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Synthesis of the C(11)-C(20) Segment of the Cytotoxic Macrolide Epothilone B

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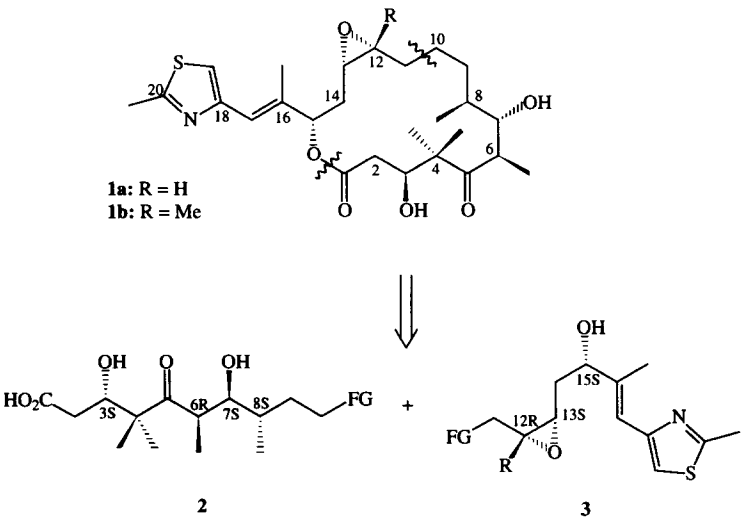
Abstract: Compound **11**, representing the C(11)-C(20) segment of the macrolide epothilone B (**1b**) has been prepared using two Wittig reactions and a Sharpless asymmetric epoxidation as the key steps.

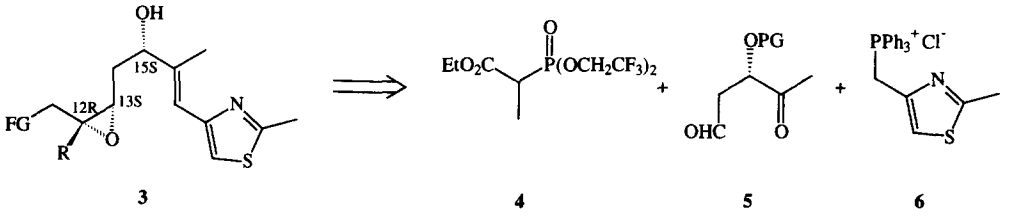
The epothilones A (**1a**) and B (**1b**), a new class of macrocyclic lactones with a taxol-like mitose inhibition, were recently isolated by Höfle and co-workers[1] and emerged as extremely promising anti-tumor agents, comparable with paclitaxel[2] (Scheme 1).

Although results of *in vivo* studies have not yet been published, it has been suggested that the epothilones offer some advantages over paclitaxel in terms of ease of formulation and potency toward multiple drug resistant cell lines.[3] The exceptional pharmacological potential of the macrolides has stimulated intensive synthetic effort,[4] which unleashed a surge of total syntheses of epothilone A.[5-7,8b] Epothilone B, which on the basis of early SAR results from natural epothilones, as well as from modified derivatives is seemingly the most active compound,[5b,8] has been synthesized very recently.[8]



Scheme 1

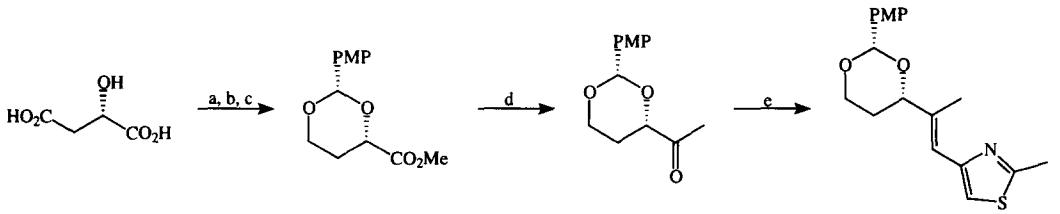
As suggested previously, the macrolide is disconnected into two fragments **2** and **3** of approximately equal complexity.[9] This modular strategy provides convergency in the synthesis and facilitates the preparation of epothilone analogues. Being fully aware of the extremely competitive situation in this area, we report on our synthesis of the fragment **3** of epothilone B, which in contrast to the existing syntheses of epothilone A and B, already contains the stereogenic centers of the epoxy unit before the connecting steps. Key steps in the synthesis of **3** are two stereoselective Wittig reactions and an asymmetric Sharpless epoxidation (Scheme 2).



3 **4** **5** **6**

Scheme 2

(S)-malic acid was transformed in one-pot fashion via the 1-methyl ester and (S)-(−)-methyl 2,4-dihydroxybutyrate[10] into the *p*-methoxybenzylidene acetal **7** (53% yield for the three steps). Addition of methyllithium furnished the methyl ketone **8** in 86% yield. Thiazolylmethyl-phosphonium salt **6**, which was easily accessible from 1,3-dichloropropanone in two steps (85% yield), was treated with **8** to give a mixture of olefination products (*E*/*Z* = 3.6:1), from which the *E*-isomer was simply separated by flash chromatography in 74% yield (Scheme 3). This result is comparable with the yields reported for the highly (*E*)-stereoselective olefination reactions with the corresponding thiazolylphosphonate[7] and -diphenylphosphine oxide.[11]



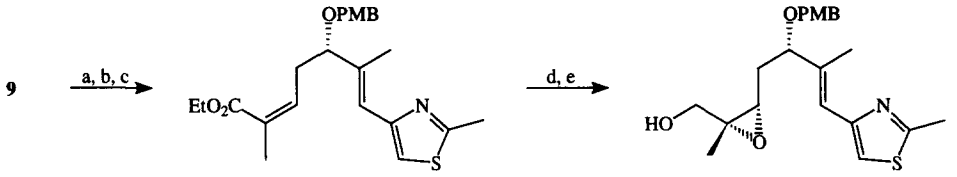
7 **8** **9**

Scheme 3

Reagents and conditions: a) TFAA, MeOH; b) BH_3·THF; c) *p*-$MeOC_6H_4CH(OMe)_2$, CSA, toluene, reflux, 6 h (53% for the three steps); d) 1 eq MeLi, THF, 2 h, -100°C (86%); e) **6**, NaHMDS, -78°C, then **8**, → 40°C, 1 h, THF (95%, *Z*/*E* = 3.6:1).

Regioselective deprotection of the terminal hydroxy group in **9** afforded the desired regioisomer in 76% yield. Swern oxidation[12] to the corresponding aldehyde, immediately followed by Wadsworth-Horner-Emmons condensation with ethyl 2-[bis(trifluoroethyl)phosphono]propionate (**4**) under Still's conditions[13]

provided the α,β-unsaturated esters (*Z*/*E* = 15:1), from which the *Z*-isomer **10** was separated in 80% yield.[14] Reduction of **10** to the (*Z*)-allylic alcohol (73% yield) and subsequent Sharpless epoxidation with the D-(−)-tartrate reagent finally delivered the epoxy alcohol **11** in 85% yield[15] (Scheme 4).



10 **11**

Scheme 4

Reagents and conditions: a) 4 eq DIBAH, CH_2Cl_2, 4 h, -20°C (89%, 5.6:1 for the desired regioisomer); b) Swern ox., 1 h, -78°C → 0°C. c) **4**, KHMDS, 18-C-6, -78°C, THF, 1 h (86% for the two steps, *Z*/*E* = 15:1); d) 3 eq DIBAH, 3h, -20°C, THF (73%); e) 4Å molecular sieve, $Ti(OiPr)_4$, D-(−)-diisopropyl tartrate, *t*BuOOH, CH_2Cl_2, 3 d, -30°C (95%, 8.5:1 for **11**).

In conclusion, the synthesis of the C(11)-C(20) fragment **3** of epothilone B, in the form of its protected derivative **11**, was achieved in 10 steps from (S)-malic acid in 13% overall yield.[16] Despite the repeated formation of stereoisomeric mixtures, large quantities of the desired compound can be prepared.

ACKNOWLEDGEMENT

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16. [2'*S*,4'*S*,1*E*]-4-[2-(4-Methoxyphenyl-1,3-dioxan-4-yl)-1-propenyl]-2-methylthiazole (**9**): ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.67 (dtd, $J_{5c,5a}$= 13.3 Hz, $J_{5e,6a}$= $J_{5e,4}$= 2.5 Hz, $J_{5e,6e}$= 1.5 Hz, 1H, 5'-H_e); 2.02 (mc, 1H, 5`-H_a); 2.10 (d, ^4J= 1.0 Hz, 3H, CH_3C=CH); 2.69 (s, 3H, 2-CH_3); 3.78 (s, 3H, OCH_3); 4.02 (td, $J_{6a,6e}\cong J_{6a,5a}\cong$ 11.5 Hz, $J_{6a,5e}$= 2.5 Hz, 1H, 6'-H_a); 4.29 (ddd, $J_{6e,6a}$= 11.5 Hz, $J_{6e,5a}$= 5.0 Hz, $J_{6e,5e}$= 1.5 Hz, 1H, 6'-H_e); 4.34 (mc, 1H, 4'-H); 5.56 (s, 1H, ArC*H*); 6.63 (mc, 1H, CH_3C=C*H*); 6.88 (mc, 2H, CH_{arom}); 6.97 (s, 1H, 5-H); 7.44 (mc, 2H, CH_{arom}); ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 15.1 (*C*H_3C=CH); 19.2 (2-CH_3); 30.2 (C-5'); 55.3 (OCH_3); 67.1 (C-6'); 81.7 (C-4'); 101.1 (Ar*C*H); 113.5 (*C*H_{arom}); 115.7 (C-5); 118.9 (CH_3C=*C*H); 127.5 (*C*H_{arom}); 131.3 (*i*-C); 139.1 (CH_3*C*=CH); 152.8 (C-4); 159.9 (CH_3O*C*); 164.4 (C-2); IR (film): 3105; 3057; 2959; 2925; 2850; 1658; 1614; 1517; 1463; 1442; 1429; 1394; 1371; 1302; 1248; 1215; 1172; 1152; 1118; 1096; 1062; 1034; 977; 830; MS (EI, 70 eV, 40°C): m/z= 331 (M^+, 40%); Anal. Calcd. for $C_{18}H_{21}NO_3S$: C, 65,23 %; H, 6,39 %; N, 4.22 %. Found: C, 65.37 %; H, 6.41 %; N, 4.40 %.

    [2*R*,3*S*,5*S*,6*E*]-2,6-Dimethyl-2,3-epoxy-5-(4-methoxyphenylmethyloxy)-7-(2-methylthiazol-4-yl)-6-hepten-1-ol (**11**): ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.40 (s, 3H, 2-CH_3); 1.76 (ddd, $J_{4a,4b}$= 14.3 Hz, $J_{4a,5}$= 10.8 Hz, $J_{4a,3}$= 9.9 Hz, 1H, 4-H_a); 2.01 (ddd, $J_{4b,4a}$ = 14.3 Hz, $J_{4b,3}$= 3.5 Hz, $J_{4b,5}$= 2.5 Hz, 1H, 4-H_b); 2.04 (d, ^4J= 1.0 Hz, 3H, 6-CH_3); 2.71 (s, 3H, 2'-CH_3); 2.76 (dd, $J_{3,4a}$= 9.9 Hz, $J_{3,4b}$= 3.5 Hz, 1H, 3-H); 3.29 (dd, $J_{OH,1b}$= 10.8 Hz, $J_{OH,1a}$= 2.0 Hz, 1H, exchange with D_2O, OH); 3.45 (dd, $J_{1a,1b}$=11.8 Hz, $J_{1a,OH}$= 2.0 Hz, 1H, 1-H_a); 3.61 (br t, $J_{1b,1a}\cong J_{1b,OH}$= 11.3 Hz, 1H, 1-H_b); 3.78 (s, 3H, OCH_3); 3.99 (dd, $J_{5,4a}$= 10.8 Hz, $J_{5,4b}$= 2.5 Hz, 1H, 5-H); 4.22 (d, *J*= 11.5 Hz, 1H, ArCH_a); 4.51 (d, *J*= 11.5 Hz, 1H, ArCH_b); 6.49 (mc, 1H, 7-H); 6.86 (mc, 2H, CH_{arom}); 7.00 (s, 1H, 5'-H); 7.22 (mc, 2H, CH_{arom}); ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 13.4 (6-CH_3); 19.2 (2'-CH_3); 20.4 (2-CH_3); 33.7 (C-4); 55.2 (OCH_3); 60.5 (C-2); 62.1 (C-3); 64.2 (C-1); 70.0 (ArCH_2); 81.3 (C-5); 113.9 (*C*H_{arom}); 116.4 (C-7); 121.7 (C-5'); 129.0 (*i*-C); 130.1 (*C*H_{arom}); 138.1 (C-6); 152.3 (C-4'); 159.5 (CH_3O*C*); 164.9 (C-2').

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