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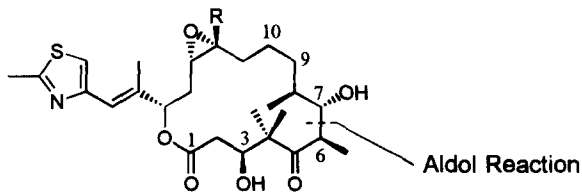
Synthesis of the C1-C9 Segment of Epothilons

Eckhard Claus, Axel Pahl, Peter G. Jones,* Hartmut M. Meyer*, Markus Kalesse*

Institut für Organische Chemie, Universität Hannover, Schneiderberg 1B, D-30167 Hannover (Germany) and *Technische Universität Braunschweig, Institut für Anorganische und Analytische Chemie, Hagenring 30, D-38106 Braunschweig (Germany)

Abstract: The C1-C9 segment of epothilons was generated by an aldol reaction between chiral aldehyde **3** and ethyl ketone **4**. Removal of the TBS protecting groups and debenzylation generated spiro ketal **13** which was analyzed by X-ray crystallography.

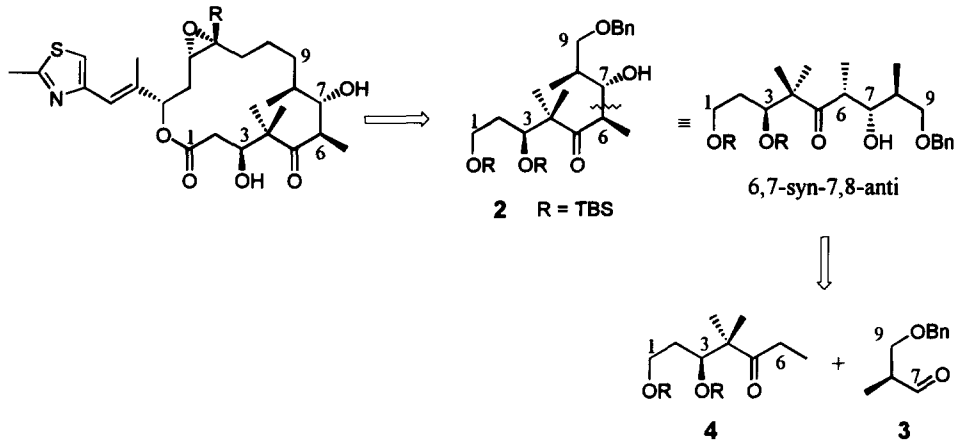
Herein we wish to report on the stereoselective synthesis of the C1-C9 fragment of epothilons (Scheme 1). The epothilons A und B (**1**) were isolated by Höfle et al.[1,2] and are considered promising anti-tumor agents since they are more active than taxol.[3] In our retrosynthetic analysis of epothilons the connection of two fragments can be made between C9 and C10. The substructure C1-C9 contains four of the seven asymmetric centres and should be easily synthesized by an aldol reaction of the key intermediates **3** and **4** (Scheme 2). A similar C6-C7 dissection has already been employed by Schinzer et al.[4] Nicolaou et al.[5] and Mulzer et al.[6] in their retrosynthetic analysis of epothilons.



Epothilones A: R = H, B: R = Me.

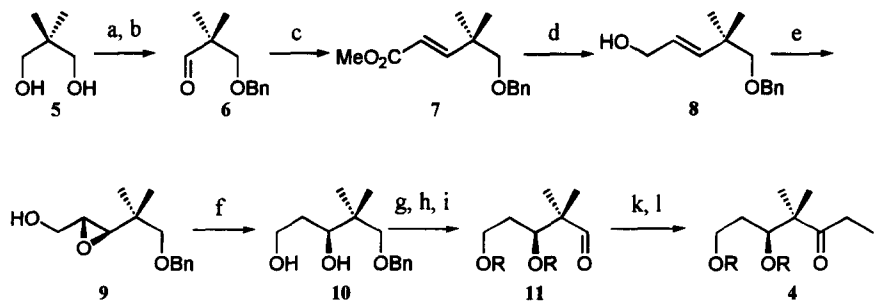
Scheme 1

Gennari, Paterson et al.[7] demonstrated that aldol reactions of *Z*-enolates with aldehyde **3** generate the desired 6,7-*syn*-7,8-*anti* configuration in the major product. However, the influence of the asymmetric center at C3 on the stereochemistry of the aldol reaction was difficult to assess. In this aldol reaction the conformation of the enolate or a Cram chelation-controlled transition state could establish the desired stereochemistry. Nevertheless, we expected the enolate geometry to govern the stereochemistry of the aldol product. Fragment **4** was synthesized starting from diol **5** (Scheme 3).



Scheme 2

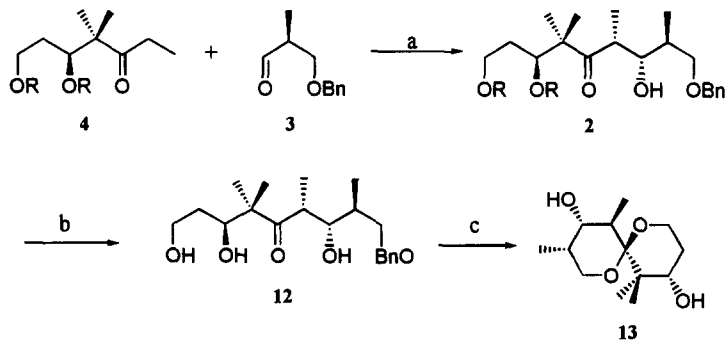
Benzylation followed by Swern oxidation generated aldehyde **6**. Wittig-Horner olefination and successive reduction with DIBAl-H gave allyl alcohol **8**, which was subjected to a Sharpless epoxidation to generate epoxide **9**.[8] Opening the epoxide with Red-Al gave the 1,3-diol,[9] which was used to determine the enantiomeric excess by ^{1}H NMR shift experiments with (+)Eu(hfc)$_3$[10] (93% ee). Protecting with TBSCl,[11] hydrogenation of the benzyl protecting group and Swern oxidation gave aldehyde **11**.[12] Addition of EtMgBr followed by oxidation yields building block **4** (Scheme 3).



Scheme 3. a) BnCl, KO*t*-Bu, dioxane, 2 h, 90 °C, 91 %; b) Swern ox., 1 h, -78 °C → 0 °C, 93 %; c) $(EtO)_2P(O)CH_2CO_2Et$, NaH, toluene/THF, 1 h, 0 °C → RT, 93 %; d) DIBAl-H, Et_2O, 3 h, -78 °C → RT, 99 %; e) Sharpless: MS 4 Å, $Ti(OiPr)_4$, (-)-diethyl tartrate, *t*BuOOH, CH_2Cl_2, -40 °C → RT, 96 %; f) Red-Al, THF, 1 h, 0 °C, 96 %; g) TBDMSCl, imidazole, DMF, 44 h, 60 °C, 98 %; h) H_2, 10 % Pd/C, EtOH, 48 h, RT, 80 %; i) Swern ox., 1 h, -78 °C → 0 °C, 97 %; k) EtMgBr, THF, 0 °C, 15 min, 82 %; l) Jones ox. 0°C, 10 min, 80 %.

Aldehyde **3** was synthesized according to literature procedure,[13] starting from (S)-(+)-3-hydroxy-2-methyl propionic acid methyl ester by protecting the alcohol as the benzyl ether followed by a reduction / oxidation

sequence. The aldol reaction was performed by reacting the lithium enolate of ethyl ketone **4** with aldehyde **3** and only one aldol product was observed.[14] X-ray crystallography was applied to determine the configuration of the new asymmetric centers. Since none of the protected derivatives of **2** gave single crystals the TBS protective groups were removed by treatment with HF and the benzyl protective group was removed by hydrogenation with H_2 Pd/C. Under hydrogenation conditions triol **12** cyclized to spiro ketal **13**, of which a single-crystal X-ray structure[15] was obtained. (Scheme 4).



Scheme 4. Aldol reaction and synthesis of spiro ketal **13**: a) LDA, THF, 15 min, -78 °C, 64 %; b) HF (48 %), MeCN, 3 h, RT, 69 %; c) H_2, Pd/C, 24 h, RT, 86 %.

Figure 1 shows the X-ray structure of spiro ketal **13**. We have thus demonstrated that the configuration of C3 can be incorporated in the ketone fragment of the epothilon precursor and that upon aldol reaction the C1-C9 segment can be generated with the desired stereochemistry.

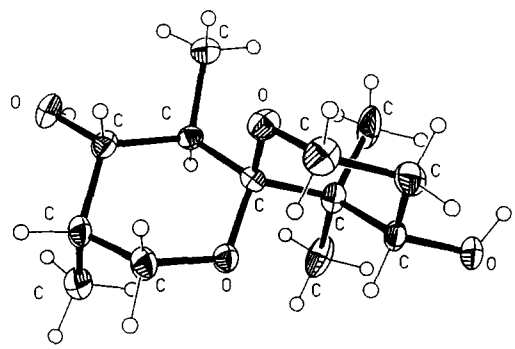


Figure 1. Molecular structure of compound **13**.

References and Notes

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10. (+)Eu(hfc)$_3$: tris[3-(heptafluoropropyl)hydroxymethylene-(+)-camphorato]europium (III).
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14. IR (Film): ν = 3028, 2956, 2928, 2856, 1684, 1472, 1256, 1100. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6 H, $SiMe_3$), 0.06 (s, 3 H, $SiMe_3$), 0.09 (s, 3 H, $SiMe_3$), 0.87 (s, 9 H, $C(CH_3)_3$), 0.88 (s, 9 H, $C(CH_3)_3$), 0.95 (d, 3 H, J = 6.8 Hz, $CHCH_3$), 1.04 (d, 3 H, J = 6.8 Hz, $CHCH_3$), 1.07 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.42-1.67 (m, 2 H, -OCH-CH_2-CH_2O), 1.81-1.90 (m, 1 H, CH-CH_3), 3.21-3.28 (m, 1 H), 3.42-3.49 (m, 2 H), 3.49-3.61 (m, 2 H), 3.61-3.68 (m, 1 H), 3.88 (dd, 1 H, J = 2.7 Hz, J =7.5 Hz, -OCH-CH_2-CH_2O-), 4.5 (d, 1 H, J = 2.6, Ph-CH_2-O-), 4.52 (d, 1 H, J = 2.6, Ph-CH_2-O-), 7.20-7.33 (m, 5 H, arom.); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = -5.3 (+, $SiCH_3$), -4.1 (+, $SiCH_3$), -3.8 (+, $SiCH_3$), 9.7 (+, CH_3), 14.0 (+, CH_3); 18.2 (Cq, $C(CH_3)_3$), 20.3 (+, CH_3), 23.0 (+, CH_3), 25.9 (+, $C(CH_3)_3$), 26.0 (+, $C(CH_3)_3$), 36.3 (+), 37.8 (-), 41.5 (+), 53.9 (Cq), 60.4 (-), 72.7 (+), 72.9 (-), 73.2 (-), 74.1 (+), 127.4 (+), 127.5 (+), 128.2 (+), 128.3 (+), 128.8 (+), 138.6 (Cq), 221.6 (Cq, Keton).
15. Crystal data for **13**: $C_{13}H_{24}O_4$, CSD - 406240, orthorhombic, $P2_12_12_1$, T = -100 °C, a = 705.05 (12), b = 1147.2 (2), c = 1572.5 (2) pm, Z = 4, D_C = 1.276 Mg/m^3, λ = 71.073 pm, μ = 0.093 mm^{-1}, crystal size 0.4 x 0.35 x 0.3 mm, θ range for data collection = 3.14 to 27.50 °, reflections collected 1908, independent 1896, data / restraints / parameters 1896 / 155 / 160, wR(F2) = 0.082, R(F) = 0.041, goodness-of-fit on F^2 = 0.898, largest diff. peak and hole 204 and -176 e.nm^{-3}. Other details can be obtained from the Fachinformationszentrum Karlsruhe, 76344 Eggenstein-Leopoldshafen, Germany. Any request for material should quote a full literature citation and the reference number CSD 406240. The absolute configuration could not be crystallographically established.

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