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Improved Synthesis of Epothilone B Employing Alkylation of an Alkyne for Assembly of Subunits

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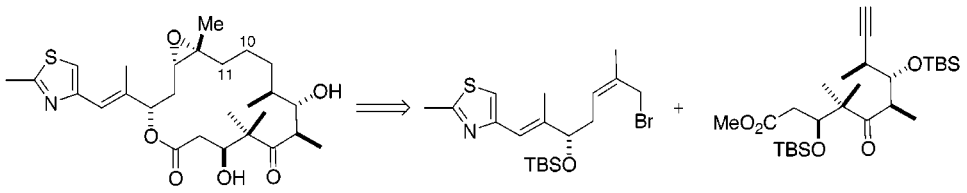
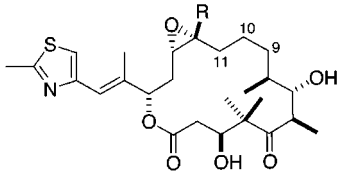
ABSTRACT

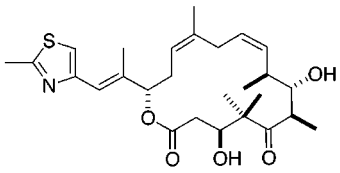


A strategy for assembling the two principal modules of epothilone B was developed that merges an allylic bromide with a terminal acetylene to fabricate the C10–C11 bond of the macrocycle. The resulting alkyne was semihydrogenated to give a seco ester previously employed in our total synthesis of epothilone B. This new approach affords a more efficient route to the naturally occurring macrolide and to its 9,10-dehydro analogue.

The extraordinary interest in the macrolides epothilone A (**1**) and B (**2**) reflects a growing awareness that these fermentation metabolites share a distinctive mechanism of cytotoxic activity with paclitaxel (Taxol), discodermolide, and eleutherobin whereby cell division is prevented by inhibition of microtubule disassembly.[1] Alongside ongoing investigations into the pivotal intracellular events triggered by epothilones[2] have been very active synthetic efforts by several groups, notably those of Danishefsky[3] and Nicolaou.[4] These studies have resulted in total syntheses of **1** and **2**, as well as a large ensemble of analogues. In addition, syntheses of **2** have been described by Schinzer,[5] Grieco,[6] Mulzer,[7] and ourselves.[8]



1, R = H
2, R = Me



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Our initial synthesis of **2** proceeded via (9*Z*)-dehydro-12,-13-deoxyepothilone B (**3**) with the goal of exploring

(1) (a) Bollag, D. M.; McQuency, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995**, *55*, 2325. (b) Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem.* **1996**, *108*, 1671; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1567. (c) Gerth, K.; Bedorf, N.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot.* **1996**, *49*, 560.

(2) (a) Bollag, D. *Exp. Opin. Invest. Drugs* **1997**, *6*, 867. (b) Su, D.-S.; Balog, A.; Meng, D.; Bertinato, P.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. *Angew. Chem.* **1997**, *109*, 2178; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2093.

(3) (a) Balog, A.; Meng, D.; Kamenecka, T.; Bertinato, P.; Su, D.-S.; Sorensen, E. J.; Danishefsky, S. J.; *Angew. Chem.* **1996**, *108*, 2976; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2801. (b) 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.* **1997**, *109*, 775; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 757. (c) Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Komenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073. (d) Balog, A.; Harris, C.; Savin, K.; Zhang, X.-G.; Chou, T.-C.; Danishefsky, S. J. *Angew. Chem.* **1998**, *110*, 2821; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2675. (e) Harris, C. R.; Kuduk, S. D.; Savin, K.; Balog, A.; Danishefsky, S. J. *Tetrahedron Lett.* **1999**, *40*, 2263.

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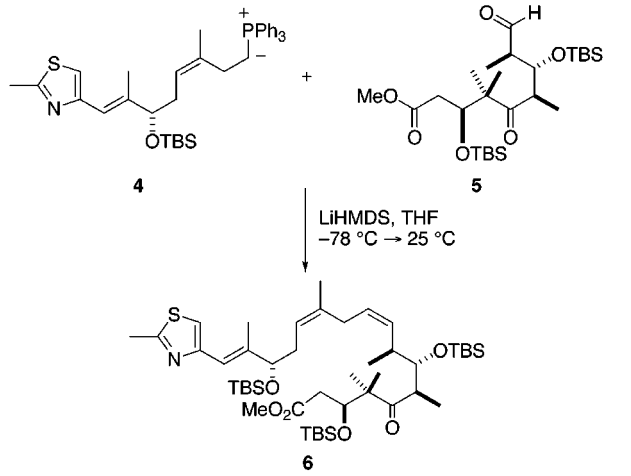
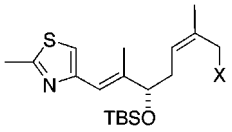
structural variants in the C9−C11 region of the macrocycle for analogue purposes. On the assumption that this domain is not intimately associated with the pharmacophore of the epothilones,[9] our expectation is that **3** should retain good biological activity.[10] On the other hand, introduction of a double bond at $\Delta^{9,10}$ distorts the macrocycle in a way that no longer permits overlay of the C9−C11 section of **3** with that of **2**. In particular, the introduction of C9−C10 unsaturation changes the antiperiplanar arrangement around these atoms in **2** to a *syn* coplanar alignment in **3**. The interplay of ring conformation with functional appendages offers a new avenue for probing structure−activity relationships in the epothilones that suggest new lines for analogue development.

Our previous strategy for assembling the requisite precursor to **3** invoked a Wittig olefination that merged the two components **4** and **5** into the seco ester **6** (Scheme 1). The

Scheme 1



aldehyde **5** was prepared by a double stereodifferentiating *anti*-Felkin aldol condensation that hinged upon chelation by a *p*-methoxybenzyl ether for directing the *Z* enolate of an ethyl ketone to the *re* face of an α-methyl aldehyde. Phosphonium bromide **4** was obtained through homologation of allylic bromide **7**, prepared by a sequence in which both *E*-trisubstituted alkene units were introduced with complete stereoselectivity. Although Wittig coupling of **4** and **5** proceeded efficiently on a >1 mmol scale, this reaction proved difficult to effect on smaller quantities of reactants. Consequently, we sought an alternative means for fusing the available subunits into **6**. This led to a plan in which a connection was to be forged between **7** or the corresponding alcohol **8** (via its mesylate) and a terminal alkyne representing the C1−C10 portion of **3**. A potential consequence of this approach was a new series of epothilone analogues embodying a C≡C unit across C9−C10.



7, X = Br
8, X = OH

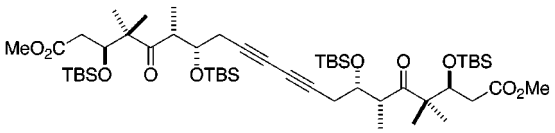
Aldehyde **5** was reacted with the anion of dimethyl diazophosphonate[11] to give alkyne **9** in good yield. Coupling of the copper(I) derivative of **9** with either bromide **7** or the mesylate of **8** required extensive experimentation (Table 1)

Table 1. Coupling of **9** with **7** and **8**

equiv of **9**	coupling partner	reagents/conditions	yield of **10** (%)[a]
1.1	**7**	5% CuI, TBAB, K_2CO_3, DMF[b]	8
1.1	**7**	20% CuI, Aliquot 336, K_2CO_3, DMF	11
1.1	**7**	50% CuI, pyrrolidine, DMF	0[c]
1.1	**8**	(a) Ms_2O, Et_3N, DMF	
		(b) 10% CuI, Na_2CO_3, TBAB, DMF	34
1.1	**8**	(a) Ms_2O, Et_3N, CH_2Cl_2	
		(b) 20% CuI, Na_2CO_3, TBAB, DMF	42
1.1	**7**	5% CuI, Et_3N, Et_2O−DMF	24
2.0	**7**	5% CuI, Et_3N, Et_2O−DMF	60

[a] Based on **7** or **8**. [b] Jeffery, T. *Tetrahedron Lett.* **1989**, *30*, 2225. [c] Product was exclusively **11**.

but was found to give dienyne **10** in good yield when a mixture of ether and DMF was employed as solvent. However, even under rigorously anhydrous and anaerobic conditions, small amounts of the diyne **11** resulting from Glaser coupling[12] of **9** were detected. Our goal with **10** was



11

to continue the synthesis with this alkyne in the form of its cobalt complex **12**, in the hope that the alkyne could be

(4) (a) Yang, Z.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. C. *Angew. Chem.* **1997**, *109*, 170; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 166. (b) Nicolaou, K. C.; Sarabia, F.; Ninkovic, S.; Yang, Z. *Angew. Chem.* **1997**, *109*, 539; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 525. (c) Nicolaou, K. C.; Winssinger, N.; Pastor, J. A.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E. *Nature* **1997**, *387*, 268. (d) Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, F.; Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I. *J. Am. Chem. Soc.* **1997**, *119*, 7960. (e) 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. (f) Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H. Yang, Z. *Angew. Chem.* **1996**, *108*, 2554, *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2399. (g) Nicolaou, K. C.; Hepworth, D.; Finley, M. R. V.; King, N. P.; Werschkun, B.; Bigot, A. *Chem. Commun.* **1999**, 519.

(5) (a) Schinzer, D.; Limberg, A.; Bauer, A.; Böhm, O. M.; Cordes, M. *Angew. Chem.* **1997**, *109*, 543; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 523. (b) Schinzer, D.; Bauer, A.; Schieber, J. *Synlett* **1998**, 861.

(6) May, S. A.; Grieco, P. *Chem. Commun.* **1998**, 1597.

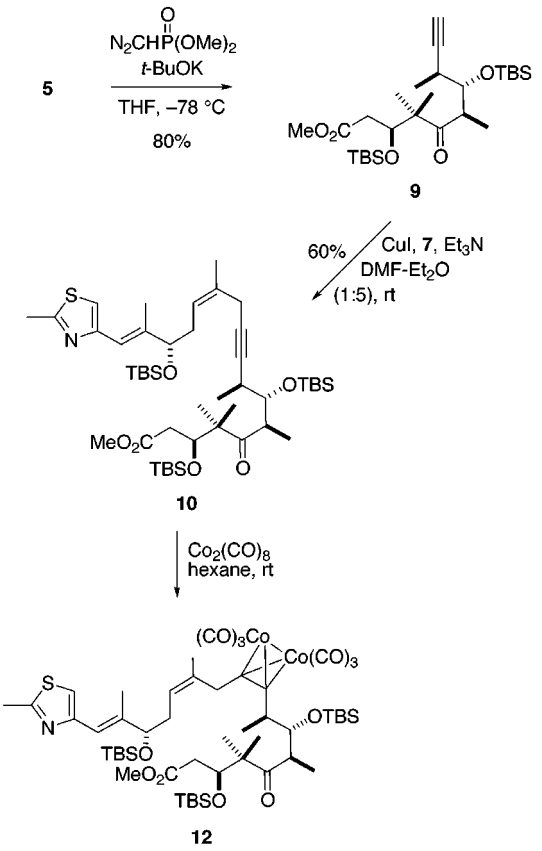
(7) Mulzer, J.; Mantoulidis, A.; Öhler, E. *Tetrahedron Lett.* **1998**, *39*, 8633.

(8) White, J. D.; Carter, R. G.; Sundermann, K. F. *J. Org. Chem.* **1999**, *64*, 684.

(9) Ojima, I.; Chakravarty, S.; Inoue, T.; Lin, S.; He, L.; Horwitz, S. B.; Kuduk, S. D.; Danishefsky, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 4256.

unmasked after macrocyclization. Unfortunately, although **12** was easily prepared by treatment of **10** with dicobaltoctacarbonyl, attempts to saponify the methyl ester of **12** led to complex mixtures (Scheme 2).

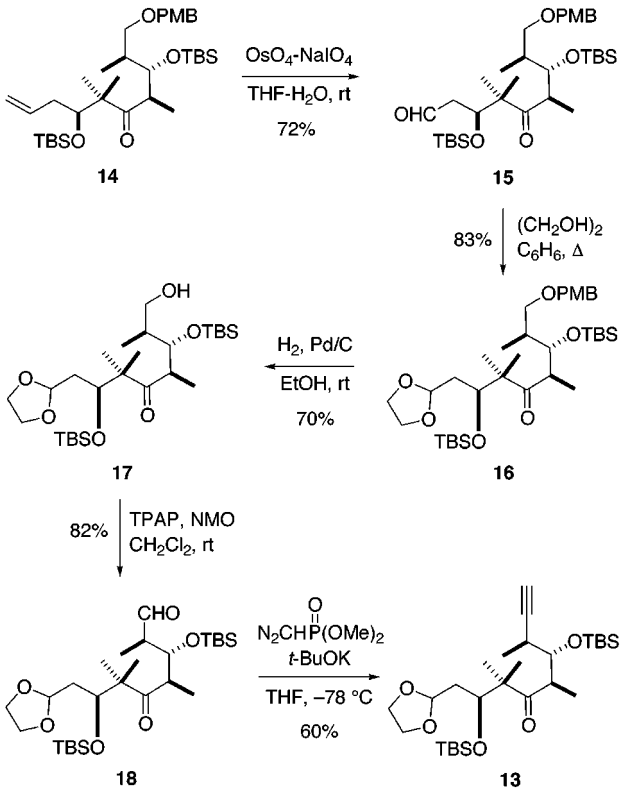
Scheme 2



In an effort to circumvent this problem, the terminal ester of **9** was replaced by an aldehyde in the guise of acetal **13**. The latter was synthesized by oxidative cleavage of alkene **14** followed by protection of aldehyde **15** as its ethylene acetal. After hydrogenolysis of **16**, the resultant alcohol **17** was oxidized to **18** which was reacted with dimethyl diazophosphonate[11] to afford **13** (Scheme 3). Disappointingly, **13** yielded no coupled product with bromide **7** under conditions that had been successful with **9**.

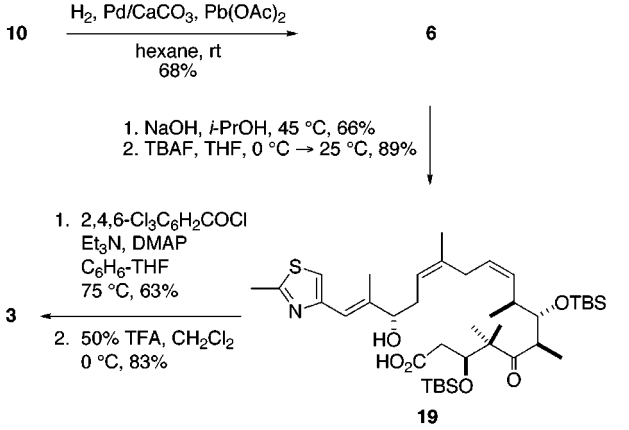
Finally, to bring this sequence into convergence with our previously published pathway to **2**,[8] alkyne **10** was semihydrogenated over Lindlar catalyst. An important requirement for success in this reaction was that it be carried out in hexane.[13] Other solvents gave little or no reaction. The

Scheme 3



resultant triene **6**, after saponification, gave the corresponding carboxylic acid, which underwent clean deprotection of the C15 TBS ether to yield seco acid **19**.[14] Macrolactonization under Yamaguchi conditions[15] followed by removal of the remaining pair of TBS ethers furnished **3** (Scheme 4). The

Scheme 4



latter has previously been reduced with diimide to yield 12,-13-deoxyepothilone B,[8] and epoxidation of this material with

(10) The results of bioassay studies with **3** will be disclosed independently.

(11) Gilbert, J. C.; Weerasooriya, V. *J. Org. Chem.* **1982**, *47*, 1837.

(12) Eglinton, G.; McCrae, W. In *Advances in Organic Chemistry*, *Methods and Results*; Raphael, R. A., Taylor, E. C., Wynberg, H., Eds.; Interscience: New York, 1963; Vol. 4, p 225.

(13) The importance of a hydrocarbon solvent for acetylene semihydrogenation was pointed out by Lindlar himself, see: Freifelder, M. *Practical Catalytic Hydrogenation, Techniques and Applications*; Wiley-Interscience: New York, 1971; p 99.

(14) Selectivity is attributed to a sterically favorable transilylation involving the carboxylate anion; the resultant silyl ester is hydrolyzed during aqueous workup.

(15) Inanaga, J.; Kirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

dimethyldioxirane as described by Danishefsky[3b] afforded **2**.

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Supporting Information Available: Experimental procedures for the preparation of **8**, **9**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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