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A radical mediated first total synthesis from 'diacetone glucose' and determination of the absolute stereochemistry of xylobovide☆

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Abstract—The first total synthesis by an intramolecular radical cyclisation protocol on a carbohydrate derived 5-hexynyl system, and determination of the absolute stereochemistry of xylobovide are reported.

Xylobovide (**1**), a bis-butyrolactone containing natural product was isolated[1] from *Xylaria obovata*. Bis-lactone **1** is an antibacterial, antifungal and phytotoxic agent, and shows activity against the phytotoxin inhibiting the germination of Eragrostistef seeds. The structure of **1** was determined from ^{1}H and ^{13}C NMR studies. Xylobovide (**1**) is a hybrid natural product, wherein the upper half resembles 4-*epi*-ethisolide,[2] while the lower half resembles canadensolide.[3] Earlier, our group reported[4] the synthesis of related natural products using a radical cyclisation protocol on carbohydrate derived 5-hexynyl systems. Herein, we report the first synthesis from 'diacetone glucose' (DAG) and determination of the absolute stereochemistry of xylobovide (**1**)[5] (Fig. 1).

From a retrosynthetic analysis of **1** (Scheme 1), it was envisaged that the bicyclic system **2** could be a late stage intermediate, while **2** could be obtained from radical cyclisation of xanthate **3**. Furthermore, compound **4** was envisaged as a precursor of **3**, while **4** could be prepared from 'diacetone glucose'. Thus the basic design involved an intramolecular radical cyclisation[6] on a 5-hexynyl system[7] to give a *cis*-fused bicyclic system with the efficient and simultaneous introduction of the *exo*-methylene group.

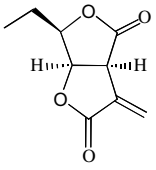
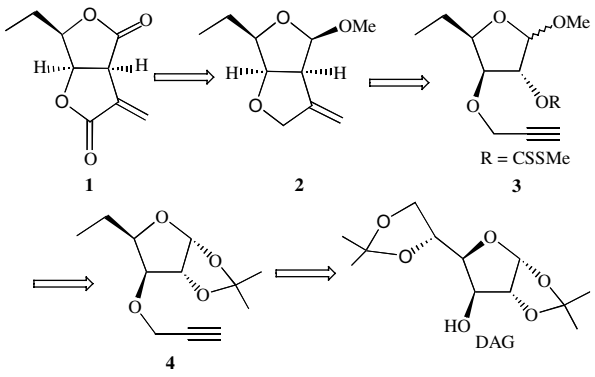


Figure 1.



Scheme 1.

Accordingly, the known[8] alcohol **5** (Scheme 2) was subjected to hydrogenation with 5% Pd–C to give **6** (71%), which on reaction with NaH and propargyl bromide furnished **7** in 82% yield, $[\alpha]_D^{25} = -40.54$ (*c* 0.8, $CHCl_3$). Methanolysis of **7** afforded a diastereomeric mixture of the α- and β-anomers **8** and **9** (1:1 ratio), respectively, which were separable by simple column chromatography. Treatment of **8** and **9** independently with NaH, CS_2 and MeI in THF gave the xanthates

Keywords: Radical cyclisation; Bis-butyrolactone; *cis*-Fused bicyclic system; 5-Hexynyl systems.
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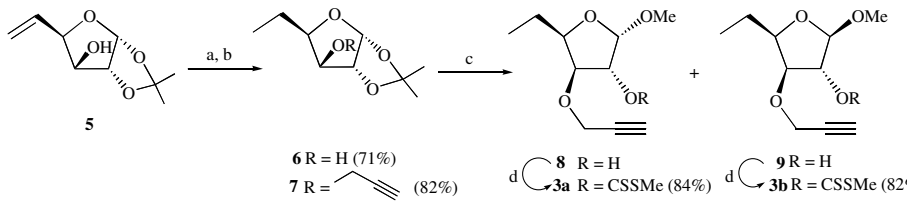
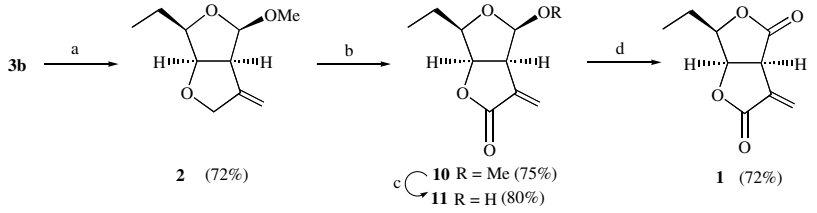


Scheme 2. Reagents and conditions: (a) 5% Pd–C, H_2, EtOH, 8 h, rt, 71%; (b) NaH, propargyl bromide, THF, 4 h, rt, 82%; (c) H^+, MeOH, 45 min, 60 °C, 86%; (d) NaH, CS_2, MeI, THF, 4 h, rt, 84% for **3a** and 82% for **3b**.



Scheme 3. Reagents and conditions: (a) *n*-Bu_3SnH, AIBN, benzene, reflux, 12 h, 72%; (b) CrO_3, pyridine, CH_2Cl_2, reflux, 2 h, 75%; (c) concd HCl, aq AcOH, 60 °C, 45 min, 80%; (d) PDC, CH_2Cl_2, reflux, 2 h, 72%.

3a in 84% yield, $[\alpha]_D^{25} = +58.5$ (*c* 0.7, $CHCl_3$), and **3b** in 82% yield, $[\alpha]_D^{25} = -78.42$ (*c* 0.6, $CHCl_3$), respectively.

Xanthates **3a** and **3b** (Scheme 3) were then treated with *n*-Bu_3SnH and AIBN in benzene at reflux, wherein **3b** underwent smooth regio- and stereoselective radical cyclisation and gave the expected *cis*-fused bicyclic system **2** in 72% yield, $[\alpha]_D^{25} = -121.12$ (*c* 0.4, $CHCl_3$), while **3a** gave a complex mixture of products perhaps due to steric hindrance. Oxidation of **2** with CrO_3–pyridine in CH_2Cl_2 furnished lactone **10** (75%), which on hydrolysis (concd HCl–aq AcOH) and further oxidation of the resultant lactol **11** with PDC in CH_2Cl_2 afforded **1** in 72% yield, which was thoroughly characterised from spectral data.

In conclusion, an efficient first total synthesis of xylobovide **1** has been achieved from DAG by an intramolecular radical cyclisation based route. This first synthesis of **1** unambiguously proves its absolute stereochemistry. Furthermore, it is evident that the intramolecular radical cyclisation on sugar derived 5-hexynyl systems is very efficient for the synthesis of natural products with structural diversity endowed with *cis*-fused bicyclic lactones having an α-methylene group.

Spectral analysis for selected compounds: *Compound **10***: $[\alpha]_D^{25} = -142.4$ (*c* 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.02 (t, 3H, $J = 7.8$ Hz, CH_3), 1.57–1.83 (m, 2H, H-7, H-7a), 3.38 (s, 3H, OCH_3), 3.54 (ddd, 1H, $J = 5.5$, 4.4, 2.0 Hz, H-3a), 3.92 (ddd, 1H, $J = 6.5$, 5.2, 2.4 Hz, H-6), 4.83 (dd, 1H, $J = 6.5$, 4.2 Hz, H-6a), 4.92 (d, 1H, $J = 5.5$ Hz, H-4), 5.64 (d, 1H, $J = 1.8$ Hz, H-8), 6.30 (d, 1H, $J = 1.8$ Hz, H-8a); ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.4, 23.1, 48.6, 56.5, 80.4, 81.9, 104.0, 124.6, 132.6, 169.8; FABMS: 199 (M^++1), 167 ($M^+ - OCH_3$); IR (neat): 1770, 1670 cm^{-1}; Analysis found C, 60.65; H, 7.15%. $C_{10}H_{14}O_4$ requires C, 60.59; H, 7.12%.

*Compound **1***: mp 102 °C, literature[1] 106 °C, $[\alpha]_D^{25} = -131.42$ (*c* 0.35, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (t, 3H, $J = 7.4$ Hz, CH_3), 1.86–1.98 (m, 2H, H-7, H-7a), 3.94 (dt, 1H, $J = 7.4$, 2.2 Hz, H-3a), 4.54 (ddd, 1H, $J = 7.5$, 5.2, 4.5 Hz, H-6), 5.12 (dd, 1H, $J = 6.7$, 4.5 Hz, H-6a), 6.16 (d, 1H, $J = 1.8$ Hz, H-8), 6.46 (d, 1H, $J = 1.8$ Hz, H-8a); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.7, 22.2, 46.2, 77.0, 84.0, 127.3, 129.9, 167.0, 172.5; FABMS: 183 (M^++1); IR (neat): 1770, 1675 cm^{-1}; Analysis found: C, 59.42; H, 5.57%. $C_9H_{10}O_4$ requires C, 59.34; H, 5.53%.

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