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# On the Introduction of a Trifluoromethyl Substituent in the Epothilone Setting: Chemical Issues Related to Ring Forming Olefin Metathesis and Earliest Biological Findings

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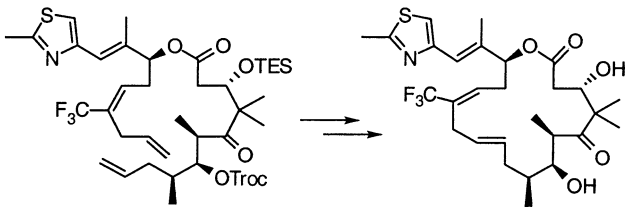
## ABSTRACT




**The disclosure herein describes the synthesis of 10,11-dehydro-13,14-desoxy-27-trifluoro-[17]epothilone B via a stereoselective ring-closing metathesis and provides early biological evaluation data pertinent to this compound.**

In the past five years, the epothilones have emerged as potential new anticancer agents.[1] Human clinical trials seeking to assess issues of toxicity, optimal dosage, and likely efficacy of several epothilones as drugs are well underway.[2] For instance, 12,13-desoxyepothilone B, initially developed in our laboratory via total synthesis, is now undergoing human clinical trials.[3] Given the massive interest in epothilones, it is not surprising that there has been a worldwide effort to synthesize new analogues, and to establish their SAR with a view to identifying and developing later generation agents for clinical evaluation.[4] Given the important role of fluorine substitution in enhancing pharmacokinetics and chemotheraputic indices of many medicinal agents,[5] it was natural to evaluate this type of structural perturbation in the epothilone series. We initially targeted

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(1) For extensive reviews in this field see: (a) Harris, C. R.; Danishefsky, S. J. *J. Org. Chem.* **1999**, *64*, 8434. (b) Nicolaou, K. C.; Roschangar, F.; Vourloumis, D. *Angew. Chem., Int. Ed.* **1998**, *37*, 2015.

(2) Chou, T. C.; O'Connor, O. A.; Tong, W. P.; Guan, Y.; Zhang, Z.-G.; Stachel, S. J.; Lee, C.; Danishefsky, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 8113.

(3) For more information about clinical trials of dEpoB, visit: *www.kosan.com*.

(4) (a) Florsheimer, A.; Altmann, K. H. *Expert Opin. Ther. Patents* **2001**, *11*, 951. (b) Chou, T. C.; Zhang, X. G.; Harris, C. R.; Kuduk, S. D.; Balog, A.; Savin, K. A.; Bertino, J. R.; Danishefky, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 15798. (c) Chou, T. C.; Zhang, X. G.; Balog, A.; Su, D.; Meng, D. F.; Savin, K.; Bertino, J. R.; Danishefsky, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 9642.

(5) (a) Ojima, I.; Inoue, T.; Chakravarty, S. *J. Fluorine Chem.* **1999**, *97*, 3. (b) Newman, R. A.; Yang, J.; Finlay, M. R. V.; Cabral, F.; Vourloumis, D.; Stephens, L. C.; Troncoso, P.; Wu, X.; Logothetis, C. J.; Nicolaou, K. C.; Navone, N. M. *Cancer Chemother. Pharmacol.* **2001**, *48*, 319.

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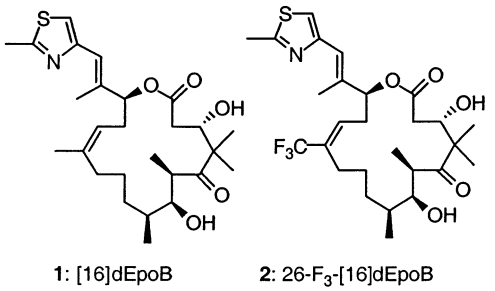
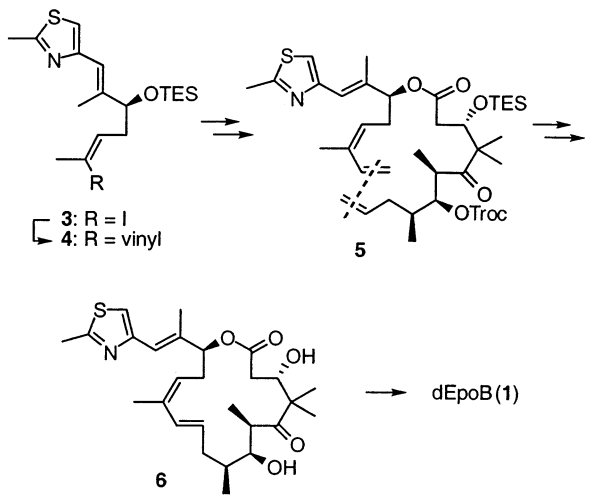



**Figure 1.** Selected epothilone analogues.

compound **2**, which is seen to correspond to a 26-trifluoro-epothilone congener for synthesis and biological evaluation. To reach compound **2**, we sought to take advantage of a highly convergent route recently reported from our laboratory for the synthesis of epothilone 490 (**6**, dehydrodesoxyEpoB) en route to dEpoB (**1**, Scheme 1).[6] In that synthesis, we

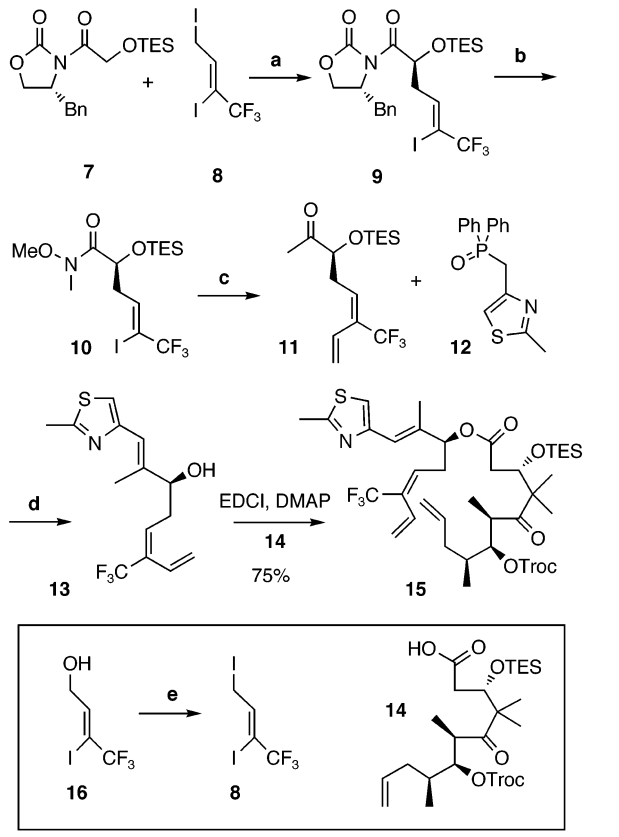
**Scheme 1**




introduced a flanking vinyl group to compound **4** via a stereospecific Stille coupling of a vinyl iodide precursor **3** with tri-*n*-butylvinylstannane. Ring closing metathesis followed by deprotection led to **6**, which was then transformed to dEpoB (**1**) via a regioselective diimide reduction.

Attention was first directed to the synthesis of **15** (Scheme 2). Alkylation of the previously reported lithium enolate of **7**[7] with iodide **8** (synthesized from the known alcohol **16**[8] using TMSI in methylene chloride) afforded **9** in 78% yield

**Scheme 2**[a]




[a] Key: (a) LHMDS, −78 °C, 78%; (b) (i) HOAc:THF:$H_2O$ (3:1:1); (ii) $CH_3ONHCH_3$, $AlMe_3$; (iii) TESCl, imidazole, DMF, 79% overall; (c) (i) vinyltributyltin, $Pd_2(dba)_3$, DMF, 80 °C, 3 h; (ii) MeMgBr, 0 °C, 40% overall; (d) (i) *n*-BuLi, THF, −78 °C, 30 min; (ii) **12**, −78 °C to room temperature, 81%; (iii) HOAc:THF:$H_2O$ (3:1:1), 76% overall; (e) TMSI, $CH_2Cl_2$, 0 °C, 92%.

and high diastereoselectivity (>25:1 de). Compound **9** was advanced in three steps to **10** as shown. Attempts to accomplish addition of methylmagnesium bromide to the Weinreb amide linkage of **10** failed to provide **11**. The breakdown of this reaction was attributed to the presence of the iodoalkene linkage. However, we could accomplish our goal by changing the order of these two C−C bond-forming steps. Thus, reaction of **10** with vinyltributyltin under Stille conditions could then be followed by addition of methyl Grignard reagent to give the desired ketone **11**. Condensation of ketone **11** with phosphine oxide **12**, followed by deprotection of the triethylsilyl ether, afforded fragment **13** in good yield. Esterification of the resulting **13** with C1−C10 acid fragment **14**[6] provided the desired **15**, in 75% yield (Scheme 2).

Unfortunately, attempts to carry out the ring-closing metathesis reaction[9] of **15** using the second generation Grubbs catalyst in methylene chloride led primarily to

(6) (a) Biswas, K.; Lin, H.; Njardarson, J. T.; Chappell, M. D.; Chou, T. C.; Guan, Y.; Tong, W. P.; He, L.; Horwitz, S. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 9825. (b) Rivkin, A.; Njardarson, J. T.; Biswas, K.; Chou, T. C.; Danishefsky, S. J. *J. Org. Chem.* **2002**, *67*, 7737.

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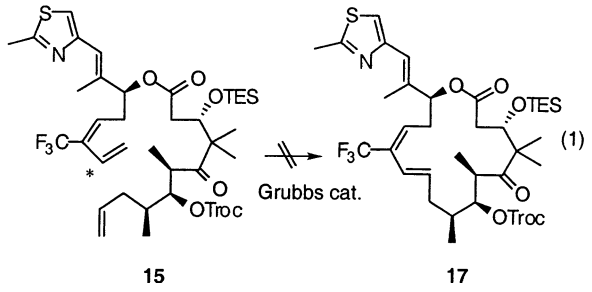
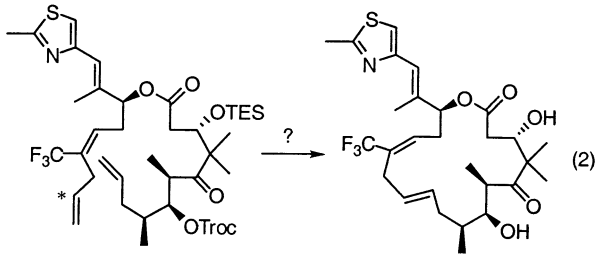
apparentdimerization of the starting material (eq 1).[10] Given




15 17

the fact that the RCM works quite well in the related setting of **5** → **6**, we naturally attributed the failure in the case of **15** to the presence of the trifluoromethyl group in a vicinal relationship to the proposed RCM reaction center (see asterisk in **15**).

It was conjectured that the detrimental impact of the resident 26-trifluoro substituent on the desired reaction might be alleviated by adding a carbon spacer between the RCM reaction center (see asterisk in **18**) and the trifluoromethyl group. Accordingly, we undertook a synthesis of **19** (eq 2) via the ring-closing metathesis of **18**, which would present the trifluoromethyl group in the context of a 17-membered ring containing a skipped (1,4)diene.




18 19

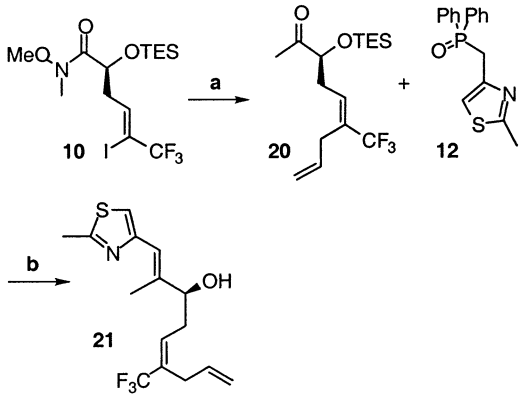
The synthesis program directed to **19** commenced with the preparation of compound **21**, which corresponds to the "O-alkyl sector" of our proposed RCM substrate (Scheme 3). We began with allylation of **10**, this time under radical reaction conditions as shown.[11] This conversion was followed by reaction of the alkylated product with methylmagnesium bromide, thus affording the required ketone **20**. Condensation of this compound with phosphine oxide **12** followed by deprotection of the triethylsilyl ether function provided **21** in good yield.

Esterification of **21** with the C1−C10 acid fragment **14** provided the proposed RCM precursor **18** in 75% yield (Scheme 4). Happily in this case, the ring-closing metathesis reaction of **18** could be accomplished using the second generation Grubbs catalyst in methylene chloride. As in the case of the conversion of **5** → **6**, the reaction provided exclusively the *trans* isomer **22** in 57% yield.[6] Finally,

(10) Dimerization occurred at 10,11-olefin, while the $CF_3$-substituted diene did not react at all.

(11) (a) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829. (b) Review: Curran, D. P. *Synthesis* **1988**, Part 1, p 417; Part 2, p 489.

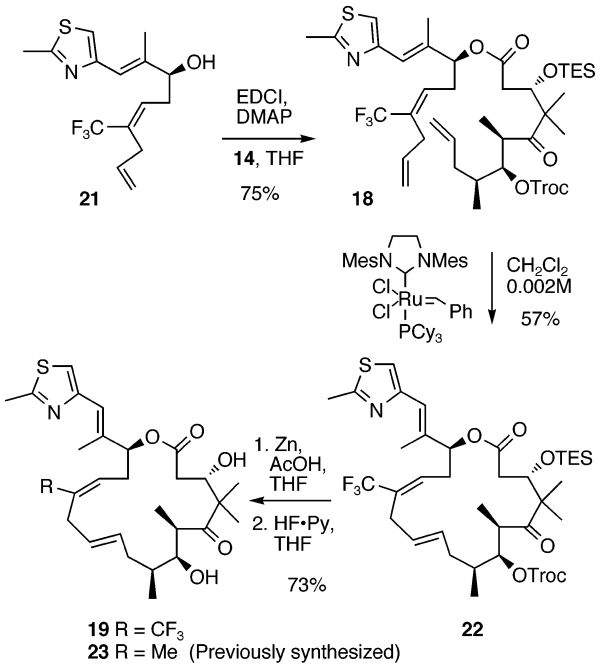
**Scheme 3**[a]




[a] Key: (a) (i) Allyltributyltin, AIBN, benzene, 80 °C, 3 h, 74%; (ii) MeMgBr, 0 °C, 69%; (b) (i) **12**, *n*-BuLi, THF, −78 °C, 30 min; (ii) **20**, −78 °C to room temperature; (iii) HOAc:THF:$H_2O$ (3:1:1), 83% overall.

reductive cleavage of the trichloroethoxycarbonyl protecting group with zinc and acetic acid, followed by deprotection of the TES ether with HF-pyridine, afforded the desired **19** containing a trifluoromethyl function at $C_{12}$, albeit in the context of the 17-membered-ring series.

**Scheme 4**




Synthetic **19** was evaluated as to its cytotoxic activity. As shown in Table 1, direct comparison of the previously reported [17]ddEpoB (**23**) with 27-$F_3$-[17]ddEpoB (**19**) indicated that the new perfluorinated compound possessed a comparably high cytotoxic potency.[12] Though the trifluoromethyl isoteric substitution had little effect on the gross

**Table 1.** In Vitro Cytotoxicities ($IC_{50}$) with Tumor Cell Lines[14]

| compd | CCRF-CEM ($IC_{50}$ ($\mu$M)) | CCRF-CEM/VBL ($IC_{50}$ ($\mu$M)) |
|---|---|---|
| 27-Tri-F-[17]ddEpoB (**19**) | 0.068 | 0.191 |
| [17]ddEpoB (**23**) | 0.040 | 0.126 |
| [16]ddEpoB (**6**) | 0.025 | 0.091 |

cytotoxic activity, *preliminary data from metabolic degradation studies in mouse plasma showed **19** to be notably more stable than is the parent **23***.[13] Since pharmokinetic issues are likely to be critical in the actual use of any epothilone agent as a drug, we take this finding to be quite encouraging. We are pursuing new departures directed to the incorporation of trifluoromethyl substituents in various epothilone settings.

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**Note Added after ASAP:** In Scheme 4, reaction **18** to **22**, bonds were added between the two chlorides and the ruthenium catalyst; the corrected version was posted on October 18, 2002.

**Supporting Information Available:** Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Compound **23** ([17]ddEpoB) was prepared in a fashion similar to compound **19** as described in ref 6b.

(13) Exposure of epothilones **19** and **23** to nude mouse and human plasma led to degradation of **23** within 30 min, while epothilone **19** remained mostly intact (see ref 2 for details) of this type of measurement. Specifics for **19** and **23** will be reported in due course.

(14) XTT assay following 72 h inhibition. CCRF-CEM is a human T-cell acute lymphoblastic leukemia cell line. The CCRF-CEM/$_{VBL100}$ cell line overexpresses *P*-glycoprotein and displays a multidrug resistance phenotype to MDR-associated oncolytics.