

A FORMAL TOTAL SYNTHESIS OF (6S,7S,9R,10R)-6,9-EPOXYNONADEC-18-ENE-7,10-DIOL FROM D-GLUCOSE

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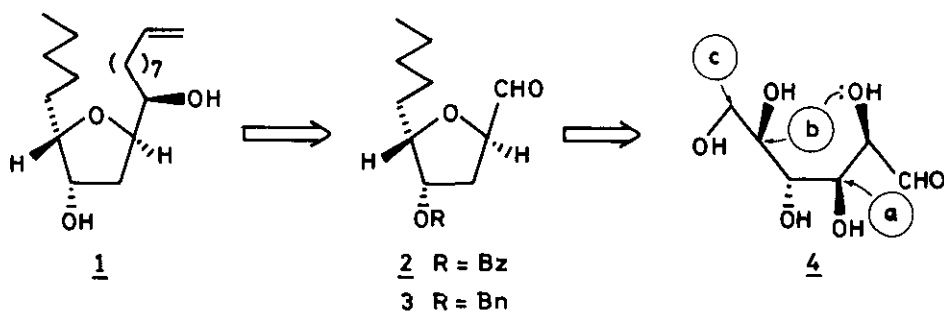
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Abstract - An enantiospecific synthesis of (2R,4S,5S)-tetrahydro-4-hydroxy-5-pentyl-2-furfuraldehyde (benzoate) (2) and (benzylate) (3), key intermediates in the synthesis of the title marine natural product (1) from D-glucose is described.

Highly functionalised tetrahydrofuran skeleton forms an integral unit of several biologically active natural products.¹ One of the distinctive features in the synthesis of these compounds is the stereocontrolled construction of tetrahydrofuran ring. A wide variety of stereospecific protocols have been developed² to prepare tetrahydrofuran derivatives, undoubtedly carbohydrates³ find a great deal of advantage due to inherent existence of sugars in furanose forms. We report an enantiospecific synthesis of (2R,4S,5S)-tetrahydro-4-hydroxy-5-pentyl-2-furfuraldehyde (benzoate) (2) and (benzylate) (3), established⁴ precursors for the synthesis of the title product (1) from D-glucose.

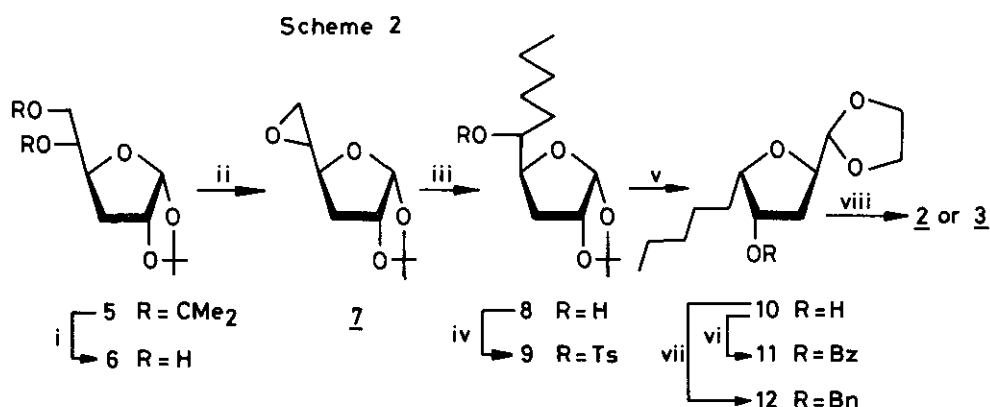
The correlation (Scheme 1) of the stereochemical centers of the target molecule

Scheme 1



(2 and 3) with those of D-glucose (4) implies that the basic premise of the strategy should involve three major synthetic operations: (a) deoxygenation at C-3, (b) formation of 2,5-anhydro ring with retention of configuration at C-2 and (c) four carbon chain extension at C-6.

Selective hydrolysis (Scheme 2) of the 5,6-isopropylidene group in 3-deoxy compound (5)⁵ was accomplished with 0.8% sulfuric acid in methanol for 18 h at room temperature in 80% yield. Subsequently, the diol (6)⁵ was treated with triphenylphosphine and diethyl azodicarboxylate under Mitsunobu condition⁶ to afford the epoxide (7) as an oil in 80% yield. The ¹H nmr data (CDCl₃) of 7 as follows: δ 1.31 (s, 3H), 1.50 (s, 3H), 1.7–2.5 (m, 2H), 3.5–4.0 (m, 3H), 4.20 (m, 1H), 4.75 (t, J = 3.5, 1H), 5.80 (d, J = 3.5, 1H); $[\alpha]_D$ -19° (c 2, EtOH). The ring opening of 7 with *n*-butylmagnesium bromide and catalytic amount of cuprous iodide at -60 °C gave 8 as an oil in 70% yield. The ¹H nmr data (CDCl₃) of 8 were as follows: δ 0.81 (t, J = 6, 3H), 1.31 (s, 3H), 1.50 (s, 3H), 0.9–2.2 (m, 10H), 4.06 (m, 2H), 4.62 (dis.t, 1H), 5.62 (d, J = 3.5, 1H); $[\alpha]_D$ +54.8° (c 1.5, CHCl₃). Compound 8 was treated with *p*-toluenesulphonyl chloride-pyridine to give the tosylate (9) as an oil in 95% yield. Compound 9 revealed the following ¹H nmr data (CDCl₃): δ 0.87 (t, J = 6, 3H), 1.25 (s, 3H),



i) 0.8% H₂SO₄, MeOH, room temperature, 18 h; ii) TPP, DEAD, C₆H₅ Me, Δ , 9 h; iii) *n*BuMgBr, CuI, -60°C, 0.5 h; iv) TsCl, Py, room temperature, 18 h; v) (CH₂OH)₂, PTSA, C₆H₆, Δ , 1.5 h; vi) BzCl, Py, room temperature, 3 h; vii) NaH, BnBr, THF, room temperature, 18 h; viii) CF₃COOH - H₂O, room temperature, 2 h.

1.43 (s, 3H), 1.0-2.25 (m, 10H), 2.43 (s, 3H), 4.20 (m, 1H), 4.56 (t, $J = 3.5$, 1H), 4.75 (m, 1H), 5.28 (d, $J = 3.5$, 1H), 7.18 (d, $J = 8$, 2H), 7.68 (d, $J = 8$, 2H); $[\alpha]_D +2.4^\circ$ (c 0.9, CHCl_3). Treatment of **9** with ethylene glycol and p-toluenesulphonic acid in refluxing benzene with azeotropic removal of water for 1.5 h afforded, as judged by tlc (Merck silica gel), a distinctly slower moving product (95%) whose structure **10** (obtained as an oil) was assigned unambiguously by spectral studies. The spectral data for **10** were as follows: ^1H nmr (CDCl_3): δ 0.81 (t, $J = 6$, 3H), 1.0-2.2 (m, 10H), 3.3-4.3 (m, 7H), 4.75 (d, $J = 7$, 1H); ms: m/z 229 (M^+-1), ir $\nu_{\text{max}}^{\text{neat}}$: 3450 cm^{-1} , $[\alpha]_D +15.2^\circ$ (c 0.6, CHCl_3). Conventional benzoylation of **10** with benzoyl chloride-pyridine afforded an oily benzoate (**11**) (100%) which was hydrolysed with aqueous trifluoroacetic acid to form rather unstable aldehyde (**2**) as an oil (90%). The ^1H nmr data of **2** were concurrent with the reported⁴ values.

In an alternative pathway, compound **10** was subjected to benzylation reaction with sodium hydride-benzyl bromide to give **12** as an oil in 90% yield. The ^1H nmr data (CDCl_3) of **12** were as follows: δ 0.87 (t, $J = 6$, 3H), 1.0-2.5 (m, 10H), 3.90 (m, 4H), 4.0-4.3 (m, 3H), 4.51 (ABq, $J = 12.8$, 2H), 4.70 ($J = 7$, 2H), 7.25 (s, 5H); $[\alpha]_D +29.9^\circ$ (c 0.7, CHCl_3). Compound **12**, on hydrolysis as described above, gave **3**, as an oil (90%). Since both the products **2** and **3** have been converted into **1** in one and two steps respectively,⁴ this study constitutes the formal total synthesis of the marine natural product (**1**).

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