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Synthesis of fused and bridged ring systems

Sy, James Nicolas Ong, Ph.D.

Iowa State University, 1988

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Synthesis of fused and bridged ring systems

by

James Nicolas Ong Sy

A Dissertation Submitted to the

Graduate Faculty in Partial Fulfillment of the

Requirements for the Degree of

DOCTOR OF PHILOSOPHY

Department: Chemistry
Major: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

For the Major Department

Signature was redacted for privacy.

For the Graduate College

Iowa State University
Ames, Iowa

1988

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OVERALL INTRODUCTION

The efficient construction of fused and bridged carbocyclic ring systems has always been a challenge for the organic chemist. We report two novel ways in synthesizing such ring systems:

1) Facile formation of cis-fused cyclopentanoids via intramolecular cyclization has been achieved.

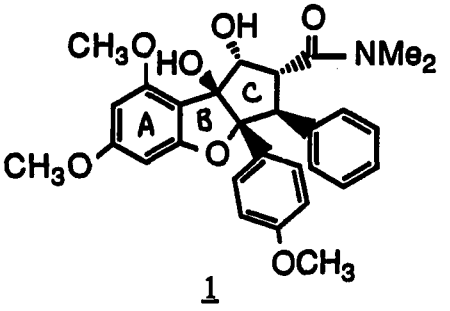
2) A novel way of constructing bridged ring systems involving a reactive enone intermediate and 1,1,3-trisubstituted dienes has been effected.

PART I. INTRAMOLECULAR CYCLIZATION STUDIES AND SYNTHETIC APPROACHES TO (±)-ROCAGLAMIDE

INTRODUCTION

Rocaglamide: Characterization and Synthetic Approaches

Rocaglamide (1) is a novel 1H-2,3,3a,8b-tetrahydro-cyclopenta[b]benzofuran isolated from the alcoholic extract of the dried roots and stems of Aglaia elliptifolia Merr. (Meliaceae). Its structure [Figure 1] and the relative stereochemistry of its substituents, have been rigorously established from spectral and single-crystal X-ray analysis.[1]



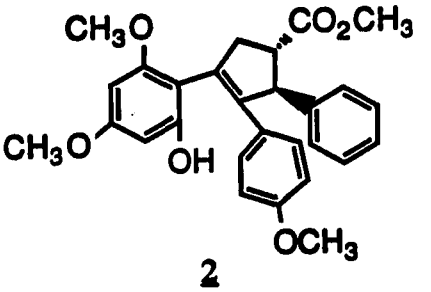
1

Figure 1. (+)-Rocaglamide

This compound has been reported to exhibit significant antileukemic activity against P388 lymphocytic leukemia in CDF_1 mice[2] and inhibitory activity *in vitro* against cells derived from human epidermoid carcinoma of the nasopharynx (KB cell).

A survey of the literature reveals that no total synthesis of this biologically active substance has yet been achieved. To this date, only two synthetic approaches to this molecule have been reported.

Trost and Saulnier[3] reported in a very brief abstract on intermediate cyclopentene 2 which was synthesized utilizing trimethylenemethane (TMM)-palladium(0) chemistry. No other details or intermediates were mentioned.



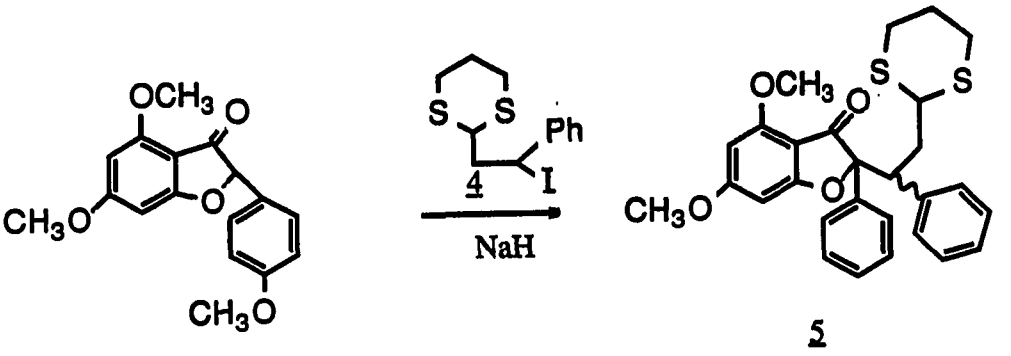
2

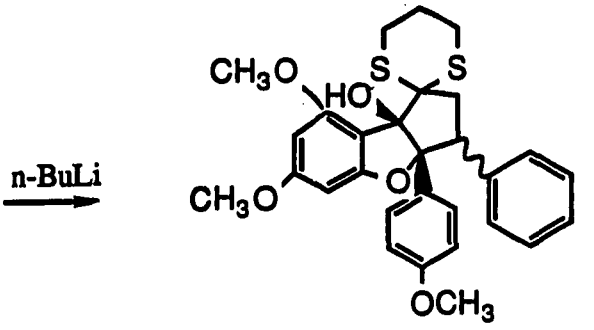
Taylor and Davey[4] reported the construction of the basic rocaglamide skeleton based on a direct 1,3-dithiane lithiation followed by intramolecular carbonyl addition. Treatment of compound 5 with n-butyl lithium in THF-HMPA at -96°C gave intermediate 6 in 64% yield. A glaring drawback of this approach is that these researchers have to work with a 1:1 diastereomeric mixture which was obtained by the coupling of two pieces 3 and 4 (Scheme 1).

Survey of Cyclopentanoid Construction and Intramolecular Cyclization Strategies

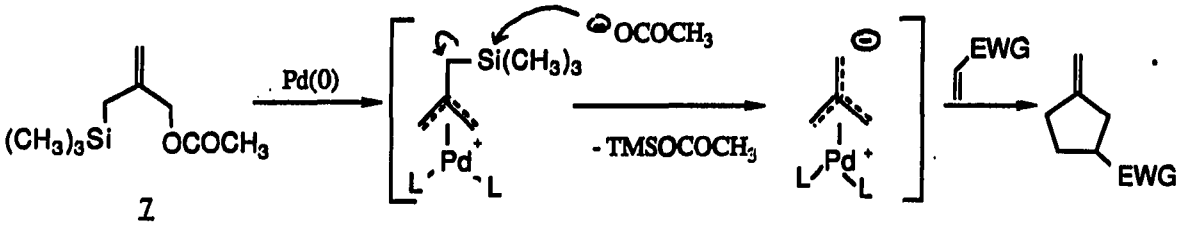
The key to any successful synthesis of rocaglamide relies on the efficient construction of the cyclopentane ring of the natural product. One, therefore, has to utilize existing methodologies for cyclopentanoid construction. A search of the literature reveals a wide array of methods that may be used to accomplish this goal.

Scheme I



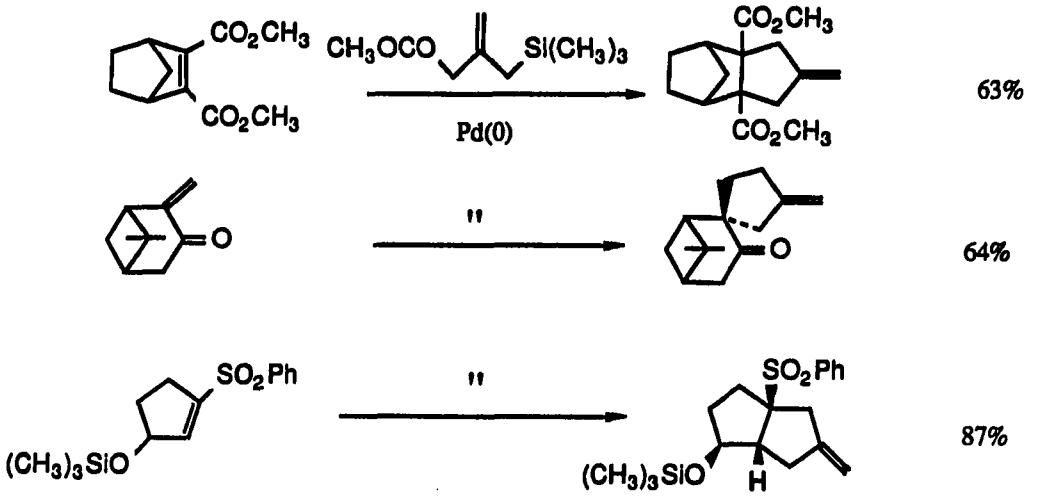


Trost and his research group[5-13] have published a series of elegant papers which revealed the development of a cycloaddition strategy for the synthesis of cyclopentanoids. Their approach was based on the silyl-substituted trimethylenemethane precursor 7. The reactive trimethylenemethane-palladium complex can directly add to give methylene cyclopentanes.[5] Trost and Chan[6,7] showed that this reactive



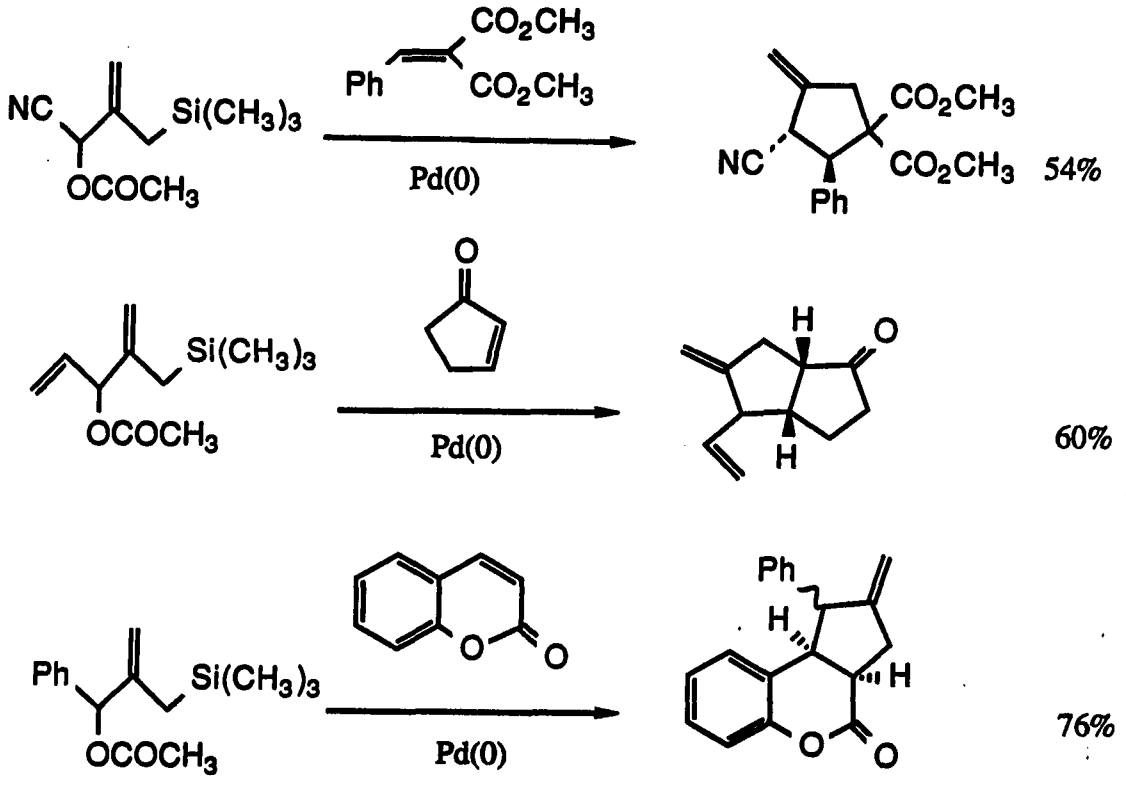
I

intermediate can add to a variety of electron-deficient olefins.

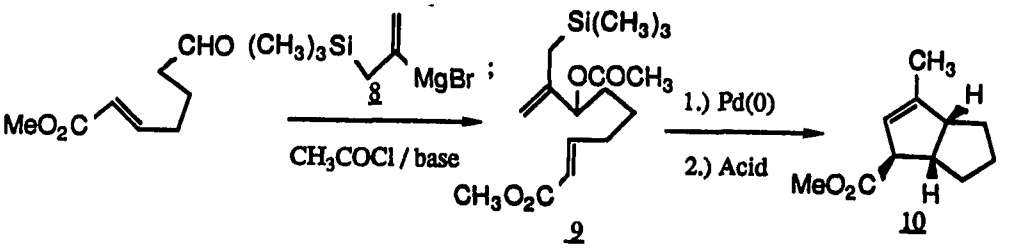


In the last case, diastereoselectivity tends to be high and can be readily explained by the attack of the trimethylenemethane (TMM) unit from the less hindered face.

Trost et al.[8] has also developed several substituted TMM units and has shown that cycloadditions also occur efficiently.

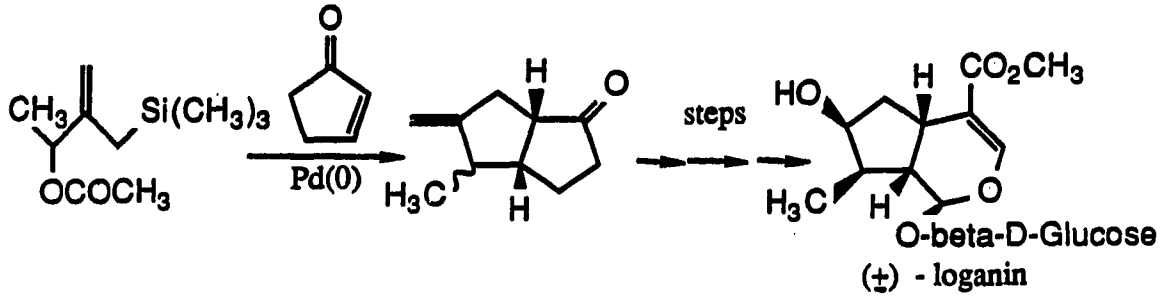


Trost and Coppola[9] demonstrated the intramolecular version of this cycloaddition strategy.

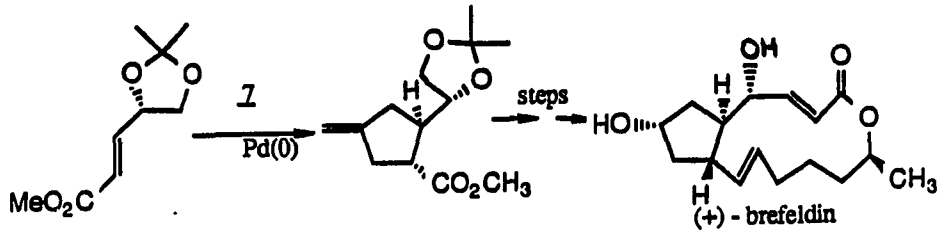


The donor conjunctive reagent 8 provides ready access to the precursor 9. This compound undergoes rapid intramolecular cycloaddition upon heating in boiling THF in the presence of a palladium catalyst to give the bicyclo[3.3.0]-octane 10 in 51% yield.

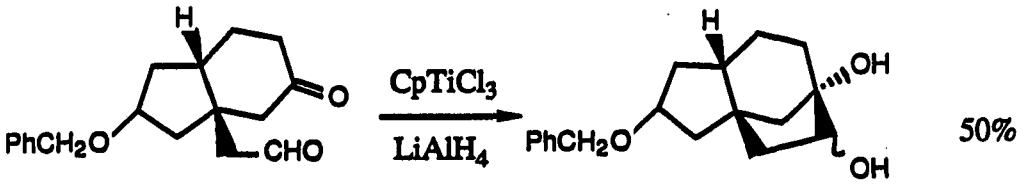
Trost and Nanninga[10] have wisely utilized their newly-developed cycloaddition to synthesize several natural products. (±)-Loganin, a key intermediate in the biosynthesis of alkaloids, was one of the iridoids made via this cyclopentanoid construction strategy.



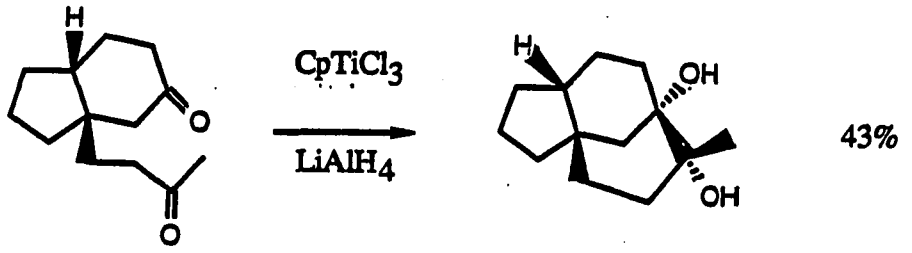
Trost et al.[11] also synthesized the macrocycle (+)-Brefeldin A.

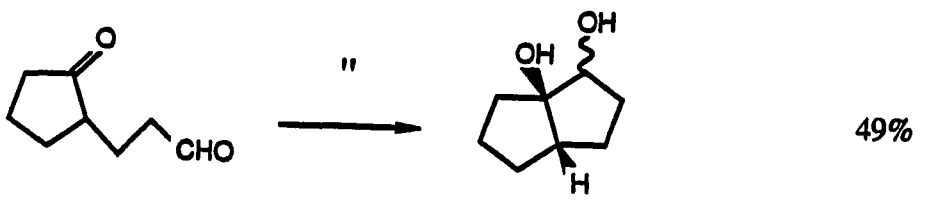


Corey et al.[14] reported a titanium-based reagent for the intramolecular pinacolic coupling of ketones and aldehydes.

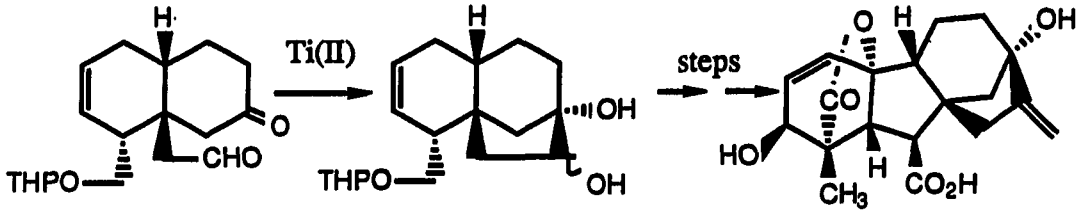


This active cyclizing reagent, formed by the reaction of cyclopentadienyltitanium trichloride and lithium aluminum chloride, can induce intramolecular reductive coupling of a wide variety of substrates.



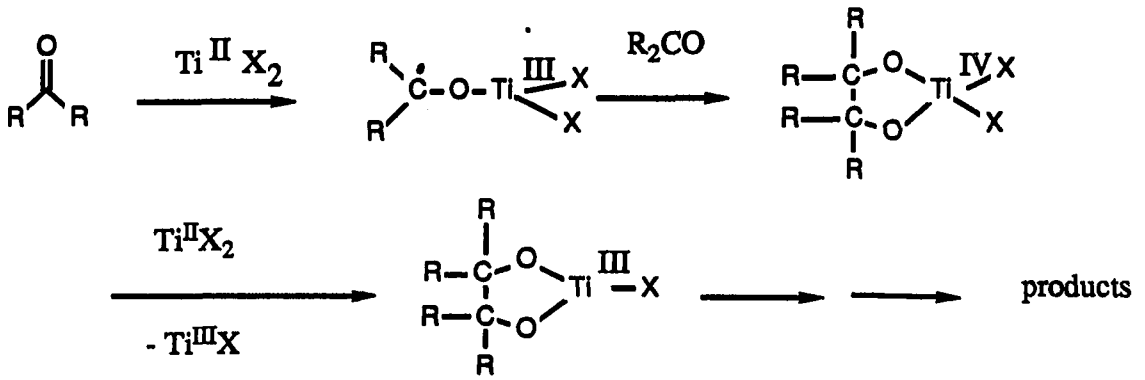


The Corey group[15] made use of this cyclization to accomplish the total synthesis of (±)-gibberellic acid.

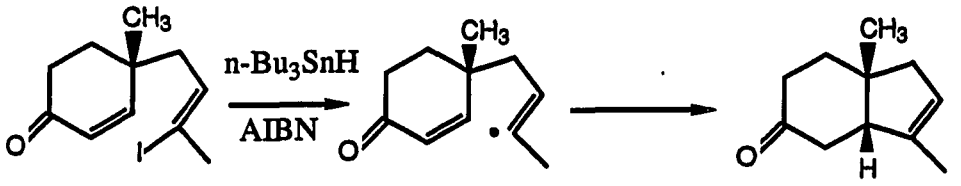


(±)- gibberellic acid

Corey believed that Ti(II) is the reactive species in these reductive couplings and has proposed the following mechanism.

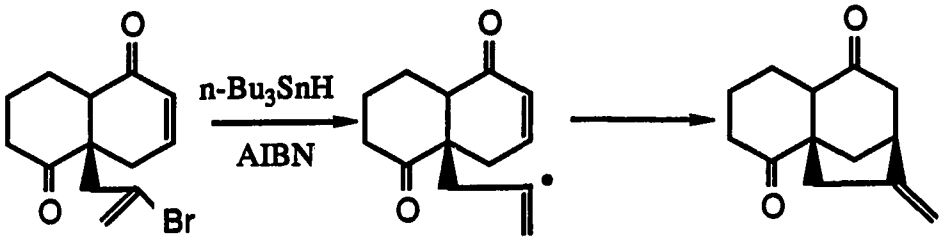


Marinovic and Ramanathan[16] demonstrated the use of vinyl radicals in the efficient construction of cyclic systems.

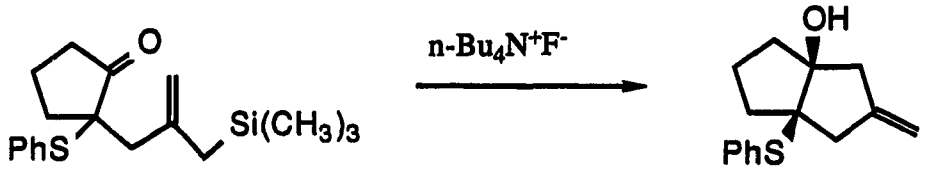


The cis-fused bicyclo[4:3.0]nonane was synthesized in good yield upon closure of the vinyl radical at the beta

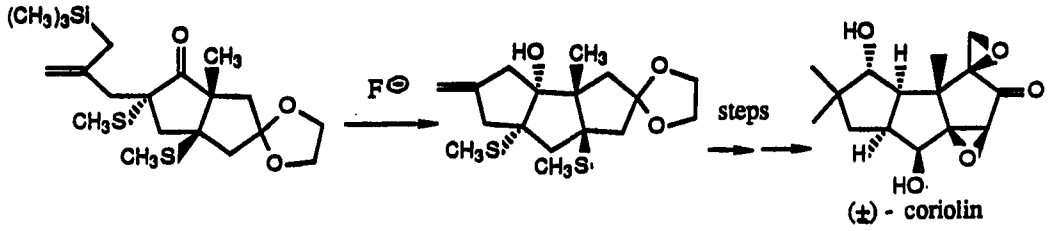
position of the enone system. They also showed the formation of a strained bicyclo[3.2.1]octane via this method.



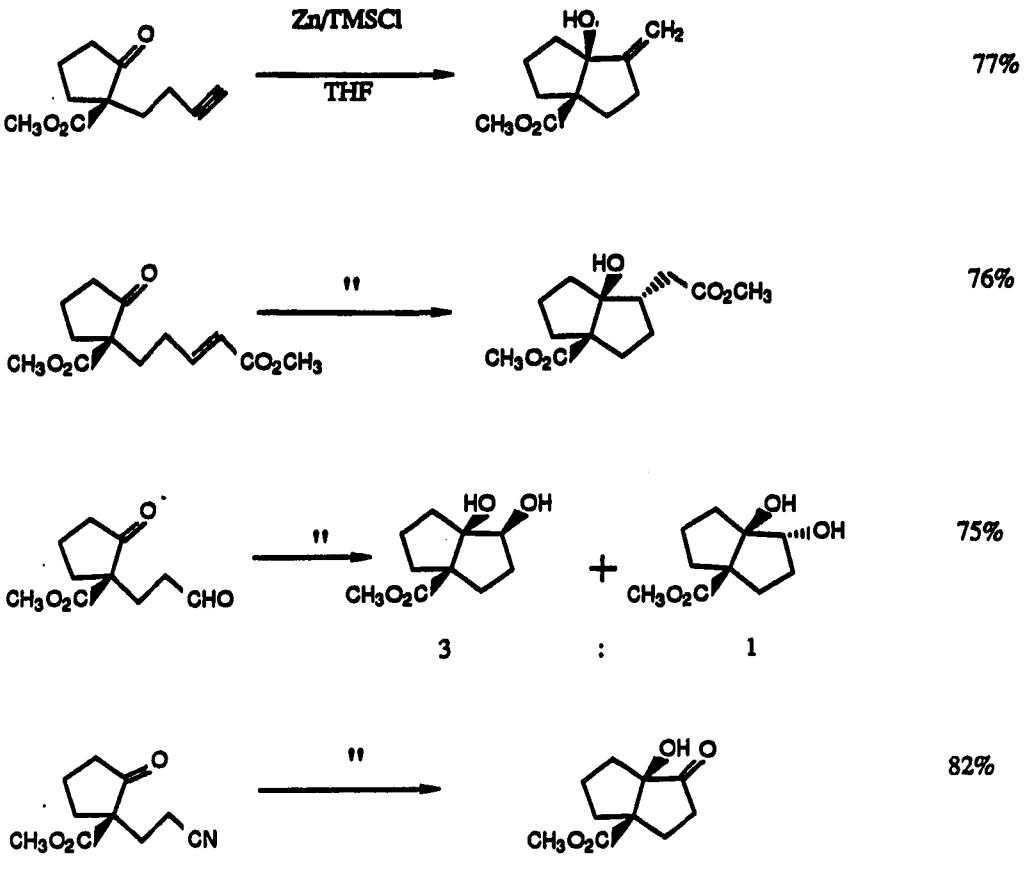
Trost and Curran[12] showed the efficient cyclization of an allylsilane which was promoted by fluoride ion. This represents a formal methylenecyclopentane annulation.



Trost and Curran[13] demonstrated the utility of this type of intramolecular cyclization in the total synthesis of (±)-coriolin. Corey and Pyne[17] described the facile

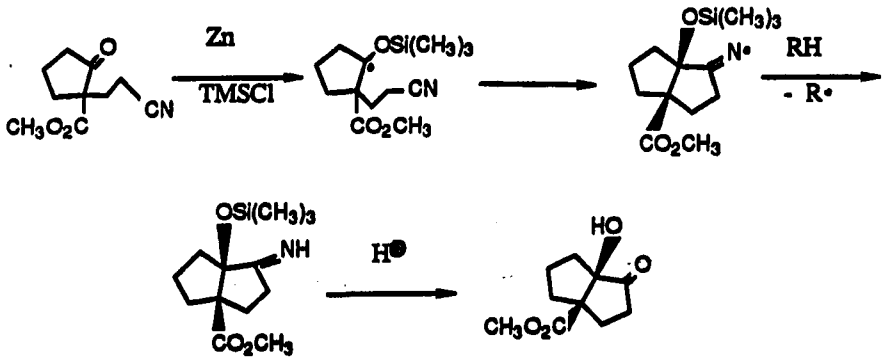


formation of cis-fused bicyclo[3.3.0]octane systems, utilizing the zinc-trimethylchlorosilane reagent to effect the desired cyclization. This new method of ring formation

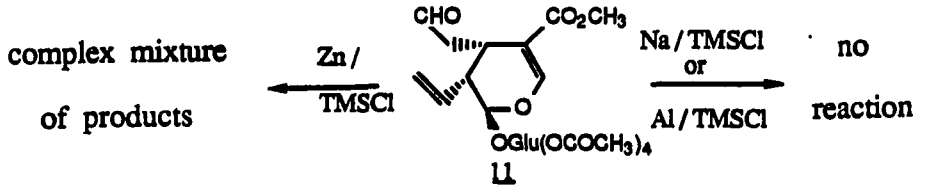


depends on the reductive activation of ketones by Zn-TMSCl and subsequent internal addition to a variety of π-unsaturated acceptors to form the 5-membered ring. The action of the reagent on the substrate is initiated by electron transfer from the metal and subsequent silylation

to generate an α-trimethylsilyloxy radical. This adds to the δ,ε-multiple bond to form the desired ring. The proposed mechanism is detailed below.



The cis ring fusion is not surprising and was assigned on the basis of literature precedent.[18] Hutchinson et al.[19] tried to apply the Corey cyclization in his synthesis of the iridoid (±)-loganin. Several unknown products were obtained, but no cyclized product was observed. Sodium or aluminum in THF with trimethylchlorosilane gave no reaction.



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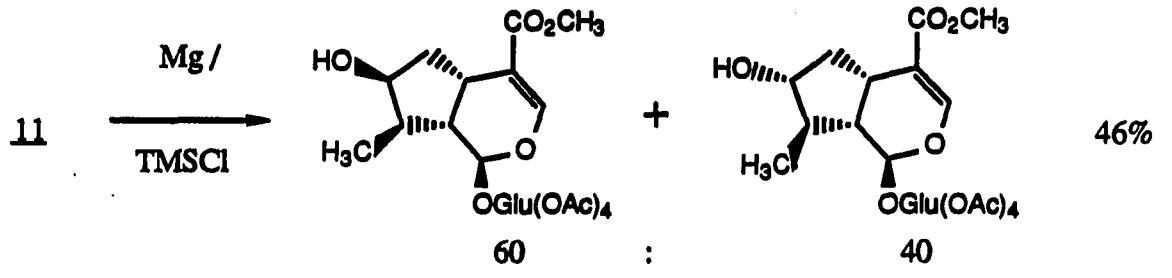
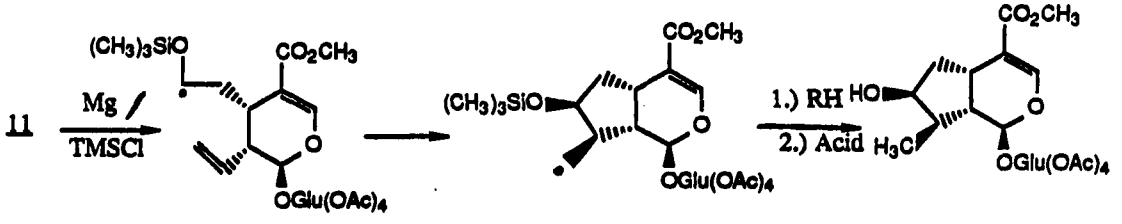
However, they was gratified to find out that a magnesium-trimethylchlorosilane mixture effected the desired cyclization. The major product was formed in 28% yield and

was identified to be the tetraacetylloganin, while the other product proved to be the 6-epi-loganin tetraacetate.

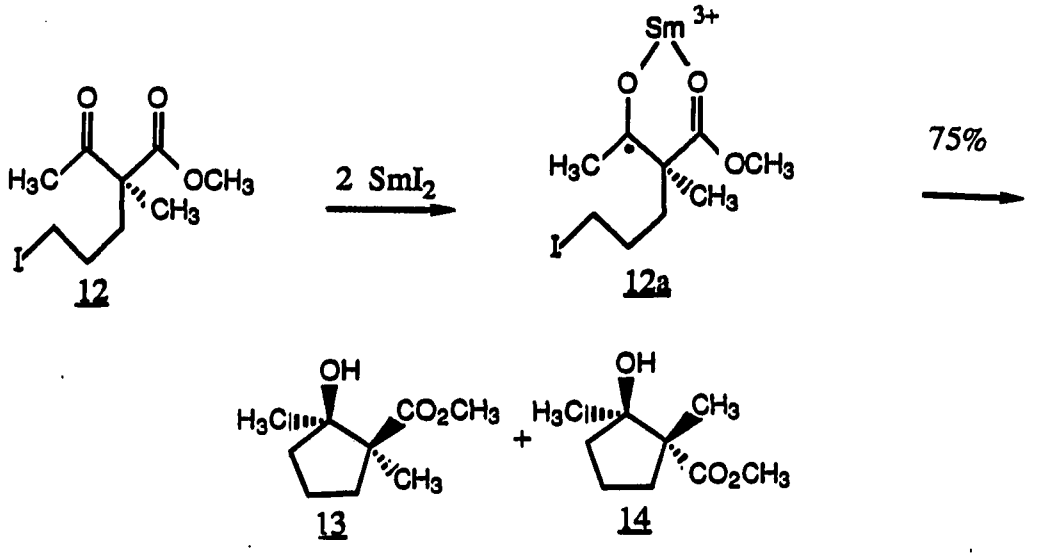


The mechanism of this cyclization parallels the proposal made by Corey and Pyne[17] for the reductive radical-induced cyclization of ketones having δ,ε π-functionality. Thus, Mg-TMSCl generates an α-trimethylsilyoxy radical by electron transfer and silylation. This adds to the double bond at the δ-position, forming a primary radical that rapidly abstracts a hydrogen atom from the solvent. This sequence of events is illustrated below.

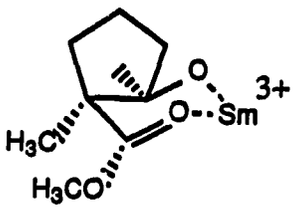


The thermodynamically favored β configuration of the methyl group at C-7 is in agreement with the results obtained for the intramolecular cyclization of 1-substituted 5-hexenyl radicals.[18]

Very recently, Molander et al.[20] reported stereocontrolled cyclization reactions mediated by samarium diiodide. They showed the facile cyclopentane ring formation of compound 12.

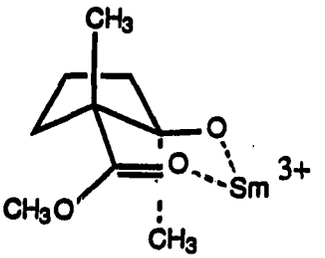


They postulated that ketyl 12a is the initial intermediate formed by electron transfer from SmI_2 to the ketone 12. Samarium diiodide also serves as a template upon which intramolecular coupling of organic halides with carbonyl substrates can be accomplished. The preferred formation of cis-fused rings is rationalized in terms of the conformations shown below.



cis conformation

15

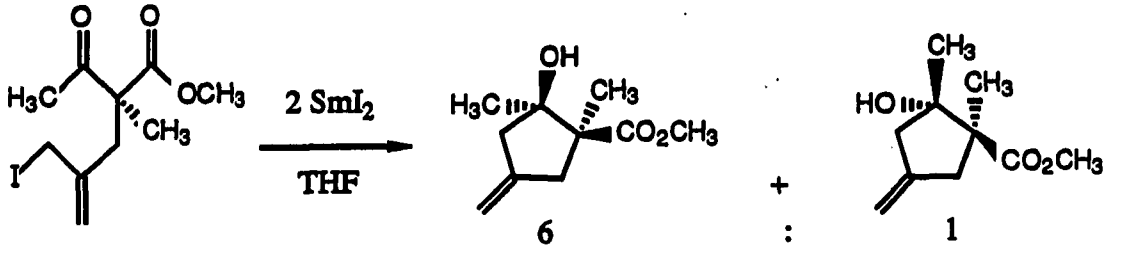


trans conformation

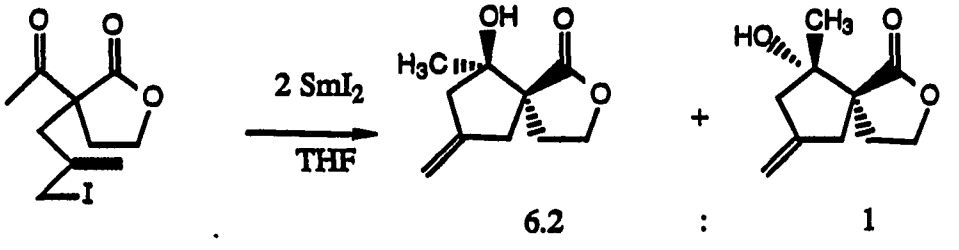
16

Conformation 16 for the trans diastereomer suffers by having both methyl groups axial on the six-membered ring defined by the chelated samarium. Conformation 15 seems to be the more favorable one, since such destabilizing factors are minimized. It is interesting to note that SmI_2 is unique in its ability to promote this type of reaction. Attempted cyclization of 12 using activated magnesium in THF gave mostly recovered starting material. The authors interpreted the success of the samarium diiodide-promoted cyclization as arising mainly from the initial electron transfer from samarium diiodide to the ketone rather than the formation of a "Grignard-type" reagent.

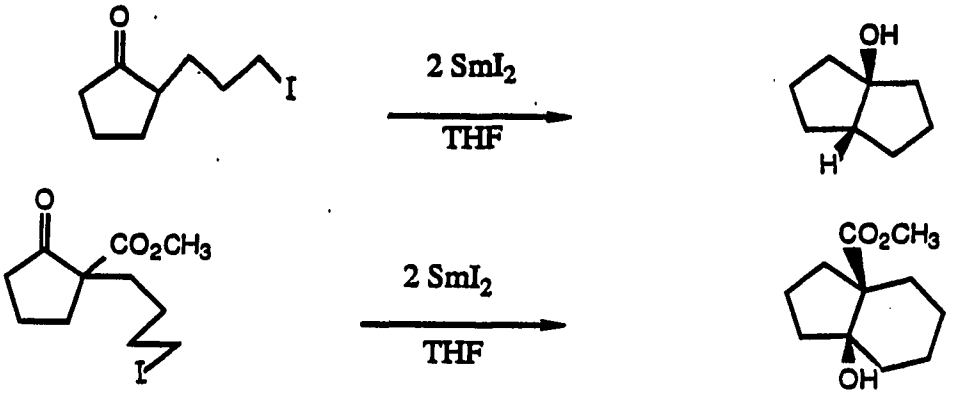
In the case of haloketone substrates, cyclization readily affords exomethylene cyclopentanes in acceptable diastereomeric ratios.



Spirocyclic ring systems have also been made via this methodology, as demonstrated by the reaction depicted below.

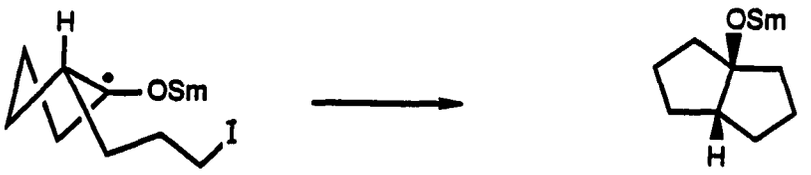


Molander and Etter[21] also utilized samarium diiodide in forming cis-fused bicyclic systems.

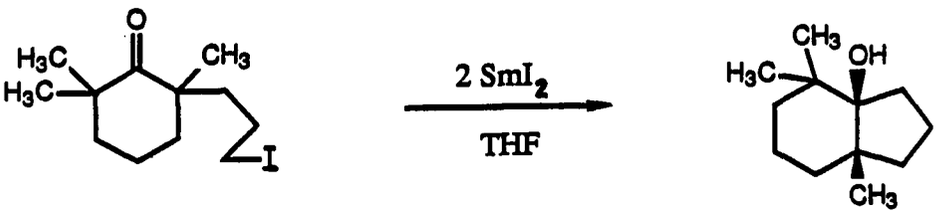


The greater facility in attaining the preferred half-chair conformation (depicted below) accounts for the exclusive formation of the cis-fused ring system. In a

trans fusion, too much strain is generated in the side chain for such cyclization to occur.



Even fully substituted, highly hindered ketones undergo cyclization with great ease.



As the foregoing published reports indicate, the literature is replete with synthetic methodologies with which one can achieve 5-membered ring closure, a necessary step in forming the C-ring of rocaglamide. One of these cyclization methods may be useful for our synthesis of rocaglamide. However, our system is functionally more complex than many of the above examples.

RESULTS AND DISCUSSION

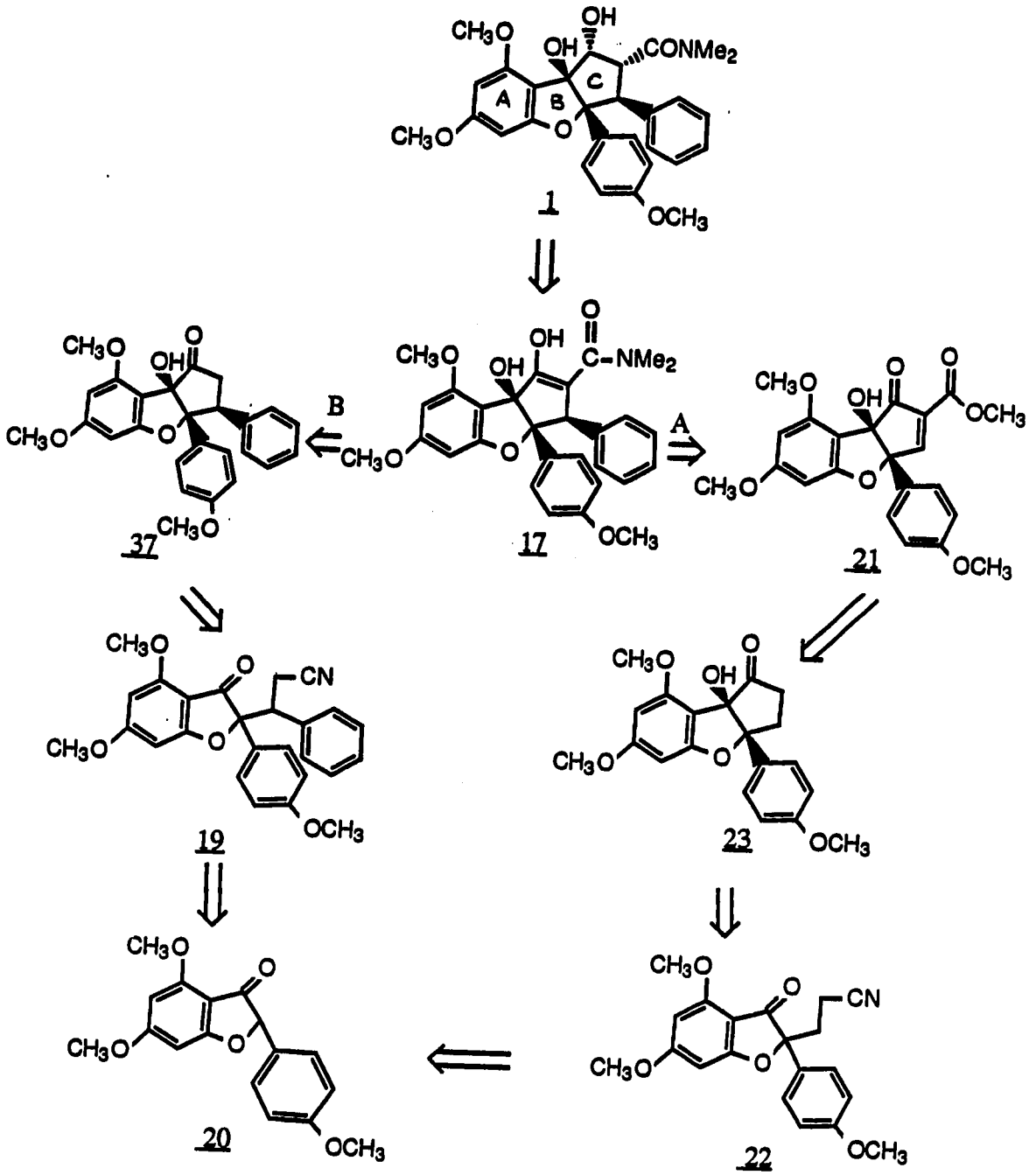
General Strategy

(±)-Rocaglamide, 1, is a highly biologically-active natural product isolated recently.[1] A very interesting feature of this molecule is the presence of five contiguous stereogenic centers in the C-ring. This feature, in fact, constitutes the foremost challenge to the successful synthesis of this compound. Another appealing aspect is that it provides a fertile testing ground for some of the ring closure methodologies published recently in the literature,[3-21] since a logical and viable approach would likely involve an intramolecular cyclization to form the C-ring.

In the process of planning our strategy toward the successful total synthesis, we envisioned two expedient routes to achieve our goal. The fact that rocaglamide has not yet yielded to any total synthesis is not perceived as a detriment, but rather emboldens us to take daring steps necessary to achieve the successful and facile synthesis. Our retrosynthetic analysis is shown in Scheme II.

In our first retrosynthetic analysis, path A, we propose that the phenyl-substituted keto amide 17 is the ultimate precursor to (±)-rocaglamide. Compound 17, in turn, is envisioned to arise from a stereoselective cuprate addition to the doubly-activated and highly reactive unsaturated

Scheme II



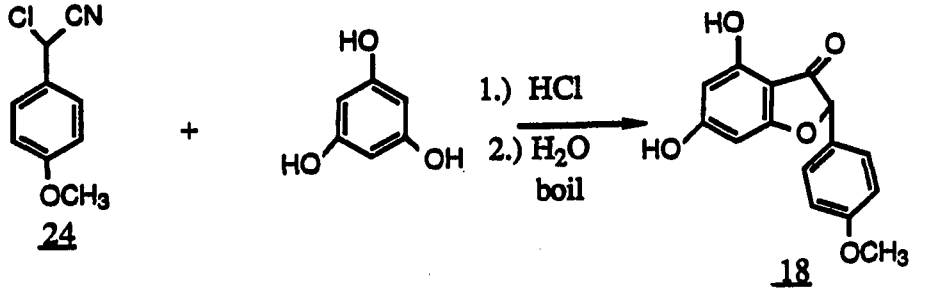
tricyclic keto ester 21, followed by a subsequent amination of the resulting keto ester with dimethylamine. The unsaturated keto ester 21 is expected to be derived from the tricyclic α-hydroxy ketone 23 via a carbomethoxylation and oxidation sequence. The bicyclic keto nitrile 22 should yield the key intermediate, cis-fused tricyclic ketone 23, by using one of the many conditions for intramolecular cyclizations that have been reported in the literature.[15,27,20] The keto nitrile 22 is readily available by the Michael reaction of benzofuranone 20 and acrylonitrile.

In our alternative retrosynthetic analysis, path B, again we reasoned that the phenyl-substituted tricyclic keto amide 17 is an advanced intermediate leading to the natural product. We anticipate that this compound should be accessible by the carbomethoxylation and subsequent amination of the tricyclic cis-fused alpha-hydroxy ketone 37. We expect compound 37 to be readily available by the intramolecular cyclization of the bicyclic keto nitrile 19. This intermediate, in turn, is to arise from the successful Michael reaction of benzofuranone 20 and cinnamonitrile. We hope that this particular reaction shows significant diastereoselectivity such that the desired diastereomer of 19 is formed in greater amount relative to the other isomers.

Substrate Preparation and Intramolecular Cyclization Studies

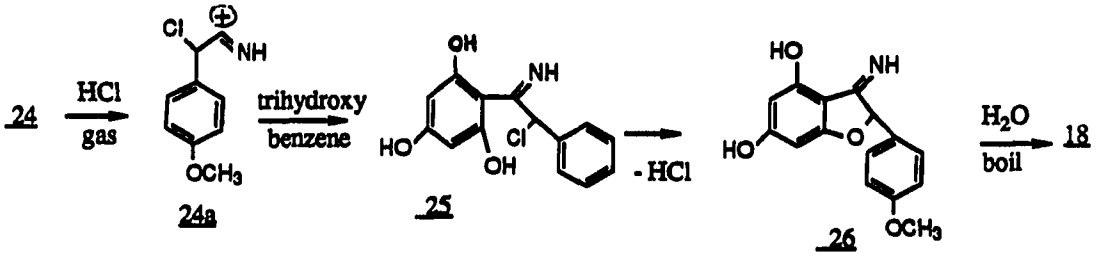
Since one of the key reactions in our synthesis involves the intramolecular cyclization of keto nitriles 19 and 22, we decided to first investigate the feasibility of that ring closure reaction.

The preparation of benzofuranone 20 can be accomplished in two steps. The Hoesch reaction of phloroglucinol and α-chloro p-methoxyphenyl acetonitrile 24 gave the arylbenzofuranone 18 in good yield.

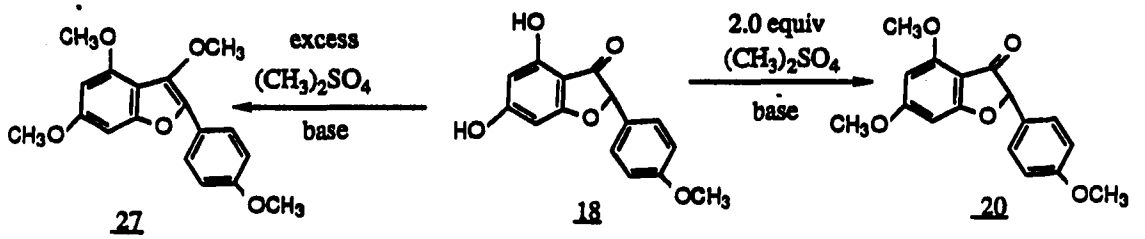


The reaction is believed to proceed via the initial protonation of the nitrile 24, which undergoes a nucleophilic attack by the electron-rich trihydroxybenzene to give the unstable intermediate 25. This compound readily cyclizes by eliminating a molecule of HCl to give the imine 26.

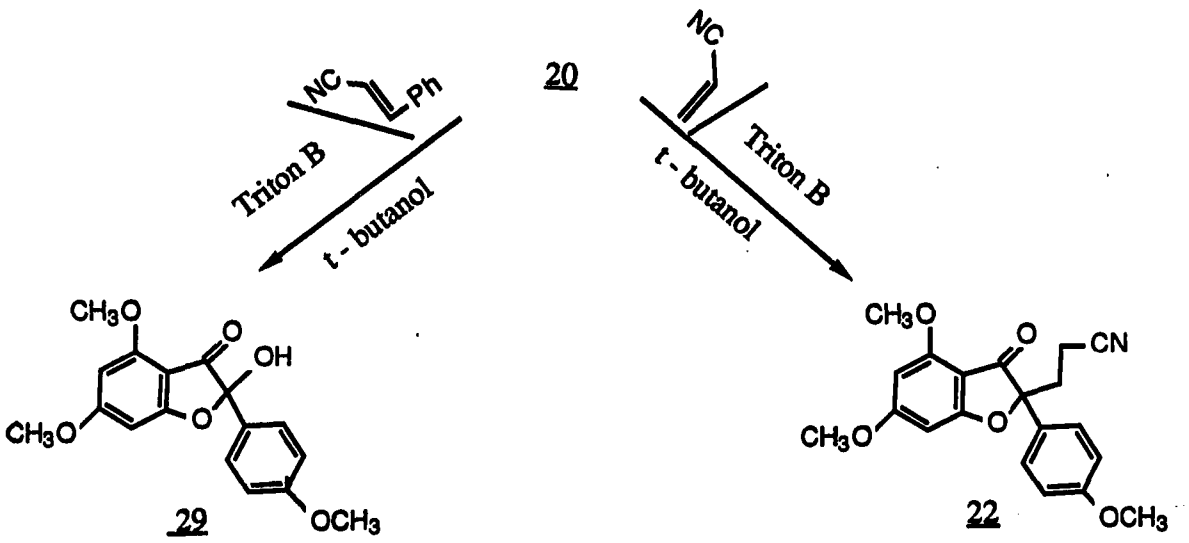
When compound 26 is boiled in water for four hours, a fine yellow precipitate of benzofuranone 18 is obtained.



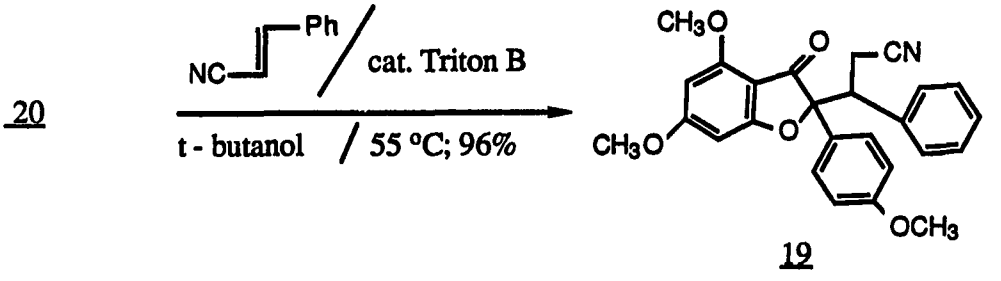
Dimethoxylation with potassium carbonate and two equivalents of dimethyl sulfate gave the aryl-substituted benzofuranone 20 in 90% yield. It is necessary to use the exact amount of dimethyl sulfate since any excess tends to give some of the trimethoxylated compound 27.



With intermediate 20 available in ample quantities, we employed the Michael reaction to form the bicyclic keto nitriles 19 and 22. While the reaction of 3-benzofuranone 20 with acrylonitrile in the presence of trimethylbenzyl-ammonium hydroxide (Triton B) gave the keto nitrile 22 in high yield, utilizing cinnamonitrile as Michael acceptor gave none of the adduct 19. Instead, the hydroxylated benzofuranone 29 is formed.

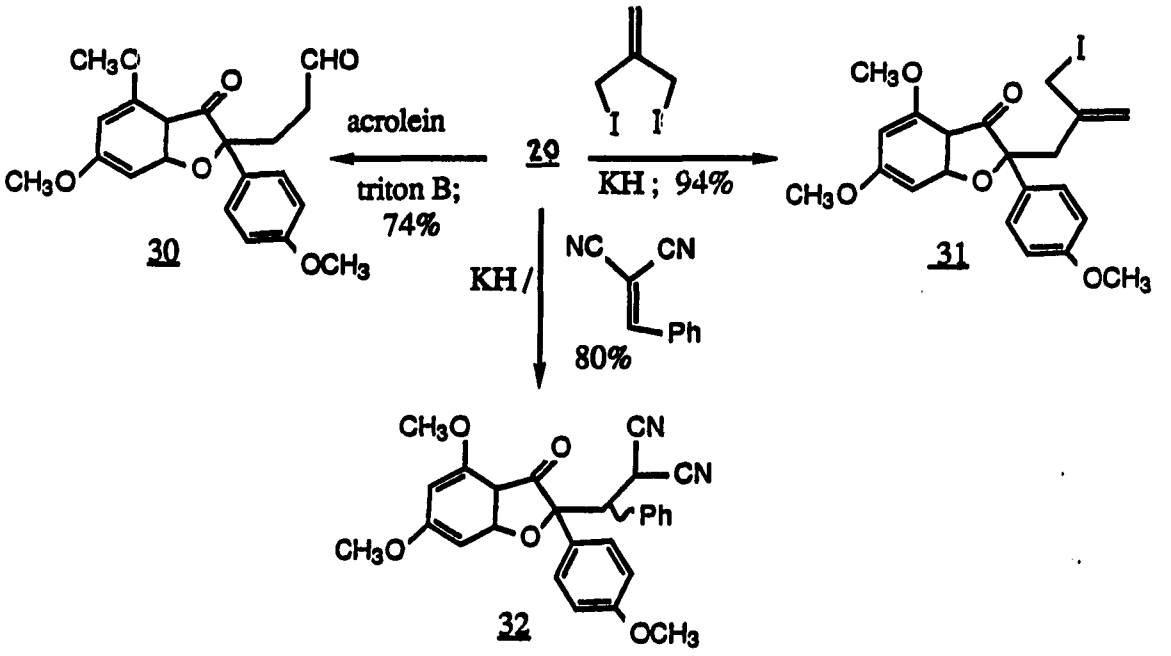


The successful preparation of the phenyl-substituted keto nitrile 19 was finally achieved in 96% yield by conducting the reaction at 55°C for 1 1/2 days using a catalytic amount of Triton B and insuring the exclusion of oxygen in the reaction mixture. Compound 19 was formed in a 5:1 ratio of diastereomers.



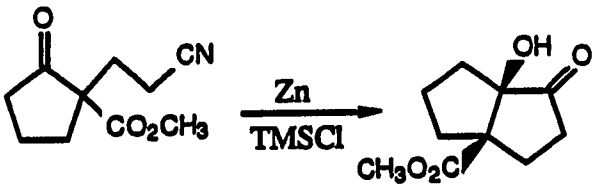
In addition to keto nitriles 19 and 22, we also prepared other substrates such as compounds 30-32. We plan to study the generality of the intramolecular cyclization reactions on more complicated systems than are reported in the

literature. The benzofuranone 31 was readily made by reacting 20 with potassium hydride and excess 3-iodo-2-iodomethyl-1-propene.

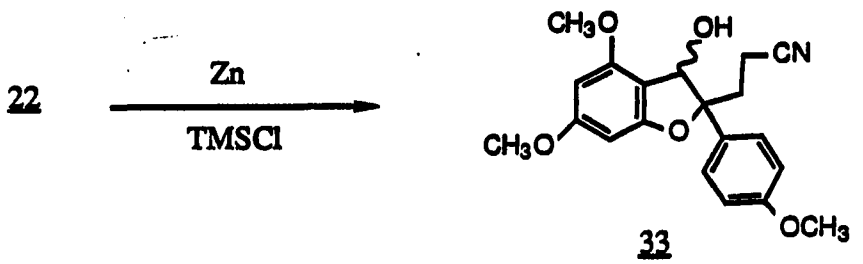


The keto aldehyde 30 was synthesized via the Michael addition of compound 20 with acrolein in the presence of potassium carbonate and Triton B. The reaction of 20 with 1,1-dicyano-2-phenyl ethylene gave a good yield of the Michael adduct 32.

With the ready availability of the substrates for intramolecular cyclization studies, we decided to try the conditions published in the literature. Corey and Pyne[17] reported the successful formation of bicyclic systems using zinc/chlorotrimethylsilane to effect such ring closures.



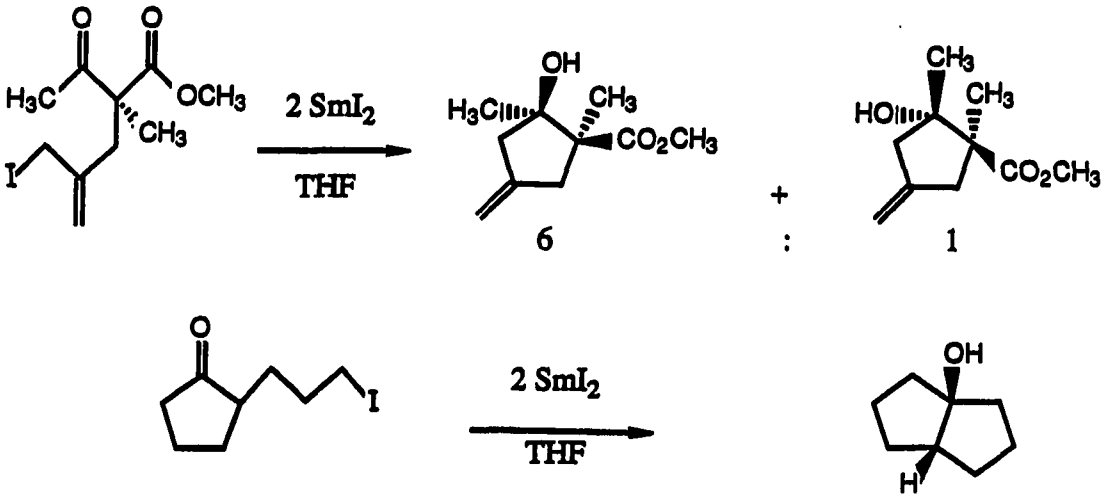
However, treatment of compound 22 with Zn/TMSCl did not yield any cyclized product; instead, a fair amount of the hydroxy nitrile 33 was obtained.



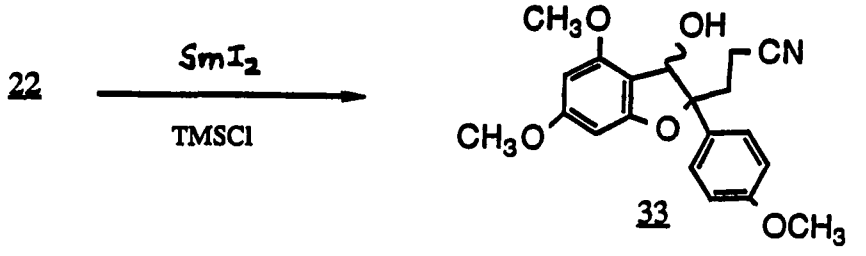
We then tried Hutchinson's modification of the Corey conditions, namely using magnesium instead of zinc as the electron donor source. Although the Wisconsin group had been successful in obtaining a loganin intermediate utilizing this method, we did not obtain any cyclized product. Instead, the magnesium/trimethylchlorosilane conditions gave a mixture of several products.

We were now a little concerned about our cyclization strategy, which we had hoped would proceed readily based on ample literature precedence. We were happy to note the report by Molander et al.[20] and Molander and Etter[21] which mentioned the facile formation of mono- and bicyclic systems

by conducting the cyclization in the presence of samarium diiodide.

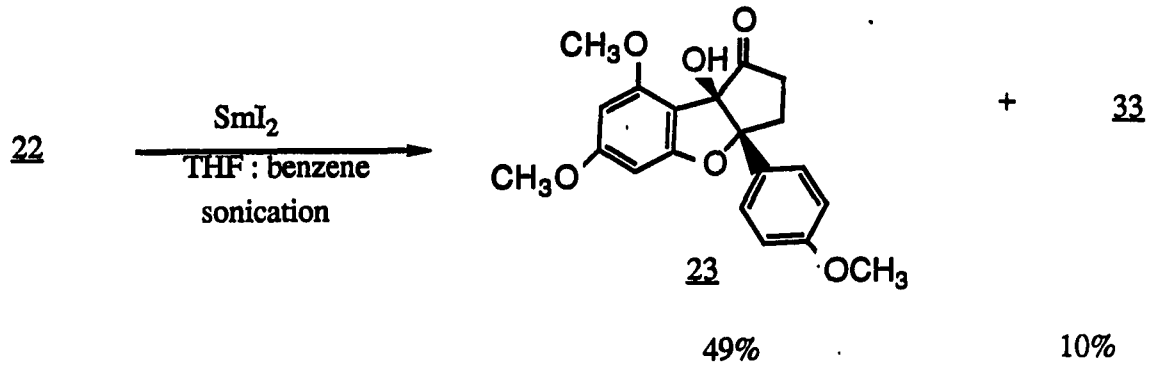


We were dismayed to find that only the uncyclized hydroxy nitrile 33 was obtained when Molander's conditions were employed.

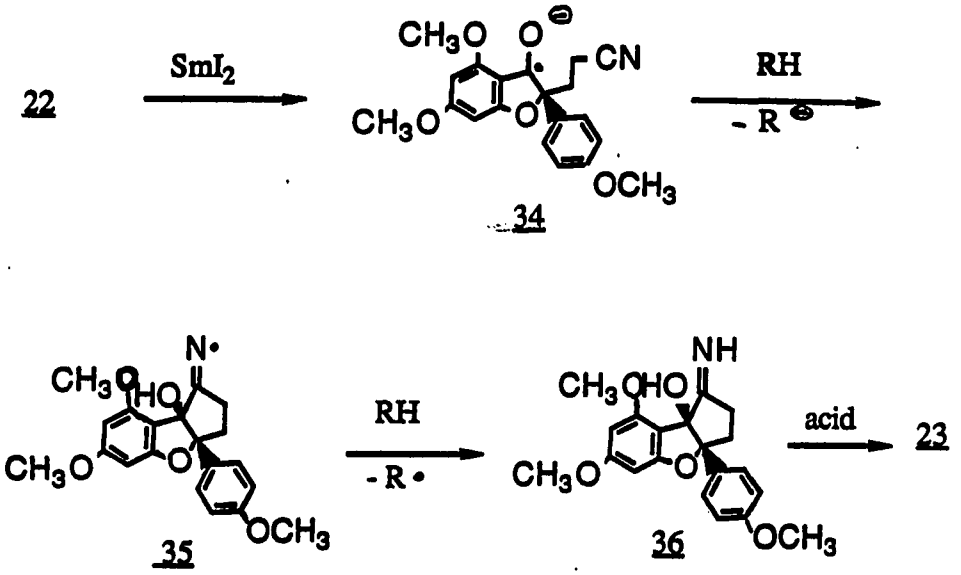


We think that the failure of our attempted cyclizations was probably due to the good hydrogen donating ability of the tetrahydrofuran solvent in which the reaction was conducted. In other words, the ketyl radical 34 is being formed, but is rapidly quenched via hydrogen atom abstraction from the solvent. The reaction must be slowed

down such that the radical has sufficient time to undergo intramolecular cyclization before being quenched by the solvent. We attempted to conduct the cyclization in poorer hydrogen donor solvents like ether and benzene, but the samarium diiodide reagent is not formed in such solvents. We then opted to run the reaction in 1:10 tetrahydrofuran: benzene cosolvent system. We were gratified to observe a 49% yield of the cyclized product 23, along with a 10% yield of hydroxy nitrile 33. We had to sonicate the reaction mixture to insure the complete solubility of the in situ generated samarium diiodide.



We believe that the initial step of the reaction involve electron donation by the samarium diiodide to the keto nitrile 22 to form the intermediate 34, which undergoes intramolecular closure to give the radical 35. Intermediate

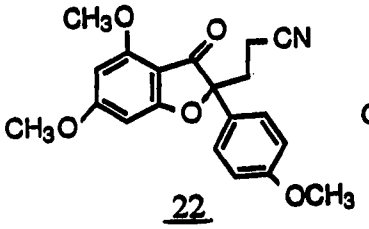
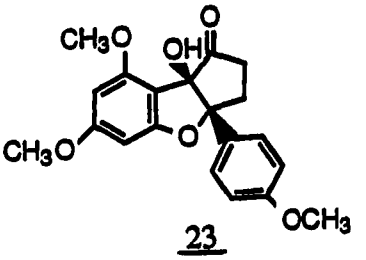
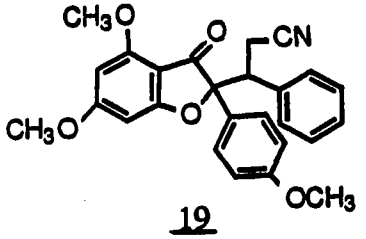
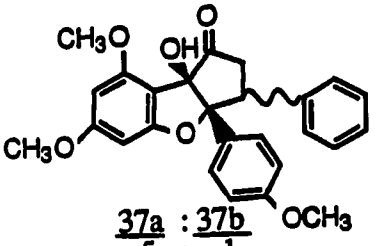
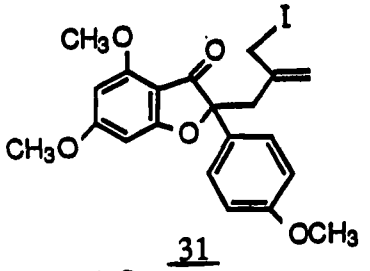
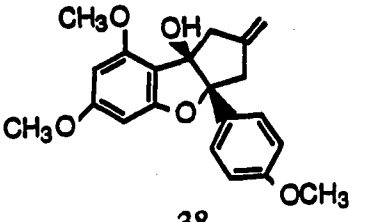
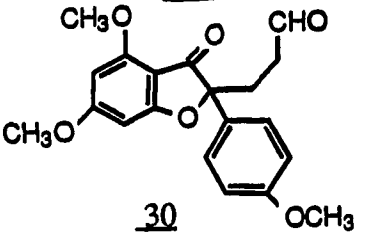
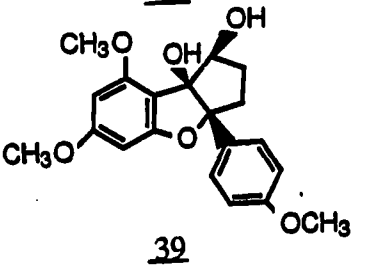
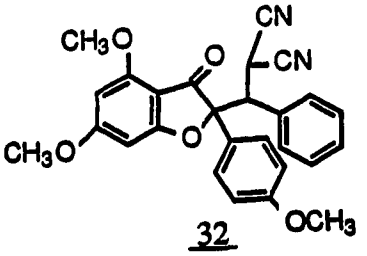
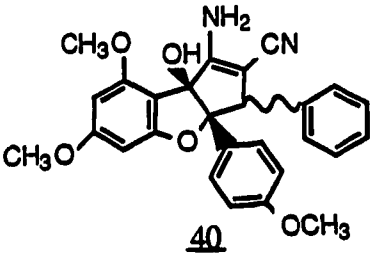


35 abstracts a hydrogen atom from the solvent to form the tricyclic imine 36. Upon acidic work-up, compound 36 is readily hydrolyzed to give the desired tricyclic ketone 23. The cis-ring fusion is assigned on the basis of literature precedence.[19-21]

With this positive result in hand, we decided to investigate the generality of this method of cyclization. Listed in Table 1 are the results of our samarium diiodide-induced intramolecular closures.

The intramolecular cyclization of 19 gave a 5:1 diastereomeric ratio of 37a:37b, reflective of the diastereoselectivity of the Michael reaction. In contrast to the ring closure of substrate 22, no sign of uncyclized

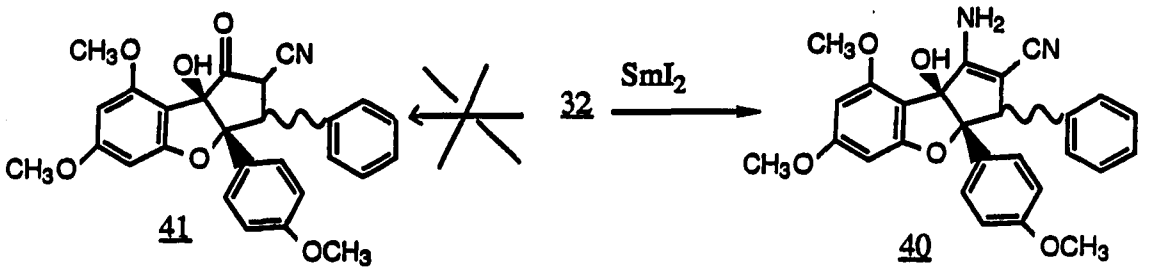
Table 1. Samarium-induced intramolecular ring closure

Substrate	Products	Yield (%)
 22	 23 + 33 (10%)	49
 19	 37a : 37b = 5 : 1	68
 31	 38	70
 30	 39	49
 32	 40	20

product was observed. This is maybe a consequence of the steric bulk of the phenyl substituent, which may hinder the hydrogen atom donation by the solvent, giving sufficient time for cyclization to occur.

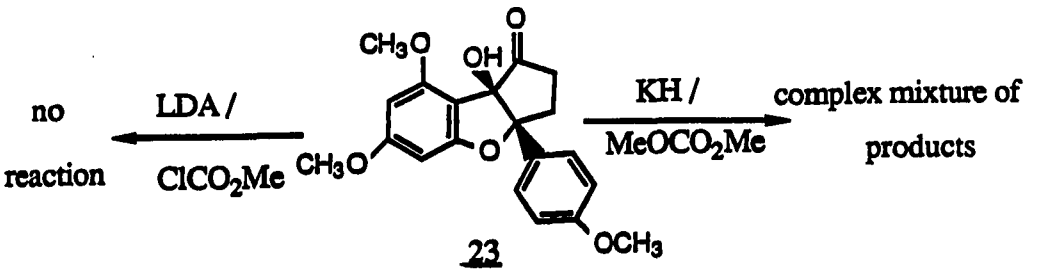
The bicyclic iodide 31 gives a good yield of the tricyclic compound 38 upon treatment with samarium diiodide. The keto aldehyde 30 also gave a decent yield of the alcohol 39. Although the stereochemistry of the secondary alcohol was not determined, we have assumed it is cis to the alcohol at the ring fusion, since samarium is reported to act efficiently as a chelating template.[20,21]

The keto dinitrile 32 gave a totally unexpected product in low yield. We had hoped to obtain the tricyclic keto nitrile 41, but obtained a small quantity of the amino nitrile 40 instead.

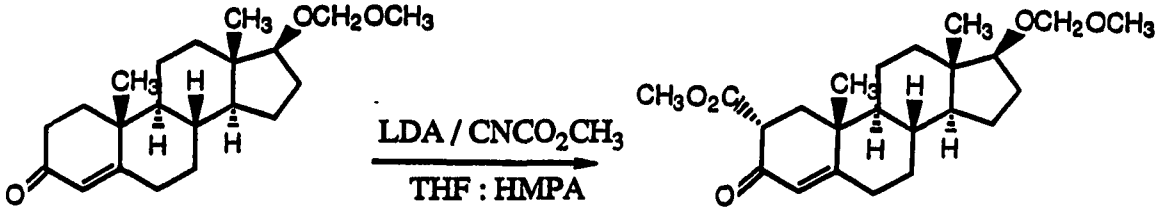


With the ready availability of compound 23, we decided to carry this intermediate on toward rocaglamide. The next important step is to incorporate a carbomethoxyl group adjacent to the ketone. We first tried the standard methods of introducing such a group. Unfortunately, reacting 23

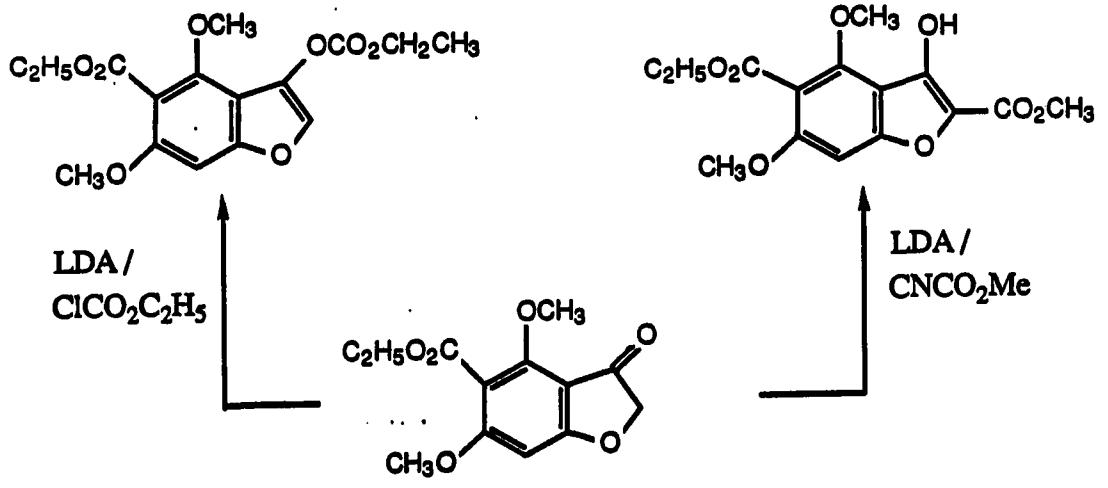
with methyl chloroformate[22] in the presence of lithium diisopropylamide only resulted in the recovery of the starting material. Treating 23 with dimethyl carbonate using potassium hydride as base gave a complex mixture of products.



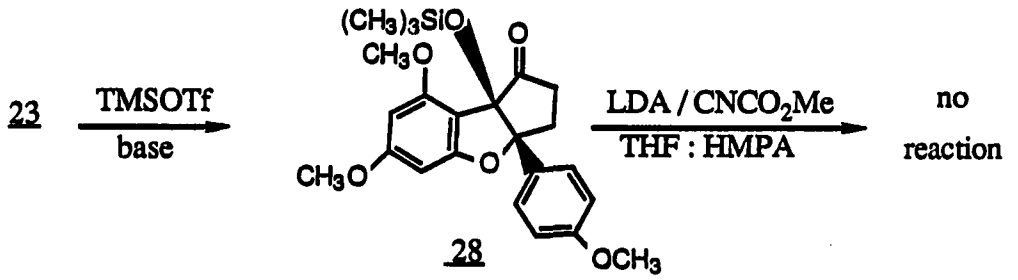
We noted with interest a recent report by Mander and Sethi[23] about an excellent carbomethoxylating agent. Methyl cyanoformate works well with hindered systems and alleviates the frequently encountered problem of competing O-acylation. This reagent reacts in a highly stereoselective manner with ketone enolates at the "softer" carbon to give β-keto esters under mild conditions. Mander and Sethi[23] utilized methyl cyanoformate to introduce the carbomethoxyl group in a steroid in good yield.



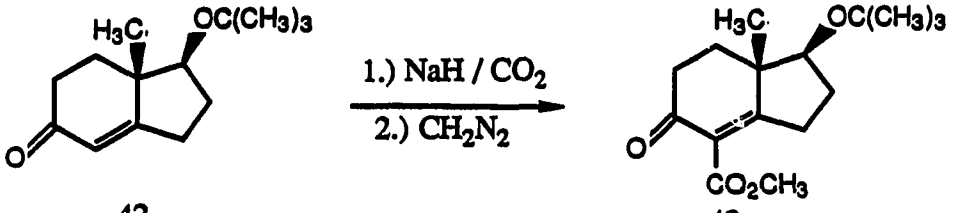
The selectivity of acylation is impressive. In his synthesis of a griseofulvin analog, Yamoto et al.[24] observed that acylation performed using ethyl chloroformate yielded mainly O-acylated product, whereas C-acylated product is obtained exclusively using methyl cyanoformate.



We were discouraged to find that the reaction of 23 with methyl cyanoformate gave only recovered starting material. Thinking that an intramolecular carbomethoxylation to the tertiary hydroxy group might be occurring, we decided to protect this alcohol before conducting the acylation. But reacting 28 with methyl cyanoformate again led to recovery of starting material.

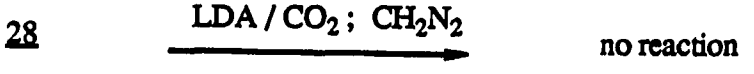


On one hand, we have to protect the tertiary alcohol to prevent any competing reaction from occurring once the desired keto ester is formed. On the other hand, by incorporating the bulky silyl protecting group, we have significantly increased the steric hindrance around the cyclopentanone ring, thus making the carbomethoxylation a substantially more difficult problem. We attempted to solve this problem by quenching the ketone enolate with carbon dioxide. We argued that CO_2 is a small enough molecule to act as a good electrophile in hindered systems. Hajos and Parrish[25] have reported the successful trapping of keto enolates in modest yield. Apparently, the relatively congested environment of the bicyclic system does not hinder the approach of the small CO_2 molecule.

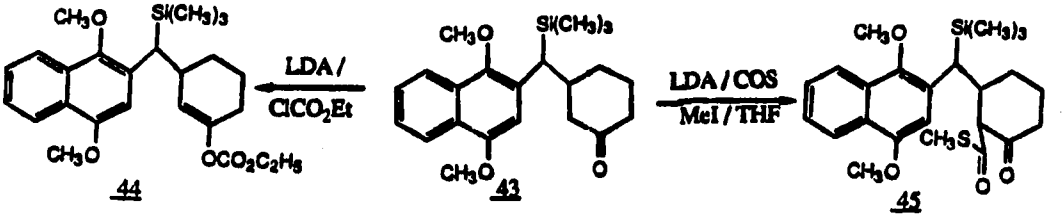


42 42a

However, the reaction of the ketone enolate of 28 with carbon dioxide/diazomethane in the presence of LDA gave only recovered starting material.

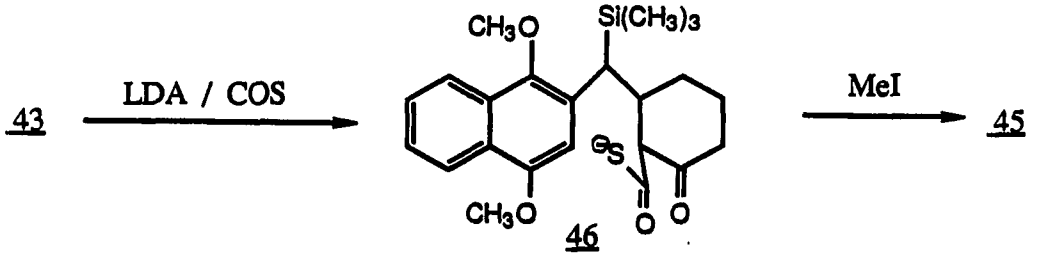


We were perplexed and concerned about this unexpected difficulty of introducing the carbomethoxyl group and were pleased to note the report of Vedejs and Nader,[26] in which they showed an efficient carboxylation of a tricyclic system.



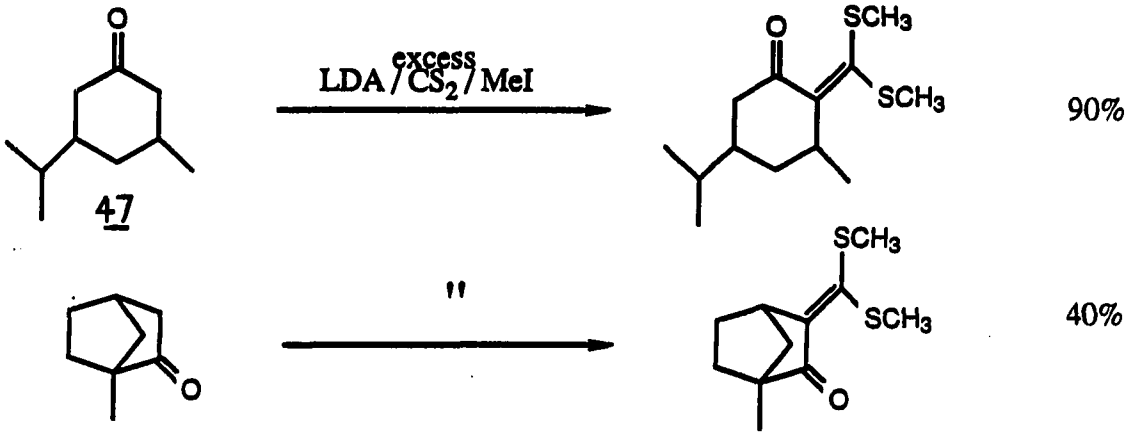
They observed that the direct carboxylation of the ketone enolate derived from 43 with carbon dioxide did not produce any keto acid after careful neutralization. Reacting 43 with LDA and ethyl chloroformate resulted only in the formation of the enol carbonate 44. They were able to solve the problem of regiospecific carboxylation by using carbon oxysulfide instead of CO_2.

Thus, treatment of the ketone enolate of 43 with COS gave the anion 46, which yielded the thioester 45 in good yield after quenching with methyl iodide.



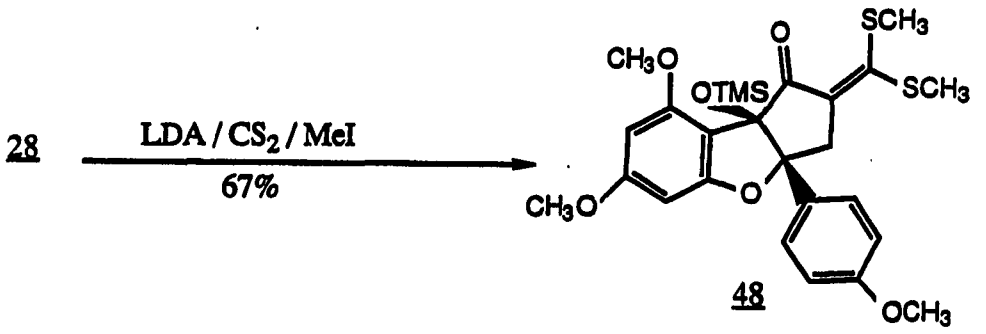
We were again dismayed to discover that only recovered starting material was observed when we attempted this methylthioester formation on our tricyclic ketone 42. The failure of these reactions due to the very congested environment of 42 requires a different tactic.

At this point, we began to doubt the feasibility of incorporating the carbomethoxyl unit and also the overall strategy. Hence, we welcomed a very recent review by Dieter[27] on α-oxo ketene dithioacetals. He reported the facile formation of α-oxo ketene dithioacetals. The reaction seems to work well on hindered systems. Shown below are some examples of relevant systems which successfully reacted with carbon disulfide/MeI.

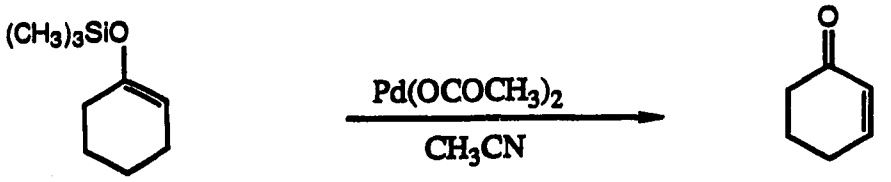


We were elated to find that the α-oxo ketene thioacetal 48 was readily formed in good yield upon treating 28 with the LDA/CS_2/MeI conditions.

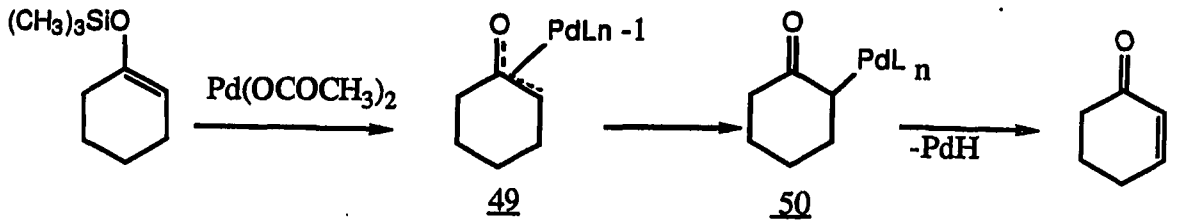
With the availability of 48, we now have to focus our attention on transforming 48 into a keto ester. A feasible



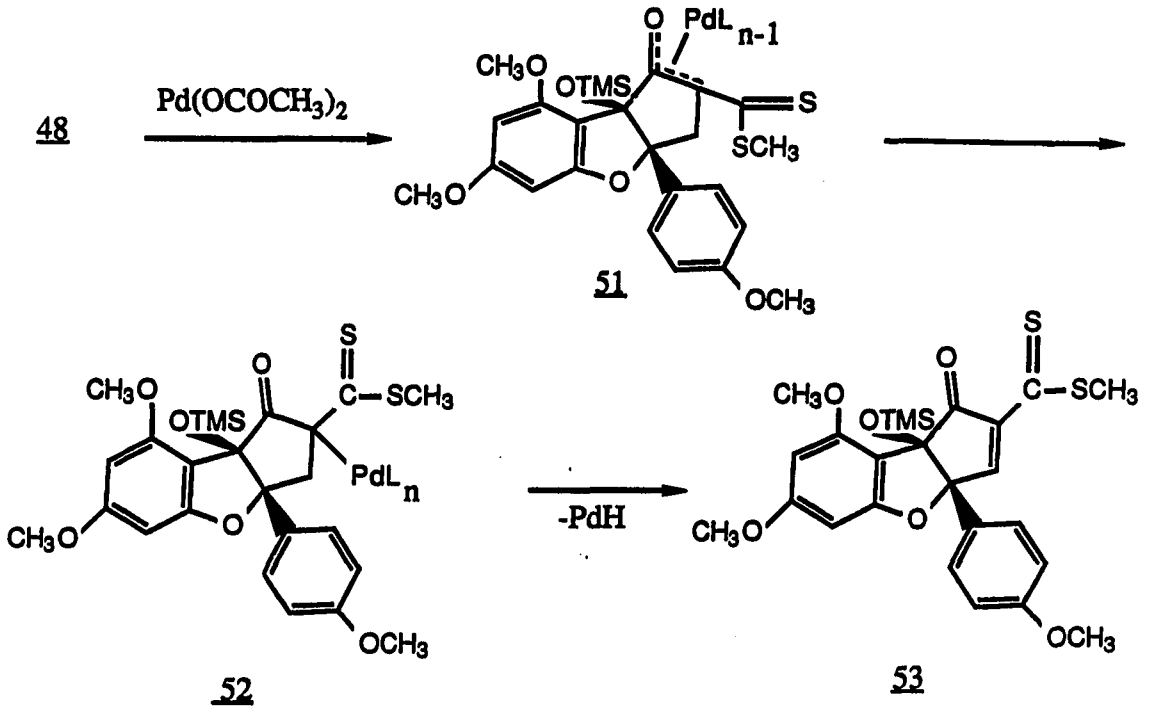
option is a palladium-catalyzed rearrangement of compound 48. The literature is replete with examples in which enol silyl ethers are readily transformed to enones.[28,29]



The palladium(II)-induced dehydrosilylation of the silyl enol ether is explained in terms of β-elimination of palladium(II)-hydride from the palladium complex 50, which in turn was derived from the oxo-π-allylpalladium(II) intermediate 49.

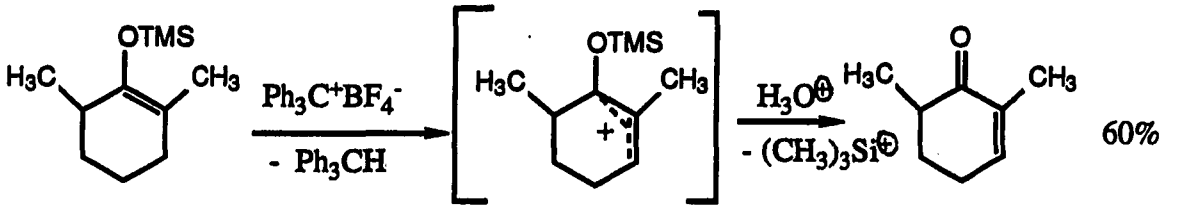


In close analogy to the above example, we had hoped to obtain the α,β-unsaturated α-thioester enone 53 through the intermediacy of the palladium complexes 51 and 52. Contrary

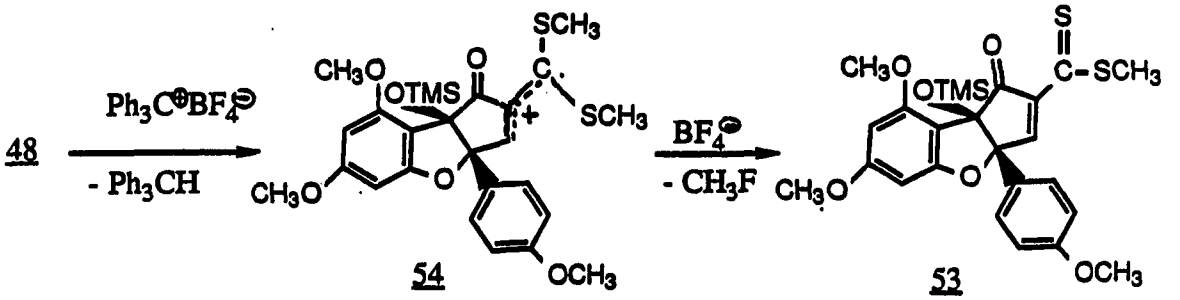


to our expectations, reaction of 48 with palladium acetate gave a complex mixture of products, none of which resembled the desired product 53.

We also tried to form the unsaturated keto ester 53 via hydride abstraction. Jung and Rathke[30] reported the conversion of enol silyl ether of ketones to enones in decent yield. They believed that the reaction proceeded via hydride abstraction with triphenyl carbenium tetrafluoroborate to afford an allylic cation, which upon acidic work-up yielded the enone.

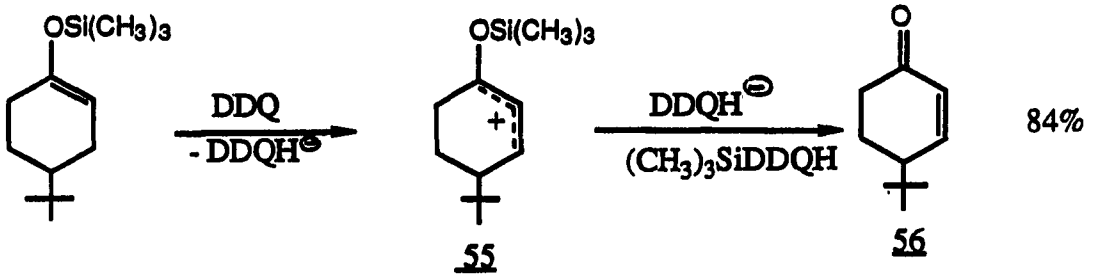


We explored the possibility of this sequence of events occurring on our substrate. We anticipated the rapid hydride abstraction by trityl tetrafluoroborate would give the allylic cation 54, which is expected to yield the desired keto ester 53. Unfortunately, the reaction of 48



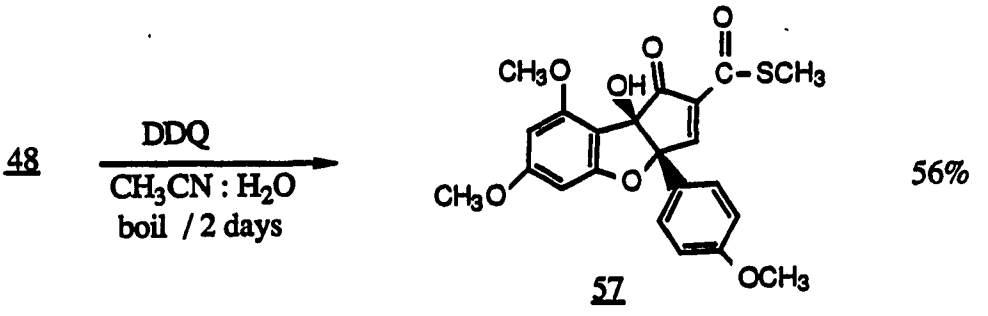
with triphenyl carbenium tetrafluoroborate resulted in a complex mixture of products.

With our options for the needed transformation rapidly diminishing, we turned our attention to a published report by Murai et al.[31] regarding the oxidation of enol silyl ethers to enones using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). In a mechanism similar to the one proposed by Jung and Rathke,[30] DDQ abstracts a hydride to yield the allylic cation 55. The silyl group of 55 then reacts with $DDQH^-$ to give the enone 56 in high yield.



55 56

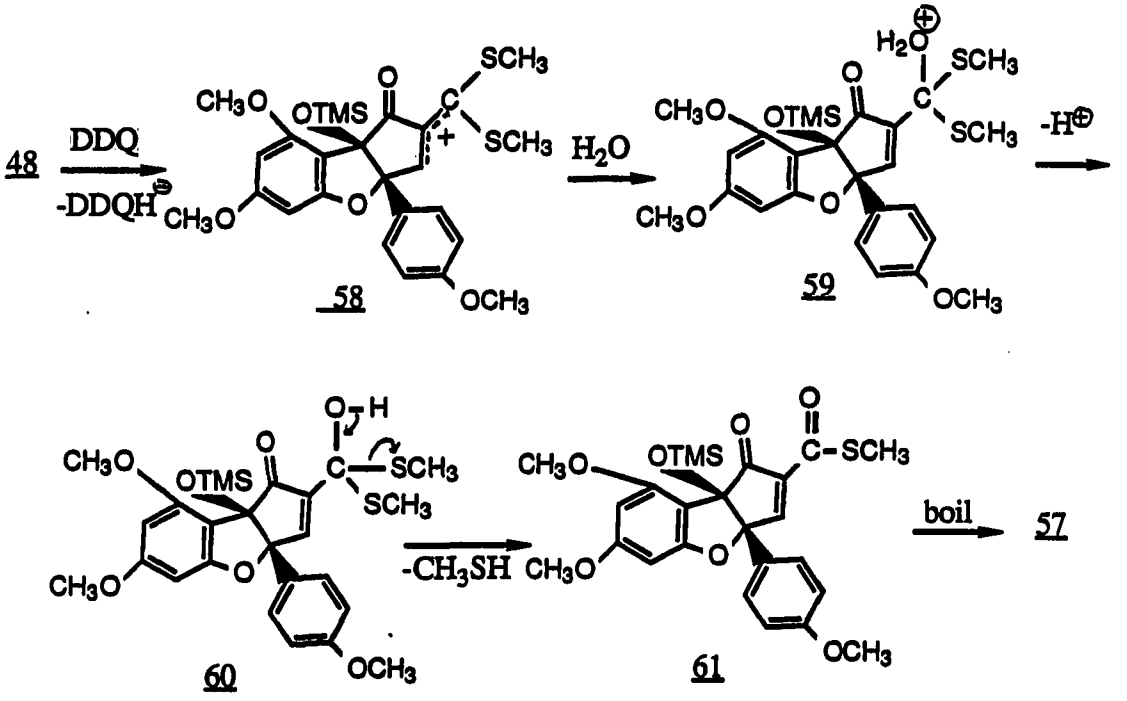
Boiling 48 in benzene in the presence of DDQ gave some of the desired enone ester 57. However, this reaction is capricious and not reproducible. When the oxidation was performed in acetonitrile:water mixture, we were extremely pleased to obtain the key intermediate 57 in 56% yield.



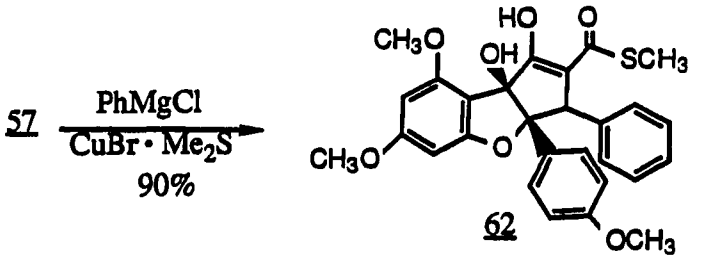
57

We believed that the reaction proceeded according to Scheme III. Initial hydride abstraction yields the allylic cation 58, which reacts with water to give intermediate 59, which leads to 61.

Scheme III

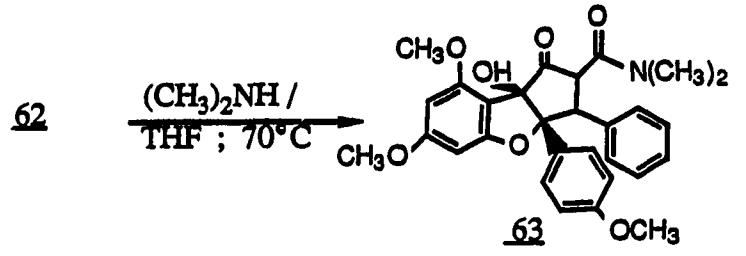


With the unsaturated keto ester 57 in hand, we are now set to introduce a phenyl group via a copper-mediated conjugate addition. We feel that the doubly activated Michael acceptor 57 should be very reactive. In fact, the reaction with phenylmagnesium chloride in the presence of copper bromide-dimethylsulfide proceeded well, as expected, giving the tricyclic keto ester 62 in high yield.



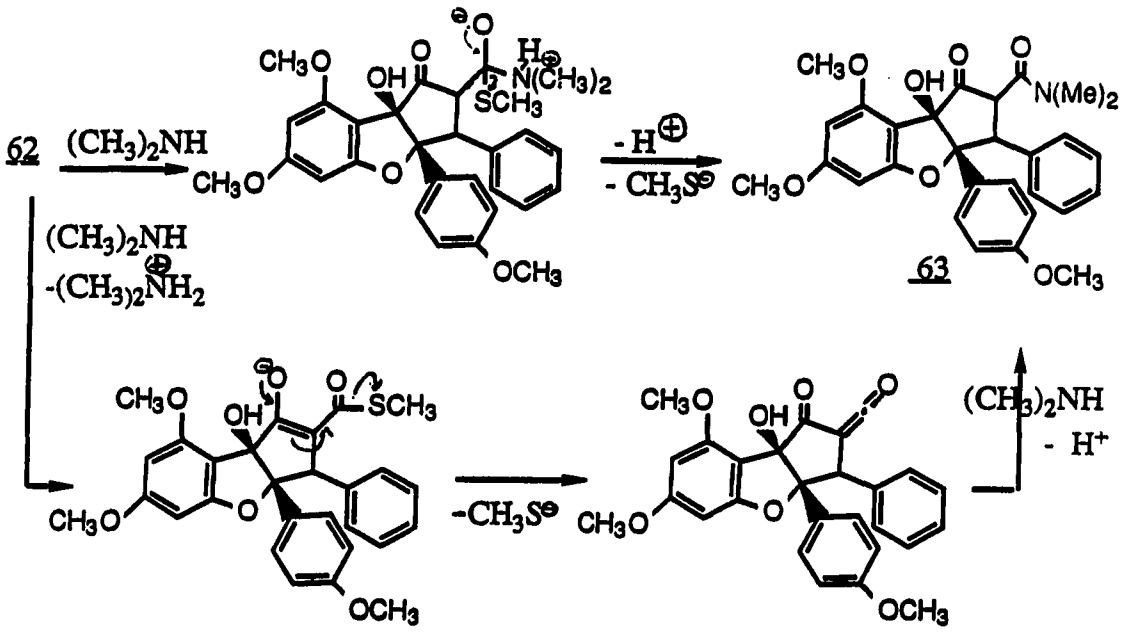
The delivery of the phenyl group is expected to occur from the convex face of the cis-fused bicyclo[3.3.0]octane, giving the desired beta-configuration of the phenyl group. On the other hand, the p-methoxyphenyl group at the ring fusion may hinder such an attack. At this point, we were unable to assign the stereochemistry of the phenyl group and have to wait until we reach the final stage of our synthesis to ascertain the stereochemistry. However, the reaction clearly produced only one diastereomer based on the spectroscopic data on hand.

Compound 62 then reacted with dimethylamine in THF at 70°C, to give key intermediate 63 in high yield.

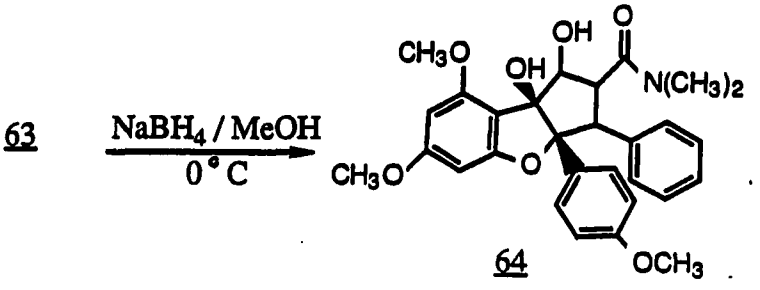


Although this mechanism is generally believed to proceed via a direct displacement of the thiomethyl moiety by dimethylamine, the formation of a ketene followed by a nucleophilic attack by the amine is also possible (please refer to Scheme IV).

Scheme IV



With the immediate precursor to the natural product in hand, treatment of compound 63 with $NaBH_4$/MeOH at 0°C gave the presumed dihydroxy amide 64 in good yield.

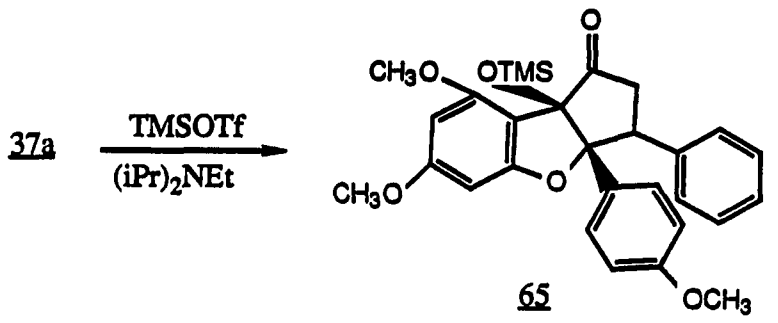


The hydride delivery is expected to occur from the exo-face of the molecule, giving the desired α-configuration of the secondary alcohol. However, we were dismayed to find

that the NMR of compound 64 does not match up with spectra of rocaglamide kindly furnished to us by Professor McPhail at Duke University. The synthetic material 64 exhibits the right molecular weight and has all the functionality present in rocaglamide. It is obvious that we have made an isomer of the natural product.

In our alternate approach to rocaglamide, we utilized the major diastereomer 37a, obtained via the samarium diiodide-induced cyclization of 19. At this point, we were unable to ascertain the relative stereochemistry of the phenyl substituent. We decided to wait until we reached the final stage of our synthesis to determine this particular stereochemistry.

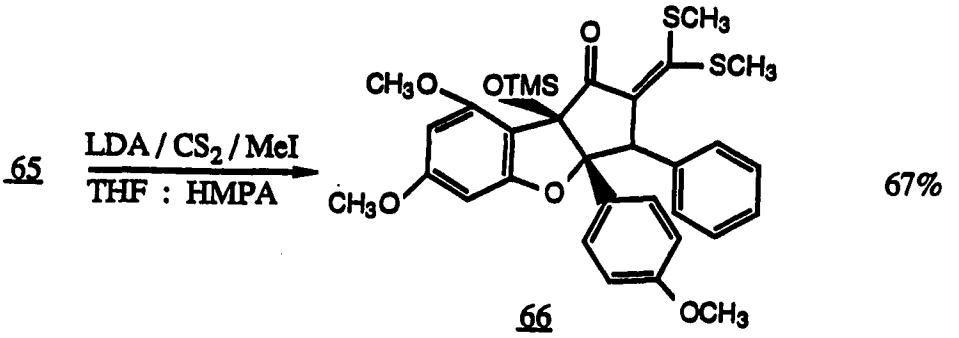
The tricyclic alcohol 37a was first silylated using trimethylsilyl trifluoromethanesulfonate. It is our experience that the subsequent alkylation proceeds much better when this protection step is performed first.



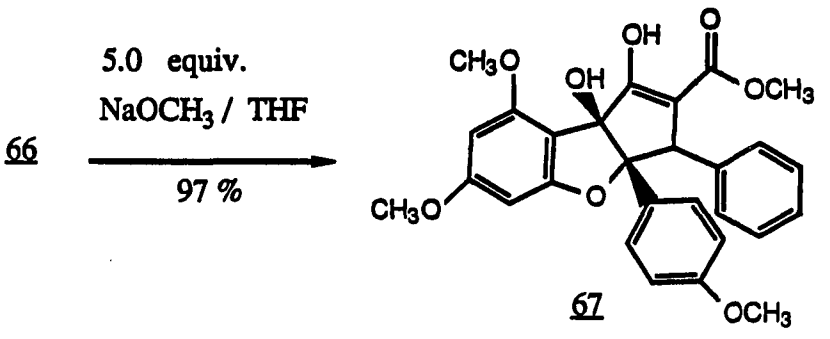
When we tried the usual carbomethoxylating conditions on ketone 65, using either lithium diisopropylamide/methyl

chloroformate or potassium hydride/dimethyl carbonate, no sign of any keto ester was observed. This is possibly due to the very congested environment of the cyclopentanone ring of 65.

We were gratified to obtain the α-oxo ketene thioacetal 66 upon treatment of the anion of 65 with carbon disulfide/methyl iodide.

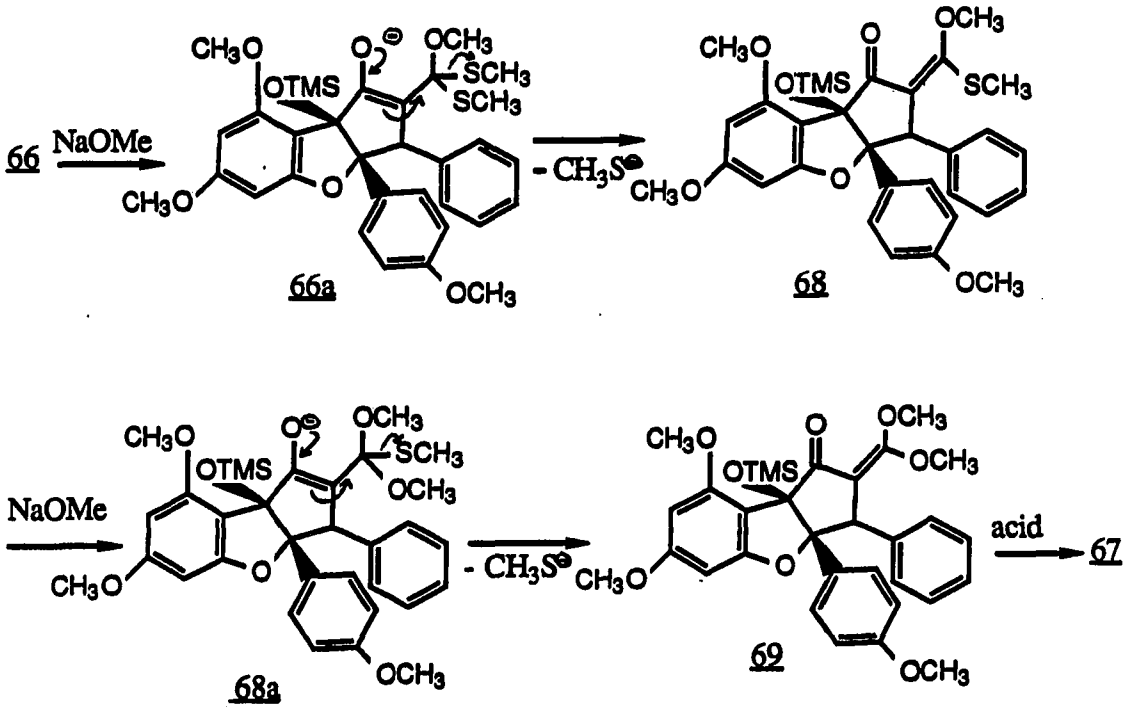


The next key step involves the conversion of compound 66 into keto ester 67. We were pleased to discover that sodium methoxide efficiently effected the transformation.



We believe that the reaction proceeds via the mechanism depicted in Scheme V.

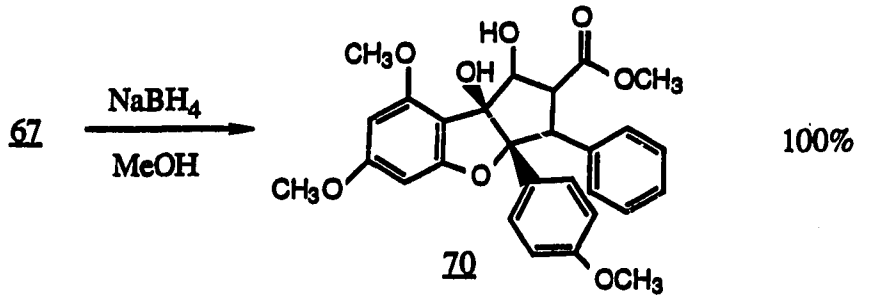
Scheme V



The methoxide anion displaces a thiomethyl anion via an addition-elimination sequence on the enone system of 66 to give compound 68. Repetition of the sequence gives 69, which yields the keto ester 67 upon acid work-up.

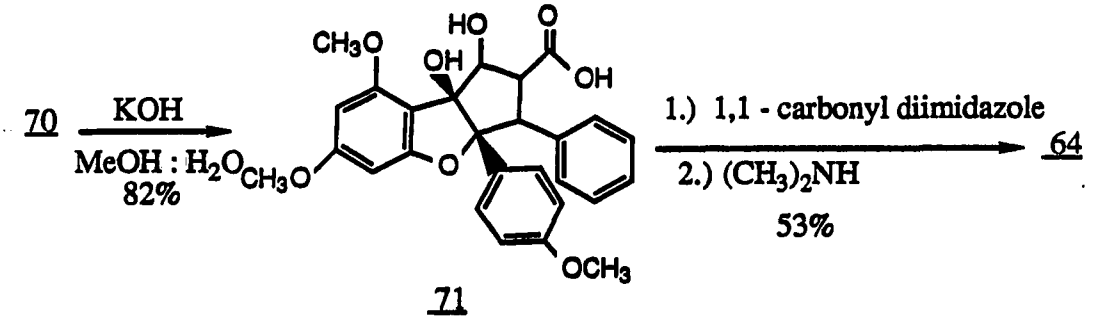
The keto group of 67 was reduced with sodium borohydride to give the alcohol 70. Hydride delivery is expected to occur from the convex face of the molecule.

With intermediate 70 in hand, we anticipated that the amination of ester 70 would proceed easily. However, treatment of 70 with excess dimethylamine in boiling tetrahydrofuran for two days gave only recovered starting



material. This probably attests to the steric congestion of the molecule. The amination conditions of Weinreb et al.[32] gave only a low yield of the amide.

We had to resort to a two-step sequence to accomplish the amide formation. Hydrolysis of the ester 70 with potassium hydroxide in methanol/water gave acid 71. Treatment of 71 with 1,1-carbonyl diimidazole, followed by dimethylamine, gave the amide 64. It was not rocaglamide!



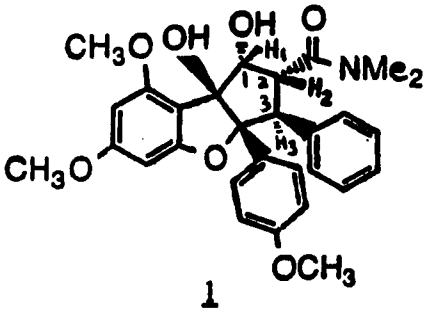
Compound 64 is the same intermediate we synthesized previously using our first approach and is an isomer of rocaglamide.

Table 2. Partial comparison of NMR data between rocaglamide and amide 64

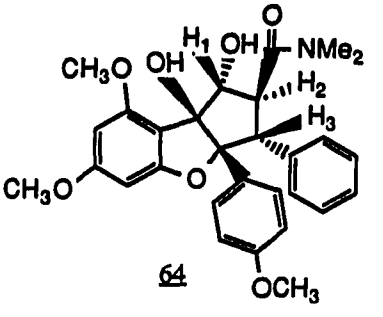
	Rocaglamide[1]	Amide 64[1]
Proton H-1[2] coupling constant	5.01 J = 6.8 Hz	4.82 J = 10 Hz
Proton H-2[2] coupling constant	3.88 J = 6.8 and 14 Hz	3.57 J = 10 and 12 Hz
Proton H-3[2] coupling constant	4.32 J = 14 Hz	4.25 J = 12 Hz
Amide methyl groups		
CH_3^a	3.31	2.99
CH_3^b	2.94	2.89

[1]Chemical shift is reported in ppm.

[2]For proton assignment, please refer to structure below.



1



64

[3]Based on the coupling constants of H-1(10 Hz), H-2 (10 and 12 Hz) and H-3 (12 Hz), we believe that the rocaglamide isomer we synthesized has the relative stereochemistry shown below. The all axial arrangement of the three protons would explain the large coupling constants observed.

Table 3. Comparison of C-13 NMR data between rocaglamide and amide 64

Rocaglamide	Amide 64
169	171.5
163.5	163.5
161	161.8
158	159.1
157.5	157.9
138.3	135.7
129	129.3
128	129.2
128	128.2
126.5	127.1
112.8	113.4
108	105.7
101.5	99.9
93.8	92.3
92.8	91.7
89	88.6
	84.6
78.5	77.3
56	
56	55.7
55.5	55.2
55	54.7
47	47.3
36.9	37.5
35.7	36.0

EXPERIMENTAL

General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl prior to usage. Methylene chloride was distilled from phosphorous pentoxide. Benzene was distilled from lithium aluminum hydride. Acetonitrile was distilled from calcium hydride. All reactions were conducted under an argon atmosphere, and all extracts were dried over anhydrous sodium sulfate. Apparatus for experiments requiring anhydrous conditions were flame-dried under a stream of argon or were dried in an oven at 150°C for 12 hours. Flash chromatography was performed on Kieselgel 60, mesh 230-400. Column chromatography was performed on Grace silica gel, grade 62, mesh 60-200. Melting points were determined on a Fischer-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 1320 Infrared Spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian EM-360 spectrometer. High field (300 MHz) proton spectra were obtained using a Nicolet Magnetics Corporation NMC-1280 spectrometer. Sonication experiments were conducted on a Branson ultrasonic cleaner. All chemical shifts are reported in δ relative to tetramethylsilane as an

internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet) and m (multiplet); addition of br indicates a broadened pattern. Carbon-13 NMR spectra were determined on a Nicolet NMC-1280 spectrometer and are reported in ppm relative to the central peak of $CDCl_3$ (77.06 ppm). High resolution mass spectra were recorded on an AEI-MS 902 high resolution mass spectrometer. Low resolution mass spectra were recorded on a Finnegan 4023 mass spectrometer. Elemental analyses were determined by Galbraith Laboratories, Inc.

4,6-Dihydroxy-4'-methoxy-2-phenyl-3-benzofuranone (18)

This compound was made via a modification of a published procedure by Katamna.[22] To a clear solution of phloroglucinol (46.0 g, 370 mmol) in ether (800 mL) at 0°C was added an ethereal solution of alpha-chloro p-methoxyphenylacetonitrile (60.0 g, 330 mmol) dropwise. After five minutes, gaseous HCl was allowed to bubble through. A precipitate began to appear after one hour. Bubbling was continued for another 2 1/2 hours. The suspension was stirred at room temperature for three days, after which the mother liquor was decanted and separated from the chalky white precipitate. This residue was triturated twice with ether and air-dried. The solid was suspended in one liter of water and boiled for three hours. The solid completely went into solution after an hour of boiling. Upon cooling

the aqueous solution, a light-yellow fluffy precipitate appeared. The precipitate was collected via a Buchner funnel, air-dried and finally vacuum-dried. This process yielded 80.03 g (88% yield) of compound 18. NMR ($CDCl_3$) δ 7.60-6.90 (q, 4 H), 6.25 (d, 1 H), 6.15 (d, 1 H), 5.60 (s, 1 H), 3.90 (s, 3 H). IR (Nujol) 3344, 3040, 1681, 1450, 1150 cm^{-1}. MS (m/e) 272 (M^+), 257, 229, 213, 136.

4,6-Dimethoxy-4'-methoxy-2-phenyl-3-benzofuranone (20)

To a solution of compound 18 (30.0 g, 110 mmol) in acetone (250 mL) was added solid potassium carbonate (34.2 g, 247 mmol) and dimethyl sulfate (20.7 mL, 220 mmol) in one portion. After stirring for two hours at reflux, the suspension was cooled and the acetone layer was separated from the excess solid potassium carbonate by filtration. The filter cake was washed thoroughly with ether (2 x 150 mL). The combined filtrate was treated successively with dilute hydrochloric acid, water and finally saturated sodium chloride. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was triturated with 5:1 hexanes:ether mixture and recrystallized in chloroform to give 28.35 g (86% yield) of compound 20. It is a light beige solid and melts at 127°C. NMR ($CDCl_3$) δ 7.30 (d, 2 H), 6.90 (d, 2 H), 6.20 (d, 1 H), 6.00 (d, 1 H), 5.40 (s, 1 H), 3.93 (s, 3 H), 3.90 (s, 3 H), 3.78 (s, 3 H).

IR ($CDCl_3$) 2940, 2830, 1690, 1610, 1590, 1508, 1460, 1250, 1210, 1150, 1100 cm^{-1}. High-resolution mass spectrum for $C_{17}H_{16}O_3$ requires 300.09978; measured 300.09992. MS (m/e) 300 (M^+), 282, 272, 257, 241, 192, 163, I35, 106.

4,6-Dimethoxy-4'-methoxy-2-phenyl-2-(3-propionitrile) 3-benzofuranone (22)

To a solution of compound 20 (9.00 g, 30.0 mmol) in t-butanol (10 mL) under argon atmosphere was added trimethylbenzyl ammonium hydroxide (3.2 mL, 90 mmol), followed immediately by the slow addition of acrylonitrile (28.3 mL, 430 mmol). After stirring for four hours, the reddish solution was neutralized with dilute hydrochloric solution and poured into a separatory funnel containing water (50 mL). The combined organic layer obtained after extracting the aqueous layer with ether was washed with saturated sodium chloride. It was then dried, concentrated in vacuo and the crude product was purified via flash column chromatography using 2:1 hexanes:ethyl acetate as eluent to obtain compound 22 (9.70 g, 91%) as a foam. NMR ($CDCl_3$) δ 7.48 (d, 2 H), 6.85 (d, 2 H), 6.25 (d, 1 H), 6.0 (d, 1 H), 3.89 (s, 3 H), 3.85 (s, 3 H), 3.75 (s, 3 H), 2.55-2.28 (m, 4 H). IR (film) 2940, 2830, 2240, 1690, 1610, 1585, 1500, 1460, 1420, 1250, 1210, 1150, 1050, 900 cm^{-1}. High-resolution mass spectrum for $C_{20}H_{19}NO_5$ requires 353.12633; measured 353.12642. C-13 NMR ($CDCl_3$) δ 194.40, 173.76,

170.17, 159.56, 159.30, 127.73, 125.82, 118.57, 113.91, 102.81, 93.30, 90.29, 88.85, 55.86, 55.81, 55.03, 33.56, 11.90.

Tricyclic alpha-hydroxy ketone 23

A solution of 1,2-diiodoethane (3.20 g, 11.4 mmol) in dry THF (10 mL) was added over 10 minutes to a round-bottom flask containing flame-dried samarium metal (3.04 g, 20.3 mmol) under argon atmosphere. An immediate formation of a dark-blue color was observed. The solution was stirred at room temperature for one hour and subjected to sonication for three hours to insure complete formation of samarium diiodide. A solution of compound 22 (3.82 g, 10.8 mmol) in benzene (100 mL) was introduced rapidly. The resulting blue solution was subjected to ultrasonication for one day. This solution was quenched with dilute hydrochloric acid and extracted twice with ether. The combined organic layer was washed with water and saturated sodium chloride. The organic layer was then dried and concentrated in vacuo. The crude product was purified by flash column chromatography using 2:1 hexanes:ethyl acetate as eluent to yield compound 23 (1.90 g, 49%) as a colorless oil. NMR ($CDCl_3$) δ 7.30 (d, 2 H), 6.90 (d, 2 H), 6.20 (d, 1 H), 6.00 (d, 1 H), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.76 (s, 3 H), 3.30 (s, br, 1 H), 2.90-2.43 (m, 4 H). IR ($CDCl_3$) 3490, 2960, 2840, 1750, 1615, 1600, 1460, 1420, 1245, 1210, 1150, 1040

cm^{-1}. High resolution mass spectrum for $C_{20}H_{20}O_6$ requires 356.12599; measured 356.12545. C-13 NMR ($CDCl_3$) δ 211.14, 164.19, 161.92, 159.17, 158.08, 129.73, 127.17, 118.90, 105.53, 96.86, 92.19, 88.71, 86.51, 55.46, 55.32, 55.03, 33.97, 33.81.

The above reaction also gave a minor product, 33, identified as the uncyclized alcohol (0.35 g, 9%). NMR ($CDCl_3$) δ 7.20 (d, 2 H), 6.80 (d, 2 H), 5.98 (d, 1 H), 5.71 (d, 1 H), 5.0 (d, 1 H), 3.87 (s, 3 H), 3.81 (s, 3 H), 3.76 (s, 3 H), 2.50-2.03 (m, 4 H). IR (film) 3350, 3000, 2925, 2820, 2238, 1615, 1580, 1500, 1450, 1400, 1240, 1200, 1105, 1030, 815, 750 cm^{-1}. High-resolution mass spectrum for $C_{20}H_{21}NO_5$ requires 355.14198; measured 355.14157.

Tricyclic α-trimethylsiloxy ketone (28)

To a solution of ketone 23 (0.28 g, 0.79 mmol) in dry benzene (10 mL) at 5°C under an argon atmosphere was added diisopropylethylamine (0.35 mL, 1.97 mmol), followed by the dropwise addition of trimethylsilyl trifluoromethanesulfonate (0.25 mL, 1.30 mmol). The solution was stirred at 5°C for six hours and then allowed to warm to room temperature over a six hour period. The solution was diluted with hexanes (60 mL) and filtered. The filtrate was concentrated in vacuo to give compound 28 (0.33 g, 98%) as a colorless oil of high purity. NMR ($CDCl_3$) δ 7.23 (d, 2 H), 6.83 (d, 2 H), 6.20 (d, 1 H), 6.00 (d, 1 H), 3.83 (s, 3 H),

3.80 (s, 3 H), 3.74 (s, 3 H), 2.70-2.30 (m, 4 H), -0.40 (s, 9 H). IR ($CDCl_3$) 2950, 2830, 1745, 1608, 1590, 1508, 1460, 1435, 1245, 1150, 1100, 1035 cm^{-1}. High-resolution mass spectrum for $C_{23}H_{28}O_6Si$ requires 428.16558; measured 428.16552. C-13 NMR ($CDCl_3$) δ 209.34, 164.54, 162.50, 159.01, 158.43, 131.19, 127.53, 113.31, 106.11, 97.57, 91.92, 89.27, 88.88, 55.51, 55.23, 55.12, 34.19, 34.12, 0.807.

4,6-Dimethoxy 2-p-anisyl 2-(3-oxopropyl) 3-benzofuranone (30)

Potassium carbonate (1.45 g, 10.5 mmol) was added in one portion to a stirred solution of compound 20 (3.00 g, 10.0 mmol) in benzene (40 mL) under argon atmosphere at room temperature. A catalytic amount of benzyltrimethyl ammonium hydroxide (0.30 mL, 0.67 mmol) was added slowly, followed by the dropwise addition of acrolein (1.12 mL, 16.6 mmol). The mixture was stirred at room temperature for three days. The solid potassium carbonate and potassium bicarbonate was filtered and the filtrate was partitioned between water and ether twice. The organic layer was treated with saturated sodium chloride solution, dried and concentrated in vacuo. The crude product obtained was purified via flash column chromatography using 1.5:1 hexanes:ethyl acetate as eluent to give compound 30 (2.64 g, 74%) as a colorless oil. NMR ($CDCl_3$) δ 9.68 (s, 1 H), 7.51 (d, 2 H), 6.84 (d, 2 H), 6.25

(d, 1 H), 6.02 (d, 1 H), 3.92 (s, 3 H), 3.89 (s, 3 H), 3.77 (s, 3 H), 3.52 (m, 4 H). IR (film) 2920, 2820, 1725, 1692, 1605, 1582, 1458, 1420, 1240, 1210, 1150, 1025 cm^{-1}. High resolution mass spectrum for $C_{20}H_{20}O_6$ requires 356.12599; measured 356.12562.

Benzofuranone 31

To hexane-washed potassium hydride (0.54 g, 4.71 mmol) in THF (20 mL) at 0°C under an argon atmosphere was added a solution of benzofuranone 20 (0.93 g, 3.10 mmol) and 3-iodo 2-iodomethyl 1-propene (3.82 g, 12.4 mmol) dropwise. The reaction mixture was stirred at 0°C for five hours. It was then partitioned twice between diethyl ether and a dilute solution of hydrochloric acid. The combined organic layer was then treated with saturated sodium chloride, dried and concentrated in vacuo. The crude product obtained was purified by flash column chromatography using 3:1 hexanes:ethyl acetate as eluent to yield compound 31 (1.40 g, 94%) as a colorless oil. NMR ($CDCl_3$) δ 7.52 (d, 2 H), 6.83 (d, 2 H), 6.26 (d, 1 H), 5.99 (d, 1 H), 5.25 (s, br, 1 H), 4.98 (s, br, 1 H), 4.96-4.85 (m, 2 H), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.75 (s, 3 H), 3.05 (m, 2 H). IR ($CDCl_3$) 3062, 2945, 2920, 2822, 1680, 1610, 1590, 1455, 1420, 1240, 1100, 1050, 900, 810, 730, 640 cm^{-1}. High-resolution mass spectrum for $C_{21}H_{21}O_5I$ requires 480.04338; measured 480.04297. C-13 NMR ($CDCl_3$) δ 195.51, 174.07, 169.98,

159.43, 159.33, 140.73, 129.26, 126.24, 119.46, 113.65, 103.40, 93.12, 92.01, 88.64, 56.03, 55.90, 55.26, 41.70, 12.04.

Benzofuranone 32

To hexane-washed potassium hydride (0.57 g, 5.0 mmol) in THF at 0°C under an argon atmosphere was added a solution of compound 20 (1.00 g, 3.33 mmol) and 1,1-dicyano 2-phenyl-ethylene (0.53 g, 3.4 mmol) in THF (20 mL) rapidly. The reaction mixture was stirred at 0°C for two hours and allowed to warm to room temperature overnight. It was diluted with ether (50 mL) and washed twice with dilute hydrochloric acid. The organic layer was dried and concentrated in vacuo. The crude product was recrystallized in chloroform to give 1.21 g (80%) of compound 32 as a pale yellow solid. The melting point range is 154°-156°C. NMR ($CDCl_3$) δ 7.51 (m, 2 H), 7.35 (d, 2 H), 7.29 (m, 3 H), 6.70 (d, 2 H), 6.47 (d, 1 H), 6.10 (d, 1 H), 4.25 (m, 2 H), 3.95 (s, 3 H), 3.89 (s, 3 H), 3.67 (s, 3 H). IR (Nujol) 2923, 2825, 2240, 1690, 1615, 1590, 1500, 1460, 1420, 1250, 1150, 1120, 903, 735 cm^{-1}. MS (m/e) 454 (M^+), 361, 300, 285, 271, 192, 164, 154, 127, 121. MS (CI, isobutane) 511 $(M+C_4H_9)^+$, 495 $(M+C_3H_5)^+$, 455 $(MH)^+$, 301, 155.

General procedure for samarium diiodide-induced cyclization

This intramolecular cyclization was conducted using a modification of the procedure reported by Molander et al.[20] and Molander and Etter.[21]

To flame-dried samarium metal powder (1.81 g, 12.0 mmol) at room temperature under an argon atmosphere was added a solution of diiodo ethane (1.89 g, 6.72 mmol) in THF (7 mL) slowly over seven minutes. The mixture was stirred for one hour until the very dark blue color of samarium diiodide persists. It was subjected to ultrasonication for three hours to insure complete formation of samarium diiodide. Benzene (30 mL) was added rapidly and ultrasonication of the reaction mixture was continued for another two hours. A solution of the substrate (3.33 mmol) in benzene (40 mL) was added rapidly. Sonication was maintained for one day. The reaction mixture was diluted with ethyl acetate (50 mL) and washed twice with dilute hydrochloric acid, once with water and finally with a saturated sodium chloride. The organic layer was dried and concentrated in vacuo. The crude product obtained was purified via flash chromatography using 2:1 hexanes:ethyl acetate as eluent.

Tricyclic alcohol 38

Following the general procedure for cyclization, the benzofuranone iodoolefin 31 (0.105 g, 0.22 mmol) was reacted with in situ generated samarium diiodide (2.7 equiv.) to

yield the desired product 38 (0.078 g, 70%). NMR ($CDCl_3$) δ 7.43 (d, 2 H), 6.95 (d, 2 H), 6.15 (d, 1 H), 6.05 (d, 1 H), 4.90 (m, br, 2 H), 3.87 (s, 3 H), 3.82 (s, 3 H), 3.77 (s, 3 H), 3.30 (m, 2 H), 2.90 (m, 2 H). IR (film) 3480, 3062, 2950, 2825, 1612, 1592, 1460, 1435, 1240, 1150, 1030, 830, 730 cm^{-1}. High-resolution mass spectrum for $C_{21}H_{22}O_5$ requires 354.14673; measured 354.14628. C-13 NMR ($CDCl_3$) δ 163.27, 160.86, 159.74, 157.74, 145.87, 131.18, 127.15, 113.66, 109.90, 108.09, 100.01, 92.13, 88.35, 88.26, 55.58, 55.45, 55.30, 47.72, 45.87.

Tricyclic ketoalcohols 37a and 37b

Following the general procedure for cyclization, benzofuranone 19 (1.43 g, 3.33 mmol) was treated with in situ generated samarium diiodide (2.70 equiv.) in THF-benzene (10:100 mL) to yield the diastereomers 37a (0.82 g, 57%) and 37b (0.16 g, 11%) after chromatographic separation.

Spectroscopic data for 37a

NMR ($CDCl_3$) δ 7.30 (d, 2 H), 7.21 (m, 3 H), 7.05 (m, 2 H), 6.85 (d, 2 H), 6.13 (d, 1 H), 5.99 (d, 1 H), 4.02 (dd, 1 H), 3.79 (s, 3 H), 3.75 (s, 3 H), 3.71 (s, 3 H), 3.38 (t, 1 H), 2.70 (dd, 1 H). IR ($CDCl_3$) 3490, 2940, 2840, 1745, 1610, 1595, 1455, 1425, 1300, 1250, 1150, 1090, 1035 cm^{-1}. High-resolution mass spectrum for $C_{26}H_{24}O_6$ requires

432.15730; measured 432.15748. C-13 NMR ($CDCl_3$) δ 209.13, 164.20, 162.21, 159.11, 158.11, 135.82, 129.12, 128.79, 128.13, 127.99, 113.38, 104.93, 98.27, 92.30, 88.48, 86.91, 55.62, 55.50, 55.39, 50.77, 39.30.

Spectroscopic data for 37b

NMR ($CDCl_3$) δ 7.18 (m, 3 H), 7.07 (d, 2 H), 7.03 (m, 2 H), 6.72 (d, 2 H), 6.35 (d, 1 H), 6.11 (d, 1 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 3.78 (m, 1 H), 3.66 (s, 3 H), 3.30 (s, br, 1 H), 3.02 (m, 1 H), 2.97 (m, 1 H). IR ($CDCl_3$) 3510, 2950, 2825, 1740, 1608, 1590, 1460, 1420, 1250, 1145, 1110 cm^{-1}. High-resolution mass spectrum for $C_{26}H_{24}O_6$ requires 432.15730; measured 432.15673. C-13 NMR ($CDCl_3$) 210.31, 164.61, 161.07, 158.68, 158.36, 137.24, 128.09, 127.97, 127.72, 127.64, 113.13, 106.63, 101.17, 96.06, 92.47, 88.68, 55.54, 55.48, 55.07, 48.67, 39.76.

Tricyclic alcohol 39

Following the general procedure for cyclization, aldehyde 30 (0.207 g, 0.58 mmol) was reacted with in situ generated samarium diiodide (2.70 equiv.) to give the cyclized product 39 (0.102, 49%). NMR ($CDCl_3$) δ 7.40 (d, 2 H), 6.88 (d, 2 H), 6.15 (d, 1 H), 6.01 (d, 1 H), 4.46 (d, 1 H), 3.88 (s, 6 H), 3.83 (s, 3 H), 3.10 (s, br, 1 H), 2.78 (m, 1 H), 2.40 (s, 1 H), 2.37 (dd, 1 H), 2.20 (s, 1 H), 2.0 (dd, 1 H). IR ($CDCl_3$) 3400 (br), 2930, 2835, 1608, 1597,

1510, 1463, 1440, 1250, 1200, 1150, 1030, 910 cm^{-1}. High resolution mass spectrum for $C_{20}H_{22}O_6$ requires 358.14164; measured 358.14099.

Tricyclic amino nitrile 40

Following the general procedure for cyclization, the dinitrile 32 (0.50 g, 1.10 mmol) was reacted with in situ generated samarium diiodide (2.70 equiv.) to give the cyclized amino nitrile 40 (0.10 g, 20%). NMR ($CDCl_3$) δ 7.40 (d, 2 H), 7.18 (m, 3 H), 6.77 (d, 2 H), 6.73 (m, 2 H), 6.10 (d, 1 H), 5.75 (d, 1 H), 5.35 (s, br, 2 H), 4.65 (s, 1 H), 3.87 (s, 3 H), 3.83 (s, 3 H), 3.75 (s, 1 H), 3.67 (s, 3 H). IR (film) 3580, 3480, 3377, 2900, 2834, 2238, 1620, 1590, 1455, 1250, 1200, 1140, 1100, 1035, 910, 750 cm^{-1}. MS (m/e) 456 (M^+), 438, 368, 299, 181, 135.

Tricyclic keto disulfide 48

n-Butyllithium (4.96 mL, 12.1 mmol) was added dropwise to a solution of diisopropylamine (1.80 mL, 12.8 mmol) in dry tetrahydrofuran (30 mL) at -40°C under an argon atmosphere. The resulting solution of lithium diisopropylamide was stirred for 15 minutes, then the tricyclic ketone 28 (1.20 g, 2.80 mmol) in THF (10 mL) was added dropwise. The yellow solution was stirred for 75 minutes, after which neat carbon disulfide (4.56 mL, 75.9 mmol) was added rapidly. The reaction mixture was stirred for five hours

and iodomethane (4.73 mL, 75.9 mmol) was added. The resulting solution was stirred while warming from -40°C to room temperature overnight. It was diluted with hexanes (200 mL) and filtered. The filtrate was concentrated in vacuo. The crude product was purified via flash column chromatography using 2:1 hexanes:ethyl acetate as eluent to give a bright yellow solid (0.92 g, 62%). Compound 48 has a melting point range of 69.5°C-72°C. NMR ($CDCl_3$) δ 7.22 (d, 2 H), 6.84 (d, 2 H), 6.21 (d, 1 H), 6.00 (d, 1 H), 3.86 (s, 3 H), 3.83 (s, 3 H), 3.73 (s, 3 H), 3.60 (d, 1 H), 2.93 (d, 1 H), 2.50 (s, 3 H), 2.45 (s, 3 H), -0.35 (9 H). IR ($CDCl_3$) 2920, 2825, 1685, 1607, 1587, 1503, 1460, 1430, 1242, 1215, 1170, 1120, 1100, 1035 cm^{-1}. High resolution mass spectrum for $C_{26}H_{32}O_6SiS_2$ requires 532.14097; measured 532.14063. C-13 NMR ($CDCl_3$) δ 193.03, 164.42, 161.83, 159.17, 158.63, 151.90, 131.22, 130.44, 127.41, 113.33, 107.27, 95.90, 92.26, 91.57, 89.29, 55.65, 55.38, 55.00, 44.96, 19.02, 17.53, 1.29. Elemental analysis calculated for $C_{26}H_{32}O_6SiS_2$: C, 58.62; H, 6.06. Found: C, 59.04; H, 6.53.

Tricyclic keto disulfide 48a

Treatment of compound 48 (0.10 g, 0.19 mmol) with tetra-n-butyl ammonium fluoride (2.2 equiv.) gave the deprotected keto disulfide 48a (0.08 g, 93%) as a bright yellow solid which melts at 179°C. NMR ($CDCl_3$) δ 7.26 (d, 2

H), 6.85 (d, 2 H), 6.19 (d, 1 H), 6.01 (d, 1 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 3.72 (s, 3 H), 3.61 (d, 1 H), 3.38 (s, 1 H), 3.00 (d, 1 H), 2.48 (s, 3 H), 2.46 (s, 3 H). IR ($CDCl_3$) 3480, 2920, 2825, 1672, 1603, 1590, 1502, 1460, 1430, 1245, 1211, 1195, 1145, 1050, 1032, 905, 780 cm^{-1}. High resolution mass spectrum for $C_{23}H_{24}O_6S_2$ requires 460.10144; measured 460.10127. Elemental analysis calculated for $C_{23}H_{24}O_6S_2$: C, 59.98; H, 5.25. Found: C, 59.83; H, 5.18. C-13 NMR ($CDCl_3$) δ 194.15, 164.22, 161.56, 159.25, 148.23, 154.88, 129.79, 128.34, 126.91, 113.62, 106.83, 94,75, 92.54, 89.22, 89.16, 55.65, 55.42, 55.20, 45.25, 19.41, 17.44.

Tricyclic enone 57

To a solution of keto disulfide 48 (0.40 g, 0.75 mmol) in acetonitrile:water (45:1 mL) was added 2,3-dicyano-5,6-dichlorobenzoquinone (0.30 g, 1.28 mmol) in one portion. The resulting dark red solution was boiled for two days. It was then concentrated in vacuo. The crude product was purified via flash column chromatography using 2.5:1 hexanes:ethyl acetate as eluent, giving compound 57 (0.18 g, 56%). This compound is a yellow powdery solid and melts at 68°-70°C. NMR ($CDCl_3$) δ 7.92 (s, 1 H), 7.27 (d, 2 H), 6.95 (d, 2 H), 6.18 (d, 1 H), 6.03 (d, 1 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 3.77 (s, 3 H), 2.42 (s, 3 H). IR ($CDCl_3$) 3435, 2920, 2830, 1730, 1715, 1615, 1590, 1500, 1460, 1435, 1300,

1250, 1105, 1030 cm^{-1}. High resolution mass spectrum for $C_{22}H_{20}O_7$ requires 428.09298; measured 428.09272. C-13 NMR ($CDCl_3$) δ 196.06, 185.64, 164.41, 160.56, 160.05, 158.40, 156.86, 140.54, 127.74, 125.07, 113.93, 105.21, 94.60, 92.82, 88.63, 86.59, 55.57, 55.19, 54.74, 11.38.

Tricyclic thioester 62

To a suspension of $CuBr \cdot Me_2S$ (0.066 g, 0.32 mmol) in diethyl ether (5 mL) under argon at 0°C was added phenyl magnesium bromide solution (0.32 mL, 0.64 mmol). The yellow suspension was stirred at 0°C for 25 minutes and then cooled to -78°C. A solution of compound 57 (0.11 g, 0.26 mmol) in ether (5 mL) was added dropwise. The reaction mixture was stirred at -78°C for one hour and then slowly warmed up to room temperature over a three hour period. It was quenched with dilute HCl (2 mL), poured into saturated ammonium chloride and extracted twice with ether (2 x 25 mL). The combined organic layer was washed with water, followed by saturated sodium chloride, dried and concentrated in vacuo. Recrystallization from 10:1 hexanes:ether mixture gave a tan powder (0.12 g, 90%) which melted at 92°-94°C. The compound exists as an 80:20 mixture of enol ester:keto ester forms. NMR ($CDCl_3$) δ 10.60 (s, br, 1 H), 7.43 (d, 2 H), 7.22 (m, 3 H), 7.06 (m, 2 H), 6.87 (d, 2 H), 6.01 (d, 1 H), 5.60 (d, 1 H), 4.78 (s, 1 H), 3.84 (s, 3 H), 3.79 (s, 3 H), 3.64 (s, 3 H), 2.25 (s, 3 H). IR ($CDCl_3$) 3400 (enol), 2922, 2830, 1750

(keto), 1670, 1617, 1595, 1505, 1495, 1460, 1250, 1215, 1150, 905 cm^{-1}. High-resolution mass spectrum for $C_{28}H_{24}O_6S$ (M^+-H_2O) requires 488.12936; measured 488.12869. MS (CI, isobutane) m/e 507 (MH^+), 489, 433, 415, 339, 311, 300, 223, 209.

Tricyclic keto amide 63

To a solution of thio ester 62 (0.12 g, 0.24 mmol) in tetrahydrofuran (3 mL) was added excess dimethylamine (1.2 mL), the solution was heated in a culture tube at 75°C for two days. The reaction mixture was concentrated in vacuo and the residue recrystallized in 5:1 hexanes:ethyl ether to give a light yellow-orange powder (0.11 g, 92%). The compound exists entirely as a keto amide (no enol amide is detected). NMR ($CDCl_3$) δ 7.35 (d, 2 H), 7.20 (m, 3 H), 7.07 (m, 2 H), 6.86 (d, 2 H), 6.16 (d, 1 H), 6.03 (d, 1 H), 4.74 (d, 1 H), 4.53 (d, 1 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 2.95 (s, 3 H), 2.86 (s, 3 H). IR ($CDCl_3$) 3350, 2920, 2830, 1743, 1635, 1610, 1590, 1505, 1460, 1250, 1215, 1145, 1030 cm^{-1}. High-resolution mass spectrum for $C_{29}H_{27}NO_6$ (M^+-H_2O) requires 485.18384; measured 485.18348. Mass spectrum (chemical ionization, isobutane) m/e 504 (MH^+), 486, 455, 311, 300, 223, 177. C-13 NMR ($CDCl_3$) δ 204.84, 166.37, 164.56, 162.08, 159.26, 158.14, 135.24, 128.89, 128.23, 128.03, 127.36, 113.37, 104.86, 97.51,

96.17, 92.59, 88.59, 87.08, 55.71, 55.19, 55.24, 54.08, 37.19, 35.99.

Tricyclic hydroxy amide 64

Sodium borohydride (0.031 g, 0.81 mmol) was suspended in methanol (3 mL) under argon at 0°C. A solution of keto amide 63 (0.0465 g, 0.092 mmol) in methanol (2 mL) was added dropwise. The resulting solution was stirred at 0°C for 10 hours and then slowly allowed to warm to room temperature over two hours. The reaction mixture was quenched with dilute HCl (2 mL) and poured into brine. The mixture was extracted twice with ether. The combined organic layer was dried and concentrated in vacuo. Recrystallization in 5:1 hexanes:ethyl ether gave a white crystalline powder (0.0436 g, 93%), melting point 108°C. NMR ($CDCl_3$) δ 7.37 (d, 2 H), 7.14 (m, 3 H), 7.03 (m, 2 H), 6.87 (d, 2 H), 6.19 (d, 1 H), 6.09 (d, 1 H), 4.80 (d, 1 H, J = 10 Hz), 4.23 (d, 1 H, J = 12 Hz), 3.81 (s, 6 H), 3.77 (s, 3 H), 3.56 (dd, 1 H, J = 10 and 12 Hz), 2.99 (s, 3 H), 2.84 (s, 3 H). IR ($CDCl_3$) 3560, 3490, 2930, 2830, 1632, 1605, 1503, 1490, 1450, 1435, 1250, 1197, 1143, 1120, 1030, 910, 730 cm^{-1}. High-resolution mass spectrum for $C_{29}H_{31}NO_7$ requires 505.21006; measured 505.20930. C-13 NMR ($CDCl_3$) δ 171.49, 163.61, 161.85, 159.08, 157.88, 135.78, 129.31, 129.23, 128.25, 127.12, 113.36, 105.70, 99.87, 92.30, 91.65, 88.57, 84.64, 77.32, 55.67, 55.19, 54.74, 47.27, 37.53, 36.03.

Benzofuranone 19

Compound 20 (7.30 g, 24.3 mmol) was suspended in t-butanol (150 mL) and maintained under an argon atmosphere. The suspension was heated at 60°C until most of the solid material went into solution. Benzyl trimethylammonium hydroxide (1.10 mL, 2.43 mmol) was added to the solution, followed by the slow addition of cinnamonitrile (3.29 mL, 24.94 mmol). The reaction mixture was heated at 60°C for two days. It was cooled and the copious chalky precipitate was separated from the t-butanol solution via filtration. The collected precipitate was triturated twice with ether. The filtrate was partitioned twice in ether and once in dilute HCl solution. The combined organic layer was treated with brine and concentrated in vacuo. The residue left after concentrating in vacuo was combined with the initial copious precipitate and carried on to the next reaction without further purification or separation of diastereomers. The spectroscopic data of the major isomer is reported. NMR ($CDCl_3$) δ 7.38 (d, 2 H), 7.45-7.15 (m, 5 H), 6.72 (d, 2 H), 6.33 (d, 1 H), 6.02 (d, 1 H), 3.89 (s, 3 H), 3.85 (s, 3 H), 3.82-3.78 (m, 1 H), 3.75 (s, 3 H), 2.92-2.84 (m, 1 H), 2.70-2.64 (m, 1 H). IR (Nujol) 2925, 2840, 2240, 1687, 1612, 1580, 1455, 1425, 1320, 1235, 1115, 1020 cm^{-1}. High-resolution mass spectrum for $C_{26}H_{23}O_5N$ requires 429.15763; measured 429.15694.

Tricyclic ketone 65

To a solution of compound 37a (0.85 g, 1.96 mmol) in dry benzene (30 mL) at 5°C under an argon atmosphere was added diisopropylethylamine (0.88 mL, 4.92 mmol) dropwise, followed by the slow addition of TMSOTf (0.63 mL, 3.25 mmol). The reaction mixture was stirred at 5°C for six hours and then slowly allowed to warm to room temperature. It was diluted with hexanes (140 mL) and filtered. The filtrate was concentrated in vacuo to give compound 65 (0.84 g, 85%) in high purity. NMR ($CDCl_3$) δ 7.25 (d, 2 H), 7.19 (m, 2 H), 6.92 (m, 2 H), 6.86 (d, 2 H), 6.04 (d, 1 H), 5.99 (d, 1 H), 3.97 (dd, 1 H), 3.81 (s, 3 H), 3.77 (s, 3 H), 3.74 (s, 3 H), 3.18 (t, 1 H), 2.55 (dd, 1 H), -0.35 (s, 9 H). IR ($CDCl_3$) 2950, 2830, 1750, 1608, 1590, 1460, 1435, 1248, 1200, 1150, 1110, 1035 cm^{-1}. High-resolution mass spectrum for $C_{29}H_{32}O_6Si$ requires 504.19683; measured 504.19635. C-13 NMR ($CDCl_3$) 207.20, 164.48, 162.82, 158.85, 157.98, 136.20, 131.67, 128.47, 128.41, 128.19, 113.15, 112.96, 105.82, 97.80, 91.75, 89.38, 88.00, 55.54, 55.23, 55.12, 52.53, 39.10, 1.32.

Tricyclic ketodisulfide 66

n-Butyllithium (2.60 mL, 6.35 mmol) was added dropwise to a solution of diisopropylamine (0.94 mL, 6.67 mmol) in dry THF (25 mL) under an argon atmosphere at -40°C. The resulting lithium diisopropylamide was stirred for 15

minutes, then hexamethylphosphoric amide (6.50 mL, 37.4 mmol) was added rapidly. After 30 minutes, a solution of compound 65 (0.80 g, 1.60 mmol) in dry tetrahydrofuran (10 mL) was added dropwise. The orange solution was stirred for 1 1/4 hours, then carbon disulfide (2.87 mL, 47.6 mmol) was added rapidly. The reaction mixture was stirred for five hours, after which methyl iodide (4.0 mL, 63.5 mmol) was introduced rapidly. The reaction mixture was allowed to warm to room temperature overnight. It was diluted with hexanes (120 mL) and washed four times with water and once with brine. The organic layer was dried and concentrated in vacuo. The crude product was purified via flash column chromatography using 2:1 hexanes:ethyl acetate as eluent to yield compound 66 (0.64 g, 67%). NMR ($CDCl_3$) δ 7.34 (d, 2 H), 7.30-6.85 (m, 5 H), 6.85 (d, 2 H), 5.88 (d, 1 H), 5.29 (d, 1 H), 4.76 (s, 1 H), 3.82 (s, 3 H), 3.76 (s, 3 H), 3.55 (s, 3 H), 2.55 (s, 3 H), 2.22 (s, 3 H), -0.35 (s, 9 H). IR (film) 2942, 2812, 1680, 1605, 1590, 1457, 1430, 1240, 1215, 1175, 1092, 1035 cm^{-1}. High-resolution mass spectrum for $C_{32}H_{36}O_6SiS_2$ requires 608.17228; measured 608.17071. C-13 NMR ($CDCl_3$) δ 192.62, 164.20, 162.02, 158.82, 157.64, 159.19, 138.59, 133.19, 132.85, 127.05, 126.83, 113.33, 113.14, 107.26, 96.74, 91.91, 91.82, 90.56, 88.01, 60.18, 55.38, 55.24, 55.14, 19.54, 17.89, 0.77.

Tricyclic keto disulfide 66a

Treatment of compound 66 (0.20, 0.33 mmol) with tetra-n-butylammonium fluoride (2.2 equiv.), gave deprotected keto disulfide 66a (0.17 g, 96%) as a yellow solid which melts at 220°C. NMR ($CDCl_3$) δ 7.37 (d, 2 H), 7.35-6.90 (m, 5 H), 6.92 (d, 2 H), 5.95 (d, 1 H), 5.37 (d, 1 H), 4.91 (d, 1 H), 3.84 (s, 3 H), 3.79 (s, 3 H), 3.58 (s, 3 H), 2.62 (s, 3 H), 2.36 (s, 3 H). IR ($CDCl_3$) 3500, 3000, 2920, 2825, 1715, 1605, 1590, 1490, 1460, 1435, 1250, 1140, 1100, 1055, 1032, 910, 730 cm^{-1}. High-resolution mass spectrum for $C_{29}H_{28}O_6S_2$ requires 536.13274; measured 536.13347. Elemental analysis calculated for $C_{29}H_{28}O_6S_2$: C, 64.91; H, 5.26. Found: C, 64.57; H, 5.26.

Tricyclic keto ester 67

To a solution of tricyclic disulfide 66 (0.12 g, 0.20 mmol) in dry THF (6 mL) at 0°C under an argon atmosphere was added a solution of sodium methoxide (0.054 g, 1.00 mmol) in THF (2 mL). The reaction mixture was stirred for 1 1/2 days. Dilute HCl solution (3 mL) was added and the mixture was stirred for five minutes. It was poured into ether (60 mL) and washed twice with saturated NaCl. The organic layer was dried and concentrated in vacuo. The crude product (0.101 g, 97%) was a light yellow foamy solid of high purity, melting point = 30°C. It exists as an 80:20 enol ester:keto ester mixture. NMR ($CDCl_3$) δ 10.65 (br, s), 7.42

(d, 2 H), 7.09 (m, 3 H), 6.90 (d, 2 H), 6.79 (m, 2 H), 5.98 (d, 1 H), 5.61 (d, 1 H), 4.67 (s, 1 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.62 (s, 3 H), 3.58 (s, 3 H). IR ($CDCl_3$) 3420, 2940, 2825, 1755, 1655, 1608, 1592, 1455, 1420, 1245, 1212, 1142, 1120, 1055, 1030, 910 cm^{-1}. High-resolution mass spectrum for $C_{28}H_{24}O_7$ requires 472.15221; measured 472.15259.

Tricyclic ester 70

To sodium borohydride (0.081 g, 2.14 mmol) in dry methanol (3 mL) at 0°C under argon was added a solution of compound 67 (0.078 g, 0.14 mmol) in methanol (5 mL) dropwise. The reaction mixture was stirred at 0°C for 10 hours. It was concentrated in vacuo. The residue was taken up in ether (25 mL) and treated with dilute HCl solution (2 mL). The organic layer was washed with brine, dried and concentrated. The crude product was recrystallized in ether:hexanes (3:1) to give ester 70 (0.0706 g, 100%) as a light yellow foamy solid which melts at 78°-80°C. NMR ($CDCl_3$) δ 7.33 (d, 2 H), 7.16 (m, 3 H), 6.94 (m, 2 H), 6.87 (d, 2 H), 6.12 (d, 1 H), 6.05 (s, 1 H), 4.77 (d, 1 H, J = 11 Hz), 4.03 (d, 1 H, J = 13 Hz), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.60 (s, 3 H), 3.24 (dd, 1 H, J = 11 and 13 Hz). IR ($CDCl_3$) 3472, 2940, 2825, 1720, 1610, 1590, 1450, 1430, 1270, 1175, 1120, 1025, 910 cm^{-1}. High-resolution mass spectrum for $C_{28}H_{28}O_8$ requires 492.17843; measured

492.17803. C-13 NMR ($CDCl_3$) 172.95, 163.93, 161.89, 159.24, 159.79, 134.84, 128.99, 128.25, 127.82, 127.15, 113.45, 105.03, 99.35, 92.53, 91.23, 88.67, 83.79, 77.25, 55.66, 55.23, 54.70, 52.12, 50.80.

Tricyclic acid 71

To ester 70 (0.17 g, 0.35 mmol) in methanol:water mixture (24:4 mL) was added solid potassium hydroxide. The solution was heated at 44°C for 10 hours. It was then neutralized with dilute HCl solution and poured into brine (50 mL). The aqueous layer was extracted three times with diethyl ether. The combined organic layer was treated with brine, dried and concentrated in vacuo. Recrystallization in chloroform gave acid 71 (0.14 g, 82%) as a white crystalline powder, which melts between 259°-261°C. NMR ($CDCl_3$) δ 7.34 (d, 2 H), 7.19 (m, 3 H), 6.97 (m, 2 H), 6.90 (d, 2 H), 6.14 (d, 1 H), 6.07 (d, 1 H), 4.79 (d, 1 H, J = 11 Hz), 4.00 (d, 1 H, J = 13 Hz), 3.79 (s, 6 H), 3.77 (s, 3 H), 3.24 (dd, 1 H, J = 11 and 13 Hz). IR ($CDCl_3$) 3460, 3550-2650 (br), 2920, 1700, 1620, 1500, 1440, 1250, 1210, 1135, 905, 730 cm^{-1}. High-resolution mass spectrum for $C_{27}H_{26}O_8$ requires 478.16278; measured 478.16274. C-13 NMR ($CDCl_3$) δ 176.34, 163.90, 161.83, 159.17, 157.81, 134.68, 129.01, 128.90, 128.24, 127.90, 113.43, 104.84, 99.25, 92.52, 91.19, 88.56, 83.56, 77.28, 55.69, 55.55, 55.23, 50.45.

Tricyclic amide 64

To a stirred solution of acid 71 (90 mg, 0.19 mmol) in methylene chloride (3 mL) at 0°C under an argon atmosphere was added pyridine (0.076 mL, 0.94 mmol). The solution was stirred for three minutes and 1,1-carbonyl diimidazole (0.16 g, 0.94 mmol) in methylene chloride (2 mL) was added. It was stirred at 0°C for five hours and then allowed to slowly warm to room temperature. The mixture was quenched with dilute HCl solution and poured into brine. The aqueous layer was extracted twice with methylene chloride (20 mL). The combined organic layer was dried and concentrated in vacuo. Recrystallization in ethyl ether:hexanes (1:5) gave a white crystalline powder (50 mg, 53%) whose physical properties are identical to amide 64.

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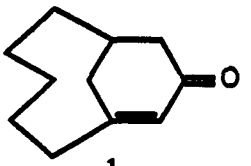
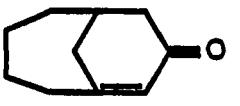
PART II. [4+2] CYCLOADDITION REACTIONS INVOLVING BRIDGEHEAD ENONES

INTRODUCTION

Ever since the extensive studies by House and co-workers[1-6] on the synthesis and reactivity of bridgehead enones in the early 1980s, these highly reactive intermediates are finding increasing uses in the area of natural products synthesis. Some of the reactive compounds that were synthesized by House are shown below.



1



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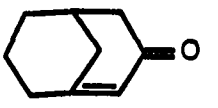
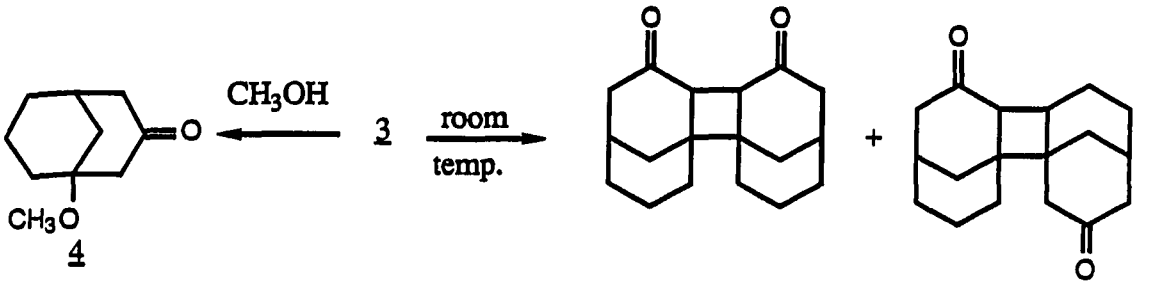


3

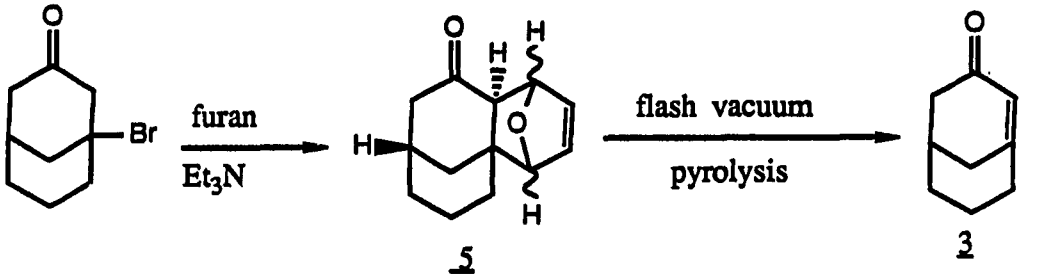
The bicyclic enones 1-3 exhibit significant differences in their behavior. Whereas enones 1 and 2 are isolable and are stable on prolonged heating, enone 3, the most strained system of the above examples, undergoes a rapid thermal [2+2] cycloaddition with itself to form dimers in the absence of any nucleophile or diene. Generation of 3 in the presence of methanol readily affords the methoxy ketone 4.



4

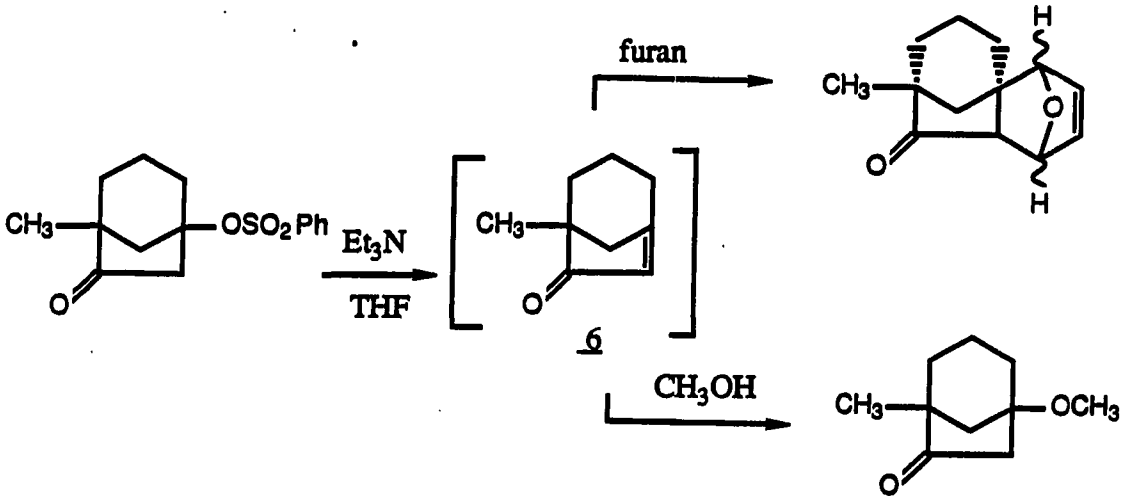
House et al.[4] used force-field calculations via Allinger's molecular mechanics program to predict the

favored conformation of these bridgehead enones. He noted that the calculated steric energies of the [5.3.1] enone 1 can be minimized with a planar enone conformation. However, for the more strained enone 3, the calculated steric energy is smaller when the enone system is distorted from planarity. House reported that the bridgehead alkene is twisted from planarity by approximately 25°. This twist is responsible for the enhancement in the electrophilicity of the enone subunit. Thus, it is not surprising that methanol and amines add readily to enone 3. This enone reacts readily with furan in a [4+2] fashion to form adduct 5. When subjected to flash vacuum pyrolysis, 5 is reported by Campbell et al.[7] to produce a stable solution of enone 3 at -78°C.

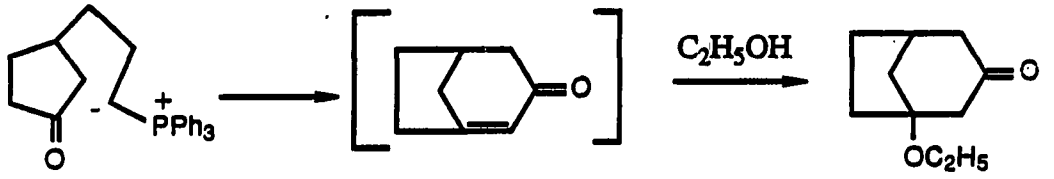


5 3

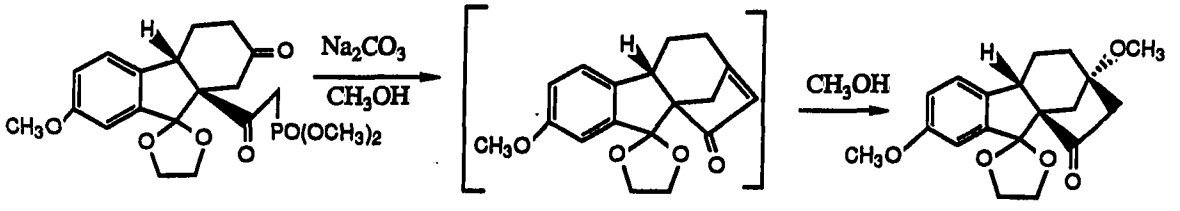
House et al.[3] also reported the synthesis of the highly strained bicyclo [3.2.1] enone 6. Although he was unable to isolate this unstable compound, he proved its fleeting existence by trapping the reactive species with methanol and furan.



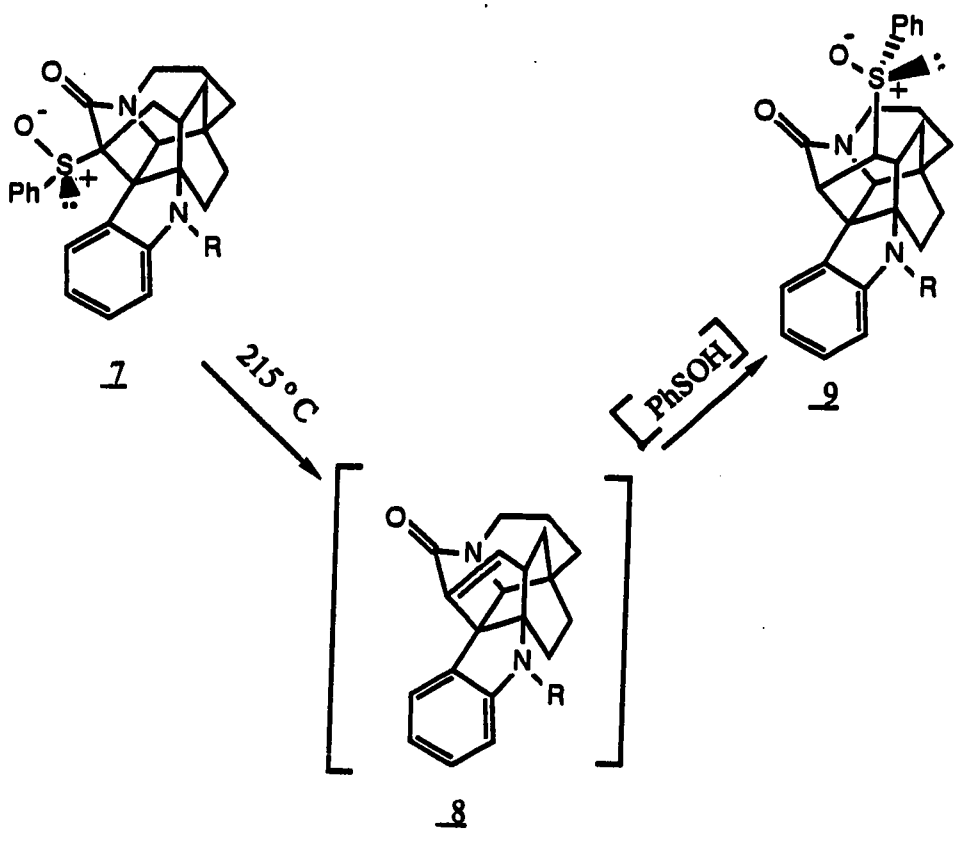
Bestmann and Schade[8] also generated a similar bicyclo [3.2.1] enone via Wittig methodology and trapped this intermediate with ethanol.



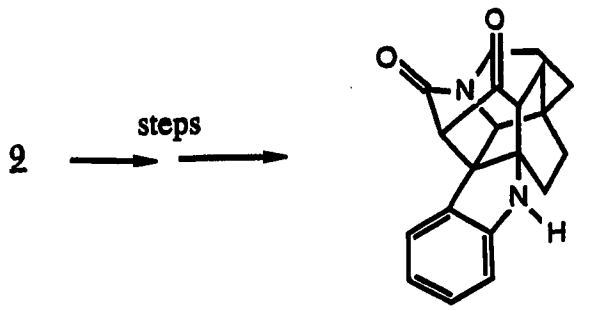
House et al.[3] applied this bridgehead enone methodology to construct a bicyclo [3.2.1] octane unit in a gibberellin skeleton.



Magnus et al.[9] was the first to report the use of a bridgehead enone in the total synthesis of a natural product. They generated the anti-Bredt compound 8 via thermolysis of the keto sulfoxide 7.

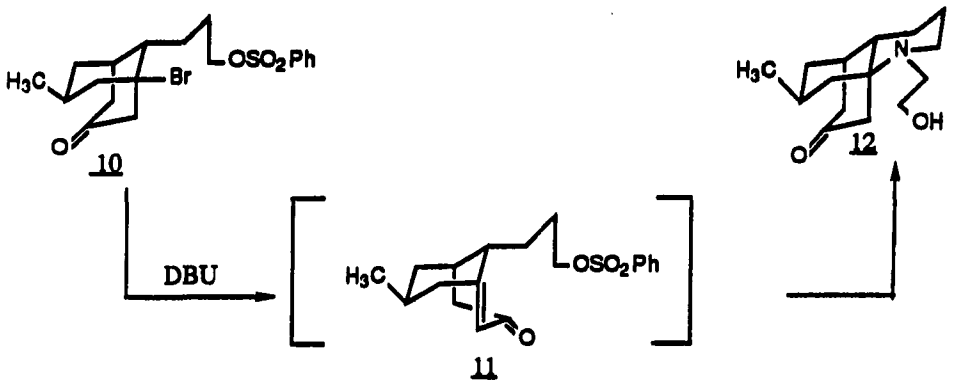


The bridgehead enone 8 was efficiently utilized to effect the 1,2-transposition of the sulfoxide group of 7 via the readdition of the benzenesulfenic acid to the torsionally strained α,β-unsaturated amide 8, to give the key intermediate 9. This compound was then carried on to accomplish an elegant synthesis of (±)-kopsanone.

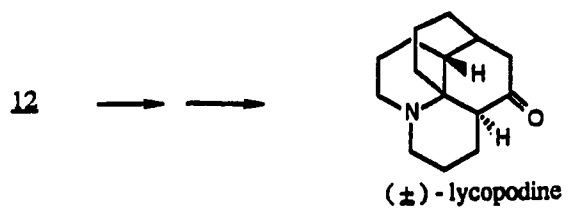


(±)-kopsanone

Kraus and Hon[10,11] also utilized bridgehead enone methodology to achieve a facile synthesis of (±)-lycopodine. Hence, treatment of the keto bromide 10 with base gives the reactive enone 11, which is rapidly trapped with 3-amino-1-propanol to yield the key intermediate 12. Compound 12 is,



in turn, transformed in two steps to (±)-lycopodine.



(±)-lycopodine

RESULTS AND DISCUSSION

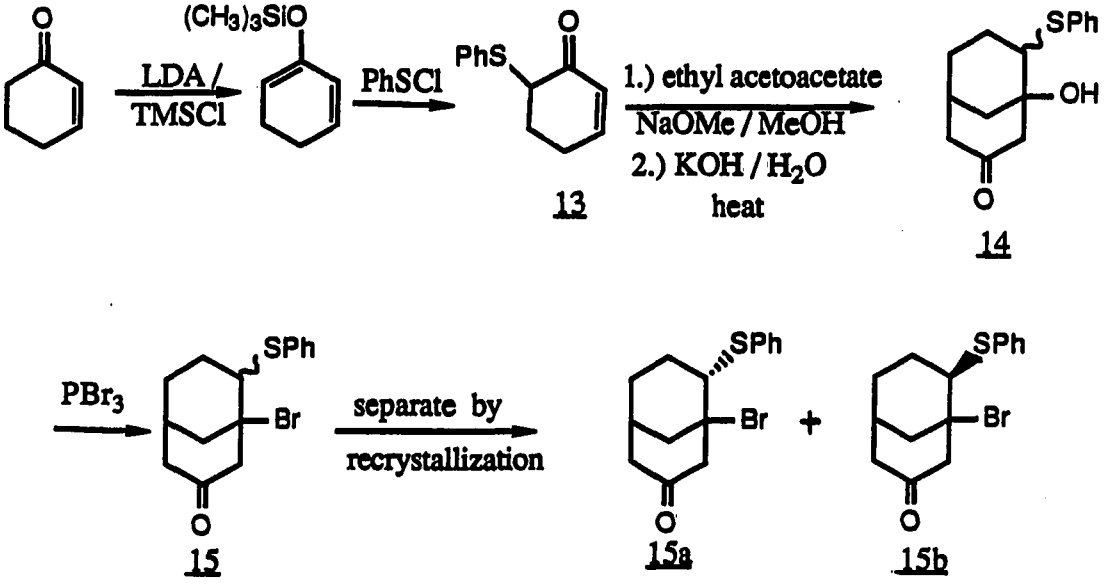
[4+2] Cycloaddition Reactions

Our interest in bridgehead enones stems chiefly from the desire to know about the reactivity of these systems in [4+2] cycloaddition reactions. Although House et al.[5] reported that furan is a good trapping agent for these reactive intermediates, no other dienes were utilized to add to these strained bicyclic systems. We are especially interested in obtaining information about the regio- and stereospecificity of these cycloaddition reactions.

The bridgehead enone precursor was readily prepared according to Scheme I. Thus, the enol silyl ether of 2-cyclohexen-1-one was reacted with benzenesulfenyl chloride to give compound 13.

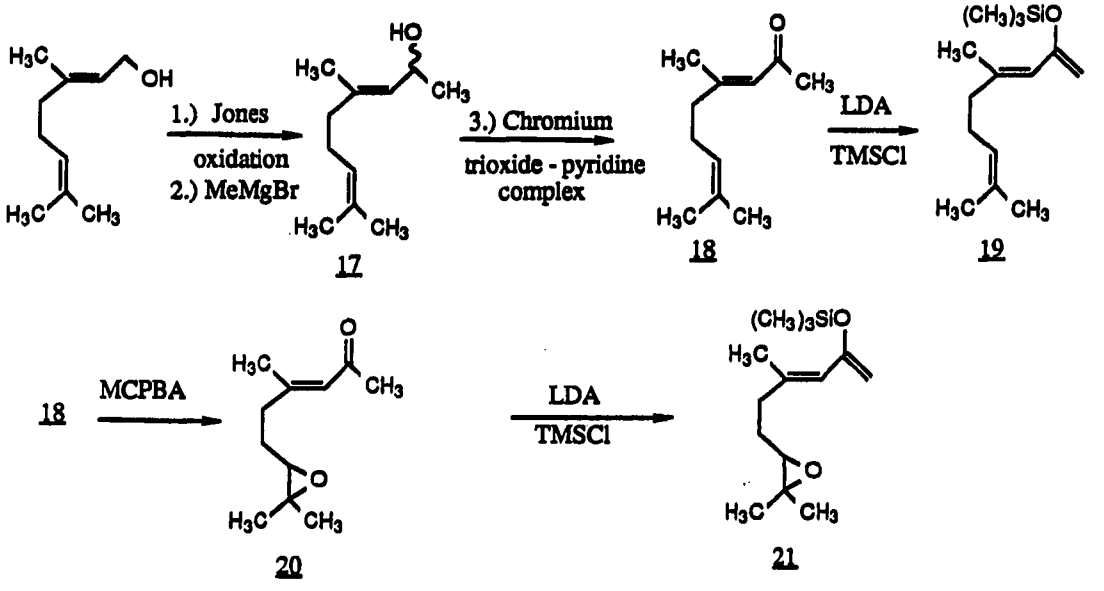
When 13 was treated with ethyl acetoacetate and sodium methoxide in boiling methanol, followed by decarbomethoxylation with potassium hydroxide, a diastereomeric mixture of bridgehead alcohol 14 was obtained. This alcohol was reacted with phosphorous tribromide to give a mixture of beta-bromo ketone 15. Recrystallization allowed the isolation of the diastereomer 15a in white crystalline form. Only this diastereomer was utilized in our cycloaddition studies.

Scheme I



Most of the dienes were prepared by treating the parent ketones with LDA and trimethylchlorosilane. The other dienes were prepared according to Scheme II.

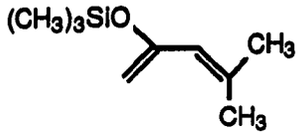
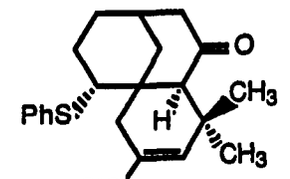
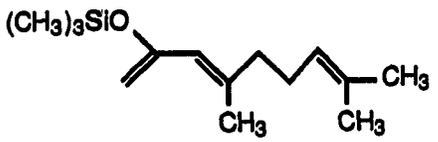
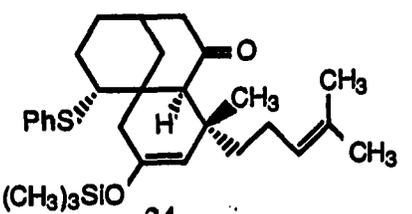
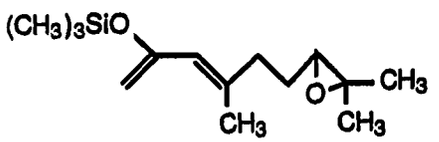
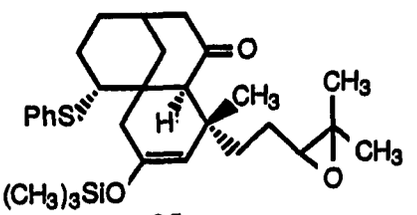
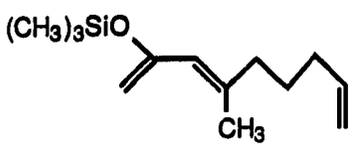
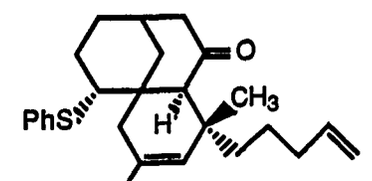
Scheme II



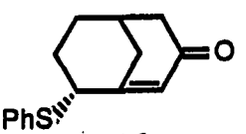
The cycloadditions were performed by generating the bridgehead enone in situ with triethylamine in the presence of excess diene. Typically, between 2- to 4-fold excess of the diene is used. The results of the cycloadditions are summarized in Table 1.

It is somewhat surprising that these 1,1,3-trisubstituted dienes can trap the bridgehead enone 16 in decent yields and with high stereoselectivity. For the assignment of stereochemistry of adduct 24, we had to resort to 2D-NMR techniques using a combination of COSY/NOESY experiments. The result of the NOESY experiment strongly supports the structure wherein the methyl group is trans to the methine proton alpha to the ketone. Specifically, the methyl group attached to the quarternary carbon shows strong interaction through space with protons Hp and Ht (please refer to structure 28 below; for COSY/NOESY results, please refer to the Appendix).

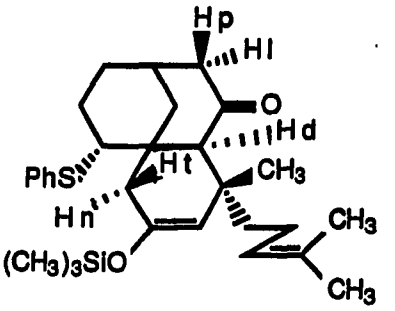
Table 1. Cycloaddition of enone 16 with 1,1,3-trisubstituted enones

Diene	Adduct	Yield
 22	 26	46%
 19	 24	46%
 21	 25	81%
 23	 27	42%

Note :



16



28

This stereochemistry signifies an exo mode of cycloaddition. This overwhelming preference for the exo addition rather than the endo mode is unusual. The general preference for the endo mode of addition in most intermolecular Diels-Alder reactions stems from the stabilization of the endo mode by secondary orbital overlap. As the figure depicted below indicates, such overlap would be difficult, if not impossible.

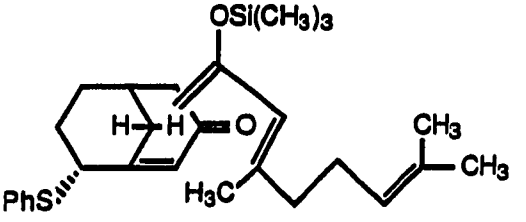
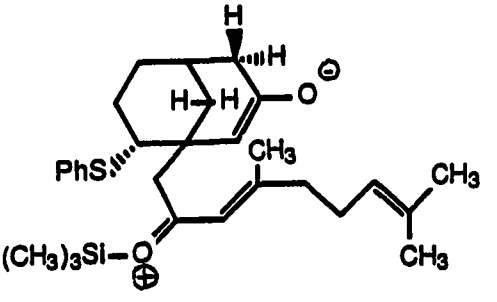


Figure 1. Endo transition state for [4+2] cycloaddition

Also, there remains the question of whether the reaction proceeds via ionic intermediates, a possible consequence of the increased electrophilicity of the bridgehead enone. We believe that the facile formation of the adducts with the tri-substituted dienes would be readily explained by ionic

intermediates. These dienes all contain a methyl group which inhibits the s-cis form of the planar diene. Generally, such a substituent renders the diene unreactive in cycloadditions. However, the methyl group would have little effect if an ionic addition was involved. Moreover, the exo stereochemistry could then be explained as illustrated below.



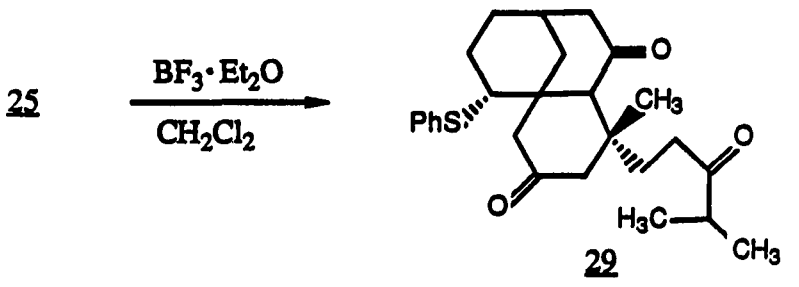
The enolate would be expected to trap the allylic cation so as to minimize non-bonded interactions between the two axial hydrogens on the bicyclo[3.3.1]nonane unit and the incoming electrophile.

Attempted Cyclization Reactions

The intramolecular cyclization of adduct 24 using mercury(II) trifluoroacetate, mercury(II) trifluoromethanesulfonate or 2,4,4,6-tetrabromo-2,5-cyclohexadienone was unsuccessful. No sign of any cyclized product was observed.

Our attempted cyclization of epoxide 25 using Lewis acids like zinc chloride, tin tetrachloride, ethylaluminum dichloride, titanium tetrachloride or diethylaluminum

chloride led only to a complex mixture of products. Reaction of adduct 25 with boron trifluoride etherate gave a low yield of the triketone 29.



EXPERIMENTAL

General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl prior to usage. Methylene chloride was distilled from phosphorus pentoxide. Benzene was distilled from lithium aluminum hydride. N,N-Dimethylformamide (DMF) was dried over 4A molecular sieves. Acetonitrile was distilled from calcium hydride. All reactions were conducted under a nitrogen atmosphere, and all extracts were dried over anhydrous sodium sulfate. The apparatus for experiments requiring anhydrous conditions was flame-dried under a steam of nitrogen or was dried in an oven at 150°C for 12 hours. Flash chromatography was performed on Kieselgel 60, mesh 230-400. Column chromatography was performed on Grace silica gel, grade 62, mesh 60-200. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-4250 or Acculab 2 spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian EM-360 spectrometer. High field (300 MHz) proton spectra were obtained using a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal

standard. Splitting patterns are designated as s (single), d (doublet), t (triplet), and m (multiplet); addition of br indicates a broadened pattern. Carbon-13 NMR spectra were determined on a JOEL FX-90Q or Nicolet NMC-1280 spectrometer and are reported in ppm relative to the central peak of $CDCl_3$ (77.06 ppm). Ultraviolet spectra were obtained on a Perkin-Elmer UV-Vis spectrophotometer. High resolution mass spectra were recorded on an AEI-MS 902 high resolution mass spectrometer. Low resolution mass spectra were recorded on a Finnegan 4023 mass spectrometer.

6-Benzenesulfenyl-2-cyclohexen-1-one 13

To a solution of 2-trimethylsiloxy-1,3-cyclohexadiene (25.9 g, 154 mmol) in 150 mL of methylene chloride was added a solution of benezenesulfenyl chloride (22.3 g, 154 mmol) in 50 mL methylene chloride dropwise at -78°C. The resulting solution was stirred at -78°C for two hours, then slowly allowed to warm to room temperature. The mixture was concentrated in vacuo and purified via flash column chromatography using 3:1 hexanes:ethyl acetate to give 28.0 g (89% yield) of product as a yellow-brown oil. NMR ($CDCl_3$) δ 7.45-6.92 (m, 5 H), 6.18-5.76 (m, 2 H), 3.81 (t, 1 H), 2.57-2.04 (m, 4 H). IR (film) 3045, 2930, 1680, 1483, 1387, 1250, 1220, 1030 cm^{-1}. High-resolution mass spectrum for $C_{12}H_{12}SO$ requires 204.28620; measured 204.28603.

1-Hydroxy-8-benzenesulfenylbicyclo[3.3.1]nonan-3-one 14

To a freshly prepared sodium methoxide (2.70 g, 50.0 mmol) in methanol (250 mL) was added ethyl acetoacetate (7.12 g, 54.6 mmol) and 6-benzenesulfenyl-2-cyclohexen-1-one 13 (10.14 g, 49.8 mmol). The resulting solution was heated at 65°C for three days. The reaction mixture was cooled to room temperature and the methanol solvent was evaporated. The residual yellowish brown oil was neutralized with dilute HCl and then extracted twice with methylene chloride. The organic layer was dried and concentrated in vacuo. The crude product was dissolved in methanol (150 mL):water (50 mL) mixture and potassium hydroxide (2.80 g, 49.8 mmol) was added. This mixture was heated at 90°C for one day. The reaction was cooled to room temperature and the mixture was concentrated in vacuo. The residual aqueous solution was brought to neutrality with dilute HCl solution and extracted twice with methylene chloride. The organic layer was dried and concentrated to afford an oily compound. The crude product was purified via flash column chromatography using 1:2 ethyl acetate:hexanes to give a 2:1 diastereomeric mixture of compound 14 (8.03 g, 61%). NMR ($CDCl_3$) δ 7.58-7.13 (m, 5 H), 3.40 (m, 1 H), 2.9-1.2 (m, 11 H). IR ($CDCl_3$) 3450, 2940, 1710, 1465, 1448, 1370, 1220, 1090, 720 cm^{-1}. Mass spectrum (m/e) 262 (M^+), 244, 234, 216, 153, 109, 77.

1-Bromo-8-benzenesulfenylbicyclo[3.3.1]nonan-3-one 15a

To a solution of compound 14 (15.4 g, 58.9 mmol) in dry ethyl ether (250 mL) was added phosphorous tribromide (6.1 mL, 64.8 mmol) dropwise at 0°C. The mixture was stirred at 0°C for one hour and allowed to warm to room temperature over three hours. The mixture was poured into ice and then extracted with methylene chloride. The organic layer was separated, dried and concentrated in vacuo. The crude product was purified via flash column chromatography using 5:1 hexanes:ethyl acetate to yield a diastereomeric mixture of the product 15 (14.5 g, 76%). Recrystallization in ether:hexanes (3:2) gave pure, white crystalline solid (7.5 g, 39%) which is identified as the major isomer 15a. NMR ($CDCl_3$) δ 7.55-7.10 (m, 5 H), 3.60-1.10 (m, 12 H). IR ($CDCl_3$) 2940, 2863, 1710, 1660, 1476, 1459, 1448, 1215, 1100, 1006, 720 cm^{-1}. High resolution mass spectrum for $C_{15}H_{17}SOBr$ requires 324.01835; measured 324.01853.

2-Hydroxy-4,8-dimethyl 3-E,7-nonadiene 17

Geranial (24.0 g, 295 mmol) was dissolved in dry ether (200 mL), the resulting solution was cooled to -78°C under nitrogen atmosphere. Methyl magnesium bromide (120 mL, 324 mmol) was added dropwise and the reaction mixture was stirred at -78°C for two hours. It was allowed to slowly warm to room temperature and then poured into dilute HCl solution (150 mL). The organic layer was separated and the

aqueous layer extracted thrice with ether. The combined organic layer was washed with water, then saturated in NaCl, dried and concentrated *in vacuo*. The crude product obtained was purified by flash column chromatography using 3:1 hexanes:ethyl acetate as eluent to obtain a light-yellow oil (22.11 g, 83%). NMR ($CDCl_3$) δ 5.25 (d, 1 H), 5.05 (br t, 1 H), 4.6 (m, 1 H), 2.12-2.0 (m, 4 H), 1.7 (s, 6 H), 1.61 (s, 3 H), 1.23 (d, 3 H). IR ($CDCl_3$) 3335, 2980, 2903, 1650, 1440, 1370, 1130, 1100, 1055, 940 cm^{-1}. High-resolution mass spectrum for $C_{11}H_{20}O$ requires 168.15142; measured 168.15177.

2-Keto-4,8-dimethyl-3-E,7-nonadiene 18

To a solution of pyridine (150 mL, 1.85 mol) in methylene chloride at 0°C under nitrogen was added chromium trioxide (93.0 g, 0.93 mol) in five portions, the resulting deep-red solution was stirred at 0°C for 10 minutes, then slowly allowed to warm to 20°C over one hour. Alcohol 17 (26.0 g, 155 mmol) in methylene chloride (50 mL) was added rapidly. An immediate separation of tarry black deposit was observed. The reaction was stirred for an additional 15 minutes at room temperature, and the organic layer was decanted and concentrated *in vacuo*. Purification of the crude product by flash column chromatography using 8:1 hexanes:ethyl acetate as eluent gave the pure product as a yellow oil (20.0 g, 78%). NMR ($CDCl_3$) δ 6.03 (s, 1 H), 5.02

(br t, 1 H), 2.10 (s, 3 H), 2.08-1.8 (m, 4 H), 2.03 (s, 3 H), 1.70 (s, 3 H), 1.60 (s, 3 H). IR (film) 2960, 2920, 1680, 1610, 1440, 1372, 1350, 1208, 1165, 1100, 962 cm^{-1}. High-resolution mass spectrum for $C_{11}H_{18}O$ requires 166.13577; measured 166.13564.

2-Trimethylsilyloxy 4,8-dimethyl 1,3-E,7 nonatriene (19)

To diisopropylamine (1.25 mL, 8.93 mmol) in dry tetrahydrofuran (20 mL) at -78°C under nitrogen was added n-BuLi (3.20 mL, 8.30 mmol) dropwise. The solution was stirred for 15 minutes and a solution of enone 18 (1.10 g, 6.62 mmol) in tetrahydrofuran (10 mL) was introduced slowly. The dark yellow solution was stirred for 40 minutes, then trimethylchlorosilane (1.29 mL, 10.0 mmol) was added neat. It was stirred for one hour at -78°C and then allowed to slowly warm to room temperature. The yellow solution was concentrated in vacuo and the residue was taken up in hexanes (150 mL). The resulting suspension was filtered and the light-yellow filtrate was concentrated in vacuo. The light-yellow oil obtained (1.44 g, 91%) was of high purity and was used in the cycloaddition reaction without further need of purification. NMR ($CDCl_3$) δ 5.60 (s, 1 H), 5.07 (br t, 1 H), 4.30 (s, 1 H), 4.20 (s, 1 H), 2.20-2.0 (m, 4 H), 1.95 (s, 3 H), 1.72 (s, 3 H), 1.64 (s, 3 H), 0.30 (s, 9 H). IR (film) 2960, 2920, 1615, 1580, 1440, 1375, 1340, 1300,

1250, 1175, 1015, 840 cm^{-1}. High resolution mass spectrum for $C_{14}H_{26}OSi$ requires 238.17530; measured 238.17562.

2-Keto 4,8-dimethyl 7,8-epoxy 3-E nonene (20)

To a solution of olefin 18 (1.00 g, 6.0 mmol) in dry methylene chloride (20 mL) under nitrogen atmosphere at -78°C was added solid meta-chloroperbenzoic acid (1.38 g, 6.6 mmol) in four portions. The resulting suspension was stirred at -78°C for two hours, then slowly allowed to warm to room temperature. It was stirred for an additional three hours at room temperature. The reaction mixture was poured into dilute $NaHCO_3$ solution and the organic layer separated. The aqueous layer was extracted twice with methylene chloride and the combined organic layer was treated with saturated $NaHCO_3$ solution, followed by saturated sodium chloride. The organic layer was concentrated in vacuo and the crude product obtained was purified via flash column chromatography using 1:1 hexanes:ethyl acetate as eluent, to give a colorless oil (0.85 g, 78%) of high purity. NMR ($CDCl_3$) δ 6.09 (s, 1 H), 2.72 (t, 1 H), 2.38-2.18 (m, 2 H), 2.18 (s, 3 H), 2.14 (s, 3 H), 1.82-1.62 (m, 2 H), 1.32 (s, 3 H), 1.26 (s, 3 H). IR (film) 2960, 2920, 1680, 1610, 1450, 1421, 1372, 1350, 1210, 1162, 1120, 1015, 910, 780 cm^{-1}. High-resolution mass spectrum for $C_{11}H_{18}O_2$ requires 182.13068; measured 182.13073.

2-Trimethylsiloxy 4,8-dimethyl 7,8-epoxy 1,3-nonadiene (21)

To diisopropylamine (1.28 mL, 9.1 mmol) in dry tetrahydrofuran (20 mL) at -78°C under nitrogen was added n-BuLi (3.50 mL, 8.30 mmol) dropwise. The solution was stirred for 15 minutes and a solution of epoxy enone 20 (1.23 g, 6.75 mmol) in tetrahydrofuran (10 mL) was introduced slowly. The yellow solution was stirred for 40 minutes, then trimethylchlorosilane (1.00 mL, 7.76 mmol) was added neat. It was stirred for one hour at -78°C and allowed to slowly warm to room temperature. The yellow solution was concentrated in vacuo. The residue was purified via flash column chromatographay using 3:1 hexanes:ethyl acetate as eluent to yield the desired product 21 (1.27 g, 74%) as a colorless oil. NMR ($CDCl_3$) δ 5.54 (s, 1 H), 4.28 (s, 1 H), 4.22 (s, 1 H), 2.66 (t, 1 H), 2.10 (m, 2 H), 1.87 (s, 3 H), 1.70 (m, 2 H), 1.34 (s, 3 H), 1.28 (s, 3 H), 0.26 (s, 9 H). IR ($CDCl_3$) 2950, 2918, 1635, 1620, 1560, 1445, 1379, 1345, 1300, 1250, 1170, 1120, 1050, 1020, 850 cm^{-1}. High resolution mass spectrum for $C_{14}H_{26}SiO_2$ requires 254.44370; measured 254.44345.

General procedure for the [4+2] cycloaddition reactions for adducts 24-27

To a mixture of the bridgehead bromide (1 equiv.) and the diene (2-4 equiv.) at 0°C was added triethylamine (1.2 equiv.) dropwise. The solution was allowed to warm to room

temperature slowly over four hours. The copious precipitate of $Et_3\overset{+}{N}HBr^-$ was removed via filtration through glass wool and the filtrate was chromatographed on silica gel using hexanes:ethyl acetate mixture as eluent.

Adduct 24

NMR ($CDCl_3$) δ 7.48-7.13 (m, 5 H), 5.33 (s, 1 H), 5.10 br t, 1 H), 3.03 (dd, 1 H), 2.99 (s, 1 H), 2.90 (dd, 1 H), 2.67 (dd, 1 H), 2.42-1.2 (m, 13 H), 1.7 (s, 3 H), 1.6 (s, 3 H), 1.35 (s, 3 H), 0.20 (s, 9 H). IR (film) 3045, 2920, 1700, 1580, 1480, 1438, 1375, 1249, 1228, 1100, 1010, 840 cm^{-1}. Mass spectrum 482 (M^+), 467, 392, 374, 283, 241, 223, 75.

Adduct 25

NMR ($CDCl_3$) δ 7.50-7.05 (m, 5 H), 5.42 (br s, 1 H), 3.12-3.0 (dd, 1 H), 3.05 (s, 1 H), 2.92 (dd, 1 H), 2.80 (m, 1 H), 2.72 (dd, 1 H), 2.63-1.20 (m, 13 H), 1.35 (s, 3 H), 1.28 (br s, 6 H), 0.23 (s, 9 H). IR ($CDCl_3$) 3048, 2940, 1700, 1580, 1480, 1452, 1438, 1378, 1250, 1100, 1050, 1010, 840, 780 cm^{-1}. High resolution mass spectrum for $C_{29}H_{42}O_3SiS$ requires 498.26241; measured 498.26199.

Adduct 26

NMR ($CDCl_3$) δ 7.42-7.15 (m, 5 H), 5.40 (br s, 1 H), 3.34 (br s, 1 H), 3.22-3.14 (dd, 1 H), 2.75 (d, 1 H), 2.40-1.80 (m, 10 H), 1.66 (br s, 6 H), 0.10 (s, 9 H). IR (film) 3055, 2930, 2860, 1702, 1560, 1480, 1460, 1445, 1402, 1380, 1250,

1220, 1180, 1150, 1090 cm^{-1}. High resolution mass spectrum for $C_{24}H_{34}O_2SSi$ requires 414.20528; measured 414.20489.

Adduct 27

NMR ($CDCl_3$) δ 7.47-7.12 (m, 5 H), 5.39 (br s, 1 H), 5.22-4.98 (m, 2 H), 4.80 (m, 1 H), 3.12-2.98 (dd, 1 H), 3.01 (s, 1 H), 2.02 (m, 1 H), 2.78 (dd, 1 H), 2.67-1.32 (m, 15 H), 1.30 (s, 3 H), 0.21 (s, 9 H). IR ($CDCl_3$) 3037, 2925, 1702, 1580, 1413, 1375, 1243, 1104, 1018, 910 cm^{-1}. High resolution mass spectrum for $C_{28}H_{40}O_2SiS$ requires 468.25184; measured 468.25248.

Attempted cyclization of epoxide 25

To epoxide 25 (0.12 g, 0.24 mmol) in dry methylene chloride (3 mL) at 0°C under nitrogen atmosphere was added a solution of $BF_3 \cdot Et_2O$ (0.05 mL, 0.41 mmol) in methylene chloride (0.50 mL) dropwise. The mixture was stirred at 0°C for three hours and allowed to slowly warm to room temperature. It was poured into brine and extracted twice with methylene chloride. The organic layer was dried and concentrated in vacuo. The crude product was purified using flash column chromatography to give triketone 29 (0.03 g, 25%). NMR ($CDCl_3$) δ 7.40-7.13 (m, 5 H), 3.13 (m, 1 H), 3.02 (m, 1 H), 2.96-1.25 (m, 18 H), 1.30 (d, 6 H), 1.24 (s, 3 H). Mass spectrum 426 (M^+), 398, 383, 370, 351, 317, 109, 77.

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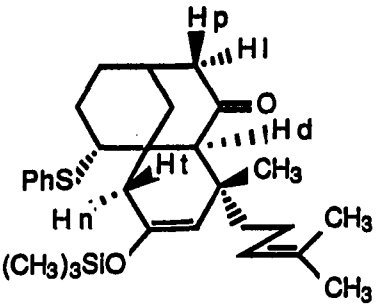
APPENDIX:

INTERPRETATION OF 2D-NMR RESULTS

2D COSY Experiment (refer to figures 2 and 3)

1. a. H_b (5.15 ppm) appears as a broad triplet, therefore, H_b is the vinylic proton.

   b. H_b is strongly coupled to two protons, H_e and H_f, therefore, H_e (2.15 ppm) and H_f (1.70 ppm) must be the allylic protons.



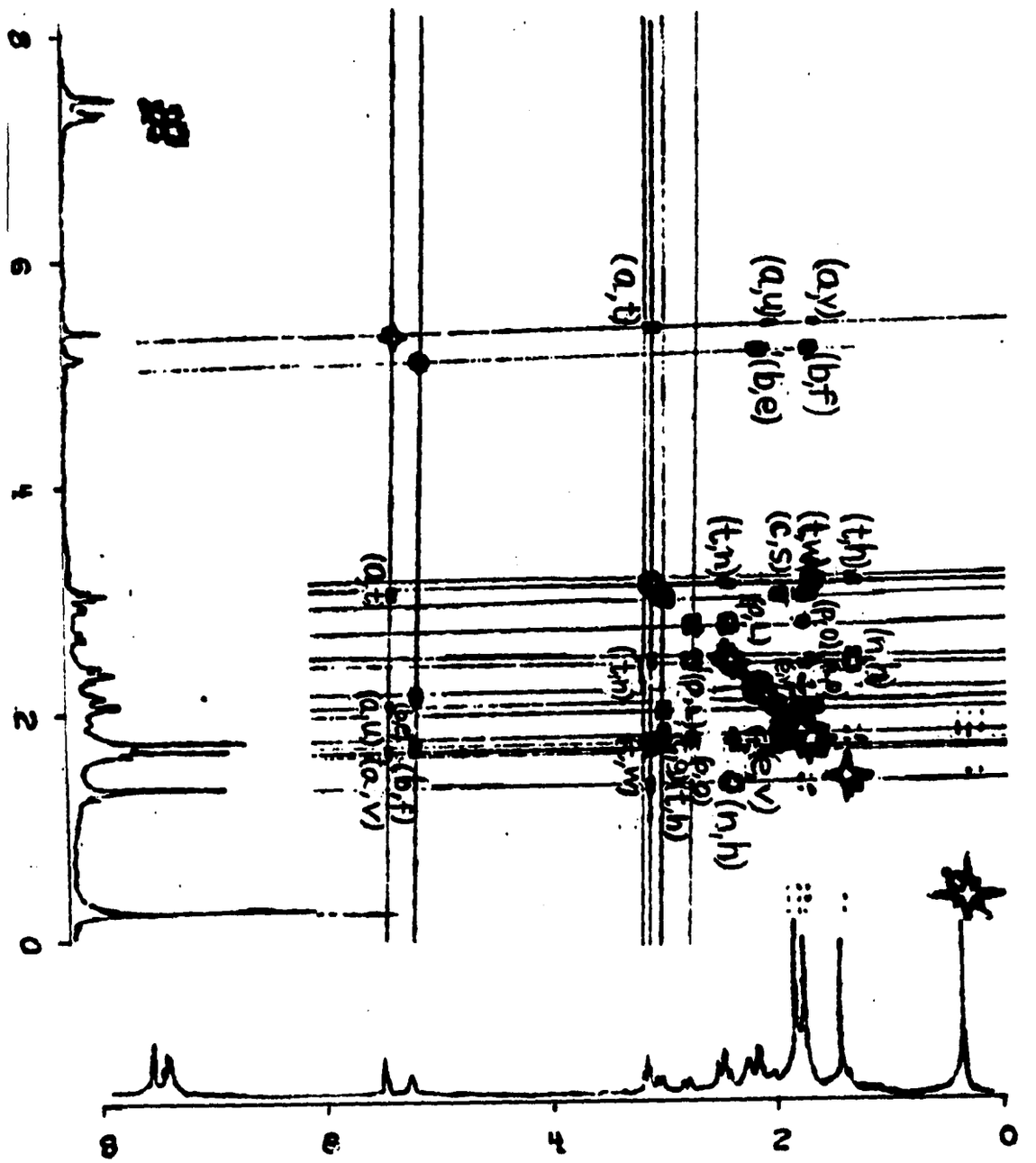
28

Figure 2. Protons assignments for adduct 24

2. a. H_a (5.40 ppm) appears as a singlet, therefore, H_a is the vinylic proton alpha to the trimethylsilyloxy group.

   b. H_a is strongly coupled to a proton, H_t, therefore, H_t (3.02 ppm) is the allylic proton alpha to the trimethylsilyloxy group.

Figure 3. 2D COSY NMR on adduct 24


8
6
4
2
0
(a,t)
(a,y)
(a,u)
(b,f)
(b,e)
(t,n)
(t,h)
(c,s)
(n,h)
(a,t)
(a,u)
(b,f)
(a,v)
(n,v)
8
6
4
2
0

c. H_a is also coupled to two other protons, therefore, based on chemical shift of these protons, H_u (2.02 ppm) and H_v (1.60 ppm) are the logical choices and are assigned as the homoallylic protons.

3. H_t (assigned earlier in 2-b) appears as a broad doublet and is coupled to three other protons, H_n, H_h and H_w, therefore, H_n (2.42 ppm) must be the other allylic proton, H_h (1.35 ppm) and H_w (1.65 ppm) are the flagpole hydrogens.

4. a. H_c (2.95 ppm) is a doublet of doublet, therefore, H_c must be the methine proton at the carbon bearing the thiophenyl group (based on chemical shift).

   b. H_c is coupled to two protons, H_s (2.00 ppm) and H_g (1.70 ppm), therefore, H_s and H_g are the methylene protons adjacent to H_c.

5. a. H_p (2.70 ppm) is a doublet of doublet, therefore, H_p must be one of the methylene protons at the carbon alpha to the ketone.

   b. H_p is coupled strongly to H_l (2.40 ppm) and weakly to H_o (1.73 ppm), therefore, H_l is the other proton at the carbon alpha to the ketone, H_o is the bridgehead proton.

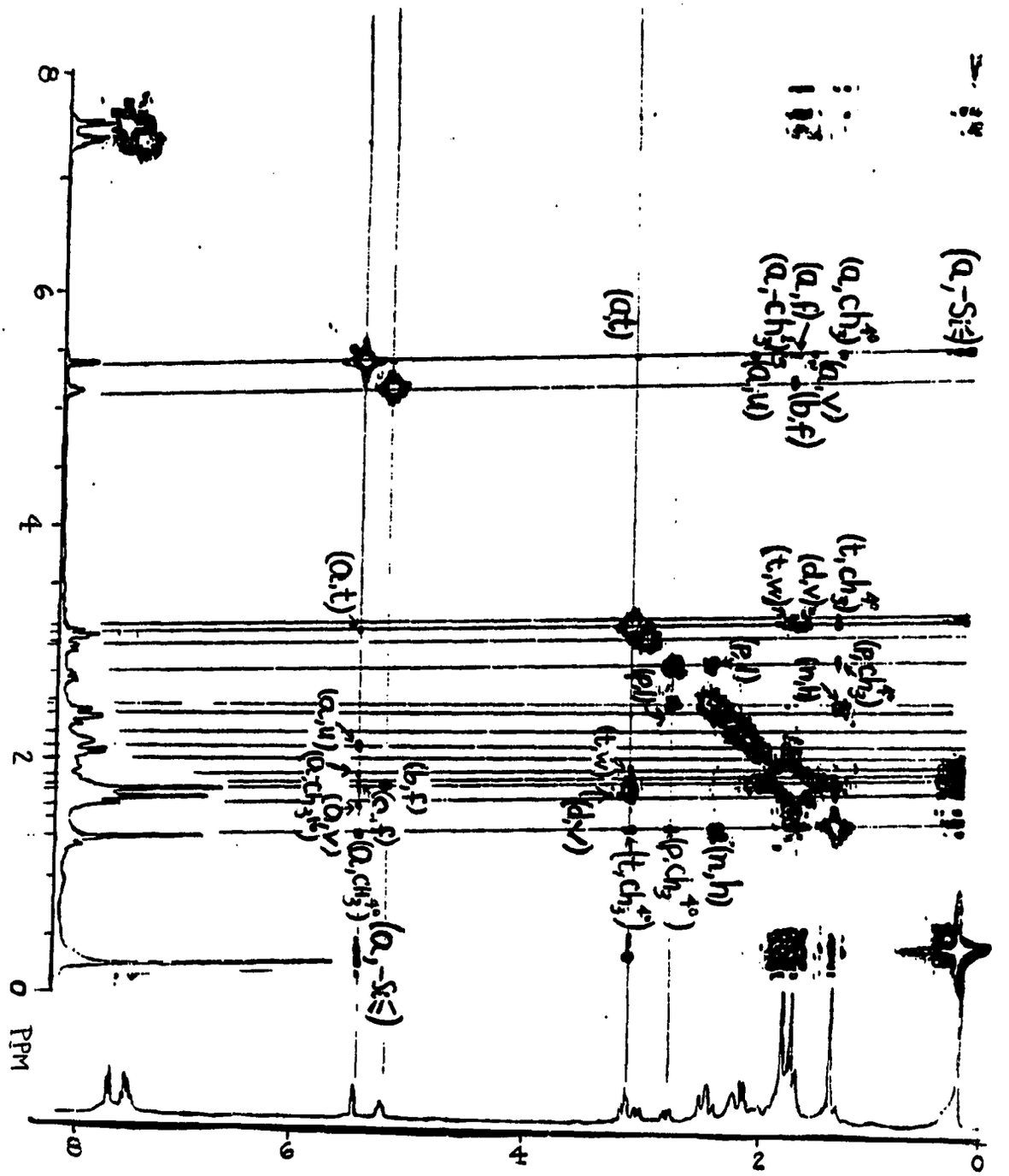
6. H_d (3.00 ppm) appears as a broad singlet, therefore, H_d must be the methine proton at carbon alpha to ketone.

2D NOESY Experiment (refer to Figures 2 and 4)

1. The following protons and groups exhibit expected interaction through space:
   a. H_a with H_t, H_u, H_f, H_f and the methyl group attached to the vinylic carbon. H_a also interacts with methyl group attached to the quarternary carbon; H_a has interaction with trimethylsilyloxy group.
   b. H_b with H_f.
   c. H_d with H_v.
   d. H_p with H_l.
   e. H_n with H_h.
   f. H_t with H_w.
2. The most significant result of this experiment shows that H_p and H_t has strong interaction through space with the methyl group attached to the quarternary carbon.

Based on the results of the above experiments, the methyl group (attached to the quarternary carbon) is trans to the methine proton alpha to the ketone. This stereochemistry suggests an exo mode of cycloaddition.

Figure 4. 2D NOESY NMR on adduct 24


PPM
8
6
4
2
0
(a,-Si)
(at)
(a,t)
(a,-Si)

CONCLUSIONS

Significant advances that resulted from our research efforts at Iowa State include:

1. An effective method for synthesizing cis-fused cyclopentanoids using samarium diiodide has been achieved.

2. Two concise approaches to the highly potent antileukemic agent rocaglamide have been developed.

3. A novel way of constructing bridged ring systems utilizing a reactive bridgehead enone intermediate and 1,1,3-trisubstituted dienes has been effected.

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