Studies Directed to the Synthesis of the Unusual Cardiotoxic Agent Kalmanol. Enantioselective Construction of the Advanced Tetracyclic 7-Oxy-5,6-dideoxy Congener

Stephane Borrelly and Leo A. Paquette*

Contribution from the Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

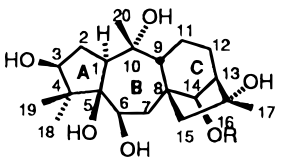
Received October 2, 1995[⊗]

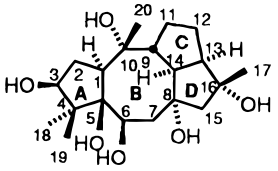
Abstract: The first synthesis of a highly functionalized B-homo-C-nor grayanotoxin closely related to kalmanol is reported. An enantiocontrolled route to the diquinane sector was first developed from (4*R*)-(+)-*tert*-butyldimethylsiloxycyclopentenone by taking advantage of the Michael acceptor properties of this enone and an α,β-unsaturated ester subsequently derived from it, *viz.*, **4** → **7** → **8**. These experiments formed the basis for more advanced substitution of the bicyclo[3.3.0]octane core. In fact, ready access was gained to the α-hydroxy esters **24**−**27**. In these advanced intermediates, it is imperative that the acetyl and carbomethoxy groups bear a trans 1,3-relationship. The neighboring OR substituent should preferably be larger than methoxy in order to guarantee 100% facial selectivity during the ensuing capture by **1** (as its lithiated derivative). This condensation leads unidirectionally to tricyclic lactones represented by **30** and **31** and sets the stage for implementation of sequential Tebbe olefination and Claisen rearrangement. This pivotal two-step process gives rise directly to the targeted tetracyclic framework. The further oxygenation of **35** can be accomplished in a highly stereoselective manner to give **3**. The characteristics of the [3.3] sigmatropic event that results in ring expansion plays a significant role in defining absolute configuration at key carbon centers which would otherwise be difficult to establish unequivocally. A total of 25 synthetic steps was involved.

The grayanotoxins are noted for their ability to open sodium channels easily and to maintain them in that condition longer than normal.[1] Their ineffectiveness on the sodium permeability of inexcitable cells or excitable cells having no sodium currents has focused attention on the existence of a receptor in a strongly hydrophobic region. The structures of these toxins cause them to be lipid-soluble and to gain ready access to the boundaries between membrane lipids and the membrane-crossing segments of the sodium channel.[2,3] Once the sodium channels are distorted, a large depolarization results, and both gating and permeation are strongly affected.[4] As a result, the strong preference for sodium ions is lessened, such that the ionic selectivity of a channel may actually be altered. The resultant impact on nerve impulses is therefore very significant.

The grayanotoxin diterpenes possess a unique tetracyclic framework which is densely populated with hydroxyl groups.[5] The functionalities essential for biological activity have been determined to reside on the A and B rings. The active binding site at or near the sodium channel may therefore possess a configuration that extends a hydrophobic anchor to this array of hydroxyl groups.[6]

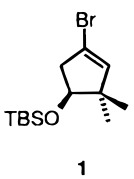
Given this historical backdrop, the isolation and characterization in 1989 of kalmanol, a new diterpenoid type having a highly oxygenated B-homo-C-nor grayanoid framework,[7] was certain to be accompanied by many questions surrounding its biological activity. Kalmanol is indeed pharmacologically active and is



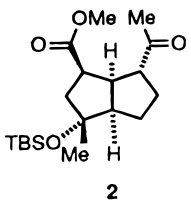


cardiotoxic as a consequence of its ability to increase the permeability of sodium ions in excitable membranes as do the grayanotoxins. Preliminary evaluation has suggested that kalmanol may be less active than grayanotoxin I. A more complete evaluation must, however, await the procurement of more material.

Consequently, kalmanol and analogs thereof merit consideration as synthetic targets. Since the biosynthetic origin of kalmanol may consist in Wagner−Meerwein rearrangement of a grayanotoxin precursor with ring contraction,[7] it is likely that these molecules share a common absolute configuration. Early efforts targeted toward kalmanol have resulted in the acquisition of both enantiomers of cyclopentenyl bromide **1** by means of an unprecedented tandem reaction sequence.[8] The advanced



1



2

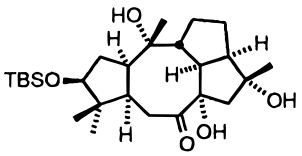
diquinane building block **2** has also been made available by

[⊗] Abstract published in *Advance ACS Abstracts,* January 15, 1996.

(1) Ku, D. D.; Akera, T.; Frank, M.; Brody, T. M.; Iwasa, J. *J. Pharmacol. Exp. Ther.* **1977**, *200*, 363.
(2) Keynes, R. D. *Sci. Am.* **1979**, 126−135.
(3) Hille, B. *Ionic Channels of Excitable Membranes*, 2nd ed.; Sinauer Assoc.: Sunderland, MA, 1992.
(4) Ulbricht, W. *Erg. Physiol. Biol. Chem. Exp. Pharmakol.* **1969**, *61*, 18.
(5) (a) Iwasa, J.; Kumazawa, Z.; Nakajima, M. *Chem. Ind.* **1961**, 511. (b) Fushiya, S.; Hikino, H.; Takemoto, T. *Tetrahedron Lett.* **1974**, *2*, 183.
(6) Masutani, T.; Seyama, I.; Narahashi, T.; Iwasa, W. *J. Pharmacol. Exp. Ther*. **1981**, *217*, 812.
(7) Burke, J. W.; Doskotch, R. W.; Ni, C.-Z.; Clardy, J. *J. Am. Chem. Soc.* **1989**, *111*, 5831.
(8) Borrelly, S.; Paquette, L. A. *J. Org. Chem.* **1993**, *58*, 2175.

0002-7863/96/1518-0727$12.00/0

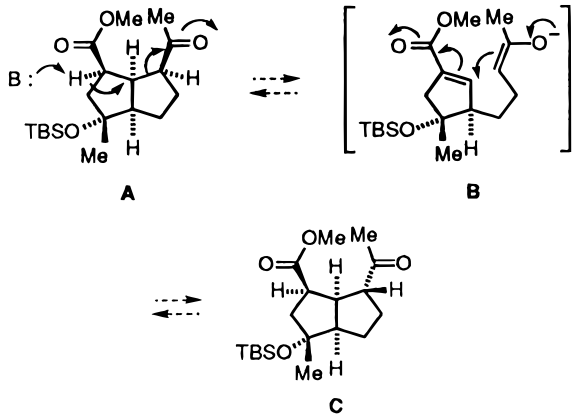
proper adaptation of Pauson−Khand technology.[9] Although the route to **2** proved to be diastereoselective, several complications associated with regiocontrol were uncovered, and the preliminary study involved racemic compounds. Herein, we report an alternate enantioselective route to a key bicyclic intermediate related to **2**, demonstrate the feasibility of a Tebbe−Claisen sequence for assembling the entire kalmanol backbone and detail the manageability of introducing most of the requisite functionality. As indicated in the title, the insights gained from this experimentation have resulted in acquisition of 7-oxy-5,6-dideoxykalmanol (**3**).[10]



3

Discussion of Results

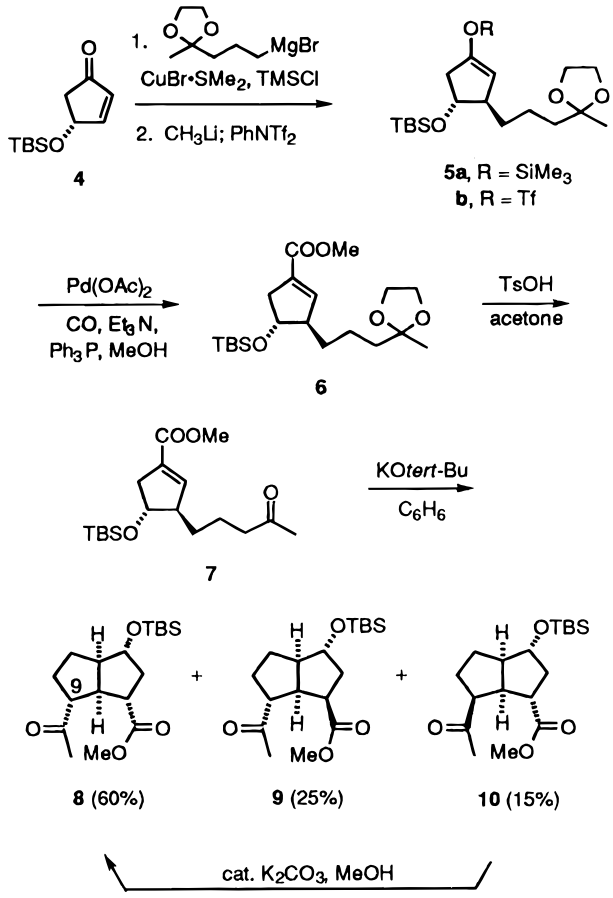
Enantiocontrolled Route to the Diquinane Subunit. An earlier reported provocative observation was the relative ease with which ester **A** undergoes epimerization to **C** under mildly basic conditions.[9] Although simple configurational inversion α to the acetyl functionality could be operational, the ring fragmentation-intramolecular Michael addition made possible by the 1,5-relationship of the two carbonyls was viewed to be



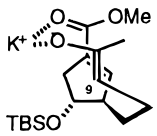
kinetically viable. Analysis of the structural features of **B** led to the decision to explore this mechanistic option directly via the known (4*R*)-(+)-*tert*-butyldimethylsiloxycyclopentenone (**4**).[11] Copper-catalyzed 1,4-addition of the Grignard reagent derived from 5-bromo-2-pentanone ethylene ketal[12] in the presence of chlorotrimethylsilane provided the silyl enol ether **5a** (Scheme 1). Rapid filtration of this sensitive intermediate through glass wool, direct regeneration of the enolate anion with methyllithium, and O-triflation[13] afforded **5b** in 91% overall yield. In order to maximize the efficiency of this conversion, it was necessary to maintain the reaction temperature below −10 °C in order to skirt the irreversible elimination of *tert*-butyldimethylsilanol made possible by enolate equilibration.

Carbomethoxylation of **5b** under 1 atm of CO in DMF[14] afforded **6** (87%), controlled hydrolysis of which provided **7** efficiently. Brief treatment of this keto ester with 0.5 equiv of potassium *tert*-butoxide in benzene resulted in the anticipated

Scheme 1



cyclization with formation of a 60:25:15 mixture of diastereomers **8**−**10**. The elevated stereoselectivity of this process can be attributed to chelation control in an aprotic solvent (see **D**) under the terms previously defined by Stork.[15] The major consequence of the involvement of **D** is predominant α introduction of the acetyl group at C-9. Treatment of the mixture with a catalytic amount of potassium carbonate in methanol resulted in the conversion of **10** into **8** and made possible the facile chromatographic separation of **8** from **9**. The stereochemical assignments to both diastereomers were corroborated by NOE analysis (see Experimental Section). No means was found to isolate **10** in a pure state and therefore to confirm its structure spectroscopically. Nevertheless, it is very unlikely that it is the β,β isomer because of the substantive strain inherent in this diquinane (MM2 calculations[9]).

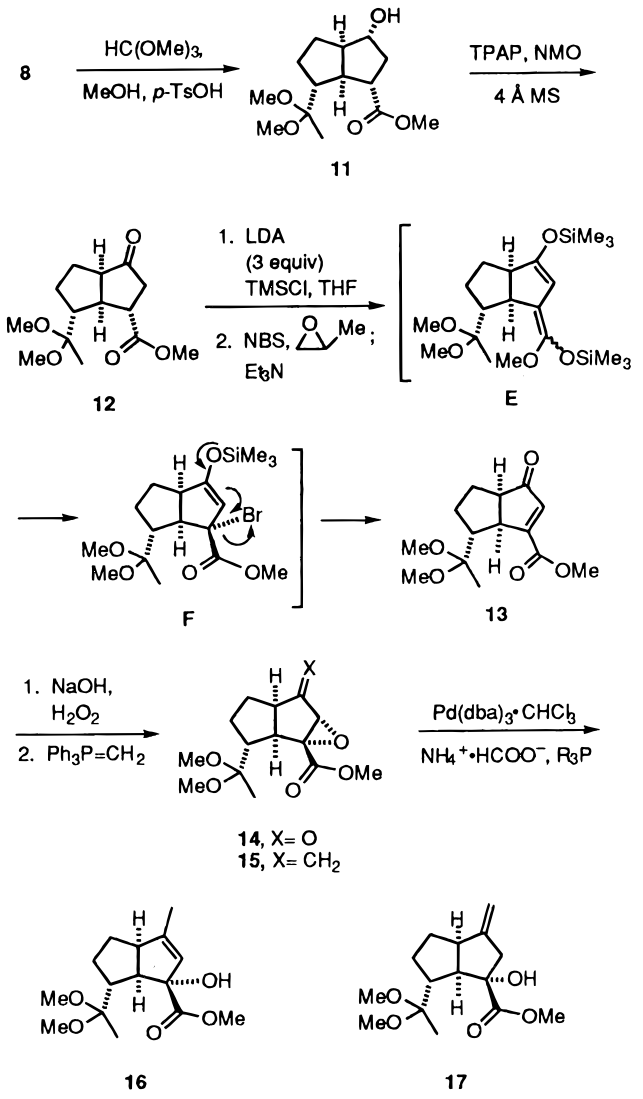


D

As the means for increasing the level of substitution in the diquinane fragment, we came to favor initial concomitant ketone protection and hydroxyl deprotection by reaction of the **8**/**9** mixture with equal proportions of trimethyl orthoformate and methanol under acidic conditions (Scheme 2). Subsequent perruthenate oxidation[16] of **11** gave rise to **12** (86%). Neither transformation impacted on the 2.3:1 (α/β) distribution. An earlier trial run with pure **8** had indicated that loss of stereo-

(9) Paquette, L. A.; Borrelly, S. *J. Org. Chem.* In press.
(10) Borrelly, S. Ph.D. Dissertation, The Ohio State University, 1995.
(11) Paquette, L. A.; Earle, M. J.; Smith, G. F. *Org. Synth.* **1995**, *73*, 36.
(12) Ponaras, A. A. *Tetrahedron Lett.* **1976**, *36*, 3105.
(13) Ritter, K. *Synthesis* **1993**, 737.
(14) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 109.
(15) Stork, G.; Winkler, J. D.; Saccomano, N. A. *Tetrahedron Lett.* **1983**, *24*, 465.
(16) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13.

Scheme 2

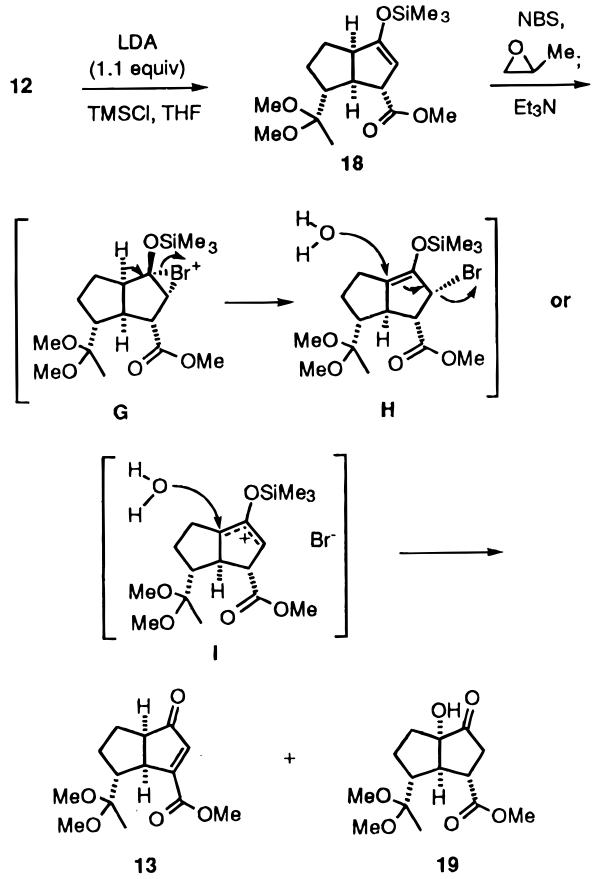


chemical integrity should not be expected. This was not a point of particular concern, however, in light of impending introduction of unsaturation adjacent to the carbomethoxy substituent.

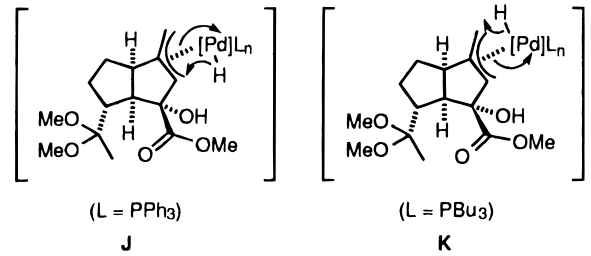
Having secured **12**, we soon recognized that *mono*-O-silylation to produce **18** was not to accommodate expedient conversion to the unsaturated keto ester **13**. Quite unexpectedly, the action of *N*-bromosuccinimide on **18** followed by the addition of triethylamine effected conversion to a 1:1 mixture of **13** and the α-hydroxy ketone **19**. Control experiments established that the oxygenation process was not the end result of the capture of molecular O_2. As illustrated in Scheme 3, the present suspicion is that **19** arises by S_N2' substitution[17] of the allylic bromine in **H**, which is generated in turn by eliminative ring opening within bromonium ion **G**. Alternatively, the possibility exists that oxyallyl cation **I** captures water regioselectively.[18]

The electron-deficient double bond in **13** proved highly receptive to alkaline peroxidation and furnished uniquely the α-isomer **14** (78%). In contrast, the olefination of **14** was a problematical step. Extensive decomposition was observed with organometallic reagents. With the more conventional Wittig

Scheme 3



process, a 50% optimized yield of the sensitive **15** could be realized. It was interesting to find that the subsequent palladium-mediated hydrogenolysis of this alkenyl oxirane exhibited a pronounced dependency on the phosphine ligand employed. Ammonium formate was used as the hydride source according to Tsuji.[19] When reduction was conducted in the presence of tributylphosphine, a separable 13:1 mixture of **16** and **17** was obtained in 91% yield. Recourse instead to triphenylphosphine redirected matters so that **17** was the only product formed with equal efficiency. The impressive regioselectivity of these processes is believed to arise as a consequence of the varied steric bulk in the π-allylpalladium intermediate. When the ligand is $(n\text{-Bu})_3P$, reductive elimination via hydride delivery to the exocyclic terminus (see **K**) is kinetically favored and



delivers the more thermodynamically stable product. On the other hand, the presence of large phenyl groups on phosphorus likely skews the complex to position the palladium center more into the environment of the exocyclic terminus such that hydride delivery to the ring carbon (as in **J**) now operates exclusively.

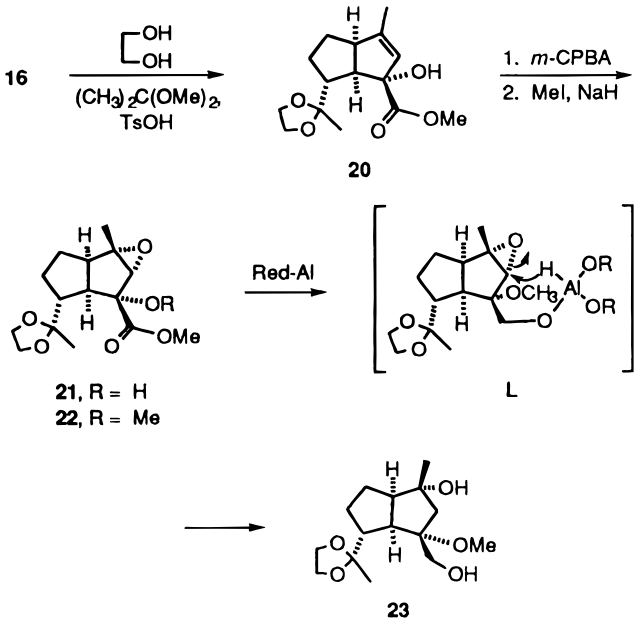
Ideally, both **16** and **17** would serve as useful precursors to the tertiary carbinol at C-16. Since the regioselective ring

(17) (a) Paquette, L. A.; Stirling, C. J. M. *Tetrahedron* **1992**, *48*, 7392. (b) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901.

(18) For other examples of *cine* substitution in oxyallyl cations, consult: (a) Hassner, A.; Naidorf-Meir, S.; Gottlieb, H. E. *J. Org. Chem.* **1993**, *58*, 5699. (b) Hassner, A.; Naidorf-Meir, S.; Gottlieb, H. E. *Tetrahedron Lett.* **1990**, *31*, 2181. (c) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1.

(19) Oshima, M.; Hirayushi, Y.; Shimizu, I.; Nisar, N.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, *111*, 6280.

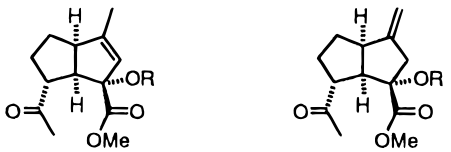
Scheme 4



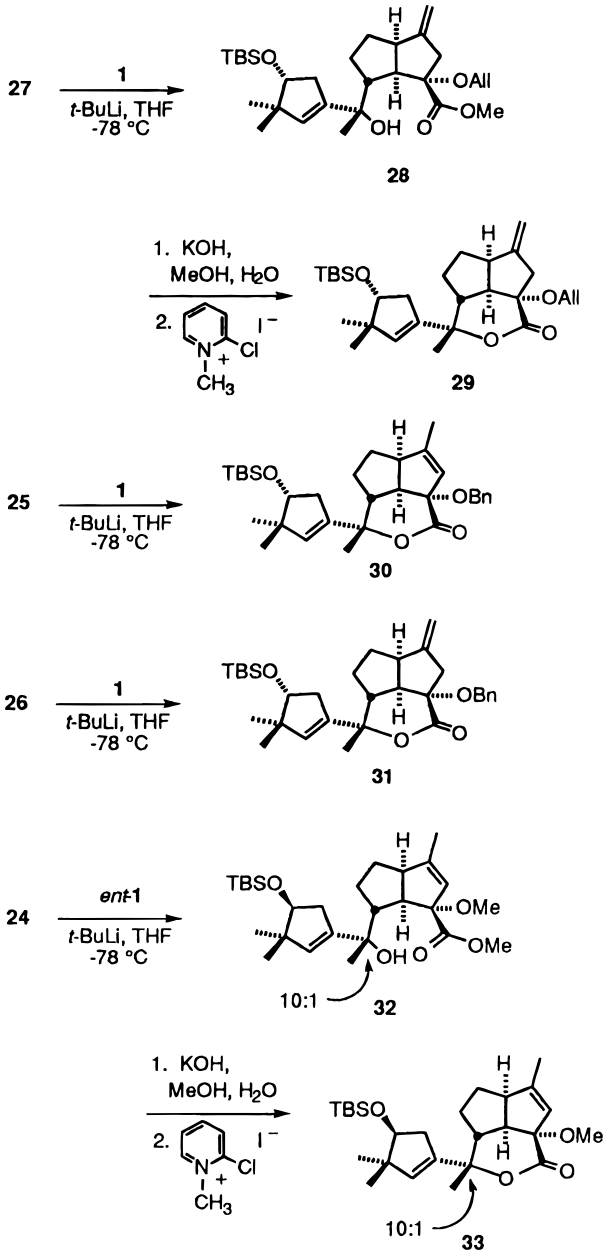
opening of terminal oxiranes is well documented,[20] the projected course of the epoxidation and reduction of **17** was not cause for concern. In contrast, the existing situation in **16** was not clear. Consequently, a preliminary scrutiny of this question was put in motion with **16** as the test case (Scheme 4). The formation of intermediates **20**−**22** was uneventful as expected. Satisfyingly, the exposure of **22** to Red-Al proceeded by initial rapid reduction of the carbomethoxy group to the primary alcohol and ensuing regiocontrolled internal hydride delivery[21] (see **L**) to cleave the oxirane ring and give rise to **23** as the sole product (94%). In light of these results, this methodology or a closely related one was deemed attractive as the means for introducing the 16-hydroxyl substituent after elaboration of the B-ring.

Tebbe−Claisen Technology. Elaboration of the Complete Tetracyclic Ring System. At this stage, the plan called for conjoining of the A-ring synthon **1** with either **16** or **17** as the means for constructing the cyclooctanoid B ring and assembling the complete framework of the target. Control of the stereochemical course of the 1,2-carbonyl addition was, of course, mandated since this event has obvious implications on the particular transition state to be adopted during the projected [3.3] sigmatropic transition state. Since little precedence was available, thorough experimental analysis of this strategic connectivity was first planned.

Beyond this, deployment of a Tebbe−Claisen sequence ultimately requires olefination of the ester carbonyl already resident in **16** and **17**. Since the nature of the substituent positioned α to this functionality could impact on the central Claisen rearrangement step, the O-substituted derivatives **24**−**27** were prepared for direct evaluation.



Scheme 5



Following halogen−metal exchange in **1** with *tert*-butyllithium, the organometallic reagent was added first to **27** in THF at −78 °C. This inverse addition resulted in the formation of hydroxy ester **28**; only trace amounts of lactone **29** were seen. In contrast, comparable processing of **25** and **26** led directly to the fully cyclized lactones **30** and **31**, respectively, in excellent yield (Scheme 5). A similar experiment involving *ent*-**1** and **24** led again predominantly to the hydroxy ester, *viz.* **32**. The conversion of **28** and **32** to their respective lactones **29** and **33** was accomplished smoothly by sequential saponification and brief treatment of the resulting hydroxy acids with Mukaiyama's reagent.[22] The overall yields from the keto esters were 85−95%.

^{1}H NMR analysis revealed that a strong bias for stereoselective nucleophilic addition was operational in all four cases. In fact, a single isomer was formed in each instance except for **32** where a 10:1 ratio of diastereomers was produced. NOE studies performed on each of the conformationally rigid lactones provided convincing evidence that all belonged to the same

(20) For example: Quartucci, J.; Rickborn, B. *J. Org. Chem.* **1964**, 29, 3165.

(21) Viti, S. M. *Tetrahedron Lett.* **1982**, *44*, 4541.

(22) (a) Mukaiyama, T.; *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 707. (b) Mukaiyama, T.; Ushui, M.; Shimada, E.; Saigo, K. *Chem. Lett.* **1975**, 1045. (c) Mukaiyama, T.; Toda, H.; Kobayashi, S. *Chem. Lett.* **1976**, 13.

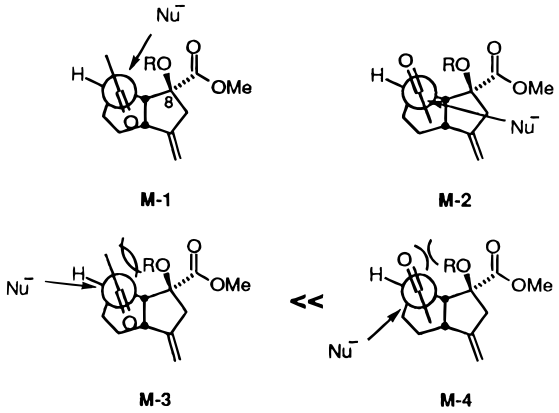


Figure 1. The four possible nucleophilic trajectories associated with **26** and **27**.

stereochemical subset. Consequently, both **1** and *ent*-**1** exhibit the same facial selectivity, indicating that the configuration of the OTBS-substituted carbon has little, if any, effect on the product distribution. Similarly, the exo or endo positioning of the double bond in ring D has no impact on selectivity, presumably as a result of its relatively remote location relative to the reaction center. Four transition state arrangements emerge as potential candidates for that which is of lower energy under these circumstances (Figure 1). Without doubt, the trajectories associated with **M-1** and **M-2** can be quickly dismissed on the basis of the high steric demands for nucleophilic attack. The geometry associated with **M-3** brings into play nonbonded steric compression between the methyl ketone and the R group situated on the protected C-8 hydroxyl. This state of affairs is minimized significantly in **M-4**. On this basis, we favor the **M-4** trajectory, which satisfyingly corresponds to the experimental results.

According to this model, the greater the size of R, the more elevated should be the stereoselectivity of nucleophilic capture. The observed diastereomeric ratios do indeed give evidence of being linked to the bulkiness of the R group. The remarkably high levels of stereoselectivity appear therefore to be linked to the restricted spatial orientation of the methyl ketone functionality, which in turn is dictated by the level of steric congestion provided by R.

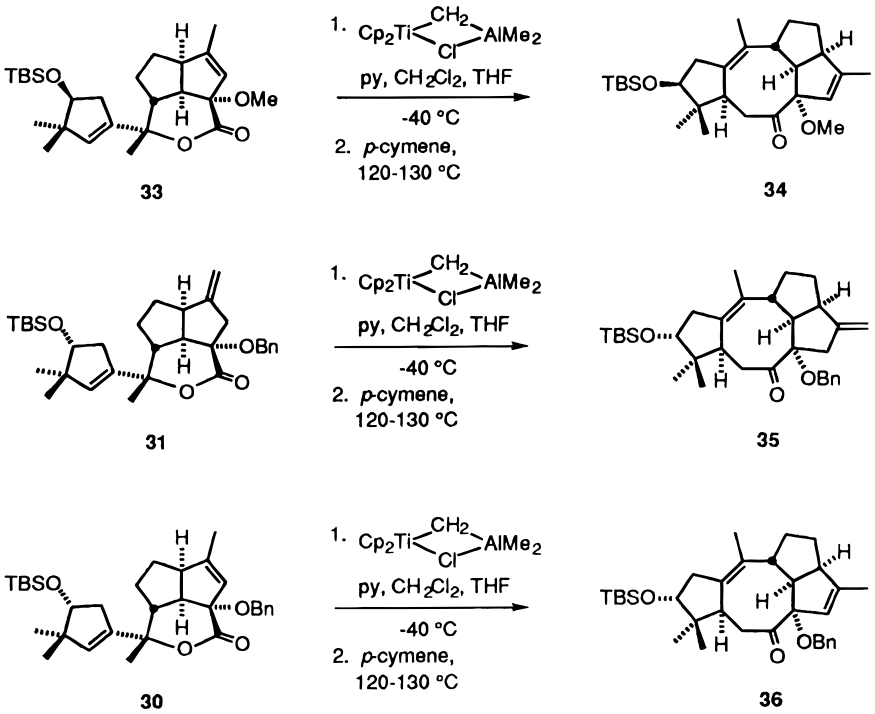
The highly stereocontrolled course of lactone formation was a most welcomed development which set the stage admirably for examination of the projected ring expansion. This central, convergent element of our strategy, shown to be highly workable in other synthetic contexts,[23,24] requires not only successful methenylation of **30**−**32** but also an ability on the part of the resulting enol ethers to participate in [3.3] sigmatropy via a suitable chair-like transition state.

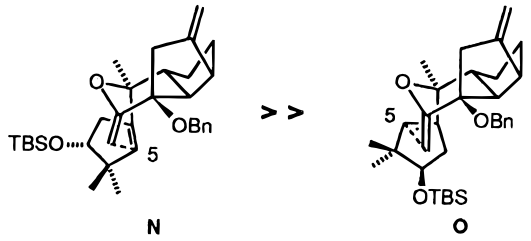
To this end, **33** was initially treated with the Tebbe reagent[25] and pyridine in a 1:1 mixture of CH_2Cl_2 and THF at −40 °C, and the exocyclic enol ether so produced[26] was purified by rapid filtration through a plug of basic alumina and heated in *p*-cymene at 120−130 °C for 2 h. Smooth conversion to **34** (as a 10:1 isomeric mixture) was observed (68% for the two steps, Scheme 6). In the same fashion, both **31** and **30** were readily transformed into **35** and **36**, respectively, in 86% overall yield. The exceptionally low temperature and short reaction times required for these conversions suggest that strain relief within the bridged diquinane components operates at the rate-determining transition states and provides a useful driving force for facilitating the electronic reorganization.

Numerous examples[24] have established that the Claisen ring expansion is controlled by an overriding thermodynamic preference for setting a *Z* double bond in the 4-cylcooctenone ring via a chair-like transition state if at all possible. From among the two geometries available to **31**, for example, the choices are to orient the cyclopentenyl unit as in **N** or **O**. In the first instance, a chair-like alignment shall develop, a *Z* double bond will be generated, and H-5 will be projected to the α-face. Option **O**, on the other hand, requires a boat-like geometry, results in the evolution of an *E* double bond, and fixes H-5 in a β-orientation. In addition, **O** suffers from steric compression between the exocyclic methylene group and the OTBS substituent. On the basis of these many factors, transition state **N** should be kinetically favored by a wide margin and apparently is. The relative stereochemistry resident in **35** follows from NOE studies performed on diepoxide **38** (see Experimental Section).

Functionalization of the Backbone. The ready formation of **35** permitted its exploitation as a precursor to **3**. The requisite

Scheme 6





N O

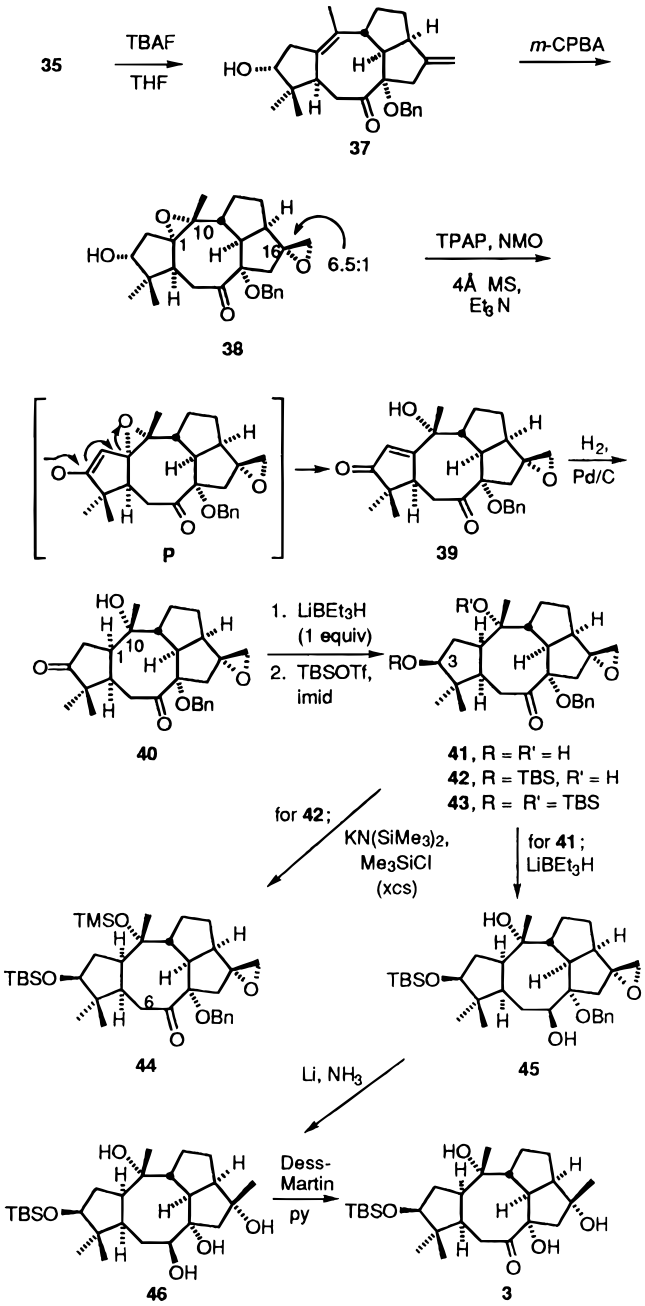
series of transformations, summarized in Scheme 7, began with the generation of hydroxy ketone **37** and its conversion to diepoxide **38**. These efficient steps straightforwardly introduced requisite oxygen atoms at both C-10 and C-16 in concurrent fashion. Furthermore, the facial selectivity of peracid attack was established by NOE methods to be as desired. Whereas reaction at the C-1/C-10 double bond was 100% α-stereoselective, the partitioning at the exocyclic C-16 site was α-selective to the extent of 87%.

Submission of **38** to perruthenate oxidation in the presence of triethylamine prompted conversion to enolate anion **P**, setting in place the opportunity for β-elimination and establishment of the proper stereochemistry for the tertiary carbinol functionality resident at C-10. With arrival at **39**, the stage was set for saturation of the enone by catalytic hydrogenation over Pd/C. In line with precedent,[27] a cis A/B ring junction was thereby established. The pair of ketone carbonyls in **40** differ appreciably in their steric screening. Advantage was taken of this feature to accomplish controlled reduction to **41** with 1 equiv of lithium triethylborohydride in cold CH_2Cl_2 solution. To demonstrate beyond reasonable doubt that the global structural features of **41** have been properly assigned, a detailed NOE analysis of this keto diol was carried out (see Experimental Section).

The action of excess *tert*-butyldimethylsilyl triflate and imidazole on **41** (under DMAP catalysis) served to make **42** available. The doubly-protected diol **43** was produced to a level of only 4%. One's ability to accomplish protection of the tertiary hydroxyl rests only on the choice of silylating agent. The conversion of **42** to **44** proceeded quite well when recourse was made to excess potassium hexamethyldisilazide and chlorotrimethylsilane. Note that silyl enol ether formation was not realized concurrently. This experiment, in fact, provided the first hint of how difficult it would be to develop sp^2 character at C-6.[10]

Next to be addressed was removal of the benzyl protecting group. Much to our delight, treatment of **45** with lithium in liquid ammonia resulted in *concomitant* cleavage of the benzyl ether and the oxirane ring. Subsequent oxidation of (−)-**46** with the Dess−Martin periodinane[28] proceeded without complication to deliver (+)-**3** (93%).

Scheme 7



Summary

Recourse to a Tebbe−Claisen reaction sequence provides a very concise route to the B-homo-C-nor grayanoid framework found uniquely in kalmanol. The diquinane subunit that forms the C/D sector of the tetracyclic ring system is conveniently assembled from the chiral building block **4** by 1,4-addition, Pd(II)-catalyzed carbonylation, and intramolecular aldol cyclization. Since it is crucial that the diquinane be adequately functionalized, particularly in connection with a 1,3-*exo*-acetyl/*endo*-carbomethoxy pattern, some preliminary chemical transformations required implementation. Some of the key lessons learned include (i) a strong diastereofacial bias exists during the 1,2-addition of metalated **1** and its enantiomer to **24**−**27**, such that lactonization often operates spontaneously; (ii) the Claisen ring expansion proceeds via a chair-like transition state, thereby generating a 4-cyclooctenone B-ring in which desirable α stereochemistry is set at C-5 with high fidelity; (iii) the introduction of hydroxyl groups at C-3, C-8, C-10, and C-15

(23) (a) Kinney, W. A; Coghlan, M. J.; Paquette, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 6868; **1985**, *107*, 7352. (b) Kang, H.-J.; Paquette, L. A. *J. Am. Chem. Soc.* **1990**, *112*, 3252. (c) Paquette, L. A.; Kang, H.-J. *J. Am. Chem. Soc.* **1991**, *113*, 2610. (d) Friedrich, D.; Paquette, L. A. *J. Org. Chem.* **1991**, *56*, 3831. (e) Paquette, L. A.; Wang, T.-Z.; Pinard, E. *J. Am. Chem. Soc.* **1995**, *117*, 1455. (f) He, W.; Pinard, E.; Paquette, L. A. *Helv. Chim. Acta* **1995**, *78*, 391.

(24) Paquette, L. A. In *Stereocontrolled Organic Synthesis*; Trost, B. M., Ed.; Blackwell Scientific Publications: Oxford, England, 1994; pp 313−336.

(25) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270.

(26) Schore, N. E. *Org. React.* **1991**, *40*, 1.

(27) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757 and relevant references cited therein.

(28) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

can be efficiently achieved in a minimum number of steps with proper stereochemistry; and (iv) application of the Dess−Martin periodinane to oxidation of a 1,2-diol for the purpose of elaborating an acyloin proceeds without evidence of carbon−carbon bond cleavage.

It can be stated with considerable assurance that the geometries adopted by such molecules as **3** and **44** are not conducive to enolization α to the carbonyl.

Finally, the total synthesis of **3** was accomplished from **4** in 25 steps and 1.6% overall yield. It is hoped that the lessons learned in this series of experiments can be successfully applied to the acquisition of kalmanol and bioactive analogs thereof.

Experimental Section

General Procedure. All manipulations were performed under a nitrogen atmosphere. Solvents were dried over 4 Å molecular sieves before distillation. Benzene, ether, THF, and toluene were distilled from sodium or sodium/benzophenone ketyl. Chlorotrimethylsilane, CH_2Cl_2, diisopropylamine, DMSO, DMF, dioxane, acetonitrile, HMPA, and triethylamine were each distilled from CaH_2. Melting points are uncorrected. Exact mass measurements were recorded on Kratos MS-30 or VG-70-2505 mass spectrometers at The Ohio State University Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. The chromatographic separations were carried out either under flash conditions on Fluka silica gel H or by gravity on Woelm silica gel 63−200. The organic extracts were dried over anhydrous Na_2SO_4. All reagents were reagent grade and purified where necessary.

(3*R*,4*R*)-4-(*tert*-Butyldimethylsiloxy)-3-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]-1-cyclopenten-1-yl Trifluoromethanesulfonate (5b). The Grignard reagent was prepared from a suspension of 5-bromo-2-pentanone ethylene ketal (14.8 g, 3 equiv) and magnesium turnings (4.3 g, 2.25 equiv) in dry THF (120 mL) according to precedent.[12] The resulting gray-green solution was transferred to a precooled (−78 °C) suspension of CuBr·Me_2S complex (2.2 g, 0.15 equiv) and dry HMPA (13 mL) in dry THF (60 mL). The resulting slurry was stirred at −78 °C for an additional hour and a precooled (−78 °C) solution of **4** (5 g, 0.0236 mol) and trimethylchlorosilane (30 mL, 10 equiv) in dry THF (70 mL) was transferred *via* cannula over 5 min. The reaction mixture was stirred at the same temperature for an additional hour and was quenched with dry triethylamine (100 mL) in hexanes (250 mL), warmed to room temperature, and concentrated by rotary evaporation to leave a black residue which was taken up in 10% Et_3N in hexanes and filtered through glass wool. The colorless oily **5a** obtained after concentration to dryness (9 g, 99%) was dissolved in dry THF (300 mL). The resulting solution was cooled to −20 °C, treated with 1.4 M MeLi (21.5 mL, 1.3 equiv) solution in ether, stirred at the same temperature for 0.5 h before the addition of a *N*-phenyltrifluoromethanesulfonimide (13 g, 1.5 equiv) solution in dry THF (100 mL), agitated at the same temperature overnight, quenched with 10% NaOH solution (100 mL), and diluted with hexanes (300 mL). The organic layer was dried, and the residue obtained after concentration was purified by silica gel chromatography (elution with 5:1 hexanes−ether) to give 9.49 g (91%) of **5b** as a colorless oil: IR (neat, cm^{-1}) 3010−2900, 2895, 1425, 1380, 1220, 1150, 1085, 840, 785; ^1H NMR (300 MHz, C_6D_6) δ 5.22 (br s, 1H), 3.81 (m, 1H), 3.53 (s, 4H), 2.52−2.32 (m, 3H), 1.63−1.58 (m, 2H), 1.43−1.33 (m, 2H), 1.27 (s, 3H), 1.24 (m, 1H), 1.11 (m, 1H), 0.89 (s, 9H), −0.028 (s, 3H), −0.075 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 144.1, 119.3, 117.3, 117.1 (q, J_{CF} = 318.45 Hz, CF_3), 107.8, 73.6, 62.6, 49.7, 39.0, 37.7, 31.3, 23.8, 22.0, 20.0, 16.0, −6.6, −6.9; HRMS *m/z* [M^+ − *t*-Bu] calcd for $C_{19}H_{33}O_6F_3Si$ 397.1294, obsd 397.1119; $[\alpha]^{20}_D$ −36.1 (*c* 3.2, $CHCl_3$).

Methyl (3*R*,4*R*)-4-(*tert*-Butyldimethylsiloxy)-3-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]-1-cyclopentene-1-carboxylate (6). A nitrogen-blanketed, magnetically stirred solution of **5b** (1.9 g, 4.3 mmol), triethylamine (1.2 mL, 2 equiv), methanol (8.6 mL, 5 equiv), triphenylphosphine (110 mg, 0.1 equiv), and palladium acetate (41 mg, 4% mol) in dry DMF (15 mL) was flushed with carbon monoxide for 5 min, kept under 1 atm of carbon monoxide for 3 h, diluted with ether(100 mL), washed with saturated NH_4Cl solution (2 × 20 mL), and dried. Purification of the residue by silica gel chromatography (elution with 2.5:1 hexanes−ether) gave 1.44 g (87%) of **6** as a colorless oil: IR (neat, cm^{-1}) 3020−2900, 2900−2760, 1720, 1630, 1440, 1360, 1250, 1110, 830, 770; ^1H NMR (300 MHz, $CDCl_3$) δ 6.66 (m, 1H), 4.09 (m, 1H), 3.94−3.88 (m, 4H), 3.71 (s, 3H), 2.86−2.78 (m, 1H), 2.64 (m, 1H), 2.47−2.38 (m, 1H), 1.73−1.61 (m, 2H), 1.50−1.25 (m, 4H), 1.29 (s, 3H), 0.86 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 165.5, 144.8, 132.8, 109.8, 77.9, 64.6, 55.3, 51.4, 40.6, 39.3, 32.4, 25.8, 23.8, 22.1, 17.9, −4.5, −4.8; HRMS *m/z* calcd for $C_{20}H_{36}O_5Si$ 384.2332, obsd 384.2332; $[\alpha]^{20}_D$ −45.6 (*c* 0.38, CH_2Cl_2). *Anal.* Calcd for $C_{20}H_{36}O_5Si$: C, 62.46; H, 9.44. Found: C, 62.58; H, 9.49.

Methyl (3*R*,4*R*)-4-(*tert*-Butyldimethylsiloxy)-3-(4-oxopentyl)-1-cyclopentene-1-carboxylate (7). A magnetically stirred solution of **6** (1.5 g, 3.9 mmol) in anhydrous acetone (30 mL) was stirred at room temperature in the presence of a catalytic amount of *p*-toluenesulfonic acid for 36 h, quenched by the addition of a few drops of triethylamine, and concentrated. The residue was purified by silica gel chromatography (elution with 1.5:1 hexanes−ether) to give 1.13 g (85%) of **7** as a colorless oil: IR (neat, cm^{-1}) 3020−2890, 2760, 1715, 1625, 1430, 1350, 1250, 1100, 1060, 830, 770; ^1H NMR (300 MHz, $CDCl_3$) δ 6.61 (m, 1H), 4.07 (m, 1H), 3.68 (s, 3H), 2.79−2.76 (m, 1H), 2.64−2.60 (m, 1H), 2.44−2.37 (m, 3H), 2.09 (s, 3H), 1.64−1.55 (m, 2H), 1.46−1.39 (m, 1H), 1.35−1.27 (m, 1H), 0.84 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 208.3, 165.3, 144.2, 133.0, 77.8, 54.9, 51.4, 43.4, 40.6, 31.5, 29.8, 25.7, 17.9, −4.5, −4.9; HRMS *m/z* [M^+] calcd for $C_{18}H_{32}O_4Si$ 340.2070, obsd 340.2064; $[\alpha]^{20}_D$ −47.7 (*c* 2.7, $CHCl_3$).

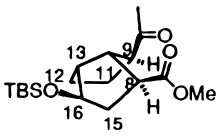
Methyl (1*S*,3*R*,3a*R*,6*S*,6a*R*)-6-Acetyl-3-(*tert*-butyldimethylsiloxy)-octahydro-1-pentalenecarboxylate (8) and Methyl (1*R*,3*R*,3a*R*,6*S*,6a*R*)-6-Acetyl-3-(*tert*-butyldimethylsiloxy)octahydro-1-pentalenecarboxylate (9). To a nitrogen-blanketed solution of **7** (1 g, 2.94 mmol) in dry benzene (55 mL) was added potassium *tert*-butoxide (165 mg, 0.5 equiv) in one portion. The reaction mixture was stirred for 10 min at room temperature and quenched by the addition of saturated NH_4Cl solution (30 mL). The organic phase was separated, dried, and concentrated. The residue was dissolved in 20 mL of dry MeOH and stirred in the presence of a catalytic amount of K_2CO_3 overnight. Solvent evaporation and purification of the residue by silica gel chromatography (elution with 2:1 hexanes−ether) gave a 2.3:1 mixture of **8** and **9** (920 mg, 92%): HRMS *m/z* [M^+] calcd for $C_{18}H_{32}O_4Si$ 340.2070, obsd 340.2076. *Anal.* Calcd for $C_{18}H_{32}O_4Si$: C, 63.49; H, 9.47. Found: C, 63.35; H, 9.41.

For **8**: IR (neat, cm^{-1}) 2950, 2880, 1730, 1710, 1430, 1360, 1250, 1160, 1100, 830, 770; ^1H NMR (300 MHz, C_6D_6) 3.81 (br d, J = 3.7 Hz, 1H), 3.42−3.34 (m, 2H), 3.38 (s, 3H), 2.60 (m, 1H), 2.42 (br q, J = 4.4 Hz, 1H), 1.99−1.90 (m, 1H), 1.89 (s, 3H), 1.88−1.78 (m, 1H), 1.75 (m, 1H), 1 68, m, 1H), 1.21 (m, 1H), 0.96 (s, 9H), 0.81 (m, 1H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 207.3, 174.5, 78.1, 55.4, 54.5, 50.8, 46.5, 44.7, 36.7, 32.6, 31.5, 28.6, 26.0, 18.2, −4.7, −4.8; $[\alpha]^{20}_D$ −10.5 (*c* 1.95, CH_2Cl_2).

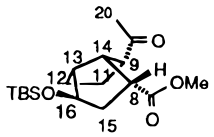
For **9**: IR (neat, cm^{-1}) 2950, 2880, 1730, 1710, 1430, 1360, 1250, 1160, 1100, 830, 770; ^1H NMR (300 MHz, C_6D_6) δ 3.61 (q, J = 5.1 Hz, 1H), 3.37 (s, 3H), 3.16 (m, 1H), 2.38 (m, 1H), 2.24 (m, 1H), 2.18 (m, 1H), 2.04 (m, 1H), 1.93 (m, 1H), 1.81 (s, 3H), 1.73−1.60 (m, 2H), 1.41 (m, 1H), 1.08 (m, 1H), 0.92 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 309.7, 174.7, 78.8, 59.3, 52.4, 51.7, 48.2, 47.2, 39.1, 30.0, 29.3, 28.4, 25.7, 17.9, −4.7, −4.8; $[\alpha]^{20}_D$ −14.8 (*c* 0.8, CH_2Cl_2).

Methyl (1*S*,3*R*,3a*R*,6*R*,6a*R*)-6-(1,1-Dimethyloxyethyl)octahydro-3-hydroxy-1-pentalenecarboxylate (11). To a solution of **8** (400 mg, 1.176 mmol) in dry methanol (15 mL) was added trimethyl orthoformate (2 mL, 15 equiv) followed by a catalytic amount of *p*-toluenesulfonic acid. The mixture was stirred for 8 h, at which time a few drops of pyridine were added. Concentration by rotary evaporation followed by silica gel chromatography (elution with 1:3 hexanes−ether) afforded **11** (297 mg, 93%) as a colorless oil: IR (neat, cm^{-1}) 3600−3100, 2865, 1715, 1430, 1375, 1250, 1150, 840; ^1H NMR (300 MHz, C_6D_6) δ 3.79 (m, 1H), 3.36 (s, 3H), 3.01 (s, 3H), 2.98 (s, 3H), 2.95 (m, 1H), 2.78 (d, J = 6.9 Hz, 1H), 2.47 (dq, J = 3.0, 8.8 Hz, 1H), 2.00−191 (m, 3H), 1.75 (m, 1H), 1.57 (m, 1H), 1.26 (m, 1H), 1.14 (s, 3H), 0.94 (m, 1H); ^{13}C NMR (75 MHz, C_6D_6) ppm 177.9, 103.7, 79.3, 54.4, 52.7, 51.5, 50.0, 48.6, 47.9, 47.5, 38.7, 30.8, 29.6, 17.7; HRMS *m/z* [M^+] calcd for $C_{14}H_{24}O_5$ 257.1389, obsd 257.1421; $[\alpha]^{20}_D$ +21.9 (*c* 0.7, CH_2Cl_2).

Methyl (1*S*,3a*R*,6*R*,6a*R*)-6-(1,1-Dimethyloxyethyl)octahydro-3-oxo-1-pentalenecarboxylate (12). A mixture of **11** (950 mg, 3.49



Irradiate	Observe	% n.O.e.
H_8	H_{14}	3.0
	α-H_{15}	2.9
	H_{16}	1.2
	α-H_{11}	3.8
	α-H_{12}	0.4
H_9	H_{14}	2.8
	α-H_{11}	1.4
	H_{16}	4.3
α-H_{11}	H_9	7.6
	α-H_{12}	1.5
	H_{16}	2.4
α-H_{12}	H_{13}	0.85
	α-H_{11}	1.4
H_{13}	H_{14}	13.5
	H_{16}	2.45
H_{14}	20-CH_3	3.6
	H_9	2.6
	H_8	2.1
	H_{13}	11.5
α-H_{15}	H_9	9.0
	H_{16}	6.3
H_{16}	α-H_{12}	3.9
	H_8	0.5
	H_9	4.3
	H_{13}	2.5
	α-H_{15}	3.1



Irradiate	Observe	% n.O.e.
H_9	α-H_{11}	3.3
	H_{16}[a]	7.7
α-H_{11}	H_9	7.7
	α-H_{12}	4.9
	H_9	3.0
	H_{13}	1.1
	H_{14}	2.1
β-H_{11}	H_{16}	10.2
	α-H_{11}	6.3
	H_9	5.7
	H_{13}	1.2
β-H_{12}	β-H_{11}	5.3
	H_{13}	5.8
H_{13}	H_{16}	2.4
	β-H_{12}	3.9
	β-H_{11}	0.9
α-H_{15}	H_8	1.0
	H_{16}	6.9
	H_9	6.2
	α-H_{12}	2.3
β-H_{15}	H_8	7.2
	H_{16}	1.9
H_{16}	α-H_{12}	3.7
	α-H_{15}	5.9
	H_9	3.0
	H_{13}	2.9

[a] Overlap with H_{14}.

mmol), *N*-methylmorpholine *N*-oxide (740 mg, 1.81 equiv), 4 Å molecular sieves (500 mg), and a catalytic amount of *N*-methylmorpholine was slurried in dry CH_2Cl_2 (60 mL) and stirred for 15 min before the addition of tetrapropylammoniumperruthenate (30 mg, 2.5% mol). The resulting mixture was stirred overnight, filtered through a small plug of Celite, and concentrated to leave a residue which was purified by silica gel chromatography (elution with 1:1 hexanes−ether). There was obtained 820 mg (86%) of **12** as a colorless solid, mp 94 °C (from hexanes): IR ($CHCl_3$, cm^{-1}) 3020−2860, 2840, 1740, 1440, 1380, 1270, 1240, 1100, 860, 815, 740; ^1H NMR (300 MHz, C_6D_6) δ 3.31 (s, 3H), 2.97−2.95 (m, 1H), 2.96 (s, 3H), 2.89 (s, 3H), 2.67 (m, 1H), 2.65−2.49 (m, 2H), 2.22 (dd, J = 18.4, 8.5 Hz, 1H), 1.98 (q, J = 7.8 Hz, 1H), 1.68−1.60 (m, 2H), 1.55−1.50 (m, 1H), 1.48−1.29 (m, 1H), 1.00 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 216.9, 175.2, 103.4, 52.1, 51.4, 50.5, 47.9, 47.6, 44.0, 40.5, 28.3, 27.7, 17.6; HRMS *m/z* [M^+] calcd for $C_{14}H_{22}O_5$ 270.1467, obsd 270.1448; $[\alpha]^{20}_D$ −49.2 (*c* 0.7, CH_2Cl_2). *Anal.* Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.24; H, 8.17.

Methyl (3a*R*,6*R*,6a*R*)-6-(1,1-Dimethoxyethyl)-3,3a,4,5,6,6a-hexahydro-3-oxo-1-pentalenecarboxylate (13). To a cold (−78 °C) solution of **12** (as a 2.3:1 isomer mixture, 91 mg, 0.34 mmol) and trimethylchlorosilane (0.22 mL, 5 equiv) in dry THF (10 mL) was added a 0.1 M LDA solution (8 mL, 2.6 equiv) in THF. The reaction mixture was stirred for 10 min before being quenched by the addition of triethylamine (1 mL) in hexanes (5 mL), allowed to warm up to room temperature, and concentrated. Filtration through a plug of glass wool followed by concentration to dryness afforded 109 mg (94%) of the corresponding silyl enol ether as a colorless oil, which was directly dissolved in dry THF (20 mL) and cooled to −78 °C. Propylene oxide (0.24 mL, 10 equiv) followed by *N*-bromosuccinimide (68 mg, 1.3 equiv) was added, and the reaction mixture was allowed to warm up to room temperature over 1 h. Et_3N (0.48 mL, 10 equiv) was added, and the resulting solution was stirred overnight, quenched with saturated $NaHCO_3$ solution (10 mL), and extracted with ether (2 × 20 mL). Drying and concentration of the organic layers afforded a residue which was purified by silica gel chromatography to give **13** (78 mg, 86%) as a colorless solid, mp 101−102 °C (from 1:2 pentane−ether): IR ($CHCl_3$, cm^{-1}) 2970, 2815, 1715, 1600, 1430, 1380, 850; ^1H NMR (300 MHz, C_6D_6) δ 6.36 (d, J = 1.3 Hz, 1H), 3.34 (s, 3H), 3.29 (m, 1H), 2.99 (s, 3H), 2.88 (s, 3H), 2.57 (m, 1H), 2.05 (q, J = 5.9 Hz, 1H), 1.79−1.72 (m, 2H), 1.48−1.39 (m, 2H), 1.09 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 210.2, 166.2, 165.3, 135.3, 102.8, 53.4, 51.4, 50.6, 48.7, 48.1, 47.9, 28.5, 27.1, 17.9; HRMS *m/z* [M^+] calcd for $C_{14}H_{20}O_5$ 268.1311, obsd 268.1311; $[\alpha]^{20}_D$ −47.9 (*c* 0.61, CH_2Cl_2). *Anal.* Calcd for $C_{14}H_{20}O_5$: C, 59.15; H, 7.10. Found: C, 59.16; H, 7.15.

Methyl (1*S*,2*S*,3a*R*,6*R*,6a*S*)-6-(1,1-Dimethoxyethyl)-2,3-epoxyoctahydro-3-oxo-1-pentalenecarboxylate (14). To a cold (−10 °C) solution of **13** (180 mg, 0.68 mmol) in CH_2Cl_2 (10 mL) and methanol (4 mL) was added 30% H_2O_2 (0.9 mL, 5 equiv) followed by 1 N NaOH solution (0.78 mL, 1.3 equiv). The resulting solution was warmed to 10 °C over 2 h, at which time saturated brine (20 mL) and CH_2Cl_2 (20 mL) were introduced. The separated organic layer was dried and concentrated. The residue was purified by silica gel chromatography (elution with 1:1 hexanes−ether) to give **14** (150 mg, 78%) as a colorless solid, mp 101−102 °C: IR (neat, cm^{-1}) 2975, 2890, 1730, 1440, 1375, 1160, 1035, 870; ^1H NMR (300 MHz, C_6D_6) δ 3.53 (s, 1H), 3.32 (s, 3H), 2.93 (t, J = 7.6 Hz, 1H), 2.88 (s, 3H), 2.85 (s, 3H), 2.46 (m, 2H), 1.81 (m, 1H), 1.36−1.33 (m, 3H), 0.94 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 208.8, 165.8, 103.1, 66.8, 59.3, 51.7, 49.5, 48.0, 47.5, 46.1, 45.5, 27.9, 25.9, 17.2; HRMS *m/z* [$M^+ - CH_3$] calcd for $C_{14}H_{20}O_6$ 269.1025, obsd 269.1017; $[\alpha]^{20}_D$ +5.1 (*c* 0.17, CH_2Cl_2). *Anal.* Calcd for $C_{14}H_{20}O_6$: C, 59.15; H, 7.10. Found: C, 59.16; H, 7.15.

Methyl (1*S*,2*S*,3a*R*,6*R*,6a*S*)-6-(1,1-Dimethoxyethyl)-2,3-epoxyoctahydro-3-methylene-1-pentalenecarboxylate (15). A nitrogen-blanketed suspension of methyltriphenylphosphonium bromide (190 mg, 1.5 equiv) in dry THF (20 mL) was treated with 1.3 M *n*-butyllithium in hexanes (0.39 mL, 1.4 equiv), stirred for 0.5 h at room temperature, and cooled to −78 °C. A cold (−78 °C) solution of **14** (100 mg, 0.354 mmol) in dry THF (20 mL) was added via cannula to the Wittig reagent. The resulting mixture was allowed to warm to room temperature over 3 h, stirred for an additional 3 h, quenched with saturated brine (30 mL), and diluted with ether (70 mL). The separated organic layer was dried and concentrated to afford a residue which was purified by silica gel chromatography (elution with 1.5:1 hexanes−ether) to give **15** as a colorless solid (49.6 mg, 50%), mp 62−63 °C: IR (CH_2Cl_2, cm^{-1}) 3035, 2980, 2890, 1735, 1655, 1445, 1375, 1155, 1040, 870; ^1H NMR (300 MHz, C_6D_6) δ 5.08 (d, J = 2.6 Hz, 1H), 4.81 (d, J = 2 Hz, 1H), 3.85 (s, 1H), 3.43 (s, 3H), 2.94 (s, 3H), 2.93 (s, 3H), 2.86 (m, 1H), 2.76−2.63 (m, 2H), 1.61−1.40 (m, 4H), 1.01 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 167.5, 151.0, 110.9, 103.7, 68.3, 64.5, 51.4, 49.8,

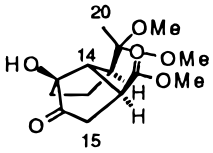
48.1, 47.5, 45.9, 44.3, 29.4, 27.6, 17.2; HRMS *m/z* [M$^+$] calcd for $C_{15}H_{22}O_5$ 282.1467, obsd 282.1478; $[\alpha]^{20}_D$ −47.5 (*c* 0.12, CH_2Cl_2).

Methyl (1*R*,3a*R*,6*R*,6a*R*)-6-(1,1-Dimethyloxyethyl)-1,3a,4,5,6,6a-hexahydro-1-hydroxy-3-methyl-1-pentalenecarboxylate (16). A solution of **15** (325 mg, 1.15 mmol), ammonium formate (148 mg, 2 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (61 mg, 5% mol), and tributylphosphine (30 μL, 5% mol) in dry dioxane was refluxed for 1 h, cooled to room temperature, filtered through a plug of Celite, and concentrated to dryness. Purification of the residue by silica gel chromatography (elution with 1:4 hexanes−ether) afforded a 13:1 mixture of **16** and **17** (297 mg, 91%).

For **16**: IR (neat, cm^{-1}) 3700−3200, 2975, 2840, 1730, 1650, 1475, 1420, 1275, 1200, 905; ^{1}H NMR (300 MHz, C_6D_6) δ 5.31 (d, J = 1.3 Hz, 1H), 3.85 (s, 1H), 3.08 (s, 3H), 3.06 (m, 1H), 3.04 (s, 3H), 3.03 (s, 3H), 2.87 (dd, J = 8.07, 6.28 Hz, 1H), 2.57 (q, J = 7 Hz, 1H), 1.78−1.54 (m, 3H), 1.57 (s, 3H), 1.44 (m, 1H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 175.8, 149.0, 127.0, 103.8, 88.6, 60.3, 54.6, 51.7, 47.9, 47.5, 46.1, 29.5, 29.2, 17.7, 15.1; HRMS *m/z* [M$^+$] calcd for $C_{15}H_{24}O_5$ 284.1624, obsd 284.1627; $[\alpha]^{20}_D$ −18.6 (*c* 0.25, CH_2Cl_2). *Anal.* Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.38; H, 8.60.

Methyl (1*S*,3a*R*,6*R*,6a*R*)-6-(1,1-Dimethoxyethyl)octahydro-1-hydroxy-3-methylene-1-pentalenecarboxylate (17). A solution of **15** (400 mg, 1.41 mmol), ammonium formate (177.6 mg, 2 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (75 mg, 5% mol), and triphenylphosphine (15 mg, 5% mol) in dry dioxane was refluxed for 1 h, cooled to room temperature, filtered through a plug of Celite, and concentrated to dryness. Purification of the residue by silica gel chromatography (elution with 1:4 hexanes−ether) afforded **17** as a colorless oil (356 mg, 91%): ^{1}H NMR (300 MHz, C_6D_6) δ 4.97 (br t, J = 1 Hz, 1H), 4.91 (br t, J = 1 Hz, 1H), 3.40 (s, 3H), 3.30 (br s, 1H), 3.28 (m, 1H), 3.11 (dq, J = 12.3, 2.5 Hz, 1H), 2.92 (s, 3H), 2.91 (s, 3H), 2.64 (br d, J = 12.4 Hz, 1H), 2.59 (m, 1H), 2.41 (br t, J = 6.3 Hz, 1H), 1.69−1.51 (m, 3H), 1.49−1.47 (m, 1H), 0.99 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 174.9, 154.1, 106.9, 104.3, 83.6, 60.4, 51.7, 50.2, 48.1, 47.3, 44.2, 43.9, 33.2, 27.5, 17.3; HRMS *m/z* [M$^+$] calcd for $C_{15}H_{24}O_5$ 284.1623, found 284.1627; $[\alpha]^{20}_D$ −25.4 (*c* 0.4, CH_2Cl_2). *Anal.* Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.38; H, 8.60.

Methyl (1*S*,3a*S*,6*R*,6a*R*)-6-(1,1-Diethoxyethyl)octahydro-3a-hydroxy-3-oxo-1-pentalenecarboxylate (19). For **19**: mp 95 °C; IR (KBr, cm^{-1}) 3600−3130, 2920, 2830, 1720, 1380, 1310, 1100, 1030, 840; ^{1}H NMR (300 MHz, C_6D_6) δ 3.33 (s, 3H), 3.08 (s, 1H), 2.97 (s, 3H), 2.95 (s, 3H), 2.68−2.47 (m, 3H), 2.31−2.22 (m, 2H), 1.83 (m, 1H), 1.63 (m, 2H), 1.44 (m, 1H), 1.24 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 214.6, 174.8, 103.6, 87.8, 55.0, 52.0, 51.6, 48.2, 47.8, 44.3, 39.4, 36.2, 27.7, 17.8; HRMS *m/z* [M$^+$] calcd for $C_{14}H_{22}O_6$ 286.1416, obsd 286.1403; $[\alpha]^{20}_D$ −26 (*c* 0.62, CH_2Cl_2).



Irradiate	Observe	% n.O.e.
H_{14}	β-H_{15}	4.0
	20-CH_3	5.8
	$COOCH_3$	1.0
	$(OCH_3)_2$	4.0

Methyl (1*R*,3a*R*,6*R*,6a*R*)-6-(2-Methyl-1,3-dioxolan)-1,3a,4,5,6,6a-hexahydro-1-hydroxy-3-methyl-1-pentalenecarboxylate (20). Ester **16** (100 mg, 0.354 mmol) was dissolved in a 1:1 mixture of dimethoxypropane and ethylene glycol (5 mL total), and a crystal of *p*-TsOH was added. This was stirred for 10 min, at which time it was diluted with ether, washed with water (3 × 5 mL), and dried. The residue obtained after concentration was purified by silica gel chromatography (elution with 1:4 hexanes−ether) to give **20** (100 mg, 98%) as a colorless oil: IR (neat, cm^{-1}) 3700−3100, 2995, 2940, 1735, 1450, 1380, 1245, 1110, 1000, 920; ^{1}H NMR (300 MHz, C_6D_6) δ 5.16 (br s, 1H), 3.93−3.89 (m, 4H), 3.76 (s, 3H), 3.17 (q, J = 8.3 Hz, 1H), 2.76 (t, J = 8.2 Hz, 1H), 2.18 (m, 1H), 1.90−1.79 (m, 2H), 1.74 (br s, 1H), 1.64−1.53 (m, 1H), 1.38−126 (m, 1H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, C6D6) ppm 176.1, 149.2, 126.7, 88.4, 65, 64.6, 59, 54.6, 51.8, 50.3, 30.9, 30.0, 23.5, 15.1; HRMS *m/z* [M$^+$] calcd for $C_{15}H_{22}O_5$ 282.1467, obsd 282.1461; $[\alpha]^{20}_D$ −9.1 (*c* 0.6, CH_2Cl_2). *Anal.* Calcd for $C_{15}H_{22}O_5$: C, 63.36; H, 8.51. Found: C, 63.38; H, 8.60.

Methyl (1*R*,2*R*,3*S*,3a*R*,6*R*,6a*R*)-2,3-Epoxyoctahydro-1-hydroxy-3-methyl-6-(2-methyl-1,3-dioxolan-2-yl)-1-pentalenecarboxylate (21). To a slurry of **20** (61 mg, 0.216 mmol) and sodium carbonate (54 mg, 3 equiv) in dry CH_2Cl_2 (10 mL) was added 95% *m*-chloroperbenzoic acid (75 mg, 2 equiv) in batches over 2 h. The reaction mixture was stirred for 2 h and quenched by the addition of a saturated aqueous solution of sodium sulfite (10 mL). The organic layer was dried and concentrated. The residue was purified by silica gel chromatography (elution with 1:4 hexanes−ethyl acetate) to give **21** (54 mg, 84%) as a colorless oil: IR (neat, cm^{-1}) 3500−3100, 2995, 2980, 2860, 1745, 1450, 1380, 1240, 1100, 1045; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96−3.89 (m, 4H), 3.80 (s, 3H), 3.43 (s, 3H), 3.20 (br s, 1H), 2.70 (m, 1H), 2.37 (dd, J = 5.6, 9.45 Hz, 1H), 1.84 (m, 2H), 1.69 (m, 1H), 1.52−1.45 (m, 2H), 1.43 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 173.7, 110.4, 85.5, 68.4, 67.3, 64.7, 55.5, 52.3, 51.5, 51.4, 30.5, 28, 22.1, 15.6; HRMS *m/z* [M$^+$] calcd for $C_{15}H_{22}O_6$ 298.1416, obsd 298.1423; $[\alpha]^{20}_D$ −17.4 (*c* 0.3, CH_2Cl_2).

Methyl (1*R*,2*S*,3*S*,3a*R*,6*R*,6a*R*)-2,3-Epoxyoctahydro-1-methoxy-3-methyl-6-(2-methyl-1,3-dioxolan-2-yl)-1-pentalenecarboxylate (22). To a nitrogen-blanketed solution of **21** (650 mg, 2.18 mmol) in dry DMF (10 mL) was added sodium hydride (157 mg, 3 equiv) followed by methyl iodide (0.34 mL, 2.5 equiv). The resulting solution was stirred for 15 min at room temperature and quenched with saturated brine (5 mL). The organic phase was extracted with ether (2 × 25 mL) and was dried. The residue obtained after concentration by rotary evaporation was purified by silica gel chromatography (elution with 1:1 hexanes−ether) to give **22** (632 mg, 93%) as a colorless oil: IR (neat, cm^{-1}) 3000−2940, 2875, 1725, 1440, 1375, 1255, 1175, 1100; $_1$H NMR (300 MHz, C_6D_6) δ 3.58−3.51 (m, 4H), 3.42 (s, 1H), 3.30 (s, 3H), 3.29 (s, 3H), 2.85 (dd, J = 9.12, 5.4 Hz, 1H), 2.67 (q, J = 9.5 Hz, 1H), 2.23 (m, 1H), 1.83 (m, 1H), 1.59−1.44 (m, 3H), 1.40 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 172.4, 111.2, 91.9, 67.3, 65.1, 65.0, 64.9, 55.9, 54.5, 51.7, 51.5, 51.0, 29.5, 28.4, 23.7, 16.0; HRMS *m/z* [M$^+$] calcd for $C_{16}H_{24}O_6$ 312.1573, obsd 312.1592; $[\alpha]^{20}_D$ −14.8 (*c* 1.04, CH_2Cl_2).

(1*R*,2*S*,3*S*,3a*R*,6*R*,6a*R*)-3-(*tert*-Butyldimethylsiloxy)octahydro-1-methoxy-3-methyl-6-(2-methyl-1,3-dioxolan-2-yl)-1-pentalen-1′-ol (23). To a cold (−10 °C) solution of **22** (33 mg, 0.106 mmol) in dry THF (6 mL) was added 3.4 M Red-Al in toluene (0.1 mL, 3 equiv). The resulting solution was heated to reflux, treated with 3.4 M Red-Al (3 × 0.1 mL) over 24 h, cooled to −10 °C, and quenched with 20% Rochelle's salt solution (1 mL). The organic phase was extracted with CH_2Cl_2 (2 × 20 mL) and dried. Concentration and purification of the residue by silica gel chromatography (elution with 25:1 dichloromethane−methanol) afforded **23** as a colorless oil (28.5 mg, 94%): IR (neat, cm^{-1}) 3540−3020, 2960−2860, 1450, 1370, 1080; ^{1}H NMR (300 MHz, C_6D_6) δ 4.16−3.80 (br s, 1H), 3.62 (br d, J = 13.2 Hz, 1H), 3.50−3.31 (m, 6H), 3.16 (s, 3H), 2.75−2.68 (m, 2H), 2.07 (m, 1H), 1.69 (dt, J = 14.2, 1.6 Hz, 1H), 1.66−1.44 (m, 3H), 1.24 (s, 3H), 1.07 (s, 3H), 1.02 (d, J = 14.3 Hz, 1H); ^{13}C NMR (75 MHz, C_6D_6) ppm 111.6, 90.3, 79.1, 64.6, 64.4, 61.9, 60.0, 52.1, 50.6, 49.8, 41.9, 31.1, 31.0, 22.7, 22.4; HRMS *m/z* [M$^+$] calcd for $C_{15}H_{26}O_6$ 255.1596, obsd 255.1606; $[\alpha]^{20}_D$ −25.4 (*c* 0.9, CH_2Cl_2)

Methyl (1*S*,3a*R*,6*R*,6a*R*)-6-Oxo-1,3a,4,5,6,6a-hexahydro-1-(methoxy)-3-methyl-1-pentalenecarboxylate (24). To a solution of **20** (274 mg, 0.97 mmol) and methyl iodide (0.12 mL, 2 equiv) in dry DMF (7 mL) was added sodium hydride (70 mg, 3 equiv). The mixture was stirred for 15 min at room temperature, quenched with saturated brine (2 mL), and diluted with ether (20 mL). The organic phase was concentrated by rotary evaporation, the residue was dissolved in acetone (10 mL), and a crystal of *p*-toluenesulfonic acid was added. Stirring was maintained for 10 min prior to quenching with 2 drops of triethylamine. Concentration and purification of the residue by silica gel chromatography (elution with 1:1.5 hexanes−ether) afforded **24** (227.5 mg, 93%) as a colorless oil: IR (neat, cm^{-1}) 2975, 2880, 1745, 1725, 1650, 1440, 1360, 1080; ^{1}H NMR (300 MHz, C_6D_6) δ 5.64 (br s, 1H), 3.45 (s, 3H), 3.31 (t, J = 7 Hz, 1H), 3.14 (s, 3H), 3.07 (m, 1H), 2.55 (q, J = 7 Hz, 1H), 1.92 (s, 3H), 1.61−1.47 (m, 3H), 1.51 (br s, 3H), 1.24 (m, 1H); ^{13}C NMR (75 MHz, C_6D_6) ppm 207.3, 172.5, 151.2, 123.9, 93.8, 55.5, 54.7, 53, 52.1, 51.1, 30.6, 28.2, 27.8, 14.7; HRMS *m/z* [M$^+$ − CH_3] calcd for $C_{13}H_{17}O_4$ 232.1127, obsd 232.1117; $[\alpha]^{20}_D$

+13.6 (*c* 0.14, CH_2Cl_2). *Anal.* Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.56; H, 8.19.

Methyl (1*S*,3a*R*,6*R*,6a*R*)-1-(Benzyloxy)-1,3a,4,5,6,6a-hexahydro-3-methyl-6-oxo-1-pentalenecarboxylate (25) and Methyl (1*S*,3a*R*,6*R*,6a*R*)-6-Oxo-octahydro-1-(benzyloxy)-3-methylene-1-pentalenecarboxylate (26). A nitrogen-blanketed solution of either **16** or **17** (142 mg, 0.5 mmol), benzyl bromide (120 μL, 2 equiv) and a catalytic amount of tetrabutylammonium iodide in dry DMF (5 mL) was treated with sodium hydride (18 mg, 1.5 equiv). The resulting mixture was stirred for 15 min, diluted with ether (20 mL), and quenched with saturated brine (10 mL). Concentration of the organic layer gave a residue which was dissolved in dry acetone (10 mL), and the resulting solution was stirred in the presence of a catalytic amount of *p*-toluenesulfonic acid for 5 min, quenched with 2 drops of triethylamine, and concentrated by rotary evaporation. Purification of the residue by silica gel chromatography (elution with 1:1 hexanes−ether) afforded either **25** or **26** (158 mg, 98%) as colorless oils.

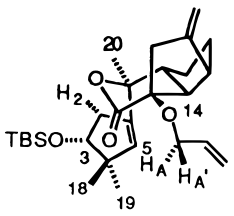
For **25**: IR (neat, cm^{-1}) 3030, 2960, 2890, 1745, 1735, 1480, 1390, 1095; ^{1}H NMR (300 MHz, C_6D_6) δ 7.37−7.35 (m, 2H), 7.17−7.03 (m, 3H), 5.64 (br s, 1H), 4.43 (d, J = 11.2 Hz, 1H), 4.38 (d, J = 11.2 Hz, 1H), 3.37 (s, 3H), 3.36 (m, 1H), 3.02 (m, 1H), 2.54 (q, J = 6.9 Hz, 1H), 1.85 (s, 3H), 1.55−1.45 (m, 3H), 1.46 (br s, 3H), 1.41−1.19 (m, 1H); ^{13}C NMR (75 MHz, C_6D_6) ppm 207.3, 172.6, 151.4, 139.4, 128.3, 127.9, 127.5, 124.4, 93.7, 67.3, 55.7, 54.7, 53.0, 51.2, 30.6, 28.2, 27.9, 14.8; HRMS *m/z* [$M^+ - C_2H_3O_2$] calcd for $C_{20}H_{24}O_4$ 269.1541, obsd 269.1537.

For **26**: IR (neat, cm^{-1}) 3030, 2960, 2890, 1745, 1735, 1480, 1390, 1095; ^{1}H NMR (300 MHz, C_6D_6) δ 7.34 (br d, J = 7.2 Hz, 2H), 7.18−7.07 (m, 3H), 4.90 (br s, 1H), 4.82 (br s, 1H), 4.40 (d, J = 11.2 Hz, 1H), 4.35 (d, J = 11.2 Hz, 1H), 3.34 (s, 3H), 3.30 (dt, J = 8.4, 1.8 Hz, 1H), 3.09 (m, 1H), 2.90 (dq, J = 16.8, 2.4 Hz, 1H), 2.77 (br d, J = 7.3 Hz, 1H), 2.57 (q, J = 8 Hz, 1H), 1.81 (m, 1H), 1.80 (s, 3H), 1.58 (m, 1H), 1.42−1.20 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6) ppm 207.0, 172.7, 154.0, 139.0, 128.3, 127.8, 127.6, 107.7, 89.0, 67.4, 55.8, 54.7, 51.4, 48.3, 39.3, 33.7, 31.3, 28.3; HRMS *m/z* [$M^+ - C_2H_3O_2$] calcd for $C_{18}H_{21}O_2$ 269.1541, obsd 269.1537; $[\alpha]^{20}_D$ −60.5 (*c* 0.83, CH_2Cl_2). *Anal.* Calcd for $C_{20}H_{24}O_4$ C, 73.19; H, 7.42. Found: C, 73.08; H, 7.42.

Methyl (1*S*,3a*R*,6*R*,6a*R*)-6-Oxo-octahydro-1-(allyloxy)-3-methylene-1-pentalenecarboxylate (27). To a nitrogen-blanketed solution of **17** (56 mg, 0.197 mmol) and a catalytic amount of tetrabutylammonium iodide in dry DMF (4 mL) was successively added sodium hydride (12 mg, 2.5 equiv) and allyl bromide (34 μL, 2 equiv). The reaction mixture was stirred for 10 min before being quenched with 5% HCl solution (10 mL) and diluted with ether (15 mL). The separated organic phase was dried and concentrated to afford a residue which was purified by silica gel chromatography (elution with 1:1 hexanes−ether) to give **27** (50.4 mg, 92%) as a colorless oil: IR (neat, cm^{-1}) 3010, 2985, 1755, 1680, 1475, 1405, 1295, 1205, 1080, 975, 905; ^{1}H NMR (300 MHz, C_6D_6) δ 5.87 (dq, J = 18.3, 5.2 Hz, 1H), 5.20 (dq, J = 18.3, 1.9 Hz, 1H), 5.00 (dq, J = 9.5, 1.7 Hz, 1H), 4.88 (br s, 1H), 4.81 (br s, 1H), 3.84 (br d, J = 1 Hz, 1H), 3.82 (br d, J = 1 Hz, 1H), 3.34 (s, 3H), 3.26 (dt, J = 8.05, 1.1 Hz, 1H), 3.12 (m, 1H), 2.87 (dq, J = 16.7, 2.5 Hz, 1H), 2.62 (br d, J = 16.7 Hz, 1H), 2.55 (q, J = 8.5 Hz, 1H), 1.80 (m, 1H), 1.79 (s, 3H), 1.58 (m, 1H), 1.41−1.19 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6) ppm 206.7, 172.4, 153.7, 135.2, 115.4, 107.3, 88.6, 66.2, 55.4, 54.4, 51.1, 48.0, 39.2, 33.4, 31.0, 28.1; HRMS *m/z* [M^+] calcd for $C_{16}H_{22}O_4$ 278.1518, obsd 278.1499; $[\alpha]^{20}_D$ −148.8 (*c* 0.66, CH_2Cl_2).

Methyl (1*R*,3a*R*,6*R*,6a*R*)-1-(Methoxy)-6-[(1*S*)-1-[(4*S*)-4-(*tert*-butyldimethylsiloxy)-3,3-dimethyl-1-cyclopenten-1-yl]-1-hydroxyethyl]-3-methylene-1-pentalenecarboxylate (28). A cold (−78 °C), argon-blanketed, magnetically stirred solution of **1** (93 mg, 1.15 equiv) in dry THF (15 mL) was treated dropwise 1.7 M *tert*-butyllithium in pentane (0.36 mL, 2.3 equiv), stirred at −78 °C for an additional 15 min, and rapidly transferred *via* cannula to a precooled (−78 °C) solution of **27** (74 mg, 0.266 mmol) in dry THF (10 mL). The reaction mixture was stirred for 1 h at −78 °C, allowed to warm to room temperature during 3 h, quenched with saturated NH_4Cl solution (10 mL), and diluted with ether (50 mL). The organic phase was dried and concentrated. The residue was purified by silica gel chromatography (elution with 2:1 hexanes−ether) to afford 91.6 mg (70%) of **28** as a colorless oil: IR (neat, cm^{-1}) 3700−3100, 3060, 2940, 2860, 1700, 1650, 1420, 1345, 1230, 1095; ^{1}H NMR (300 MHz, C_6D_6) δ 5.93 (dq, J = 18, 5.3 Hz, 1H), 5.32 (br s, 1H), 5.25 (dq, J = 18, 1.8 Hz, 1H), 4.96 (br s, 1H), 4.88 (br s, 1H), 3.98 (t, J = 6.5 Hz, 1H), 3.82 (m, 2H), 3.36 (s, 3H), 3.32 (m, 1H), 3.18 (m, 1H), 3.02 (dq, J = 15, 1.6 Hz, 1H), 2.72 (br d, J = 14.4 Hz, 1H), 2.50 (dd, J = 14.4, 6.2 Hz, 1H), 2.33 (ddd, J = 14.4, 6.3, 2.1 Hz, 1H), 2.15 (m, 1H), 1.87 (m, 1H), 1.66−1.54 (m, 3H), 1.20 (s, 3H), 1.07 (s, 3H), 1.04 (s, 3H), 0.97 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 173.3, 154.2, 145.8, 135.7, 132.8, 115.6, 106.8, 90.8, 81.1, 75.0, 66.8, 56.0, 51.1, 50.9, 48.2, 47.0, 41.1, 40.8, 34.5, 28.9, 27.2, 27.0, 26.9, 26.0, 21.0, 18.3, −4.34, −4.8; HRMS *m/z* [$M^+ + H^+$] calcd for $C_{29}H_{48}O_5Si$ 504.3271, obsd 504.3286; $[\alpha]^{20}_D$ −75.1 (*c* 0.25, CH_2Cl_2).

(3*S*,3a*R*,5a*R*,7a*R*,7b*R*)-7a-(Allyloxy)-3-[(4*S*)-4-(*tert*-butyldimethylsiloxy)-3,3-dimethyl-1-cyclopenten-1-yl]-3-methylene-3,6-pentaneleno[1,6-*cd*]pyran-1(3*H*)-one (29). To a solution of **28** (85 mg, 0.305 mmol) in THF (8 mL), methanol (3 mL), and water (3 mL) was added 5 N KOH (0.6 mL, 10 equiv). After being stirred overnight, the reaction mixture was cooled to 0 °C, carefully quenched with saturated NH_4Cl solution (10 mL), and diluted with CH_2Cl_2 (40 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic extracts were dried and concentrated to afford a white solid which was dissolved in dry CH_2Cl_2 (10 mL) and treated with 2-chloro-1-methylpyridinium iodide (310 mg, 3 equiv) and triethylamine (0.4 mL, 6 equiv). The resulting bright yellow solution was stirred for 10 min at room temperature and quenched with saturated NH_4Cl solution (3 mL). The organic extract was dried and concentrated, and the residue was purified by silica gel chromatography (elution with 1:1 hexanes−ether) to afford **29** (75 mg, 86%) as a colorless oil: IR (neat, cm^{-1}) 3045, 3005, 2970, 1795, 1415, 1360, 1310, 1270, 1240, 1200, 1055, 1015, 740; ^{1}H NMR (300 MHz, C_6D_6) δ 5.98 (dq, J = 18.1, 5.3 Hz, 1H), 5.68 (br s, 1H), 5.28 (dq, J = 18.1, 1.8 Hz, 1H), 5.04 (dq, J = 9.3, 1.7 Hz, 1H), 4.88 (br s, 1H), 4.83 (br s, 1H), 4.23 (m, 2H), 3.86 (t, J = 6.5 Hz, 1H), 3.00 (br d, J = 18.3 Hz, 1H), 2.92 (m, 1H), 2.86 (dq, J = 18.3, 2.5 Hz, 1H), 2.46 (dd, J = 14.4, 8.3 Hz, 1H), 2.35 (dd, J = 14.4, 6.3 Hz, 1H), 2.30 (ddd, J = 14.4, 6.3, 2.1 Hz, 1H), 1.91 (m, 1H), 1.55−1.28 (m, 4H), 1.24 (s, 3H), 1.23 (m, 1H), 0.98 (s, 3H), 0.94 (s, 9H), 0.89 (s, 3H), 0.02 (s, 3H), 0.008 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 171.7, 154.9, 140.4, 137.4, 135.6, 115.6, 109.3, 86.1, 86.0, 81.0, 66.9, 51.3, 51.2, 47.0, 45.1, 44.3, 41.8, 32.9, 28.3, 26.8, 26.2, 25.9, 21.1, 18.2, −4.5, −4.8; HRMS *m/z* [M^+] calcd for $C_{28}H_{43}O_4Si$ 471.2931, obsd 471.2956; $[\alpha]^{20}_D$ −115 (*c* 0.95, CH_2Cl_2).

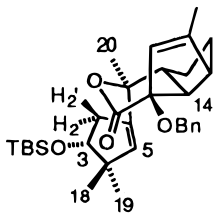


Irradiate	Observe	% n.O.e.
H_A, $H_{A'}$	H_5	5.8
	H_3	0.8
H_5	H_A, $H_{A'}$	3.3
	H_{14}	1.3
t-Bu	H_5	2.1
	H_{14}	0.45
	H_2	2.0

(3*S*,3a*R*,5a*R*,7a*R*,7b*R*)-7a-(Benzyloxy)-3-[(4*S*)-4-(*tert*-butyldimethylsiloxy)-3,3-dimethyl-1-cyclopenten-1-yl]-3a,4,5,5a,7b-hexahydro-3,6-pentaneleno[1,6-*cd*]pyran-1(3*H*)-one (30) and (3*S*,3a*R*,5a*R*,7a*R*,7b*R*)-7a-(Benzyloxy)-3-[(4*S*)-4-(*tert*-butyldimethylsiloxy)-3,3-dimethyl-1-cyclopenten-1-yl]-3-methylene-3,6-pentaneleno[1,6-*cd*]pyran-1(3*H*)-one (31). A cold (−78 °C), argon-blanketed, magnetically stirred solution of **1** (93 mg, 1.15 equiv) in dry THF (5 mL) was treated dropwise with 1.7 M *tert*-butyllithium (0.39 mL, 2.16 equiv) in pentane, stirred at this temperature for an additional 15 min, and rapidly added *via* cannula to a precooled (−78 °C) solution of **25** or **26** (87 mg, 0.267 mmol) in dry THF (5 mL). The resulting reaction mixture was stirred for 1 h at the same temperature, allowed to warm to room temperature over 2 h, quenched with saturated NH_4Cl solution (5 mL), and diluted with ether (20 mL). The organic phase was dried and concentrated,

and the residue was purified by silica gel chromatography (elution with 5:1 hexanes−ether) to afford 127 mg (88%) of either **30** or **31** as colorless oils.

For **30**: IR (neat, cm^{-1}) 3020, 2975, 2880, 1720, 1450, 1370, 1245, 1115, 830; ^1H NMR (300 MHz, C_6D_6) δ 7.41−7.36 (m, 2H), 7.35−7.06 (m, 3H), 5.65 (br s, 1H), 5.60 (br s, 1H), 5.13 (d, J = 11.4 Hz, 1H), 4.71 (d, J = 11.4 Hz, 1H), 3.93 (t, J =6.9 Hz, 1H), 2.84 (m, 1H), 2.79−2.40 (m, 2H), 2.37 (dd, J = 8.56, 6.6 Hz, 1H), 1.57−1.44 (m, 3H), 1.41 (s, 3H), 1.34−1.26 (m, 3H), 1.15 (m, 1H), 1.05 (s, 3H), 0.94 (s, 12H), 0.92 (m, 1H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 170.5, 153.9, 139.9, 139.2, 137.1, 128.5, 128.3, 127.8, 127.7, 127.3, 124.4, 90.2, 85.7, 80.9, 67.5, 51.9, 51.6, 49.7, 47.2, 41.8, 29.8, 27.1, 27.0, 26.4, 26.0, 21.1, 18.2, 14.4, −4.4, −4.8; HRMS *m/z* [M^+] calcd for $C_{32}H_{46}O_4Si$ 522.3165, obsd 522.3203; $[\alpha]^{20}_D$ +3.6 (*c* 0.98, CH_2Cl_2).

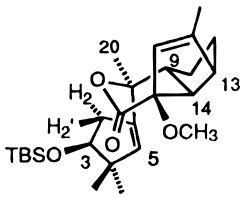


Irradiate	Observe	% n.O.e.
H_5	CHBz	0.6
	CH'Bz	1.0
	H_3	0.8
	20-CH_3	4.6
H_3	H_2	4.6
	H_5	1.3
	20-CH_3	0.6
	19-CH_3	5.3
19-CH_3	H_3	5.4
18-CH_3	H_3	1.8
	H_{14}	2.0
	$H_{2'}$	2.2
	CHBz	0.9
	Bz	3.3
	H_{13}	10.2
	H_5	2.4
20-CH_3	$H_{2'}$	3.5
	H_5	5.9

For **31**: IR (neat, cm^{-1}) 3020, 2975, 2880, 1720, 1450, 1370, 1245, 1115, 830; ^1H NMR (300 MHz, C_6D_6) δ 7.56−7.54 (d, J = 7.2 Hz, 2H), 7.27−7.12 (m, 3H), 5.80 (br s, 1H), 4.92 (m, 2H), 4.85 (d, J = 9.2 Hz, 1H), 4.78 (d, J = 9.2 Hz, 1H), 3.91 (t, J = 6.6 Hz, 1H), 3.15−2.95 (m, 3H), 2.62 (dd, J = 12.4, 7.4 Hz, 1H), 2.44−2.33 (m, 2H), 2.04 (m, 1H), 1.66−1.35 (m, 3H), 1.34 (s, 3H), 1.32 (m, 1H), 1.03 (s, 3H), 0.99 (s, 9H), 0.94 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 171.9, 154.8, 140.5, 139.1, 137.5, 128.3, 127.7, 127.6, 109.5, 86.3, 86.1, 80.9, 67.9, 51.2, 50.9, 46.9, 45.1, 44.6, 41.8, 32.9, 28.4, 26.7, 26.1, 25.9, 21.2, 18.2, −4.5, −4.9; HRMS *m/z* [M^+] calcd for $C_{32}H_{46}O_4Si$: 522.3165, obsd 522.3203; $[\alpha]^{20}_D$ −72.8(*c* 1.78, CH_2Cl_2). *Anal.* Calcd for $C_{32}H_{46}O_4Si$: C, 73.52; H, 8.87. Found: C, 73.52; H, 8.98.

Methyl (1*R*,3a*R*,6*R*,6a*R*)-1-(Methoxy)-6-[(1*S*)-1-[(4*S*)-4-(*tert*-butyldimethylsiloxy)-3,3-dimethyl-1-cyclopenten-1-yl]-1-hydroxyethyl]-1,3a,4,5,6,6a-hexahydro-3-methyl-1-pentalenecarboxylate (32). A cold (−78 °C), argon-blanketed, magnetically stirred solution of *ent*-**1** (361 mg, 1.1 equiv) in dry THF (15 mL) was treated dropwise with 1.7 M *tert*-butyllithium in pentane (1.4 mL, 2.2 equiv), stirred at −78 °C for an additional 15 min and rapidly transferred *via* cannula to a precooled (−78 °C) solution of **24** (255 mg, 1.08 mmol) in dry THF (10 mL). The resulting reaction mixture was stirred for 1 h at this temperature, allowed to warm to room temperature over 3 h, quenched with saturated NH_4Cl solution (10 mL), and diluted with ether (50 mL). The organic phase was dried and concentrated, and the residue was purified by silica gel chromatography (elution with 2:1 hexanes−ether) to afford **32** (310 mg, 60%, 92% based on recovered **24**) as a 10:1 mixture of diastereomers: IR (neat, cm^{-1}) 3700−3180, 3060, 3010−2800, 1730, 1650, 1420, 1345, 1295, 1170, 1045, 1010; ^1H NMR (300 MHz, C_6D_6) δ 5.53 (t, J = 1.3 Hz, 1H), 5.32 (s, 1H), 3.96 (t, J = 6.9 Hz, 1H), 3.42 (s, 3H), 3.28−3.21 (m, 1H), 3.18 (s, 3H), 3.03 (q, J = 7 Hz, 1H), 2.57 (dd, J = 15.18, 6.9 Hz, 1H), 2.37 (ddd, J = 15.24, 8.86, 1.9 Hz, 1H), 2.00 (m, 1H), 1.79 (m, 1H), 1.68−1.57 (m, 2H), 1.55 (br s, 1H), 1.47−1.17 (m, 2H), 1.35 (s, 3H), 1.16 (m, 1H), 1.09 (s, 3H), 1.06 (s, 3H), 0.97 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 173.1, 150.8, 145.4, 132.5, 123.4, 96.0, 80.8, 74.1, 55.6, 55.0, 52.2, 50.6, 49.7, 46.8, 40.5, 29.9, 29.0, 27.6, 26.7, 25.8, 20.9, 18.0, 15.1, −4.7, −5.1; HRMS *m/z* [$M^+ - C_2H_3O_2$] calcd for $C_{25}H_{43}O_3Si$ 419.2981, obsd 419.2999.

(3*S*,3a*R*,5a*R*,7a*S*,7b*S*)-7a-(Methoxy)-3-[(4*S*)-4-(*tert*-butyldimethylsiloxy)-3,3-dimethyl-1-cyclopenten-1-yl]-3a,4,5,5a,7b-hexahydro-3,6-pentaleno[1,6-*cd*]pyran-1(3*H*)-one (33). A solution of **32** (74 mg, 0.155 mmol) in THF (8 mL), methanol (3 mL), and water (3 mL) was treated with 5 N KOH (0.3 mL, 10 equiv), stirred overnight, cooled to 0 °C, carefully quenched with saturated NH_4Cl solution (10 mL), and diluted with CH_2Cl_2 (40 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic extracts were dried and concentrated to afford a white solid which was dissolved in dry CH_2Cl_2 (10 mL) and treated with 2-chloro-1-methylpyridinium iodide (160 mg, 3 equiv) followed by triethylamine (0.2 mL, 6 equiv). The resulting bright yellow solution was stirred for 10 min at room temperature and quenched with saturated NH_4Cl solution (3 mL). The organic extract was dried and concentrated. The residue was purified by silica gel chromatography (elution with 1:1 hexanes−ether) to afford **33** (10:1 mixture of diastereomers) (59 mg, 85%) as a colorless solid, mp 102−103 °C: IR (neat, cm^{-1}) 3030, 2915, 2820, 1770, 1410, 1345, 1295, 1260, 1170, 1010, 720; ^1H NMR (300 MHz, C_6D_6) δ 5.57 (br s, 1H), 5.49 (br s, 1H), 3.93 (t, J = 6.2 Hz, 1H), 3.52 (s, 3H), 2.85 (m, 1H), 2.64−2.40 (m, 3H), 1.59−1.42 (m, 3H), 1.41 (br t, J = 1.2 Hz, 3H), 1.27 (s, 3H), 1.26 (m, 1H), 1.15−1.02 (m, 1H), 1.05 (s, 3H), 0.99 (s, 3H), 0.97 (s, 9H), 0.06 (s, 3H), 0.035 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 170.2, 153.9, 139.2, 136.8, 123.9, 89.8, 85.8, 80.5, 52.9, 51.8, 51.6, 49.6, 47.9, 42.5, 29.8, 27.7, 27.1, 26.6, 26.0, 21.2, 18.3, 14.4, −4.5, −4.9; HRMS *m/z* [M^+] calcd for $C_{26}H_{42}O_4Si$ 447.2931, obsd 447.2900. *Anal.* Calcd for $C_{26}H_{42}O_4Si$: C, 69.91; H, 9.48. Found: C, 70.11; H, 9.52.



Irradiate	Observe	% n.O.e.
H_{14}	H_5	2.6
	H_{13}	8.2
	H_3	2.2
	$H_{2'}$	2.2
20-CH_3	H_5	3.95
	H_9	6.95
	H_2	2.8
	$H_{2'}$	1.5
OCH_3	H_{14}	4.2

(2a*R*,4a*R*,6a*R*,8*S*,10a*R*,10b*R*)-8-(*tert*-Butyldimethylsiloxy)-2,2a,4a,6,6a,7,8,9,10a,10b-decahydro-4a-(methoxy)-3,7,7,10-tetramethylcyclopenta[5,6]cycloocta[1,2,3-*cd*]pentalen-5(1*H*)-one (34). A sample of **33** (25 mg, 0.056 mmol) and pyridine (2 drops) was dissolved in dry THF (3 mL) and dry CH_2Cl_2 (3 mL) under N_2, cooled to −40 °C, and treated dropwise with 0.83 M Tebbe reagent in toluene (0.17 mL, 2.5 equiv). The solution was warmed to room temperature during 0.5 h, stirred for 1 h, cooled to −60 °C, and quenched with 10% KOH solution (1 mL). A 5% triethylamine solution in ether was added, and the mixture was filtered through a pad of basic alumina (activity I). Concentration to dryness left a residue which was dissolved in dry *p*-cymene (8 mL) and heated at 130 °C for 90 min. Purification by silica gel chromatography (elution with 8:1 hexanes−ether) afforded **34** (10:1 mixture of diastereomers) (17 mg, 68%) as a colorless oil: IR (neat, cm^{-1}) 3100−3000, 2990, 2890, 1715, 1430, 1380, 1260, 1115, 815; ^1H NMR (300 MHz, C_6D_6) δ 5.48 (br s, 1H), 3.89 (t, J = 6.4 Hz, 1H), 3.61 (m, 1H), 3.08 (m, 1H), 3.06 (s, 3H), 2.97 (s, 1H), 2.94 (d, J = 2.7 Hz, 1H), 2.61 (m, 1H), 2.52 (m, 1H), 2.19 (m, 1H), 1.93 (m, 1H), 1.55 (br s, 3H), 1.51 (br s, 3H), 1.49 (m, 1H), 1.45−1.12 (m, 2H), 1.10 (s, 3H), 1.08−1.01 (m, 1H), 0.97 (s, 9H), 0.93 (s, 3H), 0.059 (s, 3H), 0.049 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 211.7, 151.7, 136.6, 130.0, 122.3, 96.2, 79.6, 57.3, 53.6, 51.8, 47.8, 46.4, 45.8, 44.8, 42.2, 35.5, 28.6, 26.1, 21.4, 19.5, 18.3, 14.5, −4.4, −4.9; HRMS *m/z* [M^+] calcd for $C_{27}H_{44}O_3Si$ 444.3060, obsd 444.3062.

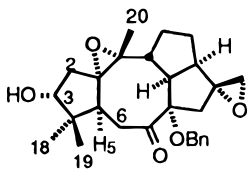
(2a*R*,4a*S*,6a*R*,8*R*,10a*R*,10b*R*)-4a-(Benzyloxy)-8-(*tert*-butyldimethylsiloxy)-2,2a,3,4,4a,6,6a,7,8,9,10a,10b-dodecahydro-7,7,10-trimethyl-3-methylenecyclopenta[5,6]cycloocta[1,2,3-*cd*]pentalen-5(1*H*)-one (35) and (2a*R*,4a*S*,6a*R*,8*R*,10a*R*,10b*R*)-8-(*tert*-Butyldimethylsiloxy)-2,2a,4a,6,6a,7,8,9,10a,10b-decahydro-4a-(benzyloxy)-3,7,7,10-tetramethylcyclopenta[5,6]cycloocta[1,2,3-*cd*]pentalen-5(1*H*)-one (36). A solution of either **31** or **30** (372 mg, 0.71 mmol) and pyridine (2 drops) in dry THF (10 mL) and dry CH_2Cl_2 (10 mL) was prepared under N_2. The mixture was cooled to −40 °C and 0.4 M Tebbe reagent (2.7 mL, 1.5 equiv) in toluene was added dropwise. The solution was warmed to room temperature over 0.5 h and stirred at the same temperature for 1 h. At this time, the reaction mixture was cooled to −60 °C and quenched with 10% KOH solution (2 mL). A 5% triethylamine solution in ether was added, and the mixture was filtered through a pad of basic alumina (activity I). Concentration to dryness left a residue which was dissolved in dry *p*-cymene (8 mL) and heated to 130 °C for 90 min. Purification by silica gel chromatography (elution with 8:1 hexanes−ether) afforded **35** or **36** (315 mg, 85%), respectively.

For **35** (9.5:1 mixture of diastereomers): IR (neat, cm^{-1}) 2950, 2930, 2850, 1700, 1460, 1350, 1240, 1100; ^1H NMR (300 MHz, C_6D_6) δ 7.39−7.21 (m, 2H), 7.19−7.08 (m, 3H), 5.49 (br s, 1H), 4.43 (d, J = 11.3 Hz, 1H), 4.21 (d, J = 11.3 Hz, 1H), 3.96 (br d, J = 12.4 Hz, 1H), 3.76 (t, J = 8.5 Hz, 1H), 3.09−3.01 (m, 2H), 2.96 (dd, J = 12.9, 3.3 Hz, 1H), 2.62 (dd, J = 16.6, 8 Hz, 1H), 2.26−2.12 (m, 3H), 1.91 (m, 1H), 1.56 (br s, 3H), 1.49 (m, 1H), 1.44 (br s, 3H), 1.31−1.08 (m, 2H), 1.05 (s, 3H), 0.95 (s, 9H), 0.87 (s, 3H), −0.07 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6) ppm 211, 152.3, 139.5, 134.1, 129.9, 128.5, 127.7, 127.4, 122.5, 96.0, 76.8, 66.6, 57.1, 53.6, 47.9, 45.5, 44.7, 44.1, 40.1, 35.5, 26.0, 25.7, 22.5, 22.4, 21.4, 18.2, 14.5, −4.3, −4.9; HRMS *m/z* [M^+] calcd for $C_{33}H_{48}O_3Si$ 520.3373, obsd 520.3377. *Anal.* Calcd for $C_{33}H_{48}O_3Si$: C, 76.10; H, 9.29. Found: C, 76.20; H, 9.55.

For **36**: IR (neat, cm^{-1}) 2950, 2930, 2850, 1705, 1460, 1360, 1240, 1150; ^1H NMR (300 MHz, C_6D_6) δ 7.27−7.24 (m, 2H), 7.18−7.09 (m, 3H), 4.92 (d, J = 1 Hz, 1H), 4.87 (d, J = 1 Hz, 1H), 4.45 (d, J = 11.7 Hz, 1H), 4.00 (d, J = 11.7 Hz, 1H), 3.87 (m, 1H), 3.72 (t, J = 8.5 Hz, 1H), 3.41 (m, 1H), 3.74−3.63 (m, 2H), 2.79 (dd, J = 13.2, 4.1 Hz, 1H), 2.59−2.54 (m, 2H), 2.25−1.79 (series of m, 5H), 1.42 (br s, 3H), 1.17−0.98 (m, 2H), 0.95 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), −0.32 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6) ppm 210.6, 154.4, 138.7, 133.5, 130.4, 128.5, 128.3, 127.2, 106.9, 94.0, 76.5, 67.3, 57.7, 49.6, 48.8, 45.6, 44.7, 44.3, 40.2, 35.4, 35.2, 32.0, 26.0, 22.3, 22.2, 21.4, −4.3, −4.9; HRMS *m/z* [M^+] calcd for $C_{33}H_{48}O_3Si$ 520.3373, obsd 520.3377; $[\alpha]^{20}_D$ +72.5 (*c* 1.06, CH_2Cl_2).

(2a*R*,4a*S*,6a*R*,8*R*,10a*R*,10b*R*)-4a-(Benzyloxy)-8-hydroxy-2,2a,3,4,4a,6,6a,7,8,9,10a,10b-dodecahydro-7,7,10-trimethyl-3-methylenecyclopenta[5,6]cycloocta[1,2,3-*cd*]pentalen-5(1*H*)-one (37). A solution of **35** (50 mg, 0.096 mmol) in THF (5 mL) was treated with a 1 M TBAF solution in THF (0.15 mL, 1.5 equiv). The reaction mixture was stirred overnight and concentrated. The residue was purified by silica gel chromatography (elution with 1:1.5 hexanes−ether) to afford **37** (35.5 mg, 91%) as a colorless oil: IR (neat, cm^{-1}) 3700−3100, 2995, 2985, 1720, 1510, 1385, 1265, 1125; ^1H NMR (300 MHz, C_6D_6) δ 7.27−7.18 (m, 2H), 7.16−7.04 (m, 3H), 4.93 (br d, J = 0.9 Hz, 1H), 4.88 (br d, J = 0.9 Hz, 1H), 4.45 (d, J = 9.7 Hz, 1H), 4.00 (d, J = 9.7 Hz, 1H), 3.85 (br d, J = 12.4 Hz, 1H), 3.54 (t, J = 8.4 Hz, 1H), 3.43 (br d, J = 17.4 Hz, 1H), 3.24−3.14 (m, 2H), 2.81 (dd, J = 12.9 Hz, 1H), 2.64−2.51 (m, 2H), 2.16−2.00 (m, 3H), 1.91−1.79 (m, 2H), 1.44 (s, 3H), 1.40−1.24 (m, 1H), 1.23−0.93 (m, 1H), 0.92−0.88 (m, 1H), 0.91 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 210.7, 154.3, 138.7, 133.5, 130.5, 128.5, 128.2, 127.8, 127.2, 106.8, 94.0, 75.9, 67.3, 57.6, 49.5, 48.8, 46.1, 44.3, 39.9, 35.3, 35.2, 32.1, 21.9, 21.8, 21.3; HRMS *m/z* [M^+] calcd for $C_{27}H_{34}O_3$ 406.2508, obsd 406.2475.

(2a*R*,3*R*,4a*S*,6a*S*,8*R*,9a*S*,10*R*,10a*R*,10b*R*)-4a-(Benzyloxy)-9a,10-epoxytetradecahydro-8-hydroxy-7,7,10-trimethylspiro[cyclopenta-[5,6]cycloocta[1,2,3-*cd*]pentalene-3(5*H*),2′-oxiran]one (38). To a slurry of **37** (40 mg, 0.098 mmol) and $NaHCO_3$ (66 mg, 8 equiv) in dry CH_2Cl_2 (5 mL) was added 90% *m*-chloroperbenzoic acid (59 mg, 3.5 equiv) in one portion. The reaction mixture was stirred at room temperature for 4 h and quenched by addition of a 10% $NaHSO_3$ solution (5 mL). The separated organic layer was dried and concentrated to leave a residue which was purified by silica gel chromatography (elution with 1:3 hexanes−ether) to afford **38** (37 mg, 86%) as a 6.5:1 mixture of diastereomers, mp 154−157 °C: IR ($CHCl_3$, cm^{-1}) 3690−3100, 3030, 2950, 2860, 1700, 1655, 1425, 1370, 1260, 1100; ^1H NMR (300 MHz, C_6D_6) δ 7.35−7.18 (m, 2H), 7.17−7.05 (m, 3H), 4.77 (d, J = 10.9 Hz, 1H), 3.88 (d, J = 10.9 Hz, 1H), 3.58 (m, 1H), 3.05 (m, 1H), 2.85 (d, J = 15.7 Hz, 1H), 2.79 (m, 1H), 2.75 (dd, J = 13.9, 4.1 Hz, 1H), 2.43−2.30 (m, 4H), 2.11 (t, J = 14 Hz, 1H), 1.74−1.26 (m, 6H), 1.20 (s, 3H), 1.06 (s, 3H), 1.03 (m, 1H), 0.98 (m, 1H), 0.74 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 210.9, 128.3, 127.7, 127.6, 127.5, 126.7, 93.7, 76.1, 72.6, 67.1, 66.0, 61.6, 53.3, 49.0, 48.7, 46.8, 45.6, 45.1, 41.6, 40.5, 33.6, 31.3, 29.0, 21.9, 21.7; HRMS *m/z* [M^+] calcd for $C_{27}H_{34}O_5$ 438.2406, obsd 438.2402.



Irradiate	Observe	% n.O.e.
H_3	α-H_6	6.9
	α-H_2	5.8
	20-CH_3	6.5
	19-CH_3	3.8
	18-CH_3	3.7
18-CH_3	H_5	7.8
	19-CH_3	5.2
19-CH_3	α-H_2	10.3
	β-H_6	2.0
	α-H_6	7.3
	18-CH_3	6.8
20-CH_3	α-H_2	5.5
	α-H_6	1.1

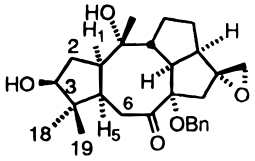
(2a*R*,3*R*,4a*S*,6a*R*,10*R*,10a*R*,10b*S*)-4a-(Benzyloxy)-2a,4,4a,6a,7,10,10a,10b-octacahydro-7,7,10-trimethyl-10-hydroxyspiro[cyclopenta-[5,6]cycloocta[1,2,3-*cd*]pentalene-3(1*H*),2′-oxirane]-5,8(2*H*,6*H*)-dione (39). A mixture of **38** (60 mg, 0.137 mmol), 97% *N*-methylmorpholine *N*-oxide (25 mg, 1.5 equiv), powdered 4 Å molecular sieves (50 mg), and a catalytic amount of *N*-methylmorpholine was stirred in dry CH_2Cl_2 (5 mL) for 15 min before the addition of tetrapropylammonium perruthenate (1.5 mg, 3% mol). The reaction mixture was stirred at room temperature for 30 min and triethylamine

(0.2 mL, 10 equiv) was added. After 1 h of stirring, the solvent was removed, and the residue was taken up in ether and filtered through a small plug of Celite. Purification by silica gel chromatography (elution with 1:6 hexanes−ether) afforded **39** (50 mg, 84%) as a colorless solid, mp 189−191 °C: IR ($CHCl_3$, cm^{-1}) 3690−3100, 3030, 2950, 2860, 1700, 1655, 1425, 1370, 1260, 1100; ^1H NMR (300 MHz, C_6D_6) δ 7.39 (br d, J = 7.2 Hz, 1H), 7.18−7.05 (m, 3H), 5.70 (s, 1H), 4.64 (d, J = 10.7 Hz, 1H), 3.85 (d, J = 10.7 Hz, 1H), 3.68 (dd, J = 14.3, 6.6 Hz, 1H), 3.27 (br t, J = 9.9 Hz, 1H), 3.06 (m, 1H), 2.60 (q, J = 9.5 Hz, 1H), 2.48−2.38 (m, 4H), 2.12 (dd, J = 14.3, 3.6 Hz, 1H), 1.73 (br d, J = 15.6 Hz, 1H), 1.43−0.81 (series of m, 5H), 1.29 (s, 3H), 1.02 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 211.0, 209.5, 183.7, 138.4, 128.7, 128.6, 128.4, 128.2, 127.9, 127.7, 93.5, 72.4, 67.6, 66.6, 54.2, 52.6, 50.3, 49.4, 48.5, 46.2, 37.5, 32.6, 30.8, 29.7, 29.5, 28.6, 20.2; HRMS *m/z* [M^+] calcd for $C_{27}H_{32}O_5$ 436.2249, obsd 436.2243; $[\alpha]^{20}_D$ −23.5 (*c* 0.71, CH_2Cl_2).

(2a*R*,3*R*,4a*S*,6a*R*,8*S*,9a*R*,10*S*,10a*R*,10b*S*)-4a-(Benzyloxy)-2a,4,4a,6a,7,10,10a,10b-octahydro-7,7,10-trimethyl-10-hydroxyspiro-[cyclopenta[5,6]cycloocta[1,2,3-*cd*]pentalene-3(1*H*),2′-oxirane]-5,8-(2*H*,6*H*)-dione (40). A solution of **39** (10 mg, 0.023 mmol) and 10% Pd/C (1 mg, 2.5% mol) in dry ethyl acetate (3 mL) was blanketed with H_2 and stirred under 1 atm of H_2 for 15 min. Removal of the catalyst by filtration through a small plug of Celite (elution with ether) followed by concentration to dryness afforded **40** (9.2 mg, 92%) as a colorless solid, mp 74−76 °C: IR ($CHCl_3$, cm^{-1}) 3700−3100, 2960, 2885, 1735, 1470, 1380, 1255, 1095, 1005, 830, 785; ^1H NMR (300 MHz, C_6D_6) δ 7.31 (br d, J = 7.2 Hz, 1H), 7.11−7.02 (m, 3 H), 4.78 (d, J = 10.9 Hz, 1 H), 3.84 (d, J = 10.9 Hz, 1 H), 3.46 (t, J = 8.2 Hz, 1 H), 3.15 (m, 1 H), 3.04 (d, J = 15.5 Hz, 1H), 2.81 (dd, J = 12.6, 3.3 Hz, 1 H), 2.51 (dd, J = 14.4, 2.7 Hz, 1 H), 2.48 (br s, 1 H), 2.45 (m, 1 H), 2.38 (dd, J = 10.5, 9.6 Hz, 1 H), 2.06 (t, J = 12.8 Hz, 1 H), 1.72 (br d, J = 15.5 Hz, 1 H), 1.66−1.42 (m, 5 H), 1.27 (m, 1 H), 1.04 (s, 3 H), 0.92 (m, 1 H), 0.74 (s, 3 H), 0.72 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 219.2, 213.2, 138.3, 128.4, 128.3, 128.2, 128.1, 127.8, 95.1, 72.2, 68.0, 65.6, 54.6, 51.7, 51.5, 49.1, 47.9, 45.8, 45.3, 40.7, 38.4, 33.4, 31.4, 29.4, 28.3, 25.1, 20.0; HRMS *m/z* [M^+] calcd for $C_{27}H_{34}O_5$ 438.2406, obsd 438.2391; $[\alpha]^{20}_D$ +69.1 (*c* 0.16, CH_2Cl_2).

(2a*R*,3*R*,4a*S*,6a*R*,8*S*,9a*R*,10*S*,10a*R*,10b*S*)-4a-(Benzyloxy)-2a,4,4a,6a,7,10,10a,10b-octahydro-7,7,10-trimethyl-10-hydroxyspiro-[cyclopenta[5,6]cycloocta[1,2,3-*cd*]pentalene-3(1*H*),2′-oxirane]-5-(2*H*,6*H*)-one (41). To a cold (−78 °C), magnetically stirred solution of **40** (10 mg, 0.023 mmol) in dry CH_2Cl_2 (2 mL) was added 1 M Superhydride in THF (25 μL, 1 equiv). After 10 min, the reaction mixture was quenched with Rochelle's salt solution (0.5 mL) and allowed to warm to room temperature. The separated organic layer was dried, and the residue obtained after concentration was purified by silica gel chromatography (elution with 1.5:1 ethyl acetate−hexanes) to afford **41** (9 mg, 90%) as a colorless solid, mp 80−81 °C: IR (KBr, cm^{-1}) 3700−3100, 2910, 2880, 1695, 1440, 1410, 1100; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (br d, J = 6.8 Hz, 1H), 7.35−7.25 (m, 3H), 4.77 (d, J = 10.9 Hz, 1H), 4.02 (d, J = 10.9 Hz, 1H), 3.53 (d, J = 3.6 Hz, 1H), 3.31 (t, J = 8.5 Hz, 1H), 2.91 (d, J = 15.6 Hz, 1H), 2.86−2.76 (m, 4H), 2.42 (q, J = 9.6 Hz, 1H), 2.19 (m, 1H), 2.04 (m, 1H), 1.98−1.79 (series of m, 5H), 1.77−1.50 (m, 3H), 1.28−1.21 (m, 2H), 1.16 (s, 3H), 0.86 (m, 1H), 0.82 (s, 3H), 0.67 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 215.4, 137.8, 128.2, 127.5, 127.4, 94.8, 80.3, 72.9, 67.8, 65.9, 54.3, 52.5, 51.7, 51.4, 47.5, 46.2, 43.1, 40.8, 35.4, 33.0, 31.7, 29.5, 29.4, 22.4, 21.2; HRMS *m/z* [M^+] calcd for $C_{27}H_{36}O_5$ 440.2563, obsd 440.2565; $[\alpha]^{20}_D$ +42.3 (*c* 0.4, CH_2Cl_2).

(2a*R*,3*R*,4a*S*,6a*R*,8*S*,9a*R*,10*S*,10a*R*,10b*S*)-4a-(Benzyloxy)-8-(*tert*-butyldimethylsiloxy)tetradecahydro-10-(*tert*-butyldimethylsiloxy)-7,7-hydroxytrimethylspiro[cyclopenta[5,6]cycloocta[1,2,3-*cd*]pentalene-3(5*H*),2′-oxiran]-5-one (42) and (2a*R*,3*R*,4a*S*,6a*R*,8*S*,9a*R*,10*S*,10a*R*,10b*S*)-4a-(Benzyloxy)-8-(*tert*-butyldimethylsiloxy)tetradecahydro-3,10-(*tert*-butyldimethylsiloxy)-7,10-trimethylspiro[cyclopenta[5,6]-cycloocta[1,2,3-*cd*]pentalene-3(5*H*),2′-oxiran]-5-one (43). Diol **41** (55 mg, 0,125 mmol) in dry DMF (5 mL) was treated with imidazole (42.5 mg, 5 equiv) and TBSOTf (375 μL, 5 equiv) in the presence of a catalytic amount of DMAP. The reaction mixture was stirred for 0.5 h before dropwise addition of saturated NH_4Cl solution (3 mL). The organic phase was extracted with ether, dried, and concentrated. Purification of the residue by silica gel chromatography (elution with 1.5:1 hexanes−ether) afforded **42** (55 mg, 93%) and **43** (3 mg, 4%).



Irradiate	Observe	% n.O.e.
β-H_2	18-CH_3	4.4
	H_3	4.9
	H_1	17.6
	H_5	7.2
H_3	β-H_2	4.6
	18-CH_3	3.7
	19-CH_3	1.9
	α-H_2	1.6
18-CH_3	H_3	7.7
	β-H_6	2.4
	β-H_2	5.2
	H_5	6.5
	19-CH_3	5.9
19-CH_3	18-CH_3	3.8
	H_3	3.4

For **42**: oil; IR (neat, cm^{-1}) 3700−3100, 2960, 2930, 2890, 1700, 1615, 1450, 1270, 1170; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (br d, J = 6.7 Hz, 1H), 7.33−7.24 (m, 3H), 4.78 (d, J = 9.1 Hz, 1H), 4.05 (d, J = 9.1 Hz, 1H), 3.57 (m, 1H), 3.31 (m, 2H), 2.95 (d, J = 15.6 Hz, 1H), 2.78 (m, 3H), 2.44 (q, J = 9.6 Hz, 1H), 2.12 (m, 1H), 1.97 (m, 1H), 1.86−1.74 (series of m, 4H), 1.56−1.51 (m, 2H), 1.20 (m, 1H), 1.10 (s, 3H), 0.92 (s, 9H), 0.85 (m, 1H), 0.74 (s, 3H), 0.74 (s, 3H), 0.068 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 215.4, 138.0, 128.1, 127.3, 94.9, 80.9, 71.9, 67.6, 66.0, 54.3, 52.6, 51.9, 51.5, 47.3, 46.4, 43.4, 40.6, 36.0, 33.3, 31.5, 29.6, 29.1, 26.1, 22.4, 22.0, 18.3, −4.6, −4.8; HRMS *m/z* [M^+] calcd for $C_{33}H_{50}O_5Si$ 554.3427, obsd 554.3427; $[\alpha]^{20}_D$ +30.3 (*c* 0.52, CH_2Cl_2).

For **43**: mp 154 °C; IR (neat, cm^{-1}) 3100−3000, 2980, 2950, 2860, 1700, 1460, 1375, 1250, 1120, 1060, 1000, 840, 770; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7.27 (m, 5H), 4.87 (d, J = 11.4 Hz, 1H), 4.03 (d, J = 11.4 Hz, 1H), 3.67 (m, 2H), 3.54 (d, J = 3.2 Hz, 1H), 3.37 (s, 1H), 3.31 (t, J = 8.4 Hz, 1H), 2.74 (m, 2H), 2.54 (dd, J = 2.5, 14 Hz, 1H), 2.37 (d, J = 13.9 Hz, 1H), 2.25 (m, 1H), 2.20−2.06 (m, 2H), 1.96−1.68 (m, 3H), 1.61−1.35 (m, 2H), 1.08 (s, 3H), 0.92 (s, 9H), 0.911 (s, 9H), 0.87 (m, 1H), 0.59 (s, 3H), 0.56 (s, 3H), 0.94−0.63 (3 s, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 213.8, 136.6, 128.4, 127.8, 127.0, 96.2, 81.3, 80.8, 71.7, 68.1, 57.0, 54.1, 53.5, 52.0, 49.5, 47.6, 43.9, 40.3, 35.7, 35.2, 31.5, 29.0, 28.6, 26.0, 25.6, 21.9, 21.6, 18.3, −3.6, −4.6, −4.8; HRMS *m/z* [M^+ − Bn] calcd for $C_{32}H_{57}O_5Si_2$ 577.3745, obsd 577.3748; $[\alpha]^{20}_D$ +29.5 (*c* 0.88, CH_2Cl_2).

(2a*R*,3*R*,4a*S*,6a*R*,8*S*,9a*R*,10*S*,10a*R*,10b*S*)-4a-(Benzyloxy)-8-(trimethylsiloxy)-10-(*tert*-butyldimethylsiloxy)-7,10-trimethylspiro-[cyclopenta[5,6]cycloocta[1,2,3-*cd*]pentalene-3(5*H*),2′-oxiran]-5-one (44). A cold (−78 °C), magnetically stirred, N_2-blanketed solution of **42** (8 mg, 0.0145 mmol) in dry THF (5 mL) was successively treated with 0.5 M potassium hexamethyldisilazide (0.6 mL, 20 equiv) in toluene followed by trimethylsilyl triflate (30 μL, 10 equiv). The resulting reaction mixture was gradually warmed to room temperature over 1 h, at which time it was treated with 10% Et_3N in ether (10 mL) and quenched with saturated $NaHCO_3$ solution (5 mL). The separated organic layer was dried and concentrated, and the residue was purified by silica gel chromatography (elution with 1.5:1 hexanes−ether) to afford **44** (7.6 mg, 83%) as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3100−3000, 2980, 2880, 1700, 1455, 1375, 1255, 1115, 1065, 1000, 840,

775; ^{1}H NMR (300 MHz, C_6D_6) δ 7.39 (d, J = 7.3 Hz, 2H), 7.17−7.02 (m, 3H), 4.89 (d, J = 9.4 Hz, 1H), 3.97 (d, J = 9.4 Hz, 1H), 3.56 (dd, J = 7.1, 10.3 Hz, 1H), 3.47 (t, J = 8.5 Hz, 1H), 3.05 (d, J = 15.6 Hz, 1H), 3.01−2.93 (m, 2H), 2.45 (s, 2H), 2.35 (q, J = 9.4 Hz, 1H), 1.78 (dd, J = 6.7, 7.6 Hz, 1H), 1.87−1.67 (m, 3H), 1.55−1.44 (m, 4H), 1.41−1.22 (m, 3H), 1.16 (s, 3H), 0.99 (s, 9H), 0.95 (s, 3H), 0.93 (m, 2H), 0.78 (s, 3H), 0.11 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 214.5, 138.7, 128.4, 128.2, 127.9, 127.5, 127.4, 95.2, 78.2, 77.2, 68.1, 65.5, 55.3, 53.2, 52.0, 51.7, 47.2, 45.7, 43.8, 40.4, 35.8, 33.9, 31.3, 29.6, 27.1, 26.2, 23.5, 23.3, 18.3, 3.4, −4.1, −4.8; HRMS *m/z* [M$^+$] calcd for $C_{36}H_{60}O_5Si_2$ 628.3979, obsd 628.3947; $[\alpha]^{20}_D$ +34.1 (*c* 0.24, CH_2Cl_2).

(2a*R*,3*R*,4a*S*,5*S*,6a*R*,8*S*,9a*R*,10*S*,10a*R*,10b*S*)-4a-(Benzyloxy)-8-(*tert*-butyldimethylsiloxy)tetradecahydro-3,10-(*tert*-butyldimethylsiloxy)-5-hydroxy-7,10-trimethylspiro[cyclopenta[5,6]cycloocta[1,2,3-*cd*]pentalene-3(5*H*),2′-oxirane] (45). To a cold (−78 °C) solution of **42** (9 mg, 0.016 mmol) in dry CH_2Cl_2 (2 mL) was added 1 M Superhydride solution in THF (80 μL, 5 equiv). The reaction mixture was allowed to warm to room temperature and quenched by addition of saturated Rochelle's salt solution (0.5 mL). The separated organic layer was dried and concentrated to afford a residue which was purified by silica gel chromatography (elution with 1:1 hexanes−ether). There was obtained 7.6 mg (85%) of **45** as a colorless solid, mp 153 °C: IR (KBr, cm^{-1}) 3700−3060, 2960, 2860, 1455, 1410, 1375, 1250, 1115, 1040; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (br d, J = 7 Hz, 1H), 7.31−7.20 (m, 3H), 4.67 (d, J = 10.8 Hz, 1H), 4.48 (m, 1H), 4.34 (d, J = 9.1 Hz, 1H), 3.59 (m, 1H), 3.42 (s, 1H), 3.18 (t, J = 8.8 Hz, 1H), 3.01 (m, 1H), 2.88 (d, J = 14.9 Hz, 1H), 2.76 (s, 2H), 2.50 (m, 1H), 2.36 (m, 1H), 2.13−2.08 (m, 2H), 1.89−1.43 (series of m, 6H), 1.27 (m, 2H), 1.17 (s, 3H), 0.92 (s, 9H), 0.86 (s, 3H), 0.73 (s, 3H), 0.1 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 139.4, 128.0, 127.5, 127.0, 87.9, 81.1, 72.8, 71.2, 66.2, 64.5, 52.3, 51.8, 49.3, 47.7, 46.9, 40.1, 36.7, 36.5, 35.0, 31.3, 29.9, 29.7, 26.1, 23.0, 22.6, 18.4, −4.6, −4.7; HRMS *m/z* [M$^+$] calcd for $C_{33}H_{52}O_5Si$ 556.3584, obsd.556.3594; $[\alpha]^{20}_D$ −27.2 (*c* 0.18, CH_2Cl_2).

(2a*R*,3*R*,4a*S*,5*S*,6a*R*,8*S*,9a*R*,10*S*,10a*R*,10b*R*)-8-(*tert*-Butyldimethylsiloxy)tetradecahydro-3,4a,10-trihydroxy-3,7,7,10-tetramethyl-[cyclopenta[5,6]cycloocta[1,2,3-*cd*]pentalene-3,4a,5,10(1*H*)-tetrol (46). Dry NH_3 (20 mL) was condensed in a 50 mL two-necked round-bottomed flask at −78 °C. Lithium pieces (3 mg, 8 equiv) were added portionwise over 10 min during which time the solution turned deep blue. The solution was stirred for an additional 20 min and **45** (30 mg, 0.054 mmol) dissolved in ether (5 mL) was rapidly introduced *via* cannula. The reaction mixture was gradually warmed to −33 °C and kept at that temperature for 0.5 h. At this time, ether (10 mL) was added, and the resulting solution was quenched by the addition of saturated NH_4Cl solution (2 mL). The separated organic layer was dried and concentrated, and the residue was purified by silica gel chromatography (elution with 1:1.75 hexanes-ethyl acetate) to afford **46** (8.5 mg, 35%) as a colorless solid, mp 212 °C: IR ($CHCl_3$, cm^{-1}) 3720−3100, 2960, 2860, 1465, 1380, 1265, 1115, 1055; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (d, J = 5.9 Hz, 1H), 3.60 (m, 1H), 3.06−3.01 (m, 2H), 2.56 (br q, J = 7.6 Hz, 1H), 2.52−2.32 (m, 2H), 2.26−2.14 (m, 3H), 2.12−1.51 (series of m, 7H), 1.54−1.38 (m, 2H), 1.29 (s, 3H), 1.28 (m, 1H), 1.14 (s, 3H), 0.95 (s, 3H), 0.93 (s, 9H), 0.92 (m, 1H), 0.75 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 83.8, 81.4, 80.5, 74.8, 72.6, 60.1, 53.2, 52.6, 48.8, 48.3, 47.9, 40.4, 36.4, 35.0, 31.1,29.4, 26.1, 25.6, 24.1, 22.8, 22.5, 18.5, −4.6, −4.65; HRMS *m/z* [M$^+$ − H_2O] calcd for $C_{26}H_{46}O_4Si$ 450.3165, obsd.450.3156 $[\alpha]^{20}_D$ −21 (*c* 0.2, CH_2Cl_2).

(2a*R*,3*R*,4a*S*,6a*R*,8*S*,9a*R*,10*S*,10a*R*,10b*R*)-8-(*tert*-Butyldimethylsiloxy)tetradecahydro-3,4a,10-trihydroxy-3,7,7,10-tetramethylspiro-[cyclopenta[5,6]cycloocta[1,2,3-*cd*]pentalen-5(1*H*)-one (3). A solution of **46** (2.8 mg, 6×10^{-3} mmol) and pyridine (1 drop) in dry CH_2Cl_2 (2 mL) was treated with the Dess−Martin periodinane reagent (3.4 mg, 1.3 equiv). After 10 min of stirring, the reaction mixture was quenched by addition of saturated $NaHCO_3$ solution (0.5 mL). The organic layer was dried, and the residue obtained after concentration to dryness was purified by silica gel chromatography (elution with 1:2 hexanes−ether) to give **3** (2.6 mg, 93%) as a highly crystalline solid, mp 156 °C: IR ($CHCl_3$, cm^{-1}) 3720−3100, 2960, 2860, 1465, 1380, 1265, 1115, 1055; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64 (dd, J = 0.7, 3.9 Hz, 1H), 3.44 (br s, 1H), 3.03 (t, J = 2.8 Hz, 1H), 2.9 (dd, J = 2.8, 12.8 Hz, 1H), 2.79 (m, 1H), 2.49 (d, J = 14.4 Hz, 1H), 2.40 (m, 1H), 2.16 (dt, J = 0.7, 2.4 Hz, 1H), 1.91 (t, J = 12.5 Hz, 1.86−1.37 (series of m, 6H), 1.31 (s, 3H), 1.26 (br s, 2H), 1.07 (s, 3H), 1.02 (s, 3H), 0.93 (s, 9H), 0.89−0.74 (m, 2H), 0.72 (s, 3H), 0.11 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 213.8, 89.5, 81.8, 81.3, 71.8, 59.4, 56.6, 53.2, 52.4, 47.6, 44.9, 42.4, 40.8, 35.9, 31.4, 29.1, 28.9, 26.1, 23.9, 22.4, 22.0, 18.4, −4.6, −4.7; HRMS *m/z* [M$^+$] calcd for $C_{26}H_{48}O_5Si$ 466.3114, obsd 466.3110 $[\alpha]^{20}_D$ +30.9 (*c* 0.39, CH_2Cl_2).

Acknowledgment. S.B. served as a Presidential Fellow during 1994−1995. This work was financially supported by the National Institutes of Health (Grant GM-30827) and the Eli Lilly Company. We thank Dr. Kurt Loening for his assistance with nomenclature.

JA9533454