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Studies directed to the total synthesis of biologically active natural products

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Studies directed to the total synthesis of biologically active natural products

by

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For the Major Department

Signature was redacted for privacy.

For the Graduate College

Iowa State University
Ames, Iowa

1990

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DEDICATION

I wish to dedicate this thesis to my parents, Ioannis and Theodora, for all their love and sacrifices.

OVERALL INTRODUCTION

The increased need for efficient syntheses of biologically active natural products has led to the development of numerous elegant synthetic methods. Our research was focused on the total synthesis of natural products and the discovery and application of new synthetic methods. We report the following advances:

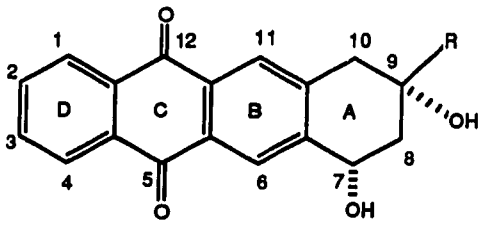
1. The synthesis of 4,11-bisdeoxydaunomycinone by a Claisen/Diels-Alder sequence.
2. The discovery of a new regiochemical control element for the Diels-Alder reaction, and its application towards the synthesis of complex alkaloids.
3. The formation of monocyclic and bicyclic systems via organosilicon-induced cyclizations, and chemoselective studies on silyl radicals.

SECTION I. THE SYNTHESIS OF 4,11-BISDEOXYDAUNOMYCINONE VIA A CLAISEN/DIELS-ALDER SEQUENCE

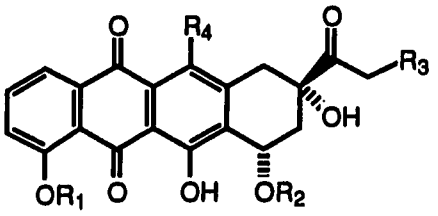
INTRODUCTION

The anthracyclines are an important class of natural products, both from a biological and a chemical perspective. The first anthracyclines were isolated in 1939 by Krassilnikov and Koreniako.[1] Since 1939 over forty members of the family have been isolated and have been the subject of numerous clinical and chemical studies.

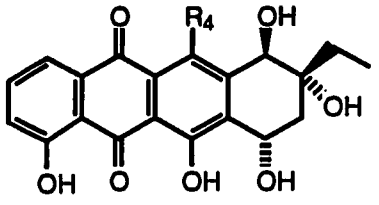
Structurally, the anthracyclines contain an anthraquinone chromophore and a linear hydrocarbon skeleton. When fully aromatized the anthracyclines exist as tetracenes. The basic carbon framework of the anthracyclines (aglycone) as well as the conventional numbering system are shown below:



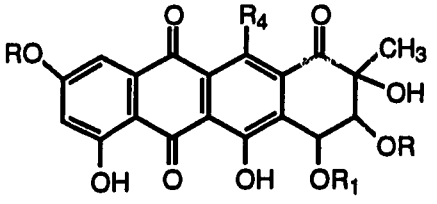
In nature, the anthracyclines exist both as glycosides, compounds that contain a carbohydrate moiety, and as aglycones, better known as anthracyclinones. The structure of some important members of the anthracycline family are shown below:



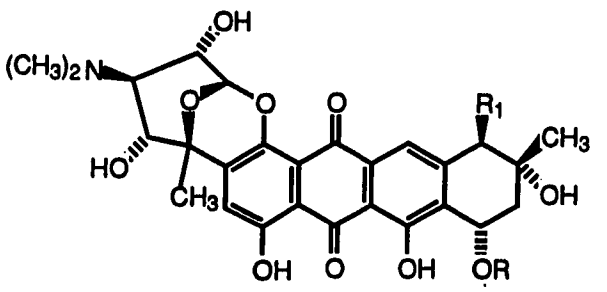
	R_1	R_2	R_3	R_4
Daunomycin	CH_3	OH	H	Daunosamine
Adriamycin	CH_3	OH	OH	Daunosamine
Carmicomycin	H	OH	H	Daunosamine



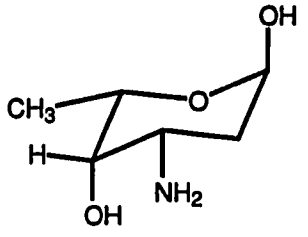
a-Citromycinone



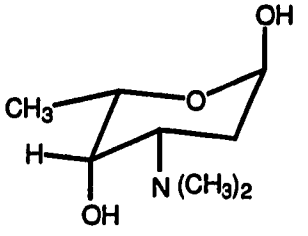
	R	R_1
Steffimycin	CH_3	2-O-Methyl-L-rhamnose
Steffimycin B	CH_3	2,4-Di-O-Methyl-L-rhamnose



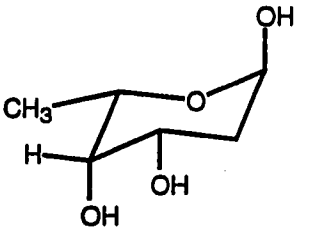
	R_1	R_2
Nogalamycin	CO_2CH_3	Nogalose
Nogamycin	H	Nogalose



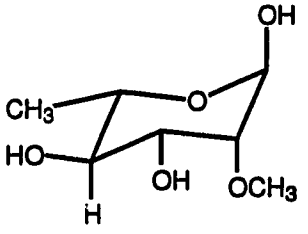
Daunosamine



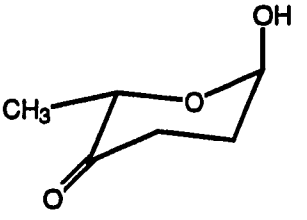
Rhodosamine



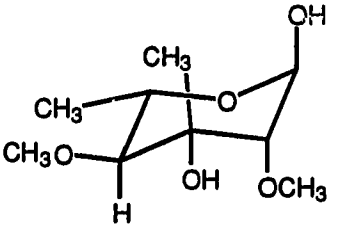
2-Deoxy-L-fucose



2-O-Methyl-L-rhamnose



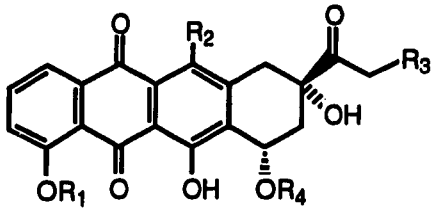
L-Cinerulose



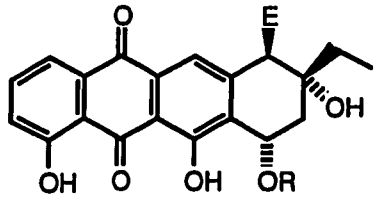
Nogalose

Recently, a second class of anthracyclines has been discovered which contain an 11-deoxy B-ring. They possess the same biological activity as the first class of anthracyclines, but do not exhibit the same toxic effects.

Significant members of this class are the aclacinomycins, isolated from Streptomyces galileus MA144-MI by Oki and coworkers,[2] and 11-deoxydaunomycin, isolated by Arcamone and coworkers from a Micromonspora peucetica strain.[3]



	R_1	R_2	R_3	R_4
11-Deoxydaunomycin	CH_3	H	H	Daunosamine
11-Deoxyadriamycin	CH_3	H	OH	Daunosamine



	E	R
Aklavinone	CO_2CH_3	H
Aclacinomycin A	CO_2CH_3	Rhodosamine + 2-deoxy-L-fucose + L-cinerulose
Aclacinomycin B	CO_2CH_3	Rhodosamine + 2-deoxy-L-fucose + cinerulose B

Biologically, the anthracyclines exhibit effective activity against breast cancer; cancers of the bladder, lung and thyroid; Hodgkin's disease; and lymphobastic and acute leukemias.[4,5] To date, the mechanism of action of the

anthracyclines and their pharmacokinetic behavior has not been completely determined.

The first anthracyclines to exhibit detectable antitumor activity were cinerubin A and cinerubin B.[6] However, the compounds were extremely toxic. The first widely-used anthracycline in clinical studies was daunomycin. It exhibited effective activity against certain leukemias. Currently, adriamycin and aclacinomycin A are some of the most successful chemotherapeutic agents.

The antitumor activity of anthracyclines and their toxicity can be modified by specific structural variations. Through structure-activity relationship tests, the active sites of the molecules can be determined, as well as changes that could lead to enhanced activity and lower toxicity.[7] The antitumor and antibacterial activity of compounds is expressed through a percent T/C factor where

$$\text{percent T/C} = \frac{\text{median survival time of test animals} \times 100}{\text{median survival time of control animals}}$$

A percent T/C value greater than 120 indicates activity, where a percent T/C value lower than 85 indicates toxicity.[8]

The information obtained from the structure-activity relationship tests has allowed the design of unnatural

anthracycline analogs with increased activity over the natural compounds. Currently, the anthracyclines attract a great volume of medical and chemical research. Of particular interest are the synthesis of recently isolated deoxyanthracyclines and the design and synthesis of new analogs.[9] The mechanism of action of the anthracyclines has been the subject of numerous reviews.[10-14] The focus of this section will be the discussion of selected recent synthetic approaches to deoxyanthracyclines.

Since their first isolation the 11-deoxyanthracyclines have been the subject of various synthetic studies. The strategic goals in their effective syntheses are as follows:

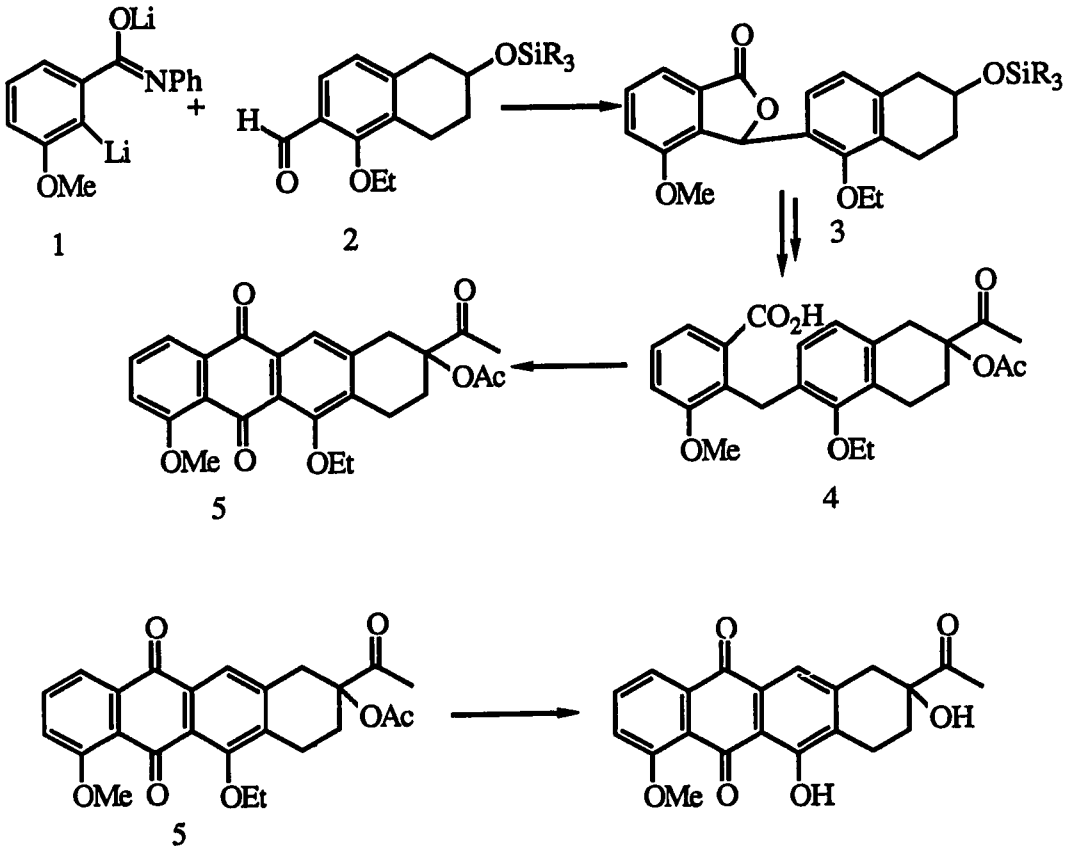
a) The regioselective construction of the carbocyclic skeleton.

b) The establishment of the functionality at C-7 and at C-9, preferably at an early stage.

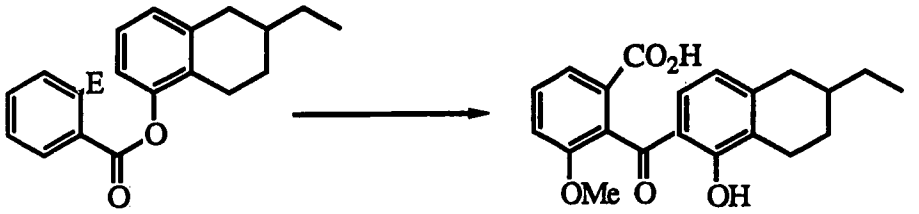
Recently, increased emphasis has been placed on accomplishing enantioselective synthesis of the natural products.

In 1981 Kende and Rizzi reported a synthesis of 11-deoxydaunomycin.[15] The synthesis is highly convergent, and it involved an AB + D ring construction strategy. The convergent step in Kende's approach was the condensation of

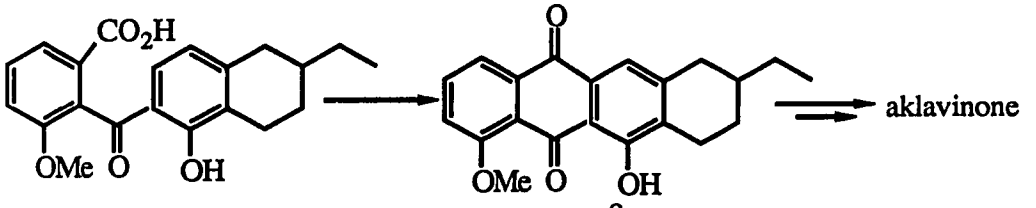
the ortholithiated benzamide 1 and the aldehyde 2. Reduction of the phthalide 3 followed a number of functional group manipulations resulted in formation of keto acid 4. Cyclization of the keto acid 4 followed by oxidation yielded the tetracyclic intermediate 5. Deprotection of the C-9 and C-6 hydroxyl sites in 5, followed by oxygenation of the C-7 position completed the synthesis. Even though the pioneering synthesis was a convergent one, the natural product was formed in 13 percent overall yield over 17 steps. A number of operations devoted to functional group manipulations was an apparent disadvantage of the route.



Confalone and Pizzolato[16] reported a synthesis of aklavinone via a different type of AB + D strategy. Aromatic ester 6 underwent an ortho-specific Fries rearrangement to produce the keto acid 7. Friedel-Crafts cyclization yielded the anthraquinone 8 in 57% yield. The approach, however, failed to introduce the functionality at ring D effectively. A rather lengthy sequence of steps afforded aklavinone from 8. The synthesis was regioselective, but the final target was formed in extremely poor overall yield.

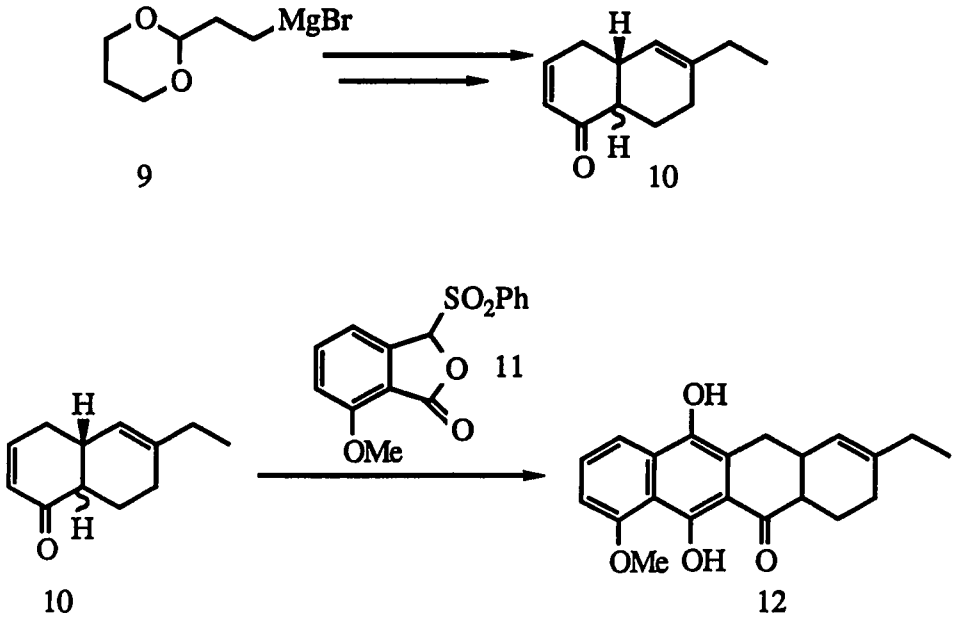


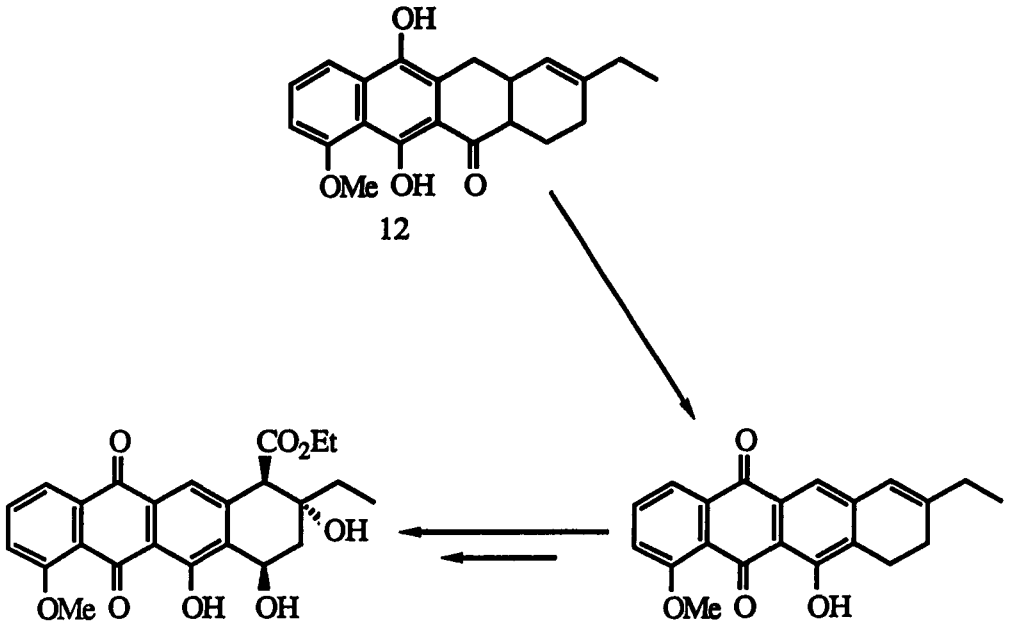
6 7



7 8

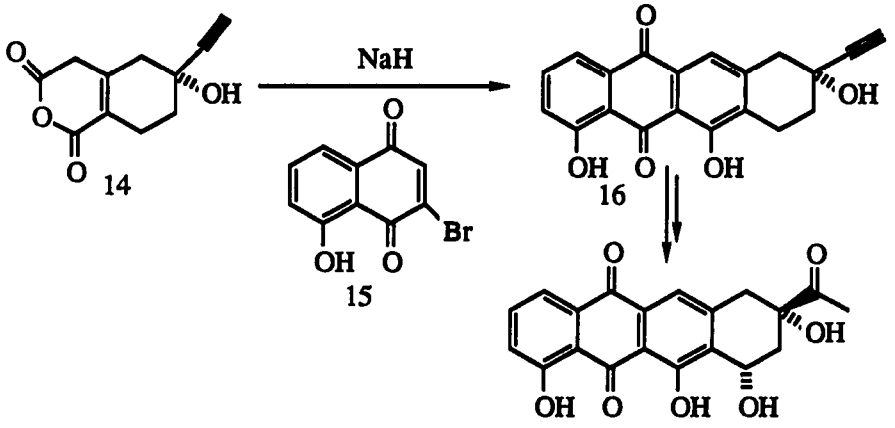
Hauser and coworkers[17] reported in 1989 a synthesis of aklavinone based on an AB + D strategy. Starting from Grignard reagent 9, naphthalenone 10 was formed which eventually became the AB ring system. Condensation of 10 with phthalidesulfone 11 yielded the tetracyclic ketone 12. Oxidation afforded the quinone 13. Conversion of quinone 13 to aklavinone required seven additional steps which completed the D-ring functionality.





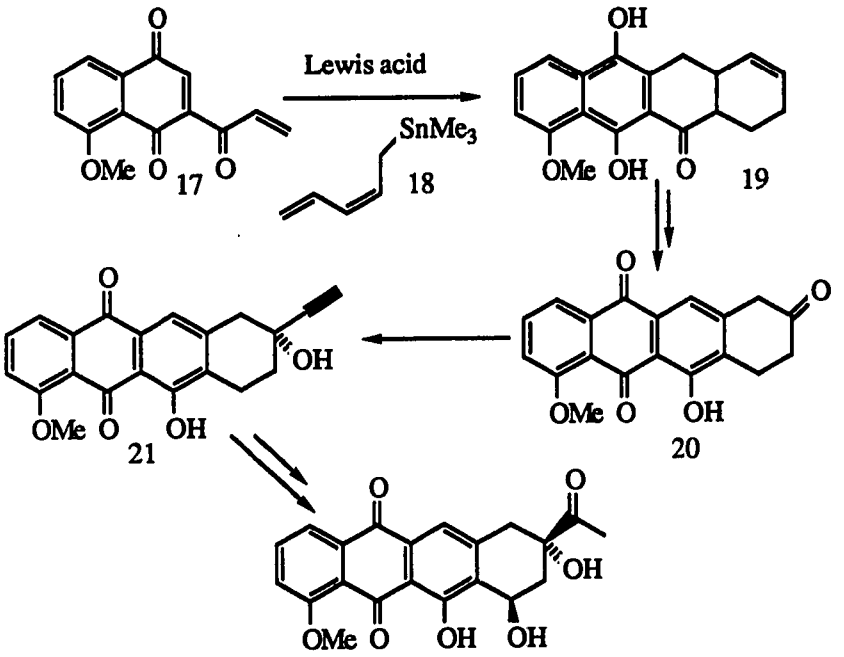
The Diels-Alder reaction has been the cornerstone of many convergent syntheses. In the synthesis of deoxyanthracyclines, the Diels-Alder reaction has served as a superior tool for the regioselective formation of the carbocyclic framework.

In 1985 Tamura and coworkers[18] synthesized 11-deoxydaunomycinone via a CD + A strategy. The key step in the sequence was the intermolecular Diels-Alder reaction of the sodium anion of anhydride 14 and 3-bromojuglone 15. Conversion of quinone 16 to the final product required two additional steps. The approach was highly efficient since the functionality at C-9 had been established prior to the key cycloaddition. The significant drawback in the route was the 32% yield in the key Diels-Alder reaction.



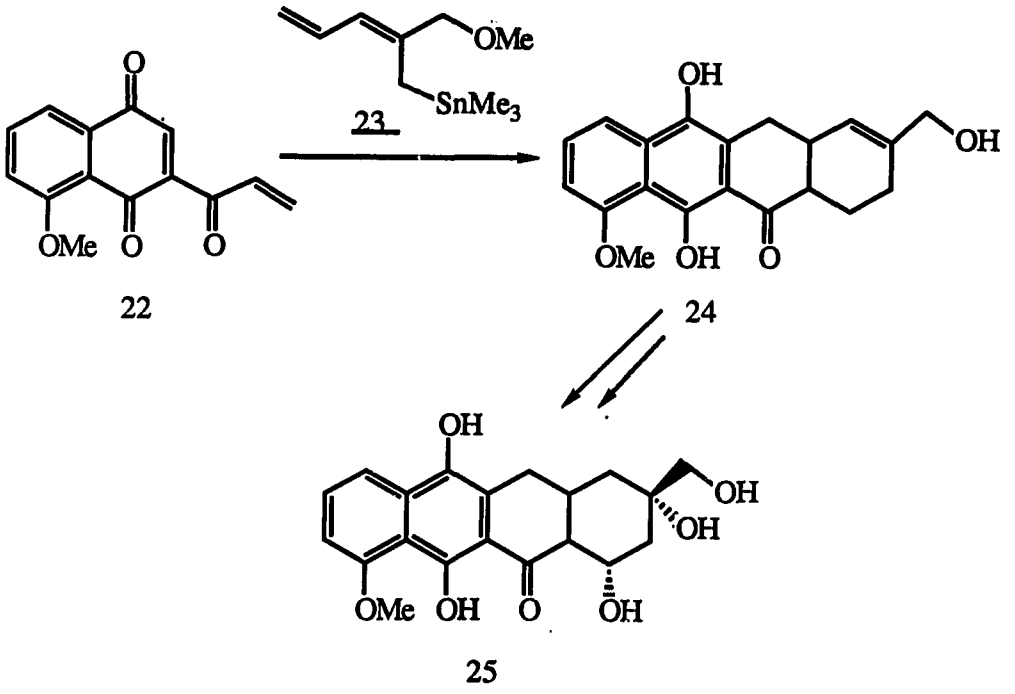
In 1989 Naruta and coworkers[19] synthesized 11-deoxyanthracyclinones via a CD→ABCD strategy. The tetracyclic framework was assembled by a clever tandem Michael/Diels-Alder reaction. Reaction of quinone 17 with pentadienyltin 18 in the presence of Lewis acids produced the tetracyclic intermediate 19. The yields reported were modest to good, varying with the Lewis acid and the amounts

used. Conversion of 19 to triketone 20 occurred in high yields. The conversion of triketone 20 to the final product was problematic. Ethynylation of 20 was an extremely difficult process. It only proceeded in 30% yield to form 21, since enolization of 20 was the major reaction. The final product was formed in three steps. In order to improve their method the authors are examining the formation of pentadienyl equivalents that include the functional groups at C-9.



Based on the same method Naruta et al.[19] recently reported an enantioselective synthesis of 11-deoxyanthracyclinone equivalent 25. The tetracyclic

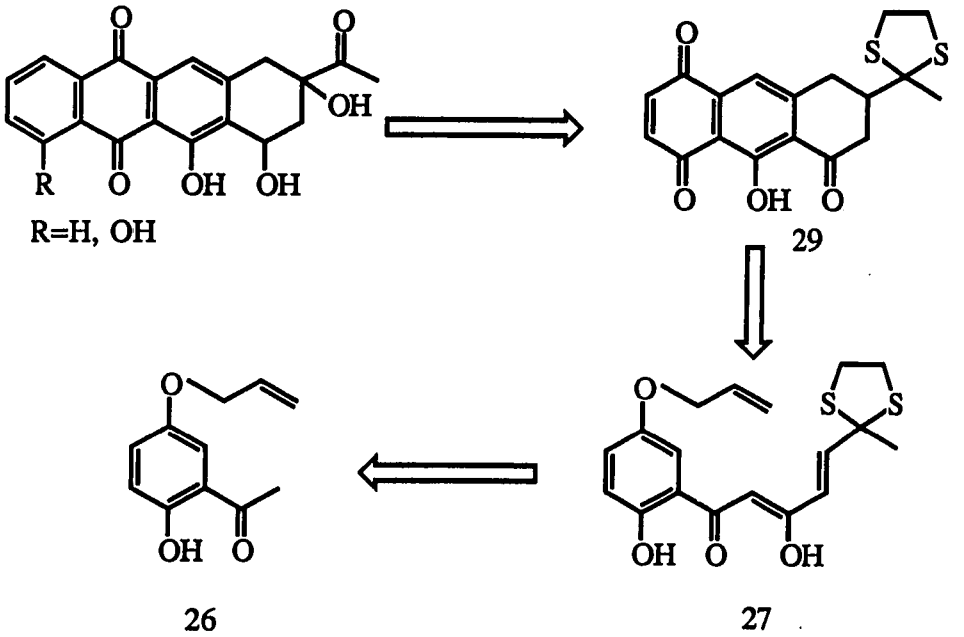
allylic alcohol 24 was formed via the tandem Michael/Diels-Alder reaction of 22 and 23, followed by methyl ether cleavage. The enantiomerically pure (92% ee) product was formed with asymmetric epoxidation of 24, reductive opening of the epoxide, and stereoselective induction of the C-7 Hydroxyl.



RESULTS AND DISCUSSION

The problem of efficient synthesis of anthracylines has been extensively studied in our laboratories. Along with the regioselective formation of the ring system, we have determined that the early introduction of the C-7 and C-9 functionality is essential for a direct synthesis.

In 1987 an extremely direct approach to 11-deoxydaunomycinone and 4,11-bisdeoxydaunomycinone was reported by our group.[20] The key step was the formation of a tricyclic intermediate via a tandem Claisen/Diels-Alder reaction. The retrosynthetic analysis is shown below:



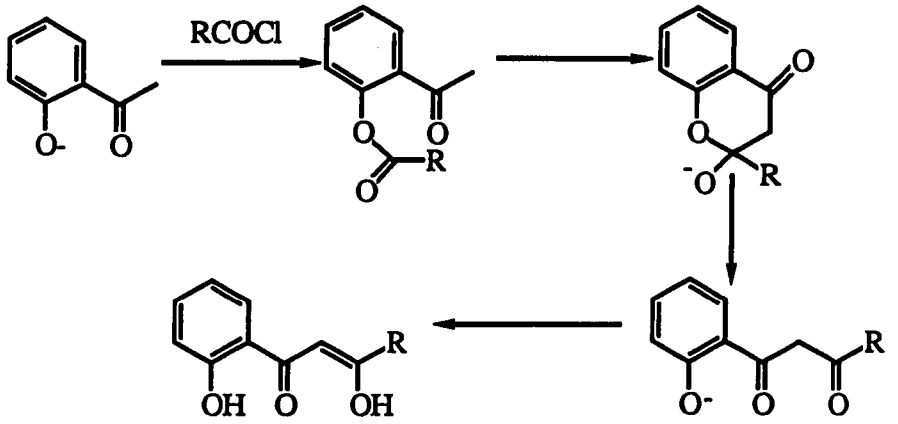
The obvious strengths of this route were the following:

a) Triketone 29 was synthesized in three steps from hydroxyacetophenone 26.

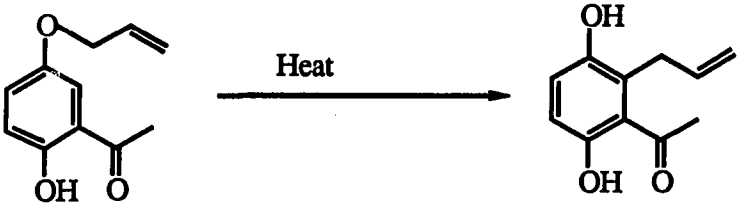
b) The tricyclic intermediate contained an oxygenated carbon at C-7 and the requisite functionality at C-9.

c) Various analogs of 11-deoxydaunomycinone in ring D could be synthesized, depending on the diene used, in the final Diels-Alder reaction.

The ß-diketones 27, required for the thermal rearrangement, were produced via an acyl transfer reaction developed by our group.[21] The detailed mechanism of the reaction involved phenoxide anion formation and its addition to the carbonyl of the acid chloride. Enolate generation and C-acylation, provided the ß-diketone.



With the ß-diketone 27 in hand, the stage was set for the tandem Claisen/Diels-Alder reaction. The Claisen rearrangement of certain o-allyl phenols with m-acyl groups is known to proceed regioselectively.[22] The 2-hydroxy-5-allyloxyacetophenone 26 undergoes Claisen rearrangement to afford 2,5-dihydroxy-6-allyl-acetophenone 31 with complete regiospecificity. It is interesting to note that when the phenol is protected the Claisen rearrangement generates a 6:4 mixture of products.[23]

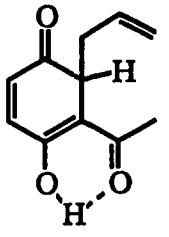


26 31

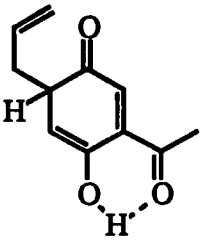
These results suggest that the hydrogen bonding between the phenol hydrogen and the carbonyl oxygen exert the dominant effect on the regioselectivity of the reaction. We feel that the absence of this hydrogen bonding forces the acyl group out of the plane of the aromatic ring. This attenuates the directing power of the acyl group.

Recently Kruse and Cha suggested that the Claisen rearrangement proceeds with intermediate A rather than

intermediate B. Intermediate A is resonance stabilized through four conjugated bonds, where B possesses only three conjugated bonds.[24]

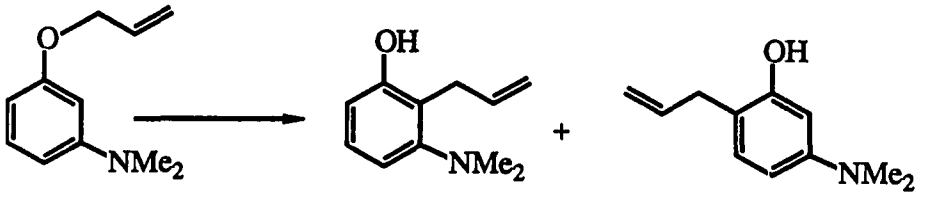


A



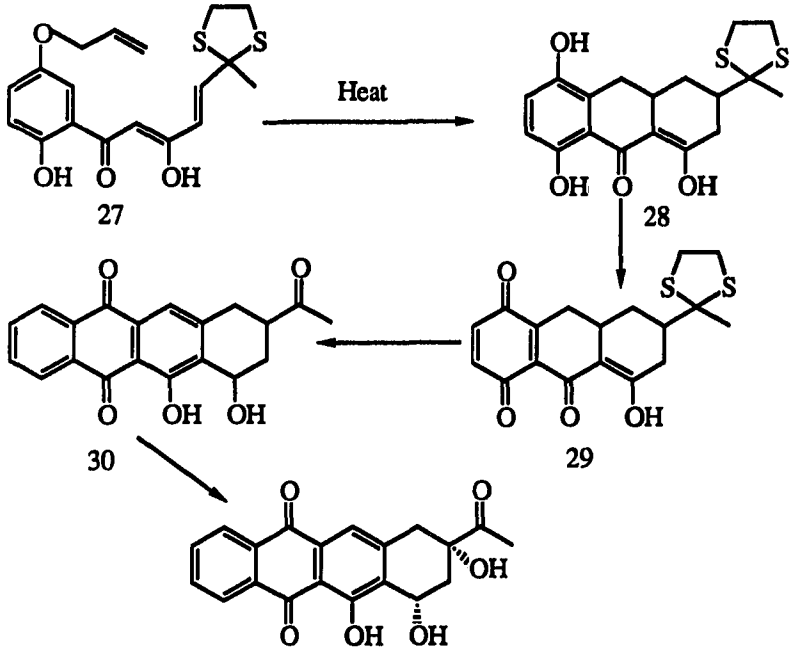
B

This explanation, however, fails to account for the formation of an equal mixture of products when a m-dimethylamino group is present.



The thermal reaction of diketone 27 afforded an 85% yield of tricyclic 28 in a 3:1 mixture of diastereomers. Oxidation of 28 to 29, selective Diels-Alders reaction, aromatization, and cleavage of the dithiane yielded

triketone 30. Triketone 30 was converted to the final product in two steps.

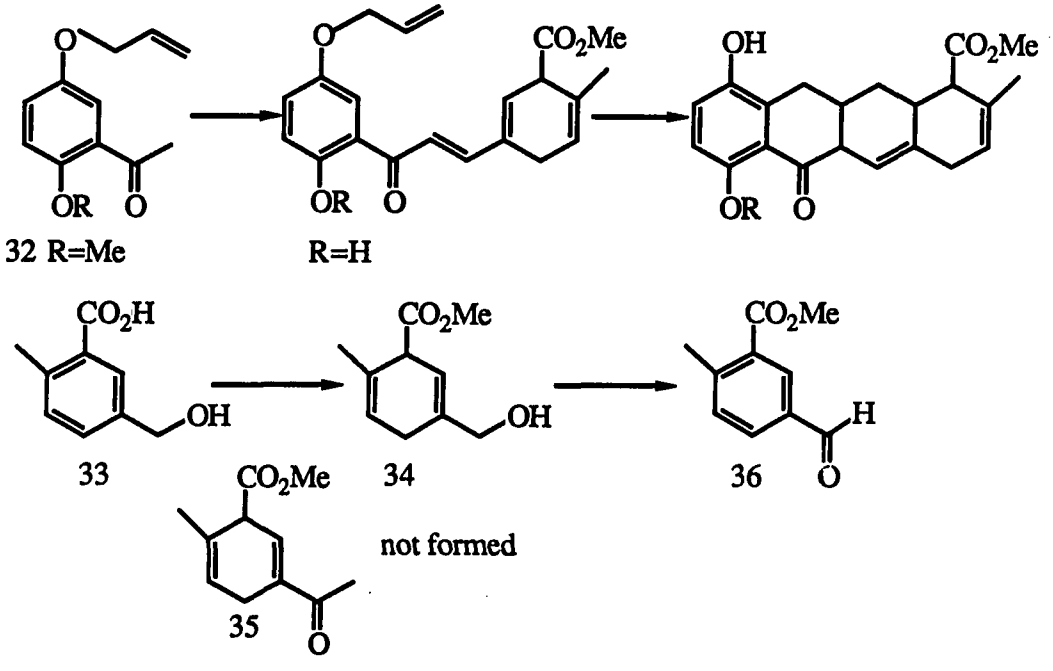


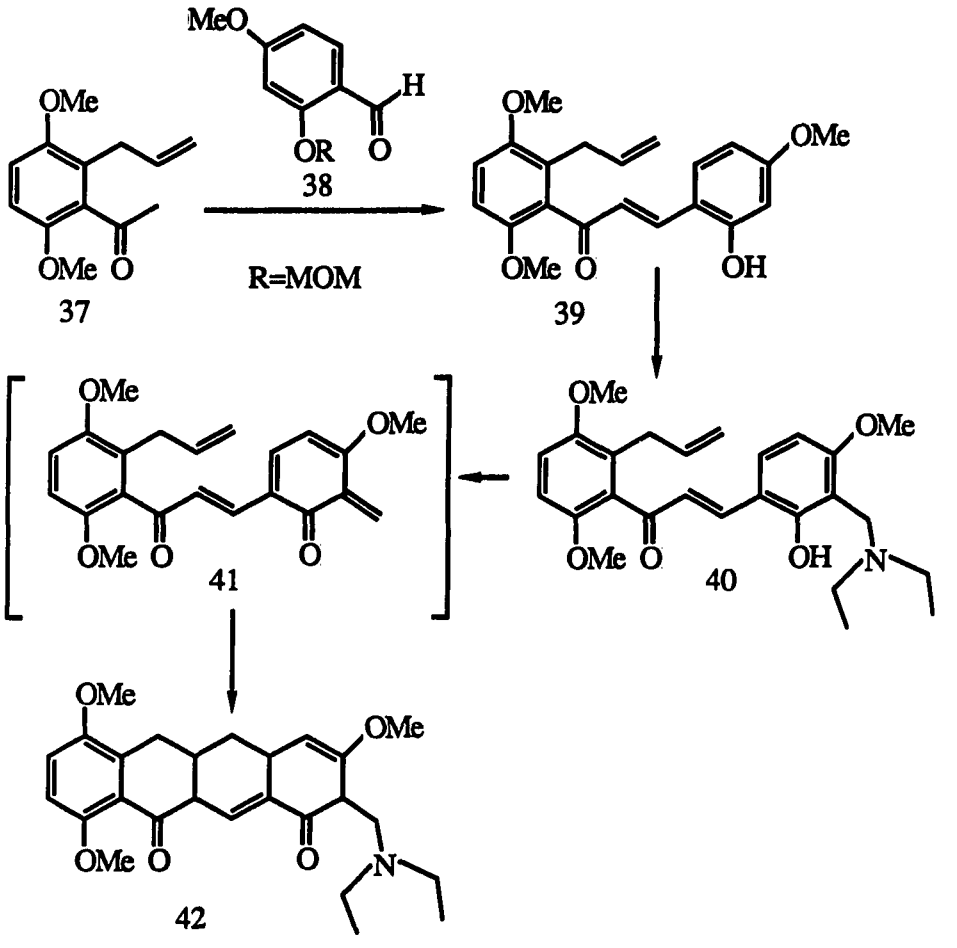
The main objective of our recent efforts has been to utilize the tandem Claisen/Diels-Alder reaction *as the tetracyclic ring system-forming operation.* Our initial targets included tetracyclic intermediates that could be converted to both anthracyclines and tetracyclines.

In an early attempt to the tetracyclines, we intended to couple acetophenone 32 with aldehyde 35. Tandem Claisen/Diels-Alder reaction should then produce a highly functionalized tetracyclic intermediate in one step. The route to the aldehyde 35 included Birch reduction of Benzoic

acid derivative 33 and oxidation of the alcohol unit 34 in 92% yield. Unfortunately, oxidation under various conditions afforded the rearomatized product 36 instead of the desired 35.

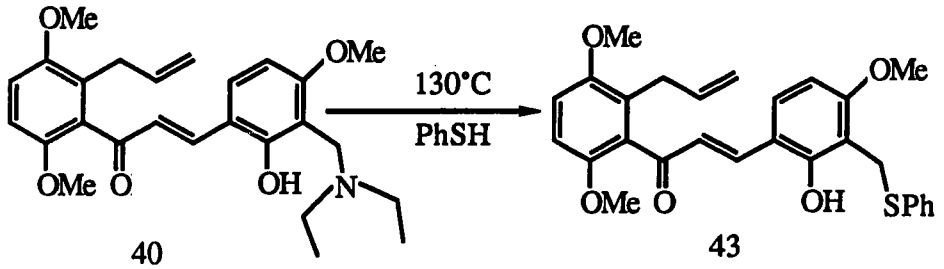
In an effort to apply a Claisen/Diels-Alder sequence towards the tetracyclic targets, we condensed acetophenone 37 with aldehyde 38. Cleavage of the methyl methoxy ether produced ketone 39 in 68% yield. Mannich condensation of ketone 39 with diethylamine and formaldehyde yielded 40 in 63%. We postulated that heating would result in elimination of the amino unit with formation of a quinone methide intermediate 41. We expected a rapid closure of the unstable intermediate, and formation of a tetracyclic compound 42 by a Diels-Alder reaction.



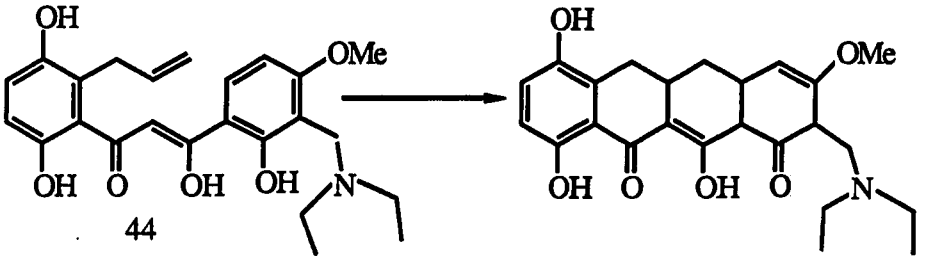


When amino ketone 40 was heated at 130°C in benzene, in the presence of benzenethiol as a trapping nucleophile, compound 43 was isolated instead of the desired 42. We reasoned that the nucleophilic addition was faster than the closure. We anticipated that construction of unit 44, which with the extended hydrogen bonding could attain a planar

transition state, would favor the Diels-Alder reaction. The new modification, however, showed no promise.



40 43

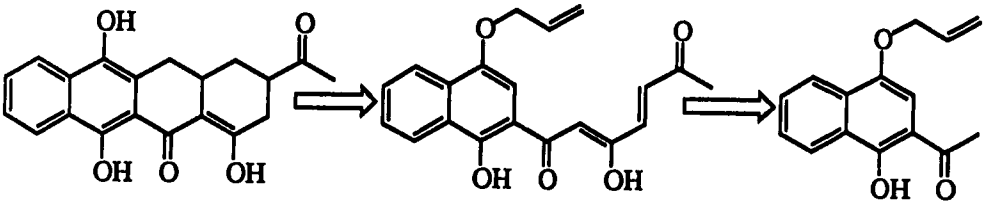


44

The formation of tricyclic intermediates from hydroxy acetophenone by acyl transfer and tandem Claisen/Diels-Alder reactions has been well documented in our laboratories. The equivalent sequence, starting with appropiately substitued naphthalenes, had not been examined. The clear strength of this sequence is that a fully functionalized tetracyclic intermediate would be formed from the tandem Claisen/Diels-Alder step. The retrosynthetic analysis is illustrated below.

The tetracylic triketone 30 could be converted to both anthracyclines and tetracyclines. Wasserman, Lu and Scott reported that tetracyclines could be generated by treatment of certain naphthalenes with singlet oxygen.[25]

To test the feasibility of the Claisen/Diels-Alder reaction in the naphthalene series, diketone 46 was synthesized by acyl transfer chemistry from ketone 45. Heating a benzene solution of ketone 46 in a degassed sealed tube afforded a complex mixture of compounds, none of which could be identified as a tetracyclic intermediate. In a effort to better understand the result, ketone 45 was heated at 230°C in benzene. Again a mixture of products was formed. The major product isolated from this mixture was naphthoquinone 48. When ketones 49 and 50 were heated, Claisen rearrangement products were formed in high yields.



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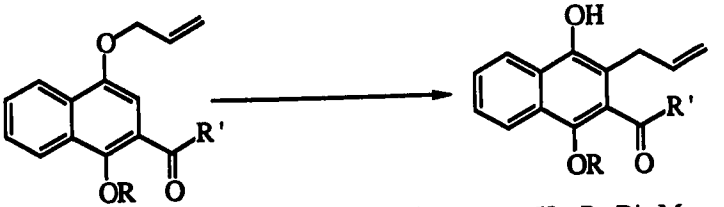
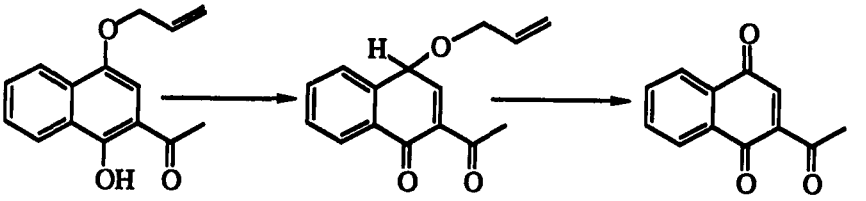


45 R=H, R'=Me, 49 R=OAc, R'=Me, 50 R=R'=Me

46 R=H, R'= CH=C(OH)-CH=CH-Me

52 R=R'=Me



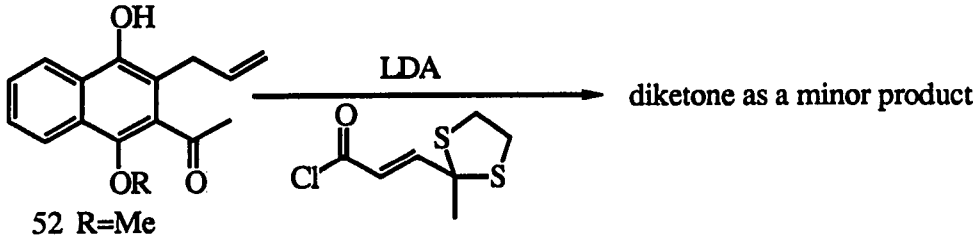
45 47 48

The results indicate that a protected phenol is required for the Claisen rearrangement to occur. We currently postulate that a retroene reaction is responsible for the formation of quinone 48 when the phenol is unprotected. Ketone 45 at elevated temperatures could tautomerize to enone 47, which in turn could eliminate propene via a retroene to produce quinone 48. This proposal is supported by chemistry reported by Hoffman.[26] The retro-ene reactions are thermodynamically favored at higher temperatures. In particular, a number of retro-ene reactions of heteroatom analogs have been reported at temperatures ranging from 100°C to 500°C. The ene cleavage of the allyl ethers has been thoroughly investigated by

Cookson and Wallis.[27] It is seen as the microscopic reverse of the "wrongly oriented" addition of carbonyl units to ene substrates.

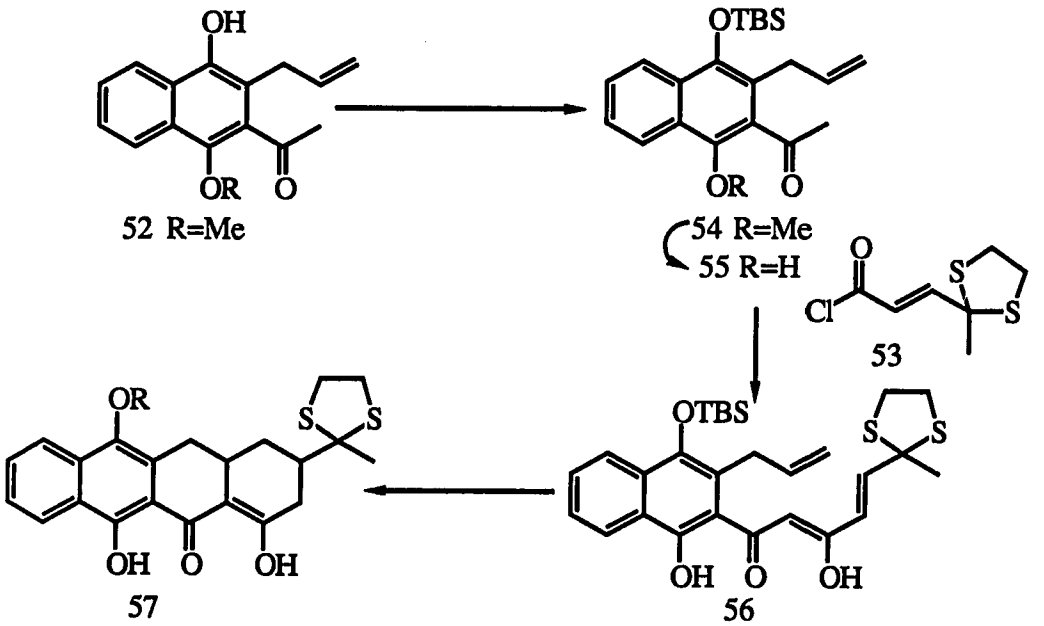
With the unexpected occurence of the retro-ene reaction, our initial synthestic plan involving the tandem Claisen/Diels-Alder reaction needed to be modified. In our previous work we had demonstrated that the tandem Claisen/Diels-Alder reaction required the planarity provided by the hydrogen bonding. The above finding, in combination with the conclusion that in the naphthlalene series the Claisen rearrangement failed with unprotected phenols led us to revise our strategy.

With compound 52 in hand, we attempted to perform intermolecular acylations. Unfortunately, treatment of the lithium enolate of 52 with acid chloride 53 or the corresponding imidazolide afforded little of the desired diketone.[28]

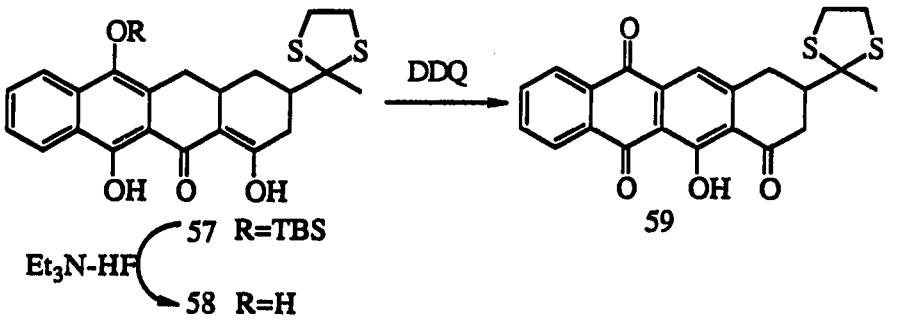


52 R=Me

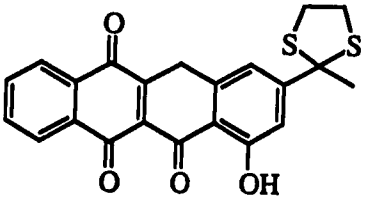
We then shifted our attention to the intramolecular acyl transfer reaction. Protection of 52 with imidazole and TBSCl afforded the silyl ether 54 in 97% yield. The deprotection of the methyl ether proceeded in modest yield at best. Treatment of 54 with Boron trichloride afforded hydroxy ketone 55 in 55% yield. Treatment of the hydroxy ketone 55 with sodium hydride and acid chloride 53, followed by the slow addition of LDA at -78°C afforded diketone 56 in 74% yield. It is important to note that the previously successful potassium tert-butoxide conditions did not work well for the particular reaction.



When a benzene solution of diketone 56 was heated in a degassed sealed tube at 210°C for three hours, a 75% yield of tetracyclic diketone 57 was produced. Cleavage of the TBS group produced a surprising result. Deprotection with tetrabutyl ammonium fluoride as the desilylating agent afforded a single compound which exhibited no cyclohexane protons in the 300 MHz NMR. Fortunately, treatment of 57 with Et_3NHF yielded 76% of naphthoquinone 58. The reaction was fairly rapid. Longer reaction times seemed to generate significant amounts of the compound produced in the tetrabutyl ammonium fluoride reaction. Oxidation of the naphthoquinone 58 with DDQ afforded 72.3% yield of anthraquinone 59 which intersects with our previous synthesis of 11-deoxyanthracyclines. The purification of 59 was a delicate task. Prolonged passage through silica gel generated again some of the unknown compound. Based on NMR, IR, and M.S. data the unknown compound was assigned as anthrone 60.

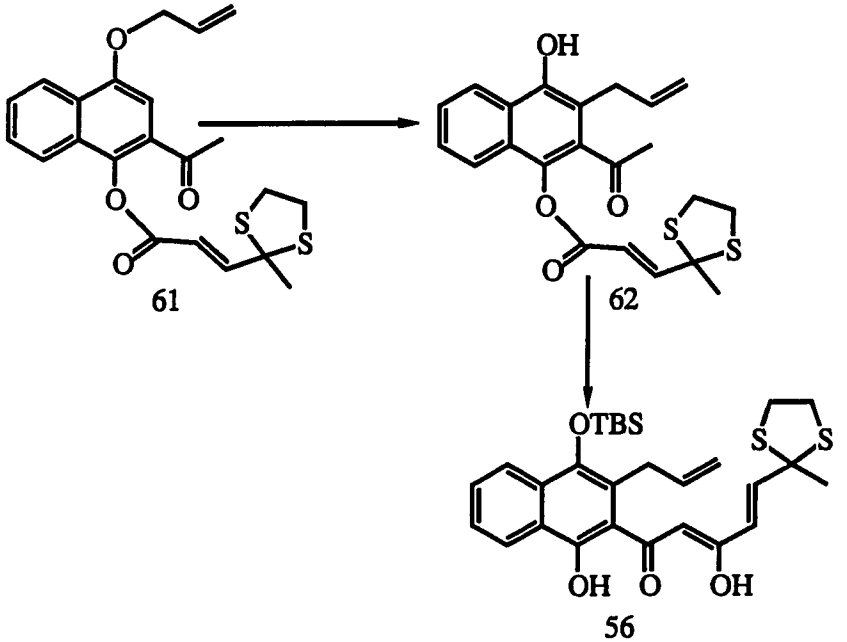


In order to produce the most expedient synthesis of our target, we critically reexamined our existing route. Often an elegant synthesis is characterized by the number and type of original and daring operations involved. The goal we established was to minimize or even eliminate the protection and deprotection steps. For this reason, we prepared ketone 61 via acylation of hydroxy ketone 45 with acid chloride 53. This intermediate allowed us to use the acyl chain as the necessary blocking unit for the Claisen rearrangement, thus, eliminating the steps involving formation and cleavage of the methyl ether. When a benzene solution of 61 was heated in a sealed tube at 240°C for 15 hours, a quantitative yield of the Claisen product 62 was obtained. This was a very welcome result, primarily because of the complexity and anticipated sensitivity of the starting material. In an attempt to transfer the acyl chain without protection of the phenol of 62, we treated the substrate with LDA, KHDMS, or potassium tertbutoxide. Unfortunately, no ß-diketone was detected as a result of these operations. Protection of the phenol 62 with TBSCl and imidazole produced, in quantitative yield, compound 56 which intersects with our previous routes.



60

Our synthesis to anthraquinone 59 proceeds in 26% overall yield in six steps from 46. The synthesis is extremely direct and highly convergent. The carbocyclic framework is assembled regioselectively via the Claisen/Diels-Alder sequence, and the functionality at C-7 and C-9 is effectively introduced at an early stage.



61 62 56

EXPERIMENTAL

General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. THF and diethyl ether were distilled from sodium benzophenone ketyl under nitrogen prior to usage. Benzene was distilled from lithium aluminum hydride. Dichloromethane was distilled from calcium hydride. Unless otherwise noted, all reactions were conducted under an argon atmosphere. Unless otherwise noted, all organic extracts were dried over anhydrous sodium sulfate. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-4250 or a Perkin-Elmer model 1320 spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian EM-360 spectrometer. High field (300 MHz) proton spectra were obtained with a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in relative to tetramethylsilane as an internal standard. Coupling constants (J) are reported in Hz. Abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet, ABq = AB quartet. 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 a Kratos model MS-50 spectrometer. Low-resolution mass spectra were recorded on a Finnegan 4023 mass spectrometer. Silica gel used for flash chromatography (72) was 230-400 mesh (Kieselgel 60) purchased from EM Science. Gravity column chromatography was performed on 60-200 mesh silica gel purchased from Davison Chemical (WR Grace Inc.). Elemental analyses were performed by Galbraith Laboratories, Inc.

1-(1-Methoxy-4-(2-propenyloxy)-2-naphthyl)ethan-1-one 57

To a solution of hydroxyketone 45 (1.51 g, 6.24 mmol) in 25 mL of acetone was added potassium carbonate(1.72g, 12.48 mmol) followed by methyl iodide (2.65g, 18.7 mmol). The mixture was heated to reflux for 12 hours. The reaction was cooled, diluted with water and acidified to pH 6 with 2N HCl. The aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried and concentrated. The crude product was purified by flash chromatography on 7:1 hexanes:ethyl acetate to afford ketone 51 in 98% yield.

NMR ($CDCl_3$): 2.80 (s, 3H), 3.90 (s, 3H), 4.6-4.8 (m, 2H), 5.2-5.6 (m, 2H), 6.1-6.4 (m, 1H), 7.1 (s, 1H), 7.5-7.9 (m,

2H), 8.1-8.2 (m, 1H), 8.25-8.4 (m, 1H).

IR (CH_2Cl_2): 1670, 1590, 910 cm^{-1}.

Mass spectrum: m/e 115, 165, 181, 198, 226, 241, 256.

High-resolution mass spectrum: m/e calculated 256.10995; measured 256.11036.

1-(4-hydroxy-1-methoxy-3-(2-propenyl)-2-naphthyl)ethan-1-one 52

A solution of ketone 51(1.56g, 6.1 mmol) in 14 mL of benzene was deoxygenated and sealed in a glass tube. The tube was heated to 240°C for 16 hours. The tube was cooled, the reaction mixture concentrated and the residue purified by flash chromatography on 6:1 hexanes:ethyl acetate to afford ketone 52 in 84% yield.

NMR ($CDCl_3$): 2.60 (s, 3H), 3.4-3.48 (m, 2H), 3.88 (s, 3H), 5.1-5.32 (m, 2H), 5.05 (s, 1H), 5.95-6.15 (m, 1H), 7.5-7.6 (m, 2H), 8.0-8.1 (m, 1H), 8.19-8.28 (m, 1H).

IR ($CDCl_3$): 1690, 1590, 1420, 890 cm^{-1}.

Mass spectrum: m/e 115, 128, 165, 198, 226, 241, 256.

High-resolution mass spectrum: calculated 256.10995; measured 256.11036.

1-[4-[(tertButyldimethylsilyl)oxy]-1-methoxy-3-(2-propenyl)-2-naphthyl]ethan-1-one 54

To a solution of ketone 52 (1.02g, 3.98 mmol) in 7 mL of DMF at 0°C was added imidazole (0.81g, 11.94 mmol) and TBSCl (1.20g, 7.96 mmol). The reaction was allowed to warm to ambient temperature and stir for 8 hours. The solution was diluted with ether, washed with brine, dried and concentrated. The crude product was purified by flash chromatography on hexanes:ethyl acetate to afford ketone 54 in 97% yield.

NMR ($CDCl_3$): 0.40 (s, 6H), 1.10 (s, 9H), 2.60 (s, 3H), 3.41-3.64 (m, 2H), 3.80 (s, 3H), 4.81-5.14 (m, 2H), 5.67-5.97 (m, 1H), 7.41-7.63 (m, 2H), 7.97-8.81 (m, 2H).

IR ($CDCl_3$): 1680, 1570, 1350, 870, cm^{-1}.

Mass spectrum: m/e 73, 165, 223, 270, 298, 313, 340, 355, 370.

High-resolution mass spectrum: calculated 370.19643; measured 370.19636.

C-13 NMR ($CDCl_3$): -2.97, -2.70, 18.70, 26.14, 26.3, 31.0, 33.1, 63.5, 116.6, 121.12, 121.9, 123.7, 127.2, 129.0, 133.3, 136.3, 145.5, 147.2, 205.7.

Elemental analysis calculated for $C_{22}H_{30}O_3Si$: C, 71.37; H, 8.17. Found: C, 71.58; H, 8.27.

White solid, melting point 70-71°C.

1-[4-tertButyldimethylsilyl)oxy]-1-hydroxy-3-(2-propenyl)-2-naphthyl]ethan-1-one 55

To a solution of ketone 54 (1.04g, 2.8 mmol) in 6 mL of methylene chloride at -78°C was added a solution of boron trichloride(1.65g, 14 mmol) in 7 mL of methylene chloride. The solution initially turned orange and then to red after the addition. The solution was stirred at -78°C for 10 minutes and then at ambient temperature for 10 minutes. The solution was diluted with water, a saturated solution of NaOAc was added and the aqueous layer extracted with ether. The combined organic layers were washed with brine, dried and concentrated. The crude product was purified by flash chromatography on 6:1 hexanes:ethyl acetate to afford ketone 55 in 55% yield.

NMR ($CDCl_3$): 0.13 (s, 6H), 1.12 (s, 9H), 2.67 (s, 3H), 3.78-3.89 (m, 2H), 4.85-5.1 (m, 2H), 5.75-5.95 (m, 1H), 7.41-7.65 (m, 2H), 7.98 (d, J=8.4 Hz, 1H), 8.40 (d, J=8.4 Hz, 1H), 13.05 (s, 1H).

IR ($CDCl_3$): 1620, 1570, 1370, 890 cm^{-1}.

Mass spectrum: m/e 167, 207, 224, 256, 281, 299, 323, 338, 356.

High-resolution mass spectrum: calculated 356.18078; measured 356.18137.

C-13 NMR ($CDCl_3$): -3.1, -2.9, 18.6, 26.1, 26.3, 31.8, 32.7, 116.1, 116.4, 120.8, 123.0, 124.4, 125.3, 127.8, 129.0, 131.4, 137.0, 141.6, 156.0, 206.1.

Elemental analysis calculated for $C_{21}H_{28}O_3Si$: C, 70.80; H, 7.92. Found: C, 70.37; H, 7.91.

Acyclic Naphtol Diketone 56

To a suspension of hexane-washed NaH (0.04g, 1.64 mmol) in 2 mL of THF was added a solution of ketone 55 (0.53g, 1.49 mmol) in THF. The resulting solution was stirred at 0°C for 15 minutes. A solution of acid chloride 53 (0.34g, 1.64 mmol) in THF was added dropwise and the solution stirred at 0°C for 30 minutes. The solution was then cooled to -78°C and LDA (3.28 mmol) in THF was added dropwise. The solution was then stirred for 15 minutes. It was diluted with water and acidified to pH 6 with 6N HCl. The aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried and concentrated. The crude product was purified by flash chromatography on 7:1 hexanes-ethyl acetate to afford ketone 56 in 74% yield.

NMR ($CDCl_3$): 0.17 (s, 6H), 1.10 (s,9H), 1.96 (s,3H), 3.40-3.75 (m, 6H), 4.9-5.1 (m,2H), 5.90-5.97 (m, 1H), 6.02 (d, J=16 Hz, 1H), 7.00 (d, J=16 Hz, 1H), 7.5-7.6 (m,2H), 7.97 (d, J=8.4 Hz, 1H), 8.34 (d, J=8.4 Hz 1H), 11.03 (s, 1H),

14.98 (s, 1H).

IR ($CDCl_3$): 1640, 1570, 1360, 910 cm^{-1}.

Mass spectrum: m/e 73, 173, 257, 299, 314, 356, 409, 439, 453, 471, 495, 510, 528.

High resolution mass spectrum: calculated 528.18244; measured 528.18244.

C-13 NMR ($CDCl_3$): -2.9, -2.5, 18.7, 26.1, 28.6, 33.4, 40.4, 64.1, 103.5, 116.1, 116.7, 120.3, 121.1, 123.0, 123.9, 124.7, 125.5, 128.2, 130.6, 136.3, 142.4, 146.6, 152.5, 174.1, 196.5.

Elemental analysis calculated for $C_{28}H_{36}O_4S_2Si$: C, 63.66; H, 6.87. Found: C, 63.38; H, 6.94.

Orange solid, melting point 180°C, dec.

4,6-Dihydroxy-11-[tertbutyldimethylsilyl)oxy]-2-(2-methyl-1,3-dithiolan-2-yl)tetrahydronaphthacene-5-one 57

A solution of ketone 56 (0.86g, 1.64 mmol) in 8 mL of benzene was degassed and sealed in a glass tube. The solution was heated to 220°C for 3 hours. The reaction mixture was cooled and concentrated. The crude product was purified by chromatography on 3:1 hexanes:ethyl acetate to afford compound 57 73% yield.

NMR ($CDCl_3$): 0.11 (s, 3H), 0.13 (s, 3H), 1.12 (s, 9H), 1.80 (s, 3H), 2.1-3.66 (m, 11 H), 7.45-7.62 (m, 2 H), 7.96 (d,

J=8.4 Hz 1H), 8.37 (d, J=8.4 Hz, 1H), 13.2 (s, 1H), 14.17 (s, 1H).

IR ($CDCl_3$): 1610, 1570, 1420, 905 cm^{-1}.

Mass spectrum: m/e 73, 91, 111, 173, 356, 409, 436, 528.

High-resolution mass spectrum: calculated 528.18244; measured 528.18340.

C-13 NMR ($CDCl_3$): -3.05, -3.056, 18.73, 26.20, 29.77, 30.77, 31.80, 32.30, 33.97, 39.36, 40.42, 40.67, 70.34, 107.71, 110.38, 122.85, 124.12, 124.68, 1125.21, 129.09, 132.27, 138.67, 157.1, 176.52, 193.05.

Elemental analysis calculated for $C_{28}H_{36}O_4S_2Si$: C, 63.66; H, 6.87. Found: C, 63.35; H, 6.89.

Orange solid, melting point 164-166°C.

4,6,11-Trihydroxy-2-(2-methyl-1,3-dithiolan-2-yl)-tetrahydronaphthacene-5-one 58

To a solution of ketone 57 (0.24g, 0.46 mmol) in 4 mL of THF was added triethylammonium hydrofluoride (0.08g, 0.69 mmol). The solution was stirred at ambient temperature until TLC indicated that the starting material was gone (approximately 1 hour). The solution was concentrated and the crude product purified by chromatography on 3:1 hexanes:ethyl acetate to afford a 76% yield of pure product that was normally taken onto the next step immediately.

NMR ($CDCl_3$): 1.89 (s, 3H), 2.25-3.58 (m, 11H), 4.65 (s, 1H), 7.4-7.75 (m, 2H), 8.01 (d, J=8.4 Hz, 1H), 8.38 (d, J=8.38 Hz, 1H), 13.21 (s, 1H), 14.01 (s, 1H).

IR ($CDCl_3$): 1730, 1420, 890 cm^{-1}.

Mass spectrum: m/e 83, 173, 239, 265, 318, 414.

High-resolution mass spectrum: calculated 414.09596; measured 414.09587.

Orange solid, melting point 225°C, dec.

5-Hydroxy-2-(2-methyl-1,3-dithiolan-2-yl)-dihydronaphthacene-4,6,11-trione 59

To a solution of the ketone from the desilylation reaction (0.14g, 0.34 mmol) in 4 mL of benzene at 5°C was added DDQ (0.16g, 0.71 mmol). The solution was allowed to warm to ambient temperature over 1 hour. The suspension was filtered and concentrated. The crude product was purified on silica gel using 2:1 hexanes:ethyl acetate to afford a 72.3% yield of quinone 59. The spectral data were identical to those described in reference 20.

1-[4-(2-propenyloxy)-1[[4,4-(ethylenedithio)-2-pentenoyl]oxy]-2-naphthyl]ethan-1-one 61

To a suspension of hexane-washed NaH (0.05g, 2.2 mmol) in 2 mL of THF at 0°C was added a solution of hydroxyketone (0.48g, 1.98 mmol) in THF. The resulting solution was stirred at 0°C for 15 minutes. Acid chloride 53 (0.46g, 2.2 mmol) was added dropwise and the solution was allowed to warm to ambient temperature over 1 hour. The solution was diluted with water. The aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried, and concentrated. The crude product was purified by chromatography on 5:1 hexanes:ethyl acetate to afford ester 61 in 87% yield.

NMR ($CDCl_3$): 2.02 (s, 3H), 2.61 (s, 3H), 3.33-3.53 (m, 4H), 4.74-4.80 (m, 2H), 5.36-5.66 (m,2H), 6.15-6.28 (m, 1H), 6.93 (d, J=15 Hz, 1H), 7.18 (s, 1H), 7.41 (d, J=15 Hz, 1H), 7.54-7.60 (m, 2H), 7.62-7.84 (m, 1H), 8.32-8.34 (m, 1H).

IR ($CDCl_3$): 1730, 1680, 1590, 1410, 890 cm^{-1}.

Mass spectrum: m/e 85, 102, 127, 155, 173, 210, 242, 414.

High-resolution mass spectrum: calculated 414.09596; measured 414.09582.

C-13 NMR ($CDCl_3$): 27.84, 27.90, 30.40, 40.3, 63.3, 69.1, 103.1, 115.2, 117.7, 122.4, 122.6, 126.9, 127.6, 127.7,

127.8, 128.4, 132.6, 140.3, 152.0, 154.5, 165.1, 197.1.

Yellow solid, melting point 85-87°C.

1-[1-[[4-(Ethylenedithio)-2-pentenoyl]oxy]-4-hydroxy-3-(2-propenyl)-2-naphthyl]ethan-1-one 62

A solution of ester 61 (0.24g 0.58 mmol) in 6 mL of benzene was degassed and sealed in a glass tube. The solution was heated to 240°C for 15 hours. The solution was cooled, concentrated and purified by chromatography with 3:1 hexanes-ethyl acetate to afford 0.237g of ester 62 (99% yield).

NMR ($CDCl_3$): 2.00 (s, 3H), 2.51, (s, 3H), 3.33-3.51 (m, 6H), 5.20-5.27 (m, 2H), 7.70 (s, 1H), 5.55-6.10 (m, 1H), 6.24 (d, J=15 Hz, 1H), 7.34 (d, J=15 Hz, 1H), 7.45-7.53 (m, 2H), 7.62-7.66 (m, 1H), 8.10-8.19 (m, 1H).

IR ($CDCl_3$): 1730, 1680, 1420, 890 cm^{-1}.

Mass spectrum: m/e 105, 173, 198, 240, 414.

High-resolution mass spectrum: calculated 414.09596; measured 414.09587.

C-13 NMR ($CDCl_3$): 27.9, 31.2, 32.3, 40.3, 63.3, 114.2, 114.7, 116.7, 120.7, 121.8, 125.5, 125.8, 126.5, 126.9, 132.6, 135.2, 135.6, 148.3, 154.7, 165.4, 203.4.

Yellow solid, melting point 154-156°C.

1-[1-[[4-(Ethylenedithio)-2-pentenoyl]oxy]-4-[(tertbutyldimethylsilyl)oxy]-3-(2-propenyl)-2-naphthyl]ethan-1-one 63

To a solution of hydroxy ester 62 (0.08g, 0.19 mmol) in 2 mL of DMF at 0°C were added imidazole (0.04g, 0.60 mmol) and TBSCl (0.04g, 0.29 mmol). The solution was allowed to warm to ambient temperature and to stir for 8 hours. The solution was then diluted with ether, washed with brine, dried, and concentrated. The ester 63 (0.096g) was isolated in 96% yield.

NMR ($CDCl_3$): 0.20 (s, 6H), 1.12 (s, 9H), 1.99 (s, 3H), 2.48 (s, 3H), 3.30-3.60 (m, 6H), 7.33 (d, J=15.3 Hz, 1 H), 7.47-7.50 (m, 2H), 7.62-7.65 (m, 1H), 8.06-8.08 (m, 1H).

IR ($CDCl_3$): 1713, 1640, 1420, 890 cm^{-1}.

Mass spectrum: m/e 73, 173, 299, 338, 376, 528.

High-resolution mass spectrum: calculated 528.18203; measured 528.18244.

C-13 NMR ($CDCl_3$): -3.03, -2.96, 18.73, 25.60, 26.06, 27.95, 31.09, 32.36, 40.40, 63.44, 67.92, 88.52, 115.11, 116.43, 120.84, 121.66, 123.55, 126.33, 126.65, 126.75, 128.64, 133.38, 136.11, 137.19, 147.40, 154.49, 164.84, 203.17.

Elemental analysis calculated for $C_{28}H_{30}O_4S_2Si$: C, 63.66; H, 6.87. Found: C, 63.55; H, 6.74.

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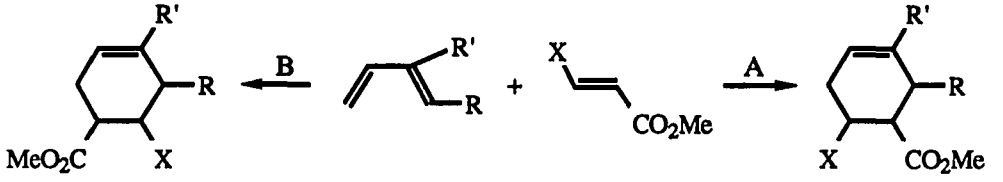
SECTION II. A NEW REGIOCHEMICAL CONTROL ELEMENT FOR THE DIELS-ALDER AND A SYNTHETIC APPROACH TO ATISINE-TYPE ALKALOIDS

INTRODUCTION

The intermolecular and intramolecular versions of the Diels-Alder reaction are superior tools for the synthesis of carbocyclic and heterocyclic systems. The regiochemistry of the Diels-Alder reaction has been the subject of the experimental and theoretical studies. In synthetic organic chemistry the possibility of the reversal of the normal regiochemical path of the reaction (A) in favor of path B, has attracted the attention of numerous researchers.

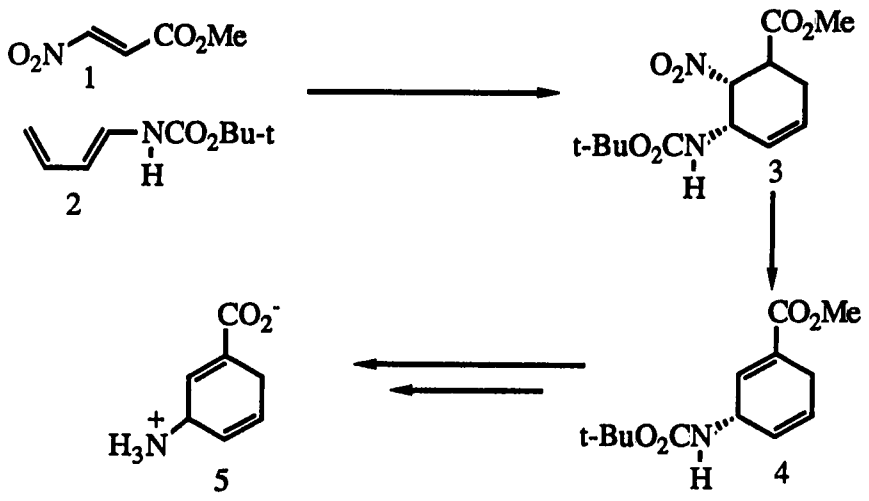


Theoretically, the regiochemistry of the Diels-Alder reaction is explained by the Frontier Molecular Orbital model (FMO). Several reviews on the FMO theory have been published.[1,2,3] It is commonly accepted that the interactions of the highest occupied orbital on the diene, and the lowest vacant orbital on the dienophile dictate the stereochemical and regiochemical outcome of the reaction.

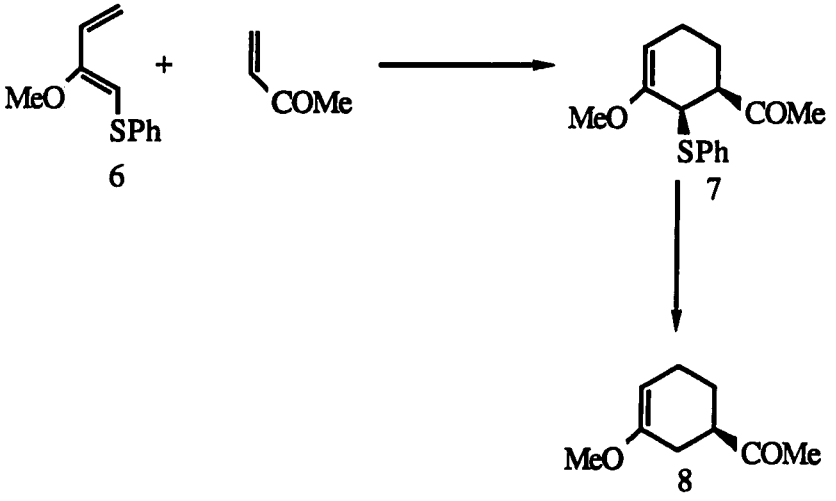
Recently Kahn and coworkers proposed a new model that explained the regioselectively in Diels-Alder reactions of electron-rich dienes and electron-poor dienophiles.[4] The

new model predicted the regiochemical outcome of the reaction, by correlating the reactivity surfaces of the diene and the dienophile. In particular, it was suggested that the electrophilic surface of the diene interacts with the nucleophilic surface of the dienophile. To determine the electrophilic surface of the diene and the nucleophilic surface of the dienophile, the substrates must be probed with a test electrophile (H+) and a test nucleophile (H-), respectively.

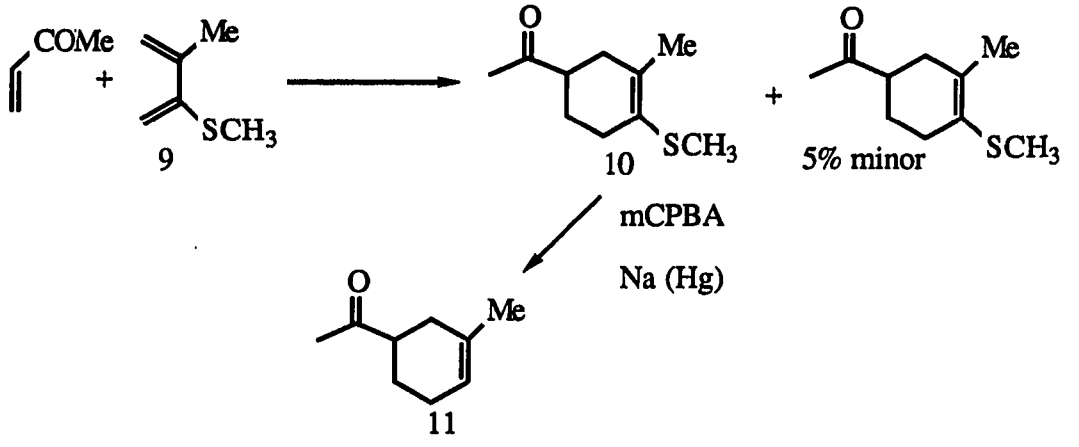
A general strategy has been developed for the reversal of the regiochemistry of the Diels-Alder. This strategy involves the temporary introduction of strongly activating groups in the diene or the dienophile. Danishefsky in 1975 reported a synthesis of isogabaculine 5.[5] The reversed substitution pattern observed in the intermediate 4 was accomplished by introducing a strong directing group (NO_2) in the dienenophile 1 prior to the cycloaddition. The Diels-Alder proceeded in 68% yield to produce nitro ester 3. Ester 4 was formed after elimination of the nitro unit, after treatment with a weak base.



In 1976 Cohen et al. reported the preparation and Diels-Alder reactions of sulfur containing diene 6.[6] Reaction with the acrylate and removal of the sulfur unit yielded the cycloaddition adduct 8, in which the methoxy group is meta oriented to the directing group of the dienophile.



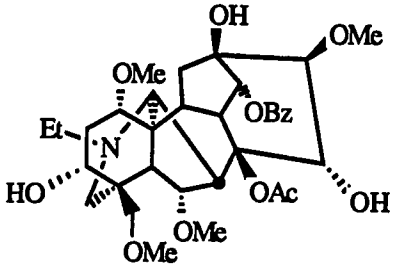
In 1985 Proteau and Hopkins reported another example of Diels-Alder reactions of sulfur containing dienes and activated dienophiles.[7] Reaction of diene 9 with methyl vinyl ketone furnished adduct 10. Removal of the sulfur moiety resulted in generation of a cyclic product 11, in which the vinyl substituent is para oriented to the carbonyl.



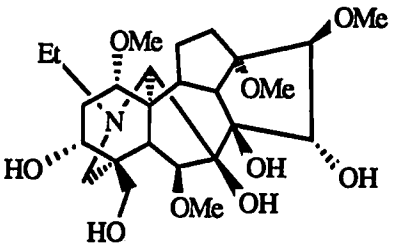
In our research efforts, we have demonstrated that path B cycloaddition products can be obtained with electron-rich dienes, by enhancing the activity of the dienophile. Certain path B reactions provide attractive intermediates for the synthesis of Aconitum alkaloids. The large family of diterpene alkaloids isolated from Aconitum roots is divided into two groups. The compounds of the first group

contain a nineteen carbon hexacyclic skeleton. The compounds of the second group contain a twenty carbon skeleton. Aconitine is the most prominent member of the first group. Aconitine has been known for over a century. A review of the studies on aconitine was published as early as 1906.[8] In 1950 aconitine was isolated from Aconitum napellus, where it was found in abundant quantities.[9] The best known compound in the second group is atisine. Atisine was first isolated by Lawson in 1937.[10] It was structurally elucidated in 1954 by Pelletier and Jacobs.[11] The structures of certain Aconitum alkaloids are shown below:

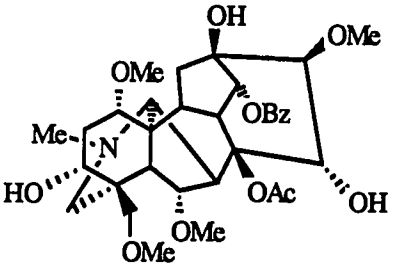
Aconitine-type alkaloids



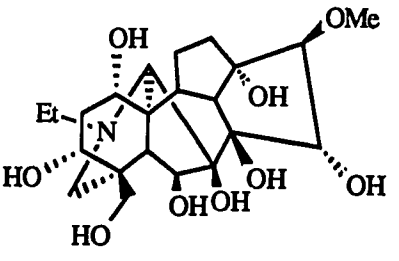
Aconitine



Lycoctonine

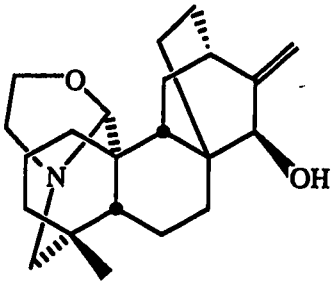


Messaconitine

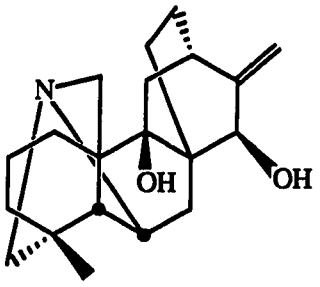


Delphilifoline

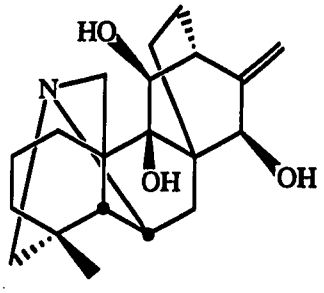
Atisine- type alkaloids



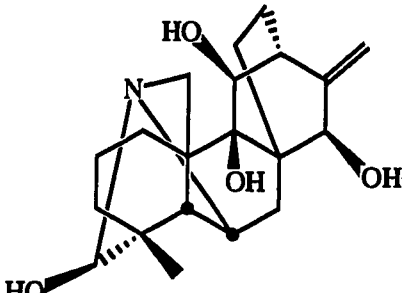
Atisine



Ignavine



Kobucine

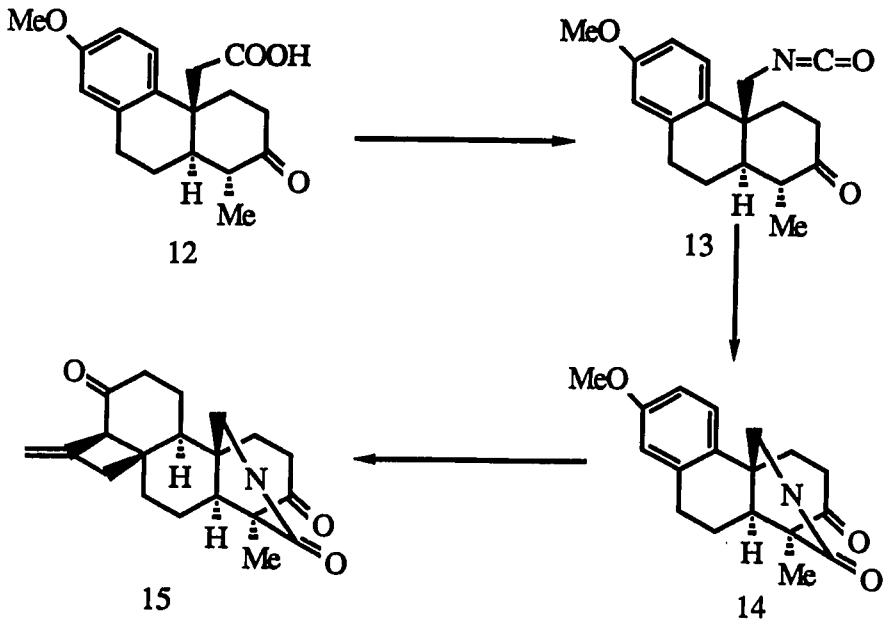


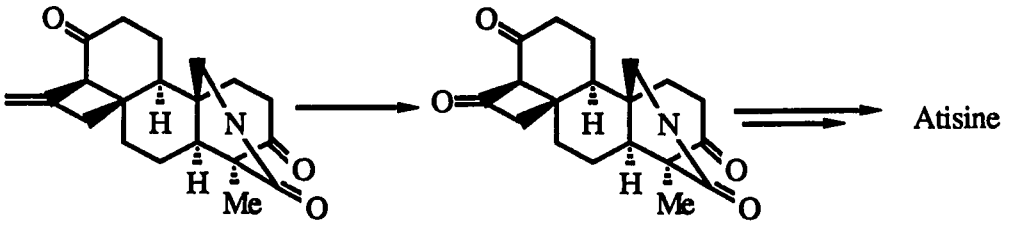
Talaticine

The Aconitum alkaloids exhibit interesting biological activity. Certain members of the family exhibit cardiac activity, others like aconotin are highly toxic. A number of Aconitum alkaloids including mesaconitine and ignavine exhibit analgesic activity.[12,13] Due to their chemical

complexity and their interesting biological properties the Aconitum alkaloids have been the subject of numerous researchers. Synthetic approaches to atisine and aconitine date as early as 1963.

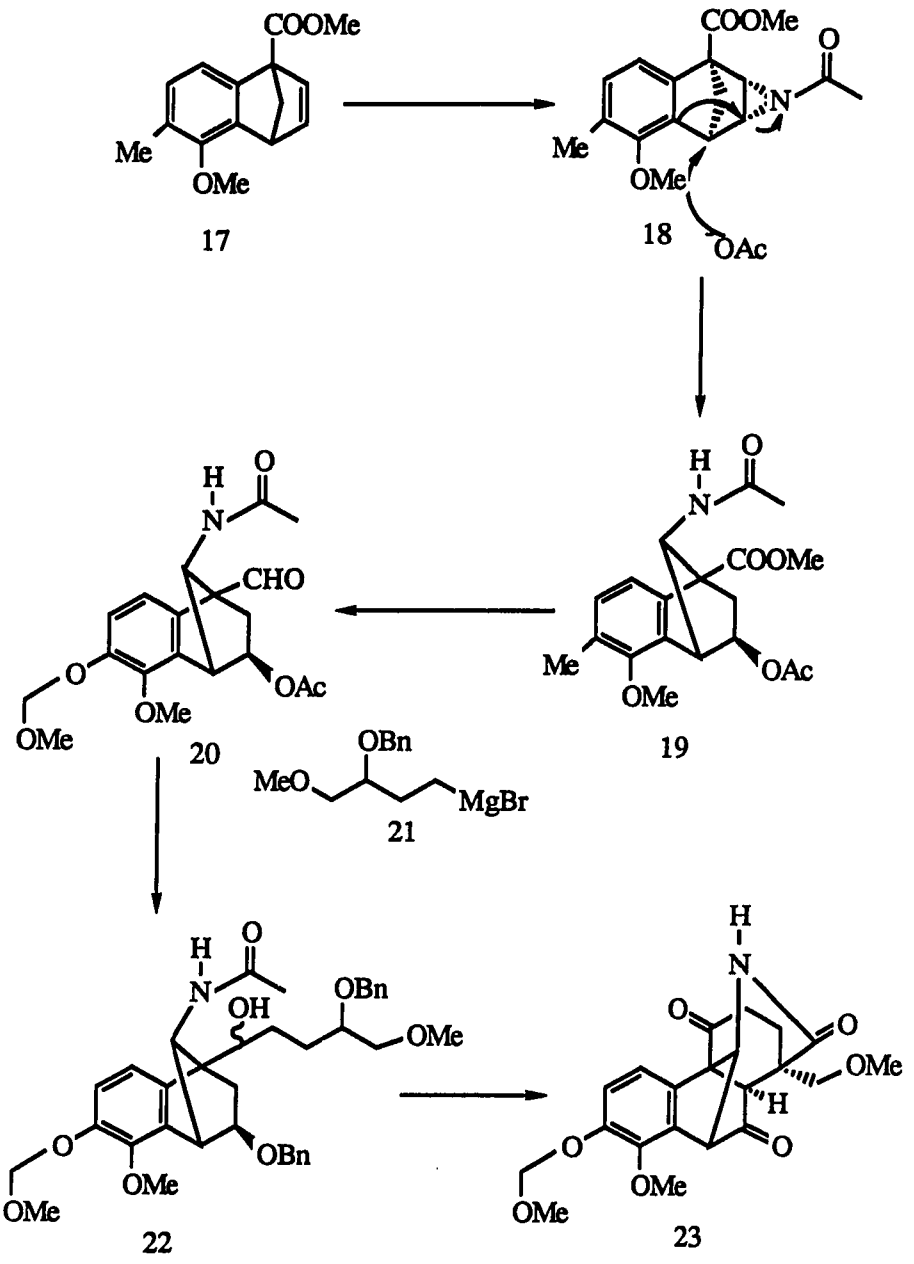
In 1964 Valenta et al. reported a synthesis of atisine.[14] Steroid type chemistry was utilized to construct the carbocyclic skeleton of the compound. The readily available ketoacid 12 was converted to the isocyanate 13. The nitrogen bridge present in the natural product was introduced via a regiospecific acid catalyzed cyclization of the isocyanate 13 to lactam 14. Birch reduction followed by allene photocycloaddition furnished stereospecifically compound 15. Oxidation afforded ketone 16 which could be transformed to atisine and Garrya alkaloids in few steps.





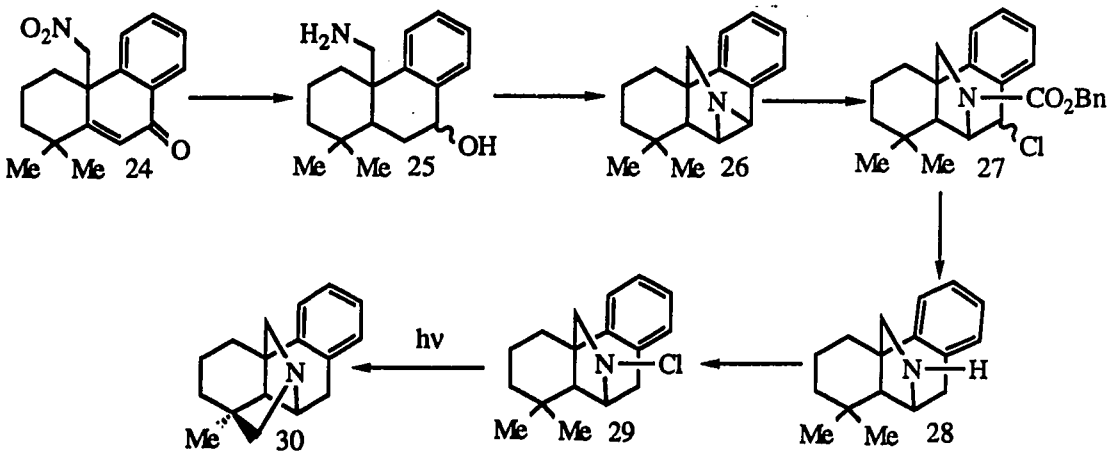
15 16

In a more recent effort Weisner's group developed a methodology that created intermediates to aconitine and napelline, such as lactam 23.[15] The key operation in this method was a formation of an aziridine and its in situ regio and stereospecific rearrangement. Treatment of olefin 17 with trimethylsilylazide resulted in formation of aziridine 18, which rearranged to amide 19 in the presence of acetic acid. It is important to note that the rearrangement required an electron releasing group in the position ortho to the methoxy group. The methyl group was chosen because it could be easily transformed to a phenol. Reduction to the aldehyde 20 and treatment with Grignard 21 generated alcohol 22 which was easily converted to lactam 23.

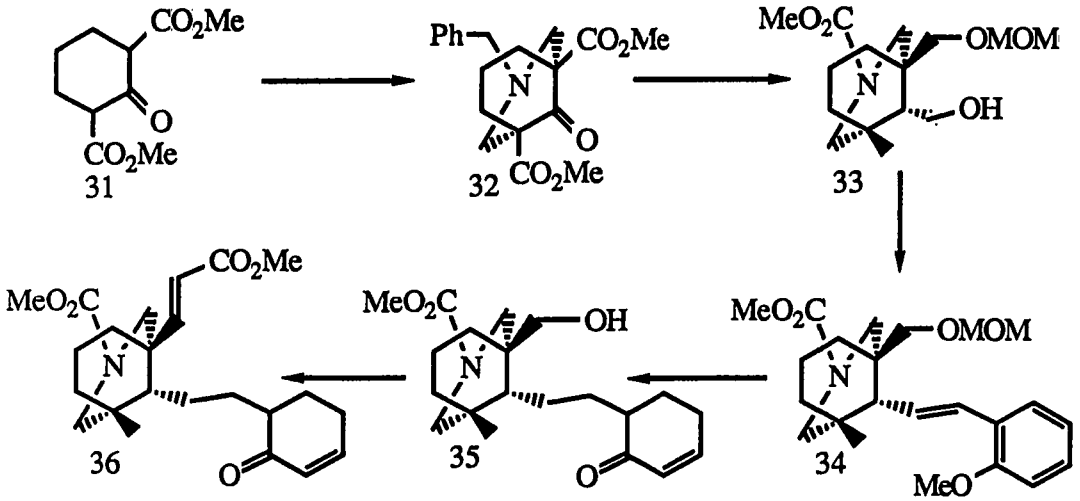


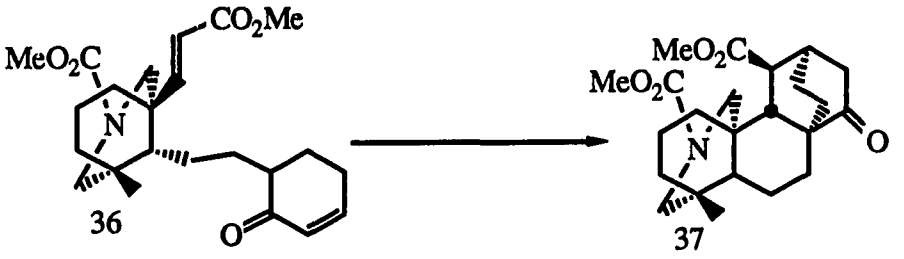
Several reviews on the Aconitum alkaloids chemistry until 1985 have been published.[16,17,18] In the more recent

years the Aconitum alkaloids continue to attract the attention of synthetic chemists. In 1985 Shibanuma and Okamoto reported a synthetic approach to the azabicyclic ring of kobusine.[19] Nitro-methylhydrophementhrone 24 was perceived as an attractive intermediate for the synthesis of the bicyclic structure. Compound 24 was obtained in four steps. Reduction of 24 with H_2/Pd-C, $NaBH_4$ and finally Raney Nickel generated methylamine 25. Dehydration of the alcohol and treatment of the amine with lead tetraacetate furnished aziridine 26. Immediate treatment of 26 with benzyl chloroformate produced stereospecifically carbamate 27. Reduction of 27 afforded amine 28, which was oxidized to the N-chloramine 29 photolysis of the N-chloramine produced the azabicyclic moiety of kobucine in 39% yield. The sequence was fairly direct, but suffered from the low yields, particularly in key reactions.



In 1988 Ihara and coworkers reported a formal total synthesis of atisine.[20] The synthesis was based on a double Mannich-double Michael reaction strategy. Double Mannich reaction of diester 31 with benzylamine and formaldehyde produced azabicyclononene 32, which corresponded to the AE part of the molecule. Several straightforward functional group manipulations generated alcohol 33 which after Swern oxidation to the aldehyde underwent Wittig coupling to yield 34. Hydrolysis of the methylmethoxy ether, hydrogenolysis of the olefin and Birch reduction furnished enone 35. Oxidation and Wittig reaction afforded ester 36, the requisite unit for the double-Michael reaction. The Michael reaction proceeded in modest yield (43%) to furnish the pentacyclic ketone 37 which had been previously transformed to atisine.[21]

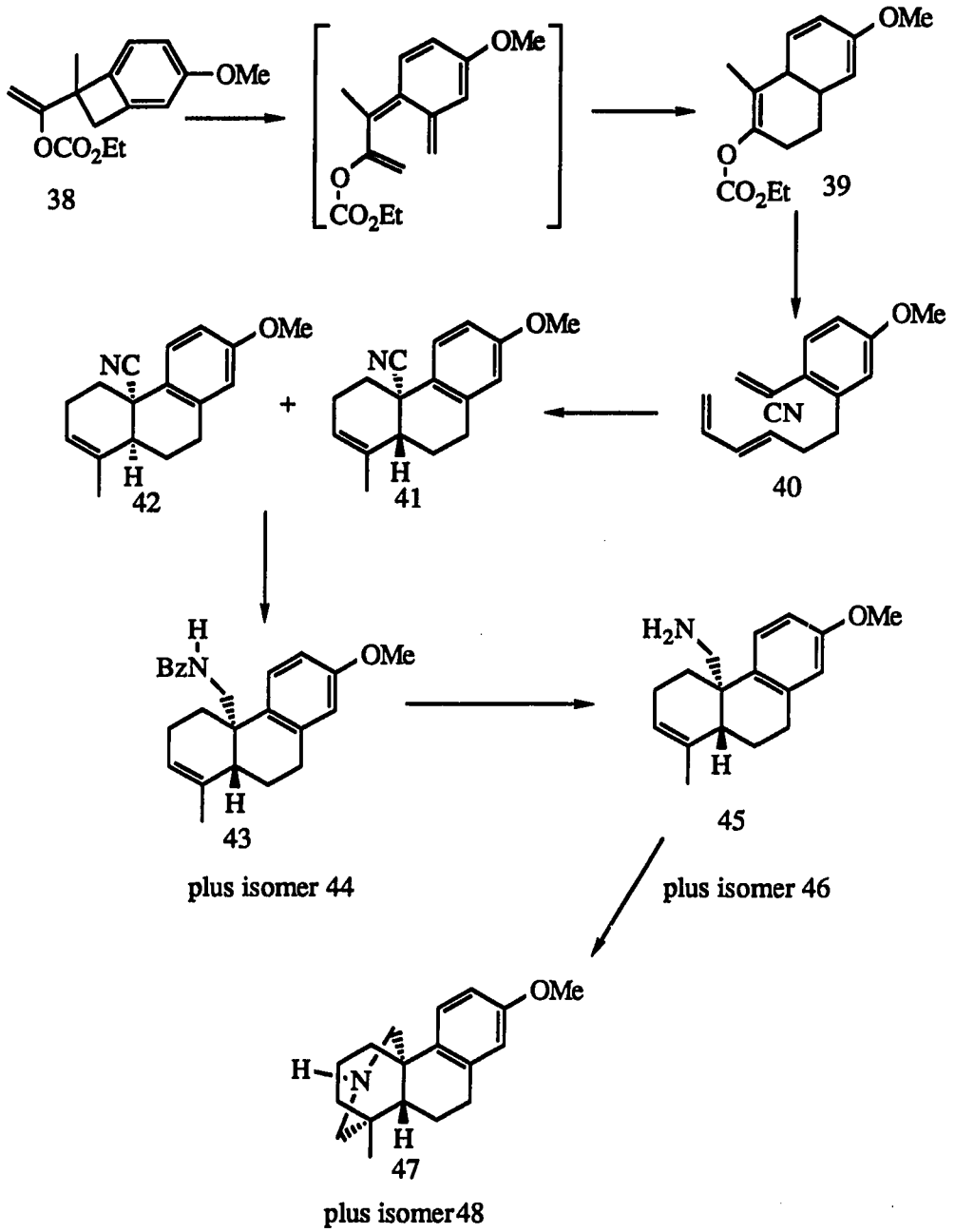




In 1989 Shishido and coworkers reported a synthesis of an advanced intermediate to atisine.[22] The intramolecular Diels-Alder reaction and the intramolecular Mannich condensation were the key steps in the synthesis.

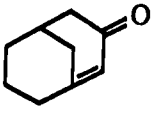
When enol carbamate 38 was heated at 180°C, it produced via a Z-O-quinodimethane the dihydronaphthalene 39. A series of seven steps led to formation of triene 40. Cycloaddition yielded compounds 41 and 42 in nearly equal amounts. Benzoates 43 and 44 were formed next, and subsequent reduction yielded secondary amines 45 and 46. Mannich reaction afforded the cyclic amines 47 and 48 regioselectively. Amine 47 is an intermediate to atisine. The poor stereoselectivity in the Diels-Alder reaction, and

the fairly large number of steps required for the synthesis of the pre-Mannich intermediates are apparent disadvantages of the strategy.



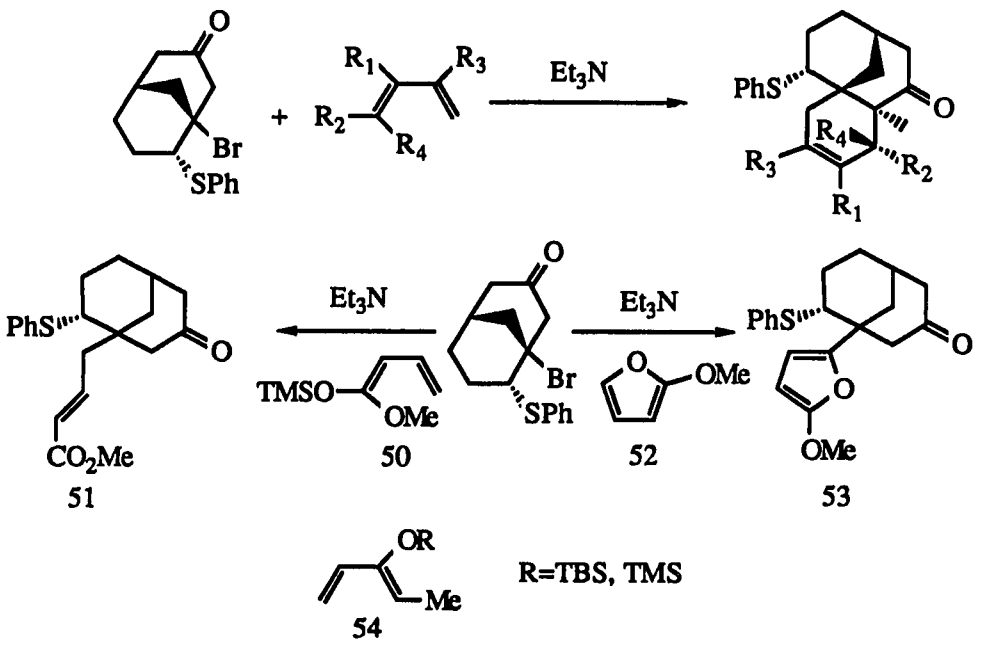
RESULTS AND DISCUSSION

Our interest in the Diels-Alder reaction of electron-rich dienes and activated dienophiles stemmed from the unexpected results which had been obtained in our laboratories, from Diels-Alder reactions of bridgehead enones. Bridgehead enones are extremely reactive dienophiles. Isolation of bridgehead enones even at low temperatures is not possible. Campbell and coworkers have detected bridgehead enone 49 in solution at -78°C. At higher temperatures the compound dimerized.[23] Bridgehead enones are very reactive towards nucleophilic addition and 4 + 2 cycloaddition, because the enone double bond is twisted from planarity by approximately 25°.



49

The regiochemistry and the stereochemistry of the bridgehead enone Diels-Alder reactions have been carefully examined by our group.[24] In situ generation of the enones and reaction with 1,1,3- trisubstituted and 1,3-disubstituted dienes afforded only exo products. Reaction of the in situ generated enone with reactive dienes 50 and 52 produced addition products 51 and 52, respectively.

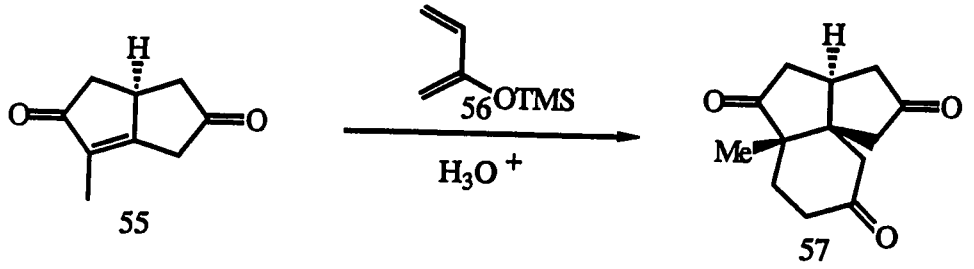


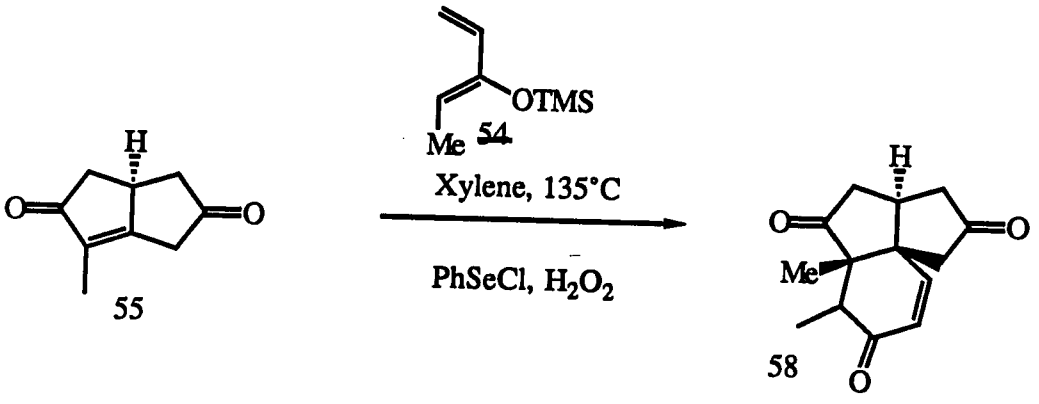
51 50 52 53 54

The Diels-Alder reactions of bridgehead enones could proceed via a polarized or even an ionic transition state. In order to examine the nature of the Diels-Alder reaction of bridgehead enones we constructed diene 54. Diene 54 and similar dienes had been used in Diels-Alder reactions with cyclic ketones. The results indicated that the regiochemistry of the Diels-Alder reaction was controlled by the methyl substituent at C-1.

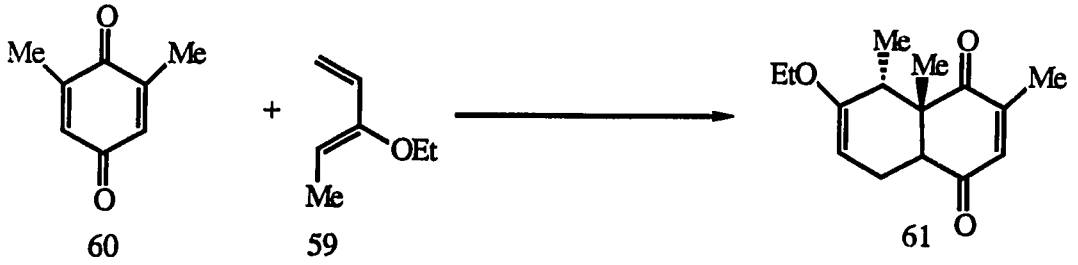
In 1981 during their synthesis of coriolin, Danishefsky's group examined the regiospecificity of the Diels-Alder reactions of enedione 55.[25] Reaction of the enedione with diene 56 produced a single product, which after hydrolysis was identified as triketone 57. When the

enedione was treated with diene 54 the product obtained after selenylation and de-selenylation was enone 58. The results clearly indicated that the methyl substituent at C-1 controlled the regiochemistry.

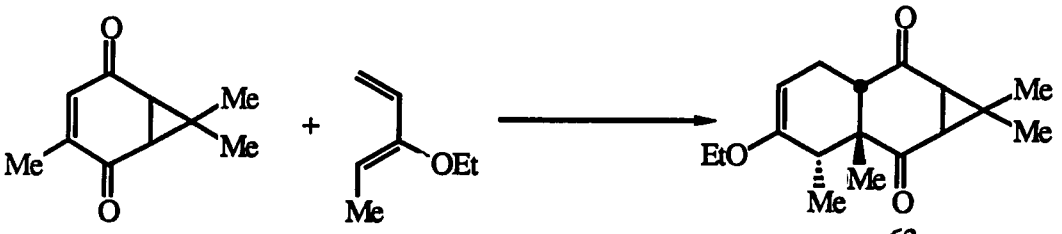




Similar results have been obtained with ethoxy substituted dienes. Schmidt and coworkers reported that the reaction of diene 59 with quinone 60 generated a single product 61.[26]

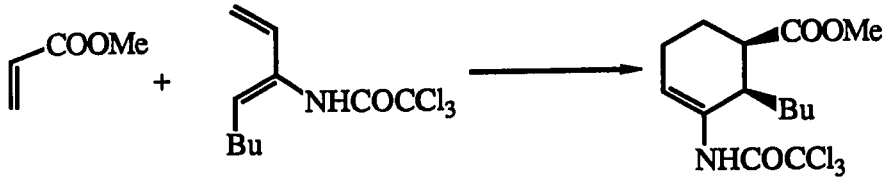


Tricyclic ketone 63 was produced by Yamakawa and coworkers via cycloaddition of 59 and ketone 62. The regiochemistry of the cycloaddition once again was determined by the C-1 substituent.[27]



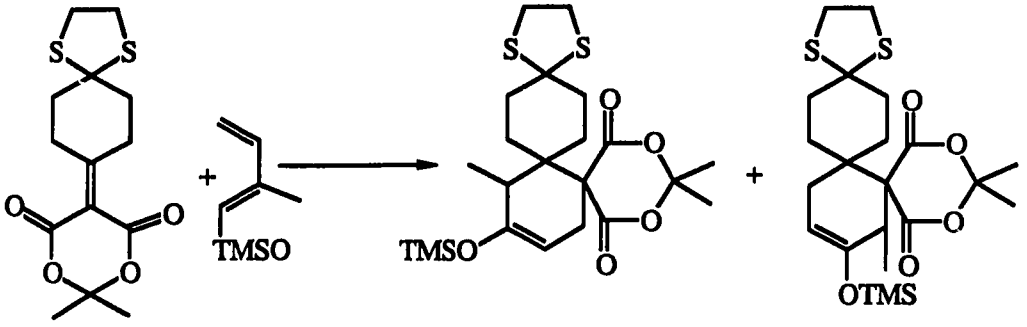
62 59 63

In 1980 Overman reported another example of a Diels-Alder reaction of dienes with heteroatoms at C-2.[28] When diene 64 was treated with methyl acrylate, the major product recovered (>80%) was ester 65. The regiochemical outcome of the reaction was dominated by the alkyl substituent at C-1.



64 65

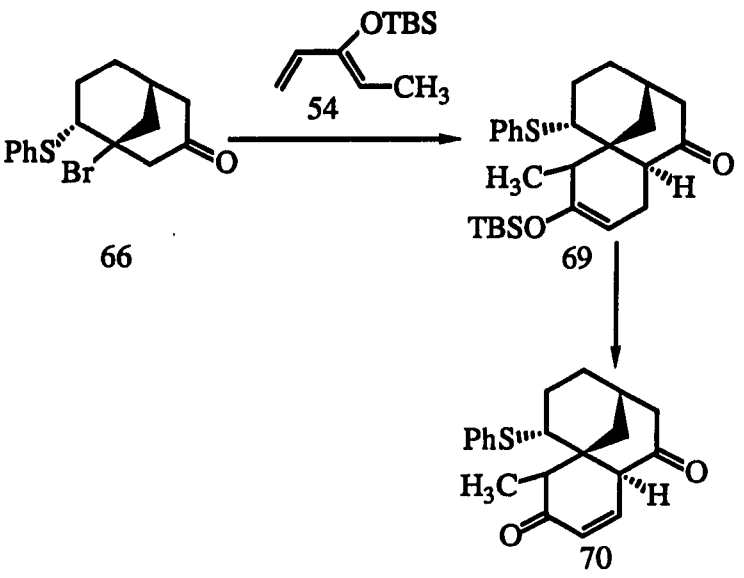
In 1977 Mock and others reported the Diels-Alder reaction of diene 54 and dienophile 66. In this case a 3:2 mixture of products 67 and 68 was obtained, which favored adduct 67.[29] The author failed to account for the selectivity observed.



66 54 67 68

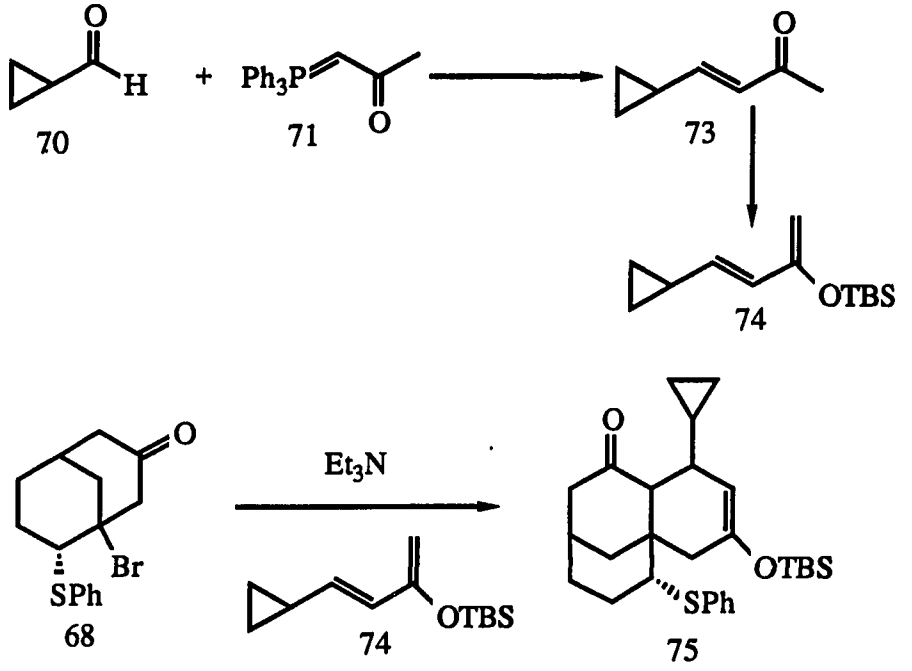
For the reaction of diene 54 with bridgehead enones we reasoned that the silyloxy substituent at C-2 would control the regiochemistry, if the transition state were polarized. Reaction of diene 54 and bridgehead bromide 66 in the presence of triethylamine at 0°C afforded a mixture of products. Treatment of the major adduct with $Pd(OAc)_2$ afforded an enone which was identified as compound 70 from NMR studies.[30] The olefinic pattern in 70 showed an AB quartet in which each peak was doubled. Decoupling studies also supported the structure of compound 70. Irradiation of the methyl doublet at 1.05 ppm resulted in the collapse of the multiplet at 3.1 ppm (assigned to the methine hydrogen α

to the methyl) and the appearance of a sharp singlet. Irradiation of the allylic tertiary hydrogen singlet at 3.7 ppm resulted in the collapse of the olefinic pattern to a simple AB quartet. The minor isomer resisted enone formation with the Saegusa conditions. However, based on decoupling experiments the product was assigned structure 69 also. Irradiation of the methyl doublet at 1.1 ppm resulted in the collapse of the multiplet at 3.0 ppm, and appearance of a sharp singlet.



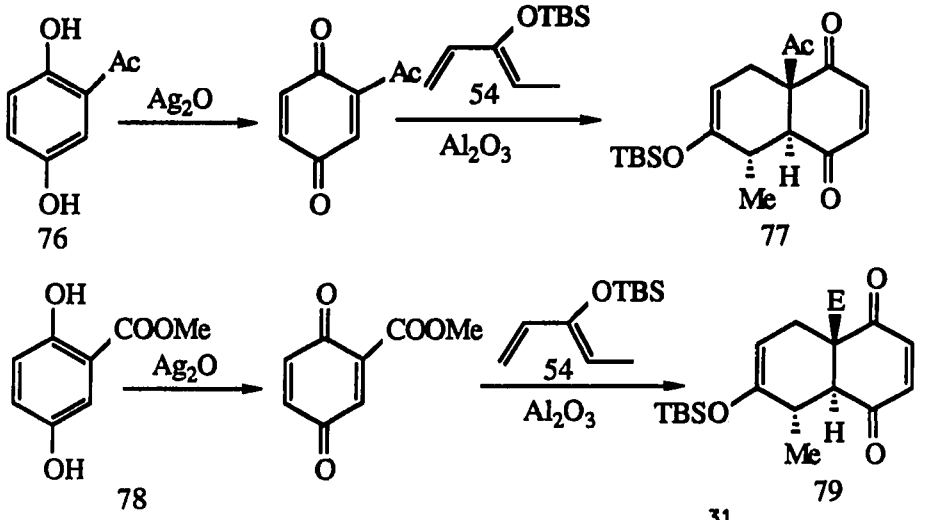
The above results indicated a possible polarized or even ionic transition state for the Diels-Alder reaction. In order to investigate the possibility of an ionic transition state we constructed diene 74. Our reasoning was

that if an ionic transition state occurred, the cyclopropane ring could open via a cyclopropylcarbinyl carbocation rearrangement. Diene 74 was prepared from enone 73 in 87% yield by reaction of 73 with lithium diisopropyl amide and TMSCl. Enone 73 was formed via a Wittig coupling of 71 and 72. The reaction of diene 74 with bridgehead bromide 68 produced ketone 75, in which the cyclopropane ring was intact.



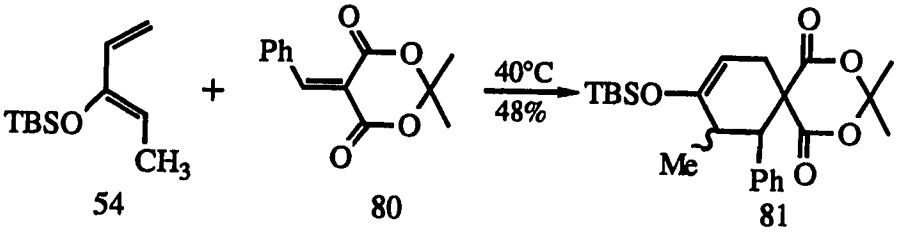
We then proceeded to investigate the Diels-Alder reactions of diene 54 with other activated dienophiles. Reaction of diene 54 with hydroquinone 76 in CH_2Cl_2 at 0°C

generated one single product with structure 77. The structure is supported again by decoupling experiments. When the methyl doublet at 0.8 ppm was irradiated, the multiplet at 2.5 ppm (assigned to the methine α to the methyl group) collapsed to a doublet. When the methine multiplet at 2.5 was irradiated, the doublet assigned to the tertiary hydrogen α to the carbonyl collapsed to a sharp singlet. Similarly, reaction of 54 with hydroquinone 78 produced 79 as a single product.



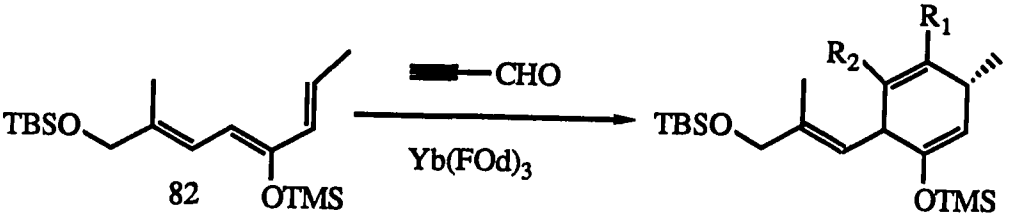
Treatment of diene 54 with compound 80[31] resulted in the formation of a mixture of isomers identified as 81. The structure is supported by NMR spectroscopy. Both isomers exhibit a doublet at 3.4 ppm, assigned to the benzylic methine proton. Irradiation of the benzylic methine at 3.4 in the major isomer resulted in the collapse of the

multiplet at 2.4 (the methine α to the methyl group) and the emergence of a quartet. Irradiation of the vinylic hydrogen resulted in the collapse of the two triplets at 2.8-3.0 ppm assigned as the allylic hydrogens and the generation of two doublets.



Structurally, dienophile 80 is closely related to compound 66 used in Mock's work, as it was described earlier. Recall that in Mock's case a mixture of products was obtained in the Diels-Alder reaction. We believe that two reasons may be responsible for the difference in selectivity of the two substrates. The presence of the phenyl group in 80 could increase the possibility of a polarized transition state existing. The alkyl substituents in dienophile 66 could dictate the formation of product 68 because of steric reasons.

We then decided to examine the Diels-Alder reactions of simple dienophiles including acrolein and cinnamaldehyde with diene 54 in the presence of Lewis acids. We reasoned that coordination of the Lewis acid with the aldehyde carbonyl would polarize the dienophile. We expected to observe Diels-Alder adducts with reversed regiochemistry. In a recent report by Takeda and coworkers, excellent regioselectivity could be achieved in a Diels-Alder reaction of a simple dienophile and a trisubstituted diene 82.[32] The uncatalyzed reaction furnished an undesirable mixture of regioisomers 83 and 84. However, in the presence of a mild Lewis acid product 83 in which the silyloxy substituent directed the cycloaddition was formed almost exclusively.



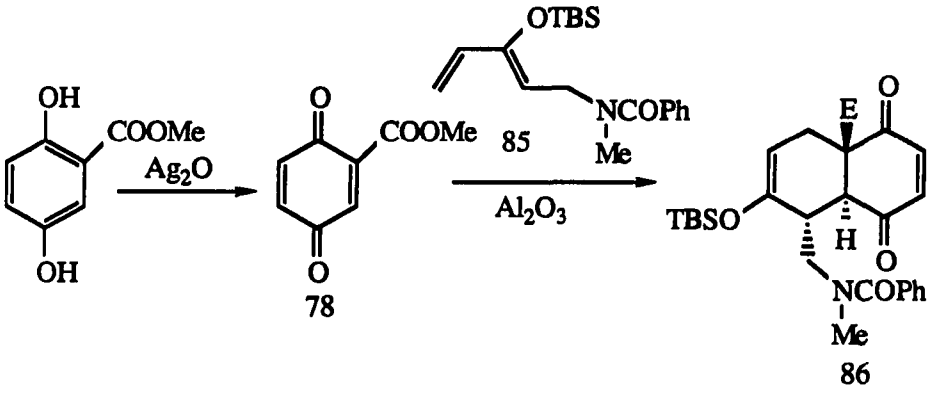
83 R_1=CHO, R_2=H

84 R_1=H, R_2=CHO

We reasoned that this result was due to polarization of the dienophile by coordination with the Lewis acid. Unfortunately, Lewis acid catalyzed reactions of diene 54 with acrolein or cinnamaldehyde, with a variety of Lewis

acids, led to decomposition products.

Next, we switched our attention to the generation of additional dienes, that could participate in reversed regiochemistry Diels-Alder reactions. Diene 85 was readily prepared as described by Levy and coworkers.[33] Treatment of diene 85 with hydroquinone 78 in the presence of silver(I) oxide afforded a single product that was identified as compound 86.

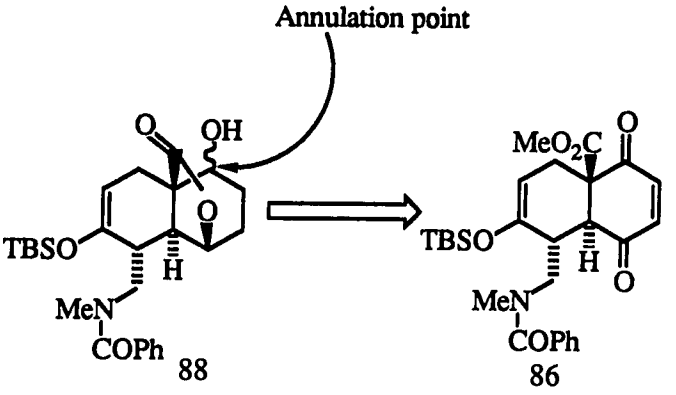


The structure is supported by NMR decoupling experiments. Irradiation of the multiplet at 3.3 ppm, assigned as the tertiary allylic hydrogen, resulted in the collapse of the doublet at 3.5 into a singlet. The doublet at 3.5 was assigned as the methine proton α to the carbonyl.

The Diels-Alder reaction of hydroquinone 78 and appropriately substituted 2-silyloxy dienes afforded an extremely direct entry to the synthesis of the tricyclic

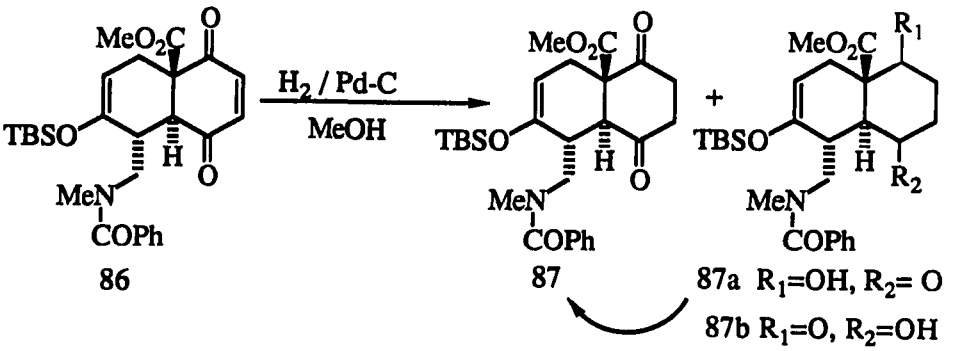
lactam-containing moiety of atisine-type alkaloids.

Initially we considered the product of the reaction of diene 85 and hydroquinone 78 as an attractive intermediate to the above targets. We envisioned that the two carbonyls in ring B could be differentiated via a reduction and in situ lactonization. The secondary alcohol of 88 could then become the handle for an annulation that would assemble ring C. The lactone carbonyl would become the site of an intramolecular nucleophilic attack by an amine to generate the lactam bridge.

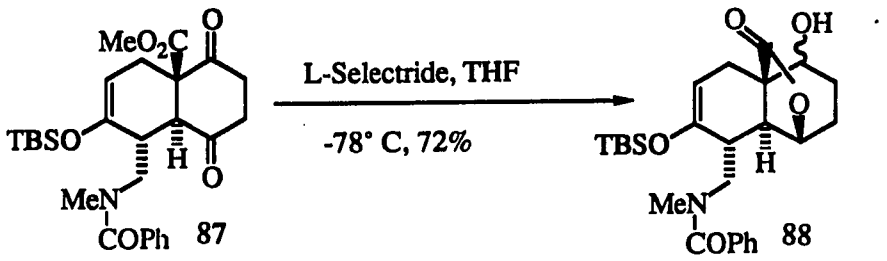


In order to test the feasibility of this strategy, we used the Diels-Alder adduct 86. Catalytic hydrogenation of 86 afforded a mixture of products in which the major compound was diketone 87 (68%). The byproduct in 29% yield

was identified as alcohol 87a or 87b by mass spectroscopy, IR and NMR spectroscopy. Oxidation of the byproduct with chromium trioxide-pyridine complex produced in quantitative yield diketone 87.



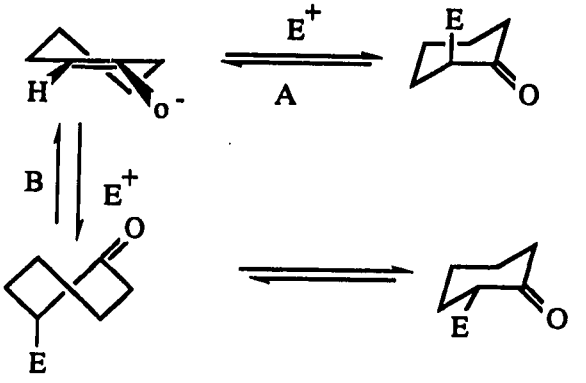
The differentiation of the two ketone carbonyls in a similar system had been accomplished as part of a synthetic approach to quasimarin.[34] L-selectride was the reagent of choice for this operation. L-selectride is known to produce axial alcohols via attack from the equatorial position of a cyclic ketone. Treatment of diketone 87 with L-selectride produced lactone 88 in a 72% yield.



Substrate 86 served well as a model system for this sequence of operations. The stability of the amide unit, however, and the fact that the amide side chain was formed exclusively in an endo orientation from the Diels-Alder reaction, prompted us to revise our strategy. In addition, we needed to revise our strategy to accommodate the introduction of the quaternary methyl group present in the natural products. We determined that a system that included the methyl group and could permit stereoselective introduction of the amine subunit was vital for an efficient synthesis.

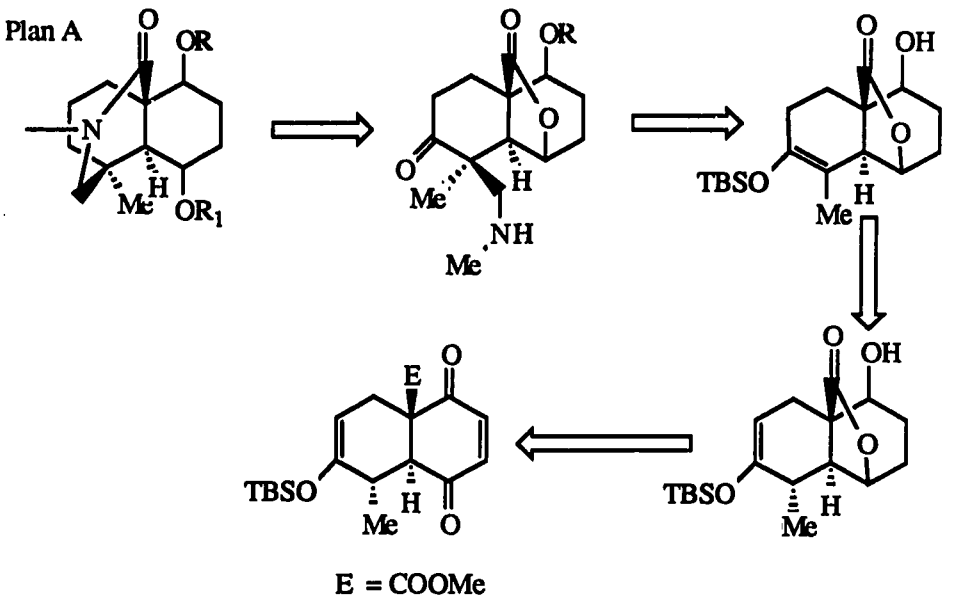
We concluded that compound 79 represented a versatile intermediate toward the synthesis of our tricyclic target. The system contained the required methyl group. Based on consideration of the stereoelectronic effect, we reasoned that the amine unit would be introduced axially. The stereoelectronic effect controls the alkylations of enolate intermediates. Strong evidence exists for the preference of axial attack of electrophiles on enol-silyl ethers.[35] In

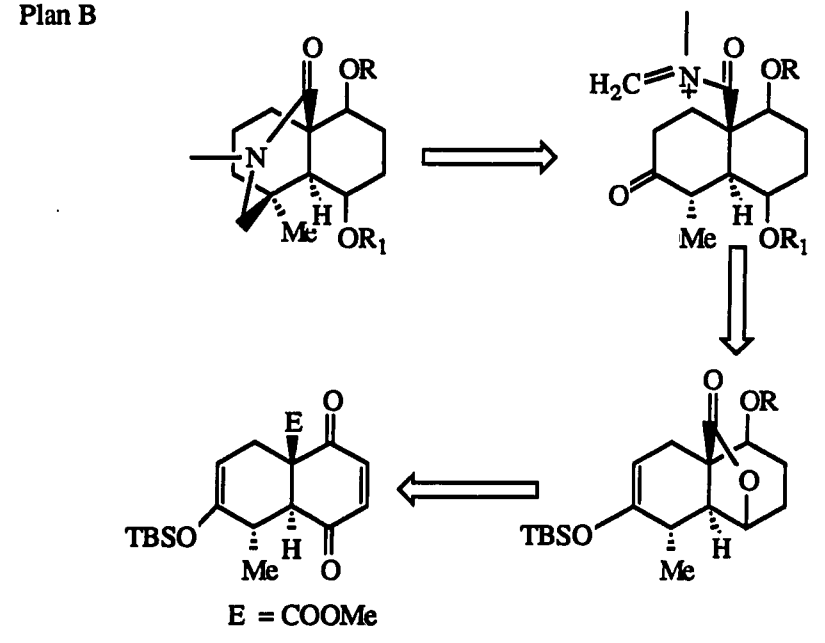
the case of cyclohexanone enolates two possible paths of attack exist.



The difference in stability between the chair-like transition state and the twist boat one, accounts for the observed axial attack of the electrophile.

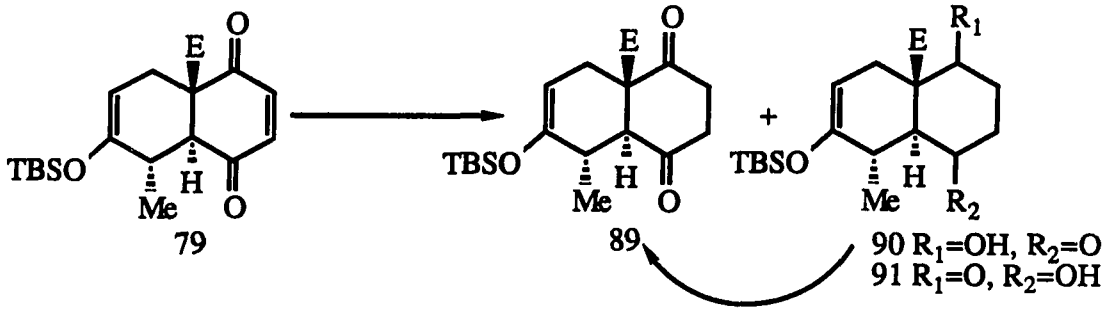
The versatility of 79 stems from the fact that the lactam bridge might also be constructed via an intramolecular closure. Recall that Wiesner's atisine synthesis formed the lactam bridge via regioselective closure of isocyanate 13. We reasoned that similar selectivity could be achieved in the related system 92. The retrosynthetic analyses of both plans are illustrated below:

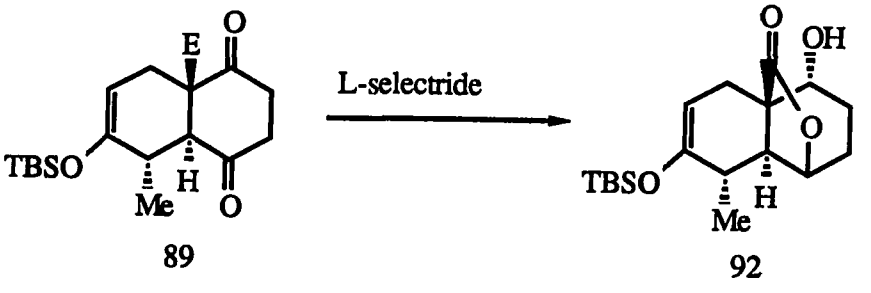




With diketone 79 in hand, we proceeded with plan A of our retrosynthetic analysis. Hydrogenation of 79 produced a

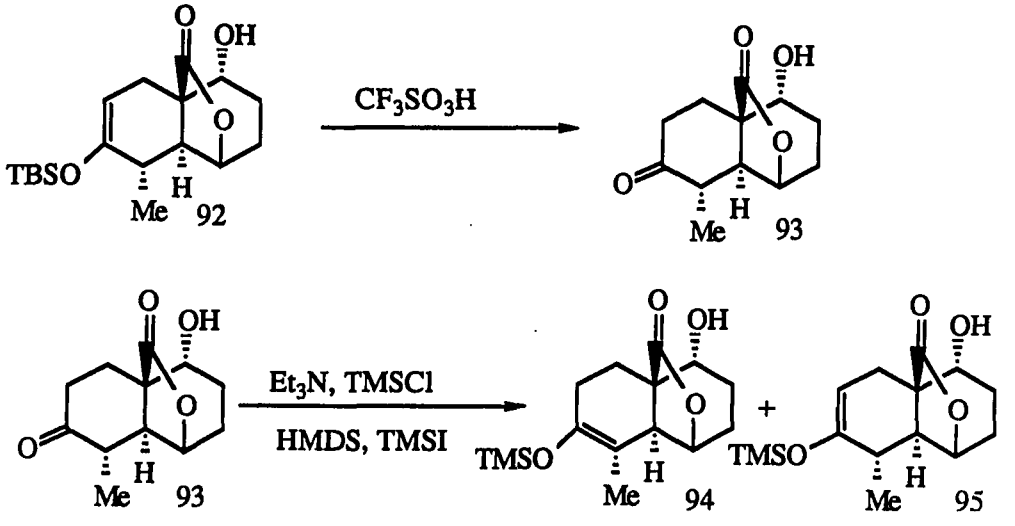
mixture of three compounds. The compounds were identified as ketone 89 (68%), alcohol 90 (12%) and alcohol 91 (6%). In situ treatment of the mixture with CrO_3/pyridine complex produced one compound, ketone 89 in quantitative yield. The L-selectride reduction and lactonization proceeded in 74% yield.





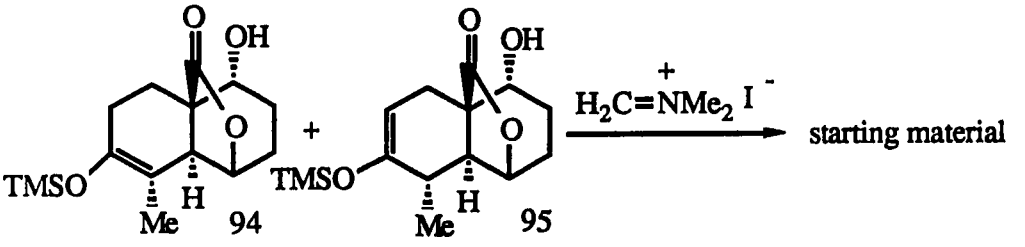
The introduction of the amine unit could be achieved via a Mannich reaction. Isomerization of the enol-silyl

ether 92 was required before the crucial reaction could be tried. Based on a recent report by Scott, we treated enol-silyl ether 92 with a catalytic amount of triflic acid.[36] Unfortunately ketone 93 was recovered in 76% yield, with no trace of the desired thermodynamic enol-silyl ether. Attempts to perform this isomerization with various acid-base complexes including DBU/CH_3COOH, or HMDS/CF_3SO_3H also failed. We then treated ketone 93 with TMSI and HMDS, conditions known to produce the thermodynamic enol-silyl ether.[37] The desired compound 94 was produced in a 4:1 mixture with its kinetic isomer 95, based on NMR spectroscopy.

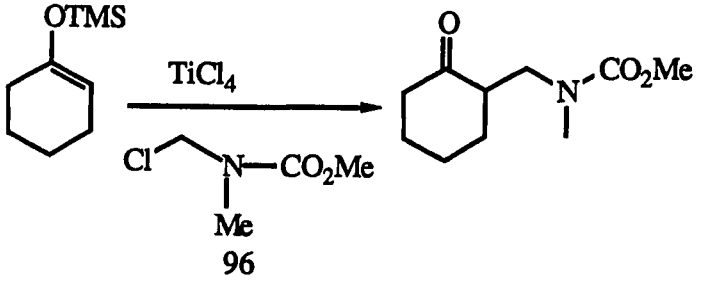


Treatment of the mixture of 94 and 95 with Eschemmoser's salt afforded to our surprise no reaction.

The enol-silyl ether was recovered in quantitative yield.

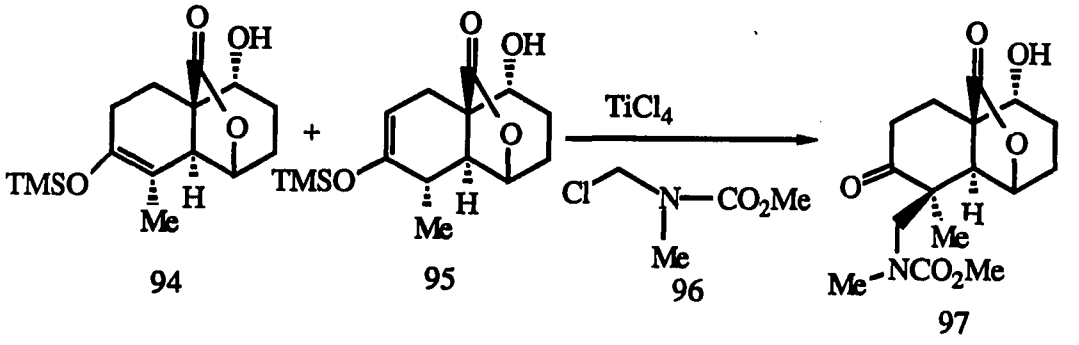


Recently, Danishefsky et al. reported a ureidoalkylation reaction of enol-silyl ethers. In this method the methyl carbamate unit was introduced via treatment of a chloromethyl carbamate with $TiCl_4$, and addition of an enol-silyl ether.[38]



We prepared chloromethyl carbamate 96 by reaction of methylamine with methyl chloroformate and treatment of the product with paraformaldehyde and HCl.[39] The crude product of the reaction was treated with $TiCl_4$ at -78°C, followed by addition of the enol-silyl ether mixture. Only ketone 97 was isolated. The yield of the reaction based on formation

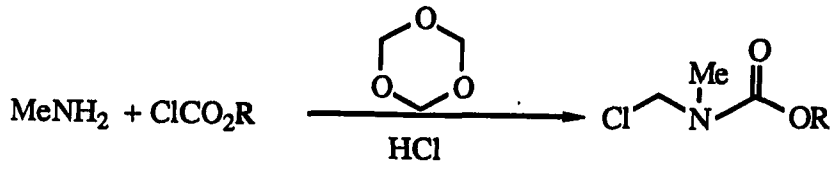
of the enol-silyl ether and ureidoalkylation was 55%-60%. Based on the stereoelectronic effect, we expected to obtain an axial carbamate unit. We reasoned that this argument could be proven chemically. We expected that cleavage of the carbamate group would result in spontaneous closure of the amine to a lactam, thus proving the stereochemistry and providing our tricyclic target.



Unfortunately, treatment of 97 with TMSI or with butanethiol and n-butyllithium according to conditions by Corey et al. yielded none of the desired product.[40] In the first case decomposition products were obtained, probably due to cleavage of the axial lactone. In the second case, starting material was obtained even after heating the reaction mixture at 90°C for 40 hours.

We then decided to form a carbamate that could be cleaved under milder conditions. Carbamates 98 and 99 were

both formed. Unfortunately in both cases ureidoalkylation failed, presumably because of cleavage of the carbamate unit by $TiCl_4$

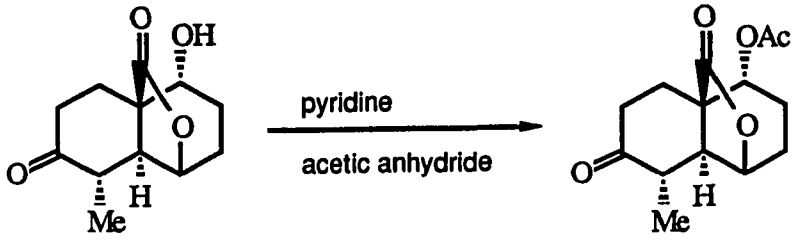


98 $R=CH_2Ph$

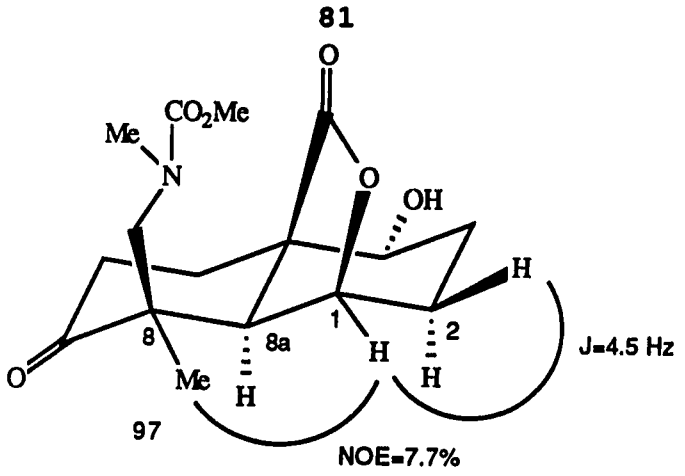
99 $R=CCl_3$

The structure of compound 97 was determined by NOE and two-dimensional NMR experiments. We first intended to locate the position of the methine on the carbon bearing the lactone oxygen. It became obvious from careful examination of lactone 93 that the methine on the carbon bearing the lactone oxygen, and the methine on the carbon bearing the hydroxyl group were located at 4.7 ppm and 3.36 ppm. In order to definitely determine the positions of the two hydrogens, we decided to protect the secondary alcohol as an acetate. We reasoned that protection of the alcohol would result in a downfield shift of the methine on the carbon bearing the alcohol, as it was previously discovered in our laboratories. Treatment of 93 with pyridine and acetic anhydride yielded neatly compound 100. Clearly the acetyl group had been introduced, based on the singlet at 2.1 ppm.

The multiplet at 3.6 had completely disappeared and a new peak had appeared at 4.9 ppm. This led us to the conclusion that the methine on the carbon bearing the lactone oxygen was at 4.7 ppm. Unexpectedly this methine appeared as a doublet with 4.5 Hz coupling constant. One would argue that the splitting pattern should have been more complicated, since coupling could occur by 3 different hydrogens. Molecular models, however, suggested that only splitting by the equatorial hydrogen at C-2 was possible. The axial proton at C-2 and the methine at C-8a were positioned at an 85° angle with respect to the C-1 proton. An 85° dihedral angle translates to zero coupling. The dihedral angle between the C-1 methine and the equatorial methine at C-2 was estimated at 45°. The calculated value for the coupling constant between two methines at such angle is 4.2 Hz. The observed coupling constant value was 4.5 Hz.



93 100



The two-dimensional COSY experiment on compound 97 indicated that the methine at 4.7 ppm was coupled to only one position at 2.2 ppm. We reasoned that a difference NOE experiment would prove the equatorial disposition of the methyl group in 97. We expected that a strong NOE should exist between the methyl group and the methine at C-1, if the methyl group were indeed equatorial. Irradiation of the methyl singlet at 1.1 ppm resulted into an 8% enhancement of the methine at 4.8 ppm. This fact suggested that the ureidoalkylation had proceeded axially, as desired. Plan B is currently being investigated.

EXPERIMENTAL

General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. THF and diethyl ether were distilled from sodium benzophenone ketyl under nitrogen prior to usage. Benzene was distilled from lithium aluminum hydride. Dichloromethane was distilled from calcium hydride. Unless otherwise noted, all reactions were conducted under an argon atmosphere. Unless otherwise noted, all organic extracts were dried over anhydrous sodium sulfate. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-4250 or a Perkin-Elmer model 1320 spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian EM-360 spectrometer. High field (300 MHz) proton spectra were obtained with a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in relative to tetramethylsilane as an internal standard. Coupling constants (J) are reported in Hz. Abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet, ABq = AB quartet. 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 a Kratos model MS-50 spectrometer. Low-resolution mass spectra were recorded on a Finnegan 4023 mass spectrometer. Silica gel used for flash chromatography (72) was 230-400 mesh (Kieselgel 60) purchased from EM Science. Gravity column chromatography was performed on 60-200 mesh silica gel purchased from Davison Chemical (WR Grace Inc.). Elemental analyses were performed by Galbraith Laboratories, Inc.

4-Cyclopropyl-3-butene-2-one 73

To a solution of aldehyde[41] 70 (0.6g, 8.6 mmol) in 10 mL of 1,2 dichloroethane was added the Wittig reagent. The reaction mixture was refluxed for 12 hours. The solution was cooled and concentrated. The crude adduct was purified by flash chromatography with hexanes:ethyl acetate 6:1 to afford 0.4g of enone 73 (43% yield).

NMR ($CDCl_3$): 0.77-0.49 (m, 2H), 1.16-0.84 (m, 2H), 1.70-1.44 (m, 1H), 2.35-1.97 (s, 3H) 6.32-6.01 (m, 2H).

IR ($CDCl_3$): 3050, 3010, 1660, 1610, 1380, 1270, 950 cm^{-1}.

Mass spectrum: m/e 43, 67, 82, 95, 110.

4-Cyclopropyl-2-tertbutyldimethylsilyloxy-1,3-butadiene 74

To a solution of lithium diisopropylamide (2.73 mmol) in 10 mL of tetrahydrofuran at -78°C, and a solution of enone 73 (0.25g, 2.27 mmol) was added dropwise. The reaction was stirred at -78°C for 30 minutes and chlorotrimethylsilane was added next (0.36g, 3.4 mmol). The reaction was stirred at -78°C for 1 hour and at ambient temperature for 30 minutes. It was then concentrated in vacuo, and the residue was dissolved in a mixture of 3:1 hexanes:ether. The precipitate was filtered through celite and the filtrate was concentrated in vacuo to afford 0.35g of enone 74 (85% yield).

NMR ($CDCl_3$): 0.24-0.17 (s, 6H), 0.50-0.35 (m, 2H), 0.87-0.67 (m, 2H), 1.54-1.34 (m, 1H) 4.26-4.06 (d, J=7.2 Hz, 2H), 5.55-5.35 (m, 1H) 6.04-5.86 (d, J=15 Hz, 1H).

IR ($CDCl_3$): 3040, 2970, 1640, 1590, 1310, 1250, 1020, 850, cm^{-1}.

Mass spectrum: m/e 45, 59, 73, 91, 106, 125, 141, 167, 182.

General Procedure for the [4 + 2] Cycloaddition Reactions for Adducts 69 and 75

To a mixture of the bridgeheaded bromide 68 (1 equivalent) and the diene (2-4 equivalent) at 0°C in methylene chloride (2 mL/mmol) triethyl amine (1.2

equivalent) dropwise. The solution was allowed to warm to room temperature slowly over four hours. The precipitate formed was removed by filtration through glass wool. The solution was concentrated in vacuo, and the residue was purified by flash chromatography with 5:1 hexanes:ethyl acetate.

Spectroscopic Data for Adducts 69 and 75

5-Benzesulfenyl-1,4,5,6,7,8,9,10,10a,-nonahydro-4-methyl-3-tertbutyldimethylsilyloxy-4a,8-methanobenzocyclooct-2-ene-10-one 69

Compound 69 was formed in an 82% yield. A varying mixture of diastereomers was obtained (8:2 at best).

NMR ($CDCl_3$): 0.13-0.08 (s, 6H) 0.9-0.86 (s, 9H) 0.98-0.94 (d, J=9 Hz, 3H), 2.43-1.40 (m, 10H), 2.9-2.68 (m, 2H), 3.15-3.06 (m, 1H) 3.35-3.19 (m, 1H), 4.80-4.67 (m, 1H), 7.42-7.18 (m, 5H).

IR ($DCDl_3$): 2960, 2930, 1700, 1460, 1200, 910, 840 cm^{-1}.

High resolution mass sprectrum for $C_{26}H_{38}O_2SiS$: calculated 442.23529; measured 442.23529.

Mass spectrum: m/e 73, 110, 167, 193, 291, 333, 385, 442.

5-Benzenesulfenyl-1-cyclopropyl-1,4,5,6,7,8,9,10,10a-nonahydro-3-trimethylsilyloxy-4a,8-methanobenzocyclooct-2-ene-10-one 75

Adduct 75 was produced in 58% yield.

NMR($CDCl_3$): 0.19-0.10 (s, 9H), 0.75-0.32 (m, 4H), 2.04-1.35 (m, 7H), 2.50-2.23 (m, 4H), 3.07-2.77 (m, 4H), 4.97-4.90 (m, 1H), 7.45-7.16 (m, 5H).

IR($CDCl_3$): 3040, 2960, 1690, 1480, 1450, 1370, 1250, 1180, 840.

High resolution mass spectrum for $C_{25}H_{34}O_2SiS$: calculated 426.20489; measured 426.20530.

Mass spectrum: m/e 73, 95, 110, 167, 185, 205, 233, 247, 273, 275, 288, 317, 368, 385, 411, 426.

5-Benzesulfenyl-3,4,5,6,7,8,9,10,10a-nonahydro-4-methyl-4a,8-methanobenzocyclooct-1-ene-3,10-dione 70

To a solution of 69 (0.20g, 0.45 mmol) in 2 mL of acetonitrile at ambient temperature was added palladium acetate. The reaction mixture was stirred at ambient temperature for 6 hours and then filtered through celite. The residue was concentrated in vacuo. Purification by flash chromatography with 3:1 hexanes:ethyl acetate afforded 0.12g of 70 (82% yield).

NMR ($CDCl_3$): 1.2-1.05 (d, J=7 Hz, 3H), 1.68-1.42 (m, 4H), 1.92-1.75 (m, 2H) 2.39-2.21 (m, 2H), 3.75-3.68 (broad S, 1H), 6.34-6.15 (d of ABq, 2H), 7.41-7.16 (m, SH).

IR ($CDCl_3$): 2950, 1710, 1670, 1380, 1020, 830, cm^{-1}.

C-13 NMR ($CDCl_3$): 26.1, 27.4, 30.4, 32.5, 45.7, 47.0, 48.1, 52.6, 55.7, 55.8, 100.1, 127.9, 129.8, 130.4, 133.5, 144.8, 200.7, 210.6.

High resolution mass spectrum for $C_{20}H_{20}O_2S$: calculated 306.13406; measured 326.13333.

Mass spectrum: m/e 67, 77, 91, 110, 121, 147, 175, 188, 216, 308, 326.

General Procedure for the [4 + 2] Cycloadditions for Adducts 76, 79, and 86

To a solution of the hydroquinone (1 equivalent) in methylene chloride (2 mL/mmol), in a light-protected flask at 0°C, was added Ag_2O. The reaction mixture was stirred for 30 minutes and a 1M solution of the diene (2-4 equivalents) in methylene chloride was added next. The reaction mixture was stirred for 30 minutes at 0°C, and overnight at ambient temperature. The mixture was filtered then through celite and the filtrate was collected and concentrated in vacuo. The adduct was purified by flash chromatography with hexanes:ethyl acetate. In situ

epimerization occurred by passage through a basic alumina column.

Spectroscopic Data for Adducts 76, 79, and 86

1-[6-(tertbutyldimethylsilyl)oxy-4a,5,8,8a-α-tetrahydro-8α-methyl-1,4-dioxo-2-naphthylethan-1-one 76

NMR ($CDCl_3$): 0.18-0.06 (s, 6H), 0.96-0.80 (m, 12H), 1.62-1.48 (m, 1H), 2.09-1.98 (s, 3H), 2.62-2.47 (m, 1H), 3.41-3.18 (dd, J=5 Hz, 1H) 3.68-3.53 (d, J=6.9 Hz, 1H), 4.83-4.57 (m, 1H), 6.81-6.6 (ABq, J=10 Hz, 2H).

IR ($CDCl_3$): 2940, 1710, 1690, 1360, 1280, 840, cm^{-1}.

High resolution mass spectrum for $C_{19}H_{28}O_4Si$: calculated 348.17569; measured 348.17519.

Mass spectrum: m/e 59, 73, 91, 117, 135, 249, 277, 305, 348.

Orange solid, melting point 117-119°C.

Methyl-6-(tertbutyldimethylsilyl)oxy-4a,5,8,8a-α-tetrahydro-8α-methyl-1,4-dioxonaphthalene-4a-β-carboxylate 79

NMR ($CDCl_3$): 0.06-0.05 (s, 3H), 0.10-0.09 (s, 3H), 1.09-0.76 (s, 9H), 1.39-1.11 (d, J=6.6 Hz, 3H), 2.45-2.36 (m, 1H), 2.91-2.82 (m, 1H), 3.10-2.92 (dd, J=6.6 Hz) 3.63-3.62 (s, 3H) 3.69-3.64 (d, J=14 Hz, 1H), 4.8-4.7 (m, 1H), 6.89-6.73 (ABq, J=10 Hz, 2H).

IR ($CDCl_3$): 2950, 2870, 1730, 1680, 1380, 1240, 1040, 840, cm^{-1}.

C-13 NMR ($CDCl_3$): -4.9, -4.2, 7.8, 18.0, 19.0, 25.13, 25.7, 28.0, 33.9, 53.6, 56.7, 62.9, 99.3, 137.3, 142.8, 153.5, 169.0, 193.6, 195.6.

High-resolution mass spectrum for $C_{10}H_{28}O_5Si$: calculated 364.17061; measured 364.17049.

Mass spectrum: m/e 59, 73, 89, 129, 141, 171, 219, 247, 257, 275, 289, 305, 364.

Methyl-6-(tertbutyldimethylsilyl)oxy-4a,5,8,8a-α-tetrahydro-8α-(methyl-N-methylbenzamide)-1,4,-dioxonaphthalene-4a-β-carboxylate 86

NMR ($CDCl_3$): 0.11-0.10 (s, 3H), 0.15-0.14 (s, 3H), 0.94-0.90 (s, 9H), 2.51-2.45 (m, 1H), 3.01-2.97 (m, 1H) 3.06-3.04 (s, 3H), 3.35-3.28 (m, 1H), 3.59-3.35 (d, J=8.5, Hz, 1H), 3.66-3.60 (s, 3H), 3.79-3.71 (dd, J=6.3 Hz, 1H), 4.26-4.16 (dd, J=2.7, 1H), 5.05-4.94 (m, 1H), 6.88-6.53 (ABq, J=10.2, 2H), 7.41-7.26 (m, 5H).

IR ($CDCl_3$): 3050, 2950, 1720, 1660, 1620, 1400, 1300, 1190, 840 cm^{-1}.

C-13 NMR ($CDCl_3$): -8.0, -6.5, 17.6, 25.3, 25.4, 27.6, 38.6, 38.7, 39.3, 49.2, 52.4, 53.0, 62.7, 95.8, 102.2, 126.4, 126.8, 128.0, 129.1, 136.2, 137.0, 142.5, 150.2, 168.7,

172.9, 193.0, 195.2.

High resolution mass spectrum for $C_{27}H_{35}NO_6Si$: calculated 497.22338; measured 497.22288.

Mass spectrum: m/e 59, 77, 105, 148, 192, 233, 303, 330, 362, 397, 440, 482, 497.

3,3,10-trimethyl-2,4-dioxa-11-phenyl-9-tertbutyldimethyl-silylspiro[5.5]undecan-8-ene-1,5-dione 81

A solution of 80 (0.35g, 1.5 mmol) and 54 (0.87g, 4.4 mmol) in 8 mL of benzene was sealed in a degassed glass tube. The solution was heated to 40°C for 12 hours. The reaction mixture was cooled and concentrated in vacuo. The residue was purified by flash chromatography with 8:1 hexanes:ethyl acetate to afford 0.31g of 81 (48% yield).

NMR ($CDCl_3$): 0.04-0.01 (s, 6H), 0.075-0.068 (d, J=6 Hz), 1.48-1.46 (s, 3H) 1.55-1.53 (s, 3H), 2.37-2.25 (m, 1H), 2.54-2.49 (m, 1H), 2.78-2.67 (m, 1H), 3.31-3.20 (d, J-8 Hz), 4.79-4.71 (m, 1H), 7.19-7.02 (m, 5H).

IR ($CDCl_3$): 2950, 1770, 1370, 1290, 1200, 870 cm^{-1}.

High resolution mass spectroscopy for $C_{24}H_{34}O_5Si$: calculated 430.21756; measured 430.21710.

Mass spectrum: m/e 75, 91, 128, 143, 203, 243, 300, 344, 372, 430.

General Procedure for the Hydrogenation Reaction for Adducts 87 and 89

To a solution of the dienone (1 equivalent) in ethanol (4 mL/mmol) was added 10% palladium on carbon catalyst (0.1 equivalent). The reaction mixture was degassed. The solution was stirred under H_2 atmosphere at room temperature for 2 hours. The mixture was filtered through celite carefully and the filtrate was concentrated in vacuo. The adduct was purified by flash chromatography with hexanes-ethyl acetate to afford the desired dione and variable amounts of biproducts. The mixture of products was oxidized with CrO_3/pyridine[42] to produce quantitatively the dione.

Spectroscopic Data for Adducts 87 and 89

Methyl-2,3,5,8,8a-α-pentahydro-8α-(methyl-N-methylbenzamide)-1,4-dioxo-7-tertbutyldimethylsilyloxynaphtalene-4a-β-carboxylate 87

Compound 87 was obtained in 90% yield.

NMR ($CDCl_3$): 0.08-0.6 (s, 3H), 0.11-0.09 (s, 3H), 0.88-0.85 (s, 9H), 2.40-2.28 (m, 1H), 3.85-2.20 (m, 5H), 3.90-3.88 (s, 3H), 3.17-3.06 (m, 1H) 3.46-3.40 (d, J=8.4 Hz, 1H), 3.61-3.59 (s, 3H), 3.73-3.62 (dd, J=6.3 Hz, 1H), 4.12-4.03 (m, 1H), 4.98-4.94 (m, 1H), 7.38-7.21 (m, 5H).

IR ($CDCl_3$): 3020, 2970, 1720, 1660, 1410, 1190, 840 cm^{-1}.

C-13 NMR ($CDCl_3$): -8.0, -6.5, 17.8, 25.6, 25.7, 25.9, 28.7, 35.8, 36.9, 38.9, 39.4, 49.6, 52.4, 52.9, 60.9, 102.7, 126.4, 128.3, 129.2, 136.5, 150.1, 169.1, 173.0, 203.3, 204.3.

High resolution mass spectrum for $C_{27}H_{37}NO_8Si$: calculated 499.23903; measured 499.23866.

Mass spectrum: m/e 77, 105, 118, 148, 341, 364, 399, 442, 484, 499.

Methyl-2,3,5,8,a-α-pentahydro-8α-methy-1,4-dioxo-7-tertbutyldimethylsilyloxynaphthalene-4a-β-carboxylate 89

Compound 89 was obtained in 84% yield.

NMR ($CDCl_3$): 0.01-0.009 (s, 3H), 0.06-0.05 (s, 3H), 0.9-0.8 (s, 9H), 1.18-1.15 (d, J=6 Hz, 3H), 2.34-2.16 (m, 1H), 3.03-2.40 (m, 7H), 3.70-3.43 (s, 3H), 4.78-4.68 (m, 1H).

IR ($CDCl_3$): 2950, 1720, 1660, 1620, 1400, 1190, 1060, 840 cm^{-1}.

C-13 NMR ($CDCl_3$): -5.81, -4.2, 17.9, 18.7, 25.1, 25.6, 25.8, 26.9, 33.1, 36.1, 36.6, 52.9, 56.3, 60.7, 99.6, 153.27, 169.1, 203.5, 204.19.

High-resolution mass spectrum for $C_{19}H_{30}O_5Si$: calculated 366.18626; measured 366.18645.

Mass spectrum: m/e 73, 89, 129, 147, 175, 203, 231, 249, 279, 309, 335, 351, 366.

General Procedure for the L-selectride Reduction for Adducts 88 and 92

A 1 M solution of the starting material in THF was added dropwise over 20 minutes to a 1 M solution of L-selectride (5 equivalents) in tetrahydrofuran at -78°C. The reaction mixture was stirred at -78°C for 3 hours and then at room temperature for 6 hours. The excess hydride was quenched with water. The reaction mixture was cooled to 0°C. A 3 M solution of NaOH was added (10 equivalents), followed by the addition of an equal volume of 30% hydrogen peroxide. The addition of the peroxide was monitored so the temperature of the reaction would not exceed 25°C. The reaction mixture was stirred at room temperature for thirty minutes. It was then poured into water and extracted with ether. The ether layer was washed with brine, dried and concentrated in vacuo. The adduct was purified with hexanes:ethyl acetate.

Spectroscopic Information for Adducts 88 and 92

7-tertbutyldimethylsilyloxy-1,3,4,5,8,8a-α-hexahydro-4α-hydroxy-8α-methyl-1β,4a-β-(epoxymethano)naphthalene-9-one 92

Compound 92 was obtained in 74% yield.

NMR ($CDCl_3$): 0.08-0.04 (s, 3H), 0.11-0.09 (s, 3H), 0.96-0.81 (s, 9H), 1.16-1.06 (d, J=6.9 Hz, 3H), 1.74-1.44 (m,

3H), 2.38-1.88 (m, 5H), 2.87-2.63 (m, 1H), 3.71-3.51 (m, 1H), 4.51-4.34 (d, J=4 Hz, 1H), 4.82-4.70 (m, 1H).

IR ($CDCl_3$): 2960, 2950, 1770, 1460, 1220, 1040, 860, 840 cm^{-1}.

C-13 NMR ($CDCl_3$): -4.5, -3.9, 17.5, 18.1, 25.1, 25.2, 25.7, 27.6, 28.7, 28.9, 33.9, 50.0, 52.3, 73.6, 79.6, 100.2, 151.1, 177.7.

High-resolution mass spectrum for $C_{18}H_{30}O_4Si$: calculated 338.19135; measured 338.19124.

Mass spectrum: m/e 59, 75, 91, 105, 117, 135, 157, 169, 219, 235, 253, 281, 320, 338.

Elemental analysis calculated for $C_{18}H_{30}O_4Si$: C, 63.86; H, 8.93. Found C, 64.30; H, 9.09.

White solid, melting point 104-106°C.

7-tertbutyldimethylsilyloxy-1,3,4,5,8,8a-α-hexahydro-4α-hydroxy-8α-(methyl-N-methylbenzamide)-1β,4a-β-(epoxymethano)naphthalene-9-one 89

Compound 89 was obtained in 73% yield.

NMR ($CDCl_3$): 0.5-0.4 (s, 3H), 0.58-0.52 (s, 3H), 0.92-0.88 (s, 9H), 1.78-1.52 (m, 3H), 2.48-2.15 (m, 5H), 2.88-2.75 (m, 1H), 3.01-2.98 (s, 3H), 3.69-3.53 (m, 1H), 4.1-3.7 (d of ABq, 2H), 4.51-4.49 (d, J=4 Hz, 1H), 4.95-4.9 (m, 1H), 7.45-7.26 (m, 5H).

IR ($CDCl_3$): 3020, 2950, 1770, 1660, 1620, 1250, 900 cm^{-1}.

Mass spectrum: m/e 77, 91, 105, 148, 192, 295, 355, 414, 446, 471.

White solid, melting point 89-91°C.

1,3,4,5,6,8,8a-α-heptahydro-4α-hydroxy-8α-methyl-1β,4a-β-(epoxymethano)naphthalene-7,9-dione 93

To a solution of 92 (0.3g, 0.86 mmol) in 5 mL of tetrahydrofuran was added triethylammonium hydrofluoride (0.2g, 1.7 mmol). The reaction was stirred at room temperature for 6 hours. The solution was concentrated in vacuo, and purified by flash chromatography with 2:1 hexanes:ethyl acetate to afford 0.15g of 93 (76% yield).

NMR ($CDCl_3$): 1.26-0.99 (d, J=8.7 Hz, 3H), 1.96-1.47 (m, 4H), 2.50-2.03 (m, 6H), 2.96-2.70 (m, 1H), 3.76-3.52 (m, 1H), 4.61-4.77 (d, J=4.5 Hz, 1H).

IR ($CDCl_3$): 2950, 1770, 1710, 1140, 1060, 940 cm^{-1}.

C-13 NMR ($CDCl_3$): 12.1, 27.8, 28.6, 37.8, 42.9, 52.0, 56.7, 73.3, 77.9, 176.5, 210.5.

High-resolution mass spectrum for $C_{12}H_{16}O_4$: calculated 224.10486; measured 224.10495.

Mass spectrum: m/e 55, 67, 81, 95, 125, 143, 168, 196, 206, 224.

Elemental analysis for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found C, 63.43; H, 7.25.

White solid, melting point 157-158°C.

1,3,4,5,6,8a,-α-hexahydro-4α-hydroxy-8α-methyl-8β-(methyl-N-methyl methylcarbamate)-1β,4a-β-(epoxymethano)naphthalene-7,9-dione 97

To a solution of 93 (0.16g, 0.672 mmol) in 5 mL of methylene chloride at 0°C was added triethylamine (0.08g, 0.79 mmol) and chlorotrimethylsilane (0.10g, 1.0 mmol). The reaction was stirred at 0°C for 1 hour and at room temperature for 6 hours. To the solution was added HMDS (0.24g, 1.48 mmol). The reaction was stirred at room temperature for 30 minutes. Iodotrimethylsilane was then added (0.13g, 0.67 mmol) at 0°C. The reaction was allowed to warm to room temperature over 1 hour, where it was stirred for 12 hours. The reaction mixture was added to a solution of carbamate 96 (0.19g, 1.36 mmol) and $TiCl_4$ (0.26g, 1.36 mmol) in 2 mL of methylene chloride at -78°C. The reaction was stirred at -78°C for 1 hour, where it was quenched by addition of water. The water layer was extracted with methylene chloride. The organic layer was washed with brine, dried and concentrated in vacuo. Purification by flash chromatography with 1:3 hexanes:ethyl

acetate afforded 0.12g of 97 (55% yield, 2 steps).

NMR ($CDCl_3$): 1.1-1.02 (s, 3H), 1.9-1.4 (m, 4H), 2.62-2.05 (m, 6H), 2.92-2.88 (s, 3H), 3.63-3.38 (ABq, J=10 Hz, 2H), 3.72-3.65 (s, 3H), 3.79-3.74 (m, 1H), 4.91-4.89 (d, J=4.5 Hz, 1H).

IR ($CDCl_3$): 2950, 1770, 1740, 1720, 1610, 1430, 1160, 840 cm^{-1}.

High-resolution mass spectrum for $C_{16}H_{23}NO_6$: calculated 325.15254; measured 325.15219.

Mass spectrum: m/e 58, 79, 102, 190, 237, 266, 294, 325.

4α-Acetoxy-1,3,4,5,6,8,8a-α-heptahydro-8α-methyl-1β,4a-β-(epoxymethano)naphthalene-7,9, dione 100

To a solution of 93 (0.01g, 0.044 mmol) was added in 1 mL of methylene chloride was added pyridine (0.005g, 0.07 mmol) and acetic anhydride (0.07g, 0.07 mmol). The solution was stirred at room temperature overnight. The solution was concentrated in vacuo, and the residue was passed through a short column with 1:3 hexanes:ethyl acetate to afford 0.01g of 100 (90% yield).

NMR ($CDCl_3$): 1.15-1.05 (d, J=6.3 Hz, 3H), 1.89-1.60 (m, 4H), 2.11-2.02 (s, 3H), 2.48-2.12 (m, 5H), 2.68-2.55 (m, 1H), 4.60-4.52 (d, J=4.5 Hz, 1H), 4.92-4.82 (m, 1H).

IR ($CDCl_3$): 2950, 1770, 1740, 1720, 1290, 1155, 1040, 980, 940 cm^{-1}.

High-resolution mass spectrum for $C_{14}H_{18}O_5$: calculated 266.1154; measured 266.1157.

Mass spectrum: m/e 53, 79, 105, 143, 178, 224, 266.

White solid, melting point 169-170°C.

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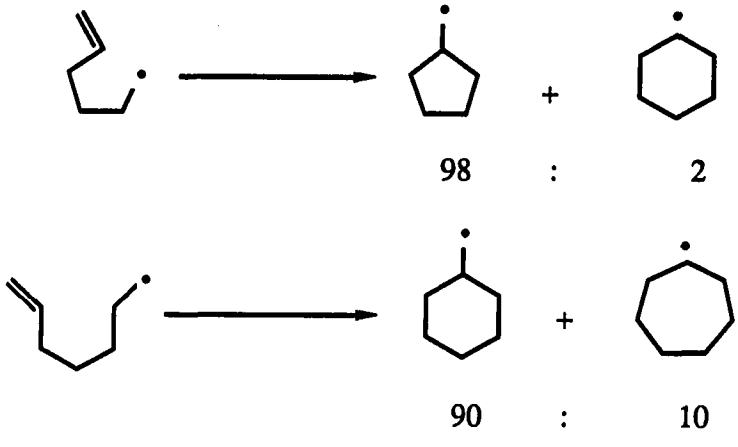
SECTION III. ORGANOSILICON RADICAL INDUCED CYCLIZATIONS

INTRODUCTION

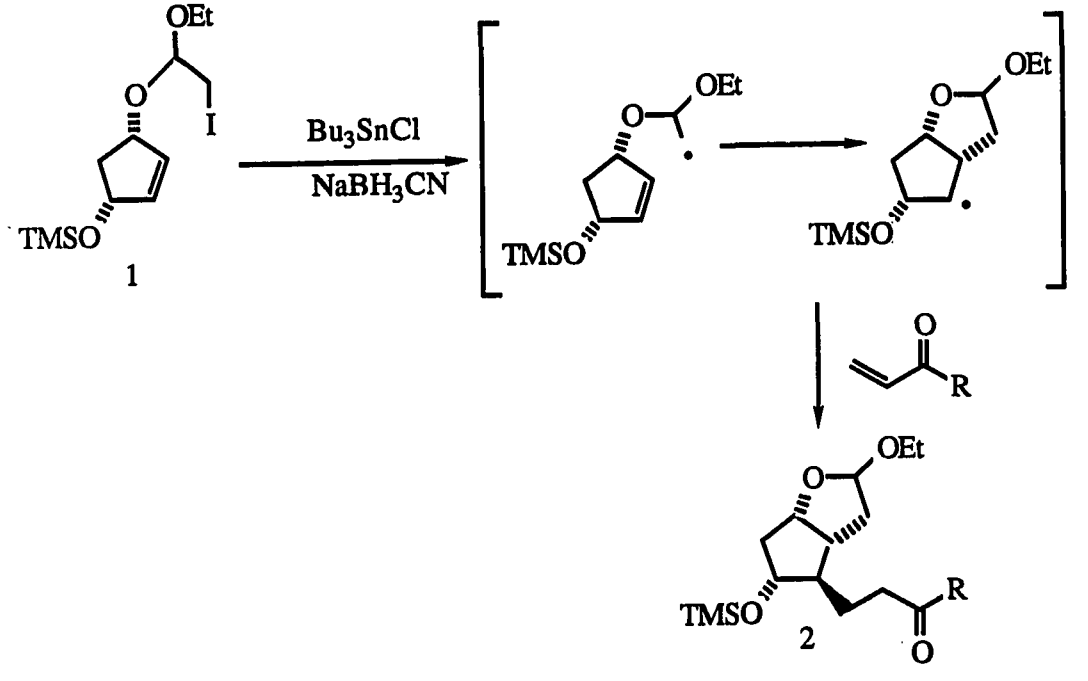
In the last decade the utility of intramolecular radical cyclizations in synthetic organic chemistry has increased tremendously. The cyclizations of the 5-hexenyl and 5-heptenyl radical systems are known to proceed with high regioselectivity. The thermodynamically less stable, smaller size rings are obtained from these operations.

Unlike cationic cyclizations, radical cyclizations favor an unsymmetrical transition state. In the transition state the distances between the radical center and the two ends of an olefin are not equal. According to Beckwith, this unsymmetrical transition state and the ring strain effects lead to faster cyclizations and to formation of the smaller rings.[1]

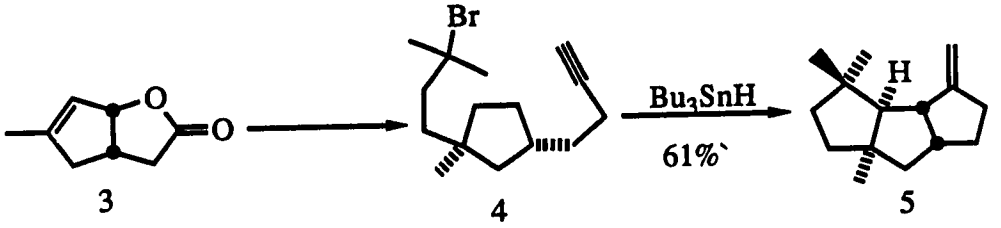


Organotin radicals are widely used today in synthetic organic chemistry. Reagents such as tributyltin hydride and triphenyltin hydride have been commonly used for the construction of complex ring systems. Several elegant sytheses of natural products have been produced based on organotin radical-induced cyclizations.

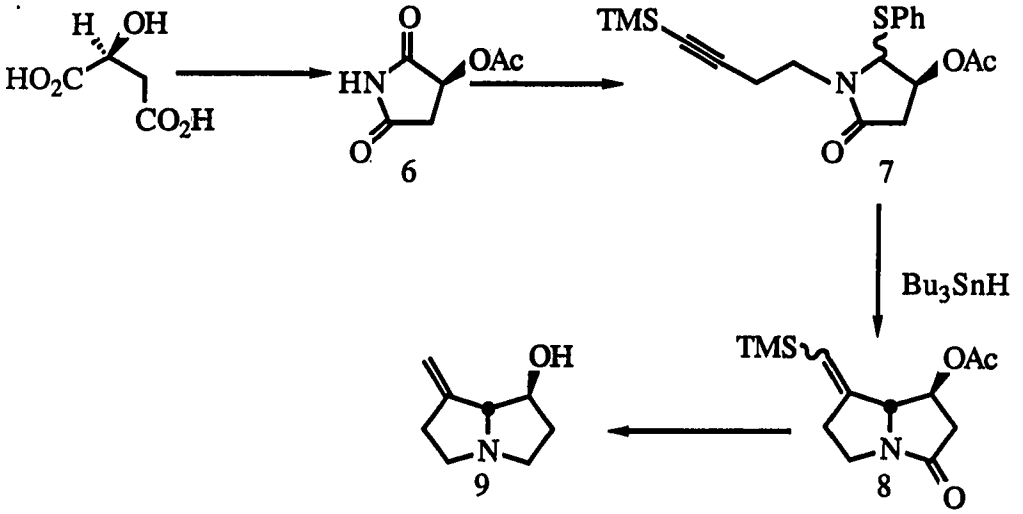
Stork and Kahn utilized an organotin radical-induced cyclization in the synthesis of Prostaglandin $F_{2\alpha}$.[2] Formation of the organotin radical resulted in cleavage of the carbon-halide bond in 1. The intramolecular cyclization proceeds in the presence of the α,β unsaturated ketone. Trapping of the alkyl radical resulted in formation of 2 stereoselectively. The final product was synthesized in two additional steps.



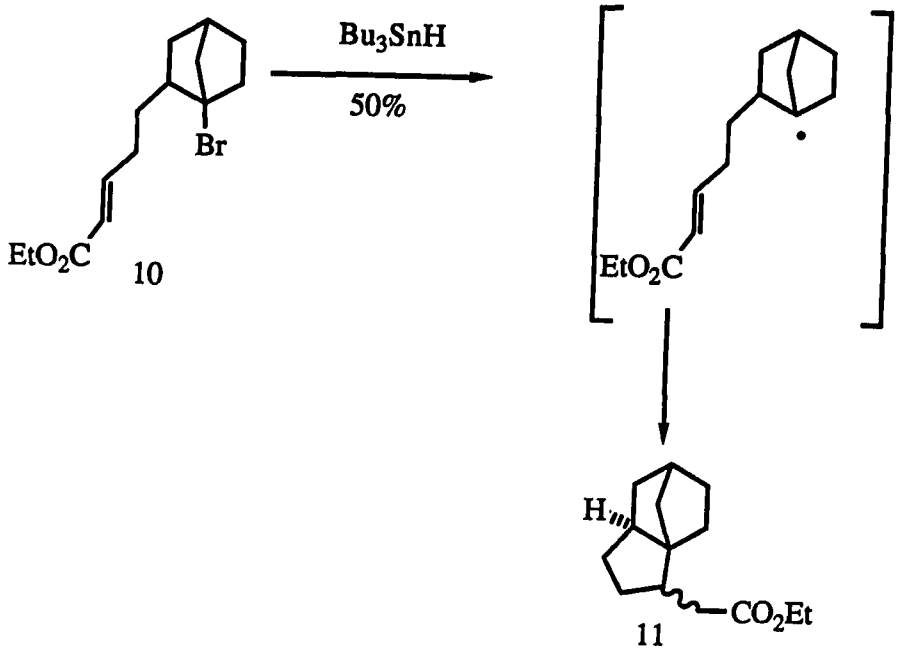
In 1985 Curran and Chen reported the synthesis of capnellene 5.[3] Bromide 4 was synthesized in a short series of steps from lactone 3. Tandem radical cyclization induced by tributyltin hydride generated the natural product in 61% yield.



Choi and Hart synthesized pyrrolizidine alkaloids, via an organotin induced-radical cyclization.[4] The radical precursor was formed from malic acid. Homolytic cleavage of the carbon-sulfur bond, followed by cyclization produced bicylic intermediate 8. The natural product was 9 produced in two steps from 8.



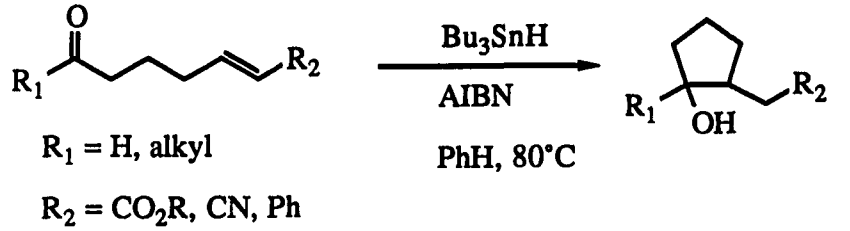
Tin mediated radical cyclizations have been utilized by our group for the formation of advanced intermediates to natural products.[5] A bridgehead radical was generated upon treatment of 10 with tributyltin hydride. Spontaneous cyclization furnished tricyclic ester 11.



The chemistry of organotin radical-mediated cyclizations has been extensively reviewed in articles by Hart and Curran, and in a comprehensive book by Giese.[6,7,8]

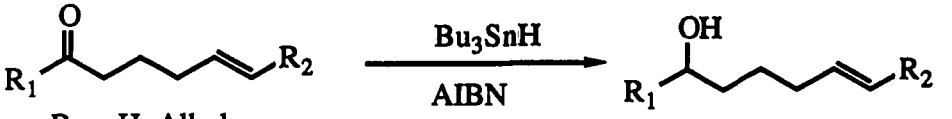
Recently, Enholm and Prasad reported the selective addition of tributyltin radicals to the oxygen end of the carbonyl group of unsaturated aldehydes and ketones.[9] The resulting o-stannyl ketyl cyclized intramolecularly in a 5-

hexenyl radical cyclization manner. The cyclization, however, occurred only in the presence of activated olefins.



R_1 = H, alkyl

R_2 = CO_2R, CN, Ph



R_1 = H, Alkyl

R_2 = Alkyl

Unlike the organotin radical-induced cyclizations, the equivalent reactions involving organosilicon radicals have not been studied. The addition of organosilicon radicals to olefins and carbonyls is a well precedented reaction. Ingold and coworkers reported comparative studies on the kinetic rates of addition of silicon, tin, and germanium radicals to olefins and carbonyls.[10] The results indicated that addition of silicon-centered radicals to carbonyls and alkenes are faster processes than the additions of tin or germanium radicals.

The hydrosilylation of alkenes is known to occur via two distinct modes: The radical process and the transition metal catalyzed process.[11] The mechanism for the radical process is shown below:

Initation $R_3SiH \xrightarrow{R'OOR'} R_3Si\bullet$

Propagation
$R_3Si\bullet + R''CH=CH_2 \longrightarrow R_3SiCH_2\text{-}\dot{C}HR''$
$R_3SiCH_2\dot{C}HR'' \xrightarrow{R_3SiH} R_3SiCH_2\text{-}CH_2R'' + R_3Si\bullet$

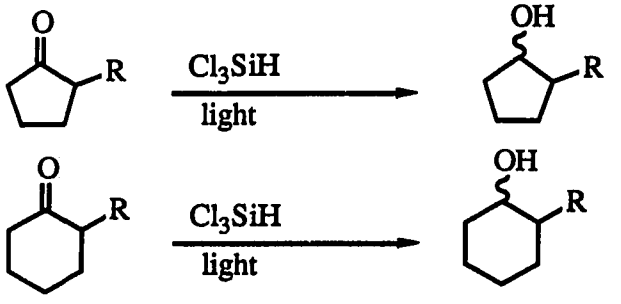
Termination $R_3Si\bullet + R_3Si\bullet \longrightarrow R_3Si\text{-}SiR_3$

The addition of silyl radicals to unsymmetrical olefins is a regiospecific reaction. It proceeds in an anti-Markovnikov mode. Addition to cyclic alkenes produces predominantly anti (trans) products. Monomers are mainly obtained from the reaction of silyl radicals and alkenes. Polymerization can be controlled by using suitable olefin-

silane ratios. However, with more reactive alkenes such as α,β unsaturated esters polymerization is a more serious problem. [12]

The silyl radical addition to carbonyl groups has been studied to a lesser extent than the addition to olefins. The strength of the carbonyl pi-bond system can hinder such reaction. However, the above negative effect can be offset by the strength of the silicon-oxygen bond (100 to 119 Kcal/mol). Nucleophilic radicals are less likely to add to carbonyls because of the polar character of the carbonyl. A more facile addition reaction can be produced by increasing the electrophilicity of the silyl radicals with electron withdrawing groups on the silicon.

Trichlorosilane is known to add to acetone under photolytic conditions. Under photochemical conditions trichlorosilane adds to alkyl cyclopentanones and alkyl cyclohexanones. [13]



Recently, Chatgilialoglou, Griller, and Lesage demonstrated that silyl radicals can be extremely useful alternatives for tin radicals in reductions of alkyl halides.[14,15,16] Tin hydrides are toxic compounds, and the formation of tin halides complicates the work up of the reductions.

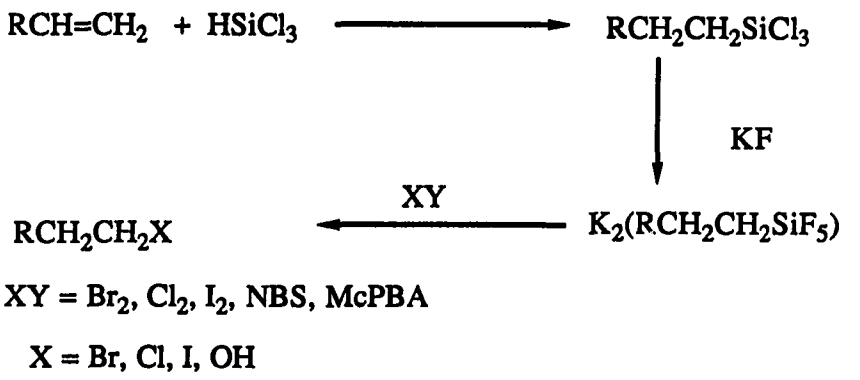
A particularly interesting reaction of silyl radicals is the halogen abstraction in acid chlorides and chloroformate esters. Elimination of carbon monoxide and carbon dioxide respectively, produces alkyl radicals.[17,18]

$$RCOCl \xrightarrow{Cl_3Si\bullet} RCO\bullet \xrightarrow{CO} R\bullet$$

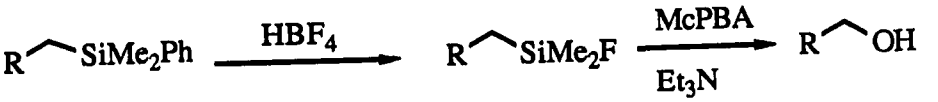
$$ROCOCl \xrightarrow{Cl_3Si\bullet} ROCO\bullet \xrightarrow{CO_2} R\bullet$$

Comprehensive reviews on the reactions of silyl radicals have been published by Wilt; and Eaborn and Bott.[19,20]

Synthetically, the carbon silicon bond has served as a precursor to alkyl halides and alcohols. Kumada and coworkers have illustrated that the trichlorosilyl group, can be transformed to a fluorosilicate. The fluorosilicates can be converted in high yields to alcohols or halides.[21]

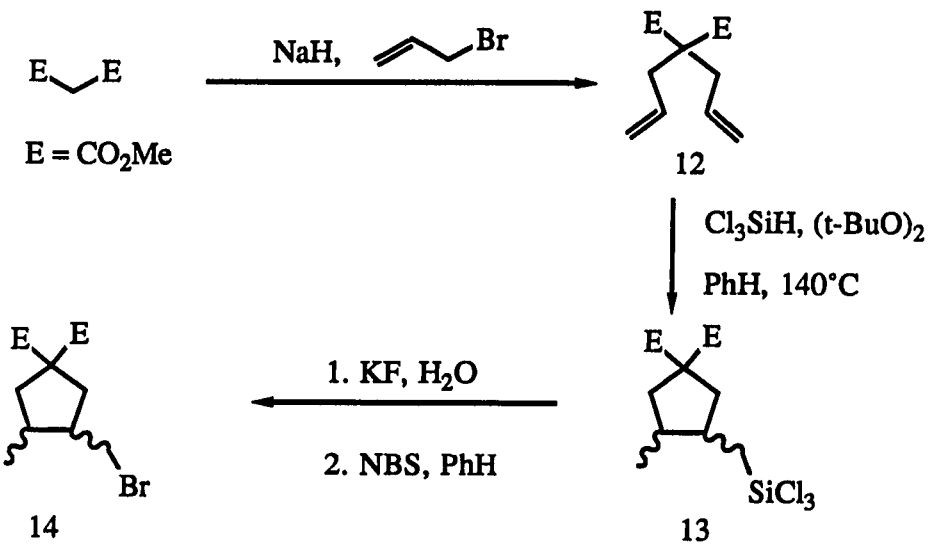


In a similar manner Fleming and coworkers have converted the dimethylphenylsilyl group to a hydroxyl group.[22] Removal of the phenyl group and oxidation of the product generate the alcohols.



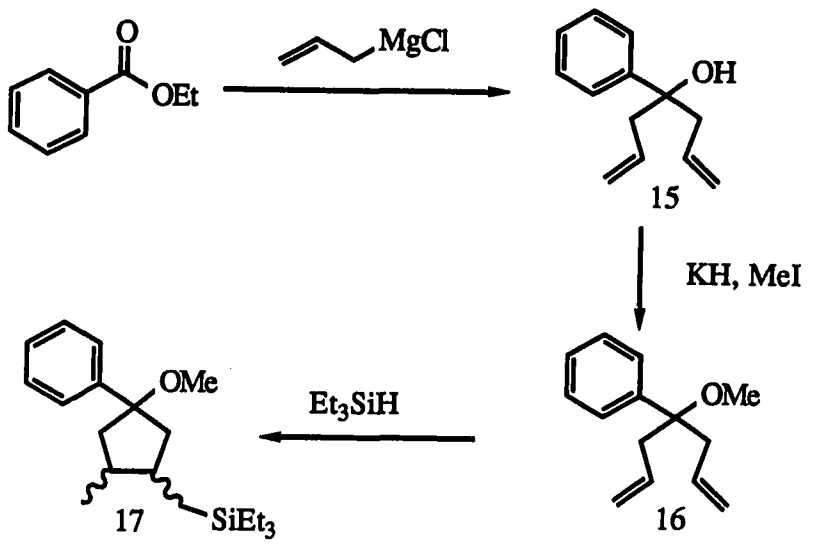
RESULTS AND DISCUSSION

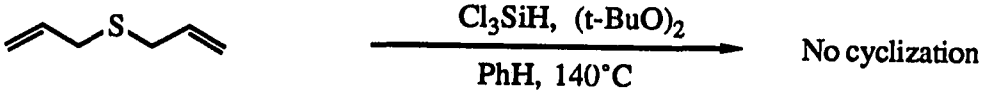
The development of new methodology is of primary importance for the progress of synthetic organic chemistry. The objective of our research was to investigate the possiblilty of chemoselective addition of silyl radicals to substrates containing both isolated carbonyls and olefins. The question of organosilicon radical-induced cyclizations of dienes was also examined. We reasoned that selective addition of silyl radicals to either olefins or carbonyl groups could be achieved by altering the electrophilicity of the silicon-centered radical. In order to examine carbon-carbon bond forming reactions induced by silyl radicals, we prepared dienes that could cyclize by a 5-hexenyl radical reaction. Simple dienes that could lead to formation of monocyclic systems were first examined. Diene 12 was prepared by double alkylation of dimethyl malonate with sodium hydride and allyl bromide. Upon treatment of 12 with trichlorosilane and di-tertbutyl peroxide at 140°C in benzene, cyclic diester 13 was obtained as a mixture of diastereomers. Intermediate 13 was transformed to the alkyl halide 14.



Similarly, diene 16 was prepared by addition of excess allyl magnesium chloride to ethyl benzoate, and treatment of the crude product 15 with excess potassium hydride and methyl iodide. When diene 16 was treated with trichlorosilane as previously described, an unexpected product was isolated. The resonance for the methyl ether was not present in the product. We reasoned that cleavage of the methyl ether had occurred due to formation of HCl.

When 16 was treated with triethylsilane, compound 17 was obtained as a diastereomeric mixture.

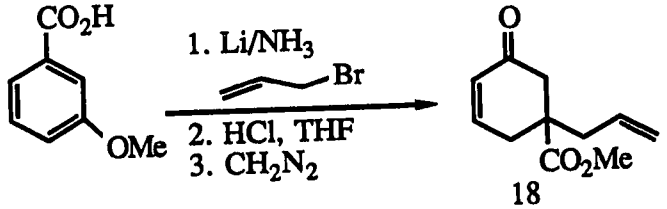




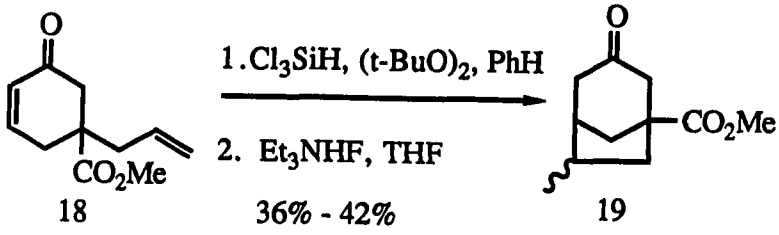
When commercially available allyl sulfide was treated with trichlorosilane using the typical reaction conditions, no cyclization products were obtained. This result implied that a geminal dimethyl effect may be required for cyclizations to occur.

We next turned our attention to the chemoselective studies. We designed systems that could permit reaction of the silyl radical with a carbonyl group or an olefin followed by cyclization. For selective addition to carbonyl groups, the more electrophilic trichlorosilyl radical was employed.

Enone 18 was prepared by alkylative Birch reduction of 3-methoxybenzoic acid, followed by acid hydrolysis and esterification with diazomethane.[23] Enone 18 was treated with trichlorosilane and tert-butyl peroxide at 140°C. After hydrolysis of the crude product with triethylammonium hydrofluoride, bicyclic ketone 19 was obtained in 36% to 42% yield as a diastereomeric mixture. This result was welcome since reaction with the terminal olefin, and 1,4-addition of the silyl radical were possible competing reactions.

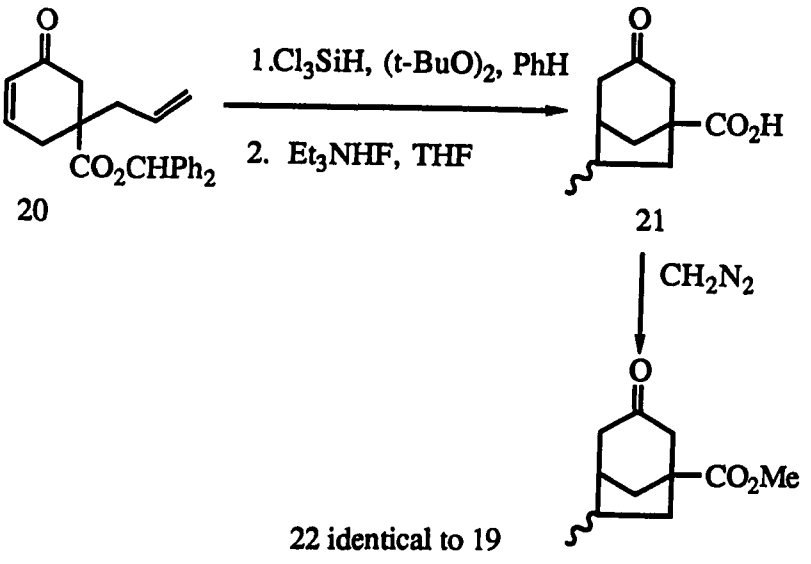


18

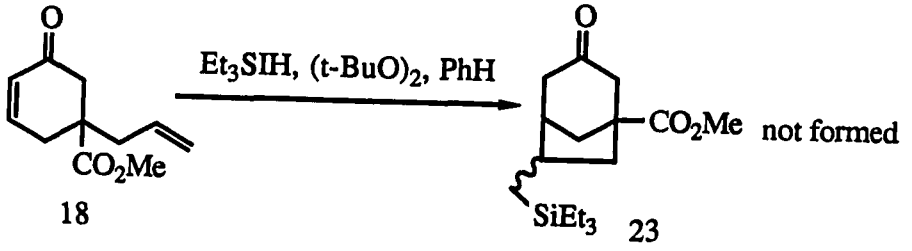


18 36% - 42% 19

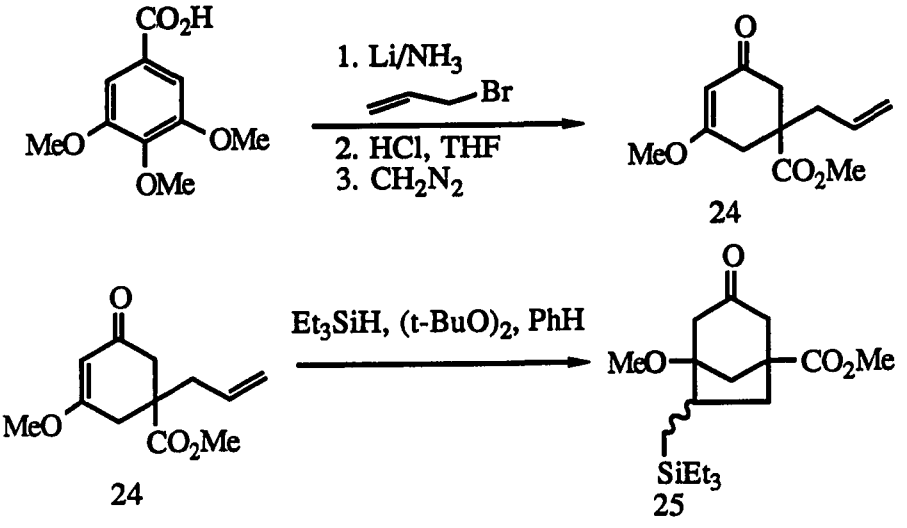
It is interesting to note that ester groups seem to be extremely unreactive toward silyl radical additions. This observation came in contrast with Baldwin and Haut's work, where ester to ether transformations occured with trichlorosilane.[24] Actually, we believe that reaction with the ester units may be reversible. When enone 20 was treated with trichlorosilane, followed by hydrolysis, a very polar compound was obtained which exhibited the doublets corresponding to a methyl group at about 1.0 ppm in the NMR. Treatment of the unknown compound with diazomethane generated ester 22 as shown by NMR, IR and mass spectroscopy. We concluded that the unknown compound was acid 21. The formation of the acid had occured via elimination of the stable diphenylmethyl radical.

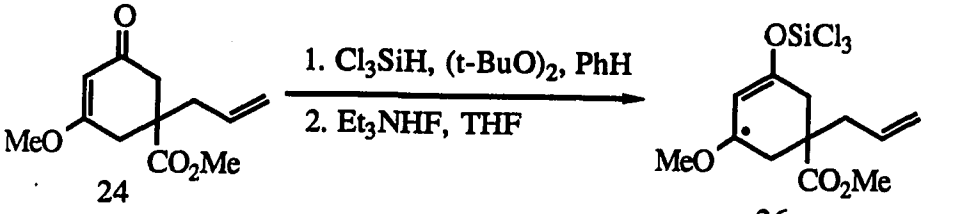


We expected that enone 18 would furnish bicyclic ketone 23 via reaction of the triethylsilyl radical selectively with the terminal olefin, followed by Michael addition of the alkyl radical. However, treatment of 18 with triethylsilane produced a complicated mixture of products. Our explanation for the result was that both addition to the terminal olefin and 1,4-addition had occurred.



We then prepared enone 24 via a similar alkylative Birch reaction, starting with 3,4,5,-trimethoxybenzoic acid. Treatment of 24 with triethylsilane clearly produced 25 as a mixture of diastereomers. The presence of the methoxy group reduced the possibility for 1,4-addition products. Treatment of 24 with trichlorosilane and hydrolysis of the crude product yielded no cylization products. We reasoned that the allylic radical 26 failed to cyclize, since it was additionally stablized by the methyl ether.

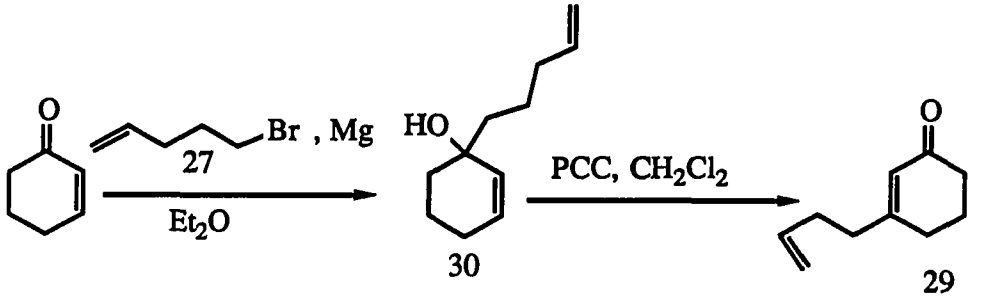




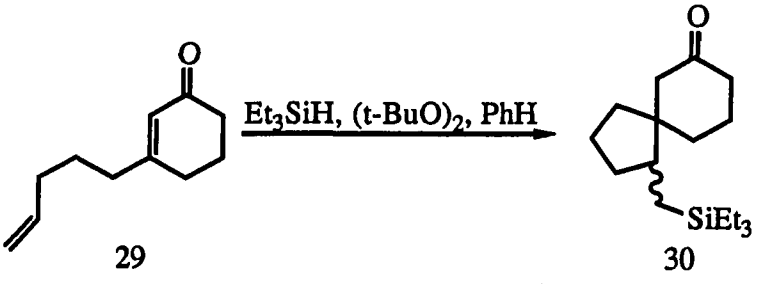
24 26

No cyclization via 26

Next we prepared enone 29 by addition of Grignard 27 to cyclohexenone followed by PCC-mediated oxidation of tertiary allylic alcohol 28.[25,26] Treatment of enone 29 with triethylsilane afforded a diastereomeric mixture of compound 30 in high yield.



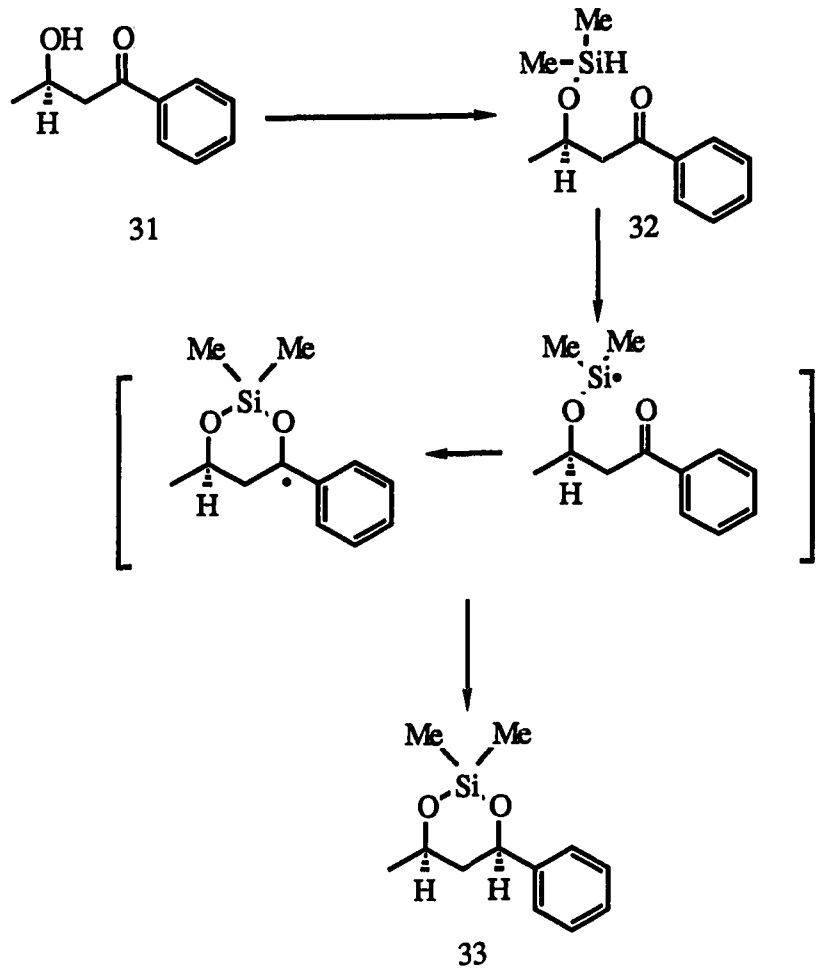
30 29



29 30

The reactions described in this unit represent the first examples of carbon-carbon bond formation mediated by addition of silyl radicals to olefins and carbonyls. We are currently involved in determining the scope and limitations of this methodology, particularly with regard to the chemoselective addition to carbonyl groups. We are in search of milder conditions for the generation of the silyl radicals with the expectation that this would result in increased selectivity for the addition reactions. Unfortunately, photolytic generation of the silyl radicals at room temperature has shown no promise. Primarily, 2 + 2 photo products were obtained from these reactions.

Based on our knowledge on the silicon radicals, we decided to extend our research to different targets. We reasoned that 1,3-syn diols could be formed by intramolecular addition of a silicon radical to a carbonyl oxygen. The strategy is illustrated below.



31 32 33

To examine our hypothesis we synthesized 32. We expected that upon formation of the silyl radical, intramolecular addition would occur. The addition of the hydrogen radical should occur syn to the ether methine, providing 33, the precursor to the 1,3-syn diols. However, treatment of 32 with tert-butyl peroxide and AIBN did not afford the desired unit. Photolysis of 32 failed to generate the silyl radical.

EXPERIMENTAL

General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. THF and diethyl ether were distilled from sodium benzophenone ketyl under nitrogen prior to usage. Benzene was distilled from lithium aluminum hydride. Dichloromethane was distilled from calcium hydride. Unless otherwise noted, all reactions were conducted under an argon atmosphere. Unless otherwise noted, all organic extracts were dried over anhydrous sodium sulfate. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-4250 or a Perkin-Elmer model 1320 spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian EM-360 spectrometer. High field (300 MHz) proton spectra were obtained with a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in relative to tetramethylsilane as an internal standard. Coupling constants (J) are reported in Hz. Abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet, ABq = AB quartet. 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 a Kratos model MS-50 spectrometer. Low-resolution mass spectra were recorded on a Finnegan 4023 mass spectrometer. Silica gel used for flash chromatography (72) was 230-400 mesh (Kieselgel 60) purchased from EM Science. Gravity column chromatography was performed on 60-200 mesh silica gel purchased from Davison Chemical (WR Grace Inc.). Elemental analyses were performed by Galbraith Laboratories, Inc.

(R,S) Dimethyl-3-methyl-4-trichlorosilylmethyl-1,1-cyclopentane dicarboxylate 13

A solution of diester 12 (0.92g, 4.33 mmol), trichlorosilane (1.18g, 8.66 mmol), and tert-butyl peroxide (0.32g, 2.16 mmol) in 15 mL of benzene was degassed and sealed in a glass tube. The solution was heated to 140°C for 18 hours. The reaction mixture was cooled and concentrated. The extremely hygroscopic product (1.26g, 84% yield) was taken on to the next step with no further purification.

NMR ($CDCl_3$): 1.04-0.98 (d, J=6.0 Hz J=7.2 Hz, 3H), 2.6-1.3 (m, 8H), 3.93-3.7 (s, 6H).

(R,S) Dimethyl-3-bromomethyl-4-methyl-1,1-cyclopentane dicarboxylate 14

To a solution of potassium fluoride (0.86g, 14.8 mmol) in 1 mL of distilled water at 0°C was added diester 13 (0.3g, 0.86 mmol). A white precipitate developed immediately. The precipitate was collected, washed with cold water-ethanol, ethanol, and ether. It was then dried in vacuo for 12 hours. To a suspension of the precipitate in 5 mL of benzene was added n-bromosuccinimide (0.2g, 1.1 mmol). The reaction mixture was stirred at ambient temperature for 2 hours. The mixture was filtered and the benzene layer was concentrated. The residue was purified by flash chromatography with 4:1 hexanes:ethyl acetate to afford 0.14g of 14 (56% yield).

NMR ($CDCl_3$): 1.04-.98 (d, J=6.0 Hz, J=7.2 Hz, 3H) 2.20-1.99 (m, 2H) 2.66-2.25 (m, 4H) 3.58-3.27 (m, 2H) 3.74-3.70 (s, 6H).

IR ($CDCl_3$): 2950, 1730, 1440, 1320 cm^{-1}.

High-resolution mass spectrum for $C_{11}H_{17}O_4Br$: calculated 292.03102; measured 292.03066.

Mass spectrum: m/e 59, 93, 145, 153, 181, 213, 233, 250, 262, 292.

4-phenyl-1,5-heptadiene-4-ol 15

To a solution of ethyl benzoate (2.8g, 19 mmol) in 19 mL of ether at 0°C was added excess allyl magnesium bromide (48 mL, 1M solution in ether) over 10 minutes. The solution was allowed to warm to ambient temperature over 1 hour, where it was stirred for 2 additional hours. The mixture was poured into ice-water, and was acidified to pH 4 with 2 N HCl. The organic layer was dried and concentrated. The residue was purified by flash chromatography with 4:1 hexanes:ethyl acetate to afford 1.6g of 15 (45% yield).
NMR($CDCl_3$): 2.15-2.1 (s, 1H), 2.78-2.45 (m, 4H), 5.27-5.00 (m, 4H), 5.75-5.51 (m, 2H), 7.45-7.2 (m, 5H).
IR ($CDCl_3$): 3050, 2950, 1070 cm^{-1}.

4-methoxy-4-phenyl-1,5-heptadiene 16

To a suspension of hexane-washed potassium hydride (0.26g, 6.4 mmol) in 7 mL of DMF at 0°C was added a solution of alcohol 15 (0.6g, 3.2 mmol) in 2 mL of DMF dropwise. The solution was stirred for 20 minutes and methyl iodide (0.68g, 4.8 mmol) was then added. The reaction was stirred for 1 hour at room temperature. The excess potassium hydride was quenched by adding isopropanol to the reaction flask. The mixture was diluted with ether, washed with brine, dried and concentrated. Purification by flash

chromatography with 9:1 hexanes:ethyl acetate afforded 0.5g of 16 (86% yield).

NMR ($CDCl_3$): 2.78-2.52 (t, 4H), 3.17-2.97 (s, 3H), 5.17-4.89 (m, 4H), 5.72-5.47 (m, 2H) 7.44-7.14 (m, 5H).

IR ($CDCl_3$): 3090, 2940, 1440, 1070 cm^{-1}.

High-resolution mass spectrum for $C_{14}H_{18}O$: calculated 202.13577; measured 202.13581.

Mass spectrum: m/e 51, 77, 91, 105, 115, 129, 161, 202.

(R,S) 1-methoxy-3-methyl-1-phenyl-4-triethylsilylmethyl cyclopentane 17

A solution of 16 (0.2g, 0.99 mmol), triethylsilane (0.23g, 1.98 mmol) and peroxide (0.07g, 0.49 mmol) was degassed and sealed in a glass tube. The solution was heated at 140°C for 18 hours. It was then cooled, concentrated, and purified by flash-chromatography with 9:1 hexanes:ethyl acetate, to afford 0.19g of 17 (60% yield).

NMR ($CDCl_3$): 2.78-2.52 (t, 4H), 3.17-2.97 (s, 3H), 5.17-4.89 (m, 4H), 5.72-5.47 (m, 2H) 7.44-7.14 (m, 5H).

IR ($CDCl_3$): 3090, 2940, 1440, 1070 cm^{-1}.

High-resolution mass spectrum for $C_{14}H_{18}O$: calculated 202.13577; measured 202.13581.

Mass spectrum (chemical ionization, ammonia): m/e 132, 157, 197, 220, 287, 304, 320, 336.

(R,S) Methyl-6-methyl-3-oxobicyclo[3.2.1]-1-octane carboxylate 19

A solution of 18 (0.44g, 2.27 mmol), trichlorosilane (0.61g, 4.54 mmol), and tert-butyl peroxide (0.17g, 1.13 mmol) in 8 mL of benzene, was degassed and sealed in a glass tube. The reaction mixture heated to 140°C for 18 hours. The solution was cooled and concentrated. The residue was dissolved in 10 mL of THF and triethylammonium hydrofluoride (0.51g, 4.24 mmol) was added to the solution at room temperature. The reaction was stirred at ambient temperature for 6 hours. The solution was concentrated, purified by flash chromatography with 5:1 hexanes:ethyl acetate to afford 0.19g of 19 (42% yield).

NMR ($CDCl_3$): 1.05-0.91 (d, J=6.9 Hz, J=6.3 Hz), 2.73-1.45 (m, 10H), 3.70-3.65 (s, 3H).

IR ($CDCl_3$): 2940, 1730, 1720, 1450, 1320, 1220 cm^{-1}.

High-resolution mass spectrum for $C_{11}H_{16}O_3$: calculated 196.10995; measured 196.10975.

Mass spectrum: m/e 59, 67, 93, 109, 137, 153, 168, 196.

(R,S) Methyl-5-methoxy-3-oxo-6-triethylsilylmethyl-biyclocyclo[3.2.1]-1-octane carboxylate 25

A solution of 24 (0.08g, 0.36 mmol), triethylsilane (0.17g, 1.43 mmol) and peroxide (0.03g, 0.18 mmol) in 2 mL

of benzene, was degassed and sealed in a glass tube. The solution was heated to 140°C for 18 hours. The reaction mixture was cooled, concentrated, and purified by flash chromatography with 5:1 hexanes:ethyl acetate, to afford 0.08g of 25 (68% yield) and 0.013g of starting material (16.5% yield).

NMR ($CDCl_3$): 0.54-0.4 (m, 8H), 0.94-0.82 (t, 9H), 2.80-2.0 (m, 9H) 3.32-3.20 (s, 3H) 3.75-3.65 (s, 3H).

IR ($CDCl_3$): 2950, 2870, 1730, 1720, 1460, 1420, 1310 cm^{-1}.

High resolution mass spectrum for $C_{18}H_{31}O_4Si$ ($M-H^+$): calculated 339.19917; measured 339.19925.

Mass spectrum (chemical ionization, ammonia): m/e 104, 134, 195, 225, 253, 296, 328, 358.

1-(4-pentenyl) 2-cyclohexen-1-ol

To a suspension of magnesium (0.22g, 9.1 mmol) in 2 mL of ether at room temperature, was added a solution of halide 27 (0.88g, 8.3 mmol) in 8 mL of ether dropwise. The reaction mixture was stirred at room temperature for 2 hours. To the reaction mixture, at room temperature, was added a solution of cyclohexenone (0.8g, 8.3 mmol) in 8 mL of ether. The reaction was stirred at ambient temperature for 1 hour, and was refluxed for 30 minutes. The reaction mixture was poured into ice-water, and was acidified to pH 4

with 2 N HCl. The aqueous layer was extracted with ether, dried, and concentrated. The adduct was purified by flash chromatography with 5:1 hexanes:ethyl acetate to afford 0.76g of 28 (74% yield).

NMR ($CDCl_3$): 2.51-1.09 (m, 13H), 5.13-4.83 (m, 2H), 5.69-5.48 (m, 1H), 6.01-5.70 (m, 2H).

IR ($CDCl_3$): 2950, 1720, 1440, 1260 cm^{-1}.

High-resolution mass spectrum for $C_{11}H_{18}O$: calculated 166.13577; measured 166.13564.

Mass spectrum: m/e 55, 79, 97, 107, 123, 148, 166.

3-(4-pentenyl) 2-cyclohexenone 29

To a solution of alcohol 28 (0.4g, 3.74 mmol) in 8 mL of methylene chloride was added pyridinium chlorochromate (2.0g, 9.34 mmol). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was filtered through celite, and concentrated. The adduct was purified by flash chromatography with 5:1 hexanes:ethyl acetate to afford 0.42g of 29 (92.5% yield).

NMR ($CDCl_3$): 1.67-1.40 (t, 2H), 2.46-1.87 (m, 10H), 5.10-4.90 (m, 2H), 5.88-5.65 (m, 1H), 5.91-5.89 (s, 1H).

IR ($CDCl_3$): 2950, 2880, 1660, 1620, 1440, 1250, 1190 cm^{-1}.

High resolution mass spectrum for $C_{11}H_{16}O$: calculated 164.12012; measured 164.11975.

Mass spectrum: m/e 53, 67, 82, 93, 108, 123, 136, 164.

(R,S) 1-triethylsilylmethyl-Spiro[4.5] decan-8-one 30

A solution of 29 (0.15g, 1.24 mmol), triethylsilane (0.3g, 2.6 mmol), and peroxide (0.09g, 0.62 mmol) in 5 mL of benzene was degassed and sealed in a glass tube. The reaction was heated to 140°C for 18 hours. The solution was cooled and concentrated. The adduct was purified by flash chromatography with 10:1 hexanes:ethyl acetate to afford 0.24g of 30 (70% yield).

NMR ($CDCl_3$): 0.59-0.39 (m, 8H), 1.01-0.83 (t, 9H), 2.54-1.1 (m, 15H)

IR ($CDCl_3$): 2940, 2870, 1700, 1410, 1120 cm^{-1}.

High-resolution mass spectrum for $C_{17}H_{32}OSi$: calculated 280.22225; measured 280.22183.

Mass spectrum: m/e 59, 67, 75, 87, 103, 115, 147, 211, 224, 237, 251, 280.

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CONCLUSIONS

Important accomplishments of our research at Iowa State University include:

1. The short and efficient synthesis of 4,11-bisdeoxydaunomycinone via a Claisen/Diels-Alder sequence.
2. The discovery of a new regiochemical control element for the Diels/Alder and an effort to the aza-tricyclic moiety of atisine-type alkaloids.
3. The formation of monocyclic and bi-cyclic rings via cyclizations induced by organosilicon radicals, and the first chemoselective studies on silyl radicals.

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