Total synthesis of 26-hydroxyepothilone B and related analogues

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A series of 26-substituted epothilones B (3, 22, 23a–n and 24a–h,j–l,o) have been constructed by total synthesis involving a selective Wittig olefination, an aldol reaction and a macrolactonization as key steps.

The novel molecular structures and impressive antitumour properties of the epothilones[1] have captured the imagination of synthetic chemists, biologists[2,3] and clinicians. Isolated[1] from myxobacterium *Sorangium cellulosum*, these substances exhibit tubulin polymerization properties[2] similar to Taxol[4] and show potent cytotoxicity against Taxol-resistant tumour cells.[3] Research in this field has resulted in the total synthesis of the naturally occurring epothilones B **1**[5–7] and A **2**,[5,7–11] and a plethora of analogues.[5–17] Owing to the higher antitumour potency of the 12-methyl bearing epothilone B **2** as compared to epothilone A **1**, this substituent (the C26 methyl group) was considered a prime candidate for modification. An expedient entry into this series of compounds was sought. Here we report such a strategy which culminated in the total synthesis of 26-hydroxydesoxyepothilone B **3**, 26-hydroxyepothilone B **22** and a series of related analogues **23a**–**n** and **24a**–**h**,**j**–**l**,**o**.

The approach to the C26-modified epothilones B followed a similar path to that developed in these laboratories[5,7] for epothilone B **1**, and involved (i) stereoselective Wittig olefination, (ii) aldol condensation and (iii) macrolactonization (Fig. 1).

Protection of **4** (Scheme 1) as a trityl (CPh_3) ether furnished **5**† in 99%. Hydroboration of **5** led to **6** (94%), which was converted to **7** by the action of PPh_3, I_2 and imidazole (90%). Stereoselective alkylation of SAMP hydrazone **8**,[18] *via* its lithio derivative, with **7** led to **9**. The transformation of **9** to **10** proceeded under the influence of MMPP[7] (91%), and reduction of the latter with DIBAL-H provided aldehyde **11** (97%).

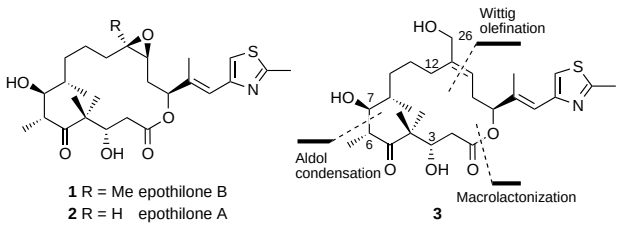
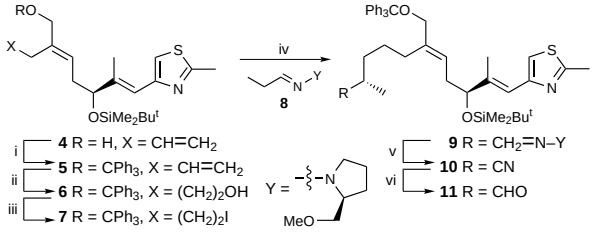


Fig. 1 Structures of **1** and **2** and retrosynthetic analysis of **3**



Scheme 1 *Reagents and conditions*: i, Ph_3CCl, DMAP, DMF, 70 °C, 1 h; ii, 9-borabicyclo[3.3.1]nonane, THF, 0 °C, 2 h, then aq. NaOH (3 M), then 30% H_2O_2; iii, I_2, imidazole, PPh_3, Et_2O–MeCN (3 : 1), 0 °C, 0.5 h; iv, **8**, LDA, THF, 0 °C, 14 h, then **7**, THF, −100 → −20 °C, 10 h; v, monoperoxyphthalic acid (Mg salt) (MMPP), MeOH–phosphate buffer (pH 7) (1 : 1), 0 °C, 1 h; vi, DIBAL-H, toluene, −78 °C, 1 h

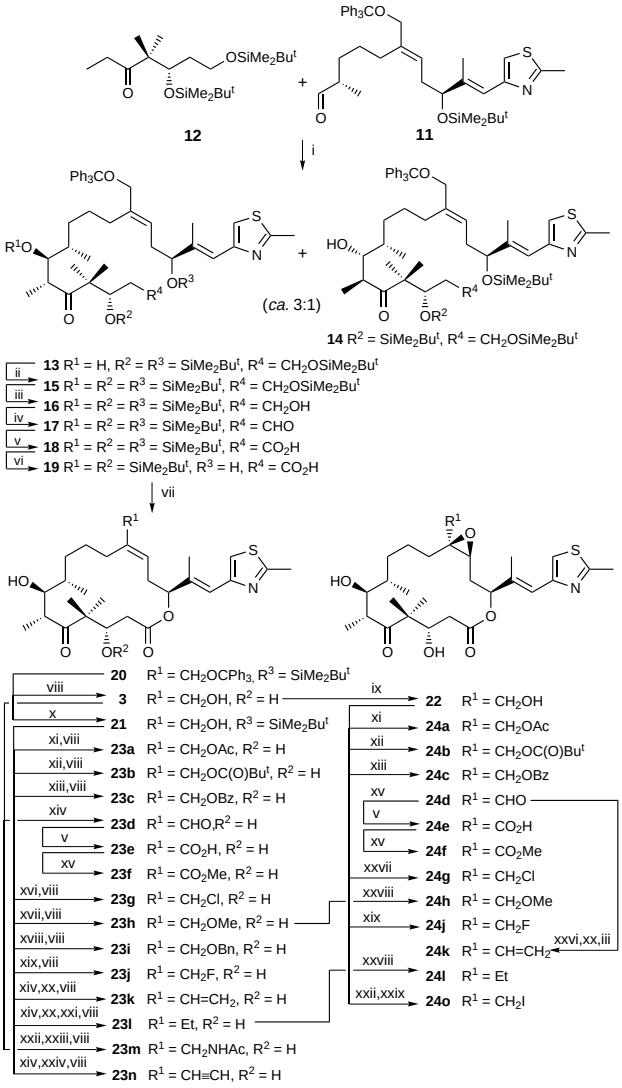
The coupling of the C1–C6 ketone fragment **12**[7,15] with **11** *via* a *syn*-selective aldol reaction (Scheme 2) furnished **13** along with its (6*S*,7*R*) diastereoisomer **14** (85% total yield, *ca.* 3 : 1). Chromatographic purification followed by silylation gave **15**. The use of buffered HF·pyridine in THF permitted selective desilylation of **15** giving **16** (74%), which was sequentially oxidized to **17**, and thence to carboxylic acid **18**. Selective desilylation at C15 was achieved by the use of Bu_4NF in THF, providing **19** (89%). The latter compound was in turn subjected to the Yamaguchi macrolactonization forming **20** (75%). Exposure of **20** to HF·pyridine in THF promoted concomitant removal of both the silyl groups and the trityl moiety, leading to **3** (78%). Alternatively, treatment of **20** with camphorsulfonic acid in MeOH–CH_2Cl_2 resulted in the selective removal of the trityl group, giving **21** (70%). Sharpless asymmetric epoxidation of **3** then gave 26-hydroxyepothilone B **22** (76%).

The availability of **3**, **21** and **22** facilitated access to a number of 26-substituted epothilones. As indicated in Scheme 3, **21** was converted to **23a**–**c** by reaction with the corresponding acid anhydride or chloride under basic conditions followed by desilylation. MnO_2 oxidation of **3** proved highly efficient, providing α,β-unsaturated aldehyde **23d** (85%). Further oxidation of **23d** with $NaClO_2$ led to carboxylic acid **23e** (98%), which was converted to **23f** by treatment with CH_2N_2 (80%). Methylation and benzylation of **21** followed by desilylation afforded **23h** (58% overall) and **23i** (35% overall), respectively. Halogenation of **21** followed by desilylation led to chloride **23g** (73% overall) or fluoride **23j** (51% overall). Alternatively, treatment of **21** with MnO_2 and reaction of the resulting aldehyde with the anion derived from Me_3SiCHN_2 followed by

Table 1 Biological activities of epothilone analogues

Compound	Induction of tubulin assembly[a] (%)	IC_{50}/nM (relative resistance)[b] Parental 1A9	Taxol-resistant PTX10	Taxol-resistant PTX22
23g	88	90	> 100	> 100
23j	83	0.65	6	4
23k	95	8.7	30	14
23l	66	60	> 100	93
24d	87	5	24	3.1
24g	69	0.25	0.50	0.55
24j	93	0.15	0.55	0.15
24k	94	0.63	4.7	0.95
24l	79	0.27	8.5	0.45
24o	41	25	55	20
Taxol	50	2	50	43
Epothilone A	72	2	19	4.2
Epothilone B	100	0.040	0.035	0.045

[a] Assays performed as in ref. 4. [b] Inhibition of human ovarian carcinoma cell growth. Assays performed as in ref. 7. Each IC_{50} value shown is an average value obtained from three independent assays.



Scheme 2 *Reagents and conditions*: i, LDA, THF, 0 °C, 15 min, then **12**, THF, −78 → −60 °C, 1 h, then **11**, THF, −78 °C; ii, $Bu^tMe_2SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h; iii, HF·pyridine, pyridine, THF, 0 → 25 °C, 4 h; iv, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 → 0 °C, 1.5 h; v, $NaClO_2$, Me_2C=CHMe, NaH_2PO_4, Bu^tOH–H_2O (5 : 1), 25 °C, 2 h; vi, Bu_4NF, THF, 25 °C, 8 h; vii, 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, 0 °C, 1 h, then add to DMAP in toluene, 75 °C, 1 h; viii, 30% HF·pyridine (v/v), THF, 0 → 25 °C, 24 h; ix, (+)-diethyl L-tartrate, $Ti(OPr^i)_4$, Bu^tOOH, −30 °C, 2 h; x, camphorosulfonic acid, MeOH–CH_2Cl_2 (1 : 1), 0 → 25 °C, 3 h; xi, Ac_2O, DMAP, EtOAc, 0 °C, 0.5 h; xii, Bu^tCOCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 0.5 h; xiii, BzCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 0.5 h; xiv, MnO_2, Et_2O, 25 °C, 3 h; xv, CH_2N_2, Et_2O, 0 °C; xvi, PPh_3, CCl_4, 75 °C, 24 h; xvii, NaH, MeI, DMF, 0 °C, 1 h; xviii, NaH, BnBr, DMF, 0 → 25 °C, 1 h; xix, DAST, CH_2Cl_2, −78 → 25 °C, 1 h; xx, $Ph_3P^+CH_3Br^-$, $(Me_3Si)_2NLi$, THF, 0 °C; xxi, H_2, Lindlar catalyst, EtOAc, room temp., 15 min.; xxii, TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 1 h; xxiii, NaN_3, DMF, 25 °C, 10 h, then PPh_3, THF, 60 °C, 8 h, then Ac_2O, CH_2Cl_2, 10 min; xxiv, Me_3SiCHN_2, then Bu^nLi, THF, −78 → 0 °C, 1 h; xxv, TEMPO (0.008 M, CH_2Cl_2), NaOCl (0.035 M, 5% aq. $NaHCO_3$), aq. KBr (0.2 M), CH_2Cl_2, 0 °C, 0.5 h; xxvi, Me_3SiCl, Et_3N, CH_2Cl_2, 0 → 25 °C, 10 h; xxvii, PPh_3, MeCN–CCl_4 (1 : 3), 25 °C, 1 h; xxviii, methyl(trifluoromethyl)dioxirane, MeCN, 0 °C; xxix, NaI, acetone, 25 °C, 10 h

the usual desilylation conditions gave **23n** (68%). The aldehyde obtained from MnO_2 oxidation of **21** (90%) was also subjected to Wittig methylenation (85%) furnishing, after desilylation, alkene **23k** (85%). A similar sequence of reactions with this aldehyde (Wittig methylation and hydrogenation followed by desilylation) provided **23l**. Conversion of **3** to the corresponding tosylate, followed by displacement with NaN_3 in DMF and reduction with PPh_3, furnished the required primary amine. The latter was then exposed to Ac_2O in CH_2Cl_2 providing the corresponding acetamide **23m** (39%, 4 steps). Similar chemistry was employed for the preparation of epothilones **24a–c, e–h** (Scheme 2). Compound **24d** was synthesized by selective oxidation of **22** with TEMPO–bleach (90%), and subsequent hydroxy protection, Wittig methylenation and deprotection allowed access to **24k** (49%, 3 steps). Iodide **24o** was prepared by selective tosylation of the primary hydroxy moiety of **22** and subsequent displacement with NaI (72%). Alternatively, treatment of **22** with DAST furnished fluoride **24j**. Reaction of **23h** and **23l** with methyl(trifluoromethyl)dioxirane provided, respectively, the epoxy methyl ether **24h** (20%) and the ethyl analogue **24l** (55%).

Table 1 shows the tubulin binding[5] and cytotoxicity properties of a selected number of the synthesized epothilones.

We thank Dr E. Hamel for a gift of purified tubulin and Dr P. Giannakakou for the cell lines. This work was supported by Novartis, the NIH, The Skaggs Institute for Chemical Biology, the CaP CURE Foundation, and the Fulbright Commission (M. R. V. F.).

Footnotes and References

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† All new compounds exhibited satisfactory spectral and exact mass data.

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Received in Corvallis, OR, USA, 11th August 1997; 7/05845D