NaOH (1.2 mL) and 30% H_2O_2 (0.8 mL) were added. The resulting mixture was stirred at 50 °C for 1 h, cooled to room temperature, and extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 10% EtOAc-hexanes, gave **14.2** (0.99 g, 93%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3513, 2956, 2868, 1603 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.45-1.98 (m, 8 H), 2.45 (ddd, *J* = 16.6, 8.1, 2.2 Hz, 1 H), 2.51-2.69 (m, 2 H), 2.73 (ddd, *J* = 16.5, 4.2, 2.2 Hz, 1 H), 3.85 (s, 3 H), 3.88 (s, 3 H), 5.06 (dd, *J* = 8.1, 4.2 Hz, 1 H), 6.93 (s, 1 H), 7.11 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 25.0 (t), 28.6 (t), 30.3 (d), 34.0 (t), 56.0 (q), 56.1 (q), 71.0 (d), 75.0 (s), 88.3 (s), 109.8 (d), 111.6 (s), 115.2 (d), 133.8 (s), 148.6 (s), 148.9 (s); exact mass (HR electrospray) *m/z* calcd for $C_{17}H_{21}{}^{79}BrNaO_3$ (M + Na) 375.0572, found 375.0572.

3-(Cyclopentylmethylene)-5,6-dimethoxy indan-1-ol (14.3).



14.2 **14.3**

A solution of Bu_3SnH (76 μL, 0.28 mmol) and AIBN (5 mg, 0.03 mmol) in PhH (3 mL) was added by syringe pump over 10 h to a stirred and heated (85 °C) solution of **14.2** (82.6 mg,

0.234 mmol) in PhH (10 mL). Stirring was continued for 2 h after the addition, and the mixture was allowed to cool to room temperature. Evaporation of solvent and flash chromatography of the residue over silica gel (1.5 x 20 cm), using 15% EtOAc-hexanes, gave **14.3** (55 mg, 85%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3383, 2949, 1605, 1500 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 1.25-2.00 (m, 9 H), 2.46-2.56 (m, 1 H), 2.58-2.73 (m, 1 H), 2.96-3.08 (m, 1 H), 3.41 (two s, 6 H), 5.05 (dd, *J* = 7.3, 3.2 Hz, 1 H), 5.82 (dt, *J* = 9.1, 2.3 Hz 1 H), 6.80 (s, 1 H), 6.91 (s, 1 H); ^{13}C NMR (C_6D_6, 75.5 MHz) δ 25.5 (t), 33.7 (t), 40.2 (t), 40.8 (d), 55.3 (q), 73.4 (d), 102.8 (d), 107.9 (d), 123.1 (d), 133.7 (s), 137.9 (s), 139.5 (s), 150.9 (s), 151.1 (s); exact mass *m/z* calcd for $C_{17}H_{22}O_3$ 274.1569, found 274.1571.

REFERENCES AND NOTES

1 (a) Chatterjee, A.; Banerjee, S. *Tetrahedron* **1970**, *26*, 2599. (b) Martens, H.; Hoornaert, G. *Synth. Commun.* **1972**, *2*, 147.

2 Ullman, E. F.; Henderson, W. A., Jr. *J. Am. Chem. Soc.* **1966**, *88*, 4942.

3 Buggle, K.; Ghogain, U. N.; O'Sulilivan, D. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2075.

4 House, H. O.; Larson, J. K.; *J. Org. Chem.* **1968**, *33*, 448.

5 Zimmerman, H. E. *J. Am. Chem. Soc.* **1956**, *78*, 1168.

6 Alesso, E. N.; Tombari, D. G.; Ibanez, A. F.; Moltrasio Iglesias, G. Y.; Aguirre, J. M. *Can. J. Chem.* **1991**, *69*, 1166.

7 Mal, D.; Bandyopadhyay, M.; Ghorai, S. K.; Datta, K. *Tetrahedron Lett.* **2000**, *41*, 3677.

8 Kitani, Y.; Morita, A.; Kumamoto, T.; Ishikawa, T. *Helv. Chim. Acta* **2002**, *85*, 1186.

9 Anstead, G. M.; Ensign, J. L.; Peterson, C. S.; Katzenellenbogen, J. A. *J. Org. Chem.* **1989**, *54*, 1485.

10 Frank, R. L.; Eklund, H.; Richter, J. W.; Vanneman, C. R.; Wennerbergm, A. N. *J. Am. Chem. Soc.* **1944**, *66*, 1.

11 Jourdan, G. P.; Dreikorn, B. A.; Hackler, E. E.; Hall, H. R.; Arnold, W. R. In *Synthesis and Chemistry of Agrochemicals II*; ACS Symposium Series; American Chemical Society: Washington, DC, 1991; p 566.

12 (a) Floyd, M. B.; Allen, G. R. *J. Org. Chem.* **1970**, *35*, 2647. (b) Galatsis, P.; Manwell, J. J.; Blackwell, J. M. *Can. J. Chem.* **1994**, *72*, 1656.

13 Hauser, F. M.; Zhou, M.; Sun, Y. *Synth. Commun.* **2001**, **31**, 77.

14 Liebeskind, L. S.; South, M. S. *J. Org. Chem.* **1980**, *45*, 5426.

15 (a) Tao, W.; Silverberg, L. J.; Rheingold, A. L.; Heck, R. F. *Organometallics* **1989**, *8*, 2550. (b) Larock, R. C.; Doty, M. J. *J. Org. Chem.* **1993**, *58*,

4579.

16 (a) Vicente, J.; Abad, J.-A.; Gil-Rubio, J. *J. Organomet. Chem.* **1992**, *436*, C9. (b) Vicente, J.; Abad, J.-A.; Gil-Rubio, J. *Organometallics* **1996**, *15*, 3509. (c) Vicente, J.; Abad, J.-A.; López-Peláez, B.; Martínez-Viviente, E. *Organometallics* **2002**, *21*, 58.

17 Fukuyama, T.; Chatani, N.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1997**, *62*, 5647.

18 Hong, P.; Cho, B.; Yamazaki, H. *Chem. Lett.* **1979**, 339.

19 Kokubo, K.; Matsumasa, K.; Miura, M.; Nomura, M. *J. Org. Chem.* **1996**, *61*, 6941.

20 Padwa, A.; Weingarten, M. D. *J. Org. Chem.* **2000**, *65*, 3722 and references therein.

21 Zweifel, G.; Backlund, S. J.; Leung, T. *J. Am. Chem. Soc.* **1978**, *90*, 5561.

22 Lacy, P. H.; Smith, D. C. C. *J. Chem. Soc. C* **1971**, 41.

23 (a) Marvel, C. S.; Hinman, C. W. *J. Am. Soc. Chem.* **1954**, *76*, 5435. (b) Hauser, F. M.; Zhou, M.; Sun, Y. *Synth. Commun.* **2001**, *31*, 77.

24 Lai, Y.; Peck, T. *Aust. J. Chem.* **1992**, *45*, 2067.

25 Grissom, J. W.; Klingberg, D.; Meyenburg, S.; Stallman, B. L. *J. Org. Chem.* **1994**, *59*, 7876.

26 Morris, J. L.; Becker, C. L.; Fronczek, F. R.; Daly, W. H.; McLaughlin, M. L. *J. Org. Chem.* **1994**, *59*, 6484.

27 Charlon, J. L.; Alauddin, M. M. *J. Org. Chem.* **1986**, *51*, 3490.

28 Clive, D. L. J.; Yu, M.; Sannigrahi, M. *J. Org. Chem.* **2004**, in press.

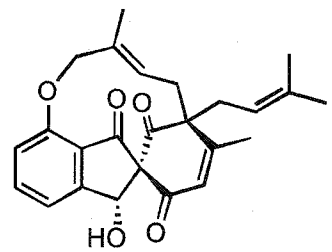
CHAPTER 3

SYNTHETIC STUDIES ON COLEOPHOMONE B

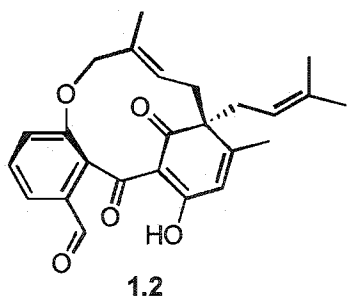
INTRODUCTION

In 1998, a research group at the Shionogi company reported in a Japanese patent[1] the discovery of three structurally novel and biologically active natural products, designated as I-1 (**1.1**), I-2 (**1.2**), and I-3 (**1.3**) (Scheme 1). These compounds were isolated from a broth produced by the fungus *Stachybothys cylindrospora* RF-5900. Interestingly, two years later a group at Merck also discovered compounds **1.1** and **1.2** from an extract of the fermentation broth of *Coleophoma sp.* MF6338, a fungus isolated from unidentified plant litter collected in Spain. The Merck researchers named the compounds coleophomone A (**1.1**) and coleophomone B (**1.2**).[2] The coleophomone family was found to show antifungal activity,[1] and inhibitory activity against both human heart chymase[1] and bacterial cell wall transglycosylase.[2]

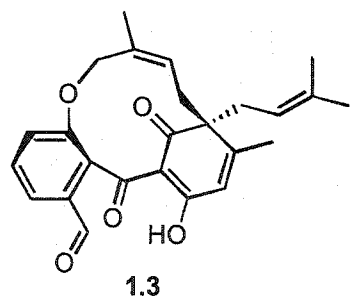
Scheme 1



1.1
coleophomone A



1.2
coleophomone B



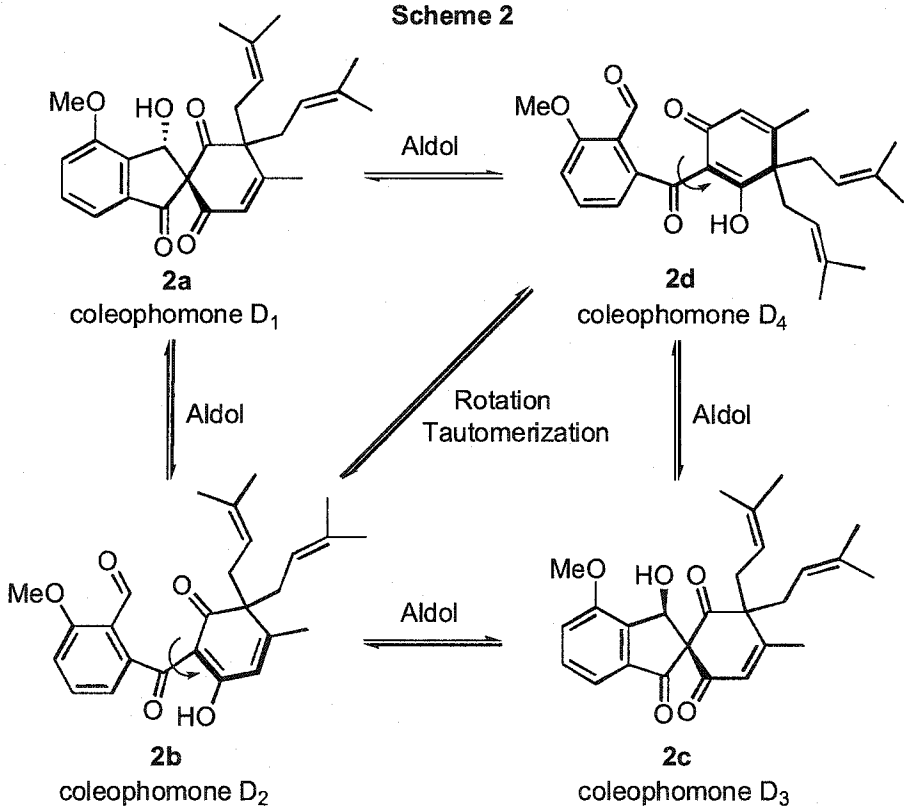
1.3
coleophomone C

The compounds possess an unusual and challenging structure, which consists of a strained and rigid

macrocycle containing a fused aryl ring, a highly unsaturated six-membered carbocycle and a tethered tricarbonyl moiety.

Coleophomone A (**1.1**) and coleophomone B (**1.2**) were reported to exist in equilibrium with each other in CH_3CN-water.[2] Coleophomone B (**1.2**) is strongly favored at pH ≥ 7 and interconversion does not occur at pH ≤ 3. Coleophomone B (**1.2**) appears to undergo a stereospecific aldol condensation to afford coleophomone A (**1.1**) since no evidence was found for the presence of another diastereoisomer of A in *in vitro* experiments.

Scheme 2



In 1999, a Japanese patent[3] from the same group at Shionogi disclosed the structure and biological activity of a related fungal metabolite, designated as I-A (**2a-d**) (Scheme 2), which was isolated from a broth produced by the fungus *Stachybothys parvispora* Hughes-1952. The compound was reported to exist as a mixture of constitutional

isomers that undergo rapid interconversion via a facile aldol-retro-aldol reaction. The compound does not have the strained macrocycle characteristic of the other metabolites and has a different substitution pattern to that of the three natural products **1.1**, **1.2** and **1.3** (Scheme 1). Coleophomone D was also reported to possess antifungal activity and inhibitory activity against human heart chymase.

Based on the unique structures and useful biological activity of these natural products, we decided to work on coleophomone B. At the start of our studies, no synthetic work was reported. However, during the course of our work, the Nicolaou group reported the total synthesis of coleophomones B and C,[4] and subsequently reported the total synthesis of coleophomone D (**2a-d**).[5] The Nicolaou group coined the names coleophomone C and coleophomone D for the Shionogi compounds I-3[1] and I-A,[3] respectively, despite the fact that I-3 and I-A were not reported by the Merck group in the *coleophoma sp.* study.[2]

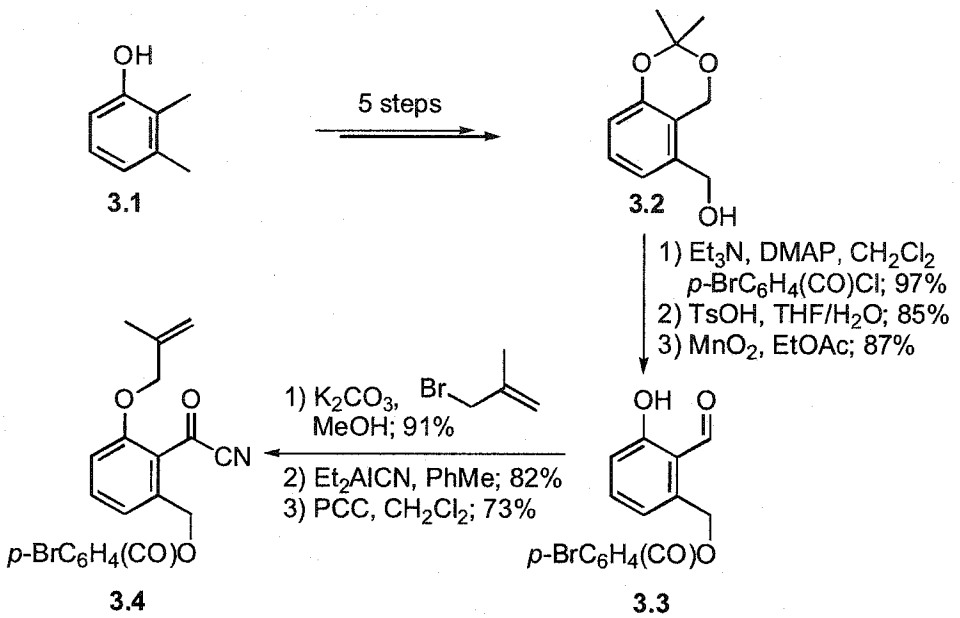
Total Syntheses of Coleophomones B, C and D by the Nicolaou Group[4,5]

Synthesis of coleophomones B and C was achieved using two key steps: a *C*-acylation of an α,β-dicarbonyl system and a ring closing metathesis. Usually an α,β-dicarbonyl system is *O*-acylated and the required *C*-acylated product is then formed by rearrangement.[4] The ring-closing metathesis was used, of course, to make the macrocyclic rings. Retrosynthetic analysis led to two building blocks that would be required: **3.4** (Scheme 3) and **4.4** (Scheme 4).

The aromatic compound **3.4** was synthesized starting from commercially available 2,3-dimethylphenol **3.1**, which was converted into hydroxy acetonide **3.2** using a five-step literature procedure. *p*-Bromobenzoylation of **3.2**, followed by deprotection of the acetonide, and MnO_2 oxidation gave the substituted benzaldehyde **3.3** in 72% overall yield.

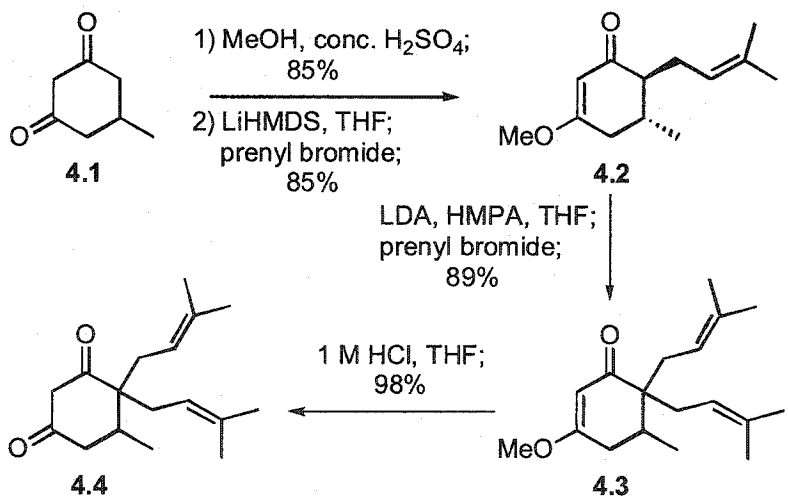
Alkylation of **3.3** with 3-bromo-2-methylpropene, and subsequent treatment with Nagata's reagent (Et_2AlCN) followed by PCC oxidation of the resulting cyanohydrin, afforded the desired acyl cyanide **3.4**, which is one of the building blocks identified in the retrosynthetic analysis.

Scheme 3



The desired 1,3-cyclohexanedione **4.4**, which is the other building block, was prepared in four steps from 5-

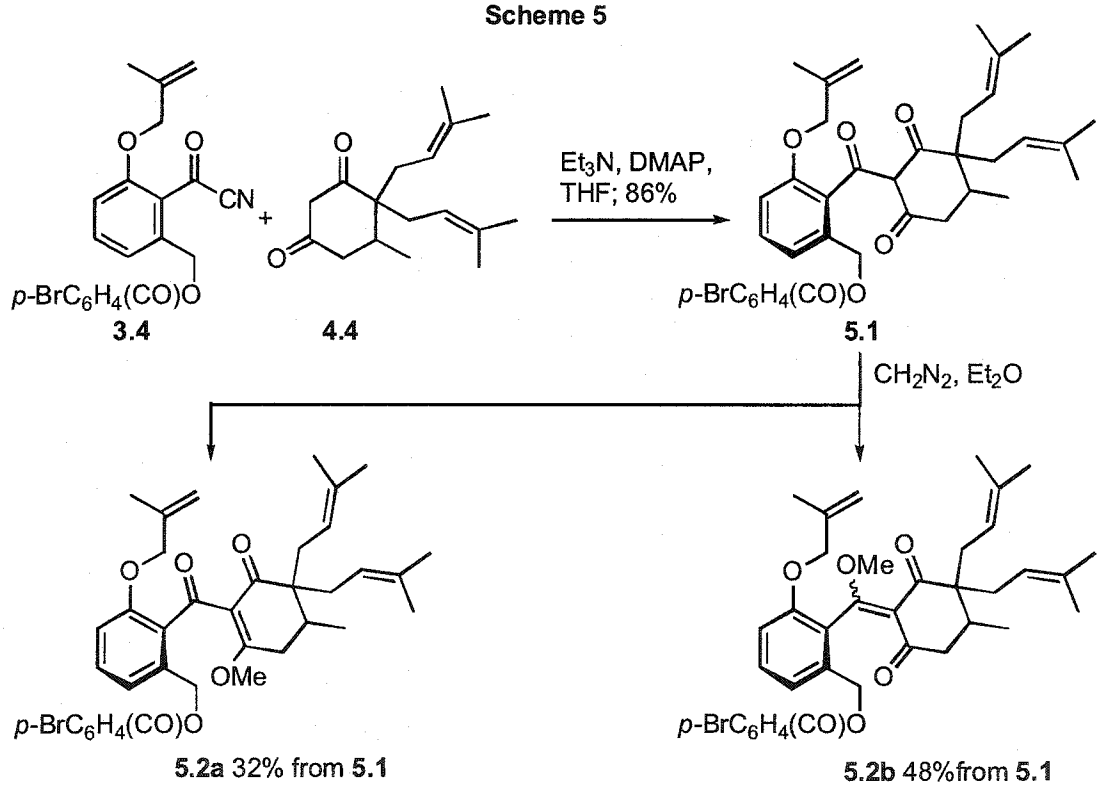
Scheme 4



methyl-1,3-cyclohexanedione **4.1**. Methylation of **4.1**, followed by alkylation of the $(Me_3Si)_2NLi$-derived enolate with prenyl bromide, furnished **4.2**. The bisalkylated analog **4.3** was made by a second alkylation with prenyl bromide of the LDA-derived enolate in the presence of HMPA. Finally, hydrolysis of the vinylogous methyl ester **4.3** with aqueous acid generated **4.4** in 98% yield.

With **3.4** and **4.4** in hand, the stage was now set for the *C*-acylation reaction (Scheme 5). Coupling of **3.4** and **4.4** afforded the desired tricarbonyl product **5.1**, and this was treated with diazomethane to give two major methoxy derivatives **5.2a,b**.

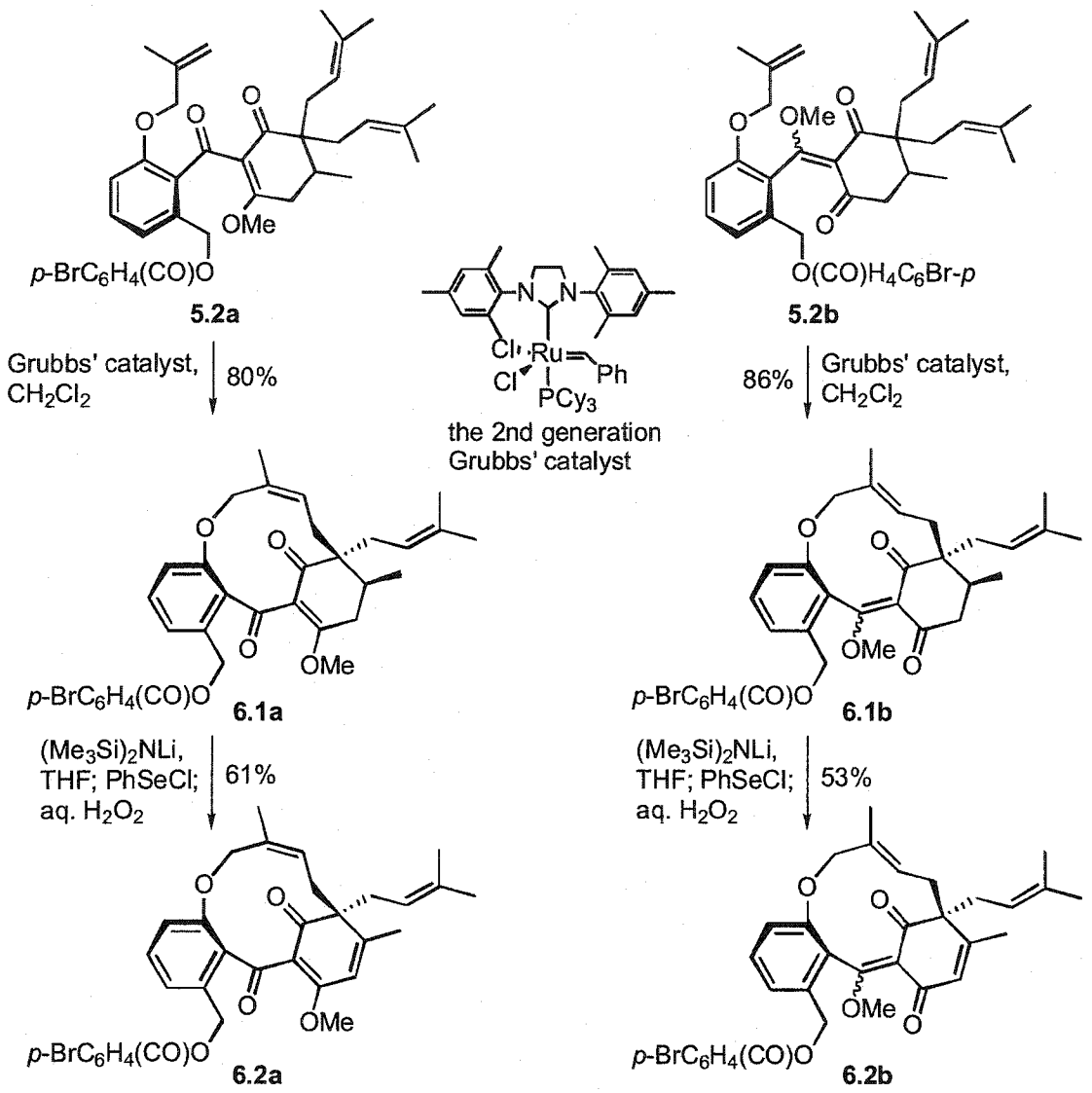
Scheme 5



Independent exposure of the two regioisomers **5.2a** and **5.2b** to the second generation Grubbs' catalyst furnished the ring-closure metathesis macrocycles **6.1a** and **6.1b** (Scheme 6). Treatment of each of these with $(Me_3Si)_2NLi$ followed by PhSeCl, and then excess of aqueous H_2O_2 resulted

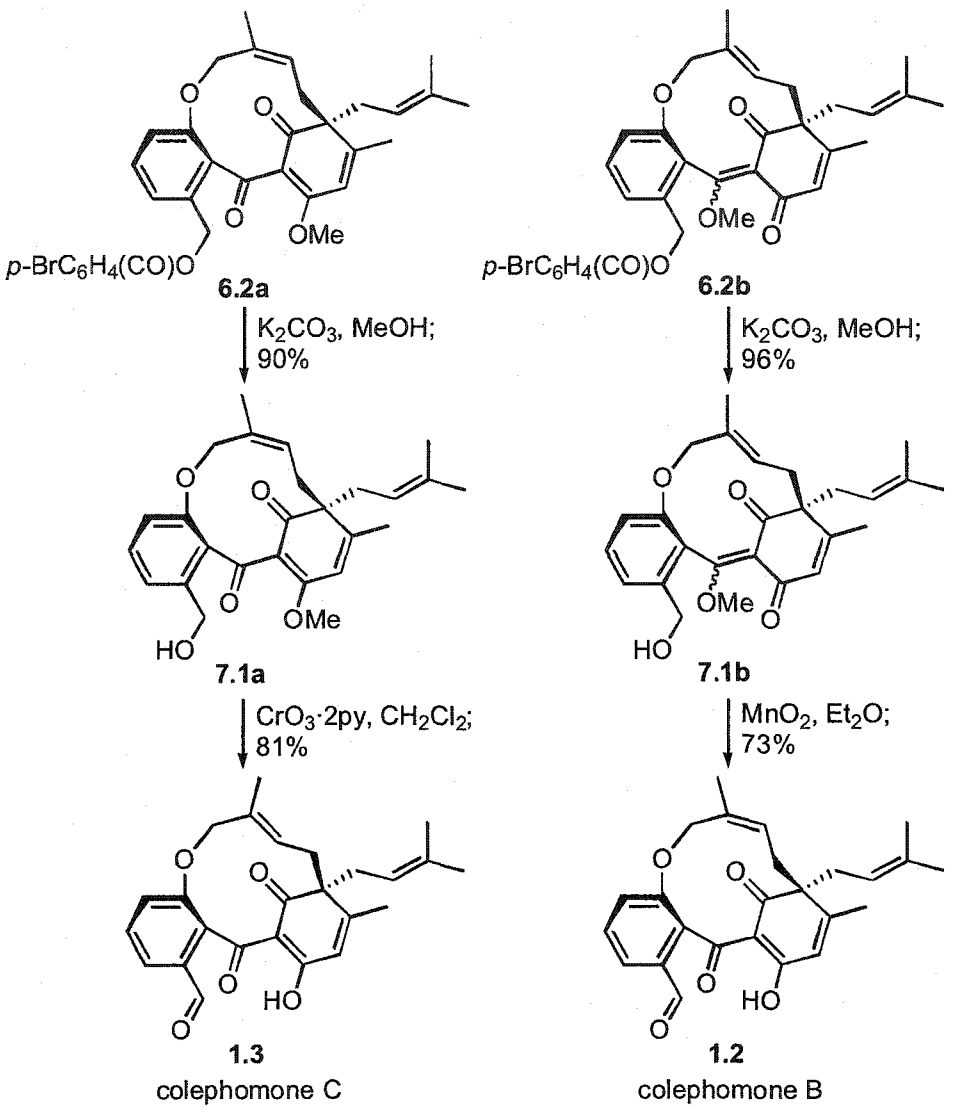
in the corresponding dienones **6.2a** and **6.2b**.

Scheme 6



Global deprotection of **6.2a** and **6.2b** with K_2CO_3 in MeOH afforded **7.1a** and **7.1b**, respectively (Scheme 7). Finally, oxidation of **7.1b** with MnO_2 gave coleophomone B (**1.2**), and oxidation of **7.1a** with Collins' reagent produced coleophomone C (**1.3**). Thus, coleophomones B and C were synthesized from the same intermediate **5.1**.

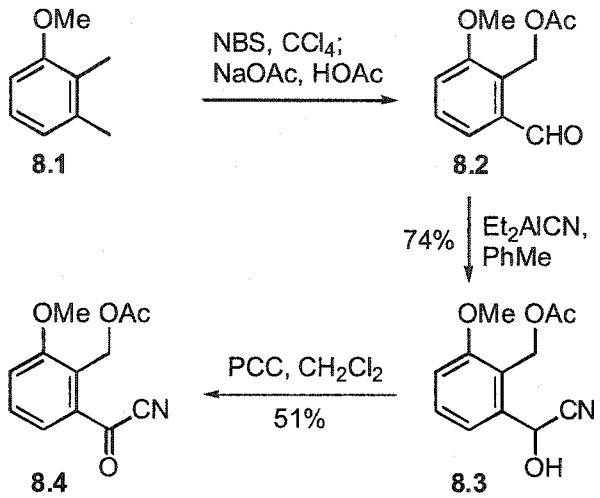
Scheme 7



Obviously, synthesis of coleophomone D benefited from the experience and knowledge gained in the above synthesis of coleophomone B and C. Two building blocks **8.4** (Scheme 8) and **9.2** (Scheme 9) were required in order to prepare coleophomone D.

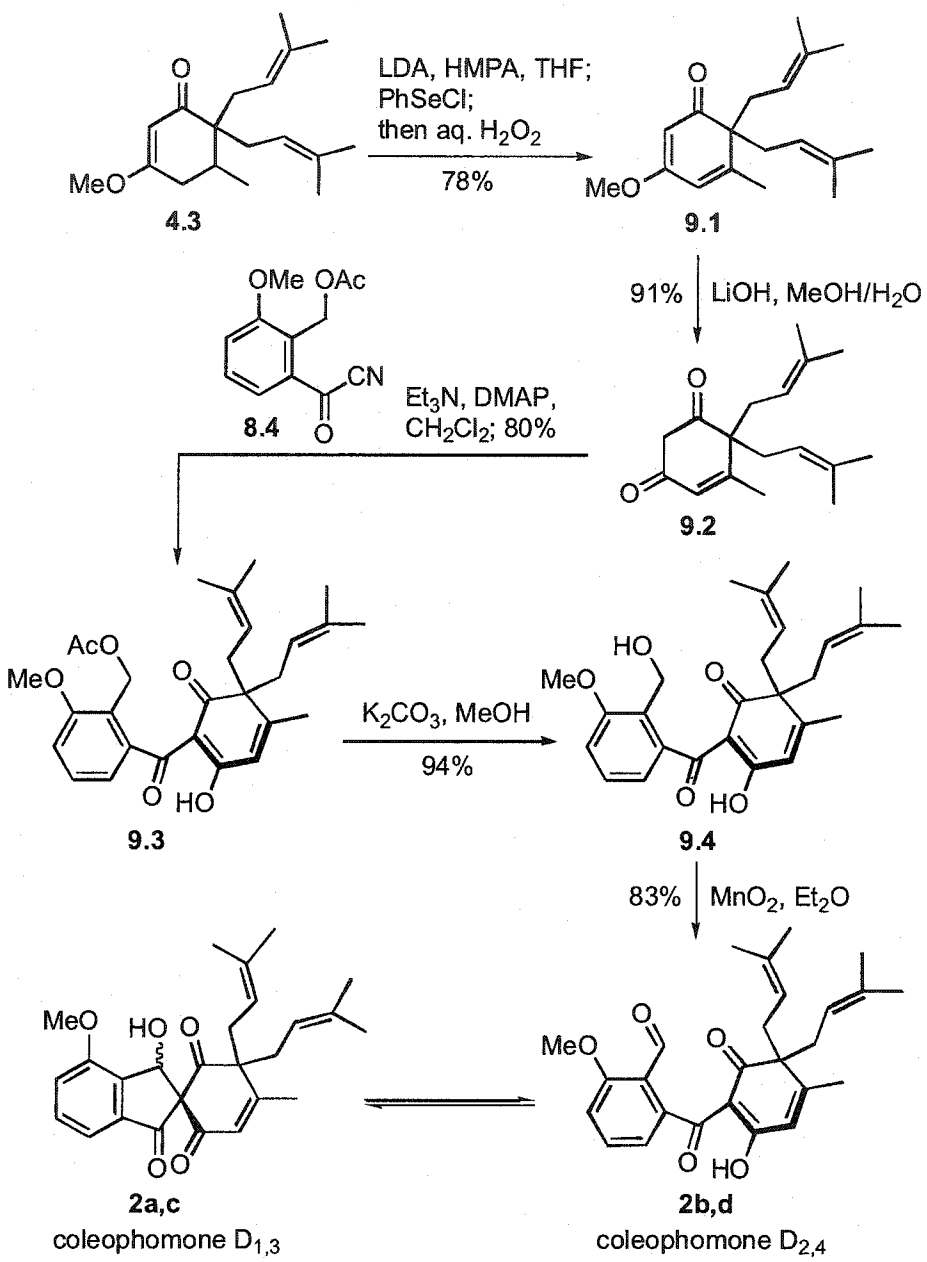
The benzoyl cyanide **8.4** was synthesized starting from 2,3-dimethylanisole (**8.1**). Conversion of **8.1** into the aldehyde **8.2**, was done using a two-step literature procedure. Treatment of aldehyde **8.2** with Nagata's reagent, followed by oxidation with PCC, resulted in the required building block **8.4** in 38% yield over two steps.

Scheme 8



The other component, 1,3-cyclohexenedione **9.2**, was made in two steps from the vinylogous ester **4.3** (Scheme 4). Treatment of **4.3** with LDA, using HMPA as an additive, followed by addition of PhSeCl, resulted in the intermediate phenyl selenide. Oxidation *in situ* with excess aqueous H_2O_2 formed the selenoxide, which underwent spontaneous *syn*-elimination to afford the desired vinylogous ester **9.1**. Hydrolysis of with LiOH in aqueous MeOH gave the required building block **9.2**. Coupling of **8.4** with **9.2** led to compound **9.3**, which was treated with K_2CO_3 in MeOH to furnish alcohol **9.4**. Finally, MnO_2 oxidation gave coleophomone D as a mixture of four structural isomers **2a-d**.

Scheme 9



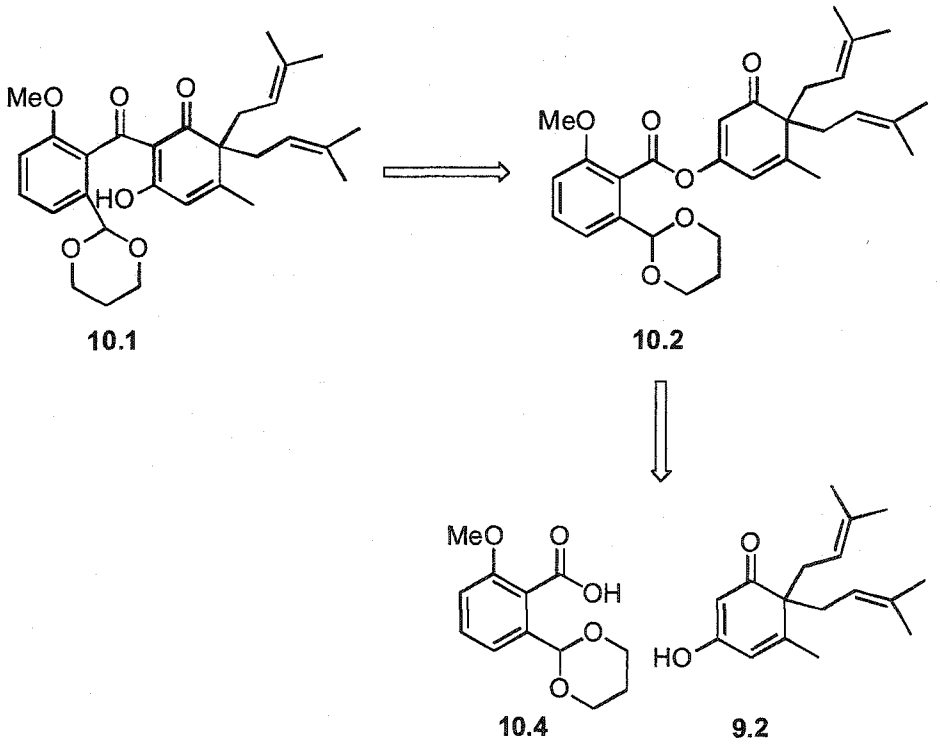
RESULTS and DISCUSSION

Synthetic Studies on Construction of the Tricarbonyl System

When we began our synthetic studies, we recognized two major challenges posed by the structure of coleophomone B. One was the problem of making the 11-membered macrocycle with the desired *trans* double bond, and the other was the construction of the tethered tricarbonyl moiety. The former might be accomplished by intramolecular alkylation or ring closing metathesis, while the latter could, perhaps, be done by an *O*-acylation-rearrangement sequence[6] or by direct formation of the critical C-C bond. We decided to work first on construction of the tricarbonyl system without the macrocycle.

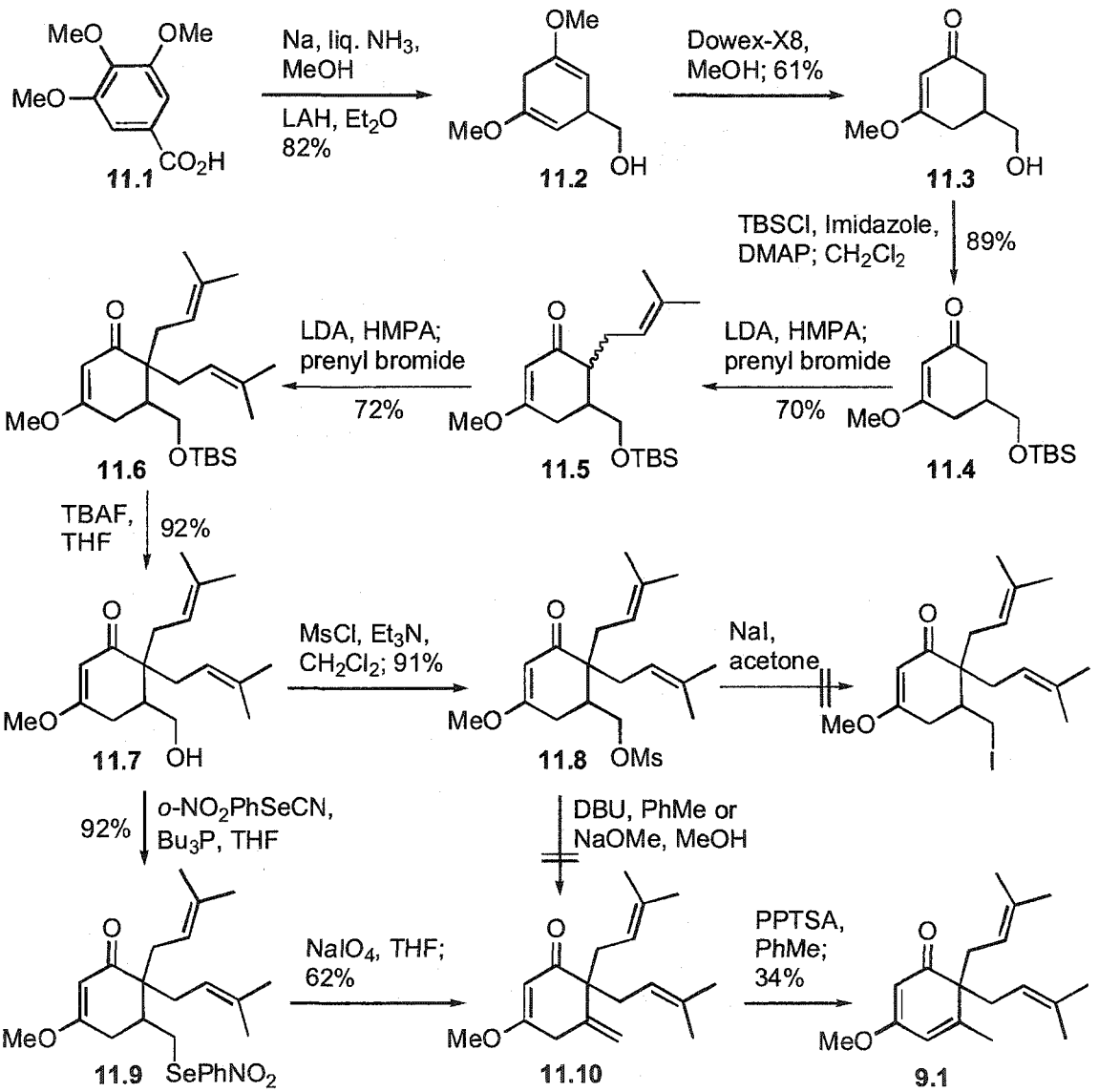
Retrosynthetically, the tricarbonyl compound **10.1** can be derived from rearrangement of the vinylogous anhydride **10.2**, which, in turn, should be accessible from two coupling fragments, the vinylogous acid **9.2** and benzoic acid **10.4** (Scheme 10).

Scheme 10



Synthesis of these two subunits was carried out in the following way. Compound **9.2** was synthesized starting from commercially available 3,4,5-trimethoxybenzoic acid (**11.1**) (Scheme 11). Following a two-step literature procedure,[7]

Scheme 11



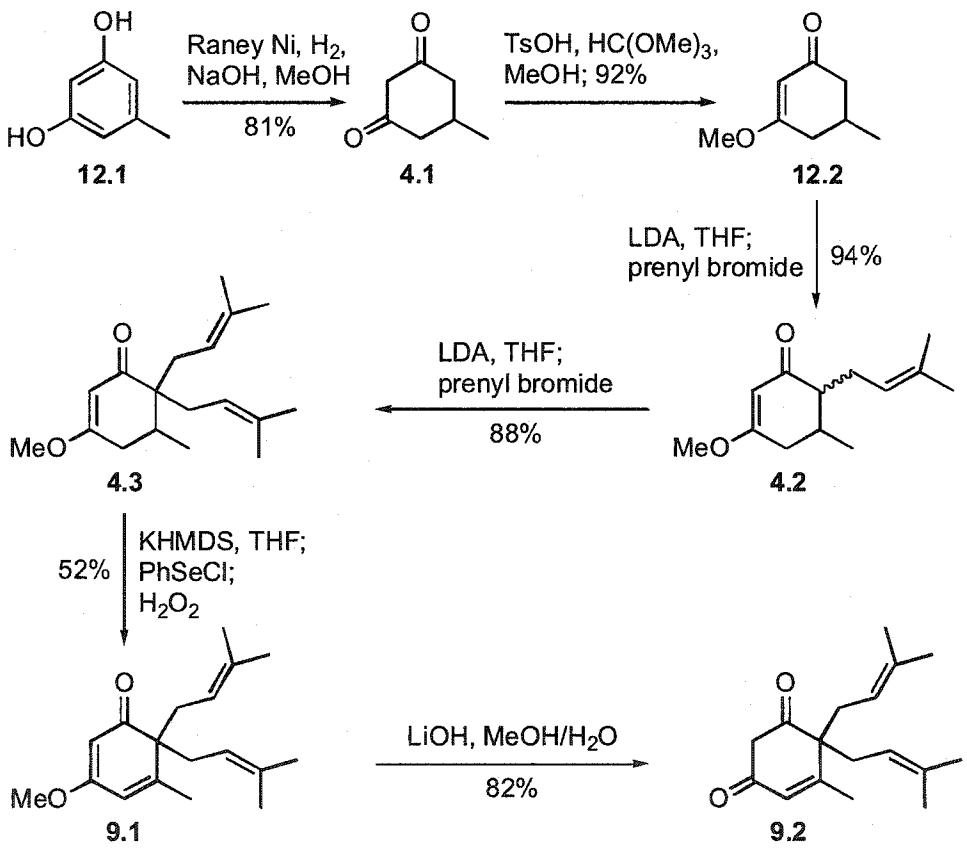
the benzoic acid **11.1** was converted into alcohol **11.2**. Exposure of **11.2** to Dowex-X8 in MeOH[8] and subsequent protection of the resulting alcohol with *t*-BuMe$_2$SiCl gave **11.4**. Treatment with LDA in the presence of HMPA as an

additive, followed by addition of prenyl bromide, afforded the alkylated product **11.5** as a mixture of two diastereoisomers. A second alkylation under the same conditions resulted in the desired compound **11.6**. At this point the *t*-$BuMe_2Si$ protecting group was removed by the action of Bu_4NF to generate alcohol **11.7** in 92% yield. Mesylation of **11.7** (MsCl, Et_3N), followed by exposure to DBU or MeONa in MeOH, led to the same unidentified compound, and none of the desired product **11.10** was detected. An attempt to replace the OMs group with I by treatment with NaI in acetone gave no reaction. Fortunately, treatment of **11.7** with *o*-nitrophenyl selenocyanate and Bu_3P[9] furnished the desired phenyl selenide **11.9** in 92% yield, and oxidation with $NaIO_4$ led to the unstable selenoxide, which underwent spontaneous *syn*-elimination, forming the exocyclic olefin **11.10** in 62% yield. Oxidation with H_2O_2, however, gave a very low yield. Finally, migration of the exocyclic carbon-carbon double bond was achieved with pyridinium *p*-toluenesulfonate and afforded the desired product **9.1** in 34% yield. In contrast, treatment of **11.10** with $RhCl_3$ gave an unidentified compound. Obviously, this route was too long and inefficient, and so we developed a shorter route to **9.2**. Unfortunately, Nicolaou's reported a similar procedure,[4,5] after we had completed our own synthesis of this subunit. Different reagents were used in some steps, but the approach is very similar indeed.

We started with commercially available 5-methylresorcinol (**12.1**) (Scheme 12). Using a literature procedure,[10] **12.1** was hydrogenated with Raney nickel under basic conditions to give the 1,3-diketone **4.1**, which was converted into the known vinylogous ester **12.2** by the literature method.[11] Alkylation of the LDA-derived enolate with prenyl bromide produced the desired product **4.2** in 94% yield as a mixture of two diastereoisomers. A second alkylation under the same conditions yielded the bisalkylated product **4.3** in 88% yield. The stage was now

set to introduce the double bond. Treatment of **4.3** with IBX[12] in DMSO gave no reaction, and use of DDQ gave a complex mixture. To our delight, phenylselenation under standard conditions and oxidation-elimination successfully introduced the desired double bond to give the vinylogous ester **9.1** in 52% yield. Finally, hydrolysis with LiOH in aqueous MeOH under reflux led to 1,3-diketone **9.2**. Hydrolysis of **9.1** with 1 N hydrochloric acid in THF for 24 h at room temperature afforded compound **9.2** in 11% yield. The poor yield under conditions of acid hydrolysis was also observed by the Nicolaou group.[5]

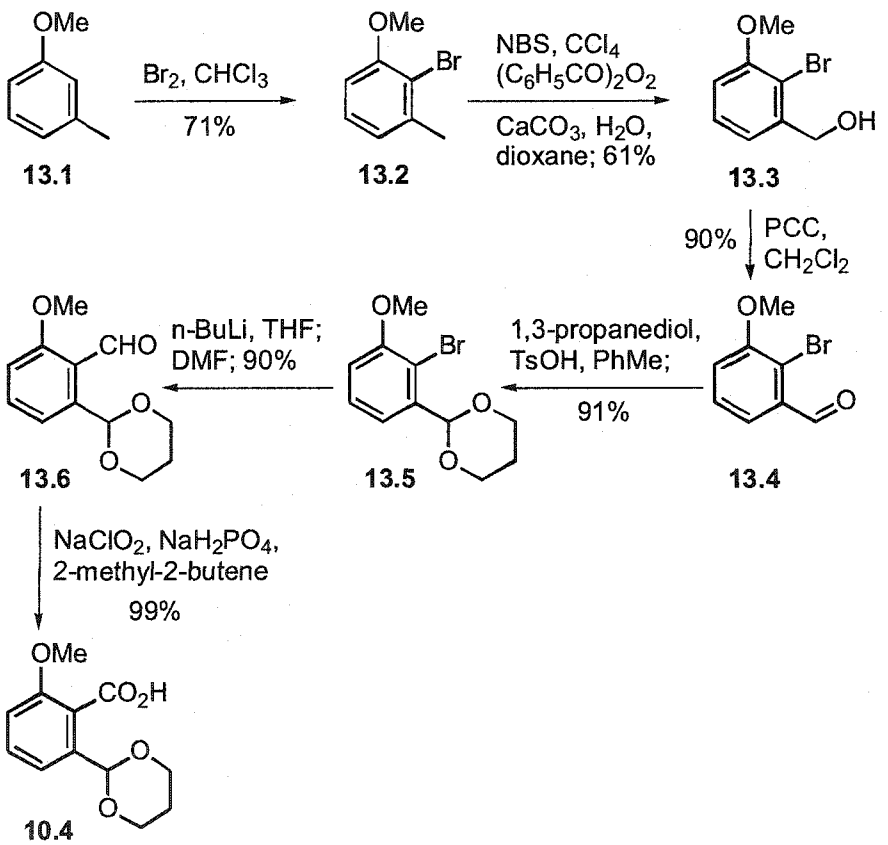
Scheme 12



With compound **9.2** in hand, we now turned our attention the synthesis of the benzoic acid subunit **10.4**. This was prepared starting from 3-methylanisole (**13.1**). Following a literature procedure,[13] bromination of **13.1** with Br_2 in

$CHCl_3$ gave bromide **13.2**. NBS bromination of **13.2**, and hydrolysis of the resulting benzyl bromide with $CaCO_3$ in aqueous dioxane under reflux afforded the known benzyl alcohol **13.3**[14] in 61% yield. PCC oxidation then furnished the known aldehyde **13.4**[14] in 90% yield. Exposure of **13.4** to 1,3-propanediol in PhMe under acid catalysis resulted in formation of the acetal **13.5**, when a Dean-Stark apparatus was used to remove the generated water. Compound **13.5** was treated with *n*-BuLi and then with DMF to yield the desired aldehyde **13.6** in 90% yield, and oxidation with $NaClO_2$ gave the benzoic acid **10.4** (99%).

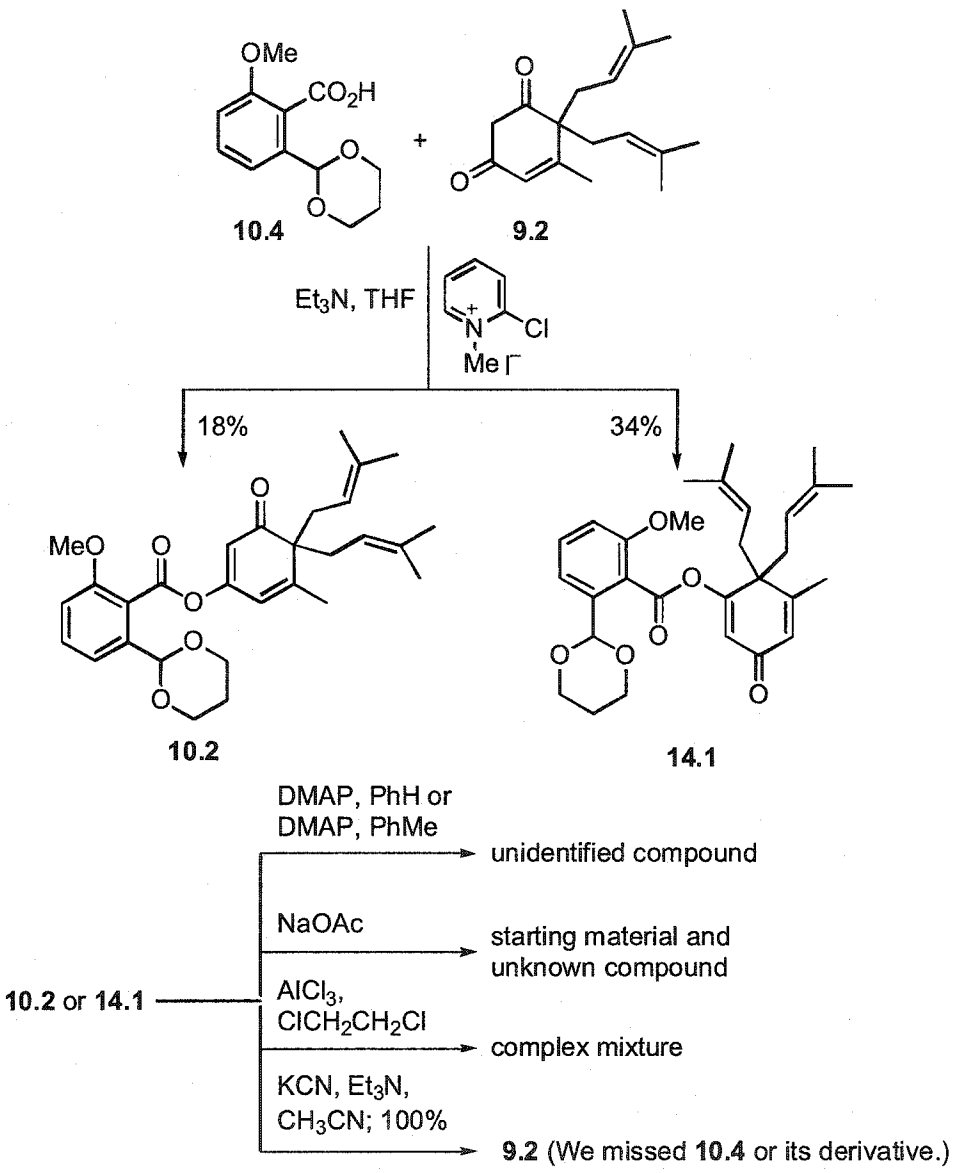
Scheme 13



Now that we had the two subunits **10.4** and **9.2**, we came to the crucial step of constructing the tricarbonyl system using *O*-acylation and rearrangement to the *C*-acylation

product. Coupling of **9.2** with **10.4** by using 2-chloro-1-methylpyridinium iodide afforded two separable products **10.2** and **14.1** (Scheme 14) in 18% and 34% yield, respectively. Treatment of **10.2** or **14.1** under various conditions and with a variety of reagents[6] did not lead to

Scheme 14

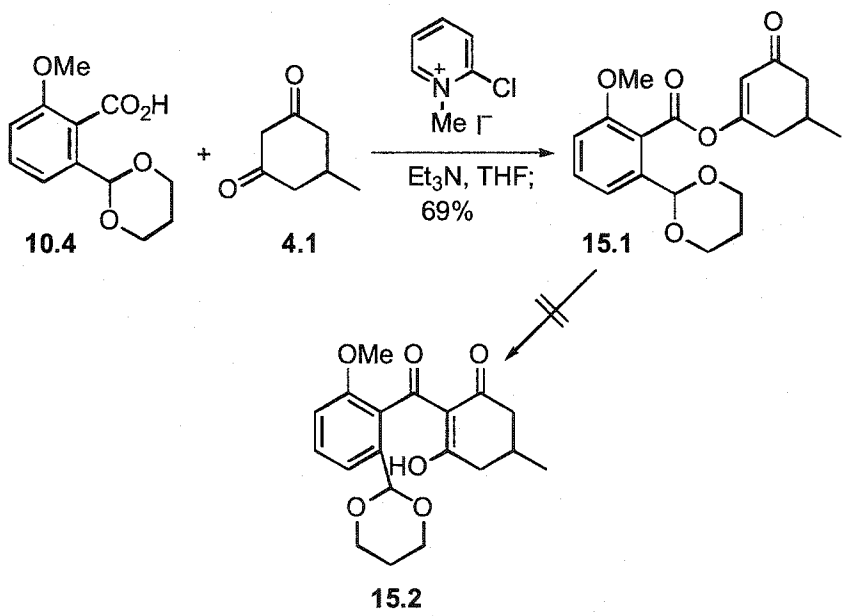


the desired rearrangement product **10.1**. Either unidentified compounds or decomposition products or starting material were obtained. Use of KCN/Et_3N gave back **9.2**. We did not detect **10.4** (or a derivative of **10.4**);

possibly, **10.4** was indeed produced, but we failed to detect it. In order to examine the possibility that the two side chains and/or the extra carbon-carbon double bond in the cyclohexenone might impede the rearrangement we studied an example in which these features are absent.

Coupling of the benzoic acid derivative **10.4** with the 1,3-diketone **4.1** gave the expected product **15.1** in 69% yield. Treatment of **15.1** under the same conditions used for **10.2** or **14.1** did not cause rearrangement to the desired triketone **15.2** (Scheme 15).

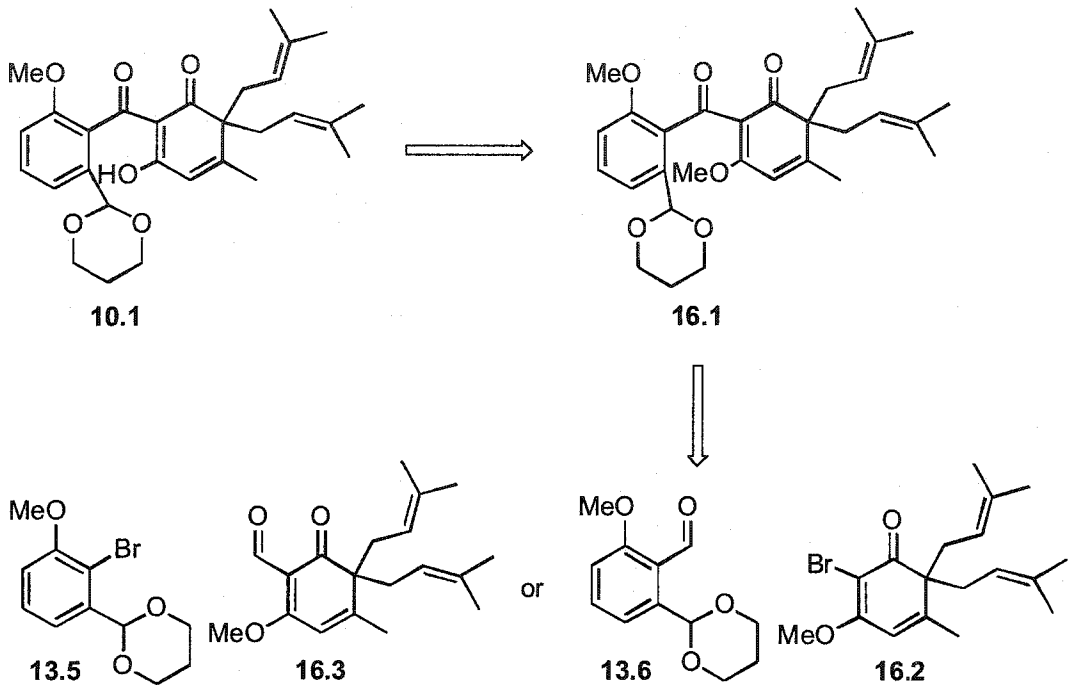
Scheme 15



Our failure to effect the rearrangement of an *O*-acylated system to a *C*-acylated product prompted us to examine direct carbon-carbon bond formation to give the tricarbonyl system. From a retrosynthetic standpoint, the tricarbonyl compound **10.1** can also be derived from the vinylogous ester **16.1**, which, in turn, can be disconnected into two simpler precursors, either the substituted benzaldehyde **13.6** and the bromide **16.2**, or bromide **13.5** and aldehyde **16.3** (Scheme 16). We already had compounds **13.5** and **13.6** in hand, and we thought that aldehyde **16.3** could

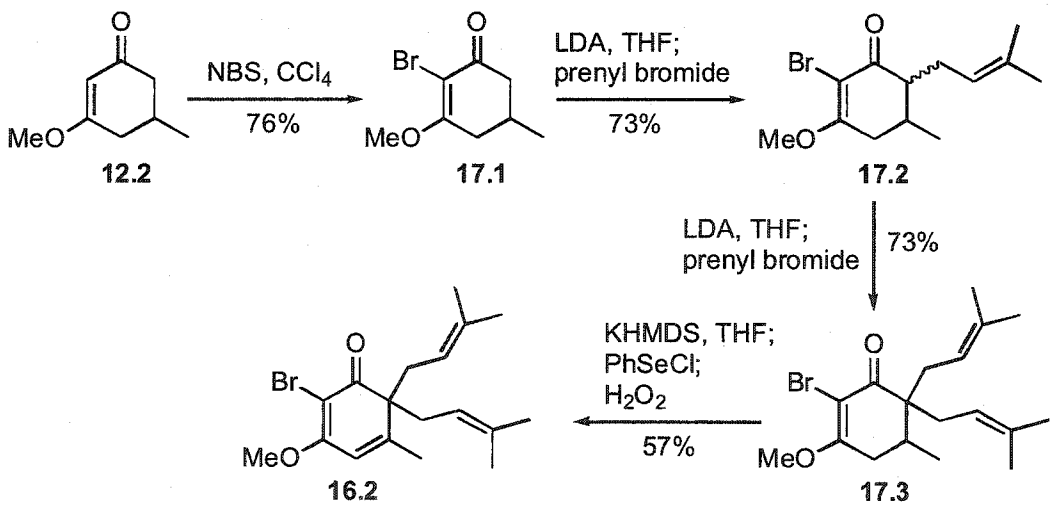
be made from bromide **16.2**, so that both approaches could be tried.

Scheme 16



Synthesis of bromide **16.2** was accomplished by starting from the vinylogous ester **12.2**. Bromination with NBS gave **17.1** in 76% yield (Scheme 17). Alkylation of the LDA-derived enolate with prenyl bromide then afforded the

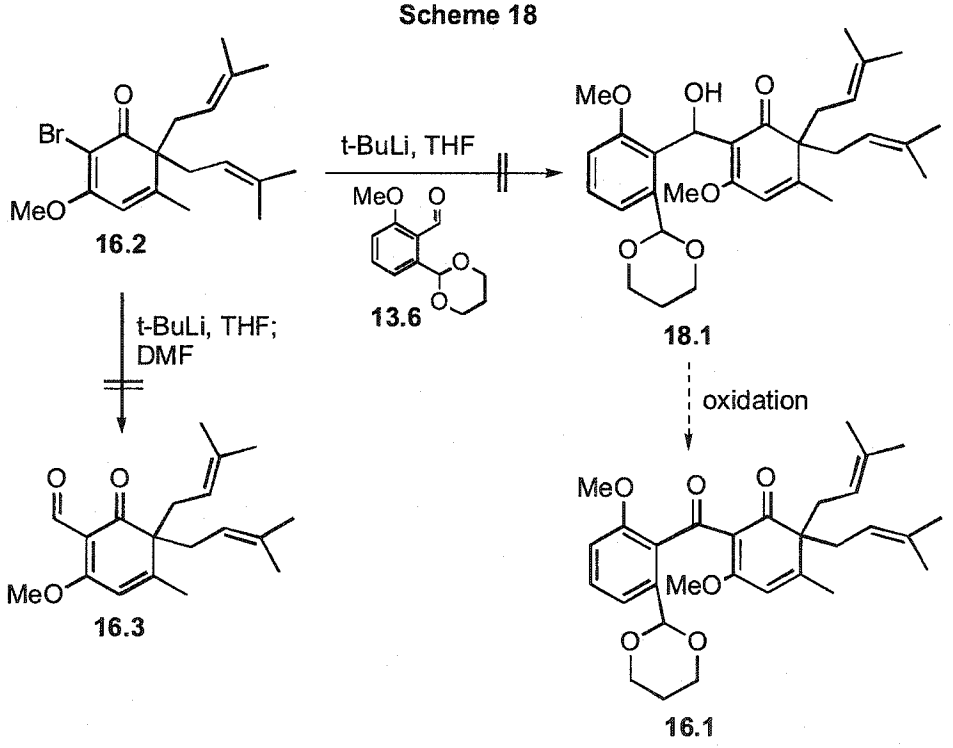
Scheme 17



alkylated product **17.2** as a mixture of diastereoisomers. A second alkylation was done under the same conditions to yield the desired product **17.3**. Generation of the phenyl selenide and oxidation, without isolation of intermediates, was used again to furnish the required compound **16.2** in 57% yield.

Following a procedure described by Pattenden,[15] bromide **16.2** was treated with *t*-BuLi at -78 °C, and the resulting oraganolithium was quenched with aldehyde **13.6**. Disappointingly, this experiment gave a complex mixture, and none of the desired alcohol **18.1** was detected. Our plan had been to oxidize **18.1** to **16.1** (Scheme 18). Treatment of **16.2** with *t*-BuLi followed by addition of DMF also failed to afford aldehyde **16.3**.

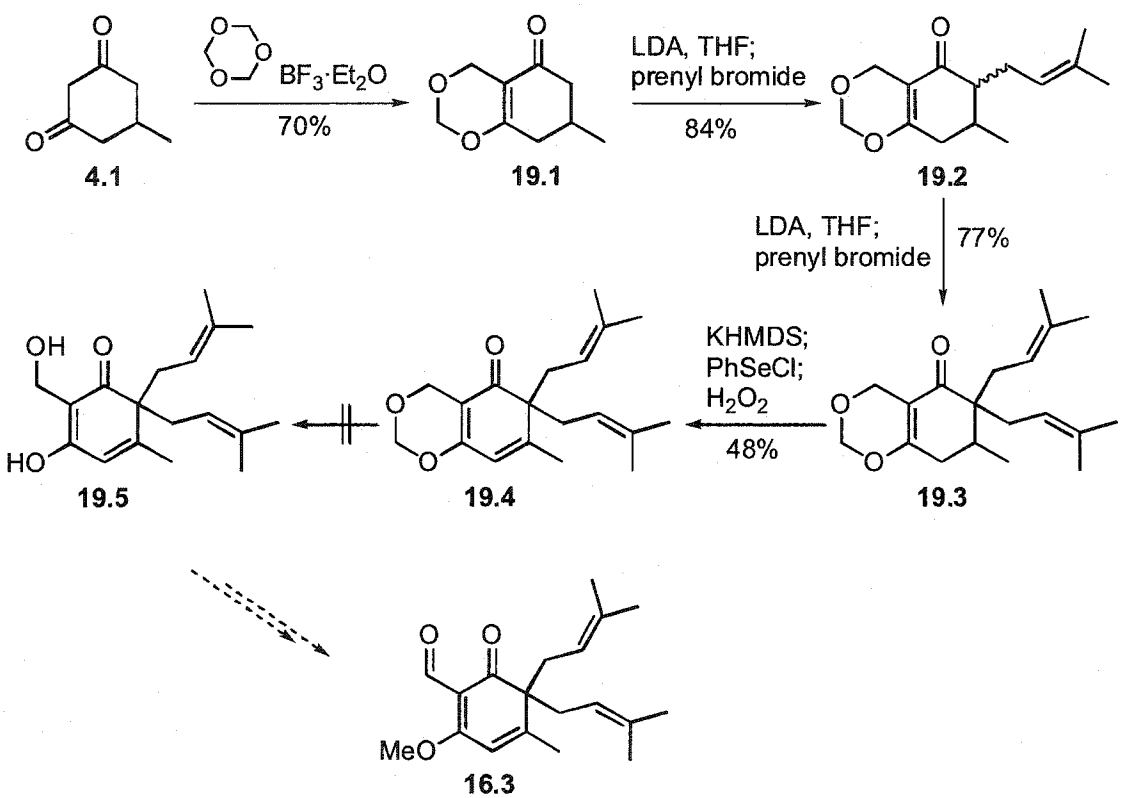
Scheme 18



The following route was then attempted to make compound **16.3**. Conversion of 1,3-diketone **4.1** into the vinylogous ester **19.1**[15] was done using a literature procedure.[16] Double alkylation with prenyl bromide gave

19.3. Once again, the phenylselenide-oxidation sequence was used to introduce a double bond, and this procedure led to **19.4**. In the next step, we encountered difficulties removing the methylene group. Treatment of **19.4** with various reagents (BCl_3, HCl, CSA, Ph_3CBF_4[17] or $PhSeSePh/NaBH_4$[18]) failed to furnish the desired product **19.5** (Scheme 19).

Scheme 19

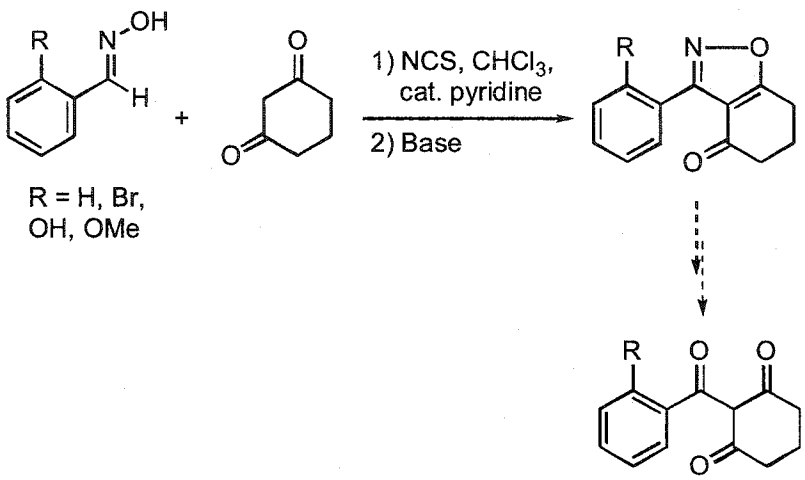


4.1 19.1 19.2 19.3 19.4 19.5 16.3

At this stage, we had to turn our attention to some other direct carbon-carbon bond formation methods in order to install the tricarbonyl moiety. As described earlier, the well-known strategy of initial *O*-acylation followed by rearrangement[6] failed to deliver the *C*-acylation product containing the tricarbonyl moiety. A direct *C*-acylation method,[19] using the preprepared intermediates involved in the usual *O*-acylation-rearrangement sequence,[6c] is also known, but rarely used to make tricarbonyl compounds. At

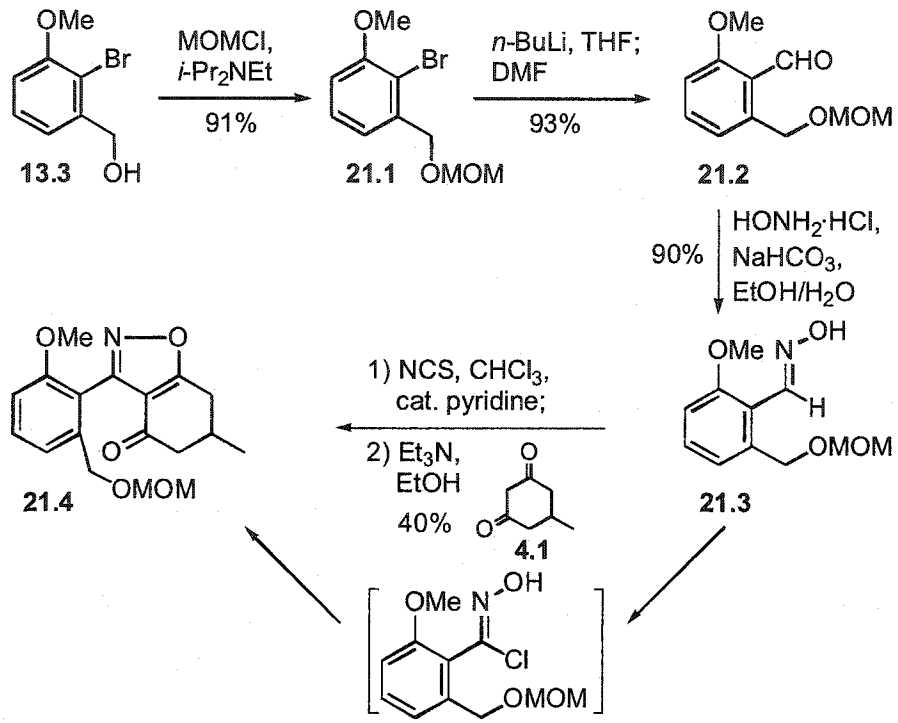
the time we decided to attempt this method, the Nikolaou group reported its successful use to construct the tricarbonyl moiety in their syntheses of coleophomones B, C and D.[4,5] At this point, a search of the literature, revealed that the methodology for making isoxazoles (Scheme 20) developed by the Suzuki group[20] might be suitable to build up the required tricarbonyl moiety.

Scheme 20



In order to test this possibility, we needed the oxime **21.3** (Scheme 21), which would then be used for condensation with 1,3-diketone **4.1**. The synthesis of **21.3** was achieved starting from the benzyl alcohol **13.3**, which we had already made in earlier work. Conversion into **21.1** was done by reaction with $MeOCH_2Cl$ in the presence of *i*-Pr_2NEt, and treatment of **21.1** with *n*-BuLi, followed by addition of DMF, gave aldehyde **21.2**. This was allowed to react with $NH_2OH \cdot HCl$ in aqueous $NaHCO_3$ solution to afford the oxime **21.3**. Chlorination of **21.3** with NCS generated the intermediate *C*-chloro oxime which, without purification, was treated with 1,3-diketone **4.1** in the presence of Et_3N in EtOH to furnish the desired product **21.4** in 40% yield (unoptimized).

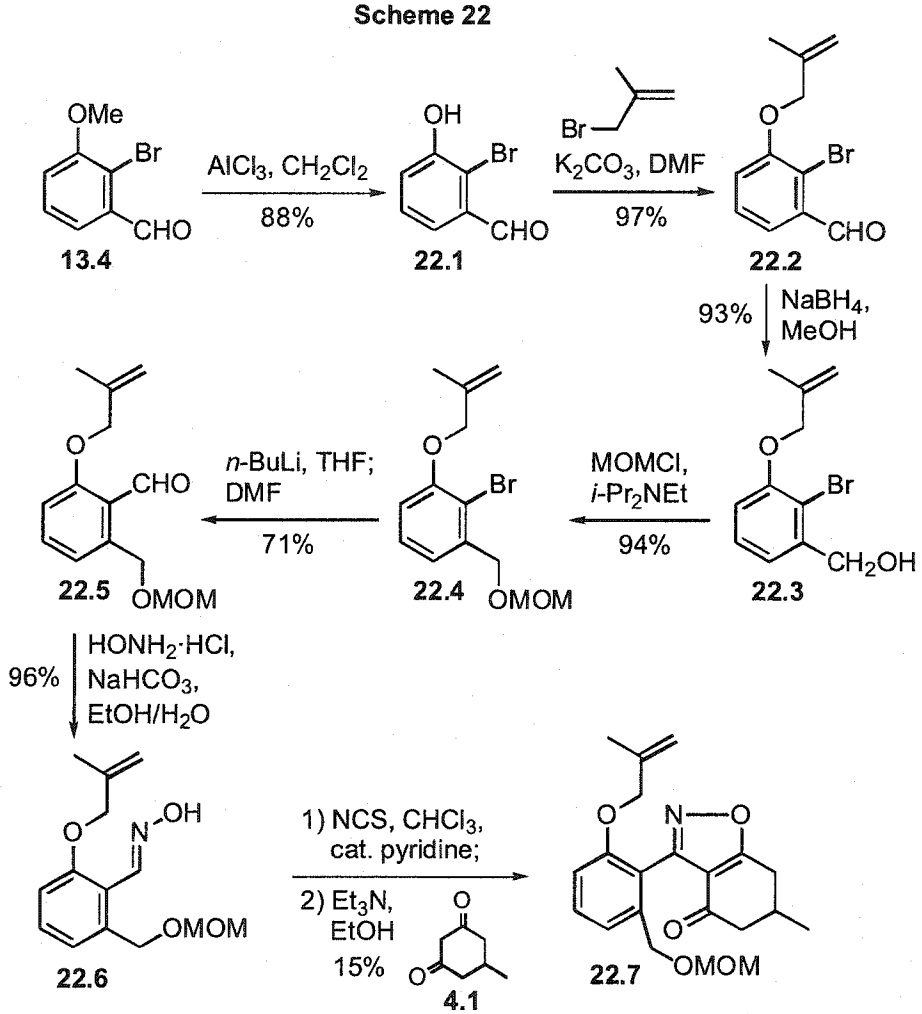
Scheme 21



Although the overall yield was not very good, the experiments gave us experience in making a chloro oxime of the type we needed. For the actual synthesis, however, we wanted to dispense with the methoxy group, and use a different protecting group that did not have to be removed, but which could take part in the macrocyclization, either by ring closing metathesis or by an alkylation process. A suitable oxime potentially satisfying this requirement is **22.6** (Scheme 22), and it was prepared from aldehyde **13.4** in six steps. Demethylation of **13.4** with $AlCl_3$ gave the known phenol **22.1**[21], which was alkylated with 3-bromo-2-methylpropene to the aldehyde **22.2** in 97% yield. Reduction with $NaBH_4$, followed by protection, afforded bromide **22.4**, and treatment of **22.4** with *n*-BuLi and DMF led to aldehyde **22.5**, which was then converted into the corresponding oxime **22.6**. Disappointedly, condensation of **22.6** with 1,3-diketone **4.1** under the same conditions as used with the model **21.3** resulted in a very low (15%) yield of isoxazole

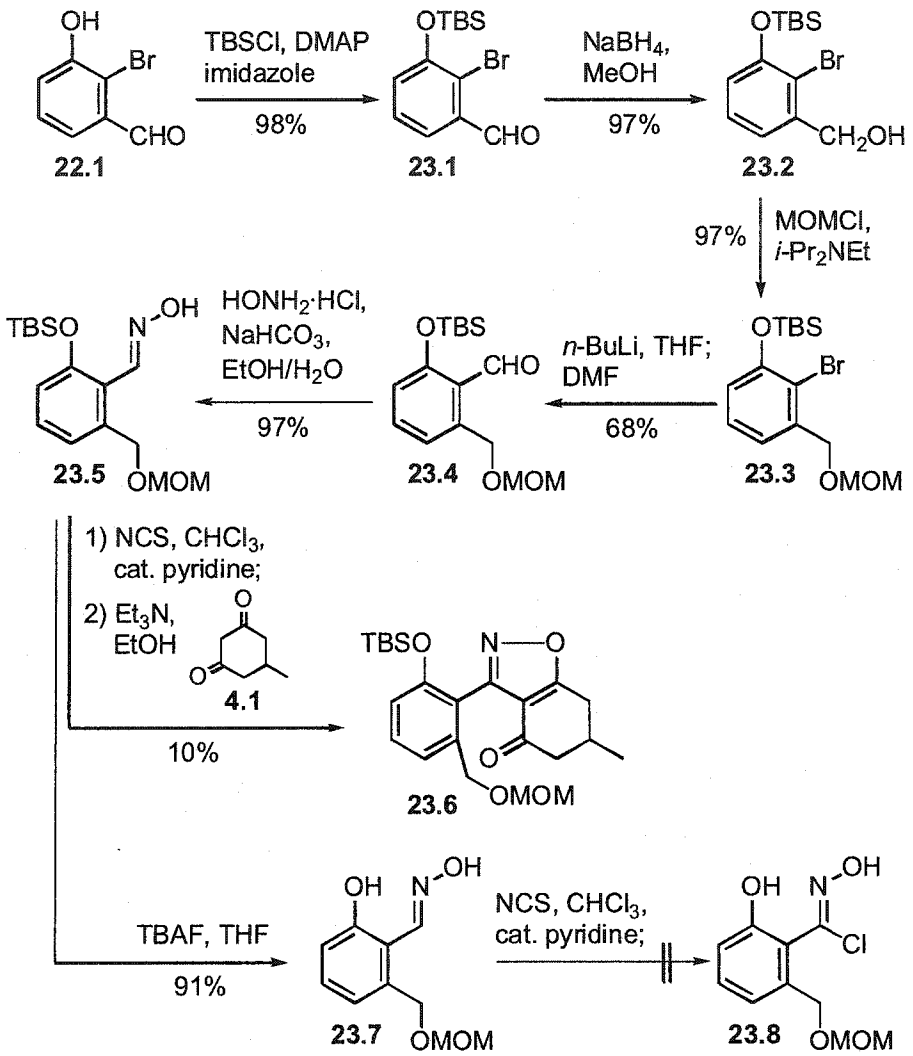
22.7 and the material contained some impurities. Attempts to optimize the reaction did not lead to any improvement. Possibly, the carbon-carbon double bond in the methylpropenyl substituent might be responsible for the intervention of side reactions. We decided to use a *t*-BuMe$_2$Si group because we believed that the methylpropenyl group could be easily reinstalled after desilylation.

Scheme 22



Following the same sequence as in Scheme 22, synthesis of oxime **23.5** (Scheme 23) was accomplished starting from phenol **22.1**. Silylation with *t*-BuMe$_2$SiCl, and NaBH$_4$ reduction gave alcohol **23.2**. Protection with MeOCH$_2$Cl afforded bromide **23.3**, which was then treated with *n*-BuLi

Scheme 23

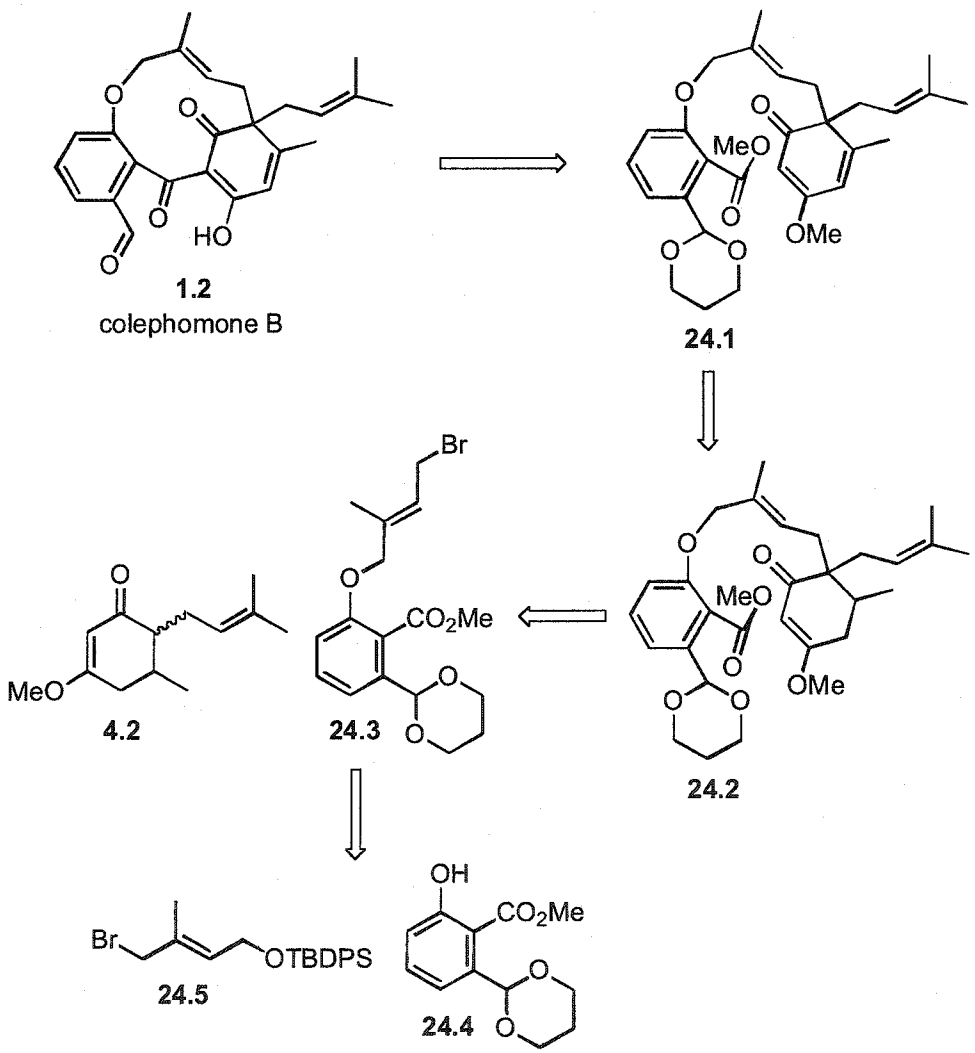


and DMF to yield aldehyde **23.4**. Formation of oxime **23.5** proceeded without incident, but, surprisingly, condensation of **23.5** with **4.1** produced the desired isoxazole **23.6** in only 10% yield, and again the material was not pure. We suspected that the bulk of the *t*-BuMe_2Si group is responsible for the low yield, and so **23.5** was desilylated with Bu_4NF to furnish oxime **23.7**. Chlorination of **23.7** with NCS produced a complex mixture, and none of the desired *C*-chloro oxime **23.8** was obtained. The previous *C*-chloro oximes prepared from **21.3**, **22.6** and **23.5** were easily handlable and their purity was checked by ^1H NMR before use.

Our results from the above studies indicated that highly substituted aromatic *C*-chloro oximes did not condense efficiently with β-diketones. Some time later, the same difficulty was also encountered by the Suzuki group, but they were able to overcome the inherent instability of the hindered chloro oximes by converting them directly to the corresponding nitrile oximes, which condensed smoothly with β-diketones.[22]

Synthetic Studies on Macrocyclization with the Tricarbonyl Moiety Tethered: Approach to Coleophomone B

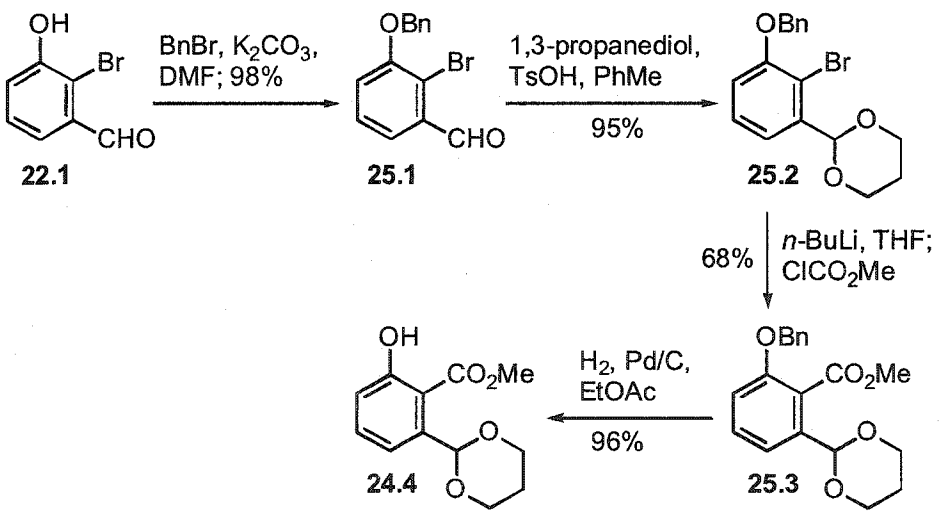
Scheme 24



As our attempts to generate the tricarbonyl system before the macrocycle had been unsuccessful, we decided to reverse the sequence, and so we examined the construction of the 11-membered macrocycle, and we decide to try to close the ring by a process that would generate the tricarbonyl system at the same time. This approach would be totally different from the Nicolaou route. According to retrosynthetic analysis, coleophomone B can be derived from the key intermediate **24.2**, which, in turn, can be disconnected into the known vinylogous ester **4.2**, and the bromide **24.3**. Bromide **24.3** can itself be derived from two subunits: phenol **24.4** and the known allyl bromide **24.5**.[23]

The subunit **24.4** was prepared from the known compound **22.1** in four steps (Scheme 25). Alkylation of phenol **22.1** with BnBr in the presence of K_2CO_3 in DMF gave the known aldehyde **25.1**,[24,25] which was protected with 1,3-propanediol under acid catalysis to yield the known acetal **25.2**.[25] Treatment with *n*-BuLi, followed by quenching with MeOCOCl, afforded ester **25.3** in 68% yield. Finally, debenzylation was done by hydrogenolysis (H_2, Pd/C) to furnish phenol **24.4** in 96% yield.

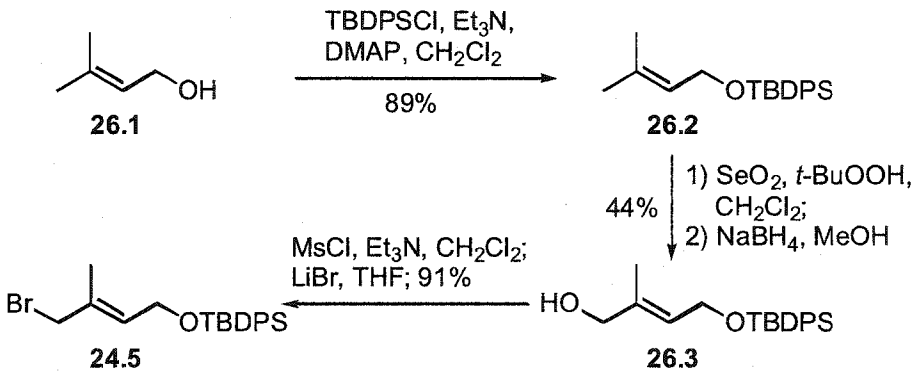
Scheme 25



The allyl bromide **24.5** was prepared from commercially

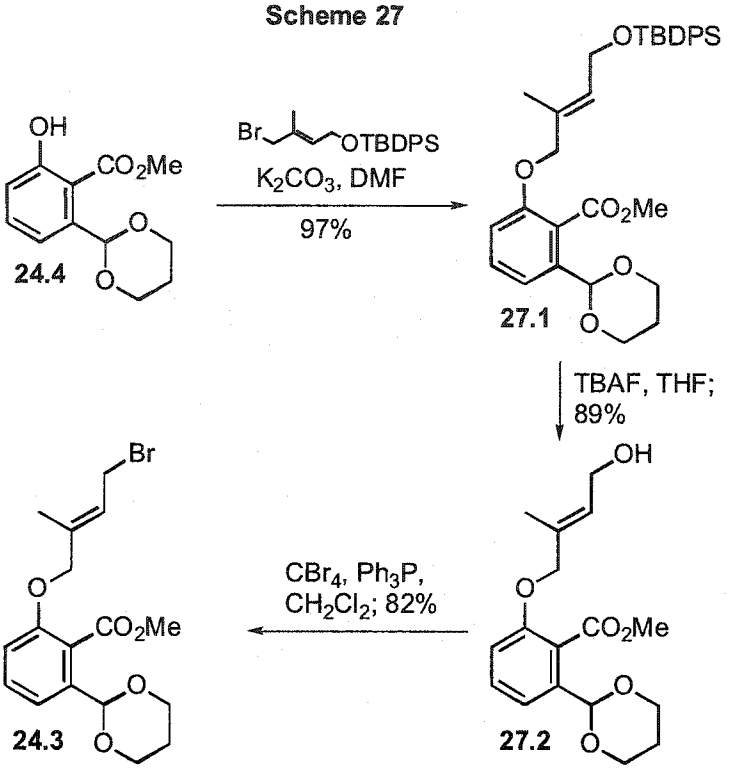
available 3-methyl-2-buten-1-ol (**26.1**) following a four-step literature procedure.[23] Silylation of **26.1** with *t*-$BuPh_2SiCl$ in the presence of Et_3N gave **26.2**. Oxidation with SeO_2/*t*-BuOOH then led to a mixture of the desired product **26.3** and the corresponding aldehyde resulting from overoxidation. It was not necessary to separate the mixture, because reduction with $NaBH_4$ generated the desired allyl alcohol **26.3** in 44% overall yield. Finally, conversion of **26.3** into bromide **24.5** was accomplished by mesylation with MsCl in the presence of Et_3N, followed by displacement with LiBr.

Scheme 26



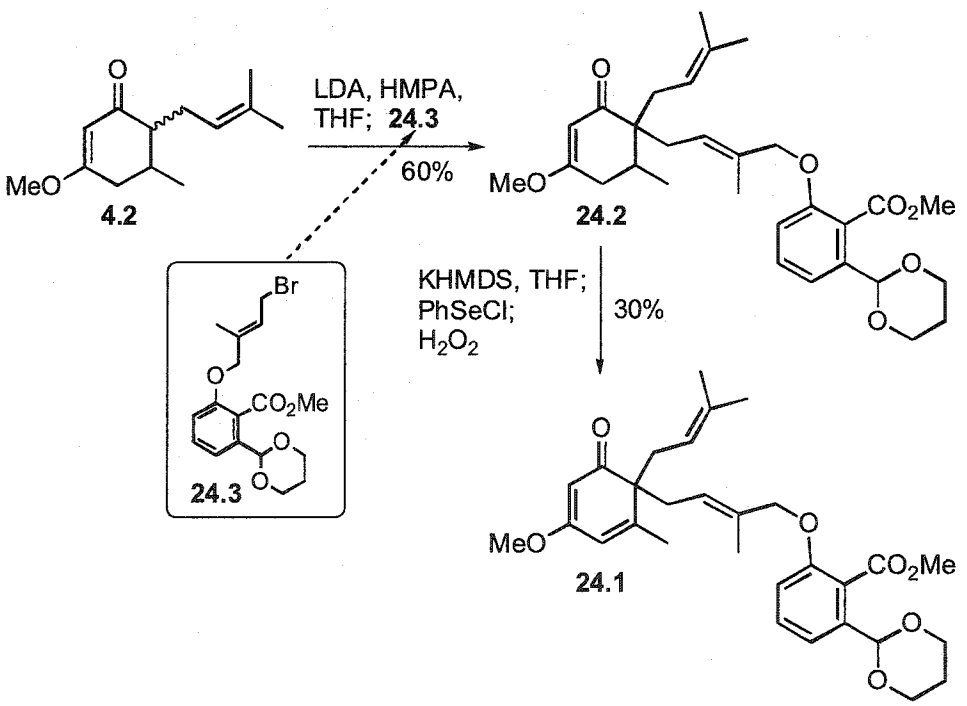
With both allyl bromide **24.5** and phenol **24.4** available, the stage was now set for synthesis of bromide **24.3** (Scheme 27). Alkylation of **24.4** with **24.5** in the presence of K_2CO_3 in DMF proceeded smoothly to give the desired ether **27.1** in 97% yield, and desilylation with Bu_4NF released the allylic alcohol **27.2**. Conversion of **27.2** into its bromide **24.3** was achieved in 82% yield by treatment with CBr_4 and Ph_3P.

Scheme 27



Next, we turned to the preparation of key intermediate **24.1**. This was obtained easily, but not in high yield.

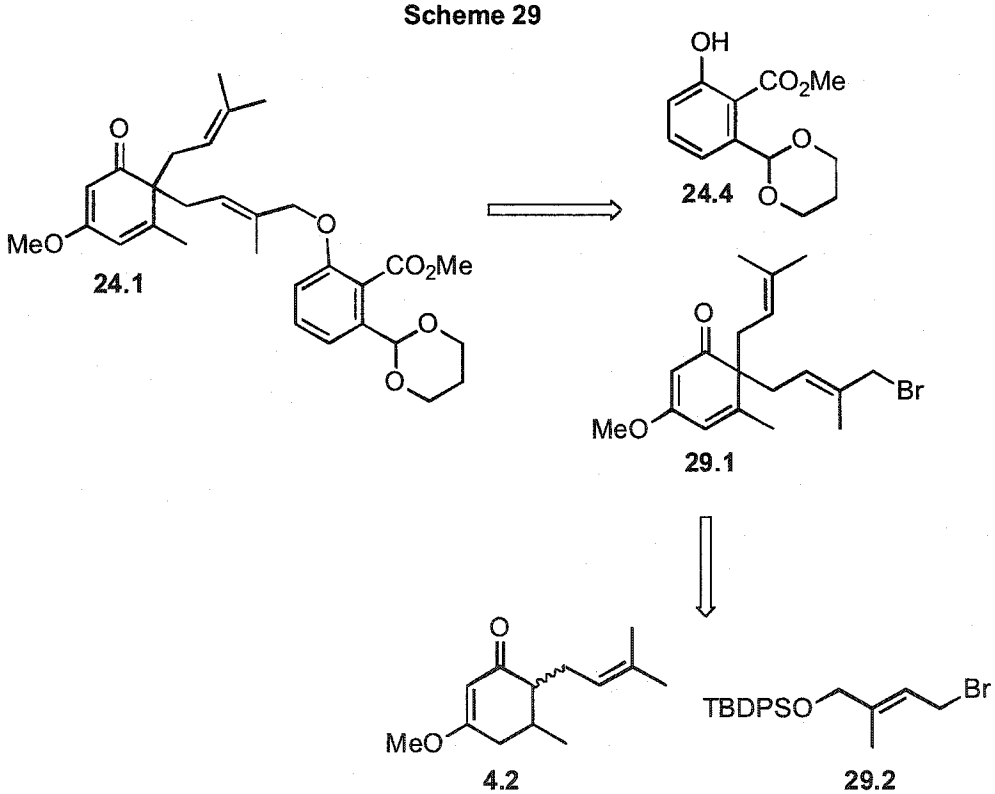
Scheme 28



The vinylogous ester **4.2** was treated with LDA, using HMPA as an additive, and addition of bromide **24.3** gave the alkylated product **24.2** in 60% yield. Once again, the double bond was introduced by phenylselenation and oxidation of the intermediate phenyl selenide. The desired product **24.1** was formed, but only in 30% yield (Scheme 28).

In order to overcome the difficulties introduced by the low yield, we attempted to modify the route. From a retrosynthetic standpoint, compound **24.1** can be disconnected into two fragments: phenol **24.4** which we had in hand, and bromide **29.1**, which can be derived by alkylation of the vinylogous ester **4.2** with the allyl bromide **29.2** (Scheme 29). Compound **4.2** was also available, as we had made it in earlier studies described above. The only remaining subunit (**29.2**) could be synthesized easily.

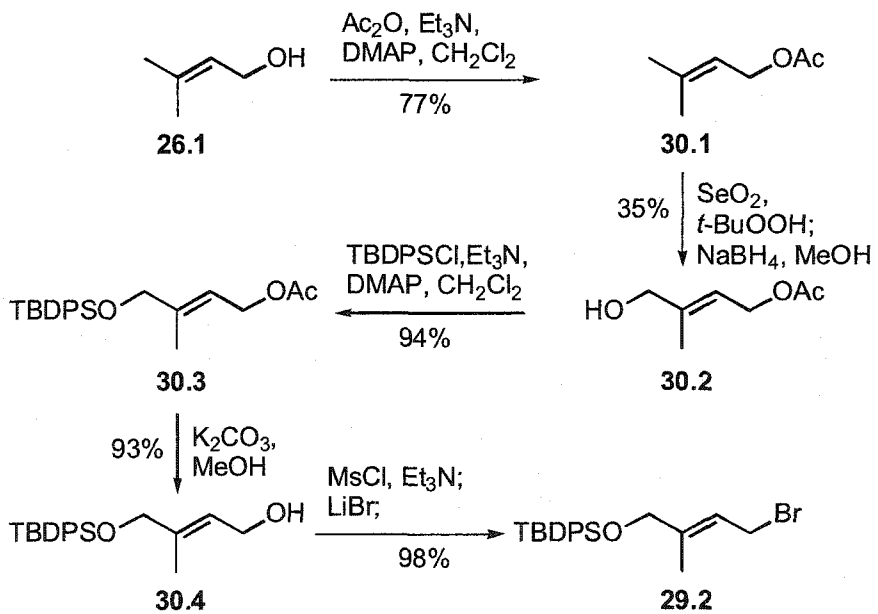
Scheme 29



Synthesis of bromide **29.2** was accomplished starting from allyl alcohol **26.1** in six steps. Acetylation of **26.1**

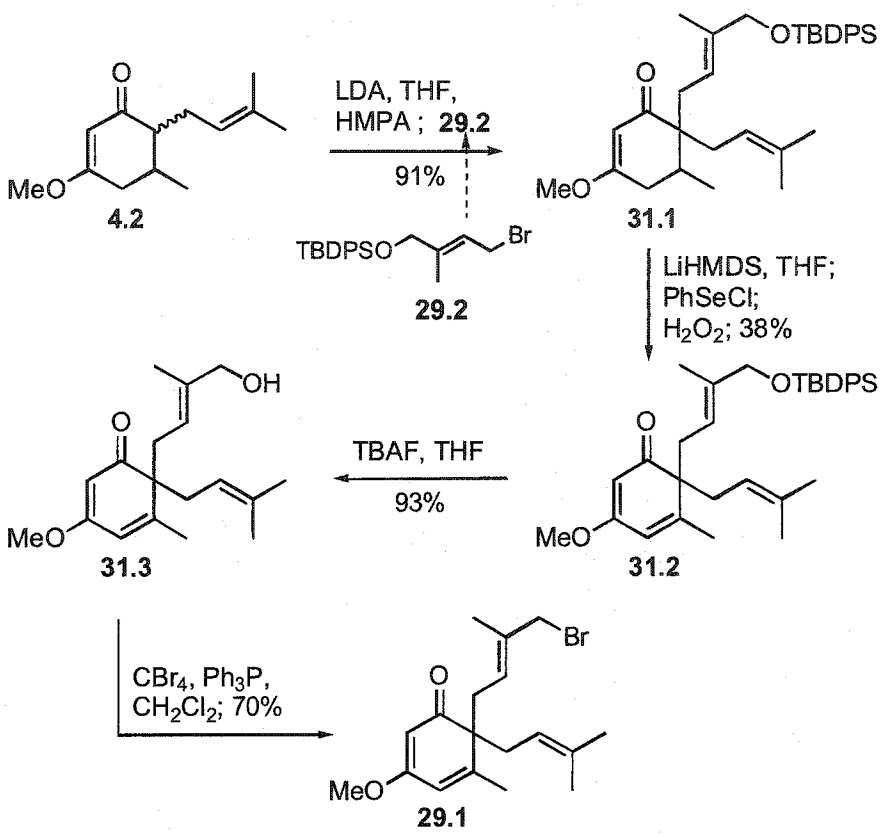
with Ac_2O gave the known acetate **30.1**[26] (Scheme 30) in 77% yield. Following a literature procedure,[27] oxidation with SeO_2/*t*-BuOOH, and subsequent reduction with $NaBH_4$, resulted in the *trans* allyl alcohol **30.2**. Silylation with *t*-$BuPh_2SiCl$ afforded the desired product **30.3**, which was deacetylated with K_2CO_3 in MeOH to generate allyl alcohol **30.4** in 93% yield. Finally, treatment first with MsCl in the presence of Et_3N, and then with LiBr afforded the crude bromide **29.2** in 98% yield. It was used in the next step without further purification. Treatment of alcohol **30.4** with CBr_4 and Ph_3P gave rise to separation problems due to the similar polarities of **29.2** and Ph_3P.

Scheme 30



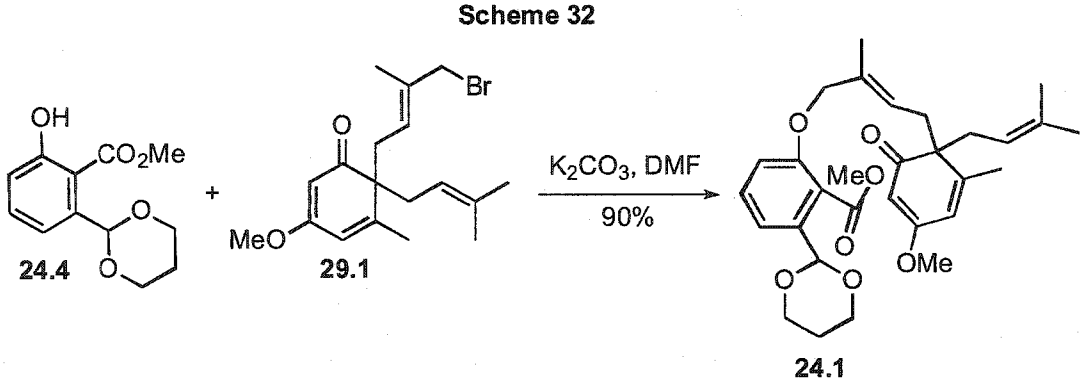
We came now to the stage of synthesizing the coupling fragment **29.1**. Vinylogous ester **4.2** was treated with LDA in the presence of HMPA, and the enolate was alkylated with bromide **29.2** to give **31.1** in 91% yield (Scheme 31). Unfortunately, introduction of the required double bond by phenylselenation and *in situ* oxidation led to the desired product **31.2** in only 38% yield. Mechanistically, only *syn*-elimination of a phenylselenoxide can generate the double

Scheme 31



bond, and the low yield in our case was probably caused by a lack of facial selectivity in the phenylselenation. Despite the low yield, we were able to obtain enough of compound **31.2** to continue our studies. Desilylation of **31.2** with Bu_4NF afforded alcohol **31.3** in 93% yield. Finally, treatment of **31.3** with CBr_4 and Ph_3P produced the corresponding bromide **29.1** in 70% yield.

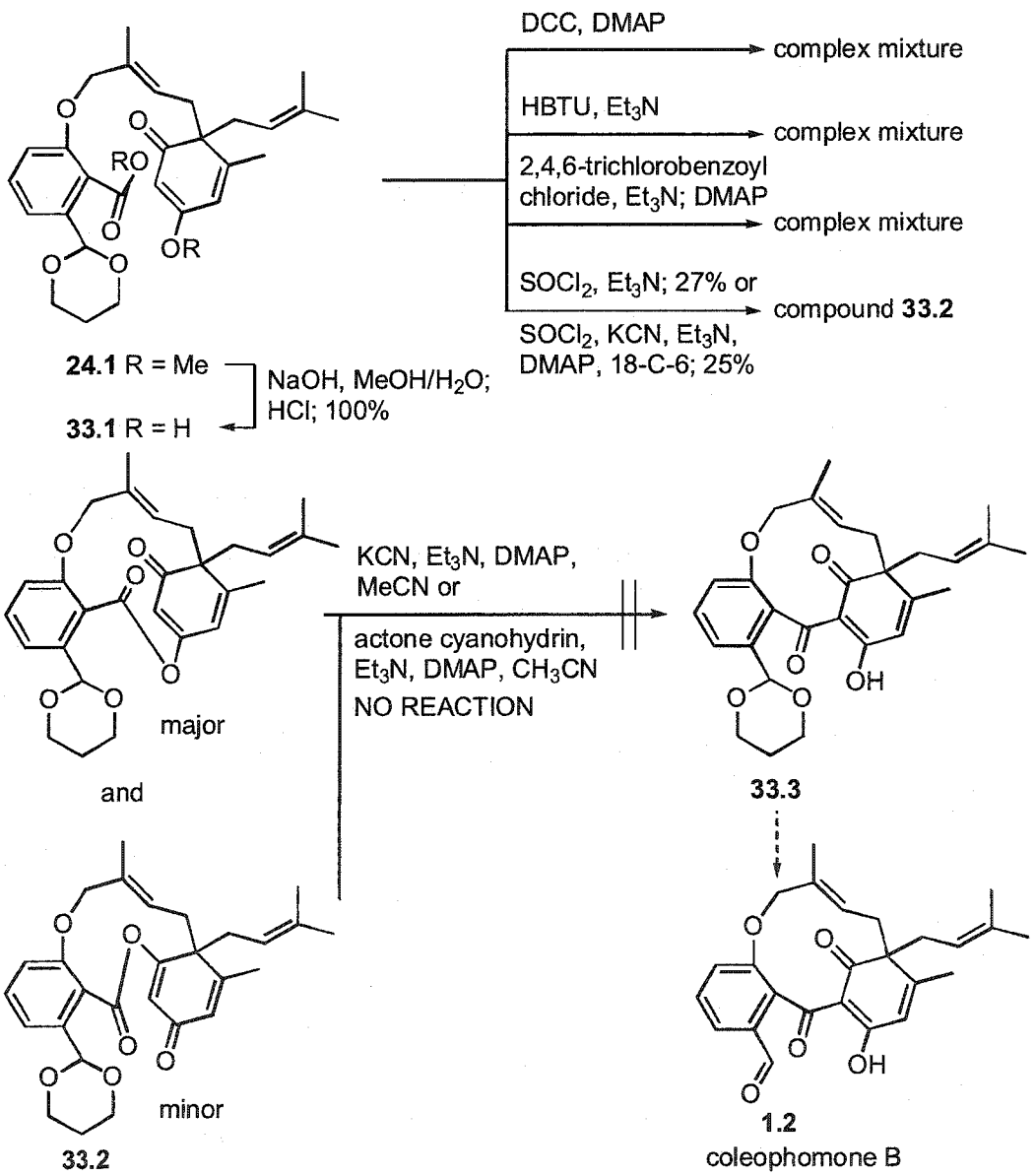
Scheme 32



At this point, phenol **24.4** was alkylated with bromide **29.1** in the presence of K_2CO_3 to give the advanced intermediate **24.1** in 90% yield (Scheme 32).

With ester **24.1** in hand, we were in a position to attempt our crucial transformation: macrocyclization with the built-in tricarbonyl moiety. Hydrolysis of ester **24.1** with NaOH in aqueous MeOH followed by acidification with hydrochloric acid gave the crude acid **33.1** in quantitative yield (Scheme 33).

Scheme 33

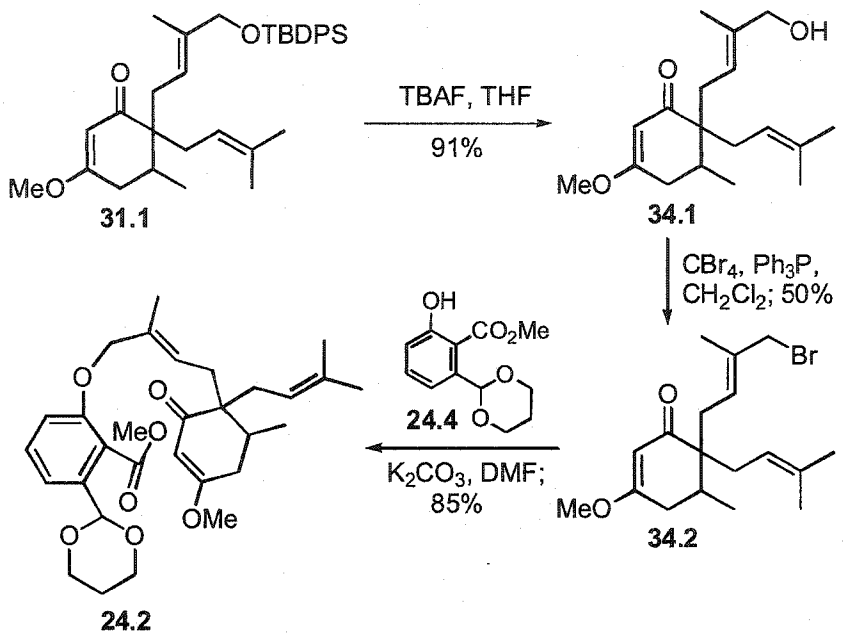


Several attempts to convert acid **33.1** to the desired product **33.3** needed for conversion into coleophomone B were unsuccessful. However, treatment with $SOCl_2$ in the presence of Et_3N gave the cyclized vinylogous anhydride **33.2** in 27% yield (unoptimized), as a mixture of two regioisomers that could not be separated. The structure of the major isomer is a tentative assignment, based on a comparison of the ^{13}C ketone carbonyl chemical shift (203.3 ppm) with the corresponding signal for **10.2** (205.5 ppm). The reference model for the minor isomer is **14.1**, which has a ketone ^{13}C signal at 187.3 ppm. The proportion of the minor isomer in the mixture was insufficient for us to obtain a ^{13}C carbonyl signal.

As a result of obtaining **33.2**, its conversion into **33.3** became the next challenge. We knew from our previous studies that attempted *O*-acylation and rearrangement[6] failed to deliver the *C*-acylation product containing the required tricarbonyl moiety, and exposure of the vinylogous anhydride **10.2** or **14.1** to KCN in the presence of Et_3N resulted in two separate pieces, which did not undergo *C*-acylation to the desired tricarbonyl product **10.1** (see Schemes 10 and 14). We hoped that if the two pieces were tethered into the same molecule, intramolecular *C*-acylation might occur. Surprisingly, treatment of **33.2** with KCN or acetone cyanohydrin in the presence of Et_3N and DMAP gave no reaction. Therefore, in order to take advantage of acyl cyanide-based *C*-acylation,[4,5,19] we treated acid **33.1** with $SOCl_2$ in the presence of KCN, Et_3N, DMAP and 18-crown-6.[28] However, only the *O*-acylation product **33.2** was obtained in 25% yield (unoptimized).

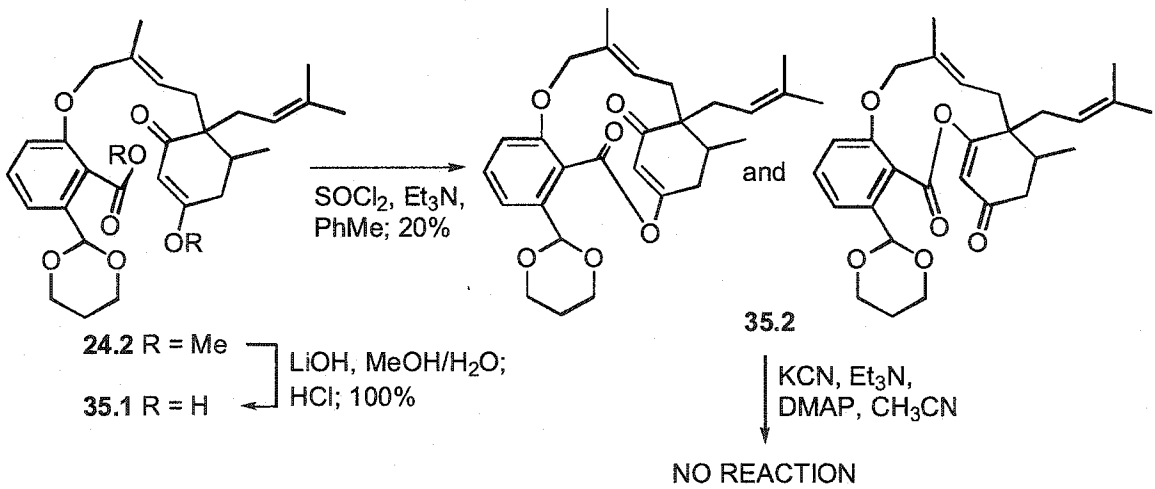
We suspected that the acetal protecting group on the benzylic position of **33.1** produced an environment that was too hindered for an acyl cyanide to be formed or for an acyl cyanide-based *C*-acylation to occur. Possibly, the extra double bond in the cyclohexenone also affected the reactivity of the vinylogous anhydride system. In order to

Scheme 34



clarify the effect of the double bond, we synthesized ester **24.2** from **31.1** in three steps (Scheme 34). Deprotection of the *t*-$BuPh_2SiO$ group with Bu_4NF in THF gave allyl alcohol **34.1** in 91% yield. Conversion of **34.1** into allyl bromide **34.2** was realized with CBr_4 and Ph_3P. Finally, alkylation of **24.4** with **34.2** in the presence of K_2CO_3 furnished ester **24.2** in 85% yield.

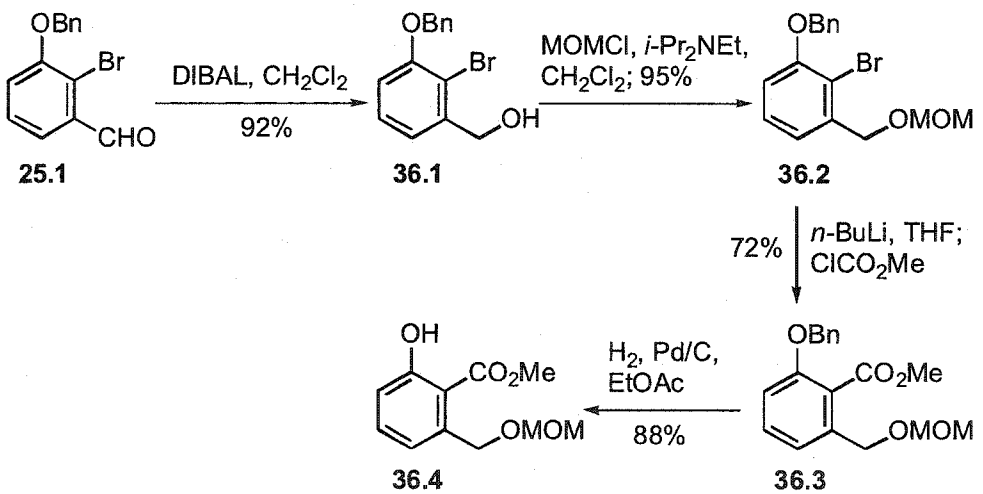
Scheme 35



Hydrolysis of **24.2** with LiOH in aqueous MeOH, followed by acidification, afforded acid **35.1** in quantitative yield and, without purification, it was treated with $SOCl_2$ to produce the *O*-acylation product **35.2** in 20% yield (unoptimized). Exposure of **35.2** to KCN in the presence of Et_3N and DMAP gave no reaction (Scheme 35).

The above result indicated that the double bond was not responsible for thwarting rearrangement of the *O*-acylation product, and so we turned our attention to the possible deleterious role of the bulky acetal protecting group. For evaluating this possibility, a smaller $MeOCH_2$ group was used to protect the benzylic hydroxyl. Reduction of aldehyde **25.1** with DIBAL resulted in alcohol **36.1**[24,29] in 92% yield. Protection with $MeOCH_2Cl$ gave the desired ether **36.2**, which was treated with *n*-BuLi and MeOCOCl to generate ester **36.3**. Finally, hydrogenolysis of **36.3** provided phenol **36.4** in 88% yield (Scheme 36).

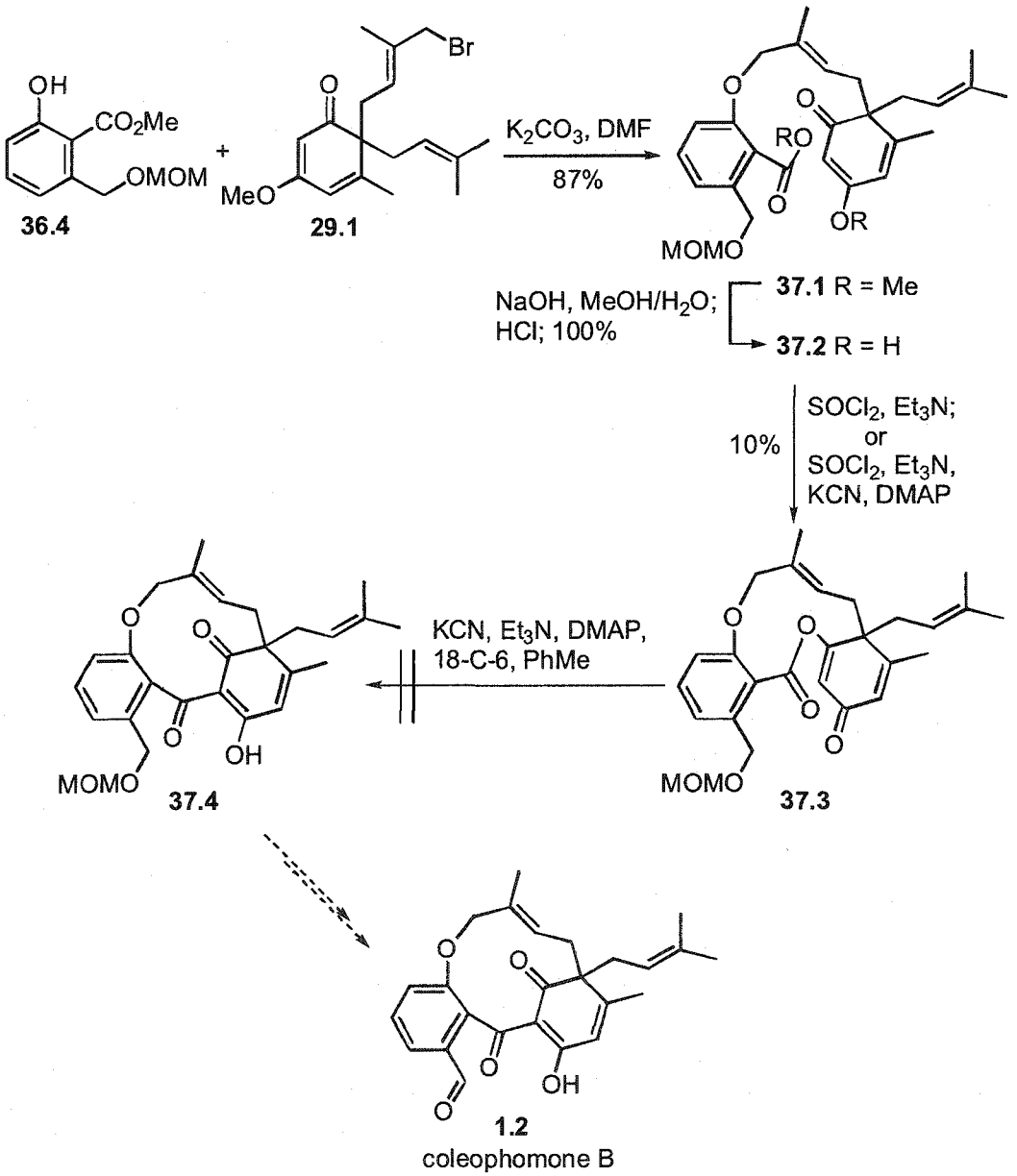
Scheme 36



The phenol was alkylated with allyl bromide **29.1** in the presence of K_2CO_3 to yield ester **37.1** (Scheme 37). Hydrolysis with NaOH in aqueous MeOH, followed by acidification, then afforded acid **37.2**, which was used without purification. Treatment with $SOCl_2$ in the presence

of Et_3N or Et_3N, DMAP and KCN produced the *O*-acylation product **37.3** in only 10% yield (unoptimized); no *C*-acylation product **37.4** was obtained. Compound **37.3** was obtained as a single isomer, and the structure was assigned based on a comparison or the ^{13}C NMR shift of the ketone carbonyl (187.4 ppm) with the corresponding value for **14.1** (187.3 ppm). Upon treatment of **37.3** with KCN in the presence of Et_3N, DMAP and 18-crown-6, no reaction occurred.

Scheme 37



Unexpectedly, compared to the bigger acetal group on the benzylic position, the $MeOCH_2$ protecting group gave rise to a lower yield of macrocyclization product, even though these macrocyclization reactions were done under the same conditions. It was clear that the protecting group change from acetal to $MeOCH_2$ on the benzylic position did not facilitate *O*-acylation-rearrangement to form the tricarbonyl system, and we decided to stop work in this area.

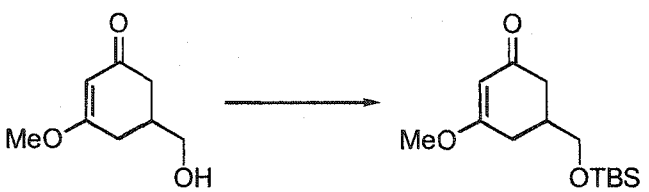
CONCLUSION

Our studies on the construction of the tricarbonyl system proved to be unsuccessful. Also, we investigated the challenging macrocyclization (based on *O*-acylation or *C*-acylation). Although we were able to generate macrocyclic systems, the advanced intermediate (**33.2**) or (**37.3**) failed to give the core structure **33.3** (or **37.4**), which was needed for conversion into coleophomone B. A number of highly substituted benzenes were made during this work.

EXPERIMENTAL

The same general procedures were used as described in Chapter 1. In many ^{1}H NMR spectra, certain spin systems are described as AB quartets even though the value of $\Delta\nu/J$ is greater than 10. Strictly, such spectra should be described as AM systems.

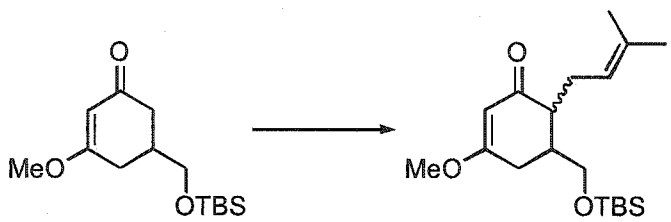
5-(*tert*-Butyldimethylsilanyloxymethyl)-3-methoxy-2-cyclohex-2-enone (11.4).



11.3 **11.4**

t-BuMe$_2$SiCl (1.29 g, 8.53 mmol) was added to a stirred and cooled (0 °C) mixture of **11.3**[8] (1.02 g, 6.56 mmol), imidazole (0.715 g, 10.5 mmol) and DMAP (40 mg, 0.33 mmol) in CH_2Cl_2 (40 mL). The cold bath was left in place but not recharged, and stirring was continued overnight. The mixture was diluted with CH_2Cl_2 (30 mL), washed with 1 N hydrochloric acid (20 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 30% EtOAc-hexanes, gave **11.4** (1.579 g, 89%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2953, 2930, 2897, 2856, 1659, 1610, 1380, 1253 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.02 (s, 6 H), 0.87 (s, 9 H), 2.14-2.41 (m, 5 H), 3.48-3.60 (m, 2 H), 3.68 (s, 3 H), 5.36 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.5 (q), 18.2 (s), 25.8 (q), 31.6 (t), 36.3 (d), 39.6 (t), 55.7 (q), 65.7 (t), 102.0 (d), 178.0 (s), 199.3 (s); exact mass (HR electrospray) *m/z* calcd for $C_{14}H_{27}O_3Si$ (M + H) 271.1729, found 271.1728.

5-(*tert*-Butyldimethylsilanyloxymethyl)-3-methoxy-6-(3-methylbut-2-enyl)cyclohex-2-enone (11.5).

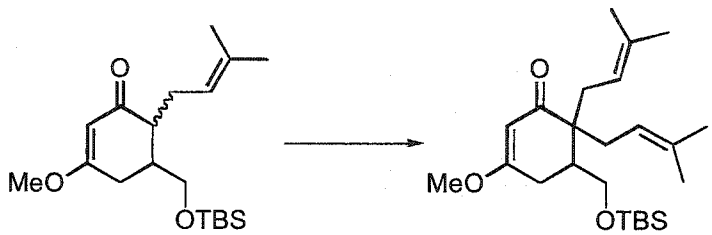


11.4 **11.5**

A solution of **11.4** (0.594 g, 2.20 mmol) in THF (2 mL) was added dropwise over 10 min to a stirred and cooled (-78 °C) solution of LDA [freshly prepared from *i*-Pr_2NH (0.37 mL, 2.64 mmol) in THF (10 mL) by addition of *n*-BuLi (0.97 mL, 2.5 M in hexanes) at -78 °C, followed by stirring at -78 °C for 1 h]. Stirring at -78 °C was continued for 1 h and HMPA (0.42 mL, 2.42 mmol) was added dropwise, followed by 3-methyl-2-butenyl bromide (0.40 mL, 3.3 mmol). The cooling bath was left in place but not recharged and stirring was continued overnight. The reaction was quenched with saturated aqueous NH_4Cl (5 mL), and the mixture was extracted with Et_2O (2 x 20 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 15% EtOAc-hexanes, gave **11.5** (0.521 g, 70%) as a 1:4.3 mixture of two diastereoisomers (^1H NMR): FTIR (CH_2Cl_2, cast) 2954, 2928, 2856, 1657, 1616, 1463, 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.01 (s, 6 H), 0.86 (s, 9 H), 1.61 (s, 3 H), 1.66 (s, 3 H), 2.00-2.55 (m, 6 H), 3.54 (d, *J* = 5.6 Hz, 2 H), 3.66 (s, 3 H), 4.88-5.15 (m, 1 H), 5.31 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.6 (q), 17.8 (q), 18.2 (s), 24.5 (t), 25.8 (q), 27.0 (t), 29.3 (t), 30.1 (t), 38.1 (d), 38.2 (d), 46.9 (d), 47.8 (d), 55.5 (q), 55.6 (q), 61.8 (t), 64.1 (t), 101.3 (d), 101.5 (d), 121.4 (d), 121.8 (d), 133.1 (s), 176.1 (s), 200.9 (s); exact mass *m/z* calcd for $C_{19}H_{34}O_3Si$ 338.2277,

found 338.2282.

5-(*tert*-Butyldimethylsilanyloxymethyl)-3-methoxy-6,6-bis(3-methylbut-2-enyl)cyclohex-2-enone (11.6).

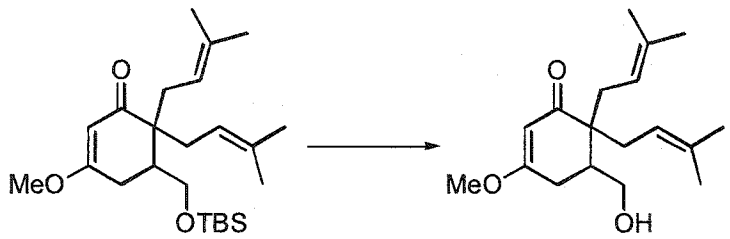


11.5 **11.6**

A solution of **11.5** (1.01 g, 2.48 mmol) in THF (2.5 mL) was added dropwise over 10 min to a stirred and cooled (-78 °C) solution of LDA [freshly prepared from *i*-Pr_2NH (0.42 mL, 2.98 mmol) in THF (12 mL) by addition of *n*-BuLi (1.1 mL, 2.5 M in hexanes) at -78 C, followed by stirring at -78 °C for 1 h]. Stirring at -78 °C was continued for 1 h and HMPA (0.55 mL, 3.1 mmol) was added dropwise, followed by 3-methyl-2-butenyl bromide (0.45 mL, 3.7 mmol). The cooling bath was left in place but not recharged, and stirring was continued overnight. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the mixture was extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 10% EtOAc-hexanes, gave **11.6** (0.729 g, 72%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2956, 2928, 2856, 1652, 1618, 1471, 1252 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ -0.05 (s, 3 H), 0.05 (s, 3 H), 0.87 (s, 9 H), 1.54 (s, 6 H), 1.64 (s, 3 H), 1.67 (s, 3 H), 2.00-2.60 (m, 7 H), 3.47 (dd, *J* = 9.7, 9.7 Hz, 1 H), 3.64-3.70 [m, 4 H, including s (3 H) at δ 3.66], 4.89-4.96 (m, 1 H), 5.03-5.10 (m, 1 H), 5.30 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.6 (q), 17.8 (q), 17.9 (q), 18.2 (s), 25.8 (q), 25.9 (q), 26.0 (q), 28.5 (t), 30.0 (t), 32.4 (t), 40.9 (d),

49.6 (s), 55.5 (q), 62.0 (t), 101.4 (d), 119.4 (d), 119.9 (d), 133.2 (s), 133.4 (s), 175.1 (s), 202.2 (s); exact mass *m/z* calcd for $C_{24}H_{42}O_3Si$ 406.2903, found 406.2899.

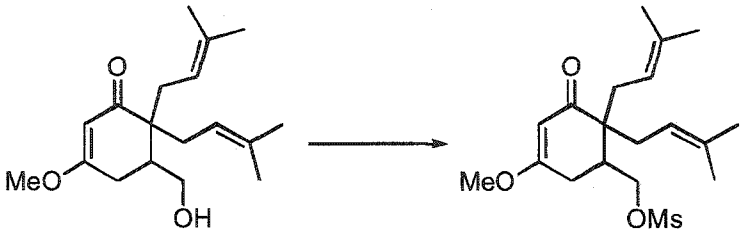
5-Hydroxymethyl-3-methoxy-6,6-bis(3-methylbut-2-enyl)-cyclohex-2-enone (11.7).



11.6 **11.7**

Bu_4NF (0.90 mL, 1.0 M in THF) was added dropwise to a stirred solution of **11.6** (0.306 g, 0.754 mmol) in THF (4 mL). Stirring was continued for 1 h, and then saturated aqueous NH_4Cl (5 mL) was added. The mixture was extracted with EtOAc (2 x 20 mL), and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 30% EtOAc-hexanes, gave **11.7** (0.220 g, 92%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3417, 2965, 2915, 1613, 1441, 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.55 (s, 3 H), 1.56 (s, 3 H), 1.63 (s, 3 H), 1.65 (s, 3 H), 1.70 (s, 1 H), 2.03 (dd, *J* = 15.3, 7.3 Hz, 1 H), 2.13 (dd, *J* = 13.9, 8.2 Hz, 1 H), 2.24-2.33 (m, 2 H), 2.48-2.68 (m, 3 H), 3.49 (dd, *J* = 10.5, 9.4 Hz, 1 H), 3.65 (s, 3 H), 3.77 (dd, *J* = 10.5, 3.0 Hz, 1 H), 4.88-4.94 (m, 1 H), 5.02-5.08 (m, 1 H), 5.30 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 17.8 (q), 17.9 (q), 25.9 (q), 26.0 (q), 28.8 (t), 30.4 (t), 32.4 (t), 41.0 (d), 49.7 (s), 55.5 (q), 62.1 (t), 101.5 (d), 119.1 (d), 119.9 (d), 133.5 (s), 133.7 (s), 175.2 (s), 202.2 (s); exact mass *m/z* calcd for $C_{18}H_{28}O_3$ 292.2039, found 292.2041.

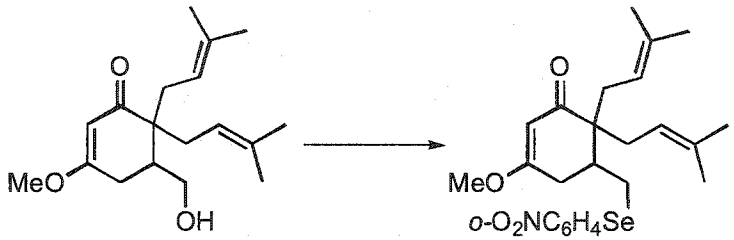
Methanesulfonic Acid 3-Methoxy-6,6-bis(3-methylbut-2-enyl)-5-oxocyclohex-3-enylmethyl Ester (11.8).



11.7 **11.8**

Et_3N (0.17 mL, 1.26 mmol), followed by MsCl (73 μL, 0.95 mmol), was added dropwise to a stirred and cooled (0 °C) solution of **11.7** (0.185 g, 0.632 mmol) in Et_2O (6 mL). The cold bath was left in place and stirring was continued for 1 h. The mixture was diluted with Et_2O (20 mL), washed with 5% hydrochloric acid (5 mL), water (5 mL) and brine (5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 25 cm), using 20% EtOAc-hexanes, gave **11.8** (0.212 g, 91%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2970, 2914, 1651, 1617, 1194 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 1.49 (s, 3 H), 1.58 (s, 3 H), 1.60 (s, 3 H), 1.61 (s, 3 H), 2.12-2.16 [m, 5 H, including s (3 H) at δ 2.09], 2.31-2.52 (m, 4 H), 2.77-2.88 (m, 1 H), 2.91 (s, 3 H), 3.92-4.04 (m, 1 H), 4.18-4.28 (m, 1 H), 5.18-5.27 (m, 2 H), 5.28 (s, 1 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 17.9 (q), 18.0 (q), 26.1 (q), 29.0 (t), 31.1 (t), 32.7 (t), 36.6 (q), 38.7 (d), 49.8 (s), 54.9 (q), 69.0 (t), 101.9 (d), 119.4 (d), 120.4 (d), 133.9 (s), 134.0 (s), 173.3 (s), 198.8 (s); exact mass *m/z* calcd for $C_{19}H_{30}O_5S$ 370.1814, found 370.1814.

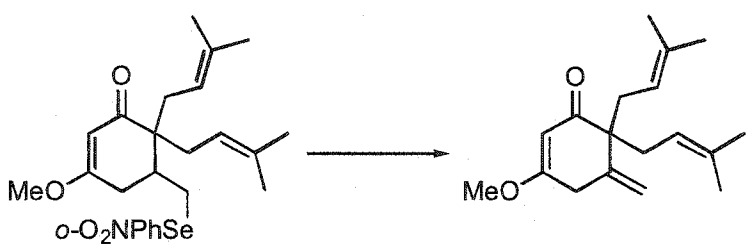
3-Methoxy-6,6-bis(3-methylbut-2-enyl)-5-(2-nitrophenylselanylmethyl)cyclohex-2-enone (11.9).



11.8 **11.9**

Bu_3P (0.10 mL, 0.42 mmol) was added dropwise to a stirred solution of **11.8** (92.5 mg, 0.317 mmol) and *o*-nitrophenyl selenocyanate (93.5 mg, 0.412 mmol) in THF (3 mL). After the addition stirring was continued for 30 min, and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 60% Et_2O-hexanes, gave **11.9** (0.139 g, 92%) as a yellow oil: FTIR (CH_2Cl_2, cast) 2967, 2912, 1651, 1617, 1512 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.60 (s, 3 H), 1.61 (s, 3 H), 1.69 (s, 3 H), 1.71 (s, 3 H), 2.24 (dd, J = 15.1, 7.8 Hz, 2 H), 2.33-2.86 (m, 6 H), 3.16-3.24 (m, 1 H), 3.62 (s, 3 H), 4.90-4.96 (m, 1 H), 5.07-5.14 (m, 1 H), 5.35 (s, 1 H), 7.28-7.50 (m, 3 H), 8.27 (d, *J* = 8.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 17.9 (q), 18.0 (q), 26.0 (q), 26.1 (q), 26.8 (t), 31.5 (t), 32.0 (t), 37.3 (d), 51.8 (s), 55.7 (q), 101.5 (d), 118.9 (d), 119.8 (d), 125.6 (d), 126.5 (d), 129.2 (d), 132.8 (s), 133.5 (d), 133.9 (s), 134.1 (s), 147.1 (s), 174.5 (s), 201.3 (s); exact mass *m/z* calcd for $C_{24}H_{31}NO_4{}^{80}Se$ 477.1418, found 477.1414.

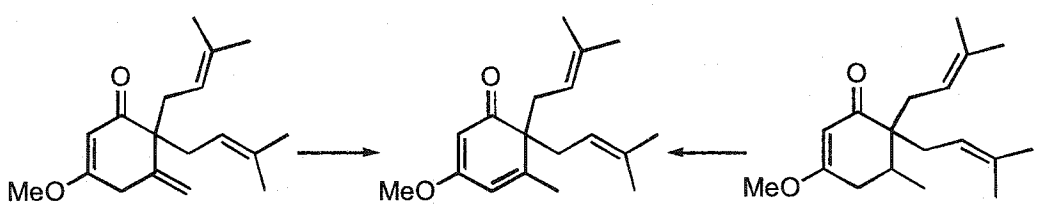
3-Methoxy-6,6-bis(3-methylbut-2-enyl)-5-methylene-cyclohex-2-enone (11.10).



11.9 **11.10**

$NaIO_4$ (0.171 g, 0.798 mmol) was added to a stirred solution of **11.9** (0.109 g, 0.228 mmol) in a mixture of MeOH (0.5 mL) and water (4 mL). Stirring was continued for 60 h, and the mixture was extracted with Et_2O (2 x 15 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 25 cm), using 10% EtOAc-hexanes, gave **11.10** (0.039 g, 62%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2967, 2912, 1661, 1618, 1441, 1215 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.59 (s, 6 H), 1.64 (s, 6 H), 2.29 (dd, *J* = 15.0, 7.6 Hz, 2 H), 2.46 (dd, *J* = 15.1, 6.0 Hz, 2 H), 3.16 (s, 2 H), 3.69 (s, 3 H), 4.82-4.85 (m, 1 H), 4.88-4.95 (m, 2 H), 5.03-5.07 (m, 1 H), 5.39 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.0 (q), 25.8 (q), 34.3 (t), 36.4 (t), 55.6 (s), 55.7 (q), 101.9 (d), 113.6 (t), 120.1 (d), 133.0 (s), 142.3 (s), 174.7 (s), 201.4 (s); exact mass *m/z* calcd for $C_{18}H_{26}O_2$ 274.1933, found 274.1933.

3-Methoxy-5-methyl-6,6-bis(3-methylbut-2-enyl)cyclohexa-2,4-dienone (9.1).



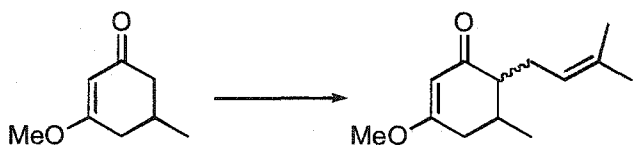
11.10 **9.1** **4.3**

Pyridinium *p*-toluenesulfonate (1 mg) was added to a stirred solution of **11.10** (15 mg, 0.054 mmol) in PhMe (2 mL). The mixture was heated at 85 °C overnight, and then allowed to cool to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (0.5 x 10 cm), using 10% EtOAc-hexanes, gave **9.1** (5.1 mg, 34%) as a colorless oil.

$(Me_3Si)_2NK$ (2.3 mL, 0.5 M in PhMe) was added dropwise

over 10 min to a stirred and cooled (-78 °C) solution of **4.3** (0.272 g, 0.990 mmol) in THF (5 mL). Stirring at -78 °C was continued for 1 h, and then a solution of PhSeCl (190 mg, 1.00 mmol) in THF (1.5 mL) was added dropwise. The cold bath was removed, and stirring was continued for 2 h. Then H_2O_2 (15%, 5 mL) was added and stirring was continued for 1.5 h. The mixture was extracted with Et_2O (2 x 20 mL), and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 25 cm), using 10% EtOAc-hexanes, gave **9.1** (0.141 g, 52%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2972, 2914, 1658, 1630, 1582, 1217 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.56 (s, 12 H), 1.90 (d, J = 3.1 Hz, 3 H), 2.25 (dd, J = 14.0, 7.0 Hz, 2 H), 2.69 (dd, J = 14.4, 6.9 Hz, 2 H), 3.72 (s, 3 H), 4.65-4.74 (m, 2 H), 5.41 (d, J = 2.0 Hz, 1 H), 6.00 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.0 (q), 19.1 (q), 25.7 (q), 38.0 (t), 55.4 (q), 57.2 (s), 99.8 (d), 118.5 (d), 120.6 (d), 133.6 (s), 155.3 (s), 171.7 (s), 204.2 (s); exact mass m/z calcd for $C_{18}H_{26}O_2$ 274.1933, found 274.1930.

3-Methoxy-5-methyl-6-(3-methylbut-2-enyl)cyclohex-2-enone (4.2).

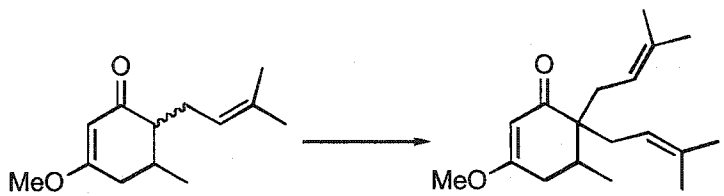


12.2 **4.2**

A solution of **12.2**[11] (2.1 g, 15 mmol) in THF (6 mL) was added dropwise over 20 min to a stirred and cooled (-78 °C) solution of LDA [freshly prepared from i-Pr_2NH (2.4 mL, 17 mmol) in THF (30 mL) by addition of n-BuLi (6.4 mL, 2.5 M in hexanes) at -78 °C, followed by stirring at -78 °C for 1 h]. Stirring at -78 °C was continued for 1 h, and then 3-methyl-2-butenyl bromide (2.60 mL, 22.1 mmol) was added.

The cooling bath was left in place but not recharged, and stirring was continued overnight. The reaction was quenched with saturated aqueous NH_4Cl (20 mL), and the mixture was extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 25 cm), using 20% EtOAc-hexanes, gave **4.2** (2.94 g, 94%) as a 1:11 mixture of two diastereoisomers (^1H NMR): FTIR (CH_2Cl_2, cast) 2964, 2927, 1654, 1615 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.93 and 1.14 (d, J = 6.5 Hz, 3 H), 1.61 and 1.66 (s, 6 H), 1.98-2.60 (m, 6 H), 3.63 (s, 3 H), 4.98-5.14 (m, 1 H), 5.28 and 5.34 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 17.7 (q), 17.8 (q), 19.8 (q), 24.3 (t), 25.8 (q), 26.8 (t), 30.3 (q), 30.7 (d), 35.0 (t), 36.1 (t), 39.3 (d), 50.7 (d), 52.4 (d), 55.5 (q), 55.6 (q), 101.2 (d), 101.4 (d), 121.3 (d), 121.9 (d), 132.9 (s), 175.9 (s), 201.0 (s); exact mass *m/z* calcd for $C_{13}H_{20}O_2$ 208.1463, found 208.1461.

3-Methoxy-5-methyl-6,6-bis(3-methylbut-2-enyl)cyclohex-2-enone (4.3).

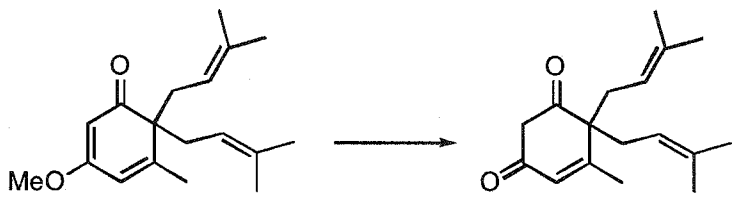


4.2 **4.3**

A solution of **4.2** (2.893 g, 13.91 mmol) in THF (6 mL) was added dropwise over 30 min to a stirred and cooled (-78 °C) solution of LDA [freshly prepared from *i*-Pr_2NH (2.23 mL, 15.8 mmol) in THF (30 mL) by addition of *n*-BuLi (5.9 mL, 2.5 M in hexanes) at -78 °C, followed by stirring at -78 °C for 1 h]. Stirring at -78 °C was continued for 1 h, and then 3-methyl-2-butenyl bromide (2.00 mL, 16.6 mmol) was added. The cooling bath was left in place but not

recharged, and stirring was continued overnight. The reaction was quenched with saturated aqueous NH_4Cl (20 mL), and the mixture was extracted with Et_2O (2 x 60 mL). The combined organic extracts were washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 25 cm), using 10% EtOAc-hexanes, gave **4.3** (3.4 g, 88%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2965, 2912, 1652, 1618, 1221 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.96 (d, *J* = 6.5 Hz, 3 H), 1.57 (s, 3 H), 1.58 (s, 3 H), 1.62 (s, 3 H), 1.66 (s, 3 H), 2.00-2.60 (m, 7 H), 3.63 (s, 3 H), 4.86-4.93 (m, 1 H), 5.02-5.09 (m, 1 H), 5.29 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 15.4 (q), 17.8 (q), 25.9 (q), 26.0 (q), 29.6 (t), 33.1 (d), 34.1 (t), 51.0 (s), 55.4 (q), 101.6 (d), 119.4 (d), 120.4 (d), 132.8 (s), 133.2 (s), 175.0 (s), 202.8 (s); exact mass *m/z* calcd for $C_{18}H_{28}O_2$ 276.2089, found 276.2090.

5-Methyl-6,6-bis(3-methylbut-2-enyl)cyclohex-4-ene-1,3-dione (9.2).

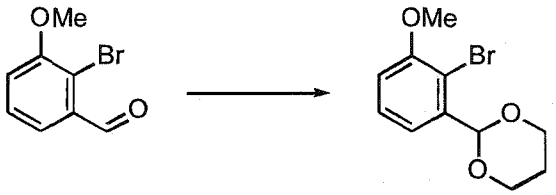


9.1 **9.2**

$LiOH \cdot H_2O$ (0.190 g, 4.52 mmol) was added to a stirred solution of **9.1** (0.310 g, 1.13 mmol) in a mixture of MeOH (6 mL) and water (2 mL). The mixture was heated at 86 °C overnight, and then allowed to cool to room temperature. The solvent was evaporated and the residue was acidified (pH = 2) with 5% hydrochloric acid and extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 60% EtOAc-hexanes, gave **9.2** (0.24 g, 82%) as a 1:2.3

mixture of two isomers (^{1}H NMR): FTIR (CH_2Cl_2, cast) 3400-2400, 1652, 1221 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.54 and 1.56 (s, 12 H), 1.89 and 2.02 (d, J = 0.9 Hz, 3 H), 2.20-2.35 (m, 2 H), 2.70-2.80 (m, 2 H), 3.22 (s, 0.6 H), 4.63-4.80 (m, 2 H), 5.71 (d, J = 0.6 Hz, 0.7 H), 6.09 (s, 0.7 H), 6.24 (s, 0.3 H), 10.4 (s, 0.6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.0 (q), 18.1 (q), 18.8 (q), 20.0 (q), 25.8 (q), 25.9 (q), 35.6 (t), 36.5 (t), 52.7 (t), 53.8 (s), 58.2 (s), 105.4 (d), 117.8 (d), 127.2 (d), 129.8 (d), 134.1 (s), 135.7 (s), 159.0 (s), 163.0 (s), 186.0 (s), 186.8 (s), 193.6 (s), 207.0 (s); exact mass m/z calcd for $C_{17}H_{24}O_2$ 260.1776, found 260.1776.

2-(2-Bromo-3-methoxyphenyl)-1,3-dioxane (13.5).

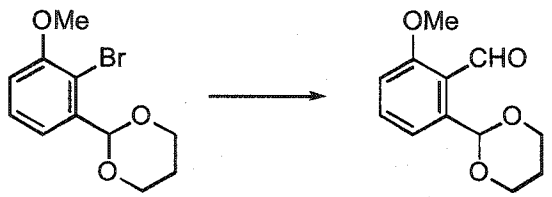


13.4 **13.5**

1,3-Propanediol (0.90 mL, 12.5 mmol), followed by $TsOH \cdot H_2O$ (19 mg, 0.10 mmol), was added to a stirred solution of **13.4**[14] (1.08 g, 5.00 mmol) in PhMe (25 mL). The mixture was refluxed for 3 h under a Dean-Stark trap. The mixture was allowed to cool to room temperature, washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 10% EtOAc-hexanes, gave **13.5** (1.25 g, 91%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2964, 2862, 1467, 1102 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40-1.47 (m, 1 H), 2.17-2.30 (m, 1 H), 3.89 (s, 3 H), 3.97-4.06 (m, 2 H), 4.24-4.29 (m, 2 H), 5.71 (s, 1 H), 6.75 (dd, J = 8.8, 3.1 Hz, 1 H), 7.23 (d, J = 3.1 Hz, 1 H), 7.39 (d, J = 8.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 25.6 (t), 55.5 (q), 67.5 (t), 100.8 (d), 112.6 (s), 112.7 (d), 117.1 (d),

133.2 (d), 138.2 (s), 159.1 (s); exact mass *m/z* calcd for $C_{11}H_{13}{}^{81}BrO_3$ 274.0028 and $C_{11}H_{13}{}^{79}BrO_3$ 272.0048, found 274.0025 and 272.0045.

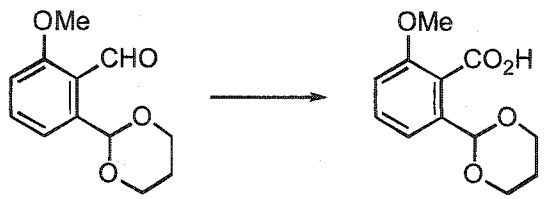
2-(1,3-Dioxan-2-yl)-6-methoxybenzaldehyde (13.6).



13.5 **13.6**

n-BuLi (2.91 mL, 2.5 M in hexanes) was added dropwise over 10 min to a stirred and cooled (-78 °C) solution of **13.5** (1.87 g, 6.86 mmol) in THF (20 mL). Stirring at -78 °C was continued for 20 min, and then DMF (10 mL) was added dropwise. The mixture was stirred for 4 h at -78 °C, the cold bath was removed and stirring was continued for 30 min. Saturated aqueous NH_4Cl (15 mL) was added and the mixture was extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 20% EtOAc-hexanes, gave **13.6** (1.39 g, 90%) as a white solid: mp 97.5-98.5 °C; FTIR (CH_2Cl_2, cast) 2953, 2864, 2740, 1684, 1602, 1089 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.43-1.49 (m, 1 H), 2.17-2.29 (m, 1 H), 3.89 (s, 3 H), 3.99-4.07 (m, 2 H), 4.23-4.28 (m, 2 H), 6.07 (s, 1 H), 6.94 (dd, *J* = 8.6, 2.6 Hz, 1 H), 7.23 (d, *J* = 2.6 Hz, 1 H), 7.85 (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 25.6 (t), 55.6 (q), 67.6 (t), 99.0 (d), 112.1 (d), 114.5 (d), 117.1 (d), 126.8 (s), 132.9 (d), 142.0 (s), 163.8 (s), 190.6 (d); exact mass *m/z* calcd for $C_{12}H_{14}O_4$ 222.0892, found 222.0892.

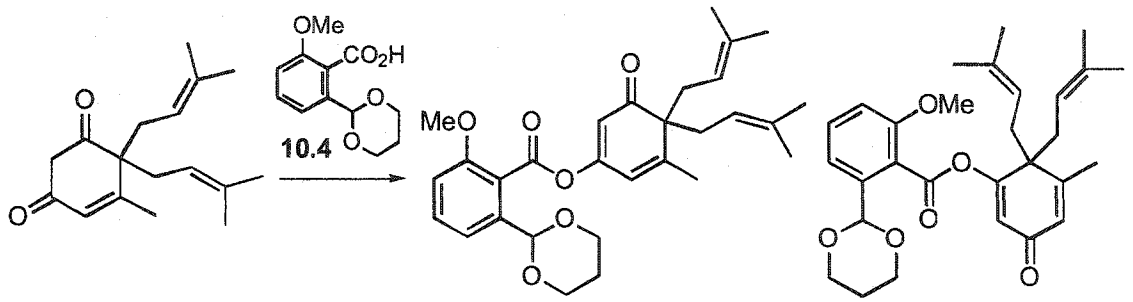
2-(1,3-Dioxan-2-yl)-6-methoxybenzoic Acid (10.4).



13.6 **10.4**

A solution of $NaClO_2$ (0.353 g, 3.90 mmol) and NaH_2PO_4 (0.538 g, 3.90 mmol) in water (4.5 mL) was added dropwise to a stirred solution of **13.6** (0.667 g, 3.00 mmol) in a mixture of *t*-BuOH (8 mL), CH_3CN (2.5 mL) and 2-methyl-2-butene (2.4 mL), and stirring was continued overnight. The solvent was evaporated to give a residue, which was diluted with water (8 ml) and extracted with hexanes (2 x 10 mL). The aqueous phase was acidified (pH = 2) with 5% hydrochloric acid, saturated with NaCl and extracted with Et_2O (2 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give **10.4** (0.707 g, 99%) as a white solid: mp 115-117 °C; FTIR (CH_2Cl_2, cast) 3500-2500, 1687, 1607 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.41-1.48 (m, 1 H), 2.16-2.31 (m, 1 H), 3.85 (s, 3 H), 4.00-4.09 (m, 2 H), 4.20-4.29 (m, 2 H), 6.34 (s, 1 H), 6.89 (dd, *J* = 8.7, 2.7 Hz, 1 H), 7.38 (d, *J* = 2.7 Hz, 1 H), 8.02 (d, *J* = 8.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 25.8 (t), 55.5 (q), 67.6 (t), 98.4 (d), 111.9 (d), 114.3 (d), 119.8 (s), 133.5 (d), 142.0 (s), 163.2 (s), 171.5 (s); exact mass *m/z* calcd for $C_{12}H_{14}O_5$ 238.0841, found 238.0841.

2-(1,3-Dioxan-2-yl)-6-methoxybenzoic Acid 5-Methyl-4,4-bis(3-methylbut-2-enyl)-3-oxocyclohexa-1,5-dienyl Ester (10.2) and 2-(1,3-dioxan-2-yl)-6-methoxybenzoic Acid 5-Methyl-6,6-bis(3-methylbut-2-enyl)-3-oxocyclohexa-1,4-dienyl Ester (14.1).



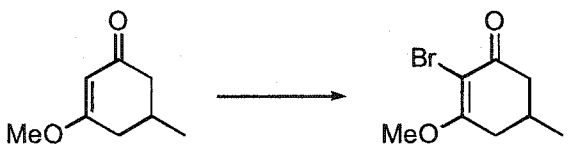
9.2 **10.2** **14.1**

Acid **10.4** (0.125 g, 0.525 mmol), 2-chloro-1-methylpyridinium iodide (0.141 g, 0.552 mmol) and Et_3N (0.18 mL, 1.28 mmol) were added in that order to a stirred solution of **9.2** (0.124 g, 0.477 mmol) in THF (9 mL). Stirring was continued overnight, and the solvent was evaporated to give a residue, which was diluted with EtOAc (30 mL). The mixture was washed with saturated aqueous NH_4Cl (5 mL) and water (5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 25 cm), using 15% EtOAc-hexanes, gave the faster-eluting isomer **10.2** (40 mg, 18%) and slower-eluting isomer **14.1** (78 mg, 34%).

Compound **10.2** had: FTIR (CH_2Cl_2, cast) 2970, 2923, 2853, 1735, 1606, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39-1.46 (m, 1 H), 1.57 (s, 6 H), 1.61 (s, 6 H), 1.97 (d, J = 1.3 Hz, 3 H), 2.14-2.28 (m, 1 H), 2.31 (dd, J = 14.3, 6.8 Hz, 2 H), 2.73 (dd, J = 14.4, 7.0 Hz, 2 H), 3.88 (s, 3 H), 3.96-4.05 (m, 2 H), 4.19-4.26 (m, 2 H), 4.76-4.83 (m, 2 H), 5.98 (d, J = 1.8 Hz, 1 H), 6.14-6.17 (m, 1 H), 6.26 (s, 1 H), 6.90 (dd, J = 8.7, 2.7 Hz, 1 H), 7.40 (d, J = 2.7 Hz, 1 H), 7.96 (d, J = 8.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.0 (q), 19.5 (q), 25.7 (q), 25.8 (t), 38.2 (t), 55.5 (q), 58.6 (s), 67.6 (t), 97.9 (d), 111.9 (d), 112.8 (d), 114.4 (d), 118.2 (d), 119.2 (s), 120.5 (d), 133.1 (d), 134.1 (s), 142.6 (s), 155.9 (s), 162.7 (s), 163.4 (s), 163.6 (s), 205.5 (s); exact mass m/z calcd for $C_{29}H_{36}O_6$ 480.2512, found 480.2510.

Compound **14.1** had: FTIR (CH_2Cl_2, cast) 2966, 2923, 2855, 1749, 1662, 1233 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.38-1.45 (m, 1 H), 1.54 (s, 6 H), 1.60 (s, 6 H), 1.91 (d, *J* = 1.2 Hz, 3 H), 2.11-2.25 (m, 1 H), 2.41 (dd, *J* = 15.1, 7.3 Hz, 2 H), 2.62 (dd, *J* = 15.1, 6.5 Hz, 2 H), 3.88 (s, 3 H), 3.94-4.04 (m, 2 H), 4.16-4.23 (m, 2 H), 4.74-4.82 (m, 2 H), 6.20-6.24 (m, 1 H), 6.26 (s, 1 H), 6.50 (d, *J* = 2.7 Hz, 1 H), 6.90 (dd, *J* = 8.7, 2.7 Hz, 1 H), 7.41 (d, *J* = 2.7 Hz, 1 H), 7.86 (d, *J* = 8.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.2 (q), 18.8 (q), 25.8 (q), 25.9 (t), 35.2 (t), 51.5 (s), 55.6 (q), 67.6 (t), 97.7 (d), 111.8 (d), 114.3 (d), 117.5 (d), 119.6 (d), 129.7 (d), 132.0 (d), 134.3 (s), 142.8 (s), 158.6 (s), 161.7 (s), 163.1 (s), 167.4 (s), 187.3 (s); exact mass *m/z* calcd for $C_{29}H_{36}O_6$ 480.2512, found 480.2506.

2-Bromo-3-methoxy-5-methylcyclohex-2-enone (17.1).



12.2 **17.1**

NBS (1.37 g, 7.70 mmol) was added in portions to a stirred and cooled (0 °C) solution of **12.2**[11] (0.982 g, 7.00 mmol) in CCl_4 (15 mL). The cold bath was removed and stirring was continued for 2 h. The solvent was evaporated to give a residue, which was diluted with CH_2Cl_2 (40 mL), and the mixture was washed with saturated aqueous $NaHCO_3$ (2 x 10 mL) and water (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 30% EtOAc-hexanes, gave **17.1** (1.165 g, 76%) as a white solid: mp 120-121.5 °C; FTIR (CH_2Cl_2, cast) 2954, 1651, 1575, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.13 (d, *J* = 5.6, 3 H), 2.14-2.34 (m, 3 H), 2.58-2.82 (m, 2 H), 3.94 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.7 (q), 28.1 (q), 34.6 (t), 44.7 (t), 55.3 (q), 102.6 (s), 172.2 (s), 190.9

(s); exact mass *m/z* calcd for $C_8H_{11}{}^{81}BrO_2$ 219.9922 and $C_8H_{11}{}^{79}BrO_2$ 217.9943, found 219.9917 and 217.9937.

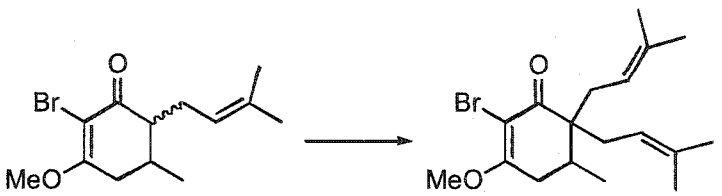
2-Bromo-3-methoxy-5-methyl-6-(3-methylbut-2-enyl)-cyclohex-2-enone (17.2).

17.1 **17.2**

A solution of **17.1** (0.269 g, 1.23 mmol) in THF (3 mL) was added dropwise over 10 min to a stirred and cooled (-78 °C) solution of LDA [freshly prepared from *i*-Pr_2NH (0.21 ml, 1.46 mmol) in THF (5 mL) by addition of *n*-BuLi (0.53 mL, 2.5 M in hexanes) at -78 °C, followed by stirring at -78 °C for 1 h]. Stirring at -78 °C was continued for 1 h, and then 3-methyl-2-butenyl bromide (0.21 mL, 1.85 mmol) was added. The cooling bath was left in place but not recharged, and stirring was continued overnight. The reaction was quenched with saturated aqueous NH_4Cl (5 mL), and the mixture was extracted with Et_2O (2 x 20 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 20% EtOAc-hexanes, gave **17.2** (0.257 g, 73%) as a 1:8 mixture of two diastereoisomers (^1H NMR): mp 85-87 °C; FTIR (CH_2Cl_2, cast) 2960, 2913, 1659, 1590, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.00 and 1.10 (d, *J* = 6.5 Hz, 3 H), 1.59, 1.62, 1.66 and 1.68 (s, 6 H), 2.08-2.84 (m, 6 H), 3.91 and 3.92 (s, 3 H), 4.98-5.12 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 17.9 (q), 19.7 (q), 25.8 (q), 27.0 (t), 30.1 (d), 33.0 (t), 52.6 (d), 55.3 (q), 102.3 (s), 120.7 (d), 133.4 (s), 170.2 (s), 192.6 (s); exact mass *m/z* calcd for $C_{13}H_{19}{}^{81}BrO_2$ 288.0548 and $C_{13}H_{19}{}^{79}BrO_2$ 286.0569, found

288.0546 and 286.0563.

2-Bromo-3-methoxy-5-methyl-6,6-bis(3-methylbut-2-enyl)cyclohex-2-enone (17.3).

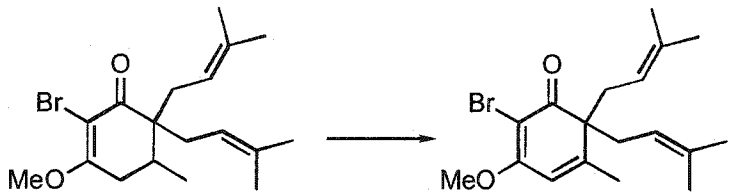


17.2 **17.3**

A solution of **17.2** (0.244 g, 0.850 mmol) in THF (2 mL) was added dropwise over 10 min to a stirred and cooled (-78 °C) solution of LDA [freshly prepared from *i*-Pr_2NH (0.14 mL, 1.0 mmol) in THF (5 mL) by addition of *n*-BuLi (0.37 mL, 2.5 M in hexanes) at -78 °C, followed by stirring at -78 °C for 1 h]. Stirring at -78 °C was continued for 1 h, and then 3-methyl-2-butenyl bromide (0.15 mL, 1.3 mmol) was added. The cooling bath was left in place but not recharged, and stirring was continued overnight. The reaction was quenched with saturated aqueous NH_4Cl (5 mL), and the mixture was extracted with Et_2O (2 x 20 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 25 cm), using 10% EtOAc-hexanes, gave **17.3** (0.22 g, 73%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2966, 2911, 1660, 1593, 1247 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.12 (d, *J* = 6.8 Hz, 3 H), 1.54 (s, 3 H), 1.58 (s, 3 H), 1.62 (s, 3 H), 1.68 (s, 3 H), 2.03 (dd, *J* = 15.0, 9.1 Hz, 1 H), 1.99 (dd, *J* = 16.2, 9.1 Hz, 1 H), 2.21 (dd, *J* = 14.7, 7.3 Hz, 1 H), 2.26-2.36 (m, 1 H), 2.46 (dd, *J* = 15.8, 9.1 Hz, 1 H), 2.58-2.66 (m, 1 H), 2.70 (dd, *J* = 17.8, 5.3 Hz, 1 H), 3.88 (s, 3 H), 4.83-4.89 (m, 1 H), 4.97-5.03 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 15.3 (q), 17.8 (q), 17.9 (q), 25.9 (q), 26.0 (q), 30.1 (t), 30.2 (t), 30.3 (d), 52.2 (s), 55.8 (q), 102.8 (s), 118.7 (d),

119.9 (d), 133.3 (s), 133.9 (s), 169.5 (s), 194.3 (s); exact mass *m/z* calcd for $C_{18}H_{27}{}^{81}BrO_2$ 356.1174 and $C_{18}H_{27}{}^{79}BrO_2$ 354.1195, found 356.1170 and 354.1184.

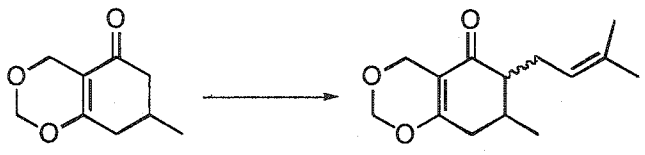
2-Bromo-3-methoxy-5-methyl-6,6-bis(3-methylbut-2-enyl)cyclohexa-2,4-dienone (16.2).



17.3 **16.2**

$(Me_3Si)_2NK$ (0.33 mL, 0.5 M in PhMe) was added dropwise over 5 min to a stirred and cooled (-78 °C) solution of **17.3** (51.1 mg, 0.144 mmol) in THF (3 mL). Stirring at -78 °C was continued for 1 h, and then a solution of PhSeCl (28.1 mg, 0.144 mmol) in THF (0.5 mL) was added dropwise. The cold bath was removed and stirring was continued for 2 h. H_2O_2 (15%, 2 mL) was added and stirring was continued for 1.5 h. The mixture was extracted with Et_2O (2 x 15 mL), and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 15% EtOAc-hexanes, gave **16.2** (28.9 mg, 57%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2969, 2914, 2856, 1645, 1539, 1274 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.54 (s, 12 H), 1.97 (d, *J* = 1.3 Hz, 3 H), 2.28 (dd, *J* = 14.4, 7.3 Hz, 2 H), 2.76 (dd, *J* = 14.4, 6.9 Hz, 2 H), 3.97 (s, 3 H), 4.57-4.64 (m, 1 H), 6.33 (d, *J* = 1.4, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.0 (q), 20.0 (q), 25.7 (q), 26.0 (q), 38.8 (t), 56.7 (q), 58.8 (s), 102.6 (s), 114.1 (d), 117.7 (d), 134.4 (s), 158.1 (s), 166.6 (s), 196.3 (s); exact mass *m/z* calcd for $C_{18}H_{25}{}^{81}BrO_2$ 354.1018 and $C_{18}H_{25}{}^{79}BrO_2$ 352.1038, found 354.1017 and 352.1037.

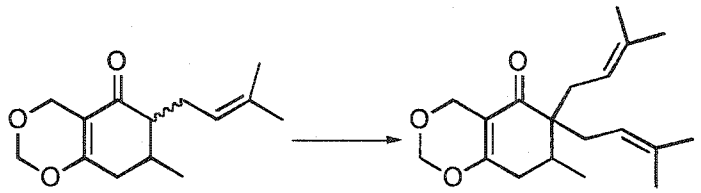
7-Methyl-6-(3-methylbut-2-enyl)-4,6,7,8-tetrahydro-benzo-[1,3]dioxin-5-one (19.2).



19.1 **19.2**

A solution of **19.1**[15] (0.835 g, 4.97 mmol) in THF (3 mL) was added dropwise over 15 min to a stirred and cooled (-78 °C) solution of LDA [freshly prepared from *i*-Pr_2NH (0.81 mL, 5.8 mmol) in THF (15 mL) by addition of *n*-BuLi (2.10 mL, 2.5 M in hexanes) at -78 °C, followed by stirring at -78 °C for 1 h]. Stirring at -78 °C was continued for 1 h, and then 3-methyl-2-butenyl bromide (0.81 mL, 7.5 mmol) was added. The cooling bath was left in place but not recharged, and stirring was continued overnight. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the mixture was extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 10% EtOAc-hexanes, gave **19.2** (0.985 g, 84%) as a 1:3 mixture of two diastereoisomers (^1H NMR): FTIR (CH_2Cl_2, cast) 2963, 2914, 2875, 1640, 1417, 1183 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.96 and 1.06 (d, J = 6.4 Hz, 3 H), 1.59, 1.62, 1.66 and 1.68 (s, 6 H), 2.00-2.60 (m, 6 H), 4.35-4.47 (m, 2 H), 4.96-5.15 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 17.7 (q), 17.8 (q), 19.8 (q), 24.3 (t), 25.8 (q), 26.4 (t), 30.0 (d), 30.4 (d), 34.0 (t), 34.7 (t), 50.4 (d), 52.1 (d), 62.8 (t), 62.9 (t), 91.3 (t), 91.4 (t), 110.6 (s), 110.7 (s), 121.1 (d), 121.7 (d), 132.9 (s), 133.0 (s), 167.8 (s), 197.6 (s); exact mass *m/z* calcd for $C_{14}H_{20}O_3$ 236.1413, found 236.1407.

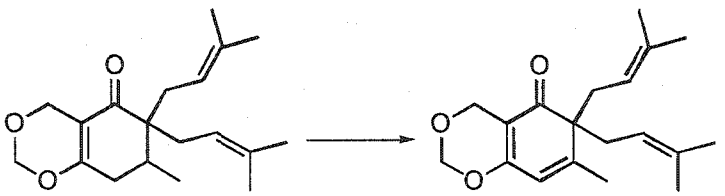
7-Methyl-6,6-bis(3-methylbut-2-enyl)-4,6,7,8-tetrahydrobenzo[1,3]dioxin-5-one (19.3).



19.2 **19.3**

A solution of **19.2** (0.985 g, 4.18 mmol) in THF (3 mL) was added dropwise over 15 min to a stirred and cooled (-78 °C) solution of LDA [freshly prepared from *i*-Pr_2NH (0.68 mL, 4.9 mmol) in THF (15 mL) by addition of *n*-BuLi (1.67 mL, 2.5 M in hexanes) at -78 °C, followed by stirring at -78 °C for 1 h]. Stirring at -78 °C was continued for 1 h, and then 3-methyl-2-butenyl bromide (0.73 mL, 6.3 mmol) was added. The cooling bath was left in place but not recharged, and stirring was continued overnight. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the mixture was extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 5% EtOAc-hexanes, gave **19.3** (0.983 g, 77%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2964, 2912, 1638, 1397, 1225 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.98 (d, J = 6.4 Hz, 3 H), 1.55 (s, 3 H), 1.58 (s, 3 H), 1.63 (s, 3 H), 1.66 (s, 3 H), 2.05 (dt, J = 14.6, 8.6, 2 H), 2.20-2.60 (m, 5 H), 4.36-4.45 (m, 2 H), 4.83-4.90 (m, 1 H), 5.00-5.06 (m, 1 H), 5.09 (AB q, $\Delta\nu_{AB}$ = 29.1 Hz, J = 5.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 15.3 (q), 17.7 (q), 17.8 (q), 25.9 (q), 26.0 (q), 29.7 (t), 31.5 (t), 32.5 (d), 32.9 (t), 51.0 (s), 63.2 (t), 91.2 (t), 110.6 (s), 119.1 (d), 120.2 (d), 132.9 (s), 133.5 (s), 166.9 (s), 199.5 (s); exact mass *m/z* calcd for $C_{19}H_{28}O_3$ 304.2039, found 304.2046.

7-Methyl-6,6-bis(3-methylbut-2-enyl)-4,6-dihydrobenzo-[1,3]dioxin-5-one (19.4).



19.3 **19.4**

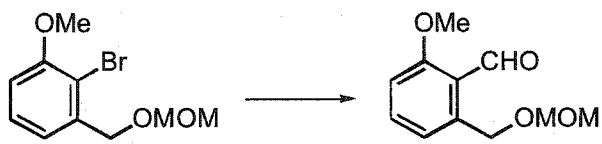
$(Me_3Si)_2NK$ (0.5 mL, 0.5 M in PhMe) was added dropwise over 5 min to a stirred and cooled (-78 °C) solution of **19.3** (66.7 mg, 0.219 mmol) in THF (2.5 mL). Stirring at -78 °C was continued for 1 h, and then a solution of PhSeCl (42 mg, 0.22 mmol) in THF (0.5 mL) was added dropwise. The cold bath was removed and stirring was continued for 2 h. H_2O_2 (15%, 2 mL) was added and stirring was continued for 1.5 h. The mixture was extracted with Et_2O (2 x 15 mL), and the combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 10% EtOAc-hexanes, gave **19.4** (36.5 mg, 55%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2969, 2911, 1656, 1598, 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.53 (s, 6 H), 1.57 (s, 6 H), 1.90 (d, *J* = 1.3 Hz, 3 H), 2.23 (dd, *J* = 14.4, 7.0, 2 H), 2.67 (dd, *J* = 14.4, 7.0, 2 H), 4.46 (s, 2 H), 4.62-4.69 (m, 1 H), 5.15 (s, 2 H), 5.97 (d, *J* = 1.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.0 (q), 19.2 (q), 25.7 (q), 37.9 (t), 57.3 (s), 62.8 (t), 91.3 (t), 108.7 (s), 118.2 (d), 119.0 (d), 133.8 (s), 155.2 (s), 164.0 (s), 200.6 (s); exact mass *m/z* calcd for $C_{19}H_{26}O_3$ 302.1882, found 302.1887.

2-Bromo-1-methoxy-3-(methoxymethoxymethyl)benzene (21.1).

13.3 **21.1**

i-Pr_2NEt (3.5 mL, 20 mmol), followed by $MeOCH_2Cl$ (1.5 mL, 20 mmol), was added dropwise to a stirred and cooled (0 °C) solution of **13.3**[14] (2.17 g, 10.0 mmol) in CH_2Cl_2 (50 mL). The cooling bath was left in place but not recharged, and stirring was continued overnight. The mixture was diluted with CH_2Cl_2 (40 mL), washed with 5% hydrochloric acid (20 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 10% EtOAc-hexanes, gave **21.1** (2.367 g, 91%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2937, 2886, 2837, 1474, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.42 (s, 3 H), 3.78 (s, 3 H), 4.61 (s, 2 H), 4.75 (s, 2 H), 6.69 (dd, *J* = 8.7, 3.1 Hz, 1 H), 7.05 (d, *J* = 3.1 Hz, 1 H), 7.40 (d, *J* = 8.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 55.4 (q), 55.5 (q), 68.8 (t), 96.2 (t), 112.9 (s), 114.6 (d), 114.7 (d), 133.1 (d), 138.4 (s), 159.1 (s); exact mass *m/z* calcd for $C_{10}H_{13}{}^{81}BrO_3$ 262.0028 and $C_{10}H_{13}{}^{79}BrO_3$ 260.0048, found 262.0032 and 260.0051.

2-Methoxy-6-(methoxymethoxymethyl)benzaldehyde (21.2).



21.1 **21.2**

n-BuLi (2.15 mL, 2.5 M in hexanes) was added dropwise over 10 min to a stirred and cooled (-78 °C) solution of **21.1** (1.30 g, 4.97 mmol) in THF (20 mL). Stirring at -78 °C was continued for 50 min, and then DMF (7.2 mL) was added dropwise. The cooling bath was left in place but not

recharged, and stirring was continued overnight. Saturated aqueous NH_4Cl (10 mL) was added and the mixture was extracted with Et_2O (2 x 40 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 20% EtOAc-hexanes, gave **21.2** (0.97 g, 93%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2943, 2842, 2700, 1687, 1602, 1568, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.40 (s, 3 H), 3.84 (s, 3 H), 4.76 (s, 2 H), 5.01 (s, 2 H), 6.91 (dd, J = 8.6, 2.6 Hz, 1 H), 7.19 (d, J = 2.6 Hz, 1 H), 7.78 (d, J = 8.6 Hz, 1 H), 10.0 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 55.6 (q), 66.7 (t), 96.3 (t), 112.4 (d), 113.5 (d), 126.8 (s), 135.8 (d), 143.4 (s), 164.1 (s), 191.1 (d); exact mass *m/z* calcd for $C_{11}H_{14}O_4$ 210.0892, found 210.0897.

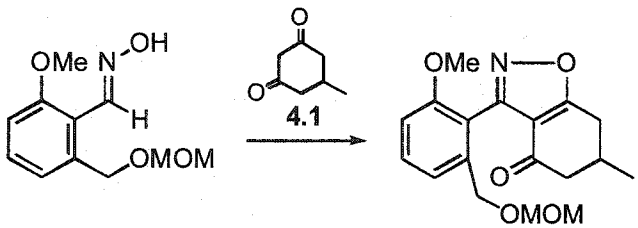
2-Methoxy-6-(methoxymethoxymethyl)benzaldehyde Oxime (21.3).

21.2 **21.3**

$NH_2OH \cdot HCl$ (0.190 g, 2.73 mmol) was added in portions to a stirred solution of $NaHCO_3$ (0.229 g, 2.73 mmol) in water (5 mL), and then a solution of **21.2** (0.546 g, 2.60 mmol) in EtOH (5 mL) was added dropwise. The mixture was stirred for 2 h and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 20% EtOAc-hexanes, gave **21.3** (0.527 g, 90%) as a white solid: mp 54-55 °C; FTIR (CH_2Cl_2, cast) 3372, 2838, 1606, 1504, 1268, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.41 (s, 3 H), 3.82 (s, 3 H), 4.70

(s, 4 H), 6.83 (dd, J = 8.6, 2.7 Hz, 1 H), 6.99 (d, J = 2.7 Hz, 1 H), 7.61 (d, J = 8.6 Hz, 1 H), 8.35 (s, 1 H), 8.44 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 55.3 (q), 55.6 (q), 67.1 (t), 95.8 (t), 113.5 (d), 114.3 (d), 122.8 (s), 129.1 (d), 138.2 (s), 148.7 (s), 160.7 (d); exact mass m/z calcd for $C_{11}H_{15}NO_4$ 225.1001, found 225.1002.

3-[2-Methoxy-6-(methoxymethoxymethyl)phenyl]-6,7-dihydro-5*H*-benzo[*d*]isoxazol-4-one (21.4).



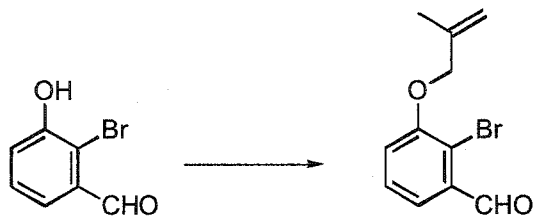
21.3 **21.4**

Pyridine (10 μL, 0.10 mmol), followed by NCS (0.148 g, 1.10 mmol), was added to a stirred solution of **21.3** (0.225 g, 1.00 mmol) in $CHCl_3$ (5 mL). The mixture was heated at 40 °C for 3 h, then cooled to room temperature, diluted with CH_2Cl_2 (20 mL), washed with water (2 x 5 mL), and dried ($MgSO_4$). Evaporation of the solvent gave the crude chloride (0.247g, 95%), which was used without purification for the next step.

A solution of the crude chloride (0.247 g, 0.95 mmol) in EtOH (1.5 mL) was added dropwise to a stirred mixture of **4.1**[10] (0.164 g, 1.25 mmol) and Et_3N (0.18 mL, 1.28 mmol) in EtOH (3 mL), and stirring was continued overnight. The mixture was diluted with EtOAc (30 mL), washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 25 cm), using 30% EtOAc-hexanes, gave **21.4** (0.12 g, 40%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2956, 2839, 1689, 1610, 1449, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.21 (d, J = 6.5 Hz, 3 H), 2.24-2.74 (m, 4 H), 3.12-3.20 (m, 1 H),

3.33 (s, 3 H), 3.84 (s, 3 H), 4.59 (s, 2 H), 4.62 (s, 2 H), 6.88 (dd, J = 8.5, 2.7 Hz, 1 H), 7.15 (d, J = 2.7 Hz, 1 H), 7.43 (d, J = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.7 (q), 30.4 (d), 31.2 (t), 46.8 (t), 55.3 (q), 55.4 (q), 66.8 (t), 95.8 (t), 112.6 (d), 113.3 (d), 114.8 (s), 117.8 (s), 132.1 (d), 139.4 (s), 158.7 (s), 161.0 (s), 181.1 (s), 191.4 (s); exact mass m/z calcd for $C_{18}H_{21}NO_5$ 331.1420, found 331.1419.

2-Bromo-3-(2-methylallyloxy)benzaldehyde (22.2).

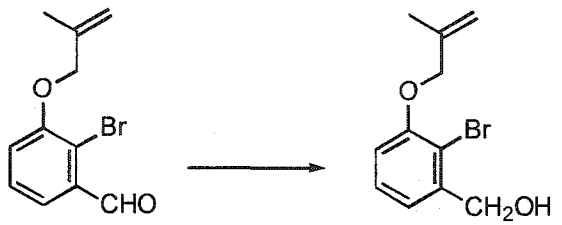


22.1 **22.2**

K_2CO_3 (1.66 g, 12.0 mmol), followed by 3-bromo-2-methylpropene (0.9 mL, 9 mmol), was added to a stirred solution of **22.1**[21] (1.21 g, 6.00 mmol) in DMF (25 mL). The mixture was heated at 60 °C for 2 h, and then cooled to room temperature. Brine (10 mL) was added and the resulting mixture was extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with water (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 10% EtOAc-hexanes, gave **22.2** (1.49 g, 97%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3080, 2975, 2916, 2865, 1694, 1590, 1453 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.80 (s, 3 H), 4.44 (s, 2 H), 4.97-5.01 (m, 1 H), 5.06-5.09 (m, 1 H), 7.04 (dd, J = 8.8, 3.2 Hz, 1 H), 7.40 (d, J = 3.2 Hz, 1 H), 7.51 (d, J = 8.8 Hz, 1 H), 10.3 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.3 (q), 72.1 (t), 113.3 (t), 113.8 (d), 117.9 (s), 123.5 (d), 133.9 (s), 134.5 (d), 139.9 (s), 158.3 (s), 191.7 (d); exact mass m/z calcd for $C_{11}H_{11}{}^{81}BrO_2$ 255.9922 and $C_{11}H_{11}{}^{79}BrO_2$ 253.9943,

found 255.9929 and 253.9942.

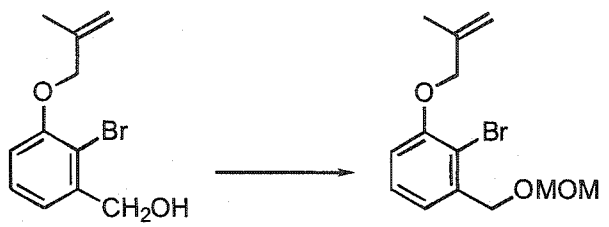
[2-Bromo-3-(2-methylallyloxy)phenyl]methanol (22.3).



22.2 **22.3**

$NaBH_4$ (0.768 g, 20.2 mmol) was added in portions to a stirred and cooled (0 °C) solution of **22.2** (1.72 g, 6.74 mmol) in a mixture of MeOH (15 mL) and CH_2Cl_2 (10 mL). The cold bath was removed and stirring was continued for 1.5 h. The reaction was quenched with water (10 mL), and the mixture was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 20% EtOAc-hexanes, gave **22.3** (1.61 g, 93%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3357, 3077, 2974, 2916, 1593, 1471 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.80 (s, 3 H), 1.97 (br s, 1 H), 4.41 (s, 2 H), 4.68 (s, 2 H), 4.96-4.98 (m, 1 H), 5.05-5.07 (m, 1 H), 6.71 (dd, *J* = 8.6, 3.1 Hz, 1 H), 7.06 (d, *J* = 3.1 Hz, 1 H), 7.38 (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.3 (q), 65.0 (t), 71.9 (t), 112.6 (s), 112.9 (t), 115.2 (d), 115.5 (d), 133.1 (d), 140.5 (s), 140.7 (s), 158.4 (s); exact mass *m/z* calcd for $C_{11}H_{13}{}^{81}BrO_2$ 258.0078 and $C_{11}H_{13}{}^{79}BrO_2$ 256.0099, found 258.0079 and 256.0099.

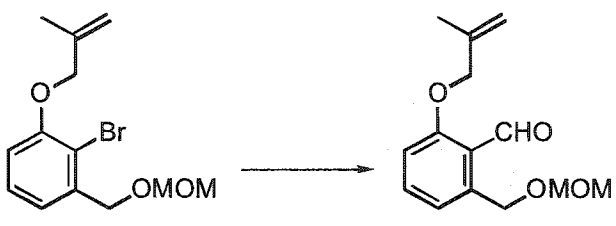
2-Bromo-1-(methoxymethoxymethyl)-3-(2-methylallyloxy)-benzene (22.4).



22.3 **22.4**

i-Pr_2NEt (3.0 mL, 18 mmol), followed by $MeOCH_2Cl$ (1.3 mL, 18 mmol), was added dropwise to a stirred and cooled (0 °C) solution of **22.3** (1.52 g, 5.92 mmol) in CH_2Cl_2 (30 mL). The cooling bath was left in place but not recharged, and stirring was continued overnight. The mixture was diluted with CH_2Cl_2 (30 mL), washed with 5% hydrochloric acid (15 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 10% EtOAc-hexanes, gave **22.4** (1.68 g, 94%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3078, 2932, 2885, 2822, 1473, 1053 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.82 (s, 3 H), 3.40 (s, 3 H), 4.40 (s, 2 H), 4.60 (s, 2 H), 4.74 (s, 2 H), 4.95-4.99 (m, 1 H), 5.04-5.08 (m, 1 H), 6.71 (dd, *J* = 8.7, 3.1 Hz, 1 H), 7.07 (d, *J* = 3.1 Hz, 1 H), 7.39 (d, *J* = 8.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 19.3 (q), 55.5 (q), 68.7 (t), 71.9 (t), 96.2 (t), 112.9 (t), 113.0 (s), 115.4 (d), 115.6 (d), 133.0 (d), 138.3 (s), 140.5 (s), 158.2 (s); exact mass *m/z* calcd for $C_{13}H_{17}{}^{81}BrO_3$ 302.0341 and $C_{13}H_{17}{}^{79}BrO_3$ 300.0361, found 302.0344 and 300.0360.

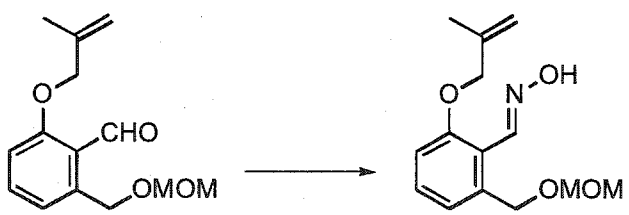
2-(Methoxymethoxymethyl)-6-(2-methylallyloxy)-benzaldehyde (22.5).



22.4 **22.5**

n-BuLi (2.4 mL, 2.5 M in hexanes) was added dropwise over 15 min to a stirred and cooled (-78 °C) solution of **22.4** (1.66 g, 5.51 mmol) in THF (20 mL). Stirring at -78 °C was continued for 1 h, and then DMF (8 mL) was added dropwise. The cooling bath was left in place but not recharged, and stirring was continued overnight. Saturated aqueous NH_4Cl (10 mL) was added and the resulting mixture was extracted with Et_2O (2 x 40 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 15% EtOAc-hexanes, gave **22.5** (0.979 g, 71%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2934, 2886, 2720, 1688, 1601, 1497, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.81 (s, 3 H), 3.40 (s, 3 H), 4.51 (s, 2 H), 4.67 (s, 2 H), 5.00 (s, 3 H), 5.07-5.10 (m, 1 H), 6.92 (dd, *J* = 8.4, 2.6 Hz, 1 H), 7.21 (d, *J* = 2.6 Hz, 1 H), 7.76 (d, *J* = 8.6 Hz, 1 H), 10.0 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.3 (q), 55.5 (q), 66.7 (t), 71.9 (t), 96.2 (t), 113.0 (d), 113.3 (t), 114.2 (d), 126.8 (s), 135.8 (d), 140.0 (s), 143.3 (s), 163.2 (s), 191.1 (d); exact mass *m/z* calcd for $C_{14}H_{18}O_4$ 250.1205, found 250.1204.

2-(Methoxymethoxymethyl)-6-(2-methylallyloxy)benzaldehyde Oxime (22.6).

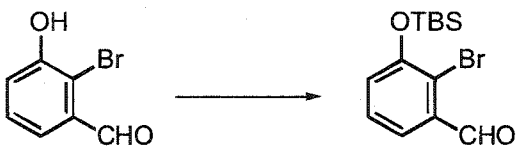


22.5 **22.6**

$NH_2OH \cdot HCl$ (0.447 g, 6.43 mmol) was added in portions to a stirred solution of $NaHCO_3$ (0.540 g, 6.43 mmol) in water (5 mL), and then a solution of **22.5** (0.946 g, 3.78 mmol) in EtOH (5 mL) was added dropwise. The mixture was stirred

for 4 h and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 20% EtOAc-hexanes, gave **22.6** (0.96 g, 96%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3369, 3079, 2944, 2887, 1605, 1453, 1268, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.81 (s, 3 H), 3.40 (s, 3 H), 4.44 (s, 2 H), 4.69 (s, 2 H), 4.71 (s, 2 H), 4.96-4.99 (m, 1 H), 5.06-5.09 (m, 1 H), 6.85 (dd, *J* = 8.5, 2.7 Hz, 1 H), 7.02 (d, *J* = 2.7 Hz, 1 H), 7.59 (d, *J* = 8.5 Hz, 1 H), 7.98 (br s, 1 H), 8.34 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.3 (q), 55.5 (q), 67.1 (t), 71.7 (t), 95.8 (t), 113.0 (t), 114.1 (d), 115.2 (d), 122.7 (s), 129.1 (d), 138.2 (s), 140.5 (s), 148.8 (d), 159.9 (d); exact mass *m/z* calcd for $C_{14}H_{19}NO_4$ 265.1314, found 265.1318.

2-Bromo-3-(*tert*-butyldimethylsilanyloxy)benzaldehyde (23.1).



22.1 **23.1**

t-$BuMe_2SiCl$ (1.15 g, 7.60 mmol) was added to a stirred and cooled (0 °C) mixture of **22.1**[21] (1.21 g, 6.00 mmol), imidazole (0.613 g, 9.00 mmol) and DMAP (36 mg, 0.30 mmol) in CH_2Cl_2 (30 mL). The cooling bath was left in place but not recharged, and stirring was continued overnight. The mixture was diluted with CH_2Cl_2 (30 mL), washed with 1 N hydrochloric acid (15 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 10% EtOAc-hexanes, gave **23.1** (1.863 g, 98%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2956, 2930, 2885, 2859, 1697, 1590, 1469, 1293 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.19 (s, 6 H), 0.96 (s,

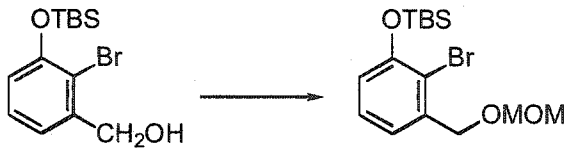
9 H), 6.93 (dd, J = 8.6, 3.1 Hz, 1 H), 7.34 (d, J = 3.1 Hz, 1 H), 7.47 (d, J = 8.6 Hz, 1 H), 10.26 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -4.5 (q), 18.1 (s), 25.5 (q), 118.3 (s), 120.4 (d), 127.6 (d), 134.1 (s), 134.6 (d), 155.6 (s), 191.7 (d); exact mass *m/z* calcd for $C_{13}H_{19}{}^{81}BrO_2Si$ 316.0317 and $C_{13}H_{19}{}^{79}BrO_2Si$ 314.0338, found 316.0317 and 314.0335.

[2-Bromo-3-(*tert*-butyldimethylsilanyloxy)]phenyl-methanol (23.2).

23.1 **23.2**

$NaBH_4$ (0.671 g, 17.7 mmol) was added in portions to a stirred and cooled (0 °C) solution of **23.1** (1.86 g, 5.90 mmol) in MeOH (20 mL). The cold bath was removed and stirring was continued for 1 h. The reaction was quenched with water (10 mL), and the resulting mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 20% EtOAc-hexanes, gave **23.2** (1.79 g, 95%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3352, 2957, 2927, 2885, 1471 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.19 (s, 6 H), 0.96 (s, 9 H), 1.94 (s, 1 H), 4.65 (s, 2 H), 6.63 (dd, J = 8.5, 3.0 Hz, 1 H), 6.96 (d, J = 3.0 Hz, 1 H), 7.34 (d, J = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -4.5 (q), 18.2 (s), 25.6 (q), 65.0 (t), 113.3 (s), 120.5 (d), 120.6 (d), 133.1 (s), 140.7 (s), 155.4 (s); exact mass *m/z* calcd for $C_{13}H_{21}{}^{81}BrO_2Si$ 318.0474 and $C_{13}H_{21}{}^{79}BrO_2Si$ 316.0494, found 318.0473 and 316.0489.

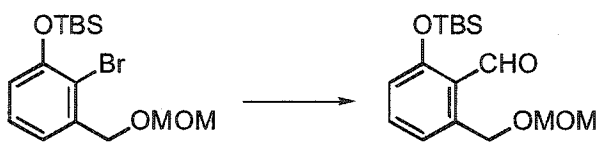
[2-Bromo-3-(methoxymethoxymethyl)phenoxy]*tert*-butyldimethylsilane (23.3).



23.2 **23.3**

i-Pr_2NEt (3.0 mL, 18 mmol), followed by $MeOCH_2Cl$ (1.3 mL, 18 mmol), was added dropwise to a stirred and cooled (0 °C) solution of **23.2** (1.79 g, 5.66 mmol) in CH_2Cl_2 (20 mL). The cooling bath was left in place but not recharged, and stirring was continued overnight. The mixture was diluted with Et_2O (70 mL), washed with 5% hydrochloric acid (15 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 10% EtOAc-hexanes, gave **23.3** (1.97 g, 97%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2954, 2930, 2885, 2822, 1471, 1057 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.18 (s, 6 H), 0.96 (s, 9 H), 3.41 (s, 3 H), 4.58 (s, 2 H), 4.73 (s, 2 H), 6.62 (dd, *J* = 8.6, 3.0 Hz, 1 H), 6.96 (d, *J* = 3.0 Hz, 1 H), 7.34 (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ -4.5 (q), 18.2 (s), 25.6 (q), 55.5 (q), 68.7 (t), 96.1 (t), 113.7 (s), 120.6 (d), 120.9 (d), 133.1 (d), 138.3 (s), 155.2 (s); exact mass *m/z* calcd for $C_{15}H_{25}{}^{81}BrO_3$ 362.07358 and $C_{15}H_{25}{}^{79}BrO_3$ 360.07562, found 362.07373 and 360.07562.

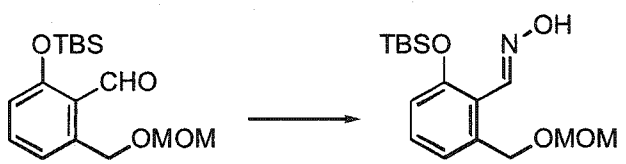
2-(*tert*-Butyldimethylsilanyloxy)-6-(methoxymethoxymethyl)benzaldehyde (23.4).



23.3 **23.4**

n-BuLi (2.1 mL, 2.5 M in hexanes) was added dropwise over 15 min to a stirred and cooled (-78 °C) solution of **23.3** (1.81 g, 5.00 mmol) in THF (20 mL). Stirring at -78 °C was continued for 1 h, and then DMF (7 mL) was added dropwise. The mixture was stirred for 1 h at -78 °C. Saturated aqueous NH_4Cl (10 mL) was added and the resulting mixture was extracted with Et_2O (2 x 40 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 15% EtOAc-hexanes, gave **23.4** (1.06 g, 68%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2954, 2886, 2720, 1693, 1601, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.24 (s, 6 H), 0.98 (s, 9 H), 3.50 (s, 3 H), 4.75 (s, 2 H), 4.98 (s, 2 H), 6.85 (dd, J = 8.3, 2.5 Hz, 1 H), 7.11 (d, J = 2.5 Hz, 1 H), 7.72 (d, J = 8.3 Hz, 1 H), 10.0 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ -4.3 (q), 18.2 (s), 25.6 (q), 55.5 (q), 66.5 (t), 96.2 (t), 118.6 (d), 119.5 (d), 127.2 (s), 135.6 (d), 143.2 (s), 161.0 (s), 191.2 (d); exact mass *m/z* calcd for $C_{16}H_{26}O_4Si$ 310.1600, found 310.1591.

2-(*tert*-Butyldimethylsilanyloxy)-6-(methoxymethoxymethyl)benzaldehyde Oxime (23.5).

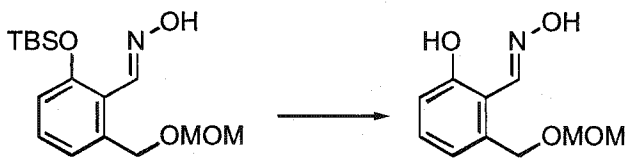


23.4 **23.5**

$NH_2OH \cdot HCl$ (0.475 g, 6.82 mmol) was added in portions to a stirred solution of $NaHCO_3$ (0.572 g, 6.82 mmol) in water (6 mL), and then a solution of **23.4** (1.06 g, 3.41 mmol) in EtOH (6 mL) was added dropwise. The mixture was stirred for 2 h, and extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with brine (10 mL),

dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 15% EtOAc-hexanes, gave **23.5** (1.08 g, 97%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3377, 2954, 2886, 2858, 1603, 1564 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.20 (s, 6 H), 0.96 (s, 9 H), 3.40 (s, 3 H), 4.66 (s, 2 H), 4.69 (s, 2 H), 6.77 (dd, *J* = 8.4, 2.6 Hz, 1 H), 6.92 (d, *J* = 2.6 Hz, 1 H), 7.54 (d, *J* = 8.4 Hz, 1 H), 7.68 (br s, 1 H), 8.34 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ -4.4 (q), 18.2 (s), 25.6 (q), 55.5 (q), 67.0 (t), 95.7 (t), 119.5 (d), 120.6 (d), 123.3 (s), 129.1 (d), 138.2 (s), 149.0 (d), 157.1 (s); exact mass *m/z* calcd for $C_{16}H_{27}NO_4Si$ 325.1709, found 325.1706.

2-Hydroxy-6-(methoxymethoxymethyl)benzaldehyde Oxime (23.7).

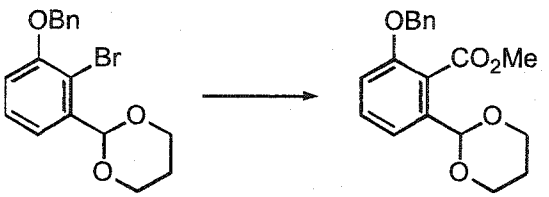


23.5 **23.7**

Bu_4NF (4.1 mL, 1.0 M in THF) was added to a stirred solution of **23.5** (1.08 g, 3.32 mmol) in THF (10 mL). Stirring was continued for 15 min, and then water (10 mL) was added. The mixture was extracted with EtOAc (3 x 25 mL), and the combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 30% EtOAc-hexanes, gave **23.7** (0.637 g, 91%) as a white solid: mp 63.5-64.5 °C; FTIR (CH_2Cl_2, cast) 3343, 3055, 2953, 2916, 2848, 1607, 1506 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.40 (s, 3 H), 4.68 (s, 2 H), 4.70 (s, 2 H), 6.76 (dd, *J* = 8.4, 2.7 Hz, 1 H), 6.94 (d, *J* = 2.7 Hz, 1 H), 7.54 (d, *J* = 8.4 Hz, 1 H), 8.31 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 55.6 (q), 67.0 (t), 95.8 (t),

114.9 (d), 115.6 (d), 122.6 (s), 129.7 (d), 138.6 (s), 149.1 (d), 157.0 (s); exact mass *m/z* calcd for $C_{10}H_{13}NO_4$ 211.0845, found 211.0850.

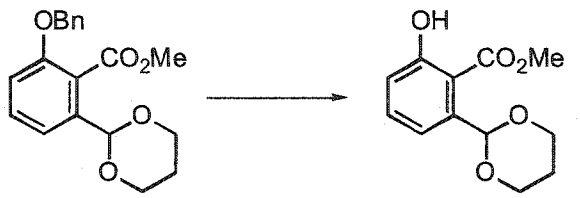
2-Benzyloxy-6-(1,3-]dioxan-2-yl)benzoic Acid Methyl Ester (25.3).



25.2 **25.3**

n-BuLi (3.3 mL, 2.5 M in hexanes) was added dropwise over 15 min to a stirred and cooled (-78 °C) solution of **25.2**[25] (2.71 g, 7.77 mmol) in THF (20 mL). Stirring was continued for 20 min, and then MeOCOCl (3.0 mL, 39 mmol) was added dropwise. Stirring at -78 °C was continued for 3 h. The cooling bath was removed and stirring was continued for 30 min. Saturated aqueous NH_4Cl (15 mL) was added and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 15% EtOAc-hexanes, gave **25.3** (1.74 g, 68%) as a white solid: mp 70-70.5 °C; FTIR (CH_2Cl_2, cast) 3032, 2952, 2853, 1719, 1605, 1266 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.40-1.46 (m, 1 H), 2.15-2.27 (m, 1 H), 3.86 (s, 3 H), 4.00-4.07 (m, 2 H), 4.20-4.26 (m, 2 H), 5.10 (s, 2 H), 6.36 (s, 1 H), 6.91 (dd, *J* = 8.7, 2.8 Hz, 1 H), 7.28-7.43 (m, 5 H), 7.49 (d, *J* = 2.8 Hz, 1 H), 7.87 (d, *J* = 8.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 26.0 (t), 51.9 (q), 67.6 (t), 70.1 (t), 98.1 (d), 112.7 (d), 114.7 (d), 120.9 (s), 127.5 (d), 128.0 (d), 128.5 (d), 132.4 (d), 136.3 (s), 141.7 (s), 161.7 (s), 166.8 (s); exact mass *m/z* calcd for $C_{19}H_{20}O_5$ 328.1311, found 328.1312.

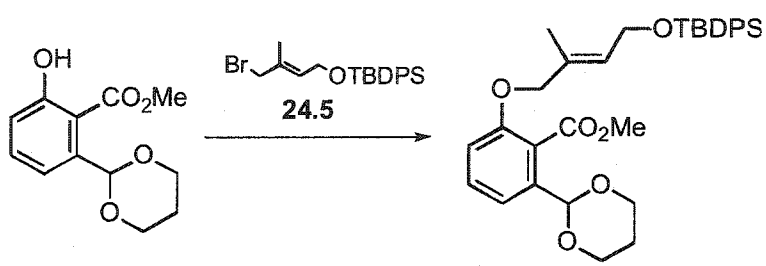
2-(1,3-Dioxan-2-yl)-6-hydroxybenzoic Acid Methyl Ester (24.4).



25.3 **24.4**

Pd-C (10%, 0.54 g) was added to a stirred solution of **25.3** (1.744 g, 5.32 mmol) in EtOAc (70 mL). The reaction flask was flushed with H_2, and the mixture was stirred under H_2 (balloon) for 3 h. The mixture was then filtered through a pad of silica gel. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 25 cm), using 30% EtOAc-hexanes, gave **24.4** (1.22 g, 96%) as a white solid: mp 132-133 °C; FTIR (CH_2Cl_2, cast) 3342, 2955, 2857, 1716, 1607, 1285 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.42-1.48 (m, 1 H), 2.17-2.28 (m, 1 H), 3.85 (s, 3 H), 4.01-4.09 (m, 2 H), 4.21-4.27 (m, 2 H), 6.08 (s, 1 H), 6.39 (s, 1 H), 6.73 (dd, *J* = 8.6, 2.7 Hz, 1 H), 7.34 (d, *J* = 2.7 Hz, 1 H), 7.81 (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 25.9 (t), 51.9 (q), 67.6 (t), 98.2 (d), 114.0 (d), 115.4 (d), 120.4 (s), 132.9 (d), 141.5 (s), 159.3 (s), 166.9 (s); exact mass *m/z* calcd for $C_{12}H_{14}O_5$ 238.0841, found 238.0835.

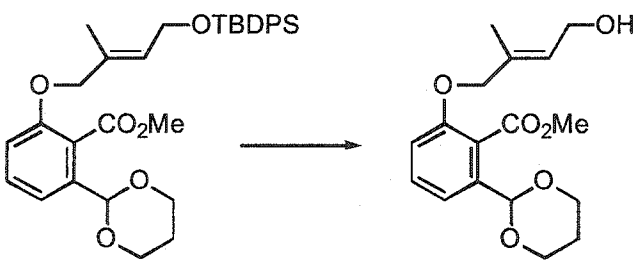
2-[(*E*)-4-(*tert*-Butyldiphenylsilanyloxy)-2-methylbut-2-enyloxy]-6-(1,3-dioxan-2-yl)benzoic Acid Methyl Ester (27.1).



24.4 **27.1**

A solution of **24.5**[23] (0.651 g, 1.61 mmol) in DMF (1 mL) was added dropwise to a stirred mixture of K_2CO_3 (0.296 g, 2.14 mmol) and **24.4** (0.261 g, 1.10 mmol) in DMF (12 mL). Stirring was continued for 4 h, and then water (10 mL) was added. The mixture was extracted with EtOAc (3 x 20 mL), and the combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 20% EtOAc-hexanes, gave **27.1** (0.597 g, 97%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3070, 2953, 2856, 1720, 1605, 1263 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.03 (s, 9 H), 1.39-1.45 (m, 1 H), 1.52 (s, 3 H), 2.15-2.26 (m, 1 H), 3.86 (s, 3 H), 3.99-4.07 (m, 2 H), 4.20-4.25 (m, 2 H), 4.27 (d, *J* = 6.1 Hz, 2 H), 4.42 (s, 2 H), 5.74-5.78 (m, 1 H), 6.35 (s, 1 H), 6.85 (dd, *J* = 8.7, 2.8 Hz, 1 H), 7.33-7.43 (m, 7 H), 7.64-7.68 (m, 4 H), 7.85 (d, *J* = 8.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 13.9 (q), 19.1 (s), 25.9 (t), 26.8 (q), 51.8 (q), 60.6 (t), 67.6 (t), 73.3 (t), 98.2 (d), 112.7 (d), 114.6 (d), 120.7 (s), 127.6 (d), 128.1 (d), 129.6 (d), 131.8 (s), 132.4 (d), 133.7 (s), 135.6 (d), 141.7 (s), 161.9 (s), 167.0 (s); exact mass *m/z* calcd for $C_{33}H_{40}O_6Si$ 560.2594, found 560.2565.

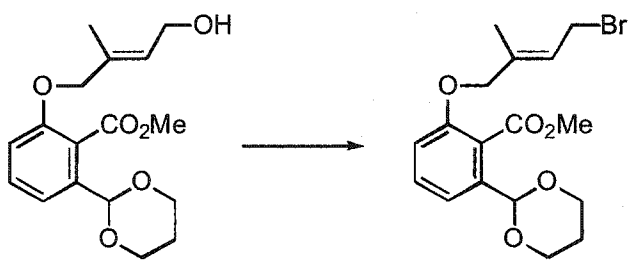
2-(1,3-Dioxan-2-yl)-6-[(*E*)-4-hydroxy-2-methylbut-2-enyloxy]benzoic Acid Methyl Ester (27.2).



27.1 **27.2**

Bu_4NF (1.2 mL, 1.0 M in THF) was added dropwise to a stirred solution of **27.1** (0.594 g, 1.06 mmol) in THF (5 mL). Stirring was continued for 30 min, and then saturated aqueous NH_4Cl (5 mL) was added. The mixture was extracted with EtOAc (2 x 20 mL), and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 50% EtOAc-hexanes, gave **27.2** (0.305 g, 89%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3421, 2952, 2856, 1719, 1605, 1269 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.36 (s, 1 H), 1.39-1.45 (m, 1 H), 1.74 (s, 3 H), 2.15-2.26 (m, 1 H), 3.85 (s, 3 H), 3.99-4.06 (m, 2 H), 4.18-4.24 (m, 4 H), 4.48 (s, 2 H), 5.75-5.80 (m, 1 H), 6.34 (s, 1 H), 6.86 (dd, *J* = 8.7, 2.8 Hz, 1 H), 7.38 (d, *J* = 2.8 Hz, 1 H), 7.85 (d, *J* = 8.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.0 (q), 25.9 (t), 51.9 (q), 59.0 (t), 67.6 (t), 73.1 (t), 98.2 (d), 112.6 (d), 114.9 (d), 120.8 (s), 127.3 (d), 132.4 (d), 133.7 (s), 141.6 (s), 161.6 (s), 166.8 (s); exact mass *m/z* calcd for $C_{17}H_{22}O_6$ 322.1416, found 322.1409.

2-[(*E*)-4-Bromo-2-methylbut-2-enyloxy]-6-(1,3-dioxan-2-yl)benzoic Acid Methyl Ester (24.3).

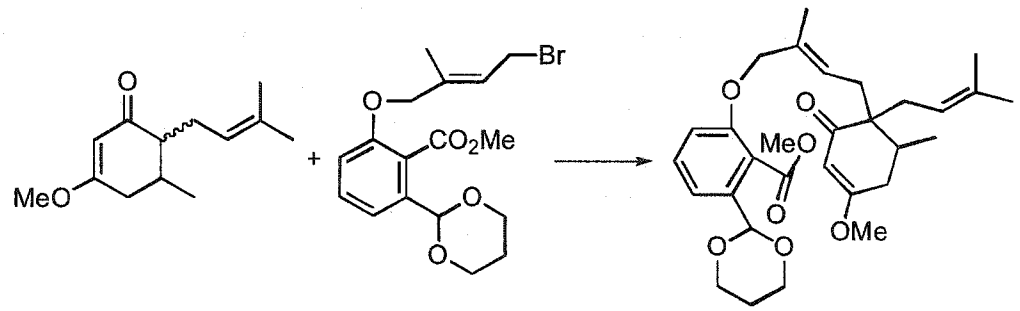


27.2 **24.3**

Ph_3P (0.268 g, 1.02 mmol), followed by CBr_4 (0.338 g, 1.02 mmol), was added to a stirred solution of **27.2** (0.253 g, 0.785 mmol) in CH_2Cl_2 (6 mL). Stirring was continued overnight and the solvent was evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm),

using 25% EtOAc-hexanes, gave **24.3** (0.249 g, 82%) as a white solid: mp 78.5-79 °C; FTIR (CH_2Cl_2, cast) 2951, 2853, 1719, 1605, 1267 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.39-1.45 (m, 1 H), 1.80 (s, 3 H), 2.14-2.26 (m, 1 H), 3.84 (s, 3 H), 3.99-4.06 (m, 4 H), 4.19-4.25 (m, 2 H), 4.48 (s, 2 H), 4.87-4.93 (m, 1 H), 6.33 (s, 1 H), 6.84 (dd, *J* = 8.8, 2.7 Hz, 1 H), 7.38 (d, *J* = 2.7 Hz, 1 H), 7.85 (d, *J* = 8.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 13.6 (q), 25.9 (t), 27.5 (t), 51.9 (q), 67.6 (t), 72.4 (t), 98.1 (d), 112.6 (d), 114.6 (d), 120.9 (s), 123.3 (d), 132.4 (d), 137.1 (s), 141.7 (s), 161.4 (s), 166.8 (s); exact mass *m/z* calcd for $C_{17}H_{21}{}^{81}BrO_5$ 386.0552 and $C_{17}H_{21}{}^{79}BrO_5$ 384.0572, found 386.0553 and 384.0571.

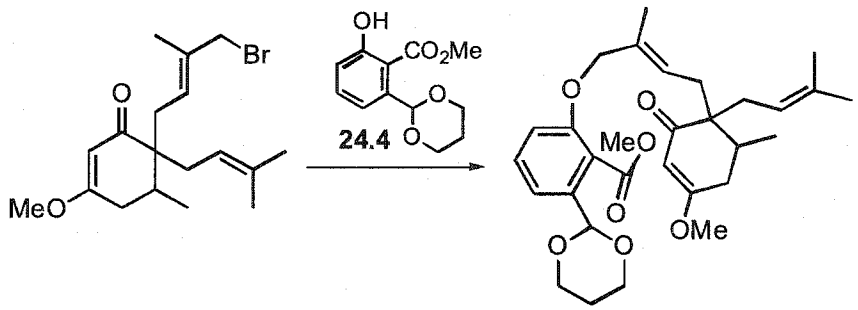
2-(1,3-dioxan-2-yl)-6-[(2*E*)-4-[4-methoxy-6-methyl-1-(3-methylbut-2-enyl)-2-oxocyclohex-3-enyl]-2-methylbut-2-enyloxy]benzoic Acid Methyl Ester (24.2).



4.2 **24.3** **24.2**

A solution of **4.2** (0.157 g, 0.756 mmol) in THF (0.5 mL) was added dropwise over 5 min to a stirred and cooled (-78 °C) solution of LDA [freshly prepared from *i*-Pr_2NH (0.12 mL, 0.86 mmol) in THF (5 mL) by addition of *n*-BuLi (0.32 mL, 2.5 M in hexanes) at -78 °C, followed by stirring at -78 °C for 1 h]. Stirring at -78 °C was continued for 1 h, and then HMPA (0.14 mL, 0.80 mmol), followed by a solution of **24.3** (0.289 g, 0.750 mmol) in THF (0.5 mL) was added. The cooling bath was left in place but not

recharged, and stirring was continued overnight. The reaction was quenched with saturated aqueous NH_4Cl (5 mL), and the mixture was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 2 cm), using 25% EtOAc-hexanes, gave **24.2** (0.230 g, 60%) as a 1:1 mixture of two diastereoisomers (^1H NMR).



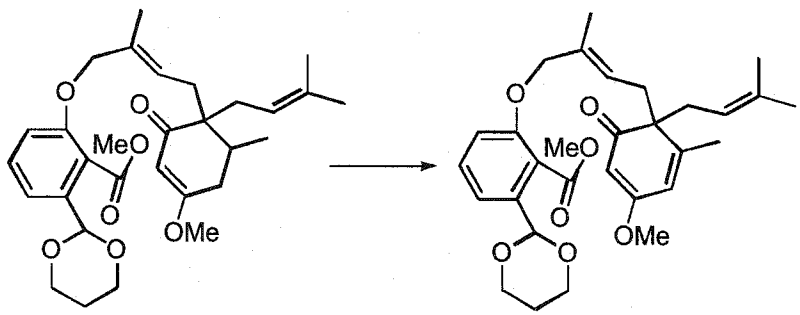
34.2 **24.2**

A solution of **34.2** (28 mg, 0.078 mmol) in DMF (0.5 mL) was added dropwise to a stirred mixture of K_2CO_3 (23 mg, 0.17 mmol) and **24.4** (19 mg, 0.081 mmol) in DMF (2 mL). Stirring was continued overnight, and then water (2 mL) was added, and the mixture was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 25 cm), using 25% EtOAc-hexanes, gave **24.2** (34 mg, 85%).

Compound **24.2** had: FTIR (CH_2Cl_2, cast) 2921, 2852, 1719, 1615, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.93 (d, J = 6.9 Hz, 1.5 H) and 0.95 (d, J = 6.4 Hz, 1.5 H), 1.37-1.43 (m, 1 H), 1.55, 1.64, 1.65 and 1.66 (s, 9 H), 2.01-2.68 (m, 8 H), 3.63 (s, 3 H), 3.83 (s, 3 H), 3.96-4.05 (m, 2 H), 4.17-4.23 (m, 2 H), 4.38 and 4.42 (s, 2 H), 4.86-5.06 (m, 1 H), 5.28 (s, 1 H), 5.30-5.53 (m, 1 H), 6.30 and 6.32 (s, 1 H), 6.80 and 6.83 (dd, J = 8.7, 2.8 Hz, 1 H), 7.32 and 7.35 (d, J = 2.8 Hz, 1 H), 7.80 and 7.83 (d, J = 8.7 Hz, 1 H);

^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 13.9 (q), 14.0 (q), 15.3 (q), 15.5 (q), 17.8 (q), 17.9 (q), 25.8 (t), 25.9 (q), 26.0 (q), 29.2 (t), 29.6 (t), 31.2 (t), 31.9 (t), 33.1 (d), 34.1 (t), 50.9 (s), 51.0 (s), 51.7 (q), 51.8 (q), 55.4 (q), 55.5 (q), 67.5 (t), 74.1 (t), 74.2 (t), 98.1 (d), 98.2 (d), 101.5 (d), 101.6 (d), 112.7 (d), 113.0 (d), 114.7 (d), 119.1 (d), 120.1 (d), 120.4 (s), 120.5 (s), 124.6 (d), 125.9 (d), 131.9 (s), 132.3 (d), 132.4 (s), 132.5 (d), 133.2 (s), 133.6 (s), 141.5 (s), 141.6 (s), 167.0 (s), 175.1 (s), 175.3 (s), 202.3 (s), 202.4 (s); exact mass *m/z* calcd for $C_{30}H_{40}O_7$ 512.2774, found 512.2766.

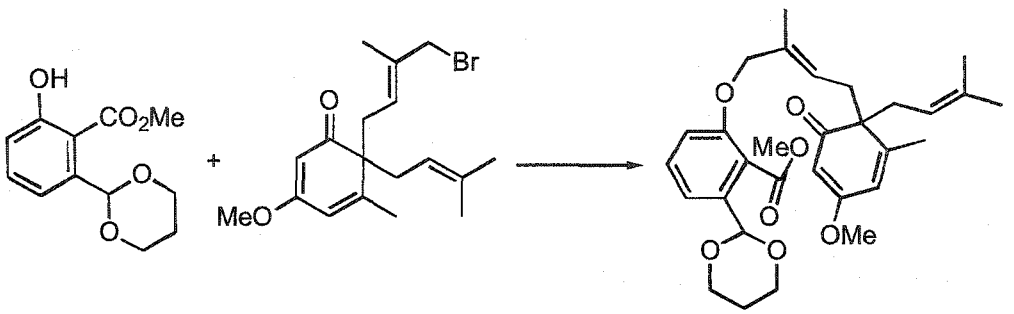
2-(1,3-Dioxan-2-yl)-6-[(2*E*)-4-[4-methoxy-6-methyl-1-(3-methylbut-2-enyl)-6-oxocyclohexa-2,4-dienyl]-2-methylbut-2-enyloxy]benzoic Acid Methyl Ester (24.1).



24.2 **24.1**

$(Me_3Si)_2NK$ (0.17 mL, 0.5 M in PhMe) was added dropwise over 5 min to a stirred and cooled (-78 °C) solution of **24.2** (37 mg, 0.073 mmol) in THF (1 mL). Stirring at -78 °C was continued for 1 h, and then a solution of PhSeCl (16 mg, 0.084 mmol) in THF (0.2 mL) was added dropwise. The cold bath was removed and stirring was continued for 1 h. H_2O_2 (30%, 1 mL) was added and stirring was continued for 1 h. The mixture was extracted with Et_2O (2 x 10 mL), and the combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using 30% EtOAc-

hexanes, gave **24.1** (11 mg, 30%) as a colorless oil.

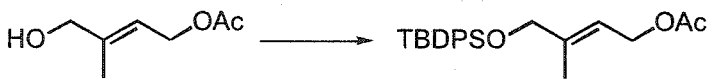


24.4 **29.1** **24.1**

Phenol **24.4** (0.153 g, 0.643 mmol), followed by K_2CO_3 (0.18 g, 1.3 mmol), was added to a stirred solution of **29.1** (0.217 g, 0.614 mmol) in DMF (5 mL). Stirring was continued overnight, and then water (5 mL) was added. The mixture was extracted with EtOAc (3 x 20 mL), and the combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 30% EtOAc-hexanes, gave **24.1** (0.281, 90%): FTIR (CH_2Cl_2, cast) 2921, 2852, 1719, 1615, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.38-1.44 (m, 1 H), 1.55 (s, 6 H), 1.67 (s, 3 H), 1.87 (d, *J* = 1.0 Hz, 3 H), 2.13-2.23 (m, 1 H), 2.26 (dd, *J* = 14.4, 7.0 Hz, 1 H), 2.32 (dd, *J* = 14.7, 7.2 Hz, 1 H), 2.68 (dd, *J* = 14.4, 7.0 Hz, 1 H), 2.76 (dd, *J* = 14.5, 6.8 Hz, 1 H), 3.67 (s, 3 H), 3.84 (s, 3 H), 3.98-4.05 (m, 2 H), 4.18-4.24 (m, 2 H), 4.31 (s, 2 H), 4.64-4.69 (m, 1 H), 5.05-5.11 (m, 1 H), 5.38 (d, *J* = 2.0 Hz, 1 H), 5.94-4.97 (m, 1 H), 6.31 (s, 1 H), 6.75 (dd, *J* = 8.8, 2.7 Hz, 1 H), 7.28 (d, *J* = 2.7 Hz, 1 H), 7.80 (d, *J* = 8.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.1 (q), 18.0 (q), 19.0 (q), 25.7 (q), 25.8 (t), 37.4 (t), 38.1 (t), 51.8 (q), 55.4 (q), 56.8 (s), 67.5 (t), 73.7 (t), 98.2 (d), 99.8 (d), 112.7 (d), 114.9 (d), 118.2 (d), 120.5 (s), 120.9 (d), 123.3 (d), 132.3 (d), 132.6 (s), 133.9 (s), 141.6 (s), 154.7 (s), 162.0 (s), 167.0 (s), 171.8 (s), 203.7 (s); exact mass (HR

electrospray) *m/z* calcd for $C_{30}H_{38}NaO_7$ (M + Na) 533.2510, found 533.2504.

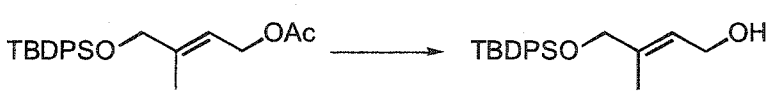
Acetic Acid (*E*)-4-(*tert*-butyldiphenylsilanyloxy)-3-methylbut-2-enyl Ester (30.3).



30.2 **30.3**

t-$BuPh_2SiCl$ (2.40 mL, 9.23 mmol) was added dropwise to a stirred and cooled (0 °C) mixture of **30.2**[27] (1.22 g, 8.45 mmol), Et_3N (1.40 mL, 10.1 mmol) and DMAP (60 mg, 0.42 mmol) in CH_2Cl_2 (30 mL). The cooling bath was left in place but not recharged, and stirring was continued overnight. The mixture was diluted with CH_2Cl_2 (40 mL), washed with 1 N hydrochloric acid (15 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 25 cm), using 10% EtOAc-hexanes, gave **30.3** (3.05 g, 94%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3071, 3049, 2958, 2857, 1741, 1428, 1232, 1112 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.06 (s, 9 H), 1.63-1.65 (m, 3 H), 2.06 (s, 3 H), 4.06 (s, 2 H), 4.64 (d, *J* = 7.1 Hz, 2 H), 5.68-5.74 (m, 1 H), 7.34-7.44 (m, 6 H), 7.64-7.68 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.6 (q), 19.2 (s), 21.0 (q), 26.8 (q), 60.9 (t), 67.9 (t), 117.4 (d), 127.6 (d), 129.6 (d), 133.5 (s), 135.5 (d), 140.3 (s), 171.0 (s); exact mass (HR electrospray) *m/z* calcd for $C_{23}H_{30}NaO_3Si$ (M + Na) 405.1862, found 405.1858.

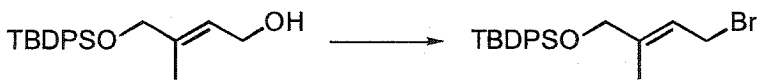
(*E*)-4-(*tert*-Butyldiphenylsilanyloxy)-3-methylbut-2-en-1-ol (30.4).



30.3 **30.4**

K_2CO_3 (2.21 g, 16.0 mmol) was added to a stirred solution of **30.3** (3.05 g, 7.98 mmol) in MeOH (20 mL). Stirring was continued for 30 min, and then saturated aqueous NH_4Cl (10 mL) was added. The mixture was extracted with Et_2O (3 x 40 mL), and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 20% EtOAc-hexanes, gave **30.4** (2.53 g, 93%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3319, 3070, 3049, 2930, 2857, 1428, 1188 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.07 (s, 9 H), 1.13 (s, 1 H), 1.61-1.63 (m, 3 H), 4.05-4.08 (m, 2 H), 4.19 (d, *J* = 7.9 Hz, 2 H), 5.70-5.76 (m, 1 H), 7.34-7.44 (m, 6 H), 7.65-7.69 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.5 (q), 19.2 (s), 26.8 (q), 59.0 (t), 68.0 (t), 122.5 (d), 127.6 (d), 129.6 (d), 133.6 (s), 135.5 (d), 137.9 (s); exact mass (HR electrospray) *m/z* calcd for $C_{21}H_{28}NaO_2Si$ (M + Na) 363.1756, found 363.1752.

***tert*-Butyldiphenyl[[(*E*)-4-bromo-2-methyl-2-butenyl]-oxy]silane (29.2).**

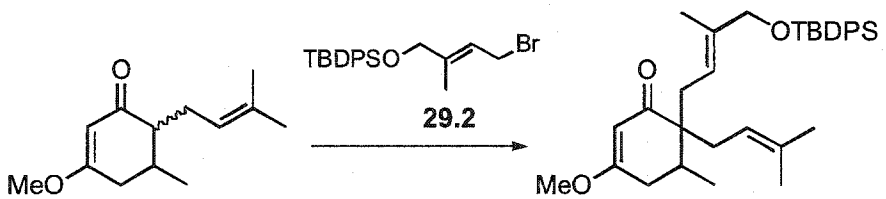


30.4 **29.2**

Et_3N (1.7 mL, 12 mmol), followed by MsCl (0.85 mL, 11 mmol), was added to a stirred and cooled (-40 °C) solution of **30.4** (2.93 g, 8.60 mmol) in CH_2Cl_2 (70 mL). Stirring at -40 °C was continued for 1 h, and then THF (20 mL) and LiBr (2.15 g, 21.5) were added. The mixture was stirred at 0 °C for 1.5 h, and then diluted with Et_2O (100 mL), washed with water (4 x 15 mL) and brine (20 mL), and dried ($MgSO_4$). Evaporation of the solvent gave crude bromide **29.2** (3.4 g, 98%), which was used without purification in the next step: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.07 (s, 9 H), 1.60-1.65 (m, 3 H), 4.02-4.12 (m, 4 H), 5.88-5.95 (m, 1 H), 7.34-7.46 (m, 6 H),

7.64-7.69 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 13.3 (q), 19.4 (s), 26.9 (q), 28.7 (t), 67.8 (t), 119.4 (d), 127.6 (d), 129.6 (d), 133.3 (s), 135.4 (d), 141.4 (s). A satisfactory mass spectrum could not be obtained and we did not measure the IR spectrum.

6-[(*E*)-4-(*tert*-Butyldiphenylsilanyloxy)-3-methylbut-2-enyl]-3-methoxy-5-methyl-6-(3-methylbut-2-enyl)cyclohex-2-enone (31.1).

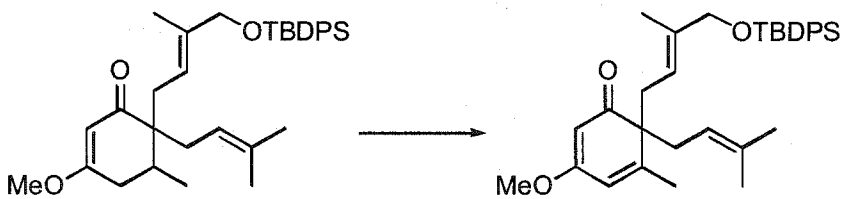


4.2 **31.1**

A solution of **4.2** (1.17 g, 5.60 mmol) in THF (4 mL) was added dropwise over 15 min to a stirred and cooled (-78 °C) solution of LDA [freshly prepared from *i*-Pr_2NH (0.90 mL, 6.44 mmol) in THF (20 mL) by addition of *n*-BuLi (3.80 mL, 1.6 M in hexanes) at -78 °C, followed by stirring at -78 °C for 1 h]. Stirring at -78 °C was continued for 1 h, and then HMPA (1.06 mL, 6.05 mmol), followed by a solution of **29.2** (3.4 g, 8.4 mmol) in THF (4 mL), was added. The cooling bath was left in place but not recharged, and stirring was continued overnight. The reaction was quenched with brine (20 mL), and the mixture was extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with water (20 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 25 cm), using 10% EtOAc-hexanes, gave **31.1** (2.71 g, 91%) as a 1:1.4 mixture of diastereoisomers (^1H NMR): FTIR (CH_2Cl_2, cast) 3070, 2959, 2855, 1653, 1618 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.98 (d, J = 6.7 Hz, 3 H), 1.02 and 1.05 (s, 9 H), 1.57, 1.61, 1.64 and 1.67 (s, 9 H),

2.01-2.68 (m, 7 H), 3.63 and 3.64 (s, 3 H), 4.01 and 4.03 (s, 2 H), 4.90-4.96 and 5.04-5.11 (m, 1 H), 5.24-5.29 and 5.44-5.51 (m, 1 H), 5.28 and 5.30 (s, 1 H), 7.32-7.46 (m, 6 H), 7.62-7.68 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 13.7 (q), 15.4 (q), 15.6 (q), 17.8 (q), 17.9 (q), 19.3 (s), 25.9 (q), 26.0 (q), 26.8 (q), 29.4 (t), 29.9 (t), 31.2 (t), 32.3 (t), 33.1 (d), 33.2 (d), 34.2 (t), 51.0 (s), 55.4 (q), 68.9 (t), 69.2 (t), 101.6 (d), 101.7 (d), 119.2 (d), 119.4 (d), 120.3 (d), 120.8 (d), 127.5 (d), 127.6 (d), 129.4 (d), 129.5 (d), 133.0 (s), 133.3 (s), 133.8 (s), 133.9 (s), 134.0 (s), 135.5 (d), 135.7 (s), 175.0 (s), 175.1 (s), 202.4 (s), 202.8 (s); exact mass (HR electrospray) *m/z* calcd for $C_{34}H_{46}NaO_3Si$ (M + Na) 553.3114, found 553.3116.

6-[(*E*)-4-(*tert*-Butyldiphenylsilanyloxy)-3-methylbut-2-enyl]-3-methoxy-5-methyl-6-(3-methylbut-2-enyl)cyclohexa-2,4-dienone (31.2).

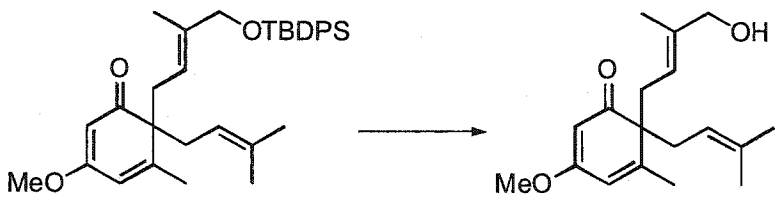


31.1 **31.2**

$(Me_3Si)_2NLi$ (0.23 mL, 1.0 M in THF) was added dropwise over 5 min to a stirred and cooled (-78 °C) solution of **31.1** (94.3 mg, 0.178 mmol) in THF (2.5 mL). Stirring at -78 °C was continued for 45 h, and then a solution of PhSeCl (41 mg, 0.214 mmol) in THF (0.2 mL) was added dropwise. The cold bath was removed and stirring was continued for 1 h. H_2O_2 (30%, 1 mL) was added and stirring was continued for 1.5 h. The mixture was extracted with Et_2O (2 x 20 mL), and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 15% EtOAc-

hexanes, gave **31.2** (35.5 mg, 38%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3070, 2959, 2856, 1658, 1582, 1218, 1112 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.98 (s, 9 H), 1.52 and 1.57 (s, 9 H), 1.91 (d, *J* = 1.2 Hz, 3 H), 2.29 (dd, *J* = 14.6, 7.0 Hz, 1 H), 2.33 (dd, *J* = 14.7, 6.8 Hz, 1 H), 2.72 (dd, *J* = 14.4, 7.0 Hz, 1 H), 2.78 (dd, *J* = 14.6, 7.0 Hz, 1 H), 3.60 (s, 3 H), 3.91 (s, 2 H), 4.68-4.73 (m, 1 H), 5.14-5.20 (m, 1 H), 5.39 (d, *J* = 2.0 Hz, 1 H), 5.98-6.01 (m, 1 H), 7.32-7.43 (m, 6 H), 7.57-7.63 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 13.7 (q), 18.0 (q), 19.1 (q), 19.2 (s), 25.7 (q), 26.7 (q), 37.5 (t), 38.3 (t), 55.3 (q), 57.1 (s), 68.0 (t), 99.9 (d), 117.6 (d), 118.4 (d), 120.8 (d), 127.5 (d), 127.6 (d), 129.5 (d), 133.6 (s), 133.7 (s), 133.8 (s), 135.4 (d), 135.5 (d), 135.7 (s), 155.1 (s), 171.7 (s), 204.0 (s); exact mass (HR electrospray) *m/z* calcd for $C_{34}H_{44}NaO_3Si$ (M + Na) 551.2957, found 551.2959.

6-[(*E*)-4-Hydroxy-3-methylbut-2-enyl)]-3-methoxy-5-methyl-6-(3-methylbut-2-enyl)cyclohexa-2,4-dienone (31.3).



31.2 **31.3**

Bu_4NF (3.60 mL, 1.0 M in THF) was added dropwise to a stirred solution of **31.2** (1.57 g, 2.97 mmol) in THF (20 mL). Stirring was continued for 1.5 h, and then saturated aqueous NH_4Cl (15 mL) was added. The mixture was extracted with EtOAc (3 x 50 mL), and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 50% EtOAc-hexanes, gave **31.3** (0.8 g, 93%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3405, 2978, 2915, 2856, 1657, 1577, 1220 cm^{-1}; ^1H NMR ($CDCl_3$, 500

MHz) δ 1.33 (br s, 1 H), 1.56 (s, 6 H), 1.62 (s, 3 H), 1.90 (d, *J* = 1.3 Hz, 3 H), 2.25 (dd, *J* = 13.4, 7.0 Hz, 1 H), 2.27 (dd, *J* = 13.7, 7.0 Hz, 1 H), 2.66 (dd, *J* = 14.4, 7.0 Hz, 1 H), 2.72 (dd, *J* = 14.7, 7.0 Hz, 1 H), 3.72 (s, 3 H), 3.85 (s, 2 H), 4.64-4.69 (m, 1 H), 4.93-4.98 (m, 1 H), 5.38 (d, *J* = 2.0 Hz, 1 H), 5.98 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.0 (q), 18.0 (q), 19.1 (q), 37.2 (t), 38.1 (t), 55.5 (q), 57.0 (s), 68.6 (t), 99.8 (d), 118.2 (d), 120.0 (d), 120.8 (d), 133.8 (s), 137.1 (s), 155.0 (s), 171.8 (s), 203.8 (s); exact mass *m/z* calcd for $C_{18}H_{26}O_3$ 290.1882, found 290.1885.

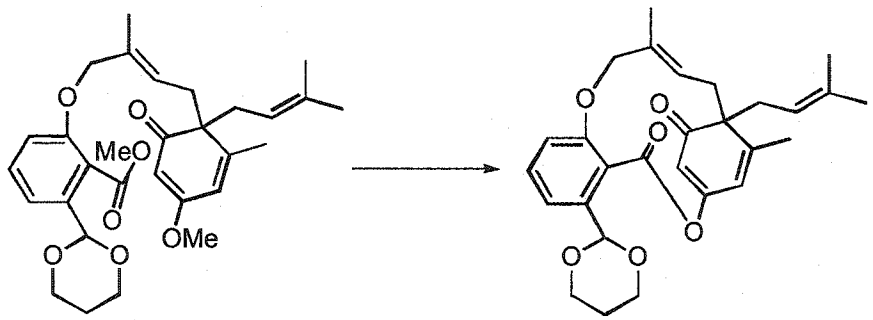
6-[(*E*)-4-Bromo-3-methylbut-2-enyl]-3-methoxy-5-methyl-6-(3-methylbut-2-enyl)cyclohexa-2,4-dienone (29.1).

31.3 **29.1**

Ph_3P (0.303 g, 1.16 mmol), followed by CBr_4 (0.384 g, 1.16 mmol), was added to a stirred solution of **31.3** (0.26 g, 0.89 mmol) in CH_2Cl_2 (6 mL). Stirring was continued overnight and the solvent was evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 15% EtOAc-hexanes, gave **29.1** (0.22 g, 70%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2921, 2854, 1658, 1581, 1219 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.55 (s, 6 H), 1.70 (s, 3 H), 1.89 (d, *J* = 1.3 Hz, 3 H), 2.21-2.29 (m, 2 H), 2.65-2.74 (m, 2 H), 3.70 (s, 3 H), 3.80 (s, 2 H), 4.63-4.69 (m, 1 H), 5.12-5.18 (m, 1 H), 5.40 (d, *J* = 2.1 Hz, 1 H), 6.00 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 15.0 (q), 18.0 (q), 19.1 (q), 25.7 (q), 37.7 (t), 37.8 (t), 55.5 (q), 56.8 (s), 99.8 (d), 118.1 (d), 121.0 (d), 125.4 (d), 134.0 (s), 134.1 (s), 154.4 (s), 171.7 (s), 203.5 (s); exact mass *m/z* calcd

for $C_{18}H_{25}{}^{81}BrO_2$ 354.1018 and $C_{18}H_{25}{}^{79}BrO_2$ 352.1038, found 354.1005 and 352.1038.

(12*E*)-5-(1,3-Dioxan-2-yl)-12,19-dimethyl-15-(3-methyl-but-2-enyl)-2,10-dioxatricyclo[13.2.2.0^{4,9}]nonadeca-1(17),4,6,8,12,18-hexaene-3,16-dione (33.2, major isomer).



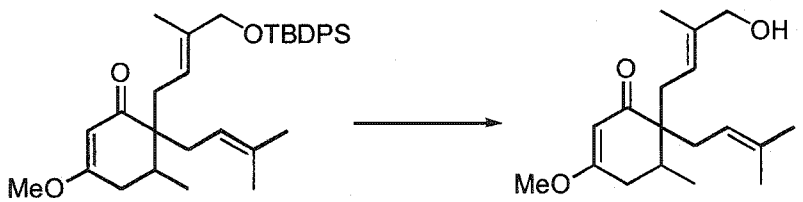
24.1 **33.2**

Aqueous NaOH (10%, 0.2 mL) was added to a stirred solution of **24.1** (47.8 mg, 0.094 mmol) in MeOH (1 mL). The mixture was heated at 85 °C overnight, and then allowed to cool to room temperature, diluted with water (3 mL), acidified (pH = 1) with 5% hydrochloric acid, and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$). Evaporation of the solvent gave crude acid (45.2 mg, ca 100%), which was used without purification in the next step.

Et_3N (60 μL, 0.43 mmol), followed by $SOCl_2$ (7.4 μL, 0.10 mmol), was added to a stirred solution of the crude acid (45.2 mg, 0.094 mmol) in PhMe (20 mL). The mixture was refluxed for 24 h, and then cooled to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 20 cm), using 20% EtOAc-hexanes, gave **33.2** (11.8 mg, 27%) as a 1:9 mixture of isomers (^1H NMR): FTIR (CH_2Cl_2, cast) 2918, 1725, 1655, 1273 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) (signals for major isomer) δ 1.42 (s, 3 H), 1.62 (s, 3 H), 1.66 (s, 3 H), 1.69-1.77 (m, 1 H), 2.04 (d, J = 1.3 Hz, 3 H), 2.10-2.18 (m, 1

H), 2.24-2.33 (m, 2 H), 2.64 (dd, *J* = 13.2, 11.3 Hz, 1 H), 3.01 (dd, *J* = 14.8, 6.0 Hz, 1 H), 3.93-4.02 (m, 1 H), 4.09 (dt, *J* = 11.3, 4.0 Hz, 1 H), 4.40-4.70 (m, 4 H), 5.07 (s, 1 H), 5.16-5.23 (m, 1 H), 5.36-5.44 (m, 1 H), 6.30-6.34 (m, 1 H), 6.59 (s, 1 H), 6.64 (d, *J* = 2.4 Hz, 1 H), 6.91 (dd, *J* = 8.5, 2.4 Hz, 1 H), 7.69 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) (signals for major isomer) δ 12.1 (q), 18.1 (q), 19.3 (q), 25.7 (q), 26.5 (t). 34.4 (t), 39.4 (t), 57.6 (s), 65.7 (t), 73.7 (t), 73.9 (t), 103.3 (d), 104.9 (d), 110.8 (d), 117.8 (d), 119.3 (d), 120.8 (d), 122.1 (d), 124.0 (s), 131.9 (d), 133.8 (s), 135.5 (s), 136.6 (s), 154.5 (s), 160.2 (s), 168.5 (s), 168.6 (s), 203.3 (s); exact mass (HR electrospray) *m/z* calcd for $C_{28}H_{32}NaO_6$ (M + Na) 487.2097, found 487.2092.

6-[(*E*)-4-Hydroxy-3-methylbut-2-enyl]-3-methoxy-5-methyl-6-(3-methylbut-2-enyl)cyclohex-2-enone (34.1).

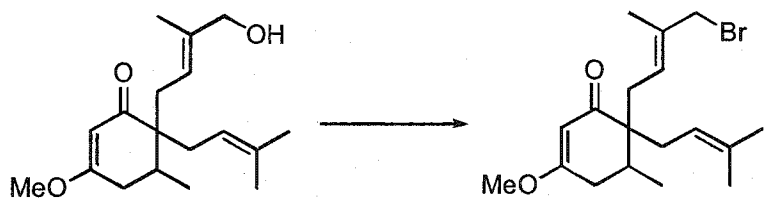


31.1 **34.1**

Bu_4NF (2.0 mL, 1.0 M in THF) was added dropwise to a stirred solution of **31.1** (0.928 g, 1.75 mmol) in THF (8 mL). Stirring was continued for 1.5 h, and then saturated aqueous NH_4Cl (10 mL) was added. The mixture was extracted with EtOAc (2 x 30 mL), and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 30% EtOAc-hexanes, gave **34.1** (0.466 g, 91%) as a 1:1.4 mixture of diastereoisomers (^1H NMR): FTIR (CH_2Cl_2, cast) 3417, 2914, 1648, 1615 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.94 (d, *J* = 6.7 Hz, 3 H), 1.54,

1.59, 1.62 and 1.64 (s, 9 H), 1.91 (br s, 1 H), 1.98-2.61 (m, 7 H), 3.63 (s, 3 H), 3.90 and 3.93 (s, 2 H), 4.83-4.89 and 4.99-5.05 (m, 1 H), 5.14-5.20 and 5.30-5.35 (m, 1 H), 5.26 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 13.8 (q), 15.4 (q), 15.6 (q), 17.8 (q), 17.9 (q), 25.9 (q), 26.0 (q), 28.8 (t), 29.5 (t), 31.1 (t), 31.5 (t), 33.0 (d), 33.1 (d), 34.0 (t), 34.1 (t), 50.9 (s), 51.0 (s), 55.4 (q), 55.5 (q), 68.9 (t), 69.0 (t), 101.5 (d), 101.6 (d), 119.1 (d), 120.2 (d), 120.8 (d), 122.0 (d), 133.0 (s), 133.5 (s), 136.4 (s), 136.9 (s), 175.2 (s), 175.3 (s), 202.6 (s); exact mass *m/z* calcd for $C_{18}H_{28}O_3$ 292.2039, found 292.2044.

6-[(*E*)-4-Bromo-3-methylbut-2-enyl)]-3-methoxy-5-methyl-6-(3-methylbut-2-enyl)cyclohex-2-enone (34.2).

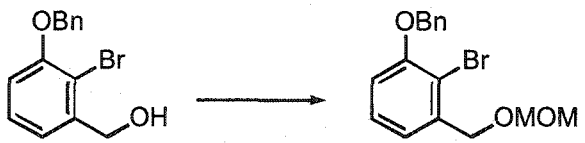


34.1 **34.2**

Ph_3P (47.4 mg, 0.181 mmol), followed by CBr_4 (61.0 mg, 0.181 mmol), was added to a stirred solution of **34.1** (45.7 mg, 0.157 mmol) in CH_2Cl_2 (4 mL). Stirring was continued for 1.5 h and the solvent was evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 15% EtOAc-hexanes, gave **34.2** (27.6 mg, 50%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2964, 2915, 1649, 1616 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.96 (d, J = 6.7 Hz, 3 H), 1.56 (s, 3 H), 1.62 and 1.65 (s, 3 H), 1.73 (s, 3 H), 2.00-2.65 (m, 7 H), 3.64 (s, 3 H), 3.89 and 3.92 (s, 2 H), 4.83-4.89 and 4.98-5.04 (m, 1 H), 5.30 (s, 1 H), 5.36-5.43 and 5.53-5.59 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.8 (q), 14.9 (q), 15.3 (q), 15.4 (q), 17.8 (q), 17.9 (q), 25.9 (q), 26.0 (q), 29.5 (t), 30.1 (t), 31.7 (t), 32.0 (t), 33.0 (d),

33.3 (d), 34.1 (t), 41.7 (t), 41.8 (t), 51.0 (s), 51.1 (s), 55.5 (q), 101.5 (d), 101.6 (d), 118.9 (d), 119.9 (d), 126.8 (d), 127.8 (d), 133.2 (s), 133.3 (s), 133.6 (s), 133.8 (s), 175.3 (s), 175.4 (s), 202.2 (s), 202.3 (s); exact mass *m/z* calcd for $C_{18}H_{27}{}^{81}BrO_2$ 356.1174 and $C_{18}H_{27}{}^{79}BrO_2$ 354.1195, found 356.1157 and 354.1189.

1-Benzyloxy-2-bromo-3-(methoxymethoxymethyl)benzene (36.2).



36.1 **36.2**

i-Pr_2NEt (2.81 mL, 16.2 mmol), followed by $MeOCH_2Cl$ (1.21 mL, 16.2 mmol), was added dropwise to a stirred and cooled (0 °C) solution of **36.1**[24,29] (2.37 g, 8.10 mmol) in CH_2Cl_2 (50 mL). The cooling bath was left in place but not recharged, and stirring was continued overnight. The mixture was diluted with CH_2Cl_2 (40 mL), washed with 5% hydrochloric acid (20 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 10% EtOAc-hexanes, gave **36.2** (2.605 g, 95%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3065, 3032, 2933, 2884, 2822, 1471 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.41 (s, 3 H), 4.61 (s, 2 H), 4.74 (s, 2 H), 5.05 (s, 2 H), 6.76 (dd, *J* = 8.8, 3.1 Hz, 1 H), 7.14 (d, *J* = 3.1 Hz, 1 H), 7.28-7.43 (m, 6 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 55.6 (q), 68.7 (t), 70.3 (t), 96.2 (t), 113.1 (s), 115.5 (d), 115.6 (d), 127.4 (d), 128.0 (d), 128.5 (d), 133.0 (d), 136.5 (s), 138.4 (s), 158.1 (s); exact mass *m/z* calcd for $C_{16}H_{17}{}^{81}BrO_3$ 338.0341 and $C_{16}H_{17}{}^{79}BrO_3$ 336.0361, found 338.0348 and 336.0365.

2-Benzyloxy-6-(methoxymethoxymethyl)benzoic Acid Methyl Ester (36.3).

36.2 **36.3**

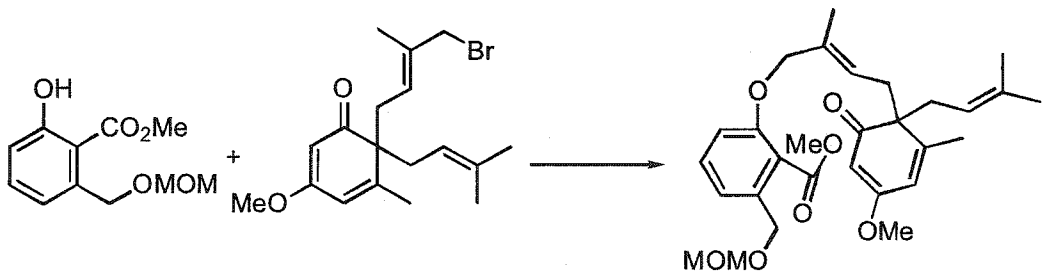
n-BuLi (0.38 mL, 2.5 M in hexanes) was added dropwise over 5 min to a stirred and cooled (-78 °C) solution of **36.2** (0.318 g, 0.944 mmol) in THF (4 mL). Stirring was continued for 40 min, and then MeOCOCl (0.37 mL, 4.7 mmol) was added dropwise. Stirring at -78 °C was continued for 3 h, and then the cooling bath was removed and stirring was continued for 1 h. Saturated aqueous NH_4Cl (5 mL) was added, and the mixture was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 10% EtOAc-hexanes, gave **36.3** (0.215 g, 72%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2949, 2885, 2822, 1713, 1603, 1268 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.38 (s, 3 H), 3.84 (s, 3 H), 4.74 (s, 2 H), 5.00 (s, 2 H), 5.12 (s, 2 H), 6.87 (dd, J = 8.7, 2.8 Hz, 1 H), 7.28-7.45 (m, 6 H), 7.96 (d, J = 8.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 51.7 (q), 55.4 (q), 67.4 (t), 70.0 (t), 96.3 (t), 112.7 (d), 113.6 (d), 120.1 (s), 127.5 (d), 128.1 (d), 128.6 (d), 133.0 (d), 136.3 (s), 143.6 (s), 162.1 (s), 166.8 (s); exact mass *m/z* calcd for $C_{18}H_{20}O_5$ 316.1311, found 316.1314.

2-Hydroxy-6-(methoxymethoxymethyl)benzoic Acid Methyl Ester (36.4).

36.3 **36.4**

Pd-C (10%, 0.273 g) was added to a stirred solution of **36.3** (0.847 g, 2.62 mmol) in EtOAc (20 mL). The reaction flask was flushed with H_2, and the mixture was stirred under H_2 (balloon) for 2.5 h. The mixture was filtered through a pad of silica gel. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 25 cm), using 25% EtOAc-hexanes, gave **36.4** (0.532 g, 88%) as a white solid: mp 93-94 °C; FTIR (CH_2Cl_2, cast) 3297, 3008, 2952, 2882, 1687, 1616, 1278 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.40 (s, 3 H), 3.83 (s, 3 H), 4.76 (s, 2 H), 4.99 (s, 2 H), 5.94 (s, 1 H), 6.74 (dd, *J* = 8.6, 2.7 Hz, 1 H), 7.15 (d, *J* = 2.7 Hz, 1 H), 7.91 (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 51.7 (q), 55.5 (q), 67.4 (t), 96.3 (t), 113.6 (d), 114.2 (d), 119.9 (s), 133.4 (d), 143.7 (s), 159.6 (s), 166.9 (s); exact mass (HR electrospray) *m/z* calcd for $C_{11}H_{14}NaO_5$ (M + Na) 249.0739, found 249.0740.

2-(Methoxymethoxymethyl)-6-[(*E*)-4-[4-methoxy-2-methyl-1-(3-methylbut-2-enyl)-6-oxocyclohexa-2,4-dienyl]-2-methylbut-2-enyloxy]benzoic Acid Methyl Ester (37.1).

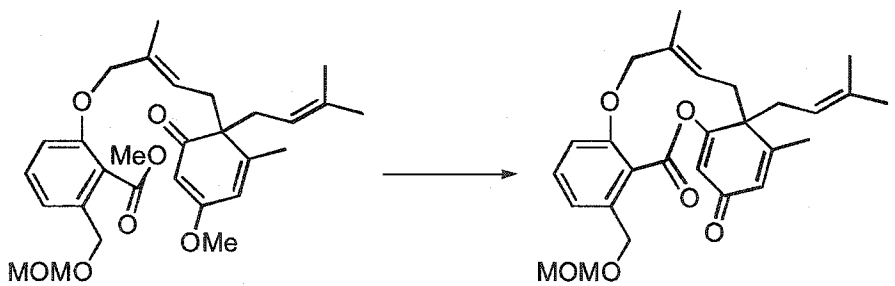


36.4 **29.1** **37.1**

Phenol **36.4** (0.124 g, 0.549 mmol), followed by K_2CO_3 (0.152 g, 1.10 mmol), was added to a stirred solution of **29.1** (0.183 g, 0.519 mmol) in DMF (5 mL). Stirring was continued overnight, and then water (5 mL) was added. The mixture was extracted with EtOAc (3 x 15 mL), and the

combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 30% EtOAc-hexanes, gave **37.1** (0.225, 87%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2947, 1713, 1658, 1580, 1267 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.54 (s, 6 H), 1.67 (s, 3 H), 1.86 (d, *J* = 1.3 Hz, 3 H), 2.24 (dd, *J* = 14.4, 7.0 Hz, 1 H), 2.32 (dd, *J* = 14.6, 7.2 Hz, 1 H), 2.67 (dd, *J* = 14.4, 7.0 Hz, 1 H), 2.76 (dd, *J* = 14.4, 6.8 Hz, 1 H), 3.38 (s, 3 H), 3.65 (s, 3 H), 3.82 (s, 3 H), 4.31 (s, 2 H), 4.62-4.69 (m, 1 H), 4.73 (s, 2 H), 4.96 (s, 2 H), 5.05-5.11 (m, 1 H), 5.36 (d, *J* = 2.1 Hz, 1 H), 5.92-5.95 (m, 1 H), 6.68 (dd, *J* = 8.7, 2.4 Hz, 1 H), 7.31 (d, *J* = 2.4 Hz, 1 H), 7.88 (d, *J* = 8.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.1 (q), 18.0 (q), 19.0 (q), 25.7 (q), 37.3 (t), 38.1 (t), 51.6 (q), 55.4 (q), 56.8 (s), 67.5 (t), 73.5 (t), 96.3 (t), 99.7 (d), 112.4 (d), 113.7 (d), 118.1 (d), 119.7 (s), 120.9 (d), 123.2 (d), 132.5 (s), 132.8 (d), 133.9 (s), 143.3 (s), 154.7 (s), 162.2 (s), 166.8 (s), 171.7 (s), 203.6 (s); exact mass *m/z* calcd for $C_{29}H_{38}O_7$ 498.2618, found 498.2610.

(7*E*)-1-(Methoxymethoxymethyl)-7,10-dimethyl-9a-(3-methylbut-2-enyl)-9,9a-dihydro-6*H*-5,14-dioxadibenzo[*a*,*e*]-cycloundecene-12,15-dione (37.3).



37.1 **37.3**

Aqueous NaOH (10%, 1 mL) was added to a stirred solution of **37.1** (119 mg, 0.238 mmol) in MeOH (3 mL). The mixture was heated at 85 °C overnight, and then allowed to

cool to room temperature, diluted with water (5 mL), acidified (pH = 1) with 5% hydrochloric acid, and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$). Evaporation of the solvent gave crude acid (112 mg, ca 100%), which was used without purification in the next step.

Et_3N (0.17 mL, 1.2 mmol), followed by $SOCl_2$ (19 μL, 0.26 mmol), was added to a stirred solution of the crude acid (112 mg, 0.238 mmol) in PhMe (45 mL). The mixture was refluxed for 48 h, and then cooled to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 20 cm), using 20% EtOAc-hexanes, gave **37.3** (11 mg, 10%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2922, 1760, 1658, 1601 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.57 (s, 6 H), 1.70 (s, 3 H), 1.87 (d, J = 0.9 Hz, 3 H), 2.36 (dd, J = 14.6, 6.2 Hz, 1 H), 2.42 (dd, J = 15.1, 6.6 Hz, 1 H), 2.69 (dd, J = 14.9, 6.9 Hz, 1 H), 2.76 (dd, J = 15.1, 7.1 Hz, 1 H), 3.35 (s, 3 H), 4.36 (s, 2 H), 4.62-4.67 (m, 1 H), 4.98 (AB q, $\Delta\nu_{AB}$ = 12.0 Hz, J = 6.2 Hz, 2 H), 5.07-5.12 (m, 1 H), 5.23 (s, 2 H), 5.74 (d, J =1.4 Hz, 1 H), 6.08-6.12 (m, 1 H), 6.78 (d, J = 1.7 Hz, 1 H), 6.93 (d, J = 8.5, 1.6 Hz, 1 H), 7.76 (d, J = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.1 (q), 18.1 (q), 18.4 (q), 25.7 (q), 34.9 (t), 35.4 (t), 50.9 (s), 56.7 (q), 69.1 (t), 73.9 (t), 94.3 (t), 106.7 (d), 107.2 (d), 117.1 (d), 117.4 (d), 118.1 (s), 122.9 (d), 127.1 (d), 129.8 (d), 132.8 (s), 134.5 (s), 149.4 (s), 156.5 (s), 163.7 (s), 170.8 (s), 174.1 (s), 187.4 (s); exact mass (HR electrospray) *m/z* calcd for $C_{27}H_{32}NaO_6$ (M + Na) 475.2097, found 475.2091.

REFERENCES AND NOTES

1 Kamigaichi, T.; Nakajima, M.; Tami, H. *Jpn. Pat.* **1998**, 10101666.

2 Wilson, K. E.; Tsou, N. N.; Guan, Z.; Ruby, C. L.; Pelaez, F.; Gorrochategui, J.; Vicente, F.; Onishi, H. R. *Tetrahedron Lett.* **2000**, *41*, 8705.

3 Kamigaichi, T.; Nakajima, M.; Tami, H. *Jpn. Pat.* **1999**, 11158109.

4 Nicolaou, K. C.; Vassilikogiannakis, G.; Montagnon, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3276.

5 Nicolaou, K. C.; Montagnon, T.; Vassilikogiannakis, G. *Chem. Commun.* **2002**, 2478.

6 *O*-Acylation and rearrangement to the *C*-acylation product with various additives is well known. For selected examples, see: (a) Akhrem, A. A.; Lakhvich, F. A.; Budai, S. I.; Khlebnicova, T. S. *Synthesis* **1978**, 925. (b) Lakhvich, F. A.; Khlebnicova, T. S.; Akhrem, A. A. *Synthesis* **1985**, 784. (c) Monte, I. F.; Burger, U. *Tetrahedron Lett.* **1996**, *37*, 1007. (d) Lakhvich, F. A.; Petrusevich, I. I.; Sergeeva, A. N. *Russ. J. Org. Chem.* **1995**, *31*, 1473.

7 Chapman, O. L.; Fitton, P. *J. Am. Chem. Soc.* **1963**, *85*, 41.

8 Kende, A. S.; Smith, C. A. *Tetrahedron Lett.* **1988**, *29*, 4217.

9 Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

10 Schiner, D.; Feßner, K.; Ruppelt, M. *Liebigs Ann. Chem.* **1992**, 139.

11 Takahashi, K.; Tanaka, T.; Suzuki, T.; Hiroma, M. *Tetrahedron* **1994**, *50*, 1327.

12 Nicolaou, K. C.; Baran, P. S.; Zhong, Y. *J. Am. Chem. Soc.* **2001**, *123*, 2525.

13 Hirota, M. *Bull. Chem. Soc. Jpn.* **1964**, 213.

14 Moorlag, H.; Meyer, A. I. *Tetrahedron Lett.* **1993**, *34*, 6993.

15 Foot, K. M.; John, M.; Pattenden, G. *Synlett* **2001**, *3*, 365.

16 Smith III, A. B.; Dorsey, B. D.; Ohba, M.; Lupo, A. T.; Malamas, M. S. *J. Org. Chem.* **1988**, *53*, 4314.

17 Barton, D. H. R.; Magnus, P. D.; Smith, G.; Streckert, G.; Zurr, D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 542.

18 Dowd, P.; Kennedy, P. *Synth. Commun.* **1981**, *11*, 935.

19 (a) Montes, I. F.; Burger, U. *Tetrahedron Lett.* **1996**, *37*, 1007. (b) Tang, Q.; Sen, S. E. *Tetrahedron Lett.* **1998**, *39*, 2249.

20 Bode, J. W.; Hachisu, Y.; Matsuura, T.; Suzuki, K. *Org. Lett.* **2003**, *5*, 391.

21 Hodgson, H. H.; Smith, E. W. *J. Chem. Soc.* **1931**, 1508.

22 Bode, J. W.; Hachisu, Y.; Matsuura, T.; Suzuki, K., *Tetrahedron Lett.* **2003**, *44*, 3555.

23 Sen, S. E.; Ewing, G. J. *J. Org. Chem.* **1997**, *62*, 3529.

24 Nicolaou, K. C.; Bunnage, M. E.; Koide, K. *J. Am. Chem. Soc.* **1994**, *116*, 8402.

25 Hollinshead, S. P.; Nichols, J. B.; Wilson, J. W. *J. Org. Chem.* **1994**, *59*, 6703.

26 Kann, N.; Rein, T.; Akermark, B. Helquist, P. *J. Org. Chem.* **1990**, *55*, 5312.

27 Mechelke, M. F.; Wiemer, D. F. *J. Org. Chem.* **1999**, *64*, 4821.

28 Childs, M. E.; Weber, W. P. *J. Org. Chem.* **1976**, *41*, 3486.

29 Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith, S. H.; Hu, H. *J. Org. Chem.* **1994**, *59*, 5147.

CHAPTER 4

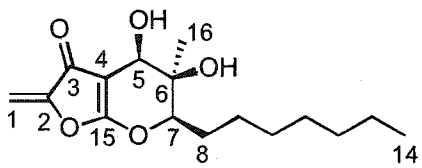
SYNTHETIC STUDIES ON BENESUDON

INTRODUCTION

Antifungal agents for crop protection have world-wide sales of at least US$ 6 billion.[1] Crompton Co., our supporting industrial partner for this project, has an important share[2] in the worldwide sales of agrochemicals, including antifungal agents. There is a growing need[3] for new antifungal agents in order to (a) combat the emergence of fungicide resistance, (b) provide more cost-effective crop treatments, (c) increase the safety levels to manufacturers, users, and consumers of treated crops, and (d) to minimize environmental effects.

Benesudon 1 (Scheme 1), a secondary metabolite of the fungus *Mollisia benesuada* (Tul.) Phill, was discovered[4] in a screening of fungal cultures for antimicrobial activity. Its novel structure was determined on the basis of NMR and mass spectral measurements. The optical rotation was reported to be -129° (*c* = 0.7, $CHCl_3$). Benesudon was found

Scheme 1



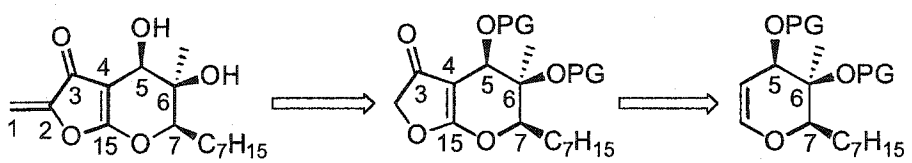
benesudon **1**

to exhibit strong antibacterial and antifungal activities. In addition, it showed cytotoxic activity (IC_{90} = 1-2 μg/mL) against a number of tumor cell lines, phytotoxic activity against *Setaria italica* and *Lepidium sativum*, and nematicidal activity against *Caenorhabditis elegans*. It was also reported that the biological activity of benesudon was immediately destroyed by reaction with L-cysteine, suggesting that the α-methylene ketone moiety is implicated in the biological activity. No synthetic work on benesudon has been reported, and the substance represents a new compound class.

RESULTS AND DISCUSSION

The structure of benesudon **1** does not appear to be especially complicated, but it is a compact and new heterocyclic system with several unusual features: three contiguous stereogenic centers, an α-methyleneketone moiety and a double bond at C(4)-C(15). Retrosynthetically, benesudon can be derived from the key intermediate **2.1**, which can be built up from the 6-membered ring compound **2.2**.

Scheme 2

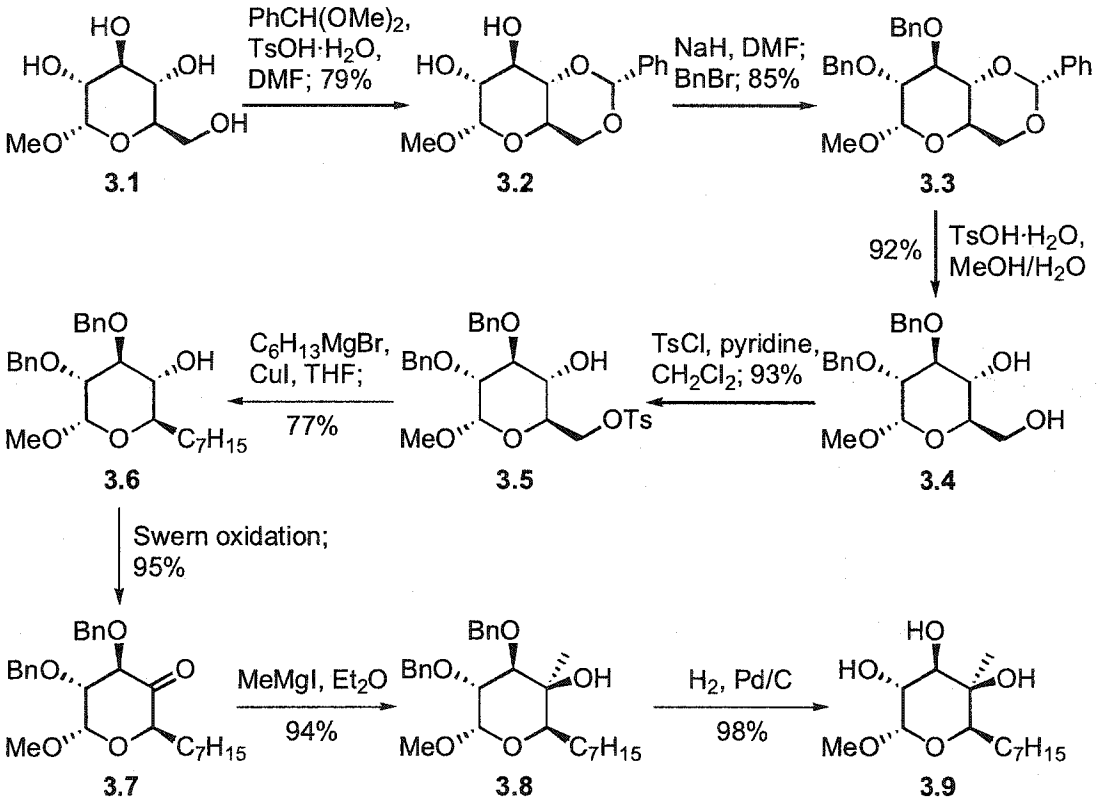


benesudon **1** **2.1** **2.2**

In order to simplify our work on the three stereogenic centers, we decided to use naturally-occurring methyl α-D-glucopyranoside **3.1** (Scheme 3) as a potential source of both the 6-membered ring, and the asymmetric centers at C(5) and C(7), and possibly also that at C(6). This decision involves the arbitrary assumption that benesudon has the same absolute configuration as D-glucose at the corresponding asymmetric centers. Following a literature procedure,[5] treatment of **3.1** with $PhCH(OMe)_2$ under acid catalysis gave compound **3.2**. Benzylation of **3.2** was achieved by deprotonation with NaH, followed by treatment with BnBr in DMF,[6] to yield the bisbenzyl ether **3.3**. Deprotection of acetal **3.3** under acidic conditions[7] liberated diol **3.4**, which was selectively protected with TsCl in the presence of pyridine to afford the expected tosylate **3.5**.[8] Installation of the hexyl sidechain was achieved by treatment of **3.5** with hexylmagnesium bromide in the presence of CuI[8] to form the desired product **3.6** in 77% yield. Swern oxidation of alcohol **3.6** provided ketone **3.7**

in high (95%) yield, and treatment with MeMgI in Et_2O gave the tertiary alcohol **3.8**. By analogy with a literature precedent,[9] we assumed that the stereochemistry of **3.8** is as shown, but later were able to prove (by X-ray analysis of an advanced intermediate) that this is indeed the case. The two benzyl protecting groups were removed by hydrogenolysis to afford triol **3.9**, which was used without purification for the next step.

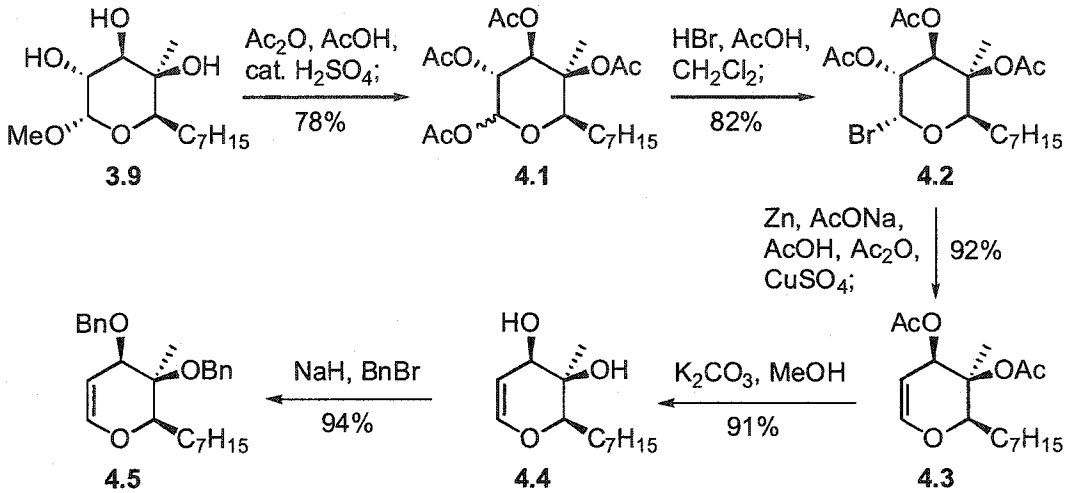
Scheme 3



Global acetylation of compound **3.9** with Ac_2O in AcOH, using a catalytic amount of concentrated H_2SO_4[10] yielded **4.1** as a mixture of two epimers (Scheme 4). The material was exposed to the action of HBr in AcOH[11] to furnish bromide **4.2**, which should be used promptly, as it decomposes on storage. Treatment of the bromide with Zn dust in AcOH[12] led to the desired product **4.3** in 92% yield. Deacetylation of **4.3** with K_2CO_3 in MeOH delivered diol **4.4**, which was

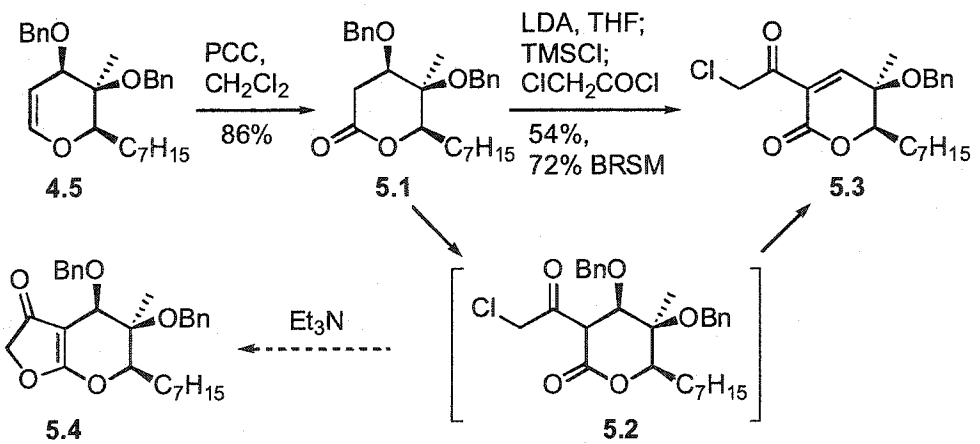
protected with BnBr to give the glucal **4.5**.

Scheme 4



With compound **4.5** in hand, we wanted to build up a 5-membered ring in order to reach the same structure type as represented by **2.1**. PCC oxidation[13] of **4.5** afforded lactone **5.1** in 86% yield. Unfortunately, when lactone **5.1** was treated with LDA, followed by Me_3SiCl and $ClCH_2COCl$ the undesired product **5.3** was formed, together with recovered **5.1**. We believed that the desired product **5.2** was first generated, but then underwent spontaneous α,β-elimination to produce **5.3**. We had hoped that the desired compound (**5.2**)

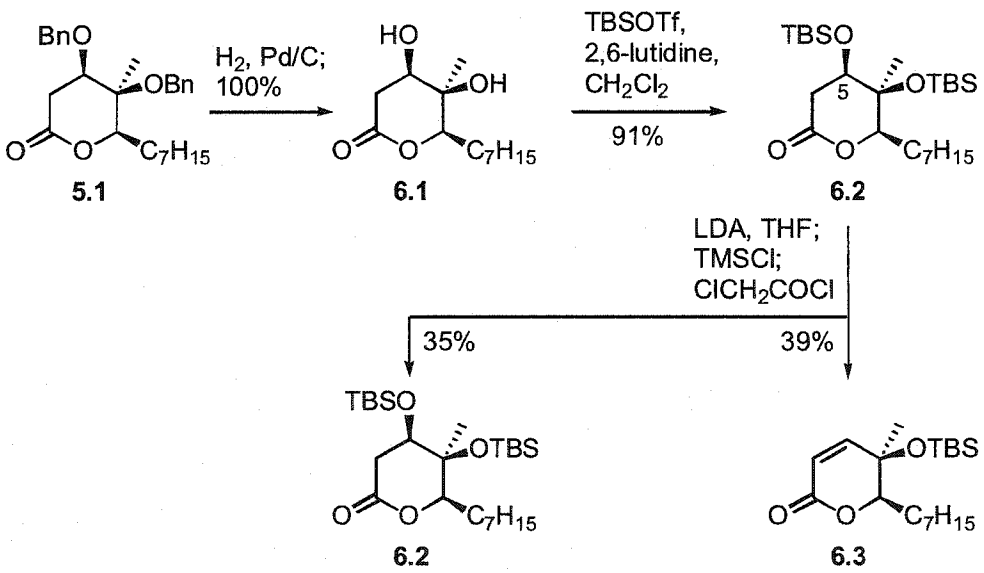
Scheme 5



would be isolable and would undergo cyclization in the presence of base (Et_3N). Such a process would generate the advanced intermediate **5.4**.

We next attempted to substitute *t*-$BuMe_2Si$ for Bn in order to determine whether the same elimination would occur. Lactone **5.1** was hydrogenated to give diol **6.1** in quantitative yield, and protection of **6.1** as its *t*-$BuMe_2Si$ ether **6.2** was achieved with *t*-$BuMe_2SiOSO_2CF_3$ in the presence of 2,6-lutidine. Treatment of **6.2** with LDA, followed by Me_3SiCl and $ClCH_2COCl$ afforded the α,β-unsaturated lactone **6.3** and starting material **6.2**. Evidently, elimination was again a facile process.

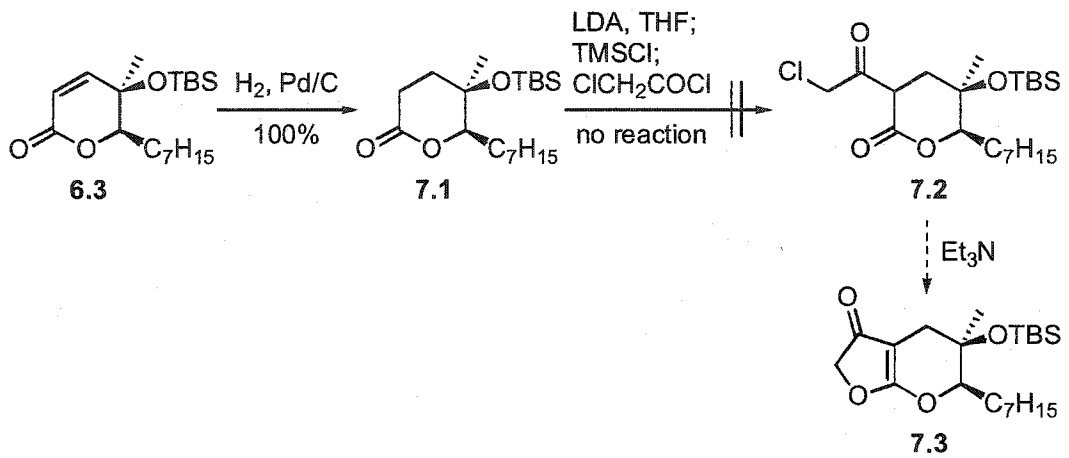
Scheme 6



Although the elimination resulted in loss of the stereogenic center at C(5), we thought that this center might be regenerated later on, after we had built up the unsaturated bicyclic system **7.3**. Hydrogenation of the α,β-unsaturated lactone **6.3** gave lactone **7.1** in quantitative yield. Surprisingly, treatment of **7.1** with LDA, followed by Me_3SiCl and $ClCH_2COCl$ gave none of the desired product **7.2**, which we had hoped convert into the bicyclic compound

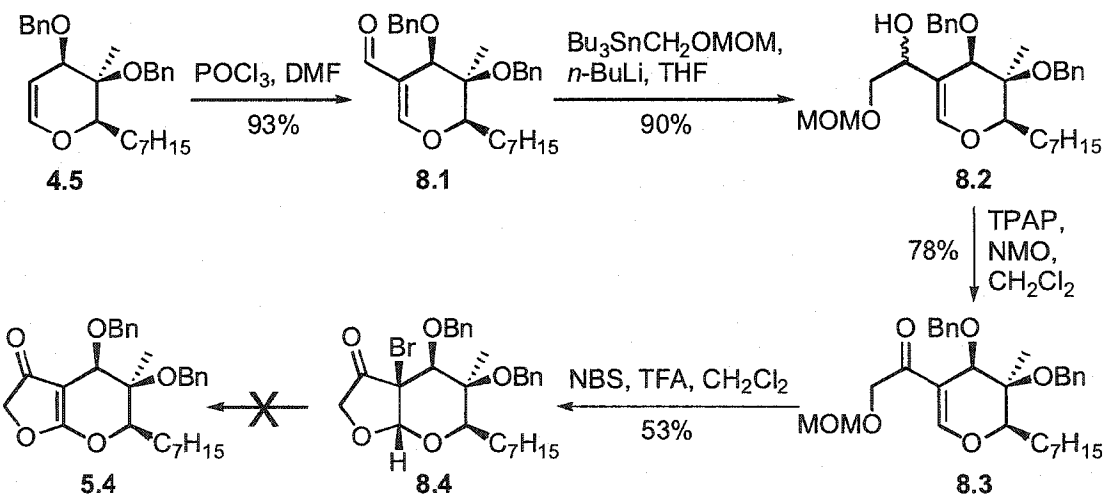
7.3 by base treatment.

Scheme 7



At this point we examined another approach (Scheme 8) for building up the 5-membered ring on compound **4.5**, so as to eventually reach the advanced intermediate **5.4**. Treatment of **4.5** with $POCl_3$ in DMF[14] provided aldehyde **8.1** in 93% yield. This aldehyde was allowed to react with the carbanion $MeOCH_2OCH_2^-$ generated *in situ* from $MeOCH_2OCH_2SnBu_3$[15] and *n*-BuLi, to give alcohol **8.2** as a mixture of two epimers. Oxidation with Pr_4NRuO_4/NMO afforded ketone **8.3** in 78% yield. We also tried some other

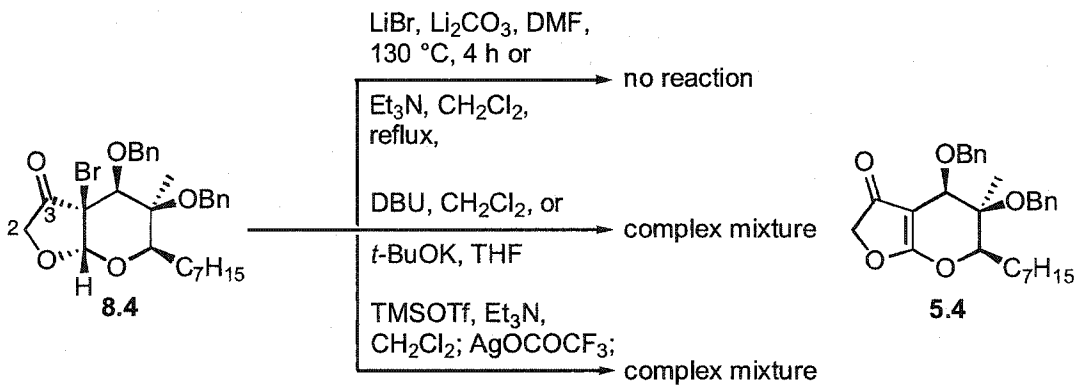
Scheme 8



oxidants, but both PCC and Dess-Martin periodinane gave a complex mixture, while MnO_2 resulted in only 50% of yield. With ketone **8.3** in hand, the stage was set for cyclization onto the 6-membered ring. To our delight, treatment of **8.3** with NBS and CF_3CO_2H furnished compound **8.4** in 53% yield, as a single isomer. The stereochemical assignment to the ring fusion is tentative, and is suggested by the chemical shift (5.45 ppm) of the acetal hydrogen. In the case of a later advanced intermediate (see compound **11.1**), we obtained an X-ray structure showing the same ring fusion stereochemistry, and in that compound the acetal **CH** signal was at 5.35 ppm.[16]

Our next task was to introduce the double bond between the two rings. Unfortunately, treatment of **8.4** under a variety of conditions and with a range of reagents failed

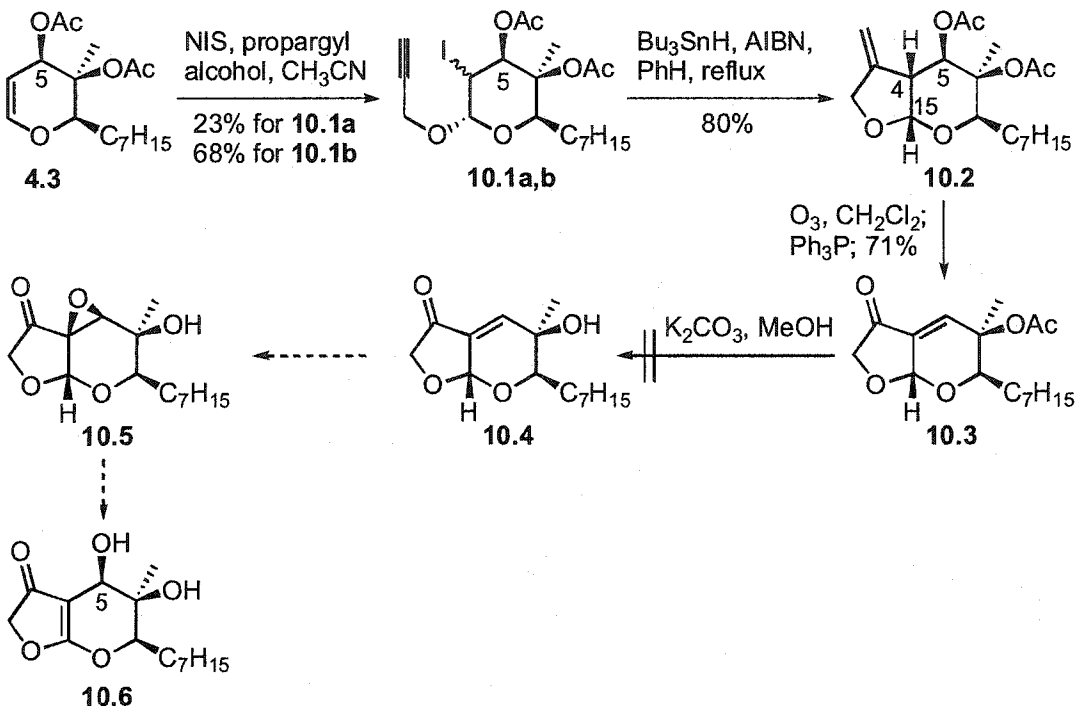
Scheme 9



to yield the desired product **5.4**. Weak bases (Et_3N or Li_2CO_3/LiBr[17]) produced no reaction while strong bases (DBU or *t*-BuOK) destroyed the starting material. In an attempt to facilitate elimination, we treated bromoketone **8.4** with $Me_3SiOSO_2CF_3$, in the hope that the derived silyl enol ether [enolization at C-(2)-C-(3)] would form, so that the desired elimination would generate a furan system and might therefore benefit from the aromatic nature of this heterocycle. Unfortunately, treatment with $Me_3SiOSO_2CF_3$ in

the presence of excess Et_3N, followed by $AgOCOCF_3$ afforded a complex mixture (Scheme 9), and so we were obliged to consider some alternative approaches for generating the desired double bond.

Scheme 10

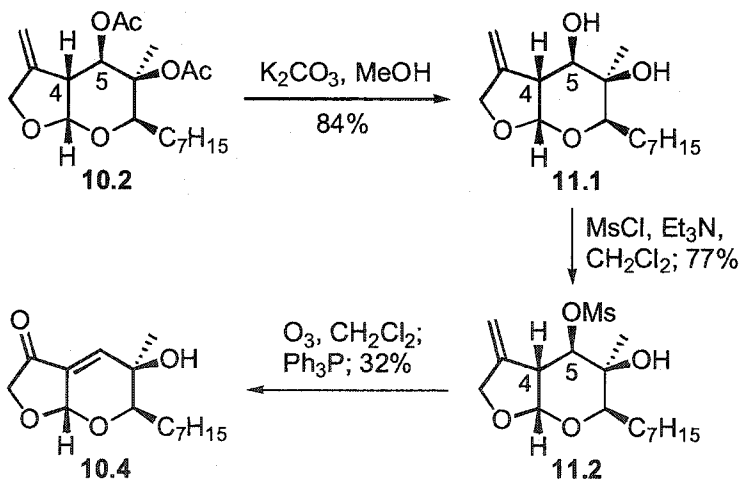


To this end, compound **4.3** was treated with NIS and propargyl alcohol to give two separable products **10.1a,b**. Both of them underwent radical cyclization, under standard conditions,[18] to yield the same product **10.2**. The stereochemistry at C(15) and C(4) was assigned as shown on the basis of an X-ray structure determination of compound **11.1** (see later, Scheme 11). Cleavage of the exocyclic double bond with O_3 generated the α,β-unsaturated ketone **10.3**, with loss of the substituent at C(5); however, we felt that it might be possible to restore this substituent, and to do so with the correct stereochemistry, at a later stage. Therefore, compound **10.3** was exposed to K_2CO_3 in MeOH in the hope of obtaining the allylic alcohol **10.4**. Surprisingly, however, none of this alcohol was obtained.

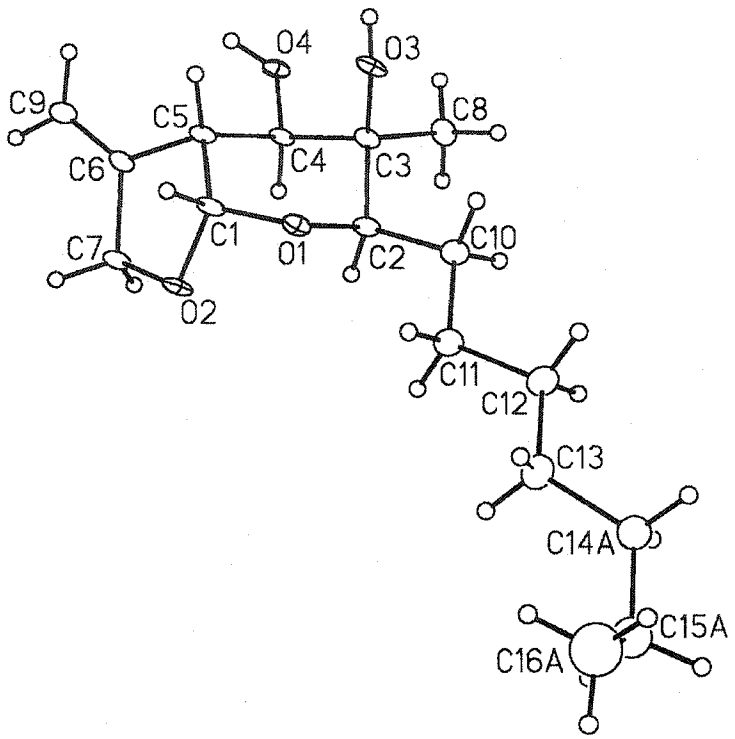
We had anticipated that compound **10.4** could be subjected to hydroxyl-directed epoxidation, from which point epoxide opening might serve to introduce the required double bond and restore the C(5) hydroxyl. The latter would, of necessity, then have the correct stereochemistry.

In order to make compound **10.4**, we modified our approach, as summarized in Scheme 11. Deacetylation of **10.2** was achieved by the action of K_2CO_3 in MeOH to give diol **11.1**. This was treated with MsCl in the presence of Et_3N to generate the monomesylate **11.2**. Only the monomesylate was formed, even in the presence of a large excess of MsCl and Et_3N. Evidently, the tertiary hydroxyl is very hindered. We expected that ozonolysis of **11.2** would result in the enone **10.4**. However, the formation of this substance was erratic, and it could not be obtained reproducibly in good yield and purity. We assume that the compound is unstable, a possibility that is consistent with the fact that deacetylation of **10.3** also failed to afford it. This unexpected difficulty with compound **10.4** forced us to abandon the plan shown in Scheme 10.

Scheme 11



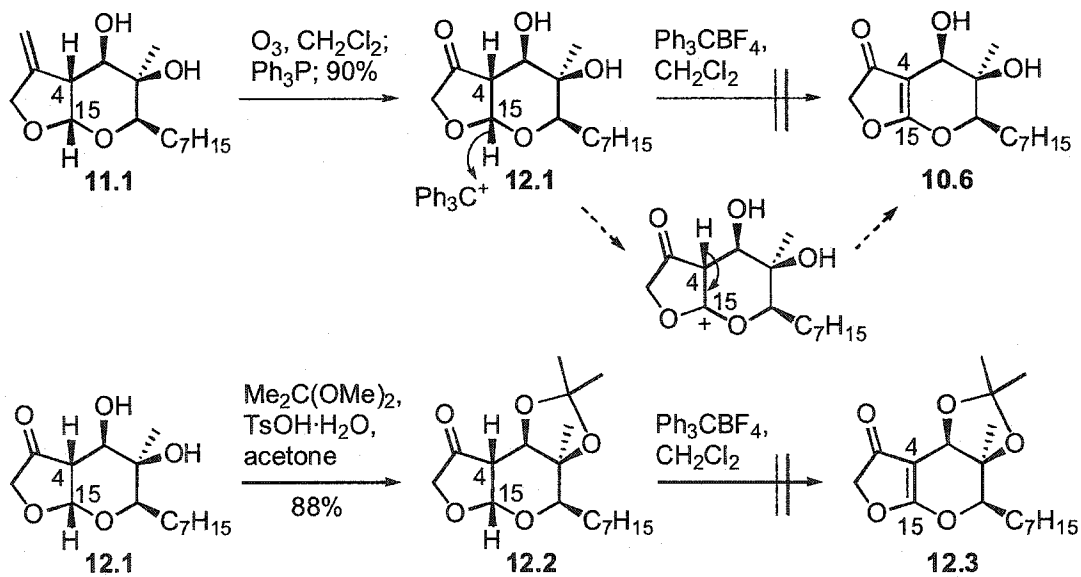
Our next approach was based on the possibility of selective hydride abstraction from C(15) (see **12.1**), followed by loss of a proton at C(4) to furnish the



X-ray Structure of Compound **11.1**

required double bond. With diol **11.1** in hand, cleavage of the exocyclic double bond with O_3 gave ketone **12.1** in 90%

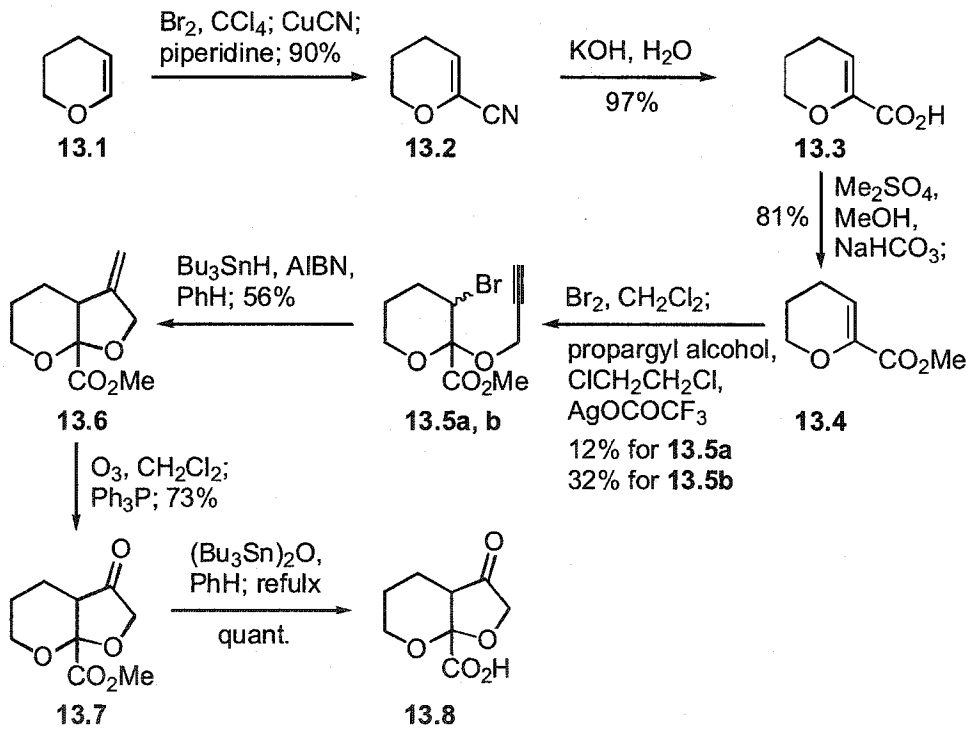
Scheme 12



yield. Treatment of **12.1** with Ph_3CBF_4[19] in CH_2Cl_2 generated a complex mixture, and none of the desired product **10.6** was obtained. Use of Ph_3CPF_6·pyridine gave no reaction. We suspected that the two free OH groups could interfere in the proposed reaction, and so diol **12.1** was treated with 2,2-dimethoxypropane in the presence of acid in order to generate compound **12.2** (88% yield). Unfortunately, Ph_3CBF_4 still destroyed this compound, and afforded a complex mixture (Scheme 12).

From the above studies, it was clear that introduction of the double bond presented a major challenge, and we turned our attention to a model compound without the three asymmetric centers.

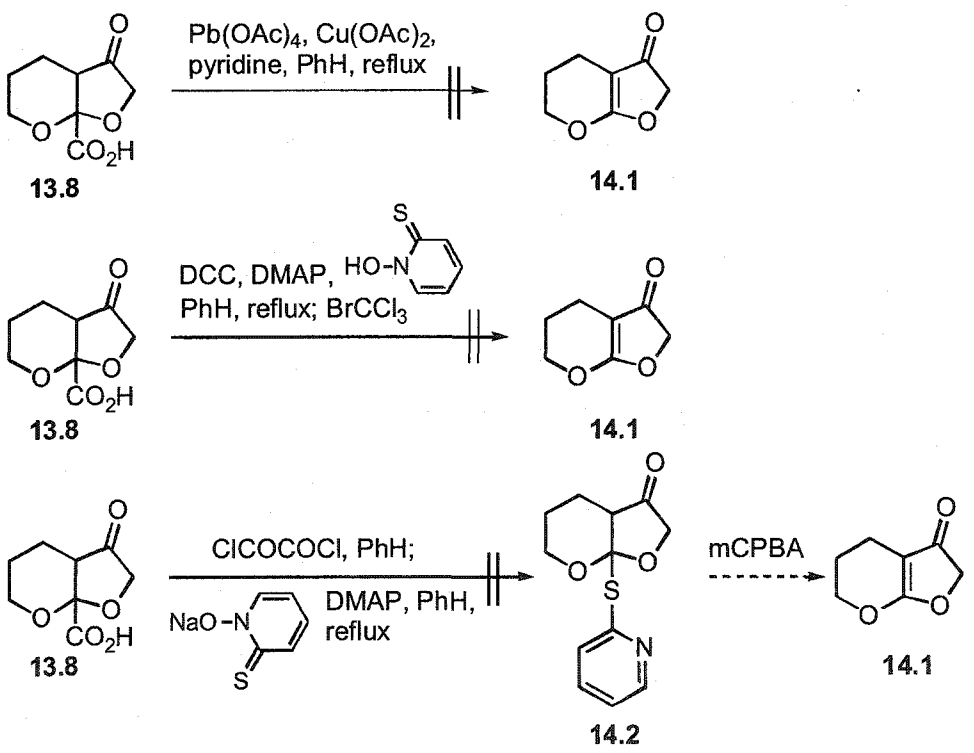
Scheme 13



Our approach started from pyran **13.1**. Following a literature procedure,[20] compound **13.1** was treated with Br_2, followed by CuCN and piperidine to give cyanide **13.2**, which was hydrolyzed to the corresponding acid **13.3**. Methylation

of **13.3** with Me_2SO_4 in the presence of $NaHCO_3$ furnished ester **13.4** in 81% yield. Using a modification of a literature procedure,[21] treatment of **13.4** with Br_2 afforded the expected dibromide, which, without purification, was allowed to react with propargyl alcohol in the presence of $AgOCOCF_3$. This process yielded two separable products **13.5a,b**. Radical cyclization under standard conditions then led to the desired product **13.6**. Cleavage of the exocyclic double bond with O_3 produced ketone **13.7** in 73% yield. Hydrolysis with LiOH in MeOH/water failed to give acid **13.8**, but demethylation of the ester was easily achieved with $(Bu_3Sn)_2O$[22] to provide acid **13.8** in quantitative yield.

Scheme 14



With acid **13.8** in hand, we wanted to introduce the double bond by Kochi oxidative decarboxylation or Barton decarboxylative halogenation, followed by elimination of HX. Treatment of acid **13.8** with $Pb(OAc)_4$ and $Cu(OAc)_2$[23]

gave a complex mixture that might have contained a trace of the desired **14.1** (loss of ^{1}H NMR signals due to the carboxyl and the adjacent hydrogen α to the ketone carbonyl). We next tried a procedure described by Barton for replacement of a carboxyl by bromine,[24] but this version of the Hunsdiecker reaction also failed to afford the desired product, **14.1**. We also examined the possibility of converting **13.8** into the sulfide **14.2**, as oxidation of **14.2** with *m*-CPBA, followed by spontaneous elimination, could generate the required **14.1**. In the event, **14.2** was not obtained, and we decided to first practice replacement of a carboxyl by a thiopyridyl group by studying a simple model compound (1-adamantanecarboxylic acid); these experiments are currently under way.

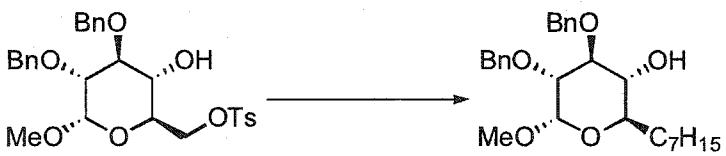
Conclusion

Benesudon represents a new compound class, and we have found that, although the majority of the carbon skeleton can be assembled, introduction of the double bond spanning the two rings is a difficult operation. Our experience suggests that a route via the carboxylic acid (cf. **14.2**) is a promising approach, and efforts to reduce this idea to practice are currently under way.

EXPERIMENTAL

The same general procedures were used as described in Chapter 1. In many ^{1}H NMR spectra, certain spin systems are described as AB quartets, even though the value of $\Delta\nu/J$ is greater than 10. Strictly, such spectra should be described as AM systems.

(2*R*,3*R*,4*S*,5*R*,6*S*)-4,5-Bisbenzyloxy-2-heptyl-6-methoxy-tetrahydropyran-3-ol (3.6).

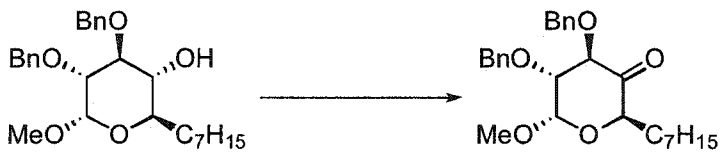


3.5 **3.6**

A solution of **3.5**[8] (12.94 g, 24.47 mmol) in THF (20 mL) was added dropwise by syringe pump over 35 min to a stirred and cooled (-25 °C) mixture of CuI (9.801 g, 51.46 mmol) and $C_6H_{13}MgBr$ (86 mL, 2.0 M in Et_2O) in THF (60 mL). [This latter solution was prepared by slow addition of the CuI to a stirred and cooled (-25 °C) solution of the Grignard reagent.] Stirring at -25 °C was continued for 5 h. The cooling bath was left in place, but not recharged, and the mixture was then allowed to warm to room temperature over ca 2 h, at which time it was poured into cooled (0 °C) saturated aqueous NH_4Cl (200 mL) and extracted with Et_2O (3 x 200 mL). The combined organic extracts were washed with brine (80 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 25 cm), using 15% EtOAc-hexanes, gave **3.6** (8.3 g, 77%) as a colorless oil: $[\alpha]_D$ = +46.8° (*c* = 2.15, $CHCl_3$); FTIR (CH_2Cl_2, cast) 3450, 3064, 3031, 2856 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.85 (t, *J* = 6.9 Hz, 3 H), 1.18-1.53 (m, 11 H), 1.74-1.83 (m, 1 H), 2.11 (d, *J* = 2.4 Hz, 1 H), 3.20 (dt, *J* = 9.2, 2.4 Hz, 1 H), 3.35 (s, 3 H), 3.45-3.53 (m, 2 H),

3.71 (t, J = 9.2 Hz, 1 H), 4.57 (d, J = 3.5 Hz, 1 H), 4.70 (AB q, $\Delta\nu_{AB}$ = 44.6 Hz, J = 12.1 Hz, 2 H), 4.85 (AB q, $\Delta\nu_{AB}$ = 149.6 Hz, J = 11.5 Hz, 2 H), 7.25-7.39 (m, 10 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.1 (q), 22.6 (t), 25.4 (t), 29.2 (t), 29.6 (t), 31.6 (t), 31.8 (t), 55.0 (q), 70.5 (d), 73.0 (t), 73.7 (d), 75.3 (t), 80.0 (d), 81.5 (d), 97.8 (d), 127.8 (d), 127.9 (d), 128.0 (d), 128.1 (d), 128.5 (d), 128.6 (d), 138.1 (s), 138.8 (s); exact mass (HR electrospray) m/z calcd for $C_{27}H_{38}NaO_5$ (M + Na) 465.2617, found 465.2617.

(2*R*,4*R*,5*R*,6*S*)-4,5-Bisbenzyloxy-2-heptyl-6-methoxy-dihydropyran-3-one (3.7).

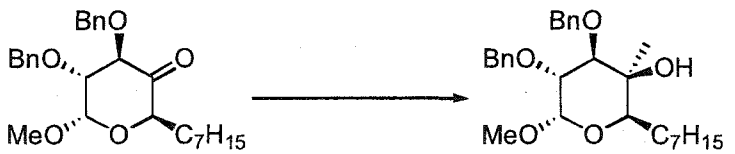


3.6 **3.7**

A solution of dry DMSO (3.71 mL, 52.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred and cooled (-78 °C) solution of $(COCl)_2$ (3.65 mL, 41.6 mmol) in CH_2Cl_2 (60 mL). Stirring at -78 °C was continued for 30 min, and then a solution of **3.6** (9.206 g, 20.81 mmol) in CH_2Cl_2 (20 mL) was added dropwise by syringe pump over 20 min. After 1 h at -78 °C, Et_3N (8.75 mL, 62.4 mmol) was injected over 15 min. The cooling bath was left in place, but not recharged, and stirring was continued overnight. The mixture was diluted with CH_2Cl_2 (50 mL) and aqueous NH_4Cl (30 mL), and the aqueous phase was extracted with CH_2Cl_2 (30 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 25 cm), using 15% EtOAc-hexanes, gave **3.7** (8.7 g, 95%) as a colorless oil: $[\alpha]_D$ = +164.7° (c = 1.75, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3064, 3032, 2953, 2856, 1726 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, J

= 6.9 Hz, 3 H), 1.18-1.56 (m, 11 H), 1.78-1.87 (m, 1 H), 3.44 (s, 3 H), 3.73 (dd, J = 10.0, 3.6 Hz, 1 H), 4.02 (dd, J = 8.4, 3.9 Hz, 1 H), 4.40 (d, J = 10.0 Hz, 1 H), 4.72 (d, J = 3.5 Hz, 1 H), 4.75 (AB q, $\Delta\nu_{AB}$ = 93.3 Hz, J = 12.3 Hz, 2 H), 4.80 (AB q, $\Delta\nu_{AB}$ = 145.5 Hz, J = 11.3 Hz, 2 H), 7.24-7.44 (m, 10 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.0 (q), 22.6 (t), 25.2 (t), 28.1 (t), 29.1 (t), 29.5 (t), 31.8 (t), 55.8 (q), 72.6 (d), 73.9(t), 74.3 (t), 80.4 (d), 82.9 (d), 98.4 (d), 127.8 (d), 127.9 (d), 128.0 (d), 128.1 (d), 128.3 (d), 128.4 (d), 137.8 (s), 138.9 (s), 203.2 (s); exact mass (HR electrospray) m/z calcd for $C_{27}H_{36}NaO_5$ (M + Na) 463.2460, found 463.2466.

(2*R*,3*S*,4*R*,5*R*,6*S*)-4,5-Bisbenzyloxy-2-heptyl-6-methoxy-3-methyltetrahydropyran-3-ol (3.8).



3.7 **3.8**

A solution of **3.7** (8.135 g, 18.49 mmol) in Et_2O (15 mL) was added dropwise by syringe pump over 30 min to a stirred and cooled (-78 °C) suspension of MeMgI (12.3 mL, 3.0 M in Et_2O) in Et_2O (60 mL). Stirring at -78 °C was continued for 2 h. The mixture was diluted with aqueous NH_4Cl (20 mL) and extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 25 cm), using 10% EtOAc-hexanes, gave **3.8** (7.9 g, 94%) as a colorless oil: $[\alpha]_D$ = +45.4° (c = 1.0, $CHCl_3$); FTIR ($CHCl_3$, cast) 3500, 3063, 3030, 2953, 2925 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, J = 6.9 Hz, 3 H), 1.14 (s, 3 H), 1.18-1.68 (m, 12 H), 2.18 (d, J = 1.6 Hz, 1 H), 3.36 (s, 3 H), 3.47 (d, J = 10.1 Hz, 1 H), 3.56 (d, J = 9.7

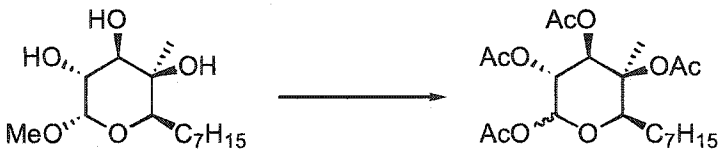
Hz, 1 H), 3.81 (dd, J = 9.6, 3.7 Hz, 1 H), 4.63 (d, J = 3.2 Hz, 1 H), 4.64 (d, J = 11.3 Hz, 1 H), 4.67 (AB q, $\Delta\nu_{AB}$ = 46.7 Hz, J = 12.0 Hz, 2 H), 5.01 (d, J = 10.9 Hz, 1 H), 7.24-7.37 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.0 (q), 22.1 (q), 22.6 (t), 26.4 (t), 27.6 (t), 29.2 (t), 29.6 (t), 31.8 (t), 55.1(q), 72.7 (d), 73.1 (t), 74.3(s), 76.2 (t), 78.1 (d), 80.9 (d), 98.0 (d), 127.8 (d), 128.1 (d), 128.2 (d), 128.3 (d), 128.4 (d), 138.3 (s); exact mass (HR electrospray) m/z calcd for $C_{28}H_{40}NaO_5$ (M + Na) 479.2768, found 479.2771.

(2*R*,3*R*,4*R*,5*R*,6*S*)-2-Heptyl-6-methoxy-3-methyl-tetrahydropyran-3,4,5-triol (3.9).

3.8 **3.9**

Pd-C (10%, 0.7 g) was added to a solution of **3.8** (14.02 g, 30.75 mmol) in MeOH (50 mL). The mixture was shaken under H_2 at 50 psi (Parr shaker) for 5 h and then filtered through a pad of silica gel. The filtrate was evaporated to give **3.9** (8.34 g, 98%) as a white solid: mp = 92-94 °C; $[\alpha]_D$ = +139.8° (c = 1.0, $CHCl_3$); FTIR ($CHCl_3$, cast) 3396, 2924, 2856 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (t, J = 6.9 Hz, 3 H), 1.17 (s, 3 H), 1.20-1.66 (m, 12 H), 2.48 (s, 1 H), 2.79 (d, J = 8.8 Hz, 1 H), 3.28 (d, J = 5.6 Hz, 1 H), 3.38 (s, 3 H), 3.41-3.50 (m, 2 H), 3.70 (dt, J = 9.2, 4.0 Hz, 1 H), 4.75 (d, J = 4.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.0 (q), 22.1 (q), 22.6 (t), 26.3 (t), 27.5 (t), 29.2 (t), 29.6 (t), 31.8 (t), 55.2(q), 70.6 (d), 73.3 (d), 73.6(s), 74.6 (d), 99.1 (d); exact mass (HR electrospray) m/z calcd for $C_{14}H_{28}NaO_5$ (M + Na) 299.1829, found 299.1829.

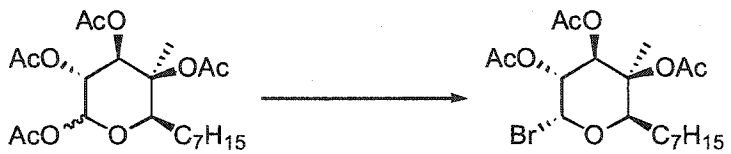
Acetic Acid (3*R*,4*R*,5*S*,6*R*)-3,4,5-Triacetoxy-6-heptyl-5-methyltetrahydropyran-2-yl Ester (4.1).



3.9 **4.1**

Concentrated H_2SO_4 (2 mL) was added dropwise to a stirred and cooled (0 °C) solution of **3.9** (18.64 g, 67.54 mmol) in a mixture of Ac_2O (80 mL) and AcOH (80 mL). The cold bath was left in place, but not recharged, and stirring was continued overnight. The mixture was poured into water (200 mL) and extracted with EtOAc (3 x 300 mL). The combined organic extracts were washed with water (100 mL), saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 25 cm), using 20% EtOAc-hexanes, gave **4.1** (22.52 g, 78%) as a 1:5 mixture of two epimers (^1H NMR): FTIR (CH_2Cl_2, cast) 2928, 2857, 1751, 1220 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.84 (t, *J* = 7.1 Hz, 3 H), 1.16-1.66 (m, 15 H), 1.94-2.13 (eight s, 12 H), 3.30 and 3.64 (dd, *J* = 9.7, 2.5 Hz, 1 H), 4.98 and 5.23 (dd, *J* = 10.0 Hz, 2 H), 5.60 and 6.30 (d, *J* = 8.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.0 (q), 19.0 (q), 19.1 (q), 20.4 (q), 20.5 (q), 20.6 (q), 20.7 (q), 20.8 (q), 20.9 (q), 22.3(q), 22.4 (q), 22.5 (t), 25.9 (t), 26.0 (t), 28.1 (t), 28.3 (t), 29.1 (t), 29.2 (t), 31.7 (t), 31.8 (t), 67.6(d), 69.2 (d), 72.0 (d), 75.5 (d), 76.5 (d), 80.3 (d), 82.4 (s), 83.2 (s), 89.6 (d), 92.3 (d), 169.0 (s), 169.1 (s), 169.4 (s), 169.7 (s), 169.9 (s), 170.3 (s), 170.5 (s); exact mass (HR electrospray) *m/z* calcd for $C_{21}H_{34}NaO_9$ (M + Na) 453.2095, found 453.2099.

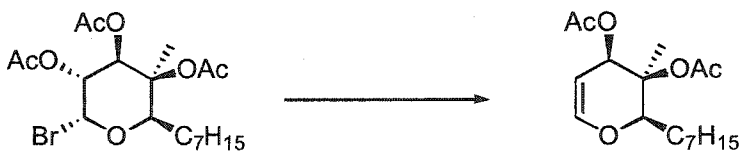
Acetic Acid (2*R*,3*R*,4*R*,5*S*,6*R*)-4,5-Diacetoxy-2-bromo-6-heptyl-5-methyltetrahydropyran-3-yl Ester (4.2).



4.1 **4.2**

A solution of HBr in AcOH (45%, 11.5 mL) was added dropwise to a solution of **4.1** (4.98 g, 11.6 mmol) in CH_2Cl_2 (45 mL). The mixture was stirred for 2 h, diluted with CH_2Cl_2 (40 mL), washed with ice-water (15 mL), saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 25 cm), using 15% EtOAc-hexanes, gave **4.2** (4.28 g, 82%) as a colorless oil: $[\alpha]_D$ = +226° (*c* = 1.0, $CHCl_3$); FTIR ($CHCl_3$, cast) 2956, 2857, 2828, 1751, 1223 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, *J* = 6.9 Hz, 3 H), 1.18-1.69 [m, 15 H, including s (3 H) at δ 1.58], 2.06 (s, 9 H), 3.82 (dd, *J* = 9.9, 2.4 Hz, 1 H), 4.94 (dd, *J* = 10.2, 4.1 Hz, 1 H), 5.33 (d, *J* = 10.2 Hz, 1 H), 6.72 (d, *J* = 3.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.0 (q), 20.6 (q), 20.7 (q), 22.3(q), 22.7 (t), 25.6 (t), 27.8 (t), 29.0 (t), 29.1 (t), 31.7 (t), 69.1 (d), 72.4 (d), 79.0 (d), 82.8 (s), 89.5 (d), 169.5(s), 170.0s), 170.1(s); exact mass (HR electrospray) *m/z* calcd for $C_{19}H_{31}{}^{79}BrNaO_7$ (M + Na) 473.1151, found 473.1155.

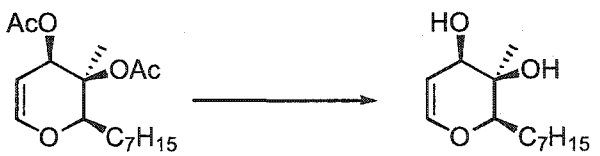
Acetic Acid (2*R*,3*S*,4*R*)-3-Acetoxy-2-heptyl-3-methyl-3,4-dihydro-2*H*-pyran-4-yl Ester (4.3).



4.2 **4.3**

Zn dust (30 g) was tipped into a stirred solution of AcONa (35 g) and AcOH (50 mL) in water (70 mL), and saturated aqueous $CuSO_4$ (10 mL) was then added. The blue color disappeared, and a solution of **4.2** (4.24 g, 9.40 mmol) in Ac_2O (15 mL) was added at a fast dropwise rate to the stirred mixture, and stirring was continued for 2 h. The mixture was diluted with CH_2Cl_2 (70 mL) and filtered. The aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 25 cm), using 10% EtOAc-hexanes, gave **4.3** (2.7 g, 92%) as a colorless oil: $[\alpha]_D$ = -106.0° (*c* = 1.0, $CHCl_3$); FTIR ($CHCl_3$, cast) 2926, 2857, 1747, 1458, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, *J* = 6.9 Hz, 3 H), 1.20-1.66 [m, 14 H, including s (3 H) at δ 1.58], 1.83-1.93 (m, 1 H), 1.99 and 2.00 (s, 6H), 4.08 (d, *J* = 10.9 Hz, 1 H), 4.90 (t, *J* = 10.2 Hz, 1 H), 5.38 (d, *J* = 5.3 Hz, 1 H), 6.26 (d, *J* = 6.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.0 (q), 20.9 (q), 21.7 (q), 21.8(q), 22.6 (t), 26.4 (t), 26.9 (t), 29.2 (t), 29.4 (t), 31.8 (t), 67.2 (d), 78.2 (s), 79.4 (d), 98.3 (d), 143.9(d), 169.5 (s), 169.9(s); exact mass (HR electrospray) *m/z* calcd for $C_{17}H_{28}NaO_5$ (M + Na) 335.1829, found 335.1828.

(2*R*,3*R*,4*R*)-2-Heptyl-3-methyl-3,4-dihydro-2*H*-pyran-3,4-diol (4.4).



4.3 **4.4**

K_2CO_3 (4.04 g, 29.2 mmol) was added to a stirred solution of **4.3** (3.04 g, 9.74 mmol) in MeOH (25 mL). After

30 min, the mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (2 x 40 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 30% EtOAc-hexanes, gave **4.4** (2.02 g, 91%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3418, 2954, 2856, 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, *J* = 6.5 Hz, 3 H), 1.20-1.80 [m, 15 H, including s (3 H) at δ 1.23], 2.01 (s, 1 H), 2.13 (d, *J* = 10.2 Hz, 1 H), 3.63 (dd, *J* = 10.2, 2.8 Hz, 1 H), 3.92 (d, *J* = 10.1 Hz, 1 H), 4.72 (dd, *J* = 6.0, 2.0 Hz, 1 H), 6.41 (d, *J* = 6.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.2 (q), 20.8 (q), 22.8 (t), 25.7 (t), 27.7 (t), 29.3 (t), 29.5 (t), 31.9 (t), 68.8 (d), 68.9 (s), 81.2 (d), 104.7 (d), 144.4(d); exact mass (HR electrospray) *m/z* calcd for $C_{13}H_{26}NaO_4$ (M + Na + H_2O) 269.1723, found 269.1722.

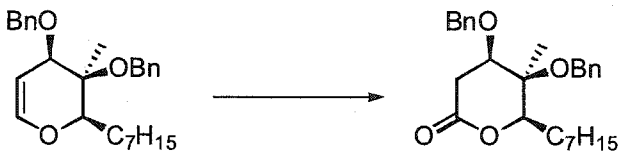
(2*R*,3*S*,4*R*)-3,4-Bisbenzyloxy-2-heptyl-3-methyl-3,4-dihydro-2*H*-pyran (4.5).

4.4 **4.5**

NaH (60% dispersion in oil, 2.11 g, 52.5 mmol) was added in portions to a stirred solution of **4.4** (2.01 g, 8.81 mmol) in DMF (40 mL). Stirring was continued for 20 min, and BnBr (2.21 mL, 26.4 mmol) was added dropwise over 5 min. The mixture was stirred overnight and then cooled to 0 °C. Water (10 mL) was added slowly to destroy the excess of NaH, and the resulting mixture was extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over

silica gel (3 x 25 cm), using 10% EtOAc-hexanes, gave **4.5** (3.37 g, 94%) as a colorless oil: $[\alpha]_D$ = +78.0° (*c* = 1.0, $CHCl_3$); FTIR ($CHCl_3$, cast) 3087, 3064, 2926, 2856, 1497, 1453 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, *J* = 6.9 Hz, 3 H), 1.20-1.37 [m, 12 H, including s (3 H) at δ 1.33], 1.46-1.58 (m, 1 H), 1.73-1.82 (m, 1 H), 1.93-2.04 (m, 1 H), 3.78 (d, *J* = 10.7 Hz, 1 H), 3.85 (d, *J* = 3.6 Hz, 1 H), 4.61 (AB q, $\Delta\nu_{AB}$ = 106.7 Hz, *J* = 11.8 Hz, 2 H), 4.68 (AB q, $\Delta\nu_{AB}$ = 77.3 Hz, *J* = 11.5 Hz, 2 H), 4.94 (dd, *J* = 6.2, 3.6 Hz, 1 H), 6.32 (d, *J* = 6.2 Hz, 1 H), 7.19-7.37 (m, 10 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.1 (q), 20.5 (q), 22.7 (t), 26.8 (t), 27.2 (t), 29.3 (t), 29.5 (t), 31.8 (t), 65.3 (t),71.2 (t), 74.0 (s), 74.8 (d), 81.6 (d), 99.2 (d), 126.9 (d), 127.2 (d), 127.3 (d), 127.5 (d), 128.1 (d), 128.2 (d), 138.8 (s), 139.9(s), 143.5 (d); exact mass (HR electrospray) *m/z* calcd for $C_{27}H_{36}NaO_3$ (M + Na) 431.2562, found 431.2564.

(4*R*,5*R*,6*R*)-4,5-Bisbenzyloxy-6-heptyl-5-methyltetrahydropyran-2-one (5.1).

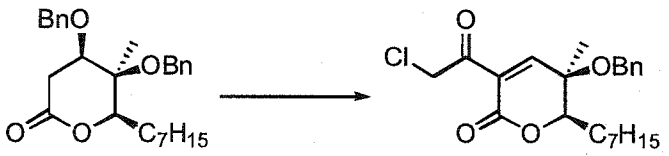


4.5 **5.1**

PCC (0.871 g, 4.04 mmol) was added to a stirred solution of **4.5** (0.822 g, 2.01 mmol) in CH_2Cl_2 (12 mL). Stirring was continued for 8 h, and the mixture was then filtered through a pad of Celite. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 25 cm), using 15% EtOAc-hexanes, gave **5.1** (0.735 g, 86%) as a white solid: mp = 43.5-44.0 °C; $[\alpha]_D$ = +21.5° (*c* = 1.0, $CHCl_3$); FTIR (CH_2Cl_2, cast) 3064, 3031, 2955, 2856, 1736, 1237 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.85 (t, *J* = 6.9 Hz, 3 H), 1.18-1.37 (m, 9 H), 1.41 (s, 3 H),

1.59-1.68 (m, 1 H), 1.82-1.92 (m, 1 H), 2.76 (dd, J = 17.6, 11.1 Hz, 1 H), 2.94 (dd, J = 17.5, 6.1 Hz, 1 H), 3.63 (dd, J = 11.1, 6.2 Hz, 1 H), 3.91 (d, J = 10.2 Hz, 1 H), 4.46 (d, J = 11.9 Hz, 1 H), 4.67 (d, J = 12.0 Hz, 2 H), 4.89 (d, J = 12.0 Hz, 1 H), 7.20-7.37 (m, 10 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.0 (q), 16.0 (q), 22.6 (t), 25.9 (t), 29.1 (t), 29.2 (t), 29.4(t), 31.8 (t), 33.5 (t), 66.7 (t), 71.9 (t), 74.6 (s), 78.5 (d), 85.3 (d), 126.7 (d), 127.1 (d), 127.6 (d), 128.0 (d), 128.2 (d), 128.5 (d), 137.4 (s), 139.3(s), 169.6 (s); exact mass m/z calcd for $C_{27}H_{36}O_4$ 424.2614, found 424.2601.

(5*R*,6*R*)-5-Benzyloxy-3-(2-chloroacetyl)-6-heptyl-5-methyl-5,6-dihydropyran-2-one (5.3).



5.1 **5.3**

A solution of **5.1** (0.212 g, 0.500 mmol) in THF (1 mL) was added dropwise over 5 min to a stirred and cooled (-78 °C) solution of LDA [freshly prepared from *i*-Pr_2NH (80 μL, 0.57 mmol) and *n*-BuLi (0.33 mL, 1.6 M in hexanes)] in THF (4 mL). Stirring at -78 °C was continued for 1 h. Then Me_3SiCl (0.31 mL, 2.5 mmol) was added dropwise and the cooling bath was removed. Stirring was continued for 1 h, by which time the mixture had attained room temperature. The mixture was evaporated under water pump vacuum (protection from moisture) to give crude trimethylsilyl enol ether, which was kept under oil pump vacuum prior to use.

A solution of the crude trimethylsilyl enol ether in THF (1 mL) was added dropwise to a stirred and cooled (0 °C) solution of $ClCH_2COCl$ (45 μL, 0.52 mmol) in THF (3 mL). The

cold bath was left in place but not recharged, and stirring was continued for 6 h. The mixture was diluted with Et_2O (30 mL), washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 25 cm), using 10% EtOAc-hexanes, gave **5.3** (0.105 g, 54%, or 72% after correction for recovered starting material) as a colorless oil and recovered starting material **5.1** (0.054 g, 25%).

Compound **5.3** had: FTIR (CH_2Cl_2, cast) 3032, 2955, 2857, 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, J = 6.5 Hz, 3 H), 1.20-1.46 (m, 9 H), 1.49 (s, 3 H), 1.66-1.80 (m, 2 H), 1.87-1.96 (m, 1 H), 4.21 (dd, J = 9.9, 2.0 Hz, 1 H), 4.49 (AB q, $\Delta\nu_{AB}$ = 32.7 Hz, J = 11.2 Hz, 2 H), 4.68 (s, 2 H), 7.21-7.34 (m, 5 H), 7.49 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.0 (q), 22.5 (t), 22.6 (q), 25.7 (t), 28.2 (t), 29.1 (t), 29.3 (t), 31.7 (t), 48.9 (t), 66.5 (t), 71.1 (s), 85.5 (d), 127.2 (d), 127.9 (d), 128.5 (d), 130.7 (s), 137.8 (s), 154.5 (d), 161.4 (s), 189.6 (s); exact mass (HR electrospray) m/z calcd for $C_{22}H_{30}{}^{35.5}ClO_4$ (M + H) 393.1827, found 393.1827.

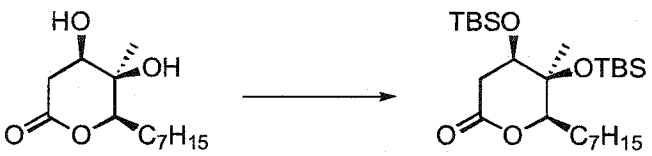
(4*R*,5*R*,6*R*)-6-Heptyl-4,5-dihydroxy-5-methyltetrahydropyran-2-one (6.1).

5.1 **6.1**

Pd-C (10%, 0.152 g) was added to a solution of **5.1** (0.347 g, 0.818 mmol) in EtOAc (10 mL). The reaction flask was flushed with H_2, and the mixture was stirred under H_2 (balloon) for 1.5 h. The mixture was filtered through a pad of silica gel and evaporated to give **6.1** (0.2 g, 100%): FTIR (CH_2Cl_2, cast) 3409, 2955, 2924, 2856, 1716 cm^{-1}; ^1H

NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, *J* = 6.8 Hz, 3 H), 1.20-1.40 [m, 12 H, including s (3 H) at δ 1.29], 1.60-1.84 (m, 3 H), 2.34 (br s, 1 H), 2.65 (dd, *J* = 17.6, 8.8 Hz, 1H), 2.67 (br s, 1 H), 2.84 (dd, *J* = 17.5, 6.6 Hz, 1 H), 3.79-3.85 (m, 1 H), 3.94 (dd, *J* = 10.4, 1.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.0 (q), 21.8 (q), 22.6 (t), 25.8 (t), 28.5 (t), 29.1 (t), 29.3 (t), 31.8 (t), 36.1 (t), 70.0(d), 70.5 (s), 83.3 (d), 170.4 (s); exact mass *m/z* calcd for $C_{13}H_{24}O_4$ 244.1675, found 244.1677.

(4*R*,5*S*,6*R*)-4,5-Bis(*tert*-butyldimethylsilanyloxy)-6-heptyl-5-methyltetrahydropyran-2-one (6.2).

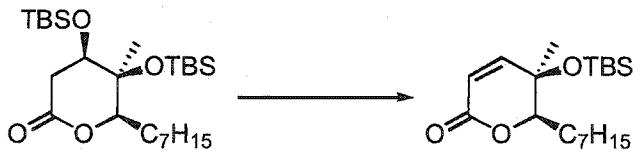


6.1 **6.2**

2,6-Lutidine (0.27 mL, 2.3 mmol), followed by *t*-$BuMe_2SiOSO_2CF_3$ (0.44 mL, 1.9 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **6.1** (0.189 g, 0.775 mmol) in CH_2Cl_2 (9 mL). The ice bath was left in place, but not recharged, and stirring was continued overnight. The mixture was diluted with CH_2Cl_2 (25 mL), washed with 5% hydrochloric acid (10 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 10% EtOAc-hexanes, gave **6.2** (0.332 g, 91%) as a white solid: mp = 79.5-80.5 °C; $[\alpha]_D$ = -14.7° (*c* = 1.0, $CHCl_3$); FTIR ($CHCl_3$, cast) 2954, 2928, 2857, 1783, 1476 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.05 and 0.09 (s, 12 H), 0.84-0.90 [m, 21 H, including two s (18 H) at δ 0.87 and δ 0.88], 1.20-1.50 [m, 15 H, including s (3 H) at δ 1.26], 2.42 (dd, *J* = 17.6, 5.5 Hz, 1 H), 2.79 (dd, *J* = 17.6, 7.3 Hz, 1 H), 3.50 (dd, *J* = 6.8, 1.4 Hz, 1 H), 4.19 (dd, *J* = 7.3, 5.5 Hz, 1 H); ^{13}C NMR

($CDCl_3$, 125.7 MHz) δ -5.2 (q), -4.4 (q), -4.3 (q), -4.1 (q), 14.0 (q), 15.2 (q), 17.9 (s), 18.3 (s), 22.6 (t), 25.6 (q), 26.0 (q), 26.3 (t), 29.1 (t), 29.8 (t), 31.8 (t), 32.9 (t), 39.2 (t), 71.1(d), 77.6 (d), 92.6 (s), 170.0 (s); exact mass (HR electrospray) *m/z* calcd for $C_{25}H_{52}NaO_4Si_2$ (M + Na) 495.3296, found 495.3299.

(5*R*,6*R*)-5-(*tert*-Butyldimethylsilanyloxy)-6-heptyl-5-methyl-5,6-dihydropyran-2-one (6.3).



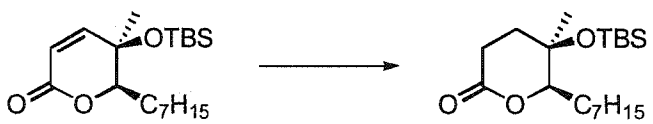
6.2 **6.3**

A solution of **6.2** (0.142 g, 0.300 mmol) in THF (1 mL) was added dropwise over 5 min to a stirred and cooled (-78 °C) solution of LDA [freshly prepared from *i*-Pr_2NH (50 μL, 0.35 mmol) and *n*-BuLi (0.20 mL, 1.6 M in hexanes)] in THF (3 mL). Stirring at -78 °C was continued for 1 h. Then Me_3SiCl (0.20 mL, 1.5 mmol) was added dropwise and the cooling bath was removed. Stirring was continued for 1 h, by which time the mixture had attained room temperature. The mixture was evaporated under water pump vacuum (protection from water) to give the crude silyl ether, which was kept under oil pump vacuum prior to use.

A solution of the crude silyl ether in THF (1 mL) was added dropwise to a stirred and cooled (0 °C) solution of $ClCH_2COCl$ (27 μL, 0.32 mmol) in THF (3 mL). The cooling bath was left in place, but not recharged, and stirring was continued for 6 h. The mixture was diluted with Et_2O (30 mL) and washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 10% EtOAc-hexanes, gave the starting material **6.2** (0.050g, 35%), and **6.3** (0.040 g, 39%,

or 60% after correction for recovered starting material) as a colorless oil. Compound **6.3** had: FTIR (CH_2Cl_2, cast) 3087, 2955, 2857, 1765 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.06 and 0.12 (s, 6 H), 0.88 (t, *J* = 7.1 Hz, 3 H), 0.90 (s, 9 H), 1.16-1.38 (m, 12 H), 1.42 (s, 3 H), 3.60 (dd, *J* = 5.9, 5.1 Hz, 1 H), 6.04 (d, *J* = 5.6 Hz, 1 H), 7.35 (d, *J* = 5.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -4.3 (q), -4.2 (q), 14.0 (q), 18.2 (s), 19.9 (q), 22.5 (t), 25.9 (q), 26.3 (t), 29.1 (t), 29.6 (t), 31.7 (t), 33.5 (t), 76.8 (d), 91.6 (s), 121.6 (d), 158.8 (d), 172.2 (s); exact mass (HR electrospray) *m/z* calcd for $C_{19}H_{36}NaO_3Si$ (M + Na) 363.2326, found 363.2325.

(5*R*,6*R*)-5-(*tert*-Butyldimethylsilanyloxy)-6-heptyl-5-methyltetrahydropyran-2-one (7.1).

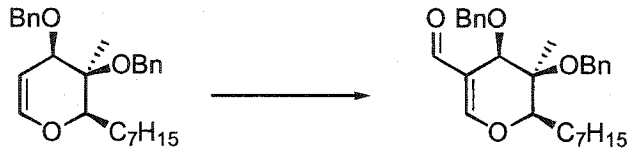


6.3 **7.1**

Pd-C (10%, 0.031 g) was added to a solution of **6.3** (0.114 g, 0.335 mmol) in EtOAc (5 mL). The reaction flask was flushed with H_2, and the mixture was stirred under H_2 (balloon) for 1 h. The mixture was then filtered through a pad of silica gel. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.5 x 20 cm), using 10% EtOAc-hexanes, gave **7.1** (0.109 g, 95%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2928, 2856, 1778 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.05 and 0.11 (s, 6 H), 0.86 (t, *J* = 7.1 Hz, 3 H), 0.88 (s, 9 H), 1.18-1.60 [m, 15 H, including s (3 H) at δ 1.30], 1.81-1.89 (m, 1 H), 1.97-2.06 (m, 1 H), 2.46-2.64 (m, 2 H), 3.55 (dd, *J* = 7.9, 3.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ -4.4 (q), -4.1 (q), 14.0 (q), 18.3 (s), 20.9 (q), 22.6 (t), 26.0 (q), 26.4 (t), 29.0 (t), 29.1 (t), 29.7 (t), 30.8 (t), 31.8 (t), 32.6 (t),

78.1(d), 89.0 (s), 176.4 (s); exact mass (HR electrospray) *m/z* calcd for $C_{19}H_{38}NaO_3Si$ (M + Na) 365.2483, found 365.2486.

(4*R*,5*S*,6*R*)-4,5-Bisbenzyloxy-6-heptyl-5-methyl-5,6-dihydro-4*H*-pyran-3-carbaldehyde (8.1).

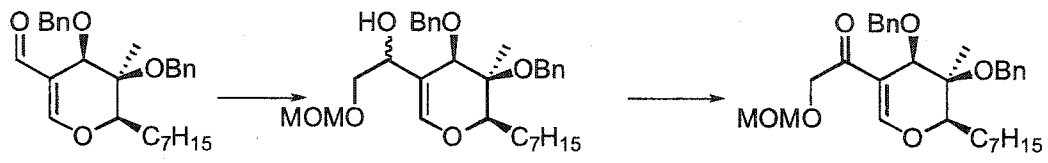


4.5 **8.1**

$POCl_3$ (0.40 mL, 4.2 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **4.5** (0.571 g, 1.40 mmol) in dry DMF (8 mL). The ice bath was left in place, but not recharged, and stirring was continued overnight. The solution was recooled to 0 °C, and saturated aqueous $NaHCO_3$ (10 mL) was added slowly. The resulting mixture was extracted with Et_2O (2 x 30 mL), and the combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 15% EtOAc-hexanes, gave **8.1** (0.565 g, 93%) as a colorless oil: $[\alpha]_D$ = +46.3° (*c* = 1.0, $CHCl_3$); FTIR ($CHCl_3$, cast) 3030, 2924, 2855, 1675, 1621, 1204 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, *J* = 6.9 Hz, 3 H), 1.21-1.40 [m, 12 H, including s (3 H) at δ 1.32], 1.48-1.58 (m, 1 H), 1.98-2.15 (m, 1 H), 4.21 (dt, *J* = 10.5, 2.1 Hz, 1 H), 4.44 (d, *J* = 1.8 Hz, 1 H), 4.58 (AB q, $\Delta\nu_{AB}$ = 57.0 Hz, *J* = 10.9 Hz, 2 H), 4.74 (AB q, $\Delta\nu_{AB}$ = 29.0 Hz, *J* = 11.5 Hz, 2 H), 7.20-7.40 (m, 10 H), 9.44 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.1 (q), 21.4 (q), 22.6 (t), 27.3 (t), 28.4 (t), 29.2 (t), 29.3 (t), 31.8 (t), 64.2 (t), 69.7 (d), 73.5 (t), 74.4 (s), 85.2(d), 119.9 (s), 127.1 (d), 127.3 (d), 127.4 (d), 128.0 (d), 128.2 (d), 138.6 (s), 139.1 (s), 164.2 (d), 190.0 (d); exact mass (HR

electrospray) *m/z* calcd for $C_{28}H_{36}NaO_4$ (M + Na) 459.2511, found 459.2511.

1-[(4*R*,5*S*,6*R*)-4,5-Bisbenzyloxy-6-heptyl-5-methyl-5,6-dihydro-4*H*-pyran-3-yl]-2-(methoxymethoxy)ethanone (8.3).



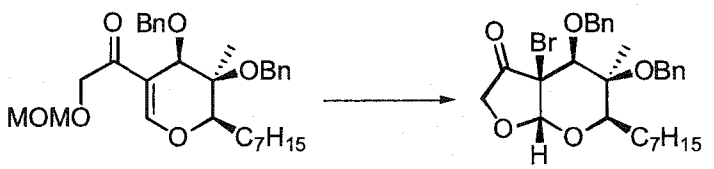
8.1 **8.2** **8.3**

n-BuLi (7.5 mL, 1.6 M in hexanes) was added dropwise to a stirred and cooled (-78 °C) solution of $MeOCH_2OCH_2SnBu_3$[15] (6.10 g, 16.7 mmol) in THF (25 mL). Stirring was continued for 30 min, and a solution of aldehyde **8.1** (0.871 g, 2.00 mmol) in THF (8 mL) was then added dropwise over 10 min. The mixture was stirred at -78 °C for an additional 2 h, and saturated aqueous $NaHCO_3$ (15 mL) was added. The resulting mixture was extracted with Et_2O (2 x 40 mL), and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 30% EtOAc-hexanes, gave **8.2** (0.926 g, 90%) as a 1:2 mixture of two epimers (^1H NMR).

NMO (0.52 g, 4.44 mmol), followed by Pr_4NRuO_4 (70 mg, 0.18 mmol), was added to a stirred solution of **8.2** (0.913 g, 1.78 mmol) in CH_2Cl_2 (9 mL). Stirring was continued for 1 h, and the mixture was filtered through a pad of silica gel. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 20 cm), using 20% EtOAc-hexanes, gave **8.3** (0.709 g, 78%) as a single isomer: $[\alpha]_D$ = +1.6° (*c* = 1.0, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3064, 3030, 2925, 2856, 1674, 1617, 1197 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, *J* = 6.9 Hz, 3 H), 1.20-1.40 [m, 12 H, including s (3 H) at δ 1.32], 1.46-1.56 (m, 1 H), 2.01-2.10

(m, 2 H), 3.40 (s, 2 H), 4.16-4.20 (m, 1 H), 4.45 (AB q, $\Delta\nu_{AB}$ = 28.0 Hz, J = 15.5 Hz, 2 H), 4.51 (d, J = 1.9 Hz, 1 H), 4.60 (AB q, $\Delta\nu_{AB}$ = 60.6 Hz, J = 11.0 Hz, 2 H), 4.72 (s, 2 H), 4.75 (AB q, $\Delta\nu_{AB}$ = 35.7 Hz, J = 11.3 Hz, 2 H), 7.18-7.35 (m, 10 H), 7.56 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.1 (q), 21.6 (q), 22.7 (t), 27.4 (t), 28.2 (t), 29.2 (t), 29.3 (t), 31.8 (t), 55.8 (q), 64.1 (t), 69.3 (t), 71.2 (d), 74.2 (t), 74.9 (s), 83.5 (d), 96.7 (t), 116.0 (s), 127.0 (d), 127.2 (d), 127.3 (d), 128.0 (d), 128.3 (d), 138.6 (s), 139.3 (s), 155.8 (d), 194.0 (s); exact mass (HR electrospray) *m/z* calcd for $C_{31}H_{42}NaO_6$ (M + Na) 533.2879, found 533.2873.

(3a*S*,4*S*,5*S*,6*R*,7a*S*)-4,5-Bisbenzyloxy-3a-bromo-6-heptyl-5-methyltetrahydrofuro[2,3-*b*]pyran-3-one (8.4).

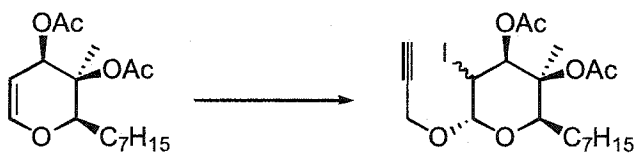


8.3 **8.4**

NBS (87 mg, 0.49 mmol) was added to a stirred and cooled (0 °C) solution of **8.3** (0.216 g, 0.423 mmol) in CH_2Cl_2 (18 mL), and CF_3CO_2H (0.16 mL, 2.08 mmol) was then added dropwise. The ice bath was left in place, but not recharged, and stirring was continued overnight. The mixture was diluted with CH_2Cl_2 (15 mL), washed with saturated $NaHCO_3$ (8 mL), water (8 mL) and brine (8 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 10% EtOAc-hexanes, gave **8.4** (0.121 g, 53%) as a single isomer: $[\alpha]_D$ = -21.2° (*c* = 1.0, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3064, 3030, 2925, 2855, 1770, 1454, 1064 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, J = 6.8 Hz, 3 H), 1.20-1.82 [m, 15 H, including s (3 H) at δ 1.29], 3.30 (dd, J = 10.1, 2.2 Hz, 1 H), 3.93 (s,

1 H), 4.23 (AB q, $\Delta\nu_{AB}$ = 27.4 Hz, J = 16.0 Hz, 2 H), 4.67 (AB q, $\Delta\nu_{AB}$ = 106.4 Hz, J = 11.9 Hz, 2 H), 4.79 (d, J = 11.4 Hz, 1 H), 5.28 (d, J = 11.4 Hz, 1 H), 5.45 (s, 1 H), 7.18-7.52 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.1 (q), 16.9 (q), 22.6 (t), 26.1 (t), 28.0 (t), 29.3 (t), 29.5 (t), 31.8 (t), 55.7 (s), 66.2 (t), 68.3 (t), 78.0 (t), 79.1 (d), 89.3 (d), 105.2 (d), 126.8 (d), 127.1 (d), 127.2 (d), 127.7 (d), 128.0 (d), 128.4 (d), 137.9 (s), 139.8 (s), 200.5 (s); exact mass (HR electrospray) *m/z* calcd for $C_{29}H_{37}{}^{79}BrNaO_5$ (M + Na) 567.1717, found 567.1714.

Acetic Acid (2*R*,3*S*,4*S*,6*S*)-3-Acetoxy-2-heptyl-5-iodo-3-methyl-6-(prop-2-ynyloxy)tetrahydropyran-4-yl Ester (10.1a,b).



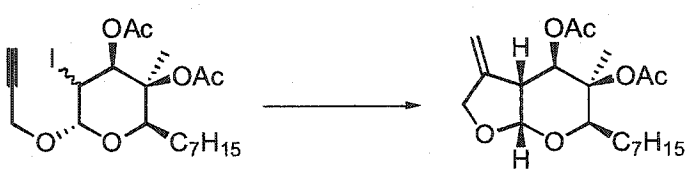
4.3 **10.1a,b**

A solution of **4.3** (1.52 g, 4.88 mmol) in CH_3CN (3 mL) was added dropwise to a stirred and cooled (-25 °C) solution of NIS (1.31 g, 5.86 mmol) and propargyl alcohol (0.30 mL, 4.91 mmol) in CH_3CN (15 mL). The cold bath was left in place, but not recharged, and stirring was continued for 24 h. The mixture was diluted with Et_2O (80 mL), washed with 10% of aqueous $Na_2S_2O_3$ (20 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 10% EtOAc-hexanes, gave the faster-eluting isomer **10.1a** (1.65 g, 68%) containing slight impurities (^{1}H NMR), and the slower-eluting isomer **10.1b** (0.55 g, 23%). Compound **10.1a** had: FTIR (CH_2Cl_2, cast) 3283, 2955, 2926, 2856, 2130, 1749, 1233 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, J = 6.8 Hz, 3 H), 1.18-1.60 [m, 15 H, including s (3 H) at δ 1.53], 2.06 (s, 3

H), 2.11 (s, 3 H), 2.45 (t, J = 2.4 Hz, 1 H), 3.63 (dd, J = 10.0, 1.7 Hz, 1 H), 4.24 (d AB q, $\Delta\nu_{AB}$ = 41.6 Hz, J = 15.6, 3.4 Hz, 2 H), 4.36 (dd, J = 11.6, 3.4 Hz, 1 H), 5.18 (d, J = 3.4 Hz, 1 H), 5.28 (d, J = 11.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.0 (q), 19.7 (q), 20.9 (q), 22.4 (q), 22.6 (t), 26.1 (d), 26.4 (t), 28.4 (t), 29.2 (t), 29.4 (t), 31.8 (t), 54.9 (t), 74.4 (d), 74.9 (d), 75.4 (d), 77.9 (s), 84.0 (s), 97.1 (d), 169.6 (s), 170.1 (s); exact mass (HR electrospray) m/z calcd for $C_{20}H_{31}INaO_6$ (M + Na) 517.1063, found 517.1064.

Compound **10.1b** had: $[\alpha]_D$ = +73.8° (c = 0.96, $CHCl_3$); FTIR (CH_2Cl_2, cast) 3273, 3030, 2955, 2925, 2855, 2120, 1746, 1233 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, J = 7.0 Hz, 3 H), 1.20-1.33 (m, 9 H), 1.44-1.62 [m, 5 H, including s (3 H) at δ 1.58], 1.75-1.85 (m, 1 H), 2.06 (s, 3 H), 2.13 (s, 3 H), 2.46 (t, J = 2.4 Hz, 1 H), 3.81 (dd, J = 11.0, 1.7 Hz, 1 H), 4.18-4.30 (m, 3 H), 5.03 (d, J = 4.0 Hz, 1 H), 5.33 (d, J = 4.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.0 (q), 20.7 (q), 21.0 (q), 22.5(q), 22.6 (t), 23.9 (d), 26.4 (t), 27.5 (t), 29.2 (t), 29.4 (t), 31.8 (t), 54.8 (t), 71.8 (d), 75.3 (d), 76.5 (d), 78.2 (s), 79.7 (s), 98.7 (d), 169.4(s); exact mass (HR electrospray) m/z calcd for $C_{20}H_{31}INaO_6$ (M + Na) 517.1063, found 517.1062.

Acetic Acid (2*S*,3*R*,4*R*,5*S*,6*R*)-5-Acetoxy-6-heptyl-5-methyl-3-methylenehexahydrofuro[2,3-*b*]pyran-4-yl Ester (10.2).



10.1a,b **10.2**

A solution of Bu_3SnH (4.51 mL, 16.8 mmol) and AIBN (0.261 g, 1.58 mmol) in PhH (30 mL) was added by syringe

pump over 10 h to a stirred and heated (85 °C) solution of **10.1a,b** (5.165 g, 10.45 mmol) in PhH (120 mL). Heating was continued for 2 h after the addition, and the mixture was then allowed to cool to room temperature. Evaporation of solvent and flash chromatography of the residue over silica gel (3 x 25 cm), using 15% EtOAc-hexanes, gave **10.2** (3.1 g, 80%): $[\alpha]_D$ = +43.9° (*c* = 1.0, $CHCl_3$); FTIR (CH_2Cl_2, cast) 2955, 2926, 2857, 1746, 1236 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.87 (t, *J* = 6.9 Hz, 3 H), 1.22-1.36 (m, 9 H), 1.52 (s, 3 H), 1.55-1.68 (m, 3 H), 2.08 (s, 3 H), 2.11 (s, 3 H), 2.77 (dd, *J* = 9.1, 5.3 Hz, 1 H), 3.73 (dd, *J* = 9.8, 2.8 Hz, 1 H), 4.29-4.34 (m, 1 H), 4.58-4.64 (m, 1 H), 4.92-4.95 (m, 1 H), 5.03 (d, *J* = 9.2 Hz, 1 H), 5.05-5.08 (m, 1 H), 5.41 (d, *J* = 4.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.1 (q), 19.3 (q), 20.7 (q), 22.3 (q), 22.6 (t), 26.2 (t), 28.7 (t), 29.2 (t), 29.4 (t), 31.8 (t), 44.3 (d), 68.2 (t), 73.8 (d), 76.6 (d), 79.8 (s), 100.5 (d), 107.9 (t), 145.5 (s), 169.8 (s), 170.5 (s); exact mass (HR electrospray) *m/z* calcd for $C_{20}H_{32}NaO_6$ (M + Na) 391.2091, found 391.2092.

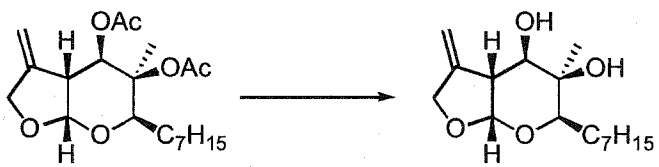
Acetic Acid (5*R*,6*R*,7a*S*)-6-Heptyl-5-methyl-3-oxo-2,3,5,7a-tetrahydro-6*H*-furo[2,3-*b*]pyran-5-yl Ester (10.3).

10.2 **10.3**

An O_3-O_2 stream was passed through a stirred and cooled (-78 °C) solution of **10.2** (25 mg, 0.068 mmol) in dry CH_2Cl_2 (3 mL) for 30 min. The solution was purged with O_2 for 10 min, and then Ph_3P (37 mg, 0.14 mmol) was added. The cooling bath was removed and stirring was continued for 3 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 10% EtOAc-

hexanes, gave **10.3** (15 mg, 71%) containing some impurities (^{1}H NMR): FTIR (CH_2Cl_2, cast) 2955, 2926, 2857, 1743, 1249, 1224 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, *J* = 6.8 Hz, 3 H), 1.20-1.80 (m, 15 H), 2.01 (s, 3 H), 3.33 (dd, *J* = 11.1, 2.2 Hz, 1 H), 4.14 (AB q, $\Delta\nu_{AB}$ = 47.8 Hz, *J* = 6.9 Hz, 2 H), 5.80 (s, 1 H), 7.20 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.1 (q), 20.9 (q), 21.2 (q), 22.6 (t), 26.2 (t), 28.3 (t), 29.2 (t), 29.6 (t), 31.8 (t), 71.1 (t), 72.5 (s), 76.8 (d), 97.1 (d), 133.8(s), 138.1 (d), 170.0 (s), 199.1 (s); exact mass (HR electrospray) *m/z* calcd for $C_{17}H_{27}O_5$ (M + H) 311.1853, found 311.1850.

(3a*R*,4*R*,5*R*,6*R*,7a*S*)-6-Heptyl-5-methyl-3-methylenehexahydrohydrofuro[2,3-*b*]pyran-4,5-diol (11.1).



10.2 **11.1**

K_2CO_3 (55 mg, 0.34 mmol) was added to a stirred solution of **10.2** (31 mg, 0.084 mmol) in MeOH (2 mL). After 30 min, the mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 30% EtOAc-hexanes, gave **11.1** (20 mg, 84%) as a white solid: mp = 99-100 °C; $[\alpha]_D$ = +39.3° (*c* = 0.6, $CHCl_3$); FTIR (CH_2Cl_2, cast) 3441, 3386, 3085, 2958, 2926, 2882 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, *J* = 7.1 Hz, 3 H), 1.22 (s, 3 H), 1.23-1.38 (m, 9 H), 1.54-1.66 (m, 3 H), 2.02 (br s, 1 H), 2.13 (br s, 1 H), 2.45 (dd, *J* = 9.0, 4.5 Hz, 1 H), 3.23 (t, *J* = 8.9 Hz, 1 H), 3.70-3.75 (m, 1 H), 4.31 (dt, *J* = 13.4, 2.2 Hz, 1 H), 4.53-4.60 (m, 1 H), 4.95-4.99 (m, 1 H), 5.21-5.25 (m, 1 H), 5.35

(d, J = 4.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.1 (q), 20.0 (q), 22.6 (t), 25.9 (t), 27.8 (t), 29.2 (t), 29.5 (t), 31.8 (t), 47.2 (d), 68.2 (t), 70.7 (s), 74.0 (d), 74.9 (d), 100.9 (d), 107.4 (t), 146.9 (s); exact mass (HR electrospray) *m/z* calcd for $C_{16}H_{28}NaO_4$ (M + Na) 307.1880, found 307.1881.

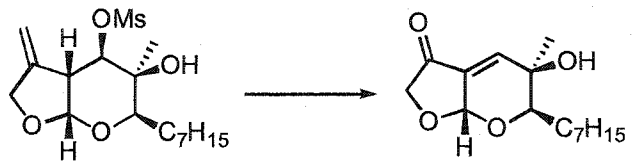
Methanesulfonic Acid (3a*R*,4*R*,5*S*,6*R*,7a*S*)-6-Heptyl-5-hydroxy-5-methyl-3-methylenehexahydrofuro[2,3-*b*]pyran-4-yl Ester (11.2).

11.1 **11.2**

Et_3N (0.87 mL, 6.2 mmol), followed by $MeSO_2Cl$ (0.24 mL, 3.1 mmol), was added dropwise to a stirred and cooled (0 °C) solution of **11.1** (0.176 g, 0.618 mmol) in CH_2Cl_2 (7 mL). The cold bath was left in place, but not recharged, and stirring was continued for 4 h. The mixture was diluted with CH_2Cl_2 (20 mL), washed with 5% of HCl (5 mL), water (5 mL) and brine (5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 25 cm), using 30% EtOAc-hexanes, gave **11.2** (0.172 g, 77%) as a colorless oil: $[\alpha]_D$ = +8.9° (*c* = 1.0, $CHCl_3$); FTIR (CH_2Cl_2, cast) 3509, 2954, 2925, 2856, 1447, 1223 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, J = 7.1 Hz, 3 H), 1.22-1.39 (m, 12 H), 1.52-1.68 (m, 3 H), 2.00 (br s, 1 H), 2.90 (dd, J = 9.7, 4.1 Hz, 1 H), 3.11 (s, 3 H), 3.81 (dd, J = 9.5, 3.0 Hz, 1 H), 4.34 (dt, J = 13.3, 2.0 Hz, 1 H), 4.58 (d, J = 9.8 Hz, 1 H), 4.61-4.67 (m, 1 H), 5.10-5.13 (m, 1 H), 5.24-5.27 (m, 1 H), 5.38 (d, J = 4.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.1 (q), 21.3 (q), 22.6 (t), 25.7 (t), 27.9 (t), 29.2 (t), 29.4 (t), 31.8 (t), 39.4 (q), 45.4 (d),

68.0 (t), 70.8 (s), 75.3 (d), 84.2 (d), 100.6 (d), 110.2 (t), 144.8 (s); exact mass (HR electrospray) *m/z* calcd for $C_{17}H_{30}NaO_6S$ (M + Na) 385.1655, found 385.1658.

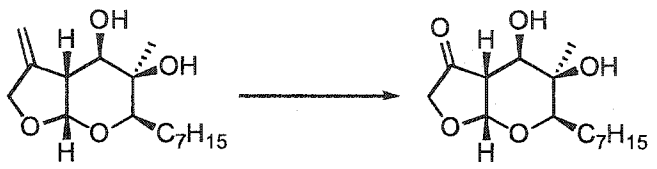
(5*R*,6*R*,7a*S*)-6-Heptyl-5-hydroxy-5-methyl-5,7a-dihydro-6*H*-furo[2,3-*b*]pyran-3-one (10.4).



11.2 **10.4**

An O_3-O_2 stream was passed through a stirred and cooled (-78 °C) solution of **11.2** (24 mg, 0.066 mmol) in dry CH_2Cl_2 (3 mL) for 30 min. The solution was purged with O_2 for 10 min, and then Ph_3P (26 mg, 0.10 mmol) was added. The cooling bath was removed and stirring was continued for 2 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 20% EtOAc-hexanes, gave **10.4** (7 mg, 32%) containing some impurities (^{1}H NMR): FTIR (CH_2Cl_2, cast) 3420, 2955, 2926, 2856, 1739, 1688 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, *J* = 7.1 Hz, 3 H), 1.24-1.44 [m, 12 H, including s (3 H) at δ 1.37], 1.59-1.72 (m, 3 H), 1.90 (br s, 3 H), 3.45 (dd, *J* = 9.5, 3.2 Hz, 1 H), 4.17 (AB q, $\Delta\nu_{AB}$ = 44.3 Hz, *J* = 6.9 Hz, 2 H), 5.82 (d, *J* = 1.7 Hz, 1 H), 6.84 (d, *J* = 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.1 (q), 22.6 (t), 24.1 (q) 26.0 (t), 27.4 (t), 29.2 (t), 29.6 (t), 31.8 (t), 66.0 (s), 71.4 (t), 77.6 (d), 97.0 (d), 135.6 (s), 139.1 (d), 199.3 (s); exact mass (HR electrospray) *m/z* calcd for $C_{15}H_{25}O_4$ (M + H) 269.1747, found 269.1748.

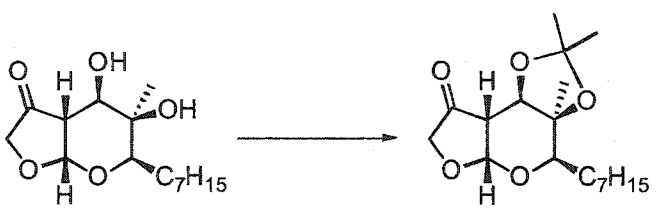
(3a*R*,4*R*,5*R*,6*R*,7a*S*)-6-Heptyl-4,5-dihydroxy-5-methyl-tetrahydrofuro[2,3-*b*]pyran-3-one (12.1).



11.1 **12.1**

An O_3-O_2 stream was passed through a stirred and cooled (-78 °C) solution of **11.1** (71.5 mg, 0.252 mmol) in dry CH_2Cl_2 (5 mL) for 20 min. The solution was purged with O_2 for 10 min, and then Ph_3P (132 mg, 0.504 mmol) was added. The cooling bath was removed and stirring was continued for 3 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexanes, gave **12.1** (65 mg, 90%) as a white solid: mp = 95-96 °C; $[\alpha]_D$ = +3.5° (*c* = 1.0, $CHCl_3$); FTIR (CH_2Cl_2, cast) 3408, 2954, 2923, 2855, 1761, 1242 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, *J* = 6.9 Hz, 3 H), 1.22-1.42 [m, 12 H, including s (3 H) at δ 1.26], 1.57-1.73 (m, 3 H), 2.04 (br s, 3 H), 2.47 (dd, *J* = 8.6, 4.7 Hz, 1 H), 2.47 (br s, 1 H), 3.55 (d, *J* = 8.7 Hz, 1 H), 3.73 (dd, *J* = 10.1, 1.8 Hz, 1 H), 4.02 (d, *J* = 7.5 Hz, 1 H), 4.35 (d, *J* = 7.5 Hz, 1 H), 5.64 (d, *J* = 4.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.1 (q), 20.7 (q), 22.6 (t), 25.9 (t), 27.7 (t), 29.2 (t), 29.4 (t), 31.8 (t), 50.2 (d), 70.3 (s), 70.6 (t), 70.9 (d), 76.0 (d), 99.1 (d), 212.8 (s); exact mass (HR electrospray) *m/z* calcd for $C_{15}H_{26}NaO_5$ (M + Na) 309.1672, found 309.1674.

(3a*S*,4*R*,5a*S*,8a*R*,8b*R*)-4-Heptyl-2,2,3a-trimethyl-tetrahydro-1,3,5,6-tetraoxa-*as*-indacen-8-one (12.2).



12.1 **12.2**

$TsOH \cdot H_2O$ (ca 1 mg) was added to a stirred solution of **12.1** (20 mg, 0.070 mmol) and $Me_2C(OMe)_2$ (50 μL, 0.70 mmol) in dry acetone (2 mL), and stirring was continued for 24 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 20 cm), using 10% EtOAc-hexanes, gave **12.2** (20 mg, 88%) as a colorless oil: $[\alpha]_D$ = -113.9° (*c* = 1.0, $CHCl_3$); FTIR (CH_2Cl_2, cast) 2981, 2955, 2926, 2856, 1757, 1209 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, *J* = 6.9 Hz, 3 H), 1.19 (s, 3 H), 1.22-1.34 (m, 9 H), 1.39 (s, 3 H), 1.43 (s, 3 H), 1.44-1.65 (m, 3 H), 2.92 (dd, *J* = 9.5, 1.6 Hz, 1 H), 3.18 (dd, *J* = 7.2, 3.0 Hz, 1 H), 4.23 (AB q, $\Delta\nu_{AB}$ = 10.8 Hz, *J* = 17.9 Hz, 2 H), 4.53 (d, *J* = 3.1 Hz, 1 H), 5.86 (d, *J* = 7.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.1 (q), 22.6 (t), 24.1 (q), 26.1 (t), 26.5 (q), 26.9 (q), 28.7 (t), 29.2 (t), 29.4 (t), 31.8 (t), 46.5 (d), 72.3 (t), 76.3 (d), 78.1 (d), 79.4 (s), 99.0 (d), 109.4 (s), 211.6 (s); exact mass (HR electrospray) *m/z* calcd for $C_{18}H_{30}NaO_5$ (M + Na) 349.1986, found 349.1985.

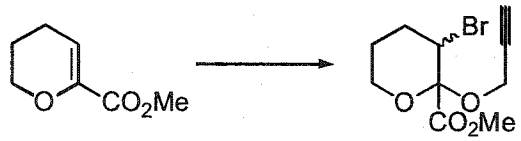
5,6-Dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester (13.4).

13.3 **13.4**

$NaHCO_3$ (5.911 g, 70.35 mmol), followed by Me_2SO_4 (7.1 mL, 75 mmol) was added to a stirred solution of acid **13.3**[20] (6.006, 46.88 mmol) in MeOH (50 mL). The mixture was refluxed for 5 h, cooled to room temperature, diluted with EtOAc (200 mL), washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.5 x 25 cm), using 15% EtOAc-hexanes, gave **13.4** (5.37, 81%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2952, 2877, 1732, 1648, 1266 cm^{-1}; ^1H NMR

($CDCl_3$, 500 MHz) δ 1.83-1.89 (m, 2 H), 2.19 (dt, *J* = 6.4, 4.2 Hz, 2 H), 3.79 (s, 3 H), 4.11 (dd, *J* = 5.2, 5.2 Hz, 2 H), 6.07 (d, *J* = 4.2 Hz, 1 H; ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 20.6 (t), 21.5 (t), 52.1 (q), 66.7 (t), 111.4 (d), 144.2 (s), 163.5 (s); exact mass *m/z* calcd for $C_7H_{10}O_3$ 142.0630, found 142.0631.

3-Bromo-2-(prop-2-ynyloxy)tetrahydropyran-2-carboxylic Acid Methyl Ester (13.5).



13.4 **13.5a,b**

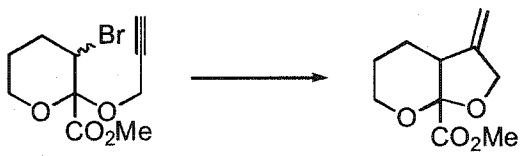
Br_2 (0.40 mL, 7.8 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a stirred solution of **13.4** (1.0 g, 7.1 mmol) in CH_2Cl_2 (30 mL), and stirring was continued for 2 h. The mixture was diluted with CH_2Cl_2 (30 mL), washed with 10% of $Na_2S_2O_3$ (10 mL), water (10 mL) and brine (10 mL), and dried ($MgSO_4$). Evaporation of the solvent gave crude bromide (1.71 g), which was used without purification in next step.

A solution of the above bromide in $ClCH_2CH_2Cl$ (5 mL) was added dropwise to a stirred mixture of $AgOCOCF_3$ (3.70 g, 14.2 mmol), 4Å molecular sieve (7 g) and propargyl alcohol (1.65 mL, 28.4 mmol) in $ClCH_2CH_2Cl$ (40 mL). Stirring was continued overnight, and the mixture was diluted with CH_2Cl_2 (30 mL), and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (15 mL) and water (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 10% EtOAc-hexanes, gave the faster-eluting isomer **13.5a** (0.236 g, 12%) and the slower-eluting isomer **13.5b** (0.63 g, 32%). Compound **13.5a** had: FTIR (CH_2Cl_2, cast) 3286, 2954, 2879, 2126, 1755, 1234 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.68-1.76 (m, 1 H), 2.36 (dq, *J* = 12.8, 4.1 Hz, 1 H), 2.45 (t, *J* = 1.5 Hz, 1 H),

3.76-3.83 [m, 4 H, including a s (3 H) at δ 3.80], 3.87 (dq, J = 12.4, 3.7 Hz, 1 H), 4.26 (dd, J = 12.4, 3.4 Hz, 1 H), 4.45 (d AB q, $\Delta\nu_{AB}$ = 108.4 Hz, J = 15.6, 2.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.9 (t), 29.2 (t), 48.4 (d), 52.2 (t), 52.9 (q), 61.9 (t), 74.3 (d), 79.6 (s), 98.9 (s), 167.3 (s); exact mass (HR electrospray) *m/z* calcd for $C_{10}H_{13}{}^{79}BrNaO_4$ (M + Na) 298.9889, found 298.9886.

Compound **13.5b** had: FTIR (CH_2Cl_2, cast) 3282, 2953, 2124, 1761, 1215 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.38-1.44 (m, 1 H), 1.97-2.05 (m, 1 H), 2.15-2.26 (m, 1 H), 2.44 (t, J = 2.4 Hz, 1 H), 2.45-2.54 (m, 1 H), 3.75-3.83 [m, 4 H, including a s (3 H) at δ 3.80], 3.89-3.96 (m, 1 H), 4.13 (d AB q, $\Delta\nu_{AB}$ = 91.5 Hz, J = 15.4, 2.5 Hz, 2 H), 4.38 (t, J = 3.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 18.9 (t), 26.9 (t), 48.9 (d), 52.1 (t), 52.7 (q), 62.2 (t), 74.7 (d), 78.4 (s), 98.0 (s), 167.2 (s); exact mass (HR electrospray) *m/z* calcd for $C_{10}H_{13}{}^{79}BrNaO_4$ (M + Na) 298.9889, found 298.9890.

3-Methylenehexahydrofuro[2,3-*b*]pyran-7a-carboxylic Acid Methyl Ester (13.6).



13.5b **13.6**

A solution of Bu_3SnH (1.14 mL, 4.28 mmol) and AIBN (50 mg, 0.30 mmol) in PhH (15 mL) was added by syringe pump over 10 h to a stirred and heated (85 °C) solution of **13.5b** (0.592 g, 2.14 mmol) in PhH (45 mL). Heating was continued for 2 h, and the mixture was allowed to cool to room temperature. Evaporation of solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 10% EtOAc-hexanes, gave **13.6** (0.239 g, 56%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2953, 2874, 1742, 1213

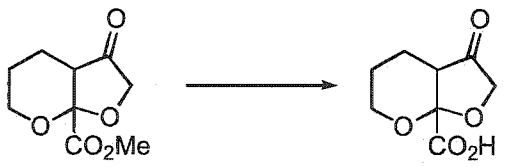
cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.29-1.41 (m, 1 H), 1.63-1.76 (m, 1 H), 1.93-2.07 (m, 1 H), 3.03-3.08 (m, 1 H), 3.59-3.66 (m, 1 H), 3.80 (s, 3 H), 3.84-3.90 (m, 1 H), 4.55-4.65 (m, 2 H), 4.97 (q, *J* = 2.6 Hz, 1 H), 5.04 (q, *J* = 2.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 19.7 (t), 22.2 (t), 43.0 (d), 52.6 (q), 64.5 (t), 71.3 (t), 103.3 (s), 104.6 (t), 146.4 (s), 168.7 (s); exact mass *m/z* calcd for $C_{10}H_{14}O_4$ 198.0892, found 198.0890.

3-Oxohexahydrofuro[2,3-*b*]pyran-7a-carboxylic Acid Methyl Ester (13.7).

13.6 **13.7**

An O_3-O_2 stream was passed through a stirred and cooled (-78 °C) solution of **13.6** (0.238 g, 1.20 mmol) in dry CH_2Cl_2 (10 mL) for 30 min. The solution was purged with O_2 for 15 min, and then Ph_3P (0.411 g, 1.56 mmol) was added. The cooling bath was removed and stirring was continued for 3 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 25 cm), using 20% EtOAc-hexanes, gave **13.7** (0.175 g, 73%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2955, 1765, 1742, 1201 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40-1.50 (m, 2 H), 1.86-1.98 (m, 1 H), 2.19-2.28 (m, 1 H), 2.91 (dd, *J* = 6.1, 2.7 Hz, 1 H), 1 H), 3.54-3.65 (m, 1 H), 3.87 (s, 3 H), 3.90-3.98 (m, 1 H), 4.23 (AB q, $\Delta\nu_{AB}$ = 19.8 Hz, *J* = 16.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.9 (t), 21.0 (t), 47.6 (d), 53.0 (q), 64.9 (t), 70.4 (t), 102.4 (s), 167.6 (s), 211.1 (s); exact mass (HR electrospray) *m/z* calcd for $C_9H_{12}NaO_5$ (M + Na) 223.5770, found 223.0581.

3-Oxohexahydrofuro[2,3-*b*]pyran-7a-carboxylic Acid (13.8).



13.7 **13.8**

$(Bu_3Sn)_2O$ (0.44 mL, 0.88 mmol) was added to a stirred solution of **13.7** (0.044 g, 0.22 mmol) in PhH (3 mL). The mixture was refluxed for 5 h, and then cooled to room temperature. The solvent was evaporated, EtOAc (10 mL) was added, and the resulting solution was extracted with saturated aqueous $NaHCO_3$ (2 x 10 mL). The aqueous phase was acidified (pH = 3) with 10% of hydrochloric acid, and then extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give **13.8** (41 mg, 100%), which was pure as judged by ^1H NMR: FTIR (CH_2Cl_2, cast) 3500-2500, 1766 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.43-1.54 (m, 2 H), 1.90-2.01 (m, 1 H), 2.16-2.26 (m, 1 H), 2.89 (dd, J = 6.3, 3.4 Hz, 1 H), 1 H), 3.70-3.77 (m, 1 H), 3.94-4.02 (m, 1 H), 4.27 (AB q, $\Delta\nu_{AB}$ = 25.2 Hz, J = 16.6 Hz, 2 H), 5.75 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.9 (t), 21.0 (t), 47.0 (d), 65.0 (t), 70.5 (t), 101.8 (s), 169.5 (s), 210.5 (s); exact mass (HR electrospray) *m/z* calcd for $C_8H_{11}O_5$ (M + H) 187.0601, found 187.0603.

REFERENCES AND NOTES

1 Hewitt, H. G. *Fungicides in Crop Protection*; CAB International: New York, NY, 1998; p 14.

2 Copping, L. G.; Hewitt, H. G. *Chemistry and Mode of Action of Crop Protection Agents*; Royal Society of Chemistry: Cambridge, England, 1998, p 5.

3 (a) See reference 1, p 9. (b) *Encyclopedia of Plant Pathology*, Maloy, O. C.; Murray, T. D., Eds.; Wiley: New York, 2001; Vol 1, p 483.

4 Thines, E.; Arendholz, W. R.; Anke, H. *J. Antibiot.* **1997**, *50*, 13.

5 Satomura, S.; Iwata, T.; Sakata, Y.; Omichi, K.; Ikenaka, T. *Carbohydr. Res.* **1988**, *176*, 107.

6 (a) Dasgupta, F.; Anderson, L. *Carbohydr. Res.* **1990**, *202*, 239. (b) Spencer, R. P.; Yu, H. K.; Cavallaro, C. L.; Schwartz, J. *J. Org. Chem.* **1997**, *62*, 4507.

7 Davis, N. J.; Flitsch, S. L. *J. Chem. Soc., Perkin Trans. 1* **1994**, *4*, 359.

8 Toshima, H.; Sato, H.; Ichihara, A. *Tetrahedron* **1999**, *55*, 2581.

9 Sato, K.; Kubo, K.; Hong, N.; Kodama, H.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 938.

10 (a) Hakamata, W.; Nishio, T.; Sato, R.; Mochizuki, T.; Tsuchiya, K; Yasuda, M.; Oku, T. *J. Carbohydr. Chem.* **2000**, *19*, 359. (b) Boger, D. L.; Honda, T. *J. Am. Chem. Soc.* **1994**, *116*, 5647.

11 (a) Maillard, P.; Huel, C.; Momenteau, M. *J. Org. Chem.* **1993**, *58*, 2774. (b) Morales, J. C.; Zurita, D.; Penadés, S. *J. Org. Chem.* **1998**, *63*, 9212.

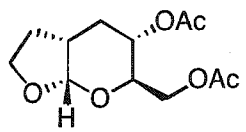
12 Renneberg, B.; Li, Y.; Laatsch, H.; Fiebig, H. *Carbohydr. Res.* **2000**, *329*, 861.

13 Rollin, P.; Sinaÿ, P. *Carbohydr. Res.* **1981**, *98*, 139.

14 Ramesh, N. G.; Balasubramanian, K. K. *Tetrahedron Lett.* **1991**, *32*, 3875.

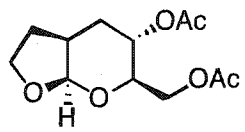
15 (a) Danheiser, R. L.; Gee, S. K.; Perez, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 806. (b) Still, W. K. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

16 The two reference compounds **i** and **ii** shown below have the indicated chemical shifts for the acetal C**H**: De Mesmaeker, A.; Hoffmann, P.; Ernst, B. *Tetrahedron Lett.* 1989, *30*, 57.



δ 5.33

i



δ 5.14

ii

17 Corey, E. J.; Hortmann, A. G. *J. Am. Chem. Soc.* **1965**, *87*, 5736.

18 Clive, D. L. J.; Manning, H. W.; Boivin, T.; Postema, M. *J. Org. Chem.* **1993**, *58*, 6857.

19 Barton, D. H. R.; Magnus, P. D.; Smith, G.; Streckert, G.; Zurr, D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 542

20 Hoffmann, H. M. R.; Giesel, K.; Lies, R.; Ismail, Z. M. *Synthesis* **1986**, 548.

21 Paulsen, H.; Wulff, A.; Brenken, M. *Liebigs Ann. Chem.* **1991**, 1127.

22 Saloman, C. J.; Mata, E. G.; Mascaretti, D. A. *J. Org. Chem.* **1994**, *59*, 7259.

23 Bacha, J. D.; Kochi, J. K. *Tetrahedron* **1968**, *24*, 2215.

24 Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.

SUMMARY OF WORK DESCRIBED IN THIS THESIS

Chapter 1 of this thesis describes the synthesis of a biologically active analog (**23**) of the ACE inhibitor A58365A. The preparation of **23** extends the generality of the route developed in our laboratory. The route has now been used to make not only the natural products (-)-A58365A (**4.1**) and (-)-A58365B (**4.2**), but also the unnatural analog **23**. Synthesis of **23** was achieved from lactone acid **11.4** and amino acid ester **24.6**, via key intermediates **25.3** and **26.2**. The fact that racemic **23** is a powerful ACE inhibitor — about half as active as (optically pure) captopril (**3.1**) — shows that the structure of (-)-A58365A (**4.1**) can be modified in a chemically significant way (substitution α to nitrogen) with retention of *in vitro* biological activity, although we have not established whether each enantiomer of **23** is an ACE inhibitor.

Chapter 2 of this thesis describes a synthetic route to 2,3-unsubstituted indenones. Although the route did not seem to be general, it worked well in some cases.

Chapter 3 of this thesis describes synthetic studies related to coleophomone B. Our studies on the construction of the tricarbonyl system proved to be unsuccessful. Also, we investigated the challenging macrocyclization (based on *O*-acylation or *C*-acylation). Although we were able to generate macrocyclic systems, the advanced intermediates **33.2** or **37.3** failed to give the core structures **33.3** or **37.4**, needed for conversion into coleophomone B. A number of highly substituted benzenes were made during this work.

Chapter 4 of this thesis describes synthetic studies on benesudon, a fungal metabolite with a very unusual structure. Although the majority of the carbon skeleton could be assembled from glucose, introduction of the double bond spanning the two rings is a difficult operation, and has not yet been achieved, although work on this task is continuing in this laboratory.