Total Synthesis of Taxol. 3. Formation of Taxol's ABC Ring Skeleton

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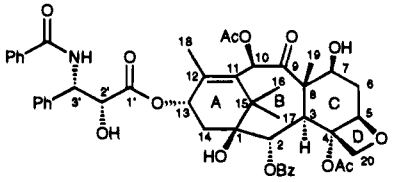
Abstract: The synthesis of Taxol's ABC ring system has been achieved. The Shapiro coupling of an aldehydic C ring synthon (**8**) with an anionic A ring synthon derived from hydrazone **9** gave, diastereoselectively, A–B conjugate **10**. Functional group manipulations and McMurry ring closure produced the highly functionalized ABC ring system **17**. Extensive attempts to optimize the McMurry reaction revealed a single predominant side reaction leading to byproducts **19** and **20**. Resolution of the C9,C10-diol (±)-**17** via its camphanyl esters provided the ABC ring system as its natural isomer (+)**17**.

Introduction

In the preceding two papers[1,2] in this series, we described our degradation and reconstruction studies with Taxol (**1**, Figure 1), preliminary investigations with rings A and C, and possible schemes for their elaboration to an appropriately functionalized ABC taxoid framework. Armed with the knowledge gained in these studies, we were now ready to attempt the final drive toward Taxol's ABC ring skeleton. As already discussed, the starting materials were defined as hydrazone **9**[2] (Scheme 2) and aldehyde **8** (Scheme 1), the synthesis of which is detailed below. The C4–C20 five-membered acetonide group was chosen as a means to protect the vicinal diol system of the intermediate and to introduce additional rigidity in the system prior to cyclization to form the 8-membered ring.

Construction of Taxol's ABC Ring Skeleton

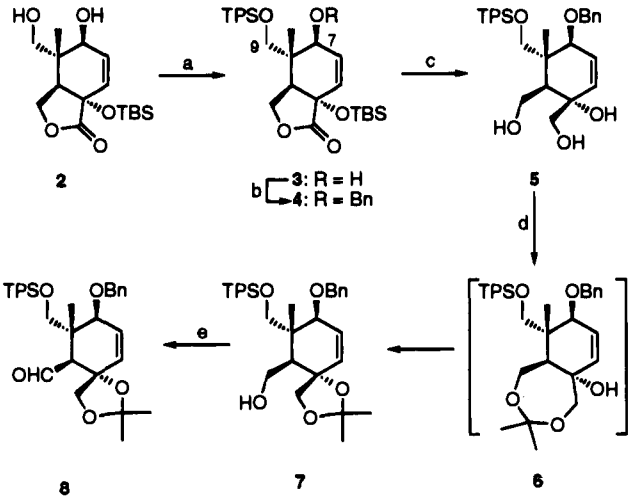
a. Synthesis of the C Ring Aldehyde 8. Scheme 1 summarizes the preparation of the targeted aldehyde **8** from the previously described intermediate **2**.[2] Thus, treatment of diol **2** with *tert*-butyldiphenylsilyl chloride (TPSCl) and imidazole[3] resulted in monosilylation of the primary alcohol, providing the C7 hydroxyl, C9 silyl ether **3** in 92% yield. Benzylation of the C7 hydroxyl group using KH and benzyl bromide[4] afforded benzyl ether **4** in 88% yield. Exhaustive reduction of the lactone ring in **4**, accompanied by removal of the C4 TBS group, resulted in the formation of triol **5** (80% yield). The crucial 5-membered ring acetonide was then installed using 2,2-dimethoxypropane in the presence of a catalytic amount of CSA[5] in methylene chloride:ether (98:2) at ambient temperature. Under these conditions, the reaction was found to be quite rapid with the initially formed 7-membered ring acetonide **6** rearranging slowly and essentially completely to the desired, and thermodynamically more stable, 5-membered ring isomer **7** (82%). Finally, TPAP–NMO oxidation[6] of the remaining hydroxyl group in **7** furnished the targeted aldehyde **8** in 97%



1: Taxol

Figure 1. Structure and numbering of Taxol (**1**).

Scheme 1. Synthesis of C Ring Aldehyde **8**[a]



[a] Reagents and conditions: (a) 1.3 equiv of TPSCl, 1.35 equiv of imidazole, DMF, 25 °C, 12 h, 92%; (b) 1.2 equiv of KH, 1.2 equiv of $PhCH_2Br$, 0.04 equiv of n-Bu_4NI, Et_2O, 25 °C, 1 h, 88%; (c) 3.0 equiv of $LiAlH_4$, Et_2O, 25 °C, 12 h, 80%; (d) 5.0 equiv of 2,2-dimethoxypropane, 0.05 equiv of camphorsulfonic acid (CSA), CH_2Cl_2:Et_2O (98:2), 25 °C, 7 h, 82%; (e) 0.05 equiv of tetrapropylammonium perruthenate (TPAP), 1.5 equiv of 4-methylmorpholine N-oxide (NMO), CH_3CN, 25 °C, 2 h, 97%. TBS = Si-t-BuMe$_2$, Bn = CH_2Ph, TPS = Si-t-BuPh$_2$.

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(1) Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624.

(2) Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634.

(3) Hanessian, S.; Lavallée, P. *Can. J. Chem.* **1975**, *53*, 2975. Hanessian, S.; Lavallée, P. *Can. J. Chem.* **1977**, *55*, 562.

(4) Kanai, K.; Sakamoto, I.; Ogawa, S.; Suami, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1529.

(5) Lipshutz, B. H.; Barton, J. C. *J. Org. Chem.* **1988**, *53*, 4495.

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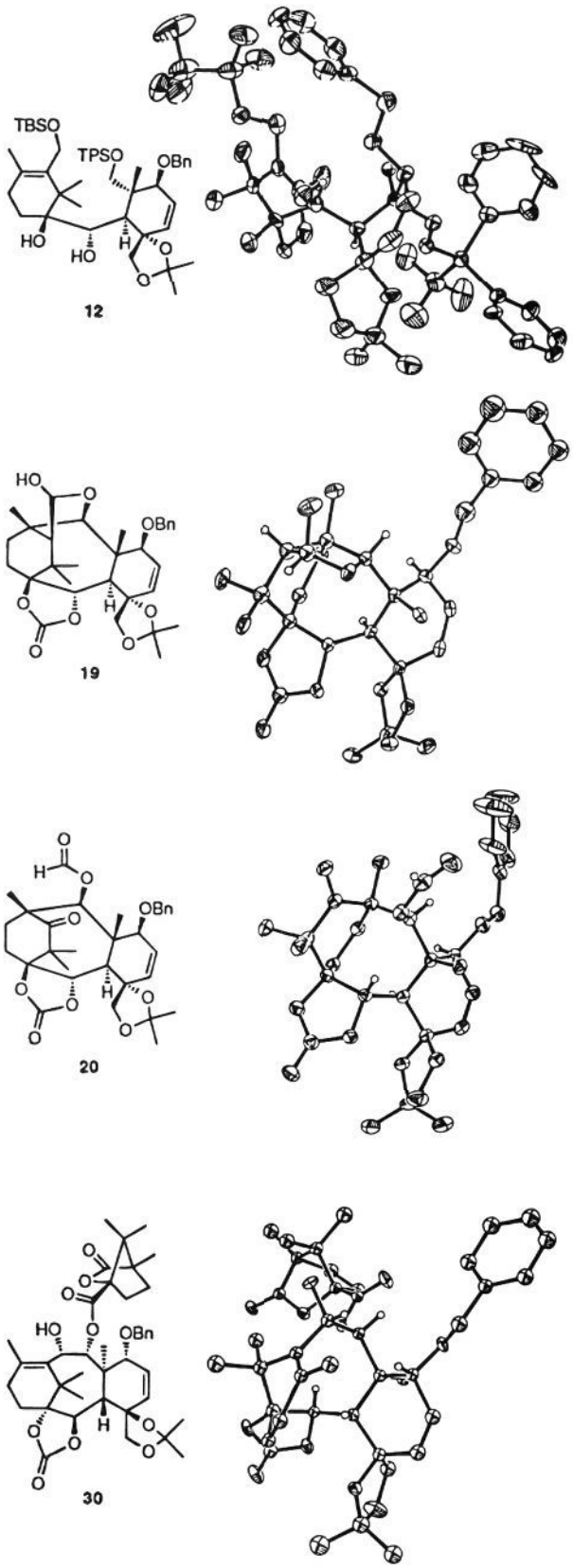
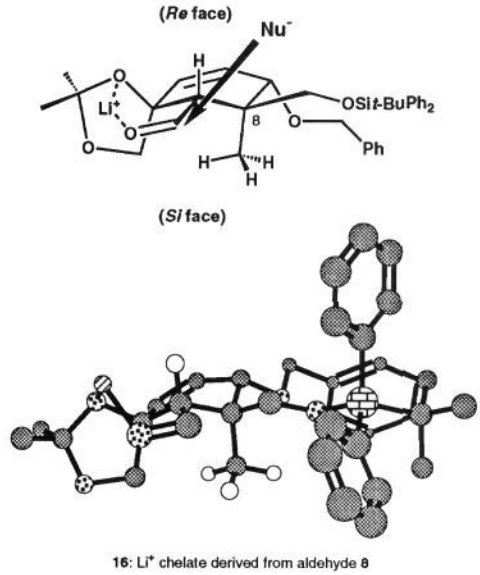


Figure 2. ORTEP drawings for compounds **12**, **19**, **20**, and **30**.

yield. Thus a rapid and efficient pathway to key intermediate **8** was established.

b. The Shapiro Coupling Reaction and Synthesis of Dialdehyde 15. The Shapiro coupling reaction[7,8] of hydrazone **9** with aldehyde **8** proceeded under the conditions specified in Scheme 2 to afford allylic alcohol **10** as a single diastereoisomer and in 82% yield. X-ray crystallographic analysis of a subsequent intermediate confirmed the stereochemical structure of **10** (*vide infra*). The stereoselectivity of this reaction can be explained by invoking the chelated intermediate **16**, depicted in Figure 3, in which the acetonide plays a crucial role. As seen in this model, the aldehyde group is fixed by the lithium template in a conformation in which nucleophilic attack can freely proceed from only one side, the *re* face, with the *si* face being blocked by the C8 methyl group.



16: Li^+ chelate derived from aldehyde **8**

Figure 3. Stereoselectivity of the Shapiro reaction. The model was generated with Chem3d. Most hydrogens are omitted for clarity.

Directed epoxidation[9] of the C1−C14 double bond in **10**, although slow, proceeded smoothly to afford the single epoxide **11** in 87% yield. Regioselective opening[10] of the epoxide group in **11** with $LiAlH_4$ resulted in the formation of diol **12** in 76% yield. The crystalline diol **12** was subjected to X-ray crystallographic analysis (see ORTEP drawing, Figure 2) confirming the assigned stereochemistry of all intermediates in Scheme 2. Exposure of **12** to excess KH and phosgene in ether:HMPA (3:1) resulted in the formation of carbonate **13** (86% yield, 58% conversion). Desilylation of **13** with fluoride ion[3] furnished diol **14** (80% yield), which was oxidized smoothly with TPAP−NMO[6] to afford the dialdehyde **15** (92% yield)—preorganized in a conformation favorable for the upcoming McMurry cyclization.[11]

c. The McMurry Cyclization and Synthesis of the ABC Ring Skeleton 17. The search for the conditions required to yield the requisite cyclized product using the McMurry pinacol

(6) Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13.

(7) Shapiro, R. H. *Org. React.* **1976**, *23*, 405. Chamberlin, A. R.; Bloom, S. H. *Org. React.* **1990**, *39*, 1. Martin, S. F.; Daniel, D.; Cherney, R. J.; Liras, S. *J. Org. Chem.* **1992**, *57*, 2523.

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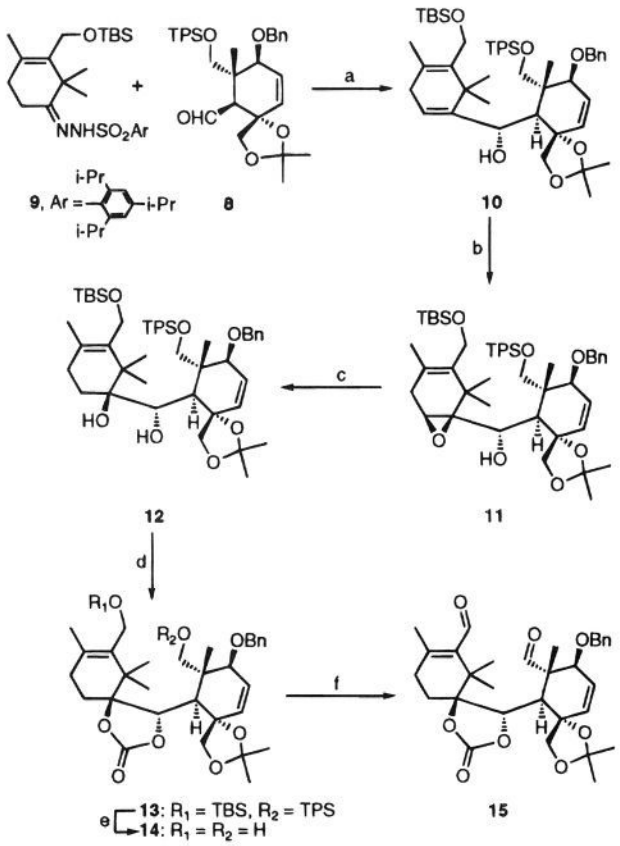
(9) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136. Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63. Rao, A. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ley, S. V., FRS, Eds.; Pergamon Press: New York, 1991; Vol. 7, p 376.

(10) Murai, S.; Murai, T.; Kato, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 8, p 871.

(11) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513. McMurry J. E. *Acc. Chem. Res.* **1983**, *16*, 405. McMurry, J. E.; Lectka, T.; Rico, J. G. *J. Org. Chem.* **1989**, *54*, 3748. McMurry, J. E.; Rico, J. G. *Tetrahedron Lett.* **1989**, *30*, 1169. Lenoir, D. *Synthesis* **1989**, 883.

Scheme 2. Shapiro Coupling of **8** with **9** and Synthesis of Dialdehyde **15**[a]

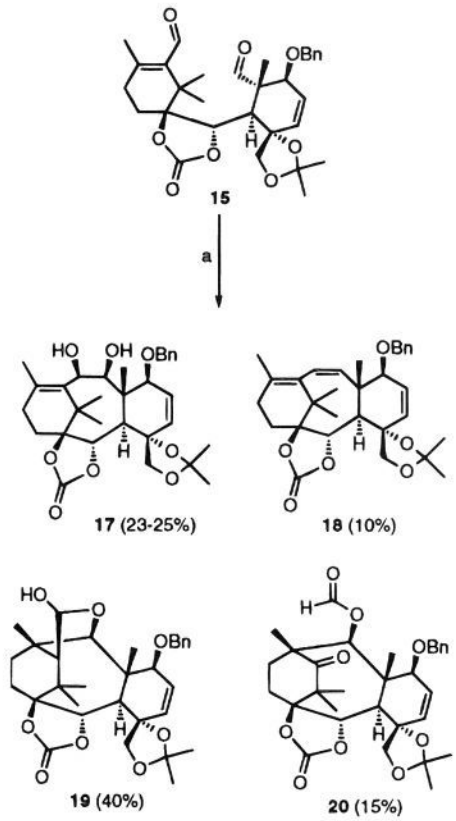


[a] Reagents and conditions: (a) 1.1 equiv of **9**, 2.3 equiv of *n*-BuLi, THF, −78 → 0 °C, 1.0 equiv of **8**, THF, −78 °C, 0.5 h, 82%; (b) 0.03 equiv of $VO(acac)_2$, 3.0 equiv of *t*-BuOOH, PhH, 4 Å molecular sieves, 25 °C, 14 h, 87%; (c) 5.0 equiv of $LiAlH_4$, 25 °C, Et_2O, 7 h, 76%; (d) 3.0 equiv of KH, Et_2O:HMPA (3:1), 1.6 equiv of phosgene (20% in toluene), 25 °C, 0.5 h, 86% based on 58% conversion; (e) 3.8 equiv of *n*-Bu_4NF (TBAF), THF, 25 °C, 14 h, 80%; (f) 0.05 equiv of tetrapropylammonium perruthenate (TPAP), 3.0 equiv of 4-methylmorpholine *N*-oxide (NMO), CH_3CN, CH_2Cl_2, (2:1), 25 °C, 2 h, 92%. TBS = Si-*t*-$BuMe_2$, TPS = Si-*t*-$BuPh_2$, Bn = CH_2Ph.

coupling methodology included varying the temperature (0 → 100 °C), solvent (e.g. THF, DME, ether) and stoichiometry, as well as the use of various bases as additives. It was finally determined that 11 equiv of $TiCl_3$•$(DME)_{1.5}$ and 26 equiv of Zn−Cu couple in DME at 70 °C provided the optimum yield of diol **17** (25%, Scheme 3). In addition to diol **17**, whose stereochemistry was assigned on the basis of a subsequent intermediate (*vide infra*), a number of other products were obtained including olefin **18** (10% yield), lactol **19** (40% yield), and formate ester **20** (15% yield). The structures of **17** and **18** were based solely upon spectroscopic evidence (except for the stereochemistry of **17** at C9 and C10 which was later confirmed, *vide infra*), whereas those of **19** and **20** were secured from both spectroscopic and X-ray crystallographic data (see ORTEP drawings, Figure 2).

Analysis of molecular models for dialdehyde **15** indicated a possible ground state conformation in which the two aldehyde moieties of **15** are in close proximity (Figure 4), thus requiring only small conformational changes to reach the geometry necessary for cyclization. Rotation around the C2−C3 carbon−carbon bond would either bring the two aldehyde groups in very close proximity, as desired, or induce strong steric interactions between ring A and the acetonide group. In contrast, dialdehyde **21** (see Figure 5 and previous paper[2] in this series, Scheme 13,

Scheme 3. McMurry Cyclization and Synthesis of Diol **17**[a]



[a] Reagents and conditions: 11 equiv of $TiCl_3$•$(DME)_{1.5}$, 26 equiv of Zn−Cu, DME, reflux, 3.5 h, then 70 °C, then **15** added over 1 h, then 70 °C, 0.5 h. Bn = CH_2Ph.

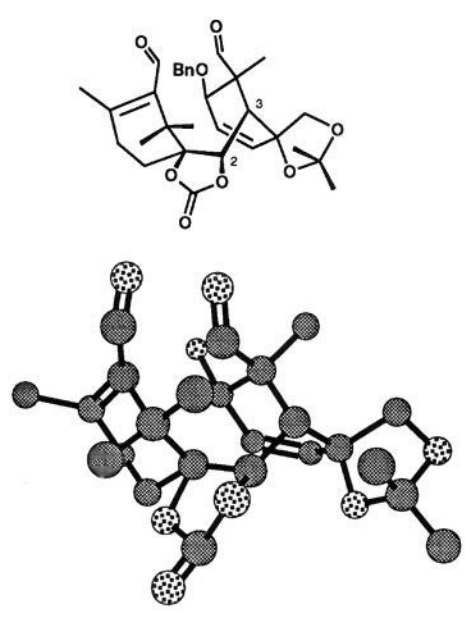


Figure 4. Possible ground state conformation of **15**. The model was generated with Chem3d. The C7 benzyl protecting group and all hydrogens are omitted for clarity. Bn = CH_2Ph.

structure **95**) offers much higher conformational freedom via rotation around the C1−C2 carbon−carbon bond. Analysis of molecular models indicated a possible ground state conformation (**21**) (Figure 5) for this compound in which the two aldehyde functionalities are far apart. Failure to cyclize to such a system

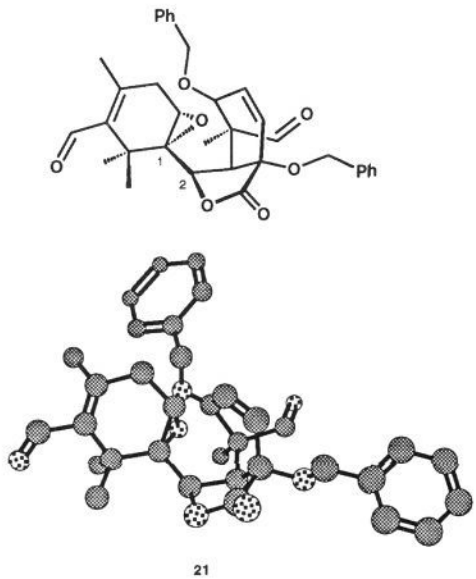


Figure 5. Possible ground state conformation of **21**. The model was generated with Chem3d. All hydrogens are omitted for clarity.

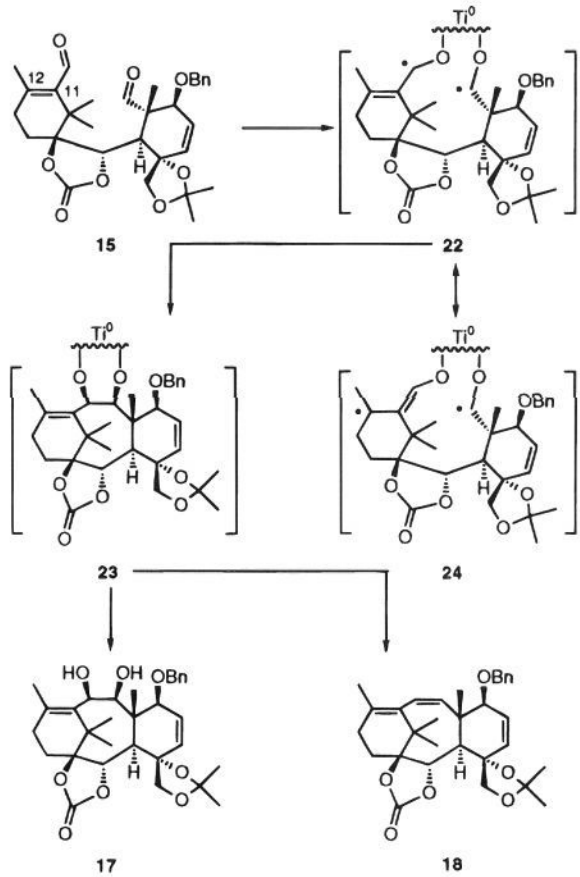
in the McMurry reaction may reflect the large entropic and enthalpic cost for the conformational change necessary for reaction to take place.

Mechanistic rationales for the formation of products **17**−**28** are shown in Schemes 4 and 5. The pathways leading to **17**−**19** are in accord with previous proposals by McMurry[11] and Kende.[12] The formation of the keto formate **20**, however, requires an additional oxygen atom which may, presumably, come from molecular oxygen introduced during workup. A speculative mechanism for its formation is proposed in Schemes 4 (**15** → **22** → **24**) and 5 (**24** → **25** → **27** → **28** → **20**).

Attempts at masking the C11−C12 double bond in order to avoid the formation of byproducts **19** and **20** were abandoned after unsuccessful early trials. Further studies along this line, however, may prove useful in controlling product formation in this reaction.

d. Resolution of ABC Ring System Diol 17. To secure enantiomerically pure intermediates for the synthesis of Taxol (**1**), we decided to attempt a resolution of the racemic diol **17** obtained from the McMurry cyclization as described above. Encouraged by a successful resolution of a similar taxoid[13] via camphanate esters,[14] we applied the sequence shown in Scheme 6 to our system. Treatment of diol (±)-**17** with an excess of (1*S*)-(−)-camphanic chloride in methylene chloride in the presence of Et_3N resulted in the formation of two diastereomeric monoesters **29** and **30** in 86% total yield (1:1 ratio). Chromatographic separation of the mixture allowed the more polar isomer (**30**, $R_f = 0.21$, silica, 15% EtOAc in PhH; $[\alpha]^{22}_D$ −133 (*c* 0.49, $CHCl_3$)) to crystallize. X-ray crystallographic analysis (see ORTEP drawing, Figure 2) revealed the absolute stereochemistry of the latter diastereoisomer and thus allowed identification of the requisite isomer for the synthesis of Taxol as the less polar diastereoisomer (**29**; $R_f = 0.26$, silica, 15% EtOAc in PhH; $[\alpha]^{22}_D$ +117 (*c* 0.54, $CHCl_3$)). Hydrolysis of this isomer (**29**) under basic conditions (K_2CO_3, MeOH) regenerated diol (+)-**17** (90% yield; $[\alpha]^{22}_D$ +187 (*c* 0.5, $CHCl_3$)), now in its enantiomerically pure form.

Scheme 4. Postulated Mechanism of the McMurry Cyclization and Formation of Products **17** and **18**



The appearance of the chiral auxiliary on the C9 hydroxyl group of these esters (**29** and **30**) was at first surprising, particularly in view of the fact that monoacetylation of diol **17** leads selectively to the C10 acetate (see following paper).[15] Inspection of molecular models revealed rather similar steric environments for these two positions, and therefore, predictions or rationalizations were not easy to make. Apparently, the more reactive allylic C10 hydroxyl group attracts the smaller acetate group, whereas only the C9 hydroxyl can accommodate the bulkier camphanate ester functionality.

Conclusion

In this paper we describe the successful construction of a suitable ring C aldehyde (**8**) and its stereoselective coupling with the ring A hydrazone (**9**) through a Shapiro reaction. Elaboration of the A−C-coupled product (**10**) led to a dialdehyde (**15**) which entered into a successful McMurry cyclization to afford ring B with retention of the C9 and C10 oxygens. Resolution of the resulting racemic ABC taxoid diol **17** through its diastereomeric camphanate esters (**29** and **30**) set the stage for an enantioselective synthesis of Taxol (**1**). The final stages of the total synthesis of this target molecule are described in the following paper.[15]

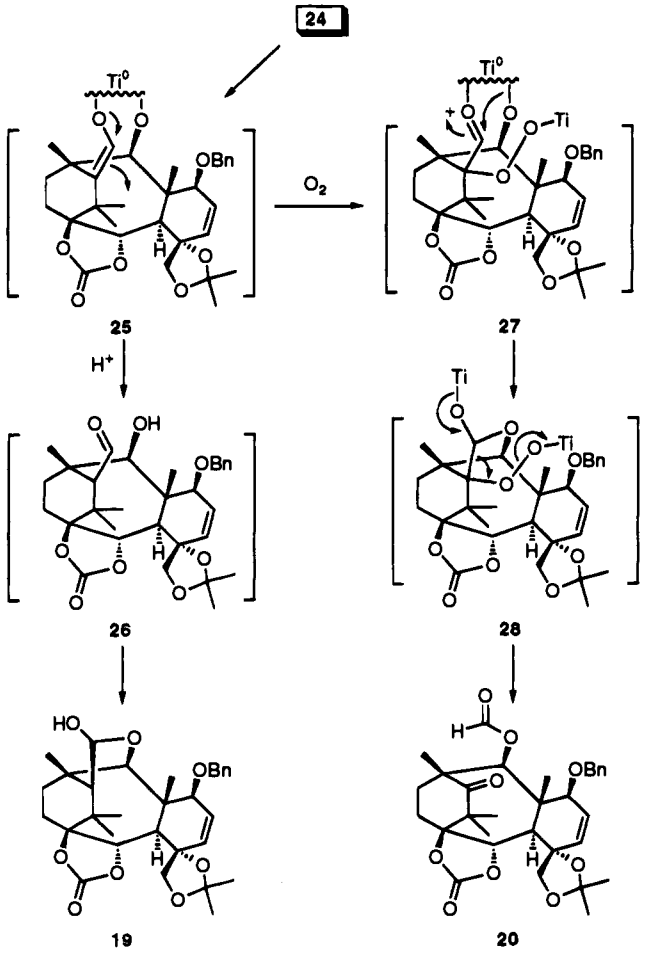
Experimental Section

General Techniques. For a description of general technique, see the first paper in this series.[1]

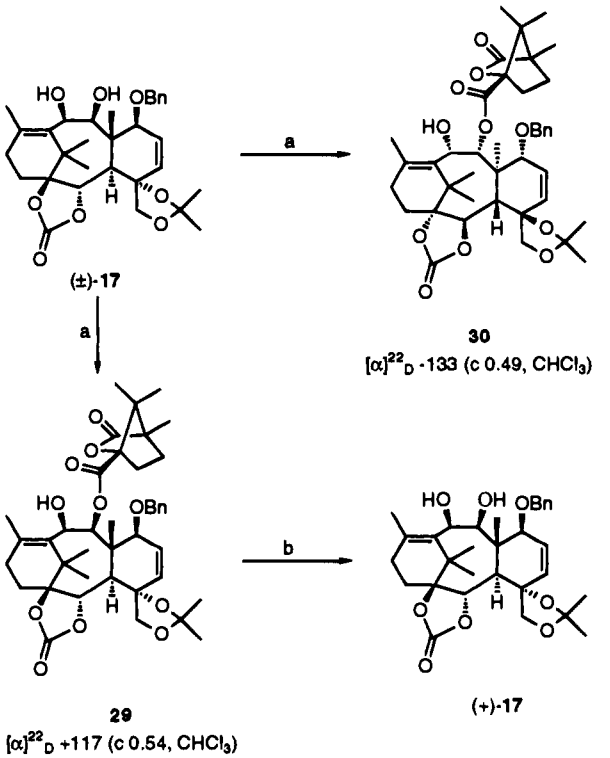
Silyl Ether 3. A solution of diol **2** (9.20 g, 28.0 mmol) in DMF (50 mL) was treated with imidazole (2.58 g, 37.9 mmol) and

(12) Kende, A. S.; Johnson, S.; Sanfilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc.* **1986**, *108*, 3513.
(13) Nicolaou, K. C.; Claiborne, C. F.; Nantermet, P. G.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1994**, *116*, 1591.
(14) Gerlach, H. *Helv. Chim. Acta* **1978**, *61*, 2773.
(15) Nicolaou, K. C.; Ueno, H.; Liu, J.-J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.* **1995**, *117*, 653.

Scheme 5. Postulated Mechanism for the Formation of Products **19** and **20**



Scheme 6. Resolution of Diol **17**[a]



[a] Reagents and conditions: (a) 5.0 equiv of (1*S*)-(−)-camphanic chloride, 20 equiv of Et_3N, 0.05 equiv of 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 25 °C, 1 h, 86%; (b) 7.0 equiv of K_2CO_3, MeOH, 25 °C, 0.5 h, 90%. Bn = CH_2Ph.

tert-butylchlorodiphenylsilane (9.46 mL, 36.0 mmol) and stirred at 25 °C for 12 h. After dilution with Et_2O (400 mL), the reaction was quenched with aqueous $NaHCO_3$ (100 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layer was washed with brine (50 mL), dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica, 30% Et_2O in petroleum ether) to give **3** (14.6 g, 92%) as a pale yellow oil: R_f = 0.41 (silica, 50% Et_2O in petroleum ether); IR (thin film) ν_{max} 3460, 2954, 2931, 2857, 1770, 1471, 1110, 1086 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65−7.55 (band, 4 H, Ar), 7.48−7.35 (band, 6 H, Ar), 5.91 (dd, J = 10.5, 2.0 Hz, 1 H, 6-H), 5.84 (dd, J = 10.5, 2.5 Hz, 1 H, 5-H), 4.58 (m, 1 H, 7-H), 4.19 (dd, J = 10.0, 6.5 Hz, 1 H, 2-H), 3.95 (dd, J = 10.0, 2.0 Hz, 1 H, 2-H), 3.61 (d, J = 10.6 Hz, 1 H, 9-H), 3.41 (d, J = 10.6 Hz, 1 H, 9-H), 2.59 (dd, J = 6.5, 2 Hz, 1 H, 3-H), 2.05 (d, J = 5.5 Hz, 1 H, 7-OH), 1.07 (s, 9 H, $SiC(CH_3)_3Ph_2$), 0.80 (s, 9 H, $SiC(CH_3)_3(CH_3)_2$), 0.69 (s, 3 H, 19-CH_3), 0.11 (s, 6 H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 136.1, 135.6, 135.5, 132.6, 132.5, 130.1, 127.9, 124.6, 74.5, 68.7, 66.6, 65.6, 47.2, 44.1, 26.9, 25.4, 19.2, 18.0, 11.0, −2.8, −3.1; FAB HRMS (NBA/NaI) *m/e* 589.2795, M + Na^+ calcd for $C_{32}H_{46}O_5Si_2$ 589.2782.

Benzyl Ether 4. A solution of alcohol **3** (21.5 g, 37.9 mmol), benzyl bromide (5.4 mL, 45.4 mmol), and *n*-Bu_4NI (0.5 g, 1.35 mmol) in Et_2O (300 mL) was treated with KH (6 g of a 30% suspension in mineral oil, 44.8 mmol, prewashed with dry Et_2O) and stirred at 25 °C for 1 h. After the reaction was quenched with MeOH (5 mL), the reaction mixture was stirred at 25 °C for 15 min. After dilution with Et_2O (200 mL), the resulting solution was washed with brine (100 mL), dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica, 10 → 30% Et_2O in petroleum ether) to give **4** (21.9 g, 88%) as a yellowish oil: R_f = 0.57 (silica, 25% Et_2O in petroleum ether); IR (thin film) ν_{max} 2956, 2925, 2849, 1773, 1467, 1101 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65−7.55 (band, 4 H, Ar), 7.45−7.25 (band, 11 H, Ar), 6.04 (dd, J = 10.0, 2.5 Hz, 1 H, 6-H), 5.82 (dd, J = 10.0, 2.5 Hz, 1 H, 5-H), 4.72 (d, J = 11.5 Hz, 1 H, OCH_2Ph), 4.58 (d, J = 11.5 Hz, 1 H, OCH_2Ph), 4.36 (dd, J = 2.5, 2.0 Hz, 1 H, 7-H), 4.08 (dd, J = 9.5, 7.0 Hz, 1 H, 2-H), 3.96 (dd, J = 9.5, 3.5 Hz, 1 H, 2-H), 3.69 (d, J = 10.6 Hz, 1 H, 9-H), 3.39 (d, J = 10.6 Hz, 1 H, 9-H), 2.66 (dd, J = 7.0, 3.5 Hz, 1 H, 3-H), 1.08 (s, 9 H, $SiC(CH_3)_3Ph_2$), 0.78 (s, 9 H, $SiC(CH_3)_3(CH_3)_2$), 0.77 (s, 3 H, 19-CH_3), 0.12 (s, 3 H, $SiC(CH_3)_3(CH_3)_2$), 0.11 (s, 3 H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 138.3, 135.6, 132.9, 132.9, 132.8, 130.0, 129.8, 128.4, 127.8, 127.7, 127.6, 127.4, 124.7, 74.5, 74.4, 72.6, 65.7, 65.6, 47.5, 43.9, 27.0, 25.5, 19.3, 18.0, 12.8, −2.8, −3.1; FAB HRMS (NBA/CsI) *m/e* 789.2395, M + Cs^+ calcd for $C_{39}H_{52}O_5Si_2$ 789.2408.

Triol 5. A solution of lactone **4** (14.7 g, 22.4 mmol) in Et_2O (150 mL) was treated with $LiAlH_4$ (66 mL of a 1 M solution in Et_2O, 66.0 mmol) and stirred at 25 °C for 12 h. After dilution with Et_2O (200 mL), the reaction mixture was cooled to −78 °C, and the reaction was quenched with aqueous NH_4Cl (100 mL). After the solution was warmed to 25 °C, the organic layer was separated, washed with brine (100 mL), dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica, 60% EtOAc in petroleum ether) to give **5** (9.8 g, 80%) as a colorless oil: R_f = 0.23 (silica, 50% EtOAc in hexanes); IR (thin film) ν_{max} 3374, 2927, 2851, 1463, 1422, 1387, 1105 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65−7.55 (band, 4 H, Ar), 7.45−7.15 (band, 11 H, Ar), 5.85 (dd, J = 10.0, 2.5 Hz, 1 H, 6-H), 5.69 (dd, J = 10.0, 1.5 Hz, 1 H, 5-H), 4.55 (d, J = 11.5 Hz, 1 H, OCH_2Ph), 4.27 (d, J = 11.5 Hz, 1 H, OCH_2Ph), 4.01 (b s, 1 H, 7-H), 3.96−3.89 (band, 3 H, 20-CH_2 and 2-H), 3.72 (d, J = 10.5 Hz, 1 H, 9-H), 3.70 (s, 1 H, 4-OH), 3.58 (m, 1 H, 2-H), 3.51 (d, J = 10.5 Hz, 1 H, 9-H), 3.45−3.35 (band, 2 H, 2-OH and 20-OH), 2.15 (dd, J = 6.5, 3.5 Hz, 1 H, 3-H), 1.09 (s, 9 H, $SiC(CH_3)_3Ph_2$), 0.89 (s, 3 H, 19-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 135.8, 135.7, 132.9, 131.2, 129.9, 129.8, 128.3, 128.2, 127.7, 127.5, 127.3, 76.2, 73.1, 71.6, 67.1, 66.7, 59.4, 48.0, 43.4, 27.0, 25.8, 19.3, 15.3; FAB HRMS (NBA/CsI) *m/e* 679.1871, M + Cs^+ calcd for $C_{33}H_{42}O_5Si$ 679.1856.

Acetonide 7. A solution of triol **5** (16.2 g, 29.6 mmol) and 2,2-dimethoxypropane (18.2 mL, 148 mmol) in CH_2Cl_2 (98 mL) and Et_2O (2 mL) was treated with camphorsulfonic acid (350 mg, 1.5 mmol) and stirred at 25 °C for 7 h. After the reaction was quenched with

aqueous $NaHCO_3$ (50 mL), the organic layer was separated, dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica, 50% Et_2O in petroleum ether) to give **7** (14.25 g, 82%) as a colorless oil: R_f = 0.51 (silica, 50% Et_2O in petroleum ether); IR (thin film) ν_{max} 3467, 2932, 2858, 1462, 1373, 1210, 1106, 1054 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66–7.60 (band, 4 H, Ar), 7.45–7.20 (band, 9 H, Ar), 7.15–7.05 (band, 2 H, Ar), 5.79 (dd, J = 10.0, 1.5 Hz, 1 H, 6-H), 5.72 (dd, J = 10.0, 2.5 Hz, 1 H, 5-H), 4.45 (d, J = 11.5 Hz, 1 H, OCH_2Ph), 4.16 (d, 9.0 Hz, 1 H, 20-H), 4.11 (d, J = 11.5 Hz, 1 H, OCH_2Ph), 3.99 (b s, 1 H, 7-H), 3.97–3.89 (band, 2 H, 2-CH_2), 3.81 (d, 9.0 Hz, 1 H, 20-H), 3.76 (A of AB, d, J = 10.5 Hz, 1 H, 9-H), 3.73 (B of AB, d, J = 10.5 Hz, 1 H, 9-H), 3.42 (b t, J = 6.0 Hz, 1 H, 2-OH), 2.14 (t, J = 4.0 Hz, 1 H, 3-H), 1.44 (s, 3 H, $C(CH_3)_2$), 1.42 (s, 3 H, $C(CH_3)_2$), 1.09 (s, 9 H, $SiC(CH_3)_3Ph_2$), 0.87 (s, 3 H, 19-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 135.9, 135.8, 132.9, 132.7, 132.5, 129.9, 129.8, 128.2, 127.7, 127.4, 127.2, 126.6, 107.9, 81.9, 75.9, 71.3, 70.0, 67.1, 58.8, 48.1, 44.2, 27.3, 27.0, 26.4, 19.3, 14.1; FAB HRMS (NBA/NaI) *m/e* 609.3028, M + Na^+ calcd for $C_{36}H_{46}O_5Si$ 609.3012.

Aldehyde 8. A solution of alcohol **7** (9.7 g, 16.5 mmol) in CH_3CN (100 mL) was treated with tetrapropylammonium perruthenate (TPAP, 290 mg, 0.83 mmol) and 4-methylmorpholine *N*-oxide (NMO, 2.91 g, 24.8 mmol) and stirred at 25 °C for 2 h. After dilution with CH_2Cl_2 (400 mL), the reaction mixture was filtered through silica gel. The resulting solution was concentrated and purified by flash chromatography (silica, 30% Et_2O in petroleum ether) to give **8** (9.37 g, 97%) as a white foam: R_f = 0.45 (silica, 30% Et_2O in petroleum ether); IR (thin film) ν_{max} 2931, 2857, 1720, 1472, 1428, 1371, 1111 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.98 (d, J = 3.5 Hz, 1 H, 2-H), 7.65–7.55 (band, 4 H, Ar), 7.47–7.22 (band, 9 H, Ar), 7.17–7.10 (band, 2 H, Ar), 5.84 (dd, J = 10.5, 1.5 Hz, 1 H, 6-H), 5.71 (dd, J = 10.5, 2.0 Hz, 1 H, 5-H), 4.50 (d, J = 11.5 Hz, 1 H, OCH_2Ph), 4.22 (d, J = 11.5 Hz, 1 H, OCH_2Ph), 4.20 (d, 9.5 Hz, 1 H, 20-H), 4.10 (dd, J = 2.0, 1.5 Hz, 1 H, 7-H), 3.84 (d, 9.5 Hz, 1 H, 20-H), 3.72 (A of AB, d, J = 10.0 Hz, 1 H, 9-H), 3.70 (B of AB, d, J = 10.0 Hz, 1 H, 9-H), 3.18 (d, J = 3.5 Hz, 1 H, 3-H), 1.42 (s, 3 H, $C(CH_3)_2$), 1.39 (s, 3 H, $C(CH_3)_2$), 1.09 (s, 9 H, $SiC(CH_3)_3Ph_2$), 1.04 (s, 3 H, 19-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.3, 138.1, 135.8, 135.8, 135.7, 135.6, 133.0, 132.9, 131.1, 129.7, 129.7, 129.5, 128.8, 128.2, 128.2, 127.6, 127.4, 127.4, 127.2, 127.2, 127.1, 108.6, 80.7, 75.4, 71.8, 70.0, 65.7, 57.6, 44.9, 26.9, 26.5, 19.3, 13.6; FAB HRMS (NBA/NaI) *m/e* 607.2865, M + Na^+ calcd for $C_{36}H_{44}O_5Si$ 607.2856.

Alcohol 10. To a solution of hydrazone **9** (28.2 g, 50.1 mmol) in THF (400 mL) at −78 °C was added dropwise *n*-BuLi (65.5 mL of a 1.6 M solution in hexanes, 105 mmol). After the reaction mixture was stirred at −78 °C for 20 min, it was allowed to warm to 0 °C, resulting in N_2 gas evolution. The resulting bright orange solution was cooled to −78 °C, and a solution of the aldehyde **8** (26.4 g, 45.1 mmol) in THF (100 mL) was slowly added via canula. The reaction mixture was stirred at −78 °C for 0.5 h, and then the reaction was quenched with aqueous NH_4Cl (50 mL). After being warmed to 25 °C, the reaction mixture was extracted with Et_2O (2 × 200 mL). The organic layer was dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica, 15% Et_2O in petroleum ether) to give **10** (31.7 g, 82%) as a colorless oil: R_f = 0.25 (silica, 10% Et_2O in petroleum ether); IR (thin film) ν_{max} 3445, 2935, 2852, 1251, 1464, 1429, 1370, 1049 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73–7.65 (band, 4 H, Ar), 7.48–7.25 (band, 11 H, Ar), 5.98 (b s, 1 H, 14-H), 5.97 (d, J = 10.0 Hz, 1 H, 5-H), 5.79 (dd, J = 10.0, 5.0 Hz, 1 H, 6-H), 4.88 (b s, 1 H, 2-H), 4.73 (d, J = 11.5 Hz, 1 H, OCH_2Ph), 4.59 (d, J = 11.5 Hz, 1 H, OCH_2-Ph), 4.45 (d, 9.5 Hz, 1 H, 20-H), 4.33 (d, J = 10.5 Hz, 1 H, 10-H), 4.29 (d, J = 3.5 Hz, 1 H, 2-OH), 4.24 (d, J = 10.5 Hz, 1 H, 10-H), 3.96 (d, 9.5 Hz, 1 H, 20-H), 3.79 (d, J = 10.0 Hz, 1 H, 9-H), 3.72 (d, J = 10.0 Hz, 1 H, 9-H), 3.70 (d, J = 5.0 Hz, 1 H, 7-H), 2.80–2.65 (band, 3 H, 3-H and 13-CH_2), 1.81 (s, 3 H, 18-CH_3), 1.43 (s, 3 H, $C(CH_3)_2$), 1.41 (s, 3 H, $C(CH_3)_2$), 1.35 (s, 3 H, 16-CH_3), 1.32 (s, 3 H, 17-CH_3), 1.25 (s, 3 H, 19-CH_3), 1.11 (s, 9 H, $SiC(CH_3)_3Ph_2$), 0.98 (s, 9 H, $SiC(CH_3)_3(CH_3)_2$), 0.15 (s, 6 H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 137.5, 137.0, 135.7, 135.7, 135.1, 133.9, 133.7, 129.4, 129.4, 129.0, 128.4, 127.8, 127.7, 127.4, 127.4, 122.6, 120.7, 106.7, 80.2, 74.1, 72.4, 71.4, 70.9, 68.4, 59.1, 46.9, 43.3, 39.2, 33.6, 28.6, 26.9, 26.7, 26.1, 26.0, 24.6, 19.4, 19.3, 19.2, 18.3, −5.3; FAB HRMS (NBA/CsI) *m/e* 983.4050 M + Cs^+ calcd for $C_{52}H_{74}O_6Si_2$ 983.4078.

Epoxide 11. A solution of allylic alcohol **10** (18.7 g, 22.0 mmol) in benzene (500 mL) was treated with 4-Å molecular sieves (2 g), VO(acac)$_2$ (175 mg, 0.66 mmol), and *t*-BuOOH (22 mL of a 3 M solution in decane, 66.0 mmol) and stirred at 25 °C for 14 h. After the reaction was quenched with Me_2S (5 mL) and aqueous NH_4Cl (300 mL), the reaction mixture was extracted with Et_2O (200 mL). The organic layer was dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica, 15% Et_2O in petroleum ether) to give **11** (16.6 g, 87%) as a colorless oil: R_f = 0.47 (silica, 15% Et_2O in petroleum ether); IR (thin film) ν_{max} 3490, 2935, 2852, 1471, 1257, 1049 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65–7.55 (band, 4 H, Ar), 7.50–7.28 (band, 11 H, Ar), 5.82 (d, J = 10.0 Hz, 1 H, 5-H), 5.74 (dd, J = 10.0, 5.0 Hz, 1 H, 6-H), 4.82 (d, J = 4.5 Hz, 1 H, 2-H), 4.70 (d, J = 11.5 Hz, 1 H, OCH_2Ph), 4.56 (d, J = 10.0 Hz, 1 H, 20-H), 4.54 (d, J = 11.5 Hz, 1 H, OCH_2Ph), 4.14 (A of AB, d, J = 11.5 Hz, 1 H, 10-H), 4.11 (B of AB, d, J = 11.5 Hz, 1 H, 10-H), 4.06 (d, J = 10.0 Hz, 1 H, 20-H), 3.85 (d, J = 10.0 Hz, 1 H, 9-H), 3.71 (d, J = 5.0 Hz, 1 H, 7-H), 3.54 (d, J = 10.0 Hz, 1 H, 9-H), 3.35 (d, J = 4.5 Hz, 1 H, 2-OH), 2.93 (s, 1 H, 14-H), 2.49 (b s, 2 H, 13-CH_2), 1.80 (s, 1 H, 3-H), 1.70 (s, 3 H, 18-CH_3), 1.41 (s, 3 H, 19-CH_3), 1.30 (s, 3 H, $C(CH_3)_2$), 1.29 (s, 3 H, $C(CH_3)_2$), 1.25 (s, 3 H, $C(CH_3)_2$), 1.24 (s, 3 H, $C(CH_3)_2$), 1.06 (s, 9 H, $SiC(CH_3)_3Ph_2$), 0.90 (s, 9 H, $SiC(CH_3)_3(CH_3)_2$), 0.08 (s, 3 H, $SiC(CH_3)_3$-$(CH_3)_2$), 0.07 (s, 3 H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 135.9, 135.6, 135.6, 135.4, 134.1, 133.7, 129.4, 129.3, 128.3, 127.7, 127.4, 127.2, 123.9, 122.0, 107.1, 79.6, 74.3, 72.3, 70.8, 69.2, 64.1, 58.8, 53.4, 44.9, 42.3, 39.6, 31.7, 28.3, 26.9, 26.1, 25.9, 25.9, 25.8, 23.2, 21.9, 19.4, 19.3, 16.8, −5.5, −5.6; FAB HRMS (NBA/CsI) *m/e* 999.4050, M + Cs^+ calcd for $C_{52}H_{74}O_7Si_2$ 999.4027.

Diol 12. A solution of epoxide **11** (20.06 g, 23.1 mmol) in Et_2O (100 mL) was treated with $LiAlH_4$ (115 mL of a 1 M solution in Et_2O, 115 mmol) and stirred at 25 °C for 7 h. After dilution with Et_2O (200 mL), the reaction mixture was cooled to −78 °C, and the reaction was quenched with EtOAc (25 mL) followed by aqueous NH_4Cl (100 mL). After warming to 25 °C, the organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica, 30% Et_2O in petroleum ether) to give **12** (15.3 g, 76%) as colorless crystals: mp 115–117 °C, from CH_2Cl_2–hexanes; R_f = 0.58 (silica, 30% Et_2O in petroleum ether); IR (thin film) ν_{max} 3468, 2955, 2857, 1471, 1367, 1254, 1052 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65–7.61 (band, 4 H, Ar), 7.42–7.28 (band, 11 H, Ar), 5.85 (d, J = 10.5 Hz, 1 H, 5-H), 5.67 (dd, J = 10.5, 5.0 Hz, 1 H, 6-H), 4.63 (d, J = 11.0 Hz, 1 H, OCH_2Ph), 4.55 (d, J = 10.0 Hz, 1 H, 20-H), 4.54 (d, J = 11.0 Hz, 1 H, OCH_2Ph), 4.18 (d, J = 4.5 Hz, 2-H), 4.16 (d, J = 11.0 Hz, 1 H, 10-H), 4.07 (d, J = 10.0 Hz, 1 H, 10-H), 3.97 (d, J = 4.5 Hz, 1 H, 2-OH), 3.87 (d, J = 11.0 Hz, 1 H, 20-H), 3.79 (d, J = 10.0 Hz, 1 H, 9-H), 3.64 (d, J = 5.0 Hz, 1 H, 7-H), 3.57 (d, J = 10.0 Hz, 1 H, 9-H), 3.22 (b s, 1 H, 1-OH), 2.23–2.04 (band, 2 H, 13-CH_2), 2.15 (s, 1 H, 3-H), 1.77–1.59 (band, 2 H, 14-CH_2), 1.67 (s, 3 H, 18-CH_3), 1.23 (s, 6 H, $C(CH_3)_2$), 1.19 (s, 3 H, 19-CH_3), 1.07 (s, 3 H, $C(CH_3)_2$), 1.06 (s, 9 H, $SiC(CH_3)_3Ph_2$), 0.98 (s, 3 H, $C(CH_3)_2$), 0.92 (s, 9 H, $SiC(CH_3)_3(CH_3)_2$), 0.09 (s, 3 H, $SiC(CH_3)_3$-$(CH_3)_2$), 0.08 (s, 3 H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 136.3, 135.7, 135.6, 135.0, 133.9, 133.7, 129.9, 129.4, 129.3, 128.3, 127.9, 127.7, 127.3, 122.6, 107.2, 79.5, 74.5, 74.3, 72.7, 72.6, 71.1, 68.8, 59.5, 47.2, 44.3, 43.6, 29.9, 28.5, 27.8, 26.9, 26.7, 25.9, 20.9, 19.3, 19.1, 19.0, 18.3, −5.4, −5.5; FAB HRMS (NBA/CsI) *m/e* 1001.4170, M + Cs^+ calcd for $C_{52}H_{76}O_7Si_2$ 1001.4184.

Carbonate 13. A solution of diol **12** (9.67 g, 11.1 mmol) in Et_2O (150 mL) and hexamethylphosphoramide (HMPA, 50 mL) was treated with KH (4.41 g of a 30% suspension in mineral oil, 33.0 mmol, prewashed with dry Et_2O) and stirred at 25 °C for 20 min, after which phosgene (10 mL of a 20% solution in toluene, 17.5 mmol) was added. The reaction mixture was stirred at 25 °C for 0.5 h. After dilution with Et_2O (300 mL), the reaction mixture was added to a half saturated solution of tartaric acid. The organic layer was separated, washed with brine (150 mL), dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica, 2% MeOH in CH_2Cl_2) to give diol **12** (4.06 g, 42%) and carbonate **13** (4.72 g, 86% based on 58% conversion) as a

yellow solid: $R_f = 0.64$ (silica, 2% MeOH in CH_2Cl_2); IR (thin film) ν_{max} 2932, 2857, 1800, 1472, 1254, 1000 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63–7.58 (band, 5 H, Ar), 7.42–7.28 (band, 10 H, Ar), 5.85 (dd, $J = 10.0, 5.0$ Hz, 1 H, 6-H), 5.79 (d, $J = 10.0$ Hz, 1 H, 5-H), 5.32 (s, 1 H, 2-H), 4.66 (d, $J = 11.5$ Hz, 1 H, OCH_2Ph), 4.36 (d, $J = 11.5$ Hz, 1 H, OCH_2Ph), 4.09 (A of AB, d, $J = 11.5$ Hz, 1 H, 20-H), 4.06 (B of AB, d, $J = 11.5$ Hz, 1 H, 20-H), 4.04 (d, $J = 9.0$ Hz, 1 H, 10-H), 3.97 (d, $J = 9.0$ Hz, 1 H, 10-H), 3.73 (d, $J = 10.5$ Hz, 1 H, 9-H), 3.62 (d, $J = 5.0$ Hz, 1 H, 7-H), 3.60 (d, $J = 10.5$ Hz, 1 H, 9-H), 2.42–2.02 (band, 4 H, 13-CH_2 and 14-CH_2), 2.26 (s, 1 H, 3-H), 1.65 (s, 3 H, 18-CH_3), 1.25 (s, 3 H, $C(CH_3)_2$), 1.24 (s, 3 H, $C(CH_3)_2$), 1.14 (s, 3 H, 19-CH_3), 1.09 (s, 3 H, $C(CH_3)_2$), 1.07 (s, 9 H, $SiC(CH_3)_3Ph_2$), 1.03 (s, 3 H, $C(CH_3)_2$), 0.88 (s, 9 H, $SiC(CH_3)_3(CH_3)_2$), 0.05 (s, 3 H, $SiC(CH_3)_3(CH_3)_2$), 0.03 (s, 3 H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 138.7, 135.7, 135.6, 134.0, 133.7, 133.5, 132.5, 130.5, 129.5, 129.4, 128.0, 127.6, 127.4, 127.3, 125.2, 107.3, 88.2, 79.7, 78.9, 73.1, 71.2, 71.2, 70.4, 59.4, 46.5, 44.2, 43.4, 29.3, 27.9, 27.0, 26.6, 25.8, 25.2, 19.3, 19.1, −5.6; FAB HRMS (NBA/CsI) *m/e* 1027.3950, M + Cs^+ calcd for $C_{53}H_{74}O_8Si_2$ 1027.3977.

Diol 14. A solution of carbonate **13** (4.72 g, 5.27 mmol) in THF (20 mL) was treated with *n*-Bu_4NF (TBAF, 20 mL of a 1.0 M solution in THF, 20.0 mmol) and stirred at 25 °C for 14 h. After dilution with Et_2O (50 mL), H_2O (50 mL) was added. The organic layer was separated, washed with brine (30 mL), dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica, 80% Et_2O in petroleum ether) to give **14** (2.29 g, 80%) as a white solid: $R_f = 0.49$ (silica, Et_2O); IR (thin film) ν_{max} 3438, 2980, 2879, 1778, 1371, 1061 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.27 (band, 5 H, Ar), 5.99 (dd, $J = 10.0, 3.5$ Hz, 1 H, 6-H), 5.89 (d, $J = 10.0$ Hz, 1 H, 5-H), 5.23 (s, 1 H, 2-H), 4.72 (d, $J = 11.0$ Hz, 1 H, OCH_2Ph), 4.42 (d, $J = 11.0$ Hz, 1 H, OCH_2Ph), 4.27 (b d, $J = 9.0$ Hz, 1 H, 10-H), 4.11 (b s, 2 H, 20-CH_2), 4.02 (d, $J = 9.0$ Hz, 1 H, 10-H), 3.69 (dd, $J = 9.5, 5.0$ Hz, 1 H, 9-H), 3.49 (d, $J = 3.5$ Hz, 1 H, 7-H), 3.25 (dd, $J = 9.5, 9.0$ Hz, 1 H, 9-H), 2.77 (dd, $J = 9.0, 5.0$ Hz, 1 H, 9-OH), 2.40–2.18 (band, 4 H, 13-CH_2 and 14-CH_2), 2.37 (s, 1 H, 3-H), 1.72 (s, 3 H, 18-CH_3), 1.47 (s, 3 H, $C(CH_3)_2$), 1.44 (s, 3 H, $C(CH_3)_2$), 1.08 (s, 3 H, 19-CH_3), 1.05 (s, 3 H, $C(CH_3)_2$), 1.03 (s, 3 H, $C(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 136.8, 133.9, 133.5, 132.8, 128.2, 127.8, 127.6, 126.2, 106.7, 88.4, 80.5, 78.8, 74.5, 71.6, 71.2, 67.9, 58.6, 44.3, 44.2, 43.5, 29.2, 27.2, 26.2, 24.5, 23.7, 20.2, 19.1, 18.5; FAB HRMS (NBA/CsI) *m/e* 675.1942, M + Cs^+ calcd for $C_{31}H_{42}O_8$ 675.1934.

Dialdehyde 15. A solution of diol **14** (0.66 g, 1.22 mmol) and 4-methylmorpholine *N*-oxide (NMO, 0.43 g, 3.67 mmol) in CH_3CN (40 mL) and CH_2Cl_2 (20 mL) was treated with 4-Å molecular sieves (50 mg) and stirred at 25 °C for 10 min. Tetrapropylammonium perruthenate (TPAP, 22 mg, 0.062 mmol) was added, and the reaction mixture was stirred at 25 °C for 2 h. After dilution with CH_2Cl_2 (100 mL), the reaction mixture was filtered through silica gel. The resulting solution was concentrated to give dialdehyde **15** (0.611 g, 92%) as a white solid: $R_f = 0.70$ (silica, 50% EtOAc in hexanes); IR (thin film) ν_{max} 2919, 1793, 1724, 1669, 1063 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2CO$) δ 10.98 (s, 1 H, 10-H), 9.40 (s, 1 H, 9-H), 7.39–7.29 (band, 5 H, Ar), 6.25 (dd, $J = 10.0, 4.5$ Hz, 1 H, 6-H), 5.84 (d, $J = 10.0$ Hz, 1 H, 5-H), 5.35 (d, $J = 2.5$ Hz, 1 H, 2-H), 4.81 (d, $J = 11.0$ Hz, 1 H, OCH_2Ph), 4.56 (d, $J = 11.0$ Hz, 1 H, OCH_2Ph), 4.28 (d, $J = 4.5$ Hz, 1 H, 7-H), 3.97 (s, 2 H, 20-CH_2), 2.91 (d, $J = 2.5$ Hz, 1 H, 3-H), 2.65 (m, 1 H, 13-H), 2.52–2.46 (band, 2 H, 13-H and 14-H), 2.23 (m, 1 H, 14-H), 2.16 (s, 3 H, 18-CH_3), 1.41 (s, 3 H, 19-CH_3), 1.29 (s, 3 H, $C(CH_3)_2$), 1.25 (s, 3 H, $C(CH_3)_2$), 1.21 (s, 3 H, $C(CH_3)_2$), 1.15 (s, 3 H, $C(CH_3)_2$); ^{13}C NMR (125 MHz, $(CD_3)_2CO$)) δ 198.9, 192.2, 155.2, 154.2, 139.5, 137.5, 133.3, 129.0, 128.4, 128.4, 109.3, 89.9, 80.4, 77.0, 72.6, 72.5, 72.2, 53.8, 46.4, 43.4, 32.4, 27.3, 26.8, 25.2, 24.1, 18.8, 18.6, 17.7; FAB HRMS (NBA/CsI) *m/e* 671.1630, M + Cs^+ calcd for $C_{31}H_{38}O_8$ 671.1621.

8-Membered Ring Intermediates 17–20. $TiCl_3 \cdot (DME)_{1.5}$ (1.53 g, 5.3 mmol) and Zn/Cu couple (1.66 g, 12.7 mmol) were transferred to a dry flask under argon (glovebag). The mixture was further dried at 140 °C, under vacuum for 10 min. Freshly distilled DME (70 mL) was then added, and the suspension was stirred at reflux for 3.5 h. After the mixture was cooled to 70 °C, a solution of dialdehyde **15** (260 mg, 0.48 mmol) in DME (25 mL) was added via syringe pump over 1 h. The reaction mixture was stirred at 70 °C for an additional 0.5 h. After cooling to 25 °C, the reaction mixture was added to a saturated solution of $NaHCO_3$ (100 mL), and the resulting mixture was stirred at 25 °C for 2 h. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 75 mL). The combined organic layer was dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica, 20 → 40% EtOAc in petroleum ether) to give products **17** (65.3 mg, 25%), **18** (24.6 mg, 10%), **19** (104.4 mg, 40%), and **20** (40.5 mg, 15%).

Diol 17: $R_f = 0.41$ (silica, 50% EtOAc in hexanes); IR (thin film) ν_{max} 3490, 2970, 1789, 1456, 1100 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42–7.31 (band, 5 H, Ar), 5.97 (dd, $J = 10.0, 1.5$ Hz, 1 H, 5-H), 5.63 (dd, $J = 10.0, 1.5$ Hz, 1 H, 6-H), 5.46 (d, $J = 5.0$ Hz, 1 H, 2-H), 4.77 (d, $J = 12.0$ Hz, 1 H, OCH_2Ph), 4.49 (d, $J = 8.5$ Hz, 1 H, 20-H), 4.39 (d, $J = 12.0$ Hz, 1 H, OCH_2Ph), 4.29 (b t, $J = 6.0$ Hz, 1 H, 10-H), 4.24 (dd, $J = 6.0, 3.0$ Hz, 1 H, 9-H), 3.80 (d, $J = 8.5$ Hz, 1 H, 20-H), 3.58 (b s, 1 H, 7-H), 2.87 (d, $J = 3.0$ Hz, 1 H, 9-OH), 2.70 (ddd, $J = 15.0, 10.5, 3.0$ Hz, 1 H, 14-H), 2.54 (ddd, $J = 20, 12.0, 3.0$ Hz, 1 H, 13-H), 2.31 (d, $J = 5.0$ Hz, 1 H, 3-H), 2.18 (d, $J = 6.0$ Hz, 1 H, 10-OH), 1.93 (ddd, $J = 20.0, 10.5, 3.0$ Hz, 1 H, 13-H), 1.78 (ddd, $J = 15.0, 12.0, 3.0$ Hz, 1 H, 14-H), 1.56 (s, 3 H, 18-CH_3), 1.42 (s, 3 H, 19-CH_3), 1.39 (s, 3 H, 16-CH_3), 1.38 (s, 3 H, 17-CH_3), 1.16 (s, 3 H, $C(CH_3)_2$), 1.05 (s, 3 H, $C(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 139.4, 137.3, 136.1, 135.6, 128.7, 128.5, 128.3, 122.0, 108.2, 93.5, 82.4, 77.9, 75.7, 74.2, 71.2, 70.4, 69.3, 46.3, 44.3, 40.0, 31.2, 28.9, 27.9, 26.8, 23.6, 21.7, 21.3, 16.0; FAB HRMS (NBA/CsI) *m/e* 673.1782, M + Cs^+ calcd for $C_{31}H_{40}O_8$ 673.1778.

Alkene 18: $R_f = 0.95$ (silica, 50% EtOAc in hexanes); IR (thin film) ν_{max} 2971, 1726 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.27 (band, 5 H, Ar), 5.93 (dd, $J = 10.5, 2.5$ Hz, 1 H, 6-H), 5.86 (b d, $J = 12.0$ Hz, 1 H, 10-H), 5.56 (dd, $J = 10.5, 1.5$ Hz, 1 H, 5-H), 5.48 (d, $J = 12.0$ Hz, 1 H, 9-H), 4.67 (d, $J = 7.0$ Hz, 1 H, 2-H), 4.65 (d, $J = 10.5$ Hz, 1 H, OCH_2Ph), 4.49 (d, $J = 8.0$ Hz, 1 H, 20-H), 4.44 (d, $J = 10.5$ Hz, 1 H, OCH_2Ph), 3.80 (d, $J = 8.0$ Hz, 1 H, 20-H), 3.68 (b s, 1 H, 7-H), 2.86 (d, $J = 7.0$ Hz, 1 H, 3-H), 2.35–2.22 (band, 3 H, 13-CH_2 and 14-H), 1.96 (m, 1 H, 14-H), 1.54 (s, 6 H, 18-CH_3 and 19-CH_3), 1.45 (s, 3 H, $C(CH_3)_2$), 1.39 (s, 3 H, $C(CH_3)_2$), 1.37 (s, 3 H, $C(CH_3)_2$), 1.07 (s, 3 H, $C(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 143.2, 137.6, 137.3, 133.4, 128.7, 128.2, 128.1, 127.7, 125.3, 122.0, 108.4, 90.6, 81.7, 75.7, 72.0, 71.0, 62.3, 47.5, 43.7, 36.3, 29.7, 29.1, 26.8, 26.6, 26.4, 24.4, 16.1, 14.4; FAB HRMS (NBA/CsI) *m/e* 639.1736, M + Cs^+ calcd for $C_{31}H_{38}O_6$ 639.1723.

Hemiacetal 19: mp 170–174 °C, 195–200 °C (corresponding aldehyde), from CH_2Cl_2–hexanes; $R_f = 0.51$ (silica, 50% EtOAc in hexanes); IR (thin film) ν_{max} 3422, 2924, 1797, 1454, 1381, 1216, 1052 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.30 (band, 5 H, Ar), 6.05 (dd, $J = 10.5, 1.0$ Hz, 1 H, 5-H), 5.71 (dd, $J = 10.5, 1.0$ Hz, 1 H, 6-H), 5.57 (d, $J = 2.0$ Hz, 1 H, 10-H), 5.20 (d, $J = 8.5$ Hz, 1 H, 2-H), 4.67 (d, $J = 11.5$ Hz, 1 H, OCH_2Ph), 4.45 (d, $J = 11.5$ Hz, 1 H, OCH_2-Ph), 4.27 (d, $J = 8.5$ Hz, 1 H, 20-H), 4.26 (s, 1 H, 9-H), 3.97 (b s, 1 H, 7-H), 3.90 (d, $J = 8.5$ Hz, 1 H, 20-H), 3.19 (d, $J = 8.5$ Hz, 1 H, 3-H), 2.42 (d, $J = 2.0$ Hz, 1 H, 11-H), 2.30–1.85 (band, 4 H, 13-CH_2 and 14-CH_2), 1.51 (s, 3 H, 16-CH_3), 1.49 (s, 3 H, 17-CH_3), 1.32 (s, 3 H, $C(CH_3)_2$), 1.24 (s, 3 H, $C(CH_3)_2$), 1.11 (s, 3 H, 18-CH_3), 1.07 (s, 3 H, 19-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 137.2, 134.0, 128.4, 128.0, 127.9, 124.0, 108.0, 98.4, 89.6, 82.5, 77.9, 74.8, 71.6, 69.6, 62.6, 45.3, 43.9, 42.2, 38.5, 38.1, 30.2, 29.0, 27.1, 26.4, 25.9, 20.3, 15.7; FAB HRMS (NBA/CsI) *m/e* 673.1760, M + Cs^+ calcd for $C_{31}H_{40}O_8$ 673.1778.

Formate Ester 20: mp 222–224 °C, from CH_2Cl_2–hexanes; $R_f = 0.59$ (silica, 50% EtOAc in hexanes); IR (thin film) ν_{max} 2986, 1799, 1728, 1383, 1139, 1058, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1 H, 9-CHO), 7.41–7.32 (band, 5 H, Ar), 6.11 (dd, $J = 10.0, 1.5$ Hz, 1 H, 5-H), 5.71 (dd, $J = 10.0, 1.0$ Hz, 1 H, 6-H), 5.54 (s, 1 H, 9-H), 5.16 (d, $J = 9.0$ Hz, 1 H, 2-H), 4.73 (d, $J = 11.5$ Hz, 1 H, OCH_2Ph), 4.52 (d, $J = 11.5$ Hz, 1 H, OCH_2Ph), 4.30 (d, $J = 8.5$ Hz, 1 H, 20-H), 4.09 (b s, 1 H, 7-H), 3.89 (d, $J = 8.5$ Hz, 1 H, 20-H), 3.42 (d, $J = 9.0$ Hz, 1 H, 3-H), 2.42–2.22 (band, 4 H, 13-CH_2 and 14-CH_2), 1.52 (s, 3 H, $C(CH_3)_2$), 1.50 (s, 3 H, $C(CH_3)_2$), 1.37 (s, 3 H, 16-CH_3), 1.28 (s, 3 H, 17-CH_3), 0.99 (s, 3 H, 18-CH_3), 0.89 (s, 3 H, 19-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.4, 158.4, 152.3, 136.6, 134.3, 128.6, 128.5, 128.2, 123.6, 108.4, 98.5, 88.1, 82.2, 77.6, 77.5, 75.5, 71.5, 69.5, 52.0,

50.6, 47.0, 43.6, 29.5, 28.9, 27.1, 25.4, 24.6, 24.6, 18.9, 15.4; FAB HRMS (NBA/CsI) *m/e* 687.1570, M + Cs^+ calcd for $C_{31}H_{38}O_9$ 687.1570.

Camphanate Esters 29 and 30. A solution of diol **17** (42 mg, 0.077 mmol) and Et_3N (0.217 mL, 1.5 mmol) in CH_2Cl_2 (3.5 mL) was treated with a catalytic amount of 4-(dimethylamino)pyridine (DMAP, 0.5 mg, 0.004 mmol) and (1*S*)-(−)-camphanic chloride (84 mg, 0.388 mmol) at 25 °C for 1 h. After dilution with Et_2O (10 mL), the reaction was quenched with aqueous $NaHCO_3$ (5 mL), and the resulting mixture was stirred at 25 °C for 15 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (10 mL), dried ($MgSO_4$), concentrated, and purified by preparative TLC (silica, 20% EtOAc in benzene) to give camphanic esters **29** and **30** (23 and 25 mg, respectively, 86% combined yield) as white solids.

Ester 29: R_f = 0.26 (silica, 15% EtOAc in benzene); $[\alpha]^{22}_D$ +117 (*c* 0.54, $CHCl_3$); IR (thin film) ν_{max} 3500, 2970, 2930, 1792, 1744, 1458, 1103, 1058, 914 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.24 (band, 5 H, Ar), 5.94 (dd, *J* = 10.5, 1.5 Hz, 1 H, 6-H), 5.74 (d, *J* = 5.0 Hz, 1 H, 9-H), 5.63 (dd, *J* = 10.5, 1.0 Hz, 1 H, 5-H), 5.51 (d, *J* = 4.5 Hz, 1 H, 2-H), 4.70 (d, *J* = 12.0 Hz, 1 H, OCH_2Ph), 4.64 (d, *J* = 8.5 Hz, 1 H, 20-H), 4.45 (d, *J* = 12.0 Hz, 1 H, OCH_2Ph), 4.36 (dd, *J* = 5.0, 3.0 Hz, 1 H, 10-H), 3.78 (d, *J* = 8.5 Hz, 1 H, 20-H), 3.70 (b s, 1 H, 7-H), 2.72 (ddd, *J* = 14.0, 10.0, 3.5 Hz, 1 H, 13-H), 2.63–2.53 (band, 1 H, 14-H), 2.56 (d, *J* = 3.0 Hz, 10-OH), 2.38 (ddd, *J* = 14.0, 11.0, 4.0 Hz, 1 H, $CH(H)CH_2$ camph.), 2.33 (d, *J* = 4.5 Hz, 1 H, 3-H), 2.12–1.88 (band, 3 H, 13-H and $CH(H)CH(H)$ camph.), 1.81 (ddd, *J* = 14.5, 12.0, 2.5 Hz, 1 H, 14-H), 1.71 (ddd, *J* = 13.5, 9.0, 4.0 Hz, 1 H, $CH(H)CH_2$ camph.), 1.62 (s, 3 H, 18-CH_3), 1.57 (s, 3 H, $OC(O)C(CH_3)$), 1.41 (s, 3 H, $(O)_2C(CH_3)_2$), 1.40 (s, 3 H, $(O)_2C(CH_3)_2$), 1.12 (s, 6 H, $C(CH_3)_2$ camph.), 1.10 (s, 3 H, 16-CH_3), 1.06 (s, 3 H, 17-CH_3), 1.00 (s, 3 H, 19-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 166.2, 153.8, 143.6, 137.1, 135.5, 132.7, 128.7, 128.5, 128.3, 122.1, 108.4, 93.4, 90.8, 82.5, 78.0, 74.9, 74.0, 74.0, 71.2, 70.9, 54.8, 54.3, 47.2, 44.8, 39.8, 31.5, 30.9, 29.0, 28.8, 28.0, 26.9, 23.6, 21.7, 21.7, 16.8, 16.8, 16.2, 9.6; FAB HRMS (NBA/CsI) *m/e* 853.2545, M + Cs^+ calcd for $C_{41}H_{52}O_{11}$ 853.2564.

Ester 30: colorless crystals, mp 240 °C, dec, from CH_2Cl_2–hexanes; R_f = 0.21 (silica, 15% EtOAc in benzene); $[\alpha]^{22}_D$ 133 (*c* 0.49, $CHCl_3$); IR (thin film) ν_{max} 3498, 2976, 1793, 1742, 1457, 1378, 1265, 1059 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.30 (band, 5 H, Ar), 5.96 (dd, *J* = 10.0, 1.5 Hz, 1 H, 6-H), 5.85 (d, *J* = 5.5 Hz, 1 H, 9-H), 5.63 (dd, *J* = 10.0, 1.0 Hz, 1 H, 5-H), 5.53 (d, *J* = 4.5 Hz, 1 H, 2-H), 4.71 (d, *J* = 12.0 Hz, 1 H, OCH_2Ph), 4.48 (d, *J* = 8.0 Hz, 1 H, 20-H), 4.46 (d, *J* = 12.0 Hz, 1 H, OCH_2Ph), 4.33 (dd, *J* = 5.5, 3.0 Hz, 1 H, 10-H), 3.79 (d, *J* = 8.0 Hz, 1 H, 20-H), 3.74 (b s, 1 H, 7-H), 2.77 (ddd, *J* = 14.0, 10.5, 3.0 Hz, 1 H, 13-H), 2.68–2.55 (band, 1 H, 14-H), 2.58 (d, *J* = 3.0 Hz, 10-OH), 2.48 (ddd, *J* = 13.5, 10.5, 4.0 Hz, 1 H, $CH(H)CH_2$ camph.), 2.36 (d, *J* = 4.5 Hz, 1 H, 3-H), 2.15–1.92 (band, 3 H, 13-H and $CH(H)CH(H)$ camph.), 1.90–1.65 (band, 2 H, 14-H and $CH(H)CH_2$ camph.), 1.72 (s, 3 H, 18-CH_3), 1.57 (s, 3 H, $OC(O)C(CH_3)$), 1.44 (s, 3 H, $(O)_2C(CH_3)_2$), 1.42 (s, 3 H, $(O)_2C(CH_3)_2$), 1.14 (s, 6 H, $C(CH_3)_2$ camph.), 1.11 (s, 3 H, 16-CH_3), 1.08 (s, 3 H, 17-CH_3), 0.98 (s, 3 H, 19-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 166.2, 153.8, 143.6, 137.1, 135.4, 132.8, 128.6, 128.3, 128.2, 122.3, 108.3, 93.4, 91.5, 82.4, 77.9, 75.2, 74.1, 73.6, 71.2, 71.1, 54.8, 54.4, 47.1, 44.7, 39.7, 31.4, 31.1, 29.0, 28.8, 27.8, 26.9, 23.5, 21.7, 21.5, 17.1, 16.8, 16.1, 9.6; FAB HRMS (NBA/CsI) *m/e* 853.2543, M + Cs^+ calcd for $C_{41}H_{52}O_{11}$ 853.2564.

Diol (+)-17. A solution of ester **29** (23 mg, 0.032 mmol) in MeOH (3.5 mL) was treated with K_2CO_3 (3.0 mg, 0.22 mmol) and stirred at 25 °C for 0.5 h. After dilution with CH_2Cl_2 (15 mL), the reaction was quenched with aqueous NH_4Cl (10 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica, 25 → 50% EtOAc in petroleum ether) to give diol (+)-**17** (15.5 mg, 90%) as a white solid: $[\alpha]^{22}_D$ +187 (*c* 0.5, $CHCl_3$).

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