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Concise Means for Accessing an Advanced Precursor to 1-Deoxypaclitaxel

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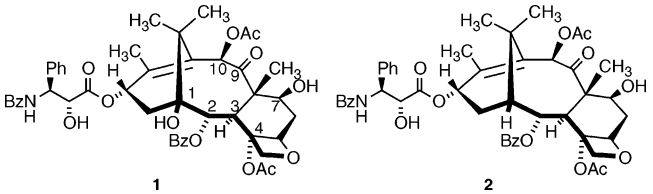
A program directed toward a total synthesis of 1-deoxypaclitaxel is described. The most direct route consists of six steps from the previously described diketone **12** and proceeds in 18% overall yield. The transformations involved in reaching the target molecule **22** consist of stereoselective α-ketol generation, an $EtAlCl_2$-catalyzed transannular hydride shift, regioselective monomesylation, and a Wagner−Meerwein 1,2-shift. The central issue of this synthesis is the sequential deployment of these highly controlled steps along the perimeter and across the interior gap of a nine-membered ring.

The substantial human health benefit offered by paclitaxel (Taxol, **1**) has spawned many studies aimed at the preparation of analogues for the purpose of elucidating structure−activity guidelines.[1] This exploratory thrust has established that reductive removal of the C-1 hydroxyl group by various protocols is not feasible because structural rearrangements are invariably triggered during attempted C−O bond cleavage.[2−5] 1-Deoxypaclitaxel (**2**) is of particular interest because a hydroxyl group no longer resides on the leading edge known to contribute to biological activity.[6] In this paper, we describe an expansion of our program aimed at synthesizing **1** from D-camphor[7] to include a companion approach to **2**. A comparable economy of steps was envisioned,[8,9] so as to allow ultimate access to reasonable amounts of the target. Ideally, both synthetic plans would share common intermediates in their early stages. The key distinction was to be the supplantation of an equilibrium-controlled α-ketol rearrangement[10] by an irreversible pinacol-type 1,2-shift.[11]



At the outset of the present undertaking, the factors cited above were sufficiently compelling to cause us to pursue a concise, enantioselective total synthesis of 1-deoxypaclitaxel. Added motivation soon surfaced with

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(11) (a) Paquette, L. A.; Elmore, S. W.; Combrink, K. D.; Hickey, E. R.; Rogers, R. D. *Helv. Chim. Acta* **1992**, *75*, 1755. (b) Paquette, L. A.; Combrink, K. D.; Elmore, S. W.; Zhao, M. *Helv. Chim. Acta* **1992**, *75*, 1772. (c) Paquette, L. A.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5203. (d) Paquette, L. A.; Wang, H.; Su, Z.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5213.

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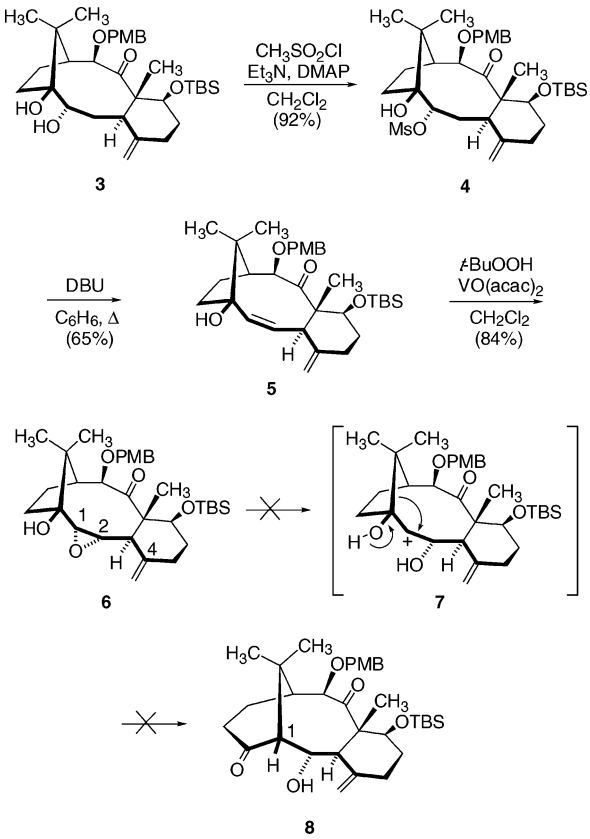
SCHEME 1

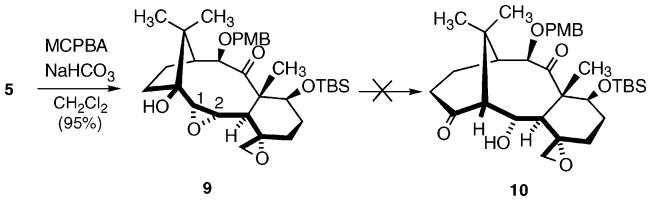


the issuance of a patent application claiming a synthesis of **2** but without exemplification.[12] The progression of events has been such that a recent report has identified **2** as a byproduct in the isolation of paclitaxel.[13] Evidently, the absence of the C-1 hydroxyl reduces activity by approximately one-third in assays involving the HCT116 and A2780 cell lines. The isolation of **2** from natural sources obviously does not solve the availability problem. Therefore, the context remains entirely favorable for proposed routes to 1-deoxypaclitaxel to be evaluated experimentally. Here we detail the assembly of a tricyclic intermediate considered to be adequately functionalized to offer the opportunity for ultimate conversion to **2**.

Results and Discussion

Exploration of the Epoxy Alcohol Option. In view of the ready availability of dihydroxy ketone **3**,[7b,14] the decision was made to install an α-epoxide moiety as in **6** for the purpose of effecting an appropriately catalyzed rearrangement to generate **8** (Scheme 1). Transformations of this type are well-known.[15] We were mindful that colinear alignment involving the antibonding C−O bond at C-1 or its p-orbital equivalent (see **7**) with the neighboring bridgehead C−C bonding orbital would prove to be crucial to our objectives.

SCHEME 2



The initial conversion of **3** to monomesylate **4** proceeded efficiently. The latter was subsequently heated with DBU in benzene for 32 h. The desired medium-ring olefin **5** was isolated chromatographically in 65% yield. Next to be addressed was the regioselective epoxidation of the intraannular double bond in **5**. On the basis of precedents,[16] it seemed reasonable that reagent attack would occur from its more open α surface. When MCPBA was found not to react regioselectively with **5**, we turned to the use of $VO(acac)_2$ and *tert*-butyl hydroperoxide in order to take advantage of the capacity of this reagent combination to oxidize allylic alcohols with high diastereoselectivity.[17] The chemistry of **6** so formed was quite extensively explored. Particularly vexing was the absence of observable chemical change in the presence of wide range of Lewis acids (e.g., Et_2AlCl, Me_3Al, $BF_3{\cdot}OEt_2$, $TiCl_4$, CSA, $HClO_4$, etc). An increase in reaction temperature to 0−40 °C only led to loss of the PMB and/or TBS protecting groups.

The unactivated nature of **6** paralleled that encountered earlier in our companion quest of paclitaxel. For reasons not yet completely understood, the presence of an exocyclic methylene group at C-4 effectively deters operation of the α-ketol rearrangement in that series.[18] The desired bridge migration does operate, however, once that substituent is converted to an epoxide. Accordingly, **5** was treated with an excess of *m*-chloroperbenzoic acid to provide diepoxide **9** (Scheme 2), the structural features of which were corroborated by NOESY NMR analysis. Exhaustive screening of different Lewis acids and select bases (including KHMDS, $Al(i\text{-}PrO)_3$, KO*t*-Bu, and the like) gave no evidence for conversion to **10**. The inoperability of the desired Wagner−Meerwein shifts may arise from improper orbital overlap since oxirane belting across C-1/C-2 in both **6** and **9** strictly rigidifies their ground-state conformation. Enhancing structural flexibility was therefore alternatively pursued in order to remediate the present complication.

Suitability of 1,2-Diol Monomesylates. We were thus motivated to explore the regioselectivity of the dihydroxylation of **5** with the OsO_4/TMEDA complex as reported by Donohoe and co-workers to attack at the

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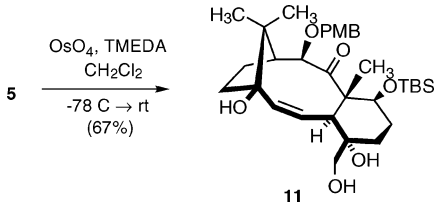
SCHEME 3



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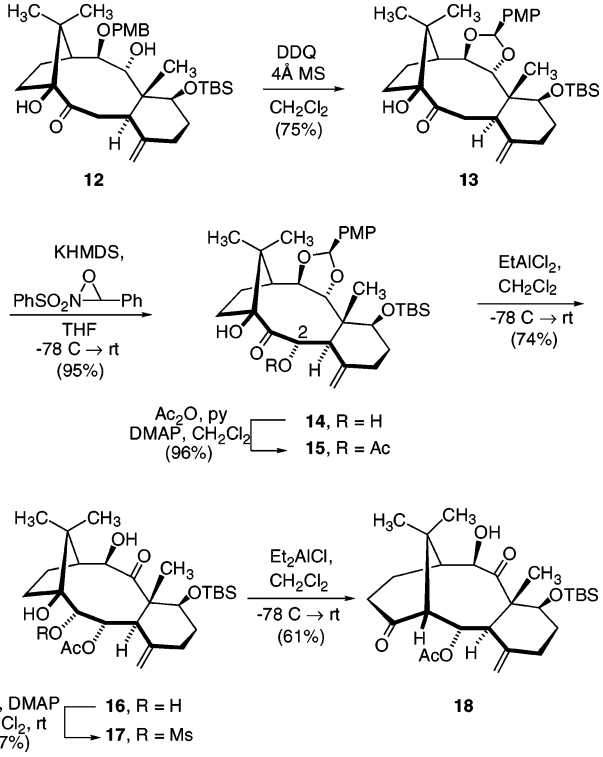
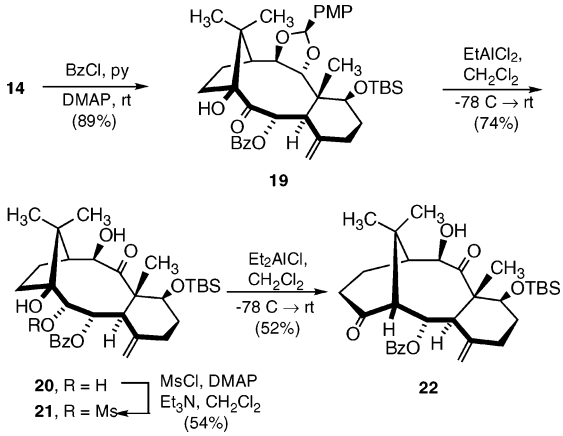


SCHEME 5



π-bonds of allylic alcohols as a result of heteroatom assistance.[19] In the event, this reaction pathway was not observed, and only **11** was produced (Scheme 3). This eventuality is believed to be the result of steric control and/or torsional constraints, as protected derivatives of **11** proved to be unreactive to various dihydroxylating conditions.[20]

At this juncture, more advanced functionalization of the previously reported **12**[18] became our immediate objective. Cyclization to the *p*-methoxyphenyl (PMP) acetal occurred on reaction with DDQ in the presence of 4 Å molecular sieves[7c,21] (Scheme 4). With **13** in hand, it was possible to bring about stereocontrolled α-hydroxylation as in **14** by exposing the potassium enolate to the Davis sulfonyloxaziridine.[22] Following acetylation to furnish **15**, the stage was set to initiate a transannular hydride shift involving migration of the well aligned β-hydrogen at C-9 to C-1. We have previously reported anionically induced variants of this useful transformation,[14] and the use of ethylaluminum dichloride served our purposes well to deliver **16** in 74% yield. This key step was matched by the very respectable regioselectivity that accompanied the monomesylation of this advanced intermediate. In line with the high level of steric shielding known to reside in the vicinity of the C-10 position, reaction with methanesulfonyl chloride materialized only at the C-2 hydroxyl to give **17**. Subsequent exposure of **17** to diethylaluminum chloride in CH_2Cl_2 provided **18** in 61% yield.

The final series of experiments gave attention to the fact that **1** and **2** carry a benzoate group at C-2. Installation of this functionality at the level of **14** would serve to eliminate a later need for the exchange of protecting groups. Indeed, this plan of action proved to be entirely workable (Scheme 5). Not only was benzoylation as in **19** easily accomplished, but the transannular hydride migration leading to **20** also proceeded well. The further progression from **20** to **21** occurred on a very favorable note as intended. Attention is called to the high level of substitution in **21** and the essentially complete overlay of its stereocenters with those resident in 1-deoxypaclitaxel (**2**).

Summary. The feasibility of devising an enantioselective route to **2** by way of a pinacol-like rearrangement has been demonstrated. The successful pathway consists of only six steps from **12** and relies on the operability of a direct transannular hydride shift, regioselective chemical activation, and 1,2-migration of the *gem*-dimethyl-substituted carbon atom. An overall yield of 18% was realized. Further advancement toward **2** must deal with the chemical complexities of A-ring functionalization and introduction of the oxetane ring. We hope to report on the final stages of this pursuit in due course.

Experimental Section

Mesylate 4. To a solution of 250 mg (0.455 mmol) of **3** in 25 mL of CH_2Cl_2 at 0 °C were added 0.32 mL (230 mg, 2.28 mmol) of triethylamine, 0.07 mL (104 mg, 0.91 mmol) of methanesulfonyl chloride, and 56 mg (0.455 mmol) of DMAP. The reaction mixture was stirred for 20 min at 0 °C, quenched with 20 mL of saturated NH_4Cl solution, and allowed to warm to room temperature. The aqueous layer was separated and extracted with CH_2Cl_2 (20 mL x 3). The organic layers were combined and dried. Purification of the residue by flash chromatography on silica gel (elution with 30% EtOAc/hexane)

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afforded 276 mg (92%) of **4** as a colorless oil: IR (neat, cm^{-1}) 3542, 1700, 1614; ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.09 (s, 1H), 5.03 (s, 1H), 4.75 (t, J = 3.0 Hz, 1H), 4.55 (dd, J = 11.2, 4.6 Hz, 1H), 4.47 (d, J = 10.9 Hz, 1H), 4.36 (d, J = 3.1 Hz, 1H), 4.12 (d, J = 10.9 Hz, 1H), 3.80 (s, 3H), 3.14−3.08 (m, 1H), 3.02 (s, 3H), 2.78−2.56 (m, 2H), 2.52−2.36 (m, 3H), 2.21−1.94 (m, 2H), 1.87−1.54 (m, 4H), 1.13 (s, 3H), 1.11 (s, 3H), 0.91 (s, 3H), 0.83 (s, 9H), 0.064 (s, 3H), 0.056 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 211.4, 159.3, 143.9, 131.6, 128.8 (2C), 114.0 (2C), 110.9, 88.5, 87.4, 87.2, 76.8, 72.7, 61.3, 57.5, 55.7, 49.1, 38.7, 36.8, 34.6, 34.3, 32.7, 31.9, 28.7, 26.5 (3C), 26.0, 18.8, 17.8, 10.1, −1.9, −2.8; HRMS *m/z* calcd for $C_{34}H_{54}O_8SSiNa^+$ 673.3201, found 673.3198; $[\alpha]^{23}_D$ −13.0 (*c* 0.47, $CHCl_3$).

Unsaturated Hydroxy Ketone 5. A 276 mg (0.425 mmol) sample of **4** was dissolved in 55 mL of benzene and treated with 0.095 mL (96.7 mg, 0.638 mmol) of DBU. The reaction mixture was heated in a 100 °C oil bath for 32 h; 20 mL of saturated NH_4Cl solution was added after return to room temperature, and stirring was maintained for 10 min. The separated aqueous layer was extracted with CH_2Cl_2 (20 mL x 3); the organic layers were combined, dried, and concentated, and the residue was purified by flash chromatography on silica gel (elution with 20% EtOAc/hexane) to give 150 mg (65%) of **5** as a colorless oil: IR (neat, cm^{-1}) 3383, 1705, 1614; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 5.54 (d, J = 12.2 Hz, 1H), 5.43 (dd, J = 12.1, 11.6 Hz, 1H), 4.98 (s, 1H), 4.76 (s, 1H), 4.64 (dd, J = 11.3, 4.5 Hz, 1H), 4.47 (d, J = 3.3 Hz, 1H), 4.41 (d, J = 11.0 Hz, 1H), 4.16 (d, J = 11.0 Hz, 1H), 3.84 (s, 3H), 3.66 (d, J = 11.4 Hz, 1H), 2.91 (d, J = 12.4 Hz, 1H), 2.67 (br q, J = 11.0 Hz, 1H), 2.49 (dq, J = 14.3, 2.4 Hz, 1H), 2.25−2.02 (m, 5H), 1.73 (qd, J = 12.5, 3.5 Hz, 1H), 1.11 (s, 3H), 1.08 (s, 6H), 0.89 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.8, 158.8, 143.9, 139.3, 131.4, 128.4 (2C), 125.1, 113.6 (2C), 110.6, 86.4, 84.1, 71.8, 65.8, 59.3, 56.2, 55.3, 51.1, 40.8, 37.1, 33.0, 31.7, 29.1, 26.4 (3C), 26.1, 18.7, 18.5, 9.5, −2.2, −2.6; HRMS *m/z* calcd for $C_{33}H_{50}O_5SiNa^+$ 577.3320, found 577.3335; $[\alpha]^{23}_D$ −21.9 (*c* 0.68, $CHCl_3$).

Epoxy Ketone 6. A 36.6 mg (0.066 mmol) sample of **5** was dissolved in 3.7 mL of dry CH_2Cl_2 and treated with 1.8 mg (0.0068 mmol) of $VO(acac)_2$ at room temperature, followed by 0.08 mL (0.136 mmol, 1.7 M) of *tert*-butylhydroperoxide in CH_2Cl_2. The mixture was stirred for 24 h; 5 mL of 10% $Na_2S_2O_3$ solution was added, and stirring was continued for 15 min. The separated aqueous layer was extracted with CH_2Cl_2 (2 mL x 3); the organic layers were combined and dried, and the crude product was purified by flash chromatography on silica gel (elution with 15% EtOAc/hexane) to afford 31.7 mg (84%) of **6** as a colorless oil: IR (neat, cm^{-1}) 3388, 1697, 1614; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.11 (s, 1H), 5.04 (s, 1H), 4.66 (dd, J = 11.2, 4.8 Hz, 1H), 4.49 (d, J = 3.8 Hz, 1H), 4.32 (d, J = 10.9 Hz, 1H), 4.19 (d, J = 10.9 Hz, 1H), 3.82 (s, 3H), 3.13 (dd, J = 10.7, 4.4 Hz, 1H), 3.01 (d, J = 1.3 Hz, 1H), 2.86−2.82 (m, 1H), 2.52−2.43 (m, 3H), 2.19−1.72 (m, 6H), 1.28 (s, 3H), 1.18 (s, 3H), 1.11 (s, 3H), 0.90 (s, 3H), 0.13 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.9, 161.1, 144.5, 133.5, 130.6 (2C), 115.9 (2C), 113.5, 88.0, 85.8, 76.6, 73.7, 63.9, 60.7, 59.3, 57.5, 56.4, 50.0, 42.4, 35.2, 34.2, 33.2, 32.0, 28.8 (3C), 25.8, 21.1, 19.9, 12.4, 0.0 (2C); HRMS *m/z* calcd for $C_{33}H_{50}O_6SiNa^+$ 593.3269, found 593.3271; $[\alpha]^{23}_D$ −51.0 (*c* 0.20, $CHCl_3$).

Diepoxide 9. To a solution of 10 mg (0.018 mmol) of **5** in 0.5 mL of CH_2Cl_2 at 0 °C were added 10 mg (0.12 mmol) of $NaHCO_3$ and 10 mg (0.044 mmol) of MCPBA. The reaction mixture was allowed to stir for 12 h with the bath warming to room temperature, at which point 2 mL of 10% $Na_2S_2O_3$ solution was added and stirring was continued for 15 min. The aqueous layer was separated and extracted with CH_2Cl_2 (5 mL x 3). The organic layers were combined, dried, and evaporated. The residue was purified by flash chromatography on silica gel (elution with 50% EtOAc/hexane) to afford 10 mg (95%) of **9** as a white glassy solid: IR (neat, cm^{-1}) 1703, 1614, 1514; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 4.66 (dd, J = 10.7, 4.2 Hz, 1H), 4.47 (d, J = 3.9 Hz, 1H), 4.31 (d, J = 10.8 Hz, 1H), 4.20 (d, J = 10.9 Hz, 1H), 3.82 (s, 3H), 3.13 (d, J = 4.0 Hz, 1H), 2.84−2.79 (m, 4H), 2.54 (br q, J = 12.7 Hz, 1H), 2.35 (d, J = 10.0 Hz, 1H), 2.20−2.05 (m, 3H), 1.96−1.80 (m, 4H), 1.49 (s, 3H), 1.25 (s, 3H), 1.11 (s, 3H), 0.91 (s, 9H), 0.15 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0, 161.2, 133.4, 130.6 (2C), 115.9 (2C), 88.0, 85.5, 78.3, 73.8, 61.1, 60.5, 60.4, 57.6, 57.5, 56.2, 52.9, 49.8, 38.8, 34.5, 33.4, 32.7, 31.9, 28.8 (3C), 25.8, 21.1, 19.3, 12.9, 0.0 (2C); HRMS *m/z* calcd for $C_{33}H_{50}O_7SiNa^+$ 609.3218, found 609.3211; $[\alpha]^{23}_D$ −22.8 (*c* 0.60, $CHCl_3$).

Triol 11. To a solution of 10 mg (0.018 mmol) of **5** in 2.0 mL of CH_2Cl_2 at −78 °C were added 0.0033 mL (2.51 mg, 0.0216 mmol) of TMEDA and 5.5 mg (0.0216 mmol) of OsO_4 in 0.1 mL of CH_2Cl_2. The reaction mixture was stirred for 1 h at −78 °C, allowed to warm to room temperature, and freed of solvent. The residue was taken up in 2 mL of THF, treated with 20 mg of $Na_2S_2O_4$ dissolved in 2 mL of H_2O, and stirred for 1 h at room temperature. The separated aqueous layer was extracted with CH_2Cl_2 (3 mL x 3); the organic layers were combined and dried, and the residue was purified by flash chromatography on silica gel (elution with EtOAc/hexane, gradient from 70% to 80%) to afford 7.0 mg (67%) of **11** as a white amorphous solid: IR (neat, cm^{-1}) 3474, 1698, 1514; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.71 (d, J = 12.0 Hz, 1H), 5.38 (t, J = 12.2 Hz, 1H), 4.56 (dd, J = 11.0, 4.2 Hz, 1H), 4.44 (d, J = 2.4 Hz, 1H), 4.32 (d, J = 10.9 Hz, 1H), 4.09 (d, J = 10.8 Hz, 1H), 3.83−3.72 (m, 2H), 3.82 (s, 3H), 3.33 (d, J = 12.5 Hz, 1H), 2.89−2.82 (m, 2H), 2.65 (br q, J = 11.7 Hz, 1H), 2.51 (br, 1H), 2.28 (br d, J = 13.6 Hz, 1H), 2.12−1.98 (m, 3H), 1.77−1.44 (m, 4H), 1.13 (s, 3H), 1.07 (s, 3H), 1.06 (s, 3H), 0.84 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5, 161.0, 146.2, 133.3, 130.6 (2C), 124.5, 115.8 (2C), 88.3, 86.3, 75.7, 74.1, 65.8, 61.1, 58.4, 57.4, 53.6, 45.7, 38.8, 35.0, 34.1, 31.9, 31.5, 28.4 (3C), 28.2, 20.7, 20.5, 14.4, 0.0, −0.9; HRMS *m/z* calcd for $C_{33}H_{54}O_7SiNa^+$ 611.3375, found 611.3403; $[\alpha]^{23}_D$ −30.9 (*c* 0.33, $CHCl_3$).

Acetalization of 12. To a solution of 650 mg (1.14 mmol) of **12** in 60 mL of CH_2Cl_2 at room temperature was added 1.7 g of 4 Å molecular sieves. At the same time, 284 mg (1.25 mmol) of DDQ in 50 mL of CH_2Cl_2 was treated with 1.7 g of 4 Å molecular sieves. Both suspensions were stirred for 1 h before the DDQ suspension was cannulated into the suspension containing **12**. The mixture was stirred for 24 h prior to quenching with 50 mL of saturated $NaHCO_3$ solution and 50 mL of CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2 (20 mL x 3). The organic layers were combined, dried, and evaporated to give the crude product. Purification by flash chromatography on silica gel (elution with 15% EtOAc/hexane) afforded 490 mg (75%) of **13** as a colorless oil: IR (neat, cm^{-1}) 3535, 1674, 1615; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 5.79 (s, 1H), 4.97 (s, 1H), 4.67 (s, 1H), 4.34−4.30 (m, 2H), 3.81 (s, 3H), 3.67 (d, J = 9.0 Hz, 1H), 3.11 (s, 1H), 2.94 (dd, J = 15.4, 2.2 Hz, 1H), 2.86−2.76 (m, 2H), 2.69−2.55 (m, 2H), 2.44 (dt, J = 13.6, 4.2 Hz, 1H), 2.30−2.23 (m, 1H), 2.14−2.07 (m, 2H), 2.06−1.97 (m, 1H), 1.74−1.64 (m, 2H), 1.17 (s, 3H), 1.16 (s, 3H), 1.04 (s, 3H), 0.95 (s, 9H), 0.16 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.3, 162.2, 148.4, 131.6, 130.3 (2C), 115.6 (2C), 111.2, 102.2, 89.6, 85.0, 83.8, 75.4, 57.2, 50.8, 50.1, 47.0, 46.9, 42.5, 35.8, 34.2, 32.8, 31.3, 28.4 (3C), 27.4, 21.4, 20.9, 14.6, 0.0, −0.6; HRMS *m/z* calcd for $C_{33}H_{50}O_6SiNa^+$ 593.3269, found 593.3271; $[\alpha]^{23}_D$ 6.1 (*c* 0.93, $CHCl_3$).

α-Oxygenation of 13. A 500 mg (0.877 mmol) sample of **13** was dissolved in 45 mL of THF, cooled to −78 °C, treated with 3.50 mL (1.75 mmol) of 0.5 M KHMDS solution in toluene, and stirred for 10 min at that temperature. At this point, 458 mg (1.75 mmol) of the Davis reagent dissolved in 20 mL of

THF was added and the reaction mixture was allowed to warm to room temperature over a period of 2 h, treated with 40 mL of saturated NH_4Cl solution, and stirred for 15 min. The aqueous layer was separated and extracted with CH_2Cl_2 (20 mL x 3). The combined organic layers were dried and evaporated to leave a residue that was purified by flash chromatography on silica gel (elution with 30% EtOAc/hexane) to afford 489 mg (95%) of **14** as a colorless oil: IR (neat, cm^{-1}) 2948, 2857, 1674, 1615; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 5.76 (s, 1H), 5.26 (s, 1H), 4.84 (s, 1H), 4.54 (d, J = 11.5 Hz, 1H), 4.28−4.23 (m, 2H), 3.86 (s, 3H), 3.67 (d, J = 9.0 Hz, 1H), 3.20−3.12 (m, 1H), 2.78−2.70 (m, 2H), 2.62−2.44 (m, 2H), 2.19−1.99 (m, 3H), 1.80−1.60 (m, 2H), 1.20(s, 3H), 1.18 (s, 3H), 1.13 (s, 3H), 0.93 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.9, 162.9, 145.8, 132.0, 130.8 (2C), 116.3 (2C), 113.6, 103.0, 89.7, 84.7, 84.6, 81.1, 75.0, 57.8, 51.7, 50.3, 49.9, 48.3, 36.4, 34.5, 31.9, 31.4, 28.8 (3C), 27.2, 22.2, 21.3, 17.3, 0.0, −0.5; HRMS *m/z* calcd for $C_{33}H_{50}O_7SiNa^+$ 609.3218, found 609.3222; $[\alpha]^{23}_D$ 0.62 (*c* 0.81, $CHCl_3$).

Acetylation of 14. To a solution of 23.6 mg (0.040 mmol) of **14** in 2.5 mL of CH_2Cl_2 at room temperature were added 0.05 mL (0.619 mmol) of pyridine, 0.012 mL (0.127 mmol) of acetic anhydride, and 5 mg (0.041 mmol) of DMAP. The reaction mixture was allowed to stir for 12 h, quenched with 3 mL of saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2 (5 mL x 3). The combined organic layers were dried and evaporated to leave a residue that was purified by flash chromatography on silica gel (elution with 25% EtOAc/hexane). There was isolated 24.3 mg (96%) of **15** as a colorless oil: IR (neat, cm^{-1}) 3478, 1753, 1690, 1615; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 5.75 (s, 1H), 5.67 (d, J = 12.1 Hz, 1H), 5.03 (s, 1H), 4.49 (s, 1H), 4.26−4.23 (m, 2H), 3.82 (s, 3H), 3.80 (d, J = 9.2 Hz, 1H), 3.05 (ddd, J = 14.8, 10.2, 3.5 Hz, 1H), 2.82 (d, J = 12.2 Hz, 1H), 2.77 (br d, J = 11.6 Hz, 1H), 2.62−2.52 (m, 1H), 2.48−2.42 (m, 1H), 2.22−2.15 (m, 1H), 2.11−1.96 (m, 2H), 2.06 (s, 3H), 1.81−1.72 (m, 1H), 1.70−1.62 (m, 1H), 1.20 (s, 3H), 1.16 (s, 6H), 0.92 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.5, 172.1, 163.3, 144.5, 132.3, 131.1 (2C), 116.7 (2C), 112.9, 103.6, 89.9, 85.3, 85.2, 81.3, 74.8, 58.2, 52.2, 50.3, 49.0, 48.2, 35.8, 34.6, 32.1, 31.5, 29.1 (3C), 27.6, 23.8, 22.5, 21.5, 18.2, 0.0, −0.3; HRMS *m/z* calcd for $C_{35}H_{52}O_8SiNa^+$ 651.3324, found 651.3336; $[\alpha]^{23}_D$ −9.6 (*c* 0.95, $CHCl_3$).

Isomerization of 15 to 16. A solution containing 11.2 mg (0.018 mmol) of **15** dissolved in 2.0 mL of dry CH_2Cl_2 was cooled to −78 °C, treated with 0.09 mL (0.09 mmol) of 1.0 M $EtAlCl_2$ solution in hexane, and stirred for 5 min at −78 °C. The dry ice bath was removed, and the reaction vessel was allowed to warm to room temperature over a period of 15 min and treated with 2 mL of MeOH followed by 6 mL of 1.0 M KNa tartrate solution. The mixture was stirred for 15 min; the separated aqueous layer was extracted with CH_2Cl_2 (3 mL x 3), and the organic layers were combined and dried to give the crude product, purification of which by flash chromatography on silica gel (elution with 25% EtOAc/hexane) afforded 6.8 mg (74%) of **16** as a colorless oil: IR (neat, cm^{-1}) 3472, 1742, 1673; ^1H NMR (400 MHz, $CDCl_3$) δ 5.27 (d, J = 11.8 Hz, 1H), 5.09 (s, 1H), 4.44 (s, 1H), 4.43 (br s, 1H), 4.27 (br s, 1H), 4.26 (dd, J = 11.2, 4.6 Hz, 1H), 3.61 (br s, 1H), 3.23 (d, J = 11.8 Hz, 1H), 2.74−2.60 (m, 2H), 2.50−2.39 (m, 2H), 2.17−2.06 (m, 2H), 2.10 (s, 3H), 1.99−1.93 (m, 1H), 1.76−1.68 (m, 1H), 1.63−1.52 (m, 1H), 1.21 (s, 3H), 1.03 (s, 3H), 0.92 (s, 3H), 0.80 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.3, 174.8, 142.8, 111.9, 81.6, 79.7, 77.6, 77.3, 71.7, 60.4, 54.7, 50.0, 46.4, 35.4, 33.1, 31.4, 27.8, 26.0 (3C), 23.8, 21.3, 18.3, 17.7, 11.9, −2.5, −4.8; HRMS *m/z* calcd for $C_{27}H_{46}O_7SiNa^+$ 533.2905, found 533.2935; $[\alpha]^{23}_D$ −94.2 (*c* 0.85, $CHCl_3$).

Mesylate 17. To a solution of 10.0 mg (0.020 mmol) of **16** in 1.0 mL of CH_2Cl_2 at room temperature were added 12.2 mg (0.100 mmol) of DMAP and 0.003 mL (0.039 mmol) of methanesulfonyl chloride. The reaction mixture was stirred for 2 h prior to quenching with 2 mL of saturated NH_4Cl solution and then stirred for 15 min at room temperature. The separated aqueous layer was extracted with CH_2Cl_2 (3 mL x 3); the organic layers were combined, dried, and evaporated, and the residue was purified by flash column chromatography on silica gel (elution with 30% EtOAc/hexane). There were isolated 2.9 mg of unreacted **16** and 6.7 mg (57%) of **17** as a white amorphous solid: IR (neat, cm^{-1}) 3468, 1747, 1684; ^1H NMR (400 MHz, $CDCl_3$) δ 5.75 (d, J = 1.1 Hz, 1H), 5.18 (d, J = 1.4 Hz, 1H), 4.89 (d, J = 3.0 Hz, 1H), 4.67 (d, J = 2.5 Hz, 1H), 4.47 (br s, 1H), 4.37 (br s, 1H), 4.22 (dd, J = 11.2, 4.5 Hz, 1H), 3.19 (dt, J = 12.9, 3.5 Hz, 1H), 3.08 (s, 3H), 2.95 (br s, 1H), 2.73−2.61 (m, 1H), 2.53 (ddd, J = 15.6, 10.8, 4.4 Hz, 1H), 2.37 (dt, J = 13.1, 3.8 Hz, 1H), 2.19−1.92 (m, 3H), 2.10 (s, 3H), 1.89−1.75 (m, 2H), 1.61−1.50 (m, 1H), 1.19 (s, 3H), 1.17 (s, 3H), 1.03 (s, 3H), 0.76 (s, 9H), 0.02 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.7, 168.7, 137.4, 115.7, 87.2, 85.7, 77.3, 74.8, 70.2, 59.9, 55.8, 47.5, 39.7, 37.8, 34.6, 32.5, 31.5, 30.3, 24.3 (3C), 23.9, 19.8, 16.6, 16.2, 9.3, −4.5, −6.5; HRMS *m/z* calcd for $C_{28}H_{48}O_9SSiNa^+$ 611.2681, found 611.2691; $[\alpha]^{23}_D$ −26.2 (*c* 0.51, $CHCl_3$).

Conversion of 17 to 18. A 3.5 mg (0.006 mmol) sample of **17** was dissolved in 0.5 mL of dry CH_2Cl_2, cooled to −78 °C, and treated with 0.06 mL (0.06 mmol) of 1.0 M Et_2AlCl solution in hexane. The reaction mixture was stirred for 5 min at −78 °C and allowed to warm to room temperature over a period of 45 min prior to the addition of 2 mL of 1.0 M tartaric acid solution. After 15 min, the separated aqueous layer was extracted with CH_2Cl_2 (3 mL x 3); the organic layers were combined, dried, and evaporated, and the crude product was purified by flash chromatography on silica gel (elution with 20% EtOAc/hexane) to afford 1.8 mg (61%) of **18** as a colorless oil: IR (neat, cm^{-1}) 3490, 1732, 1704; ^1H NMR (500 MHz, $CDCl_3$) δ 5.27 (dd, J = 11.0, 5.5 Hz, 1H), 5.08 (s, 1H), 4.68 (br, 1H), 4.39 (s, 1H), 3.87 (d, J = 11.0 Hz, 1H), 3.80 (t, J = 2.6 Hz, 1H), 3.16 (br, 1H), 2.73−2.60 (m, 3H), 2.44 (td, J = 11.8, 7.1 Hz, 1H), 2.29−2.27 (m, 2H), 2.19−2.13 (m, 1H), 2.03 (s, 3H), 1.95−1.89 (m, 1H), 1.86−1.81 (m, 1H), 1.71−1.68 (m, 1H), 1.40 (s, 3H), 1.09 (s, 3H), 1.00 (s, 3H), 0.95 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 221.5, 210.4, 170.9, 145.2, 111.8, 80.6, 75.6, 70.7, 63.2, 59.0, 53.3, 42.9, 38.1, 36.0, 34.1, 33.2, 32.6, 28.4, 26.6 (3C), 21.7, 18.8, 17.9, 14.5, −3.0, −3.9; HRMS *m/z* calcd for $C_{27}H_{44}O_6SiNa^+$ 515.2799, found 515.2808; $[\alpha]^{23}_D$ −89.7 (*c* 0.12, $CHCl_3$).

Benzoylation of 14. To a solution of 115 mg (0.196 mmol) of **14** in 3.0 mL of dry pyridine at room temperature were added 0.20 mL (242 mg, 1.72 mmol) of benzoyl chloride and 24 mg (0.196 mmol) of DMAP. The reaction mixture was allowed to stir for 19 h, quenched in turn with 10 mL of saturated $NaHCO_3$ solution, 10 mL of H_2O, and 20 mL of CH_2Cl_2, and stirred for 15 min prior to extraction of the aqueous layer with CH_2Cl_2 (25 mL x 3). The combined organic layers were dried and evaporated to leave the crude product, purification of which by flash chromatography on silica gel (elution with 15% EtOAc/hexane) afforded 120 mg (89%) of **19** as a colorless oil: IR (neat, cm^{-1}) 3556, 1728, 1689, 1615; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.0 Hz, 2H), 7.57−7.53 (m, 1H), 7.44−7.36 (m, 4H), 6.90 (d, J = 8.0 Hz, 2H), 5.93 (d, J = 12.0 Hz, 1H), 5.77 (s, 1H), 4.98 (s, 1H), 4.59 (s, 1H), 4.30−4.27 (m, 2H), 3.88 (d, J = 9.2 Hz, 1H), 3.80 (s, 3H), 3.21−3.14 (m, 1H), 2.99 (d, J = 12.0 Hz, 1H), 2.84 (s, 1H), 2.79 (d, J = 11.6 Hz, 1H), 2.67−2.56 (m, 1H), 2.48−2.41 (m, 1H), 2.25−1.98 (m, 3H), 1.82−1.64 (m, 2H), 1.22 (s, 6H), 1.14 (s, 3H), 0.92 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.5, 168.0, 163.3, 144.0, 136.2, 132.7 (2C), 132.4, 132.3, 131.4 (2C), 131.1 (2C), 116.7 × 2, 113.4, 103.7, 90.0, 85.4, 85.3, 81.8, 74.8, 58.2, 52.3, 50.5, 49.1, 48.4, 35.8, 34.6, 32.2, 31.9, 29.1 (3C), 27.8, 22.5, 21.5, 18.3, 0.0, −0.3; HRMS *m/z* calcd for $C_{40}H_{54}O_8SiNa^+$ 713.3480, found 713.3474; $[\alpha]^{23}_D$ +58.4 (*c* 1.1, $CHCl_3$).

Isomerization of 19. To a solution of 244 mg (0.354 mmol) of **19** (azeotropically dried with benzene and evacuated for 2 h) in 38.0 mL of dry CH_2Cl_2 at −78 °C was added 1.42 mL (1.42 mmol) of 1.0 M $EtAlCl_2$ solution in hexane. The reaction mixture was allowed to stir for 5 min at −78 °C, warmed to room temperature over a period of 15 min, quenched by adding 20 mL of MeOH and 40 mL of 1.0 M KNa tartrate solution, and stirred for 20 min. The separated aqueous layer was extracted twice with 20 mL of CH_2Cl_2. The organic layers were combined, dried, and evaporated to leave the crude product, which was purified by flash chromatography on silica gel (elution with 15% EtOAc/hexane) to afford 150 mg (74%) of **20** as a white foam: IR (neat, cm^{-1}) 3474, 1719, 1602; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93−7.91 (m, 2H), 7.52−7.50 (m, 1H), 7.39−7.35 (m, 2H), 5.47 (d, J = 11.8 Hz, 1H), 4.98 (s, 1H), 4.56 (d, J = 5.6 Hz, 1H), 4.46 (s, 1H), 4.41 (t, J = 4.2 Hz, 1H), 4.27−4.21 (m, 2H), 3.66 (d, J = 5.6 Hz, 1H), 3.51 (s, 1H), 3.35 (d, J = 11.8 Hz, 1H), 2.72−2.65 (m, 2H), 2.44−2.34 (m, 2H), 2.14−2.05 (m, 2H), 1.93−1.89 (m, 1H), 1.76−1.74 (m, 1H), 1.60−1.54 (m, 1H), 1.20 (s, 3H), 0.95 (s, 3H), 0.87 (s, 3H), 0.75 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.4, 169.8, 142.3, 134.1, 130.5 (2C), 129.4, 128.9 × 2, 112.6, 81.7, 79.7, 78.3, 71.6, 60.5, 54.7, 50.0, 46.5, 35.5, 33.1, 31.7, 27.8, 26.2, 26.0 (3C), 24.0, 18.3, 17.8, 11.9, −2.5, −4.7; HRMS *m/z* calcd for $C_{32}H_{48}O_7SiNa^+$ 595.3062, found 595.3074; $[\alpha]^{23}_D$ −29.1 (*c* 1.18, $CHCl_3$).

Mesylate 21. To a solution of 1.2 g (2.1 mmol) of **20** in 100 mL of dry CH_2Cl_2 at 0 °C were added 563 mg (4.6 mmol) of DMAP, 0.32 mL (4.2 mmol) of methanesulfonyl chloride, and 0.99 mL of triethylamine in order. The mixture was allowed to stir for 20 min at 0 °C and then quenched with 100 mL of saturated $NaHCO_3$ solution at 0 °C. The mixture was allowed to warm to room temperature over a period of 15 min. The separated aqueous layer was extracted twice with 50 mL of CH_2Cl_2. The organic layers were combined, dried, and evaporated. Purification of the residue by flash chromatography on silica gel (elution with 35% EtOAc/hexane) afforded 270 mg of unreacted **20** and 740 mg (54%) of **21** as a white foam: IR (neat, cm^{-1}) 3470, 1723, 1686, 1602; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05−8.03 (m, 2H), 7.57−7.54 (m, 1H), 7.45−7.42 (m, 2H), 5.97 (br s, 1H), 5.33 (br s, 1H), 5.17 (d, J = 3.0 Hz, 1H), 4.83 (d, J = 2.8 Hz, 1H), 4.52 (d, J = 2.9 Hz, 1H), 4.41 (t, J = 3.6 Hz, 1H), 4.25 (dd, J = 10.7, 4.8 Hz, 1H), 3.24−3.20 (m, 1H), 3.10 (s, 1H), 3.02 (s, 3H), 2.71−2.60 (m, 1H), 2.58−2.53 (m, 1H), 2.45−2.42 (m, 1H), 2.25−2.19 (m, 1H), 2.09−2.03 (m, 2H), 1.92−1.77 (m, 2H), 1.62−1.56 (m, 1H), 1.28 (s, 3H), 1.20 (s, 3H), 1.01 (s, 3H), 0.74 (s, 9H), 0.01 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.3, 166.3, 138.9, 133.7, 130.4 (2C), 129.9, 128.9 (2C), 117.4, 89.0, 87.4, 78.9, 76.4, 72.6, 61.4, 57.5, 49.2, 42.0, 39.4, 35.9, 34.2, 32.9, 31.6, 25.8 (3C), 25.6, 18.1, 17.9, 11.0, −3.0, −4.9; HRMS *m/z* calcd for $C_{33}H_{50}O_9SSiNa^+$ 673.2837, found 673.2830; $[\alpha]^{23}_D$ −0.9 (*c* 1.0, $CHCl_3$).

Conversion of 21 to 22. To a solution of 740 mg (1.14 mmol) of **21** (azeotropically dried with benzene and evacuated for 2 h) in 114 mL of dry CH_2Cl_2 at −78 °C was added 11.4 mL (11.4 mmol) of 1.0 M Et_2AlCl solution in hexane. The reaction mixture was allowed to stir for 5 min at −78 °C, warmed to room temperature over a period of 1.5 h, quenched with 120 mL of 1.0 M tartaric acid aqueous solution, and stirred for 20 min. The separated aqueous layer was extracted twice with 60 mL of CH_2Cl_2. The organic layers were combined, dried, and concentrated to leave the crude product. Purification by flash chromatography on silica gel (elution with 15% EtOAc/hexane) afforded 334 mg (52%) of **22** as a white foam: IR (neat, cm^{-1}) 3490, 1710, 1646, 1602; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02−7.99 (m, 2H), 7.54−7.42 (m, 1H), 7.40−7.38 (m, 2H), 5.45 (dd, J = 10.0, 4.2 Hz, 1H), 4.92 (s, 1H), 4.56 (t, J = 7.9 Hz, 1H), 4.40 (s, 1H), 4.04 (d, J = 10.0 Hz, 1H), 3.78 (br s, 1H), 3.20 (d, J = 8.1 Hz, 1H), 2.72−2.60 (m, 3H), 2.36−2.26 (m, 3H), 2.19−2.13 (m, 1H), 1.93−1.87 (m, 1H), 1.76−1.72 (m, 2H), 1.45 (s, 3H), 1.11 (s, 3H), 1.04 (s, 3H), 0.90 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 222.0, 210.4, 166.3, 143.9, 133.3, 130.8, 130.3 (2C), 128.7 (2C), 113.4, 80.2, 76.2, 70.8, 63.4, 58.6, 53.7, 41.9, 38.1, 36.1, 34.5, 32.5, 31.4, 28.3, 26.5 (3C), 26.1, 18.7, 18.1, −3.1, −4.0; HRMS *m/z* calcd for $C_{32}H_{46}O_6SiNa^+$ 577.2956, found 577.2919; $[\alpha]^{23}_D$ −92.7 (*c* 1.0, $CHCl_3$).

Supporting Information Available: High-field ^1H and ^{13}C NMR spectra for all compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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