ELSEVIER

Carbohydrate Research 314 (1998) 277–281

CARBOHYDRATE RESEARCH

Note

A concise synthesis of *neo*-inositol

Andrew M. Riley, David J. Jenkins, Barry V.L. Potter *

Wolfson Laboratory of Medicinal Chemistry, Department of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, UK

Received 9 October 1998; accepted 27 November 1998

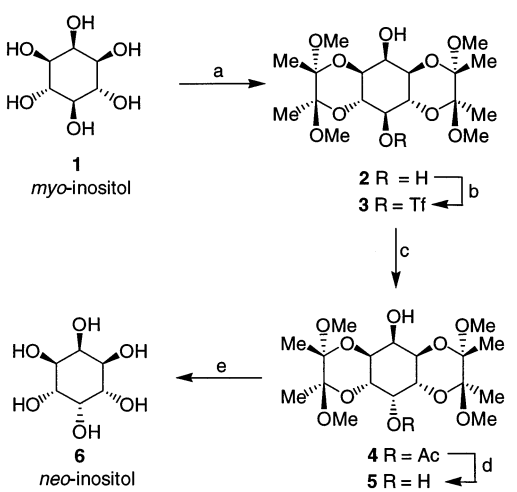
Abstract

neo-Inositol was prepared on a multigram scale in five steps from *myo*-inositol without recourse to column chromatography. The synthesis includes a large-scale preparation of 1,6:3,4-bis-[*O*-(2,3-dimethoxybutane-2,3-diyl)]-*myo*-inositol and a high-yielding inversion of configuration at C-5 employing solvolysis of the 5-triflate ester in aqueous dimethylacetamide.

Keywords: *neo*-Inositol; *myo*-Inositol; Inversion; Dimethylacetamide

Inositols are hexahydroxycyclohexanes. Of the nine possible inositols, *myo*-inositol (**1**, Scheme 1) is widespread in nature and cheaply available, while D- and L-*chiro*-inositol can be obtained from the naturally occurring methyl ethers (+)-pinitol and (−)-quebrachitol, respectively [1]. The remaining six inositols are rare, although *epi*-inositol has been synthesised from **1** [2], and multigram-scale routes to *allo*- [3], *muco*- [4], and *scyllo*- [5] inositols have recently been developed. A simple one-step synthesis of *cis*-inositol from tetrahydroxyquinone has also been described [6].

In 1955, it was reported [7] that acid hydrolysis of (+)-3,4:5,6-di-*O*-isopropylidene-1,2-anhydro-*allo*-inositol gave L-*chiro*-inositol together with an equal amount of a previously unknown inositol, which had a very low solubility in cold water and could therefore be isolated from the mixture by crystallisation. The authors proposed the structure **6** and the name *neo*-inositol for the new inositol, which has since been found in mammalian tissues [8] and plants [9]. More recently, a small-scale



Scheme 1. (a) Butanedione, MeOH, $CH(OMe)_3$, (±)-10-camphorsulphonic acid, reflux; (b) trifluoromethanesulphonic anhydride, pyridine, CH_2Cl_2, −78 °C to rt; (c) 50:1 dimethylacetamide–H_2O, 50 °C; (d) NaOMe, MeOH, reflux; (e) 4:1 AcOH–H_2O, reflux; Tf, trifluoromethanesulphonyl.

* Corresponding author. Tel.: +44-1225-826639; fax: +44-1225-826114.

E-mail address: b.v.l.potter@bath.ac.uk (B.V.L. Potter)

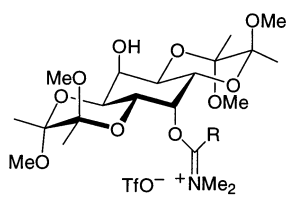
0008-6215/98/$ - see front matter
PII: S0008-6215(98)00317-6

synthesis via enzymatic oxidation of chlorobenzene has been reported [10] in which **6** was again isolated from a mixture of inositols by crystallisation. An X-ray crystallographic study has since accounted for the low aqueous solubility of **6** in terms of its unusually compact and stable crystal structure [11]. However, little is known of the biology of **6**, perhaps in part due to its limited availability. Here we report a concise synthetic route leading exclusively to **6**. The synthesis requires no column chromatography and is easily carried out on a multigram scale.

The synthesis begins with the symmetrical bis(butane-2,3-diacetal) of *myo*-inositol (**2**). The application of the butane-2,3-diacetal (BDA) protecting group for the selective protection of *trans*-1,2-diols in various monosaccharide derivatives was first demonstrated by Montchamp et al. [12]. These authors also reported the first synthesis of **2** on a 1 g scale by acid-catalysed reaction of *myo*-inositol with 2,2,3,3-tetramethoxybutane (TMB) in refluxing methanol for 135 h in the presence of trimethyl orthoformate as a dehydrating agent. It was later shown [13] that BDA protection of various monosaccharide derivatives could be achieved more conveniently by using cheap and commercially available butanedione in place of TMB. Applying this method to *myo*-inositol on a similar scale, we found that the two methods produced similar results, with a complex mixture of products gradually equilibrating to give **2** as the major product after a few days. However, on scale-up excessively long reaction times (up to 2 weeks) became necessary to produce comparable yields of **2**. Furthermore, it was found that long reaction times led to the gradual accumulation of a less polar by-product, which was difficult to remove. For large-scale production of **2**, therefore, it was preferable to use moderate reaction times (20–96 h). The modest yield (27–31%) is acceptable considering the low cost of the starting materials, convenience of the method, and ease of isolation. Because diol **2** has very low solubility in methanol, while the other major product [DL-1,6:4,5-bis-*O*-(2,3-dimethoxybutane-2,3-diyl)-*myo*-inositol], and various minor by-products at this stage are all soluble, the product is simply filtered off from the cooled reaction mixture and dried, typically giving 30–35 g of highly pure **2** from 50 g of *myo*-inositol.

The next step required the regioselective introduction of a suitable leaving group at C-5. Reaction of **2** with methanesulphonyl chloride or methanesulphonic anhydride was slow and not particularly regioselective, while the reaction with tosyl chloride was too sluggish to be of practical use. In contrast, the reaction of **2** with 1.3 equivalents of trifluoromethanesulphonic anhydride was rapid and highly selective, giving the 5-monotriflate **3** as the major product. The triflate **3** proved to be quite stable and could be isolated by crystallisation from ether in 76% yield. Further quantities of **3** could be isolated by chromatography of the mother liquors but, for the multigram-scale route, chromatography was not used.

Reaction of the monotriflate **3** with caesium acetate in DMF at 50 °C proceeded with inversion of configuration at C-5 to give the acetate **4** in moderate yield, but substantial amounts of a by-product with a similar R_f to that of **4** were also produced together with amounts of the *neo*-diol **5**. The by-product proved to be the monoformate ester of **5**, suggesting that DMF itself was reacting as a nucleophile, in competition with acetate anion, presumably to give an iminium triflate salt (**3a**), which was hydrolysed to the labile formate ester on aqueous work-up.



3a R = H; **3b** R = Me

The use of aqueous DMF as a formate anion equivalent in reaction with certain tosylates has recently been explored [14]. It seemed likely therefore, that the use of aqueous dimethylacetamide (DMA) might have a similar effect, but yielding the desired acetate **4** via iminium triflate **3b**. Indeed, it was reported 40 years ago [15] that β-cholestanyl tosylate, when heated in DMA at 78 °C for 92 h, gave α-cholestanyl acetate, albeit it in low yield. In the present case, it was found that **4** could be obtained in excellent yield simply by stirring

the triflate **3** in aqueous DMA at 50 °C for 3 h. The reaction occurred with total inversion of configuration and no elimination product was detectable. Apart from evaporation of solvents, followed by an aqueous work-up to remove dimethylammonium triflate, no further purification was necessary.

The acetate group was removed by dissolving **4** in refluxing dry methanol (the solubility of **4** in cold methanol was low) and then adding a catalytic amount of sodium methoxide. Like its *myo*-inositol epimer, the symmetrical *neo*-diol **5** had low solubility in methanol, and precipitated from the reaction mixture as it formed. Finally, the BDA protecting groups were cleaved using refluxing 80% aqueous acetic acid. Crystallisation from boiling water gave *neo*-inositol in an overall yield of 60% from **2**.

In summary, we have described a practical route to a rare inositol. The synthesis exemplifies the use of the recently introduced BDA protecting group, which should find further use in inositol chemistry. Furthermore, the efficient inversion of configuration via solvolysis of a triflate ester in aqueous DMA may be worthy of wider evaluation for general synthetic utility.

Experimental

General methods.—Thin-layer chromatography (TLC) was performed on pre-coated plates (E. Merck TLC aluminium sheets silica 60 F_{254}) with detection by phosphomolybdic acid in MeOH followed by heating. CH_2Cl_2 and pyridine were purchased in anhydrous form. Melting points (uncorrected) were determined using a Reichert–Jung hot stage microscope apparatus. ^1H and ^{13}C NMR spectra were recorded on a Jeol GX270 or EX400 NMR spectrometer. FAB mass spectra were recorded at the University of Bath using *m*-nitrobenzyl alcohol as the matrix. Microanalysis was carried out by the Microanalysis Service, University of Bath.

*Preparation of 1,6:3,4-bis-[*O*-(2,3-dimethoxybutane-2,3-diyl)]*-myo-*inositol* (**2**) *[12].*—To a stirred suspension of *myo*-inositol (50.0 g, 277 mmol) in MeOH (500 mL) was added trimethyl orthoformate (200 mL), butanedione (50 mL, 570 mmol) and (±)-10-camphorsulphonic acid (1 g). The mixture was heated under reflux for 24 h and then allowed to cool. The precipitate was filtered off and washed sequentially with MeOH (200 mL) and Et_2O (200 mL) and allowed to dry, giving the diol **2** as a white solid (32.0 g, 78.3 mmol, 28%) whose ^1H and ^{13}C NMR spectra matched those previously reported [12]; mp > 300 °C with sublimation and decomposition, lit > 330 °C [12]; R_f 0.24 (EtOAc); R_f 0.29 (2:1 $CHCl_3$–acetone).

*1,6:3,4-bis-[*O*-(2,3-dimethoxybutane-2,3-diyl)]-5-*O*-trifluoromethanesulphonyl-*myo*-inositol* (**3**).—To a stirred suspension of diol **2** (22.0 g, 53.9 mmol, previously dried at 75 °C) in dry CH_2Cl_2 (150 mL) and dry pyridine (13 mL) at −78 °C under N_2 was added a solution of trifluoromethanesulphonic anhydride (20.0 g, 70.9 mmol) in dry CH_2Cl_2 (100 mL) dropwise over 1 h. The cooling bath was removed and stirring was continued for a further 12 h, after which time only a trace of solid remained and TLC (1:1 EtOAc–hexane) showed almost total conversion of **2** (R_f 0.05) into a major product (R_f 0.36) and traces of two minor products (R_f 0.54 and 0.65). The solution was diluted with CH_2Cl_2 (200 mL) and water (400 mL) and the organic layer was separated and washed with 1.0 M HCl, satd $NaHCO_3$ and brine (400 mL of each), dried ($MgSO_4$) and concentrated under reduced pressure to give an off-white foam. Co-evaporation with toluene removed traces of pyridine. The residue was taken up in Et_2O (~100 mL) and the slightly cloudy solution was filtered, giving a clear solution which was refrigerated at −20 °C. A first crop of crystalline monotriflate **3** (16.4 g) was collected after 24 h, and concentration of the mother liquor gave further crops of **3** (total yield 22.1 g, 40.9 mmol, 76%). The crystalline monotriflate was stable at room temperature but decomposed on heating, so no mp could be obtained; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.30 (s, 6 H, Me), 1.34 (s, 6 H, Me), 2.54 (br s, 1 H, exch D_2O, OH), 3.25 (s, 6 H, OMe), 3.26 (s, 6 H, OMe), 3.62 (dd, 2 H, $J_{1,6}$ and $J_{3,4}$ 10.1, $J_{1,2}$ and $J_{3,2}$ 2.4 Hz, H-1 and H-3), 4.07 (t, 1 H, H-2), 4.26 (dd, 2 H, $J_{4,5}$ and $J_{6,5}$ 9.8 Hz, H-4

and H-6), 4.81 (t, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.39 (Me), 17.54 (Me), 47.97 (OMe), 48.19 (OMe), 66.17 (2 × inositol C), 68.05 (2 × inositol C), 68.40 (inositol C-2), 84.71 (inositol C-5), 99.63 (2 × BDA quaternary C), 100.33 (2 × BDA quaternary C), 118.60 (J_{CF} 320 Hz, CF_3); FABMS m/z 509.2 [$(M - MeO)^+$, 100%], 101.1 (85%); FABMS m/z 692.3 [$(M + NBA - H)^-$, 70%], 471.2 (60%), 149.1 [$CF_3SO_3^-$, 100%]; Anal. Calcd for $C_{19}H_{31}F_3O_{12}S$: C, 42.22; H 5.78. Found: C, 42.2; H, 5.82.

2-O-*acetyl*-*1,6:3,4*-*bis*-O-*(2,3-dimethoxybutane-2,3-diyl)*-neo-*inositol* (**4**).—A solution of **3** (16.6 g, 30.7 mmol) in dimethylacetamide (100 mL) and water (2 mL) was stirred at 50 °C for 3 h, after which time TLC (EtOAc) showed total conversion of starting material (R_f 0.60) into a product (R_f 0.48). The solvents were removed by evaporation in vacuo at 50 °C to give an off-white solid. The solid was taken up in CH_2Cl_2 (200 mL), washed with water (2 × 200 mL), dried ($MgSO_4$) and concentrated by evaporation under reduced pressure to give **4** as a white solid (13.2 g, 29.3 mmol, 95%), which was used in the next step without further purification. Crystals from EtOH (needles) sublime above 200 °C to give new crystals with mp 262–265 °C; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.23 (s, 6 H, Me), 1.31 (s, 6 H, Me), 2.12 (s, 3 H, Ac), 2.44 (br s, 1 H, exch D_2O, OH), 3.24 (s, 6 H, OCH_3), 3.26 (s, 6 H, OCH_3), 3.92 (dd, 2 H, $J_{4,3}$ and $J_{6,1}$ 10.3, $J_{4,5}$ and $J_{6,5}$ 2.8 Hz, H-4 and H-6), 4.07–4.14 (m, 3 H, H-1, H-3 and H-5), 5.46 (t, 1 H, J 2.9 Hz, H-2); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 17.50 (2 × Me), 17.63 (2 × Me), 21.11 [*Me*C(O)O], 47.94 (4 × OMe), 65.10 (2 × inositol C), 67.12 (2 × inositol C), 68.83 (inositol C), 69.59 (inositol C), 99.53 (2 × BDA quaternary C), 99.79 (2 × BDA quaternary C), 170.46 (C=O); FABMS m/z 473.2 [$(M + Na)^+$, 30%], 419.2 [$(M - MeO)^+$, 100%], 101.1 (70%); Anal. Calcd for $C_{20}H_{34}O_{11}$: C, 53.32; H 7.61. Found: C, 53.3; H, 7.62.

1,6:3,4-*bis*-O-*(2,3-dimethoxybutane-2,3-diyl)*-neo-*inositol* (**5**).—To a stirred solution of **4** (13.2 g, 29.3 mmol) in refluxing dry MeOH (300 mL) under N_2 was added a catalytic amount of NaOMe (100 mg). After 1 h at reflux, a white precipitate of diol **5** began to appear, and after 5 h TLC (EtOAc) showed that no monoacetate (R_f 0.48) remained. Heating was discontinued and the solution was stirred overnight. The white precipitate was filtered off, washed with MeOH and dried to give the diol **5** as a white solid (11.9 g, 29.1 mmol, 99%) which was used in the next step without further purification. **5** Sublimes above 250 °C to give crystals with mp > 300 °C (dec); R_f 0.24 (EtOAc); R_f 0.40 (2:1 $CHCl_3$–acetone); ^1H NMR (Me_2SO-d_6, 270 MHz) δ 1.18 (s, 12 H, Me), 3.13 (s, 12 H, OMe), 3.74 (br s, 4 H, H-1, H-3, H-4 and H-6) 3.81 (br d, 2 H, J 4.6 Hz, H-2 and H-5), 4.77 (d, 2 H, J 4.6 Hz, exch D_2O, 2 × OH); ^{13}C NMR (Me_2SO-d_6, 67.8 MHz) δ 17.87 (4 × Me), 47.42 (4 × OMe), 66.67 (C-1, C-3, C-4, C-6), 67.59 (C-2 and C-5), 98.83 (4 × BDA quaternary C); FABMS m/z 431.1 [$(M + Na)^+$, 30%], 377.1 [$(M - OMe)^+$, 100%], 101.0 (70%). An analytical sample was obtained by sublimation: Anal. Calcd for $C_{18}H_{32}O_{10}$: C, 52.93; H 7.90. Found: C, 52.7; H, 7.96.

Neo-*inositol* (**6**).—A stirred suspension of **5** (11.3 g, 27.7 mmol) in 80% v/v aq AcOH (250 mL) was heated at reflux. The solid dissolved to give a clear solution and after a few min a precipitate began to appear, accompanied by a yellow coloration (butanedione). After 4 h, heating was discontinued and solvents were removed by evaporation in vacuo at 50 °C. Co-evaporation with toluene removed remaining traces of acetic acid giving a white solid (~ 5 g), which was recrystallised from boiling water to give *neo*-inositol (**6**) as colourless crystals (4.19 g, 23.3 mmol, 84%); mp > 300 °C with sublimation and decomposition, lit 315 °C (dec) [7]; ^1H NMR (D_2O, 400 MHz) δ 3.66 (br s, 4 H, H-1, H-3, H-4 and H-6), 3.95 (br s, 2 H, H-2 and H-5); Anal. Calcd for $C_6H_{12}O_6$: C, 40.00; H 6.71. Found: C, 39.8; H, 6.72.

Acknowledgements

We thank the Wellcome Trust for Programme Grant Support (045491).

References

[1] W. Tegge, C.E. Ballou, *Proc. Natl. Acad. Sci. USA*, 86 (1989) 94–98.
[2] T. Posternak, *Helv. Chim. Acta*, 29 (1946) 1991.
[3] M. Desjardins, L.E. Brammer Jr., T. Hudlicky, *Carbohydr. Res.*, 304 (1997) 39–42.
[4] L.E. Brammer Jr., T. Hudlicky, *Tetrahedron: Asymmetry*, 9 (1998) 2011–2014.
[5] C. Husson, L. Odier, Ph.J.A. Vottéro, *Carbohydr. Res.*, 307 (1998) 163–165.
[6] S.J. Angyal, L. Odier, M.E. Tate, *Carbohydr. Res.*, 266 (1995) 143–146.
[7] S.J. Angyal, N.K. Matheson, *J. Am. Chem. Soc.*, 77 (1955) 4343–4346.
[8] W.R. Sherman, S.L. Goodwin, K.D. Gunnell, *Biochemistry*, 10 (1971) 3491–3499.
[9] R. Mukherjee, E.M. Axt, *Phytochemistry*, 23 (1984) 2682–2684.
[10] (a) M. Mandel, T. Hudlicky, *J. Chem. Soc., Perkin Trans. 1*, (1993) 741–743. Corrigendum: (1993) 1537. (b) T. Hudlicky, M. Mandel, J. Rouden, R.S. Lee, B. Bachmann, T. Dudding, K.J. Yost, J.S. Merola, *J. Chem. Soc., Perkin Trans. 1*, (1994) 1553–1567.
[11] S.J. Angyal, D.C. Craig, *Carbohydr. Res.*, 263 (1994) 149–154.
[12] J.-L. Montchamp, F. Tian, M.E. Hart, J.W. Frost, *J. Org. Chem.*, 61 (1996) 3897–3899.
[13] A. Hense, S.V. Ley, H.M.I. Osborn, D.R. Owen, J.-F. Poisson, S.L. Warriner, K.E. Wesson, *J. Chem. Soc., Perkin Trans. 1*, (1997) 2023–2031.
[14] S.C. Suri, S.L. Rogers, K.V. Radhakrishnan, V. Nair, *Synth. Commun.*, 26 (1996) 1031–1039.
[15] F.C. Chang, R.T. Blickenstaff, *J. Am. Chem. Soc.*, 80 (1958) 2906.