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Diosphenol-Based Approach to the A-Ring Functionalization of Advanced Taxol Precursors

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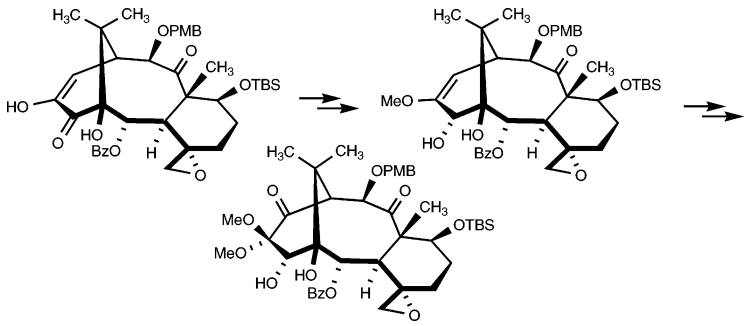

Several different approaches to the A-ring functionalization of an advanced, highly functionalized diosphenol precursor to Taxol are described. The first phase of the undertaking consists of an assessment of those reagents conducive to reaction at the enolic oxygen (silylation, methylation, allylation, and acylation). Transformations involving an alternative attack at the enol carbon center (bromination, selenation) have also been defined. Sodium borohydride reduction operates from the β-face of C-14 as long as the C-1 hydroxyl is not protected so as to offer steric exclusion. Complications associated with various aspects of these methodological undertakings are addressed. The most advanced oxygenation achievements were realized by way of a noteworthy sequence involving epoxidation of the *O*-methyl ether, methanolysis under mildly acidic conditions, and regioselective oxidation of diol **38** to give **39**.

Introduction

A direct consequence of the continuing role of Taxol (**5**) as an important resource in the battle against cancer is the inspiration for the development of improved new synthetic routes to the parent drug as well as to structural analogues thereof. This high level of interest has spilled over to our laboratories where the goal for several years has been to develop an approach based on the readily available (+)-camphor derivative **1** that is more abbreviated than any of the six prior completed syntheses of this powerful cytotoxic agent.[1−6] To the present time, **1** has been successfully transformed in 15 steps and 5.7% overall yield to **2**,[7] to which an oxetane D-ring has been fused as in **3** with an outlay of only six more transformations (Scheme 1).[8] Already quite apparent at this point is the essentially complete overlay of functionality and stereocenters in **3** and the ultimate target **5**.

The remaining challenge associated with the overall plan involves the proper modification of ring A. An assortment of interim objectives must be met. The conversion of **2** to **5** requires, inter alia, reductive deoxygenation at C-14, α-hydroxylation at C-13, and the introduction of a methyl group and bridgehead double bond involving C-12. One possible tactic

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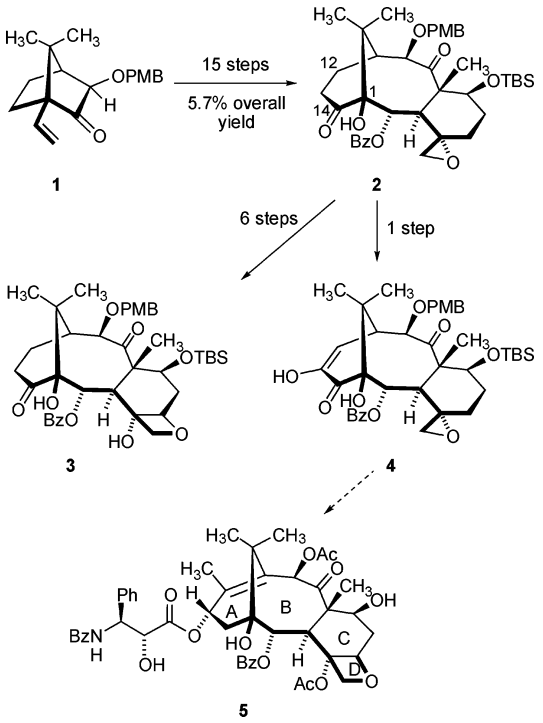
SCHEME 1

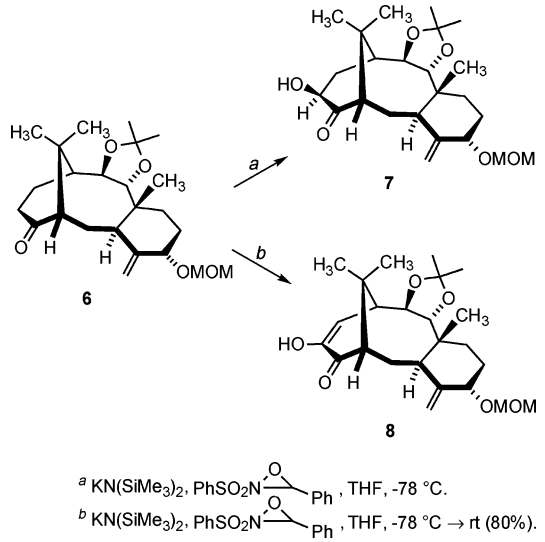


that attracted our attention was the possible intermediacy of diosphenol **4**, which we anticipated would be available in a single maneuver via the direct oxygenation of **2**. Indeed, the steric shielding in existence about the C11−C15 sector of **2** proved not to be an insurmountable problem. As a result, it is possible to describe herein the unique reactivity patterns made evident in our study of this advanced intermediate.

Results and Discussion

Literature precedent with regard to diosphenols is, for our purposes, rich yet somewhat lacking. A significant number of their syntheses have made their appearance, but many begin from the corresponding α-hydroxy ketone, α,*β*-epoxy ketone, α,α-dibromo ketone, or other functionalized substrate not applicable here.[9] Presently, it was mandatory for reasons of reaction economy that **2** be the immediate precursor of **4**. As part of our earlier quest of taxusin,[10] it was determined that the

SCHEME 2



deprotonation of **6** with an equivalent of potassium hexamethyldisilazide in the presence of the Davis oxaziridine[11] formed α-hydroxy ketone **7** when the reaction mixture was quenched at −78 °C (Scheme 2). If warming of the reaction mixture to room temperature occurred prior to the protonation, **7** advanced through a process of autoxidation[12] to generate the diosphenol **8**.

In the taxusin study, the conversion to **8** proved to be a high-yielding and reliable oxidative process (80%), the attractive features of which did not carry over to the comparable generation of **4**. It was not until many sets of reaction conditions were tested[13] that an acceptable yield of **4** was realized. The continued use of potassium hexamethyldisilazide and the oxaziridine or oxygen gave rise most often to yields of **4** in the 30−35% range and was quite variable and unreliable in its outcome. Attempts to effect the direct oxidation of **2** with selenium dioxide[14] in refluxing dioxane or *tert*-butyl alcohol were met with the formation of complex mixtures and were clearly a move in the wrong direction. It is likely that under such reaction conditions the bridgehead hydroxyl is not merely a standby spectator. Ultimately, it was determined that the exposure of **2** dissolved in dry THF to 2 equiv of potassium

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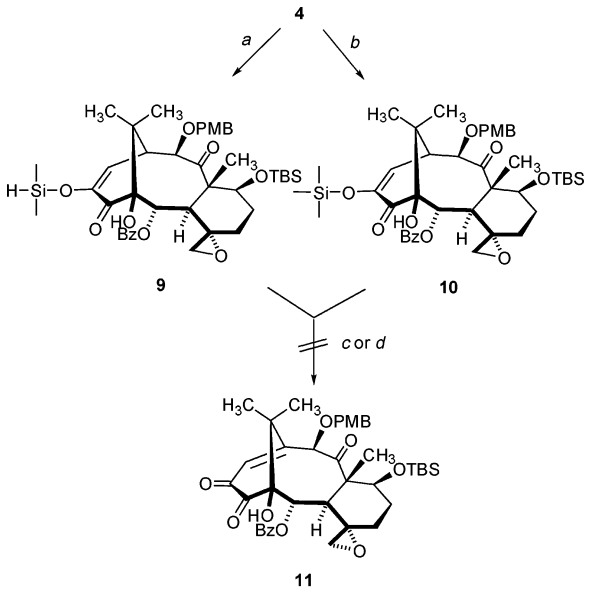
SCHEME 3



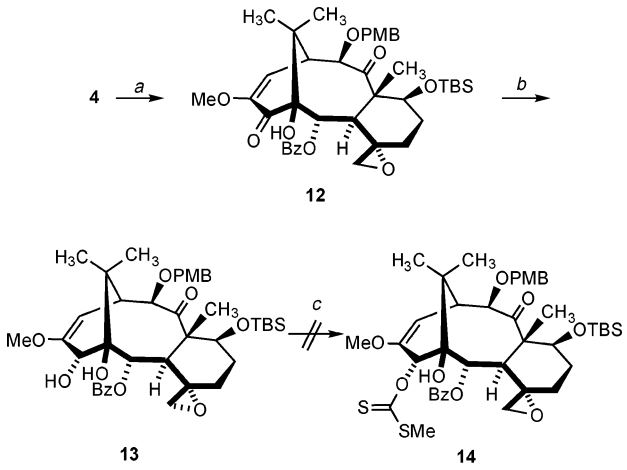
[a] DMSCl, DMAP, Et_3N, CH_2Cl_2, 0 °C (82%). [b] TMSCl, Et_3N, CH_2Cl_2. [c] $Pd(OAc)_2$, 1,4-benzoquinone, CH_3CN, rt or Δ. [d] IBX:NMO (1:1), DMSO, rt.

tert-butoxide at −78 °C under an atmosphere of oxygen was notably effective (84% of **4**).

With this development in hand, it seemed appropriate to explore some of the options available for engaging electrophilic capture of the enol subunit in **4** at both its oxygen and carbon atoms. The obvious first choice involved the generation of silyl enol ethers **9** and **10** by conventional reaction with chlorodimethylsilane (DMSCl) or trimethyl homologues thereof (TMSCl) (Scheme 3). Although **9** was amenable to chromatographic purification,[15] **10** was not and was therefore used directly as generated. In neither case were conditions found to effect conversion to enedione **11** by either the Saegusa method[16] or oxidation with IBX.[17] One of the deterrents to the positioning of a double bond in the interior of ring A may be a less than ideal alignment of the bridgehead C−H bond.

The *O*-methylation of **4** with diazomethane in ether proved unsuccessful when no additive was present. Attempts to achieve catalysis with fluoroboric acid[18] offered no advantage. However, the presence of silica gel[19] served usefully to activate the system, with stirring at room temperature for 1 h delivering **12** in 98% yield (Scheme 4). Chemoselective reduction of the C-14 carbonyl group in **12** was next realized under Luche conditions,[20] with delivery of hydride occurring from the exo surface to produce alcohol **13**. Advancement in this manner was intended to be a route that would lead to effective deoxygenation at this site. For this tactic to be successful, access to xanthate **14** or a closely related compound type was required. Radical

SCHEME 4



[a] CH_2N_2, SiO_2, Et_2O, rt (98%). [b] $NaBH_4$, $CeCl_3 \cdot 7\ H_2O$, 10:1 EtOH-THF, 0 °C (60% conv, 80% yield). [c] KH, 18-cr-6, CS_2, CH_3I, Δ.

reduction with tri-*n*-butyltin hydride[21] was to follow. Unfortunately, the generation of **14** could not be accomplished, with extensive screening resulting most often in the recovery of unreacted **13**. More forcing conditions induced decomposition. This conversion was not expected to be straightforward because of prevailing steric congestion. It was not entirely clear what role electronic factors could be playing to reduce reactivity levels.

To accord some attention to this aspect of the problem, diosphenol **4** was subjected to bromination with pyridinium hydrotribromide[22] in CH_2Cl_2 at 0 °C.[19] Smooth conversion to **15** ensued (Scheme 5). The presence of the bromine substituent did not impede the subsequent reaction with diazomethane to deliver **16**. In fact, this step proceeded very well at a temperature of only 0 °C (compare the need for 20 °C in the case of **12**) and was the first indication that the change in the reactivity profile accompanying brominative substitution at C-12 could hold interest. The subsequent Luche reduction of **16** was marked by an enhanced rate of consumption of this ketone compared to **12**. The accelerated response to sodium borohydride and cerium trichloride may originate from the greater electronegativity of the halogen atom, which by electron withdrawal renders the nearby C-14 site more susceptible to nucleophilic attack. These features also facilitate xanthate formation to give **18**.

Effort was next directed to the reductive desulfurization of **18** because the bromine atom resident at C-12 in **19** could potentially serve as a handle for double bond installation. Xanthate reduction was initially attempted under the standard Barton deoxygenation protocol involving *n*-Bu_3SnH as the reducing hydride and AIBN as the initiation source.[23] At the elevated temperature required to activate AIBN, decomposition of the starting material was observed. The initiation was then carried out with Et_3B so that the reaction could be executed at low temperature. Again, decomposition was observed. A series of reductions were attempted using a phosphine borane, specifically *n*-Bu_3P-BH_2, a reagent reported by Barton to reduce

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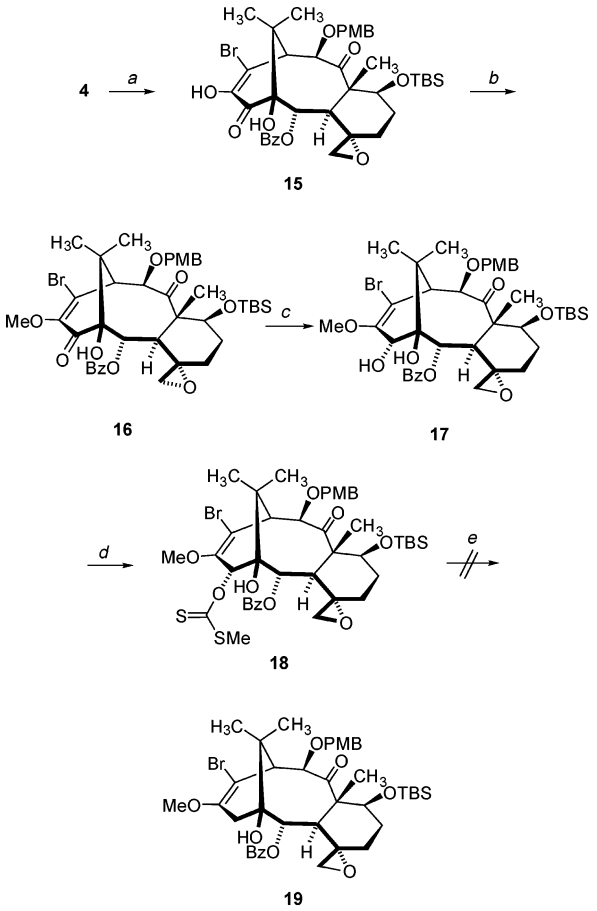
SCHEME 5

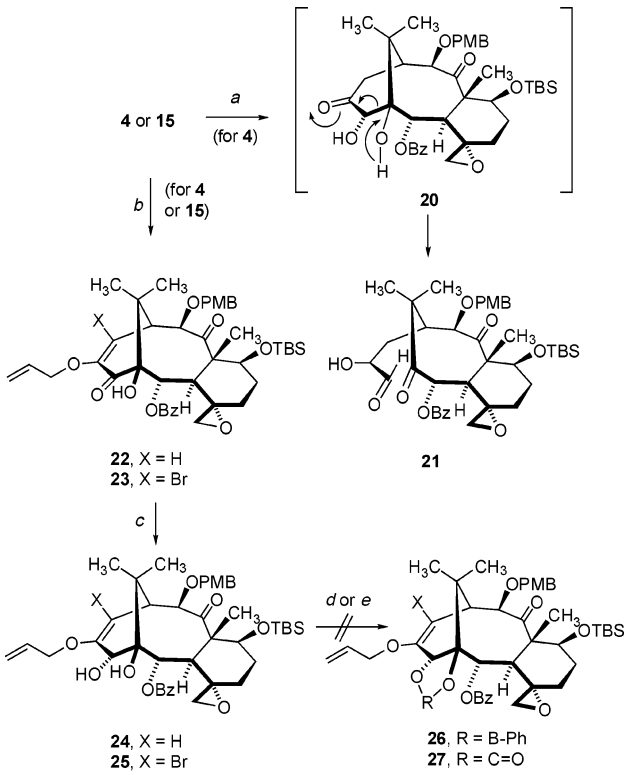


[a] Py•HBr_3, py, CH_2Cl_2, 0 °C (71%). [b] CH_2N_2, SiO_2, Et_2O, 0 °C (95%). [c] $NaBH_4$, $CeCl_3$•7 H_2O, 10:1 EtOH-THF, 0 °C (77% conv, 76% yield). [d] KH, 18-cr-6, CS_2, rt, 3 h (83% conv, 60% yield). [e] See text.

xanthate functionalities in the presence of halogens.[24] This was an attractive alternative because tin reagents seemed to be detrimental to our system, and we attributed this result to the alkenyl bromide moiety present at C12−C13 in **18**. All of the conditions utilizing heat to activate the reaction again resulted in decomposition. At times, it was slow to occur, but no useable material was isolated out of any of the reaction mixtures. Photochemical reduction was attempted through the employment of a phosphoramide radical, which could be generated by irradiation of HMPA. Runs at varying times were carried out using a quartz reaction vessel, but again, decomposition was observed even at the shortened reaction time of 5 min. Changing to a reaction tube made of Vycor glass, which allows 50% of the light to pass through, again led to decomposition of the starting material in a rapid manner. One final reaction was carried out using RaNi in EtOH, in the hope that cleavage of the xanthate would occur. As with the previous attempts, no useable compounds were isolated from the reaction mixture.

In the course of investigating this strategy, the *O*-allyl derivatives **22** and **23** were prepared by reaction of **4** or **15** with allyl iodide and potassium carbonate in DMF at room temperature. By that time, we had already come to recognize that Luche reduction of the unprotected diosphenol triggers an undesirable retro-aldol cleavage as **20** → **21**[25] (Scheme 6). As before,

SCHEME 6



[a] $NaBH_4$, EtOH, $CeCl_3$•7 H_2O. [b] Allyl iodide, K_2CO_3, DMF, rt (76% for **22**, 75% for **23**). [c] $NaBH_4$, $CeCl_3$•7 H_2O, EtOH, 0 °C (50% for **25**). [d] $PhB(OH)_2$, CH_2Cl_2, rt. [e] KH, $COCl_2$, ether-HMPA, rt.

recourse to ethanol as solvent proved necessary to prolong the lifetime of the $NaBH_4$[26] and allow reduction to proceed properly. With the availability of **24** and **25**, an examination of diol protection maneuvers was made possible. The advantages derived from diol protection have not escaped the attention of others.[1−6] However, in the earlier examples, the A-ring was already somewhat "flattened" due to the presence of the bridgehead double bond. For the substrates presently in hand, neither **24** nor **25** possess this structural feature. As molecular models show, the A-ring in these intermediates is constituted instead of a highly folded conformation that very effectively blockades the structural underside. As a result, our efforts to achieve conversion to cyclic boronate esters such as **26** or cyclic carbonates of type **27** were uniformly thwarted. These targeted transformations would likely not be problematic if the configuration at C-14 featured instead a β-oriented hydroxyl as in **28**. Regrettably, Meerwein−Ponndorf−Verley reduction of **22** and **23** could not be successfully realized under a variety of modifications.

We next directed our attention to a different strategy adapted from Winkler's synthesis of ingenol that was used to install an α,β-unsaturated-α-methyl ketone structural motif.[27] The short sequence of steps, originally reported by the Tsuji group,[28] is

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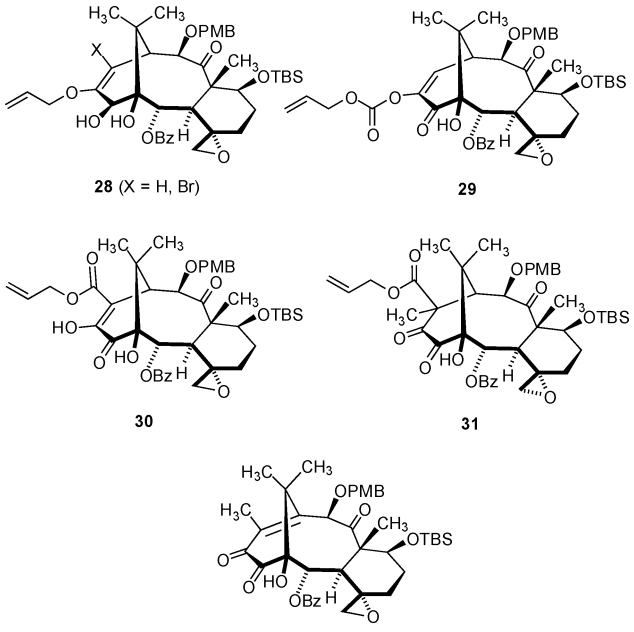
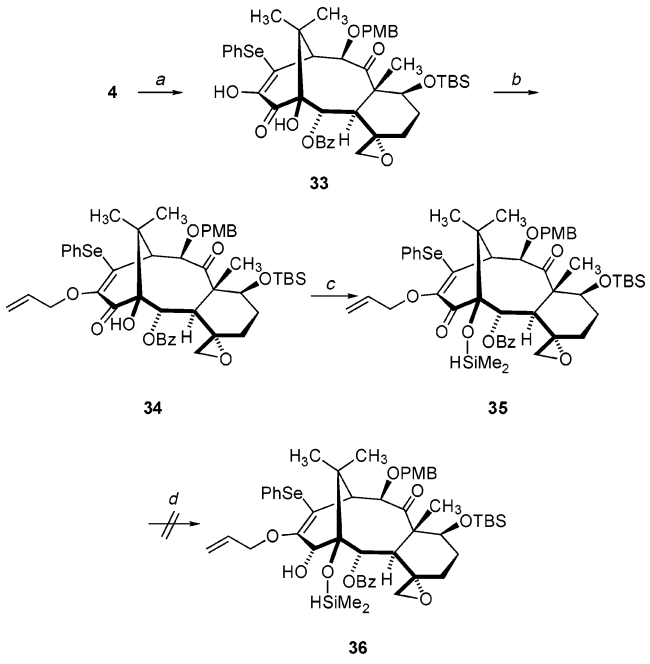
based on a $Pd(OAc)_2$-catalyzed oxidative decarboxylation. The proper outcome would require that we first be able to generate ester **30**, perhaps via the *O*-acylated intermediate **29**. Subsequent *C*-methylation as in **31** would be followed by the key transformation that would hopefully lead to α-diketone **32**. At the



experimental level, treatment of **4** with lithium hexamethyldisilazide and allyl cyanoformate[29] eventuated in decomposition with no evidence for the generation of **30**. In contrast, acylation with allyl chloroformate in the presence of triethylamine and DMAP[30] gave rise to **29** in 80% yield. Although this outcome was encouraging, we were singularly unsuccessful in bringing about the Pd(II)-promoted installation of the C11−C12 double bond.[28] We assume that the appreciable steric congestion and conformational rigidity preclude the normal operation of the acyl shift.

Another initiative for mastering the rather densely substituted A-ring domain involved turning to organoselenium chemistry. The plan was to introduce a phenylseleno group as in **33** as a prelude to functionality manipulation and selenoxide elimination[31] (Scheme 7). We had earlier utilized a related tactic in our taxusin synthesis.[10] Operationally, the formation of **33** from **4** proceeded quite smoothly. This step was followed by *O*-allylation to provide **34**. In a move designed to deter future complications stemming from undesirable retro-aldol A-ring cleavages (i.e., selenated variants of the **20** → **21** bond scission), a means for protecting the C-1 hydroxyl was sought. Although **34** proved to be totally unreactive toward chlorotrimethylsilane, coupling to the less sterically demanding dimethyl congener[32] as in **35** could be achieved quantitatively. However, the consequences of installing the dimethylsilyl group in this fashion

SCHEME 7



[a] $LiN(SiMe_2)_2$, PhSeCl, THF, 0 °C (82%). [b] Allyl iodide, K_2CO_3, DMF, rt (80%). [c] Me_2SiHCl, py, rt (100%). [d] $NaBH_4$, EtOH, $CeCl_3 \cdot 7\ H_2O$.

soon surfaced. Reduction of the C-14 carbonyl group proved not to be an attainable goal. Exposure of **35** to such reagents as $LiBH_4$, DIBAL-H, and BH_3 led to no reaction. The only observable change occurred with $LiAlH_4$ at room temperature, where wholesale decomposition materialized. None of the several TLC spots proved to be attributable to carbinol **36**.

Seeing no way to render this sequence feasible, we resorted instead to a totally different approach involving intermediates more extensively oxygenated in the A-ring. This objective led us to consider the suitability of epoxy ether **37** as an advanced intermediate. Once we recognized that *m*-chloroperbenzoic acid was incapable of effecting the targeted epoxidation satisfactorily, we were drawn to the possibility of utilizing dimethyldioxirane[33] for this conversion. The initial outcome was encouraging, although the yield was modest (Scheme 8). The first modification designed to improve matters involved the alternate use of methyl(trifluoromethyl)dioxirane, the reactivity of which is reported to be 1000 times that of DMDO.[34] Indeed, a faster reaction ensued, but without an improvement in the yield of **37**. Ultimately, the efficiency with which **37** was generated was enhanced to the 45% level simply by using more dilute solutions of DMDO. The stereochemistry of **37** was assigned on the basis of HMBC, COSY, and HMQC data (Figure 1).

The corresponding bromine-containing alcohol **17** proved inert to DMDO. In the presence of the fluorinated oxidant, cleavage of the PMB ring was operational.[35]

One of the nice features of the epoxidation reaction leading to **37** is that it defines the regioselectivity of the ring opening that occurs upon exposure to mildly acidic methanol. In the presence of pyridinium *p*-toluenesulfonate at 0 °C, conversion

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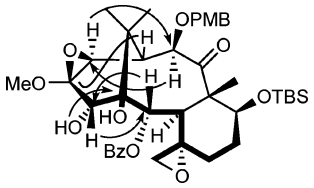


FIGURE 1. HMBC correlations present in **37**.

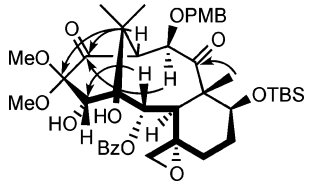
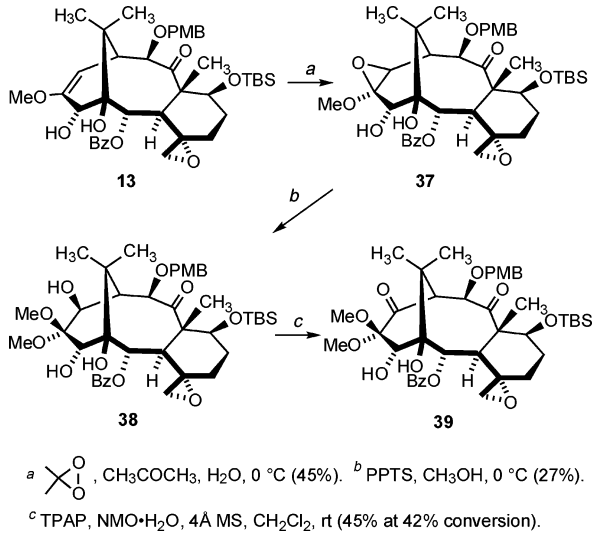


FIGURE 2. HMBC correlations Present in **39**.

SCHEME 8



[a] , CH_3COCH_3, H_2O, 0 °C (45%). [b] PPTS, CH_3OH, 0 °C (27%).
[c] TPAP, NMO•H_2O, 4Å MS, CH_2Cl_2, rt (45% at 42% conversion).

to acetal **38** takes place. Attempts to increase the efficiency of this useful reaction by "softening" the conditions were to no avail. Other possible promoters such as camphorsulfonic acid were met with decomposition. Lowering the temperature to below 0 °C was also not a practical option because of very low reaction rates. Nevertheless, sufficient quantities of **38** were available to pursue the possible regioselective oxidation of this triol. We were extremely pleased with the results of a first attempt in this direction which involved tetrapropylammonium perruthenate (TPAP)[36] as the catalyst and NMO as the oxidant. In accord with expectations, the reaction occurred selectively at the less-congested C-12 position to deliver **39**. The long-range correlation data are summarized in Figure 2.

Convincingly, we established the precise position of the newly introduced carbonyl group. The feasibility of this oxidative conversion serves as exemplary evidence that the controlled activation of C-12 is possible. Further advancement toward **5** must now deal with the complexities associated with introduction of the bridgehead double bond at this rather late stage of taxane construction. We hope to report on the further optimization of the three steps contained in Scheme 8 as well as on the final stages of the pursuit of **5** in due course.

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Experimental Section

Oxidation of 2 to Diosphenol 4. A solution of **2** (246 mg, 0.348 mmol) in anhydrous THF (25 mL) was placed in a flame-dried round-bottomed flask under N_2, cooled to −78 °C, treated with sublimed potassium *tert*-butoxide (678 mg, 0.69 mmol) in one portion, and stirred at low temperature for 30 min. The N_2 was replaced with a balloon of O_2, and the reaction mixture was purged with O_2 until complete conversion was observed (typically 45−60 min). Saturated NH_4Cl solution (20 mL) and ethyl acetate (20 mL) were introduced, and the product was extracted into ethyl acetate (3 × 20 mL), washed with brine (40 mL), and concentrated to leave a residue that was purified by flash chromatography (elution with 25−50% ethyl acetate/hexanes) to furnish **4** (212 mg, 80%) as a colorless oil: IR (neat, cm^{-1}) 3424, 1728, 1682, 1614; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 7.2 Hz, 2H), 7.65 (t, J = 7.4 Hz, 1H), 7.53 (t, J = 7.8 Hz, 2H), 7.40 (d, J = 8.6 Hz, 2H), 6.34 (d, J = 6.5 Hz, 1H), 6.11 (s, 1H), 5.56 (d, J = 3.8 Hz, 1H), 4.68 (d, J = 10.8 Hz, 1H), 4.55 (s, 1H), 4.24 (dd, J = 10.5, 5.6 Hz, 1H), 4.17 (d, J = 10.8 Hz, 1H), 3.87 (s, 3H), 3.69 (d, J = 3.7 Hz, 1 Hz), 3.51 (s, 1H), 3.26 (d, J = 6.3 Hz, 1H), 2.88 (d, J = 4.3 Hz, 1H), 2.43 (d, J = 4.4 Hz, 1H), 2.09−2.05 (m, 1H), 1.79−1.67 (m, 1H), 1.58−1.54 (m, 1H), 1.52−1.48 (m, 1H), 1.48 (s, 3H), 1.23 (s, 3H), 1.14 (s, 3H), 0.90 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 208.3, 190.0, 165.3, 159.8, 149.1, 134.0 (2C), 130.4, 130.3, 129.7 (2C), 129.5, 129.2 (2C), 120.9, 114.3 (2C), 84.2, 81.1, 74.4, 73.2, 79.2, 58.3, 58.2, 55.7, 54.7, 53.4, 41.6, 39.7, 32.8, 30.2, 29.7, 26.3 (3C), 20.7, 18.6, 11.6, −1.8, −3.6; EI HRMS m/z $C_{40}H_{52}O_{10}Si$ (M^+) calcd 721.3403, obsd 721.3414; $[\alpha]^{22}_D$ +17.2 (c 0.59, $CHCl_3$).

***O*-Methylation of 4.** To a solution of 100 mg of **4** in 10 mL of dry ether at room temperature was added 100 mg of silica gel and 5 mL of an ethereal CH_2N_2 solution (prepared from 600 mg of KOH, 3 mL of water, 5 mL of ether, and 500 mg of *N*-nitrosomethylurea). The reaction mixture was stirred for 1 h and freed of solvent under a house vacuum. The remaining silica gel was slurried in 5 mL of ether and filtered through a small plug of silica gel, which was rinsed with 40 mL of ether and 10 mL of CH_2Cl_2 to ensure that all the material had been eluted. Solvent evaporation yielded 100 mg (98%) of **12** as a cloudy oil: IR (neat, cm^{-1}) 3492, 1728, 1694, 1634; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 7.1 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.42 (d, J = 8.6 Hz, 2H), 6.97 (d, J = 8.6 Hz, 2H), 5.84 (d, J = 6.1 Hz, 1H), 5.64 (d, J = 5.4 Hz, 1H), 4.71 (d, J = 10.9 Hz, 1H), 4.32 (dd, J = 9.6, 6.8 Hz, 1H), 4.13 (d, J = 10.9 Hz, 1H), 3.88 (2, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 3.21 (d, J = 5.4 Hz, 1H), 3.19 (d, J = 6.2 Hz, 1H), 2.73 (d, J = 3.6 Hz, 1H), 2.54 (d, J = 3.6 Hz, 1H), 2.16−2.09 (m, 1H), 1.93−1.87 (m, 1H), 1.73−1.67 (m, 4H), 1.16 (s, 3H), 1.11 (s, 3H), 1.10−1.05 (m, 1H), 0.93 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.6, 194.5, 166.0, 159.9, 152.0, 134.0, 130.3 (2C), 130.2 (2C), 129.5, 129.2, 129.8 (2C), 119.5, 114.4 (2C), 85.3, 82.3, 74.0, 72.7, 72.1, 57.4, 56.2, 55.7, 55.6, 55.0, 54.0, 41.8, 30.4, 28.0, 26.3 (3C), 22.0, 18.6, 12.7, −1.7, −3.7; EI HRMS m/z $C_{41}H_{54}O_{10}SiNa$ (M^+) calcd 757.3378, obsd 757.3364; $[\alpha]^{22}_D$ +23.0 (c 0.37, $CHCl_3$).

Luche Reduction of 12. A solution of **12** (148 mg, 0.201 mmol) in 13 mL of absolute ethanol and 1.3 mL of dry THF was prepared at room temperature. To this solution was added $CeCl_3 \cdot 7H_2O$ (150 mg, 0.403 mmol), and once homogeneous, the solution was cooled to 0 °C. This mixture was treated with $NaBH_4$ (15 mg, 0.403 mmol), stirred for 30 min, treated with a second portion of $NaBH_4$ (15 mg, 0.403 mmol), stirred for 2 h at 0 °C, carefully quenched with 3 mL of saturated NH_4Cl solution, diluted with 5 mL of CH_2Cl_2, and transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were washed with brine and freed of solvent under reduced pressure. The resulting oil was purified by column chromatography on silica gel (6:1 to 3:1 hexanes/ethyl acetate) to yield 59 mg of unreacted **1** (60% conversion) and 79 mg (89%) of **13** as a cloudy

oil: IR (neat, cm^{-1}) 3425, 1732, 1718, 1652; ^1H NMR (500 MHz, C_6D_6) δ 8.20 (d, $J = 7.6$ Hz, 2H), 7.57 (d, $J = 8.4$ Hz, 2H), 7.04 (t, $J = 7.2$ Hz, 1H), 6.95 (t, $J = 7.8$ Hz, 2H), 6.86 (d, $J = 8.5$ Hz, 2H), 5.92 (d, $J = 2.1$ Hz, 1H), 5.19 (d, $J = 12.8$ Hz, 1H), 4.99 (s, 1H), 4.95 (d, $J = 10.5$ Hz, 1H), 4.59 (d, $J = 4.4$ Hz, 1H), 4.56 (s, 1H), 4.41 (d, $J = 12.6$ Hz, 1H), 4.36 (d, $J = 10.5$ Hz, 1H), 4.14 (dd, $J = 10.5$, 4.5 Hz, 1H), 3.30 (s, 3H), 3.26 (s, 3H), 3.19−3.15 (m, 2H), 2.76 (s, 1H), 1.93 (d, $J = 4.5$ Hz, 1H), 1.78−1.73 (m, 1H), 1.65−1.63 (m, 1H), 1.57 (s, 3H), 1.43 (s, 3H), 1.40−1.34 (m, 1H), 1.12 (s, 3H), 0.91 (s, 9H), 0.89−0.86 (m, 1H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 208.0, 164.6, 159.9, 158.0, 133.4, 131.3 (2C), 130.4, 130.1 (2C), 129.4 (2C), 129.1 (2C), 128.6, 114.3, 98.9, 86.4, 77.4, 76.5, 74.5, 73.7, 73.1, 60.7, 60.5, 54.9, 54.8, 54.3, 53.8, 40.6, 36.5, 30.7, 29.9, 26.2 (3C), 20.2, 18.6, 11.0, −2.1, −3.6; ES HRMS *m/z* $C_{41}H_{56}O_{10}SiNa$ $(M + Na)^+$ calcd 759.3535, obsd 759.3507; $[\alpha]^{20}_D$ −43.6 (*c* 0.32, $CHCl_3$).

Bromodiosphenol 15. A solution of **4** (107 mg, 0.148 mmol) and pyridine (24 μL, 0.297 mmol) in 10 mL of CH_2Cl_2 was cooled to 0 °C. To the solution was added solid pyr·HBr_3 (47 mg, 0.148 mmol), and the solution was stirred for 1 h, quenched with saturated $NaHCO_3$ solution, and diluted with CH_2Cl_2 and H_2O. The solution was transferred to a separatory funnel, and the aqueous layer was extracted with 3 × 25 mL of CH_2Cl_2. The combined organic fractions were washed with brine, dried, and concentrated under reduced pressure and high vacuum. The resulting yellow oil was purified by column chromatography on silica gel (5:1 hexanes/ethyl acetate) to yield 84 mg (71%) of **15** as a clear oil: IR (neat, cm^{-1}) 3405, 1731, 1613; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, $J = 7.2$ Hz, 2H), 6.95 (d, $J = 8.6$ Hz, 2H), 6.75 (s, 1H), 5.49 (d, $J = 2.9$ Hz, 1H), 5.02 (d, $J = 0.9$ Hz, 1H), 4.68 (d, $J = 7.1$ Hz, 1H), 3.87 (s, 3H), 3.72 (d, $J = 4.8$ Hz, 1H), 3.41 (s, 1H), 3.58 (s, 1H), 3.00 (d, $J = 4.4$ Hz, 1H), 2.37 (d, $J = 4.8$ Hz, 1H), 2.12−2.09 (m, 1H), 1.85−1.70 (m, 2H), 1.37 (s, 3H), 1.29 (s, 3H), 1.16 (s, 3H), 0.88 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.3, 192.3, 164.7, 148.5, 133.6, 130.1 (2C), 129.8, 129.4 (2C), 129.0, 128.8 (2C), 128.6, 121.3, 113.7 (2C), 82.6, 80.1, 75.3, 72.7, 72.0, 62.7, 58.0, 55.3, 52.7, 42.5, 38.1, 35.0, 30.0, 29.1, 26.0 (3C), 19.6, 18.2, 10.5, −2.4, −4.2; ES HRMS *m/z* $C_{40}H_{51}BrO_{10}SiNa$ $(M + Na)^+$ calcd 821.2327, obsd 821.2376; $[\alpha]^{20}_D$ −41.3 (*c* 0.12, $CHCl_3$).

***O*-Allylation of 4.** A solution of **4** (100 mg, 0.14 mmol) and K_2CO_3 (95 mg, 0.69 mmol) in 20 mL of dry DMF was cooled to 0 °C, treated with neat allyl iodide (40 μL, 0.416 mmol), warmed to room temperature, stirred for 1 h, and treated with 10% aqueous $NaHSO_3$ solution (∼5 mL) until the solution was clear. The reaction mixture was diluted with ethyl acetate, transferred to a separatory funnel, and extracted with the same solvent (3 × 25 mL). The organic fractions were combined, washed with brine, dried, and concentrated under reduced pressure, and the resulting oil was purified by column chromatography on silica gel (5−20% ethyl acetate in hexanes) to give 80 mg (76%) of **22** as a colorless oil: IR (neat, cm^{-1}) 1724, 1510, 1248; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, $J = 7.2$ Hz, 2H), 7.61 (t, $J = 7.4$ Hz, 1H), 7.49 (dd, $J = 7.8$, 7.7 Hz, 1H), 7.39 (d, $J = 8.5$ Hz, 2H), 6.95 (d, $J = 8.6$ Hz, 2H), 6.09−6.03 (m, 1H), 5.82 (d, $J = 6.2$ Hz, 1H), 5.62 (d, $J = 5.4$ Hz, 1H), 5.43 (dd, $J = 17.2$, 1.2 Hz, 1H), 5.36 (dd, $J = 10.5$, 1.0 Hz, 1H), 4.69 (d, $J = 11.0$ Hz, 1H), 4.41−4.29 (m, 2H), 4.19−4.08 (m, 1H), 3.87 (s, 1H), 3.84 (s, 3H), 3.17 (d, $J = 5.3$ Hz, 1H), 3.14 (d, $J = 5.7$ Hz, 1H), 2.74 (d, $J = 5.7$ Hz, 1H), 2.51 (d, $J = 3.6$ Hz, 1H), 2.20−2.05 (m, 1H), 1.91−1.81 (m, 1H), 1.75−1.70 (m, 1H), 1.64 (s, 3H), 1.13 (s, 3H), 1.09 (s, 3H), 1.08−1.03 (m, 1H), 0.91 (s, 3H), 0.11 (s, 3H), 0.09 (s, 9H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.2, 194.1, 165.1, 159.5, 156.3, 150.5, 143.7, 133.5, 132.1, 129.9 (2C), 129.8 (2C), 129.1 (2C), 128.7 (2C), 120.6, 119.0, 113.9, 84.6, 81.4, 73.5, 72.3, 71.7, 69.6, 57.0, 55.3, 41.7, 41.5, 40.3, 31.9, 31.0, 27.7, 25.9 (3C), 22.7, 21.6, 18.2, 14.1, 12.3, −2.1, −4.1; ES HRMS *m/z* $C_{43}H_{56}O_{10}SiNa$ $(M + Na)^+$ calcd 783.3535, obsd 783.3517.

Reduction of 23. A solution of **23** (9 mg, 0.01 mmol) and $CeCl_3 \cdot H_2O$ (20 mg, 0.054 mmol) in 2 mL of ethanol at 0 °C was treated with $NaBH_4$ (4 mg, 0.11 mmol), stirred for 3 h, quenched with saturated NH_4Cl solution, diluted with CH_2Cl_2, and transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were washed with brine, dried, and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel (5−20% ethyl acetate/hexanes) to yield 4 mg (50%) of **25** as a clear oil: IR (film, cm^{-1}) 3378, 1728, 1511; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (dd, $J = 8.0$, 0.91 Hz, 2H), 7.62 (d, $J = 7.5$ Hz, 1H), 7.49 (dd, $J = 7.8$, 7.5 Hz, 1H), 7.39 (d, $J = 8.6$ Hz, 2H), 6.91 (d, $J = 8.6$ Hz, 2H), 6.16−6.09 (m, 1H), 5.48−5.41 (m, 3H), 5.30 (dd, $J = 10.4$, 1.1 Hz, 1H), 5.03 (d, $J = 1.0$ Hz, 1H), 4.81−4.75 (m, 1H), 4.62 (d, $J = 10.6$ Hz, 1H), 4.46 (d, $J = 2.1$ Hz, 1H), 4.35−4.24 (m, 2H), 4.20 (dd, $J = 7.7$, 3.2 Hz, 1H), 3.84 (s, 3H), 3.30 (dd, $J = 4.1$, 1.8 Hz, 1H), 3.17 (s, 1H), 2.59 (s, 1H), 2.54 (d, $J = 4.3$ Hz, 1H), 2.12−1.98 (m, 2H), 1.76−1.64 (m, 1H), 1.28 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H), 0.91−0.87 (m, 1H), 0.85 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 207.8, 164.5, 159.1, 156.3, 152.3, 143.7, 134.2, 133.7, 130.6 (2C), 130.1 (2C), 129.1 (2C), 128.9 (2C), 118.7, 113.9, 113.7, 108.8, 75.5, 72.8, 72.4, 71.3, 68.7, 60.8, 59.3, 55.3, 54.2, 41.6, 36.2, 31.0, 29.7, 25.9 (3C), 22.7, 19.4, 18.2, 14.1, 10.2, −2.5, −4.2; ES HRMS *m/z* $C_{43}H_{57}BrO_{10}SiNa$ $(M + Na)^+$ calcd 863.2797, obsd 863.2833; $[\alpha]^{21}_D$ −9.52 (*c* 0.42, $CHCl_3$).

***O*-Acylation of 4 with Allyl Chloroformate.** A 10 mL conical flask was charged with 1 mL of CH_2Cl_2, allyl chloroformate (10 μL, 0.083 mmol), and DMAP (20 mg, 0.167 mmol). To the cloudy white solution was added **4** (6 mg, 0.008 mmol) dissolved in 500 μL of CH_2Cl_2 via cannula, and the reaction mixture was stirred at room temperature for 2 h, then quenched with saturated NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic extracts were washed with brine, dried, and concentrated under reduced pressure to give a yellow residue that was purified by column chromatography on silica gel (10:1 to 2:1 hexanes/ethyl acetate) to give 5.3 mg (80%) of **29** as a colorless oil: IR (neat, cm^{-1}) 3507, 1769, 1727, 1616; ^1H NMR (500 MHz, C_6D_6) δ 8.20 (d, $J = 7.1$ Hz, 2H), 7.46 (d, $J = 8.6$ Hz, 2H), 7.10−6.98 (m, 3H), 6.85 (d, $J = 8.7$ Hz, 2H), 6.37 (d, $J = 6.4$ Hz, 1H), 5.92 (d, $J = 5.0$ Hz, 1H), 5.67−5.60 (m, 2H), 5.10 (dd, $J = 10.5$, 1.1 Hz, 1H), 4.93 (dd, $J = 10.4$, 1.1 Hz, 1H), 4.74 (d, $J = 10.2$ Hz, 1H), 4.45−4.35 (m, 3H), 4.06 (d, $J = 10.2$ Hz, 1H), 3.78 (s, 1H), 3.34 (d, $J = 4.9$ Hz, 1H), 3.29 (s, 3H), 3.11 (d, $J = 1.5$ Hz, 1H), 2.92 (d, $J = 4.1$ Hz, 1H), 2.17 (d, $J = 4.1$ Hz, 1H), 1.91−1.85 (m, 1H), 1.74 (s, 3H), 1.55−1.45 (m, 1H), 1.40−1.28 (m, 4H), 1.15−1.05 (m, 4H), 0.93 (s, 9H), −0.02 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 207.0, 192.9, 165.1, 160.1, 153.0, 146.1, 139.6, 133.5, 130.4, 130.1, 130.0 (2C), 130.0 (2C), 129.0 (2C), 128.6 (2C), 119.3, 114.3, 83.1, 82.0, 73.8, 73.2, 72.8, 69.7, 65.5, 57.3, 57.0, 54.8, 53.1, 41.5, 41.3, 30.2, 30.0, 29.0, 26.2 (3C), 21.2, 18.5, 1.4, −2.0, −4.0; ES HRMS *m/z* $C_{44}H_{56}O_{12}$-SiNa $(M + Na)^+$ calcd 827.3433, obsd 827.3436; $[\alpha]_D^{20}$ +25.2 (*c* 0.08, $CHCl_3$).

Phenylselenation of 4. A solution of **4** (200 mg, 0.277 mmol) in 28 mL of THF was cooled to −78 °C in a 50 mL conical flask. Lithium hexamethyldisilazide (416 μL of 1.0 M in THF, 0.416 mmol) was added, and the reaction mixture was stirred for 15 min. Neat phenylselenenyl chloride (79 mg, 0.416 mmol) was added, and the reaction mixture was stirred for 30 min, quenched with saturated NH_4Cl solution, and transferred to a separatory funnel. The aqueous layer was extracted with 3 × 25 mL of CH_2Cl_2, and the combined organic extracts were dried and concentrated under reduced pressure. The resulting dark orange residue was purified by chromatography on silica gel (neat hexanes, then 5:1 hexanes/ethyl acetate) to give 200 mg (82%) of **33** as a pale orange oil: IR (film, cm^{-1}) 3420, 1734, 1669; ^1H NMR (500 MHz, C_6D_6) δ 8.15 (d, $J = 7.6$ Hz, 2H), 7.49 (dd, $J = 7.6$, 1.9 Hz, 2H), 7.32 (d, $J = 8.6$ Hz, 2H), 7.06 (d, $J = 7.4$ Hz, 1H), 7.00 (t, $J = 7.4$ Hz, 1H),

6.90−6.85 (m, 2H), 6.79 (d, J = 8.6 Hz, 2H), 5.90 (d, J = 2.7 Hz, 1H), 5.12 (s, 1H), 4.64 (d, J = 9.3 Hz, 1H), 4.37 (dd, J = 10.9, 4.9 Hz, 1H), 4.19 (J = 2.5 Hz, 1H), 3.86 (d, J = 9.5 Hz, 1H), 3.58 (s, 1H), 3.54 (s, 1H), 3.30 (s, 3H), 3.29 (s, 1H), 2.94 (d, J = 4.9 Hz, 1H), 1.95 (d, J = 5.2 Hz, 1H), 1.82−1.60 (m, 3H), 1.48 (s, 3H), 1.43 (s, 3H), 1.18−1.10 (m, 1H), 0.98 (s, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.8, 192.7, 164.7, 158.9, 148.0, 135.1 (2C), 130.3, 130.1, 130.0, 129.9 (2C), 129.8 (2C), 129.3, 128.9 (2C), 113.4, 88.6, 83.2, 79.7, 75.3, 72.0, 71.8, 60.7, 58.1, 55.3, 52.6, 50.2, 42.1, 37.7, 30.2, 29.7, 28.9, 26.7, 26.2, 25.9 (3C), 19.7, 18.2, −2.4, −3.1; ES HRMS m/z $C_{46}H_{56}O_{10}$SeSiNa $(M + Na)^+$ calcd 899.2700, obsd 899.2763; $[\alpha]_D^{19}$ -28.5 (c 1.2, $CHCl_3$).

Epoxidation of 13. A 50 mL round-bottomed flask containing **13** (155 mg, 0.210 mmol), $NaHCO_3$ (265 mg, 3.15 mmol), 10.5 mL of acetone, and 10.5 mL of H_2O was cooled to 0 °C with vigorous stirring. To this solution was added Oxone (645 mg, 1.05 mmol), and the reaction mixture was stirred for 2 h, filtered through a plug of silica gel, and transferred to a separatory funnel. The aqueous layer was extracted with 3 × 10 mL of ethyl acetate, and the combined organic fractions were washed with brine, dried, and concentrated under reduced pressure. The resulting oil was purified by chromatography on silica gel (5:1 hexanes/ethyl acetate) to yield 20 mg of unreacted **13** and 62 mg (45%) of **37** as a colorless oil: IR (neat, cm^{-1}) 3378, 1728, 1611; ^{1}H NMR (500 MHz, C_6D_6) δ 8.29 (d, J = 8.2 Hz, 2H), 7.61 (d, J = 8.6 Hz, 2H), 7.21 (d, J = 7.8 Hz, 1H), 7.13 (d, J = 7.8 Hz, 2H), 6.95 (d, J = 8.2 Hz, 2H), 5.98 (d, J = 1.9 Hz, 1H), 5.72 (d, J = 13.3 Hz, 1H), 4.96 (d, J = 10.6 Hz, 1H), 4.56 (s, 1H), 4.44 (d, J = 13.3 Hz, 1H), 4.38 (d, J = 10.6 Hz, 1H), 4.19 (dd, J = 11.4, 4.7 Hz, 1H), 4.08 (s, 1H), 3.84 (s, 3H), 3.70 (s, 1H), 3.45 (s, 3H), 3.43 (s, 1H), 3.27 (d, J = 4.7 Hz, 1H), 3.13 (s, 1H), 2.98 (s, 1H), 2.35 (t, J = 13.7 Hz, 1H), 2.12 (d, J = 4.7 Hz, 1H), 1.80−1.78 (m, 1H), 1.77 (s, 3H), 1.63 (s, 1H), 1.59 (s, 1H), 1.52 (s, 1H), 1.44−1.40 (m, 1H), 1.38 (s, 1H), 1.00 (s, 3H), 0.96−0.88 (m, 1H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.5, 165.3, 159.6, 133.4, 130.7, 130.1 (2C), 129.7, 129.4 (2C), 129.1 (2C), 128.8 (2C), 113.9, 84.8, 85.0, 77.8, 76.0, 74.1, 73.0, 67.4, 61.3, 60.6, 59.8, 57.7, 54.5, 53.5, 51.5, 39.3, 37.9, 35.2, 30.2, 29.4, 25.9 (3C), 21.3, 20.3, 18.2, 13.4, 10.6, −2.4, −4.0; ES HRMS m/z $C_{41}H_{56}O_{11}$SiNa $(M + Na)^+$ calcd 775.3484, obsd 775.3496; $[\alpha]_D^{18}$ -22.1 (c 0.10, $CHCl_3$).

Acetalization of 37. A solution of **37** (51 mg, 0.068 mmol) in 6.7 mL of methanol was cooled to 0 °C, and PPTS (9 mg, 0.03 mmol) was added. The reaction mixture was stirred for 3 h, quenched with saturated NH_4Cl solution, diluted with CH_2Cl_2, and transferred to a separatory funnel. The aqueous layer was extracted with 3 × 25 mL of CH_2Cl_2, and the combined organic extracts were washed with brine, dried, and concentrated under reduced pressure to give an oil, which was purified by chromatography on silica gel to give 12 mg of unreacted **37** and 11 mg (27%) of **38** as a colorless oil: IR (neat, cm^{-1}) 3429, 1727, 1611; ^{1}H NMR (500 MHz, C_6D_6) δ 8.34 (d, J = 7.1 Hz, 2H), 7.67 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 7.5 Hz, 1H), 7.11 (d, J = 7.5 Hz, 2H), 6.95 (d, J = 8.2 Hz, 2H), 6.03 (d, J = 2.3 Hz, 1H), 5.23 (d, J = 12.9 Hz, 1H), 4.98 (d, J = 11.0 Hz, 1H), 4.89 (s, 1H), 4.69 (s, 1H), 4.64 (d, J = 10.6 Hz, 1H), 4.39 (dd, J = 11.4, 4.7 Hz, 1H), 4.28 (d, J = 13.3 Hz, 1H), 3.47 (s, 1H), 3.41 (s, 3H), 3.36 (s, 3H), 3.29 (dd, J = 4.5, 1.7 Hz, 1H), 3.28 (s, 1H), 3.20 (s, 3H), 3.09 (s, 1H), 2.12−2.06 (m, 1H), 2.05 (d, J = 4.7 Hz, 1H), 1.89−1.80 (m, 1H), 1.64 (s, 3H), 1.62 (s, 3H), 1.61−1.58 (m, 1H), 1.40 (s, 3H), 1.04 (s, 9H), 1.02−0.97 (m, 1H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 207.8, 164.4, 159.6, 133.2, 130.9 (2C), 130.1 (2C), 129.9 (2C), 129.2, 128.8 (2C), 113.9, 98.7, 86.9, 80.1, 78.9, 54.7, 72.7, 72.1, 62.7, 61.2, 60.2, 54.5, 53.2, 50.2, 48.5, 40.1, 38.9, 35.6, 30.4, 25.8 (3C), 22.9, 21.0, 18.2, 14.1, 10.8, −2.5, −4.0; ES HRMS m/z $C_{42}H_{60}O_{12}$SiNa $(M + Na)^+$ calcd 807.3746, obsd 807.3719; $[\alpha]_D^{18}$ -31.4 (c 0.4, $CHCl_3$).

Regioselective Oxidation of 38. A solution containing **38** (21 mg, 0.027 mmol), NMO·H_2O (7 mg, 0.05 mmol), and 4 Å molecular sieves (100 mg) in 2.7 mL of CH_2Cl_2 was treated with TPAP (2.4 mg, 0.0067 mmol) at room temperature. The reaction mixture was stirred overnight and filtered through a plug of silica gel (eluent CH_2Cl_2). The filtrate was concentrated under reduced pressure, and the oil was purified chromatographically on silica gel (5−25% ethyl acetate/hexanes) to give 12 mg of **38** (42% conversion) and 4 mg (45%) of **39** as a colorless oil: IR (neat, cm^{-1}) 3397, 1731, 1702; ^{1}H NMR (500 MHz, C_6D_6) δ 8.31 (d, J = 7.1 Hz, 2H), 7.64 (d, J = 8.6 Hz, 2H), 7.18 (t, J = 7.6 Hz, 1H), 7.09 (t, J = 7.8 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 6.12 (d, J = 2.6 Hz, 1H), 5.58 (d, J = 2.0 Hz, 1H), 5.46 (d, J = 13.5 Hz, 1H), 5.10 (d, J = 10.1 Hz, 1H), 4.65 (d, J = 10.3 Hz, 1H), 4.53 (d, J = 13.4 Hz, 1H), 4.35 (dd, J = 11.2, 4.7 Hz, 1H), 3.93 (s, 3H), 3.41 (s, 3H), 3.40 (s, 1H), 3.27 (s, 3H), 3.22 (d, J = 4.4 Hz, 1H), 3.06 (s, 1H), 2.85 (d, J = 1.5 Hz, 1H), 2.46 (t, J = 13.2 Hz, 1H), 2.07 (d, J = 4.5 Hz, 1H), 1.80−1.74 (m, 2H), 1.71 (s, 3H), 1.56 (s, 3H), 1.37 (s, 3H), 1.00 (s, 9H), 0.94−0.87 (m, 1H), 0.22 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.3, 203.9, 164.2, 159.7, 133.3, 130.8, 130.1 (2C), 129.6, 129.4, 128.8 (2C), 128.1 (2C), 113.9 (2C), 98.5, 82.7, 81.9, 78.1, 74.2, 73.1, 72.5, 64.2, 61.9, 60.9, 54.5, 53.7, 52.6, 51.4, 42.3, 38.5, 34.2, 30.0, 25.9 (3C), 20.2, 18.2, 10.7, −2.7, − 4.4; ES HRMS m/z $C_{42}H_{58}O_{12}$SiNa $(M + Na)^+$ calcd 805.3590, obsd 805.3566; $[\alpha]^{21}_D$ −30.0 (c 0.14, $CHCl_3$).

Supporting Information Available: Experimental procedures and high-field ^{1}H/^{13}C NMR spectral data for all compounds whose preparation is not detailed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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