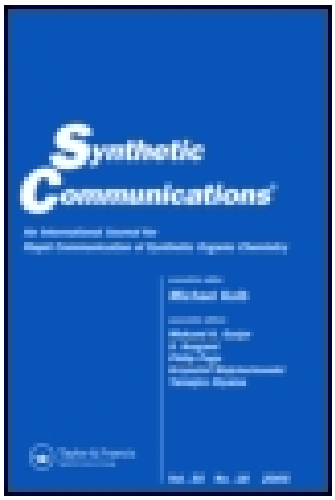

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Improved Routes for the Preparation of Pentaerythritol Mono-*O*-benzyl Ether

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Abstract: Two new efficient routes for the synthesis of pentaerythritol monobenzyl ether are described. In one route, the known mono-*O*-benzylidenepentaerythritol (**5**) is selectively benzylated via its dibutylstannylene acetal and then the benzylidene acetal is hydrolized. In the other route, compound **5** is reduced directly to the monobenzyl ether using $EtAlCl_2$-Et_3SiH.

Keywords: Dibutylstannylene acetal, ethylaluminum dichloride, mono-*O*-benzylpentaerythritol, pentaerythritol, selective reduction

INTRODUCTION

There has been intense interest recently in the use of pentaerythritol (**1**) and its derivatives as scaffolds for the construction of a wide range of clusters and dendrimers.[1–13] Monosubstituted derivatives are highly useful because they can act as branching points in dendrimer synthesis; the three hydroxyls can be transformed into branches and the original substituent can be removed or reacted further to allow extension of the growing dendrimer in the inward direction.

Monosubstituted derivatives of pentaerythritol can be prepared directly in good yields[14,15] based on the reagent employed if 0.5 equiv or less of the reagent is used, particularly if the reagent employed is hindered, such as t-butyldimethylsilyl chloride.[14] Direct reaction with greater amounts of reagent leads to mixtures.[16] One general approach is available to

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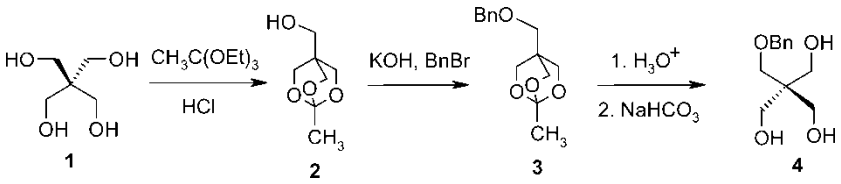


Scheme 1. Synthesis of pentaerythritol mono-*O*-benzyl ether via the orthoester. [17]

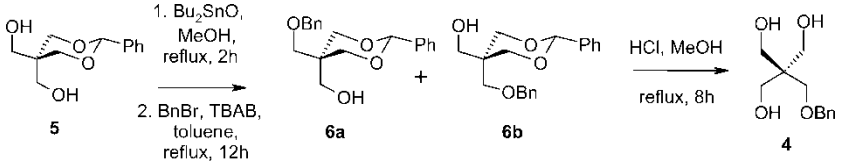
monosubstituted derivatives. As shown in Scheme 1, Dunn et al.[17] formed pentaerythritol orthoacetate (**2**), which can be converted into any other monosubstituted derivative by the appropriate reaction followed by acid hydrolysis.[18–20] However, orthoester **2** is quite acid labile,[21] is also known to polymerize rapidly at higher temperatures,[20] and is therefore difficult to store or purify.

We now introduce two efficient alternative routes to pentaerythritol mono-*O*-benzyl ether (**4**) that avoid the use of orthoester (**2**).

RESULTS AND DISCUSSION

Mono-*O*-benzylidenepentaerythritol (**5**) can be prepared conveniently on a very large scale.[22] Dibutylstannylene acetals are formed readily from diols and are known to have a high preference for the formation of monoalkyl derivatives.[23–25] In the case of mono-*O*-benzylidenepentaerythritol (**5**), reaction with 1 equiv of dibutyltin oxide in refluxing methanol for 2 h, followed by methanol removal and treatment of the resulting product with benzyl bromide and tetrabutylammonium bromide in toluene, gave a mixture of the diasteroisomeric mono-*O*-benzyl ethers **6a** and **6b** in 73% yield as a 3:2 ratio of *cis*/*trans* isomers (Scheme 2). These isomers were separated by column chromatography on silica gel.

The structures of the isomers were assigned from their NMR spectra. It is well-known that in 1,3-dioxanes, the ^{1}H NMR signals of methyl and alkyl groups at the C-5 position are more deshielded if the group is axial than if it is equatorial,[26–30] unlike the situation for cyclohexane substituents. We have shown that for ^{13}C NMR chemical shifts the situation is reversed;

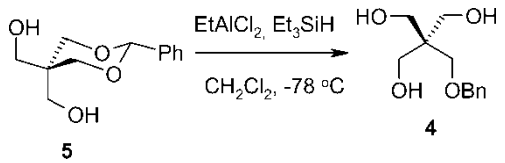


Scheme 2. Formation of the mono-*O*-benzylpentaerythritol via selective monobenzylation.

equatorial carbons attached to the C-5 position are more deshielded than those of their axial counterparts.[31] On this basis, the major isomer, compound **6a** (62.8 ppm, CH_2OH), was assigned the structure that had the phenyl and hydroxymethyl groups *cis*, and the minor isomer, compound **6b** (65.2 ppm, CH_2OH), was assigned the structure with the phenyl and hydroxymethyl groups *trans* (see Scheme 2). The ^1H NMR chemical shifts were entirely in accord with these assignments; the signal of the CH_2 in the CH_2OH group was less shielded when it was axial in **6a** (4.04 ppm) than when it was equatorial in **6b** (3.41 ppm); that of the CH_2 in the CH_2OBn group was more shielded when it was equatorial in **6a** (3.31 ppm) than when it was axial in **6b** (3.88 ppm); even the benzyl CH_2s fit this trend (4.49 ppm for **6a**, 4.54 ppm for **6b**), although the difference is small. It should be noted that substitution on the equatorial oxygen atom was preferred slightly over substitution on the axial oxygen atom (3/2).

Benzylidene acetals can be removed by acid hydrolysis or by hydrogenolysis.[32,33] The most commonly used conditions for acid hydrolysis are reflux in 80% aqueous AcOH,[34] stirring with 90% aqueous CF_3CO_2H acid in CH_2Cl_2 at room temperature,[35] and reaction with 1% I_2 in CH_3OH (w/v) at room temperature or at reflux.[36] Unfortunately, none of these methods work efficiently for the hydrolysis of the diasteroisomeric mixture **6a** and **6b**. However, it was found that treatment the diasteroisomeric mixture **6a** and **6b** with conc. HCl in 80% aqueous MeOH at reflux for 8 h furnished the desired mono-*O*-benzyl ether **4** in 74% yield (Scheme 2).

The second route for the production of pentaerythritol monobenzyl ether (**4**) is to partially reduce mono-*O*-benzylidenepentaerythritol (**5**). Benzylidene acetals can be transformed into the mono-*O*-benzyl ethers of the corresponding diols by various reducing agents, most commonly $LiAlH_4$-$AlCl_3$,[37] $NaCNBH_3$-HCl,[38] Et_3SiH-TFA,[39] Et_3SiH-$BF_3{\cdot}Et_2O$,[40] and DIBAL.[41] Most of these methods are ineffective if hydroxyl groups are present in the substrate being reduced. It was found here that ethylaluminum dichloride, a Lewis acid recently introduced for this type of reaction,[42] was quite effective for **5** with Et_3SiH as a reducing agent, giving the mono-*O*-benzyl ether **4** in 85% yield after column chromatography (Scheme 3). This method is shorter and has the advantages of ease of reaction, high yield, and the use of the easily prepared and stable mono-*O*-benzylidenepentaerythritol. However, for large-scale preparations, ethylaluminium dichloride is costly.



5 4

Scheme 3. Formation of mono-*O*-benzyl ether **4** via reductive cleavage of acetal **5**.

EXPERIMENTAL

Melting points were determined with a Fisher-Johns melting-point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 K in 5-mm NMR tubes on Bruker AC 250-MHz or Avance 500 NMR spectrometers operating at 250.13 or 500.13 and 62.9 or 125.76 MHz, respectively, on solutions in chloroform-*d*. Chemical shifts are given in parts per million (ppm) (± 0.01 ppm) relative to that of tetramethylsilane (TMS) (0.00 ppm) in the case of ^{1}H NMR spectra and to the central line of chloroform-*d* (77.16 ppm) for the ^{13}C NMR spectra. All assignments were confirmed by ^{1}H-^{1}H and ^{1}H-^{13}C correlation spectroscopy, heteronuclear multiple quantum correlation, or heteronuclear multiple bond correlation experiments. Exact masses were measured on a CEC 21-110B mass spectrometer using electron impact ionization (70 eV). MeOH was dried by distillation from magnesium turnings. Dichloromethane was first dried with calcium chloride and then refluxed over calcium hydride for 1 h, followed by distillation. Toluene was dried by refluxing over calcium hydride, followed by distillation. Benzylidene acetals were visualized on TLC by quenching of fluoresence or by spraying the plate with a solution of 0.2% *p*-methoxyphenol in ethanol/2 N H_2SO_4 (1/1, v/v)[43] and heating until color developed. Other compounds were visualized by quenching of fluoresence where applicable and/or were located by spraying with a solution of 2% ceric sulfate in 1 M sulfuric acid followed by heating until color developed. Compounds were purified on silica gel TLC standard grade (230–400 mesh) by flash chromatography using specified eluents.

Trans-5-Benzyloxymethyl-*cis*-5-hydroxymethyl-2-phenyl-1,3-dioxane and *cis*-5-Benzyloxymethyl-*trans*-5-hydroxymethyl-2-phenyl-1,3-dioxane (6a and 6b, respectively)

A suspension of mono-*O*-benzylidenepentaerythritol (**5**)[22] (1.5 g, 6.7 mmol) and dibutyltin oxide (1.66 g, 6.7 mmol, 1 eq) in methanol (350 mL) was refluxed until a clear solution was obtained. Reflux was then continued for 2 h. The solution was concentrated, and the residue was suspended in dry toluene (250 mL). Benzyl bromide (1.2 mL, 10 mmol, 1.5 eq) and tetrabutylammonium bromide (2.16 g, 6.7 mmol, 1 eq), were added, and the mixture was refluxed for 12 h, then cooled to room temperature, and stirred with water (250 mL). The organic layer was dried ($MgSO_4$) and concentrated to dryness. The oily residue was fractionated by flash column chromatography on silica gel (EtOAc–hexanes, 1:5). First to elute was compound **6a** as a colorless syrup (930 mg, 44.2%); $R_F = 0.24$ (EtOAc–hexanes, 1:4); ^{1}H NMR 7.46–7.27 (m, 10H, PhH), 5.42 (s, 1H, acetal H), 4.49 (s, 2H, $PhCH_2O$), 4.16, 3.79 (AB q, 4H, $J = 12.5$ Hz, 2 dioxane CH_2), 4.04 (d, 2H, $J = 7.5$ Hz, CH_2OH), 3.31 (s, 2H, CH_2OBn), 2.22 (t, 1H, OH); ^{13}C NMR 138.2–126.1 (PhC), 101.8 (acetal C), 73.6 ($PhCH_2O$), 71.4 (CH_2OBn), 69.8

(C-4 and C-6, dioxane), 62.7 (CH_2OH), 38.9 (C quat). EI HRMS calcd. for $C_{19}H_{22}O_4$: 314.1518. Found: 314.1514.

The second component, **6b**, was also a colorless syrup (600 mg. 28.5%): $R_F = 0.18$ (EtOAc–hexanes, 1:4); ^{1}H NMR7.42–7.25 (m, 10H, PhH), 5.35 (s, 1H, acetal H), 4.54 (s, 2H, $PhCH_2O$), 4.11, 3.69 (AB q, 4H, $J = 12.5$ Hz, 2 dioxane CH_2), 3.41 (d, 2H, $J = 5$ Hz, CH_2OH), 3.88 (s, 2H, CH_2OBn), 2.73 (t, 1H, OH); ^{13}C NMR 138.2–126.1 (PhC), 101.9 (acetal C), 73.6 ($PhCH_2O$),71.3 (CH_2OBn), 70.2 (C-4 and C-6, dioxane), 65.1 (CH_2OH), 38.6 (qC). EI HRMS calcd. for $C_{19}H_{22}O_4$: 314.1518. Found: 314.1505.

2-(Benzyloxymethyl)-2-(hydroxymethyl)-1,3-propanediol (4)[17]

Method A

The oily mixture of compounds **6a** and **6b** obtained prior to chromatographic separation (0.13 g, 0.41 mmol) was dissolved in CH_3OH (35 mL) and treated with concentrated HCl (6 ml) and H_2O (8 mL). The resulting reaction mixture was stirred at reflux temperature for 8 h. After being cooled to room temperature, MeOH was removed by evaporation, and the resulting residue was dissolved in CH_2Cl_2 (25 mL) and washed with saturated $NaHCO_3$ (50 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (6 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. Purification by flash column chromatography using EtOAc as eluant gave the title compound as a colorless viscous oil (70 mg, 75%); $R_F = 0.22$ (EtOAc); ^{1}H and ^{13}C NMR chemical shifts agreed with literature values[17] (average differences ± 0.09 ppm and ± 0.6 ppm, respectively).

Method B

To a stirred solution of mono-*O*-benzylidenepentaerythritol (**5**)[22] (0.30 g, 1.34 mmol, dried by co-evaporation with dry toluene) in dry dichloromethane (30 mL), Et_3SiH (1.56 mmol, 1.2 eq, 0.25 mL) was added, and the solution was cooled to -78°C. $EtAlCl_2$ (1.8 M in toluene, 4.3 mmol, 3.3 eq, 2.4 mL) was added dropwise, and the reaction mixture was stirred at -78°C for 40 min under nitrogen. It was quenched with saturated $NaHCO_3$ (80 mL) and extracted with dichloromethane (5 × 35 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to a residue that was purified as in method A, yield 0.25 g, 85%.

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REFERENCES

1. Newkome, G. R.; Lin, X. F.; Weis, C. D. *Tetrahedron: Asymmetry.* **1991**, *2*, 957–960.
2. Langer, P.; Ince, S. J.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3913–3915.
3. Padias, A. B.; Hall, H. K.; Tomalia, D. A.; McConnell, J. R. *J. Org. Chem.* **1987**, *52*, 5305–5312.
4. Hanessian, S.; Qiu, D. X.; Prabhanjan, H.; Reddy, G. V.; Lou, B. L. *Can. J. Chem.* **1996**, *74*, 1738–1747.
5. Hanessian, S.; Huynh, H. K.; Reddy, G. V.; Duthaler, R. O.; Katopodis, A.; Streiff, M. B.; Kinzy, W.; Oehrlein, R. *Tetrahedron* **2001**, *57*, 3281–3290.
6. Lindhorst, T. K.; Dubber, M.; Krallmann-Wenzel, U.; Ehlers, S. *Eur. J. Org. Chem.* **2000**, 2027–2034.
7. Constable, E. C.; Housecroft, C. E.; Cattalini, M.; Phillips, D. *New J. Chem.* **1998**, *22*, 193–200.
8. Dagron, F.; Lubineau, A. *J. Carbohydr. Chem.* **2003**, *22*, 481–500.
9. Lemcoff, N. G.; Fuchs, B. *Org. Lett.* **2002**, *4*, 731–734.
10. Ivannikova, T.; Bintein, F.; Malleron, A.; Juliant, S.; Cerutti, M.; Harduin-Lepers, A.; Delannoy, P.; Auge, C.; Lubineau, A. *Carbohydr. Res.* **2003**, *338*, 1153–1161.
11. Schmidt, M.; Dobner, B.; Nuhn, P. *Eur. J. Org. Chem.* **2002**, 669–674.
12. Liu, B.; Roy, R. *Tetrahedron* **2001**, *57*, 6909–6913.
13. Esnault, J.; Mallet, J. M.; Zhang, Y. M.; Sinaÿ, P.; Le Bouar, T.; Pincet, F.; Perez, E. *Eur. J. Org. Chem.* **2001**, 253–260.
14. Hanessian, S.; Prabhanjan, H.; Qiu, D. X.; Nambiar, S. *Can. J. Chem.* **1996**, *74*, 1731–1737.
15. Lehmann, J.; Weitzel, U. P. *Carbohydr. Res.* **1996**, *294*, 65–94.
16. Ueno, Y.; Takeba, M.; Mikawa, M.; Matsuda, A. *J. Org. Chem.* **1999**, *64*, 1211–1217.
17. Dunn, T. J.; Neumann, W. L.; Rogic, M. M.; Woulfe, S. R. *J. Org. Chem.* **1990**, *55*, 6368–6373.
18. Findeis, R. A.; Gade, L. H. *Dalton Trans.* **2003**, 249–254.
19. Findeis, R. A.; Gade, L. H. *Eur. J. Inorg. Chem.* **2003**, 99–110.
20. Rockendorf, N.; Sperling, O.; Lindhorst, T. K. *Aust. J. Chem.* **2002**, *55*, 87–93.
21. Wuts, P. G. M.; Greene, T. W. *Protective Groups in Organic Synthesis*; Wiley: New York, 1999.
22. Issidorides, C. H.; Gulen, R. C. Monobenzalpentaerythritol. In *Organic Syntheses Collected Volume IV*; Rabjohn, N., Ed.; Wiley: New York, 1963; pp. 679–681.
23. David, S.; Thiéffry, A.; Veyrières, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1796–1801.
24. Nagashima, N.; Ohno, M. *Chem. Pharm. Bull.* **1991**, *39*, 1972–1982.
25. Grindley, T. B. *Adv. Carbohydr. Chem. Biochem.* **1998**, *53*, 17–142.
26. Cai, J. Q.; Davies, A. G.; Schiesser, C. H. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1151–1156.
27. Weber, E. *J. Org. Chem.* **1982**, *47*, 3478–3486.
28. Crabb, T. A.; Porssa, M.; Elmore, N. F. *Magn. Reson. Chem.* **1991**, *29*, 613–618.
29. Eliel, E. L.; Martin, R. J. L. *J. Am. Chem. Soc.* **1968**, *90*, 682–689.
30. Coxon, A. C.; Stoddart, J. F. *J. Chem. Soc., Perkin Trans. 1* **1977**, 767–785.
31. Al-Mughaid, H.; Grindley, T. B.; Robertson, K. N.; Cameron, T. S. *Can. J. Chem.* **2003**, *81*, 505–516.
32. Gelas, J. *Adv. Carbohydr. Chem. Biochem.* **1981**, *39*, 71–156.

33. Clode, D. M. *Chem. Rev.* **1979**, *79*, 491–513.
34. Ogawa, T.; Nakabayashi, S.; Sasajima, K. *Carbohydr. Res.* **1981**, *95*, 308–312.
35. Colonna, B.; Harding, V. D.; Nepogodiev, S. A.; Raymo, F. M.; Spencer, N.; Stoddart, J. F. *Chem. Eur. J.* **1998**, *4*, 1244–1254.
36. Szarek, W. A.; Zamojski, A.; Tiwari, K. N.; Ison, E. R. *Tetrahedron Lett.* **1986**, *27*, 3827–3830.
37. Lipták, A.; Jodál, I.; Harangi, J.; Nánási, P. *Acta Chim. Hung.* **1983**, *113*, 415–422.
38. Garegg, P. J.; Hultberg, H.; Wallin, S. *Carbohydr. Res.* **1982**, *108*, 97–101.
39. Deninno, M. P.; Etienne, J. B.; Duplantier, K. C. *Tetrahedron Lett.* **1995**, *36*, 669–672.
40. Debenham, S. D.; Toone, E. J. *Tetrahedron: Asymmetry* **2000**, *11*, 385–387.
41. Lizarzaburu, M. E.; Kurth, M. J.; Nantz, M. H. *Tetrahedron Lett.* **1999**, *40*, 8985–8988.
42. Balakumar, V.; Aravind, A.; Baskaran, S. *Synlett* **2004**, 647–650.
43. Herzner, H.; Eberling, J.; Schultz, M.; Zimmer, J.; Kunz, H. *J. Carbohydr. Chem.* **1998**, *17*, 759–776.