Total Synthesis and Antitumor Activity of 12,13-Desoxyepothilone F: An Unexpected Solvolysis Problem at C15, Mediated by Remote Substitution at C21

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A new epothilone analogue, 12,13-desoxyepothilone F (dEpoF, 21-hydroxy-12,13-desoxyepothilone B, 21-hydroxyepothilone D), was synthesized and evaluated for antitumor potential. A convergent strategy employed for the semipractical synthesis of 12,13-desoxyepothilone B (dEpoB) has been utilized to yield an amount of dEpoF sufficient for relevant biological studies. The results from an in vitro assay reveal that this new analogue is highly active against various tumor cell lines with a potency comparable to that of dEpoB. In particular, the growth of resistant tumor cells is inhibited by dEpoF at concentrations where paclitaxel (Taxol) is basically ineffective. A preliminary assessment of its in vivo activity is also promising. The new analogue, containing an additional hydroxyl group at C21, exhibits advantages over other epothilones in terms of water solubility, and can serve as a readily functionalizable handle to produce other useful compounds for pertinent biological studies.

The epothilones are a family of naturally occurring cytotoxic macrolides that were isolated from the mycobacterium *Sorangium cellulosum*.[1,2] Despite apparently minimal structural homology with the taxoids, the epothilones manifest biological effects similar to those of paclitaxel (Taxol; Taxol is a registered trademark of Bristol-Meyers Squibb) on microtubule and cultured cells.[3] While these two classes of compounds seemingly share the same mode of action, the epothilones retain remarkable potency against multi-drug-resistant tumor cells.[4,5] They may also offer advantages relative to paclitaxel in terms of formulatabililty. Due to the exciting potential of the epothilones for clinical development, they have attracted considerable attention in cancer research as possible agents for cancer chemotherapy.[6]

Given the biological ramifications of the epothilones, it is hardly surprising that they have engendered a great deal of attention from the standpoint of total synthesis. Indeed, several total syntheses of naturally occurring epothilones have been accomplished.[7−21] Subsequently, syntheses of numerous analogues have served to establish a rather detailed map of the structure−activity relationships (SARs) based on in vitro and in vivo[22] assays.[6] Recently, extensive in vivo experiments demonstrated that the less cytotoxic 12,13-desoxyepothilone B (**2b**, dEpoB) (Figure 1) manifests a more promising therapeutic profile than does epothilone B (**1b**, EpoB) itself.[23,24] In our studies in mice, the desoxy compound, dEpoB, was well tolerated and is virtually curative against otherwise resistant xenograft tumors. Although the desoxy derivatives are present as minor components from fermentation, the more biologically significant dEpoB is apparently scarce in that it is a secondary constituent within a family of minor B components from

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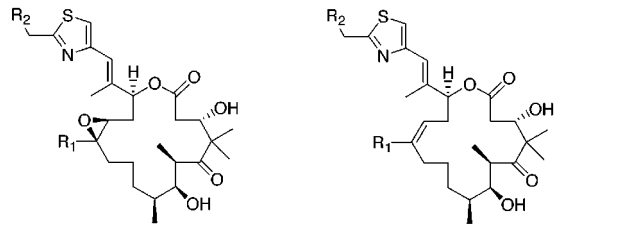

1

1a R_1 = H, R_2 = H, Epothilone A
1b R_1 = CH_3, R_2 = H, Epothilone B
1c R_1 = H, R_2 = OH, Epothilone E
1d R_1 = CH_3, R_2 = OH, Epothilone F

2

2a R_1 = H, R_2 = H, Epothilone C
2b R_1 = CH_3, R_2 = H, Epothilone D
2c R_1 = H, R_2 = OH, Desoxyepothilone E
2d R_1 = CH_3, R_2 = OH, Desoxyepothilone F

Figure 1. Structures of epothilones and desoxyepothilones.

fermentation. While our previous studies relied entirely on the fully synthetic dEpoB,[25,26] it is of interest to note the emerging possibility that biotransformation may, someday, be able to deliver significant amounts of 12,13-desoxyepothilones (vide infra).

Among the structural variants isolated from fermentation are epothilones E and F, each of which possesses a 21-hydroxyl group.[14,27,28] Preliminary in vitro SAR studies on these compounds show that these more oxidized epothilones retain the biological activity of the A and B systems. Despite the putative role of the thiazole as a key pharmacophore,[29] the 21-hydroxyl group does not abrogate binding.[30] Another particularly inviting prospect associated with having a primary hydroxyl group is that of enhanced aqueous solubility, thereby providing major simplifications in issues of formulation. Furthermore, the primary hydroxyl group could be utilized as a staging point for further elaboration.

A recent study by Höfle et al. described a method to functionalize C21 starting with epothilone B itself via *N*-oxidation, acylation, and Polonovsky-like rearrangement.[30] Thus, it is now possible to convert some epothilones to their corresponding 21-hydroxy analogues. However, access to a 21-hydroxylated epothilone bearing 12,13-unsaturation by the Höfle method is still limited due to the vulnerability of the C12−C13 double bond to epoxidation by the same sorts of peroxy reagents which are necessary to achieve *N*-oxide formation. The *N*-oxide of the thiazole is required for the Polonovsky rearrangement sequence, which leads ultimately to the 21-hydroxy group. Indeed, in the total syntheses of EpoA and EpoB, the 12,13-epoxide was introduced by treatment of the corresponding deoxy systems with either peracids or, preferably, 2,2-dimethyldioxirane. Thus, it would appear that to reach dEpoF by partial synthesis requires one to start with EpoB. The latter would be advanced to EpoF by the Höfle technology. Deoxygenation of the 12,13-oxido linkage with a 21-oxygen-based function already in place would then be required. Also to be considered in the future is the possibility that recent biosynthetic routes to the epothilone family, using heterologous expression in surrogate microbial hosts, could effectively address the problem of reaching dEpoF.[31,32]

In light of these promising prospects, and lacking access to fermentation-derived EpoB, we came to favor a total synthesis of dEpoF, at least as a temporary expedient to provide material for the all-critical preliminary assessments of biological utility. Herein, we report the total synthesis of 12,13-desoxyepothilone F (**2d**) and provide evaluations which point to its promise as an antitumor agent.

Our synthesis adopted a strategy similar to that of our previous dEpoB synthesis. In that effort, two fragments of roughly equal complexity served as key building blocks (Scheme 1). While the preparation of the "alkyl" wing (**3**) required de novo construction of the thiazole moiety, we envisioned that the "acyl" sector (**4**), available from our previous synthesis of dEpoB, would serve for the polypropionate domain.

The synthesis of the alkyl wing commenced with protection of the known thiazole (**5**)[33] with a Troc group (Scheme 2). It was anticipated that this group could be cleaved concurrently with deprotection of a hydroxyl group at C7. In the event, ester **6** was reduced with Dibal-H to provide aldehyde **7**. Homologation of this compound via phosphorane **8** led to aldehyde **9**.

Asymmetric addition of the allyl unit was accomplished by the Brown protocol,[34] thereby establishing the (*S*)-configuration of the carbinol in **10** with high ee (>95%). Selective dihydroxylation of the terminal olefin, followed by the cleavage of the resultant diol, gave rise to aldehyde **11**. Although the iodoethenylation reaction[35] produced the iodoalkene function with the desired (*Z*)-geometry, the Troc protective group proved quite unstable under these conditions. Thus, the crude product was directly treated with lithium hydroxide to give alcohol **13**, which in turn was converted to **3** in serviceable yield.

The union of the two key fragments **3** and **4** was achieved through a Pd-catalyzed Suzuki coupling reaction to generate diketone **14** in 60−75% yield (Scheme 3).[36−38] Alternatively, alcohol **13** could be directly employed for this reaction. The resultant product, following reprotection of the 21-hydroxyl function with a Troc group, afforded diketone **14**. After removal of the TBS group, diketone **15** was subjected to a ruthenium-mediated asymmetric hydrogenation reaction in methanol using a modified Noyori catalyst.[39,40] Indeed, the desired diol **16** was produced as a single diastereomer. *However, remarkably, an approximately equal quantity of the methyl ether* ***17*** *was also produced as a single stereoisomer, though of unproven configuration*.[41] The use of commercially avail-

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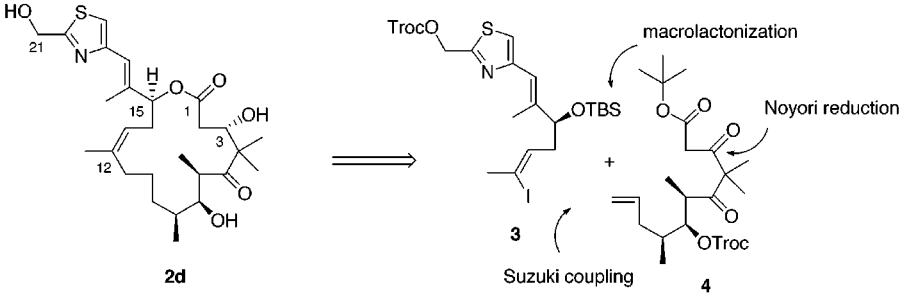
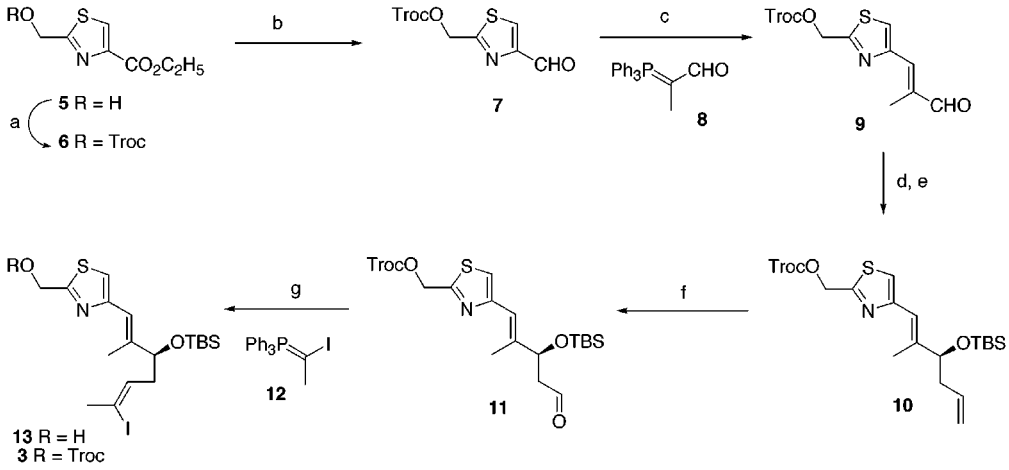
Scheme 1. Retrosynthetic Analysis



Scheme 2. Synthesis of the Left Wing[a]



[a] Reagents and conditions: (a) Cl_3CCH_2OCOCl, Pyr, CH_2Cl_2, 0 °C, 0.5 h, 95%; (b) Dibal-H, CH_2Cl_2, −78 °C, 10 h, 80%; (c) **8**, C_6H_6, 80 °C, 3 h, 89%; (d) (+)-Icp$_2$(allyl), pentane, −100 °C, 74% (>95% ee); (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C to rt, 2 h, 95%; (f) (i) 1% OsO_4, NMO, H_2O−THF, 0 °C, 12 h; (ii) $Pb(OAc)_4$, C_6H_6, 0 °C, 1 h, 82%; (g) (i) **12**, THF, −78 to −30 °C, then LiOH, THF−H_2O, rt, 61%; (ii) Cl_3CCH_2OCOCl, Pyr, CH_2Cl_2, 0 °C, 95%.

able catalyst, $\{RuCl_2(BINAP)\}_2$,[42] resulted in the formation of a complex mixture in which the major component was the C16−C17 reduced product **18**. Under a variety of different conditions, the formation of the methyl ether could not be avoided. Since it was conceivable that methanolic HCl had induced solvolysis of the C15 hydroxy group, it was hoped that recourse to ethanol as the solvent would minimize the surprising solvolysis process. While the yield of diol **16** was improved, the reaction, under these conditions, is significantly slower and the conversion to product is poor. The use of a C15 TBS ether, **14**, as the substrate provided only marginal improvement. These results stand in contrast with the synthesis of dEpoB where no such solvolysis reaction was encountered.

The asymmetric Noyori reduction using $Et_2NH_2[\{(R)\text{-BINAP})RuCl\}_2Cl_3]$[43,44] as catalyst is known to be critically dependent on the amount of acid present.[45] In the case of the dEpoB synthesis, the presence of stoichiometric HCl was absolutely required for achieving reduction at C3 in a chemo- and diastereoselective fashion.[25] We surmise that the addition of stoichiometric acid resulted in protonation of the thiazole moiety, thereby preventing the inactivation of the ruthenium catalyst. It is also possible that, in the dEpoB total synthesis, it is protonation of the thiazole which effectively protects the vulnerable C15 allylic alcohol from solvolysis. Ironically, with a less basic thiazole which is less effective in buffering the acid, the solvolysis risk factor is enhanced. We note that, in contrast to the situation pertaining to the synthesis of dEpoB, Noyori reduction at C3 of substrate **16** can be conducted with substoichimetric HCl. However, solvolysis still proceeded even in the presence of HCl in concentrations as low as 20 mol %. This result again suggests that the 21-hydroxymethyl-substituted thiazole moiety may not be an effective base to scavenge HCl. It is interesting that a subtle difference at the thiazole has such a strong effect on the reactivity of a seemingly remote alcohol. Presumably, this difference arises from an electronic effect, though there could be a conformational component.

While this very surprising susceptibility to solvolysis of **16** and related congeners at C15 was certainly for the moment detrimental to the efficiency of our total synthesis, we moved on to our goal. Having established all of the necessary stereocenters, the *tert*-butyl ester was unmasked with simultaneous protection of the C3 and

(41) While it is likely that the solvolysis reaction proceeded with inversion of stereochemistry, the rigorous elucidation of the stereochemistry of the presumed **17** at C15 has not been accomplished despite considerable effort.

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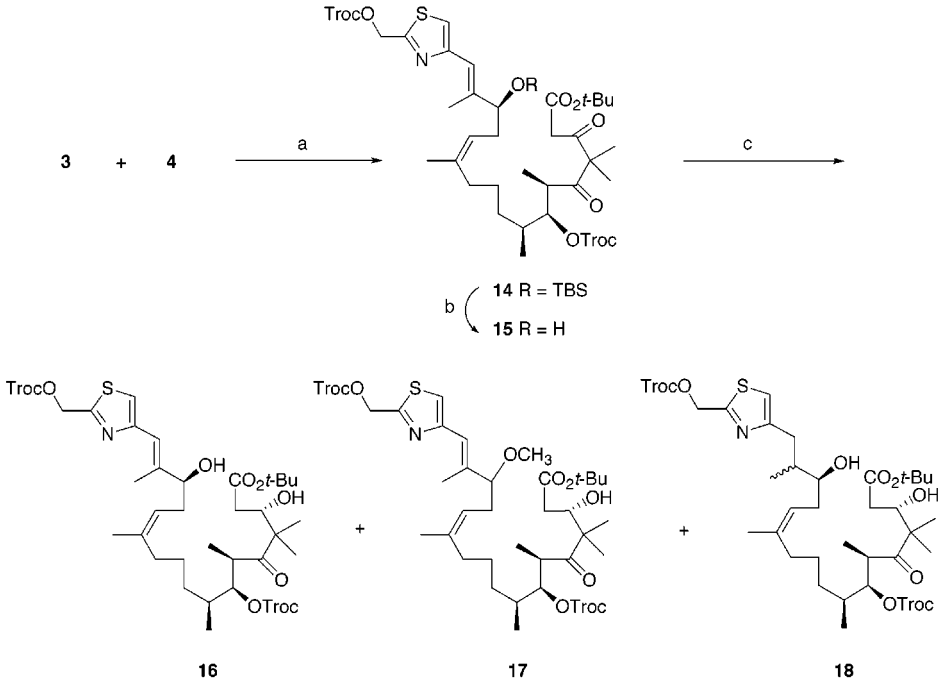
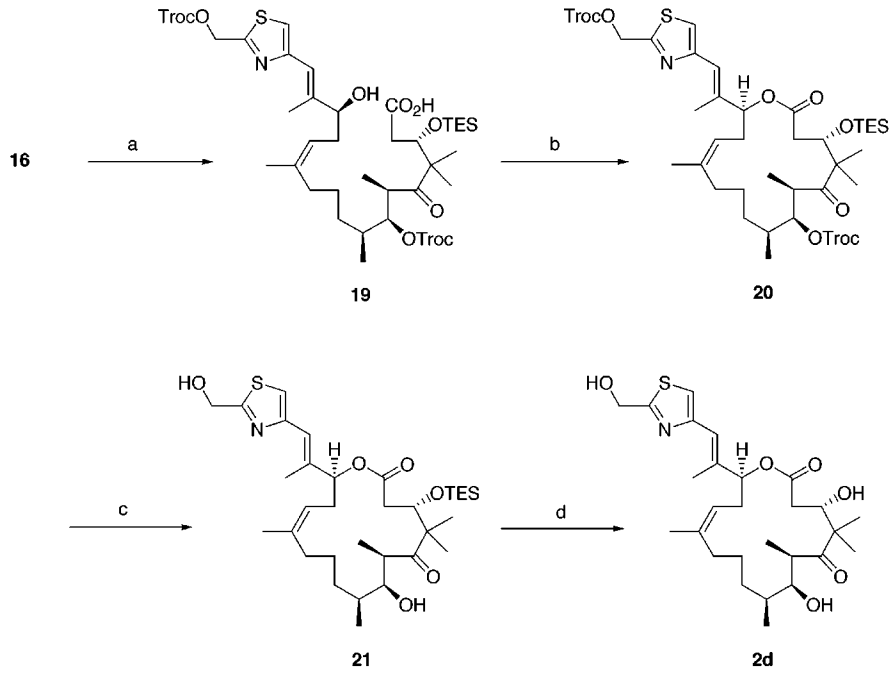
Scheme 3. *B*-Alkyl Suzuki Coupling and Noyori Asymmetric Hydrogenation[a]



[a] Reagents and conditions: (a) 9-BBN−H, THF, 25 °C, then $(dppf)PdCl_2 \cdot CH_2Cl_2$, $AsPh_3$, Cs_2CO_3, THF−DMF−H_2O, 2 h, 65%; (b) HCl−CH_3OH, 2 h, 84%; (c) 5% $Et_2NH_2[\{(R)\text{-(BINAP)RuCl}\}_2Cl_3]$, HCl−$CH_3OH$, H_2 (1200 psi), rt, 8 h, 49% of **16** and 42% of **17**.

Scheme 4. Completion of the Synthesis of dEpoF (2d)[a]



[a] Reagents and conditions: (a) (i) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C to rt, 8 h, (ii) HCl−CH_3OH, 0 °C, 70%; (b) 2,4,6-trichlorobenzoyl chloride, $(C_2H_5)_3N$, then 4-DMAP, toluene, slow addition, 3 h, 60−70%; (c) Zn, AcOH−THF, rt, 1 h, 86% or cat. NiI_2/SmI_2, THF, −78 to −40 °C, 87%; (d) HF·pyridine, THF, 0 °C to rt, 91%.

C15 alcohols by TESOTf (Scheme 4). Selective desilylation of the C15 TES group with methanolic HCl provided **19**, setting the stage for cyclization. Macrolactonization of this seco-acid, according to the Yamaguchi protocol,[46,47] afforded fully protected lactone **20** in 60−70% yield. The removal of the two Troc protecting groups was performed through the agency of samarium(II) iodide[48] or zinc, both in good yields. Finally, standard fluoride-induced removal of the C3 silyl group yielded the desired 12,13-desoxyepothilone F (**2d**).

The fully synthetic dEpoF has been evaluated against a variety of cell types to evaluate its antitumor potential. As shown in Table 1, dEpoF exhibited high cytotoxicity

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Table 1. Potency of dEpoF, dEpoB, and Taxol against Various Tumor Cell Growths in Vitro

tumor cell lines	IC_{50} (μM)[a] dEpoF	dEpoB	paclitaxel	others
		Human T-cell AL Leukemia		
CCRF-CEM	0.0027	0.0095	0.0021	0.00063,[b] 0.290[c]
CCRF-CEM/VBL_{100}	0.047 (17.4×)	0.017 (1.8×)	4.140 (1971×)	0.332[b] (527×)
CCRF-CEM/VM_1	0.0049 (1.8×)	0.014 (1.5×)	0.0066 (3.18×)	3.44[c] (117×)
CCRF−CEM/Taxol	0.0053 (2.0×)	0.0162 (1.7×)	0.120 (57×)	
		Hamster Lung Fibroblasts		
DC-3F	0.0017	0.0019	0.0135	0.00025[d]
DC-3F/ADII	0.0136 (8.0×)	0.0073 (3.8×)	0.583 (43.2×)	0.00153[d] (61.2×)
DC-3F/ADX	0.0223 (13.1×)	0.0288 (15.2×)	20.19 (1496×)	0.4092[d] (1637×)
		Human CM Leukemia		
K562	0.0021	0.0036	0.0029	
		Human Mammary Carcinoma		
MX-1	0.0042	0.0221	0.0394	0.00184[e]

[a] Cell growth inhibition was measured by XTT tetrazonium assay after 72 h of incubation for cell growth as described previously in ref 23. The values were determined with six to seven concentrations of each drug using a computer program. The cross-resistances are shown in parentheses. [b] Vinblastin (VBL). [c] Etoposide (VP-16). [d] Actinomycin D (AD). [e] Epothilone B (EpoB).

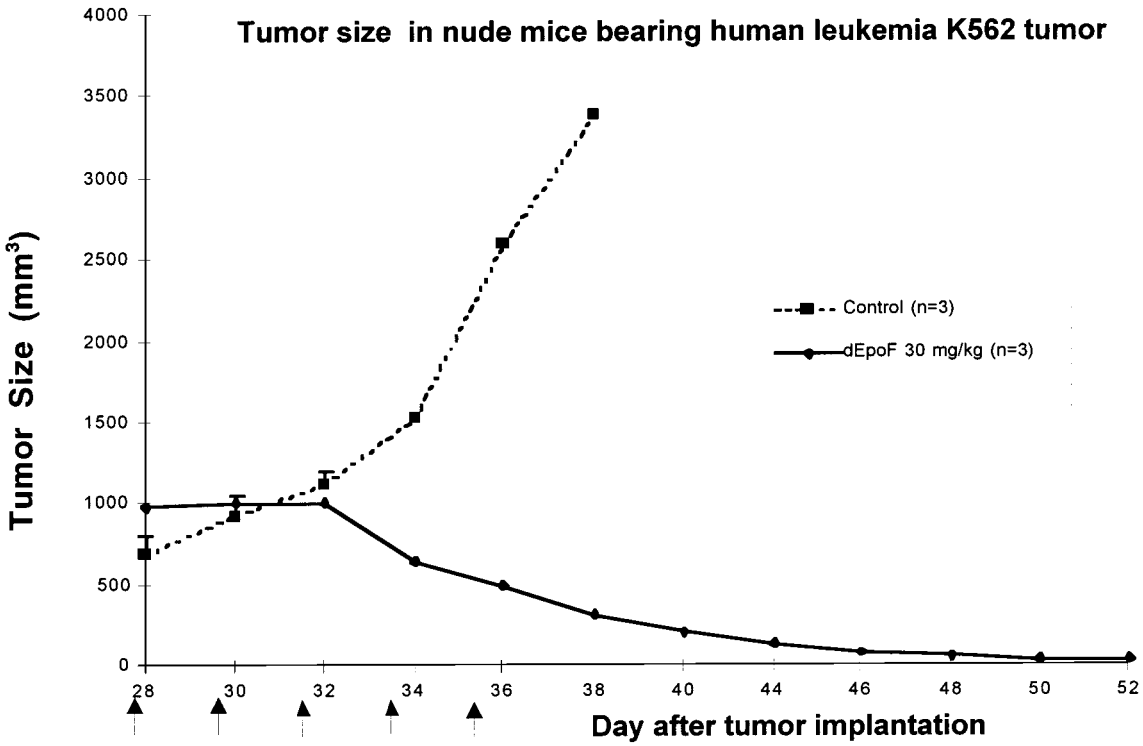

Figure 2. Therapeutic effect of dEpoF in nude mice bearing human leukemia K562 xenograft.

activity against a range of sensitive and resistant tumor cell lines tested. In particular, high potency and relatively low cross-resistances were observed for dEpoF against sensitive and MDR cell lines, respectively. Direct comparison of dEpoF with dEpoB indicates that the new compound possesses a comparable potency. It is noteworthy that dEpoF consistently outperforms other anticancer agents such as Taxol, vinblastine, etoposide, and actinomycin in inhibiting the growth of MDR tumor cells.

We then turned our attention to the in vivo efficacy of dEpoF. Thus, the therapeutic effect of dEpoF was evaluated in athymic mice bearing a human leukemia K562 xenograft. The animal experiments were performed according to the slow IV infusion protocol developed in our previous studies.[23,24] As depicted in Figure 2, treatment of the mice with dEpoF (30 mg/kg) readily induced reduction in the size of the tumor to the point of remission. While the preliminary in vivo results with this sensitive tumor clearly look promising, more revealing experiments are necessary to assess its full promise.

With the encouraging biological results, we next examined the aqueous solubility of dEpoF using an HPLC-based method.[49] *Indeed, dEpoF was found to be 2.5 times more water soluble than dEpoB*. Although literature estimates of paclitaxel aqueous solubility vary considerably,[50] it has been noted that epothilones are approximately 30 times more water soluble than paclitaxel.[1] Considering these observations and the problems associated with paclitaxel administration, the present analogue appears to be a promising candidate that may bring significant improvement in the formulation of the active drug.

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(50) Straubinger, R. M. In *Taxol: Science & Applications*; Suffness, M., Ed.; CRC Press: Boca Raton, FL, 1995; p 237.

In summary, a new epothilone analogue which possesses an additional hydroxy group at the 21-position has been obtained by total synthesis, using the strategy based on the convergent merger of the two key fragments by *B*-alkyl Suzuki coupling and subsequent macrolactonization. Compared to the dEpoB synthesis, the synthesis of dEpoF described here suffers, for the moment, from a surprising acid-induced susceptibility of the C15 allylic alcohol to solvolysis (under conditions required for reduction of the C3 ketone with high asymmetric induction). Nevertheless, an amount of dEpoF sufficient for biological studies has been successfully produced. The in vitro and in vivo tumor growth inhibition experiments demonstrated the new analogue possesses high antitumor activity. Given the promising in vivo profile of the closely related dEpoB, the need for further investigation with dEpoF is apparent. Experiments along these lines are underway.

Experimental Section

General Procedures. All commercial materials were used without further purification unless otherwise noted. The following solvents were obtained from a dry solvent system and used without further drying: THF, diethyl ether, methylene chloride, toluene and benzene. All reactions were performed under a positive pressure of prepurified dry argon gas. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 400 and 100 MHz, respectively. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F254 plates, and flash chromatography was performed using the indicated solvent on E. Merck silica gel 60 (40−63 μm) or Sigma H-type silica gel (10−40 μm).

Preparation of 6. To a solution of ethyl 2-(hydroxymethyl)-thiazole-4-carboxylate[33] (**5**; 38.4 g, 0.205 mol) and pyridine (41 mL, 0.053 mol) in CH_2Cl_2 (100 mL) was slowly added 2,2,2-trichloroethyl chloroformate (32 mL, 0.23 mol) at 0 °C. After the resulting mixture was stirred for 30 min, the reaction was quenched by the addition of 10% aq $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with 2 N HCl, 10% aq $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated. The residue was then recrystallized in ethanol (50 mL) to yield a light yellow solid (35 g). The mother liquor was concentrated and chromatographed to afford an additional amount (35 g) of ethyl ester **6** (95%): mp 82.5−83.0 °C; IR (film) 2981, 1765, 1718, 1236 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 5.64 (s, 2H), 4.85 (s, 2H), 4.55 (q, J = 7.1 Hz, 2H), 1.45 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 161.0, 153.5, 147.5, 128.8, 94.0, 77.2, 66.5, 61.7, 14.4; HRMS calcd for $C_{10}H_{10}Cl_3NO_5SNa$ (M + Na^+) 383.9242, found 383.9237.

Preparation of 7. To a solution of ester **6** (23 g, 0.063 mol) in CH_2Cl_2 (200 mL) was added a solution of Dibal-H (1.0 M in CH_2Cl_2, 120 mL) at −78 °C over 0.5 h. After the addition, the resulting mixture was placed in a freezer at −78 °C for 10 h. The excess Dibal-H was quenched with acetic acid (5 mL) and warmed to rt, and the mixture was stirred with satd aq Rochelle's salt (150 mL) until the suspension disappeared and a clear two-phased solution was formed. The organic layer was washed with 10% aq $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. Purification by column chromatography on SiO_2 (toluene/ethyl acetate, 6:1) afforded aldehyde **7** as a light yellow syrup (16 g, 80%): IR (film) 1762, 1699, 1384 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 8.23 (s, 1H), 5.55 (s, 2H), 4.83 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.3, 164.6, 154.9, 153.5, 153.1, 128.6, 93.9, 66.2; LRMS calcd for $C_8H_6Cl_3NO_4SNa$ (M + Na^+) 341.6, found 341.9.

Preparation of 9. To a solution of aldehyde **7** (21.0 g, 0.0660 mol) in benzene (300 mL) was added **8** (20.6 g, 0.0660 mol). The resulting mixture was heated at reflux for 3 h, cooled to rt, and concentrated. Purification by flash column chromatography on SiO_2 (hexanes/ethyl acetate, 4:1) yielded aldehyde **9** as a clear oil (21.0 g, 89%): IR (film) 1764, 1679, 1628, 1437 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1H), 7.67 (s, 1H), 7.30 (s, 1H), 5.58 (s, 2H), 4.88 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 163.1, 153.5, 152.1, 140.1, 139.3, 124.2, 94.0, 77.1, 66.4, 11.0; LRMS calcd for $C_{11}H_{10}Cl_3NO_4S$ (M + H^+) 359.6, found 360.1.

Asymmetric Brown Allylation. A solution of aldehyde **9** (9.20 g, 25.7 mmol) in anhydrous ether (50 mL) was cooled to −100 °C. A pentane solution of (+)-diisopinocampheylallylborane[34] (1.5 equiv, 150 mL) was added dropwise to the vigorously stirred aldehyde solution. After the addition was complete, the reaction mixture was stirred for 1.5 h and warmed to −50 °C. A solution of 30% aq H_2O_2 (20 mL) and 10% aq $NaHCO_3$ (50 mL) were added, and the resulting turbid mixture was stirred at 25 °C for 8 h. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with satd aq $Na_2S_2O_3$ and brine, dried ($MgSO_4$), filtered, and concentrated. Purification by flash column chromatography on SiO_2 (hexanes/ethyl acetate, 10:1) afforded the alcohol as a clear oil (7.65 g, 74%). The ee of the alcohol was determined to be 95% by derivatizing to the corresponding Mosher ester: $[\alpha]^{25}_D$ −2.5 (*c* 1.00, $CHCl_3$); IR (film) 3382, 2958, 1763, 1384, 1239, 820 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 1H), 6.59 (s, 1H), 5.77−5.87 (m, 1H), 5.62 (s, 2H), 5.16 (d, J = 17.0 Hz, 1H), 5.01 (d, J = 11.0 Hz, 1H), 4.82 (s, 2H), 4.23 (m, 1H), 2.43−2.49 (m, 1H), 2.36−2.40 (m, 1H), 2.07 (s, 3H), 1.90 (s, 1H); HRMS calcd for $C_{14}H_{17}Cl_3N_1O_4Si$ (M + H^+) 399.9943, found 399.9927.

Preparation of 10. To a mixture of the alcohol prepared as above (7.65 g, 19.1 mmol) and 2,6-lutidine (10 mL, 86 mmol) in CH_2Cl_2 (50 mL) was added dropwise TBSOTf (15 mL, 0.066 mol) at −78 °C. After the addition, the reaction mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was poured into 2 N HCl and extracted with ether. The combined organic layers were washed with 10% aq $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography on SiO_2 (hexane → hexanes/ethyl acetate, 20:1) provided TBS ether **10** as a colorless oil (9.39 g, 95%): $[\alpha]^{25}_D$ −2.2 (*c* 1.00, $CHCl_3$); IR (film) 1767, 1239, 1076 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 1H), 6.49 (s, 1H), 5.79 (m, 1H), 5.52 (s, 2H), 5.04 (d, J = 17.9 Hz, 1H), 5.01 (d, J = 8.5 Hz, 1H), 4.82 (s, 2H), 4.16 (t, J = 6.1 Hz, 1H), 2.39−2.30 (m, 2H), 2.01 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 152.8, 152.6, 142.1, 134.0, 116.9, 116.0, 115.5, 92.9, 77.0, 65.5, 40.2, 24.6, 17.1, 12.9, −5.7, −6.0; HRMS calcd for $C_{20}H_{31}Cl_3NO_4SSi$ (M + H^+) 514.0808, found 514.0790.

Dihydroxylation of 10. To a mixture of alkene **10** (20.6 g, 0.0400 mol), H_2O (21 mL), and *N*-methylmorpholine *N*-oxide (50% in THF, 10 mL, 0.048 mol) in *t*-BuOH (155 mL) was added OsO_4 (1 wt % in THF, 20.3 mL, 0.78 mmol) at 0 °C. After the resulting mixture was stirred for 12 h, Na_2SO_3 (∼10 g) and water (5 mL) were added. The resulting solution was stirred at 25 °C for 30 min and then extracted with ether. The combined extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by flash chromatography on SiO_2 provided a 1:1 diastereomeric mixture of the diol as a colorless, viscous oil (18.8 g, 85%): IR (film) 3396, 1764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 0.5H), 7.16 (s, 0.5H), 6.61 (s, 0.5H), 6.53 (s, 0.5H), 5.51 (s, 2H), 4.82 (s, 2H), 4.49−4.45 (m, 1H), 3.94 (m, 1H), 3.61 (m, 1H), 3.45 (m, 1H), 2.04 (s, 3H), 1.92−1.55 (m, 4H), 0.93 (s, 4.5H), 0.92 (s, 4.5H), 0.14 (s, 1.5H), 0.13 (s, 1.5H), 0.07 (s, 1.5H), 0.04 (s, 1.5H); HRMS calcd for $C_{20}H_{32}O_6Cl_3NSSiNa$ (M + Na^+) 570.0682, found 570.0694.

Preparation of 11. To a suspension of the diol prepared as above (18.0 g, 0.032 mol) and Na_2CO_3 (8.67 g, 0.081 mol) in benzene (500 mL) was added $Pb(OAc)_4$ (19.1 g, 0.043 mol) portionwise at 0 °C over the course of 5 min. After being stirred for 15 min, the mixture was filtered through a SiO_2 pad to afford aldehyde **11** (14.0 g, 82%). The product was directly subjected to the next reaction: $[\alpha]^{25}_D$ −11.0 (*c* 1.00, $CHCl_3$); IR (film) 1765, 1724, 1678 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ

9.80 (s, 1H), 7.16 (s, 1H), 6.58 (s, 1H), 5.51 (s, 2H), 4.82 (s, 2H), 4.69 (dd, J = 6.5, 3.2 Hz, 1H), 2.74 (ddd, J = 12.6, 6.5, 2.3 Hz, 1H), 2.53 (ddd, J = 12.5, 3.2, 1.6 Hz, 1H), 2.06 (s, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 154.0, 153.8, 142.0, 118.9, 118.3, 94.5, 77.5, 74.1, 66.9, 50.5, 26.1, 18.5, 14.7, −4.4, −4.7; HRMS calcd for $C_{19}H_{29}Cl_3NO_5SSi$ (M + H$^+$) 516.0601, found 516.0604.

Preparation of 3. To a suspension of (ethyl)triphenylphosphonium iodide (7.90 g, 17.9 mmol) in THF (150 mL) was added *n*-butyllithium (7.17 mL, 2.5 M in hexane, 17.9 mmol) at ambient temperature. After disappearance of the solid material, the red solution was cannulated into a vigorously stirred solution of iodine (4.54 g, 17.9 mmol) in THF (150 mL) at −78 °C. The resulting dark brown suspension was stirred for 5 min and allowed to warm gradually to −30 °C. A solution of NaHMDS (17.3 mL, 1.0 M in THF) was added dropwise to afford a dark red solution. Then, a solution of aldehyde **11** (3.10 g, 5.98 mmol) in THF (10 mL) was slowly added, and stirring was continued at −30 °C for 30 min. The reaction mixture was diluted with pentane (100 mL), filtered through a pad of Celite, and concentrated. Purification by flash column chromatography on SiO_2 (hexane/ethyl acetate, 15:1) afforded vinyl iodide **3** as a yellow syrup (1.50 g, 38%): $[\alpha]^{25}_D$ +4.5 (*c* 1.00, $CHCl_3$); IR (film) 1764, 1249, 1067 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 1H), 6.45 (s, 1H), 5.43 (s, 2H), 5.39 (t, J = 6.6 Hz, 1H), 4.75 (s, 2H), 4.15 (dd, J = 12.2, 5.7 Hz, 1H), 2.42 (s, 3H), 2.34−2.37 (m, 2H), 2.00 (s, 3H), 0.83 (s, 9H), 0.05 (s, 3H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 154.2, 153.8, 142.9, 132.0, 118.1, 117.4, 102.5, 77.1, 66.6, 43.7, 33.7, 25.8, 18.2, 14.3, 13.6, −4.6, −5.0; FAB-HRMS calcd for $C_{21}H_{32}Cl_3INO_4SSi$ (M + H$^+$) 653.9311, found 653.9931.

Preparation of 13. To a suspension of (ethyl)triphenylphosphonium iodide (5.05 g, 12.1 mmol) in THF (30 mL) was added a solution of NaHMDS (12 mL, 1.0 M in THF) at ambient temperature. After being stirred for 5 min, the dark red solution was cooled to −78 °C and cannulated into a vigorously stirred solution of iodine (3.02 g, 11.9 mmol) in THF (50 mL) at −78 °C to form a dark brown suspension. After 5 min, a solution of NaHMDS (11 mL, 1.0 M in THF) was added, and the resulting red solution was stirred for 0.5 h. A solution of aldehyde **11** (3.12 g, 6.04 mmol) in THF (30 mL) was added via cannula, and the mixture was allowed to warm to −20 °C over 1 h, at which point TLC analysis indicated complete consumption of the starting aldehyde. The reaction was quenched by the addition of satd aq NH_4Cl (0.5 mL) and hexanes (50 mL), and the resulting precipitates were removed by a short pad of silica gel. The filtrate was concentrated under reduced pressure to give 4.05 g of light yellow oil.

The crude mixture, obtained from above, was dissolved in aqueous THF (1:1, 10 mL). Then, lithium hydroxide monohydrate (0.510 g, 12.2 mmol) was added, and the resultant mixture was stirred at 25 °C for 4 h. The two-phased solution was poured into satd aq NH_4Cl and extracted with ethyl acetate. The combined organic layers were washed with 10% aq $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on SiO_2 (hexanes/ethyl acetate, 3:1) afforded alcohol **13** as a light yellow oil (1.78 g, 61%): $[\alpha]^{25}_D$ +6.4 (*c* 2.00, $CHCl_3$); IR (film) 3272, 1252, 1068 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 1H), 6.49 (s, 1H), 5.45 (td, J = 6.6, 1.4 Hz, 1H), 4.94 (s, 2H), 4.21 (t, J = 6.4 Hz, 1H), 2.48 (s, 3H), 2.43−2.31 (m, 2H), 2.02 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 153.2, 142.4, 132.0, 118.4, 115.8, 102.5, 77.1, 62.1, 43.6, 33.6, 25.8, 18.2, 14.3, −4.7, −5.0; FAB-MS calcd for $C_{18}H_{31}INO_2SSi$ (M + H$^+$) 480.0890, found 480.0908.

Preparation of 14 (Characterized as a 1.8:1 Mixture of Keto−Enol* Tautomers). To a solution of 9-BBN-H (0.774 g, 6.34 mmol) in THF (5 mL) was added a solution of tricarbonyl **4** (2.80 g, 5.43 mmol) in THF (5 mL). After the resulting mixture was stirred at 25 °C for 1 h, TLC analysis indicated the complete consumption of the starting olefin **4**. In a separate flask containing vinyl iodide **3** (3.25 g, 4.53 mmol), (dppf)$PdCl_2$·CH_2Cl_2 (0.370 g, 0.453 mmol), $AsPh_3$ (0.139 g, 0.454 mmol), and Cs_2CO_3 (2.21 g, 6.78 mmol) was added degassed DMF (5 mL). The resulting red suspension was purged with a stream of argon gas for 20 min. Water (2 mL) was added to the borane solution, prepared above, and stirring was continued for 10 min to quench the excess 9-BBN-H. Then, the solution of the alkylborane was added rapidly to the vigorously stirred solution containing the vinyl iodide. After 2 h, the reaction mixture was diluted with ether, washed with water and brine, dried ($MgSO_4$), and concentrated. Purification by flash column chromatography on SiO_2 (hexanes/ethyl acetate, 10:1) gave **14** as a light yellow viscous oil (3.26 g, 65%): $[\alpha]^{25}_D$ −21.0 (*c* 4.46, $CHCl_3$); IR (film) 1759, 1721, 1698, 1462 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.60* (s, 1H), 7.12 (s, 1H), 7.10* (s, 1H), 6.46 (s, 1H), 5.49 (s, 2H), 5.10 (t, J = 6.9 Hz, 1H), 4.86−4.80 (m, 3H), 4.74−4.67 (m, 2H), 4.05 (t, J = 6.1 Hz, 1H), 3.47 (d, J = 16.2 Hz, 1H), 3.40 (d, J = 16.2 Hz, 1H), 3.35−3.25 (m, 1H), 2.25−2.15 (m, 2H), 1.99 (s, 3H), 1.99−1.86 (m, 2H), 1.73−1.60 (m, 5H), 1.48 (s, 3H), 1.48−1.27 (m, 15H), 1.09* and 1.07 (d, J = 6.9 Hz, 3H), 0.93* and 0.90 (d, J = 7.4 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7, 209.6, 203.1, 178.4, 172.6, 166.2, 161.2, 154.2, 154.1*, 154.0, 153.6, 143.6, 136.6*, 136.5, 121.7, 117.9, 117.1, 94.7*, 94.6, 94.1, 90.6, 82.9*, 81.9, 81.6*, 78.7, 77.1, 66.6, 63.6, 54.3, 46.5, 41.9*, 41.5, 35.3, 34.8*, 34.6, 32.1, 31.7, 31.2*, 30.6*, 28.2, 27.9, 25.8, 25.1*, 25.0, 23.5*, 23.4, 22.7*, 22.1*, 21.5, 20.8, 18.8*, 18.2, 16.0*, 15.7, 14.1, 12.8*, 11.4; FAB-MS calcd for $C_{43}H_{66}Cl_6NO_{11}SSi$ (M + H$^+$) 1042.2257, found 1042.2304.

Preparation of 15 (Characterized as a 3.3:1 Mixture of Keto−Enol* Tautomers). TBS ether **14** (0.265 g, 0.254 mmol) was dissolved in 0.5 N HCl in MeOH (25 mL). The reaction was stirred at 25 °C and closely monitored by TLC for completion. After 2 h, the reaction mixture was poured into 10% aq $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. Alcohol **15** was purified by flash column chromatography on SiO_2 (hexanes/ethyl acetate, 2:1) to afford a clear viscous oil (0.198 g, 84%): $[\alpha]^{25}_D$ −27.2 (*c* 1.33, $CHCl_3$); IR (film) 3545, 3411, 1759, 1717, 1698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.60* (s, 1H), 7.16 (s, 1H), 7.13* (s, 1H), 6.57 (s, 1H), 5.50 (s, 2H), 5.15 (t, J = 7.0 Hz, 1H), 4.87−4.81 (m, 4H), 4.81 (s, 2H), 4.76−4.68 (m, 2H), 4.13−4.10 (m, 1H), 3.48 (d, J = 16.2 Hz, 1H), 3.41 (d, J = 16.2 Hz, 1H), 3.35−3.26 (m, 1H), 2.31 (t, J = 6.4 Hz, 2H), 2.05 (s, 3H), 2.03−1.99 (m, 2H), 1.75−1.61 (m, 5H), 1.59* and 1.49 (s, 3H), 1.41−1.39 (m, 11H), 1.36 (s, 3H), 1.34* (s, 3H), 1.28* (s, 3H), 1.10* and 1.08 (d, J = 6.8 Hz, 3H), 0.92 and 0.88* (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7*, 209.6, 203.2, 178.5*, 172.6*, 166.3, 161.3, 154.3, 154.2*, 153.8, 153.6, 142.7, 139.2*, 139.0, 120.4, 118.1, 117.6, 117.3*, 94.7*, 94.6, 94.1, 90.6*, 83.0*, 82.0, 81.7*, 77.2, 77.1, 66.6, 63.6, 54.3*, 46.6, 42.0*, 41.6, 34.8*, 34.7, 34.1, 32.1, 30.6, 28.3, 27.9, 25.1*, 25.0, 23.6, 22.7*, 22.2*, 21.6, 20.9, 16.0*, 15.7, 14.6, 13.6*, 12.9*, 11.5; LRMS calcd for $C_{37}H_{51}Cl_6NO_{11}SNa$ (M + Na$^+$) 950.1, found 950.4.

Preparation of 16 and 17. Diketone **15** (0.302 g, 0.325 mmol) was dissolved in 0.12 N HCl in MeOH (3.5 mL, 0.42 mmol) at 25 °C. The ruthenium catalyst[44] (0.048 M in THF, 0.034 mmol) was then added, and the mixture was transferred to a Parr apparatus. The vessel was purged with H_2 for 10 min and then pressurized to 1200 psi. After 8 h at 25 °C, the reaction was returned to atmospheric pressure and poured into satd aq $NaHCO_3$ (15 mL). After extraction with CH_2Cl_2, the combined organic layers were dried (Na_2SO_4) and concentrated. Purification by flash chromatography on SiO_2 (hexanes/ethyl acetate, 2:1) gave the less polar methyl ether **17** as a clear oil (0.152 g, 49%) and the more polar hydroxy ester **16** as a green syrup (0.126 g, 42%).

Characterization of 16: $[\alpha]^{25}_D$ +6.43 (*c* 2.54, $CHCl_3$); IR (film) 3518, 1759, 1726, 1704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 1H), 6.57 (s, 1H), 5.50 (s, 2H), 5.14 (t, J = 6.4 Hz, 1H), 4.86−4.80 (m, 4H), 4.71 (d, J = 12.0 Hz, 1H), 4.15−4.10 (m, 1H), 3.49−3.40 (m, 1H), 2.39−2.20 (m, 5H), 2.04 (s, 3H), 2.04−1.98 (m, 2H), 1.73−1.68 (m, 1H), 1.68 (s, 3H), 1.49−1.44 (m, 2H), 1.44 (s, 9H), 1.19−1.13 (m, 10H), 1.09 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.0, 172.5, 161.4, 154.3, 153.7, 153.6, 142.8, 139.1, 120.3, 118.0, 117.6, 94.7, 83.1, 81.4, 77.1, 72.9, 66.5, 51.9, 41.5, 37.3,

34.7, 34.1, 32.2, 31.2, 28.1, 25.2, 23.6, 21.9, 19.2, 16.2, 14.6, 12.3; FAB-MS calcd for $C_{37}H_{53}Cl_6NO_{11}SNa$ (M + Na^+) 952.1368, found 952.1383.

Characterization of 17: $[\alpha]^{25}_D$ +15.0 (*c* 4.70, $CHCl_3$); IR (film) 3520, 1759, 1729, 1704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 1H), 6.57 (s, 1H), 5.50 (s, 2H), 5.15 (t, *J* = 7.2 Hz, 1H), 4.86−4.81 (m, 4H), 4.71 (d, *J* = 11.9 Hz, 1H), 4.14−4.10 (m, 1H), 3.44−3.30 (m, 2H), 3.22 (s, 3H), 2.37 (dd, *J* = 16.2, 2.1 Hz, 1H), 2.23 (dd, *J* = 16.1, 10.7 Hz, 1H), 2.25−2.18 (m, 1H), 1.97 (s, 3H), 1.94 (m, 2H), 1.68 (m, 1H), 1.63 (s, 3H), 1.44 (s, 9H), 1.41 (m, 1H), 1.19 (s, 3H), 1.15 (s, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.0, 172.5, 161.4, 154.3, 153.6, 153.5, 140.4, 137.0, 120.7, 117.7, 94.7, 87.6, 83.0, 81.4, 77.2, 77.1, 72.9, 66.6, 56.3, 51.9, 41.5, 37.4, 32.6, 32.2, 31.2, 28.1, 25.0, 23.4, 21.8, 19.3, 16.2, 13.3, 12.2; LRMS calcd for $C_{38}H_{55}Cl_6NO_{11}SNa$ (M + Na^+) 968.2, found 968.3.

Preparation of 19. To a solution of diol **16** (0.495 g, 0.531 mmol) in CH_2Cl_2 (5 mL) were added 2,6-lutidine (0.870 mL, 7.47 mmol) and TESOTf (0.840 mL, 3.72 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 0.5 h and then allowed to warm to 25 °C. After being stirred at 25 °C for 8 h, the reaction mixture was diluted with CH_2Cl_2 (40 mL) and poured into 1 N HCl (20 mL). The organic layer was separated, washed with a phosphate buffer solution (20 mL, pH 7), dried (Na_2SO_4), and concentrated. The crude TES derivative was then dissolved in THF (5 mL) and treated with a solution of 0.1 N HCl in MeOH (2.2 mL) at 0 °C. Additional methanolic HCl was added in small portions, and approximately 5 mL of 0.1 N HCl was required for completion. The reaction mixture was diluted with CH_2Cl_2, washed with phosphate buffer (pH 7), dried (Na_2SO_4), and concentrated. Purification on a SiO_2 column (hexanes/ethyl acetate, 1:1) afforded acid **19** as a colorless sticky oil (0.370 g, 70%): $[\alpha]^{25}_D$ −30.3 (*c* 2.34, $CHCl_3$); IR (film) 3389, 1759, 1734, 1705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1H), 6.62 (s, 1H), 5.50 (s, 2H), 5.11 (t, *J* = 6.6 Hz, 1H), 4.87 (d, *J* = 12.0 Hz, 1H), 4.81 (s, 2H), 4.73 (dd, *J* = 8.0, 3.6 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.31 (dd, *J* = 7.4, 2.4 Hz, 1H), 4.14−4.10 (m, 1H), 3.44−3.40 (m, 1H), 2.58 (d, *J* = 16.8 Hz, 1H), 2.32−2.23 (m, 3H), 2.02 (s, 3H), 2.02−1.96 (m, 2H), 1.74−1.67 (m, 1H), 1.67 (s, 3H), 1.46−1.35 (m, 2H), 1.32−1.23 (m, 2H), 1.23 (s, 3H), 1.14−1.06 (m, 1H), 1.08 (s, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.97−0.92 (m, 12H), 0.62 (q, *J* = 7.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.2, 175.9, 161.7, 154.2, 153.6, 142.7, 139.1, 120.4, 118.0, 117.4, 94.8, 81.9, 77.2, 77.1, 76.8, 73.9, 66.4, 54.0, 41.4, 39.5, 34.7, 34.1, 32.1, 31.7, 24.7, 23.5, 22.5, 19.3, 15.7, 14.8, 14.2, 11.2, 6.9, 5.0; FAB-MS calcd for $C_{39}H_{60}Cl_6NO_{11}SSi$ (M + H^+) 988.1788, found 988.1755.

Preparation of 20. Triethylamine (0.360 mL, 2.60 mmol) and 2,4,6-trichlorobenzoic acid (0.528 g, 2.15 mmol) were added to a solution of hydroxy acid **19** (0.426 g, 0.430 mmol) in THF (9.0 mL). The mixture was stirred for 15 min at 25 °C and then diluted with toluene (40 mL). The resultant solution was taken up in a syringe and added to a previously prepared solution of DMAP (0.525 g, 4.30 mmol) in toluene (400 mL) via syringe pump over 3 h. After the addition was complete, the reaction mixture was stirred for 1 h, then filtered with a short pad of Celite, and concentrated. Flash chromatography on SiO_2 (hexanes/ethyl acetate, 2:1) afforded macrolactone **20** as a white foam (0.196 g, 64%): mp 71.2−72.9 °C; $[\alpha]^{25}_D$ +1.5 (*c* 0.98, $CHCl_3$); IR (film) 1762, 1736, 1700, 1382, 1245, 1107, 928 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1H), 6.54 (s, 1H), 5.49 (s, 2H), 5.20−5.16 (m, 2H), 5.04 (d, *J* = 10.1 Hz, 1H), 4.84 (d, *J* = 12.0 Hz, 1H), 4.81 (s, 2H), 4.76 (d, *J* = 12.0 Hz, 1H), 4.06 (d, *J* = 10.0 Hz, 1H), 3.35−3.27 (m, 1H), 2.77−2.63 (m, 3H), 2.47 (t, *J* = 9.9 Hz, 1H), 2.12 (s, 3H), 2.04 (dd, *J* = 14.5, 7.8 Hz, 1H), 1.76−1.66 (m, 4H), 1.66 (s, 3H), 1.19 (s, 3H), 1.14 (s, 3H), 1.12 (d, *J* = 6.7 Hz, 3H), 1.04−0.97 (m, 5H), 0.88 (t, *J* = 8.1 Hz, 9H), 0.58 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 170.7, 161.5, 154.6, 153.3, 140.5, 139.6, 119.2, 118.3, 94.8, 86.5, 80.1, 77.1, 76.1, 66.5, 53.6, 45.6, 39.2, 35.5, 32.3, 31.7, 31.2, 27.4, 24.7, 23.4, 23.0, 18.7, 16.3, 14.8, 6.9, 5.2; FAB-MS calcd for $C_{39}H_{58}Cl_6NO_{10}SSi$ (M + H^+) 970.1682, found 970.1648.

Preparation of 21. Procedure A. The mixture of samarium metal (0.126 g, 0.838 mmol) and iodine (0.170 g, 0.838 mmol) in THF (8 mL) was stirred vigorously at reflux for 2 h. During this period of time, the reaction mixture progressed from a dark orange to an olive green to a deep blue color. The deep blue solution was cooled to rt, and a catalytic amount of NiI_2 (2.6 mg, 0.0083 mmol) was added. After being stirred for 5 min at rt, the mixture was cooled to −78 °C. A solution of macrolactone **20** (81.5 mg, 0.0838 mmol) in THF (2 mL) was cannulated to the SmI_2/NiI_2 solution, and stirring was continued for 1 h. After being stirred at −40 °C for 2 h, the reaction mixture was poured into 1 N HCl and extracted with ethyl acetate. The combined organic layers were washed with 10% aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. Flash chromatography on SiO_2 (hexanes/ethyl acetate, 2:1) yielded diol **21** as a colorless oil (45.3 mg, 87%).

Procedure B. To a suspension of activated zinc dust (0.261 g, 3.84 mmol) in acetic acid (2 mL) was added a solution of macrolactone **20** (0.196 g, 0.201 mmol) in THF (1.0 mL) at 25 °C. After being stirred for 1.5 h, the reaction mixture was diluted with ethyl acetate and filtered with a plug of cotton to remove the excess zinc. The filtrate was then washed with 10% aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexanes/ethyl acetate, 2:1) afforded diol **21** (0.108 g, 86%): $[\alpha]^{25}_D$ −52.0 (*c* 1.38, $CHCl_3$); IR (film) 3374, 1742, 1693 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 1H), 6.54 (s, 1H), 5.15 (dd, *J* = 9.9, 5.6 Hz, 1H), 5.06 (d, *J* = 9.9 Hz, 1H), 4.93 (s, 2H), 4.09 (dd, *J* = 9.8, 3.0 Hz, 1H), 3.87 (t, *J* = 2.8 Hz, 1H), 3.09−3.03 (m, 2H), 2.80−2.64 (m, 4H), 2.47−2.40 (m, 1H), 2.09 (s, 3H), 2.09−2.06 (m, 1H), 1.88−1.63 (m, 2H), 1.63 (s, 3H), 1.42−1.12 (m, 4H), 1.15 (s, 3H), 1.13 (d, *J* = 6.6 Hz, 3H), 1.12 (s, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.88 (t, *J* = 8.0 Hz, 9H), 0.65−0.50 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.3, 170.8, 169.8, 152.4, 139.3, 139.2, 120.3, 118.9, 116.5, 79.3, 77.2, 75.8, 73.6, 62.1, 53.6, 43.0, 39.5, 39.0, 32.8, 32.3, 31.2, 26.1, 24.2, 22.6, 22.5, 16.5, 15.3, 14.2, 14.0, 7.0, 5.3; LRMS calcd for $C_{33}H_{55}NO_6SSiNa$ (M + Na^+) 644.4, found 644.5.

12,13-Desoxyepothilone F (2d). TES ether **21** (82 mg, 0.132 mmol) was dissolved in THF (2 mL) in a polyethylene vessel and cooled to 0 °C. The resultant solution was treated with HF·pyridine (1.5 mL) while being closely monitored by TLC. After being stirred at 0 °C for 1 h and at rt for 0.5 h, the reaction mixture was diluted with ethyl acetate (30 mL) and poured into satd aq $NaHCO_3$ (20 mL). The organic layer was separated and washed once with 1 N HCl, 10% aq $NaHCO_3$, and brine and dried ($MgSO_4$). Flash chromatography on SiO_2 (hexanes/ethyl acetate, 1:2) yielded 12,13-desoxyepothilone F (**2d**) as a white foam (61 mg, 91%): mp 172.4−174.0 °C; $[\alpha]^{25}_D$ −63.3 (*c* 1.83, $CHCl_3$); IR (film) 3408, 1729, 1688, 1468, 1451, 1252 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 1H), 6.58 (s, 1H), 5.24 (d, *J* = 8.8 Hz, 1H), 5.12 (dd, *J* = 9.5, 4.8 Hz, 1H), 4.87 (d, *J* = 4.5 Hz, 1H), 4.87 (d, *J* = 4.5 Hz, 2H), 4.44 (br s, 1H), 4.32−4.28 (m, 1H), 3.78 (d, *J* = 5.8 Hz, 1H), 3.68 (m, 1H), 3.12 (qd, *J* = 6.8, 1.9 Hz, 1H), 3.07 (d, *J* = 1.6 Hz, 1H), 2.60 (dt, *J* = 15.2, 9.8 Hz, 1H), 2.45 (dd, *J* = 14.4, 11.2 Hz, 1H), 2.32−2.22 (m, 3H), 2.04 (s, 3H), 1.92−1.85 (m, 2H), 1.75−1.64 (m, 2H), 1.64 (s, 3H), 1.32 (s, 3H), 1.29−1.21(m, 4H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.04 (s, 3H), 0.99 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.7, 170.3, 170.0, 152.3, 139.7, 138.4, 120.9, 118.4, 116.4, 78.7, 74.2, 72.0, 61.4, 53.7, 41.5, 39.6, 38.5, 32.4, 31.7, 31.5, 25.2, 23.1, 22.9, 17.6, 16.1, 15.6, 13.4; HRMS calcd for $C_{27}H_{42}NO_6S$ (M + H^+) 508.2733, found 508.2739.

Aqueous Solubility of dEpoF and dEpoB. An excess (1.0 mg) of epothilone(s) was suspended and sonicated in distilled water (1.0 mL) at 25 °C for 1 h. The suspension was centrifuged (12 G) for 30 min, and the clear supernatant (5.0 μL) was analyzed by reversed-phase HPLC (Eclipse XDB-C18, 4.6 × 250 mm, λ = 250 nm, methanol:water = 65:35). Alternatively, the suspension was filtered with a microfilter (0.45 μm), and the filtrate (5.0 μL) was analyzed by HPLC. The calibration curve was obtained from a plot of the absorption against the concentration of standard epothilone solutions in methanol. On the basis of the standard calibration curve,

the solubilities of dEpoF and dEpoB were determined to be 25 μg/mL (49 μM) and 10 μg/mL (19 μM), respectively.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all characterized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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