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Synthesis of the C^6–C^{21} fragment of epothilone analogues

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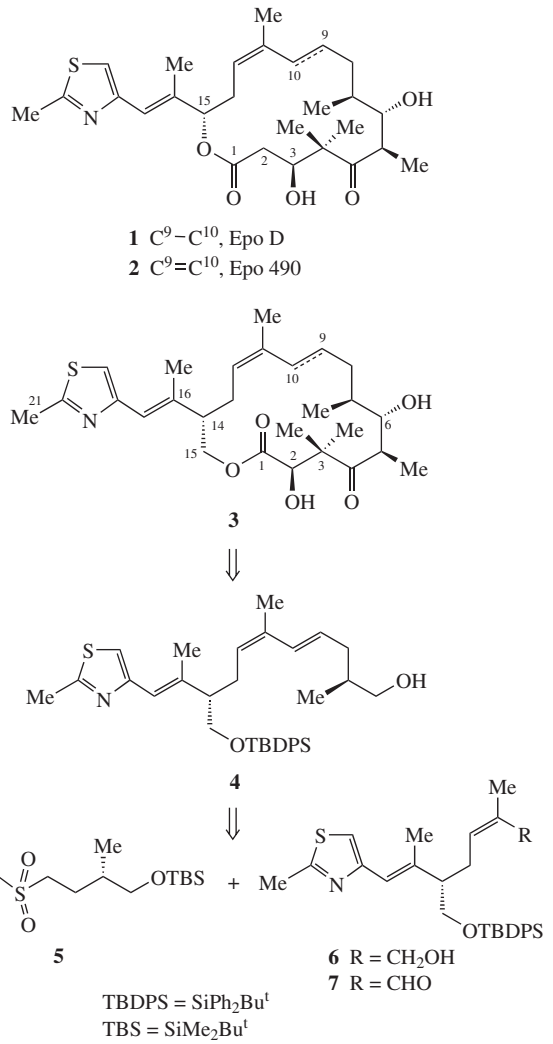
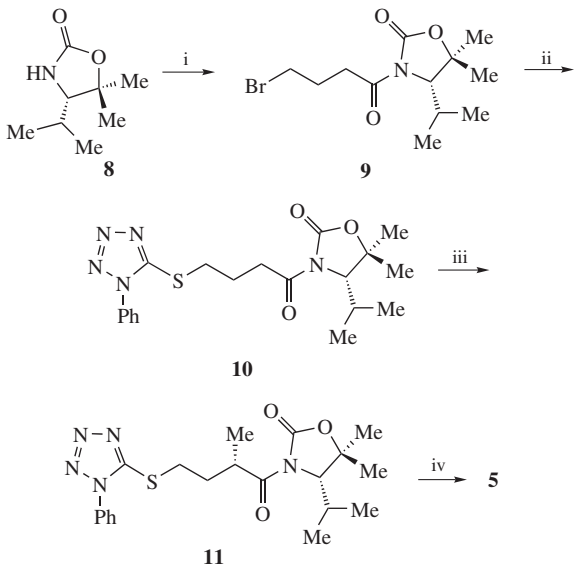
(2*S*,4*E*,6*Z*,9*S*,10*E*)-9-[*tert*-Butyl(diphenyl)silyloxymethyl]-2,6,10-trimethyl-11-(2-methylthiazol-4-yl)undeca-4,6,10-trien-1-ol, a key precursor for epothilone analogues, was prepared by multi-step synthesis using the Julia–Kocienski olefination at the key step.

Among microtubule stabilizing natural products (taxol, discodermolide, dictyostatin),[1–4] the sixteen-membered epothilones (Epo)[5] are one of the most prospective candidates for drug development (Scheme 1).[6,†] Many different epothilone analogues have been synthesized and studied,[6–9] thus providing a rather comprehensive understanding of the structure–activity relationship for epothilone class of compounds. We concentrated on the synthesis of a novel type epothilone structure **3** in which the methylene unit is isosterically displaced in the C^{15}–C^3 fragment.[10] Once we obtained the northern C^{10}–C^{21} fragment of an Epo analogue **6**,[10] we planned to synthesize the C^6–C^9 chiral block, which seemed promising to be coupled with C^{10}–C^{21} carbon chain. The Julia–Kocienski olefination[11] as the coupling strategy was chosen, therefore sulfone **5** was required. The chiral building block **4** can be used in the total synthesis of an Epo D analogue **1** since the selective C^9–C^{10} double bond reduction in unsaturated analogue Epo 490 **2**[12] is possible.[12]



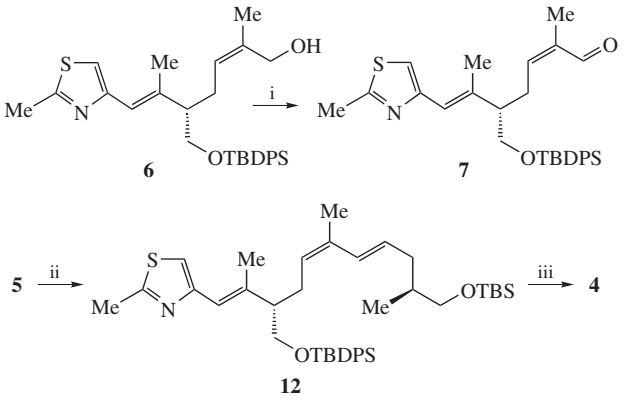
Scheme 1

4-Bromobutyryl chloride was used as a starting compound for the synthesis of compound **5** (Scheme 2).† To introduce the chiral center in the target molecule, the Evans asymmetric alkylation[13] was chosen. The chiral auxiliary **8** was prepared from L-valine as described.[14] 4-Bromobutyryl chloride reacted with lithium derivative of **8** giving bromo amide **9**. Subsequent substitution of bromine by the action of 1-phenyl-1*H*-tetrazole-5-thiol in the presence of Na_2CO_3 resulted in sulfide **10**. Methylation of the sodium enolate of **10** with MeI at –78 °C furnished a mixture of diastereomers in a ratio of 1:10 (according to ^{1}H NMR) with the predominance of the (*S*)-isomer **11**. Reduction of **11** with $LiAlH_4$ provided an inseparable mixture of products (by TLC analysis) which was subjected to oxidation with H_2O_2 in the



Scheme 2 *Reagents and conditions*: i, BuLi, –80 °C, 40 min, then $Br(CH_2)_3C(O)Cl$, –80 °C, 2 h, 84%; ii, 1-phenyl-1*H*-tetrazole-5-thiol, Na_2CO_3, acetone, room temperature, 12 h, 88%; iii, $NaN(SiMe_3)_2$ (NaHMDS), –78 °C, 1 h, then MeI, –70 °C for 2 h, 85%; iv, $LiAlH_4$, THF, 5 °C, 30 min, room temperature, 1 h, then $(NH_4)_6Mo_7O_{24}\cdot4H_2O$, 30% aqueous H_2O_2, EtOH, room temperature, 12 h, then Bu^tSiMe_2Cl (TBSCl), imidazole, DMAP, CH_2Cl_2, room temperature, 8 h (65% yield for 3 steps).

† For experimental details and characteristics of compounds obtained, see Online Supplementary Materials.



Scheme 3 *Reagents and conditions*: i, 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO), $PhI(OAc)_2$, CH_2Cl_2, room temperature, 6 h, 93%; ii, KHMDS, –78 °C for 20 min, then **7**, –78 °C, 30 min, 86%; iii, *p*-TSA, MeOH–CH_2Cl_2 (1:1), 15 °C, 12 h, 95%.

presence of ammonium heptamolybdate in EtOH.[15] After standard workup the crude product was treated with TBSCl followed by the separation of the resulting sulfone **5** and recovered oxazolidinone **8** using column chromatography.

The careful oxidation of thiazole-containing alcohol **6** was achieved under mild conditions by the action of $PhI(OAc)_2$ under TEMPO catalysis (Scheme 3).† The coupling **5** + **7** was accomplished using the Julia–Kocienski method. The coupling proceeds rapidly affording *E*-isomer **12** exclusively (^{1}H NMR, $J_{C^9H–C^{10}H}$ 15.6 Hz). Upon analysis of the ^{1}H and ^{13}C NMR spectra of **12**,‡ none of the other isomers was detected.

Finally, the selective hydrolysis of the TBS-protecting group in **12** has been achieved in MeOH–CH_2Cl_2 solution under *p*-TSA catalysis. Thus, the synthesized C^6–C^{21} fragment as monoprotected diol **4** ‡ can be used for the further selective transformations.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2014.11.022.

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‡ *4-{(1*E*,3*S*,5*Z*,7*E*,10*S*)-11-[*tert*-Butyl(dimethyl)silyloxy]-3-[*tert*-butyl(diphenyl)silyloxymethyl]-2,6,10-trimethylundeca-1,5,7-trien-1-yl}-2-methyl-1,3-thiazole* **12**. 1.5 M solution of KHMDS in THF (1.1 ml, 1.65 mmol) was added to a stirred solution of sulfone **5** (0.34 g, 0.83 mmol) in dry THF (15 ml) under Ar at –78 °C. After stirring this mixture for 20 min, aldehyde **7** (0.32 g, 0.63 mmol) was added *via* cannula as a solution in THF (5 ml). The mixture was stirred for 30 min at –78 °C, then the cooling bath was removed, and the mixture was allowed to warm to room temperature. A saturated aqueous solution of NH_4Cl (20 ml) was added, the layers were separated, the aqueous one was extracted with ethyl acetate (3×20 ml), the combined organic phase was dried over $MgSO_4$, filtered and evaporated. Purification of the residue by column chromatography (9% ethyl acetate–light petroleum) afforded **12** (0.38 g, 86%) as a colourless liquid. R_f (20% ethyl acetate–light petroleum) 0.62; $[\alpha]_D^{20}$ –1.3 (*c* 1.53, CH_2Cl_2). IR (Nujol mull, ν_{max}/cm^{-1}): 3428, 2956, 2929, 2857, 1462, 1112, 837, 702, 505. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.04 (s, 6H), 0.87 (d, 3H, *J* 7.0 Hz), 0.90 (s, 9H), 1.04 (s, 9H), 1.72–1.74 (m, 1H), 1.76 (s, 3H), 1.89–1.90 (m, 1H), 1.91 (s, 3H), 2.23–2.64 (m, 4H), 2.70 (s, 3H), 3.41–3.43 (m, 2H), 3.67–3.72 (m, 2H), 5.20 (t, 1H, *J* 7.0 Hz), 5.57–5.68 (m, 1H), 6.35 (s, 1H), 6.45 (d, 1H, *J* 15.6 Hz), 6.83 (s, 1H), 7.33–7.40 (m, 6H), 7.65 (d, 4H, *J* 6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: –5.4, 14.2, 16.6, 18.3, 19.1, 19.2, 20.7, 26.0, 26.9, 27.5, 36.3, 37.0, 52.3, 66.1, 67.9, 114.5, 120.6, 126.3, 127.6, 128.5, 129.0, 129.5, 132.7, 133.8, 135.7, 141.0, 153.5, 164.1. MS (APCI), *m/z*: 721 (66), 704 (100), 689 (24, MH$^+$). Found (%): C, 71.28; H, 8.76; N, 1.89; S, 4.62. Calc. for $C_{41}H_{61}NO_2SSi_2$ (%): C, 71.56; H, 8.93; N, 2.04; S, 4.66.

*(2*S*,4*E*,6*Z*,9*S*,10*E*)-9-[*tert*-Butyl(diphenyl)silyloxymethyl]-2,6,10-trimethyl-11-(2-methyl-1,3-thiazol-4-yl)undeca-4,6,10-trien-1-ol* **4**. *p*-TSA (0.01 g, 0.08 mmol) was added to an ice-bath cooled solution of compound **12** (0.26 g, 0.38 mmol) in MeOH–CH_2Cl_2 (1:1, 20 ml). The mixture was stirred at 15 °C for 12 h, then it was quenched with solid $NaHCO_3$ and filtered. The filtrate was evaporated and the residue was purified by column chromatography (30% ethyl acetate–light petroleum) to provide **4** (0.21 g, 95%) as a light yellow oil. R_f (20% ethyl acetate–light petroleum) 0.21; $[\alpha]_D^{20}$ –0.7 (*c* 1.14, CH_2Cl_2). IR (Nujol mull, ν_{max}/cm^{-1}): 3374, 2956, 2929, 2857, 1428, 1112, 702, 505. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.92 (d, 3H, *J* 7.0 Hz), 1.05 (s, 9H), 1.72–1.73 (m, 1H), 1.76 (s, 3H), 1.91 (s, 3H), 1.98–2.05 (m, 1H), 2.19–2.31 (m, 2H), 2.40–2.59 (m, 2H), 2.71 (s, 3H), 3.41–3.51 (m, 2H), 3.65–3.73 (m, 2H), 5.22 (t, 1H, *J* 7.0 Hz), 5.63–5.68 (m, 1H), 6.34 (s, 1H), 6.48 (d, 1H, *J* 15.6 Hz), 6.84 (s, 1H), 7.35–7.41 (m, 6H), 7.65 (d, 4H, *J* 6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.7, 16.9, 19.1, 19.3, 20.7, 26.9, 27.6, 36.1, 37.0, 52.4, 66.1, 67.7, 114.5, 120.5, 126.8, 127.6, 128.3, 128.9, 129.6, 132.6, 133.8, 135.7, 141.1, 153.4, 164.2. MS (APCI), *m/z*: 575 (31, MH$^+$), 557 (100). Found (%): C, 73.20; H, 8.05; N, 2.36; S, 5.54. Calc. for $C_{35}H_{47}NO_2SSi$ (%): C, 73.25; H, 8.25; N, 2.44; S, 5.59.