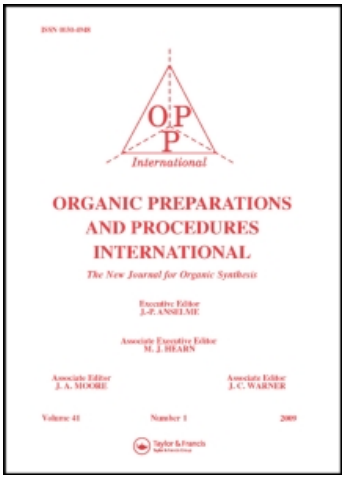

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SYNTHESIS OF 2-0-PROTECTED GLYCEROL DERIVATIVES

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SYNTHESIS OF 2-*O*-PROTECTED GLYCEROL DERIVATIVES

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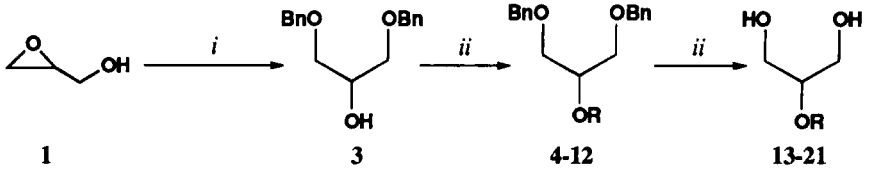
Symmetrical 2-*O*-protected glycerols are important structural units that have been incorporated into compounds with biological applications, such as water soluble *o*-carboranes,[1] and 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG, ganciclovir) and analogues.[2] As part of our program involving enantiotopic group differentiation of prochiral molecules,[3] we were interested in studying 2-*O*-protected glycerol derivatives and we have devised a practical synthesis of these compounds proceeding from glycidol (1) and 1,3-di-*O*-benzylglycerol (3) (Eq. 1).



1 3 4-12 13-21 (1)

i) NaH, THF, BnBr, TBAI, Rt, 10 hrs b) NaH, BnOH, DMF, 120°, 16 hrs. ii) See Table.

There are a number of methods for preparing 2-*O*-protected glycerols. Those based on 1,3-*O*-benzylideneglycerol,[4] proceed in low yields[5] due to competitive formation of 1,2-*O*-benzylideneglycerol isomers, and would be expected to restrict the choice of protecting groups to those which are not acid labile. Those based on 1,3-di-*O*-tritylglycerol[6] would be expected to restrict the choice of protecting groups for similar reasons. Those based on 1,3-di-*O*-benzylglycerol[7] (3) appear to be compatible with the largest selection of protecting groups, excluding only those groups sensitive to reductive cleavage conditions.

A number of 2-*O*-protected-1,3-dibenzylglycerol derivatives (**4-12**) have been synthesized (Table) in good to excellent yield. A survey of commonly encountered protecting groups such as the acetyl (Ac), benzoyl (Bz), *tert*-butyldimethylsilyl (TBDMS), *p*-toluenesulfonyl (Ts), ethoxymethyl (CH_2OEt), and methylthiomethyl (MTM) groups was carried out in order to demonstrate the flexibility of this route.[8] Removal of the benzyl groups was straightforward giving 2-*O*-protected-glycerol derivatives **13-17** (Table) in quantitative yield.

TABLE. Synthesis of 2-*O*-Protected Glycerol Derivatives

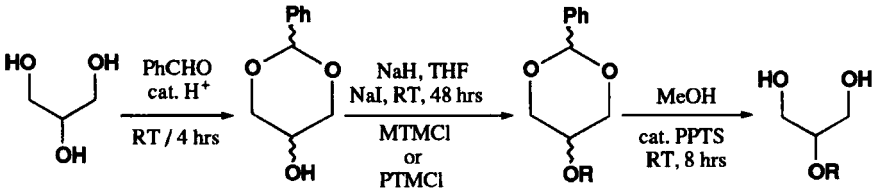
Cmpd	*ii* / (RT / 8-12 hrs)	Yield (%)	Diol	*iii*[a]	Yield (%)
4, R = Ac	Ac_2O / CH_2Cl_2 / Et_3N / DMAP	75	**13**	A	100
5, R = Bz	BzOH / CH_2Cl_2 / DCC / DMAP	88	**14**	A	100
6, R = TBDMS	TBDMSCl / DMF / imidazole	92	**15**	A	100
7, R = Ts	*p*-TsCl / CH_2Cl_2 / Et_3N / DMAP	86	**16**	A	100
8, R = CH_2OEt	$EtOCH_2Cl$ / CH_2Cl_2 / *i*Pr_2NEt	82	**17**	A	100
9, R = BOM	BOMCl / CH_2Cl_2 / *i*Pr_2NEt	78	**18**	B	-
10, R = Bn	NaH / BnBr / THF / TBAI	93	**19**	B	-
11, R = PMB	NaH / PMBCl / THF / TBAI	87	**20**	B	70
12, R = MTM	NaH / MTMCl / THF / NaI	72	**21**	C	30

a) A = H_2, $Pd(OH)_2$-C, EtOAc, RT, 8-12 hrs; B = H_2, Pd-C, EtOAc, RT, 8-12 hrs; C = Na, NH_3, -40°, 30 min.

It was felt that it might be possible to selectively debenzylate the 2-*O*-protected-glycerol derivatives **9-11** containing groups known to be labile to hydrogenolysis conditions, such as the benzyloxymethyl (BOM), benzyl (Bn) and *p*-methoxybenzyl (PMB) groups. We were able to selectively debenzylate the *p*-methoxybenzyl derivative **11** with 10% Pd/C in EtOAc to give diol **20** (see Table) in good yield.[9] No selectivity was achieved when using 20% $Pd(OH)_2$/C as catalyst. The origin of this selectivity is unknown at present. However, the highly selective hydrogenolysis of a benzyl group in the presence of a *p*-methoxybenzyl group using Raney Ni as catalyst has been reported.[10]

The benzyl groups of the methylthiomethyl derivative **12**, could not be removed by hydrogenolysis with either 10% Pd/C or 20% $Pd(OH)_2$/C as catalyst, presumably due to catalyst poisoning by the sulfur group. Although numerous debenzylation strategies were attempted,[11] the only method that afforded diol **21** was Birch reduction using sodium in liquid ammonia (see Table). It was apparent that an alternative strategy would be required in order to obtain reasonable quantities of diols **21** and **26** containing the methylthiomethyl (MTM) or phenylthiomethyl (PTM) groups.

A reliable route to these compounds was developed, proceeding from glycerol (**22**) and 1,3-*O*-benzylideneglycerols **23a-b** (Eq. 2).



(2)

22 **23a-b**

24a-b : R = MTM, 70 % **21** : R = MTM, 73 %
25a-b : R = PTM, 55 % **26** : R = PTM, 75 %

EXPERIMENTAL SECTION

Unless otherwise noted, all reactions were carried out in dry glassware under an atmosphere of argon. Tetrahydrofuran and hexane were distilled from sodium/benzophenone ketyl; dimethylformamide, triethylamine, and N,N-diisopropylethylamine were distilled from CaH_2. Glycidol and benzyl bromide were freshly distilled prior to use. Methanol was dried over CaH_2 and freshly distilled from magnesium methoxide prior to use. Other reagents were purchased (Aldrich) and were used without further purification. The phrase normal workup is the equivalent of extraction with Et_2O (5 mL), washing the organic extract with sat. $NaHCO_3$ solution (3 mL) followed by sat. brine solution (3 mL), drying (Na_2SO_4), filtration, and evaporation to dryness *in vacuo*. Thin-layer chromatography was carried out on silica gel 60 F_{254} aluminum sheets (Merck 5554). Developed plates were visualized by staining with a 4% solution of phosphomolybdic acid in ethanol. Flash chromatography was performed using Merck 9385 silica gel 60 (230-400 mesh). Infrared spectra were recorded on a MB-100 Fourier transform infrared spectrophotometer between NaCl plates. ^1H and ^{13}C NMR spectra were recorded using Bruker AC-200 or AM-250 spectrometers using $CDCl_3$ as solvent; tetramethylsilane (^1H, δ 0.0) or $CDCl_3$ (^{13}C, δ 77.0) were used as internal references. Melting points were determined with a meltemp. melting point apparatus and are uncorrected. Mass spectra were recorded on a Kratos MS890 mass spectrometer. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

Benzyl 2,3-Epoxypropyl Ether (2).- A solution of glycidol (50.0 g, 0.675 mol) in THF (250 mL) was added to a suspension of NaH (30.0 g, 0.745 mol, 60% in oil), prewashed with hexane, in THF (1500 mL) and stirred at 0°. After hydrogen evolution had ceased, solid tetrabutylammonium iodide (5.25 g, 14.20 mmol) was added in one portion. Benzyl bromide (84.50 mL, 0.710 mol) was added dropwise and the mixture was stirred for 10 hrs at RT. The mixture was quenched with aqueous ammonium chloride (100 mL) and extracted with ether (2 x 500 mL). The combined organic extracts were washed with H_2O (2 x 500 mL), brine (500 mL), dried (Na_2SO_4) and concentrated using a rotary evaporator. The crude product was distilled through a short-path Vigreux column apparatus to give benzylated glycidol **2** (108.7 g, 89%) as a colorless liquid,[12] bp. 120-122° at 1.0 mm, lit.[13] bp. 105° at 0.4 mm. When benzyl chloride was substituted for benzyl bromide in the above procedure, the yield of 2 dropped to 60%.

1,3-Dibenzyloxy-2-propanol (3).- A solution of benzyl alcohol (31.6 mL, 0.305 mol) in DMF (50 mL) was added to a suspension of NaH (24.4 g, 0.610 mol, 60% in oil), prewashed with hexane, in DMF (300 mL) and stirred at 0°. After hydrogen evolution had ceased, benzylated glycidol **2** (10.0 g, 0.061 mol) was slowly added and the mixture was stirred at 120° for 16 hrs. After cooling, the mixture was quenched with aqueous ammonium chloride (50 mL) and extracted with ether (2 x 200 mL). The combined organic extracts were washed with H_2O (4 x 200 mL), brine (200 mL), dried (Na_2SO_4) and concentrated using a rotary evaporator. The excess benzyl alcohol was removed by bulb to bulb distillation, (air bath temperature 70-100°, 1.5 mm.) giving **3** (15.8 g, 95%) as a pale yellow oil, which exhibited spectral data identical with that previously reported.[7b]

1,3-Dibenzyloxy-2-propyl Acetate (4) and 1,3-Dibenzyloxy-2-*p*-toluenesulfonyloxypropane (7).- To a solution of alcohol **3** (272 mg, 1.0 mmol) in CH_2Cl_2 (3 mL) at 0°, triethylamine (0.167 mL, 1.2 mmol), DMAP (2.5 mg, 0.02 mmol), and acetic anhydride (0.128 mL, 1.1 mmol) for **4** or *p*-toluenesulfonyl chloride (210 mg, 1.1 mmol) for **7** were sequentially added. The mixture was stirred for 8-10 hrs at RT. Normal workup followed by flash chromatography with hexane/EtOAc (10:1) as the eluent

afforded pure **4** (236 mg, 75%) or pure **7** (367 mg, 86%).

1,3-Dibenzyloxy-2-propyl Acetate (4).- IR (neat): υ = 1739, 1096, 743, 699 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.36-7.22 (m, 10 H), 5.21 (quintet, 1 H, *J* = 5.1 Hz), 4.52 (ABq, 4 H, Δδ = 0.04 ppm, *J* = 12.1 Hz), 3.63 (d, 4 H, *J* = 5.1 Hz), 2.07 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.45, 137.91, 128.33, 127.57, 73.20, 71.47, 68.57, 21.11; MS, EI: *m/e* 314 (M^+, 4), 221 (35), 105 (100), 91 (87).

Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.36; H, 6.94

1,3-Dibenzyloxy-2-*p*-toluenesulfonyloxypropane (7).- IR (neat): υ = 1356, 1180, 1107, 814, 745, 685 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.77-7.75 (m, 2 H), 7.35-7.17 (m, 13 H), 4.75 (quintet, 1 H, *J* = 5.1 Hz), 4.43 (ABq, 4 H, Δδ = 0.06 ppm, *J* = 14.3 Hz), 3.65 (d, 4 H, *J* = 5.1 Hz), 2.37 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 144.46, 137.64, 129.52, 128.33, 127.94, 127.68, 127.58, 79.58, 73.34, 68.72, 21.60; MS, EI: *m/e* 426 (M^+, 12), 335 (79), 181 (66), 155 (65), 105 (43), 91 (100).

Anal. Calcd for $C_{24}H_{26}SO_5$: C, 67.58; H, 6.14. Found: C, 67.31; H, 6.35

1,3-Dibenzyloxy-2-propyl Benzoate (5).- To a solution of alcohol **3** (272 mg, 1.0 mmol) in CH_2Cl_2 (3 mL) at 0°, DCC (217 mg, 1.05 mmol), DMAP (2.5 mg, 0.02 mmol), and benzoic acid (128 mg, 1.05 mmol) were sequentially added. The mixture was stirred for 8 hrs at RT. Normal workup followed by flash chromatography with hexane/EtOAc (10:1) as the eluent afforded pure **5** (331 mg, 88%). IR (neat): υ = 1719, 1269, 1099, 741, 707 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.09-8.05 (m, 2 H), 7.61-7.20 (m, 13 H), 5.46 (quintet, 1 H, *J* = 5.1 Hz), 4.57 (ABq, 4 H, Δδ = 0.04 ppm, *J* = 12.2 Hz), 3.78 (d, 4 H, *J* = 5.1 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.99, 137.98, 132.94, 130.18, 129.75, 128.32, 128.28, 127.55, 73.22, 72.21, 68.70; MS, EI: *m/e* 271 (M^+- C_7H_5O, 1), 212 (6), 123 (5), 105 (100), 91 (91), 77 (42).

Anal. Calcd for $C_{24}H_{24}O_4$: C, 76.57; H, 6.43. Found: C, 76.47; H, 6.31

1,3-Dibenzyloxy-2-*tert*-butyldimethylsiloxypropane (6).- To a solution of alcohol **3** (272 mg, 1.0 mmol) in DMF (5 mL) at 0°, imidazole (163.4 mg, 2.4 mmol), and TBDMSCl (166 mg, 1.1 mmol) were sequentially added. The mixture was stirred for 10 hrs at RT, and was then extracted with ether (10 mL), washed with aqueous $NaHCO_3$ (2 x 5 mL), brine (5 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator. The residue was purified by flash chromatography with hexane/EtOAc (20:1) as the eluent to afford pure **6** (356 mg, 92%). IR (neat): υ = 1112, 1024, 739, 698 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 7.43-7.23 (m, 10 H), 4.53 (s, 4 H), 4.02 (quintet, 1 H, *J* = 5.3 Hz), 3.55 (A of ABX, 2 H, *J* = 5.0, 9.8 Hz), 3.48 (B of ABX, 2 H, *J* = 5.6, 9.8 Hz), 0.88 (s, 9 H), 0.07 (s, 6 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.45, 128.25, 127.52, 127.42, 73.33, 72.36, 71.13, 25.82, 18.18, -4.71; MS, EI: *m/e* 386 (M^+, 22), 293 (33), 181 (68), 131 (63), 123 (63), 105 (87), 91 (100).

Anal. Calcd for $C_{23}H_{34}SiO_3$: C, 71.46; H, 8.87. Found: C, 71.28; H, 8.77

1,3-Dibenzyloxy-2-ethoxymethoxypropane (8) and 1,3-Dibenzyloxy-2-benzyloxymethoxypropane (9).- To a solution of alcohol **3** (272 mg, 1.0 mmol) in CH_2Cl_2 (3 mL) at 0°, *N,N*-diisopropylethylamine (0.210 mL, 1.2 mmol), and chloromethyl ethyl ether (0.102 mL, 1.1 mmol) for **8** or chloromethyl benzyl ether (0.153 mL, 1.1 mmol) for **9** were sequentially added. The mixture was stirred for 8 hrs at RT. Normal workup followed by flash chromatography with

hexane/EtOAc (10:1) as the eluent afforded pure **8** (271 mg, 82%) or pure **9** (314 mg, 80%).

1,3-Dibenzyloxy-2-ethoxymethoxypropane (8).- IR (neat): 1078, 741, 699 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 7.35-7.21 (m, 10 H), 4.80 (s, 2 H), 4.53 (s, 4 H), 3.98 (quintet, 1 H, J = 5.1 Hz), 3.66-3.55 (m, 6 H), 1.15 (t, 3 H, J = 7.1 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.13, 128.18, 127.43, 94.56, 74.83, 73.21, 70.15, 63.07, 14.90; MS, EI: *m/e* 330 (M^+, 35), 299 (73), 271 (71), 193 (87), 181 (99), 105 (84), 91 (100).

Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.81; H, 7.83

1,3-Dibenzyloxy-2-benzyloxymethoxypropane (9).- IR (neat): 1105, 1039, 741, 699 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 7.36-7.21 (m, 15 H), 4.89 (s, 2 H), 4.63 (s, 2 H), 4.54 (s, 4 H), 4.04 (quintet, 1 H, J = 5.0 Hz), 3.64-3.59 (m, 4 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.19, 137.91, 128.33, 127.87, 127.58, 94.17, 75.03, 73.36, 70.27, 69.41; MS, EI: *m/e* 392 (M^+, 7), 271 (72), 193 (81), 181 (99), 105 (80), 91 (100).

Anal. Calcd for $C_{25}H_{28}O_4$: C, 76.50; H, 7.19. Found: C, 76.43; H, 6.97

1,2,3-Tribenzyloxypropane (10), 1,3-Dibenzyloxy-2-(4-methoxyphenyl)methoxypropane (11) and 1,3-Dibenzyloxy-2-methylthiomethoxypropane (12).- A solution of alcohol **3** (272 mg, 1.0 mmol) in THF (5 mL) was added to a suspension of NaH (80 mg, 2.0 mmol, 60% in oil), prewashed with hexane, in THF (15 mL) and stirred at 0°. After hydrogen evolution had ceased solid tetrabutylammonium iodide (7.3 mg, 0.02 mmol) for **10** and **11** or solid sodium iodide (0.165 g, 1.1 mmol) for **12** was added in one portion. Benzyl bromide (0.143 mL, 1.2 mmol) for **10**, *p*-methoxybenzyl chloride (0.163 mL, 1.2 mmol) for **11** or chloromethyl methyl sulfide (0.092 mL, 1.1 mmol) for **12** was added dropwise and the mixture was stirred for 12 hrs at RT. The mixture was then quenched with aqueous ammonium chloride (3 mL) and extracted with ether (2 x 10 mL). The combined organic extracts were washed with H_2O (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated using a rotary evaporator. The residue was purified by flash chromatography with hexane/EtOAc (15:1) for **10** and **12** or hexane/EtOAc (12:1) for **11** as the eluent to afford pure **10** (337 mg, 93%), exhibiting spectral data identical with that previously reported,[7c] pure **11** (341 mg, 87%) or pure **12** (239 mg, 72%).

1,3-Dibenzyloxy-2-(4-methoxyphenyl)methoxypropane (11). IR (neat): 1081, 825, 743, 699 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.31-7.25 (m, 12 H), 6.87-6.82 (m, 2 H), 4.62 (s, 2 H), 4.53 (s, 4 H), 3.91-3.72 (m, 1 H), 3.79 (s, 3 H), 3.68-3.53 (m, 4 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.11, 138.31, 130.76, 129.34, 128.30, 127.57, 127.52, 113.68, 76.83, 73.33, 71.88, 70.36, 55.23; MS, EI: *m/e* 392 (M^+, 15), 302 (100), 271 (66), 181 (65), 105 (42), 91 (81).

Anal. Calcd for $C_{25}H_{28}O_4$: C, 76.50; H, 7.19. Found: C, 76.35; H, 7.38

1,3-Dibenzyloxy-2-methylthiomethoxypropane (12).- IR (neat): 1080, 740, 698 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.38-7.21 (m, 10 H), 4.79 (s, 2 H), 4.54 (s, 4 H), 4.11 (tt, 1 H, J = 5.1, 4.8 Hz), 3.65 (A of ABX, 2 H, J = 5.1, 8.3 Hz), 3.55 (B of ABX, 2 H, J = 4.8, 8.3 Hz), 2.14 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.16, 128.31, 127.57, 74.46, 74.21, 73.34, 70.15, 13.68; MS, EI: *m/e* 333 (M^++ 1, 53), 319 (76), 271 (87), 229 (88), 193 (100), 181 (96), 91 (87)

Anal. Calcd for $C_{19}H_{24}SO_3$: C, 68.64; H, 7.28. Found: C, 68.89; H, 7.43

General Procedure for Preparation of 2-*O*-Protected Glycerols (13-17).- A mixture of dibenzyl ether **4-8** (1.0 mmol) and 20% $Pd(OH)_2/C$ (0.05-0.10 eq) in EtOAc (3 mL) was stirred for 8-12 hrs under one atmosphere of hydrogen at RT. The mixture was then filtered by gravity, concentrated using a rotary evaporator, and dried *in vacuo* to afford the corresponding diol in quantitative yield (**13, 14, 16, 17**, as colorless oils; **15** as a white solid (mp. = 61-62°)).

1,3-Dihydroxy-2-propyl Acetate (13).- IR (neat): 3381, 1726, 734 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 4.89 (quintet, 1 H, J = 4.9 Hz), 3.76 (d, 4 H, J = 4.9 Hz), 2.11 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.48, 74.99, 61.48, 20.99; MS, EI: *m/e* 135 (M^++1, 9), 117 (87), 103 (20), 43 (100).

Anal. Calcd for $C_5H_{10}O_4$: C, 44.77; H, 7.51. Found: C, 44.66; H, 7.39

1,3-Dihydroxy-2-propyl Benzoate (14).- IR (neat): 3394, 1710, 720 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 8.03-7.97 (m, 2 H), 7.54-7.31 (m, 3 H), 5.11 (quintet, 1 H, J = 4.9 Hz), 3.86 (d, 4 H, J = 4.9 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.69, 133.22, 129.67, 128.33, 75.54, 61.68; MS, EI: *m/e* 197 (M^++1, 48), 179 (44), 123 (7), 105 (28), 92 (100), 91 (98).

Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.20; H, 6.17. Found: C, 60.80; H, 6.36

2-*tert*-Butyldimethylsiloxy-1,3-propanediol (15).- IR ($CHCl_3$): 3413, 1216, 761 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 3.75 (quintet, 1 H, J = 4.8 Hz), 3.58 (d, 4 H, J = 4.8 Hz), 0.85 (s, 9 H), 0.06 (s, 6 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 72.43, 63.83, 25.73, 18.03, -4.78; MS, EI: *m/e* 207 (M^++1, 78), 189 (29), 171 (51), 131 (100), 75 (84).

Anal. Calcd for $C_9H_{22}SiO_3$: C, 52.18; H, 10.74. Found: C, 51.93; H, 10.39

2-*p*-Toluenesulfonyloxy-1,3-propanediol (16).- IR (neat): 3409, 1350, 1179, 779, 733, 673 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 7.83-7.79 (m, 2 H), 7.35-7.31 (m, 2 H), 4.54 (quintet, 1 H, J = 4.7 Hz), 3.82-3.69 (m, 4 H), 2.42 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 145.16, 133.12, 129.91, 127.82, 82.61, 61.30, 21.55; MS, EI: *m/e* 247 (M^++1, 49), 229 (55), 155 (94), 91 (100).

Anal. Calcd for $C_{10}H_{14}SO_5$: C, 48.77; H, 5.73. Found: C, 48.88; H, 5.74

2-Ethoxymethoxy-1,3-propanediol (17).- IR (neat): 3386, 1061 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 4.81 (s, 2 H), 3.74-3.63 (m, 7 H), 1.25 (t, 3 H, J = 7.1 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 95.59, 82.14, 64.02, 62.87, 14.96; MS, EI: *m/e* 151 (M^++1, 79), 133 (7), 117 (91), 105 (100), 59 (89).

Anal. Calcd for $C_6H_{14}O_4$: C, 47.99; H, 9.39. Found: C, 48.12; H, 9.21

2-(4-Methoxyphenyl)methoxy-1,3-propanediol (20).- 1,3-Dibenzyloxy-2-(4-methoxyphenyl) methoxypropane (**11**) (393 mg, 1.0 mmol) was added to a suspension of 10% Pd/C (0.05 eq) in EtOAc (3 mL). The mixture was stirred for 18 hrs under one atmosphere of hydrogen at RT. The mixture was then filtered by gravity and concentrated using a rotary evaporator. The residue was purified by flash chromatography with hexane/EtOAc (4:1-1:5) as the eluent to afford pure diol **20** (149 mg, 70%), as a white solid (mp. = 37-40°). IR (neat): 3385, 1067, 825, cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.31-7.25 (m, 2 H), 6.92-6.87 (m, 2 H), 4.59 (s, 2 H), 3.81 (s, 3 H), 3.76-3.71 (m, 4 H), 3.58 (quintet, 1 H, J = 4.7 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.48, 129.47, 114.02, 78.85, 71.66, 62.32, 55.28; MS, EI: *m/e* 213 (M^++1, 1), 137 (19), 121 (100), 107 (2), 91 (5), 77 (8).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.00; H, 7.58

2-Methylthiomethoxy-1,3-propanediol (21).- To a solution of benzyl ether **12** (800 mg, 2.4 mmol) in liquid ammonia (50 mL) and THF (5 mL) at -40° was added small quantities of sodium (115 mg, 5.0 mmol) until a permanent blue color was observed. Stirring was continued for an additional 15 min. The mixture was then quenched by the portionwise addition of solid ammonium chloride and the ammonia was allowed to evaporate overnight. The residue was purified by flash chromatography with hexane/EtOAc (3:1-1:4) as the eluent to afford pure **21** (46 mg, 30%) as a colorless oil. IR (neat): 3368, 1055 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 4.78 (s, 2 H), 4.53 (s, 4 H), 3.78-3.60 (m, 5 H), 2.21 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 78.24, 74.55, 62.17, 14.04; MS, EI: *m/e* 153 (M^++1, 8), 105 (61), 61 (100).

Anal. Calcd for $C_5H_{12}SO_3$: C, 39.45; H, 7.95. Found: C, 39.15; H, 7.77

***trans*- and *cis*-5-Hydroxy-2-phenyl-1,3-dioxane (23a-b).**- This material was prepared by a modification of the method reported by Baggett.[14] Thus a biphasic mixture of glycerol (400 g, 4.34 mol) and benzaldehyde (430 mL, 4.23 mol) was treated with conc. HCl (10 drops). The mixture was stirred at 120-130° with azeotropic removal of water until it was homogeneous (3-4 hours). The mixture was cooled and allowed to stand at RT overnight. To this mixture was added benzene (300 mL)/petroleum ether bp 80-100° (700 mL), and the mixture was stored for two days at 0°. The semi-solid white crystals isolated were recrystallized (3X) from a solution of benzene/pet ether (210 mL/590 mL) to afford a 1:1 mixture of **23a** and **23b** (130 g, 17%) as a white solid. This material exhibited spectral data in accord with literature values.[14]

***trans*- and *cis*-5-Methylthiomethoxy-2-phenyl-1,3-dioxane (24a-b) and *trans*- and *cis*-2-Phenyl-5-phenylthiomethoxy-1,3-dioxane (25a-b).**- A solution of 1,3-dioxanes **23a-b** (10 g, 0.055 mol) in THF (30 mL) was added to a suspension of NaH (4.44 g, 0.111 mol, 60% in oil), prewashed with hexane, in THF (120 mL) and the mixture was stirred at 0°. After hydrogen evolution had ceased solid sodium iodide (8.32 g, 0.055 mol) was added in small quantities. Chloromethyl methyl sulfide (4.65 mL, 0.055 mol) for **24-a-b** or chloromethyl phenyl sulfide (7.43 mL, 0.055 mol) for **25a-b** was added dropwise and the mixture was stirred for 48 hrs at RT. The mixture was then quenched with aqueous ammonium chloride (35 mL) and extracted with ether (2 x 100 mL). The combined organic extracts were washed with H_2O (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated using a rotary evaporator. The residue was purified by flash chromatography with hexane/EtOAc (10:1-3:1) as the eluent to afford *trans*-5-methylthiomethoxy-2-phenyl-1,3-dioxane **24a** (4.20 g, 34%) as a yellow oil and *cis*-5-methylthiomethoxy-2-phenyl-1,3-dioxane **24b** (4.31 g, 36%) as a white solid (mp. = 64-66°) or *trans*-2-phenyl-5-phenylthiomethoxy-1,3-dioxane **25a** (4.61 g, 28%) as a pale yellow solid (mp. = 57-59°) and *cis*-2-phenyl-5-phenylthiomethoxy-1,3-dioxane **25b** (2.76 g, 27%) as a white solid (mp. = 68-69°).

***trans*-5-Methylthiomethoxy-2-phenyl-1,3-dioxane (24a).**- IR ($CHCl_3$): 1066, 753, 695 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 7.49-7.33 (m, 5 H), 5.40 (s, 1 H), 4.65 (s, 2 H), 4.42-4.36 (m, 2 H), 3.96 (tt, 1 H, J = 5.1, 10.3 Hz), 3.67-3.63 (m, 2 H), 2.15 (s, 3 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 137.49,

128.77, 128.06, 125.93, 101.05, 74.27, 68.69, 66.36, 13.69; MS, EI: *m/e* 240 (M^+, 26), 193 (42), 162 (40), 105 (96), 91 (57), 77 (44), 61 (100).

Anal. Calcd for $C_{12}H_{16}SO_3$: C, 59.98; H, 6.71. Found: C, 60.03; H, 6.81

***cis*-5-Methylthiomethoxy-2-phenyl-1,3-dioxane (24b).**- IR ($CHCl_3$): 1067, 755, 699 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.51-7.31 (m, 5 H), 5.56 (s, 1 H), 4.80 (s, 2 H), 4.32-4.26 (m, 2 H), 4.12-4.06 (m, 2 H), 3.77 (tt, 1 H, *J* = 1.3, 3.3 Hz), 2.17 (s, 3 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 137.88, 128.70, 127.97, 125.93, 101.09, 72.51, 68.72, 66.68, 13.42; MS, EI: *m/e* 240 (M^+, 4), 193 (85), 162 (59), 105 (98), 91 (65), 77 (57), 61 (100). *Anal.* Calcd for $C_{12}H_{16}SO_3$: C, 59.98; H, 6.71. Found: C, 60.15; H, 6.89.

***trans*-2-Phenyl-5-phenylthiomethoxy-1,3-dioxane (25a).**- IR ($CHCl_3$): 1089, 757, 697 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.49-7.25 (m, 10 H), 5.39 (s, 1 H), 5.03 (s, 2 H), 4.43-4.36 (m, 2 H), 4.05 (tt, 1 H, J = 1.3, 3.4 Hz), 3.67-3.59 (m, 2 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 137.58, 135.12, 130.21, 129.03, 128.97, 128.24, 127.02, 126.06, 101.24, 75.15, 69.78, 67.03; MS, EI: *m/e* 302 (M^+, 26), 162 (23), 123 (70), 105 (100), 91 (99), 77 (73).

Anal. Calcd for $C_{17}H_{18}SO_3$: C, 67.52; H, 6.00. Found: C, 67.54; H, 6.05

***cis*-2-Phenyl-5-phenylthiomethoxy-1,3-dioxane (25b).**- IR ($CHCl_3$): 1087, 759, 699 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.54-7.16 (m, 10 H), 5.54 (s, 1 H), 5.18 (s, 2 H), 4.35-4.29 (m, 2 H), 4.13-4.07 (m, 2 H), 3.84 (tt, 1 H, J = 1.6 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 137.94, 135.44, 129.88, 128.95, 128.84, 128.11, 126.68, 126.04, 101.23, 73.18, 68.54, 67.14; MS, EI: *m/e* 302 (M^+, 21), 193 (54), 123 (68), 105 (77), 91 (100), 77 (69). *Anal.* Calcd for $C_{17}H_{18}SO_3$: C, 67.52; H, 6.00. Found: C, 67.64; H, 6.01.

2-Methylthiomethoxy-1,3-propanediol (21) and 2-Phenylthiomethoxy-1,3-propanediol (26).- To a solution of 1,3-dioxanes **24a-b** (2.00 g, 8.32 mmol) or 1,3-dioxanes **25a-b** (2.84 g, 9.38 mmol) in methanol (40 mL) was added pyridinium *p*-toluenesulfonate (0.234 g, 0.938 mmol). The mixture was stirred for 8 hrs after which Na_2CO_3 (0.1 g, 1 mmol) was added and the mixture was stirred for an additional 10 min. The mixture was filtered through a Celite® pad and concentrated using a rotary evaporator. The residue was purified by flash chromatography with hexane/EtOAc (3:1-1:5) as the eluent to afford pure diol **21** (0.925 g, 73%) as a colorless oil (spectral properties identical to those presented above) or pure diol **26** (1.51 g, 75%) as a colorless oil.

2-Phenylthiomethoxy-1,3-propanediol (26).- IR (neat): 3381, 1050, 743, 699 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 7.50-7.45 (m, 2 H), 7.34-7.23 (m, 3 H), 5.13 (s, 2 H), 3.85 (tt, 1 H, J = 4.2, 5.3 Hz), 3.77 (A of ABX, 2 H, J = 4.2, 11.9 Hz), 3.67 (B of ABX, 2 H, J = 5.3, 11.9 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 134.96, 129.98, 129.04, 126.92, 78.12, 74.87, 61.77; MS, EI: *m/e* 213 (M^++1, 39), 195 (55), 181 (58), 108 (65), 91 (100).

Anal. Calcd for $C_{10}H_{14}SO_3$: C, 56.05; H, 6.59. Found: C, 56.35; H, 6.85

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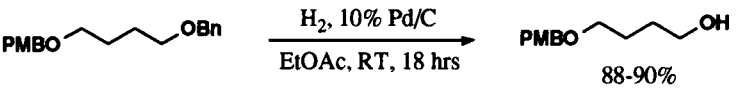
8. The acetyl, benzoyl and *p*-toluenesulphonyl derivatives have been previously prepared from the 1,3-O-benzylideneglycerol intermediate.[15,16] In the case of the acetyl and benzoyl derivatives, removal of the benzylidene group under the conditions employed resulted in partial acyl transfer.

9. In order to investigate this chemoselectivity, 1,4-butanediol was differentially protected with the *p*-methoxybenzyl and benzyl group. Hydrogenolysis of this compound with 10% Pd/C in EtOAc under a hydrogen atmosphere resulted in highly selective deprotection of the benzyl group



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