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%).

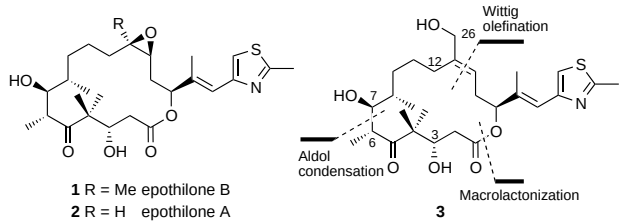
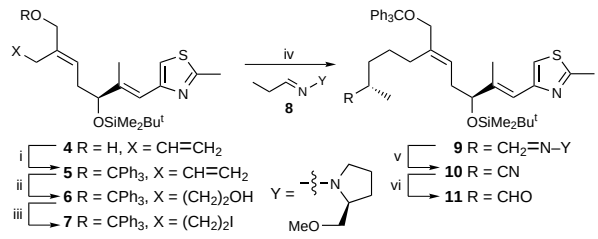


Fig. 1 Structures of **1** and **2** and retrosynthetic analysis of **3**



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

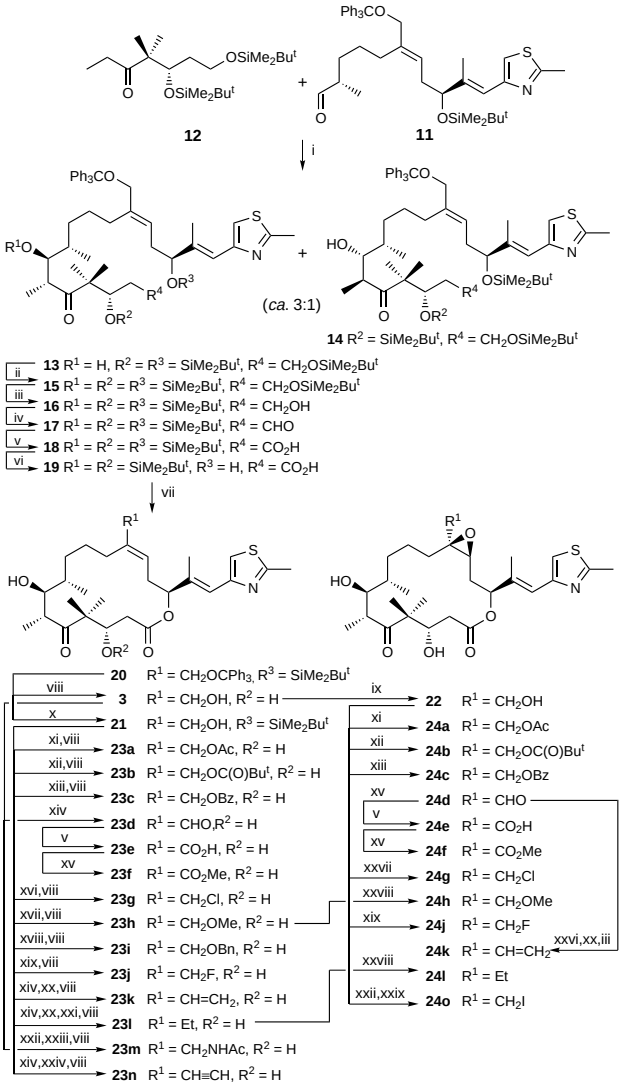
The coupling of the C1–C6 ketone fragment **12**[7,15] with **11** *via* a *syn*-selective aldol reaction (Scheme 2) furnished **13** along with its (6*S*,7*R*) diastereoisomer **14** (85% total yield, *ca.* 3 : 1). Chromatographic purification followed by silylation gave **15**. The use of buffered 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.

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Footnotes and References

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

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