Bicyclic Systems Related to Taxol. A Direct Means for Implementing C-2 Oxygenation and Demonstration of the Feasibility of α-Ketol Equilibration in a Fully Oxygenated B-Ring Setting

Qingbei Zeng, Simon Bailey, Ting-Zhong Wang, and Leo A. Paquette*

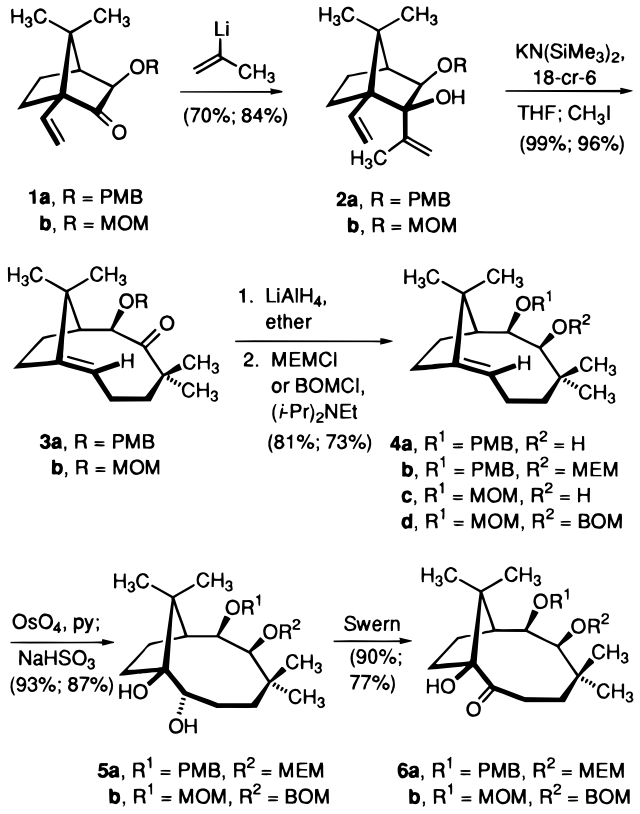
Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

Received August 26, 1997[⊗]

The feasibility of α-ketol equilibration in a fully oxygenated B-ring setting for the rapid, enantioselective construction of an A/B bicyclic model related to Taxol has been examined. The key elements associated with this successful venture include selection of a proper array of protecting groups for the four hydroxyl groups present, suitable catalysis of the 1,2-pinacol-like shift, and an intrinsic dependence on the thermodynamic stabilities of the two α-ketol isomers. The key conversion of **13** to **14** is seen to be unidirectional and consequently to offer useful potential serviceability as more advanced thrusts toward Taxol are mounted.

Previous studies from this laboratory have dealt with the design and development of a unique strategy for the synthesis of advanced taxane structures.[1] These investigations have established the feasibility of incorporating all of the essential features of taxusin,[2] as well as the several added oxygenated sites of Taxol, either separately or in tandem.[3] If the option is exercised to form the C-ring via an aldol cyclization, efficiency would be well-served if the C-2 oxygen substituent were introduced after this cyclization and prior to bridge migration. The preceding paper details the consequences of involving the thiophenyl group as an oxygen surrogate at that site.[4] Unfortunately, the propensity for transannular cyclization following elimination of the sulfur substituent cannot be sufficiently controlled for our purposes. In this paper, this problem is addressed from the perspective of enolate oxygenation in a bicyclic model system. Not only is the protocol shown to be feasible, but the added functionality is demonstrated not to impede the subsequent 1,2-bridge migration that establishes the desired structural framework.

Scheme 1



Results and Discussion

The Interplay of Protecting Groups. These studies began by reacting the 3-[(*p*-methoxybenzyl)oxy] ketone **1a** with 2-lithiopropene (Scheme 1). As usual, the apical methyl and flanking *exo*-OR substituents resident in this enantiopure derivative of D-camphor cause endo attack to be the sterically feasible direction for 1,2-addition to

[⊗] Abstract published in *Advance ACS Abstracts,* December 15, 1997.

(1) For reviews on this subject, see: (a) *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I., Chen, T. T., Ojima, I., Vyas, D. M., Eds.; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1995. (b) *Taxol® Science and Applications*; Suffness, M., Ed.; CRC Press: Boca Raton, FL, 1995. (c) Boa, A. N.; Jenkins, P. R.; Lawrence, N. J. *Contemp. Org. Synth.* **1994**, *1*, 47. (d) Nicolaou, K. C.; Dai, W. M.; Guy, R. K. *Angew. Chem.* **1994**, *33*, 15. (e) Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. *Progress in the Chemistry of Organic Natural Products*; Springer-Verlag: New York, 1993; Vol. 61. (f) Paquette, L. A. *Studies in Natural Products Chemistry*; Elsevier: Amsterdam, 1992, Vol. 11, pp 3−69. (g) Swindell, C. S. *Org. Prep. Proced. Int.* **1991**, *23*, 465−543.

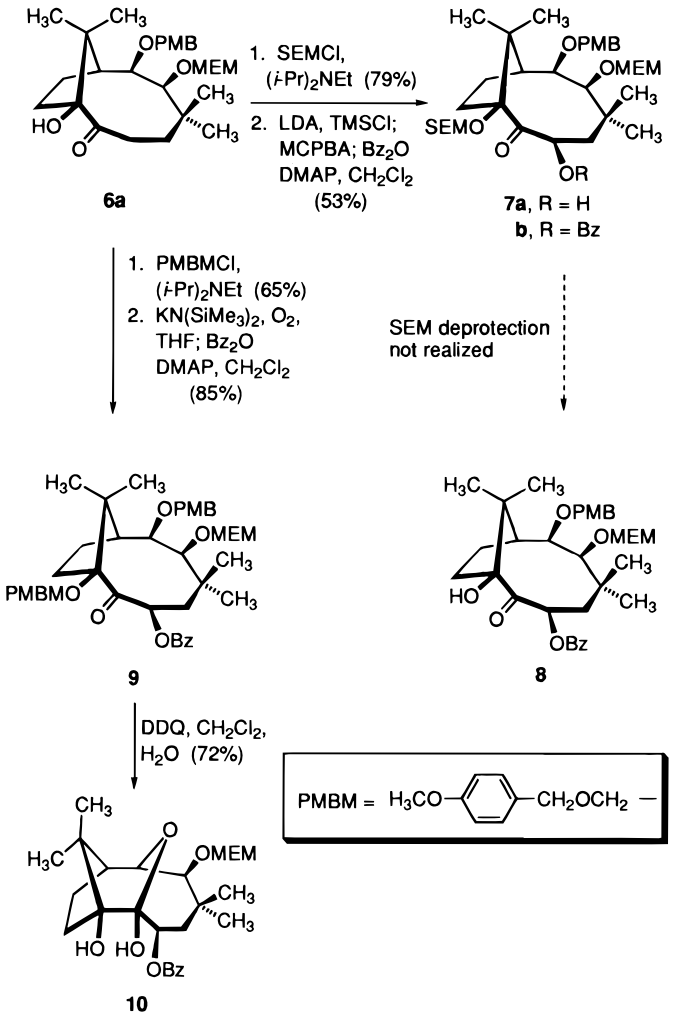
(2) (a) Paquette, L. A.; Zhao, M. *J. Am. Chem. Soc.* **1993**, *115*, 354. (b) Paquette, L. A.; Zhao, M.; Friedrich, D. *Tetrahedron Lett.* **1992**, *33*, 7311. (c) Paquette, L. A.; Combrink, K. D.; Elmore, S. W.; Zhao, M. *Helv. Chim. Acta* **1992**, *75*, 1772. (d) Paquette, L. A.; Elmore, S. W.; Combrink, K. D.; Hickey, E. R.; Rogers, R. D. *Helv. Chim. Acta* **1992**, *75*, 1755. (e) Elmore, S. W.; Combrink, K. D.; Paquette, L. A. *Tetrahedron Lett.* **1991**, *32*, 6679.

(3) (a) Paquette, L. A.; Montgomery, F. J.; Wang, T.-Z. *J. Org. Chem.* **1995**, *60*, 7857. (b) L. A. Paquette, L. A.; Bailey, S. *J. Org. Chem.*, **1995**, *60*, 7849. (c) Paquette, L. A.; Su, Z.; Bailey, S.; Montgomery, F. J. *J. Org. Chem.* **1995**, *60*, 897. (d) Elmore, S. W.; Paquette, L. A. *J. Org. Chem.* **1995**, *60*, 889. (e) Paquette, L. A.; Huber, S. K.; Thompson, R. C. *J. Org. Chem.* **1993**, *58*, 6874. (f) Elmore, S. W.; Paquette, L. A. *J. Org. Chem.* **1993**, *58*, 4963.

(4) Johnston, J. N.; Tsui, H.-C.; Paquette, L. A. *J. Org. Chem.* **1998**, *63*, 127−134.

S0022-3263(97)01592-2 CCC: $15.00
Published on Web 01/09/1998

Scheme 2



the carbonyl group. This reaction trajectory delivered **2a**, the alkene subunits in which are in adequate proximity for participation in [3,3] sigmatropic rearrangement. When this isomerization was performed under anionic conditions and followed directly by in situ methylation, **3a** was isolated in 99% yield. Alkylation of the regiodirected enolate in this fashion did away with an irrelevant stereogenic center while simultaneously simulating C-8 of the taxanes. Ketone **3a** prefers to reside in its "carbonyl-up" conformation, with the result that lithium aluminum hydride reduction proceeds with attack from the more open α-surface (NOE analysis).

With arrival at **4a**, the decision was made to distinguish R^1 from R^2 by formation of the MEM derivative **4b**. Subsequent dihydroxylation of the bridgehead double bond furnished **5a** and set the stage for arrival at α-ketol **6a** by Swern oxidation.

As shown in Scheme 2, protection of the bridgehead hydroxyl in **6a** as the SEM derivative made possible formation of the silyl enol ether and Rubottom oxidation[5] of this intermediate with *m*-chloroperbenzoic acid. Without purification of **7a** generated in this manner, benzoylation was effected to deliver **7b** in 53% overall yield for the three steps. NOE studies on **7b** and related polyoxygenated intermediates made clear that the benzoyloxy substituent was oriented β and therefore in a configuration unnatural to Taxol (see Figure 1). This feature was considered to be inconsequential to the outcome of the pending α-ketol equilibration experiments (see below).

Preliminary to these studies, it was necessary to remove the SEM functionality from **7b**. However, this immediate goal was never realized. Under a variety of conditions, **7b** was recovered unchanged; attempts to force matters resulted in decomposition.

As a consequence, the decision was made to protect the bridgehead carbinol as the [(*p*-methoxybenzyl)oxy]methyl (PMBM) derivative in advance of conversion to **9** in good yield (85%). We had envisioned selective removal of the PMBM residue as a prelude to bridge migration. However, this approach had to be abandoned when it was recognized that DDQ oxidation of **9** led to competitive deprotection of both the PMBM and PMB groups with

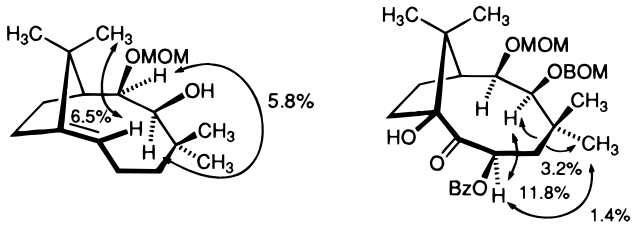
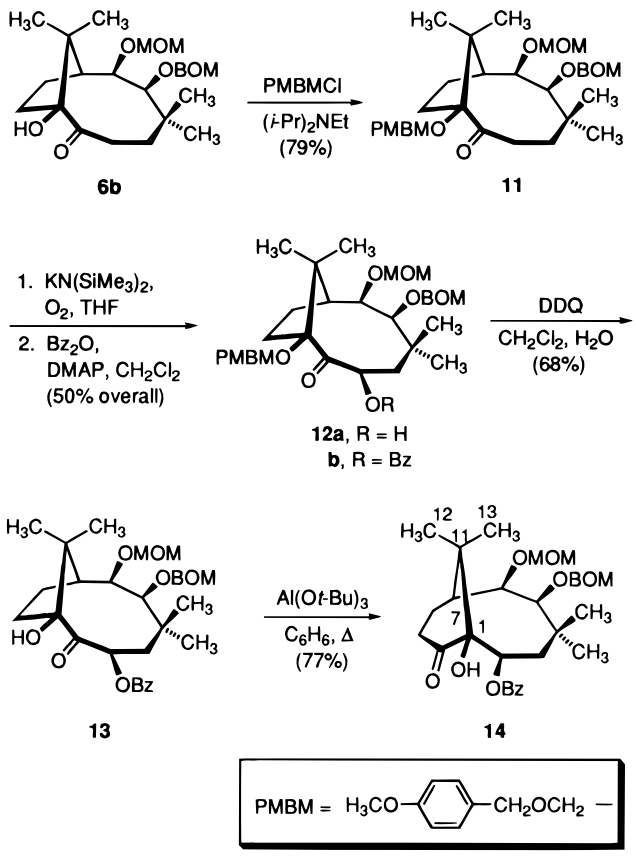


Figure 1. Representative results of NOE measurements. The data shown are for **4c** and **13**.

(5) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319.

Scheme 3



formation of the transannular hemiketal **10**. Accordingly, we returned to the deployment of alternative hydroxyl protection schemes where these complications would not surface.

Arrival at the Targeted α-Ketol. The previously described MOM-protected ketone **1b**[3d] was transformed by an analogous oxy-anionic Cope pathway to **3b** in highly efficient fashion (96%, Scheme 1). Once hydride reduction had been accomplished, the resultant free hydroxyl in **4c** was transformed into the (benzyloxy)-methyl (BOM) derivative as in **4d** in advance of dihydroxylation and Swern oxidation as before.

For the purposes already mentioned above, it was considered desirable to protect the bridgehead hydroxyl in **6b** with PMBM chloride, particularly in view of the established ready removability of this protective functionality at a more advanced stage. Indeed, arrival at **11** lent itself suitably to α-oxygenation and formation of **12b** (Scheme 3). Chemoselective removal of the PMBM group was now realized cleanly without obvious deleterious involvement of the other functionality present. With the circumvention of this earlier problem, the production of **13** was achieved conveniently. The time had now come to assess the workability of the α-ketol rearrangement in the highly oxygenated context found in this bicyclic system.

As a direct outgrowth of our earlier studies,[2b,c] we were well-apprised of the stereoelectronic demands of this 1,2-shift and, more importantly, its total dependence on thermodynamic factors. The first of these issues was facilitated by making recourse to aluminum tri-*tert*-butoxide in order to achieve dual coordination of the Al atom to the neighboring oxygen centers. This alignment adjusts the relative geometry of the C═O group to encourage migration of the dimethyl-substituted methano carbon. While this eventuality is conducive to expediting the conversion of **13** to **14**, it is independent of the question of which isomer is the more stable. In actuality, heating **13** with Al(O*t*-Bu)$_3$ in benzene resulted in unidirectional conversion to **14**. The structural features of **14** were established by semiselective DEPT studies at 300 MHz. Particularly diagnostic was the experiment that involved irradiation of the proton on C-12, which resulted in the appearance of strong ^3J coupling to C-1, C-7, and C-13. Migration of the ethano bridge was thereby excluded. The energy difference is therefore clearly of sufficient magnitude to cause the bicyclo[5.3.1]-undecane form to dominate completely over the bicyclo-[6.2.1]undecane option.

This protocol is consequently seen to be accommodating of our broadly defined goals of producing serviceable precursors to Taxol through implementation of a dual rearrangement pathway. This direct solution to the expeditious construction of the required A/B framework is currently being developed in more advanced tri- and tetracyclic intermediates. The results of these studies will be reported in due course.

Experimental Section

General Methods. Melting points are uncorrected. The column chromatographic separations were performed with Woelm silica gel (230−400 mesh). 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 and ^{13}C NMR. The high-resolution and fast-atom-bombardment spectra were recorded at The Ohio State University Campus Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark or at Atlantic Microlab, Inc., Norcross, GA.

(1*S*,3*R*,4*S*)-3-[(*p*-Methoxybenzyl)oxy]-7,7-dimethyl-1-vinyl-2-norbornanone or (1*S*,3*R*,4*S*)-3-[(*p*-Methoxybenzyl)oxy]-7,7-dimethyl-1-vinylbicyclo[2.2.1]heptan-2-one (1a). To a solution of (1*S*,3*R*,4*S*)-3-hydroxy-7,7-dimethyl-1-vinyl-2-norbornanone[3d] (5.85 g, 32.5 mmol) in ether (100 mL) was added *p*-methoxybenzyl trichloroacetimidate (18.43 g, 65 mmol) followed by camphorsulfonic acid (710 mg, 3.0 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 72 h, quenched with 1 N HCl (50 mL), agitated for 25 min, and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with saturated $NaHCO_3$ solution and H_2O, dried, and evaporated. Chromatography of the residue on silica gel (elution with 15% ethyl acetate in hexanes) gave **1a** (8.67 g, 89%) as a colorless oil: IR (film, cm^{-1}) 1760, 1620, 1520; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 10.5 Hz, 2 H), 7.26 (d, J = 10.6 Hz, 2 H), 5.87 (dd, J = 17.7, 11.1 Hz, 1 H), 5.39 (dd, J = 11.1, 1.6 Hz, 1 H), 5.23 (dd, J = 17.1, 1.6 Hz, 1 H), 4.80 (d, J = 11.5 Hz, 1 H), 4.62 (d, J = 11.5 Hz, 1 H), 3.79 (s, 3 H), 3.50 (s, 1 H), 2.14 (d, J = 4.2 Hz, 1 H), 2.00 (m, 2 H), 1.46 (m, 2 H), 1.13 (s, 3 H), 0.90 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 216.1, 159.2, 131.8, 130.1, 129.3, 119.0, 113.7, 83.2, 72.4, 63.5, 55.2, 48.4, 48.2, 25.1, 24.7, 21.4, 20.1; MS *m*/*z* (M^+) calcd 300.1725, obsd 300.1772; $[\alpha]^{25}_D$ −78.8 (*c* 2.1, $CHCl_3$). Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.94; H, 8.10.

(1*S*,2*R*,7*E*)-2-[(*p*-Methoxybenzyl)oxy]-4,4,11,11-tetramethylbicyclo[6.2.1]undec-7-en-3-one (3a). *n*-Butyllithium (10.7 mL of 1.6 M in hexanes, 17.1 mmol) was added to a solution of 2-bromopropene (1.52 mL, 17.1 mmol) in dry THF (30 mL) at −78 °C. After 75 min of stirring, a solution of **1a** (3.52 g, 11.4 mL) in the same solvent (10 mL) was introduced and the reaction mixture was maintained at −78 °C for 30 min, warmed to −30 °C during 1 h, quenched with saturated $NaHCO_3$ solution, and brought to rt. The separated aqueous phase was extracted with ether, and the combined organic

phases were washed with brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 9:1 hexanes/ethyl acetate) furnished the *exo*-alcohol **2a** (2.74 g, 70%) as a colorless oil: IR (film, cm^{-1}) 3499, 1609, 1515, 1255, 1108; ^1H NMR (300 MHz, C_6D_6) δ 7.16 (d, $J = 9$ Hz, 2 H), 6.77 (m, 3 H), 5.29 (dd, $J = 10$, 1 Hz, 1 H), 5.07 (dd, $J = 16$, 1 Hz, 1 H), 4.87 (s, 2 H), 4.40 (d, $J = 11$ Hz, 1 H), 4.31 (d, $J = 11$ Hz, 1 H), 3.96 (s, 1 H), 3.57 (s, 1 H), 3.34 (s, 3 H), 2.10 (s, 3 H), 1.95 (d, $J = 6$ Hz, 1 H), 1.69 (m, 2 H), 1.55 (s, 3 H), 1.34 (m, 1 H), 0.92 (m, 1 H), 0.85 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 159.6, 150.3, 138.0, 130.0, 129.3, 114.2, 113.9, 109.0, 85.0, 84.4, 72.2, 58.1, 54.5, 51.6, 48.7, 24.4, 24.0, 22.6, 22.3, 21.4; MS *m/z* (M^+) calcd 342.2195, obsd 342.2199; $[\alpha]^{20}_D$ −17.1 (*c* 1.5, $CHCl_3$). Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.16; H, 8.83. Found: C, 77.56; H, 8.99.

Potassium hexamethyldisilazide (51.7 mL of 0.5 M in toluene, 25.9 mmol) was added to the above alcohol (5.90 g, 17.3 mmol) and 18-crown-6 (5.13 g, 20.7 mmol) in dry THF (170 mL) at −78 °C. The mixture was warmed to 0 °C during 1 h, returned to −78 °C, treated with methyl iodide (5.5 mL, 68 mmol), and stirred at that temperature for 1 h prior to being quenched with saturated $NaHCO_3$ solution. The separated aqueous phase was extracted with ether, and the combined organic layers were washed with brine, dried, and evaporated. The residue was purified by chromatography on silica gel (elution with 9:1 hexanes/ethyl acetate) to provide **3a** (6.05 g, 99%) as a colorless oil: IR (film, cm^{-1}) 1697, 1514, 1258, 1091; ^1H NMR (300 MHz, C_6D_6) δ 7.31 (d, $J = 9$ Hz, 2 H), 6.78 (d, $J = 9$ Hz, 2 H), 4.97 (dd, $J = 12$, 4 Hz, 1 H), 4.44 (d, $J = 9$ Hz, 1 H), 3.86 (d, $J = 9$ Hz, 1 H), 3.81 (d, $J = 1$ Hz, 1 H), 3.29 (s, 3 H), 2.46 (dt, $J = 13$, 4 Hz, 1 H), 2.31 (m, 2 H), 2.13 (m, 1 H), 1.95 (m, 3 H), 1.64 (s, 3 H), 1.40 (m, 1 H), 1.20 (m, 1 H), 1.00 (s, 3 H), 0.95 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 214.8, 159.4, 144.4, 131.1, 129.1, 124.4, 113.8, 88.5, 71.1, 56.4, 54.5, 46.2, 46.0, 44.7, 31.6, 26.5, 26.1, 25.5, 23.6, 20.6, 19.2; MS *m/z* (M^+) calcd 356.2351, obsd 356.2344. Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.14; H, 9.00.

(1*E*,6*S*,7*R*,8*S*)-7-[(*p*-Methoxybenzyl)oxy]-6-[(2-methoxyethoxy)methoxy]-5,5,11,11-tetramethylbicyclo[6.2.1]-undec-1-ene (4b). A solution of **3a** (3.07 g, 8.62 mmol) in cold (0 °C), anhydrous ether (130 mL) was treated with lithium aluminum hydride (668 mg, 17.6 mmol), stirred at this temperature for 1 h, quenched with brine (3 mL), and allowed to warm to rt until gas evolution ceased. Anhydrous $MgSO_4$ (6 g) was added, and the white solids were filtered off and washed repeatedly with ethyl acetate. The filtrate was concentrated and the residue was passed down a short silica gel column. The resulting alcohol **4a** was dissolved in DMF (30 mL), and this solution was treated sequentially with diisopropylethylamine (7.3 mL, 41.9 mmol), methoxyethoxymethyl chloride (2.4 mL, 21.3 mmol), and tetra-*n*-butylammonium iodide (3.2 g, 8.7 mmol). This mixture was heated at 60 °C for 4 h, cooled to rt, treated with saturated $NaHCO_3$ solution, and extracted with ether. The combined organic layers were washed with brine, and the residue was subjected to chromatography on silica gel (elution with 15% ethyl acetate in hexanes) to give **4b** (3.15 g, 81%) as a colorless oil: IR (film, cm^{-1}) 1610, 1515; ^1H NMR (300 MHz, C_6D_6) δ 7.20 (d, $J = 7$ Hz, 2 H), 6.78 (d, $J = 7$ Hz, 2 H), 5.71 (br d, $J = 9$ Hz, 1 H), 5.11 (d, $J = 6$ Hz, 1 H), 5.04 (d, $J = 6$ Hz, 1 H), 4.40 (d, $J = 10$ Hz, 1 H), 4.15 (d, $J = 10$ Hz, 1 H), 3.95 (m, 1 H), 3.75 (d, $J = 3$ Hz, 1 H), 3.64 (m, 1 H), 3.44 (m, 2 H), 3.35 (s, 3 H), 3.16 (s, 3 H), 3.12 (m, 1 H), 2.53 (m, 2 H), 2.16 (m, 4 H), 1.80 (s, 3 H), 1.25 (m, 3 H), 1.22 (s, 3 H), 1.20 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 159.3, 142.6, 130.9, 129.1, 119.4, 113.8, 100.4, 93.5, 89.9, 72.0, 71.7, 68.3, 58.4, 54.4, 53.8, 44.4, 40.5, 38.1, 36.7, 26.9, 26.6, 25.9, 24.3, 23.1, 21.1; MS *m/z* (M^+) calcd 446.3033, obsd 446.3056; $[\alpha]^{25}_D$ −109 (*c* 1.4, $CHCl_3$). Anal. Calcd for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48. Found: C, 72.49; H, 9.49.

(1*S*,2*S*,6*S*,7*R*,8*S*)-7-[(*p*-Methoxybenzyl)oxy]-6-[(2-methoxyethoxy)methoxy]-5,5,11,11-tetramethylbicyclo[6.2.1]-undecane-1,2-diol (5a). A solution of **4b** (3.40 g, 7.62 mmol) in pyridine (100 mL) was cooled in a cold water bath while osmium tetraoxide (2.0 g, 7.87 mmol) was added. The black mixture was stirred at rt for 1.5 h, carefully treated with several portions of saturated $NaHSO_3$ solution (total of 130 mL), stirred overnight, and diluted with brine. The product was extracted into ethyl acetate, the combined extracts were washed twice with brine, and the residue obtained after workup was chromatographed on silica gel (elution with 50% ethyl acetate in hexanes). There was isolated 3.4 g (93%) of diol **5a** as a white solid: mp 121−122 °C; IR ($CHCl_3$, cm^{-1}) 3640, 3565, 1620; ^1H NMR (300 MHz, C_6D_6) δ 7.35 (d, $J = 9.0$ Hz, 2 H), 6.84 (d, $J = 9.0$ Hz, 2 H), 4.71 (m, 2 H), 4.62 (m, 2 H), 4.04 (d, $J = 9.0$ Hz, 1 H), 3.89 (s, 1 H), 3.67 (m, 3 H), 3.36 (m, 5 H), 3.16 (s, 3 H), 2.79 (m, 1 H), 2.62 (br s, 1 H), 2.30 (m, 2 H), 1.98 (m, 1 H), 1.67 (m, 3 H), 1.59 (s, 3 H), 1.45 (s, 3 H), 1.40 (m, 3 H), 1.30 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 159.3, 131.4, 129.3, 113.7, 95.8, 87.2, 86.8, 81.6, 74.4, 73.5, 72.0, 67.6, 58.5, 54.5, 50.9, 48.7, 37.4, 35.8, 32.7, 31.1, 27.1, 26.9, 24.6, 22.4, 20.8; MS *m/z* (M^+ − SEMOH) calcd 374.2458, obsd 374.2449; $[\alpha]^{25}_D$ −37.0 (*c* 1.7, $CHCl_3$). Anal. Calcd for $C_{27}H_{44}O_7$: C, 67.47; H, 9.23. Found: C, 67.24; H, 9.25.

(1*S*,6*S*,7*R*,8*S*)-1-Hydroxy-7-[(*p*-methoxybenzyl)oxy]-6-[(2-methoxyethoxy)methoxy]-5,5,11,11-tetramethylbicyclo[6.2.1]undecan-2-one (6a). A solution of dimethyl sulfoxide (0.15 mL, 2.10 mmol) in CH_2Cl_2 (6 mL) cooled to −78 °C was treated with oxalyl chloride (0.13 mL, 1.49 mmol). After 10 min, diol **5a** (216 mg, 0.45 mmol) dissolved in CH_2Cl_2 (3 mL) was introduced, and the mixture was stirred for 15 min before triethylamine (2.5 mL) was added and stirring continued for 15 min at 0 °C. After dilution with ether, the organic phase was washed with brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 40% ethyl acetate in hexanes) provided **6a** (193 mg, 90%) as a colorless oil: IR (film, cm^{-1}) 3480, 1695, 1615, 1520; ^1H NMR (300 MHz, C_6D_6) δ 7.32 (d, $J = 9$ Hz, 2 H), 6.85 (d, $J = 9$ Hz, 2 H), 4.58 (m, 4 H), 4.09 (d, $J = 9$ Hz, 1 H), 3.83 (s, 1 H), 3.57 (m, 2 H), 3.35 (m, 5 H), 3.15 (s, 3 H), 2.82 (m, 1 H), 2.10 (m, 6 H), 1.52 (m, 1 H), 1.39 (s, 3 H), 1.37 (s, 3 H), 1.35 (s, 3 H), 0.99 (m, 1 H), 0.90 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 214.0, 159.6, 131.2, 129.7, 113.9, 96.1, 90.1, 86.6, 81.9, 73.8, 72.3, 67.9, 58.7, 54.7, 51.4, 50.1, 37.9, 34.5, 34.0, 32.0, 30.2, 27.1, 24.4, 22.6, 21.8; MS *m/z* (M^+) calcd 478.2930, obsd 478.2941; $[\alpha]^{25}_D$ −51.0 (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{27}H_{42}O_7$: C, 67.76; H, 8.84. Found: C, 67.48; H, 8.70.

(1*S*,3*R*,6*S*,7*R*,8*S*)-3-Hydroxy-7-[(*p*-methoxybenzyl)oxy]-6-[(2-methoxyethoxy)methoxy]-5,5,11,11-tetramethyl-1-[[2-(trimethylsilyl)ethoxy]methoxy]bicyclo[6.2.1]undecan-2-one Benzoate (7b). To a solution of **6a** (30 mg, 0.063 mmol) in CH_2Cl_2 (0.3 mL) containing diisopropylethylamine (0.3 mL) was added SEMCl (0.2 mL, 1.13 mmol). The reaction mixture was stirred at rt for 24 h, diluted with ethyl acetate, washed with water, and dried. The concentrated residue was purified by chromatography on silica gel (elution with 20% ethyl acetate in hexanes) to deliver the protected α-ketol (30 mg, 79%), which was used directly.

n-Butyllithium (0.12 mL of 2.5 M in hexanes, 0.30 mmol) was added at −78 °C to a solution of diisopropylamine (0.06 mL, 0.43 mmol) in THF (2 mL) under N_2 and stirred in the cold for 1 h prior to addition of the above material (60 mg, 0.20 mmol) dissolved in THF (2 mL). The resulting solution was stirred for 1.5 h at −78 °C, at which point neat chlorotrimethylsilane (0.12 mL, 0.95 mmol) was introduced. After an additional 20 min, the cooling bath was removed and the reaction mixture was allowed to warm to rt, treated with triethylamine (0.5 mL), diluted with ethyl acetate, washed with saturated $NaHCO_3$ solution, dried, and concentrated. The residue was dissolved in CH_2Cl_2 (2 mL), treated with *m*-chloroperbenzoic acid (32 mg, 0.186 mmol) in the presence of sodium bicarbonate (10 mg), stirred at 20 °C for 1.5 h, quenched with saturated $NaHCO_3$ solution, diluted with ethyl acetate, washed with water, and dried. The concentrated residue was taken up in THF (5 mL), treated with a solution of tetra-*n*-butylammonium fluoride in THF (0.8 mL of 1 M, 0.8 mmol), and evaporated to leave an oil, which was dissolved in CH_2Cl_2 (2 mL) and treated with benzoic anhydride (170 mg, 0.75 mmol) in the presence of 4-(dimethylamino)pyridine (50

mg, 0.41 mmol). The resulting solution was stirred overnight, diluted with ethyl acetate, washed with saturated $NaHCO_3$ solution and water, dried, and concentrated. Chromatography of the residue on silica gel (elution with 20% ethyl acetate in hexanes) gave **7b** (38 mg, 53% overall) as a colorless oil: IR (film, cm^{-1}) 1713, 1611, 1513, 1291, 1248, 1091; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, J = 7.2, 1.3 Hz, 2 H), 7.59 (t, J = 7.3 Hz, 1 H), 7.46 (t, J = 7.8 Hz, 2 H), 7.28 (d, J = 8.3 Hz, 2 H), 6.88 (d, J = 8.6 Hz, 2 H), 5.19 (d, J = 5.9 Hz, 1 H), 4.75−4.64 (m, 3 H), 4.59 (d, J = 4.4 Hz, 2 H), 4.52 (d, J = 7.3 Hz, 1 H), 4.08 (d, J = 9.8 Hz, 1 H), 3.88 (s, 1 H), 3.81 (s, 3 H), 3.78−3.62 (m, 2 H), 3.55−3.44 (m, 3 H), 3.36 (s, 3 H), 3.17−3.12 (m, 1 H), 2.86−2.85 (m, 1 H), 2.56−2.49 (m, 2 H), 2.45−2.34 (m, 1 H), 1.95−1.85 (m, 1 H), 1.81 (dd, J = 16.5, 6.5 Hz, 1 H), 1.28 (s, 3 H), 1.26 (s, 3 H), 1.21 (s, 3 H), 1.03 (s, 3 H), 0.99−0.85 (m, 3 H), 0.00 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 207.4, 166.3, 159.1, 133.3, 130.6, 129.8, 129.3, 129.2, 129.1, 128.4, 113.6, 96.7, 95.6, 92.9, 86.3, 81.7, 73.4, 71.7, 70.8, 67.6, 65.4, 59.0, 55.2, 52.8, 50.3, 37.4, 36.7, 34.3, 30.4, 27.1, 23.8, 23.3, 21.6, 18.1, −1.5; FAB MS m/z (M^+) calcd 728.40, obsd 728.50; $[\alpha]^{22}_D$ −8.5 (c 0.25, $CHCl_3$).

(1*S*,3*R*,6*S*,7*R*,8*S*)-3-Hydroxy-7-[(*p*-methoxybenzyl)oxy]-1-[[(*p*-methoxybenzyl)oxy]methoxy]-6-[(2-methoxyethoxy)methoxy]-5,5,11,11-tetramethylbicyclo[6.2.1]undecan-2-one Benzoate (9). Freshly prepared [(*p*-methoxybenzyl)oxy]methyl chloride (0.2 mL, 1.0 mmol) was added to a solution of **6a** (33 mg, 0.069 mmol) in CH_2Cl_2 (0.5 mL) containing tetra-*n*-butylammonium iodide (270 mg, 1.88 mmol) and diisopropylethylamine (0.3 mL, 3.0 mmol). The reaction mixture was stirred at rt for 24 h, quenched with water, and extracted with ethyl acetate. The combined organic layers were washed with water, dried, and concentrated. Purification of the residue by chromatography on silica gel (elution with 40% ethyl acetate in hexanes) gave the protected α-hydroxy ketone (28 mg, 65%), which was used directly.

Oxygen was bubbled through a solution of this material (90 mg, 0.143 mmol) and 18-crown-6 (200 mg, 0.529 mmol) in dry THF (10 mL) for 2 min at −78 °C. Potassium hexamethyldisilazide (0.5 mL of 0.5 M in toluene, 0.25 mmol) was introduced with continued bubbling of oxygen at this temperature for 20 min, followed by triphenylphosphine (240 mg, 0.92 mmol). The reaction mixture was stirred at −78 °C for 20 min, quenched with water, warmed to rt, and extracted with ethyl acetate. The combined organic phases were dried and concentrated to leave a residue that was dissolved in CH_2Cl_2 (5 mL), treated with DMAP (100 mg, 0.819 mmol) and benzoic anhydride (200 mg, 0.885 mmol), stirred at rt for 4 h, quenched with water, and extracted with ethyl acetate. The extracts were washed with water, dried, and concentrated. Purification of the residue by chromatography on silica gel (elution with 30% ethyl acetate in hexanes) gave **9** as a colorless oil (89 mg, 85% overall): IR (film, cm^{-1}) 1712, 1612, 1513, 1248, 1032; ^1H NMR (300 MHz, $CDCl_3$) δ 8.06−8.01 (m, 2 H), 7.59−7.54 (m, 1 H), 7.48−7.40 (m, 2 H), 7.38−7.19 (m, 4 H), 6.89−6.82 (m, 4 H), 5.18 (d, J = 5.6 Hz, 1 H), 4.79−4.64 (m, 5 H), 4.61 (d, J = 5.2 Hz, 3 H), 4.47 (d, J = 11.4 Hz, 1 H), 4.09 (d, J = 9.8 Hz, 1 H), 3.89 (s, 1 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.70−3.66 (m, 2 H), 3.50−3.44 (m, 1 H), 3.36 (s, 3 H), 3.25−3.12 (m, 1 H), 2.91−2.83 (m, 1 H), 2.65−2.27 (m, 3 H), 1.96−1.50 (m, 2 H), 1.30 (s, 6 H), 1.21 (s, 3 H), 1.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 207.3, 166.3, 159.1, 133.3, 130.6, 130.3, 129.8, 129.4, 129.3, 129.1, 128.3, 113.7, 113.6, 96.9, 95.6, 92.7, 86.3, 81.7, 73.4, 71.7 70.8, 69.6, 67.6, 59.0, 55.2, 52.8, 50.3, 37.4, 36.7, 34.4, 30.5, 27.1, 23.7, 23.3, 21.6; MS molecular ion too fleeting for accurate measurement; $[\alpha]^{22}_D$ −42.7 (c 0.06, $CHCl_3$).

(1*R*,2*S*,5*S*,6*R*,7*S*,10*R*)-7-[(*p*-Methoxyethoxy)methoxy]-8,8,12,12-tetramethyl-11-oxatricyclo[4.4.1.1^{2,5}]dodecane-1,2,10-triol Benzoate (10). DDQ (25 mg, 0.110 mmol) was added to a mixture of **9** (17 mg, 0.023 mmol) in CH_2Cl_2 (4 mL) and water (0.2 mL). The resulting suspension was stirred at rt for 5 h, quenched with saturated sodium bisulfite solution, and extracted with ether. The combined organic layers were washed with saturated sodium bicarbonate solution and water, dried, and concentrated. Chromatography of the residue on silica gel (elution with 40% ethyl acetate in hexanes) gave **10** (7.7 mg, 72%) as a colorless oil: IR (film, cm^{-1}) 3450, 1717, 1281, 1011; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09−8.06 (m, 2 H), 7.62−7.52 (m, 1 H), 7.49−7.44 (m, 2 H), 5.45−5.43 (m, 1 H), 4.75 (d, J = 7.2 Hz, 1 H), 4.66 (d, J = 7.2 Hz, 1 H), 4.49 (dd, J = 8.1, 1.8 Hz, 1 H), 3.97 (s, 1 H), 3.80−3.71 (m, 1 H), 3.69−3.64 (m, 1 H), 3.59−3.52 (m, 3 H), 3.39 (s, 3 H), 2.27−2.21 (m, 1 H), 1.98−1.60 (m, 4 H), 1.40 (s, 3 H), 1.31 (s, 3 H), 1.26−1.08 (m, 3 H), 1.04 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 165.0, 133.4, 129.8, 128.5, 101.5, 96.7, 86.4, 81.7, 80.0, 71.7, 67.4, 59.0, 46.1, 43.6, 40.1, 39.1, 32.3, 30.3, 28.3, 23.6, 22.5, 20.4, 19.4; MS m/z (M^+) calcd 462.2617, obsd 462.2625; $[\alpha]^{22}_D$ −40.0 (c 0.01, $CHCl_3$).

(1*S*,2*S*,3*R*,4*S*)-2-Isopropenyl-3-(methoxymethoxy)-7,7-dimethyl-1-vinylbicyclo[2.2.1]heptan-2-ol (2b). A solution of *tert*-butyllthium in pentane (20 mL of 1.7 M, 34 mmol) was added to 2-bromopropene (2.07 g, 17.1 mmol) dissolved in cold (−78 °C), dry THF (25 mL) under N_2. After 20 min at that temperature, a solution of **1b**[3d] (2.74 g, 12.2 mmol) in dry THF (10 mL) was introduced and the reaction mixture was stirred at −78 °C for 30 min, allowed to warm slowly to rt, quenched with water, and extracted with ether. The combined extracts were washed with water, dried, and concentrated in advance of chromatographic purification on silica gel (elution with 5% ethyl acetate in hexanes). There was obtained 2.7 g (84%) of **2b** as a colorless oil: IR (film, cm^{-1}) 3528, 1635, 1458, 1388, 1370, 1280; ^1H NMR (300 MHz, $CDCl_3$) δ 6.36−6.26 (m, 1 H), 5.15−5.10 (m, 1 H), 4.98−4.90 (m, 1 H), 4.87 (s, 1 H), 4.76 (s, 1 H), 4.71−4.62 (m, 2 H), 4.09 (s, 3 H), 3.33 (d, J = 1.8 Hz, 3 H), 3.20 (d, J = 1.8 Hz, 1 H), 1.89 (d, J = 3.4 Hz, 1 H), 1.75 (s, 3 H), 1.69 (d, J = 8.7 Hz, 2 H), 1.19 (s, 3 H), 1.17−0.98 (m, 2 H), 0.69 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 149.6, 137.3, 114.4, 109.5, 96.4, 84.8, 83.6, 57.7, 55.4, 51.4, 49.7, 24.2, 23.9, 22.3, 21.9, 21.2; MS m/z (M^+) calcd 266.1882, obsd 266.1877; $[\alpha]^{22}_D$ −12.8 (c 1.5, $CHCl_3$).

(1*S*,2*R*,7*E*)-2-(Methoxymethoxy)-4,4,11,11-tetramethylbicyclo[6.2.1]undec-7-en-3-one (3b). A solution of potassium hexamethyldisilazide in THF (36.8 mL of 0.5 M, 18.4 mmol) was added to a solution of **2b** (2.45 g, 9.21 mmol) and 18-crown-6 (3.5 g, 13.2 mmol) in dry THF (100 mL) at −78 °C under N_2. The reaction mixture was stirred at −78 °C for 15 min, warmed to 9 °C for 15 min, returned to −78 °C, and treated with methyl iodide (3 mL, 48 mmol). After an additional hour at this temperature, water was introduced and the product was extracted into ether after arrival at rt. The combined ethereal solutions were washed with water, dried, and concentrated to leave a residue, chromatography of which on silica gel (elution with 10% ethyl acetate in hexanes) provided 2.36 g (96%) of **3b** as a colorless oil: IR (film, cm^{-1}) 1688, 1472, 1461, 1390, 1144; ^1H NMR (300 MHz, $CDCl_3$) δ 4.82−4.78 (m, 1 H), 4.52 (d, J = 7.0 Hz, 1 H), 4.29 (d, J = 7.0 Hz, 1 H), 4.13 (d, J = 1.0 Hz, 1 H), 3.28 (s, 3 H), 2.54−2.50 (m, 1 H), 2.37−2.24 (m, 3 H), 2.17−2.14 (m, 2 H), 2.06−2.01 (m, 1 H), 1.74−1.65 (m, 1 H), 1.44−1.39 (m, 1 H), 1.28 (s, 3 H), 1.19 (s, 3 H), 1.06 (s, 3 H), 0.98 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 216.2, 144.2, 124.2, 94.7, 84.3, 55.8, 55.4, 46.3, 45.9, 44.5, 31.6, 26.4, 26.2, 25.2, 23.4, 20.7, 18.6; MS m/z (M^+) calcd 280.2038, obsd 280.2051; $[\alpha]^{22}_D$ −112.3 (c 1.1, $CHCl_3$).

(1*S*,2*R*,3*S*,7*E*)-2-(Methoxymethoxy)-4,4,11,11-tetramethylbicyclo[6.2.1]undec-7-en-3-ol (4c). Lithium aluminum hydride (645 mg, 17.0 mmol) was added to a solution of **3b** (2.26 g, 8.07 mmol) in ether (130 mL) at 0 °C under N_2. The resulting suspension was stirred in the cold for 1 h, quenched with water (3 mL), dried, and concentrated to give **4c** as a colorless oil (2.10 g, 93%): IR (film, cm^{-1}) 3496, 1462, 1386, 1280; ^1H NMR (300 MHz, $CDCl_3$) δ 5.31−5.26 (m, 1 H), 4.70 (d, J = 6.9 Hz, 1 H), 4.59 (d, J = 6.9 Hz, 1 H), 3.81−3.78 (m, 1 H), 3.38 (s, 3 H), 3.36−3.31 (m, 1 H), 2.74 (d, J = 2.8 Hz, 1 H), 2.58−2.50 (m, 1 H), 2.36−2.27 (m, 1 H), 2.13−1.91 (m, 5 H), 1.38 (s, 3 H), 1.36−1.13 (m, 2 H), 1.09 (s, 3 H), 1.06 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 142.8, 119.1, 96.2, 88.0, 84.7, 55.8, 54.7, 43.9, 38.2, 38.1, 37.6, 26.5, 25.7, 23.4, 23.1, 21.5; MS m/z (M^+) calcd 282.2194, obsd 282.2193; $[\alpha]^{22}_D$ −61.5 (c 0.3, $CHCl_3$).

(1*E*,6*S*,7*R*,8*S*)-6-[(Benzyloxy)methoxy]-7-(methoxymethoxy)-5,5,11,11-tetramethylbicyclo[6.2.1]undec-1-

ene (4d). Alcohol **4c** (500 mg, 0.604 mmol) was dissolved in DMF (5 mL) containing diisopropylethylamine (2 mL). The resulting solution was treated with tetra-*n*-butylammonium iodide (440 mg, 1.19 mmol) and benzyl chloromethyl ether (184 mg, 1.18 mmol), stirred at rt for 1 h and at 60 °C for 30 min, returned to rt, quenched with saturated $NaHCO_3$ solution, and extracted with ether. The combined extracts were washed with water, dried, and concentrated. Chromatography of the residue on silica gel (elution with 5% ethyl acetate in hexanes) gave **4d** as a colorless oil (520 mg 73%): IR (film, cm^{-1}) 1475, 1146, 1089, 1039; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.27 (m, 5 H), 5.41−5.36 (m, 1 H), 5.03 (d, J = 6.6 Hz, 1 H), 4.86−4.83 (m, 2 H), 4.63−4.55 (m, 2 H), 4.54 (d, J = 6.9 Hz, 1 H), 3.67 (d, J = 3.7 Hz, 1 H), 3.47−3.40 (m, 1 H), 3.37 (s, 3 H), 2.57−2.51 (m, 1 H), 2.41−2.35 (m, 1 H), 2.14−1.95 (m, 4 H), 1.45 (s, 3 H), 1.44−1.32 (m, 1 H), 1.29−1.21 (m, 1 H), 1.13 (s, 3 H), 1.10 (s, 3H), 1.08−1.03 (m, 1 H), 0.94 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 143.1, 138.2, 128.3, 127.8, 127.5, 119.2, 99.1, 95.8, 94.4, 87.9, 70.6, 56.0, 54.8, 44.2, 39.6, 38.3, 36.9, 26.9, 26.4, 25.6, 24.5, 23.5, 20.7; MS m/z (M^+) calcd 402.2770, obsd 402.2742; $[\alpha]^{22}_D$ −93.0 (*c* 0.3, $CHCl_3$).

(1*S*,2*S*,6*S*,7*R*,8*S*)-6-[(Benzyloxy)methoxy]-7-(methoxymethoxy)-5,5,11,11-tetramethylbicyclo[6.2.1]undecane-1,2-diol (5b). A solution of **4d** (350 mg, 0.91 mmol) in pyridine (10 mL) was treated with osmium tetraoxide (270 mg, 1.06 mmol) in pyridine (3 mL) at 0 °C. The reaction mixture was stirred in the cold for 40 min, treated with a solution of sodium dithionite (2.3 g, 13.2 mmol) in water, stirred for an additional 12 h, and extracted with ether. The combined organic extracts were washed with water, dried, and concentrated in advance of chromatographic purification on silica gel (elution with 40% ethyl acetate in hexanes). There was isolated 345 mg (87%) of **5b** as a colorless oil: IR (film, cm^{-1}) 3452, 1477, 1454, 1385, 1360, 1150; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.27 (m, 5 H), 4.75 (d, J = 7.1 Hz, 2 H), 4.64−4.54 (m, 4 H), 4.22 (d, J = 9.6 Hz, 1 H), 3.77 (s, 1 H), 3.59 (d, J = 10.1 Hz, 1 H), 3.37 (s, 3 H), 2.90−2.85 (br, 1 H), 2.79−2.70 (m, 1 H), 2.55−2.45 (br, 1 H), 2.26−2.18 (m, 1 H), 2.03−1.90 (m, 2 H), 1.62−1.46 (m, 3 H), 1.36−1.33 (m, 1 H), 1.29 (s, 3 H), 1.25−1.22 (m, 1 H), 1.11 (s, 3 H), 1.03 (s, 3 H), 0.90 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 137.7, 128.3, 127.7, 127.5, 95.8, 94.9, 87.1, 83.4, 81.4, 74.1, 69.9, 55.7, 50.9, 48.6, 37.1, 35.7, 32.4, 30.9, 26.8, 26.3, 24.1, 22.1, 20.2; MS m/z (M^+ − MOMH − BOMH) calcd 236.1824, obsd 236.1803; $[\alpha]^{22}_D$ −6.9 (*c* 0.5, $CHCl_3$).

(1*S*,6*S*,7*R*,8*S*)-6-[(Benzyloxy)methoxy]-1-hydroxy-7-(methoxymethoxy)-5,5,11,11-tetramethylbicyclo[6.2.1]undecan-2-one (6b). Oxalyl chloride (0.27 mL, 3.09 mmol) was added to a solution of DMSO (0.31 mL, 4.37 mmol) in CH_2Cl_2 (10 mL) under N_2 at −78 °C and stirred for 15 min prior to the introduction of **5b** (390 mg, 0.93 mmol) dissolved in CH_2Cl_2 (5 mL). After 15 min, triethylamine (5 mL) was added and the mixture was warmed to 0 °C, subsequently quenched with water, and extracted with ether. The combined organic extracts were washed with water, dried, and concentrated, making possible chromatographic purification on silica gel (elution with 40% ethyl acetate in hexanes) to give 301 mg (77%) of **6b**, a colorless oil: IR (film, cm^{-1}) 3456, 1694, 1152, 1091; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.28 (m, 5 H), 4.84 (d, J = 7.3 Hz, 1 H), 4.80 (d, J = 6.5 Hz, 1 H), 4.73 (d, J = 7.2 Hz, 1 H), 4.67 (s, 2 H), 4.62 (d, J = 6.5 Hz, 1 H), 4.42 (d, J = 9.8 Hz, 1 H), 4.11 (s, 1 H), 3.93 (s, 1 H), 3.42 (s, 3 H), 2.99−2.91 (m, 1 H), 2.48−2.42 (m, 1 H), 2.35−2.21 (m, 2 H), 2.19−2.00 (m, 3 H), 1.80−1.73 (m, 1 H), 1.65−1.56 (m, 1 H), 1.17 (s, 3 H), 1.12 (s, 6 H), 0.98 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 214.5, 137.7, 128.4, 127.8, 127.7, 95.8, 95.0, 89.8, 82.8, 81.6, 70.1, 55.8, 51.1, 50.1, 37.5, 34.1, 33.5, 31.6, 29.9, 27.1, 23.8, 22.4, 21.1; MS m/z (M^+ − CH_3OH) calcd 402.2406, obsd 402.2384; $[\alpha]^{22}_D$ −28.2 (*c* 0.30, $CHCl_3$).

(1*S*,3*R*,6*S*,7*R*,8*S*)-6-[(Benzyloxy)methoxy]-3-hydroxy-1-[[(*p*-methoxybenzyl)oxy]methoxy]-7-(methoxymethoxy)-5,5,11,11-tetramethylbicyclo[6.2.1]undecan-2-one Benzoate (12b). Alcohol **6b** (250 mg, 0.59 mmol) was dissolved in CH_2Cl_2 (3 mL) containing diisopropylethylamine (1.5 mL) and treated sequentially with tetra-*n*-butylammonium iodide (1.2 g, 17.4 mmol) and freshly prepared *p*-methoxybenzyl chloromethyl ether (0.5 mL, ∼2.6 mmol). The resulting mixture was stirred at rt for 24 h, quenched with saturated $NaHCO_3$ solution, and extracted with ethyl acetate. The combined extracts were washed with water, dried, and concentrated. Chromatography (silica gel, elution with 40% ethyl acetate in hexanes) gave **11** (205 mg, 61%) as an oily mixture of atropisomers, which was used directly.

Oxygen was bubbled through a solution of **11** (25 mg, 0.043 mmol) and 18-crown-6 (40 mg, 0.15 mmol) in THF at 0 °C for 1 min prior to the introduction of potassium hexamethyldisilazide (0.4 mL of 0.5 M in toluene, 0.2 mmol). This mixture was stirred at 0 °C with continued bubbling of oxygen, treated with triphenylphosphine (40 mg, 0.15 mmol), quenched 10 min later with water, and extracted with ethyl acetate. The combined extracts were washed with water, dried, and concentrated. The residue was taken up in CH_2Cl_2 (0.5 mL), treated with DMAP (10 mg, 0.08 mmol) and benzoic anhydride (15 mg, 0.066 mmol), stirred for 2 h, quenched with saturated $NaHCO_3$ solution, and extracted with ethyl acetate. The combined organic layers were processed in the usual way (SiO_2, elution with 20% ethyl acetate in hexanes) to deliver **12b** as a colorless oil (15 mg, 50%): IR (film, cm^{-1}) 1712, 1248, 1099, 1026; ^1H NMR (300 MHz, $CDCl_3$) δ 8.11−8.02 (m, 2 H), 7.60−7.54 (m, 1 H), 7.49−7.41 (m, 2 H), 7.37−7.30 (m, 5 H), 7.29−7.24 (m, 2 H), 6.87−6.83 (m, 2 H), 5.29 (d, J = 5.7 Hz, 1 H), 4.85−4.59 (m, 9 H), 4.48−4.43 (m, 2 H), 3.93 (s, 1 H), 3.79 (s, 3 H), 3.45 (s, 3 H), 3.21−3.14 (m, 1 H), 2.97−2.91 (m, 1 H), 2.60−2.32 (m, 3 H), 1.92−1.79 (m, 2 H), 1.31 (s, 3 H), 1.30 (s, 3 H), 1.19 (s, 3 H), 1.06 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 207.3, 166.3, 159.1, 137.6, 133.3, 130.3, 129.8, 129.4, 129.1, 128.4, 127.7, 113.7, 96.8, 95.9, 95.0, 92.7, 82.9, 81.8, 70.7, 70.1, 69.6, 56.0, 55.2, 52.8, 50.6, 37.4, 36.6, 34.5, 30.5, 27.1, 23.6, 23.3, 21.4; MS molecular ion too fleeting for accurate measurement; $[\alpha]^{22}_D$ −54.2 (*c* 0.15, $CHCl_3$).

(1*S*,3*R*,6*S*,7*R*,8*S*)-6-[(Benzyloxy)methoxy]-1,3-dihydroxy-7-(methoxymethoxy)-5,5,11,11-tetramethylbicyclo[6.2.1]undecane-2-one 3-Benzoate (13). DDQ (72 mg, 0.32 mmol) was added to a mixture of **12b** (56 mg, 0.080 mmol), CH_2Cl_2 (8 mL), and water (0.4 mL), stirred at rt for 5 h, treated with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic phases were washed with water, dried, and concentrated. Chromatography of the residue on silica gel (elution with 10% ethyl acetate in hexanes) gave **13** as a colorless oil (30 mg, 68%): IR (film, cm^{-1}) 3477, 1705, 1600, 1289, 1260, 1159; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04−7.97 (m, 2 H), 7.53−7.48 (m, 1 H), 7.45−7.30 (m, 2 H), 7.29−7.26 (m, 5 H), 5.33 (d, J = 5.6 Hz, 1 H), 4.77−4.70 (m, 2 H), 4.66 (d, J = 7.2 Hz, 1 H), 4.62−4.50 (m, 2 H), 4.38 (d, J = 9.9 Hz, 1 H), 3.97 (s, 1 H), 3.89 (s, 1 H), 3.36 (s, 3 H), 2.95−2.83 (m, 2 H), 2.52 (d, J = 16.2 Hz, 1 H), 2.29−1.96 (m, 2 H), 1.83−1.71 (m, 2 H), 1.16 (s, 3 H), 1.13 (s, 3 H), 1.12 (s, 3 H), 0.98 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 210.3, 166.1, 137.6, 133.4, 129.8, 129.0, 128.4, 127.7, 95.9, 95.1, 90.1, 82.8, 81.7, 70.4, 70.1, 55.9, 51.5, 50.2, 36.9, 36.7, 34.7, 33.3, 26.9, 23.5, 22.2, 20.7; MS molecular ion too fleeting for accurate measurement; $[\alpha]^{22}_D$ +5.2 (*c* 0.34, $CHCl_3$).

(1*S*,2*R*,3*S*,6*R*,7*S*)-3-[(Benzyloxy)methoxy]-6,7-dihydroxy-2-(methoxymethoxy)-4,4,11,11-tetramethylbicyclo[5.3.1]undecan-8-one 6-Benzoate (14). A mixture of **13** (13 mg, 0.023 mmol) and aluminum tri-*tert*-butoxide (23 mg, 0.093 mmol) in benzene (1 mL) was refluxed for 2 h, cooled to rt, treated with 1 N HCl solution (2 mL), and extracted with ethyl acetate. The combined organic extracts were washed with saturated $NaHCO_3$ solution and water, dried, and concentrated. Chromatography of the residue on silica gel (elution with 15% ethyl acetate in hexanes) afforded **14** (10 mg, 77%) as a colorless oil: IR (film, cm^{-1}) 3490, 1713, 1273, 1108; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 7.2 Hz, 2 H), 7.57−7.52 (m, 1 H), 7.44−7.36 (m, 2 H), 7.35−7.27 (m, 5 H), 5.71 (d, J = 8.1 Hz, 1 H), 5.06 (d, J = 6.6 Hz, 1 H), 4.83−4.79 (m, 2 H), 4.69−4.61 (m, 3 H), 4.31 (d, J = 8.7 Hz, 1 H), 3.85 (s, 1 H), 3.81 (s, 1 H), 3.44 (s, 3 H), 3.25−2.98 (m, 2 H), 2.50−2.48 (m, 1 H), 2.23−2.12 (m, 2 H), 1.98−1.95 (m, 1 H), 1.62 (s, 3 H), 1.58 (s, 1 H), 1.28 (s, 3 H), 1.14 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.2, 164.8, 137.9, 133.2, 129.8, 129.4,

128.3, 127.8, 127.6, 96.4, 96.1, 86.8, 82.5, 80.8, 71.7, 70.2, 56.5, 47.5, 42.5, 41.2, 37.6, 33.3, 30.2, 29.4, 28.9, 25.2, 25.0; MS *m*/*z* (M^+ − OBOM) calcd 417.2277, obsd 417.2303; $[\alpha]^{22}_D$ +84.8 (*c* 0.07, $CHCl_3$).

Acknowledgment. We thank the National Cancer Institute for their generous support of this research by means of Grant CA 63344.

Supporting Information Available: Copies of the high-field ^1H NMR and ^{13}C NMR spectra of all new compounds not accompanied by elemental analyses (23 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.

JO971592F