Tetrahedron Letters, Vol.32, No.49, pp 7309-7312, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

Highly Diastereoselective Bis-Hydroxylation of a Protected Conduritol B: A Short Route to *myo*-Inositol Derivatives.

Odón Arjona[a], Alfonso de Dios[a], Roberto Fernández de la Pradilla[b]*, and Joaquín Plumet [a]*.

[a] Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense, 28040 Madrid, Spain.

[b] Instituto de Química Orgánica, C.S.I.C., Juan de la Cierva 3, 28006 Madrid, Spain.

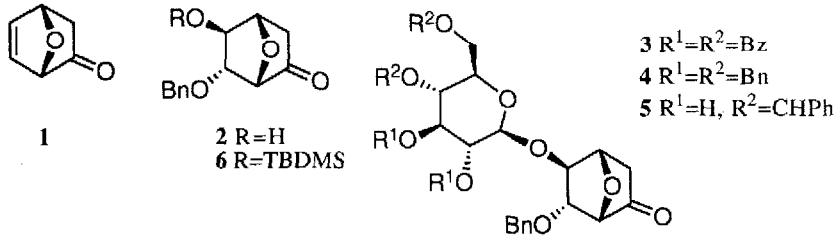
Key words: Glycosyl-7-oxanorbornanes; Stereoselective Reduction; Conduritol B; Bis-Hydroxylation; *myo*-Inositol Derivatives

Abstract: *Model studies on a synthesis of glycosylinositols via glycosyloxanorbornanes have resulted in a short and highly stereoselective synthesis of conveniently protected myo-inositols from 7-oxanorbornen-2-one featuring a highly diastereoselective catalytic osmylation of a protected Conduritol B.*

Despite the recent appearance of numerous reports on the preparation of differentially protected *myo*-inositols[1-3], these molecules remain challenging synthetic targets. This high level of interest, sustained by the recognized biological importance of inositol phosphates[4] and glycosyl-phosphatidylinositol derivatives[5,6], along with our involvement in the chemistry of 7-oxanorbornenes[7], versatile synthetic intermediates[8], motivated the research described here.

Our strategy envisioned glycosylation of ketone **2** (Scheme 1), prepared in 3 steps (65% overall)[9] from readily available optically pure 7-oxanorbornen-2-one **1**[10], followed by cleavage of the oxygen bridge as described by Vogel[11] and subsequent reduction to the allylic alcohol and hydroxylation of the double bond. The recent disclosure of Martín-Lomas' protocol to prepare a 1,6 differentially protected *myo*-inositol from a Conduritol B starting material[3a], prompted us to submit our preliminary results in this field.

At the initial stage of this investigation, racemic materials were employed[12], to establish if resolution could be achieved upon glycosylation, thus shortening considerably the synthesis. Also, due to the symmetry of the target molecule, one diastereoisomer would lead to a 1,4-substitution pattern and the other one to a



1

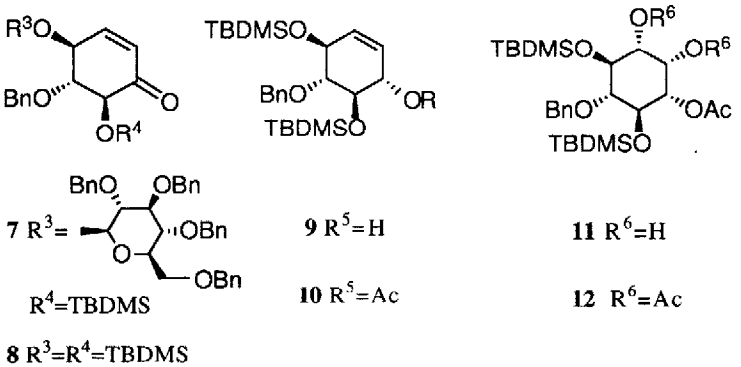
2 R=H
6 R=TBDMS

3 $R^1=R^2=Bz$
4 $R^1=R^2=Bn$
5 $R^1=H$, $R^2=CHPh$

Scheme 1

1,6-pattern which are both of interest[5,6]. In this context, glycosylation of **2** with commercially available α-D-glucopyranosyl bromide tetrabenzoate ($HgBr_2$, $Hg(CN)_2$, C_6H_6, 70°C, 4Å molecular sieves, 5 h, 79%)[13] afforded **3** as a mixture of diastereomers separable by flash chromatography. Similarly, PhSeOTf promoted glycosylation[14] (Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside, CH_3CN, -40°C, 4Å molecular sieves, 2 h, β:α *ca.* 4:1, 75%) produced a good yield of **4** as a mixture of anomers. Separation of isomers at this stage was possible but cumbersome. Having explored the reactivity of this hydroxyl group, we sought a more efficient separation procedure. To this end, and to avoid a participating group at C-2 (see below) we prepared benzylidene derivative **5** from **3** by conventional methods (1. NaOMe/MeOH; 2. $PhCH(OMe)_2$, pTsOH, C_6H_6). Trituration of the mixture of diastereomers of **5** with $CHCl_3$ provided a solution of one isomer and a solid residue of the other isomer, both practically pure as determined by ^1H NMR ($CDCl_3$ and CD_3COCD_3 respectively)[15]. The remarkable simplicity of this separation is noteworthy. Also, it should be mentioned that these oxanorbornanic glycosides are potential precursors of rare disaccharides[8].

While the treatment of benzoylated glycoside **3** with Et_3N/TMSOTf, under Vogel's conditions[11], resulted in traces of the desired enone and extensive decomposition, perbenzylated glycoside **4** afforded a 74% yield of enone **7** (Scheme 2). Thus, it appears that the above conditions are not compatible with a participating group at C-2. Having secured that cleavage of the oxygen bridge could be effected in the presence of a carbohydrate moiety in the molecule, we turned our attention to the reduction-hydroxylation sequence. Considering the controversial results in the literature about these reductions[16] and to facilitate analysis of the spectral data we prepared model enone **8** from alcohol **2** (1. TBDMSCl, DMF, Imidazole; 2. Et_3N/TBDMSOTf, C_6H_6, 89% overall].



Scheme 2

Reduction under Luche's conditions[17] ($NaBH_4/CeCl_3$, MeOH, 0°C, 90%) provided a 94:6 mixture of epimers favoring Conduritol B derivative **9**. The selectivity of the process appears to depend on the nature of the protecting group at C-5, quite remote from the reactive center[16]; this may be tentatively attributed to a conformational phenomenon. At any rate, reduction with $LiAl[OC(CH_3)_3]_3H$ (THF, -78° to RT, 12 h, 98%) afforded exclusively **9** in a stereospecific manner.

At this stage, and in view of previous efforts in the literature[18,19] we reasoned that the only possibility of achieving a useful diastereoselectivity in the hydroxylation of the very "symmetrical" double bond of **9** was to protect the free alcohol with a small and electron withdrawing group. Thus, the reaction between acetate **10** and a catalytic amount of OsO_4 (Acetone:Water, 8:1, Et_3NO, RT, 24 h, 60%), was examined, and, to our delight, the practically single diol **11** (diastereoselectivity=91:9) was obtained[20]. The structure of **11** was conclusively established by acetylation to *meso*-triacetate **12**[21]. Since the selective manipulation of hydroxyls at C-1 and C-2 in *myo*-inositol derivatives is well documented[22] and positions 4 and 6 may be readily differentiated earlier in the synthesis, this outstanding selectivity found enables us to prepare totally differentiated *myo*-inositol derivatives in a highly efficient manner. Furthermore, our route allows for the

equally facile synthesis of both enantiomers and should be amenable to the preparation of analogues[23] by early manipulation of the furan nucleus or the oxabicyclic precursor.

In conclusion, the selectivity of the catalytic bis-hydroxylation of Conduritol B derivatives may be controlled by the appropiate choice of protecting groups. We are currently exploring the generality of this phenomenon as well as the completion of the synthesis of model glycosyl-inositols outlined here and the extension of the methodology to aminoglycosyl derivatives.

Acknowledgment. This research was supported by D.G.I.C.Y.T. (Grant PB89-0099) and by the C.S.I.C. We thank the Comunidad de Madrid for a doctoral fellowship to A.d.D.

References and notes.

1. For reviews see: a) Potter, B.V.L. *Nat. Prod. Rep.* **1990**, *7*, 1-24. b) Billington, D.C. *Chem. Soc. Rev.* **1989**, *18*, 83.
2. For recent reports from *myo*-inositol, see: a) Dreef, C.E.; Tuinman, R.J.; Lefeber, A.W.M.; Elie, C.J.J.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron* **1991**, *47*, 4709-4722. b) Watanabe, Y.; Fujimoto, T.; Shinohara, T.; Ozaki, S. *J. Chem. Soc., Chem. Commun.* **1991**, 428-429. c) Zapata, A.; Fernández de la Pradilla, R.; Martín-Lomas, M.; Penadés, S. *J. Org. Chem.* **1991**, *56*, 444-447. d) Gilbert, I.H.; Holmes, A.B. *Tetrahedron Lett.* **1990**, *31*, 2633-2634.
3. For recent reports from other starting materials see: a) Jaramillo, C.; Martín-Lomas, M. *Tetrahedron Lett.* **1991**, *32*, 2501-2504. b) Ley, S.V.; Parra, M.; Redgrave, A.J.; Sternfeld, F. *Tetrahedron* **1990**, *46*, 5995-5026. c) Carless, H.A.J.; Busia, K. *Tetrahedron Lett.* **1990**, *31*, 3449-3452. d) Akiyama, T.; Takechi N.; Ozaki, S. *Tetrahedron Lett.* **1990**, *31*, 1433-1434.
4 See ref. 1. See also: a) Ferguson, M.A.J.; Williams, A.F. *Ann. Rev. Biochem.* **1988**, *57*, 285. b) Berridge, M.J. *Ibid.* **1987**, *56*, 159.
5. a) Saltiel, A.R.; Cuatrecasas, P. *Am. J. Physiol.* **1988**, *255*, C1. b) Mato, J.M.; Kelly, K.L.; Abler, A.; Jarret, L. *J. Biol. Chem.* **1987**, *262*, 2131-2137. c) Ferguson, M.A.J.; Homans, S.W.; Dwek, R.A.; Rademacher, T.W. *Science* **1988**, *239*, 753. d) Homans,S.W.; Edge, C.J.; Ferguson, M.A.J.; Dwek, R.A.; Rademacher, T.W. *Biochemistry* **1989**, *28*, 2881.
6. For recent synthetic efforts see: a) Mukarata, C.; Ogawa,T. *Tetrahedron Lett.* **1991** *32*, 671-674 and previous papers by this group. b) Berlin, W.K.; Zhang, W.-S.; Shen, T.Y. *Tetrahedron* **1991**, *47*, 1-20. c) Elie, C.J.J.; Verduyn, R,; Dreef, C.E.; Brounts, D.M.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron* **1990**, *46*, 8243-8254 and previous papers by this group. d) Mootoo, D.R.; Konradsson, P.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1989**, *111*, 8540-8542.
7. a) Arjona, O.; de Dios, A.; Fernández de la Pradilla, R.; Mallo, A.; Plumet, J. *Tetrahedron* **1990**, *46*, 8179-8186. b) Arjona, O.; Fernández de la Pradilla, R.; Pita-Romero, I.; Plumet, J.; Viso, A. *Ibid.* **1990**, *46*, 8199-8206. c) Arjona, O.; Fernández de la Pradilla, R.; Martín-Domenech, A.; Plumet, J. *Ibid.* **1990**, *46*, 8179-8186.
8. a) Vogel, P. *Bull. Soc. Chim. Belg.* **1990**, *99*, 395-439. b) Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett* **1990**, 173-185. c) Neff, D.-P.; Chen, Y.; Vogel, P. *Helv. Chim. Acta* **1991**, *74*, 508-516. d) Jeganathan, S.; Vogel, P. *J. Org. Chem.* **1991**, *56*, 1133-1142. e) Reymond, J.-L.; Pinkerton, A.A.; Vogel, P. *J. Org. Chem.* **1991**, *56*, 2128-2135.
9. Le Drian, C.; Vogel, P. *Helv. Chim. Acta* **1987**, *70*, 1703-1720.
10. a) See reference 8a. b) Reymond, J.-L.; Vogel, P. *Tetrahedron: Asymmetry* **1990**, *1*, 729-736. c) Saf, R.; Faber, K.; Penn, G.; Griengl, H. *Tetrahedron* **1988**, *44*, 389-392.
11. Le Drian, C.; Vieira, E.; Vogel, P. *Helv. Chim. Acta* **1989**, *72*, 338-347.
12. For simplicity, only one enantiomer or diastereomer is despicted. The yields are not optimized.
13. Flowers, H.M. *Methods in Carbohydrate Chemistry*, Vol. VI, p.474, Academic Press: New York, 1972.
14. Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1990**, *202*, 165-175.

15. This straightforward separation was carried out on a "clean" mixture of **5** previously filtered through silica gel. Additionally separation could also be achieved by flash chromatography. Some representative data follows:
5A (Rf 0.20, AcOEt:Hexane, 2:1), ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.13 (*d*, 1H, *J*=17.8 Hz, H_{3endo}); 2.47 (*ddd*, 1H, *J*=17.8, 6.7, 1.5 Hz, H_{3exo}); 4.39 (*d*, 1H, *J*=7.7 Hz, anomeric); 5.52 (*s*, 1H, benzylidene).
5B (Rf 0.13, AcOEt:Hexane, 2:1), ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 2.14 (*d*, 1H, *J*=17.8 Hz, H_{3endo}); 2.45 (*ddd*, 1H, *J*=17.8, 6.7, 1.6 Hz, H_{3exo}); 4.68 (*d*, 1H, *J*=7.7 Hz, anomeric); 5.59 (*s*, 1H, benzylidene).
16. a) Jaramillo, C.; Fernández de la Pradilla, R.; Martín-Lomas, M. *Carbohydr. Res.* **1991**, *209*, 296-298 and references cited therein. b) See ref. 3c.
17. Gemal, A.L.; Luche, J.L. *J. Am. Chem. Soc.* **1981**, *103*, 5454-5459.
18. a) See ref. 3c. b) Chida, N.; Ohtsuka, M.; Nakazawa, K.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1989,** 436-438. c) Ley, S.V. *Pure & Appl. Chem.* **1990**, *62*, 2031-2034 and references cited therein.
19. a) Evans, D.A.; Kaldor, S.W. *J. Org. Chem.* **1990**, *55*, 1698-1700. b) Cha , J.K.; Christl, W.J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247-2255.
20. A small amount of product resulting from acetate migration to C-2 (<7%) was detected in the ^{1}H NMR spectrum of the crude reaction mixture. These isomers provided the same triacetate **12**.
21. ^{1}H NMR ($CDCl_3$, 300 MHZ) δ: -0.012 (*s*, 6H, Me_2Si); 0.02 (*s*, 6H, Me_2Si); 0.76 (*s*, 18H, 2 ^{t}BuSi); 2.04 (*s*, 6H, 2 AcO); 2.17 (*s*, 3H, AcO); 3.34 (*t*, 1H, *J*=9.1 Hz, H5); 4.05 (*dd*, 2H, *J*=10.0, 9.1 Hz, H4, H6); 4.89 (*dd*, 2H, *J*=10.0, 2.9 Hz, H1, H3); 4.92 (*s*, 2H, $PhCH_2$); 5.51 (*t*, 1H, *J*=2.9 Hz, H2); 7.28 (*m*, 5H, H-Ar).
22. For recent reports in which hydroxyls 1 and 2 are diferentiated, see: a) Estevez, V.A.; Prestwich, G.D. *Tetrahedron Lett.* **1991**, *32*, 1623-1626. b) Schultz, C.; Metschies, T.; Gerlach, B.; Stadler, C.; Jastorff, B. *Synlett* **1990,** 163-165.
23. For recent references dealing with *myo*-inositol analogues, see: a) Baker, R.; Carrick, C.; Leeson, P.D.; Lennon, I.C.; Liverton, N.J. *J. Chem. Soc., Chem. Commun.* **1991**, 298-300. b) Kozikowski, A.P.; Fauq, A.H.; Powis, G.; Melder, D.C. *J. Am. Chem. Soc.* **1990**, *112*, 7403-7404. c) Falck, J.R.; Abdali, A.; Wittenberger, J. *J. Chem. Soc., Chem. Commun.* **1990**, 953-954.

(Received in UK 19 September 1991)