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Probing the SAR of dEpoB via Chemical Synthesis: A Total Synthesis Evaluation of C26-(1,3-dioxolanyl)-12,13-desoxyepothilone B

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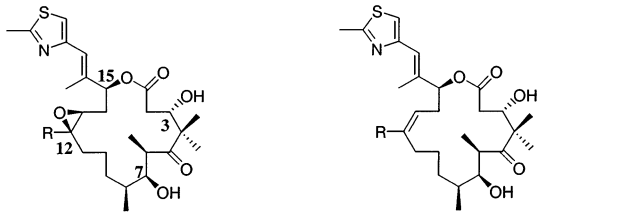
Received March 14, 2002

A practical total synthesis of 26-(1,3-dioxolanyl)-12,13-desoxyepothilone B (26-dioxolanyl dEpoB) was accomplished in a highly convergent manner. A novel sequence was developed to produce the vinyl iodide segment **17** in high enantiomeric excess, which was used in a key *B*-alkyl Suzuki merger. Subsequently, a Yamaguchi macrocyclization formed the core lactone, while a selective oxidation and a late stage Noyori acetalization incorporated the dioxolane functionality. Sufficient amounts of synthetic 26-dioxolane dEpoB were produced using this sequence for an in vivo analysis in mice containing xenograft CCRF−CEM tumors.

Introduction

The epothilones have evoked considerable interest in the chemical and biological communities since the discovery that their potent antitumor activity is derived from a paclitaxel-like mode of action.[1] Paclitaxel, a microtubule stabilizing agent that is approved for use against breast and ovarian cancer, is also being evaluated against other tumor types. However, the poor water solubility of paclitaxel and its susceptibility to multidrug resistance hampers the effectiveness of this drug. The fact that the epothilones manifest increased solubility and enhanced efficacy in a number of multidrug resistant (MDR) cell lines[2] has prompted a search, through total synthesis, for promising epothilone congeners.[3]

This laboratory[4] and several others,[5] upon successfully completing the total syntheses of epothilone A and B (Figure 1, **1** and **2**, respectively), embarked on the synthesis of selected analogues with the hope of establishing a thorough understanding of epothilone structure−activity relationships (SAR).[6] Through extensive in vivo biological testing, it was found that compounds lacking the 12,13-epoxide functionality [dEpoA (**3**) and dEpoB (**4**)], though less cytotoxic than the epoxy analogues, demonstrated an enhanced therapeutic range, due to a lower toxicity profile. In particular, dEpoB was essentially curative against a number of otherwise resistant xenograft tumors in mice.[2]



1 R = H, epothilone A, EpoA
2 R = CH_3, epothilone B, EpoB
3 R = H, 12,13-desoxyepothilone A, dEpoA
4 R = CH_3, 12,13-desoxyepothilone B, dEpoB

FIGURE 1. Epothilones.

It was previously known that dEpoB, which contains a methyl group at C-12, has superior biological activity to dEpoA (**3**, R = H).[7] With one modification having such a profound effect, it seemed justified to further explore 12,13-desoxy analogues with variations of substitution at this position. A number of modifications containing

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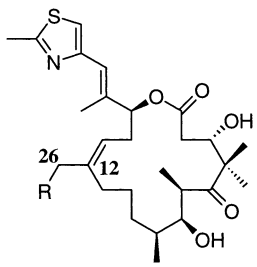
10.1021/jo020180q CCC: $22.00
Published on Web 10/10/2002

polar and nonpolar functionalities were incorporated at C-12 utilizing varying tether lengths (Table 1).[3c] Incorporation of polar alcohol functional groups in the C-12 domain (**5**−**7**) increased the MDR susceptibility, and the compounds were presumably transported out of the cell by the drug efflux transport protein, PgP. However, the incorporation of ethylene glycol acetals (**8**, **9**) resulted in retention of activity against the vinblastine resistant tumor line. A particularly intriguing result was the discovery that the analogue containing a C-12 ethylidene acetal (**8**) was found to have *activity superior to dEpoB* in the CCRF−CEM cell line, while still retaining comparable efficacy against the resistant CRCF−CEM/VBL line.[8] Following this study, compound **8** was identified as a promising candidate and selected as the first C-26-modified epothilone analogue to undergo advanced in vivo studies in our laboratories.[9]

TABLE 1. In Vitro Activity of C-26-Modified Epothilone Analogues



Cmpd #	R	CCRF-CEM IC_{50} (nM)	CRCF-CEM/VBL IC_{50} (nM)	Resistance[a]
4	H	9.5	17	1.8
5	OH	49	>2000	>50
6	CH_2OH	32	1033	33
7	$(CH_2)_2OH$	9.5	167	18
8		4.3	20	4.7
9		80	409	5.1
	Paclitaxel	2.1	4140	1971

[a] Resistance is defined as [IC_{50} CCRF−CEM/VBL]/[IC_{50} CCRF−CEM].

Results and Discussion

Synthesis. To meet the demands on material for advanced biological testing, an efficient and scalable synthesis of compound **8** was required. The initial planning for the synthesis involved key components previously utilized in the synthesis of dEpoB (Figure 2).[10] The polypropionate segment **B** would be constructed first from

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(8) CCRF−CEM is a human T-cell acute lymphoblastic leukemia cell line. CCRF−CEM/VBL cell line demonstrates cross-resistance to paclitaxel, adriamycin, and etoposide and was developed after continuous exposure of CCRF−CEM cells to increasing and sublethel concentrations (IC_{50}) of vinblastine.

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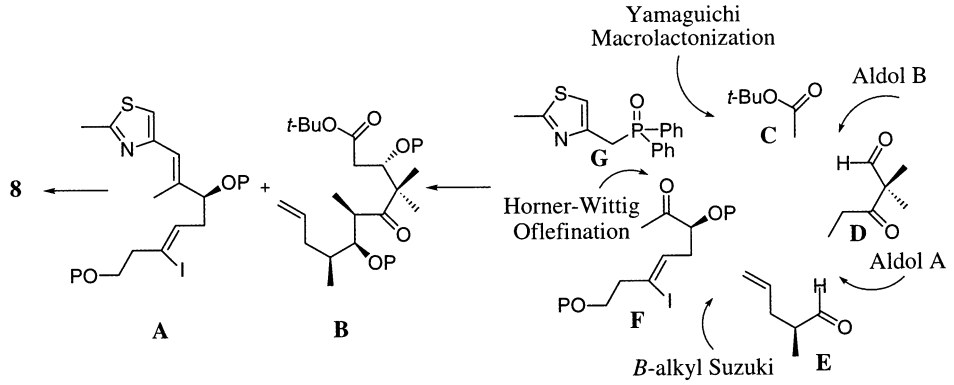
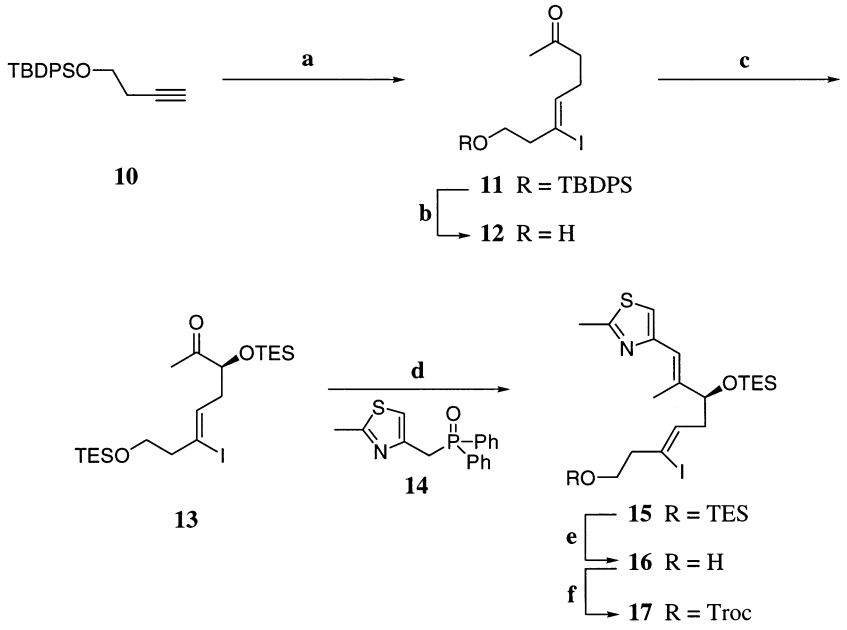


FIGURE 2. Synthesis plan for 26-dioxolane dEpoB.

SCHEME 1. Synthesis of the Vinyl Iodide Segment[a]



[a] Reagents and conditions: (a) (i) *B*-I-9-BBN, (ii) methyl vinyl ketone, (iii) 3 N NaOH, PhMe, 100 °C, 86%; (b) HF·pyr, THF, 77%; (c) (i) TMSI, HMDS, CH_2Cl_2, −15 °C, (ii) OsO_4, AD-mix-α, $MeSO_2NH_2$, *tert*-butyl alcohol:H_2O (1:1), 0 °C; (iii) HOAc, H_2O, (iv) TESCl, imidazole, DMF, 50% overall (88% ee); (d) **14**, *n*-BuLi, THF, −78 °C, 30 min, then **13**, −78 °C → rt, 86%; (e) HOAc, MeOH, 0 °C, 80%; (f) TrocCl, pyridine, 0 °C, 86%.

an aldol reaction between the lithium enolate of fragment **D** and aldehyde **E**. A second aldol utilizing a chiral titanium enolate of *tert*-butyl acetate **C** would set the C-3 stereochemistry and would provide the *O*-acyl sector **B**, thus equipped for a *B*-alkyl Suzuki coupling.[11] The alkyl region of the molecule **A** would initially require generation of the chiral alcohol **F**, which would undergo a Horner−Wittig olefination with phosphine oxide **G** to generate the trisubstituted olefin in segment **A**. With both segments in hand, a *B*-alkyl Suzuki coupling would successfully connect the fragments. Following a Yamaguchi macrolactonization,[12] the core structure would be complete. Finally, conversion of the primary alcohol into the ethylene glycol acetal would provide the final target.

The synthesis commenced with conversion of butynol **10** to the desired vinyl iodide ketone (**11**, Scheme 1). Utilizing the protocol developed by Suzuki,[13] the carbon framework of the hydroxy ketone segment was assembled in one step with the desired cis olefin geometry. The use of the *tert*-butyldiphenylsilyl ether proved to be vital, since it was the only protecting group found to be robust enough to survive the iodo−boration step. Eventually a trichloroethoxycarbonyl would be the protecting group desired at this position. However, owing to its incompatibility with phosphorus ylides, it was installed following the Horner−Wittig olefination (vida infra).[14] The silyl protecting group was removed by treatment with HF·

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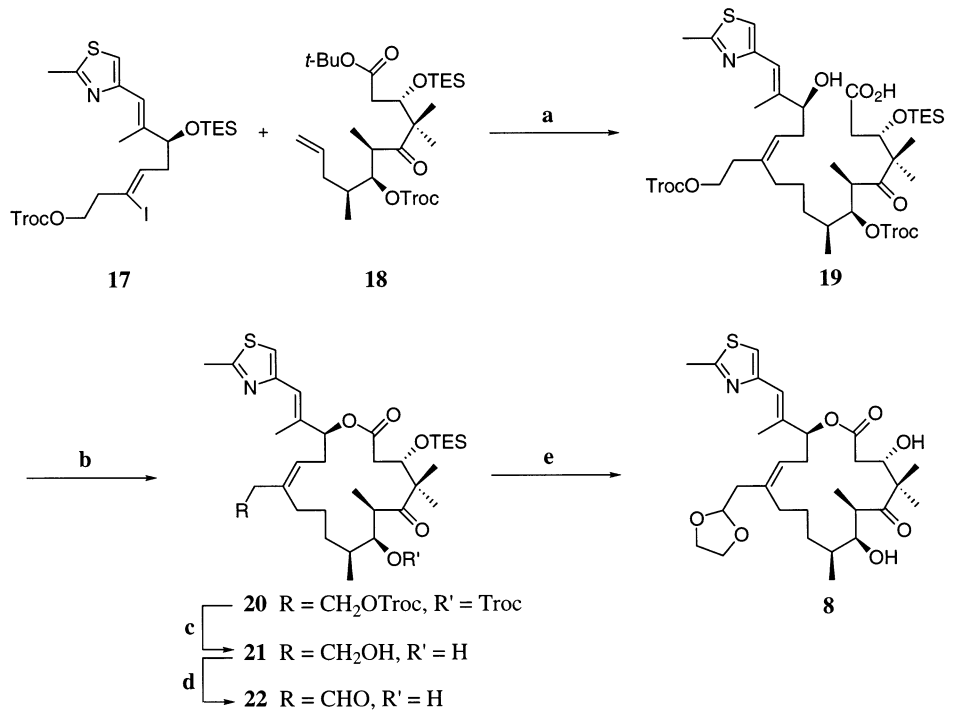
SCHEME 2. Completion of the Total Synthesis of 26-Dioxolane dEpoB[a]



[a] Reagents and conditions: (a) (i) **18**, 9-BBN dimer, THF, (ii) **17**, $PdCl_2dppf{\cdot}CH_2Cl_2$, $AsPh_3$, Cs_2CO_3, DMF, H_2O, 0 C → rt, (iii) TESOTf, 2,6-lutidine, CH_2Cl_2, (iv) 0.12 N HCl, MeOH, 0 °C, 35% overall; (b) 2,4,6-trichlorobenzoyl chloride, Et_3N, 4-DMAP, THF, PhMe, 65%; (c) Zn, HOAc, THF, sonication, 60%; (d) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 81%; (e) (i) $(TMSOCH_2)_2$, TMSOTf, CH_2Cl_2, −78 °C, (ii) HF·pyr, THF, 69% overall.

pyridine, giving rise to the free alcohol **12** in 77% yield. At this point, the thermodynamic trimethylsilyl enol ether was generated with concomitant protection of the primary alcohol using trimethylsilyl iodide and hexamethyldisilazane.[15] The intermediate enol ether was dihydroxylated using Sharpless' procedure[16] to provide an inseparable mixture of the desired diol contaminated with methane sulfonamide. Next, the mixture was silylated using triethylsilyl chloride and imidazole to provide the pure α-hydroxy ketone **13** in 50% overall yield (88% ee).[17] The Horner olefination of ketone **13** was stereoselectively accomplished (the undesired olefin isomer was not detected) in 86% yield utilizing the lithium anion of phosphine oxide **14**.[18] Prior to the pivotal Suzuki coupling, it would be necessary to differentiate the two hydroxy groups. Toward this end, the primary TES ether was selectively removed by treatment with dilute acetic acid in methanol at 0 °C and then reprotected as the trichloroethoxycarbonate in 86% yield, thereby affording vinyl iodide segment **17**.

Fragments **17** and **18** (Scheme 2) were connected using a *B*-alkyl Suzuki coupling[11] as shown. Following deprotection of the *tert*-butyl ester utilizing TESOTf, the resulting silyl ester and C-15 TES ether functions were selectively cleaved using dilute HCl in methanol. *seco*-Acid **19** underwent a Yamaguchi macrocyclization[12] to provide the fully protected lactone **20**. Treatment with activated zinc in acetic acid[19] successfully removed both Troc protecting groups, and subsequent oxidation utilizing TEMPO and $PhI(OAc)_2$ selectively oxidized the primary alcohol in excellent yield (81%).[20] Acetalization using Noyori's conditions[21] proceeded smoothly with concomitant scrambling of the C-3 protecting group to a mixture of TMS and TES silyl ethers. The crude mixture was treated with HF·pyridine to provide the final target in 69% overall yield for the final two steps. This synthesis has proved to scale-up to the levels we required and has produced 50 mg of the final product (**8**) for in vivo biological testing.

Biological Evaluations. The therapeutic effect of 26-dioxolane dEpoB was initially examined in nude mice containing xenograft CCRF−CEM tumors (Figure 3). The animal experiments were performed according to the slow i.v. infusion protocol developed previously in these laboratories.[2] Initial dosing at 30 mg/kg afforded some retardation of tumor growth. However, increased dosing presented no additional reduction in tumor size; in fact,

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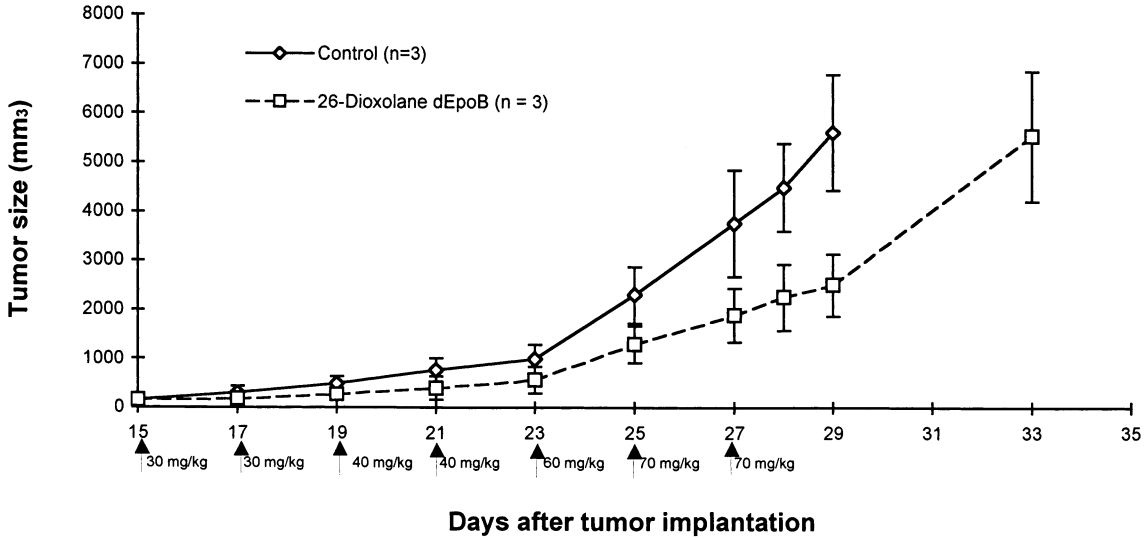

FIGURE 3. Therapeutic effect of treatment with 26-dioxolane dEpoB. CCRF−CEM tumor cells (1×10^7 in 0.2 mL) were introduced in nude mice by inoculation on day 0. Mice were treated with 26-dioxolane dEpoB, 6 h i.v. infusion, 30 mg/kg on days 15 and 17, 40 mg/kg on days 19 and 21, 60 mg/kg on day 23, and 70 mg/kg on days 25 and 27 ($n = 3$). The control mice received vehicle only.

at dosing levels of 70 mg/kg after 25 days, the tumor growth resumed until experiment termination at day 33. This result was in stark contrast to the effects of dEpoB, which provided complete tumor regression after 14 days.[2] By the limited effects of the drug at increased dosing, it is possible that the dioxolane functionality is chemically unstable or increases drug metabolism. It would be necessary to resolve this important issue of potential in vivo instability before compound **8** can be developed further.

Conclusion

In summary, the efficient total synthesis of promising in vitro candidate 26-dioxolane dEpoB was achieved in order to provide material for advanced in vivo biological studies. A highly enantioselective sequence was developed for the generation of the vinyl iodide segment **17**. The synthesis relied on a key *B*-alkyl Suzuki merger and subsequent macrocyclization to form the core lactone, while a selective oxidation and late stage acetalization incorporated the dioxolane functionality. Sufficient amounts of synthetic 26-dioxolane dEpoB were produced using this sequence for an in vivo analysis in murine models. For the moment, 26-dioxolane dEpoB did not abrogate tumor growth, even at elevated dosing, in mice containing xenograft CCRF−CEM tumors.

Experimental Section

General Methods. Reagents obtained from commercial suppliers were used without further purification unless otherwise noted. The following solvents were obtained from a dry solvent system and used without further drying: tetrahydrofuran, methylene chloride, diethyl ether, benzene, and toluene. All air- and water-sensitive reactions were performed in flame-dried glassware under a positive pressure of prepurified argon gas. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or C_6D_6 at 400 and 100 MHz, respectively. Optical rotations were obtained at 22 ± 2 °C. Analytical thin-layer chromatography was performed on silica gel 60 plates. Compounds that were not UV active were visualized by dipping the plates in a ceric ammonium molybdate or *p*-anisaldehyde solution and heating. Silica gel chromatography was performed using the indicated solvent on silica gel (grade 1740, type 60A, 170−400 mesh).

Compound 11. A solution of 1.0 M *B*-Iodo-9-BBN (47.0 mL, 47.0 mmol) in hexane was treated with a solution of alkyne **10** (14.28 g, 46.3 mmol) in hexane (46 mL) and allowed to stir at room temperature for 80 min. Methyl vinyl ketone (11.5 mL, 138.2 mmol) was then added and the reaction was stirred for an additional 3 h. The reaction mixture was concentrated, redissolved in toluene (60 mL), and treated with 3 N NaOH (25 mL). The biphasic solution was warmed to 100 °C and stirred for 5.5 h. The reaction mixture was cooled to room temperature, poured into H_2O (100 mL), and extracted with diethyl ether (3 × 100 mL). The combined extracts were washed with water and then brine, dried over $MgSO_4$, filtered, and concentrated. The resulting syrup was purified by silica gel chromatography (20:1 hex:EtOAc) to provide **11** (20.16 g, 86%) as a clear syrup: IR (thin film) 3070, 2956, 2930, 2856, 1718, 1589, 1472, 1428, 1361, 1161, 1111 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.63 (m, 4H), 7.42−7.35 (m, 6H), 5.59 (t, $J = 6.8$ Hz, 1H), 3.75 (t, $J = 6.1$ Hz, 2H), 2.67 (t, $J = 6.1$ Hz, 2H), 2.49 (t, $J = 7.3$ Hz, 2H), 2.35 (q, $J = 7.1$ Hz, 2H), 2.11 (s, 3H), 1.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.5, 135.6, 135.3, 133.6, 129.6, 127.6, 105.9, 62.2, 48.0, 41.9, 30.7, 29.8, 26.8, 19.2; HRMS (EI+) calcd for $C_{24}H_{35}INO_2Si$ $(M + NH_4)^+$ 524.1482, found 524.1494.

Compound 12. A solution of ketone **11** (19.73 g, 39.0 mmol) in THF (250 mL) was treated with HF·pyridine (18.5 mL) and stirred at room temperature for 6.5 h. The reaction mixture was then poured into saturated $NaHCO_3$ (200 mL) and extracted with EtOAc (3 × 200 mL). The combined extracts were washed with saturated $NaHCO_3$ and then brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography (2:1 hex:EtOAc) to provide alcohol **12** (8.03 g, 77%) as a clear syrup: IR (thin film) 3414, 2920, 1714, 1645, 1418, 1365, 1282, 1258, 1230, 1163, 1096, 1047 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (t, $J = 6.7$ Hz, 1H), 3.72 (t, $J = 5.8$ Hz, 2H), 2.68 (t, $J = 5.7$ Hz, 2H), 2.54 (t, $J = 7.2$ Hz, 2H), 2.38 (q, $J = 6.8$ Hz, 2H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.0, 135.9, 105.6, 60.7, 47.8, 41.7, 30.6, 29.8; HRMS (EI+) calcd for $C_8H_{14}IO_2$ $(M + H)^+$ 269.0038, found 269.0046.

Compound 13. A solution of alcohol **12** (4.03 g, 15.0 mmol) in CH_2Cl_2 (80 mL) was cooled to −15 °C, treated with 1,1,1,3,3,3-hexamethyldisilazane (11.5 mL, 54.5 mmol) and trimethylsilyl iodide (6.5 mL, 46 mmol), and stirred at −15 °C for 40 min and then room temperature for 20 min. The

reaction mixture was diluted with cold saturated $NaHCO_3$ (80 mL) and extracted with Et_2O (2 × 100 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated to provide a mixture of silyl enol ether isomers (5.871 g) which was used without further purification.

A homogeneous solution of $K_3Fe(CN)_6$ (13.18 g, 40.0 mmol), K_2CO_3 (5.52 g, 39.9 mmol), $MeSO_2NH_2$ (1.39 g, 14.2 mmol), $(DHQ)_2PHAL$ (0.524 g, 0.673 mmol), and OsO_4 (2.5 wt % in *tert*-butyl alcohol, 1.37 mL, 0.134 mmol) was cooled to 0 °C and treated with the crude silyl enol ether. After 80 min, the reaction mixture was quenched with saturated Na_2SO_3 (130 mL), warmed to room temperature, and stirred for 30 min. The reaction mixture was extracted with EtOAc (3 × 150 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated The crude product was dissolved in 4:1 THF:H_2O (100 mL), treated with HOAc (2 mL), and allowed to stir overnight. The reaction mixture was coevaporated with toluene and the residue was purified by silica gel chromatography (1:1 hex:EtOAc) to provide a mixture of diol and $MeSO_2NH_2$ (3.155 g).

The crude product and imidazole (3.03 g, 44.5 mmol) were dissolved in DMF (20 mL) and treated with TESCl (5.6 mL, 33.3 mmol). The reaction mixture was stirred at room temperature for 1 h and then poured into H_2O (20 mL) and extracted with EtOAc (3 × 25 mL). The combined extracts were washed with H_2O and then brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography (1:1 hex:EtOAc) to provide the bis-TES ether **13** (3.875 g, 50% overall) as a clear oil: $[\alpha]^{22}_D$ 0.1° (*c* 0.90, $CHCl_3$); IR (thin film) 2954, 2910, 2876, 1718, 1457, 1417, 1352, 1239, 1104, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.59 (t, J = 6.6 Hz, 1H), 4.08 (t, J = 6.3 Hz, 1H), 3.70 (t, J = 6.7 Hz, 2H), 2.68 (t, J = 6.6 Hz, 2H), 2.48−2.39 (m, 2H), 2.17 (s, 3H), 0.96−0.87 (m, 18H), 0.63−0.48 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.8, 131.6, 107.0, 77.4, 61.8, 48.4, 41.8, 25.3, 6.7, 6.7, 4.7, 4.4; HRMS (EI+) calcd for $C_{20}H_{42}IO_3Si_2$ $(M + H)^+$ 513.1717, found 513.1700.

Compound 15. A solution of phosphine oxide **14**[18] (1.82 g, 5.82 mmol) in THF (70 mL) at −78 °C was treated with *n*-BuLi (1.6 M, 3.6 mL, 5.8 mmol) dropwise and stirred for 30 min. A solution of ketone **13** (2.00 g, 3.90 mmol) in THF (20 mL) was added via cannula to the previously prepared red-orange lithiated phosphine oxide solution and stirred at −78 °C. After 50 min, the reaction was warmed to room temperature, stirred for an additional 50 min, and then quenched with saturated $NaHCO_3$ (50 mL). The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 × 100 mL). The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography (10:1 hex:EtOAc) to provide **15** (2.04 g, 86%) as a clear syrup: $[\alpha]^{22}_D$ 9.43° (*c* 1.05, $CHCl_3$); IR (thin film) 2953, 2910, 2874, 1506, 1457, 1413, 1377, 1238, 1182, 1094, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.46 (s, 1H), 5.58 (t, J = 6.6 Hz, 1H), 4.20 (t, J = 6.4 Hz, 1H), 3.68 (t, J = 7.0 Hz, 2H), 2.69−2.65 (m, 5H), 2.39−2.35 (m, 2H), 2.00 (s, 3H), 0.92 (t, J = 3.9 Hz, 18H), 0.60−0.53 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 153.0, 141.6, 133.7, 118.9, 115.2, 105.2, 77.0, 62.0, 48.4, 43.7, 19.2, 14.1, 6.8, 6.7, 4.8, 4.3; HRMS (EI+) calcd for $C_{25}H_{47}INO_2SSi_2$ $(M + H)^+$ 608.1911, found 608.1919.

Compound 16. A solution of **15** (2.30 g, 3.79 mmol) in MeOH (41 mL) at 0 °C was treated with HOAc (1.00 mL, 17.4 mmol.). After 11 h, the reaction mixture was quenched with Et_3N (2.7 mL, 19.4 mmol), warmed to room temperature, and absorbed onto silica gel (10 g). Purification by silica gel chromatography provided **16** (1.498 g, 80%) as a clear syrup: $[\alpha]^{22}_D$ −7.9° (*c* 1.34, $CHCl_3$); IR (thin film) 3342, 2952, 2910, 2874, 1502, 1460, 1414, 1376, 1239, 1184, 1070, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.42 (s, 1H), 5.65 (t, J = 6.8 Hz, 1H), 4.24 (t, J = 6.2 Hz, 1H), 3.67 (m, 2H), 2.74−2.63 (m, 5H), 2.56 (s br, 1H), 2.43 (t, J = 6.7 Hz, 2H), 1.97 (s, 3H), 0.93 (t, J = 8.0 Hz, 9H), 0.58 (q, J = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 152.6, 141.3, 134.2, 119.1, 115.0, 107.1, 76.4, 60.4, 48.5, 43.4, 19.0, 14.3, 6.8, 4.7; HRMS (EI+) calcd for $C_{19}H_{33}INO_2SSi$ $(M + H)^+$ 494.1046, found 494.1032.

Compound 17. A solution of **16** (1.29 g, 2.62 mmol) and pyridine (0.45 mL, 5.56 mmol) in CH_2Cl_2 (13 mL) at 0 °C was treated with 2,2,2-trichloroethyl chloroformate (0.50 mL, 3.63 mmol). After 10 min at 0 °C, the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was then washed with saturated $NaHCO_3$ (2 × 15 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (10:1 hex:EtOAc) provided **17** (1.52 g, 86%) as a light yellow oil: $[\alpha]^{22}_D$ 9.1° (*c* 1.00, $CHCl_3$); IR (thin film) 2954, 2908, 2874, 1759, 1502, 1452, 1392, 1242, 1071, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.47 (s, 1H), 5.69 (t, J = 6.6 Hz, 1H), 4.73 (s, 2H), 4.31 (t, J = 6.7 Hz, 2H), 4.21 (t, J = 6.3 Hz, 1H), 2.86 (t, J = 6.6 Hz, 2H), 2.69 (s, 3H), 2.46−2.36 (m, 2H), 2.00 (s, 3H), 0.92 (t, J = 8.0 Hz, 9H), 0.58 (q, J = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 153.7, 152.8, 141.3, 135.3, 118.9, 115.3, 102.4, 94.3, 76.6, 76.6, 67.4, 44.0, 43.6, 19.2, 14.1, 6.8, 4.7; HRMS (EI+) calcd for $C_{22}H_{34}Cl_3INO_4SSi$ $(M + H)^+$ 668.0093, found 668.0095.

Compound 19. A solution of **18** (1.63 g, 2.57 mmol) in degassed THF (5.0 mL) was added to a flask containing 9-BBN dimer (0.477 g, 1.95 mmol) and stirred for 3 h, after which time excess 9-BBN dimer was quenched by the addition of degassed H_2O (1.55 mL, 86.1 mmol). The reaction was stirred for 20 min and then cannulated into a suspension of **17** (1.46 g, 2.18 mmol), Cs_2CO_3 (1.07 g, 3.28 mmol), $AsPh_3$ (0.134 g, 0.44 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.182 g, 0.22 mmol) in degassed DMF (12 mL) at 0 °C. After addition of the borane solution, the reaction mixture was warmed to room temperature and stirred for 5 h. Then additonal $AsPh_3$ (0.131 g, 0.43 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.181 g, 0.22 mmol) were added, and the reaction mixture was allowed to stir. After 15 h the reaction mixture was poured into Et_2O (50 mL) and washed with H_2O (2 × 25 mL). The aqueous layer was back-extracted with Et_2O (2 × 25 mL). The combined Et_2O extracts were dried over $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (10:1 hexanes:EtOAc) provided a mixture of product (1.97 g) and borane impurities, which was carried on to the next step without further purification.

A solution of the crude product in CH_2Cl_2 (16 mL) at 0 °C was treated with 2,6-lutidine (1.20 mL, 10.3 mmol) and then TESOTf (1.10 mL, 4.86 mmol) and allowed to stir for 15 min, after which the reaction was warmed to room temperature and stirred for 21 h. Then, the reaction was washed with saturated $NaHCO_3$ (3 × 25 mL), dried over $MgSO_4$, filtered, and concentrated. 2,6-Lutidine was removed by repeated coevaporation with toluene. A solution of the resulting syrup in THF (16 mL) at 0 °C was treated with small portions of 0.12 N HCl in MeOH over the course of 4 h (10.0 mL total) until starting material was completely consumed, after which the reaction was poured into saturated $NaHCO_3$ (25 mL). The reaction was then diluted with H_2O (25 mL) and extracted with $CHCl_3$ (3 × 25 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (1:1 → 3:1 EtOAc:hex) provided **19** (0.760 g, 35% overall) as a clear syrup: $[\alpha]^{22}_D$ −52.0° (*c* 1.10, CH_2Cl_2); IR (thin film) 3420, 2957, 2865, 1756, 1700, 1652, 1456, 1385, 1249, 1062 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.70 (s, 1H), 5.20 (t, J = 7.0 Hz, 1H), 4.90 (d, J = 12.0 Hz, 1H), 4.73 (s, 2H), 4.68 (dd, J = 2.6, 8.5 Hz, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.45−4.42 (m, 1H), 4.23 (t, J = 7.0 Hz, 2H), 4.09 (dd, J = 5.0, 7.5 Hz, 1H), 3.42−3.39 (m, 1H), 2.68 (s, 3H), 2.54 (dd, J = 1.8, 16.9 Hz, 1H), 2.38−2.22 (m, 5H), 2.15−2.03 (m, 2H), 1.98−1.92 (m, 4H), 1.73−1.69 (m, 1H), 1.48−1.41 (m, 2H), 1.30−1.23 (m, 2H), 1.13 (s, 3H), 1.09−1.07 (m, 6H), 0.98 (d, J = 6.2 Hz, 3H), 0.94 (t, J = 7.9 Hz, 9H), 0.66−0.60 (m, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ 214.1, 175.2, 165.3, 154.9, 154.4, 153.1, 142.3, 137.0, 124.6, 118.9, 115.3, 95.5, 95.2, 81.1, 77.2, 76.8, 76.7, 73.3, 67.9, 55.1, 40.5, 40.3, 35.9, 35.0, 34.2, 32.3,

30.6, 24.9, 22.8, 18.1, 17.9, 15.7, 14.9, 11.5, 7.4, 5.6; HRMS (EI+) calcd for $C_{40}H_{62}Cl_6NO_{11}SSi$ $(M + H)^+$ 1002.1944, found 1002.1900.

Compound 20. A solution **19** (0.731 g, 0.728 mmol) in THF (11 mL) was sequentially treated with Et_3N (0.62 mL, 4.45 mmol) and 2,4,6-trichlorobenzoyl chloride (0.57 mL, 3.65 mmol). After 15 min, the reaction was diluted with toluene (21 mL) and added by syringe pump (3.5 mL/h) to a solution of 4-DMAP (0.938 g, 7.68 mmol) in toluene (800 mL). After addition was complete, the syringe was rinsed with toluene (2 mL) and the reaction mixture was stirred for an additional hour and then placed in a freezer (−15 °C) overnight. The reaction mixture was then filtered through Celite and concentrated. Purification by silica gel chromatography (10:1 → 7:1 hex:EtOAc) provided **20** (0.466 g, 65%) as a white foam: $[\alpha]^{22}_D$ −6.4° (*c* 1.48, CH_2Cl_2); IR (thin film) 2956, 2876, 1759, 1698, 1652, 1456, 1386, 1246, 1158, 1106, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.51 (s, 1H), 5.28 (dd, J = 6.9, 9.2 Hz, 1H), 5.16 (d, J = 10.2 Hz, 1H), 5.05 (d, J = 10.1 Hz, 1H), 4.83 (d, J = 12.0 Hz, 1H), 4.77−4.70 (m, 3H), 4.29−4.20 (m, 2H), 4.04 (d, J = 9.4 Hz, 1H), 3.31−3.26 (m, 1H), 2.76−2.60 (m, 6H), 2.45−2.31 (m, 4H), 2.14−2.04 (m, 5H), 1.84−1.67 (m, 4H), 1.16 (s, 3H), 1.12 (s, 3H), 1.10 (d, J = 6.7 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H), 0.86 (t, J = 7.9 Hz, 9H), 0.55 (q, J = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ 211.8, 170.5, 164.6, 155.1, 154.4, 153.5, 139.5, 138.0, 122.5, 120.6, 117.1, 95.6, 95.2, 86.5, 80.3, 76.7, 76.6, 67.6, 53.3, 45.8, 39.4, 35.7, 35.1, 32.6, 31.4, 30.1, 30.1, 27.8, 24.9, 23.0, 18.9, 16.3, 15.0, 7.3, 5.8; HRMS (EI+) calcd for $C_{40}H_{60}Cl_6NO_{10}SSi$ $(M + H)^+$ 984.1838, found 984.1822.

Compound 21. A solution of **20** (0.327 g, 0.331 mmol) in HOAc (3.3 mL) was treated with excess nanosize zinc (4 spatula tips) and sonicated for 10 min. The reaction mixture was filtered through Celite, coevaporated with toluene, and purified by silica gel chromatography (1:1 → 1:3 hex:EtOAc) to provide **21** (0.126 g, 60%) as a white foam: $[\alpha]^{22}_D$ −65.0° (*c* 0.54, CH_2Cl_2); IR (thin film) 3420, 2951, 2875, 1694, 1456, 1380, 1301, 1240, 1196, 1158, 1107, 1065, 1040, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.53 (s, 1H), 5.25 (dd, J = 5.6, 10.0 Hz, 1H), 4.08 (dd, J = 4.4, 8.3 Hz, 1H), 3.83 (s br, 1H), 3.66−3.58 (m, 2H), 3.05−3.01 (m, 1H), 2.92 (s br, 1H), 2.76−2.65 (m, 6H), 2.41−2.30 (m, 2H), 2.18−2.05 (m, 5H), 1.91−1.86 (m, 1H), 1.74−1.60 (m, 3H), 1.40−1.35 (m, 2H), 1.26−1.18 (m, 2H), 1.14 (s, 3H), 1.12−1.10 (m, 6H), 1.00 (d, J = 7.0 Hz, 3H), 0.86 (t, J = 7.9 Hz, 9H), 0.58−0.47 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.1, 170.6, 164.6, 152.4, 139.4, 138.1, 122.8, 119.8, 116.2, 79.2, 75.7, 73.6, 60.2, 53.7, 43.2, 39.6, 39.0, 38.5, 32.6, 32.4, 29.0, 26.2, 23.8, 22.6, 19.2, 16.7, 15.2, 14.0, 7.0, 5.2; HRMS (EI+) calcd for $C_{34}H_{58}NO_6SSi$ $(M + H)^+$ 636.3754, found 636.3731.

Compound 22. A solution of **21** (0.0458 g, 0.0720 mmol) and iodobenzene diacetate (0.118 g, 0.366 mmol) in CH_2Cl_2 (2.0 mL) was treated with TEMPO (1.0 mg, 0.0064 mmol) at room temperature. After 2 h, the reaction mixture was concentrated to approximately 1 mL and purified by silica gel chromatography (4:1 → 2:1 hex:EtOAc) to provide **22** (0.0370 g, 81%) as a white foam: $[\alpha]^{22}_D$ −82.1° (*c* 0.42, CH_2Cl_2); IR (thin film) 3421, 2954, 2876, 1740, 1695, 1652, 1456, 1380, 1242, 1182, 1158, 1107, 1070, 1012 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.58 (t, J = 2.2 Hz, 1H), 6.95 (s, 1H), 6.54 (s, 1H), 5.32 (dd, J = 5.9, 10.0 Hz, 1H), 5.09 (d, J = 9.9 Hz, 1H), 4.07 (t, J = 6.4 Hz, 1H), 3.83 (s br, 1H), 3.12 (dd, J = 2.2, 15.9 Hz, 1H), 3.05−3.02 (m, 1H), 2.94 (d, J = 15.6 Hz, 1H), 2.91−2.85 (m, 1H), 2.81−2.69 (m, 5H), 2.55−2.43 (m, 1H), 2.18 (dd, J = 5.5, 14.0 Hz, 1H), 2.10 (s, 3H), 1.96−1.87 (m, 1H), 1.79−1.60 (m, 2H), 1.42−1.33 (m, 1H), 1.28−1.22 (m, 2H), 1.15 (s, 3H), 1.13−1.11 (m, 6H), 0.87 (t, J = 7.9 Hz, 9H), 0.60−0.48 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.9, 200.1, 170.6, 164.7, 152.3, 137.8, 134.8, 125.9, 120.0, 116.3, 78.9, 75.7, 73.6, 53.6, 50.6, 43.3, 39.5, 38.4, 32.5, 30.2, 29.6, 25.9, 24.0, 22.6, 19.2, 16.7, 15.2, 14.1, 7.0, 5.2; HRMS (EI+) calcd for $C_{34}H_{55}NO_6SSi$ $(M + H)^+$ 634.3598, found 634.3606.

Compound 8. A solution of **22** (37.0 mg, 0.0584 mmol) in CH_2Cl_2 (2.0 mL) at −78 °C was successively treated with 1,2-bis(trimethylsilyloxy)ethane (0.073 mL, 0.298 mmol) and trimethylsilyl trifluoromethanesulfonate (0.014 mL, 0.0760 mmol). After 30 min, the reaction mixture was poured into saturated $NaHCO_3$ (5 mL) and warmed to room temperature, and then the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated. The resulting syrup was dissoved in THF (2.0 mL), treated with HF·pyridine (0.20 mL), and stirred for 20 min. The reaction was poured into cold saturated $NaHCO_3$ (5 mL) and extracted with EtOAc (4 × 5 mL). The combined extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (1:1 hexanes:EtOAc) provided **8** (22.8 mg, 69% overall) as a white foam: $[\alpha]^{22}_D$ −86.2° (*c* 0.97, $CHCl_3$); IR (thin film) 3502, 2925, 1734, 1684, 1558, 1456, 1249, 1141, 1039, 1008 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.55 (s, 1H), 5.27 (dd, J = 4.7, 10.0 Hz, 1H), 5.19 (d, J = 8.8 Hz, 1H), 4.87 (t, J = 5.0 Hz, 1H), 4.28 (d, J = 10.0 Hz, 1H), 3.96−3.88 (m, 2H), 3.85−3.77 (m, 2H), 3.68 (s br, 1H), 3.62 (s br, 1H), 3.16−3.11 (m, 1H), 3.03 (s br, 1H), 2.68−2.60 (m, 4H), 2.46−2.19 (m, 7H), 2.03−1.98 (m, 4H), 1.73−1.60 (m, 2H), 1.31−1.27 (m, 5H), 1.16 (d, J = 6.8 Hz, 3H), 1.04 (s, 3H), 0.98 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.7, 170.4, 165.0, 151.9, 139.1, 137.4, 124.0, 119.1, 115.6, 103.8, 78.6, 73.9, 72.2, 64.8, 64.7, 53.6, 41.6, 40.4, 39.6, 38.1, 32.5, 31.6, 30.2, 25.4, 22.9, 19.0, 17.8, 15.9, 15.8, 13.3; HRMS (EI+) calcd for $C_{30}H_{45}NO_7S$ $(M + H)^+$ 564.2995, found 564.3004.

Acknowledgment. This research was supported by the National Institutes of Health [Grants CA-28824 (S.J.D.) and CA-08748 (T.-C.C.)]. Postdoctoral Fellowship support is gratefully acknowledged by M.D.C. (NIH, 1 F32 GM19972-01), C.R.H. (American Cancer Society, PF-98-173-001), S.D.K. (U.S. Army Breast Cancer Research Fellowship, DAMD 17-98-1-1854), A.B. (NIH, CA-GM 72231), F. Z. (Upjohn Pharmacia Predoctoral Fellowship), S. J. S. (NIH, F32 CA81704), and C.B.L. (U.S. Army, Grant DAMD 17-98-1-8155). The authors wish to thank Dr. George Sukenick (NMR Core Facility, Sloan-Kettering Institute) for mass spectral and NMR analysis.

Supporting Information Available: ^1H and ^{13}C NMR spectra of selected intermediates (**8**, **11**−**13**, **15**−**17**, **19**−**22**).This material is available free of charge via the Internet at http://pubs.acs.org.

JO020180Q