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Total synthesis of verbalactone: an efficient, carbohydrate-based approach

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ABSTRACT

A carbohydrate-based strategy for the total synthesis of verbalactone has been described. (3*R*,5*R*)-3,5-dihydroxydecanoic acid was dimerised under Yamaguchi conditions to provide verbalactone in an overall yield of 17% starting from 3-deoxy-1,2:5,6-di-*O*-isopropylidine-α-D-glucofuranose.

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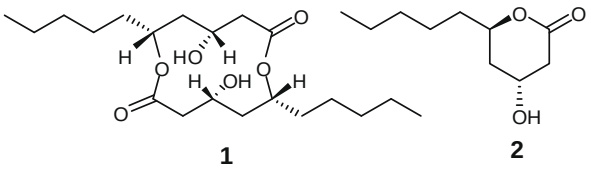
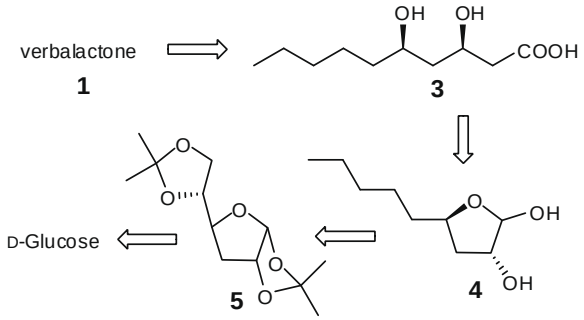
Verbalactone (**1**) is a novel macrocyclic dimer lactone with *C*2-symmetry and it exhibits interesting antibacterial activity. Verbalactone was isolated[1] by Mitaku et al from the roots of *Verbascum undulatum*. The structure and the absolute stereochemistry of **1** were determined as 4*R*, 6*R*, 10*R*, 12*R* by spectral methods (1D and 2D NMR, MS) and chemical correlation spectroscopy. The molecule has a NMR profile very similar to (+)-(3*R*,5*R*)-dihydroxy-5-decanolide (**2**).[2]



1 **2**

The unique dimeric lactone, verbalactone (**1**), has attracted several organic chemists[3–5] to develop its total synthesis. Interesting structural complexity and our continued interest in the area of synthesis of bioactive natural products containing 1,3 polyol systems using carbohydrate-based strategies[6] prompted us to undertake the synthesis of **1**. Herein, we report a simple and efficient total synthesis of verbalactone adopting the chiral pool approach.



Retrosynthetic analysis for Verbalactone

The retrosynthetic analysis delineated above indicated that verbalactone (**1**) can easily be synthesized exploiting Yamaguchi's lactonization on the key monomer seco acid, (3*R*,5*R*)-3,5-dihydroxy decanoic acid **3,** which can in turn be derived from D-glucose via intermediates **5** and **4** (Scheme 1).

The synthesis of seco acid **3** started with the preparation of 3-deoxy-1,2;5,6-di-*O*-isopropylidene- α-D-glucofuranose **5** from D-glucose.[7] Selective deprotection of the 5,6-*O*-isopropylidene group of compound **5** with 0.8% H_2SO_4 in MeOH at ambient temperature afforded the C5–C6 diol in 94% yield. Oxidative cleavage by using sodium metaperiodate followed by subsequent Wittig olefination with butyltriphenyl phosphorane provided alkene **6** in the ratio 3:7 (*E*/*Z*). Hydrogenation of alkene **6** using Raney-Ni in ethanol and then hydrolysis of the 1,2-*O*-isopropylidine

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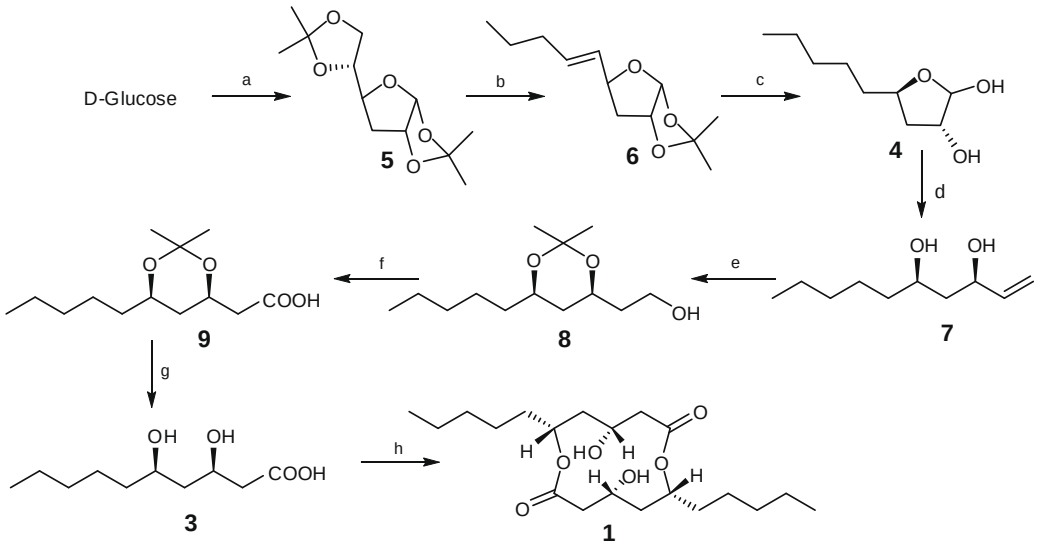

Scheme 1. Reagents and conditions: (a) Ref. 7; (b) (i) 0.8% aq H_2SO_4, MeOH, rt, 16 h, 95%; (ii) $NaIO_4$ on silica gel, CH_2Cl_2, 96%; (iii) $C_4H_9P^+Ph_3Br^-$, *n*-BuLi, THF, 0 °C, 81%; (c) (i) Raney-Ni, ethanol, 98%; (ii) 4% aq H_2SO_4, THF, 60 °C, 3 h, 94%; (d) $CH_3P^+Ph_3I^-$, *n*-BuLi, THF, 0 °C → rt, 80%; (e) (i) CSA (cat), 2,2-dimethoxypropane, CH_2Cl_2, 0 °C, 15 min, 98%; (ii) BH_3-DMS, THF, 0 °C, 4 h, 76%; (f) (i) Dess–Martin periodinane, CH_2Cl_2, 0 °C → rt, 1 h, 92%; (ii) $NaClO_2$, $NaH_2PO_4.2H_2O$, 30% H_2O_2, $^tBuOH:H_2O$ (3:1), 0 °C → rt, 3 h, 95%; (g) CSA (5 mol %), MeOH, rt, 30 min, 80%; (h) (i) 2,4,6-trichlorobenzoylchloride, Et_3N, THF, rt, 3 h; (ii) DMAP (30 equiv), toluene, reflux, 4 h, 60% (over two steps).

group with 4% aq sulfuric acid in THF at 60 °C afforded the diastereomeric lactol **4**.

One-carbon Wittig homologation of lactol **4** at 0 °C with in situ-generated methylenetriphenyl phosphorane yielded *syn*-1,3-diol **7**, thus providing the desired ten-carbon chain of the verbalactone monomer. In the ^1H NMR of diol **7**[8], the C4 methylene protons resonated separately as two distinguishable doublets of triplets indicating a 1,3-*syn*-relationship. This was further substantiated in the ^{13}C NMR studies of its isopropylidene derivative where the isopropylidene methyl carbons showed two separate signals at 30.2 and 19.8 ppm. The *syn*-1,3-diol **7** was transformed quantitatively into its isopropylidene derivative with 2,2-dimethoxypropane in the presence of catalytic camphor sulfonic acid (CSA). Selective hydroboration[9] of this acetonide derivative of **7** with BH_3-DMS reagent at 0 °C afforded primary alcohol **8** in 76% yield (9% of its regioisomer). The alcohol **8** on treatment with Dess–Martin periodinane gave the corresponding aldehyde, which on further oxidation[10] with sodium chlorite in the presence of 30% H_2O_2 and sodium dihydrogen phosphate dihydrate gave acid **9**. The spectral and analytical data[11] of **9** were in full agreement with the reported[5] compound. The unmasking of the 1,3-isopropylidine group was achieved by treating **9** with cat. CSA in anhydrous methanol and by carefully controlling the pH (=6) during work-up[3,5] to provide the (3*R*,5*R*)-3,5-dihydroxydecanoic acid **3**.

Finally, the synthesis of verbalactone was successfully completed using Yamaguchi's macrolactonization[12] to obtain **1** in 60% yield from **3** as a colorless oil $[\alpha]_D^{25}$ 9.1 (*c* 0.9, $CHCl_3$) along with monomer lactone **2** (22%). The ^1H and ^{13}C NMR spectra as well as other analytical data of synthetic **1** were identical with those of the natural product.[1]

In conclusion, an expeditious and economic total synthesis of verbalactone has been achieved in 17% overall yield by adopting the chiral pool approach.

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8. *Spectral data for compound* **7**: $[\alpha]_D^{25}$ −2.8 (*c* 1, $CHCl_3$); ^1H NMR δ: (400 MHz, $CDCl_3$): 5.92–5.84 (m, 1H), 5.25 (dt, *J* = 17.1, 1.3 Hz, 1H), 5.10 (dt, *J* = 10.5, 1.3 Hz, 1H), 4.42–4.34 (m, 1H), 3.93–3.84 (m, 1H), 3.15 (br s, 1H), 3.03 (br s, 1H), 1.67 (dt, *J* = 14.6, 2.8 Hz, 1H), 1.58 (dt, *J* = 14.6, 9.7 Hz, 1H), 1.51–1.39 (m, 2H), 1.25–1.35 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ: (100 MHz, $CDCl_3$): 140.7 (d), 114.3 (t), 73.7 (d), 72.5 (d), 42.8 (t), 38.0 (t), 31.8 (t), 25.0 (t), 22.5 (t), 14.0 (q); IR ($CHCl_3$): ν = 3368, 3012, 2932, 2860, 1647, 1424, 1216 cm^{-1}; MS (ESI): *m/z* 195.1 ([M + Na]$^+$).
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11. *Spectral data for compound* **9**: $[\alpha]_D^{25}$ +12.4 (*c* 0.5, $CHCl_3$); ^1H NMR δ: (400 MHz, $CDCl_3$): 4.33–4.25 (m, 1H), 3.88–3.79 (m, 1H), 2.57 (dd, *J* = 15.8, 7.0, 1H), 2.46 (dd, *J* = 15.8, 5.5, 1H), 1.55–1.24 (m, 10H), 1.45 (s, 3H), 1.39 (s, 3H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ: (100 MHz, $CDCl_3$): 176.0 (s), 99.0 (s), 68.8 (d), 65.8 (d), 41.2 (t), 36.3 (t), 36.2 (t), 31.7 (t), 30.0 (q), 24.5 (t), 22.6 (t), 19.7 (q), 14.0 (q); IR ($CHCl_3$): ν = 3019, 2931, 1713, 1382, 1216 cm^{-1}; MS (ESI): *m/z* 267.5 ([M +Na]$^+$).
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