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

Mukund K. Gurjar* and Prathama S. Mainkar

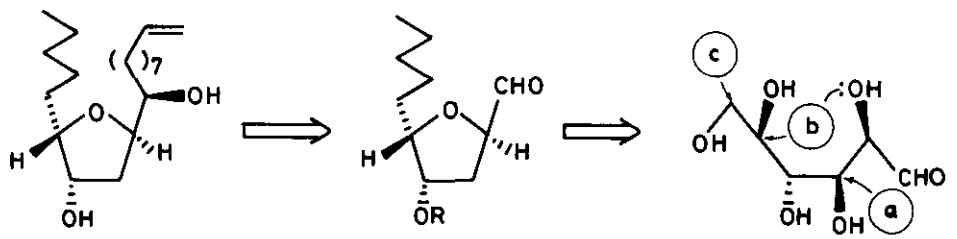
Indian Institute of Chemical Technology, Hyderabad 500 007, India

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 developed[2] to prepare tetrahydrofuran derivatives, undoubtedly carbohydrates[3] 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), established[4] 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

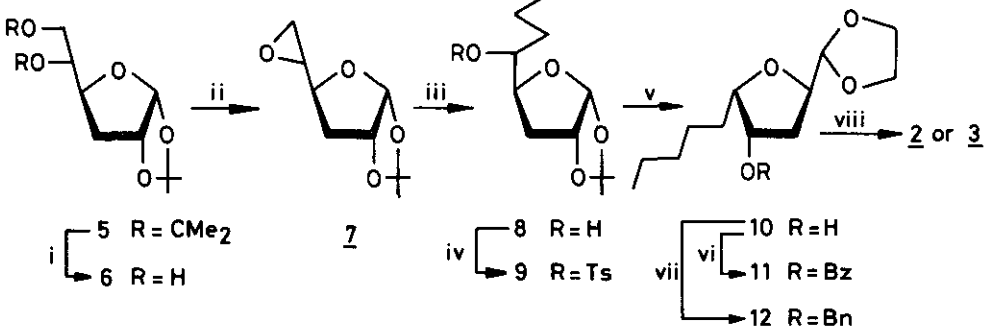


1 2 R = Bz 3 R = Bn 4

(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 condition[6] to afford the epoxide (**7**) as an oil in 80% yield. The ^{1}H nmr data ($CDCl_3$) 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 ^{1}H nmr data ($CDCl_3$) 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, $CHCl_3$). 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 ^{1}H nmr data ($CDCl_3$): δ 0.87 (t, J = 6, 3H), 1.25 (s, 3H),

Scheme 2



i) 0.8% H_2SO_4, MeOH, room temperature, 18 h; ii) TPP, DEAD, C_6H_5Me, Δ, 9 h; iii) nBuMgBr, CuI, -60°C, 0.5 h; iv) TsCl, Py, room temperature, 18 h; v) $(CH_2OH)_2$, PTSA, C_6H_6, Δ, 1.5 h; vi) BzCl, Py, room temperature, 3 h; vii) NaH, BnBr, THF, room temperature, 18 h; viii) $CF_3COOH - H_2O$, 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° (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: ^{1}H 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 ν_{max}^{neat}: 3450 cm^{-1}, $[\alpha]_D$ +15.2° (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 ^{1}H nmr data of **2** were concurrent with the reported[4] 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 ^{1}H 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° (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**).

One of the authors (MKG) thanks CSIR for generous financial support under **'Young Scientist Award Scheme'.**

REFERENCES

1. J. W. Westley, "Polyether Antibiotics : Naturally Occurring Acid Ionophores", Vols. I and II, Marcel Dekker, New York, 1982.
2. T. L. B. Boivin, Tetrahedron, 1987, **43**, 3309.
3. S. Hanessian, "The Total Synthesis of Natural Products : Chiron Approach", Pergamon Press, Oxford, 1983 ; A, Vasella, "Modern Synthetic Methods", 1980 (ed. R. Scheffold), Vol. 2, Otto Salle Verlag, Frankfurt am Main, p. 173.

4. D. R. Williams, Y. Harigaya, J. L. Moore, and A. D'Sa, J. Am. Chem. Soc., 1984, **106**, 2641 ; S. Hatakeyama, K. Sakurai, K. Saizo, and S. Takano, Tetrahedron Lett., 1985, **26**, 1333.

5. M. K. Gurjar and V. J. Patil, Indian J. Chem., 1986, **25B**, 596.

6. O. Mitsunobu, Synthesis, 1981, 1.

Received, 23rd October, 1989