New Chemical Synthesis of the Promising Cancer Chemotherapeutic Agent 12,13-Desoxyepothilone B: Discovery of a Surprising Long-Range Effect on the Diastereoselectivity of an Aldol Condensation

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Abstract: The epothilones are naturally occurring cytotoxic molecules that possess the remarkable ability to arrest cell division through the stabilization of microtubule assemblies. Our *in vivo* studies with 12,13-desoxyepothilone B (dEpoB), have established that the desoxy compound is well tolerated and virtually curative against a variety of sensitive and resistant xenograft tumors in animal models. In light of these discoveries, we sought a chemical synthesis of dEpoB that would be able to support a serious and substantial discovery research program directed toward the clinical development of this molecule. The overall strategy for this endeavor assumed the ability to synthesize dEpoB from three constructs which include an achiral β,δ-diketo ester construct **A**, an (*S*)-2-methylpentenal moiety **B**, and the thiazoyl-containing vinyl iodide moiety **C**. We envisioned that a diastereoselective aldol condensation between an achiral C5−C6 (*Z*)-metalloenolate derived from construct **A** and an (*S*)-2-methylalkanal fragment, **B**, would generate the desired C6−C7 bond. Second, a *B*-alkyl Suzuki coupling between the vinyl iodide construct **C** and an alkyl borane would form the C11−C12 bond. Finally, a late-stage reduction of the C3 ketone to the requisite C3 alcohol with high asymmetric induction would permit us to introduce the β,δ-diketo ester fragment **A**, into the synthesis as a readily accessible achiral building block. The governing concepts for our new synthesis are described herein.

Introduction

Epothilones A (**1**, EpoA) and B (**2**, EpoB), Scheme 1, are cytotoxic macrolide natural products[1,2] which exhibit biological effects that parallel those of Taxol (paclitaxel) and Taxotere (docetaxel).[3−6] The epothilones were first isolated from the mycobacterium *Sorangium cellulosum* that were harvested off the shores of the Zambezi River in South Africa.[1,2] Taxol (paclitaxel) and Taxotere (docetaxel) are clinically effective antineoplastic agents[7] whose chemical structure is significantly different than the epothilones. The primary target of the taxanes, and presumably the epothilones, is the microtubule which is vital for mitosis, motility, secretion, and proliferation.[8] Recently, it was established that the taxanes also induce several early response and cytokine genes, and it has been demonstrated that gene expression is dramatically influenced by taxoid chemical structure.[9] Consequently, some of the pharmacological effects of paclitaxel may originate because of its effect on gene expression and not exclusively from stabilization of microtubule assemblies. The observed anticancer effects of the epothilones are also attributed to their ability to stabilize microtubule assemblies although minimal data on the physiological effects of the epothilones on gene expression has been reported in the literature.[9]

The taxoids and epothilones demonstrate analogous effects in their ability to arrest cellular mitosis and to induce the formation of hyperstable tubulin polymers in both cultured cells and microtubule protein.[10] Thus epothilones A and B competitively inhibited the binding of [^{3}H]paclitaxel to tubulin polymers.[11] This result was interpreted to suggest binding of the

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epothilones and taxanes at the same site, although binding in an overlapping or allosteric site could not be ruled out through these experiments.

Perhaps the most intriguing discovery encountered during an early investigation of the epothilones is that EpoB is notably more potent (both *in vitro* and *in vivo*) than paclitaxel in inhibiting cell growth.[10] Moreover, while the cellular mechanism of the epothilones and the taxanes is apparently the same, the epothilones stand out in their ability to retain activity against multidrug-resistant (MDR) cell lines and tumors where paclitaxel and other major chemotherapeutic agents fail.[9,10]

Recognizing that the epothilones, or suitably modified derivatives, might find status as cancer chemotherapy agents, we embarked in a multidisciplinary pursuit to investigate these compounds. Included in our objectives was the goal of total synthesis of the epothilones and their analogues, which was accomplished first by us[12] and subsequently by others.[13] While the epothilones are available by fermentation,[1,2] the more active epothilone B is particularly scarce, and thus we sought chemical synthesis as a means for our laboratory to gain access to this series of compounds and their analogues for *in vitro* and *in vivo* analysis.

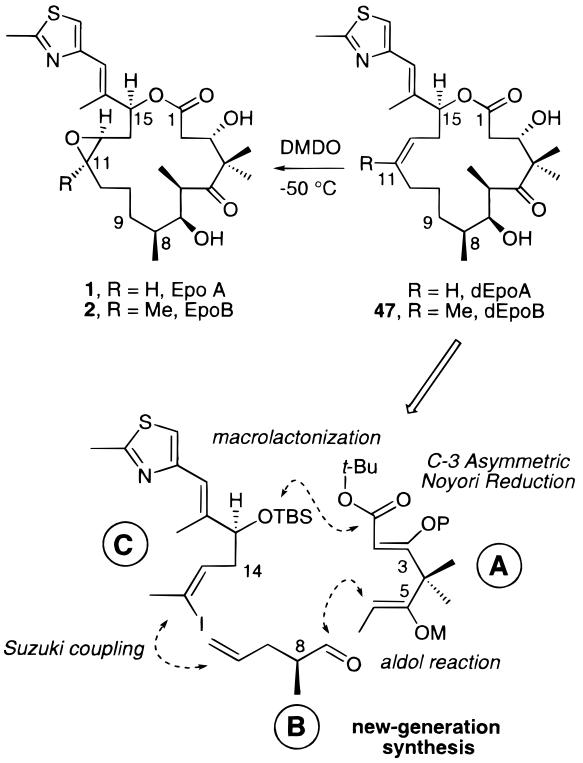
This account begins with a brief synopsis of our early synthetic efforts toward this end. In the following contribution, we shall enumerate our findings regarding our recently accomplished practical chemical synthesis of epothilone B and its congeners.[14]

Background

From the outset, it was readily apparent that unlike the structurally complex taxanes, the less forbidding structure of the epothilones could be better suited for rapid development of structure−activity comparisons (SAR) through chemical synthesis. Consequently, the initial goal of our synthetic program was to realize a total chemical synthesis of the epothilones (and their analogues) that would provide material for preliminary biological testing, both *in vitro* and *in vivo*. We were hopeful that the SAR data would identify congeners of the naturally occurring epothilones with enhanced chemotherapeutic efficacy. In addition to considerations of potency, we were particularly interested in the MDR-reversing ability of our synthetic targets in comparison to their MDR-susceptible taxoid counterparts.[10]

Notwithstanding the less intimidating architecture of the epothilones relative to the taxoids, we foresaw several synthetic issues concerning this venture that would require careful attention and much experimentation. The structures of the epothilones invite retrosynthetic dissection into two domains. Thus the polypropionate domain (C1−C8) and the "*O*-alkyl" sector (C12−C15) of the lactone are joined through a third achiral "hinge" region (C9−C11) which consists of three

Scheme 1. Retrosynthetic Disconnections of the New Synthesis of the Epothilones through the Merger of Constructs **A**, **B**, and **C**



contiguous methylene groups (Scheme 1). The polypropionate sector (C1−C8) comprises four discontiguous stereocenters flanked by two relatively labile β-hydroxy carbonyl moieties. The *O*-alkyl sector contains the C12−C13 *cis*-epoxide moiety that is insulated by a single methylene group from C15. The latter bears an allylic alcohol and an α,β-unsaturated thiazole linkage.

Scheme 1 outlines the retrosynthetic strategy that was employed for our newly developed chemical synthesis of the epothilones. Although, the structural issues addressed above were not insurmountable, several significant obstacles were encountered during the course of our pursuit.

The synthesis of the C1−C11 domain of the epothilones has proven most challenging, and indeed, this region had been the scene of many variations in strategy and synthetic design.[13a,15] In our first synthesis of the C1−C11 polypropionate domain, we chose to contain the stereocenters at C6, C7, and C8 in a rigid cyclic template with the general structure **5**, Scheme 2.[16,17] The requisite cyclic template was synthesized as outlined in Scheme 2 via a Lewis Acid catalyzed diene−aldehyde cyclocondensation (LACDAC)[18] reaction which enabled us to accomplish the central goal of stereospecificity by translating the absolute stereochemistry of the template to C6, C7, and C8 of epothilone.[12,16,17,19] Through a series of steps, the resultant dihydropyran-4-one, **5**, could be converted to the desired

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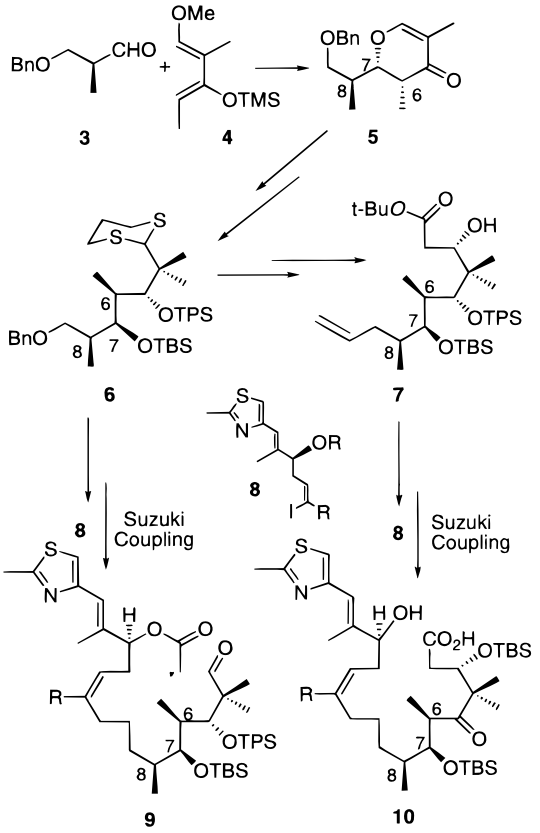
Scheme 2. First Generation Synthesis of the Epothilones Using Lewis Acid Catalyzed Diene−Aldehyde Cyclocondensation (LACDAC) Chemistry



epothilone precursors, **9** or **10**, through a *B*-alkyl Suzuki coupling with an appropriate thiazole-containing vinyl iodide, **8**. Although this route proved rather lengthy, the first successful synthesis of both epothilones A and B, performed in these laboratories, was achieved through this strategy, utilizing either macroaldolization or macrolactonization reactions.

A New Synthesis of Epothilone B. While our initial synthetic enterprise in the epothilone field afforded fully synthetic epothilone B in quantities necessary for *in vitro* cytoxicity and tubulin binding studies, it was only through a tenacious effort that suitable amounts could be prepared for extensive *in vivo* studies against xenografts of human tumors in nude mice. Our initial *in vivo* studies of the parent agent suggested some potentially serious toxicity problems and an all too narrow window of possible therapeutic advantage.[20b−d] Fortunately however, experiments with 12,13-desoxyepothilone B (dEpoB) were more promising (*vide infra*).[20a,b] Surprisingly, these studies revealed that although the *in vivo* and *in vitro* potency of dEpoB is lower than **2**, the 12,13-desoxy system dramatically outperforms paclitaxel *in vivo*. We were further enticed to pursue this direction of research when our preliminary *in vivo* studies established that the desoxy compounds were well tolerated and virtually curative against a variety of xenograft tumors.[20] Moreover, in parallel studies with drug resistant xenografts, dEpoB was clearly superior to paclitaxel.[20] In light of these findings, we sought a chemical synthesis of dEpoB that would be able to support a serious and substantial discovery research program directed toward the clinical development of this apparently useful compound. Toward this end, we undertook a major departure from our original academic syntheses. The governing concepts for our new synthesis are detailed below.

Our overall strategy for this endeavor assumed the ability to synthesize dEpoB from the three constructs **A**, **B**, and **C** through the key steps outlined in Scheme 1. We envisioned two possible routes in confronting this challenge: First, a *B*-alkyl Suzuki merger of constructs **B** and **C**, followed by a post-Suzuki aldol condensation between the Suzuki-coupled product (**B** + **C**) and the enolate of **A**, {e.g., [**A** + (**B** + **C**)]} (Scheme 1). Our second itinerary projected a key aldol condensation between constructs **A** and **B**, followed by Suzuki coupling to effect the merger of the aldolate (**A** + **B**) with the vinyl iodide, **C**, {e.g., [(**A** + **B**) + **C**]} (Scheme 1).

Consequently, our new synthetic strategy hinged on three vital requirements, each of which was crucial to the success of the venture. Our stipulations assumed that the troublesome C1−C11 polypropionate domain could be assembled through an aldol condensation of the C5−C6 (*Z*)-metalloenolate construct **A** (or its equivalent) with the chiral aldehyde **B** or the post-Suzuki aldehyde (**B** + **C**). Fulfilling this goal would require a high level of asymmetric control in the aldol reaction as well as excellent regiocontrol in the addition of chiral aldehyde **B** or the post-Suzuki aldehyde (**B** + **C**) to enolate **A**. Our second tenet assumed the ability to perform successfully a *B*-alkyl Suzuki merger (*vide infra*) between a construct of the form **B** or the elaborate aldol condensation product (**A** + **B**) and vinyl iodide **C**. Finally, a late-stage reduction of the C3 ketone to the requisite C3 alcohol with high asymmetric induction would be essential. The ability to successfully control the desired C3 stereochemistry through catalytic asymmetric reduction was a necessary element as it permitted us to introduce the C1−C7 fragment, **A**, into the synthesis as a readily accessible achiral building block.

Dianion Equivalents Corresponding to the Polypropionate Domain. Two tactical approaches emerged during the evolution of our synthesis. Initially the aldol reaction was performed directly between aldehyde **13a**[21] and the dianion **12** derived from tricarbonyl **11**. In this way, it was indeed possible to generate the (*Z*)-lithium enolate of **11**, which underwent successful aldol condensation as shown in Scheme 3.[22] Unfortunately, the resultant C7 β-hydroxyl functionality tended to cyclize to the C3 carbonyl group, thereby affording a rather unmanageable mixture of hydroxy ketone **14a** and lactol **14b** products. Lactol formation could be reversed following treatment of the crude aldol product under the conditions shown (Scheme 3); however, under these conditions an inseparable 3−4:1 mixture of diastereomeric products, **15**(**a** or **b**):**16** (**a** or **b**), was obtained. Progress along this avenue was further impeded when it later became apparent that neither C7-acetate nor C7-TES-protecting groups were compatible with the remainder of the synthesis. Attempts to introduce more durable blocking groups at the C7 hydroxyl center, by diversion of the desired hydroxy ketone **14a**, were unsuccessful.

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(21) Aldehyde **13a** was readily prepared according to the procedure outlined in: Lin, N.-H.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am Chem. Soc.* **1996**, *118*, 9062.

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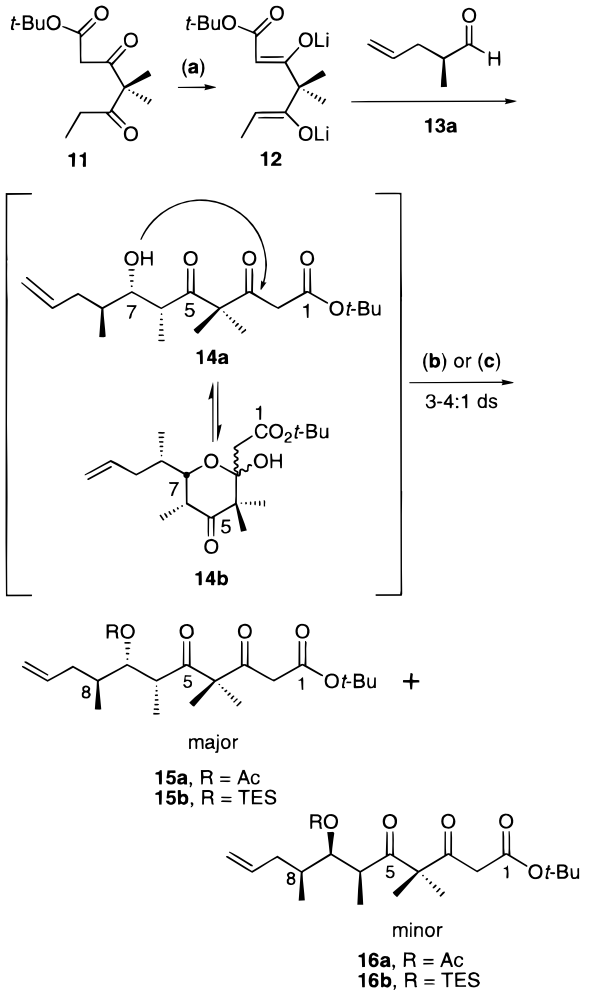
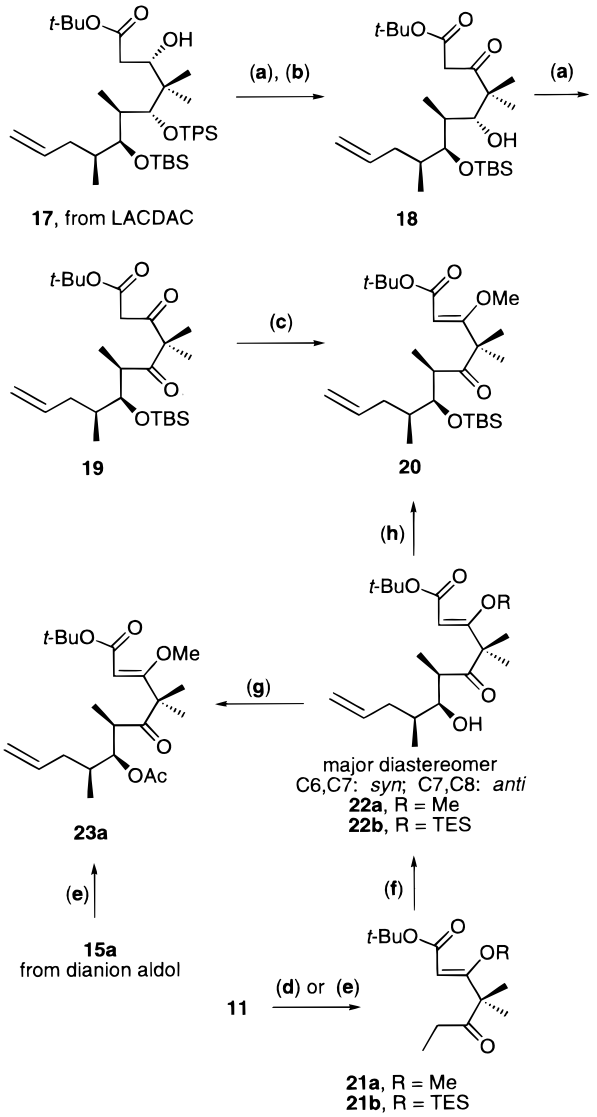
Scheme 3[a]



[a] (a) 2.2 equiv LDA, −50 °C, (*S*)-2-methyl-4-pentenal (**13a**), (*ca.* 60%); (b) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 18 h, (60%, two steps); (c) TESCl, imidazole, DMF, 18 h, (60%, two steps).

Although our initial attempts in this regard proved unavailing, we were able to confirm that the critical aldol reaction between the dienolate **12** and (*S*)-aldehyde **13a** did indeed provide the desired C6−C7 syn stereochemistry concurrent with C7−C8 anti relationship (by anti-Felkin−Anh addition) as the major diastereomer. Initially, we sought to confirm the resident stereochemistry at C6, C7, and C8 by converging the protected aldolate products **15a** or **15b** with compound **19** which could be prepared independently (Scheme 4) from previously characterized intermediates in our LACDAC route.[12,20,23] Unfortunately, it was not possible to prepare the C7 TBS-protected compound, **19**, using our aldol chemistry due to complications arising from hemiacetal formation (*vida supra*). Likewise, several attempts to hydrolyze the C7-TBS of **19** resulted in decomposition of the tricarbonyl system. However, comparison of the ^{1}H NMR spectra of compounds **15b** (C7-TES-protected, aldol chemistry) and **19** (C7-TBS-protected, LACDAC chemistry) revealed similar chemical shifts and multiplicities of coupling constants which suggested the likelihood of correspondence at the level of stereochemistry. This finding encouraged us to pursue our course of research. However, to ascertain unambiguously that the major diasteroemer in the aldol reaction between **11** and **13** was indeed the desired compound would require a more rigorously supported argument.

Scheme 4[a]



[a] (a) Dess Martin, (86−88%); (b) HF·pyridine, (90%); (c) dimethyl sulfate, K_2CO_3, reflux (50%); (d) NaH, TESOTf, −30 °C (73%); (e) $TMSCHN_2$, *i*-Pr_2NEt, MeOH, CH_3CN, (74%); (f) (*S*)-2-methyl-4-pentenal (**13a**), LDA, −120 °C, (50−60% of major diastereomer); (g) Ac_2O, DMAP, Et_3N, (98%); (h) TBSOTf, 2,6-lutidine, (87%).

Realizing that the major impediment in this regard was the untoward lactolization of **14a** to the hemiacetal, **14b**, we considered the possibility of simply engaging the C3-carbonyl group of the nucleophile in another functional arrangement such as an enol ether (Scheme 4). In this way, unwanted cyclization would not occur, and the C7-hydroxyl group could be readily protected with a more robust moiety. Initially, methyl enol ether (**21a**) and triethylsilyl (TES) enol ether (**21b**)[14] protecting groups proved useful for our purposes (Scheme 4). Rewardingly, **21a** and **21b** each successfully underwent the aldol coupling with (*S*)-aldehyde **13a** to afford a 1:5−6 mixture of diastereomers that were separable by flash column chromatography. Given the circumvention of the difficulties encountered by undesired engagement of the C7-hydroxyl moiety, the latter could be readily protected as triethylsilyl (TES), acetate (Ac), or (*tert*-butyldimethylsilyl) TBS ethers. As a result, we were able to converge the polypropionate domain (prepared through our aldol

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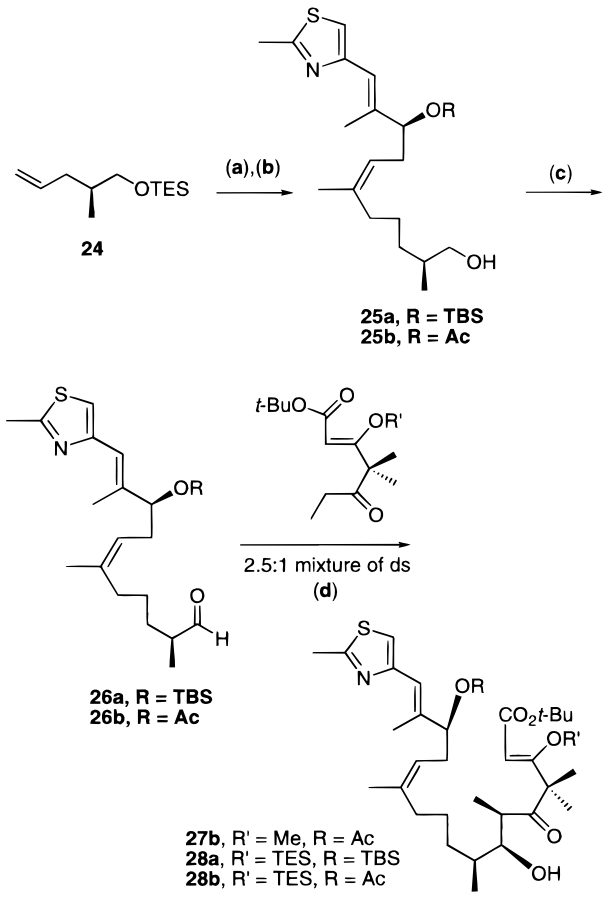
chemistry) with compound **20**, prepared from previously characterized intermediates in our LACDAC synthesis of the polypropionate region (Scheme 4).[12,20] In the event, the tricarbonyl system **19**, obtained from the previously described LACDAC chemistry, was successfully converted to the methyl enol ether **20**, and this compound displayed an identical ^{1}H NMR with the TBS-protected aldolate isolated from the aldol condensation of methyl enol ether **21a** and aldehyde **13a** (Scheme 4). Similarly, the C7-protected aldolate product, isolated from the aldol condensation of the methyl enol ether **21a** and aldehyde **13a**, exhibited identical ^{1}H NMR with methyl enol ether **23a** derived from C7 acetate **15a** (obtained from the aldol reaction of tricarbonyl **11** and aldehyde **13a**). These results demonstrated conclusively that the aldol reactions provided both good diastereoselectivity and the requisite syn connectivity between the stereocenters at C6−C7 and the necessary anti relationship relative to the resident chirality at C8. We shall digress at a later point to discuss the apparent reason for this unexpected anti-Felkin−Anh diastereoselection.

Aldol Condensation Following Suzuki Coupling. Having confirmed the ability to successfully perform the coupling of enolate **A** and chiral aldehyde **B**, generating the required C7−C8 stereochemical relationship, we sought to address the prospect of performing the aldol condensation on the highly elaborate chiral aldehyde formed from the merger of constructs **B** and **C**, Scheme 1. In the event, we were able to prepare the requisite aldehyde beginning with the C1 TES-protected alcohol, **24** (Scheme 5). The TES ether **24**[24] readily underwent hydroboration with 9-BBN and subsequent *B*-alkyl Suzuki coupling with vinyl iodide **C**[25] in good yield and with good stereochemical integrity about the olefin to afford **25a** or **25b**. Selective TBAF[26] deprotection of the C1 TES-protecting group and subsequent Swern oxidation[27] afforded the desired aldehyde, **26a** or **26b**. Aldol condensation of aldehyde **26** with the lithium enolate of either **21a** or **21b** afforded consistently a 2.5:1 mixture of diastereomeric products (C7−C8, anti:syn) in 62−68% combined yield. Attempts to lower reaction temperature and modify the solvent and/or base proved ineffective at improving the apparent diastereoselectivity of the coupling step. Given the poor diastereoselectivity observed in the coupling reaction of **12** and **26a/b**, we redirected our attention toward the more successful coupling observed between enol ethers **21a/b** and the pre-Suzuki aldehyde **13a**.

Synthesis of C1−C11 Polypropionate Domain. With the desired C1−C11 domain, **22a/b**, in hand, we initially attempted to effect the synthesis of dEpoB with the C3 TES enol ether, **22b** (Scheme 4). We felt that a C3 TES enol ether intermediate would be advantageous as this group could be readily removed under mild conditions. While we did accomplish our first total synthesis of dEpoB with material prepared via this route, our initial success in this regard did not translate well upon attempted scale-up (>1.0 g). On larger scales, the aldol reaction between **21b** and aldehyde **13a** proved to be troublesome. In time we learned that the resultant C3 TES enol ether in **22b** was prone to decomposition under the very basic conditions of the aldol reaction and, moreover, was quite sensitive to silica gel chromatography.

Scheme 5[a]



[a] (a) 9-BBN, **24**; then **C**, Cs_2CO_3, $Pd(dppf)_2Cl_2$, Ph_3As, H_2O; (b) TBAF, 0 °C, (82% (two steps)); (c) oxalyl chloride, DMSO; Et_3N, (87%); (d) LDA, **21a** or **21b**, −100 °C; R = Me, (62%, 2.5:1 mixture of diastereomers); R = TES, (68%, 2.5:1 mixture of diastereomers), major diastereomer shown.

As a result of this apparent failure, we investigated the usefulness of the methyl enol ether linkage discussed above.[28] We were happy to discover that the requisite methyl enol ether, **21a**, could be readily prepared in multigram quantities from trimethylsilyl diazomethane, $TMSCHN_2$, with Hunig's base in high yield (Scheme 4).[29] Likewise, hydrolysis of the C3 methyl enol ether could be effected, without epimerization at C6, by the use of *p*-toluenesulfonic acid (*p*-TSA) in acetone at room temperature (Scheme 6).

At this point, we directed our attention to an appropriate protecting group for the C7 alcohol. We were concerned that the highly acidic nature of the Noyori reduction protocol (*vide infra*) would not be compatible with the survival of silyl (TES or TBS) functionality at C7. Therefore, we considered a more robust functionality at C7 such as acetate; however, on the basis of preliminary studies, we foresaw difficulty in successfully removing the C7 acetate from the lactonized dEpoB precursor without concomitant destruction of a highly advanced macrocycle. Hence, we sought a more dischargeable functionality to protect the C7 alcohol. At this point, we directed our attention toward slightly more labile protecting groups that would still be expected to survive the acidic conditions of the asymmetric Noyori reduction. We investigated the use of both chloroacetyl

(24) The C-1 TES ether was readily prepared from the Overman alcohol described in ref 21 by the use of TESOTf and 2,6-lutidine in CH_2Cl_2 at −78 °C for 30 min.

(25) See Supporting Information for the synthesis of the previously characterized vinyl iodide and its precursors.

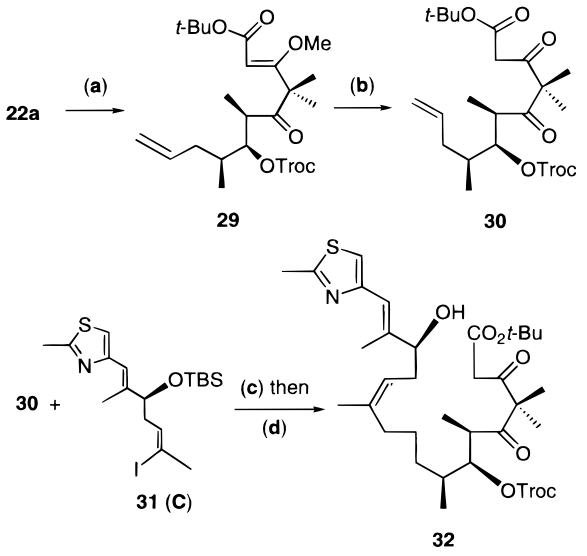
(26) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549.

(27) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.

(28) Harris, C. R.; Kuduk, S. D.; Savin, K.; Balog, A.; Danishefsky, S. J. *Tetrahedron Lett.* **1999**, *40*, 2263.

(29) Aoyama, T.; Terasawa, S.; Sudo, K.; Shiori, T. *Chem. Pharm. Bull.* **1984**, *32*, 3759.

Scheme 6[a]



[a] (a) TrocCl, pyridine, CH_2Cl_2, 0 °C; (b) *p*-TSA, acetone, rt, 6 h, (87%, two steps); (c) 9-BBN, **30**; Cs_2CO_3, $Pd(dppf)_2Cl_2$, Ph_3As, DMF, **31(C)**, H_2O, (ca. 75%); (d) 0.5 M HCl/MeOH, (85%).

and methoxyacetyl moieties; however, these too proved ineffective as they were difficult to remove without concomitant destruction of the macrocycle by ring-opening at the lactone or retro-aldol of the β-hydroxy carbonyl moieties.

We finally turned our attention to a 2,2,2-trichlorethyoxycarbonate (Troc)-protecting group at C7. Indeed a similar protective moiety had been utilized by Evans, *et al*.[30] in the total synthesis of the macrolide antibiotic cytovaricin. We were pleased to discover that the Troc function could readily be introduced through the action of compound **22a** (or **22b**) with TrocCl and pyridine in CH_2Cl_2 (Scheme 6). However, we foresaw difficulties in the standard reductive removal of the Troc-protecting group (Zn/HOAc/heat), given the possibility of concurrent reduction of the C5 ketone under the strongly reducing conditions. However, the Evans report demonstrates the ability of the mild reducing agent samarium(II) iodide, SmI_2,[31] to cleanly remove a 2,2,2-trichloroethoxycarbamate, and we hoped to extend this protocol to the reductive removal of the C7 Troc-protected alcohol of epothilone B. We anticipated that with these mild reaction conditions (SmI_2, −78 °C) the sterically encumbered C5 ketone would not be reduced in the absence of an added proton source. With the C7 issue addressed, we could direct our focus toward the merger of the highly elaborate C1−C11 domain with the vinyl iodide moiety, **C**, through a *B*-alkyl Suzuki coupling.

***B*-Alkyl Suzuki Merger.** The second fundamental component of our new total synthesis of epothilone B involved a very ambitious *B*-alkyl Suzuki[32] merger, Scheme 6. The hope was to couple the previously described vinyl iodide[12,20,33] **31(C)** and the rather elaborate tricarbonyl **30** to gain access to the requisite C15 hydroxy ester in preparation for end-game macrolactonization. We were somewhat apprehensive that the tricarbonyl arrangement might be sensitive to the hydroboration conditions necessary for the preparation of the organoborane at C11. However, our concerns were allayed as the coupling step was accomplished without difficulty. The crude *B*-alkyl Suzuki-coupled product was best characterized as the C15 alcohol after hydrolysis of the TBS-protecting group to afford the requisite C15-hydroxy ester **32**. With this elaborate acyclic precursor (**32**) in hand, we now directed our thoughts to the asymmetric reduction of the C3 ketone.

Stereoselective Noyori Reduction. Indeed, the selective asymmetric reduction of the C3 ketone now loomed as the key issue on which the completion of the synthesis of dEpoB hinged. The choice of a suitable reducing agent for this transformation would be determined with the goal of optimizing diastereoselectivity and chemoselectivity. Selective asymmetric reduction of the C3 ketone without concomitant reduction of the ketone at C5 would be imperative. Furthermore, concurrent reduction of the two olefinic moieties present in the acyclic precursor **32** must be avoided.

We soon directed our focus toward the excellent chiral recognition displayed by the atropisomeric [2,2′-bis(diarylphosphino)-1,1′binaphthyl]ruthenium {Ru(BINAP)} species which has been used occasionally in the total synthesis of several naturally occurring molecules.[34] Noyori[35] and others[36] have demonstrated that these Ru(BINAP) derivatives possess the remarkable ability to catalyze the asymmetric reduction of β-keto esters. Because of the inherent ability of the ruthenium species to chelate the 1,3-dicarbonyl arrangement, it is readily evident that β-keto esters that contain functionality in the δ-position could affect the stereo- and regiocontrol of the catalyst upon reduction due to competing coordination modes and multiple ligation possibilities with Ru(BINAP) in a system such as ours. We were encouraged to discover that in the reduction of β,δ-diketo esters, the C3 ketone is at first selectively hydrogenated to give the 3-hydroxy ester and then subsequently the C5-carbonyl group is hydrogenated to afford the dihydroxy ester.[37] We were hopeful that the presence of the *gem*-dimethyl functionality in **32** would preclude subsequent reduction of the C5 ketone under the Noyori reduction conditions.

Recognizing that the conditions of the Noyori reduction may also effect the facile reduction of isolated olefinic moieties present in the molecule, we were concerned that asymmetric reduction of the C3 ketone might be complicated by undesired reduction of the C12−C13 and C15 allylic olefin species. However, we were pleased to find that under mild conditions, the modified Noyori catalyst $[RuCl_2(BINAP)]_2{\cdot}NEt_3$], prepared by heating $Ru(COD)Cl_2$, BINAP, and Et_3N at 140 °C in toluene, would catalyze the hydrogenation of the 3-oxo group in our substrate without simultaneous reduction of remote di- and trisubstituted olefins.[38] Encouraged by these previous examples, we set out to attempt the asymmetric reduction on our β,δ-diketo ester system.

(30) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

(31) Molander, G. A. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley and Sons: New York, 1994; Vol. 46, p 211.

(32) (a) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314. (b) For an excellent review, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (c) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014.

(33) Su, D.-S.; Meng, D.; Bertinato, P.; Balog, A.; Sorensen, E. J.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 757.

(34) (a) Taber, D. F.; Deker, P. B.; Silverberg, L. J. *J. Org. Chem.* **1992**, *57*, 5990. (b) Taber, D. F.; Silverberg, L. J.; Robinson, E. D. *J. Am. Chem. Soc.* **1991**, *113*, 6639. (c) Schreiber, S. L.; Kelly, S. E.; Porco, J. A.; Sammakia, T.; Suh, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 6210. (d) Taber, D. F.; Wang, Y. *J. Am. Chem. Soc.* **1997**, *119*, 22.

(35) Noyori, R. *Tetrahedron* **1994**, *50*, 4259 and references therein.

(36) Ager, D. J.; Laneman, S. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3327 and references therein.

(37) (a) Shao, L.; Seki, T.; Kawano, H.; Saburi, M. *Tetrahedron Lett.* **1991**, *32*, 7699. (b) Shao, L.; Kawano, H.; Saburi, M.; Uchida, Y. *Tetrahedron* **1993**, *49*, 1997.

(38) (a) Taber, D. F.; Silverberg, L. J. *Tetrahedron Lett.* **1991**, *32*, 4227. (b) Taber, D. F.; Silverberg, L. J.; Robinson, E. D. *J. Am. Chem. Soc.* **1991**, *113*, 6639.

Development of Conditions and Substrate. It was soon apparent that the asymmetric Noyori reduction of various diketo esters in this series was critically dependent upon the amount of acid present in the reaction. Thus, the presence of stoichiometric acid was required for reduction of the C3 ketone with both good diastereo- and chemoselectivity. In the absence of acid, no reduction of the ketone was observed. However, complete reduction of both olefinic moieties was apparent upon inspection of the ^{1}H NMR spectrum of the crude reaction product. In the presence of only 0.5 equiv of HCl, the diastereoselectivity of the asymmetric reduction was quite poor, resulting in a reaction mixture comprising a 4:1 mixture of diastereomeric products at C3 along with an appreciable amount of product resulting from hydrogenation of the C11−C12 double bond.

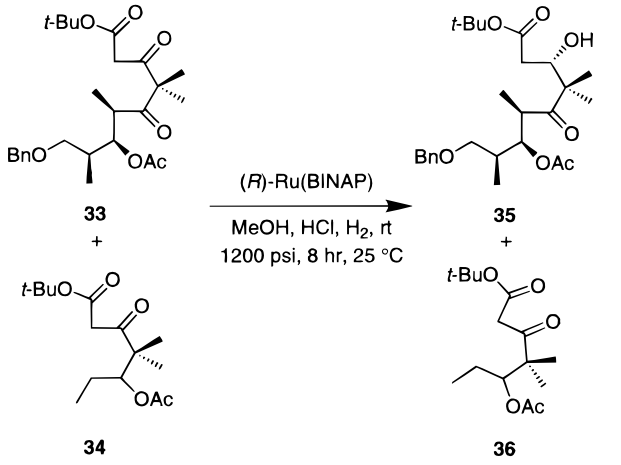
There are numerous reports citing the dramatic dependence of the Noyori reduction upon the presence of added strong acid.[34c,36,39] Moreover, it is reported that the addition of Et_3N may retard the hydrogenation, but upon re-acidification, the original reaction rates are reestablished.[36] These failures have been attributed to the presence of low-level basic impurities in the substrate.[36,39] In our hands, the presence of stoichiometric HCl was absolutely required for both reduction at C3 and good diastereoselectivity in the reduction. We suspect that the presence of the basic thiazolium nitrogen perhaps coordinates the ruthenium catalyst, resulting in slow reaction rates and poor levels of asymmetric reduction. However, upon the addition of stoichiometric HCl, the thiazole moiety is perhaps protonated, resulting in reestablishment of the appropriate catalytic cycle.

At 25 °C and pressures greater than 1300 psi, the chemoselectivity of the reduction was poor, resulting in the reduction of both alkene groups. Pressures below 1000 psi (and ambient temperature) resulted in dramatically slower rates of reduction along with poorer diastereoselectivity in the reduction at C3. While there are reports of asymmetric Noyori reductions at elevated temperatures (*ca.* 80 °C) occurring at even lower pressures (50 psi),[36] we encountered decomposition of the epothilone substrates at these elevated temperatures. As a result, our standard Noyori asymmetric reductions were performed at 25 °C and 1200 psi.

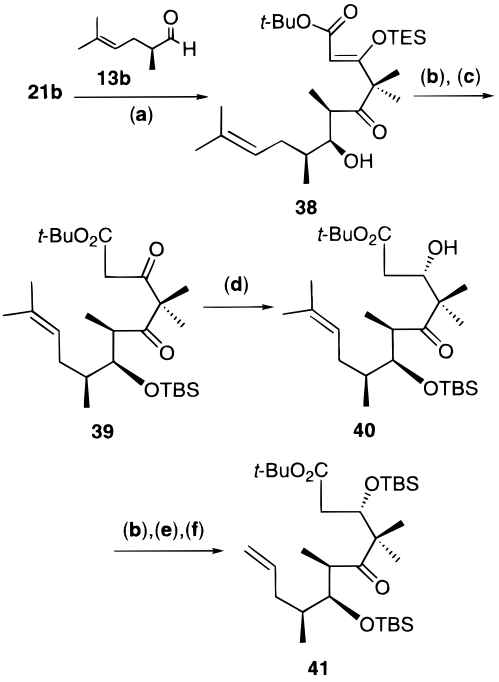
We were surprised to discover that the nature of the substrate played a significant role in the observed chemo- and stereoselectivity. However, since it is the BINAP ligand that provides the chiral environment and induces enantioselectivity through differentiation of the possible diastereomeric transition states, it should not be surprising that the observed stereo- and chemoselectivity in the reduction of these chiral ketonic substrates is markedly affected by the preexisting steric requirements and stereogenic centers present in the substrate. Indeed, we were fascinated to discover that the carbonyl group at C5 was never reduced under any of the attempted reaction conditions but was absolutely necessary for the reduction of the C3-carbonyl. We attribute this result to the presence of the *gem*-dimethyl functionality bridging the adjoining carbonyl groups. Thus, in a competition study between the two β-ketoesters, **33** and **34**, tricarbonyl **33** was completely reduced at C3, whereas the β-ketoester **34**, with C5 in the alcohol oxidation state, was unwavering toward reduction (Scheme 7).

Thus, with these preliminary results in hand, we were prepared to examine the asymmetric Noyori reduction in the context of the total synthesis of dEpoB. Initially, we sought to perform the asymmetric Noyori reduction on the pre-Suzuki aldolate product **15a** (eq 1); however, as anticipated, the terminal olefin in **15a** was rapidly reduced even under mild reaction conditions. Since there have been reports of chemoselective reduction of β-ketoesters in the presence of trisubstituted olefinic species,[34b,38a] we prepared the analogous substrate **38** containing a trisubstituted double bond (Scheme 8). Thus, the aldol condensation of 5,5-methyl-4-pentenal[40] with **21b**, afforded a 4.5:1 mixture of diastereomeric aldol products (**38**, major diastereomer) which could be separated by flash column chromatography. After protection of the C7 alcohol as the TBS ether, the resultant trisubstituted olefin, **39**, could be cleanly reduced under our standard Noyori reduction conditions to provide a single diastereomer **40** (by ^{1}H NMR) in good yield.

Scheme 7. Competition Experiment of β,δ-Diketo Ester and β-Keto Ester Substrates Demonstrate Necessity of C5-Ketone in the Noyori Reduction of These Systems



Scheme 8[a]

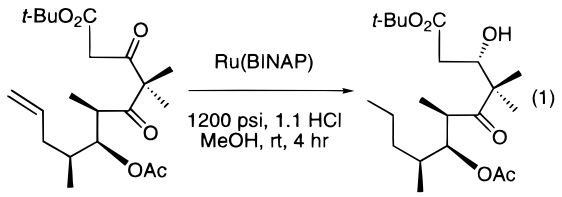


[a] (a) (*S*)-5,5-dimethyl-4-pentenal (**13b**), LDA, (60%, major diastereomer); (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, (95%); (c) 0.1 M HCl/MeOH, (87%); (d) *R*-(BINAP)$RuCl_2$, 1200 psi, 1.1 equiv HCl, MeOH, rt, 7−8 h, (87−88%); (e) O_3, DMS, (86%); (f) $Ph_3P{=}CH_2$, (96%).

(39) King, S. A.; Thompson, A. S.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1992**, *57*, 6689.

(40) Aldehyde **13b** was readily prepared according to the procedure outlined in ref 21.

Protection of the C3 alcohol as the TBS ether and subsequent ozonolysis and Wittig reaction afforded the previously characterized **41**[12,20] (Scheme 8) which could be subjected to *B*-alkyl Suzuki coupling and constituted a formal total synthesis of epothilone B.



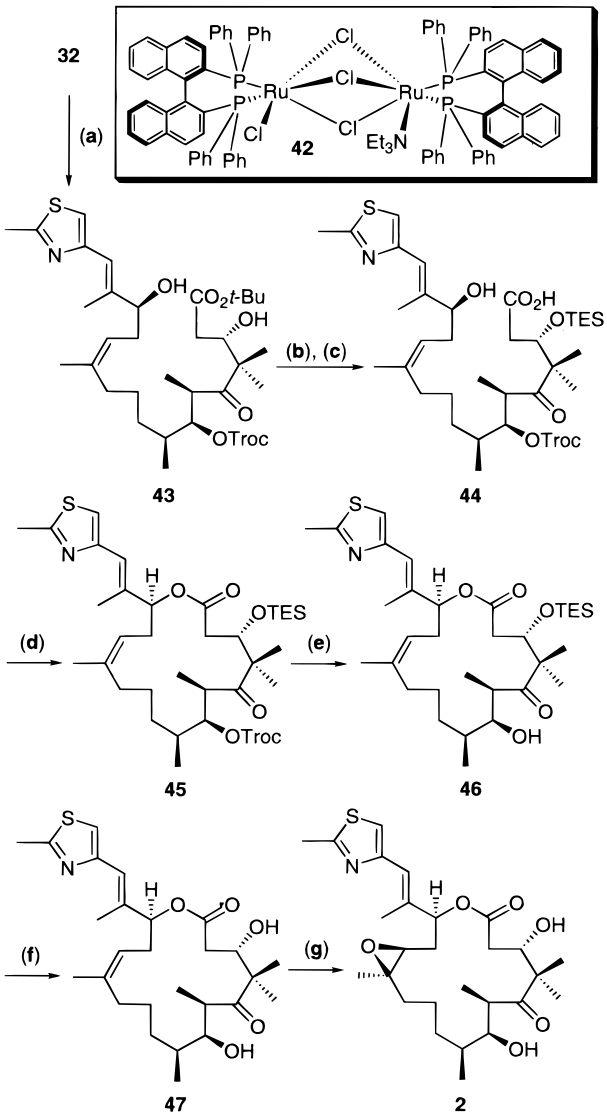
15a **37**

Although, the asymmetric Noyori reduction on the pre-Suzuki aldolate product proved effective for the formal total synthesis of dEpoB in Scheme 8, we felt that the synthesis could be made more concise by performing the asymmetric reduction on the post-Suzuki substrate, **32**. Indeed, the Noyori reduction of ketone **32** with the dimerized Noyori catalyst $[RuCl_2((R)\text{-BINAP})]_2[NEt_3]$ (**42**) afforded the desired diol **43** with excellent diastereoselectivity (>95:5, no minor diastereomer observed by ^1H NMR). An additional benefit of avoiding the ancillary ozonolysis and Wittig transformations (compare Schemes 8 and 9) was also realized. Having successfully controlled the C3 stereochemistry by reduction of the late-stage intermediate **32**, we were in a position to continue with the completion of the synthesis of dEpoB (and EpoB).

Completion of the dEpoB (EpoB) Synthesis. With these critical issues addressed, no significant obstacles remained in the total synthesis and the conversion of **43** to dEpoB (**47**), Scheme 9. Thus, using previously developed methods, the dihydroxy ester **43** was protected at C3 and C15 as the triethylsilyl ether and the *tert*-butyl ester successfully hydrolyzed to the triethylsilyl ester through the agency of triethylsilyl trifluoromethanesulfonate (TESOTf) and 2,6-lutidine.[20,23] The resultant C3,C15-bis(triethylsilyl)-protected diol was selectively hydrolyzed to the requisite C15-hydroxy acid **44**. Subsequent macrolactonization of **44** under Yamaguchi conditions[41] afforded the fully protected macrolactone **45**. We were pleased to find that samarium (II) iodide deprotection of the 2,2,2-trichloroethoxy carbonate (Troc) **45** at C7 proceeded smoothly to afford the desired C7 alcohol **46** in excellent yield.[42] Finally, standard HF·pyridine deprotection of the C3 triethylsilyl group afforded the desired dEpoB **47**. The C12−C13 olefin could be selectively epoxidized[20] to afford the natural product epothilone B (**2**) with the usual high degree of chemo- and stereoselectivity. For our purposes, however, dEpoB was the target molecule.

Remarkable Long-Range Effects on the Diastereoface Selectivity Observed in Aldol Condensations. Traditional models for diastereoface selectivity were first proposed by Cram and later by Felkin for predicting the stereochemical outcome of aldol reactions occurring between an enolate and chiral aldehyde.[43] During our investigations directed toward a practical synthesis of dEpoB, we were puzzled to discover an unforeseen bias in the relative diastereoface selectivity observed in the aldol condensation between the (*Z*)-lithium enolate **B** and α-methyl aldehyde **C**, Schemes 3 and 4. The aldol reaction proceeds with

Scheme 9[a]



[a] (a) $[RuCl_2((R)\text{-BINAP})]_2[NEt_3]$ (**42**), H_2, 1200 psi, MeOH, HCl, 25 °C, 7 h, (82−88%); (b) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C to rt; (c) then 0.1 N HCl/MeOH (70−77%, two steps); (d) 2,4,6-trichlorobenzoyl chloride, TEA, 4-DMAP, $PhCH_3$, (78%); (e) SmI_2, cat. NiI_2, −78 °C, THF, (90−95%); (f) HF·pyridine, THF, 0 °C, (98%); (g) DMDO, CH_2Cl_2 (80%).

the expected simple diastereoselectivity providing exclusively the C6−C7 syn stereochemistry, however, the C7−C8 relationship of the principal product was anti (Schemes 3 and 4).[44] Indeed, the diastereoselectivity exhibited in the aldol condensation between **A** and **B** (Scheme 1) occurred with the opposite sense of diastereoface addition to that predicted, according to the models for relative face diastereoselection encompassed in the Felkin rules.[45] We were prompted to investigate the cause for this unanticipated but fortunate occurrence.

A survey of the previous literature revealed that Evans,[46] Hoffman,[47] Heathcock,[22c,44] and Roush[48] have examined similar systems in the recent past. Their studies demonstrated that the Felkin−Anh rules for diastereoselection fail to adequately rationalize the results of many reactions involving (*Z*)-*O*-enolates

(41) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. (b) Mulzer, J.; Mareski, P. A.; Buschmann, J.; Luger, P. *Synthesis* **1992**, 215.

(42) (a) Molander, G. A.; Harris, C. R. *J. Org. Chem.* **1997**, *62*, 7418. (b) Machrouhi, F.; Namy, J.-L.; Kagan, H. B. *Synlett* **1996**, 633.

(43) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 2819 and references therein.

(44) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 111−213.

(45) (a) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (b) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

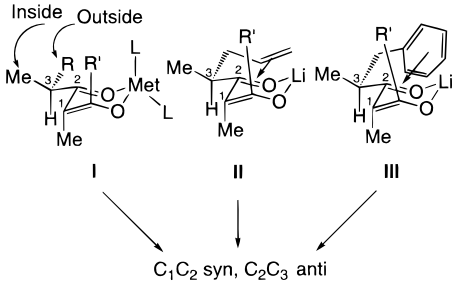


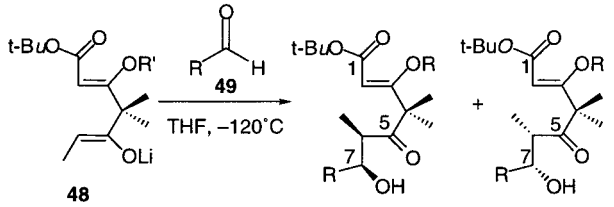
Figure 1. Proposed transition-state models for the aldol condensation of aldehydes **49** and enolate **48** in Table 1.

((*Z*)-crotylboronates)[47a,b] and allylboron reagents[47,48] with α-branched chiral aldehydes. Examination of the Felkin−Anh transition state demonstrated the presence of a destabilizing gauche-pentane interaction which causes the anti-Felkin−Anh product to be formed preferentially.[46]

Further examination revealed that our data were reconcilable when viewed in the above context. In the early 1980s, Evans[46] proposed a transition-state model based on the above findings which is supported by our recent discoveries. However, recently, Roush has proposed a more refined model to account for attrition in anti selectivity with α-methyl chiral aldehydes.[49] The Roush model proposes that in the reacting Curtin−Hammett conformer, the R group (larger group) of the aldehyde is distanced from the R′ group of the enolate (**I**) to avoid an unfavorable, potentially serious *syn*-pentane interaction (Figure 1). Thus, the basis of the Roush model focuses on minimization of steric interactions between the largest functional groups of the enolate and the α-branched aldehyde in the reacting ensemble. Consequently, the observed *anti*-Felkin−Anh selectivity displayed in these reactions is typical for such "α-methyl" aldehydes. When the R group is approximately equal to the methyl center in its effective A-value, the selectivity for the anti-product must correspondingly deteriorate.

Our discoveries using aldehyde **13a** and related congeners were unique in that our substrate aldehydes lack the typical resident protected alcohol derivative that is usually involved in fashioning anti diastereoface selectivity (Table 1).[50] Rather, the conformational bias in our substrates is apparently the result of a very particular relationship between the formyl moiety and the unsaturation in the pendant side chain. As a result of our studies, we are prompted to speculate that the presence of unsaturation at C4−C5 in the aldehyde moiety (present in both **13a** and **13b**, Table 1, entries a and b) provides a subtle stabilizing, nonbonded interaction between the unsaturation in the aldehyde and the carbonyl of the enolate (Figure 1, **II**).[51] This interaction can be envisioned to stabilize the transition state leading to the observed major anti-Felkin diastereomer **51**.

Table 1. Diastereoselectivities Observed in the Aldol Reaction of Enolate **48** (R′ = Me or TES) with Aldehyde **49**



Entry	Aldehyde R =	Ratio (**50**:**51**) (C7-C8) (*syn*:*anti*)	
a		1	5.5
b		1	4.5
c		1	1.3
d		1	2.0
e		1	3.3
f		11	1.0
g		1	2.0
h		1	4.0
i		1	5.0
j		1	2.1
k		1	1.2
l		1	2.8
m		1	4.2
n		1	5.0
o		1	5.4
p		1	1.2

Indeed previous examination of aldol reactions of chiral α-methyl aldehydes has suggested that nonbonded interactions play an important role in determining aldehyde diastereofacial selectivities in the reaction of (*Z*)-enolates.[52]

The results of several aldol reactions between the enolate **48** and various other aldehydes (**49**) are depicted in Table 1. Our extensive studies using various substrates identified a trend in the consequences of varying the tether length between the formyl group and the site of unsaturation. Amazingly, reduction of the double bond of the side chain led to sharply diminished selectivity affording a 1.3:1 mixture of diastereomeric products (entry c). Likewise, lengthening of the tether beyond that found in entry a or b, led to a 2:1 ratio of diastereomers (entry d). Given these discoveries, the diminished diastereoselectivities observed in the aldol condensation of **26a** or **26b** and **21a** or **21b** (Scheme 5), containing unsaturation in a similar position, it is not surprising. By contrast, shortening the tether (entry f) gave strong syn diastereoface selectivity consistent with previous findings with particular aldehyde **49f**.[53] The results of entry g, in which similar steric factors are virtually equivalent (propyl

(46) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.

(47) (a) Hoffmann, R. W.; Zeiss, H.-J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 218. (b) Hoffmann, R. W.; Weidmann, U. *Chem. Ber.* **1985**, *118*, 3966. (c) Hoffmann, R. W.; Brinkmann, H.; Frenking, G. *Chem. Ber.* **1990**, *123*, 2387. (d) Brinkmann, H.; Hoffmann, R. W. *Chem. Ber.* **1990**, *123*, 2395. (e) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555.

(48) (a) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422. (b) Roush, W. R.; Adam, M. A.; Harris, D. J. *J. Org. Chem.* **1985**, *50*, 2000. Roush, W. R.; Palkoitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348. (c) Roush, W. R. In *Comprehensive Organic Synthesis*, Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 1.

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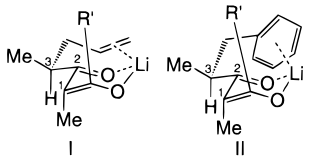

Figure 2. Potential transition state for diastereoselective aldol reaction involving a potential lithium cation bridging the olefin (I) or aryl moiety (II).

versus 2-propenyl at the branching site) demonstrate a small, but clear preference for the C7−C8 anti product, presumably reflecting the special effect of the olefin−aldehyde interaction. The Roche aldehyde,[54] (entry h) a substrate well-known for its tendency to favor the anti-Felkin−Anh adduct,[55] performs as expected to afford a 4:1 mixture of anti:syn diasteromeric products (entry h).

We next wondered whether the unsaturation site could be encompassed in the context of a properly positioned benzenoid linkage (Figure 1, **III**). We were intrigued to discover that excellent diastereoface selectivity was obtained in the aldol condensation of the (*Z*)-lithium enolate with the benzyl substituted formyl moiety, entry i. Recognizing that functional group substitution about the aromatic ring would dramatically affect the donating ability of the ring, we examined the effects of *para*-positioned functional groups on the resultant C7−C8 relationship (entries m−p, Table 1). Indeed, some minor slippage in the anti:syn ratio is seen in the electron deficient *p*-bromo substrate (entry m). The benchmark ratio, seen in entry i, is restored with the electron rich *p*-methoxy substrate (entry n), while a small improvement was realized with the *p*-dimethylamino derivative (entry o). Moreover, in the strongly electron-deficient *p*-nitrophenyl substrate (entry p), the C7−C8 anti selectivity is severely abrogated. Clearly, the "aryl effect" is closely coupled to the electron-donating ability of the ring.

By contrast with the reconcilable data observed with para-substituted substrates, a range of ortho substituents (entries j−l, Table 1) all resulted in significant weakening of the C7−C8 anti selectivity. We take these data to suggest that ortho substitution results in some steric inhibition of the rotamer in which the faces of the aromatic ring and formyl group are parallel (Figure 1, **III**).

To interpret these experiments, we suggest that our data points to a stabilizing through-space interaction of a donor olefinic linkage with the formyl function as the likely source of preference of conformers **II** and **III**, leading to the sense of attack anticipated by the Roush model.[48]

An alternative hypothesis for the enhanced anti-Felkin−Anh diastereoselectivity that is also supported by these experiments has been suggested, wherein a Li cation bridges the olefin (or π system of the aryl moiety) and the enolate (Figure 2).[56] Thus, intramolecular bridging in the transition state could indeed enhance the facial approach of the enolate that leads to the C7−C8 anti diastereomer.

Synthesis of Epothilone Analogues. Taxol (paclitaxel) is currently a front line therapeutic agent against a variety of solid forms of cancer including ovarian, breast, colon, lung, and liver neoplasms.[57] As previously discussed, although the epothilones are chemically dissimilar to the taxanes, they function with a paclitaxel-like mechanism. Both families of agents apparently lead to the arrest of cell division and cell death by stabilizing cellular microtubule assemblies; however, the epothilones have demonstrated the capacity to retain activity against multidrug-resistant (MDR) cell lines and tumors where paclitaxel fails. The multidrug-resistance (MDR) phenotype is characterized by broad-spectrum resistance to structurally and mechanistically diverse anticancer agents.[11]

Acquired resistance to paclitaxel and other commonly used cancer chemotherapy agents may be mediated by multiple mechanisms including mutations in microtubule proteins[9,11] and overexpression of the energy-dependent drug transport protein, P-glycoprotein (PgP).[58] Although certain MDR reversal agents appear promising when co-administered with the anticancer agent,[59] a search for paclitaxel analogues with improved performance *in vitro* and *in vivo* has met with only limited success.[3,5]

Our ongoing research program in this field focuses on the relationship between epothilone and paclitaxel in the context of tumors with the MDR resistance phenomena. Toward this end, we have applied our rather more practical synthesis toward the preparation of both dEpoB and similarly promising epothilone congeners in an effort to provide these compounds in quantities suitable for both *in vitro* and more importantly *in vivo* studies.

The synthesis of one such novel analogue was made possible by using a modified route of the total synthesis described above (Scheme 4, 6, and 9). The novel analogue **58**, which bears a fused phenyl ring at C12−C13 was prepared as outlined in Scheme 10. The synthesis of this analogue centered on the preparation of the aryl iodide moiety, **56**, and required little modification from our newly described synthesis. Thus, zinc-mediated nucleophilic addition[60] of 2-iodobenzylbromide **53**[61] with aldehyde **52**[12,20] afforded racemic **54** in 67% yield. Oxidation of **54** followed by asymmetric reduction to **56** afforded only modest enantioselectivities. The highest enantiomeric excess observed for the reduction of **55** by methods that are generally effective using (*R*)-2-methyl-CBS-oxazaborolidine[62] was 60%. While far from ideal, this enantioselectivity margin was sufficient for our purposes.

Protection of the resultant alcohol as the TBS enol ether provided the desired thiazole moiety, **56**, suitable for Suzuki coupling. Palladium-mediated Suzuki coupling of the aryl iodide **56** and polypropionate **30** afforded the hydroxy ester **57** which could be hydrolyzed to the desired C15-hydroxy acid for Yamaguchi macrolactonization (not shown). The diastereomeric products (4:1 mixture of diastereomers, epimers at C15 resulting from incomplete enantioselective reduction) could be separated by flash column chromatography after macrolactonization to afford, as the major product, the analogue containing the desired

(53) The stereochemistry of the major diastereomer (**50f**) obtained in the aldol condensation of **48** with **49f** was confirmed by comparing the aldol product **50f** to the identical compound prepared through an independent synthesis with known stereochemistry.

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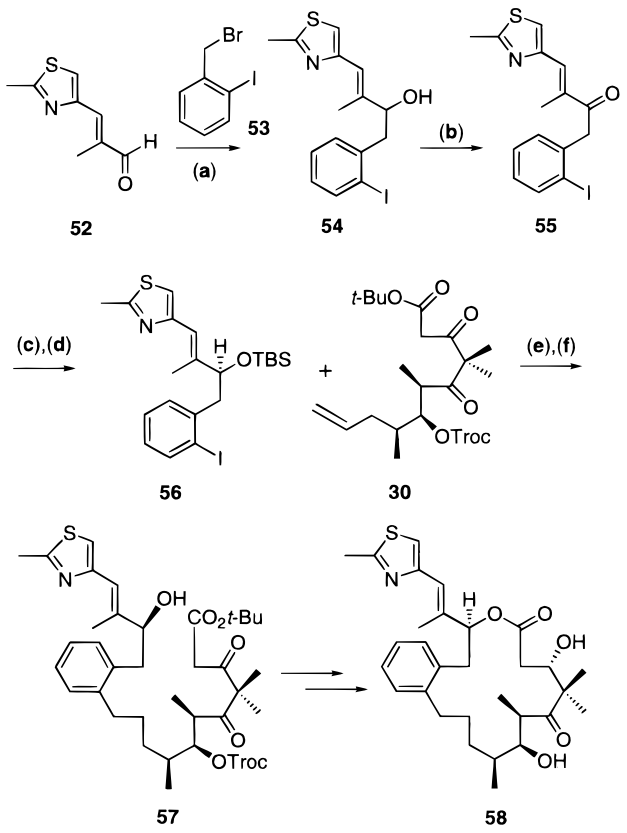
Scheme 10[a]



[a] (a) Zn, CuCN, LiCl, THF, then $BF_3{\cdot}OEt_2$, **52**, (67%); (b) Swern oxidation (90%); (c) CBS reduction, 60% ee, (89%); (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, (90%); (e) 9-BBN, THF, 2 h, then **56**, $Pd(dppf)_2Cl_2$, Cs_2CO_3, Ph_3As, H_2O, DMF, rt, 6 h, (70%); (f) 0.5 M HCl/MeOH, THF, rt, 6 h (85%).

"natural" stereochemistry at C15.[63] The remainder of the synthesis was performed according to the previous protocols described in Scheme 9 to obtain analogue **58**.

Conclusions

We have described a practical total synthesis of dEpoB (EpoB) that has supported the synthesis of both this agent and several epothilone analogues in sufficient quantity to perform pertinent *in vivo* studies on several human xenograft tumors in mice, the results of which have been published elsewhere.[14,20,23] Our fully chemical synthesis comprises three key components, each critical to the completion of the synthesis. These include a diastereoselective aldol reaction, *B*-alkyl Suzuki reaction, and a modified asymmetric Noyori reaction. Surprisingly, the aldol reaction developed in this total synthesis exhibits enhanced diastereofacial selectivity for formation of the anti-Felkin−Anh diastereomer. Continued examination of this novel aldol reaction is ongoing in our laboratories. These studies are being conducted in the context of a continued program intended to discover the optimal epothilone derivative for full-scale clinical development. With this accomplished, the total synthesis effort will be conducted on multigram scales.

The chemical synthesis described herein has proved useful for the discovery of the biological attributes of this promising compound. As a result of these studies, we have designated dEpoB as a leading candidate for clinical application. Further development of an epothilone as a potential clinical candidate continues to remain the main focus of our research.

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Experimental Section

General. All commercial materials were used without further purification unless otherwise noted. The following solvents were obtained from a dry solvent system (passed through a column of alumina) and used without further drying: THF, diethyl ether (Et_2O), CH_2Cl_2, toluene, and benzene. All reaction were performed under an atmosphere of prepurified dry Ar(g). NMR (^1H, ^{13}C) spectra were recorded on Bruker AMX-400 MHz, Bruker Advance DRX-500 MHz, reference to TMS (^1H NMR, δ 0.00) or $CDCl_3$ (^{13}C NMR, δ 77.0) peaks unless otherwise stated. LB = 1.0 Hz was used before Fourier transformation for all the ^{13}C NMR. IR spectra were recorded with a Perkin-Elmer 1600 series-FTIR spectrometer, and optical rotations were measured with a Jasco DIP-370 digital polarimeter using 10-cm path length cell. Low-resolution mass spectral analysis were performed with a JEOL JMS-DX-303 HF mass spectrometer. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F254 plates (0.25 mm). Compounds were visualized by dipping the plates in a cerium sulfate−ammonium molybdate solution or *p*-anisaldehyde solution followed by heating. Flash column chromatography was performed using the indicated solvent on E. Merck silica gel 60 (40−63 mm) or Sigma H-Type silica gel (10−40 mm).

***tert*-Butyl (6*R*,7*S*,8*S*,12*Z*,15*S*,16*E*)-3,5-Dioxo-15-hydroxy-17-(2-methylthiazol-4-yl)-4,4,6,8,12,16-hexamethyl-(2,2,2-trichloroethoxycarbonyl)pentadeca-12,16-dieno-ate (32).** 9-BBN dimer (1.58 g, 6.50 mmol) was dissolved in 20 mL of dry THF. Then, tricarbonyl **30** (4.46 g, 8.64 mmol) in THF (15 mL) was added in small portions over a 45 min period to the solution of 9-BBN at 25 °C. After 2 h, TLC analysis revealed the complete consumption of the starting olefin.

In a separate flask, containing the vinyl iodide **31** (4.0 g, 8.64 mmol) and DMF (60 mL), were added successively and with vigorous stirring: Cs_2CO_3 (5.6 g, 17.3 mmol), $AsPh_3$ (0.53 g, 1.71 mmol), $Pd(dppf)_2Cl_2$ (1.40 g, 1.71 mmol), and H_2O (4.6 mL, 0.25 mol). Then, H_2O (1 mL, 56 mmol) was added to the borane solution, prepared above, to quench the excess 9-BBN. Then, the solution of alkyl borane was added rapidly by syringe to the vigorously stirred solution containing the vinyl iodide. After 2 h, the reaction TLC analysis revealed that the reaction was complete. The reaction mixture was poured into Et_2O (300 mL), washed with H_2O (3 × 200 mL) and brine (1 × 50 mL), and dried over anhydrous $MgSO_4$. This crude product was purified by flash column chromatography on SiO_2, eluting with hexanes/ethyl acetate (18:1 to 13:1 to 10:1) to afford the TBS-protected coupled product as an impure mixture which was taken onto the next step without further purification.

The crude TBS-protected coupled product was dissolved in 0.5 M HCl in MeOH (100 mL) at 25 °C. The reaction was monitored by TLC for completion, and after 3.5 h (disappearance of starting TBS ether), the mixture was poured into a solution of saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ (4 × 60 mL). The combined organic layers were washed once with brine (50 mL) and dried over anhydrous $MgSO_4$. The diol was purified by flash column chromatography on SiO_2, eluting with hexanes/ethyl acetate (4:1 to 3:1 to 2:1) to give the pure product **32** as a clear oil (3.96 g, 5.4 mmol, 62% for two steps): ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.56 (s, 1H), 5.16 (t, J = 6.9 Hz, 1H), 4.83 (d, J = 11.9 Hz, 1H), 4.75 (dd, J = 3.4, 8.0 Hz, 1H), 4.70 (d, J = 11.9 Hz, 1H), 4.14 (t, J = 6.4 Hz, 1H), 3.45 (q, J = 13.2 Hz, 2H), 3.32 (m, 1H), 2.72 (s, 3H), 2.32 (t, J = 6.5 Hz, 2H), 2.04 (s, 3H), 2.01 (m, 2H), 1.74 (m, 2H), 1.69 (s, 3H), 1.45 (s, 9H), 1.38 (s, 6H), 1.09 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.51, 203.04, 166.15, 164.39, 154.14, 152.72, 141.71, 138.24, 120.70, 118.76, 115.28, 94.54, 81.85, 77.31, 76.57, 63.41, 54.16, 46.47, 41.48, 34.56, 33.95, 31.98, 31.53, 27.85, 24.85, 23.45, 21.47, 20.75, 19.04, 15.60, 14.33, 11.35; IR (neat) 3546, 3395, 1756, 1717, 1699, 1644, 1621, 1506, 1456, 1251 cm^{-1}; LR-FAB calcd for $C_{34}H_{50}Cl_3NO_8S$ 737.2; found 738.5 $[M + H]^+$.

***tert*-Butyl (3*S*,6*R*,7*S*,8*S*,12*Z*,15*S*,16*E*)-5-Oxo-3,15-dihydroxy-17-(2-methylthiazol-4-yl)-4,4,6,8,12,16-hexamethyl-(2,2,2-trichloro-**

ethoxycarbonyl)pentadeca-12,16-dienoate (43). The diketone **32** (3.12 g, 4.22 mmol) was dissolved in 0.15 N HCl in MeOH (36 mL, 1.3 equiv) at 25 °C. The (*R*)-RuBINAP catalyst[40] (0.045 M in THF, 8.0 mL, 0.36 mmol) was then added and the mixture transferred to a Parr apparatus. The vessel was purged with H_2 for 5 min and then pressurized to 1200 psi. After 12−14 h at 25 °C, the reaction was returned to atmospheric pressure and poured into a saturated solution of $NaHCO_3$. This mixture was extracted with $CHCl_3$ (4 × 50 mL), and the combined organic layers were dried over anhydrous $MgSO_4$. The product was purified by flash column chromatography on silica gel, eluting with hexanes/ethyl acetate (4:1 to 2:1) to give 2.53 g (81%) of the hydroxy ester **43** as a green foam: $[\alpha]_D = -32.4°$ (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.55 (s, 1H), 5.15 (t, J = 6.9 Hz, 1H), 4.85 (t, J = 5.3 Hz, 1H), 4.81 (d, J = 12.0 Hz, 1H), 4.71 (d, J = 12.0 Hz, 1H), 4.12 (m, 2H), 3.43 (m, 2H), 2.70 (s, 3H), 2.37 (dd, J = 2.2, 6.2 Hz, 1H), 2.30 (t, J = 6.7 Hz, 2H), 2.24 (dd, J = 10.6, 16.2 Hz, 1H), 2.03 (s, 3H), 1.99 (m, 2H), 1.68 (s, 3H), 1.44 (s, 9H), 1.18 (s, 3H), 1.16 (s, 3H), 1.09 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.95, 172.39, 164.39, 154.21, 152.74, 141.70, 138.33, 120.59, 118.77, 115.27, 94.64, 82.98, 81.26, 76.51, 72.78, 51.82, 41.40, 37.36, 34.66, 33.96, 32.08, 31.10, 30.20, 27.96, 25.06, 23.45, 21.73, 21.07, 19.17, 19.01, 16.12, 15.16, 14.33, 12.17; IR (neat) 3434.0, 1757.5, 1704.5, 1249.9, 1152.8 cm^{-1}; LR-FAB calcd for $C_{38}H_{52}Cl_3NO_8S$ 739.2; found 740.5 $[M + H]^+$.

(3*S*,6*R*,7*S*,8*S*,12*Z*,15*S*,16*E*)-5-Oxo-3,15-bis(triethylsilyloxy)-17-(2-methylthiazol-4-yl)-4,4,6,8,12,16-hexamethyl-(2,2,2-trichloroethoxycarbonyl)pentadeca-12,16-dienoic acid. 2,6-Lutidine (3.8 g, 35.6 mmol) and TESOTf (4.7 g, 17.8 mmol) were added successively to a cooled solution of the diol **43** (4.4 g, 5.90 mmol) in CH_2Cl_2 (50 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 5 min and then warmed to room temperature and stirred for 1 h. Then 2,6-lutidine (8.9 g, 83.2 mmol) and TESOTf (10.9 g, 41.6 mmol) were added successively to a −78 °C cooled solution. The reaction was stirred at room temperature for 8 h and then quenched with saturated aqueous NH_4Cl and subjected to an aqueous workup. The crude product was concentrated in vacuo and the 2,6-lutidine removed on high vacuum pump and then subjected directly to the next set of reaction conditions: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.66 (s, 1H), 5.04 (t, J = 6.93 Hz, 1H), 4.90 (d, J = 12.0 Hz, 1H), 4.77 (dd, J = 7.99, 3.21 Hz, 1H), 4.66 (d, J = 12.0 Hz, 1H), 4.46 (m, 1H), 4.10 (dq, J = 12.3, 7.11 Hz, 2H), 3.42 (m, 1H), 2.70 (s, 3H), 2.60 (dd, J = 16.7, 2.34 Hz, 1H), 2.34 (dd, J = 16.7, 7.94 Hz, 1H), 2.27 (dd, J = 14.0, 6.97 Hz, 1H), 2.18 (m, 1H), 2.09 (m, 1H), 2.04 (s, 1H), 1.95 (s, 3H), 1.82 (m, 2H), 1.61 (s, 3H), 1.44 (m, 2H), 1.27−1.22 (m, 4H), 1.14 (d, J = 8.45 Hz, 3H), 1.11 (d, J = 6.81 Hz, 2H), 1.04 (d, J = 6.88 Hz, 2H), 1.15−1.01 (m, 2H), 0.94 (t, J = 7.92 Hz, 18H), 0.65−0.57 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.11, 175.34, 165.00, 154.14, 152.80, 142.60, 136.84, 121.31, 118.79, 114.60, 94.77, 81.60, 79.06, 76.64, 73.87, 54.19, 41.18, 39.56, 35.09, 34.52, 32.29, 31.95, 24.76, 23.62, 22.55, 18.95, 18.64, 15.87, 13.69, 11.33, 6.94, 6.83, 5.07, 4.76; IR (neat) 3100−2390, 1756.8, 1708.8, 1459.3, 1250.6, 816.1 cm^{-1}.

(3*S*,6*R*,7*S*,8*S*,12*Z*,15*S*,16*E*)-5-Oxo-15-hydroxy-3-(triethylsilyloxy)-17-(2-methylthiazol-4-yl)-4,4,6,8,12,16-hexamethyl-(2,2,2-trichloroethoxycarbonyl)pentadeca-12,16-dienoic acid (44). The crude bis-(triethylsilyl)ether (above) was dissolved in 30 mL of THF and then cooled to 0 °C. Then, 20 mL of 0.12 M HCl/MeOH was added. The reaction mixture was stirred at 0 °C for 3 min and maintained at 0 °C for the duration. The reaction was monitored closely by TLC analysis. Methanolic HCl (0.12 M) was added in small portions (5 mL), and roughly 1.3 equiv of 0.12 M HCl was required for the hydrolysis of the C-15 TBS ether (approximately 65 mL, total). The reaction was complete in approximately 30 min. The reaction was quenched by pouring into a solution of saturated aqueous $NaHCO_3$ and subjected to an aqueous workup. Flash column chromatography with 40% EtOAc/hexanes afforded the desired carboxylic acid **44** (3.61 g, 4.51 mmol) in 76% yield (two steps): $[\alpha]_D = -22.4°$ (*c* 0.58, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.69 (1, s), 5.11 (t, J = 6.9 Hz, 1H), 4.91 (d, J = 12.0 Hz, 1H), 4.71 (dd, J = 3.1, 8.2 Hz, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.42 (d, J = 5.9 Hz, 1H), 4.10 (m, 1H), 3.43 (m, 1H), 2.71 (s, 3H), 2.57 (dd, J = 2.1, 10.5 Hz, 1H), 2.25 (m, 3H), 2.11 (m, 1H), 1.98 (s, 3H), 1.95 (m, 2H), 1.72 (m 1), 1.67 (s, 3H), 1.45 (m, 2H), 1.16 (s, 3H), 1.13 (s, 3H), 1.09 (d, J = 6.7 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H), 0.95 (t, J = 7.9 Hz, 9H), 0.64 (dq, J = 2.3, 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.11, 176.00 (165.10, 154.18, 152.35, 142.24, 138.55, 120.74, 118.21, 115.02, 94.76, 81.91, 76.86, 76.63, 73.95, 54.08, 41.28, 39.64, 34.73, 34.16, 32.02, 31.67, 24.71, 23.41, 22.49, 19.17, 18.62, 15.71, 14.86, 11.20, 6.93, 5.05); IR (neat) 3400−2390, 1755.9, 1703.8, 1250.4, 735.4 cm^{-1}; LR-FAB calcd for $C_{36}H_{58}Cl_3NO_8SSi$ 797.3; found 800.6 $[M + H]^+$.

12,13-Deoxy-7-(2,2,2-trichloroethoxycarbonyl)-3-(triethylsilyloxy)-epothilone B (45). Triethylamine (0.61 g, 6.03 mmol) and 2,4,6-trichlorobenzoyl chloride (1.2 g, 5.0 mmol) were added to a solution of the hydroxy acid **44** (780 mg, 1.0 mmol) in 14 mL of THF. The reaction mixture was stirred for 15 min at room temperature and then diluted with 25 mL of dry toluene. The resultant solution was added slowly dropwise, via syringe pump, over 3 h to a previously prepared, stirred solution of DMAP (1.3 g, 10.6 mmol) in 700 mL of dry toluene. After the addition of the substrate was complete, the reaction was stirred for an additional 0.5 h and then concentrated in vacuo. Flash column chromatography of the crude product with 10% EtOAc/hexanes afforded the desired macrolactone **45** (464 mg, 0.60 mmol) in 60% yield: $[\alpha]_D = -2.6°$ (*c* 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.53 (s, 1H), 5.20 (m, 2H), 5.04 (d, J = 10.2 Hz, 1H), 4.84 (d, J = 12.0 Hz, 1H), 4.78 (d, J = 12.0 Hz, 1H), 4.07 (m, 1H), 3.32 (m, 1H), 2.86−2.63 (m, 3H), 2.70 (s, 3H), 2.48 (m, 1H), 2.11 (s, 3H), 2.04 (dd, J = 6.17, 14.7 Hz, 1H), 1.73 (m, 4H), 1.66 (s, 3H), 1.25 (m, 2H), 1.19 (s, 3H), 1.15 (s, 3H), 1.12 (d, J = 6.68 Hz, 3H), 1.01 (d, J = 6.83 Hz, 3H), 0.89 (t, J = 8.00 Hz, 9H), 0.58 (q, J = 7.83 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.75, 170.66, 164.62, 154.60, 152.52, 140.29, 138.44, 119.81, 119.38, 116.28, 94.84, 86.44, 80.14, 76.59, 76.10, 53.55, 45.89, 39.23, 35.47, 32.39, 31.69, 31.57, 31.16, 29.68, 27.41, 25.00, 23.44, 22.94, 19.23, 18.66, 16.28, 14.83, 6.89, 5.22; IR (neat) 1760.5, 1742.6, 1698.0, 1378.8, 1246.2, 1106.0, 729.8 cm^{-1}; LR-FAB calcd for $C_{36}H_{57}Cl_3NO_7SSi$ 780.3; found 780.5.

12,13-Deoxy-3-(triethylsilyloxy)epothilone B (46). Samarium metal (4.2 g, 28.2 mmol) and iodine (5.2 g, 20.5 mmol) in 250 mL of dry THF were stirred together vigorously at reflux for 2.5 h. During this period of time, the reaction mixture progressed from a dark orange to an olive green to deep blue color. The resultant deep blue solution of SmI_2 was used directly in the following reaction. A catalytic amount of NiI_2 (0.61 g) was added in one portion to the vigorously stirred solution of SmI_2. The reaction mixture was stirred 5 min at room temperature and then cooled to −78 °C in a a dry ice/acetone bath. Then, the macrolactone **45** (3.0 g, 3.8 mmol), in 40 mL of dry THF, was added over 1 min to the rapidly stirred, cold solution of SmI_2/NiI_2.[44] The resultant deep blue solution was maintained at −78 °C with continued vigorous stirring for 2 h. TLC analysis at this time revealed the complete consumption of the starting material and formation of a single, lower R_f product. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and subjected to an aqueous workup. Flash column chromatography with 25% EtOAc/hexanes afforded the desired C-7 alcohol, **46**, (1.88 g, 3.12 mmol) in 82% yield: $[\alpha]_D = -64.5°$ (*c* 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.54 (s, 1H), 5.15 (m, 1H), 5.05 (d, J = 10.15 Hz, 1H), 4.08 (dd, J = 10.1, 2.66 Hz, 1H), 3.87 (m, 1H), 3.01 (s, 1H), 3.06 (m, 1H), 2.83−2.65 (m, 3H), 2.70 (s, 3H), 2.44 (m, 1H), 2.10 (s, 3H), 2.07 (m, 1H), 1.83 (m, 1H), 1.77 (m, 1H), 1.71 (m, 1H), 1.64 (s, 3H), 1.60 (s, 1H), 1.37 (m, 1H), 1.31 (m, 1H), 1.20 (m, 1H), 1.15 (s, 3H), 1.14 (m, 5H), 1.02 (d, J = 7.02 Hz, 3H), 0.89 (t, J = 7.97 Hz, 9H), 0.64−0.52 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.34, 170.73, 164.59, 152.46, 139.07, 138.49, 120.48, 119.54, 116.00, 79.31, 75.81, 73.48, 53.62, 42.98, 39.48, 39.01, 32.85, 32.41, 31.20, 26.12, 24.26, 22.01, 22.46, 19.18, 16.44, 15.30, 13.99, 6.98 (3), 5.27 (3); IR (neat) 3524.0, 1740.3, 1693.4, 1457.2, 1378.4, 733.2 cm^{-1}; LR-FAB calcd for $C_{33}H_{56}NO_5SSi$ 606.4; found 606.5 $[M + H]^+$.

12,13-Deoxyepothilone B (47). The C-3 TES-protected alcohol **46** (2.04 g, 3.37 mmol) was dissolved in 60 mL of THF in a plastic reaction vessel and cooled to 0 °C in an ice bath. The resultant solution was treated with 14 mL of HF·pyridine. The reaction mixture was stirred for 5 h at 0 °C and then quenched by being poured into a saturated aqueous solution of $NaHCO_3$. An aqueous workup followed by flash column chromatography with 10% EtOAc/hexanes afforded the desired

desoxyepothilone B **47** (1.5 g, 3.05 mmol) in 91% yield. The resultant product exhibited a ^{1}H NMR spectrum identical to desoxyepothilone B prepared previously in this laboratory.

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Supporting Information Available: Experimental procedures for the preparation of *tert*-butyl 4-methyl-3-oxopentanoate, **11**, **15**, **16**, **18**−**23**, **29**−**31**, **38**, **41**, **49a**−**p**, **50**/**51a**−**p**, and **54**−**58** as well as characterization data are included (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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