Stereoselective Syntheses of Epothilones A and B via Directed Nitrile Oxide Cycloaddition[1]

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The search for molecules which mimic the activity of the highly successful anticancer drug Taxol has inspired impressive research activity with particular emphasis by synthetic chemists on the leading candidates, discodermolide and the epothilones.[2] Herein we describe concise, fully stereocontrolled syntheses of epothilones A and B featuring diastereoselective, hydroxyl directed cycloadditions and convergent fragment couplings. This strategy provides an expedient route to the constituent fragments that furthers the ongoing, intense investigations aimed at developing a scalable approach.

The epothilones present two major stereochemical obstacles to their effective syntheses. The first, construction of the C_3-C_8 region, has enjoyed intense scrutiny, particularly in the elegant studies by Danishefsky.[3] Additionally, notable approaches have been documented by Nicolaou,[4] Schinzer,[5] Grieco,[6] White,[7] Panek,[8] and Shibasaki.[9] An important advance in this field was recently reported by Mulzer,[10] who described a highly stereoselective aldol addition involving a C_7-C_{15} epoxy aldehyde fragment.[11] Approaches to the second obstacle, construction of the $C_{12}-C_{15}$ *cis*-homoallylic epoxy alcohol, uniformly rely on the stereoselective synthesis of the olefin and its oxidative functionalization. While this approach has seen considerable use, it encounters some difficulties associated with the stereocontrolled synthesis of the *cis*-olefin as well as drawbacks of the ultimate stereoselective epoxidation.

The emerging limitations of contemporary, stereoselective organic transformations (i.e., aldol, allylation, epoxidation) to a practical epothilone synthesis prompted us to develop and explore new reaction methodology for the facile introduction of stereochemical complexity. The application of a directed nitrile oxide cycloaddition was inspired by the work of Kanemasa,[12] who has reported the diastereoselective cycloaddition reaction of simple aromatic nitrile oxides and allylic alcohols. Initial attempts to utilize this method with nonaromatic nitrile oxides, in particular those possessing the accompanying functionality required to effect a convergent synthesis, were unsuccessful. In subsequent studies we identified conditions which allowed for highly stereoselective cycloaddition for a variety of reaction partners, including highly functionalized ones. In this regard, the cycloadditions of the versatile oxime **5** with chiral allylic alcohols is key to our strategy, affording a highly convergent assembly of the epothilone subunits **4a,b**. Combined with Mulzer's diastereoselective aldol coupling, this approach provides concise syntheses of the epothilones (Figure 1).

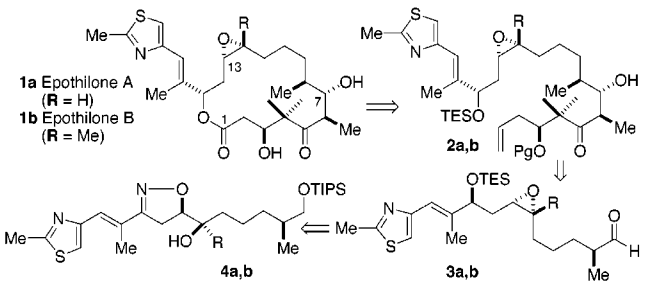
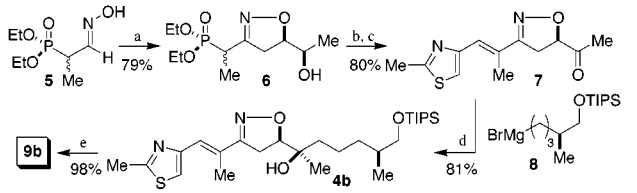


Figure 1.

Scheme 1[a]



[a] Conditions: (a) *tert*-BuOCl, CH_2Cl_2; then 1.3 equiv of (*R*)-3-buten-2-ol, 3.3 equiv of ^{i}PrOH, 3.0 equiv of EtMgBr, room temperature; (b) LiCl, DBU, 2-methylthiazole-4-carboxaldehyde, CH_3CN, room temperature; (c) TPAP, NMO, CH_2Cl_2, room temperature; (d) THF, −78 °C; (e) TESOTf, Hünig's base, CH_2Cl_2, 0 °C.

Oxidation of **5** to the nitrile oxide was followed by highly diastereoselective cycloaddition with commerically available (*R*)-3-butene-2-ol to furnish **6** in 79% yield as a single isoxazoline diastereomer (Scheme 1). Introduction of the thiazole side chain utilizing Roush−Masamune conditions[13] followed by Ley oxidation[14] of the secondary alcohol provided ketone **7** as a crystalline solid. Chelation-controlled Grignard coupling with **8**[15] proceeded smoothly to afford the epothilone B C_6-C_{15} fragment **4b** in 81% yield and >10:1 dr.[16]

The construction of the C_6-C_{15} subunit for epothilone A commmenced with the addition of 3-methylbutyn-3-ol[17] to aldehyde **11** (>20:1 dr) to furnish **12** following treatment of the crude product with BzCl (Scheme 2). Acetylene deprotection of **12** (K_2CO_3, catalytic 18-crown-6) followed by $LiAlH_4$ reduction of the propargylic benzoate directly afforded allylic alcohol **13**.

(1) Dedicated to Professor David A. Evans on the occasion of his 60th birthday.

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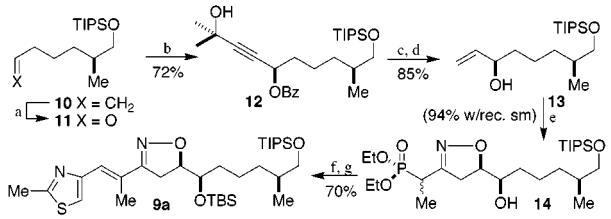
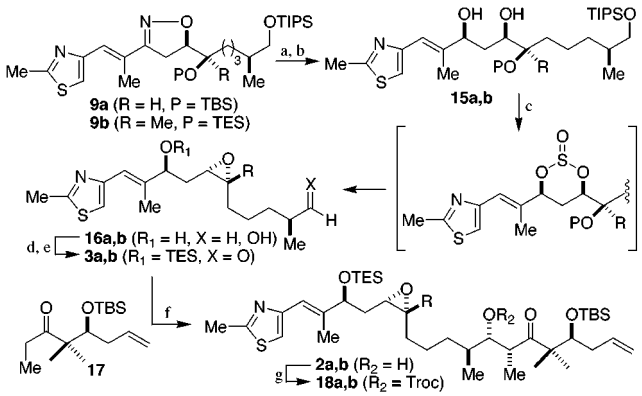
Scheme 2[a]



[a] Conditions: (a) O_3, CH_2Cl_2, PPh_3; (b) 2.1 equiv of 3-methylbutyn-3-ol, 2.1 equiv of (+)-*N*-methylephedrine, 2.0 equiv of $Zn(OTf)_2$, NEt_3, room temperature; then BzCl, NEt_3; (c) catalytic 18-crown-6, K_2CO_3, $PhCH_3$, reflux; (d) $LiAlH_4$, Et_2O; (e) 1.3 equiv of **5**, 3.0 equiv of EtMgBr, 3.3 equiv of ^iPrOH, CH_2Cl_2; (f) TBSOTf, Hünig's base, CH_2Cl_2, 0 °C; (f) LiCl, DBU, 2-methylthiazole-4-carboxaldehyde, CH_3CN, room temperature.

Scheme 3[a]



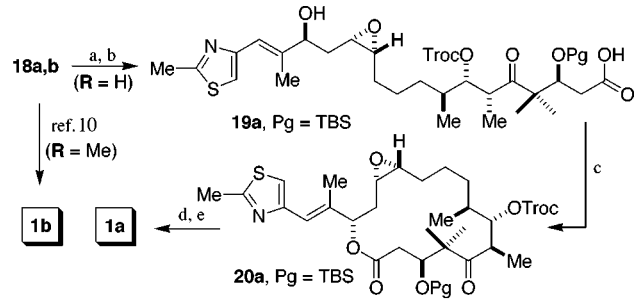
[a] Conditions: (a) SmI_2, THF, 0 °C, 75−76%; (b) Et_3B, $NaBH_4$, THF−MeOH, −78 °C, 88−90%; (c) $SOCl_2$, NEt_3; then $Bu_4NF{\cdot}3H_2O$, THF, reflux, 77%; (d) TESCl, NEt_3, CH_2Cl_2, 75-79%; (e) 3:3:1 AcOH:THF:H_2O, room temperature; then TPAP, NMO, CH_2Cl_2 64−81%; (f) 1.5 equiv of **17**, 1.5 equiv of LDA, then **3**, −78 °C, 86%; (g) TrocCl, pyr, CH_2Cl_2, 0 °C, 91%.

We were pleased to observe that this allylic alcohol underwent clean, diastereoselective cycloaddition, which after protection and olefination afforded **9a**.

The completion of the syntheses of both epothilones subsequently followed a parallel course (Scheme 3). Although reduction of isoxazolines to β-hydroxy-ketones[18] is well-precedented, this transformation is virtually unknown for conjugated isoxazolines.[19] All attempts to effect this transformation on **9a,b** with conventional reagents (Raney-Ni, $Mo(CO)_6$, O_3) were unsuccessful due to competing reaction of the conjugated olefin. We were pleased to discover that treatment of **9a,b** with SmI_2 (THF, 0 °C) resulted in clean reduction of the N−O bond without injury to the olefin.[20]

Reduction of the resulting ketone[21] (Et_3B, $NaBH_4$) provided *syn*-diol **15a,b** and left us to differentiate the two hydroxyl groups

Scheme 4[a]



[a] Conditions: (a) OsO_4, NMO, $^tBuOH-THF-H_2O$; then $Pb(OAc)_4$, EtOAc, 86%; (b) HF·pyr, pyr, THF, 0 °C; then $NaOCl_2$, 2-methyl-2-butene−^tBuOH, 76%; (c) 2,4,6-trichlorobenzoyl chloride, NEt_3, DMAP, room temperature, 74%; (d) Zn, NH_4Cl, MeOH, room temperature, 84%; (e) 3:1 (pyr[HF·pyr]), 35−40 °C, 7 days, 38% at 40% conversion.

in anticipation of the key epoxide formation. We discovered a convenient solution by 1,3-cyclic *sulfite* formation followed by the action of $Bu_4NF{\cdot}3H_2O$ in refluxingTHF to effect, in one pot, desilylation, ring formation, and loss of SO_2. This reaction resulted in clean formation of β-hydroxy epoxide **16a,b** in 77% overall yield and provided considerable advantages over the corresponding cyclic sulfate,[22] as it avoids both the oxidation step and sulfonic acid hydrolysis in the presence of the labile epoxide.

Following transformation of **16a,b**, aldehydes **3a,b** were poised for stereoselective aldol couplings. Although the aldol addition of **17** to **3b** has precedence in the work of Mulzer, the success of the corresponding reaction in the epothilone A series was far from clear given the abundance of remote effects in related systems.[3,10] However, both **3a** and **3b** underwent smooth aldol coupling with **17**[4b] to provide **2a,b** in 86% yield and >10:1 dr (^1H, ^{13}C NMR analysis).

With a formal synthesis of epothilone B in hand, epothilone A was completed, confirming the stereochemistry of the aldol reaction and the viability of our approach. Following transformation of **18a** to seco-acid **19a**, macrolactonization was effected in 74% yield. Although C_7-OTroc deprotection proceeded without incident, the C_3-OTBS proved remarkably recalcitrant. Careful optimization of HF·pyr conditions (3:1 pyr:[HF·pyr], 40 °C) afforded synthetic epothilone A (**1a**) identical with the reported data (^1H, ^{13}C, IR, HRMS, $[\alpha]_D$).

In summary, we have reported the expedient, completely stereocontrolled total synthesis of epothilone A (21 steps) and the concise construction of the fully assembled epothilone B backbone **2a** (11 steps), constituting its formal synthesis (18 steps in total). As well, we have introduced and established a powerful, directed nitrile oxide cycloaddition which utilizes readily available, stable starting materials to achieve a convergent and highly diastereoselective coupling under operationally simple reaction conditions. These studies provide a timely contribution to the development of a practical synthetic approach to the epothilones and analogues.

Acknowledgment. We are grateful to Prof. Mulzer for copies of spectra for **2b** and **3b** and to Boehringer-Ingelheim for a generous gift of (*R*)-3-buten-2-ol. Support has been provided by generous funds from the ETH, Kontaktgruppe für Forschungsfragen (KGF), Merck, and Hoffmann-La Roche. J.W.B. thanks the National Science Foundation (USA) for a predoctoral fellowship.

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

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