Pergamon

Tetrahedron Letters 41 (2000) 7635–7638

TETRAHEDRON LETTERS

A novel highly stereoselective total synthesis of epothilone B and of its (12*R*,13*R*) acetonide

Johann Mulzer,* Gunter Karig and Peter Pojarliev

Institut für Organische Chemie der Universität Wien, Währinger Strasse 38, A-1090 Vienna, Austria

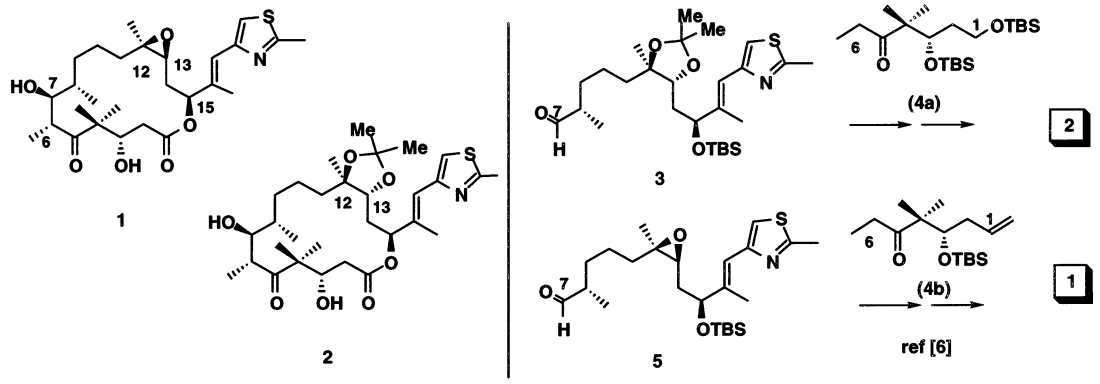
Received 13 July 2000; accepted 31 July 2000

Abstract

Stereoselective syntheses of epothilone B (**1**) and its novel derivative **2** are described. Key steps are the formation of intermediate **3** via Sharpless AD-reaction and Davis–Evans-hydroxylation.

Keywords: asymmetric synthesis; antitumor compounds; oxazolidinone; hydroxylation.

Epothilone B (**1**)[1] shows outstanding microtubule binding affinities and cytotoxity against tumor cells and multiple drug resistant tumor cell lines.[2] The role of **1** as a potential paclitaxel successor has initiated intense interest in its synthesis, resulting in several total syntheses of **1** and numerous derivatives thereof.[2b] In this respect, variations of the 12,13-section have proven particularly fruitful, resulting in the exchange of the epoxide, among others, for a *Z* double bond (epothilone D) or a cyclopropane moiety.[3] It occurred to us to bridge the 12,13-bond by a larger heterosubstituted ring, which should allow more conformational flexibility. In this paper we present a stereoselective synthesis of the novel *trans*-12,13-acetonide analogue **2** of epothilone B.

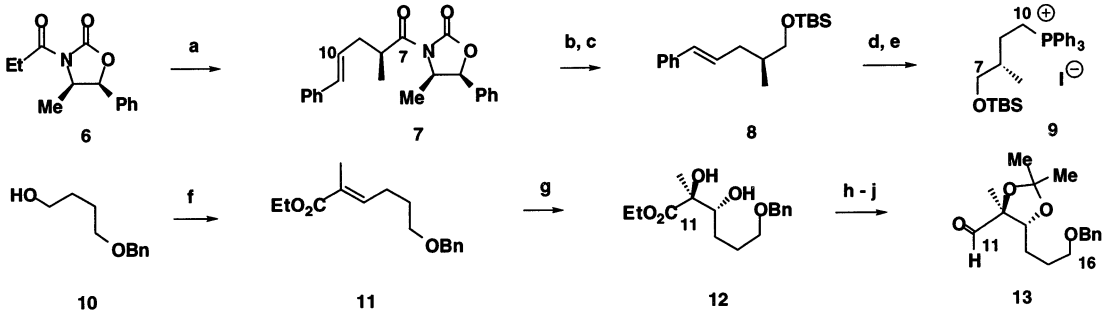


* Corresponding author. Fax: +431-4277-52189; e-mail: johann.mulzer@univie.ac.at

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01318-6

Additionally we report a highly stereoselective synthesis of epothilone B (**1**) itself. Both syntheses make use of aldehyde **3**. In the synthesis of **2**, aldehyde **3** is directly coupled with the known ketone **4a**,[4], whereas in the synthesis of **1**, aldehyde **3** is first converted into the epoxy derivative **5**, which is then coupled with the known ketone **4b**[4] following our previous route.[5]

The key fragments for the synthesis of **3** are the phosphonium salt **9** (containing C7–C10) and the aldehyde **13** (containing C11–C16) (Scheme 1). Known oxazolidinone **7**[6] was converted into the TBS–ether **8**, which was converted into phosphonium salt **9**. The key step in the synthesis of aldehyde **13** was the Sharpless AD-reaction[7] of enoate **11**, which was obtained from the protected butanediol **10** as shown.

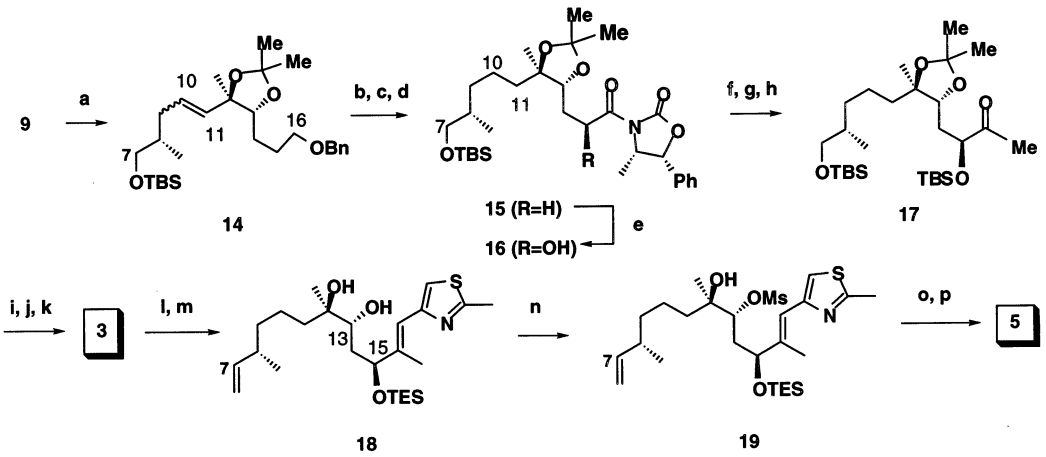


Scheme 1. *Reagents and conditions*: (a) 1.1 equiv. NaHMDS, THF, then cinnamyl bromide, −78°C to rt, 4 h, 76% (>96:4 dr). (b) 1.2 equiv. $LiBH_4$, 1.1 equiv. H_2O, Et_2O, 0°C to rt, 2 h, 90%. (c) TBSCl, imidazole, DMF, rt, 3 h, 99%. (d) O_3, CH_2Cl_2/EtOH (9:1), −78°C, 2 min, then 3.7 equiv. $NaBH_4$, −78°C to rt, 5 h, 97%. (e) i. 3 equiv. imidazole, 1.5 equiv. PPh_3, 1.5 equiv. I_2, Et_2O/MeCN (3:1), 0°C, 30 min, ii. 1.5 equiv. PPh_3, neat, 90°C, 5 h, 76%. (f) i. DMSO, oxalyl chloride, triethylamine, ii. 1.1 equiv. ethyl-2-(triphenylphosphoranyliden)-propionate, THF, 80°C, 4 h, 84%. (g) AD-mix β, $MeSO_2NH_2$, *t*BuOH/H_2O (1:1), rt, 12 h, 96% (>98% ee). (h) $(MeO)_2CMe_2$, CSA, rt, 12 h, 99%. (i) 3 equiv. DIBAH, THF, 0°C to rt, 12 h, 94%. (j) Dess–Martin-periodinane, pyridine, CH_2Cl_2, 0°C, 4 h, 97%

The synthesis of the key aldehydes **3** and **5** (Scheme 2) was started with a Wittig reaction between **9** and **13**, which furnished olefin **14** as a mixture of *E*/*Z* isomers, which was converted into the oxazolidinone **15**. Asymmetric hydroxylation of the sodium enolate of **15** was achieved with Davis' oxaziridine[8] to form **16** with 92% de at C15. The oxazolidinone moiety in **16** was replaced by the Weinreb-amide, and after protecting the 15-hydroxy group as a TBS ether, addition of MeLi furnished methyl ketone **17**. *E* selective Wittig reaction (*E*/*Z* 30:1), selective monodesilylation of the 7-TBS ether and Dess–Martin-oxidation furnished key intermediate **3**. To form the epoxide **5**, aldehyde **3** was converted into olefin **18** by Wittig reaction, global *O*-deprotection and selective protection of the 15-OH with 3 equivalents of TESCl. Selective mesylation of the 13-OH was achieved to generate intermediate **19**. On treatment with potassium carbonate the desired epoxide was formed and, via dihydroxylation and ensuing glycol cleavage, the 7-olefin was selectively oxidized to aldehyde **5**.[9]

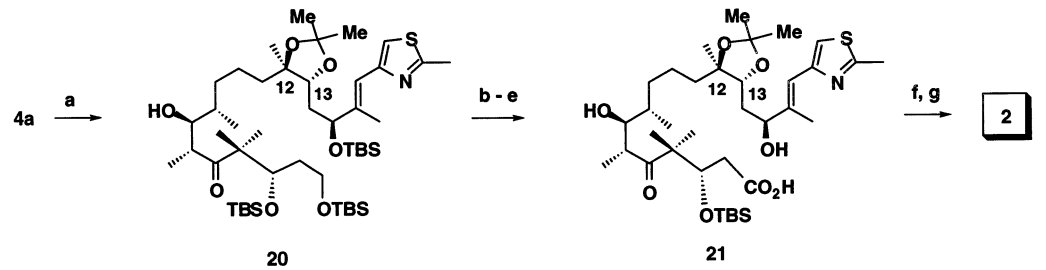
The aldol reaction of **3** with ketone **4a** gave adduct **20** (Scheme 3). The main diastereomer was separated by chromatography and converted via seco acid **21** into **2**[9] via the methodology developed earlier.[4] Similarly, ketone **4b** and aldehyde **5** were coupled to generate **1** as described previously.[5]

In conclusion, we have presented efficient syntheses of **1** and **2**, which establish the stereogenic centers at C3, 6, 12, 13, and 15 independently with high diastereoselectivity by using external sources of chirality. Only centers C6 and 7 are determined during the aldol addition by internal



Scheme 2. *Reagents and conditions*: (a) 1.1 equiv. NaHMDS, THF, 0°C, 30 min, then **13**, 0°C to rt, 30 min, 87% over two steps. (b) H_2, Pd/Al_2O_3 cat., EtOH, 3 bar, rt, 36 h, 91%. (c) 4 equiv. $NaIO_4$, 0.05 equiv. $RuCl_3$–H_2O, CCl_4/MeCN/H_2O (2:2:3), rt, 80 min, 88%. (d) 1.1 equiv. NEt_3, 1.0 equiv. PivCl, Et_2O, −78 to 0°C, 1 h, then Li-salt of (4*S*,5*R*)-4-methyl-5-phenyl-1,3-oxazolidinone, THF, −78 to 0°C, 1 h, 80%. (e) 1.4 equiv. NaHMDS, THF, −78°C, 1 h, then 1.8 equiv. Davis oxaziridine, −84°C, 5 min, then CSA, −84°C to rt, 10 min, 66% (>96:4 dr). (f) 4 equiv. $H_2N(OMe)MeCl$, 8 equiv. *i*PrMgCl, THF, −10 to 0°C, 1 h, 94%. (g) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 1 h, 97%. (h) 1.1 equiv. MeLi, THF, −78°C, 90 min, 91%. (i) 5 equiv. (2′-methyl thiazol-4′-yl)-methyl-tri-*n*-butyl-phosphonium chloride, 5 equiv. KHMDS, THF, −78 to 45°C, 1 h, 98% (*E*/*Z* 30:1). (j) 1 equiv. CSA, CH_2Cl_2/MeOH (1:1), 0°C, 7 h, 97%. (k) 1.3 equiv. Dess–Martin-periodinane, pyridine, CH_2Cl_2, 0°C, 4 h, 97%. (l) triphenylmethylphosphonium iodide, *n*BuLi, hexane–THF, then EtOH, 1 M HCl, 75%. (m) NEt_3, triethylchlorosilane, 25°C, 3 h. (n) NEt_3, methanesulfonylchloride, −15°C, 4 h, 81%. (o) methanol, potassium carbonate, 25°C, 1 h, 90%. (p) osmium tetroxide, NMO, THF, *tert*-BuOH, 0°C, 16 h, then sodium periodate, EtOH, H_2O, 25°C, 1 h, 62%

stereoinduction. In the synthesis of **2**, this induction is 6:1, and in the case of **1** it is >95:5.[5] Our introduction of the 12,13-epoxide is also highly stereocontrolled and in this respect more reliable than the direct epoxidation of epothilone D, which gives varying diastereomeric ratios between 5:1 and 20:1.[2b] Hence we have achieved the *first totally stereoselective* synthesis of **1**.



Scheme 3. *Reagents and conditions*: (a) LDA, THF, −78°C, 45 min, then **3**, 20 min, 70% (6:1). (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 12 h, 93%. (c) CSA, CH_2Cl_2/MeOH (1:1), 0°C, 8 h, 84%. (d) i. 1.3 equiv. Dess–Martin-periodinane, pyridine, CH_2Cl_2, 0°C, 2 h, ii. 5 equiv. $NaClO_2$, $NaHPO_4$, 2,3-dimethyl-but-2-ene, *t*BuOH/H_2), rt, 50 min, 93%. (e) 4 equiv. TBAF, THF, rt, 12 h. (f) 1.2 equiv. 2,4,6-trichlorobenzoyl chloride, 2 equiv. NEt_3, toluene, rt, 2 h, then add to a solution of 10 equiv. DMAP in toluene, 110°C, 3 h, 50% over two steps. (g) 15% CF_3CO_2H in CH_2Cl_2, −18 to 0°C, 6 h, 80%

Acknowledgements

Financial support by the FWF (Austrian Science Foundation) and the Schering AG, Berlin, is gratefully acknowledged.

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9. Analytical data: **2**: ^{1}H NMR (400 MHz, $CHCl_3$): $\delta = 0.98$ (d, $J = 7.1$ Hz, 3H), 1.08 (s, 3H), 1.10 (s, 3H), 1.12 (s, 3H), 1.14 (d, $J = 6.8$ Hz, 3H), 1.18–1.42 (m, 4H), 1.34 (s, 3H), 1.55–1.67 (m, 3H), 1.91 (ddd, $J = 15.7$, 3.3, 1.8 Hz, 1H), 1.99 (s, 3H), 2.10 (ddd, $J = 15.7$, 7.8, 4.0 Hz, 1H), 2.45–2.59 (m, 3H), 2.8 (s, 3H), 3.28 (dq, $J = 6.8$, 5.8 Hz, 1H), 3.57 (br, 1H), 3.72 (t, $J = 4.0$ Hz, 1H), 3.99 (dd, $J = 7.8$, 1.5 Hz, 1H), 4.15 (dd, $J = 10.7$, 2.6 Hz, 1H), 5.47 (br, 1H), 6.57 (s, 1H), 6.92 (s, 1H), ^{13}C NMR (100 MHz, $CHCl_3$): $\delta = 13.58$, 16.73, 16.92, 18.97, 19.07, 20.83, 21.17, 21.58, 26.48, 28.55, 31.16, 32.77, 36.05, 38.88, 40.30, 43.41, 53.15, 71.74, 74.14, 75.33, 76.21, 77.21, 106.14, 114.94, 117.43, 137.00, 152.24, 164.55, 169.69, 219.76. $[\alpha]_D^{20} = -37.6$ ($c = 0.6$, $CHCl_3$). HRMS calcd for $C_{30}H_{47}NO_7S$: 565.3073, found 565.3081. **5**: ^{1}H NMR (400 MHz, $CHCl_3$): $\delta = 0.61$ (q, $J = 7.8$ Hz, 6H), 0.94 (t, $J = 7.8$ Hz, 9H), 1.09 (d, $J = 7.0$ Hz, 1H); 1.27 (s, 3H); 1.32–1.53 (m, 5H), 1.60 (ddd, $J = 14.0$, 7.0, 4.0 Hz, 1H); 1.66–174 (m, 1H); 1.89 (ddd, $J = 14.0$, 9.0, 4.5 Hz, 1H), 2.02 (s, 3H), 2.33 (m, 1H), 2.70 (s, 3H), 2.89 (dd, $J = 7.0$, 4.5 Hz, 1H), 4.34 (dd, $J = 9.0$, 4.0 Hz, 1H); 6.93 (s, 1H), 9.91 (d, $J = 2.0$ Hz, 1H). ^{13}C NMR (100 MHz, $CHCl_3$): $\delta = 5.2$, 7.2, 13.7, 14.2, 19.6, 22.6, 23.2, 31.0, 33.3, 36.4, 46.7, 61.1, 62.4, 76.5, 115.8, 119.2, 142.6, 153.4, 164.9, 205.2. $[\alpha]_D^{20} = -10.6$ ($c = 1.0$, $CHCl_3$). HRMS calcd for $C_{24}H_{41}NO_3SSi$: 451.2576, found 451.2559.