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A Delicate Balance of Energetics. Subtleties Associated with α-Ketol-Based Bridge Migration To Afford 9-Keto-10*β*-*p*-methoxybenzyloxytaxanes

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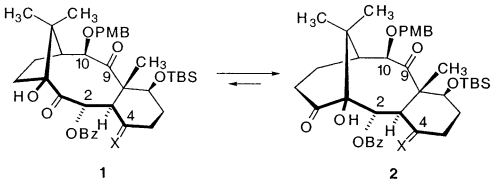
The feasibility of the title reaction has been pursued for the purpose of advancing a concise total synthesis of Taxol. Of the two closely related series examined, the first featured an *exo*-methylene group at C4. The second consisted of an α-epoxide at that site. Strikingly, the olefinic construct proved inert to attempted α-ketol rearrangement. In contrast, the oxiranyl derivative isomerized smoothly. The reaction sequence associated with arrival at taxane **18** is short (15 steps from a D-camphor derivative) and notably efficient. The thermodynamic issues that are raised by this investigation have been clarified by an assessment of molecular mechanics-derived (MM3) steric energy calculations.

As noted in the preceding paper,[1] a central challenge in a total synthesis of Taxol based on D-camphor as the starting material is that of gaining proper control in the operation of a necessary α-ketol rearrangement.[2] The potential complications can be concisely summarized in the response of 9,10-acetal derivatives to the action of aluminum alkoxides. When this functionality is transfused, steric strain considerations preclude operation of the key 1,2-carbon shift, in line with molecular mechanics (MM3) calculations. Comparable scrutiny of a representative cis acetal revealed that the α-ketol rearrangement is now so facile that prior oxygenation at C2 is not feasible. Three potential modifications have more recently been entertained by us to confront the issue of framework equilibration in the proper direction, viz. **1** → **2**. First, the acetal protecting group across C9 and C10 should be supplanted with a noncyclic equivalent such as that illustrated. The avoidance of a heterocyclic ring in this locale was expected to make available added conformational mobility that could be used to advantage. As well, the α-ketol rearrangement should be attempted only after the C2 hydroxyl had been transformed into a benzoate group (as is already present in taxol). On the basis of precedent,[1,3] it seemed unlikely that bridge migration would be deterred under these circumstances. Beyond that, retroaldol fragmentation of ring B would be precluded if the targeted pathway was slowed kinetically.[1] Finally, the opportunity to modify the chemical nature of X was viewed to be a useful adjunct in view of the striking electronic transmission effects we have observed in compounds having generic formulas reflected by **1** and **2**.[4] As matters have turned out, it is precisely the subtle characteristic associated with chemical manipulations at C4 that exert the greatest control on unilateral progression in the direction of the taxanes.



Results and Discussion

The Consequences of C4 *exo*-Methylene Substitution. One available option was to arrive at our objectives by placement of an *exo*-methylene group at C4 in an otherwise suitably functionalized isotaxane, with the ultimate goal of utilizing this unsaturated center to craft the oxetane ring. This retrosynthetic consideration led us back to the conveniently available dihydroxy ketone **3**.[1,5] A primary concern was that **3** would be notably prone to transannular hemiketal formation. Such proved not to be the case, thereby permitting Swern oxidation to be entirely workable (Scheme 1). We expected that the base-promoted enolization of **4** would proceed regioselectively along the leading edge[6] and provide a suitable means for activating C2. Indeed, the deprotonation of this diketone with potassium hexamethyldisilazide and ensuing oxidation with the Davis sulfonyloxaziridine[7] afforded **5** in 98%

(1) Paquette, L. A.; Hofferberth, J. E. *J. Org. Chem*. **2003**, *68*, 2266.
(2) Paquette, L. A.; Hofferberth, J. E. *Org. React.*, in press.
(3) Zeng, Q.; Bailey, S.; Wang, T. Z.; Paquette, L. A. *J. Org. Chem*. **1998**, *63*, 137.
(4) Paquette, L. A.; Zhao, M.; Montgomery, F.; Zeng, Q.; Wang, T. Z.; Elmore, S.; Combrink, K.; Wang, H.-L.; Bailey, S.; Su, Z. *Pure Appl. Chem*. **1998**, *70*, 1449.
(5) Hofferberth, J. E.; Lo, H. Y.; Paquette, L. A. *Org. Lett*. **2001**, *3*, 1777.
(6) Paquette, L. A.; O'Neil, S. V.; Guillo, N.; Zeng, Q.; Young, D. G. *Synlett* **1999**, 1857.
(7) (a) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703. (b) Davis, F. A.; Chen, B.-C. *Chem. Rev*. **1992**, *92*, 919.

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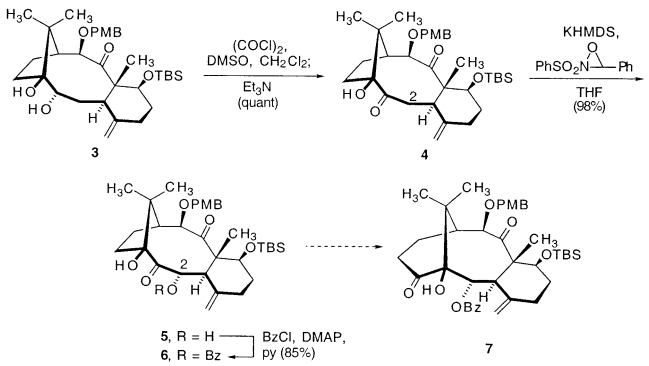
SCHEME 1



yield. No attempt was made to promote the base-catalyzed rearrangement of **4** as this process does not advance the synthesis.

Attempts to bring about the α-ketol rearrangement of **5** led as anticipated to a complex mixture of products. The need for suitable protection of the C2 hydroxyl was thereby again implicated.[1] Conversion to monobenzoate **6** occurred smoothly with benzoyl chloride and pyridine in the presence of DMAP. The spectral characterization of **6** was initially hampered by the fact that this compound exists as a mixture of atropisomers at room temperature. Variable-temperature ^{1}H NMR studies removed all ambiguities and confirmed that esterification had occurred uniquely at C2. Quite unexpectedly, exposure of **6** to a significant number of potential promoters did not result in isomerization to the taxane system **7**. After the expenditure of considerable effort at this point, it was made clear that an alternative thrust had to be implemented.

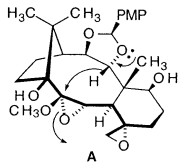
Exploration of an Alternative C2-Hydroxylation Protocol. Undertaken concurrently with the preceding investigation was a plan to bring about the oxidation of C2 by prior generation of an enol ether. This tactic, which envisioned isomerization of the derived oxirane, was considered likely to involve concurrent epoxidation of the exo-methylene group that resides on the periphery of ring C. The introduction of an additional oxygen in this manner could serve to expedite ultimate generation of the oxetane ring.

The early aspects of this phase of investigation involved the known ketone **8**.[1] The synthesis of **10** began with the highly regioselective *O*-methylation of **8**. Thus, treatment with 2 equiv of potassium *tert*-butoxide in DMF at 0 °C followed by dimethyl sulfate[8] afforded enantiomerically pure **9** in 58% yield (Scheme 2).

Exposure of **9** in turn to dimethyl dioxirane at 0 °C[9] gave rise to **12**, thereby demonstrating that initial reaction with this oxidant proceeds via attack at the exocyclic π-bond. When attempts were made to force this reaction by allowing it to proceed at room temperature, oxidative cleavage of the PMP acetal occurred with formation of benzoate ester **11**.

Under buffered *m*-CPBA conditions, the surprisingly recalcitrant methyl enol ether functionality was seen to experience epoxidation. The resulting product **10** proved to be not only a robust compound but spectacularly crystalline as well. Single-crystal X-ray diffraction measurements conducted on **10** unequivocally corroborated the fact that both oxiranes had formed on the α-surface in line with steric approach control involving the lowest energy conformer.

Considerable effort was expended for the purpose of uncovering ways to effect bridge migration within **10**. Such reagents as aluminum tri-*tert*-butoxide, zinc chloride, and potassium *tert*-butoxide had no effect. In contrast, boron trifluoride etherate, camphorsulfonic acid, diethylaluminum chloride, pyridinium *p*-toluenesulfonate, and triethylsilyl triflate uniformly transformed **10** into **13** in quantitative yield. The structure of **13** was confirmed crystallographically. As shown in **A**, this transformation can be economically rationalized in terms of an acetal oxygen-assisted transannular hydride shift from C9 to C1 with configurational inversion during the ring opening.



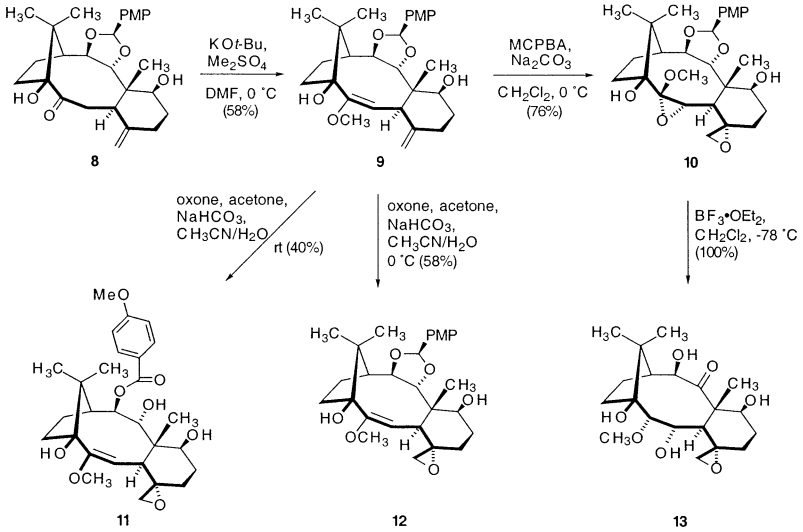
Realization of an α-Ketol Rearrangement. In the spirit of our routing paradigm, **4** was transformed into the benzyl enol ether **14** in order to probe its utility. In the ensuing treatment of **14** with an excess of MCPBA, we discovered that the single diepoxide **15** could be generated with essentially the same stereocontrol and efficiency as in the *O*-methyl series (Scheme 3). The important distinction between **10** and **15** is the inherent stability of the latter toward transannular migrations. The absence of a hydrogen at C9 is, of course, responsible for the inoperability of this otherwise troublesome process.

To pave the way for construction of a taxane derivative, **15** was admixed with a catalytic quantity of camphorsulfonic acid in CH_2Cl_2 at room temperature. Opening of the oxirane ring with loss of the benzyl group materialize readily and the α,α′-dihydroxy ketone array contained in **16** was established in 95% yield. With this chemistry worked out, the time had arrived to bring about benzoylation at C2 and the all-important bridge migration. The implementation of both steps took place uneventfully and a path to taxane **18** was made clear. It may well be possible to transform **6** into **18**. This pathway was not examined because of the limiting scale of the α-hydroxylation step (**4** → **5**), an undesirable feature not associated with the epoxidation of enol ether **14**.

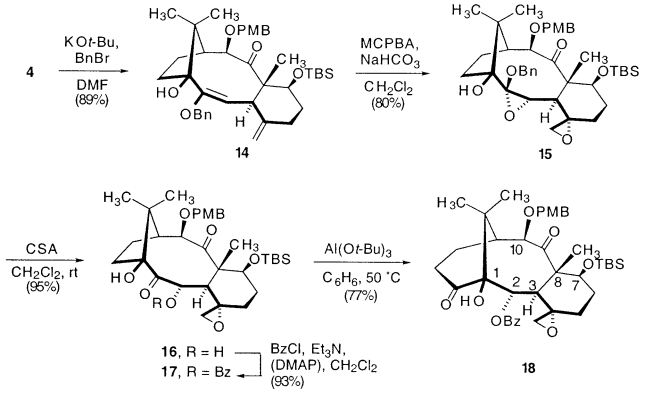
Steric Strain Considerations. While **6** was recalcitrant to equilibration with its isomeric taxane counterpart **7**, the structurally related epoxide **17** proved notably amenable to conversion to **18**. To the extent that MM3 calculations dealing with these polycyclic systems can be relied upon to provide guidance regarding relative thermodynamic stabilities, the contrasting energetic preference profiles must necessarily be viewed with special interest. For the *exo*-methylene triads **6**, **7**, and **19** (Scheme 4), the data infer that placement of an exocyclic double bond at C4 causes the undesired isomer **19** to be

(8) Paquette, L. A. Broadhurst, M. J. *J. Org. Chem*. **1973**, *38*, 1886.
(9) Troisi, L.; Cassidei, L.; Lopez, L.; Curci, R. *Tetrahedron Lett*. **1989**, *30*, 257.

SCHEME 2



SCHEME 3



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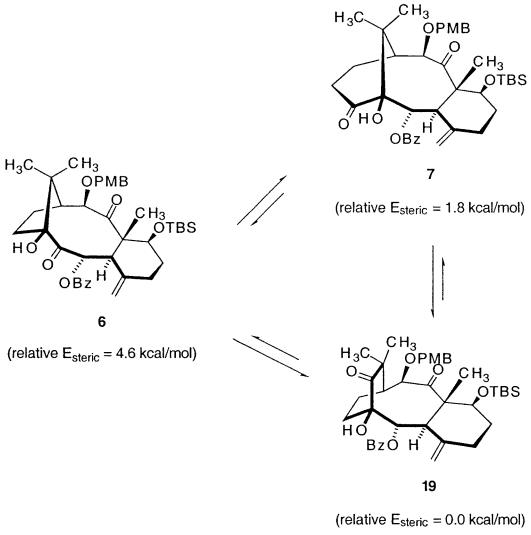
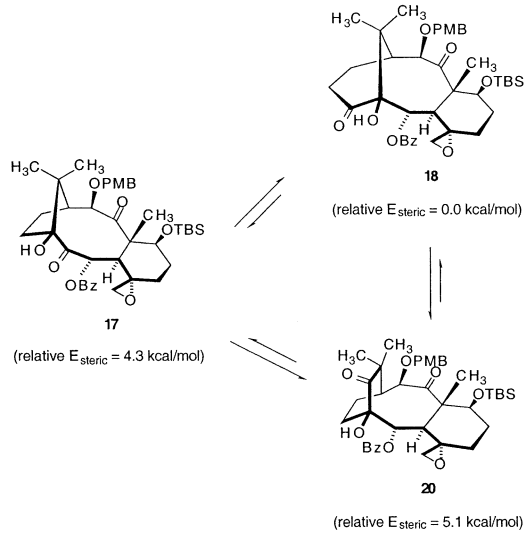


the global energy minimum. The positioning of an sp^2-hybridized carbon at C4 is seen to cause both **7** and **19** to be less strained than **6**, the more so for **19**. Since we saw no hint indicating that the **6** → **7** isomerization was operative, the prevailing thermodynamic imbalance could reflect a somewhat greater relative E_s value for **7**, though not in excess of that realized for **19**.

SCHEME 5



Simple modulation of the hybridization of C4 from trigonal to that offered by an oxiranyl carbon switches the relative ordering of **18** and **20** (Scheme 5). Thus, the minimally strained conformer in this subgroup is computed to be the taxane derivative. The thermodynamic favoring of **18** is reflected in the fact that it is indeed the heavily dominant α-ketol under equilibrating conditions. A logical outgrowth of these findings is the promise that MM3-derived steric strain values offer a reasonable level of suggestive insight to warrant their acquisition prior to embarking on a synthetic undertaking based on preparative-scale equilibration.

Conclusions. Presented herein is a unified synthetic approach to a highly functionalized taxane system that is well poised for A-ring functionalization and introduction of the oxetane D-ring. The successful strategy exploited and extended our early investigations of the α-ketol rearrangement in bridgehead contexts. The dramatic interrelationship between the presence of a double bond or an oxirane ring at C4 and the inherent capacity for 1,2-shifting was not expected to be so sharply demarcated. Notably, the isomerization that leads to **18** pro-

vides important insight into our capacity to carry many chiral centers and oxygenated appendages directly correlatable to the taxol substitution pattern and stereochemistry through a key framework isomerization step. The further development of our targeted objectives will be the subject of future reports.

Experimental Section

Swern Oxidation of 3. To a solution of oxalyl chloride (69 μL, 0.79 mmol) in CH_2Cl_2 (2.5 mL) cooled to −78 °C was added a solution of DMSO (112 μL, 1.6 mmol) in CH_2Cl_2 (2.5 mL). The resulting solution was stirred for 20 min, treated with a solution of **3** (45 mg, 0.079 mmol) in CH_2Cl_2 (2.5 mL) via cannula, stirred for 1 h at −78 °C, and slowly warmed to −50 °C over 30 min. After 3 h at this temperature, the solution was returned to −78 °C, and freshly distilled Et_3N (330 μL, 2.4 mmol) was added prior to warming to rt over 1 h, quenching with water, and extraction with dichloromethane (3 × 40 mL). The combined organic layers were dried, filtered, and freed of solvent. The yellow residue was chromatographed over silica gel (elution with 9% EtOAc in hexanes) to give **4** as a white solid (45 mg, quant): mp 150−151 °C; IR (neat, cm^{-1}) 3488, 1705, 1680, 1609; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.1 Hz, 2 H), 6.83 (d, *J* = 8.1 Hz, 2 H), 4.99 (s, 1 H), 4.68 (s, 1 H), 4.62 (dd, *J* = 11.4, 4.1 Hz, 1 H), 4.58 (d, *J* = 2.5 Hz, 1 H), 4.33 (d, *J* = 10.8 Hz, 1 H), 4.15 (d, *J* = 10.8 Hz, 1 H), 3.78 (s, 3 H), 3.30 (d, *J* = 10.2 Hz, 1 H), 3.09 (s, 1 H), 2.88 (dd, *J* = 15, 2.5 Hz, 1 H), 2.78 (d, *J* = 12 Hz, 1 H), 2.63−2.60 (m, 2 H), 2.49 (d, *J* = 13 Hz, 1 H), 2.24−2.09 (m, 5 H), 1.66−1.65 (m, 1 H), 1.13 (s, 3 H), 1.06 (s, 3 H), 1.01 (s, 3 H), 0.85 (s, 9 H), 0.07 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.9, 210.9, 158.7, 144.2, 130.8, 128.4, 113.4, 100.1, 87.4, 85.2, 76.9, 71.4, 59.6, 55.1, 54.2, 49.6, 43.9, 37.0, 34.0, 31.9, 31.5, 30.1, 26.3, 25.6, 18.6, 18.5, 9.14, −2.32, −2.50; ES HRMS *m*/*z* $(M + Na)^+$ calcd 593.3274, obsd 593.3269; [α] −25.8 (*c* 0.08, $CHCl_3$).

α-Oxygenation of 4. To a solution of **4** (43 mg, 0.075 mmol) in THF (30 mL) at −78 °C were added a solution of KHMDS (0.45 M in toluene, 840 μL, 0.38 mmol) and Davis' oxaziridine (98 mg, 0.38 mmol). The reaction mixture was slowly warmed to 10 °C over 2 h, quenched with saturated NH_4Cl solution, and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with 1 N HCl, and dried, filtered, and evaporated. The residue was chromatographed over silica gel (elution with 8% EtOAc in hexanes) to give **5** as a clear oil (43 mg, 98%): IR (neat, cm^{-1}) 3400, 1704, 1614, 1514; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.0 Hz, 2 H), 6.91 (d, *J* = 8.6 Hz, 2 H), 5.14 (s, 1 H), 5.09 (s, 1 H), 4.60 (dd, *J* = 11.3, 4.3 Hz, 1 H), 4.51 (s, 1 H), 4.50 (d, *J* = 10.2 Hz, 1 H), 4.42 (d, *J* = 2.9 Hz, 1 H), 4.20 (d, *J* = 10.8 Hz, 1 H), 3.85 (s, 3 H), 3.81 (d, *J* = 9.0 Hz, 1 H), 3.29 (s, 1 H), 3.12−3.10 (m, 1 H), 3.02 (s, 1 H), 2.82−2.79 (m, 1 H), 2.54−2.50 (m, 1 H), 2.49−2.45 (m, 1 H), 2.23−2.11 (m, 3 H), 2.04−2.00 (m, 1 H), 1.78−1.70 (m, 1 H), 1.28 (s, 3 H), 1.21 (s, 3 H), 1.13 (s, 3 H), 0.91 (s, 9 H), 0.13 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.5, 211.4, 158.9, 139.3, 130.9, 128.5 (2C), 113.8, 113.6 (2C), 88.7, 86.3, 76.9, 72.1, 60.3, 56.1, 55.2, 50.3, 43.5, 34.7, 33.3, 31.8, 31.7, 26.3, 25.2 (3C), 25.8, 19.0, 18.5, 11.1−2.4, −2.9; ES HRMS *m*/*z* $(M + Na)^+$ calcd 609.3218, obsd 609.3204; [α] +0.8 (*c* 0.89, $CHCl_3$).

Benzoylation of 5. To a solution of **5** (12 mg, 0.020 mmol) and DMAP (1 crystal, cat) in dry pyridine (0.2 mL) was added benzoyl chloride (24 μL, 0.2 mmol). The solution was stirred for 6 h, and the reaction mixture was diluted with water and EtOAc. The aqueous layer was extracted with EtOAc (3 × 30 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and freed of solvent under reduced pressure. The residue was chromatographed on silica gel (3−5% EtOAc in hexanes) to give 10.8 mg (85%) of **6** as a colorless solid, mp 143−145 °C, and return 2 mg (15%) of unreacted **5**.

For **6**: ^1H NMR (500 MHz, C_6D_6, 40 °C) δ 8.11 (d, *J* = 7.2 Hz, 2 H), 7.43 (d, *J* = 8.5 Hz, 2 H), 7.07 (t, *J* = 7.4 Hz, 1 H), 7.00 (t, *J* = 8.1 Hz, 2 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 6.17 (d, *J* = 5.3 Hz, 1 H), 5.21 (s, 1 H), 4.95 (s, 1 H), 4.73 (d, *J* = 8.7 Hz, 2 H), 4.45 (dd, *J* = 11.4, 4.4 Hz, 1 H), 4.37 (s, 1 H), 4.28 (d, *J* = 10.6 Hz, 1 H), 4.09−4.04 (m, 1 H), 4.61 (d, *J* = 4.4 Hz, 1 H), 3.33 (s, 3 H), 3.03−2.98 (m, 1 H), 2.55−2.50 (m, 1 H), 2.29−2.24 (m, 1 H), 2.05−1.88 (m, 3 H), 1.86−1.78 (m, 1 H), 1.70 (s, 3 H), 1.65−1.56 (m, 1 H), 1.49−1.41 (m, 1 H), 1.39 (s, 3 H), 1.23 (s, 3 H), 0.85 (s, 9 H), 0.01 (s, 3 H), −0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.0, 159.4, 133.9, 131.2, 130.4 (2C), 129.6, 128.92 (2C), 128.91 (2C), 114.1 (2C), 89.5, 72.9, 55.7, 34.9, 31.8, 30.1, 26.5, 26.0, 23.1, 18.8, 11.3, −2.8 (due to atropisomerism not all carbons are apparent); ES HRMS *m*/*z* $(M + Na)^+$ calcd 713.3480, obsd 713.3504.

Selective *O*-Methylation of 8. Potassium *tert*-butoxide (27 mg, 0.24 mmol) was placed under high vacuum in a 50 mL round-bottomed flask for 1 h. After the solid was blanketed with dry N_2, anhydrous DMF (10 mL) was added to achieve dissolution at rt. After being cooled to 0 °C, a solution of **8** (56 mg, 0.121 mmol) in dry DMF (3 mL) was added, stirring was maintained at this temperature for 30 min, dimethyl sulfate (23 μL, 0.24 mmol) was introduced, and the solution was stirred for another 30 min at 0 °C. Sodium hydroxide (2 N, 3 mL) was added, the product was extracted into Et_2O (2 × 10 mL), the combined organic extracts were dried, filtered, and concentrated, and the residue was subjected to flash chromatography on silica gel (elution with 7:1 hexane/EtOAc) to afford **9** (40.9 mg, 71%) as a colorless oil: IR (neat, cm^{-1}) 3271, 1754, 1725; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.7 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 h), 5.75 (s, 1 H), 4.94 (s, 1 H), 4.76 (s, 1 H), 4.62 (d, *J* = 11.7 Hz, 1 H), 4.58 (s, 1 H), 4.22 (m, 4 H), 3.80 (s, 3 H), 3.68 (s, 1 H), 3.63 (s, 3 H), 2.93 (m, 2 H), 2.63 (m, 1 H), 2.40 (m, 1 H), 2.12 (t, *J* = 8.5 Hz, 2 H), 2.04 (m, 1 H), 1.90 (m, 1 H), 1.57 (m, 1 H), 1.13 (s, 3 H), 1.10 (s, 3 H), 1.08 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4, 157.3, 145.5, 130.2, 128.0, 113.8, 110.7, 99.7, 96.2, 87.0, 85.2, 84.2, 72.6, 55.3, 54.6, 51.5, 50.0, 42.7, 41.4, 35.4, 32.8, 30.2, 29.9, 26.0, 20.0, 13.0; ES HRMS $(M + Na)^+$ calcd 493.2566, obsd 493.2562; [α] −9.2 (*c* 4.2, $CHCl_3$).

Diepoxidation of 9. To a solution of **9** (4.8 mg, 0.01 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added $NaHCO_3$ (8.4 mg, 0.1 mmol) and *m*-CPBA (8.7 mg, 0.05 mmol). The mixture was stirred vigorously at 0 °C for 28 h, quenched with saturated $NaHCO_3$ solution (10 mL), and extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (elution with 1:2 hexane/EtOAc) gave **10** (3.9 mg, 76%) as a white crystalline solid: mp 138−140 °C; IR (neat, cm^{-1}) 1678, 1590; ^1H NMR (500 MHz, C_6D_6) δ 7.45 (d, *J* = 8.5 Hz, 2 H), 6.81 (d, *J* = 8.5 Hz, 2 H), 5.84 (s, 1 H), 4.53 (d, *J* = 9.7 Hz, 1 H), 4.18 (s, 1 H), 4.04 (dd, *J* = 2.1, 9.7 Hz, 1 H), 3.98 (m, 1 H), 3.32 (s, 3 H), 3.04 (d, *J* = 10.8 Hz, 1 H), 2.91 (s, 1 H), 2.90 (s, 3 H), 2.88 (br s, 2 H), 2.43 (t, *J* = 11.1 Hz, 1 H), 2.30 (d, *J* = 4.5 Hz, 1 H), 2.10 (t, *J* = 6 Hz, 2 H), 1.99 (d, *J* = 10.7 Hz, 1 H), 1.96 (m, 1 H), 1.79 (m, 2 H), 1.55 (s, 3 H), 1.34 (s, 3 H), 1.30 (s, 3 H), 1.16 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ 160.6, 129.2, 128.2, 113.8, 99.8, 86.0, 85.3, 84.2, 83.3, 72.0, 58.4, 55.3, 54.8, 50.5, 50.0, 48.9, 47.9, 42.3, 38.3, 32.2, 31.6, 31.2, 28.8, 23.7, 21.4, 14.0; ES HRMS *m*/*z* $(M + Na)^+$ calcd 525.2464, obsd 525.2462; [α] −3.2 (*c* 0.23, $CHCl_3$). Crystallographic details for **10** are provided as Supporting Information.

Oxidation of 9 with Oxone at Room Temperature. To a solution of **9** (8.1 mg, 0.017 mmol) in CH_3CN (5 mL) and H_2O (1 mL) at rt were added $NaHCO_3$ (14.3 mg, 0.17 mmol), acetone (6.3 μL, 0.086 mmol) and oxone (52 mg, 0.086 mmol). The reaction mixture was stirred vigorously for 24 h and diluted 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 1:3 hexane/EtOAc) to deliver **11** (3.4 mg, 40%) as a

colorless oil: IR (neat, cm^{-1}) 3428, 1703, 1603; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 8.8 Hz, 2 H), 6.91 (d, J = 8.8 Hz, 2 H), 5.56 (dd, J = 2,8, 7.7 Hz, 1 H),4.29 (dd, J = 0.9, 5 Hz, 1 H), 4.19 (d, J = 11 Hz, 1 H), 4.11 (d, J = 4 Hz, 1 H), 4.09 (d, J = 7.2 Hz, 1 H), 3.86 (s, 3 H), 3.55 (s, 3 H), 3.09 (d, J = 12 Hz, 1 H), 2.89 (d, J = 3 Hz, 1 H), 2.74 (d, J = 16 Hz, 1 H), 2.62 (d, J = 4.4 Hz, 1 H), 2.58 (m, 1 H), 2.41 (m, 1 H), 2.20 (m, 1 H), 1.95 (m, 1 H), 1.91 (m, 3 H), 1.80 (m, 1 H), 1.40 (m, 1 H), 1.22 (s, 3 H), 1.17 (s, 3 H), 1.05 (s, 3 H); ES HRMS m/z $(M + Na)^+$ calcd 525.2464, obsd 525.2452; [α] −18.3 (c 0.3, $CHCl_3$).

Oxidation with Oxone at 0 °C. To a solution of **9** (10 mg, 0.021 mmol) in CH_3CN (5 mL) and H_2O (1 mL) at 0 °C were added $NaHCO_3$ (17.6 mg, 0.21 mmol), acetone (3 μL, 0.042 mmol), and Oxone (26 mg, 0.042 mmol), respectively. The solution mixture was stirred vigorously at 0 °C for 7 h. Saturated $NaHCO_3$ solution (10 mL) was added to the mixture. The resulting aqueous solution was extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. Concentration of the filtrate followed by flash chromatography on silica gel (elution with 2:1 hexane/EtOAc) afforded epoxy ether **12** (5.9 mg, 58%) as a colorless oil: IR (neat, cm^{-1}) 1607, 1513; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 8.7 Hz, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 5.75 (s, 1 H), 4.50 (br s, 1 H), 4.22 (dd, J = 2.1, 9.7 Hz, 1 H), 4.14 (m, 3 H), 3.80 (s, 3 H), 3.61 (s, 1 H), 3.55 (s, 3 H), 2.94 (d, J = 12 Hz, 1 H), 2.90 (s, 1 H), 2.87 (d, J = 18 Hz, 1 H), 2.61 (d, J = 4.3 Hz, 1 H), 2.60 (m, 1 H), 2.40 (m, 1 H), 2.20 (m, 1 H), 1.93 (m, 2 H), 1.78 (m, 1 H), 1.71 (m, 1 H), 1.40 (m, 1 H), 1.22 (s, 3 H), 1.13 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 160.6, 130.6, 128.4, 114.2, 100.1, 92.5, 86.9, 85.6, 84.7, 72.6, 57.9, 55.7, 54.9, 52.0, 50.4, 50.2, 43.4, 39.2, 36.0, 32.4, 29.0, 26.3, 20.4, 13.6; ES HRMS m/z $(M + Na)^+$ calcd 509.2515, obsd 509.2513; [α] −3.5 (c 1.13, $CHCl_3$).

Boron Trifluoride-Catalyzed Isomerization of 10. A solution of **10** (2.8 mg, 56 μmol) in dry CH_2Cl_2 (3 mL) at −78 °C under N_2 was treated with boron trifluoride etherate (10 mL of 1.1 M in benzene, 0.011 mmol), stirred for 5 h at −78 °C, and quenched with saturated $NaHCO_3$ solution (5 mL) prior to extraction with EtOAc (2 × 10 mL). The combined organic extracts were dried, filtered, and freed of solvent. The residue was purified by flash chromatography on silica gel (elution with 1:5 hexane/EtOAc) to furnish **13** (2.2 mg, 100%) as a white solid: mp 214−215 °C; IR (neat, cm^{-1}) 3506, 1660, 1437; ^1H NMR (500 MHz, DMSO-d_6) δ 5.04 (d, J = 5.2 Hz, 1 H), 4.48 (s, 1 H), 4.30 (br s, 2 H), 4.09 (t, J = 5.6 Hz, 1 H), 4.02 (dd, J = 6.9, 14.3 Hz, 1 H), 3.66 (s, 1 H), 3.43 (s, 1 H), 3.19 (s, 3 H), 2.92 (m, 2 H), 2.82 (s, 1 H), 2.79 (s, 1 H), 2.42 (d, J = 11.7 Hz, 1 H), 2.21 (m, 2 H), 1.77 (m, 3 H), 1.63 (m, 1 H), 1.24 (d, J = 15.4 Hz, 1 H), 1.13 (s, 3 H), 0.91 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 216.3, 81.7, 78.8, 78.1, 74.3, 68.2, 62.9, 58.7, 55.3, 54.3, 51.5, 49.3, 41.1, 33.3, 31.3, 29.4, 28.4, 23.3, 17.6, 11.7; ES HRMS m/z $(M + Na)^+$ calcd 407.2046, obsd 407.2048; [α] −29 (c 0.37, $CHCl_3$). Crystallographic details for **13** are provided in the Supporting Information.

***O*-Benzylation of 4.** Potassium *tert*-butoxide (154 mg, 1.4 mmol) was placed under high vacuum in a 100 mL round-bottomed flask for 1 h. After the solid had been blanketed with dry N_2, anhydrous DMF (20 mL) was added to achieve dissolution at rt. The reaction mixture was cooled to 0 °C, treated with a solution of **4** (400 mg, 0.7 mmol) in dry DMF (10 mL), and stirred at the same temperature for 30 min. Benzyl bromide (0.17 mL, 1.4 mmol) was added, and the solution was stirred for another 30 min at 0 °C prior to quenching with NaOH solution (10 mL). After 5 min, the product was extracted into Et_2O (2 × 10 mL), the combined organic extracts were dried, filtered, and concentrated, and the residue was flash chromatographed on silica gel (elution with 6:1 hexane/Et_2O) to provide **14** (412 mg, 89%) as a white solid: mp 157−158 °C; IR (neat, cm^{-1}) 1705, 1703, 1609, 1514; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42−7.34 (m, 7 H), 6.90 (d, J = 8.6 Hz, 2 H), 4.95 (s, 1 H), 4.74 (d, J = 11 Hz, 1 H), 4.72 (s, 1 H), 4.69 (d, J = 11 Hz, 1 H), 4.68−4.66 (m, 2 H), 4.50 (d, J = 3.2 Hz, 1 H), 4.42 (d, J = 11 Hz, 1 H), 4.17 (d, J = 11 Hz, 1 H), 3.84 (s, 3 H), 3.72 (d, J = 12 Hz, 1 H), 3.57 (s, 1 H), 2.96 (d, J = 12 Hz, 1 H), 2.75−2.70 (m, 1 H), 2.50 (d, J = 10 Hz, 1 H), 2.30−2.23 (m, 3 H), 2.16−2.11 (m, 1 H), 2.11−2.03 (m, 1 H), 1.73−1.69 (m, 1 H), 1.11 (s, 3 H), 1.09 (s, 3 H), 1.07 (s, 3 H), 0.89 (s, 9 H), 0.13 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.2, 158.7, 157.1, 144.2, 136.3, 131.2, 128.5, 128.3, 128.0, 113.5, 110.7, 97.8, 86.3, 85.1, 76.9, 71.8, 69.9, 59.9, 57.0, 55.2, 51.7, 39.0, 35.6, 32.9, 31.6, 26.4, 26.3, 19.3, 18.5, 9.5, −2.2, −2.8; ES HRMS m/z $(M + Na)^+$ calcd 683.3744, obsd 683.3736; [α] −74 (c 0.3, $CHCl_3$).

Diepoxidation of 14. A solution of **14** (103 mg, 0.16 mmol) in CH_2Cl_2 (30 mL) at 0 °C was treated with $NaHCO_3$ (250 mg, 1.5 mmol) and *m*-CPBA (138 mg, 0.8 mmol). The reaction mixture was stirred vigorously at 0 °C for 36 h prior to quenching with saturated $NaHCO_3$ solution (10 mL). The product was extracted into EtOAc (2 × 30 mL), the combined organic extracts were dried and filtered, and the concentrate was flash chromatographed on silica gel (elution with 4:1 hexane/EtOAc) to afford **15** (88 mg, 80%) as a white solid: mp 133−134 °C; IR (neat, cm^{-1}) 1703, 1509; ^1H NMR (500 MHz, C_6D_6) δ 7.46 (d, J = 8.6 Hz, 2 H), 7.23 (d, J = 7.4 Hz, 2 H), 7.14−7.11 (m, 2 H), 7.09−7.02 (m, 1 H), 6.79 (d, J = 8.6 Hz, 2 H), 4.54 (d, J = 10.6 Hz, 1 H), 4.51 (d, J = 3.6 Hz, 1 H), 4.45 (dd, J = 4.3, 11.3 Hz, 1 H), 4.35 (s, 2 H), 4.32 (d, J = 10.8 Hz, 1 H), 3.28 (s, 3 H), 3.04 (d, J = 10.8 Hz, 1 H), 2.86−2.84 (m, 1 H), 2.78 (d, J = 3.6 Hz, 1 H), 2.53 (d, J = 10.8 Hz, 1 H), 2.45−2.40 (m, 1 H), 2.23−2.22 (d, J = 4.4 Hz, 1 H), 2.19−2.10 (m, 2 H), 1.76−1.72 (m, 2 H), 1.63 (s, 1 H), 1.62 (s, 3 H), 1.60−1.49 (m, 2 H), 1.22 (s, 3 H), 1.14 (s, 3 H), 1.11−1.05 (m, 1 H), 0.83 (s, 9 H), −0.01 (s, 3 H), −0.05 (s, 3 H); ^{13}C NMR (500 MHz, C_6D_6) δ 209.2, 159.6, 138.1, 133.5, 131.5, 128.9, 128.8, 128.5, 114.1, 86.6, 86.5, 85.9, 76.6, 72.0, 65.2, 58.5, 57.9, 56.4, 55.4, 54.8, 50.0, 49.3, 37.0, 32.6, 32.5, 32.1, 30.7, 26.6, 23.9, 21.0, 18.9, 10.7, −2.16, −2.23; ES HRMS m/z $(M + Na)^+$ calcd 715.3642, obsd 715.3632; [α] −34.5 (c 0.87, $CHCl_3$).

Acid Treatment of 15. A solution of **15** (320 mg, 0.46 mmol) in CH_2Cl_2 (50 mL) was treated with CSA (214 mg, 0.92 mmol), stirred for 24 h under N_2, and quenched with saturated $NaHCO_3$ solution (5 mL). The product was extracted into EtOAc (2 × 50 mL), the combined organic extracts were dried and filtered, and the concentrate was purified by flash chromatography on silica gel (elution with 2:1 hexane/EtOAc) to give **16** (263 mg, 95%) as a white solid: mp 177−179 °C; IR (neat, cm^{-1}) 3424, 1701, 1507; ^1H MMR (500 MHz, $CDCl_3$) δ 7.27 (d, J = 8.7 Hz, 2 H), 6.85 (d, J = 8.7 Hz, 2 H), 4.58 (dd, J = 4.1, 11.1 Hz, 1 H), 4.45 (s, 1 H), 4.43 (d, J = 7.5 Hz, 1 H), 4.18−4.14 (m, 1 H), 4.11 (d, J = 7.1 Hz, 1 H), 4.07 (d, J = 2.5 Hz, 1 H), 3.80 (s, 3 H), 3.79 (s, 1 H), 3.68 (dd, J = 1.5, 4.6 Hz, 1 H), 3.18 (d, J = 4.7 Hz, 1 H), 3.09−3.06 (m, 1 H), 2.80−2.71 (m, 2 H), 2.58 (d, J = 4.7 Hz, 1 H), 2.22−2.11 (m, 2 H), 2.10−2.04 (m, 2 H), 1.89−1.84 (m, 1 H), 1.36−1.34 (m, 1 H), 1.33 (s 3 H), 1.15 (s, 3 H), 1.02 (s, 3 H), 0.86 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.0, 209.9, 158.9, 130.7, 128.4, 113.6, 88.5, 85.9, 76.9, 76.1, 72.1, 60.6, 60.0, 55.9, 55.2, 53.2, 50.1, 38.4, 34.3, 34.0, 31.9, 30.1, 26.1, 25.8, 18.8, 18.4, 11.2, −2.4, −3.1; ES HRMS m/z $(M + Na)^+$ calcd 625.3173, obsd 625.3167; [α] −16 (c 0.64, $CHCl_3$).

Benzoylation of 16. To a solution of **16** (265 mg, 0.44 mmol) in CH_2Cl_2 (30 mL) were added Et_2N (0.30 mL, 2.2 mmol), DMAP (5.0 mg, 0.044 mmol), and benzoyl chloride (0.10 mL, 0.88 mmol) sequentially under N_2. The reaction mixture was stirred for 12 h, and saturated $NaHCO_3$ solution (20 mL) was introduced prior to extraction of the product into EtOAc (2 × 50 mL). The combined organic extracts were dried and filtered. The concentrate was flash chromatographed on silica gel (elution with 5:1 hexane/EtOAc) to afford **17** (291 mg, 94%) as a colorless oil: IR (neat, cm^{-1}) 3448, 1730, 1706, 1513; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67−7.62 (m, 2 H), 7.54−7.52 (m, 2 H), 7.42 (s, 1 H), 7.36 (d, J = 8.6 Hz, 2 H), 6.92 (d, J = 8.6 Hz, 2 H), 5.66 (d, J = 2.3 Hz, 1 H), 4.65 (dd, J = 4.3, 11.4 Hz,

1 H), 4.57 (d, J = 10.7 Hz, 1 H), 3.86 (s, 3 H), 3.79 (d, J = 4.3 Hz, 1 H), 3.60 (s, 1 H), 3.31 (d, J = 12.7 Hz, 1 H), 2.98−2.88 (m, 1 H), 2.75−2.70 (m, 1 H), 2.65 (d, J = 4.9 Hz, 1 H), 2.34−2.27 (m, 2 H), 2.17−2.12 (m, 2 H), 1.94−1.86 (m, 1 H), 1.50−1.47 (m, 1 H), 1.26 (s, 3 H), 1.25 (s, 6 H), 0.89 (s, 9 H), 0.15 (s, 3 H), 0.14 (s, 3 H); ES HRMS m/z $(M + Na)^+$ calcd 729.3435, obsd 729.3435; [α] +2.4 (c 1.3, $CHCl_3$).

α-Ketol Rearrangement of 17. A solution of **17** (10 mg, 0.014 mmol) in dry benzene (10 mL) was treated with aluminum isopropoxide (7.1 mg, 0.028 mmol) and the reaction mixture was stirred at 50 °C under N_2 for 24 h, cooled to rt, and quenched with 3% HCl (5 mL). The product was extracted into EtOAc (2 × 20 mL), the combined organic extracts were dried and filtered, and the concentrate was flash chromatographed on silica gel (elution with 6:1 hexane/EtOAc) to furnish **18** (5.5 mg, 55%) as a colorless oil alongside an isomer (4 mg), which was put to the same reaction procedure again to yield and additional crop of **18** (2.2 mg, 22%): IR (neat, cm^{-1}) 3494, 1734, 1514; ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 7.6 Hz, 2 H), 7.63 (t, J = 7.3 Hz, 1 H), 7.50 (t, J = 7.6 Hz, 2 H), 7.37 (t, J = 8.5 Hz, 2 H), 6.93 (d, J = 8.5 Hz, 2 H), 5.64 (d, J = 6.3 Hz, 1 H), 4.13 (d, J = 4.3 Hz, 1 H), 4.06 (d, J = 10.7 Hz, 1 H), 3.86 (s, 3 H), 3.42 (d, J = 6.3 Hz, 1 H), 2.86−2.83 (m, 2 H), 2.80 (d, J = 3.3 Hz, 1 H), 2.63 (d, J = 3.3 Hz, 1 H), 2.49−2.41 (m, 1 H), 2.29−2.21 (m, 2 H), 2.12−2.05 (m, 1 H), 1.97−1.93 (m, 1 H), 1.76 (s, 3 H), 1.77−1.71 (m, 1 H), 1.15 (s, 3 H), 1.07−1.04 (m, 1 H), 1.02 (s, 3 H), 0.94 (s, 9 H), 0.15 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.8, 209.4, 165.1, 159.4, 133.5, 129.6, 129.5, 128.7, 128.4, 113.8, 84.3, 84.0, 73.3, 71.8, 70.5, 57.5, 56.5, 55.2, 54.3, 52.2, 43.1, 42.0, 38.1, 30.9, 27.7, 27.3, 26.7, 25.9, 23.0, 18.2, 12.1, −1.8, −4.2; ES HRMS m/z $(M + Na)^+$ calcd 729.3429, obsd 729.3492; [α] +60.7 (c 0.27, $CHCl_3$).

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Supporting Information Available: Details surrounding the X-ray crystallographic analysis of **10** and **13** including experimental protocols, ORTEP diagrams, crystallographic data, and tables of bond lengths and bond angles, atomic coordinates, and thermal parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

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