Stereoselective Total Synthesis of Decytospolides A and B Starting from D-Mannitol[1])

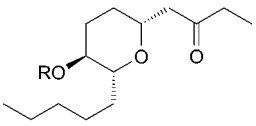
by **Malampati Srilatha** and **Biswanath Das***

Natural Products Chemistry Division, CSIR- Indian Institute of Chemical Technology, Hyderabad-500 007, India (phone: +91-40-7193434; fax: +91-40-7160512; e-mail: biswanathdas@yahoo.com)

The stereoselective total synthesis of decytospolides A and B, two naturally occurring pyran derivatives, has been achieved using D-mannitol as the starting material. The intramolecular oxa-*Michael* reaction has been employed to construct the tetrahydropyran ring of the molecules and *Weinreb* amide formation to generate their side chain with a keto function.

Introduction. – Two new tetrahydropyran derivatives, decytospolides A and B (**1** and **2**, resp.; *Fig.*) were isolated [1] from *Cytospora* sp., an endophytic fungus from *Ilex canariensis*. The cytotoxic properties of these two compounds were evaluated, and **2** was found to be active against the tumor cell lines, A549 and QGY [1].

In continuation of our work [2] on the stereoselective construction of natural products, we have recently accomplished the total synthesis of **1** and **2**. While our synthetic work was in progress, some reports on the synthesis of these molecules appeared [3]. Herein, we report our alternative total synthesis of **1** and **2** starting from D-mannitol (*Fig.*).



1 R = H
2 R = Ac

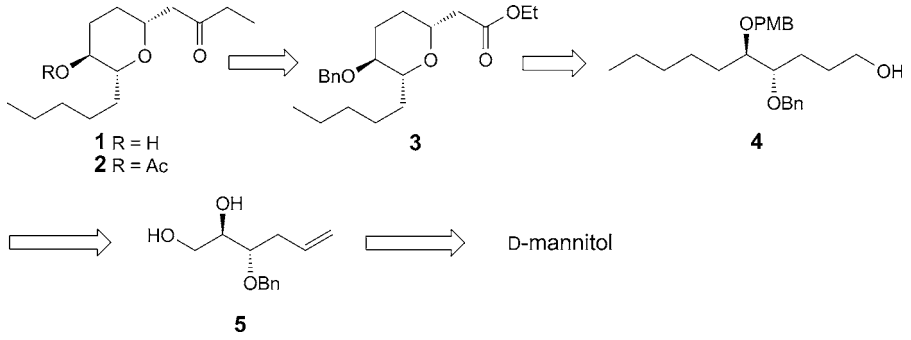
Figure. *Structures of decytospolides A and B* (**1** and **2**, resp.)

Results and Discussion. – The retrosynthetic analysis (*Scheme 1*) indicates that the compounds **1** and **2** can be prepared from the ester **3**, which in turn can be obtained from the alcohol **4**. The alcohol **4** can be generated from the ene-diol **5** derived from D-mannitol.

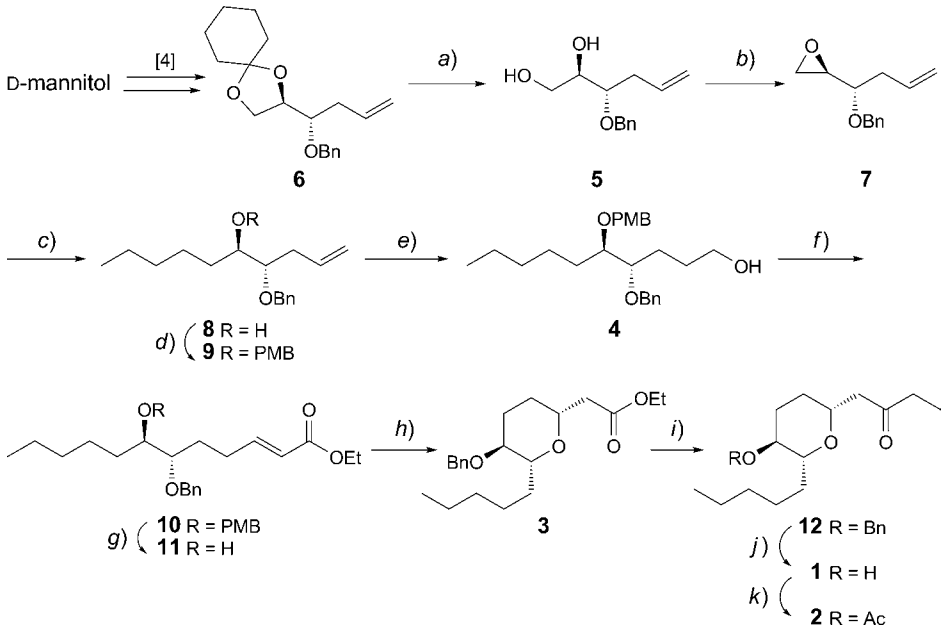
Our synthesis was initiated (*Scheme 2*) by converting D-mannitol to the alkene **6** as described in [4]. The acetal group of the latter was subsequently deprotected with *Dowex 50* in MeOH to furnish the ene-diol **5**. Selective tosylation of the primary OH group of **5** with TsCl, Et_3N, and a catalytic amount of Bu_3SnO, followed by treatment

[1]) Part 77 in the series, 'Synthetic studies on natural products'.

Scheme 1. *Retrosynthetic Analysis of* **1** *and* **2**



Scheme 2. *Synthesis of Decytospolides A and B*



a) *Dowex H*$^+$ resin, MeOH, r.t., 20 h; 91%. *b*) *i*) Et_3N, Bu_3SnO, TsCl, dry CH_2Cl_2, 0° – r.t., 2 h; 89%; *ii*) K_2CO_3, dry MeOH, r.t., 1 h; 94%. *c*) BuMgBr, dry THF, 0° – r.t., 3 h, 93%. *d*) NaH, 4-Methoxybenzyl chloride (PMBCl), THF, 0° – r.t., 8 h; 85%. *e*) *i*) $BH_3 \cdot Me_2S$, dry THF, 0° – r.t., 3 h; *ii*) NaOH, 30% H_2O_2, 2 h; 87%. *f*) *i*) 2-Iodoxybenzoic acid (IBX), CH_2Cl_2, r.t., 3 h; *ii*) $Ph_3P{=}CHCOOEt$, benzene, reflux, 3 h; overall 88%. *g*) 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), CH_2Cl_2/H_2O (9:1), 0° – r.t., 1 h; 86%. *h*) ^{t}BuOK, dry THF, −20°, 1 h; 73%. *i*) *i*) (MeO)MeNH·HCl, ^{i}PrMgCl, THF, −20°, 1 h; *ii*) EtMgI, dry THF, 0° – r.t., 2 h; overall 76%. *j*) Li, Naphthalene, dry THF, −25°, 2 h; 86%. *k*) Ac_2O, Et_3N, CH_2Cl_2, 0° – r.t., 4 h; 90%.

with K_2CO_3 in dry MeOH, afforded the chiral epoxide **7**. The epoxy ring of **7** was opened with BuMgBr to give the secondary alcohol **8**, and its free OH group was protected as 4-methoxybenzyl (PMB) ether **9**. Next, **9** was treated with $BH_3 \cdot Me_2S$ and

subsequently with alkaline H_2O_2 to afford the primary alcohol **4**, which underwent oxidation with 2-iodoxybenzoic acid (IBX). The corresponding aldehyde was subjected to *Wittig* olefination with $Ph_3P{=}CHCOOEt$ to form the major (*E*)-isomer of the α,β-unsaturated ester **10** ((*E*)/(*Z*) 95:5) [5]. The PMB group of **10** was removed using DDQ to yield the hydroxy ester **11**. The latter was treated with ^{t}BuOK in dry THF to undergo an oxa-*Michael* reaction [6] to give the tetrahydropyran derivative **3** [7]. Thus, the skeleton of the target molecules, **1** and **2**, has been constructed. Compound **3** was then transformed to the corresponding *Weinreb* amide using (MeO)MeNH · HCl and ^{i}PrMgCl in THF, which was then treated with EtMgI in THF to afford the ketone **12** [8]. Removal of the Bn group of **12** yielded the naturally occurring decytospolide A (**1**), and the acetylation of the latter furnished decytospolide B (**2**). The optical and spectroscopic properties of **1** and **2** were found to be identical to those reported earlier [1][3].

In conclusion, we have described the stereoselective total synthesis of two natural tetrahydropyran derivatives, decytospolides A and B (**1** and **2**, resp.), starting from D-mannitol and by applying intramolecular oxa-*Michael* reaction and *Weinreb* amide formation as the key steps.

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Experimental Part

General. All commercially available reagents were used directly without further purification unless otherwise stated. The solvents used were all of anal. reagent grade and were distilled under N_2 where necessary. All reactions were performed in pre-dried apparatus under N_2. TLC: *Merck* silica-gel *60* F_{254} plates. Column chromatography (CC): silica gel 60–120 mesh (SiO_2; *Qingdao Marine Chemical*, P. R. China). Optical rotations: *JASCO DIP 360* digital polarimeter at 25°. IR Spectra: *Perkin-Elmer RX* FT-IR spectrophotometer. NMR Spectra: *Gemini* 200 MHz spectrometer with TMS as internal standard, in $CDCl_3$; the chemical shifts, δ in ppm; the coupling constants, *J* in Hz. ESI-MS: *VG-Autospecmicromass.* HR-MS: *QSTAR XL*, Hybrid MS system (*Applied Biosystems*).

*(2*R*,3*S*)-3-(Benzyloxy)hex-5-ene-1,2-diol* (**5**). To a soln. of **6** (10.5 g, 34.77 mmol) in MeOH (4 × 20 ml) was added *Dowex* H^+ resin (90 g), and the mixture was stirred at r.t. for 20 h. After completion of the reaction, the mixture was filtered, and MeOH was evaporated under reduced pressure to afford a crude product, which was purified by CC to afford pure **5** (7.0 g, 91%). $[\alpha]_D^{25} = +33.9$ ($c = 1.0$, $CHCl_3$). IR: 3410, 1641, 1453, 1211, 1074. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.49–7.40 (*m*, 2 H); 7.38–7.24 (*m*, 3 H); 5.92–5.78 (*m*, 1 H); 5.19–5.02 (*m*, 2 H); 4.64 (*d*, *J* = 14.0, 1 H); 4.49 (*d*, *J* = 14.0, 1 H); 4.23–4.19 (*m*, 1 H); 3.78–3.68 (*m*, 2 H); 3.62–3.54 (*m*, 1 H); 2.50–2.31 (*m*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 138.0; 134.1; 128.4; 127.9; 117.9; 80.1; 72.2; 63.1; 34.7. ESI-MS: 245 ($[M + Na]^+$). Anal. calc. for $C_{13}H_{18}O_3$ (222.13): C 70.24, H 8.16; found: C 70.14, H 8.14.

*(2*R*)-2-[(1*S*)-1-(Benzyloxy)but-3-en-1-yl]oxirane* (**7**). For spectral data, see [4b].

*(4*S*,5*R*)-4-(Benzyloxy)dec-1-en-5-ol* (**8**). Compound **7** (5.0 g, 24.51 mmol) was dissolved in dry THF (2 × 20 ml), and the mixture was cooled to 0°. BuMgBr (Mg: 44.12 mmol, BuBr: 36.76 mmol) was added slowly, and the mixture was stirred at the same temp. for 3 h. After completion of the reaction, the mixture was treated with sat. aq. NH_4Cl soln. (20 ml) and extracted with CH_2Cl_2 (3 × 30 ml). The combined extracts were dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by CC to afford **8** (5.97 g, 93%). $[\alpha]_D^{25} = +4.3$ ($c = 1.0$, $CHCl_3$). IR: 3450, 1608, 1513, 1251. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.38 (*s*, 5 H); 5.95–5.85 (*m*, 1 H); 5.13–5.04 (*m*, 2 H); 4.59 (*q*, *J* = 14.0, 2 H); 3.82–3.75 (*m*, 1 H); 3.45–3.40 (*m*, 1 H); 2.46–2.38 (*m*, 1 H); 2.33–2.26 (*m*, 1 H); 1.51–1.42 (*m*, 2 H); 1.35–1.23 (*m*, 6 H); 0.88 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 138.5; 135.4; 129.4; 128.4;

127.9; 117.1; 82.0; 71.9; 71.1; 33.3; 31.8; 31.7; 25.9; 22.5; 14.1. ESI-MS: 285 ($[M+Na]^+$). Anal. calc. for $C_{17}H_{26}O_2$ (262.19): C 77.82, H 9.99; found: C 77.69, H 9.94.

1-({[(4S,5R)-4-(Benzyloxy)dec-1-en-5-yl]oxy}methyl)-4-methoxybenzene (**9**). Compound **8** (5.8 g, 22.14 mmol) in dry THF (20 ml) was added to a suspension of NaH (1.33 g, 33.2 mmol) in THF (2 × 20 ml) under N_2 at 0°, and the mixture was stirred for 30 min. To this mixture, 4-methoxybenzyl chloride (PMBCl; 3.6 ml, 26.56 mmol) was added, and the mixture was stirred for 8 h at r.t. The reaction was quenched with sat. aq. NH_4Cl soln. (20 ml), and the mixture was extracted with AcOEt. The org. layer was washed with H_2O (20 ml), brine (10 ml), dried (Na_2SO_4), evaporated in *vacuo*, and purified by CC to afford **9** (7.35 g, 85%). $[\alpha]_D^{25} = +5.0$ ($c = 0.3$, $CHCl_3$). IR: 1611, 1511, 1460, 1246. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.38–7.30 (*m*, 5 H); 7.27 (*d*, *J* = 8.0, 2 H); 6.85 (*d*, *J* = 8.0, 2 H); 5.93–5.84 (*m*, 1 H); 5.13–5.04 (*m*, 2 H); 4.59 (*q*, *J* = 14.0, 2 H); 4.45 (*q*, *J* = 14.0, 2 H); 3.79 (*s*, 3 H); 3.56–3.52 (*m*, 1 H); 3.50–3.46 (*m*, 1 H); 2.47–2.40 (*m*, 1 H); 2.37–2.31 (*m*, 1 H); 1.68–1.34 (*m*, 2 H); 1.32–1.20 (*m*, 6 H); 0.88 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 159.2; 138.8; 135.9; 131.0; 129.2; 128.1; 127.9; 127.2; 117.0; 113.9; 80.1; 79.9; 72.2; 72.0; 55.2; 35.1; 32.0; 30.4; 25.2; 22.3; 13.9. ESI-MS: 405 ($[M+Na]^+$). Anal. calc. for $C_{25}H_{34}O_3$ (382.25): C 78.49, H 8.96; found: C 78.40, H 8.85.

(4S,5R)-4-(Benzyloxy)-5-[(4-methoxybenzyl)oxy]decan-1-ol (**4**). To a stirred soln. of **9** (7.0 g, 17.9 mmol) in dry THF (3 × 20 ml), $BH_3 \cdot Me_2S$ (1.1 ml, 17.9 mmol) was added at 0°, and the mixture was stirred for 3 h at the same temp. Aq. 3M NaOH (6.7 ml), followed by 30% H_2O_2 (6.7 ml), was added at 0°. After stirring for 2 h at 0° and 12 h at r.t., the mixture was extracted with AcOEt (3 × 20 ml). The org. layer was washed with H_2O (20 ml) and brine (10 ml). The combined org. layers were dried (Na_2SO_4), evaporated *in vacuo*, and purified by CC to afford **4** (6.2 g, 87%). $[\alpha]_D^{25} = -1.2$ ($c = 2.0$, $CHCl_3$). IR: 3432, 1612, 1513, 1459, 1249. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.38–7.20 (*m*, 7 H); 6.86 (*d*, *J* = 8.0, 2 H); 4.69 (*d*, *J* = 14.0, 1 H); 4.62 (*d*, *J* = 14.0, 1 H); 4.52 (*d*, *J* = 14.0, 1 H); 4.46 (*d*, *J* = 14.0, 1 H); 3.78 (*s*, 3 H); 3.60–3.45 (*m*, 4 H); 2.98 (br. *s*, 1 H); 1.74–1.42 (*m*, 6 H); 1.36–1.18 (*m*, 6 H); 0.89 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 159.0; 138.3; 130.9; 129.3; 128.5; 128.0; 127.6; 113.5; 80.8; 79.9; 71.8; 71.6; 62.3; 55.0; 31.9; 30.7; 28.9; 26.5; 25.3; 22.2; 14.0. ESI-MS: 423 ($[M+Na]^+$). Anal. calc. for $C_{25}H_{36}O_4$ (400.26): C 74.96, H 9.06; found: C 74.90, H 9.02.

Ethyl (2E,6S,7R)-6-(Benzyloxy)-7-[(4-methoxybenzyl)oxy]dodec-2-enoate (**10**). To a stirred soln. of 2-iodoxybenzoic acid (IBX; 6.0 g, 15.0 mmol) in DMSO (5 ml) at r.t., **4** dissolved in CH_2Cl_2 (2 × 20 ml) was added. After completion of the reaction (TLC), the mixture was filtered with Et_2O and concentrated. The residue, an aldehyde, was directly used for next step.

To a stirred soln. of the aldehyde (5.6 g, 14.1 mmol) in benzene (3 × 20 ml), $Ph_3P{=}CHCOOEt$ (6.37 g, 18.29 mmol) was added, and the mixture was heated to 60° for 2 h, and then concentrated in *vacuo*. The residue was purified by CC to give **10** (6.2 g, overall 88%). $[\alpha]_D^{25} = -10.1$ ($c = 2.2$, $CHCl_3$). IR: 2928, 1717, 1606, 1513, 1460, 1255, 1169. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.40–7.20 (*m*, 7 H); 7.00–6.82 (*m*, 3 H); 5.78 (*d*, *J* = 16.0, 1 H); 4.69 (*d*, *J* = 12.0, 1 H); 4.61 (*d*, *J* = 12.0, 1 H); 4.51–4.42 (*m*, 2 H); 4.17 (*q*, *J* = 7.0, 2 H); 3.82 (*s*, 3 H); 3.58–3.43 (*m*, 2 H); 2.44–2.30 (*m*, 1 H); 2.28–2.14 (*m*, 1 H); 1.87–1.75 (*m*, 1 H); 1.70–1.57 (*m*, 2 H); 1.50–1.41 (*m*, 2 H); 1.39–1.20 (*m*, 8 H); 0.89 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 166.9; 159.1; 149.0; 138.5; 131.0; 129.6; 128.2; 128.0; 127.8; 121.6; 113.8; 80.2; 79.9; 72.1; 72.0; 61.1; 55.2; 32.1; 30.5; 28.1; 28.0; 25.9; 23.8; 14.1; 14.0. ESI-MS: 491 ($[M+Na]^+$). Anal. calc. for $C_{29}H_{40}O_5$ (468.29): C 74.33, H 8.60; found: C 74.29, H 8.52.

Ethyl (6S,7R,2E)-6-(Benzyloxy)-7-hydroxydodec-2-enoate (**11**). To a stirred soln. of **10** (4.0 g, 8.54 mmol) in CH_2Cl_2/H_2O 9:1 (40 ml), DDQ (2.33 g, 10.26 mmol) was added at 0°, and the soln. was stirred for 30 min at r.t. The reaction was quenched with sat. $NaHCO_3$ soln. (20 ml), and the mixture was extracted with CH_2Cl_2 (2 × 20 ml), and washed with H_2O (30 ml) and brine (10 ml). The combined org. layers were dried (Na_2SO_4), concentrated, and purified by CC to afford **11** (2.5 g, 86%). $[\alpha]_D^{25} = -20.8$ ($c = 2.2$, $CHCl_3$). IR: 3454, 1719, 1664, 1455, 1272. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.40–7.28 (*m*, 5 H); 7.0–6.89 (*m*, 1 H); 5.79 (*d*, *J* = 16.0, 1 H); 4.52 (*d*, *J* = 12.0, 1 H); 4.49 (*d*, *J* = 12.0, 1 H); 4.17 (*q*, *J* = 7.0, 2 H); 3.89–3.81 (*m*, 1 H); 3.37–3.30 (*m*, 1 H); 2.46–2.32 (*m*, 1 H); 2.30–2.17 (*m*, 1 H); 1.85–1.72 (*m*, 1 H); 1.66–1.56 (*m*, 1 H); 1.50–1.22 (*m*, 11 H); 0.89 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 166.8; 148.9; 138.2; 128.1; 127.3; 121.5; 81.2; 71.9; 71.1; 60.2; 32.2; 31.8; 29.9; 28.2; 27.0; 26.1; 22.8; 14.1; 14.0. ESI-MS: 371 ($[M+Na]^+$). Anal. calc. for $C_{21}H_{32}O_4$ (348.23): C 72.38, H 9.26; found: C 72.30, H 9.21.

*Ethyl [(2*R*,5*S*,6*R*)-5-(Benzyloxy)tetrahydro-6-pentyl-2*H*-pyran-2-yl]acetate* (**3**). A soln. of **11** (2.0 g, 5.75 mmol) in dry THF (20 ml) was added to a stirred suspension of *t*BuOK (1.29 g, 11.49 mmol) in dry THF (10 ml) at $-20°$, and the mixture was stirred for 1 h. The reaction was quenched with sat. aq. NH_4Cl (10 ml), and the mixture was extracted with AcOEt (30 ml), and washed with H_2O (10 ml) and brine (5 ml). The combined org. layers were dried (Na_2SO_4), concentrated, and purified by CC to afford **3** (1.46 g, 73%). $[\alpha]_D^{25} = +25.4$ ($c = 1.0$, $CHCl_3$). IR : 3452, 2926, 2856, 1738, 1187, 1086. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.88–7.29 (*m*, 5 H); 4.62 (*d*, *J* = 12.0, 1 H); 4.46 (*d*, *J* = 12.0, 1 H); 4.13 (*q*, *J* = 7.0, 2 H); 3.81–3.70 (*m*, 1 H); 3.24–3.16 (*m*, 1 H); 3.12–3.02 (*m*, 1 H); 2.52 (*dd*, *J* = 12.0, 8.0, 1 H); 2.39 (*dd*, *J* = 12.0, 6.0, 1 H); 2.25–2.20 (*m*, 1 H); 1.92–1.76 (*m*, 2 H); 1.49–1.20 (*m*, 12 H); 0.92–0.81 (*m*, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 172.2; 139.3; 129.0; 127.5; 127.3; 81.7; 74.4; 70.8; 70.7; 60.5; 41.1; 32.2; 31.7; 30.9; 29.8; 25.0; 23.2; 14.6; 14.5. ESI-MS: 371 ($[M + Na]^+$). Anal. calc. for $C_{21}H_{32}O_4$ (348.23): C 72.38, H 9.26; found: C 72.25, H 9.21.

*1-[(2*R*,5*S*,6*R*)-5-(Benzyloxy)tetrahydro-6-pentyl-2*H*-pyran-2-yl]butan-2-one* (**12**). To a stirred soln. of (MeO)MeNH·HCl (0.4 g, 4.3 mmol) in dry THF at $-20°$, ^{i}PrMgCl (Mg, 14.36 mmol; ^{i}PrCl, 14.36 mmol) in dry THF was added slowly, and the mixture was stirred for 1 h, and **3** (0.5 g, 1.4 mmol) dissolved in THF was added slowly. The stirring was continued for 1 h. After completion, the mixture was filtered with Et_2O and concentrated. The residue (the *Weinreb* amide) was directly used for the next step.

The *Weinreb* amide (0.45 g, 1.2 mmol) was dissolved in dry THF (5 ml), and the mixture was cooled to 0°. To this, EtMgI (Mg, 2.23 mmol; EtI, 1.85 mmol) in THF was added slowly at 0°, and the mixture was stirred at r.t. for 2 h. After completion of the reaction, the mixture was treated with sat. aq. NH_4Cl (5 ml) and extracted with CH_2Cl_2 (30 ml). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by CC to afford **12** (0.36 g, overall 76%). $[\alpha]_D^{25} = +32.2$ ($c = 0.5$, $CHCl_3$). IR: 3456, 2926, 2854, 1716, 1457, 1258, 1085. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.38–7.30 (*m*, 5 H); 4.52 (*d*, *J* = 12.0, 1 H); 4.47 (*d*, *J* = 12.0, 1 H); 3.78–3.71 (*m*, 1 H); 3.20–3.15 (*m*, 1 H); 3.08–3.02 (*m*, 1 H); 2.70–2.61 (*m*, 1 H); 2.53–2.42 (*m*, 2 H); 2.41–2.36 (*m*, 1 H); 2.26–2.22 (*m*, 1 H); 1.91–1.82 (*m*, 1 H); 1.80–1.74 (*m*, 1 H); 1.61–1.55 (*m*, 2 H); 1.38–1.21 (*m*, 7 H); 1.04 (*t*, *J* = 7.0, 3 H); 0.89 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 210.2; 139.1; 130.1; 128.3; 127.6; 81.2; 78.4; 74.1; 70.7; 48.2; 37.0; 31.8; 31.7; 30.8; 30.2; 24.9; 23.2; 14.6; 7.8. ESI-MS: 355 ($[M + Na]^+$). Anal. calc. for $C_{21}H_{32}O_3$ (332.24): C 75.86, H 9.70; found: C 75.75, H 9.67.

*1-[(2*R*,5*S*,6*R*)-Tetrahydro-5-hydroxy-6-pentyl-2*H*-pyran-2-yl]butan-2-one* (**1**) [3]. To a soln. of naphthalene (0.15 g, 1.2 mmol) in THF (5 ml) was added Li metal (0.01 g, 0.9 mmol) in small pieces. The mixture was stirred at r.t. under Ar, until Li metal was completely dissolved (*ca.* 3 h). The resulting dark green soln. of lithium naphthalenide was then cooled to $-25°$, and then **12** (0.1 g, 0.3 mmol) in THF (4 ml) was added dropwise over 5 min. The resulting mixture was stirred at $-25°$ for 2 h. The reaction was quenched with sat. aq. NH_4Cl (3 ml). The resulting soln. was extracted with Et_2O (2 × 10 ml). The combined extracts were washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was then purified by CC to afford **1** (62 mg, 86%). $[\alpha]_D^{25} = +12.3$ ($c = 0.7$, $CHCl_3$). IR: 3422, 2933, 2862, 1711, 1459. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.80–3.64 (*m*, 1 H); 3.31–3.21 (*m*, 1 H); 3.07–2.98 (*m*, 1 H); 2.66 (*dd*, *J* = 15.0, 8.0, 1 H); 2.55–2.43 (*m*, 2 H); 2.37 (*d*, *J* = 15.0, 5.0, 1 H); 2.12–2.04 (*m*, 1 H); 1.85–1.69 (*m*, 2 H); 1.65 (br. *s*, 1 H); 1.50–1.37 (*m*, 2 H); 1.36–1.23 (*m*, 7 H); 1.05 (*t*, *J* = 7.2, 3 H); 0.86 (*t*, *J* = 6.8, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 210.1; 82.3; 74.5; 70.6; 48.4; 36.8; 33.0; 31.7; 31.6; 30.8; 25.0; 22.5; 14.2; 7.6. ESI-MS: 265 ($[M + Na]^+$). Anal. calc. for $C_{14}H_{26}O_3$ (242.19): C 69.38, H 10.81; found: C 69.30, H 10.75.

*(2*R*,3*S*,6*R*)-Tetrahydro-6-(2-oxobutyl)-2-pentyl-2*H*-pyran-3-yl Acetate* (**2**) [3]. To a stirred soln. of **1** (30 mg, 0.12 mmol) in dry CH_2Cl_2 (2 ml), Et_3N (0.02 ml, 0.18 mmol) was added at 0°, and the mixture was stirred for 20 min. Ac_2O (0.01 ml, 0.15 mmol) was added at 0°. The mixture was warmed to r.t., stirred for 4 h, and then diluted with CH_2Cl_2 (25 ml). The org. layer was washed with H_2O (5 ml) and brine (2 ml), dried (Na_2SO_4), and concentrated, and the residue was subjected to CC to obtain **2** (32 mg, 90%). $[\alpha]_D^{25} = +22.2$ ($c = 1.0$, $CHCl_3$). IR: 2928, 2856, 1739, 1460, 1372. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.47–4.41 (*m*, 1 H); 3.80–3.74 (*m*, 1 H); 3.25–3.20 (*m*, 1 H); 2.68 (*dd*, *J* = 15.0, 8.0, 1 H); 2.54–2.42 (*m*, 2 H); 2.39 (*dd*, *J* = 15.0, 5.0, 1 H); 2.17–2.11 (*m*, 1 H); 2.03 (*s*, 3 H); 1.77–1.72 (*m*, 1 H); 1.64–1.56 (*m*, 1 H); 1.52–1.30 (*m*, 2 H); 1.34–1.18 (*m*, 7 H); 1.02 (*t*, *J* = 7.2, 3 H); 0.86 (*t*, *J* = 6.8, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$):

209.9; 170.2; 79.4; 74.3; 72.1; 48.2; 37.1; 31.9; 31.7; 30.7; 29.3; 24.8; 22.5; 21.3; 14.2; 7.5. ESI-MS: 307 ($[M+Na]^+$). Anal. calc. for $C_{16}H_{28}O_4$ (284.20): C 67.57, H 9.92; found: C 67.49, H 9.84.

REFERENCES

[1] S. Lu, P. Sun, T. Li, T. Kurtán, A. Mándi, S. Antus, K. Krohn, S. Draeger, B. Schutz, Y. Yi, L. Li, W. Zhang, *J. Org. Chem* **2011**, *76*, 9699.

[2] J. N. Kumar, B. Das, *Tetrahedron Lett*. **2013**, *54*, 3865; C. R. Reddy, B. Veeranjaneyulu, S. Nagendra, B. Das, *Helv. Chem. Acta* **2013**, *96*, 505; C. R. Reddy, B. Das, *Tetrahedron Lett.* **2014**, *55*, 67; P. Jangili, J. Kashanna, G. C. Kumar, Y. Poornachandra, B. Das, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 325.

[3] P. R. Krishna, R. Nomula, D. V. Ramana, *Tetrahedron Lett.* **2012**, *53*, 3612; P. J. Reddy, A. S. Reddy, J. S. Yadav, B. V. S. Reddy, *Tetrahedron Lett.* **2012**, *53*, 4054; D. Clarisse, F. Fache, *Tetrahedron Lett.* **2014**, *55*, 2221; J. Zeng, Y. J. Tan, J. Ma, M. L. Leow, D. Tirtorahardjo, X.-W. Liu, *Chem. – Eur. J.* **2014**, *20*, 405.

[4] A. Sharma, S. Gamre, S. Chattopadhyay, *Tetrahedron Lett.* **2007**, *48*, 3705; S. Bujaranipalli, G. Chander Eppa, S. Das, *Synlett* **2013**, *24*, 1117; D. Ramesh, S. Rajaram, P. Prabhakar, U. Ramulu, D. K. Reddy, Y. Venkateswarlu, *Helv. Chim. Acta* **2011**, *94*, 1226; P. R. Krishna, P. V. Arun Kumar, *Helv. Chim. Acta* **2012**, *95*, 1623.

[5] B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863; B. Das, B. Veeranjaneyulu, P. Balasubramanyam, M. Srilatha, *Tetrahedron: Asymmetry* **2010**, *21*, 2762.

[6] N. Wahlström, J. Slätt, B. Stensland, A. Ertan, J. Bergman, T. Janosik, *J. Org. Chem.* **2007**, *72*, 5886; F. C. Nising, S. Bräse, *Chem. Soc. Rev.* **2012**, *41*, 988.

[7] H. Fuwa, A. Saito, M. Sasaki, *Angew. Chem., Int. Ed.* **2010**, *49*, 3041.

[8] J. S. Yadav, S. Das, J. S. Reddy, N. Thrimurtulu, A. R. Prasad, *Tetrahedron Lett.* **2010**, *51*, 4050; J. M. Williams, R. B. Jobson, N. Yasuda, G. Marchesini, U.-H. Dolling, E. J. J. Grabowski, *Tetrahedron Lett.* **1995**, *36*, 5461; K. R. Prasad, P. Anbarasan, *Tetrahedron: Asymmetry* **2006**, *17*, 850.

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