A Highly Stereoselective Synthesis of Epothilone B

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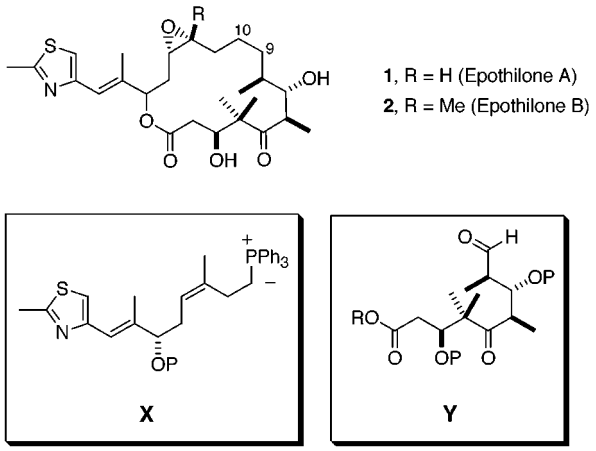
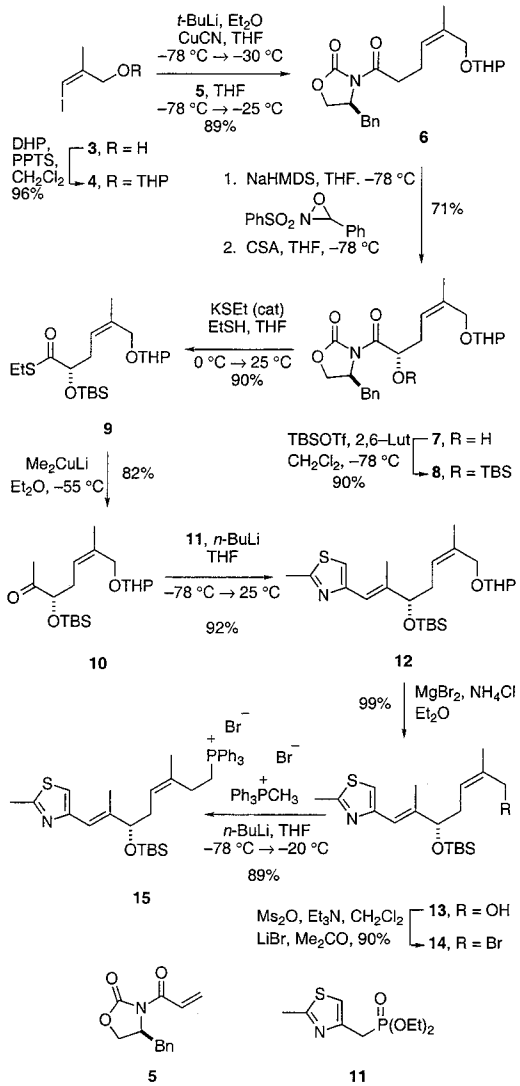
Epothilones A (**1**) and B (**2**) were discovered by Höfle and co-workers[1] during the course of an examination of metabolites of the cellulose-degrading myxobacterium *Sorangium cellulosum* (Myxococcales) as potential antifungal agents.[2] Although the antifungal spectrum of **1** and **2** proved to be quite narrow, scientists at Merck found that these macrolides exhibit a high level of cytotoxicity.[3] The novel



structures and potential utility of the epothilones as chemotherapeutic agents has stimulated intense interest in their synthesis, resulting in four total syntheses of **2**[4] and several as yet incomplete approaches to this structure.[5] Our plan for the synthesis of **2** differs from other pathways in assembling the macrolide from two segments, X and Y, which are first connected at C9−C10 before macrolactonization. Fragment X is constructed around a preformed (*Z*) trisubstituted alkene, thus circumventing stereochemical problems that have afflicted previous routes. The (*Z*)-9,10 olefin arising from convergence of X with Y confers rigidity on the one portion of the epothilone macrocycle that exhibits flexibility.

Synthesis of fragment X began from (*Z*)-3-iodo-2-methyl-2-propen-1-ol (**3**), prepared in geometrically pure form from propargyl alcohol.[6] After protection as **4**, the iodoalkene was converted to the corresponding cuprate, which underwent clean conjugate addition to (*S*)-3-acryloyl-4-benzyl-2-oxazolidinone (**5**)[7] to yield **6**. Hydroxylation[8] of the sodium enolate derived from **6** with Davis' oxaziridine[9] gave **7**, the configuration of which was confirmed by oxidative degradation to dimethyl (*S*)-malate.[10] Protection of alcohol **7** as silyl ether **8**, followed by exposure to catalytic potassium thioethoxide in ethanethiol,[11] afforded **9** along with recovered oxazolidinone (93%). Treatment of thioester **9** with lithium dimethylcuprate furnished ketone **10**, which upon Horner−Emmons condensation with phosphonate **11**[12] produced diene **12** in excellent yield, accompanied by 5% of its (*Z*,*Z*) isomer. Removal of the tetrahydropyranyl ether was accomplished with magnesium bromide,[13] and the liberated alcohol **13** was converted to bromide **14**. Homologation of **14** to phosphonium bromide **15** using triphenylmethylenephosphorane completed the synthesis of fragment X.



Fragment Y was prepared along lines already established by Mulzer[5a] and Meyer[5b] in their approach to **1** and entailed as a key construction the aldol condensation of the known ketone **16**[4a] with aldehyde **17**.[5a] This double stereodifferen-

(1) Höfle, G.; Bedorf, N.; Gerth, H.; Reichenbach (GBF), DE-B 4138042, 1993; *Chem. Abstr.* **1993**, *120*, 52841.

(2) Höfle, G.; Bedorf, N.; Steinmeth, H.; Schomburg, D.; Gerth. H.; Reichenbach, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1567.

(3) For a recent review of the chemical biology of epothilones, see: Nicolaou, K. C.; Roschangar, F.; Vourloumis, F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2014.

(4) (a) 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. (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) May, S. A.; Grieco, P. *Chem. Commun.* **1998**, 1597. (d) Schinzer, D.; Bauer, A.; Schieber, J. *Synlett* **1998**, 861.

(5) (a) Mulzer, J.; Mantoulidis, A. *Tetrahedron Lett.* **1996**, *37*, 9179. (b) Claus, E.; Pahl, A.; Jones, P. G.; Meyer, H. M.; Kalesse, M. *Tetrahedron Lett.* **1997**, *38*, 1359. (c) Gabriel, T.; Wessjohann, L. *Tetrahedron Lett.* **1997**, *38*, 1363. (d) Taylor, R. E.; Haley, J. D. *Tetrahedron Lett.* **1997**, *38*, 2061. (e) Brabander, J. D.; Rosset, S.; Bernardinelli, G. *Synlett* **1997**, 824. (f) Chakraborty, J. K.; Dutta, S. *Tetrahedron Lett.* **1998**, *39*, 101. (g) Liu, Z.-Y.; Yu, C.-Z.; Yang, J. D. *Synlett* **1997**, 1383. (h) Liu, Z.-Y.; Yu, C.-Z.; Wang, R.-F.; Li, G. *Tetrahedron Lett.* **1998**, *39*, 5261. (i) Mulzer, J.; Mantoulidis, A.; Öhler, E. *Tetrahedron Lett.* **1997**, *38*, 7725. (j) Bijoy, P.; Avery, M. A. *Tetrahedron Lett.* **1998**, *39* 1209.

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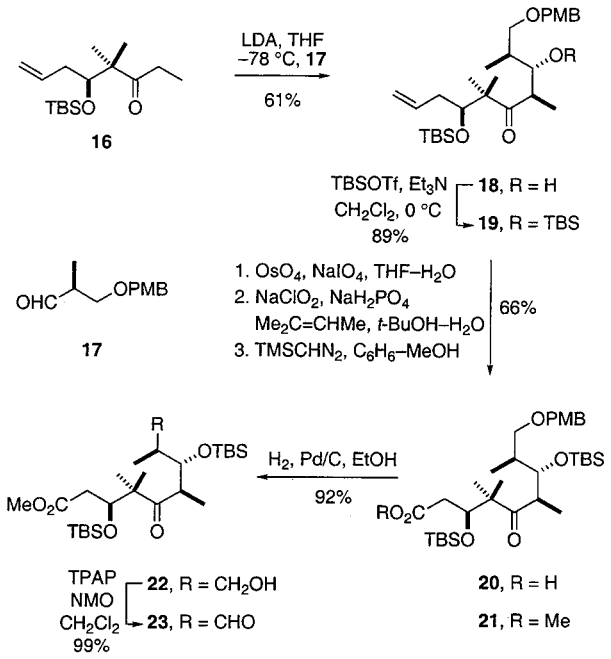
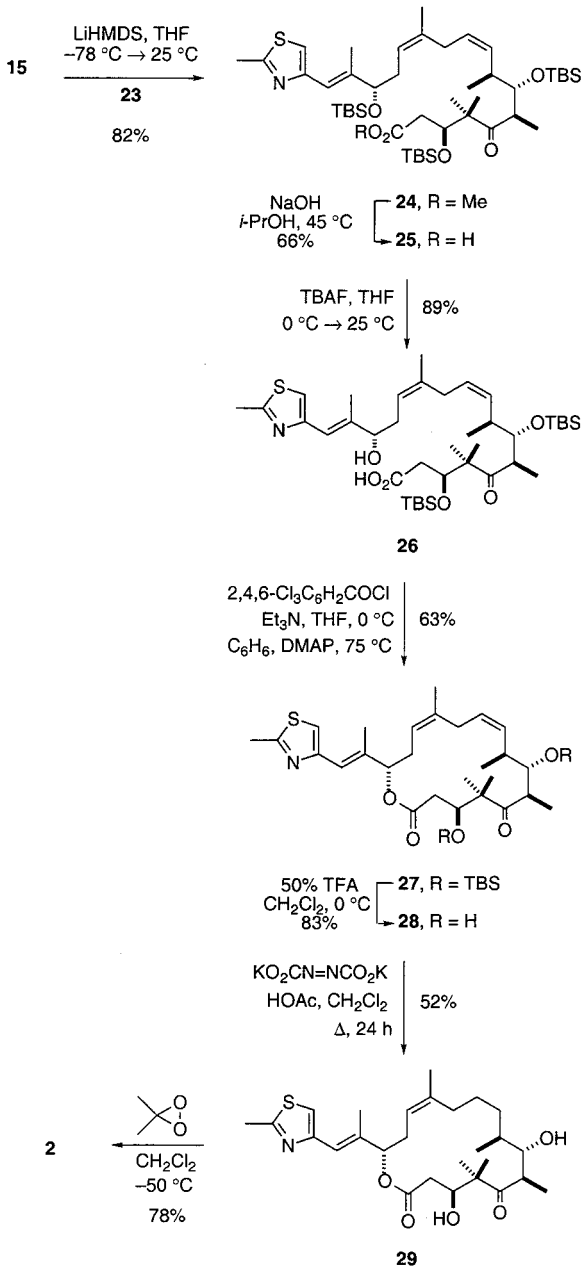
tiating reaction proceeded in good yield to give *anti*-Felkin product **18** as the *sole* stereoisomer. An important contribution to the stereoselectivity of this condensation is made by the *p*-methoxybenzyl (PMB) ether of **17**, since the TBS-protected version of this aldehyde resulted only in a 3:2 mixture of **18** and its Felkin diastereomer, respectively. The favorable outcome with **17** is consistent with chelation of the aldehyde carboxyl with both the lithium enolate from **16** and the PMB ether.[14] After protection of **18** as tris ether **19**, the terminal olefin was cleaved oxidatively to carboxylic acid **20**, which was converted to its methyl ester **21**. Hydrogenolysis of the PMB ether and oxidation of the resultant alcohol **22** yielded aldehyde **23.**



Wittig coupling of the ylide from **15** with aldehyde **23** at low temperature afforded triene **24** as a single stereoisomer in excellent yield. After saponification to carboxylic acid **25** deprotection was accomplished with tetra-*n*-butylammonium fluoride. Macrolactonization of seco acid **26** was carried out under Yamaguchi's conditions[15] to furnish **27**, from which both silyl ethers were cleaved with acid to yield 9,10-dehydrodesepoxyepothilone B (**28**). Selective hydrogenation of the disubstituted olefin of **28** with diimide gave the known lactone **29**,[16,17] which underwent epoxidation with dimethyldioxirane to produce **2**. Characterization data for **29** matched those in the literature,[4a,b] and the NMR spectra of **2** were in excellent agreement with those of natural material.



In summary, we have completed a convergent synthesis of epothilone B (**2**) that generates all seven of its asymmetric centers in a completely stereoselective fashion. In addition, clean *Z* configuration at the 12,13-double bond is incorporated by this pathway. Finally, the *Z* olefin at C9−C10 affords a locus at which exploratory structural modifications can now be made.

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Supporting Information Available: Full characterization data and experimental procedures for all compounds.

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(6) Duboudin, J. G.; Jousseaume, B.; Bonakdar, A. *J. Organomet. Chem.* **1979**, *168*, 227.
(7) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1998**, *110*, 1238.
(8) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346.
(9) Davis, F. A.; Chaltophadhyay, S.; Towson, J. C.; Lol, S.; Reddy, T. *J. Org. Chem.* **1988**, *53*, 2087.
(10) Ozonolysis of **7** followed by oxidation and exposure to (trimethylsilyl)-diazomethane gave a methyl ester that upon treatment with magnesium methoxide afforded dimethyl (*S*)-malate, $[\alpha]^{23}_D = +3.5$ (*c* 1.20).
(11) Evans, D. A.; Ripin, D. H. B.; Johnson, J. S.; Shaughnessy, E. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2117.
(12) Schinzer, D.; Limberg, A.; Böhm, O. M. *Chem.—Eur. J.* **1996**, *2*, 1477.
(13) Kim, S.; Park, J. H. *Tetrahedron Lett.* **1987**, *28*, 439.
(14) For an analogous example of stereocontrolled aldol condensation via double chelation, see: White, J. D.; Porter, W. J.; Tiller, T. *Synlett* **1993**, 535.
(15) Inanaga, J.; Kirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(16) **29**: −86.7 (*c* 0.19, $CHCl_3$) (lit.[6a] −91.5 (*c* 0.30, $CHCl_3$)).
(17) Nicolaou, K. C.; Finlay, M. R. V.; Ninkovic, S.; Sarabia, F. *Tetrahedron* **1998**, *54*, 7127.