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Synthesis of Epothilones via a Silicon-Tethered RCM Reaction

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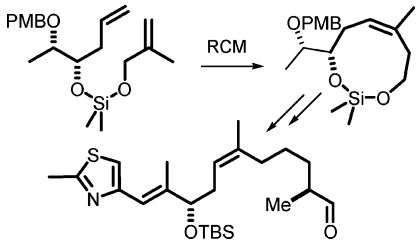
ABSTRACT



A short synthesis of epothilone B and D is reported. The key step for generating the C12–13-trisubstituted *Z*-double bond uses a ring-closing metathesis reaction of a disiloxane to form a nine-membered silicon-tethered ring.

Epothilones such as **1** and **2** (Figure 1) are forthcoming anticancer drugs with high cytotoxic activity combined with low multidrug resistance.[1] Although these compounds can be procured from fermentation quite efficiently, the constant search for more biologically active derivatives has inspired an ever-increasing amount of total syntheses.[2] All of these routes, some of which are well-suited for the larger scale, must cope with the nontrivial problem of introducing a (*Z*)-double bond into the C12−C13 position. Among the various approaches, Danishefsky's Miyaura−Suzuki coupling[3] of vinyl iodide **3** with borane **4** to olefin **5** has found widespread application, notwithstanding the low overall yield (43% for the preparation of **3**, and 77% for the coupling) (Scheme 1).

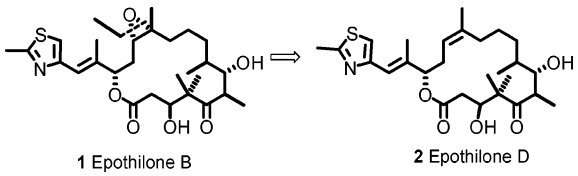
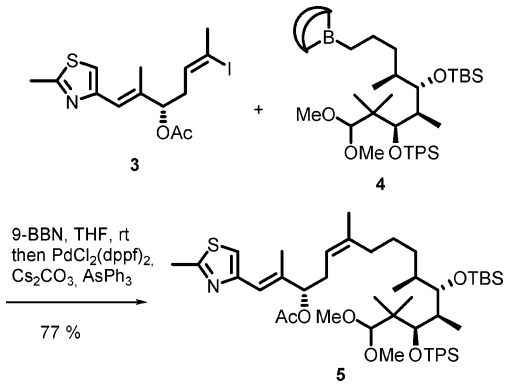


Figure 1. Epoxidation of epothilone D.

Scheme 1. Danishefsky Approach to the 12,13-Double Bond



Following the standard aldol disconnection[2] of **2** into the northern fragment **7** and a southern fragment **8** (Scheme 2)

(1) Höfle, G.; Bedorf, N.; Gerth, K.; Reichenbach, H. (GBF), DE-B 4138042, **1993**; *Chem. Abstr*. **1993**, *120*, 52841. Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 1567.

(2) For reviews, see: (a) Nicolaou, K. C.; Roschangar, F.; Vourloumis, D. Angew. *Chem., Int. Ed*. **1998**, *37*, 2014. (b) Mulzer, J. *Monatsh. Chem.* **2000**, *131*, 205. (c) Altmann, K.-H. *Org. Biomol. Chem*. **2004**, *2*, 437. For most recent syntheses, see: (d) Scheid, G.; Ruijter, E.; Konarzycka-Bessler, M.; Bornscheuer, U. T.; Wessjohann, L. A. *Tetrahedron: Asymmetry* **2004**, *15*, 2861. (e) Jung, J.-J.; Kache, R.; Vines, K. K.; Zheng, Y.-S.; Bijoy, P.; Valluri, M.; Avery, M. A. *J. Org. Chem*. **2004**, *69*, 9269.

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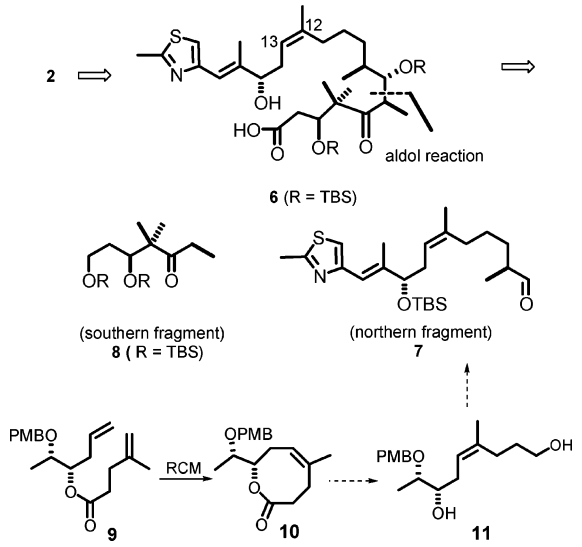
Scheme 2. Retrosynthetic Considerations



it occurred to us that the ring-closing metathesis (RCM)[4] of an ester such as **9** would incorporate the C12−C13 double bond into an eight-membered lactone **10** with (*Z*)-configuration because the ring strain is lower than in the case of the (*E*)-isomer.

Moreover, **10** could serve for a chain elongation via diol **11** toward aldehyde **7**, which constitutes the northern fragment of **6** in Nicolaou's[5] and our synthesis[6] (Scheme 2). Hence, diolefinic esters **9** and **14**, serving as RCM precursors, were prepared in 2 and 4 steps, respectively, from lactate **12** in overall yields of 61% and 44% and subjected to RCM with either the Grubbs catalyst[7] **a** or the Grubbs−Hoveyda catalyst **b**[8] (Figure 2). Lactate **12** was obtained from

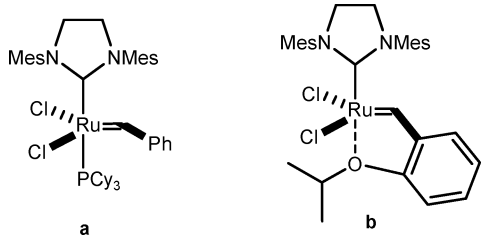


Figure 2. Structure of catalysts **a** and **b**.

commercially available (*S*)-methyllactate via protection with Bundle's reagent.

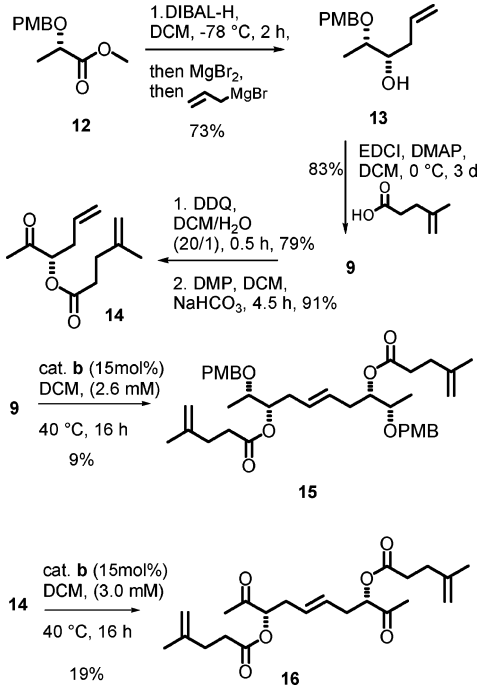
(3) (a) Meng, V.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073. (b) For a variation, cf. Schinzer, D.; Bauer, A.; Schieber, J. *Chem.—Eur. J.* **1999**, *5*, 2492.

(4) (a) Cf. Kalesse, M.; Gerlach, K.; Quitschalle, M. *Tetrahedron Lett.* **1999**, *40*, 3553. (b) Reviews on RCM: Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592. Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.

(5) Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He, Y.; Vallberg, H.; Finlay, M. R. V.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 7974.

In both cases, only dimers **15** and **16** were isolated in 9 and 19% yield (Scheme 3). From this result we concluded

Scheme 3. Attempted RCM of Diolefins **9** and **14**

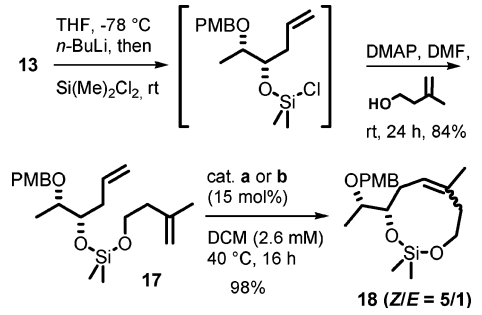


that the RCM was not able to overcome the ring strain in the transition state.

Hence, our idea was to induce strain relief by using a silicon tether. As silicon is bigger in size and has got more polarizable soft d-orbitals, its bonds are more easily distorted. Thus, cyclization causes less ring strain, and RCM seemed to be more facile.[9] Of course, we chose the tether in a form to get ready access to aldehyde **7**.

Thus, disiloxane **17** emerged as a suitable RCM substrate, which was prepared from alcohol **13**[4a] in one pot in 84% yield. RCM of **17** gave the nine-membered ring olefin **18** quantitatively with a *Z*/*E* ratio of 5/1 (Scheme 4).[10] Yields

Scheme 4. Silicon-Tethered RCM

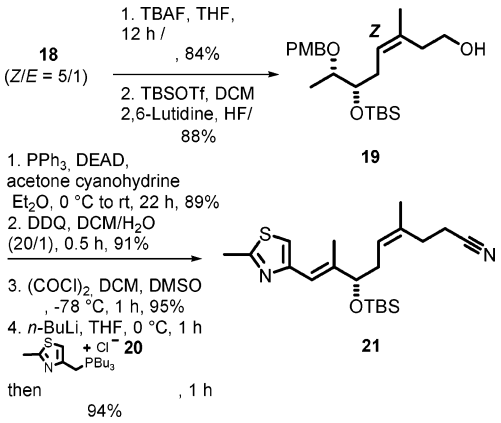


for RCM turned out to be strongly dependent on the rate of catalyst addition. Quantitative yields where only obtained

when the catalyst was added over 16 h. By contrast, addition of catalyst in one portion reduced the yield to 50%.

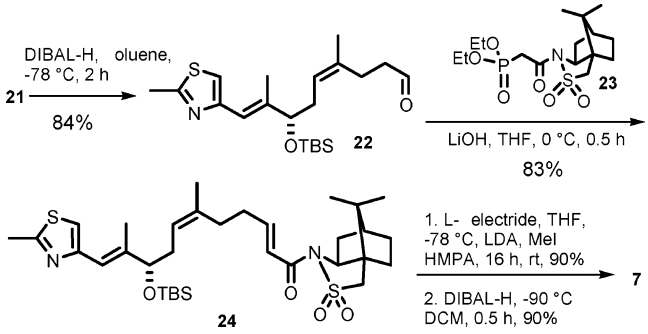
Without separation, the *E*/*Z* mixture of **18** was desilylated to give a stereoisomeric mixture of *E* and *Z* diols, separable by column chromatography. The *Z*-diol was thus obtained in 82% overall yield from **17**. In one pot, the *Z*-diol was converted into the di-TBS-ether and then mono-deprotected to give **19** in 88% yield. One-carbon chain elongation of **19** was accomplished by a Mitsunobu reaction with acetone cyanohydrin in 92% yield.[11] *p*-Methoxybenzyl (PMB) deprotection, oxidation to the ketone and (*E*)-selective Wittig reaction with phosphonium salt **20** generated thiazole nitrile **21** (overall yield of 81% for the three steps) (Scheme 5).

Scheme 5. Chain Elongation and Introduction of the Thiazole Moiety



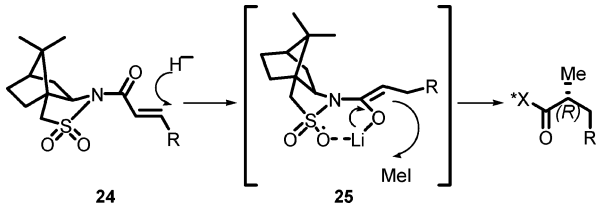
Nitrile **21** was reduced to aldehyde **22** (84% yield), which was subjected to a Horner−Wadsworth−Emmons reaction with Oppolzer's chiral phosphonate **23** to give enone **24** in 79% yield. A one-pot 1,4-reduction/methylation sequence[12] followed by reduction with DIBAL-H applied to **24** led to aldehyde **7** with a diastereoselectivity greater than 95% and 81% yield for the two steps (Scheme 6). The analytical data

Scheme 6. Completion of the Northern Fragment **7**



of **7** perfectly matched those described.[5,6] The stereochemical outcome of the tandem 1,4-reduction−methylation sequence is rationalized via a chelate induced chirality transfer within enolate **25** (Scheme 7). By using this procedure, aldehyde **7**

Scheme 7. Stereoselectivity of the Tandem 1,4 Reduction Methylation



was available in 11 steps from alcohol **13** (overall yield 25%).

The endgame of the synthesis proceeds as described earlier[6] (Scheme 2). In an aldol reaction aldehyde **7** is connected with ketone **8**. An additional five steps lead to seco acid **6**, which after Keck lactonization and desilylation gives **2**, which is epoxidized with *m*-CPBA (5/1 selectivity) to **1**. In conclusion, we present a short route to **2** and **1** in 21/22 steps (longest linear sequence 18/19 steps) and with an overall yield of 9%.

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

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(6) (a) Mulzer, J.; Mantoulidis, A.; Öhler, E. *Tetrahedron Lett.* **1996**, *37*, 9179. (b) Mulzer, J.; Mantoulidis, A.; Öhler, E. *J. Org. Chem.* **2000**, *65*, 7456.

(7) Schwab, B.; Grubbs, R. K.; Ziller, J. W. *J. Am. Chem Soc.* **1996**, *118*, 100.

(8) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem Soc.* **2000**, *122*, 8168. (b) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973.

(9) (a) Harrison, B. A.; Verdine, G. L. *Org. Lett.* **2001**, *3*, 2157. (b) Boiteau, J. G.; Van de Weghe, P.; Eustache, J. *Tetrahedron Lett.* **2001**, *42*, 239. For RCM with a sulfonate tether, see: (c) Le Flohic, A.; Meyer, C.; Cossy, J. *Org. Lett.* **2005**, *7*, 339.

(10) (a) Promo, M. A.; Hoye, T. R. *Tetrahedron Lett.* **1999**, *40*, 1429. (b) Evans, P. A.; Cui, J.; Buffone, G. P. *Angew. Chem., Int. Ed.* **2003**, *42*, 1734.

(11) (a) Wilk, B. *Synth. Commun.* **1993**, *23*, 2481. (b) Tsunoda, T.; Uemoto, K.; Nagino, C.; Kawamura, M.; Kaku, H.; Ito, S. *Tetrahedron Lett.* **1999**, *40*, 7355.

(12) (a) Oppolzer, W.; Poli, G. *Tetrahedron Lett.* **1986**, *27*, 4717. (b) Martin, H. J.; Drescher, M.; Mulzer, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 581.