Tetrahedron Letters, Vol. 34, No. 17, pp. 2827-2830, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

The Alkylation of Dibutylstannylene Derivatives of 1,2-O-Isopropylidene-myo-inositol.[1]

Jill Gigg, Roy Gigg*, and Eloisa Martin-Zamora

Laboratory of Lipid and General Chemistry,
National Institute for Medical Research, Mill Hill, London NW7 1AA, U.K.

Abstract: Benzylation (or allylation) of 1,2-*O*-isopropylidene-*myo*-inositol in the presence of an excess of dibutyltin oxide gives, as major products, the readily isolable 3,4,6- (**12**) and 3,5,6-tri-*O*-alkyl (**13**) derivatives which are valuable intermediates for the synthesis of inositol phosphates of the phosphatidylinositol cycle.

The intense interest[2] in the biology of the inositol phosphates has resulted in considerable chemical research[3] on the synthesis of derivatives of *myo*-inositol.

We have described[4] the one-pot alkylation of dibutylstannylene derivatives of *myo*-inositol with allyl and crotyl bromides which provides[4] practical routes for the synthesis of 1,3,4-tri- and 1,3,4,5- and 1,3,4,6-tetra-*O*-allyl (crotyl) derivatives of *myo*-inositol which have been used[5] for the synthesis of inositol phosphates.

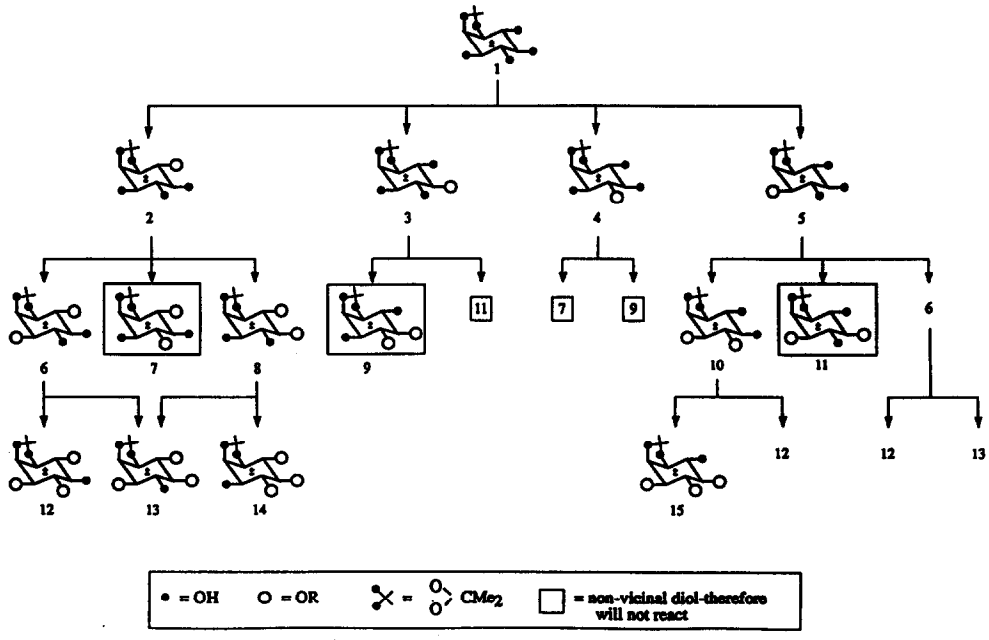
The direct alkylation of racemic 1,2-*O*-isopropylidene-*myo*-inositol[6] (**1**) under similar conditions was of interest and as all of the vicinal diols in this molecule are *trans*-equatorial it was difficult to predict the outcome of the reaction. As can be seen from the Scheme, if the reaction is carried out with an excess of reagents, there are four theoretical trialkylated products **12-15** and three potential dialkylated products **7, 9** and **11** which, because they contain no vicinal diol, would be expected to accumulate in the product.

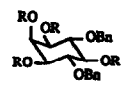
When racemic **1** was treated with an excess of benzyl bromide and dibutyltin oxide in the presence of tetrabutylammonium bromide in refluxing acetonitrile (using a Soxhlet containing molecular sieve 3A to remove water)[4] only two major products were observed [t.l.c. (ether-light petroleum, 2:1), Rfs 0.8 and 0.7 together with minor products 0.6, 0.5, 0.2 and 0.1] and these were readily isolated by column chromatography on silica gel. They were shown to be identical with the products obtained by the tin-mediated benzylation of racemic 3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-*myo*-inositol[7] **6** (R=Bn) i.e. they were compounds **12** (R=Bn, Rf 0.8, m.p. 80-81°, 40% yield) and **13** (R=Bn, Rf 0.7, m.p. 60-61°, hygroscopic, 30% yield). The structures were assigned as described below.

The two other possible tri-*O*-benzyl derivatives **14** and **15** (R=Bn) were present in minor proportions and co-chromatographed (Rf 0.6). Compound **15** (R=Bn) has been prepared previously[8] and the presence of compound **14** (R=Bn) together with this was indictated after removal of the *O*-isopropylidene group and preparation of the mixed triacetates. ^{1}H-N.m.r. showed the presence of the symmetrical triacetate derived from **14** (R=Bn) together with the known[8] triacetate derived from **15** (R=Bn).

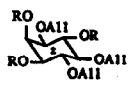
The product with Rf 0.5 (m.p. 97-98°; diacetate, m.p. 110-111°) was shown to be **7** (R=Bn). Acidic hydrolysis gave the tetraol **16** (m.p. 138-140°) and the ^{1}H-n.m.r. spectrum of the tetraacetate **17** (m.p. 189-190°) indicated its symmetrical structure. The other polar products were not investigated.

Tin-Mediated Alkylation of 1,2-O-Isopropylidene-myo-Inositol With Excess Reagents

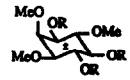




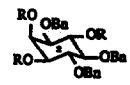
16 R = H
17 R = Ac



18 R = H
19 R = Ac
20 R = Me

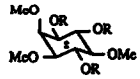


21 R = H
22 R = Ac

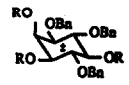


23 R = H
24 R = Ac
25 R = Bz

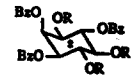
26 R = H
27 R = Me



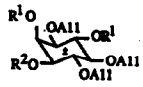
28 R = H
29 R = Ac



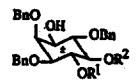
30 R = H
31 R = Ac
32 R = Bz



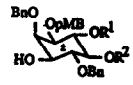
33 R = H
34 R = PO (OBn)$_2$



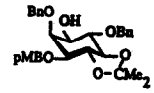
35 R^1 = R^2 = Bn
36 R^1 = H; R^2 = pMB
37 R^1 = Bn; R^2 = pMB



38 R^1 = R^2 = H
39 R^1, R^2 = CMe$_2$



40 R^1 = R^2 = H
41 R^1, R^2 = CMe$_2$



42

All = CH_2-CH = CH_2; Bn = CH_2Ph; Bz = COPh; pMB = $CH_2Ph(pOMe)$

When the benzylation reaction was performed with **1** and two equivalents of dibutyltin oxide, the highly crystalline compound **6** (R=Bn) was readily isolated in *ca.* 45% yield from the reaction mixture and this is a superior route to **6** (R=Bn) than that described previously[7]. We have shown[9a] that compound **6** (R=Bn) is readily resolved *via* the bis-camphanates and that the chiral compounds **6** (R=Bn) can be used[9b] for the preparation of *myo*-inositol derivatives suitable for the synthesis of inositol phosphates.

The tin-mediated reaction of **1**, using excess reagents, with allyl bromide as the alkylating agent gave similar results. When allyl bromide was used as the solvent in this reaction, in place of acetonitrile, the rate was enhanced. The two major products were again **12** and **13** (R=All) [t.l.c. (ether-light petroleum, 3:1), Rfs 0.8 and 0.7] each obtained in *ca.* 30% yield.

The structure of syrupy **13** (R=All; Rf 0.7) was established by acidic hydrolysis to the known[4] crystalline racemic 1,4,5-tri-*O*-allyl-*myo*-inositol **18** (which gave known[4] triacetate **19**). Methylation of **18** gave **20** and this on deallylation[10] with Pd/C gave 1,2,4-tri-*O*-methyl-*myo*-inositol **21** which gave the triacetate **22** (m.p. 157-159°). Acidic hydrolysis of **13** (R=Bn), described above, gave the triol **23** (m.p. 119-120°; triacetate **24**, m.p. 112-113°) which on methylation and subsequent debenzylation followed by acetylation also gave **22** thus establishing the structure of **13** (R=Bn).

Hydrolysis of the syrupy **12** (R=All, Rf 0.8) gave the triol **26** (m.p. 120-122°). Methylation of this gave **27** and subsequent deallylation gave 1,2,5-tri-*O*-methyl-*myo*-inositol **28** which gave the triacetate **29** (m.p. 161-163°). Acidic hydrolysis of the product **12** (R=Bn), described above, gave the triol **30** (monohydrate, m.p. 83-84°; triacetate **31**, m.p. 85-86°). Methylation of **30** and subsequent debenzylation followed by acetylation of the product also gave the triacetate **29** thus establishing the structure of **12** (R=All).

Benzoylation of **30** gave **32** (m.p. 129-130°) and benzoylation of **23** gave **25** (m.p. 146-147°). Compound **25** is being used as a model compound for the synthesis of 1,4,5-IP_3 *via* compounds **33** and **34** especially as the chiral derivatives are available from chiral **6** (R=Bn)[9a]. The route to 1,4,5-IP_3 *via* chiral **33** and **34**, obtained from *chiro*-inositol, has been described[11a] by Ballou and Tegge and chiral **33** has also been prepared by Bruzik and Tsai[11b].

Benzylation of **18** gave the known[7] 1,4,5-tri-*O*-allyl-2,3,6-tri-*O*-benzyl-*myo*-inositol **35** which has been used[7] for the preparation of 1,2,4-tri-*O*-benzyl-*myo*-inositol **38** which is readily resolved[5a,c,12] *via* the camphanates of the *O*-isopropylidene derivate **39** and is an intermediate[5d] for the synthesis of 1,4,5-IP_3. Tin-mediated *p*-methoxybenzylation of **18** gave **36** (m.p. 53-55°) and this on benzylation gave syrupy **37**. Deallylation[10] of **37** gave **40** (m.p. 124-125°; triacetate, m.p. 127-128°) which can also be resolved[5c] *via* the camphanates of the *O*-isopropylidene derivative **41**. The chiral derivative **42**[5c] of **41** is being used[13] as an intermediate for the synthesis of phosphatidylinositol 3-phosphate, 4,5-bisphosphate and 3,4,5-trisphosphate. The chiral derivatives of **30** [available from chiral **6** (R=Bn)[9a]] will also serve for the preparation of chiral **32** and hence D- and L-*myo*-inositol 1,4,6-trisphosphates which are also components[14] of the phosphatidylinositol cycle.

Acknowledgements; We thank Perstorp Pharma, Perstorp, Sweden for support (to J.G.) and NATO for a Research Fellowship to E.M-Z. who is a visiting scientist from the University of Seville, Spain.

References;

1. The Allyl Group for Protection in Carbohydrate Chemistry, Part 28. For Part 27 see reference 5(d).
2. Majerus,P.J. *Ann. Review Biochem.*, **1992**, *61*, 225-250: Putney,J.W. Ed.; *Inositol Phosphates and Calcium Signalling* (Vol. 26 of Advances in Second Messenger and Phosphoprotein Research), Raven Press, N.Y., 1992: Fisher,S.K.; Heacock,A.M.; Agranoff,B.W. *J. Neurochem.*, **1992**, *58*, 18-38: Berridge,M.J. *Nature (London)*, **1993**, *361*, 315-325.
3. Reitz,A.B. Ed.; *Inositol Phosphates and Derivatives* (Vol. 463 of ACS Symposium Series) ACS, Washington DC, 1991: *Carbohydr. Res.*, **1992**, *234* (Special Issue on Second Messengers).
4. Desai,T.; Gigg,J.; Gigg,R.; Payne,S.; Penades,S.; Rogers,H.J. *Carbohydr. Res.*, **1991**, *216*, 197-209.
5. (a) Desai,T.; Gigg,J.; Gigg,R.; Payne,S. *Carbohydr. Res.*, **1992**, *225*, 209-228: (b) Desai,T.; Gigg,J.; Gigg,R.; Payne,S. *Carbohydr. Res.*, **1992**, *228*, 65-79: (c) Desai,T.; Gigg,J.; Gigg,R.; Payne,S.; Penades,S. *Carbohydr. Res.*, **1992**, *234*, 1-21: (d) Desai,T.; Fernandez-Mayoralas,A.; Gigg,J.; Gigg,R.; Payne,S. *Carbohydr. Res.*, **1992**, *234*, 157-175.
6. Gigg,J.; Gigg,R.; Payne,S.; Conant,R. *Carbohydr. Res.*, **1985**, *142*, 132-134.
7. Gigg,J.; Gigg,R.; Payne,S.; Conant,R. *J. Chem. Soc. (Perkin Trans. I)*, **1987**, 423-429.
8. Desai,T.; Fernandez-Mayoralas,A.; Gigg,J.; Gigg,R.; Payne,S. *Carbohydr. Res.*, **1990**, *205*, 105-123.
9. Desai,T.; Gigg,J.; Gigg,R.; Martin-Zamora,E. *Abstracts XVIth International Carbohydrate Symposium, Paris, France, July 5-10*, **1992** (a) A150; (b) A151.
10. Boss,R.; Scheffold,R. *Angew. Chem. Int. Ed. Engl.*, **1976**, *15*, 558-559.
11. (a) Tegge,W.; Ballou,C.E. *Proc. Nat. Acad. Sci.*, **1989**, *86*, 94-98; Ballou,C.E.; Tegge,W. *ACS Symposium Series*, **1991**, *463*, 33-42; (b) Bruzik,K.S.; Tsai,M-D. *J. Amer. Chem. Soc.*, **1992**, *114*, 6361-6374.
12. Gigg,J.; Gigg,R.; Payne,S.; Conant,R. *J. Chem. Soc. (Perkin Trans. I)*, **1987**, 1757-1762.
13. Desai,T.; Fernandez-Mayoralas,A.; Gigg,J.; Gigg,R.; Jaramillo,C.; Payne,S.; Penades,S.; Schnetz,N. *ACS Symposium Series*, **1991**, *463*, 86-102.
14. Stephens,L.R.; Downes,C.P. *Biochem. J.*, **1990**, *265*, 435-452.

(Received in UK 3 March 1993)