Chiral Synthesis of the C_3-$_{13}$ Segment of Epothilone A

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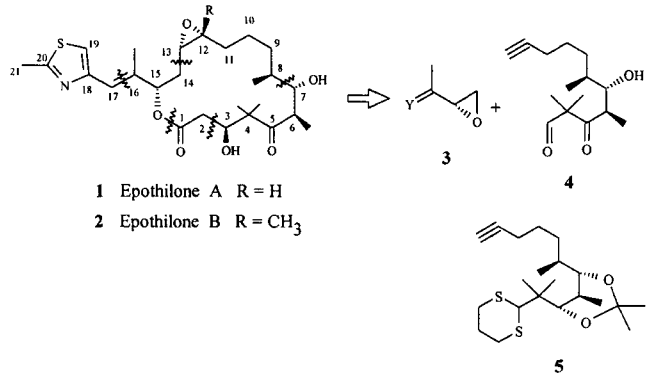
Received 18 September 1997

Abstract: Synthesis of the title compound using inexpensive geraniol as starting material in 13 steps and in 10.6% overal yield is described.

Epothilone A and B are a new class of macrolides, which possess striking biological activities.[1] Most importantly, Merk scientists discovered that epothilones have all the biological effects of taxol with the same mechanism of action and a much greater toxicity against p-glycoprotein-expressing multiple drug resistant cells.[2] But the structure is totally different from the taxol.

Epothilones are first isolated by Höfle's group from myxobacteria *sorangium celulosum*.[1] Due to their very interesting biological activities and new structure, these biological analogues of taxol immediately attracted much attention from chemists and biologists. Several groups have reported their approach to the epothilones.[3-8] Herein we report our preliminary result for epothilone A synthesis.

Retrosynthetic analysis was shown in **scheme 1**.



1 Epothilone A R = H

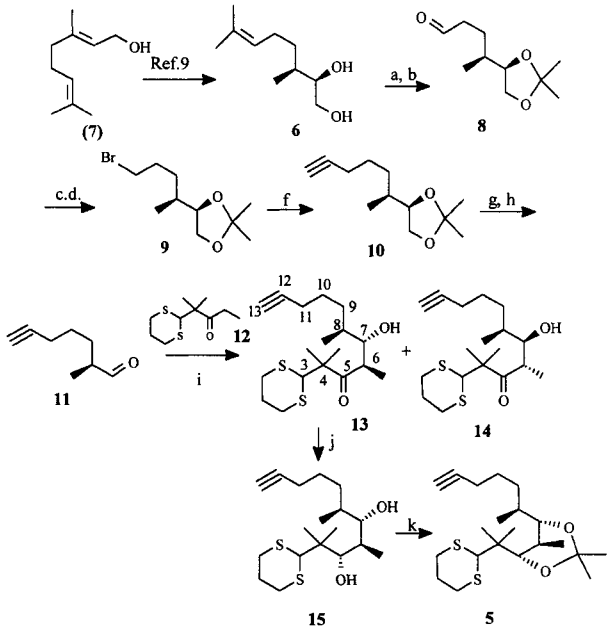
2 Epothilone B R = CH_3

Scheme 1

This strategy is different from all reported so far in literature for introduction of the desired *cis* double bond at $C_{12\text{-}13}$. Major point for this strategy is to synthesize the related compound (**5**), which is suitable for coupling with other segments by acetylide reaction.

Synthesis of the fragment (**5**) began with compound (**6**), which can be obtained by known procedure from inexpensive geraniol (**7**) in 76% yields by two steps.[9] Protection of the diol (**6**) with acetonide followed by cleavage of the double bond with ozone gave an aldehyde (**8**).[10] With the common reactions, the aldehyde (**8**) was converted into bromide (**9**), which alkylated monosodium acetylide [11] to give compound (**10**). At this stage, we decided to connect compound (**10**) with the ketone (**12**)† for introduction of necessary two chiral centers at the C_6 and C_7. Deprotection of the compound (**10**), followed by cleavage of the resulted diol produced an aldehyde (**11**), which without purification, underwent aldol condensation with the enolate of ketone (**12**) to afford the desired compound (**13**) and isomer (**14**) in the ratio of 2.5:1. ^{1}H n.m.r. spectrum of compounds (**13**)‡ and (**14**)§ were well distinguished and the major one was assigned to be (**13**),[12] which has all carbons of the $C_{3\text{-}13}$ segment and two different functional groups at two ends for further coupling with other fragments. Compound (**13**) was converted into compound (**5**) by reduction and protection.

Thus an efficient synthesis of the $C_{3\text{-}13}$ segment (**5**) of epothilone A using geraniol as starting material has been achieved, and preparation of other fragments as well as coupling them for epothilone A synthesis are in progress.



Scheme 2. *Reagents and conditions*: a, 2, 2-dimethoxypropane (3.1eq.), H_2SO_4(c) (cat.), acetone, 0°C→r.t., 0.5h, 81.5%; b, O_3, CH_2Cl_2, -78°C, 45 min, then Me_2S (3eq.) -78°C →r.t. overnight, 92%; c, $LiAlH_4$ (0.5eq.), Et_2O, 0 °C, 35 min, 100%; d, TsCl (1.1eq.), Pyr., -10 °C→ r.t., 6h; e, LiBr (2eq.), acetone, reflux, 45 min, 83.1% two steps; f, Na (1.5eq.), acetylene, liquid ammonium, -40 °C →-30 °C, 2h, 68%; g, HOAc-H_2O (4:1), 80°C, 1h, 100%; h, H_5IO_6 (1.2eq.), Et_2O, RT, 0.5h, 81%; i, LAD (3eq.), (**12**) (1.5eq.), THF, -78°C →-38°C, 50 min, then (**11**) in THF, -78°C, 30 min, (**13**) (62.5%), (**14**) (25.1%); j, $LiBH_4$ (3eq.), Et_2O, -45°C →-35°C, 3.5h, 90%; k, TsOH (0.2eq.), 2, 2-dimethoxypropane (2.5eq.), DMF, r,t., 30h, 69.5%

References and Notes

† Preparation of (**12**): Boron trifluoride etherate (0.37ml, 3.0mmol) and 1,3-propanedithiol (6ml, 59.88mmol) were added accordingly to the solution of 2, 2-dimethyl-3-keto pentaldehyde (2.664g, 20.8mmol) in 60ml of dry dichloromethane, and the reaction mixture was stirred at room temperature for 36 hours, then was concentrated on rotatory evaporator, and purified through flash colunm chromatography to afford (**12**) 4.122g (91%). m.p.: 65.5 -66.0 °C; ^{1}H n.m.r. (90MHz, $CDCl_3$): δ 4.36 (s, 1H), 3.02-2.75 (m, 4H), 2.48 (q, J = 7.5Hz, 2H), 2.18-1.76(m, 2H), 1.24 (s, 6H), 1.02 (t, J = 7.5Hz, 3H); m/z 218 (M^+, 3.19), 189 (1.00), 161 (18.46), 119 (100.00); i.r. (KBr): 1699, 1462, 1422, 1279, 1095, 910, 775; elemental analysis: calcd C 55.03 H 8.32, found C 55.06 H 8.42.

‡ (**13**): R_f = 0.35, petroleum ether : ethyl acetate = 86:14; oil; $[\alpha]_D^{20}$ -17.97° (c=4.52, $CHCl_3$); ^{1}H n.m.r. (300MHz, C_6D_6): δ 4.47 (d, 1H, J = 2.30Hz, 3-H), 3.66 (dd, 1H, J= 8.88 and 1.64Hz, 7-H), 3.20-3.35 (brs, 1H, OH), 3.10-3.18 (m, 1H, 6-H), 2.30-2.51 (m, 4H, 1'-S-CH_2), 2.08 (dd, 2H, J= 7.14 and 2.69Hz, 11-H), 1.88 (d, 1H, J= 2.68Hz, 13-H), 1.25-1.70 (m, 13H, singlets at 1.34, 1.33, 3H each), 1.15 (d, 3H, J= 6.81Hz, 6-CH_3), 0.75 (d, 3H, J= 6.73Hz, 8-CH_3); m/z 342 (M^+, 3.60), 253 (0.64), 247 (0.41), 235 (1.74), 217 (2.21), 181 (0.58), 161 (35.90), 119 (100.00); i.r. (film): 3506, 3300, 1736, 1688, 1463, 1243, 1020, 993; HRMS: calcd 342.1687, found 342.1695.

[§](**14**): R_f = 0.30, petroleum ether : ethyl acetate = 86:14; oil; $[\alpha]_D^{20}$ +6.00° (c=4.30, $CHCl_3$); ^1H n.m.r. (300MHz, C_6D_6): δ 4.56 (s, 1H, 3-H), 3.80 (dd, 1H, J= 7.67 and 2.87Hz, 7-H), 3.18-3.28 (m, 1H, 6-H), 2.70-3.00 (brs, 1H, OH), 2.30-2.52 (m, 4H, 1'-S-CH_2), 1.96-2.02 (m, 2H, 11-H), 1.87 (t, 1H, J= 2.69Hz, 13-H), 1.30-1.70 (m, 13H, singlets at 1.40, 1.35, 3H each), 1.14 (d, 3H, J=7.00Hz, 6-CH_3), 1.10 (d, 3H, J=6.59Hz, 8-CH_3); m/z 342 (M^+, 2.62), 325 (1.13), 247 (0.45), 235 (2.84), 217 (2.38), 181 (0.66), 161 (34.00), 119 (100.00); i.r. (film): 3503, 3301, 1736, 1693, 1463, 1423, 1370, 1243, 981; HRMS: calcd 342.1687, found 342.1658.

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12 The assignment using NOSEY and NOE techniques will be published elsewhere.