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Total Synthesis of Epothilone B

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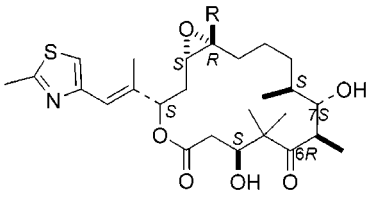
ABSTRACT



Epothilone A, **1**, R = H
Epothilone B, **2**, R = Me

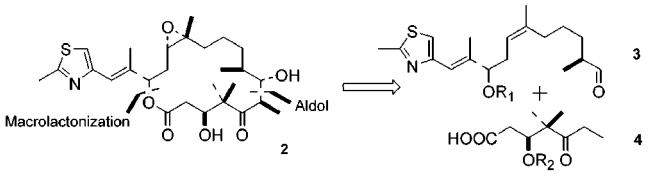
A convergent and stereoselective total synthesis of epothilone B (2) is described. The key steps are Normant reaction, Wadsworth–Emmons reaction of a methyl ketone 14 with the phosphonate reagent 7, diastereoselective aldol condensation of aldehyde 3 with enolate 4 to form the C6–C7 bond, and macrolactonization.

The novel molecular structure and fascinating biological activity of Epothilones A and B, isolated and characterized by Höfle et al. from the myxobacterium *Sorangium cellulosum*, have evoked a great deal of interest.[1] Along with their antifungal and microtubule binding properties, these compounds have the advantages of better solubility than that of taxol, the ability to be obtained in multigram quantities, and increased potency over taxol multidrug-resistant cancer cell lines.[2,3] The numbers of completed syntheses, partial syntheses, and patents being published on these compounds is remarkable.[4−6]

The (*Z*)-olefin, an essential feature for the synthesis of epothilone B, as reported in the literature, was prepared either by classical Wittig olefination methods or ring closing olefin metathesis approaches. Herein we report a unique and stereoselective method to generate the trisubstituted (*Z*)-olefin geometry by modifiction of a classical Normant alkyne cupration and electrophile trap.

Retrosynthetic disconnection of epothilone B indicated to us that synthons **3** and **4** could serve as key intermediates, which could be coupled together via a double-diastereoselective aldol condensation (Scheme 1) and macrolactonization to furnish the target framework.

Scheme 1



The synthesis of aldehyde unit **3**, the northern hemisphere of epothilone B, is based on the retrosynthetic strategy indicated in Scheme 2. Thus, ring opening of epoxide **5** by the Normant-derived vinyl cuprate **6** should lead to an alcohol whose oxidation to ketone could be followed by a Wadsworth−Emmons olefination reaction. Finally, the α-methyl

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(3) Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995**, *55*, 2325−2333.
(4) Reviews: (a) Nicolaou, K. C.; Roschangar, F.; Vourloumis, D. *Angew. Chem.* **1998**, *110*, 2121−2153; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2014−2045. (b) Mulzer, J. *Chem. Mon.* **2000**, *131*, 205−238.

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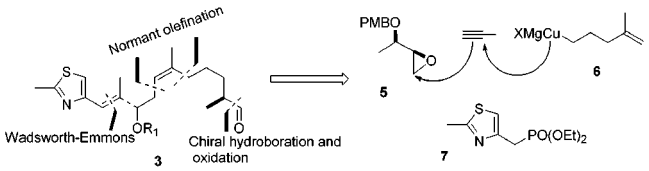
Scheme 2

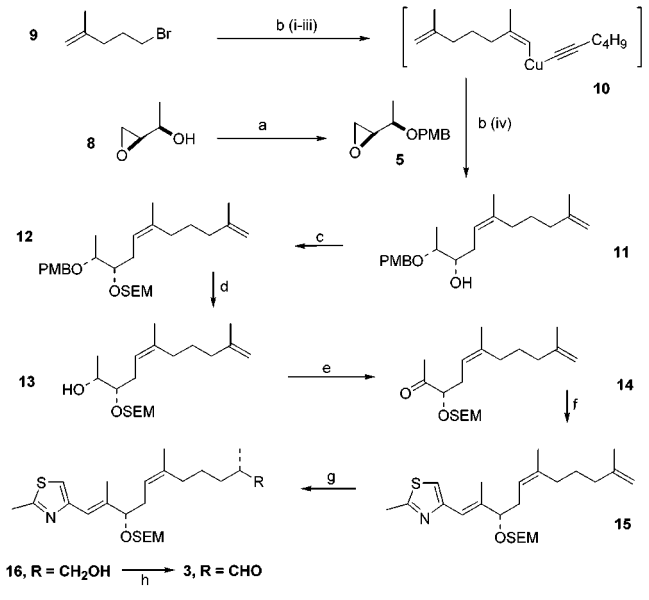


carboxaldehyde could be generated by a chiral hydroboration−oxidation sequence to provide **3**.

The synthesis of fragment **3** (Scheme 3) was commenced by protection of (2*S*,3*R*)-1,2-epoxy-3-butanol **8** as its *p*-methoxybenzyl (PMB) ether. This was achieved by treating compound **8** with sodium hydride and PMB bromide to give **5** in 85% yield.[7]

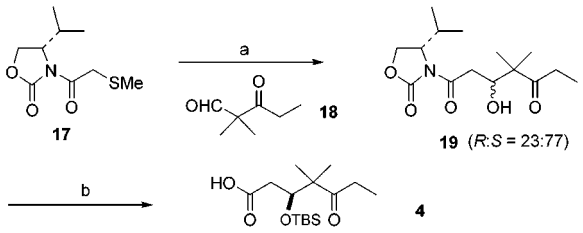
The Normant coupling reaction with epoxide **5** was performed conveniently as follows.[8] After forming the Grignard reagent from the reported bromide **9**, addition of CuBr−DMS complex and stirring for several hours at low temperature led to a black solution of cuprate reagent. Condensation of propyne (g) into the cuprate solution at low temperature was followed by addition of lithiohexyne. Alkylation of the resultant vinyl cuprate **10** was accomplished over the course of 1 day at −25 °C following addition of epoxide **5**. Chromatography of the crude product provided the diastereomerically pure (*Z*)-alkene **11** in 76% yield. The

Scheme 3[a]



[a] (a) PMB−Br, NaH, Bu_4N−I, THF, 0 °C, 85%; (b) (i) Mg, ether, rt, (ii) CuBr−DMS, ether, DMS, −45 °C, 3 h, (iii) propyne, −45 to −23 °C, 4 h, then lithiohexyne, −78 °C, 1 h, (iv) epoxide **5**, −78 °C, 1 h, −25 °C, 24 h, 76%; (c) SEMCl, DIPEA, DCM, 0 °C, 92%; (d) DDQ/water (8:2), 88%; (e) DMSO, $(COCl)_2$, DCM, TEA, −78 °C, 85%; (f) **7**, *n*-BuLi, THF, then **14**, 72%; (g) $(i\text{-PC})_2BH$, THF, 0.5 h, aqueous $NaBO_3$; and (h) DMSO, $(COCl)_2$, DCM, TEA, −78 °C, 92%.

Scheme 4[a]



[a] (a) (i) Bu_2BOTf, DIPEA, CH_2Cl_2, 0 °C then add **17** at −78 °C, (ii) Raney Ni, acetone, 60 °C, 45 min, 70% combined; (b) (i) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 95%; (ii) LiOH, H_2O_2, THF/H_2O, rt, 82%.

alcohol moiety of alkenol **11** was derivatized with SEMCl and DIPEA to provide a SEM ether, **12**. Removal of the PMB ether of **12** with DDQ left the SEM ether intact to give the alcohol **13**. Oxidation of **13** was then effected under Swern conditions to afford the methyl ketone **14** in 85% yield. Wadsworth−Emmons olefination of ketone **14** with the known phosphonate **7** led to the production of diastereomerically clean triene **15** in 72% yield.[9] Finally, diastereoselective hydroboration of the triene **15** using $(i\text{-PC})_2BH$[10] followed by oxidative workup and subsequent Swern oxidation of the resulting alcohol **16** furnished the enantiomerically pure aldehyde **3** in 92% yield.

For the aldol condensation shown in Scheme 1, the silyl-protected keto acid **4** was required. This acid could be prepared as reported in our earlier work via an Evans enantioselective aldol condensation.[6] The dibutylboron enolate of the reported oxazolidinone **17** reacted with keto aldehyde **18** to give an α-thiomethyl amide aldol intermediate. Desulfuration was readily accomplished using Raney Ni, providing the corresponding *R*:*S* aldol adducts **19** in a 23:77 ratio, respectively (70% yield). After silylation with TBDMSOTf and removal of the auxiliary, we obtained **4** in good overall yield.

The optimum conditions for the aldol condensation of keto acid **4** with aldehyde **3** required generation of the dilithio

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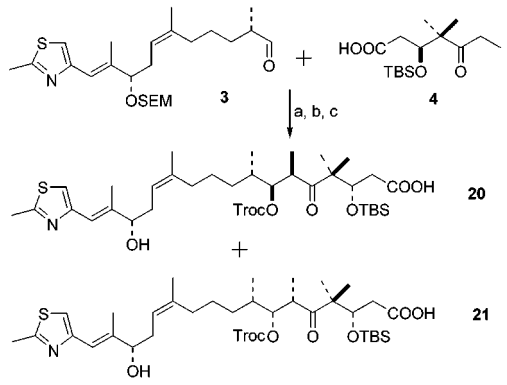
Scheme 5[a]



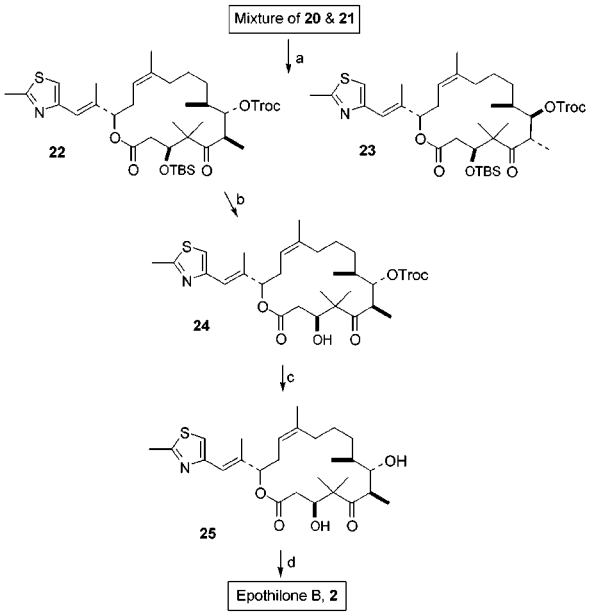
[a] (a) LDA, **4**, THF, −78 to −40 then to −78 °C, $ZnCl_2$, **3**, −78 to −50 °C, 0.5 h; (b) TrocCl, Py, DCM, 0 °C; (c) TFA/DCM (3:7), −20 °C, 1 h, 63% (three steps).

derivative of **4** with LDA (−78 to −40 °C) followed by metal exchange with anhydrous $ZnCl_2$ at −78 °C.[11] Thereupon, reaction of aldehyde **3** with the transmetalated enolate of **4** led to formation of polar adducts best handled as follows.

Treatment of the aldol mixture with 1.2 equiv of TBSCl and excess TrocCl in pyridine furnished a mixture of fully protected products. Upon exposure to trifluoroacetic acid at −20 °C, deprotection of the SEM ether with simultaneous deprotection of TBS esters occurred. At this stage the aldol product mixture could be conveniently separated from the unreacted keto acid **4** by flash column chromatography giving adducts **20** and **21** in a 2:1 diastereomeric ratio.

The mixture of hydroxy acids was then subjected to macrolactonization using the Yamaguchi method[12] to obtain the corresponding lactones as shown in Scheme 6. The two lactones **22** and **23** were readily separated by flash column chromatography, and **22** was characterized by conversion to natural product. Selective deprotection of the of the TBS group from **22** using HF−Py followed by chromatographic purification gave the desired Troc alcohol **24**. Removal of

Scheme 6[a]



[a] (a) 2,4,6-$Cl_3C_6H_2COCl$, TEA, THF, DMAP, toluene, rt, 1 h; (b) HF−Py, DCM, rt, 95%; (c) Zn, aqueous NH_4Cl, MeOH, reflux, 92%; (d) [methyl(trifluoromethyl)]dioxirane, MeCN, 0 °C, 56%.

the Troc group was effected using Zn and aqueous NH_4Cl in MeOH to provide the diol **25**, epothilone D.[13] Finally, treatment of **25** with methyl (trifluoromethyl)dioxirane[13] led cleanly to epothilone B **2**, whose properties were identical to reported spectral and physical data for the natural product.[14]

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Supporting Information Available: Data for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Yang, D.; Wong, M.-K.; Yip, Y.-C. *J. Org. Chem.* **1995**, *60*, 3887−3889.

(14) See Supporting Information. For synthetic epothilone B (**2**): $[\alpha]^{25}_D = -31°$ (*c* 0.25, $CHCl_3$); lit.[5a] $[\alpha]^{25}_D = -31°$ (*c* 0.045, $CHCl_3$).