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Carbohydrate Research 339 (2004) 2607–2610
Carbohydrate RESEARCH

Note

Syntheses of monohydroxy benzyl ethers of polyols: tri-*O*-benzylpentaerythritol and other highly benzylated derivatives of symmetrical polyols

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Received 3 June 2004; accepted 17 August 2004
Available online 18 September 2004

Abstract—Symmetrical polyols can be converted into benzyl ethers with one free hydroxyl group in good yield by reaction of the monodibutylstannylene acetal with excess benzyl bromide in the presence of tetrabutylammonium bromide and diisopropylethylamine in xylene. The reaction pathway involves initial benzylation of the dibutylstannylene acetal to give benzyl and bromodibutylstannyl ethers; if a hydroxyl group remains unsubstituted, the latter ether ring closes and reacts further.
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Keywords: Dibutylstannylene; Pentaerythritol; Tri-*O*-benzylpentaerythritol; Dipentaerythritol; Trihydroxymethylethane

General methods for the isolation of single hydroxyl groups from symmetrical polyols are of considerable interest[1–7] because the products are amenable to further selective conversions to a wide variety of products including dendrimers,[4,8] clusters,[5,6,9] ligands,[10–12] and liquid crystals.[13] Benzyl groups are among the most desirable protecting groups because of their persistence under many reaction conditions and because highly selective deprotection is facile.[14]

Dibutylstannylene acetals have been shown to be useful for selective functionalization and chemical manipulation of diols and polyols.[15–17] They can be prepared by reaction of diols with dibutyltin oxide in refluxing methanol or by refluxing in benzene or toluene with azeotropic removal of water. They have served as convenient intermediates for the formation of monobenzyl ethers from diols or polyols by reaction with benzyl bromide either in benzene or toluene in the presence of added nucleophiles, such as tetrabutylammonium bromide,[18,19] or in dimethylformamide in the presence of cesium fluoride[20,21] to give good yields of monosubstituted products. David demonstrated that the bis(dibutylstannylene) acetal of pentaerythritol can serve as an intermediate for making the dibenzyl derivative.[22] We now show that the mono(dibutylstannylene) acetal of pentaerythritol and other symmetrical polyols can be used to produce polybenzylated derivatives with one unsubstituted hydroxyl group.

We are interested[23] in developing the chemistry of pentaerythritol (**1**), dipentaerythritol (**2**), and related molecules as cores of clusters and dendritic wedges. We now report that the tri-*O*-benzyl ether of **1** (**4**) is obtained in good yield (73%) on treatment of its monodibutylstannylene acetal with excess benzyl bromide (16 equiv), tetrabutylammonium bromide, and *N*,*N*-diisopropylethylamine (DIEA) in *o*-xylene for 12 h at reflux (Scheme 1). These conditions evolved from an initial attempt to obtain the mono-*O*-benzyl ether by treatment of the monodibutylstannylene acetal with 1 equiv of benzyl bromide with tetrabutylammonium bromide in toluene.[18] Despite the 1:1 stoichiometry, this attempt yielded a mixture of mono-, di-, and tri-*O*-benzyl ethers, similar to results of Nagashima and Ohno[21] in reactions with glycerol. Experiments conducted with excess benzyl bromide at lower temperatures (e.g., at reflux in toluene) and in the absence of base gave mixtures of the di- and tri-*O*-benzyl ethers.

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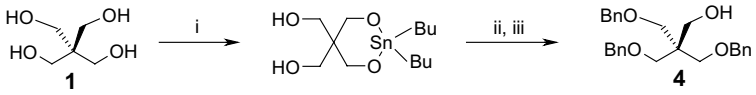
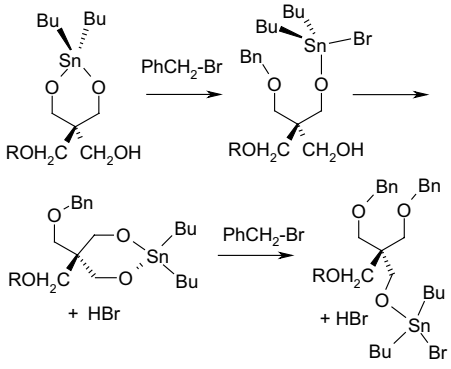
doi:10.1016/j.carres.2004.08.006



Scheme 1. Synthesis of tri-*O*-benzylpentaerythritol. Reagents and conditions: (i) Bu_2SnO (1 equiv), MeOH, reflux, 2 h; (ii) benzyl bromide (16 equiv), *o*-xylene, tetrabutylammonium bromide (1 equiv), reflux 2 h; (iii) add diisopropylethylamine (4 equiv), reflux 12 h, 73%.

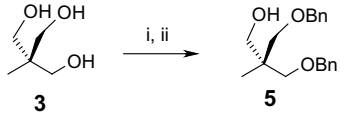


Scheme 2. Probable reaction pathway for multiple benzylation of pentaerythritol.

A probable reaction pathway is shown in Scheme 2. It is well established that dibutylhalostannyl ethers are intermediates in the reactions of stannylene acetals.[24,25] Multiple substitution occurs here because, as long as a free hydroxyl group remains, the intermediate from the initial benzylation, the bromodibutylstannyl ether, can undergo an intramolecular nucleophilic displacement of bromide to give another reactive stannylene acetal. The base (DIEA) is necessary to ensure complete conversion, presumably because it removes hydrogen bromide. As with other reactions of stannylene acetals,[17,26] there is a strong preference for reaction with the cyclic stannylene acetal rather than the product bromodibutylstannyl ether. After workup, this results in products in which one hydroxyl remains unsubstituted. It appears that the second substitution is faster than the first, while the third is slower than the second, probably for steric reasons. Nagashima and Ohno reported that benzylation of glycerol in DMF with 1 equiv of the benzylating agent using cesium fluoride as catalyst gave about equal amounts of the mono and disubstituted products,[21] in agreement with our observations.

Liu and Roy have reported[9] the isolation of compound **4** in lower yield from the reaction of pentaerythritol with substoichiometric amounts of benzyl bromide and sodium hydride in DMF followed by chromatography.

Other symmetrical polyols react in the same way. The same conditions with 2,2-dihydroxymethyl-1-propanol (**3**), gave a 72% yield of the di-*O*-benzyl derivative (**5**) (Scheme 3).



Scheme 3. Synthesis of 2,2-bis(benzyloxymethyl)-1-propanol. Reagents and conditions: (i) Bu_2SnO (1 equiv), MeOH, reflux, 2 h; (ii) benzyl bromide (6 equiv), *o*-xylene, tetrabutylammonium bromide (1 equiv), diisopropylethylamine (6.5 equiv), reflux 12 h, 72%.

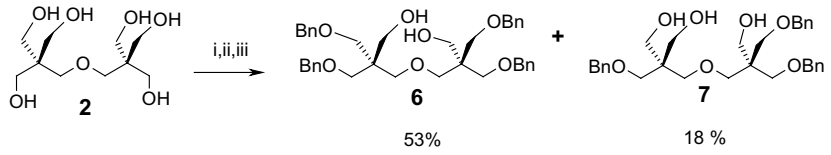
Dipentaerythritol (**2**) contains two pentaerythritol units separated by an anhydro bridge. Exposure of the bisdibutylstannylene acetal of **2** to the same conditions as for the monodibutylstannylene acetal of **1** gave 2,2,6,6-tetrakis(benzyloxymethyl)-4-oxa-1,7-heptanediol (**6**) and 2,2,6-tris(benzyloxymethyl)-4-oxa-1,7-heptanediol (**7**) in yields of 53% and 18.3%, respectively (Scheme 4). Presumably, steric hindrance slows the last substitution. The observation that only the symmetrical tetrakis derivative was formed suggests either that stannylene acetals do not form across oxygen atoms from the two halves of dipentaerythritol, a span that would require a 10-membered ring, or that such acetals are less reactive.

Symmetrical polyols can be converted into benzyl ethers with one free hydroxyl group in good yield by reaction of the monodibutylstannylene acetal with excess benzyl bromide in the presence of tetrabutylammonium bromide and diisopropylethylamine in xylene. The reaction is thought to proceed in stepwise fashion through reaction with the dibutylstannylene acetal followed by ring closure of the resulting bromodibutylstannyl ether with a remaining free hydroxyl group. Non-symmetrical polyols give mixtures of regioisomers under these conditions.

1. Experimental

1.1. General methods

^1H and ^{13}C NMR spectra were recorded at 300 K in 5 mm NMR tubes on a Bruker AC-250 MHz spectrometer operating at 250.13 and 62.9 MHz, respectively. 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 ^1H NMR spectra, and to the central line of chloroform-*d* (δ 77.23) for the ^{13}C NMR spectra. All assignments were confirmed by



Scheme 4. Reaction with dipentaerythritol. Reagents and conditions: (i) Bu_2SnO (2 equiv), MeOH, reflux, 2 h; (ii) benzyl bromide (16 equiv), *o*-xylene, tetrabutylammonium bromide (2 equiv); (iii) add diisopropylethylamine (6.5 equiv), reflux 12 h, 72%.

COSY, HETCOR, HMQC, or HMBC experiments. The EI exact masses were measured on a CEC 21-110B mass spectrometer using electron ionization (70 eV). The ES exact masses were measured by positive ion mode electrospray ionization on a Micromass ZabSpec Hybrid Sector-TOF mass spectrometer. The liquid carrier (MeOH) was infused into the electrospray source by means of a Harvard syringe pump at a flow rate of 10 μL/min. *o*-Xylene was dried by refluxing over calcium hydride followed by distillation. MeOH was dried with Mg/iodine, followed by distillation. *N*,*N*-Dimethylformamide was stored over activated 4 Å molecular sieves for 72 h. It was distilled under reduced pressure over freshly activated 4 Å molecular sieves. Compounds were visualized by quenching of fluorescence or by spraying the plate with a soln[27] of 0.2% *p*-methoxyphenol in 1:1 EtOH–2 N H_2SO_4 and heating on a hot plate until color developed. Other compounds were visualized by UV where applicable and/or were located by spraying with a soln of 2% ceric ammonium sulfate in 1 M H_2SO_4 followed by heating on a hot plate until color developed. Compounds were purified on silica gel (TLC standard grade, 230–400 mesh) by flash chromatography using specified eluents.

1.2. 2,2,2-Tris(benzyloxymethyl)ethanol (4)

A suspension of pentaerythritol (**1**) (1.36 g, 9.99 mmol) and dibutyltin oxide (2.50 g, 10.0 mmol, 1.01 equiv) in dry MeOH (300 mL) was refluxed until a clear soln was obtained. Reflux was continued for a further 100 min. Evaporation of the solvent gave the crude stannylene derivative to which was added *o*-xylene (250 mL), benzyl bromide (19 mL, 160 mmol, 16 equiv), and tetrabutylammonium bromide (3.2 g, 9.9 mmol), and the mixture was refluxed in a Dean–Stark apparatus for 2 h. Freshly distilled diisopropylethylamine (7.0 mL, 40 mmol) was added and the resulting soln was refluxed in a Dean–Stark apparatus for 12 h, then cooled to room temperature, and stirred with water (50 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel (1:3 EtOAc–hexanes) to afford the title compound (2.92 g, 73%) as a syrup: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.11–7.60 (m, 3 × PhH, 15H), 4.60 (s, 3 × $PhCH_2O$, 6H), 3.95 (s, CH_2OH, 2H), 3.72 (s, 3 × CCH_2O, 6H); ^{13}C NMR (62.1 MHz, $CDCl_3$): δ 126.4–133.3 (PhC), 73.6 (3 × $PhCH_2O$), 70.8 (3 × CCH_2O), 65.8 (CH_2OH), 45.0 (Cquat). ESMS found *m*/*z* 429.2047 [M+Na^+]. Calcd for $C_{26}H_{30}O_4Na$ 429.2042.

1.3. 2,2-Bis(benzyloxymethyl)-1-propanol (5)

A suspension of 2,2-bis(hydroxymethyl)-1-propanol (**3**) (0.63 g, 5.2 mmol) and dibutyltin oxide (1.24 g, 4.98 mmol, 1.05 equiv) in dry MeOH (150 mL) was boiled under reflux until a clear soln was obtained. Reflux was then continued for 100 min. Evaporation of the solvent gave the crude stannylene derivative, which was suspended in dry *o*-xylene (50 mL). Benzyl bromide (3.6 mL, 30 mmol), tetrabutylammonium bromide (1.6 g, 5.0 mmol), and freshly distilled diisopropylethylamine (6.0 mL, 34 mmol) were added and the mixture was refluxed for 12 h in a Dean–Stark apparatus, then cooled to room temperature, and stirred with water (100 mL). The organic layer was dried over $MgSO_4$ and concentrated. Flash column chromatography of the residue on silica gel with 1:4 EtOAc–hexanes as the eluent afforded the title compound (**5**, 1.08 g, 72%) as a syrup: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.11–7.30 (m, 2 × PhH, 10H), 4.59 (s, 2 × $PhCH_2O$, 4H), 3.71 (s, CH_2OH, 2H), 3.61 (AB quartet, *J* 8.85 Hz, 4H, 2 × CCH_2O,), 1.06 (s, CH_3, 3H); ^{13}C NMR (62.1 MHz, $CDCl_3$): δ 127.3–138.3 (PhC), 74.2 (2 × $PhCH_2O$), 73.3 (2 × CCH_2O), 68.2 (CH_2OH), 40.7 (Cquat), 17.4 (CH_3). EIMS found *m*/*z* 300.1730 [M^+]. Calcd for $C_{19}H_{24}O_3$ 300.1725.

1.4. 2,2,6,6-Tetrakis(benzyloxymethyl)-4-oxa-1,7-heptanediol (6) and 2,2,6-tris(benzyloxymethyl)-4-oxa-1,7-heptanediol (7)

A suspension of dipentaerythritol (**2**) (0.25 g, 0.98 mmol) and dibutyltin oxide (0.54 g, 2.2 mmol, 2.2 equiv) in dry MeOH (400 mL) was boiled under reflux until a clear soln was obtained (2 h). Evaporation of the solvent gave the crude stannylene derivative, which was taken up in *o*-xylene (250 mL). Benzyl bromide (1.9 mL, 15.7 mmol, 16 equiv) and tetrabutylammonium bromide (0.63 g, 2.0 mmol) were added and the mixture was refluxed in a Dean–Stark apparatus for 2 h. Freshly distilled diisopropylethylamine (0.7 mL, 4 mmol) was added and the resulting soln was refluxed for 12 h, then cooled to room

temperature, and stirred with water (175 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was separated by flash column chromatography on silica gel (1:1 EtOAc–hexanes). First to elute (R_f 0.57, 1:1 EtOAc–hexanes) was compound **5** (0.32 g, 53%), a syrup: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.25–7.36 (m, 4 × PhH, 20H), 4.45 (s, 4 × $PhCH_2O$, 8H), 3.67 (s, 2 × CH_2OH, 4H), 3.46 (s, 4 × CCH_2OBn, 8H), 3.40 (s, CCH_2OCH_2C, 4H); ^{13}C NMR (62.1 MHz, $CDCl_3$): δ 127.6–138.4 (4 × PhC), 73.7 (4 × $PhCH_2O$), 72.0 (CCH_2OCH_2C), 71.0 (4 × CCH_2OBn), 65.9 (2 × CH_2OH), 45.3 (2 × Cquat). ESMS found *m/z* 637.3148 [M+Na$^+$]. Calcd for $C_{38}H_{46}O_7Na$ 637.3141.

The second component (R_f 0.17, 1:1 EtOAc–hexanes) was compound **6**, which crystallized upon standing, mp 64–66 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.25–7.30 (m, 3 × PhH, 15H), 4.45, 4.46 (s, 3 × $PhCH_2O$, 6H), 3.67, 3.62 (s, 3 × CH_2OH, 6H), 3.47, 3.48 (s, 3 × CCH_2OBn, 6H), 3.45, 3.46 (s, CCH_2OCH_2C, 4H); ^{13}C NMR (62.1 MHz, $CDCl_3$): δ 127.6–138.4 (3 × PhC), 73.8, 73.7 (3 × $PhCH_2O$, 72.5, 72.1 (CCH_2OCH_2C), 71.2, 71.5 (3 × CCH_2OBn), 65.5, 64.8 (3 × CH_2OH), 45.2, 45.3 (2 × Cquat). ESMS found *m/z* 547.2668 [M+Na$^+$]. Calcd for $C_{31}H_{40}O_7Na$ 547.2672.

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada for financial support. NMR spectra were recorded at the Atlantic Region Magnetic Resonance Centre.

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