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First stereoselective total synthesis of decytospolides A and B

P. Janardhan Reddy, A. Srinivas Reddy, J. S. Yadav, B. V. Subba Reddy *

Natural Products Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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ABSTRACT

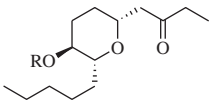
The first stereoselective total synthesis of decytospolides **A** and **B** has been accomplished starting from *n*-hexanal. The key steps involved in this synthesis are Horner–Wittig reaction, Sharpless asymmetric epoxidation, and oxa-Michael reaction.

The 2,6-disubstituted tetrahydropyran containing natural products such as phorboxazoles,[1] (−)-centrolobine,[2] bryostatins,[3] leucascandrolide A,[4] and neopeltolide[5] are found to exhibit promising biological properties which make them attractive synthetic targets to organic chemists.[6] In particular, decytospolides **A** and **B** were isolated recently from *Cytospora* sp., an endophytic fungus from *Ilex canariensis* (Fig. 1).[7] Decytospolide **B** shows strong cytotoxicity than decytospolide **A**. However, to date, there have been no reports on the total synthesis of decytospolides **A** and **B**.

Following our interest on the synthesis of biologically active natural products having tetrahydropyran ring system,[8] we, herein report a stereoselective total synthesis of decytospolides **A** and **B** employing Horner–Wittig reaction and intramolecular oxa-Michael reaction as key steps.

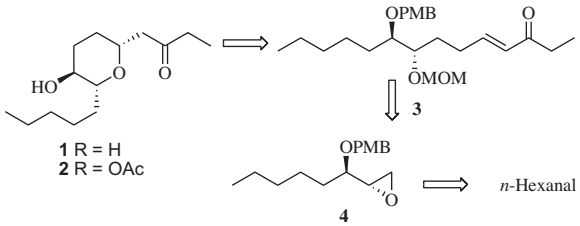
In our retrosynthetic analysis, we assume that decytospolides **A** and **B** could be prepared by oxa-Michael addition of secondary alcohol onto α,β-unsaturated ketone **3**. The Michael acceptor **3** could in turn be obtained from epoxide **4** by utilizing two consecutive reactions like allyl Grignard and Horner–Wittig reactions (Scheme 1).

Our synthetic approach for the total synthesis of decytospolides **A** and **B** is outlined in Scheme 2. We began our synthesis from *n*-hexanal. Accordingly, *n*-hexanal was converted into epoxide **7** in three steps using known procedures. Regioselective ring opening[9] of epoxy alcohol **7**,[10] with *p*-methoxybenzyl alcohol in the presence of $Ti(O^iPr)_4$ gave the diol **8** in 82% yield. Selective protection of primary alcohol **8** with *p*-toluenesulfonyl chloride, triethylamine, and a catalytic amount of dibutyltin oxide gave the tosylate which then treated with a base to afford the epoxide **4** in 81% yield, over two steps. Epoxide **4** was then subjected to allylation with allylmagnesium bromide in the presence of a catalytic amount of CuI to afford the secondary alcohol **9** in 90% yield.[11] Alcohol **9** was protected as its MOM ether **10** using MOM-Cl and DIPEA in the presence of a catalytic amount of DMAP. Oxidative cleavage of terminal olefin **10** using OsO_4, 2,6-lutidine, and $NaIO_4$ gave the aldehyde in a single step,[12] which was subsequently homologated by Horner–Wittig reaction with dimethyl 2-oxobutanephosphonate in the presence of NaH and 18-crown-6 to afford the α,β-unsaturated ketone **3** in 80% yield over two steps.[13]



1 R = H
2 R = OAc

Figure 1. Structure of decytospolides **A** and **B**.



1 R = H
2 R = OAc

Scheme 1. Retrosynthesis of decytospolides **A** and **B**.

* Corresponding author. Fax: +91 40 27160512.
E-mail address: yadavpub@iict.res.in (B.V. Subba Reddy).

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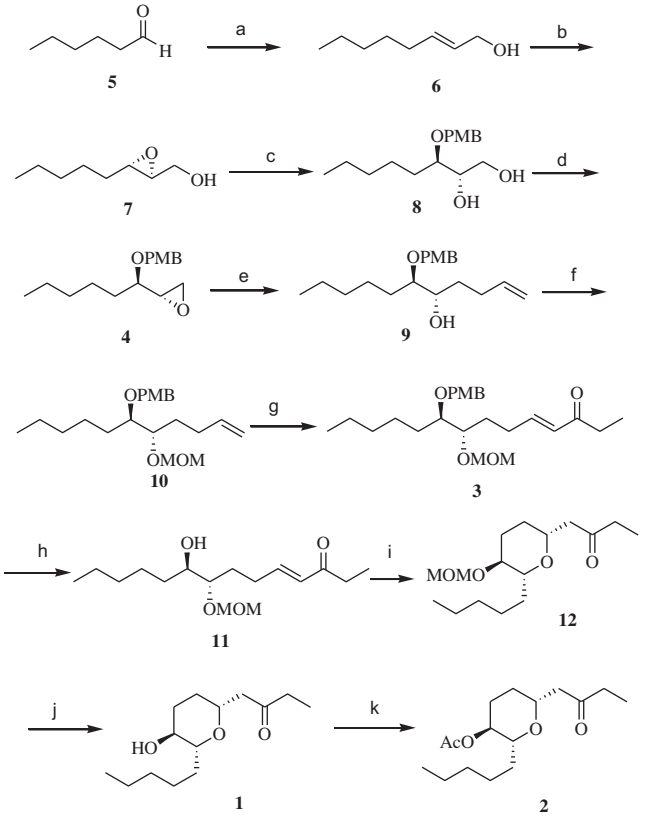

Scheme 2. Synthesis of decytospolides **A** and **B**. Reagents and conditions: (a) (i) PPh_3 = $CHCO_2Et$, CH_2Cl_2, 25 °C, 6 h; (ii) DIBAL-H, CH_2Cl_2, 25 °C, 2 h; (b) $Ti(O^iPr)_4$, (+)-DIPT, *t*-BuOOH, CH_2Cl_2, −20 °C, 6 h; (c) $Ti(O^iPr)_4$, PMB-OH, toluene, reflux, 2 h; (d) (i) TsCl, Et_3N, CH_2Cl_2, 25 °C, 3 h; (ii) NaH, THF, 28 °C, 4 h; (e) allylMgBr, CuI, THF, −30 °C, 2 h; (f) MOM-Cl, DIPEA, CH_2Cl_2, 23 °C, 6 h; (g) (i) OsO_4, 2,6-lutidine, $NaIO_4$, 2 h; (ii) $CH_3CH_2COCH_2PO(OMe)_2$, NaH, 18-Crown-6, 28 °C, 6 h; (h) DDQ, CH_2Cl_2:H_2O (10:1), 3 h; (i) KO^tBu, THF, −20 °C, 0.5 h; (j) $BF_3.OEt_2$, $(CH_3)_2S$, −10 °C, 1 h; (k) pyridine, Ac_2O, 28 °C, 18 h.

Oxidative deprotection of *p*-methoxybenzyl ether **3** with DDQ[14] followed by base induced intramolecular oxa-Michael reaction of the resulting alcohol (KO^tBu, THF, −20 °C) gave the tetrahydropyran ring **12** as a sole product in 70% yield over two steps.[15] Finally, the removal of MOM group from compound **12** using $BF_3.OEt_2$ and DMS[16] afforded the title compound **1**, decytospolide **A** in 85% yield, which was then acetylated under standard conditions to furnish the decytosploide **B** in 90% yield (Scheme 2). The optical rotation and spectral data of synthetic compounds **1** and **2**[17] are identical with those of natural products.[7]

In summary, we have demonstrated a highly stereoselective total synthesis of decytospolides A and **B** using a readily accessible starting material, *n*-hexanal involving Horner–Wittig reaction, Sharpless asymmetric epoxidation and intramolecular oxa-Michael reaction as the key steps. Our approach provides an easy access for decytospolides A and **B**.

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17. Spectral data for *decytospolide* ***A*** (***1***): $[\alpha_D^{20}]$ +8.3 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.80–3.69 (1H, m), 3.32–3.21 (1H, m), 3.03 (1H, dt, *J* = 9.0, 2.2 Hz), 2.66 (1H, dd, *J* = 15.0, 8.1 Hz), 2.55–2.44 (2H, m), 2.39 (1H, dd, *J* = 15.0, 4.9 Hz), 2.13–2.03 (1H, m), 1.88–1.16 (12H, m), 1.04 (3H, t, *J* = 7.3 Hz), 0.88 (3H, t, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 210.0, 82.1, 74.0, 70.5, 48.3, 37.0, 32.9, 31.9, 31.8, 31.2, 24.9, 22.6, 14.0, 7.5; IR (neat): ν_{max} 3422, 2933, 2862, 1711, 1459 cm^{-1}; ESI-MS: *m*/*z* 265 $[M+Na]^+$; HRMS (ESI) Calcd for $C_{14}H_{26}O_3Na$ 265.17742. Found: 265.17718; *decytospolide* ***B*** (***2***): $[\alpha_D^{20}]$ +22.6 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 4.51–4.39 (1H, m), 3.83–3.72 (1H, m), 3.25 (1H, dt, *J* = 9.3, 2.4 Hz), 2.68 (1H, dd, *J* = 15.1, 7.9 Hz), 2.48 (2H, m), 2.38 (1H, dd, *J* = 15.2, 4.9 Hz), 2.20–2.10 (1H, m), 2.04 (3H, s), 1.81–1.19 (11H, m), 1.04 (3H, t, *J* = 7.3 Hz), 0.87 (3H, t, *J* = 6.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 209.8, 170.2, 79.3, 74.2, 72.0, 48.2, 37.2, 31.9, 31.7, 30.8, 29.3, 24.8, 22.6, 21.1, 14.0, 7.4; IR(neat): ν_{max} 2928, 2856, 1739, 1460, 1372 cm^{-1}; ESIMS: *m*/*z* 307 $[M+Na]^+$; HRMS (ESI) Calcd for $C_{16}H_{28}O_4Na$ 307.18798. Found: 307.18799.
1-((2R,5S,6R)-5-(Methoxymethoxy)-6-pentyl-tetrahydro-2H-pyran-2-yl)butan-2-one (***12***): $[\alpha_D^{20}]$ +7 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 4.72 (1H, d, *J* = 6.8 Hz), 4.60 (1H, d, *J* = 6.8 Hz), 3.80–3.69 (1H, m), 3.37 (3H, s), 3.24–3.08 (2H, m), 2.65 (1H, dd, *J* = 15.1, 8.1 Hz), 2.55–2.33 (3H, m), 2.23–2.13 (1H, m), 1.86–1.69 (1H, m), 1.55–1.18 (10H, m), 1.04 (3H, t, *J* = 7.1 Hz), 0.87 (3H, t, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 209.9, 95.2, 80.5, 75.6, 74.0 55.5, 48.3, 37.0, 32.0, 31.8, 31.0, 30.0, 24.9, 22.6, 14.0, 7.4; IR (neat): ν_{max} 2933, 1714, 1459, 1377 cm^{-1}; ESIMS: *m*/*z* 309 $[M+Na]^+$; HRMS (ESI) Calcd for $C_{16}H_{30}O_4Na$ 309.20363. Found: 309.20336.
(8S,9R,E)-9-(4-Methoxybenzyloxy)-8-(methoxymethoxy) tetradec-4-en-3-one (***3***): $[\alpha_D^{20}]$ +12.5 (*c* 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.29–7.23 (2H, m), 6.90–6.80 (3H, m), 6.16–6.08 (1H, m), 4.78 (1H, d, *J* = 6.7 Hz), 4.64–4.59 (2H, m), 4.45 (1H, d, *J* = 10.5 Hz), 3.80 (3H, s), 3.70–3.63 (1H, m), 3.48–3.38 (4H, m), 2.56 (2H, q, *J* = 14.3 Hz), 2.49–2.35 (1H, m), 2.33–2.16 (1H, m), 1.87–1.21 (10H, m) 1.10 (3H, t, *J* = 7.5 Hz), 0.88 (3H, t, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.0, 159.1, 146.5, 130.8, 130.1, 129.4, 113.7, 96.3, 80.3, 78.4, 71.9, 55.8, 55.2, 33.2, 31.9, 30.7, 29.0, 28.8, 25.6, 22.6, 14.0, 8.1; IR (neat): ν_{max} 3423, 2957, 2927, 1709, 1605 cm^{-1}; ESI-MS: *m*/*z* 407 $[M+Na]^+$.