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Synthesis of the C(1)-C(9) Segment of the Cytotoxic Macrolides Epothilon A and B

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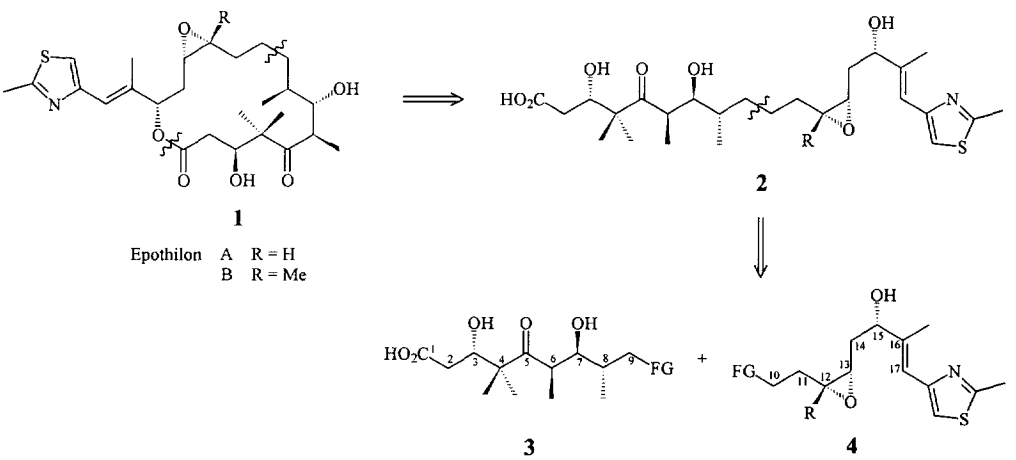
Abstract: The C(1)-C(9) segment **3** of the macrolides epothilon A and B **1**, two new cytotoxic natural products, has been synthesized in a direct manner. Key steps in the synthesis are a stereoselective aldol reaction of **6** and **7** and a Brown allylation of **9**. Copyright © 1996 Published by Elsevier Science Ltd

The epothilons A and B, two recently discovered cytotoxic macrolides, were isolated from the myxobacterium *Sorangium-cellulosum* culture So ce901 by Höfle and co-workers[1]. A combination of spectroscopic techniques and X-ray crystallographic analysis on epothilon B defined its structure as a 16-membered macrolide, with a side-chain containing a thiazole ring[2].



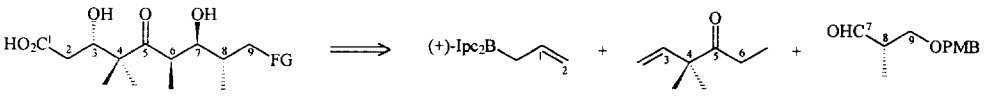
scheme 1

In addition to the antifungal activity against oomycetae (*Plasmopara viticola, Phytophthora infestans*), the epothilons exhibit antimitotic activity by inhibition of microtubule polymerization to the same extent as taxol. The macrolides show cytotoxicity against mice fibroblasts (cell line L929, epothilon B: IC_{50}= 2 $ngmL^{-1}$), which results in desintegration of the cell nucleus and apopotose[3]. An *in-vitro* anticancer screening of the epothilons also displayed promising activity and selectivity against breast and colon tumor cell lines.

The potent biological activity and the possibility of gaining access to analogues with enhanced antitumor effects and lower toxicity provided the incentive for our synthesis on epothilon A and B.

A retrosynthetic analysis of the macrolides is shown in scheme 1, with the first disconnection, opening of the macrocycle, provided the functionalized epothilon precursor **2**. Cleavage of the C(9)-C(10) bond generates the two fragments **3** and **4** with comparable size.

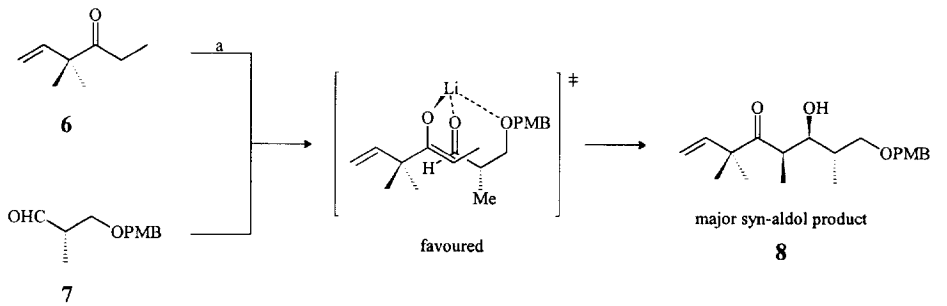
Herein we describe our stereoselective synthesis of the advanced intermediate **3**. The C(1)-C(9) fragment itself can be disconnected retrosynthetically at the C(2)-C(3) and C(6)-C(7) bonds to generate three easy available fragments **5**, **6** and **7** (scheme 2).



3 **5** **6** **7**

scheme 2

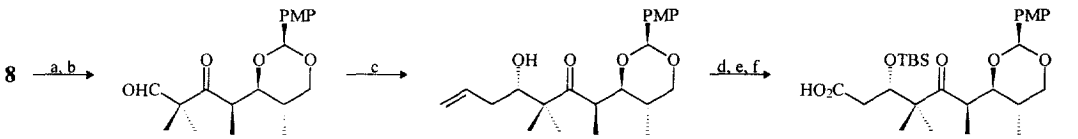
The synthesis of **3** started from methyl 3-hydroxy-(2S)-methylpropionate, which after protection of the hydroxyl group with p-methoxy-benzyl 2,2,2-trichloroacetimidate (PMBTCAI)[4] in 94% yield, was reduced with DIBAL-H to the alcohol (92%)[5]. Swern oxidation[6] afforded the aldehyde **7**, which was used without further purification, because chromatography of analogous compounds on silica gel is reported to cause partial racemization[7]. Treatment of the crude aldehyde with the lithium enolate of Mori's reagent[8] **6**, readily prepared in one step (75%) by reaction of the Grignard reagent obtained from prenyl chloride with propionyl chloride, gave the syn-aldol adducts **8** and **8`** as a 79:21 mixture of diastereomers in good yield (87% over two steps) (scheme 3).



scheme 3

Reagents and conditions: a) LDA, -90°C for 30 min, then addition of 7, 15 min, THF.

The secondary alcohol was protected as the benzylidene acetal by treatment of **8** with dichlorodicyano-benzoquinone (DDQ) under anhydrous conditions (89%)[9]. Ozonolysis of the terminal vinyl group delivered aldehyde **9** (93%), which underwent Brown allylboration[10] to give, after oxidative workup (NaOOH, 5 equiv.), the allylic alcohols **10** and **10`** (74%) in 81:19-diastereoselectivity. After separation by HPLC, the hydroxyl group was protected as TBS ether in almost quantitative yield. The synthesis of **11** was completed by ozonolysis of the double bond and Pinnick oxidation[11] of the aldehyde with sodium chlorite, which afford acid **11**[12] in 95% overall yield from allylation product **10** (scheme 4).



9 **10** **11**

scheme 4

Reagents and conditions: a) DDQ, 4Å molecular sieve, -20°C→r.t., 2h, CH_2Cl_2, (89%). b) O_3, -78°C→r.t., Me_2S workup, CH_2Cl_2/MeOH (20:1), (93%). c) Allyl-B[(+)-Ipc]$_2$, -78°C, 1h, Et_2O, oxidative workup, (74%). d) TBSOTf, 2,6-lutidine, 0°C, 2h, CH_2Cl_2, (99%). e) O_3, -78°C→r.t., CH_2Cl_2/MeOH (20:1), Ph_3P workup, (99%). f) $NaClO_2$, NaH_2PO_4, 2,3-dimethyl-but-2-ene, 3h, tert.-butanol-water (97%).

In conclusion, the synthesis of the C(1)-C(9) fragment **3,** as ist protected derivative **11,** was achieved in 9 steps from the commercial available methyl 3-hydroxy-(2S)-methylpropionate in 27% overall yield.

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12. Data for **8**: $[\alpha]_D^{20}$= - 14.2 (c= 0.675, $CHCl_3$); **MS** (EI, 70eV, 80°C): m/z= 334 (M^+, 0.3%); **^{1}H NMR** (400 MHz, $CDCl_3$): 0.93 (d, *J*= 6.8 Hz, 3H); 1.04 (d, *J*= 6.8 Hz, 3H); 1.22 (s, 3H); 1.25 (s, 3H); 1.81 (br.m, 1H); 3.15 (qd, *J*= 7.0, 2.4 Hz, 1H); 3.45 (dd, *J*= 9.0, 6.4 Hz, 1H); 3.51 (m, 1H); 3,52 (s, 1H); 3.59 (dd, *J*= 9.2, 4.0 Hz, 1H); 3.80 (s, 3H); 4.44 (dd, *J*= 16.4, 11.6 Hz, 2H); 5.20 (d, *J*= 17.2 Hz, 1H); 5.20 (d, *J*= 10.8 Hz, 1H); 5.88 (dd, *J*= 17.2, 10.6 Hz, 1H); 6.88 (dt, *J*= 11.4, 2.8 Hz, 2H); 7.25 (dt, *J*= 10.6, 1.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): 10.7, 14.1, 23.0, 23.2, 36.1, 41.0, 51.6, 55.1, 72.4, 72.8, 73.3, 113.7, 115.1, 129.1, 130.5, 141.4, 159.0, 218.5; **IR** (film): 3497, 2971, 2935, 2876, 1692, 1633, 1613, 1586, 1514, 1463, 1414, 1378, 1363, 1302, 1248, 1173, 1087, 1036, 1010, 992, 981, 923, 824, 756; Anal. Calcd. for $C_{20}H_{30}O_4$: C, 72.26%; H, 8.49%. Found: C, 72.02%; H, 8.41%.

Data for **10**: **MS** (EI, 70eV, 80°C): m/z= 376 (M^+, 0.26%); **^{1}H NMR** (250 MHz, $CDCl_3$): 0.87 (d, *J*= 6.7 Hz, 3H); 1.17-1.25 (m, 9H); 2.04 (m, 2H); 2.22 (m, 1H); 2.76 (d, *J*= 5.4 Hz, 1H); 3.40 (qd, *J*= 7.1, 3.0 Hz, 1H); 3.49 (t, *J*= 11.2 Hz, 1H); 3.73 (dd, *J*= 10.0, 3.0 Hz, 1H); 3,79 (s, 1H); 3.81 (mc, 1H); 4.07 (dd, *J*= 11.3, 4.8 Hz, 1H); 5.02 (m, 1H); 5.08 (m, 1H); 5.41 (s, 1H); 5.80 (m, 1H); 6.87 (dt, *J*= 8.8, 2.8 Hz, 2H); 7.37 (dt, *J*= 8.9, 2.8 Hz, 2H); **^{13}C NMR** (62,5 MHz, $CDCl_3$): 12.7, 13.6, 19.0, 21.7, 21.7, 22.0, 31.7, 35.9, 43.6, 52.5, 55.1, 67.5, 72.9, 75.4, 83.6, 100.8, 113.4, 117.0, 127.1, 130.5, 135.8, 159.7, 216.8; **IR** (film): 3484, 3074, 2960, 2838, 1703, 1640, 1615, 1588, 1518, 1463, 1391, 1369, 1303, 1250, 1172, 1126, 1110, 1077, 1034, 992, 914, 874, 829, 784; Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.185%; H, 8.57%. Found: C, 69.99%; H, 8.52%.

Data for **11**: **MS** (EI, 70eV, 280°C): m/z= 509 (M^+, 5.2%); **^{1}H NMR** (250 MHz, $CDCl_3$): 0.03 (s, 3H); 0.06 (s, 3H); 0.82 (d, *J*= 6.9 Hz, 3H); 0.85 (s, 9H); 1.12 (s, 3H); 1.15 (d, *J*= 7.2 Hz, 3H); 1.22 (s, 3H); 2.03 (mc, 1H); 2.31 (dd, *J*= 16.5, 6.6 Hz, 1H); 2.46 (dd, *J*= 16.2, 3.6 Hz, 1H); 3.28 (qd, *J*= 6.9, 3.0 Hz, 1H); 3.49 (t, *J*= 11.0 Hz, 1H); 3.76 (s, 3H); 3.77 (dd, *J*= 9.9, 3.0 Hz, 1H); 4.08 (dd, *J*= 11.3, 4.7 Hz, 1H); 4.57 (dd, *J*= 6.6, 3.6 Hz, 1H); 5.39 (s, 1H); 6.84 (dt, *J*= 9.1, 2.2 Hz, 2H); 7.34 (dt, *J*= 8.8, 1.9 Hz, 2H); **^{13}C NMR** (62,5 MHz, $CDCl_3$): 11.6, 12.5, 18.0, 19.1, 22.5, 25.8, 31.3, 39.2, 43.2, 53.5, 55.1, 72.7, 72.9, 82.1, 100.6, 113.4, 127.1, 130.7, 159.6, 176.8, 214.1; **IR** (film): 2959, 2936, 2883, 2855, 1707, 1616, 1588, 1519, 1464, 1429, 1388, 1371, 1360, 1313, 1251, 1220, 1172, 1160, 1123, 1101, 1077, 1041, 1029, 1010, 996, 982, 952, 939, 836, 776, 687, 670; Anal. Calcd. for $C_{27}H_{44}O_7Si$: C, 63.75%; H, 8.72%. Found: C, 63.63%; H, 8.91%.

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