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Synthesis of the Northern Hemisphere of Epothilone A by a ten-membered Ring Closing Metathesis Reaction

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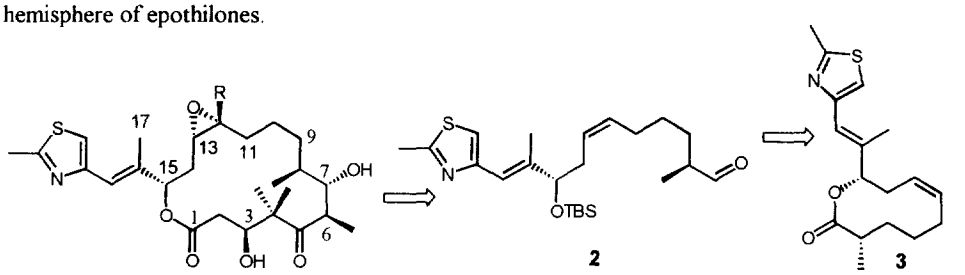
Abstract: The synthesis of the strained epothilone analog containing a ten-membered ring as well as the northern hemisphere of epothilone A is described. This approach, using the ring closing metathesis reaction, is a solution to the lack of stereocontrol observed in the ring closing metathesis reaction utilized in the synthesis of the epothilone backbone by other groups.

The epothilones,[1] macrolides isolated from the myxobacteria *Sorangium cellulosum* by Höfle, Reichenbach *et al.*,[2] have drawn much attention because their biological activity is closely related to taxol and both compounds stabilize microtubule. The important biological activities of epothilones[3] have not only stimulated the total synthesis[4] of these compounds but also the search for derivatives and analogs.[5] Conformational investigations indicate that strained epothilone analogs can exhibit some of the structural features of the parent natural product and be used to evaluate the structure for evaluating the structure activity relationship. Thus there is increasing interest in the efficient synthesis of advanced intermediates and strained analogs containing either the northern or southern hemisphere of epothilones.



1 epothilones A: R=H, B: R=Me

Scheme 1

Herein we report the synthesis of a constrained epothilone analog **3** and the northern (C7-C15) hemisphere which contains the thiazole moiety (Scheme 1). Epothilone A analog **3** and aldehyde **2** are derived from the PMB-protected alcohol **8** and 6-heptenoic acid (Scheme 2). The ring closing metathesis reaction (RCM), leading to the 10-membered lactone[6] **11**, can be converted to aldehyde **2**, an advanced intermediate in the Nicolaou total synthesis of epothilone A (Scheme 3).

The synthesis of **3** (Scheme 3) involves protection of (*S*)-ethyl lactate with PMB-trichloroacetimidate followed by reduction with $LiAlH_4$ and subsequent Swern oxidation. Addition of allyltrimethylsilane to the so-generated

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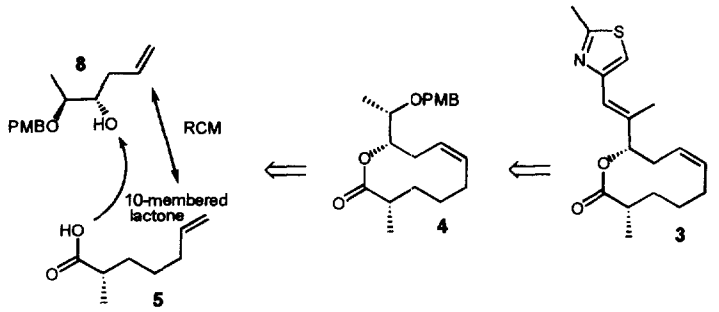
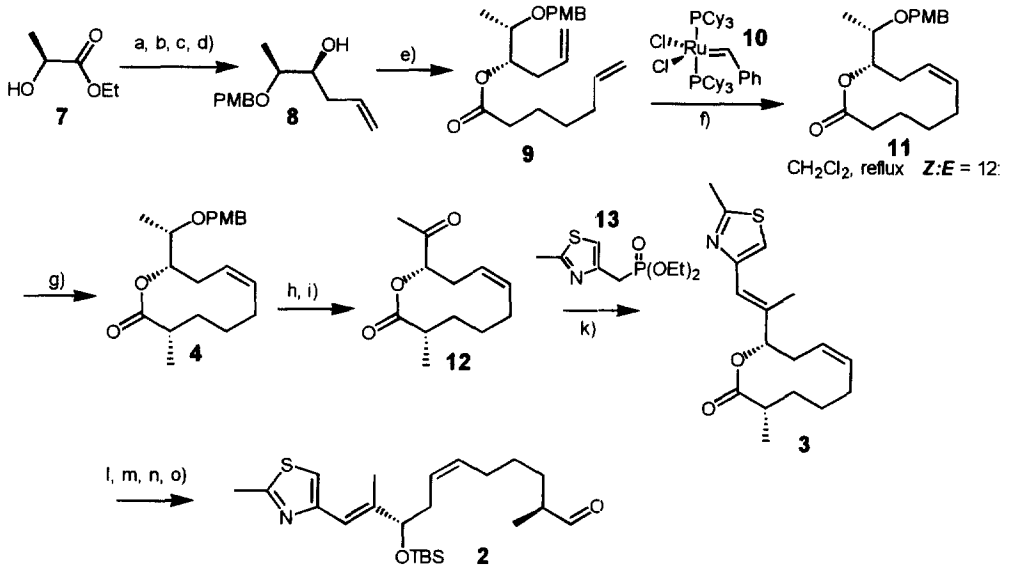
aldehyde provides secondary alcohol **8** in a diastereoselective addition (de = 91%) with the desired diastereomer as the major compound.[7]



Scheme 2

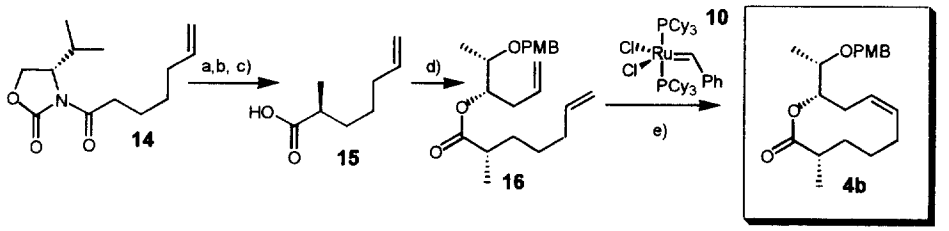
In order to obtain the 10-membered epothilone analog esterification with 6-heptenoic acid was performed under standard conditions[8] and the subsequent ring closing metathesis reaction with Grubbs' catalyst[9] gave the desired *Z*-isomer as the major compound (*Z*/*E* = 12:1). The isomers could be separated by flash chromatography. In the case of the 10-membered RCM reaction the best *Z*/*E* ratio (12:1) was obtained when the reaction was performed in refluxing CH_2Cl_2.



Scheme 3: a) PMB trichloroacetimidate, CSA, CH_2Cl_2, 0 °C→r.t., 88%; b) $LiAlH_4$, Et_2O, 0 °C→r.t., 74%; c) Swern oxidation, 77%; d) allyltrimethylsilane, $SnCl_4$, CH_2Cl_2, -78 °C, 88%; e) 6-heptenoic acid, DCC, DMAP, CH_2Cl_2, r.t., 94%; f) ring closing metathesis, 0.22 eq **10**, high dilution, CH_2Cl_2, reflux, 3h, 63%, Z:E = 12:1; g) NaHMDS, THF, MeI, -78 °C, 82%; h) DDQ, CH_2Cl_2/H_2O 18:1, r.t., 1h, 98%; i) TPAP, NMO, 3 Å sieves, CH_2Cl_2, r.t., 1h, 83%; k) **13**, BuLi, -78 °C→r.t. 2h, 65%; l) $LiAlH_4$, Et_2O, 0 °C, 1h, 95%; m) TBDMS triflate, lutidine,CH_2Cl_2, -78 °C, 91%; n) CSA, CH_2Cl_2/MeOH 1:1, 0 °C, 92%; o) Dess-Martin periodinane, CH_2Cl_2, 0 °C, 1h, 93%.

Computational analysis of both isomers which showed the *Z*-isomer to be 9 kcal/mol less in energy than the *E*-isomer indicating that the *Z*-isomer is the thermodynamically controlled product. Evidence supporting the thermodynamic preference for the *Z*-isomer is demonstrated by the fact that subjecting the doubled bond isomers to additional RCM conditions isomerizes the *E*-isomer to the *Z*-isomer.

The *Z*-isomer was methylated diastereoselectively at C8 without the aid of any additional chiral auxiliary.[10] The stereochemistry of the methylation at C8 was assigned by comparison to the RCM product using (S)-2-methyl 6-heptenoic acid in the esterification step. In order to obtain 2-(*S*)-methyl-6-heptenoic acid (**15**), the Evans derivative with 6-heptenoic acid was methylated, reduced with $LiAlH_4$ [11] and then oxidized to the chiral acid. The ^1H and ^{13}C-NMR signals of both compounds **4** and **4b** were identical, indicating that the methylation had generated the desired stereochemistry at C8.



Scheme 4: a) NaHMDS, THF, -78 °C, MeI, 73%; b) $LiAlH_4$, Et_2O, 0 °C, 76%; c) PDC, CH_2Cl_2, r.t., 61%; d) **8**, DCC, DMAP, CH_2Cl_2, r.t., 92%; e) RCM, high dilution, CH_2Cl_2, reflux, 53%.

Deprotecting the PMB group of **4** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), followed by tetra-*n*-propylammonium perruthenate (TPAP) oxidation generated ketone **12** which was then subjected to a Horner-Emmons reaction with thiazole **13** to establish the 10-membered epothilone analog **3** in 65% yield. In order to obtain aldehyde **2,** lactone **3**[12] was reduced with $LiAlH_4$ and the resulting diol was protected with 3 eq. TBDMS-triflate and lutidine in CH_2Cl_2. Deprotection of the primary alcohol with CSA as described by Nicolaou *et al.* followed by Dess-Martin oxidation established aldehyde **2**[13] (Scheme 3).

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12. Lactone **3**: $[\alpha]^{20}_{D}$ -88.0° (c = 0.6 in $CHCl_3$); FTIR ($CHCl_3$) 2924, 2856, 1720, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.59 (d, *J* = 0.48 Hz, 1H), 5.40-5.55 (m, 2H), 5.37 (t, *J* = 4.2 Hz, 1H), 2.73 (s, 3H), 2.33-2.43 (m, 1H), 2.20-2.33 (m, 2H), 2.11 (s, 3H), 1.96-2.08 (m, 2H), 1.55-1.80 (m, 4H), 1.22 (d, *J* = 7.15 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.30, 164.64, 152.74, 136.77, 135.03, 123.24, 119.00, 115.80, 77.20, 42.45, 32.06, 31.91, 29.68, 27.55, 19.34, 19.22, 16.47; HRMS m/e calcd for $C_{17}H_{23}N_1O_2S_1$ (M^+ + 1) 305.1449, found 305.1449.

13. Aldehyde **2**: $[\alpha]^{20}_{D}$ = +11.1° (c 0.7, $CHCl_3$); IR ($CHCl_3$) 2928, 2856, 1460, 1388, 1256, 1184, 1076, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.57 (d, *J* = 2 Hz, 1H), 6.90 (s, 1H), 6.43 (s, 1H), 5.34-5.42 (m, 2H), 4.07-4.13 (m, 1H), 2.68 (s, 3H), 2.22-2.34 (m, 3H), 1.9-2.07 (m, 2H), 1.97 (d, *J* = 1.2 Hz, 3H), 1.57-1.73 (m, 2H), 1.27-1.42 (m, 3H), 1.05 (d, *J* = 9 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), -0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.1, 164.4, 153.1, 142.1, 130.6 126.5, 118.9, 115.0, 78.6, 46.2, 34.7, 30.1, 27.3, 26.9, 25.8, 19.2, 18.2, 13.9, 13.3, -4.7, -5.0; HRMS m/e calcd for $C_{23}H_{39}N_1O_2Si_1S_1$ 421.2470, found 421.2470.