SYNTHETIC STUDIES ON THE PHOMOIDRIDES

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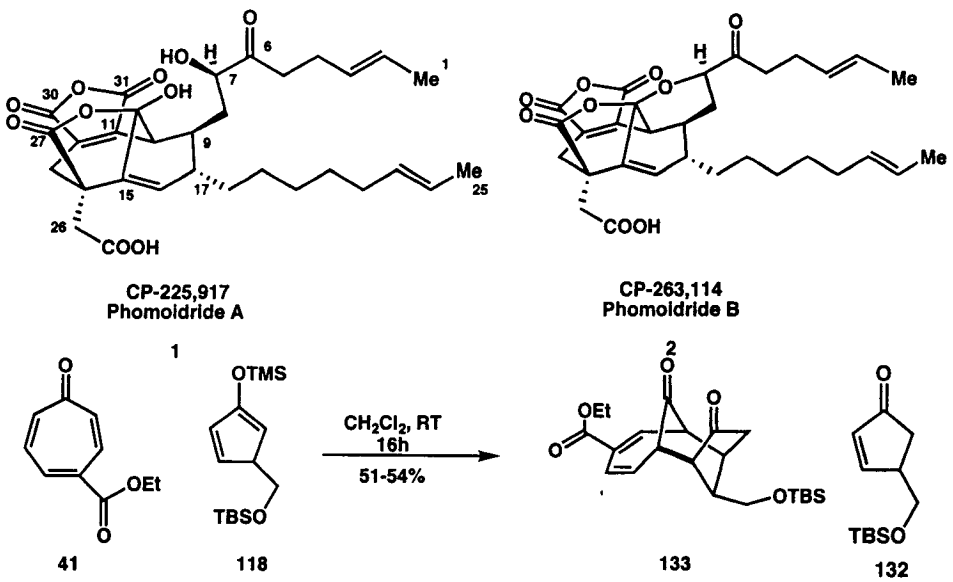
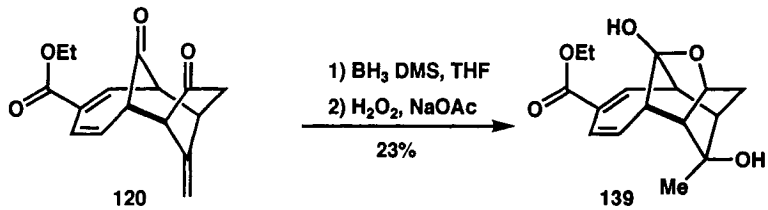
Abstract

A model study for the synthesis of the fungal metabolites phomoidride A and B is presented. Building on previous studies from our group, the carbocyclic core of these molecules was constructed using a [6+4] cycloaddition between tropone **41** and the silyl enol ether of 2-cyclopenten-1-one. Efforts to install the C-17 phomoidride sidechain on substrates derived from this carbocycle met with limited success. This led us to revise our strategy by employing the novel 5-substituted cyclopentadiene **118**. In contrast to the known instability of 5 substituted cyclopentadienes towards [1,5] hydrogen shifts, the 2-silyloxy moiety of **118** imparted remarkable thermal stability on the diene. A practical method was developed for the multigram-scale synthesis of cyclopentenone **132**, a useful synthon and precursor to **118**. Diene **118** underwent smooth [6+4] cycloaddition with tropone **41** at 23 °C to give **133** in 51-54% yield.



Attempts to install the C-17 stereocenter of the phomoidrides through hydroboration of alkene **120** were thwarted by low yields. Remarkably, significant amounts of Markovnikoff products (9-23%) were isolated after the hydroboration of **120** and related alkenes with BH_3·DMS. We undertook a series

of DFT studies (B3LYP/6-31G*) to understand the origins of reduced anti-Markovnikoff selectivity. These studies suggested that the bridging ketones and remote diene both contributed to this phenomenon. These studies led us to synthesize carbocycle **158**. In line with predictions, hydroboration of saturated diketone **158** was completely selective for the anti-Markovnikoff product.



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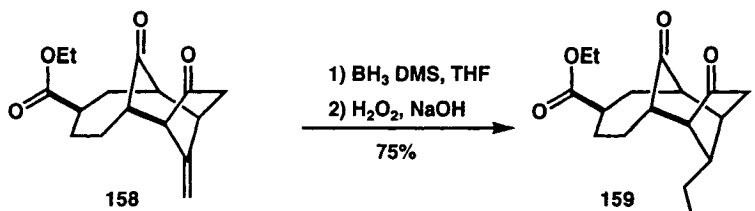
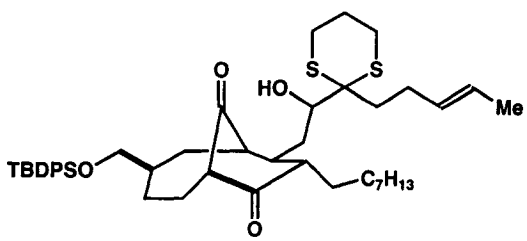


158 159

The C-17 sidechain of the phomoidrides was successfully extended through a conjugate addition reaction. Compound **189**, which contains the correct stereochemistry of the C-9 and C-17 sidechains, represents our furthest progress to date on the molecules.



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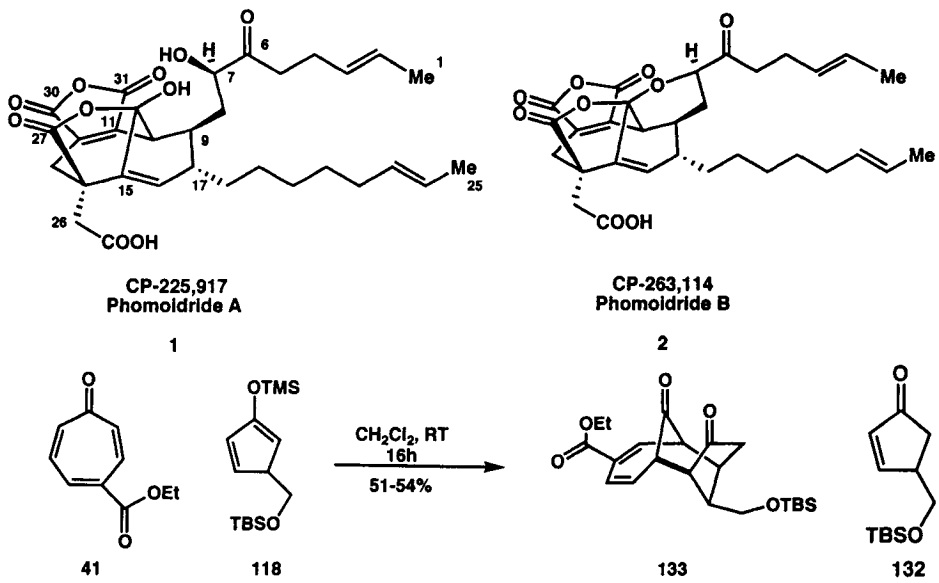
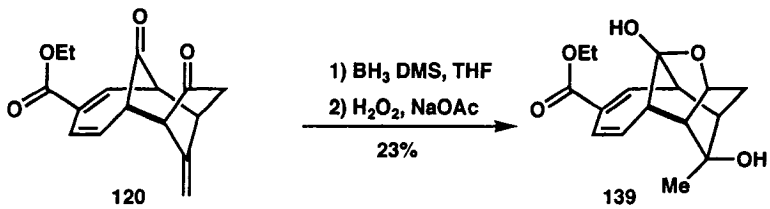
Résumé

Une étude modèle pour la synthèse des métabolites fongiques phomoidrides A et B est présentée. Se basant sur de précédentes études de notre groupe, le noyau carbocyclique de ces molécules fut construit en utilisant une cycloaddition [6+4] entre la tropone **141** et l'éther d'énol silylé de la 2-cyclopenten-1-one. Sur de tels substrats, les efforts pour installer la chaîne latérale phomoidride C17 n'ont rencontré qu'un succès limité. Ceci nous amena à réviser notre stratégie et à employer le nouveau cyclopentadiène **118**, substitué en position 5. Contrastant avec l'instabilité notoire des cyclopentadiènes substitués en position 5, causée par un rapide transfert [1,5] d'hydrogène, le cyclopentadiène **118** possède une remarquable stabilité thermique, grâce à son groupe silyloxy en position 2. Le diène **118** réagit aisément lors d'une cycloaddition [6+4] avec la tropone **141** à 23°C et donne l'adduit **133** dans un rendement de 51-54%. Une méthode pratique fut développée pour la synthèse de multiples grammes du synthon **132**, obtenu en trois étapes à partir du cyclopentadiène.



Les tentatives pour intaller le stéréocentre C-17 des phomoidrides au moyen d'une hydroboration de l'alcène **120** furent contrecarrées par de faibles

rendements. Remarquablement, des quantités significatives (9-23%) de produit d'hydroboration Markovnikoff furent isolées après l'hydroboration de **120** et d'alcènes similaires au moyen de BH_3•DMS. Nous avons entrepris une série d'études DFT (B3LYP/6-31G*) afin de comprendre les origines de la sélectivité réduite pour l'addition anti-Markovnikoff. Ces études ont suggéré que la cétone pontée et le diène contribuaient tous deux au phénomène observé. Nous avons ainsi été amenés à synthétiser le carbocycle **158**. En accord avec les prédictions des calculs moléculaires, l'hydroboration de la dicétone saturée **158** fut complètement sélective en faveur du produit d'addition anti-Markovnikoff.



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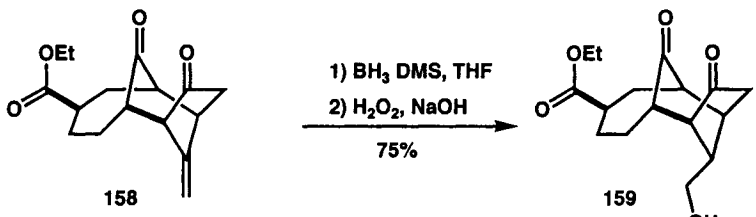
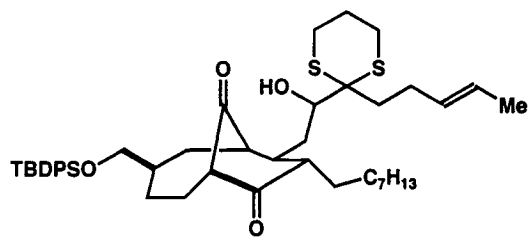


158 159

La chaîne latérale C-17 des phomoidrides fut prolongée avec succès au moyen d'une addition conjuguée. Le composé **189**, contenant la stéréochimie correcte pour les chaînes latérales C-9 et C17, représente actuellement nos progrès les plus avancés vers les molécules désirées.



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Acknowledgments

Many people made this work possible. I would especially like to thank my thesis supervisor, Prof. James L. Gleason, for giving me the opportunity to work on such an ambitious project. His integrity, rigor, and devotion to his field is truly exemplary. Jim is an excellent teacher and spares no effort in the training of his graduate students. I am truly fortunate to have been able to study organic chemistry in his group. These have been the best years of my life.

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I would like to thank my mother Judy, father Alex, brother Andrew and the rest of my family for their support during my time at McGill. Finally, two people deserve special mention. My wife Janet Macdonald is an incredible person. Her wit, intelligence, infectious energy and wisdom has been a tremendous blessing to my life. Lastly, I would like to thank my good friend Dr. Larry Whitlow. I met Larry at a very difficult time in my life. He has been like a second father to me, and given me the courage to do things I had previously not thought possible. This is for you, Lar.

List of Abbreviations

Å	Angstrom
Ac	acetyl
AcOH	acetic acid
atm	atmosphere
Bu	butyl
Ar	aryl
°C	degrees Celsius
CAN	cerium ammonium (IV) nitrate
cm	centimetre
COSY	correlation spectroscopy
d	deuterium
δ	part per million
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DFT	density functional theory
DIBAL	diisobutylaluminum hydride
DMAD	dimethylacetylene dicarboxylate
DMDO	dimethyldioxirane
DMF	N, N-dimethylformamide
DMAP	4-dimethylaminopyridine
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
E	entgegen
equiv	equivalents
ent	enantiomeric
Et	ethyl
EtOAc	ethyl acetate
FMO	frontier molecular orbitals
FT	Fourier transform

G	Gibbs free energy
g	gram
h	hour
HMBC	heteronuclear multiple-bond correlation
NaHMDS	sodium hexamethyldisilylamide
HMPA	hexamethylphosphorous triamide
HMQC	heteronuclear multiple-quantum coherence
HOMO	highest-occupied molecular orbital
HPLC	high-pressure liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	Hertz
i	iso
IR	infrared
J	coupling constant in Hertz
Kcal	kilocalorie
L	litre
LDA	lithium diiisopropylamide
LUMO	lowest unoccupied molecular orbital
M	molarity
m	minutes
m	meta
mCPBA	*m*-chloroperbenzoic acid
Me	methyl
MeOH	methanol
MeCN	acetonitrile
mg	milligram
MHz	megahertz
mL	millilitre
μL	microlitre

mmol	millimole
mol	moles
MS	mass spectroscopy/ molecular sieves
NBS	N-bromosuccinimide
NMO	N-methylmorpholine N-oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
o	ortho
p	para
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	part per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
R	rectus
R_f	retention factor
s	second
S	sinister
TFA	trifluoroacetic acid
TBS	tert-butyldimethylsilyl
TBDPS	tert-butyldiphenylsilyl
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl
TPAP	tetrapropylammonium perruthenate
TS	transition state
Tf	trifluoromethanesulfonyl
UV	ultraviolet
Z	zussamen

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CHAPTER ONE

1.1 Isolation and biological activity

In 1997 researchers at Pfizer reported the isolation of two new fungal metabolites, CP-225,917 (**1**) and CP-263,114 (**2**) (later renamed phomoidride A and B, respectively, Figure **1-1**).[1] These molecules were obtained from the culture broth of a sterile *Phoma* species collected from a juniper branch near Dripping Springs, Texas, along with the previously decribed zaragozic acid A (squalestatin I).[2] The relative stereochemistry of **1** and **2** was elucidated by a host of analytical techniques, including extensive NMR spectroscopy. The absolute stereochemistry was later determined by Nicolaou *via* total synthesis (*vide infra*). Subsequent investigation by Danishefsky and Sulikowski showed that the C-7 (S) epimers of **1** and **2** are also present in the fungal broth.[3] [4] These compounds were then given the names phomoidrides C and D.

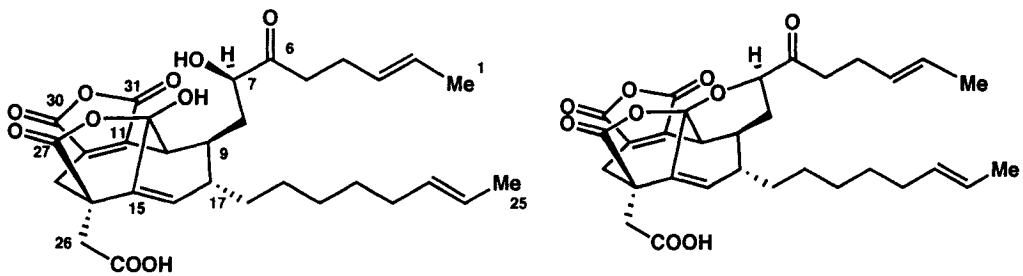


Figure 1-1. Structure of the phomoidrides[5].

The phomoidrides possess a dense array of oxygenated functional groups. Notable features include a bicyclo[4.3.1] ring system, a maleic anhydride moiety, a quaternary carbon center contained within a δ-lactol, two partially unsaturated

side-chains, and, intriguingly, a bridgehead olefin. Structures **1** and **2** are differentiated by closure of the C-7 hydroxyl in **2** upon the bridging hemiacetal. Indeed, the Pfizer team demonstrated that **1** could be converted to **2** by treatment with methanesulfonic acid.[6] Compounds **1** and **2** were proposed to belong to the nonadride family of natural products (Figure **1.2**), a small group of fungal metabolites including glaucanic acid (**3**),[7] glauconic acid (**4**), byssochlamic acid (**5**),[8] scytalidic acid,[9] rubratoxins A (**6**) [10] and B (**7**) [11], casteneinolide,[12] and heveadride (**8**). [13] Their inclusion in this family, combined with their isolation from *Phoma sp.* led the Pfizer team to suggest the name "phomoidrides" for these two natural products.[14]

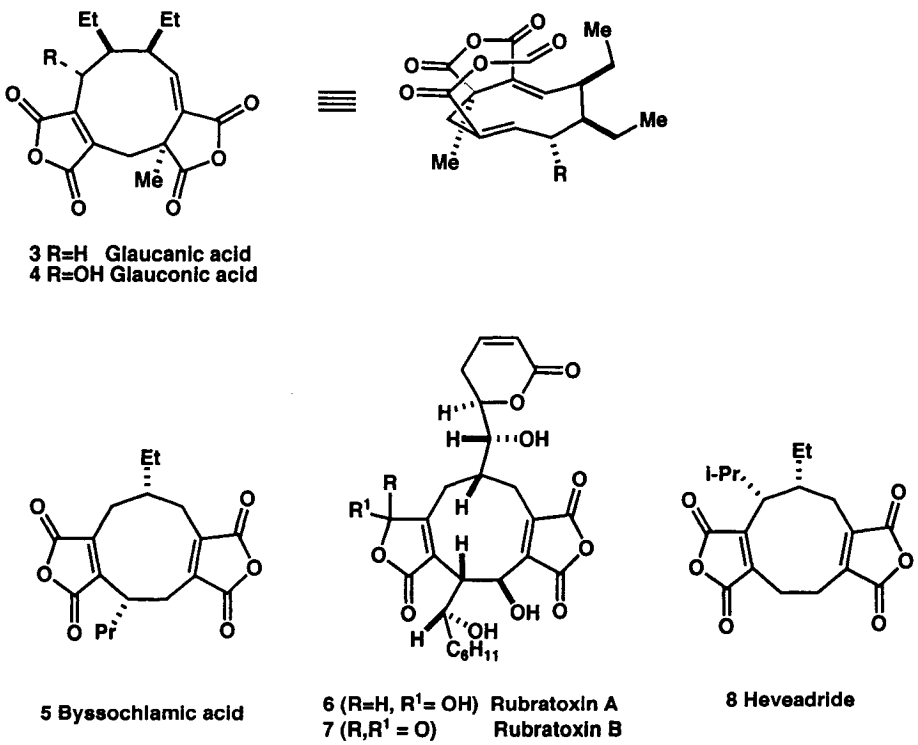


Figure 1-2. Nonadrides.

The biological activity profile of the phomoidrides is noteworthy.[15] These molecules possess interesting dual activity, being inhibitors of both squalene synthase and Ras farnesyl transferase. Phomoidrides A and B inhibit squalene synthase (SQS) from rat liver microsomes with IC_{50} values of 43 μM and 160 μM respectively. They inhibit Ras farnesyl transferase from rat brain with IC_{50} values of 6 and 20 μM. The discovery of novel inhibitors for both of these enzymes is of considerable current interest.

Discovery of novel SQS inhibitors may result in new treatments for cardiovascular disease, which is currently the leading cause of death in North America. SQS induces head-to-head dimerization of farnesyl pyrophosphate (FPP) to form squalene. Squalene is further metabolized into cholesterol and by extension, other steroids. High levels of serum cholesterol are associated with cardiovascular disease. In humans, a considerable portion of serum cholesterol is derived from *de novo* biosynthesis. Squalene synthase represents the first committed step of cholesterol biosynthesis from farnesyl pyrophosphate. Inhibition of this enzyme, therefore, may lead to lowered serum cholesterol and thus a lowered risk of heart disease. Recent evaluation of SQS inhibitors have shown promise in animal models.[16]

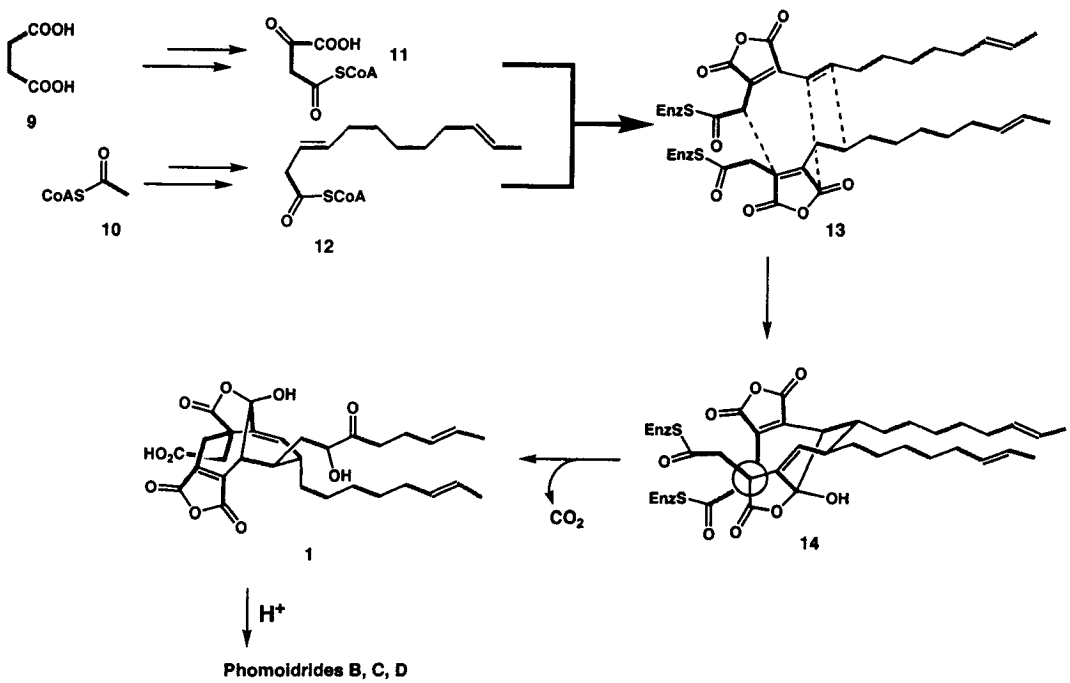
Interest in inhibitors of Ras farnesyl transferase stems from its implications in cancer.[17] Ras, a GTP-hydrolyzing protein, functions like a molecular switch. It is activated by binding to GTP. Once activated, it participates in signal transduction pathways controlling cell growth,

differentiation, apoptosis, and other events. Mutated forms of Ras are found in over 30% of human cancers. In the mutated form, GTPase activity is lost. This leads to accumulation of Ras in the active form and contributes to tumor formation. In order to function, Ras must be localized in the cell membrane. This is commonly achieved by farnesylation. Numerous Ras farnesyl transferase inhibitors have been explored as potential anti-cancer drugs. [18] Recently, results of the first clinical studies with various farnesyl transferase inhibitors have been presented.[19] These preliminary results show that farnesyl transferase inhibitors are successful at inhibiting tumor growth. However, their lack of cytotoxicity remains a concern for applications in tumor regression.

1.2 Biosynthesis

Sulikowski has proposed that the phomoidrides are formed through the decarboxylative head-to-head dimerization of two C-16 units (Scheme **1-1**).[20] Sulikowski's proposal was inspired by Sutherland's earlier studies on the biosynthesis of the closely related nonadride glauconic acid, which was proposed to arise from the dimerization of two C-9 units.[21] The C-16 units (**13**) are proposed to originate from the condensation between oxaloacetyl-CoA **11** and C_{12} carboxylic acid derivative **12**. To test this proposal, Sulikowski's group fed ^{13}C labeled succinic acid (**9**) and ^{13}C labeled acetyl-CoA (**10**) to the phomoidride producing fungus ATCC 74256. The ^{13}C labeled phomoidrides produced in this manner had a labeling pattern consistent with this proposal. In this manner,

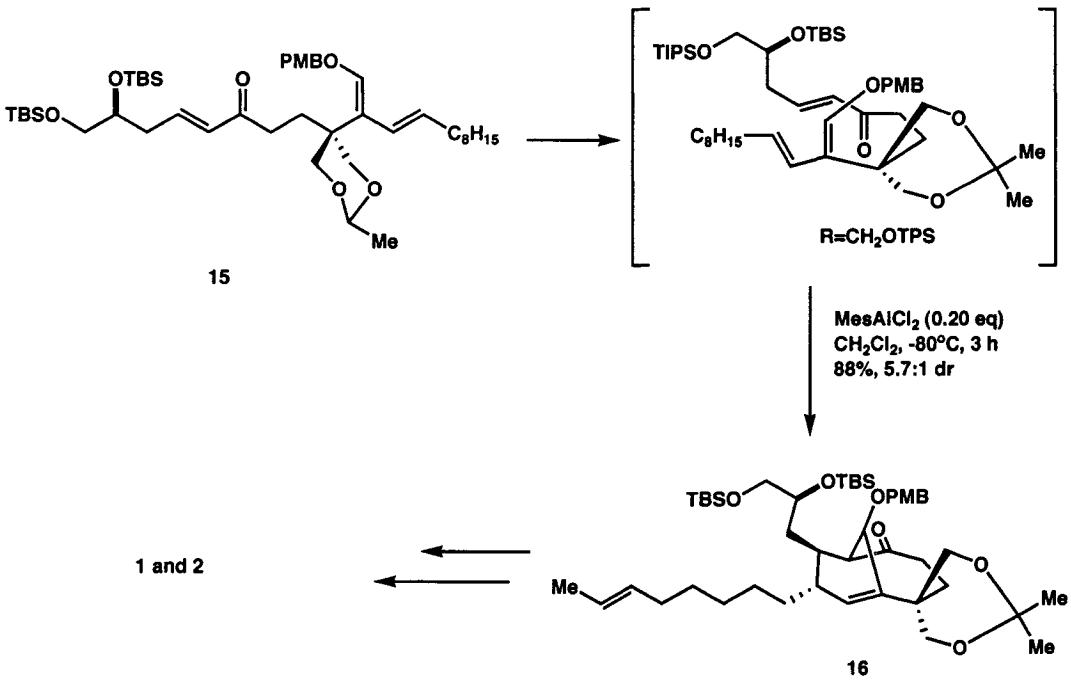
Sulikowski established that carbons C12-C14 and C27-30 all originate from succinic acid, and the remaining carbons arise from acetyl-CoA. These studies also suggested that phomoidride A is formed first, and phomoidrides B, C, and D are formed later in the biosynthetic pathway. The groups of Sulikowski [22] and Baldwin [23] have attempted biomimetic syntheses of the phomoidrides based on these studies, but have not yet succeeded in constructing the carbocyclic core. Although the putative C-16 precursor has been identified, the mechanism of the dimerization to generate the phomoidride core, and the timing of the decarboxylation event remain to be definitively established.



Scheme 1-1. Sulikowski's proposed biosynthesis of the phomoidrides.

1.3 Total Syntheses of the Phomoidrides

The highly unusual structure of the phomoidrides has inspired a great deal of creative effort from the synthetic organic community. To date, over 20 research groups have published synthetic studies on these molecules. It is beyond the scope of this introduction to give a thorough account of all of this work. A comprehensive review of synthetic approaches to the phomoidrides was recently published by Wood.[24] Four total syntheses have been accomplished, and these will be summarized below.

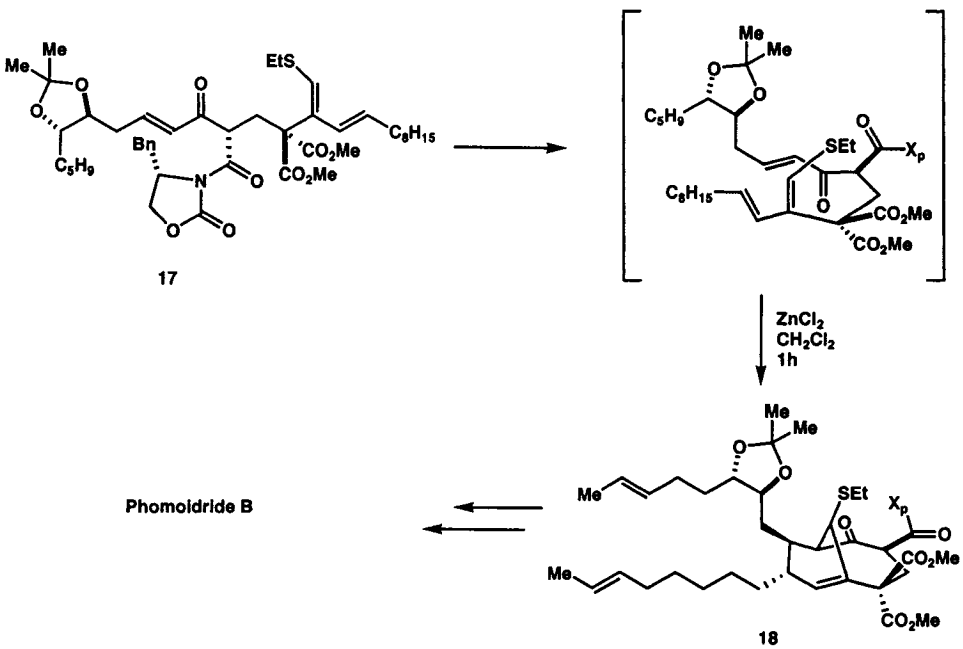


Scheme 1-2. Nicolaou's intramolecular Diels-Alder approach to the phomoidrides

The first total synthesis of phomoidrides A and B was reported in 1999 by the Nicolaou group (Scheme **1-2**).[25] The key step of this synthesis was the intramolecular Diels-Alder reaction of open-chain precursor **15**. The resulting cycloadduct **16** contains the [4.3.1] bicyclic core, the bridgehead olefin, and the C-17 and C-9 sidechains of **1**, all with correct stereochemistry. The C-9 sidechain was then extended through the addition of a dithiane. Other noteworthy features of this work involve the development of a novel tandem sequence to install the maleic anhydride, and a new method for Arndt-Eistert homologation of acids using acyl mesylates.[26] The synthesis also led to the development of a range of new transformations mediated by iodine(V). After completion of the synthesis, the Nicolaou workers developed an enantioselective route that established the absolute configuration of the phomoidrides as enantiomeric to that shown in Figure **1-1**.[27]

Fukuyama also reported a synthesis of phomoidride B using a similar intramolecular Diels-Alder reaction (Scheme **1-3**).[28] Like the Nicolaou route, the IMDA of **17** formed the [4.3.1] bicyclic core, the bridgehead olefin, and established the stereochemistry of the two side chains. The incorporation of a chiral auxiliary allowed for a route to the molecules in enantiopure form. The acyl group appended to the chiral auxiliary of **18** was then used to forge the maleic anhydride. The usage of a highly functionalized IMDA precursor allowed for a synthesis incorporating relatively few oxidation/reduction steps, protecting group

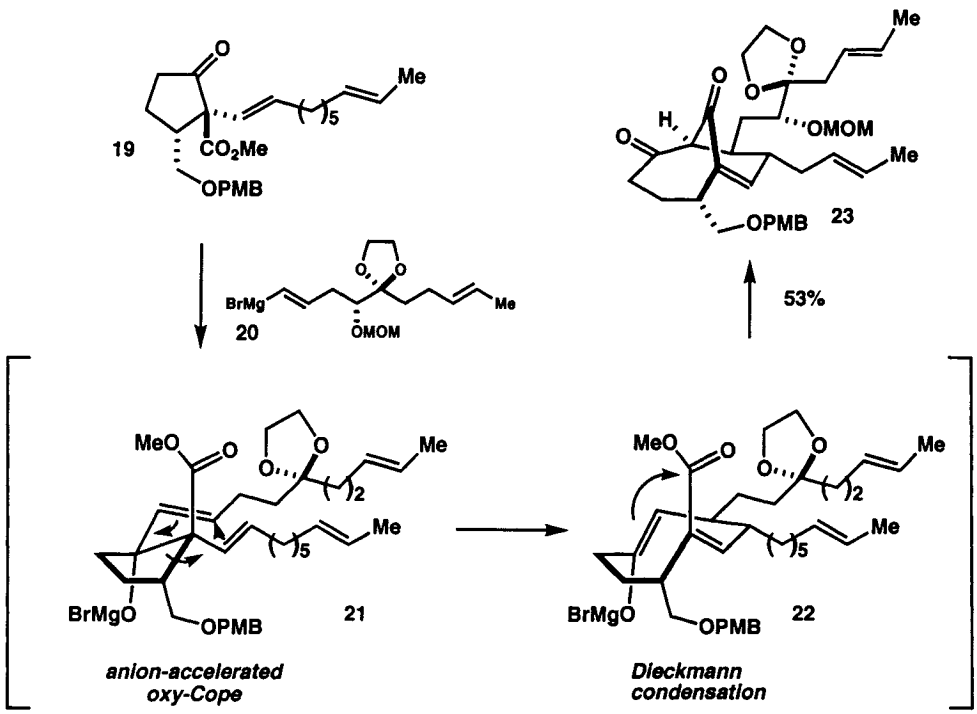
manipulations, and C-C bond forming reactions on the functionalized phomoidride core.



Scheme 1-3. Fukuyama's intramolecular Diels-Alder en route to phomoidride B.

Shair reported the synthesis of *ent*-phomoidride B in 2000 using a fascinating tandem reaction as the key step (Scheme **1-4**).[29] The sequence is initiated by the addition of vinyl Grignard **20** to ketone **19**, which then performs an oxy-Cope rearrangement. Dieckmann closure of the resulting enolate of **22** upon the pendant ester then generates the highly functionalized [4.3.1] bicyclic core structure **23**. In a subsequent publication, the Shair group further extended this methodology to the synthesis of other [*m.n.*1] bicyclic cores, including the [5.3.1] bicyclic core present in the taxane ring system.[30] A second tandem process involving TMSOTf-catalyzed addition of trimethyl orthoformate installed the

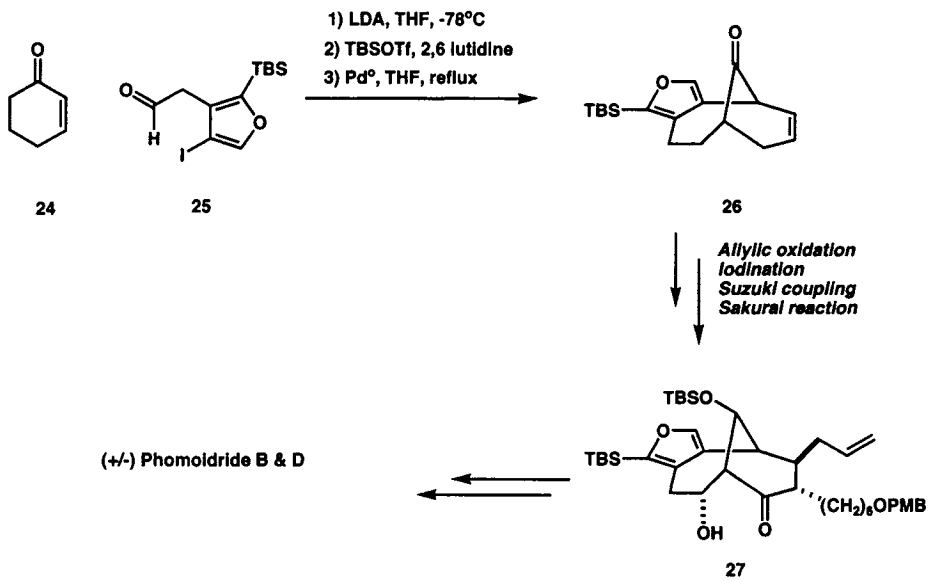
quaternary center and formed the ∂-lactol acetal system. The synthesis was completed *via* Arndt-Eistert homologation of the C-26 acid and Pd-catalyzed carbonylation to generate the maleic anhydride.



Scheme 1-4. Shair's tandem reaction to build the phomoidride core.

The fourth total synthesis of the phomoidrides was reported by Danishefsky (Scheme **1-5**).[31] The key step of this route was a tandem aldol/Heck processs, a sequence also used in his total synthesis of Taxol.[32] The resulting core structure **26** lacked both the C-17 and C-9 side chains, which were appended through Suzuki and Sakurai reactions respectively to form **27**. The quaternary center was formed through a [2+2] cycloaddition followed by sulfuration and

Baeyer-Villiger oxidation. The C-9 side chain was extended through Grignard addition / oxidation. After oxidation of the furan to the maleic anhydride and elaboration of this structure to the final product, it was found that the stereochemistry at C-7 was opposite to that found in the natural product. Subsequent work by the Danishefsky group showed that this epimeric product was actually a component of the fungal broth, and was later named phomoidride D. Danishefsky then developed a 7-step sequence to convert this compound to phomoidride B, thereby completing the synthesis.

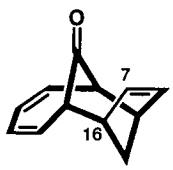


Scheme 1-5. Danishefsky's tandem Aldol-Heck route to the phomoidrides .

The phomoidrides have been one of the most hotly pursued synthetic targets of the past 10 years. Like "classic" targets such as strychnine, Taxol, and the enediynes before them, they have inspired the discovery and application of new strategies and methodologies in organic chemistry.

1.4 Inspiration for a synthetic strategy

Our inspiration for a synthesis of the phomoidrides came from an analysis of Cookson and Ito's [6+4] cycloadduct of tropone and cyclopentadiene (**28**, Figure **1-3**). We recognized that cleavage of the bond between C-7 and C-16 of **28** (phomoidride numbering) would reveal the [4.3.1] bicyclic core present in the phomoidrides (**29**). This challenged us to investigate the application of a [6+4] cycloaddition approach to the phomoidrides, which will be discussed in greater detail below.



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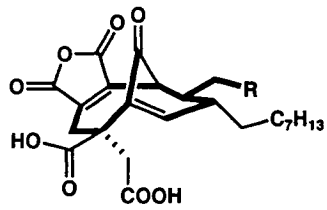
Cookson/Ito [6+4] product



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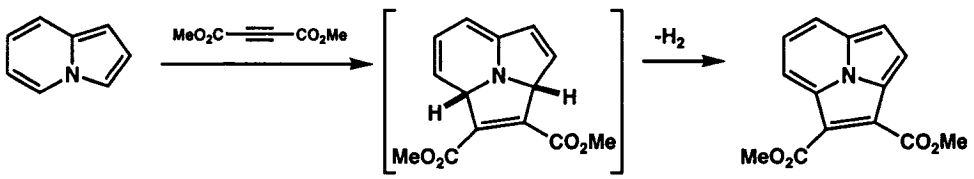
Phomoidride open form

Figure 1-3. Comparison of Cookson & Ito's [6+4] cycloadduct to the phomoidride core.

1.5 [6+4] cycloadditions [33]

Woodward and Hoffmann's seminal 1965 papers laid the foundation for our modern understanding of pericyclic reactions.[34] The recognition of the importance of orbital symmetry unified a great deal of empirical data into a simple set of rules governing the chemical reactivity of π systems.[35] Woodward and Hoffmann established a set of selection rules for cycloaddition reactions.[36] Due to orbital symmetry considerations, only cycloadditions containing a total of

[4n+2] π electrons are thermally allowed if the addition is suprafacial at both reactive termini. The set where n=1 contains a host of important 6-electron pericyclic reactions, including the Diels-Alder reaction and 1,3-dipolar cycloadditions. The ability of these reactions to generate up to four stereocenters, join together complex fragments, and tolerate a wide degree of substitution make them among the most powerful tools available to synthetic organic chemists. Interestingly, higher-order processes — cases where n >1 — were barely known at the time of Woodward and Hoffmann's proposal. Among the few examples were Boekelheide's ten-electron [8+2] cycloaddition between indolazine **30** and DMAD (Scheme **1-6**) to produce tricyclic intermediate **31**.[37] In contrast, the ten-electron [6+4] cycloaddition had never been observed.[38] Three predictions were made about this process: the reaction should be thermally allowed, it should be concerted, and the main cycloadduct should have *exo* selectivity due to repulsion between secondary orbitals in the *endo* transition state.

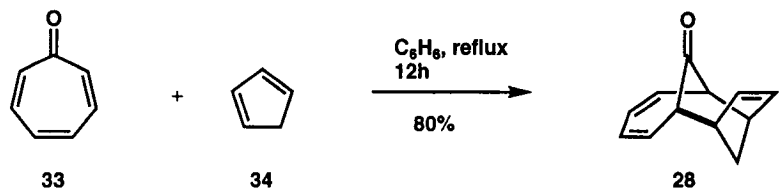


30 31 32

Scheme 1-6. Boekelheide's [8+2] cycloaddition.

Discovery of the [6+4] cycloaddition did not take long. The next year, both Cookson and Ito independently reported that tropone **33** combined with cyclopentadiene in refluxing benzene to give [6+4] cycloadduct **28** in 80% yield

(Scheme **1-7**).[39,40] In accord with predictions, the stereochemistry of the [6+4] adduct was exclusively *exo*. The *endo* mode of [6+4] addition was not observed.



33 34 28

Scheme 1-7. Cookson & Ito's [6+4] cycloaddition.

The course of the [6+4] cycloaddition can be predicted by frontier-molecular-orbital (FMO) theory.[41] The LUMO of tropone is depicted in Figure **1-4**.[42] The LUMO coefficients for tropone are largest on C-2 and C-7. In the [6+4] cycloaddition, these carbons form σ bonds with the diene termini, which are the sites of highest electron density in the HOMO of the diene. The transition states for the *exo* and *endo* modes of the [6+4] cycloaddition between tropone and cyclopentadiene are depicted in Figure **1-5**. The *exo* selectivity for the [6+4] is rationalized by the presence of repulsive orbital overlap between the secondary orbitals in the *endo* transition state. The extent to which secondary orbital interactions govern the selectivity of this reaction remains a matter of debate. [43]

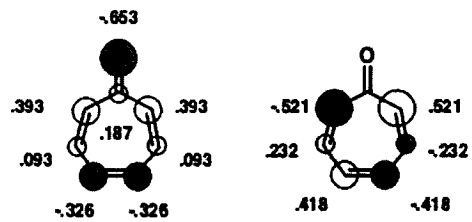


Figure 1-4. Frontier molecular orbitals of tropone.

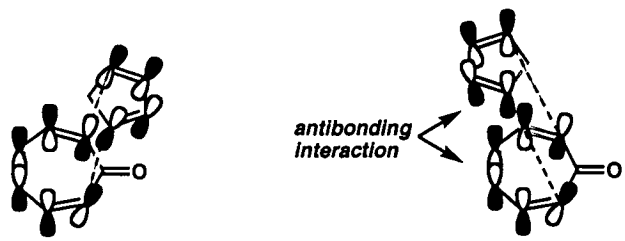
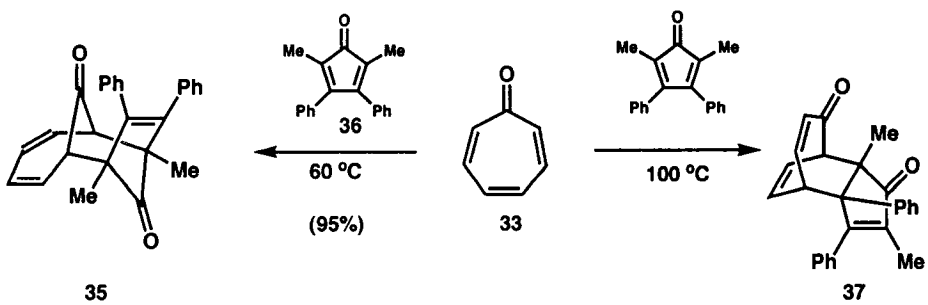


Figure 1-5. *Exo* vs. *Endo* transition states in the [6+4] cycloaddition.

The [6+4] cycloaddition is often accompanied by competitive formation of [4+2] products. The dominant byproducts are inverse electron-demand Diels-Alder cycloadducts in which tropone acts as a 4π donor and the diene as a 2π donor. Houk and Woodward found that higher temperatures favor this [4+2] pathway (Scheme **1-8**).[44] When tropone **33** was heated at 60 °C with cyclopentadieneone **36**, the [6+4] product **35** was obtained exclusively. However, when the reaction temperature was raised to 100 °C, [4+2] adduct **37** was obtained. Kinetic data and theoretical calculations strongly suggest that the barrier of the [6+4] process is lower than that of the [4+2] process, but the [4+2] products possess a lower ground-state energy. Consistent with these observations, Ito found that extended heating of the [6+4] cycloadduct **28** at 145 °C gave a mixture of [4+2] adducts, presumably through cycloreversion and recombination.[45] Extended heating of these [4+2] adducts did not result in the formation of new products. The kinetic parameters of the [6+4] cycloaddition have been measured and found to be similar to that of the Diels-Alder reaction, consistent with a

concerted pathway.[46,47] Houk has calculated the activation energy of the [6+4] cycloaddition reaction between cyclopentadiene and tropone to be 20.7 kcal/mol (B3LYP/6-31G*). [48]



Scheme 1-8. Houk and Woodward's [6+4] cycloaddition.

Garst examined the scope of the [6+4] cycloaddition between tropone and a variety of dienes (Table **1-1**).[49] In general, the [6+4] pathway was favored when the reaction was conducted at lower temperatures using sterically undemanding, electron-rich dienes. The stereochemistry of the [6+4] adducts was *exo* in all cases. Higher temperatures, electron-withdrawing diene substituents, or *cis* substitution on the diene terminus led to formation of the [4+2] product. Furans were not found to undergo [6+4] cycloaddition, likely owing to the facile reversibility of the cycloaddition. It had been noted previously that the [6+4] pathway is very sensitive to steric effects, as only [4+2] cycloadducts have been observed with 2-substituted tropones (e.g. 2-chlorotropone)[50] or 5,5 disubstituted cyclopentadienes.

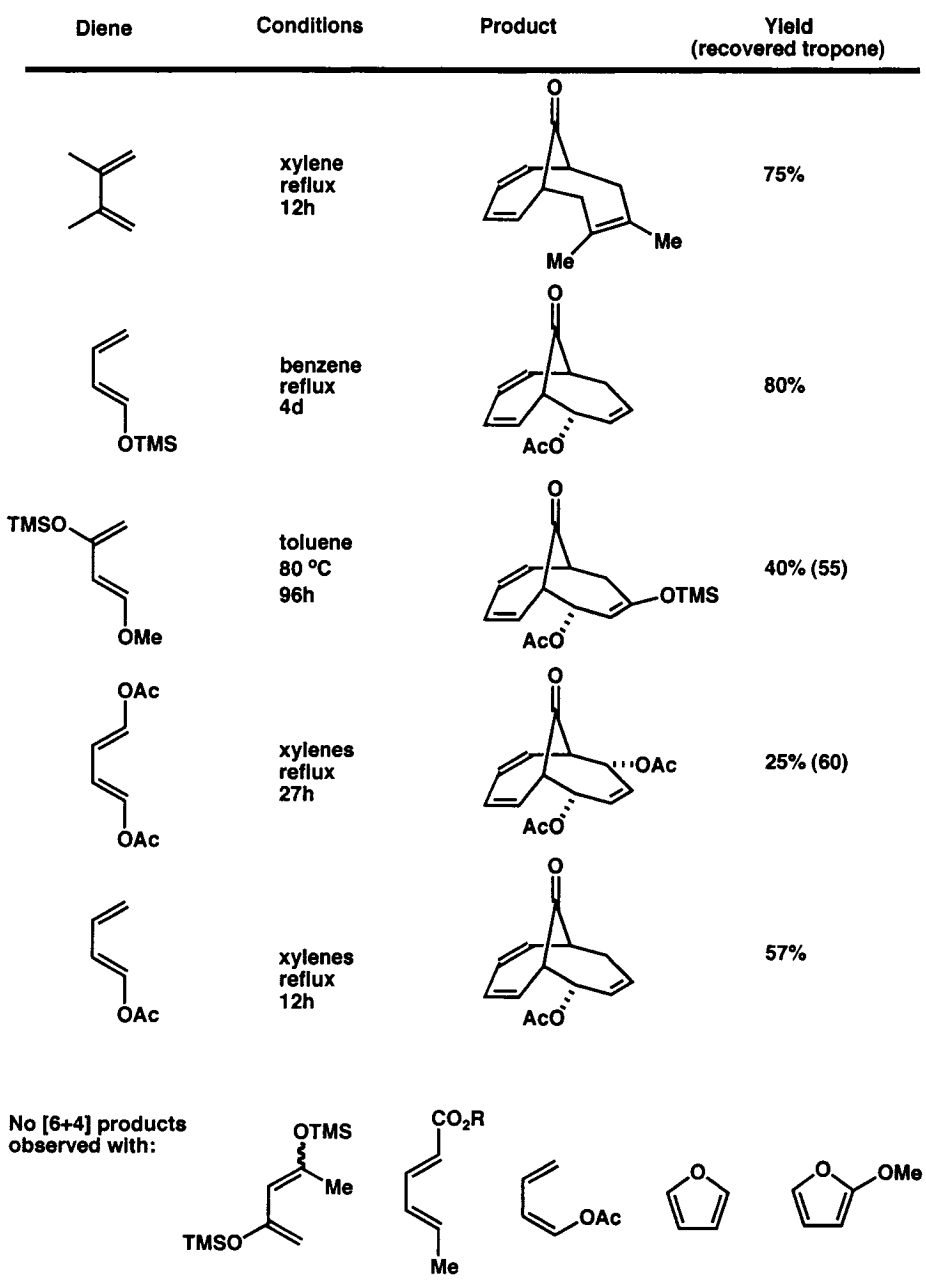
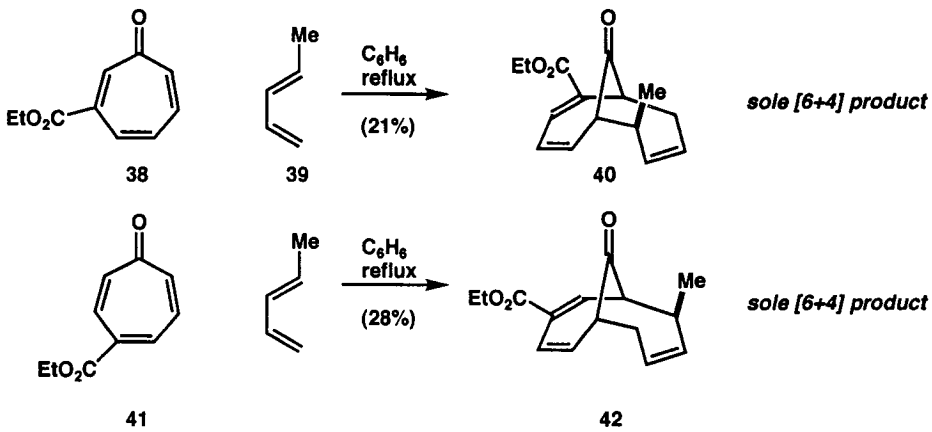


Table 1-1. Garst's study of the scope of the [6+4] cycloaddition.

In a subsequent study, Garst and Houk examined the [6+4] cycloaddition between substituted dienes and substituted tropones (Scheme **1-9**).[51] Best yields were obtained with electron-poor tropones and electron-rich dienes. Electron-rich tropones were found to be extremely unreactive, requiring forcing conditions and long reaction times. With substituted dienes and tropones, the regioselectivity of the [6+4] cycloaddition could be predicted by FMO theory. The reaction of 3-substituted tropone **38** with **39** gave [6+4] cycloadduct **40** exclusively. When 4-substituted tropone **41** was used, adduct **42** was obtained. Like the Diels-Alder reaction, the major adduct is that which arises from maximum overlap of the FMOs of the two addends.

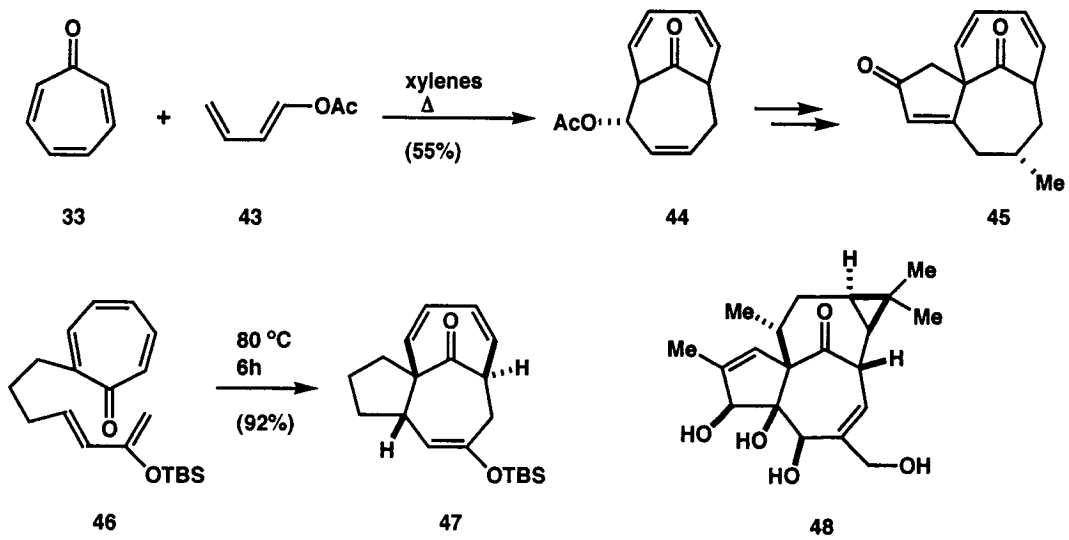


Scheme 1-9. Frontier molecular orbital control in the [6+4] cycloaddition.

The [6+4] cycloaddition can be accelerated by the use of acid catalysts. Ito found that the [6+4] cycloaddition of tropone and cyclopentadiene proceeded at room temperature in the presence of *para*-toluenesulfonic acid with 65% yield.[44] Ito also found that p-TsOH reduced the periselectivity of the process, as various

[4+2] products were produced in 15% yield. Despite intermittent failed attempts of Lewis acids in the [6+4] cycloaddition,[48] the first comprehensive study of Lewis acid catalysis was not reported until 2001 by our group. In certain cases, we found that Lewis acid catalysis can be beneficial for both yield and periselectivity in the [6+4] cycloadditions of substituted tropones (*vide infra*). Rigby subsequently published a study of Lewis-acid catalysis of [6+4] cycloadditions, including one example of modest enantioselective induction using BINAL.[52]

Despite its power, the limited scope of the [6+4] cycloaddition has limited its application toward total synthesis endeavors. Rigby has pioneered the application of the [6+4] cycloaddition toward the total synthesis of the ingenane diterpenes, including ingenol (**48**).[53] In an early example, Rigby reported the synthesis of the ingenol core **45** *via* the intermolecular [6+4] cycloaddition of tropone with 1-acetoxybutadiene **43** (Scheme **1-10**). Funk reported a high-yielding intramolecular [6+4] cycloaddition of **46** to give ingenol model system **47**.[54] In spite of a great deal of creative effort, however, neither approach has yet achieved a total synthesis of ingenol.



33 43 44 45 46 47 48

Scheme 1-10. Funk and Rigby's approaches to ingenol (**48**)

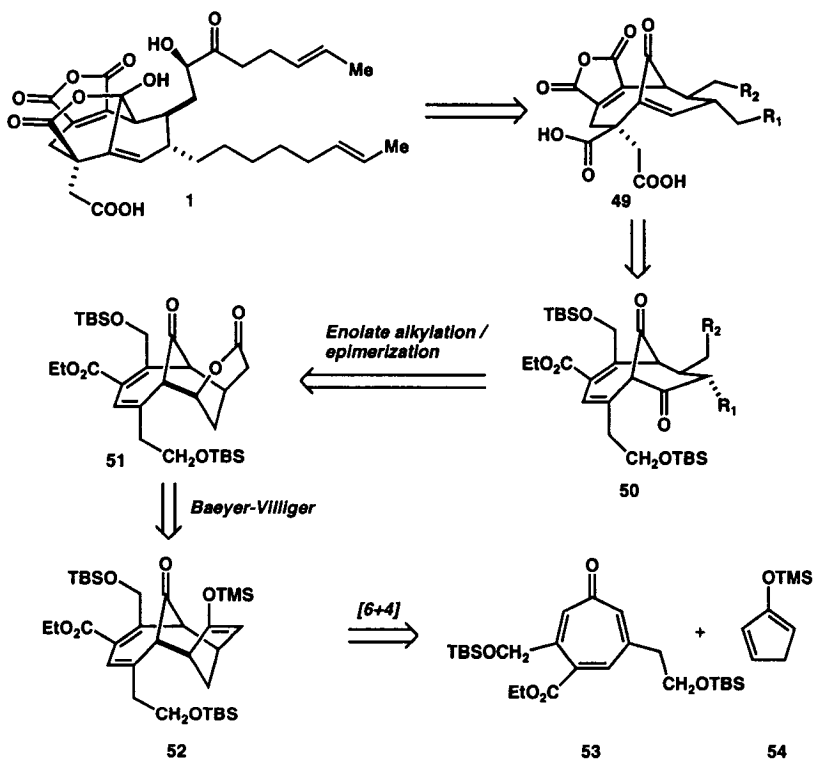
1.6 Retrosynthetic analysis and preliminary studies

We hypothesized that a highly convergent approach to the phomoidrides could potentially be realized through the union of suitably functionalized tropone and cyclopentadiene components. In addition to the high degree of convergency, we were also attracted by the fact that the powerful [6+4] transform has seen little use in total synthesis endeavors. Thus, development of this strategy would hold the promise of development of the [6+4] cycloaddition as a powerful tool, and provide opportunities for discovery.

The proper design of each component is crucial for the success of the synthesis. Higher yields of [6+4] cycloadducts are obtained when the diene component is cyclic and electron-rich, and the tropone component includes an electron-withdrawing group. Furthermore, as with any cycloaddition, the

substitution pattern of each component must be designed such that the desired regioisomer is produced exclusively.

A [6+4] cycloaddition that both conforms to these restraints and maps well onto the phomoidride target structure is shown in Scheme **1-11**. The target tropone **53** contains an ester at C-4 and a neighboring one-carbon alcohol at C-3 that can be later oxidized to the ester oxidation state. Direct incorporation of the maleic anhydride on the tropone is avoided due to regioselectivity concerns (*vide infra*). The tropone also contains a two-carbon alcohol on C-6 that would be used to install the quaternary center at a later stage, possibly *via* a 5-*exo* trig radical process.



Scheme1-11. Retrosynthetic analysis of the phomoidrides

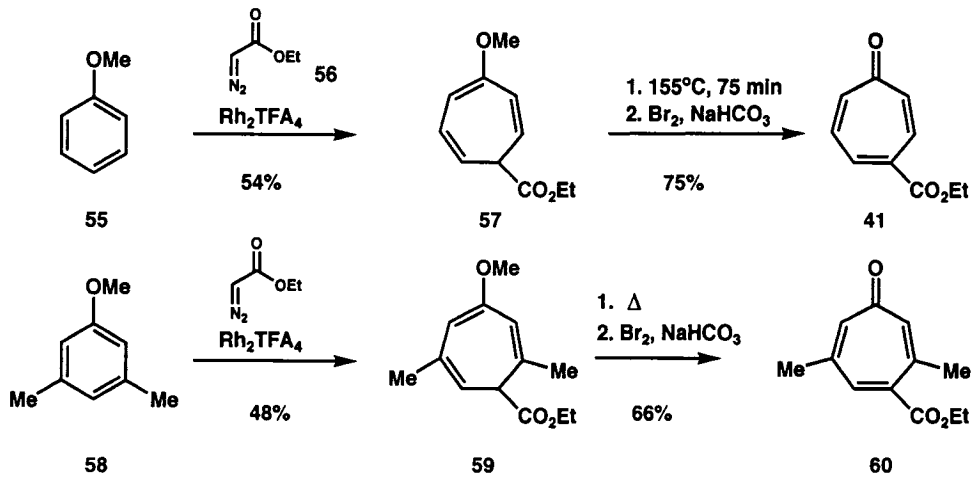
Baeyer-Villiger oxidation was envisioned as the method to cleave the C(7)-C(16) bond of [6+4] cycloadduct **52**. With this transformation in mind, silyl enol ether **54** was selected as the diene component. The [6+4] cycloaddition of this electron-rich diene with tropone produces a new silyl enol ether on the bridge carbon, which could be cleaved with acid to reveal a bridging ketone at C7. The anticipated Baeyer-Villiger would then produce lactone **51**. In addition to revealing the top sidechain, cleavage of the resulting lactone would provide an alcohol. Upon oxidation of this alcohol to a ketone, it was hoped that the C-17 sidechain could be installed *via* alkylation of a kinetic enolate. Epimerization of the sidechain to form **50**, followed by dehydration, would then provide the bridgehead olefin. The timing for installation of the quaternary center, maleic anhydride, and the C-7 sidechain was left open at this point.

A notable feature of this design is that a significant portion of the functional groups on the left-hand side of the molecule are incorporated on the tropone component. This avoids intermolecular carbon-carbon bond forming reactions on the core, which have proven problematic in some syntheses. The right-hand half of the molecule, by contrast, requires significant elaboration. In effect, we are testing the hypothesis that it may be easier to install most of the left-hand half in the key step, and build the right-hand half on the resulting carbocycle.

There are two major challenges associated with this approach. First of all, the few methods reported to date for the synthesis of substituted tropones are

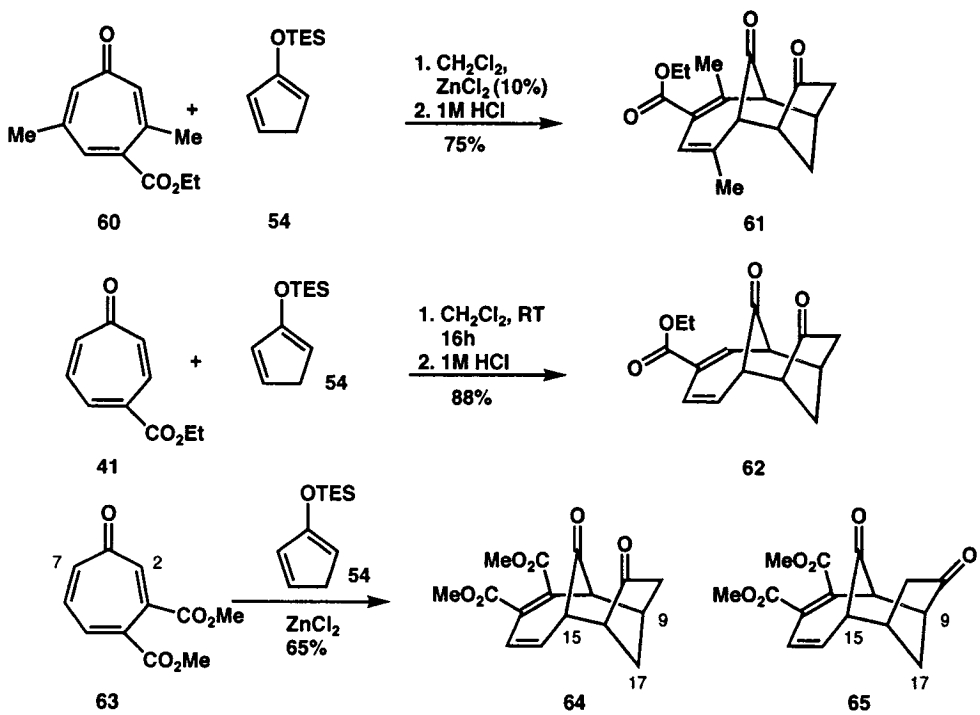
unlikely to be satisfactory for a multigram synthesis of **53**. This necessitates the development of a new method for tropone synthesis. The second major challenge is that a significant portion of the right-hand half must be installed after the [6+4] cycloaddition. After considerable deliberation, it was decided to develop a route towards the right hand half first, using a simplified tropone as a model system. Success with the model system would provide an impetus for the development of a method for the synthesis of tropone **53**, which we would then employ in a total synthesis using the knowledge gained during our model studies.

The results of Dr. Ljubomir Isakovic's model study are presented here.[55] Tropones **41** and **60** were selected as the most synthetically accessible analogues to **53** (Scheme **1-12**). Tropone **41** is readily available on multigram scale using Anicaux' adaptation of the Buchner aromatic ring-expansion reaction of anisole as the key step.[56] Isomerization of the resulting heptatriene, followed by oxidation with Br_2 [57] gave the tropone in good yield. Tropone **60** is obtained in similar fashion through the use of 3,5-dimethylanisole **58**. Unfortunately, the scope of the ring-expansion reaction is limited by the necessity of using the anisole as solvent (20 equivalents relative to ethyl diazoacetate **56**). This requirement likely makes adaptation of this method to a synthesis of substituted tropone **53** infeasible.



Scheme 1-12. Synthesis of tropones.

The [6+4] cycloadditions of **41** and **60** were then studied (Scheme **1-13**). To our great encouragement, the [6+4] cycloaddition of **60** and **54** proceeded in 75% yield. Interestingly, addition of Lewis acid was found to be crucial to the success of this transformation. In the absence of $ZnCl_2$, the yield was 54% and tropone was not completely consumed. Cycloaddition of **41** proceeded in higher yield with identical regioselectivity, without the need for addition of a Lewis acid. The [6+4] cycloaddition of tropone **63** was also examined.[58] In contrast to the regioselective cycloadditions of **61** and **40**, reaction of tropone **63** with **54** provided a 1:1 mixture of regioisomers **64** and **65**. Calculations show that the presence of the additional ester substituent at C-3 causes the C-2 and C-7 carbons to have similar coefficient magnitudes in the LUMO. The electronic properties of this tropone therefore disfavor direct installation of the maleic anhydride on the tropone.



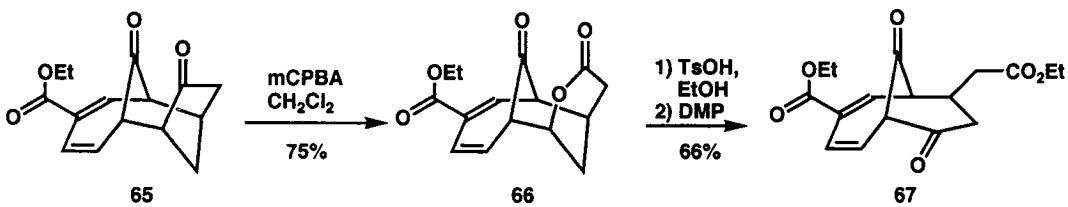
Scheme 1-13. [6+4] cycloadditions of substituted tropones.

1.7 Functionalization of the core

Owing to the greater availability of tropone **41**, model studies were continued with its [6+4] cycloadduct **62** (Scheme **1-14**). It was quickly discovered that cleavage of the crucial C_{16}—C_7 bond was a very straightforward process. Addition of mCPBA to diketone **62** led to a site-selective and regioselective Baeyer-Villiger reaction to give lactone **66** in 78% yield. Remarkably, neither attack at the bridgehead ketone nor epoxidation of the double bonds were observed. The presence of the ester presumably renders the diene less susceptible towards attack by electrophiles. Inspection of models also reveals that the diene

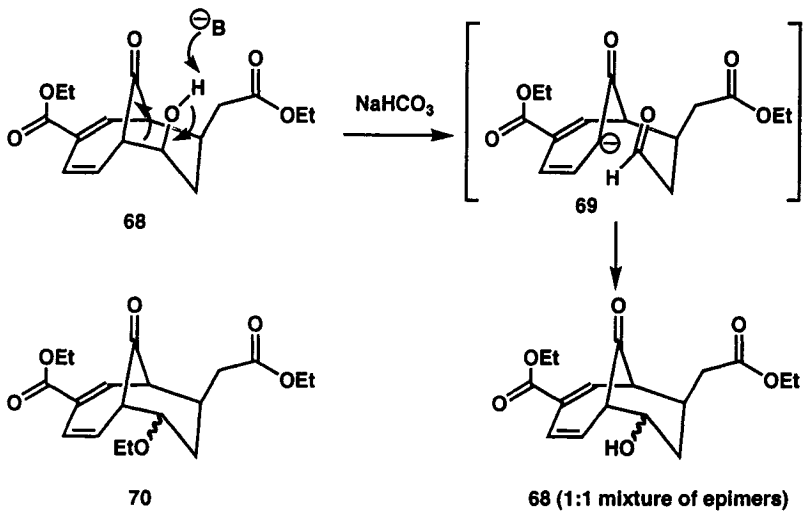
blocks the Bürghi-Dunitz trajectory towards the ketone on the 1-carbon bridge, protecting it from attack.

The resulting lactone could be opened under acidic conditions to give alcohol **68** in 75% yield, and the alcohol easily oxidized to diketone **67** in 88% yield. Interestingly, the alcohol was found to be very sensitive to base. Even brief treatment with $NaHCO_3$ led to rapid epimerization of the C(16) alcohol. Presumably this occurs through a facile retro-aldol / aldol process proceeding through intermediate aldehyde **69** (Scheme **1-15**). When the lactone opening reaction was performed under acidic conditions, epimerization was not observed. However, significant amounts of a byproduct **70** were obtained that accounts for the relatively modest yield (75%) of this reaction. Byproduct **70** likely forms through trapping of an intermediate oxonium ion by ethanol, followed by expulsion of water and subsequent re-closure.



65 66 67

Scheme 1-14. Elaboration of the [6+4] cycloadduct to ketone **67**.



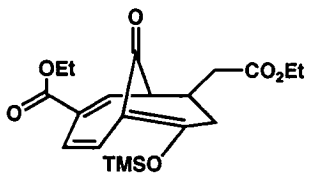
Scheme 1-15. Base-induced retro-aldol epimerization of alcohol **68**

Formation of the bridgehead alkene was briefly investigated, and found to be remarkably straightforward (Scheme **1-16**). Mesylation of alcohol **68**, followed by treatment with DBU in refluxing benzene gave bridgehead alkene **71** in 84% yield. This is a rare example of a *syn* elimination, presumably occurring through an E_{1cb} mechanism.

Scheme 1-16. Installation of bridgehead olefin.

With diketone **67** in hand, it was expected that generation of the less substituted enolate using NaHMDS followed by alkylation would form the crucial C-17 C-C bond. This was not the case. It was found that treatment of **67** with an excess of NaHMDS followed by trapping with TMSCl led to the bridgehead silyl

enol ether **72**. In contrast, usage of a deficit of base (0.9 eq) and allowing 30 min for enolate equilibration followed by trapping gave the less substituted enol ether **73**. The generation of the more substituted enolate through addition of an excess of base is generally not observed. Shea discovered similar anomalous reactivity of a bridgehead enolate in a [5.3.1] cyclic system during his synthetic work on Taxol.[59] He rationalized this behavior as resulting from acidification of the bridgehead proton through its better overlap (99° vs. 144° for the methylene protons according to MM2) with the π^* of the ketone. We subsequently learned that other groups working on the phomoidrides had encountered anomalous bridgehead reactivity in similar systems.[60]



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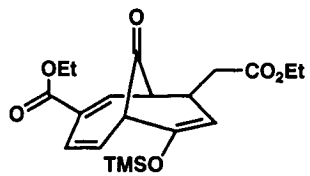
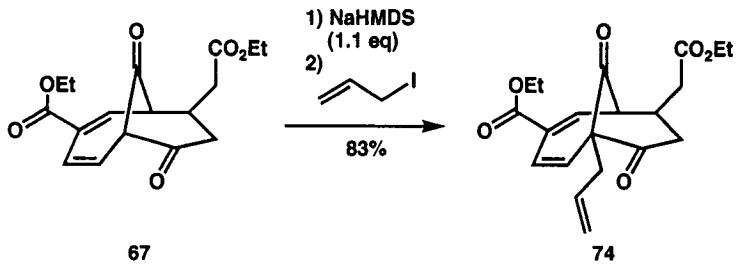


73

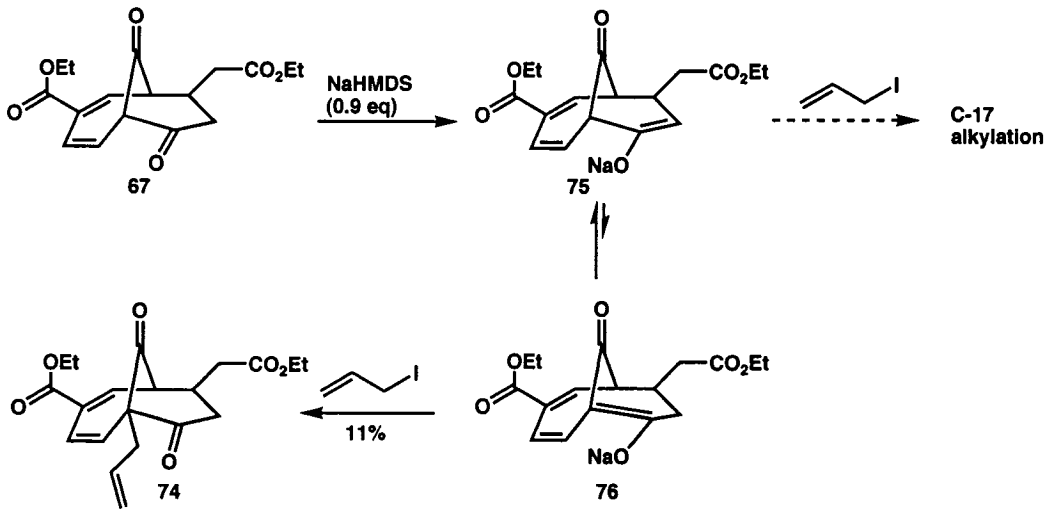
Figure 1-16. Silyl enol ethers derived from diketone **67**

As expected, treatment of diketone **67** with NaHMDS (1.1 eq) followed by addition of allyl iodide led to bridgehead allylation product **74** in 83% yield (Scheme **1-17**). In accordance with enolate trapping experiments, it was expected that treatment of **67** with 0.9 equivalents of base followed by addition of allyl iodide would provide the desired C-17 alkylation product. Instead, the only product isolated from the reaction was **74**, the result of bridgehead allylation. This unexpected result must result from Curtin-Hammet behavior of the

equilibrating mixture of enolates (Scheme **1-18**). Although enolate **75** is the major species in solution under these conditions, it is much less reactive than bridgehead enolate **76**. The result is dominant bridgehead alkylation.



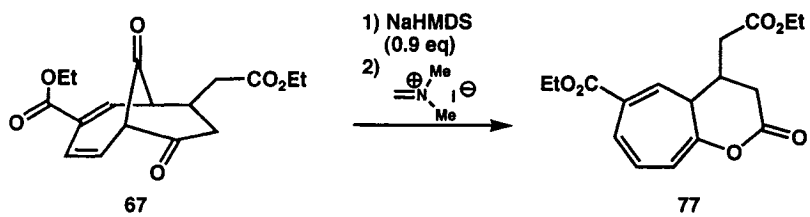
Scheme 1-17. Bridgehead alkylation of diketone **67**.



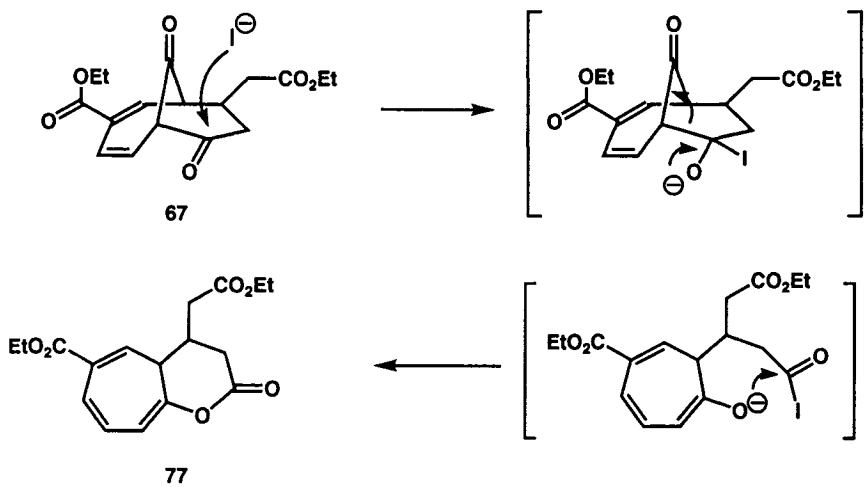
Scheme 1-18. Proposed rationale for bridgehead alkylation.

Despite many attempts, selective alkylation at C-17 could not be achieved. The high reactivity of the bridgehead position was not confined to alkyl halides. Michael addition with methyl vinyl ketone gave a 2:1 ratio of addition products with the bridgehead isomer predominating. Interestingly, treatment of the enolate of **67** with Eschenmoser's salt led to a complete fragmentation of the ring

(Scheme **1-20**). A mechanism for this transformation is presented in Scheme **1-21**. We were later to discover that similar retro-Dieckmann pathways were encountered by the Shair group. [61]



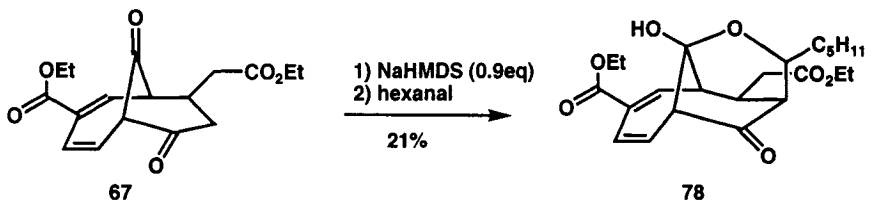
Scheme 1-20. Retro-Dieckmann reaction.



Scheme 1-21. Proposed mechanism of the retro-Dieckmann reaction.

The only reaction that appeared to possess regioselectivity for the C-17 position was aldol reaction with hexanal. Hemiacetal **78** was obtained as the sole product, albeit in low yield (Scheme **1-22**). Further functionalization of this product was prevented by an inability to open the stable hemiacetal.[62] In an attempt to circumvent these difficulties, the Mukaiyama aldol reaction of **73** was attempted using hexanal dimethyl acetal and a variety of Lewis acids.

Unfortunately, the silyl enol ether **73** was found to be inert towards these conditions.



67 78

Scheme 1-22. Aldol reaction.

Dr. Isakovic also briefly explored an alternative C-17 bond forming strategy employing a substituted cyclopentadiene in the [6+4] cycloaddition. This strategy will be discussed in more depth in Chapter 3.

1.8 Summary

Previous work in the laboratory by Ljubomir Isakovic demonstrated the viability of a [6+4] cycloaddition approach for the synthesis of the core. However, attempts to install the C-17 sidechain with the desired regioselectivity in high yield were unsuccessful. At the conclusion of Dr. Isakovic's tenure, the primary challenge was installation of the C-17 sidechain. Attempts to achieve this bond construction using a continuation of this strategy are outlined in Chapter 2.

References

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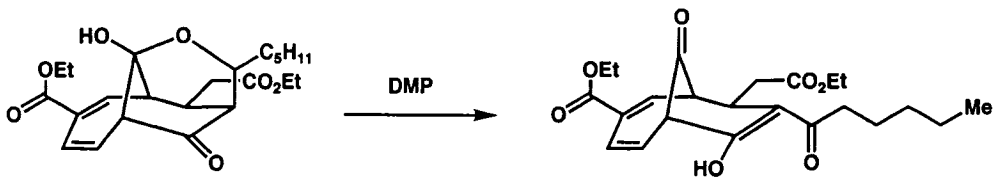
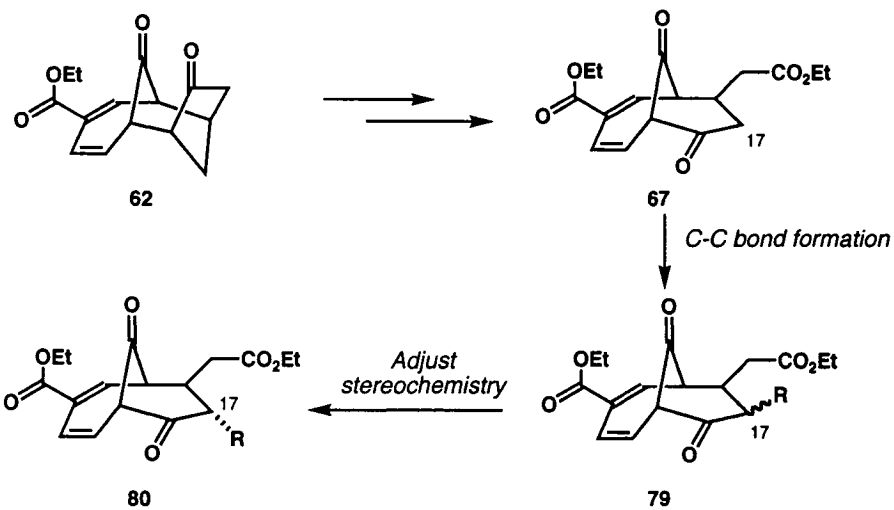


CHAPTER TWO

2.1 Introduction

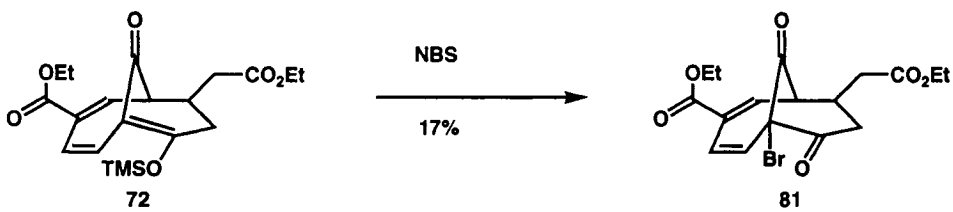
Previous work in this laboratory by Dr. Ljubomir Isakovic established the viability of [6+4] cycloadditions for constructing the carbocyclic core of the phomoidrides. Due to the ready availability of tropone **41,** we continued to focus attention on constructing the right-hand half of the molecule. Our concern at the outset was to continue attempts to add the sidechain (or an appropriate surrogate) upon the core diketone **67** (Scheme **2-1**). Although these efforts eventually met with limited success, they nevertheless led to several interesting observations that would later prove valuable during our progress toward the right-hand half detailed in Chapter 3.



Scheme 2-1. General plan for installation of the C—17 sidechain.

2.2 Blocking the bridgehead position

Noting the propensity of the diketone system for undesired bridgehead reactivity, our first plan was to install a blocking group at this position. Treatment of silyl enol ether **72** with NBS at 0 °C yielded bridgehead bromide **81** (Scheme **2-2**). Although the yield was low, it provided enough material to allow exploratory alkylation chemistry using this substrate. Unfortunately, treatment of the enolate obtained by addition of 1.1 eq. NaHMDS (with or without HMPA as a cosolvent) led either to no reaction or destruction of the substrate. This was not pursued further.



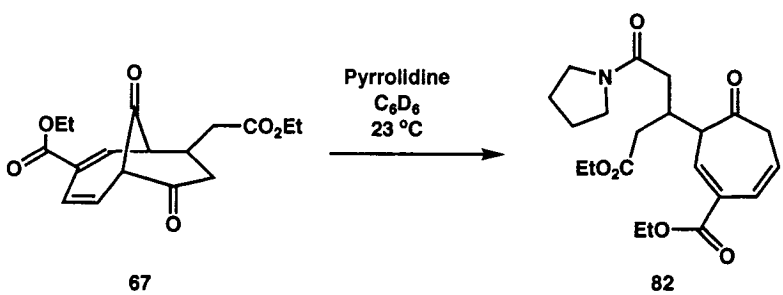
Scheme 2-2. Protection of the bridgehead position via bromination of **72**.

2.3 Further investigation of the aldol reaction

As discussed in section **1.7**, the aldol reaction between **67** and hexanal was the only carbon-carbon bond forming reaction that appeared to possess the desired regioselectivity for the C-17 carbon. We decided to investigate this reaction further, hoping to find optimal conditions for this key step. Unfortunately, in our hands the yield was never observed to exceed 25%. We found that the remainder of the mass balance was present in the aqueous layer after workup. Analysis of this fraction showed a mixture of carboxylic acids that lacked the characteristic

resonances of the bicyclo[4.3.1] ring system. This was a strong indication that the ring had undergone retro-Dieckmann fragmentation.

Retro-Dieckmann fragmentation also prevailed during attempts to install the sidechain via a Stork enamine reaction (Scheme **2-3**). When pyrrolidine (2 eq) was added to diketone **67**, the solution quickly turned black. Within 5 minutes, both ^{1}H and COSY NMR clearly indicated that the diketone had undergone fragmentation. IR of the resulting product showed a strong peak at 1638 cm^{-1}, consistent with the formation of amide **82**. [1]



67 **82**

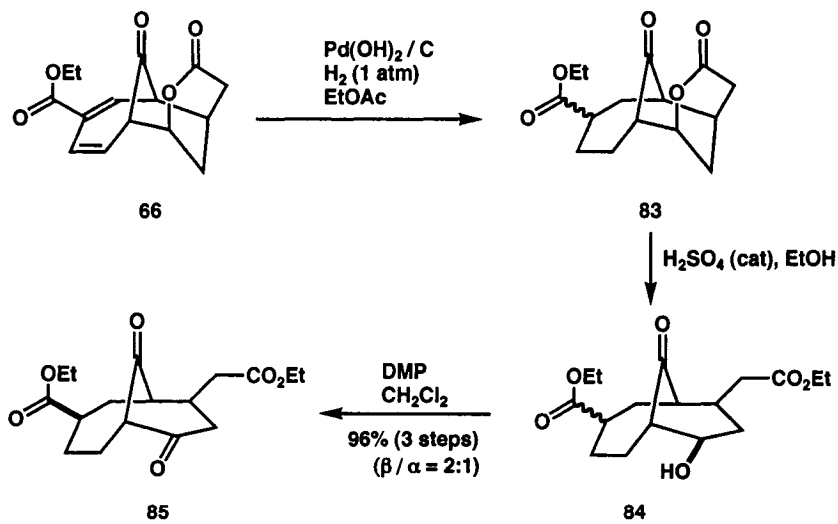
Scheme 2-3. Retro-Dieckmann reaction to form amide **82**.

2.4 Saturation of the carbocyclic core

The unexpected reactivity of the bridgehead enolate **76** coupled with the tendency of the diketone **67** to undergo fragmentation led us to modify our approach. We hoped to ameliorate both of these undesired reaction pathways through saturation of the ring system. We reasoned that removal of the diene moiety should make the bridgehead proton less acidic. Furthermore, the propensity towards retro-Dieckmann fragmentation should also be reduced, as the

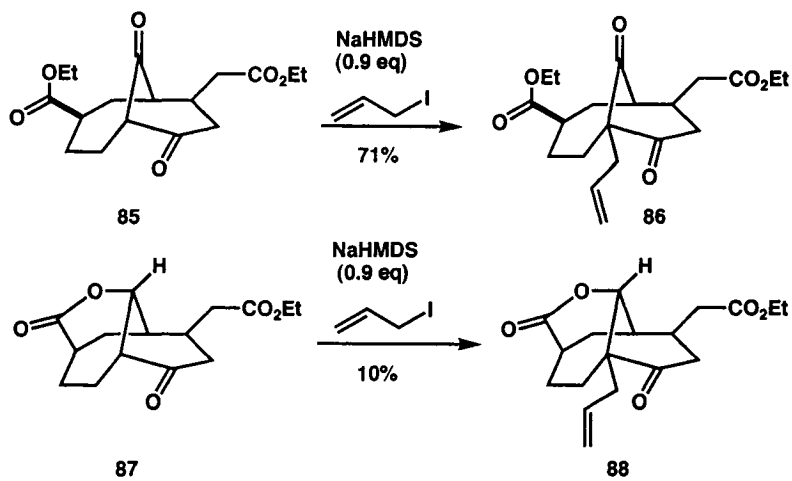
enolate resulting from fragmentation would no longer be stabilized by resonance with the diene.

The saturated analogue of the diketone was synthesized in three steps from unsaturated lactone **66** (Scheme **2-4**). Hydrogenation over $Pd(OH)_2/C$ resulted in a 2:1 mixture of epimeric lactones **83** which could not be separated. The lactone was opened under acidic conditions to give alcohol **84**. Oxidation of the alcohol with DMP as before gave saturated diketone **85**. The sequence proceeded in 96% yield over three steps. At this point, the ester epimers could be separated through silica gel column chromatography. The higher yield for this sequence is a function of the greater stability of the saturated system towards both the acid-catalyzed lactone-opening step and silica gel. The β–orientation of the ester group was established through reduction of the bridging ketone with $NaBH_4$ followed by heating with PPTS to give a lactone.[2]



Scheme 2-4. Synthesis of saturated diketone **82**.

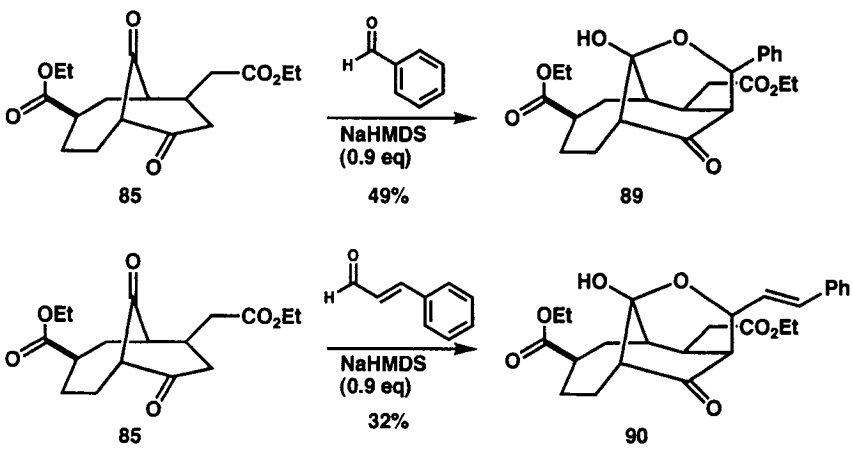
To our dismay, hydrogenation of the diene did not significantly change the behavior of the resulting enolates. Addition of NaHMDS (1.1 eq) followed by quenching with TMSCl led to trapping of the bridgehead silyl enol ether as before. Likewise, trapping of the enolate under conditions of thermodynamic control (0.9 eq NaHMDS) gave the less substituted silyl enol ether. Preferential reaction of electrophiles at the bridgehead position remained a problem (Scheme **2-5**). Attempted alkylation of the C-17 carbon under thermodynamic conditions (0.9 eq NaHMDS) with allyl iodide resulted in bridgehead allylated diketone **86** in 71% yield. Lactone **87** was also synthesized but found to allylate at the bridgehead position to give **88** in 10% yield.



Scheme 2-5. Bridgehead allylation of ketones **85** and **87**.

Some success was achieved with the aldol reaction of diketone **85** (Scheme **2-6**). Addition of benzaldehyde gave aldol addition product **89** in 49% yield, where addition to the desired position was observed. Similarly, addition of cinnamaldehyde also gave a 32% yield of **90**. In both of these cases the majority

of the remaining mass balance consisted of unreacted starting material. Encouragingly, neither retro-Dieckmann reaction nor formation of the bridgehead aldol product were observed.

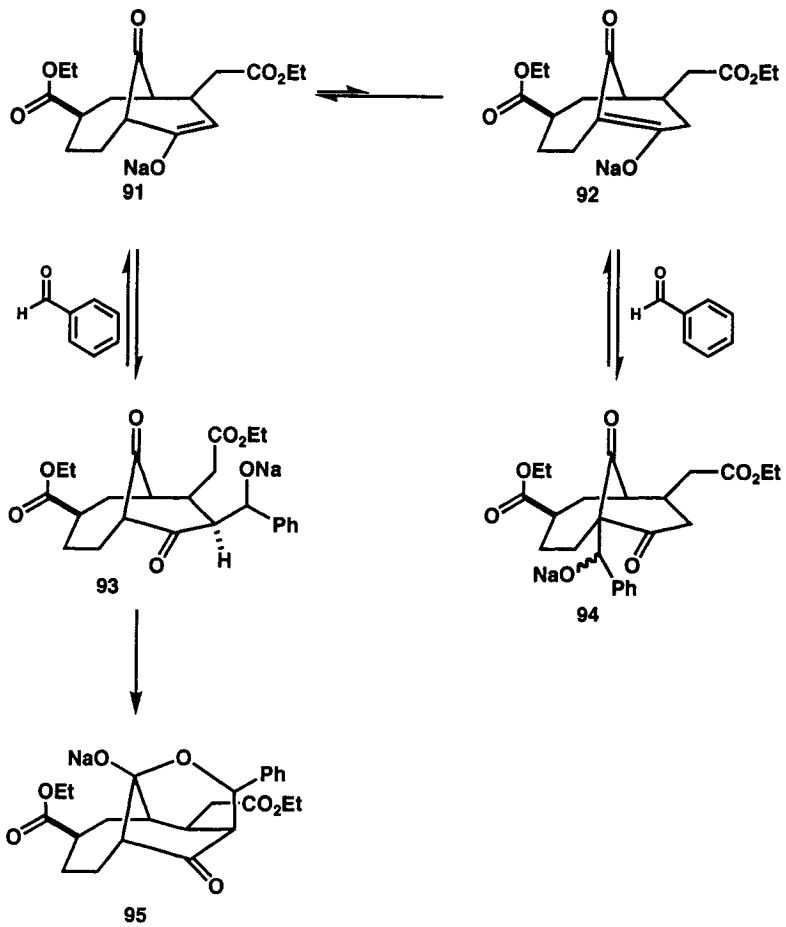


Scheme 2-6. Successful aldol reactions of diketone **85**.

Unfortunately, attempts to extend the success of the aldol reaction to aliphatic aldehydes more closely resembling the C-17 sidechain met with failure. For example, reaction of the enolate of **85** with hexanal (1.1 eq) at –40 ^{0}C resulted in a complex mixture of aldol adducts. A significant portion of the product mixture consisted of products derived from reaction at the bridgehead. This stands in contrast to the reaction of diketone **67** with hexanal, where bridgehead reaction products underwent rapid retro-Dieckmann fragmentation. This provided further evidence that hydrogenation was successful in stabilizing the diketone.

The contrast in product distribution between aliphatic and aromatic aldehydes is noteworthy. In light of our previous observations with bridgehead enolates, we view it as unlikely that there is a significant regiochemical difference

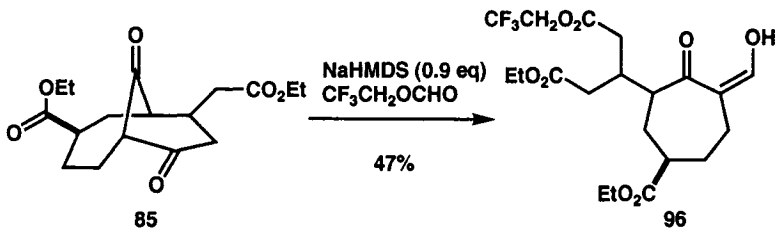
between aliphatic and aromatic aldehydes. Instead, we propose that the observed regioselectivity of the reaction with aromatic aldehydes is due to an equilibrium aldol/retro-aldol process (Scheme **2-7**). Initial (unselective) aldol reaction would give a mixture of C-17 and C-15 aldolates **93** and **94**. Retro-aldol reaction of the bridgehead aldolate **94** would regenerate the enolate **92**. In contrast, retro-aldol reaction of the C-17 aldolate **93** is prevented by trapping of the product as the stable hemiacetal. In this manner, all of the bridgehead aldolate should be eventually converted to **95**. The aldol/retro-aldol equilibrium with aliphatic aldehydes is evidently more complex, as evidenced by the lack of a single regioisomer. This is likely due to the possibility for proton transfer from the aldehyde to the equilibrating ketone enolate. Further work is required to confirm this mechanistic hypothesis.



Scheme 2-7. Proposed rationale for C-17 regioselectivity of aldol reactions.

Although the hydrogenated diketone exhibited greater stability towards retro-Dieckmann fragmentation than the unsaturated system, rearrangement was still observed under certain conditions. For example, attempted formylation of **82** with 2,2,2-trifluoroethyl formate[3] led to the isolation of triester **96** in 47% yield (Scheme **2-8**). Once again, the bridgehead position of the enolate was the most reactive. Attachment of an electron-withdrawing acyl moiety to the bridgehead

evidently facilitates the subsequent retro-Dieckmann step by stabilizing the resulting enolate.

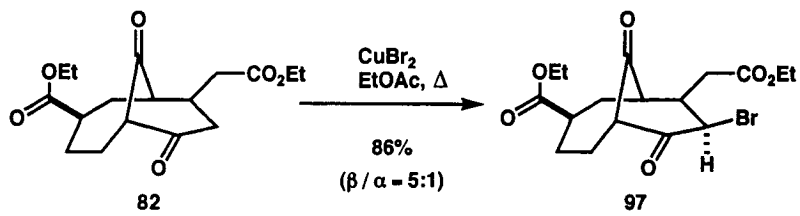


85 96

Scheme 2-8. Formylation / retro-Dieckmann reaction of **85**

In analogy to the unsaturated system, attempts to forge the desired C-17 bond by reaction of the silyl enol ether of the thermodynamic enolate with carbon electrophiles under various conditions (Eschenmoser's salt[4]; $Yb(OTf)_3$ / formaldehyde[5] ; hexanal / $TiCl_4$) either led to cleavage of the silyl enol ether or recovery of starting material.[6] In addition, blocking of the bridgehead position with a bromine atom followed by alkylation was unsuccessful. Finally, trapping of the thermodynamic enolate with allyl chloroformate followed by treatment with $Pd_2(dba)_3$ / PPh_3 predominantly afforded products of bridgehead allylation.[7]

Although carbon-carbon bond formation at C-17 met with failure, we found that treatment of diketone **85** with $CuBr_2$ in refluxing EtOAc[8] generated bromide **97** in 86% yield as a 5:1 (β/α) mixture of isomers [9] (Scheme **2-9**). The β-orientation of the bromide was established by NOE of the C-17 proton at 4.64 ppm to the C-12 proton on the underside of the molecule at 2.60 ppm. Gratifyingly, bridgehead bromination was not observed.



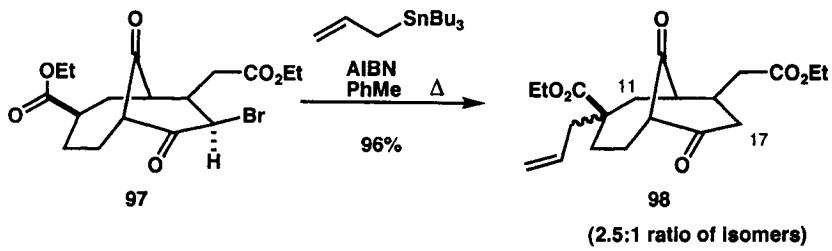
Scheme 2-9. Regioselective bromination of diketone **85**.

2.5 Attempts at free-radical carbon-carbon bond formation

The accessibility of bromide **97** opened up a new avenue for C-C bond formation. Aliphatic halides are excellent substrates for free-radical carbon-carbon bond formation. Since free radicals tend not to equilibrate once formed, we hypothesized that generation of a free radical at the desired carbon would not be complicated by the regioselectivity problems that plagued our enolate chemistry.

Using the procedure of Keck,[10] we attempted allylation of **97** under free-radical conditions. To our initial satisfaction, addition of allyltributyltin in refluxing toluene with AIBN gave two products (ratio 2.5:1) which clearly contained an allyl group and lacked the characteristic resonance at 4.64 ppm in the ^1H spectrum. The mixture of compounds was difficult to separate and characterize. However, treatment with $NaBH_4$ yielded a mixture of separable alcohols. Re-oxidation gave clean samples of each. Extensive 1-D and 2-D NMR spectroscopy revealed the structure of the allylated products to be the 2.5:1 mixture of epimers **98**. To our great surprise, allylation had occurred on the opposite side of the molecule.

Our assignment of **98** was supported by experimental and spectroscopic methods. HMQC and COSY NMR spectroscopy revealed C-17 to be a methylene carbon (^{13}C NMR: 41.9 ppm ; ^{1}H NMR: 2.27, 2.88 ppm). HMBC showed correlations between the methylene protons of the allyl moiety (^{1}H NMR: 2.22 ppm) and the ester carbonyl (^{13}C NMR: 173.4 ppm). The major product contained the allyl moiety on the α face, as evidenced by a NOE between the allyl methylene protons, the C-17 methylene protons, and the α-oriented proton at C-11. When **98** was subjected to the $CuBr_2$ reaction, a new bromide was isolated whose 1-D and 2-D NMR characteristics further supported the structure assignment.



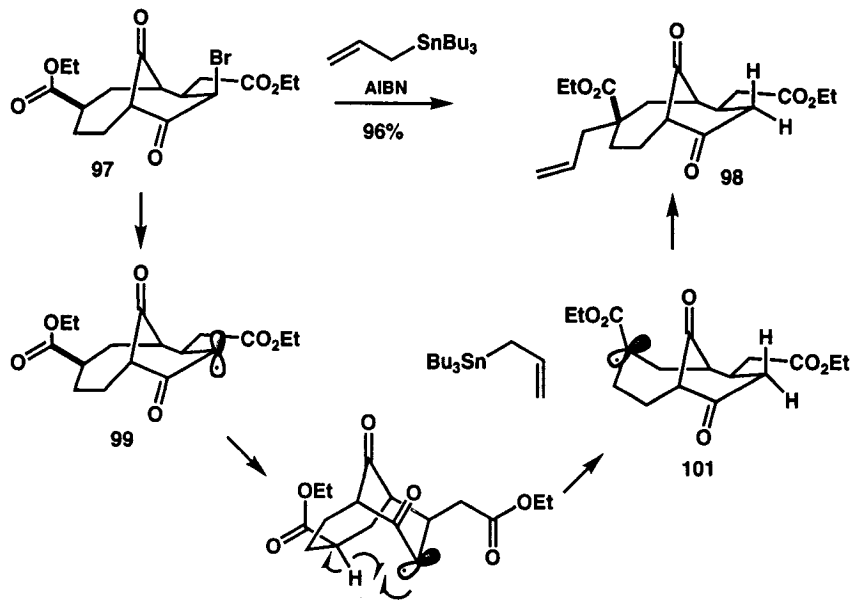
97 **98**

(2.5:1 ratio of isomers)

Scheme 2-10. Free-radical allylation of **97**.

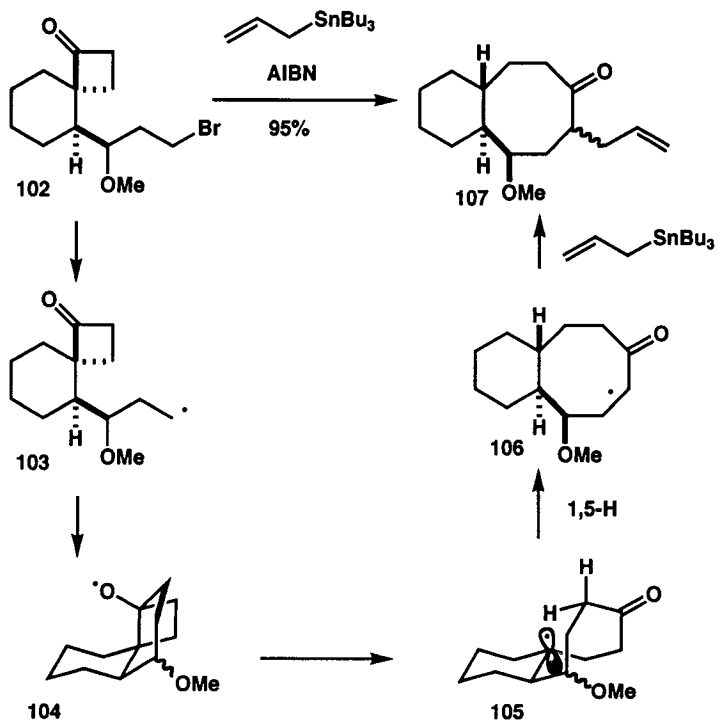
A proposed mechanism for the allylation reaction is indicated in Scheme **2-11**. Abstraction of the bromide by the tributyltin radical generates the corresponding radical **100**. A 1,5-hydrogen translocation then occurs, whereby the radical then abstracts a hydrogen atom from the underside of the molecule, six atoms away, generating the more stable tertiary α-ester radical **101**. Allylation of the radical by allyltributyltin then occurs with a modest (2.5:1) preference for the

α-face to give **98**, indicating a kinetic preference for attack on the twist-boat conformation in the 7-membered ring.



Scheme 2-11. Proposed mechanism for remote allylation.

Intramolecular rearrangements using the allyltributyltin method are known.[11] A similar hydrogen translocation was observed by Cha during his studies on the generation of fused ring systems from the free-radical promoted reaction of ω-bromoalkyl cyclobutanones (Scheme **2-12**).[12]



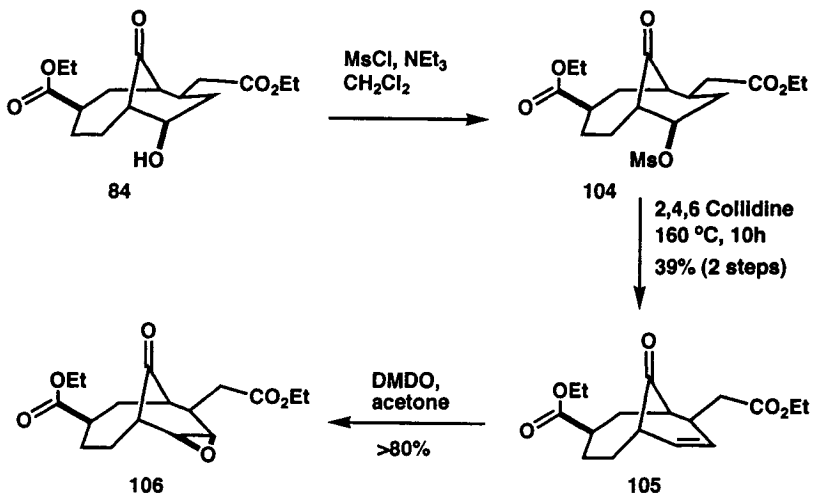
Scheme 2-12. Hydrogen translocation during Cha's synthesis of fused cyclooctanones.

2.6 Attempted Bridgehead Olefin Formation

With alcohol **84** in hand, we attempted to install the bridgehead olefin through a two step mesylation/elimination process analogous to that described for compound **68**. Interestingly, when the resulting mesylate **104** was heated with 2,4,6-collidine at 160 °C for 1 h, the disubstituted alkene **105** was formed in 39% yield (Scheme **2-13**). In contrast to **68**, which eliminates to the bridgehead olefin through a presumed E_{1cb} process, an E2 mechanism is favored in this case. The

removal of the diene in **84** likely makes the barrier to formation of the bridgehead anion prohibitively high relative to the competing E2 process.

Alkene **105** could be smoothly converted to epoxide **106** by treatment with a solution of DMDO in acetone. Unfortunately, attempts to form the C-17 bond by addition of carbon-based nucleophiles (e.g. lithium dibutylcuprate/BF_3, lithium acetylide / BF_3) were unsuccessful.

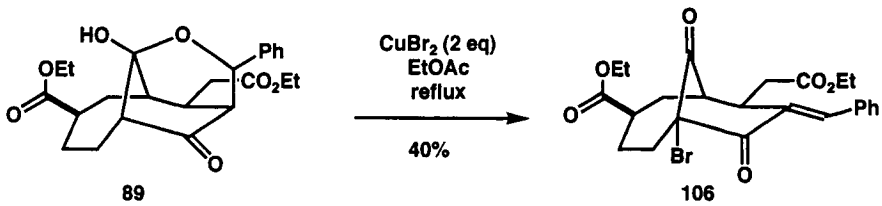


Scheme 2-13. Mesylation-elimination and alkene epoxidation.

2.7 Elimination of Benzaldehyde Aldol Adduct

An interesting reaction was observed during the attempted bromination of benzaldehyde aldol adduct **89**. Heating with $CuBr_2$ in refluxing EtOAc for 18h resulted in the isolation of enone **106** in 40% yield (Scheme **2-14**). Although it was not investigated, installation of the C-17 stereocenter could presumably be achieved via conjugate reduction of the enone. In light of the difficulties we

experienced with the aldol reaction of saturated diketone **85** with aliphatic aldehydes, however, this reaction was not explored further.



Scheme 2-14. $CuBr_2$-promoted elimination of aldol adduct **89** to give enone **106**.

2.8 Summary

Although saturation of the ring system greatly stabilized it toward destructive retro-Dieckmann pathways, it did not overcome the tendency of the enolates to alkylate on the bridgehead carbon. Some success was achieved with the aldol reaction of non-enolizable aldehydes, but attempts to extend these successes to aldehydes more useful for synthesis of the C-17 sidechain met with failure. Regioselective bromination on C-17 could be achieved using $CuBr_2$. Unfortunately, attempts to alkylate under free radical conditions led to an interesting intramolecular hydrogen abstraction followed by allylation.

The difficulty of forming a carbon-carbon bond on these and related substrates led us to modify our approach by using a 5-substituted cyclopentadiene in the [6+4] cycloaddition. This strategy will be detailed in Chapter 3.

References

[1] Hydrogenation of diketone **67** with $Pd(OH)_2$ in EtOH also resulted in fragmentation.

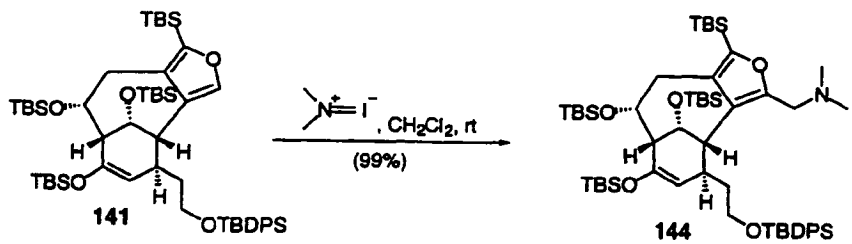
[2] No epimerization of esters were observed under these conditions.

[3] Zayia, G.H. ; *Org. Lett.* **1999**, *1*, 989

[4] Danishefsky, S. ; Kitahara, T. ; McKee, R. ; Schuda, P.F. ; *J. Am. Chem. Soc.* **1976**, *98*, 6715

[5] Kobayashi, S. ; Hachiya, I. ; *J. Org. Chem.* **1994**, *59*, 3590

[6] After the completion of this research, we became aware that the Danishefsky laboratory encountered similar difficulties forming the C—17 bond using a silyl enol ether: Kwon, Ohyun, Ph.D. thesis, Columbia University, 2001.



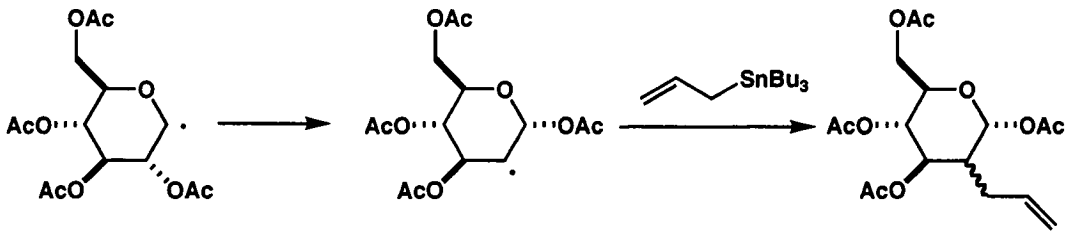
[7] Tsuji, J. ; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140 ; Nicolaou, K.C. ; Vassilikogiannakis, G.; Magerlein, W.; Kranich, R. *Angew. Chem. Int. Ed.* **2001**, *40*, 2482

[8] Bamford, S.J. ; Luker, T. ; Speckamp, W. N. ; Hiemstra, H. *Org. Lett.* **2000**, *2*, 1157; Kochi, J.K. *J. Am. Chem. Soc.* **1955**, *77*, 5274

[9] When this reaction was attempted on diketone **67**, retro-Dieckmann cleavage occurred.

[10] Keck, G.E. ; Yates, J.B. *J. Am. Chem. Soc.*, **1982**, *104*, 5829

[11] Giese, B. in "Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds", Pergamon. New York: **1986** p. 101. The following example is noted (as "B.Giese, unpublished results"):



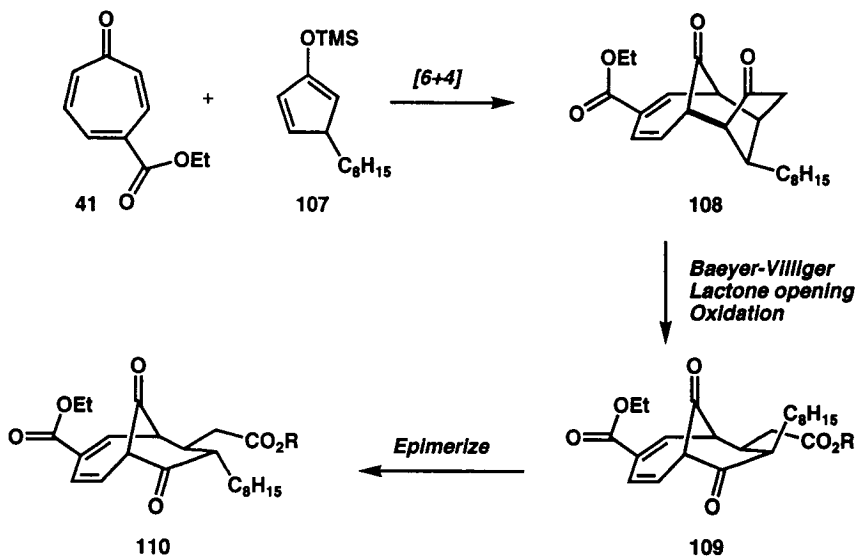
[12] Oh, H.O.; Lee, H. I.; Cha, J. K. *Org. Lett.* **2002**, *4*, 3707

CHAPTER THREE

3.1 Introduction

In Chapter 2 we described our attempts to install the crucial C-17 sidechain upon the bicyclic core of a phomoidride model system. The formation of this carbon-carbon bond upon the bicyclic core proved to be an exceptionally difficult task. After considerable deliberation, we realized that the convergency of our synthesis would be greatly improved if we could include that C—C bond on the cyclopentadiene component of our [6+4] cycloaddition.

Early experiments in this area had been performed by Ljubomir Isakovic. The plan pursued by Dr. Isakovic called for installation of the eventual C-17 sidechain on the diene **107**, which would be derived from an enone as in earlier studies (Scheme **3-1**). The key [6+4] cycloaddition would be followed by Baeyer-Villiger oxidation, lactone opening, and oxidation as described for the analogous



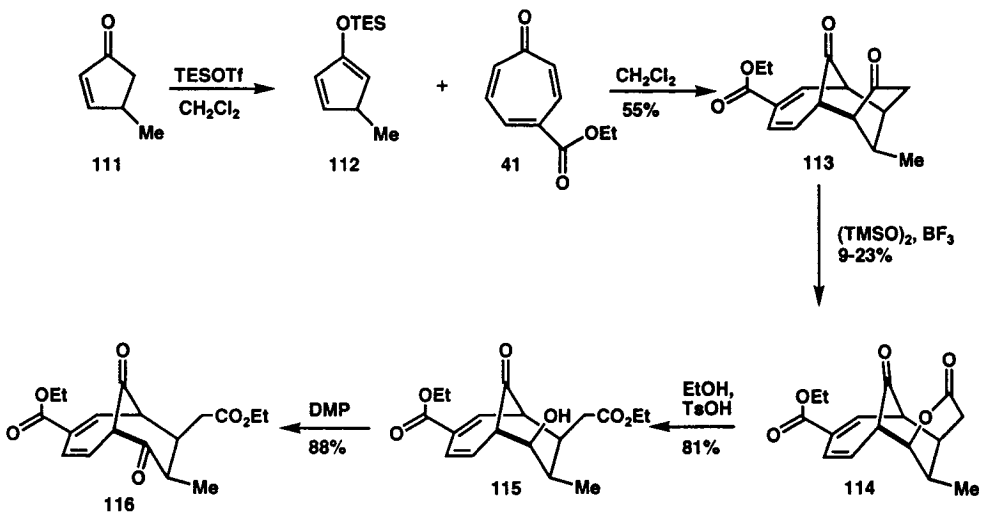
Scheme 3-1. Ljubomir Isakovic's plan for installation of the C-17 sidechain.

unsubstituted diene series to give diketone **109**. The proper C-17 stereochemistry would then be established by epimerization, as it was thought that protonation should occur preferentially from the concave face of the bicycle.

A potential concern raised by this approach was the known thermal instability of 5-substituted cyclopentadienes.[1] Dienes in this class undergo a facile [1,5] hydrogen shift to give the more substituted diene. McLean and Haynes measured the activation energy for the rearrangement of 5-methylcyclopentadiene to be 20.4 ± 0.3 kcal/mol, and Katagiri and co-workers noted that 5-[(benzyloxy)methyl]cyclopenta-1,3-diene showed complete rearrangement over 24 h.[2] Although these dienes have proven to be invaluable for certain synthetic applications, particularly in Corey's pioneering work in the prostaglandin field [3], their notorious instability typically requires cold-room facilities for workup and purification. A further drawback is that they are best synthesized through alkylation of highly toxic thallium cyclopentadienide salts.

The execution of Dr. Isakovic's plan is shown in Scheme **3-2**. Diene **112** was synthesized by forming the silyl enol ether of the known, simplified enone **111** with TESOTf. Remarkably, silyloxy groups were found to impart sufficient stability to 5-substituted cyclopentadienes to enable their synthesis and handling at room temperature. The diene was observed to undergo clean [6+4] cycloaddition with tropone **41** at room temperature, affording cycloadduct **113** in 55% yield. The reason for the stabilizing influence of the silyloxy group is not fully understood. An explanation that invokes FMO theory rationalizes the [1,5]

hydrogen shift as an interaction of the HOMO of the C-H bond with the LUMO of the diene. Using this interpretation, the presence of the silyloxy group thus raises the energy of the diene LUMO, retarding the sigmatropic rearrangement. Prof. James Gleason has performed DFT studies on an analogous 5-substituted cyclopentadiene that show that the barrier to [1,5] H shift increases by 1.6 kcal/mol when the electronically similar -OH substituent is present.



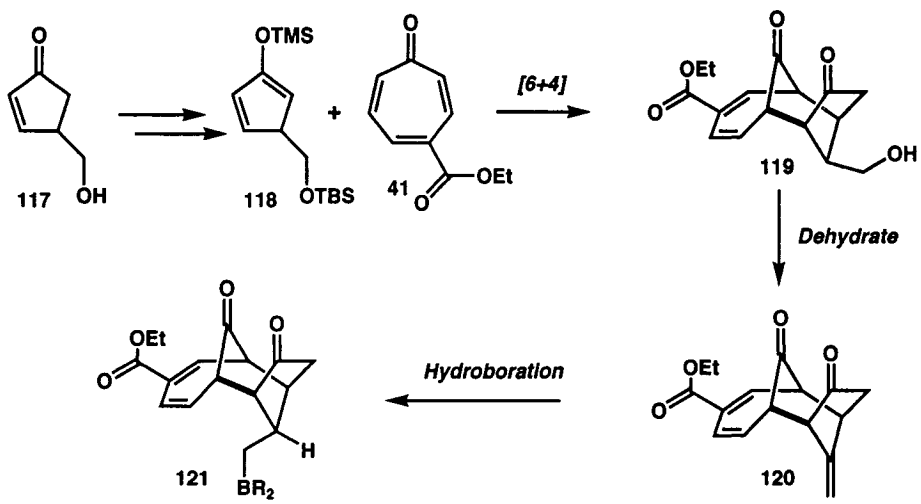
Scheme 3-2. Application of the original synthetic plan using simplified enone **111**.

With access to [6+4] cycloadduct **113** secured, Dr. Isakovic then pursued the plan developed for the unsubstituted diene. Unfortunately, the Baeyer-Villiger oxidation that worked so well on the unsubstituted system was problematic for diketone **113**. Evidently, the ß-oriented methyl group shields the ketone from nucleophilic attack. After a number of unsuccessful attempts, it was eventually found that the Baeyer-Villiger proceeded to lactone **114** with $(TMSO)_2$

in the presence of excess $BF_3 \cdot Et_2O$.[4] Unfortunately, the yields and reproducibility of this reaction were very poor. Opening of the lactone and following oxidation of the resulting alcohol **115** to the ketone **116** proceeded with satisfactory yields, but several attempts at epimerization (NEt_3/CH_2Cl_2, NaHMDS/THF, $TMSOTf/NEt_3$) failed to effect this transformation. The proton adjacent to the ketone is buried on the concave underside of the molecule, greatly hindering enolization.

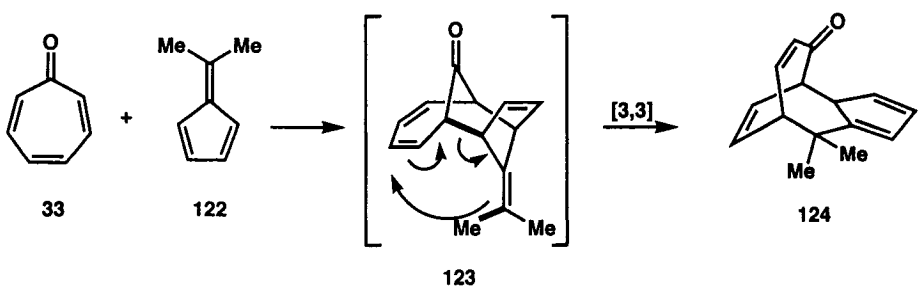
3.2 Development of a New Synthetic Route for Installation of the C-17 Sidechain

We returned to the substituted cyclopentadiene approach after performing the experiments outlined in Chapter 2. With Dr. Isakovic's results in mind, we re-designed the synthesis of the diene such as to incorporate a substituent that would allow for adjustment of stereochemistry before the Baeyer-Villiger step. Our plan was to synthesize known enone 117, protect the primary alcohol and then trap its kinetic enolate as before to deliver diene **118**. After the key [6+4] cycloaddition with tropone **41**, dehydration of the primary alcohol on the resulting cycloadduct **119** would afford a new terminal alkene **120**. The concavity of this terminal alkene would then be exploited to generate the desired C—17 stereochemistry. Overwhelming literature precedent gave us confidence that the desired stereochemistry could be established through the anti-Markovnikoff selective hydroboration of the terminal alkene. Oxidation of the resulting borane **121** would then provide a handle that could be further extended to provide the full sidechain.



Scheme 3-3. Revised plan for C—17 sidechain installation.

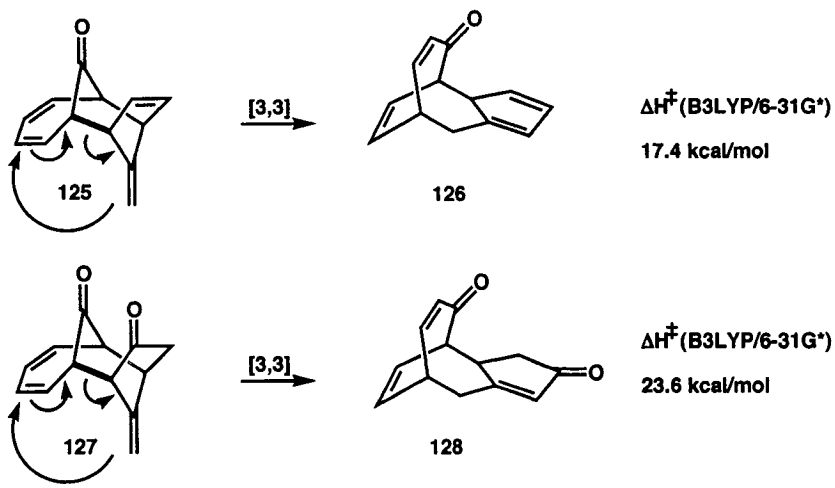
Our decision to adopt this strategy was not without some trepidation, as prior work from Houk's laboratory showed that the [6+4] cycloaddition of tropone **33** with dimethylfulvene **122** formed a 1:1 adduct **124** (Scheme **3-4**). [5] It was speculated, but not conclusively demonstrated, that **124** might be the product of a [6+4] cycloaddition (with tropone acting as the 6π component) to give **123** followed by a facile Cope rearrangement. [6]



Scheme 3-4. Houk's proposed Cope rearrangement for [6+4] adduct **123**.

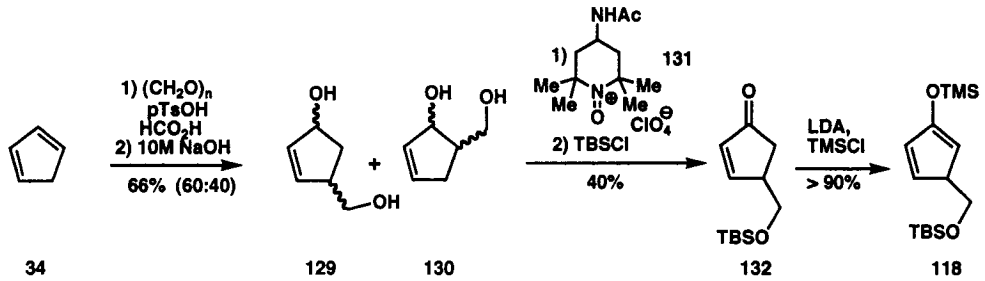
We were concerned about the possibility for a destructive Cope rearrangement and wished to learn if it would be a problem in our synthesis.

Towards this end, Prof. James Gleason studied the Cope rearrangements of **125** and **127** by DFT. It was found that the barrier to the Cope rearrangement was indeed low enough to be a concern. In **125**, which possesses an alkene on the two-carbon bridge, the barrier to rearrangement was calculated to be 17.4 kcal/mol, meaning that it should be facile even below room temperature.[7] In diketone **127**, an analogue of our synthetic intermediate, the barrier is considerably higher (23.4 kcal/mol). The contrast in stability is noteworthy. The destabilizing influence of the bridging alkene substitutent may be a reflection of increased ring strain, or slightly shorter distances between the reactive termini (DFT calculated distance: 3.59 Å vs. 3.65 Å for the diketone). These calculations gave us sufficient cause for optimism that with careful handling we could minimize the problematic Cope rearrangement. This turned out to be the case.



Scheme 3-5. Calculation of energies for Cope rearrangements **125** and **127**.

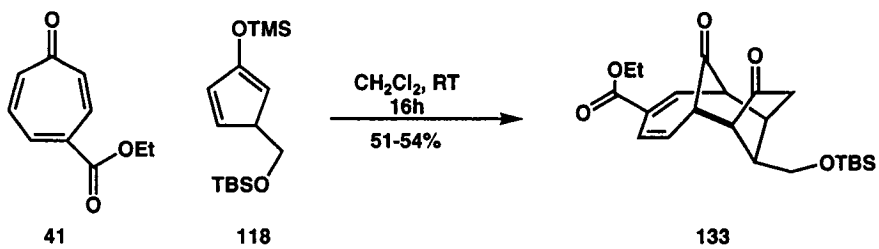
Our next concern was to secure access to large quantities of enone **117**. To our dismay, we found that none of the several reported procedures for the synthesis of **117** were satisfactory for this purpose.[8] After considerable effort, we eventually developed a very practical three-step protocol that allowed for rapid access to large quantities (>20g / batch) of protected alcohol **132** using inexpensive starting materials (Scheme **3-6**). The Prins reaction of formaldehyde and cyclopentadiene developed by Sutherland provided a 60:40 mixture of 1,4, and 1,3 diols **129** and **130**.[9] After distillation, this mixture was submitted to oxidation by Bobbitt's N-oxo ammonium salt **131** which showed exquisite selectivity for the allylic alcohol.[10] This seldom-used but splendid oxidant was key for the success of this route. In addition to its bench-stability and inexpensive preparation on large scale, the reagent is colorimetric, allowing for facile monitoring of the reaction by observing the disappearance of its distinctive bright-yellow colour. Furthermore, the simple workup (filtration) provides a white solid that can easily be re-oxidized and recycled. Numerous other oxidants known to be selective for secondary and/or allylic alcohols were found to be inferior for this transformation. [11]



Scheme 3-6. Synthesis of diene **118**.

Diene **118** was synthesized by protection of the primary alcohol with TBSCl and trapping of its kinetic enolate with TMSCl. Monitoring of a solution of diene **118** in $CDCl_3$ found that 80% of the diene remained after 20 h, confirming both our calculations and the analogous observations of Dr. Isakovic.

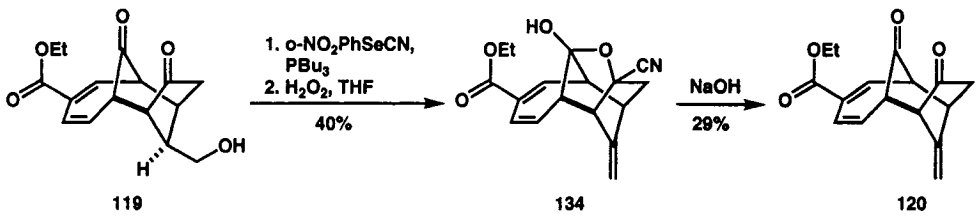
The [6+4] cycloaddition of tropone **41** and diene **118** was then investigated (Scheme **3-7**). Best results were obtained with a 2- to 3-fold excess of diene **118** and a minimal amount of solvent in CH_2Cl_2 at room temperature. Under these conditions, [6+4] cycloaddition proceeded rapidly and was usually complete within 1 h. After cleavage of the silyl enol ether with AcOH/THF/H_2O, the [6+4] cycloadduct **133** was obtained in reliable 51-54% yield.



Scheme 3-7. Successful [6+4] cycloaddition of tropone **41** and diene **118**.

Alkene **120** was synthesized in 3 steps from alcohol **119** (Scheme **3-8**). Selenation of **119**, followed by treatment with H_2O_2 using Grieco's conditions

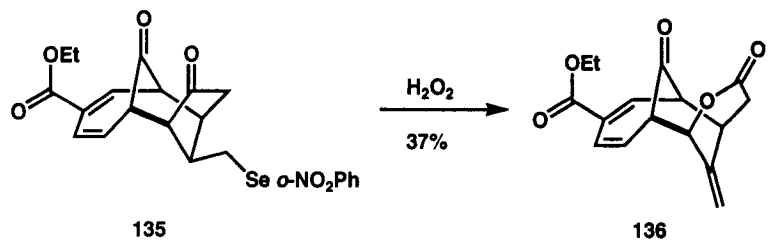
gave an alkene in 40% overall yield.[12] Treatment of the crude reaction mixture with zinc in acetic acid was necessary to remove the aromatic selenenic acid byproduct of the reaction.



119 134 120

Scheme 3-8. Synthesis of diketone **120**.

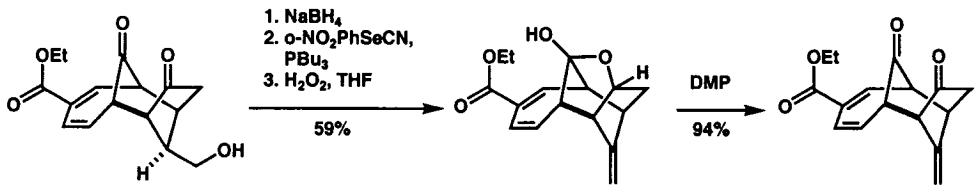
Interestingly, the major product of the elimination reaction was found to be cyanohydrin **134**, in which the HCN generated by the Grieco reaction added to diketone **120**. Minor amounts (5-10%) of the corresponding diketone were also present. The bridging ketone appears to be unusually susceptible to nucleophilic attack. Indeed, the formation of the cyanohydrin was fortunate in that it protected the diketone during the subsequent oxidation step. It was found, for example, that oxidation of diketone selenide **135** led to significant amounts of the Baeyer-Villiger product **136** (Scheme **3-9**). After considerable experimentation, it was found that the cyanohydrin could be cleaved by washing with a cold, dilute solution of NaOH. Yields for this process were modest, however, as the resulting diketone quickly decomposed in the presence of strong base.



135 136

Scheme 3-9. Selenoxide elimination / Baeyer-Villiger reaction of diketone selenide **135**.

An alternative, higher-yielding four-step protocol for the synthesis of **120** was developed that avoided this final, low-yielding step (Scheme **3-10**). Reduction of **119** with $NaBH_4$ followed by the Grieco dehydration gave hemiketal **137**, which could be oxidized to **120** with DMP in 55% overall yield.



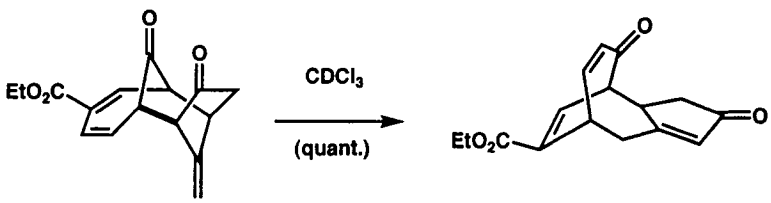
119 137 120

Scheme 3-10. Improved synthesis of diketone **120**.

3.3 Cope rearrangement of diketone 120

As predicted by our theoretical studies, diketone **120** slowly transformed to a new product **138** when left in $CDCl_3$ at room temperature (Scheme **3-11**). This product was a tricyclic bis-enone, the product of the expected Cope rearrangement. The half-life of this process was measured to be ~63 h at 23 °C. Among the several molecules studied, this rearrangement appears to be particular to diketone **120**. No Cope rearrangement was observed for cyanohydrin **134**, ester

136, or hemiketal **137**, even when each were heated at 60 °C for 12 h. The reaction would seem to be driven by relief of ring strain and possibly generation of conjugation in the cyclopentenone. Though not amenable to prolonged storage, the diketone possessed enough thermal stability at room temperature for us to investigate the anticipated hydroboration.



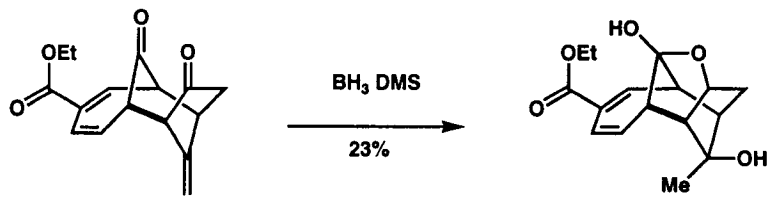
120 **138**

Scheme 3-11. Cope rearrangement of diketone **120**.

3.4 Hydroboration Studies

With diketone **120** in hand, our initial plan was to perform a hydroboration with 9-BBN, followed by the well-precedented Pd-catalyzed cross coupling with an alkyl iodide to install the sidechain.[13] However, we found that 9-BBN did not perform the hydroboration and instead it merely reduced the ketone on the two-carbon bridge to give **137**. The resulting alcohol failed to undergo hydroboration with 9-BBN. A similar result was obtained when hydroboration was attempted with catecholborane and Wilkinson's catalyst.[14] However, when diketone **120** was treated with BH_3·DMS, the starting material was observed to disappear over 2 h. Oxidation with H_2O_2 and mild basic workup gave a new product in 23% yield, which was the major product in the ^1H NMR of the crude reaction mixture. The

remainder of the mass balance was composed of a complex mixture of polar byproducts that frustrated our attempts at purification and characterization. To our great surprise, the structure of this major product was determined to be **139**, the Markovnikoff product of hydroboration-oxidation (Scheme **3-12**). As anticipated, hydroboration proceeded from the convex face of the diketone, as shown by the NOE between the methyl group and the protons of the diene. Of further interest in this reaction is the reduction of the carbonyl to give the hemiacetal. Further experiments are required to establish the order in which the hydroboration and ketone reduction events occur. Among the hydroboration reagents attempted, only BH_3·DMS was observed to give a relatively clean reaction. Hydroboration using BH_2Br and BH_2Cl gave complex mixtures.



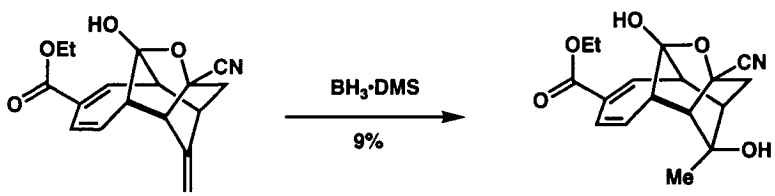
120 139

Scheme 3-12. Hydroboration of **120** giving unanticipated Markovnikoff product **139**

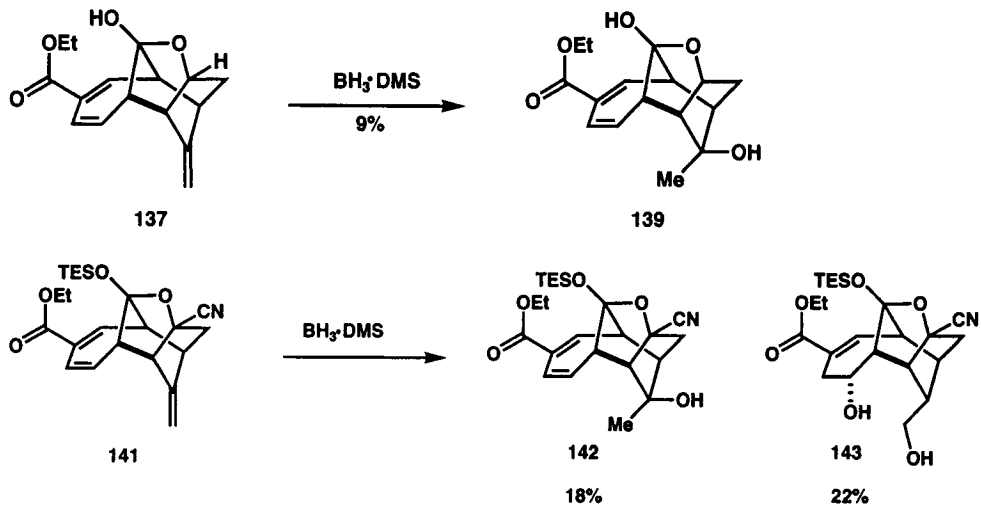
Surprisingly, Markovnikoff products were observed in the hydroboration of other alkenes in our series (Scheme **3-13**). Hydroboration of cyanohydrin **134** with BH_3·DMS provided Markovnikoff product **140** in 9% yield. To address the possibility that the nitrile in **134** may be directing the hydroboration towards the Markovnikoff product, we also investigated the hydroboration of alcohol **137**.

The isolation of Markovikoff product **139** in identical 9% yield suggests that the influence of a heteroatom is not a requirement for the formation of this product. Despite the low yields, the Markovnikoff products were prominent in the ^{1}H NMR of the crude reaction mixtures. Our attempts at isolation and characterization of the products in this reaction were hampered by the instability of the Markovnikoff adducts towards silica gel and the presence of a number of other polar byproducts that could not be separated.

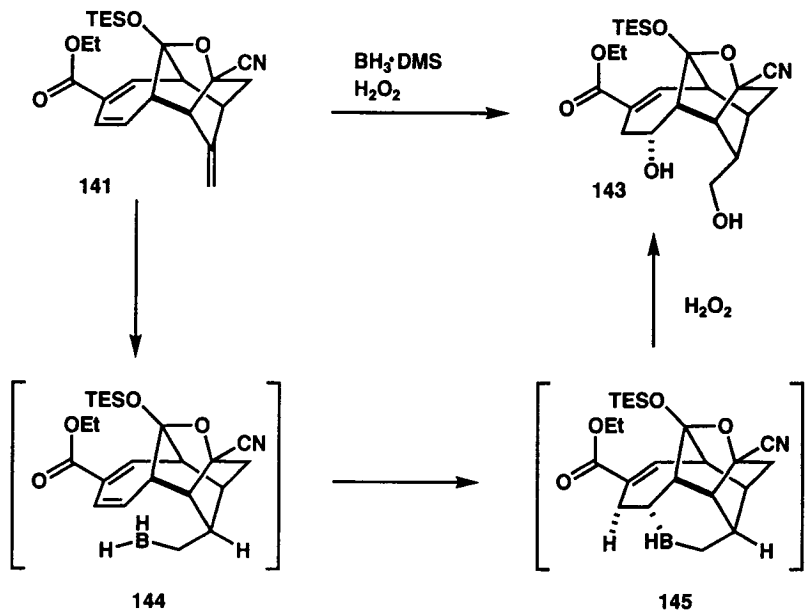
We surmised that the complex mixtures observed with **134** and **137** may have been a result of hydroxyl-directed hydroboration upon the top face of the diene. To prevent this possibility, the cyanohydrin was protected with a TES group to give **141**. Hydroboration of **141** with BH_3·DMS was found to be considerably cleaner, leading to Markovnikoff product **142** and anti-Markovnikoff product **143** in 18% and 22% yields, respectively. Interestingly, the initial anti-Markovnikoff hydroboration product delivered BH on the underside of the molecule to the more electron-rich double bond, resulting in a diol after oxidative workup (Scheme **3-14**).



134 **140**



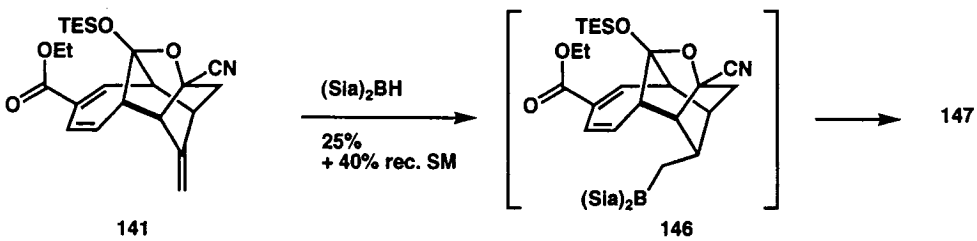
Scheme 3-13. Hydroborations giving Markovnikoff products.



Scheme 3-14. Rationale for formation of diol **143**.

Finally, we investigated the use of a sterically hindered hydroborating reagent on this system. Disiamylborane was prepared according to the procedure

of Brown.[15] Hydroboration of cyanohydrin **141** with Sia_2BH led to the isolation of a product **147** in which two of the starting alkenes had disappeared (Scheme **3-15**). The Markovnikoff hydroboration product **142** was not observed. Despite our best efforts, we have been unable to conclusively determine the structure of **147**. Based on COSY and HMBC correlations, we believe it to be an anti-Markovnikoff hydroboration product that has undergone a subsequent, as yet unidentified transformation. These results tentatively indicate that anti-Markovnikoff selectivity can be restored on **141** by employing a sufficiently bulky hydroborating reagent.



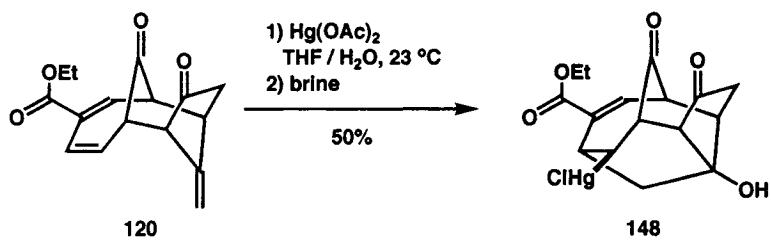
Scheme 3-15. Hydroboration of cyanohydrin **141** with diisoamylborane.

3.5 Other Studies

Noting the anomalous reactivity of **120**, we wondered if it would show abnormal reactivity under other conditions known to be selective for Markovnikoff reactivity. The hydration of alkenes in the presence of mercury salts (oxymercuration) is known to be selective for Markovnikoff addition.[16] Stirring **120** in 1:1 THF/H_2O in the presence of $Hg(OAc)_2$ led to the formation of a new product in 50% yield. ^1H NMR showed that two of the alkenes had disappeared.

Extensive 1-D and 2-D spectroscopy revealed the presence of a new tertiary alcohol, and HMBC correlations showed that a new C-C bond had formed on the underside of the molecule. The structure was shown to be **148**, the result of an apparent cationic cyclization followed by trapping by solvent (Scheme **3-16**). We know of no precedent for this beautiful ring system, somewhat reminiscent of adamantane. The mechanism for formation of **148** is not known with certainty. Mechanistic proposals accounting for cationic cyclization / solvent trapping must account for the intermediacy of a highly unstable bridgehead cation. Further studies are warranted on this fascinating transformation.

The chloride salt **148** crystallized as colourless prisms. We were gratified to find that X-ray crystal diffraction confirmed our NMR structure assignment (Figure **3-1**).



120 148

Scheme 3-16. Oxymercuration of diketone **120**.

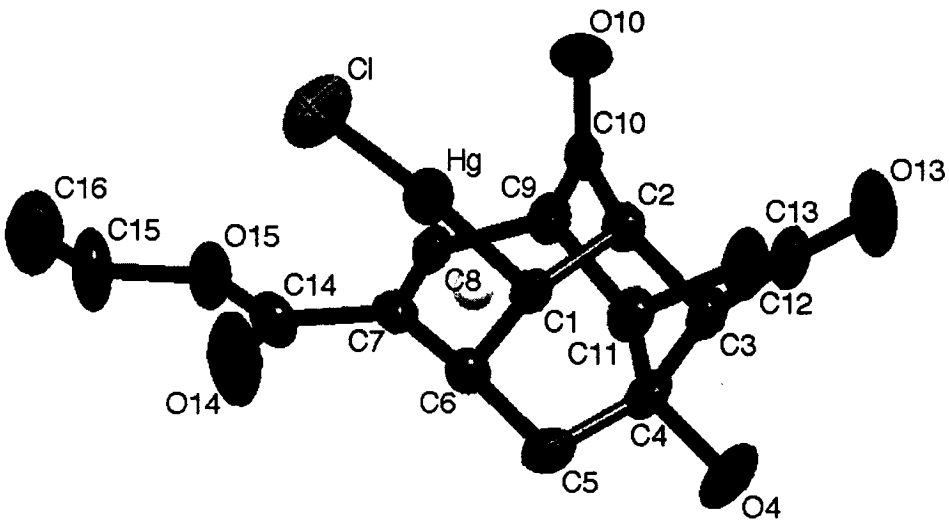


Figure 3-1. ORTEP diagram of oyxmercuration product **148**.

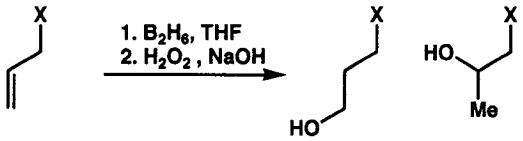
3.6 Regioselectivity in Hydroboration Reactions

The predictable regioselectivity of the hydroboration reaction has made it one of the most useful reactions in organic chemistry.[17] The mechanism of this reaction has been the subject of numerous experimental[18,19,20] and theoretical studies.[21,22,23] Much of the theoretical work suggests the existence of a weakly bound olefin-borane π complex along the reaction pathway. The rate determining step of the reaction is the progression of this π complex to an early, 4-membered hydroboration transition state (TS). Fehlner has measured the rate of reaction of BH_3 with ethylene in the gas phase and estimated the barrier of the reaction to be 2-3 (+/-2) kcal/mol. In substituted systems, the regioselectivity is determined by

the relative energies of the Markovnikoff and anti-Markovnikoff transition states, with formation of the B-C bond at the more nucleophilic carbon. Good correlation has been found between the regioselectivity of the reaction and the relative sizes of the HOMO coefficients of the olefin.[24] In the simplest substituted case, the hydroboration of 1-propene with BH_3, there is 94:6 selectivity for the primary alcohol. Houk calculated transition states leading to both products in this reaction (RHF/3-21G), finding the anti-Markovnikoff TS to be 3.6 kcal/mol lower in energy than the Markovnikoff TS, consistent with experiment. The tendency of the new B-C bond to be formed on the less substituted carbon can be further augmented by the use of sterically hindered boranes.[25]

Markovnikoff hydroboration is known to occur when electron withdrawing or partially positive substitutents are present on the olefin. For example, the hydroboration of 3,3,3-trifluoropropene proceeds with 74% selectivity for the Markovnikoff product, [26] Brown and Knights studied the effects of allylic substituents on regioselectivity and found a strong correlation between electron-withdrawing character and Markovnikoff selectivity (Scheme **3-17**).[27] Brown found, however, that these electronic preferences could be overcome by the use of thexylborane. Predominant Markovnikoff hydroboration is also observed in vinyl halides (60-95%) and in styrenes with electron-withdrawing substitutents.[28] [29] Silyl substituents have a similar effect on regioselectivity. The Markovnikoff product is observed almost exclusively (87-92%) in the

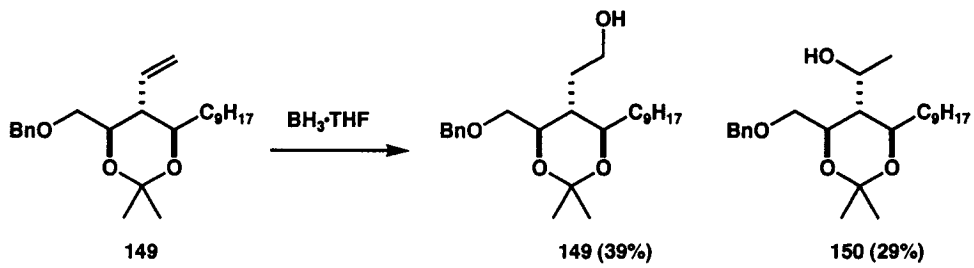
hydroboration of 1-(trimethylsilyl)cyclopentene and 1-(trimethylsilyl)cyclohexene.[30]



X	1° : 2°
H	94: 6
OEt	81: 19
Cl	60: 40
OTs	55: 45
CF_3	30: 70

Scheme 3-17. Hydroboration study of Brown and Knights.

In addition, deviations from anti-Markovnikoff selectivity are occasionally found in the presence of Lewis basic functionality.[31] For example, Suzuki ascribed origin of the poor regioselectivity observed in the hydroboration of alkene **149** with BH_3·THF to complexation of BH_3 with the pendant benzyloxy moiety, which then directed the hydroboration via a chairlike transition state to give secondary alcohol **150** as a mixture of stereoisomers (Scheme **3-18**).[32] The poor regioselectivity in this case could be overcome by use of the bulky hydroborating reagent dicyclohexylborane.



149 149 (39%) 150 (29%)

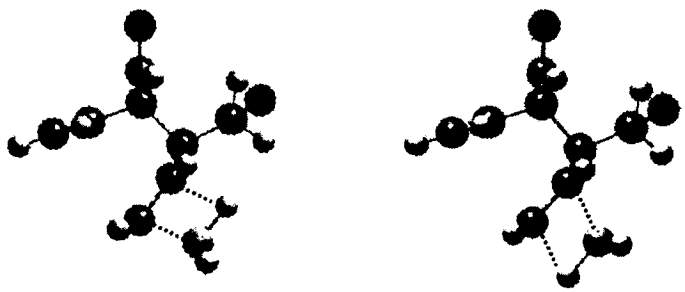
Scheme 3-18. Suzuki's benzyloxy-directed hydroboration.

3.7 Theoretical studies

The isolation of significant amounts of Markovnikoff hydroboration products **139**, **140**, and **142** is highly unusual. We wanted to understand the reasons for this seemingly aberrant reactivity, as hydroborations of 1,1 disubstituted alkenes generally give primary alcohols at the 98-99% selectivity level.[33]

To further understand our anomalous hydroboration reaction, calculations were performed by Prof. James L. Gleason at the B3LYP/6-31G* level. Using 1-propene as a model, the study found the π complex of BH_3 with 1-propene and found that the anti-Markovnikoff TS was lower in energy than the Markovnikoff by 2.8 kcal/mol. For 2-methyl-1-propene, the anti-Markovnikoff TS was lower in energy by 4.8 kcal/mol. These values are in accord with those calculated in previous theoretical studies.

With these results in hand, the transition state energies for the Markovnikoff and anti-Markovnikoff hydroboration of diketone **127** were calculated (B3LYP/6-31G*), (Figure **3-2**). Remarkably, these calculations found that the Markovnikoff hydroboration TS was lower in energy by 0.32 kcal/mol! Interestingly, the Markovnikoff TS is slightly later than the anti-Markovnikoff TS, an observation also made by Houk and Lipscomb.[34] This is presumably due to steric factors. [20, 21]



Anti-Markovnikoff

C_{18}-B 1.695 Å

C_{17}-H_B 1.675 Å

Markovnikoff

C_{17}-B 1.76 Å

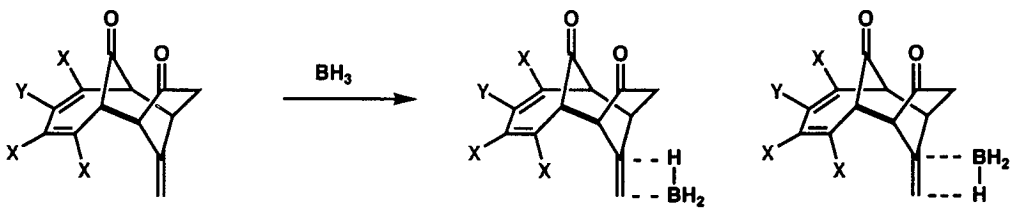
C_{18}-H_B 1.72 Å

Figure 3-2 Calculated Markovnikoff and anti-Markovnikoff transition states for **127.**

The TS for the hydroboration of the unsubstituted diene analogues of cyanohydrin **137** and alcohol **140** were then calculated, and also found to favor Markovnikoff addition.

We were especially curious about which structural or electronic features in these molecules were responsible for the reversal of selectivity. Essentially, we were trying to find the source of the 4.8 kcal/mol difference between isobutylene and our alkenes. The effect of substitution on the diene was investigated first (Scheme **3-19**). Comparing the data for **150, 151** and **152** shows that the preference for Markovnikoff hydroboration is predicted to increase with the number of electron withdrawing groups on the diene. Strongly π donating substituents, such as in **153**, do not seem to exert any undue influence. Using DFT it was possible to systematically examine the effect of removing various

substituents on the selectivity of the reaction. The results of these calculations are shown in Figure **3-3**. Parent alkene **127** showed a slight preference for Markovnikoff hydroboration. Removing the diene to give **154** led to a sharp restoration of anti- Markovnikoff selectivity, a net change of 1.72 kcal/mol. Removing the bridging ketones, as in **155**, had an almost identical effect on the predicted selectivity. Finally, these effects were found to be cumulative: removing both the diene and the ketones, in **156**, led to an anti-Markovnikoff transition state that was more stable than the Markovnikoff TS by 3.0 kcal/mol. We conclude that the presence of both the bridging ketones and the remote diene are the main factors for the erosion of anti-Markovnikoff selectivity found in the hydroboration of these compounds.



#	X	Y	Prediction	Energy Difference
127	H	H	Markovnikoff	0.32 kcal/mol
151	H	CO_2H	Markovnikoff	0.59 kcal/mol
152	CN	CN	Markovnikoff	1.75 kcal/mol
153	OR	OR	Markovnikoff	0.74 kcal/mol

Scheme 3-19. Effect of electronegative alkene substituents on calculated hydroboration transition states.

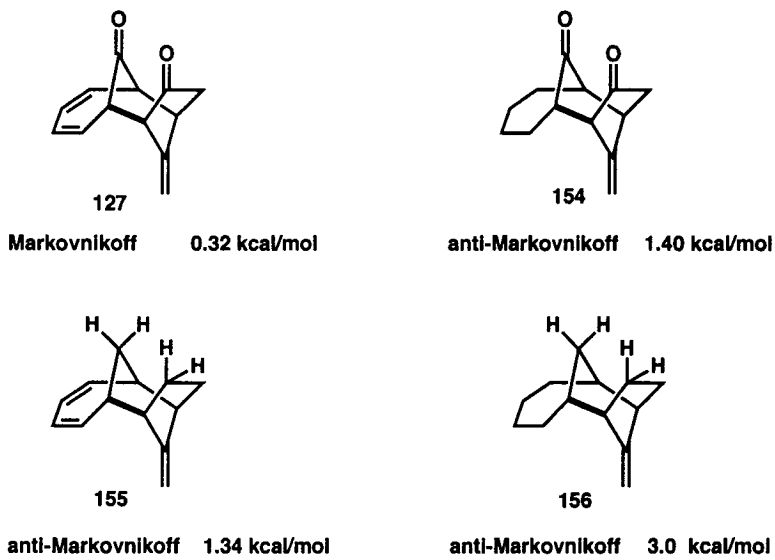


Figure 3-3. Effect of diene and diketone substituents on calculated hydroboration transition states.

It is likely that the cage-like structure of the alkene also plays a role in the reversal of regioselectivity. As discussed above, hydroboration results in a new C-H bond that is typically formed on the carbon best able to stabilize positive charge. Anti-Markovnikoff selectivity is generally observed in hydroborations because hyperconjugative stabilization of positive charge increases with the degree of substitution on carbon. However, the developing positive charge in the anti-Markovnikoff TS of diketone **127** is poorly stabilized by the bridgehead C-H bonds, as they lie in the plane of the olefin. Furthermore, the proximal C-C bonds attached to the diene and ketone possess the proper orientation for

hyperconjugation, but the presence of the electron-withdrawing substituents (e.g. ketone, diene) greatly reduces their stabilizing influence.

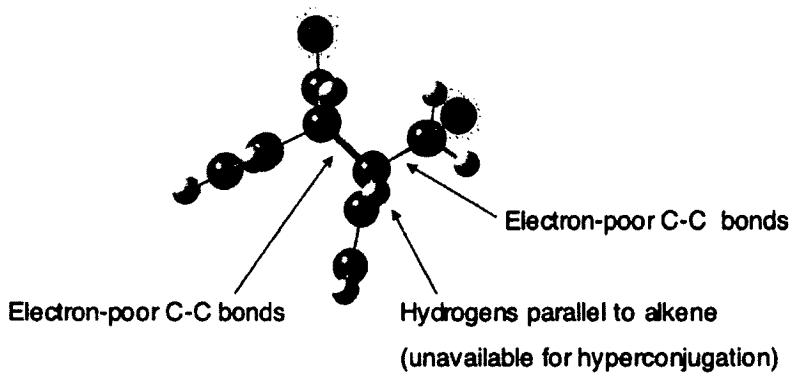


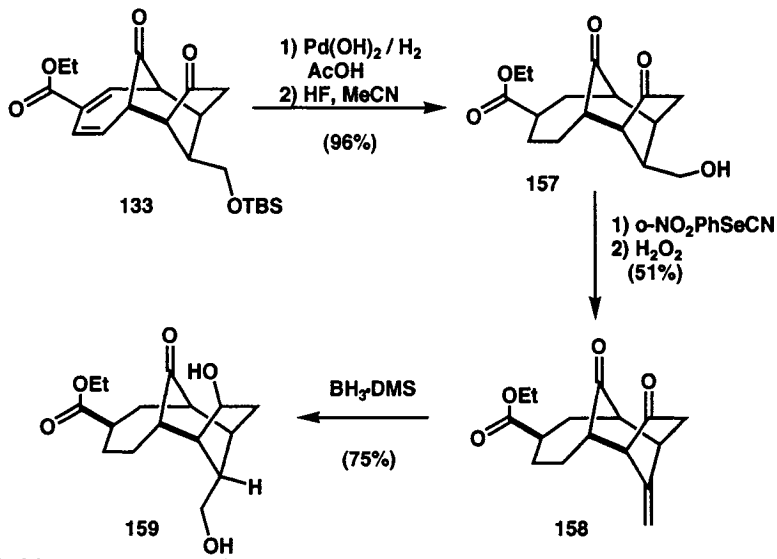
Figure 3-4. Rationalization for eroded hydroboration anti-Markovnikoff selectivities.

To summarize, we believe that the unusual erosion of anti-Markovnikoff selectivity in the hydroboration of olefins in this series is due to the presence of electron withdrawing substituents and their placement relative to the reacting center due to the cage-like structure of the molecule (Figure **3-4**). Partial positive charge is not stabilized to the same extent on the interior olefinic carbon as it is on a "normal" trisubstituted olefinic carbon, resulting in complete loss of anti-Markovnikoff selectivity.

3.8 Successful Installation of the C-17 Stereocenter

With these results in mind, we turned our efforts toward the installation of the proper stereochemistry of the C-17 sidechain. According to our theoretical

studies, removal of the diene should restore strong anti-Markovnikoff selectivity. Alkene **158** was therefore synthesized in 4 steps from [6+4] cycloadduct **133** (Scheme **3-20**). Treatment of **133** with $Pd(OH)_2$ under a balloon of H_2 in AcOH resulted in a 2:1 mixture of epimers favoring the ester in the β configuration. Hydrogenation in either EtOAc or EtOH was considerably slower at atmospheric pressure. The resulting mixture was directly submitted to deprotection conditions using HF in MeCN, leading to a 96% yield of **157** over two steps. The mixture of epimers was then submitted to Grieco conditions as before (PBu_3 / *o*-$NO_2PhSeCN$) to yield the primary selenides as mixtures of cyanohydrins and diketones. The cyanohydrins from this reaction were considerably more labile than that in the unsaturated system; they could be removed simply by stirring with NEt_3 for 30 min. The resulting mixture of diketones was then oxidized with H_2O_2 and heated to reflux in THF for 24 h. After treatment of the crude reaction mixture with zinc dust in AcOH to remove residual arylselenide impurities and subsequent column chromatography, the alkenes **158** were obtained in 51% yield for the selenation/oxidation sequence. The epimeric alkenes could be separated at this stage. As the slower-eluting β-epimer was the major product of this reaction, we chose to carry this compound forward to the hydroboration step.



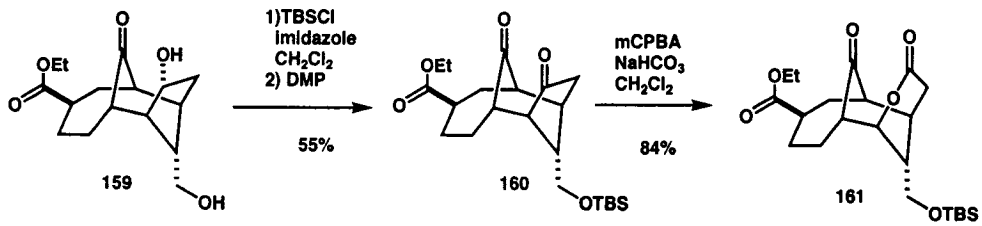
Scheme 3-20. Installation of C-17 stereocenter via hydroboration with BH_3·DMS.

To our great satisfaction, hydroboration of alkene **158** with BH_3·DMS resulted in a 75% yield of primary alcohol **159**. Remarkably, we had completely changed the product distribution of the hydroboration reaction and significantly increased the yield simply by removing the remote diene.

3.9 Baeyer-Villiger Reaction

With the hydroboration product **159** in hand, and the C-17 stereocenter established, we then set out to re-investigate the Baeyer-Villiger reaction. The primary alcohol of diol **159** was protected with TBSCl, and the secondary alcohol then oxidized to give diketone **160** in 55% yield over two steps (Scheme **3-21**). [35] To our delight, treatment of **160** with mCPBA in CH_2Cl_2 for 24 h gave lactone

161 in 84% yield. With the sidechain stereochemistry adjusted, the Baeyer-Villiger reaction was now successful.



Scheme 3-21. Baeyer-Villiger sequence to produce lactone **161**.

3.10 Summary

Revising our synthetic plan to accommodate 5-hydroxymethyl-substituted diene **118** provided access to key diketone alkene **120**. Attempts to hydroborate **120** and a series of related olefins led to the highly unusual observation of products resulting from Markovnikoff hydroboration. In order to understand this anomalous reactivity in more detail, a series of DFT studies were performed that suggested that anti-Markovnikoff selectivity was eroded by the presence of the bridging ketones and the remote diene. The studies predicted that removal of the diene would restore anti-Markovnikoff selectivity. Confirming these predictions, saturated diketone **158** was synthesized and found to undergo anti-Markovnikoff hydroboration in 75% yield. This adjustment of sidechain stereochemistry allowed for fruitful Baeyer-Villiger oxidation of the bridging ketone to give lactone **161**. In short, our revised strategy had allowed for the successful installation of the C-9 and C-17 stereocenters with proper stereochemistry. Our

application of this strategy towards the synthesis of the right-hand half of the phomoidrides is detailed in Chapter 4.

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[7] Houk monitored the [6+4] cycloaddition of tropone and 6,6-dimethylfulvene in THF at 50 °C over 48 h and did not observe the formation of an intermediate such as **123** when the reaction was followed by NMR. However, our calculations indicate the lifetime of this species would be extremely short at this temperature.

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[33] We subsequently found that Bobbitt's reagent was effective in selectively oxidizing the secondary alcohol of this substrate.

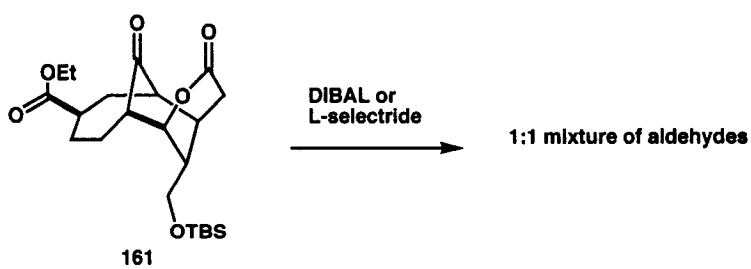
CHAPTER FOUR

4.1 Introduction

With the proper stereochemistry of the C-9 and C-17 sidechains established, we turned our thoughts toward completion of the right-hand half of the phomoidrides. The challenge before us was to devise a route to extend both sidechains, as well as introduce the bridgehead olefin. Our progress toward this goal is described below.

4.2 Reduction of the C-12 Ester

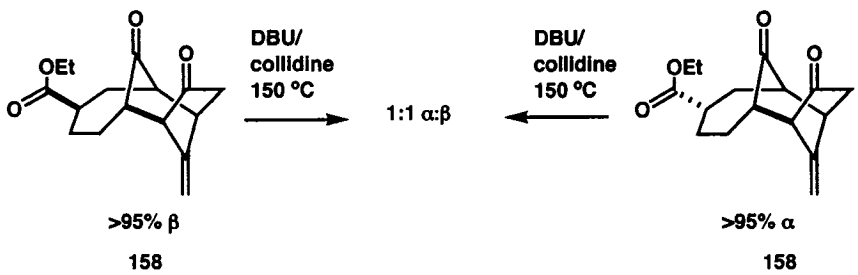
Planning the route ahead from lactone **161** immediately presented us with a difficult obstacle. Owing to the precedents of Nicolaou,[1] Danishefsky,[2] and Leighton,[3] we were confident that the C-9 sidechain could be extended through reduction of lactone **161** to an aldehyde and subsequent addition of a lithiated dithiane. In order to bring this strategy to practice, we first needed to investigate whether the lactone moiety of **161** could be reduced selectively in the presence of the C-12 ester. Despite ample precedent for this transformation,[4] several attempts to reduce the lactone selectively with DIBAL and L-Selectride resulted in competitive C-12 ester reduction (Scheme **4-1**). An approximate 1:1 mixture of aldehydes was obtained.



161

Scheme 4-1 Unselective reduction of lactone **161**.

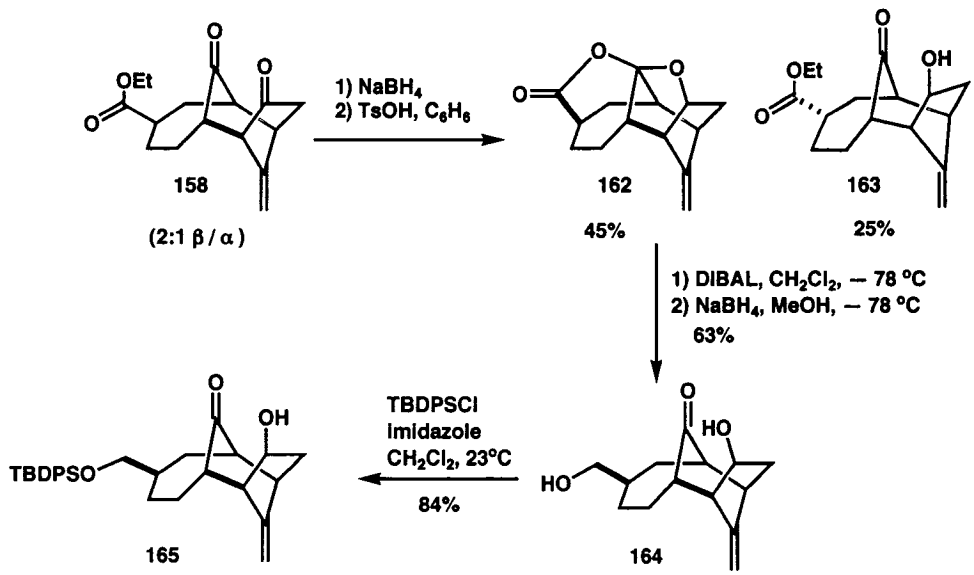
The ester on C-12 presented two additional difficulties that eventually led us to decide upon its removal. The first problem was that the 2:1 mixture of isomers **158** could only be separated after extensive (and tedious) column chromatography. Even then, minor amounts of the undesired α-ester epimer were inevitably present, complicating spectral analysis. A second concern was our finding that the 2:1 mixture of isomers could not be enriched by epimerization (Scheme **4-2**). In fact, the 2:1 mixture of epimers must represent a kinetic preference exhibited by the hydrogenation catalyst, as treatment of either epimer with base under forcing conditions led to a 1:1 mixture. With these results in mind, it was of obvious concern to us that addition of a strong base – a lithiated dithiane, for example – might cause partial epimerization of the ester. We concluded that reduction of the ester down to the alcohol oxidation state was necessary.



Scheme 4-2 Epimerization either C-12 ester of **158** gives a 1:1 mixture.

We then devised a route by which the C-12 epimers of **158** could be easily separated (Scheme **4-3**). Diketone **158** was reduced with $NaBH_4$ and then treated with TsOH in boiling benzene to afford lactone **162** and alcohol **163**. The lactone and alcohol were easily separated by silica gel chromatography. DIBAL reduction

of lactone **162** led to the formation of a stable hemiacetal, which was further reduced to the alcohol **164** with $NaBH_4$.The alcohol was then protected as the TBDPS ether **165** in 84% yield. The spectra of **164** and **165** were complicated by ring-chain tautomerism. In $CDCl_3$ at 23°C, the tautomers of **165** existed as a 60:40 mixture favoring the open form.



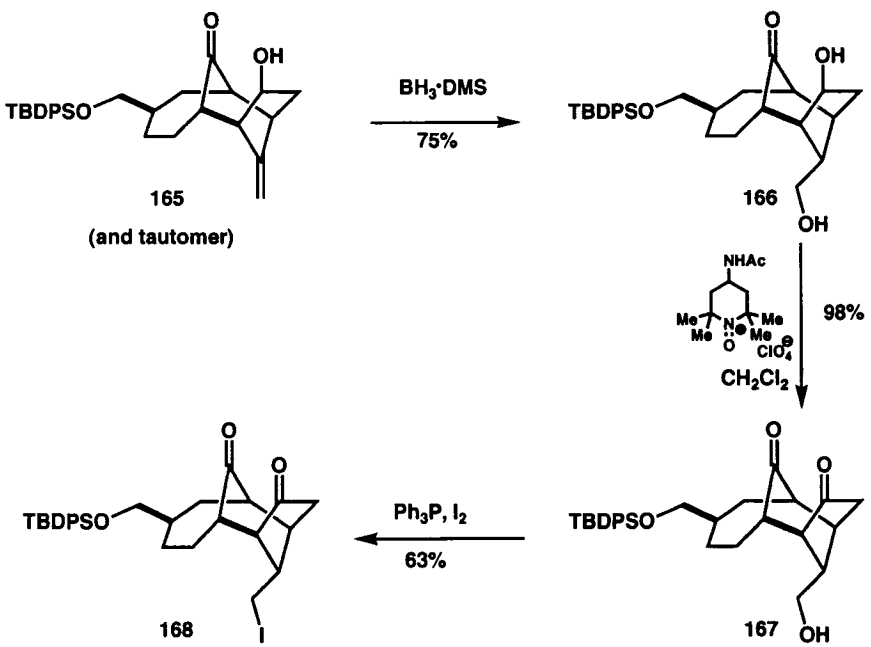
Scheme 4-3 Separation of C-12 epimers and subsequent TBDPS protection

4.3 Attempts to Elongate the C-17 Sidechain

With protected alcohol **165** in hand, we considered our options toward completing the right-hand half. The plan that seemed most direct was to hydroborate the alkene of **165** and use the resulting functionality to elongate the C-17 sidechain. This would be followed by Baeyer-Villiger oxidation, extension

of the C-9 sidechain, and installation of the bridgehead olefin. We describe our attempts to elongate the C-17 sidechain below.

Alkene **165** underwent smooth hydroboration with BH_3·DMS to give alcohol **166** in 75% yield (Scheme **4-4**). Remarkably, the secondary alcohol of the diol could be oxidized preferentially to the ketone (**167**) by the usage of Bobbitt's reagent in near-quantitative yield. The resulting alcohol was successfully transformed into the alkyl iodide **168** by treatment with PPh_3 / I_2 in 63% yield. The corresponding alkyl bromide could also be formed, in 40% yield using PPh_3 / NBS.



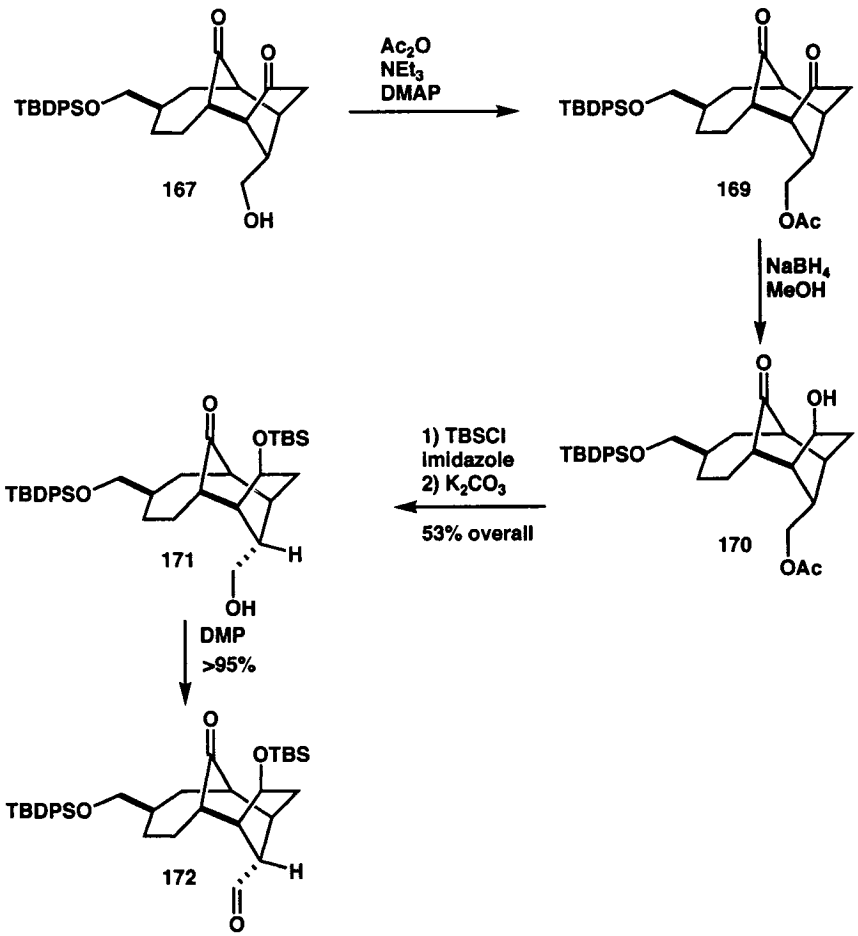
Scheme 4-4 Synthesis of alkyl iodide **168**.

With iodide **168** in hand, we attempted to extend the C-17 sidechain through the application of organotransition metal chemistry. We were particularly hopeful that Fu's $Ni(COD)_2$-catalyzed cross-coupling of organozinc reagents with hindered alkyl iodides would succeed in our case.[5] In our hands, however, these conditions resulted in reduction of the iodide rather than formation of the desired C—C bond. Similarly, attempts at using "higher-order" cuprates to forge this bond,[6] as well as attempted displacement with cyanide also failed. The primary halide appears to be too hindered for nucleophilic displacement to be fruitful. Extension of the C-17 sidechain from the iodide could not be achieved.

Having failed to extend the chain through the scission of an appropriate σ bond, we considered the options available for C—C bond formation if the C—17 carbon was at a higher oxidation state. As a second attempt at C—C bond formation, we speculated that we might be able to extend the chain via addition of a carbon-based nucleophile to an aldehyde. We envisioned a number of sequences involving Wittig-type reagents or Grignard reagents that would be suitable for installing the C—17 sidechain. In the case of Grignard addition, we felt that the convergency afforded by direct addition would outweigh the inconvenience of having to include an additional deoxygenation step.

Since harder nucleophiles were to be employed using this plan, we prepared the alcohol **171** as a precursor where the bridging ketone had been protected in its reduced form. Alcohol **171** was prepared in four steps from ketone **167** in 53% overall yield (Scheme **4-5**). The alcohol was then oxidized to the

aldehyde **172** using Dess-Martin periodinane. We quickly found that **172** was extremely sensitive to base, which precluded usage of the normal workup procedure (aqueous $NaHCO_3$ / $Na_2S_2O_3$) for this reaction. Fortunately, we discovered that the aldehyde could be obtained cleanly by simple concentration of the reaction mixture and trituration with hexanes. As silica gel chromatography also destroyed the aldehyde, this extract was used directly in subsequent reactions without further purification. Yields obtained in this manner exceeded 95%.



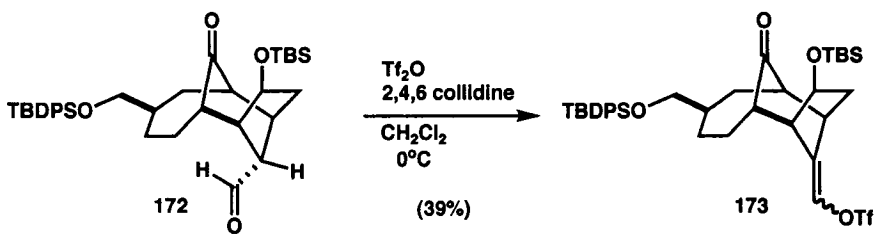
Scheme 4-5 Synthesis of aldehyde **172**.

The instability of aldehyde **172** towards base and acids was due to its extreme tendency to enolize. We observed that solutions of **172** in were stable in $CDCl_3$ for at least 24h, but addition of excess NEt_3 immediately resulted in the disappearance of the aldehyde peak to give two new peaks at 6.22 and 6.44 ppm, which are presumably the E and Z aldehyde enolates (1:1 ratio, stereochemistry not determined). The unusual ability of the mild base NEt_3 to effect enolization of an aldehyde is clearly facilitated by the relief of transannular strain in this case. [7]

The facile enolization of **172** frustrated all of our attempts to extend the bottom sidechain. To our dismay, aldehyde **172** did not undergo clean reaction with a host of conditions surveyed (MeMgBr, vinylMgBr, MeLi, $Ph_3P{=}CH_2$, MeLi $CeCl_3$, Petasis olefination). After workup, the original aldehyde was not recovered.[8] Especially discouraging was the failure of the organocerium reagents, which are well-known to effect addition to enolization-prone ketones and aldehydes.[9] A final testament to the capricious nature of aldehyde **172** was our observation of enolization products while attempting to form a hydrazone with 2,4,6-trimethylbenzenesulfonylhydrazide. [10] The desired hydrazone did not form.

We eventually decided to attempt to use this facile enolization to our advantage. The formation of the enol triflates of **172** could be effected under remarkably mild conditions (Scheme **4-6**). Treatment of **172** with 2,4,6 collidine / Tf_2O resulted in a 39% yield of a 1:1 mixture of two new triflates (structure not assigned) believed to be **173**. The modest yield was a function of the extreme sensitivity of the enol triflate to silica gel. It should be further noted that

formation of triflates of this nature usually require strong amide base and either $PhNTf_2$ or Comins' reagent.[11] The cross coupling of this enol triflate using Fürstner's conditions ($Fe(acac)_3$, MeMgBr) was explored.[12] Conditions for the successful bond formation were not found, however.



Scheme 4-6 Facile enol triflate formation from aldehyde **172**

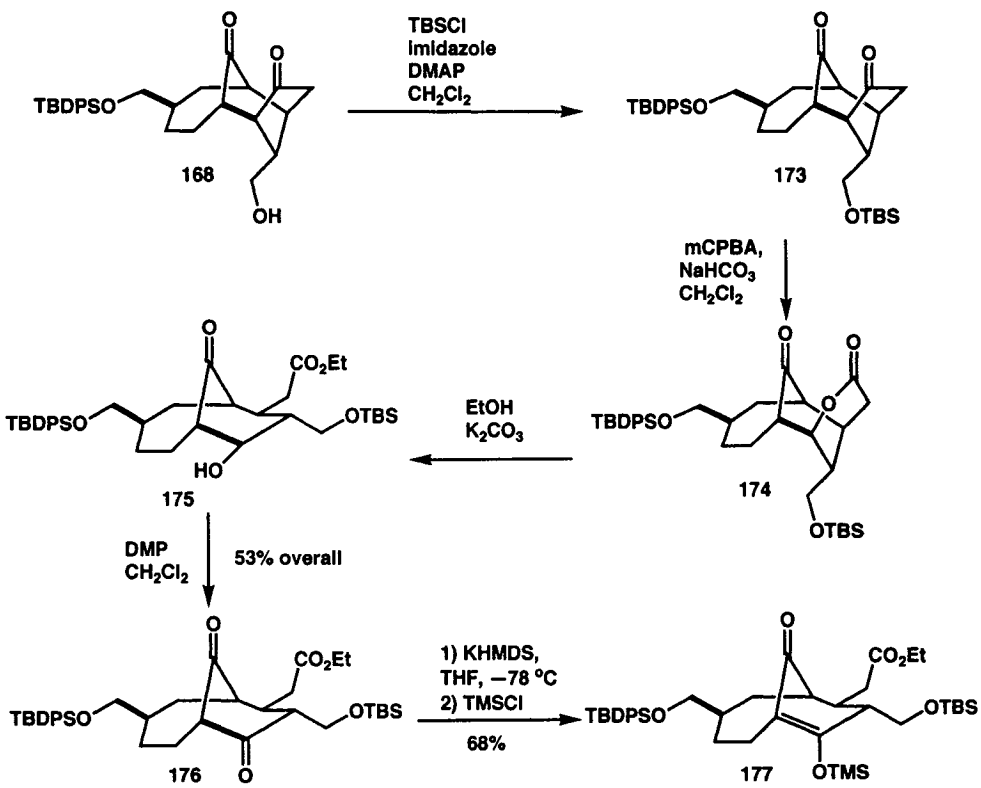
4.4 Attempted Bridgehead Olefin Formation

We pursued a second synthetic study concurrent with our efforts to extend the C-17 sidechain directly. Although, as in section **4.3**, it ultimately was not the method eventually used to extend the sidechain, key observations made during the course of this investigation paved the way for our eventual success in this endeavor.

Our strategy called for an early Baeyer-Villiger reaction to form the lactone. Opening of the lactone would then be followed by oxidation of the alcohol and installation of the bridgehead olefin via reduction of an enol triflate.[13] This plan thus obviated any need to protect the alcohol revealed after lactone

opening. Given our experience with bridgehead enolates described in Chapters 1 and 2, we were confident in our ability to trap the bridgehead enol triflate. We also anticipated that this plan would facilitate installation of the C—17 sidechain. Our difficulties in extending the C—17 with iodide **168** and aldehyde **172** stemmed from the hindered position of the C—18 carbon. After the lactone-opening step, the C—18 carbon would no longer be constrained on the crowded underside of the ring. Instead, models suggested that the sidechain would reside on the equatorial position of a boat cyclohexane. With the side-chain in a sterically less demanding position, we believed that we could then activate the alcohol and install the sidechain via the methods attempted previously after bridgehead olefin formation.

Alcohol **167** was protected as its TBS ether **173** and subjected to the Baeyer-Villiger oxidation and lactone opening to give alcohol **175** (Scheme **4-7**). Alcohol **175** was oxidized by DMP to give diketone **176** in 53% yield over the four steps. When treated with KHMDS and TMSCl, the silyl enol ether **177** formed in 68% yield. The selective, high-yielding formation of the bridgehead silyl enol ether led us to believe that installation of the corresponding triflate would be a facile process.



Scheme 4-7 Synthesis of diketone **176** and silyl enol ether **177**.

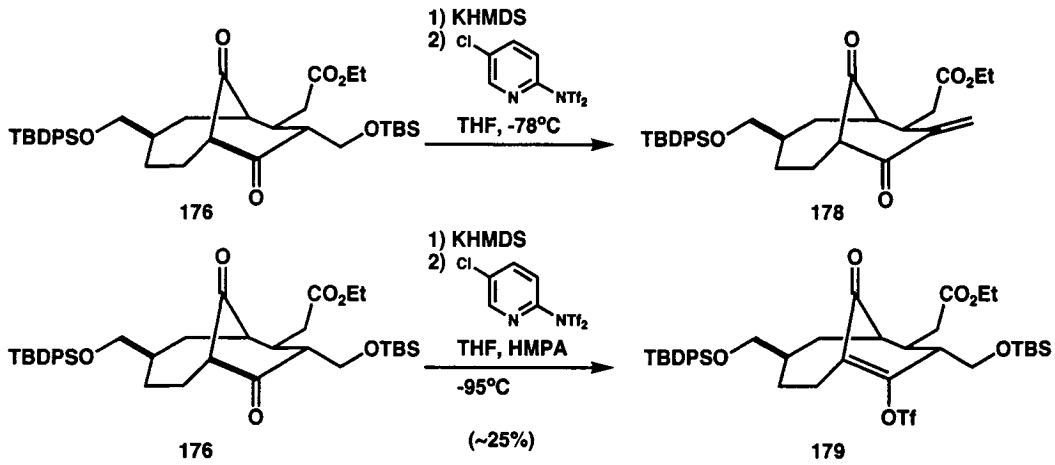
Unfortunately, formation of the corresponding triflate was beset by very low yields. Addition of excess KHMDS to diketone **176**, followed by trapping with Comins' reagent[14] did not lead to the isolation of any of the desired triflate. Instead, the resulting crude mixture showed several new peaks in the olefin region. Although none of these products could be isolated and purified, the majority of the mass balance of the reaction consisted of products lacking the characteristic TBS resonance at around 0.1 ppm.

The observation of products lacking the TBS resonance led us to investigate the possibility that the enolate was undergoing β-elimination of the

OTBS group to give an enone. Evidence for a destructive pathway was provided when solutions of diketone **176** stirring with a slight excess of KHMDS in THF were monitored over time at –78 °C by TLC. Under these conditions, the slow appearance of new, lower-R_f spots were observed. After workup, ^{1}H NMR spectroscopy of the crude reaction mixture showed the appearance of new resonances at 5.53 and 6.27 ppm, identical to those observed in the crude reaction mixture of the attempted triflations.[15] In addition, COSY of the mixture showed a weak correlation between these two peaks, consistent with an exocyclic alkene **178** (Scheme **4-9**). Unfortunately, the exocyclic alkene was unstable towards silica gel chromatography and could not be isolated to confirm this structure assignment.

We found that β elimination could be greatly retarded by forming the enolate at –95 °C in the presence of HMPA. Under these conditions, very little decomposition was observed by TLC. Unfortunately, the enolate did not possess sufficient reactivity at this temperature to make triflation a high-yielding process. The desired triflate **179** was obtained in only ~25% yield and was difficult to separate from several other unidentified reaction products.

Along similar lines, attempts to form the corresponding enol phosphate with $(PhO)_2P(O)Cl$ under identical conditions led to the undesired ß-elimination. Elimination was also observed during attempted Shapiro reaction of the tosylhydrazone of diketone **176**.

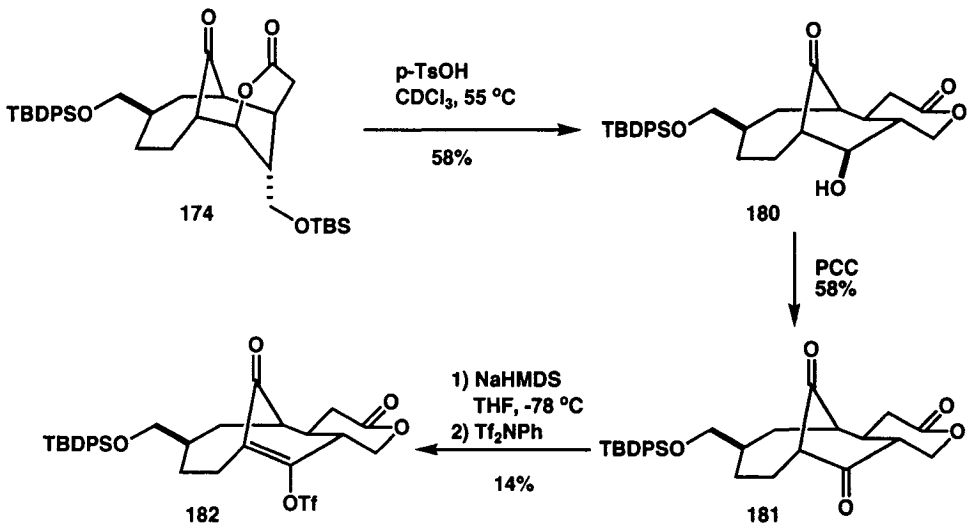


Scheme 4-9 Destructive β-elimination observed during attempted triflation of **176**, and successful formation of triflate **179**.

A concurrent route proceeded via conversion of **174** was to lactone **180** in 58% yield by heating with TsOH in $CDCl_3$ (Scheme **4-10**). Unfortunately, we found that this system was even more prone to β-elimination than the open-chain system. Oxidation of **180** proceeded well with PCC. Oxidation could also be achieved with Dess-Martin periodinane, but subjection of the resulting diketone to the basic workup conditions led to the isolation of polar, olefinic byproducts that were clearly carboxylic acids resulting from β-elimination. As with **176**, attempted formation of the bridgehead enol triflate from **181** with $PhNTf_2$ led to poor yields.

Unfortunately, the small quantities of triflates obtained from these two routes did not allow us to conclusively investigate the feasibility of their reduction

to bridgehead olefins. Clearly, a new route was required that avoided the problematic β-elimination.



Scheme 4-10. Triflate formation from lactone **174**.

4.5 Successful Elongation of the C-17 Sidechain

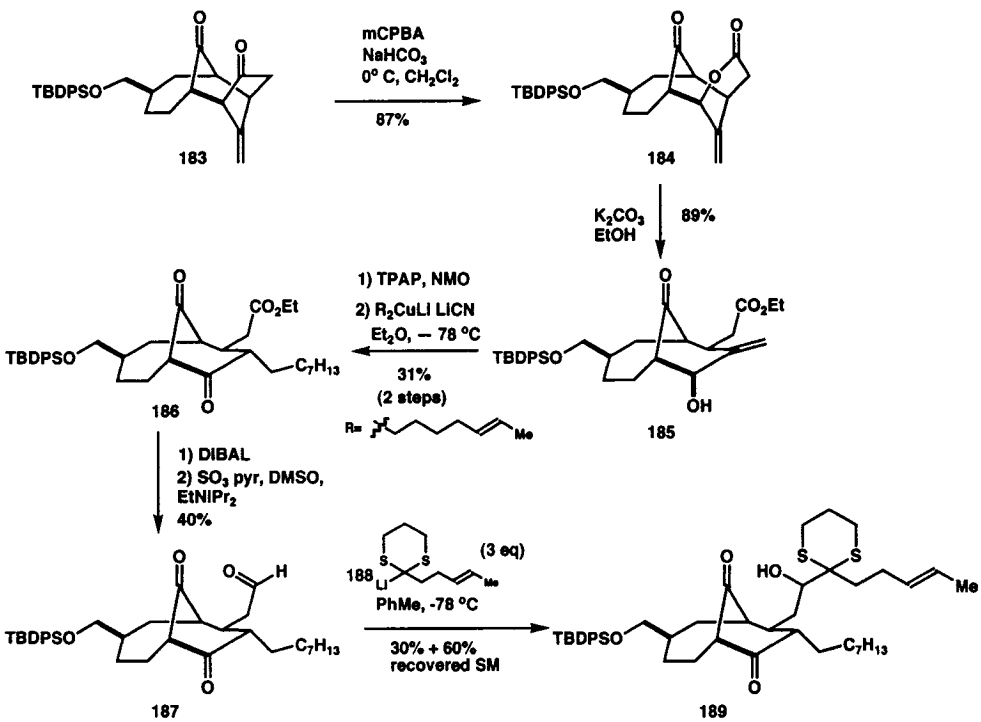
The problems encountered with β-elimination of diketone **176** and the difficulty of C—C bond formation with alkyl iodide **168** and aldehyde **172** eventually led us to re-evaluate our hydroboration strategy. Although the stereochemistry of C—17 could be reliably established via hydroboration, our experiences led us to conclude that installation of a heteroatom at C-18 could not be turned to our advantage. We therefore sought other options.

One simple solution to the sidechain problem presented itself. If Baeyer-Villiger oxidation of the TBDPS-protected analogue of alkene **158** could be

performed, then we could open the lactone and oxidize the resulting alcohol to give the previously encountered enone **178**. It was hoped that the enone would successfully undergo conjugate addition with a dialkylcuprate to extend the chain, followed by protonation of resulting enolate on the convex face to give the correct C—17 stereochemistry.

Alkene **183** was obtained directly through oxidation of **165** with Bobbitt's reagent. To our delight, treatment of **183** with 1 equivalent of mCPBA at 0 °C indeed gave lactone **184** in 87% yield (Scheme **4-11**). Maintenance of low temperature was key to the success of the Baeyer-Villiger reaction, as higher temperatures led to a major product lacking the exocyclic alkene believed to be an epoxide. Lactone **184** could be opened to alcohol **185** under conditions analogous to those developed previously in 89% yield. Lactone opening was attended by minor amounts (~20%) of the epimerized α-alcohol, which presumably arose through the previously described retro-aldol/ aldol process. Oxidation of the alcohol with DMP or Bobbitt's reagent was sluggish, but TPAP/NMO[16] led to clean formation of an enone **181** whose spectral characteristics agreed with those obtained through the β-elimination process described above. Owing to its sensitivity to silica gel chromatography the crude enone was not purified, but immediately subjected to conjugate addition with the dialkylcuprate derived from 1-iodo-*trans*-5-heptene and CuCN. Rewardingly, the reaction proceeded to generate diketone **186** in 31% yield over the two steps. The stereochemistry of the sidechain is assigned based on the strong coupling constant (11.5 Hz) observed

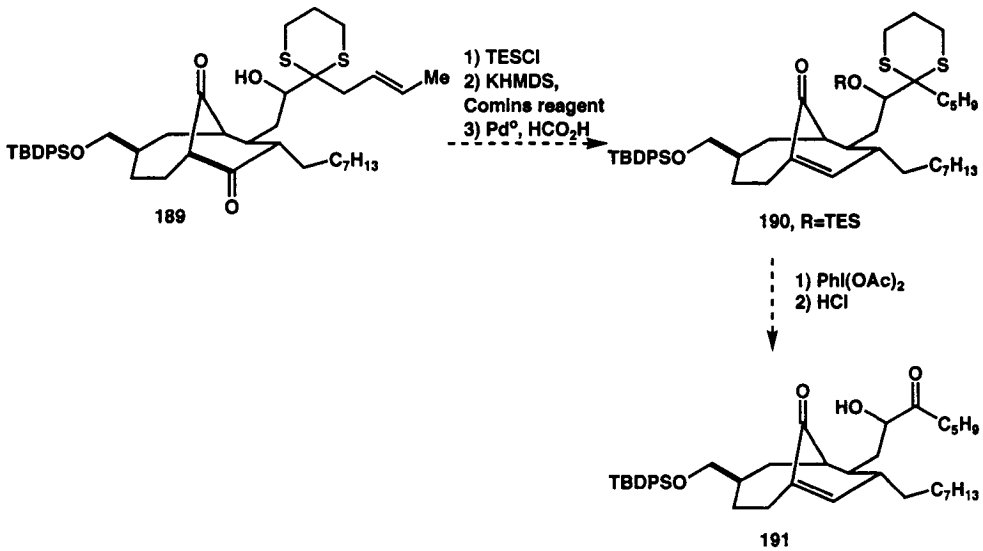
between C—17 and C—9. The conjugate addition product was then exhaustively reduced with DIBAL and then re-oxidized to diketoaldehyde **187** under Parikh-Doering conditions. Gratifyingly, it was found that **187** underwent selective addition of dithiane **188** at the aldehyde position to afford **189** as a mixture of alcohols.



Scheme 4-11 Synthesis of enone **181** and successful conjugate addition.

Structure **189** currently represents our point of furthest progress toward the phomoidride right-hand half. The remaining objectives are bridgehead olefin formation and deprotection of the dithiane protecting group. A plausible route toward the completion of the right-hand half from diketone **189** is presented in Scheme **4-12**. Protection of the alcohol of **189**, followed by reduction of the

bridgehead enol triflate would afford alkene **190**. Deprotection of the dithiane **190** using $PhI(OAc)_2$ and removal of the TES group would afford **191**, which contains the completed phomoidride right-hand half.



Scheme 4-12. Possible route for completion of the phomoidride right hand half.

4.6 Summary and Conclusion

Despite the tremendous efforts expended in installing the C-17 stereocenter via hydroboration, a satisfactory method for extending the sidechain from the resulting alcohol could not be achieved. Attempts to extend the chain directly via iodide **168** were impeded by the crowded steric environment on the underside of the molecule. By contrast, elaboration of the hydroboration product to diketone **176** led to problematic β-elimination of the protected alcohol. Retracing our steps, we found a remarkably straightforward solution to this problem. Selective Baeyer-Villiger of **183**, followed by subsequent oxidation and

conjugate addition afforded diketone **186**, which contains the entire C-17 sidechain with correct stereochemistry. After reduction and re-oxidation, the C—9 sidechain was then extended through addition of lithiated dithiane **188**. A plausible route for installation of the bridgehead olefin has been proposed.

With only bridgehead olefin formation and dithiane deprotection remaining, the synthesis of the right-hand half of the phomoidrides beginning with a [6+4] cycloaddition has largely been solved. With the considerable intelligence gathered from this model study in hand, it remains to develop an effective, scalable synthesis of trisubstituted tropone **53** and employ the powerful [6+4] cycloaddition towards a total synthesis of the phomoidrides.

References

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[7] Addition of TMSCl led to the isolation of an oil whose spectral characteristics were consistent with a silyl enol ether.

[8] Typically, a variable mixture of isomeric aldehydes were obtained, whose structures were not fully determined.

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[15] Several other minor peaks were also observed in the olefinic region, but these products have not been identified.

[16] For a review of this reagent, see: Ley, S.V.; Norman, J.; Griffith, W.P.; Marsden, S.P. *Synthesis* **1994**, 639

Contributions to Knowledge

1. The application of a [6+4] cycloaddition approach toward the total synthesis of a phomoidride model system is presented. This strategy is notable for its rapid assembly of the phomoidride carbocyclic core. Highlights of this synthesis include 1) the facile [6+4] cycloaddition of tropone **41** with 5-substituted cyclopentadiene **118** to establish the phomoidride core structure, 2) the selective Baeyer-Villiger oxidation of diketone alkene **183** to establish the C—9 side chain and 3) subsequent conjugate addition and dithiane addition reactions to install the entire C—17 and C—19 side-chains with proper stereochemistry.

2. The hydroboration of a series of 1,1-disubstituted alkenes led to the isolation of products resulting from Markovnikoff addition in 9-23% yield. Examples of Markovnikoff products formed by hydroboration on this class of alkenes are extremely rare. We believe that the erosion in anti-Markovnikoff selectivity is caused by the relative placement of electron-withdrawing functionality on the cage-like structure of these molecules. Remarkably, removal of the remote diene substituent led to complete restoration of anti-Markovnikoff hydroboration selectivity.

3. A large-scale route to the synthesis of the useful synthon **132** was developed in three steps from cyclopentadiene. The key step of this route was the selective oxidation of the allylic alcohol of a 1,4 diol by 4-acetylamino-2,3,6,6-tetramethylpiperidine-1-oxoammonium perchlorate (Bobbitt's reagent).

4. The application of 5-substituted cyclopentadiene **118** in a room-temperature cycloaddition is presented. Compared to other 5-

substituted cyclopentadienes, [1,5] hydrogen shift is very slow. The scope of this useful synthon in Diels-Alder cycloadditions is currently being explored by our laboratory.

5. Several remarkable reactions were discovered. These include the room-temperature Cope rearrangement of **120**, the oxymercuration of **120**, selective oxidation of the 2° alcohol of diol **166** using Bobbitt's reagent, remote allylation of diketone **97**, and the facile enolization of aldehyde **172**.

Experimental Section

General Procedures. All reactions were performed in flame-dried or oven-dried round bottom flasks fitted with rubber septa under a positive pressure of argon with magnetic stirring, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary (so noted) solutions were deoxygenated by alternate freeze (liquid nitrogen)/evacuation/argon-flush/thaw cycles (FPT, ≥three iterations). Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or by exposure to an ethanolic phosphomolybdic acid (PMA), an aqueous solution of ceric ammonium molybdate (CAM), an aqueous solution of potassium permanganate (Mn), or a solution of 3,5-dinitrophenylhydrazine solution followed by heating. Organic solutions were concentrated by rotary evaporation at ~25 Torr (water aspirator). Flash column chromatography was performed as described by Still et al. [1] using Silicycle 60 Å silica gel (230-400 mesh).

Materials. Commercial reagents and solvents were used as received with the following exceptions. Ethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl at 760 Torr under a dinitrogen atmosphere. Triethylamine, acetonitrile, toluene, dichloromethane, and diisopropylamine were distilled from calcium hydride at 760 Torr. HMPA was distilled from CaH_2 under an argon atmosphere on to activated 4 Å molecular sieves. $CDCl_3$ was stored over freshly activated 4 Å molecular sieves. All other deuterated solvents were obtained from sealed ampoules and used as received. Triflic anhydride was distilled from P_2O_5 immediately prior to use. Allyl iodide, benzaldehyde, and cinnamaldehyde were passed through basic alumina immediately prior to use. Solutions of *n*-butyllithium, *t*-butyllithium, NaHMDS,

[1] Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923

and KHMDS were titrated in Et_2O using 2,2-dipyridyl as indicator. N-bromosuccinimide was recrystallized from hot distilled water immediately prior to use. mCPBA was recrystallized twice from CH_2Cl_2 and stored at 0 °C. *o*-$NO_2PhSeCN$ was prepared according to the procedure of Sharpless.[2] Disiamylborane was prepared according to the procedure of Brown.[3] Dimethyldioxirane was prepared according to the procedure of Adam. [4]

Instrumentation. Proton nuclear magnetic resonance (^1H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) were recorded with a Varian Unity-500 (500 MHz), Varian Mercury-400 (400 MHz), or Varian Mercury-300 (300 MHz) NMR spectrometer. Chemical shifts for protons are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, C_6HD_5: δ 7.15, CD_2HCN: δ 1.93). Chemical shifts for carbon are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$: δ 77.0, C_6D_6: δ 128.0, CD_3CN: 117.7). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constant(s) in Hertz (Hz). Infrared spectra were recorded with a Nicolet Avatar 360 FTIR spectrometer. Melting points (MP) were obtained on a Gallenkamp melting point apparatus in open capillaries and are uncorrected. High-resolution mass spectroscopy was performed by Dr. Gaston Boulay (Université de Sherbrooke), Dr. Mike Evans (Université de Montreal), or by Dr. Alain LeSimple (Mass Spectrometry Unit at McGill University).

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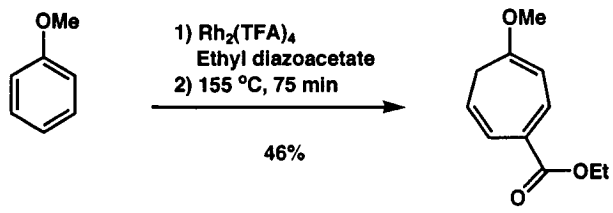

Heptatriene **57**:

To anisole (110 mL, 1.01 mol) was added $Rh_2(TFA)_4$ (155 mg, 0.234 mmol). The emerald-green solution was placed under argon and maintained under a slight positive pressure via a needle attached to a Schlenk line. To the solution was added ethyl diazoacetate (5.0 mL, 47.5 mmol) over 8 h via syringe pump. As ethyl diazoacetate was added, gas evolved and the solution turned brown. After stirring overnight, the reaction mixture was concentrated. Column chromatography (1% EtOAc / hexanes to 5% EtOAc / hexanes in 1% increments) gave the desired 4-ester heptatriene (8.51 g, 46%) contaminated with a small amount (~10% of the 3-isomer). The spectral characteristics of this compound agreed with those of Anciaux et. al. [5]

The neat heptatriene containing a stirbar was placed in a tube with a Teflon screw-cap and hydroquinone (~10 mg) added. The tube was filled with argon, sealed, and then placed into an oil bath (155 °C) with moderate stirring. The heptatriene slowly turned yellow. After 75 min, the heating bath was removed. NMR of the oil showed complete conversion to the isomerized heptatriene. The heptatriene was then carried forward to the oxidation step.

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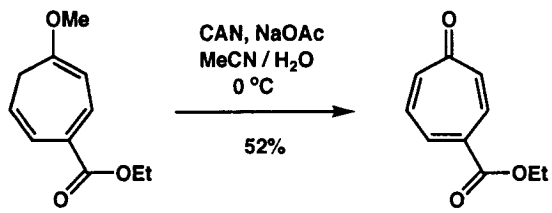
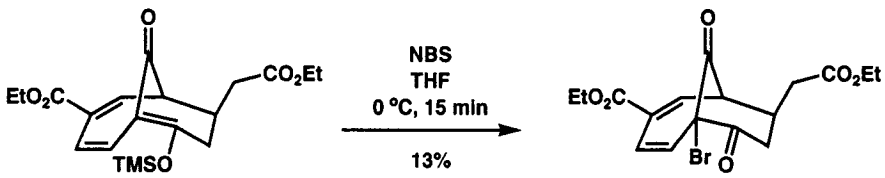


Tropone **41:**

To heptatriene **57** (5.16 g, 26.6 mmol) and NaOAc (8.2 g, 100 mmol) in 70/30 acetonitrile / water (250 mL) at 0 °C was added CAN (28.8 g, 52.5 mmol). The orange solution was stirred vigorously until all the CAN had dissolved (~3 min) and then for 10 minutes further. After exactly 10 minutes, the solution was quenched with 4:1 ethyl acetate / CH_2Cl_2 (200 mL) and partitioned with brine (200 mL). The aqueous layer was extracted further with 4:1 EtOAc / CH_2Cl_2 (2 x 200 mL). The organic layers were then washed with saturated $NaHCO_3$ solution (2 x 200 mL), 50% saturated $Na_sS_2O_3$ (2 x 200 mL) and saturated ammonium chloride (1 x 200 mL). The organic layers were dried (Na_2SO_4) and filtered. A trace amount of hydroquinone was added, and the mixture was then concentrated to give a brown oil. Column chromatography (30% EtOAc / hexanes to 40% EtOAc / hexanes) gave tropone **41** (2.47 g, 52.1%) as a brown crystalline solid, along with 1.62 g (31%) of recovered heptatriene **57**. The tropone was used immediately in the cycloaddition.

Spectral characteristics agreed with those reported by Garst et. al. [6]

[6] Garst, M.E.; Roberts, V.A.; Prussin, C. *Tetrahedron*, **1983**, *39*, 581



Bromo diketone **81**:

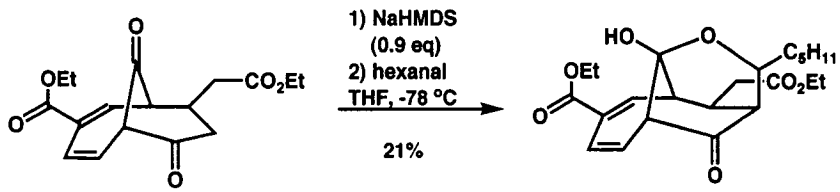
To diketone **67** (88 mg, 0.274 mmol) at –78° C was added NaHMDS (0.280 μL of a 1.07 M solution in THF, 0.300 mmol). The solution turned black almost immediately. After 30 min the reaction was quenched with TMSCl (150 μL, 1.18 mmol) and stirred for 5 min, as the solution slowly turned red. The solution was warmed to room temperature and concentrated. The oily solid was taken up in pentane, filtered and concentrated to give bridgehead silyl enol ether.**72** (83 mg, 77%).

The silyl enol ether was dissolved in THF (1 mL) and cooled to 0^0 C. After 15 minutes, NBS (52.4 mg, 0.294 mmol) was added. After 30 minutes, the reaction mixture was poured into a seperatory funnel containing saturated $NaHCO_3$ (5 mL), $Na_2S_2O_3$ (2 mL), and Et_2O (5 mL). After collecting the organic layer, the aqueous layer was extracted further with Et_2O (2 x 10 mL). The organic layers were then washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered and concentrated to give 87 mg of a black oil. Purification by column chromatography (30% ethyl acetate / hexanes) gave bromide **81** (14 mg, 13% over two steps).

^{1}H NMR (300 MHz, $CDCl_3$, 23 °C) 7.15 (d, 1H, 8.0), 6.68 (d, 1H, 12.0), 5.82 (d, 1H, J=12.0), 4.29 (q, 2H, J=7.1), 4.16 (q, 2H, J=7.1), 3.84 (dd, 1H, J=8.0, 3.4), 2.93 (dd, 1H, J=15.3, 5.6), 2.82 (m, 1H), 2.62 (dd, 1H, J=15.3, 5.3), 2.36 (d, 2H, J=6.9), 1.35 (t, 3H, J=7.1), 1.27 (t, 3H, J=7.1)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 195.6, 194.7, 170.2, 164.9, 136.1, 129.5, 127.6, 123.4, 82.5, 62.1, 61.4, 54.5, 40.0, 38.1, 32.9, 14.2, 14.2

TLC (50% EtOAc / hexanes) $R_f = 0.59$ (UV, Mn)

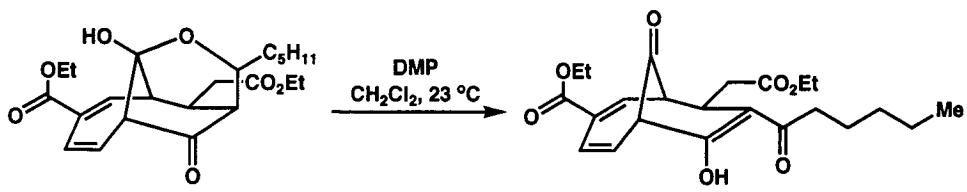


Hexanal aldol adduct **78**:

To diketone **67** (41.8 mg, 0.130 mmol) in THF (1.0 mL) at –78 °C was added NaHMDS (0.140 mL of a 0.85 M solution in THF, 0.119 mmol) dropwise. The solution turned deep red. After 30 min, freshly distilled hexanal (0.080 mL, 0.666 mmol) was added dropwise over 5 min. After 2h the reaction was quenched with NH_4Cl (5 mL) and allowed to warm to room temperature. The solution was extracted with EtOAc (3 x 5 mL), dried (Na_2SO_4), filtered and concentrated. Silica gel column chromatography (20% EtOAc / hexanes) gave hexanal aldol adduct **78** (10.6 mg, 21%) as a pale yellow oil.

^1H NMR (300 MHz, $CDCl_3$, 23 °C) 7.23 (d, 1H, J=8.8), 6.64 (d, 1H, J=13.1), 5.93 (dd, 1H, J=12.0, 6.9), 4.24 (q, 2H, J=7.1), 4.13 (q, 2H, J=7.2), 3.34-3.37 (m, 1H), 2.92 (ddd, 1H, J=8.8, 8.4, 2.5), 2.63 (d, 1H, J=7.5), 2.35 (dd, 1H, J=7.2, 7.0), 2.14-2.20 (m, 1H), 2.08 (s, 1H), 1.2 – 1.60 (obs, 12H), 1.25-1.34 (m, 6H)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 206.3, 170.9, 166.7, 138.3, 130.2, 125.8, 122.8, 96.2, 71.4, 63.7, 61.7, 61.4, 48.7, 46.2, 37.6, 35.5, 35.0, 31.7, 25.0, 22.8, 22.7, 14.4, 14.2



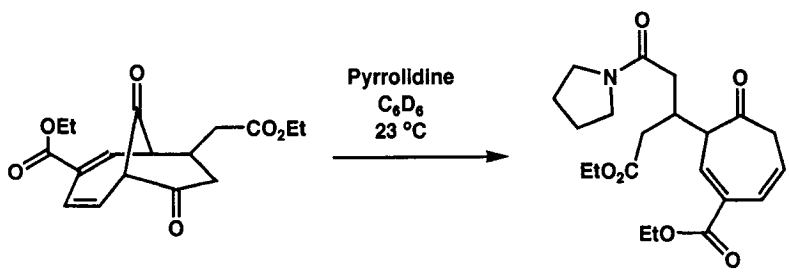
Opened hexanal aldol adduct **192**:

To aldol adduct **78** (8.2 mg, 0.020 mmol) in CH_2Cl_2 (1.0 mL) was added DMP (79.4 mg, 0.184 mmol). The mixture was stirred for 90 min whereupon the reaction was quenched with a solution of Et_2O (3 mL), saturated aqueous $NaHCO_3$ (3 mL) and saturated aqueous $Na_2S_2O_3$ (1.0 mL). After 1h the reaction mixture was transferred to a seperatory funnel, and extracted with EtOAc (3 x 5 mL). The organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated to give crude **192** as a yellow oil.

^{1}H NMR (400 MHz, 23 °C) 6.80 (d, 1H, J=5.3), 6.74 (d, 1H, J=10.9), 6.06 (dd, 1H, J=10.9, 10.8), 4.10-4.24 (m, 4H), 4.01 (dd, 1H, J=10.8, 1.9), 3.62-3.65 (m, 1H), 3.54-3.58 (ddd, 1H, J=9.6, 4.0, 2.5), 2.45-2.57 (m, 2H), 2.31-2.42 (m, 3H), 2.18 (s, 1H), 1.58-1.70 (m, 3H), 1.16-1.38 (m, 11H)

^{13}C NMR (75 MHz, 23 °C) 198.7, 180.3, 170.7, 165.6, 135.9, 128.8, 125.9, 123.0, 107.6, 61.7, 61.3, 56.1, 55.9, 39.5, 38.2, 36.5, 31.4, 24.7, 22.5, 14.2, 14.2, 14.0

IR (thin film, 23 °C) 2926.7 (m), 2854.3 (m), 1727.6 (s), 1604.9 (w), 1464.6 (w), 1373.4 (w), 1251.7 (m), 1185.0, 1095.2, 1046.6

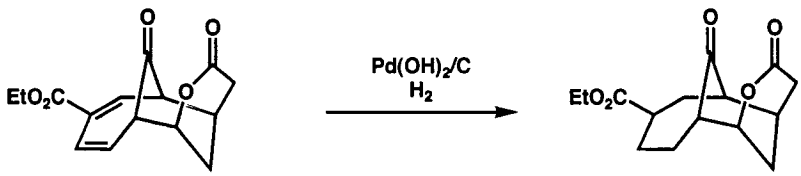


Retro-Dieckmann amide **82**:

To diketone **67** (50.6 mg, 0.16 mmol) in benzene-d_6 in an NMR tube at 23 °C was added pyrrolidine (30 μL, 0.36 mmol) in ~0.4 mL benzene-d_6 . Within 5 minutes, the solution had turned black. The NMR of the solution showed that starting material had been completely consumed.

^{1}H NMR (300 MHz, C_6D_6, 23 °C) 7.21 (d, 1H, J=6.4), 7.05 (d, 1H, J=9.0), 5.23 (dt, 1H, J=9.0, 7.8), 4.12-4.19 (m, 1H), 3.84-4.01 (m, 4H), 3.26 (dd, 1H, J=6.6, 6.0), 3.15-3.23 (m, 1H), 2.42-2.98, 2.26 (d, 1H, J=18.4), 1.96-2.10 (m, 2H), 1.31-1.37 (m, 1H), 1.10-1.25 (m, 2H), 0.87-1.00 (m, 6H)

FTIR (neat, 23 °C) 2976.9 (s), 2748.7 (m), 1727.4 (s), 1633.2 (s), 1444.9 (m), 1369.3 (m), 1254.9 (s), 1030.5 (m)



Saturated lactone **83**:

To lactone **66** (2.2g, 7.9 mmol) in ethyl acetate (20 mL) at 23 oC was added 20% $Pd(OH)_2$ on carbon (450 mg). The flask was placed under an atmosphere of H_2 (via balloon, 3 evacuate / refill cycles) and stirred rapidly. After 19h, the reaction was filtered through Celite and concentrated to give a yellow oil. This was carried through to the lactone opening step without further purification.

^1H NMR (300 MHz, $CDCl_3$, 23 °C) 4.72 (s, 1H), 4.65* (s, 1H), 4.05 (q, 2H, J=7.1), 3.11* (d, 1H, J=12.2), 2.69-2.84 (m), 2.35-2.53 (m), 1.74-2.20 (m), 1.20-1.40 (m), 1.17 (t, 3H, J=7.1)

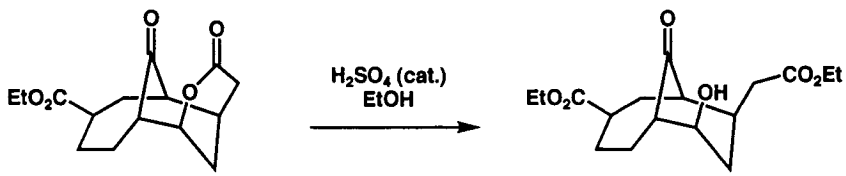
^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 209.87, 174.00, 167.43, 80.63, 60.84, 54.62, 52.75, 43.92, 39.46, 34.41, 34.07, 28.84, 23.70, 23.56, 14.10

^{13}C NMR of minor isomer (75 MHz, $CDCl_3$, 23 °C) 210.16, 174.41, 167.57, 81.17, 60.77, 55.54, 52.70, 42.65, 36.61, 34.46, 30.05, 29.39, 27.67, 24.20, 14.1

FTIR (neat, 23° C) 2927.8 (m), 1728.19 (s), 1452.5 (w), 1379.8 (w), 1250.1 (m), 1227.4 (m), 1184.6 (m), 1074.4 (m), 1044.1 (m)

HRMS (FTMS, H^+) Expected for $C_{15}H_{21}O_5^+$: 281.1383 Found: 281.1384

TLC (50% Ethyl acetate / hexanes) $R_f = 0.10$ (25% H_2SO_4)



Saturated alcohol **84**:

To lactone **84** in anhydrous ethanol (20 mL) was added concentrated H_2SO_4 (2 drops via pipet). The solution was stirred for 22h at room temperature, after which was added pH 7 buffer (10 mL) and brine (10 mL). This was then extracted with EtOAc (1 x 20 mL). The organic layer was washed with brine (2 x 20 mL), and the aqueous layers back-extracted once more with EtOAc (1 x 40 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated to give 2.5 g of a yellow oil. This was carried through to the oxidation step without further purification.

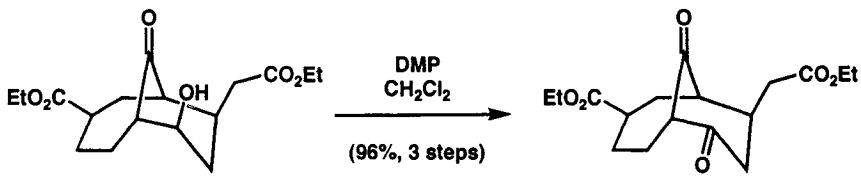
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 4.07-4.17 (m, 4H), 3.45 (dd, 1H, J=13.9, 5.6), 2.5-2.67 (m, 3H), 2.47-2.54 (m, 2H), 2.29-2.43 (m, 3H), 2.19-2.26 (m, 1H), 1.97-2.10 (m, 2H), 1.84 (dd, 1H, J=13.8, 12.0), 1.32-1.49 (m, 2H), 1.14-1.29 (m, 6H),

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C) 215.8, 174.95, 172.67, 74.05, 60.90, 60.81, 56.51, 53.14, 43.69, 41.43, 34.17, 33.54, 33.00, 28.89, 26.17, 14.35, 14.29

FTIR (neat, 23 °C) 3447.1 (br), 2980.0 (m), 2938.4 (m), 1728.2 (s), 1451.9 (w), 1375.5 (m), 1227.43 (m), 1180.5 (m), 1029.6 (m)

HRMS (FTMS, H^+) Expected for $C_{17}H_{27}O_6^+$: 327.1797 Found: 327.1802

TLC (50% Ethyl acetate / hexanes) R_f = 0.37 (Mn)



Saturated diketone **85**:

To the crude alcohol **84** (~2.5 g) in CH_2Cl_2 (40 mL) was added Dess-Martin periodinane (5.13g, 11.9 mmol). A slight exotherm was noted upon addition of this reagent. After 2h, the reaction was quenched with a biphasic mixture of Et_2O (120 mL), saturated $NaHCO_3$ (120 mL), and saturated $Na_2S_2O_3$ (40 mL) (added all at once) and stirred until the organic phase was clear (20 min). The mixture was poured into a seperatory funnel and the organic phase removed. The aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic phases were then dried (Na_2SO_4), filtered, and concentrated. Column chromatography (20% EtOAc / hexanes) gave 2.48 g (7.7 mmol, 96% from **84**) of diketone **85** as a ~2:1 mixture of epimers.

See Appendix A for copies of spectra and structural assignment

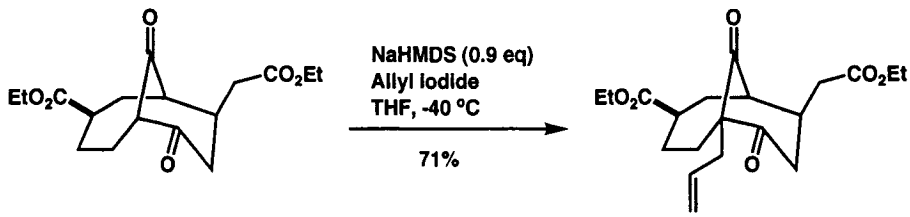
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 4.10-4.16 (m, 4H), 3.26 (dd, 1H, J=8.2, 5.4), 2.82 (dd, 1H, J=13.2, 4.9), 2.66-2.71 (m, 2H), 2.59-2.65 (m, 1H), 2.47 (dd, 1H, J=12.8, 5.4), 2.31 (dd, 1H, J=12.8, 7.9), 2.19-2.26 (m, 2H), 2.03-2.11 (m, 2H), 1.98 (ddd, 1H, J=14.8, 4.5, 4.0), 1.85-1.92 (m, 1H), 1.55-1.63 (m, 1H), 1.26 (t, 3H, J=7.1) , 1.24 (t, 3H, J= 7.1)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 208.60, 205.80, 173.58, 170.88, 62.31, 61.00, 60.93, 52.17, 43.82, 42.63, 39.86, 31.70, 29.99, 28.28, 24.68, 14.26, 14.23

FTIR (neat, 23° C) 2980.8 (m), 2939.3 (m), 1729.73 (s), 1451.25(w), 1377.7 (m), 1252.9 (m), 1184.1 (m), 1027.7 (m)

HRMS (FTMS, H^+) Expected for $C_{17}H_{25}O_6^+$: 325.1646 Found: 325.1646

TLC (50% Ethyl acetate / hexanes) R_f = 0.52 (Mn)



Bridgehead allylation product **86**:

In a flame-dried flask, diketone **85** (38.5 mg, 0.119 mmol) was dried azeotropically with toluene (2 x 1 mL). The diketone was dissolved in THF (1.0 mL) and cooled to -78^0C. NaHMDS (105 μL of a 1.07 M solution in THF, 0.112 mol) was added dropwise to give a faint yellow solution. After 25 minutes, the flask was warmed to -40^0C. After a further 10 mL, allyl iodide (20 μL, 0.22 mmol, freshly passed through alumina) was added. After 1h the reaction was quenched with saturated NH_4Cl (3 mL) and extracted with Et_2O (3 x 3 mL), dried (Na_2SO_4), filtered and concentrated. Column chromatography (20% EtOAc / hexanes) yielded allylated diketone **86** (31 mg, 71%) as a clear oil.

See Appendix A for copies of spectra

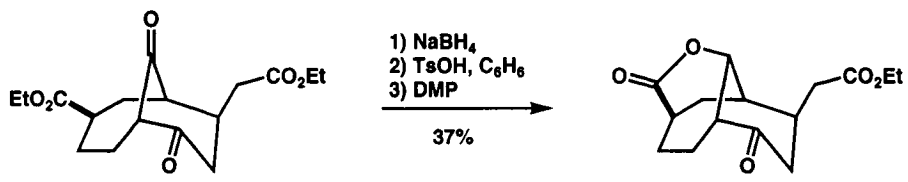
^{1}H NMR (500 MHz, $CDCl_3$, 23 °C) 5.70-5.79 (m, 1H), 5.03-5.11 (m, 2H), 4.15 (q, 2H, J=7.1), 4.11 (q, 2H, J=7.1), 2.81 (dd, 1H, J=13.2, 4.3), 2.62-2.71 (m, 2H), 2.58 (dd, 1H, J=10.8, 7.5), 2.44-2.48 (m, 2H), 2.28 (dd, J=15.5, 8.0), 2.11 (dd, 1H, J=11.0, 11.2), 2.05 (dd, 1H, J=11.5, 4.7), 1.95-2.00 (m, 3H), 1.75-1.82 (m, 1H), 1.42-1.52 (m, 2H), 1.27 (t, 3H, J=7.1), 1.24 (t, 3H, J=7.1)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 209.41, 207.21, 173.64, 170.92, 133.34, 119.10, 65.84, 60.95, 60.85, 52.68, 44.63, 42.53, 40.05, 38.06, 31.98, 31.57, 29.09, 27.97, 14.25, 14.22

FTIR (neat, 23 °C) 2980.8 (m), 2938.9 (m), 1730.6 (s), 1698.9 9s), 1447.2 (m), 1377.7 (m), 1266;0 (m), 1181.0 (s), 1030.4 (m), 920.1 (w)

HRMS (FTMS, Na^+) Expected for $C_{20}H_{28}O_6Na^+$: 387.17795 Found: 387.17781

TLC (50% Ethyl acetate / hexanes) $R_f = 0.60$ (UV, Mn)



Lactone ketone **87**:

To diketone **85** (183.9 mg, 0.567 mmol) in MeOH (2.0 mL) containing $CeCl_3 \cdot 7H_2O$ (27.6 mg, 0.074 mmol) at –78 °C was added $NaBH_4$ (39.8 mg, 1.05 mmol). After 30 min the reaction was quenched with saturated aqueous NH_4Cl (3 mL). The mixture was extracted with EtOAc (3 x 10 mL), dried (Na_2SO_4), filtered and concentrated to give 195 mg of a white foam.

The crude mixture of diols was dissolved in DMF (5 mL). PPTS (13 mg, 0.052 mmol) and activated 4 Å molecular sieves (10 mg). The solution was heated to 80 °C. After 36 h, the mixture was filtered through Celite and concentrated. A solution of pH 7 buffer (10 mL) was added, and the aqueous layer extracted with EtOAc (3 x 10 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated. Column chromatography (30% EtOAc / hexanes to 90% EtOAc / hexanes in 10% increments gave a lactone (145 mg) as a mixture of alcohols.

The lactone was dissolved in CH_2Cl_2 (5.0 mL), and DMP (445 mg, 1.03 mmol) added. After 3 h, the reaction was quenched with a solution containing Et_2O (15 mL), saturated aqueous $NaHCO_3$ (15 mL), and saturated aqueous $Na_2S_2O_3$ (5 mL) and stirred until the organic layer became clear (30 min). The aqueous layer was extracted with EtOAc (2 x 15 mL), dried (Na_2SO_4), filtered and concentrated. Column chromatography (20% EtOAc / hexanes to 40% EtOAc / hexanes in 10% increments) gave lactone **84** (59.3 mg, 37%) as fine white needles, along with a ~1:1 mixture of epimeric starting diketones (41%).

See Appendix A for copies of spectra and structural assignment

^1H NMR (400 MHz, $CDCl_3$, 23 °C) 5.04 (dd, 1H, J=9.0, 5.5), 4.15 (q, 2H, J=7.1), 3.11 (dd, 1H, J=8.5, 7.5), 2.94 (dd, 1H, J=7.3, 7.0), 2.61 (dd, 1H, J=15.0, 6.3),

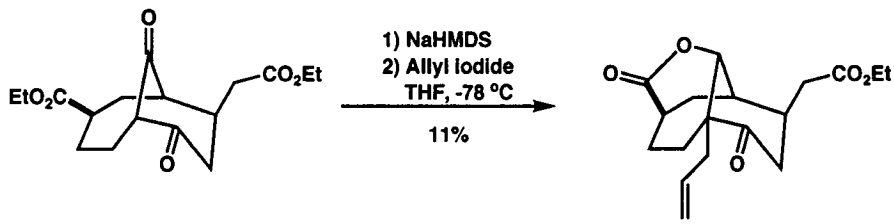
2.53-2.57 (m, 1H), 2.38-2.46 (m, 4H), 2.29 (dd, 1H, J=15.0, 5.2), 2.16-2.21 (m, 1H), 2.09 (d, 1H, J=14), 1.67-1.76 (m, 1H), 1.43-1.57 (m, 2H), 1.27 (t, 3H, J=7.1)

^{13}C NMR (100 MHz, $CDCl_3$, 23 °C) 208.92, 173.03, 170.86, 75.74, 61.01, 49.71, 41.15, 39.43, 38.70, 34.11, 33.70, 32.30, 28.79, 22.29, 14.30

FTIR (neat, 23 °C) 2927.1 (m), 1730.37 (s), 1464.8 (m), 1380.0 (m), 1266.2 (m), 1182.1 (m), 1043.3 (m)

HRMS (FTMS, Na^+) : $C_{15}H_{20}O_5Na^+$: 303.12009 Found: 303.12030

TLC (50% Ethyl acetate / hexanes) $R_f = 0.26$ (Mn)



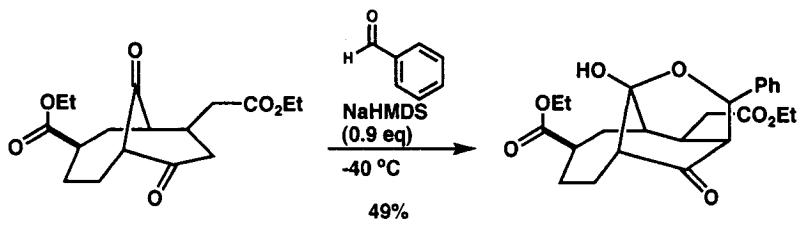
Allylated lactone **88**:

To lactone ketone **87** (26.1 mg, 0.093 mmol) in THF (1.0 mL) at –78 °C was added NaHMDS (135 μL of a 0.83 M solution in THF, 0.112 mmol). After 30 min, allyl iodide (20 μL, 0.22 mmol, freshly passed through basic alumina) was added dropwise. After 2 h the reaction was quenched with pH 7 phosphate buffer (5 mL) and warmed to room temperature. The solution was extracted with EtOAc (3 x 5 mL), dried (Na_2SO_4), filtered and concentrated to give a bright yellow residue (26.5 mg). The residue was purified by silica gel column chromatography (0% EtOAc / hexanes to 40% EtOAc / hexanes in 10% increments) to give allylated lactone **88** (3.0 mg, 11%) along with starting lactone **87** (2.5 mg, 9%).

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 5.59-5.71 (m, 1H), 5.19 (d, 1H, J=11.6), 5.15 (d, 1H, J=18.4), 4.83 (d, 1H, J=6.0), 4.15 (q, 2H, J=7.1), 2.91 (dd, 1H, J=7.0, 6.8), 2.60 (dd, 2H, J=14.8, 5.3), 2.47-2.54 (m, 2H), 2.40-2.42 (m, 1H), 2.36 (dd, 1H, J=8.8, 5.6), 2.34-2.40 (m, 1H), 2.29-2.33 (m, 1H), 2.22 (dd, 1H, J=13.2, 9.0), 2.14-2.19 (m, 1H), 1.91-1.97 (m, 1H), 1.42-1.55 (m, 3H), 1.27 (t, 3H, J=7.1)

^{13}C NMR (100 MHz, $CDCl_3$, 23 °C) 210.9, 173.4, 170.9, 132.5, 120.5, 78.5, 78.5, 61.0, 55.0, 43.1, 41.0, 39.6, 38.4, 33.8, 32.6, 30.9, 28.3, 14.3

FTIR (neat, 23 °C) 2929.3 (m), 2360.5 (m), 2348.0, 1733.2 (s), 1458.5 (w), 1375.8 (w), 1176.7 (m), 1039.6 (m), 920.4 (w)



Benzaldehyde aldol adduct **86**:

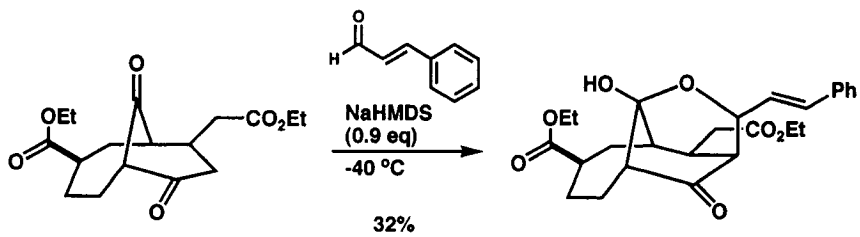
The diketone **82** (44.2 mg, 0.136 mmol) was dried via removal of benzene (2 x 1 mL). THF (1.0 mL) was added and the solution cooled to -78^0 C. NaHMDS (115 μL of a 1.07 M solution in THF, 0.123 mmol) was added dropwise. The reaction mixture became yellow. After 15 minutes the flask was warmed to -40^0 C. After a further 15 minutes, benzaldehyde (22 μL, 0.21 mmol) was added. The yellow solution was then stirred for 1h, and quenched with pH 7 phosphate buffer (5 mL). The mixture was extracted with Et_2O (3 x 10 mL), dried (Na_2SO_4), filtered and concentrated. Column chromatography (gradient, 20% EtOAc / hexanes to 50% EtOAc / hexanes) yielded **86** (28.9 mg, 49%). The remainder contained unreacted starting material.

See Appendix A for copies of spectra

^{1}H NMR (400 MHz, $CDCl_3$, 23° C) 7.26-7.32 (m, 5H), 5.39 (s, 1H), 4.19 (q, 2H, J=7.1), 4.11 (q, 2H, J=7.1), 3.66 (s, 1H), 2.84 (s, 1H), 2.71-2.76 (m, 1H), 2.72 (d, 1H, J=2.3), 2.69 (s, 1H), 2.24-2.32 (m, 2H), 2.14-2.20 (m, 1H), 2.00-2.13 (m, 2H), 1.89-1.97 (m, 3H), 1.81 (ddd, 1H, J=14.1, 3.2, 3.0), 1.22-1.32 (m, 6H)

^{13}C NMR (75 MHz, $CDCl_3$, 23° C) 209.77, 175.60, 170.90, 140.42, 128.48, 127.60, 125.04, 100.97, 71.40, 61.07, 60.68, 56.84, 53.05, 47.71, 40.4, 37.80, 34.16, 30.69, 28.41, 21.60, 14.30, 14.25

TLC (50% Ethyl acetate / hexanes) $R_f = 0.59$ (UV, Mn)



Cinnemaldehyde aldol adduct **89**:

To diketone **85** (57.8 mg, 0.180 mmol, dried azeotropically 1 x 1 mL toluene) in 1.0 mL THF at –78 ^{0}C was added NaHMDS (125 μL of a 1.15 M solution in THF, 0.144 mmol) dropwise. This was stirred for 15 minutes at –78^{0}C and then warmed to –40^{0}C for 15 min. Cinnemaldehyde (30 μL, 0.24 mmol) was then added. The reaction mixture turned slightly brown over 1h, whereupon the solution was quenched with pH 7 phosphate buffer (1 mL). The mixture was extracted with EtOAc (3 x 5 mL), dried (Na_2SO_4), filtered and concentrated. Purifcation by column chromatography (5% → 10% → 20% →30% EtOAc / hexanes) gave hemiacetal **89** (21.5 mg, 32%) along with unreacted starting material.

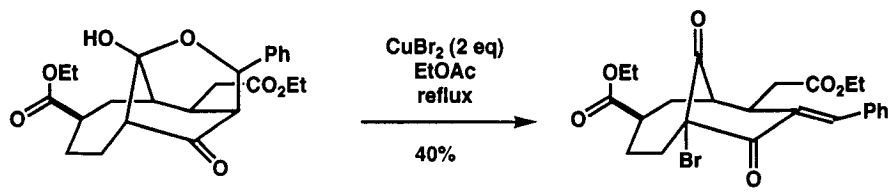
^{1}H NMR (300 MHz, $CDCl_3$, 23 °C) 7.26-7.39 (m, 5H), 6.66 (d, 1H, J=15.8), 6.04 (dd, 1H, J=15.8, 5.3), 4.94 (d, 1H, J=5.3), 4.17 (q, 2H, J=7.1), 4.11 (q, 2H, J=7.1), 3.48 (s, 1H), 2.81 (d, 1H, J=9.3), 2.62-2.66 (m, 2H), 2.44-2.56 (m, 1H), 2.07-2.30 (m, 4H), 1.88-2.07 (m, 3H), 1.79 (d, 1H, J=14.2), 1.19-1.32 (m, 6H)

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C) 195.5, 175.7, 171.0, 131.9, 128.5, 127.9, 126.5, 100.8, 70.8, 61.1, 60.7, 56.7, 52.0, 47.6, 40.2, 37.8, 33.9, 28.5, 21.4, 14.3, 14.2

FTIR (neat, 23 °C) 3454.4(br), 2979.3 (m), 2930.8 (m), 1729.2 (s), 1449.8 (w), 1370.9 (w), 1296.59 (m), 1233.3 (m), 1178.9 (m), 1030.6 (m), 972.8 (m)

HRMS (FTMS, Na^+) Expected for $C_{26}H_{32}O_7Na^+$: 479.2037 Found: 479.2040

TLC (50% EtOAc / hexanes) $R_f = 0.46$ (UV, Mn)



Dehydrated benzaldehyde aldol adduct **106**:

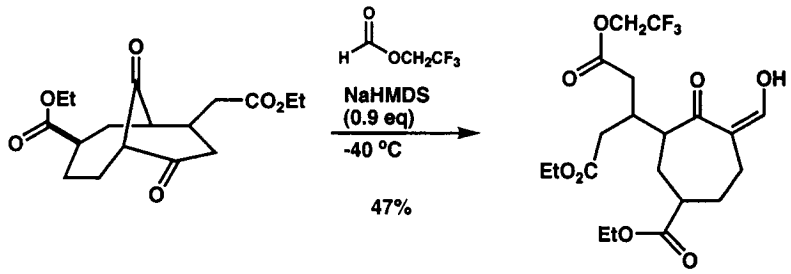
To benzaldehyde aldol adduct **89** (20.6 mg, 0.048 mmol) in EtOAc (2.0 mL) at 45°C was added $CuBr_2$ (26.4 mg, 0.12 mmol). The solution was heated to reflux, and slowly turned green as the reaction progressed. After 18h the reaction mixture was filtered through Celite and a short pad of silica, and concentrated. Column chromatography (20% EtOAc / hexanes) gave 9.2 mg (40%) of **106** as an oil.

^{1}H NMR (300 MHz, $CDCl_3$, 23 °C) 7.96 (s, 1H), 7.56-7.60 (m, 2H), 7.45-7.50 (m, 3H), 4.11-4.25 (m, 4H), 3.90 (d, 1H, J=12.5), 3.32-3.40 (m, 1H), 2.91-2.98 (m, 1H), 2.65-2.78 (m, 2H), 2.61 (dd, 1H, J=18.0, 3.1), 2.39 (dd, 1H, J=18.0, 11.6), 2.25-2.33 (m, 2H), 1.48-1.63 (m, 2H), 1.29 (m, 6H)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 202.08, 193.17, 171.39, 170.64, 144.07, 133.66, 132.40, 130.84, 130.52, 129.14, 67.07, 61.17(2), 48.93, 40.98, 36.91, 35.81, 35.77, 28.44, 27.65, 14.24, 14.18

FTIR (neat, 23 °C) 2926.0 (m), 2654.6 (w), 1730.9 (s), 1684.4 (m), 1589.6 (m), 1446.0 (m), 1374.5 (m), 1194.5 (m), 1024.3 (w), 755.0 (w), 693.7 (w)

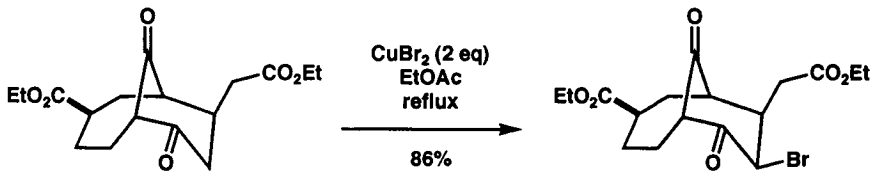
TLC (50% EtOAc / hexanes) $R_f = 0.66$ (UV, Mn)



Formate **96**:

To diketone **85** (104 mg, 0.32 mmol) in Et_2O (1.0 mL) at –78 °C was added NaHMDS (270 μL of a 1.07 M solution in THF, 0.29 mmol). The yellow slurry was stirred for 20 min and then warmed to –40 °C. After 15 min at this temperature, 2,2,2-trifluoroethyl formate (150 μL, 1.54 mmol) was added. The solution became clear within 5 min. After 90 min, the solution was quenched with pH 7 buffer (~0.1 mL) and concentrated. Silica gel column chromatography (20% EtOAc / hexanes) gave formate **96** (64 mg, 47%).

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 14.3 (d, 1H, J=9.6), 7.37 (d, 1H, J=9.6), 4.43 (q, 2H, J=6.8), 4.06-4.22 (m, 4H), 2.97-3.01 (dd, 1H, J=7.6, 3.8), 2.85-2.89 (m, 1H), 2.83-2.87 (m, 1H), 2.59-2.75 (m, 3H), 2.41 (dd, 1H, J=13.6, 11.2), 2.27 (dd, 2H, J=12.8, 8.8), 2.07-2.13 (m, 2H), 1.63 (dd, 1H, J=10.8, 9.6), 1.52-1.56 (m, 1H), 1.25 (t, 3H, J=7.1), 1.23 (t, 3H, J=7.1)



Bromoketone **97**:

To diketone **85** (96 mg, 0.296 mmol) in ethyl acetate (4.0 mL) at 50 °C was added $CuBr_2$ (154 mg, 0.690 mmol). The solution was stirred vigorously and slowly turned green as the reaction progressed. After 6h, ethyl acetate (20 mL) was added. The solution was filtered through Celite and silica gel, then concentrated. Column chromatography (50% EtOAc / hexanes) gave bromide **97** (103 mg, 86%) as a ~5:1 mixture of bromine epimers.

See Appendix A for copies of spectra

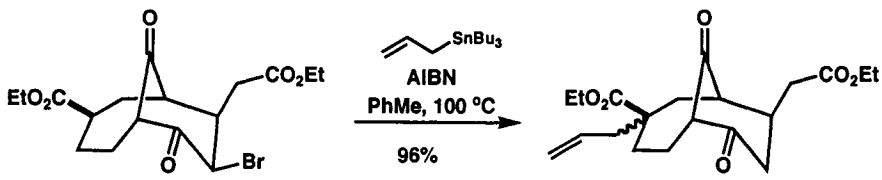
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 4.66 (d, 1H, J=2.3), 4.19 (q, 2H, J=7.1), 4.11 (q, 2H, J=7.1), 3.57 (ddd, 1H, J=12.4, 5.4, 1.6), 2.72-2.77 (m, 1H), 2.66 (dd, 1H, J=17.8, 8.8), 2.50-2.61 (m, 2H), 2.54 (dd, 1H, J=17.8, 4.4), 2.46 (dddd, 1H, J=14.8, 12.4, 5.6, 2.6), 2.19 (d, 1H, J=14.0), 2.09 (ddd, 1H, J=14.3, 4.5, 4.0), 1.76 (1H, J=14.0, 14.0, 5.6, 2.5), 1.40-1.49 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$, 23 °C) 205.91, 198.69, 173.54, 170.42, 61.33, 61.06, 57.82, 54.36, 49.97, 43.26, 36.71, 33.18, 31.31, 28.43, 25.60, 14.24, 14.24

FTIR (neat, 23 °C) 2981.4 (m), 2935.9 (m), 1727.8 (s), 1451.4 (m), 1377.4 (m), 1243.51 (m), 1184.6 (m), 1026.24 (m)

HRMS (EI) Expected for $C_{17}H_{23}BrO_6^+$ 402.0678 Found: 402.0671

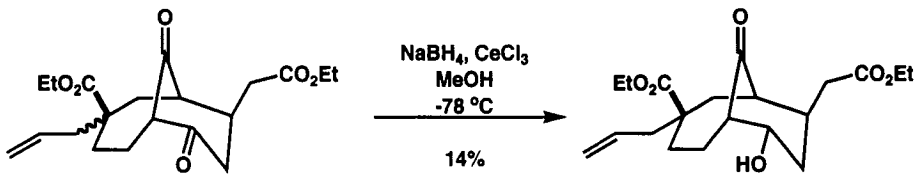
TLC (50% Ethyl acetate / hexanes) R_f = 0.63 (UV, Mn)



Allylated diketone **98**:

Bromide **97** (101 mg, 0.25 mmol, >95% β-Br) in toluene (2.0 mL, degassed FPT) containing allyltributyltin (330 mg, 1.0 mmol) was heated to 100 °C, whereupon AIBN (2 mg) was added. Further aliquots of AIBN were added at 20 minute intervals. After 1 h, the reaction was cooled and the toluene removed by evaporation. Column chromatography (0% → 10% → 20% EtOAc / hexanes) gave 87 mg (96%) of a mixture of allylated compounds **98** (~2.5 : 1)

The crude mixture of allylated compounds was inseparable by column chromatography (0% EtOAc / hexanes to 20% EtOAc / hexanes in 10 % increments). Therefore it was submitted to the following reduction / purification / oxidation sequence.



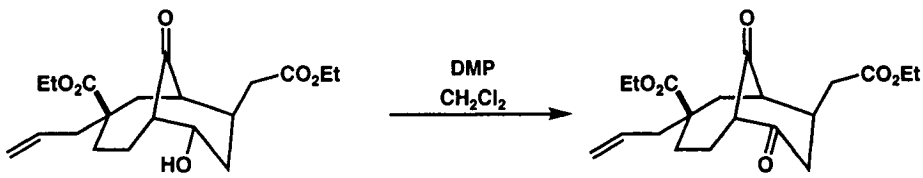
Reduced allylated ketone **194**:

To a mixture of allylated diketones **98** (59 mg, 0.059 mmol) in MeOH (1.0 mL) was added $CeCl_3 \cdot 7H_2O$ (12 mg). The solution was cooled to –78 °C, and then $NaBH_4$ (19 mg, 0.5 mmol) was added. After 10 min, the reaction was quenched with saturated NH_4Cl (10 mL) and warmed to room temperature. The mixture was extracted with EtOAc (3 x 10 mL), dried (Na_2SO_4), filtered and concentrated. Column chromatography (0% → 40% EtOAc / hexanes in 10% increments) gave a clean fraction of alcohol **194** (8 mg, 14%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 5.61-5.72 (m, 1H), 5.09 (d, 1H, J=10.1), 5.06 (d, 1H, J=18.1), 4.13 (q, 2H, J=7.1), 4.12 (q, 2H, J=7.1), 4.09-4.15 (obs, 1H), 2.92 (dd, 1H, J=14.8, 8.1), 2.57 (dd, 1H, J=9.0, 8.8), 2.38-2.47 (m, 2H), 2.30 (dd, 1H, J=14.4, 9.5), 2.23-2.27 (m, 1H), 2.20 (d, 1H, J=7.0), 2.17 (d, 1H, 8.8), 2.09-2.15 (m, 1H), 2.07 (s, 1H), 1.93-2.00 (m, 1H), 1.82 (d, 1H, J=6.0), 1.67-1.80 (m, 3H), 1.60 (d, 1H, J=5.1), 1.26 (t, 3H, J=7.1), 1.25 (t, 3H, J=7.1)

1-D NOE (irradiation at 4.15 ppm): 2.93, 2.18, 1.78, 1.58, 1.26

TLC (50% EtOAc / hexanes) $R_f = 0.39$ (Mn)



α-allyl diketone **98**:

To alcohol **194** (10 mg, 0.027 mmol) in CH_2Cl_2 (0.5 mL) was added Dess-Martin periodinane (25 mg, 0.058 mmol). After 1h, the reaction was quenched with $NaHCO_3$ (3 mL), Et_2O (3 mL), and $Na_2S_2O_3$ (1 mL) (all one portion) and stirred for 20 minutes. The mixture was then extracted with Et_2O (3 x 5 mL), dried (Na_2SO_4), filtered and concentrated to give diketone **98** (10 mg) as a single isomer which was used without further purification in the bromination step.

See Appendix A for copies of spectra and structural assignment

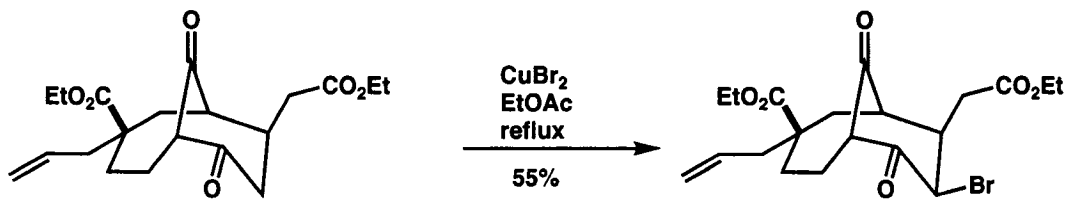
^1H NMR (400 MHz, $CDCl_3$, 23 °C) 5.57-5.69 (m, 1H), 5.09 (d, 1H, J=10.7), 5.03 (d, 1H, J=15.4), 4.07-4.16 (m, 4H), 3.10 (dd, 1H, J=4.8, 4.8), 2.88 (dd, 1H, J=16.8, 7.8), 2.85-2.93 (m, 1H), 2.53 (d, 1H, J=9.5), 2.45-2.51 (m, 1H), 2.40 (dd, 1H, J=18.0, 6.5), 2.19-2.30 (m, 4H), 2.09 (d, 1H, J=14.8), 1.88-1.97 (m, 1H), 1.37-1.45 (m, 1H), 1.20-1.29 (m, 6H), 1.09-1.16 (m, 1H)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 208.86, 207.48, 173.36, 171.00, 131.95, 119.34, 62.67, 60.93, 60.89, 51.41, 49.36, 47.96, 41.91, 39.72, 35.73, 33.58, 32.39, 25.42, 14.24 (2)

FTIR (neat, 23 °C) 2978.9 (m), 2932.1 (m), 1729.7 (s), 1702.4 (s), 1446.7 (w), 1376.6 (w), 1181.9 (m), 1026.9 (m)

HRMS (FTMS, H^+) Expected for $C_{20}H_{29}O_6^+$: 365.1957 Found: 365.1959

TLC (50% EtOAc / hexanes) $R_f = 0.67$ (UV, Mn)



Brominated allylated diketone **195**:

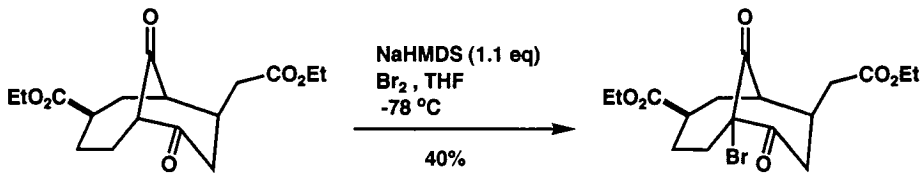
To diketone **98** (10 mg, 0.027 mmol) in ethyl acetate (2 mL) at 50 °C was added $CuBr_2$ (15 mg, 0.064 mmol) with rapid stirring. The reaction slowly turned a deep green colour. After 2h, the reaction was cooled, filtered through Celite, and the solvent removed through rotary evaporation. Column chromatography (5% to 15% EtOAc / hexanes in 5% increments) gave brominated diketone **195** (6.7 mg, 55%) of a 6.8:1 mixture of bromine epimers,

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 5.54-5.65 (m, 1H), 5.08 (dd, 1H, J=10.0, 1.9), 5.02 (dd, 1H, J=16.8, 1.8), 4.47 (d, 1H, J=6.8), 4.06-4.21 (m, 4H), 3.16 (dd, 1H, J=5.0, 4.3), 2.98 (dd, 1H, J=9.3, 8.7), 2.75 (1H, d, J=12.5), 2.47-2.57 (m, 3H), 2.36-2.43 (m, 1H), 2.20 (d, 2H, J=7.4), 2.08 (d, 1H, J=14.2), 1.89-1.99 (m, 1H), 1.47-1.55 (m, 1H), 1.30 (t, 3H, J=7.1), 1.25 (t, 3H, J=7.1), 1.01 (dd, 1H, J=15.2, 9.3)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 206.51, 196.66, 173.04, 170.56, 131.74, 119.47, 61.18, 60.93, 60.33, 56.41, 53.05, 49.10, 47.77, 45.29, 37.79, 37.36, 32.81, 23.75, 14.23 (2)

FTIR (neat, 23 °C) 2979.1 (m), 2928.0 (m), 1724.5 (s), 1445.8 (w), 1376.7 (w), 1199.5 (m), 1096.6 (w), 1025.3 (m)

TLC (33% EtOAc / hexanes) $R_f = 0.33$ (Mn)



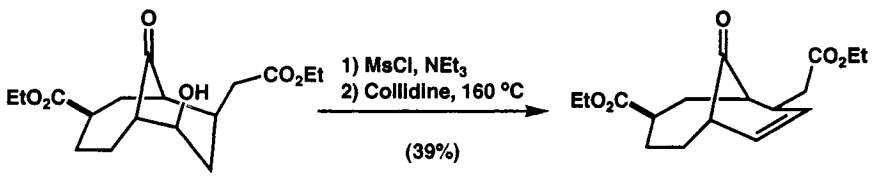
Saturated bridgehead bromide **196**:

To diketone **85** (42.5 mg, 0.131 mmol) in THF (1.0 mL) at –78 °C was added NaHMDS (150 μL of a 1.07 M solution in THF, 0.160 mmol) dropwise. After stirring 20 min, a solution of Br_2 (130 μL of a 1.0 M solution in THF) was added dropwise until the brown colour persisted. After 2 minutes, the solution was quenched with 5 mL of a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. After 10 min at –78 ^{0}C the mixture was warmed to room temperature, thawed, and extracted with EtOAc (3 x 10 mL). The collected organic layers were dried (Na_2SO_4), filtered and concentrated to give 49 mg of a crude mixture. Column chromatography (10% EtOAc / CH_2Cl_2) gave 23 mg of bromide **196** as a yellow oil along with 16 mg of starting diketone.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 4.08-4.21 (m, 4H), 2.98 (ddd, 1H, J=7.8, 7.2, 3.2), 2.88 (dd, 1H, J=15.6, 6.6), 2.72-2.77 (m, 1H), 2.57-2.67 (m, 2H), 2.28-2.49 (m, 5H), 1.89-1.94 (m, 1H), 1.60 (dddd, J=14.8, 7.2, 2.7), 1.31-1.35 (m, 1H), 1.24-1.29 (m, 4H)

^{13}C NMR (100 MHz, $CDCl_3$, 23 °C) 201.8, 199.1, 172.1, 170.6, 69.2, 61.1, 61.0, 50.8, 40.7, 40.6, 40.3, 33.3, 31.3, 31.2, 27.6, 14.3, 14.2

TLC (10% EtOAc / CH_2Cl_2) $R_f = 0.63$ (UV, Mn)



Disubstituted alkene **105**:

To alcohol **84** (80 mg, 0.26 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C was added NEt_3 (0.9 mL, 0.64 mmol) and methanesulfonyl chloride (0.4 mL, 0.5 mmol). After 30 min the reaction was quenched with saturated aqueous NH_4Cl (5 mL). The mixture was then extracted with EtOAc (3 x 10 mL), dried (Na_2SO_4) filtered and concentrated to give a crude mesylate (123 mg).

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): 4.93-4.98 (m, 1H), 4.01-4.16 (m, 4H), 3.07-3.10 (m, 1H), 2.98 (s, 3H), 2.82-2.91 (m, 1H), 2.59-2.64 (m, 1H), 2.48-2.54 (m, 1H), 2.39-2.48 (m, 2H), 2.29 (dd, 1H, J=13.2, 7.4), 1.97-2.09 (m, 2H), 1.83-1.89 (m, 1H), 1.61 (ddd, 1H, J=12.4, 8.2, 7.5), 1.32-1.46 (m, 2H), 1.16-1.24 (m, 7H)

^{13}C NMR (100 MHz, $CDCl_3$, 23 °C) 210.8, 173.9, 171.4, 81.3, 60.8, 60.8, 53.3, 52.5, 43.3, 40.6, 38.9, 33.0, 32.3, 32.2, 28.3, 25.9, 14.3, 14.2

TLC (80% EtOAc / hexanes): $R_f = 0.66$ (Mn)

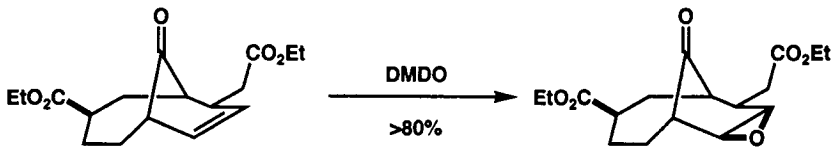
A portion of this crude mixture (54 mg, ~0.13 mmol) was dissolved in 2,4,6-collidine (2.0 mL) and heated to 160 °C for 10 h. Upon removal from heat, saturated aqueous $CuSO_4$ (10 mL) and EtOAc (10 mL) were added. The organic layer was then washed with 1 M HCl (2 x 10 mL), saturated aqueous $NaHCO_3$ (1 x 10 mL), and brine (1 x 10 mL). The organic layer was then dried (Na_2SO_4), filtered and concentrated to give a yellow oil (34 mg). Silica gel column chromatography (0% to 20% EtOAc / hexanes in 5% increments, pipet column) gave alkene **104** (16 mg, 39%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 5.85 (dd, 1H, J=9.6, 5.9), 5.70 (dd, J=9.6, 3.7), 4.06-4.15 (m, 4H), 2.90-2.98 (m, 2H), 2.75-2.78 (dd, 1H, J=8.8, 5.4), 2.28 (dd, 1H, J=10.0, 7.5), 2.30-2.44 (m, 2H), 1.87-2.03 (m), 1.63-1.73 (m), 1.23-1.27 (m)

^{13}C NMR (100 MHz, $CDCl_3$, 23 °C) 212.90, 173.33, 171.30, 130.59, 129.23, 60.63 (2), 51.19, 49.00, 42.88, 41.07, 39.45, 32.54, 28.57, 26.94, 14.30, 14.26

FTIR (neat, 23 °C) 2980 (m), 2931 (m), 1730 (s), 146 (m), 1373 (m), 1286 (s), 1176 (s), 1030 (m)

TLC (33% Ethyl acetate / hexanes) R_f = 0.48 (UV, Mn)



Epoxide **106**:

To alkene **105** (18 mg, 0.058 mmol) was added a solution of DMDO in acetone (1.5 mL of a 0.058 M solution of DMDO, 0.09 mmol). The clear solution was stirred for 18h and then concentrated. Purification by silica gel chromatography (0% to 30% EtOAc / hexanes in 10% increments) gave a mixture of epoxides (15.4 mg, 81%). The remainder of the material was unreacted alkene.

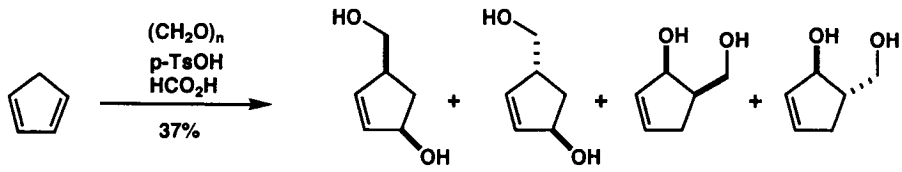
For the slower-eluting major epoxide:

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 4.17 (q, 2H, J=7.1), 4.11 (q, 2H, J=7.1), 3.46 (dd, 1H, J=3.8, 3.0), 3.42 (dd, 1H, J=4.0, 3.0), 3.10-3.15 (m, 1H), 2.83-2.89 (m, 1H), 2.64-2.71 (m, 1H), 2.63 (dd, 1H, J=16.6, 8.4), 2.42 (dd, 1H, J=16.6, 6.5), 2.32 (dd, 1H, J=6.8, 5.5), 2.06-2.18 (m, 1H), 2.04 (d, 1H, J=14.3), 1.88 (ddd, 1H, J=14.0, 11.2, 4.9), 1.51-1.69 (m, 2H), 1.24-1.30 (m, 6H)

^{13}C NMR (100 MHz, $CDCl_3$, 23 °C) 210.54, 174.01, 171.43, 60.85 (2), 58.48, 53.90, 49.71, 47.15, 42.96, 38.18, 36.03, 34.05, 28.51, 24.47, 14.31, 14.28

FTIR (neat, 23 °C) 2923.3 (s), 2852.3 (m), 1730.1 (s), 1455.5 (w), 1375.5 (w), 1179.7 (m), 1095.5 (m), 1027.6 (m)

TLC (50% EtOAc / hexanes) $R_f = 0.36$ (Mn)



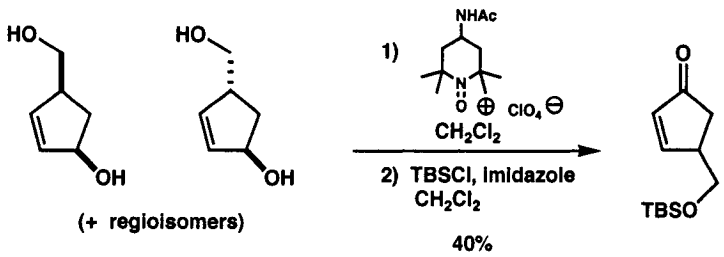
Mixture of diols **129** and **130**:

The mixture of diols was obtained through a modification of the procedure of Saville-Stones et. al. [7]

Paraformaldehyde (88g, 0.978 mol)) was added to 95-97% formic acid (500g, 420mL, 10.3 mol) in a 2L flask under argon with stirbar and reflux condenser. The mixture was heated to reflux until clear, then cooled to room temperature. p-toluenesulfonic acid (0.3 g) was added. The mixture was cooled in an ice bath, the reflux condenser replaced with a 250 mL dropping funnel, and cracked cyclopentadiene (50g, 0.760 mmol) added dropwise over 20 minutes. The ice bath was removed, whereupon the mixture quickly turned black. After stirring overnight (16h) the solution was cooled in an ice bath, and 10M NaOH (1.2L) was added dropwise with effective stirring. After completion of the addition (approximately 5h) the mixture is composed of an amber liquid with black sludge floating on top. The sludge was filtered off with a large, stand-alone Buchner filter, and the flask washed with water (300 mL). The resulting amber liquid was acidified to pH 5-6, and concentrated under reduced pressure (note: it is imperative to concentrate to complete dryness, as residual water will dissolve the sodium formate and cause problems during the distillation step). The solid was washed thoroughly with acetonitrile (2 x 500 mL) and the resulting solution was concentrated to give approximately 60g of an amber oil. Distillation of the oil through a Vigreux column (110°C / 0.1 mm Hg) afforded 32.0 g (281 mmol, 37%) of a clear, pale yellow oil. NMR spectroscopy revealed an approximate 3:2 ratio

[7] (*Tetrahedron*, **1994**, *50*, 6695-6704).

of 1,4 (**129**)and 1,3 diols (**130**) in agreement with Stones et. al. The mixture of diols was submitted without further purification to the Bobbitt oxidation step.



TBS-protected enone **132**:

To 32.0 g (280 mmol) of diols (60:40 ratio of 1,4 to 1,3) in CH_2Cl_2 (500 mL) was added 99.5 g (308 mmol, 1.10 eq) of Bobbitt's reagent **131** in two 50 g portions. After the addition was complete, a further 1000 mL CH_2Cl_2 was added. After 3h, the yellow slurry was filtered, washed with CH_2Cl_2 (2 x 500 mL), and concentrated to yield 36 g of a dark brown oil. NMR of the crude reaction mixture revealed the major product to be alcohol **117**, whose spectrum agreed with reported values. [8]

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 7.70 (dd, 1H, J=5.5, 2.1), 6.23 (dd, 1H, J=5.5, 1.9), 3.67-3.77 (m, 2H), 3.16-3.17 (m, 1H), 2.48 (dd, 1H, J=18.5, 6.5), 2.17 (dd, 1H, J=18.5, 1.7)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 210.34, 166.18, 134.99, 64.03, 44.06, 37.54

FTIR (neat, 23 °C) 3407 (br), 2926.96 (w), 2871.8 (w), 1707.43 (s), 1670.9 (m), 1584.83 (w), 1406.81 (w), 1349.51 (w) 1188.54 (w) 1059.98 (w), 1032.45 (w), 940.74 (w), 786.90 (w)

For convenience, the above mixture of crude alcohols was divided into two approximately equal batches. The following procedure is illustrative. The crude mixture (18 g) was dissolved in CH_2Cl_2 (1000 mL). Imidazole (15.92 g, 234

[8] Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945

mmol), TBSCl (31 g, 206 mmol), and DMAP (0.291 g, 2.4 mmol) were then added. A white solid quickly precipitated from the solution. After 3h, the mixture was poured into a 4L separatory funnel and washed with H_2O (1L), 1M HCl (1L), H_2O (1L), saturated $NaHCO_3$ (1L) and brine (1L). The organic layer was dried (Na_2SO_4), filtered and concentrated to give a brown oil (approximately 40g). Column chromatography (0% to 10% EtOAc / hexanes in 2% increments (1L per run), followed by flushes of 15% EtOAc / hexanes and 20% EtOAc / hexanes) gave desired enone **132** (11.82 g), as a pale yellow oil. The yield from the second protection, run under essentially identical conditions (reaction time 4h) gave 13.63g of **132** for a total yield of 25.45 g (40%, 66% of theoretical yield).

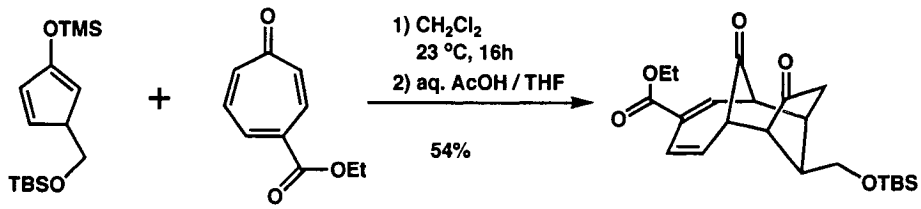
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 7.67 (dd, 1H, J= 5.6, 2.5), 6.21 (dd, 1H, J=5.6, 1.9), 3.74 (dd, 1H, J=10.0, 5.6), 3.61 (dd, 1H, J= 10.0, 6.6), 3.13 (m, 1H), 2.45 (dd, 1H, J=18.4, 6.5), 2.12 (dd, 1H, J=18.4, 2.2), 0.89 (s, 9H), 0.06 (s, 6H)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 209.69, 166.01, 134.92, 64.84, 44.19, 37.47, 25.75, 18.21, -5.41

FTIR (neat, 23 °C) 2954.44 (m) 2928.83 (m), 2856.85 (m), 1716.95 (s) 1471.94 (w), 1254.31 (m), 1183.76 (w), 1093..61 (m), 837.79 (s), 776.77 (m)

HRMS (FTMS, H^+) Expected for $C_{12}H_{23}O_2Si^+$: 227.1460 Found: 227.1462

TLC (10% EtOAc / hexanes) R_f = 0.27 (UV, Mn)



Diene **118**:

To N,N-diisopropylamine (7.2 mL, 51.6 mmol) in 150 mL THF at –20 °C was added n-butyllithium (18.0 mL of a 2.45 M solution in hexanes, 44.1 mmol). After 15 min, the solution was cooled to –78 °C. After a further 15 minutes, a cooled, yellow solution of enone **132** (9.21 g, 40.7 mmol) in THF (30 mL, followed by 2 x 10 mL rinse) was added via cannula over 8 min. During the addition the solution slowly turned from yellow to red. After 30 minutes, TMSCl (7.0 mL, 55 mmol) was added, and the solution turned yellow. After 5 minutes, the solution was allowed to warm to room temperature and then concentrated under reduced pressure. The resulting oil and salt byproducts were triturated with pentane and filtered. The yellow oil, now free of salts, was taken up in 100 mL pentane, washed with H_2O (3 x 50 mL) and pH 7 phosphate buffer (3 x 50 mL) until at neutral pH, dried with Na_2SO_4, filtered, and concentrated to give 12.16 g (99% crude yield) of the diene **118**.

See Appendix A for copies of spectra

^{1}H NMR (400 MHz, $CDCl_3$ 23 °C) 6.39 (d, 1H, J=5.6), 6.19 (d, 1H, J=5.6), 5.22 (d, 1H, J=1.6), 3.58 (dd, 1H, J=9.1, 8.4), 3.49 (dd, 1H, J=9.1, 8.4), 3.25 (t, 1H, J=8.4), 0.91 (s, 9H), 0.25 (s, 9H)

[6+4] cycloadduct **133**:

To tropone **41** (2.51 g, 14.1 mmol) in CH_2Cl_2 (10 mL) at 23 °C was added diene **118** (12.16 g, 40.8 mmol) in CH_2Cl_2 (5 mL, followed by 2 x 5 mL rinse). The reaction mixture was stirred at -5^0 C overnight, during which it turned dark brown. The next day the solvent was removed under reduced pressure. THF (100

mL), H_2O (30 mL) and glacial acetic acid (30 mL) were added, and the mixture was stirred at room temperature. After 1h, TLC analysis indicated complete removal of the silyl enol ether. Ethyl acetate (100 mL) and brine (100 mL) were added, and the organic phase washed with saturated $NaHCO_3$ until the aqueous layer was no longer acidic followed by a final wash with brine. The organic phase was then dried (Na_2SO_4), filtered, and concentrated. Column chromatography (gradient, 5% EtOAc / hexanes to 50% EtOAc / hexanes) yielded the cycloadduct **133** (3.09 g, 54% yield) along with 2.2 g (9.7 mmol) of enone **132**.

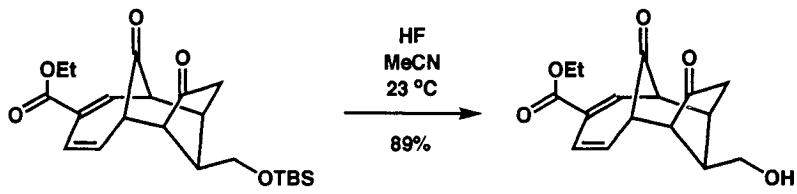
^1H NMR (400 MHz, $CDCl_3$ 23 °C) 6.99 (d, 1H, J=8.0), 6.72 (d, 1H, J=11.9), 5.78 (dd, 1H, J= 11.9, 7.7), 4.26 (t, 2H, J=7.1), 3.67 (dd, 1H, J=10.8, 3.6), 3.61 (dd, 1H, J=10.8, 3.6), 3.37 (m, 2H), 2.85-2.91 (m, 2H), 2.80 (dd, 1H, J=18.8, 7.5), 2.56 (s, 1H), 2.24 (dd, 1H, J=2.2, 18.8), 1.32 (t, 3H, J=7.1), 0.84 (s, 9H), 0.01 (s, 6H), 0.00 (s, 6H)

^{13}C NMR (75 MHz, $CDCl_3$ 23 °C) 213.50, 205.52, 165.97, 135.02, 131.57, 126.75, 125.77, 63.59, 61.65, 60.13, 57.43, 57.24, 44.26, 42.90, 39.61, 25.81, 18.22, 14.26, -5.49, -5.50

FTIR (neat, 23 °C) 2953.77 (m), 2938.56 (m), 2857.48 (m), 1748.64 (s), 1718.64 (s), 1469.27 (w), 1409.8 (w), 1364.51 (w), 1257.60 (s), 1240.3 (s), 1110.44 (m), 1049.32 (m), 838.48 (s), 778.26 (m)

HRMS: (FTMS, Na^+) Calculated for $C_{22}H_{32}SiO_5Na^+$: 427.19041 Found: 427.19112

TLC: (20% ethyl acetate/hexanes) Rf= 0.31 (UV, Mn)



Diketone alcohol **119**:

To diketone **133** (56.0 mg, 0.138 mmol) in acetonitrile (1.0 mL) at 0 °C was added HF (0.22 mL of a 2.5% solution in MeCN, 0.28 mmol). The solution slowly warmed to room temperature over 4h, after which it was quenched with saturated $NaHCO_3$ solution (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to give a yellow oil. Column chromatography (70% EtOAc / hexanes) gave 35.6 mg (0.123 mmol, 89%) of alcohol **119** as a white oil.

See Appendix A for copies of spectra and structural assignment

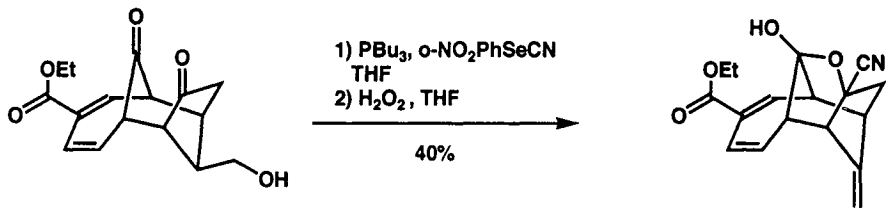
^{1}H NMR (400 MHz, 23 °C): 7.00 (1H, d, 8.1 Hz) 6.73 (1H, d, 12.1 Hz) 5.78 (1H, dd, 7.61, 10.6 Hz) 4.26 (2H, q, 7.1 Hz) 3.63 (2H, dd, 7.6, 2.5 Hz) 3.38-3.43 (2H, m), 2.94 (2H, m) 2.75 (1H, dd, 19.4, 7.3 Hz) 2.64 (1H, m) 2.32 (1H, d, 19.4 Hz) 1.34 (3H, t, 7.1 Hz)

^{13}C NMR (100 MHz, 23 °C) : 214.4, 205.57, 166.07, 134.89, 131.53, 126.48, 125.79, 62.49, 61.86, 59.71, 57.20, 57.20 (degenerate), 43.86, 42.06, 39.57, 14.26

HRMS(EI): Calculated for $C_{16}H_{18}O_5$: 290.1154 Found 290.1160

FTIR: 3466.10 (br), 2957.77 (m), 1743.80 (s), 1715.48 (s) 1259.86 (m), 1242.16 (m), 1082.23 (w), 1045.99 (m), 733.04 (m)

TLC: (70% Ethyl acetate/hexanes) R_f = 0.39



Alkene cyanohydrin **134**:

To alcohol **119** (485.3 mg, 1.67 mmol) in THF 8.0 mL was added o-NO_2PhSeCN (0.420 g, 1.85 mmol) and 3Å MS (0.509 g). The brown suspension was stirred for 30 min at 0 °C whereupon freshly distilled PBu_3 (0.460 mL, 1.82 mmol) was added dropwise. The reaction mixture immediately turned reddish purple, which slowly faded to brown over time. After 2h the reaction was partitioned between EtOAc (20 mL) and H_2O (20 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Column chromatography (20% EtOAc / hexanes to 80% EtOAc / hexanes in 20% increments) gave 516 mg (61%) of the selenide cyanohydrin **198** as a yellow foam. The cyanohydrin was typically contaminated with a minor amount of the inseperable diketone (ratio ~5:1).

For the selenide cyanohydrin **198**:

TLC: (50% Ethyl acetate/hexanes) $R_f = 0.38$ (UV, Mn)

^{13}C NMR (100 MHz, 23 °C) 166.16, 147.32, 137.54, 133.45, 130.97, 130.75, 129.39, 127.22, 127.14, 126.26, 125.95, 118.13, 101.14, 74.72, 61.55, 57.31, 54.88, 49.64, 48.03, 44.70, 39.77, 27.82, 14.33

To the purified selenide (468 mg, 0.926 mmol) in THF (5.0 mL) at 23 °C was added 50% H_2O_2 (0.110 mL, 1.6 mmol). The solution slowly developed a bright yellow colour and a white precipitate crashed out of solution. After 4 days, glacial

acetic acid (20 mL) and zinc powder (275 mg, 4.2 mmol) were added. The grey slurry was stirred for 30 minutes and then poured into a separatory funnel. Ethyl acetate (50 mL) was added, and the layers were separated. The organic layer was washed with $NaHCO_3$ (3 x 50 mL) and the aqueous layer back extracted with ethyl acetate (50 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. Column chromatography (0% EtOAc / hexanes to 40% EtOAc / hexanes in 10% increments) gave **134** as a colourless powder (182 mg, 66% yield).

See Appendix A for copies of spectra and structural assignment

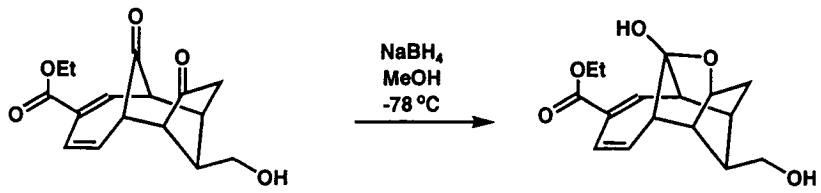
^{1}H NMR: (400 MHz, 23 °C) 6.78 (d, 1H, 8.4 Hz), 6.58 (d, 1H, 12.5 Hz), 5.54 (dd, 12.4, 7.2 Hz), 5.07 (s, 1H), 4.68 (s, 1H), 4.22 (q, 2H, 7.2 Hz), 3.47 (d, 1H, J=6.42 Hz), 3.23 (m, 1H), 3.07 (s, 1H), 2.87 (m, 2H), 2.50 (d, 1H, 11.7 Hz), 2.01 (dd, 1H, 11.7, 3.52 Hz), 1.32 (t, 3H, J=7.2 Hz)

^{13}C NMR: (100.6 MHz, 23 °C) 166.70, 145.41, 136.11, 130.04, 126.35, 125.83, 118.00, 110.37, 101.28, 74.61, 61.48, 56.41, 55.93, 50.02, 48.01, 47.44, 14.31

FTIR (neat, 23 °C) 3411.5 (br, OH), 2982.1 (m, C-H), 2247.0 (w, CN), 1711.3 (s, C=O), 1241.2 (s), 1054.7 (s), 759.9 (s)

HRMS (EI): Calculated for $C_{17}H_{17}N_1O_4$: 299.1157 Obtained 299.1163

TLC (50% Ethyl acetate/hexanes) R_f = 0.67 (UV, Mn)



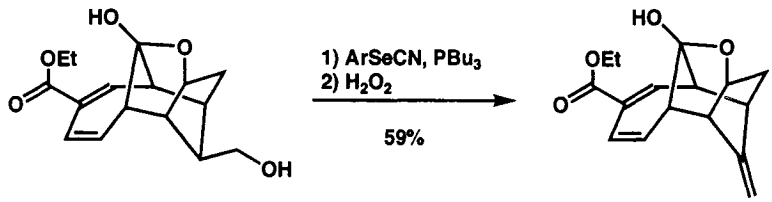
Reduced [6+4] cycloadduct **199**:

To alcohol **119** (70.0 mg, 0.241 mmol) in MeOH (1.0 mL) at –78 °C was added $NaBH_4$. After 45 min, saturated NH_4Cl (10 mL) was added. The solution was warmed to room temperature, and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to give a crude oil **199** that was submitted without purification to the next step.

^1H NMR (300 MHz, $CDCl_3$, 23 °C) 6.88 (d, 1H, J=8.6), 6.64 (dd, 1H, J=12.6, 1.1), 5.75 (dd, 1H, J=12.6, 7.1), 4.47-4.57 (m, 1H), 4.20 (q, 2H, J=7.1), 3.39 (d, 2H, J=7.5), 2.84-2.93 (m, 1H), 2.75-2.84 (m, 1H), 2.64 (dd, 1H, J=5.9. 5.4), 2.51-2.54 (m, 1H), 2.46 (t, 1H, J=7.5), 2.01-2.09 (1H, obs), 1.85 (dt, 1H, J=12.9, 3.5), 1.31 (t, 3H, J=7.1)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 167.2, 139.5, 130.3, 129.5, 126.2, 99.6, 77.8, 63.3, 61.3, 55.2, 50.9, 46.7, 44.8, 43.5, 40.2, 14.2

TLC (100% Ethyl acetate / hexanes) $R_f = 0.21$ (UV, Mn)



Alcohol **137**:

To alcohol **199** (102.4 mg, 0.350 mmol) in THF (2.0 mL) was added o-NO_2PhSeCN (87.4 mg, 0.384 mmol) and 4Å molecular sieves. After stirring for 30 min, the brown mixture was cooled to –78 °C and PBu_3 (0.100 mL, 0.615 mmol) was added dropwise. A wine-red colour was observed upon addition of the PBu_3. The mixture was left to warm slowly overnight, during which the wine-red colour faded to brown. The next day, the volatile liquids were removed via rotary evaporation and the crude mixture carried through to the next step.

To the crude selenide in THF (1.5 mL) at room temperature was added 50% H_2O_2 (0.050 mL, 0.73 mmol). After 4 h, dimethyl sulfide (~0.25 mL, excess) was added to quench the remaining H_2O_2, and the reaction mixture was stirred at room temperature. After 10 d (analysis of aliquot by ^{1}H NMR) the reaction mixture was concentrated. AcOH (1 mL) was then added, followed by zinc dust (50 mg, 7.6 mmol), and the mixture was stirred vigorously for 30 min. the yellow colour of the o-NO_2PhSeOH quickly dissipated. After 30 min, the slurry was filtered through Celite and concentrated. Silica gel column chromatography (30% EtOAc / hexanes to 40% EtOAc / hexanes) gave alcohol **137** (57 mg, 0.21 mmol, 59%) as a pale yellow oil.

See Appendix A for copies of spectra

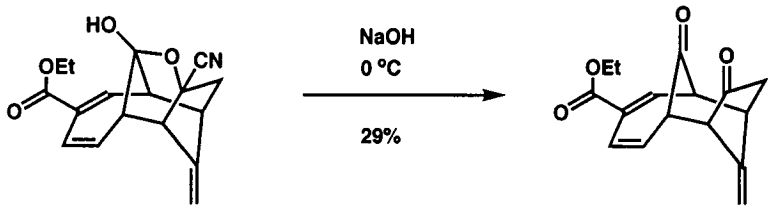
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 6.80 (d, 1H, J=8.4), 6.53 (dd, 1H, J= 12.4, 1.1), 5.55 (dd, 1H, J= 12.4, 7.0), 4.94 (s, 1H), 4.68 (m, 1H), 4.53 (s, 1H), 4.21 (q, 2H, J=7.2, 1.8), 3.10 (m, 1H), 3.03 (m, 1H), 2.82 (m, 1H), 2.78 (s, 1H), 2.72 (m, 1H), 2.17 (d, 1H, J=12.0), 1.62 (dt, 1H, J=12.0, 3.6)

^{13}C NMR (100 MHz, $CDCl_3$, 23 °C) 167.14, 149.47, 137.45, 129.64, 127.80, 125.27, 107.75, 99.37, 77.58, 61.18, 57.34, 51.41, 49.66, 47.56, 43.82, 14.34

FTIR (neat, 23 °C) 3390.57 (br), 2917.15 (s), 2849.14 (s), 1713.33 (m), 1462.07 (m), 1380.48 (w), 1232.32 (w), 1113.95 (m), 755.53 (w), 721.38 (w), 619.02 (w)

HRMS (FTMS, H^+) Calculated for $C_{16}H_{19}O_4^+$: 275.12752 Found: 275.12779

TLC (50% Ethyl acetate / hexanes) $R_f = 0.26$



Diketone **120**:

Cyanohydrin **134** (36 mg, 0.12 mmol) was dissolved in 10 mL ethyl acetate and transferred to a separatory funnel. This was washed with ice-cold 1M NaOH (3 x 10 mL). The aqueous layer turned canary yellow. After the three washes, the organic phase was washed with 10 mL saturated NH_4Cl. The organic layer was dried (Na_2SO_4), filtered, and concentrated to give a brown oil. This was purified by column chromatography (20% EtOAc / hexanes) to give 9.7 mg (29%) of diketone **120** as a colourless oil.

See Appendix A for copies of spectra

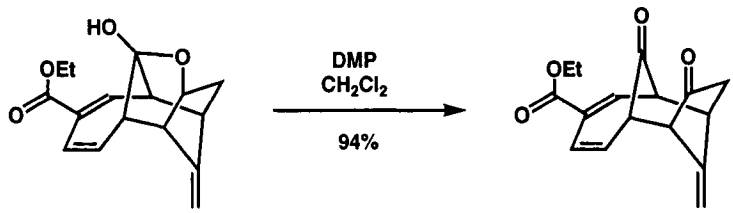
^{1}H NMR: (400MHz, $CDCl_3$, 23 °C) 6.85 (d, 1H, J=7.4), 6.62 (d, 1H, J=6.62) 5.57 (dd, 1H, J=12.0, 7.1), 5.22 (s, 1H), 5.13 (s, 1H), 4.24 (q, 2H, J=6.9) 3.48-3.50 (m, 2H), 3.21 (d, 1H, J=7.3Hz) 2.98 (m, 1H), 2.82 (dd, 1H, J=18.8, 7.4) 2.62 (d, 1H, J=18.8Hz) 1.33 (t, 3H, J=6.9)

^{13}C NMR: (75 MHz, $CDCl_3$, 23 °C) 210.06, 204.49,166.31, 142.36, 133.71, 130.89, 125.47, 124.63, 115.74 61.60, 60.24, 59.87, 59.43, 49.15, 46.24, 14.16

FTIR (neat, 23 °C) 2924.45 (m), 1751.22 (s), 1714.76 (s)m 1310.78 9w), 1252.88 (s), 1234.84 (s), 1086.41 (w), 1049.81 (m), 781.65 (w), 716.08 (w)

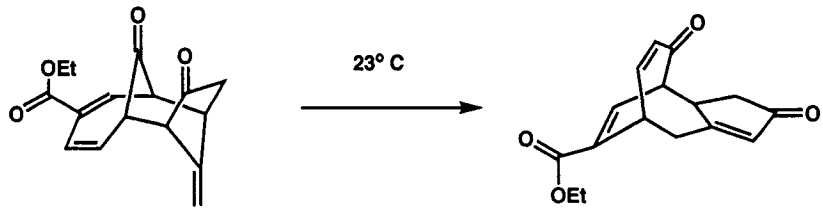
HRMS (EI) Calculated for $C_{16}H_{16}O_4$: 272.1048 Found: 272.1042

TLC: (50% Ethyl acetate/hexanes) R_f= 0.76 (UV, Mn)



Alternative experimental for diketone **120**:

To alcohol **137** (25 mg, 0.091 mmol) in CH_2Cl_2 (1.0 mL) was added DMP (205 mg, 0.477 mmol). After 50 min, the reaction was quenched with a mixture of Et_2O (3 mL), saturated aqueous $NaHCO_3$ (3 mL), and saturated aqueous $Na_2S_2O_3$ (1 mL) and stirred until the organic layer became clear (45 min). Brine (10 mL) was added, and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Silica gel column chromatography (10% EtOAc / hexanes to 30% EtOAc / hexanes in 10% increments) gave the desired diketone **120** (23.4 mg, 94%) as a clear, pale-yellow oil.



Cope rearrangement product **138**:

The formation of the Cope rearrangement product **138** could be observed by monitoring a solution of purified diketone **120** in $CDCl_3$ by NMR at 23 °C. Approximately 90% conversion to the rearranged product occurred over 10 days.

See Appendix A for copies of spectra and structural assignment

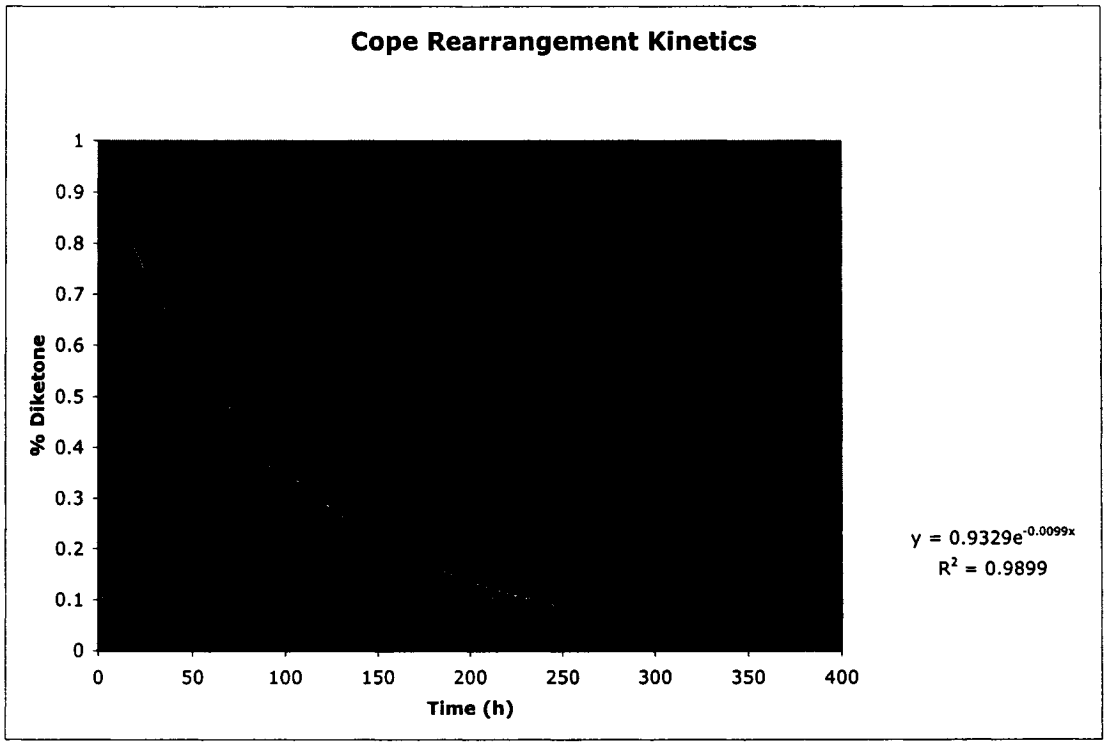
^{1}H NMR: (300 MHz, $CDCl_3$, 23 °C) 7.30 (dd, 1H, J=9.0, 1.7), 6.77 (dd, 1H, J= 11.7, 9.0), 6.04 (dd, 1H, J=11.7, 1.4), 5.97 (dd, 1H, J=1.8, 1.7), 4.26 (q, 2H, J=7.1), 4.26 (m, 1H), 3.51 (ddd, 1H, J=9.0, 3.3, 1.4), 3.19 (m, 1H), 3.00 (dd, 1H, J=14.4, 5.4), 2.70 (d, 1H, J=14.4), 2.63 (dd, 1H, J=19.2, 6.70), 2.32 (dd, 1H, J= 19.2, 2.8), 1.34 (t, 3H, J=7.1)

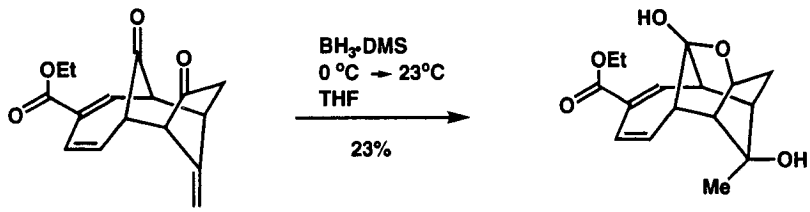
^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): 204.66, 193.02, 176.09, 165.57, 147.18, 141.21, 138.68, 136.20, 133.23, 61.73, 56.55, 42.60, 39.24, 36.06, 34.45, 14.32

HRMS (EI) Calculated for $C_{16}H_{16}O_4$: 272.1048 Found: 272.1042

FTIR: 2979.17 (w), 2929.65 (w), 1706.4 (s) 1650.05 (m) 1613.43 (w), 1391.66 (w) 1254.94 (s)

TLC: 50% Ethyl acetate/hexanes $R_f = 0.39$


Cope Rearrangement Kinetics
% Diketone
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
50
100
150
200
250
300
350
400
Time (h)
y = 0.9329e-0.0099x
R2 = 0.9899



Markovnikoff hydroboration product **139**:

To a solution of diketone **120** (23.4 mg, 0.086 mmol) in THF (0.5 mL) at 0 °C was added borane-dimethylsulfide complex (20 μL, 0.19 mmol). After 15 minutes the ice bath was removed. After 2h, a solution of 50% H_2O_2 (40 μL) in EtOH (1 mL) was added. Gas evolution was observed. After 30 minutes, triethanolamine (30 mg) was then added, and the solution stirred overnight. The reaction was partitioned with brine (10 mL) and extracted with EtOAc (5 x 10 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated. Column chromatography (30%-50%-70%-90%-100% ethyl acetate/hexanes gave Markovnikoff hydroboration product **139** (5.7 mg, 23%) along with 8mg of a complex mixture of more polar byproducts that could not be separated.

See Appendix A for copies of spectra

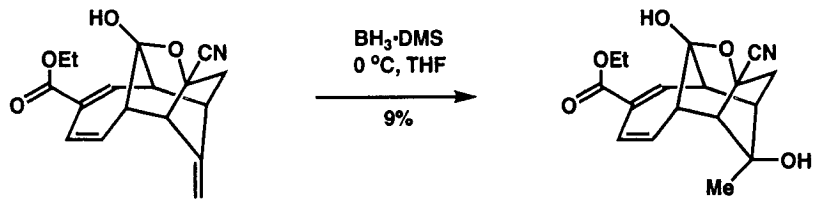
^{1}H NMR (500 MHz, $CDCl_3$, 23 °C) 6.95 (d, 1H, J=8.7), 6.63 (d, 1H, J=12.2), 5.90 (dd, 1H, J=12.2, 7.9), 4.64 (s, 1H), 4.21 (t, 2H, J=7.1), 2.89-2.94 (m, 1H), 2.88 (s, 1H), 2.76 (dd, 1H, J=12.5, 7.5), 2.72 (ddd, 1H, J=12.0, 4.0, 3.6), 2.57-2.60 (m, 1H), 2.30 (s, 1H), 1.92 (d, 1H, J=12.0), 1.79 (s, 1H), 1.62 (s, 3H), 1.31 (t, 3H, J=7.1)

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C) 167.02, 140.22, 137.55, 130.89, 126.47, 99.45, 80.32, 78.91, 61.31, 55.96, 54.22, 51.80, 49.27, 40.71, 23.37, 14.19

FTIR (neat, 23 ° C) 3399.68 (br), 2927.43 (m), 1709.06 (s), 1449.45 (w), 1369.42 (m), 1263.95 (s), 1235.90 (s), 1111.12 (m), 1057.92 (m), 1034.49 (m), 1010.20 (m), 903.88 (w), 744.88 (m)

HRMS (FTMS, H^+) Expected for $C_{16}H_{21}O_5^+$: 293.1838 Found: 293.13835

TLC (100% Ethyl acetate) $R_f = 0.32$ (UV, Mn)



Markovnikoff hydroborated cyanohydrin **140**:

To cyanohydrin **134** (40 mg, 0.13 mmol) in THF (1.3 mL) was added borane-dimethyl sulfide complex (25 μL, 0.26 mmol). After 3h a white precipitate was observed. The reaction was cooled to 0 ^{0}C, whereupon a solution of NaOAc (50 mg, 0.6 mmol, ~5 equiv) and 50% H_2O_2 (50 μL, 0.73 mmol, 5 equiv) in EtOH (1 mL) was added. Vigorous gas evolution was observed. The solution was stirred overnight. After 16 h, the reaction was partitioned with brine (10 mL) and extracted with ethyl acetate (4 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. Column chromatography (10% EtOAc / hexanes to 100% EtOAc / hexanes in 10% increments) yielded the Markovnikoff hydroboration product **140** (3.8 mg, 9%) as a clear oil.

See Appendix A for copies of spectra

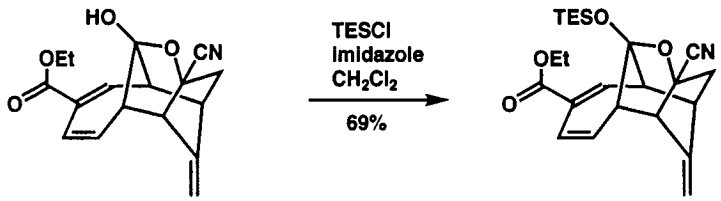
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 6.93 (d, 1H, J=8.2) 6.69 (d, 1H, J=12.2 Hz), 5.87 (dd, 1H, J=12.2, 6.4 Hz), 4.23 (q, 2H, J=7.1 Hz), 3.16 (dd, 1H, J=11.6, 4.2 Hz), 3.04 (s, 1H), 2.96 (s, 2H), 2.44 (s, 1H), 2.24 (d, 1H, 11.6), 1.64 (s, 3H), 1.41 (s, 1H) 1.33 (t, 3H, J=7.1 Hz)

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C) 166.59, 137.77, 131.39, 128.64, 127.40, 118.43, 101.29, 79.65, 75.89, 61.57, 61.45, 54.88, 50.45, 49.39, 45.40, 22.97, 14.16

FTIR (neat, 23 °C) 3431.8 (br), 2927.59 (m), 2853.1 (w), 2246.76 (w), 1786.0 (w), 1709.8 (s), 1447.9 (w), 1370.1 (w), 1268.1 (s), 1238.5 (s), 1191.7 (m), 1152.8 (m), 1109.63 (w), 1045.3 (m), 903.45 (m), 748.66 (m)

HRMS (CI, H^+) Calculated for $C_{17}H_{19}NO_5^+$: 318.1341 Found 318.1341

TLC (50% Ethyl acetate / hexanes) Rf = 0.26 (UV, Mn)



Protected cyanohydrin **141**:

Cyanohydrin **134** (41 mg, 0.136 mmol) was dissolved in CH_2Cl_2 (2.0 mL). Imidazole (19.6 mg, 0.288 mmol) was added, then TESCl (46 μL) was added dropwise. A white precipitate formed. After 3h the reaction was partitioned with brine (10 mL) and extracted with ethyl acetate (1 x 10 mL). The organic layer was then dried (Na_2SO_4), filtered and concentrated. Column chromatography (0% EtOAc / hexanes to 20% EtOAc / hexanes in 10 % increments) gave 39.0 mg (69%) of the protected cyanohydrin **141** as a pale yellow oil.

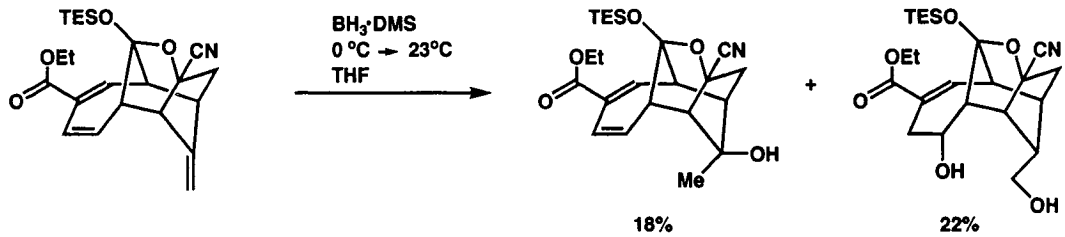
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 6.69 (d, 1H, J=7.0), 6.49 (dd, 1H, J=12.5, 1.2), 5.47 (dd, 1H, J=12.5, 7.1), 4.99 (s, 1H), 4.61 (s, 1H), 4.20 (q, 1H, J=7.2), 3.36 (dd, 1H, J=7.1, 1.5), 3.14 (m, 1H), 2.72 (m, 2H), 2.42 (d, 1H, J=11.7), 1.94 (dd, 1H, J=11.7, 3.8), 1.30 (t, 2H, J=7.2), 0.91 (t, 6H, J=7.6), 0.62 (q, 6H, J=7.6)

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C) 167.14, 146.36, 136.98, 129.83, 126.46, 126.05, 118.48, 109.59, 102.31, 74.53, 61.10, 57.34, 55.72, 51.81, 48.07, 47.54, 14.12, 6.65, 5.93

FTIR (neat, 23 °C) 2956.36 (m), 2877.08 (m) 2246.91 (w), 1714.51 (s) 1390.35 (m), 1259.13 (s) 1236.35 (s), 1189.08 (m), 1056.40 (m), 1000.09 (m) 832.75 (m), 747.38 (m)

HRMS (FTMS) Calculated for $C_{23}H_{32}SiO_4N^+$ 414.20857 Found: 414.20951

TLC (10% EtOAc / hexanes) R_f = 0.45 (UV, Mn)



Hydroboration of protected cyanohydrin **141**:

Protected cyanohydrin **141** (42.3 mg, 0.101 mmol) was dried azeotropically with PhMe (3 x 0.5 mL) dissolved in THF (1.0 mL), and cooled to 0 °C. Borane-dimethylsulfide complex (20 μL, 0.211 mmol) was then added dropwise. After 10 minutes the ice bath was removed, and the reaction allowed to warm to room temperature. After 70 minutes at 23 °C, the reaction again cooled to 0 °C and quenched with a solution of sodium perborate (80 mg, 0.52 mmol) in H_2O (2.0 mL). Vigorous bubbling ensued. After 3h, triethanolamine (0.1 g) in 1 mL H_2O was added. After a further 1h, saturated $Na_2S_2O_3$ (1 mL) was added and the solution stirred for 15 min, whereupon the reaction was partitioned with saturated NH_4Cl (10 mL) and extracted with EtOAc (5 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Column chromatography (20% EtOAc / hexanes to 100% EtOAc / hexanes in 20% increments) gave tertiary alcohol **142** (7.7 mg, 18%), diol **143** (10.0 mg, 22%) and starting cyanohydrin **141** (5.7 mg, 13%).

For the tertiary alcohol **142**:

See Appendix A for copies of spectra and structural assignment

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 6.85 (d, 1H, *J*=9.67), 6.60 (d, 1H, J=12.9), 5.79 (dd, 1H, J=12.9, 6.2), 4.23 (q, 2H, J=7.0), 3.11 (dd, 1H, J= 11.5, 3.8) 2.86 (m, 2H), 2.80 (m, 1H), 2.36 (s, 1H), 2.18 (d, 1H, J=11.5), 1.63 (s, 3H), 1.31 (t, 3H, J=7.0), 0.90 (t, 6H, J=7.8), 0.60 (q, 9H, J=7.8)

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C) 166.93, 139.26, 131.30, 128.99, 127.12, 118.90, 102.29, 79.7, 75.86, 61.27, 61.24, 55.66, 52.19, 49.58, 45.53, 23.09, 14.18, 6.71, 5.91

FTIR (neat, 23 °C) 3500.14 (br), 2956.94 (m), 2877.18 (m), 2246.78 (w), 1712.96 (s), 1458.71 (w), 1385.28 (m), 1268.84 (m), 1240.56 (s), 1194.65 (m), 1070.67 (m), 1046.44 (m), 1005.47 (m), 904.04 (w), 826.64 (w), 742.99 (m)

HRMS (FTMS, H^+) Expected for $C_{23}H_{34}O_5SiN^+$: 432.2201 Found: 432.2201

TLC (1:2 Ethyl acetate / hexanes) $R_f = 0.36$ (UV, Mn)

For the diol **143**:

See Appendix A for copies of spectra and structural assignment

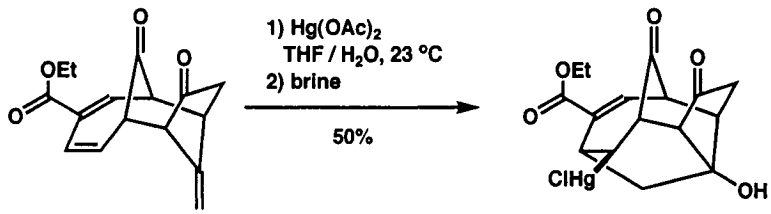
^1H NMR (400 MHz, $CDCl_3$, 23 °C) 6.72 (dd, 1H, J=5.2, 2.9), 4.74 (dm, J=11.6), 4.27 (dd, 1H, J=11.5, 4.5), 4.21 (t, J=7.1), 3.42 (dd, 1H, J=11.6, 5.6), 3.28-3.33 (m, 1H), 3.19 (dm, 1H, J=17.6), 2.99 (dd, 1H, J=17.6, 2.5), 2.92-2.98 (m, 1H), 2.62 (s, 1H), 2.51 (s, 1H), 2.25 (d, 1H, J=11.5), 2.05-2.09 (m, 1H), 1.95 (dd, 1H, J=11.2, 3.5), 1.32 (t, 3H, J=7.1), 0.93 (t, 9H, J=7.9), 0.64 (q, 6H, J=7.9)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 167.7, 138.8, 130.6, 118.7, 104.2, 75.3, 68.9, 61.4, 60.9, 52.8, 50.1, 50.0, 48.6, 46.9, 42.4, 33.7, 14.3, 7.0, 6.2

FTIR (neat, 23 °C) 3401.67 (br), 2955.08 (s), 2877.72 (m), 2245.32 (w), 1705.93 (s), 1458.83 (w), 1385.11 (m), 1296.47 (m), 1269.11 (m), 1235.99 (s), 1185.42 (m), 1065.65 (m), 1013.38 (s), 847.42 (m), 828.20 (m), 740.32 (s)

HRMS (FTMS, H^+) Expected for $C_{23}H_{36}O_6SiN^+$: 450.2309 Found: 450.2306

TLC (80% Ethyl acetate / hexanes) R_f = 0.46 (UV, Mn)



Oxymercuration product **148**:

To diketone **120** (23.8 mg, 0.0875 mmol) in 1:1 THF / H_2O (1 mL) at 23 °C was added $Hg(OAc)_2$ (30.4 mg, 0.095 mmol). A yellow precipitate slowly formed over 10 min. The yellow suspension was stirred overnight, whereupon brine (10 mL) was added. Extraction with EtOAc (3 x 10 mL), followed by drying of the organic layers (Na_2SO_4), filtration and conentration gave 43.8 mg of a crude yellow solid. Column chromatography (20% to 100% EtOAc in 20% increments) yielded organomercury compound **148** (24 mg, 50%) which crystallized from CH_3CN as colourless prisms.

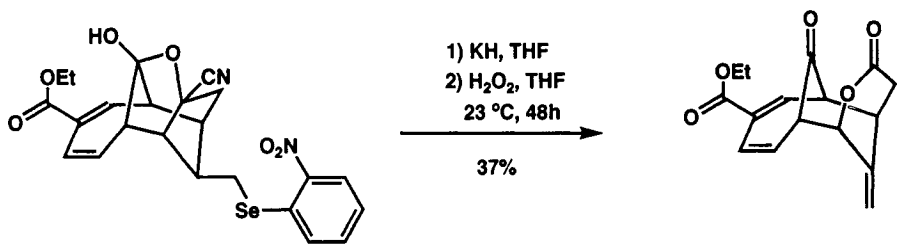
See Appendix A for copies of spectra and structural assignment

^1H NMR: (500 MHz, CD_3CN, 23 °C) 7.11 (d, 1H, J=9.9), 4.26 (q, 2H, J=7.1), 3.82 (m, 1H), 3.36 (d, 1H, J=9.9), 3.30 (m, 1H), 3.12 (dd, 1H, J=18.5, 7.1), 3.05 (dd, 1H, J=4.4, 4.0), 2.60-2.63 (m, 1H), 2.47-2.50 (m, 1H), 2.26-2.28 (m, 2H), 2.11 (d, 1H, J=18.5), 1.67 (s, 1H), 1.34 (t, 3H, J=7.1)

^{13}C NMR (75 MHz, CD_3CN, 23 °C) 215.71, 209.72, 167.31, 146.11, 137.37, 74.91, 62.54, 62.19, 60.85, 57.30, 45.03, 44.40, 39.01, 37.48 (2), 14.37

FTIR (neat, 23 °C) 3445.5 (br), 2925.3 (m), 2852.6 (w), 1745.9 (s), 1699.9 (s), 1650.22 (w), 1558.22 (w), 1540.5 (w), 1507.8 (w), 1457.5 (w), 1277.8 (w), 1237.5 (m), 1071.9 (m), 912.39 (m), 741.2 (m)

TLC: (100% Ethyl acetate) $R_f = 0.54$ (UV, Mn)



Lactone **136**:

To the selenide cyanohydrin **198** (224.5 mg, 0.447 mmol) in THF (2.0 mL) was added 30% KH dispersion in mineral oil (144 mg of dispersion, 1.08 mmol). The reaction mixture bubbled and then turned a dark orange. After 15 minutes the reaction was quenched with saturated NH_4Cl (10 mL) and the aqueous layer extracted with EtOAc (3 x 10 mL), dried (Na_2SO_4), filtered, and concentrated to give a crude selenide diketone **135**(220 mg) which was submitted without purification to the next step.

For the selenide diketone **135**:

^1H NMR: (300 MHz, $CDCl_3$, 23 °C) 8.19 (dd, 1H, J=7.1, 1.4), 7.27-7.48 (m, 3H), 6.89 (d, 1H, J=8.1), 6.56 (d, 1H, J=12.6), 5.69 (dd, 1H, J=12.6, 7.8), 4.15-4.28 (m, 2H), 3.30-3.42 (m, 2H), 3.06 (dd, 1H, J=8.1, 7.6), 2.94-3.00 (m, 1H), 2.69-2.85 (m, 4H), 2.35 (dd, 1H, J=19.8, 1.9), 1.23 (t, 3H, J=7.1)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): 213.10, 204.47, 165.49, 147.30, 137.81, 134.47, 131.51, 130.66, 129.29, 126.30, 126.03, 125.81, 61.90, 60.10, 59.34, 57.20, 44.36, 43.03, 36.32, 26.87, 14.28

To the crude selenide diketone (220 mg, 0.460 mmol) in THF (2.0 mL) was added 30% H_2O_2 (450 μL, 3.97 eq). After 48 hours of stirring at 23 °C, the solution was concentrated and then purified by column chromatography (10% EtOAc / hexanes to 100% EtOAc / hexanes in 10% increments) to give 49.5 mg (37%) of the

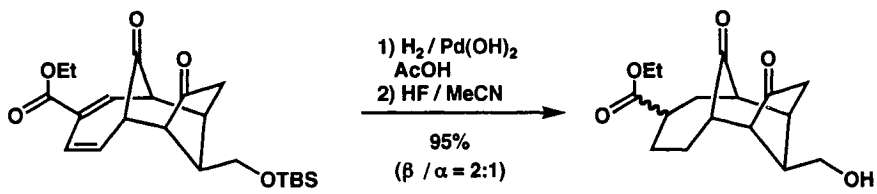
lactone **136** as colourless crystals. The compound was found to be unstable towards silica gel.

^{1}H NMR: (300 MHz, $CDCl_3$, 23 °C): 6.80 (1H, d, 8.5 Hz) 6.60 (1H, d,12.0 Hz) 5.61 (1H, dd, 12.0, 8.4 Hz), 5.35 (1H, s) 5.34 (1H, s), 4.89 (1H, d, 2.7 Hz) 4.22 (2H, q, 7.2 Hz), 3.83 (1H, ddd, 3.3, 2.7, 8.4 Hz) 3.52 (1H, ddd, 8.1, 3.3, 1.7 Hz) 3.00-3.07 (m, 2H) 2.83 (d, 1H, 17.5 Hz), 1.31 (3H, t, 7.2 Hz)

^{13}C NMR: (75 MHz, $CDCl_3$, 23 °C) 202.98, 165.97, 165.84, 136.07, 133.92, 129.64, 125.92, 122.71, 119.92, 83.27, 61.76, 60.61, 60.18, 43.04, 38.32, 14.22

HRMS (EI) Calculated for $C_{16}H_{16}O_5$: 288.0998 Found: 288.1003

TLC (50% Ethyl acetate/hexanes) R_f = 0.34 (UV, Mn)



Saturated [6+4] cycloadduct **157**:

To cycloadduct **133** (3.91 g, 9.67 mmol) in glacial acetic acid (20 mL) was added 20% Pd/OH (0.313 g). The black suspension was placed under an atmosphere of H_2 (balloon). After 48h of vigorous stirring at room temperature, the reaction mixture was filtered through Celite, washed with EtOAc, and concentrated to give 3.60 g of a pale yellow oil. NMR analysis indicated partial deprotection of the primary TBS group. The oil was taken up in MeCN (50 mL) and a solution of HF (9.0 mL of a 5% solution of 48% aqueous HF in MeCN, 10.8 mmol) was added. After 3h the reaction was quenched with 50 mL saturated $NaHCO_3$ and extracted with EtOAc (3 x 50 mL). The organic phase was washed with saturated NH_4Cl solution (50 mL) which was then back-extracted with EtOAc (2 x 50 mL). The combined organic layers were dried (Na_2SO_4) filtered and concentrated. The resulting milky oil was run through a plug of silica gel eluting with 80% EtOAc / hexanes and concentrated to obtain 2.67 g (95%) of a 2:1 mixture of alcohols **157** as a colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$, 23 °C) 4.10* (q, 2H, J=7.1), 4.16 (q, 2H, J=7.1), 3.66-3.76 (m), 3.51-3.62* (m, 2H), 2.94-3.08 (m), 2.69-2.91* (m), 2.65-2.69* (m), 2.55* (d, 1H, J=7.1), 2.44-2.47* (m), 2.17-2.33 (m), 1.86-2.09* (m), 1.44-1.59* (m), 1.23* (t, 3H, J=7.1)

* donates major isomer

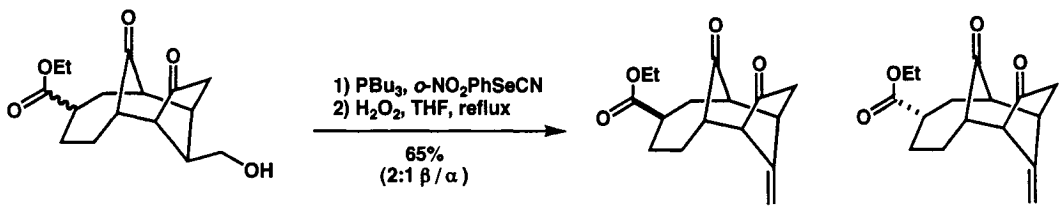
^{13}C NMR (125 MHz, $CDCl_3$, 23 °C) (β-ester epimer, major product) 215.59, 211.36, 174.63, 62.86, 60.85, 56.24, 55.96, 52.06, 45.24, 41.50, 40.61, 39.67, 31.63, 28.23, 25.60, 14.09

(α-ester epimer, minor product) 215.9, 211.6, 175.0, 62.90, 60.82, 55.65, 53.72, 53.29, 43.07, 39.7, 39.4, 38.85, 30.49, 29.9, 28.34, 14.1

FTIR (neat, 23 °C) 3469 (br), 2937 (m), 2872.7 (w), 1743.1 (s, br) 1449.93 (w) 1380.8 (w), 1189.0, 1085.7 (w), 1032.2 (s)

HRMS(EI): Calculated for $C_{16}H_{22}O_5$: 294.1467 Found 294.1473

TLC: (50% Ethyl acetate/hexanes) $R_f = 0.16$ (Mn)



Alkenes **158** a and **158** b:

To the alcohol **157** (1.22 g , 4.15 mmol of a 2:1 mixture of epimers) in THF at 23°C was added o-NO_2PhSeCN (1.04 g, 4.58 mmol) and 4Å molecular sieves (1.29 g). The brown solution was cooled to –70 °C and PBu_3 (1.20 mL, 4.75 mmol) was added dropwise, causing the solution to slowly turn bright red. The reaction was allowed to warm to room temperature overnight, whereupon the reaction mixture was filtered, washed with ethyl acetate (200 mL) and concentrated. The brown oil was purified via flash column chromatography (20% EtOAc / hexanes to 100% EtOAc / hexanes in 20% increments) to give 1.58 g (76.3%) of selenide as crystalline yellow cubes (mp 142 °C).

The selenide (1.58 g, 3.11 mmol) was taken up in THF (30 mL) at 23 °C whereupon 50% H_2O_2 (0.45 mL, 6.61 mmol) was added. The reaction mixture slowly changed colour from bright yellow to pale yellow. After stirring overnight (16h), dimethyl sulfide (1.14 mL, 15.5 mmol) was added. When TLC and starch paper indicated complete consumption of H_2O_2 (~1h) the reaction mixture was heated to reflux. After 24h, the solution was allowed to cool and then concentrated under reduced pressure. The residue was taken up in glacial acetic acid (10 mL) and Zn dust (0.6 g) added to reduce the seleninic acid contaminant. After 30 minutes, the slurry was filtered through Celite and concentrated. The residue was further dissolved in EtOAc (10 mL), washed with saturated $NaHCO_3$ (10 mL), 1M HCl (10 mL), and brine (10 mL), dried (Na_2SO_4), and concentrated. NMR analysis indicated a mixture of cyanohydrins and diketones. The cyanohydrins were removed by dissolving the mixture in CH_2Cl_2 (10 mL) and

NEt_3 (3 mL) and stirring for 30 min at room temperature. After concentration and removal of the selenium-containing byproducts through a plug of silica, the 2:1 mixture of olefinic diketones **158** was obtained as a colourless oil (745 mg, 88% for the oxidation, 65% over 2 steps). The epimeric olefins could be separated through repeated column chromatography (10% EtOAc / hexanes to 50% EtOAc / hexanes in 10% increments).

α-ester epimer **158a** (minor product, faster eluting)

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 5.33 (s, 1H), 5.31 (s, 1H), 4.09 (q, 2H, J=7.1), 3.03 (d, 1H, J=11.9), 2.96-2.99 (m, 2H), 2.74-2.76 (m, 1H), 2.58 (dd, 1H, J=18.8, 7.1), 2.28-2.42 (m, 2H), 2.30 (d, 1H, J=18.8), 2.14 (ddd, 1H, J=12.4, 12.0, 3.2), 2.07 (ddd, 1H, J= 14.4, 6.8, 3.0), 1.91 (d, 1H, J=12.4), 1.66-1.83 (m, 2H), 1.23 (t, 3H, J=7.1)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 210.46, 210.11, 174.88, 146.04, 112.94, 60.68, 59.94, 55.63, 53.87, 46.38, 45.15, 43.20, 31.32, 29.38, 28.59, 14.22

FTIR (neat, 23 °C) 2933.77 (m) 1750.31 (s), 1727.40 (s), 1675.95 (w), 1443.72 (w), 1316.26 (m), 1237.02 (m), 1187.99 (s), 1127.40 (w) 1028.71 (w), 909.70 (w)
HRMS (EI) : Calculated for $C_{16}H_{20}O_4$ 276.1361 Found: 276.1366

TLC: (50% Ethyl acetate/hexanes) $R_f = 0.72$ (Mn)

β-ester **158b** (major product, slower eluting)
See Appendix A for copies of spectra
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 5.47 (s, 1H), 5.20 (s, 1H), 4.10 (q, 2H, J=7.1) 3.24 (ddd, 1H, 12.0, 4.2, 3.7 Hz) 3.12 (ddd, 1H, 6.7, 3, 3), 3.03 (d, 1H, J=10.3 Hz), 2.85 (m, 2H), 2.56 (ddd, 1H, J=18.8, 7.2, 1 Hz) 2.28 (d, 1H, 18.8 Hz), 2.22

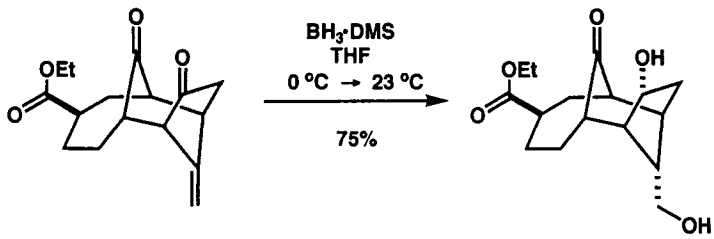
(m, 1H), 2.13 (d, 1H, 13.9 Hz), 2.06 (d, 1H, 12.9 Hz), 1.9 (ddd, 1H, 14, 13.1, 6.3 Hz), 1.57 (dd, 1H, 13.5, 2.8 Hz), 1.25 (t, 3H, 7.1 Hz)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 210.66, 210.03, 174.80, 147.09, 112.64, 60.71, 60.61, 56.42, 54.22, 47.64, 45.90, 42.52, 33.32, 28.44, 25.83, 14.25

FTIR (neat, 23 °C) 2921.18 (m), 2851.41 (s), 1746.28 (s), 1730.97 (s), 1650.74 (w) 1511.57 (w), 1457.07 (w), 1264.85(m), 1190.48 (w), 741.96 (s)

HRMS (EI) : Calculated for $C_{16}H_{20}O_4$ 276.1361 Found: 276.1366

TLC : 0.62 (50% Ethyl acetate / hexanes)



Diol **159**:

To olefinic diketone **158b** (27 mg, 0.097 mmol) in THF (1.0 mL) at 23 °C was added borane dimethylsulfide complex (18μL, 0.190 mmol). After 2h, the reaction was quenched by addition of NaOAc (30 mg), EtOH (1.0 mL), and 50% H_2O_2 (30 μL, 0.44 mmol). Vigorous gas evolution followed, and the reaction was then left to stir overnight. The next day, the reaction mixture was partitioned with ethyl acetate (15 mL) and brine (10 mL). The organic fraction was collected, and the aqueous fraction extracted a further two times with 10 mL EtOAc. The collected organic layers were dried (Na_2SO_4), filtered and concentrated, and purified by column chromatography (50% EtOAc / hexanes to 100% EtOAc / hexanes) to give 22 mg (75%) of diol **159** as a colourless foam.

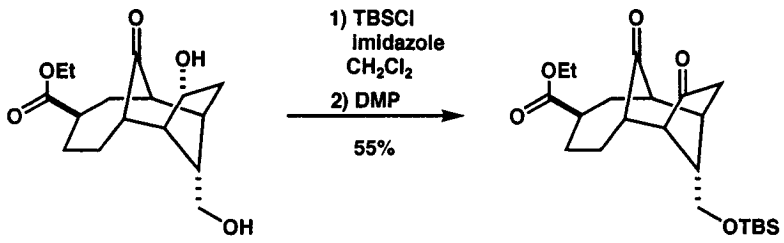
See Appendix A for copies of spectra and structural assignment

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 4.27-4.36 (m, 2H), 4.22 (dd, 1H, J=10.0, 7.5), 4.09 (q, 2H, J=7.1), 3.08 (d, 1H, J=13.6), 2.98 (s, 1H), 2.94 (ddd, 1H, J=12.8, 4.8, 2.0), 2.77 (d, 1H, J=7.3), 2.49-2.54 (m, 1H), 2.49 (dd, 1H, J=14.8, 3.5), 2.42-2.46 (m, 1H), 2.04-2.13 (m, 3H), 1.93 (dd, 1H, J=6.0, 1.8), 1.79-1.83 (m, 1H), 1.67 (d, 1H, J=12.4), 1.56 (m,1H), 1.23 (t, 3H, J=7.1), 1.07 (dd, 1H, J=14.8, 4.0)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 215.32, 175.08, 72.94, 62.15, 60.83, 56.84, 47.29, 46.71, 45.01, 44.25, 41.90, 41.86, 28.82, 27.92, 22.17, 14.24

A minor contaminant in the spectra (~20%) is the hemiacetal tautomer. This was not fully characterized, but was inferred from the peak at δ 4.55 in the ^{1}H spectrum and peaks at δ 104.1 and 77.5 in the ^{13}C spectrum.

HRMS (EI) Calculated for $C_{16}H_{24}O_5$: 296.1624 Found: 296.1619



TBS-protected diketone **160**:

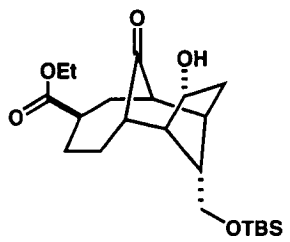
To a clear yellow solution of diol **159** (50 mg, 0.169 mmol) at 0 °C in CH_2Cl_2 (1.0 mL) was added imidazole (19.3 mg, 0.283 mmol), TBSCl (29 mg, 0.192 mmol), and DMAP (one crystal, ~5 mg). Upon addition of TBSCl the solution became cloudy. After 1 h the reaction was partitioned with brine (10 mL). Ethyl acetate (10 mL) was added. The organic phase was washed with 1 M HCl (1 x 10 mL), saturated aqueous $NaHCO_3$ (1 x 10 mL), and saturated NH_4Cl (1 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude silyl ether was carried immediately through to the next step without chromatography.

To the silyl ether **199** in CH_2Cl_2 (1.5 mL) at 0 °C was added DMP (95 mg, 0.22 mmol). After 2 h, a mixture of Et_2O (4 mL), saturated aqueous $NaHCO_3$ (1.5 mL) and saturated aqueous $Na_2S_2O_3$ (1.5 mL) was added. The mixture was stirred until the organic layer became clear (45 min). Brine (10 mL) was added, and the mixture extracted with EtOAc (3 x 10 mL). The organic layers were combined and dried (Na_2SO_4), filtered and concentrated. Column chromatography (10% ethyl acetate / hexanes to 20% ethyl acetate / hexanes) gave diketone **160** (37.5 mg, 55%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 4.22-4.35 (m, 2H), 4.10 (q, 2H, J=7.1), 2.97 (dddd, 1H, J=11.6, 11.6, 6.0, 2.3), 2.82-2.89 (m, 2H), 2.76 (d, 1H, J=12.4), 2.70 (dd, 1H, J=6.8, 3.4), 2.49 (dd, 1H, J=17.6, 6.4), 2.24-2.32 (m, 1H), 1.97-2.16 (m,

5H), 1.69 (dddd, 1H, J=14.4, 13.6, 3.9, 3.5), 1.49-1.59 (m, 1H), 1.23 (t, 3H, J=7.1), 0.91 (s, 9H), 0.10 (s, 3H), 0.10 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 213.1, 211.3, 174.6, 61.4, 60.8, 54.9, 54.4, 50.8, 48.1, 45.0, 44.1, 39.5, 29.1, 27.7, 25.9, 22.8, 18.3, 14.2, -5.1

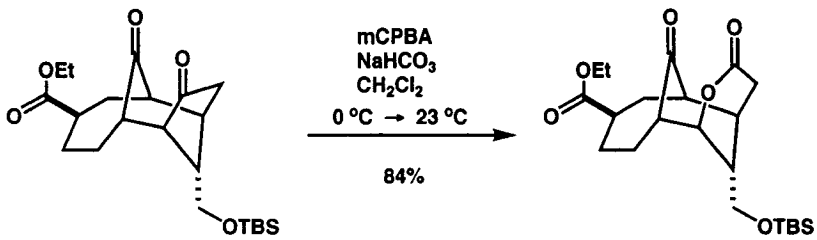


TBS-protected alcohol **199**:

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 4.16-4.32 (m, 3H), 4.11 (q, 2H, J=7.2 Hz), 3.08 (d, 1H, 12.5 Hz), 2.97 (m, 1H), 2.77 (d, 1H, J=8.3 Hz), 2.47 (m, 3H), 1.90-2.09 (m, 4H), 1.84 (m, 2H), 1.66 (m, 1H), 1.25 (t, 3H, J=7.2 Hz), 1.06 (dd, 1H, J=13.9, 4.3 Hz), 0.93 (s, 9H), 0.11 (s, 6H)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 215.55, 175.02, 73.28, 62.16, 60.65, 57.08, 47.47, 46.91, 44.87, 44.21, 42.07, 41.79, 28.94, 27.94, 25.98, 22.35, 18.30, 14.27, -5.05, -5.10

TLC (50% Ethyl acetate/hexanes) R_f = 0.58 (Mn)



Lactone **161**:

To diketone **160** (37 mg, 0.091 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C was added $NaHCO_3$ (25 mg, 0.300 mmol) and mCPBA (27 mg of a 75% mixture (0.12 mmol)). After 14 h, a further portion of mCPBA was added (5.1 mg, 0.022 mmol) and the solution was stirred a further 12h. The reaction was quenched with $Na_2S_2O_3$ (5 mL) and the layers partitioned with EtOAc (5 mL). The organic layer was washed with $NaHCO_3$ (5 mL), and brine (5 mL), then dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash column chromatography (10% EtOAc / hexanes to 50% EtOAc / hexanes in 10% increments) to give 32 mg (84%) of lactone **161** as a colourless foam.

See Appendix A for copies of spectra

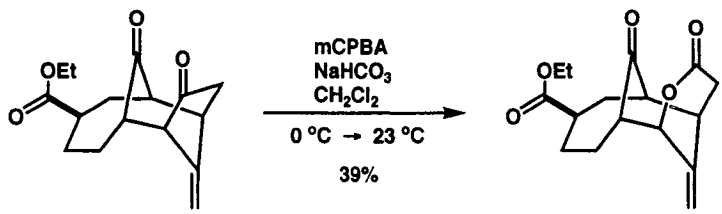
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 4.89 (dd, 1H, J=5.9, 2.4), 4.20 (m, 2H, J=9.7 Hz), 4.12 (q, 2H, J=7.4 Hz), 3.23 (d, 1H, 12.2 Hz), 2.99 (dd, 1H, 18.5, 7.0 Hz), 2.90 (d, 1H, J=7.6 Hz), 2.82 (m, 1H), 2.57-2.62 (m, 3H), 2.0-2.2 (m, 4H), 1.97 (d, 1H, 13.4 Hz), 1.58 (m, 1H), 1.26 (q, 3H, 7.4 Hz), 0.94 (s, 9H), 0.14 (s, 6H)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 210.44, 174.01, 167.92, 80.88, 62.36, 61.00, 54.95, 52.57, 43.73, 43.59, 41.78, 35.93, 30.84, 27.47, 25.90, 20.57, 18.25, 14.24, -5.14

FTIR (neat, 23 °C) 2953.20 (m), 2929.70 (m), 2856.32 (m), 1734.33 (s), 1471.13 (w), 1351.82 (w), 1251.68 (m), 1168.90 (m), 1095.38 (m), 1024.07 (m), 837.83 (s), 778.62 (m)

HRMS (CI, H^+): Calculated for $C_{22}H_{37}O_6Si_1^+$: 425.2359 Found : 425.2359

TLC: (50% Ethyl acetate/hexanes) $R_f = 0.68$ (Mn)



Lactone alkene **200**:

To diketone **158a**(31 mg, 0.11 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added $NaHCO_3$ (17.0 mg, 0.202 mmol) and mCPBA (34.7 mg of 75% mCPBA, 0.151 mmol)). The ice bath was removed after 15 min and the reaction allowed to stir for 5h at 23 °C, whereupon the reaction was partitioned with 10 mL brine and extracted with EtOAc (3 x 10 mL). The combined aqueous layers were washed with 1:1 $NaHCO_3$ / $Na_2S_2O_3$ (20 mL) and the organic phase dried with Na_2SO_4, filtered and concentrated. The residue was purified via column chromatography (10% EtOAc / hexanes to 60% EtOAc / hexanes) to give 12.6 mg (39%) of lactone **200** as a colourless oil.

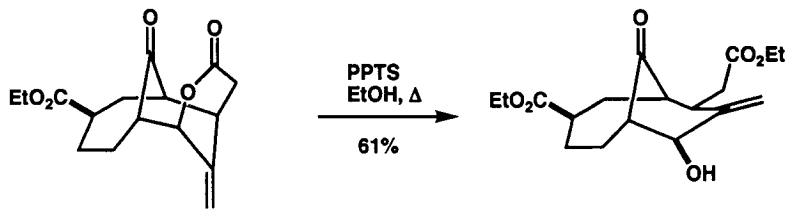
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 5.56 (s, 1H), 5.47 (s, 1H), 4.78 (dd, 1H, J=3.6, 2.1), 4.11 (q, 2H, J=7.1), 3.36 (dm, 1H, J=12.3), 2.97 (m, 1H), 2.93 (dd, 1H, J=16.6, 6.6), 2.81-2.89 (m, 2H), 2.78 (d, 1H, J=16.6), 2.21 (ddd, 1H, J=11.6, 11.3, 4.8), 2.10 (m, 2H), 1.87 (ddd, 1H, J=13.2, 13.1, 5.6), 1.27-1.33 (m, 2H), 1.23 (t, 3H, J=7.1)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 208.91, 174.34, 166.72, 139.00, 117.62, 84.60, 60.89, 55.23, 54.28, 42.38, 42.07, 41.75, 35.83, 29.15, 23.99, 14.24

FTIR: (neat, 23 °C) 2931.84 (m), 1730.43 (s), 1449.05 (w), 1367.79 (w), 1218.00 (w), 1162.45 (m), 1064.34 (w), 1029.45 (m), 1002.55 (w), 930.7 (w)

HRMS (EI) : Calculated for $C_{16}H_{20}O_5$: 292.1311 Found: 292.1315

TLC (50% Ethyl acetate/hexanes) $R_f = 0.39$



Allylic alcohol **201**:

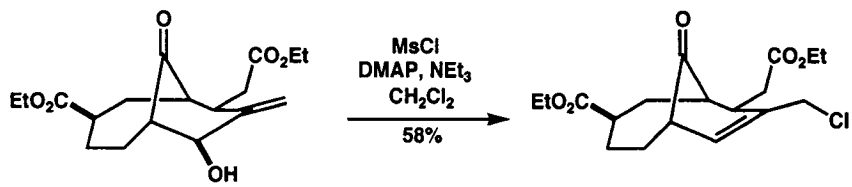
To lactone **200** (9 mg, 0.031 mmol) at 23 °C in EtOH (2.0 mL) was added PPTS (1.5 mg, 0.006 mmol). The solution was refluxed for 10 hours, then let to sit at room temperature overnight. The reaction mixture was partitioned with brine (10 mL) and exracted with ethyl acetate (3 x 10 mL). The organic layer was washed with 9:1 brine /$NaHCO_3$ solution (10 mL), dried (Na_2SO_4), filtered and concentrated. Column chromatography (10% EtOAc / hexanes to 70% EtOAc / hexanes, in 10% increments) yielded 6.4 mg (61%) of alcohol **201** as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 5.56 (s, 1H), 5.47 (s, 1H), 4.78 (dd, 1H, J=3.6, 2.3), 4.10 (q, 2H, J=7.1), 3.36 (dm, 1H, J=12.2), 2.96-2.99 (m, 1H), 2.94 (dd, 1H, J=16.7, 6.6), 2.81-2.87 (m, 2H), 2.78 (d, 1H, J=6.6), 2.17-2.25 (ddd, 1H, J= 12.4, 11.2, 4.4) 2.06-2.13 (m, 2H), 1.87 (ddd, 1H, J=14.4, 13.2, 5.7), 1.26-1.33 (m, 2H), 1.23 (t, 3H, J=7.1)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 211.93, 174.79, 172.18, 144.71, 119.32, 80.79, 60.83, 60.71, 54.78, 52.68, 45.36, 43.63, 42.66, 36.75, 29.31, 24.87, 14.40, 14.28

FTIR (23 °C, neat) 3448.93 (br), 2924.60 (s), 2854.86 (m), 1729.81 (s), 1453.46 (w), 1372.35 (w), 1302.08 (s), 1248.65 (w), 1178.41 (m), 1027.04 (m)

TLC: (50% Ethyl acetate/hexanes) $R_f = 0.53$



Allylic chloride **202**:

To alkene **201** (4.6 mg, 0.013 mmol) in CH_2Cl_2 (0.5 mL) at 23^0 C was added DMAP (~1 mg), triethylamine (15 μL, 0.17 mmol), and methanesulfonyl chloride (10 μL, 0.013 mmol). After stirring at RT for 7h, the mixture was quenched with saturated ammonium chloride solution (10 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layers were dried (Na_2SO_4), filtered, and concentrated. Column chromatography (0% to 70% EtOAc / hexanes in 10% increments) yielded 2.7 mg (58%) of allylic chloride **202** as a colourless oil.

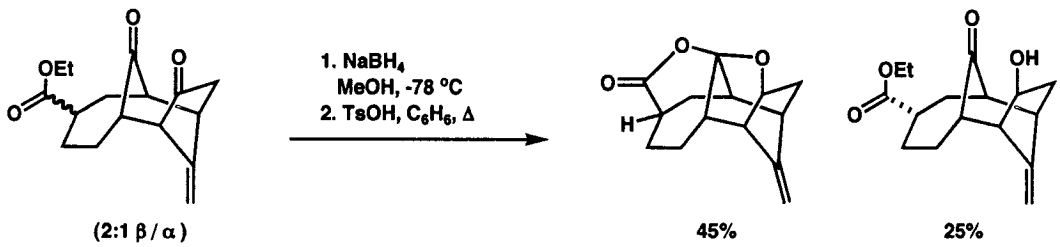
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 5.84 (d, 1H, J=2.8), 4.08-4.16 (m, 6H), 3.09-3.12 (m, 1H), 2.91-2.98 (m, 2H), 2.85-2.91 (m, 1H), 2.45-2.52 (m, 1H, 2.36 (dd, 1H, J=16.5, 5.0), 2.24 (dd, 1H, J=16.5, 9.0), 2.06-2.12 (m, 1H), 1.88-1.94 (m, 1H), 1.79 (d, 1H, J=14), 1.70-1.76 (m, 1H), 1.60-1.65 (m, 1H), 1.24-1.27 (m, 6H)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 212.10, 172.89, 171.16, 136.60, 131.48, 60.91, 60.68, 50.27, 48.83, 47.20, 42.02, 41.27, 37.71, 30.37, 27.99, 27.14, 14.24

FTIR (neat, 23 °C)2979.79 (w), 2929.61 (m), 2857.62 (w), 1729.84 (s), 1445.92 (m), 1374.88 (m), 1306.10 (w), 1261.43 (w), 1233.09 (m), 1176.81 (m), 1027.36 (m), 699.11 (w),

HRMS (FTMS, H^+) Expected for $C_{18}H_{26}O_5Cl^+$: 357.14571 Found: 357.14633

TLC (20% EtOAc / hexanes) R_f = 0.25 (Mn)



(2:1 β / α) 45% 25%

Lactone **162**:

To the 2:1 mixture of epimeric alkenes **158** (729 mg, 2.64 mol) in MeOH (12.0 mL) at –78° C was added $NaBH_4$ (112 mg, 2.96 mmol). The mixture was stirred for 45 minutes whereupon saturated NH_4Cl (10 mL) was added. The mixture was allowed to warm to room temperature. The aqueous mixture was then extracted with EtOAc (3 x 10 mL), dried (Na_2SO_4), filtered, and concentrated to give approximately 800 mg of a crude mixture of alcohols. The crude alcohols were dissolved in benzene (15 mL) and p-TsOH (51 mg, 0.27 mmol) was added. The solution was heated to reflux for 16 hours and then concentrated. Column chromatography (20% EtOAc / hexanes to 60% EtOAc / hexanes in 20% increments) gave 275 mg (45%) of the lactone **162** as white prisms, along with 188 mg (25%) of the epimeric alcohol/ester **163**.

Lactone **162**:

See Appendix A for copies of spectra

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 5.09 (s, 1H), 4.73 (s, 1H), 4.65-4.67 (m, 1H), 2.94 (dd, 1H, J=5.5, 5,4), 2.77 (dd, 1H, J=8.0, 7.7), 2.59 (s, 1H), 2.31-2.37 (m, 1H), 2.11-2.19 (m, 1H), 1.87-2.03 (m, 5H), 1.57-1.63 (m, 1H), 1.49-1.54 (m, 2H)

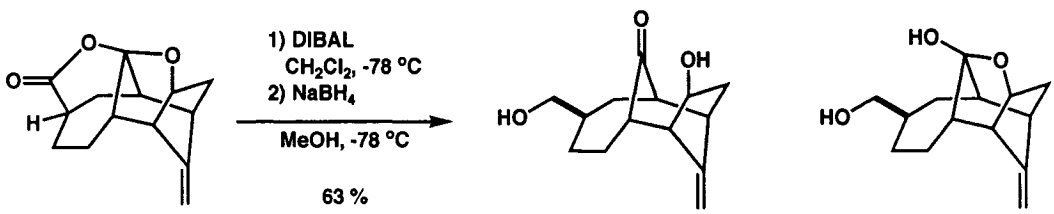
^{13}C NMR (100 MHz, $CDCl_3$, 23 °C) 173.27, 149.78, 108.64, 105.85, 76.89, 48.87, 47.71, 46.32, 42.94, 40.86, 38.24, 26.89, 21.82, 19.76

FTIR (neat, 23 °C) 2924.19(s), 2854.06(m), 1758.81 (s), 1176.35 (w), 1101.03 (s), 913.3 (m), 744.78 (s)

HRMS (EI) Expected for $C_{14}H_{16}O_3^+$: 232.1099 Found: 232.1094

TLC (50% Ethyl acetate / hexanes) R_f = 0.62 (Mn)

m.p. 106 ^{0}C



Diol **164**:

To lactone **163** (817 mg, 3.52 mmol) in CH_2Cl_2 (10.0 mL) at –78 °C was added DIBAL (4.8 mL of a 1.0 M solution in toluene, 4.80 mmol). After 1h the reaction was quenched with saturated sodium potassium tartrated solution in water (10 mL). After warming to room temperature, the solution was extracted with EtOAc (3 x 10 mL), dried, filtered and concentrated to give a crude foam that consisted mostly of an intermediate hemiacetal **203**.

The acetal was dissolved in MeOH (15 mL) at –78 °C and $NaBH_4$ (179 mg, 4.7 mmol) was slowly added. After 1h, a further 48 mg (1.2 mmol) of $NaBH_4$ was added. After a further 30 min, the reaction was quenched with saturated NH_4Cl solution (10 mL) and warmed to room temperature. The solution was warmed to room temperature and extracted with EtOAc (3 x 10 mL), dried (Na_2SO_4) filtered and concentrated. Column chromatography (50% EtOAc / hexanes, then 80% EtOAc / hexanes, then 100% EtOAc / hexanes, followed by a 10% MeOH / EtOAc flush) gave the desired diol **164** (526 mg, 63%) as a mixture of tautomers in $CDCl_3$, along with starting lactone (55 mg, 7%) and a number of other polar compounds (presumably triols) that were not fully characterized.

See Appendix A for copies of spectra

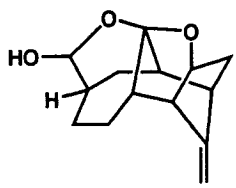
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 5.11 (s), 4.99 (s), 4.96 (s), 4.66 (s), 4.56 (br), 4.37 (br), 3.27-3.41 (m), 3.17-3.25 (m), 2.67-2.79 (m), 2.54-2.61 (m), 2.38-2.52 (m), 2.07-2.20 (m), 1.93-2.02 (m), 1.84-1.92 (m), 1.65-1.79 (m), 1.43-1.61 (m), 1.21-1.36 (m)

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C) 215.1, 154.5, 150.8, 110.1, 105.8, 104.9, 76.3, 70.9, 69.4, 68.7, 58.7, 54.1, 50.6, 50.3, 49.4, 49.1, 47.1, 46.5, 42.8, 40.8, 39.2, 38.5, 34.1, 33.4, 28.6, 27.8, 25.8, 23.5

FTIR (neat, 23 °C) 3363.41 (br), 2931.66 (s), 2862.75, 1700.29 (s), 1445.21 (w), 1138.24 (m), 1054.97 (m) 888.05 (m)

HRMS (FTMS, H^+) Expected for $C_{14}H_{21}O_3^+$: 237.1490 Found: 237.1485

TLC (80% Ethyl acetate / hexanes) $R_f = 0.25$ (Mn)



Hemiacetal **203**:

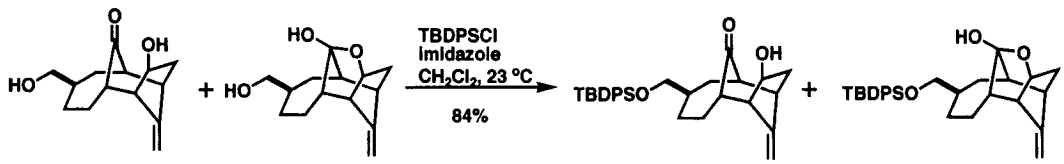
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 5.19 (d, 1H, J=2.6), 5.03 (s, 1H), 4.65 (s, 1H), 4.56-4.58 (m, 1H), 3.35 (s, 1H), 2.82 (dd, 1H, J=6.6, 6.0), 2.44-2.47 (m, 1H), 2.43 (m, 1H), 2.09-2.18 (m, 2H), 1.99 (d, 1H, J=11.8), 1.92-1.98 (m, 2H), 1.75-1.80 (m, 1H), 1.48 (dd, 1H, J=4.0, 3.6), 1.46 (ddd, 1H, J=11.6, 4.0, 3.6), 1.29 (dd, 1H, J=13.5, 8.5), 1.22-1.24 (m, 1H)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 151.81, 106.34, 103.32, 97.67, 77.19, 51.05, 49.11, 47.14, 41.73, 41.56, 35.02, 26.43, 20.61, 20.13

FTIR (neat, 23 °C) 3403.7 (br) 2926.1 (s) 1717.2 (w), 1116.87 (m) 1090.8 (m) 1076.5 (w)l, 1011.5 (s), 976.6 (s) 911.4 (m) 884.6 (m), 873.9 (m)

HRMS (EI) Expected for $C_{14}H_{18}O_3^+$: 234.1256 Found: 234.1250

TLC (50% EtOAc / hexanes) R_f = 0.32 (Mn)



TBDPS-protected alcohol **165**:

To the diol **164** (50 mg, 0.21 mmol) in CH_2Cl_2 (2.0 mL) was added imidazole (17.7 mg, 0.260 mmol) and TBDPSCl (0.231 mmol). The solution was stirred for 3 hours at 23 °C, whereupon the reaction was partitioned with 1M HCl(10 mL) and EtOAc (10 mL). The organic layer was washed further with saturated $NaHCO_3$ (10 mL) and saturated NH_4Cl (10 mL), then dried (Na_2SO_4), filtered and concentrated. Purification via flash chromatography (30% EtOAc / hexanes) gave 84 mg (84%) of the protected alcohol as a colourless foam. The alcohol **165** exhibited ring-chain tautomerism (~60/40 mixture of ketone-alcohol and hemiacetal in $CDCl_3$ solution).

See Appendix A for copies of spectra

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 7.59-7.67 (m, 8H), 7.34-7.43 (m, 10H), 5.05* (s, 1H), 4.96*(s, 1H), 4.90 (s, 1H), 4.65 (s, 1H), 4.52-4.56 (m, 1H), 4.34-4.39* (m, 1H), 3.32-3.38 (m, 4H), 3.20* (d, 2H, J=12.2), 2.75 (dd, 1H, J=6.6, 5.6), 2.71*(d, 1H, J=3.3), 2.39-2.62 (m), 2.10-2.22 (m), 1.85-2.01 (m), 1.42-1.79 (m), 1.25-1.37 (m), 1.06 (s, 9H), 1.05 (s, 9H), 0.85-0.95 (m)

note: due to the 60:40 ratio of tautomers, no attempt was made to deconvolute the multiplets.

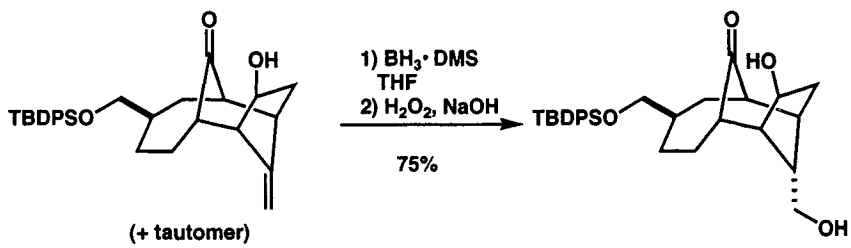
^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 215.48*, 154.88*, 151.09, 135.78, 135.75, 134.32, 134.04, 129.79, 129.69, 127.82, 127.77, 110.06*, 105.82, 105.4, 76.56, 71.25*, 70.29, 69.77*, 59.16*, 54.42*, 50.92, 50.57, 49.74,* 49.49, 47.54, 46.93*, 43.14, 41.14*, 39.58*, 38.81, 34.67*, 33.86, 28.96*, 28.17, 27.24(2)*, 26.28*, 23.98, 19.75, 19.71*

*denotes resonance of alcohol-ketone tautomer

FTIR (neat, 23 °C); 3345.34 (br), 2931.56 (m), 2856.97 (m), 1701.09 (w), 1427.45 (w), 1109.30 (s), 975.83 (w), 887.49 (w), 822.32 (w), 702.54 (s) 505.3 (m)

HRMS (FTMS, H^+) Expected for $C_{30}H_{39}O_3Si^+$: 475.2664 Found: 475.2663

TLC (20% Ethyl acetate / hexanes) $R_f = 0.14$



Diol **166**:

To alkene **165** (822 mg, 1.74 mmol) in THF (8.8 mL) at 23 °C was added borane dimethylsulfide complex (330 μL, 3.48 mmol). After 80 min the reaction was cooled to 0 °C. A solution containing EtOH (2 mL), 1M NaOH (2 mL), and 50% H_2O_2 (300 μL, 4.4 mmol) was then slowly added. Vigorous gas evolution was observed. Atfer 90 min, saturated aqueous NH_4Cl (10 mL) and saturated aqueous $Na_2S_2O_3$ (10 mL) were added. The mixture was extracted with EtOAc (3 x 15 mL), dried (Na_2SO_4), filtered, and concentrated. Column chromatography (20% EtOAc / hexanes to 100% EtOAc / hexanes in 20% increments followed by 5% MeOH / EtOAc flush) gave 640 mg (75.0 %) of diol **166** as a white foam. In $CDCl_3$ at 23 °C the diol contained ~20% of the ring-closed tautomer.

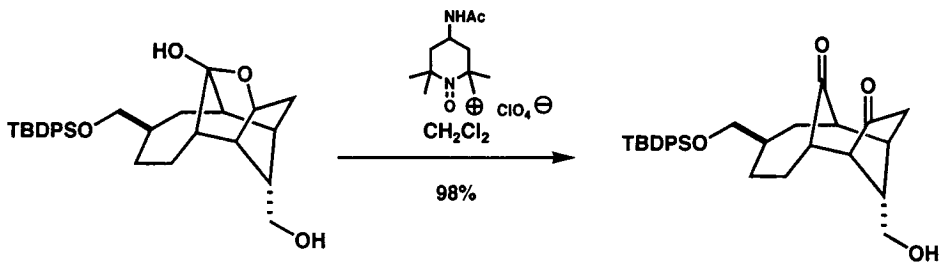
^{1}H NMR (500 MHz, $CDCl_3$, 23 °C) 7.61-7.64 (m, 4H), 7.37-7.44 (m, 6H), 4.26-4.31 (m, 2H), 4.14 (dd, 1H, J=10.0, 7.5), 3.43 (dd, 1H, J=10.0, 5.5), 3.05 (dm, 1H, J=12.5), 2.68 (J=7.6), 2.49-2.52 (m, 1H), 2.43-2.48 (m, 1H), 2.36-2.39 (m, 1H), 2.09-2.16 (m, 1H), 2.09 (s, 1H, hydroxyl), 2.03 (dd, 1H, J=14.5, 14.5), 1.92 (d, 1H, J=15.0), 1.75-1.78 (m, 1H), 1.70 (dd, 1H, J=15.0, 6.2), 1.53-1.60 (m, 1H), 1.41 (m, 1H), 1.25 (s, 1H, hydroxyl), 1.04 (s, 9H), 1.02-1.12 (m, 2H),

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 216.45, 135.47, 133.69, 133.42, 129.54, 129.51, 127.56, 73.22, 69.72, 62.21, 57.31, 47.47, 46.92, 45.07, 42.28, 42.11, 41.24, 29.89, 27.80, 26.94, 22.40, 19.32

FTIR (neat, 23 °C) 3396.1 (br), 2930.3 (s) 2857.1 (s) 1698.73 (s) 1471.2 (w) 1427.7 (s) 1110.8 (s) , 1027 (w), 1007,.1 (w), 823.2 (w), 702.4 (m) 739.3 (s) 612.8 (w) 505.1 (s)

HRMS (FTMS, Na^+) Expected for $C_{30}H_{40}O_4SiNa^+$: 515.2588 Found: 515.2588

TLC (80% Ethyl acetate / hexanes) $R_f = 0.17$ (UV, Mn)



Diketone alcohol **167**:

To diol **166** (262 mg, 0.532 mmol), which had been previously filtered through Celite in order to remove any solid impurities, in CH_2Cl_2 (3.0 mL) at 23 °C was added Bobbitt's reagent (342 mg, 1.06 mmol). The yellow suspension was stirred vigorously for 48h, whereupon it was filtered through Celite and washed thoroughly with several portions of CH_2Cl_2. Concentration afforded the diketone-alcohol **167** (256.4 mg, 98%) as a white foam.

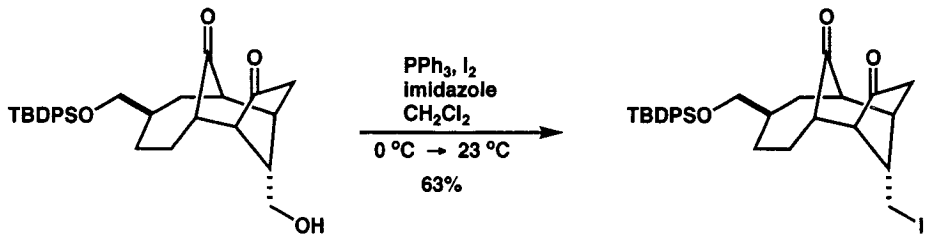
^{1}H NMR (500 MHz, $CDCl_3$, 23 °C) 7.59-7.62 (m, 4H), 7.35-7.45 (m, 6H), 4.31-4.35 (m, 1H), 4.17-4.22 (m, 1H), 3.45 (dd, 1H, J=10.0, 5.4), 3.33 (dd, 1H, J=10.0, 6.6), 2.71-2.79 (m, 3H), 2.48 (dd, 1H, J=18.5, 6.4), 2.33 (s, 1H), 2.19-2.24 (m, 1H), 2.05-2.13 (m, 2H), 2.02 (d, 1H, J=18.5), 1.92 (d, 1H, J=14.5), 1.76 (dd, 1H, J=14.5, 6.2), 1.58 (dd, 1H, J=14.5, 14.4), 1.47 (m, 1H), 1.43 (dd, 1H, J=4.5, 4.4), 1.04-1.11 (m, 1H), 1.03 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 213.31, 212.15, 135.42, 133.55, 133.27, 129.57, 129.53, 127.55, 69.48, 61.37, 55.14, 54.32, 50.85, 48.19, 45.02, 41.29, 40.02, 30.07, 27.60, 26.89, 22.84, 19.27

FTIR (neat, 23 °C) 3471.09 (br), 2930.79 (m), 2857.41 (m), 1747.51 (m), 1710.99 (m), 1469.60 (w), 1427.56 (s), 1109.40 (m), 1029.08 (w), 740.79 (w), 704.13 (m), 505.56 (m)

HRMS (EI, H^+) Expected for $C_{30}H_{39}O_4Si^+$: 491.2617 Found: 491.2617

TLC (50% Ethyl acetate / hexanes) R_f = 0.26 (UV, Mn)



Diketone iodide **168**:

To PPh_3 (71.8 mg, 0.274 mmol) and imidazole (21.0 mg, 0.308 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C was added I_2 (68.3 mg, 0.269 mmol). After 15 minutes, a solution of alcohol **167** (44.4 mg, 0.0905 mmol) in CH_2Cl_2 (0.5 mL) was added via cannula, followed by a rinse (2 x 0.5 mL). The reaction was allowed to warm overnight. After 24h, a solution of 1:1 $NaHCO_3$ / $Na_2S_2O_3$ (10 mL) was added. This was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ($NaSO_4$), filtered, and concentrated. Column chromatography (10% EtOAc / hexanes to 20% EtOAc / hexanes) gave 34.4 mg (63%) of iodide **168** as white crystals.

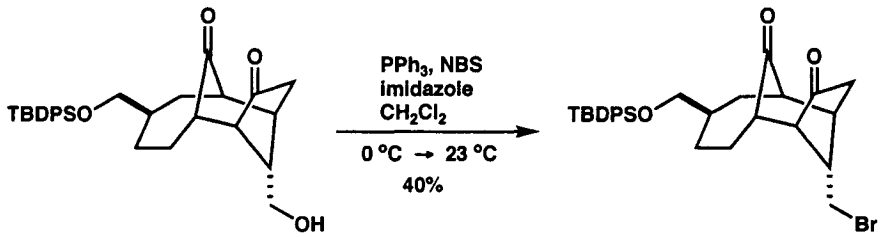
^{1}H NMR (500 MHz, $CDCl_3$, 23 °C) 7.62 (m, 4H), 7.41 (m, 6H), 3.97 (dd, 2H, J= 7.2, 3.5), 3.44 (dd, 1H, J= 11.0, 5.6), 3.37 (dd, 1H, J=11.0, 6.0) 2.89 (m, 1H), 2.77-2.84 (m, 2H), 2.53 (dd, 1H, J=17.3, 6.5), 2.40 (dd, 1H, J=8.5, 8.5), 2.09 (d, 1H, J=17.3), 2.04-2.17 (m, 2H), 1.97 (dd, 1H, J=15.5, 6.8), 1.8 (d, 1H, J=15.5), 1.73 (ddd, 1H, J=15.0, 14.5, 2.8), 1.55-1.59 (m, 1H), 1.09 (m, 1H), 1.05 (s, 9H), 0.86 (m, 1H)

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C) 212.53, 211.68, 135.56, 135.54, 133.43, 129.74, 127.74, 127.73, 69.68, 56.56, 55.09, 50.86, 48.71, 44.91, 42.66, 42.14, 29.69, 27.57, 26.87, 22.70, 19.26, 7.12

FTIR (neat, 23 °C) 2928.6(m), 2855.7 (m), 2360.51 (m) 2339.98 (m), 1750.01 (s) 1714.91 (s) 1108.94 (s), 989.9 (w), 823.1 (m), 742.7 (s), 703.28 (s) 505.73 (s)

HRMS(FTMS, Na^+): Expected for $C_{30}H_{37}O_3SiNaI^+$: 623.14472 Found: 623.14489

TLC (20% Ethyl acetate / hexanes) $R_f = 0.24$ (UV, Mn)



Diketone bromide **204**:

To alcohol **167** (86 mg, 0.118 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C was added NBS (25.3 mg, 0.136 mmol) and then PPh_3 (34.7 mg, 0.132 mmol). Upon addition of PPh_3 the reaction mixture turned yellow. After 24 h, CH_2Cl_2 was added (10 mL), and this was then washed with water (10 mL), saturated $Na_2S_2O_3$ (10 mL), and brine (10 mL). The organic layer was dried with $NaSO_4$, filtered, and concentrated. Column chromatography (10% EtOAc / hexanes to 20% EtOAc / hexanes) gave 25.9 mg (40%) of bromide **204** as white crystals.

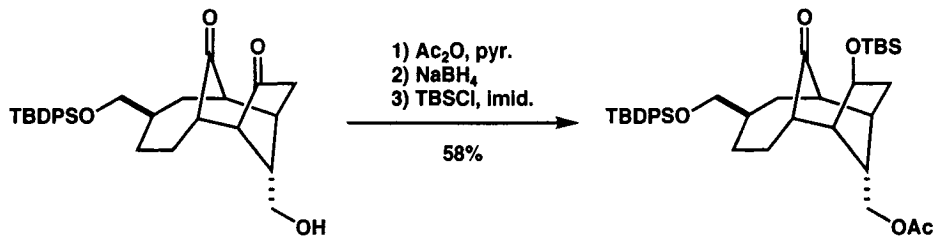
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 7.62 (d, 4H, J=7.7), 7.37-7.45 (m, 6H), 4.15 (dd, 2H, J=8.8, 2.7), 3.47 (dd, 1H, J=9.6, 5.5), 3.38 (dd, 1H, J=9.6, 6.1), 2.92 (m, 1H,), 2.83 (m, 3H), 2.55 (dd, 1H, J=18.8, 6.5), 2.47 (dd, 1H, J=8.8, 9.0), 2.10 (d, 1H, J=18.8), 2.08-2.18 (m, 2H), 1.91 (dd, 2H, J=14.8, 5.1), 1.67 (ddd, 1H, J=14.4, 14.4, 2.7), 1.55-1.60 (m, 1H), 1.13 (m, 1H), 1.06 (s, 9H). 0.89 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$, 23 °C) 212.11, 211.38, 135.45, 135.42, 133.39, 133.30, 129.65, 127.64, 127.64, 69.67, 55.68, 55.05, 50.81, 48.38, 44.34, 42.05, 41.42, 33.02, 29.81, 27.61, 26.96, 22.86, 19.36

FTIR (neat, 23 °C) 2931.12 (br), 2856.90 (m), 1751.41 (s), 1712.75 (m), 1427.6 (w), 1109.46 (s), 910.64 (w), 739.41 (s), 704.13 (s), 505.52 (m)

HRMS(FTMS, Na^+) Expected for $C_{30}H_{37}O_3NaBrSi^+$: 575.15819 Found: 575.15876

TLC (20% Ethyl acetate / hexanes) R_f = 0.26 (UV, Mn)



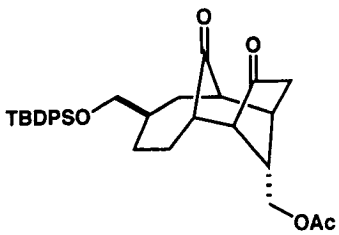
TBS-protected acetate **169**:

To alcohol **167** (94.7 mg, 0.193 mmol) in CH_2Cl_2 (2.0 mL) was added pyridine (30 μL, 0.37 mmol), acetic anhydride (40 μL, 0.42 mmol) and DMAP (5 mg, 0.04 mmol). The mixture was stirred overnight, whereupon it was quenched with 0.5M HCl (10 mL), and partitioned with EtOAc (10 mL). The aqueous layer was removed, and the organic layer washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), The organic layer was dried (Na_2SO_4), filtered, and concentrated to give crude acetate **169** (99 mg) as a clear oil. This was used without purification in the subsequent reduction step.

To crude acetate **169** (99 mg, ~0.19 mmol) in MeOH (5.0 mL) at –78 °C was added $NaBH_4$ (19.0 mg, 0.502 mmol). The solution turned slightly yellow. After 1h, the reaction was quenched with 50% saturated NH_4Cl (10 mL) and warmed to room temperature. The aqueous layer was extracted with EtOAc (3 x 10 mL), dried ($NaSO_4$), filtered and concentrated to give 103 mg of crude alcohol **170**. The alcohol was a mixture of ring-chain tautomers in $CDCl_3$.

To alcohol **170** (103 mg, ~ 0.19 mmol) in CH_2Cl_2 at 23 °C was added imidazole (50.8 mg, 0.746 mmol), TBSCl (104 mg, 0.690 mmol), and DMAP (11 mg, 0.090 mmol). As TBSCl was added, a white precipitate came out of solution. The mixture was stirred vigorously for 22h, whereupon the reaction was observed not to go to completion. Additional DMAP (31 mg, 0.25 mmol) was added and the reaction stirred for a further 12h, after which it was diluted with EtOAc (10 mL). The organic layer was washed with 0.5 M HCl (10 mL), saturated aqueous

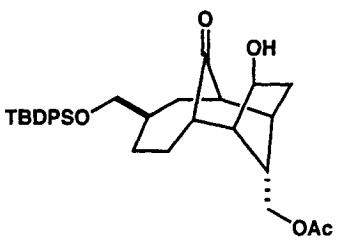
$NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and concentrated. Column chromatography (10% Ethyl acetate / hexanes to 50% ethyl acetate / hexanes in 10% increments) gave silylated acetate **205** (72.4 mg, 58% over three steps) as a clear oil, along with starting alcohol **170** (30mg, 29%).



Acetate **169**:

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 7.61-7.64 (m, 4H), 7.36-7.44 (m, 6H), 4.91 (dd, 1H, J=11.2, 7.5), 4.72 (dd, 1H, J=11.2, 7.2), 3.44 (dd, 1H, J=9.6, 5.5), 3.38 (dd, 1H, J=9.6, 3.4), 2.74-2.86 (m, 3H), 2.50 (dd, 1H, J=18.8, 6.4), 2.27-2.33 (m, 1H), 2.18-2.25 (m, 1H), 2.12 (s, 3H), 2.07-2.17 (m, 1H), 2.06 (d, 1H, J=18.8), 1.86 (dd, 1H, J=15.2, 5.3), 1.55-1.73 (m, 3H), 1.09-1.14 (m, 2H), 1.05 (s, 9H)

TLC (50% Ethyl acetate / hexanes) R_f = 0.73 (UV, Mn)

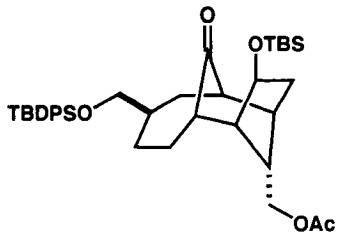


Acetate alcohol **170**:

The compound existed as a mixture of ring-chain tautomers, which led to obscuring of signals in the aliphatic region. No attempt was made to deconvolute the multiplets.

^{1}H NMR (300 MHz, $CDCl_3$, 23 °C) 7.61-7.66 (m, 4H), 7.34-7.44 (m, 6H), 4.79 (dd, 1H, J=11.1, 7.2), 4.69 (dd, 1H, J=11.1, 7.7), 4.49-4.59 (m, 1H), 4.23-4.33 (m, 1H), 3.28-3.44 (m, 2H), 3.07 (d, 1H, J=13.0), 2.79-2.92 (m, 1H), 2.70 (d, 1H, J=9.0), 2.59-2.66 (m, 1H), 2.28-2.41 (m), 2.17-2.27 (m), 2.10 (s,3H), 2.09 (s, 3H), 1.78-1.91 (m), 1.76 (d, 1H, J=7), 1.71 (d, 1H, J=7.6), 1.58-1.67 (m), 1.46-1.57 (m), 1.36-1.44 (m), 1.03 (s, 9H), 0.82-1.15 (m)

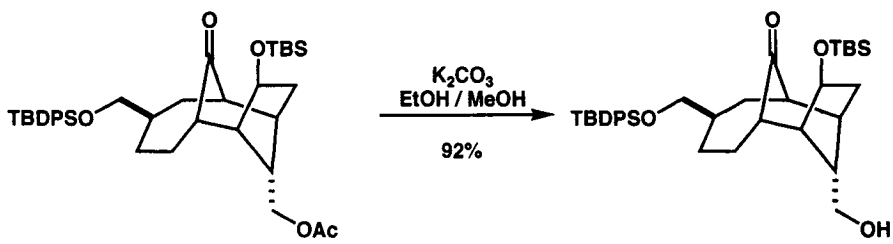
TLC (50% Ethyl acetate / hexanes) $R_f = 0.15$ (UV, Mn)



TBS-protected acetate **205**:

^{1}H NMR (300 MHz, $CDCl_3$, 23 °C) 7.61-7.69 (m, 4H), 7.34-7.47 (m, 6H), 4.81 (dd, 1H, J=11.1, 7.3), 4.65 (dd, 1H, J=11.1, 3.8), 4.16-4.26 (m, 1H), 3.31-3.44 (m, 2H), 3.05 (d, 1H, J=13.8), 2.67 (d, 1H, J=8.5), 2.29-2.39 (m, 2H), 2.11-2.22 (m, 1H), 2.10 (s, 3H), 1.96-2.06 (m, 1H), 1.81 (d, 1H, J=12.6), 1.72 (dd, 1H, J=14.7, 6.5), 1.45-1.62 (m, 2H), 1.19-1.26 (m, 2H), 1.05 (dd, 1H, obs), 1.03 (s, 9H), 0.86 (s, 9H), 0.10 (s, 3H), 0.01 (s, 3H)

TLC (20% Ethyl acetate / hexanes) $R_f = 0.85$ (UV, Mn)



TBS-protected diol **171**:

To acetate **205** (100 mg, 0.154 mmol) in EtOH (4 mL) was added K_2CO_3 (45 mg, 0.32 mmol). After 15 min, MeOH (2 mL) was added. After stirring for 4h, the reaction was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give a crude extract which was purified using column chromatography (10% EtOAc / hexanes to 40% EtOAc /hexanes in 10% increments) to give alcohol **171** (86.6 mg, 92%) as an oil that formed colourless crystals upon standing. In addition, starting acetate (6 mg, 6%) was also obtained.

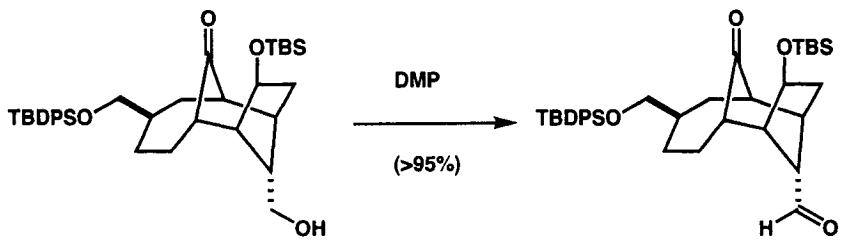
See Appendix A for copies of spectra

^{1}H NMR (300 MHz, $CDCl_3$, 23 °C) 7.59-7.67 (m, 4H), 7.35-7.46 (m, 6H), 4.17-4.33 (m, 2H), 4.09 (dd, 1H, J=10.2, 7.1), 3.43 (dd, 1H, J=9.9, 5.2), 3.31 (dd, 1H, J=9.9, 6.5), 3.03 (d, 1H, J=13), 2.63 (d, 1H, J=8.4), 2.40 (s, 1H), 2.24-2.37 (m, 2H), 1.93-2.13 (m, 2H), 1.86 (d, 1H, J=14.1), 1.74 (dd, 1H, J=7.5, 7.4), 1.63 (dd, 1H, J=14.6, 5.8), 1.52 (dddd, 1H, J=14.4, 14.3, 3.3, 2.9), 1.31-1.46 (m, 1H), 1.17-1.23 (m, 1H), 1.03-1.10 (m, 1H), 1.04 (s, 9H), 0.87 (s, 9H), 0.01 (s, 3H), -0.01 (s, 3H)

FTIR (neat, 23 °C) 3441.3 (br), 2930.8 (s), 2857.1 (s), 1702.0 m), 1469.7 (m), 1427.9 (m), 1361.2 (m), 1252.4 (m), 1156.5 (m), 1109.1 (s), 877.1 (m), 836.5 (m), 776.6 (m), 703.4 (s), 505.1 (w)

HRMS (FTMS, Na^+) Expected for $C_{36}H_{54}Si_2O_4Na^+$: 629.34516 Found: 629.34529

TLC (20% Ethyl acetate / hexanes) R_f = 0.32 (UV, Mn)



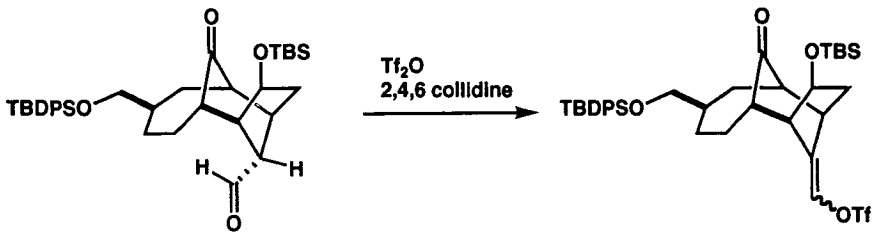
Aldehyde **172**:

To alcohol **171** (15.7 mg, 0.0259 mmol) in CH_2Cl_2 (1.0 mL) was added Dess-Martin periodinane (20 mg, 0.0465 mmol). After 30 min, the reaction was concentrated under reduced pressure and triturated with hexanes (3 x 10 mL). The washings were gravity-filtered through a small fritted glass funnel and washed further with hexanes. Concentration gave crude aldehyde **172** (16 mg, >95%) as a clear oil with only trace amounts of DMP-related impurities.

See Appendix A for copies of spectra

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 10.11 (s, 1H), 7.59-7.63 (m, 4H), 7.35-7.42 (m, 6H), 4.19-4.28 (m, 1H), 3.32 (d, 2H, J=5.47), 3.13 (d, 1H, J=13.6), 2.92-2.96 (m, 1H), 2.80-2.83 (m, 1H), 2.71 (d, 1H, J=7.5), 2.37-2.40 (m, 1H), 2.20 (dd, 1H, J=3.5, 3.1), 1.93-2.00 (m, 1H), 1.73-1.82 (m, 2H), 1.62-1.73 (m, 2H), 1.36-1.46 (m, 1H), 1.17 (dd, 1H, J=14.0, 3.7), 1.02 (s, 9H), 1.01-1.04 (m, 1H), 0.89 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H)

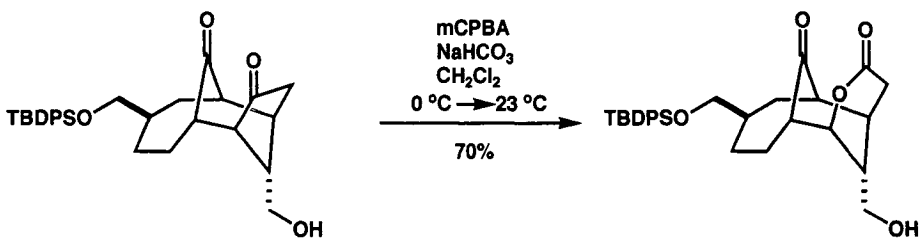
TLC (20% EtOAc / hexanes) $R_f = 0.55$ (UV, Mn)



Triflate **173**:

To aldehyde **172** (20.2 mg, 0.033 mmol) in CH_2Cl_2 at 0 °C was added 2,4.6-collidine (40 μL, 0.33 mmol) and freshly distilled Tf_2O (60 μL, 0.36 mmol) The solution immediately turned dark yellow. After 1h, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and partitioned with EtOAc (10 mL). The organic phase was collected and washed with 10% aqueous $KHSO_4$ (3 x 10 mL), then brine (1 x 10 mL), dried (Na_2SO_4), filtered and concentrated. The crude reaction mixture was filtered through a short plug of silica gel to give the 1:1 mixture of triflates (9.6 mg, 39%). The triflates were found to be extremely labile to silica gel; exposure of more than a few seconds resulted in their cleavage to an aldehyde isomeric to **172**.

^1H NMR (400 MHz, $CDCl_3$, 23 °C) Could not be fully characterized due to inability to purify; key resonances at 6.30 and 5.94 (ratio 1:1.4) are believed to be from the enol triflate protons.



Lactone alcohol **206**:

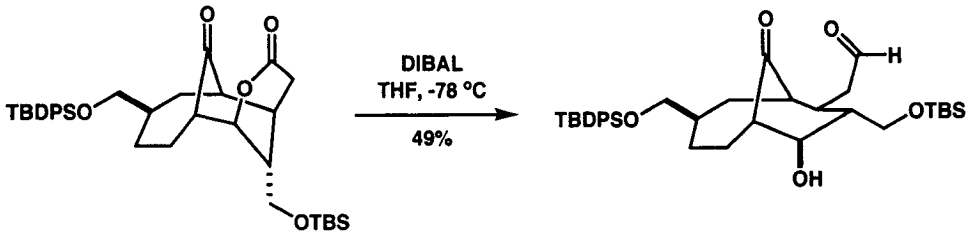
To alcohol 167 (6.0 mg, 0.012 mmol) in CH_2Cl_2 at 23 °C was added $NaHCO_3$ (5.1 mg, 0.060 mmol) and mCPBA (4.8 mg of ~80% pure mCPBA, 0.022 mmol). The suspension was stirred rapidly at room temperature for 48h, whereupon it was diluted with ethyl acetate (10 mL) and extracted with saturated $NaHCO_3$ solution (3 x 10 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated. Column chromatography (20% - 50% - 80% - 100% EtOAc / hexanes) gave 4.3 mg (70%) of lactone **206**.

^1H NMR (400 MHz, $CDCl_3$, 23 °C) 7.59-7.62 (m, 4H), 7.35-7.44 (m, 6H), 4.89 (dd, 1H, J=6.0, 2.8), 4.17 (dd, 1H, J=10.5, 8.0), 4.00 (dd, 1H, J=10.5, 6.0), 3.43 (dd, 1H, J=10.0, 5.9), 3.34 (dd, 1H, J=10.0, 6.3), 3.19 (d, 1H, 12.8), 2.97 (dd, 1H, J=18.5, 6.9), 2.76 (d, 1H, J=6.6), 2.54 (d, 1H, J=18.5), 2.47-2.50 (m, 2H), 2.04 (dd, 1H, J=14, 13), 1.84-1.97 (m, 2H), 1.74 (d, 1H, J=14), 1.48-1.62 (m, 2H), 1.37 (dd, 1H, J=15,14), 1.24 (s, 1H), 1.03 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C) 211.67, 168.18, 135.59, 133.64, 133.41, 129.73, 127.72, 80.90, 69.07, 62.42, 55.39, 52.25, 43.82, 41.64, 41.03, 36.44, 32.33, 27.44, 26.87, 20.55, 19.23

FTIR (neat, 23 °C) 3458.65 (br), 2930.03 (s), 2857.22 (m), 1716.98 (s), 1469.87 9w), 1427.36 (w), 1358.09 (w), 1240.76 (s), 1173.29 (w), 1109.49 (s), 986.53 (m), 822.86 (w), 739.93 (m), 703.83 (s), 613.60 (m), 505.22 (m)

TLC (80% Ethyl acetate / hexanes) R_f = 0.56 (UV, Mn)



Aldehyde **207**:

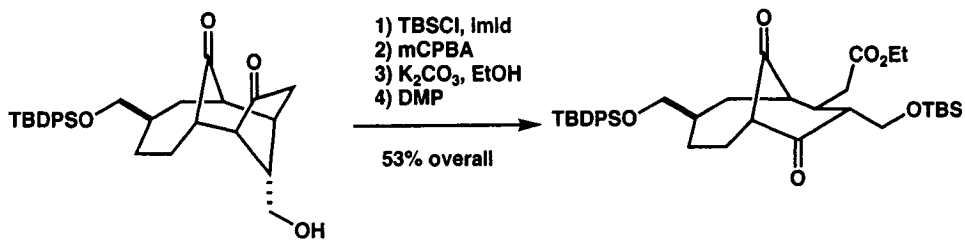
To lactone **206** (0.016 g, 0.026 mmol) in THF (0.5 mL) at –78 °C was added DIBAL (1.5 M in PhMe, 180 μL, 0.27 mmol). The solution was stirred for 15 minutes and then saturated potassium sodium tartrate solution was added (2 mL). The reaction mixture was stirred rapidly for 30 min at room temperature, whereupon brine (10 mL) was added and the liquid extracted with Et_2O (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Column chromatography (50% EtOAc / pentane) gave 7.9 mg (49%) alcohol-aldehyde **207**. The remainder of the mass balance was primarily unreacted starting material.

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C) 9.75 (s, 1H), 7.60-7.63 (m, 4H), 7.35-7.44 (m, 6H), 3.93 (d, 1H, J=8.2), 3.75 (dd, 1H, J= 10.0, 3.6), 3.62 (dd, 1H, J=10.0, 6.9), 3.42 (m, 2H), 2.84 (s, 1H), 2.58-2.66 (m, 2H), 2.50 (ddd, 1H, J=17.5, 4.9, 1.8), 2.34 (dd, 1H, J=17.5, 3.8), 2.25-2.32 (m, 2H), 1.81-1.90 (m, 3H), 1.24-1.26 (m, 1H), 1.03 (s, 9H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C) 214.62, 200.24, 135.37, 133.33, 129.51, 127.51, 76.71, 68.27, 64.01, 56.67, 53.82, 49.20, 47.01, 40.67, 31.52, 28.72, 28.31, 27.23, 26.86, 19.27, 18.17, -5.51

FTIR (neat, 23 °C) 3433.23 (br), 2928.22 (s), 2856.23 (s), 1715.89 (s), 1468.41 (w), 1427.38 (w), 1255.53 (w), 1110.08 (s), 836.04 (m), 779.24 (w), 703.19 (m)

TLC (50% Ethyl acetate / hexanes) R_f = 0.58 (UV, Mn)



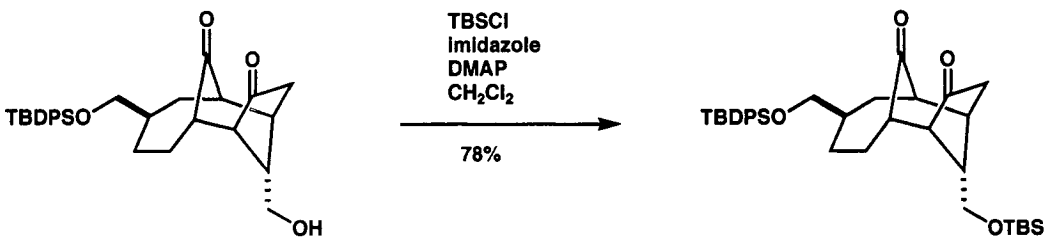
Diketone **176**:

To alcohol (129.7 mg, 0.264 mmol) in CH_2Cl_2 (2.0 mL) at 23 °C was added imidazole (25.8 mg, 0.378 mmol), TBSCl (56.0 mg, 0.371 mmol) and DMAP (4 mg, 0.033 mmol). A precipitate formed upon addition of TBSCl. After stirring for 2h, the suspension was diluted with EtOAc (10 mL) and washed sequentially with 1 M HCl (10 mL), saturated $NaHCO_3$ (10 mL), and brine (1 x 10 mL). Drying of the organic layer (Na_2SO_4) followed by filtration and concentration gave a clear oil consisting almost exclusively of **173**.

The unpurified silyl ether **173** was dissolved in CH_2Cl_2 and cooled to 0 °C. Solid $NaHCO_3$ (93 mg, 1.1 mmol) and ~80% pure mCPBA (82.3 mg of 80% pure mCPBA, corresponding to 0.381 mmol mCPBA) were then added with rapid stirring. After stirring overnight, a white precipitate had formed, and TLC indicated completion of the reaction. The reaction was partitioned with EtOAc (10 mL) and washed with saturated $NaHCO_3$ (2 x 10 mL), and brine (1 x 10 mL). Drying of the organic layer (Na_2SO_4) followed by filtration and concentration gave 180 mg of an oil which corresponded to lactone **174** contaminated with a small amount of mCBA.

To crude lactone **174** in EtOH (10 mL) was added K_2CO_3 (45 mg, 0.33 mmol). The white suspension was stirred at 23 °C for 24 h, whereupon brine (20mL) and EtOAc (20 mL) were added. The organic layer was collected, and the aqueous layer further extracted with EtOAc (2 x 10 mL), dried (Na_2SO_4), filtered and concentrated to give crude alcohol **175** .

Crude alcohol **175** was dissolved in CH_2Cl_2 (2.0 mL) at 23 °C. Dess-Martin periodinane (216 mg, 0.503 mmol) was added. After 3h, the solution was quenched with a mixture of Et_2O (6 mL), saturated $NaHCO_3$ (6 mL) and saturated $Na_2S_2O_3$ (2 mL) and stirred until the organic phase became clear (15 min). Brine (10 mL) was added, and the mixture extracted with EtOAc (3 x 10 mL), dried (Na_2SO_4) filtered and concentrated. Column chromatography (10% EtOAc / hexanes to 30% EtOAc / hexanes in 10% increments) gave pure diketone **176** (93.0 mg, 0.140 mmol, 53% over 4 steps) as a clear oil.



TBS-protected diketone **173**:

To alcohol **172** (43.3 mg, 0.088 mmol) in CH_2Cl_2 (1 mL) at 23 °C was added imidazole (11.1 mg, 0.161 mmol), TBSCl (15.0 mg, 0.099 mmol) and DMAP (2 mg). A white precipitate quickly formed. The mixture was stirred for 4h and then partitioned with EtOAc (10 mL). The organic layer was washed with 1M HCl (10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL), then dried (Na_2SO_4), filtered and concentrated. Purification via flash column chromatography (10% EtOAc / hexanes to 20% EtOAc / hexanes) gave 41.4 mg (0.068 mmol, 78%) of TBS protected diketone **173** as a clear oil.

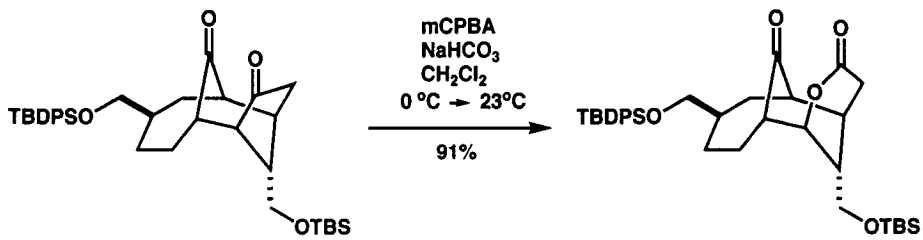
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 7.55-7.64 (m, 4H), 7.32-7.42 (m, 6H), 4.39 (dd, 1H, J=10.0, 8.0), 4.28 (dd, 1H, J=10.0, 8.0), 3.41 (dd, 1H, J=10.0, 5.2), 3.29 (dd, 1H, J=10.0, 6.5), 2.69-2.82 (m, 4H), 2.48 (dd, 1H, J=18.5, 6.3), 2.24-2.27 (m, 2H), 2.02-2.09 (m, 1H), 2.01 (d, 1H, J=18.5), 1.93 (d, 1H, J=15.0), 1.82 (dd, 1H, J=15.0, 6.2), 1.67 (dd, 1H, J=14.6, 14.5), 1.49 (m, 1H), 1.07 (m, 1H), 1.02 (s, 9H), 0.90 (s, 9H), 0.09 (s, 6H)

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C) 213.95, 212.79, 135.52, 133.47, 133.44, 129.68, 127.68, 69.51, 61.61, 55.28, 54.45, 50.94, 48.31, 45.28, 41.67, 39.97, 30.11, 27.72, 26.83, 25.88, 22.76, 19.26, 18.19, -5.14, -5.20

FTIR (neat, 23 °C) 2930.5 (m), 2856.9 (m), 1751.8 (m), 1713.5 (m), 1469.6 (w), 1427.8 (w), 1254.7 (w), 1108.7 (s), 837.6 (m), 777.26 (w), 738.9 (w), 703.5 (m), 505.3 (w)

HRMS (CI, H^+) Expected for $C_{36}H_{53}O_4Si_2^+$: 605.3482 Found: 605.3468

TLC (20% Ethyl acetate / hexanes) $R_f = 0.52$ (UV, Mn)



Lactone **174**:

To diketone **173** (41.4 mg, 0.0685 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C was added $NaHCO_3$ (11.6 mg, 0.138 mmol) and then mCPBA (21.4 mg of ~80% pure mCPBA, 0.099 mmol). The solution was stirred for 8h, during which a white precipitate slowly appeared. The mixture was partitioned with ethyl acetate (10 mL) and saturated $NaHCO_3$ (10 mL). The organic phase was further washed with saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and concentrated. Flash column chromatography (10% EtOAc / hexanes to 20% EtOAc / hexanes) gave 38.8 mg (91%) of the desired lactone **174** as a colorless oil.

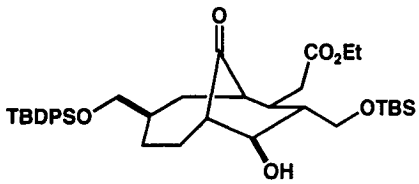
^{1}H NMR (500 MHz, $CDCl_3$, 23 °C) 7.61 (dd, 4H, J=6.8, 7.0), 7.35-7.45 (m, 6H), 4.93 (d, 1H, J=2.7), 4.29 (dd, 1H, J=10.0, 9.6), 4.07 (dd, 1H, J=10.0, 7.9), 3.41 (dd, 1H, J=10.0, 5.8), 3.32 (dd, 1H, J=10.0, 6.4), 3.21 (m, 1H), 3.19 (m, 1H), 2.98 (dd, 1H, J=18.5, 7.1), 2.78 (d, 1H, J=7.5), 2.57 (d, 1H, J=18.5), 2.50-2.56 (m, 1H), 2.47 (d, 1H, J=6.6) 2.02-2.14 (m, 2H), 1.91 (d, 1H, J=14.8), 1.80 (d, 1H, J=14.7), 1.53-1.61 (m, 2H), 1.48 (dd, 1H, J=14.0, 15.1), 1.03 (s, 9H), 0.93 (s, 1H), 0.13 (s, 6H)

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C) 211.64, 168.35, 162.64, 135.48, 133.35, 133.33, 129.70, 127.67, 80.97, 68.97, 62.57, 55.42, 52.27, 43.86, 41.68, 41.45, 36.35, 32.32, 27.49, 26.80, 25.81, 20.29, 19.22, 18.12, -5.23, -5.30

FTIR (neat, 23 °C) 2930.67 (s), 2856.93 (m), 1738.32 (s), 1469.63 (w), 1427.55 (w), 1255.02 (m), 1170.93 (w), 1110.37 (s), 1028.83 (w), 838.03 (s), 778.49 (m), 738.41 (m), 703.54 (m), 505.23 (m)

HRMS(FTMS, H^+) : Calculated for $C_{36}H_{53}O_5Si_2^+$: 621.34260 Found: 621.34261

TLC (20% Ethyl acetate / hexanes) $R_f = 0.27$ (UV, Mn)



Alcohol **175**:

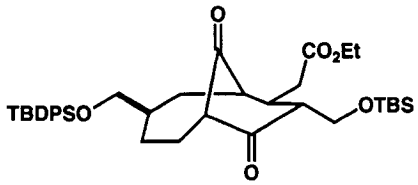
^{1}H NMR (500 MHz, $CDCl_3$, 23 °C) 7.59-7.64 (m, 4H), 7.35-7.45 (m, 6H), 4.11 (q, 2H, J=7.1), 3.96 (d, 1H, J=8.2), 3.92 (dd, 1H, J=9.4, 3.7), 3.67 (dd, 1H, J=9.4, 8.5), 3.45 (dd, 1H, J=10.0, 5.7), 3.38 (dd, 1H, J=10.0, 6.3), 3.21 (s, 1H), 2.59 (dd, 1H, J=9.3, 8.7), 2.45-2.51 (m, 1H), 2.23-2.38 (m, 3H), 2.29 (dd, 1H, J=16.5, 5.8), 1.80-1.91 (m, 3H), 1.39-1.53 (m, 3H), 1.24 (t, 3H, J=7.1), 1.03 (s, 9H), 0.91 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C) 214.98, 171.97, 135.56, 135.55, 133.62, 133.57, 129.62, 127.64, 77.77, 68.39, 65.00, 60.73, 56.41, 53.36, 48.60, 40.51, 36.69, 31.65, 31.27, 28.40, 27.49, 26.84, 25.81, 19.24, 18.10, 14.21, -5.60, -5.64

FTIR (neat, 23 °C) 3449.36 (br), 2929.97 (s), 2857.08 (s), 1733.57 (s), 1713.61 (s), 1469.37 (w), 1427.50 (w), 1253.85 (m), 1180.05 (m), 1110.53 (s), 853.24 (m), 778.35 (w), 740.77 (w), 703.47 (m), 612.59 (w), 505.46 (m)

HRMS (FTMS, H^+) Calculated for $C_{38}H_{59}O_6Si_2^+$: 667.38367 Found: 667.38447

TLC (33% Ethyl acetate / hexanes) $R_f = 0.44$ (UV, Mn)



Diketone **176**:

See Appendix A for copies of spectra

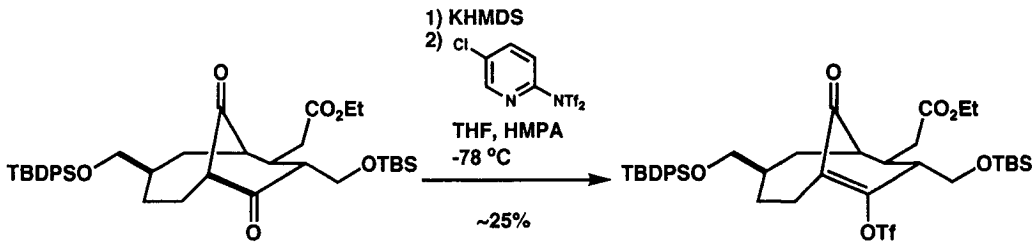
^{1}H NMR (500 MHz, $CDCl_3$, 23 °C) 7.59-7.62 (m, 4H), 7.34-7.44 (m, 6H), 4.19 (dd, 1H, J=10.5, 3.1), 4.09 (dq, 2H, J=7.1, 1.6), 3.81 (dd, 1H, J=10.5, 3.4), 3.45 (dd, 1H, J=10.0, 5.7), 3.40 (dd, 1H, J=10.0, 6.2), 3.23 (dd, 1H, J=10.0, 6.1), 2.75-2.79 (m, 2H), 2.60 (dd, 1H, J=16.5, 2.4), 2.48 (dd, 1H, J=16.5, 6.1), 2.40 (ddd, 1H, J=11.2, 3.3, 3.2), 2.01-2.10 (m, 1H), 1.83-1.99 (m, 4H), 1.55 (ddd, 1H, J=13.6, 13.2, 3.9), 1.23 (t, 3H, J=7.1) 1.12-1.17 (m, 1H), 1.04 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C) 210.18, 205.62, 171.54, 135.56, 135.52, 133.50, 129.67, 127.67, 67.89, 62.91, 60.63, 58.71, 53.16, 52.22, 39.44, 36.32, 32.74, 31.24, 28.09, 26.83, 25.80, 23.07, 19.25, 18.1, 14.18, -5.59, -5.69

FTIR (neat, 23 °C) 2929.67 (s), 2856.82 (s), 1732.32 (s), 1705.70 (s), 1469.09 (w), 1427.21 (w), 1253.35 (w), 1178.80 (w), 1109.94 (s), 1030.72 (w), 836.06 (m), 778.99 (w), 740.90 (w), 703.18 (s)

HRMS (FTMS, NH_4^+) Expected for $C_{38}H_{60}O_6NSi_2^+$: 682.39432 Found: 682.39537

TLC (20% Ethyl acetate / hexanes) $R_f = 0.40$ (UV, Mn)



Triflate **179**:

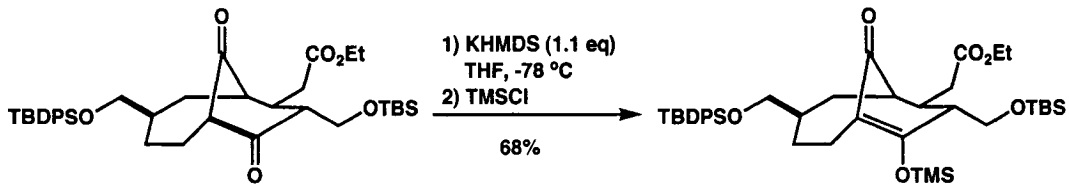
Diketone **176** (6.9 mg, 0.010 mmol) was dried azeotropically with PhMe (3 x 1 mL) and dissolved in THF (0.2 mL). Freshly distilled HMPA (20 μL) was then added. The solution was taken to –95 °C with a MeOH / liquid N_2 ice bath. KHMDS (25 μL of a 0.5 M solution in PhMe, 0.013 mmol) was added dropwise. After 25 min, a solution of freshly distilled Comins' reagent (51 mg, 0.13 mmol) in THF (50 μL) was cannulated into the reaction mixture. After 90 min at –90 °C, the reaction was quenched with H_2O (1 mL) and slowly warmed to room temperature. Et_2O (10 mL) and water (10 mL) were added, and the organic layer removed. The aqueous layer was further extracted with Et_2O (2 x 10 mL) and the combined organic extracts washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered and concentrated. The crude reaction mixture was purified by silica gel chromatography (0% to 30% ethyl acetate / pentane in 10% increments) to give several impure fractions containing the desired triflate. These fractions were re-purified to give triflate **179** (~2 mg, ~25%) accompanied by minor impurities.

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C) 7.57-7.64 (m, 4H), 7.34-7.46 (m, 6H), 4.13 (q, 2H, J=7.1), 4.05 (d, 1H, J=11.3), 3.79 (d, 1H, J=11.3), 3.42 (d, 2H, J=5.9), 2.68-2.71 (m, 1H), 2.58 (d, 1H, J=17), 2.51-2.55 (m, 2H), 2.34-2.48 (m, 3H), 1.91 (d, 1H, J=13.6), 1.83 (dd, 1H, J=14, 7.5), 1.57-1.61 (m, 1H), 1.41-1.46 (m, 1H), 1.24 (t, 3H, J=7.1), 1.11-1.18 (m, 1H), 1.04 (s, 9H), 0.87 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H)

FTIR (neat, 23 °C) 2928.53 (s), 2856.83 (s), 1731.59 (s), 1467.85 (w), 1423.43 (m), 1247.30 (m), 1213.39 (s), 1141.13 (m), 1110.65 (s), 836.03 (m), 703.12 (m), 611.52 (w), 506.37 (m)

HRMS (FTMS, H^+) Expected for $C_{39}H_{56}O_8Si_2F_3S^+$: 797.31895 Found: 797.31811

TLC (5% Ethyl acetate / hexanes) $R_f = 0.43$ (Mn, UV)



Silyl enol ether **177**:

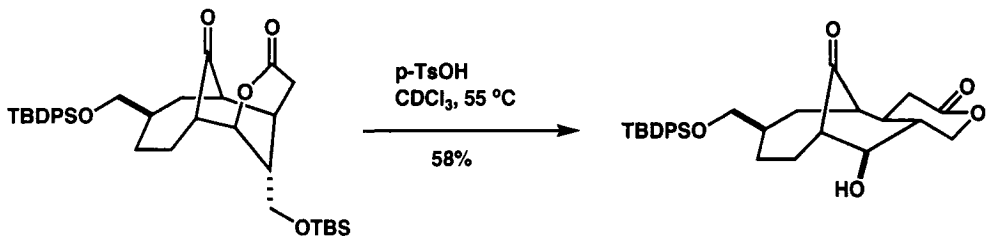
Diketone **176** (6.0 mg, 0.0090 mmol) was dried azeotropically with PhMe (3 x 1 mL) and then dissolved in THF (0.5 mL). The solution was cooled to –78 °C. KHMDS (21 μL of a 0.5 M solution in PhMe was added. After 30min, the solution was quenched with TMSCl (50 μL, 0.39 mmol). After 10 min, the solution was warmed to room temperature and concentrated. Trituration with pentane and filtration gave 4.5 mg (68%) of silyl enol ether **177** as a clear oil.

See Appendix A for copies of spectra

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C) 7.62 (d, 4H, J=6.7), 7.35-7.42 (m, 6H), 4.10 (q, 2H, J=7.1), 3.90 (dd, 1H, J=10.5, 3.8), 3.82 (dd, 1H, J=10.5, 5.0), 3.41 (d, 2H, J=6.3), 2.76 (dd, 1H, J=16.0, 3.6), 2.56-2.60 (m, 1H), 2.38 (dd, 1H, J=16.0, 9.0), 2.13-2.34 (m, 4H), 1.85 (d, 1H, J=13.6), 1.74 (dd, 1H, J=13.5, 7.2), 1.46-1.57 (m, 2H), 1.24-1.33 (m, 2H), 1.22 (t, 3H, J=7.1), 1.06 (m, 1H), 1.03 (s, 9H), 0.89 (s, 9H), 0.23 (s, 6H), 0.06 (s, 3H), 0.05 (s, 3H)

FTIR (neat, 23 °C) 2929.3 (m), 2586.7 (m), 1733.2 (s), 1703.8 (m), 1468.7 (w), 1427.4 (w), 1387.7 (w), 1252.9 (m), 1109.7 (s), 842.9 (m), 703.3 (m)

TLC (20% Ethyl acetate / hexanes) $R_f = 0.55$ (UV, Mn)



Alcohol lactone **180**:

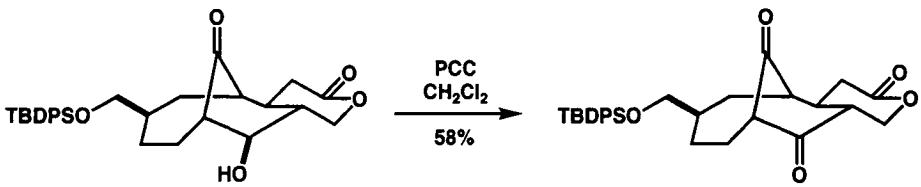
Lactone **174** (11.0 mg, 0.0177 mmol) was dissolved in $CDCl_3$ (0.5 mL) and p-TsOH (3.6 mg, 0.019 mmol) added in an NMR tube. The tube was heated to 55 °C for 24h and monitored by NMR spectroscopy. The reaction was quenched by rinsing the contents of the NMR tube into $NaHCO_3$ (5 mL) and extracting with EtOAc (3 x 5 mL). The organic phase was dried with Na_2SO_4, filtered, and concentrated. Column chromatography (10% EtOAc / hexanes to 100% EtOAc / hexanes) gave 5.4 mg (58%) of alcohol **180** as a clear oil.

^1H NMR (500 MHz, $CDCl_3$, 23 °C) 7.58-7.61 (m, 4H), 7.35-7.44 (m, 6H), 4.72 (dd, 1H, J=11.0, 5.1), 4.08 (dd, 1H, J=11.2, 11.0), 3.58 (s, 1H), 3.38-3.45 (m, 2H), 2.80 (dd, 1H, J=16.5, 4.3), 2.57-2.61 (m, 1H), 2.24-2.31 (m, 1H), 2.09-2.21 (m, 2H), 1.89 (dd, 1H, J=6.0, 6.0), 1.86 (d, 1H, J=4.8), 1.77 (d, 1H, J=14.0), 1.67-1.75 (m, 2H), 1.34 (dd, 1H, J=13.5, 3.6), 1.21-1.31 (m, 2H), 1.02 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 212.94, 168.84, 135.41, 133.34, 129.65, 127.56, 75.94, 72.45, 68.26, 57.74, 54.69, 41.87, 40.15, 36.52, 31.97, 31.80, 28.32, 27.40, 26.88, 19.22

HRMS(FTMS, Na^+) Expected for $C_{30}H_{38}O_5SiNa^+$: 529.23732 Found: 529.23807

TLC (80% Ethyl acetate / hexanes) R_f = 0.43 (UV, Mn)



Diketone lactone **181**:

To alcohol **180** (5.6 mg, 0.011 mmol) in CH_2Cl_2 (1.0 mL) was added pyridinium chlorochromate (13 mg, 0.060 mmol). The reaction mixture slowly turned dark brown. After stirring overnight, the suspension was filtered through Celite and washed with CH_2Cl_2. Silica gel chromatography (50% EtOAc / hexanes) yielded 3.2 mg (58%) of **181** as a colourless film.

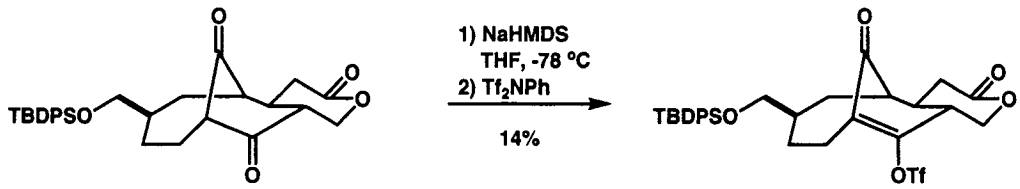
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 7.61 (d, 4H, J=7.6), 7.37-7.44 (m, 6H), 4.77 (dd, 1H, J=12.0, 5.1), 4.35 (dd, 1H, J=12.0, 11.2), 3.46 (d, 2H, J=6.2), 3.33 (d, 1H, J=9.2), 2.89 (dd, 1H, J= 17.6, 5.1), 2.54-2.60 (m, 2H), 2.14-2.36 (m, 3H), 1.89 (d, 1H, J=14.4), 1.80 (d, 1H, J=13.6), 1.70-1.76 (m, 1H), 1.28-1.38 (m, 2H), 1.06 (s, 9H), 0.93-1.00 (obs, 1H)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 207.64, 203.48, 167.72, 135.42, 135.35, 133.16, 129.72, 127.62, 68.25, 68.01, 61.70, 54.17, 47.06, 39.37, 36.85, 32.87, 32.17, 30.97, 28.51, 26.87, 24.66, 19.20

FTIR (neat, 23 °C) 2927.64 (m), 2856.52 (m), 1729.78 (s), 1706.06 (s), 1427.58 (w) 1223.03 (w), 1110.54 (s) 704.01 (m)

HRMS(FTMS, Na^+) Expected for $C_{30}H_{36}O_5NaSi^+$: 527.22159 Found: 527.22242

TLC (50% Ethyl acetate / hexanes) R_f = 0.59 (UV, Mn)



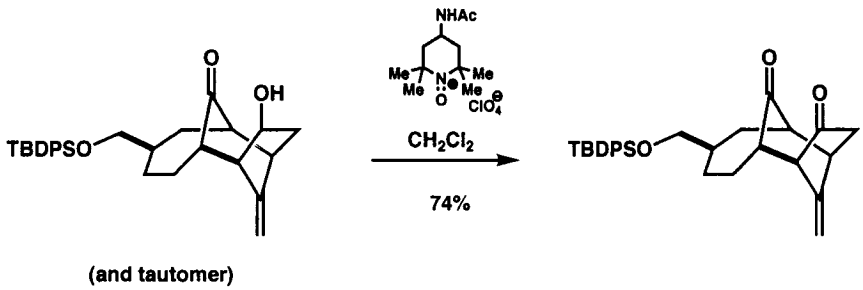
Triflate **182**:

Diketone **181** (8.2 mg, 0.016 mmol) was dried azeotropically with PhMe (2 x 1mL) and then dissolved in THF (0.5 mL). The flask was placed in a dry ice – acetone bath at –78 °C . After allowing the solution to cool completely, NaHMDS (20 μL of a 1.06 M solution in PhMe, 0.022 mmol) was added. The solution slowly turned pale yellow. After 30 min, the reaction was quenched with solid $PhNTf_2$ (57 mg, 0.159 mmol). The ice bath was removed and the solution allowed to warm to room temperature. The reaction mixture was then concentrated under reduced pressure. Pipet column chromatography (10% EtOAc to 80% EtOAc / hexanes in 20% increments) afforded 1.5 mg (14%) of triflate **182** as a clear oil.

See Appendix A for copies of spectra

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 7.59-7.61 (d, 4H, J=7.4), 7.37-7.45 (m, 6H), 4.72 (dd, 1H, J=11.2, 5.1), 4.29 (dd, 1H, J=11.6, 11.2), 3.53 (dd, 1H, J=10.4, 5.7), 3.45 (dd, 1H, J=10.4, 6.2), 2.88 (dd, 1H, J=18.0, 5.1), 2.69-2.77 (m, 1H), 2.43-2.49 (m, 2H), 2.38 (dd, 1H, J=18.0, 13.0), 2.20-2.29 (m, 1H), 1.71-1.88 (m, 3H), 1.22-1.36 (obs), 1.07 (s, 9H), 1.07-1.14 (m, 1H)

TLC (20% Ethyl acetate / hexanes) $R_f = 0.28$



(and tautomer)

Diketone olefin **183**:

To alcohol **165** (128 mg, 0.270 mmol) in CH_2Cl_2 was added Bobbitt's reagent (2 eq). The yellow slurry was stirred vigorously. After 48h, the reaction mixture was filtered through a pad of Celite and rinsed thoroughly with CH_2Cl_2. After concentration, the crude residue was purified via silica gel column chromatography (10% EtOAc / hexanes to 30% EtOAc / hexanes in 10% increments) to give diketone **183** (94 mg, 0.20 mmol, 74%) as a clear oil.

See Appendix A for copies of spectra and structural assignment

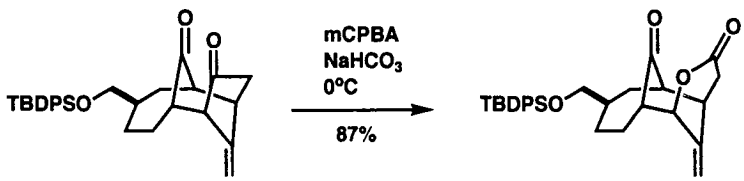
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 7.64-7.66 (m, 4H), 7.39-7.47 (m, 6H), 5.36 (s, 1H), 5.15 (s, 1H), 3.40 (dd, 2H, J=10.4, 1.9), 3.09 (d, 1H, J=7.0), 3.04 (d, 1H, J=11.8), 2.85 (s, 1H), 2.82 (d, 1H, J=3.9), 2.56 (dd, 1H, J=18.6, 6.9), 2.44-2.49 (m, 1H), 2.29 (d, 1H, J=18.6), 2.14-2.21 (m, 1H), 1.98 (d, 1H, J=13.9), 1.77 (d, 1H, J=14.8), 1.49 (dd, 1H, J=14.8, 13.9), 1.41 (ddd, 1H, J=13.6,13.6, 6.1), 1.08 (s, 9H), 0.88-0.95 (dd, 1H, J=14.6, 12.4)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 211.4, 211.4, 147.4, 135.5, 133.7, 133.6, 129.6, 127.6, 112.2, 69.2, 60.8, 57.2, 54.4, 47.8, 46.1, 39.3, 34.4, 28.2, 26.8, 26.0, 19.3

FTIR (neat, 23 °C) 2932.5 (m), 2857.2 (m), 1750.4 (s), 1711.0 (s), 1470.1 (w), 1427.8 (m), 1109.8 (s), 823.3 (m), 740.7 (m), 704.0 (s), 613.3 (w), 505.5 (m)

HRMS (FTMS, Na^+) Expected for $C_{30}H_{36}SiO_3Na^+$: 495.23230 Found: 495.23259

TLC (50% Ethyl acetate / hexanes) $R_f = 0.81$ (UV, Mn)



Lactone olefin **184**:

To diketone **183** (46.9 mg, 0.099 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C was added $NaHCO_3$ (16.8 mg, 0.200 mmol). After stirring for 10 min, mCPBA (21.5 mg of ~80% mCPBA, 0.10 mmol) was added. The mixture was stirred overnight at 0 °C. After 16h, saturated aqueous $Na_2S_2O_3$ (2 mL) was added. After stirring 30 min, the mixture was partitioned with saturated aqueous $NaHCO_3$ (10 mL) and EtOAc (10 mL). The organic layer was washed further with saturated aqueous $NaHCO_3$ (10 mL), dried (Na_2SO_4), filtered and concentrated. Column chromatography (20% EtOAc / hexanes) gave 42.1 mg (87%) of lactone **184** as a colourless oil.

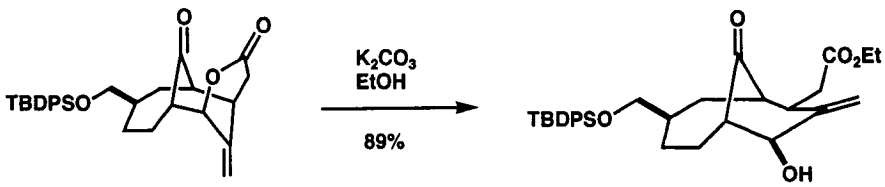
See Appendix A for copies of spectra

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 7.59-7.62 (m,4H), 7.35-7.45 (m, 6H), 5.40 (s, 1H), 5.38 (s, 1H), 4.76 (dd, 1H, J=3.6, 2.2), 3.35 (dd, 2H, J=6.8, 1.3), 3.29-3.31 (m, 1H), 2.91 (dd, 1H, J=16.8, 6.5), 2.86-2.88 (m, 1H), 2.78-2.80 (m, 1H), 2.76 (d, 1H, 16.8), 2.04-2.19 (m, 2H), 1.97 (dddd, 1H, J=13.6, 3.6, 3.6, 1.5), 1.73 (d, 1H, J=14.6), 1.40 (ddd, 1H, J=13.6, 13.2, 5.5), 1.16-1.23 (m, 1H), 1.04 (s, 9H), 0.85-0.95 (m, 1H)

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C) 210.3, 167.3, 139.9, 135.5, 133.6, 133.5, 129.7, 127.7, 117.1, 84.9, 68.9, 55.9.54.3, 42.6, 41.9, 38.7, 36.9, 28.9, 26.8, 23.9, 19.3

FTIR (neat, 23 °C) 2931.3 (m), 2857.4 (m), 1740.0 (s), 1711.2 (m), 1427.0 (m), 1364.5 (m), 1217.4 (m), 1158.7 (m), 1109.7 (s), 1006.9 (m), 1003.9 (m), 914.0(m), 736.9 (m), 704.0 9s), 505.8 (m)

TLC (50% Ethyl acetate / hexanes) $R_f = 0.53$ (UV, Mn)



Allylic alcohol **185**:

To lactone **184** (42.3 mg, 0.086 mmol) in EtOH (10 mL) at 23 °C was added K_2CO_3 (19.8 mg, 0.14 mmol) with rapid stirring. After 6 h, the reaction mixture was filtered through a pad of Celite and concentrated. Column chromatography (10% EtOAc / hexanes to 20% EtOAc / hexanes) gave alcohol **185** (40.4 mg, 89%) as a 5:1 mixture of β and α isomers.

For the β-alcohol (major component):

See Appendix A for copies of spectra

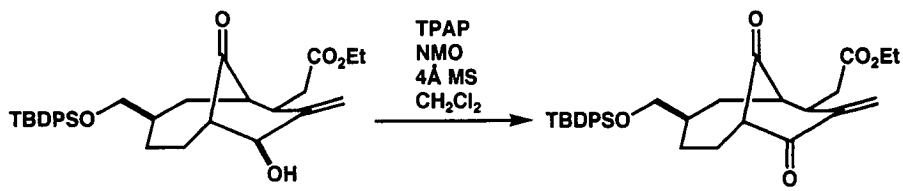
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 7.60-7.63 (m, 4H), 7.35-7.42 (m, 6H), 5.19 (s, 1H), 5.16 (s, 1H), 4.28 (d, 1H, J=3.8), 4.13 (t, 2H, J=7.2), 3.35-3.40 (m, 2H), 2.94-3.03 (m, 2H), 2.62-2.72 (m, 2H), 2.54-2.59 (m, 1H), 2.06-2.16 (m, 1H), 1.92 (d, 1H, J=13.6), 1.81-1.87 (m, 1H), 1.71-1.78 (m, 1H), 1.38 (ddd, 1H, J=12.8, 12.4, 4.8), 1.26 (t, 3H, J=7.2), 1.16-1.26 (m, 1H), 1.04 (s, 9H), 0.86-0.95 (m, 1H)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 202.1, 172.4, 145.1, 135.5, 133.7, 129.6, 127.6, 118.9, 81.0, 68.8, 60.7, 54.9, 53.2, 45.6, 43.7, 39.4, 37.5, 29.1, 26.8, 24.9, 19.2, 14.3

FTIR (neat, 23 °C) 3437.3 (br), 2928.3 (s), 2857.2 (m), 1731.1 (s), 1703.1 (s), 1567.3 (w), 1468.8 (w), 1427.2 (m), 1389.9 (m), 1371.0 (m), 1301.2 (m), 1251.3 (m), 1162.6 (m), 1113.4 (s), 1037.1 (m), 823.0 (m), 740.4 (m), 703.54 (s), 614.74 (m), 505.6 (s)

HRMS (FTMS, Na^+): Expected for $C_{32}H_{42}SiO_5Na^+$: 557.26880 Found: 557.26937

TLC (50% Ethyl acetate / hexanes) $R_f = 0.63$ (UV, Mn)



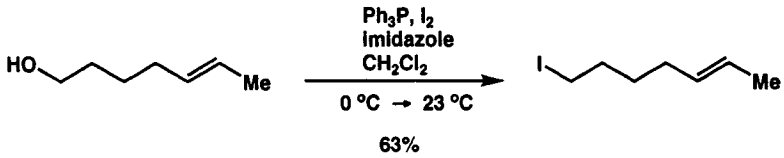
Enone **178**:

To alcohol **185** (11 mg, 0.021 mmol) in CH_2Cl_2 containing 4 Å molecular sieves) was added N-methylmorpholine N-oxide (15 mg, 0.14 mmol), and TPAP. The amount of tarry TPAP was not measured exactly, but was enough to barely cover the tip of a standard spatula (~5 mg) which was placed directly in solution. The solution became black. After 3 h, water (5 mL) was added, along with $NaSO_3$ (~20 mg). After stirring 10 min, the reaction was partitioned with brine (10 mL) and extracted with EtOAc (2 x 10 mL). The crude reaction mixture was placed under vacuum for 1 h to remove all traces of residual N-methylmorpholine, and then carried forward directly to the conjugate addition step.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) 7.55-7.62 (m, 4H), 7.32-7.44 (m, 6H), 6.27 (s, 1H), 5.51 (s, 1H), 4.09 (t, 2H, J=7.1), 3.36-3.42 (m, 2H), 3.24-3.29 (m, 1H), 2.81 (s, 1H), 2.47 (dd, 1H, J=16.2, 6.0), 2.34 (dd, J=16.2, 7.7), 2.16-2.26 (m, 1H), 1.92 (d, 1H, J=14.4), 1.79-1.84 (m, 1H), 1.60-1.73 (m, 2H), 1.22 (t, 3H, J=7.1), 1.03 (s, 9H), 0.85-0.89 (m, 1H).

FTIR (23 °C, neat) 2928.2 (s), 2855.8 (s), 1729.9 (s), 1692.1 9 (m), 1368.4 (w), 1427.4 (m), 1375.6 (m), 1176.1 (m), 1109.3 (s), 911.2 (w), 822.7 (w), 737.3 (m), 703.6 (s)

TLC (20% Ethyl acetate / hexanes) $R_f = 0.40$ (UV, Mn)



Alkyl iodide **192**:

To a clear solution of Ph_3P (1.878 g, 7.16 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added I_2 (1.634 g, 6.44 mmol). A precipitate formed, and the solution turned dark orange. After 10 minutes at this temperature, imidazole 559 mg, 8.21 mmol) was added, causing the solution to turn deep yellow over two minutes. After 10 minutes, a solution of *trans*-hept-5-ene-1-ol [9] (676 mg, 5.93 mmol) in CH_2Cl_2 (10 mL followed by 10 mL rinse) was added via cannula. Upon addition of alcohol, the colour disappeared instantaneously. A white precipitate remained. The solution was allowed to warm to room temperature overnight. After 12h, 1:1 saturated $Na_sS_sO_3$ / saturated $NaHCO_3$ (30 mL) was added and the mixture extracted with diethyl ether (3 x 30 mL). The organic phases were washed with brine (30 mL), dried (Na_2SO_4) and concentrated to give an oily white solid. This was purified on a short plug of silica (hexanes → 5% EtOAc / hexanes) to give iodide **187** (905 mg, 63%) as a colourless oil.

^1H NMR (400 MHz, $CDCl_3$, 23 °C) 5.36-5.46 (m, 2H), 3.18 (td, 2H, J=7.0, 2.1), 1.99 (dd, 2H, J=9.5, 6.5), 1.79-1.85 (m, 2H), 1.63 (m, 3H), 1.41-1.48 (m, 2H)

^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) 130.48, 125.38, 33.05, 31.51, 30.45, 18.02, 7.21

FTIR (neat, 23 °C) 3020.24 (m), 2958.03 (s), 2930.76 (s), 2853.31 (m), 1450.48 (m), 1208.35 (m), 1187.13 (m), 965.26 (s)

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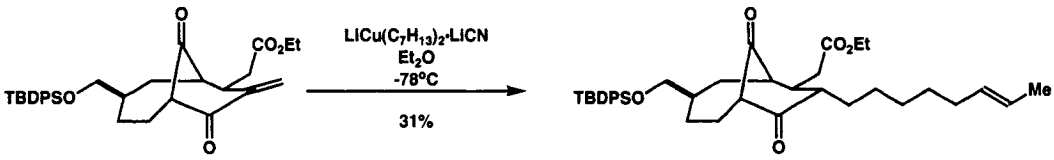
[9] Denmark, S. E.; Cramer, C. J.; Dappen, M.S. *J. Org. Chem.* **1987**, *52*, 877

HRMS(FTMS) of Ag complex: Expected for $C_7H_{13}AgI^+$: 330.91086 Found: 330.91074

TLC (100% Hexanes) Rf = 0.64 (UV, Mn)



Conjugate addition product **186**:

To iodide **192** (60 mg, 0.26 mmol) in Et_2O (0.5 mL) at –78 °C was added t-BuLi (260 μL of a 2.00 M solution in pentane, 0.52 mmol). A white mist was observed as the *t*-BuLi was added. After 15 min, the clear solution was cannulated into a slurry of CuCN (28.0 mg, 0.31 mmol) in Et_2O (0.5 mL) at –78 °C. Over 5 min, the colour of the solution went from clear to bright yellow. The yellow solution was stirred for a further 30 min, after which a solution of diketone **178** (~11 mg, 0.021 mmol) in Et_2O (0.5 mL + 0.5 mL rinse) was added dropwise via cannula. The colour changed from bright yellow to a darker, brownish yellow. After 15 min, saturated aqueous NH_4Cl (1 mL) was added, and the solution slowly warmed to room temperature. After stirring for 10 min at 23 °C, a further portion of saturated aqueous NH_4Cl solution (10 mL) was added, and the mixture extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na_2SO_4, filtered and concentrated. Column chromatography (pipet column, 10% EtOAc to 30% EtOAc in 10% increments) gave enone **186** (4.1 mg, 31% over two steps) as a clear oil.

See Appendix A for copies of spectra and structural assignment

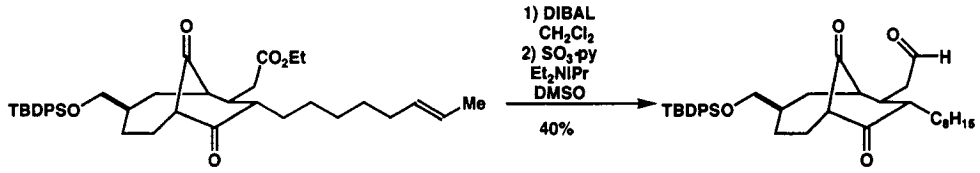
^1H NMR (500 MHz, $CDCl_3$, 23 °C) 7.59-7.65 (m, 4H), 7.35-7.44 (m, 6H), 5.39-5.42 (m, 2H), 4.13 (q, 2H, J=7.2), 3.40 (d, 2H, J=6.4), 3.10 (d, 1H, J=8.7), 2.77 (m), 2.55 (dd, 1H, J=16.0, 3.9), 2.41 (dd, 1H, J=16.0, 7.6), 2.27 (ddd, 1H, J=11.5, 7.8, 2.6), 2.08-2.15 (m, 1H), 1.91-2.04 (m, 4H), 1.79 (d, 2H, J=15), 1.73-1.77 (m, 1H), 1.64 (s, 3H), 1.61-1.64 (m, 1H), **xXX** 1.27-1.30 (m), 1.25 (t, 3H, J=7.2), 1.12-1.20 (m), 1.03 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C) 210.4, 207.5, 171.4, 135.6, 135.5, 133.5, 131.4, 129.7, 127.7, 124.8, 67.8, 61.4, 60.8, 53.5, 52.7, 38.0, 37.7, 36.3, 34.3, 32.5, 29.4, 29.3, 28.1, 26.8, 26.8, 26.5, 22.7, 19.2, 17.9, 14.2

FTIR (neat, 23 °C) 2927.7 (s), 2855.9 (s), 1734.0 (s), 1708.2 (s), 1461 (m), 1427 (m), 1159 j(m), 1110 (s), 704 (s), 505.4 (m)

HRMS (FTMS, Na^+) Calculated for $C_{39}H_{54}O_5SiNa^+$: 653.36276 Found: 653.36327

TLC (20% Ethyl acetate / hexanes) $R_f = 0.63$ (UV, Mn)



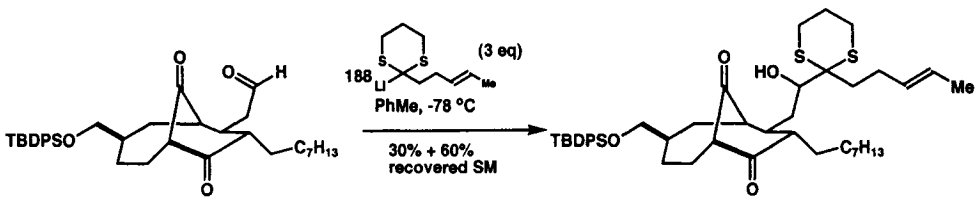
To diketone **186** (26.0 mg, 0.041 mmol) in CH_2Cl_2 (1.0 mL) at −78 °C was added DIBAL (1.0 M solution in toluene, 120 μL, 3.0 equiv) and the reaction followed by TLC. After 60 min a further 80 μL was added. After a further 30 min, the excess DIBAL was quenched with saturated potassium sodium tartrate (1.0 mL) and the mixture allowed to warm to room temperature. Brine (10 mL) was added, and the reaction mixture extracted with EtOAc (6 x 10 mL), dried (Na_2SO_4), filtered and concentrated. The crude reaction mixture, which consisted primarily of an aldehyde by ^{1}H NMR, was immediately carried forward to the next step.

The crude mixture of alcohols (27 mg, 0.041 mmol) was dissolved in CH_2Cl_2 (1.0 mL) and cooled to 0 °C. In sequence were added DMSO (80 μL, 1.0 mmol), Et*i*Pr_2 (100 μL, 0.71 mmol), and sulfur trioxide pyridine complex (67 mg, 0.43 mmol). After 1 h the reaction was partitioned with brine (10 mL), extracted with diethyl ether (3 x 10 mL), dried (Na_2SO_4), filtered and concentrated. Column chromatography (5% → 10% → 20% → 30% EtOAc / hexanes) gave 10.0 mg (40%, 2 steps) of aldehyde **187** as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C) 9.82 (s, 1H), 7.59-7.63 (m, 4H), 7.35-7.44 (m, 6H), 5.39-5.42 (m, 2H), 3.43 (dd, 1H, *J*=10.0, 6.3), 3.39 (dd, 1H, *J*= 10.0, 7.2), 3.11 (d, 1H, *J*=9.5), 2.73 (dd, 1H, *J*= 18.5, 3.5), 2.57-2.65 (m, 2H), 2.22 (ddd, 1H, *J*=11.5, 8.0, 2.4), 2.07-2.16 (m, 2H), 1.90-1.97 (m, 3H), 1.85 (d, 1H, J=14.7), 1.78 (dt, 1H, *J*=14.5, 4.9), 1.67-1.73 (m, 1H), 1.64 (d, 3H, J=3.5), 1.49 (ddd, 1H, J=14.5, 12.0, 5.2), 1.43 (d, 1H, J=12), 1.25-1.39 (m), 1.09-1.21 (m), 1.04 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C) 210.2, 207.1, 199.7, 135.6, 135.5, 133.5, 131.3, 129.7, 127.7, 124.8, 67.6, 61.4, 54.0, 52.7, 48.1, 37.7, 34.3, 34.0, 32.4, 29.3, 29.3, 26.9, 26.8, 22.6, 19.2, 17.9

TLC (33% EtOAc / hexanes) : $R_f = 0.6$ (UV, Mn)



To aldehyde **187** (5.1 mg, 0.0087 mmol) in PhMe (50 μL) in a 5 mL flame dried flask without a stirbar at −78 °C was added 45 μL (0.021 mmol) of a 0.476 M canary-yellow solution of dithiane **188** (generated by addition of 180 μL of a 2.2 M solution of *t*-BuLi in pentane to a solution of 78 μL of dithiane precursor in 0.60 mL THF at –78 °C). The addition was performed dropwise on to the small pool of solvent and not along the sides of the flask. Care was taken not to allow the dithiane solution to warm so as to lose the canary yellow colour. After 15 min a mixture of H_2O and Et_2O (2 mL, 1:1) was added, and after warming to room temperature the mixture was concentrated under vacuum. Column chromatography (pipet column, 5% → 10% → 20% → 30% EtOAc / hexanes) gave 2.4 mg (30%) of dithiane **189** as a mixture of isomers in addition to 2.8 mg (60%) recovered starting material.

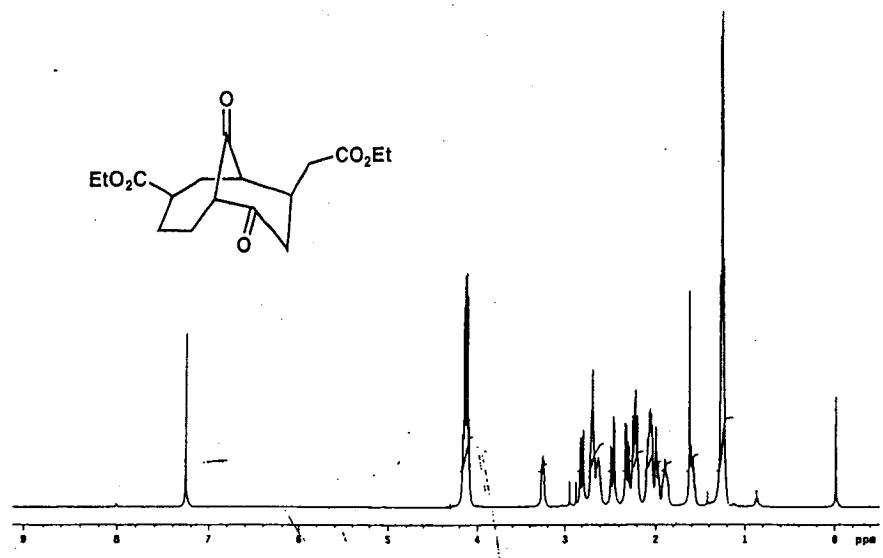
^{1}H NMR (500 MHz, $CDCl_3$, 23 °C) See Appendix for proton spectrum

FTIR (KBr pellet, 23 °C) 2926, 2855, 1727, 1701, 1111, 910

TLC (33% EtOAc / hexanes) : $R_f = 0.8$ (UV, Mn)

HRMS (FTMS, Na^+): Expected for $C_{46}H_{66}O_4NaS_2Si^+$ = 797.40704 Found: 797.40640

APPENDIX B: SELECTED SPECTRA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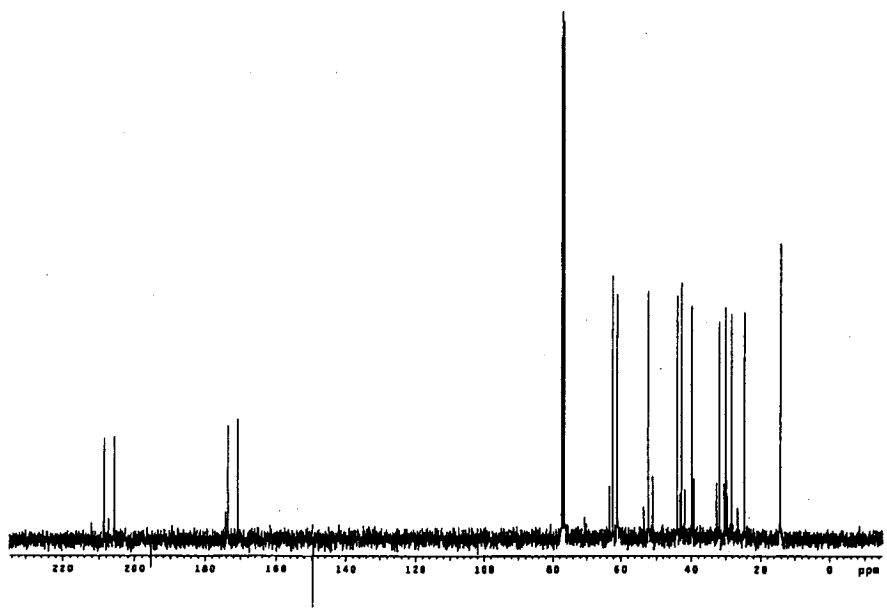
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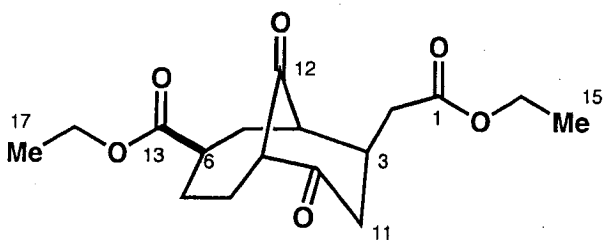
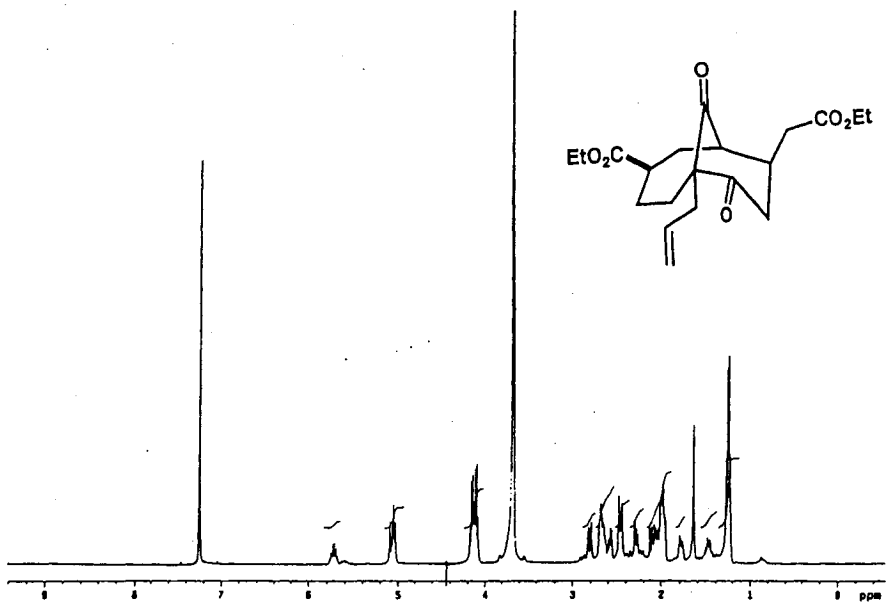


Pos. #	^{13}C shift	H no.	^{1}H shift	^{1}H-^{1}H correlations	HMBC	NOE
1	170.9	0			2, 3, 14	
2	39.9	2	2.31	2a, 3	4, 3, 1	
			2.47	2b		2a, 3, 4, 5a
3	30.0	1	2.63	2a, 11a	4, 3, 5, 2, 11	
4	52.2	1	2.69		3, 5, 11, 9	
5	31.7	2	1.98	5a	7	
			2.08			
6	42.6	1	2.68		4, 5, 7, 8	
7	28.3	2	1.60	8a, 7b, 8b, 6	5, 6, 8, 9	7a, 8b, 6, 9
			2.05			
8	24.7	2	1.88	8a, 7a	6, 7, 9	8a, 6, 7a (-), 7b, 9
			2.19			
9	62.3	1	3.26	8a, 8b	4, 7, 8, 11	8b, 8a, 7a
10	205.8	0			8, 9,	
11	43.8	2	2.22		2, 3	
			2.82	11a		2.22
12	208.6	0			4, 5, 8, 9	
13	173.6	0			5, 6	
14	61.0	2	4.14	15	1, 15	
15	14.2	3	1.26	14	14	
16	61.0	2	4.10	17	13, 17	
17	14.2	3	1.23	16	16	

(-) indicates negative NOE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8
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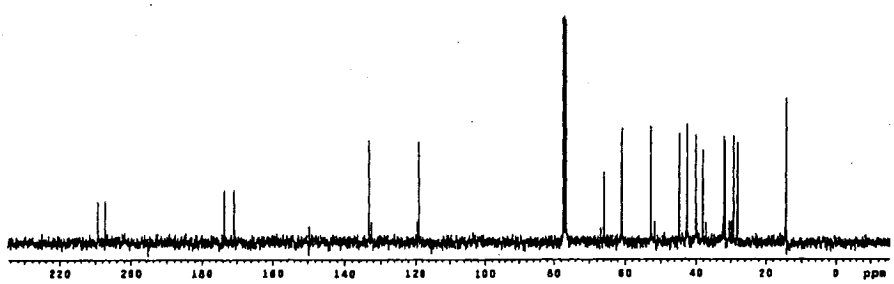
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160
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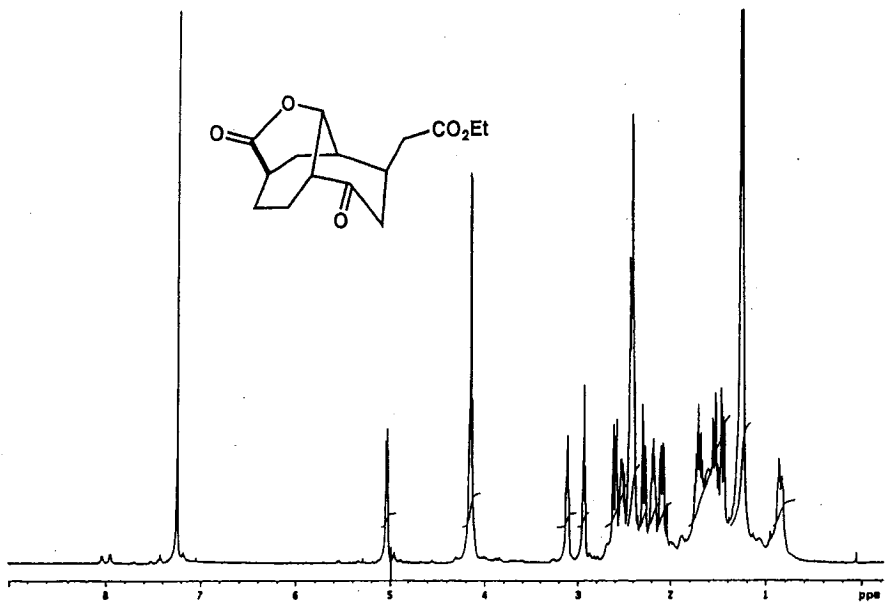
120
100
80
60
40
20
0
ppm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O
CO_2Et
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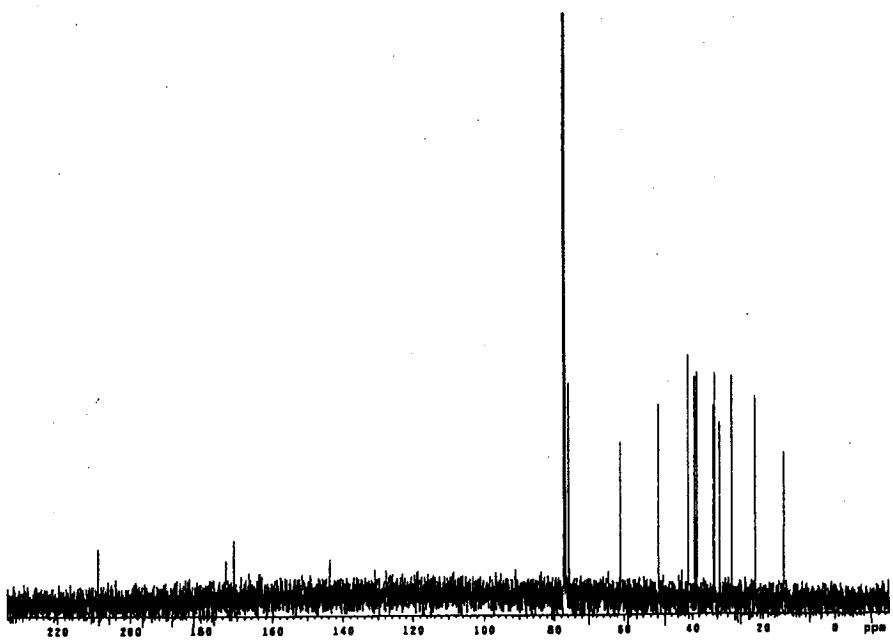
7
6
5
4
3
2
1
ppm

9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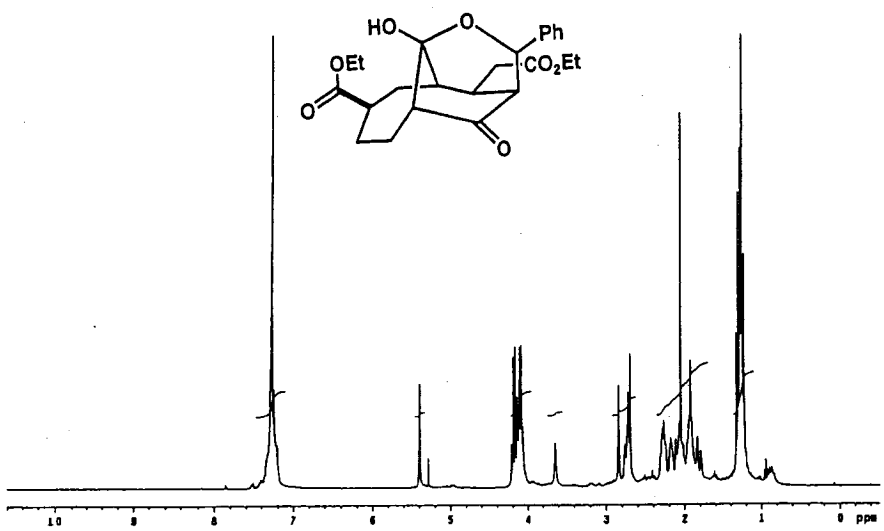
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9
8
7
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4
3
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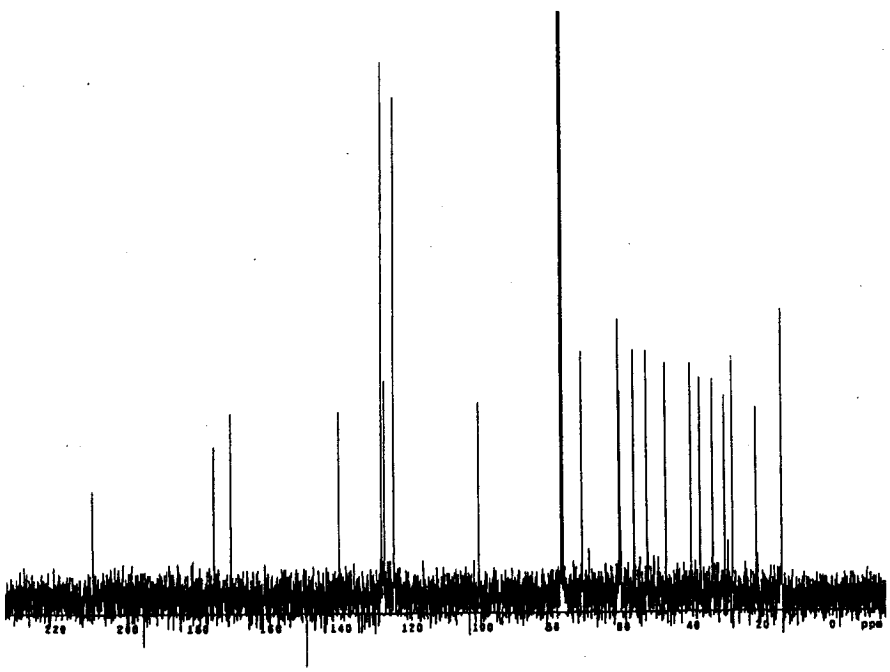
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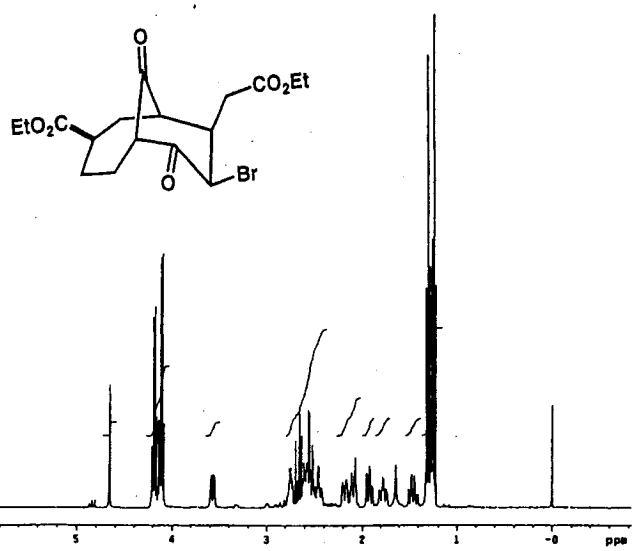
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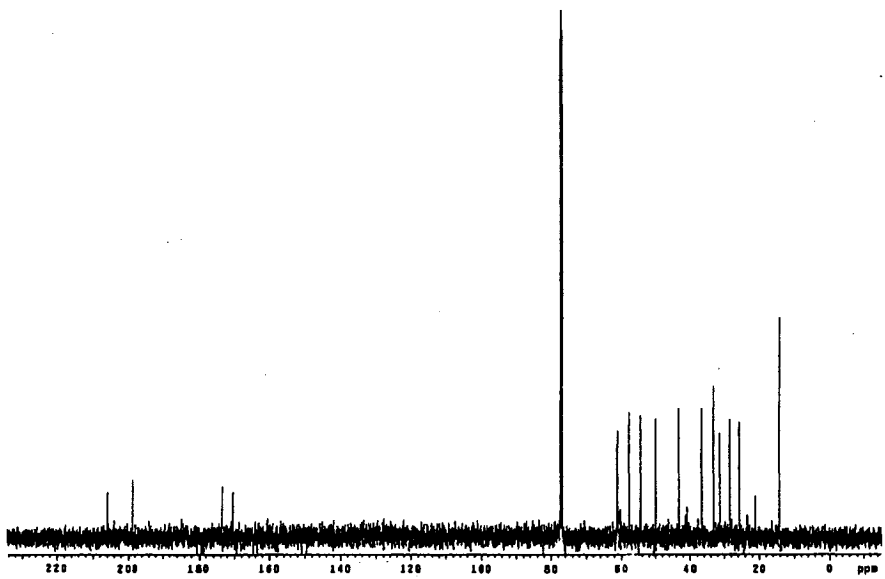
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40
20
0
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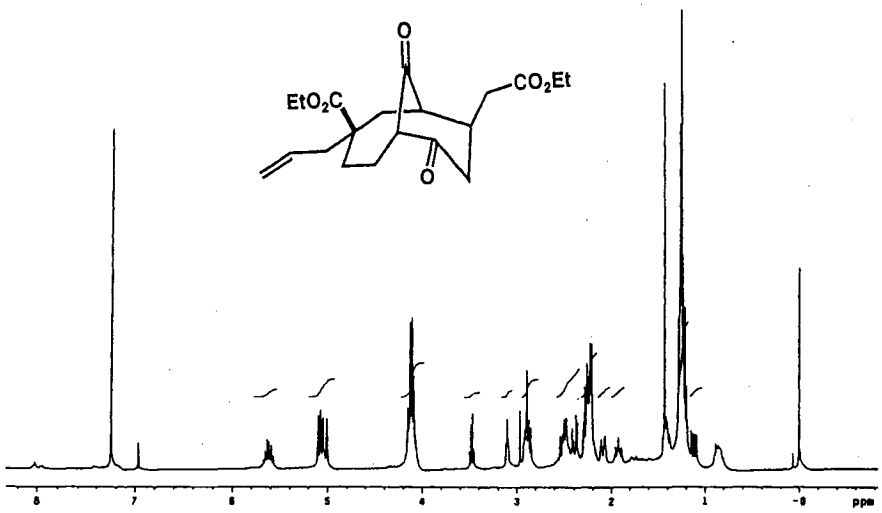
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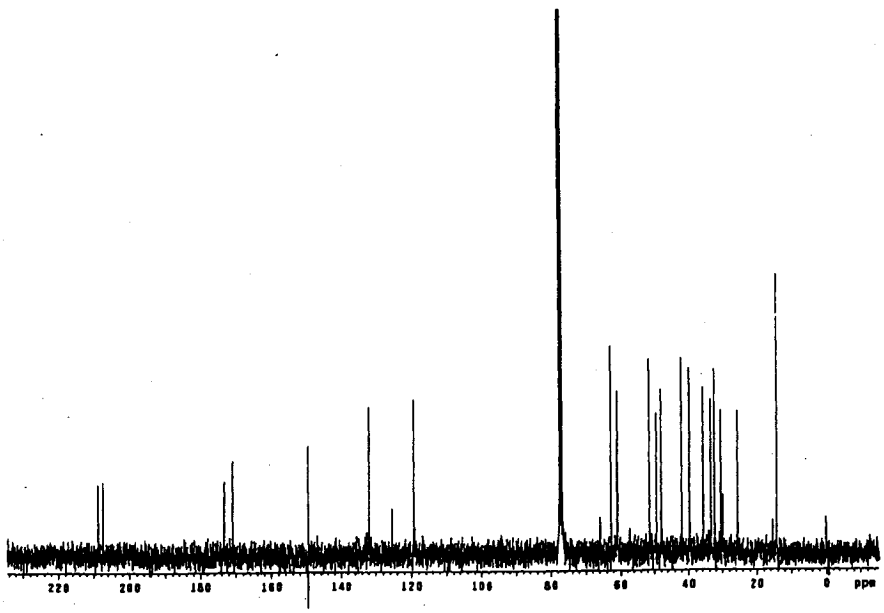
EtO2C
CO2Et
O
8
7
6
5
4
3
2
1
0
ppm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200
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60
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20
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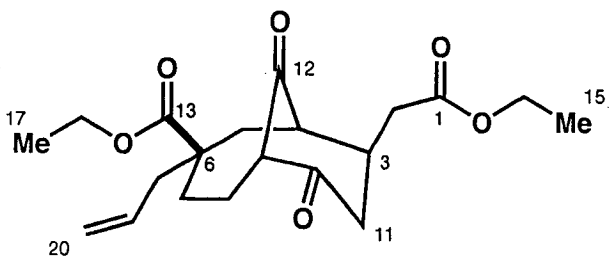
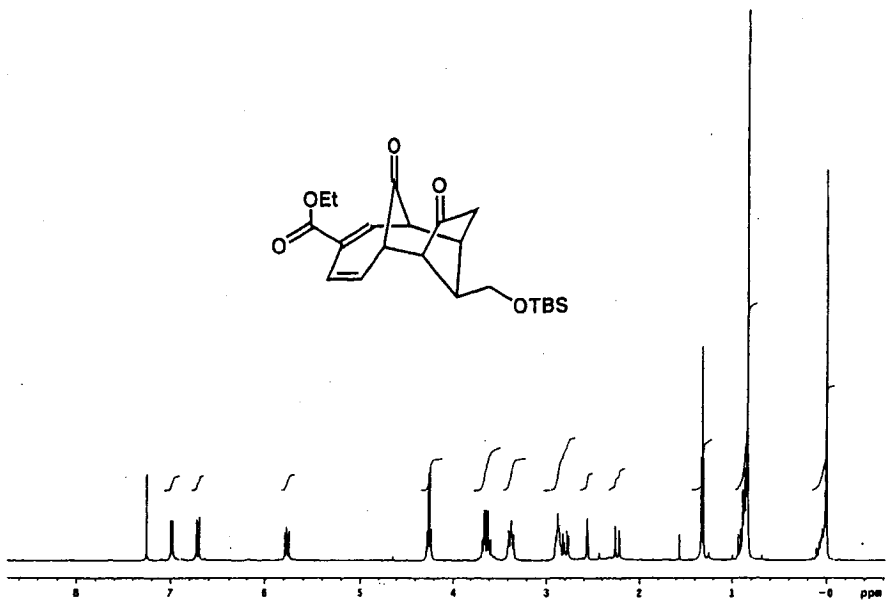


Pos. #	^{13}C shift	H no.	^{1}H shift	^{1}H-^{1}H correlations	HMBC	NOE
1	171.0	0			14	
2	39.7	2	2.19	2b, 3		
			2.40	2a, 3		
3	32.4	1	2.48	2a, 2b		
4	51.4	1	2.86	5a	5	
5	35.7	2	1.13	5b, 4	13, 18	7a, 5b, **11b**[1], **18**
			2.53	5a		5a, 4
6	49.4	0			**18**	
7	33.6	2	1.43	7b, 8a		7b, 5a, 18, 19, 11b
			2.09	7a, 8a, 8b		
8	25.4	2	1.93	7a, 7b, 8b		
			2.24			
9	62.7	1	3.10	8a, 8b		8a, 8b
10	207.5	0				
11	41.9	2	2.27	11b		
			2.88	3, 11a		
12	208.9	0			5	
13	173.4	0			5, **18**	
14	60.9	2	4.13	15		
15	14.2	3	1.25	14		
16	60.9	2	4.13	17		
17	14.2	3	1.25	16		
18	48.0	2	2.22	19, 20	5, 6, 19, 20	
19	132.0	1	5.64	20		
20	119.3	2	5.06	19		

[1] Despite overlap with **4** at this resonance, the coupling pattern on this signal (dd, J=16.8, 7.8) is unambiguously that of **11b.**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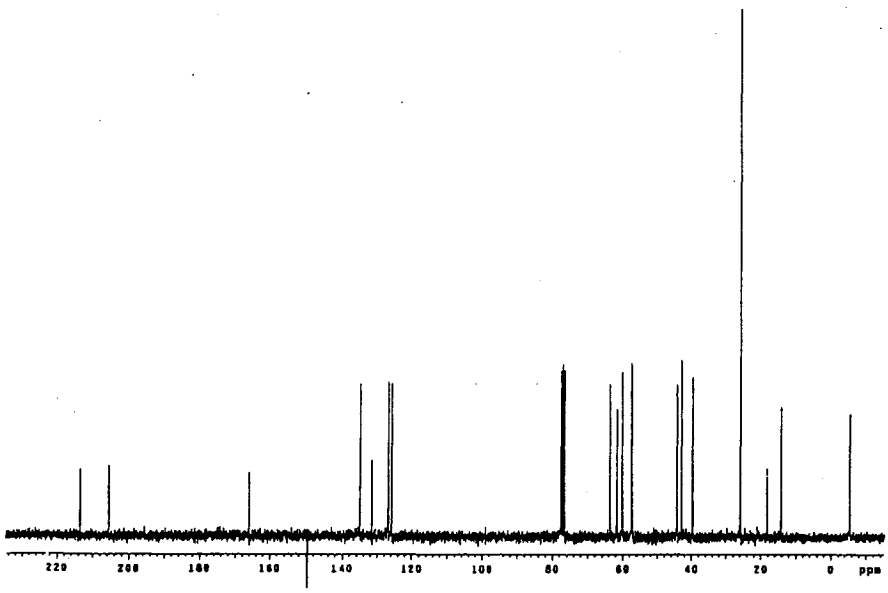
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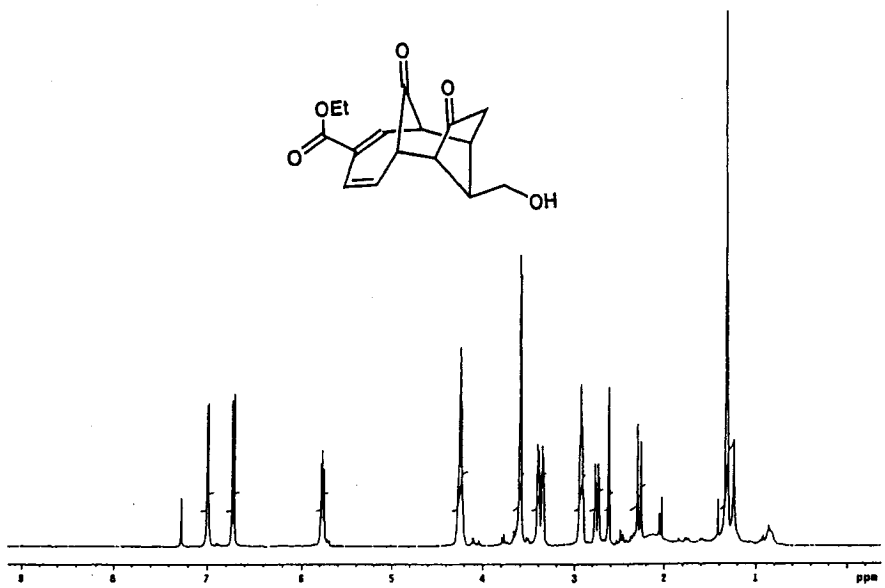
ppm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OH
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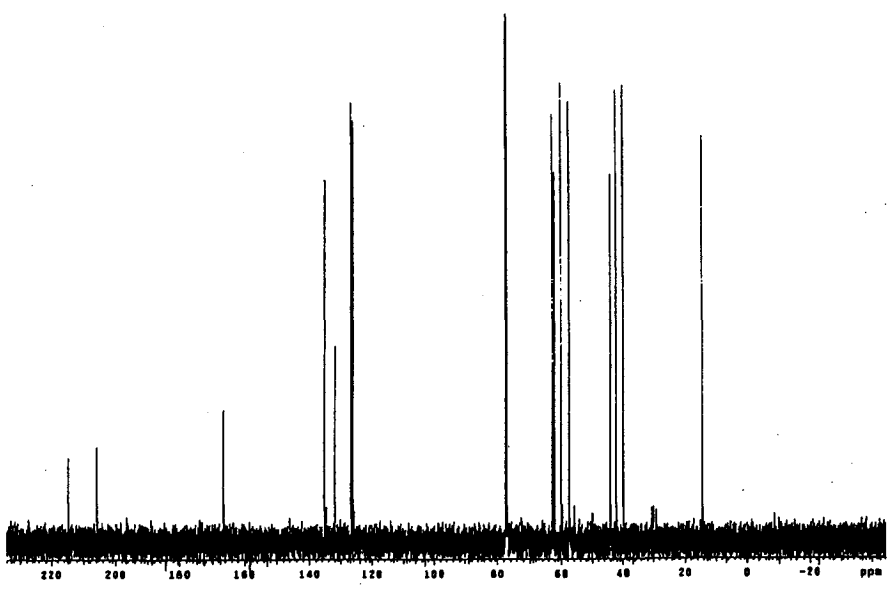
4
3
2
1
ppm

20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20
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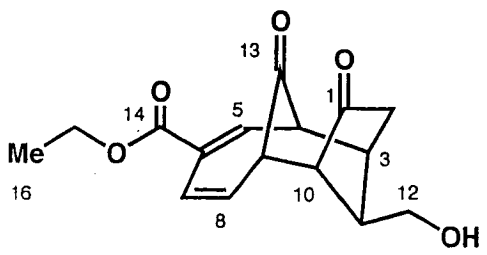
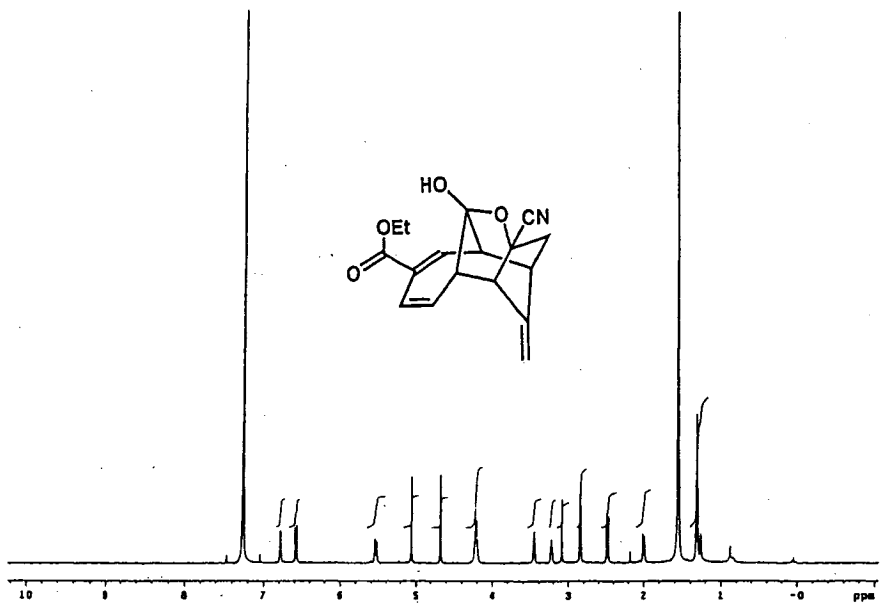
-20
ppm



Pos. #	^{13}C shift	H no.	^{1}H shift	^{1}H-^{1}H correlations	HMBC	NOE
1	214.4	0				
2	43.9	2	2.32			
			2.75			
3	42.1	1	2.94			
4	59.7	1	3.40			
5	134.9	1	7.00			
6	131.5	0				
7	125.8	1	6.73			
8	126.5	1	5.78			
9	57.2	1	3.40			
10	57.2	1	2.64			
11	39.6	1	2.94			
12	62.5	2	3.63			
13	205.6	0				
14	166.1	0				
15	61.9	2	4.26			
16	14.3	3	1.34			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CN
OEt
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8
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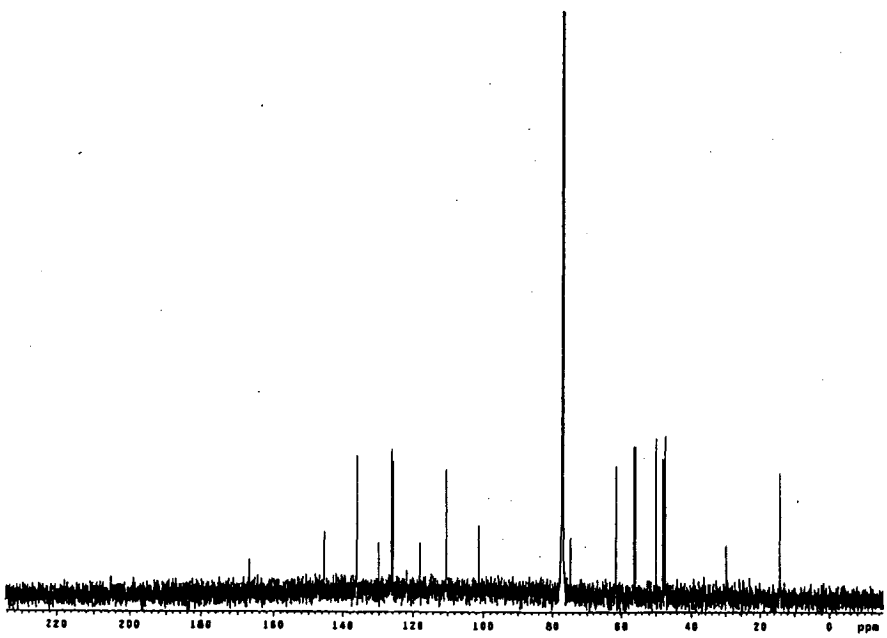
6
5
4
3
2
1
-0
ppm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100
80
60
40
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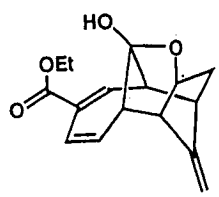
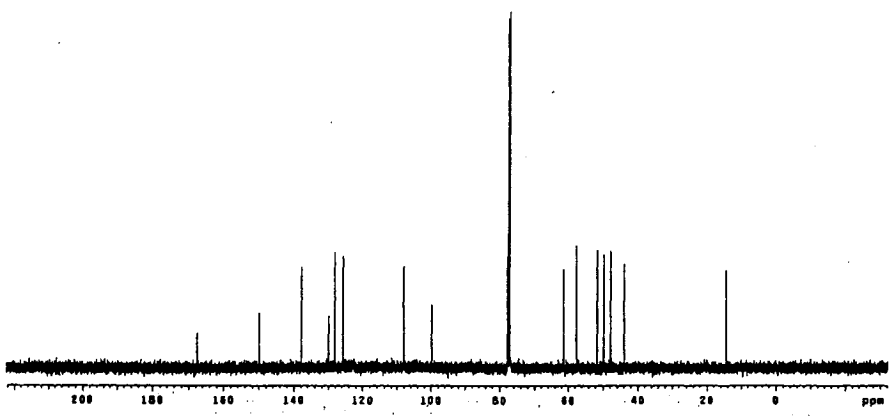
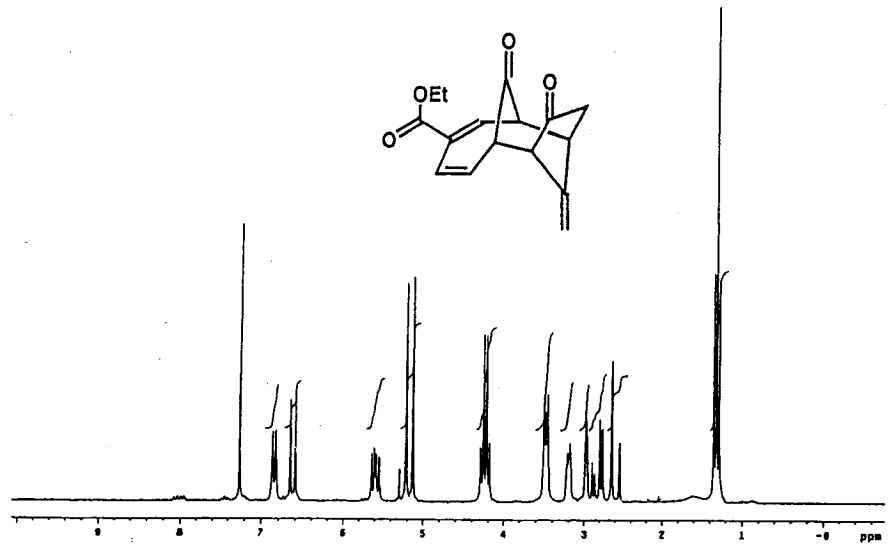
0
ppm

32



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O
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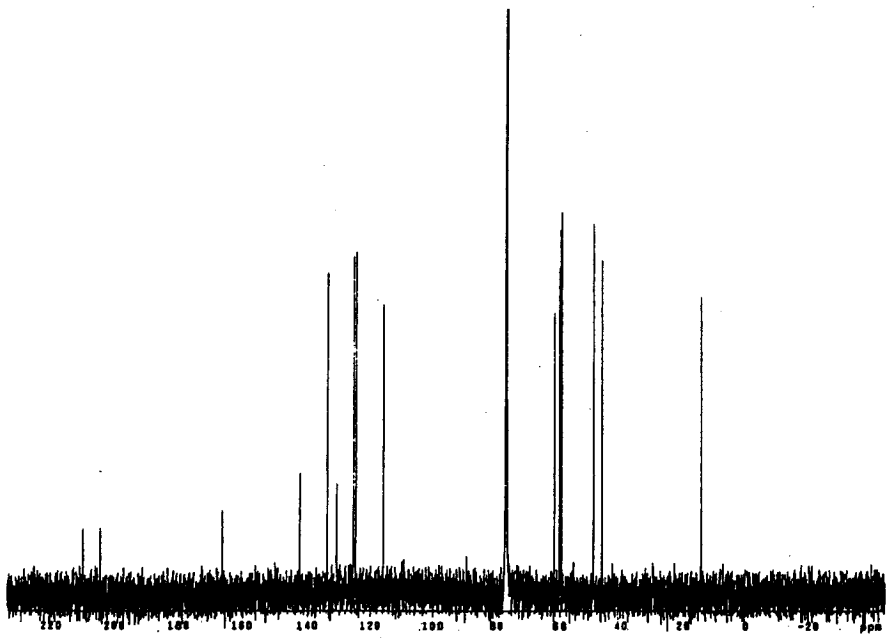
8
7
6
5
4
3
2
1
-0
ppm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-20
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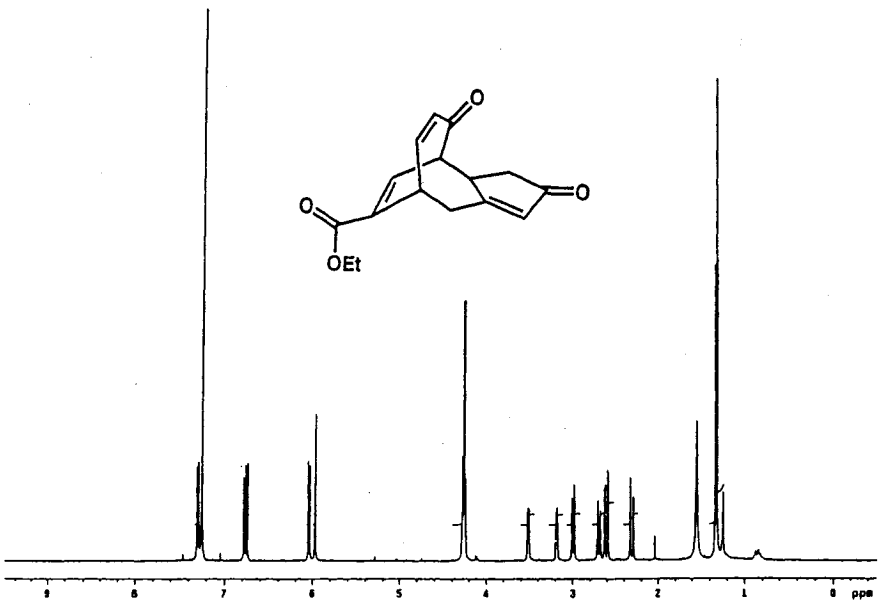
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OEt
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0
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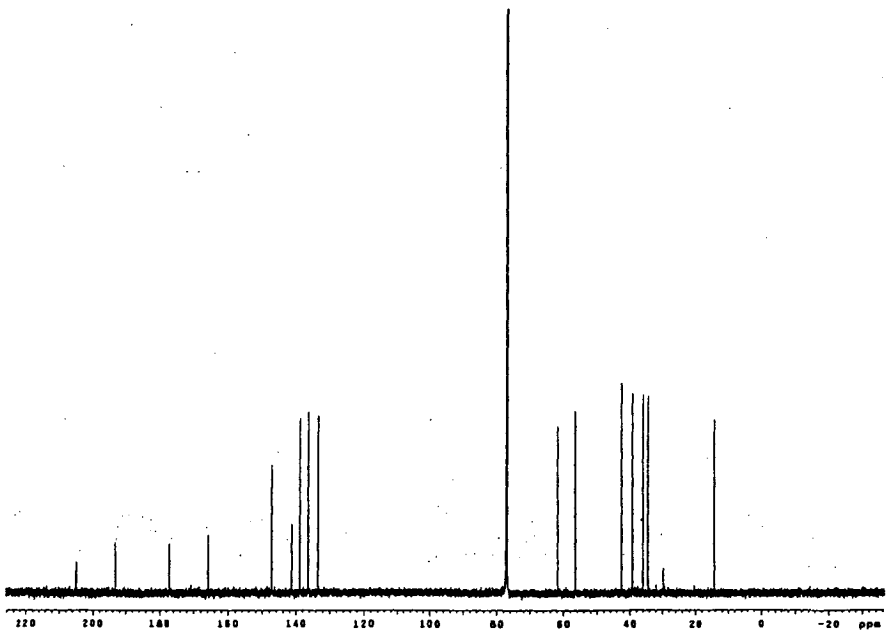
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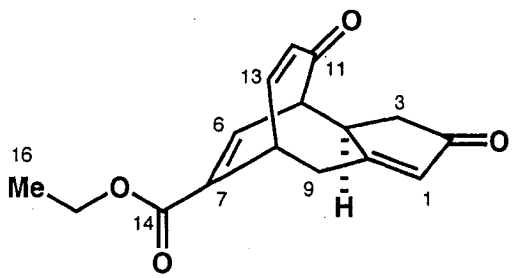
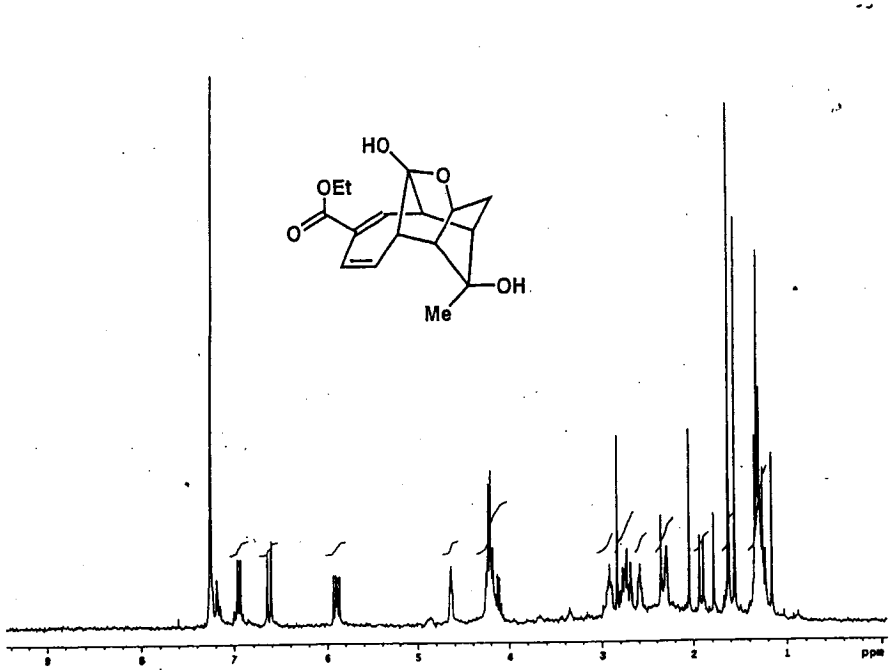
ppm



Pos. #	^{13}C shift	H no.	^{1}H shift	^{1}H-^{1}H correlations	HMBC	NOE
1	136.2	1	5.97		9	
2	204.7	0			1,	
3	39.2	2	2.32	3b	1, 5, 4, 2	4, 5, 3b,
			2.63	4, 3a,		
4	42.6	1	3.19	13	1, 3, 5,	5, 3
5	56.5	1	3.51	13	6, 12,	4, 3a, 6
6	138.7	1	7.30	5,	5	5
7	141.2	0			13, 5, 9	
8	36.0	1	4.26		13, 12, 6,	
9	34.4	2	2.70	9b	1, 4, 8, 5, 7	
			3.00	9a, 8		8,9a, 1
10	176.1	0			5, 9	
11	193.0	0			4, 12, 13	
12	133.2	1	6.04	13		
13	147.2	1	6.77	8, 12	8	8, 12
14	165.6	0			6, 15	
15	61.7	2	4.26	16	14, 16	
16	14.3	3	1.34	15	15	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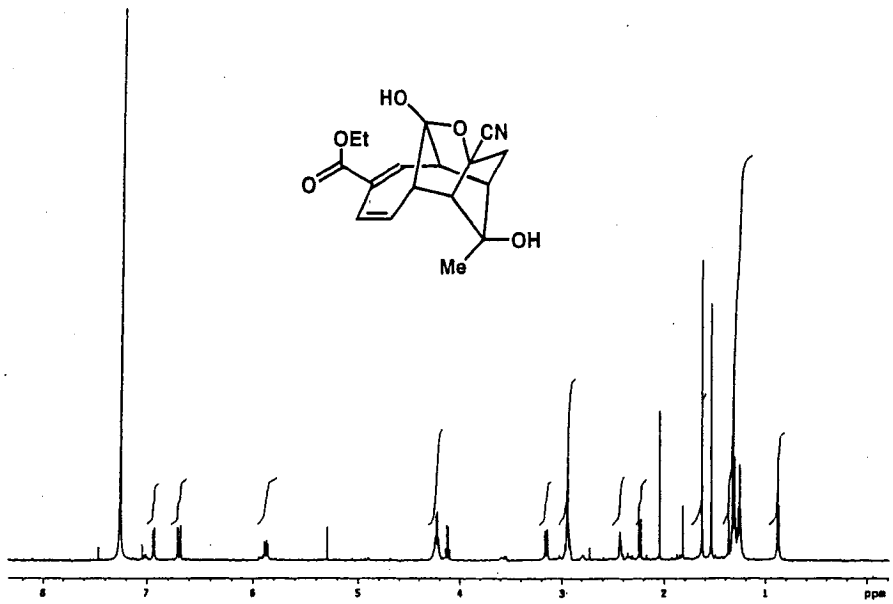
OH
Me
ppm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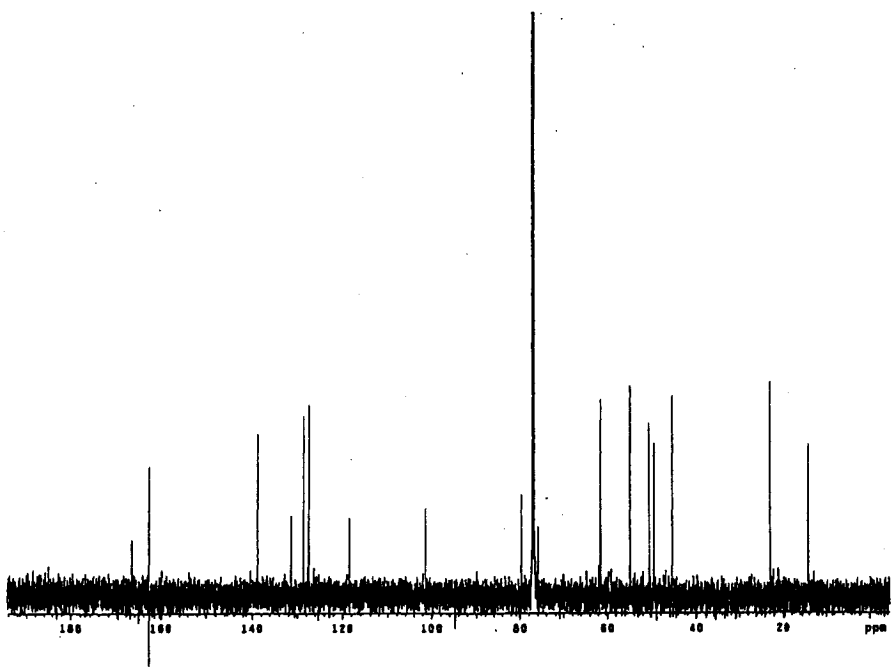
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140
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80
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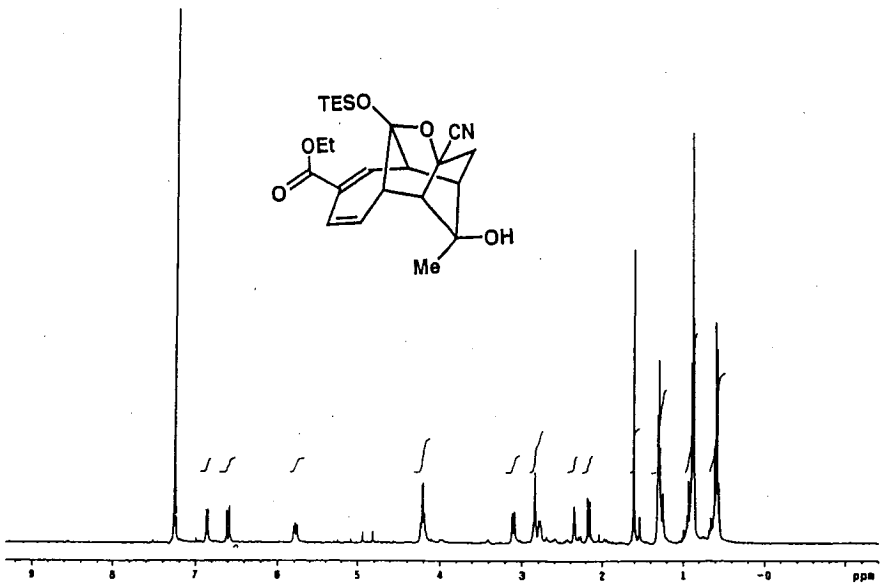
40
20
ppm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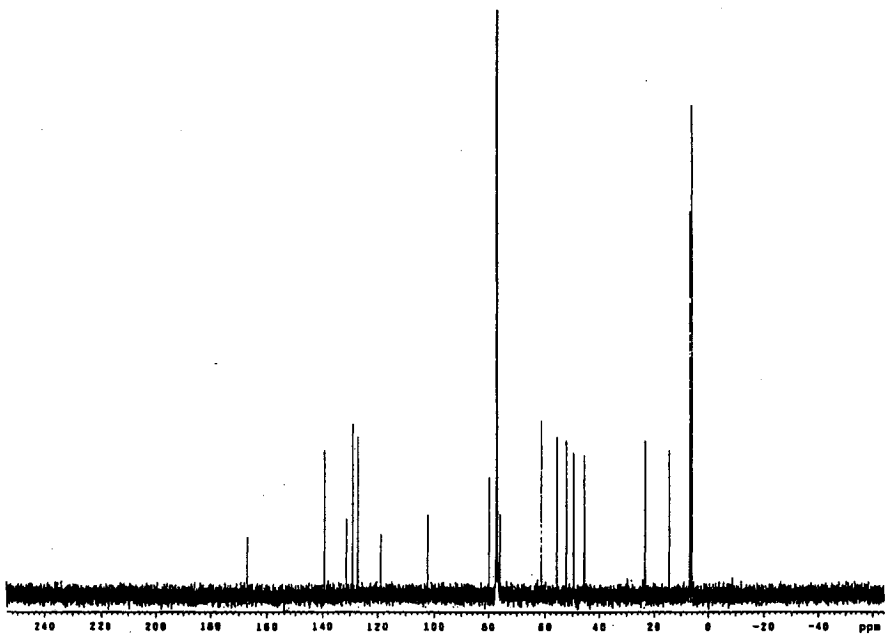
ppm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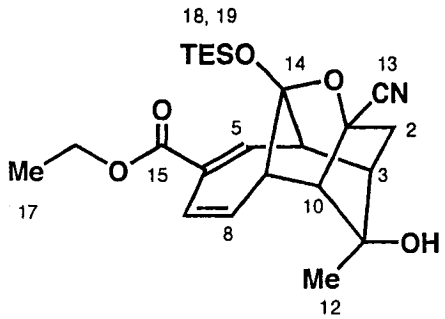
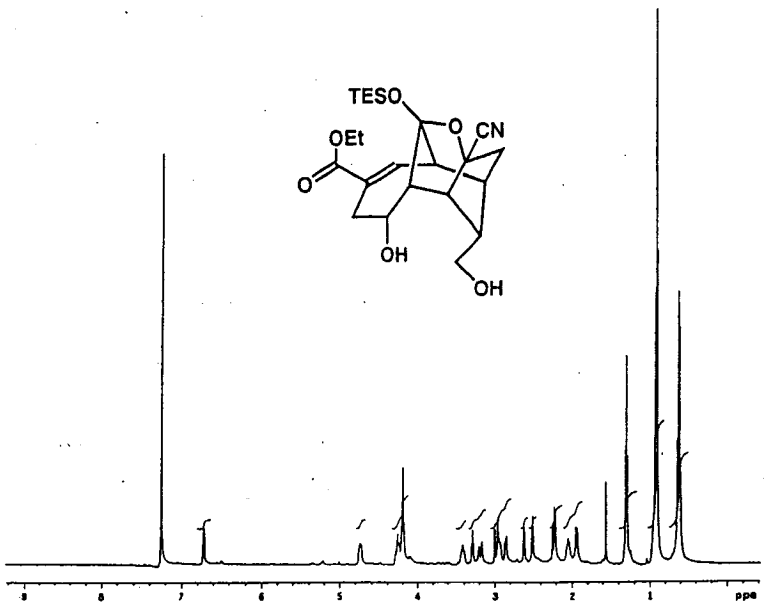
ppm



Pos. #	^{13}C shift	H no.	^{1}H shift	^{1}H-^{1}H correlations	HMBC	NOE
1	75.9	0			1	
2	45.5	2	2.18	2b		2b, 3, 4
			3.11	2a, 3	1, 4, 11	2a, 3, 10
3	49.6	0	2.36	2b	2, 12	
4	52.2	1	2.80	5	2	
5	139.3	1	6.85		15, 7, 14	
6	131.1	0				
7	127.1	1	6.60	8	15, 5	**8, 12**
8	129.0	1	5.79	7, 9	14	
9	61.2	1	2.86			
10	55.9	1	2.86			2b
11	79.7	0			2, 12	
12	23.1	3	1.63			3, **5, 7, 8**, 10
13	118.9	0				
14	102.3	0			5, 8	
15	166.9	0			5, 7, 16	
16	61.2	2	4.23	17	15, 17	
17	14.2	3	1.31	16	16	
18	6.7	6	0.90	19		
19	5.9	9	0.60	18		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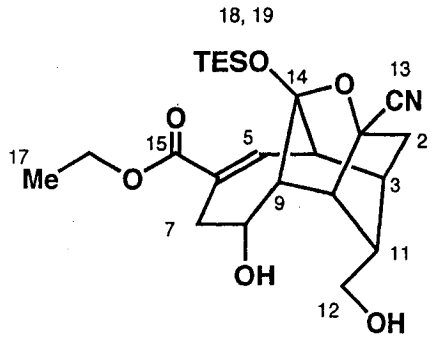
OH
OH
ppm



Pos. #	^{13}C shift	H no.	^{1}H shift	^{1}H-^{1}H correlations	HMBC	NOE
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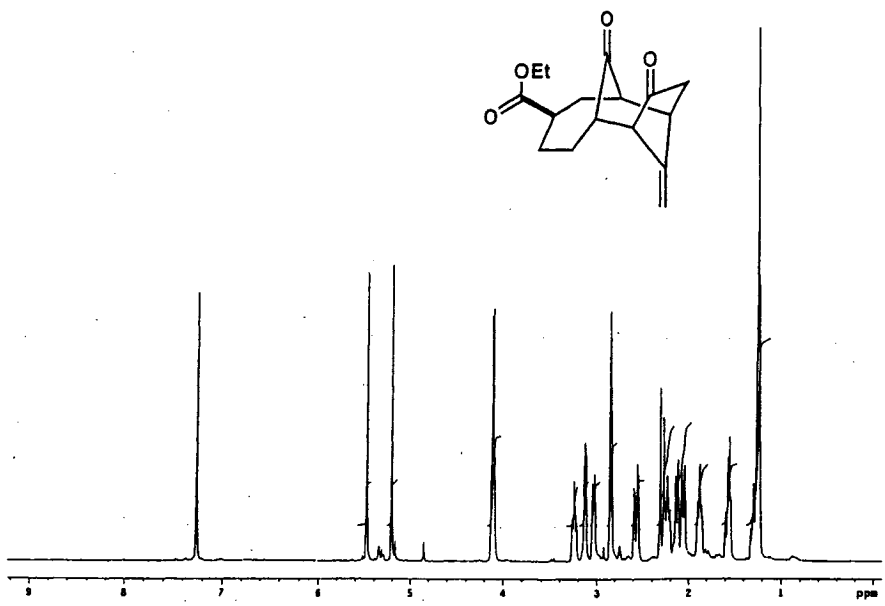
2	46.9	2	1.95	2b, 3	1, 3, 11	
			2.25	2a		
3	42.4	1	2.51	2a	2, 10, 11	
4	50.1	1	2.62	5	3	2a, 3, 5
5	138.8	1	6.72	4	4	3, 4
6	130.6	0			4, 5, 7	
7	33.7	2	2.99	7b	5, 6	
			3.19	7a		
8	68.9	1	4.74			7a, 7b, **9** (s)
9	52.8	1	2.95		10, 11	
10	48.6	1	3.30		2, 11, 12	
11	50.0	1	2.07	12b	2, 9, 10, 12	
12	60.9	2	3.42	12b	2, 11	3, 11, 12b
			4.27	11, 12a		12a
13	118.7	0				
14	104.2	0				
15	167.7	0				
16	61.4	2	4.21	17	15	
17	14.3	3	1.32	16		
18	0.64	6	6.2	19		
19	0.93	9	7.0	18		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9
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6
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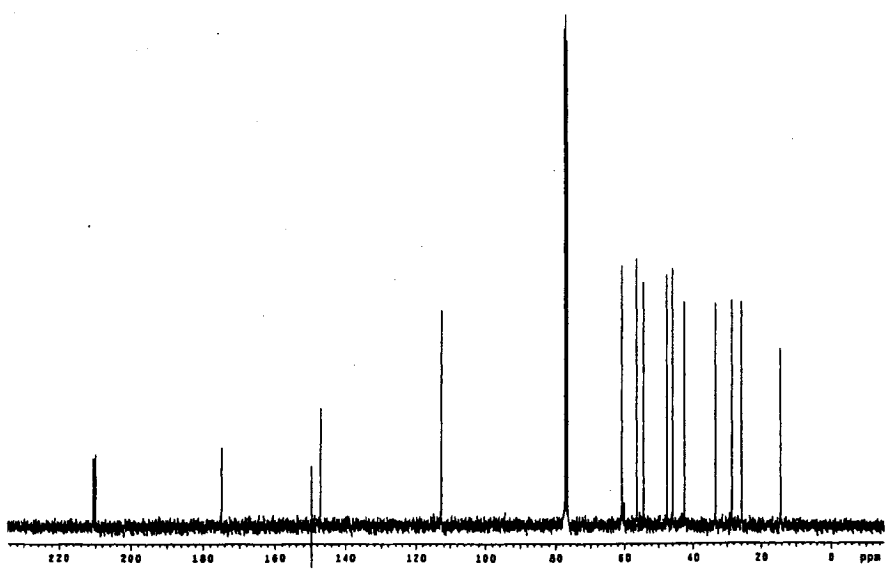
2
1
ppm

47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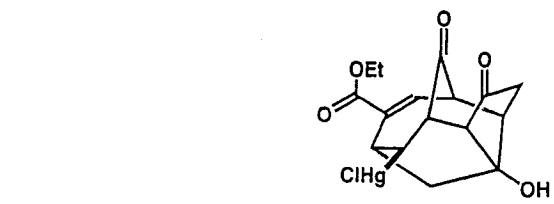
ppm


O
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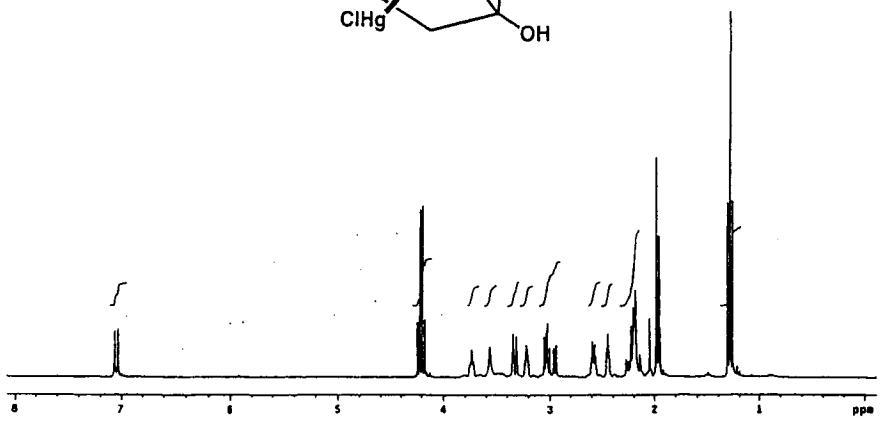
O
O
ClHg
OH


8
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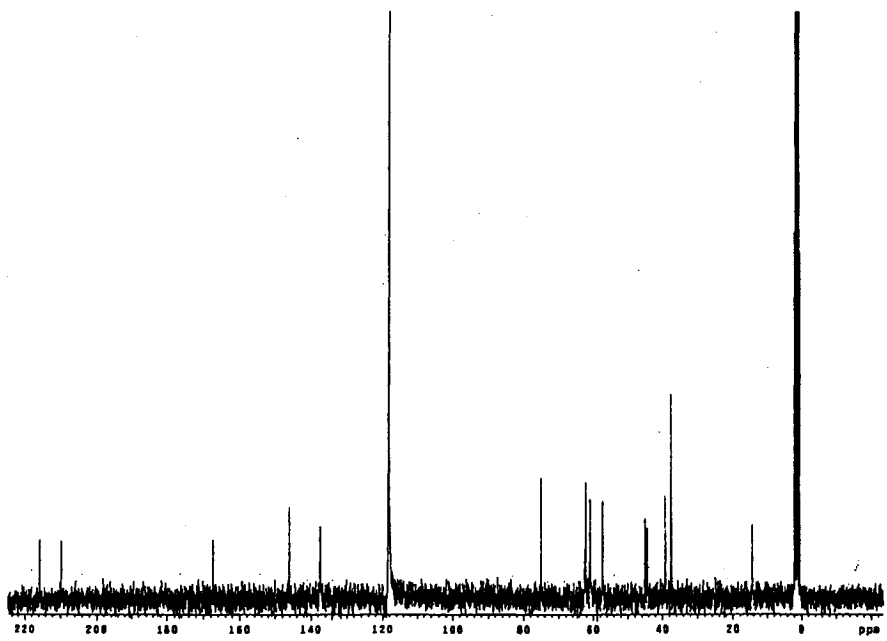
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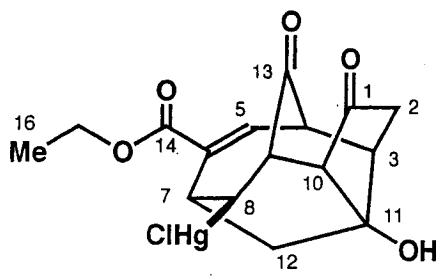
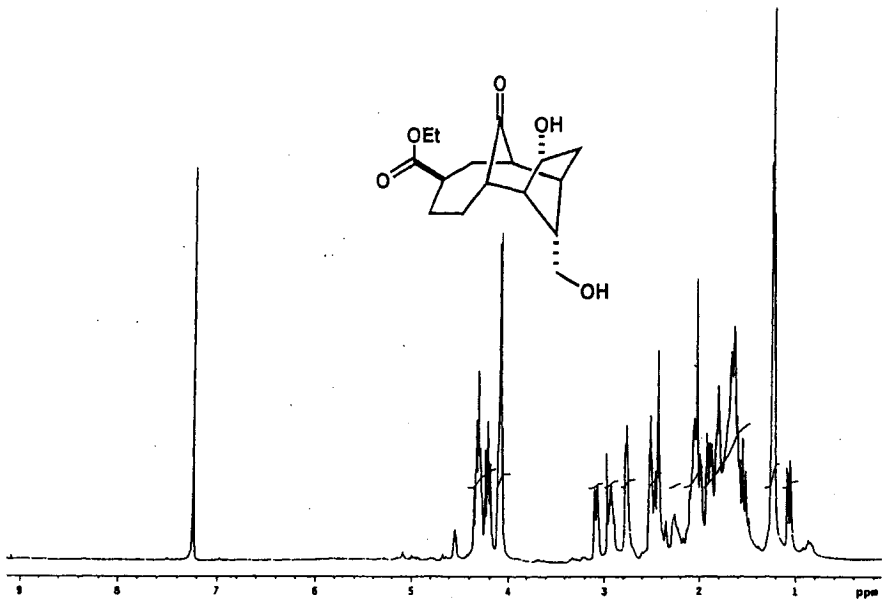
ppm



Pos. #	^{13}C shift	H no.	^{1}H shift	^{1}H-^{1}H correlations	HMBC	NOE
1	215.7	0			2a, 2b, 3	
2	45.0	2	2.11	2b		
			3.12	2a, 3		
3	44.4	1	2.62	2b		
4	57.3	1	3.36	5	13	
5	137.3	1	7.11	4		
6	146.1	0			5,12	
7	37.5	1	3.82	8, 12	12, 5	8, 12
8	60.8	1	3.05	7, 9		
9	60.6	1	3.30	8, 10		
10	44.4	1	2.49	9		
11	74.9	0			12, 7, 9	
12	39.0	2	2.27	7		
13	209.7	0			5, 4, 3, 8	
14	167.3	0			5, 7	
15	62.5	2	4.26	16		
16	14.4	3	1.34	15		


O
OEt
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OH
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6
5
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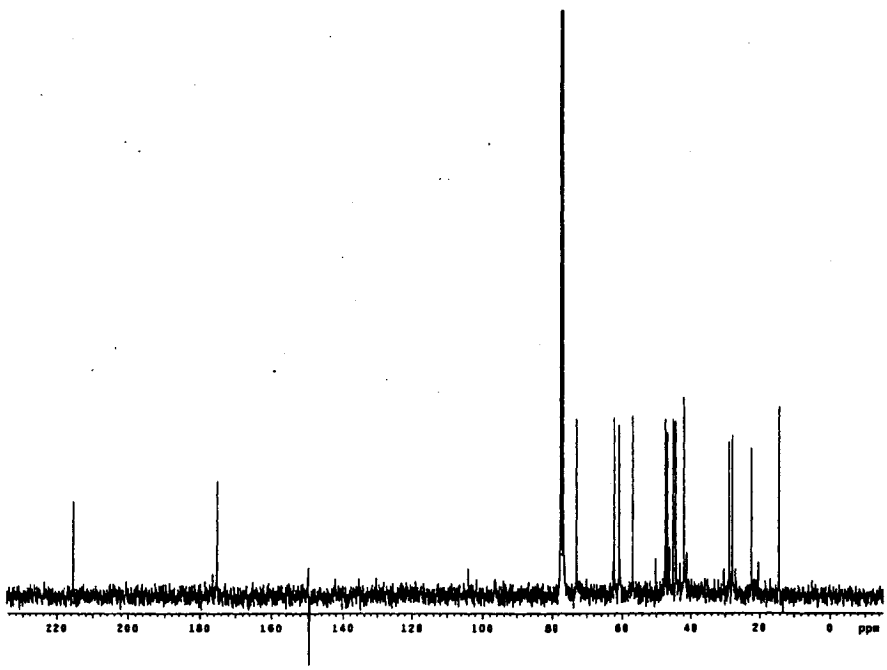
3
2
1
ppm


220
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60
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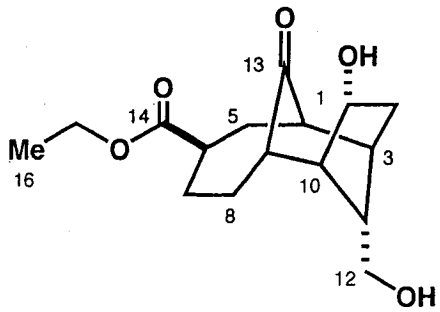

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3	41.9	1	2.45			
4	56.8	1	2.77	3, 5a,	2, 5,	
5	28.8	2	1.93	5, 6	6	
			2.10			
6	44.2	1	2.94	5a, 7a		**12**
7	28.0	2	1.56	7a	5	
			2.06			
8	22.2	2	1.67	7b	7	
			2.11			
9	47.3	1	3.10	10, 8a, 8b		8b (-), 10
10	46.7	1	2.53			
11	45.0	1	1.81		12, 4, 2	1, 2a, **2b** (-), 3, 10, 12
12	62.1	2	4.22	11	11	
			4.32			
13	215.3	0			4	
14	175.1	0			6, 15	
15	60.8	2	4.09	16		
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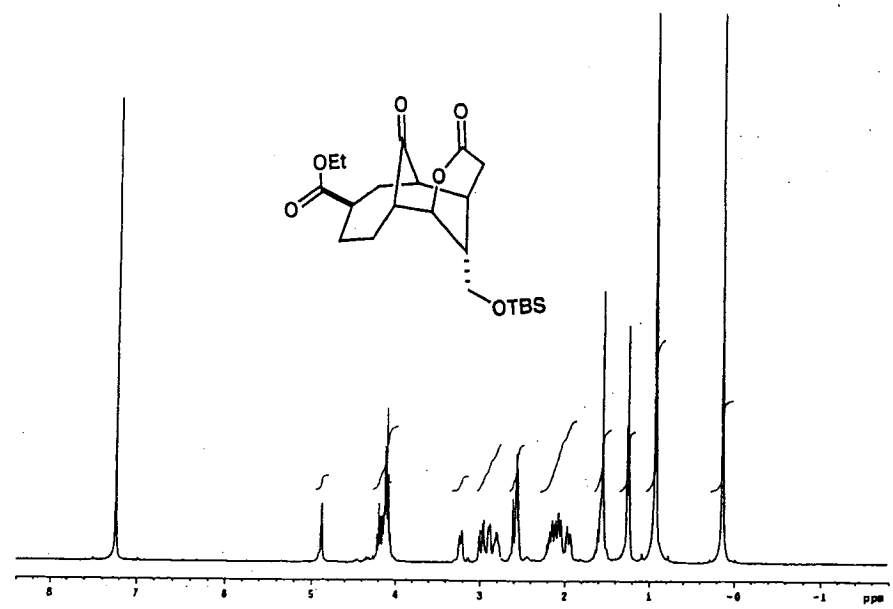
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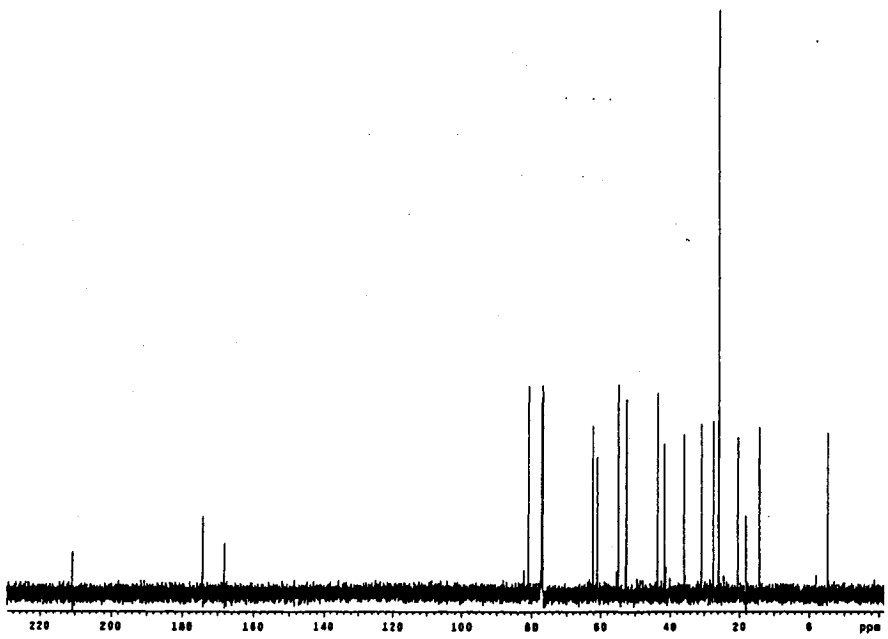
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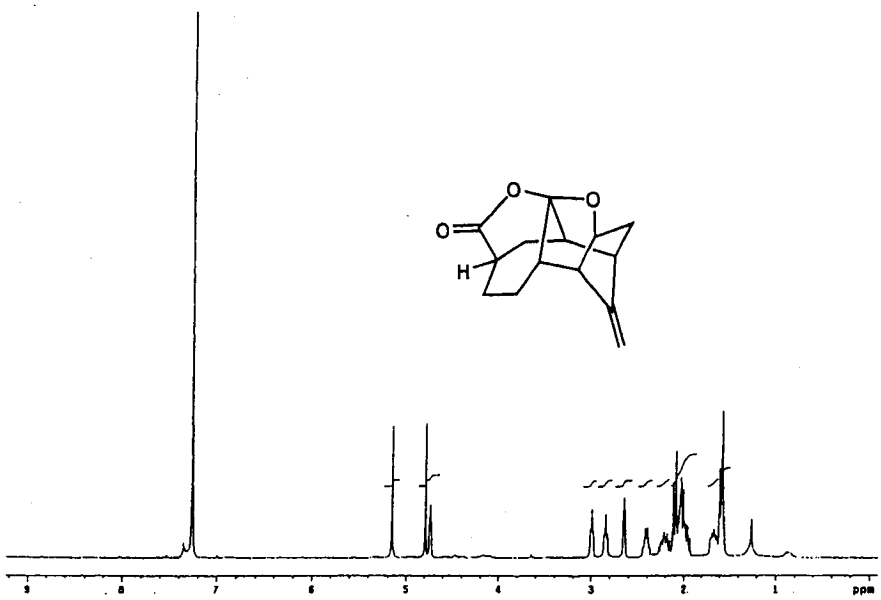
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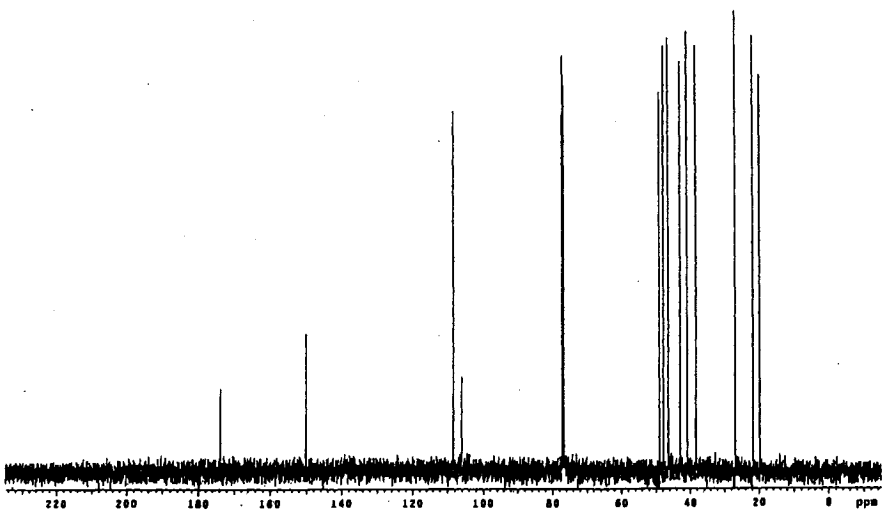
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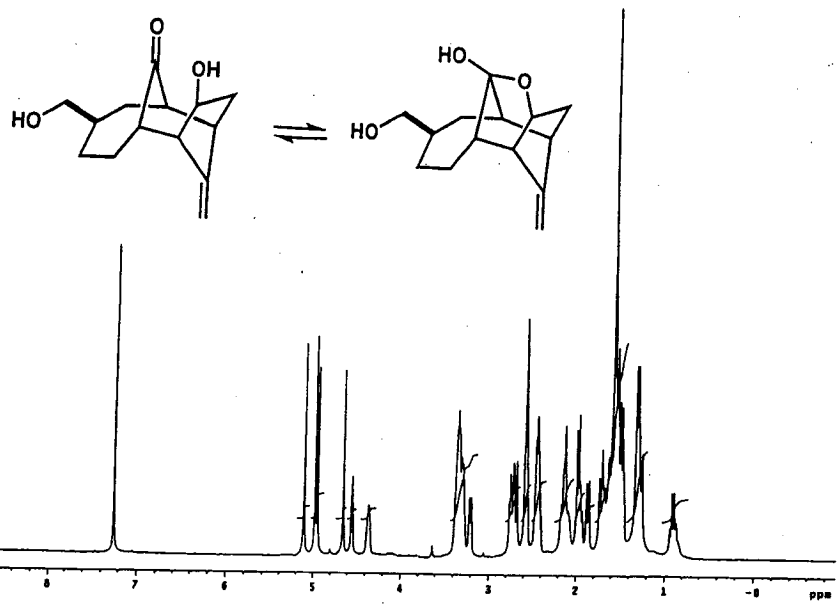
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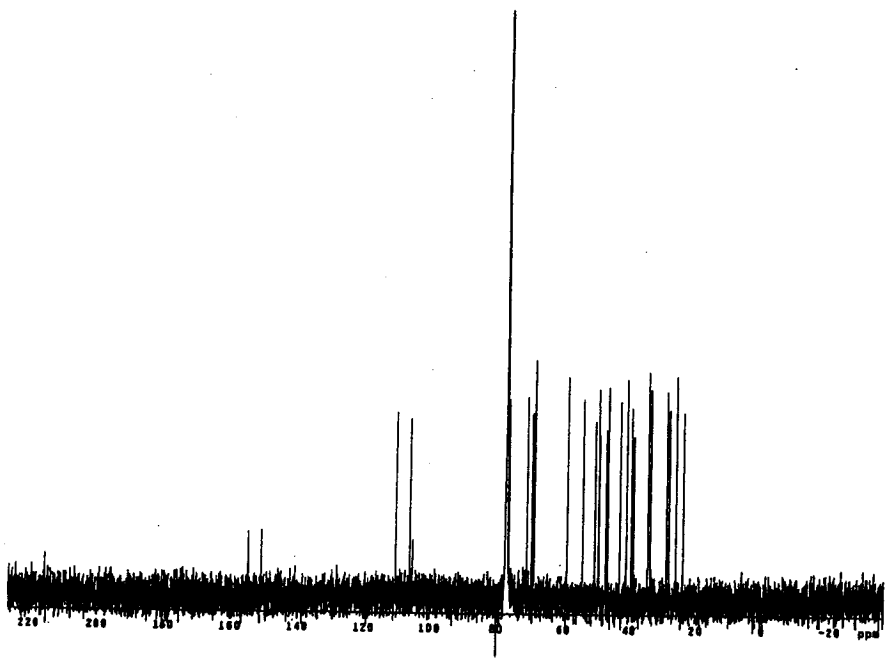
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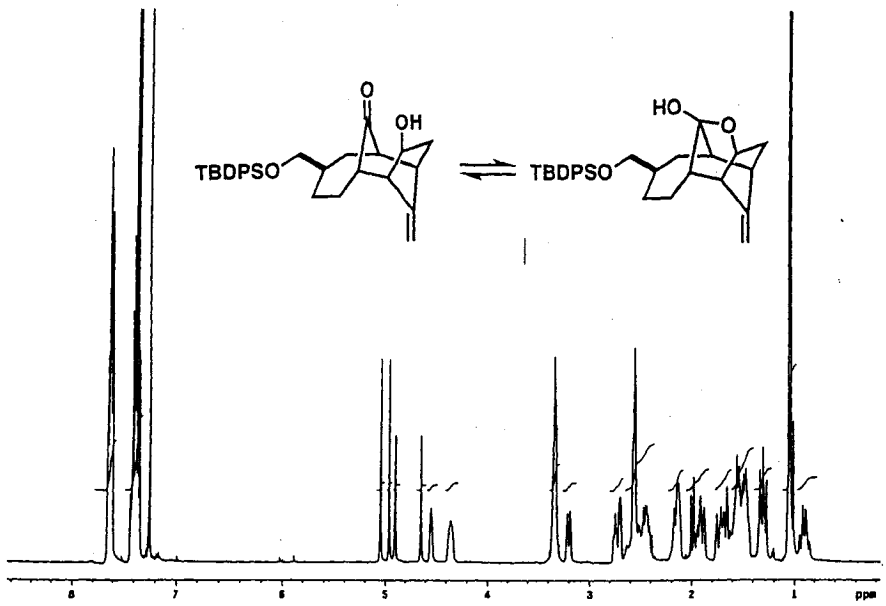
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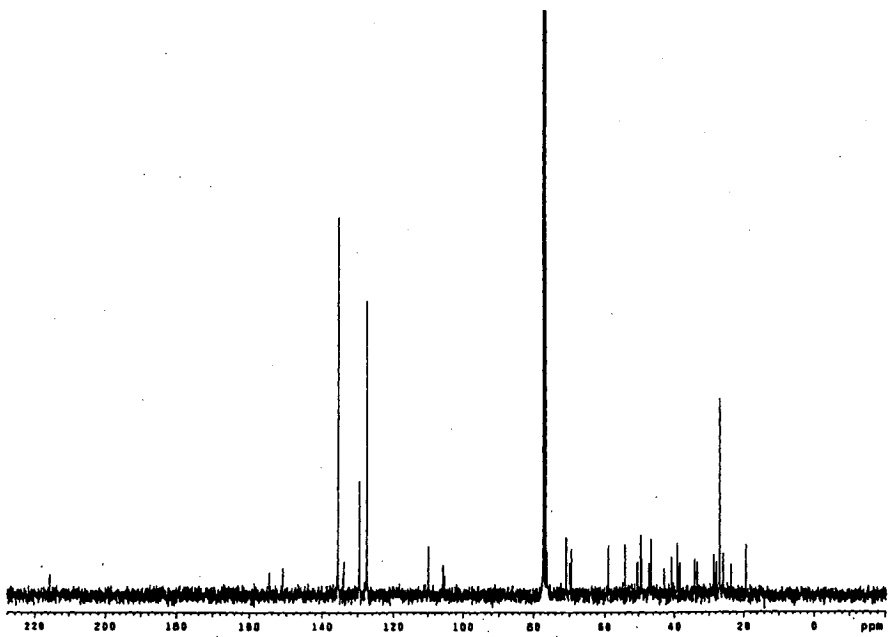
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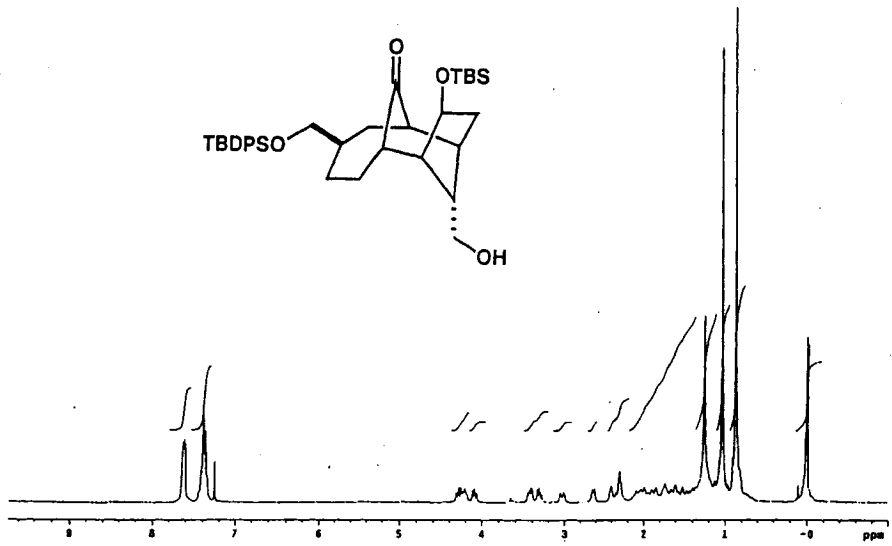
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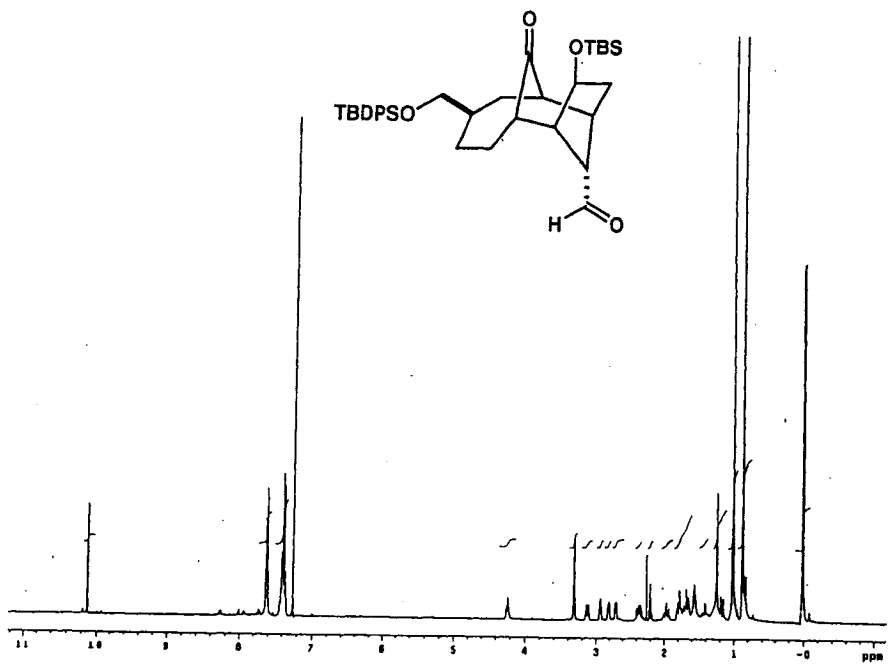
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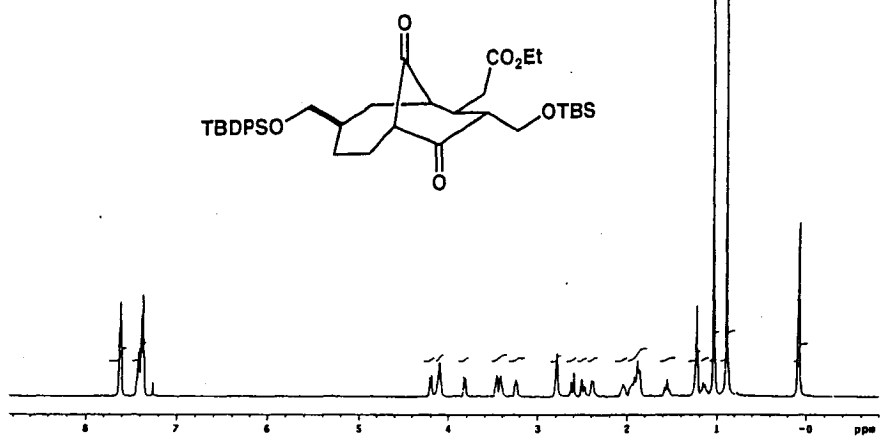
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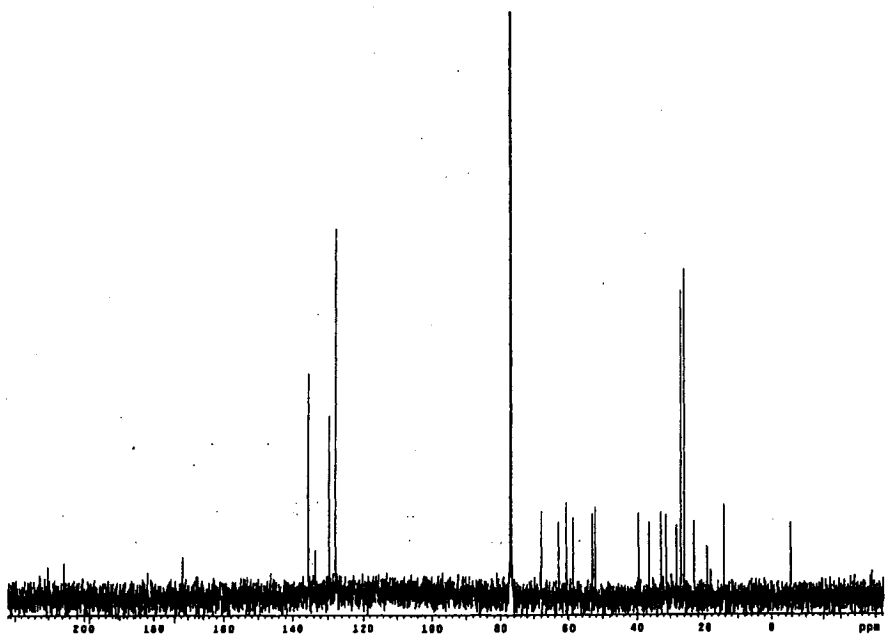
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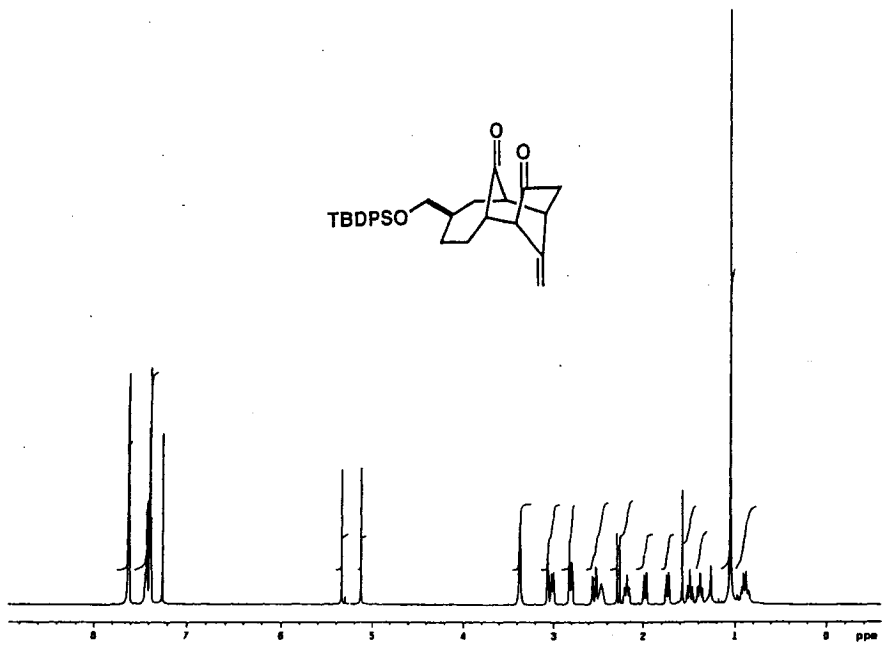
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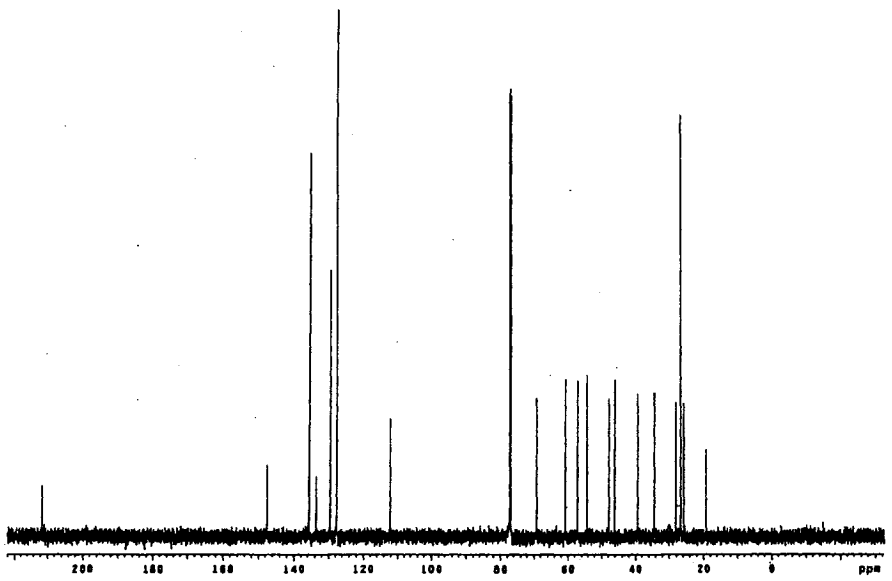
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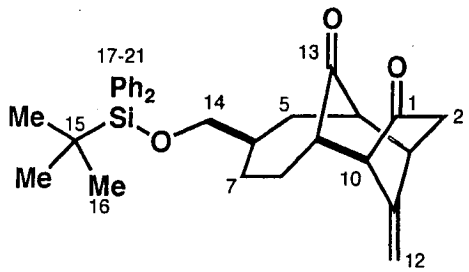

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			2.56	2a, 3		
3	46.1	1	3.09	2b	2, 5, 12	
4	57.2	1	2.82		2, 5	
5	34.4	2	1.41	4, 5b, 6	14	
			1.98	5a		5a, 6, 4, 14, 19
6	39.3	1	2.46	5a, 14		
7	28.2	2	0.92	7b, 8a	14	7b, 8b, 5a, 14
			1.77	7a, 8a, 8b		7a, 14, 6, 8a, 8b, 19
8	26.0	2	1.49	8b, 7b, 7a		
			2.18	8a, 9		
9	54.4	1	3.04	8b, 10		
10	60.8	1	2.85	9		
11	147.4	0			2	
12	112.2	2	5.15		3, 9, 10	10, 8a, 12b
			5.36			3, 6, 12b
13	211.4	0				
14	69.2	2	3.40	6	5, 6, 7	
15	19.3	0			16	
16	26.8	9	1.08			
17	133.7	0				
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20	129.6	2	7.43	19		
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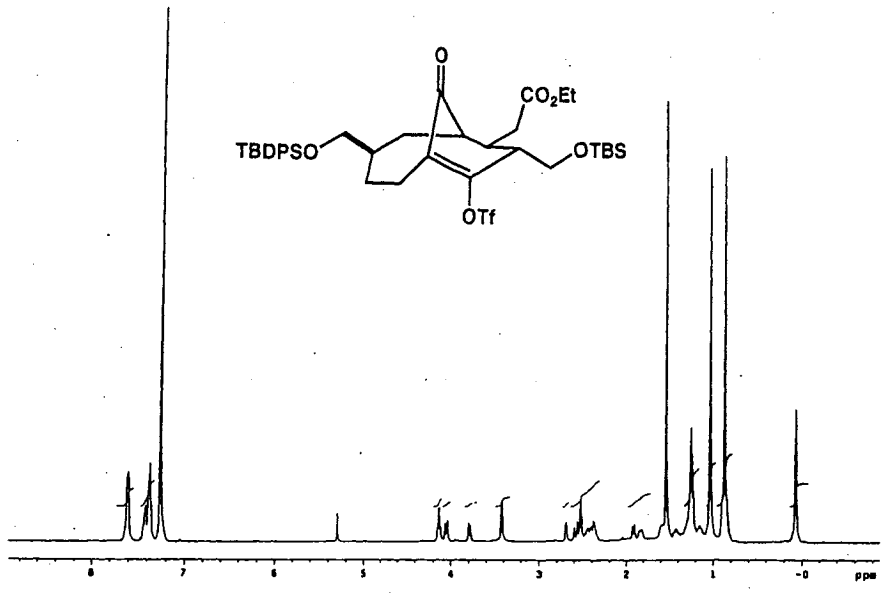
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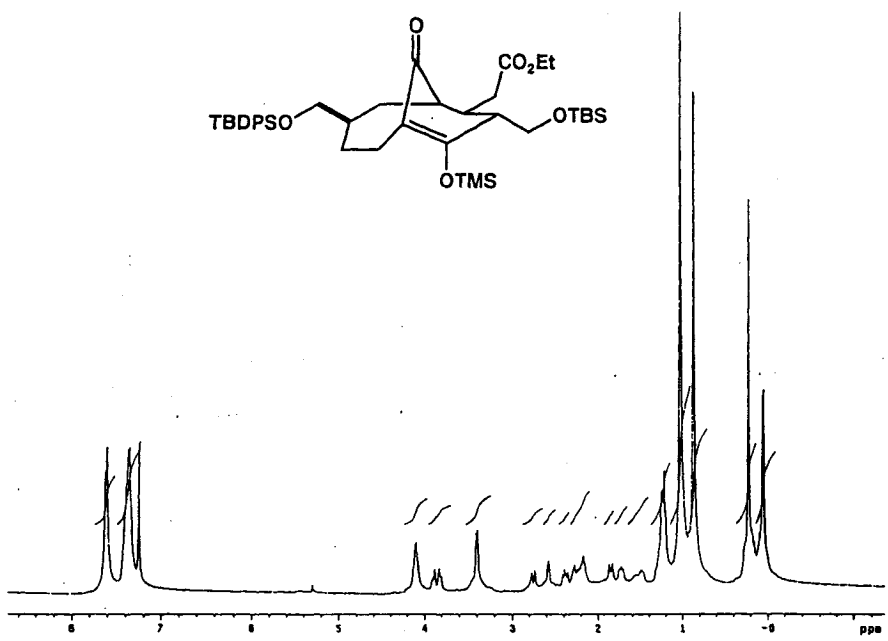
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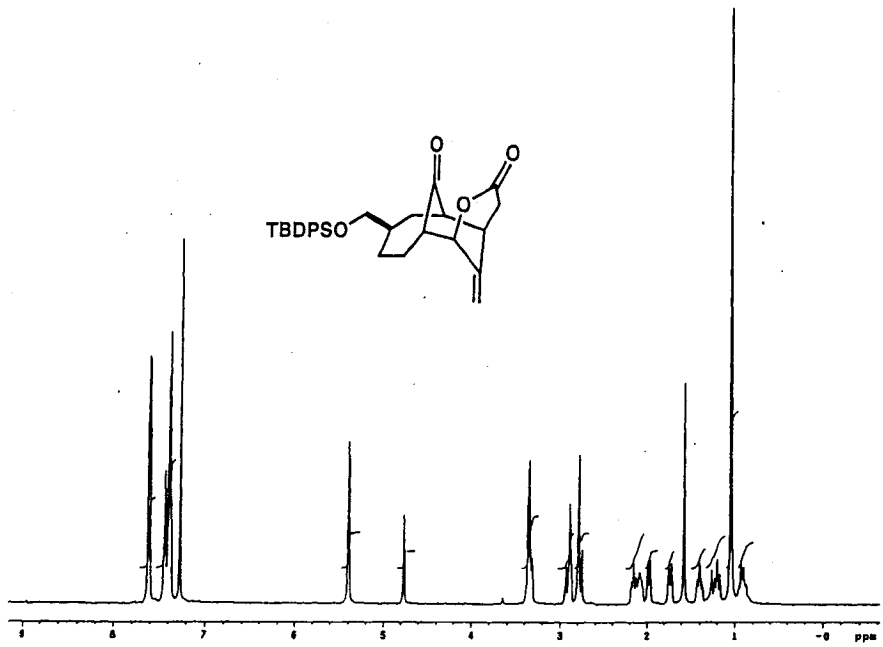
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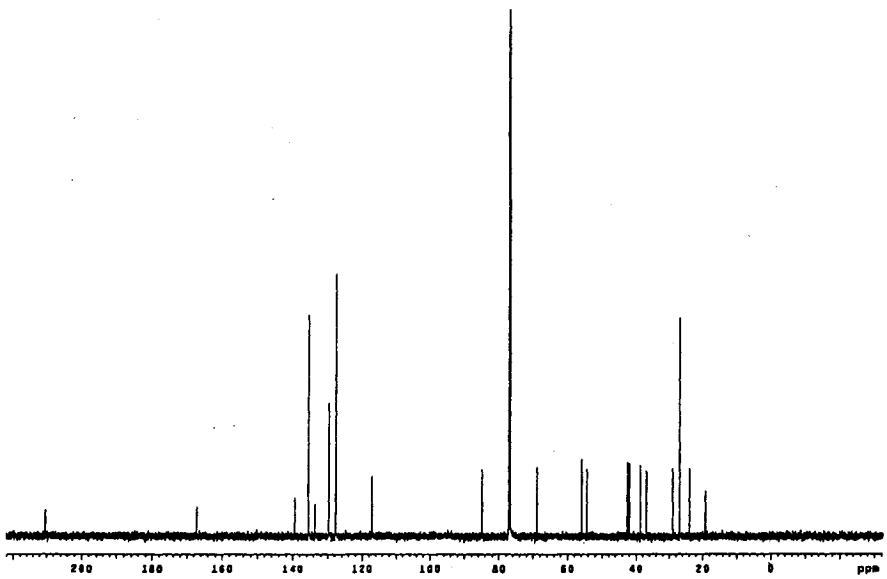
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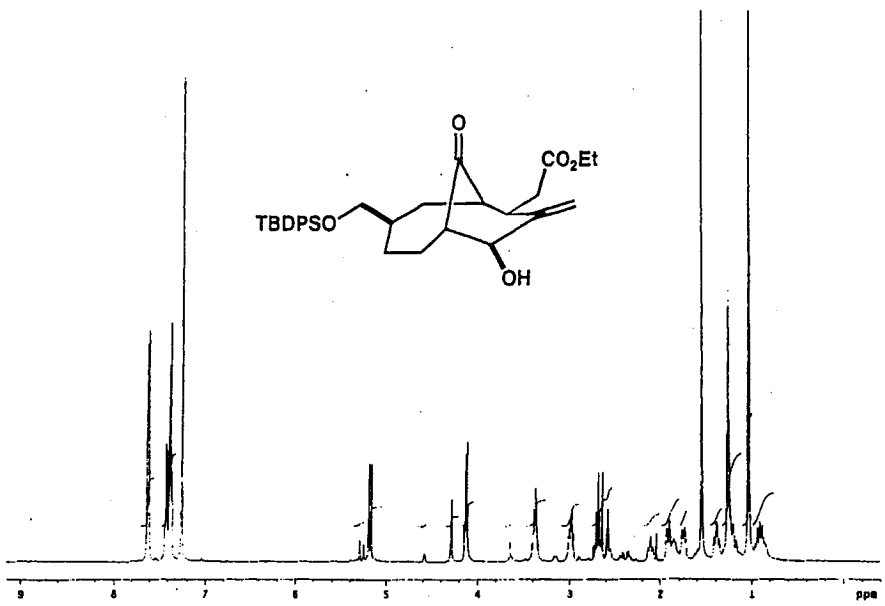
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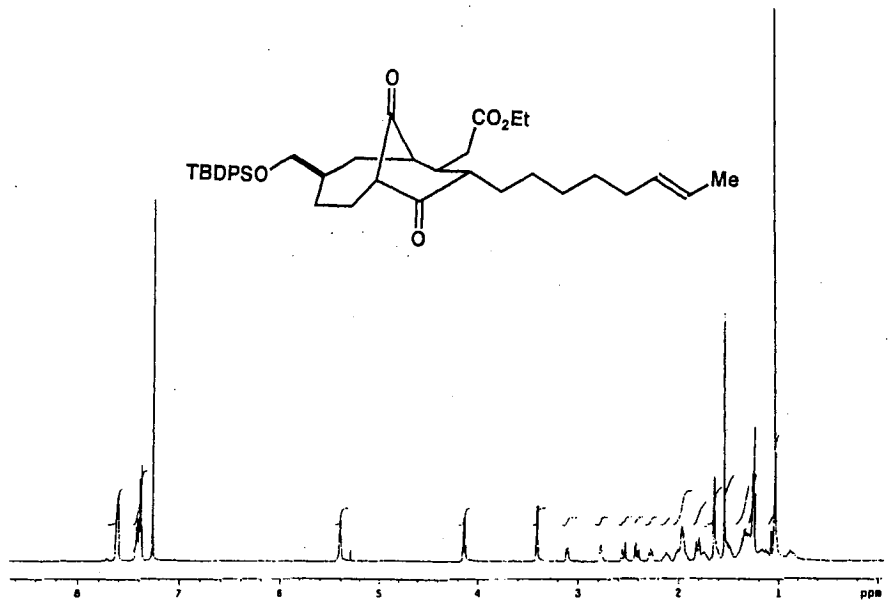
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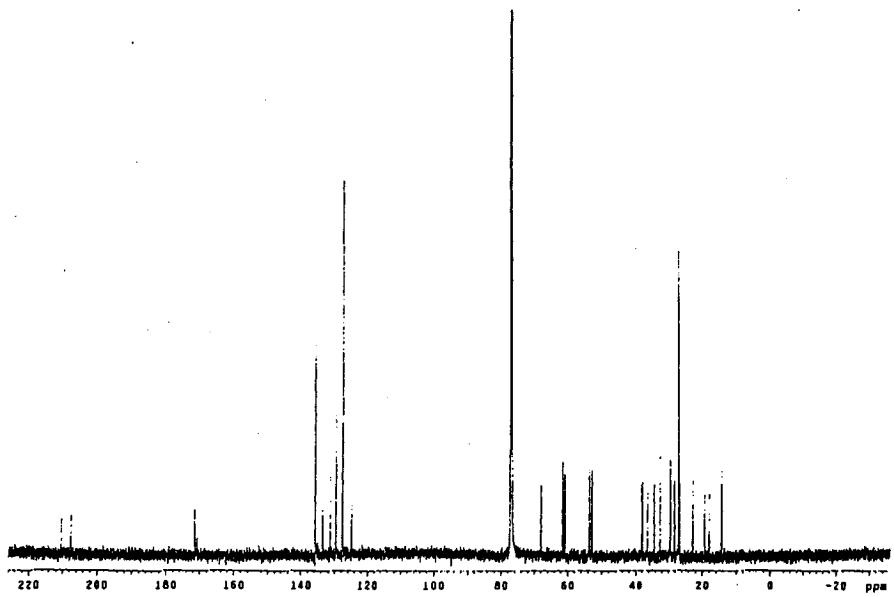
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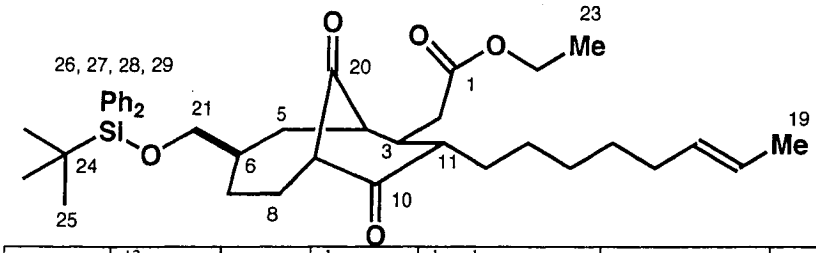

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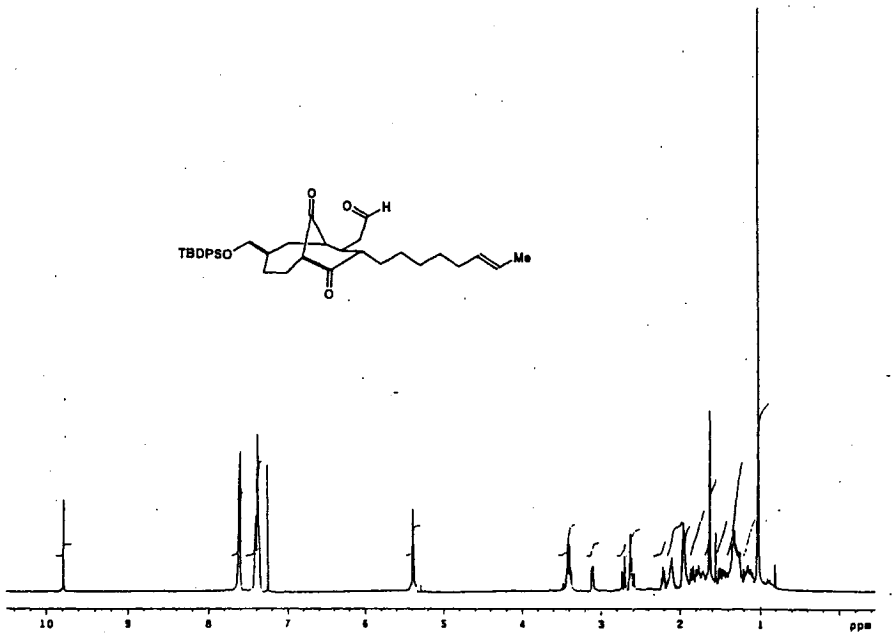
4	53.5	1	2.77	3, 5a, 5b	3, 5	2a, 2b, **11**, 3, 5a, 5b
5	34.3	2	1.49	5b	4, 7, 21	
			1.79	5a		
6	37.7	1	1.64			
7	28.1	2	1.11	7b	5, 8, 21	
			1.80			
8	22.7	2	1.95		7, 9	
			2.12	2a		
9	61.4	1	3.10	8a	7, 8	8a, 8b, **11**
10	207.5	-			9, 11	
11	52.7	1	2.27	3, 12b	3, 12	**4**, **9**, 2a, 2b,
12	26.5	2	1.52		11	
			1.75	11		
13	29.3*	2				
14	26.8*	2				
15	29.4	2	1.31		16	
16	32.5	2	1.97			
17	131.4	1	5.40		15, 16, 19	16
18	124.8	1	5.40		16, 19	19
19	17.8	3	1.64			
20	210.4	-			4, 5	
21	67.8	2	3.40	6	5, 6, 7	
22	60.8	2	4.13	23		
23	14.2	3	1.25	22		
24	19.2				17, 18	
25	26.8	9	1.05			
26	133.5	-				
27	135.6	2	7.63	28		
28	135.5	2	7.63	28		
29	129.7	2	7.40	29		
30	127.7	4	7.40	27, 28, 30		

* may be interchanged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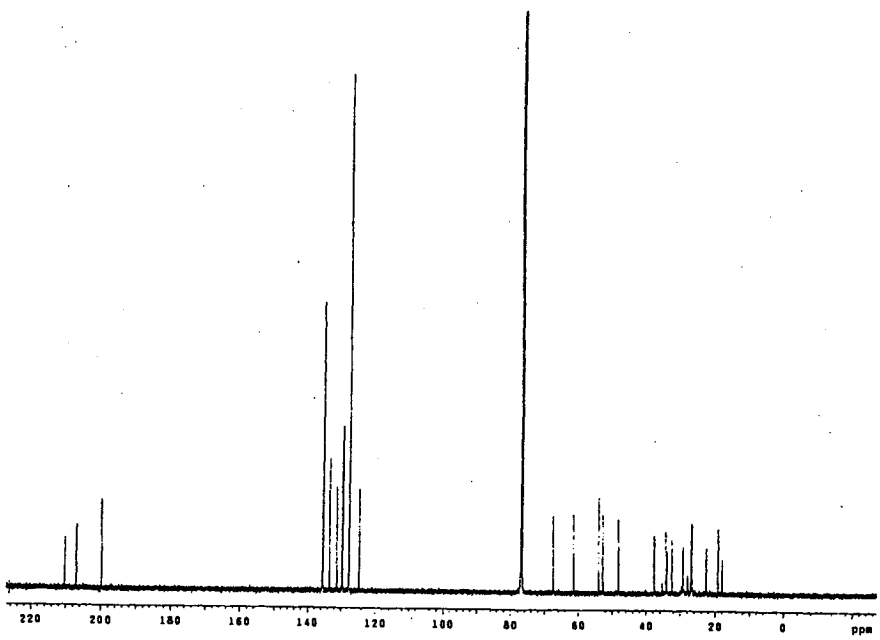
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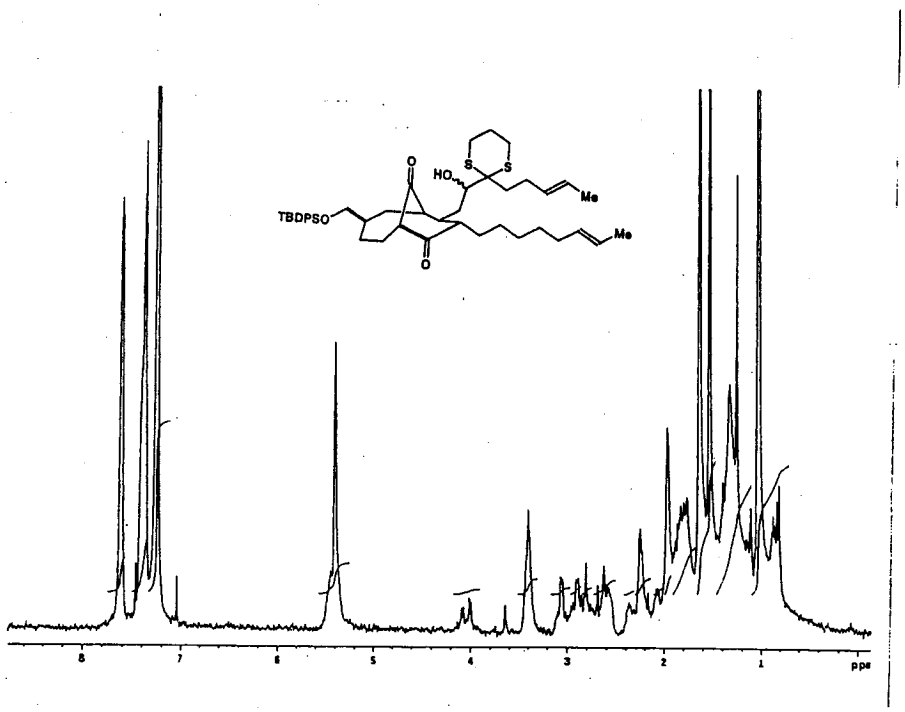
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2
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ppm

APPENDIX B: LEWIS ACID CATALYZED CYCLOADDITIONS

The author was engaged in a study of Lewis acid catalyzed cycloadditions immediately prior to beginning Ph.D. studies in this laboratory which culminated in the following paper (Isakovic, L.; Ashenhurst, J. A.; Gleason, J. L. *Organic Letters* **2001**, *3*, 4184). In addition to the work detailed in the published study, a considerable amount of effort was expended investigating various Lewis acids and solvents on the [6+4] cycloaddition of tropone with cyclopentadiene. It is the purpose of this Appendix to provide a further layer of detail in addition to that already published.

As discussed in Chapter 1, Cookson and Ito independently discovered that tropone combines with cyclopentadiene in refluxing benzene to afford [6+4] cycloadduct **A** in 80% yield. Subsequently, Ito found that protic acids promote this reaction. Ito discovered that protic acids considerably reduce the periselectivity of the reaction, and was able to characterize both *exo* and *endo* [4+2] cycloadducts **B** and **C** (attended by their respective double-bond isomers). During the course of our studies we found that the periselectivity of the reaction was highly dependent on both solvent and the identity of the Lewis acid. Stronger Lewis acids promoted the [4+2] cycloadditions to a greater extent. We also discovered that certain Lewis acids could promote an *additional* [4+2] cycloaddition, namely that of the [4+2] cycloadducts with a further equivalent of cyclopentadiene to give pentacycles such as **D**. No attempt was made to characterize or separate the various isomers of **D**. Table **B** presents a number of different reaction conditions and Lewis acids that were investigated during the course of this study. The optimal solvent was found to be CH_2Cl_2 with $Sc(OTf)_3$ as Lewis acid. Stronger Lewis acids or more polar solvents led to poorer selectivity for the [6+4] cycloadduct.

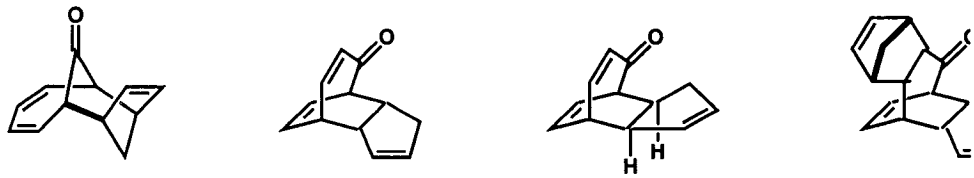

Figure A. Structures of [6+4] and [4+2] adducts

Prof. James L. Gleason compared the transition states of the Lewis-acid catalyzed [6+4] and [4+2] cycloadditions of tropone and cyclopentadiene using DFT [B3LYP/6-31G*]. The calculations were performed using a protonated tropone as a model for Lewis

acid activation. The greater preponderance of [4+2] cycloadducts in the presence of a Lewis acid catalyst can be rationalized by comparing the activation energies of the catalyzed and uncatalyzed reactions. In the absence of Lewis acid, the activation energies of the [6+4] cycloaddition and [4+2] (endo) cycloaddition are 20.7 kcal/mol and 23.5 kcal/mol respectively. In the presence of Lewis acid (with H^+ as a model) the activation energies are lowered to 7.5 and 7.9 kcal/mol respectively. Thus, the presence of an acid catalyst lowers the activation energy of the Diels-Alder to a greater extent than the [6+4] cycloaddition. These calculations were performed with a fully protonated, unsolvated tropone which would be expected to be a good model for a strong Lewis acid. Indeed, strong Lewis acids (e.g. BF_3) were observed to afford greater amounts of [4+2] adducts. These results indicate that there will be a limit to practical Lewis acid acceleration of the [6+4] cycloaddition due to increasing competition from the [4+2] pathway.

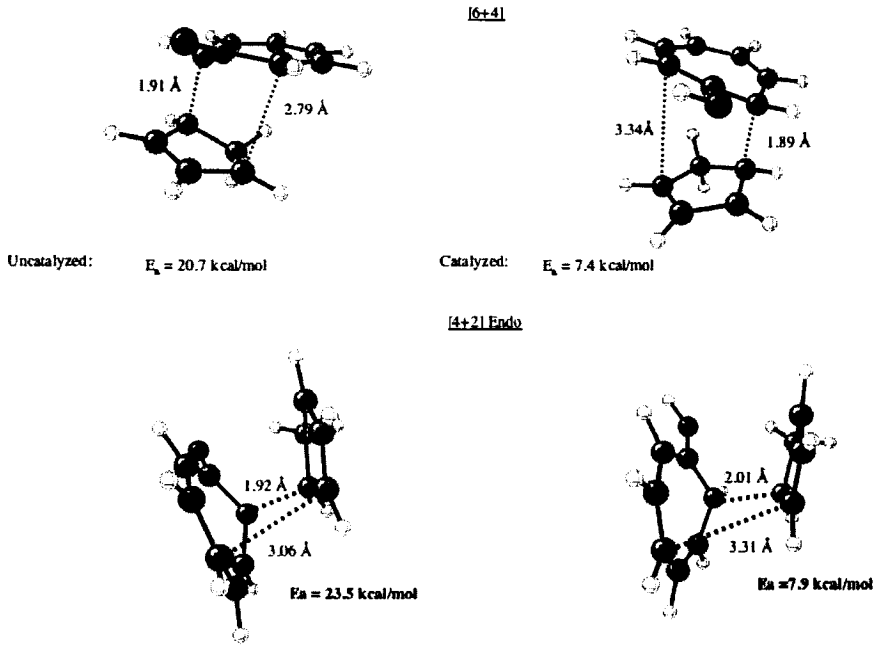

Figure B. Calculated transition states for [6+4] and [4+2] cycloadditions

Table **A**: Reactions run in various solvents at room temperature

L.A.	Solvent	Time	[6+4]	[4+2] **B**	[4+2] **C**	**D**	Ratio
-	MeCN	20	5%				
	MeCN	84	16%	6%	3%	4%	55:45
	CH_2Cl_2	24	6%				
	H_2O	36	21%	4%			84:16
	THF	24	3%				
	MeOH	20	12%				
	PhMe	7	1%				

All reactions run at 0.2 M in respective solvent with tropone (1 mmol) and cyclopentadiene (5 mmol) at 21 °C for the time period (in hours) indicated. Ratio refers to the ratio of [6+4] to [4+2] products.

Table **B**: Lewis-acid catalyzed [6+4] cycloadditions of tropone and cyclopentadiene.

L.A.	Solvent	Time	[6+4]	[4+2] **B**	[4+2]**C**	**D**	Ratio
$Sc(OTf)_3$	**CH_2Cl_2**	**6**	**55**	**9**	**5**	**17**	**64:36**
	MeCN	14	29	16	8		55:45
$Yb(OTf)_3$	CH_2Cl_2	24	58%	21%	7%	<1%	67:33
	MeCN	24	32%	21%	9%		52;48
$La(OTf)_3$	CH_2Cl_2	24	44%	17%	8%	2%	62;38
	THF	24	23%	15%	8%		50:50
$ZnCl_2$	CH_2Cl_2	24	14%	2%	2%		78:22
	MeCN	144	49%	16%	8%		67:33
$Cu(OTf)_3$	CH_2Cl_2	4	35%	5%	5%	33%	45:55
$Eu(OTf)_3$	CH_2Cl_2	24	18%	5%	2%	5%	60:40
	MeCN	24	25%	13%	8%	22%	37:63
$Zn(OTf)_3$	MeCN	24	29%	24%	11%		45:55
Et_2AlCl	CH_2Cl_2	1.5	33%	2%	1%	18%	61:39
BF_3 Et_2O	CH_2Cl_2	1.5	26%	5%	3%	32%	39:61
$Y(OTf)_3$	CH_2Cl_2	3	37%	14%	9%	21%	46:54
$Ce(OTf)_3$	CH_2Cl_2	8	43%	18%	9%	11%	53:47
$Sm(OTf)_3$	CH_2Cl_2	9	31%	16%	9%	<1%	55:45
$Nd(OTf)_3$	CH_2Cl_2	10	40%	19%	10%	12%	49:51
$Ho(OTf)_3$	CH_2Cl_2	3.5	38%	9%	6%	27%	47:53
$Sn(OTf)_3$	CH_2Cl_2	1.5	39%	7%	6%	36%	44:56
$Sn(OTf)_3$ [a]	CH_2Cl_2	3.5	37%	4%	4%	28%	51:49
[b]	CH_2Cl_2	24	36%	20%	8%	<1%	56:44
	MeCN	1	17%	5%	5%	33%	28:72
	PhMe	1	25%	14%	9%	18%	38;62

All reactions run at 0.2 M in indicated solvent with Lewis acid (0.1 mmol), tropone(1 mmol) and cyclopentadiene (5 mmol) at 21 °C. Notes: [a] −78 °C to −20 °C ; [b] −20 °C.

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Application of Lewis Acid Catalyzed Tropone [6+4] Cycloadditions to the Synthesis of the Core of CP-225,917

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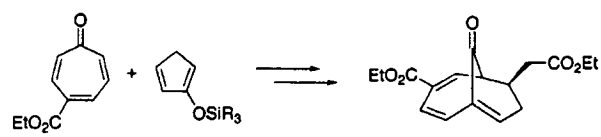
Received September 25, 2001

ABSTRACT



The carbocyclic core of CP-225,917 and CP-263,114 is accessible through the [6+4] cycloaddition of a tropone with a 2-substituted cyclopentadiene. Examination of this reaction has revealed for the first time that this cycloaddition process is catalyzed by Lewis acids, including lanthanide triflates. Cycloadditions of several mono-, di-, and trisubstituted tropones with 2-silyloxycyclopentadienes using $ZnCl_2$ catalysis are found to proceed in good yield and, in many cases, with excellent diastereoselectivity. Subsequent transformation to the core of the CP-molecules involves a site-selective Baeyer–Villiger oxidation of a tricyclic diketone, followed by a syn-elimination process.

The [6+4] cycloaddition of tropone with a diene[1] is a potentially powerful tool for natural product synthesis.[2] The reaction can be used to rapidly generate bicyclo[4.4.1]-undecanone structures and, if more complex reacting partners are used in conjunction with selective carbon–carbon cleaving reactions, holds the potential for the synthesis of other ring structures as well as linear molecules.[3] Despite this potential, relatively few synthetic efforts have utilized the tropone cycloaddition strategy.[4] This is mainly due to low yields and poor periselectivities, which are observed with more functionalized tropones and dienes.[2]

CP-225,917 and CP-263,114 (Figure 1) are an interesting set of natural products isolated by the Pfizer research group.[5]

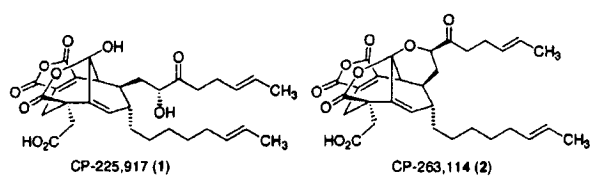


Figure 1. Structure of CP-225,917 and CP-263,114.

These fungal metabolites possess inhibitory activity against squalene synthetase and Ras farnesyl transferase, and they have been the focus of significant synthetic research[6] that has culminated in several recent total syntheses.[7] Our retrosynthetic analysis of this molecule (Scheme 1) indicated that the bicyclo[4.3.1]decadienone core of these molecules

(1) Cookson, R. C.; Drake, B. V.; Hudec, J.; Morrison, A. *J. Chem. Soc., Chem. Commun.* **1966**, 15.

(2) (a) Garst, M. E.; Roberts, V. A.; Prussin, C. *Tetrahedron* **1983**, *39*, 581. (b) Garst, M. E.; Roberts, V. A.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 3882. (c) Rigby, J. H. *Org. React.* **1997**, *49*, 331.

(3) For related modifications of tropylium [6+4] adducts, see: (a) Rigby, J. H.; Fales, K. R. *Tetrahedron Lett.* **1998**, *39*, 1525. (b) Rigby, J. H.; Fales, K. R. *Tetrahedron Lett.* **1998**, *39*, 5717.

(4) Rigby, J. H.; Rege, S. D.; Sandanayaka, V. P.; Kirova, M. *J. Org. Chem.* **1996**, *61*, 842.

(5) (a) Dabrah, T. T.; Kaneko, T.; Massefski, W., Jr.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594. (b) Dabrah, T. T.; Harwood, H. J., Jr.; Huang, L. H.; Jankovich, N. D.; Keneko, T.; Li, J.-C.; Linjdsey, S.; Moshier, P. M.; Subashi, T. A.; Therrien, M.; Watts, P. C. *J. Antibiot.* **1997**, *50*, 1.

(6) For a review, see: Starr, J. T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1415.

(7) (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Fong, K. C.; He, Y.; Yoon, W. H.; Choi, H.-S. *Angew. Chem, Int. Ed.* **1999**, *38*, 1676. (b) Nicolaou, K. C.; Jung, J.-K.; Yoon, W. H.; He, Y.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1829. (c) Meng, D.; Tan, Q.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3197. (d) Chen, C.; Layton, M. E.; Sheehan, S. M.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 7424. (e) Waizumi, N.; Itoh, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2000**, *122*, 7825.

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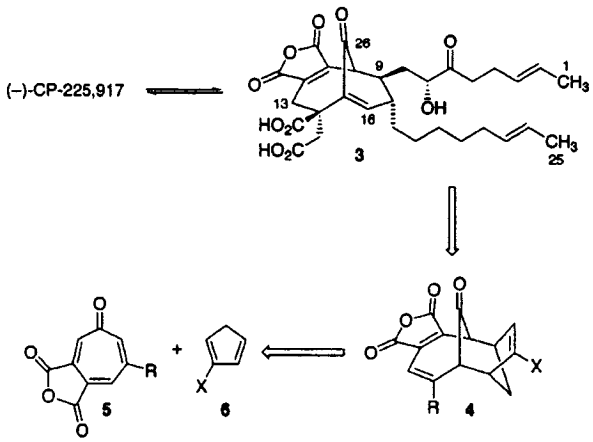
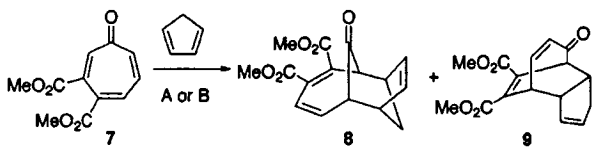
Scheme 1



might be accessed by a [6+4] cycloaddition between a functionalized tropone and an appropriately substituted cyclopentadiene. This cycloaddition would furnish tricyclic structure **4** that, upon selective carbon−carbon bond cleavage in the two-carbon bridge, might produce the desired carbocyclic framework of the natural product. In this letter, we disclose our preliminary examination of [6+4] tropone cycloadditions relevant to the synthesis of the CP-molecules, including the first examples of Lewis acid catalysis in this class of reactions. Furthermore, we demonstrate a highly site-selective Baeyer−Villiger oxidation that allows the cycloadducts to be transformed into the carbocyclic core of the CP-molecules.

Application of a tropone cycloaddition to the synthesis of the CP-ring system would ideally utilize a trisubstituted tropone containing electron-withdrawing groups at the 3- and 4-positions (e.g., **5**). As a model for this system, cycloadditions of diester tropone **7** were studied.[8] Cycloaddition of **7** with cyclopentadiene proceeded rapidly in toluene at reflux (Scheme 2). The reaction was complete in less than 2

Scheme 2[a]



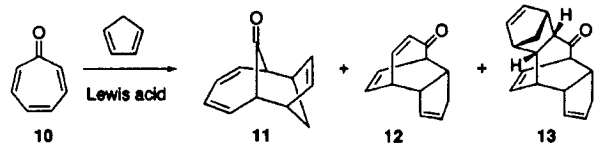
[a] Key: (A) PhMe, reflux, 2 h, 51% **8**, 1.5:1 ratio of **8**/**9**. (B) 10% $ZnCl_2$, Et_2O, 3 h, 62% **8**, 3:1 ratio of **8**/**9**.

h, but NMR analysis indicated that a mixture of [6+4] and [4+2] cycloadducts had formed in a 1.5:1 ratio. Although these cycloadducts could not be separated, the [4+2] adduct **9** could be selectively reduced in the presence of the [6+4] cycloadduct **8** with $NaBH_4/CeCl_3$ in methanol at −78 °C. Chromatographic separation then provided the desired [6+4] cycloadduct in 51% yield. The yield of the [6+4] cycloadduct could be improved by running the reaction in the presence of a Lewis acid. When the cycloaddition was conducted in ether in the presence of 10 mol % $ZnCl_2$, the reaction proceeded to completion within 3 h at room temperature and resulted in an improved ratio of cycloadducts (3:1) favoring the desired [6+4] adduct. Selective reduction of the minor product, as described above, allowed the desired adduct to be isolated in an improved 62% yield. As with most tropone [6+4] cycloadditions, both the catalyzed and the uncatalyzed reactions occurred exclusively with exo-stereoselectivity.[9]

The observation of Lewis acid catalysis in tropone [6+4] cycloadditions is noteworthy. Although there is a single report of Brønsted acid catalysis in the cycloaddition of tropone with cyclopentadiene,[10] a study by Garst et al. concluded that Lewis acids were not useful for mediating this reaction.[2a] Rigby has developed related [6+4] cycloadditions of cycloheptatriene η^1-tricarbonylchromium complexes,[11] and Trost has shown that palladium TMM complexes undergo [6+3] cycloadditions with tropone;[12] however, to our knowledge, no examples of Lewis acid catalysis exist for simple tropone [6+4] cycloadditions. In light of this, we chose to study Lewis acid catalyzed cycloadditions of tropone (**10**) with cyclopentadiene.

In the reaction between tropone (**10**) and cyclopentadiene, no acceleration above the background rate was observed when $ZnCl_2$ was employed as a catalyst in ether. Switching to methylene chloride as the solvent afforded a small amount of cycloadduct **11** along with lesser amounts of [4+2] adduct **12**. Examining a range of Lewis acids revealed that several lanthanides as well as Et_2AlCl catalyzed the reaction at significantly higher rates (Table 1). The best results were

Table 1. Lewis Acid Catalysis in Tropone Cycloadditions



entry	Lewis acid[a]	time	11	12	13
1	$ZnCl_2$	24 h	14%	4%	
2	Et_2AlCl	1.5 h	33%	3%	18%
3	$La(OTf)_3$	24 h	44%	25%	2%
4	$Yb(OTf)_3$	19 h	58%	28%	trace
5	$Sc(OTf)_3$	6 h	55%	14%	17%
6	$Sc(OTf)_3$	24 h[b]	59%	38%	

[a] All reactions conducted with 5 equiv of cyclopentadiene in the presence of 10 mol % Lewis acid in CH_2Cl_2 at 21 °C. [b] Reaction contained 1 equiv of H_2O.

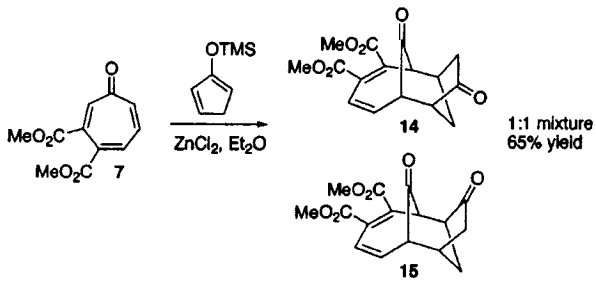
achieved with ytterbium triflate and scandium triflate, the latter of which gave nearly complete consumption of tropone within 6 h, resulting in a 55% yield of **11**. This was accompanied by **12** (14%) and 2:1 adduct **13** (17%), which arises from the Diels−Alder reaction of **12** with cyclopenta-

(8) Tropone **7** was prepared as described: Roberts, V. A.; Garst, M. E. *J. Org. Chem.* **1985**, *50*, 893.

diene. Interestingly, addition of 1 equiv of water moderates the acidity of the scandium triflate, resulting in complete suppression of the 2:1 adduct (Table 1, entry 6).[13] Although the periselectivity in these reactions is not absolute, they represent the first example of Lewis acid catalysis in tropone [6+4] cycloadditions. Employing the scandium triflate conditions in the cycloaddition of **7** with cyclopentadiene afforded a 4:1 ratio of cycloadducts and a 60% isolated yield of **8**.

As indicated in the retrosynthetic analysis depicted in Scheme 1, it was desirable to conduct the cycloaddition with a 2-substituted cyclopentadiene. Cycloaddition of **7** with 2-trimethylsilyloxycyclopentadiene[14] proceeded rapidly in ether in the presence of $ZnCl_2$ (Scheme 3). After aqueous

Scheme 3

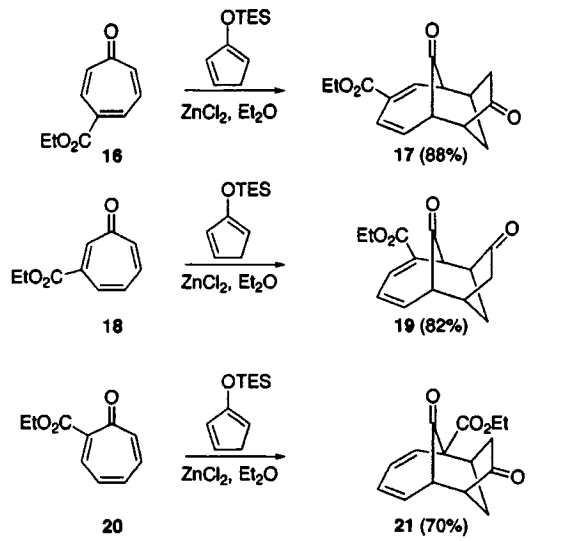


acidic workup to hydrolyze the initially formed silyl enol ether, the product was isolated in 65% yield as a 1:1 mixture of regioisomeric ketones. It has been shown that tropones display "even" regioselectivity when electron-withdrawing groups are placed in the 3- or 4-position.[2b,15] In this example, the two ester groups exert equal and opposite directing influences on the regioselectivity of the reaction, resulting in a poorly selective cycloaddition.

In comparison to the above results, cycloaddition of the 4-substituted tropone **16**[16] with 2-triethylsilyloxy-cyclopentadiene under identical conditions afforded adduct **17** in 88% yield. Similarly, the 3-substituted tropone **18** and the 2-substituted tropone **20** underwent regioselective cycloadditions with excellent yields. In all cases, only the "even" regioisomer is formed in these cycloadditions. The cycloaddition of **20** is particularly noteworthy. In many cases, 2-substituted tropones give predominantly [4+2] cycloadducts.[17] 2-Chlorotropone shows disparate reactivity, giving the [4+2] adduct with cyclopentadiene[18] and the [6+4] adduct with 1,3-cyclohexadiene.[19] Although **20** shows excellent [6+4] selectivity with 2-silyloxycyclopentadiene, reaction with cyclopentadiene resulted in mainly the [4+2] adduct. It is important to note that the cycloaddition reactions using 2-silyloxycyclopentadiene are also efficient in the absence of $ZnCl_2$, proceeding to completion within 24 h at 21 °C (vs instantaneous reaction in the presence of Lewis acid).

For a successful route to the CP-molecules to be realized, it will be necessary to use a 3,4,6-substituted tropone (cf. Scheme 1). To this end, tropone **22** was prepared by rhodium acetate catalyzed reaction of ethyl diazoacetate with 3,5-

Scheme 4



dimethylanisole, followed by oxidation of the adduct with bromine (see Supporting Information for details). It was expected that **22** would serve as a useful model for the total synthesis, as hydroxymethyl groups in the 3- and 6-positions might eventually be oxidized at a late stage in the synthesis. The reaction of **22** was much slower than that of either the mono- or disubstituted tropones, requiring 18 h for complete reaction. Although the periselectivity of the reaction was slightly reduced, with the [4+2] adduct being isolated in 5% yield, the desired [6+4] cycloadduct could be isolated in good yield (75%). It should be noted that Lewis acid catalysis is crucial to the success of this reaction. In its absence, the

(9) Houk, K. N.; Woodward, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 4145.

(10) Ito, S.; Sakan, K.; Fujise, Y. *Tetrahedron Lett.* **1970**, *11*, 2873. Ito et al. reported that reaction of tropone and cyclopentadiene in the presence of pTsOH afforded a 65% yield of **11** and a 15% yield of a mixture of [4+2] adducts, although the solvent, temperature, and amount of catalyst were not specified. We have found that use of 10% pTsOH in toluene afforded a 40% yield of **11** along with 38% of the [4+2] adduct, **12**.

(11) Rigby, J. H.; Ateeq, H. S.; Charles, N. R.; Cuisiat, S. V.; Ferguson, M. D.; Henshilwood, J. A.; Krueger, C.; Ogbu, C. O.; Short, K. M.; Heeg, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 1382. For a thermal version using a catalytic amount of chromium, see: Rigby, J. H.; Fiedler, C. *J. Org. Chem.* **1997**, *62*, 6106.

(12) Trost, B. M.; Seoane, P. R. *J. Am. Chem. Soc.* **1987**, *109*, 615.

(13) Kobayashi, S.; Hachiya, I.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1993**, *24*, 3755.

(14) 2-Trimethylsilyloxycyclopentadiene and 2-triethylsilyloxy-cyclopentadiene were prepared by silylation of 2-cyclopentenone with the corresponding silyl triflates and triethylamine. See: Plenio, H.; Aberle, C. *Organometallics* **1997**, *16*, 5950.

(15) "Even" or "odd" regioselectivity in this case refers to the number of atoms along the shortest path between the functional groups in the cycloadduct.

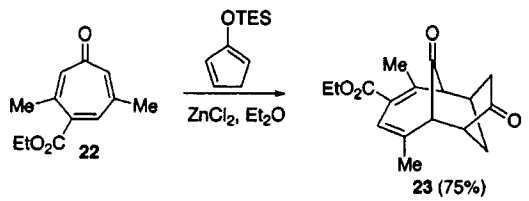
(16) Tropones **16**, **18**, and **20** were prepared by rhodium acetate catalyzed reaction of ethyl diazoacetate with anisole to give three cycloheptatrienes, which may be separated by chromatography and individually oxidized with bromine to afford the tropones. See: (a) Garst, M. E.; Roberts, V. A. *J. Org. Chem.* **1982**, *47*, 2188. (b) Anciaux, A. J.; Demonceau, A.; Noels, A. F.; Hubert, A. J.; Warin, R.; Teyssie, P. *J. Org. Chem.* **1981**, *46*, 873.

(17) Rigby, J. H.; Moore, T. L.; Rege, S. *J. Org. Chem.* **1986**, *51*, 2400.

(18) Ito, S.; Sakan, K.; Fujise, Y. *Tetrahedron Lett.* **1969**, *10*, 715.

(19) Fujise, Y.; Mazaki, Y.; Shiokawa, T.; Fukazawa, Y.; Ito, S. *Tetrahedron Lett.* **1984**, *25*, 3611.

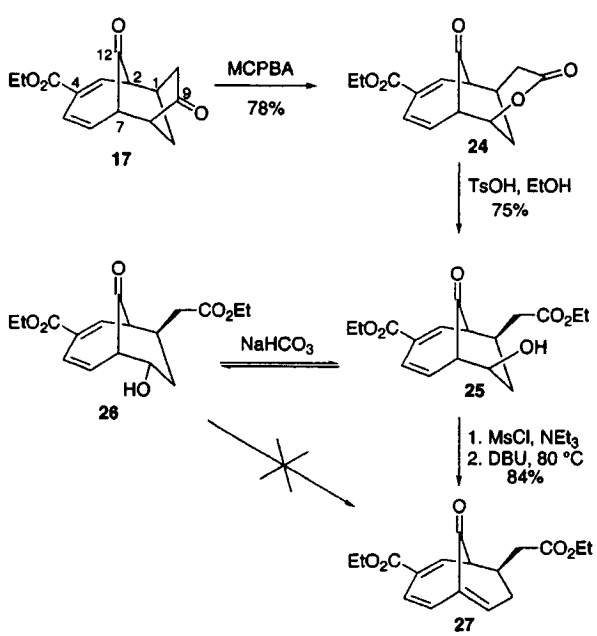
Scheme 5



tropone was not completely consumed and only a 50% yield of cycloadduct was isolated.

The success of the cycloaddition strategy hinges on the ability to effect a selective carbon–carbon bond cleavage to reveal a [4.3.1]bicyclic system. We studied this process using tricyclic diketone **17**. To our delight, treatment of **17** with 1 equiv of MCPBA in methylene chloride results in clean conversion of the diketone into lactone **24** (Scheme 6). The reaction is highly site selective, with no other

Scheme 6



oxidation products being isolated. The site selectivity in the reaction is striking and may be explained by two cooperating factors. First, molecular modeling (MM2 and PM3) calculations indicate that oxidation at C9 should be favored by at least 10 kcal/mol, as oxidation at C12 would be accompanied by a large increase in bond angle strain (See Scheme 6 for numbering). Second, formation of the requisite tetrahedral intermediate at C12 is greatly disfavored as the ketone does not undergo nucleophilic attack readily. One side of this ketone is flanked by the two-carbon bridge, preventing any nucleophile from approaching from that direction. On the opposite face, molecular models indicate that the C4–C5 bond lies almost directly along the Burgi–Dunitz trajectory,[20] thus greatly hindering nucleophilic attack from that side. The C9 ketone, although blocked on one side by the C12 carbonyl group, is completely unhindered on the outer face, thus permitting addition of MCPBA to take place. Similar site selectivity has been observed for $LiAlH_4$ reductions of an analogous diketone.[21]

Hydrolysis of the lactone in **24** was best achieved by treatment with acid in ethanol to provide **25** in 75% yield. Interestingly, the method of workup for the acidic hydrolysis is important. If saturated $NaHCO_3$ is added directly to the reaction mixture, the product is invariably isolated as a mixture of alcohol diastereomers **25** and **26**. A similar result is obtained if pure **25** is treated with a mixture of $NaHCO_3$ in ethanol/water. The stereoisomer in these cases presumably arises by a retro-aldol/aldol sequence. Exposure of the mixture of epimeric alcohols **25** and **26** to acid in ethanol cleanly reconverts the mixture back to a single stereoisomer (**25**). The retro-aldol cleavage problem is exacerbated if stronger base is used. Attempted transesterification of **24** with K_2CO_3/MeOH led to complete decomposition of the starting material.

Installation of the bridgehead olefin turned out to be a straightforward process. Mesylation of **25** under standard conditions followed by heating in toluene in the presence of DBU at 80 °C furnished the alkene **27** in 84% yield via an apparent syn-elimination.[22] If the elimination was carried out for extended reaction times or at higher temperatures (e.g., 150 °C, collidine), deconjugation of the olefin occurred. The stereochemistry of the leaving group is very important in this reaction. When the epimeric alcohol **26** was subjected to identical reaction conditions, no elimination of the intermediate mesylate was observed.

In conclusion, we have developed a tropone cycloaddition route to the core of CP-225,917 and CP-263,114. These studies have for the first time revealed that tropone cycloadditions may be effected using Lewis acid catalysts. The cycloadducts may be further transformed to the desired bridgehead enone by a site-selective Baeyer–Villiger oxidation followed by a straightforward ring-opening and elimination sequence. The application of this method to a total synthesis of the CP-molecules is in progress, and results will be reported in due course.

Acknowledgment. We thank NSERC and FCAR for funding of this research.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016814H

(20) (a) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. J. *J. Am. Chem. Soc.* **1973**, *95*, 5065. (b) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563.

(21) Li, Z.-H.; Mori, A.; Kato, N.; Takeshita, H. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2778.

(22) For related eliminations, see: (a) Warnhoff, E. W.; Wong, C. M.; Tai, W. T. *J. Org. Chem.* **1967**, *32*, 2664. (b) Carruthers, W.; Qureshi, M. I. *J. Chem. Soc. C* **1970**, 2238. (c) Buchanan, G. L.; Jamieson, G. *Tetrahedron* **1972**, *28*, 1129. (d) Meng, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 1485.

Appendix C: Crystal structure determination data for oxymercuration product **148**

Table 7. Crystal data and structure refinement for **148**.

Identification code	ja13m
Empirical formula	C16 H17 Cl Hg O5
Formula weight	525.34
Temperature	566(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 8.0732(10) A alpha = 90 deg. b = 19.991(2) A beta = 98.149(2) deg. c = 10.1257(12) A gamma = 90 deg.
Volume	1617.7(3) A^3
Z, Calculated density	4, 2.157 Mg/m^3
Absorption coefficient	9.701 mm^-1
F(000)	1000
Crystal size	0.40 x 0.20 x 0.10 mm
Theta range for data collection	2.04 to 28.13 deg.
Limiting indices	-10<=h<=10, -26<=k<=26, -12<=l<=13
Reflections collected / unique	14193 / 3763 [R(int) = 0.0433]
Completeness to theta = 28.13	95.0 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3763 / 0 / 208
Goodness-of-fit on F^2	1.027
Final R indices [I>2sigma(I)]	R1 = 0.0289, wR2 = 0.0646
R indices (all data)	R1 = 0.0483, wR2 = 0.0742
Largest diff. peak and hole	1.046 and -0.716 e.A^-3

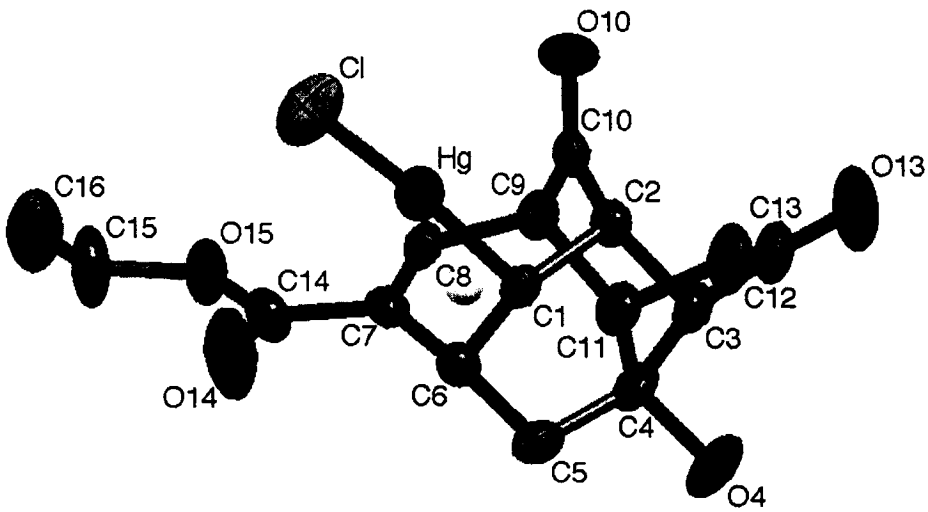

O10
Cl
C10
Hg
C9
C2
O13
C16
C15
O15
C13
C14
C8
C12
C1
C7
C11
C3
O14
C6
C4
C5
O4

Table 8. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for jaa1708.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Cl	760(2)	5354(1)	11670(1)	62(1)
Hg	1961(1)	5695(1)	9823(1)	37(1)
C(1)	3332(6)	6057(2)	8383(4)	29(1)
C(2)	2364(6)	6490(2)	7283(4)	29(1)
C(3)	3665(6)	6849(2)	6530(5)	35(1)
C(4)	4749(6)	6325(3)	5966(5)	39(1)
O(4)	5993(5)	6701(2)	5401(4)	59(1)
C(5)	5590(6)	5834(3)	6974(6)	41(1)
C(6)	4416(6)	5511(2)	7857(5)	32(1)
C(7)	3416(6)	4948(2)	7160(5)	30(1)
C(8)	2420(6)	5010(2)	5997(4)	29(1)
C(9)	2003(6)	5664(2)	5310(5)	30(1)
C(10)	1192(6)	6092(2)	6287(4)	28(1)
O(10)	-309(4)	6121(2)	6244(4)	46(1)
C(11)	3452(6)	6052(3)	4810(5)	36(1)
C(12)	2743(9)	6695(3)	4136(6)	51(2)
C(13)	2790(7)	7186(3)	5294(5)	46(1)
O(13)	2195(7)	7740(2)	5241(5)	70(1)
C(14)	3493(7)	4296(3)	7881(5)	40(1)
O(14)	4141(8)	4233(2)	9017(5)	88(2)
O(15)	2726(5)	3795(2)	7198(4)	48(1)
C(15)	2604(10)	3169(3)	7907(7)	69(2)
C(16)	1923(12)	2651(4)	6964(10)	106(3)

Table 9. Bond lengths [A] and angles [deg] for **148**.

Cl-Hg	2.3272(14)
Hg-C(1)	2.081(5)
C(1)-C(2)	1.534(6)
C(1)-C(6)	1.540(7)
C(2)-C(10)	1.508(6)
C(2)-C(3)	1.558(6)
C(3)-C(13)	1.506(7)
C(3)-C(4)	1.526(7)
C(4)-O(4)	1.437(6)
C(4)-C(5)	1.506(8)
C(4)-C(11)	1.555(7)
C(5)-C(6)	1.535(7)
C(6)-C(7)	1.502(7)
C(7)-C(8)	1.335(6)
C(7)-C(14)	1.491(7)
C(8)-C(9)	1.496(6)
C(9)-C(10)	1.524(6)
C(9)-C(11)	1.547(7)
C(10)-O(10)	1.208(6)
C(11)-C(12)	1.527(8)
C(12)-C(13)	1.526(8)
C(13)-O(13)	1.205(7)
C(14)-O(14)	1.200(7)
C(14)-O(15)	1.321(6)
O(15)-C(15)	1.453(7)
C(15)-C(16)	1.462(10)
C(1)-Hg-Cl	171.19(13)
C(2)-C(1)-C(6)	113.9(4)
C(2)-C(1)-Hg	116.0(3)
C(6)-C(1)-Hg	112.4(3)
C(10)-C(2)-C(1)	113.3(4)
C(10)-C(2)-C(3)	108.5(4)
C(1)-C(2)-C(3)	107.8(4)
C(13)-C(3)-C(4)	102.8(4)
C(13)-C(3)-C(2)	110.1(4)
C(4)-C(3)-C(2)	109.2(4)
O(4)-C(4)-C(5)	109.7(4)
O(4)-C(4)-C(3)	105.1(4)
C(5)-C(4)-C(3)	114.9(4)
O(4)-C(4)-C(11)	108.6(4)
C(5)-C(4)-C(11)	118.1(4)
C(3)-C(4)-C(11)	99.3(4)
C(4)-C(5)-C(6)	114.4(4)
C(7)-C(6)-C(1)	113.5(4)
C(7)-C(6)-C(5)	112.1(4)
C(1)-C(6)-C(5)	109.4(4)
C(8)-C(7)-C(14)	119.5(4)
C(8)-C(7)-C(6)	124.1(4)
C(14)-C(7)-C(6)	116.3(4)
C(7)-C(8)-C(9)	124.1(4)
C(8)-C(9)-C(10)	106.1(4)
C(8)-C(9)-C(11)	117.3(4)

C(10)-C(9)-C(11)	110.2(4)
O(10)-C(10)-C(2)	121.9(4)
O(10)-C(10)-C(9)	121.7(4)
C(2)-C(10)-C(9)	116.3(4)
C(12)-C(11)-C(9)	108.4(4)
C(12)-C(11)-C(4)	102.1(4)
C(9)-C(11)-C(4)	112.9(4)
C(11)-C(12)-C(13)	103.4(4)
O(13)-C(13)-C(3)	125.8(5)
O(13)-C(13)-C(12)	126.2(6)
C(3)-C(13)-C(12)	108.0(5)
O(14)-C(14)-O(15)	122.1(5)
O(14)-C(14)-C(7)	122.8(5)
O(15)-C(14)-C(7)	115.0(4)
C(14)-O(15)-C(15)	117.0(5)
O(15)-C(15)-C(16)	109.4(6)

Symmetry transformations used to generate equivalent atoms:

Table 10. Anisotropic displacement parameters (A^2 x 10^3) for jaa1708.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
Cl	78(1)	80(1)	31(1)	-3(1)	17(1)	-25(1)
Hg	46(1)	40(1)	25(1)	-1(1)	8(1)	-1(1)
C(1)	30(2)	25(3)	30(2)	-7(2)	3(2)	-5(2)
C(2)	37(2)	26(2)	25(2)	-3(2)	10(2)	0(2)
C(3)	41(3)	23(2)	43(3)	-5(2)	12(2)	-8(2)
C(4)	38(3)	35(3)	48(3)	-6(2)	23(2)	-10(2)
O(4)	63(3)	51(3)	71(3)	-10(2)	40(2)	-24(2)
C(5)	32(3)	41(3)	53(3)	-11(2)	11(2)	-7(2)
C(6)	31(2)	30(3)	33(3)	-5(2)	0(2)	2(2)
C(7)	30(2)	29(3)	33(2)	-2(2)	10(2)	6(2)
C(8)	35(2)	23(2)	29(2)	-4(2)	11(2)	-4(2)
C(9)	38(3)	28(2)	25(2)	-3(2)	3(2)	-4(2)
C(10)	33(3)	25(2)	26(2)	3(2)	3(2)	1(2)
O(10)	30(2)	56(3)	52(2)	-8(2)	6(2)	5(2)
C(11)	48(3)	32(3)	31(3)	-4(2)	17(2)	-3(2)
C(12)	77(4)	39(3)	41(3)	5(3)	18(3)	-5(3)
C(13)	62(4)	31(3)	48(3)	9(2)	19(3)	-7(3)
O(13)	115(4)	36(3)	63(3)	12(2)	23(3)	7(3)
C(14)	46(3)	34(3)	37(3)	5(2)	2(2)	9(2)
O(14)	127(5)	56(3)	66(3)	22(2)	-40(3)	-10(3)
O(15)	67(3)	27(2)	48(2)	3(2)	6(2)	-3(2)
C(15)	104(6)	28(3)	74(5)	16(3)	13(4)	1(4)
C(16)	105(7)	62(5)	140(8)	31(6)	-18(6)	-17(5)

Table 11. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for jaa1708.

	x	y	z	U(eq)
H(1A)	4143	6364	8872	35
H(2A)	1719	6827	7695	34
H(3A)	4347	7167	7110	42
H(4A)	6208	6512	4727	88
H(5A)	6482	6063	7542	49
H(5B)	6097	5483	6504	49
H(6A)	5121	5319	8632	38
H(8A)	1957	4624	5587	34
H(9A)	1155	5577	4536	37
H(11A)	3999	5779	4194	43
H(12A)	1608	6628	3696	62
H(12B)	3430	6851	3487	62
H(15A)	1881	3226	8587	82
H(15B)	3703	3036	8343	82
H(16A)	1851	2237	7431	158
H(16B)	2644	2596	6295	158
H(16C)	828	2781	6547	158