Total Synthesis of 26-Fluoro-epothilone B

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Abstract: An efficient synthesis of the epothilone B derivative 26-fluoroepothilone B (**1**) was realized by early introduction of the synthetically demanding fluoromethyl epoxide function. The presence of a fluoro substituent results in a remarkable increase in the stability of the epoxide, which tolerates the wide range of reaction conditions required for the fragment coupling step and end game transformations.

Key words: epothilone, total synthesis, fluorine, epoxides, substituent effects

Epothilone compounds (e.g. epothilones A and B) represent a class of microtubule inhibitors with the remarkable ability to inhibit the growth of multidrug-resistant human tumor cell lines at low nanomolar or even subnanomolar concentrations. To explore the therapeutic potential of epothilone-type agents, natural epothilones and numerous structural analogs thereof have been synthesized by a multitude of research groups.[1]

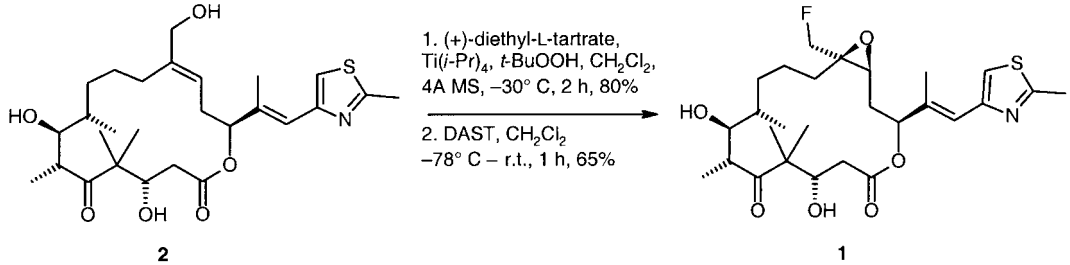
Among those analogs, whose in vivo activity has been assessed in human tumor models, 26-fluoroepothilone B (**1**)[2] has emerged as a promising drug candidate, which exhibits high efficacy at well tolerated dose levels.

For further biological profiling and pharmacological evaluation larger quantities of compound **1** were required. The original synthesis of **1** as reported by the Nicolaou group[2b,c] was based on the epoxidation of the advanced allylic alcohol **2** under Katsuki–Sharpless[3] conditions and subsequent fluorination with DAST[4] in moderate yield (Scheme 1).

However, we felt that the introduction of fluorine at the very end of the synthesis could pose a significant problem upon scale-up and we have thus devised an alternative strategy for the synthesis of **1**, which is outlined in Scheme 2. Our retrosynthetic analysis of **1** is characterized by three key features: a) avoidance of the late stage fluorination step by the early introduction of the fluorine substituent, b) the diastereoselective installation of the epoxide moiety, and c) the diastereoselective construction of the aldol substructure (Scheme 2).

Disconnection at the ester moiety and the C6–C7 aldol unit gives aldehyde **3** and ethyl ketone **4**. The acetonide fragment **4** has been developed by Schinzer[5] for a highly diastereoselective aldol coupling in the total synthesis of epothilones A and B and it has also been successfully applied in the synthesis of other epothilone analogs.[6] The fluoro epoxide **3** is derived from an allylic alcohol, which is the Wittig product formed by reaction of stabilized ylide **5** and the known aldehyde **6**.[7]

Starting from caprolactone (**7**), the phosphorane **5** was prepared via a readily scalable route in 27% yield over 10 steps without the need for any chromatographic purification (Scheme 3). Thus, caprolactone was hydrolyzed and treated in situ with benzylchloride to give benzyl protected hydroxy acid **8**.[8] Conversion of this acid to the acid chloride and coupling to the L-phenylalanine-derived Evans auxiliary **10** gave imide **11**. Diastereoselective methylation and subsequent reductive removal of the auxiliary gave *S*-alcohol **13**, which was obtained in 87% ee as determined by chiral HPLC. A two-step deprotection/protection sequence led to alcohol **15**, which was converted



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Scheme 1 Nicolaou synthesis of 26-fluoroepothilone B

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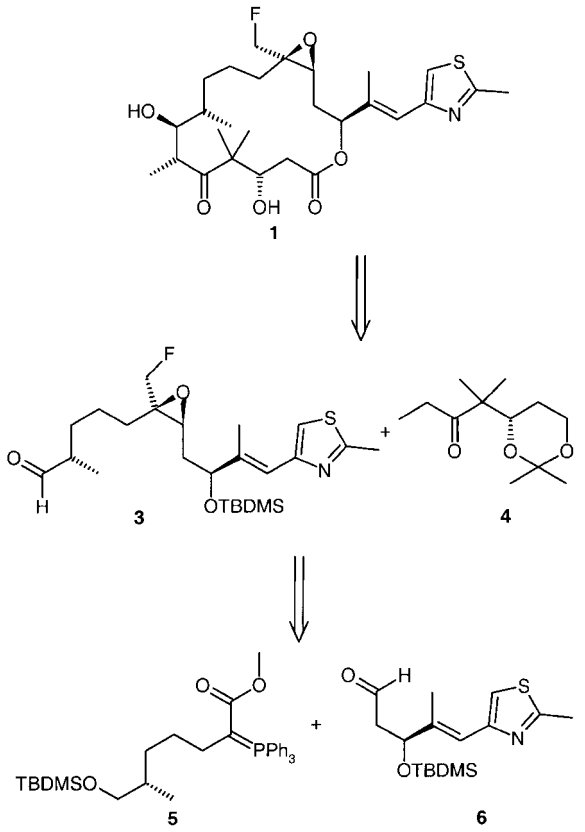


Scheme 2 Retrosynthetic analysis

to the iodide **16**, whose treatment with triphenylphosphine gave the corresponding phosphonium salt. Finally ylide **5** was obtained through reaction of the phosphonium salt with KHMDS and in situ acylation of the resulting (monosubstituted) phosphorane with methylchloroformate.

Coupling of aldehyde **6** and fragment **5** according to ref.[2c] gave α,β-unsaturated ester **17a**, which was reduced to the allylic alcohol **18a** (Scheme 4). Katsuki–Sharpless epoxidation of **18a** gave epoxy alcohol **19a** as a single diastereomer in excellent yield. Subsequent fluorination with DAST provided the desired product **20a** in 26% yield, but in addition significant amounts of the side product **21** (Figure 1) were also isolated.

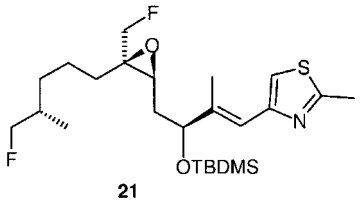
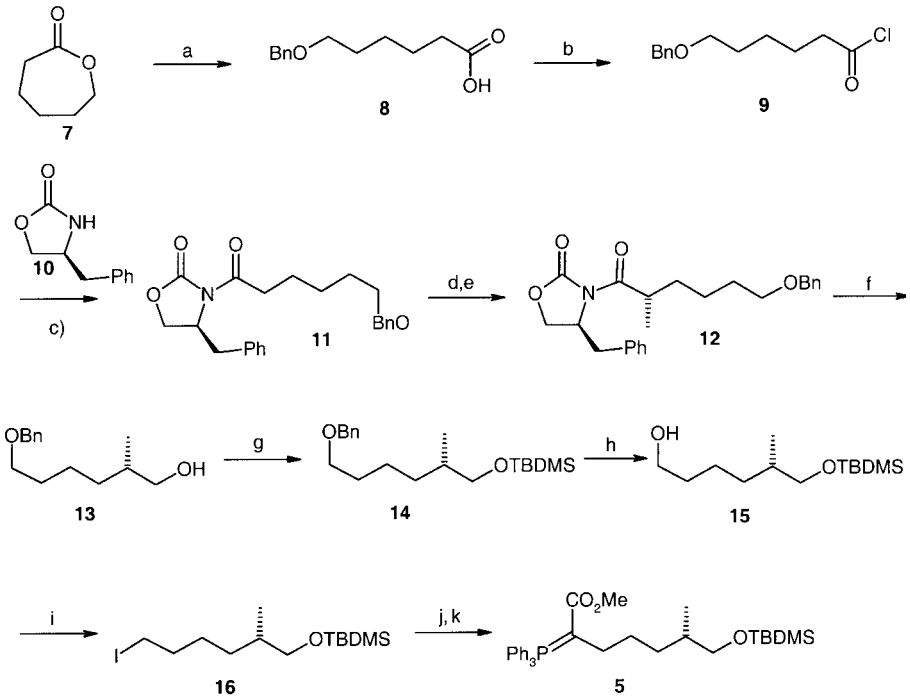
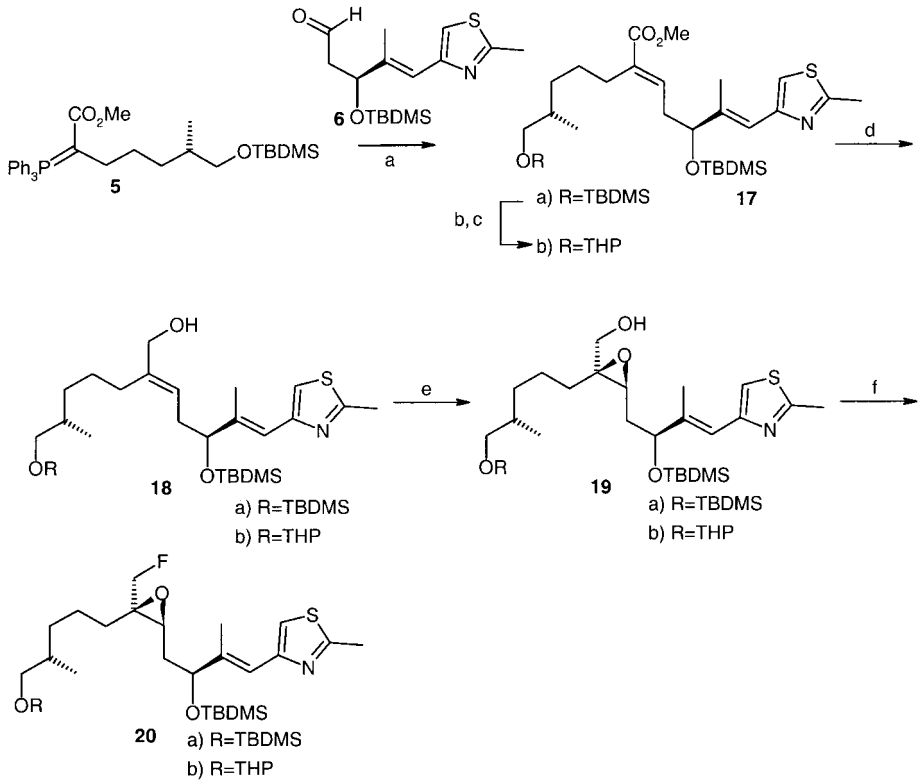


Figure 1 Bis-fluoro epoxide side product **21**

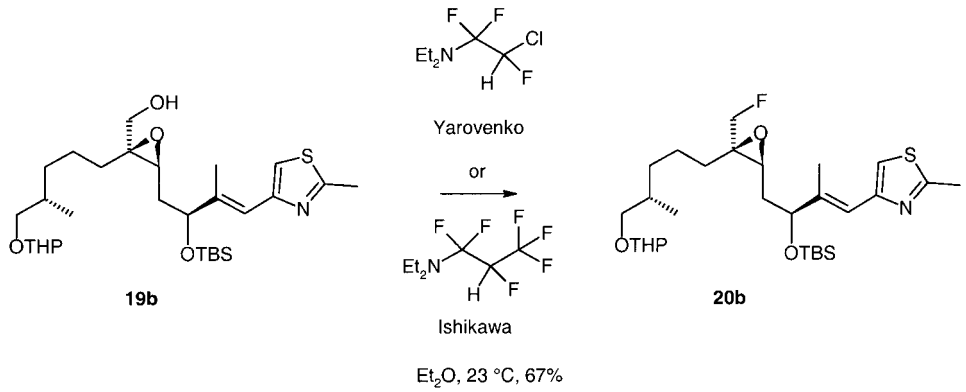
Formation of **21** can be rationalized by fluoride–mediated deprotection of the primary hydroxyl group and its subsequent fluorination with DAST. We thus hypothesized that competing bis-fluorination would be avoided, if the more stable THP group was used to protect the primary alcohol function. Gratifyingly, the implementation of this alternative protection scheme resulted in a clean and repro-



Scheme 3 *Reaction conditions*: a) KOH/BnCl, toluene, reflux (76%); b) $(COCl)_2$, toluene, 23 °C; c) **10**, hexyl-Li, then silica gel filtration (87%, from acid **8**); d) NaHDMS, THF, –78 °C; e) MeI, –78 °C (81%); f) $LiAlH_4$, THF, 0 °C, silica gel filtration (79%, 87% ee); g) TBDMSCl, imidazole, DMF, 23 °C (79%); h) H_2 (3.5 bar), $Pd(OH)_2/C$, THF, 23 °C (100%); i) PPh_3, imidazole, I_2, CH_3CN, toluene, 0 °C, (97%); j) PPh_3, 100 °C; k) KHMDS, $ClCO_2CH_3$, THF, 0 °C, –78°C (quant.).



Scheme 4 *Reaction conditions*: a) **6**, Toluene, 40 °C (quant.); b) TFA, H_2O, THF, 23 °C; c) dihydropyrane, PPTS, CH_2Cl_2, 23 °C (65%, chromatography); d) DIBALH, THF, –78 °C–0 °C (R = TBDMS: 76% over 4 steps; R = THP: quant.); e) (+)-diethyl-L-tartrate, Ti(O*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2, 4 Å MS, –30 °C, 2 h (R = TBDMS, R = THP; 70%, silica gel filtration); f) DAST, CH_2Cl_2, 23 °C (R = TBDMS: 26%, R = THP: 70%).



Scheme 5 Alternative fluorinating reagents

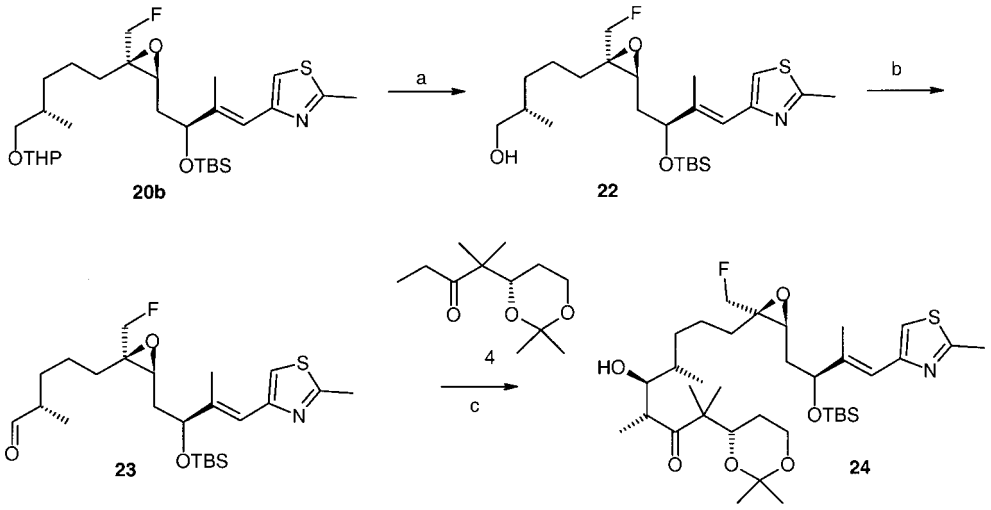
ducible fluorination protocol affording the protected fluoro epoxide **20b** in 70% yield.

Alternative reagents for fluorine introduction were also investigated. Reaction of the epoxy alcohol with the Yarovenko[9] or the Ishikawa[10] reagents led to comparable results as the reaction with DAST (Scheme 5).

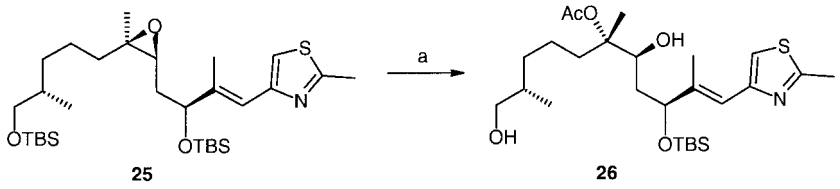
With the fluoro epoxide **20b** in hand, we then investigated the coupling of the anion of ethyl ketone **4** with aldehyde **23**, which was obtained after selective removal of the THP protecting group from intermediate **20b** with PPTS and subsequent Swern oxidation of the resulting alcohol (Scheme 6). Gratifyingly, reaction of **23** with the lithium enolate of **4** at low temperature gave the aldol product **24** in 77% yield as a single diastereomer.

The elaboration of **24** into 26-fluoroepothilone B **1** was guided by the chemistry previously employed by Schinzer et al. in their formal synthesis of epothilone B.[11] However, it should be kept in mind that in contrast to this prior work, all steps were carried out in the presence of the epoxide function.

The presence of a fluoro substituent leads to a remarkable enhancement in epoxide stability towards acid and base. The epoxide function remained unaffected by the reaction conditions required to remove the THP, the acetonide and TBDMS protecting groups downstream in the synthesis



Scheme 6 *Reaction conditions*: a) PPTS, EtOH, 65 °C; b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C; c) **4**, LDA, –78 °C (77%, chromatography).



Scheme 7 Sensitivity of the methyl epoxide moiety in **25** toward aq HOAc. Reaction conditions: a) HOAC, THF, H2O (85%)

[conditions a) in Scheme 6, conditions a), c) and h) in Scheme 8]. In contrast, the methyl substituted epoxide moiety in the model substrate **25** (Scheme 7) proved to be labile in the presence of Brønsted and Lewis acids as well as in the presence of TBAF. For example, treatment of **25** with HOAC in addition to the expected TBDMS removal from the primary hydroxyl group led to rapid regioselective opening of the epoxide to give product **26**. Treatment with PPTS, TFA, $BF_3{\cdot}Et_2O$, or CAN all gave analogous ring opening, which was observed even under very mild acidic conditions (Montmorillonite K10 in CH_2Cl_2).[12] Treatment of **25** with TBAF led to a complex mixture.

In contrast, cleavage of the acetonide moiety in **24** proceeded cleanly and the corresponding diol **27a** was converted to the mono protected alcohol **28**. Swern oxidation afforded aldehyde **29**, which was further oxidized to the carboxylic acid **30** with sodium chlorite. The protected allylic alcohol was selectively desilylated with TBAF and the resulting *seco* acid **31** was subjected to Yamaguchi macrolactonization conditions at elevated temperature as previously reported for other epothilone derivatives.[13] The macrolactone **32** was obtained in 62% yield. Final cleavage of the remaining silyl groups required long reaction times in HF·pyridine and 26-fluoroepothilone B (**1**) was isolated in 45% yield.

In conclusion, we have reported an improved total synthesis of the promising epopthilone B analogue 26-fluoroepothilone B. This approach allowed the preparation of **1** for biological studies, making use of the remarkable stability of the fluoro-methyl epoxide towards a variety of reaction conditions. As a consequence, the fluorination reaction, which requires harsh reaction conditions, could be carried out at an early stage in the synthesis on a substrate less sensitive than **2**. In addition, all stereocenters were constructed using highly diastereoselective transformations.

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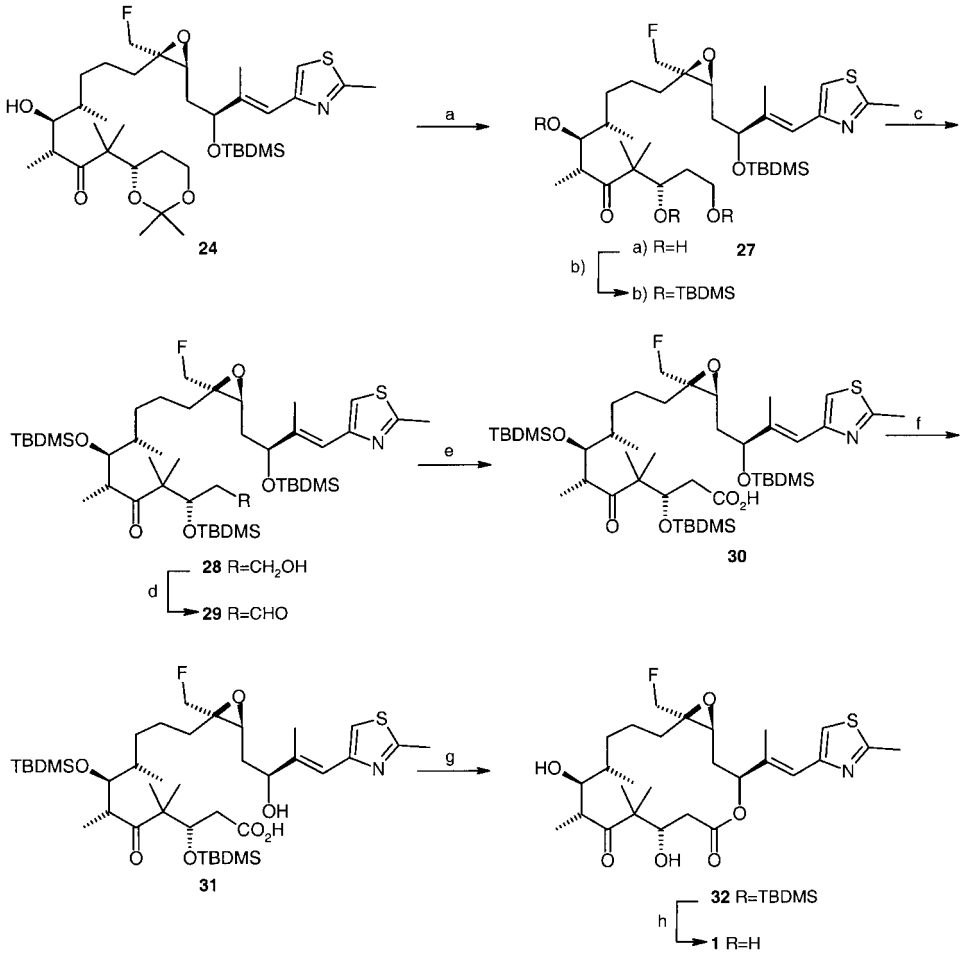

Scheme 8 Final steps; *Reaction conditions*: a) PPTS, EtOH, 55 °C (70%, chromatography); b) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, –10 °C (81%, chromatography); c) CSA, CH_2Cl_2, MeOH, 23 °C (89%, chromatography); d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C (88%, chromatography); e) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH, 23 °C (89%, chromatography); f) Bu_4NF, THF, 0 °C–23 °C (88%, chromatography); g) trichloro-benzoyl chloride, Et_3N, DMAP, toluene, 75 °C (62%, chromatography); h) HF–pyridine, THF, 23 °C (45%, chromatography).

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