Total Syntheses of Epothilones A and B

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Abstract: Convergent, stereocontrolled total syntheses of the microtubule-stabilizing macrolides epothilones A (**2**) and B (**3**) have been achieved. Four distinct ring-forming strategies were pursued (see Scheme 1). Of these four, three were reduced to practice. In one approach, the action of a base on a substance possessing an acetate ester and a nonenolizable aldehyde brought about a remarkably effective macroaldolization see (**89** → **90** + **91**; **99** → **100** + **101**), simultaneously creating the C2−C3 bond and the hydroxyl-bearing stereocenter at C-3. Alternatively, the 16-membered macrolide of the epothilones could be fashioned through a C12−C13 ring-closing olefin metathesis (e.g. see **111** → **90** + **117**; **122** → **105** + **123**) and through macrolactonization of the appropriate hydroxy acid (e.g. see **88** → **93**). The application of a stereospecific *B*-alkyl Suzuki coupling strategy permitted the establishment of a *cis* C12−C13 olefin, thus setting the stage for an eventual site- and diastereoselective epoxidation reaction (see **96** → **2**; **106** → **3**). The development of a novel cyclopropane solvolysis strategy for incorporating the geminal methyl groups of the epothilones (see **39** → **40** → **41**), and the use of Lewis acid catalyzed diene−aldehyde cyclocondensation (LACDAC) (see **35** + **36** → **37**) and asymmetric allylation (see **10** → **76**) methodology are also noteworthy.

The introduction of taxol (paclitaxel) (**1**) into cancer chemotherapy is testimony to the synergism of broadly based contributions from many areas of scientific expertise *en route* to the clinic. The original isolation and structure work, which also served to identify the cytotoxicity of the drug, was accomplished by Wall and co-workers.[1] In a seminal paper, Horwitz identified the *in vitro* mode of action of taxol, demonstrating its ability to stabilize microtubule assemblies.[2] This finding gave impetus to a wider range of pharmacological investigations of critical importance. The development of improved methods from phytochemical sources for obtaining baccatin III, and improved chemical methods for converting baccatin III to paclitaxel, provided the drug in ample quantities for human trials.

On the basis of favorable findings that issued from these evaluations, paclitaxel, developed by the Bristol Myers-Squibb Co., was approved for chemotherapeutic application against ovarian carcinomas. Since then, this drug has been undergoing extensive evaluations for other indications and is being incorporated in a variety of clinical contexts. Though it is often not a curative agent, paclitaxel is emerging as a useful main line chemotherapeutic resource. There being no evidence to the contrary, it is assumed that the *in vivo* mode of action and antitumor properties of paclitaxel arise from inhibition of cellular mitosis through the Horwitz mechanism. The question of whether or not this mode of action is actually operative in the human patient is not easily addressed.

Although having many advantages, paclitaxel is not an ideal drug.[3] One major problem with this agent, useful as it is, has to do with difficulties in its formulation. Paclitaxel is a rather insoluble substance in water, thereby necessitating awkward forms of clinical administration. Perhaps even more serious is the fact that paclitaxel is subject to a significant attenuation of therapeutic value through the onset of multiple drug resistance (MDR). Although there has been extensive structure−activity work in the paclitaxel area, to our knowledge the only modified compound presently being evaluated in human clinical trials is the close relative, taxotere.[4]

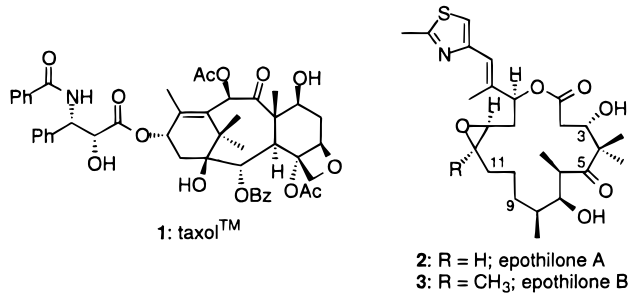

Figure 1. Structures of taxol (**1**) and epothilones A (**2**) and B (**3**).

Given the high interest engendered by taxoids as a consequence of their clinical usefulness, the search for new agents that function by a comparable mechanism is of great interest. It is in this connection that the recently discovered bacterial metabolites epothilone A (**2**) and B (**3**) have attracted considerable attention. These compounds were first identified as antifungal cytotoxic agents by Höfle and co-workers.[5] During the course of a screening program aimed at the identification of substances with a paclitaxel-like mode of action, a group based at Merck found that the epothilones are powerful cytotoxic agents which function through stabilization of cellular microtubules.[6] The strong implication of the Merck research effort was that the epothilones share in the paclitaxel mode of action.

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Indeed, these compounds seem to adhere to the "taxol binding domains" of the microtubule assemblies. In light of the possibility that the epothilones, or suitably modified derivatives, might find a role in cancer chemotherapy, this series also merits multidisciplinary attention. Among the scientific enterprises which we felt to be warranted in the case of the epothilones would be research directed to their total synthesis.

Unlike the situation with paclitaxel, where it was clear from the outset that total synthesis would be unlikely to impact upon the actual availability of the drug itself,[7] the simpler structures of the epothilones invited the hope that chemical synthesis could improve accessibility to the desired agents. Thus, organic chemistry could contribute to the development of an epothilone-based drug effort through a highly efficient total synthesis or possibly by delivering much simpler structures that still manifest chemotherapeutically useful biological activity.

Moreover, several intrinsically challenging chemical issues require attention in any total synthesis venture aimed at the epothilones. Quickly recognized in the case of epothilone A is the presence of a thiazole moiety, a *cis*-epoxide (C12−C13) and, somewhat unusual for a macrolide, the presence of geminal methyl groups at C4. Not the least noteworthy feature of the synthesis problem is inherent in the array of three contiguous methylene groups which serves to insulate the two domains of the epothilones that bear stereochemical imprints. The acyl section, numbered from carbons 1−8, presents a constellation of four chiral centers whose proper emplacement would require careful management. An agenda dealing with the synthesis of this domain must also include programs for elaborating and maintaining a potentially unstable β-hydroxy ester linkage at C3. The oxidation state at C3 must be cleanly differentiated from that at C5 where a ketonic group is to emerge. This entire polypropionate sector is insulated by carbons 9, 10, and 11 from the chiral *O*-alkyl domain comprising carbons 12−15. The already mentioned *cis*-epoxide, connecting carbons 12 and 13 (disubstituted in the case of epothilone A and trisubstituted in the case of epothilone B), is insulated by a single methylene group from carbon 15, which bears an allylic alcohol and a thiazole-based version of an α-methyl styryl linkage.

None of these issues in isolation pose an insurmountable obstacle to the capabilities of contemporary organic chemistry. However, taken together, they constitute a significant challenge to the goal of a stereocontrolled total synthesis of the epothilones. Below, we provide a summary of our activities that eventually accomplished this goal[8] for the first time for both epothilone A[8c] and epothilone B.[8e] In a concurrent time frame, studies from other laboratories accomplished these goals.[9,10] Moreover, the field of epothilone synthesis has spawned a host of interesting disclosures of potential impact on the long term total synthesis goal.[11]

Overall Synthetic Strategies

In pursuit of this program, a variety of initiatives were considered for assembling epothilone systems, including the natural products themselves. It is well to identify the main themes that were followed, often in parallel. In the earliest phase, our thinking was much influenced by the presence of the achiral domain encompassing carbons 9, 10, and 11. As noted above, this achiral region insulates the chiral "*O*-alkyl and acyl" sectors of the molecule from one another. We felt that the presence of this spacer element would pose a considerable difficulty in communicating stereochemical information from one chiral locus to the other. *Rather, it seemed appropriate to build the two chiral domains independently and to join them through carbon−carbon bond formation somewhere in the C9−C11 sector*. In this way, the integrity of chiral centers at C8 and C12, that are terminal to their respective chiral enclaves, would not be placed at risk in the crucial "merger" phase. One obvious possibility which presented itself in this regard was that of ring-forming olefin metathesis[12−14] (see approach I, Scheme 1). In this connection we were mindful of a seminal precedent disclosed by Hoveyda et al. in the context of synthesizing a macrolactam. Indeed, other laboratories, active in the epothilone field recognized, as did we, the potential pertinence of olefin metathesis to the epothilone area.[13]

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(11) For studies toward a total synthesis of the epothilones, see: (a) Mulzer, J.; Mantoulidis, A. *Tetrahedron Lett.* **1996**, *37*, 9179. (b) Claus, E.; Pahl, A.; Jones, P. G.; Meyer, H. M.; Kalesse, M. *Tetrahedron Lett*. **1997**, *38*, 1359. (c) Gabriel, T.; Wessjohann, L. *Tetrahedron Lett*. **1997**, *38*, 1363. (d) Taylor, R. E.; Haley, J. D. *Tetrahedron Lett*. **1997**, *38*, 2061. (e) De Brabander, J.; Rosset, S.; Bernardinelli, G. *Synlett* **1997** (July), 824.

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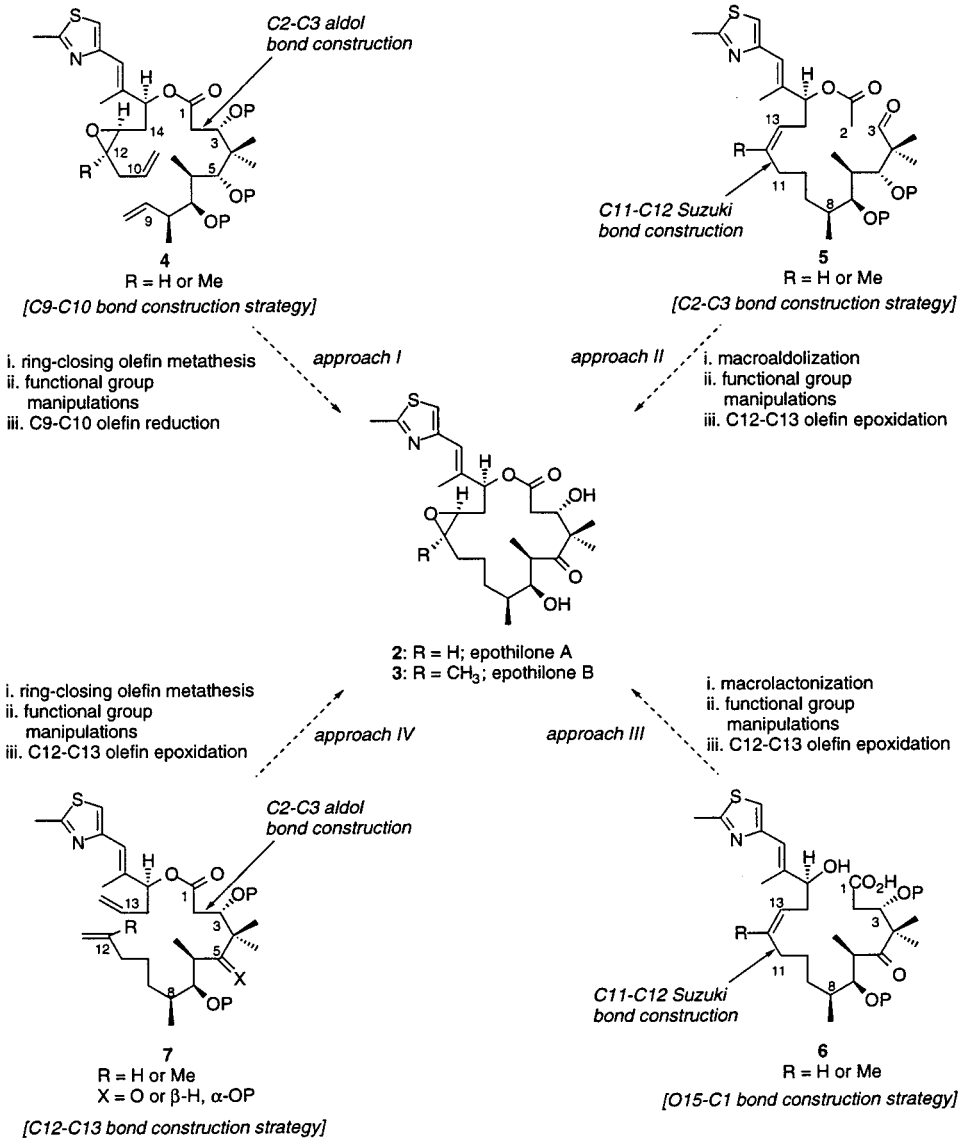
(14) For recent examples of ring-closing olefin metathesis, see: (a) Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Pätzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251. (b) Fürstner, A.; Langemann, K. *J. Org. Chem*. **1996**, *61*, 3942.

Scheme 1. Bond Construction Strategies for Total Synthesis of Epothilone A (**2**) and B (**3**)



Refining the matter still further, we directed our attentions to a construction in which the olefin metathesis bond would join carbons 9 and 10 (see **4**). An alternative approach wherein carbons 10 and 11 would be joined seemed riskier. The latter construction would have involved substrates in which there was an allylic relationship between the epoxide and the C10−C11 unsaturation in both the starting material and the product. Accordingly, the olefin metathesis prospectus that we came to favor called for a precursor of the general type **4** (P = unspecified protecting group). The resultant olefin would comprise carbons 9 and 10 of the goal system. Reduction of the olefin, followed by appropriate functional group manipulations, would then lead to target systems **2** and **3**.

As will be shown, some surprising limitations in the ring-forming olefin metathesis reaction surfaced as we attempted to reduce this line of thinking to practice. When the full dimensions of the obstacles associated with a C9−C10 bond construction through ring-closing olefin metathesis were revealed, we came to focus on a fundamentally different assembly strategy wherein a double bond would be established between carbons 12 and 13 through ring-closing olefin metathesis. In this prospectus, the thiazole bearing chiral domain would display sp^3 asymmetry only at C-15. Carbons 12 and 13 would first be presented in the form of a *cis*-olefin, hopefully *en route* to a properly configured epoxide.

We also had occasion to contemplate an alternative synthetic logic, i.e. that of cross coupling, *wherein a bond would be fashioned between future carbons 11 and 12*. Specifically, we came to favor a *B*-alkyl Suzuki motif[15] to achieve this goal. In this line of reasoning, the fragments entering into this Suzuki coupling would be implied by a structure of the type **5**. From such a seco-compound, the 16-membered macrolide ring could be established through an intramolecular aldol addition,[16] giving rise to the C2−C3 bond (approach II). Alternatively, one could envision a post-Suzuki coupling structure of the type **6** which could set the stage for macrolide construction through macrolactonization[17] (approach III).

As will eventually be shown, the double bond at C-12 and C-13, either in the di- or trisubstituted series, could be very

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(16) For a prior instance of a keto aldehyde macroaldolization, see: Hayward, C. M.; Yohannes, D.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 9345.

(17) For a review of methods for constructing macrolides, see: Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569. The first macrolactonization in this series was demonstrated (though unknown to us at the time of our experiments) by Nicolaou and associates (reference 9c).

effectively exploited for introduction of the β-epoxide required for the final targets. As this feasibility was established, we also directed efforts to establishment of the C12−C13 bond through a ring-closing olefin metathesis reaction. An assessment of this interesting possibility would require the construction of a diolefin of the general type **7** (see approach IV, Scheme 1). This subgoal was accomplished. We now proceed to describe the progress attained in pursuing each of these strategies.

The First Generation Ring-Closing Olefin Metathesis Strategy (Approach I, Scheme 1)

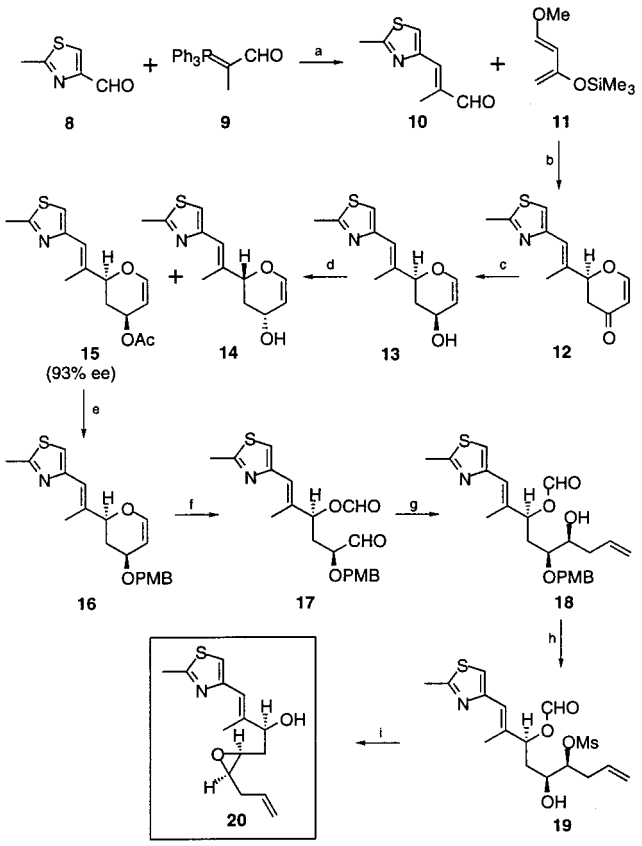
As was alluded to above, several options for constructing the 16-membered macrolide ring of the epothilones were considered as we contemplated strategies for a total synthesis. Initially, we favored a strategy wherein the C9−C10 would be fashioned during the course of the macrocyclization event. It was our hope that a structure of the general type **4** (see Scheme 1) could be induced to undergo a ring-closing olefin methathesis (RCM). Our considerations for favoring such an approach were several. In synthesizing and merging the subunits leading to **4**, all of the stereochemical problems associated with an epothilone total synthesis would have been overcome. The unsaturation at C9−C10 that would emerge from a successful ring-closing olefin metathesis could conceivably be removed by reduction *en route* to the epothilones, or used to introduce new functionality for the purpose of synthesizing novel analog structures.

As will be shown (*vide infra*), the guiding paradigm, *i.e.* the possibility of creating a C9−C10 double bond during the course of an intramolecular RCM process, was not reducible to practice in a substrate having adequate functionality to reach the natural products. Nonetheless, many of our perceptions pertinent to the epothilone stereochemical problem and, indeed, some of the very compounds used in the pursuit of approach I, did find application to variations for the successful total syntheses. Hence, we describe here the findings pertinent to approach I, Scheme 1.

We defined goal system **20** (see Scheme 2) as a milestone compound under the approach I program. A structure of this genre would be joined to an acyl fragment (*vide infra*) to establish a precursor of the type hitherto generalized as **4**. Our path commenced with the known aldehyde **8**,[18] which was elongated in a Wittig-type construction with the commercially available phosphorane **9**, leading to **10** in 83% yield (see Scheme 2).[8a] At this stage, it was of interest to us to take advantage of a line of chemistry that our laboratory had innovated in the 1980s.[19] Thus, aldehyde **10** served as a "heterodienophile" in the context of a Lewis acid catalyzed diene−aldehyde cyclocondensation (LACDAC) reaction with the synergistic butadiene **11**.[20] The reaction proceeded quite smoothly, giving rise to the racemic dihydropyrone **12** in a yield of 65%.

Reduction of compound **12** via conditions that we had introduced some years ago for synthesizing artificial glycals bearing equatorial alcohols at C3 (glucose numbering),[21] led to racemic **13**. Here we were able to take advantage of more recently introduced methodology, wherein racemic glycals, derived by total synthesis rather than from carbohydrate sources, could be effectively resolved by lipase-mediated kinetic resolution.[22] In the event, we chose to carry out a kinetic resolution

Scheme 2[a]



[a] (a) C_6H_6, reflux (83%); (b) *trans*-1-methoxy-3-((trimethylsilyl)oxy)-1,3-butadiene (**11**), $BF_3{\cdot}OEt_2$, CH_2Cl_2; then CSA (65%); (c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C → rt (99%); (d) Lipase-30, vinyl acetate, DME, rt, (−)-**15** (45%; 93% ee); (e) (i) K_2CO_3, MeOH, rt; (ii) PMBCl, NaH, DMF, 0 °C → rt (97% overall); (f) 3,3-dimethyldioxirane, K_2CO_3, CH_2Cl_2, 0 °C; then $NaIO_4$, H_2O/THF (92%); (g) allyl triphenylstannane, $SnCl_4$, CH_2Cl_2, −78 °C (98% of **18** + epimer (4:1)); (h) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C; (ii) DDQ, CH_2Cl_2/H_2O (20:1), 0 °C → rt (93% overall); (i) (i) $LiN(SiMe_3)_2$, THF, −78 → 0 °C; (ii) K_2CO_3, MeOH/H_2O (78% of the *cis* epoxide); PMB = *p*-$MeOC_6H_4CH_2$; Ms = SO_2CH_3.

through acetylation in the "forward sense". Following protocols of Wong,[23] the racemic alcohol was used in a transesterification experiment with vinyl acetate under the influence of Lipase-30 to afford alcohol **14** and acetate **15**. Of course, at this stage, we were in no position to assert the assignments of the absolute configuration to the antipodal glycal and glycal acetates with rigorous confidence. Rather, our tentative formulations arose from extensive precedents that had been garnered in our laboratory some years ago in this general area.[22] The presumed 3*S*-acetate **15** was subjected to deacetylation, giving rise to *ent*-**14**. The latter was subjected to the action of sodium hydride and *p*-methoxybenzyl chloride to afford **16**. In principle, it was initially supposed that compound **14** in the 3*R* series could be utilized in the synthesis program. However, as will be shown, an alternate route not requiring resolution to reach the desired 3*S* pyranoid series (cf. **16**) became available, and the possibility of recycling the 3*R* series available from the lipase chemistry was not pursued.

The next phase of the program called for disconnection of the C1−C2 bond of the artificial glycal **16** in such a fashion that C3 would emerge as C13 of the projected *cis*-epoxide **20**. We proceeded as follows. Drawing once again on chemistry that we had introduced in an earlier era for different purposes,[24]

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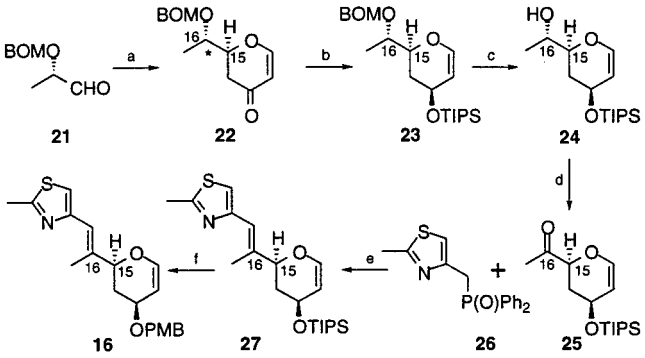
(24) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1381.

Scheme 3[a]



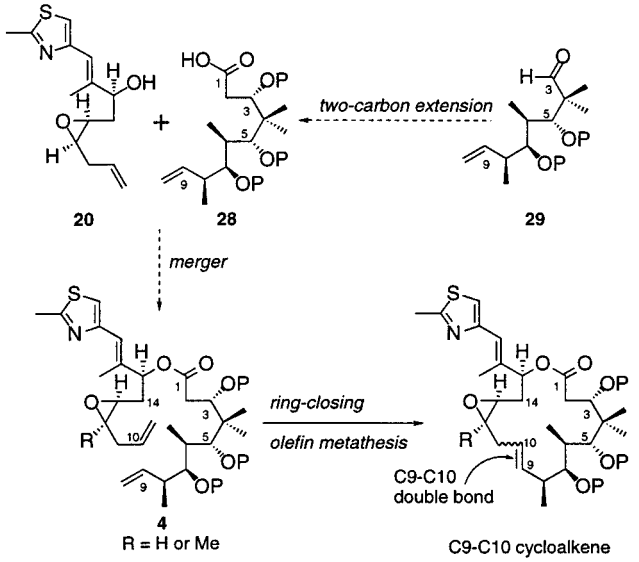
[a] (a) *trans*-1-Methoxy-3-((trimethylsilyl)oxy)-1,3-butadiene (**11**), $MgBr_2 \cdot OEt_2$, THF, −10 °C; then AcOH, H_2O (93%); (b) (i) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C; (ii) TIPSCl, imidazole, DMF, 0 °C → rt (87% overall); (c) Na^0, NH_3 (l), THF, −78 °C; then MeOH, −78 → 25 °C (92%); (d) Dess−Martin periodinane, pyridine, CH_2Cl_2, rt (98%); (e) **26**, *n*-BuLi, THF, −78 °C; then **25**, THF, −78 °C → rt (87%); (f) (i) *n*-Bu_4NF, THF, rt; (ii) PMBCl, NaH, DMF, 0 °C → rt (97% overall); BOM = CH_2OCH_2Ph; TIPS = Si*i*-Pr_3; PMB = *p*-$MeOC_6H_4CH_2$.

reaction of **16** with 3,3-dimethyldioxirane gave rise to an intermediate epoxide which, on oxidative solvolysis with sodium metaperiodate, afforded a 92% yield of aldehyde **17**. It was hoped that the emergence of the future oxygen at C15 (epothilone numbering) in the form of the formate ester would serve to prevent hemiacetal formation with the aldehyde group. Such a complicating event would have been anticipated if the C15 oxygen were free. While there was considerable apprehension as to whether the formate protecting device would be equal to the challenges with which it would be confronted, in practice this group survived during reaction of compound **17** with allyltriphenylstannane.[25] There was obtained a 96% yield of a 4:1 mixture of diastereomers at the future C12. The major product was assumed (and demonstrated on the basis of subsequent events) to be **18** in the relative configurational sense. Compound **18** was then subjected to mesylation, followed by deprotection of the *p*-methoxybenzyl group to give the hydroxy mesylate **19**. Finally, the sequence was completed by cyclization of the hydroxy mesylate with lithium hexamethyldisilazide. In this way, goal system **20** was obtained. Since compound **20** was indeed a *cis*-epoxide, the assignments of relative stereochemistry to compounds subsequent to the intermediate **12** had been substantiated. As for the absolute configuration of **20**, this assignment was proven by a sharply modified route (*vide infra*), which was undertaken to avoid the need for any resolution.

The pursuit of this modified route was also motivated by the desire to demonstrate still another dimension to the cyclocondensation reaction.[19] The concept involved the leveraging of chirality of heterodienophiles in the LACDAC reaction to create a pyran matrix of defined absolute configurations. This accomplished, the original asymmetries of the hetereodienophile can be abrogated, depending on the needs of the synthesis.

To teach this lesson, we proceeded as follows. Cyclocondensation of the known lactaldehyde derivative **21**[26] with **11** under mediation by magnesium bromide etherate gave rise to a 93% yield of a dihydropyrone (see Scheme 3). On the basis of earlier work,[27] we formulated this pyrone to be structure **22**. The importance of this assignment lies in the statement that it

Scheme 4. A C9−C10 Bond Construction through Ring-Closing Olefin Metathesis



makes about the absolute stereochemistry of the center destined to become C15. This center was presumed to be *S* as a consequence of α-chelation control in the cyclocondensation reaction. It will be appreciated that we had introduced an sp^3 chiral element which was *per se* unneeded, at the future trigonal C16 center (see the indicated carbon atom in **22**).

Compound **22** was integrated within the main synthetic pathway as follows. The ketone function of the dihydropyrone was reduced, as before, and the resultant alcohol at C3 (glycal numbering) was protected as its triisopropylsilyl ether (TIPS) derivative **23**. The benzyloxymethyl (BOM) group was discharged through the action of sodium in liquid ammonia and the alcohol function in the resultant **24** was subjected to oxidation using the Dess−Martin periodinane procedure.[28] This sequence provided **25** in 90% yield. This compound was, in turn, successfully condensed with phosphine oxide **26**[8a] in a Horner reaction,[29] thereby producing the elongated structure **27**. For purposes of stereochemical correlation, the silyl group was cleaved (*n*-Bu_4NF), and the resultant alcohol was reprotected as its *p*-methoxybenzyl ether. At this stage, we had achieved an alternate synthesis of compound **16** in a way that rigorously defined the relative stereochemistry as well as the absolute configuration. The conversion of intermediate **16** to **20** has already been discussed above.

With these successes as a platform, it was appropriate to focus on the construction of the acyl fragment projected for the olefin metathesis step. For this purpose, it would be appropriate to reach a carboxylic acid (cf. **28**, Scheme 4**)** for joining to alcohol **20** to reach system type **4**. We further presumed at the planning level that acid **28** would arise by a two carbon extension of a generic aldehyde (cf. **29**). In this section of the molecule, we would also be dealing with incorporation of the geminal methyl groups at the future C4 as well as the implementation of the appropriate chirality at carbons 6, 7, and 8. The chirality at C3 would have to be established during the course of the two carbon homologation alluded to above.

(25) For a review of allylations, see: Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

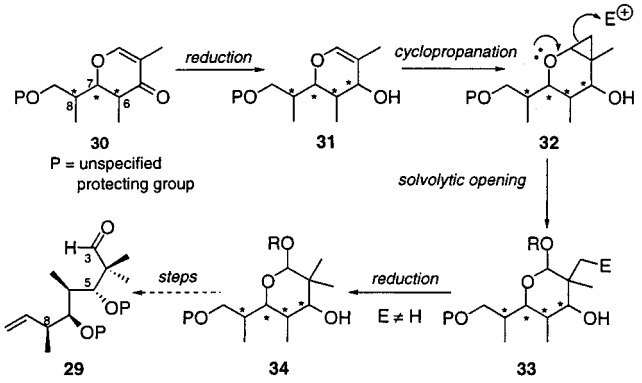
(26) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846.

(27) (a) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F. *J. Am. Chem. Soc.* **1984**, *106*, 2455. (b) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1256.

(28) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (c) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549. (d) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(29) For examples, see: (a) Lythgoe, B.; Nambudiry, M. E. N.; Ruston, S.; Tideswell, J.; Wright, P. W. *Tetrahedron Lett.* **1975**, 3863. (b) Lythgoe, B. *Chem. Soc. Rev.* **1981**, 449. (c) Toh, H. T.; Okamura, W. H. *J. Org. Chem.* **1983**, *48*, 1414. (d) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovic, M. R. *J. Org. Chem.* **1986**, *51*, 3098.

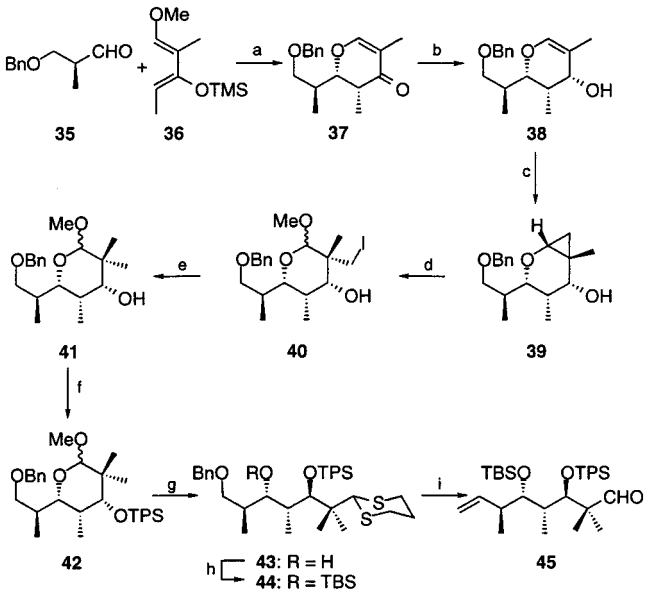
Scheme 5. General Strategy for a Synthesis of the Polypropionate Domain of the Epothilones



A central goal of our plan was the attainment of stereospecificity in the management of chirality at carbons 6, 7, and 8. As our thinking evolved (*vide infra*), it seemed that control over these issues could be facilitated if our scheme included a temporary chirality element at C5. Though C5 is destined to become a ketone, the temporary sp^3-associated chirality at this center would be very valuable in the management of stereochemistry in this region and in the introduction of the geminal methyl groups at C4. The possibility of using a dihydropyrone to address this problem presented itself.[8b] The thought was to translate the C-6, -7, and -8 domain of epothilone to correspond to dihydropyrone **30** (see Scheme 5). The latter could be accessed through cyclocondensation chemistry (*vide infra*). Hence, an artificial glycal (cf. **30**) was seen to be an exploitable intermediate *en route* to subgoal structure **29**. *More specifically, the thought was to utilize a C5 alcohol to facilitate and direct a cyclopropanation of the glycal double bond* (see **31** → **32**, Scheme 5).[30,31] A regiospecific solvolytic fragmentation of the cyclopropane ring in **32**[32] would then provide, in gross terms, an aldehyde equivalent of the type **33**. In the event that the crucial cyclopropane solvolysis step would be conducted in an oxidative sense (i.e. $E^+ \neq H$), it would then be necessary to effect a reduction of **33** to reach a compound of the type **34**. The latter would then be advanced, as appropriate, to reach the desired aldehyde **29**. This general thinking is summarized in Scheme 5.

In practice, titanium-mediated cyclocondensation of the known and optically pure β-(benzyloxy)isobutyraldehyde **35**[33] with diene **36**,[34] following a protocol previously devised in our laboratory,[35] gave rise to dihydropyrone **37** (see Scheme 6).[8b] Reduction of this compound with lithium aluminum hydride in ether provided glycal **38**. The hydroxyl group was then used

Scheme 6[a]



[a] (a) $TiCl_4$, CH_2Cl_2, −78 °C; then CSA, PhH, rt (87%); (b) $LiAlH_4$, Et_2O, −78 °C (91%); (c) Et_2Zn, CH_2I_2, Et_2O, rt (93%); (d) NIS (7 equiv), MeOH, rt; (e) *n*-Bu_3SnH, AIBN (cat.), PhH, reflux (80% from **39**; (f) Ph_3SiCl, imidazole, DMF, rt (97%); (g) 1,3-propanedithiol, $TiCl_4$, CH_2Cl_2, −78 → −40 °C (78%); (h) *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, 0 °C (98%); (i) (i) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), CH_2Cl_2/H_2O (19:1), rt (89%); (ii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; then Et_3N, −78 °C → 0 °C (90%); (iii) CH_3PPh_3Br, $NaN(SiMe_3)_2$, $PhCH_3$, 0 °C → rt (76%); (iv) $PhI(OCOCF_3)_2$, $CH_2Cl_2/CH_3CN/H_2O$, rt (85%); Bn = CH_2Ph; TMS = $SiMe_3$; TPS = $SiPh_3$; TBS = Si*t*-$BuMe_2$.

to direct a cyclopropanation under modified Conia−Simmons−Smith conditions[31a] to afford cyclopropano derivative **39**. Oxidative solvolytic fragmentation of this cyclopropane was accomplished through the agency of *N*-iodosuccinimide in methanol to provide methyl glycoside **40**.[8b] Reductive deiodination of this compound led to the branched artificial methyl glycoside **41**, after which triphenylsilylation afforded the protected derivative **42**.

At this stage, it was timely to cleave the pyran ring with a view toward liberating the future aldehyde corresponding to C3 of the epothilones. Advancement *en route* to this goal involved subjecting compound **42** to the combined action of 1,3-propanedithiol and titanium(IV) chloride. This protocol led to the formation of the dithioacetal **43**.[36] Protection of the future C7 alcohol as shown (see compound **44**) was followed by olefin formation and liberation of the aldehyde function. In this way the specific compound **45** was in hand.

The next stage in the pursuit of approach I involved a two-carbon expansion starting with aldehyde **45**. The goal was the production of an acylation partner for alcohol **20** *en route* to a competent substrate for ring-closing olefin metathesis. In an early experiment, aldehyde **45** was treated with the lithium enolate of *tert*-butyl acetate (Rathke anion, see Scheme 7).[37]

(30) (a) Winstein, S.; Sonnenberg, J. *J. Am. Chem. Soc.* **1961**, *83*, 3235. (b) Dauben, W. G.; Berezin, G. H. *J. Am. Chem. Soc.* **1963**, *85*, 468. (c) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53. (d) For recent examples of oxygen-directed cyclpropanations of glycals, see: Hoberg, J. O.; Bozell, J. J. *Tetrahedron Lett.* **1995**, *36*, 6831. (e) For an excellent review of substrate-directable chemical reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(31) For selected examples of glycal cyclopropanations, see: (a) Boeckman, R. K., Jr.; Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1991**, *113*, 5337. (b) Murali, R.; Ramana, C. V.; Nagarajan, M. *J. Chem. Soc., Chem. Commun.* **1995**, 217. (c) Henry, K. J., Jr.; Fraser-Reid, B. *Tetrahedron Lett.* **1995**, *36*, 8901. (d) Hoberg, J. O.; Claffey, D. J. *Tetrahedron Lett.* **1996**, *37*, 2533. (e) Timmers, C. M.; Leeuwenburgh, M. A.; Verheijen, J. C.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron: Asymmetry* **1996**, *7*, 49. (f) Scott, R. W.; Heathcock, C. H. *Carbohydr. Res.* **1996**, *291*, 205. (g) For an excellent review of cyclopropanes in synthesis, see: Wong, H. N. C.; Hon, M.-Y.; Tse, C.-H.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.

(32) (a) Collum, D. B.; Mohamadi, F.; Hallock, J. S. *J. Am. Chem. Soc.* **1983**, *105*, 6882. (b) Collum, D. B.; Still, W. C.; Mohamadi, F. *J. Am. Chem. Soc.* **1986**, *108*, 2094. (c) For an important early study, see: Wenkert, E.; Mueller, R. A.; Reardon, E. J., Jr.; Sathe, S. S.; Scharf, D. J.; Tosi, G. *J. Am. Chem. Soc.* **1970**, *92*, 7428.

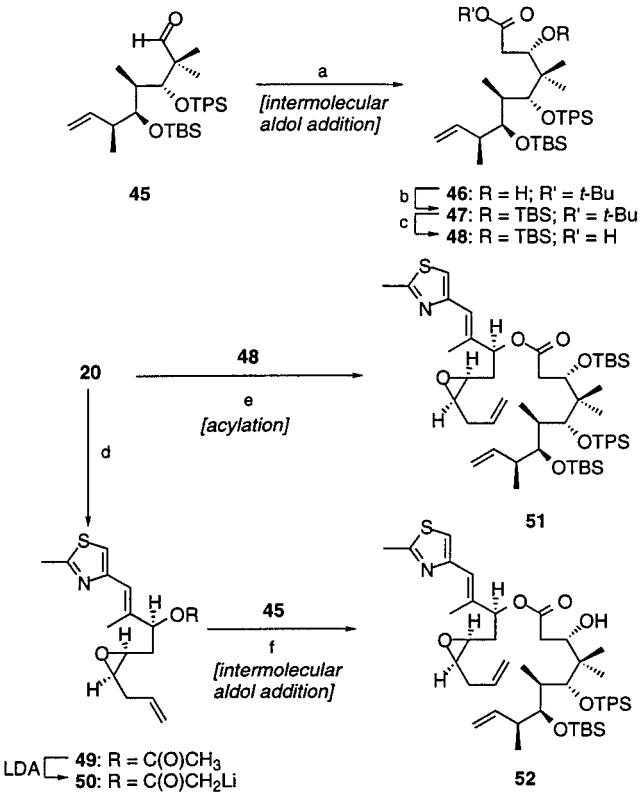
(33) (a) Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505. (b) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (c) Meyers, A. I.; Babiak, K. A.; Campbell, H. L.; Comins, D. L.; Fleming, M. P.; Henning, R.; Heuschmann, M.; Hudspeth, J. P.; Kane, J. M.; Reider, P. J.; Roland, D. M.; Shimizu, K.; Tomioka, K.; Walkup, R. D. *J. Am. Chem. Soc.* **1983**, *105*, 5015. (d) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.

(34) Danishefsky, S. J.; Yan, C.-F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M., Jr.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001.

(35) (a) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1256. (b) Danishefsky, S. J.; Myles, D. C.; Harvey, D. F. *J. Am. Chem. Soc.* **1987**, *109*, 862.

(36) For an example, see: Egbertson, M.; Danishefsky, S. J. *J. Org Chem.* **1989**, *54*, 11.

Scheme 7[a]



[a] (a) *t*-BuOC(O)CH_2Li, THF, 0 °C (90%; *ca*. 2.5:1 mixture of C-3 epimers in favor of **46**); (b) *t*-BuMe_2SiOTf, 2,6-lutidine, CH_2Cl_2, rt; (c) TESOTf, 2,6-lutidine, CH_2Cl_2, rt (90% overall); (d) Ac_2O, Et_3N, 4-DMAP, CH_2Cl_2, rt (94%); (e) **48**, EDC, CH_2Cl_2, 4-DMAP, rt; then **20** (78%); (f) **45** + **49**, LDA, THF, −78 °C (2−6:1 mixture of C3 epimers in favor of **52**; 85%); TBS = Si*t*-BuMe_2; TPS = $SiPh_3$.

There was thus generated a mixture of diastereomeric alcohols at the carbon destined to become C3 of epothilone. The major product was shown to have the required 3*S* configuration. The alcohol function in compound **46** was successfully protected as the *tert*-butyldimethylsilyl (TBS) ether derivative (see compound **47**). At this stage, it was possible to cleave the *tert*-butyl ester function to generate the acid **48**.

The coupling of the previously described alcohol **20** with acid **48** was conducted under the influence of 1-(3-(dimethylamino)-propyl)-3-ethylcarbodiimide hydrochloride (EDC) to produce, at long last, the proposed metathesis substrate **51** (see Scheme 7). It was also of interest to investigate the possibility of a more concise construction of a possible metathesis substrate. This approach started with acetylation of compound **20** to provide **49**. This acetate, when treated with lithium diisopropylamide, generated a presumed lithium ester enolate (see proposed structure **50**). This enolate underwent successful union with aldehyde **45** to produce a mixture of C3 epimers with the desired compound **52** predominating. A particularly interesting and efficient method for conducting the coupling of **49** and **45** involved merger of the two units in a "Barbier" sense.[38] *In this mode, the aldehyde and the ester would be concurrently exposed to the action of lithium diisopropylamide*. It was felt that such a treatment might be successful since the aldehyde is nonenolizable. In the event, an 85% yield of a ca. 5:1 mixture of C3 epimers was obtained with the major product being the 3*S* compound shown. This experiment was to have significant implications for our intramolecular aldol addition strategy which will be discussed under approach II.

(37) Rathke, M. W.; Sullivan, D. F. *J. Am. Chem. Soc*. **1973**, *95*, 3050.

(38) For a prior instance of a Barbier aldol reaction, see: Linde, R. G., II; Jeroncic, L. O.; Danishefsky, S. J. *J. Org. Chem*. **1991**, *56*, 2534.

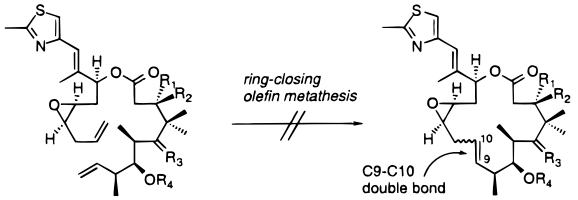
We now had in hand substrates **51** and **52**. Surprisingly, when these substrates were submitted to a range of conditions and catalysts designed to bring about ring-closing olefin metathesis, no convincing indication could be garnered for the presence of cyclized systems even to a small extent. While we could not exclude the possibility that trace amounts of desired products had been produced, the overwhelming bulk of the material was clearly of a very complicated nature, suggesting probable oligomerization. In any case, neither the protected system **51**, nor the structure bearing a free C3 alcohol in **52** served as usable substrates *en route* to epothilone A.

We did not take the setbacks in this early skirmishing with substrates **51** and **52** to necessarily establish the nonviability of the concept. We hoped that the feasibility of the RCM reaction could be sharply influenced by the nature and stereochemistry of the "decorating" substituents along the acyl chain. It seemed possible that certain substrates might be more amenable to cyclization in that conformational factors (in these variants) might help to predispose proximity between the terminal vinyl groups, or that properly selected substituents would be less conformationally obtrusive in the cyclic products which we were hoping to form on metathesis. In that spirit, we synthesized a wide variety of compounds as potential participants in the RCM reaction.[39] Unfortunately, none of these candidate substrates produced workable amounts of cyclized product. At best, mass spectrometric analysis indicated the possible formation of some desired materials. However, attempted isolation of traces of RCM products (assuming they were actually present) from very complex mixtures proved to be unsuccessful.

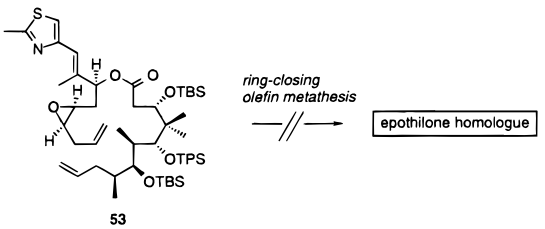
These facts, however disheartening, forced us to conclude that the row of substituents projecting from C3 through C8 had created an unmanageable problem of steric hindrance with respect to participation of the C9 double bond in the metathesis process. To probe this matter further, we went so far as to synthesize a compound which would, in itself, not constitute a promising intermediate for reaching epothilone. However, we thought that the study of the olefin metathesis possibility with this substrate could shed more light on the failures of the previously described entries. Accordingly, we synthesized compound **53**[40] in which the vinyl group on the acyl side was insulated from the secondary methyl group at C8 by another methylene group. Unhappily, homologous olefin **53** also failed to undergo ring-closing olefin metathesis.[40]

As described elsewhere,[8b] we went on to demonstrate to our satisfaction that the "culprit" in preventing the ring forming olefin metathesis reaction was the network of functionality between C3 and C8. There was nothing inherently unworkable

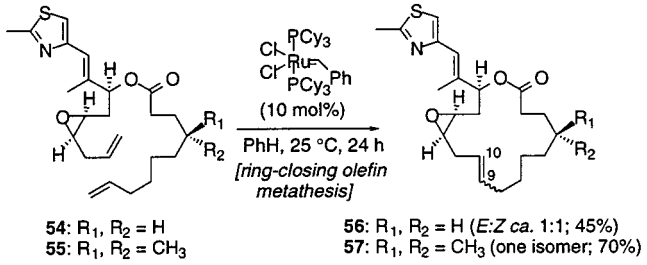
(39) For specific substrates tested in ring-closing olefin metathesis reactions, see Supporting Information.



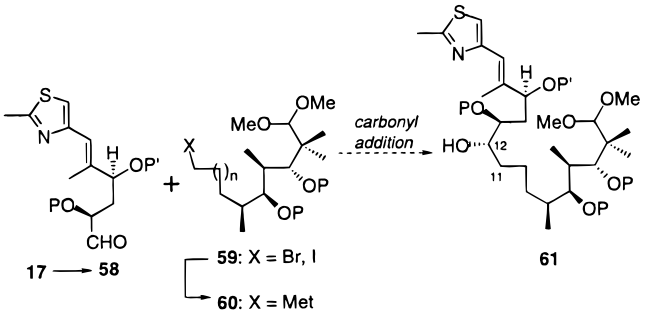
(40) Compound **53** was not a successful substrate for ring-closing olefin metathesis.



Scheme 8. Construction of the Compounds **56** and **57** through Ring-Closing Olefin Methathesis



Scheme 9. Intermolecular Carbonyl Addition Strategy for the Construction of the C11−C12 Bond



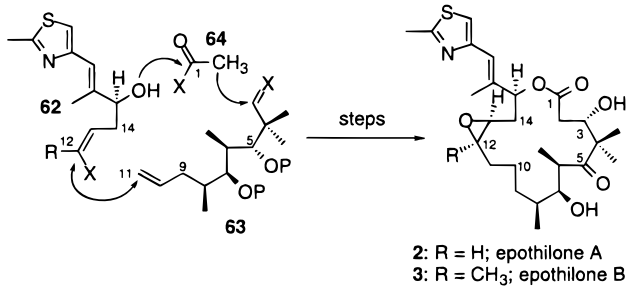
about inclusion of the homoallylic epoxide or the thiazolyl function, which were situated in the alkyl sector of the proposed premacrolide substrate. This "probable cause" argument was demonstrated by successful ring-closing metathesis reactions of substrates **54** and **55** (see Scheme 8). Unfortunately, while products **56** and **57**, respectively, could be obtained from such reactions in excellent yields, they did not display significant biological activity, either in tubulin binding or in cell-culture cytotoxicity studies.

We were now in the horns of what seemed to be an unsolvable dilemma. Those substrates in which olefin metathesis, leading to a C9−C10 cycloalkene (see Scheme 8), could be conducted provided products with nonuseful biological profiles. Conversely, those substrates which were functionalized in the spirit of serious potential epothilone precursors failed to undergo ring-closing olefin metathesis. It was when the full scope of this conundrum became clear that approach I was set aside in favor of other options.

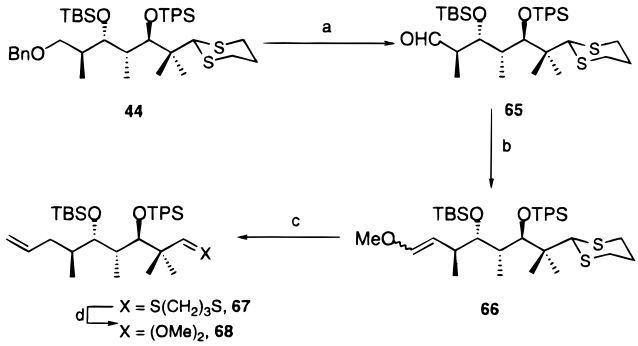
Since we had demonstrated the ability to generate a protected aldehyde of the type **17** (Scheme 2), we turned to the possibility of a convergent coupling of this sort of system (generalized as **58**) with a conventional nucleophile in the form of a metallo derivative (generalized as **60**) (see Scheme 9). In the ideal scenario, **60** would be derived from **59**, in which case a product such as **61** could be anticipated.

In practice, it proved possible to synthesize potential probe compounds for such metalation reactions (i.e. systems of the type **59**). Surprisingly, at no point were we able to accomplish the metalation of any such derivative to produce a competent organometallic nucleophile corresponding to **60**. In all cases, either unreacted aldehyde was recovered with the protonated metal species or decomposition took place. These failures were documented, not only in attempted couplings to the relatively sophisticated electrophile **17**, but even with much simpler electrophiles. We could garner little evidence to show that we had achieved metalation either in the series $n = 0$ or $n = 1$. These failures, suggesting problems in accessing external agents to the terminus of **59**, mirrored some of the difficulties which were soon to be encountered in the Suzuki coupling scheme (*vide infra*). Fortunately, this problem could be overcome in a novel way.

Scheme 10. C11−C12 Suzuki Bond Construction



Scheme 11[a]



[a] (a) (i) DDQ, CH_2Cl_2/H_2O (89%); (ii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; then Et_3N, −78 → 0 °C (90%); (b) $MeOCH_2PPh_3Cl$, *t*-BuOK, THF, 0 °C → rt (86%); (c) (i) *p*-TSOH, dioxane/H_2O, 50 °C (99%); (ii) CH_3PPh_3Br, NaHMDS, $PhCH_3$, 0 °C → rt (76%); (d) PhI(O-$COCF_3)_2$, MeOH/THF, rt, 0.25 h (92%); Bn = CH_2Ph; TPS = $SiPh_3$; TBS = Si*t*-$BuMe_2$.

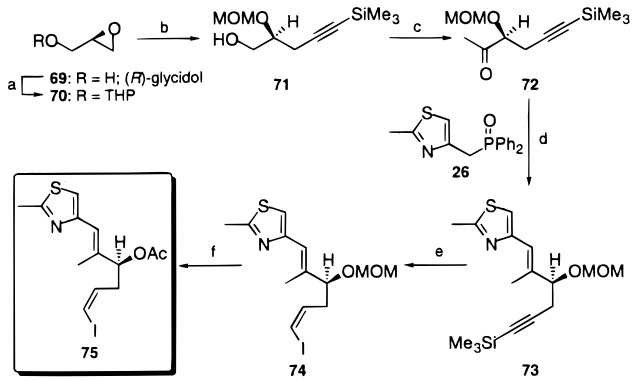
B-Alkyl Suzuki Strategy (Approaches II and III, Scheme 1)

We now report the results of the first successful syntheses of epothilones A and B which were achieved by the alkyl Suzuki method. The concept is generalized in Scheme 10 anticipating a synthesis of epothilones A and B. Through some as yet unspecified method, we envisioned a route to a *Z*-haloalkene **62**. Furthermore, it was expected that the chemistry would lend itself to construction of a terminal vinyl system in the context of a protected C3 substructure, generalized as system **63**. Construction of the C11−C12 bond would be the hallmark of the scheme and would be accomplished through a *B*-alkyl Suzuki coupling[15] (*vide infra*). Also to be dealt with would be a two carbon insert corresponding to carbons 1 and 2 of epothilone (see **64**). The appendage **64** could be incorporated in the scheme at several stages. If these carbon−carbon bond producing maneuvers were to be realized, there would also remain the need for introduction of the C12−C13 β-epoxide through the action of a suitable oxidizing agent. It was from these perceptions that our overall strategy for reaching epothilone A emerged. With suitable modification, a route to epothilone B was also embraced under this paradigm.

In practice, we turned to aldehyde **65** (Scheme 11). Compound **65** had been previously described as arising from **44** and had been converted to terminal vinyl compound **45** (Scheme 6). Now, the same aldehyde was successfully coupled to (methoxymethyl)triphenylphosphorane to give rise to **66**.[8c] The latter was then subjected to sequential hydrolysis and Wittig reactions to afford **67**. Finally, it proved possible to convert the dithiane linkage protecting C3 to the dimethyl acetal **68**. Here it was envisioned that the future C3 aldehyde could be revealed from the dimethyl acetal even in a mutlifunctionalized substrate.

With this chemistry in hand, we turned our attentions to the other projected Suzuki coupling partner. The specific version

Scheme 12[a]



[a] (a) Dihydropyran, PPTS, CH_2Cl_2, rt (73%); (b) (i) $Me_3SiCCLi$, $BF_3{\cdot}OEt_2$, THF, −78 °C (76%); (ii) MOMCl, *i*-Pr_2NEt, $Cl(CH_2)_2Cl$, 55 °C (85%); (iii) PPTS, MeOH rt (95%); (c) (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; then Et_3N, −78 → rt; (ii) MeMgBr, Et_2O, 0 °C → rt (85% for two steps); (iii) TPAP, NMO, 4 Å mol sieves, CH_2Cl_2, 0 °C → rt (93%); (d) **26**, *n*-BuLi, THF, −78 °C; then **72**, THF, −78 °C → rt (97%); (e) (i) *N*-iodosuccinimide, $AgNO_3$, $(CH_3)_2CO$ (64%); (ii) dicyclohexylborane, Et_2O, AcOH (65%); (f) (i) PhSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt (86%); (ii) Ac_2O, pyr, 4-DMAP, CH_2Cl_2, rt (99%); PPTS = pyridinium *p*-toluenesulfonate; MOMCl = methoxymethyl chloride; TPAP = tetra-*n*-propylammonium perruthenate; NMO = *N*-methylmorpholine *N*-oxide.

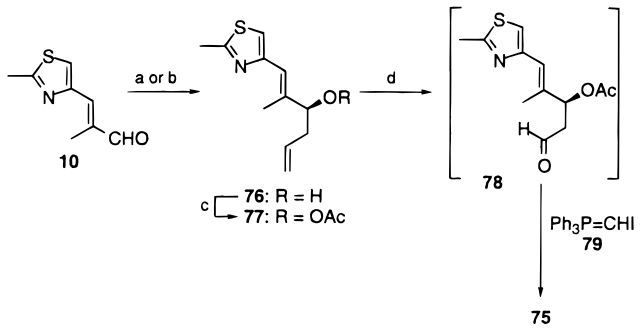
of the generic structure **62** which was settled upon was the iodoacetate (see **75**, Scheme 12). Needless to say, it would be necessary to "deliver" this compound with the appropriate olefin geometry and in optically pure form for melding into the epothilone synthesis. In theory, depending on the coupling modality, we could utilize either enantiomeric version at C15; each enantiomer could be interfaced into the synthesis, subject to whether inversion or retention would be required at C15.

In our first route,[8c] we anticipated retention of configuration at this center (see Scheme 12). Accordingly, our program started with the commercially available *R*-(+)-glycidol (**69**).[41] The hydroxyl group was protected in the form of a THP ether (see compound **70**). In a defining step, the epoxide linkage was used to alkylate the lithium salt of (trimethylsilyl)acetylene, under the conditions described, to give rise to compound **71**. It will be recognized that the chiral center of glycidol is retained *en route* to coupling partner **75**.

The next phase involved the classical transformation of the primary alcohol linkage to a methyl ketone. This was accomplished, as indicated, to provide ketone **72**. Drawing from an important precedent (see **25** + **26** → **27**, Scheme 3),[8a] we could accomplish the introduction of the thiazolyl nucleus through an Emmons reaction[29] of phosphine oxide **26** with methyl ketone **72**. In the concluding phase of this synthesis, silyl acetylene **73** was converted to the corresponding iodoalkyne which, upon reduction,[42] gave rise to the *cis*-iodoalkene **74**. Finally, cleavage of the MOM protecting group, as shown, followed by acetylation, produced the desired *cis*-vinyl iodide **75**.

When the general concept of the alkyl Suzuki coupling proved to be fruitful (*vide infra*), more concise syntheses of **75** were achieved. For this purpose, we returned to the enal **10**, a substance employed in an earlier stage of the synthesis.[8a] Allylation of this compound with tri-*n*-butylstannane in the presence of the (*S*)-BINOL enantiodirecting ligand, as described by Keck,[43] gave rise to the allylated product **76** in greater than

Scheme 13[a]



[a] (a) Allyltri-*n*-butylstannane, (*S*)-(−)-BINOL, $Ti(Oi\text{-}Pr)_4$, CH_2Cl_2, −20 °C (60%; >95% ee); (b) $[(-)\text{-Ipc}]_2BCH_2CHCH_2$, Et_2O, −100 °C; then 3 N NaOH, 30% H_2O_2 (83%; >95% ee); (c) Ac_2O, 4-DMAP, Et_3N, CH_2Cl_2 (96%); (d) (i) OsO_4, NMO, 0 °C; (ii) $NaIO_4$, THF/H_2O, rt (iii) **79**, THF, −78 → 0 °C (50% overall).

95% enantiomeric excess (see Scheme 13). Alternatively, we could effect an asymmetric allylation of enal **10** through the use of Brown's procedure.[44,9b] These transformations were generally faster and higher yielding but, of course, lacked the feature of implementation of chirality through catalytic means. The optical purity of allylic alcohol **76** prepared by allyl boration, was established by formation of the Mosher ester and subsequent analysis by ^1H and ^{19}F NMR spectroscopy. Eventually, the assignment and extent of optical purity were corroborated by interfacing this product with compound **75** derived from the glycidol route. Protection of carbinol **76** afforded acetate **77**. In a very delicate set of transformations, this homoallylic acetate was subjected to oxidative cleavage, as shown, to generate the putative β-acetoxy aldehyde **78**. That we had resorted, in the first instance, to the glycidol route reflected our fears that such a structure would be nonviable given its projected vulnerability to β-elimination of the cinnamyl-like acetoxy function. However, in practice, this difficulty could be managed. Wittig-type reaction with the known phosphorane **79**[45] gave rise to **75**. Certainly, this route proved to be more concise for reaching compound **75** than the *R*-glycidol based route shown in Scheme 12. The actual practicality of the process will depend on the feasibility of the scale up of the conversion of **77** to the vulnerable **78** *en route* to **75**.

Even while this work was in progress, we were investigating a variation wherein the hypothetical Suzuki coupling would be conducted with a more advanced coupling partner, better positioned to reach epothilone itself. For this purpose, we returned to the acetal **68** which was deprotected to give rise to aldehyde **80** (see Scheme 14). This compound was condensed with lithio *tert*-butyl acetate[37] (i.e. the Rathke anion). There was produced a 63% yield of **81**, as well as its C3 stereoisomer (**82**, not shown here) in a ratio of approximately 2:1. The undesired C3 epimer could be oxidized to the corresponding ketone with Dess−Martin periodinane[28] and subsequently reduced in a stereoselective fashion to give the desired C3 alcohol exclusively. The major product **81** was subjected to the action of buffered HF·pyridine, whereupon the triphenylsilyl function was selectively cleaved from the C5 oxygen. It was further possible to selectively silylate the C3 alcohol through the combined action of TBS triflate and 2,6-lutidine, providing compound **83**. At this point, the C5 alcohol in compound **83** was oxidized to produce the ketone **84**. Finally, the *tert*-butyl

(41) For an excellent review of the chemistry of glycidol, see: Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437.

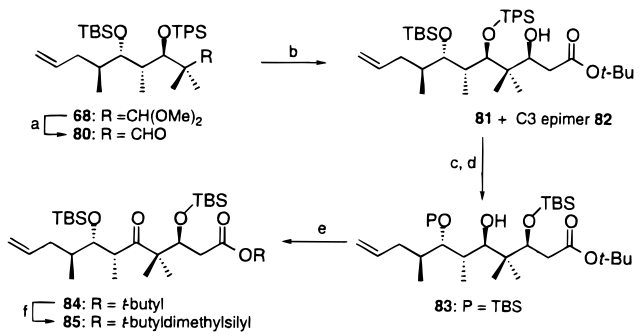
(42) Corey, E. J.; Cashman, J. R.; Eckrich, T. M.; Corey, D. R. *J. Am. Chem. Soc.* **1985**, *107*, 713.

(43) Keck, G. E. Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467.

(44) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.

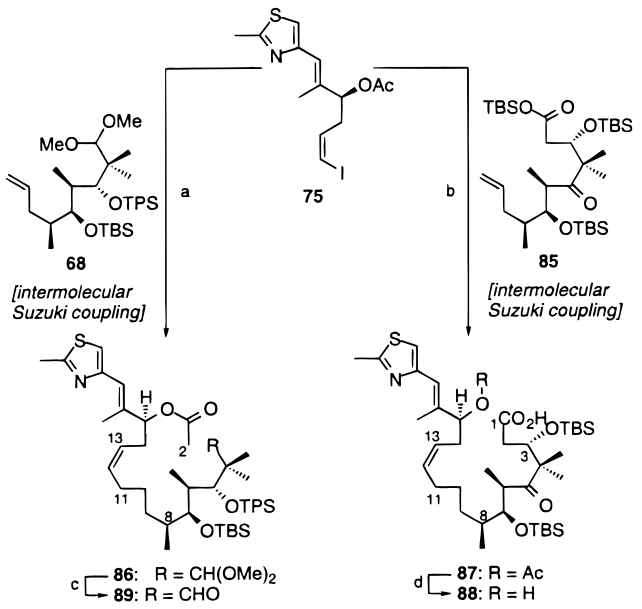
(45) (a) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173. (b) Stork, G.; Zhao, K. *J. Am. Chem. Soc.* **1990**, *112*, 5875. (c) Chen, J.; Wang, T.; Zhao, K. *Tetrahedron Lett.* **1994**, *35*, 2827.

Scheme 14[a]



[a] (a) *p*-TsOH, dioxane/H_2O (5:1), 50 °C (81% overall); (b) *tert*-butyl acetate, LDA, THF, −78 °C, (95%; *ca.* 2:1 mixture of C-3 epimers); (c) HF·pyr, pyr, THF, rt (98%); (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, −30 °C (96%); (e) Dess−Martin periodinane, CH_2Cl_2, rt (89%); (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt (93%); TPS = $SiPh_3$; TBS = Si*t*-BuMe_2.

Scheme 15[a]



[a] (a) **68**, 9-BBN, THF, rt; then **75**, $PdCl_2(dppf)_2$, Cs_2CO_3, Ph_3As, H_2O/DMF, rt (75%); (b) **85**, 9-BBN, THF, rt; then **75**, $PdCl_2(dppf)_2$, Cs_2CO_3, Ph_3As, H_2O/DMF, rt (56%); (c) *p*-TsOH, dioxane/H_2O, 50 °C (85%); (d) K_2CO_3, MeOH/H_2O (84%); 9-BBN = 9-borabicyclo-[3.3.1]nonane; dppf = 1,1′-bis(diphenylphosphino)ferrocene; TPS = $SiPh_3$; TBS = Si*t*-BuMe_2.

ester could be converted to the *tert*-butyldimethylsilyl ester (see compound **85**) through the agency of TBS triflate and 2,6-lutidine.

We were now in a position to probe the feasibility of establishing the C11−C12 bond by Suzuki coupling in several contexts. Compound **68** was subjected to the action of 9-BBN (see Scheme 15). Remarkably, even the hydroboration of this terminal olefin required surprisingly coercive conditions. This slowness of hydroboration is reminiscent of the difficulties previously discussed in Scheme 9 for metalation of systems of the type **59** as a route to **60**. Fortunately, the hydroboration of **68** could be conducted under more vigorous conditions (as demonstrated by independent oxidative quenching experiments that revealed the anti-Markovnikov hydration product).

Having convinced ourselves that compound **68** had indeed been successfully hydroborated, we now conducted the last phase of the Suzuki reaction under mediation by palladium(II) chloride−1,1′-bis(diphenylphosphino)ferrocene (dppf) in the presence of the (*Z*)-vinyl iodide **75** as shown (Scheme 15). Gratifyingly, there was obtained a 72% yield of the acetate **86**.[8c] Within the limits of our detection, there had been no loss of stereointegrity of the C11−C12 double bond. The remarkable versatility of the *B*-alkyl Suzuki reaction[15] was further demonstrated by successful coupling of keto ester **85** with **75**. Under these circumstances, the TBS ester was cleaved during the course of the reaction, and the acetate was subsequently cleaved through the action of K_2CO_3 in aqueous methanol to give rise to the hydroxy acid **88**.

Our attentions would next be directed to the construction of the 16-membered ring. It was felt that our chances for achieving a stereoselective epoxidation would be better if the framework of the ring system were already in place when the oxidation of the C12−C13 double bond would be conducted. In our first attempt at macrocyclization, we favored a bold possibility. *The thought was to close the ring by connecting the methyl group of the acetate ester (C2) with the aldehyde center (C3) in a construct to be derived from compound* ***86***. That such a prospect could be even considered, arose from the fact that the *gem*-dimethyl substitution at C4 blocks the possibility of deprotonation of the aldehyde function. It will be recalled that earlier, in converting compound **45** to **52** (Scheme 7), we had exploited this principle by conducting an ester enolate aldol coupling under Barbier-type conditions.[38] Here, we would be drawing from the same concept in a macroaldolization step. To set the stage for this interesting ring-forming possibility, the acetal function in compound **86** was cleaved, thus revealing the electrophilic C3 aldehyde (see **86** → **89**, Scheme 15). In the crucial event, deprotonation of compound **89** (see Scheme 16) was accomplished through the action of potassium hexamethyldisilazide in THF at −78 °C. Remarkably, these conditions allow a stereoselective macroaldolization, resulting in the selective formation (6:1) of the desired (*S*)-C3 alcohol **90**. In some small scale experiments, compound **90** was the *only* product noted at the analytical level. However, optimal results from the standpoint of yield were actually obtained when the aldolate intermediate derived from cyclization was quenched at 0 °C or even at room temperature. When the quenching experiment was conducted at lower temperature, greater amounts of the undesired epimer **91** were obtained with an increase in mass recovery. Apparently, aldolate equilibration favors the formation of the desired 3*S* alcohol, whereas conditions more nearly approximating kinetic control give rise to lower degrees of stereoselectivity. At higher temperatures, it would seem that there is virtually no kinetic control in the stereochemistry of the macroaldolization step; the diastereomeric ratios observed indicate that equilibration occurs. While it is interesting to ponder and sort out methods to control stereoselectivity, in practice, the undesired epimer **91** could be utilized in our synthesis. Thus, oxidation of **91** to the ketone **92** set the stage for a diastereoselective reduction with $NaBH_4$ to provide the desired epimer **90** in high yield. Presumably, this outcome reflects the directing effects of the C5-OTPS function.

Cleavage of the triphenylsilyl ether in **90** could be conducted selectively, producing the C3−C5 diol (see compound **93**). Selective protection of the C3 hydroxyl in this compound was readily achieved, thus exposing the C5 alcohol in **94** for oxidation to a ketone. There was then produced di-TBS C12−C13 desoxyepothilone (**95**). Cleavage of the two silyl protecting groups could be accomplished, giving rise to desoxyepothilone A (**96**).

The whole scheme was now at considerable risk as we approached the matter of epoxidation of the C12−C13 double bond. We had hoped that oxidation would occur from the desired β-face on the basis of local conformational preferences that rendered this face of the molecule more accessible (see substructure **96** in Figure 2).[46] We further hoped to maximize our opportunities for stereocontrol by conducting the reaction

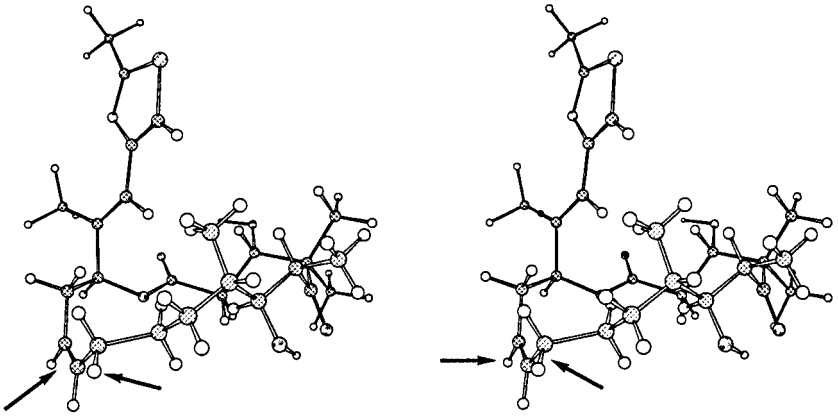


Figure 2. Macromodel minimized stereoview of desoxyepothilone A (**96**).

at low temperature. Given our many successful applications of the oxidizing powers of 3,3-dimethyldioxirane[24] it was not unnatural that we would turn to this reagent.

In practice, the major product of this reaction was the long sought after epothilone A (see **96** → **2**, Scheme 16), *confirmed by spectral and chromatographic comparisons of this material with authentic epothilone A kindly provided by Professor Höfle*. The first total synthesis of epothilone A had thus been accomplished. Two very minor products in the epoxidation were also isolated. One is the corresponding α-epoxide between C12 and C13. Still another product is one in which this epoxide linkage is present, but is accompanied by an epoxide functionality at C16−C17.

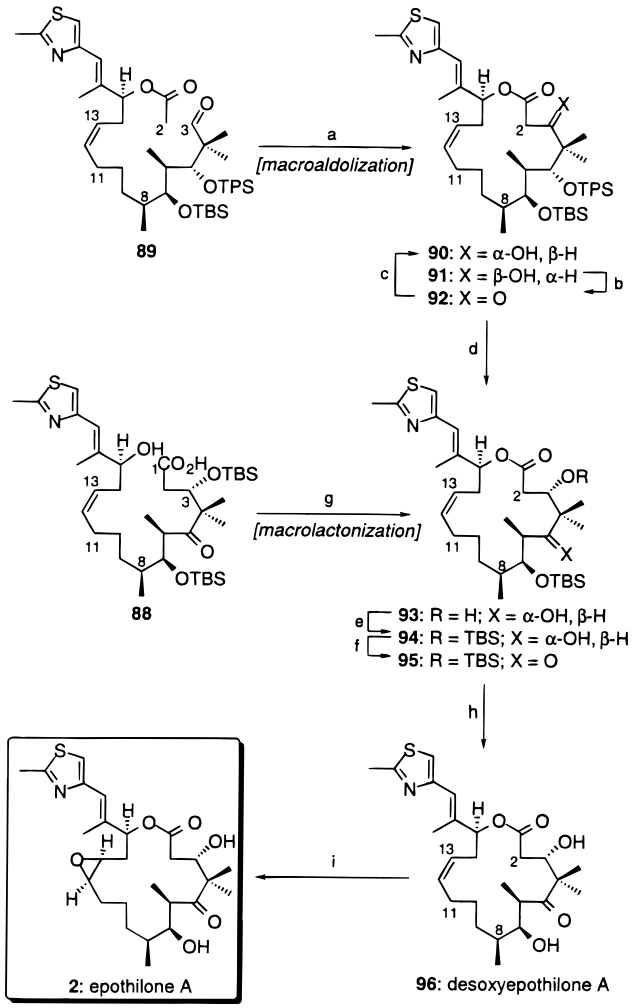
Although we had achieved the epoxidation reaction with high stereoselectivity, our reasoning based on model **96** can be questioned. Nicolaou and co-workers studied the use of the more conventional *m*-chloroperoxybenzoic acid.[9b,c] The use of this reagent produced mixtures of α and *β* epoxides. Hence, the factors controlling the facial sense of epoxidation are rather more subtle than is reflected in modeling of gross steric accessibility as suggested in **96**, since the course of oxygen delivery is strongly reagent dependent. However, we did have at our disposal a protocol for highly stereoselective epoxidation in the desired sense.

Having demonstrated the macroaldol route, we turned to the possibility of macrolactonization. This goal brought us back to compound **88** which, under Yamaguchi conditions,[47] led to the previously encountered **95**. Thus, we now had available to us two routes to enter the desoxyepothilone series in the form of compound **95** and, shortly thereafter, epothilone itself.

We next turn to our total synthesis of epothilone B (**3**) (see Scheme 17).[8e] We had hoped that this synthesis could be accomplished using, as much as possible, the chemistry that had served so well for the synthesis of epothilone A (**2**).[8c] Indeed, our route started with compound **77**, which was cleaved to the corresponding aldehyde **78**. Condensation of this aldehyde with the appropriate Wittig reagent[45c] gave rise to compound **97**, albeit in only 43% yield. Fortunately, the reaction was highly stereoselective, giving rise to the required *Z*-isomer as the only product. The stage was now set for the key Suzuki coupling. In this instance, we confined ourselves to acetal olefin **68**. Once again, hydroboration of **68** as before was followed by coupling of the resultant borane with (*Z*)-vinyl iodide **97**, giving rise to compound **98** in 77% yield. Cleavage of the acetal linkage led to aldehyde **99**. Once again, aldol condensation occurred in much the same manner as previously noted for compound **89**, thus allowing us to enter into the desoxyepothilone B series.

The protocols to reach desoxyepothilone B from cyclized material were already in hand from our synthesis of the A compound, **90**. Thus, in the case at hand, cleavage of the C5 TPS ether generated the diol **103**, which upon resilylation of

Scheme 16[a]

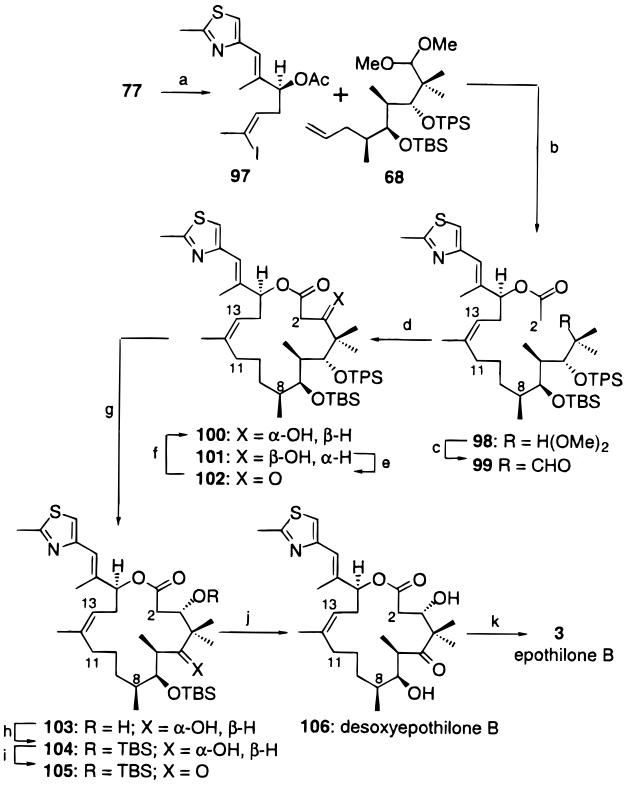


[a] (a) KHMDS, THF, −78 °C, 0.001M (51%, 6:1 α/*β*); (b) Dess−Martin periodinane, CH_2Cl_2, rt; (c) $NaBH_4$, MeOH, THF, −78 °C → rt (80% for two steps); (d) HF·pyridine, pyridine, THF, rt (99%); (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, −30 °C (93%); (f) Dess−Martin periodinane, CH_2Cl_2, rt (84%); (g) 2,4,6-trichlorobenzoyl chloride, TEA, 4-DMAP, toluene, rt (88%); (h) HF·pyridine, THF, rt (99%); (i) 3,3-dimethyldioxirane, CH_2Cl_2, −35 °C (49%; ≥16:1 mixture of diastereomers in favor of **2**); TPS = $SiPh_3$; TBS = Si*t*-BuMe_2.

(46) Molecular modeling was performed with MacroModel version 5.5; The MMZ force field was used with a Monte Carlo random walk conformational search.

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

Scheme 17[a]



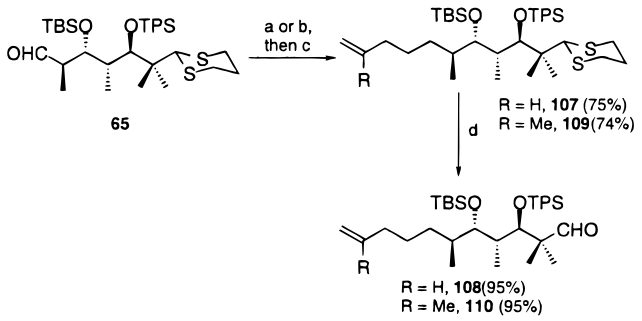
[a] (a) (i) OsO_4, NMO, $(CH_3)_2CO/H_2O$, 0 °C; (ii) $Pb(OAc)_4$, Na_2CO_3, C_6H_6, 0 °C → rt; (iii) $Ph_3P{=}C(I)CH_3$, THF, −20 °C (43% from **77**; *Z* geometrical isomer only); (b) **68**, 9-BBN, THF, rt; then **97**, $PdCl_2(dppf)_2$, Cs_2CO_3, Ph_3As, DMF/H_2O, rt (77%); (c) *p*-TsOH, dioxane/H_2O, 55 °C (71%); (d) KHMDS, THF, −78 °C (60%; **100**:**101**/2.1:1); (e) Dess−Martin periodinane, CH_2Cl_2, rt; (f) $NaBH_4$, MeOH, rt (67% for two steps); (g) HF·pyridine, pyridine, THF, rt (94%); (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, −30 °C (89%); (i) Dess−Martin periodinane, CH_2Cl_2, rt (87%); (j) HF·pyridine, THF, rt (92%); (k) 3,3-dimethyldioxirane, CH_2Cl_2, −50 °C (97%; ≥20:1 mixture of diastereomeric *cis*-epoxides in favor of **3**); NMO = *N*-methylmorpholine *N*-oxide; 9-BBN = 9-borabicyclo[3.3.1]nonane; dppf = 1,1′-bis(diphenylphosphino)ferrocene; KHMDS = $KN(SiMe_3)_2$; TPS = $SiPh_3$; TBS = Si*t*-$BuMe_2$.

the exposed C3 hydroxyl group gave the product **104**. Oxidation of the C5 alcohol led to desoxyepothilone B *bis* (TBS) ether (compound **105**). Cleavage of the silyl blocking groups at C3 and C7 was accomplished, as shown, thereby allowing us to reach desoxyepothilone B (**106**). For obvious reasons, we turned to the use of dimethyl dioxirane in the oxidation of this compound. Happily, *this reaction was even more regio- and stereoselective, producing epothilone B (**3**) identical in all respects with an authentic sample, kindly provided by Professor Höfle*.

The Second Generation Ring-Closing Olefin Metathesis Strategy (Approach IV, Scheme 1)

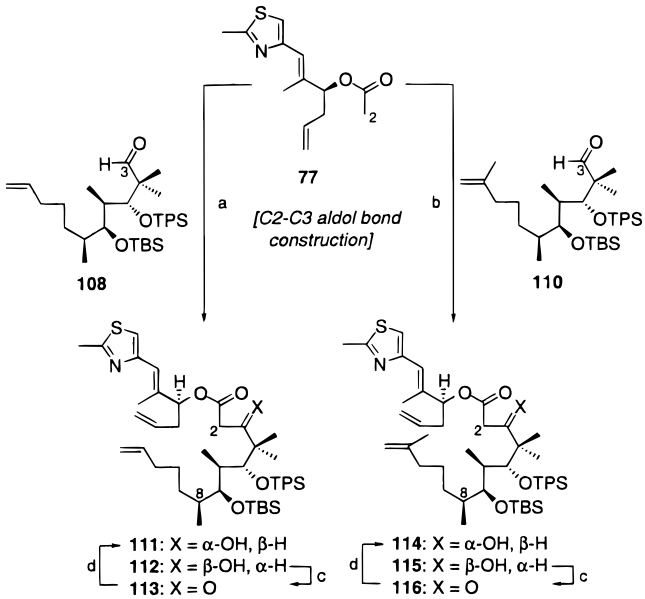
Even though we had accomplished our primary goals of synthesizing epothilones A and and B, it was still of interest to reinvestigate the possibility of intramolecular olefin metathesis.[8d] However, in this case we would be focusing on elaborating the C11−C12 double bond in the course of the metathesis reaction. Since we had known that epoxidation of this double bond could be conducted in a highly stereoselective and favorable direction, we were obviously more disposed to consider syntheses where this double bond would be elaborated in the decisive cyclization step. Toward this end, we returned to thioacetal aldehyde **65**. This compound was itself converted to product **107** through butenylation and deoxygenation at C9 (see Scheme 18). The C3 aldehyde function could be liberated by cleavage of the dithiane, as indicated, to provide aldehyde **108**.

Scheme 18[a]



[a] (a) 3-Butenylmagnesium bromide, Et_2O, −78 → 0 °C; (b) 4-iodo-2-methyl-1-butene, *t*-BuLi (2.1 equiv), Et_2O, −78 → −50 °C; then **65**, Et_2O, −78 → 0 °C; (c) (i) thiocarbonyl diimidazole, 4-DMAP, 95 °C; (ii) *n*-Bu_3SnH, AIBN, C_6H_6, 80 °C; (d) (i) $(CF_3CO_2)_2IC_6H_5$, MeOH/THF, rt; (ii) *p*-TsOH, dioxane/H_2O, 50 °C.

Scheme 19[a]



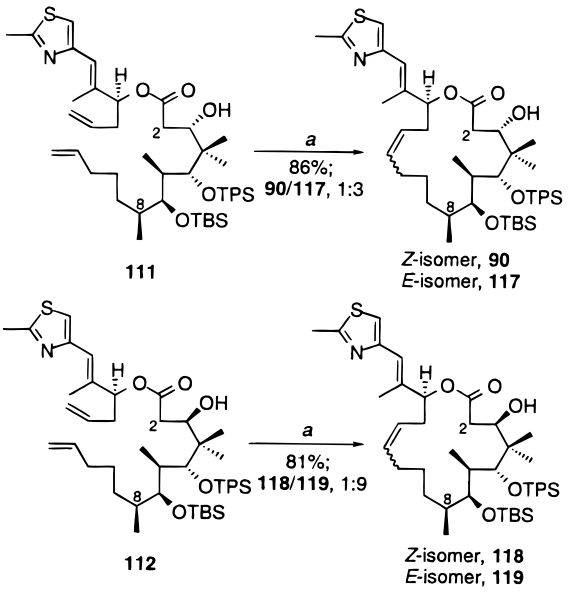
[a] (a) LDA, THF, −78 °C (65%; **111**:**112**/1:1); (b) LDA, THF, −78 °C (70%; **114**:**115**/*ca*. 1:1); (c) Dess−Martin periodinane, CH_2Cl_2, rt; (d) $NaBH_4$, MeOH, THF, −78 °C → rt (*ca*. 92% for two steps).

In order to probe the applicability of such a construction to the total synthesis of epothilone B, we returned to aldehyde dithiane **65**. The latter was converted to compound **109** by isobutenylation and deoxygenation. Once again, cleavage of the dithiane linkage provided aldehyde **110**.

With compounds **77** as well as **108** and **110** in hand, assembly of substrates for RCM were possible. To simplify the initial merger step, we turned, once again, to an intermolecular aldol condensation of the ester enolate, derived from **77**, with aldehydes **108** and **110** (see Scheme 19). In practice, the coupling could be readily conducted to give a mixture of stereoisomers at C3. The product, bearing the *S* configured alcohol, could be separated. The *R*-alcohol, in each case, was recycled through an oxidation/reduction sequence as shown.

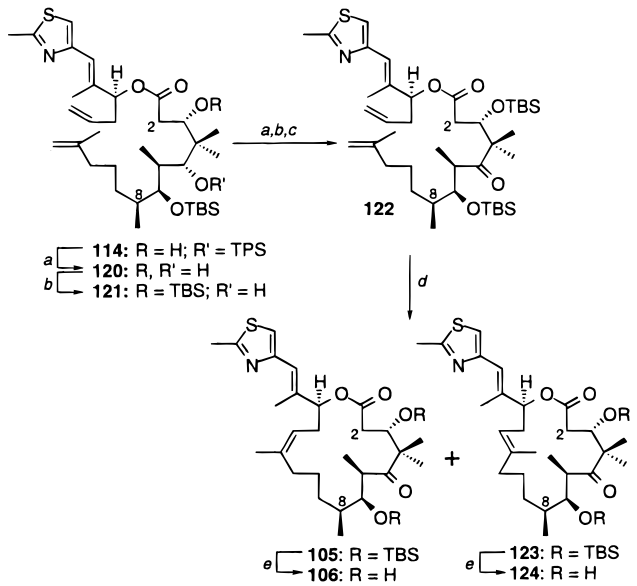
Indeed, with increased spacing between the C12 olefin and the branched positions of the polypropionate domain (see compound **111**), olefin metathesis chemistry proved to be successful.[8d] Cyclizations were conducted as described in Scheme 20 for compounds **111** and **112**. In these studies, we took recourse to both the ruthenium-based catalyst of Grubbs[12b] and the molybdenum-based catalyst of Schrock[12a] to mediate metathesis. In our work, the ruthenium-based system proved to be generally more efficacious for constructing the disubstituted double bonds with the properly configured (3*S*) alcohol.

Scheme 20[a]



[a] (a) $RuBnCl_2(PCy_3)_2$, 50 mol %, C_6H_6, 0.001 M rt, 24 h.

Scheme 21[a]

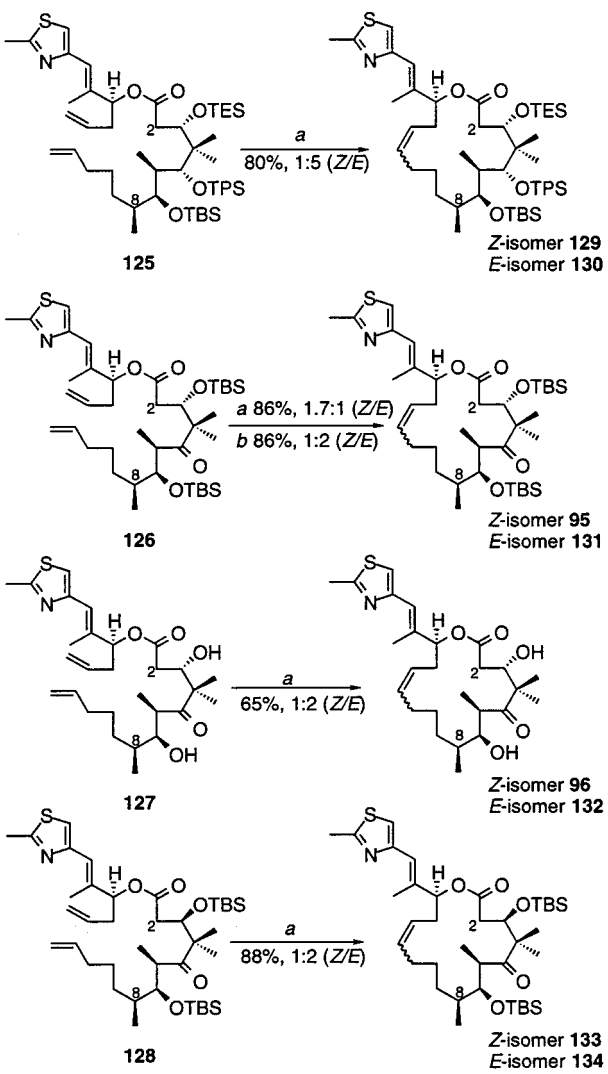


[a] (a) HF·pyr, pyr, THF, rt (93%); (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −30 °C (85%); (c) Dess−Martin periodinane, CH_2Cl_2 (94%); (d) $Mo(CHMe_2Ph)(N(2,6\text{-}(i\text{-}pr)_2C_6H_3))(OCMe(CF_3)_2)_2$ 20 mol %, C_6H_6, 0.001 M, 55 °C, 2 h, 86%, **105**/**123** 1:1; (e) HF·pyr, THF, rt, 2 h, 90%.

Although the yields of cyclized products were generally quite good, it was unfortunate that the resultant C12−C13 olefins were produced as a serious mixtures of *E*/*Z* isomers (**90**:**117**). The *Z* compounds could be correlated with earlier intermediates arising from the previously described *B*-alkyl Suzuki pathway. The *E* compounds were independently deprotected and converted to the corresponding *E* desoxyepothilone systems, as shown in Scheme 23 (*vide infra*).

Olefin metathesis was also attempted on compound **114** (see Scheme 21).[8e] In the event, this substrate failed to cyclize with the ruthenium-based system described by Grubbs,[12b] or the molybdenum based catalyst described by Schrock.[12a] However, when compound **122**, derived from **124** as shown, was treated with the Schrock catalyst, cyclization was successful producing a 1:1 mixture of *Z* and *E* isomers **105** and **123**.[8e] These products were independently processed, as shown, leading to the previously encountered *Z*-desoxyepothilone B (**106**) and *E*-desoxyepothilone B (**124**).

Scheme 22[a]

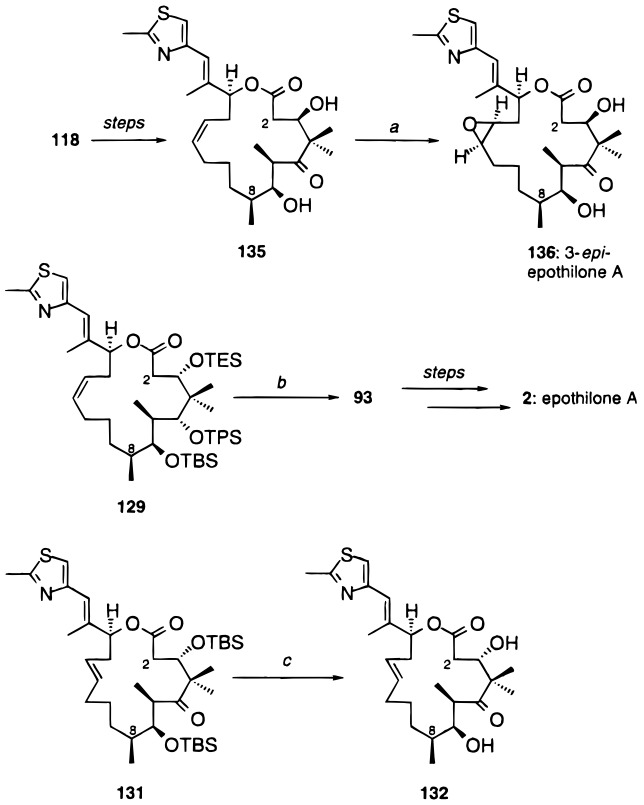


[a] (a) $RuBnCl_2(PCy_3)_2$, 50 mol %, C_6H_6, 0.001 M, rt, 4 h; (b) $Mo(CHMe_2Ph)(N(2,6\text{-}(i\text{-}pr)_2C_6H_3))(OCMe(CF_3)_2)_2$ 20 mol %, C_6H_6, 0.001 M, rt, 1 h, 86%.

As seen with substrates **111** and **112**, a point mutation of stereochemistry at C3 had tilted the process toward substantial stereoselectivity. Unfortunately, it was the 3-*epi* substrate (**112**) in which a high stereochemical margin was obtained, and, in fact, the unnatural *E*-double bond isomer was favored. We then mounted a considerable effort toward improving the stereoselectivity of the olefin metathesis reaction with the goal of reaching the natural *Z* series from the "natural" 3*S* carbinol precursor.

Unfortunately, no hypothesis emerged to guide our experiments in crafting the remote functions in the C3−C7 sector. Accordingly, we took recourse to intermediates that were accessible from the synthetic studies already in place. In this respect, we had occasion to prepare compounds **125** to **128** and to study their olefin metathesis.[8d] Using our collection of substrates, we were able to observe effects on the stereochemical course of olefin metatheses as a function of the nature of the substituents along the acyl chain. However, the only decisive perturbations favoring significant stereoselectivity were in the transformations of **112** to **118** and **119** (Scheme 20) as well as **125** to **129** and **130** (Scheme 22), each of which resulted in the predominant formation of the unnatural *E* compounds.

Scheme 23[a]



[a] (a) 3,3-Dimethyldioxirane, CH_2Cl_2, −30 °C, 70%, 3:1 β/α; (b) HF·pyr, THF, rt, 93%; (c) HF·pyr, pyr, THF, rt, 92%.

As is seen from the data, there is a sensitivity of olefin geometry to variation of substituents at even some distance from the terminal vinyl groups. Presumably, the consequence of these structural permutations reflect subtle effects on the sense of presentation of the vinyl group of one sector to the terminal metal−carbene complex[12] derived from the other sector. In this connection, it is also interesting that the olefin geometry ratio is also sensitive to the catalyst employed (see ratio of **95**:**131**) when this question was probed.

Compounds **118**, **129**, and **131** were processed as shown to afford 3-*epi*-epothilone A (**136**), epothilone A, and (*E*)-12,13-desoxyepothilone A (**132**) (Scheme 23). The results of evaluations of the biological profiles of these epothilone analogs have been published elsewhere[8d,e] and provide a basis for the development of new classes of structurally simpler and synthetically more accessible agents.

Summary

Several total syntheses of epothilones A and B have been described herein. These constructions involved union at either the C11−C12 bond (*B*-alkyl Suzuki coupling) or the C12−C13 bond (ring-forming olefin metathesis). Our routes differ from all others in several important respects. First, the stereochemistry of the polypropionate region accrues from the LACDAC reaction[19] and cyclic matrices elaborated therefrom. *Ultimately, all sterochemistry in this domain is induced from the single chiral center, readily derivable "Roche aldehyde" derivative* ***35*** *using sound principles formulated in our group many years ago*.[19]

Of particular importance is that C8 is incorporated in this dynamic. By contrast, the other syntheses have taken recourse to separate syntheses of α-methyl aldehydes, using chiral auxiliaries, to "deliver" the C8 chiral center to the synthetic pool. Furthermore, our syntheses uniquely provide strict control over the geometry of the double bonds of epothilone B as well as A, through adaptations of the B-alkyl Suzuki reaction. Recourse to the separation of *E*:*Z* isomer mixtures arising from olefin metathesis is, at least in our hands, seriously disabling in terms of throughput of significant amounts of material.

A stereoselective conversion of desoxyepothilone A and B to the epoxides in the natural series has been accomplished with the use of dimethyldioxirane (see conversion of **96** → **2** and **106** → **3**). Also illustrated in these studies were the power of catalytic asymmetric allylation (**10** → **76**), the flexibility of glycidol as a multifacated member of the chiral pool (see **69** → **75**), and the power of the LACDAC reaction in assembling polypropionate frameworks (see **35** + **36** → **45**, **68** and **85**). The rather novel cyclopropanation of a glycal (**38** → **39**) followed by oxidative solvolysis (**39** → **40**) and reduction (**40** → **41**) as a route to the introduction of quaternary branching is also deserving of attention. Given the generality of the issues which have been addressed, it is likely that the lessons garnered here would find application to other problems in organic synthesis.

Experimental Section

General. All commercial materials were used without further purifications unless otherwise noted. The following solvents were distilled under positive pressure of dry nitrogen immediately before use: THF and diethyl ether from sodium/potassium−benzophenone ketyl, CH_2Cl_2, toluene, and benzene from CaH_2. All the reactions were performed under N_2 atmosphere. NMR (^{1}H, ^{13}C) spectra were recorded on Bruker AMX-400 MHz, Bruker Avance DRX-500 MHz, referenced to TMS (^{1}H-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 of 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 pathlength 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 F_{254} plates (0.25 mm). Compounds were visualized by dipping the plates in a cerium sulfate−ammonium molybdate 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). Melting points are obtained with Electrothermal melting point apparatus (series no. 9100) and are uncorrected.

Preparation of Compound 68. A solution of (methoxymethyl)-triphenylphosphonium chloride (2.97 g, 8.55 mmol) in THF (25 mL) at 0 °C was treated with KO^{t}Bu (8.21 mL, 1 M in THF, 8.1 mmol). The mixture was stirred at 0 °C for 30 min. Aldehyde **65** (3.10 g, 4.07 mmol) in THF (10 mL) was added, and the resulting solution was allowed to warm to rt and stirred at this temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (40 mL), and the resulting solution was extracted with Et_2O (3 × 30 mL). The combined Et_2O fractions were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel eluting with 5% Et_2O in hexanes to yield the methyl enol ether **66** (2.83 g, 86%) as a colorless foam.

To a solution of the methyl enol ether **66** (2.83 g, 3.50 mmol) in dioxane/H_2O (9:1, 28 mL) was added pTSA·H_2O (1.0 g, 5.30 mmol), and the resulting mixture was heated to 50 °C for 2 h. After cooling to rt, the mixture was diluted with Et_2O (50 mL) and washed successively with saturated aqueous $NaHCO_3$ (15 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated to provide the corresponding aldehyde (2.75 g, 99%) as a colorless foam: $[\alpha]_D$ = +1.74 (*c* = 0.77, $CHCl_3$); IR (film) 2929, 1725, 1428, 1253, 1115, 1039 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.31 (d, *J* = 3.4 Hz, 1 H), 7.68 (dd, *J* = 7.8, 1.4 Hz, 6 H), 7.45−7.37 (band, 9 H), 4.60 (d, *J* = 6.8 Hz, 1 H), 4.20 (s, 1 H), 3.51 (d, *J* = 6.7 Hz, 1 H), 2.68 (d, *J* = 14.0 Hz, 1 H), 2.60 (d, *J* = 13.5 Hz, 1 H), 2.37 (m, 1 H), 2.24 (m, 1 H), 1.90 (m, 1 H), 1.81 (m, 2 H), 1.68 (m, 2 H), 1.52 (m, 1 H), 1.32 (s, 3 H), 1.14−1.03 (band, 6 H), 0.86 (s, 9 H), 0.75 (d, *J* = 6.9 Hz, 3 H), −0.03 (s, 3 H), −0.06 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.8, 136.0, 134.6, 130.1, 128.0, 77.6, 76.2, 59.5, 45.1, 44.7, 43.8,

31.8, 30.9, 30.5, 26.3, 25.9, 22.5, 20.9, 18.6, 17.9, 14.7, −3.0, −3.5; HRMS calcd for $C_{39}H_{56}O_3S_2Si_2$: 692.3210; found: 731.2828 (M + K).

Methyltriphenylphosphonium bromide (1.98 g, 5.54 mmol) in THF (50 mL) at 0 °C was treated with lithium bis(trimethylsilyl)amide (5.04 mL, 1 M in THF, 5.04 mmol), and the resulting solution was stirred at 0 °C for 30 min. The aldehyde (2.00 g, 2.52 mmol), prepared above, in THF (5.0 mL) was added, and the mixture was allowed to warm to room temperature and stirred at this temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (15 mL) and extracted with Et_2O (3 × 20 mL). The combined Et_2O fractions were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel eluting with 5% Et_2O in hexanes to afford compound **67** (1.42 g, 76%) as a colorless foam.

A solution of the dithiane **67** (1.0 g, 1.34 mmol), prepared above, in MeOH/THF (2:1, 13 mL) was treated with [bis(trifluoroacetoxy)-iodobenzene] (0.865 g, 2.01 mmol) at rt. After 15 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (25 mL). The mixture was extracted with Et_2O (3 × 25 mL), and the combined Et_2O fractions were washed once with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel eluting with 5% Et_2O in hexanes provided compound **68** (0.865 g, 92%) as a colorless foam: $[\alpha]_D = +1.74$ ($c = 0.77$, $CHCl_3$); IR (film) 1428, 1252, 1114, 1075, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.61 (dd, $J = 7.9$, 1.4 Hz, 6 H), 7.38 (s, 9 H), 5.47 (m, 1 H), 4.87 (d, $J = 10.0$ Hz, 1 H), 4.76 (d, $J = 15.9$ Hz, 1 H), 4.30 (d, $J = 3.7$ Hz, 1 H), 3.95 (s, 1 H), 3.56 (dd, $J = 7.5$, 1.4 Hz, 1 H), 3.39 (s, 3 H), 2.84 (s, 3 H), 2.02 (m, 1 H), 1.64 (m, 2 H), 1.34 (m, 1 H), 1.11 (s, 3 H), 1.02 (d, $J = 7.4$ Hz, 3 H), 0.90 (s, 3 H), 0.85 (s, 9 H), 0.62 (d, $J = 6.8$ Hz, 3 H), −0.04 (s, 3 H), −0.05 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.3, 135.8, 135.0, 129.9, 127.8, 114.9, 110.5, 60.1, 55.6, 46.5, 43.9, 36.8, 34.2, 26.3, 19.6, 18.6, 17.1, 16.16, 13.9, −2.9, −3.8; HRMS calcd for $C_{39}H_{58}O_4Si_2$: 646.3873; found: 685.3491 (M + K).

Preparation of Compound 76. A mixture of (*S*)-(−)-1,1′-bi-2-naphthol (0.259 g, 0.91 mmol), Ti(O-*i*-Pr)$_4$ (261 mL; 0.90 mmol), and 4 Å sieves (3.23 g) in CH_2Cl_2 (16 mL) was heated at reflux for 1 h. The mixture was cooled to rt, and aldehyde **10** was added. After 10 min, the suspension was cooled to −78 °C, and allyltri-*n*-butyltin (3.60 mL, 11.6 mmol) was added. The reaction mixture was stirred for 10 min at −78 °C and then placed in a −20 °C freezer for 70 h. Saturated aqueous $NaHCO_3$ solution (2 mL) was added, and the mixture was stirred for 1 h, poured over Na_2SO_4, and then filtered through a pad of $MgSO_4$ and Celite. The crude material was purified by flash chromatography (hexanes/ethyl acetate, 1:1) to give alcohol **76** as a yellow oil (1.11 g, 60%): $[\alpha]_D = -15.9$ (*c* 4.9, $CHCl_3$); IR (film) 3360, 1641, 1509, 1434, 1188, 1017, 914 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 25 °C) δ 6.92 (s, 1 H), 6.55 (s, 1 H), 5.82 (m, 1 H), 5.13 (dd, $J = 17.1$, 1.3 Hz, 1 H), 5.09 (d, $J = 10.2$ Hz, 1 H), 4.21 (t, $J = 6.0$ Hz, 1 H), 2.76 (br s, 1 H), 2.69 (s, 3 H), 2.40 (m, 2 H), 2.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ 164.5, 152.6, 141.5, 134.6, 119.2, 117.6, 115.3, 76.4, 39.9, 19.0, 14.2; HRMS calcd for $C_{11}H_{15}NOS$: 209.0874 found: 209.0872 (M + H).

Preparation of Compound 77. To a solution of alcohol **76** (0.264 g; 1.26 mmol) in CH_2Cl_2 (12 mL) were added 4-DMAP (0.015 g, 0.098 mmol), Et_3N (0.45 mL; 3.22 mmol), and Ac_2O (0.18 mL; 1.90 mmol). After 2 h, the reaction was quenched by the addition of H_2O (20 mL) and extracted with EtOAc (4 × 20 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated. Flash chromatography on SiO_2 (EtOAc/hexanes, 1:3) afforded acetate **77** as a yellow oil (0.302 g; 96%): $[\alpha]_D = -40.0$ (*c* 7.3, $CHCl_3$); IR (film) 1738, 1505, 1436, 1370, 1236, 1019 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 25 °C) δ 6.95 (s, 1 H), 6.52 (s, 1 H), 5.72 (m, 1 H), 5.33 (t, $J = 6.6$ Hz, 1 H), 5.10 (ddd, $J = 17.1$, 3.1, 1.5 Hz, 1 H), 5.07 (ddd, $J = 10.2$, 3.3, 1.7 Hz, 1 H), 2.70 (s, 3 H), 2.48 (dt, $J = 5.9$, 1.3 Hz, 2 H), 2.08 (s, 3 H), 2.07 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ 170.1, 164.5, 152.4, 137.0, 133.4, 120.6, 117.6, 116.2, 77.9, 37.5, 21.1, 19.1, 14.7; HRMS calcd for $C_{13}H_{17}O_2NS$: 251.0980; found: 251.0983 (M^+).

Preparation of Compound 75. To a solution of acetate **77** (0.099 g; 0.39 mmol) in acetone (10 mL) at 0 °C were added H_2O (4 drops), OsO_4 (2.5% wt in butyl alcohol; 0.175 mL; 0.018 mmol), and *N*-methylmorpholine *N*-oxide (0.069 g; 0.59 mmol). The mixture was stirred at 0 °C for 2 h and then quenched with saturated aqueous Na_2SO_3 solution (10 mL). The solution was poured into H_2O (10 mL) and extracted with EtOAc (8 × 10 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated.

To a solution of the crude diol in THF/H_2O (4 mL, 3:1) was added $NaIO_4$ (0.260 g; 1.22 mmol). After 1.25 h, the reaction mixture was quenched with H_2O (10 mL) and concentrated. The aqueous layer was extracted with EtOAc (5 × 10 mL) and dried over $MgSO_4$. Flash chromatography (SiO_2, EtOAc/hexanes, 1:1) on a short pad of silica gave the crude aldehyde **78** as a yellow oil (0.080 g) which contained unidentified byproduct(s). This mixture was used without further purification.

To a solution of $(Ph_3P^+CH_2I)I^-$ (0.100 g; 0.19 mmol) in THF (0.25 mL) at rt was added sodium bis(trimethylsilyl)amide (1 M soln in THF, 0.15 mL, 0.15 mmol). To the resulting solution at −78 °C were added HMPA (0.022 mL; 0.13 mmol) and the crude aldehyde **78** from the previous step (0.016 g) in THF (0.25 mL). The reaction mixture was then stirred at rt for 30 min. After the addition of saturated aqueous NH_4Cl (10 mL), and the solution was extracted with EtOAc (4 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by preparative thin-layer chromatography (prep-TLC) (EtOAc/hexanes, 2:3) to give the vinyl iodide **75** as a yellow oil (0.014 g; 50% for three steps).

Preparation of Compound 80. The acetal **68** (0.930 g, 1.44 mmol) was dissolved in dioxane/H_2O (9:1, 20 mL), and *p*TSA·H_2O (0.820 g, 4.32 mL) was added. The mixture was heated at 55 °C for 2 h. After cooling to rt, the solution was poured into Et_2O (200 mL) and washed once with saturated aqueous $NaHCO_3$ solution (30 mL) and once with brine (30 mL) and dried over anhydrous $MgSO_4$. Purification by flash chromatography on silica gel eluting with hexanes/ethyl acetate (9:1) gave 0.702 g (81%) of the aldehyde **80** as a white foam: $[\alpha]_D = -12.8$ ($c = 3.4$, $CHCl_3$); IR (film) 2929, 1722, 1472, 1429, 1256, 1115, 1059 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.76 (s, 1 H), 7.71 (d, $J = 6.4$ Hz, 6 H), 7.42 (m, 9 H), 5.49 (m, 1 H), 4.87 (m, 1 H), 4.75 (m, 1 H), 4.08 (d, $J = 1.6$ Hz, 1 H), 3.56 (dd, $J = 1.6$, 8.7 Hz, 1 H), 2.18 (m, 1 H), 1.70 (m, 1 H), 1.46 (m, 2 H), 1.10 (s, 3 H), 0.89 (d, $J = 6.4$ Hz, 3 H), 0.79 (s 9 H), 0.60 (d, $J = 6.5$ Hz, 3 H), −0.8 (s, 3 H), −0.83 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.5, 137.6, 135.6, 134.2, 130.0, 127.9, 115.4, 80.7, 76.4, 51.7, 43.5, 38.2, 34.9, 26.1, 20.9, 20.1, 18.5, 15.5, 12.9, −3.3, −3.9; HRMS calcd for $C_{37}H_{52}O_3S_2$: 600.3455; found: 623.3333 (M + Na).

Preparation of Compound 81. The aldehyde **80** (0.702 g, 1.17 mmol) was dissolved in THF (50 mL), and *tert*-butyl acetate (1.26 mL, 9.36 mmol) was added. The solution was cooled to −78 °C, and LDA (2.0 M soln, 3.51 mL, 7.02 mmol) was added. After 20 min, the reaction was quenched with MeOH (10 mL) and H_2O (100 mL). The mixture was extracted with Et_2O (3 × 100 mL). The combined organics were washed once with brine (30 mL) and dried over anhydrous $MgSO_4$. The crude mixture contained a 2:1 ratio (**81**:**82**) of diastereomers. Purification was done by flash chromatography on silica gel eluting with hexanes/ethyl acetate (19:1) to give 0.527 g (63%) of the desired isomer **81** as a white foam: $[\alpha]_D = -11.2$ ($c = 1.4$, $CHCl_3$); IR (film) 3493, 2929, 1710, 1429, 1153, 1115, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35 (dd, $J = 1.2$, 7.6 Hz, 6 H), 7.38 (m, 9 H), 5.50 (m, 1 H), 4.86 (d, $J = 9.5$ Hz, 1 H), 4.73 (d, $J = 17.1$ Hz, 1 H), 4.09 (d, $J = 3.5$ Hz, 1 H), 3.93 (br d, $J = 10.0$ Hz, 1 H), 3.75 (d, $J = 7.1$ Hz, 1 H), 3.34 (d, $J = 2.6$ Hz, 1 H), 2.29 (dd, $J = 2.5$, 16.4 Hz, 1 H), 2.18 (m, 2 H), 1.67 (m, 2 H), 1.44 (m, 1 H), 1.41 (s, 9 H), 1.05 (d, $J = 7.4$ Hz, 3 H), 0.95 (s, 3 H), 0.86 (s, 12 H), 0.64 (d, $J = 6.7$ Hz, 3 H), −0.03 (s, 3 H), −0.05 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.2, 138.0, 136.7, 134.8, 129.8, 127.6, 115.0, 81.2, 78.8, 75.9, 71.3, 44.4, 43.5, 38.0, 37.2, 34.9, 28.0, 26.3, 21.2, 20.5, 18.8, 16.0, 14.1, −3.0, −4.1; HRMS calcd for $C_{43}H_{64}O_5Si_2$: 572.4293; found: 573.4390 (M + H).

Preparation of Compound 83. The alcohol **81** (0.110 g, 0.0153 mmol) was treated with pyridine buffered HF·pyridine solution (3.0 mL) (stock solution was prepared from 20 mL of THF, 11.4 mL of pyridine, and 4.2 g of hydrogen fluoride−pyridne (Aldrich Co.)) at rt and stirred for 2 h. The reaction mixure was poured into saturated aqueous $NaHCO_3$ (50 mL) and extracted with ether (3 × 50 mL). The organic layer was washed in sequence with saturated aqueous $CuSO_4$ (3 × 10 mL) and saturated aqueous $NaHCO_3$ (10 mL) and then dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by

flash chromatography on silica gel eluting with hexanes/ethyl acetate (7:1) to give the corresponding diol (0.070 g, 98%) as a white foam.

The diol (0.231 g, 0.48 mmol) was dissolved in CH_2Cl_2 (5.0 mL) and cooled to −30 °C. 2,6-Lutidine (0.168 mL, 1.44 mmol) was added followed by TBSOTf (0.131 mL, 0.570 mmol). After 1 h at −30 °C, the reaction was poured into Et_2O (300 mL), washed once with 1 N HCl (50 mL), once with saturated aqueous $NaHCO_3$ (50 mL), and once with brine (30 mL), and dried over anhydrous $MgSO_4$. Purification by flash chromatography on silica gel eluting with hexanes/ethyl acetate (20:1) gave alcohol **83** (0.276 g, 96%) as a clear oil: $[\alpha]_D = -5.4$ ($c = 0.9$, $CHCl_3$); IR (film) 3466, 2930, 1728, 1462, 1369, 1254, 1156 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.76 (m, 1 H), 4.99 (m, 2 H), 4.15 (t, $J = 4.4$ Hz, 1 H), 3.91 (d, $J = 4.0$ Hz, 1 H), 3.60 (bs, 1 H), 3.75 (dd, $J = 3.3$, 7.8 Hz, 1 H), 2.81 (dd, $J = 4.7$, 17.3 Hz, 1 H), 2.41 (m, 1 H), 2.22 (dd, $J = 4.2$, 17.3 Hz, 1 H), 1.88 (m, 1 H), 1.73 (m, 2 H), 1.45 (s, 9 H), 0.94 (d, $J = 7.0$ Hz, 3 H), 0.92 (s, 3 H), 0.90 (s, 9 H), 0.89 (s, 12 H), 0.85 (s, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.1, 138.2, 115.5, 80.8, 77.7, 74.4, 46.3, 43.7, 40.9, 38.7, 37.9, 39.7, 28.1, 26.2, 26.0, 19.5, 19.2, 18.5, 18.1, 16.9, 15.1, −3.9, −4.1, −4.2, −4.9; HRMS calcd for $C_{31}H_{64}O_5Si_2$: 572.4293; found: 573.4390 (M + H).

Preparation of Compound 85. The alcohol **83** (0.275 g, 0.46 mmol) was dissolved in CH_2Cl_2 (5.0 mL), and Dess−Martin periodinane (0.292 g, 0.690 mmol) was added. After 2 h, a 1:1 mixture of saturated aqueous $NaHCO_3$/saturated aqueous $Na_2S_2O_3$ (2.0 mL) was added. After 10 min, the mixture was poured into Et_2O (40 mL), and the organic layer was washed with brine (3.0 mL) and dried over anhydrous $MgSO_4$. Purification by flash chromatography on silica gel eluting with hexanes/ethyl acetate (19:1) gave ketone **84** (0.244 g, 89%) as a clear oil.

The olefin **84** (0.420 g, 0.76 mmol) was dissolved in CH_2Cl_2 (10 mL) and treated successively with 2,6-lutidine (1.75 mL, 15 mmol) and TBSOTf (1.72 mL, 7.5 mmol). After 7 h, the reaction was poured into Et_2O (150 mL), washed successively with 0.2 N HCl (25 mL) and brine (20 mL), and dried over anhydrous $MgSO_4$. The residue was purified by flash chromatography on a short pad of silica gel with fast elution with hexanes/ethyl acetate (20:1) to give TBS ester **85** (0.611 g, 93%) as a clear oil. The purification must be done quickly to avoid hydrolysis of the silyl ester: $[\alpha]_D = -35.4$ ($c = 0.4$, $CHCl_3$); IR (film) 2930, 1730, 1692, 1472, 1367, 1253, 1155, 1084 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.73 (m, 1 H), 4.97 (m, 2 H), 4.33 (dd, $J = 3.8$, 5.5 Hz, 1 H), 3.78 (dd, $J = 1.9$, 7.3 Hz, 1 H), 3.19 (m, 1 H), 2.53 (dd, $J = 3.8$, 17.3 Hz, 1 H), 2.25 (m, 2 H), 1.85 (m, 1 H), 1.40 (m, 1 H), 1.24 (s, 3 H), 1.07 (s, 3 H), 1.04 (d, $J = 6.8$ Hz, 3 H), 0.92 (s, 12 H), 0.91 (s, 9 H), 0.87 (s, 9 H), 0.26 (s, 3 H), 0.26 (s, 3 H), 0.10 (s, 3 H), 0.06 (s, 6 H), 0.05 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 217.1, 170.6, 137.2, 115.0, 79.8, 77.1, 73.2, 52.9, 45.0, 40.8, 37.5, 34.7, 27.5, 25.6, 25.4, 22.4, 19.7, 17.9, 17.6, 17.3, 14.9, −4.2, −4.3, −4.9, −5.4.

Preparation of Compound 87. To a solution of olefin **85** (0.053 g, 0.081 mmol) in THF (0.8 mL) was added 9-BBN (0.5 M soln in THF, 0.323 mL, 0.162 mmol). In a separate flask, the iodide **75** (0.036 g, 0.097 mmol) was dissolved in DMF (1.0 mL). Cs_2CO_3 (0.053 g, 0.162 mmol) was then added with vigorous stirring followed by sequential addition of Ph_3As (0.0025 g, 0.0081 mmol), $PdCl_2(dppf)_2$ (0.0067 g, 0.0081 mmol), and H_2O (0.052 mL, 2.91 mmol). After 4 h, the borane in THF was added to the iodide mixture in DMF. The reaction quickly turned dark brown in color and slowly became pale yellow after 2 h. The reaction was then poured into saturated aqueous NH_4Cl (10.0 mL) and extracted with $CHCl_3$ (3 × 30 mL). The combined organics were washed with H_2O (2 × 50 mL) and once with brine (50 mL) and dried over anhydrous $MgSO_4$. Purification by flash chromatography on silica gel eluting with hexanes/ethyl acetate (4:1 → 3:1) gave 0.036 g (56%) of the coupled product **87** as a pale yellow oil: $[\alpha]_D = -29.2$ ($c = 0.3$, $CHCl_3$); IR (film) 3500−2600, 1738, 1710, 1691, 1236, 988 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.95 (s, 1 H), 6.59 (s, 1 H), 5.49 (m, 1 H), 5.31 (m, 1 H), 5.25 (dd, $J = 5.7$, 7.7 Hz, 1 H), 4.38 (dd, $J = 3.8$, 6.5 Hz, 1 H), 3.78 (dd, $J = 1.9$, 6.7 Hz, 1 H), 3.13 (m, 1 H), 2.71 (s, 3 H), 2.49 (m, 2 H), 2.42 (m, 1 H), 2.31 (dd, $J = 6.5$, 16.3 Hz, 1 H), 2.07 (s, 3 H), 2.04 (s, 3 H), 1.95 (m, 1 H), 1.89 (m, 2 H), 1.48 (m, 3 H), 1.21 (s, 3 H), 1.15 (m, 2 H), 1.12 (s, 3 H), 1.06 (d, $J = 6.9$ Hz, 3 H), 0.90 (s, 12 H), 0.88 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 217.9, 176.7, 170.2, 164.9, 152.2, 137.6, 132.7, 123.9, 120.3, 115.9, 78.4, 73.6, 53.5, 45.0, 40.1, 38.8, 31.0, 30.6, 27.9, 27.7, 26.2, 26.0, 23.5, 21.9, 21.2, 19.2, 18.9, 18.4, 18.1, 17.5, 15.7, 14.9, −3.7, −3.9, −4.3, −4.7; HRMS calcd for $C_{40}H_{71}O_6NSSi_2$: 765.4490; found: 766.4571 (M + H).

Preparation of Compound 88. The acetate **87** (0.035 g, 0.044 mmol) was dissolved in MeOH/H_2O (2:1, 1.5 mL), and K_2CO_3 (0.050 g) was added. After 3 h, the reaction was diluted with saturated aqueous NH_4Cl (5.0 mL) and extracted with $CHCl_3$ (5 × 10 mL). The hydroxy acid **88** was purified by flash chromatography on silica gel eluting with hexanes/ethyl acetate (4:1 → 2:1) to give the pure hydroxy acid **88** (0.030 g, 84%): $[\alpha]_D = -19.8$ ($c = 16.5$, $CHCl_3$); IR (film) 3600−2450, 1710, 1700, 1472, 1253, 988 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.95 (s, 1 H), 6.64 (s, 1 H), 5.55 (m, 1 H), 5.42 (m, 1 H), 4.39 (dd, $J = 3.6$, 6.4 Hz, 1 H), 4.15 (t, $J = 6.7$ Hz, 1 H), 3.79 (dd, $J = 1.7$, 6.9 Hz, 1 H), 3.13 (m, 1 H), 2.71 (s, 3 H), 2.49 (dd, $J = 3.6$, 16.4 Hz, 1 H), 2.40 (m, 2 H), 2.31 (dd, $J = 6.5$, 16.4 Hz, 1 H), 2.11 (m, 1 H), 2.01 (s, 3 H), 1.38 (m, 3 H), 1.20 (s, 3 H), 1.15 (m, 2 H), 1.13 (m, 3 H), 1.12 (s, 3 H), 1.05 (d, $J = 6.8$ Hz, 3 H), 0.91 (d, $J = 6.7$ Hz, 3 H), 0.87 (s, 9 H), 0.10 (s, 3 H), 0.06 (s, 6 H), 0.05 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 218.0, 176.2, 165.0, 152.5, 141.8, 133.2, 124.9, 118.9, 115.2, 73.5, 53.6, 44.9, 40.1, 38.9, 33.3, 30.8, 28.0, 27.9, 26.2, 26.0, 23.5, 19.2, 18.9, 18.5, 18.2, 17.4, 15.9, 14.5, −3.7, −3.8, −4.2, −4.6; HRMS calcd for $C_{38}H_{69}O_6NSSi_2$: 723.4384; found: 746.4285 (M + Na).

Preparation of Compound 89. To a solution of the the olefin **68** (0.680 g, 1.07 mmol) in THF (8.0 mL) was added 9-BBN (0.5 M soln in THF, 2.99 mL, 1.50 mmol). In a separate flask, the iodide **75** (0.478 g, 1.284 mmol) was dissolved in DMF (10.0 mL). Cs_2CO_3 (0.696 g, 2.14 mmol) was then added with vigorous stirring followed by sequential addition of Ph_3As (0.034 g, 0.111 mmol), $PdCl_2(dppf)_2$ (0.091 g, 0.111 mmol), and H_2O (0.693 mL, 38.5 mmol). After 4 h, the borane solution was added to the iodide mixture in DMF. The mixture quickly turned dark brown in color and slowly became pale yellow after 2 h. The reaction was then poured into H_2O (100 mL) and extracted with Et_2O (3 × 50 mL). The combined organics were washed with H_2O (2 × 50 mL) and once with brine (50 mL) and dried over anhydrous $MgSO_4$. Purification by flash chromatography on silica gel eluting with hexanes/EtOAc (7:1) gave 0.630 g (75%) of the coupled product **86** as a pale yellow oil. This compound could not be separated completely from residual borane impurities and was taken forward in impure form.

The acetate **86** (0.610 g, 0.770 mmol) was dissolved in dioxane/H_2O (9:1, 15 mL), and *p*TSA·H_2O (0.442 g, 2.32 mmol) was added. The mixture was then heated to 55 °C. After 3 h, the mixture was cooled to rt and poured into Et_2O. This solution was washed once with saturated $NaHCO_3$ (30 mL) and once with brine (30 mL) and dried over anhydrous $MgSO_4$. Purification by flash chromatography on silica gel eluting with hexanes/EtOAc (7:1) gave 0.486 g (85%) of the aldehyde **89** as a pale yellow oil: $[\alpha]_D = -18.7$ ($c = 0.53$, $CHCl_3$); IR (film) 1737, 1429, 1237, 1115, 1053 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.74 (s, 1 H), 7.61 (dd, $J = 7.8$, 1.2 Hz, 6 H), 7.38 (m, 9 H), 6.94 (s, 1 H), 6.53 (s, 1 H), 5.39 (m, 1 H), 5.31 (m, 1 H), 5.29 (t, $J = 6.9$ Hz, 1 H), 4.61 (d, $J = 4.3$ Hz, 1 H), 3.50 (dd, $J = 5.2$, 2.6 Hz, 1 H), 2.70 (s, 3 H), 2.48 (m, 2 H), 2.14 (m, 1 H), 2.09 (s, 3 H), 2.07 (s, 3 H), 1.83 (m, 2 H), 1.41 (m, 1 H), 1.18 (m, 1 H), 1.01 (s, 3 H), 0.99 (s, 3 H), 0.91 (d, $J = 7.4$ Hz, 3 H), 0.85 (s, 9 H), 0.69 (m, 1 H), 0.58 (d, $J = 6.8$ Hz, 3 H), −0.05 (s, 3 H), −0.06 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.46, 170.01, 164.49, 152.46, 137.10, 135.60, 134.22, 132.55, 130.65, 127.84, 123.82, 120.66, 116.19, 81.09, 78.47, 76.73, 51.66, 43.14, 38.98, 30.99, 30.42, 27.63, 26.10, 21.15, 20.92, 20.05, 19.15, 18.49, 15.12, 14.70, 12.75, −3.25, −4.08; HRMS calcd for $C_{50}H_{69}O_5NSSi_2$: 851.4435; found: 890.4100 (M + K).

Preparation of Compounds 90 and 91. To a solution of the acetate−aldehyde **89** (0.084 g, 0.099 mmol) in THF (99 mL) at −78 °C was added potassium bis(trimethylsilyl)amide (0.5 M in toluene, 1.0 mL, 0.5 mmol) dropwise. The resulting solution was stirred at −78 °C for 30 min. Then the reaction mixure was transfered via cannula to a short pad of silica gel and washed with Et_2O. The residue was purified by flash chromatography (silica, 12% EtOAc in hexane) to give the 3*S* product **90** and the 3*R* product **91** in a 6:1 ratio in 51% combined yield:

Compound 90: $[\alpha]_D = -39.4$ (*c* 0.52, $CHCl_3$); IR (film) 3508, 1733, 1428, 1254, 1113, 1034 cm^{-1}; ^1H NMR (500 MHz, C_6D_6, 60 °C) δ 7.85 (dd, $J = 7.3$, 2.1 Hz, 6 H), 7.22 (m, 9 H), 6.54 (s, 1 H), 6.49 (s, 1 H), 5.53 (d, $J = 6.0$ Hz, 1 H), 5.42 (m, 2 H), 4.22 (d, $J =$

5.9 Hz, 1 H), 4.19 (d, J = 3.5 Hz, 1 H), 4.17 (br s, 1 H), 2.58 (m, 1 H), 2.45 (m, 2 H), 2.31 (s, 3 H), 2.29 (m, 2 H), 2.13 (s, 3 H), 2.00 (m, 2 H), 1.81 (m, 1 H), 1.56 (m, 1 H), 1.35−1.28 (band, 2 H), 1.24 (d, J = 7.1 Hz, 3 H), 1.20 (m, 1 H), 1.11 (s, 3 H), 1.07−0.92 (band, 13 H), 0.88 (d, J = 6.7 Hz, 3 H), 0.12 (s, 6 H); ^{13}C NMR (125 MHz, C_6D_6, 60 °C) δ 171.1, 164.3, 153.7, 137.4, 136.6, 136.0, 130.1, 128.5, 125.5, 120.2, 116.7, 78.5, 75.8, 72.8, 44.6, 41.6, 38.3, 32.7, 31.8, 30.1, 28.5, 27.9, 26.6, 22.2, 21.3, 18.9, 18.8, 15.8, 15.7, 1.30, −2.76, −3.66; HRMS calcd for $C_{50}H_{69}O_5NSSi_2$: 851.4435; found: 852.4513 (M + H).

Compound 91: $[\alpha]_D$ = −53.9 (*c* 0.37, $CHCl_3$); IR (film) 2927, 1734, 1428, 1114, 1036 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6, 60 °C) δ 7.82 (m, 6 H), 7.22−7.19 (band, 9 H), 6.59 (s, 1 H), 6.53 (s, 1 H), 5.58−5.53 (band, 2 H), 5.49 (m, 1 H), 4.39 (d, J = 9.7 Hz, 1 H), 3.98 (d, J = 4.7 Hz, 1 H), 3.86 (dd, J = 1.9, 5.6 Hz, 1 H), 3.59 (br s, 1 H), 2.49−2.43 (band, 3 H), 2.34−2.26 (band, 6 H), 2.18 (s, 3 H), 1.98 (m, 2 H), 1.51 (m, 1 H), 1.50−1.30 (band, 2 H), 1.21−1.19 (band, 6 H), 1.03−0.99 (band, 10H), 0.85 (d, J = 5.4 Hz, 3 H), 0.78 (s, 3 H), 0.10 (s, 3 H), 0.07 (s, 3 H); HRMS calcd for $C_{50}H_{69}O_5NSSi_2$: 851.4435; found: 852.4489 (M + H).

Preparation of Compound 93. The lactone **90** (0.032 g, 0.0376 mmol) was treated with pyridine-buffered HF·pyridine solution (1 mL) (stock solution was prepared from 20 mL of THF, 11.4 mL of pyridine, and 4.2 g of hydrogen fluoride−pyridne (Aldrich Co.)) at room temperature for 2 h. The reaction mixure was poured into saturated aqueous $NaHCO_3$ (15 mL) and extracted with Et_2O (3 × 30 mL). The organic layer was washed in sequence with saturated aqueous $CuSO_4$ (3 × 10 mL) and saturated aqueous $NaHCO_3$ (10 mL) and then dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (silica, 25% EtOAc in hexane) to give diol **93** (0.022 g, 99%) as a white foam: $[\alpha]_D$ = −111.7 (*c* = 0.7, $CHCl_3$); IR (film) 3463, 2928, 1729, 1253 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz, 60 °C) δ 6.65 (s, 1 H), 6.57 (s, 1 H), 5.50 (dd, J = 2.58, 9.42 Hz, 1 H), 5.39 (m, 2 H), 4.34 (s, 1 H), 4.07 (dd, J = 2.2, 9.9 Hz, 1 H), 3.47 (t, J = 4.5 Hz, 1 H), 3.11 (br s, 1 H), 2.69 (m, 2 H), 2.57 (m, 2 H), 2.31 (s, 3 H), 2.18 (m, 6 H), 2.0 (m, 1 H), 1.78 (m, 1 H), 1.53 (m, 2 H), 1.27 (m, 1 H), 1.09 (d, J = 4.5 Hz, 3 H), 0.98 (m, 15H), 0.91 (s, 3 H), 0.14 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR (C_6D_6, 125 MHz, 60 °C) δ 171.4, 164.3, 153.8, 137.8, 133.2, 128.5, 125.8, 120.3, 116.6, 83.2, 78.7, 75.8, 73.9, 42.6, 40.9, 39.4, 35.5, 34.4, 32.3, 28.1, 26.3, 22.5, 22.4, 18.8, 18.6, 17.0, 16.5, 15.5, −3.6, −4.4; LRMS calcd for $C_{32}H_{55}O_5NSSi$: 593.4; found: 616.3 (M + Na).

Preparation of Compound 94. To a cooled (−30 °C) solution of diol **93** (0.029 g, 0.048 mmol) and 2,6-lutidine (0.017 mL, 0.147 mmol) in anhydrous CH_2Cl_2 (1.0 mL) was added TBSOTf (0.015 mL, 0.065 mmol). The resulting solution was then stirred at −30 °C for 30 min. The reaction was quenched with 0.5 M HCl (10 mL) and extracted with Et_2O (15 mL). The ether layer was washed with saturated aqueous $NaHCO_3$ (5 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash chromatogrphy (silica, 8% EtOAc in hexane) afforded TBS ether **94** (0.032 g, 93%) as white foam: $[\alpha]_D$ = −21.7 (*c* 0.35, $CHCl_3$); IR (film) 3471, 2928, 1742, 1253, 1076 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6, 38 °C) δ 6.62 (s, 1 H), 6.53 (s, 1 H) 5.49−5.46 (band, 3 H), 4.41 (br s, 1 H), 4.10 (br s, 1 H), 3.49 (br s, 1 H), 2.70−2.64 (band, 2 H), 2.44 (dd, J = 16.1, 6.5 Hz, 1 H), 2.34 (d, J = 15.5 Hz, 1 H), 2.28 (s, 3 H), 2.22−2.15 (band, 5H), 2.02 (m, 1 H), 1.81 (m, 1 H), 1.68 (m, 1 H), 1.50 (m, 1 H), 1.34 (m, 1 H), 1.18 (s, 3 H), 1.14 (d, J = 20.9 Hz, 3 H), 1.02−0.98 (band, 23 H), 0.90 (s, 3 H), 0.16−0.15 (band, 9 H), 0.10 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6, 43 °C) δ 171.3, 164.2, 153.9, 137.9, 133.0, 127.9, 120.1, 116.6, 78.9, 75.1, 44.7, 41.0, 32.8, 31.9, 27.9, 27.6, 26.4, 26.2, 25.9, 21.7, 18.9, 18.51, 18.49, 17.4, 15.53, −3.4, −3.6, −4.3, −4.4; HRMS calcd for $C_{38}H_{69}O_5NSSi_2$: 707.4435; found: 746.4062 (M + K).

Preparation of Compound 95. To a solution of alcohol **94** (0.030 g, 0.0424 mmol) in CH_2Cl_2 (2.0 mL) at 25 °C was added Dess−Martin periodinane (0.036 g, 0.0848 mmol) in one portion. The resulting solution was then allowed to stir at 25 °C for 1.5 h. The reaction was quenched by the addition of 1:1 saturated aqueous $NaHCO_3$:$Na_2S_2O_3$ (10 mL) and stirred for 5 min. The mixture was then extracted with Et_2O (3 × 15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (silica, 8% EtOAc in hexane) provided ketone **95** (0.025 g, 84%) as white foam: $[\alpha]_D$ = −21.93 (*c* = 1.4, $CHCl_3$); IR (film): 2928, 1745, 1692, 1254, 1175, 836 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.97 (s, 1 H), 6.57 (s, 1 H), 5.53 (dt, J = 3.4, 11.1 Hz, 1 H), 5.37 (dd, J = 16.4, 9.9 Hz, 1 H), 5.00 (d, J = 10.3 Hz, 1 H), 4.02 (d, J = 9.7 Hz, 1 H), 3.89 (d, J = 8.7 Hz, 1 H), 3.00 (m, 1 H), 2.82 (d, J = 6.5 Hz, 1 H), 2.71 (m, 5H), 2.36 (q, J = 10.7 Hz, 1 H), 2.12 (, 3 H), 2.07 (dd, J = 8.2 Hz, 1 H), 1.87 (bs, 1 H), 1.49 (m, 3 H), 1.19 (m, 5H), 1.14 (s, 3 H), 1.08 (d, J = 6.8 Hz, 3 H), 0.94 (m, 12 H), 0.84 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 3 H), 0.07 (s, 3 H), −0.09 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 218.7, 170.1, 164.5, 152.6, 137.9, 133.9, 124.8, 119.6, 115.9, 72.7, 53.2, 43.9, 41.0, 40.3, 32.9, 32.3, 28.4, 27.1, 26.3, 26.1, 26.0, 19.2, 19.1, 18.3, 18.2, 17.1, 16.0, 15.2, 14.3, −4.2, −4.4, −4.6, −4.8; HRMS calcd for $C_{38}H_{67}O_5NSSi_2$: 705.4315, found: 706.4357 (M + H).

Macrolactonization To Produce Compound 95. To a solution of hydroxy acid **88** (0.094 g, 0.133 mmol) in THF (1 mL) were added Et_3N (0.11 mL, 0.79 mmol) and 2,4,6-trichlorobenzoyl chloride (0.104 mL, 0.66 mmol). The mixture was stirred at rt for 0.25 h, diluted with toluene (15 mL), and added dropwise over a period of 3 h to a solution of DMAP (0.167 mg, 1.37 mmol) in toluene (50 mL). After complete addition, the mixture was stirred for additional 0.5 h and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel eluting with hexanes/ethyl acetate (9:1) gave 0.081 g (88%) of the previously described lactone **95**.

Preparation of Compound 96. To a solution of TBS ether **95** (0.027 g, 0.038 mmol) in THF (1.0 mL) at 25 °C in a plastic vial was added dropwise HF·pyridine (0.5 mL). The resulting solution was allowed to stir at 25 °C for 2 h. The reaction mixture was diluted with chloroform (2 mL) and very slowly added to saturated aqueous $NaHCO_3$ (20 mL). The mixture was extracted with $CHCl_3$ (20 mL × 3). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (silica, 30% EtOAc in hexane) provided diol **96** (0.018 g, 99%) as white foam: $[\alpha]_D$ = −84.7 (*c* = 0.85, $CHCl_3$); IR (film): 3493, 2925, 1728, 1689, 1249 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.96 (s, 1 H), 6.59 (s, 1 H), 5.44 (dt, J = 4.3, 10.4 Hz, 1 H), 5.36 (dt, J = 5.1, 10.2 Hz, 1 H), 5.28 (dd, J = 1.7, 9.8 Hz, 1 H), 4.11 (d, J = 7.2 Hz, 1 H), 3.74 (s, 1 H), 3.20 (d, J = 4.5 Hz, 1 H), 3.14 (dd, J = 2.2, 6.8 Hz, 1 H), 3.00 (s, 1 H), 2.69 (m, 4 H), 2.49 (dd, J = 11.3, 15.1 Hz, 1 H), 2.35 (dd, J = 2.5, 15.1 Hz, 1 H), 2.27 (m, 1 H), 2.05 (m, 1 H), 2.04 (s, 3 H), 2.01 (m, 1 H) 1.75 (m, 1 H), 1.67 (m, 1 H), 1.33 (m, 4 H), 1.21 (s, 1 H), 1.19 (m, 2 H), 1.08 (d, J = 7.0 Hz, 3 H), 1.00 (s, 3 H), 0.93 (d, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 226.5, 176.5, 171.1, 158.2, 144.7, 139.6, 131.1, 125.7, 122.0, 84.6, 80.2, 78.6, 59.4, 47.9, 45.4, 44.6, 38.5, 37.9, 33.7, 33.6, 28.7, 25.1, 25.0, 21.9, 21.7, 19.6; HRMS calcd for $C_{26}H_{39}O_5NS$ 477.2549, found 478.2627 (M + H).

Preparation of Epothilone A (2). To a cooled (−50 °C) solution of desoxyepothilone A (**96**) (0.009 g, 0.0189 mmol) in dry CH_2Cl_2 (1 mL) was added freshly prepared 3,3-dimethyldioxirane (0.95 mL, 0.1 M in acetone). The resulting solution was allowed to warm to −30 °C for 2 h. A stream of nitrogen was then bubbled through the solution to remove excess dimethyldioxirane. The residue was purified by flash chromatography (silica, 40% EtOAc in hexane) and afforded epothilone A (**2**) (0.0046 g, 49%) as colorless solid and 0.0003 g of the *cis*-epoxide diastereomer: $[\alpha]_D$ = −41.6 (*c* = 0.51, MeOH); IR (film): 3464, 2926, 1737, 1689, 978, 755 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.00 (s, 1 H), 6.56 (s, 1 H), 5.39 (dd, J = 9.2, 2.0 Hz, 1 H), 4.16 (br d, J = 10.0 Hz, 1 H), 3.73 (dd, J = 8.6, 4.2 Hz, 1 H), 3.59 (br s, 1 H), 3.21 (m, 1 H), 2.99 (m, 1 H), 2.87 (m, 1 H), 2.68 (s, 3 H), 2.50−2.44 (band, 2 H), 2.38 (dd, J = 15.0, 3.2 Hz, 1 H), 2.14−2.08 (band, 4 H), 1.86 (m, 1 H), 1.75−1.66 (band, 3 H), 1.55 (m, 1 H), 1.41 (m, 4 H), 1.35 (s, 3 H), 1.14 (d, J = 6.9 Hz, 3 H), 1.06 (s, 3 H), 0.98 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 220.2, 170.9, 165.6, 152.4, 138.1, 120.2, 116.7, 77.2, 74.9, 73.4, 57.8, 55.1, 53.7, 39.5, 36.8, 32.1, 30.9, 30.1, 27.7, 23.8, 22.0, 20.2, 19.3, 17.3, 15.6, 14.3; HRMS calcd for $C_{26}H_{39}O_6NS$: 493.2498, found: 494.2578 (M + H).

Preparation of Compound 97. To a suspension of ethyltriphenylphosphonium iodide (0.250 g, 0.60 mmol) in THF (6 mL) was added *n*BuLi (2.5 M soln in hexanes, 0.24 mL, 0.60 mmol) at rt. After disappearance of the solid material, the solution was added to a mixture of iodine (0.152 g, 0.60 mmol) in THF (4 mL) at −78 °C. The resulting suspension was vigorously stirred for 5 min at −78 °C and then warmed to −20 °C and treated with sodium bis(trimethylsilyl)amide (1 M soln in THF, 0.56 mL, 0.56 mmol). The resulting red solution was stirred for 5 min followed by the slow addition of aldehyde **78** (0.074 g, 0.30

mmol). The mixture was stirred at −20 °C for 40 min, diluted with pentane (50 mL), filtered through a pad of Celite, and concentrated in vacuo. Purification of the residue by flash column chromatography (hexanes/ethyl acetate, 85:15) gave 0.141 g (43% overall from acetate **77**) of the vinyl iodide **97** as a yellow oil: $[\alpha]_D = -20.7$ (*c* 2.45, $CHCl_3$); IR (film) 2920, 1738, 1369, 1234 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.98 (s, 1 H), 6.53 (s, 1 H), 5.43 (t, $J = 6.5$, 5.4 Hz, 1 H), 5.35 (t, $J = 6.6$, 6.5 Hz, 1 H), 2.71 (s, 3 H), 2.58−2.50 (band, 5H), 2.08 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 164.6, 152.4, 136.9, 130.3, 120.7, 120.6, 116.4, 103.6, 40.3, 33.7, 19.2, 19.1, 14.9; HRMS calcd for $C_{14}H_{18}O_2NIS$: 391.0103; found: 392.0181 (M + H).

Preparation of Compound 98. To a solution of olefin **68** (0.977 g, 1.55 mmol) in THF (3 mL) was added 9-BBN (0.5 M soln in THF, 3.4 mL, 1.7 mmol). In a separate flask, iodide **97** (0.749 g, 1.92 mmol) was dissolved in DMF (5 mL). Cs_2CO_3 (1.154 g, 3.54 mmol) was then added with vigorous stirring followed by sequential addition of $PdCl_2(dppf)_2$ (0.162 g, 0.198 mmol), Ph_3As (0.061 g, 0.20 mmol), and H_2O (0.42 mL, 23.4 mmol). After 5 h, the borane solution was added to the iodide mixture in DMF. The reaction quickly turned dark brown in color and slowly became pale yellow after 3 h. The solution was then poured into H_2O (10 mL) and extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with H_2O (3 × 15 mL), brine (1 × 20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography (hexanes/ethyl acetate, 9:1) gave the coupled product **98** (1.073 g; 77%) as a yellow oil: IR (film) 2931, 1738, 1429, 1239, 1072, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (m, 15 H), 6.98 (s, 1 H), 6.59 (s, 1 H), 5.30 (t, $J = 6.9$ Hz, 1 H), 5.15 (t, $J = 6.7$ Hz, 1 H), 4.38 (d, $J = 3.5$ Hz, 1 H), 4.02 (s, 1 H), 3.60 (m, 2 H), 3.41 (t, $J = 6.9$ Hz, 2 H), 2.88 (s, 3 H), 2.79 (s, 3 H), 2.41 (m, 2 H), 2.16−2.10 (band, 6 H), 1.80 (m, 2 H), 1.70 (s, 3 H), 1.30−1.01 (band, 6 H), 0.85 (s, 15H), 0.73 (d, $J = 6.8$ Hz, 3 H), 0.62 (d, $J = 6.7$ Hz, 3 H), 0.00 (br s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 164.5, 152.7, 138.6, 137.5, 135.8, 135.3, 129.9, 127.8, 120.6, 119.1, 116.2, 110.6, 110.5, 78.9, 77.8, 63.3, 60.4, 60.2, 55.5, 46.6, 43.9, 43.4, 38.0, 32.3, 31.7, 30.4, 26.2, 26.1, 26.0, 23.6, 21.3, 19.6, 19.4, 19.2, 18.6, 17.1, 15.8, 15.4, 14.8, 14.2, 13.6, −2.9, −3.9, −4.1; HRMS calcd for $C_{53}H_{77}O_6NSSi_2$ 911.5010, found 950.4613 (M + K).

Preparation of Compound 99. The acetal **98** (0.069 g, 0.077 mmol) was dissolved in dioxane/H_2O (9:1, 1 mL), and *p*TSA·H_2O (0.045 g, 0.237 mmol) was added. The mixture was then heated to 55 °C. After 3 h, the mixture was cooled to rt, poured into saturated aqueous $NaHCO_3$, and extracted with Et_2O (4 × 15 mL). The combined ether extracts were washed with saturated aqueous $NaHCO_3$ (1 × 30 mL), brine (1 × 30 mL), dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (hexanes/EtOAc, 3:1) gave aldehyde **99** (0.046 g, 71%) as a pale yellow oil: $[\alpha]_D = -13.3$ (*c* 0.95, $CHCl_3$); IR (film) 3070, 2929, 2856, 1737, 1429, 1238, 1116, 1056 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1 H), 7.71−7.69 (band, 6 H), 7.52−7.44 (band, 9 H), 7.01 (s, 1 H), 6.60 (s, 1 H), 5.31 (t, $J = 6.6$ Hz, 1 H), 5.12 (t, $J = 6.9$ Hz, 1 H), 4.85 (d, $J = 4.5$ Hz, 1 H), 3.58 (br s, 1 H), 2.77 (s, 3 H), 2.47 (m, 2 H), 2.14 (s, 3 H), 2.13 (s, 3 H), 1.87 (m, 2 H), 1.72 (s, 3 H), 1.49 (m, 1 H), 1.30 (m, 2 H), 1.10 (m, 1 H), 1.09 (s, 3 H), 1.06 (s, 3 H), 0.98 (d, $J = 1.5$ Hz, 3 H), 0.92 (s, 9 H), 0.80 (m, 2 H), 0.65 (d, $J = 6.7$ Hz, 3 H), 0.02 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.7, 170.2, 164.6, 152.6, 138.4, 137.4, 135.7, 135.1, 134.9, 134.3, 130.1, 127.9, 120.6, 119.2, 116.2, 81.2, 78.9, 51.7, 43.1, 39.1, 32.3, 31.7, 30.9, 26.1, 26.0, 23.6, 21.3, 20.8, 20.2, 19.2, 18.6, 14.9, 14.8, 12.8, 0.00, −3.2, −4.0; HRMS calcd for $C_{51}H_{71}O_5NSSi_2$ 865.4592, found 904.4201 (M + K).

Preparation of Compounds 100 and 101. To a solution of aldehyde **99** (0.290 g, 0.341 mmol) in THF (34 mL) at −78 °C was added potassium bis(trimethylsilyl)amide (0.5 M soln in toluene, 3.4 mL, 1.7 mmol). The solution was stirred at −78 °C for 1 h and then quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3 × 15 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. Flash column chromatography (hexanes/EtOAc, 7:1) gave 0.120 g of the desired α-alcohol **100** and 0.055 g of *β*-alcohol **101** (60% combined yield) as pale yellow oils.

Conversion of Compound 101 to Compound 100. To a solution of *β*-alcohol **101** (0.075 g, 0.088 mmol) in 0.5 mL of CH_2Cl_2 at rt was added Dess−Martin periodinane (0.188 g, 0.44 mmol). The resulting solution was stirred at rt for 1 h and then treated with Et_2O (2 mL) and saturated aqueous $NaHCO_3$:$Na_2S_2O_3$ (3 mL, 1:1), poured into H_2O (20 mL), and extracted with Et_2O (4 × 10 mL). The combined ether solutions were washed with H_2O (1 × 30 mL), brine (1 × 30 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. To a solution of crude ketone **102** in MeOH/THF (2 mL, 1:1) at −78 °C was added $NaBH_4$ (0.017 g, 0.447 mmol). The resulting solution was stirred at rt for 1 h, quenched with saturated aqueous NH_4Cl (10 mL), and extracted with Et_2O (3 × 15 mL). The organic layers were dried with $MgSO_4$, filtered, and concentrated. Flash column chromatography (hexanes/ethyl acetate, 9:1) gave 0.052 g (67%) of the α-alcohol **100** as a pale yellow oil and 0.009 g of *β*-alcohol **101**.

Compound 100: $[\alpha]_D = -45.4$ (*c* 1.0, $CHCl_3$); IR (film) 3490, 2929, 2856, 1729, 1428, 1114, 1037, 708 cm^{-1}; ^1H NMR (500 MHz, C_6D_6, 60 °C) δ 7.85 (m, 6 H), 7.22 (m, 9 H), 6.55 (s, 1 H), 6.49 (s, 1 H), 5.56 (br d, $J = 6.9$ Hz, 1 H), 5.25 (m, 1 H), 4.24 (br s, 1 H), 4.17 (m, 2 H), 2.60 (m, 1 H), 2.47 (m, 2 H), 2.29−2.22 (band, 6 H), 2.15 (s, 3 H), 2.08 (m, 2 H), 1.96 (m, 1 H), 1.84 (br s, 1 H), 1.68 (s, 3 H), 1.43 (m, 1 H), 1.32 (m, 2 H), 1.24 (d, $J = 7.1$ Hz, 3 H), 1.11 (s, 6 H), 1.04 (s, 9 H), 0.91 (d, $J = 6.3$ Hz, 3 H), 0.12 (s, 6 H); HRMS calcd for $C_{51}H_{71}O_5NSSi_2$: 865.4591; found: 866.4716 (M + H).

Preparation of Compound 103. The silyl ether **100** (0.210 g, 0.247 mmol) was dissolved in HF·pyridine/pyridine/THF (15 mL). The solution was stirred at rt for 2 h and then diluted with Et_2O (1 mL), poured into a mixture of Et_2O/saturated $NaHCO_3$ (20 mL, 1:1), and extracted with Et_2O (4 × 10 mL). The Et_2O extracts were washed with saturated aqueous $CuSO_4$ (3 × 30 mL), saturated aqueous $NaHCO_3$ (1 × 30 mL), and brine (1 × 30 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography (hexanes/EtOAc, 9:1) gave diol **103** (0.141 g, 94%) as a pale yellow oil: $[\alpha]_D = -41.7$ (*c* 0.65, $CHCl_3$); IR (film) 3460, 2928, 1728, 1252, 1037, 757 cm^{-1}; ^1H NMR (500 MHz, C_6D_6, 58 °C) δ 6.69 (s, 1 H), 6.56 (s, 1 H), 5.51 (dd, $J = 9.4$, 3.0 Hz, 1 H), 5.20 (m, 1 H), 4.30 (br s, 1 H), 4.10 (dd, $J = 9.7$, 2.6 Hz, 1 H), 3.50 (br s, 1 H), 3.07 (br s, 1 H), 2.74 (t, $J = 9.6$, 5.7 Hz, 1 H), 2.70 (dd, $J = 16.0$, 3.5 Hz, 1 H), 2.52 (dd, $J = 16.0$, 9.7 Hz, 1 H), 2.31−2.25 (band, 4 H), 2.24 (s, 3 H), 2.22−2.18 (band, 3 H), 1.91 (m, 1 H), 1.81 (m, 1 H), 1.61−1.58 (band, 4 H), 1.50 (m, 1 H), 1.37 (m, 2 H), 1.11 (d, $J = 6.9$ Hz, 3 H), 1.04 (d, $J = 7.0$ Hz, 3 H), 0.99 (s, 12 H), 0.93 (s, 3 H), 0.16 (s, 3 H), 0.14 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6, 58 °C) δ 171.3, 164.3, 153.9, 138.2, 137.6, 122.1, 120.4, 116.6, 82.8, 79.2, 73.8, 42.7, 39.5, 34.0, 32.9, 31.8, 26.3, 22.4, 21.9, 18.8, 18.6, 17.0, 15.5, −3.5, −4.5; LRMS calcd for $C_{33}H_{57}O_5NSSi$ 607.4, found 608.4 (M + H).

Preparation of Compound 104. To a solution of diol **103** (0.0066 g, 0.011 mmol) in 0.5 mL of CH_2Cl_2 at −78 °C were added 2,6-lutidine (7 μL, 0.060 mmol) and TBSOTf (5 μL, 0.022 mmol). The resulting solution was stirred at −30 °C for 0.5 h and then quenched with H_2O (5 mL) and extracted with Et_2O (4 × 10 mL). The ether solutions were washed with 0.5 M HCl (1 × 10 mL) and saturated aqueous $NaHCO_3$ (1 × 10 mL), dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (hexanes/EtOAc, 93:7) gave alcohol **104** (0.0070 g, 89%) as a pale yellow oil: $[\alpha]_D = -2.6$ (*c* 3.15, $CHCl_3$); IR (film) 3453, 2929, 1726, 1252, 1030 cm^{-1}; ^1H NMR (500 MHz, C_6D_6, 60 °C) δ 7.15 (s, 1 H), 6.66 (s, 1 H), 6.58 (s, 1 H), 5.54 (t, $J = 6.8$, 6.7 Hz, 1 H), 5.21 (m, 1 H), 4.64 (br s, 1 H), 3.80 (br s, 1 H), 2.99 (m, 1 H), 2.84 (dd, $J = 14.0$, 6.7 Hz, 1 H), 2,45 (dd, $J = 14.1$, 1.5 Hz, 1 H), 2.37 (s, 3 H), 2.29 (s, 3 H), 2.17−2.08 (band, 4 H), 1.80 (m, 1 H), 1.70−1.60 (band, 4 H), 1.49 (m, 1 H), 1.12−1.08 (band, 5H), 1.04 (d, $J = 6.8$ Hz, 3 H), 1.00−0.90 (band, 25H), 0.18 (s, 3 H), 0.12 (s, 3 H), 0.11 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 171.2, 164.1, 154.2, 138.8, 121.4, 120.8, 116.6, 80.1, 77.6, 74.7, 44.7, 41.8, 33.5, 32.5, 31.9, 27.1, 26.4, 26.8, 23.3, 20.2, 18.9, 18.4, 18.3, 17.4, 15.1, −3.8, −4.3, −4.4; LRMS calcd for $C_{39}H_{71}NO_5SSi_2$: 721.5; found: 722.7 (M + H).

Preparation of Compound 105. To a solution of alcohol **104** (0.107 g, 0.148 mmol) in CH_2Cl_2 (3 mL) at rt was added Dess−Martin periodinane (0.315 g, 0.743 mmol). The resulting solution was stirred at rt for 2 h, treated with Et_2O (1 mL) and saturated aqueous $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ (2 mL, 1:1), poured into H_2O (20 mL), and extracted with Et_2O (4 × 10 mL). The ether solution was washed with saturated aqueous $NaHCO_3$ (1 × 20 mL), dried with $MgSO_4$, filtered, and concentrated. Flash column chromatography (hexanes/EtOAc, 9:1) gave ketone **105** (0.092 g, 87%) as a pale yellow oil: $[\alpha]_D = -18.7$ (*c* 3.65, $CHCl_3$); IR (film) 2931, 2856, 1742, 1696, 1463, 1255, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.85 (s, 1 H), 6.46 (s,

1 H), 5.06 (t, J = 8.4, 7.7 Hz, 1 H), 4.86 (d, J = 10.0 Hz, 1 H), 3.92 (d, J = 9.3 Hz, 1 H), 3.78 (d, J = 8.9 Hz, 1 H), 2.92 (m, 2 H), 2.69 (d, J = 15.5 Hz, 1 H), 2.60−2.55 (band, 1 H), 2.36 (m, 1 H), 2.06 (d, J = 3.5 Hz, 1 H), 2.00−1.93 (band, 5H), 1.63−1.58 (band, 6 H), 1.44 (m, 2 H), 1.15 (s, 3 H), 1.08 (s, 3 H), 1.03 (s, 3 H), 0.99 (d, J = 6.8 Hz, 3 H), 0.87 (d, J = 6.9 Hz, 3 H), 0.85−0.73 (band, 12 H), 0.00−0.06 (band, 9 H), −0.21 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.1, 171.2, 164.5, 152.5, 140.6, 138.8, 119.3, 119.1, 115.9, 79.8, 76.2, 53.4, 39.1, 32.5, 31.9, 31.4, 29.2, 27.4, 26.3, 26.1, 24.5, 24.3, 23.0, 19.1, 18.7, 18.6, 17.8, 15.3, −3.3, −3.7, −5.6; LRMS calcd for $C_{39}H_{69}O_5NSSi_2$: 719.4; found: 720.6 (M + H).

Preparation of Compound 106. To a solution of ketone **105** (0.092 g, 0.128 mmol) in THF (4.5 mL) at 0 °C was added HF·pyridine (2.25 mL) dropwise. The solution was stirred at rt for 2 h, diluted with $CHCl_3$ (2 mL), poured into saturated aqueous $NaHCO_3/CHCl_3$ (20 mL, 1:1) slowly, and extracted with $CHCl_3$ (4 × 10 mL). The combined $CHCl_3$ layers were dried with $MgSO_4$, filtered, and concentrated. Flash column chromatography (hexanes/EtOAc, 3:1) gave desoxyepothilone B (**106**)-(0.057 g, 92%) as a pale yellow oil: $[\alpha]_D$ = −61.4 (*c* 2.85, $CHCl_3$); IR (film) 3465, 2969, 1735, 1691, 1377, 1181, 1148 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (s, 1 H), 6.58 (s, 1 H), 5.21 (d, J = 9.3 Hz, 1 H), 5.15 (dd, J = 10.7, 5.5 Hz, 1 H), 4.28 (br d, J = 9.2 Hz, 1 H), 3.80−3.50 (band, 3 H), 3.17 (m, 1 H), 3.16 (br s, 1 H), 2.69 (s, 3 H), 2.66−2.61 (band, 3 H), 2.46 (dd, J = 14.6, 3.4 Hz, 1 H), 2.34−2.22 (band, 3 H), 2.18 (s, 3 H), 2.07 (s, 3 H), 1.88 (m, 1 H), 1.75 (m, 1 H), 1.34 (s, 3 H), 1.02 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.6, 210.7, 170.4, 164.9, 151.9, 139.1, 138.4, 120.8, 119.3, 115.6, 78.9, 74.1, 72.3, 69.4, 53.7, 53.4, 41.7, 39.6, 38.3, 32.5, 31.7, 29.2, 22.9, 19.0, 18.0, 15.7; HRMS calcd for $C_{27}H_{41}NO_5NS$: 491.2705; found $C_{27}H_{42}NO_5S$: 492.2782 (M + H).

Preparation of Epothilone B (3). To a solution of desoxyepothilone B (**106**) (0.090 g, 0.183 mmol) in CH_2Cl_2 (1.8 mL) at −78 °C was added freshly prepared dimethyldioxirane (0.087 M soln in acetone, 3.60 mL, 0.313 mmol) dropwise. The resulting solution was warmed to −50 °C for 1 h, and another portion of dimethyldioxirane (1.0 mL, 0.087 mmol) was added. After stirring at −50 °C for additional 1.5 h, any excess dimethyldioxirane and solvent were removed by a stream of N_2 at −50 °C. The crude reaction mixture was determined to be >20:1 ratio of diastereomeric *cis*-epoxides by ^{1}H NMR spectroscopy. The resulting residue was purified by flash column chromatography (hexanes/EtOAc, 1:1) to give epothilone B (**3**) (0.090 g, 97%) as a white solid: $[\alpha]_D$ = −31.0 (*c* 0.045, $CHCl_3$); mp 93.6−94.7 °C; IR (film) 3454, 2962, 1727, 1690, 1263, 978 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (s, 1 H), 6.52 (s, 1 H), 5.43 (dd, J = 7.7, 2.4 Hz, 1 H), 4.22 (m, 2 H), 3.78 (t, J = 4.3 Hz, 1 H), 3.30 (m, 1 H), 2.81 (dd, J = 7.5, 4.6 Hz, 1 H), 2.70 (s, 3 H), 2.54 (m, 1 H), 2.37 (d, J = 12.7 Hz, 1 H), 2.09 (s, 3 H), 1.93 (m, 1 H), 1.72 (m, 2 H), 1.49 (m, 2 H), 1.43 (m, 3 H), 1.37 (s, 3 H), 1.32 (s, 3 H), 1.17 (d, J = 6.8 Hz, 3 H), 1.08 (s, 3 H), 1.01 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.5, 170.5, 165.1, 151.7, 137.5, 119.6, 116.1, 74.1, 72.8, 69.5, 61.6, 61.3, 53.7, 53.0, 42.9, 39.1, 36.3, 32.2, 32.0, 31.7, 30.6, 29.2, 22.7, 22.3, 19.6, 19.0, 17.1, 15.7, 13.7; LRMS calcd for $C_{27}H_{41}O_5NS$ 507.3, found 508.4 (M + H).

Preparation of Compound 109. To a solution of *tert*-butyllithium (3.6 mL of a 1.7 M solution in Et_2O; 6.08 mmol) in Et_2O (5 mL) at −78 °C was added a solution of 4-iodo-2-methyl-1-butene (0.596 g; 3.04 mmol) in Et_2O (20 mL). After 0.5 h, a solution of aldehyde **65** (1.03 g; 1.52 mmol) in Et_2O (5 mL) was added. After 5 min at −78 °C, the cooling bath was removed, and the solution was allowed to warm to 0 °C and stirred for 0.5 h. The reaction mixture was then poured into saturated aqueous NH_4Cl solution (100 mL) and extracted with Et_2O (2 × 100 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (silica, 5−7% Et_2O/hexanes) to give a 3:1 mixture of diastereomeric alcohols (1.01 g; 89%) as a white foam.

A solution of the mixture of alcohols prepared above (1.01 g, 1.35 mmol), thiocarbonyl diimidazole (0.801 g, 4.05 mmol), and 4-DMAP (0.164 g, 1.35 mmol) in THF (10 mL) was heated to 90 °C. A stream of N_2 was then used to evaporate the THF completely. The sticky residue was maintained at 90 °C for 2 h, cooled to rt, and diluted with CH_2Cl_2 (5 mL). Purification of the residue by flash chromatography (SiO_2, 20% EtOAc:hexane) provided an epimeric mixture of thionoimidazolides (1.25 g, 99%) as a pale yellow foam.

A solution of the mixture of thionoimidazolides prepared above (1.25 g, 1.34 mmol), *n*-Bu_3SnH (0.66 mL, 2.01 mmol), and AIBN (0.022 g, 0.13 mmol) in benzene (14 mL) was refluxed for 1 h. The reaction mixture was cooled to rt and diluted with Et_2O (14 mL). To this solution, DBU (0.32 mL, 2.01 mmol) was added, and the resulting mixture was titrated with a solution of iodine in Et_2O until the solution color turned yellow and white precipitate formed. This slurry was filtered through a 5 cm thick pad of silica gel and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 25% CH_2Cl_2:hexanes) to give the dithiane **109** (0.823 g, 84%) as a white foam: $[\alpha]_D$ = 5.97 (*c* 15.9, $CHCl_3$); IR (film) 2931, 1428, 1252, 1114, 1057 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (dd, J = 7.8, 1.3 Hz, 6 H), 7.45−7.38 (band, 9 H), 4.69 (s, 1 H), 4.64 (s, 1 H), 4.56 (d, J = 3.9 Hz, 1 H), 4.16 (s, 1 H), 3.53 (d, J = 5.2 Hz, 1 H), 2.71 (d, J = 13.4 Hz, 1 H), 2.54−2.43 (band, 2 H), 2.08 (m, 1 H), 1.79−1.73 (band, 4 H), 1.73 (s, 3 H), 1.66−1.61 (band, 2 H), 1.35 (s, 3 H), 1.32 (m, 1 H), 1.16 (s, 1 H), 1.03 (d, J = 7.3 Hz, 3 H), 0.91−0.85 (band, 11 H), 0.65 (d, J = 6.8 Hz, 3 H), −0.03 (s, 3 H), −0.05 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.3, 135.9, 134.9, 129.8, 127.8, 109.3, 77.4, 77.1, 38.0, 37.8, 31.0, 30.4, 29.6, 26.2, 25.9, 25.5, 22.6, 22.4, 20.9, −3.1, −4.0; HRMS calcd for $C_{43}H_{64}O_2S_2Si_2$: 732.3886; found: 755.3784 (M + Na).

Preparation of Compound 110. A solution of compound **109** (0.95 g, 1.3 mmol) in MeOH/THF (2:1, 18 mL) was treated with [bis-(trifluoroacetoxy)iodobenzene] (1.118 g, 2.6 mmol) at rt. After 15 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (25 mL). The mixture was extracted with Et_2O (3 × 25 mL), and the organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in dioxane/water (5:1, 12 mL) and treated with *p*TSA·H_2O (0.74 g, 3.9 mmol), and the resulting mixture was heated at 50 °C for 2 h. After cooling to rt, the mixture was diluted with Et_2O (50 mL) and washed successively with aqueous $NaHCO_3$ (15 mL) and brine (20 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash chromatography (SiO_2, 25% CH_2Cl_2:hexanes) afforded aldehyde **110** (0.79 g, 95%) as a white foam: $[\alpha]_D$ = −15.2 (*c* 11.8, $CDCl_3$); IR (film) 2931, 1722, 1472, 1429 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1 H), 7.64 (d, J = 6.6 Hz, 6 H), 7.46−7.37 (band, 9 H), 4.69 (s, 1 H), 4.59 (s, 1 H), 4.04 (d, J = 4.2 Hz, 1 H), 3.52 (dd, J = 5.3, 2.5 Hz, 1 H), 2.16 (m, 1 H), 1.77 (m, 2 H), 1.70 (s, 3 H), 1.54 (m, 1 H), 1.44−1.26 (band, 3 H), 1.00 (s, 6 H), 0.92−0.80 (band, 15H), 0.62 (d, J = 6.8 Hz, 3 H), 0.08 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.6, 146.0, 135.7, 134.4, 130.1, 127.9, 109.6, 81.1, 76.9, 51.7, 43.3, 38.9, 38.0, 30.4, 26.2, 25.6, 22.4, 21.1, 20.1, 18.6, 15.1, 12.8, −3.2, −4.0; HRMS calcd for $C_{40}H_{58}O_3Si_2$ 642.3925, found 665.3842 (M + Na).

Preparation of Compound 114. To a solution of acetate **77** (0.285 g, 1.16 mmol) and aldehyde **110** (0.49 g, 0.772 mmol) in THF (1 mL) at −78 °C was added LDA (2 M soln in THF, 0.772 mL, 1.54 mmol). The yellow mixture was stirred at −78 °C for 40 min and then quenched with saturated aqueous NH_4Cl (10 mL). The mixture was extracted with Et_2O (3 × 15 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (SiO_2, 6% EtOAc:hexanes) provided α-alcohol **114** (0.239 g, 35%) and *β*-alcohol **115** (0.238 g, 35%).

To a solution of *β*-alcohol **115** (0.238 g, 0.27 mmol) in CH_2Cl_2 (3 mL) was added Dess−Martin periodinane (0.689 g, 1.62 mmol) at rt. The resulting solution was stirred for 1 h and then quenched by the addition of 1:1 saturated aqueous $NaHCO_3$:$Na_2S_2O_3$ (10 mL). The mixture was extracted with Et_2O (3 × 10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting C-3 ketone **116** was *immediately* dissolved in a mixture of MeOH (4 mL) and THF (2 mL) and cooled to −78 °C. Sodium borohydride (0.102 g, 2.7 mmol) was then added, and the mixture was allowed to warm to rt and stirred for 1 h. The reaction was then quenched with saturated aqueous NH_4Cl (10 mL). The mixture was extracted with ether (3 × 15 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (SiO_2, 8% EtOAc:hexanes) provided α-alcohol **114** (0.230 g, 92%): $[\alpha]_D$ = −45.3 (*c* 0.29, $CHCl_3$); IR (film) 3502, 2927, 1715, 1428 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 6.5 Hz, 6 H), 7.45−7.30 (band, 9 H), 6.93 (s, 1 H), 6.50 (s, 1 H), 5.65 (m, 1 H), 5.31 (t, J = 6.7 Hz, 1 H), 5.05 (m, 2 H), 4.69 (s, 1 H), 4.63 (s, 1 H), 4.13 (d, J = 3.5 Hz, 1 H), 4.00 (m, 1 H), 3.73 (d, J = 4.5 Hz, 1 H), 3.25 (d, J = 2.5 Hz, 1 H), 2.71 (s, 3 H), 2.42 (m,

4 H), 2.06 (m, 1 H), 2.02 (s, 3 H), 1.87−1.78 (band, 2 H), 1.75 (s, 3 H), 1.70 (m, 1 H), 1.31−1.20 (band, 2 H), 1.12 (m, 1 H), 1.02 (d, J = 8.0 Hz, 3 H), 0.96 (s, 3 H), 0.91 (s, 3 H), 0.79 (s, 9 H), 0.60 (d, J = 7.0 Hz, 3 H), −0.06 (s, 3 H), −0.07 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.1, 164.6, 152.4, 146.2, 136.4, 135.7, 134.9, 133.2, 129.8, 127.7, 121.4, 117.9, 116.5, 109.4, 79.0, 78.7, 76.3, 71.8, 44.2, 43.0, 38.7, 38.0, 37.4, 36.5, 30.4, 26.2, 26.1, 25.7, 22.5, 21.0, 20.5, 19.2, 18.5, 15.2, 14.5, 13.4, −3.1, −4.3; HRMS calcd for $C_{53}H_{75}O_5NSSi_2$: 893.4904, found: 932.4529 (M + K).

Preparation of Compound 120. The aldol product **114** (0.219 g, 0.27 mmol) was treated with buffered HF·pyridine in THF (8.0 mL) at rt (the stock solution was prepared from 20 mL THF, 11.4 mL pyridine and 4.2 g hydrogen fluoride−pyridne (Aldrich Co.)). After 2 h, the reaction was poured into saturated aqueous $NaHCO_3$ and extracted with Et_2O. The organic layer was washed in sequence with saturated aqueous $CuSO_4$ (3 × 30 mL) and saturated aqueous $NaHCO_3$ (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (silica, 10 → 20% EtOAc in hexane) to give diol **120** (0.15 g, 93%) as a white foam: $[\alpha]_D = -40.5$ (c 3.8, $CDCl_3$); IR (film) 3457, 2930, 1732, 1472, 1386, 1252 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (s, 1 H), 6.51 (s, 1 H), 5.72 (m, 1 H), 5.35 (t, J = 6.7 Hz, 1 H), 5.08 (m, 2 H), 4.68 (s, 1 H), 4.65 (s, 1 H), 4.07 (d, J = 10.0 Hz, 1 H), 3.92 (br s, 1 H), 3.80 (br s, 1 H), 3.49 (br s, 1 H), 2.68 (s, 3 H), 2.61−2.45 (band, 4 H), 2.07 (d, J = 1.2 Hz, 3 H), 2.01 (br s, 1 H), 1.69 (s, 3 H), 1.55 (m, 1 H), 1.36 (m, 1 H), 0.99 (d, J = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.80 (s, 3 H), 0.09 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 164.5, 152.5, 145.8, 136.8, 133.3, 120.9, 117.7, 116.3, 109.8, 78.5, 41.5, 38.0, 37.5, 37.1, 32.9, 25.9, 25.5, 22.3, 21.1, 19.1, 18.2, 16.1, 14.6, −4.4; LRMS calcd for $C_{35}H_{61}O_5NSSi$: 635.4; found: 658.5 (M + Na).

Preparation of Compound 121. To a cooled (−30 °C) solution of diol **120** (0.110 g, 0.173 mmol) and 2,6-lutidine (0.121 mL, 1.04 mmol) in anhydrous CH_2Cl_2 (2 mL) was added TBSOTf (0.119 mL, 0.519 mmol). The resulting solution was then stirred at −30 °C for 30 min. The reaction was quenched with 0.5 M HCl (50 mL) and extracted with Et_2O (150 mL). The Et_2O layer was washed with saturated aqueous $NaHCO_3$ (50 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash chromatogrphy (silica, 5 → 8% EtOAc in hexane) afforded TBS ether **121** (0.112 g, 85%) as white foam: $[\alpha]_D = -33.7$ (c 1.6, $CHCl_3$); IR (film) 3478, 2929, 1737, 1471, 1253 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (s, 1 H), 6.50 (s, 1 H), 5.71 (m, 1 H), 5.30 (t, J = 6.8 Hz, 1 H), 5.08 (m, 2 H), 4.67 (s, 1 H), 4.65 (s, 1 H), 4.20 (m, 1 H), 3.81 (br s, 1 H), 3.40 (br s, 1 H), 2.90 (dd, J = 17.2, 3.9 Hz, 1 H), 2.69 (s, 3 H), 2.47 (m, 2 H), 2.35 (dd, J = 17.2, 5.4 Hz, 1 H), 2.07 (s, 3 H), 2.01 (m, 2 H), 1.99 (m, 1 H), 1.69−1.60 (band, 4 H), 1.54−1.48 (band, 2 H), 1.25 (m, 1 H), 0.94 (d, J = 7.0 Hz, 3 H), 0.91 (s, 3 H), 0.89−0.87 (band, 12 H), 0.86 (s, 3 H), 0.83 (s, 9 H), 0.07 (s, 3 H), 0.02 (s, 3 H), 0.01 (s, 3 H), −0.05 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 164.5, 152.5, 146.2, 136.7, 133.4, 121.2, 117.8, 116.4, 109.7, 78.7, 78.1, 74.4, 43.4, 39.8, 38.1, 37.5, 32.9, 26.0, 25.9, 25.6, 22.4, 19.9, 19.2, 18.2, 18.1, 14.2, −4.0, −4.2, −4.22, −4.9; HRMS calcd for $C_{41}H_{75}O_5NSSi_2$: 749.4904, found: 788.4518 (M + K).

Preparation of Compound 122. To a solution of alcohol **121** (0.110 g, 0.147 mmol) in CH_2Cl_2 (2.0 mL) at rt was added Dess−Martin periodinane (0.249 g, 0.583 mmol) in one portion. The resulting solution was then allowed to stir at 25 °C for 1.5 h. The reaction was quenched by the addition of 1:1 saturated aqueous $NaHCO_3$:$Na_2S_2O_3$ (10 mL) and stirred for 5 min. The mixture was then extracted with Et_2O (3 × 15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (silica, 6% EtOAc in hexane) provided ketone **122** (0.099 g, 94%) as white foam: $[\alpha]_D = -55.1$ (c 0.85, $CHCl_3$); IR (film) 2929, 1737, 1695, 1253 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (s, 1 H), 6.49 (s, 1 H), 5.70 (m, 1 H), 5.29 (t, J = 6.8 Hz, 1 H), 5.05 (m, 2 H), 4.68 (s, 1 H), 4.65 (s, 1 H), 4.34 (dd, J = 5.9, 3.4 Hz, 1 H), 3.72 (d, J = 5.4 Hz, 1 H), 3.15 (m, 1 H), 2.70 (s, 3 H), 2.53−2.42 (band, 3 H), 2.28 (dd, J = 17.0, 6.1 Hz, 1 H), 2.06 (s, 3 H), 1.99 (m, 2 H), 1.69 (s, 3 H), 1.41 (m, 1 H), 1.33−1.29 (band, 3 H), 1.25−1.21 (band, 4 H), 1.04−1.02 (band, 6 H), 0.92−0.83 (band, 21 H), 0.10 (s, 3 H), 0.05 (s, 3 H), 0.03 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 164.5, 152.5, 146.0, 136.7, 133.4, 121.1, 117.8, 116.4, 109.8, 78.6, 77.7, 74.0, 53.3, 45.2, 40.3, 38.7, 38.3, 37.5, 31.6, 26.2, 26.0, 25.6, 23.1, 22.4, 20.3, 19.3, 18.5, 18.2, 17.1, 15.5, 14.5, −3.6, −3.8, −4.3, −4.7; HRMS calcd for $C_{41}H_{73}O_5NSSi_2$: 747.4748; found: 786.4362 (M + K).

Preparation of Compound 124. To a solution of diene **122** (0.015 g; 0.02 mmol) in dry, degassed benzene (20 mL) at rt was added Schrock's metathesis catalyst [Mo(CHMe$_2$Ph)(*N*-(2,6-(*i*-Pr)$_2$C$_6$H$_3$))-(OCMe(CF$_3$)$_2$)$_2$] (0.0038 g; 0.005 mmol) in a dry box. The reaction mixture was then warmed to 55 °C and stirred for 2 h. The reaction mixture was concentrated in vacuo, and the residue was purified by flash chromatography (silica, 4% EtOAc/hexanes) to give an inseparable 1:1 mixture of stereoisomeric alkenes **105** and **123** (0.013 g; 86%).

To a solution of the mixture of alkenes prepared above (0.013 g; 0.018 mmol) in THF (1 mL) was added HF·pyridine (0.5 mL), and the resulting solution was stirred for 1.5 h. The reaction mixture was then poured into saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with chloroform (3 × 30 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (silica, 30% EtOAc/hexanes) to give an equimolar mixture of stereoisomeric alkenes **106** and **124** (0.008 g; 90%). The mixture was separated by preparative thin-layer chromatography (2% MeOH/CH_2Cl_2, four elutions). **124**: IR (film) 3484, 2922, 1732, 1693, 1464, 1260 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (s, 1 H), 6.57 (s, 1 H), 5.30 (m, 1 H), 5.11 (t, J = 6.7 Hz, 1 H), 4.32 (d, J = 10.0 Hz, 1 H), 3.67 (m, 1 H), 3.29−3.25 (band, 3 H), 2.70 (s, 3 H), 2.65−2.45 (band, 5 H), 2.16 (m, 1 H), 2.07 (s, 3 H), 1.98 (m, 1 H), 1.73−1.61 (band, 3 H), 1.60 (s, 3 H), 1.31 (m, 1 H), 1.28 (s, 3 H), 1.17 (d, J = 6.8 Hz, 3 H), 1.05 (s, 3 H), 0.98 (d, J = 7.0 Hz, 3 H); HRMS calcd for $C_{27}H_{41}O_5NS$: 491.2705; found: 492.2795 (M + H).

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Supporting Information Available: Experimental procedures for the preparation of compounds **10**, **12**, **13**, **15**, **16**−**20**, **22**, **24**, **27**, **37**−**44**, **55**−**57**, **65**, **70**−**75**, **107**, **108**, **111**, **112**, **117**−**119**, and **125**−**136** as well as full characterization data are included (60 pages). See any current masthead page for ordering and Internet access instructions.

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