On the Interactivity of Complex Synthesis and Tumor Pharmacology in the Drug Discovery Process: Total Synthesis and Comparative in Vivo Evaluations of the 15-Aza Epothilones

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The total syntheses of 12,13,15-desoxy-15(*S*)-aza-epothilone B (aza-dEpoB; dEpoB-lactam) and 12,13,15-desoxy-15(*R*)-aza-epothilone B (15-epi-aza-dEpoB; 15-epi-dEpoB-lactam) have been accomplished via a highly convergent strategy. We have also successfully oxidized 12,13,15-desoxy-15(*S*)-aza-epothilone B to aza-epothilone B (aza-EpoB; EpoB-lactam). Aza-epothilone B has been advanced to phase I clinical trials by the Bristol-Myers Squibb group. Our synthesis is efficient and was amenable to the production of significant quantities of these lactams. Using our fully synthetically derived lactams, in vitro and in vivo studies were conducted in comparison with advanced clinical candidates, 12,13-desoxyepothilone B and 12,13-desoxyepothilone F, also derived by total synthesis.

Introduction

The epothilones are a class of cytotoxic macrolides that have emerged as highly promising new anticancer agents. Although structurally dissimilar to paclitaxel (taxol), the epothilones apparently function through an analogous mechanism involving inhibition of cellular division by stabilization of microtubule assemblies, thereby leading to cell death.[1] Paclitaxel is currently employed as a frontline chemotherapeutic agent. However, concerns for its therapeutic index in conjunction with formulation difficulties arising from its lack of solubility in aqueous media render it less than ideal.

By comparison, the epothilones potentially enjoy a greater therapeutic profile as well as increased water solubility, making them attractive agents for clinical development.[2] While the naturally occurring compound, epothilone B (**1**, EpoB), is the most potent member of this family, it possesses, at least in xenograft mice, a worrisomely narrow therapeutic index.[3,4] We appreciate that projections of chemotherapeutic opportunities from rodents to humans in a clinical setting are beset with uncertainties. Nonetheless, we strongly preferred moving forward with compounds which provide more obvious windows of opportunity. In a potentially important discovery, we demonstrated in the context of xenograft mice that the somewhat less potent 12,13-desoxyepothilone B (**3a**, dEpoB) exhibits a much enhanced therapeutic range relative to epothilone B, due to a reduction in its toxic dose levels.[5] For instance, dEpoB is tolerated in nude mice at dose levels of 25 mg/kg, whereas in the case of EpoB tolerable dose levels are only 0.6 mg/kg.

Preliminary stability studies of dEpoB in murine plasma did suggest that the lactone ring may be a locus of instability. However, further studies carried out with human plasma provided a different perspective on these initial findings. In fact, even after 24 h, the concentration of dEpoB in human plasma was determined to be 9-fold higher than the IC_{50} value in vitro.[6] To provide further insight into the issue of plasma stability of the epothilones, we elected to synthesize the corresponding lactam and to assess its antitumor activity. In addition to assessments of ring stability, we wished to undertake a direct biological comparison between the epoxide containing epothilones with their desoxy counterparts. The synthesis of aza-EpoB and aza-dEpoB would allow us a two-stage comparison between the two drug series.

Recently, the Bristol-Myers Squibb company (BMS) has advanced the 15-desoxy-15-aza analogue of epothilone B (**2**, aza-EpoB) as a clinical candidate for cancer therapy.[7,8] BMS gained access to the lactam from epothilone B (**1**) via an elegantly devised and executed three-step,

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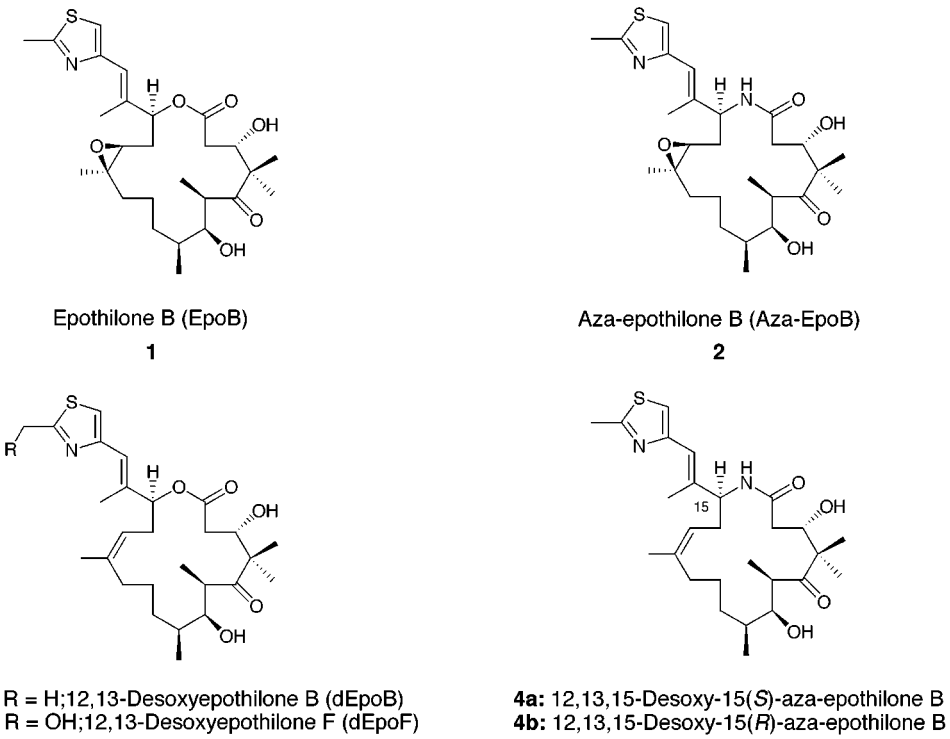
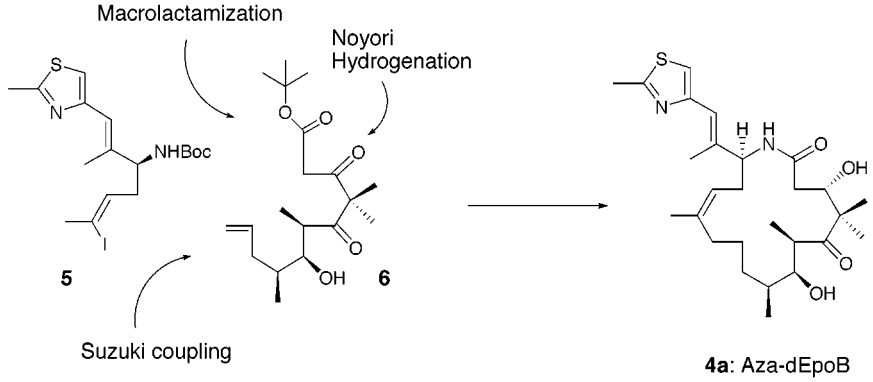


Figure 1. Structure of Epothilones.

Scheme 1. Synthetic Analysis



"one-flask" transformation. While remarkably efficient, the BMS partial synthesis route may be limited with respect to development, since it starts from fully elaborated natural product.

We note that independently the BMS and the Schinzer groups have recently published fully synthetic routes toward the analogous 15-aza-epothilone A system, lacking the 12-methyl group, based on a ring closing metathesis (RCM) reaction. However the RCM chemistry results in varying *E*:*Z* mixtures of the C12,13-olefin geometry. The need to separate such closely related congeners seriously complicates the prospects of producing pure product in quantity by total synthesis.[8,9] Synthesis of aza-dEpoB via ring closing metathesis could well be even more awkward in attempting to generate a trisubstituted olefin of the B-type (dEpoB). We recently communicated our results pertaining to a total synthesis of aza-dEpoB (**4a**).[10] Herein, we report the total synthesis of aza-EpoB (**2**) and provide the first evaluations as to its in vivo antitumor action based on in vivo comparison with dEpoB (**3a**).

The initial planning for a total synthesis of aza-EpoB (**2**) envisioned a convergent strategy similar to that employed in our synthesis of 12,13-desoxyepothilone B (**3a**, dEpoB). Along those lines, fragments of roughly equal complexity were expected to serve as key building blocks (Scheme 1). While the preparation of the alkyl sector **5** would require *de novo* construction to accommodate the new goal, we envisioned that the acyl sector **6**, available from our previous synthesis of dEpoB, could serve for the polypropionate domain.[11] The union of the two key fragments **5** and **6** was to be achieved through a palladium catalyzed *B*-alkyl Suzuki coupling. A ruthenium mediated asymmetric hydrogenation would provide highly selective access to the desired stereochemistry at

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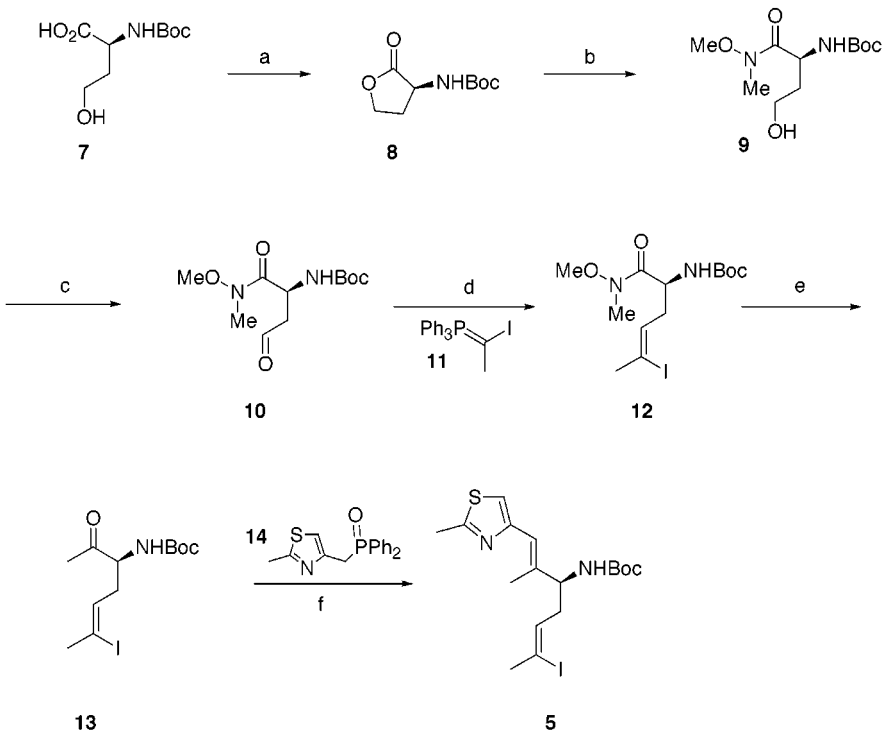
Scheme 2. Olefination Reaction of Aza-Ketone[a]



[a] Reagents and conditions: (a) DIPC, HOBt, THF, 84%; (b) *N*,*O*-dimethylhydroxylamine, $AlMe_3$, benzene, 92%; (c) oxalyl chloride, DMSO, CH_2Cl_2, 94%; (d) **11**, THF, −78 °C to −30 °C, 35%; (e) MeMgBr, Et_2O, 0 °C, 67%; (f) **14**, *n*-BuLi, −78 °C, 18%.

C-3. Deprotection followed by macrolactamization would then lead to aza-EpoB in short order. As will be seen, implementation of these seemingly conservative ideas proved to be anything but straightforward in the lactam series and success was attained only after extensive retrofitting, though with high efficiency.

Our initial route for the synthesis of alkyl fragment **5** was based on the Horner-like olefination used to construct the alkyl fragment for the synthesis of dEpoB (Scheme 2).[12] The synthesis commenced with cyclization of *N*-Boc-L-homoserine (**7**) to produce lactone **8**. Ring opening to form the Weinreb amide (**9**)[13] followed by oxidation of the nascent hydroxy group produced aldehyde **10** in good yield. Olefination with the known phosphorane **11** yielded vinyl iodide **12**, albeit in low yield.[14] Elaboration to the methyl ketone **13** required for the olefination reaction proceeded smoothly. Unfortunately, the actual olefination reaction to produce alkyl fragment **5** occurred in an unsatisfactory 18% yield. It was theorized that the acidic N−H proton of the carbamate compromised the efficiency of the reaction. Unfortunately, when the reaction was carried out on the benzyl-protected carbamate, there was no improvement in the yield.

To circumvent the problems of the olefination reaction, described above, a Mitsunobu based strategy for the installation of the C-15 (epothilone numbering system) amine was developed. It relied on the alkyl fragment used for the synthesis of dEpoB (Scheme 3). The opposite enantiomer (*R* instead of *S* hydroxyl configuration) of the TES-protected vinyl-iodide alkyl fragment (**15**), used in the synthesis of dEpoB, is readily accessible through our recently developed methods.[12] Deprotection of the silyl ether (**15**) was easily accomplished using AcOH/THF/water. It should be noted that the corresponding C-15 *tert*-butyldimethylsilyl ether was surprisingly resistant to deprotection. More forcing conditions led to considerable decomposition. This finding prompted us to explore the use of triethylsilyl protection for the hydroxyl group. Transformation of the free alcohol (**16**) to the corresponding azide (**17**) was accomplished using Thompson's procedure.[15] This protocol resulted in an 85% yield of azide **17** with complete displacement and minimal elimination product. In contrast, inversion using standard Mitsunobu conditions[16] led to a 66% yield of the azide. This reaction was accompanied by significant amounts of triene via elimination. Next, triphenylphosphine mediated Staudinger reduction of the azide followed by protection of the nascent amine as the *tert*-butyl carbamate yielded the requisite partner (**5**) for the subsequent *B*-alkyl Suzuki coupling. Unfortunately, the palladium catalyzed *B*-alkyl Suzuki reaction occurred in a disappointing 10% yield. This low yield may well reflect formation of a stable intermediate derived from intramolecular chelation of the palladium to the carbamate, after oxidative insertion.

To avoid formation of potential palladacycle intermediates in the *B*-alkyl Suzuki reaction, the cross-coupling was carried out using the corresponding azido-alkyl

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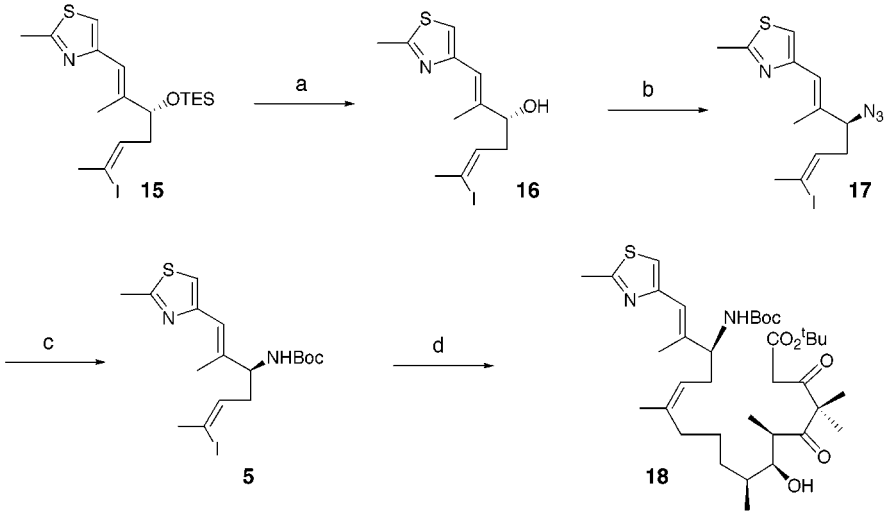
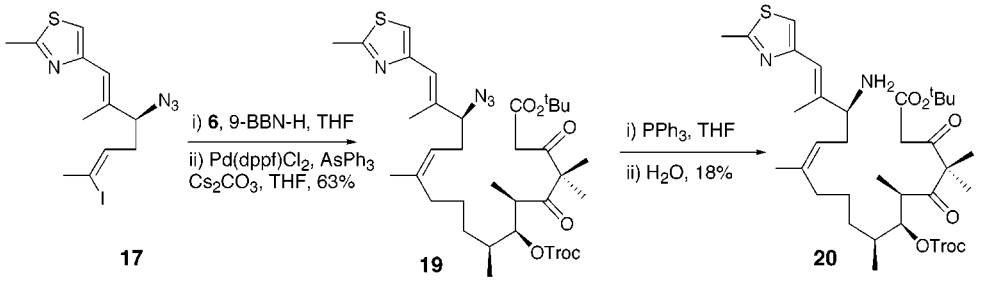
Scheme 3. Suzuki Coupling of Vinyl Iodide 5 with Acyl Sector 6[a]



[a] Conditions: (a) HOAc/THF/H_2O, 98%; (b) diphenylphosphoryl azide, DBU, toluene, 85%; (c) (i) PPh_3, THF, H_2O, 92%; (ii) Boc_2O, MeCN, 65%; (d) (i) **6**, 9-BBN−H, THF; (ii) $Pd(dppf)Cl_2$, $AsPh_3$, Cs_2CO_3, DMF, 10%.

Scheme 4. Suzuki Coupling with Azide Fragment



fragment **17**. Gratifyingly, the palladium catalyzed cross-coupling proceeded smoothly producing the azido-ester **19** in 63% yield despite the possibility of ionization of the azide group to form a π-allylpalladium species (Scheme 4).[17] However, the subsequent Staudinger reduction of azide **19** afforded amino ester **20** in a disappointing 18% yield. This depressed yield may reflect inter- or intramolecular Schiff base formation of the incipient amine with the β-keto ester.

To circumvent the problems which we associated with possible Schiff base formation, the β-keto ester was temporarily masked as its corresponding enol ether (**21**) (Scheme 5). Since the penultimate step in the synthesis of the acyl fragment **6**[12] was to involve the hydrolysis of the methyl enol ether **21**, this circumvention actually shortened the synthesis. We were pleased to find that the palladium catalyzed *B*-alkyl Suzuki cross-coupling reaction not only proceeded smoothly, but was effected in higher yield than with the corresponding β-keto ester. This finding, as to the preferred timing for coupling, was subsequently incorporated in a further improvement of the synthesis of dEpoB. As hoped for, by masking the β-keto ester as the corresponding enol ether, we were able to accomplish a 98% yield for the subsequent Staudinger reduction of azide **22**. After protection of the nascent amine as its *tert*-butyl carbamate (**23**), the β-keto ester **18** was then be liberated by transfer hydrolysis.

The β-keto ester **18** was then subjected to a ruthenium-mediated asymmetric hydrogenation reaction in methanol using a modified Noyori catalyst (Scheme 6).[18] Indeed, the desired diol **24** was produced apparently as a single diastereomer in 78% yield. However, the necessity of acid in the hydrogenation medium (for protonation of the thiazole moiety) resulted in the formation of minor amounts of deprotected amine products. This undesired hydrolysis reaction was circumvented by employing recrystallized catalyst. This precaution resulted in an increased reaction rate, thus minimizing the time of exposure to the acidic solution. Simultaneous deprotection of the *tert*-butyl carbamate and the *tert*-butyl ester was performed through the agency of trifluoroacetic acid in dichloromethane to afford amino acid **25**. The latter was used for the subsequent cyclization reaction without purification. Macrolactamization mediated by HATU in dichloromethane produced the Troc-protected lactam in 90% yield.[19] It should be noted that the use of other solvents (i.e., DMF, THF) also resulted in macrocyclization. However, varying degrees of a byproduct, which purportedly resulted from transfer of the tetramethyluronium fragment of HATU to the C3 hydroxyl of the cyclized adduct, limited access to the desired material. Fortunately, treatment of the urea adduct with aqueous acid (acetic acid/THF/water) released the cyclized product **26**. Deprotection of the C7 Troc-group by sonication with

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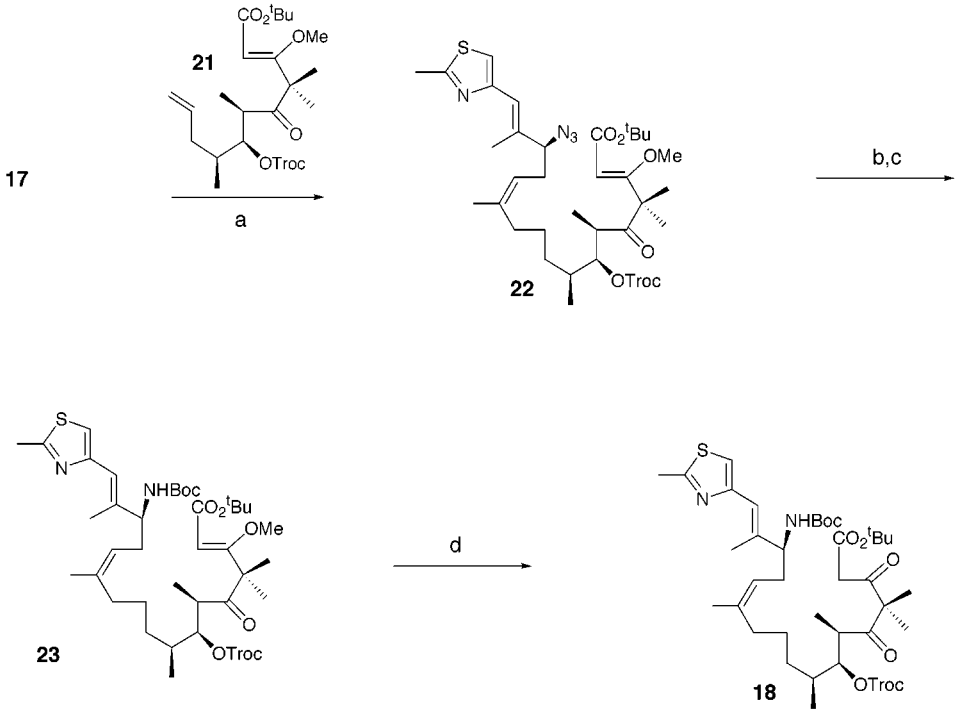
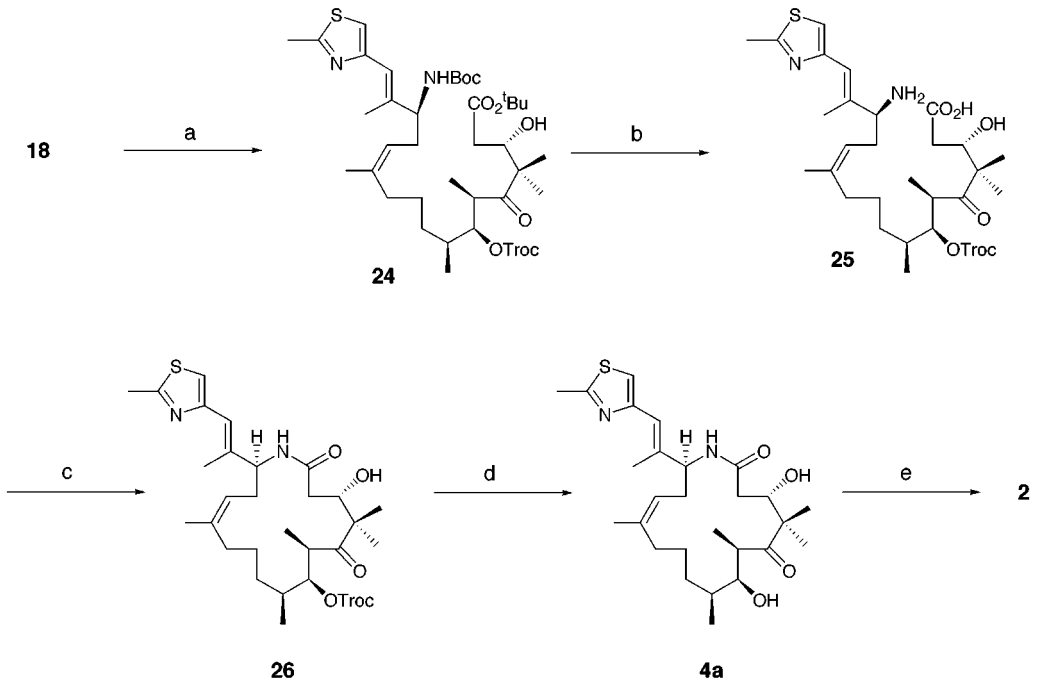
Scheme 5. Suzuki Coupling of Azido Vinyl-iodide 17 with Methyl Enol Ether 21[a]



[a] Conditions: (a) (i) **21**, 9-BBN−H, THF; (ii) $Pd(dppf)Cl_2$, $AsPh_3$, Cs_2CO_3, DMF, 78%; (b) PPh_3, H_2O, THF, 98%; (c) Boc_2, MeCN, 70%; (d) *p*-TSOH, Acetone, 82%.

Scheme 6. Synthesis of Aza-EpoB (2)[a]



[a] Conditions: (a) 2% $Et_2NH_2[\{((R)\text{-BINAP})RuCl\}_2Cl_3]$, HCl-MeOH, H_2, 1250 psi, 78%; (b) TFA, CH_2Cl_2; (c) HATU, Hoat, DIPEA, CH_2Cl_2, 90%; (d) Zn dust, HOAc, 88%; (e) DMDO, CH_2Cl_2, 70%.

zinc dust afforded fully deprotected 12,13,15-desoxy-15-(*S*)-aza-epothilone B (**4a**) in 88% yield.[20] Finally, epoxidation of the 12,13-olefinic linkage using 2,2-dimethyldioxirane at −50 °C yielded fully synthetic aza-epothilone B (**2**) *as a single diastereomer*.

To probe stereochemical permutations on biological activity of the lactam series further, we synthesized the C15-(*R*) antipode by using the enantiomeric chiral auxiliary for the alkylation[12] to produce the C15 epimeric vinyl-iodide fragment of **15**. The consequences of permutating the C15 configuration in both the lactam and lactone series could then be assessed.[4]

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Table 1. Potency of dEpoB (3a), Aza-EpoB (2), Aza-dEpoB (4a), 15-Epi-aza-dEpoB (4b), and Taxol against Various Tumor Cell Growth in Vitro

	IC_{50} (μM)[a]				
Tumor Cell Lines	dEpoB	Aza-EpoB	Aza-dEpoB	15-epi-aza-dEpoB	Taxol
			Human T-cell AL Leukemia		
CCRF−CEM	0.0095	0.0021	0.0278	0.119	0.0012
CCRF−CEM/VBL_{100}	0.017 (5 ×)	2.99 (1423 ×)	0.997 (35.8 ×)	0.551 (4.6 ×)	5.17 (4308 ×)
CCRF−CEM/VM_1	0.014 (1.5 ×)	0.039 (18.6 ×)	NA	NA	0.0066 (3.18 ×)
CCRF−CEM/Taxol	0.0162 (1.2 ×)	0.171 (81.4 ×)	0.791 (38.4 ×)	NA	0.339 (282.5 ×)
			Hampster Lung Fibroblasts		
DC-3F	0.0025	0.0087	NA	NA	0.0135
DDC-3F/ADX	0.0091 (2.8 ×)	0.288 (33.1 ×)	NA	NA	0.583 (43.2 ×)
DC-3F/ADII	0.0484 (19.4 ×)	2.380 (274 ×)	NA	NA	20.19 (1496 x)
			Human CM Leukemia		
K562	0.0069	0.0040	0.0024	NA	0.0029
			Human Mammary Carcinoma		
MX-1	0.0221	0.0024	NA	NA	0.0394

[a] Cell growth inhibition was measured by XTT tetrazonium assay after 72 h incubation for cell growth. The values were determined with six to seven concentrations of each drug using a computer program. The cross-resistances are shown in parentheses.

Biological Evaluations

Fully synthetic aza-epothilone B (**2**, aza-EpoB), 12,13,-15-desoxy-15(*S*)-aza-epothilone B (**4a**, aza-dEpoB), and the epimeric 12,13,15-desoxy-15(*R*)-aza-epothilone B (**4b**, 15-epi-aza-dEpoB) have been evaluated in the context of a variety of cell types to evaluate their antitumor potential. As shown in Table 1, direct comparison of aza-EpoB with dEpoB showed that aza-EpoB was slightly more potent in vitro in the base leukemia cell lines (CCRF−CEM), 0.0021 and 0.0095 μM, respectively.[21] However, aza-EpoB exhibited markedly reduced activity in our multidrug-resistant cell lines (CCRF−$CEM/_{VBL100}$, CCRM-$CEM/_{VM1}$, and CCRF−$CEM/_{Taxol}$) as compared with dEpoB. Additionally, as we have noted with epothilone B (containing the C12,13-epoxide) compared with dEpoB (without the epoxide), aza-dEpoB was about 10-fold less potent than the epoxide containing aza-EpoB.

The effect of inversion of stereochemistry at C15 was also investigated in both the lactone[4] and lactam (**4b**) desoxy series. In both systems, inversion of configuration at C15 resulted in a further reduction in activity in all cell lines tested.

We then progressed to in vivo evaluations of aza-EpoB (**2**). Initially, the therapeutic effect of aza-EpoB was examined in nude mice bearing human mammary MX-1 xenograft (Figure 2).[22] The animal experiments were performed according to the slow i.v. infusion protocol developed in our previous studies.[5,23] A dosage of 6 mg/kg demonstrated some inhibition in tumor growth, but no significant reduction in tumor mass was noted. Upon cessation of treatment, the tumor resumed its growth. At elevated dosage levels (9 mg/kg), approaching the maximally tolerated dose levels, similar inhibitory effects were seen, with no major regression in tumor size.

Next, the therapeutic efficacy of aza-EpoB was evaluated in athymic mice bearing a human leukemia K562 xenograft. As depicted in Figure 3, treatment of the mice with aza-EpoB (6 mg/kg) inhibited tumor growth but did not lead to a dramatic reduction in the size of the tumor. In contrast, further treatment of the same mice with dEpoF (**3b**), at a dose of 30 mg/kg, readily induced tumor reduction to the point of remission.[24] While the preliminary in vivo results with this type of sensitive tumor suggests aza-EpoB to be less effective than dEpoB or dEpoF, more revealing experiments are necessary to assess its full biological potential. However, these in vivo biological results, in conjunction with the previous in vivo results obtained for EpoB,[5] suggest that once again the epoxide functionality might be imparting considerable toxicity, in vivo, as compared with the corresponding desoxy systems.

In summary, we have succeeded in entering the aza-dEpoB series through total chemical synthesis, using a strategy based on the convergent merger of two key fragments by *B*-alkyl Suzuki coupling and subsequent macrolactamization. We have also successfully oxidized aza-dEpoB to aza-EpoB to study both its in vitro and in vivo activity. The synthesis has proven to be efficient and amenable to production scales commensurate with those required for animal studies. As such, aza-dEpoB was shown to exhibit reduced in vitro activity as compared with dEpoB. In contrast, in murine systems aza-EpoB was slightly more active than dEpoB in nonresistant cell lines but was not effective toward our multidrug-resistant cell lines. dEpoB and dEpoF also proved superior in our in vivo models where aza-EpoB failed to produce strong curtailment in tumor progression and, furthermore, gave rise to unacceptable toxicity at elevated doses.

While further studies are warranted in terms of translation from the murine to the human setting, for the moment, systems containing the 12,13-oxido linkage such as EpoB (**1**) or the aza system (**2**) are not as promising as are 12,13-desoxyagents. These matters will be sorted out with greater definition as clinical trails commence with the lactonic 12,13-desoxy compounds, allowing for direct comparisons with results achieved via 12,13-oxido agents.

(21) The CCRF-CEM/paclitaxel cell line was developed at this institute (T.-C. Chou) after continuous exposure of CCRF-CEM cells with increasing and sublethal (IC_{50}−IC_{90}) concentrations of paclitaxel for 10 months.

(22) MX-1 is a well-characterized human mammary adenocarcinoma that has been used for many years as part of the National Cancer Institute's screening panel of experimental tumors.

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(24) In all in vitro and in vivo experiments performed to date, dEpoF has demonstrated comparable activity to dEpoB with the additional benefit of increased aqueous solubility.

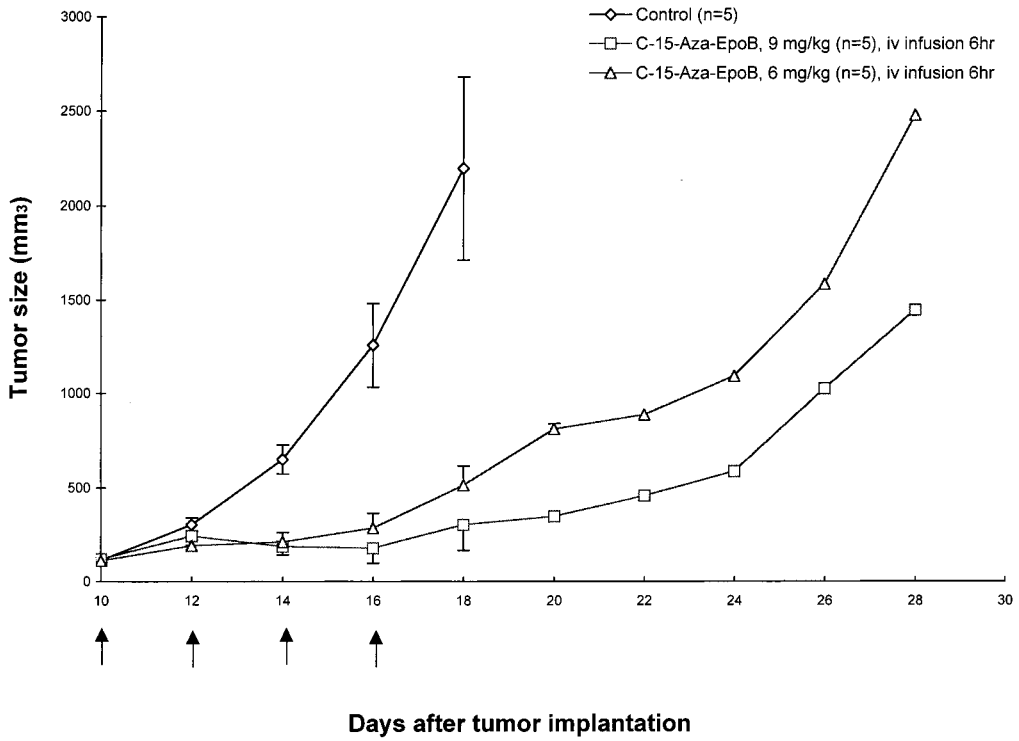

Figure 2. Therapeutic effect of treatment with aza-EpoB (6 mg/kg and 9 mg/kg). MX-1 tumor cells (1×10^7 in 0.2 mL) were inoculated to nude mice on day 0. Mice were treated with 6 or 9 mg/kg aza-EpoB, 6 h-i.v. infusion on days 10, 12, 14, and 16 ($n = 5$). The control mice ($n = 5$) received vehicle only.

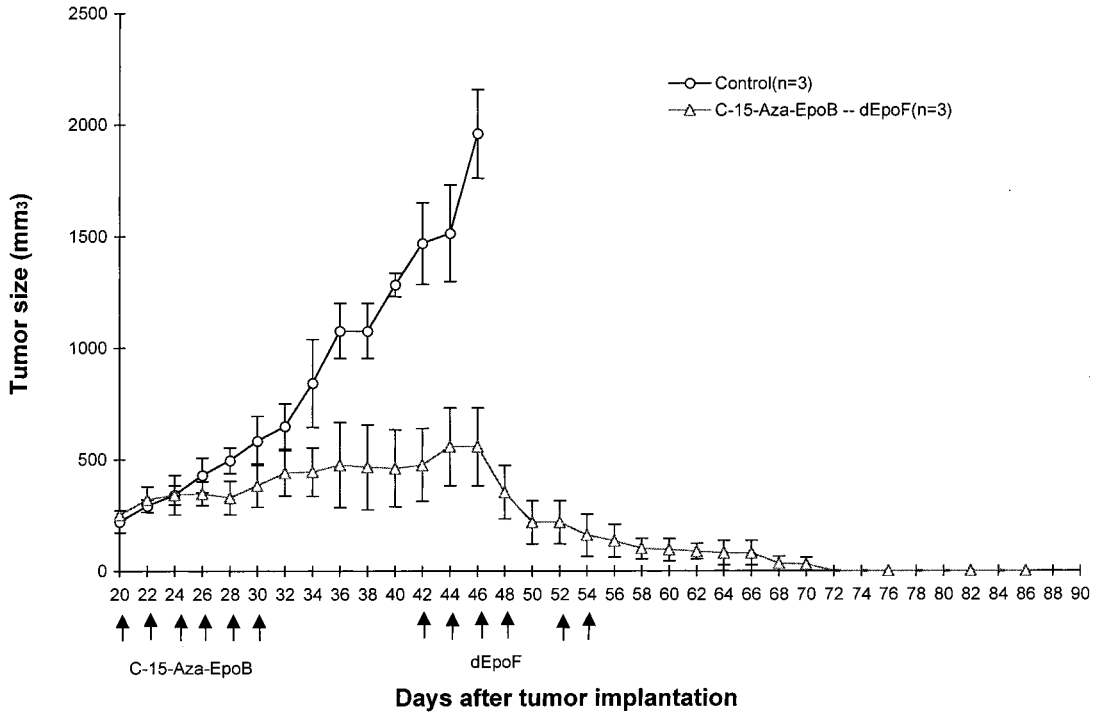

Figure 3. Therapeutic effect of sequential treatment with aza-EpoB and dEpoF. K562 tumor cells (1×10^7 in 0.2 mL) were inoculated to nude mice on day 0. Mice were treated with 6 mg/kg aza-EpoB, 6 h-i.v. infusion on days 20, 22, 24, 26, 28, and 30 (△, $n = 3$). The same group of mice were then treated with 30 mg/kg dEpoF, 6 h-i.v. infusion on days 42, 44, 46, 48, 52, and 54 (△, $n = 3$). On day 76, all three mice were tumor free. The control mice (○, $n = 3$) received vehicle only.

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 16. TES-protected alcohol **15** (2.28 g, 4.92 mmol) was dissolved in HOAc/THF/H_2O (3:1:1, 50 mL) and stirred at room temperature for 8 h. The solvent was then removed in vacuo. The oily residue was dissolved in EtOAc (100 mL) and excess acid was neutralized by the addition of sat. $NaHCO_3$ (50 mL). The organic layer was removed and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with sat. $NaHCO_3$ (1 × 50 mL) and brine (1 × 50 mL) and then dried ($MgSO_4$). The solution was filtered and concentrated in vacuo. Chromatography on silica gel (30% EtOAc/hexanes) provided alcohol **16** (1.71 g, 99%) as a yellow oil: $[\alpha]_D$ + 4.9 (*c* 1.0, $CHCl_3$); R_f = 0.19 in 40% EtOAc/hexanes; IR (neat) 3332, 2947, 1737, 1651, 1506, 1432, 1270, 1188, 1100, 1049, 969, 881, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 1H), 6.58 (s, 1H), 5.44 (t, *J* = 6.5 Hz, 1H), 4.28 (t, *J* = 6.4 Hz, 1H), 2.72 (s, 3H), 2.51 (s, 3H), 2.44 (m, 2H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 152.4, 141.6, 131.5, 118.9, 115.5, 103.1, 76.1, 42.4, 33.7, 19.0, 14.4; LRMS (+electrospray): 371.9 $[M + Na]^+$, 349.9 $[M + H]^+$. HRMS cald for $C_{12}H_{17}NSOI$, 350.0077, found 350.0071.

Preparation of 17. The allylic alcohol **16** (1.74 g, 4.99 mmol) was dissolved in toluene (30 mL) and cooled to 0 °C. Diphenylphosphoryl azide (1.65 g, 5.98 mmol) was added followed by DBU (0.91 g, 5.98 mmol). The reaction mixture was stirred at 0 °C for 2 h. The solution was then warmed to 25 °C followed by the addition of ethyl acetate (100 mL). The organic layer was washed with H_2O (1 × 30 mL), sat. $NaHCO_3$ (1 × 50 mL), and brine (1 × 50 mL) sequentially. The organic layer was then dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel (7.5% EtOAc/hexanes) provided azide **17** (1.58 g, 85%) as a light yellow oil: $[\alpha]_D$ −21.3 (*c* 1.0, $CHCl_3$); R_f = 0.68 in 40% EtOAc/hexanes; IR (neat) 3104, 2914, 2094, 1650, 1504, 1427, 1243, 1183, 1103, 1031, 960, 877, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.52 (s, 1H), 5.44 (t, *J* = 6.5 Hz, 1H), 4.07 (t, *J* = 7.0 Hz, 1H), 2.70 (s, 3H), 2.49 (s, 3H), 2.41 (m, 2H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 151.8, 136.1, 130.5, 122.2, 116.8, 103.8, 69.5, 40.0, 33.6, 19.2, 14.4; LRMS (+electrospray): 397.1 $[M + Na]^+$, 375.1 $[M + H]^+$, 332.0. HRMS cald for $C_{12}H_{16}N_4SI$, 375.0142, found 375.0139.

Preparation of 5. To a solution of azide **17** (0.074 g, 0.198 mmol) dissolved in THF (3 mL) was added triphenylphosphine (0.062 g, 0.237 mmol). The reaction mixture was stirred at 25 °C for 24 h. Water (0.014 g, 0.792 mmol) was then added and the reaction was heated to 65 °C for 4 h. The solution was cooled, acidified with 1 N HCl, and extracted with ethyl acetate (3 × 30 mL). The aqueous layer was then basified using 1N NaOH followed by extraction with ethyl acetate (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel (5% methanol/chloroform) provided the free amine (0.069 g, 100%).

Characterization of amine: $[\alpha]_D$ −7.7 (*c* 1.0, $CHCl_3$); R_f = 0.30 in 10% MeOH/$CHCl_3$; IR (neat) cm^{-1} 3368, 3287, 2912, 1650, 1504, 1432, 1182, 1063, 870, 731; ^1H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.48 (s, 1H), 5.45 (t, *J* = 6.6 Hz, 1H), 3.53 (t, *J* = 6.8 Hz, 1H), 2.69 (s, 3H), 2.48 (s, 3H), 2.34 (m, 2H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 152.8, 142.9, 132.1, 118.8, 115.2, 103.1, 58.9, 42.6, 33.7, 19.1, 14.7; LRMS (+electrospray): 370.9 $[M + Na]^+$, 349.0 $[M + H]^+$, 331.9. HRMS cald for $C_{12}H_{17}N_2SI$, 348.0159, found 349.0241.

To a solution of free amine (0.069 g, 0.198 mmol), as prepared above, dissolved in acetonitrile (2 mL) was added di-*tert*-butyl dicarbonate (0.065 g, 0.297 mmol) followed by triethylamine (0.024 g, 0.238 mmol). The reaction was stirred at 25 °C for 1.5 h. The solvent was then removed in vacuo. Chromatography on silica gel (15% EtOAc/Hexanes) provided the protected amine **5** (0.065 g, 73%) as a yellow oil: $[\alpha]_D$ −8.0 (*c* 1.0, $CHCl_3$); R_f = 0.58 in 40% EtOAc/hexanes; IR (neat) 3336, 2975, 2925, 1698, 1504, 1366, 1248, 1170, 1045, 873, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.46 (s, 1H), 5.37 (t, *J* = 6.5 Hz, 1H), 4.68 (br s, 1H), 4.28 (br s, 1H), 2.70 (s, 3H), 2.45 (s, 3H), 2.39 (m, 2H), 2.06 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 155.6, 153.1, 139.8, 131.6, 119.4, 116.1, 104.2, 79.9, 57.1, 41.4, 34.2, 28.8, 19.6, 16.5; LRMS (+electrospray): 470.9 $[M + Na]^+$, 448.8 $[M + H]^+$. HRMS cald for $C_{17}H_{26}N_2O_2SI$, 449.0761, found 449.0766.

Preparation of 22. To a solution of enol ether **21** (5.80 g, 11.22 mmol) in THF (25 mL) was added 9-BBN dimer (2.10 g, 8.63 mmol). After the resulting mixture was stirred at 25 °C for 1 h, TLC analysis indicated the complete consumption of the starting olefin **21**. In a separate flask containing vinyl iodide **17** (3.22 g, 8.63 mmol), (dppf)$PdCl_2$·CH_2Cl_2 (0.705 g, 0.862 mmol), $AsPh_3$ (0.264 g, 0.862 mmol), and Cs_2CO_3 (4.21 g, 12.94 mmol) was added degassed DMF (30 mL). Water (5 mL) was added to the borane solution 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 ethyl acetate (300 mL), washed with H_2O (1 × 250 mL) and brine (1 × 100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel (10% EtOAc/Hexanes) provide **22** as a yellow oil (4.56 g, 70%): $[\alpha]_D$ −13.8 (*c* 1.0, $CHCl_3$); R_f = 0.38 in 20% EtOAc/hexanes; IR (neat) 2953, 2924, 2096, 1756, 1707, 1623, 1245, 1149, 972 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 1H), 6.53 (s, 1H), 5.23 (s, 1H), 5.12 (t, *J* = 6.8 Hz, 1H), 4.89 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.84 (m, 1H), 4.72 (d, *J* = 12.0 Hz, 1H), 3.97−3.91 (m, 2H), 3.93 (s, 3H), 3.27 (m, 1H), 2.73 (s, 3H), 2.41 (m, 1H), 2.22−2.15 (m, 2H), 2.10 (s, 3H), 2.00 (t, *J* = 7.7 Hz, 1H), 1.92−1.78 (m, 2H), 1.70 (s, 3H), 1.50 (s, 9H), 1.58−1.41 (m, 2H), 1.34 (s, 3H), 1.27 (s, 3H), 1.13 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 211.6, 172.1, 165.0, 154.4, 152.4, 138.6, 137.6, 137.1, 122.3, 120.3, 116.8, 98.0, 95.0, 82.9, 80.3, 76.9, 71.1, 62.5, 56.2, 41.6, 35.0, 32.3, 31.7, 28.4, 25.2, 24.2, 23.7, 22.2, 19.4, 16.2, 14.6, 12.6; LRMS (+electrospray): 799.2 $[M + Na]^+$, 777.2 $[M + H]^+$. HRMS cald for $C_{35}H_{52}Cl_3N_4O_7S$, 777.2622, found 776.2544.

Preparation of 23. To a solution of Suzuki product **22** (4.10 g, 5.36 mmol) dissolved in THF (100 mL) was added triphenylphosphine (2.81 g, 10.71 mmol). The solution was heated to 40 °C for 19 h. Water (2 mL) was added followed by heating at 65 °C for 4 h. Silica gel (70 g) was added and the solvent was removed in vacuo. Chromatography on silica gel (1.5% MeOH/chloroform containing 0.5% triethylamine) to afford the reduced amine (3.9 g, 98%): $[\alpha]_D$ −4.4 (*c* 1.0, $CHCl_3$); R_f = 0.30 in 10% methanol/chloroform (containing 1% triethylamine); IR (neat) 2973, 2936, 1759, 1709, 1438, 1368, 1249, 1198, 1149, 1119 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.48 (s, 1H), 5.20 (s, 1H), 5.11 (t, *J* = 6.8 Hz, 1H), 4.86 (d, *J* = 12.0 Hz, 1H), 4.81 (dd, *J* = 7.7, 3.9 Hz, 1H), 4.70 (d, *J* = 12.0, 1H), 3.90 (s, 3H), 3.39 (t, *J* = 7.2 Hz, 1H), 3.25 (m, 1H), 2.69 (s, 3H), 2.24−2.11 (m, 2H), 2.02 (s, 3H), 2.00−1.94 (m, 2H), 1.70−1.61 (m, 1H), 1.67 (s, 3H), 1.49−1.40 (m, 4H), 1.47 (s, 9H), 1.37−1.20 (m, 2H), 1.31 (s, 3H), 1.24 (s, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6, 172.1, 165.0, 154.3, 153.4, 144.1, 137.8, 133.2, 122.0, 118.6, 115.1, 97.9, 95.0, 82.9, 80.3, 76.9, 62.5, 60.1, 56.2, 41.6, 35.0, 34.4, 32.4, 31.7, 28.4, 25.2, 23.7, 23.5, 23.1, 22.2, 19.4, 16.2, 15.1, 12.6; LRMS (+electrospray): 773.2 $[M + Na]^+$, 751.3 $[M + H]^+$.]$^+$. HRMS cald for $C_{35}H_{54}Cl_3N_2O_7S$, 751.2717, found 751.2683.

To a solution of the amine (3.30 g, 4.48 mmol), as prepared above, dissolved in acetonitrile (100 mL) was added di-*tert*-butyl dicarbonate (1,37 g, 6.27 mmol) followed by triethylamine (0.91 g, 8.57 mmol). The reaction mixture was stirred at RT for 16 h. The solution was then diluted with EtOAc (100 mL) and washed with 1 N HCl (1 × 100 mL), sat. Na_2CO_3 (1 × 100 mL), and brine (1 × 100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel (10% EtOAc/hexanes) afforded **23** (2.66 g, 70%) as a white foam: $[\alpha]_D$ −14.5 (*c* 1.0, $CHCl_3$); R_f = 0.60 in 40% EtOAc/hexanes; IR (neat) 2978, 2948, 1757, 1710, 1366, 1247, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.43 (s, 1H), 5.20 (s, 1H), 5.08 (t, *J* = 6.0 Hz, 1H), 4.87 (d, *J* = 12.0 Hz, 1H), 4.81 (dd, *J* = 7.6, 3.8 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 4.65−4.59 (m, 1H), 4.14−4.11 (m, 1H), 3.90 (s, 3H), 3.25 (dd, *J* = 6.8, 3.8

Hz, 1H), 2.70 (s, 3H), 2.32 (m, 1H), 2.24−2.21 (m, 1H), 2.04 (s, 3H), 1.96−1.94 (m, 2H), 1.55−1.43 (m, 3H), 1.66 (s, 3H), 1.48 (s, 9H), 1.42 (s, 9H), 1.37−1.20 (m, 2H), 1.31 (s, 3H), 1.25 (s, 3H), 1.10 (d, J = 6.9 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.6, 172.2, 165.1, 164.5, 154.4, 153.3, 120.5, 118.9, 115.5, 97.9, 95.0, 82.9, 80.4, 76.9, 62.5, 56.3, 41.6, 35.0, 32.2, 31.8, 28.6, 28.4, 25.3, 23.8, 23.5, 23.1, 19.4, 16.2, 12.6; LRMS (+electrospray): 873.2 $[M + Na]^+$, 851.2 $[M + H]^+$. HRMS cald for $C_{40}H_{62}Cl_3N_2O_9S$, 851.3241, found 851.3250.

Preparation of 18. To a solution of enol ether **23** (0.309 g, 0.363 mmol) dissolved in acetone (9 mL) was added *p*-toluenesulfonic acid (0.083 g, 0.436 mmol). The solution was stirred at RT for 22 h. The reaction was neutralized by the addition of sat. $NaHCO_3$ and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel (15% EtOAc/Hexanes) afforded β-keto-ester **18** as a white foam (0.250 g, 82%): $[\alpha]_D$ −36.8 (*c* 1.0, $CHCl_3$); R_f = 0.28 in 10% EtOAc/toluene; IR (neat) 2968, 2948, 1758, 1710, 1367, 1250, 1164, 1060, 927, 816, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ *12.61 (s, 1H), 6.91 (s, 1H), 6.43 (s, 1H), 5.14−5.07 (m, 1H), 4.88−4.66 (m, 4H), 4.11 (m, 1H), 3.49 (d, J = 16.2 Hz, 1H), 3.42 (d, J = 16.0 Hz, 1H), 3.31−3.29 (m, 1H), 2.69 (s, 3H), 2.33−2.17 (m, 2H), 2.04 (s, 3H), 2.04−1.96 (m, 2H), 1.72−1.61 (m, 2H), *1.65 and 1.63 (s, 3H), 1.45 (s, 9H), 1.42 (s, 9H), 1.24 (s, 9H), *1.10 and 1.08 (d, J = 8.5 Hz, 3H), 0.92 and *0.88 (d, J = 8.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8, 203.4, 178.7, 166.5, 164.5, 154.4, 153.2, 140.2, 138.3, 120.6, 118.9, 115.5, 94.9, 82.2, 77.3, 76.9, 63.8, 60.6, 46.8, 41.8, 34.9, 32.3, 32.2, 31.5, 28.6, 28.2, 23.7, 22.4, 21.8, 21.1, 19.4, 15.9, 14.4, 11.6; LRMS (+electrospray): 837.5 $[M + H]^+$, 859.6 $[M + Na]^+$. HRMS cald for $C_{39}H_{60}Cl_3N_2O_9S$, 837.3084, found 837.3108 (*corresponds to enol tautomer).

Preparation of 24. Diketone **18** (1.234 g, 1.48 mmol) was dissolved in 0.12 N HCl in MeOH (24.6 mL, 2.95 mmol) at 25 °C. The solution was then sparged with argon gas for 30 min. The ruthenium catalyst (0.150 g, 0.089 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 18 h at 25 °C, the reaction was returned to atmospheric pressure and poured into sat. aq $NaHCO_3$ (60 mL). After extraction with EtOAc (3 × 100 mL), the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel (20% EtOAc/Hexane) afforded the hydroxy ester **24** (0.955 g, 78%) as a white foam: $[\alpha]_D$ −33.5 (*c* 1.0, $CHCl_3$); R_f = 0.20 in 20% EtOAc/hexanes; IR (neat) 3385, 2974, 2936, 1758, 1703, 1504, 1471, 1455, 1367, 1249, 1161, 1051, 926, 817, 733 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.42 (s, 1H), 5.08 (t, J = 6.7 Hz, 1H), 4.85 (t, J = 5.7 Hz, 1H), 4.82 (d, J = 12.0 Hz, 1H), 4.71 (d, J = 12.0 Hz, 1H), 4.66 (br s, 1H), 4.15−4.09 (m, 2H), 3.46−3.39 (m, 2H), 2.70 (s, 3H), 2.39−2.21 (m, 4H), 2.03 (s, 3H), 1.98−1.94 (m, 2H), 1.73−1.71 (m, 1H), 1.65 (s, 3H), 1.44 (s, 9H), 1.42 (s, 9H), 1.37−1.20 (m, 2H), 1.18 (s, 3H), 1.16 (s, 3H), 1.09 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.2, 172.7, 164.4, 154.5, 153.2, 140.2, 138.3, 120.6, 120.5, 118.9, 115.5, 95.0, 83.3, 81.6, 77.3, 76.9, 73.2, 52.1, 41.7, 37.6, 35.0, 32.5, 32.3, 31.5, 28.6, 28.3, 25.4, 25.3, 23.7, 22.2, 19.3, 16.4, 12.4; LRMS (+electrospray): 861.2 $[M + Na]^+$, 832.2 $[M + H]^+$. HRMS cald for $C_{39}H_{62}Cl_3N_2O_9S$, 839.3241, found 839.3278.

Preparation of 25. To a solution of the bis-Boc protected amino acid (0.738 g, 0.880 mmol) dissolved in CH_2Cl_2 (20 mL) was added trifluoroacetic acid (10 mL). The solution was stirred at RT for 2 h followed by concentration in vacuo. The crude material was used without further purification: $[\alpha]_D$ +3.4 (*c* = 1.0, $CHCl_3$); R_f = 0.5 in 75:15:10 ^{t}BuOH: HCOOH: H_2O; IR (neat) 3076, 2971, 1757, 1668, 1378, 1255, 1187, 926, 818 cm^{-1}; ^{1}H NMR (400 MHz, DMF_{d7}) δ 8.61 (br s, 3H), 7.48 (s, 1H), 6.67 (s, 1H), 5.14 (t, J = 6.8 Hz, 1H), 5.03 (d, J = 12.4 Hz, 1H), 4.98 (d, J = 12.3 Hz, 1H), 4.88 (t, J = 6.6 Hz, 1H), 4.28 (dd, J = 9.8, 1.1 Hz, 1H), 4.00 (m, 1H), 3.63−3.60 (m, 1H), 2.70 (s, 3H), 2.68−2.66 (m, 2H), 2.49 (dd, J = 15.4, 2.0 Hz, 1H), 2.26 (s, 3H), 2.25−2.21 (m, 1H), 2.12−2.04 (m, 2H), 1.78−1.71 (m, 1H), 1.67 (s, 3H), 1.59−1.17 (m, 5H), 1.24 (s, 3H), 1.14 (s, 3H), 1.09 (d, J = 6.7 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.9, 171.6, 161.0, 161.3, 154.8, 143.9, 143.0, 142.9, 118.2, 116.7, 94.8, 83.9, 73.2, 58.8, 53.6, 52.2, 42.3, 36.5, 34.8, 32.2, 30.4, 27.8, 25.2, 23.8, 23.6, 22.5, 18.7, 16.4, 16.1, 14.1; LRMS (+electrospray): 705.1 $[M + Na]^+$, 683.1 $[M + H]^+$. HRMS cald for $C_{30}H_{45}Cl_3N_2NaO_7S$, 705.1910, found 705.1936.

Preparation of 26. The crude mixture, obtained from above, was dissolved in DMF (10 mL) and further diluted with CH_2Cl_2 (500 mL). Then HOAt (0.359 g, 2.64 mmol) was added followed by diisopropylethylamine (1.02 g, 7.92 mmol) and finally HATU (0.359 g, 2.64 mmol). The resultant mixture was stirred at 25 °C for 16 h. The reaction mixture was then washed with H_2O (1 × 100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was then dissolved in HOAc/THF/H_2O (3:1:1, 30 mL) for 30 min. The reaction mixture was concentrated in vacuo, neutralized with sat. aq $NaHCO_3$, and extracted using EtOAc (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel (45% EtOAc/Hexanes) afforded Troc-protected aza-dEpoB (**26**) (0.479 g, 79%) and Troc-protected C-15-epi-aza-dEpoB, from 88% ee asymmetric dihydroxylation, (0.065 g, 11%) as a white foam.

Characterization for Troc-protected aza-dEpoB **26**: $[\alpha]_D$ −16.3 (*c* 1.0, $CHCl_3$); R_f = 0.35 in 70% EtOAc/Hexanes; IR (neat) 3318, 2932, 1758, 1620, 1370, 1248, 1143, 1069, 926 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (s, 1H), 6.92 (d, J = 7.80 Hz, 1H), 6.51 (s, 1H), 5.18 (t, J = 7.8 Hz, 1H), 5.08 (d, J = 7.7 Hz, 1H), 4.79 (s, 2H), 4.64−4.63 (m, 1H), 4.34 (dd, J = 10.9, 7.0 Hz, 1H), 4.05 (d, J = 9.0 Hz, 1H), 2.68 (s, 3H), 2.52−2.46 (m, 2H), 2.31−2.21 (m, 3H), 2.09 (s, 3H), 1.98−1.92 (m, 1H), 1.69 (s, 3H), 1.65−1.51 (m, 4H), 1.35 (s, 3H), 1.37−1.20 (m, 2H), 1.17 (d, J = 6.8 Hz, 3H), 1.09 (s, 3H), 0.99 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.3, 170.7, 165.9, 154.5, 140.0, 139.6, 120.7, 118.4, 115.6, 94.9, 84.9, 76.8, 73.0, 56.4, 52.9, 43.8, 39.6, 38.7, 32.0, 31.8, 30.8, 27.2, 24.1, 22.0, 21.3, 19.2, 17.6, 16.9, 16.0; LRMS (+electrospray): 687.0 $[M + Na]^+$, 665.1 $[M + H]^+$. HRMS cald for $C_{30}H_{44}Cl_3N_2O_6S$, 665.1985, found 665.2002.

Characterization for Troc-protected C-15-epi-aza-dEpoB: $[\alpha]^{22}_D$ −1.50 (*c* 1.0, $CHCl_3$; R_f = 0.61 in 70% EtOAc/Hexanes; IR (neat) 3315, 2966, 1759, 1696, 1646, 1526, 1466, 1382, 1248, 1183, 925, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.40 (s, 1H), 6.34 (d, J = 5.8 Hz, 1H), 5.15 (t, J = 7.0 Hz, 1H), 4.92 (d, J = 12.0 Hz, 1H), 4.84−4.77 (m, 1H), 4.74 (d, J = 12.0 Hz, 1H), 4.69−4.60 (m, 1H), 4.57−4.52 (m, 1H), 3.40−3.35 (m, 1H), 2.71 (s, 3H), 2.34−2.09 (m, 3H), 2.07 (s, 3H), 1.97−1.91 (m, 3H), 1.70 (s, 3H), 1.43−1.20 (m, 6H), 1.33 (s, 3H), 1.17 (d, J = 6.9 Hz, 3H), 1.04 (s, 3H), 0.98 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.9, 172.5, 164.9, 154.8, 152.6, 139.7, 139.0, 120.8, 118.4, 115.8, 94.8, 77.1, 71.8, 55.9, 54.3, 53.6, 52.9, 45.9, 38.8, 34.7, 32.1, 31.8, 30.8, 24.7, 22.5, 19.3, 16.6, 15.7; LRMS (+electrospray) 687.0 $[M + Na]^+$, 665.2 $[M + H]^+$. HRMS cald for $C_{30}H_{44}Cl_3N_2O_6S$, 665.1985, found 665.1988.

Preparation of 4a. To a solution of Troc-protected aza-dEpoB (0.038 g, 0.057 mmol) dissolved in THF/HOAc (1:3, 6 mL) was added a spatula tip of activated nanosized zinc. The reaction mixture was then sonicated at 25 °C for 2 h. The solution was filtered to remove the zinc metal followed by concentration in vacuo. The residue was then dissolved in EtOAc (20 mL) and neutralized with sat. aq $NaHCO_3$ (10 mL). The aqueous layer was extracted using EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel (60% EtOAc/Hexanes) afforded aza-dEpoB (0.025 g, 88%) as a white foam.

Characterization for aza-dEpoB (**4a**) $[\alpha]_D$ −61.9 (*c* 0.5, $CHCl_3$); R_f = 0.55 in 100% EtOAc; IR (neat) 3330, 2929, 1690, 1634, 1510, 1456, 1381, 1147, 732 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.46 (s, 1H), 5.99 (d, J = 6.5 Hz, 1H), 5.13 (t, J = 7.6 Hz, 1H), 4.31 (dd, J = 11.6, 6.8 Hz, 1H), 4.06 (d, J = 8.9 Hz, 1H), 3.82−3.74 (m, 2H), 3.14 (q, J = 6.9 Hz,

1H), 2.99 (s, 1H), 2.69 (s, 3H), 2.48−2.31 (m, 3H), 2.25−2.21 (m, 1H), 2.06 (s, 3H), 2.07−2.00 (m, 1H), 1.77−1.69 (m, 4H), 1.69 (s, 3H), 1.31 (s, 3H), 1.34−1.20 (m, 2H), 1.17 (d, $J = 6.9$ Hz, 3H), 1.11 (s, 3H), 1.00 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 221.2, 170.6, 164.8, 152.8, 139.7, 120.8, 118.7, 115.7, 74.5, 73.9, 56.6, 53.1, 42.6, 40.5, 38.5, 32.7, 31.7, 31.5, 25.8, 23.3, 22.9, 20.2, 19.3, 16.8, 15.9, 13.7; LRMS (+electrospray): 513.2 $[M + Na]^+$, 491.1 $[M + H]^+$. HRMS cald for $C_{27}H_{42}N_2O4_S$, 490.2865, found 490.2856.

Characterization for 15 (*R*)-aza-dEpoB (**4b**): $[\alpha]^{22}_D$ 30.9 (*c* 1.0, $CHCl_3$); $R_f = 0.43$ in 70% EtOAc; IR (neat) 3339, 2966, 1685, 1644, 1520, 1454, 1377, 1184, 979, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.31 (s, 1H), 5.77 (d, $J = 8.4$ Hz, 1H), 5.06 (t, $J = 7.2$ Hz, 1H), 4.98 (s, 1H), 4.71−4.68 (m, 1H), 4.22 (d, $J = 10.4$ Hz, 1H), 3.51 (d, $J = 6.0$ Hz, 1H), 3.16 (dd, $J = 11.9$, 7.0 Hz, 1H), 2.96 (s, 1H), 2.71 (s, 3H), 2.47−2.40 (m, 2H), 2.17−2.02 (m, 2H), 2.08 (s, 3H), 1.96−1.87 (m, 2H), 1.77−1.75 (m, 1H), 1.70 (s, 3H), 1.58−1.50 (m, 2H), 1.34 (s, 3H), 1.34−1.20 (m, 2H), 1.14 (d, $J = 6.8$ Hz, 3H), 1.07 (s, 3H), 0.94 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 221.3, 172.0, 164.7, 152.6, 140.3, 138.7, 119.4, 118.4, 115.7, 73.2, 72.2, 54.8, 54.0, 41.5, 39.0, 36.7, 32.0, 31.8, 31.2, 25.1, 24.2, 23.0, 19.3, 17.2, 15.5, 14.4, 12.4; LRMS (+electrospray): 513.0 $[M + Na]^+$, 491.1 $[M + H]^+$. HRMS cald for $C_{27}H_{42}N_2O4_S$, 490.2865, found 490.2863.

Preparation of 2. Aza-dEpoB (0.025 g, 0.051 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled to −78 °C. 2,2-Dimethyldioxirane (0.6M, 0.11 mmol) was added slowly. The reaction mixture was allowed to warm to −50 °C and stirred for 1 h. Excess DMDO was quenched at −50 °C by the addition of dimethyl sulfide (0.1 mL) and warmed to RT. Chromatography on silica gel (80% EtOAc/Hexanes) afforded fully synthetic aza-EpoB (0.018 g, 69%) as a white foam: $[\alpha]_D$ −34.1 (*c* 1.0, $CHCl_3$); $R_f = 0.4$ in 100% EtOAc; IR (neat) 3319, 2931, 1661, 1643, 1536, 1453, 1372, 1185, 753 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.83 (d, $J = 8.0$ Hz, 1H), 6.55 (s, 1H), 4.66−4.64 (m, 1H), 4.25 (d, $J = 6.2$ Hz, 1H), 4.03−4.01 (m, 1H), 3.83−3.81 (m, 1H), 3.38−3.33 (m, 1H), 2.81 (dd, $J = 7.2$, 6.4 Hz, 1H), 2.70 (s, 3H), 2.62 (br s, OH, 1H), 2.43 (dd, $J = 14.7$, 9.3 Hz, 1H), 2.32 (dd, $J = 14.7$, 2.9 Hz, 1H), 2.13 (s, 3H), 2.04−1.97 (m, 4H), 1.69−1.38 (m, 5H), 1.34 (s, 3H), 1.27 (s, 3H), 1.17 (d, $J = 6.9$ Hz, 3H), 1.12 (s, 3H), 0.99 (d, $J = 7.0$ Hz, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 221.0, 170.6, 165.0, 152.6, 137.8, 119.4, 116.2, 75.0, 74.1, 61.4, 61.1, 54.7, 52.4, 43.9, 40.4, 38.0, 31.9, 31.8, 30.7, 23.9, 23.1, 21.7, 21.6, 19.4, 17.3, 17.1, 14.5; LRMS (+electrospray) 529.0 $[M + Na]^+$, 507.0 $[M + H]^+$. HRMS cald for $C_{27}H_{42}N_2O_5S$, 506.2814, found 506.2796.

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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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