Tetrahedron Letters,Vol.30,No.29,pp 3869-3872,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

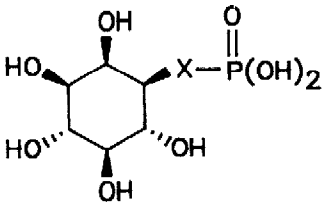
THE SYNTHESIS OF (±)myo-INOSITOL-1-PHOSPHONATE

Janusz J. Kulagowski

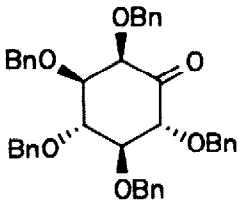
Merck Sharp and Dohme Research Laboratories,
Terlings Park, Eastwick Road, Harlow, Essex, CM20 2QR

Summary - The synthesis of a phosphonate analogue of (±)-myo-inositol-1-phosphate using Horner-Emmons methodology is described.

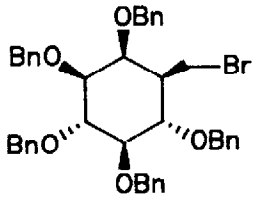
Phosphonates have found widespread use as isosteric[1,2], analogues of biologically active phosphates. Since phosphonates lack a scissile P-O bond, the main advantage gained over the corresponding phosphates in enzymic studies is a stability towards the action of phosphatases. As part of our interest in phosphoinositide (PI) metabolism[3] we required a non-hydrolysable analogue of myo-inositol-1-phosphate (1), one of the key intermediates in the phosphoinositide cycle[4]. Since the enzyme inositol monophosphatase which hydrolyses (1) has been reported to not be enantioselective[5], a synthesis of racemic phosphonate (2) was undertaken.



(1) X = O
(2) X = CH_2



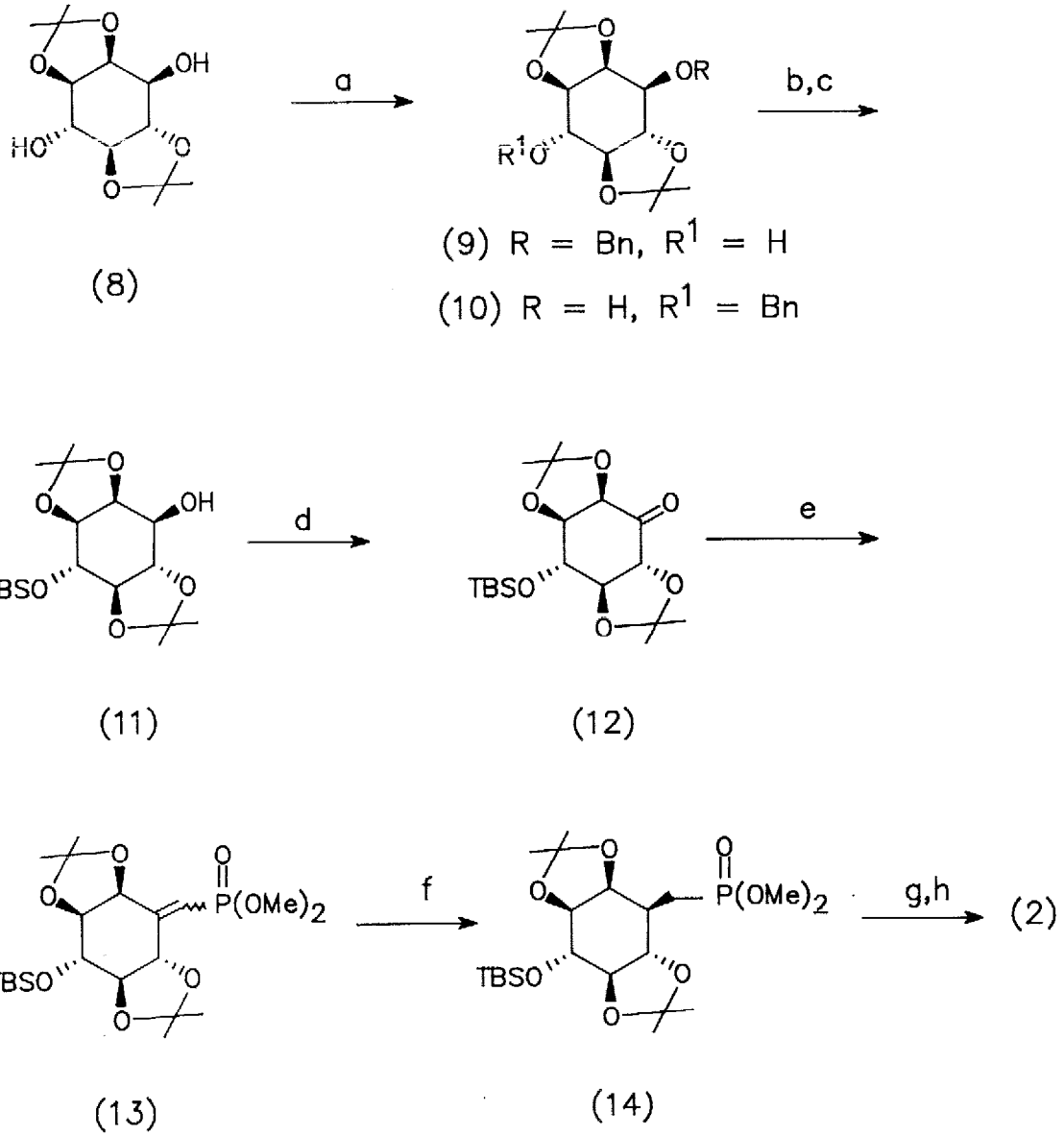
(3) Bn = CH_2Ph



(4)

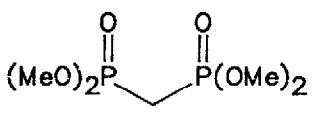
Our initial efforts focussed on the ketone (3)[6] and the bromomethyl derivatives (4)[7] as key intermediates in the synthetic scheme. It was anticipated that a phosphonate moiety could be introduced via Horner-Emmons methodology in the case of the former or an Arbusov reaction in the latter case. In the event, attempted addition of the anion of methylene bisphosphonate (5) to the ketone (3) gave only the phenol (6), whereas heating the bromide (4) with trimethyl phosphite led to isolation of the bicyclic derivative (7), as the only isolable product.

SCHEME

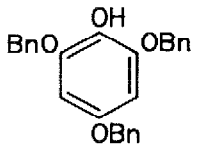


a) NaH, BnBr, DMF, 25°; 45% of (9). b) DBU, TBSCl, DMF, 60°; 99%. c) $Pd(OH)_2$, 50psi H_2, EtOH, NEt_3, 25°; 98%. d) NCS, Me_2S, PhMe, -23°, then NEt_3, 25°; 83%. e) n-BuLi, (5), THF, 0°; 73%. f) PtO_2, latm. H_2, EtOAc, 25°; 99%. g) TMSBr, CH_2Cl_2, 25°. h) 2:1 CF_3CO_2H/H_2O, 25°; 78% from (13).

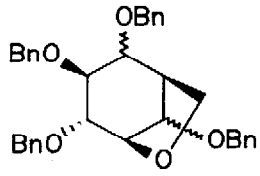
These results suggested that a rigid analogue of the ketone (3) was required.



(5)



(6)



(7)

The preparation of such a derivative and its transformation into (2) is outlined in the Scheme. Treatment of the diol (8)[8] with sodium hydride and benzyl bromide gave dibenzylated material, starting diol and a 9:1 mixture of monobenzyl derivatives[9] (9)[10] and (10)[11]. The major isomer was isolated by recrystallisation, the remaining hydroxyl silylated with t-butyl dimethylsilyl chloride, and the benzyl group removed by hydrogenolysis. Oxidation of the resulting alcohol (11)[12] to the required ketone (12)[13] could be carried out most effectively using the procedure of Corey and Kim[14]. Other methods of oxidation were found to give incomplete reaction, leading to inseparable mixtures of (11) and (12), or led to epimerisation of positions adjacent to the carbonyl group. Addition of (12) to the lithium salt of (5) then gave the vinyl phosphonate (13)[15] as a mixture of double bond isomers. The success of this reaction was found to be critically dependent on the order of addition; reversing the order led to mixtures of endocyclic olefins. Hydrogenation of (13) over platinum resulted in exclusive addition of hydrogen from the α-face, giving the desired myo-inositol stereochemistry at C-1. Transesterification of the phosphonate (14)[16] with bromotrimethylsilane followed by acid hydrolysis afforded (2)[17]. The biological activity of this compound will be reported in due course.

Acknowledgement - The author would like to thank Drs. R. Baker and P. Leeson for helpful discussions, Dr. R. Herbert for providing nmr data, and Mrs. E. Brawn for assistance with preparation of the manuscript.

References and Notes

1. R. Engel, Chem. Rev., 1977, 77, 349.

2. M.G. Blackburn, Chem. Ind. (London), 1981, 134; M.G. Blackburn, D.E. Kent, and and F. Kolkmann, J. Chem. Soc., Perkin Trans.I, 1984, 1119.

3. D.C. Billington, R. Baker, J.J. Kulagowski and I.M. Mawer, J. Chem. Soc. Chem. Commun., 1987, 314; D.C. Billington and R. Baker, J. Chem. Soc. Chem. Commun., 1987, 1011.

4. M.J. Berridge and R.F. Irvine, Nature (London), 1984, 312, 315; A.A. Abdel-Latif, Pharmacol. Rev., 1986, 38, 227.

5. L.M. Hallcher and W.R. Sherman, J. Biol. Chem., 1980, 255, 10896.

6. S.S. Yang, T.R. Beattie, P.L. Durette, T.F. Gallagher, T-Y. Shen, U.S. Pat. 4,515,722, 1985.

7. Prepared in 93% yield by treatment of the corresponding alcohol with PPh_3/CBr_4. For the synthesis of the alcohol see ref. 6.

8. J. Gigg, R. Gigg, S. Payne and R. Conant, Carbohydrate Res., 1985, 142, 132.

9. J. Gigg, R. Gigg, S. Payne and R. Conant, J. Chem. Soc., Perkin Trans. 1, 1987, 423.

10. (9 'H nmr ($CDCl_3$) δ 1.34 (3H, s), 1.46 (3H, s), 1.49 (3H, s), 1.55 (3H, s), 2.50 (1H, d, J = 2.6Hz), 3.26 (1H, dd, J = 9.8, 9.8Hz), 3.80 (1H, dd, J = 10.2, 4.3Hz), 3.81 (1H, m), 3.88 (1H, m), 4.05 (1H, dd, J = 9.8, 9.8Hz), 4.32 (1H, dd, J = 4.4, 4.4Hz), 4.81 (1H, d, J = 12.5Hz), 4.89 (1H, d, J = 12.5Hz), 7.26-7.43 (5H, m).

11. (10) 'H nmr ($CDCl_3$) δ 1.36 (3H, s), 1.39 (3H, s), 1.46 (3H, s), 1.48 (3H, s), 2.34 (1H, d, J = 8.8Hz), 3.41 (1H, dd, J = 10.4, 9.6Hz), 3.67 (1H, dd, J = 10.4, 6.0Hz), 3.80 (1H, dd, J = 10.0, 9.6Hz), 4.00 (1H, ddd, J = 10.1, 8.9, 4.6Hz), 4.20 (1H, dd, J = 6.0, 5.0Hz), 4.47 (1H, dd, J = 5.0, 4.6Hz), 4.82 (2H, s), 7.26-7.41 (5H, m).

12. (11) 'H nmr ($CDCl_3$) δ 0.10 (3H, s), 0.11 (3H, s), 0.91 (9H, s), 1.36 (3H, s), 1.41 (3H, s), 1.51 (3H, s), 1.57 (3H, s), 2.32 (1H, d, J = 8.8Hz), 3.25 (1H, dd, J = 9.6, 9.4Hz), 3.76 (1H, dd, J = 10.0, 9.8Hz), 3.79 (1H, dd, J = 10.5, 6.1Hz), 3.96 (1H, ddd, J = 10.0, 8.8, 4.6Hz), 4.02 (1H, dd, J = 5.9, 5.0Hz), 4.43 (1H, dd, J = 5.0, 4.8Hz).

13. (12) 'H nmr ($CDCl_3$). δ 0.14 (3H, s), 0.16 (3H, s), 0.93 (9H, s), 1.34 (3H, s), 1.44 (3H, s), 1.47 (3H, s), 1.54 (3H, s), 3.64 (1H, dd, J = 11.1, 9.8Hz), 4.14 (1H, dd, J = 9.8, 4.1Hz), 4.27 (2H, m), 4.58 (1H, d, J = 11.2Hz).

14. E.J. Corey and C.U. Kim, J. Amer. Chem. Soc., 1972, 94, 7586.

15. (13; minor isomer) 'H nmr ($CDCl_3$), δ 0.09 (6H, s), 0.88 (9H, s), 1.35 (3H, s), 1.39 (3H, s), 1.52 (3H, s), 1.56 (3H, s), 3.67 (1H, dd, J = 7.5, 6.0Hz), 3.71 (3H, d, J = 11.1Hz), 3.74 (3H, d, J = 11.1Hz), 4.17 (2H, m), 4.55 (1H, m), 5.12 (1H, m), 6.01 (1H, d, J = 15.5Hz).
(13; major isomer) 'H nmr ($CDCl_3$), δ 0.11 (3H, s), 0.12 (3H, s), 0.91 (9H, s), 1.36 (3H, s), 1.47 (3H, s), 1.49 (6H, s), 3.44 (1H, dd, J = 10.0, 10.0Hz), 3.71 (3H, d, J = 11.2Hz), 3.75 (3H, d, J = 11.2Hz), 3.89 (1H, dd, J = 10.0, 5.8Hz), 4.06 (1H, dd, J = 5.7, 5.6Hz), 4.40 (1H, m), 4.46 (1H, d, J = 5.6Hz), 5.89 (1H, d, J = 14.4Hz).

16. (14) 'H nmr ($CDCl_3$), δ 0.10 (6H, s), 0.91 (9H, s), 1.34 (3H, s), 1.37 (3H, s), 1.39 (3H, s), 1.46 (3H, s), 2.17 (2H, m), 2.31 (1H, m), 3.25 (1H, dd, J = 10.3, 9.4Hz), 3.50 (1H, dd, J = 10.8, 9.4Hz), 3.73 (3H, d, J = 10.8Hz), 3.74 (3H, d, J = 10.8Hz), 3.78 (1H, m), 3.93 (1H, dd, J = 6.4, 4.9Hz), 4.47 (1H, dd, J = 4.9, 4.2Hz).

17. (2) 'H nmr (D_2O), δ 1.80 (1H, m), 1.99 (1H, m), 2.14 (1H, ddd, J = 17.4, 15.2, 2.5Hz), 3.30 (1H, dd, J = 9.1, 8.1Hz), 3.40 (1H, dd, J = 9.9, 9.4Hz), 3.53 (1H, dd, J = 9.9, 2.9Hz), 3.60 (1H, dd, J = 10.0, 8.9Hz), 4.17 (1H, dd, J = 2.6, 2.5Hz),

(Received in UK 26 May 1989)