Total synthesis of (−)-epothilone B

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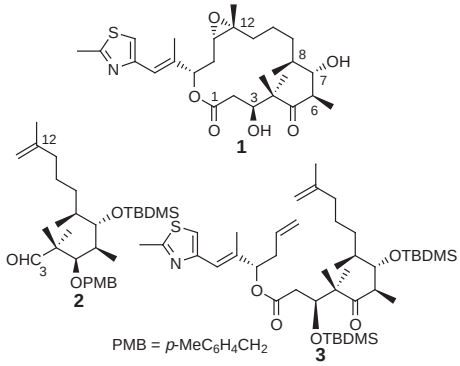
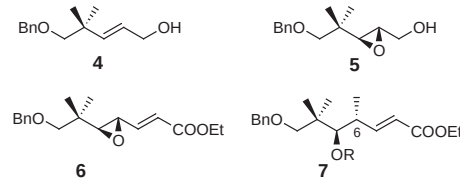
The sixteen-membered ring macrolide (−)-epothilone B 1 has been synthesized by a route which features stereospecific methylation of an (*E*)-γ,δ-epoxy acrylate, the use of a double asymmetric reaction employing (*R*,*R*)-diisopropyltartrate and (*E*)-crotylboronate, and ring closure by means of an olefin metathesis reaction.

(–)-Epothilone B **1**, isolated by Höfle and co-workers[1] from the myxobacteria *Sorangium cellulosum* strain 90, has been the object of intense synthetic activity.[2,3] The excitement surrounding the epothilones stems, in part, from research conducted at the Merck Research Laboratories by Bollag[4] and co-workers who demonstrated that the epothilones function *via* a paclitaxel-like mode of action by binding to and stabilizing cell microtubule assemblies. Particularly significant has been the finding[4] that (−)-epothilone B appears to be effective against a number of drug-resistant tumor cell lines. We detail below an intramolecular olefin metathesis strategy for the construction of (−)-epothilone B which features preparation of the C(3)-C(12) fragment **2** and its elaboration into **3**, and subsequent conversion of **3** into **1**.

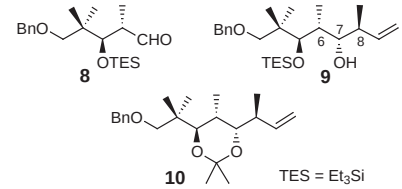


Synthesis of the chiral C(3)-C(12) fragment **2** commenced with the optically active epoxide **5**, $[\alpha]_D^{25}$ −10.1 (*c* 2.5, $CHCl_3$), which was prepared from allylic alcohol **4**[5] *via* a Sharpless epoxidation[6] [diethyl L-tartrate (0.26 equiv.), $Ti(O\text{-}Pr^i)_4$ (0.2 equiv.), Bu^tOOH (3.0 equiv.), CH_2Cl_2, 4 Å mol sieves, −40 °C (8 h) → −10 °C (8 h)]. With the ready availability of **5**, efforts were focused on introduction of the C(6) methyl group. Toward this end, **5** was transformed, in 87% overall yield, into the (*E*)-γ,δ-epoxy acrylate **6** *via* a Swern oxidation [DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 1 h, then Et_3N, 0 °C, 1 h] and an (*E*)-selective Horner–Wadsworth–Emmons reaction [NaH, THF, $(EtO)_2POCH_2CO_2Et$, 0 °C, 1 h, then RCHO, THF, 0 °C, 30 min]. Treatment of a 0.07 M solution of **6** in 1,2-dichloroethane in the presence of 6.0 equiv. of water cooled to −30 °C with 10.0 equiv. of Me_3Al (2.0 M in hexane) gave rise to **7** (R = H), $[\alpha]_D^{25}$ +11.7 (*c* 2.5, $CHCl_3$), as the sole product in 87% yield.[7] The methylation of **6** is stereospecific, proceeding with net inversion of configuration about C(6). Note that, in the absence of water, the transformation of **6** into **7** (R = H) does not proceed to any appreciable extent.

Elaboration of the remaining two stereocenters at C(7) and C(8) necessitated conversion of substrate **7** into aldehyde **8** which was realized (95% overall yield) *via* a three step protocol

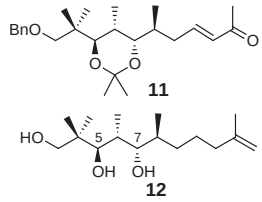


[TESOTf, 2,6-lutidine, CH_2Cl_2, 45 min, then OsO_4 (catalytic), NMO, acetone–water–Bu^tOH (2:5:1), 7 h, followed by $NaHSO_3$, 14 h, then $Pb(OAc)_4$, C_6H_6, 15 min]. Exposure of **8** to (*R*,*R*)-diisopropyltartrate and (*E*)-crotylboronate[8] in toluene [−78 °C (3 h) → room temp. (12 h)] in the presence of 4 Å molecular sieves gave rise to **9**, $[\alpha]_D^{25}$ −8.6 (*c* 2.1, $CHCl_3$), as the sole product in 93% yield, thus establishing the required *syn*,*anti* arrangement about C(6)–C(7) and C(7)–C(8). Prior to functionalization of the $\Delta^{9,10}$ terminal olefin, the triethylsilyl ether was cleaved (TBAF, THF, 30 min) and the resulting 1,3-*anti* diol was converted, upon exposure (15 min) to 2,2-dimethoxypropane and catalytic TsOH, into the 1,3-*anti* acetonide **10**, $[\alpha]_D^{25}$ +11.6 (*c* 1.7, $CHCl_3$), in 93% overall yield. The stereochemical assignment for the *anti* acetonide follows from the ^{13}C NMR spectrum of **10**. The observed chemical shifts for the acetonide carbons (δ 23.4, 25.7 and 100.1) in **10** are in excellent agreement with previous data from independent studies on 1,3-*anti* acetonides by Rychnovsky[9] and Evans.[10]

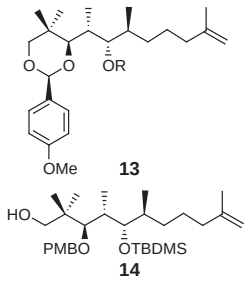


Completion of the synthesis of the C(3)-C(12) fragment **2** was realized as follows. Hydroboration [catecholborane, $(PPh_3)_3RhCl$ (catalytic), THF, 45 min; NaOH, H_2O_2][11] of **10** followed by oxidation (Swern conditions) and subsequent Horner–Wadsworth–Emmons condensation (THF, 4 h) of the resulting aldehyde with the sodium anion derived from diethyl (2-oxopropyl)phosphonate gave rise, in 55% overall yield, to **11**, $[\alpha]_D^{25}$ +26.0 (*c* 1.05, $CHCl_3$). Enone **11** was transformed (77% overall) into triol **12** *via* a three step sequence [H_2, 10% Pd/C, EtOH–EtOAc (1:1), 5 h, then $Ph_3P{=}CH_2$, THF, 3 h, then 1.0 M HCl–THF (1:1), 50 °C, 3 h] which set the stage for selective protection of the C(5) and C(7) hydroxy groups, which proved critical for completion of the total synthesis of epothilone B since the 1,3-diol acetonide present in **11** was not compatible with the olefin metathesis reaction in the late stages of the synthesis.

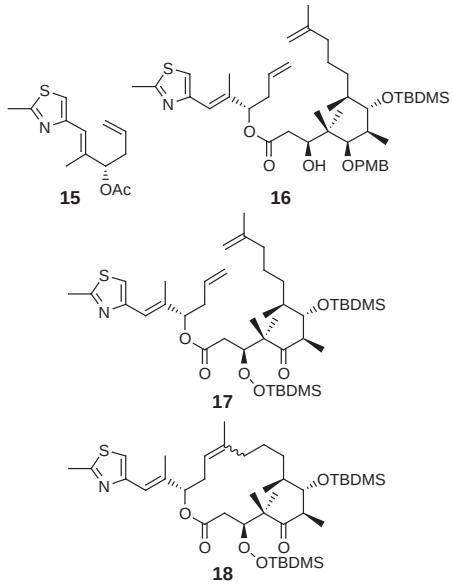
Exposure (30 min) of **12** to *p*-anisaldehyde dimethylacetal in benzene containing catalytic TsOH gave rise (90%) to **13** (R = H) which, upon silylation [TBDMSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 4 h], provided (94%) **13** (R = TBDMS), $[\alpha]_D^{25}$ +19.7 (*c* 3.9, $CHCl_3$). Protection of the C(5) hydroxy group as its 4-methoxybenzyl (PMB) ether was realized *via* regioselective



reductive ring cleavage[12] of the 1,3-dioxane ring of the 4-methoxybenzylidene acetal **13** (R = TBDMS). Thus, a 0.04 M solution of **13** (R = TBDMS) in CH_2Cl_2 , cooled to −78 °C, was treated with 10.0 equiv. of a 1.0 M solution of DIBAL-H in CH_2Cl_2. After warming to −15 °C (1.5 h), a 75% yield of primary alcohol **14** was isolated. Oxidation (Swern conditions) of **14** provided the intact C(3)-C(12) fragment **2**, $[\alpha]_D^{25}$ −7.6 (*c* 4.6, $CHCl_3$), in 98% yield.

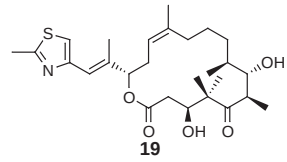


In order to complete the total synthesis of **1**, the ester enolate derived (LDA, THF, −78 °C) from the known acetate **15**[2] was condensed with **2** giving rise (83%) to a readily separable mixture (1.7 : 1) of diastereomers favoring **16**, $[\alpha]_D^{25}$ −28.6 (*c* 1.4, $CHCl_3$), possessing the correct configuration at C(3). Protection [TBDMSOTf, 2,6-lutidine, CH_2Cl_2, −50 °C, 4 h] of the C(3) hydroxy group, followed by cleavage [DDQ, CH_2Cl_2–H_2O (18 : 1), 0 °C, 3 h] of the C(5) 4-methoxybenzyl ether and subsequent Dess–Martin oxidation gave rise to **17**, $[\alpha]_D^{25}$ −44.0 (*c* 2.4, $CHCl_3$), in 65% overall yield.



Ring closure to complete the formation of the sixteen-membered ring of **1** was realized by an intramolecular olefin metathesis reaction.[13,14] Exposure (4 h) of a 0.001 M solution of **17** in benzene (heated to 55 °C) to 20 mol% of the molybdenum-based catalyst [$Mo(CHMe_2Ph)\{N(2,6\text{-}Pr^i_2C_6H_3)\}\{OCMe(CF_3)_2\}_2$] of Schrock[13] afforded in 55% yield a 1 : 1 mixture of *Z* and *E* isomers (*cf.* **18**) which could be separated by preparative TLC. Upon treatment of the enantiomerically pure *Z*-isomer with HF·pyridine (THF, 3 h), a 60% yield of pre-epothilone B **19** was obtained. Epoxidation (dimethyldioxirane,[15] CH_2Cl_2, −50 °C, 4 h) of **19** provided crystalline **1**, mp 93–94 °C (lit.,[2] 93.6–94.7 °C), $[\alpha]_D^{25}$ −32.2 (*c* 0.09, $CHCl_3$) [lit.,[2] −31.0 (*c* 0.045, $CHCl_3$)] in 86% yield. The ^{1}H NMR spectrum of synthetic **1** was identical in all respects with a spectrum of natural (-)-epothilone B.

We thank Professor S. Danishefsky for helpful discussions and the ^{1}H NMR spectra of natural (−)-**1** and synthetic (−)-**17**. This research was supported by a grant from the U.S. NIH (CA 28865).



Notes and References

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