

## Total Synthesis of Epothilones B and D

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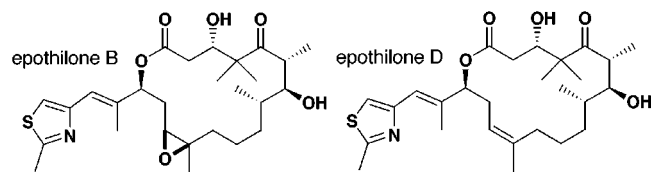
## ABSTRACT



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.<sup>1</sup> The combination of their potent biological activity and their relatively simple structure has stimulated substantial interest from the synthetic community.<sup>2</sup> 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).<sup>3</sup>

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<sup>3b,f,g,l</sup> or Wittig olefination<sup>3c</sup> strategies which have shown little geometric selectivity. Alternative selective routes, which proceed through intermediate trisubstituted vinyl halides, have been prone to low yields.<sup>3a,b,f,i,j,l</sup> To date, Nicolaou<sup>3d,k</sup> and Mulzer's<sup>3q</sup> use of stabilized-Wittig and Horner–Emmons



These structural units, common to biologically active natural products, have for a long time and continue to

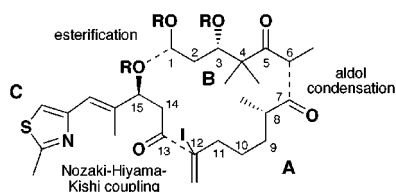
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reagents has been shown to offer the most reliable combination of high geometric selectivity and overall yield. We have chosen to explore an alternative route which relies on a Nozaki–Hiyama–Kishi (NHK) coupling<sup>4</sup> for the formation of the C12–C13 carbon–carbon bond and a thionyl chloride induced allylic rearrangement<sup>5</sup> 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<sup>6</sup> 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  $\beta$ -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.<sup>6a</sup> Previously we had generated the C15 allylic alcohol using Keck's Ti·BINOL-catalyzed allylation.<sup>7a</sup> However, in this case we chose to use Brown's asymmetric allylboration<sup>7b</sup> which we found more suitable

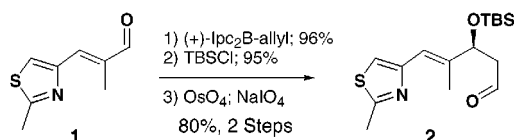
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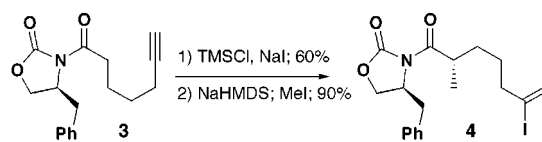
**Scheme 1**



for large-scale synthetic work. As shown in Scheme 1 exposure of conjugated aldehyde **1** to (+)Ipc<sub>2</sub>B(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**.<sup>8</sup>

The construction of fragment **A** proceeded with use of Evan's chiral enolate alkylation chemistry.<sup>9</sup> 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,<sup>10</sup> provided the internal vinyl iodide in 60% yield (31% recovered starting material), Scheme 2. Generation of

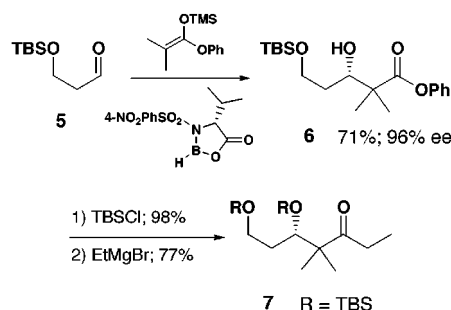
**Scheme 2**



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.<sup>6b</sup> 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

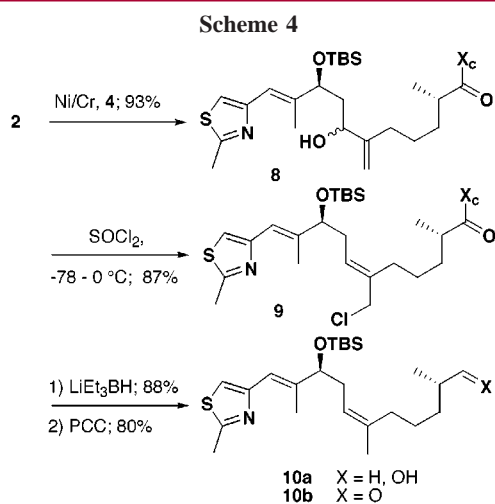
**Scheme 3**



which exploits the elegant chemistry of Kiyooka.<sup>11</sup> 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.<sup>3q</sup> 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<sup>12</sup> to provide the desired ethyl ketone **7** directly.

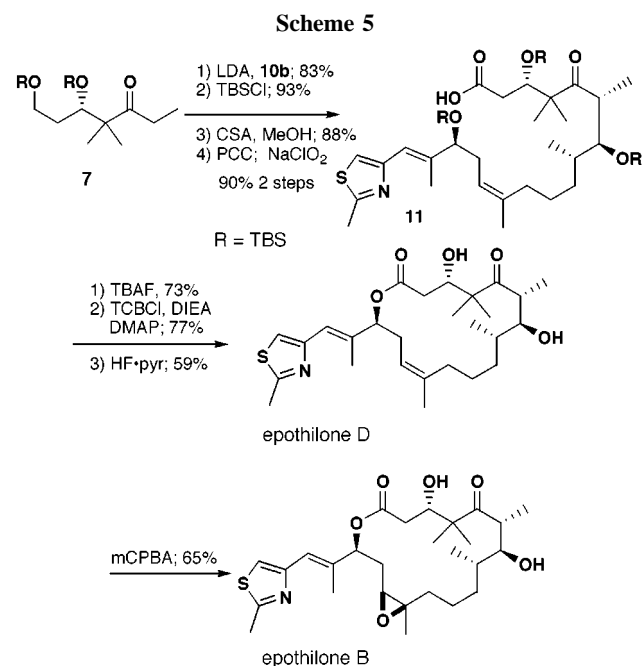
With all three fragments in hand, we next chose to explore the convergence of fragments **A** and **C**, Scheme 4. Inter-



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<sub>3</sub>BH 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 epoxythilones

**D** and **B** by Schinzer,<sup>3l</sup> Mulzer,<sup>3q</sup> and Nicolaou<sup>3d</sup> and thus represents a formal total synthesis of epoxythilones **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



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<sup>13</sup> to provide the 16-membered lactone in 77% yield. Deprotection of the C3 and C7 silyl ethers was carried out using HF·pyr, providing epoxythilone **D**. Finally, incorporation of the C12–C13 epoxide was carried out by exposure to mCPBA, yielding epoxythilone **B** in 65% yield. This material was identical to an authentic sample of epoxythilone **B**.

In summary, we have completed a convergent synthesis of the natural products epoxythilone **B** and **D**.<sup>14</sup> 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

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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,<sup>15</sup> 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 <sup>1</sup>H and <sup>13</sup>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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