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Total Synthesis of Epothilones B and D

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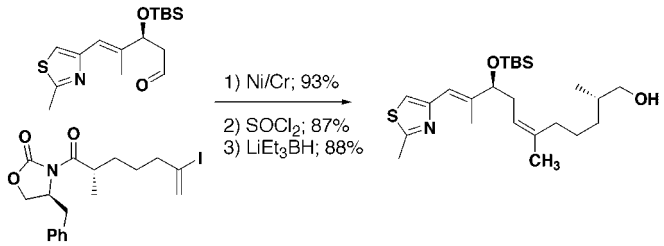
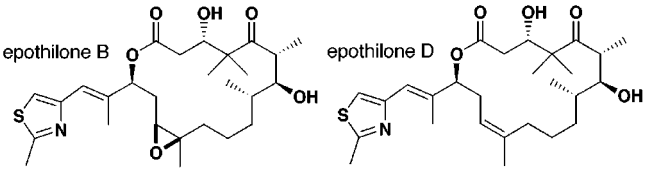
ABSTRACT



A highly convergent total synthesis of the natural products epothilone B and D is described. The route is highlighted by efficient generation of a C12–C13 trisubstituted olefin which exploits a sequential Nozaki–Hiyama–Kishi coupling and a stereoselective thionyl chloride rearrangement.

Epothilones B and D represent exciting new leads in the search for novel cancer chemotherapeutic agents.[1] The combination of their potent biological activity and their relatively simple structure has stimulated substantial interest from the synthetic community.[2] Several total syntheses of these macrolide natural products have been reported. Critical to a practical approach to epothilone B is a convergent strategy which allows for the selective construction of the C12−C13 trisubstituted olefin (epoD).[3]



These structural units, common to biologically active natural products, have for a long time and continue to represent a significant synthetic challenge. Previous syntheses of the epothilones B and D have explored methods for construction of this region through either olefin metathesis[3b,f,g,l] or Wittig olefination[3c] strategies which have shown little geometric selectivity. Alternative selective routes, which proceed through intermediate trisubstituted vinyl halides, have been prone to low yields.[3a,b,f,i,j,l] To date, Nicolaou[3d,k] and Mulzer's[3q] use of stabilized-Wittig and Horner−Emmons

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(2) (a) For a recent review of efforts to synthesize the epothilones, see: Mulzer, J. *Monatsh. Chem.* **2000**, *131*, 205.

(3) (a) Su, D.-S.; Meng, D.; Bertinato, P.; Balog, A.; Sorensen, E. J.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 757. (b) Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073. (c) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E. *Nature* **1997**, *387*, 268. (d) Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He, Y.; Vallberg, H.; Finlay, M. R. V.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 7974. (e) Balog, A.; Harris, C. R.; Savin, K.; Zhang, X.-G.; Chou, T.-C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2675. (f) Schinzer, D.; Bauer, A.; Schieber, J. *Synlett* **1998**, 861. (g) May, S. A.; Grieco, P. A. *Chem. Commun.* **1998**, 1597. (h) Mulzer, J.; Mantoulidis, A.; Öhler, E. *Tetrahedron Lett.* **1998**, *39*, 8633. (i) White, J. D.; Carter, R. G.; Sundermann, K. F. *J. Org. Chem.* **1999**, *64*, 684. (j) White, J. D.; Sundermann, K. F.; Carter, R. G. *Org. Lett.* **1999**, *1*, 1431. (k) Nicolaou, K. C.; Hepworth, D.; Finlay, M. R. V.; King, N. P.; Werschkun, B.; Bigot, A. *Chem. Commun.* **1999**, 519. (l) Schinzer, D.; Bauer, A.; Schieber, J. *Chem. Eur. J.* **1999**, *5*, 2492. (m) Harris, C. R.; Kuduk, S. D.; Balog, A.; Savin, K.; Danishefsky, S. J. *Tetrahedron Lett.* **1999**, *40*, 2263. (n) Harris, C. R.; Kuduk, S. D.; Balog, A.; Savin, K.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 7050. (o) Martin, H. J.; Drescher, M.; Mulzer, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 581. (p) Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 10521. (q) Mulzer, J.; Mantoulidis, A.; Öhler, E. *J. Org. Chem.* **2000**, *65*, 7456.

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reagents has been shown to offer the most reliable combination of high geometric selectivity and overall yield. We have chosen to explore an alternative route which relies on a Nozaki−Hiyama−Kishi (NHK) coupling[4] for the formation of the C12−C13 carbon−carbon bond and a thionyl chloride induced allylic rearrangement[5] to control the trisubstituted olefin geometry. Herein we report the application of these methods for the total synthesis of epothilones B and D.

The connectivity analysis which guides our synthetic strategy is outlined in Figure 1. Similar to our approach to

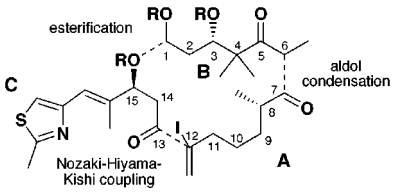

Figure 1. Connectivity analysis.

epothilone A, we chose a convergent route[6] which has assembled the 16-membered macrolide from three fragments of similar complexity. Simplification of epothilone D was considered through three strategic disconnections.

First, the C5−C7 β-hydroxy ketone could be formed, in a synthetic direction, from an aldol reaction between the enolate of the C5 ketone and a C7 chiral aldehyde. An additional disconnection through the C12−C13 olefin reveals the necessary chiral aldehyde **A** for the C7−C12 fragment. Retrosynthetic disconnection of the ester (lactone) linkage then exposes a C1−C6 fragment such as chiral ketone **B**. This leaves behind our choice for the side chain, aldehyde **C**. Novel to this approach to epothilone D is the formation of the C12−C13 trisubstituted olefin through a sequential NHK coupling followed by a stereoselective allylic rearrangement. While we considered using this coupling in the macrocyclization, a late-stage reductive cleavage of the allylic chloride would have provided a significant challenge.

Thiazole fragment **C** was prepared using a method similar to one that we have reported.[6a] Previously we had generated the C15 allylic alcohol using Keck's Ti·BINOL-catalyzed allylation.[7a] However, in this case we chose to use Brown's asymmetric allylboration[7b] which we found more suitable

(4) (a) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048. (b) Jin, H.; Uenishi, J.-I.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644.

(5) Caserio, F. F.; Dennis, G. E.; DeWolfe, R. H.; Young, W. G. *J. Am. Chem. Soc.* **1955**, *77*, 4182. From a mechanistic perspective, this reaction has been restudied on numerous occasions. However, to the best of our knowledge only Johnson has exploited the stereoselectivity of this interesting reaction from a synthetic perspective; Johnson, W. S.; Li, T.-T.; Harbert, C. A.; Bartlett, W. R.; Herrin, T. R.; Staskun, B.; Rich, D. H. *J. Am. Chem. Soc.* **1970**, *92*, 4461. See also: Taylor, R. E.; Ciavarri, J. P.; Hearn, B. R. *Tetrahedron Lett.* **1998**, *39*, 9361.

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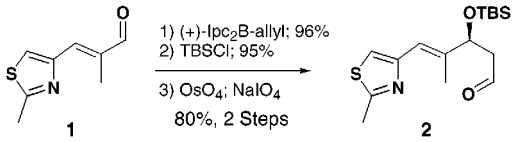
(7) (a) Keck, G. E.; Geraci, L. S. *Tetrahedron Lett.* **1993**, *34*, 7827. (b) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.

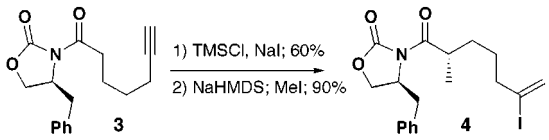
Scheme 1



for large-scale synthetic work. As shown in Scheme 1 exposure of conjugated aldehyde **1** to (+)Ipc_2B(allyl) gave the corresponding allylic alcohol in excellent yield (>91% ee by chiral gc analysis) on a multigram scale. The secondary alcohol was protected as a *tert*-butyldimethylsilyl ether under classic conditions, and a two-step oxidative cleavage provided aldehyde **2**.[8]

The construction of fragment **A** proceeded with use of Evan's chiral enolate alkylation chemistry.[9] Alkyne **3** was prepared from commercially available 6-heptynoic acid using the unsymmetric anhydride method. Hydrogen iodide addition, using trimethylsilyl chloride/sodium iodide in aqueous acetonitrile,[10] provided the internal vinyl iodide in 60% yield (31% recovered starting material), Scheme 2. Generation of

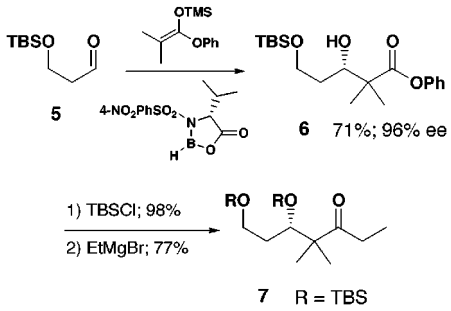
Scheme 2



the enolate was then accomplished with NaHMDS, and alkylation with methyl iodide generated in the C8 stereogenic center in 90% yield (>96:4 dr).

We had previously reported an efficient route to the chiral ketone necessary for the preparation of epothilone A.[6b] However, the synthesis of the chiral starting material for that route was dependent on an enzymatic resolution of a secondary alcohol which was found to make large-scale production tedious. Scheme 3 describes an alternative route

Scheme 3

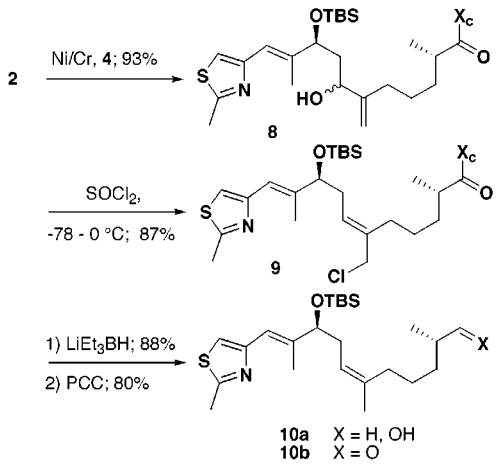


which exploits the elegant chemistry of Kiyooka.[11] The reaction of 2-methyl-1-phenoxy-1-trimethylsilyloxy-1-pro-

pene with readily available aldehyde **5** under the influence of Kiyooka's chiral boron reagent (100 mol %) provided aldol adduct **6** in 71% yield (96% ee by chiral GC analysis). A similar route to this chiral fragment has been recently reported by Mulzer.[3q] Our original contribution to preparation of this fragment is the use of the phenoxy−ketene acetal which not only provides higher enantioselectivity than the commercially available methoxy−ketene acetal but also allows for a one-step ester-to-ketone conversion. Protection of the secondary alcohol was followed by exposure to ethylmagnesium bromide in the presence of triethylamine[12] to provide the desired ethyl ketone **7** directly.

With all three fragments in hand, we next chose to explore the convergence of fragments **A** and **C**, Scheme 4. Inter-

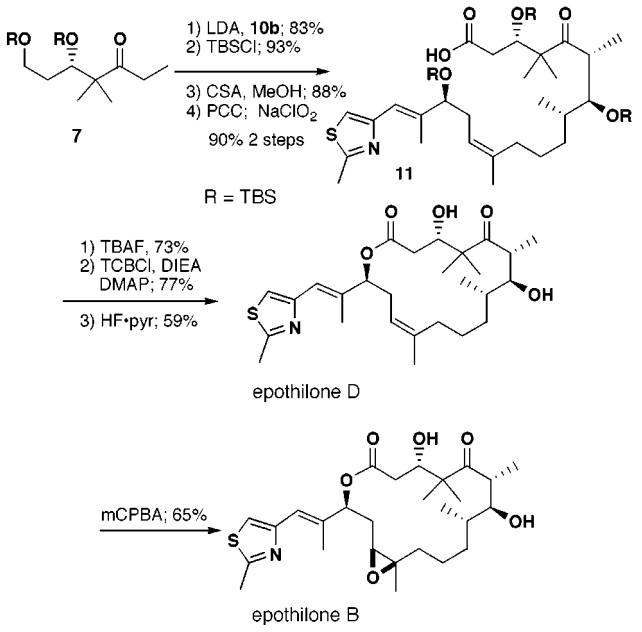
Scheme 4



molecular Ni/Cr coupling of vinyl iodide **4** with aldehyde **2** (2 equiv) provided the desired allylic alcohol **8** in 93% yield as a mixture of diastereomers (1:1). Exposure of this mixture to thionyl chloride in ether−pentane provided the desired primary chloride **9** in 87% yield. While the olefin geometry was completely selective, a small amount of the secondary allylic chloride could be observed in the crude proton NMR spectrum. After exploration of a number of hydride reducing agents, we ultimately found that $LiEt_3BH$ not only reductively cleaved the chiral auxiliary but also efficiently reduced the allylic chloride in 88% yield, providing primary alcohol **10a** which contained ~10% of an unidentified inseparable isomer. Presumably a small amount of epimerization of the C8 stereogenic center occurred during the reductive cleavage. Oxidation with PCC then provided aldehyde **10b**. While this intermediate has been previously converted to epothilones D and B by Schinzer,[3l] Mulzer,[3q] and Nicolaou[3d] and thus represents a formal total synthesis of epothilones B and D, we chose to complete the total synthesis by the following synthetic sequence.

As highlighted in Scheme 5, the completion of the total

Scheme 5



synthesis began with an aldol reaction. The lithium enolate of ethyl ketone **7** was generated by exposure to LDA at −78 °C. Addition of aldehyde **10b** provided the desired *syn,anti*-aldol adduct as the major product in 83% yield and 8:1 selectivity. After protection of the C7 hydroxyl as a TBS ether, the primary alcohol was liberated by exposure to acidic methanol solution. The C1-carboxylic acid was generated by two-step oxidation in 90% yield. Subsequent selective removal of the C15 TBS ether was then accomplished with TBAF. Macrolactonization proceeded efficiently using the Yamaguchi method[13] to provide the 16-membered lactone in 77% yield. Deprotection of the C3 and C7 silyl ethers was carried out using HF•pyr, providing epothilone D. Finally, incorporation of the C12−C13 epoxide was carried out by exposure to mCPBA, yielding epothilone B in 65% yield. This material was identical to an authentic sample of epothilone B.

In summary, we have completed a convergent synthesis of the natural products epothilone B and D.[14] The route is highlighted by the efficient generation of a C12−C13 trisubstituted olefin which exploits a sequential Nozaki−Hiyama−Kishi coupling and a stereoselective thionyl chloride rearrangement. The chemistry described in this Letter

(8) Aldehyde **2** was previously reported by Nicolaou (ref 3d).
(9) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
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(11) Kiyooka, S.-I.; Kira, H.; Hena, M. A. *Tetrahedron Lett.* **1996**, *37*, 2597.
(12) Kikkawa, I.; Yorifuji, T. *Synthesis* **1980**, 877.
(13) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(14) Satisfactory spectroscopic and HRMS data have been obtained for all compounds.
(15) Taylor, R. E.; Zajicek, J. *J. Org. Chem.* **1999**, *64*, 7224.

has led to an 18-step synthesis of epothilone D and allowed for the preparation of significant quantities of the desired material for biological, conformational,[15] and structure/conformation−activity studies. The application of this chemistry to the preparation of novel epothilone analogues will be reported in due course.

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Supporting Information Available: Full experimental and ^{1}H and ^{13}C NMR spectra for compounds **8**, **9**, and **10a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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