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Easy Access to the Epothilone Family – Synthesis of Epothilone B

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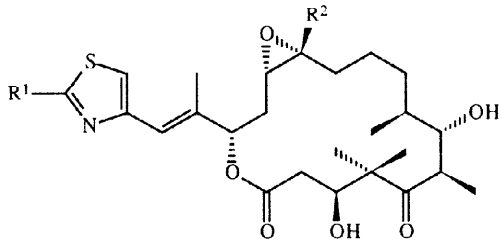
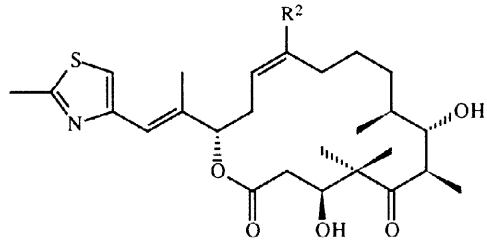
Abstract: An easy access to four out of five naturally occurring epothilones (A-E, **1-5**) is reported. Key steps are an enantioselective Mukaiyama type aldol reaction, (*E*)- and (*Z*)-selective olefinations, and a sulfone alkylation.

Keywords: natural products; macrolides; antitumour compounds; Mukaiyama reaction.

Soon after their isolation from the myxobacteria *Sorangium cellulosum* strain So ce90 [1] the epothilones A-E (**1-5**) have been propelled into the forefront of chemical, biological and medical research, in consequence of their eminent cytotoxic activity against tumor cells, taxol-like mitose inhibition and toxity against multiple drug-resistant tumor cell lines [2]. Several total syntheses of **1/2** [3], **3/4** [4] and **5** [5], in addition to a formal synthesis of **3/4** [4c] and the preparation of major fragments [6] have been reported.



R^1 = Me, R^2 = H epothilone A (**1**)
R^1 = Me, R^2 = Me epothilone B (**3**)
R^1 = CH_2OH, R^2 = H epothilone E (**5**)



R^2 = H epothilone C (**2**)
R^2 = Me epothilone D (**4**)

In continuation of earlier work [7] we report an easy access to epothilones A-D which is illustrated by the preparation of the most active member, epothilone B (**3**) and its synthetic precursor epothilone D (**4**). The retrosynthetic concept is based on the disconnection into three fragments **6**, **7** and **8**, which are connected successively via a sulfone alkylation between **6** and **7** and an aldol addition between **7** (via the C7-aldehyde) and **8** (**Scheme 1**).

Fragment **6** was prepared from commercially available (2*S*)-hydroxy butyrolactone **9** via silylation and addition of methyl lithium to form hemiacetal **10**, which was converted into olefin **11** (*E*)-stereoselectively by use of the tri-*n*-butyl phosphonium salt [8] (**Scheme 2**). Swern oxidation furnished the labile C13-aldehyde to which a Still-Gennari olefination [9] was applied. Depending on the phosphonate reagent the epothilones **1-4** can be developed by analogous sequences. For brevity's sake it may suffice to show the conversion of enoate **12** into **3**.

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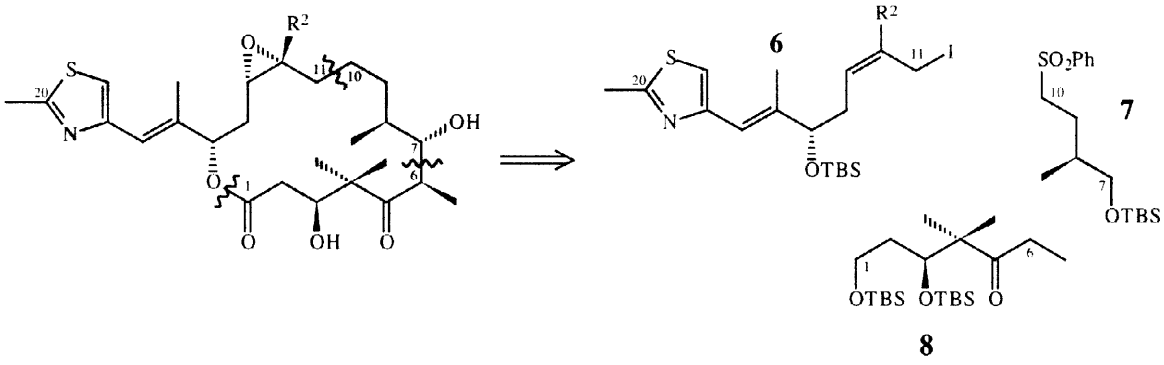
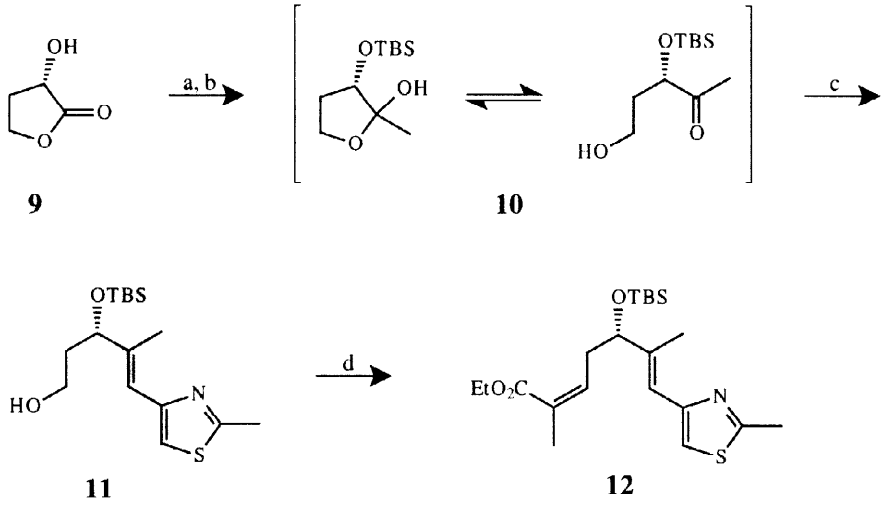


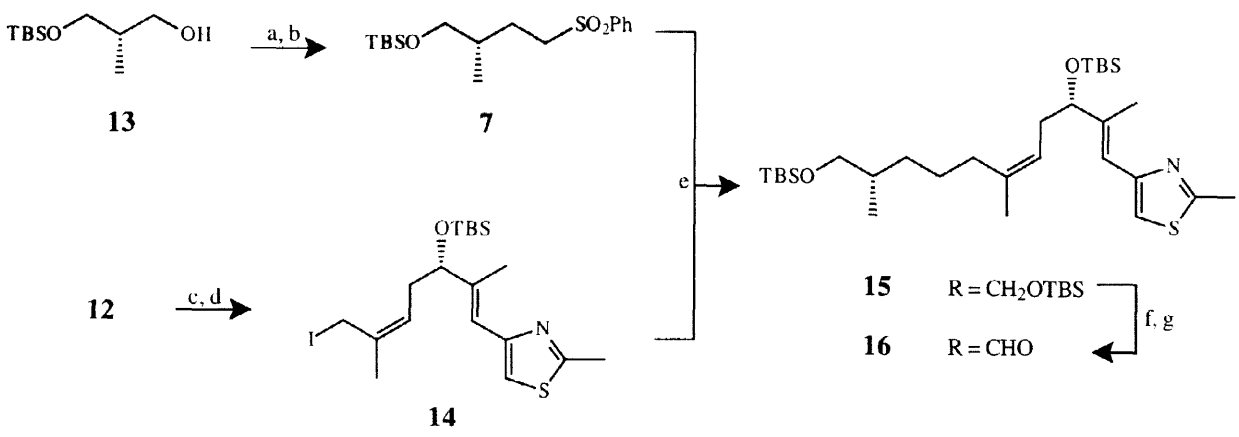
Scheme 1



Scheme 2. *Reagents and conditions*: **a**) TBSCl, imidazole, DMF, 0°C, 2.5 h, 99%. **b**) MeLi, THF, -78°C, 1.5 h, 88%. **c**) (2-Methyl thiazol-4-yl-methyl)-tri-*n*-butyl-phosphonium chloride, NaHMDS, THF, -78°C→55°C, 1 h, 71% (only the (*E*)-isomer was found). **d**) i) Swern ox., ii) ethyl 2-[bis(2,2,2-trifluoroethyl)phosphono]propionate, KHMDS, 18-crown-6, THF, -78°C, 1 h, 89% (only the (*Z*)-isomer was found).

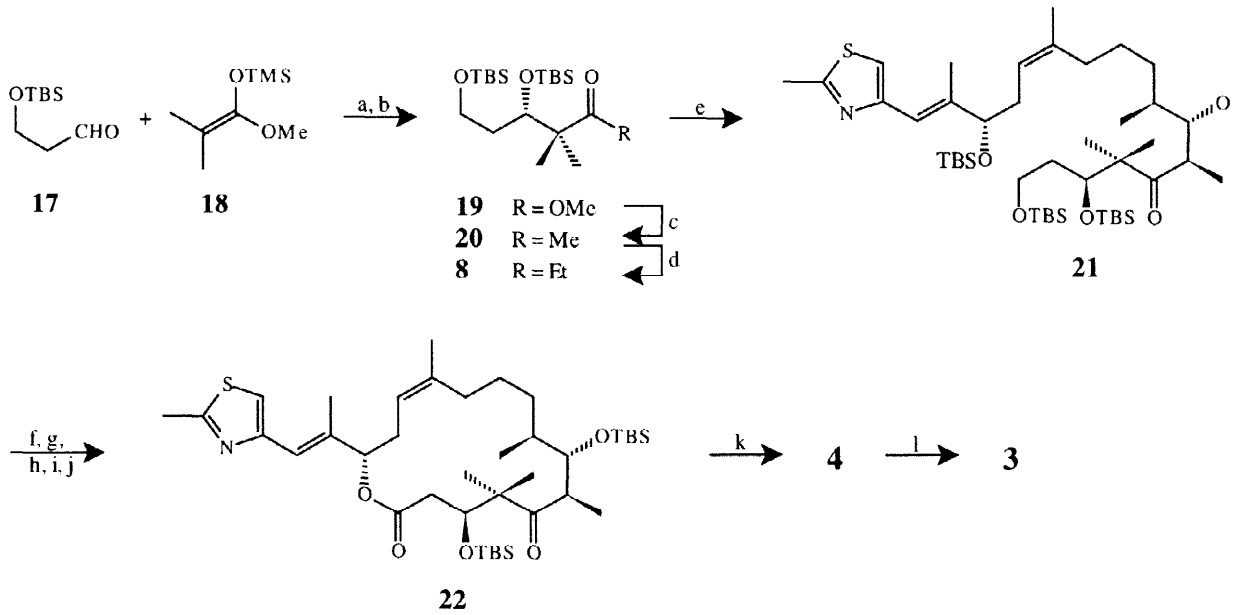
Scheme 2

To this end, sulfone **7** was prepared from the monoprotected diol **13** [10] (**Scheme 3**). **12** was reduced to the allylic alcohol, converted into the unstable iodide **14**, and immediately coupled with monodeprotonated **7**. After reductive removal of the sulfone group the C7-C21-fragment **15** was obtained. Selective mono-desilylation and Dess-Martin oxidation furnished aldehyde **16**, which was used immediately for the aldol reaction. To this end, the C1-C6-fragment **8** was prepared in a novel and efficient way (**Scheme 4**). The (*S*)-selective Mukaiyama aldol addition of the commercially available methyl trimethylsilyl dimethylketene acetal **18** to the known aldehyde **17** [11] was mediated by the chiral borane reagent formed *in situ* from N-tosyl-D-valine and BH_3-THF to furnish ester **19** in 88% yield with >90% ee according to chiral HPLC [12]. After silylation, **19** was first converted into the methyl ketone **20** and subsequently, via methylation of the enolate, into the desired ethyl ketone **8** (72% yield for three steps). A variety of other residues R were also introduced by this alkylation.



Scheme 3. *Reagents and conditions*: **a**) TosCl, pyr, 0°C, 3.5 h, 93%. **b**) $PhSO_2CH_2Li$, THF, -20°C→r.t., 12 h, 96%. **c**) DIBAH, THF, 0°C, 2.5 h, 98%. **d**) 1.3 eq Ph_3P, 1.35 eq imidazole, 1.4 eq I_2, CH_3CN/Et_2O (3:2), r.t.,1 h. **e**) i) **7**, KHMDS, 18-crown-6, THF, -78°C, 1 h, then **14**, 1 h, ii) 5% Na/Hg, MeOH/THF (2:1), Na_2HPO_4, -15°C→r.t., 2 h, (61% yield for two steps). **f**) 1 eq CSA, $MeOH/CH_2Cl_2$ (1:1), 0°C, 5 h, 99%. **g**) 1.3 eq Dess-Martin-periodinane, CH_2Cl_2, 0°C.

Scheme 3



Scheme 4. *Reagents and conditions*: **a**) 1 eq N-Tos-D-valine, 1 eq BH_3·THF, CH_2Cl_2, r.t., 30 min, then **17** (1 eq) and **18** (1.1 eq), -78°C, 4 h, 88% (ca. 95% recovered N-Tos-D-valine). **b**) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 2 h, 99%. **c**) $TMSCH_2Li$, pentane, 0°C, 4 h, then MeOH, 1 h, r.t., 97%. **d**) LDA, THF, -78°C, 30 min, then MeI, -78°C to r.t., 85%. **e**) LDA, THF, -78°C, then **16**, -95°C, 2 h, 69% (4:1). **f**) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 3 h, quant. **g**) 1 eq CSA, $MeOH/CH_2Cl_2$ (1:1), 0°C, 4 h, 87%. **h**) i) 1.3 eq Dess-Martin-periodinane, CH_2Cl_2, 0°C, 2 h, ii) 5 eq $NaClO_2$, Na_2HPO_4, 2,3-dimethyl-but-2-ene, tert.-butanol-water, 40 min, 96%. **i**) 5 eq TBAF, THF, r.t., 10 h, 55%. **j**) 2 eq EDCI, 3 eq DMAP, 2 eq DMAP·HCl, $CHCl_3$, reflux,17 h, 69%. **k**) excess buffered HF-pyridine, THF, r.t., 36 h, 96%. **l**) 1.5 eq mCPBA, $CHCl_3$, -18°C, 5 h, 81%.

Scheme 4

The aldol addition of **8** to the aldehyde **16** [4b] gave diastereoisomer **21** (69%) with 4:1-selectivity, identical in all respects with the compound described by Nicolaou [4b]. After silylation, selective desilylation furnished the primary alcohol, which was converted into the seco acid by two-step oxidation at C1 and desilylation at C15-position. Macrolactonization, under modified Keck condition [13], furnished **22** (69%), which was desilylated to give epothilone D (**4**). Epoxidation with mCPBA resulted in the formation of a 4:1-mixture of epothilone B (**3**) and its 12,13-epimer in 81% yield, which were separated by HPLC to give **3** identical in every respect with the natural product. Epoxidation with dimethyldioxirane apparently leads to higher stereoselectivity [4a].

In conclusion, we have presented the first uniform synthetic approach to the epothilone family which is unusually short (23 steps overall, 18 steps in the longest linear sequence) and high-yielding. Except the aldol addition and the epoxidation each step proceeds with high stereoselectivity. These attributes provide our synthesis with a clear advantage over those reported so far. We are now in a position for concise elaboration of derivatives in useful amounts for *in vivo* examination, which are currently under investigation.

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Dedicated to Prof. E. J. Corey on the occasion of his 70th birthday

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