JOC Article

Effect of 9,10-Cyclic Acetal Stereochemistry on Feasible Operation of the α-Ketol Rearrangement in Highly Functionalized Paclitaxel (Taxol) Precursors†

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The convergent, stereocontrolled synthesis of enantiopure stereoisomeric 9,10-cyclic acetals, whose designed role was to serve as potential precursors to Taxol, is reported. These advanced intermediates are multiply functionalized and carry a bridgehead α-ketol array which was key to isomerization into the proper framework. In agreement with relative strain energy values obtained by MM3 calculations, a dichotomy was observed between these two families. While the trans-fused acetals failed to undergo bridge migration, their cis counterparts did so efficiently. In fact, isomerization was sufficiently rapid that oxygenation at C2 was now precluded. The operation of several unusual transannular hydride shifts is also detailed.

The synthetic planning and strategy associated with our exploration of concise routes to taxusin,[1] paclitaxel (Taxol),[2] and their analogues have been based on the substantial scaffolding power of the anionic oxy-Cope rearrangement and the feasibility of regiocontrolled 1,2-carbon shifts in advanced bridged intermediates. While the first of these tactics has been widely exploited and is well understood mechanistically,[3] the adaptability of the α-ketol rearrangement to complex target synthesis is far less advanced.[4] Certainly, bridgehead α-keto carbinols are recognized for their ability to isomerize under a variety of conditions.[4,5] However, since this isomerization is equilibrium-controlled, thermodynamics plays an obvious key role in determining the direction in which bond reorganization will proceed preferentially. As a consequence of our early investigations of this process, aluminum alkoxides were determined to be notably efficacious promoters.[6,7] After noting the ready, near-quantitative conversion of **1** to **2** in refluxing benzene containing 3 equiv of $Al(O\text{-}i\text{-}Pr)_3$,[6] we turned our attention to **3** where the B/C ring fusion was now trans as in all taxanes (Scheme 1). Heating this α-ketol with either $Al(O\text{-}i\text{-}Pr)_3$ or $Al(O\text{-}t\text{-}Bu)_3$ in benzene for 3 h resulted in its total consumption. At this point, the reaction mixture was constituted of 15% of **4** and 85% of **5**. Extension of the reaction time to 12 h afforded pure **5** in 93% isolated yield.[7]

Although the thermodynamic bias in this system was not in line with our objectives, two subsequent observations proved highly encouraging (Scheme 2). The substantially more functionalized diketo alcohol **6** was found to isomerize smoothly in the desired manner and furnish exclusively **7** (94%).[8] Of added importance was the **8** → **9** isomerization.[9] Although the C-ring is lacking in this example, the benzoate functionality residing adjacent to the ketone carbonyl was found not to impede bridge migration. Taxol (**10**) carries an α-oriented benzoate group at C-2.[10]

One of the synthetic routes projected by us for the enantioselective synthesis of **10** involves the construction from D-camphor of stereoisomeric 9,10-*p*-methoxybenzylidene (PMP) acetals[11] otherwise functionalized to a level exemplified by **11** and **14** (Table 1). MM3 calculations suggested that an interesting dichotomy may distinguish these compound families. In the trans series, isotaxane **11** is estimated to be 4.6 kcal/mol *less* sterically strained than **12** and approximately 3 kcal/mol *less* thermodynamically favored than the undesirable bond shift

† After common usage of the term taxol for nearly two decades, it was selected as a registered trademark by Bristol-Myers Squibb. This fact is recognized when Taxol is cited in this paper.

(1) (a) Paquette, L. A.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5203. (b) Paquette, L. A.; Wang, H.-L.; Su, Z.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5213.

(2) For a summary of the early progress, consult: 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.

(3) (a) Paquette, L. A.; *Tetrahedron* **1997**, *53*, 13971. (b) Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609.

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(6) Paquette, L. A.; Elmore, S. W.; Combrink, K. D.; Hickey, E. R.; Rogers, R. D. *Helv. Chim. Acta* **1992**, *75*, 1755.

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(10) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.

(11) Taxane numbering is used throughout for simplicity. Where isotaxanes are involved, the operation of 1,2-bridge migration must be anticipated.

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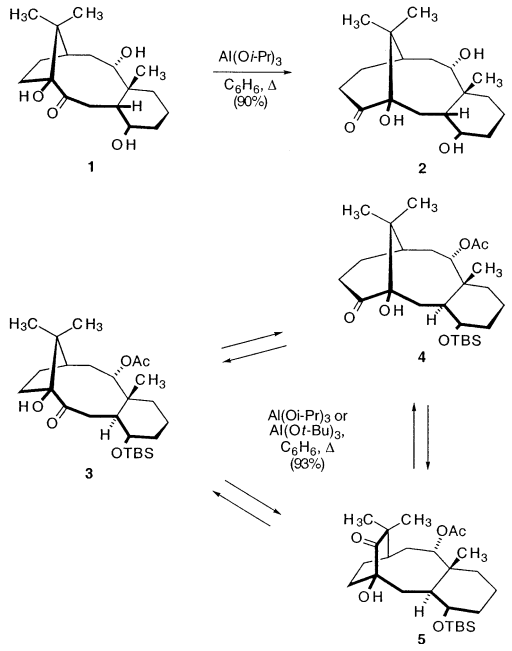
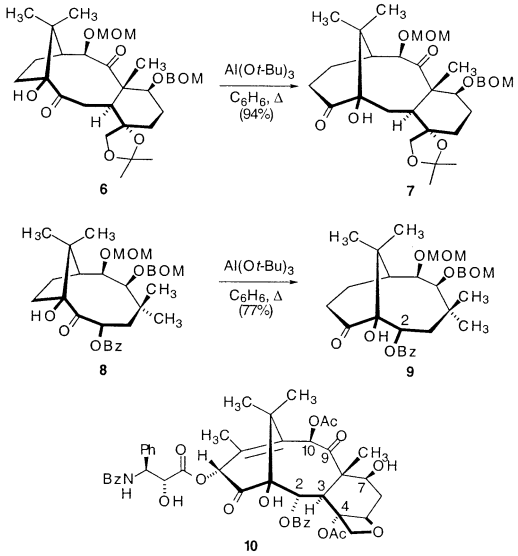
SCHEME 1



SCHEME 2

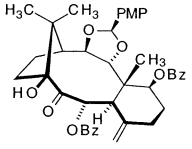
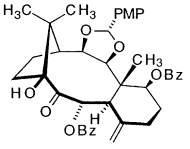
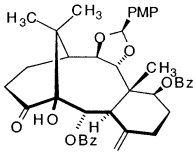
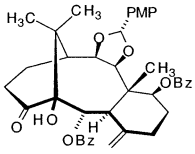
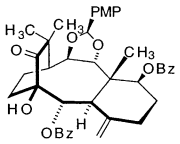
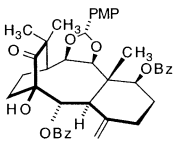


isomer **13**. The steric energy gaps arrived at when a cis-locked PMP acetal is involved are smaller in magnitude. Although **16** is predicted to be the least stable isomer by more than 2 kcal/mol, it is difficult to conjecture which candidates will be favored under equilibrating conditions. In this paper, we describe a convergent approach to these potential Taxol precursors and document their differing response to α-ketol rearrangement.

Results and Discussion

Assembly of the Common Tricyclic Precursor. The critical role planned for a common precursor demanded that a concise route be developed. This objective was met by initial hydride reduction of the known ester **17**[12] and protection of the primary hydroxyl so generated as the TBS ether (Scheme 3). A two-step procedure for the conversion of **18** into **20** was accomplished by coupling

TABLE 1. Relative Steric Strain Energies Estimated by MM3 Calculations

trans series	relative E_S, kcal/mol	cis series	relative E_S, kcal/mol
 **11**	2.9	 **14**	0.0
 **12**	7.5	 **15**	0.2
 **13**	0.0	 **16**	2.5

the vinyllithium intermediate generated by halogen−metal exchange in **18** to dimethylformamide[13] followed by Wittig condensation of aldehyde **19** with (iodomethylene)triphenylphosphorane.[14,15] Attention then shifted to the lithiation of **20** and subsequent coupling to readily available, enantiopure norbornanone **21**.[9] As expected,[16] addition to the carbonyl group proceeded only from the endo direction under steric control without loss of geometrical configuration about the double bond.[8,17] Alcohol **22** underwent ready [3.3] sigmatropic rearrangement when treated with potassium hexamethyldisilazide and 18-crown-6 in THF at low temperature. The necessary adoption of an endo-chair transition state[18] resulted in the highly stereoselective generation of an enolate anion whose in situ methylation gave rise to **23** in 81% yield. Entry of the alkyl group proceeded from the less sterically congested π-surface.[8,17] With **23** in hand, we were able to take advantage of the more elevated tendency of this bridgehead double bond to become engaged in reaction. A three-step sequence involving regioselective dihydroxylation with osmium tetraoxide, reaction with phosgene in the presence of pyridine to generate a cyclic carbonate, and desilylation in the presence of a Dowex resin produced **26** in good overall yield. These tactics made possible subsequent Swern oxidation[19] to deliver keto

(12) Harris, G. D., Jr.; Herr, R. J.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 5452.
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(14) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173.
(15) Paquette, L. A.; Shih, T.-L.; Zeng, Q.; Hofferberth, J. E. *Tetrahedron Lett.* **1999**, *40*, 3519.
(16) Elmore, S. W.; Paquette, L. A. *J. Org. Chem.* **1995**, *60*, 889.
(17) (a) Paquette, L. A.; Bailey, S. *J. Org. Chem.* **1995**, *60*, 7849. (b) Johnston, J. N.; Tsui, H.-C.; Paquette, L. A. *J. Org Chem.* **1998**, *63*, 129.
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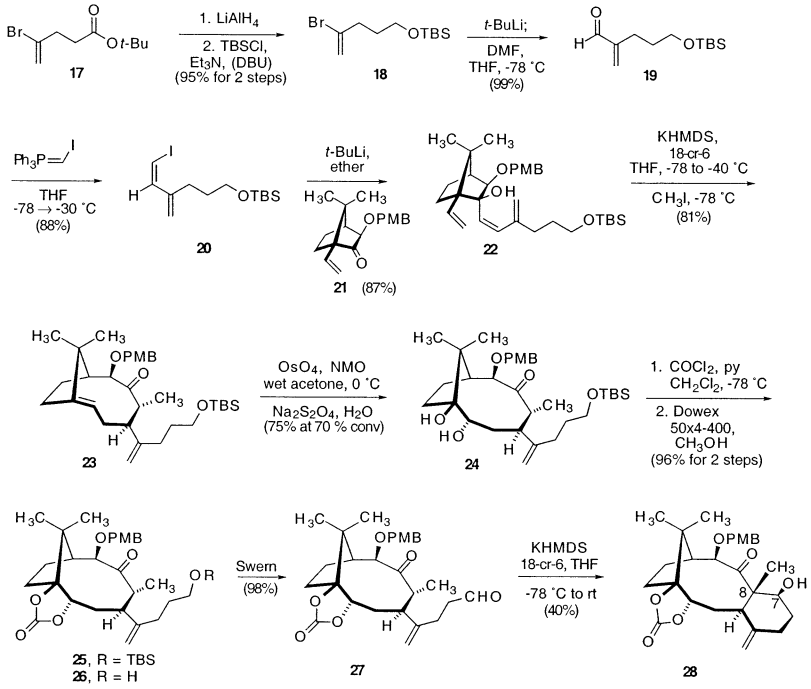
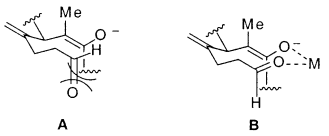
SCHEME 3

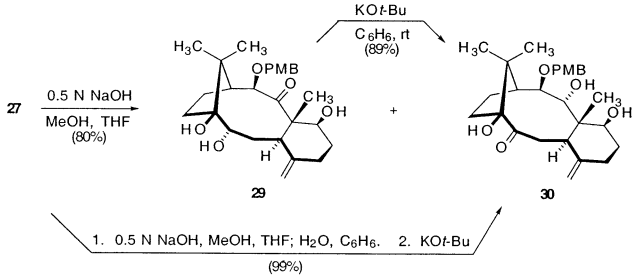


aldehyde **27**. The candidate reaction for elaborating the fully functionalized C ring was the intramolecular aldol. It was expected that this ring closure would be properly stereocontrolled by virtue of the steric destabilization of the pseudoaxial aldehyde conformer **A** relative to its pseudoequatorial counterpart **B**.[20] The possible operation of metal counterion chelation also favors involvement of the latter transition state. In early experiments, treatment of **27** with lithium hexamethyldisilazide was indeed found to give rise to **28**, albeit in modest yield. Note that the newly established stereocenters at C7 and C8 conform precisely in absolute configuration to the structural features resident in Taxol (**10**).



To improve the efficiency of the aldol cyclization, possible catalysis by several other bases was screened. The use of 0.5 N NaOH in 2.3:1 methanol/THF was met not only with a doubling of efficiency but was also accompanied by formation of a 6:1 mixture of **29** and the transannular hydride shift product **30** (Scheme 4).[21] *In an important development, the discovery was made that potassium tert-butoxide in benzene is capable of bringing about the wholesale conversion of* ***29*** *to* ***30****. In final optimized form, the conversion of* ***27*** *to* ***30*** *can be performed in a single operation in nearly quantitative yield, providing material of sufficient purity for use in subsequent steps without recourse to chromatography.* Crystallographic data are available for both **29** and **30**.[21]

SCHEME 4



Advancement into the Trans Series. With technology available for the preparation of **30** in quantity, this advanced intermediate was oxidized with DDQ in dry ether containing 4 Å molecular sieves.[22] As a consequence of the presence of a neighboring free hydroxyl, the benzylic carbocation so generated was trapped intramolecularly to provide the PMP acetal **31**[23] (Scheme 5). The endo projection of the PMP group in **31** was confirmed by NOE analysis (see structure). Selective protection of the secondary hydroxyl resident in **31** with benzyloxymethyl (BOM) chloride[24] led to the isolation of **32** (43%) and **33** (18%). Following chromatographic purification, the bridgehead α-ketol **32** was deprotonated with 10 equiv of potassium hexamethyldisilazide in THF at −78 °C. Activation of the anionic species by means of 30 equiv of 18-crown-6 preceded oxygenation of the cold solution.[25]

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SCHEME 5

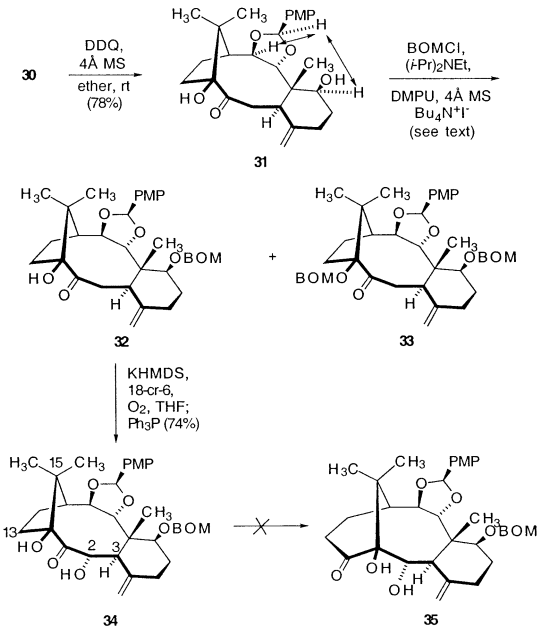
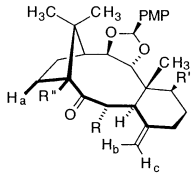


TABLE 2. Chemical Shift Data for C2-Oxygenated *trans*-9,10-Isotaxane PMP Acetals (300 MHz, $CDCl_3$, δ)

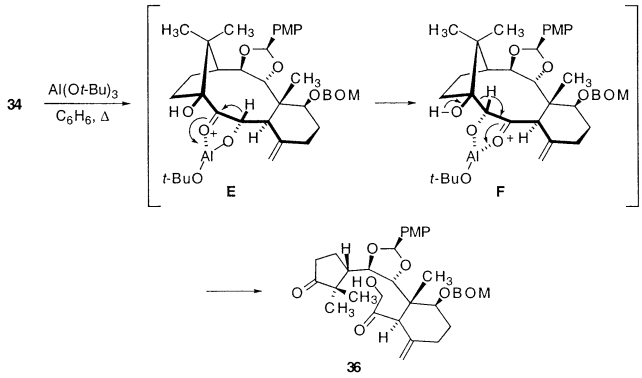


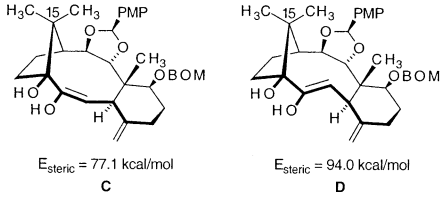
R	R′	R″	H_a	H_b	H_c
H	OH	OH	2.25	5.02	4.70
OH	OH	OH	**3.15**	5.29	4.86
OH	OBn	OH	**3.08**	5.26	4.85
OH	OBn	OBn	**3.42**	5.22	4.86
OTES	OTES	OH	**3.17**	5.16	4.65
OAc	OAc	OH	**3.00**	5.12	4.57
OBz	OBz	OH	**3.15**	5.07	4.66

After short-term exposure of the reaction mixture to triphenylphosphine, the resultant colorless oil was shown to be **34**. This chemical transformation was accompanied by two significant changes in the ^{1}H NMR spectrum (recorded in $CDCl_3$). In the first instance, the absorptions attributable to the exomethylene protons were displaced from their original location (δ 5.02 and 4.71 ppm) to more downfield positions (δ 5.26 and 4.85 ppm), presumably as a direct consequence of the proximity of the newly introduced C2 hydroxyl. Also, COSY analysis revealed the new carbinyl proton having a chemical shift of 4.55 ppm to be coupled to the newly introduced hydroxyl proton as well as to H3. Still more convincing was the striking downfield shift of $H_{13\alpha}$ that is observed when C2 is oxygenated from the α direction (Table 2).

This structural assignment was also in line with MM3 calculations involving the minimum energy conformations for enols **C** and **D** corresponding to the enolates presumably involved in the oxidation. Following adaptation of the Monte Carlo conformational searching protocol, additional minimization was accomplished through use of the full-matrix Newton Raphson method. This direct comparison revealed the *E*-enol with a steric energy of 77.1 kcal/mol to be substantially favored relative to the *Z*-enol (E_s = 94.0 kcal/mol). Additionally, the intracyclic double bond in **C** is projected upward in the direction of C15 such that only the α-surface can be approached without encountering severe nonbonded steric compression.

SCHEME 6





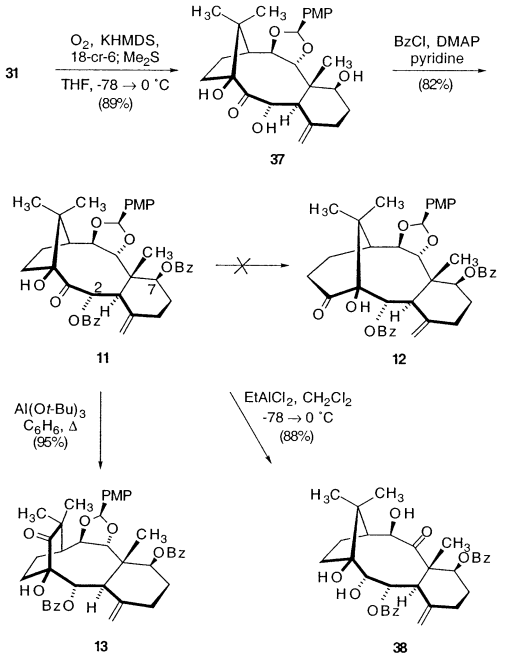
It will be recognized that the strongly basic conditions applied to **32** will result in initial generation of the α-keto alkoxide. Notably, bridge migration operated neither at this stage nor when the dianion was subsequently generated. This lack of a sufficient driving force for rearrangement foreshadowed the properties inherent to **34**.

Heating **34** with Al(O-*t*-Bu)$_3$ in benzene under conditions known to isomerize structurally related systems resulted in its rapid consumption. Detailed NMR analysis of the product did not support the formation of **35** but was entirely consistent with the generation of the ring-cleaved product **36** (Scheme 6). Thus, it appeared that a Lewis acid-promoted 1,2-hydride shift as in **E** was kinetically favored, thereby giving rise to **F**, an intermediate amenable to retroaldol fragmentation. The precise status of the several functional groups in **36** were deduced by the application of nOe and HNDC techniques (see the Supporting Information).

Several attempts were made to render this ring-fragmentation process nonoperational.[26] Of these, the specific fate of dibenzoate **11** proved to be particularly informative (Scheme 7). Introduction of the C2 α-hydroxyl into **31** followed the now-established protocol to successfully deliver **37**. The steric congestion present in this triol conveniently allowed for efficient dibenzoylation to operate at C2 and C7. With **11** available in this manner, reaction with aluminum trialkoxide in the manner defined in **E** is no longer possible. However, opportunities for α-ketol rearrangement were not similarly precluded. Notwithstanding, in no instance was conversion to taxane

(26) Hofferberth, J. E. Ph.D. Dissertation, The Ohio State University, 2002.

SCHEME 7



12 achieved. In one of the survey experiments, **11** was heated with aluminum tri-*tert*-butoxide in benzene. Under these conditions, isomerization to **13** (95%) was prevalent. Alternative treatment of **11** with the more potent Lewis acid ethylaluminum dichloride in CH_2Cl_2 at low temperature afforded **38**. This eventuality is the result of a transannular hydride shift process that is accorded mechanistic rationalization in the sequel.[27] The structural assignments to **11**, **13**, and **38** are fully consistent with the HMBC studies compiled in the Supporting Information.

The preferential isomerization of **11** to **13** is consistent with the MM3-derived steric energy values found in Table 1. Once the equilibration of **11** is initiated, the system advances in the direction of the global energy minimum, which in this instance happens not to be a taxane.

Probe of Reactivity in the Cis Series. To address the matter of preparing a cis PMP-acetal related to **32**, we began by subjecting **30** to regioselective silylation and base-promoted transannular hydride migration.[21] In turn, **39** was reduced with $LiAlH_4$ in order to achieve stereoselective introduction of the C9 hydroxyl on the β face[1a] (Scheme 8). DDQ oxidation of triol **40** in dry ether led quantitatively to the desired benzylidine acetal **41**. The conformational rigidity of this intermediate was particularly conducive to NOE analysis, this technique serving to confirm the overall stereochemical relationships of its functional groups, most relevantly at C-9 and the PMP-substituted carbon. Swern oxidation of **41** proved to be a reasonably sluggish process, but extended reaction times had to be skirted because of side-product formation. At this stage, we had need to introduce an α-hydroxyl at C2 to correspond to the Taxol substitution profile. Oxidation of **42** under the predescribed basic conditions afforded **43** in 76% yield.

The conversion of **42** to **43** implies that the alkoxide of **42** is particularly prone to α-ketol rearrangement. The rapidity with which 1,2-bridge migration operates precludes oxygenation of the enolate of **42**. Instead, α-oxygenation occurs only after the taxane framework has been adopted.[1b]

Overview. Considerable process has been achieved in our appreciation of the energetics that can conspire to facilitate or disallow operation of the α-ketol rearrangement in bridgehead α-hydroxy ketones. A trans-locked PMP-acetal introduces steric strain too elevated for ready isomerization to the taxane ring system. On the other hand, the corresponding cis acetal is so prone to structural change that proper C2 oxygenation cannot be accomplished. Neither scenario is conducive to a concise synthesis of Taxol. In the following paper,[27] additional subtleties associated with this chemistry are presented and a workable advance involving a favorable rearrangement arising from a derivative of **39** (where it appears as **3**) is therein documented.

Experimental Section

Vinyl Bromide 18. To a slurry of lithium aluminum hydride (2.75 g, 66 mmol) in ether (60 mL) was added dropwise a solution of **17** in ether (40 mL) at a rate such that a gentle reflux was maintained. The reaction mixture was stirred for 3 h and carefully quenched with water (8 mL) and 1 N NaOH (2.5 mL). The resulting suspension was stirred for 3 h to obtain a flocculent white precipitate. The slurry was filtered, the filtrate was dried and evaporated, and the residue was dissolved in dry CH_2Cl_2 (200 mL). To the resulting solution were added freshly distilled Et_3N (9.2 mL, 66 mmol), DBU (2.0 mL, 13.2 mmol), and *tert*-butyldimethylsilyl chloride (10.93 g, 72.5 mmol). The cloudy reaction mixture was stirred overnight, diluted with CH_2Cl_2 (200 mL), and washed with 5% HCl (200 mL), saturated $NaHCO_3$ solution (200 mL), and brine (200 mL). The organic layer was dried, filtered, and freed of solvent to leave a residue that was chromatographed over silica gel (elution with 2% EtOAc in hexane) to give **18** (15.74 g, 95% for two steps) as a clear oil: IR (neat, cm^{-1}) 1256, 1206, 1104; ^1H NMR (300 MHz, $CDCl_3$) δ 5.57 (s, 1 H), 5.40 (s, 1 H), 3.64 (t, J = 6.1 Hz, 2 H), 2.52 (t, J = 7.2 Hz, 2 H), 1.75 (tt, J = 7.2, 6.1 Hz, 1 H), 0.90 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 128.2, 62.6, 31.0, 26.1 (3C), 24.5, 18.7, −5.1 (2C); EI HRMS m/z (M^+) calcd 278.0701, obsd 278.0672.

Aldehyde 19. A solution of **18** (10.0 g, 35.8 mmol) in THF (300 mL) was cooled to −78 °C, and *tert*-butyllithium (1.42 M in pentane, 53.6 mL, 76.1 mmol) was added in one portion. The resulting mixture was stirred for 30 min, and neat DMF (27.7 mL, 358 mmol) was introduced at a rate of 0.5 mL/min. Following the addition, stirring was maintained for 3 h at −78 °C prior to quenching with saturated NH_4Cl solution (200 mL) and extraction of the aqueous phase with ether (3 × 200 mL). The combined organic layers were washed with water (200 mL) and brine (200 mL), dried, and filtered. The solvent was removed under reduced pressure, and the residue was chromatographed over silica gel (elution with 10% EtOAc in hexane) to give **19** as a yellow oil (8.05 g, 99%): ^1H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1 H), 5.57 (s, 1 H), 5.40 (s, 1 H), 3.64 (t, J = 6.1 Hz, 2 H), 2.52 (t, J = 7.2 Hz, 2 H), 1.75 (tt, J = 7.2, 6.1 Hz, 2 H), 0.90 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.8, 140.5, 128.2, 62.6, 31.0, 26.1 (3C), 24.5, 18.7, −5.1 (2C).

Iodobutadiene 20. To a suspension of iodomethyltriphenylphosphonium iodide (9.10 g, 17.1 mmol) in THF (150 mL) cooled to 0 °C was added a solution of sodium hexamethyldisilazide (0.79 M in THF, 21.6 mL, 17.1 mmol). The ylide solution was stirred for 20 min and cooled to −78 °C. The reaction flask was covered with aluminum foil to avoid

(27) Paquette, L. A.; Lo, H. Y.; Hofferberth, J. E.; Gallucci, J. C. *J. Org. Chem.* **2003**, *68*, 2276.

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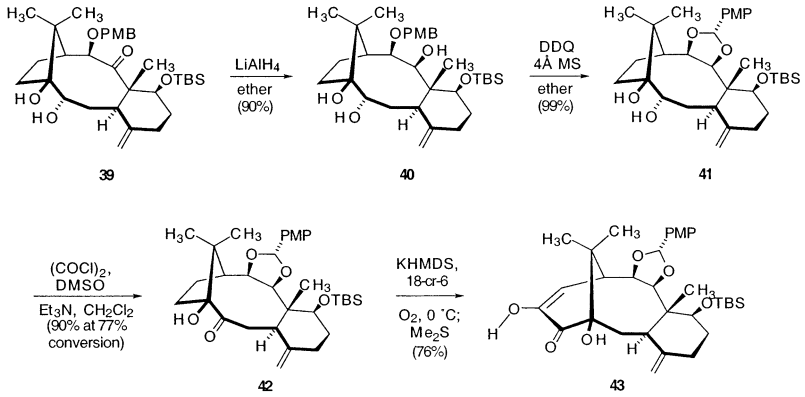

exposure to light, and a solution of **19** (3.0 g, 13.1 mmol) in THF (50 mL) was introduced via cannula. The reaction mixture was stirred for 3 h and warmed to −30 °C. At this temperature, saturated NH_4Cl solution (200 mL) was introduced, and the aqueous layer was extracted with ether (3 × 100 mL). The combined organic layers were washed with brine (200 mL), dried, and freed of solvent under reduced pressure. The residue was chromatographed over silica gel in an aluminum foil-wrapped column (elution with 10% EtOAc in hexane) to give **20** as a clear yellow oil (4.08 g, 88%) which decomposed rapidly in light or in the dark at rt. However, the iodide can be preserved for up to 72 h by immediately freezing it in benzene. For **20**: ^{1}H NMR (300 MHz, C_6D_6) δ 6.58 (d, J = 8.5 Hz, 1 H), 6.26 (d, J = 8.5 Hz, 1 H), 5.19 (s, 1 H), 5.05 (s, 1 H), 3.53 (t, J = 7.8 Hz, 2 H), 2.19 (t, J = 7.8 Hz, 2 H), 1.55−1.71 (m, 2 H), 0.80 (s, 9 H), 0.00 (s, 6 H).

Convergent Synthesis of Norbornanol 22. A stirred solution of **20** (4.6 g, 13 mmol) in dry ether (100 mL) at −78 °C was treated with *tert*-butyllithium (1.1 M in pentane, 23.6 mL, 26 mmol), stirred for 2 min, and admixed with a solution of **21** (4.6 g, 16 mmol) in dry ether (150 mL) via cannula. The reaction mixture was stirred for 3 h at −78 °C, warmed to 0 °C over 30 min, quenched with saturated NH_4Cl solution (250 mL), and extracted with ether (3 × 150 mL). The combined organic layers were dried, filtered, and freed of solvent under reduced pressure. The residue was chromatographed over silica gel (elution with 1−3.5% EtOAc in hexane) to afford **22** as a yellowish oil (6.57 g, 96%) alongside recovered **21** (0.51 g).

For **22**: IR (neat, cm^{-1}) 3511, 1608, 1507; ^{1}H NMR (300 MHz, C_6D_6) δ 7.23 (d, J = 8.6 Hz, 2 H), 6.79 (d, J = 8.6 Hz, 2 H), 6.55 (dd, J = 17.8, 11.0 Hz, 1 H), 5.80 (d, J = 12.6 Hz, 1 H), 5.68 (d, J = 12.6 Hz, 1 H), 5.35 (dd, J = 11.0, 2.2 Hz, 1 H), 5.18 (s, 1 H), 5.09 (dd, J = 17.8, 2.2 Hz, 1 H), 4.96 (s, 1 H), 4.38 (dd, J = 18.6, 10.8 Hz, 2 H), 3.67 (s, 1 H), 3.58 (t, J = 6.3 Hz, 2 H), 3.52 (s, 1 H), 3.33 (s, 3 H), 2.26 (t, J = 9.6 Hz, 2 H), 1.92 (d, J = 4.6 Hz, 1 H), 1.78−1.60 (m, 3 H), 1.58 (s, 3 H), 1.48−1.44 (m, 1 H), 0.99 (s, 9 H), 0.96−0.91 (m, 2 H), 0.84 (s, 3 H), 0.07 (s, 6 H); ^{13}C NMR (75 MHz, C_6D_6) δ 160.1, 146.9, 137.1, 136.1, 131.3, 130.3, 129.8 (2C), 117.3, 114.6 (2C), 114.0, 88.4, 83.2, 71.7, 63.3, 60.5, 55.2, 50.6, 49.1, 34.5, 32.1, 26.5, 26.0, 24.7, 23.2, 22.9, 18.9 (3C), −4.8 (2C); EI HRMS m/z (M^+) calcd 526.3478, obsd 526.3455; [α] −105.4 (c 1.06, $CHCl_3$).

Anionic Rearrangement and Methylation of 22. A dry 1 L round-bottomed flask was charged with 18-cr-6 (10.1 g, 38 mmol) pumped down under high vacuum for 24 h and filled with an argon atmosphere. A solution of **22** (5.78 g, 11 mmol) in THF (380 mL) was added, and the reaction mixture was cooled to −78 °C, treated with a solution of potassium hexamethyldisilazide (0.48 M in toluene, 68 mL, 33 mmol) via cannula over 4 min, allowed to warm to −40 °C over 1 h, and stirred at that temperature for 25 min. The reaction vessel was returned to −78 °C, and a solution of freshly distilled MeI (6.8 mL, 110 mmol) in THF (70 mL) was added. The reaction mixture was stirred for 3 h at −78 °C, quenched by the addition of brine, and extracted with ether (3 × 250 mL). The combined organic layers were dried, filtered, and evaporated. The residue was chromatographed over silica gel (elution with 1.5% EtOAc in hexane) to give **23** as a yellowish oil (4.8 g, 81%): IR (neat, cm^{-1}) 1710, 1613, 1514; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J = 8.5 Hz, 2 H), 6.84 (d, J = 8.6 Hz, 2 H), 5.32 (dd, J = 11.7, 4.6 Hz, 1 H), 4.92 (s, 1 H), 4.87 (s, 1 H), 4.52 (d, J = 12.0 Hz, 1 H), 4.01 (d, J = 12.0 Hz, 1 H), 3.79 (s, 3 H), 3.68 (dd, J = 6.5, 3.8 Hz, 2 H), 3.61 (d, J = 1.6 Hz, 1 H), 2.72 (dd, J = 8.2, 3.6 Hz, 1 H), 2.70−2.10 (m, 8 H), 1.85−1.65 (m, 2 H), 1.61−1.45 (m, 2 H), 1.22 (s, 3 H), 1.06 (s, 3 H), 1.03 (d, J = 7.2 Hz, 3 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.0, 159.2, 150.8, 148.4, 130.9, 129.2 (2C), 122.9, 113.9 (2C), 111.9, 89.8, 71.2, 63.6, 55.5, 54.9, 53.3, 45.9, 45.7, 32.2, 30.5, 30.4, 26.8, 26.3, 26.2 (3C), 26.1, 23.8, 20.5, 18.6, −5.0 (2C); FAB LRMS m/z ($M + H$)$^+$ calcd 541.37, obsd 541.38; [α] −21.2 (c 1.68, $CHCl_3$).

Dihydroxylation of 23. To a solution of **23** (1.6 g, 2.9 mmol) in acetone (800 mL) at 0 °C were added NMO·H_2O (805 mg, 5.9 mmol), OsO_4 (254 mg, 0.89 mmol), and water (1 mL). The reaction mixture was stirred for 5 days at 0 °C, quenched with 10% sodium dithionite solution (50 mL), and stirred for 2 h at 0 °C prior to dilution with water and extraction with CH_2Cl_2 (3 × 300 mL). The combined organic layers were dried, filtered, and evaporated to leave a residue that was chromatographed over silica gel (elution with 14% EtOAc in hexane) to give **24** as a pale tan oil (900 mg, 54%, 75% at 70% conversion) and unreacted **23** (470 mg, 30%); IR (neat, cm^{-1}) 3416, 1700, 1612, 1514; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J = 8.6 Hz, 2 H), 6.85 (d, J = 8.6 Hz, 2 H), 4.98 (s, 1 H), 4.91 (s, 1 H), 4.45 (d, J = 11.5 Hz, 1 H), 4.09 (d, J = 11.5 Hz, 1 H), 3.88 (s, 1 H), 3.79 (s, 3 H), 3.65−3.57 (m, 3 H), 3.35 (s, 1 H), 2.89 (s, 1 H), 2.76−2.70 (m, 1 H), 2.68−2.35 (m, 3 H), 2.14−2.01 (m, 3 H), 1.95−1.80 (m, 3 H), 1.70−1.56 (m, 3 H), 1.09 (s, 3 H), 1.04 (s, 3 H), 1.00 (d, J = 6.7 Hz, 3 H), 0.89 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.1, 159.4, 149.4, 130.2, 129.4 (2C), 113.9 (2C), 111.9, 90.6, 83.1, 71.2, 69.3, 62.6, 56.4, 55.4, 50.2, 48.4, 37.0, 34.9, 32.8, 32.0, 31.7, 30.1, 28.6, 26.2 (3C), 18.5, 17.0, 9.7, −5.1 (2C); FAB LRMS m/z ($M + H$)$^+$ calcd 575.38, obsd 575.35; [α] +175.7 (c 0.94, $CHCl_3$).

Cyclic Carbonates 25 and 26. To a solution of **24** (1.1 g, 1.9 mmol) in CH_2Cl_2 (120 mL) at −78 °C were added pyridine (1.5 mL, 19 mmol) and a solution of phosgene (1.9 M in toluene, 5.0 mL, 9.6 mmol). The reaction mixture was stirred for 15 min at −78 °C and quenched by the addition of water (100 mL). After reaching rt, the reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried, filtered, and evaporated to give **25** as a tan oil. This material was directly dissolved in methanol (100 mL), and Dowex 50X4-400 (350 mg) was added. The suspension was stirred for 2.5 h, filtered, and freed of solvent to leave a residue that was chromatographed on silica gel (elution with 35−45% EtOAc

in hexane) to give **26** as a colorless oil (890 mg, 96% for two steps).

For **25**: IR (neat, cm^{-1}) 1805, 1704, 1611, 1510; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, J = 8.7 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 5.04 (s, 1 H), 4.88 (s, 1 H), 4.46 (dd, J = 12.5, 3.5 Hz, 1 H), 4.38 (d, J = 11.3 Hz, 1 H), 4.06 (d, J = 11.3 Hz, 1 H), 3.93 (s, 1 H), 3.79 (s, 3 H), 3.66−3.57 (m, 2 H), 2.69−2.57 (m, 3 H), 2.34 (dd, J = 6.7, 1.9 Hz, 1 H), 2.26−2.00 (m, 5 H), 1.85−1.56 (m, 4 H), 1.17 (s, 6 H), 1.01 (d, J = 6.7 Hz, 3 H), 0.90 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.4, 159.4, 152.9, 148.1, 129.4 (3C), 113.8 (2C), 112.1, 93.8, 89.5, 76.8, 70.9, 62.1, 55.2, 54.5, 49.2, 48.8, 34.9, 31.7, 31.6, 31.4, 29.3, 28.5, 27.9, 25.9 (3C), 18.3, 15.9, 8.3, −5.3 (2C); FAB LRMS m/z (M^+) calcd 600.35, obsd 600.28; [α] +28.2 (c 3.2, $CHCl_3$).

For **26**: IR (neat, cm^{-1}) 3520, 1797, 1700, 1611, 1509; ^1H NMR (300 MHz, C_6D_6) δ 7.19 (d, J = 8.6 Hz, 2 H), 6.86 (d, J = 8.6 Hz, 2 H), 5.04 (s, 1 H), 4.87 (s, 1 H), 4.43 (dd, J = 9.0, 3.9 Hz, 1 H), 4.42 (d, J = 11.5 Hz, 1 H), 4.09 (d, J = 11.5 Hz, 1 H), 3.91 (s, 1 H), 3.79 (s, 3 H), 3.63 (dt, J = 6.1, 1.7 Hz, 2 H), 2.67−2.55 (m, 3 H), 2.33−1.92 (m, 5 H), 1.84−1.55 (m, 5 H), 1.16 (s, 6 H), 0.99 (d, J = 6.7 Hz, 3 H), OH not apparent; ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.6, 159.6, 153.2, 148.3, 129.9 (2C), 129.5, 114.1 (2C), 112.3, 94.1, 89.0, 77.0, 71.0, 62.2, 55.5, 54.6, 49.4, 48.9, 35.2, 31.9, 31.6, 31.4, 29.6, 28.6, 28.2, 16.1, 8.5; EI HRMS m/z (M^+) calcd 486.2617, obsd 486.2617; [α] +40.8 (c 2.7, $CHCl_3$).

Aldehyde 27. To a solution of oxalyl chloride (0.57 mL, 6.6 mmol) in CH_2Cl_2 (25 mL) at −78 °C was added a solution of DMSO (0.93 mL, 13 mmol) in CH_2Cl_2 (25 mL). The resulting solution was stirred for 10 min, and a solution of **26** (800 mg, 1.6 mmol) in CH_2Cl_2 (25 mL) was added via cannula. After 1 h at −78 °C, freshly distilled Et_3N (2.2 mL, 16 mmol) was introduced, stirring was maintained for 20 min at −78 °C, and warming to rt ensued over 1 h, prior to quenching with water and extraction with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried, filtered, and evaporated to leave a yellow residue that was chromatographed over silica gel (elution with 25−30% EtOAc in hexane) to give **27** (780 mg, 98%) as a colorless oil: IR (neat, cm^{-1}) 1801, 1721, 1705, 1612, 1509; ^1H NMR (300 MHz, $CDCl_3$) δ 9.80 (s, 1 H), 7.21 (d, J = 8.6 Hz, 2 H), 6.87 (d, J = 8.6 Hz, 2 H), 5.01 (s, 1 H), 4.94 (s, 1 H), 4.45 (dd, J = 12.3, 3.4 Hz, 1 H), 4.42 (d, J = 11.5 Hz, 1 H), 4.11 (d, J = 11.6 Hz, 1 H), 3.95 (s, 1 H), 3.81 (s, 3 H), 2.69−2.62 (m, 4 H), 2.36−2.14 (m, 6 H), 1.82−1.77 (m, 2 H), 1.65−1.55 (m, 1 H), 1.19 (s, 6 H), 1.01 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.4, 200.8, 159.7, 153.1, 147.2, 129.8 (2C), 129.5, 114.1 (2C), 112.3, 94.0, 89.2, 76.9, 71.1, 55.5, 54.6, 49.5, 48.8, 42.5, 36.3, 31.6, 29.6, 28.7, 28.3, 27.2, 16.1, 8.7; EI HRMS m/z (M^+) calcd 484.2461, obsd 484.2452; [α] +40.0 (c 0.6, $CHCl_3$).

Aldol Cyclization of 27 Promoted by Potassium Hexamethyldisilazide. A dry 25 mL round-bottomed flask was charged with **27** (24 mg, 0.050 mmol), 18-cr-6 (70 mg, 0.25 mmol), and dry THF (2 mL). The resulting solution was cooled to −78 °C, and potassium hexamethyldisilizide (0.5 M in toluene, 109 μL, 0.055 mmol) was added. The reaction mixture was warmed to rt over 3 h, stirred overnight, quenched with saturated NH_4Cl solution, and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried, filtered, and evaporated to leave a residue that was chromatographed over silica gel (elution with 10−30% EtOAc in hexane) to give **28** (9.7 mg, 40%) as a colorless oil: IR (neat, cm^{-1}) 3482, 1801, 1779, 1696, 1612; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8.6 Hz, 2 H), 6.86 (d, J = 8.6 Hz, 2 H), 5.04 (s, 1 H), 4.81 (s, 1 H), 4.71 (dd, J = 12.4, 3.7 Hz, 1 H), 4.47 (d, J = 11.8 Hz, 1 H), 4.46 (d, J = 2.7 Hz, 1 H), 4.16−4.09 (m, 2 H), 3.81 (s, 3 H), 2.71−2.43 (m, 4 H), 2.18−1.80 (m, 7 H), 1.59−1.54 (m, 1 H), 1.34−1.27 (m, 1 H), 1.24 (s, 3 H), 1.16 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.6, 158.9, 153.1, 144.8, 130.9, 128.8 (2C), 113.7 (2C), 111.6, 93.6, 84.6, 76.2, 75.5, 70.7, 58.9, 55.3, 53.9, 48.7, 37.4, 34.3, 32.2, 31.8, 28.7, 28.3, 25.6, 16.3, 9.4; EI HRMS m/z (M^+) calcd 484.2461, obsd 484.2461; [α] −12.7 (c 0.34, $CHCl_3$).

Aldol Cyclization of 27 Promoted by Sodium Hydroxide. Transannular Hydride Shift. A solution of **27** (119 mg, 0.25 mmol) in methanol (4 mL) was treated with THF (800 μL) and 0.5 N NaOH (2.5 mL, 1.2 mmol), stirred overnight, quenched with saturated NH_4Cl solution, and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried, filtered, and freed of solvent under reduced pressure. The residue was chromatographed over silica gel (elution with 15% EtOAc in hexane) to give **29** (77 mg, 68%) and **30** (14 mg, 12%), both as white solids.

For **29**: mp 155−156 °C; IR (neat, cm^{-1}) 3431, 1691, 1642, 1612; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 8.7 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 4.99 (s, 1 H), 4.86 (s, 1 H), 4.51 (d, J = 12.1 Hz, 1 H), 4.41 (d, J = 2.9 Hz, 1 H), 4.18−4.11 (m, 2 H), 3.85−3.83 (m, 1 H), 3.80 (s, 3 H), 3.14 (s, 1 H), 2.77−2.65 (m, 3 H), 2.54−2.40 (m, 2 H), 2.20−1.37 (m, 9 H), 1.08 (s, 6 H), 1.00 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.4, 159.1, 145.9, 131.5, 129.0 (2C), 113.9 (2C), 111.1, 86.1, 83.6, 75.8, 71.1, 69.4, 59.6, 56.4, 55.5, 49.4, 38.6, 34.5, 33.8, 32.4, 32.2, 29.9, 26.2, 17.3, 9.8; ES HRMS m/z $(M + Na)^+$ calcd 481.2566, obsd 481.2572; [α] −153.7 (c 0.35, $CHCl_3$).

For **30**: mp 158−160 °C; IR (neat, cm^{-1}) 3406, 1681, 1644, 1613; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 8.7 Hz, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 4.97 (s, 1 H), 4.89 (s, 1 H), 4.67 (d, J = 10.7 Hz, 1 H), 4.63 (s, 1 H), 4.43 (d, J = 10.9 Hz, 1 H), 4.39 (s, 1 H), 4.03 (dd, J = 11.1, 4.5 Hz, 1 H), 3.80 (s, 3 H), 3.75 (dd, J = 9.5, 1.8 Hz, 1 H), 3.54 (d, J = 9.1 Hz, 1 H), 3.08 (s, 1 H), 2.93−2.86 (m, 1 H), 2.77−2.60 (m, 3 H), 2.58−2.45 (m, 1 H), 2.41−2.34 (m, 1 H), 2.24−1.99 (m, 3 H), 1.88−1.82 (m, 1 H), 1.80−1.65 (m, 1 H), 1.60−1.46 (m, 1 H), 1.14 (s, 3 H), 1.05 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.2, 159.8, 146.8, 129.8 (2C), 129.1, 114.3 (2C), 110.1, 87.7, 83.0, 77.6, 73.7, 73.6, 55.5, 50.3, 48.9, 44.7, 44.2, 39.7, 34.4, 31.4, 31.0, 30.4, 25.8, 19.3, 12.5; EI HRMS m/z $(M - H)^+$ calcd 457.2590, obsd 457.2545; [α] −37.6 (c 1.54, $CHCl_3$).

Conversion of 29 to 30. To a solution of **29** (36 mg, 0.079 mmol) in dry benzene (20 mL) was added potassium *tert*-butoxide (5.0 mg, 0.044 mmol). The suspension was stirred for 30 min and quenched with pH 8 buffer (NH_4Cl/NH_4OH, saturated). The resulting biphasic suspension was stirred for 10 min, and the aqueous layer was removed. To the organic phase was added $MgSO_4$, and the suspension was stirred for 10 min, filtered, and freed of solvent under reduced pressure to give **30** (32 mg, 89%). ^1H NMR analysis of this material indicated it to be >98% pure).

Direct Conversion of 27 to 30. To a solution of **27** (786 mg, 1.6 mmol) in methanol (16.3 mL) were added THF (5.5 μL) and 0.5 N NaOH (16.3 mL, 8.1 mmol). The resulting solution was stirred overnight, quenched with saturated NH_4Cl solution, and extracted with benzene (3 × 330 mL). The combined organic layers were dried and filtered. To this benzene solution was added potassium *tert*-butoxide (330 mg, 2.9 mmol), and the suspension was stirred for 30 min, quenched with pH 8 buffer (NH_4Cl/NH_4OH, saturated), and stirred 20 min longer. The separated organic layer was dried and freed of solvent under reduced pressure to give **30** (728 mg, 99%).

The structural assignments to both **29** and **30** were confirmed by three-dimensional crystallographic analysis.[21]

DDQ Oxidation of 30. To a solution of **30** (2.4 g, 5.2 mmol) in dry ether (450 mL) were added 4 Å molecular sieves (2 g). In a separate flask, a solution of DDQ (1.3 g, 5.8 mmol) in dry ether (400 mL) was prepared, and to it were added 4 Å molecular sieves (1 g). Both suspensions were stirred separately for 1 h. While both were being vigorously stirred, the DDQ suspension was cannulated into the solution of **30**. The resulting suspension turned rapidly from yellow to green. After 6 h, saturated NH_4Cl solution was introduced, and the product was extracted into ether (3 × 300 mL). The combined organic layers were dried, filtered, and evaporated to leave a waxy

yellow solid that was recrystallized from methanol to give **31** (1.8 g, 78%) as white rods: mp 171−174 °C; IR (neat, cm^{-1}) 3486, 1682, 1644, 1614; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 8.6 Hz, 2 H), 6.90 (d, J = 8.6 Hz, 2 H), 5.75 (s, 1 H), 5.02 (s, 1 H), 4.70 (s, 1 H), 4.39 (dd, J = 9.6, 1.9 Hz, 1 H), 4.20−4.16 (m, 2 H), 3.85 (d, J = 9.6 Hz, 1 H), 3.80 (s, 3 H), 3.05−2.95 (m, 2 H), 2.90−2.50 (m, 4 H), 2.45−2.35 (m, 1 H), 2.30−2.22 (m, 1 H), 2.20−2.05 (m, 2 H), 2.00−1.90 (m, 1 H), 1.80−1.70 (m, 1 H), 1.65−1.50 (m, 1 H), 1.17 (s, 3 H), 1.15 (s, 3 H), 1.00 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.5, 160.9, 146.3, 128.8, 128.6 (2C), 114.1 (2C), 110.2, 100.3, 87.3, 84.9, 83.1, 72.2, 55.5, 48.7, 47.8, 44.9, 43.5, 40.2, 34.4, 31.6, 30.9, 29.3, 25.5, 19.9, 12.8; EI HRMS m/z (M^+) calcd 456.2512, obsd 456.2515; [α] −8.2 (*c* 2.4, $CHCl_3$).

BOM Protection of 31. To a solution of **31** (65 mg, 0.14 mmol) in DMPU (2.5 mL) were added 4 Å molecular sieves (100 mg), Hunig's base (490 μL, 2.8 mmol), and BOMCl (221 μL, 1.4 mmol). The flask was shielded from light with aluminum foil, and tetra-*n*-butylammonium iodide (5.0 mg, 0.014 mmol) was added. The reaction mixture was warmed to 70 °C, stirred for 16 h, treated with additional BOMCl (100 μL, 0.64 mmol), and stirred at 70 °C for an additional 24 h. The flask was cooled to rt, and methanol was added. The resulting suspension was stirred for 1 h, water and saturated NH_4Cl solution were added, the product was extracted into EtOAc (3 × 30 mL), and the combined organic layers were dried, filtered, and evaporated. The remaining DMPU was removed under high vacuum and the yellow residue was chromatographed on silica gel (elution with 6−10% EtOAc in hexane) to give **32** as a pale yellow oil (30 mg, 43%) and **33** as a pale yellow glass (15 mg, 18%) alongside unreacted **31** (10 mg, 15%).

For **32**: IR (neat, cm^{-1}) 3500, 1674, 1644, 1614; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41−7.30 (m, 7 H), 6.91 (d, J = 8.4 Hz, 2 H), 5.73 (s, 1 H) 5.03 (d, J = 6.8 Hz, 1 H), 5.02 (s, 1 H), 4.95 (d, J = 6.8 Hz, 1 H), 4.76 (d, J = 11.8 Hz, 1 H), 4.71 (s, 1 H), 4.63 (d, J = 11.9 Hz, 1 H), 4.32 (d, J = 8.8 Hz, 1 H), 4.04 (dd, J = 11.3, 4.2 Hz, 1 H), 3.84 (s, 3 H), 3.71 (d, J = 8.8 Hz, 1 H), 3.13 (s, 1 H), 2.97 (dd, J = 15.3, 1.9 Hz, 1 H), 2.86 (dd, J = 15.4, 12.6 Hz, 1 H), 2.77 (d, J = 11.4 Hz, 1 H), 2.71 (d, J = 12.1 Hz, 1 H), 2.65−2.59 (m, 1 H), 2.49−2.46 (m, 1 H), 2.35−2.26 (m, 2 H), 2.17−2.10 (m, 2 H), 1.74−1.63 (m, 2 H), 1.24 (s, 3 H), 1.20 (s, 3 H), 1.14 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.5, 160.5, 146.4, 137.6, 129.2, 128.6 (2C), 128.5, 128.3 (2C), 127.9 (2C), 113.7 (2C), 109.7, 100.9, 93.7, 87.6, 82.8, 81.7, 79.1, 70.0, 55.3, 48.8, 48.1, 44.8, 44.3, 41.3, 34.4, 30.8, 29.3, 28.0, 25.4, 19.4, 12.9; ES HRMS m/z ($M + Na)^+$ calcd 599.2985, obsd 599.2991; [α] −27.6 (*c* 1.21, $CHCl_3$).

For **33**: IR (neat, cm^{-1}) 1688, 1644, 1614, 1518; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.27 (m, 12 H), 6.86 (d, J = 8.7 Hz, 2 H), 5.63 (s, 1 H), 4.97 (d, J = 6.8 Hz, 1 H), 5.90 (d, J = 6.8 Hz, 1 H), 4.87 (s, 1 H), 4.83 (d, J = 7.6 Hz, 1 H), 4.71 (d, J = 11.8 Hz, 1 H), 4.64 (d, J = 7.6 Hz, 1 H), 4.55 (d, J = 11.9 Hz, 1 H), 4.49 (d, J = 3.1 Hz, 2 H), 4.42 (s, 1 H), 4.22 (dd, J = 9.0, 1.1 Hz, 1 H), 3.96 (dd, J = 11.1, 4.1 Hz, 1 H), 3.89 (d, J = 9.0 Hz, 1 H), 3.80 (s, 3 H), 2.90 (d, J = 13.1 Hz, 1 H), 2.70−2.43 (m, 4 H), 2.42−2.23 (m, 4 H), 2.06−1.98 (m, 1 H), 1.74−1.57 (m, 2 H), 1.29 (s, 3 H), 1.17 (s, 3 H), 1.08 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.8, 160.5, 146.5, 137.7, 129.6, 128.7 (2C), 128.4 (2C), 128.3 (2C), 127.9 (2C), 127.8 (2C), 127.7, 127.6, 113.7 (2C), 109.5, 100.8, 93.8, 92.1, 90.4, 82.6, 81.9, 79.2, 70.6, 70.0, 55.3, 50.1, 48.1, 46.5, 44.5, 41.5, 34.3, 29.5, 29.3, 29.0, 28.1, 26.3, 20.0, 13.0; ES HRMS m/z ($M + Na)^+$ calcd 719.3560, obsd 719.3497; [α] −11.6 (*c* 1.35, $CHCl_3$).

α-Oxygenation of 32. To a solution of **32** (29 mg, 0.050 mmol) and 18-cr-6 (135 mg, 0.50 mmol) in dry THF (20 mL) at −78 °C was added a solution of potassium hexamethyldisilazide (0.42 M in toluene, 600 μL, 0.25 mmol). Dry molecular oxygen was bubbled through the solution for 10 min, and the flask was allowed to warm to 0 °C over 5 min. Molecular oxygen was again introduced for 5 min, at which point the reaction was complete by TLC analysis. The hydroperoxide was reduced by the addition of triphenylphosphine (40 mg) and vigorous stirring for 10 min prior to quenching with half-saturated brine and extraction with EtOAc (3 × 30 mL). The combined organic layers were dried, filtered, and freed of solvent under reduced pressure. The residue was chromatographed on silica gel (elution with 15−25% EtOAc in hexane) to give **34** (22 mg, 74%) as a colorless oil: IR (neat, cm^{-1}) 3426, 1673, 1615, 1589; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−7.30 (m, 7 H), 6.86 (d, J = 8.7 Hz, 2 H), 5.69 (s, 1 H), 5.26 (s, 1 H), 4.96 (d, J = 6.8 Hz, 1 H), 4.88 (d, J = 6.8 Hz, 1 H), 4.85 (s, 1 H), 4.70 (d, J = 11.9 Hz, 1 H), 4.59 (d, J = 11.9 Hz, 1 H), 4.55 (dd, J = 11.5, 2.2 Hz, 1 H), 4.25 (dd, J = 8.8, 2.0 Hz, 1 H), 3.97 (dd, J = 10.7, 4.4 Hz, 1 H), 3.80 (s, 3 H), 3.62 (d, J = 8.8 Hz, 1 H), 3.08 (ddd, J = 14.6, 10.3, 3.6 Hz, 1 H), 3.03 (s, 1 H), 2.69 (d, J = 11.8 Hz, 1 H), 2.66 (d, J = 11.5 Hz, 1 H), 2.61 (d, J = 2.2 Hz, 1 H), 2.54−2.46 (m, 1 H), 2.45−2.42 (m, 1 H), 2.33−2.30 (m, 1 H), 2.17−1.99 (m, 2 H), 1.72−1.66 (m, 1 H), 1.65−1.48 (m, 1 H), 1.20 (s, 3 H), 1.19 (s, 3 H), 1.16 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.1, 171.3, 160.7, 143.8, 137.8, 128.9 (2C), 128.8 (2C), 128.6, 128.1 (2C), 128.0, 114.0 (2C), 111.9, 101.0, 93.8, 87.4, 82.1, 81.8, 78.8, 70.3, 55.6, 49.4, 49.3, 47.5, 45.3, 35.1, 29.5, 29.1, 28.8, 24.8, 19.9, 14.5; ES HRMS m/z ($M + Na)^+$ calcd 615.2935, obsd 615.2912; [α] −30.2 (*c* 0.33, $CHCl_3$).

B-Ring Fragmentation of 34. A solution of **34** (3.0 mg, 5.0 μmol) in dry benzene (1 mL) was treated with aluminum tri-*tert*-butoxide (5.8 mg, 0.024 mmol), stirred at reflux for 50 min, and quenched with saturated Rochelle's salt solution. The product was extracted into EtOAc (3 × 10 mL), and the combined organic layers were dried, filtered, and freed of solvent under reduced pressure. The residue was chromatographed on silica gel (elution with 6−12% EtOAc in hexane) to give **36** as a cloudy oil (2.4 mg, 80%): IR (neat, cm^{-1}) 3446, 1732, 1615, 1517; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60−7.27 (m, 7 H), 6.85 (d, J = 8.8 Hz, 2 H), 5.50 (s, 1 H), 4.98 (s, 1 H), 4.82 (d, J = 6.7 Hz, 1 H), 4.77 (d, J = 6.7 Hz, 1 H), 4.63 (d, J = 11.6 Hz, 1 H), 4.53 (s, 1 H), 4.52 (d, J = 11.6 Hz, 1 H), 4.46 (d, J = 7.0 Hz, 1 H), 4.25 (dd, J = 12.7, 3.1 Hz, 1 H), 4.21 (dd, J = 12.7, 3.1 Hz, 1 H), 4.08 (d, J = 6.7 Hz, 1 H), 3.80 (s, 3 H), 3.60 (dd, J = 7.3, 3.3 Hz, 1 H), 3.34 (s, 1 H), 3.06 (t, J = 3.1 Hz, 1 H), 2.50−1.85 (m, 8 H), 1.67−1.55 (m, 1 H), 1.34 (s, 3 H), 1.08 (s, 3 H), 1.03 (s, 3 H); ES HRMS m/z ($M + Na)^+$ calcd 615.2928, obsd 615.2975.

α-Oxygenation of 31. Through a solution of **31** (250 mg, 0.55 mmol) and 18-crown-6 (1.2 g, 4.5 mmol) in dry THF (60 mL) at −78 °C was bubbled dry molecular oxygen for 3 min. With continued bubbling, a solution of potassium hexamethyldisilazide (0.50 M in toluene, 6.6 mL, 3.3 mmol) was added. The reaction mixture was stirred with continuous bubbling for 10 min at −78 °C. The bubbling was arrested and under an atmosphere of O_2 the solution was warmed to 0 °C and stirred for 1 h. Dimethyl sulfide (1 mL) was introduced, and the solution was stirred at rt for 1 h, quenched with water, and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried, filtered, and evaporated under reduced pressure. The residue was chromatographed on silica gel (elution with 15−35% EtOAc in hexane) to give **37** (230 mg, 89%) as clear needles: mp 91−93 °C; IR (neat, cm^{-1}) 3422, 1682, 1652, 1615; ^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), 5.29 (s, 1 H), 4.86 (s, 1 H), 4.55 (d, J = 11.2, 2.5 Hz, 1 H), 4.37 (dd, J = 9.7, 2.3 Hz, 1 H), 4.17−4.12 (m, 1 H), 3.99 (s, 1 H), 3.82 (d, J = 9.7 Hz, 1 H), 3.80 (s, 3 H), 3.15 (ddd, J = 11.6, 10.8, 4.2 Hz, 1 H), 2.98 (s, 1 H), 2.84−2.80 (m, 2 H), 2.69 (d, J = 11.2 Hz, 1 H), 2.62−2.48 (m, 1 H), 2.43−2.37 (m, 1 H), 2.11−1.97 (m, 3 H), 1.69−1.52 (m, 2 H), 1.18 (s, 3 H), 1.16 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.3, 160.9, 143.5, 128.9, 128.5 (2C), 114.1 (2C), 112.4, 101.1, 86.9, 83.9, 82.8, 78.7, 72.4, 55.5, 49.1, 48.1, 47.0, 43.8, 35.6, 32.9, 29.4, 29.0, 24.6, 20.3, 13.9; ES HRMS m/z ($M + Na)^+$ calcd 495.2359, obsd 495.2352; [α] −10.6 (*c* 0.75, $CHCl_3$).

Dibenzoylation of 37. To a solution of **37** (90 mg, 0.19 mmol) and DMAP (2.0 mg, 0.018 mmol) in dry pyridine (4 mL) was added benzoyl chloride (200 μL, 1.7 mmol). The reaction mixture was stirred for 12 h, diluted with water and CH_2Cl_2, and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried, filtered, and evaporated under reduced pressure. The residue was chromatographed on silica gel (elution with 8% EtOAc in hexane) to give **11** (106 mg, 82%) as clear needles: mp 135−137 °C; IR (neat, cm^{-1}) 3486, 1713, 1614, 1518; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 7.2 Hz, 2 H), 7.98 (d, J = 7.2 Hz, 2 H), 7.62−7.47 (m, 2 H), 7.46−7.42 (m, 4 H), 6.77 (d, J = 8.7 Hz, 2 H), 6.69 (d, J = 8.7 Hz, 2 H), 5.99 (d, J = 11.9 Hz, 1 H), 5.52 (dd, J = 10.8, 4.4 Hz, 1 H), 5.07 (s, 1 H), 5.05 (s, 1 H), 4.66 (s, 1 H), 4.26 (dd, J = 9.3, 2.0 Hz, 1 H), 3.91 (d, J = 9.3 Hz, 1 H), 3.74 (s, 3 H), 3.19−3.12 (m, 1 H), 3.11 (d, J = 11.9 Hz, 1 H), 2.80 (s, 1 H), 2.77 (d, J = 11.7 Hz, 1 H), 2.67−2.59 (m, 1 H), 2.45−2.43 (m, 1 H), 2.28−2.12 (m, 3 H), 1.81−1.61 (m, 2 H), 1.50 (s, 3 H), 1.22 (s, 3 H), 1.14 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 206.9, 165.4, 164.9, 160.7, 141.5, 133.1, 133.0 (2C), 130.7 (2C), 130.0 (2C), 129.9, 129.8 (2C), 129.4, 128.9, 128.5 (2C), 128.4 (2C), 113.5, 111.5, 101.1, 86.9, 82.3, 82.1, 78.7, 73.7, 54.5, 49.0, 47.4, 47.0, 45.0, 35.0, 29.4, 29.2, 28.8, 24.4, 20.1, 14.8; ES HRMS m/z $(M + Na)^+$ calcd 703.2883, obsd 703.2878; [α] +57.7 (c 0.98, $CHCl_3$).

α-Ketol Rearrangement of 11. To a solution of **11** (2.0 mg, 0.0029 mmol) in dry benzene (5 mL) was added aluminum tri-*tert*-butoxide (10 mg, 0.040 mmol). The resulting solution was stirred at reflux for 2 h, treated with a saturated solution of Rochelle's salt, stirred for an additional 20 min, and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried, filtered, and evaporated under reduced pressure. The residue was chromatographed on silica gel (elution with 8% EtOAc in hexane) to give **13** as a cloudy oil (2.0 mg, quant). Proton NMR analysis indicated the product to be contaminated with a copolar impurity (~5% by integration) making the $[\alpha]_D$ value for the mixture meaningless and it was not measured. For **13**: IR (film, cm^{-1}) 3480, 1714, 1651, 1616; ^1H NMR (500 MHz, $CDCl_3$) δ 8.00−7.96 (m, 4 H), 7.55 (t, J = 7.4 Hz, 1 H), 7.50 (t, J = 7.5 Hz, 1 H), 7.49 (t, J = 7.4 Hz, 2 H), 7.34 (t, J = 8.1 Hz, 1 H), 6.93 (d, J = 8.7 Hz, 2 H), 6.65 (d, J = 8.7 Hz, 2 H), 5.76 (d, J = 9.4 Hz, 1 H), 5.51 (dd, J = 8.5, 4.6 Hz, 1 H), 5.34 (s, 1 H), 5.08 (s, 1 H), 4.71 (s, 1 H), 4.43 (d, J = 8.3 Hz, 1 H), 3.75 (d, J = 5.5 Hz, 1 H), 3.74 (d, J = 5.4 Hz, 1 H), 3.16 (s, 1 H), 2.84 (d, J = 9.4 Hz, 1 H), 2.76 (d, J = 11.1 Hz, 1 H), 2.73−2.65 (m, 2 H), 2.48−2.35 (m, 2 H), 2.29−2.20 (m, 1 H), 2.04−1.98 (m, 1 H), 1.95−1.88 (m, 1 H), 1.85−1.75 (m, 1 H), 1.46 (s, 3 H), 1.44 (s, 3 H), 1.39 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.8, 167.4, 165.0, 160.4, 143.0, 133.4, 133.2, 130.4, 130.1 (2C), 129.9 (2C), 128.9 (2C), 128.6 (2C), 128.3 (2C), 128.1 (2C), 127.7, 113.6, 113.1, 102.2, 84.6, 82.7, 77.9, 73.4, 72.9, 55.4, 47.4, 47.3, 46.1, 42.7, 34.2, 30.2, 28.4, 25.5, 24.7, 23.2, 16.9; ES HRMS m/z $(M + Na)^+$ calcd 703.2883, obsd 703.2882.

Conversion of 11 to 38. To a solution of **11** (42 mg, 0.061 mmol) in CH_2Cl_2 (3 mL) at −78 °C was added a solution of ethylaluminum dichloride (1 M in hexane, 490 μL, 0.49 mmol). The resulting solution was allowed to warm to 0 °C over 3 h, treated with methanol (2 mL), diluted with saturated Rochelle's salt solution, and extracted with CH_2Cl_2 (3 × 30 mL). The combine organic layers were dried, filtered, and freed of solvent. The residue was chromatographed on silica gel (elution with 8% EtOAc in hexane) to give **38** (30.3 mg, 88%) as a white solid: mp 128−132 °C; IR (neat, cm^{-1}) 3470, 1716, 1602, 1584; ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 8.3 Hz, 2 H), 7.91 (dd, J = 8.2, 1.3 Hz, 2 H), 7.64 (t, J = 7.4 Hz, 1 H), 7.60 (t, J = 7.5 Hz, 1 H), 7.51−7.45 (m, 4 H), 5.61 (d, J = 11.7 Hz, 1 H), 5.58 (dd, J = 11.2, 4.3 Hz, 1 H), 5.18 (s, 1 H), 4.74 (d, J = 5.8 Hz, 1 H), 4.64 (s, 1 H), 3.54 (t, J = 4.3 Hz, 1 H), 3.95 (d, J = 4.7 Hz, 1 H), 3.74 (d, J = 5.6 Hz, 1 H), 3.60 (d, J = 11.7 Hz, 1 H), 3.52 (s, 1 H), 2.86−2.80 (m, 1 H), 2.76−2.70 (m, 1 H), 2.59−2.53 (m, 2 H), 2.42−2.32 (m, 2 H), 2.23−2.16 (m, 1 H), 1.91−1.87 (m, 1 H), 1.77−1.72 (m, 1 H), 1.56 (s, 3 H), 1.04 (s, 3 H), 0.94 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 215.3, 169.8, 165.7, 141.8, 134.3, 133.9, 130.6 (2C), 130.1 (2C), 129.6, 129.2, 129.0 (2C), 128.9 (2C), 113.5, 81.8, 80.2, 78.1, 71.9, 60.8, 54.9, 50.1, 47.1, 35.2, 32.0, 31.7, 28.9, 27.8, 24.2, 17.5, 14.6; ES HRMS m/z $(M+Na)^+$ calcd 585.2464, obsd 585.2472; [α] −122.0 (c 0.75, $CHCl_3$).

Hydride Reduction of 39. To a solution of **39** (52 mg, 0.087 mmol) in ether (5 mL) was added a solution of lithium aluminum hydride (1 M in ether, 437 μL, 0.44 mmol) in three equal portions at 5 min intervals. The reaction mixture was stirred for 5 min, carefully treated with methanol (1 mL), diluted with saturated Rochelle's salt solution, and extracted with ether (3 × 15 mL). The combined organic layers were dried, filtered, and evaporated under reduced pressure. The residue was chromatographed on silica gel (elution with 8−12% EtOAc in hexane) to give **40** (47 mg, 90%) as white needles: mp 148−149 °C; IR (neat, cm^{-1}) 3519, 1700, 1653, 1612; ^1H NMR (500 MHz, C_6D_6) δ 7.32 (d, J = 8.1 Hz, 2 H), 6.90 (d, J = 8.5 Hz, 2 H), 5.13 (s, 1 H), 4.97 (s, 1 H), 4.85 (s, 1 H), 4.60 (d, J = 10.1 Hz, 1 H), 4.50 (d, J = 10.2 Hz, 1 H), 4.07 (s, 1 H), 3.89 (dd, J = 10.9, 5.0 Hz, 1 H), 3.74 (d, J = 16.9 Hz, 1 H), 3.69 (s, 1 H), 3.41 (s, 3 H), 3.27 (s, 1 H), 3.11 (d, J = 12.2 Hz, 1 H), 2.76 (s, 1 H), 2.50−2.10 (m, 5 H), 2.00−1.62 (m, 6 H), 1.58 (s, 3 H), 1.47 (s, 3 H), 1.28 (s, 3 H), 1.06 (s, 9 H), 0.16 (s, 3 H), 0.15 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 159.6, 149.2, 145.6, 130.5 (2C), 114.0 (2C), 108.4, 87.2, 85.9, 78.0, 77.5, 73.6, 72.0, 54.8, 54.5, 47.5, 46.4, 40.2, 34.6, 33.6, 32.6, 32.1, 25.9, 25.8 (3C), 25.4, 19.4, 11.1, 1.1, −3.1, −4.8; ES HRMS m/z $(M + Na)^+$ calcd 597.3587, obsd 597.3592; [α] −68.6 (c 1.45, $CHCl_3$).

DDQ Oxidation of 40. To a solution of **40** (60 mg, 0.10 mmol) in dry ether (55 mL) were added 4 Å molecular sieves (~100 mg). In a separate flask, a solution of DDQ (119 mg, 0.52 mmol) in dry ether (55 mL) was prepared, and to it were added 4 Å molecular sieves (100 mg). Both suspensions were stirred separately for 1 h. While both were stirring vigorously, the DDQ suspension was cannulated into the solution of **40**. The resulting suspension, which turned rapidly from yellow to green, was stirred for 8 h, quenched with saturated NH_4Cl solution, and extracted with ether (3 × 100 mL). The combined organic layers were dried, filtered, and evaporated. The waxy yellow solid residue was recrystallized from methanol to give **41** as a glass (59 mg, 99%): IR (neat, cm^{-1}) 3562, 1722, 1613, 1511; ^1H NMR (500 MHz, C_6D_6) δ 7.48 (d, J = 8.4 Hz, 2 H), 6.78 (d, J = 8.7 Hz, 2 H), 6.12 (s, 1 H), 5.04 (s, 1 H), 4.87 (s, 1 H), 4.34 (d, J = 5.8 Hz, 1 H), 4.29 (t, J = 5.7 Hz, 1 H), 3.95 (s, 1 H), 3.57 (dd, J = 10.9, 5.0 Hz, 1 H), 3.34 (s, 3 H), 3.10 (dd, J = 16.5, 3.0 Hz, 1 H), 2.93 (ddd, J = 12.5, 5.7, 3.6 Hz, 1 H), 2.62 (s, 1 H), 2.26 (d, J = 9.9 Hz, 1 H), 2.22−2.01 (m, 4 H), 1.80−1.70 (m, 2 H), 1.59−1.55 (m, 1 H), 1.48−1.38 (m, 3 H), 1.37 (s, 3 H), 1.35 (s, 3 H), 1.07 (s, 3 H), 0.66 (s, 9 H), −0.10 (s, 3 H), −0.22 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 159.8, 148.8, 133.7, 127.0 (2C), 113.7 (2C), 108.7, 98.9, 86.6, 81.4, 80.6, 77.4, 74.0, 56.1, 54.5, 46.4, 45.7, 39.8, 34.5, 33.2, 32.9, 32.3, 25.9, 25.5 (3C), 23.0, 18.5, 17.5, 11.4, −3.9, −5.4; ES HRMS m/z $(M + H)^+$ calcd 573.3606, obsd 573.3587; [α] +117.8 (c 0.37, $CHCl_3$).

Swern Oxidation of 41. To a solution of oxalyl chloride (20 μL, 0.23 mmol) in CH_2Cl_2 (2.5 mL) at −78 °C was added a solution of DMSO (32 μL, 0.45 mmol) in CH_2Cl_2 (2.5 mL). The reaction mixture was stirred for 20 min, a solution of **41** (26 mg, 0.045 mmol) in CH_2Cl_2 (5 mL) was introduced by cannula, and stirring was maintained for 1 h at −78 °C prior to slow warming to −40 °C over 30 min and recooling to −78 °C. Freshly distilled Et_3N (94 μL, 0.68 mmol) was added, and stirring was maintained at −78 °C for 30 min followed by warming to rt over 1 h. Thirty minutes later, water was added and the product was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried, filtered, and evaporated under reduced pressure. The yellow residue was chromatographed on silica gel (elution with 2% EtOAc in hexane) to

give **42** as a white solid (18 mg, 70%, 90% at 77% conversion) and unreacted **41**(6 mg, 23%).

For **42**: mp 86−88 °C; IR (neat, cm^{-1}) 3436, 1684, 1508; ^1H NMR (500 MHz, C_6D_6) δ 7.45 (d, J = 8.6 Hz, 2 H), 6.79 (d, J = 8.6 Hz, 2 H), 6.06 (s, 1 H), 5.09 (s, 1 H), 5.05 (s, 1 H), 4.83 (s, 1 H), 4.37 (d, J = 5.6 Hz, 1 H), 4.33 (t, J = 5.7 Hz, 1 H), 4.04 (d, J = 15.4 Hz, 1 H), 3.51 (dd, J = 10.9, 4.9 Hz, 1 H), 3.35 (s, 3 H), 3.09 (dd, J = 15.4, 11.0 Hz, 1 H), 3.05−3.00 (m, 1 H), 2.76 (d, J = 11.7 Hz, 1 H), 2.17−2.11 (m, 2 H), 2.08−1.99 (m, 1 H), 1.90−1.87 (m, 1 H), 1.63−1.58 (m, 1 H), 1.55−1.40 (m, 3 H), 1.39 (s, 3 H), 1.23 (s, 3 H), 1.02 (s, 3 H), 0.66 (s, 9 H), −0.11 (s, 3 H), −0.23 (s, 3 H);^{13}C NMR (75 MHz, C_6D_6) δ 212.2, 159.9, 144.6, 133.2, 126.9 (2C), 113.8 (2C), 109.8, 99.2, 89.5, 81.8, 80.5, 74.1, 56.7, 54.6, 48.2, 45.9, 40.5, 39.4, 36.7, 31.4 (2C), 25.5, 25.4 (3C), 24.5, 19.2, 17.5, 10.5, −3.9, −5.5; ES HRMS m/z $(M + Na)^+$ calcd 593.3269, obsd 593.3234; [α] +20.8 (c 0.43, $CHCl_3$).

If the reaction mixture is allowed stand at rt for longer than 30 min before the water quench, **41** will be completely consumed.

For **i**: colorless solid; mp 160−162 °C; IR (neat, cm^{-1}) 3572, 1717, 1510; ^1H NMR (500 MHz, C_6H_6) δ 9.56 (s, 1 H), 7.48 (d, J = 8.7 Hz, 2 H), 6.80 (d, J = 8.7 Hz, 2 H), 6.10 (s, 1 H), 4.84 (s, 1 H), 4.82 (s, 1 H), 4.35 (d, J = 5.6 Hz, 1 H), 4.13 (t, J = 5.3 Hz, 1 H), 3.36 (dd, J = 10.7, 5.0 Hz, 1 H), 3.34 (s, 3 H), 2.40 (dd, J = 16.3, 3.1 Hz, 1 H), 2.36 (ddd, J = 10.7, 6.4, 2.6 Hz, 1 H), 2.15−2.06 (m, 3 H), 1.97−1.92 (m, 2 H), 1.78−1.72 (m, 1 H), 1.60−1.57 (m, 1 H), 1.54−1.48 (m, 1 H), 1.43 (s, 3 H), 1.30−1.26 (m, 1 H), 1.21−1.17 (m, 1 H), 1.13 (s, 3 H), 0.93 (s, 3 H), 0.69 (s, 9 H), −0.12 (s, 3 H), −0.31 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 200.4, 160.2, 148.2, 134.1, 127.4 (2C), 114.1 (2C), 108.6, 99.0, 81.1, 80.9, 75.8, 59.6, 57.1, 54.9, 47.9, 46.3, 43.7, 34.7, 32.2, 30.0, 27.8, 27.6, 25.9 (3C), 22.3, 20.5, 17.9, 12.5, −3.9, −5.0; ES HRMS m/z $(M + Na)^+$ m/z calcd 571.3449, obsd 571.3466; [α] +22.0 (c 0.63, $CHCl_3$).

α-Ketol Rearrangement/Oxidation of 42. Through a solution of 18-cr-6 (160 mg, 0.60 mmol) in dry THF (2.5 mL) at 0 °C was bubbled dry molecular oxygen for 1 min. With continued bubbling, a solution of potassium hexamethyldisilazide (0.45 M in toluene, 500 μL, 0.23 mmol) was added followed by a solution **42** (13 mg, 0.023 mmol) in dry THF (2.5 mL). The reaction mixture was stirred with continuous bubbling for 30 min at 0 °C. Dimethyl sulfide (300 μL) was introduced, and the solution was stirred at 0 °C for 5 min at rt for an additional 5 min, quenched with water, and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried, filtered, and evaporated. The residue was chromatographed on silica gel (elution with 2−3% EtOAc in hexane) to give **43** as an oily solid (10.2 mg, 76%); IR (neat, cm^{-1}) 3460, 1679, 1659, 1612; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 8.7 Hz, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 6.22 (s, 1 H), 6.10 (d, J = 6.3 Hz, 1 H), 5.85 (s, 1 H) 4.86 (s, 1 H), 4.70 (s, 1 H), 4.41 (dd, J = 5.7, 3.0 Hz, 1 H), 4.36 (d, J = 5.7 Hz, 1 H), 3.83 (s, 3 H), 3.23 (dd, J = 10.9, 4.9 Hz, 1 H), 3.13−3.11 (m, 2 H), 3.03 (dd, J = 15.2, 3.4 Hz, 1 H), 2.72 (s, 1 H), 2.24−2.20 (m, 1 H), 1.83−1.76 (m, 2 H), 1.72−1.69 (m, 1 H), 1.56 (s, 3 H), 1.53−1.46 (m, 1 H), 1.21 (s, 3 H), 0.91 (s, 3 H), 0.57 (s 9 H), −0.05 (s, 3 H), −0.30 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 159.7, 149.2, 147.1, 132.9, 127.0 (2C), 118.5, 114.0 (2C), 108.1, 99.0, 81.0, 79.6, 78.8, 74.8, 55.5, 52.6, 46.4, 42.8, 40.8, 34.9, 33.9, 31.9, 28.7, 25.6 (3C), 20.7, 17.7, 11.6, −3.6, −5.0; ES HRMS m/z $(M + Na)^+$ calcd 607.3062, obsd 607.3055; [α] +12.7 (c 0.77, $CHCl_3$).

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Supporting Information Available: Selected ^1H NMR data for **36** and HMBC correlations for **11**, **13**, and **38**. This material is available free of charge via the Internet at http://pubs.acs.org.

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