Stereoselective Syntheses of Epothilones A and B via Nitrile Oxide Cycloadditions and Related Studies

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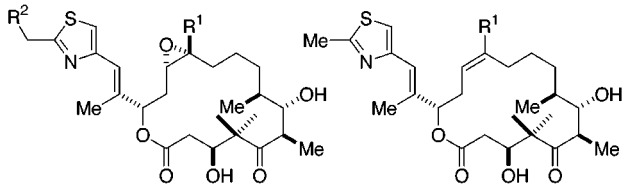
The expedient and fully stereocontrolled synthesis of epothilones A and B are described. The routes described make extensive study of nitrile oxide cycloadditions as surrogates for aldol addition reactions and have led to the realization of a highly convergent synthesis based on the Kanemasa hydroxyl-directed nitrile oxide cycloaddition. As well, our synthetic efforts have led to the development of new reaction methodologies and served as the proving ground for several modern methods for asymmetric carbon−carbon bond formation.

Background and Introduction

The epothilone natural products (**1a**−**f**) are structurally unique polyketide macrolides which share with Taxol the ability to induce tubulin polymerization and associated cellular effects (Chart 1). This extraordinary biologically activity has led to the development of anticancer chemotherapeutics, as evidenced by the phenomenal success of Taxol as a clinical drug. The inherent limitations of Taxol, in particular the emergence of cancer cell lines resistant to Taxol, has placed the identification and study of alternatives at the forefront of chemistry and biology. It is therefore no surprise that the discovery of the epothilones and the recognition of their potent biological activity has prompted interest in the synthesis and pharmacological study of these exciting molecules.[1]

The epothilones were first isolated from cultures of *Sorangium cellulosum* collected from the banks of the Zambesi river in South Africa, by Höfle and co-workers at the Gesellschaft für Biotechnologische Forschung (GBF−Braunschweig) in 1987.[2] Although the potent cytotoxicity of these molecules was recognized and preliminary investigations made, they were deemed too toxic for further study.[3] It was not until 1995 that Bollag and co-workers rediscovered the epothilones using a newly developed assay to screen for molecules which exhibit tubulin polymerization activity that significant interest in the epothilones was generated.[4] Although the epothilones were the first nontaxoid molecules for which this unique mode of action was identified, a number of other molecules which bind to the same or overlapping binding site on the microtubules have been subsequently identified. In addition to the diterpenoids eleutherobin and sarcodicytin,[5] the polyketide natural products discodermolide (**2**)[6] and laulimalide (**3**)[7] show similar biological activity to the epothilones. As well, rhizoxin (**4**) is a complex polyketide macrolide known to bind to tubulin but which acts as an inhibitor of microtubule assembly rather than as a promoter (Chart 2). [8]

Chart 1



1a R^1, R^2 = H Epothilone A
1b R^1 = Me, R^2 = H Epothilone B
1e R^1 = H, R^2 = OH Epothilone E
1f R^1 = Me, R^2 = OH Epothilone F

1c R = H, Epothilone C
1d R = Me, Epothilone D

Although the gross structure of the epothilones had been independently deduced by both Höfle and by Bollag, serious synthetic efforts toward these molecules had to wait for the disclosure of the relative and absolute stereochemistry. Initial progress toward the full structure determination of the epothilones was reported by Georg,[9] but the final structure was obtained by X-ray diffraction analysis of epothilone B by Höfle and co-workers.[2a] Taken together, these studies identified the structurally unique features of the epothilones including their abundance of functional groups. The epothilones also possess several uncommon structural features including the C_4 *gem*-dimethyl group, the thiazole moiety, a *cis*-epoxide, and the C_9−C_{11} spacer region which effectively divides these molecules into two discrete regions of stereochemical and functional complexity.

As is often the case in natural products synthesis the unique structure and important biological activity con-

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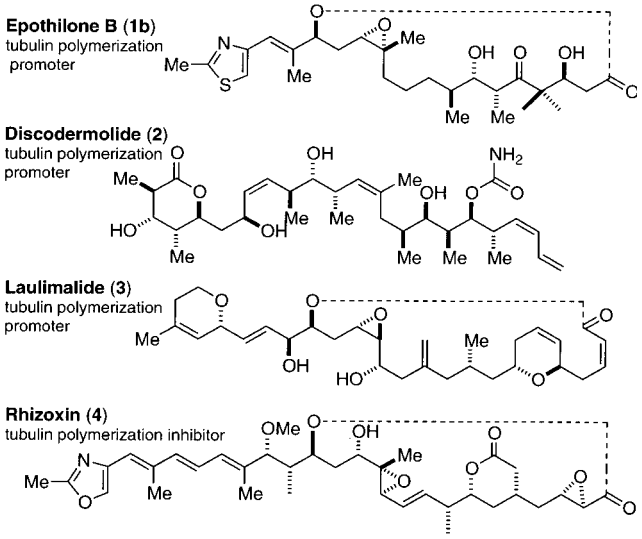
Chart 2



spired to make the epothilones attractive targets for total synthesis. Within six months of the first disclosure of the relative stereochemistry of the epothilones the Danishefsky,[10] Nicolaou,[11] and Schinzer[12] groups each independently completed the total synthesis of epothilone A and, shortly thereafter, epothilone B.[13,14] The impressive efforts toward their total synthesis, both by academic research groups as well as by pharmaceutical companies,[15,16,17] have resulted in a broader understanding of the role of the functional and stereochemical features leading to the physiological effects of the epothilones. These studies, which include both analogue synthesis as well as elegant degradation studies, have made the epothilones the subject of intense synthetic scrutiny, and several promising analogues have been prepared.[15,18]

The published synthetic routes to the epothilones have been reviewed.[1] In general, the published syntheses fall into one of three approaches. The macrocyclic ring-closing metathesis approach has been reported by Nicolaou,[11] Schinzer,[24a] Danishefsky,[19] Grieco,[20] and Lerner.[21] This strategy takes advantage of the rapid assembly of the necessary subunits, their convergent coupling, macrocyclization, and stereoselective epoxidation. The second approach, pioneered by Danishefsky[10,22] and continued by White,[23] Schinzer,[24] Shibasaki,[25] and Panek,[26] recognized a disconnection at or near the $C_{12}-C_{13}$ *cis*-olefin of epothilones C and D to achieve a convergent coupling of two stereochemically advanced fragments. The convergent aldol approach, pioneered by Nicolaou[27] and by Mulzer,[28,29] takes advantage of the full aldol retron at C_5-C_7 of the epothilone backbone and joins the appropriate fragments at their point of greatest functional and stereochemical complexity. The various approaches underscore the persistent limitations of modern asymmetric synthesis that demand a balance between convergency and efficient stereochemical control. A major current objective in epothilone syntheses is the development of a strategy to achieve a *concise, convergent, and fully stereocontrolled* approach.

We now report a full account of our studies toward this goal, culminating in the expedient and stereoselective syntheses of epothilones A and B.[30] Critical to the success of this endeavor has been the development and application of new methodologies and strategies suitable for the construction of functionally and stereochemically complex molecules. Our efforts have also focused on the exploration and advancement of the use of nitrile oxides as surrogates for aldol addition reactions.

Synthetic Plan

Our initial synthetic planning of routes for the epothilones benefited from early reports highlighting the unique difficulties in controlling the stereochemistry of the critical polypropionate region. Although we considered a convergent aldol coupling at C_5-C_7 to be an attractive synthetic disconnection, the first generation syntheses that had been reported documented the difficulties in stereoselectively accomplishing the necessary *anti*-Felkin aldol addition.[31] Likewise, although all of the initial approaches had employed a stereoselective epoxidation reaction as the final step, we believed that early

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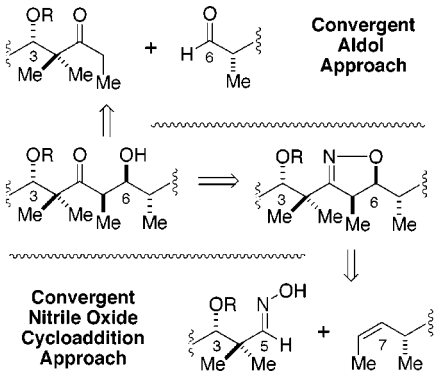
Scheme 1



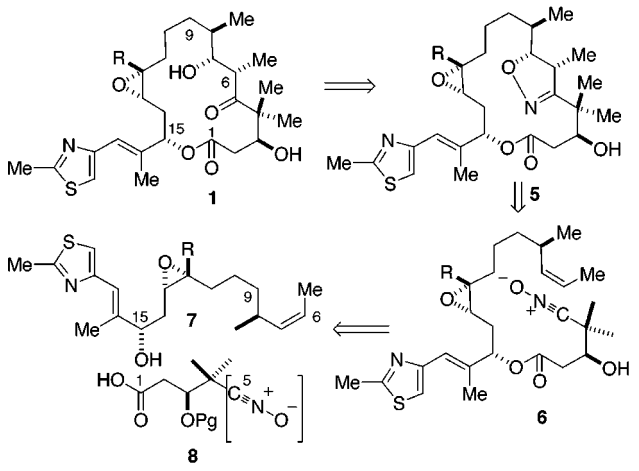
introduction of the epoxide functionally would be advantageous.

Initial Approach. Closer analysis of the epothilone structure revealed the potential use of a nitrile oxide cycloaddition approach to be particularly promising.[32] In analogy to strategies employing aldol couplings, the use of a nitrile oxide cycloaddition would lead to a disconnection of the epothilones at their point of greatest stereochemical and functional complexity, and a single reaction step would suffice for the construction of two bonds, two stereocenters, and two functional groups in the correct oxidation state (Scheme 1). This was predicated on the known transformation of isoxazolines to β-hydroxy ketones via N−O bond reduction and imine hydrolysis. Importantly, the necessary precursors, a *cis*-olefin and a nitrile oxide, would be readily accessible and amenable to concise, convergent synthetic routes.

This use of a strategy based on nitrile oxide cycloaddition, however, was not without considerable concerns. Although its successful implementation would undoubtedly lead to convergency, issues of regioselectivity, chemoselectivity, and reactivity of the unactivated *cis*-double bond would have to be addressed. Although it is true that unactivated di- and trisubstituted olefins are notoriously poor reaction partners in dipolar cycloadditions, this limitation typically stems from the tendency of the nitrile oxide to undergo competing decomposition or dimerization in preference to cycloaddition. The nonproductive decomposition pathways depend on the sterics associated with the nitrile oxides; hindered nitrile oxide are known to be ideal reaction partners even with unactivated olefins. Because we would require a tertiary nitrile oxide at C_5, these precedents offered considerable promise for the application of this methodology for epothilone synthesis. The use of *cis*-olefins also presents questions of regiochemistry, particularly if they are not substituted by electronically activating groups. However, we found promising precedent for steric control of this reaction in Martin's report that the reaction of a similarly substituted *cis*-olefin and a tertiary nitrile oxide provided the cycloadduct as a single regioisomer.[33]

In hopes of achieving a convergent approach to the epothilones, we planned to introduce the thiazole side chain early in the synthetic route. This presented,

Scheme 2



however, an additional site of unsaturation where the nitrile oxide could potentially react. We anticipated the trisubstituted olefin to be considerably less reactive than the requisite *cis*-olefin, given the reported chemoselective oxidation of a *cis*-olefin in the presence of the thiazole side chain which enabled the late-stage epoxidation of epothilones C and D to form epothilones A and B.[1] However, we felt that we could further influence the chemoselectivity, regioselectivity, and ultimately stereoselectivity of the cycloaddition by effecting a macrocyclic, ring-closing, nitrile oxide cycloaddition (Scheme 2). Importantly, a number of elegant applications of macrocyclic nitrile oxide cycloadditions of simpler systems in remarkably good yields and with complete regiochemical control further persuaded us to pursue such a route. [34]

These considerations and precedents led to our first retrosynthetic analysis of the epothilones. In addition to providing an alternative to the problematic aldol reaction, we felt the use of an intramolecular nitrile oxide approach limited superfluous protection group manipulation and divided the epothilone structure into two accessible fragments, designated as the C_1-C_5 fragment (**8**) and the C_6-C_{15} fragment (**7**). With these two subunits as targets, we initiated our synthetic efforts toward the epothilones. Although this initial approach proved untenable, the route employed for the fragment synthesis proved useful in developing a successful and convergent strategy to the epothilones. Indeed, the chemistry we developed in the synthesis of the C_6-C_{15} fragment in the context of the macrocyclic nitrile oxide cycloaddition approach was directly applicable to an alternative and fully stereocontrolled route. Following the landmark disclosure by Mulzer that introduction of the $C_{12}-C_{13}$ epoxide prior to a convergent aldol reaction resulted in the successful realization of a highly diastereoselective fragment coupling, we readily adapted our initial route to take advantage of this development.[29] Further refinements in our synthetic approach ultimately led to the total synthesis of epothilone A (21 steps) and a formal synthesis of epothilone B (18 steps in total) based on Mulzer's stereocontrolled convergent aldol approach (Scheme 3). These routes, as well as our studies toward the macrocyclic nitrile oxide approach, make extensive use of new reaction methodologies.

Preliminary Studies

Fragment Synthesis: The C_6-C_{15} Fragment. Our initial attempts to achieve a workable synthesis focused

(31) For a more detailed analysis of the challenges in controlling the stereochemical outcome of this aldol reaction, see Wu, Z.; Zhang, F.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *24*, 4505−4508.

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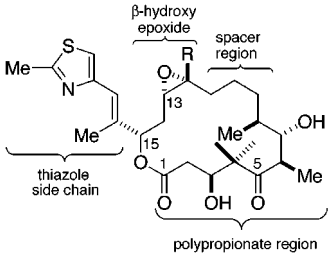
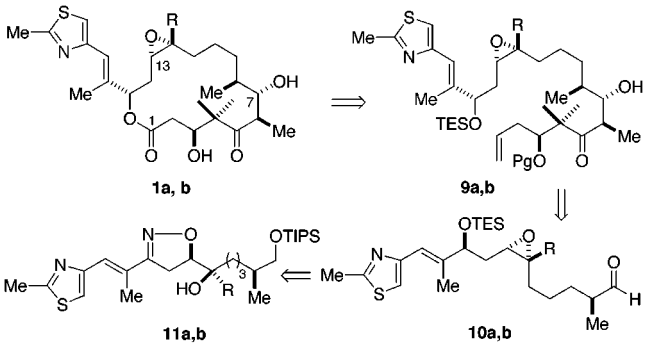
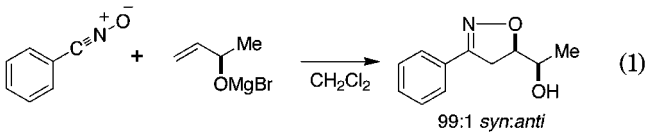


Figure 1.

Scheme 3



on aldol methodology including both catalytic, asymmetric aldol reactions as well as chiral reagent-based approaches. As in the case of the C_3-C_8 polypropionate region, we found these methodologies to be limited either by their stereoselectivity or their practicality, and we sought to explore less established chemistry to achieve a novel and expedient synthesis. In this regard, we were intrigued by the report of a powerful, yet seemingly overlooked hydroxy-directed nitrile oxide cycloaddition reaction reported by Kanemasa (eq 1).[35] A short series



(1)

of publications documented important effects of Mg(II) ion on the course of nitrile oxide cycloaddition of benzonitrile oxide with an allylic alkoxide including a significant increase in the rate of the cycloaddition and a stabilization of the reactive nitrile oxide by coordination of the magnesium ion to the Lewis basic oxygen (Figure 2).[36] Furthermore, the allylic alkoxide was proposed to coordinate to the magnesium and to promote a pseudo-intramolecular reaction with the magnesium ion acting as a transient tether. Importantly, with chiral allylic alcohols, an impressive degree of *syn*-stereoselectivity (99:1 syn:anti) in the cycloaddition was observed, and it is noteworthy that even substituted, unactivated olefins react under these conditions at 0 °C or below.

Although a viable experimental protocol for the preparative use of this reaction was not the focus of Kanemasa's studies, his observations provided the basis for

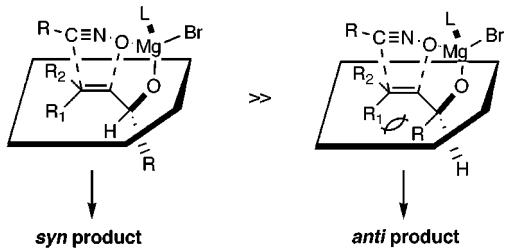
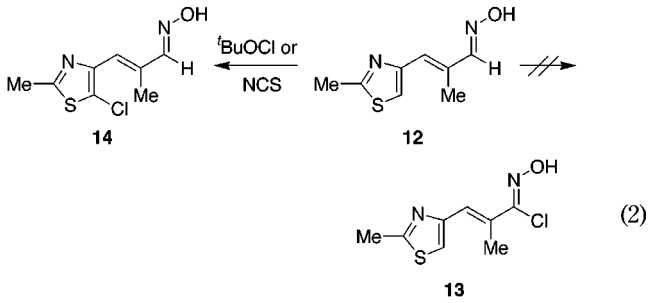


Figure 2.

our development of operationally simple, broadly applicable reaction conditions which enabled the highly diastereoselective cycloaddition with a wide range of reaction partners, including aliphatic and C-alkynyl nitrile oxides.[37] However, our attempts to extend this chemistry to the requisite thiazole-containing oxime **12** were thwarted by the inability to selectively generate the nitrile oxide precursor. After our initial attempts at cycloaddition failed to provide any cycloadducts, we reinvestigated the chlorination (NCS) of oxime **12** and noted that chlorination occurred selectively on the aromatic ring to give **14** (eq 2). Attempts to effect successful



(2)

oxidation with milder halogenating agents, such as *tert*-BuOCl or NBS, gave identical results.

As an alternative, we sought a nitrile oxide precursor which would allow introduction of the sensitive thiazole at a later stage. In this regard the nitrile oxide derived from readily prepared oxime **17**[38] was chosen for the late stage introduction of the thiazole.[39] At the outset, we had serious concerns with the use of this phosphonate, as it was expected to be highly base sensitive. However, hydroximinoyl chloride **18** prepared from oxime **17** underwent diastereoselective nitrile oxide cycloaddition to give **20** as a single syn diastereomer at the isoxazoline oxygen (Scheme 4). Oxime **17** proved to be a stable, versatile nitrile oxide precursor critical to achieving an efficient, convergent synthesis of C_6-C_{15} epothilone subunit **21** and became the cornerstone of our epothilone syntheses (Scheme 5).

The successful implementation of this strategy necessitated convenient access to the appropriate allylic alcohols such as **24**. Although chiral allylic alcohols are valuable synthetic building blocks, there exist remarkably few methods for their general, enantioselective synthesis. By far the most common method, kinetic

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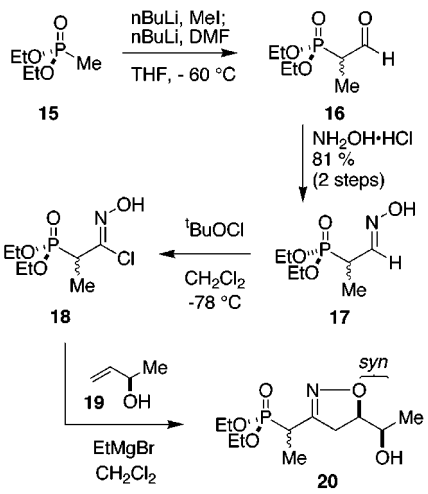
(38) For a single step, high yielding preparation of the corresponding aldehyde from diethylmethyl phosphonate, see Aboujaoude, E. E.; Collignon, N. *Synthesis* **1983**, 635.

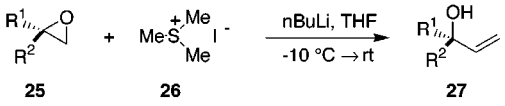
(39) For the use of a related phosphonate-containing nitrile oxide in a thermal cycloaddition, see: Tsuge, O.; Kanemasa, S.; Suga, H. Nakagawa, N. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2463.

Scheme 4



resolution, reliably provides the desired product in high enantiomeric excess.[40] In our case, however, the presence of an additional stereocenter in allylic alcohol **24** made such a strategy unappealing. The leading alternative, the asymmetric addition of carbanions to an appropriate aldehyde,[41] appeared promising; however, cumbersome preparations of the chiral vinylorganometallic along with less than optimal chiral induction rendered such an approach less than ideal.

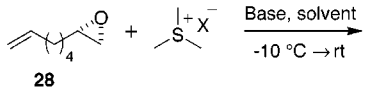
Monosubstituted chiral epoxides have recently become easy to access in high enantiopurity, and we sought a procedure for the direct conversion of a terminal epoxide to the corresponding allylic alcohol.[42] In this respect, the single step conversion of epoxides to allylic alcohols reported by Mioskowski and Falck seemed promising. This protocol, the addition excess Corey−Chaykovsky dimethylsulfonium methylide to epoxides and aldehydes, directly affords chiral allylic alcohols but was unexploited apart from the original disclosure (eq 3).[43,44] Thus, we

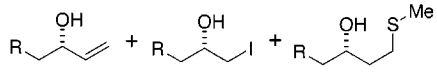


(3)

were prompted to conduct an investigation of this reaction before applying it to the synthetic strategy en route to the epothilones. Using commercially available **28** as our model epoxide, we were initially disappointed to find that the reported reaction conditions gave the corresponding allylic alcohol **29** in less than 10% yield (Table 1, entry 1). However, we noted that changing the solvent from the reported THF to Et_2O resulted in a dramatic improvement in consumption of the starting material (entry 2), albeit the product formed was contaminated with significant amounts of the corresponding iodohydrin. Further attempts to influence the product distribution by variation of reaction solvent and base did not lead to

Table 1. Optimization of the Epoxide Opening





entry	X	solvent	base	% **29**	% **30**	% **31**
1	I	THF	^{n}BuLi	10	trace	—
2	I	Et_2O	^{n}BuLi	70	30	—
3	I	1:1 Et_2O/hex	^{n}BuLi	complex mixture		
4	I	Et_2O	EtMgBr	—	30−40	—
5	I	Et_2O	NaH	no reaction		
6	I	Et_2O	KH	no reaction		
7	OSO_3Me	Et_2O	^{n}BuLi	no reaction		
8	OSO_3Me	THF	^{n}BuLi	no reaction		
9	OSO_3Me	DME	^{n}BuLi	no reaction		
10	OSO_2CF_3	Et_2O	^{n}BuLi	82	—	trace

marked improvements (entries 3−6). Reasoning that changing the counteranion associated with the trialkyl sulfonium salt from iodide to a nonnucleophilic alternative would preclude formation of such byproducts, we conducted the epoxide-opening reaction with commercially available trimethylsulfonium methyl sulfate; however, the insolubility of this salt rendered the reaction unworkable (entries 7−9). In contrast, the use of trimethyl sulfonium triflate, prepared by reaction of dimethyl sulfide and methyl triflate, proved optimal. The desired allylic alcohol product was reliably obtained in preparatively useful scales in >80% yield with traces of thioether **31** (>1%) as the only detectable side-product (entry 10).

Having developed suitable conditions for the conversion of a terminal epoxide to the corresponding homologous allylic alcohol, we were ready to commence with the synthesis of the necessary fragment **24**. The synthesis began with the convenient alkylation of (*R,R*)-pseudoephedrine-derived amide **32** with readily available iodide **33** (89%) to give **34** as a single diastereomer, as previously described by Myers (Scheme 6).[45] Reduction of the chiral amide with the BuLi/NH_3•BH_3 afforded alcohol **35** in 99% yield.[46] Oxidation of **35** under Ley conditions (TPAP, NMO, 4 Å MS)[47] followed by Wittig olefination (Ph_3EtPI, $NaNH_2$) afforded the *cis*-olefin **36** in 84% yield and >95% ee as a 13:1 mixture of cis:trans diastereomers. The integrity of the methine stereocenter through the series of reactions was confirmed following desilylation, Mosher ester formation,[48] GC (Hewlett-Packard HP-5 siloxane column) analysis, and comparison to an authentic, racemic sample.[49]

Terminal epoxide **42** was assembled by reaction of (*R*)-glycidol tosylate and Grignard **38** as shown in Scheme 7.[50] The organomagnesium reagent was procured by conversion of silyl ether **36** to bromide **37** (PPh_3•Br_2,

(40) For a comprehensive review, see Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1−300.

(41) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1988**, *29*, 5645−5648.

(42) (a) Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 1, 6086−6087. (b) Tokunaga, M.; Larrow J. F.; Kakiuchi, F.; Jacobsen E. N. *Science* **1997**, *277*, 936−938.

(43) Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Martel, J. P.; Legall, T.; Shin, D.-S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 5449.

(44) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 7, 1353−1364.

(45) (a) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496−6511. (b) Myers, A. G.; Yang, B. H.; Chen, H. *Org. Synth.* **1999**, *77*, 22.

(46) (a) Myers, A. G.; Yang, B. H.; Chen, H. *Org. Synth.* **1999**, *77*, 29. (b) Myers, A. G.; Yang, B. H.; Kopecky, D. *Tetrahedron Lett.* **1996**, *37*, 3623.

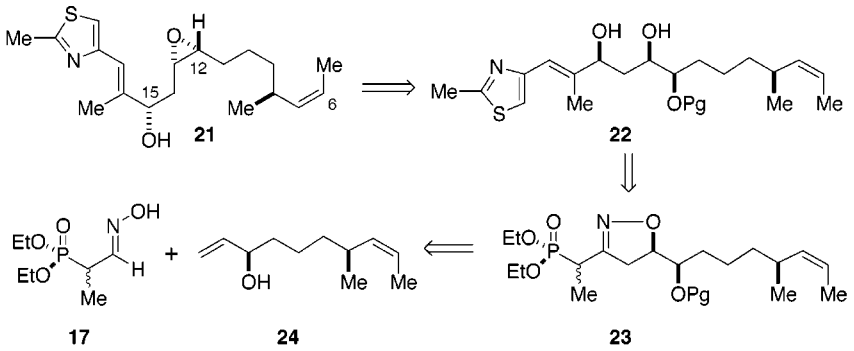
(47) Griffen, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *Chem Commun.* **1987**, 1625.

(48) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

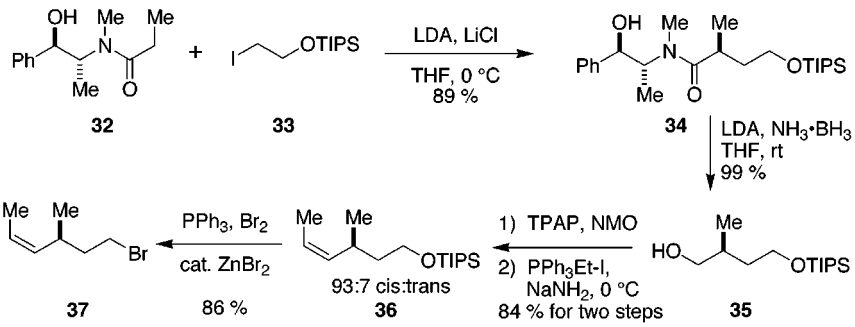
(49) The preparation of this alcohol has been reported: Reitz, A. B,; Nortey, S. O.; Maryanoff, B. E.; Liotta, D.; Monaham, R. *J. Org. Chem.* **1987**, *52*, 4191.

(50) (a) Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 1295. (b) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437.

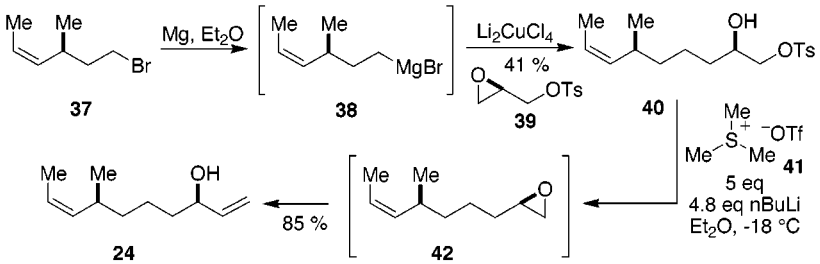
Scheme 5



Scheme 6



Scheme 7



catalytic $ZnBr_2$),[51] Grignard formation (Mg, Et_2O), and copper-catalyzed epoxide opening of commercially available (*R*)-tosyl-glycidol (**39**) to afford hydroxy tosylate **40**.[52] Although terminal epoxide **42** could be isolated following the Grignard coupling simply by allowing the reaction to warm to room temperature, the instability of epoxide **42** prompted us to develop conditions for in situ epoxide formation and opening to give the chiral allylic alcohol **24**. In this regard, treatment of **40** with 5 equiv of **41** and 4.8 equiv of *n*-BuLi according to our optimized procedure cleanly afforded allylic alcohol **24** in 85% yield.

With **18** and **24** in hand, we were poised to conduct the critical hydroxyl-directed nitrile oxide cycloaddition. Although such cycloadditions had never been documented on substrates possessing the complexity of these reaction partners, the dipolar cycloaddition reaction proceeded smoothly (2 days, rt), providing isoxazoline **23** in 77% yield (Scheme 8). The secondary alcohol in **23** was protected as a TBS-ether (^{t}BuMe$_2$SiOTf, ^{i}Pr$_2$EtN) to afford **43**. Following a survey of bases and reaction conditions, the use of LiHMDS was identified as optimal in terms of yield and stereoselectivity for the reaction of aldehyde **44** and phosphonate **43**. Under these conditions, the formation byproducts by Cannizaro reaction was minimized, and *trans*-**45** was isolated in 87% yield along with 9% of the minor *cis*-diastereomer, which could be readily separated by chromatography on silica gel.

The preparation of **45** constitutes the completion of the C_6-C_{15} carbon backbone of fragment **21**. However, the subsequent unmasking of the isoxazoline to furnish the corresponding hydroxy ketone proved difficult. Although the reduction of isoxazolines to β-hydroxy-ketones is a well-studied transformation, surprisingly, it was virtually unknown for isoxazolines in which C=N is conjugated with an exocyclic C=C or C≡C. Moreover, for the substrate at hand (**45**) the presence of both a conjugated and a nonconjugated olefin provided a particularly challenging case for chemoselective reduction (Scheme 9).

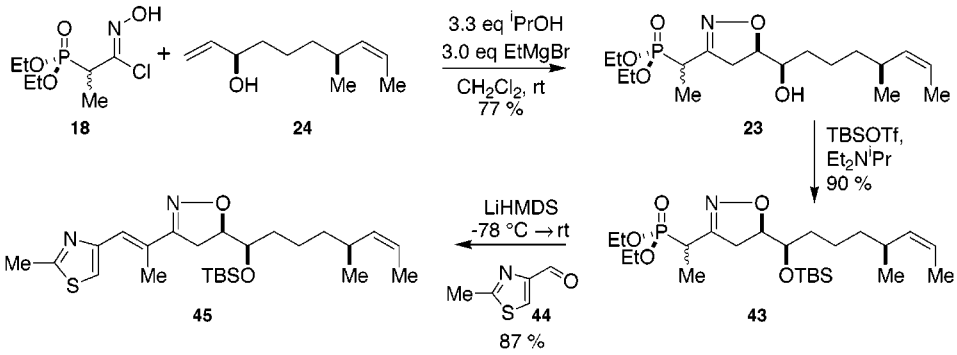
Torssell and co-workers had examined the reduction of 3-vinyl-substituted isoxazolines and noted that the commonly employed reagents, such as Raney-Ni, $TiCl_3$, and Zn/AcOH, result in concomitant reduction of the olefin and N−O bond.[53] As an alternative, a two-step protocol was developed involving *N*-alkylation of the isoxazoline followed by electrochemical reduction of the resulting *N*-alkyl isoxazolinium. Because the compatibility of the reactive thiazole to such conditions was of

(51) Aizpurua, J. M.; Cossio, F. P.; Palomo, C. *J. Org. Chem.* **1986**, *51*, 1, 4941−4943.

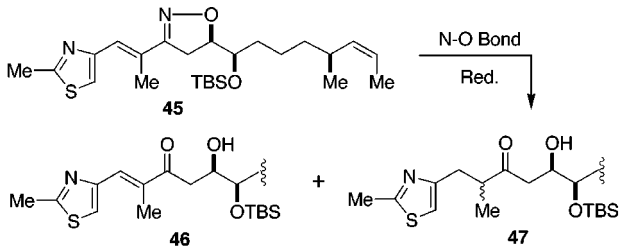
(52) We are grateful to Diacel coporation for a generous gift of (*R*)-tosyl-glycidol.

(53) Isager, P.; Thomsen, I.; Torsell, K. G. B. *Acta Chem. Scand.* **1990**, *44*, 806

Scheme 8

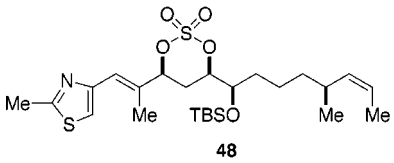


Scheme 9



some concern, we proceed to examine a number of other reduction protocols. In this respect, $Mo(CO)_6$ in CH_3CN has recently emerged as a useful reagent for N−O bond cleavage for isoxazoles and isoxazolines.[54] This reagent, indeed, did provide the desired conjugated ketone **46**, albeit in at best 35−40% isolated yield despite extensive attempts at optimization. A critical problem with this reaction was the low mass balance following reaction workup. Following the lead of previous reports that yields of similar reductions were improved by absorbing the crude reaction mixture onto silica gel and exposure to air (1−2 days) led to the isolation of **46** (40−50% yield) contaminated with saturated ketone **47** (30%) and 20% recovered starting material (**45**).[55] A mild, selective, workable solution to the isoxazoline reductive cleavage to furnish hydroxy ketone **46** eventually emerged from our studies. Thus smooth cleavage of the isoxazoline N−O could be effected with 3−4 equiv of SmI_2 in THF at 0 °C, followed by imine hydrolysis with $B(OH)_3$ to give the desired conjugated ketone (**46**) in 75% yield.[56]

Following 1,3-syn reduction of ketone **46** under Prasad conditions (Et_3B, MeOH, $NaBH_4$),[57] a key chemoselectivity issue presented itself: differentiating two secondary hydroxyl groups in anticipation of epoxide formation. Although considerable work could be relied upon for the differentiation of secondary alcohols, the fact that the desired series of reactions would necessitate not only hydroxyl group differentiation, but also activation, epoxide formation, and deprotection encouraged a novel solution. An attractive approach would be the formation of a bis-activated derivative, in which selective C−O cleavage would lead to the desired epoxide. In this regard, the obvious candidate, a cyclic sulfate, could be prepared in moderate yield; however, the desired hydroxy epoxide could not be isolated following treatment of **48** with fluoride sources and attempts at subsequent sulfate hydrolysis.[58,59]



We soon decided to focus our attention on the less reactive, and rarely studied, 1,3-cyclic *sulfite* which could be readily prepared in one step from diol **49** and had been an intermediate in the formation of the cyclic sulfate **48** (Scheme 10). We were pleased to discover that treatment of the unpurified cyclic sulfite with excess $TBAF{\cdot}3H_2O$ in refluxing THF cleanly led to the formation of the desired epoxide in 80% yield.[60] This expedient transformation from triol to β-hydroxy epoxide effects, in a single reaction vessel, cyclic sulfite formation, desilylation, ring closure to form the epoxide, and SO_2 extrusion, completing the synthesis of **21**.[61,62] The successful formation of epoxide **21** allowed us to confirm the sense of stereoinduction observed in the hydroxyl-directed nitrile oxide cycloaddition. Analysis by ^1H NMR spectroscopy of the coupling constant of the vicinal epoxide protons ($J = 4.2$ Hz) was consistent with that of a *cis*-epoxide.

The Nitrile Oxide Fragment. The sensitivity of the thiazole ring toward halogenation presented an obstacle to the generation of the requisite nitrile oxide precursor from an oxime; thus, other protocols for the introduction

(54) (a) Baraldi, P. G.; Barco, A.; Benetti, S.; Manfredini, S.; Simoni, D. *Synthesis* **1987**, 276. (b) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351−3354.

(55) (a) Guarna, A.; Guidi, A.; Goti, A.; Brandi, A.; De Sarlo, F. *Synthesis* **1989**, 175−178(b) Trost, B. M.; Chupak, L. S.; Lübbers, T. *J. Am. Chem. Soc.* **1998**, *120*, 1732−1740.

(56) Bode, J. W.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 1587−1590.

(57) (a) Chen, K.-M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923−1926.

(58) For a review of the chemistry of cyclic sulfates, see Lohray, B. B. *Synthesis* **1992**, 1035−1052.

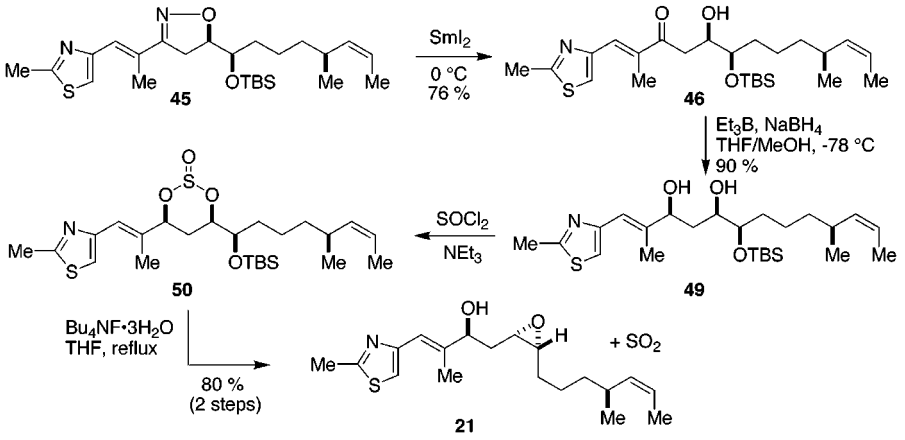
(59) While the suspected byproducts were not isolated, we surmised that the acidic conditions required to hydrolyze the resulting sulfate may result in degradation of the newly formed epoxide, perhaps via intramolecular cyclization.

(60) An epoxide has been implicated as a transient intermediate following the treatment of related 1,2-cyclic sulfates with TBAF: Ko, S. Y.; Malik, M. *Tetrahedon Lett.* **1993**, *34*, 4675−4678.

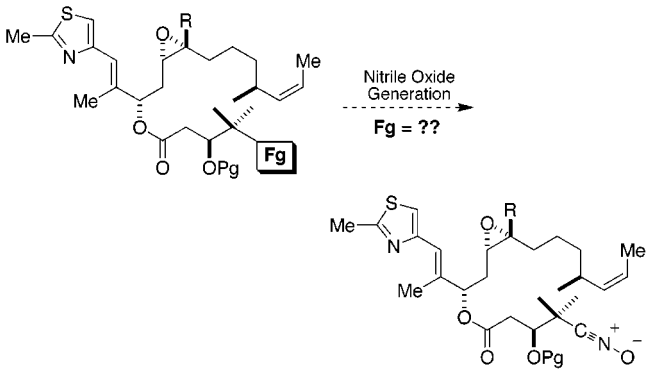
(61) The presence of the silyl group is not essential for this transformation; the corresponding hydroxy-cyclic sulfite undergoes the same reaction under the identical conditions and can be observed as an intermediate in this reaction.

(62) In a somewhat related example, a 1-hydroxy,4-mesyloxy,5-silyloxy-protected triol system undergoes desilylation, epoxide formation, and 5-*exo* epoxide opening to afford a substituted tetrahydrofuran under similar reaction conditions (Hori, K.; Kazuno, H.; Nomura, K.; Yoshii, E. *Tetrahedron Lett.* **1993**, *34*, 2183−2186.). In our case, we do not observe any tetrahydrofuran formation which would arise from 5-*endo* opening of the epoxide.

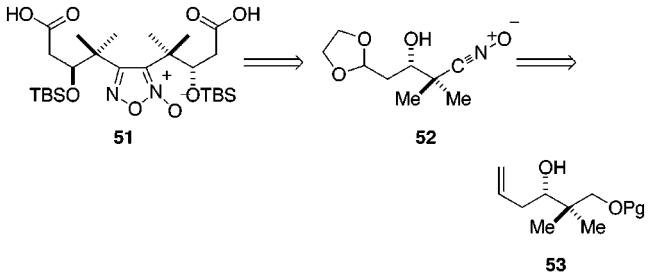
Scheme 10



Scheme 11

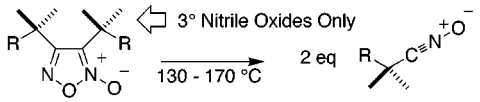


Scheme 12



of this functionality were sought.[63] The other general method for nitrile oxide synthesis, the Mukaiyama–Hoshino method,[64] involves the dehydration of primary nitroalkanes. Unfortunately, while this method appeared at first to be viable, it necessitated the preparation of a neopentyl nitro (Scheme 11). The difficulty in synthesizing such substrates, as well as concerns about the dehydration step, encouraged us to seek novel solutions to the preparation of nitrile oxides in functionally rich molecules.[65]

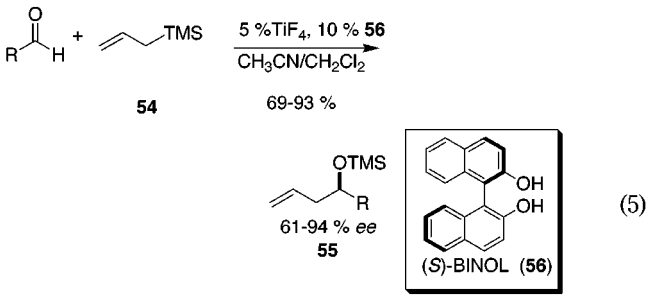
The fact that the desired cycloaddition reaction required a tertiary nitrile oxide led us to investigate a protocol reported by Curran in which nitrile oxides are generated thermally from a furoxan dimer. This reaction involves cracking the nominal nitrile oxide dimer to provide the reactive species, a process which Curran had demonstrated to be viable only for very highly substituted nitrile oxides (eq 4).[66] Further analysis revealed a number



(4)

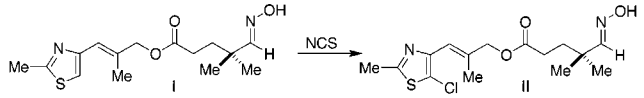
of key advantages to an approach that relied on such a fragmentation reaction to furnish the reactive nitrile oxide thermally in situ. The use of a furoxan dimer as a nitrile oxide precursor would serve as a stable masking group for the nitrile oxide. Moreover, it would allow the generation of the nitrile oxide under very high dilution conditions, favoring formation of the macrocyclic ring and disfavoring the two major nitrile oxide decomposition pathways, both of which are intermolecular: dimerization (which would be inconsequential as it would return starting furoxan), and isocyanate formation. Even more attractive was that these conditions allowed Curran to achieve nitrile oxide cycloaddition of similarly substituted *cis*-olefins in good yields.[67] With this nitrile oxide precursor, a furoxan dimer, as our target, we commenced our preparation of C_1–C_5 fragment **51** (Scheme 12).

The presence of a *gem*-dimethyl group in the desired nitrile oxide **52** presented the ideal opportunity to apply the enantioselective TiF_4–BINOL catalyzed addition of allyl trimethylsilate to aldehydes (eq 5).[68] This reaction



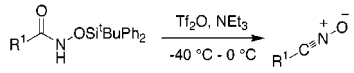
(5)

(63) A model study of the oxime chlorination reinforced our concerns about this approach to the nitrile oxide:

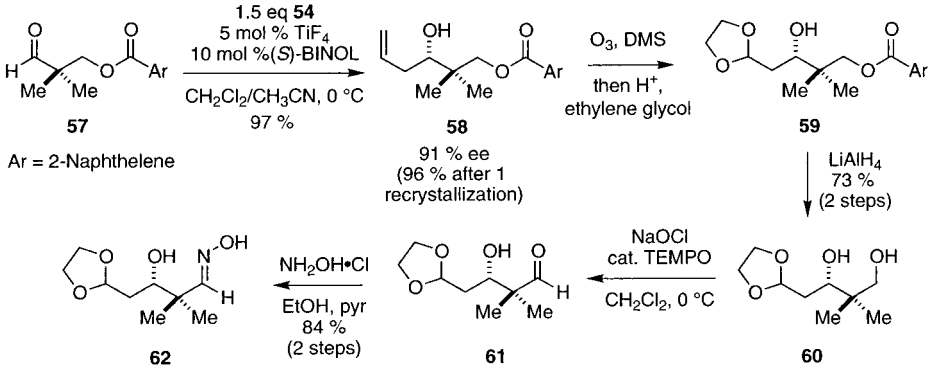


(64) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.

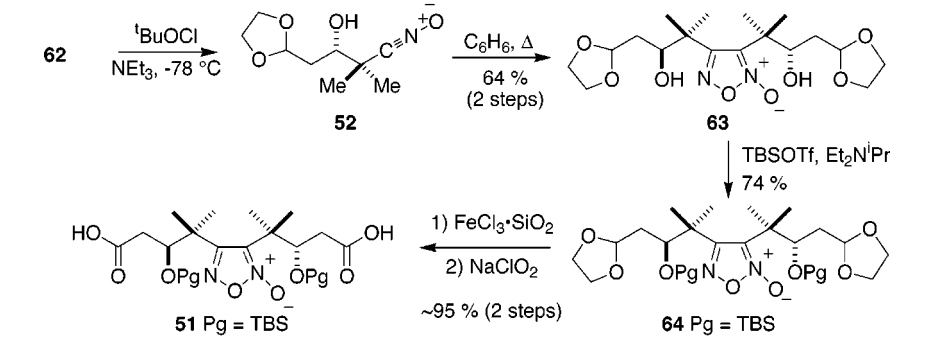
(65) These and other difficulties in the preparation of nitrile oxides encountered during our synthesis of the epothilones led to the development of a novel, general method for nitrile oxide generation from *O*-TBDPS hydroxamates: Muri, D.; Bode, J. W.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 539–542.



Scheme 13



Scheme 14



offers several advantages over related processes including the commercial availability of the ligand, the metal, and allyl silane; the single step, in situ, preparation of the active catalyst; the low toxicity of the allyl silane as compared to the corresponding and often utilized allylstanne reagents; and the ability to run this reaction at high concentration at 0 °C. This was found to be particularly effective, in terms of both yield and enantioselectivity, for the allylsilylation of sterically demanding aldehydes such as those required for an epothilone total synthesis.

Following preliminary results which suggested this reaction would function well with a suitably functionalized aldehyde, we identified aldehyde **57** as an optiminal substrate in terms of yield, enantioselectivity, and the possibility to enrichment the enantiopurity by recrystallization. Noteworthy is the ability to perform this reaction on a preparative scale (40 mmol) using 5 mol % catalyst and at high substrate concentration (approximately 4 M).

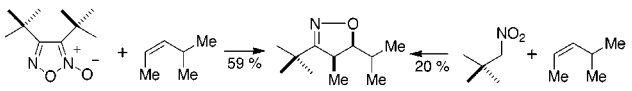
With substantial quantities of **58** available, its elaboration to **52** was subsequently investigated (Scheme 13). Ozonolytic cleavage of the double bond followed by in situ protection afforded acetal **59** which was reductively deprotected ($LiAlH_4$) to furnish diol **60** in 73% overall yield. Selective oxidation of the primary alcohol (catalytic TEMPO, NaOCl, catalytic KBr) cleanly afforded hydroxy aldehyde **61** which was converted directly to its corresponding oxime (**62**).[69]

Nitrile oxide formation was readily achieved by oxime chlorination with *tert*-BuOCl and deprotonation with Et_3N to provide stable, chromatographically isolatable nitrile oxide **52** (Scheme 14). In practice, however, the cleanly formed nitrile oxide was taken directly to the dimerization step. Refluxing a concentrated solution (1.0 M) of **52** in benzene for 18 h resulted in clean formation of the UV active, more polar (TLC), unsymmetrical dimer **63**.[70] Protection of the secondary hydroxyls (TBSOTf, Hünig's base) proceeded smoothly to give **64**. Selective acetal hydrolysis in the presences of the TBS ethers was achieved by the action of $FeCl_3$•SiO_2 in acetone.[71] Finally, Lindgrin oxidation of the dialdehyde to the diacid proceeded without incident to give **51**, completing the synthesis of the C_1-C_5 subunit.

Intramolecular, Ring-Closing Nitrile Oxide Cycloaddition. In preparation for the key step, nitrile oxide fragment **51** and olefin fragment **21** were coupled under standard ester forming conditions to provide the unsymmetrical diester **65** (Scheme 15). Upon heating a dilute (0.00014 M) solution of dimeric diester **65** in C_6H_6 at 150 °C for 36 h, a product of nitrile oxide cycloaddition was

(66) Curran, D. P.; Fenk, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 7, 6023−6028.

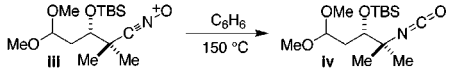
(67) For example, Curran obtained a 59% yield in a related cycloaddition of 1.1 equiv of a *cis*-olefin using a furoxan as the nitrile oxide precursor. In contrast, the same cycloaddition using a nitro compound as the nitrile oxide precursor and excess olefin afforded the product in only 20% yield:



(68) Gauthier, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2363.

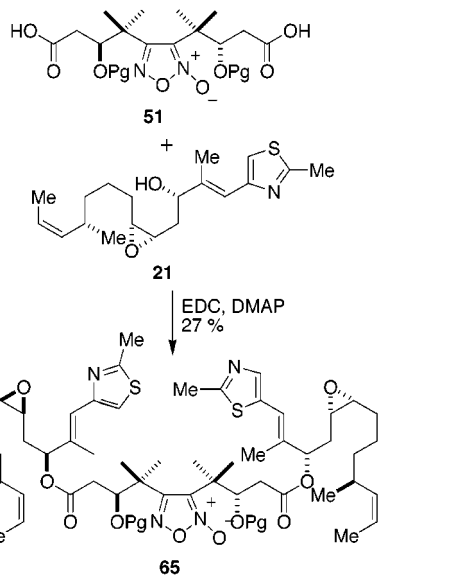
(69) (a) Anelli, P. L., Biffi, C., Montanari, F. Quici, S. *J. Org. Chem.* **1987**, *52*, 2559−2562. (b) For a review of TEMPO mediated oxidations, see de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153−1174.

(70) Attempts to dimerize a more sterically hindered nitrile oxide failed to provide the desired furoxan dimer and the isocyanate was isolated in good yield:

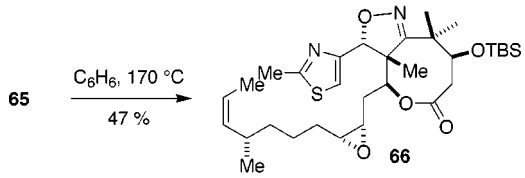


(71) Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem.* **1986**, *51*, 404.

Scheme 15



Scheme 16



obtained as a single regio- and stereoisomer in 47% yield.[72] Unfortunately, upon closer analysis of both the crude reaction mixture and the isolated products, we found that cycloaddition had occurred exclusively on the more highly substituted olefin (Scheme 16).[73,74] This result prompted us to reevaluate the use of a nitrile oxide cycloaddition reaction for the macrocyclization step and subsequently led to the development of a convergent route that relied on diastereoselective nitrile oxide cycloadditions to assemble the constituent fragments and lactonization of a seco-acid to furnish the desired macrocycle.

The Convergent Aldol Approach. The disclosure by Mulzer of a highly stereoselective convergent aldol coupling in the context of an epothilone B total synthesis provided an intriguing precendent for a new approach to the epothilones built upon chemistry developed for the synthesis of the C_6-C_{15} fragment. Mulzer reported that while the aldol reaction of aldehyde **67** with a $C_{12}-C_{13}$ olefin proceeded with only 4:1 dr, the aldol with aldehyde **69** containing a $C_{12}-C_{13}$ epoxide gave the desired *anti*-Felkin product in >10:1 dr and 91% yield which could be readily transformed to epothilone B (Scheme 17).[29]

Given the abundance of remote effects in related aldol reactions, however, we could not be confident that the same approach would be amenable to the epothilone A series. Fortunately, our previously prepared subunit **21** was readily converted to the appropriate aldehyde (**70**) and tested in this respect. Following protection of the secondary alcohol as its TES-ether, we were pleased to find that the *cis*-olefin, which had refused to undergo 1,3-dipolar cycloaddition, could be selectively dihydroxylated (catalytic OsO_4, NMO) and the unpurified diol cleaved ($Pb(OAc)_4$)to the requisite aldehyde (Scheme 18).

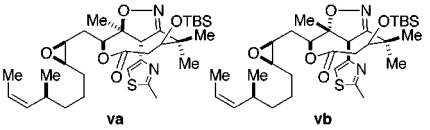
Aldehyde **70** undergoes highly diastereoselective aldol coupling with 1.5 equiv of **68** at −78 °C (Scheme 19). Importantly, we found this reaction to be reliable, consistently affording the desired product in >10:1 dr. With a solution to the synthesis of the critical polypropionate region in hand, we opted to revisit our epothilone A synthesis.

Second Generation Syntheses of Epothilones A and B. The Total Synthesis of Epothilone A. The successful total synthesis of epothilone A began with the preparation of aldehyde **73** from known chiral alcohol **72** (Scheme 20).[27] Although our initial report of highly asymmetric alkyne additions to aldehydes were not readily extended to unbranched, aliphatic substrates,[75a] we have recently developed conditions for the enantioselective addition 3-methylbutyn-2-ol which appeared promising for the synthesis of the requisite chiral allylic alcohol.[75b] In this regard, aldehyde **73** undergoes clean, highly diastereoselective (>20:1 dr) alkyne addition under the reported conditions. Following protection of the unpurified secondary alcohol as a benzoate ester, propargylic ester **75** was obtained in 72% yield. Extrusion of acetone (K_2CO_3, catalytic 18-crown-6) and treatment of the ester with $LiAlH_4$ provided chiral allylic alcohol **77** directly in 81% overall yield from **75**.

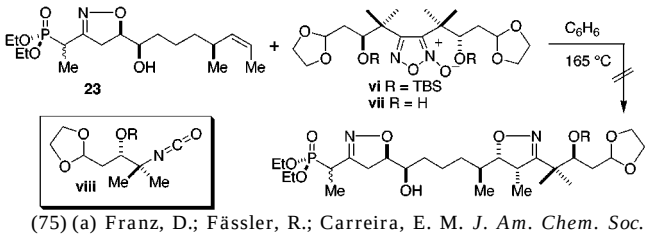
Treatment of **77** with the nitrile oxide derived from **18** proceeded cleanly (58% conversion after 48 h, 94% recovery of **77**) to give cycloadduct **78** as a single syn diastereomer at the isoxazoline oxygen (Scheme 21). Condensation of **79** with aldehyde **44** under Roush−Masamune conditions proceeded in good yield,[76] but as a 6:1 mixture of olefin stereoisomers which were not readily separated by column chromatography. With the hope that the isomers could be separated following reduction of the isoxazoline to the β-hydroxy ketone the mixture was submitted to our recently developed selective isoxazoline reduction with SmI_2. Following the reaction, analysis of the crude reaction mixture revealed

(72) All of the starting dimer had been consumed and the bulk of the remaining material was identified as uncyclized nitrile oxide **(6** in Scheme 2).

(73) The other potential product, endo-cyclization of the nitrile oxide onto the trisubstituted to give nine membered ring lactone **v** was discounted on the basis of ^{13}C NMR DEPT experiments which clearly showed that the eight membered ring had been formed.



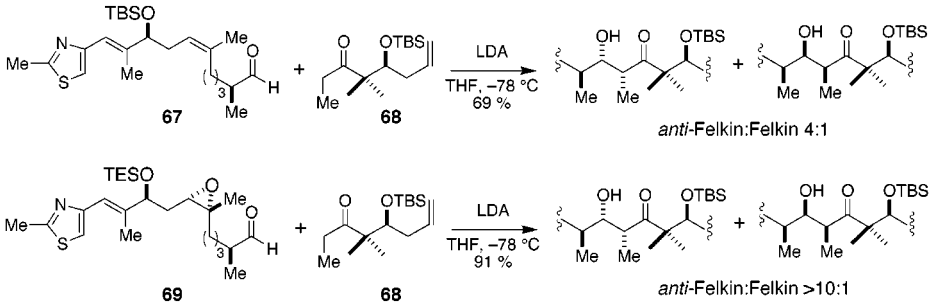
(74) Attempts to effect an *intermolecular* nitrile oxide cycloaddition on the unactivated *cis*-olefin revealed the pronounced unreactivity of this double bond. Reaction of either **vi** or **vii** with olefin **23** under the conditions reported by Curran for intermolecular nitrile oxide cycloaddition quantitatively returned the starting olefin unchanged and the nitrile oxides were consumed by clean conversion to isocyanate **viii**.



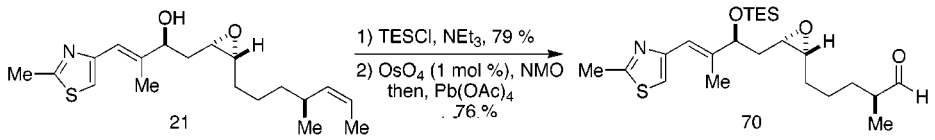
(75) (a) Franz, D.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806−1807. (b) Boyall, D.; Lopez, F.; Sasaki, H. Frantz, D.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 4233−4236.

(76) Blanchette M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183

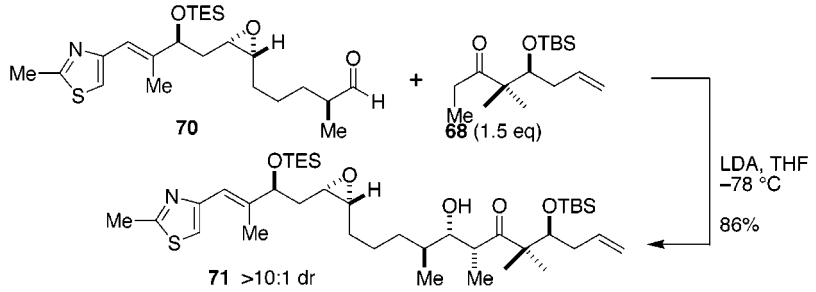
Scheme 17



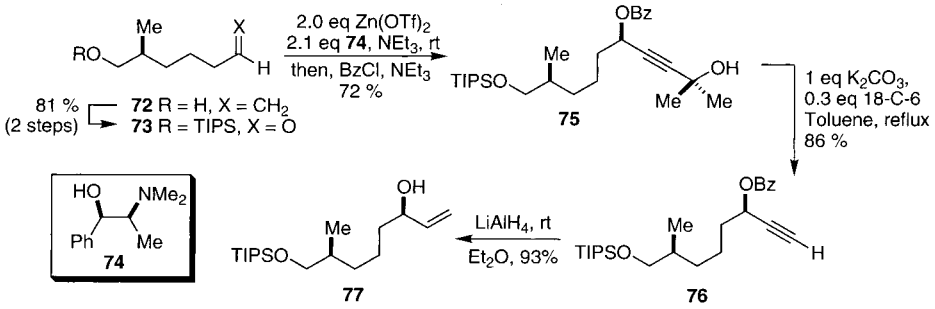
Scheme 18



Scheme 19



Scheme 20



a 9:1 mixture of the *E* and *Z* olefin stereoisomers, from which the desired *E*-isomer was isolated in 75% yield.[77]

Reduction of the *β*-hydroxy ketone to the 1,3-syn diol was followed by our protocol for diol differentiation and epoxide formation via a cyclic sulfite to afford **84** in 70% overall yield (Scheme 22). Following bis-*O*-TES protection, the primary silyl group was selectively removed and the unpurified alcohol oxidized to the previously prepared aldehyde **70** in 84% yield.

Following highly diastereoselective coupling of **68** and **70**, aldol adduct **71** was protected as its C7-OTroc ester and the terminal olefin oxidized to the corresponding aldehyde in good yield (Scheme 23).[78] Selective deprotection of the C_{15}-OTES and Lindgrin oxidation of the aldehyde provided *seco*-acid **87**. We were pleased to find that this compound undergoes clean macrolactonization under modified Yamaguchi conditions, affording 16-membered macrolide **88** in 74% yield. The C_7-OTroc ester was rapidly removed, even at room temperature, under conditions similar to those reported by Yamada for Troc deprotection of a sensitive molecule.[79] This procedure routinely provided the desired product in >80% yield along with traces of the dichlorocarbonate ester (Scheme 24).[80]

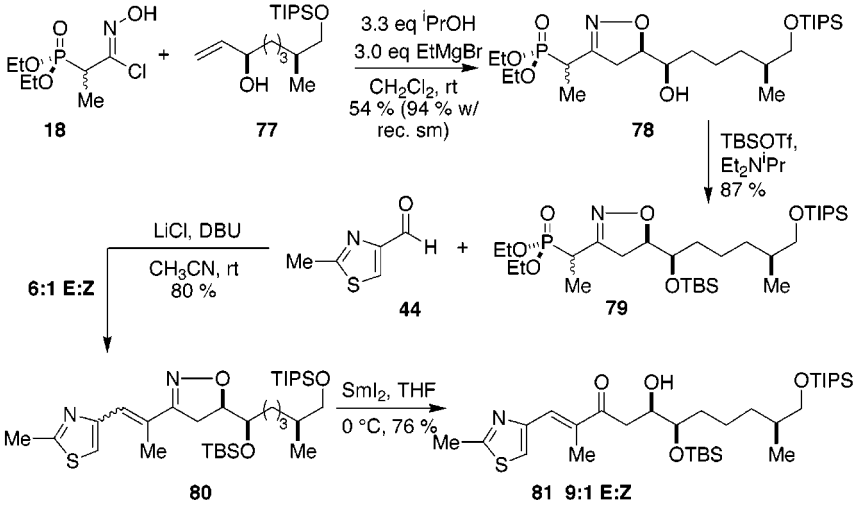
In comparison to the facile deprotection of the C_7-OTroc ester, removal of the remaining C_3-OTBS protective group proved to be challenging. In contrast to the corresponding transformation of epothilone C, which lacks the $C_{12}-C_{13}$ epoxide functionality, deprotection of epothilone A was hampered by pronounced acid and base sensitivity. In this regard, reagents such as AcOH, 1:10 aq. HF:CH_3CN, CF_3COOH (−20 °C in CH_2Cl_2), HF·NEt_3, and HF·pyr (molar rations <2:1 pyr:HF) all resulted in

(77) Upon reduction of a related (*Z*)-conjugated isoxazoline, we observed formation of the corresponding (*E*) product as >25% of the reaction mixture. It is not clear, however, if this isomerization occurs during the isoxazoline reduction or upon hydrolysis of the resulting imine.

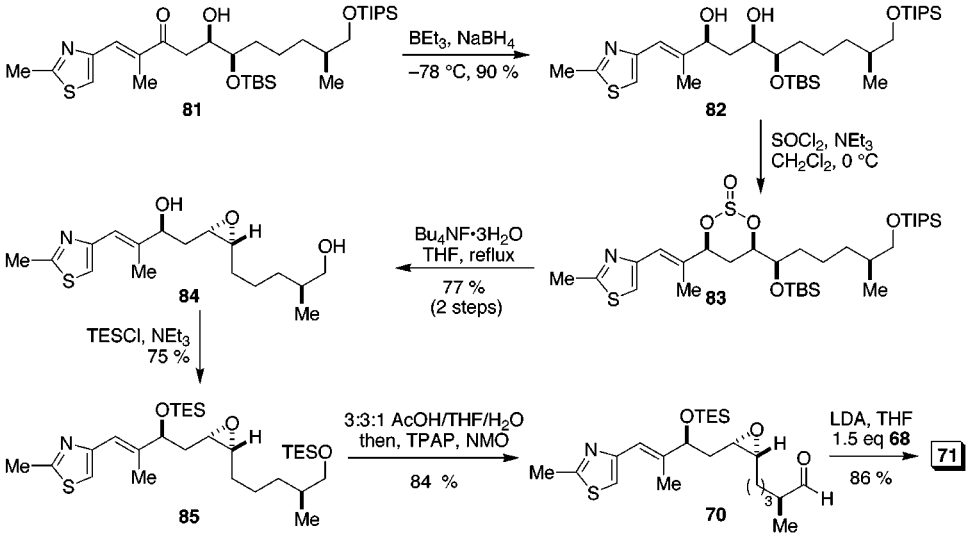
(78) The final steps of Mulzer's epothilone B synthesis were modified and employed for the completion of epothilone A.

(79) Wakamatsu, K.; Kigoshi, H.; Niyama, K.; Niwa, H.; Yamada, K. *Tetrahedron* **1986**, *42*, 5551−5558.

Scheme 21



Scheme 22



destruction of the sensitive epoxide moiety.[81] Likewise, the highly hindered nature of the silyl ether rendered numerous reagents for silyl deprotection ineffective for this transformation, including TBAF−AcOH (THF, 50 °C), TBAF−(2-fluorophenol) (THF, 50 °C), TBAF−HF (THF, 50 °C), NH_4F−HF (DMF:NMP, 45 °C), NH_4F (MeOH, 60 °C), and 0.1 M periodic acid. This difficult transformation was finally accomplished by the use of a 3:1 mixture of HF·pyr in pyridine at 40 °C (Scheme 25).[82] These conditions resulted in slow but clean deprotection to afford epothilone A (40% conversion after 7 days) whose spectral characteristics (^{1}H NMR, ^{13}C NMR, IR, HRMS, $[\alpha]_D$). were identical in all respects to those reported for natural material

Formal Synthesis of Epothilone B. The increasing importance of epothilone B and related analogues in the development of new anticancer chemotherapeutics motivated us to pursue a concise synthesis of this molecule. An important feature of our synthetic approach to the epothilones is its ready extension to the synthesis of related structures. Previously prepared isoxazoline **20** (see Scheme 4) proved to be the ideal starting point for the epothilone B synthesis as this material could be readily synthesized in enantiomerically pure form using commercially available (*R*)-3-buten-2-ol (**19**) (Scheme 26).[83] Following olefination and oxidation of the secondary alcohol, ketone **92** was obtained as highly crystalline solid which was stereochemically pure following a single recrystallization (Et_2O).

Using conditions reported by Curran for nucleophilic additions to similar 2-acyl-Δ^2-isoxazolines,[84] we were pleased to find that chelation controlled Grignard addition of **93** to ketone **92** proceeded in good yield and >10:1

(80) Attempts to eliminate this byproduct by modification of the reaction reaction solvent (MeOH or EtOH), reaction temperature (rt or 80 °C) and by careful drying of the reaction components uniformly failed to change the product distribution. Attempts to deprotected the dichlorocarbonate ester by resubmission to the reaction condition or via reduction with SmI_2 were equally unsuccessful, and the protected compound was recovered unchanged. These results, however, were more curious than consequential as the desired deprotection product was consistently obtained in >80% yield regardless of the conditions employed.

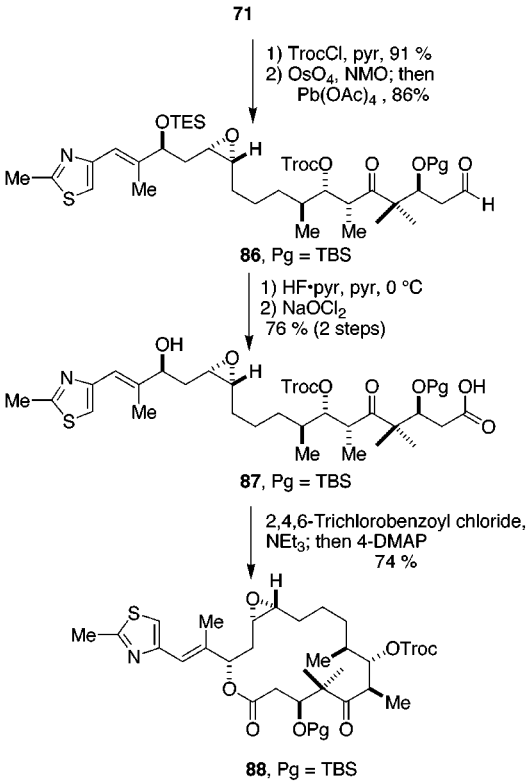
(81) Up until this point in the synthesis, the epoxide had proven to be a robust, trouble-free functional group which at no point exhibited any notable reactivity, even in the presence of acids (AcOH) and strong bases (TBAF, THF, reflux).

(82) Mulzer has also reported the use of HF·pyr to effect the deprotection of C_3-OTBS of epothilone B. Similarly long reaction times were necessary for this deprotection.

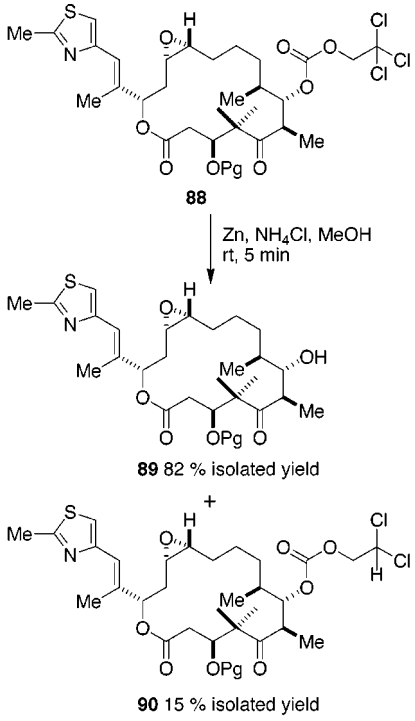
(83) We are grateful to Boehringer-Ingelheim for a generous gift of (*R*)-3-buten-2-ol.

(84) Curran, D. P.; Zhang, J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2613−2625.

Scheme 23



Scheme 24

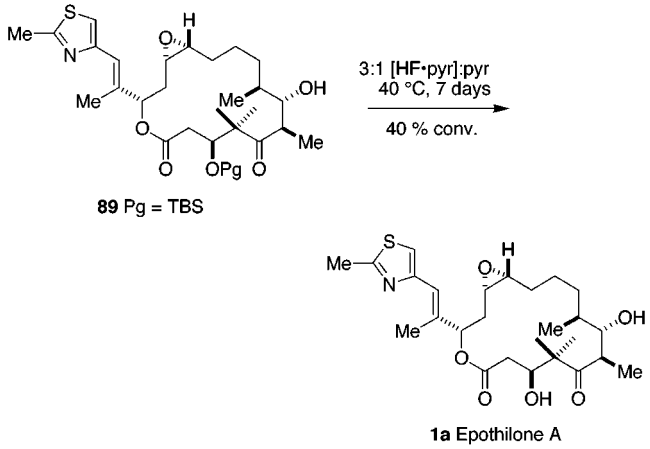


dr to give the desired syn relationship between the isoxazoline oxygen and the resulting tertiary alcohol (Scheme 27).[85] To obtain consistently high diastereoselectivity, it was essential that the solution of the Grignard reagent was cooled to −78 °C prior to its addition to the ketone. The use of the isoxazoline as a masking group and as a platform for controlling the stereochemistry of the Grignard addition highlights the unique advantages enabled by the nitrile oxide approach to the epothilones.

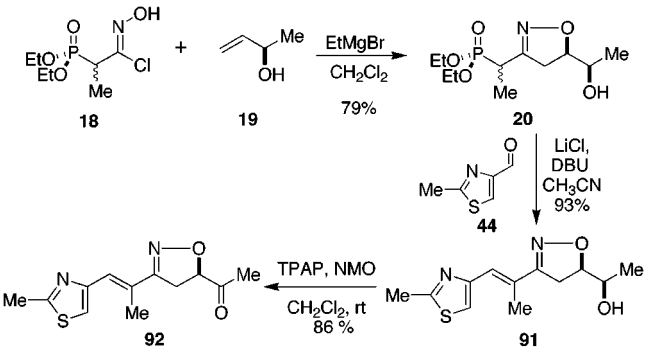
Following protection of the tertiary alcohol (TESOTf, Hünig's Base), the epothilone B synthesis converged with our previously described route to epothilone A. In this regard isoxazoline reduction (SmI_2, THF), stereoselective ketone reduction, epoxide formation (via the 1,3-cyclic sulfite), TES protection, and aldehyde preparation all proceeded without incident to provide the previously reported epoxy aldehyde **69** (Scheme 28).

Although Mulzer has described the highly diastereoselective aldol coupling of aldehyde **69** and ketone **68**, we have confirmed the highly selective nature of this reaction which consistently gives the product in good yield and excellent diastereoselectivity (Scheme 29). The ability of the remote epoxide moiety to influence the

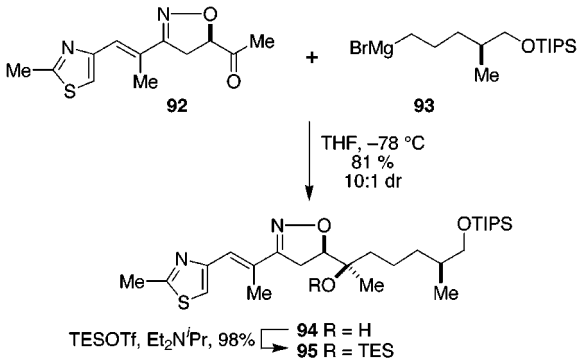
Scheme 25



Scheme 26

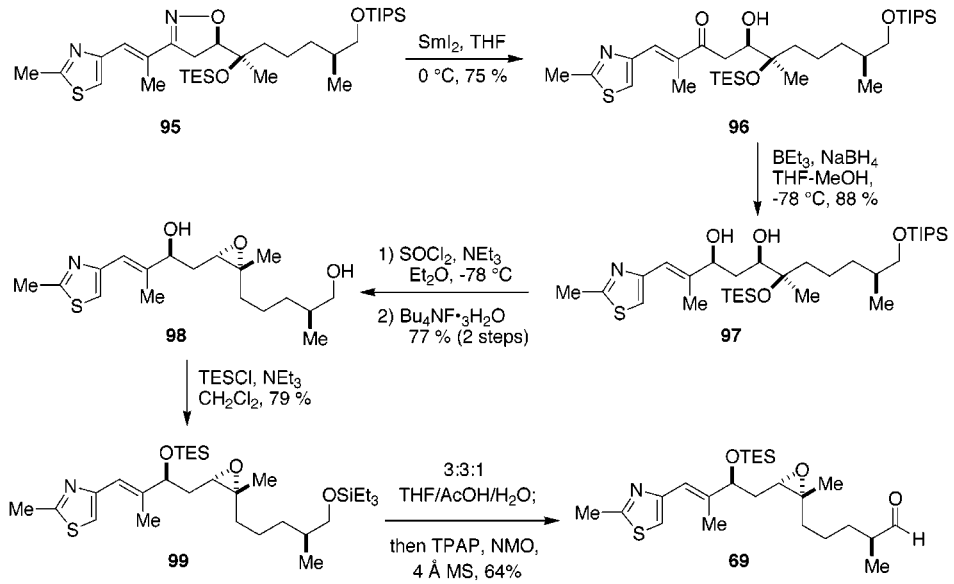


Scheme 27

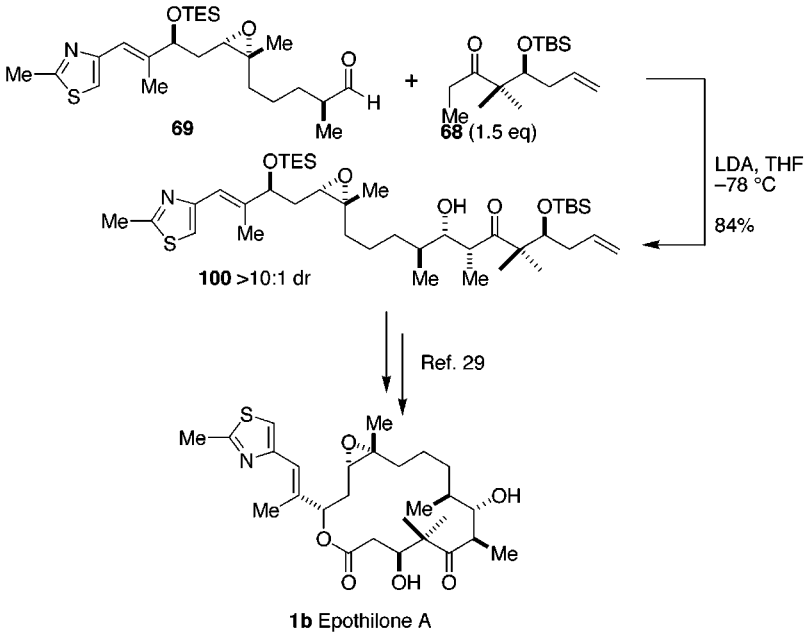


(85) The sense of stereoinduction was confirmed by conversion of this compound to aldehyde **69** (vida supra) and comparison to the spectral data of this known compound (see ref 29). We are grateful to Prof. Mulzer for kindly providing copies of spectral data for **69** and aldol adduct **100**.

Scheme 28



Scheme 29



course of this reaction represents yet another remarkable long-range effect discovered in the course of synthetic efforts toward these molecules. It is significant in that it enables the successful realization of a highly convergent approach to epothilone B with complete stereocontrol at all seven chiral centers. Furthermore, the successful application of this coupling reaction completed the highly convergent and fully stereocontrolled synthesis of the epothilone B carbon backbone (11 steps) and constitutes the expedient formal synthesis of this molecule.

Conclusions

In summary, we have described the concise, stereocontrolled total synthesis of epothilone A (21 steps) and the formal synthesis of epothilone B (18 steps in total) using hydroxyl-directed nitrile oxide cycloadditions and Mulzer's highly diastereoselective convergent aldol coupling. These studies constitute an important contribution to the development of efficient and scalable approaches to the epothilones and analogues. The syntheses described have proven to be fertile ground for the discovery and advancement of novel methodologies including: (1) a new method for nitrile oxide generation,[65] (2) a chemoselective protocol for isoxazoline reduction,[56] and (3) a new procedure for epoxide formation via 1,3-cyclic sulfites. As well, we have studied, advanced and debuted a number of powerful carbon−carbon bond forming reactions in the context of a complex molecule synthesis, namely (1) the diastereoselective Kanemasa hydroxyl directed nitrile oxide cycloaddition, (2) the Falck−Mioskowski allylic alcohol synthesis, (3) the TiF_4−BINOL-catalyzed enantioselective allylsilylation of aldehydes, and (4) the Zn-$(OTf)_2$−*N*-Me-ephedrine-mediated asymmetric alkyne addition. Given the ongoing, intense investigations in academic and industrial research laboratories on the chemistry and biology of the epothilones, the results presented substantively contribute to development of a

workable, stereocontrolled synthesis of this important class of natural products.

Acknowledgment. We are grateful to Prof. Mulzer for copies of spectra for **69** and **100** and to Boehringer-Ingelheim and Diacel Corporation for a generous gifts. Dr. Don Gautier is gratefully acknowledge for his work on of the asymmetric allyl silylation reaction. Support has been provided by generous funds from the ETH, Kontaktgruppe für Forschungsfragen (KGF), and Hoffman-La Roche. J.W.B. thanks the National Science Foundation for a predoctoral fellowship.

Supporting Information Available: Complete experimental procedures, spectral data, and structure correlation for all relevant compounds (PDF). This material available free of charge via the Internet at http://pubs.acs.org.

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