Enantiospecific Total Synthesis of Natural (+)-Taxusin. 2. Functionalization of the A-Ring and Arrival at the Target

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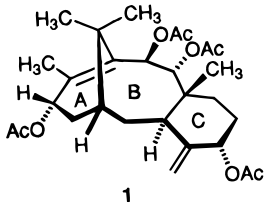
Abstract: A total synthesis of (+)-taxusin (**1**) has been realized by virtue of the development of a practical route for complete functionalization of the A ring. To achieve this goal, it proved necessary to devise a strategy that would enable chemical transformations to proceed in a very congested environment. The successful pathway from **2** required 19 steps consisting principally of chemoselective oxidation and reduction maneuvers of various types. The requisite methyl substituent was introduced by 1,2-addition of the methylcerate reagent to a C(12) ketone intermediate. Several tactics that ultimately proved unsatisfactory are also discussed in an effort to set important boundary limits on chemical reactivity. The pivotal roles played by samarium diiodide and tetrapropylammonium perruthenate in permitting the deployment of appropriate chemical changes are noteworthy.

The preceding paper details a convergent strategy for the concise construction of taxane systems.[1] The specific focus of these initial chemical studies was taxusin (**1**), whose carbocyclic framework and fully functionalized B and C rings were assembled in only 17 steps. The building block approach developed in the early phases of this investigation was expected to have important consequences in an anticipated parallel synthesis of taxol. Indeed, good progress has been made on the elaboration of more highly oxygenated intermediates as required of that target.[2] The development of this useful methodology has given impetus to the need for practical



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methodology designed to introduce the characteristic substitution pattern resident in ring A. The schemes detailed below constitute the most elaborate investigation devoted to this topic yet reported. The knowledge gained in this final drive to taxusin is of general chemical interest in that it addresses simultaneously the twin issues of severe steric screening and bridgehead unsaturation on chemical reactivity. These factors are recognized to impact heavily on this structural sector.

Consideration of Metal-Promoted Exocyclic to Endocyclic Olefin Isomerization

The first of the intrinsically challenging issues to be addressed is the most noteworthy feature of the taxusin A-ring, its strained double bond. Since a possible agenda dealing with synthetic efforts in this domain could include the migration of an exocyclic π-bond to the proper internal site, we were led to gain some perspective of the energetic imbalances separating these isomers. Molecular mechanics calculations[3] were therefore performed on compounds **A**−**C** as depicted in Table 1. Although these three compounds are clearly not related as conformers or diastereomers, and the comparison of their strain energies is therefore subject to pitfalls,[4] the greater stability of **A** relative to **B** proved adequately attractive to us to warrant experimental evaluation. In view of the thermodynamic relationship of **A** to **C**, one might speculate that taxanes as a class represent hyperstable olefins.[5]

Refining the matter still further, we directed our attention to enolate oxidation studies involving **2**.[1] In line with earlier observations,[2c] it was possible to effect the α-oxygenation of this ketone with the sulfonyl oxaziridine popularized by Davis.[6] By maintenance of the reaction temperature at −78 °C, **3** was reproducibly obtained in 50% yield (Scheme 1). The occasion also presented itself to examine the direct oxygenation of the enolate of **2** at 0 °C in THF solution. At this higher temperature, more advanced oxidation became operative and the useful α-diketone **4** was obtained directly (80%). Although **3** proved to be unresponsive to possible α-ketol rearrangement, access to **5a** could be gained alternatively by the reduction of **4** with lithium aluminum hydride. No hydride attack was anticipated at C(13) because the enol positioned there will have been rapidly transformed into its enolate anion and transiently protected from nucleophilic attack. Indeed, the regioselective conversion of **4** into **5a** was accomplished in 65% yield alongside 28% of unreacted α-diketone.

To this point, the hydroxyl oxygen in **5a** has played a highly instrumental role in furthering the synthetic strategy to this

(1) Paquette, L. A.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5203.
(2) Elmore, S. W.; Combrink, K. D.; Paquette, L. A. *Tetrahedron Lett.* **1991**, *32*, 6679. (b) Paquette, L. A.; Combrink, K. D.; Elmore, S. W.; Zhao, M. *Helv. Chim. Acta* **1992**, *75*, 1772. (c) Elmore, S. W.; Paquette, L. A. *J. Org. Chem.* **1993**, *58*, 4963; **1995**, *60*, 889. (d) Paquette, L. A.; Huber, S. K.; Thompson, R. C. *J. Org. Chem.* **1993**, *58*, 6874. (e) Paquette, L. A.; Bailey, S. *J. Org. Chem.* **1995**, *60*, 7849. (f) Paquette, L. A.; Montgomery, F. J.; Wang, T.-Z. *J. Org. Chem.* **1995**, *60*, 7857. (g) Zeng, Q.; Bailey, S.; Wang, T.-Z.; Paquette, L. A. *J. Org. Chem.* **1998**, *63*, 3, in press.
(3) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Canfield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440. The illustrations were generated with Chem 3-D (Cambridge Scientific Co., Inc., Cambridge, MA).
(4) Taber, D. F. *Tetrahedron Lett.* **1993**, *34*, 1883.
(5) Maier, W. F.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 1891.
(6) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919.

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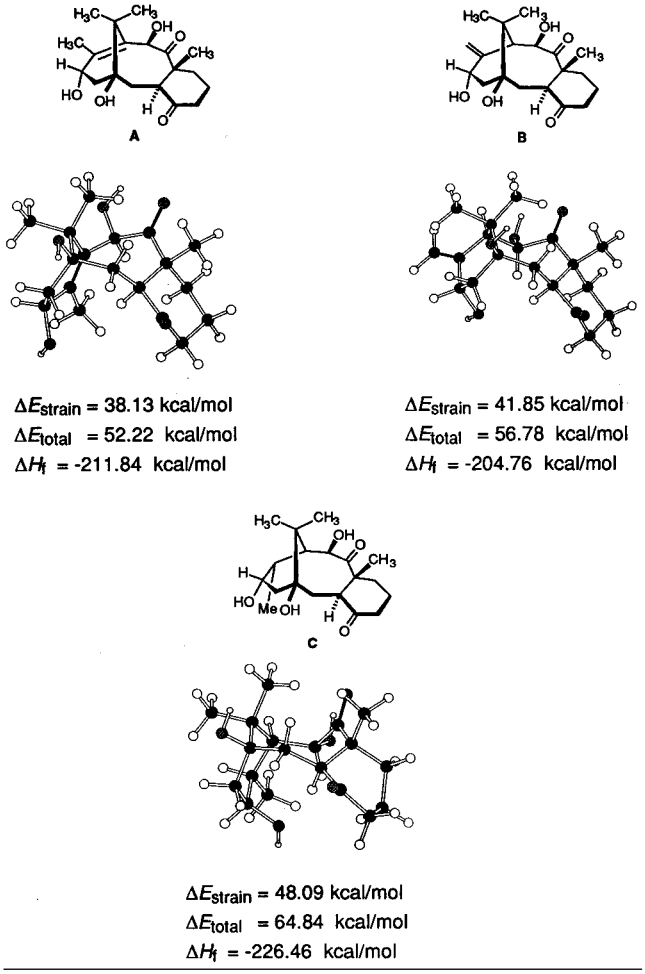
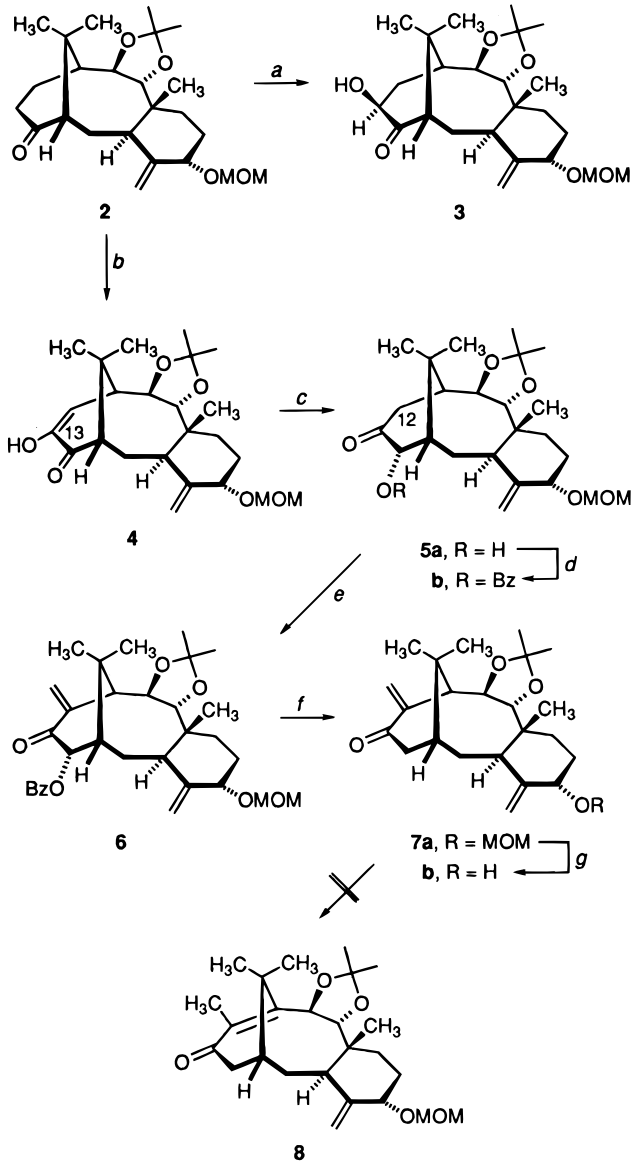
Table 1. Global Minimum Energy Conformations of an Endocyclic Unsaturated (**A**), Exocyclic Unsaturated (**B**), and Fully Saturated Taxane Systems as Obtained Using the Model KS 2.96 Software Package and Chem 3-D output



advanced stage. Initially responsible for driving the pinacol-like bridge migration, this oxygen center subsequently made possible useful adjustment of the oxidation level in ring A. However, its role had not yet been played out in that benzoylation as in **5b** was necessary in order to guide regioselective deprotonation exclusively to the C(12)-position. Indeed, the sequential exposure of **5b** to lithium diisopropylamide and freshly prepared monomeric formaldehyde solution[7] led efficiently to **6** alone (86%). At this stage, the benzoate group had accomplished its worthwhile function and was reductively cleaved by reaction with samarium iodide in a mixture of THF and methanol at −78 °C.[8] It is noteworthy that enone **7a** is not further reduced by this reagent under the conditions employed.

Of the limited number of known methods for olefin isomerization, that involving rhodium trichloride[9] appeared best suited to our needs. However, heating **7** with $RhCl_3$ in various solvents with or without added triethylamine failed to give **8**. Prolonged heating in the absence of base resulted in loss of the MOM protecting group, a likely consequence of acid buildup as the catalyst experiences slow degradation. No conditions were found to bring about the desired isomerization. Other reagents such as $[(Ph_3P)_3RhCl]$ and $Pd(OAc)_2/Ph_2PCH_2CH_2PPh_2$ promoted no observable chemical change. One of the deterrents to migration of the double bond into the interior of ring A may be a less than ideal stereoelectronic alignment of an allylic C−H bond.

Scheme 1



Introduction of the C(12)-Methyl Substituent

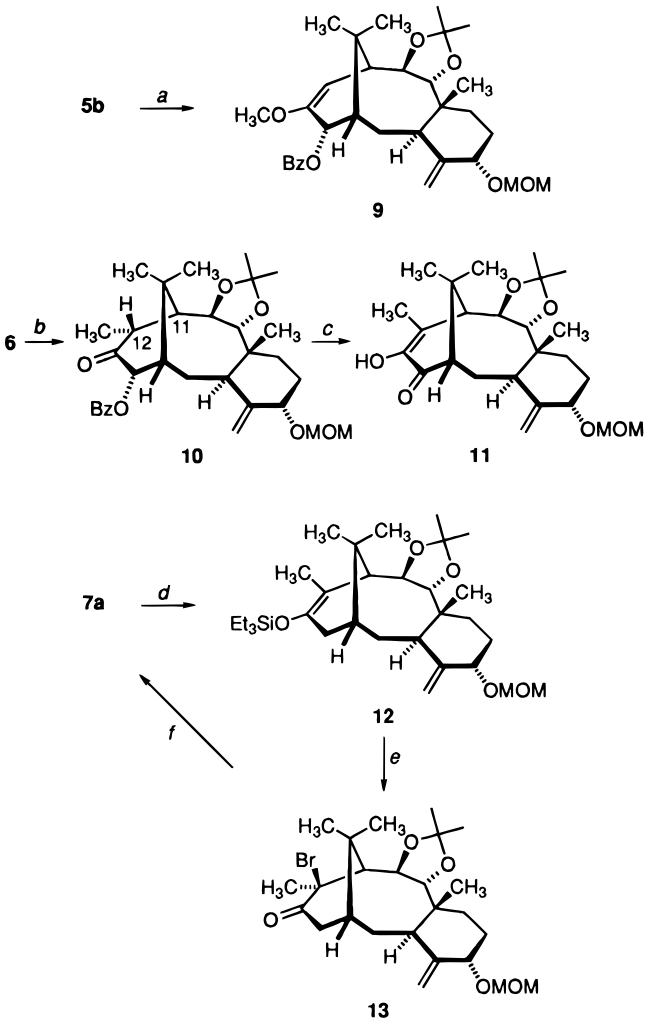
In view of this development, it seemed appropriate to explore C-methylation prior to generation of the enone segment. The potential for undesired competing elimination in the exocyclic direction did not escape our attention. The pursuit of this strategy began by conventional alkylation of the enolate anion of **5b**. This reactive intermediate proved to be very prone to

(7) Schlosser, M.; Jenny, T.; Guggisberg, Y. *Synlett* **1990**, 704.

(8) (a) Molander, G. A. *Org. React.* **1994**, *46*, 211. (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (c) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135, 5259. (d) Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573.

(9) (a) Andrieux, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 359. (b) Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102. (c) Genet, J. P.; Ficini, J. *Tetrahedron Lett.* **1979**, 1499.

Scheme 2



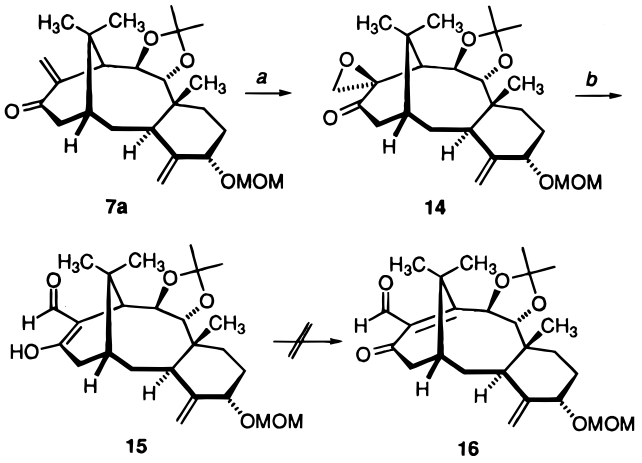
[a] LDA, THF, HMPA; CH_3I, -78° → 0 °C (92%). [b] $[Ph_3PCuH]_6$, Me_3SiCl, C_6H_6 (82%). [c] LDA, THF; C_6H_5SeCl, -78° → 0 °C (56%). [d] $[(C_6H_5)_3P]_3RhCl$, $(C_2H_5)_3SiH$, C_6H_6, reflux (93%). [e] NBS, propylene oxide, THF, 0° → 25 °C (74%). [f] DBU, THF, rt (75%).

O-alkylation, giving rise to **9** in 92% yield (Scheme 2). This eventuality conforms to the driving force underlying rehybridization of the carbon atoms in ring A from sp^3 to sp^2 status whenever possible. The previously discussed conversion of **2** to **4** constitutes a related example.

Some advancement toward our goal was alternatively realized by exploiting the susceptibility of **6** to stoichiometric conjugate reduction with triphenylphosphine copper hydride hexamer.[10] Exposure of benzene solutions of this enone to this hydride source in the presence of chlorotrimethylsilane or phenylselenenyl chloride led cleanly to **10** without evidence for significant incorporation of either electrophile. The configuration at C(12) was ascertained by NOE methods. Attempts to force selenenylation by deprotonation of **10** with excess lithium diisopropylamide followed by PhSeCl returned only the oxidation product **11**.

This complication was skirted by exploiting the Ojima 1,4-hydrosilylation protocol.[11] Treatment of **7a** with triethylsilane and chlorotris(triphenylphosphine)rhodium(II) in refluxing benzene gave in 93% yield the desired silyl enol ether **12**. Rather unexpectedly, all attempts to bring about the selenenylation of **12** with PhSeCl, PhSeBr, and CH_3SeBr were not at all promising. However, a bromine atom could be suitably introduced by exposure of **12** to *N*-bromosuccinimide in the presence of propylene oxide, whose role it was to serve as an acid scavenger. The resulting α-bromo ketone **13** proved responsive to the action of DBU in THF at room temperature. However, dehydrobromination in this fashion returned only **7a**. Recourse to other reagent combinations such as LiBr and Li_2CO_3 in DMF or LiF and Li_2CO_3 in HMPA resulted in the generation of very complex product mixtures. These findings should not be construed to be evidence for an inability to introduce the bridgehead double bond by an elimination process (see below). Nor do they necessarily shed light on the thermodynamic issues surrounding Table 1. What is clear is that the availability of three methyl protons fosters facile kinetically controlled antiperiplanar E_2 elimination in the exocyclic direction.

Scheme 3



[a] 30% H_2O_2, K_2CO_3, CH_3OH, H_2O (99%). [b] $LiBH(C_2H_5)_3$, THF, -78° → 10 °C (55%).

Consideration of Dual Activation as a Tool for Possible Introduction of the Bridgehead Olefinic Bond

A different agenda for realizing the direct introduction of C(11)−C(12) unsaturation emerged from the concept of dual activation. The guiding paradigm was the discovery of a completely stereoselective epoxidation of **7a** with alkaline hydrogen peroxide[12] and the remarkable conversion of **14** to **15** under conditions of attempted lithium triethylborohydride reduction[13] (Scheme 3). Although this reagent has displayed an ability to attack labile epoxides prone to electrophilic rearrangement in advance of structural isomerization,[14] the only characterizable product in the present instance was the enolic β-keto aldehyde **15**. By comparison, exposure of **14** to LDA or to diethylaluminum tetramethylpiperidide gave rise to complex reaction mixtures. Also, whereas zinc iodide alone

(10) (a) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291. (b) Koenig, T. M.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett.* **1990**, *31*, 3237. (c) Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett.* **1989**, *30*, 5677.

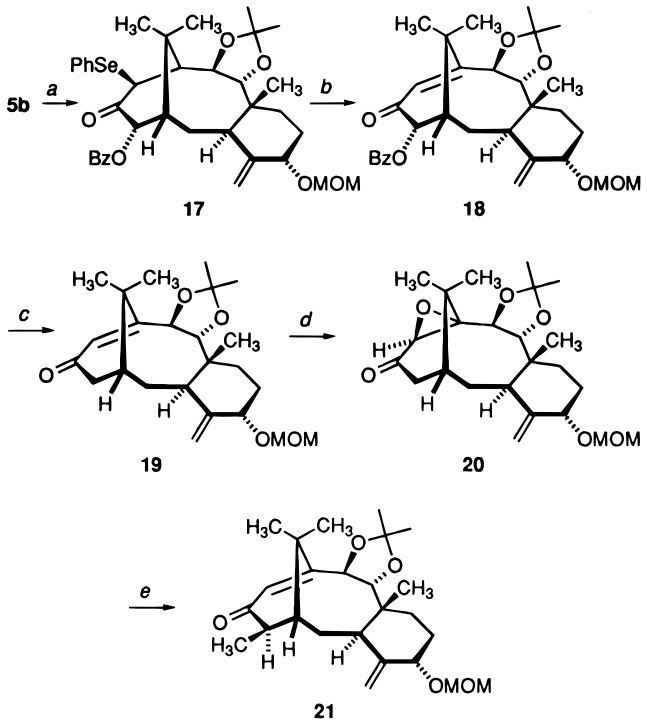
(11) (a) Ojima, I.; Kogure, T.; Nihonyanagi, M.; Nagai, Y. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3506. (b) Ojima, I.; Kogure, T. *Organometallics* **1982**, *1*, 1390.

(12) Solladié, G.; Hutt, J. *J. Org. Chem.* **1987**, *52*, 3560.

(13) Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1.

(14) (a) Krishnamurthy, S.; Schubert, R. M.; Brown, H. C. *J. Am. Chem. Soc.* **1973**, *95*, 8486. (b) Kitamura, M.; Isobe, M.; Ichikawa, Y.; Goto, T. *J. Am. Chem. Soc.* **1984**, *106*, 3252.

Scheme 4



[a] LiN(*i*-Pr)$_2$, THF; C_6H_5SeBr, -78° → 25 °C (92%). [b] 30% H_2O_2, HOAc, 0 °C (92%). [c] SmI_2, THF, CH_3OH, -78 °C (82%). [d] 30% H_2O_2, K_2CO_3, CH_3OH, 0° → 5 °C (79%). [e] LiN(*i*-Pr)$_2$; CH_3Li, THF, -78° → 0 °C.

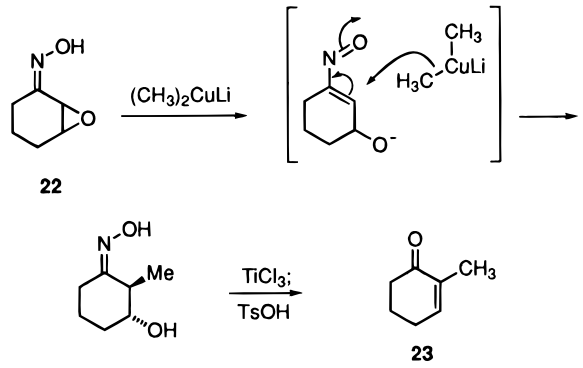
elicited no chemical change in **14**, the co-addition of lithium iodide did indeed lead to **15**, but with decreased efficiency.

The strong implication provided by these results is that the heightened steric congestion localized on both surfaces of ring A precludes operation of normal attack trajectories. Without doubt, this steric crowding also impacts heavily on the reactivity of **15**. The inherent problem is reflected, for example, in our inability to effect its oxidation to **16** with a variety of reagents including phenylselenenyl chloride[15] and DDQ,[16] despite widespread reports of their utility in related contexts. The pertinence of an inability to access **16** led us to consider introduction of the bridgehead olefinic bond in advance of any C(12) substituent.

Response of a Hindered Bridgehead Epoxide to Lithium Dimethylcuprate

Phenylselenenylation of the lithium enolate of **5b** with *freshly prepared* phenylselenyl bromide[17] afforded **17** in 92% yield (Scheme 4). Subsequent elimination of the derived selenoxide proceeded with equal efficiency to deliver **18**. In contrast to the fate of **17**, which experiences exclusive cleavage of the PhSe group under conditions of samarium iodide reduction, **18** undergoes chemoselective loss of the benzoate functionality to give **19** (82%). Despite the successful acquisition of enone **19** in a very direct way, one cannot lose sight of the fact that steric inhibition of an array of potential synthetic transformations continues to be observed. An example is the inertness of **19** to α-iodination upon treatment with I_2 in a mixture of pyridine and CCl_4.[18] More forceful conditions typified by bromine in pyridine or treatment with ICl and NaN_3[19] led to decomposition. The pursuit of this objective was motivated by an expectation that the halogen, once installed, could be substituted by a methyl group.

The possibility of utilizing epoxy ketone **20** surfaced when **19** was found to be amenable to epoxidation with 30% hydrogen peroxide and K_2CO_3 in methanol at 0 °C. The projected use of **20** that most attracted our attention was the reaction of lithium dimethylcuprate with epoxy oximes such as **22** reported by Corey and co-workers.[20] This route to **23**, when applied in the present context, would skirt the need for heavily encumbered backside attack by $(CH_3)_2CuLi$ on the epoxide ring. In practice, however, we were singularly unsuccessful in attempts to generate an oxime from **20**.



This setback prompted consideration of the direct opening of the oxirane ring in **20** with cuprate reagents.[21] The general consequence of these studies, which also included the higher-order $(CH_3)_2Cu(CN)Li_2$,[22] was reductive cleavage to the β-hydroxy ketone.[23] Since it seemed that a modest change in the nature of the reaction substrate might render the desired reaction more amenable, **20** was deprotonated with LDA prior to the addition of methyllithium.[24] When no observable change occurred up to 0 °C, CH_3MgBr was additionally introduced followed by warming to room temperature. Under these circumstances, a methyl group was indeed incorporated. However, it was immediately evident following spectroscopic analysis of this product that the C(14)-methylated compound (**21**) had formed by S_N2' addition to the enolate anion followed by the β-elimination of water.

Extended Oxygenation of the A-Ring: Net C(11) Methylation

The successful union of a methyl substituent to **20**, although incorrectly positioned, suggested the viability of a route in which coupling to an enol triflate was to figure prominently. Construction of the appropriate intermediate began with oxidation

(15) For example: Liotta, D.; Barnum, C.; Puleo, R.; Zima, G.; Bayer, C.; Kezar, H. S., III *J. Org. Chem.* **1981**, *46*, 2920.
(16) For example: Kende, A. S.; Blacklock, T. J. *Tetrahedron Lett.* **1980**, *21*, 3119.
(17) Reich, H. J.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 5813.
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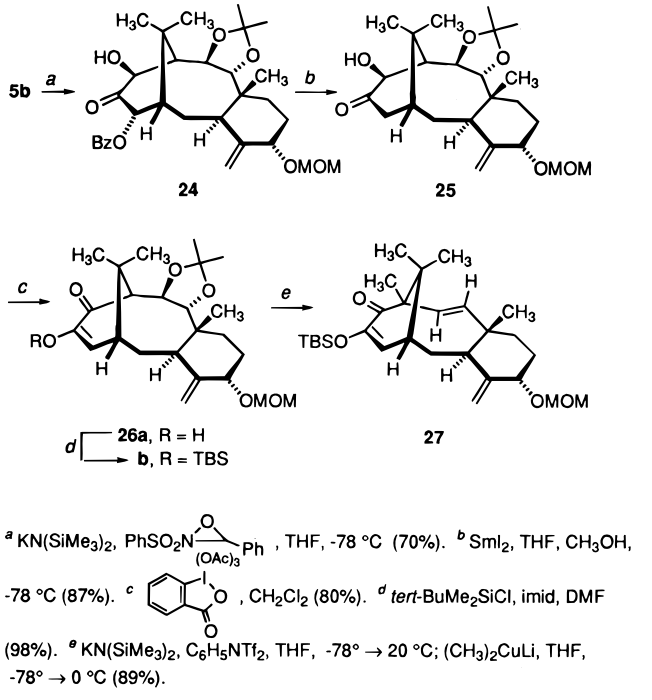
(19) McIntosh, J. M. *Can. J. Chem.* **1971**, *49*, 3045.
(20) Corey, E. J.; Melvin, L. S., Jr.; Haslanger, M. F. *Tetrahedron Lett.* **1975**, 3117.
(21) See, for example: (a) Acker, R.-D. *Tetrahedron Lett.* **1977**, 3407. (b) Huynh, C.; Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, 1503. (c) Fuchs, P. L. *J. Org. Chem.* **1976**, *41*, 2935. (d) Szajewski, R. P. *J. Org. Chem.* **1978**, *43*, 1819. (e) Lipshutz, B. H.; Kozlowski, J.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 2305. (f) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.
(22) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. *Tetrahedron Lett.* **1982**, *23*, 3755.
(23) Zhao, M. Unpublished work performed in this laboratory.
(24) Wender, P. A.; Erhardt, J. M.; Letendre, L. J. *J. Am. Chem. Soc.* **1981**, *103*, 2114.

Scheme 5



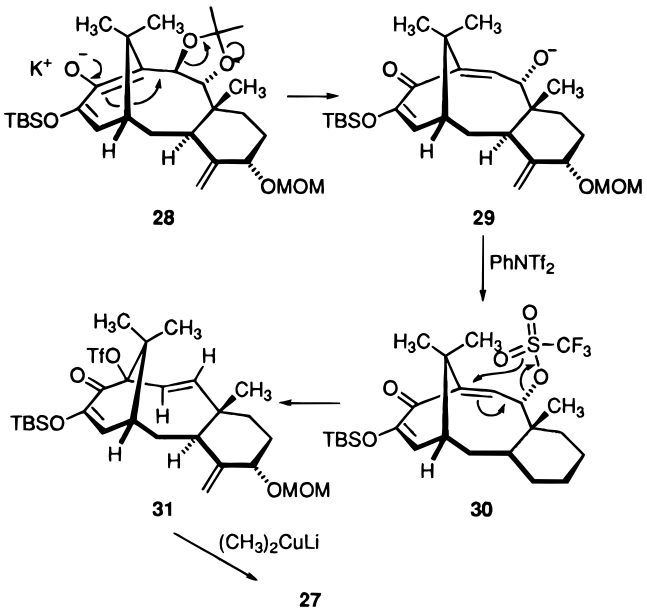
of **5b** to the α-hydroxy ketone **24**. The Davis oxaziridine approach provided **24** as the major product (70%, Scheme 5). Selective removal of the α-benzoyloxy group with samarium iodide followed by careful oxidation with the Dess−Martin periodinane[25] furnished the α-diketone **26a**. The ^{1}H NMR spectrum of this advanced intermediate revealed its wholesale adoption of the enol structure shown. In $CDCl_3$, the hydrogen-bonded OH proton appears as a sharp singlet at δ 5.94, and the vinylic C(14) proton is displayed as a doublet with $J = 6.9$ Hz. As a consequence of these structural features, it proved an easy matter to accomplish O-silylation to give **26b**.

Initial attempts to produce the targeted enol triflate by reaction of **26b** with LDA followed by *N*-phenyltriflimide[26] resulted in no reaction. When recourse was made instead to potassium hexmethyldisilazide as the base, a clean spot-to-spot transformation occurred (TLC analysis). When attempts to purify this product resulted in decomposition, the assumed triflate was not isolated, but treated directly with lithium dimethylcuprate in a one-pot procedure. To our delight, a methyl-substituted compound could be isolated in 89% yield. However, ^{1}H NMR analysis clearly showed this material to be the C(11)-methyl derivative **27**.

This outcome prompted closer investigation of the triflate generation step. The instability of the enolate of **26b** was initially ascertained on the basis of the complete fading within minutes of the yellow color that develops immediately after introduction of the $KN(SiMe_3)_2$. Also, TLC analysis at this early stage showed **26b** to be totally consumed before the triflimide was ever introduced. Indeed, the ^{1}H NMR spectrum of the unpurified triflate bore little resemblance to that of **26b**. Most striking was the Scheme 6 appearance of two mutually coupled doublets at δ 6.28 and 5.85. The large coupling constant of 17.8 Hz suggested that β-elimination had occurred with loss of acetone and introduction of an α,β double bond in ring B (see **29** in Scheme 6). This occurrence sets the stage for O-triflation of the alkoxide anion to generate **30**, rearrangement of which

(25) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
(26) Ritter, K. *Synthesis* **1993**, 735.

Scheme 6

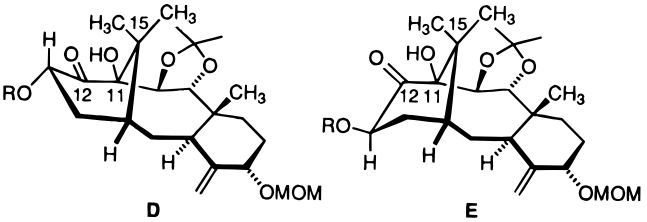


via the illustrated six-membered transition state would deliver the observed triflate. The ultimate conversion to **27** rests finally on an alkylative substitution at that bridgehead carbon adjacent to the ketone carbonyl.

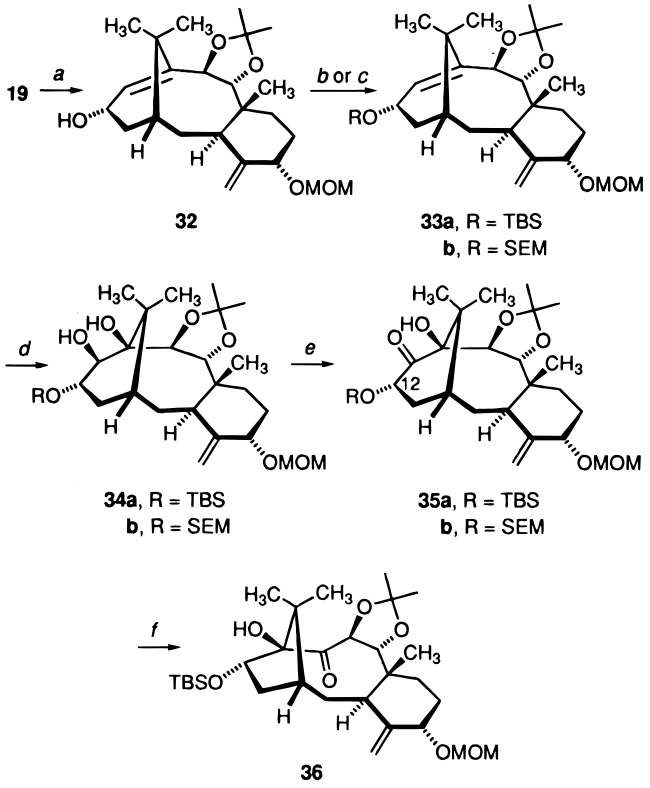
The Successful Dihydroxylation Pathway

At this stage, our thinking was much influenced by the sensitivity of ketone **26b** to strong base. Notwithstanding, it seemed appropriate to entertain the notion that introduction of the C(12)-methyl could be accomplished by 1,2-addition to a ketone structurally related to **26**. Toward this goal, **19** was reduced with Dibal-H to the α-alcohol **32**, which was amenable to protection as either the TBS or SEM derivative (Scheme 7). Dihydroxylation with osmium tetraoxide then provided diols **34a** and **34b**, perruthenate oxidation of which afforded **35a** and **35b**, respectively, thereby setting the stage for the projected nucleophilic methyl addition to C(12). An unanticipated limitation to this strategy surfaced when **35a** was treated with methylmagnesium bromide in ether at 0 °C. Although a rapid reaction ensued, the product proved to be isomeric with **35a**, indicating, of course, that the intended 1,2-addition had not materialized. Rather, the Grignard reagent had functioned as a base and promoted an α-ketol rearrangement to deliver **36**, the carbonyl group in which is sufficiently congested to ward off attack by the excess organometallic.

Although the facility with which this framework reorganization operates appeared to represent an insurmountable obstacle to arrival at **1**, increased attention to the conformational features of these taxane intermediates spawned a resolution to the synthetic goal. Specifically, the presence of an α-oxygenated substituent at C(13) was recognized to favor a boatlike A-ring arrangement as in **D** in order to skirt steric compression on the molecular interior. However, adoption of this conformation has



Scheme 7



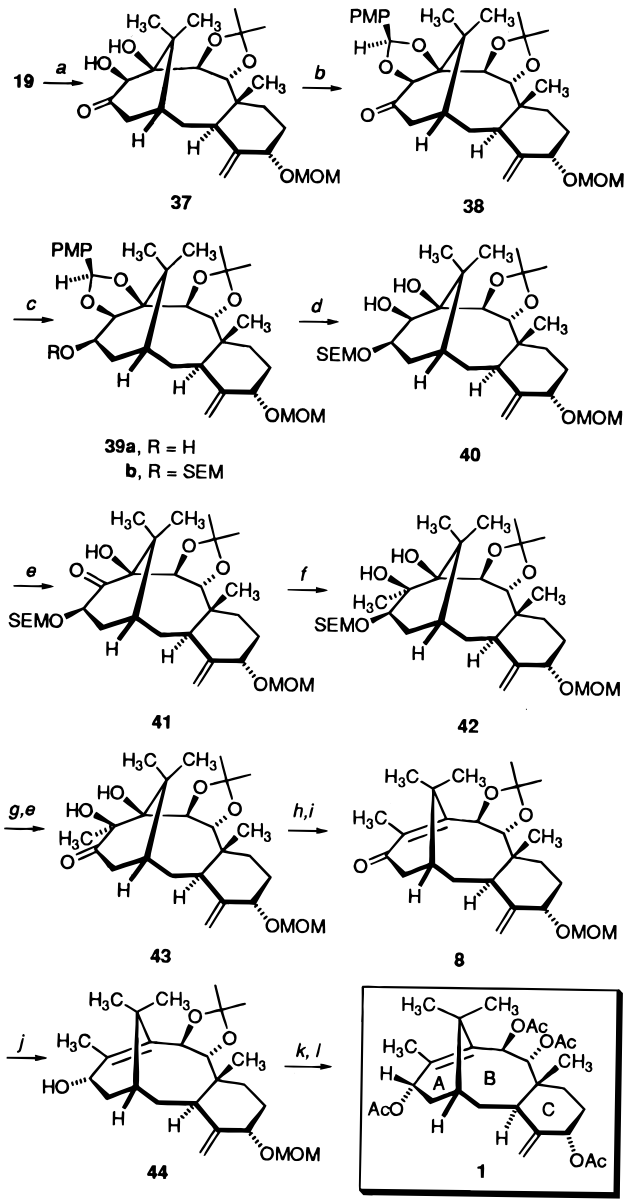
[a] (i-Bu)$_2$AlH, C_6H_6 (86%). [b] TBSOTf, py (99%). [c] SEMCl, (i-Pr)$_2$NEt (91%). [d] OsO_4, py; $NaHSO_3$: **a** (73%); **b** (100%). [e] TPAP, NMO, CH_2Cl_2: **a** (86%); **b** (93%). [f] CH_3MgBr, ether, 0 °C (63%).

the effect of disrupting a reasonable stereoalignment between the carbonyl π-cloud and the C(11)−C(15) σ bond. Accordingly, it is very likely that bridge migration operates only when the chair topology is attained and is necessarily accompanied by a substantial release of nonbonded strain. Conversely, a β-substituent at C(13) is best accommodated in a chairlike A-ring setting (see **E**). However, no unusual steric driving force to isomerization of the α-hydroxy ketone rearrangement is now apparent. Were this the actual scenario, then the 13β-substituted intermediate could be sufficiently long-lived to experience capture of the Grignard reagent.

The reversal in stereochemistry required to test this hypothesis was easily realized in the manner summarized in Scheme 8. Dihydroxylation of the bridgehead enone **19** afforded **37**, which was transformed into acetal **38**. The fusion of a dioxolane ring in this manner renders hydride attack from the α-surface more kinetically favored and delivers **39a**. The ensuing SEM protection and PMP removal steps proceeded quite smoothly to make diol **40** easily available. At this point, we were again able to take advantage of the selective oxidizing power of the TPAP reagent to provide **41** (92%) without detectable overoxidation. This compound was in turn successfully condensed with the cerate derived from methyllithium, thereby producing **42** in 83% yield. Although these conditions led most efficiently to **42**, neither methyllithium alone nor methylmagnesium bromide gave any evidence for inducing α-ketol rearrangement. Thus, the impact exerted by the stereochemistry of substitution at C(13) is notably influential on A-ring reactivity.

Spurred on by these developments, we proceeded to convert **42** by conventional means into ketone **43** and to implement removal of the neighboring hydroxyl groups therein. The best sequence uncovered involved preliminary reductive cleavage

Scheme 8



[a] OsO_4, py; $NaHSO_3$ (66%). [b] p-$CH_3OC_6H_4CH(OCH_3)_2$, CSA, DMF, 50 °C (100%). [c] $LiAlH_4$, ether; SEMCl, (i-Pr)$_2$NEt (81%). [d] DDQ, PPTS, CH_3OH, H_2O (91%). [e] TPAP, NMO, CH_2Cl_2 (92%). [f] CH_3Li, $CeCl_3$, THF, -78 °C (83%). [g] TBAF, THF (86%). [h] SmI_2, THF, MeOH (72%). [i] $SOCl_2$, py, DMAP (64%). [j] (i-Bu)$_2$AlH, CH_2Cl_2 (67%). [k] $LiBF_4$, H_2O, CH_3CN, 45 °C, 2 h (51%). [l] Ac_2O, DMAP, Et_3N, CH_2Cl_2 (85%).

of the α-OH with samarium iodide in THF.[8] This accomplished, β-elimination was induced with thionyl chloride in pyridine.

At this juncture, it was timely to reduce **8** so as to introduce the α-hydroxyl at C(13) in advance of the deprotection steps.[27] Concomitant hydrolytic removal of the MOM and acetonide protecting groups was accomplished by treatment with lithium tetrafluoroborate in wet acetonitrile.[28] However, the sensitivity of the resulting tetraol to acidic environments, likely due to the allylic functionality resident in both rings A and C, required that very careful attention be paid to reaction conditions. In

(27) For stereochemical precedence, consult inter alia: (a) Hara, R.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1996**, *118*, 9186. (b) Mukaiyama, T.; Shiima, I.; Iwadare, H.; Sakoh, H.; Tani, Y.; Hasegawa, M.; Saitoh, K. *Proc. Japan Acad., Ser. B* **1997**, *73*, 95.

(28) Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635.

the final analysis, a 5% level of water, a reaction temperature of 45 °C, and a total exposure time not exceeding 2 h were found to be near optimal. Finally, acetylation of this highly polar penultimate intermediate under standard conditions gave (+)-taxusin (**1**), $[\alpha]^{25}_D$ +105.5 (*c* 0.09, $CHCl_3$), which exhibited ^{1}H NMR, ^{13}C NMR, and IR spectra indistinguishable from those of natural taxusin, $[\alpha]^{25}_D$ +103.8 (*c* 0.16, $CHCl_3$).

Summary

A total synthesis of naturally occurring (+)-taxusin that is intrinsically different from the routes to (−)-taxusin[29] and (±)-taxusin[27a] reported earlier has been completed. The present approach proceeds from **2**[1] in 19 steps and 1.3% overall yield. The successful protocol features chemoselective oxidation/reduction processes of varied type within the confines of the A ring, and proper introduction of the C(12) methyl substituent via an organocerate reagent. A number of ancillary studies have demonstrated certain tactics to be unsatisfactory for use in the extremely congested and rather strained environment present in the A-ring sector of taxane intermediates. These include possible isomerization of an exocyclic double bond to the internal bridgehead position, dehydrogenation of a β-dicarbonyl system, and cuprate attack on an epoxy ketone. Several rearrangement reactions are now recognized to be capable of implementation. The transformations of **26b** into **27** and of **35b** into **36** are exemplary.

In the final analysis, our route to **1** (36 steps) is somewhat longer than those developed by Holton (31 steps)[29] and Kuwajima (25 steps).[27a] Work continues on the development of a workable strategy that would transform ketones such as **2** more directly into products having the C(11)−C(14) functionality characteristic of the taxane family of diterpenoids.

Experimental Section

For general methods, consult ref 1.

(3*S*,4a*R*,6*S*,8*S*,10*S*,11*R*,12*R*,12a*R*)-Dodecahydro-8-hydroxy-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-12a,13,13-trimethyl-4-methylene-6,10-methanobenzocyclodecen-7(1*H*)-one (3). To a solution of **2** (41 mg, 0.10 mmol) in dry THF (3 mL) cooled to −78 °C was added potassium hexamethyldisilazide (0.22 mL of 0.5 M in toluene, 0.11 mmol). After 30 min, the reaction mixture was treated with the Davis oxaziridine[6] (29 mg in 2 mL of THF), and stirring was continued for 30 min prior to quenching with cold saturated NH_4Cl solution. TLC analysis at this point indicated that conversion had proceeded only to approximately the 60% level. The product was extracted into ethyl acetate/hexanes (1:1), dried, concentrated, and chromatographed on silica gel to give 21 mg (50%) of **3**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.09 (br s, 1 H), 4.82 (br s, 1 H), 4.50 (d, J = 9.1 Hz, 1 H), 4.43 (d, J = 6.4 Hz, 1 H), 4.40 (d, J = 6.4 Hz, 1 H), 4.29 (d, J = 9.8 Hz, 1 H), 4.22 (dd, J = 3.2, 9.8 Hz, 1 H), 4.13 (t, J = 2.8 Hz, 1 H), 3.63 (s, 1 H), 3.30 (s, 3 H), 2.56−2.47 (m, 2 H), 2.34−2.15 (m, 3 H), 2.01 (dd, J = 6.8, 15.9 Hz, 1 H), 1.90−1.56 (m, 4 H), 1.40 (s, 6 H), 1.37 (s, 3 H), 0.98 (s, 3 H), 0.93 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 215.0, 148.0, 112.3, 106.6, 92.8, 83.0, 81.8, 76.7, 72.8, 58.4, 55.2, 46.5, 40.3, 39.2, 37.9, 37.8, 35.7, 28.3, 27.4, 26.8, 26.5, 25.2, 22.6, 17.4; FAB MS *m*/*z* (M^+ + 1) calcd 423.28, obsd 423.38.

(3*S*,4a*R*,6*S*,10*S*,11*R*,12*R*,12a*R*)-2,3,4,4a,5,6,10,11,12,12a-Decahydro-8-hydroxy-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-12a,13,13-trimethyl-4-methylene-6,10-methanobenzocyclodecen-7(1*H*)-one (4). A solution of **2** (252 mg, 0.62 mmol) and 18-crown-6 (246 mg, 0.93 mmol) in dry THF (31 mL) was oxygenated with O_2 for 30 min and treated with potassium hexamethyldisilazide (1.86 mL of 0.5 M in toluene, 0.93 mmol) at 0 °C. After 10 min of stirring, the reaction mixture was quenched with saturated NH_4Cl solution, and the product was extracted into ether prior to drying. Following solvent evaporation, the residue was subjected to chromatography on silica gel (elution with 1:4 ether/ hexanes) to provide 209 mg (80%) of **4** as a white solid, mp 165−166 °C; IR ($CHCl_3$, cm^{-1}) 3460, 1677, 1660; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (d, J = 6.6 Hz, 1 H), 5.89 (s, 1 H), 5.05 (s, 1 H), 4.86 (s, 1 H), 4.37 (d, J = 6.7 Hz, 1 H), 4.33 (d, J = 6.7 Hz, 1 H), 4.27 (d, J = 9.7 Hz, 1 H), 4.12 (br s, 1 H), 4.02 (d, J = 9.7 Hz, 1 H), 3.31 (s, 3 H), 2.96 (d, J = 6.6 Hz, 1 H), 2.67 (br d, J = 3.7 Hz, 1 H), 2.38 (dd, J = 2.0, 6.4 Hz, 1 H), 2.12 (ddd, J = 2.0, 6.4, 16.0 Hz, 1 H), 1.81−1.56 (m, 5 H), 1.41 (s, 6 H), 1.34 (s, 3 H), 1.20 (s, 3 H), 0.88 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 198.7, 148.9, 147.2, 118.4, 112.6, 104.8, 92.2, 83.6, 78.0, 75.5, 55.1, 54.0, 45.3, 38.2, 36.9, 36.5, 35.5, 28.8, 27.5, 25.1, 24.5, 23.5, 17.2; MS *m*/*z* (M^+) calcd 420.2512, obsd 420.2507; $[\alpha]^{23}_D$ +28.5 (*c* 1.04, $CHCl_3$).

Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.55; H, 8.63. Found: C, 68.35; H, 8.65.

(3*S*,4a*R*,6*S*,7*S*,10*S*,11*R*,12*R*,12a*R*)-Dodecahydro-7-hydroxy-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-12a,13,13-trimethyl-4-methylene-6,10-methanobenzocyclodecen-8(2*H*)-one (5a). A slurry of lithium aluminum hydride (53 mg, 1.39 mmol) in anhydrous ether (20 mL) was treated with **4** (195 mg, 0.464 mmol) in ether (16 mL), stirred for 30 min, and cooled to −78 °C prior to a methanol quench (2 mL). Saturated NH_4Cl solution (4 mL) was next introduced and the temperature was allowed to rise to 25 °C. The aqueous phase was extracted with 1:1 ethyl acetate/hexanes (3 × 20 mL), and the combined organic layers were dried and concentrated. Chromatographic purification on silica gel (gradient elution with 33−50% ethyl acetate in hexanes) returned 54 mg (28%) of unreacted **4** and provided 128 mg (65%) of **5a**, a colorless solid of mp 192−194 °C: IR ($CHCl_3$, cm^{-1}) 3500, 1704; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.08 (br s, 1 H), 5.00 (br s, 1 H), 4.67 (d, J = 6.9 Hz, 1 H), 4.63 (d, J = 6.9 Hz, 1 H), 4.35 (br d, J = 7.6 Hz, 1 H), 4.31 (d, J = 9.8 Hz, 1 H), 4.13 (t, J = 2.8 Hz, 1 H), 3.90 (d, J = 9.8 Hz, 1 H), 3.37 (s, 3 H), 3.15 (d, J = 2.6 Hz, 1 H), 3.03 (ddd, J = 1.3, 9.7, 18.1 Hz, 1 H), 2.62 (d, J = 18.1 Hz, 1 H), 2.54 (d, J = 9.7 Hz, 1 H), 2.35 (t, J = 6.7 Hz, 1 H), 2.23 (ddd, J = 1.5, 6.1, 15.5 Hz, 1 H), 1.83−1.51 (m, 6 H), 1.46 (s, 3 H), 1.37 (s, 3 H), 1.36 (s, 3 H), 1.29 (s, 3 H), 0.87 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 209.9, 146.5, 113.0, 105.1, 92.8, 83.4, 82.7, 75.6, 74.0, 55.0, 49.6, 45.9, 44.1, 39.1, 38.9, 37.4, 35.0, 28.3, 27.6, 26.8, 26.7, 25.3, 19.6, 17.7; MS *m*/*z* (M^+) calcd 422.2668, obsd 422.2665; $[\alpha]^{23}_D$ −99.2 (*c* 1.02, $CHCl_3$).

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.06. Found: C, 68.28; H, 9.13.

(3*S*,4a*R*,7*S*,10*S*,11*R*,12*R*,12a*R*)-Dodecahydro-7-hydroxy-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-12a,13,13-trimethyl-4-methylene-6,10-methanobenzocyclodecen-8(2*H*)-one Benzoate (5b). A solution of **5a** (78 mg, 0.185 mmol), 4-(dimethylamino)pyridine (2 mg), and benzoyl chloride (60 mg, 0.43 mmol) in pyridine (2 mL) was stirred overnight, quenched with water, and extracted with 1:1 ethyl acetate/hexanes. The combined organic layers were dried and concentrated, and the residue was chromatographed on silica gel (elution with 1:3 ethyl acetate/hexanes) to give **5b** (83 mg, 85%) as a white foam: IR (neat, cm^{-1}) 1720; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (dd, J = 1.3, 8.0 Hz, 2 H), 7.55 (tt, J = 1.3, 7.4 Hz, 1 H), 7.41 (d, J = 7.5 Hz, 1 H), 5.90 (d, J = 6.9 Hz, 1 H), 5.26 (br s, 1 H), 5.02 (br s, 1 H), 4.52 (d, J = 7.3 Hz, 1 H), 4.47 (d, J = 7.5 Hz, 1 H), 4.34 (d, J = 9.8 Hz, 1 H), 4.23 (br s, 1 H), 3.98 (d, J = 9.8 Hz, 1 H), 3.23 (s, 3 H), 3.13 (dd, J = 10.2, 18.5 Hz, 1 H), 2.66 (d, J = 18.5 Hz, 1 H), 2.60 (d, J = 9.6 Hz, 1 H), 2.37 (t, J = 6.4 Hz, 1 H), 2.24 (ddd, J = 1.7, 6.0, 16.3 Hz, 1 H), 2.08 (d, J = 4.5 Hz, 1 H), 1.83−1.57 (m, 5 H), 1.51 (s, 6 H), 1.40 (s, 3 H), 1.31 (s, 3 H), 0.92 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 202.0, 165.8, 148.5, 133.3, 130.1, 129.3, 128.2, 112.3, 105.0, 93.2, 83.2, 82.8, 75.3, 75.0, 54.8, 48.4, 45.4, 45.0, 39.4, 38.7, 38.0, 35.1, 28.7, 27.6, 26.7, 26.4, 25.3, 20.7, 17.6; MS *m*/*z* (M^+) calcd 526.2930, obsd 526.2911; $[\alpha]^{23}_D$ −51.4 (*c* 1.10, $CHCl_3$).

Anal. Calcd for $C_{31}H_{42}O_7$: C, 70.70; H, 8.04. Found: C, 70.83; H, 8.19.

(3*S*,4a*R*,6*S*,7*S*,10*R*,11*R*,12*R*,12a*R*)-Dodecahydro-7-hydroxy-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-12a,13,13-trimethyl-4-methylene-6,10-methanobenzocyclodecen-8(2*H*)-one Benzoate (6). A solution of **5b** (82 mg, 0.156 mmol) in dry THF (5 mL) was cooled

(29) Holton, R. A.; Juo, R. R.; Kim, H. B.; Williams, A. D.; Harusawa, S.; Lowenthal, R. E.; Yogai, S. *J. Am. Chem. Soc.* **1988**, *110*, 6558.

to −78 °C, treated with lithium diisopropylamide (0.67 mL in THF, 0.17 mmol), and stirred for 30 min at which point freshly prepared monomeric formaldehyde solution (1.5 mL, ca. 1 mmol) was introduced. The reaction mixture was allowed to warm to 0 °C for 1 h, quenched with saturated NH_4Cl solution, and extracted with 1:1 ethyl acetate/hexanes. The combined organic layers were dried and concentrated, and the residue was chromatographed on silica gel (elution with 1:4 ethyl acetate/hexanes) to afford **6** (72 mg, 86%) as a white foam, mp 145−147 °C (from hexanes containing ethyl acetate): IR ($CHCl_3$, cm^{-1}) 1723, 1703; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, J = 1.5, 7.4 Hz, 2 H), 7.56 (tt, J = 1.4, 7.4 Hz 1 H), 7.42 (t, J = 7.4 Hz, 2 H), 6.41 (br s, 1 H), 5.96 (d, J = 7.0 Hz, 1 H), 5.60 (t, J = 1.3 Hz, 1 H), 5.24 (br s, 1 H), 4.99 (br s, 1 H), 4.49 (d, J = 7.3 Hz, 1 H), 4.47 (d, J = 7.3 Hz, 1 H), 4.29 (d, J = 9.9 Hz, 1 H), 4.22 (t, J = 2.9 Hz, 1 H), 4.02 (d, J = 9.9 Hz, 1 H), 3.25 (s, 3 H), 3.24 (s, 1 H), 2.37 (t, J = 6.8 Hz, 1 H), 2.22 (ddd, J = 1.7, 5.7, 16.3 Hz, 1 H) 2.07 (br d, J = 3.6 Hz, 1 H), 1.82−1.53 (m, 5 H), 1.51 (s, 3 H), 1.43 (s, 3 H), 1.36 (s, 3 H), 1.33 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 192.7, 166.0, 148.1, 147.0, 133.2, 130.2, 129.4, 128.3, 128.2, 112.3, 104.9, 93.3, 84.0, 83.3, 75.2, 74.3, 54.9, 50.9, 47.2, 39.5, 39.3, 36.3, 35.4, 28.7, 27.5, 26.8, 25.8, 25.2, 20.3, 17.3; MS m/z (M^+) calcd 538.2930, obsd 538.2935; $[\alpha]^{23}_D$ −91.1 (c 1.03, hexanes).

Anal. Calcd for $C_{32}H_{42}O_7$: C, 71.35; H, 7.86. Found: C, 71.31; H, 7.87.

(3*S*,4a*R*,6*R*,10*R*,11*R*,12*R*,12a*R*)-Dodecahydro-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-12a,13,13-trimethyl-4,9-dimethylene-6,10-methanobenzocyclodecen-8(2*H*)-one (7a). To a solution of **6** (70 mg, 0.13 mmol) in a mixture of THF (5 mL) and methanol (2.5 mL) cooled to −78 °C was added dropwise a 0.10 M solution of samarium iodide in THF until a blue color persisted (ca. 3 mL); the mixture was quenched with saturated NH_4Cl solution and extracted with 1:1 ethyl acetate/hexanes. The combined extracts were dried and evaporated, and the residue was purified by chromatography on silica gel (elution with 1:4 ethyl acetate/hexanes) to deliver 44 mg (91%) of **7a** as an off-white solid, mp 130 °C (dec): IR ($CHCl_3$, cm^{-1}) 1684; ^1H NMR (300 MHz, $CDCl_3$) δ 6.43 (t, J = 1.4 Hz, 1 H), 5.52 (t, J = 1.4 Hz, 1 H), 5.11 (d, J = 1.2 Hz, 1 H), 4.95 (d, J = 1.2 Hz, 1 H), 4.41 (d, J = 7.1 Hz, 1 H), 4.34 (d, J = 7.1 Hz, 1 H), 4.22 (d, J = 9.8 Hz, 1 H), 4.13 (t, J = 3.0 Hz, 1 H), 4.01 (d, J = 9.8 Hz, 1 H), 3.30 (s, 3 H), 3.11 (br s, 1 H), 2.67 (dd, J = 8.1, 19.8 Hz, 1 H), 2.01 (d, J = 19.8 Hz, 1 H), 1.95−1.82 (m, 2 H), 1.81−1.57 (m, 5 H), 1.53−1.43 (m, 1 H), 1.40 (s, 3 H), 1.37 (s, 3 H), 1.33 (s, 3 H), 1.05 (s, 3 H), 0.87 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 197.6, 147.5, 146.6, 127.2, 112.7, 104.7, 92.6, 84.9, 83.6, 75.1, 55.0, 49.7, 41.2, 39.9, 39.2, 38.7, 35.5, 34.5, 28.3, 27.4, 26.8, 25.3, 25.1, 25.0, 17.4; MS m/z (M^+) calcd 418.2719, obsd 418.2723; $[\alpha]^{23}_D$ −96.9 (c 0.87, $CHCl_3$).

Anal. Calcd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 72.00; H, 9.16.

(3*S*,4a*R*,6*R*,10*R*,11*R*,12*R*,12a*R*)-Dodecahydro-3-hydroxy-11,12-(isopropylidenedioxy)-12a,13,13-trimethyl-4,9-dimethylene-6,10-methanobenzocyclodecen-8(2*H*)-one (7b). A mixture of **7a** (4 mg) and rhodium trichloride trihydrate (2 mg) was placed under high vacuum for 1.5 h, blanketed with N_2, and taken up in acetonitrile (4 mL). The mixture was refluxed for 2 h, cooled to room temperature, and freed of solvent. The residue was purified by chromatography on silica gel (elution with 1:2 ethyl acetate/hexanes) to furnish 3 mg (75%) of **7b**: ^1H NMR (300 MHz, C_6D_6) δ 6.44 (t, J = 1.5 Hz, 1 H), 5.23 (t, J = 1.5 Hz, 1 H), 4.88 (br s, 1 H), 4.61 (br s, 1 H), 4.24 (d, J = 9.7 Hz, 1 H), 4.13 (d, J = 9.7 Hz, 1 H), 4.09 (br s, 1 H), 3.18 (br s, 1 H), 2.37 (dd, J = 7.4, 18.8 Hz, 1 H), 2.06 (d, J = 18.8 Hz, 1 H), 2.09−1.98 (m, 2 H), 1.84−1.77 (m, 1 H), 1.64−1.45 (m, 6 H), 1.41 (s, 3 H), 1.33 (s, 3 H), 1.24 (s, 3 H), 0.92 (s, 3 H), 0.80 (s, 3 H); MS m/z (M^+) calcd 374.2458, obsd 374.2442.

(3*S*,4a*R*,6*S*,7*S*,10*S*,11*R*,12*R*,12a*R*)-1,2,3,4,4a,5,6,7,10,11,12,12a-Dodecahydro-11,12-(isopropylidenedioxy)-8-methoxy-3-(methoxymethoxy)-12a,13,13-trimethyl-4-methylene-6,10-methanobenzocyclodecen-7-ol Benzoate (9). A cold (−78 °C) solution of **5b** (15 mg, 0.028 mmol) in dry THF (2 mL) was treated with lithium diisopropylamide (0.20 mL in THF, 0.034 mmol) and stirred for 1 h, at which point dry HMPA (0.12 mL) and freshly distilled methyl iodide (0.01 mL, 0.16 mmol) were introduced sequentially. The reaction mixture was allowed to warm to 0 °C during 1 h, quenched with saturated NH_4Cl solution, and extracted with hexanes. The combined organic phases were dried and evaporated, whereupon the residue was chromatographed on silica gel (elution with 1:4 ethyl acetate/hexanes) to furnish 14.1 mg (92%) of **9** as a white solid, mp 145−146 °C: IR ($CHCl_3$, cm^{-1}) 1710; ^1H NMR (300 MHz, C_6D_6) δ 8.38−8.33 (m, 2 H), 7.15−7.13 (m, 3 H), 6.24 (td, J = 1.9, 6.9 Hz, 1 H), 5.10 (br s, 1 H), 4.94 (d, J = 6.8 Hz, 1 H), 4.72 (s, 1 H), 4.44 (d, J = 6.8 Hz, 1 H), 4.41 (dd, J = 1.4, 5.8 Hz, 1 H), 4.31 (d, J = 9.8 Hz, 1 H), 4.29 (s, 1 H), 4.07 (d, J = 9.8 Hz, 1 H), 3.51 (br d, J = 4.5 Hz, 1 H), 3.21 (s, 3 H), 3.12 (s, 3 H), 2.74 (d, J = 4.5 Hz, 1 H), 1.98−1.60 (m, 6 H), 1.45 (s, 3 H), 1.42 (s, 3 H), 1.39−1.23 (m, 1 H), 1.33 (s, 3 H), 1.16 (s, 3 H), 0.97 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 166.6, 152.9, 150.0, 132.8, 131.0, 130.7, 111.7, 104.6, 100.4, 93.6, 83.9, 80.5, 77.2, 70.1, 54.9, 54.3, 44.1, 43.9, 38.7, 37.4, 36.5, 35.0, 31.9, 29.1, 27.8, 27.1, 25.73, 25.67, 23.0, 20.9, 17.6, 14.3; MS m/z (M^+) calcd 540.3087, obsd 540.3071; $[\alpha]^{23}_D$ −113.8 (c 0.90, CH_2Cl_2).

(3*S*,4a*R*,6*S*,10*R*,11*R*,12*R*,12a*R*)-2,3,4,4a,5,6,10,11,12,12a-Decahydro-8-hydroxy-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-9,12a,13,13-tetramethyl-4-methylene-6,10-methanobenzocyclodecen-7(1*H*)-one (11). To a solution of **6** (8.5 mg, 16 μmol) in dry benzene (2 mL) were added chlorotrimethylsilane (0.01 mL) and a solution of $[Ph_3PCuH]_6$ (22 mg, 0.011 mmol) in dry benzene (2 mL). After 1.5 h of stirring, the color had completely faded, the reaction mixture was quenched with saturated $NaHCO_3$ solution, stirred overnight, and extracted with hexanes. After drying and evaporation, **10** was isolated as a white foam (7.0 mg, 82%): ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (dd, J = 1.4, 7.4 Hz, 2 H), 7.55 (tt, J = 1.4, 7.4 Hz, 1 H), 7.41 (br t, J = 7.4 Hz, 2 H), 5.90 (d, J = 7.1 Hz, 1 H), 5.24 (br s, 1 H), 5.02 (br s, 1 H), 4.54 (d, J = 7.2 Hz, 1 H), 4.48 (d, J = 9.7 Hz, 1 H), 4.41 (d, J = 7.2 Hz, 1 H), 4.19 (br s, 1 H), 4.08 (dd, J = 1.4, 9.7 Hz, 1 H), 3.25−3.16 (m, 1 H), 3.19 (s, 3 H), 2.51 (br d, J = 7.7 Hz, 1 H), 2.45 (br t, J = 6.6 Hz, 1 H), 2.31−2.23 (m, 1 H), 1.98 (br d, J = 5.8 Hz, 1 H), 1.82−1.56 (m, 4 H), 1.62 (s, 3 H), 1.57 (s, 3 H), 1.40 (s, 3 H), 1.32 (s, 3 H), 1.29 (d, J = 6.7 Hz, 3 H), 0.92 (s, 3 H).

A solution of the above material (5.4 mg, 10.0 μmol) in dry THF (1.5 mL) at −78 °C was treated with lithium diisopropylamide (0.19 mL in THF, 30 μmol), stirred for 1 h at this temperature prior to the addition of phenylselenenyl chloride (10 mg, 50 μmol), allowed to warm to 0 °C, quenched with saturated $NaHCO_3$ solution, and extracted with hexanes. The combined organic phases were dried and concentrated to leave a residue which was chromatographed on silica gel (elution with 1:5 ethyl acetate/hexanes) to give 2.4 mg (56%) of **11** as a white solid: ^1H NMR (300 MHz, C_6D_6) δ 6.16 (s, 1 H), 4.99 (br s, 1 H), 4.78 (br s, 1 H), 4.58 (d, J = 6.8 Hz, 1 H), 4.50 (d, J = 6.8 Hz, 1 H), 4.30 (d, J = 9.7 Hz, 1 H), 4.19 (t, J = 2.7 Hz, 1 H), 4.12 (d, J = 9.7 Hz, 1 H), 3.20 (s, 3 H), 2.72−2.69 (m, 2 H), 2.16 (dd, J = 1.5, 6.6 Hz, 1 H), 2.05 (ddd, J = 2.2, 6.6, 15.6 Hz, 1 H), 1.91 (s, 3 H), 1.88−1.75 (m, 2 H), 1.69−1.50 (m, 2 H), 1.46 (ddd, J = 1.8, 5.7, 15.6 Hz, 1 H), 1.39 (s, 3 H), 1.30 (m, 3 H), 1.18 (s, 3 H), 0.91 (s, 6 H); MS m/z (M^+) calcd 434.2669, obsd 434.2681.

(3*S*,4a*R*,6*R*,10*S*,11*R*,12*R*,12a*R*)-9-Bromododecahydro-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-9,12a,13,13-tetramethyl-4-methylene-6,10-methanobenzocyclodecen-8(2*H*)-one (13). To a mixture of **7a** (10 mg, 23.9 μmol) and tris(triphenylphosphine)rhodium chloride (1 mg) under N_2 were added benzene (1 mL) and triethylsilane (0.1 mL). The mixture was refluxed for 2 h, cooled, and freed of benzene and excess silane in vacuo. The residue was purified by chromatography on silica gel (elution with 1:10 ether/hexanes) to give **12** as a colorless oil (12 mg, 93%): ^1H NMR (300 MHz, C_6D_6) δ 5.06 (br s, 1 H), 4.86 (d, J = 7.1 Hz, 1 H), 4.84 (br s, 1 H), 4.78 (d, J = 7.1 Hz, 1 H), 4.40 (d, J = 9.8 Hz, 1 H), 4.33 (br s, 1 H), 4.29 (d, J = 9.8 Hz, 1 H), 3.33 (s, 3 H), 3.10 (br s, 1 H), 2.56 (br s, 1 H), 2.30−2.20 (m, 1 H), 2.08−1.58 (series of m, 8 H), 1.84 (br s, 3 H), 1.48 (s, 3 H), 1.41 (s, 3 H), 1.39 (s, 3 H), 1.10 (s, 3 H), 1.03 (s, 3 H), 0.97 (t, J = 7.9 Hz, 9 H), 0.58 (q, J = 7.9 Hz, 6 H).

A solution of **12** (5.0 mg, 9.3 μmol) and propylene oxide (3 drops) in THF (2 mL) at 0 °C was treated with *N*-bromosuccinimide (2 mg, 11 μmol) and allowed to warm to 25 °C during 2 h. An additional 2 mg of NBS was introduced; after another 3 h, the reaction mixture was quenched with saturated $NaHCO_3$ solution and brine, and the

product was extracted into ether. The combined organic layers were dried and concentrated to leave a residue which was chromatographed on silica gel (elution with 1:10 ether/hexanes). There was isolated 3.4 mg (74%) of **13** as a white solid: ^{1}H NMR (300 MHz, C_6D_6) δ 4.93 (br s, 1 H), 4.71 (d, J = 7.4 Hz, 1 H), 4.70 (d, J = 7.4 Hz, 1 H), 4.66 (br s, 1 H), 4.49 (d, J = 9.7 Hz, 1 H), 4.28 (d, J = 9.7 Hz, 1 H), 4.19 (t, J = 2.6 Hz, 1 H), 3.41 (br s, 1 H), 3.22 (s, 3 H), 2.77 (dd, J = 7.8, 18.5 Hz, 1 H), 2.42 (s, 3 H), 1.90 (d, J = 18.9 Hz, 1 H), 1.79−1.43 (series of m, 8 H), 1.57 (s, 3 H), 1.38 (s, 3 H), 1.31 (s, 3 H), 1.30 (s, 3 H), 0.86 (s, 3 H); FAB MS *m*/*z* calcd 498.20, obsd 498.41.

Conversion of 13 to 7a. A solution of **13** (10 mg, 0.02 mmol) in dry THF (4 mL) was treated with 4 drops of DBU and stirred overnight at 25 °C. After the addition of saturated NH_4Cl solution, the product was extracted into ethyl acetate/hexanes (1:1), and the combined organic phases were dried and evaporated. Chromatography of the residue on silica gel afforded 6.3 mg (75%) of **7a** as a white solid, mp 135 °C (dec), identical with the compound of the same structure described earlier.

(3*S*,4a*R*,6,9*R*,10*S*,11*R*,12*R*,12a*R*)-Dodecahydro-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-12a,13,13-trimethyl-4-methylenespiro[6,10-methanobenzocyclodecene-9(8*H*),2′-oxiran]-8-one (14). To a cold (0 °C) solution of **7a** (100 mg, 0.239 mmol) in methanol (10 mL) were added water (5 mL) and 30% hydrogen peroxide (0.5 mL). Potassium carbonate (150 mg) was introduced and the mixture was stirred for 4 h, quenched with saturated NH_4Cl solution, and freed of methanol in vacuo. The product was extracted into ethyl acetate (3 × 20 mL), washed with water (10 mL) and brine (10 mL), dried, evaporated, and chromatographed on silica gel. There was obtained 103 mg (99%) of **14** as a white solid, mp 146−148 °C: IR ($CHCl_3$, cm^{-1}) 1710; ^{1}H NMR (300 MHz, C_6D_6) δ 4.97 (br s, 1 H), 4.70 (br s, 3 H), 4.29 (d, J = 9.7 Hz, 1 H), 4.22 (br t, J = 3 Hz, 1 H), 4.15 (d, J = 9.7 Hz, 1 H), 3.69 (d, J = 6.2 Hz, 1 H), 3.23 (s, 3 H), 2.71 (d, J = 6.2 Hz, 1 H), 2.50 (dd, J = 7.7, 19.2 Hz, 1 H), 2.35 (br s, 1 H), 1.94−1.77 (m, 4 H), 1.69−1.41 (m, 5 H), 1.36 (s, 3 H), 1.27 (s, 3 H), 1.21 (s, 3 H), 1.14 (s, 3 H), 0.92 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 203.4, 148.0, 112.5, 105.3, 93.2, 82.9, 80.8, 75.1, 60.2, 55.0, 52.5, 50.6, 42.5, 40.7, 39.7, 39.4, 37.0, 33.3, 28.7, 27.7, 26.9, 25.8, 25.6, 25.1, 17.9; MS *m*/*z* (M^+) calcd 434.2668, obsd 434.2633; $[\alpha]^{23}_D$ −158.5 (*c* 1.00, $CHCl_3$).

Anal. Calcd for $C_{25}H_{38}O_6$: C, 69.10; H, 8.81. Found: C, 69.46; H, 8.88.

(3*S*,4a*R*,6*R*,10*S*,11*R*,12*R*,12a*R*)-1,2,3,4,4a,5,6,7,10,11,12,12a-Dodecahydro-8-hydroxy-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-12a,13,13-trimethyl-4-methylene-6,10-methanobenzocyclodecene-9-carboxaldehyde (15). A solution of **14** (5.5 mg, 12.7 μmol) in dry THF (1 mL) was cooled to −78 °C, treated with lithium triethylborohydride (0.20 mL of 0.1 M in THF), stirred at −10 °C for 3 h, and quenched with saturated NH_4Cl solution. Extraction with 1:1 ethyl acetate/hexanes was followed by drying and evaporation of the combined extracts, and chromatography of the residue on silica gel (elution with 1:4 ether/hexanes) to give 3 mg (55%) of **15**: ^{1}H NMR (300 MHz, C_6D_6) δ 15.4 (d, J = 2 Hz, 1 H), 8.82 (d, J = 2 Hz, 1 H), 4.97 (br s, 1 H), 4.72 (d, J = 6.9 Hz, 1 H), 4.68 (br s, 1 H), 4.60 (d, J = 6.9 Hz, 1 H), 4.21 (br s, 1 H), 4.19 (d, J = 9.6 Hz, 1 H), 3.95 (d, J = 9.6 Hz, 1 H), 3.20 (s, 3 H), 2.86 (br s, 1 H), 2.51 (br s, 1 H), 2.30 (dd, J = 8.2, 19.9 Hz, 1 H), 1.80−1.73 (m, 2 H), 1.76 (d, J = 19.9 Hz, 1 H), 1.60−1.54 (m, 2 H), 1.45 (t, J = 3.9 Hz, 2 H), 1.39 (s, 3 H), 1.35 (br s, 1 H), 1.27 (s, 3 H), 1.24 (s, 3 H), 0.91 (s, 3 H), 0.73 (s, 3 H); MS *m*/*z* (M^+) calcd 434.2668, obsd 434.2676.

(3*S*,4a*R*,6*S*,7*S*,9*Z*,11*R*,12*R*,12a*R*)-1,3,4,4a,5,6,7,11,12,12a-Decahydro-7-hydroxy-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-12a,13,13-trimethyl-4-methylene-6,10-methanobenzocyclodecen-8(2*H*)-one Benzoate (18). To a solution of **5b** (100 mg, 0.19 mmol) in dry THF (5.0 mL) at −78 °C was added lithium diisopropylamide (1.7 mL of 0.16 M in THF, 0.27 mmol). After 3 min, phenylselenenyl bromide (0.2 M in THF) was introduced until the color persisted. The reaction mixture was allowed to warm to room temperature during 1 h, at which point saturated $NaHCO_3$ solution was added and the product was extracted into 1:3 ethyl acetate/ hexanes. The combined extracts were dried and evaporated. Purification of the residue by chromatography on silica gel afforded 119 mg (92%) of **17** as a white foam: ^{1}H NMR (300 MHz, C_6D_6) δ 8.33−8.29 (m, 2 H), 7.66−7.61 (m, 2 H), 7.13−7.07 (m, 3 H), 6.95−6.90 (m, 3 H), 6.50 (d, J = 6.2 Hz, 1 H), 5.20 (br s, 1 H), 4.87 (br s, 1 H), 4.77 (d, J = 7.4 Hz, 1 H), 4.61 (d, J = 7.4 Hz, 1 H), 4.31 (br s, 2 H), 4.28 (d, J = 9.8 Hz, 1 H), 4.03 (d, J = 4.0 Hz, 1 H), 4.12 (s, 1 H), 3.07 (s, 3 H), 2.35 (br d, J = 4.9 Hz, 1 H), 2.04−1.96 (m, 2 H), 1.84−1.76 (m, 2 H), 1.67−1.55 (m, 2 H), 1.49 (s, 3 H), 1.46−1.37 (m, 1 H), 1.34 (s, 3 H), 1.27 (s, 3 H), 1.20 (s, 3 H), 0.92 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 200.0, 165.7, 149.0, 135.8, 133.2, 131.2, 130.6, 130.2, 129.3, 128.9, 128.7, 128.4, 111.9, 105.0, 93.8, 84.4, 83.5, 75.5, 73.1, 54.8, 52.6, 52.1, 48.6, 39.5, 39.3, 37.7, 36.0, 29.1, 27.6, 26.8, 26.5, 25.8, 20.6, 17.7.

A solution of the above material (119 mg, 0.17 mmol) in THF (4.0 mL) was cooled to 0 °C, treated with acetic acid (3 drops) and 30% hydrogen peroxide (0.1 mL), and stirred at 0 °C for 1 h. The THF was removed on a rotary evaporator, and the residue was neutralized with saturated $NaHCO_3$ solution and processed in the usual way to give **18** (85 mg, 92%) as a white solid, mp 156−157 °C: IR ($CHCl_3$, cm^{-1}) 1720, 1680; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 8.0 Hz, 2 H), 7.54 (t, J = 7.4 Hz, 1H), 7.40 (dd, J = 7.4, 8.0 Hz, 2 H), 6.25 (d, J = 5.7 Hz, 1 H), 6.24 (s, 1 H), 5.13 (s, 1 H), 4.80 (s, 1 H), 4.54 (d, J = 9.3 Hz, 1 H), 4.46 (d, J = 7.0 Hz, 1 H), 4.33 (d, J = 9.3 Hz, 1 H), 4.27 (d, J = 20 Hz, 1 H), 4.16 (br s, 1 H), 3.26−3.24 (m, 1 H), 3.24 (s, 3 H), 2.71−2.61 (m, 1 H), 2.15−2.08 (m, 1 H), 1.89−1.64 (m, 5 H), 1.69 (s, 3 H), 1.60 (s, 3 H), 1.50 (s, 3 H), 1.43 (s, 3 H), 0.90 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 194.1, 166.1, 164.1, 149.7, 133.3, 132.4, 130.1, 129.2, 128.2, 111.7, 108.6, 92.8, 82.0, 79.4, 76.0, 73.9, 55.0, 51.0, 41.2, 40.5, 37.0, 35.8, 28.5, 27.0, 26.7, 24.9, 24.3, 20.9, 17.4; MS *m*/*z* (M^+) calcd 524.2774, obsd 524.2769; $[\alpha]^{23}_D$ +25.5 (*c* 1.00, $CHCl_3$).

Anal. Calcd for $C_{31}H_{40}O_7$: C, 70.97; H, 7.68. Found: C, 71.06; H, 7.76.

(3*S*,4a*R*,6*R*,9*Z*,11*R*,12*R*,12a*R*)-1,3,4,4a,5,6,7,11,12,12a-Decahydro-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-12a,13,13-trimethyl-4-methylene-6,10-methanobenzocyclodecen-8(2*H*)-one (19). To a solution of **18** (399 mg, 0.76 mmol) in 1:1 tetrahydrofuran−methanol (40 mL) cooled to −78 °C was added 0.12 M samarium diiodide solution in THF via a syringe pump (0.25 mL/min). The progress of reaction was monitored by TLC, and the mixture was quenched with saturated $NaHCO_3$ solution (5 mL) and extracted with ethyl acetate when no **18** remained. The combined organic phases were washed with brine, dried, and concentrated to leave a residue, purification of which by chromatography on silica gel (elution with 3:1 hexanes/ethyl acetate) gave **19** (108 mg, 82%) as a colorless crystalline solid, mp 194−195 °C (from 2:1 hexanes/ethyl acetate): IR (neat, cm^{-1}) 1671; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (s, 1 H), 5.07 (s, 1 H), 4.81 (s, 1 H), 4.48 (d, J = 9.3 Hz, 1 H), 4.37 (d, J = 6.7 Hz, 1 H), 4.27 (d, J = 6.7 Hz, 1 H), 4.22 (d, J = 9.3 Hz, 1 H), 4.10 (t, J = 2.6 Hz, 1 H), 3.29 (s, 3 H), 3.05 (br d, J = 3.1 Hz, 1 H), 2.88 (dd, J = 9.5, 6.7 Hz, 1 H), 2.25 (m, 1 H), 1.92−1.55 (series of m, 7 H), 1.59 (s, 3 H), 1.48 (s, 3 H), 1.41 (s, 3 H), 1.27 (s, 3 H), 0.87 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 199.7, 162.0, 149.6, 131.5, 112.2, 108.2, 92.0, 82.1, 79.9, 75.9, 55.1, 43.4, 40.6, 40.3, 40.0, 36.8, 35.3, 28.4, 27.0, 26.7, 26.5, 24.9, 23.4, 17.5; MS *m*/*z* (M^+) calcd 404.2563, obsd 404.2567; $[\alpha]^{24}_D$ +90.9 (*c* 0.74, $CHCl_3$).

(3*S*,4a*R*,6*R*,9*S*,10*R*,11*S*,12*R*,12a*R*)-9,10-Epoxydodecahydro-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-12a,13,13-trimethyl-4-methylene-6,10-methanobenzocyclodecen-8(2*H*)-one (20). To a solution of **19** (8.5 mg, 0.021 mmol) in methanol (2 mL) at 0−5 °C were added 30% hydrogen peroxide (5 drops) and potassium carbonate (5 mg). The reaction mixture was stirred overnight at 0 °C, quenched with 1% citric acid, and extracted with 1:3 ethyl acetate/hexanes. The combined extracts were dried, evaporated, and chromatographed on silica gel to give 7.0 mg (79%) of **20** as white crystals, mp 184−186 °C: IR ($CHCl_3$, cm^{-1}) 1721; ^{1}H NMR (300 MHz, C_6D_6) δ 4.89 (s, 1 H), 4.58 (s, 1 H), 4.48 (d, J = 6.6 Hz, 1 H), 4.37 (d, J = 6.6 Hz, 1 H), 4.23 (d, J = 9.8 Hz, 1 H), 4.09 (t, J = 2.7 Hz, 1 H), 3.40 (d, J = 9.8 Hz, 1 H), 3.13 (s, 3 H), 2.96 (s, 1 H), 2.88−2.86 (m, 1 H), 2.41 (dd, J = 7.6, 20.1 Hz, 1 H), 1.70 (d, J = 20.1 Hz, 1 H), 1.70−1.37 (m, 7 H), 1.44 (s, 3 H), 1.41 (s, 3 H), 1.29 (s, 3 H), 0.89 (s, 3 H), 0.75 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 205.9, 149.4, 111.4, 107.6, 92.9, 83.5, 81.6, 76.5, 58.8, 55.0, 54.5, 44.5, 41.9, 39.1, 38.5, 38.0, 28.6,

28.1, 27.2, 26.7, 25.6, 25.5, 24.5, 17.4; MS *m*/*z* (M^+) calcd 420.2513, obsd 420.2514.

(3*S*,4a*R*,6*R*,7*R*,9*Z*,11*R*,12*R*,12a*R*)-1,3,4,4a,5,6,7,11,12,12a-Decahydro-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-7,12a,13,13-tetramethyl-4-methylene-6,10-methanobenzocyclodecen-8(2*H*)-one (21). A solution of **20** (2 mg, 4.7 μmol) in dry THF (1 mL) was cooled to −78 °C and treated with lithium diisopropylamide (0.10 mL, 30 μmol). After 30 min, methyllithium (0.04 mL of 1.4 M in ether, 56 μmol) was introduced, and the reaction mixture was allowed to warm to 0 °C during 3 h and stirred overnight at this temperature. At this point, no reaction was evident by TLC analysis. Methylmagnesium bromide (0.05 mL of 3 M in ether, 150 μmol) was added and the reaction mixture was stirred at room temperature for 3 h prior to being quenched with saturated NH_4Cl solution. The product was extracted into 1:3 ethyl acetate/hexanes, dried, and concentrated. Purification of the residue by chromatography on silica gel afforded 1 mg of **21**: IR (neat, cm^{-1}) 1691; ^1H NMR (500 MHz, C_6D_6) δ 6.11 (s, 1 H), 4.91 (s, 1 H), 4.62 (s, 1 H), 4.52 (d, J = 6.5 Hz, 1 H), 4.44 (d, J = 9.4 Hz, 1 H), 4.36 (d, J = 6.5 Hz, 1 H), 4.19 (d, J = 9.4 Hz, 1 H), 4.07 (t, J = 3 Hz, 1 H), 3.20 (br s, 1 H), 3.13 (s, 3 H), 1.90 (q, J = 7.3 Hz, 1 H), 1.90−1.43 (series of m, 7 H), 1.42 (s, 3 H), 1.40 (s, 3 H), 1.35 (s, 3 H), 1.35 (d, J = 7.3 Hz, 3 H), 1.07 (s, 3 H), 0.92 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) ppm 201.6, 160.1, 150.8, 131.3, 111.8, 108.0, 92.8, 82.5, 80.1, 76.8, 55.0, 50.2, 46.7, 40.6, 40.1, 37.3, 36.4, 28.8, 27.3, 26.9 (2 C), 25.4, 23.6, 19.4, 17.8; MS *m*/*z* (M^+) calcd 418.2720, obsd 418.2726.

(3*S*,4a*R*,6*S*,7*S*,9*S*,10*R*,11*R*,12*R*,12a*R*)-Dodecahydro-7,9-dihydroxy-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-12a,13,13-trimethyl-4-methylene-6,10-methanobenzocyclodecen-8(2*H*)-one 7-Benzoate (24). A cold (−78 °C), magnetically stirred solution of **5b** (70 mg, 0.133 mmol) in dry THF (5 mL) was treated with potassium hexamethyldisilazide (0.32 mL of 0.5 M in toluene, 1.2 equiv) and, 30 min later, with the Davis oxaziridine (52 mg, 0.20 mmol) dissolved in 1 mL of dry THF. The reaction mixture was stirred at −78 °C for 1 h, quenched with saturated NH_4Cl solution, and extracted with 1:3 ethyl acetate/hexanes. The combined extracts were dried and concentrated to leave a residue which was subjected to chromatography on silica gel (elution with 1:3 ethyl acetate/hexanes). There was obtained 50 mg (70%) of **24**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.07−8.03 (m, 2H), 7.58−7.53 (m, 1 H), 7.44−7.39 (m, 2 H), 6.10 (d, J = 7.1 Hz, 1 H), 5.16 (br s, 1 H), 4.88 (br s, 1 H), 4.49 (d, J = 7.1 Hz, 1 H), 4.41 (d, J = 7.1 Hz, 1 H), 4.28−4.25 (m, 2 H), 4.22 (br s, 1 H), 4.06 (d, J = 9.8 Hz, 1 H), 3.27 (s, 3 H), 2.58 (s, 1 H), 2.43 (br t, J = 5.3 Hz, 1 H), 2.13−2.06 (m, 1 H), 1.83−1.59 (m, 6 H), 1.49 (s, 3 H), 1.46 (s, 3 H), 1.41 (s, 3 H), 1.35 (s, 3 H), 0.90 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 206.3, 165.9, 147.6, 133.3, 130.2, 129.1, 128.2, 112.0, 104.9, 93.3, 82.9, 81.6, 78.9, 75.8, 72.5, 55.0, 50.4, 47.8, 39.2, 39.1, 36.7, 34.2, 28.6, 27.3, 26.7, 26.4, 25.3, 19.9, 17.3; MS *m*/*z* (M^+) calcd 540.2723, obsd 540.2712.

(3*S*,4a*R*,6*R*,9*S*,10*R*,11*R*,12*R*,12a*R*)-Dodecahydro-9-hydroxy-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-12a,13,13-trimethyl-4-methylene-6,10-methanobenzocyclodecen-8(2*H*)-one (25). A vigorously stirred solution of **24** (50 mg, 0.092 mmol) in a cold (−78 °C) mixture of THF (4 mL) and methanol (2 mL) was treated dropwise with a solution of samarium iodide (0.1 M in THF) until the reaction mixture was no longer UV-active, quenched with saturated NH_4Cl solution, and extracted with 1:3 ethyl acetate/hexanes. The combined extracts were dried and evaporated prior to chromatographic purification of the residue on silica gel. There was isolated 34 mg (87%) of **25**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.14 (d, J = 1.3 Hz, 1 H), 4.90 (d, J = 1.3 Hz, 1 H), 4.46 (d, J = 6.5 Hz, 1 H), 4.28 (d, J = 6.5 Hz, 1 H), 4.23−4.16 (m, 4 H), 3.27 (s, 3 H), 2.81 (dd, J = 9.7, 19.8 Hz, 1 H), 2.42 (dd, J = 1.1, 3.5 Hz, 1 H), 2.31 (br s, 1 H), 2.07−2.03 (m, 1 H), 1.91−1.59 (m, 8 H), 1.40 (s, 3 H), 1.36 (s, 3 H), 1.34 (s, 3 H), 0.92 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 214.8, 148.6, 112.0, 104.8, 92.7, 83.5, 81.4, 77.6, 76.8, 55.2, 53.7, 42.5, 39.0, 38.6, 38.4, 37.0, 33.7, 28.3, 27.2, 26.7, 25.4, 24.9, 24.8, 17.6; MS *m*/*z* (M^+) calcd 422.2669, obsd 422.2654.

(3*S*,4a*R*,6*R*,10*S*,11*R*,12*R*,12a*R*)-2,3,4,4a,5,6,10,11,12,12a-Decahydro-8-hydroxy-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-12a,13,13-trimethyl-4-methylene-6,10-methanobenzocyclodecen-9(1*H*)-one (26a). A solution of **25** (30 mg, 0.071 mol) in CH_2Cl_2 (3 mL) was treated with the Dess−Martin periodinane (1.5 equiv), stirred for 1 h, and quenched with saturated $NaHCO_3$ solution. The product was extracted into 1:2 ethyl acetate/hexanes, dried, concentrated, and chromatographed on silica gel (elution with 1:4 ethyl acetate/hexanes) to give 24 mg (80%) of **26a**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.94 (s, 1 H), 5.74 (d, J = 6.9 Hz, 1 H), 5.10 (br s, 1 H), 4.88 (br s, 1 H), 4.43 (d, J = 6.9 Hz, 1 H), 4.24 (d, J = 6.9 Hz, 1 H), 4.24 (d, J = 9.7 Hz, 1 H), 4.13 (br s, 1 H), 4.08 (dd, J = 1.0, 9.7 Hz, 1H), 3.30 (s, 3 H), 2.86 (s, 1 H), 2.46 (dt, J = 1.6, 6.9 Hz, 1 H), 2.10 (br s, 1 H), 1.94−1.86 (m, 1 H), 1.80−1.44 (m, 5 H), 1.42 (s, 3 H), 1.40 (s, 3 H), 1.35 (s, 3 H), 1.16 (s, 3 H), 0.93 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 197.2, 148.3, 147.5, 117.5, 112.7, 105.4, 92.2, 82.8, 77.7, 75.5, 56.4, 55.1, 44.1, 38.5, 37.71, 37.67, 35.7, 28.3, 27.4, 26.7, 25.2, 24.9, 22.4, 18.0; MS *m*/*z* (M^+) calcd 420.2512, obsd 420.2523.

(3*S*,4a*R*,6*R*,10*S*,11*R*,12*R*,12a*R*)-8-(*tert*-Butyldimethylsiloxy)-2,3,4,4a,5,6,10,11,12,12a-decahydro-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-12a,13,13-trimethyl-4-methylene-6,10-methanobenzocyclodecen-9(1*H*)-one (26b). A mixture of **26a** (24 mg, 0.057 mmol), imidazole (100 mg, 1.47 mmol), and *tert*-butyldimethylsilyl chloride (70 mg, 0.46 mmol) in DMF (1 mL) was stirred overnight at room temperature, quenched with water (5 mL), and extracted with hexanes (10 mL). The organic solution was dried over sodium sulfate and sodium bicarbonate, then concentrated. Purification of the residue by chromatography on silica gel delivered 30 mg (98%) of **26b** as a white solid: IR ($CHCl_3$, cm^{-1}) 1675; ^1H NMR (300 MHz, C_6D_6) δ 5.52 (d, J = 6.9 Hz, 1 H), 5.03 (s, 1 H), 4.73 (d, J = 7.1 Hz, 1 H), 4.71 (s, 1 H), 4.66 (d, J = 7.1 Hz, 1 H), 4.45 (dd, J = 0.7, 9.8 Hz, 1 H), 4.26 (br s, 1 H), 4.24 (d, J = 9.8 Hz, 1 H), 3.31 (s, 3 H), 3.00 (s, 1 H), 2.30 (br s, 1 H), 1.93−1.80 (m, 3 H), 1.66−1.41 (m, 4 H), 1.39 (s, 3 H), 1.29 (s, 3 H), 1.23 (s, 3 H), 0.99 (s, 9 H), 0.98 (s, 6 H), 0.42 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 196.2, 150.1, 148.7, 125.8, 112.2, 105.3, 92.7, 83.2, 78.5, 75.7, 58.2, 55.1, 45.1, 39.0, 38.0, 37.3, 35.9, 28.9, 27.7, 26.8, 25.8, 25.7, 24.7, 22.7, 18.7, 18.4, −3.6, −4.5; MS *m*/*z* (M^+) calcd 534.3377, obsd 534.3356.

(3*S*,4a*S*,6*R*,10*R*,11*E*,12a*S*)-8-(*tert*-Butyldimethylsiloxy)-2,3,4,4a,5,6,10,11,12,12a-octahydro-3-(methoxymethoxy)-10,12a,13,13-tetramethyl-4-methylene-6,10-methanobenzocyclodecen-9(1*H*)-one (27). To a solution of **26b** (8.8 mg, 0.016 mmol) in cold (−78 °C), dry THF (2 mL) was added potassium hexamethyldisilazide (0.15 mL of 0.5 M in toluene, 0.075 mmol). After 30 min, a solution of *N*-phenyltriflimide (30 mg, 0.084 mmol) in dry THF (1 mL) was introduced, and the reaction mixture was allowed to warm to −20 °C over 2 h. A solution of lithium dimethylcuprate was prepared by adding methyllithium−lithium bromide complex (0.25 mL of 1.5 M in ether) to a slurry of copper(I) bromide−dimethyl sulfide complex (45 mg, 0.22 mmol) in dry THF (2 mL) at 0 °C, followed by stirring for 10 min. The original reaction mixture was returned to −78 °C, treated with the cuprate solution, allowed to warm to 0 °C during 1.5 h, diluted with hexanes (20 mL), and filtered through a pad of Florisil. The filtrate was concentrated and the residue was purified by chromatography on silica gel to furnish **27** (7 mg, 89%) as a white solid: IR (neat, cm^{-1}) 1703; ^1H NMR (300 MHz, C_6D_6) δ 6.28 (d, J = 17.8 Hz, 1 H), 5.85 (d, J = 17.8 Hz, 1 H), 5.63 (d, J = 5.7 Hz, 1 H), 4.94 (s, 1 H) 4.67 (d, J = 6.5 Hz, 1 H), 4.60 (t, J = 1.4 Hz, 1 H), 4.54 (d, J = 6.5 Hz, 1 H), 4.10 (t, J = 2.8 Hz, 1 H), 3.26 (s, 3 H), 2.91 (br d, J = 9.0 Hz, 1 H), 2.15 (dt, J = 4.4, 13.5 Hz, 1 H), 1.95−1.90 (m, 1 H), 1.88−1.80 (m, 1 H), 1.68−1.60 (m, 1 H), 1.51−1.47 (m, 2 H), 1.40−1.33 (m, 1 H), 1.24 (s, 3 H), 1.06 (s, 9 H), 0.89 (s, 3 H), 0.82 (s, 3 H), 0.78 (s, 3 H), 0.35 (s, 3 H), 0.29 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 199.7, 151.6, 148.1, 140.0, 135.6, 124.7, 110.6, 93.4, 77.2, 55.2, 53.1, 50.7, 49.4, 45.8, 42.2, 33.1, 29.3, 28.4, 26.8, 26.0, 22.7, 19.5, 18.6, 11.1, −4.1; MS *m*/*z* (M^+) calcd 474.3169, obsd 474.3814.

(3*S*,4a*R*,6*R*,9*S*,10*S*,11*S*,12*R*,12a*R*)-Dodecahydro-9,10-dihydroxy-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-12a,13,13-trimethyl-4-methylene-6,10-methanobenzocyclodecen-8(2*H*)-one (37). A solution of **19** (110.5 mg, 0.273 mmol) in THF (3.0 mL) at −18 °C was treated with pyridine (92.8 μL, 1.148 mmol) and osmium tetraoxide (73.0 mg, 0.287 mmol), stirred for 2 h, quenched with 20% $NaHSO_3$ solution (10 mL), stirred overnight, and extracted with ethyl acetate. Following the predescribed workup, purification by chromatography

on silica gel (elution with 2:1 hexanes/ethyl acetate) furnished 79.1 mg (66%) of **37** as a white solid, mp 139−141 °C: IR (neat, cm^{-1}) 3349, 1713; ^1H NMR (300 MHz, $CDCl_3$) δ 5.13 (s, 1 H), 4.87 (s, 1 H), 4.49 (d, J = 6.5 Hz, 1 H), 4.40 (d, J = 9.4 Hz, 1 H), 4.36 (d, J = 6.5 Hz, 1 H), 4.23 (d, J = 4.8 Hz, 1 H), 4.15 (t, J = 2.3 Hz, 1 H), 4.03 (d, J = 9.4 Hz, 1 H), 4.02 (s, 1 H), 4.00 (s, 1 H), 3.27 (s, 3 H), 2.88 (dd, J = 19.0, 10.1 Hz, 1 H), 2.48 (br d, J = 2.7 Hz, 1 H), 2.15 (m, 1 H), 1.93−1.60 (m, 7 H), 1.42 (s, 3 H), 1.37 (s, 3 H), 1.34 (s, 3 H), 0.95 (s, 3 H), 0.92 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 210.6, 148.6, 112.0, 105.8, 92.7, 82.7, 81.9, 79.1, 77.9, 76.5, 55.2, 43.1, 42.7, 39.1, 39.0, 38.7, 30.7, 28.2, 27.0, 26.7, 25.4, 25.2, 22.5, 17.7; MS m/z (M^+) calcd 438.2617, obsd 438.2613; $[\alpha]^{24}_D$ −52.8 (c 1.0, $CHCl_3$).

Anal. Calcd for $C_{24}H_{38}O_7$: C, 65.71; H, 8.74. Found: C, 65.61; H, 8.68.

(3*S*,4a*R*,6*R*,9*S*,10*R*,11*S*,12*R*,12a*R*)-Dodecahydro-11,12-(isopropylidenedioxy)-9,10-[(*R*)−(*p*-methoxybenzylidene)dioxy]-3-(methoxymethoxy)-12a,13,13-trimethyl-4-methylene-6,10-methanobenzocyclodecen-8(2*H*)-one (38). A solution of **37** (24.3 mg, 0.055 mmol) in DMF (1.0 mL) containing camphorsulfonic acid (3.0 mg) and *p*-methoxybenzylidene dimethyl acetal (50.0 mg, 0.275 mmol) was heated at 50−55 °C for 6 h, cooled to room temperature, quenched with saturated $NaHCO_3$ solution (5 mL), and stirred overnight. The product was extracted into ethyl acetate, the combined organic phases were washed with brine, dried, and concentrated, and the residue was purified by chromatography on silica gel (elution with 5:1 hexanes/ethyl acetate) to afford **38** as a colorless crystalline solid (30.5 mg, 100%), mp 111−112 °C: IR (neat, cm^{-1}) 1709, 1613; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.37 (m, 2 H), 6.87−6.82 (m, 2 H), 5.93 (s, 1 H), 5.15 (s, 1H), 4.90 (s, 1 H), 4.66 (s, 1 H), 4.47 (d, J = 6.6 Hz, 1 H), 4.42 (d, J = 9.3 Hz, 1 H), 4.36 (d, J = 9.3 Hz, 1 H), 4.32 (d, J = 6.6 Hz, 1 H), 4.19 (s, 1 H), 3.79 (s, 3 H), 3.27 (s, 3 H), 2.87 (dd, J = 20.0, 9.5 Hz, 1 H), 2.23 (m, 2 H), 1.96−1.68 (m, 7 H), 1.48 (s, 3 H), 1.46 (s, 3 H), 1.40 (s, 3 H), 1.07 (s, 3 H), 0.94 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 207.7, 160.8, 147.9, 129.2 (2 C), 127.7, 113.6 (2 C), 112.0, 105.3, 102.5, 92.6, 87.0, 84.6, 83.2, 79.3, 76.1, 55.3, 55.2, 44.3, 42.0, 39.7, 39.5, 38.4, 30.5, 28.3, 27.1, 26.6, 25.5, 24.8, 22.9, 17.5; MS m/z (M^+) calcd 556.3036, obsd 556.3006; $[\alpha]^{24}_D$ −45.7 (c 1.0, $CHCl_3$).

(3*S*,4a*R*,6*R*,8*R*,9*R*,10*S*,11*S*,12*R*,12a*R*)-Tetradecahydro-11,12-(isopropylidenedioxy)-9,10-[(*R*)-(*p*-methoxybenzylidene)dioxy]-3-(methoxymethoxy)-12a,13,13-trimethyl-4-methylene-6,10-methanobenzocyclodecen-8-ol (39a). Lithium aluminum hydride (83 μL of 1.0 M in THF, 0.083 mmol) was added to a solution of **38** (30.5 mg, 0.055 mmol) in dry ether (5.0 mL) at 0 °C. The reaction mixture was quenched with saturated Na_2SO_4 solution, stirred for an additional hour, filtered through a cake of Celite, and eluted with ether. The combined organic filtrates were evaporated to afford pure **39a** as a colorless oil (28.5 mg, 93%): IR (neat, cm^{-1}) 3516; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48−7.43 (m, 2 H), 6.90−6.86 (m, 2 H), 5.95 (s, 1 H), 5.12 (s, 1 H), 4.89 (s, 1 H), 4.50 (d, J = 6.5 Hz, 1 H), 4.47 (d, J = 6.5 Hz, 1 H), 4.41 (d, J = 7.3 Hz, 1 H), 4.34 (d, J = 9.3 Hz, 1 H), 4.29−4.20 (m, 3 H), 3.80 (s, 3 H), 3.33 (s, 3 H), 3.16 (s, 1 H), 2.26−2.17 (m, 1 H), 2.06−1.99 (m, 2 H), 1.87−1.58 (m, 7 H), 1.45 (s, 6 H), 1.43 (s, 3 H), 1.37 (s, 3 H), 0.90 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 160.9, 148.3, 129.1 (2 C), 128.5, 113.8 (2 C), 111.9, 104.9, 101.8, 92.6, 84.3, 82.9, 80.9, 79.4, 76.0, 63.0, 55.2, 55.1, 44.0, 40.6, 39.0, 38.3, 31.9, 30.8, 28.1, 27.0, 26.6, 25.8, 25.4, 24.6, 17.7; MS m/z (M^+) calcd 558.3193, obsd 558.3183; $[\alpha]^{24}_D$ −48.4 (c 6.9, $CHCl_3$).

Trimethyl-[2-[[[(3*S*,4a*R*,6*R*,8*R*,9*R*,10*S*,11*S*,12*R*,12a*R*)-tetradecahydro-11,12-(isopropylidenedioxy)-9,10-[(*R*)−(*p*-methoxybenzylidene)-dioxy]-3-(methoxymethoxy)-12a,13,13-trimethyl-4-methylene-6,10-methanobenzocyclodecen-8-yl]oxy]methoxy]ethyl]silane (39b). A solution of **39a** (28.5 mg, 0.051 mmol) in CH_2Cl_2 (1.0 mL) was treated with diisopropylethylamine (177 μL, 1.017 mmol) and SEM chloride (135 μL, 0.765 mmol), stirred for 16 h, quenched with saturated $NaHCO_3$ solution, and extracted with ethyl acetate. The combined organic phases were washed with brine, dried, and concentrated. The residue was chromatographed on silica gel (elution with 10:1 hexanes/ethyl acetate) to give **39b** as a colorless oil (29.6 mg, 87%): IR (neat, cm^{-1}) 1248, 1093, 1033; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52−7.47 (m, 2 H), 6.87−6.82 (m, 2 H), 5.89 (s, 1 H), 5.13 (s, 1 H), 4.91 (s, 1 H), 4.76−4.58 (m, 4 H), 4.42 (d, J = 7.8 Hz, 1 H), 4.37−4.30 (m, 2 H), 4.21−4.18 (m, 2 H), 3.79 (s, 3 H), 3.63 (td, J = 10.0, 6.5 Hz, 1 H), 3.45 (td, J = 10.0, 6.5 Hz, 1 H), 3.36 (s, 3 H), 2.21−2.14 (m, 1 H), 2.08 (br s, 1 H), 1.99−1.93 (m, 1 H), 1.89−1.60 (m, 7 H), 1.43 (s, 3 H), 1.42 (s, 3 H), 1.38 (s, 3 H), 1.35 (s, 3 H), 0.89 (s, 3 H) 0.92−0.78 (m, 2 H), −0.04 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 160.6, 148.4, 129.5 (2 C), 129.4, 113.4 (2 C), 111.9, 104.8, 101.8, 95.3, 92.7, 84.4, 83.0, 81.5, 79.9, 76.0, 68.9, 64.9, 55.2, 55.1, 44.0, 40.3, 39.3, 38.3, 32.2, 30.7, 28.2, 27.1, 26.6, 25.7, 25.5, 24.4, 18.0, 17.6, −1.5 (3 C); MS m/z (M^+) calcd 688.4006, obsd 688.4032; $[\alpha]^{25}_D$ +28.1 (c 2.7, $CHCl_3$).

Anal. Calcd for $C_{38}H_{60}O_9Si$: C, 66.24; H, 8.78. Found: C, 66.19; H, 8.86.

(3*S*,4a*R*,6*R*,8*R*,9*R*,10*S*,11*S*,12*R*,12a*R*)-Dodecahydro-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-12a,13,13-trimethyl-4-methylene-8-[[2-(trimethylsilyl)ethoxy]methoxy]-6,10-methanobenzocyclodecene-9,10(2*H*)-diol (40). A solution of **39b** (13.1 mg, 0.019 mmol), pyridinium *p*-toluenesulfonate (44 mg, 0.175 mmol), and DDQ (39.3 mg, 0.173 mmol) in methanol (2.0 mL) was stirred for 12 h, quenched with saturated $NaHCO_3$ solution (3 mL), evaporated to remove methanol, and extracted with brine, dried, and concentrated. The residue was chromatographed on silica gel (elution with 5:1 hexanes/ethyl acetate) to afford **40** as a colorless oil (9.9 mg, 91%): IR (neat, cm^{-1}) 3467 (br); ^1H NMR (300 MHz, $CDCl_3$) δ 5.13 (s, 1 H), 4.85 (s, 1 H), 4.79 (d, J = 8.0 Hz, 1 H), 4.77 (s, 2 H), 4.60 (s, 2 H), 4.20 (m, 2 H), 3.83 (d, J = 5.0 Hz, 1 H), 3.81 (d, J = 8.0 Hz, 1 H), 3.70 (s, 1 H), 3.73−3.59 (m, 2 H), 3.35 (s, 3 H), 2.91 (br s, 1 H), 2.50 (d, J = 8.2 Hz, 1 H), 2.19 (m, 1 H), 1.99 (t, J = 8.2 Hz, 1 H), 1.90−1.51 (m, 7 H), 1.46 (s, 3 H), 1.43 (s, 3 H), 1.41 (s, 3 H), 1.32 (s, 3 H), 0.91 (s, 3 H), 0.96−0.88 (m, 2 H), 0.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 150.3, 112.3, 109.6, 94.6, 92.7, 81.9, 80.5, 77.4, 76.2, 74.6, 74.5, 65.5, 55.1, 43.1, 41.3, 40.0, 39.1, 32.5, 29.2, 28.2, 27.8, 26.9, 26.6, 25.0, 24.4, 18.1, 17.4, −1.4 (3 C); MS m/z (M^+) calcd 570.3588, obsd 570.3571; $[\alpha]^{25}_D$ −71.4 (c 1.75, $CHCl_3$).

(3*S*,4a*R*,6*R*,8*R*,10*R*,11*S*,12*R*,12a*R*)-Dodecahydro-10-hydroxy-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-12a,13,13-trimethyl-4-methylene-8-[[2-(trimethylsilyl)ethoxy]methoxy]-6,10-methanobenzocyclodecen-9(1*H*)-one (41). Tetrapropylammonium perruthenate (1.8 mg, 0.005 mmol), *N*-methylmorpholine *N*-oxide (7.4 mg, 0.063 mmol), and 4 Å molecular sieves (7.4 mg) were added to a solution of **40** (12.0 mg, 0.021 mmol) in CH_2Cl_2 (1.0 mL); the reaction mixture was stirred for 5 h before being diluted with hexanes (1.0 mL), filtered through a pad of silica gel, and eluted with 5:1 hexanes/ethyl acetate. The combined organic filtrates were evaporated to give **41** as a colorless oil (11.0 mg, 92%): IR (neat, cm^{-1}) 3535, 1732; ^1H NMR (300 MHz, $CDCl_3$) δ 5.18 (s, 1 H), 4.89 (s, 1 H), 4.83 (d, J = 7.2 Hz, 1 H), 4.79 (d, J = 7.2 Hz, 1 H), 4.65 (m, 4 H), 4.24 (t, J = 2.8 Hz, 1 H), 4.05 (d, J = 7.1 Hz, 1 H), 3.72 (s, 1 H), 3.72−3.59 (m, 2 H), 3.35 (s, 3 H), 2.53 (d, J = 6.8 Hz, 1 H), 2.30−2.19 (m, 1 H), 2.10−1.42 (m, 8 H), 1.39 (s, 3 H), 1.36 (s, 3 H), 1.25 (s, 3 H), 1.03 (s, 3 H), 0.96 (s, 3 H), 0.97−0.82 (m, 2 H), 0.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 209.6, 149.8, 112.2, 111.3, 94.9, 92.5, 82.4, 79.9, 77.6, 76.1, 75.4, 65.6, 55.1, 43.2, 42.0, 41.1, 39.1, 33.7, 30.7, 28.3, 27.0, 26.5, 26.4, 24.8, 22.6, 18.0, 17.4, −1.5 (3 C); MS m/z (M^+-CH_3) calcd 553.3256, obsd 553.3226; $[\alpha]^{25}_D$ −39.7 (c 0.78, $CHCl_3$).

(3*S*,4a*R*,6*R*,8*R*,9*R*,10*R*,11*S*,12*R*,12a*R*)-Dodecahydro-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-9,12a,13,13-tetramethyl-4-methylene-8-[[2-(trimethylsilyl)ethoxy]methoxy]-6,10-methanobenzocyclodecene-9,10(2*H*)-diol (42). A slurry of dried cerium(III) chloride (1.18 mmol) in anhydrous THF (3.0 mL) at −78 °C was treated with methyllithium (759 μL of 1.4 M in ether, 1.06 mmol) and stirred for 2 h. A solution of **41** (51.3 mg, 0.09 mmol) in THF (1.0 mL) was introduced, followed 30 min later with water (5 mL). The product was extracted into ethyl acetate and the combined organic phases were dried and concentrated to leave a residue, purification of which by chromatography on silica gel (elution with 4:1 hexanes/ethyl acetate) afforded recovered **41** (8.1 mg, 16%) and **42** (44.0 mg, 83%), the latter as a white solid, mp 116−117 °C: IR (neat, cm^{-1}) 3474; ^1H NMR (300 MHz, C_6D_6) δ 5.03 (s, 1 H), 4.95 (d, J = 8.0 Hz, 1 H), 4.90 (d, J = 6.8 Hz, 1 H), 4.84 (d, J = 6.8 Hz, 1 H), 4.74 (d, J = 7.2 Hz, 1 H), 4.70 (s, 1 H), 4.66 (d, J = 7.2 Hz, 1 H), 4.27 (t, J = 2.9 Hz, 1 H), 4.17 (d, J = 8.0 Hz, 1 H), 4.11 (dd, J = 11.9, 6.5 Hz, 1 H), 3.86 (s, 1 H),

3.75−3.60 (m, 2 H), 3.35 (s, 3 H), 2.68 (dd, J = 7.5, 0.4 Hz, 1 H), 2.45−2.36 (m, 2 H), 1.93−1.79 (m, 3 H), 1.82 (s, 3 H), 1.72−1.53 (m, 5 H), 1.49 (s, 3 H), 1.40 (s, 3 H), 1.30 (s, 3 H), 1.26 (s, 3 H), 0.95−0.88 (m, 2 H), 0.93 (s, 3 H), −0.07 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 150.9, 111.8, 109.2, 94.7, 93.2, 82.8, 79.5, 79.3, 79.2, 77.3, 76.2, 65.4, 55.0, 43.3, 42.1, 41.7, 39.4, 34.9, 30.5, 28.5, 21.8, 27.1, 26.7, 26.2, 25.4, 23.4, 18.2, 17.7, −1.5 (3 C); MS m/z (M^+ − H) calcd 583.3634, obsd 583.3650; $[\alpha]^{24}_D$ −78.3 (c 0.59, $CHCl_3$).

(3*S*,4a*R*,6*R*,9*S*,10*R*,11*S*,12*R*,12a*R*)-Dodecahydro-9,10-dihydroxy-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-9,12a,13,13-tetramethyl-4-methylene-6,10-methanobenzocyclodecen-8(2*H*)-one (43). A solution of **42** (60.5 mg, 0.104 mmol) in THF (3.0 mL) containing tetra-*n*-butylammonium fluoride (2.0 mL of 1.0 M in THF, 2.0 mmol) was refluxed for 3 days, cooled, quenched with water (5 mL), and extracted with brine, dried, and concentrated. Purification of the residue by chromatography on silica gel (elution with 2:1 hexanes/ethyl acetate) furnished the alcohol (44.5 mg, 86%) as a white solid, mp 144−146 °C: IR (neat, cm^{-1}) 3470; ^{1}H NMR (300 MHz, C_6D_6) δ 4.99 (s, 1 H), 4.98 (d, J = 8.1 Hz, 1 H), 4.75 (d, J = 6.6 Hz, 1 H), 4.67 (s, 1 H), 4.63 (d, J = 6.6 Hz, 1 H), 4.22 (m, 1 H), 4.19 (t, J = 2.8 Hz, 1 H), 4.13 (d, J = 8.1 Hz, 1 H), 3.94 (s, 1 H), 3.18 (s, 3 H), 2.65 (br d, J = 6.1 Hz, 1 H), 2.41−2.32 (m, 1 H), 2.11−1.99 (m, 1 H), 1.91−1.79 (m, 2 H), 1.72−1.19 (series of m, 5 H), 1.60 (s, 3 H), 1.42 (s, 3 H), 1.33 (s, 3 H), 1.26 (s, 3 H), 1.21 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 150.6, 111.8, 109.2, 92.9, 83.1, 79.6, 79.0, 77.3, 76.5, 72.1, 55.1, 43.2, 41.9, 41.7, 38.7, 34.2, 34.0, 28.8, 27.2, 27.0, 26.7, 25.9, 25.1, 22.7, 17.5; MS m/z (M^+) calcd 454.2930, obsd 454.2915; $[\alpha]^{24}_D$ −73.1 (c 0.80, $CHCl_3$).

A solution of this alcohol (4.5 mg, 0.01 mmol) in CH_2Cl_2 (1.0 mL) was treated with 4 Å molecular sieves (3.5 mg), *N*-methylmorpholine *N*-oxide (3.5 mg, 0.03 mmol), and tetrapropylammonium perruthenate (1.0 mg, 0.003 mmol) at 0 °C and allowed to warm slowly to 15 °C during overnight stirring. The mixture was filtered through a pad of silica gel, eluted with 2:1 hexanes/ethyl acetate, and evaporated. Chromatography of the residue on silica gel (elution with 4:1 hexanes/ethyl acetate) gave **43** as a colorless oil (3.0 mg, 67%): IR (neat, cm^{-1}) 1715; ^{1}H NMR (300 MHz, C_6D_6) δ 5.07 (d, J = 7.2 Hz, 1 H), 5.04 (s, 1 H), 4.88 (d, J = 7.2 Hz, 1 H), 4.75 (d, J = 8.2 Hz, H), 4.66 (s, 1 H), 4.28 (t, J = 2.7 Hz, 1 H), 3.97 (d, J = 8.2 Hz, 1 H), 3.96 (s, 1 H), 3.28 (s, 3 H), 3.12 (dd, J = 16.2, 9.0 Hz, 1 H), 2.71 (s, 1 H), 2.14 (br d, J = 4.9 Hz, 1 H), 1.93−1.38 (series of m, 8 H), 1.65 (s, 3 H), 1.50 (s, 3 H), 1.31 (s, 3 H), 1.20 (s, 3 H), 1.16 (s, 3 H), 0.87 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 208.2, 149.6, 112.5, 109.1, 93.2, 83.0, 82.9, 78.5 (2 C), 75.3, 55.0, 43.0, 42.5, 41.3, 40.2, 37.7, 33.9, 28.8, 26.9 (2 C), 26.7, 25.6, 24.8, 20.7, 17.8; MS m/z (M^+) calcd 452.2774, obsd 452.2773; $[\alpha]^{24}_D$ −121.7 (c 0.23, $CHCl_3$).

(3*S*,4a*R*,6*R*,9*Z*,11*R*,12*R*,12a*R*)-1,3,4,4a,5,6,7,11,12,12a-Decahydro-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-9,12a,13,13-tetramethyl-4-methylene-6,10-methanobenzocyclodecen-8(2*H*)-one (8). To a solution of **43** (10.2 mg, 0.023 mmol) in 2.0 mL of THF/methanol (1:1) at −78 °C was added samarium(II) iodide (2.4 mL of 0.085 M in THF, 0.203 mmol) until the mixture became green in color. After being warmed to room temperature and stirred for an additional 2 h, the mixture was quenched with saturated $NaHCO_3$ solution (2 mL) and extracted with ethyl acetate. The combined organic phases were washed with brine, dried, and concentrated to leave a residue, purification of which by chromatography on silica (elution with 6:1 hexanes/ethyl acetate) afforded the β-hydroxy ketone (7.1 mg, 72%) as a white solid, mp 112−113 °C: IR (neat, cm^{-1}) 3494, 1700; ^{1}H NMR (300 MHz, C_6D_6) δ 5.10 (d, J = 7.2 Hz, 1 H), 5.05 (s, 1 H), 4.89 (d, J = 7.2 Hz, 1 H), 4.69 (d, J = 8.1 Hz, 1H), 4.67 (s, 1 H), 4.29 (t, J = 2.8 Hz, 1 H), 4.08 (s, 1 H), 3.90 (d, J = 8.3 Hz, 1 H), 3.29 (s, 3 H), 2.81 (q, J = 6.4 Hz, 1 H), 2.34 (dd, J = 16.4, 9.3 Hz, 1 H), 2.18 (dd, J = 6.6, 1.4 Hz, 1 H), 1.92−1.79 (m, 3 H), 1.66 (t, J = 8.5 Hz, 1 H), 1.64−1.36 (m, 4 H), 1.35 (s, 3 H), 1.32 (s, 3 H), 1.30 (d, J = 6.4 Hz, 3 H), 1.24 (s, 3 H), 1.20 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 209.5, 150.1, 112.3, 109.7, 93.1, 83.2, 78.6, 76.9, 75.5, 55.6, 55.0, 43.1, 42.8, 42.6, 41.4, 37.3, 32.0, 28.9, 27.0, 26.6, 26.5, 24.7, 23.8, 18.0, 7.9; MS m/z (M^+) calcd 436.2825, obsd 436.2819; $[\alpha]^{24}_D$ −107.4 (c 0.47, $CHCl_3$).

The above material (9.4 mg, 0.021 mmol) was dissolved in pyridine (0.5 mL), cooled to 0 °C, and treated with 4-(dimethylamino)pyridine (2.6 mg, 0.021 mmol) and thionyl chloride (45.7 μL, 0.65 mmol). The reaction mixture was stirred at room temperature for 16 h, quenched with cold water (2 mL), and extracted with ethyl acetate. The combined organic phases were washed with brine, dried, and concentrated. Purification of the residue was accomplished by chromatography on silica gel (elution with 5:1 hexanes/ethyl acetate) to give **8** (5.8 mg, 64%) as a white solid, mp 157−158 °C: IR (neat, cm^{-1}) 1670; ^{1}H NMR (300 MHz, C_6D_6) δ 5.01 (d, J = 9.2 Hz, 1 H), 4.89 (s, 1 H), 4.58 (s, 1 H), 4.50 (d, J = 6.6 Hz, 1 H), 4.35 (d, J = 6.6 Hz, 1 H), 4.28 (d, J = 9.2 Hz, 1 H), 4.09 (t, J = 2.8 Hz, 1 H), 3.11 (s, 3 H), 2.97 (m, 1 H), 2.77 (dd, J = 19.3, 7.3 Hz, 1 H), 2.16 (s, 3 H), 1.95−1.64 (m, 5 H), 1.58−1.24 (m, 3 H), 1.46 (s, 3 H), 1.45 (s, 3 H), 1.41 (s, 3 H), 1.06 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 198.8, 152.9, 150.4, 138.8, 111.6, 107.7, 92.5, 83.1, 76.6, 76.3, 54.9, 41.7, 40.3, 40.20, 40.17, 37.3, 35.4, 28.8, 27.4, 27.0, 26.7, 26.4, 24.5, 17.6, 14.1; MS m/z (M^+) calcd 418.2719, obsd 418.2721; $[\alpha]^{24}_D$ +122.4 (c 0.17, $CHCl_3$).

(3*S*,4a*R*,6*R*,8*S*,9*Z*,11*R*,12*R*,12a*R*)-1,2,3,4,4a,5,6,7,8,11,12,12a-Dodecahydro-11,12-(isopropylidenedioxy)-3-(methoxymethoxy)-9,12a,13,13-tetramethyl-4-methylene-6,10-methanobenzocyclodecen-8-ol (44). A solution of **8** (3.4 mg, 0.008 mmol) in CH_2Cl_2 (1.0 mL) cooled to −78 °C was treated with Dibal-H (12 μL of 1.0 M in hexanes, 0.012 mmol), stirred for 10 min, quenched with saturated NH_4Cl solution, and extracted with ethyl acetate. The combined organic phases were washed with brine, dried, and concentrated. The residue was subjected to chromatography on silica gel (elution with 4:1 hexanes/ethyl acetate) to furnish pure **44** (2.3 mg, 67%) as a white solid, mp 143−145 °C: IR (neat, cm^{-1}) 3487; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.05 (s, 1 H), 4.87 (d, J = 9.4 Hz, 1 H), 4.75 (s, 1 H), 4.60 (s, 2 H), 4.58−4.35 (m, 1 H), 4.16 (d, J = 9.4 Hz, 1 H), 4.11 (t, J = 2.6 Hz, 1 H), 3.33 (s, 3 H), 2.96 (m, 1 H), 2.85 (ddd, J = 15.4, 10.3, 9.1 Hz, 1 H), 2.68 (d, J = 11.2 Hz, 1 H), 2.05 (d, J = 1.3 Hz, 3 H), 1.90−1.03 (series of m, 8 H), 1.50 (s, 3 H), 1.46 (s, 3 H), 1.42 (s, 3 H), 1.00 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 150.6, 142.7, 135.2, 110.9, 106.7, 94.1, 82.9, 78.9, 75.4, 68.7, 55.4, 40.3, 39.5, 39.0, 36.6, 36.4, 32.7, 27.5, 27.4, 27.3, 27.0, 26.0, 25.2, 17.4, 16.7; MS m/z (M^+) calcd 420.2876, obsd 420.2886; $[\alpha]^{24}_D$ +136.7 (c 0.060, $CHCl_3$).

(+)-Taxusin (1). A magnetically stirred solution of **44** (2.2 mg, 0.005 mmol) in acetonitrile (1.0 mL) was treated with water (50 mL) and lithium tetrafluoroborate (3.1 mg, 0.033 mmol), heated at 45 °C for 2 h, returned to room temperature, and diluted with brine (1 mL). The product was extracted into ethyl acetate, and the combined organic phases were dried and concentrated to leave a residue which was chromatographed on silica gel (elution with 1:2 hexanes/ethyl acetate) to afford the tetraol (0.9 mg, 51%) as a white solid, mp 209−211 °C: IR (neat, cm^{-1}) 3416 (br); ^{1}H NMR (300 MHz, CD_3OD) δ 5.03 (s 1 H), 4.74 (d, J = 9.6 Hz, 1 H), 4.56 (s, 1 H), 4.35 (m, 1 H), 4.21 (t, J = 2.5 Hz, 1 H), 3.95 (d, J = 9.6 Hz, 1 H), 2.77 (m, 1 H), 2.05 (d, J = 1.3 Hz, 3 H), 1.77−1.57 (m, 7 H), 1.47 (s, 3 H), 1.22 (m, 2 H), 1.00 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (75 MHz, CD_3OD) ppm 155.9, 140.5, 139.0, 110.2, 80.1, 75.8, 73.7, 69.6, 45.0, 41.6, 40.2, 37.9, 37.0, 33.3, 31.6, 28.7, 26.9, 26.8, 18.2, 16.9; MS m/z (M^++H) calcd 335.2222, obsd 335.2224; $[\alpha]^{25}_D$ +133.3 (c 0.045, CH_3OH).

A cold (0 °C) solution of the above tetraol (1.4 mg, 0.004 mmol) in CH_2Cl_2 (1.0 mL) was treated with DMAP (1.0 mg, 0.008 mmol), triethylamine (17 μL, 0.125 mmol), and acetic anhydride (7.8 μL, 0.083 mmol), and stirred at room temperature for 20 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution, the product was extracted into ethyl acetate, and the combined organic phases were washed with brine, dried, and concentrated. Purification of the residue by chromatography on silica gel (elution with 2:1 hexanes/ethyl acetate) afforded **1** (1.8 mg, 85%): IR (neat, cm^{-1}) 1738, 1240; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (d, J = 10.7 Hz, 1 H), 5.90−5.84 (br m, 1 H), 5.87 (d, J = 10.7 Hz, 1 H), 5.36 (t, J = 2.4 Hz, 1 H), 5.21 (s, 1 H), 4.85 (s, 1 H), 3.00 (br d, J = 5.5 Hz, 1 H), 2.79 (dt, J = 14.6, 9.9 Hz, 1 H), 2.16 (s, 3 H), 2.11 (d, J = 11.4 Hz, 3 H), 2.07 (s, 3 H), 2.05 (s, 3 H), 2.01 (s, 3 H), 1.87−1.50 (m, 7 H), 1.62 (s, 3 H), 1.11 (s, 3 H), 1.06 (dd, J = 14.8, 7.3 Hz, 1 H), 0.75 (s, 3 H); ^{13}C NMR (75 MHz,

$CDCl_3$) ppm 170.4, 169.94, 169.91, 148.8, 137.0, 134.8, 114.1, 77.2, 76.3, 72.5, 70.7, 42.9, 40.3, 39.3, 38.0, 31.9, 31.1, 28.3, 27.34, 27.31, 27.28, 21.8, 21.5, 21.0, 20.8, 17.7, 14.8; $[\alpha]^{25}_D$ +105.5 (*c* 0.09, $CHCl_3$).

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Supporting Information Available: Experimental details for the preparation of **32**−**36** as well as final calculated atomic coordinates for **A**−**C** in Table 1 (9 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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