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Chemical Modification of a Highly Functionalized Taxane. The Consequences of an Absent Bridgehead Double Bond on Oxetane D-Ring Construction

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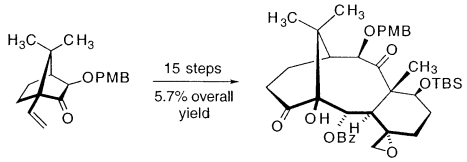
An oxetane D-ring has been fused to the framework of the highly functionalized taxane **2**. The synthetic route is based on a trimethylsilyl triflate-promoted epoxide-opening step, followed by stereocontrolled, regioreversed oxirane formation and reductive transposition of this intermediate with bis(cyclopentadienyl)titanium(III) chloride. This last key step provides for the convenient implementation of additional hydroxyl groups ultimately conducive to intramolecular S_N2 reaction. Tangential features of the route outlined herein include specific rearrangement reactions and a retro-aldol cleavage of ring A.

In our synthetic effort directed toward Taxol, we targeted a short route that was also sufficiently flexible to permit practical access to analogues. The combined application of anionic oxy-Cope[1] and α-ketol rearrangements[2] has been shown to fulfill our early expectations in that a convergent route from enantiomerically pure **1** to tricyclic diketone **2** has been realized in only 15 steps and 5.7% overall yield.[3,4] This notably efficient pathway also allows for incorporation of the absolute configuration of (+)-camphor into the target compounds. In light of the high level of substitution in **2** and the essentially complete overlay of its stereocenters with those resident in Taxol (**5**),[5] the former was considered to be a good candidate for forward progress.



1 **2**

Consideration of the chemical complexities to be dealt with does not make apparent which of two possible directions to advance on first. Completion of the western sector translates into immediate investigation of A-ring chemistry. The second option involves the eastern sector of **2** and gives priority to proper introduction of the oxetane ring. Of the six prior successful de novo syntheses of taxol,[6−11] all but one entails construction of the strained heterocyclic ring late in the overall scheme after the bridgehead (C11−C12) double bond has been installed. The alternative ploy utilized by Danishefsky comprised

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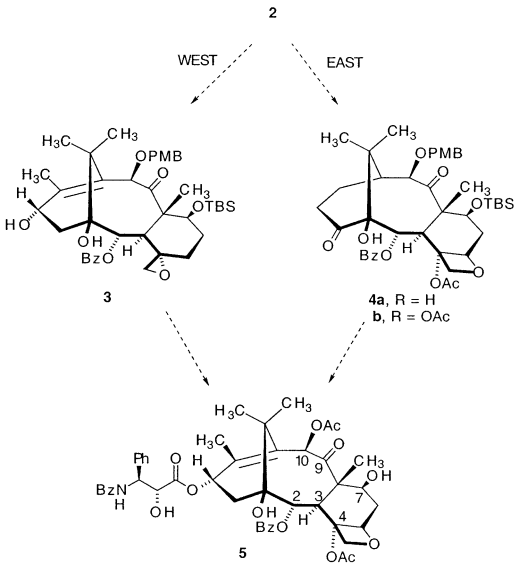
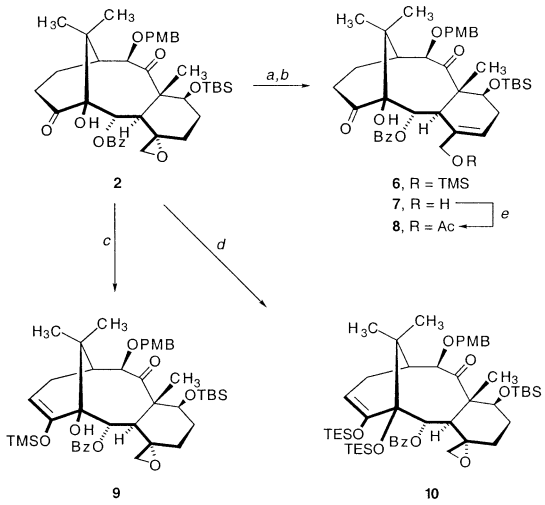
early introduction of the oxetane D-ring with the Wieland−Miescher ketone serving as the matrix.[8] Since no attention had yet been paid to 11,12-dihydro systems, we decided to proceed from **2** in the general direction of **4**. A comparative analysis would thereby be enabled. The presence of bridgehead unsaturation in **5** and its immediate congeners flattens the A-ring sector and thereby releases nonbonded steric compression throughout the core structure to an appreciable level. On the other hand, **2**, **4**, and relatives thereof are not subject to comparable diminution of steric strain and have a very crowded hemispherical topology. The challenges associated with this plan of action form the subject of this paper.

Results and Discussion

The first attempts made to carry **2** forward involved the isomerization of its epoxide to the ring-cleaved allylic alcohol. In view of precedent,[8] aluminum isopropoxide was initially resorted to. However, only wholesale decomposition was seen in refluxing benzene or toluene. Subsequently, various alternative methods were probed including MICA,[12] diethylaluminum tetramethylpiperidide,[13] lithium amide bases,[14] and boron trifluoride etherate with and without added DBU. All of these reagents except for the Lewis acid combination led again to decomposition. These observations prompted our consideration of the trimethylsilyl triflate−DBU tandem[15,16] to realize our goal. When these conditions were applied in the predescribed manner, only silyl enol ether **9** was isolated (91%, Scheme 1). An increase in the amount of the silyl triflate resulted only in bis-silylation as exemplified by **10**. However, more careful control of reaction conditions, particularly the addition of triflic acid as a co-catalyst, proved successful. The reactivity of the epoxide is significantly enhanced by protonolysis and conversion to **6** proceeds effectively as long as conditions remain acidic even after the addition of DBU. Product **6** was expectedly sensitive to chromatographic conditions. Practical considerations led us to hydrolyze **6** directly to allylic alcohol **7**, this two-step conversion proceeding in an acceptable 75% overall yield.



SCHEME 1[a]



[a] Key: (a) TMSOTf, 2,6-lutidine, TfOH, −78 to 0 °C (55%); (b) CSA, CH_2Cl_2, rt (55%); (a, b) as above, no intermediate workup (75% for two steps); (c) TMSOTf, 2,6-lutidine, DBU, 0 °C (91%); (d) TESOTf, DBU, 0 °C (68%); (e) Ac_2O, Et_3N, DMAP, CH_2Cl_2 (100%).

All attempts to bring about the dihydroxylation of **7** with osmium tetraoxide were to no avail, undoubtedly a direct consequence of the considerable steric hindrance in the vicinity of the endocyclic double bond. In the case of ruthenium tetraoxide, which has a smaller size, uncontrolled oxidation was noted and considerable C-ring cleavage ensued. An unexpected observation was the formation of α,*β*-unsaturated aldehyde **11** when **7** was exposed to OsO_4 in the presence of DABCO as an accelerating ligand (Scheme 2).

Foreshadowed by the above experiments was the need to effect translocation of the double bond to the somewhat less crowded external position. Initially, a path adapted from Mukaiyama et al.[10] was pursued. Exposure of **7** to the action of triphenylphosphine and carbon tetrabromide did indeed furnish primary bromide **12**. However, **12** totally resisted CuBr-promoted allylic rearrangement to **13** when heated in acetonitrile for extensive periods of time. The thermodynamic bias in favor of **12** can also be reasoned in terms of the heightened crowding in **13**.

Concurrent studies of the epoxidation of **7** with *m*-CPBA revealed that α-epoxidation to give **14** could be accomplished efficiently. The stereochemistry of **14** was unequivocally established by $^1H-^1H$ COSY and $^1H-^1H$ NOESY experiments (see **A**). Beyond this objective, attempts were made to epoxidize acetate **8** with *m*-CPBA, dimethyl dioxirane, and via the halohydrin. In light of the singular lack of reactivity of this substrate and of bromide **12**, it was made clear that precoordination of the peracid to the allylic hydroxyl in **7** is a likely

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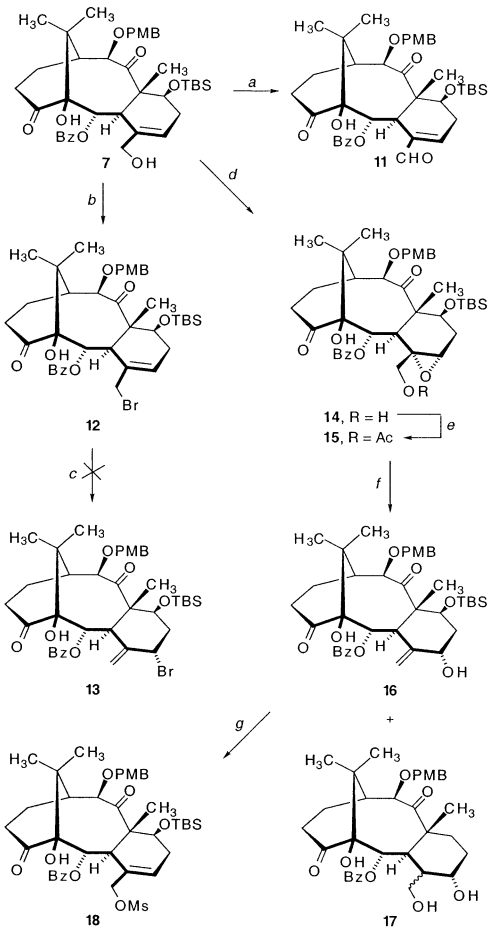
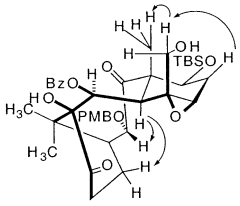
SCHEME 2[a]



[a] Key: (a) OsO_4, DABCO, THF, rt; $Na_2S_2O_4$ (90%); (b) PPh_3, CBr_4, CH_2Cl_2, rt (96%); (c) CuBr, CH_3CN, 50 °C to reflux; (d) *m*-CPBA, $NaHCO_3$, CH_2Cl_2 (90%); (e) Ac_2O, DMAP, Et_3N (100%); (f) Cp_2TiCl_2, Zn, $ZnCl_2$, THF (82%; **16**/**17** = 1:1.2); (g) MsCl, Et_3N, DMAP, CH_2Cl_2 (100%).

prerequisite to oxirane formation. Under no conditions was any sign of the β-epoxide found.



A

When arrival at the halo epoxide could be realized neither by the epoxidation of **12** nor by reaction of **14** with triphenylphosphine and iodine, the role of **14** as a key intermediate was pursued. Bis(cyclopentadienyl)-titanium(III) chloride has been shown to react cleanly with epoxy alcohols to deliver allylic alcohols in which the original OH group is transposed.[17] Of the various conditions explored by us for the formation of **16** (Table 1), the use of a substantial excess of all three necessary

TABLE 1. Conditions Examined for the Reductive Deoxygenation of 14

run	conditions	*T*, °C	yield, %	product ratio **16**/**17**
a	1.2 equiv of Cp_2TiCl_2, 5 equiv of activated Zn, 1.2 equiv of $ZnCl_2$, THF	25	82	1:1.2
b	10 equiv of Cp_2TiCl_2, 20 equiv of activated Zn, 10 equiv of $ZnCl_2$, THF	25	72	1:0
c	1.2 equiv of Cp_2TiCl_2, 5 equiv of activated Zn, 1.2 equiv of $ZnCl_2$, THF	0	NR[a]	
d	5 equiv of Cp_2TiCl_2, THF	25	NR[a]	

[a] NR signifies that no observable reaction was seen.

reagents (run b) proved particularly efficacious in delivering **16** (72% yield) without contamination by diol **17**. The insufficiency of titanocene reagent apparent in runs a and c conforms to the proposed mechanistic analysis of this process,[17,18] where the involvement of at least two equiv of the titanium complex is believed to be involved. Also relevant to these studies is the observation that epoxy acetate **15** was unaffected by this reagent combination, in conformity with the proposition that the OH functionality is the initial site of reaction.

When an opportunity presented itself to bring about the mesylation of **16** under conventional conditions, quantitative conversion to **18** was noted. The ready isomerization observed with sulfonate ester formation was not matched by acetylation.[19] This dichotomy suggests that mesylation also occurs with derivatization of the secondary alcohol. However, ionization to the allylic cation is now energetically feasible, with covalent capture subsequently materializing at the less crowded primary site.

The time had now arrived to examine the dihydroxylation of **16**. This chemistry was initially pursued by exposure of the allylic alcohol to osmium tetraoxide in a THF/pyridine solvent system. The presence of pyridine was essential to the reaction, which however resulted in formation of osmate ester **19** (Scheme 3). Rather unexpectedly, this substance was highly resistant to controlled hydrolysis. Conditions were not found to bring about its conversion to the triol, cyclic carbonate, or TMS-protected tetrol. When aqueous acetone served as the reaction medium, conversion to **21** was seen. The formation of this ring-cleaved product is presumably the result of overoxidation of the dihydroxy aldehyde level followed by retro-aldol cleavage and intramolecular transesterification. This unwanted side reaction was curtailed to some degree (**20**/**21** = 1:1.1) through use of ruthenium trichloride−sodium periodate.[20] To our delight, substitution of DABCO for pyridine as the accelerating ligand for OsO_4 gave rise to **20** as the sole observable product in 75% yield after chromatography.

This tetraol was integrated into the main synthetic pathway by quantitative monosilylation of the primary

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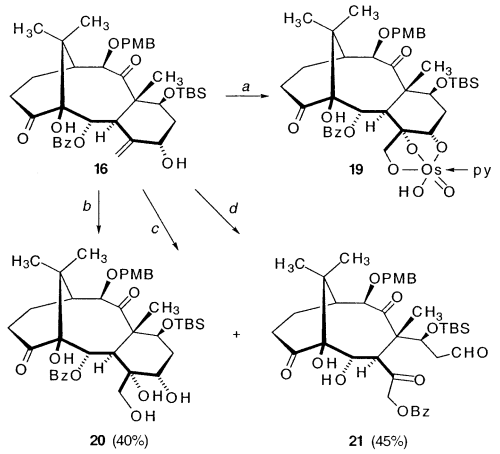
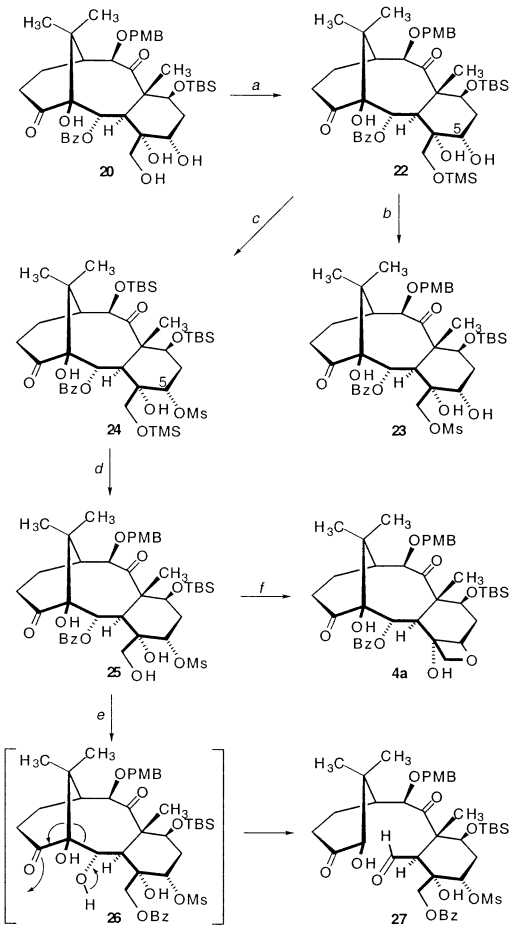
SCHEME 3[a]



[a] Key: (a) OsO_4, THF/py, rt; $Na_2S_2O_4$ (75% at 65% conversion); (b) OsO_4, DABCO, THF, rt (75%); (c) $RuCl_3$, $NaIO_4$, CH_3CN, H_2O, EtOAc (85%; **20**/**21** = 1:1.1); (d) OsO_4, H_2O, acetone; $Na_2S_2O_4$ (71%).

SCHEME 4[a]



[a] Key: (a) TMSCl, 2,6-lutidine, CH_2Cl_2, −78 °C (100%); (b) MsCl, py, rt (85%); (c) MsCl, DMAP, CH_2Cl_2, (90%); (d) CSA, CH_2Cl_2, rt (95−100%); (e) $(n\text{-Bu})_4NOAc$, CH_2Cl_2, rt (70%) or DMAP, THF, rt (82%); (f) $Al(O\text{-}t\text{-Bu})_3$, C_6H_6, rt (54%).

hydroxyl group as in **22** (Scheme 4). For the purpose of transforming the OH at C-5 into a leaving group, **22** was exposed to methanesulfonyl chloride in pyridine at room temperature. Quite unexpectedly, these conditions proved conducive to loss of the trimethylsilyl substituent and its transformation into a mesylate. This undesired reaction was skirted by performing the activation step in CH_2Cl_2 solution with DMAP as the activator. The regioselectivity associated with the formation of **24** has its origins in steric accessibility as usual. Deprotection of the primary alcohol to deliver **25** proceeded without incident.

The final stage of the pursuit of **28** was to involve intramolecular S_N2 displacement with configurational inversion at C-5. This goal proved more elusive than projected. Recourse to tetra-*n*-butylammonium acetate in butanone at 25 °C in an adaptation of Nicolaou's best conditions for construction of the Taxol D-ring[7] caused rapid decomposition. In an interesting development, a change in solvent to CH_2Cl_2 exhibited a profound effect on the reaction pathway. Under these circumstances, benzoyl migration occurred to generate **26**, thereby making possible retro-aldol fragmentation of the A-ring with conversion to **27** (70%).[19] The same transformation accompanied the use of DMAP in THF at room temperature (82% yield). At this point, the timely observation was made that the exposure of **25** to aluminum *tert*-butoxide in benzene promoted the desired ring closure and furnished **4a**. Accordingly, the feasibility of laterally fusing an oxetane ring onto **2** has been demonstrated. The assembly process required eight laboratory operations and proceeded in 18% overall yield. The effectiveness of the titanium(III)-mediated reductive deoxygenation of **14** to give **16** was demonstrated in a highly functionalized structural setting, and augurs well for its exploitation in other complex settings. The successful route reflects a number of deterrents brought on by substantive steric congestion. The adaptations made necessary by these factors resulted in modest prolongation of the synthetic pathway. We anticipate more favorable consequences once the A-ring is suitably modified[6−11] and hope to be in a position to report on this matter soon.

Experimental Section

Epoxide Ring Opening in 2. To a solution of **2** (10.7 mg, 0.15 μmol) in dry toluene (5 mL) were added 2,6-lutidine (1.6 μL, 0.015 mmol) and TMSOTf (5.4 μL, 0.03 mmol) at −78 °C under N_2. Trific acid (0.13 μL, 0.15 μmol) was added, and the solution was stirred at −78 °C for 3 h. DBU (2 μL, 0.015 mmol) was introduced, the reaction flask was immediately transferred from the dry ice−acetone bath to an ice water bath, stirring at this temperature was maintained for 5 h, and saturated $NaHCO_3$ solution (10 mL) was added. After 10 min, the resulting mixture was extracted with EtOAc (2 × 20 mL), the combined organic extracts were dried and filtered, and the residue was subjected to flash chromatography on silica gel (elution with 8:1 hexane/EtOAc) to afford **6** (6.4 mg, 55%) as a colorless oil: IR (neat, cm^{-1}) 3491, 1729, 1701, 1513; ^1H NMR (500 MHz, C_6D_6) δ 8.18−8.16 (m, 2 H), 7.46 (d, J = 8.6 Hz, 2 H), 7.05−7.02 (m, 3 H), 6.84 (d, J = 8.6 Hz, 2 H), 6.27 (d, J = 4.3 Hz, 1 H), 5.67 (br s, 1 H), 4.65 (d, J = 10.2 Hz, 1 H), 4.49 (d, J = 3.8 Hz, 1 H), 4.30 (d, J = 12.1 Hz, 1 H), 4.22 (s, 1 H), 4.19 (br s, 1 H), 4.14 (d, J = 12.1 Hz, 1 H), 3.95 (t, J = 7.7 Hz, 1 H), 3.88 (d, J = 10.3 Hz, 1 H), 3.26 (s, 3 H), 3.26−3.24 (m, 1 H), 2.64−2.59 (dd, J = 6.8, 18.3 Hz, 1 H), 2.29 (br s, 1 H), 2.09−2.05 (m, 3 H), 1.79−1.77 (m, 1 H), 1.77 (s, 3 H), 1.34 (s, 3 H), 0.93 (s, 9 H), 0.76 (s, 3 H), 0.19 (s, 9 H), 0.00 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 212.1, 209.2, 164.5, 159.6, 153.1, 135.9, 132.8, 130.5, 129.8, 129.5, 128.5, 126.9, 113.8, 84.7, 83.5, 73.6, 72.0, 71.5, 66.2, 57.7, 54.4, 51.9, 43.0,

40.4, 38.4, 30.9, 30.7, 27.9, 25.9, 22.5, 18.3, 12.0, −0.1, −2.1, −4.1; ES HRMS *m/z* (M − Me_3Si + Na + H) calcd 739.3429, obsd 729.3439; $[\alpha]^{20}_D$ +19 (*c* 0.22, $CHCl_3$).

Hydrolysis of 6 to 7. A 10 mg (0.013 mmol) sample of **6** in 5 mL of CH_2Cl_2 was treated with 15 mg (0.642 μmol) of CSA. The reaction mixture was stirred for 30 min at rt, quenched with a saturated solution of aqueous $NaHCO_3$, transferred to a separatory funnel, and extracted with EtOAc. The combined organic extracts were dried, filtered, and concentrated under reduced pressure to give a residue that was purified by column chromatography on silica gel (elution with 5:1 hexane/EtOAc) to give 5.0 mg (55%) of **7** as a colorless oil: IR (neat, cm^{-1}) 3488, 1725, 1514; ^1H NMR (500 MHz, C_6D_6) δ 8.11 (d, *J* = 7.9 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.08−6.98 (m, 3 H), 6.84 (d, *J* = 8.4 Hz, 2 H), 6.25 (d, *J* = 4.3 Hz, 1 H), 5.36 (br s, 1 H), 4.67 (d, *J* = 10.2 Hz, 1 H), 4.48 (d, *J* = 4.1 Hz, 1 H), 4.23 (d, *J* = 12 Hz, 1 H), 4.20 (s, 1 H), 4.14 (br s, 1 H), 3.97−3.94 (m, 2 H), 3.84 (d, *J* = 12 Hz, 1 H), 3.34−3.27 (m, 1 H), 3.27 (s, 3 H), 2.59 (dd, *J* = 6.6, 18.3 Hz, 1 H), 2.35−2.28 (m, 1 H), 2.08−1.99 (m, 3 H), 1.86−1.76 (m, 1 H), 1.72 (s, 3 H), 1.33 (s, 3 H), 0.94 (s, 9 H), 0.91−0.89 (m, 1 H), 0.77 (s, 3 H), 0.02 (s, 3 H), −0.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.8, 210.6, 165.0, 159.3, 136.5, 133.2, 129.7, 129.6, 129.5, 128.6, 126.8, 113.8, 84.3, 83.4, 73.2, 71.9, 71.6, 66.6, 57.5, 55.2, 52.1, 43.1, 39.3, 38.2, 30.9, 30.8, 27.6, 25.9, 22.6, 18.3, 14.1, 11.9, −1.9, −3.9; ES HRMS *m/z* $(M + Na)^+$ calcd 729.3429, obsd 729.3411; $[\alpha]^{20}_D$ −2.3 (*c* 0.64, $CHCl_3$).

Direct Conversion of 2 to 7. To a solution of **2** (10 mg, 0.014 mmol) in dry toluene (5 mL) were added 2,6-lutidine (1.6 μL, 0.014 mmol) and TMSOTf (5.4 μL, 0.028 mmol) at −78 °C under N_2. Triflic acid (0.13 μL, 0.15 μmol) was added, and the solution was stirred at −78 °C for 3 h. DBU (2 μL, 0.015 mmol) was introduced, the reaction flask was immediately transferred from the dry ice−acetone bath to an ice−water bath, stirring at this temperature was maintained for 5 h, and saturated $NaHCO_3$ solution (10 mL) was added. After 10 min, the resulting mixture was extracted with EtOAc (2 × 20 mL), and the combined organic extracts were dried and filtered. CSA (16 mg, 0.07 mmol) was added, and the solution was stirred at rt for 1 h prior to quenching with saturated $NaHCO_3$ solution (20 mL). After 10 min, the resulting mixture was extracted with EtOAc (2 × 20 mL), the combined organic phases were dried and filtered, and the concentrate was subjected to flash chromatography on silica gel (elution with 2:1 hexane/EtOAc) to give **7** (7.5 mg, 75%) as a colorless oil identical to the material isolated above.

Silyl Enol Ether 9. To a solution of **2** (10 mg, 0.014 mmol) in dry toluene (5 mL) were added 2,6-lutidine (1.6 μL, 0.014 mmol) and TMSOTf (5.4 μL, 0.028 mmol) at −78 °C under N_2. The solution was stirred at −78 °C for 3 h, DBU (9.6 μL, 0.07 mmol) was added, and the reaction flask was immediately transferred from the dry ice−acetone bath to an ice−water bath. After 5 h of stirring at this temperature, saturated $NaHCO_3$ solution (10 mL) was added, and the mixture was stirred for 10 min, extracted with EtOAc (2 × 20 mL), dried, and filtered. Concentration of the filtrate followed by flash chromatography on silica gel (elution with 12:1 hexane/EtOAc) furnished **9** (9.9 mg, 91%) as a colorless oil: IR (neat, cm^{-1}) 1724, 1513; ^1H NMR (500 MHz, C_6D_6) δ 8.27−8.25 (m, 2 H), 7.44 (d, *J* = 8.6 Hz, 2 H), 7.14−7.11 (m, 3 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 5.93 (br s, 1 H), 4.926−4.921 (m, 1 H), 4.77 (d, *J* = 10.6 Hz, 1 H), 4.60 (d, *J* = 4.6 Hz, 1 H), 4.43 (br s, 1 H), 4.20 (d, *J* = 10.6 Hz, 1 H), 3.44 (br s, 1 H), 3.30 (s, 3 H), 3.09 (d, *J* = 4.3 Hz, 1 H), 2.94 (s, 1 H), 2.55 (dd, *J* = 3.8, 15.2 Hz, 1 H), 2.28−2.26 (m, 1 H), 2.17−2.11 (m, 2 H), 1.92−1.89 (m, 1 H), 1.71 (s, 3 H), 1.55−1.51 (m, 1 H), 1.38 (s, 3 H), 1.33−1.25 (m, 2 H), 1.15 (s, 3 H), 0.94 (s, 9 H), 0.24 (s, 9 H), 0.03 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 209.4, 164.9, 159.5, 149.8, 132.9, 130.9, 130.4, 130.0, 129.4, 128.4, 128.3, 113.7, 103.1, 77.7, 74.0, 72.5, 71.1, 57.8, 54.4, 51.7, 50.6, 40.3, 30.7, 30.2, 30.1, 29.9, 29.8, 25.9, 22.4, 18.2, 11.8, −0.1, −2.2, −4.2; EI HRMS $(M + 1)^+$ calcd 779.4005, obsd 779.3986; $[\alpha]^{20}_D$ +23 (*c* 0.24, $CHCl_3$).

Bis-silylation of 2. To a solution of **2** (3.1 mg, 0.004 mmol) in dry toluene (2 mL) were added DBU (2.8 μL, 0.02 mmol) and TESOTf (2 μL, 0.009 mmol) at −78 °C under N_2. The solution was slowly warmed to 0 °C during 2 h prior to quenching with saturated $NaHCO_3$ solution (10 mL). After 10 min, the mixture was extracted with EtOAc (2 × 20 mL), and the combined organic phases were dried and filtered. Concentration of the filtrate followed by flash chromatography on silica gel (elution with 20:1 hexane/EtOAC) afforded **10** (2.5 mg, 68%) as a colorless oil: ^1H NMR (500 MHz, C_6D_6) δ 8.40−8.38 (m, 2 H), 7.46 (d, *J* = 8.5 Hz, 2 H), 7.29−7.17 (m, 3 H), 6.83 (d, *J* = 8.5 Hz, 2 H), 5.93 (d, *J* = 4.0 Hz, 1 H), 4.96 (d, *J* = 3 Hz, 1 H), 4.77 (d, *J* = 10.4 Hz, 1 H), 4.59 (d, *J* = 4.8 Hz, 1 H), 4.39−3.38 (m, 1 H), 4.18 (d, *J* = 10.4 Hz, 1 H), 3.40 (d, *J* = 4.0 Hz, 1 H), 3.27 (s, 3 H), 3.05 (br s, 1 H), 2.59 (dd, *J* = 4.0, 15.8 Hz, 1 H), 2.31−2.29 (m, 1 H), 2.12 (dd, *J* = 5.3, 18 Hz, 1 H), 2.04 (d, *J* = 4.1 Hz, 1 H), 1.88−1.85 (m, 1 H), 1.62 (s, 3 H), 1.55−1.51 (m, 1 H), 1.39 (s, 3 H), 1.28 (m, 2 H), 1.14 (t, *J* = 7.4 Hz, 9 H), 1.13−1.08 (m, 9 H), 0.94 (s, 9 H), 0.81 (t, *J* = 7.9 Hz, 9 H), 0.77−0.64 (m, 3 H), 0.59−0.51 (m, 3 H), 0.00 (s, 3 H), −0.03 (s, 3 H).

Acetylation of 7. A solution of **7** (5 mg, 0.007 mmol) in CH_2Cl_2 (3 mL) was treated sequentially with Et_3N (3 μL, 0.021 mmol), acetic anhydride (0.8 μL, 0.008 mmol), and DMAP (0.1 mg, 0.8 μmol), stirred at rt for 1 h, and quenched with saturated $NaHCO_3$ solutions (10 mL). After 3 min of stirring, the mixture was extracted with EtOAc (2 × 20 mL), the combined organic phases were dried and filtered, and the residue was subjected to flash chromatography on silica gel (elution with 10:1 hexane/EtOAc) to afford **8** (5.3 mg, 100%) as a colorless oil: IR (neat, cm^{-1}) 3482, 1733, 1252; ^1H NMR (400 MHz, C_6D_6) δ 8.30 (d, *J* = 8.2 Hz, 2 H), 7.57 (d, *J* = 8.6 Hz, 2 H), 7.19−7.11 (m, 3 H), 6.97 (d, *J* = 8.6 Hz, 2 H), 6.40 (d, *J* = 5.1 Hz, 1 H), 5.61 (br s, 1 H), 4.87 (d, *J* = 4.3 Hz, 1 H), 4.82 (d, *J* = 10.2 Hz, 1 H), 4.77 (d, *J* = 13.5 Hz, 1 H), 4.63 (br s, 1 H), 4.57 (d, *J* = 13.5 Hz, 1 H), 4.37 (s, 1 H), 4.20 (t, *J* = 7.6 Hz, 1 H), 4.13 (d, *J* = 10.2 Hz, 1 H), 3.96−3.86 (m, 1 H), 3.40 (s, 3 H), 2.83 (dd, *J* = 6.4, 18.4 Hz, 1 H), 2.43 (br s, 1 H), 2.23−2.14 (m, 3 H), 2.02−1.97 (m, 1 H), 1.90 (s, 3 H), 1.76 (s, 3 H),1.46 (s, 3 H), 1.06 (s, 9 H), 0.91 (s, 3 H), 0.12 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 213.3, 209.5, 170.6, 164.8, 159.9, 134.4, 133.3, 130.7, 130.4, 130.2, 130.0, 129.0, 124.9, 114.1, 84.4, 84.1, 74.0, 71.99, 71.94, 67.5, 57.9, 54.7, 52.1, 43.1, 42.3, 38.5, 31.2, 31.1, 28.1, 26.2, 23.1, 23.1, 20.7, 18.6, 12.4, −1.8, −3.8; ES HRMS *m/z* $(M + Na)^+$ calcd 771.3534, obsd 771.3562; $[\alpha]^{20}_D$ +3.2 (*c* 0.47, $CHCl_3$).

Unsaturated Aldehyde 11. A solution of **7** (2.8 mg, 0.004 mmol) in THF (2 mL) containing DABCO (0.9 mg, 0.008 mmol) was treated with OsO_4 (1 mg, 0.004 mmol) at rt. After 6 h, $Na_2S_2O_4$ (3.5 mg, 0.02 mmol) dissolved in water (2 mL) was introduced, and stirring was maintained for 3 h. The resulting mixture was extracted with EtOAc (2 × 10 mL), the combined organic phases were dried and filtered, and the residue was purified by flash chromatography on silica gel (elution with 6:1 hexane/EtOAc) to give **11** (2.5 mg, 90%) as a colorless oil: IR (neat, cm^{-1}) 3459, 1724, 1514; ^1H NMR (400 MHz, C_6D_6) δ 9.26 (s, 1 H), 7.84 (d, *J* = 8.6 Hz, 2 H), 7.54−7.50 (m, 1 H), 7.38 (t, *J* = 7.8 Hz, 2 H), 7.27−7.25 (m, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 6.49 (br s, 1 H), 5.78 (d, *J* = 5.5 Hz, 1 H), 4.59−4.54 (m, 2 H), 4.44 (br s, 1 H), 4.22 (s, 1 H), 4.01−3.97 (m, 2 H), 3.79 (s, 3 H), 3.37 (m, 1 H), 2.92 (dd, *J* = 6.0, 17 Hz, 1 H), 2.50 (d, *J* = 5.2 Hz, 1 H), 2.45−2.38 (m, 2 H), 2.25 (br s, 1 H), 1.87 (dd, *J* = 7.6, 13.8 Hz, 1 H), 1.57 (s, 3 H), 1.23 (s, 3 H), 1.00 (s, 3 H), 0.92 (s, 9 H), 0.12 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 209.9, 209.5, 192.3, 164.9, 159.4, 141.7, 140.8, 133.3, 130.0, 129.5, 129.2, 128.5, 113.9, 83.9, 83.8, 71.7, 71.6, 71.5, 55.6, 55.2, 52.1, 43.5, 38.3, 37.4, 31.3, 30.6, 29.6, 27.9, 25.8, 23.2, 18.3, 12.4, −1.9, −4.0; ES HRMS *m/z* $(M + Na)^+$ calcd 727.3272, obsd 727.3286; $[\alpha]^{20}_D$ +36 (*c* 0.46, $CHCl_3$).

Allylic Bromide 12. A solution of **7** (8.5 mg, 0.012 mmol) in dry CH_2Cl_2 (6 mL) was treated with PPh_3 (6.3 mg, 0.024 mmol) and CBr_4 (12 mg, 0.036 mmol) under N_2. The solution was stirred at rt for 20 min, saturated $NaHCO_3$ solution (10 mL) was added, and the reaction mixture was warmed to rt and extracted with EtOAc (2 × 20 mL). The combined organic phases were dried and filtered. Flash chromatography of the residue on silica gel (elution with 12:1 hexane/EtOAc) furnished **12** (8.9 mg, 96%) as a colorless oil: IR (neat, cm^{-1}) 1729, 1699, 1513; ^1H NMR (500 MHz, C_6D_6) δ 8.05 (d, J = 7.3 Hz, 2 H), 7.44 (d, J = 8.6 Hz, 2 H), 7.06−7.04 (m, 1 H), 6.97−6.94 (m, 2 H), 6.84 (d, J = 8.6 Hz, 2 H), 6.23 (d, J = 4.6 Hz, 1 H), 5.54 (br s, 1 H), 4.67 (d, J = 10.4 Hz, 1 H), 4.62 (d, J = 4.3 Hz, 1 H), 4.33 (d, J = 10.5 Hz, 1 H), 4.27 (br s, 1 H), 4.15 (s, 1 H), 4.01 (t, J = 7.5 Hz, 1 H), 3.97 (d, J = 10.5 Hz, 1 H), 3.96 (d, J = 10.4 Hz, 1 H), 3.59−3.51 (m, 1 H), 3.27 (s, 3 H), 2.69 (dd, J = 6.7, 18.7 Hz, 1 H), 2.26 (s, 1 H), 2.06−1.98 (m, 1 H), 1.93−1.92 (m, 2 H), 1.78−1.73 (m, 1 H), 1.69 (s, 3 H), 1.31 (s, 3 H), 0.93 (s, 9 H), 0.76 (s, 3 H), −0.02 (s, 3 H), −0.09 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.3, 210.4, 164.7, 159.4 134.8, 133.4, 132.2, 129.9, 129.7, 129.3, 129.2, 128.7, 113.8, 83.4, 83.1, 73.1, 71.6, 71.5, 57.1, 55.3, 51.8, 42.8, 39.2, 38.7, 37.3, 31.3, 31.0, 27.2, 25.8, 22.8, 18.3, 12.6, −1.9, −4.0; ES HRMS m/z $(M + Na)^+$ calcd 791.2585, obsd 791.2570; $[\alpha]^{20}_D$ +13 (c 0.88, $CHCl_3$).

Epoxidation of 7. To a solution of **7** (4 mg, 5.7 μmol) in CH_2Cl_2 (4 mL) at 0 °C were added $NaHCO_3$ (2.4 mg, 0.029 mmol) and *m*-CPBA (2 mg, 0.011 mmol). The mixture was stirred vigorously at 0 °C for 48 h, quenched with saturated $NaHCO_3$ solution (10 mL), and extracted with EtOAc (2 × 20 mL). The combined organic phases were dried, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (elution with 2:1 hexane/EtOAc) to afford **14** (3.6 mg, 90%) as a colorless oil: IR (neat, cm^{-1}) 1731, 1700, 1514; ^1H NMR (500 MHz, C_6D_6) δ 8.12 (d, J = 7.4 Hz, 2 H), 7.45 (d, J = 8.6 Hz, 2 H), 7.04−7.01 (m, 1 H), 6.95−6.92 (m, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 5.99 (d, J = 1.8 Hz, 1 H), 4.70 (d, J = 10.4 Hz, 1 H), 4.47 (s, 1 H), 4.39−4.36 (dd, J = 5.4, 10.4 Hz, 1 H), 4.14 (d, J = 10.4 Hz, 1 H), 4.11 (s, 1 H), 4.00 (d, J = 12.7 Hz, 1 H), 3.97 (br s, 1 H), 3.57 (s, 1 H), 3.28 (s, 3 H), 3.16−3.08 (m, 2 H), 2.57−2.51 (m, 1 H), 2.51 (d, J = 9 Hz, 1 H), 2.16−2.10 (m, 2 H), 1.76−1.71 (m, 1 H), 1.63 (s, 1 H), 1.47−1.44 (m, 1 H), 1.41 (s, 3 H), 1.31 (s, 3 H), 0.88 (s, 9 H), 0.69 (s, 3 H), 0.00 (s, 3 H), −0.03 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 212.9, 208.5, 164.4, 159.6, 133.0, 130.5, 129.9, 129.8, 129.3, 128.7, 113.8, 88.0, 81.8, 72.7, 72.1, 70.5, 62.7, 59.7, 57.9, 57.6, 54.4, 52.4, 43.2, 41.4, 36.5, 29.8, 29.5, 27.4, 25.8, 20.8, 18.2, 10.0, −2.3, −4.0; ES HRMS m/z $(M + Na)^+$ calcd 745.3378, obsd 745.3328; $[\alpha]^{20}_D$ −12 (c 0.23, $CHCl_3$).

Acetylation of 14. A solution of **14** (6.7 mg, 0.009 mmol) in dry CH_2Cl_2 (5 mL) was treated with Et_3N (13 μL, 0.09 mmol), DMAP (0.1 mg, 0.9 μmol), and Ac_2O (4.3 μL, 0.045 mmol) at rt under N_2, stirred for 1 h, quenched with saturated $NaHCO_3$ solution (10 mL), and extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (elution with 5:1 hexane/EtOAc) to afford **15** (7 mg, 100%) as a colorless oil: IR (neat, cm^{-1}) 3462, 1734, 1514; ^1H NMR (500 MHz, C_6D_6) δ 8.19−8.17 (m, 2 H), 7.44 (d, J = 8.6 Hz, 2 H), 7.08−7.06 (m, 3 H), 6.04 (d, J = 2.2 Hz, 1 H), 4.72 (d, J = 12.6 Hz, 1 H), 4.68 (d, J = 10.5 Hz, 1 H), 4.46 (s, 1 H), 4.35 (dd, J = 5.3, 10.3 Hz, 1 H), 4.23 (d, J = 12.6 Hz, 1 H), 4.21 (s, 1 H), 4.14 (d, J = 10.5 Hz, 1 H), 3.69 (s, 1 H), 3.38−3.29 (m, 1 H), 3.28 (s, 3 H), 2.82 (s, 1 H), 2.61 (dd, J = 8.9, 19 Hz, 1 H), 2.49 (d, J = 9.2 Hz, 1 H), 2.13−2.10 (m, 2 H), 1.76−1.71 (m, 1 H), 1.69 (s, 3 H), 1.54−1.52 (m, 1 H), 1.42 (s, 3 H), 1.41 (s, 3 H), 0.89 (s, 9 H), 0.68 (s, 3 H), 0.00 (s, 3 H), −0.02 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 212.3, 208.3, 169.6, 164.5, 159.6, 133.0, 130.5, 130.0, 129.3, 128.7, 116.4, 113.8, 88.1, 81.9, 72.5, 72.0, 70.2, 65.2, 58.1, 57.7, 56.8, 54.4, 52.3, 43.3, 41.6, 36.5, 29.9, 29.6, 27.5, 25.8, 20.8, 19.9, 18.2, 10.3, −2.4, −4.1; ES HRMS m/z $(M + Na)^+$ calcd 787.3484, obsd 787.3480; $[\alpha]^{20}_D$ +4.4 (c 0.58, $CHCl_3$).

Titanium-Promoted Deoxygenation/Reduction of 14. Activated zinc powder (2.2 mg, 0.035 mmol), $ZnCl_2$ (1.1 mg, 8.3 μmol), and Cp_2TiCl_2 (2.1 mg, 8.3 μmol) were transferred in a flame-dried 10 mL round-bottomed flask equipped with a stirrer bar from a drybox. Dry THF (2 mL) was introduced, and the mixture was stirred at rt under N_2 for 1 h while the color changed from red to green. The green solution was transferred to a solution of **14** (5 mg, 7.0 μmol) in dry THF (1 mL), stirred for another 10 min, and treated with 3% HCl (5 mL). After 10 min, the mixture was extracted with EtOAc (2 × 20 mL); the combined organic extracts were dried, filtered, and concentrated; and the residue was purified by flash chromatography on silica gel (elution with 5:1 hexane/EtOAc) to furnish **16** (1.9 mg, 39%) and **17** (2.1 mg, 43%), both as colorless oils.

For **16**: IR (neat, cm^{-1}) 3470, 1718, 1508; ^1H NMR (500 MHz, C_6D_6) δ 8.09 (m, 2 H), 7.43 (d, J = 8.4 Hz, 2 H), 7.07−6.98 (m, 3 H), 6.83 (d, J = 7.9 Hz, 2 H), 6.03 (d, J = 7.9 Hz, 1 H), 5.22 (s, 1 H), 4.89 (s, 1 H), 4.77−4.75 (m, 1 H), 4.73 (d, J = 9.3 Hz, 1 H), 4.62−4.55 (m, 1 H), 4.37 (s, 1 H), 4.28 (d, J = 8.5 Hz, 1 H), 4.10 (d, J = 10.1 Hz, 1 H), 3.89−3.85 (m, 1 H), 3.26 (s, 3 H), 2.93−2.90 (m, 1 H), 2.57−2.54 (m, 1 H), 2.40−2.30 (m, 1 H), 2.24 (br s, 1 H), 1.98−1.96 (m, 1 H), 1.84−1.83 (m, 1 H), 1.66−1.63 (m, 2 H), 1.55 (s, 3 H), 1.27 (s, 3 H), 0.94 (s, 9 H), 0.73 (s, 3 H), 0.40 (s, 3 H), 0.00 (s, 3 H); ES HRMS m/z $(M + Na)^+$ calcd 729.3435, obsd 729.3387; $[\alpha]^{20}_D$ +16 (c 0.63, $CHCl_3$).

For **17**: IR (neat, cm^{-1}) 3473, 1718, 1702, 1509; ^1H NMR (500 MHz, C_6D_6) δ 8.06−9.01 (m, 2 H), 7.41 (d, J = 8.6 Hz, 2 H), 7.04−7.00 (m, 3 H), 6.81−6.77 (m, 2 H), 5.99 (d, J = 3.5 Hz, 1 H), 4.81 (d, J = 3.9 Hz, 1 H), 4.78−4.75 (m, 1 H), 4.71 (d, J = 10.3 Hz, 1 H), 4.14 (d, J = 10.3 Hz, 1 H), 3.97 (dd, J = 4.1, 10.6 Hz, 1 H), 3.97 (s, 1 H), 3.84 (s, 1 H), 3.56 (dd, J = 2.2, 10.4 Hz, 1 H), 3.45−3.43 (m, 1 H), 3.42 (dd, J = 3.4, 11.7 Hz, 1 H), 3.21 (s, 3 H), 3.12−3.08 (m, 1 H), 2.42−2.38 (m, 1 H), 2.25 (s, 1 H), 1.95−1.90 (m, 2 H), 1.69−1.60 (m, 1 H), 1.43 (s, 3 H), 1.39 (s, 3 H), 1.30−1.10 (m, 3 H), 0.92 (s, 9 H), 0.69 (s, 3 H), 0.03 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.8, 211.4, 165.2, 159.3, 133.2, 129.87, 129.83, 129.6, 113.8, 82.7, 82.5, 74.4, 71.2, 71.1, 67.7, 66.1, 60.4, 55.2, 51.7, 42.7, 39.6, 38.3, 36.9, 32.9, 30.7, 29.6, 27.2, 25.9, 22.1, 18.3, 8.9, −2.5, −4.0; ES HRMS m/z $(M + Na)^+$ calcd 747.3540, obsd 747.3467; $[\alpha]^{20}_D$ +18 (c 0.25, $CHCl_3$).

Improved Preparation of 16. Activated zinc powder (8 mg, 0.12 mmol), $ZnCl_2$ (8 mg, 0.06 mmol), and Cp_2TiCl_2 (15 mg, 0.06 mmol) were transferred in a flame-dried 10-mL round-bottomed flask equipped with a stirrer bar from a drybox. Dry THF (2 mL) was introduced, and the mixture was stirred at rt under N_2 for 1 h while the color changed from red to green. The green solution was transferred to neat **14** (4.5 mg, 0.006 mmol), and the solution was stirred for 10 min prior to treatment with 3% HCl (5 mL). After 10 min, the resulting mixture was extracted with EtOAc (2 × 20 mL); the combined organic extracts were dried, filtered, and concentrated; and the residue was purified by flash chromatography on silica gel (elution with 5:1 hexane/EtOAc) to provide **16** (3 mg, 72%) as the only product.

Mesylation of 16 with Allylic Reagent. To a solution of **16** (2.0 mg, 2.8 μmol) in dry CH_2Cl_2 (3 mL) were added Et_3N (7.8 μL, 0.056 mmol), DMAP (6.8 mg, 0.056 mmol), and methanesulfonyl chloride (2.2 μL, 0.028 mmol) at rt under N_2. The reaction mixture was stirred for 1 h, diluted with saturated $NaHCO_3$ solution (10 mL), stirred for 10 min, and extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (elution with 5:1 hexane/EtOAc) to give **18** (2.1 mg, 100%) as a colorless oil: IR (neat, cm^{-1}) 3482, 1724, 1699, 1514; ^1H NMR (500 MHz, C_6D_6) δ 8.11−8.09 (m, 2 H), 7.46 (d, J = 8.6 Hz, 2 H), 7.08−7.00 (m, 3 H), 6.85 (d, J = 8.6 Hz, 2 H), 6.22 (d, J = 4.7 Hz, 1

H), 5.66 (d, J = 6.7 Hz, 1 H), 4.74 (d, J = 12.1 Hz, 1 H), 4.69−4.65 (m, 2 H), 4.59 (d, J = 4.2 Hz, 1 H), 4.20 (s, 1 H), 4.11 (s, 1 H), 4.07 (dd, J = 5.4, 10.0 Hz, 1 H), 4.01 (d, J = 10.3 Hz, 1 H), 3.28 (s, 3 H), 3.27 (m, 1 H), 2.62 (dd, J = 6.6, 18.6 Hz, 1 H) 2.39 (s, 3 H), 2.26−2.25 (m, 1 H), 2.07−1.91 (m, 3 H), 1.80−1.79 (m, 1 H), 1.66 (s, 3 H), 1.30 (s, 3 H), 0.93 (s, 9 H), 0.75 (s, 3 H), 0.07 (s, 3 H), −1.84 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.8, 210.2, 164.6, 159.4, 133.5, 131.5, 130.6, 129.8, 129.6, 129.3, 128.8, 113.9, 83.4, 83.2, 73.4, 73.1, 71.7, 71.2, 57.4, 55.2, 51.8, 42.7, 40.4, 38.2, 37.9, 31.4, 30.9, 27.4, 25.8, 22.7, 18.3, 11.8, −1.9, −4.0; ES HRMS m/z $(M + Na)^+$ calcd 807.3210, obsd 807.3198; $[\alpha]^{20}_D$ +7.3 (c 0.66, $CHCl_3$).

Osmate Ester 19. To a solution of **16** (8.3 mg, 0.012 mmol) in THF (2 mL) and pyridine (1 mL) was added neat OsO_4 (3.3 mg, 0.013 mmol) at 0 °C. The reaction mixture was stirred for 20 min, treated with saturated sodium hydrosulfite solution (5 mL), and stirred for 3 h. Following extraction with EtOAc (2 × 10 mL), the combined organic phases were dried, filtered, and concentrated. Flash chromatography of the residue on silica gel (elution with EtOAc) afforded **19** (4.7 mg, 83% at 65% conversion) as a pale brown oil along with 2.9 mg (35%) of recovered **16**.

For **19**: IR (neat, cm^{-1}) 3451, 1718, 1512; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42−8.40 (m, 2 H), 7.36−7.29 (m, 5 H) 6.86−6.84 (m, 2 H), 5.73 (d, J = 2.7 Hz, 1 H), 4.95−4.92 (m, 1 H), 4.92 (s, 1 H), 4.78 (dd, J = 4.8, 11.8 Hz, 1 H), 4.57 (br s, 1 H), 4.50 (d, J = 10.7 Hz, 1 H), 4.19 (d, J = 2.7 Hz, 1 H), 4.10 (d, J = 8.4 Hz, 1 H), 4.02 (s, 1 H), 3.98 (d, J = 7.4 Hz, 1 H), 3.78 (s, 3 H), 3.53−3.48 (m, 1 H), 2.52 (s, 1 H), 2.37−2.30 (m, 5 H), 2.03−1.91 (m, 2 H), 1.34 (s, 3 H), 1.10 (s, 3 H), 0.85 (s, 3 H), 0.82 (s, 9 H), 0.07 (s, 3 H), 0.00 (s, 3 H); $[\alpha]^{20}_D$ −89 (c 0.24, $CHCl_3$).

Osmium Tetraoxide Oxidation of 16. To a solution of **16** (2 mg, 2.8 μmol) in THF (2 mL) and DABCO (0.6 mg, 5.6 μmol) was added neat OsO_4 (0.7 mg, 2.8 μmol) at rt. As the reaction mixture turned to bright red, it was stirred for 24 h, treated with sodium dithionite (4.9 mg, 0.028 mmol) in water (2 mL), stirred 3 h longer, and extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (elution with 1:1 hexane/EtOAc) to give **20** (1.8 mg, 75%) as a colorless oil: IR (neat, cm^{-1}) 3470, 1719, 1706, 1514; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 7.2 Hz, 2 H), 7.54−7.52 (m, 1 H), 7.44−7.40 (m, 2 H), 7.26 (d, J = 8.5 Hz, 2 H), 6.81 (d, J = 8.5 Hz, 2 H), 5.71 (d, J = 5.8 Hz, 1 H), 4.79 (d, J = 4.0 Hz, 1 H), 4.55 (dd, J = 4.3, 11.6 Hz, 1 H), 4.43 (d, J = 10.5 Hz, 1 H), 4.06 (d, J = 10.6 Hz, 1 H), 3.99 (s, 1 H), 3.87 (br s, 1 H), 3.82 (d, J = 5.8 Hz, 1 H), 3.74 (s, 3 H), 3.56 (d, J = 10.2 Hz, 1 H), 3.43−3.41 (m, 1 H), 3.36 (s, 1 H), 3.16−3.06 (m, 1 H), 2.77 (s, 1 H), 2.77−2.72 (m, 1 H), 2.36−2.26 (m, 2 H), 2.18−2.16 (m, 1 H), 1.94−1.93 (m, 1 H), 1.88−1.80 (m, 1 H), 1.80−1.70 (m, 1 H), 1.30 (s, 3 H), 1.03 (s, 3 H), 0.87 (s, 3 H), 0.78 (s, 9 H), 0.01 (s, 3 H), −0.06 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.3, 208.9, 165.2, 159.4, 152.8, 133.8, 129.8, 129.5, 128.98, 128.9, 113.8, 84.2, 81.6, 75.2, 74.0, 73.5, 71.5, 67.2, 62.9, 58.7, 55.2, 51.3, 42.1, 38.9, 38.0, 32.9, 31.0, 29.6, 25.7, 22.7, 18.2, 10.0, −2.1, −4.2; ES HRMS m/z $(M + Na)^+$ calcd 763.3490, obsd 763.3432; $[\alpha]^{20}_D$ +5.2 (c 0.56, $CHCl_3$).

Ruthenium Tetraoxide-Promoted Oxidation of 16. A solution of **16** (5 mg, 7.0 μmol) in 1:1 acetonitrile/EtOAc (2 mL) cooled to 0 °C was treated via cannula with a solution of ruthenium trichloride (0.1 m, 0.49 μmol) and sodium periodate (1.5 mg, 7.0 μmol) in water (0.5 mL). The reaction mixture was stirred at 0 °C for 2 min, treated with a saturated solution of sodium dithionite (5 mL), and extracted with EtOAc (2 × 5 mL). The combined organic phases were processed as described above to give 2.5 mg (40%) of **20** and 2.7 mg (47%) of **21**.

For **21**: colorless oil; IR (neat, cm^{-1}) 3446, 1717, 1515; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.61 (s, 1 H), 8.06−8.04 (m, 2 H), 7.63−7.60 (m, 1 H), 7.52−7.49 (m, 2 H), 7.294−7.290 (m, 2 H), 6.95−6.93 (m, 2 H), 4.82 (d, J = 10.6 Hz, 1 H), 4.19 (d, J = 2.5 Hz, 1 H), 4.07 (s, 1 H), 3.86 (s, 3 H), 3.43 (s, 1 H), 3.34−3.27 (m, 1 H), 2.44−2.40 (m, 2 H), 2.38−2.29 (m, 2 H), 2.21−2.05 (m, 1 H), 1.94−1.89 (m, 1 H), 1.81−1.79 (m, 1 H), 1.58 (s, 3 H), 1.51 (s, 3 H), 0.97 (s, 3 H), 0.83 (s, 9 H), −0.04 (s, 3 H), −0.18 (s, 3 H); ES HRMS m/z $(M + Na)^+$ calcd 761.3333, obsd 761.3340; $[\alpha]^{20}_D$ −53 (c 0.16, $CHCl_3$).

Ring Cleavage of 16 with Osmium Tetraoxide. To a solution of **16** (2 mg, 2.8 μmol) in acetone (1 mL) and H_2O (0.2 mL) was added neat OsO_4 (0.8 mg, 3.1 μmol). The solution was stirred at rt for 5 h, sodium dithionite solution (5 mL) was introduced, and after 3 h the resulting mixture was extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried, filtered, and concentrated. The residue was subjected to flash chromatography on silica gel (elution with 1:1 hexane/EtOAc) to furnish **21** (1.5 mg, 71%) as a colorless oil identical to the material isolated above.

Monosilylation of 20. To a solution of **20** (2.0 mg, 2.7 μmol) in CH_2Cl_2 (2 mL) were added 2,6-lutidine (9.4 μL, 0.081 mmol) and TMSCl (3.4 μL, 0.027 mmol) sequentially at −78 °C under N_2. The reaction mixture was stirred at this temperature for 20 min, saturated $NaHCO_3$ solution (5 mL) was introduced, and stirring was maintained for 10 min prior to extraction with EtOAc (2 × 10 mL). The combined organic extracts were dried, filtered, and concentrated. Flash chromatography of the residue on silica gel (elution with 10:1 hexane/EtOAc) afforded **22** (2.2 mg, 100%) as a colorless oil: IR (neat, cm^{-1}) 3452, 1723, 1252; ^{1}H NMR (400 MHz, C_6D_6) δ 8.39−8.19 (m, 2 H), 7.45 (d, J = 8.6 Hz, 2 H), 6.99−6.96 (m, 3 H), 6.79 (d, J = 13.7 Hz, 2 H), 6.15−6.13 (m, 1 H), 5.05 (d, J = 3.9 Hz, 1 H), 4.85 (dd, J = 5.0, 11.6 Hz, 1 H), 4.70 (d, J = 10.1 Hz, 1 H), 4.32 (s, 1 H), 4.24 (d, J = 10.1 Hz, 1 H), 4.11 (d, J = 5.2 Hz, 1 H), 3.88 (d, J = 10.2 Hz, 1 H), 3.72 (s, 1 H), 3.69 (s, 1 H), 3.37 (d, J = 10.3 Hz, 1 H), 3.26 (s, 3 H), 2.84 (br s, 1 H), 2.56 (dd, J = 6.8, 19 Hz, 1 H), 2.31 (br s, 1 H), 2.28−2.25 (m, 1 H), 2.16−2.03 (m, 2 H), 1.84−1.78 (m, 2 H), 1.67 (s, 3 H), 1.31 (s, 3 H), 0.92 (s, 9 H), 0.76 (s, 3 H), 0.01 (s, 3 H), 0.00 (s, 3 H), −0.34 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 210.8, 208.3, 177.6, 165.5, 159.6, 132.8, 130.2, 130.1, 129.8, 128.4, 113.7, 84.2, 82.9, 74.2, 73.9, 71.1, 67.6, 62.9, 59.0, 54.4, 51.4, 42.3, 38.9, 37.7, 33.2, 30.8, 28.2, 25.7, 22.6, 18.2, 10.1, −1.7, −2.3, −4.6; ES HRMS m/z $(M + Na)^+$ calcd 835.3885, obsd 835.3837; $[\alpha]^{20}_D$ +3.1 (c 0.37, $CHCl_3$).

Desilylative Mesylation of 22. To a solution of **22** (2 mg, 2.0 μmol) in pyridine (2 mL) was added MsCl (2 μL, 0.02 mmol) at 0 °C. The solution was warmed to rt, stirred for 24 h, and quenched with $NaHCO_3$ solution (5 mL). The resulting mixture was extracted with EtOAc (2 × 10 mL), and the combined organic extracts were dried, filtered, and concentrated. Flash chromatography of the residue on silica gel (elution with 1:1 hexane/EtOAc) afforded **23** (2 mg, 100%) as a colorless oil: ^{1}H NMR (500 MHz, C_6D_6) δ 8.18 (d, J = 7.2 Hz, 2 H), 7.42 (d, J = 8.6 Hz, 2 H), 7.04−6.96 (m, 3 H), 6.82 (d, J = 8.6 Hz, 2 H), 6.10 (d, J = 5 Hz, 1 H), 4.64 (d, J = 10 Hz, 1 H), 4.73 (dd, J = 5.1, 11.5 Hz, 1 H), 4.64 (d, J = 10 Hz, 1 H), 4.53 (d, J = 12 Hz, 1 H), 4.29 (d, J = 12 Hz, 1 H), 4.25 (s, 1 H), 4.18 (d, J = 10 Hz, 1 H), 4.12 (d, J = 4.8 Hz, 1 H), 4.09 (br s, 1 H), 3.30 (s, 1 H), 3.26 (s, 3 H), 3.26−3.25 (m, 1 H), 2.55 (dd, J = 7.1, 18 Hz, 1 H), 2.41 (br s, 2 H), 2.27−2.13 (m, 2 H), 2.12−2.08 (m, 2 H), 1.75 (s, 3 H), 1.74−1.73 (m, 1 H), 1.58 (s, 3 H), 1.27 (s, 3 H), 0.91 (s, 9 H), 0.72 (s, 3 H), −0.037 (s, 3 H), −0.039 (s, 3 H); ES HRMS m/z $(M + Na)^+$ calcd 841.3265, obsd 841.3295.

Silyl-Protected Mesylate 24. To a solution of **22** (2 mg, 0.002 mmol) in CH_2Cl_2 (20 mL) were added DMAP (48 mg, 0.4 mmol) and methanesulfonyl chloride (2 μL, 0.02 mmol) sequentially at 0 °C. The reaction mixture was warmed to rt, stirred for 24 h, and quenched with saturated $NaHCO_3$ solution (5 mL). The product was extracted into EtOAc (2 × 10 mL), the combined organic extracts were dried, filtered, and concentrated, and the residue was flash chromatographed (elution with 5:1 hexane/EtOAc) to afford **24** (1.9 mg, 90%) as a colorless oil: IR (neat, cm^{-1}) 3461, 1724, 1513; ^{1}H NMR (500 MHz, C_6D_6) δ 8.11 (d, J = 7.2 Hz, 2 H), 7.50 (d, J = 8.6 Hz, 2 H), 7.05−7.02 (m, 1 H), 6.98−6.95 (m, 2 H), 6.90 (d, J = 8.6 Hz, 2 H), 6.15−6.13 (m, 1 H), 5.11 (d, J = 3.6 Hz, 1 H), 5.06

(d, J = 3.6 Hz, 1 H), 4.89 (dd, J = 5.1, 11.6 Hz, 1 H), 4.77 (d, J = 10.3 Hz, 1 H), 4.40 (d, J = 10.3 Hz, 1 H), 4.26 (s, 1 H), 4.08 (d, J = 5 Hz, 1 H), 3.87 (d, J = 11.1 Hz, 1 H), 3.67 (d, J = 11.1 Hz, 1 H), 3.51−3.47 (m, 1 H), 3.36 (s, 1 H), 3.29 (s, 3 H), 2.68−2.61 (m, 2 H), 2.53 (s, 3 H), 2.36 (br s, 1 H), 2.12−2.04 (m, 2 H), 2.02−1.90 (m, 1 H), 1.73 (s, 3 H), 1.30 (s, 3 H), 0.89 (s, 9 H), 0.74 (s, 3 H), 0.08 (s, 3 H), −0.02 (s, 3 H), −0.32 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 211.4, 207.3, 165.0, 159.7, 145.7, 145.2, 133.2, 130.1, 130.0, 128.7, 114.0, 83.9, 83.4, 82.8, 74.7, 73.9, 71.5, 67.5, 64.3, 58.8, 54.4, 51.6, 45.1, 43.2, 37.3, 34.0, 29.8, 29.5, 28.0, 25.6, 22.4, 18.1, 10.6, −1.3, −2.8, −4.8; ES HRMS m/z $(M + Na)^+$ calcd 913.3660, obsd 913.3643; $[\alpha]^{20}_D$ +32 (c 0.33, $CHCl_3$).

Desilylation of 24. A solution of **24** (1 mg, 0.001 mmol) in CH_2Cl_2 (1 mL) was treated with CSA (0.5 mg, 0.002 mmol) at rt, stirred for 2 h, and quenched with saturated $NaHCO_3$ solution (3 mL) prior to extraction with EtOAc (2 × 10 mL). The combined organic extracts were dried, filtered, and evaporated. The residue was subjected to flash chromatography on silica gel (elution with 2:1 hexane/EtOAc) to give **25** (0.9 mg, 95−100%) as a colorless oil: IR (neat, cm^{-1}) 3456, 1706, 1359, 1260; ^{1}H NMR (500 MHz, C_6D_6) δ 8.14 (d, J = 7.3 Hz, 2 H), 7.48 (d, J = 8.6 Hz, 2 H), 7.08−7.05 (m, 1 H), 7.03−7.00 (m, 2 H), 6.88 (d, J = 8.6 Hz, 2 H), 6.08 (d, J = 5.1 Hz, 1 H), 5.05 (d, J = 3.4 Hz, 1 H), 4.80 (dd, J = 4.9, 11.5 Hz, 1 H), 4.75−4.73 (m, 2 H), 4.36 (d, J = 10.2 Hz, 1 H), 4.26 (s, 1 H), 4.20 (s, 1 H), 3.96 (d, J = 5 Hz, 1 H), 3.48 (d, J = 11.8 Hz, 1 H), 3.46−3.42 (m, 1 H), 3.29 (s, 3 H), 3.23 (s, 1 H), 3.07 (d, J = 11.4 Hz, 1 H), 3.07 (d, J = 11.4 Hz, 1 H), 2.59 (dd, J = 6.6, 18 Hz, 1 H), 2.51−2.49 (m, 1 H), 2.47 (s, 3 H), 2.33 (br s, 1 H), 2.05−2.00 (m, 1 H), 1.92−1.87 (m, 1 H), 1.76−1.63 (m, 1 H), 1.55 (s, 3 H), 1.27 (s, 3 H), 0.90 (s, 9 H), 0.70 (s, 3 H), 0.06 (s, 3 H), −0.01 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 214.3, 210.2, 167.6, 162.5, 136.0, 132.8, 132.7, 132.5, 131.5, 116.7, 86.5, 86.1, 85.2, 77.5, 76.8, 74.3, 70.3, 66.2, 61.5, 57.2, 54.4, 45.0, 43.0, 40.0, 39.9, 36.6, 33.4, 30.6, 28.4, 25.1, 20.9, 13.3, 0.00, −2.0; ES HRMS m/z $(M+Na)^+$ calcd 841.3265, obsd 841.3238; $[\alpha]^{20}_D$ +7 (c 0.25, $CHCl_3$).

Oxetane 28. To a solution of **25** (2.5 mg, 0.003 mmol) in dry benzene (5 mL) was added Al(O-t-Bu)$_3$ (3.7 mg, 0.015 mmol) at rt under N_2. The reaction mixture was stirred for 10 h, treated with 3% HCl (5 mL), and extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried, filtered, and evaporated. The residue was purified by flash chromatography on silica gel (elution with 3:1 hexane/EtOAc) to afford **28** (1.2 mg, 54%) as a colorless oil: IR (neat, cm^{-1}) 3464, 1724, 1514; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 7.4 Hz, 2 H), 7.55−7.44 (m, 1 H), 7.42−7.40 (m, 2 H), 7.37 (d, J = 8.6 Hz, 2 H), 6.96 (d, J = 8.6 Hz, 2 H), 5.88−5.81 (m, 1 H), 4.81 (d, J = 6.5 Hz, 1 H), 4.73 (d, J = 10.9 Hz, 1 H), 4.63 (dd, J = 4.9, 10.9 Hz, 1 H), 4.32 (s, 1 H), 4.26 (d, J = 10.9 Hz, 1 H), 4.09−4.06 (m, 1 H), 3.88 (s, 3 H), 3.86−3.83 (m, 1 H), 3.70−3.65 (m, 1 H), 3.50−3.47 (m, 1 H), 2.91−2.90 (m, 1 H), 2.81−2.78 (m, 2 H), 2.38−2.32 (m, 2 H), 2.30−2.27 (m, 1 H), 2.20−2.03 (m, 1 H), 1.90−1.83 (m, 1 H), 1.40 (s, 3 H), 1.11 (s, 3 H), 0.96 (s, 3 H), 0.93 (s, 9 H), 0.15 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (150 MHz, C_6D_6) δ 208.5, 206.6, 159.9, 133.4, 132.5, 131.0, 130.2, 129.9, 129.7, 129.3, 114.0, 79.5, 71.7, 71.0, 60.9, 54.6, 51.0, 42.6, 40.4, 40.0, 37.8, 37.0, 34.1, 29.6, 29.2, 25.8, 22.9, 18.3, 14.1, 10.2, −2.0, −4.2; ES HRMS m/z $(M + Na)^+$ calcd 745.3384, obsd 745.3381; $[\alpha]^{20}_D$ +36 (c 0.17, $CHCl_3$).

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Supporting Information Available: Copies of the high field ^{1}H NMR spectra of all compounds reported herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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