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Synthesis of the thiazole-containing C^{11}–C^{21}-block of a *gem*-dimethylcyclopropane derivative of epothilones

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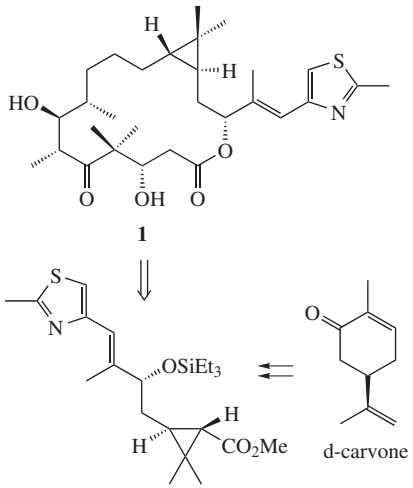
The synthesis of key chiral block for a *gem*-dimethylcyclopropane analogue of epothilones from *R*-carvone has been developed.

Currently, epothilones and, especially, their analogues are considered high-activity clinically acceptable anticancer drugs with Taxol-like (tubulin-polymerising) mechanism of action.[1–3] An extremely fruitful approach to epothilones modification involves isosteric replacement, in particular, replacement of the epoxy moiety, which is responsible for chemical lability and high toxicity, with a cyclopropane moiety.[4–10] We also intended to synthesize a new *gem*-dimethylcyclopropane analogue of epothilone A **1**. This paper describes the synthesis of a key precursor, namely, thiazole-containing segment **2**,† from d-carvone (Scheme 1) (*cf.* ref. 11).

Chlorocyclohexenone **3**, which is readily accessible from d-carvone,[12] was the starting compound. It is evident that functionalization of compound **3** enables chemo rational 'movement' towards block **2**. The dihydroxylation of the double bond of compound **3** *via* a ketodiol followed by its selective oxidative cleavage allows one to generate an α-ketol system suitable for olefination with a thiazole-containing phosphonate. Afterwards, a cyclopropane moiety in the products can be created by intramolecular 1,3-S_N2-replacement of chlorine with carboxyenolates in the Me_2Cl-containing centre (Scheme 2).



Scheme 1

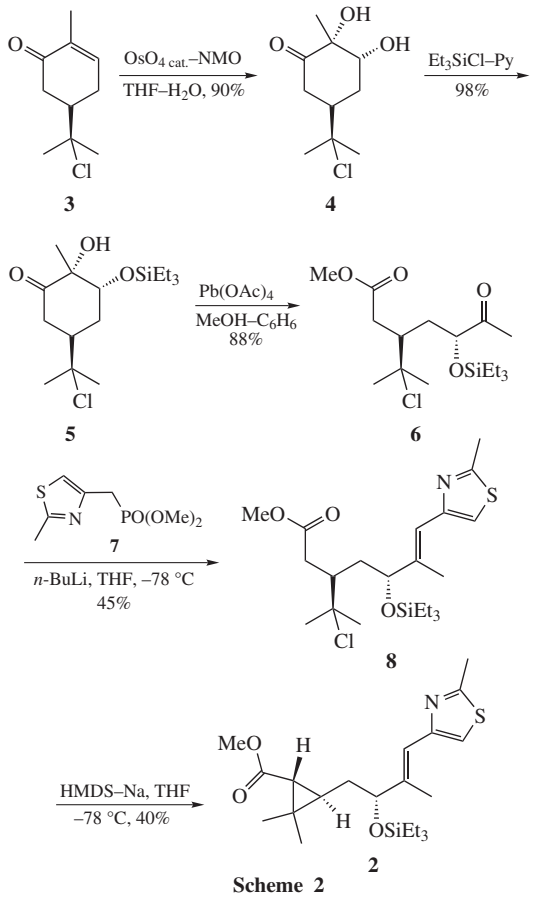
The above approach was implemented as follows: carvone derivative **3** was oxidized with the $OsO_{4\ cat.}$–NMO system[13] to give ketodiol **4**‡ and, subsequently, monosilyl derivative **5**.§ After that, ketol **5** was converted to methyl ester **6**¶ by treatment with lead tetraacetate in a benzene–methanol mixture.[14]

Condensation of **6** with the anion of phosphonate **7**[15] in THF at –78 °C gave olefin **8**,†† which underwent smooth intramolecular cyclization to target cyclopropane **2** upon deprotonation with sodium hexamethyldisilazide in THF at –78 °C.

† NMR spectra were recorded on a Bruker AM-300 spectrometer at 300 (^{1}H) and 75.47 MHz (^{13}C), using TMS as the internal standard. IR spectra were recorded on an IR Prestige-21 Fourier Transform Shimadzu spectrophotometer from samples prepared as thin films or dispersed in Nujol. Mass spectra were recorded on a Shimadzu LCMS-2010 spectrometer. Optical rotations were measured at 25 °C on a Perkin–Elmer 341 polarimeter. Commercial *R*-(–)-carvone (*ee* 98%, Aldrich), and synthesized[12] (5*R*)-5-(1-chloro-1-methylethyl)-2-methylcyclohex-2-en-1-one **3** with $[\alpha]_D^{20}$ –42.4 (*c* 1.1, $CHCl_3$) were used.

*Methyl (1*R*,3*R*)-2,2-dimethyl-3-{(2*R*,3*E*)-3-methyl-4-(2-methylthiazol-4-yl)-2-[(triethylsilyl)oxy]but-3-en-1-yl}cyclopropanecarboxylate* **2**. A 2 M solution of HMDS–Na in THF (0.06 ml, 0.12 mmol) was added dropwise at –78 °C to a solution of ester **8** (0.03 g, 0.065 mmol) in THF (2 ml) and the reaction mixture was stirred for 1.5 h at the same temperature. The mixture was warmed to room temperature and decomposed by adding a saturated NH_4Cl solution. THF was evaporated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried with $MgSO_4$ and the solvent was evaporated. The reaction product was purified by column chromatography on silica gel using EtOAc–light petroleum (1:9) as the eluent. Yield ~40%, colourless oil; $[\alpha]_D^{20}$ –165.0 (*c* 0.867, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.60 (q, 6H, CH_2Si, *J* 7.76 Hz), 0.95 (t, 9H, Me, *J* 7.76 Hz), 1.12 (s, 3H) and 1.19 (s, 3H, *gem*-Me), 1.45 (ddd, 1H, 3-CH, *J* 6.7, 6.5 and 7.0 Hz), 1.62 (ddd, 1H, 1′-CH_2, *J* 5.7, 7.0 and 14.0 Hz), 1.71 (d, 1H, 1-CH, *J* 7.0 Hz), 1.74 (ddd, 1H, 1′-CH_2, *J* 6.2, 6.5 and 14.0 Hz), 2.0 (s, 3H, Me), 2.71 (s, 3H, $Me_{thiazole}$), 3.61 (s, 3H, OMe), 4.18 (dd, 1H, OCH, *J* 6.2 and 5.7 Hz), 6.47 (s, 1H, =CH), 6.92 (s, 1H, $=CH_{thiazole}$). ^{13}C NMR, δ: 4.76 ($SiCH_2$), 6.87 (Me), 13.98 (Me), 19.20 ($Me_{thiazole}$), 20.79 and 21.51 (*gem*-Me), 27.32 (2-C), 30.53 (1-C), 32.49 (3-C), 35.84 (1′-C), 51.21 (OMe), 78.39 (2′-C), 115.09 ($=CH_{thiazole}$), 118.79 (4′-C), 141.99 (3′-C), 153.08 (4-$C_{thiazole}$), 164.29 (2-$C_{thiazole}$), 173.13 (CO_2Me). MS (CIAD), *m/z*: 424 $[MH]^+$, 292 $[MH – HOSiEt_3]^+$.

‡ *(2*R*,3*R*,5*R*)-5-(1-Chloro-1-methylethyl)-2,3-dihydroxy-2-methylcyclohexan-1-one* **4**. OsO_4 (1 mg) and then (15 min later) *N*-methylmorpholine *N*-oxide (NMO) (1.5 g, 11.11 mmol) were successively added with stirring to a solution of chloride **1** (1.0 g, 5.36 mmol) in an acetone–water mixture (4:1, 10 ml). The reaction mixture was stirred for 8 h; acetone was evaporated; saturated Na_2SO_3 solution was added to the residue, the mixture was stirred for 30 min, and reaction products were extracted with EtOAc, dried with $MgSO_4$, and concentrated. The solid residue was recrystallized from a light petroleum–ethyl acetate mixture (10:1). Yield 82% (0.97 g), white crystals, mp 96–97 °C. $[\alpha]_D^{20}$ +43.4 (*c* 1.335, $CHCl_3$). IR (ν/cm^{-1}): 3427, 2924, 2852, 1722, 1458, 1386, 1369, 1260, 1240, 1141, 1085, 1047, 883, 567. ^{1}H NMR ($CDCl_3$) δ: 1.47 (s, 3H, Me), 1.58 and 1.63 (2s, 6H, *gem*-Me), 2.03 (t, 1H, *J* 12.8 Hz) and 2.30 (m, 1H, 4-CH_2), 2.43 (m, 1H, 5-CH), 2.67–2.70 (m, 2H, 6-CH_2), 2.98 (br. s, 1H, OH), 4.07 (t, 1H, OCH, *J* 2.7 Hz), 4.21 (s, 1H, OH). ^{13}C NMR, δ: 23.08 (Me), 29.34 (4-C), 31.16 and 31.45 (*gem*-Me), 38.55 (6-C), 44.75 (5-C), 74.22 (C–Cl), 75.03 (3-C), 78.13 (2-C), 212.95 (C=O).



Scheme 2

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§ *(2*R*,3*R*,5*R*)-5-(1-Chloro-1-methylethyl)-2-hydroxy-2-methyl-3-[(triethylsilyl)oxy]cyclohexanone* **5**. Et_3SiCl (0.36 ml, 2.04 mmol) was added with stirring to a solution of diol **4** (0.3 g, 1.36 mmol) in pyridine (3 ml). The reaction mixture was stirred until the starting compound was consumed (~2 h, TLC monitoring). The solution was then concentrated and the residue was separated on a column with silica gel using EtOAc–light petroleum (1:5) as the eluent. Yield 98% (0.45 g), colourless oil. $[\alpha]_D^{20}$ –7.2 (*c* 1.55, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.56 (q, 6H, CH_2Si, *J* 7.96 Hz), 0.89 (t, 9H, Me, *J* 7.96 Hz), 1.36 (s, 3H, Me), 1.54 and 1.57 (2s, 2×3H, *gem*-Me), 2.03 (m, 2H, 4-CH_2), 2.36 (m, 1H, 5-CH), 2.60 (d, 1H, *J* 3.5 Hz) and 2.67 (d, 1H, 6-CH_2, *J* 13.9 Hz, ^2J 15.0 Hz), 3.51 (s, 1H, OH), 4.02 (t, 1H, OCH, *J* 2.9 Hz). ^{13}C NMR, δ: 4.70 ($SiCH_2$), 6.72 (Me), 22.52 (Me), 31.19 and 31.24 (*gem*-Me), 32.11 (4-C), 39.10 (6-C), 45.17 (5-C), 73.10 (C–Cl), 77.64 (3-C), 78.44 (2-C), 212.42 (C=O).

¶ *Methyl (3*R*,5*R*)-3-(1-chloro-1-methylethyl)-6-oxo-5-[(triethylsilyl)oxy]-heptanoate* **6**. Lead tetraacetate (3.46 g, 7.77 mmol) was added with stirring to a solution of compound **5** (0.65 g, 1.94 mmol) in a dry MeOH–benzene mixture (1:1, 20 ml). The reaction mixture was stirred for 15 min, then ethylene glycol (3–4 drops) and water (10 ml) were added and the mixture was stirred for another 10 min. The mixture was extracted with EtOAc; the combined organic extracts were dried with $MgSO_4$ and the solvent was evaporated. The product was purified by column chromatography on silica gel using EtOAc–light petroleum (1:5) as the eluent. Yield 88% (0.62 g), colourless oil. $[\alpha]_D^{20}$ +9.42 (*c* 3.81, $CHCl_3$). IR (ν/cm^{-1}): 2955, 2912, 2878, 1735, 1717, 1458, 1435, 1415, 1373, 1352, 1294, 1240, 1194, 1159, 1113, 1105, 1011, 978, 889, 826, 743, 729, 594, 571, 516. ^{1}H NMR ($CDCl_3$) δ: 0.58 (q, 6H, CH_2Si, *J* 7.76 Hz), 0.93 (t, 9H, Me, *J* 7.74 Hz), 1.48 (s, 3H) and 1.53 (s, 3H, *gem*-Me), 2.15 (s, 3H, 7-Me), 1.58 (dd, 1H, *J* 6.40 and 2.20 Hz) and 2.00 (ddd, 1H, 4-CH_2, *J* 2.20 and 6.40 Hz, ^2J 17.2 Hz), 2.24 (m, 1H, 3-CH), 2.36 (dd, 1H, *J* 4.76 and 15.93 Hz) and 2.60 (dd, 1H, 2-CH_2, J 6.41 and 15.92 Hz), 3.66 (s, 3H, OMe), 4.05 (dd, 1H, OCH, *J* 6.6 and 7.5 Hz). ^{13}C NMR, δ: 4.63 ($SiCH_2$), 6.71 (Me), 24.65 (7-Me), 30.11 and 30.91 (*gem*-Me), 36.55 (4-C), 36.78 (2-C), 43.22 (3-C), 51.77 (OMe), 73.93 (C–Cl), 77.89 (5-C), 173.11 (CO_2Me), 211.15 (C=O).

†† *Methyl (3*R*,5*R*,6*E*)-3-(1-chloro-1-methylethyl)-6-methyl-7-(2-methylthiazol-4-yl)-5-[(triethylsilyl)oxy]hept-6-enoate* **8**. A 3 N solution of *n*-BuLi in hexane (0.3 ml, 9.0 mmol) was added at –78 °C with stirring under argon to a solution of phosphonate **7** (0.09 g, 0.41 mmol) in dry THF (5 ml). The reaction mixture was stirred for 30 min, then a solution of ketone **6** (0.1 g, 0.27 mmol) in THF (5 ml) was added dropwise at –78 °C. The reaction mixture was warmed to room temperature and stirred for another 2 h. A saturated solution of NH_4Cl was added, THF was evaporated from the aqueous layer, the reaction products were extracted with EtOAc (3×10 ml), the combined extracts were dried with $MgSO_4$, and the solvent was evaporated. The product was purified in a column with SiO_2 using EtOAc–light petroleum (1:3) as the eluent. Yield 45% (0.03 g), colourless oil. $[\alpha]_D^{20}$ –13.3 (*c* 0.9, $CHCl_3$). IR (ν/cm^{-1}): 2953, 2912, 2875, 1732, 1458, 1436, 1414, 1361, 1238, 1165, 1112, 1076, 1004, 974, 844, 741, 729, 686. ^{1}H NMR ($CDCl_3$) δ: 0.59 (q, 6H, CH_2Si, *J* 7.76 Hz), 0.94 (t, 9H, Me, *J* 7.5 Hz), 1.51 (s, 3H) and 1.55 (s, 3H, *gem*-Me), 1.55–1.72 (overlapped m, 1H, 4-CH), 2.02 (s, 3H, 7-Me), 2.18–2.30 (m, 2H, 4-CH, 3-CH), 2.47 (dd, 1H, 2-CH_2, *J* 4.14 and 16.29 Hz) and 2.63 (dd, 1H, 2-CH_2, *J* 7.98 and 16.29 Hz), 2.71 (s, 3H, $Me_{thiazole}$), 3.66 (s, 3H, OMe), 4.24 (t, 1H, OCH, *J* 6.7 Hz), 6.47 (s, 1H, =CH), 6.96 (s, 1H, $=CH_{thiazole}$). ^{13}C NMR, δ: 4.74 ($SiCH_2$), 6.84 (Me), 13.36 (Me), 19.17 ($Me_{thiazole}$), 30.35 and 30.69 (*gem*-Me), 37.05 (4-C), 38.41 (2-C), 44.08 (3-C), 51.67 (OMe), 74.47 (C–Cl), 78.21 (5-C), 115.42 (7-C), 120.24 ($=CH_{thiazole}$), 141.19 (6-C), 152.89 (4-$C_{thiazole}$), 164.32 (2-$C_{thiazole}$), 173.42 (CO_2Me).