

Synthesis of the C⁶–C²¹ fragment of epothilone analogues

Ruslan F. Valeev,* Radmir F. Bikzhanov and Mansur S. Miftakhov

Institute of Organic Chemistry, Ufa Scientific Centre of the Russian Academy of Sciences, 450054 Ufa, Russian Federation. Fax: +7 347 235 6066; e-mail: rusl0@yandex.ru

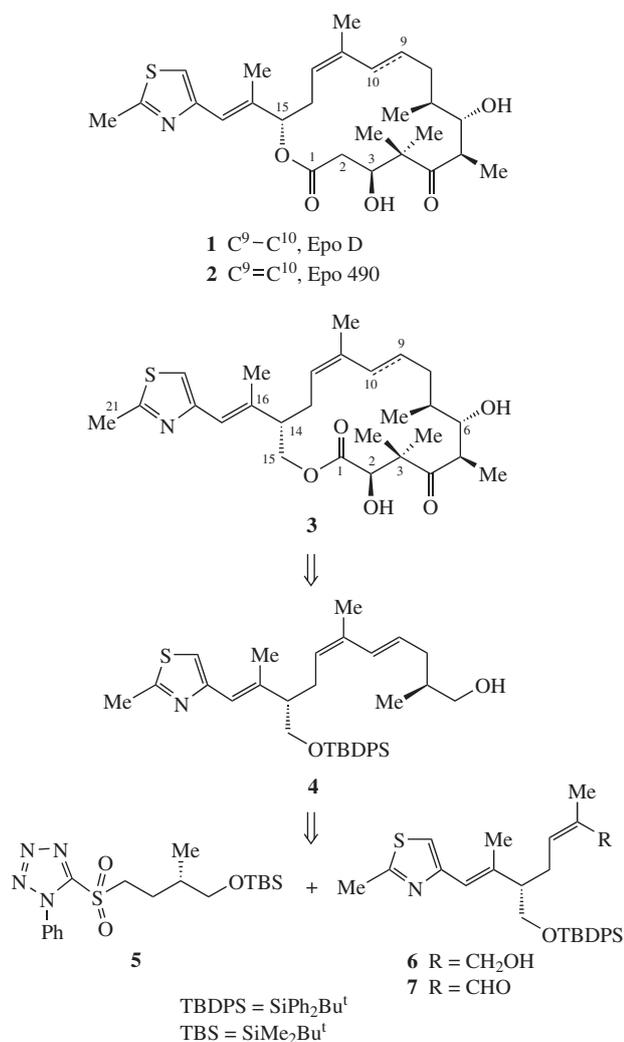
DOI: 10.1016/j.mencom.2014.11.022

(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.

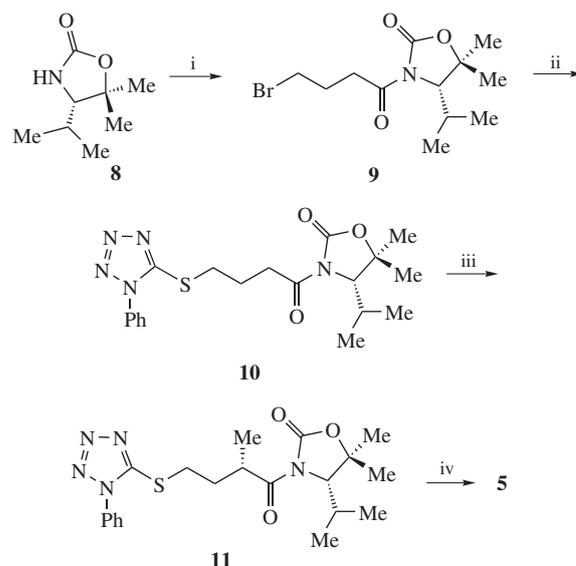
Among microtubule stabilizing natural products (taxol, discodermolide, dictyostatin),^{1–4} the sixteen-membered epothilones (Epo)⁵ are one of the most prospective candidates for drug development (Scheme 1).^{6,7} Many different epothilone analogues have been synthesized and studied,^{6–9} thus providing 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 C¹⁵–C³ fragment.¹⁰ Once we obtained the northern C¹⁰–C²¹ fragment of an Epo analogue **6**,¹⁰ we planned to synthesize the C⁶–C⁹ chiral block, which seemed promising to be coupled with C¹⁰–C²¹ carbon chain. The Julia–Kocienski olefination¹¹ 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 C⁹–C¹⁰ double bond reduction in unsaturated analogue Epo 490 **2**¹² is possible.¹²

4-Bromobutyl 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 alkylation¹³ was chosen. The chiral auxiliary **8** was prepared from L-valine as described.¹⁴ 4-Bromobutyl 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 Na₂CO₃ 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 ¹H NMR) with the predominance of the (*S*)-isomer **11**. Reduction of **11** with LiAlH₄ provided an inseparable mixture of products (by TLC analysis) which was subjected to oxidation with H₂O₂ in the

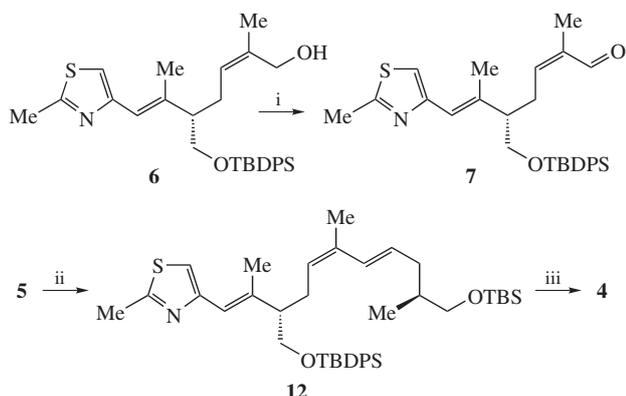


Scheme 1



Scheme 2 Reagents and conditions: i, BuLi, –80 °C, 40 min, then Br(CH₂)₃C(O)Cl, –80 °C, 2 h, 84%; ii, 1-phenyl-1*H*-tetrazole-5-thiol, Na₂CO₃, acetone, room temperature, 12 h, 88%; iii, NaN(SiMe₃)₂ (NaHMDS), –78 °C, 1 h, then MeI, –70 °C for 2 h, 85%; iv, LiAlH₄, THF, 5 °C, 30 min, room temperature, 1 h, then (NH₄)₆Mo₇O₂₄·4H₂O, 30% aqueous H₂O₂, EtOH, room temperature, 12 h, then Bu[†]SiMe₂Cl (TBSCl), imidazole, DMAP, CH₂Cl₂, 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), $\text{PhI}(\text{OAc})_2$, 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, $\text{MeOH}-\text{CH}_2\text{Cl}_2$ (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 $\text{PhI}(\text{OAc})_2$ 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 (^1H NMR, $J_{\text{C}^9\text{H}-\text{C}^{10}\text{H}}$ 15.6 Hz). Upon analysis of the ^1H 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 $\text{MeOH}-\text{CH}_2\text{Cl}_2$ 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.

References

- 1 D. G. I. Kingston, *Chem. Biol.*, 2004, **11**, 153.
- 2 F. Feyen, F. Cachoux, J. Gertsch, M. Wartmann and K.-H. Altmann, *Acc. Chem. Res.*, 2008, **41**, 21.
- 3 C. R. Harris and S. J. Danishefsky, *J. Org. Chem.*, 1999, **64**, 8434.
- 4 C. Monti, O. Sharon and C. Gennari, *Chem. Commun.*, 2007, 4271.
- 5 K. Gerth, N. Bedorf, G. Höfle, H. Irshik and H. Reichenbach, *J. Antibiotics*, 1996, **49**, 560.
- 6 J. Mulzer, K.-H. Altmann, G. Höfle, R. Müller and K. Prantz, *C. R. Chim.*, 2008, **11**, 1336.
- 7 A. Conlin, M. Fornier, C. Hudis, S. Kar and P. Kirkpatrick, *Nat. Rev. Drug Discov.*, 2007, **6**, 953.
- 8 F. Cachoux, T. Isarno, M. Wartmann and K. H. Altmann, *Angew. Chem. Int. Ed.*, 2005, **44**, 7469.
- 9 A. Rivkin, F. Yoshimura, A. E. Gabarda, T. C. Chou, H. J. Dong, W. P. Tong and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2003, **125**, 2899.
- 10 R. F. Valeev, R. F. Bikzhanov, N. Z. Yagafarov and M. S. Miftakhov, *Tetrahedron*, 2012, **68**, 6868.
- 11 P. R. Blakemore, W. J. Cole, P. J. Kocienski and A. Morley, *Synlett.*, 1998, **1**, 26.
- 12 K. Biswas, H. Lin, J. T. Njardarson, M. D. Chappell, T.-C. Chou, Y. Guan, W. P. Tong, L. He, S. B. Horwitz and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2002, **124**, 9825.
- 13 D. A. Evans, M. D. Ennis and D. J. Mathre, *J. Am. Chem. Soc.*, 1982, **104**, 1737.
- 14 S. D. Bull, S. G. Davies, S. Jones and H. J. Sangane, *J. Chem. Soc., Perkin Trans. 1*, 1999, 387.
- 15 B. M. Trost, D. Amans, W. M. Seganish and C. K. Chung, *J. Am. Chem. Soc.*, 2009, **131**, 17087.

[‡] 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-thiazol-4-yl]undeca-4,6,10-trien-1-ol **4**. 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, $\nu_{\text{max}}/\text{cm}^{-1}$): 3428, 2956, 2929, 2857, 1462, 1112, 837, 702, 505. ^1H 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 $\text{C}_{41}\text{H}_{61}\text{NO}_2\text{SSi}_2$ (%): C, 71.56; H, 8.93; N, 2.04; S, 4.66.

Received: 11th April 2014; Com. 14/4347

(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 $\text{MeOH}-\text{CH}_2\text{Cl}_2$ (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, $\nu_{\text{max}}/\text{cm}^{-1}$): 3374, 2956, 2929, 2857, 1428, 1112, 702, 505. ^1H 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 $\text{C}_{35}\text{H}_{47}\text{NO}_2\text{SSi}$ (%): C, 73.25; H, 8.25; N, 2.44; S, 5.59.