Synthesis of 16-desmethylepothilone B: improved methodology for the rapid, highly selective and convergent construction of epothilone B and analogues

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During a synthesis of 16-desmethylepothilone B new methods for the convergent and highly stereoselective synthesis of epothilone B and analogues were developed.

Due to their great potential as anticancer drugs with a paclitaxel-like mechanism of action, the epothilones have recently been at the focus of widespread scientific investigations.[1] In particular, significant attention has concerned chemical synthesis of the epothilone natural products, which we and others have successfully achieved.[1–3] In connection with on-going studies in the epothilone area we were interested in preparing analogues of epothilone B containing less conformationally restrained heteroaromatic side-chains, in particular the 16-desmethyl analogue **1** (Fig 1). Since this endeavour required a complete resynthesis of the epothilone macrocycle we took this opportunity to develop new methods for the swift assembly of epothilone B analogues with improved selectivities and yields.

Our aims were to combine the benefits of our highly modular and convergent approach to epothilone A and analogues *via* olefin metathesis,[1] which allowed for extremely rapid macrocycle construction, with the improved stereoselectivities inherent in our macrolactonisation strategy to epothilone B.[1] We envisioned that our approach to epothilone B analogues could be made more convergent by employing a fully functionalised C7–C12 fragment in a highly selective olefination reaction to construct the C12–C13 bond. This approach would also allow access to C26 modified analogues as previously described.[1,3*a*] Furthermore, we wished to retain a hydroxy group at the C26 position until a late stage in the synthesis and thus profit from a chemo-, regio- and stereo-selective Sharpless epoxidation.[1,3*a*] In adopting this route we were aware that a method for subsequent deoxygenation at the C26 position (adjacent to the epoxide) would have to be developed. Finally, we hoped to improve the pivotal aldol coupling step which provides the stereocentres at C6 and C7 of the macrocycle. Previously we have found this reaction to be somewhat capricious.

The thiazole aldehyde fragment **6a**† was prepared in an analogous fashion to the related epothilone B fragment with minor changes in experimental conditions (Scheme 1). An asymmetric allylboration was the key step used to introduce the stereogenic centre at C15.‡ The regioselectivity of the dihydroxylation was lower than in the epothilone B series which slightly impaired the overall yield for this fragment. The fully functionalised phosphorane **14** was prepared in short order from commercially available **7** without the need for chiral auxiliaries.

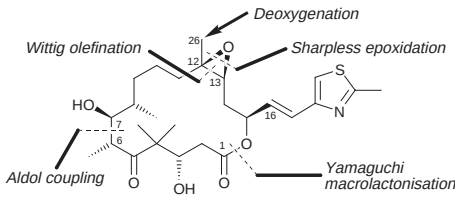
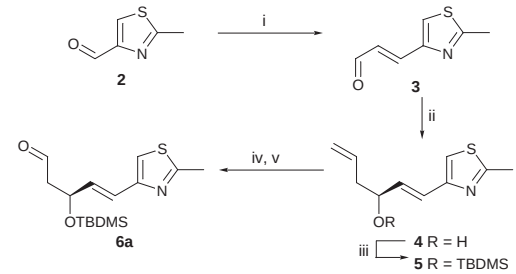


Fig. 1 Numbering and bond disconnections for **1**.

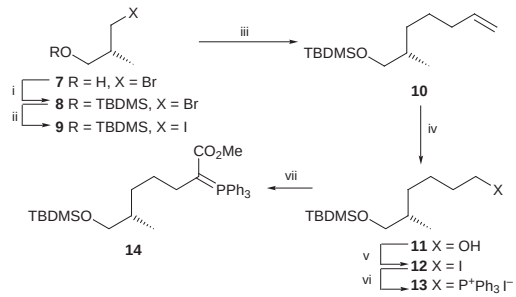


Scheme 1 *Reagents and conditions*: Ph_3P=CHCHO, CH_2Cl_2, reflux, 12 h, 82%; ii, (+)-Ipc_2B(allyl), CH_2Cl_2, Et_2O, pentane, −100 °C, 2 h, 100%; iii, TBDMSCl, imidazole, DMF, 0 → 25 °C, 2 h, 99%; iv, OsO_4 (cat.), NMO, THF, Bu^tOH, H_2O, 25 °C, 12 h, 68%; v, $NaIO_4$, MeOH, H_2O, 0 → 25 °C, 1 h, 89% (Ipc = isopinocampheyl).

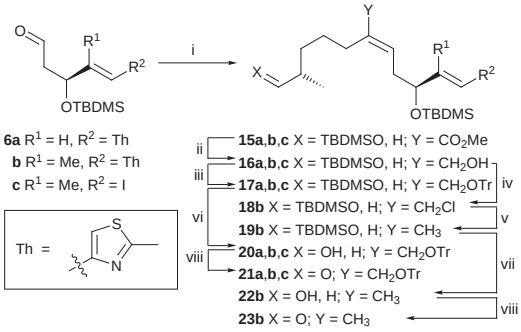
The reaction sequence includes an efficient cuprate coupling,[4] and a chloroformate quench of an unstabilised ylide[5] as the key steps (Scheme 2). Control of temperature during the latter reaction is critical to obtain phosphorane of good quality.§

The all-important Wittig coupling of **14** and **6a** proceeded smoothly with excellent yield and selectivity ($E:Z > 30:1$ in all cases) to provide the coupled product **15a**, which was processed to **21a** (Scheme 3). We have since extended this approach to the natural epothilone B series **23b**, the 26-hydroxyepothilone B series **21b** and the highly flexible vinyl iodide series **21c**, which we have shown to be invaluable for producing heterocycle-modified epothilones.[1,3*b*,*c*] This route also enabled us to approach the highly epimerisation-prone aldehydes **21a**-**c** and **23b** through stereochemically 'safe' alcohol oxidation procedures.¶

We reasoned that the moderate and variable stereoselectivities obtained in the coupling of **24** with chiral aldehydes such as **21a**–**c** and **23b** may be due, at least in part, to the reversible nature of aldol reactions using ketone-derived lithium enolates.[7] In an attempt to alleviate such problems we have performed the reaction with an excess of enolate,‖ very short reaction time and a rapid low temperature quench (AcOH). Gratifyingly, the



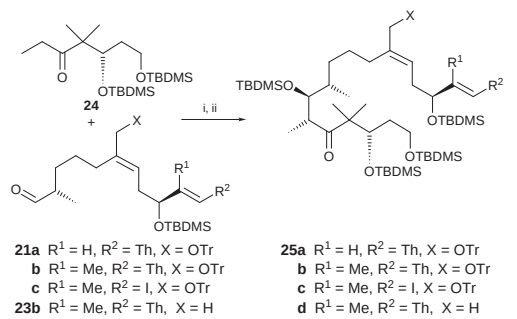
Scheme 2 *Reagents and conditions*: TBDMSCl, imidazole, DMF, 0 → 25 °C, 1 h; ii, NaI, acetone, reflux, 12 h, 99% (2 steps); iii, CH_2=$CHCH_2CH_2MgBr$, Li_2CuCl_4 (cat.), THF, 0 °C, 1 h, 96%; iv, (a) O_3, CH_2Cl_2, −78 °C, then PPh_3; (b) $NaBH_4$, EtOH, 0 °C, 30 min., 91% (2 steps); v, I_2, PPh_3, CH_3CN, Et_2O, 0 → 25 °C, 1 h, 100%; vi, PPh_3, neat, 100 °C, 2 h; vii, KHMDS, THF, 0 °C, 30 min, then MeOCOCl, −78 °C, 3 h (*ca.* 100%, 2 steps, unpurified).



Scheme 3 *Reagents and conditions*: i, **14** (1.3 equiv. based on **12**), C_6H_6, reflux, 18 h, 84–93%; ii, DIBAL-H, THF, −78 °C, 3 h, 71–95%; iii, TrCl, DMAP, DMF, 70 °C, 18 h, 82–95%; iv, CCl_4, PPh_3, reflux, 18 h, 80%; v, $LiEt_3BH$, THF, −78 °C, 1 h, 92%; vi, HF•Py.Py, THF, 25 °C, 4 h, 66–73%; vii, CSA, MeOH, 25 °C, 1 h, 95%; viii, SO_3•Py, DMSO, Et_3N, THF, 0 °C, 1 h.

application of these conditions to aldehydes **21a–c** and **23b** lead to significant amelioration of stereoselectivity which was naturally accompanied by an improved yield of the desired aldol stereoisomer in each case (Scheme 4, Table 1). Intermediates **25a–d** were obtained in good overall yields after subsequent TBDMS-protection. Under these closely defined conditions the aldol reaction is highly reproducible and applicable to multigram quantities. These results, in terms of diastereoselectivities and yields, are at least as good as those obtained by Schinzer and co-workers in their epothilone B syntheses.[2b] Since our approach features a rather convenient protecting group strategy, we believe this development renders our modified route the most effective solution to date for epothilone B.

The TBDMS-protected aldol product **25a** was processed through to 26-hydroxy-16-desmethylepothilone B **30** in the same fashion as our published route to 26-hydroxyepothilone B (Scheme 5).[3a] As projected, the Sharpless epoxidation proceeded with complete stereo- and regio-control at the C12–C13 position. It should be noted that for this analogue series, competitive side-chain epoxidation would likely have been problematic upon use of conventional oxidants. In order to complete the synthesis, removal of the C26 hydroxy group was required. This was achieved by initial conversion to iodide **31** followed by reductive deiodination with $NaBH_3CN$[7] to provide

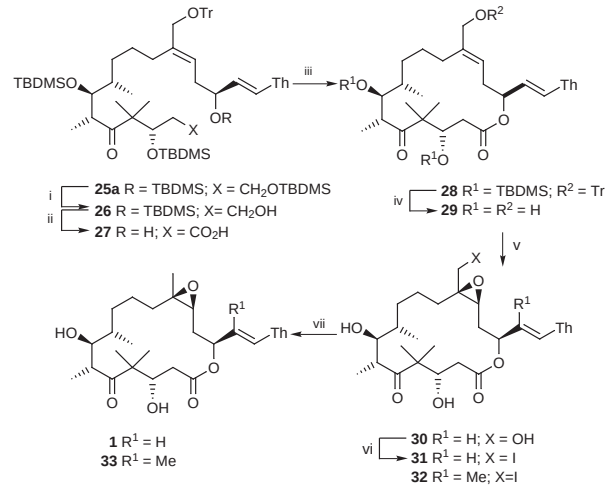


Scheme 4 *Reagents and conditions*: i, LDA (2.4 equiv.), **24** (2.3 equiv.), THF, −78 → −40 °C, 1 h, then add **21** or **23**, THF −78 °C, 2 min, then AcOH, −78 → 0 °C; ii, TBDMSOTf, 2,6-lutidine, THF, −78 → 0 °C, 1 h.

Table 1 Yields and stereoselectivities for aldol reactions

Aldehyde	Selectivity[a]	Aldol product (%)[b]	**25** (%) (2 steps)[c]
21a	⩾10 : 1	76	72
21b	⩾15 : 1	77	73
21c	⩾10 : 1	79	75
23b	⩾10 : 1	71	67

[a] Conservative estimates based upon mass recovery of the major isomer relative to all other polar impurities. [b] Often contaminated with small amounts (= 5%) of starting aldehyde. Yields are compensated. [c] Single stereoisomer free from traces of aldehyde and other impurities.



Scheme 5 *Reagents and conditions*: i, HF•Py.Py, THF, 25 °C, 3 h, 87% (after 1 recycle); ii, (a) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 30 min, then Et_3N, −78 → 0 °C, 30 min; (b) $NaClO_2$, Me_2C=CHMe, NaH_2PO_4, Bu^tOH–H_2O, 25 °C, 2 h; (c) TBAF, THF, 25 °C, 12 h, *ca.* 100% (3 steps); iii, 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, 0 °C, 1 h, then add to DMAP in toluene, 75 °C, 1 h, 73%; iv, HF•Py, THF, 0 → 25 °C, 24 h, 78%; v, (+)-diethyl L-tartrate, $Ti(Pr^iO)_4$, Bu^tOOH, CH_2Cl_2, 4 Å MS, −30 °C, 2 h, 80%; vi, (a) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 → 25 °C, 1 h; (b) NaI, acetone, 25 °C, 15 h, 91% (2 steps); vii, $NaBH_3CN$, HMPA, 45 °C, 40 h, 67–70%.

our desired analogue **1** in good overall yield. Furthermore, this deoxygenation sequence has also been demonstrated for the production of epothilone B (**33**) itself from our previously reported iodide **32**. Thus, all of the synthetic methodology described herein is applicable to epothilone B, which renders our approach now *highly selective at every step*, and significantly increases the speed of access to this and related structures. Work is currently underway to assess the biological activity of **1** and related analogues of epothilone B.

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Notes and references

† All new compounds exhibited satisfactory spectral and exact mass data.
‡ The ee was shown to be ⩾97% by chiral HPLC (Chiralcel OD-H column) by comparison with the racemate.
§ Due to high polarity and complex NMR spectra **14** was not purified as characterized. We observed full mass return for **12** → **14** and used the material crude using quantities assuming purity.
¶ The aldehydes were freshly prepared and not purified prior to use.
‖The unreacted ketone **24** is easily recovered by chromatography.

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