Synthesis of the C7–C17 Segment of Epothilones by a 10-membered Ring Closing Metathesis Reaction

Kai Gerlach, Monika Quitschalle and Markus Kalesse*

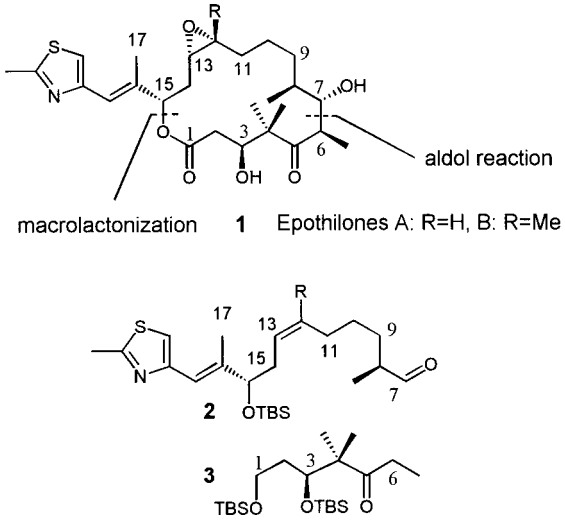
Institut für Organische Chemie, Universität Hannover, Schneiderberg 1b, 30167 Hannover (Germany)

FAX: +49-(0)511 762 4643; E-mail: Kalesse@mbox.oci.uni-hannover.de

Received 22 July 1998

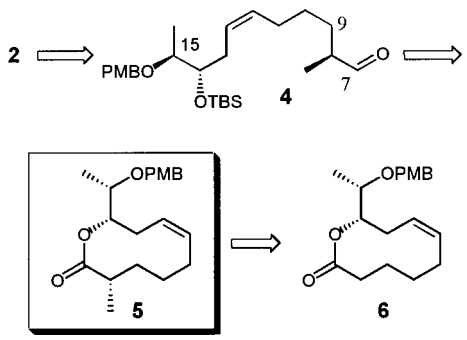
Abstract: The synthesis of the C7-C17 segment of epothilones employing a ring closing metathesis is described. Our approach utilizes the stereoselective methylation of the 10-membered lactone, generated by ring closing metathesis, for introducing the methyl group at C8 and provides an efficient access to strained epothilone derivatives, as well as to the C7-C17 segment of epothilones.

The fascinating biological activities of the epothilones,[1] isolated and characterized by Höfle, Reichenbach *et al.* at the GBF,[2] have initiated a variety of different projects throughout the scientific community yielding in the total synthesis of epothilones[3] and epothilone derivatives as well as various partial solutions.[4] Our strategy in the total synthesis of epothilones employs the aldol reaction between C6 and C7 and a macrolactonization for the ring closure (Scheme 1). With a practical synthesis for the ethyl ketone fragment **3** in our hands,[4b] we evaluated different strategies in order to establish a short and efficient route to the northern (C7-C17) segment, suitable for the aldol reaction.



Scheme 1

We envisioned that the ring closure of compound **10** to generate the 10-membered lactone **6** as the key step will provide an efficient access to the C7-C17 segment of epothilones as well as to strained epothilone derivatives (Scheme 2). The synthesis of this strained 10-membered lactone could be 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. Even though it was not obvious whether such a ring closure metathesis reaction would be successful since only three examples of a 10-membered ring closing metathesis reaction had been published at that time, the results of Fürstner *et al*. on synthesizing a 10-membered lactone by a ring closing metathesis indicated that this route can lead to the desired product.[5] In order to synthesize the desired precursor **10** we chose (*S*)-ethyl lactate (**7**)as the starting material from the chiral pool. Addition of allyltrimethylsilane should generate the desired stereochemistry at C15 in good stereoselectivity and the hydroxyl group of (S)-ethyl lactate could later be oxidized and used in the Wittig reaction for introducing the thiazole moiety.

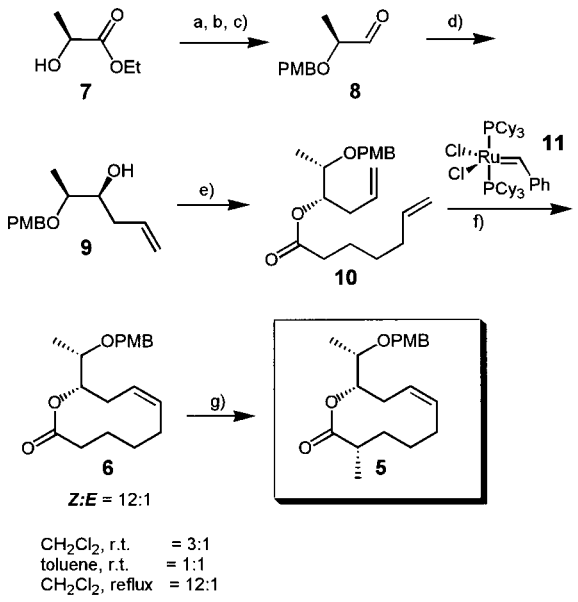


Scheme 2

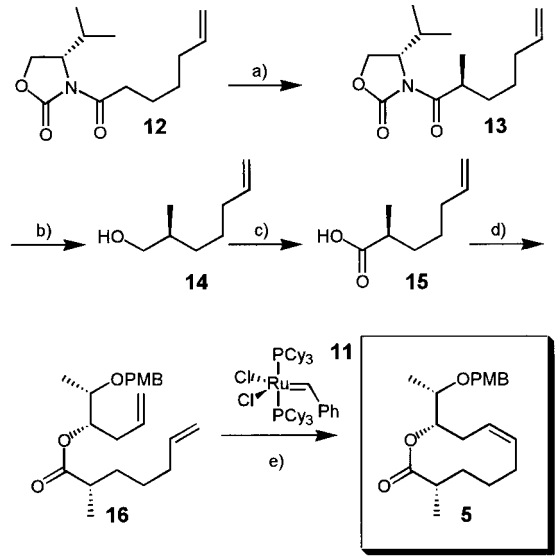
Here we report the synthesis of the C7-C17 segment of epothilone A, starting from (S)-ethyl lactate (**7**) and employing the ring closing metathesis reaction as the key step to generate the *Z* double bond of epothilone in a rare 10-membered ring closing reaction. Subsequent methylation establishes the desired carbon skeleton of the northern hemisphere of epothilones (Scheme 3). (*S*)-Ethyl lactate (**7**) was protected with PMB-trichloroacetimidate followed by reduction and subsequent Swern oxidation generated aldehyde **8**, which was transformed into the secondary alcohol **9** by stereoselective addition (de = 91%) of allyltrimethylsilane with $SnCl_4$ as Lewis acid.[6] Esterification with 6-heptenoic acid under standard conditions provided diene **10** which was subjected to a ring closing metathesis reaction (RCM) using Grubbs' ruthenium-based catalyst (**11**).[7] The choice of the solvent and the reaction temperature had significant influence on the stereochemical outcome of the metathesis reaction.[8] High dilution technique in refluxing CH_2Cl_2 gave the best *Z/E* ratio (12:1), whereas reaction in toluene only gave a 1:1 mixture of both stereoisomers.

In order to introduce the methyl group at C8 stereoselectively we followed two strategies. The more straightforward approach was to establish the methyl group right from the beginning by asymmetric methylation of the 6-heptenoic acid according to Evans´ protocol (Scheme 4).[9] Cleavage of the chiral auxiliary with $LiAlH_4$ followed by oxidation with PDC provided 2-(*S*)-methyl-6-heptenoic acid (**15**) which was esterified with alcohol **9** and subsequently subjected to a ring closing metathesis reaction yielding lactone **5**.

The second route made use of the conformation of the 10-membered ring which was methylated stereoselectively[10] without the need of any additional chiral auxiliary as shown in Scheme 3. Both strategies were employed in the synthesis of **5** and compound **5** derived from 2-methyl-6-heptenoic acid (**15**) was used to assign the stereochemistry of the methylation of **6**. The alkylation of compound **6** gave only one stereoisomer and both products gave identical NMR signals and the same optical rotation, indicating that the alkylation of **6** with NaHMDS and CH_3I generated the desired compound.[11]



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, high dilution, CH_2Cl_2, reflux, 54%, ***Z:E*** = 12:1; g) NaHMDS, THF, MeI, -78 °C, 82%.



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) **9**, DCC, DMAP, CH_2Cl_2, r.t., 92%; e) RCM, high dilution, CH_2Cl_2, reflux, 53%.

This strategy allows access to the northern fragment of epothilones without the necessity of employing chiral auxiliaries for the introduction of the C8-methyl group. Taking into account that the metathesis reaction provides a rapid access to the C7-C17 segment of epothilones with the *Z*-double bond in a very good *Z/E* ratio and no chiral auxiliary is necessary for establishing the desired stereochemistry at C8, we now have a convenient strategy for generating the northern hemisphere and the carbon framework of strained epothilones.

References and Notes

1. Bollag, D.M.; McQueney, P.A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.E.; Lazarides, C.; Woods, M. *Cancer Res*. **1995**, *55*, 2325-2333.
2. a) Höfle, G.; Bedorf, N.; Gerth, K.; Reichenbach, H. DE-4138042, 1993 [Chem. Abstr. 1993, 120, 52841]; b) Gerth, K.; Bedorf, N.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot*. **1996**, *49*, 560-563; c) Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem.* **1996**, *108*, 1671-1673, *Angew. Chem. Int. Ed. Engl*. **1996**, *35*, 1567-1569; d) Schinzer, D. *Eur. Chem. Cron*. **1996**, *1*, 7-10; e) Kalesse, M. *Eur. Chem. Cron*. **1997**, *2*, 7-11; f) Wessjohann, L. *Angew. Chem*. **1997**, *109*, 739-742, *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 739-742.
3. a) Balog, A.; Meng, D.; Kamencka, T.; Bertinato, P.; Su, D.-S.; Sorensen, E.J.; Danishefsky, S.J. *Angew. Chem*. **1996**, *108*, 2976-2978; *Angew. Chem. Int. Ed. Engl*. **1996**, *35*, 2801.2803; b) Nicolaou, K.C.; He, Y.; Vourloumis, D.; Vallberg, H.; Yang, Z. *Angew. Chem*. **1997**, *109*, 170-172; *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 166-168; c) Schinzer, D.; Limberg, A.; Bauer, A.; Böhm, O.; Cordes, M. *Angew. Chem*. **1997**, *109*, 543-544; *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 523-524; d) Nicolaou, K.C.; Sarabia, F.; Nincovic, S.; Yang, Z. *Angew. Chem.* **1997**, *109*, 539-540; *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 525-527; e) Su, D.-S.; Meng; D.; Bertinanto, P.; Balog, A.; Sorensen, E.J.; Danishefsky, S.J.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horowitz, S.B. *Angew. Chem*. **1997**, *109*, 775-777; *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 775-777; f) Nicolaou, K.C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakatou, P.; Hamel, E. *Nature* **1997**, *387*, 268-272.
4. a) Mulzer, J.; Mantoulidis, A. *Tetrahedron Lett*. **1996**, *37*, 9179-9182; b) Claus, E.; Pahl, A.; Jones, P.G.; Meyer, H.H.; Kalesse, M.; *Tetrahedron Lett*. **1997**, *38*, 1359-1362; c) Gabriel, T.; Wessjohann, L.; *Tetrahedron Lett.* **1997**, *38*, 1363-1366; d) Taylor, R.E.; Haley, J.D. *Tetrahedron Lett*. **1997**, *38*, 2061-2064; e) De Brabander, J.; Rosset, S.; Bernardinelli, G. *Synlett* **1997**, 824-826; f) Chakraborty, T.K.; Dutta, S.; *Tetrahedron Lett*. **1998**, *39*, 101-104; g) Bijoy, P.; Avery, M.A. *Tetrahedron Lett*. **1998**, *39*, 209-212; h) Liu, Z.-Y.; Yu, C.-Z.; Yang, J.-D. *Synlett* **1997**, 1383-1384; i) Liu, Z.-Y.; Yu, C.-Z.; Wang, R.-F.; Li, G. *Tetrahedron Lett*. **1998**, *39*, 5261-5264.
5. For ring closing metathesis reactions yielding 10-membered rings see: a) Fürstner, A.; Müller, T. *Synlett* **1997**, 1010-1012; b) Chang, S.; Grubbs, R.H. *Tetrahedron Lett*. **1997**, *38*, 4757-4760; c) Oishi, T.; Nagumo, Y.; Hirama, M. *Chem. Commun*. **1998**, 1041-1042.
6. Heathcock, C.H.; Kiyooka, S.-i.; Blumenkopf, T.A. *J. Org. Chem*. **1989**, *49*, 4214-4222.
7. Nguyen, S.T.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc*. **1993**, *115*, 9858-9859.
8. *Experimental procedure for the ring closing metathesis reaction*. To a refluxing solution of $RuCl_2(PCy_3)_2CHC_6H_5$ (95 mg, 0.115 mmol, 20 mol%) in CH_2Cl_2 (160 mL) is added a solution of diene **10** (200 mg, 0.577 mmol) in CH_2Cl_2 (20 mL) over a period of 1 h. After refluxing for 3 h the mixture is concentrated *in vacuo*. The crude product is purified by column chromatography (pentane/EtOAc 60:1) to provide the desired compound as a colourless oil (99 mg, 0.312 mmol, 54%).
   Spectroscopic data for compound **6**: IR ($CHCl_3$): 2932, 2860, 1720, 1612, 1512, 1444, 1248, 1172, 1032, 824 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.22-7.28, 2H, PMB), 6.84-6.89 (m, 2H, PMB), 5.38-5.50 (m, 2H, H-7, H-8), 4.90 (dd, *J*=10.67, 6.03 Hz, 1H, H-10), 4.57 (d, *J*=11.67 Hz, 1H, CH_2-*p*-$MeOC_6H_4$),

4.47 (d, *J*=11.67 Hz, 1H, C*H*$_2$-*p*-MeOC$_6$H$_4$), 3.65 (quin., *J*=6.35 Hz, 1H, H-11), 3.80 (s, 3H, MeO), 2.07-2.46 (m, 6H), 1.86-2.00 (m, 1H), 1.58-1.78 (m, 3H), 1.22 (d, *J*=6.4 Hz, 3H, H-12); ^{13}C-NMR (100 MHz, DEPT, CDCl$_3$): δ (ppm) = 174.44 (C, C-2), 159.08 (C, PMB), 134.57 (CH, PMB), 130.66 (C, PMB), 129.21 (CH, PMB), 124.07 (CH, C-7), 113.73 (CH, C-8), 75.58 (CH, C-11), 74.38 (CH, C-10), 70.96 (CH$_2$, *C*H$_2$-*p*-MeO-C$_6$H$_4$), 55.20 (CH$_3$, MeO), 35.27 (CH$_2$, C-3), 28.54 (CH$_2$), 26.72 (CH$_2$), 25.25 (CH$_2$, C-5), 23.49 (CH$_2$, C-4), 16.15 (CH$_3$, C-12); MS (EI, 70 eV, RT) *m/z* : 318 (M$^+$, 3), 182 (8), 153 (1), 137 (58), 121 (100), 95 (4), 80 (7); HR MS (C$_{19}$H$_{26}$O$_4$): calcd. 318.18311, found 318.18212.

9. Limberg, A. **1998** *Doktorarbeit* Universität Braunschweig.
10. For the stereoselective alkylation of medium ring enolates see: Still, W.C.; MacPherson, L.J.; Harada, T.; Callahan, J.F.; Rheingold, A.L. *Tetrahedron* **1984**, *40*, 2275-2281.
11. *Experimental procedure for the synthesis of compound* **5**. To a solution of lactone **6** (78 mg, 0.245 mmol) in THF (0.25 mL) is added dropwise NaHMDS (0.35 mL, 1 M in THF, 0.35 mmol, 1.4 eq) at -78 °C. After stirring for 1 h at -78 °C CH$_3$I (0.1 mL, 1.6 mmol, 6.5 eq) is added and stirring is continued for 5 h. After addition of water at -78 °C the mixture is allowed to warm to room temp. Extraction with MTB ether, drying over MgSO$_4$, evaporation and column chromatography on silica gel (PE/EtOAc 80:1) provides **5** as a colourless oil (67 mg, 0.201 mmol, 82%). [a]$_D^{20}$ = -11.3° (c=1, CHCl$_3$); IR (CHCl$_3$): 3000, 2972, 2936, 2856, 1720, 1612, 1512, 1460, 1248, 1172, 1068, 1036 cm^{-1}; ^{1}H-NMR (400 MHz, CDCl$_3$): δ (ppm) = 7.22-7.28 (m, 2H, PMB), 6.84-6.89 (2H, PMB), 5.38-5.53 (m, 2H, H-7, H-8), 4.85 (dt, *J*=7.15, 4.64 Hz, H-10), 4.54 (d, *J*=11.42 Hz, 1H, C*H*$_2$-*p*-MeO-C$_6$H$_4$), 4.50 (d, *J*=11.42 Hz, 1H, C*H*$_2$-*p*-MeO-C$_6$H$_4$), 3.80 (s, 3H, MeO), 3.69 (quin., *J*=6.35 Hz, 1H, H-11), 2.31-2.42 (m, 1H), 1.99-2.26 (m, 3H), 1.86-1.99 (m, 1H), 1.69-1.82 (m, 1H), 1.54-1.68 (m, 2H), 1.45-1.54 (m, 1H), 1.23 (d, *J*=6.4 Hz, 3H, H-12), 1.19 (d, *J*=7.02 Hz, 3H, H-13); ^{13}C-NMR (100 MHz, DEPT, CDCl$_3$): δ (ppm) = 176.78 (C, C-2), 159.08 (C, PMB), 134.93 (CH, PMB), 130.77 (C, PMB), 129.08 (CH, PMB), 123.44 (CH, C-7), 113.71 (CH, C-8), 75.49 (CH, C-11), 74.58 (CH, C-10), 55.25 (CH$_3$, MeO), 42.20 (CH, C-3), 41.27 (CH$_2$, *C*H$_2$-*p*-MeO-C$_6$H$_4$), 32.10 (CH$_2$, C-6), 27.37 (CH$_2$, C-9), 26.07 (CH$_2$, C-5), 25.47 (CH$_2$, C-4), 18.93 (CH$_3$, C-13), 16.46 (CH$_3$, C-12); MS (EI, 70 eV, RT) *m/z* : 333 (M$^+$+1, 2), 332 (M$^+$, 12), 196 (8), 137 (69), 121 (100), 95 (9), 85 (12), 68 (7); HR MS (C$_{20}$H$_{28}$O$_4$): calcd. 332.19876, found: 332.19912.