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Synthesis of the northern fragment of an epothilone D analogue from (−)-carvone

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ABSTRACT

A simple and effective synthesis of the chiral thiazole-containing fragment of an epothilone D analogue from (−)-carvone is described.

1. Introduction

Among microtubule stabilizing natural products (taxol, discodermolide, dictyostatin),[1–4] the epothilones (Epo)[5] are one of the most perspective candidates for a new antitumour agents. Six Epo derivatives are now at various stages of clinical assay,[6] including the Epo B lactam analogue ixabepilone,[7] which received FDA approval for the treatment of patients with locally advanced or metastatic breast cancer in 2007. The main shortcomings of the natural Epo for practical application are poor metabolic and chemical stability, toxicity and lipophilicity. The poor metabolic stability of Epo is expressed in a rapid in vivo lactone ring hydrolysis, the chemical instability is due to the epoxide-containing side chain (nucleophilic ring opening) and the 'southern' β-hydroxy ester fragment (dehydratation reactions and possible allylic ester transformations).

Accordingly, we concentrated on the synthesis of a novel Epo D lactam analogue **3**, in which the epoxide functional group is absent (toxicity reduction) and the methylene unit is isosterically displaced in the C^{15}–C^{3} fragment (chemical stabilization). Danishefsky and co-workers previously reported the synthesis of 12,13-desoxy analogue of **1**[8] and a lactam analogue **2**, which exhibited increased microtubulin stabilizing and advanced anticancer activity in comparison with natural Epo B **1**. Therefore, a new Epo derivative **3** is also of interest to SAR assay development.[9] This paper describes the synthesis of the thiazole-containing fragment **4** from the inexpensive natural terpene (−)-carvone **5** Scheme 1.

2. Results and discussion

(−)-Carvone is considered as a very convenient chiral starting compound for the synthesis of **4**. It has a trisubstituted *cis*-double bond, the correct stereochemistry at the chiral centre, the isopropylidene moiety as a methyl ketone equivalent and the keto group suitable for the chemoselective oxidative cleavage.

To transform (−)-carvone into α-hydroxy ketones **10a**,**b** suitable for the oxidative ring cleavage, Rubottom methodology was used (transformation of a ketone into an α-hydroxy ketone via silyl enol ether formation, followed by epoxidation and rearrangement).[10] α-Hydroxylation of ketones of the carvone series was reported previously.[11] The acetonide **7**, derived from epoxide **6**[12] was converted into TMS-enol ester **8** followed by m-CPBA oxidation, which yielded the TMS-protected α-hydroxy ketone **9**. Deprotection of the TMS–ether gave a mixture of isomeric hydroxy ketones **10a** and **10b** in a ratio of 10:1 (epimers at the hydroxyl-carrying centre). At the same time, the diastereomeric ratio (3:2) established during the formation of epoxide **6** was found to be unchanged by ^{13}C NMR spectroscopic analysis Scheme 2.

The mixture of **10a** and **10b** was then subjected to oxidative cleavage by the action of lead tetraacetate[13] in MeOH/C_6H_6 and the crude product was reduced using Luche conditions[14] ($NaBH_4$–$CeCl_3$). This reaction sequence gave the acetonide ester **12** in a good yield (88%). Acetonide ester deprotection followed by oxidative cleavage according to the procedure described above produced β-hydroxy ketone **14** Scheme 3.

The thiazole-containing phosphonium and phosphonate reagents **15a**–**c** were tested in the Wittig olefination reaction of

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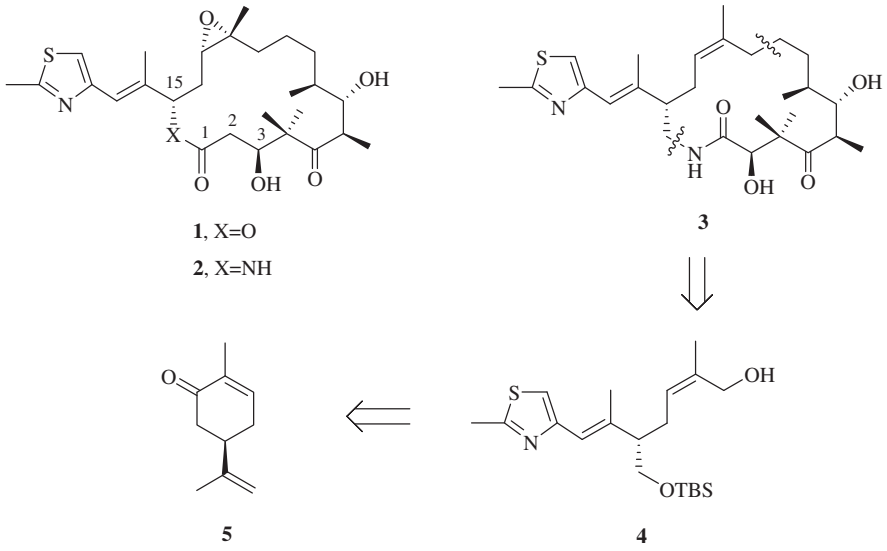


Scheme 1. Retrosynthetic analysis of the nothern fragment of the Epo D analogue **4**.

hydroxy ketone **14**. It was found that ylides **15a** and **15b** had low activity in the olefination reaction while **15c** smoothly reacted with ketone **14** producing the (*E*)-olefin[15] **16** in high yield. Subsequent hydroxyl protection and DIBAL-H reduction reactions afforded the target alcohol **4** Scheme 4 Table 1.

3. Conclusion

We have developed a synthesis of an Epo D analogue fragment from the known (−)-carvone. The prepared fragment will be used for the total synthesis of a novel Epo D analogue in our future investigations.

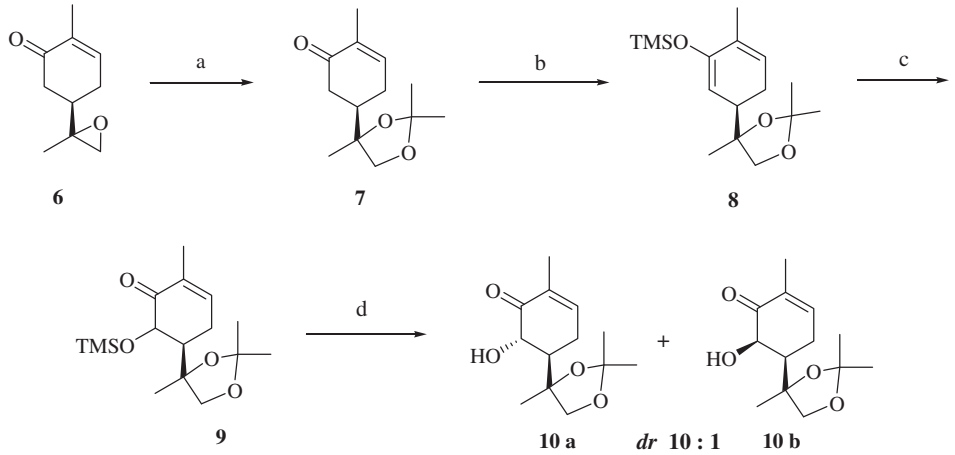
4. Experimental

4.1. General

Solvents were purified and dried before used by standard procedures. Reagents were generally the best quality commercial grade and used without further purification unless otherwise indicated. All reactions were carried in oven-dried glassware. TLC was performed using Sorbfil STC-1A 110 μm layer, silica gel 5–17 precoated foil plates. Column chromatography was carried out using 210–280 mesh silica gel. Optical rotations were measured using the sodium D line at 589 nm on a Perkin Elmer, Model 241 MC polarimeter. IR (infrared spectra) was recorded on a Shimadzu IRPrestige-21 spectrometer as a Nujol mull or as neat thin films on KBr plates. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker AM-300 (300 MHz for ^{1}H and 75.47 MHz for ^{13}C) as solutions in $CDCl_3$ (Aldrich Chemical Company; spectra grade). Mass spectra were recorded on Shimadzu LCMS QP-2010EV (APCI) spectrometer. Elemental analyses were carried on a Euro EA 3000 CHNS-analyzer.

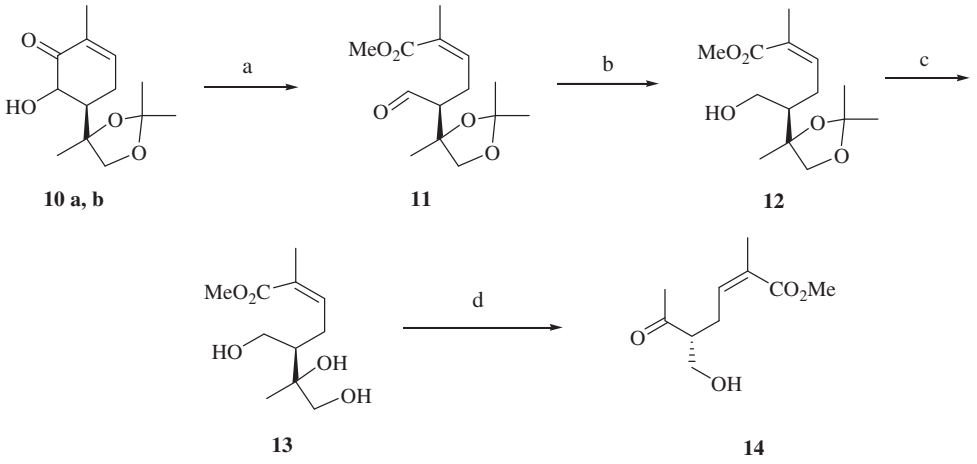
4.2. (5*R*,4′*RS*)-2-Methyl-5-(2′,2′4′-trimethyl-1′,3′-dioxolan-4′-yl)cyclohex-2-en-1-one (7)

To a stirred solution of **6**[12] (7.00 g, 42.2 mmol) in dry acetone (60 mL) was added $BF_3 \cdot Et_2O$ (9.53 g, 84.3 mmol) under Ar at room



a) $BF_3 \cdot OEt_2$, Me_2CO, rt, 1 h, 93%; b) LDA, TMSCl, THF, - 78 °C, 1 h, quant.; c) m-CPBA, 1 M aq. $NaHCO_3$, CH_2Cl_2, 10 °C, 2 h, 93%; d) TBAF, THF, 0-10 °C, 20 min, 83%.

Scheme 2. Synthesis of hydroxy ketones **10a**,**b** via the Rubottom reaction.



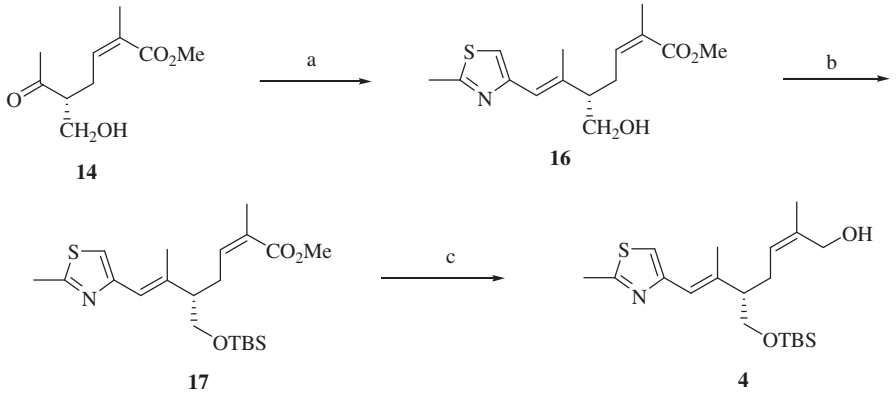
a) $Pb(OAc)_4$, MeOH-C_6H_6 (1:1), 0 °C to rt, 20 min, 92%; b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 5 °C to rt, 1 h, 96%; c) 1% aq. HCl, THF, 50 °C, 5 h, 85%; d) $Pb(OAc)_4$, MeOH-C_6H_6 (1:1), 0 °C to rt, 20 min, 96%.

Scheme 3. Oxidative cleavage of hydroxy ketones **10a,b** and synthesis of the desired compound **14**.

temperature. The reaction was monitored by TLC (20% ethyl acetate/petroleum ether) and after stirring for 1 h, $NaHCO_3$ was added following, which the solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (50 mL), washed with water (40 mL), dried over $MgSO_4$ and concentrated. Purification of the product by column chromatography (10% ethyl acetate/petroleum ether) afforded **7** (8.78 g, 93%, a mixture of diastereoisomers at $C^{4\prime}$ in a ratio of 3/2) as a light yellow oil; [Found: C, 69.4; H, 8.7. $C_{13}H_{20}O_3$ requires C, 69.64; H, 8.93%]; R_f (20% ethyl acetate/petroleum ether) 0.53; ν_{max} (Nujol mull) 2934, 2876, 1676, 1379, 1369, 1250, 1211, 1059, 733 cm^{-1}; δ_H (300 MHz, $CDCl_3/CHCl_3$): 1.27 (1.8H, s, C*Me*), 1.30 (1.2H, s, C*Me*), 1.38 (3H, s, OC*Me*), 1.41 (3H, s, OC*Me*), 1.79 (3H, s,=C*Me*), 2.18–2.26 (3H, m,=CHC*H*, CH_2CH, C*H*C=O), 2.44–2.66 (2H, m,=CHC*H*, C*H*C=O), 3.71 (0.4H, d, *J* 2.0 Hz, OC*H*), 3.73 (0.6H, d, *J* 2.0 Hz, OC*H*), 3.88–3.93 (1H, m, OC*H*), 6.73–6.75 (0.4H, m,=C*H*), 6.78–6.80 (0.6H, m,=C*H*); δ_C (75 MHz, $CDCl_3/CHCl_3$) 15.5, 21.8, 22.6, 26.5, 26.8, 27.2, 27.7, 39.4, 40.2, 43.3, 43.5, 72.1, 72.4, 81.6, 81.8, 109.3, 135.1, 135.3, 144.2, 144.8, 199.0, 199.6; *m*/*z* (APCI) 225 (18, MH^+), 167 (100), 149 (52%).

4.3. Trimethyl (3*R*,4′*RS*)-{[6-methyl-3-(2′,2′,4′-trimethyl-1′,3′-dioxolan-4′-yl)cyclohexa-1,5-dien-1-yl]oxy}silane (8)

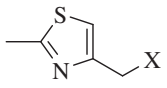
A solution of diisopropylamine (9.37 mL, 67.0 mmol) in tetrahydrofuran (40 mL) was cooled to −78 °C, a 2.0 M solution of n-butyllithium in hexane (33.5 mL, 67.0 mmol) was added dropwise under stirring, the mixture was stirred for 30 min at −10 °C and cooled to −78 °C, and a solution of compound **7** (7.50 g, 33.5 mmol) in tetrahydrofuran (10 mL) was added dropwise. The mixture was allowed to warm up to −40 °C, stirred for 40 min at that temperature, and cooled to −78 °C, chloro(trimethyl)silane (8.50 mL, 67.0 mmol) was added dropwise. The mixture was stirred for 1 h at −70 °C until the initial compound disappeared and was then treated with a saturated aqueous solution of sodium chloride. The organic phase was separated, the aqueous phase was extracted with methylene chloride (2×30 mL), and the extracts were combined with the organic phase, dried over $MgSO_4$, filtered, and evaporated to provide **8** (9.91 g, quant.) as a yellow oil. The product was used in the next step without chromatographic purification.



a) ***i.*** **15c**, NaHMDS, THF, - 78 °C, 1 h; ***ii***. **14**, - 78 to - 30 °C, 12 h, 86%; b) TBSCl, imidazole, DMAP, CH_2Cl_2, rt, 4 h, 96%; c) DIBAL-H, CH_2Cl_2, - 78 to - 30 °C, 1 h, 80%.

Scheme 4. Synthesis of the target compound **4**.

Table 1
The testing of thiazole-containing phosphonium and phosphoranium reagents **15a**–**c** in the Wittig olefination reaction of **14**



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Entry	X	Yield of **16**, %
a		20
b	$P^+Ph_3Cl^-$	53
c	$P^+Bu_3Cl^-$	86

4.4. (4′*RS*,5*R*,6*RS*)-2-Methyl-5-(2′,2′,4′-trimethyl-1′,3′-dioxolan-4′-yl)-6-[(trimethylsilyl)oxy]cyclohex-2-en-1-one (9)

Crude compound **8** (9.91 g, 33.5 mmol) was dissolved in methylene chloride (40 mL), a 1 M aqueous solution of $NaHCO_3$ (33 mL) was added, and 70% *m*-chloroperoxybenzoic acid (10.7 g, 43.5 mmol) was added in three portions (at 15-min intervals) under stirring at 10 °C. The mixture was stirred for 2 h at 10 °C then a saturated aqueous solution of $Na_2S_2O_3$ was added, the mixture was stirred for 15 min, and the organic phase was separated, washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered, and evaporated to provide **9** (9.71 g, 93%) as a yellow oil. The product was used in the next step without chromatographic purification.

*4.4.1. (5R,6S,4′RS)-6-Hydroxy-2-methyl-5-(2′,2′,4′-trimethyl-1′,3′-dioxolan-4′-yl)cyclohex-2-en-1-one (**10a**) (a mixture of diastereoisomers at $C^{4\prime}$ in a ratio of 3/2).* A solution of compound **9** (9.71 g, 31.1 mmol) in tetrahydrofuran (30 mL) was cooled to 0 °C, a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (31 mL, 31.1 mmol) was added dropwise under stirring, and the mixture was stirred for 20 min at 10 °C and treated with a saturated solution of sodium chloride. The organic phase was separated and the aqueous phase was extracted with methylene chloride (2×30 mL), the extracts were combined with the organic phase, dried over $MgSO_4$, filtered, and evaporated. Purification of the product by column chromatography (15% ethyl acetate/petroleum ether) afforded a mixture of **10a** and **10b** in a ratio of 10/1 (6.20 g, 83%) as a light yellow oil; [Found: C, 64.8; H, 8.2. $C_{13}H_{20}O_4$ requires C, 65.0; H, 8.33%]; R_f (20% ethyl acetate/petroleum ether) 0.19; ν_{max} (Nujol mull) 3468, 2982, 2934, 2884, 1678, 1377, 1254, 1213, 1055, 870 cm^{-1}; δ_H (300 MHz, $CDCl_3/CHCl_3$) 1.26 (1.2H, s, C*Me*), 1.29 (1.2H, s, OC*Me*), 1.33 (1.8H, s, C*Me*), 1.36 (1.2H, s, OC*Me*), 1.37 (1.8H, s, OC*Me*), 1.40 (1.8H, s, OC*Me*), 1.77 (3H, s,=C*Me*), 2.13–2.25 (2H, m,=CHC*H*, CH_2CH), 2.38–2.44 (1H, m,=CHC*H*), 3.72–3.74 (1H, m, OC*H*), 3.82–3.91 (1H, m, OC*H*), 4.01 (0.4H, d, *J* 9.5 Hz, C*H*OH), 4.12 (0.6H, d, *J* 9.5 Hz, C*H*OH), 6.66–6.67 (0.6H, m,=C*H*), 6.76–6.77 (0.4H, m,=C*H*); δ_C (75 MHz, $CDCl_3/CHCl_3$) 13.9, 15.2, 19.6, 24.2, 26.2, 26.6, 26.8, 27.0, 27.1, 27.4, 48.8, 50.2, 71.8, 74.3, 76.6, 81.4, 82.3, 108.1, 109.6, 132.5, 133.0, 144.4, 146.4, 199.8, 200.3; *m*/*z* (APCI) 241 (21, MH^+), 183 (100), 165 (63%).

*4.4.2. (5R,6R,4′RS)-6-Hydroxy-2-methyl-5-(2′,2′,4′-trimethyl-1′,3′-dioxolan-4′-yl)cyclohex-2-en-1-one (**10b**) (a mixture of diastereoisomers at $C^{4\prime}$ in a ratio of 3/2).* R_f (20% ethyl acetate/petroleum ether) 0.19; ν_{max} (Nujol mull) 3468, 2982, 2934, 2884, 1678, 1377, 1254, 1213, 1055, 870 cm^{-1}; δ_H (300 MHz, $CDCl_3/CHCl_3$) 1.26 (1.2H, s, C*Me*), 1.29 (1.2H, s, OC*Me*), 1.33 (1.8H, s, C*Me*), 1.36 (1.2H, s, OC*Me*), 1.37 (1.8H, s, OC*Me*), 1.40 (1.8H, s, OC*Me*), 1.71 (3H, s,=C*Me*), 2.13–2.25 (2H, m,=CHC*H*, CH_2CH), 2.60–2.66 (1H, m,=CHC*H*), 3.64–3.66 (1H, m, OC*H*), 3.82–3.91 (1H, m, OC*H*), 4.05 (0.4H, d, *J* 1.8 Hz, C*H*OH), 4.08 (0.6H, d, *J* 1.8 Hz, C*H*OH), 6.66–6.67 (0.6H, m,=C*H*), 6.76–6.77 (0.4H, m,=C*H*); δ_C (75 MHz, $CDCl_3/CHCl_3$) 13.9, 15.2, 19.6, 20.3, 20.6, 24.2, 26.2, 26.8, 27.1, 27.4, 52.7, 54.1, 72.0, 74.8, 75.9, 81.4, 82.3, 111.4, 113.1, 135.2, 136.8, 144.9, 146.4, 199.8, 200.3.

4.5. Methyl (2*Z*,5*R*,4′*RS*)-2-methyl-6-oxo-5-(2′,2′,4′-trimethyl-1′,3′-dioxolan-4′-yl)hex-2-enoate (11)

Lead tetraacetate (13.0 g, 29.3 mmol) was added with stirring at 0 °C to a solution of the isomeric mixture of **10a** and **10b** (5.40 g, 22.5 mmol) in methanol–benzene (1:1, 40 mL), the mixture was stirred for 20 min at room temperature, ethylene glycol (0.42 g, 6.77 mmol) and water (30 mL) were added, and the mixture was stirred for 10 min and treated with ether (40 mL). The extract was dried over $MgSO_4$, filtered, and evaporated to provide **11** (5.59 g, 92%) as a yellow oil. The product was used in the next step without chromatographic purification.

4.6. Methyl (2*Z*,5*R*,4′*RS*)-6-hydroxy-2-methyl-5-(2′,2′,4′-trimethyl-1′,3′-dioxolan-4′-yl)hex-2-enoate (12)

Compound **11** (5.59 g, 20.7 mmol) was dissolved in methanol (30 mL), $CeCl_3 \cdot 7H_2O$ (7.71 g, 20.7 mmol) was added with stirring, the mixture was cooled to 5 °C, $NaBH_4$ (0.79 g, 20.7 mmol) was added, then the mixture was stirred for 1 h at room temperature. The mixture was then treated with water (60 mL), stirred for 15 min, saturated with sodium chloride, then extracted with ethyl acetate (3×30 mL), dried over $MgSO_4$, filtered, and evaporated. Purification of the product by column chromatography (30% ethyl acetate/petroleum ether) afforded **12** (5.41 g, 96%, a mixture of diastereoisomers at $C^{4\prime}$ in a ratio of 3/2) as a colourless oil; [Found: C, 61.7; H, 8.7. $C_{14}H_{24}O_5$ requires C, 61.76; H, 8.82%]; R_f (30% ethyl acetate/petroleum ether) 0.22; ν_{max} (Nujol mull) 3449, 2957, 2938, 1717, 1456, 1432, 1356, 1321 cm^{-1}; δ_H (300 MHz, $CDCl_3/CHCl_3$) 1.31 (3H, s, OC*Me*), 1.38 (3H, s, OC*Me*), 1.33 (1.2H, s, C*Me*), 1.42 (1.8H, s, C*Me*), 1.79–1.83 (1H, m, CH_2CH), 1.90 (3H, s,=C*Me*), 2.40–2.52 (1H, m,=CHC*H*), 2.63–2.74 (1H, m,=CHC*H*), 3.60–3.64 (1H, m, C*H*OH), 3.72–3.83 (5H, m, CO_2Me, OC*H*, C*H*OH), 3.95 (0.4H, d, *J*=8.6 Hz, OC*H*), 3.99 (0.6H, d, *J*=8.6 Hz, OC*H*), 5.90–6.01 (1H, m,=C*H*); δ_C (75 MHz, $CDCl_3/CHCl_3$) 20.5, 21.8, 23.6, 26.6, 27.1, 26.8, 27.6, 48.4, 48.9, 51.4, 62.0, 62.2, 72.6, 73.7, 83.5, 84.2, 108.9, 109.1, 128.0, 128.5, 141.2, 142.1, 186.3; *m*/*z* (APCI) 273 (12, MH^+), 215 (100), 197 (41%).

4.7. Methyl (2*Z*,5*R*,6*RS*)-6,7-dihydroxy-5-(hydroxymethyl)-2,6-dimethylhept-2-enoate (13)

To a stirred solution of **12** (4.80 g, 17.6 mmol) in tetrahydrofuran (20 mL) was added 1% aqueous HCl (7 mL) at room temperature. The mixture was heated to 50 °C and after stirring for 5 h, $NaHCO_3$ and $MgSO_4$ were added, the tetrahydrofuran was decanted, and the remaining white precipitate was washed with ethyl acetate (3×30 mL). The combined organic phase was evaporated and the resulting light yellow oil was purified by column chromatography (ethyl acetate) to provide **13** (3.48 g, 85%, a mixture of diastereoisomers at C^6 in a ratio of 3/2) as a colourless oil; [Found: C, 56.7; H, 8.5. $C_{11}H_{20}O_5$ requires C, 56.90; H, 8.62%]; R_f (ethyl acetate) 0.23; ν_{max} (Nujol mull) 3401, 3381, 2953, 1713, 1454, 1435, 1246, 1209, 1136, 1049 cm^{-1}; δ_H (300 MHz, $CDCl_3/CHCl_3$) 1.17 (1.2H, s, C*Me*), 1.19 (1.8H, s, C*Me*), 1.80–1.87 (1H, m, CH_2CH), 1.89 (1.8H, s,=C*Me*), 1.91 (1.2H, s,=C*Me*), 2.23–2.36 (1H, m,=CHC*H*), 2.41–2.46 (1H, m,=CHC*H*), 3.54–3.64 (1H, m, CC*H*OH), 3.72 (1.2H, s, CO_2Me), 3.74 (1.8H, s, CO_2Me), 3.75–3.85 (3H, m, CH_2OH, CC*H*OH), 5.87–5.99 (1H, m,=C*H*); δ_C (75 MHz, $CDCl_3/CHCl_3$) 20.6, 21.1, 24.1, 26.5, 26.7, 45.6, 48.4, 51.8, 52.0, 60.0, 62.1, 66.6, 68.5, 74.0, 76.0, 128.7, 128.8, 141.9, 141.9, 176.6; *m*/*z* (APCI) 277 (81), 261 (100), 231 (13, $[M-H]^-$), 173 (30%).

4.8. Methyl (2*Z*,5*R*)-5-(hydroxymethyl)-2-methyl-6-oxohept-2-enoate (14)

Lead tetraacetate (7.94 g, 17.9 mmol) was added with stirring at 0 °C to a solution of **13** (3.20 g, 13.8 mmol) in methanol–benzene (1:1, 30 mL), the mixture was stirred for 20 min at room temperature, ethylene glycol (0.25 g, 4.03 mmol) and water (20 mL) were added, and the mixture was stirred for 10 min and then treated with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and evaporated, purification of the residue by column chromatography (30% ethyl acetate/petroleum ether) afforded **14** (2.64 g, 96%) as a light yellow oil; [Found: C, 59.8; H, 7.8. $C_{10}H_{16}O_4$ requires C, 60.0; H, 8.0%]; R_f (ethyl acetate) 0.51; $[\alpha]_D^{20}$ +15.7, (*c* 0.8, CH_2Cl_2); ν_{max} (Nujol mull) 3412, 2953, 1718, 1701, 1458, 1437, 1264, 1244, 1204, 1132 cm^{-1}; δ_H (300 MHz, $CDCl_3/CHCl_3$) 1.89 (3H, s,=C*Me*), 2.22 (3H, s, *Me*C=O), 2.23–2.24 (1H, m,=CHC*H*), 2.69–2.74 (2H, m,=CHC*H*, CH_2CH), 3.73 (3H, s, CO_2Me), 3.78 (2H, br s, CH_2OH), 5.85–5.90 (1H, m,=CH); δ_C (75 MHz, $CDCl_3/CHCl_3$) 20.1, 26.9, 28.8, 51.1, 54.0, 61.5, 128.8, 139.0, 168.0, 210.6; *m*/*z* (APCI) 201 (32, MH^+), 183 (58), 139 (100), 109 (39%).

4.9. Methyl (2*Z*,5*S*,6*E*)-5-(hydroxymethyl)-2,6-dimethyl-7-(2′-methyl-1′,3′-thiazol-4′-yl)hepta-2,6-dienoate (16)

A 1 M solution of NaHMDS in tetrahydrofuran (18.8 mL, 18.8 mmol) was added at −78 °C with stirring under an argon atmosphere to a solution of tributylphosphonium reagent **15c** (6.56 g, 18.8 mmol) in dry tetrahydrofuran (20 mL). The reaction mixture was stirred for 1 h, then a solution of ketone **14** (1.50 g, 7.50 mmol) in tetrahydrofuran (5 mL) was added dropwise at −78 °C. The reaction mixture was stirred for 2 h at −78 °C, warmed to −30 °C and stirred for another 12 h. A saturated aqueous solution of NH_4Cl (50 mL) was added, the layers were separated, the aqueous layer was extracted with ethyl acetate (3×30 mL), the combined organic phase was dried over $MgSO_4$, filtered, and evaporated, purification of the residue by column chromatography (30% ethyl acetate/petroleum ether) afforded **16** (1.90 g, 86%) as a light yellow oil; [Found: C, 60.8; H, 7.0; N, 4.7; S, 10.8. $C_{15}H_{21}NO_3S$ requires C, 61.02; H, 7.12; N, 4.75; S, 10.85%]; R_f (50% ethyl acetate/petroleum ether) 0.22; $[\alpha]_D^{20}$ +3.6, (*c* 1.7, CH_2Cl_2); ν_{max} (Nujol mull) 3360, 3041, 2986, 1713, 1479, 1422, 1242, 1199 cm^{-1}; δ_H (300 MHz, $CDCl_3/CHCl_3$) 1.88 (3H, s,=C*Me*), 2.02 (3H, s,=C*Me*), 2.43–2.50 (1H, m,=CHC*H*), 2.51–2.64 (1H, m,=CHC*H*), 2.70 (3H, s, N=C*Me*), 2.72–2.83 (1H, m, CH_2CH), 3.64–3.68 (2H, m, CH_2OH), 3.73 (3H, s, CO_2Me), 5.93 (1H, t, *J* 7.0 Hz,=C*H*), 6.40 (1H, s,=C*H*), 6.91 (1H, s,=C*HS*); δ_C (75 MHz, $CDCl_3/CHCl_3$) 16.0, 19.1, 20.6, 29.7, 51.4, 52.0, 64.1, 115.3, 121.4, 128.1, 140.1, 140.7, 152.7, 164.5, 168.2; *m*/*z* (APCI) 296 (12, MH^+), 277 (100), 219 (19%).

4.10. Methyl (2*Z*,5*S*,6*E*)-5-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2,6-dimethyl-7-(2′-methyl-1′,3′-thiazol-4′-yl)hepta-2,6-dienoate (17)

To a solution of **16** (1.50 g, 5.08 mmol), imidazole (0.76 g, 11.2 mmol) and DMAP (0.31 g, 2.54 mmol) in methylene chloride (25 mL) at room temperature was added TBSCl (1.15 g, 7.63 mmol), and the mixture was stirred until the starting compound was consumed (~4 h, TLC monitoring). The solution was then concentrated and the residue was purified by column chromatography (6% ethyl acetate/petroleum ether) to provide **17** (2.0 g, 96%) as a colourless oil; [Found: C, 61.5; H, 8.4; N, 3.3; S, 7.7. $C_{21}H_{35}NO_3SSi$ requires C, 61.61; H, 8.56; N, 3.42; S, 7.82%]; R_f (10% ethyl acetate/petroleum ether) 0.18; $[\alpha]_D^{20}$ +1.3, (*c* 1.37, CH_2Cl_2); ν_{max} (Nujol mull) 2951, 2928, 2857, 1715, 1252, 1134, 1105, 837, 775, 368 cm^{-1}; δ_H (300 MHz, $CDCl_3/CHCl_3$) 0.07 (6H, s, $SiMe_2$), 0.91 (9H, s, $SiCMe_3$), 1.91 (3H, s,=C*Me*), 2.02 (3H, s,=C*Me*), 2.43–2.52 (1H, m,=CHC*H*), 2.64–2.72 (1H, m,=CHC*H*), 2.74 (3H, s, N=C*Me*), 2.79–2.87 (1H, m, CH_2CH), 3.61–3.74 (2H, m, CH_2OSi), 3.76 (3H, s, CO_2Me), 6.00 (1H, t, *J* 7.0 Hz,=C*H*), 6.41 (1H, s,=C*H*), 6.91 (1H, s,=C*HS*); δ_C (75 MHz, $CDCl_3/CHCl_3$) -5.5, 16.2, 18.1, 19.0, 20.6, 25.8, 29.8, 51.1, 52.2, 65.7, 114.6, 120.7, 127.2, 140.5, 141.6, 153.2, 164.1, 168.3; *m*/*z* (APCI) 410 (16, MH^+), 310 (100), 296 (10%).

4.11. (2*Z*,5*S*,6*E*)-5-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-2,6-dimethyl-7-(2′-methyl-1′,3′-thiazol-4′-yl)hepta-2,6-dien-1-ol (4)

To a stirred solution of **17** (1.60 g, 3.91 mmol) in methylene chloride (15 mL) at −78 °C was added a 73% solution of DIBAL-H in hexane (2.4 mL, 9.78 mmol), the reaction mixture was warmed to −30 °C and stirred for 1 h. A solution of MeOH–H_2O (1:1, 30 mL) was added dropwise, the mixture was allowed to warm to room temperature and stirred for another 1 h. The white precipitate, which formed was then filtered and washed with hot methylene chloride (5×20 mL). The phases of the combined filtrate were separated, the aqueous phase was saturated with NaCl and extracted with methylene chloride (3×20 mL). The combined organic phase was dried over $MgSO_4$, filtered and evaporated, the residue was purified by column chromatography (20% ethyl acetate/petroleum ether) to provide **4** (1.19 g, 80%) as a colourless oil; [Found: C, 62.8; H, 9.1; N, 3.5; S, 8.3. $C_{20}H_{35}NO_2SSi$ requires C, 62.99; H, 9.19; N, 3.67; S, 8.40%]; R_f (25% ethyl acetate/petroleum ether) 0.19; $[\alpha]_D^{20}$ +19.4, (*c* 2.17, CH_2Cl_2); ν_{max} (Nujol mull) 3433, 3053, 2980, 2927, 2856, 1265, 739, 704, 385 cm^{-1}; δ_H (300 MHz, $CDCl_3/CHCl_3$) 0.02 (6H, s, $SiMe_2$), 0.87 (9H, s, $SiCMe_3$), 1.77 (3H, s,=C*Me*), 1.94 (3H, s,=C*Me*), 2.20–2.39 (3H, m,=CHCH_2, CH_2CH), 2.67 (3H, s, N=C*Me*), 3.56–3.61 (1H, m, C*H*OSi), 3.68–3.71 (1H, m, C*H*OSi), 4.00 (1H, d, *J* 12.0 Hz, C*H*OH), 4.18 (1H, d, *J* 12.0 Hz, C*H*OH), 5.23 (1H, t, *J* 7.0 Hz,=C*H*), 6.25 (1H, s,=C*H*), 6.83 (1H, s,=C*HS*); δ_C (75 MHz, $CDCl_3/CHCl_3$) -5.6, 17.2, 18.0, 18.8, 21.2, 26.3, 27.7, 51.4, 61.1, 65.1, 114.2, 119.9, 125.3, 135.9, 140.9, 152.7, 164.2; *m*/*z* (APCI) 382 (13, MH^+), 336 (100), 277 (16%).

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