An Abbreviated, Highly Stereocontrolled Route to Precursors of Taxol. Elaboration of a Fully Functionalized C Ring by Means of Intramolecular Aldol Cyclization

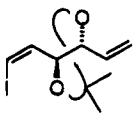
Leo A. Paquette,* Francis J. Montgomery, and Ting-Zhong Wang

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

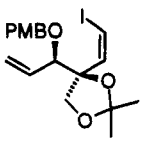
Received July 25, 1995[⊗]

The asymmetric synthesis of an advanced taxol precursor is reported. The scheme involves the conversion of (*R*)-glyceraldehyde acetonide into the (*Z*)-vinyl iodide **2**, transmetalation of this intermediate, and 1,2-addition to the D-camphor derivative **11** from the endo direction. This convergent coupling gives rise to exo alcohol **12**, which undergoes anionic oxy-Cope rearrangement at low temperatures. In situ methylation of the resulting enolate anion delivers **13**, which is chemoselectively transformed into aldehyde **18**. In a key step, the aldol cyclization of **18** proceeds without β-elimination to deliver a tricyclic product in which proper absolute configuration is adopted at the two stereogenic centers being newly introduced. Following protection of the hydroxyl substituent as in **19b**, the α-hydroxy ketone **21** is heated with aluminum tri-*tert*-butoxide in benzene in order to effect near-quantitative rearrangement to the taxol-like isomer **22**.

The development of an expedient total synthesis of taxol is a central focus of current research in this laboratory. As detailed in the preceding paper,[1] the sequential adaptation of anionic oxy-Cope and α-ketol rearrangements constitutes an effective means for the rapid elaboration of rings A and B in their proper absolute configuration. The C ring can be constructed from suitably substituted cyclohexenyl anions,[2] but the resultant cis B/C ring fusion necessitates the implementation of additional steps to set the natural trans stereochemistry. Maneuvers of this type can be completely bypassed if an acyclic *Z* vinyl iodide such as **1** is utilized.[1] Due principally to the presence in **1** of an acetal substructure, complications arise subsequent to its convergent coupling with a derivative of D-camphor. Reductive cleavage and β-elimination of the acetonide operate at inopportune times. Also, inadequate provision has been made for direct ultimate incorporation of the requisite oxetane ring with minimal fanfare.



1



2

This first effort has led us to consider **2** as a second-generation vinyl iodide. As will be detailed herein, **2** is readily available in enantiopure condition from inexpensive D-glyceraldehyde acetonide and enters readily without degradation into the key [3,3] sigmatropic and 1,2-Wagner–Meerwein transpositions. Further, the substitution plan in **2** is fully compatible with those reactions that culminate in assembly of a C ring optimally functionalized for arrival at taxol.

Results and Discussion

Preparation of Vinyl Iodide 2. In 1978, Depezay and Le Merrer reported that the anion produced by halogen–metal exchange of 3,3-diethoxy-2-bromo-2-propene (**3**)[3] with *n*-butyllithium in THF reacts with enantiomerically pure **4** at −70 °C to give the diastereomeric alcohols **5a** and **5b** in a 7:3 ratio (Scheme 1).[4] More recently, Su and Tamm carried out the same coupling with (*S*)-glyceraldehyde acetonide and realized an identical product distribution.[5] Since **5a** was the diastereomer of interest, we were delighted to find that a simple change to ether as solvent furnished **5a** in excess of 10:1 over **5b**. With this product ratio, no attempt was made to remove the **5b** at this stage. As the synthesis advanced, the major component was progressively enriched to the point where no contaminant was discernible.

Subsequent oxidation with *tert*-butyl hydroperoxide and vanadyl acetylacetonate cleanly afforded the epoxide **6a**,[6] which was converted to its *p*-methoxybenzyl ether and transformed into the stereochemically homogeneous diol **7** when heated with KOH in aqueous DMSO. Following straightforward cyclization to **8**, iodide **9** was formed by the Garegg–Samuelson protocol.[7] The production of **8** and **9** as anomeric mixtures is of no long-range consequence since the ensuing reductive cleavage of **9** with zinc in refluxing methanol[8] leads to the formation of aldehyde **10** with destruction of this stereogenic center.

[⊗] Abstract published in *Advance ACS Abstracts,* November 1, 1995.

(1) Paquette, L. A.; Bailey, S. *J. Org. Chem.* **1995**, *60*, 7849.

(2) (a) Paquette, L. A.; Combrink, K. D.; Elmore, S. W.; Rogers, R. D. *J. Am. Chem. Soc.* **1991**, *113*, 1335. (b) Paquette, L. A.; Elmore, S. W.; Combrink, K. D.; Hickey, E. R.; Rogers, R. D. *Helv. Chim. Acta* **1992**, *75*, 1755. (c) Paquette, L. A.; Combrink, K. D.; Elmore, S. W.; Zhao, M. *Helv. Chim. Acta* **1992**, *75*, 1772. (d) Elmore, S. W.; Paquette, L. A. *J. Org. Chem.* **1993**, *58*, 4963. (e) Paquette, L. A.; Thompson, R. C. *J. Org. Chem.* **1993**, *58*, 4952. (f) Paquette, L. A.; Huber, S. K.; Thompson, R. C. *J. Org. Chem.* **1993**, *58*, 6874. (g) Su, Z.; Paquette, L. A. *J. Org. Chem.* **1995**, *60*, 764. (h) Elmore, S. W.; Paquette, L. A. *J. Org. Chem.* **1995**, *60*, 889. (i) Paquette, L. A.; Su, Z.; Bailey, S.; Montgomery, F. J. *J. Org. Chem.* **1995**, *60*, 897.

(3) Smith, A. B., III; Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M., Jr.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 1505.

(4) (a) Depezay, J.-C.; Le Merrer, Y. *Tetrahedron Lett.* **1978**, 2865. (b) Depezay, J.-C.; Le Merrer, Y. *Carbohydr. Res.* **1980**, *83*, 51.

(5) Su, Z.; Tamm, C. *Helv. Chim. Acta* **1995**, *78*, 1278. *Tetrahedron*, in press.

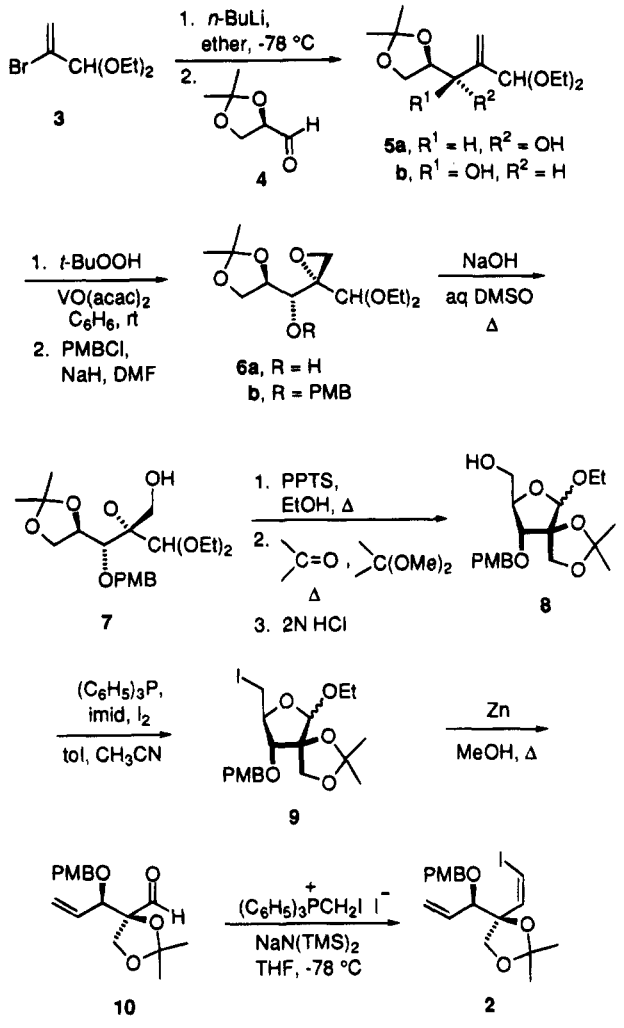
(6) Depezay, J.-C.; Duréault, A. *Tetrahedron Lett.* **1978**, 2869.

(7) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866. For a more recent application, see Corbett, D. F.; Dean, D. K.; Robinson, S. R. *Tetrahedron Lett.* **1993**, *34*, 1525.

(8) (a) Gallos, J. K.; Goga, E. G.; Koumbis, A. E. *J. Chem. Soc., Perkin Trans. 1* **1994**, 613. (b) Gallos, J. K.; Koftis, T. V.; Koumbis A. E. *J. Chem. Soc., Perkin Trans. 1* **1994**, 611.

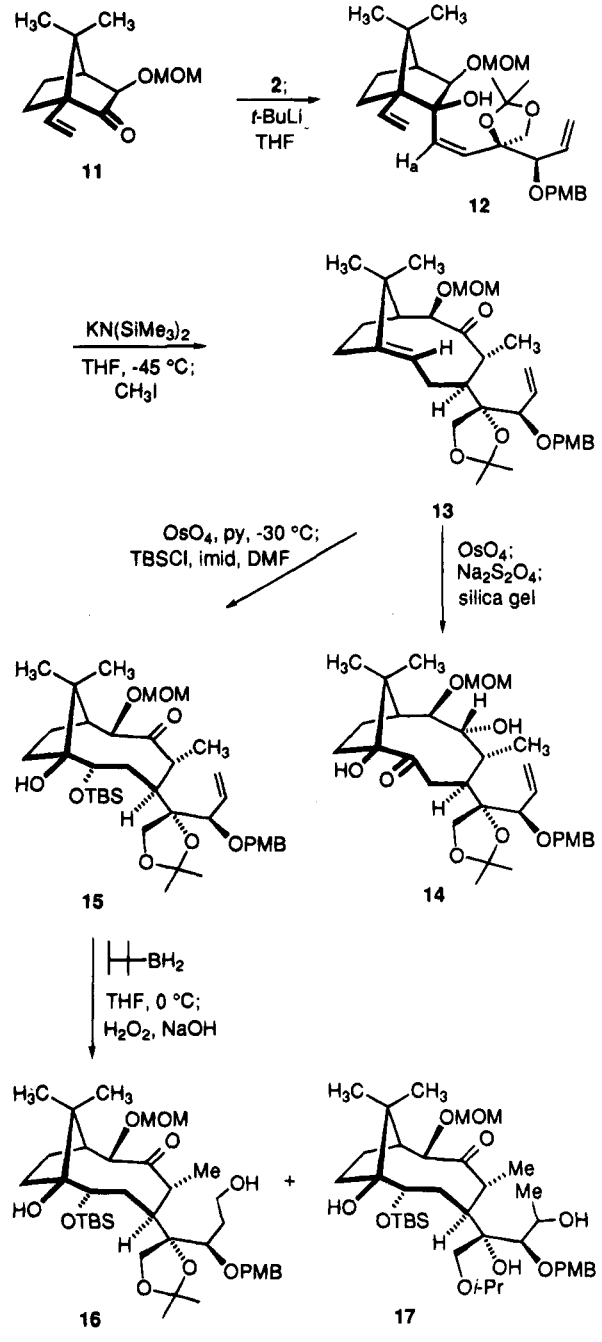
0022-3263/95/1960-7857$09.00/0

Scheme 1



With arrival at **10**, the stringent requirement to produce the homologated *Z* vinyl iodide **2** was met as before[1] by Wittig condensation with (iodomethylene)-triphenylphosphorane.[9] The ^{1}H NMR spectrum of **2** in C_6D_6 at 300 MHz revealed the coupling constant between the two protons isolated in the iodoethylene fragment to be 8.8 Hz, clearly consistent with the *J* value expected for this isomer. The *E* isomer of **2**, produced in minor amounts during the olefination process, features a coupling constant of 14.4 Hz between these same protons. Halogen–metal exchange of **2** proceeded efficiently with *tert*-butyllithium in THF. The resultant vinyl organometallic was treated with ketone **11**, and alcohol **12** was produced in 70% overall yield (Scheme 2). The identity of **12** was determined by double irradiation of the vinyl proton doublet (J_{cis} = 13.4 Hz) due to H_a at δ 5.62 (in C_6D_6), which led to signal enhancement of the two nearest endo protons attached to the norbornyl framework and located at δ 3.29 (5.2%) and δ 2.19–2.08 (5.8%). In addition, the couping of (*E*)-**2** to **11** produced the distinctively different trans carbinol (J_{trans} = 15.5 Hz). The endo trajectory followed in the course of this 1,2-addition was expected to render this intermediate susceptible to anionically driven oxy-Cope rearrangement via an endo-chair transition state arrangement.[10] In fact, subjection of **12** to the action of potassium hexamethyldisilazide in

Scheme 2

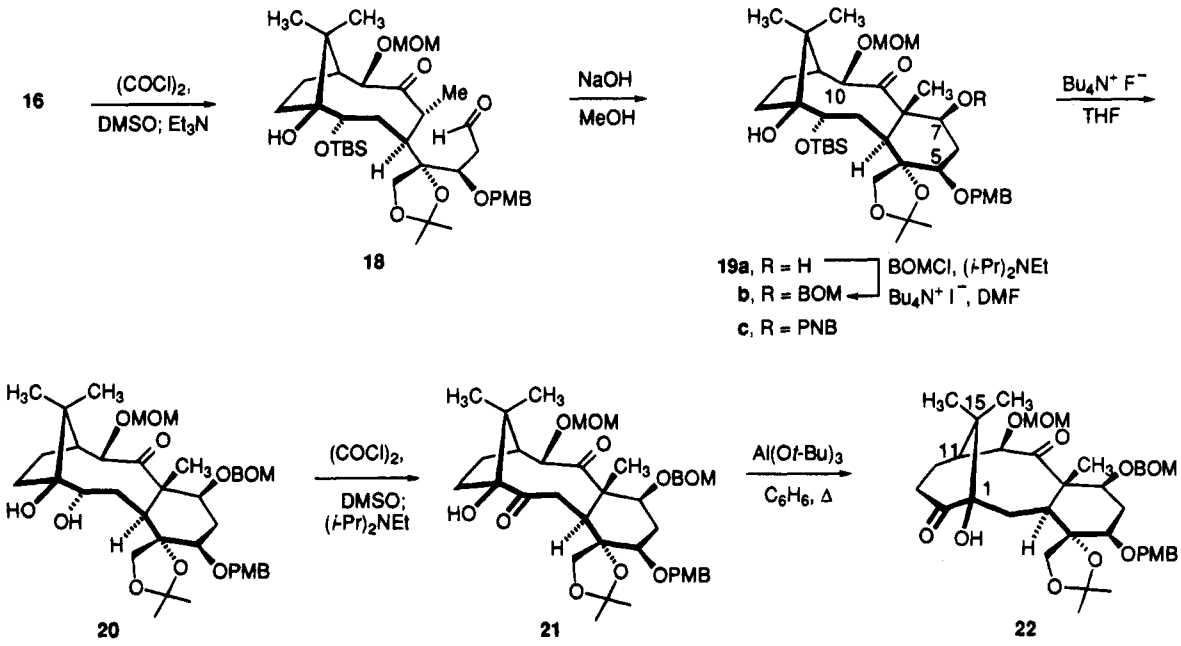


THF containing 18-crown-6 prompted the [3,3] sigmatropic event to occur very rapidly, even at −45 °C. When the enolate anion regiospecifically generated in this manner was treated with methyl iodide in advance of workup, direct conversion to **13** occurred efficiently (91%). NMR studies including detailed NOE analysis confirmed that methylation had indeed been realized on the less sterically congested α surface of the structure syn to the adjoining tertiary proton.

The feasibility of dihydroxylating **13** selectively at its bridgehead olefin site was next addressed. When the osmate ester was hydrolyzed with sodium dithionite and purification was effected by chromatography on silica gel, the rearranged keto diol **14** was isolated. Evidently, a suprafacial transannular hydride shift had taken place when the initially-formed product was adsorbed on the column. In order to circumvent this undesirable reaction, **13** was osmylated instead in pyridine and treated directly

(9) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173.
(10) Paquette, L. A.; Pegg, N. A.; Toops, D.; Maynard, G. D.; Rogers, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 277.

Scheme 3



with *tert*-butyldimethylsilyl chloride following dithionite hydrolysis. Silyl protection of the secondary alcohol in this manner permitted **15** (71%) to be obtained without difficulty.

The distinction between **14** and **15** is easily recognized by ^{1}H NMR. The characteristic narrow doublet (J = 1.6 Hz) for the proton geminal to the MOM group in **13** which appears at δ 3.97 (in $CDCl_3$) is closely mirrored in the spectrum of **15** (s, δ 4.17). For **14**, the additional neighboring proton causes the multiplicity of the C(*H*)-OMOM signal to become a widely-spaced doublet (J = 8.2 Hz) centered at δ 3.35.

Consideration now had to be given to the closure of ring C. The planned hydroboration–oxidation was accomplished with thexylborane at 0 °C. The regioselectivity of this functionalization reaction was such that primary alcohol **16** was formed as the major product (67%) alongside its secondary isomer **17** (16%). Since attempts to lower the relative amounts of **17** by decreasing the reaction temperature only served to increase its preponderance, the possibility exists that the neighboring OPMB group may be exerting a modest directing effect. Swern oxidation of **16** gave rise to aldehyde **18** (Scheme 3), thereby setting the stage for aldol cyclization. After preliminary screening of a variety of conditions, the use of sodium hydroxide in methanol was judged most suitable since only one product was formed in 85% yield. The conversion of **19a** to its *p*-nitrobenzoate **19c** caused H-7 to be shifted to lower field clear of other signals, thereby enabling unambiguous NMR analysis. Of particular note is the appearance of H-7 in this derivative as a doublet of doublets (J = 11.5 and 3.8 Hz) consistent with an axial–axial and axial–equatorial stereochemical disposition relative to vicinal protons. Additional NOE studies showed the following integral enhancements: H-7 → H-10, 16%; H-10 → H-7, 16%; H-7 → H-5, 7%; H-5 → H-7, 5%. These observations are uniquely consistent with the presence of an axial methyl group at C-8 and an equatorial oxido substituent at C-7. Thus, the aldol ring closure proceeds with the proper establishment of all of the many stereocenters present in the entire western sector of taxol!

With these stereochemical issues resolved, the 7-hydroxyl group in **19a** was protected as its BOM derivative **19b** prior to removal of the TBS ether (75%). The oxidation of diol **20** under conventional Swern conditions could not be forced to proceed to completion without competitive formation of side products. Matters were substantially improved when diisopropylethylamine was utilized as base and reaction was allowed to proceed at −78 °C for 1 h prior to slow warming to 0 °C during an equivalent period of time. When these guidelines were adhered to, **21** was isolated in 73% yield accompanied by 10% of unreacted **20**.

In order to arrive at our synthetic goal, **21** was heated with an excess of aluminum tri-*tert*-butoxide in benzene for 12 h in order to bring about an α-ketol rearrangement.[2b,11] Appropriate bond migration took place to deliver **22** in 94% yield. The identification of this product as a taxane derivative rests solidly on the results of selective DEPT experiments. Thus, irradiation of the apical methyl group that resonates at 0.96 ppm in ^{1}H NMR led to enhancement of the ^{13}C NMR signals appearing at 83.0 (C-1), 51.8 (C-11), 42.9 (C-15), and 22.9 ppm (CH_3). In addition, irradiation of the methyl signal appearing at 0.99 ppm had an identical effect on the same three carbons (C-1, C-11, C-15) in addition to a fourth at 29.6 ppm (CH_3). If the other possible isomer had formed, J_3 coupling would have been required to operate at the carbonyl carbon,[2b] but it does not.

Conclusion

The present study provides an important backdrop for gaining an understanding of those structural features conducive to a short stereocontrolled route to taxol and congeners thereof. The very evident convergency of the process leads in only ten steps from bicyclic ketone **11** to

(11) Elmore, S. W.; Combrink, K. D.; Paquette, L. A. *Tetrahedron Lett.* **1991**, *32*, 6679.

(12) (a) Baer, E.; Fischer, H. O. L. *J. Biol. Chem.* **1939**, *128*, 463. (b) Kierstead, R. W.; Faraone, A.; Mennona, F.; Mullin, J.; Guthrie, R. W.; Crowley, H.; Simko, B.; Blaber, L. C. *J. Med. Chem.* **1983**, *26*, 1561. (c) Hertel, L. W.; Grossman, C. S.; Kroin, J. S. *Synth. Commun.* **1991**, *21*, 151. (d) Schmid, C. R.; Bryant, J. D. *Org. Synth.* **1995**, *72*, 6.

the highly functionalized taxane **22**. Recourse to vinyl iodide **2** is enabling in two important respects. Its acyclic nature and array of substituents provide much less steric impedance than a cyclohexenyl ring system to operation of the oxy-Cope rearrangement, such that formation of the A/B ring network can be accomplished well below 0 °C. Also, no β-elimination is observed during the aldol reaction associated with the elaboration of ring C. Furthermore, the configurations at atoms C-4 and C-5 are such that the stereogenic centers being generated at C-7 and C-8 during this cyclization adopt the features present in the naturally occurring taxanes. Therefore, the protocol described herein indicates that D-camphor and D-glyceraldehyde hold considerable promise as enantiopure building blocks of the proper absolute configuration for taxol construction. More advanced investigations in this area are in progress and 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 (300 MHz) and ^{13}C NMR (75 MHz). The high-resoution 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.

(*S*)-2-[(*R*)-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]hydroxymethyl]glycidaldehyde Diethyl Acetal (6a).[6] *n*-Butyllithium (162 mL of 1.6 M in hexanes, 259 mmol) was added during 30 min to a stirred solution of **3**[3] (52.05 g, 249 mmol) in ether (500 mL) at −78 °C under nitrogen. After 30 min, **4**[12] (27.0 g, 207 mmol) was introduced in neat condition followed by an ether rinse (10 mL). The reaction mixture was stirred at −78 °C for 2 h, allowed to warm to rt overnight, and quenched with pH 7 buffer. The separated aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were dried and concentrated. Chromatography of the residue on silica gel (elution with 20% ethyl acetate in hexanes) afforded 48.4 g (90%) of a >10:1 mixture of **5a** and **5b**.[4]

tert-Butyl hydroperoxide (56.4 mL of 5 M in CH_2Cl_2, 282 mmol) was added carefully to a chilled solution of the above carbinol mixture (49.0 mL, 188 mmol) in benzene (500 mL) containing vanadyl acetylacetonate (1.25 g, 4.71 mmol). The reaction mixture was stirred at rt for 12 h, quenched with 10% Na_2SO_3 solution (400 mL), and vigorously agitated 30 min longer. The aqueous layer was extracted with CH_2Cl_2, and the combined organic phases were dried and concentrated. Product purification by chromatography on silica gel (elution with 25–30% ethyl acetate in hexanes) furnished 52.5 g (84%) of **6a** as a colorless oil: IR (neat, cm^{-1}) 3476, 1372, 1158, 1111, 1066; ^{1}H NMR (300 MHz, C_6D_6) δ 4.48 (s, 1 H), 4.28 (dd, *J* = 7.2, 4.2 Hz, 1 H), 4.19–4.03 (m, 3 H), 3.57–3.25 (m, 4 H), 2.89 (d, *J* = 4.2 Hz, 1 H), 2.86 (d, *J* = 5.3 Hz, 1 H), 2.73 (d, *J* = 5.3 Hz, 1 H), 1.39 (s, 3 H), 1.27 (s, 3 H), 0.99 (td, *J* = 7.0, 1.2 Hz, 6 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 109.4, 103.3, 75.6, 70.5, 67.1, 64.1, 63.8, 59.6, 47.1, 26.8, 25.7, 15.3 (2 C); MS *m*/*z* (M$^+$ − CH_3) calcd 261.1338, obsd 261.1340; [α]$^{23}_D$ +5.8 (*c* 1.2, $CHCl_3$).

(*S*)-2-[(*R*)-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl][(*p*-methoxybenzyl)oxy]methyl]glycidaldehyde Diethyl Acetal (6b). Epoxy alcohol **6a** (22.0 g, 79 mmol) was dissolved in dry DMF (200 mL), treated with sodium hydride (2.9 g, 121 mmol) in several portions with external cooling (ice bath), and stirred at rt for 30 min. *p*-Methoxybenzyl chloride (18 mL, 133 mmol) was added dropwise and the mixture was stirred for 1 h before being carefully quenched with saturated NH_4Cl solution. Following dilution with water (400 mL), the mixture was extracted with ether (3 × 150 mL), and the combined organic layers were twice washed with brine prior to drying and concentration. Chromatography of the residue on silica gel (elution with 15% ethyl acetate in hexanes) gave 27.1 g (85%) of **6b** as a colorless oil: IR (neat, cm^{-1}) 1514, 1249, 1112, 1066; ^{1}H NMR (300 MHz, C_6D_6) δ 7.33 (d, *J* = 8.7 Hz, 2 H), 6.79 (d, *J* = 8.7 Hz, 2 H), 4.75 (d, *J* = 2.1 Hz, 2 H), 4.52–4.46 (m, 2 H), 4.31 (d, *J* = 4.2 Hz, 1 H), 4.13 (dd, *J* = 8.0, 7.3 Hz, 1 H), 4.05 (dd, *J* = 8.0, 6.7 Hz, 1 H), 3.62–3.28 (m, 4 H), 3.30 (s, 3 H), 2.70 (d, *J* = 5.7 Hz, 1 H), 2.55 (d, *J* = 5.7 Hz, 1 H), 1.49 (s, 3 H), 1.35 (s, 3 H), 1.07 (t, *J* = 7.1 Hz, 3 H), 1.00 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 160.1, 131.7, 130.0, 114.3, 109.2, 103.0, 77.0, 76.3, 75.4, 66.1, 64.4, 63.7, 60.0, 55.0, 45.8, 27.0, 26.1, 15.7, 15.6; MS *m*/*z* (M$^+$ − CH_3) calcd 381.1904, obsd 381.1909; [α]$^{23}_D$ +21.7 (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{21}H_{32}O_7$: C, 63.62; H, 8.14. Found: C, 63.70; H, 8.19.

2-*C*-(Hydroxymethyl)-4,5-*O*-isopropylidene-3-*O*-(*p*-methoxybenzyl)-D-arabinose Diethyl Acetal (7). A solution of **6b** (25.0 g, 63.1 mmol) in DMSO (150 mL) was treated with 3 M NaOH (150 mL), refluxed for 4.5 h, returned to rt, and carefully neutralized with 5% HCl to pH 8. The mixture was extracted with CH_2Cl_2 (3 × 150 mL), and the combined organic phases were washed with brine, dried, and concentrated. Chromatography of the residue on silica gel (elution with 40% ethyl acetate in hexanes) afforded 22.1 g (84%) of **7** as a colorless solid: mp 80–81 °C; IR (film, cm^{-1}) 3482, 1515, 1249, 1102, 1052; ^{1}H NMR (300 MHz, C_6D_6) δ 7.33 (d, *J* = 8.6 Hz, 2 H), 6.80 (d, *J* = 8.6 Hz, 2 H), 5.07 (d, *J* = 10.7 Hz, 1 H), 4.66 (td, *J* = 7.2, 2.5 Hz, 1 H), 4.63 (d, *J* = 10.7 Hz, 1 H), 4.62 (s, 1 H), 4.42 (t, *J* = 7.8 Hz, 1 H), 4.21 (dd, *J* = 8.1, 6.7 Hz, 1 H), 3.88 (dd, *J* = 11.6, 6.5 Hz, 1 H), 3.74 (dd, *J* = 11.6, 6.9 Hz, 1 H), 3.56–3.11 (m, 4 H), 3.31 (s, 3 H), 3.07–2.93 (m, 2 H), 1.48 (s, 3 H), 1.34 (s, 3 H), 0.99 (t, *J* = 7.0 Hz, 3 H), 0.91 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 159.7, 131.6, 129.4, 114.1, 107.9, 106.6, 79.2, 77.2, 76.5, 75.4, 67.2, 65.9, 64.9, 63.5, 54.8, 26.7, 25.2, 15.5, 15.4; MS *m*/*z* (M$^+$) calcd 368.1835, obsd 368.1878; [α]$^{23}_D$ +5.7 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{21}H_{34}O_8$: C, 60.85; H, 8.27. Found: C, 60.93; H, 8.29.

(5*S*,8*R*,9*R*)-6-Ethoxy-9-[(*p*-methoxybenzyl)oxy]-2,2-dimethyl-1,3,7-trioxaspiro[4.4]nonane-8-methanol (8). Diol **7** (39.5 g, 95.3 mmol) and pyridinium *p*-toluenesulfonate (1.4 g, 4.8 mmol) were dissolved in ethanol (400 mL), refluxed for 4 h, and freed of solvent in vacuo. The residue was taken up in 1:1 acetone/2,2-dimethoxypropane (400 mL), refluxed for 2 h, cooled, poured into CH_2Cl_2 (500 mL), and washed with saturated $NaHCO_3$ solution followed by 2 N HCl (2×). Purification of the residue by chromatography on silica gel (elution with 45–50% ethyl acetate in hexanes) gave 31.7 g (90%) of **8** as a colorless, oily anomeric mixture. More careful purification led to separation of the two products.

For the more polar anomer: IR (neat, cm^{-1}) 3483, 1613, 1515, 1372, 1250, 1174, 1103, 1037; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4 Hz, 2 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 4.76 (d, *J* = 11.2 Hz, 1 H), 4.67 (s, 1 H), 4.51 (d, *J* = 11.2 Hz, 1 H), 4.43 (d, *J* = 7.2 Hz, 1 H), 4.40 (d, *J* = 8.8 Hz, 1 H), 3.89 (d, *J* = 8.8 Hz, 1 H), 3.80–3.76 (m, 2 H), 3.79 (s, 3 H), 3.68–3.61 (m, 2 H), 3.49 (dd, *J* = 11.9, 4.5 Hz, 1 H), 2.30–2.05 (br s, 1 H), 1.49 (s, 3 H), 1.43 (s, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 159.4, 129.9, 129.4, 113.9, 110.1, 104.0, 87.9, 80.9, 77.4, 73.2, 67.1, 64.5, 63.2, 55.2, 26.8, 26.0, 15.1; MS *m*/*z* (M$^+$) calcd 368.1835, obsd 368.1834; [α]$^{23}_D$ −16.0 (*c* 1.02, $CHCl_3$). Anal. Calcd for $C_{19}H_{28}O_7$: C, 61.94; H, 7.66. Found: C, 61.76; H, 7.75.

For the less polar anomer: IR (neat, cm^{-1}) 3486, 1613, 1515, 1372, 1249, 1091; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 4.93 (s, 1 H), 4.63 (d, *J* = 11.7 Hz, 1 H), 4.52 (d, *J* = 11.7 Hz, 1 H), 4.35 (d, *J* = 9.7 Hz, 1 H), 4.18 (d, *J* = 9.7 Hz, 1 H), 4.02 (q, *J* = 4.3 Hz, 1 H), 3.81–3.78 (m, 1 H), 3.80 (s, 3 H), 3.77–3.68 (m, 2 H), 3.57–3.46 (m, 2 H), 2.00–1.85 (br s, 1 H), 1.37 (s, 6 H), 1.20 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 159.5, 129.7, 129.6, 113.9, 110.3, 107.1, 90.0, 83.0 (2 C), 72.7, 64.6, 63.2, 62.7, 55.2, 26.4, 25.8, 15.0; MS *m*/*z* (M$^+$) calcd 368.1835, obsd 368.1817; [α]$^{23}_D$ +93.1 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{19}H_{28}O_7$: C, 61.94; H, 7.66. Found: C, 61.75; H, 7.73.

(5*S*,8*S*,9*R*)-6-Ethoxy-8-(iodomethyl)-9-[(*p*-methoxybenzyl)oxy]-2,2-dimethyl-1,3,7-trioxaspiro[4.4]nonane (9). Al-

cohol **8** (3.98 g, 10.8 mmol) was dissolved in toluene (40 mL) and acetonitrile (10 mL). Triphenylphosphine (6.9 g, 26.3 mmol) and imidazole (2.5 g, 36.7 mmol) were introduced, the reaction mixture was heated nearly to the reflux temperature, and iodine (5.5 g, 21.6 mmol) was added in several portions. After 1 h of heating, the mixture was cooled to rt, diluted with ether (100 mL), washed twice with water, dried, and concentrated. Chromatography of the residue on silica gel (elution with 10% ethyl acetate in hexanes) furnished **9** (4.6 g, 89%) as a colorless, oily mixture of two diastereomers. Rechromatography of a small sample of the mixture (elution with 12.5% ethyl acetate in hexanes) led to separation of the individual anomers.

For anomer A: IR (neat, cm^{-1}) 1613, 1514, 1451, 1372, 1249, 1211, 1174, 1093, 851; ^1H NMR (300 MHz, C_6D_6) δ 7.20 (d, J = 8.6 Hz, 2 H), 6.75 (d, J = 8.6 Hz, 2 H), 5.09 (s, 1 H), 4.54 (d, J = 11.5 Hz, 1 H), 4.48 (d, J = 11.5 Hz, 1 H), 4.47 (d, J = 11.0 Hz, 1 H), 4.37 (d, J = 11.0 Hz, 1 H), 4.14 (dd, J = 10.8, 5.8 Hz, 1 H), 3.88 (d, J = 4.3 Hz, 1 H), 3.72 (dq, J = 9.7, 7.1 Hz, 1 H), 3.35 (s, 3 H), 3.29 (dq, J = 9.7, 7.1 Hz, 1 H), 3.23 (dd, J = 10.0, 6.1 Hz, 1 H), 3.13 (dd, J = 10.0, 6.1 Hz, 1 H), 1.39 (s, 3 H), 1.33 (s, 3 H), 1.04 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 160.0, 130.2, 129.9, 114.2, 110.4, 108.1, 90.7, 87.1, 82.6, 72.6, 65.2, 63.4, 54.8, 26.7, 25.9, 15.1, 6.9; MS m/z (M^+) calcd 478.0852, obsd 478.0854; $[\alpha]^{23}_D$ +39.7 (c 1.00, $CHCl_3$). Anal. Calcd for $C_{19}H_{27}IO_6$: C, 47.71; H, 5.69. Found: C, 48.10; H, 5.80.

For anomer B: IR (neat, cm^{-1}) 1612, 1515, 1458, 1372, 1251, 1101; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 8.7 Hz, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 4.76 (d, J = 11.0 Hz, 1 H), 4.73 (s, 1 H), 4.58 (d, J = 11.0 Hz, 1 H), 4.36 (d, J = 8.8 Hz, 1 H), 4.21 (d, J = 6.4 Hz, 1 H), 3.88 (d, J = 8.8 Hz, 1 H), 3.86–3.74 (m, 2 H), 3.80 (s, 3 H), 3.58 (qd, J = 7.1, 10.0 Hz, 1 H), 3.21 (d, J = 5.7 Hz, 1 H), 3.19 (d, J = 5.7 Hz, 1 H), 1.49 (s, 3 H), 1.42 (s, 3 H), 1.26 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 159.5, 129.7, 129.6, 113.9, 110.2, 103.9, 88.3, 82.7, 79.8, 73.1, 67.1, 63.8, 55.3, 26.7, 26.1, 15.0, 8.3; MS m/z (M^+) calcd 478.0852, obsd 478.0845; $[\alpha]^{23}_D$ −24.6 (c 1.22, $CHCl_3$). Anal. Calcd for $C_{19}H_{27}IO_6$: C, 47.71; H, 5.69. Found: C, 48.11; H, 5.75.

(4*S*)-4-[(*Z*)-2-Iodovinyl]-4-[(1*R*)-1-[(*p*-methoxybenzyl)-oxy]allyl]-2,2-dimethyl-1,3-dioxolane (2). Zinc dust (18.0 g, 275 mmol) was added to a solution of **9** (15.0 g, 31.1 mmol) in methanol (220 mL), refluxed for 1.5 h, cooled, filtered, and evaporated. The residue was taken up in ether (300 mL), washed twice with brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 20% ethyl acetate in hexanes) provided 9.1 g (95%) of aldehyde **10** which was used directly in the next step.

To a suspension of (iodomethyl)triphenylphosphonium iodide[13] (24.3 g, 45.8 mmol) in dry THF (200 mL) was added sodium hexamethyldisilazide (43 mL of 1.0 M) at rt. The resultant reddish solution was cooled to −78 °C, aldehyde **10** (9.1 g, 29.7 mmol) dissolved in THF (50 mL) was introduced, and stirring was maintained at this temperature for 1.5 h prior to quenching with saturated NH_4Cl solution (50 mL). The reaction mixture was allowed to warm to rt, hexanes (500 mL) were added, and the precipitates were removed by filtration. The filtrate was washed twice with brine, dried, and evaporated. Purification of the residue by chromatography on silica gel (elution with 7% ethyl acetate in hexanes) yielded 9.1 g (71%) of **2** as a viscous, colorless oil: IR (neat, cm^{-1}) 1612, 1514, 1381, 1371, 1302, 1248, 1211, 1172, 1110, 1066, 1037, 829, 755; ^1H NMR (300 MHz, C_6D_6) δ 7.20 (d, J = 8.6 Hz, 2 H), 6.78 (d, J = 8.6 Hz, 2 H), 6.59 (d, J = 8.8 Hz, 1 H), 6.03 (d, J = 8.8 Hz, 1 H), 5.89 (ddd, J = 17.4, 10.3, 7.1 Hz, 1 H), 5.26 (ddd, J = 17.4, 1.9, 1.1 Hz, 1 H), 5.22 (ddd, J =10.3, 1.9, 0.8 Hz, 1 H), 4.52 (d, J = 11.4 Hz, 1 H), 4.30 (d, J = 8.7 Hz, 1 H), 4.25 (d, J = 11.4 Hz, 1 H), 4.09 (d, J = 7.1 Hz, 1 H), 4.03 (d, J = 8.7 Hz, 1 H), 3.31 (s, 3 H), 1.43 (s, 3 H), 1.35 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 159.8, 142.7, 134.6, 130.8, 129.7, 119.4, 114.0, 110.4, 85.6, 82.9, 77.0, 71.5, 71.1, 54.8, 27.0, 25.9; MS m/z (M^+) calcd 430.0641, obsd 430.0688; $[\alpha]^{23}_D$ −43.9 (c 1.1, $CHCl_3$). Anal. Calcd for $C_{18}H_{23}IO_4$: C, 50.25; H, 5.39. Found: C, 50.64; H, 5.49.

In addition, 1–2% of the E vinyl iodide was also isolated: colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (m, 2 H), 6.89 (m, 2 H), 6.75 (d, J = 14.4 Hz, 1 H), 6.44 (d, J = 14.4 Hz, 1 H), 5.72 (ddd, J = 17.2, 10.4, 7.8 Hz, 1 H), 5.41 (dd, J = 10.4, 1.5 Hz, 1 H), 5.30 (dd, J = 17.2, 1.1 Hz, 1 H), 4.55 (d, J = 11.4 Hz, 1 H), 4.26 (d, J = 11.4 Hz, 1 H), 4.11 (d, J = 8.9 Hz, 1 H), 3.81 (s, 3 H), 3.79 (d, J = 8.9 Hz, 1 H), 3.68 (d, J = 7.8 Hz, 1 H), 1.41 (s, 3 H), 1.38 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 159.2, 144.4, 133.8, 129.9, 129.4, 120.6, 113.7, 110.7, 86.8, 83.0, 77.5, 71.7, 70.2, 55.2, 26.8.

(1*S*,2*S*,3*R*,4*S*)-2-[(*Z*)-2-[(4*S*)-4-[(1*R*)-1-[(*p*-Methoxybenzyl)oxy]allyl]-2,2-dimethyl-1,3-dioxolan-4-yl]vinyl]-3-(methoxymethoxy)-7,7-dimethyl-1-vinyl-2-norbornanol (12). A cold (−78 °C) solution of **2** (1.05 g, 2.44 mmol) in dry THF (12 mL) was treated with *tert*-butyllithium (3.2 mL of 1.7 M in hexanes, 5.44 mmol). After 2 min, ketone **11**[2h] (500 mg, 2.23 mmol) dissolved in THF (3 mL) was introduced via syringe. The yellow reaction mixture was stirred for 20 min, warmed to rt, quenched with saturated $NaHCO_3$ solution, and extracted with ether. The combined organic phases were washed with brine (2x), dried, and concentrated. Chromatography of the residue (silica gel, elution with 10% ethyl acetate in hexanes) afforded 836 mg (70%) of **12** as a colorless oil: IR (neat, cm^{-1}) 3446, 1515, 1251, 1175, 1148, 1114, 1045; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.1 Hz, 2 H), 6.87 (d, J = 8.1 Hz, 2 H), 6.21 (dd, J = 16.9, 9.9 Hz, 1 H), 5.76 (ddd, J = 17.5, 10.7, 6.8 Hz, 1 H), 5.54 (d, J = 13.4 Hz, 1 H), 5.44 (d, J = 13.4 Hz, 1 H), 5.30 (d, J = 9.9 Hz, 1 H), 5.25 (d, J = 16.9 Hz, 1 H), 5.17 (dd, J = 10.7, 1.7 Hz, 1 H), 4.93 (dd, J = 17.5, 1.7 Hz, 1 H), 4.51 (d, J = 11.2 Hz, 1 H), 4.42 (d, J = 11.2 Hz, 1 H), 4.39 (s, 1 H), 4.34 (d, J = 6.8 Hz, 1 H), 4.25 (d, J = 9.8 Hz, 1 H), 4.20 (d, J = 9.8 Hz, 1 H), 4.19 (d, J = 6.5 Hz, 1 H), 3.95 (d, J = 6.5 Hz, 1 H), 3.80 (s, 3 H), 3.40 (s, 1 H), 3.23 (s, 3 H), 1.86–1.60 (m, 3 H), 1.51–1.43 (m, 1 H), 1.40 (s, 3 H), 1.35 (s, 3 H), 1.27 (s, 3 H), 1.13–1.04 (m, 1 H), 0.75 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 159.4, 137.4, 137.3, 134.5, 130.7, 130.1, 129.5, 118.8, 116.1, 113.7, 108.4, 96.4, 90.1, 84.5, 83.7, 83.5, 72.4, 71.4, 60.1, 55.2, 55.0, 51.0, 50.4, 27.0, 25.5, 25.3, 24.3, 22.2, 21.9; MS m/z (M^+) calcd 528.3087, obsd 528.3080; $[\alpha]^{23}_D$ −27.8 (c 1.23, $CHCl_3$). Anal. Calcd for $C_{31}H_{44}O_7$: C, 70.43; H, 8.39. Found: C, 70.71; H, 8.47.

(1*S*,2*R*,4*R*,5*S*,7*E*)-5-[(4*S*)-4-[(1*R*)-1-[(*p*-Methoxybenzyl)-oxy]allyl]-2,2-dimethyl-1,3-dioxolan-4-yl]-2-(methoxymethoxy)-4,11,11-trimethyl-bicyclo[6.2.1]undec-7-en-3-one (13). A cold (−45 °C) solution of **12** (656 mg, 1.24 mmol) and 18-crown-6 (650 mg, 2.46 mmol) in dry THF (15 mL) was treated with potassium hexamethyldisilazide (5 mL of 0.5 M in toluene), stirred for 25 min at this temperature, and cooled to −78 °C. Methyl iodide (0.6 mL, 9.6 mmol) was introduced and the mixture was stirred at −78 °C for 1 h prior to being quenched with saturated NH_4Cl solution. The product was extracted into ether, and the combined ethereal solutions were dried and concentrated. Chromatography of the residue on silica gel (elution with 15% ethyl acetate in hexanes) gave **13** as a colorless oil (615 mg, 91%); IR (neat, cm^{-1}) 1711, 1613, 1514, 1248, 1042; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J = 8.6 Hz, 2 H), 6.84 (d, J = 8.6 Hz, 2 H), 6.01 (ddd, J = 17.0, 10.8, 6.1 Hz, 1 H), 5.35 (d, J = 17.0 Hz, 1 H), 5.34 (d, J = 10.8 Hz, 1 H), 5.15 (dd, J = 11.7, 4.2 Hz, 1 H), 4.70 (d, J = 8.4 Hz, 1 H), 4.60 (d, J = 6.9 Hz, 1 H), 4.54 (d, J = 11.0 Hz, 1 H), 4.35 (d, J = 6.9 Hz, 1 H), 4.31 (d, J = 11.0 Hz, 1 H), 4.10 (d, J = 8.4 Hz, 1 H), 4.02 (d, J = 6.1 Hz, 1 H), 3.97 (d, J = 1.6 Hz, 1 H), 3.79 (s, 3 H), 3.30 (s, 3 H), 2.68–2.12 (m, 8 H), 1.59 (s, 3 H), 1.54 (m, 1 H), 1.50 (s, 3 H), 1.18 (s, 3 H), 1.05 (s, 3 H), 1.05 (d, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.2, 159.0, 146.8, 135.1, 130.7, 129.0, 124.2, 117.5, 113.6, 107.9, 94.9, 87.6, 86.3, 82.7, 71.0, 70.8, 55.6, 55.2, 54.5, 46.9, 45.8, 45.4, 29.1, 28.6, 26.9, 26.8, 26.3, 23.3, 19.4, 17.0; MS m/z (M^+) calcd 542.3244, obsd 5422.3251; $[\alpha]^{23}_D$ −27.9 (c 1.0, $CHCl_3$). Anal. Calcd for $C_{32}H_{46}O_7$: C, 70.82; H, 8.54. Found: C, 70.85; H, 8.53.

(1*S*,4*S*,5*R*,6*R*,7*R*,8*S*)-1,6-Dihydroxy-4-[(4*S*)-4-[(1*R*)-1-[(*p*-methoxybenzyl)oxy]allyl]-2,2-dimethyl-1,3-dioxolan-4-yl]-2-(methoxymethoxy)-5,11,11-trimethylbicyclo[6.2.1]-

(13) Seyferth, D.; Heeren, J. K.; Singh, G.; Grim, S. O.; Hughes, W. B. *J. Organomet. Chem.* **1966**, *5*, 267.

undecan-2-one (14). Osmium tetraoxide (18 mg, 0.070 mmol) was added at 0 °C to a solution of **13** (37 mg, 0.068 mmol) in a mixture of acetone (2.5 mL), *tert*-butyl alcohol (0.15 mL), and water (0.3 mL). After 1 h, a solution of sodium dithionite (100 mg, 0.57 mmol) in H_2O (1.5 mL) was introduced and the dark-colored mixture was stirred at rt for 4.5 h prior to extraction with ethyl acetate. The combined organic phases were washed twice with brine, dried, and evaporated. After a preliminary filtration of the residue through silica gel (elution with 50% ethyl acetate in hexanes), more careful chromatography (elution with 30% ethyl acetate in hexanes) completed the isomerization and delivered 15 mg (40%) of **14** as a colorless solid: mp 108–109 °C; IR ($CHCl_3$, cm^{-1}) 3550, 3470, 1685, 1620; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (m, 2 H), 6.86 (m, 2 H), 6.10 (m, 1 H), 5.50 (dt, J = 6.6, 1.5 Hz, 1 H), 5.46 (d, J = 1.4 Hz, 1 H), 4.70 (d, J = 6.7 Hz, 1 H), 4.63 (d, J = 11.3 Hz, 1 H), 4.56 (d, J = 6.7 Hz, 1 H), 4.30 (d, J = 11.3 Hz, 1 H), 4.08 (dd, J = 3.3, 1.5 Hz, 1 H), 4.03 (d, J = 9.3 Hz, 1 H), 3.80 (s, 3 H), 3.75 (d, J = 9.3 Hz, 1 H), 3.43 (s, 1 H), 3.38 (s, 3 H), 3.35 (d, J = 8.2 Hz, 1 H), 3.10 (m, 3 H), 2.67 (m, 2 H), 2.48 (m, 3 H), 2.20 (m, 1 H), 1.91 (m, 2 H), 1.42 (s, 3 H), 1.35 (s, 3 H), 1.11 (s, 3 H), 1.05 (s, 3 H), 0.90 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 218.4, 159.2, 134.3, 130.0, 129.1, 118.5, 113.8, 108.3, 97.0, 87.8, 87.4, 85.7, 82.8, 72.3, 71.9, 66.6, 56.1, 55.2, 53.0, 49.4, 41.4, 37.4, 35.7, 30.6, 30.5, 27.7, 26.7, 26.4, 18.4, 11.9; MS m/z (M^+) calcd 576.3298, obsd 576.3332.

(1*S*,2*R*,4*R*,5*S*,7*S*,8*S*)-7-(*tert*-Butyldimethylsiloxy)-8-hydroxy-5-[(4*S*)-4-[(1*R*)-1-[(*p*-methoxybenzyl)oxy]allyl]-2,2-dimethyl-1,3-dioxolan-4-yl]-2-(methoxymethoxy)-4,11,11-trimethylbicyclo[6.2.1]undecan-3-one (15). Osmium tetraoxide (1.28 g, 5.07 mmol) was added portionwise to a stirred solution of **13** (1.75 g, 5.07 mmol) in cold (−30 °C) pyridine (50 mL), stirred at this temperature for 1.5 h, and allowed to warm to rt. After an additional 2.5 h, 50 mL of a 20% sodium dithionite solution was introduced and the mixture was stirred overnight, diluted with water (50 mL), and extracted with ethyl acetate (2 × 100 mL and 2 × 50 mL). The combined organic extracts were dried, filtered, and evaporated, and the residue was dissolved in DMF (1.5 mL) containing imidazole (1.55 g, 22.8 mmol). This solution was treated with *tert*-butyldimethylsilyl chloride (2.29 g, 15.2 mmol), stirred for 2 h, poured into saturated $NaHCO_3$ solution (50 mL), and extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with 1 N HCl (50 mL), dried, and evaporated. Chromatography of the residue on silica gel (elution with 15 → 20% ethyl acetate in hexanes) afforded 2.49 g (71%) of **15** as a colorless oil; IR (neat, cm^{-1}) 3464, 1704, 1515, 1252, 1037, 1012; ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, J = 8.5 Hz, 2 H), 6.85 (d, J = 8.5 Hz, 2 H), 6.20 (ddd, J = 17.6, 10.8, 3.8 Hz, 1 H), 5.52 (d, J = 17.6 Hz, 1 H), 5.50 (d, J = 17.6 Hz, 1 H), 4.63 (d, J = 11.1 Hz, 1 H), 4.50 (d, J = 7.0 Hz, 1 H), 4.32 (d, J = 7.0 Hz, 1 H), 4.32 (d, J = 11.0 Hz, 1 H), 4.17 (s, 1 H), 4.16–4.15 (m, 2 H), 4.05 (d, J = 9.1 Hz, 1 H), 3.80 (s, 3 H), 3.78 (d, J = 9.1 Hz, 1 H), 3.68 (dd, J = 12.0, 2.6 Hz, 1 H), 3.26 (s, 3 H), 3.17 (qd, J = 6.2, 1.8 Hz, 1 H), 2.68 (br d, J = 12.0 Hz, 1 H), 2.46–2.39 (m, 2 H), 2.27–2.20 (m, 1 H), 2.09 (t, J = 12 Hz, 1 H), 1.91–1.79 (m, 2 H), 1.54 (td, J = 12, 2.6 Hz, 1 H), 1.44 (s, 3 H), 1.38 (s, 3 H), 1.07 (s, 3 H), 0.97 (s, 3 H), 0.95 (d, J = 6.2 Hz, 3 H), 0.87 (s, 9 H), 0.13 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.3, 159.3, 134.4, 129.8, 129.1, 117.4, 113.8, 108.6, 95.0, 87.1, 86.5, 82.9, 72.9, 69.7, 66.4, 56.3, 55.6, 55.2, 50.1, 46.4, 33.6, 32.3, 31.9, 29.9, 28.0, 27.5, 26.3, 25.7, 18.0, 17.0, 10.0, −3.4, −4.7; MS m/z (M^+) calcd 690.4163, obsd 690.4150; $[\alpha]^{23}_D$ +30.9 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{38}H_{62}O_9Si$: C, 66.05; H, 9.04. Found: C, 66.17; H, 9.25.

(1*S*,2*R*,4*R*,5*S*,7*S*,8*S*)-7-(*tert*-Butyldimethylsiloxy)-8-hydroxy-5-[(4*S*)-4-[(1*R*)-3-hydroxy-1-[(*p*-methoxybenzyl)oxy]propyl]-2,2-dimethyl-1,3-dioxolan-4-yl]-2-(methoxymethoxy)-4,11,11-trimethylbicyclo[6.2.1]undecan-3-one (16) and (1*S*,2*R*,4*R*,5*S*,7*S*,8*S*)-7-(*tert*-Butyldimethylsiloxy)-5-[(1*S*,2*R*)-1,3-dihydroxy-1-(isopropoxymethyl)-2-[(*p*-methoxybenzyl)oxy]butyl]-8-hydroxy-2-(methoxymethoxy)-4,11,11-trimethylbicyclo[6.2.1]undecan-3-one (17). Borane–tetrahydrofuran complex (2.08 mL of 1 M in THF, 2.08 mmol) was added to 2,3-dimethyl-2-butene (2.08 mL of 1 M in THF, 2.08 mmol) at 0 °C under N_2. After 30 min, a solution of **15** (248 mg, 359 μmol) was introduced via cannula followed by 1 mL of THF as rinse. After 2 h of stirring at 0 °C, the reaction mixture was carefully treated with NaOH (3.1 mL of 2 M) and then hydrogen peroxide (1.27 mL, 30%). After an additional 15 min, 5 mL of 10% Na_2SO_3 solution was added, stirring was continued for 15 min, and the mixture was poured into saturated $NaHCO_3$ solution. The products were extracted into CH_2Cl_2 (3×), and the combined organic layers were dried and concentrated to leave a residue which was chromatographed on silica gel. Elution with 35–50% ethyl acetate in hexanes afforded 167 mg (67%) of **16** and 40 mg (16%) of **17**.

For **16**: colorless oil; IR (neat, cm^{-1}) 3459, 1700, 1251, 1037, 1011; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, J = 8.5 Hz, 2 H), 6.84 (d, J = 8.5 Hz, 2 H), 4.62 (d, J = 11.1 Hz, 1 H), 4.55 (d, J = 7.0 Hz, 1 H), 4.46 (d, J = 11.1 Hz, 1 H), 4.35 (d, J = 7.0 Hz, 1 H), 4.17 (s, 2 H), 4.05 (d, J = 9.2 Hz, 1 H), 3.91–3.72 (m, 5 H), 3.79 (s, 3 H), 3.28 (s, 3 H), 3.11 (q, J = 3.7 Hz, 1 H), 2.78 (d, J = 13.1 Hz, 1 H), 2.55–2.50 (m, 2 H), 2.26–2.07 (m, 4 H), 1.98–1.83 (m, 3 H), 1.58 (t, J = 12.2 Hz, 1 H), 1.47 (s, 3 H), 1.39 (s, 3 H), 1.09 (s, 3 H), 0.99 (s, 3 H), 0.94 (d, J = 6.3 Hz, 3 H), 0.87 (s, 9 H), 0.14 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 211.9, 159.3, 129.9, 129.2, 113.8, 108.7, 99.7, 87.5, 87.1, 82.0, 81.3, 74.4, 69.7, 66.7, 60.5, 56.1, 55.8, 55.2, 50.2, 47.2, 33.5, 33.0, 32.3, 32.1, 29.9, 28.1, 27.9, 26.3, 25.7, 18.0, 17.0, 10.3, −3.4, −4.7; MS m/z (M^+) calcd 708.4269, obsd 708.4253; $[\alpha]^{23}_D$ +26.3 (*c* 1.00, $CHCl_3$).

For **17**: colorless oil; IR (neat, cm^{-1}) 3458, 1700, 1515, 1037, 1012, 835; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J = 8.5 Hz, 2 H), 6.87 (d, J = 8.5 Hz, 2 H), 4.68 (d, J = 10.6 Hz, 1 H), 4.52 (d, J = 7.0 Hz, 1 H), 4.50 (d, J = 10.6 Hz, 1 H), 4.34 (d, J = 7.0 Hz, 1 H), 4.20 (d, J = 8.6 Hz, 1 H), 4.19 (s, 1 H), 4.09 (ddt, J = 9.1, 9.1, 6.5 Hz, 1 H), 3.80 (s, 3 H), 3.70 (dd, J = 11.9, 2.4 Hz, 1 H), 3.63 (sept, J = 6.1 Hz, 1 H), 3.56 (d, J = 9.1 Hz, 1 H), 3.53 (d, J = 8.6 Hz, 1 H), 3.41 (d, J = 9.1 Hz, 1 H), 3.26 (s, 3 H), 2.92 (q, J = 6.0 Hz, 1 H), 2.76 (d, J = 12.8 Hz, 1 H), 2.54–2.44 (m, 2 H), 2.35–2.26 (m, 1 H), 2.03 (t, J = 12.8 Hz, 1 H), 1.97–1.80 (m, 2 H), 1.76 (t, J = 12.8 Hz, 1 H), 1.41 (d, J = 6.0 Hz, 3 H), 1.22 (s, 3 H), 1.20 (s, 3 H), 1.16 (d, J = 6.5 Hz, 3 H), 1.10 (s, 3 H), 0.99 (s, 3 H), 0.89 (s, 9 H), 0.16 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.2, 159.5, 129.5, 129.4, 113.9, 94.8, 87.3, 85.0, 82.1, 77.9, 75.7, 72.9, 70.3, 68.3, 68.1, 56.0, 55.6, 55.2, 50.4, 47.7, 34.3, 32.8, 31.6, 30.1, 28.2, 25.8, 21.7, 21.6, 21.2, 18.1, 17.0, 11.1, −3.2, −4.8; MS m/z (M^+) calcd 710.4425, obsd 710.4410.

(*βR*,4*S*)-4-[(1*S*,2*S*,4*S*,5*R*,7*R*,8*S*)-2-(*tert*-Butyldimethylsiloxy)-1-hydroxy-7-(methoxymethoxy)-5,11,11-trimethyl-6-oxobicyclo[6.2.1]undec-4-yl]-*β*-[(*p*-methoxybenzyl)oxy]-2,2-dimethyl-1,3-dioxolane-4-propionaldehyde (18). Oxalyl chloride (13.6 mL of 0.2 M in CH_2Cl_2, 3.17 mmol) was added to DMSO (15.9 mL of 0.2 M in CH_2Cl_2, 3.17 mmol) at −78 °C under N_2, the solution was stirred for 15 min, and alcohol **16** (643 mg, 907 μmol) in CH_2Cl_2 (7 mL) was introduced via cannula. After 30 min, triethylamine (6.94 mL of 0.5 M in CH_2Cl_2, 3.47 mmol) was added and the reaction mixture was stirred at 0 °C for 10 min prior to being poured into water (50 mL) and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried and concentrated, and the residue was chromatographed on silica gel. Elution with 30% ethyl acetate in hexanes afforded **18** (618 mg, 96%) as a colorless oil: IR (neat, cm^{-1}) 3461, 1726, 1700, 1586, 1514, 1251, 1097, 1038, 1011, 836; ^1H NMR (300 MHz, $CDCl_3$) δ 9.88 (s, 1 H), 7.15 (d, J = 8.6 Hz, 2 H), 6.84 (d, J = 8.6 Hz, 2 H), 4.57 (d, J = 7.0 Hz, 1 H), 4.51 (d, J = 11.1 Hz, 1 H), 4.40 (d, J = 11.1 Hz, 1 H), 4.37 (d, J = 7.0 Hz, 1 H), 4.35 (m, 1 H), 4.17 (s, 1 H), 4.15 (s, 1 H), 4.02 (d, J = 9.2 Hz, 1 H), 3.82 (d, J = 9.2 Hz, 1 H), 3.79 (s, 3 H), 3.74 (dd, J = 12.1, 2.6 Hz, 1 H), 3.30 (s, 3 H), 3.13 (qd, J = 6.2, 2.1 Hz, 1 H), 3.06 (dd, J = 15.9, 3.1 Hz, 1 H), 2.82 (ddd, J = 16.7, 7.6, 1.7 Hz, 1 H), 2.72 (d, J = 13.2 Hz, 1 H), 2.59–2.49 (m, 2 H), 2.29–2.19 (m, 1 H), 2.11 (t, J = 12.8 Hz, 1 H), 1.92–1.74 (m, 2 H), 1.58 (td, J = 12.8, 2.6 Hz, 1 H), 1.43 (s, 3 H), 1.37 (s, 3 H), 1.09 (s, 3 H), 1.00 (s, 3 H), 0.95 (d, J = 6.2 Hz, 3 H), 0.88 (s, 9 H), 0.14 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 211.6, 199.4, 159.4, 129.4, 129.3, 113.8, 109.0, 95.1, 87.6, 86.6, 82.0, 77.4, 73.6, 69.6, 66.6, 56.0,

55.8, 55.2, 50.2, 47.4, 45.2, 33.2, 32.2, 32.1, 29.9, 28.5, 27.9, 26.2, 25.7, 18.0, 17.0, 10.2, −3.4, −4.7; MS m/z (M^+) calcd 706.4112, obsd 706.4142; $[\alpha]^{23}_D$ +16.3 (c 0.88, $CHCl_3$).

(2′*R*,4*S*,4′*S*,4′a*S*,6′*R*,7′*S*,10′*S*,11′*S*,12′a*S*)-11′-(*tert*-Butyldimethylsiloxy)dodecahydro-4′,10′-dihydroxy-2′-[(*p*-methoxybenzyl)oxy]-6′-(methoxymethoxy)-2,2,4′a,13′,13′-pentamethylspiro[1,3-dioxolane-4,1′(5′*H*)-[7,10]methanobenzocyclodecen]-5′-one (19a). A solution of **18** (491 mg, 694 μmol) in methanol (15 mL) and THF (2 mL) was treated with sodium hydroxide (5.6 mL of 0.5 M, 2.78 mmol) at 0 °C, stirred at rt for 12 h, poured into water, and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried and evaporated to leave a residue which was chromatographed on silica gel (elution with 32 → 35% ethyl acetate in hexanes) to furnish **19a** (419 mg, 85%) as a white solid: mp 212−214 °C; IR (film, cm^{-1}) 3448, 1699, 1514, 1251, 1065, 1039, 1004, 836, 738; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.6 Hz, 2 H), 6.87 (d, J = 8.6 Hz, 2 H), 4.59 (d, J = 7.4 Hz, 1 H), 4.58 (s, 2 H), 4.54 (d, J = 7.4 Hz, 1 H), 4.47 (s, 1 H), 4.23 (s, 1 H), 4.18 (d, J = 8.6 Hz, 1 H), 4.15−4.09 (m, 1 H), 3.89 (d, J = 8.6 Hz, 1 H), 3.88 (dd, J = 11.5, 2.9 Hz, 1 H), 3.81 (s, 3 H), 3.51 (dd, J = 12.4, 4.2 Hz, 1 H), 3.33 (s, 3 H), 2.57−2.45 (m, 2 H), 2.37−2.26 (m, 4 H), 2.18 (dt, J = 12.4, 4.2 Hz, 1 H), 1.96−1.85 (m, 1 H), 1.75−1.53 (m, 3 H), 1.50 (s, 3 H), 1.44 (s, 3 H), 1.09 (s, 6 H), 1.04 (s, 3 H), 0.89 (s, 9 H), 0.19 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.6, 159.2, 130.2, 129.3, 113.8, 109.2, 95.1, 87.1, 83.8, 82.0, 80.5, 72.6, 72.1, 69.1, 64.4, 59.4, 56.5, 56.1, 55.3, 49.8, 37.8, 33.9, 32.3, 32.2, 29.6, 27.6, 26.9, 26.6, 25.8, 18.0, 17.3, 10.1, −3,4, −4.4; MS m/z (M^+) calcd 706.4112, obsd 706.4124; $[\alpha]^{23}_D$ −13.9 (c 1.0, $CHCl_3$). Anal. Calcd for $C_{38}H_{62}O_{10}Si$: C, 64.56; H, 8.84. Found: C, 64.53; H, 8.79.

(2′*R*,4*S*,4′*S*,4′a*S*,6′*R*,7′*S*,10′*S*,11′*S*,12′a*S*)-4′-[(Benzyloxy)-methoxy]-11′-(*tert*-butyldimethylsiloxy)dodecahydro-10′-hydroxy-2′-[(*p*-methoxybenzyl)oxy]-6′-(methoxymethoxy)-2,2,4′a,13′,13′-pentamethylspiro[1,3-dioxolane-4,1′(5′*H*)-[7,10]methanobenzocyclodecen]-5′-one (19b). A solution of **19a** (80.2 mg, 113 μmol), chloromethyl benzyl ether (197 μL, 1.73 mmol), tetra-*n*-butylammonium iodide (84 mg, 227 μmol), and diisopropylethylamine (590 μL, 3.40 mmol) in DMF (0.6 mL) was stirred overnight a rt, heated at 50 °C for 1 h, cooled, and quenched with saturated $NaHCO_3$ solution. The product was extracted into CH_2Cl_2 (3×), and the combined organic layers were dried and concentrated. The residue was purified by chromatography on silica gel (elution with 20% ethyl acetate in hexanes) to provide **19b** (81.1 mg, 86%) as a viscous, colorless oil: IR (film, cm^{-1}) 3456, 1701, 1251, 1148, 1099, 1040, 1004; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5 H), 7.21 (d, J = 8.6 Hz, 2 H), 6.84 (d, J = 8.6 Hz, 2 H), 4.74 (d, J = 7.5 Hz, 1 H), 4.65 (d, J = 7.5 Hz, 1 H), 4.62 (d, J = 11.6 Hz, 1 H), 4.55 (d, J = 2.3 Hz, 1 H), 4.50 (s, 2 H), 4.41 (d, J =, 7.1 Hz, 1 H), 4.39 (d, J = 11.6 Hz, 1 H), 4.28 (d, J = 7.1 Hz, 1 H), 4.20 (s, 1 H), 4.15 (d, J = 8.6 Hz, 1 H), 3.92 (dd, J = 11.5, 3.8 Hz, 1 H), 3.95−3.87 (m, 1 H), 3.88 (d, J = 8.6 Hz, 1 H), 3.78 (s, 3 H), 3.45 (dd, J = 12.4, 4.0 Hz, 1 H), 3.32 (s, 3 H), 2.70 (dt, J = 13.0, 4.0 Hz, 1 H), 2.57−2.25 (m, 5 H), 1.99−1.88 (m, 1 H), 1.76−1.53 (m, 3 H), 1.49 (s, 3 H), 1.43 (s, 3 H), 1.13 (s, 3 H), 1.08 (s, 3 H), 1.02 (s, 3 H), 0.89 (s, 9 H), 0.18 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.5, 159.1, 137.6, 130.1, 129.3, 128.4, 127.8, 127.7, 113.7, 109.2, 95.2, 93.9, 86.9, 81.9, 81.3, 80.7, 80.3, 71.8, 69.7, 69.1, 64.3, 57.9, 55.8, 55.7, 55.2, 49.8, 37.8, 32.2, 32.1, 31.8, 29.3, 26.9, 26.7, 26.6, 25.8, 18.0, 17.6, 11.3, −3.4, −4.4; MS m/z (M^+) calcd 826.4687, obsd 826.4716; $[\alpha]^{23}_D$ −12.5 (c 1.0, $CHCl_3$).

(2′*R*,4*S*,4′*S*,4′a*S*,6′*R*,7′*S*,10′*S*,11′*S*,12′a*S*)-11′-(*tert*-Butyldimethylsiloxy)dodecahydro-10′-hydroxy-2′,4′-bis[(*p*-methoxybenzyl)oxy]-6′-(methoxymethoxy)-4′-[(*p*-nitrobenzoyl)oxy]-2,2,4′a,13′,13′-pentamethylspiro[1,3-dioxolane-4,1′(5′*H*)-[7,10]methanobenzocyclodecen]-5′-one (19c). *p*-Nitrobenzoyl chloride (79 mg, 424 μmol) was added portionwise to a magnetically stirred solution of **19a** (18 mg, 25.4 μmol) in 1:1 pyridine/DMF (2 mL) containing a catalytic quantity of 4-(dimethylamino)pyridine. The reaction mixture was heated at 50 °C for 3 h, cooled, quenched with saturated $NaHCO_3$ solution, and extracted with ethyl acetate (3×). The combined organic phases were washed with 1 N HCl, dried, and concentrated. Chromatography of the residue on silica gel (elution with 20% ethyl acetate in hexanes) gave **19c** (15 mg, 69%) as a viscous, colorless oil: IR (film, cm^{-1}) 3461, 1733, 1700, 1531, 1267, 1090, 1040, 1005; ^1H NMR (300 MHz, C_6D_6) δ 7.81 (d, J = 8.7 Hz, 2 H), 7.74 (d, J = 8.7 Hz, 2 H), 7.30 (d, J = 8.5 Hz, 2 H), 6.87 (d, J = 8.5 Hz, 2 H), 5.58 (dd, J = 11.5, 3.8 Hz, 1 H), 4.73 (d, J = 2.9 Hz, 1 H), 4.50 (d, J = 11.0 Hz, 1 H), 4.44 (s, 1 H), 4.43 (d, J = 11.0 Hz, 1H), 4.34 (d, J = 8.5 Hz, 1 H), 4.29 (dd, J = 12.2, 2.6 Hz, 1 H), 4.23 (d, J = 7.0 Hz, 1 H), 4.13 (d, J = 7.0 Hz, 1 H), 4.08 (d, J = 8.5 Hz, 1 H), 3.73 (dd, J = 12.3, 4.1 Hz, 1 H), 3.35 (s, 3 H), 2.86 (s, 3 H), 2.79−2.70 (m, 6 H), 2.51−2.33 (m, 2 H), 1.98−1.76 (m, 2 H), 1.57 (s, 6 H), 1.46 (s, 3 H), 1.45 (s, 3 H), 1.38 (s, 3 H), 0.94 (s, 9 H), 0.34 (s, 3 H), 0.27 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 211.5, 163.5, 159.9, 150.7, 135.7, 130.2, 129.5, 128.0, 123.5, 114.2, 109.8, 93.9, 87.1, 82.5, 81.1, 80.0, 76.2, 72.2, 69.8, 64.7, 57.4, 56.9, 54.9, 54.7, 50.4, 38.3, 32.8, 32.5, 30.4, 30.0, 27.1, 27.0, 26.9, 25.9, 18.3, 18.2, 12.2, −3.2, −4.3; MS m/z (M^+) calcd 855.4225, obsd 855.4177; $[\alpha]^{23}_D$ +30.4 (c 1.66, $CHCl_3$). Anal. Calcd for $C_{45}H_{65}NO_{13}Si$: C, 63.13; H, 7.65. Found: C, 63.52; H, 8.05.

(2′*R*,4*S*,4′*S*,4′a*S*,6′*R*,7′*S*,10′*S*,11′*S*,12′a*S*)-4′-[(Benzyloxy)-methoxy]dodecahydro-10′11′-dihydroxy-2′-[(*p*-methoxybenzyl)oxy]-6′-(methoxymethoxy)-2,2,4′a,13′,13′-pentamethylspiro[1,3-dioxolane-4,1′(5′*H*)-[7,10]methanobenzocyclodecen]-5′-one (20). Tetra-*n*-butylammonium fluoride (200 μL of 1 M in THF, 200 μmol) was added to a magnetically stirred solution of **19b** (81 mg, 98 μmol) in dry THF (4 mL) at rt under N_2. After 30 min, the reaction mixture was poured into water and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried and concentrated, and the residue was purified by chromatography on silica gel (elution with 40% ethyl acetate in hexanes) to afford **20** (52.2 mg, 75%) as a white foam: IR (film, cm^{-1}) 3438, 1699, 1514, 1249, 1148, 1098, 1034; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7.27 (m, 5 H), 7.21 (d, J = 8.6 Hz, 2 H), 6.84 (d, J = 8.6 Hz, 2 H), 4.76 (d, J = 7.5 Hz, 1 H), 4.69 (d, J = 7.5 Hz, 1 H), 4.62 (d, J = 11.7 Hz, 1 H), 4.55−4.45 (m, 4 H), 4.42 (d, J = 7.3 Hz, 1 H), 4.27 (d, J = 7.3 Hz, 1 H), 4.20 (d, J = 8.8 Hz, 1 H), 4.04 (dd, J = 11.6, 4.2 Hz, 1 H), 3.83 (d, J = 8.8 Hz, 1 H), 3.78 (s, 3 H), 3.66 (dd, J = 6.2, 3.6 Hz, 1 H), 3.38 (dd, J = 12.2, 4.1 Hz, 1 H), 3.31 (s, 3 H), 2.78−2.68 (m, 2 H), 2.58−2.52 (m, 1 H), 2.33−2.26 (m, 2 H), 2.10−2.02 (m, 1 H), 1.95−1.70 (m, 3 H), 1.61−1.51 (m, 1 H), 1.47 (s, 6 H), 1.12 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 211.4, 159.1, 137.5, 129.9, 129.2, 129.1, 128.4, 127.8, 113.7, 109.7, 95.1, 94.2, 86.5, 84.7, 81.0, 80.5, 80.2, 71.2, 71.0, 69.8, 64.8, 58.6, 56.0, 55.6, 55.2, 48.1, 36.8, 32.6, 32.2, 31.3, 29.7, 27.6, 26.6, 25.9, 17.0, 11.6; MS m/z (M^+ − CH_3) calcd 697.3588, obsd 697.3591; $[\alpha]^{23}_D$ −36.0 (c 1.92, $CHCl_3$). Anal. Calcd for $C_{40}H_{56}O_{11}$: C, 67.39; H, 7.92. Found: C, 67.04; H, 8.12.

(2′*R*,4*S*,4′*S*,4′a*S*,6′*R*,7′*S*,10′*S*,11′*S*,12′a*S*)-4′-[(Benzyloxy)-methoxy]octahydro-10′-hydroxy-2′-[(*p*-methoxybenzyl)-oxy]-6′-(methoxymethoxy)-2,2,4′a,13′,13′-pentamethylspiro[1,3-dioxolane-4,1′(2′*H*)-[7,10]methanobenzocyclodecene]-5′,11′(3′*H*,6′*H*)-dione (21). DMSO (150 μL, 2.10 mmol) was added dropwise to a cold (−78 °C), magnetically stirred solution of oxalyl chloride (5.25 mL of 0.2 M in CH_2Cl_2, 1.05 mmol) under N_2. After 15 min, diol **20** (150 mg, 210 μmol) was introduced via cannula in CH_2Cl_2 (2 × 2 mL). After a further 20 min, diisopropylethylamine (3.67 mL, 21 mmol) was added slowly and the reaction mixture was kept at −78 °C for 1 h, allowed to warm slowly to 0 °C over 1 h, and quenched with H_2O (5 mL). The product was extracted into CH_2Cl_2 (3×), dried, concentrated, and columned on silica gel (elution with 30 → 40% ethyl acetate in hexanes) to afford 110 mg (73%) of **21** and 15 mg (10%) of unreacted **20** (81% based on recovered **20**).

For **21**: IR (film, cm^{-1}) 3446, 1709, 1683, 1515, 1248, 1212, 1148, 1097, 1039, 1001; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.28 (m, 5 H), 7.21 (d, J = 8.6 Hz, 2 H), 6.84 (d, J = 8.6 Hz, 2 H), 4.80 (d, J = 7.6 Hz, 1 H), 4.70 (d, J = 7.6 Hz, 1 H), 4.64 (s, 1 H), 4.63 (d, J = 12.2 Hz, 1 H), 4.54 (d, J = 11.1 Hz, 1 H), 4.49 (d, J = 11.1 Hz, 1 H), 4.42 (d, J = 12.2 Hz, 1 H), 4.38 (d, J = 7.2 Hz, 1 H), 4.27 (d, J = 7.2 Hz, 1 H), 4.15 (d, J = 8.9 Hz, 1 H), 4.12 (dd, J = 9.0, 1.6 Hz, 1 H), 3.83 (d, J = 8.9 Hz, 1 H),

3.78 (s, 3 H), 3.53 (dd, J = 12.3, 3.3 Hz, 1 H), 3.31 (s, 3 H), 3.20 (dd, J = 16.4, 2.9 Hz, 1 H), 2.91 (dd, J = 10.0, 2.9 Hz, 1 H), 2.76–2.63 (m, 5 H), 2.51 (dd, J = 16.4, 10.0 Hz, 1 H), 2.08–1.97 (m, 2 H), 1.41 (s, 3 H), 1.40 (s, 3 H), 1.10 (s, 3 H), 1.05 (s, 3 H), 1.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 214.7, 210.7, 159.2, 137.5, 129.8, 129.3, 128.5, 127.8, 127.7, 113.8, 109.3, 95.2, 94.2, 88.1, 86.4, 80.3, 79.8 (2 C), 71.9, 69.8, 64.2, 58.0, 55.7, 55.4, 55.2, 50.1, 40.7, 36.2, 32.3, 31.1, 30.7, 27.1, 26.4, 26.3, 18.3, 10.7; MS m/z ($M^+ - CH_3$) calcd 695.3431, obsd 695.3423; $[\alpha]^{23}_D$ −23.6 (c 1.03, $CHCl_3$).

(1′*S*,3*R*,4*S*,4′a*S*,6′*R*,10′*S*,12′a*S*)-1′-[(Benzyloxy)methoxy]-decahydro-6′-hydroxy-3′-[(*p*-methoxybenzyl)oxy]-11′-(methoxymethoxy)-2,2,12′a,13′,13′-pentamethylspiro[1,3-dioxolane-4,4′(1′*H*)-[6,10]methanobenzocyclodecene]-7′,12′-dione (22). A solution of **21** (17.4 mg, 24.5 μmol) and aluminum tri-*tert*-butoxide (18 mg, 73.4 mmol) in benzene (2 mL) was refluxed for 12 h, cooled, quenched with 1 N HCl, and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried, filtered, and evaporated to leave a residue that was chromatographed on silica gel (elution with 35% ethyl acetate in hexanes) to give 16.4 mg (94%) of **22** as a colorless film; IR (neat, cm^{-1}) 3477, 1802, 1705, 1613, 1515, 1383, 1249, 1213, 1150, 1041, 737; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.27 (m, 5 H), 7.19 (d, J = 8.6 Hz, 2 H), 6.83 (d, J = 8.6 Hz, 2 H), 4.85 (d, J = 4.5 Hz, 1 H), 4.70 (s, 2 H), 4.63 (d, J = 12.3 Hz, 1 H), 4.52 (d, J = 11.0 Hz, 1 H), 4.51 (s, 1 H), 4.46 (d, J = 11.0 Hz, 1 H), 4.44 (d, J = 12.3 Hz, 1 H), 4.44 (d, J = 7.7 Hz, 1 H), 4.40 (d, J = 7.7 Hz, 1 H), 4.13–4.08 (m, 1 H), 4.11 (d, J = 8.4 Hz, 1 H), 3.78 (s, 3 H), 3.72 (d, J = 8.4 Hz, 1 H), 3.73–3.78 (m, 1 H) 3.41 (s, 3 H), 2.88–2.77 (m, 2 H), 2.71 (dt, J = 13.2, 4.1 Hz, 1 H), 2.59–2.57 (m, 1 H), 2.43 (ddd, J = 19.7, 12.8, 6.9 Hz, 1 H), 2.32–2.19 (m, 2 H), 2.08–2.01 (m, 1 H), 1.98–1.91 (m, 2 H), 1.37 (s, 3 H), 1.31 (s, 3 H), 1.21 (s, 3 H), 0.99 (s, 3 H), 0.96 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.9, 209.6, 159.1, 137.6, 130.0, 129.1, 128.4, 127.8, 127.7, 113.7, 109.9, 94.3, 93.8, 87.0, 83.0, 79.8, 77.4, 76.8, 71.2, 69.8, 64.7, 58.4, 56.1, 55.2, 51.8, 42.9, 38.9, 37.9, 33.1, 31.8, 29.6, 28.3, 27.4, 26.8, 22.9, 10.1; MS m/z ($M^+ - CH_3$) calcd 695.3431, obsd 695.3442; $[\alpha]^{23}_D$ +8.9 (c 0.89, $CHCl_3$).

Acknowledgment. We are grateful to the National Institutes of Health for their financial support (Grant CA-63344), to Dr. Kurt Loening for providing assistance with nomenclature, and to Dr. Zhuang Su and Prof. Christoph Tamm for disclosure of their results described in reference 5 in advance of publication.

Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra of those compounds for which analytical data are not provided (14 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.

JO951359M