Stereocontrolled Oxygenation of Camphor Derivatives as a Prelude to the Complete β-Ring Functionalization of Potential Precursors to Taxol and Structural Analogs Thereof

Steven W. Elmore[1] and Leo A. Paquette*

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

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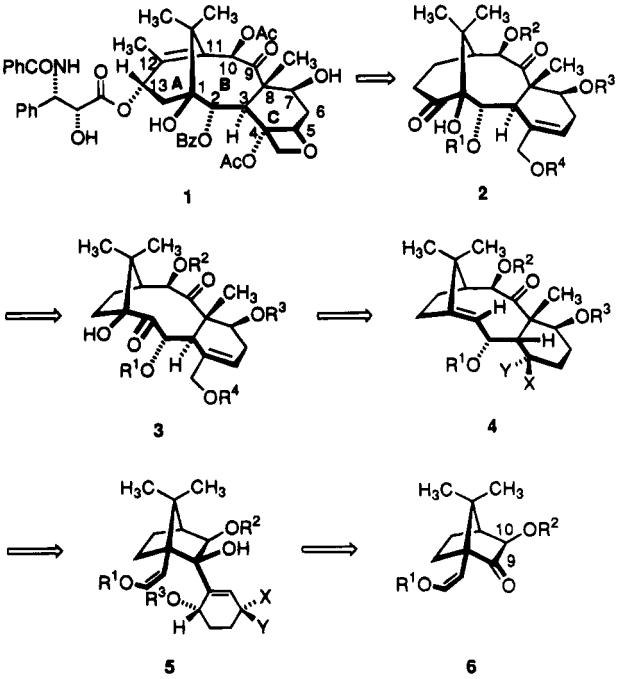
The possibility of realizing the predominant exo α-hydroxylation of camphor-related ketones is described. Both the direct oxidation of enolate anions with 1-phenyl-*N*-(phenylsulfonyl)oxaziridine or exposure of the derived silyl enol ethers to dimethyl dioxirane are conducive to exo attack. Following conversion to MOM derivatives, the acidity of the α-carbonyl proton is reduced sufficiently to allow *direct* condensation of these hindered ketones with cyclohexenyllithium reagents. The subsequent anionic oxy-Cope rearrangement of the resulting exo carbinols results in direct conversion to tricyclic products that feature the characteristic C-2,C-9,C-10 B-ring oxygenation pattern resident in taxol. Further, the stereogenic centers are introduced in their proper absolute configuration. The steric demands of the [3,3] sigmatropic shift are discussed and the stereochemical features conducive to the minimization of steric compression subjected to experimental verification.

Taxol (**1**), a structurally remarkable diterpenoid produced by the Pacific yew *Taxus brevifolia*,[2a] has developed into an antitumor agent indispensable to the regime provided to patients beset with refractory ovarian cancer.[2b] Our involvement with a projected synthesis[3] of this exciting cytotoxic agent has relied on the utilization of *D*-(+)-camphor for construction of the entire western and central sectors of **1**.[4a] The generic approach, outlined in Scheme 1, has been developed with a view to arriving rapidly at the requisite carbocyclic framework in its proper absolute configuration by tandem application of anionic oxy-Cope sigmatropy, *viz.* **5** → **4**,[4b] and an α-ketol rearrangement exemplified by the conversion of **3** to **2**.[6] In the developmental phases of our investigation, we have observed that all of the oxy-Cope rearrangements follow the identical "endo-chair" transition state profile[7] to give products having the structural features found in **4**. The complete array of functional groups has not been present, however, and appropriate enhancement of the level of substitution has more recently been undertaken.

Scheme 1



The highly convergent nature of Scheme 1 allows for considerable diversification in the structural features of the key intermediates **2**–**6**. Since the C-9 carbonyl present in taxol originates directly from the keto group of the camphor-derived precursor (the numbering depicted in **6** is designed to reflect this relationship), this structural component requires no further attention. Introduction of an α-oriented C-O bond at C-2 is intimately linked to the geometry of the bridgehead vinyl ether double bond in **6**.[8] Indeed, the stereospecificity of the oxy-Cope rearrangement has been relied upon to translate the olefin geometry at this site with complete configurational fidelity into either α (as shown) or β stereochemistry (from the *E* isomer) in **4**.

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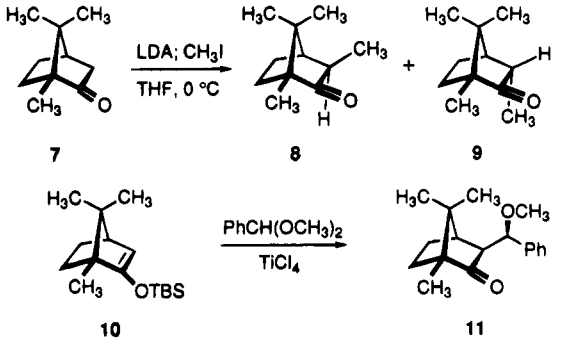
Further, our strategy is based upon the expectation that suitable installation in **6** of an exo OR^2 group α to the ketone carbonyl would provide an expedient means for introducing the β-oriented C-10 substituent in taxol. A number of salient observations have previously been reported concerning the stereoselectivity with which camphor and select derivatives thereof undergo methylation and aldol condensation.[9] The most recent detailed analysis by Money and co-workers concludes that three key factors are involved in directing the exo or endo capture of an electrophile: (a) the presence of endo substituents including hydrogen on the rear ethano bridge directs exo attack; (b) the syn apical methyl group serves to sterically bias the system toward kinetically favored endo approach; (c) prevailing enolate geometry can be influential, particularly if the carbanionic center already carries a substituent. The relative importance of these factors as far as camphor itself is concerned would appear to be in the order given. Thus, sequential treatment of **7** with LDA and CH_3I gives rise to a 4:1 mixture of **8** and **9**.[10] In a related experiment, Mukaiyama reaction of **10** provided the exo product **11**.[11]

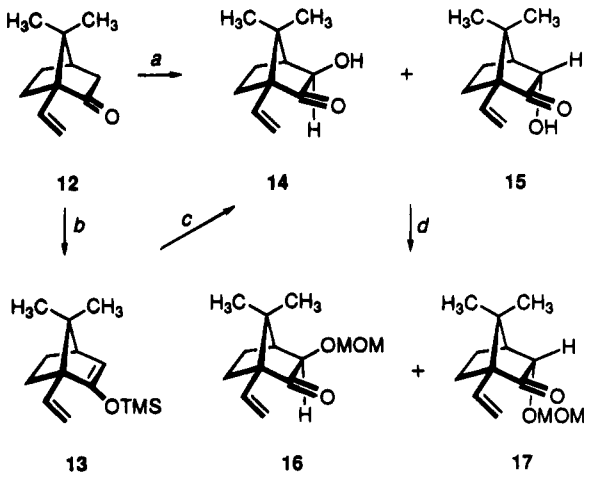


7 8 9 10 11

Results

C-10 Oxygenation. As noted above, delivery of the proper C-10 configuration for taxol requires that the α-hydroxylation occur from the exo surface. In line with precedent, when the enolate anion generated from **12**[12] was exposed to 1-phenyl-*N*-(phenylsulfonyl)oxaziridine[13] at −78 °C, high-field NMR analysis showed that the ratio of exo to endo epimers was 5:1 (Scheme 2). More impressive still was the degree of stereoselectivity achieved by oxidation of the derived silyl enol ether **13**. Treatment of **13** with a solution of dimethyl dioxirane[14] in acetone at −78 °C followed by warming to rt and brief exposure to tetra-*n*-butylammonium fluoride produced predominantly **14** (94:6) with an efficiency of 84%. The vinyl group in **13** proved to be unreactive to the dioxirane even when this oxidant was present in large excess at 20 °C. Protection of the hydroxyl functionality in **15** as the methoxymethyl ether[15] gave the highly exo-enriched coupling partner **16**.

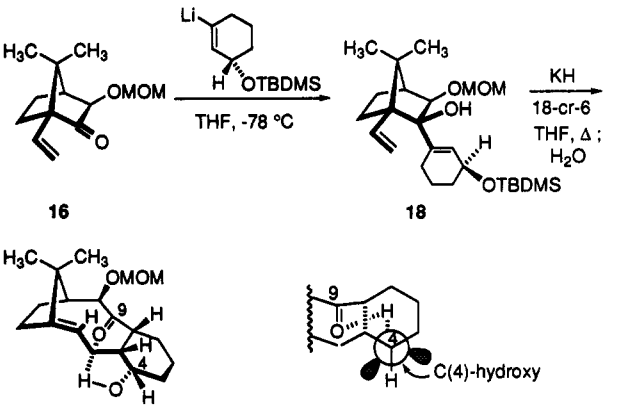
Scheme 2



12 14 15 13 16 17

[a] $KN(SiMe_3)_2$, THF, −78 °C; $PhSO_2N$(oxaziridine) [b] $LiN(i\text{-}Pr)_2$, THF, −78 °C; Me_3SiCl, −78 °C → rt. [c] dimethyldioxirane, acetone, −78 °C → rt; TBAF, THF, rt. [d] MOMCl, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, 0 °C → rt.

Scheme 3



16 18

19

C(4)-H: δ 3.77 (dddd, J = 11.0, 3.1, 3.1, 4.4 Hz)
C(4)-OH: δ 5.42 (d, J = 11.0 Hz)

The alkoxy substituent in **16** and **17** plays an important role in those processes involving anionic addition to their respective carbonyl groups. In the parent ketone **12**, it is necessary to mediate the capture of organolithium nucleophiles with cerium trichloride in order to inhibit competing enolization. The substantial decrease in the acidity of the α proton (relative to **12**) when the OMOM group is present as in **16** accommodates the direct addition of vinyl anions. The added steric blockade present in **17** effectively deters any condensation whatsoever. As a consequence, there exists no practical need to separate this minor constituent of the product mixture. If desired, **17** may be recovered in a pure state after **16** has been consumed in reaction.

On exposure of **16** to 1-lithio-3(*S*)-(*tert*-butyldimethylsiloxy)cyclohexene, the normal endo approach was adopted to produce **18** in excellent yield (Scheme 3). The atropselectivity of the impending anionic oxy-Cope rearrangement involving **18** proved to be a source of interesting speculation. Earlier findings had established that the presence of an α substituent at C-4 was conducive to formation of the "carbonyl-up" conformer under conditions of kinetic control.[5,7] Adoption by the β-OMOM substituent at C-10 of an equatorial disposition can

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(13) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.
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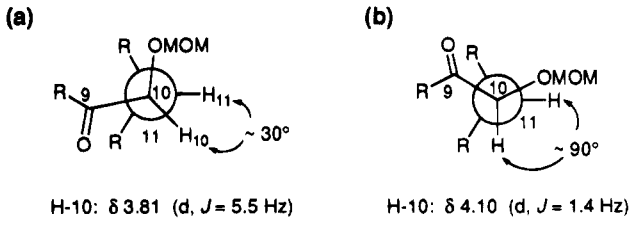


Figure 1. Dihedral angles between the H-10 and H-11 protons in (a) the carbonyl-down conformation of **19** and (b) the carbonyl-up conformation of **20**.

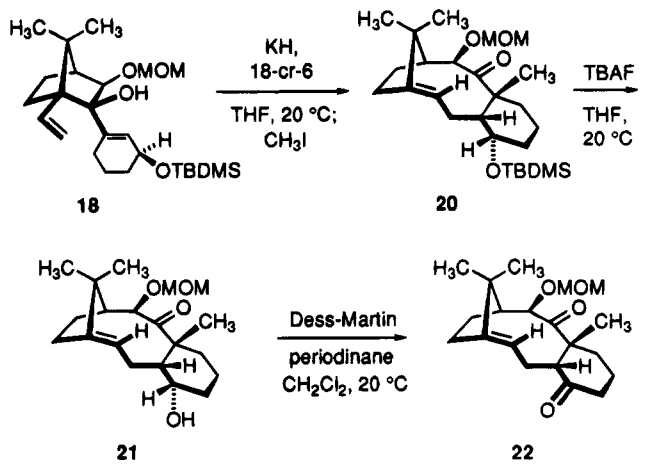
reasonably be expected to reinforce this preference. Following the admixture of **18** with KH and 18-crown-6 in THF solution, no reaction was detected until the reflux temperature was reached. After 3 h of heating, a rearrangement product having a higher polarity than anticipated due to desilylation was formed. NMR analysis involving complete proton decoupling and C/H correlation culminated in the formulation of **19** as shown. This compound is characterized by a transannular hydrogen bond between its carbonyl oxygen and the axially disposed C-4 carbinol. Evidently, cleavage of the *tert*-butyldimethylsilyl protecting group under the basic reaction conditions was followed by thermal atropisomerization to the carbonyl-down conformer in order to take advantage of the resultant close proximity of its two most polar groups. In C_6D_6 solution, the hydroxyl proton appears as a sharp downfield doublet that is strongly coupled to the vicinal C-4 methine proton (see Scheme 3).

A consequence of the B-ring conformation in **19** is the thrusting of the C-10 β-OMOM substituent into a quite crowded pseudoaxial position. Illustrated in Figure 1 is the characteristic dihedral angle between the geminal proton H-10 and the neighboring bridgehead hydrogen H-11 considered responsible for the doublet observed for H-10. The distinctive vicinal coupling displayed in **19** is diagnostic of the carbonyl-down geometry. It is not clear whether this conformation prevails as the energy minimum or as a direct result of the transannular hydrogen bond.

When the rearrangement of **18** was further investigated, sigmatropy was found actually to take place at 20 °C. This rapid conversion to product had earlier gone undiagnosed because the rearranged protonated isomer happens to be indistinguishable from the starting alcohol by TLC analysis. The enolate anion generated under these conditions reacted smoothly with iodomethane at 20 °C to afford **20** (Scheme 4). The chemical shift of H-10 in this ketone is shifted to appreciably lower field than that in **19** (Figure 1). Further, the greatly reduced coupling between H-10 and H-11 suggests the adoption of a dihedral angle approaching 90°. These facts are ideally accommodated by the carbonyl-up conformation. The added torsional barrier to σ-bond rotation introduced by the angular methyl group, coupled with the absence of thermal input during the sigmatropic rearrangement, allows for isolation of the kinetically favored carbonyl-up atropisomer. The greater thermodynamic stability of the carbonyl-down conformation is consistent with the response of other 4α-OR analogs.[5-7]

Deprotection of the silyl ether functionality in **20** could be accomplished by treatment with TBAF at rt. Since heating was not required, alcohol **21** maintains the conformational integrity of its precursor. Oxidation of **21** with the Dess–Martin periodinane reagent[16] proceeded without diffficulty to deliver diketone **22**. Both **21** (δ 4.07, J = 1.3 Hz) and **22** (δ 5.03, J = 1.2 Hz) display a multiplicity pattern for H-10 closely comparable to that seen for **20**.

Scheme 4



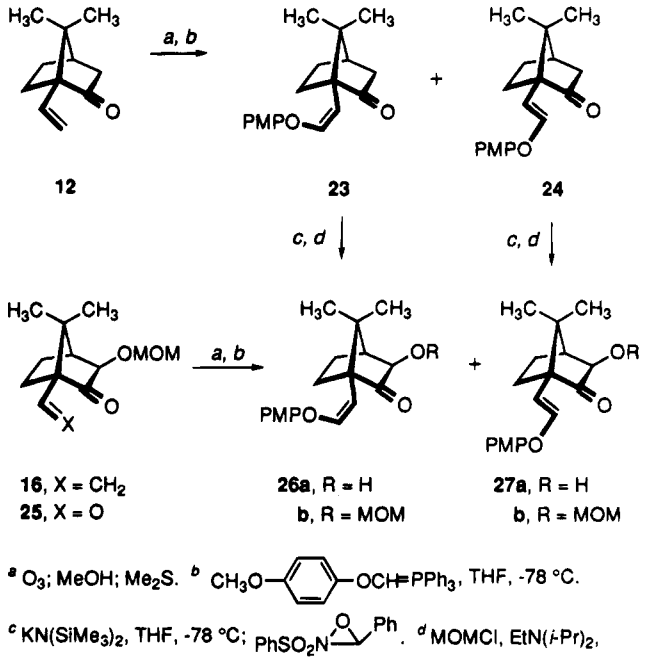
Dual C-2 and C-10 Oxygenation. The feasibility of transforming ketone **12** into the enol ethers **23** and **24** by ozonolysis and chemoselective condensation with an aryloxy Wittig reagent had previously been demonstrated in this laboratory.[8] Should the exo oxygenation of these intermediates prove feasible, it would be of interest to address the attractive question of possible concurrent introduction of the C-2 and C-10 oxygen functionality in taxol. As a direct consequence of the heightened reactivity of the bridgehead double bonds in **23** and **24**, dimethyl dioxirane could not be employed as the oxidant. Alternatively, the enolate of **23** entered into reaction with Davis' sulfonyl oxaziridine to give a 5:1 mixture of the exo and endo epimers of **26a**; similarly, **24**$^-$ afforded a 7:1 mixture of the exo and endo epimers of **27a** (Scheme 5). Despite the ease with which MOM protection could be realized as in **26b** and **27b**, we came to favor the alternative route which involved initial ozonolytic cleavage of the olefinic bond in **16** because higher yields were reproducibly realized. Further, the Wittig olefination of **25** exhibited no cis/trans selectivity, providing a 1:1 mixture of **26b** and **27b**.

The C-10 methoxymethoxy substituent in **18** is not involved directly in the six-membered endo-chair transition state of the anionic oxy-Cope rearrangement and does not affect its outcome. On the other hand, a bridgehead enol ether is intimately involved in the sigmatropic process and impacts on the structural reorganization both electronically and sterically. When the starting configuration is *Z*, the OPMP group adopts a pseudoaxial orientation as the critical geometry is reached and is ultimately incorporated stereoselectively as an α-C-2 substituent in the tricyclic product. For the *E* isomer, the OPMP group is projected pseudoequatorially and eventuates as the β epimer. The consequences of these differences were examined separately.

Ketone **26b** was condensed both with the (*S*)-OMOM-substituted cyclohexenyllithium **28** and with the (*R*)-*p*-methoxybenzyl ether analog **29** (Scheme 6). When carbinol **30** was subjected to a variety of oxy-Cope conditions, thermal input was required to elicit a reaction that was dominated by decomposition. In this particular example, the allylic OMOM and OPMP substituents must

(16) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

Scheme 5



[a] O_3; MeOH; Me_2S. [b] CH_3O—C6H4—$OCH{=}PPh_3$, THF, -78 °C. [c] $KN(SiMe_3)_2$, THF, -78 °C; $PhSO_2N$(O)CHPh. [d] MOMCl, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, 0 °C → rt.

Scheme 6

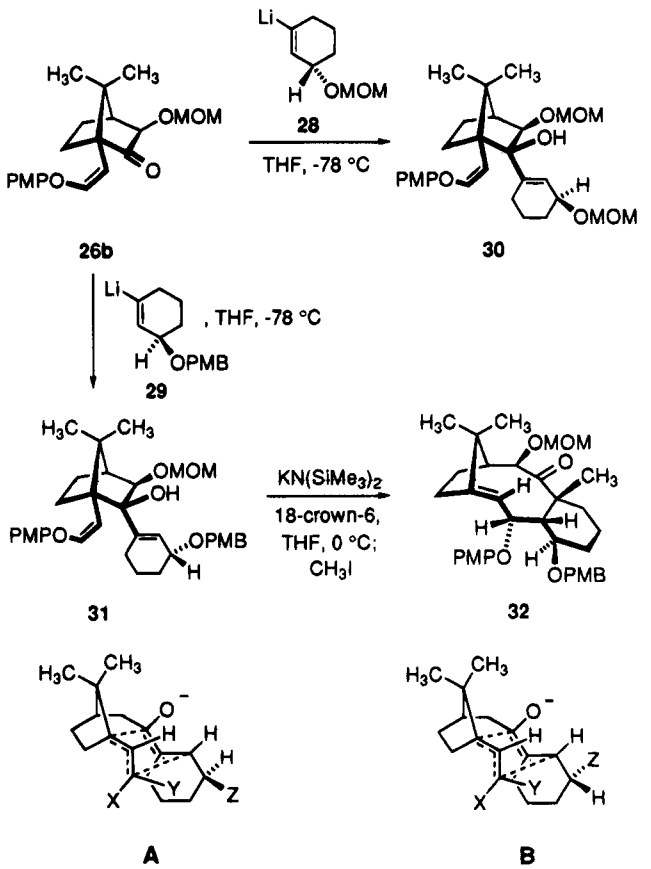
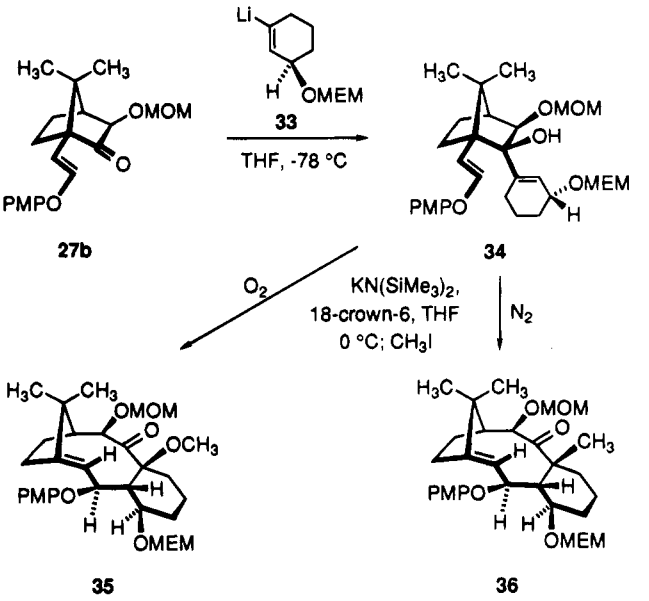


Figure 2. Depiction of endo-chair transition states showing the degree of steric compression as a function of the *S*- (**A**) and *R*-configuration (**B**) in the cyclohexenyl subunit.

necessarily be brought into close proximity in order to effect the electronic reorganization and the steric congestion is significant as seen in structure **A** of Figure 2. The level of steric compression should be further compounded in the *E* enol ether series.

Scheme 7



A simple and effective solution to this problem is to utilize the epimeric C-ring synthon **29**. By positioning *Z* in **B** (Figure 2) distal from X and Y, steric congestion is avoided. Indeed, once the potassium salt of **31** had formed in the presence of 18-crown-6, oxy-Cope rearrangement proceeded well at 0 °C. The ^1H NMR spectrum of **32** (in $CDCl_3$ solution) is characterized by the appearance of H-10 as a broadened singlet at δ 4.29. This data point is consistent with a carbonyl-up conformation of the nine-membered ring that results in the axial orientation of the C-2 OPMP group and equatorial character for the C-10 OMOM substituent. Ketone **32** contains a B-ring that is fully functionalized along the lines of taxol.

The trans enol ether **27b** was subjected to a similar sequence in order to assess its propensity for rearrangement. To better differentiate blocking groups, the (*R*)-methoxyethoxymethyl (OMEM) derivative **33** was used. Alcohol **34** was produced in 84% yield (Scheme 7). The anionically-promoted sigmatropic rearrangement of **34** proceeded under very mild conditions as the reaction mixture was being warmed from −78 °C to 0 °C. The greater ease of structural isomerization in this instance could be the result of orienting the OPMP side chain equatorially in the endo-chair transition state. If the oxy-Cope process was performed in the presence of air, enolate oxidation occurred readily.[17] Ensuing methylation delivered the methoxy product **35** in 69% yield. Proper attention to performing the reaction under a dry N_2 atmosphere furnished **36** instead (82%). The singlet nature of H-10 in **36** (δ 4.19 in $CDCl_3$) is indicative that the carbonyl-up conformation is once again adopted. As a consequence, both ether groups reside equatorially on the B ring.

Summary. The camphor-derived unsaturated ketones **12**, **23**, and **24** have proven amenable to α-oxygenation either by means of Davis' oxaziridine reagent or by use of dimethyl dioxirane to deliver principally the exo α-hydroxy ketone. No need exists to separate the respective minor endo diastereomer at this stage or after MOM protection because each is totally unreactive toward

(17) Paquette, L. A.; DeRussy, D. T.; Pegg, N. A.; Taylor, R. T.; Zydowsky, T. M. *J. Org. Chem.* **1989**, *54*, 4576.

cyclohexenyllithium reagents. In fact, carbinols **18**, **30**, **31**, and **34** are produced efficiently and are easily purified. A useful feature of the reactivity of ketones **16**, **26b**, and **27b** is the drastically reduced acidity of their α proton as a result of the presence of the OMOM substituent. Consequently, recourse need be made no longer to organocerium intermediates. Significantly, the neighboring OMOM group does not inhibit ensuing oxy-Cope rearrangement, thereby allowing the 9-keto-10-β-hydroxy substitution characteristic of taxol to be quickly established. When a bridgehead vinyl ether is also present, steric factors that gain importance in the endo-chair transition state can be best relieved by involving 3(*R*)-substituted cyclohexenyllithiums. In this way, unusually high levels of steric compression in the vicinity of those atoms involved in the [3,3] sigmatropic process are skirted and rapid conversion to tricyclic products carrying the complete array of B ring substituents present in taxol can be realized.

Experimental Section

General Considerations. Melting points are uncorrected. The column chromatographic separations were performed with Woelm silica gel (230–400 mesh) or Florisil (100–200 mesh) as indicated. Solvents were reagent grade and in most cases dried prior to use. The purity of all compounds was shown to be >95% by TLC and high-field ^{1}H (300 MHz) and ^{13}C NMR (75 MHz). The high-resolution and fast-atom-bombardment mass spectra were obtained at The Ohio State University Campus Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

(1*S*,3*R*,4*S*)-3-Hydroxy-7,7-dimethyl-1-vinyl-2-norbornanone (14). A. Oxaziridine Oxidation. A solution of potassium hexamethyldisilazide (79.1 mL of 0.5 M, 39.6 mmol) in THF (100 mL) was cooled to −78 °C under N_2. Into this solution was cannulated 5.00 g (30.4 mmol) of **12** dissolved in 100 mL of THF. The resulting solution was stirred for 15 min at −78 °C and allowed to warm to 0 °C. After 1 h at this temperature, the solution was recooled to −78 °C and a solution of 1-phenyl-*N*-(phenylsulfonyl)oxaziridine (11.93 g, 45.7 mmol) in 50 mL of THF was introduced. After 1 h, the solution was allowed to warm to 0 °C and quenched with saturated NH_4Cl solution. The layers were separated, and the organic phase was washed with water and brine prior to drying. The resulting mixture was separated by column chromatography on silica gel (gradient elution from 20:1 to 5:1 petroleum ether–ethyl acetate) to yield 4.70 g (86%) of an inseparable 5:1 mixture of **14** and **15**.

B. Dimethyl Dioxirane Oxidation. To a flame-dried vessel was added 0.62 mL (4.42 mmol) of freshly distilled diisopropylamine and 5 mL of THF under N_2. The solution was cooled to −78 °C and treated with 2.75 mL of 1.6 M *n*-butyllithium (4.40 mmol). The solution was briefly allowed to warm to 0 °C, recooled to −78 °C, and treated via cannula with a 5 mL THF solution containing 145 mg (0.883 mmol) of **12**. After 1 h, an excess (1.10 mL, 8.83 mmol) of freshly distilled trimethylchlorosilane was added via syringe and the mixture was warmed to rt. Triethylamine (1 mL) was added and the mixture was concentrated in vacuo. The residue was filtered through coarse Florisil (elution with 10:1 petroleum ether–ethyl acetate), and the filtrate was concentrated. The resulting crude silyl enol ether **13** was dissolved in 10 mL of reagent grade acetone under N_2, and the resulting solution was cooled to −78 °C. Dimethyl dioxirane (25 mL of a 0.1 M solution in acetone) was introduced and the solution was warmed to rt. The reaction mixture was concentrated in vacuo to afford silylated and unsilylated products, which were dissolved in 10 mL of THF and treated with 0.5 mL of 1 M (5.0 mmol) TBAF in THF at rt. Desilylation was instantaneous. Layers were formed by dilution with brine and ether, and the separated organic phase was washed with water and brine and then dried. Purification of the residue by column chromatography on silica gel (elution with 5:1 petroleum ether–ethyl acetate) gave 0.133 g (83.6%) of a 94:6 mixture of **14** and **15** as a colorless solid, mp 99–101 °C.

For **14**: IR (CCl_4, cm^{-1}) 3460, 3085, 1751, 1641, 1480, 1470, 1454, 1393, 1373, 1310, 1133, 1110, 1086, 1045, 994, 968, 920; ^{1}H NMR (300 MHz, C_6D_6) δ 5.90 (dd, *J* = 17.7, 11.2 Hz, 1H), 5.25 (dd, *J* = 11.2, 1.7 Hz, 1H), 5.14 (dd *J* = 17.7, 1.7 Hz, 1H), 3.45 (v br s 1H [OH]), 3.55 (s, 1H), 1.91 (d, *J* = 4.7 Hz, 1H), 1.57 (m, 2H), 1.25–1.08 (m, 1H), 1.11 (s, 3H), 0.93 (m, 1H), 0.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 217.5, 132.5, 118.5, 77.8, 63.2, 50.0, 48.6, 25.0 (2xCH_2), 21.6, 20.3; MS *m*/*z* (M^+) calcd 180.1150, obsd 180.1154. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.03; H, 8.94.

(1*S*,3*R*,4*S*)-3-(Methoxymethyl)-7,7-dimethyl-1-vinyl-2-norbornanone (16). A solution of 3.03 g (16.8 mmol) of a 5:1 mixture of **14** and **15** together with 43.6 mL (0.252 mol) of diisopropylethylamine in 100 mL of CH_2Cl_2 was cooled to 0 °C before being treated dropwise with 12.8 mL (0.168 mol) of chloromethyl methyl ether. The reaction mixture was allowed to warm to rt overnight and was diluted with brine. After separation of the layers, the organic phase was washed with water, 5% HCl, water, and brine prior to drying. Purification of the residue by column chromatography on silica gel (gradient elution from 10:1 to 5:1 petroleum ether–ethyl acetate) gave an undetermined amount of starting material along with 2.50 g (66%) of an inseparable 6:1 mixture of **16** and **17** as a colorless oil.

For **16**: IR ($CHCl_3$, cm^{-1}) 1752, 1640, 1468, 1454, 1440, 1392, 1373, 1199, 1284, 1251, 1214, 1151, 1113, 919; ^{1}H NMR (300 MHz, C_6D_6) δ 5.91 (dd, *J* = 11.2, 17.7 Hz, 1H), 5.26 (dd, *J* = 11.2, 1.7 Hz, 1H), 5.16 (dd, *J* = 17.7, 1.7 Hz, 1H), 4.65 (ABq, *J* = 6.5, Δν = 78.7 Hz, 2H), 3.58 (s, 1H), 3.22 (s, 3H), 1.84 (br d, *J* = 4.3 Hz, 1H), 1.60–1.56 (series of m, 2H), 1.27–1.06 (m, 1H), 1.09 (s, 3H), 0.90 (m, 1H), 0.65 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 213.8, 132.7, 118.6, 96.6, 81.0, 63.0, 55.2, 49.0, 48.4, 25.3, 24.9, 21.5, 20.1; MS *m*/*z* (M^+) calcd 224.1412, obsd 224.1417. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.83; H, 9.05.

(1*S*,2*S*, 3*R*,4*S*)-2-[(*S*)-3-(*tert*-Butyldimethylsiloxy)-1-cyclohexen-1-yl]-3-(methoxymethoxy)-7,7-dimethyl-1-vinyl-2-norbornanol (18). A 5 mL THF solution containing 55 mg (0.190 mmol) of 1-bromo-3(*S*)-(*tert*-butyldimethylsiloxy)cyclohexene was cooled to −78 °C before 0.22 mL of a 1.7 M solution of *tert*-butyllithium in pentane (0.380 mmol) was added dropwise via syringe. The resulting yellow solution was stirred at this temperature for 15 min before 2 mL of a THF solution containing 36 mg (0.160 mmol) of **16** (admixed with a small amount of **17**) was introduced via cannula. After 15 min, the reaction mixture was quenched with 1.5 mL of saturated NH_4Cl solution and allowed to warm to rt. The separated organic phase was washed with water and brine and then dried. Concentration gave a colorless oil that was purified by column chromatography on silica gel (elution with 10:1 petroleum ether–ethyl acetate) to give an undetermined amount of unreacted **17** and 51 mg (73%) of **18** as a colorless oil: $[\alpha]^{21}_D$ = −49.5° (*c* 1.5, $CHCl_3$); IR (CCl_4, cm^{-1}) 3535, 1632, 1472, 1389, 1369, 1340, 1280, 1252, 1151, 1129, 1079, 1037; ^{1}H NMR (300 MHz, C_6D_6) δ 5.81 (m, 1H), 5.23 (dd, *J* = 2.0, 11.1 Hz, 1H), 5.03 (dd, *J* = 2.0, 18.0 Hz, 1H), 3.30 (s, 1H), 3.09 (s, 3H), 2.54 (ddd, *J* = 5.4, 6.9, 17.6 Hz, 1H), 2.18 (ddd, *J* = 5.4, 6.6, 17.7 Hz, 1H), 1.87 (d, *J* = 4.8 Hz, 1H), 1.77 - 1.48 (series m, 5H), 1.46 (s, 3H), 1.43 (m, 1H), 1.22 (m, 1H), 0.98 (s, 9H), 0.95 (m, 1H), 0.78 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 144.8, 138.4, 124.4, 114.2, 96.5, 85.1, 83.0, 67.3, 58.7, 55.3, 51.8, 50.0, 32.7, 26.7, 26.1, 24.7, 24.4, 22.7, 22.6, 19.9, 18.4, −4.4 (2C); MS *m*/*z* (M^+) calcd 436.3010, obsd 436.3000. Anal. Calcd for $C_{25}H_{44}O_4Si$: C, 68.76; H, 10.16. Found: C, 68.85; H, 10.16.

(1*S*,4a*R*,6*R*,7*S*,10*E*,12a*R*)-2,3,4,4a,6,7,8,9,12,12a-Decahydro-1-hydroxy-6-(methoxymethoxy)-13,13-dimethyl-7,10-methanobenzocyclodecen-5(1*H*)-one (19). Neat potassium hydride (13 mg, 0.329 mmol) was suspended in 2 mL of THF under N_2 in a flame-dried vessel. A 3 mL THF solution containing 18-crown-6 (104 mg, 0.289 mmol) and **18** (29 mg, 65.7 μmol) was added slowly to the suspension at rt. After 1

h, the reaction vessel was placed in an oil bath, heated to a gentle reflux for 3 h, cooled to rt, and quenched with aqueous NH_4Cl solution. After separation of the layers, the organic phase was washed with water and brine and then dried. Column chromatography of the residue on Florisil (gradient elution from 5:1 to 3:1 petroleum ether–ethyl acetate) gave 10.4 mg (53%) of **19** as a colorless oil: ^1H NMR (300 MHz, C_6D_6) δ 5.42 (d, J = 5.42 Hz, 1H), 5.14 (m, 1H), 4.21 (ABq, J = 6.5 Hz, $\Delta\nu$ = 46.9 Hz, 2H), 3.81 (d, J = 5.5 Hz, 1H), 3.77 (dddd, J = 11.0, 4.4, 3.1, 3.1 Hz, 1H), 3.30 (br t, J = 6.5 Hz, 1H), 3.03 (s, 3H), 2.77 (ddd, J = 13.2, 13.2, 10.7 Hz, 1H), 2.20 (m, 1H), 2.12 (m, 1H), 2.00 (m, 1H), 1.92 (m, 1H), 1.90–1.50 (series of m, 6H), 1.36 (s, 3H), 1.29–1.12 (series of m, 3H), 0.94 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 215.9, 146.1, 123.4, 96.0, 88.5, 66.7, 55.7, 54.3, 45.8, 45.3, 44.9, 34.6, 27.9, 27.2, 26.5, 24.0, 23.4, 22.0, 15.5.

(1*S*,4a*R*,6*R*,7*S*,10*E*,12a*R*)-1-(*tert*-Butyldimethylsiloxy)-2,3,4,4a,6,7,8,9, 12,12a-decahydro-6-(methoxymethoxy)-4a,13,13-trimethyl-7,10-methano-benzocyclodecen-5(1*H*)-one (20). Neat potassium hydride (10 mg, 0.24 mmol) was suspended in 2 mL of THF under N_2 in a flame-dried vessel. A 2 mL THF solution containing 18-crown-6 (76 mg, 0.289 mmol) and **18** (21 mg, 48.1 μmol) was added slowly to the suspension at rt. The reaction mixture was stirred at rt for 30 min before an excess (0.10 mL) of freshly distilled iodomethane was introduced. After an additional 30 min, the resulting white suspension was quenched with 1 mL of saturated NH_4Cl solution. The layers were separated, and the organic phase was washed with brine and dried. Column chromatography of the residue on Florisil (elution with 10:1 petroleum ether–ethyl acetate) gave 19 mg (86%) of **20** as a colorless solid: mp 118–119 °C; $[\alpha]^{21}_D$ = −133.2° (c 2.2, $CHCl_3$); IR (CCl_4, cm^{-1}) 1685, 1471, 1392, 1372, 1360, 1258, 1145, 1103, 1084, 1046; ^1H NMR (300 MHz, C_6D_6) δ 5.09 (dd, J = 4.0, 12.2 Hz, 1H) 4.42 (s, 2H), 4.14 (ddd, J = 5.3, 5.3, 10.6 Hz, 1H), 4.10 (d, J = 1.4 Hz, 1H), 3.13 (s, 3H), 2.83 (ddd, J = 4.8, 4.8, 12.2 Hz, 1H), 2.63 (ddd, J = 4.5, 4.5, 13.8 Hz, 1H), 2.49–2.34 (series of m, 2H), 2.21 (br d, J = 7.9 Hz, 1H), 2.01 (m, 2H), 1.70 (s, 3H), 1.67–1.15 (series of m, 7H), 1.05 (s, 3H), 1.04 (s, 3H), 0.97 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6) ppm 214.9, 144.4, 126.0, 95.0, 84.0, 69.6, 56.4, 55.3, 51.9, 51.6, 46.8, 29.7, 26.6, 26.3, 26.0, 25.1, 24.6, 24.5, 23.8, 20.4, 19.5, 18.3, −4.6, −4.7; MS m/z (M^+) calcd 450.3165, obsd 450.3133. Anal. Calcd for $C_{26}H_{46}O_4Si$: C, 69.28; H, 10.29. Found: C, 69.27; H, 10.12.

(1*S*,4a*R*,6*R*,7*S*,10*E*,12a*R*)-2,3,4,4a,6,7,8,9,12,12a-Decahydro-1-hydroxy-6-(methoxymethoxy)-4a,13,13-trimethyl-7,10-methanobenzocyclodecen-5(1*H*)-one (21). A 20 mL THF solution containing 225 mg (0.50 mmol) of **20** under a N_2 atmosphere was cooled to 0 °C. To this was added 2.50 mL (2.50 mmol) of 1 M TBAF in THF, and the resulting reaction mixture was allowed to warm to rt, stirred for 22 h, and diluted with brine and ether. The separated organic phase was dried and concentrated. The crude residue was purified by column chromatography on Florisil (elution with 3:1 petroleum ether–ethyl acetate) to yield 160 mg (95%) of **21** as a colorless solid: mp 114–115 °C; $[\alpha]^{21}_D$ = −134.5° (c 1.4, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3611, 1682, 1474, 1448, 1392, 1373, 1144, 1101, 1039; ^1H NMR (300 MHz, C_6D_6) δ 5.02 (dd, J = 4.1, 12.1 Hz, 1H), 3.12 (s, 3H), 2.69 (ddd, J = 4.9, 4.9, 12.2 Hz, 1H), 2.45 (ddd, J = 4.7, 4.7, 13.6 Hz, 1H), 2.32 (m, 2H), 2.19 (br d, J = 7.8 Hz, 1H), 2.07–1.90 (series of m, 2H), 1.72 (s, 3H), 1.49–1.12 (series of m, 7H), 1.03 (s, 3H), 0.96 (s, 3H), 0.87 (m, 1H); ^{13}C NMR (75 MHz, C_6D_6) ppm 215.2, 144.5, 125.9, 94.9, 83.8, 68.2, 56.4, 55.3, 51.5, 51.1, 46.8, 28.8, 26.6, 26.2, 25.0, 24.6, 24.1, 23.8, 20.4, 19.5; MS m/z ($M^+ - H_2 - OCH_2OCH_3$) calcd 273.1854, obsd 273.1908. Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.45; H, 9.58.

(4a*R*,6*R*,7*S*,10*E*,12a*R*)-2,3,4,4a,6,7,8,9,12,12a-Decahydro-6-(methoxymethoxy)-4a,13,13-trimethyl-7,10-methanobenzocyclodecene-1,5-dione (22). Dess-Martin periodinane[16] (202 mg, 0.475 mmol) was suspended in 20 mL of CH_2Cl_2 under N_2, and a solution of **21** (123 mg, 0.366 mmol) in 10 mL of CH_2Cl_2 was introduced via cannula at rt. After 30 min, 20 mL of saturated $NaHSO_3$ solution was added and the resulting mixture was stirred for 45 min (until both layers were clear). The separated organic phase was washed with water and brine prior to drying. Concentration left a residue that was subjected to column chromatography on Florisil (gradient elution from 5:1 to 1:1 petroleum ether–ethyl acetate) to give 87 mg (71%) **22** as a colorless solid: mp 95–98 °C; $[\alpha]^{21}_D$ = −287.1° (c 1.1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 1703, 1685 (sh), 1474, 1449, 1392, 1375, 1144, 1100, 1039; ^1H NMR (300 MHz, C_6D_6) δ 4.77 (dd, J = 3 .7, 12.1 Hz, 1H), 4.30 (ABq, J = 7.0 Hz, $\Delta\nu$ = 20.6 Hz, 2H), 4.03 (d, J = 1.2 Hz, 1H), 3.24 (dd, J = 5.2, 12.4 Hz, 1H), 3.07 (s, 3H), 2.28 (ddd, J = 12.6, 12.6, 12.6 Hz, 1H), 2.22–1.88 (series of m, 7H), 1.64 (m, 1H), 1.58 (s, 3H), 1.39–1.21 (series of m, 4H), 0.98 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 213.7, 209.7, 145.5, 123.3, 95.3, 84.5, 62.9, 55.6, 55.4, 52.2, 46.3, 36.0, 30.2, 26.6, 26.0, 25.2, 24.8, 24.0, 21.1, 19.3; MS m/z ($M^+ - OCH_2OCH_3$) calcd 273.1854, obsd 273.1843. Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.64; H, 8.99.

(1*S*,3*R*,4*S*)-3-Hydroxy-1-[(*Z*)-2-(*p*-methoxyphenoxy)vinyl]-7,7-dimethyl-2-norbornanone (26a). A solution of 2.33 mL of 0.5 M potassium hexamethyldisilazide in toluene (1.16 mmol) and 10 mL of THF was cooled to −78 °C under N_2. Into this solution was cannulated 175 mg (0.583 mmol) of **23**[8] in 10 mL of THF, and the resulting solution was stirred for 15 min at −78 °C before it was allowed to warm to 0 °C. After 15 min at this temperature, the solution was recooled to −78 °C and a solution of 457 mg (1.75 mmol) of 1-phenyl-*N*-(phenylsulfonyl)oxaziridine in 5 mL of THF was added to the reaction vessel. After 1 h, the solution was allowed to warm to 0 °C before being quenched with saturated NH_4Cl solution. The separated organic phase was washed with water and brine prior to drying. The resulting multicomponent mixture was separated by silica gel chromatography (gradient elution from 10:1 to 3:1 petroleum ether–ethyl acetate) to give 95 mg (52%) of a 5:1 mixture of the exo and endo isomers of **26a**. Resubjecting this mixture to column chromatography gave pure exo isomer **26a** as a colorless solid: mp 97–99 °C; $[\alpha]^{21}_D$ = +53.6° (c 1.0, CCl_4); IR (CCl_4, cm^{-1}) 3580, 3458, 1751, 1667, 1505, 1466, 1455, 1442, 1397, 1224; ^1H NMR (300 MHz, C_6D_6) δ 6.82 (m, $^1/_2$ AA′, 2H), 6.66 (m, $^1/_2$ AA′, 2H), 6.33 (d, J = 6.8 Hz, 1H), 4.76 (d, J = 6.8 Hz, 1H), 3.51 (s, 1H), 3.28 (s, 3H), 2.73 (br s, 1H), 2.46 (m, 1H), 1.88 (d, J = 4.5 Hz, 1H), 1.70 (m, 2H), 1.18 (s, 3H), 1.12 (m, 1H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 216.2, 156.0, 151.8, 145.8, 118.1, 115.0, 103.6, 77.7, 61.2, 55.2, 49.2, 26.0, 25.8, 21.7, 21.3; MS m/z (M^+) calcd 302.1519, obsd 302.1513.

(1*S*,3*R*,4*S*)-3-(Methoxymethoxy)-1-[(*Z*)-2-(*p*-methoxyphenoxy)vinyl]-7,7-dimethyl-2-norbornanone (26b). A solution of 28 mg (87 μmol) of **26a** and 0.60 mL (3.48 mmol) of diisopropylethylamine in 3 mL of CH_2Cl_2 was cooled to 0 °C before being treated dropwise with 0.13 mL (1.74 mmol) of chloromethyl methyl ether. The reaction mixture was allowed to warm to rt overnight and diluted with brine. After separation of the layers, the organic phase was washed water and brine prior to drying. Purification of the residue by column chromatography on silica gel (elution with 3:1 petroleum ether–ethyl acetate) gave 27 mg (88%) of **26b** as a colorless oil: $[\alpha]^{21}_D$ = +88.6° (c 1.1, CCl_4); IR (CCl_4, cm^{-1}) 1758, 1667, 1505, 1466, 1455, 1441, 1397, 1216; ^1H NMR (300 MHz, C_6D_6) δ 6.83 (br d, J = 9.0 Hz, 2H), 6.66 (br d, J = 9.0 Hz, 2H), 6.34 (d, J = 6.8 Hz, 1H), 4.82 (d, J = 6.5 Hz, 1H), 4.79 (d, J = 6.8 Hz, 1H), 4.55 (d, J = 6.5 Hz, 1H), 3.66 (s, 1H), 3.27 (s, 3H), 3.24 (s, 3H), 2.47 (m, 1H), 1.85 (d, J = 4.4 Hz, 1H), 1.68 (m, 2H), 1.20 (s, 3H), 1.03 (m, 1H), 0.93 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 213.2, 156.0, 151.8, 145.9, 118.1 (2 C), 115.0 (2 C), 103.9, 96.6, 80.9, 61.2, 55.2, 55.1, 49.1, 48.4, 26.1, 25.6, 21.7, 21.2; MS m/z (M^+) calcd 346.1780, obsd 346.1772. Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 68.87; H, 7.59.

(1*S*,3*R*,4*S*)-3-(Methoxymethoxy)-1-[(*E*)-2-(*p*-methoxyphenoxy)vinyl]-7,7-dimethyl-2-norbornanone (27b). A 50 mL THF solution containing 22.0 mL of 0.5 M potassium hexamethyldisilazide in toluene (11.0 mmol) under N_2 was cooled to −78 °C and treated via cannula with a 20 mL THF solution of **24**[8] (1.577 g, 5.51 mmol). The resulting mixture was stirred for 15 min, allowed to warm briefly to 0 °C, and recooled to −78 °C. After an additional 30 min, 4.32 g (16.5 mmol)

1-phenyl-*N*-(phenylsulfonyl)oxaziridine dissolved in 30 mL of THF was introduced. The mixture was stirred for 2 h, allowed to warm to 0 °C, and quenched by the addition of saturated NH_4Cl solution. The layers were separated, and the organic phase was washed with water and brine and then dried. The residue was passed through a plug of silica gel and directly carried into the protection step.

The unpurified product from above was dissolved in 60 mL of CH_2Cl_2 under N_2 and treated sequentially with 10.8 mL (62.0 mmol) of diisopropylethylamine and 3.2 mL (41.4 mmol) of chloromethyl methyl ether at 0 °C. The mixture was allowed to warm to rt overnight, partitioned between brine and CH_2Cl_2, and separated into layers. The organic phase was washed with water and brine prior to drying. The crude concentrate was purified by column chromatography on silica gel (gradient elution from 5:1 to 2:1 petroleum ether–ethyl acetate) to give 0.989 g (69%) of a 7:1 exo:endo mixture of **27b** as a colorless oil.

For the exo isomer **27b**: colorless oil; $[\alpha]^{21}_D = +38.7°$ (*c* 2.7, $CHCl_3$); IR (CCl_4, cm^{-1}) 1757, 1668, 1505, 1466, 1454, 1441, 1226, 1039; ^1H NMR (300 MHz, $CDCl_3$) δ 6.95 (m, $^1/_2$ AA′, 2H), 6.83 (m, $^1/_2$ AA′, 2H), 6.63 (d, J = 12.5 Hz, 1H), 5.20 (d, J = 12.5 Hz, 1H), 4.83 (d, $^1/_2$ ABq, J = 6.6 Hz, 1H), 4.72 (d, $^1/_2$ ABq, J = 6.6 Hz, 1H), 3.77 (s, 3H), 3.71 (s, 1H), 3.41 (s, 3H), 2.17 (d, J = 4.6 Hz, 1H), 2.05 (m, 1H), 1.91 (m, 1H), 1.56 (m, 1H), 1.44 (m ,1H), 1.07 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 215.0, 155.3, 151.0, 146.7, 117.8 (2C), 114.6 (2C), 104.6, 96.5, 81.1, 59.9, 55.5, 55.4, 48.4, 47.9, 26.9, 25.0, 21.1, 20.1; MS m/z (M^+) calcd 346.1780, obsd 346.1785. Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 69.31; H, 7.62.

(1*S*,3*R*,4*S*)-3-(Methoxymethyl)-7,7-dimethyl-2-norbornanone-1-carboxaldehyde (25). A 120 mL (5:1) CH_2Cl_2–MeOH solution of **16** (3.08 g, 13.7 mmol) was cooled to −78 °C and treated with an 8 psi stream of ozone. After 3 h, the reaction mixture became blue and was treated with 5.0 mL (68.7 mmol) of dimethyl sulfide. The cooling bath was removed, and the mixture was allowed to stir at rt overnight. Dilution with brine was followed by separation of the layers. The organic phase was washed with water and brine and then dried and concentrated to leave an oily residue that was purified by column chromatography on silica gel (gradient elution from 5:1 to 3:1 petroleum ether–ethyl acetate) to give **25** (2.08 g, 67%) followed by 680 mg of an unidentified compound.

For **25**: ^1H NMR (300 MHz, $CDCl_3$) δ 9.93 (s, 1H), 4.81 (d, $^1/_2$ AB_q, J = 6.7 Hz, 1H), 4.70 (d, $^1/_2$ AB_q, J = 6.7 Hz, 1H), 3.73 (s, 1H), 3.39 (s, 3H), 2.24 (dt, J_t = 13.0, J_d = 3.4 Hz, 1H), 2.14, (d, J = 4.4 Hz, 1H), 2.07 (m, 1H), 1.57 (ddd, J = 4.3, 9.2, 13.5 Hz, 1H), 1.30 (ddd, J = 3.3, 9.2, 12.5 Hz, 1H), 1.34 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.3, 201.1, 96.7, 81.5, 69.8, 55.6, 50.1, 24.6, 22.8, 21.8, 20.5; MS m/z (M^+) calcd 226.1205, obsd 226.171.

Upon treatment of **25** (1.01 g, 4.48 mmol) in cold (−78 °C) THF solution (23 mL) with the ylide prepared from 4.36 g (10.04 mmol) of (*p*-methoxyphenoxy)methylphosphonium chloride and 6.69 mL of 1.6 M *n*-butyllithium in hexanes (10.70 mmol) via cannula under N_2 for 2 h, followed by quenching with saturated NH_4Cl solution, extraction into CH_2Cl_2, drying, concentration, and chromatography on silica gel (elution with 10 → 15% ethyl acetate in hexanes), there were obtained 340 mg (22%) of **26b** and 830 mg (53%) of **27b**. The ^1H NMR spectra of these materials were identical to those described above.

(1*S*,2*S*,3*R*,4*S*)-3-(Methoxymethoxy)-2-[(*S*)-3-(methoxymethoxy)-1-cyclohexen-1-yl]-1-[(*Z*)-2-(*p*-methoxyphenoxy)vinyl]-7,7-dimethyl-2-norbornanol (30). A 10 mL THF solution containing 35.0 mg (0.158 mmol) of **28-Br** under N_2 was cooled to −78 °C and treated dropwise with 0.19 mL (0.317 mmol) of 1.7 M *tert*-butyllithium. The resulting yellow solution was stirred at this temperature for 30 min before introduction of a 2 mL THF solution of **26b** (18 mg, 53 μmol) via cannula. After 2 h, the solution was warmed to rt and quenched with saturated NH_4Cl solution. The layers were separated, and the organic phase was washed with water and brine prior to drying. Purification of the concentrate on Florisil (gradient elution from 10:1 to 5:1 petroleum ether–ethyl acetate) gave 21 mg (83%) of **30** as a colorless oil: $[\alpha]^{21}_D$ = −66.6° (*c* 1.3, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3522, 1664, 1504, 1466, 1442, 1224, 1180, 1102, 1073, 1036, 917, 829; ^1H NMR (300 MHz, C_6D_6) δ 6.85 (m, $^1/_2$ AA′, 2H), 6.67 (m, $^1/_2$ AA′, 2H), 6.31 (d, J = 7.2 Hz, 1H), 6.01 (m, 1H), 5.42 (d, J = 7.2 Hz, 1H), 4.64 (s, 2H), 4.41 (ABq, J = 6.5 Hz, $\Delta\nu$ = 15.4 Hz, 2H), 4.23 (s, 1H), 4.15 (s, 1H), 3.38 (s, 1H), 3.27 (s, 3H), 3.25 (s, 3H), 3.09 (s, 3H), 2.79 (m, 1H), 2.65 (m, 1H), 2.45 (m, 1H), 1.84 (d, J = 4.9 Hz, 1H), 1.87–1.60 (series of m, 3H), 1.57 (s, 3H), 1.35–1.16 (series of m, 2H), 1.04 (s, 3H), 1.01–0.83 (series of m, 2H); ^{13}C NMR (75 MHz, C_6D_6) ppm 155.7, 152.1, 146.5, 142.0, 121.9, 117.6 (2C), 115.0 (2C), 110.0, 96.7, 95.4, 85.4, 83.6, 71.9, 57.0, 55.3, 55.1, 54.9, 53.1, 49.1, 29.5, 26.6, 26.4, 25.0, 23.7, 22.7, 20.0; MS FAB m/z (M^+ + 1) calcd 489.2851, obsd 489.50.

(1*S*,2*S*,3*R*,4*S*)-2-[(*R*)-3-[(methoxybenzyl)oxy]-1-cyclohexen-1-yl]-3-(methoxymethoxy)-1-[(*Z*)-2-(*p*-methoxyphenoxy)vinyl]-7,7-dimethyl-2-norbornanol (31). A solution of 220 mg (0.735 mmol) of 1-bromo-3-(*R*)-(*p*-methoxybenyloxy)-cyclohexene (**29**) in 10 mL of THF was cooled to −78 °C and treated dropwise with 0.90 mL of 1.7 M *tert*-butyllithium (1.50 mmol) in pentane. After 15 min, **26b** (170 mg, 0.50 mmol) was introduced as a 5 mL THF solution, and the resulting mixture was stirred for 20 min. Addition of 1.5 mL of saturated NH_4Cl solution was followed by warming of the mixture to rt. The layers were separated, and the organic phase was washed with water and brine and then dried. Column chromatography of the concentrate on silica gel (elution with 5:1 petroleum ether–ethyl acetate) gave 217 mg (78%) of **31** as a colorless oil: $[\alpha]^{21}_D$ = +17.1° (*c* 1.9, $CHCl_3$); IR (thin film, cm^{-1}) 3517, 1664, 1612, 1505, 1464, 1441, 1389, 1243, 1219, 1180, 1150, 1102, 1074, 1036; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, $^1/_2$ AA′, 2H), 6.88 (m, $^1/_2$ AA′, 2H), 6.36 (d, J = 7.1 Hz, 1H), 5.81 (m, 1H), 5.04, (d, J = 7.1 Hz, 1H), 4.74 (d, $^1/_2$ ABq, J = 6.5 Hz, 1H), 4.68 (d, $^1/_2$ ABq, J = 6.5 Hz, 1H), 4.51 (AB_q, J = 11.6, $\Delta\nu$ = 12.5 Hz, 2H), 4.11 (s, 1H), 4.01 (m, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.39 (s, 3H), 2.31 (m, 3H), 1.87 (d, J = 5.0 Hz, 1H), 1.90–1.67 (series of m, 3H), 1.63–1.42 (series of m, 3H), 1.27 (s, 3H), 1.04 (ddd, J = 4.6, 4.8, 13.3 Hz, 1H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 159.0, 155.0, 151.6, 145.7, 141.6, 131.3, 129.1 (2C), 122.0, 117.2 (2C), 114.6 (2C), 113.7 (2C), 109.1, 96.7, 85.1, 83.6, 73.7, 69.4, 56.5, 55.7, 55.6, 55.2, 52.6, 48.6, 28.5, 26.2, 26.0, 24.7, 23.2, 22.1, 20.6; MS FAB m/z (M^+ + 1) calcd 565.3164, obsd 565.48. Anal. Calcd for $C_{34}H_{44}O_7$: C, 72.32; H, 7.85. Found: C, 72.01; H, 7.89.

(1*R*,4a*R*,6*R*,7*S*,10*E*,12*R*,12a*R*)-2,3,4,4a,6,7,8,9,12,12a-Decahydro-1-[(*p*-methoxybenzyl)oxy]-6-(methoxymethoxy)-12-(*p*-methoxyphenoxy)-4a,13,13-trimethyl-7,10-methanobenzocyclodecen-5(1*H*)-one (32). A mixture of 18-crown-6 (51 mg, 0.20 mmol) and **31** (22 mg, 39 μmol) was dissolved in 5 mL of THF under N_2. After passing N_2 through the solution for 30 min, it was cooled to 0 °C and treated dropwise with 0.31 mL of 0.5 M (0.156 mmol) potassium hexamethyldisilazide. After 45 min, 0.5 mL of freshly distilled methyl iodide was added by syringe and the solution was allowed to warm to rt. Dilution with ether and saturated NH_4Cl solution was followed by separation of the layers. The organic phase was washed with water and brine and then dried. Purification of the residue by column chromatography on silica gel (elution with 5:1 petroleum ether–ethyl acetate) yielded 18 mg (78%) of **32** as a colorless solid: mp 122–124 °C; $[\alpha]^{21}_D$ = −134.1° (*c* 1.2, $CHCl_3$); IR (thin film, cm^{-1}) 1681, 1613, 1506, 1223, 1040, 822; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, $^1/_2$ AA′, 2H), 6.85 (m, $^1/_2$ AA′, 2H), 6.79 (s, 4H), 4.91 (m, 1H), 4.84 (m, 1H), 4.56 (d, $^1/_2$ ABq, J = 11.3 Hz, 1H), 4.54 (d, $^1/_2$ ABq, J = 6.9 Hz, 1H), 4.38 (d, $^1/_2$ ABq, J = 11.3 Hz, 1H), 4.35 (d, $^1/_2$ ABq, J = 6.9 Hz, 1H), 4.29 (s, 1H), 3.79 (s, 3H), 3.77 (m, 1H), 3.75 (s, 3H), 3.31 (s, 3H), 3.27 (m, 1H), 3.22 (m, 1H), 2.44 (m, 1H), 2.21–1.64 (series of m, 8H), 1.40 (s, 3H), 1.38 (s, 3H), 1.26 (m, 1H), 1.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 217.6, 158.9, 153.8, 151.6, 146.3, 131.1, 128.8, 124.6, 115.6, 114.5, 113.8, 94.7, 82.9, 79.8, 77.8, 70.3, 55.7, 55.6, 55.2, 55.0, 50.4, 47.0, 27.8, 27.5, 27.1, 26.5, 25.7, 24.0, 19.1,

17.9; MS m/z (M^+) calcd 578.3243, obsd 578.3270. Anal. Calcd for $C_{35}H_{46}O_7$: C, 72.64; H, 8.01. Found: C, 72.84; H, 8.04.

1-[[[(*R*)-3-Bromo-2-cyclohexen-1-yl]oxy]methoxy]-2-methoxyethane (33-Br). A 30 mL CH_2Cl_2 solution of (*R*)-3-bromo-2-cyclohexenol (0.76 g, 4.29 mmol, 80% ee)[6a] under N_2 was cooled to 0 °C and treated sequentially with 11.2 mL (64.4 mmol) of diisopropylethylamine and 4.9 mL (42.9 mmol) of methoxyethoxymethyl chloride. The solution was warmed to rt and stirred for 12 h. After dilution with water, the layers were separated, and the organic phase was washed with water and brine prior to drying. Concentration gave a brown oil that was purified by column chromatography on silica gel (elution with 5:1 petroleum ether–ethyl acetate) to give 0.82 g (72%) of **33-Br** as a slightly yellow oil; IR (CCl_4, cm^{-1}) 1646, 1451, 1363, 1326, 1200, 1173, 1110, 1040, 936, 908; ^1H NMR (300 MHz, $CDCl_3$) δ 6.15 (m, 1H), 4.74 (br s, AB_q, 2H), 4.12 (m, 1H), 3.68 (m, 2H), 3.53 (t, J = 4.6 Hz, 1H), 3.37 (s, 3H), 2.40 (m, 2H), 1.92–1.58 (4H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 129.5, 127.1, 94.0, 71.9, 71.7, 66.8, 58.9, 35.1, 27.7, 20.6; MS FAB m/z ($M^+ + 1$) calcd 265.04, obsd 265.05.

(1*S*,2*S*,3*R*,4*S*)-2-[(*R*)-3-[2-Methoxyethoxy)methoxy]-1-cyclohexen-1-yl]-3-(methoxymethoxy)-1-[(*E*)-2-(*p*-methoxyphenoxy)vinyl]-7,7-dimethyl-2-norbornanol (34). Vinyl bromide **33-Br** (0.300 g, 1.13 mmol) was dissolved in 10 mL of THF under N_2, and the resulting solution was cooled to −78 °C. After dropwise treatment with 1.40 mL of 1.7 M *tert*-butyllithium (2.37 mmol), the mixture was left to stir for 1.5 h. A solution of **27b** (0.169 g, 0.488 mmol) in 5 mL of THF was then introduced via cannula. After 30 min at −78 °C, the vessel was allowed to come to rt and the reaction mixture was quenched with saturated NH_4Cl solution. The layers were separated, the organic phase was washed with water and brine, and the aqueous washings were extracted with ether. The combined organic solutions were dried and concentrated to leave a yellow oil, purification of which was effected by column chromatography on Florisil (gradient elution from 5:1 to 2:1 petroleum ether–ethyl acetate) to give 0.217 g (84%) of **34** as a colorless oil: $[\alpha]^{21}_D$ = +51.6° (*c* 1.1, CCl_4); IR (CCl_4, cm^{-1}) 3532, 1664, 1505, 1465, 1441, 1389, 1368, 1291, 1226, 1151, 1106, 1040, 947, 923; ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (m, 1/2 AA′, 2H), 6.83 (m, 1/2 AA′, 2H), 6.27 (d, J = 12.6 Hz, 1H), 5.77 (d, J = 12.6 Hz, 1H), 5.74 (s, 1H), 4.81 (ABq, J = 7.0, $\Delta\nu$ = 7.5 Hz, 2H), 4.72 (ABq, J = 6.5, $\Delta\nu$ = 13.5 Hz, 2H), 4.21 (m, 1H), 4.14 (s, 1H), 3.77 (s, 3H), 3.72 (m, 2H), 3.57 (m, 2H), 3.39 (s, 3H), 3.38 (s, 3H), 2.24 (m, 2H), 1.95 (d, J = 4.9 Hz, 1H), 1.87 (m, 1H), 1.75 (m, 2H), 1.60–1.43 (series of m, 4H), 1.30 (m, 1H), 1.25 (s, 3H), 1.10 (m, 1H), 0.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 155.1, 151.6, 145.6, 143.4, 121.9, 117.6 (C), 114.7 (2C), 111.4, 96.7, 94.2, 84.8, 83.4, 72.6, 71.8, 66.8, 59.0, 55.7, 55.6, 55.4, 51.7, 49.2, 29.3, 26.8, 25.6, 24.3, 22.6, 22.1, 20.4; MS FAB m/z ($M^+ + 1$) calcd 533.3133, obsd 533.47. Anal. Calcd for $C_{30}H_{44}O_8$: C, 67.65; H, 8.33. Found: C, 67.61; H, 8.37.

(1*R*,4a*S*,6*R*,7*S*,10*E*,12*S*,12a*R*)-2,3,4,4a,6,7,8,9,12,12a-Decahydro-4a-methoxy-1-[(2-methoxyethoxy)methoxy]-6-(methoxymethoxy)-12-(*p*-methoxyphenoxy)-13,13-dimethyl-7,10-methanobenzocyclodecen-5(1*H*)-one (35). A 10 mL THF solution containing 67 mg of **34** (0.126 mmol) and 0.166 g of 18-crown-6 (0.629 mmol) under N_2 was cooled to −78 °C. The reaction mixture was treated dropwise with 1.0 mL of 0.5 M potassium hexamethyldisilazide in toluene (0.500 mmol), and the mixture was allowed to warm to rt. After 15 min, TLC analysis showed that all the substrate had been consumed to give a much more polar species. The solution was cooled to 0 °C, treated with 0.5 mL of freshly distilled methyl iodide, warmed to rt for 1 h, and quenched with brine. The layers were separated, and the organic phase was washed with water and brine prior to drying. Concentration gave a yellow oil that was purified by column chromatography on Florisil (gradient elution from 3:1 to 1:1 petroleum ether–ethyl acetate) to give 49 mg (69%) of **35** as a colorless oil: $[\alpha]^{21}_D$ = +10.8° (*c* 1.3, CCl_4); IR (CCl_4, cm^{-1}) 1705, 1506, 1465, 1227, 1180, 1147, 1109, 1043; ^1H NMR (300 MHz, $CDCl_3$) δ 6.75 (s, 4H), 4.88 (d, J = 9.1 Hz, 1H), 4.79 (ABq, J = 6.9, $\Delta\nu$ = 20.4 Hz, 2H), 4.65 (t, J = 10.2 Hz, 1H), 4.49 (ABq, J = 6.7, $\Delta\nu$ = 22.2 Hz, 2H), 4.26 (d, J = 1.5 Hz, 1H), 4.19 (s, 1H), 3.76 (m, 2H), 3.73 (s, 3H), 3.64 (s, 3H), 3.59 (m, 2H), 3.38 (s, 3H), 3.33 s, (3H), 2.92 (br d, J = 9.9 Hz, 1H), 2.55 (m, 2H), 2.35 (m, 2H), 2.20 (br d, J = 7.2 Hz, 1H), 2.10 (m, 1H), 1.95–1.45 (series of m, 3H), 1.25 (m, 1H), 1.32 (s, 3H), 1.09 (s, 3H), 0.85 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 210.6, 154.0, 146.7, 125.7, 116.6 (2C), 114.5 (2C), 95.3, 93.9, 88.3, 85.3, 75.6, 72.3, 71.8, 66.7, 62.2, 59.0, 55.7, 55.6, 55.4, 51.7, 46.1, 26.6, 25.7, 24.9, 23.9, 19.1, 16.6; MS m/z (M^+) calcd 562.3141, obsd 562.3151.

(1*R*,4a*R*,6*R*,7*S*,10*E*,12*S*,12a*R*)-2,3,4,4a,6,7,8,9,12,12a-Decahydro-1-[(2-methoxyethoxy)methoxy]-6-(methoxymethoxy)-12-(*p*-methoxyphenoxy)-4a,13,13-trimethyl-7,10-methanobenzocyclodecen-5(1*H*)-one (36). A solution of 117 mg of **34** (0.220 mmol) and 290 mg of 18-crown-6 (1.10 mmol) in 20 mL of THF was vigorously deoxygenated by bubbling N_2 through it for 2 h. The reaction mixture was then cooled to −78 °C, treated dropwise with 1.75 mL of 0.5 M potassium hexamethyldisilazide in toluene (0.879 mmol) and allowed to warm to 0 °C. After 1 h, TLC analysis showed complete substrate consumption to give a species of very similar polarity. The solution was treated with 2.0 mL of freshly distilled methyl iodide and stirred for 10 min at 0 °C before being warmed to rt. The reaction mixture was stirred for 1 h and quenched with saturated NH_4Cl solution. The layers were separated, and the organic phase was washed with water and brine prior to drying. Concentration gave a yellow oil that was purified by column chromatography on triethylamine-washed silica gel (gradient elution from 3:1 to 1:1 petroleum ether–ethyl acetate) to give 11 mg (9%) of **35** as well as 98 mg (82%) of **36** as a colorless oil; $[\alpha]^{21}_D$ = −38.8° (*c* 1.4, CCl_4); IR (CCl_4, cm^{-1}) 1688, 1506, 1466, 1454, 1441, 1393, 1377, 1362, 1287, 1226, 1146, 1105, 1044, 1018, 974; ^1H NMR (300 MHz, $CDCl_3$) δ 6.76 (s, 4H), 4.83 (d, J = 9.2 Hz, 1H), 4.79 (ABq, J = 6.8, $\Delta\nu$ = 24.0 Hz, 2H), 4.68 (t, J = 10.0 Hz, 1H), 4.51 (d, 1/2 ABq, J = 7.0 Hz, 1H), 4.31 (d, 1/2 ABq, J = 7.0 Hz, 1H), 4.30 (m, 1 H), 4.19 (s, 1H), 3.74 (s, 3H), 3.73 (m, 2H), 3.58 (m, 2H), 3.39 (s, 3H), 3.30 (s, 3H), 2.84 (br d, J = 9.7 Hz, 1H), 2.59 (m, 1H), 2.35 (m, 2H), 2.17 (br d, J = 6.9 Hz, 1H), 1.84–1.40 (series of m, 7H), 1.36 (s, 3H), 1.30 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 215.9, 153.7, 152.7, 145.9, 126.6, 116.4 (2C), 114.4 (2C), 94.5, 93.6, 82.5, 77.4, 72.9, 71.7, 66.7, 58.9, 55.5, 55.1, 53.1, 50.1, 46.4, 28.2, 26.8, 25.9, 25.7, 25.3, 23.9, 18.7, 17.0; MS m/z (M^+) calcd 546.3192, obsd 546.3172. Anal. Calcd for $C_{31}H_{46}O_8$: C, 68.11; H, 8.48. Found: C, 67.87; H, 8.52.

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Supplementary Material Available: 300-MHz ^1H NMR and 75-MHz ^{13}C NMR spectra of those compounds lacking combustion data (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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