Total Synthesis of (1-^{13}C)-Glycerol

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SUMMARY

A simple, inexpensive synthesis of (1-^{13}C)-glycerol is described.

Key Words: Glycerol, Carbon-13, potassium cyanide.

INTRODUCTION

Glycerol labelled with ^{13}C in C-1 was required in these laboratories for a number of experiments - investigations of the biosyntheses of mould metabolites, nuclear magnetic resonance studies of whole cells, and as a synthetic intermediate in the preparation of other labelled compounds such as nicotinic acid[1]. Because relatively large amounts of compound (10mg-1g) were required, the commercially available (1,3-$^{13}C_2$)-glycerol was prohibitively expensive. In the n.m.r. investigation a second label was actually undesirable as ^{13}C-^{13}C coupling would complicate the spectra. Thus a simple, high-yielding synthesis of (1-^{13}C)-glycerol was sought. Literature syntheses of (1-^{14}C)-glycerol were not generally adaptable to work with ^{13}C, being either too low yielding[2] or most suitable for larger scales.[3] However, the general strategy used in these syntheses, that of forming a cyanohydrin of the required carbon skeleton from labelled potassium cyanide and a suitable aldehyde, was also employed in the synthesis described in this paper.

RESULTS

Glycolaldehyde diethyl acetal (1) is commercially available and was treated with sodium hydride and benzyl chloride to give the hydroxy-protected

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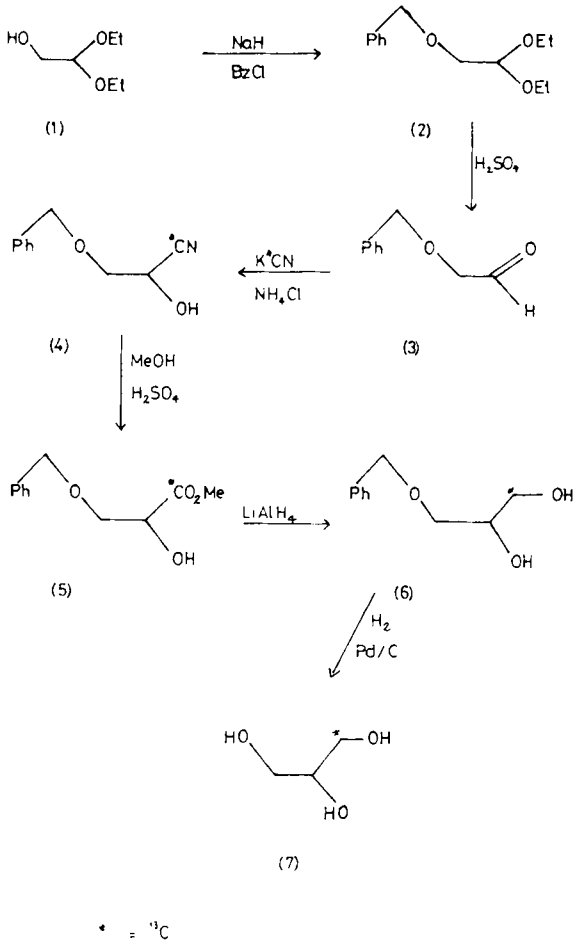
SCHEME



acetal (2) (see scheme). The benzyl protecting group was used because it is resistant to acid, base and reducing agents, is readily removed by hydrogenolysis, and because it renders the synthetic intermediates soluble in organic solvents. The acetal function was hydrolysed with dilute sulphuric acid to give 2-benzyloxyacetaldehyde (3).

Compound (3) was treated with potassium (^{13}C)-cyanide, which is a very inexpensive source of ^{13}C, in a two phase system to give the cyanohydrin (4) in very high yield. On treatment with methanol in the presence of sulphuric

acid for 10 days at reflux, the ester (5) was obtained. Various procedures including distillation and chromatography were used in an effort to purify the ester, but these all resulted in considerable loss of material; simple washing of the methanolic solution with hexane gave the best results. After treatment in this way the ester was reduced with lithium aluminium hydride to give the diol (6) which was easily deprotected by hydrogenolysis to give (1-^{13}C)-glycerol (7) in 22% yield from potassium (^{13}C)-cyanide.

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EXPERIMENTAL

Nuclear magnetic resonance spectra (^{1}H and ^{13}C) were recorded on a Bruker WM250 instrument at 250MHz and 63MHz respectively, using deuteriated chloroform as solvent unless otherwise stated, and with tetramethylsilane as internal standard. Infra-red spectra were determined in chloroform solution on a Beckmann IR-8 or a Perkin-Elmer 421 and mass spectra on a Varian MAT CH-5 instrument. Solutions were dried over anhydrous sodium sulphate.

2-Benzyloxydiethyl acetal (2)[4]

Glycolaldehyde diethyl acetal (7ml, 6.22g, 46mmole) was dissolved in dry tetrahydofuran with stirring. Sodium hydride (80% in oil, 1.95g, 65mmole) was added, followed by benzyl chloride (5.1ml, 55mmole). The mixture was stirred overnight at room temperature, then poured into water (100ml). The aqueous solution was extracted with dichloromethane (4 x 50ml), and the combined organic layers were dried and evaporated to give almost pure (2) which could be distilled (100-110°, 0.6 torr, bulb to bulb). Yield 8.37g (80%). δ 7.31

(5H, bs, ArH), 4.67 (1H, t, J=5.5Hz, $CH(OEt)_2$), 4.58 (2H, s, $PhCH_2$), 3.64 (4H, q, J=7.5Hz, CH_2Me), 3.50 (2H, d, J=5.5Hz, $BzOCH_2$), 1.24 (6H, t, J=7.5Hz, CH_3). ν 3010(w), 2920 (m), 2890 (m), 1605 (w), 1585 (w), 1497 (w), 1455 (w). m/e 193, 178, 148, 121, 103, 91 (100%).

2-Benzyloxyacetaldehyde (3)

2-Benzyloxydiethyl acetal (200mg) was suspended in water (7ml). Concentrated sulphuric acid (0.2ml) was added and the suspension was stirred vigorously at room temperature overnight. It was then extracted with dichloromethane (3 x 5ml), and the combined organic layers were dried and evaporated. Distillation (82-83°, 0.1 torr; lit[5] 112°, 10 torr) yielded pure (3), 62mg, 46%. δ 9.76 (1H, t, J=1.5Hz, CHO), 7.38 (5H, s, ArH), 4.64 (2H, s, $PhCH_2O$), 4.09 (2H, d, J=1.5Hz, CH_2CHO). ν 3030 (m), 2930 (m), 1735 (s), 1595 (m). m/e 150 (M^+), 149, 136, 120, 107, 91 (100%).

3-Benzyloxy-2-hydroxypropionitrile

2-Benzyloxyacetaldehyde (300mg, 2 mmole) was dissolved in chloroform (3ml). Potassium cyanide (117mg, 1.8 mmole) and ammonium chloride (110mg) were added, followed by water (3ml). The mixture was stirred overnight at room temperature. The aqueous layer was extracted with dichloromethane (3 x 7ml) and these extracts combined with the chloroform layer, dried and evaporated *in vacuo* at room temperature to give a yellow oil, which was shown by n.m.r. to be almost pure (4). All attempts to purify this material resulted in considerable losses so it was used crude in the next reaction. Found 177.095 (M^+) (Required for $C_{10}H_{11}NO_2$ 177.0790); δ 7.37 (5H, s, ArH), 4.62 (2H, s, $PhCH_2$), 4.53 (1H, t, J=4Hz, CHCN), 3.68 (2H, d, J=4Hz, CH_2CHCN), 3.51 (1H, bs, OH). ^{13}C δ137.2 ($(CH)_5CCH_2O$), 127-129 (remaining Ar), 118.6 (CN), 73.8 (CH_2), 70.8 (CH_2), 60.7 (CHOH). ν 3350 (bs), 3090 (m), 3060 (m), 3030(m), 2920 (s), 2870 (s), 2250 (w), 1605 (w), 1585 (w). m/e 177, 108, 107, 91 (100%).

(1-^{13}C)-3-Benzyloxy-2-hydroxypropionitrile (4)

As above, with potassium (^{13}C) cyanide. δ7.37 (5H, m, ArH), 4.62 (2H, s, $PhCH_2$), 4.53 (1H, dt, J=4Hz, 6.5Hz, CHCN), 3.68 (2H, d, J=4Hz, 0.5Hz, CH_2CHCN), 1.8 (1H, bs, OH). ^{13}C δ 137.1 (CCH_2O), 127-129 (Ar), 118.5 (CN,

strong), 73.6 (CH_2), 70.7 (CH_2), 60.5 (d, J=61Hz, CHOH). m/e 178, 149, 136, 107, 105, 91 (100%).

Methyl 3-benzyloxy-2-hydroxypropionate

3-Benzyloxy-2-hydroxypropionitrile (crude from 200mg (2)) was dissolved in Analar methanol (15ml), and sulphuric acid (0.5ml) was added. The solution was stirred at reflux for 10 days. (The reaction may be followed by n.m.r. - working up small quantities which are returned to the reaction medium after analysis). Water (5ml) was then added and most of the methanol was removed *in vacuo*. The aqueous solution was extracted with dichloromethane (4 x 10ml) and the combined organic layers were dried and evaporated to give a yellow oil. Neither distillation (120-125°, 0.1 torr) nor chromatography effected significant purification so the product, which was already almost pure by n.m.r., was used without purification in the next reaction. Found 210.0892 (Required for $C_{11}H_{14}O_4$ 210.0892). δ7.33 (5H, bs, Ar), 4.60 (2H, s, $ArCH_2$), 4.38 (1H, t, J=4Hz, $CHCO_2Me$), 3.82 (3H, s, Me), 3.74 (2H, d, J=4Hz, CH_2CH), 2.30 (1H, bs, OH). ^{13}C δ173.0 (C=O), 137.7 (CCH_2O-), 126-129 (Ar), 73.5 (CH_2), 71.3 (CH_2), 70.8 (CHOH), 52.4 (CH_3). ν 3250 (br), 3025, 1720 (s), 1627 (m), 1583 (w), 1540 (m). m/e 210 (M^+), 162, 149, 122, 107, 105, 91 (100%).

(1-^{13}C)-Methyl 3-benzyloxy-2-hydroxypropionate (5)

As above, using (1-^{13}C)-3-benzyloxy-2-hydroxypropionitrile. δ7.33 (5H,bs,Ar), 4.60 (2H, s, $ArCH_2$), 4.38 (1H, dt, J=6Hz, 4Hz, $CHCO_2Me$), 3.82 (3H, d, J=4Hz, CO_2CH_3), 3.74 (2H, d, J=4Hz, CH_2CH), 2.18 (1H, bs, OH). ^{13}C δ173.0 (strong, C=O), 137.6 (CCH_2O), 126-129 (Ar), 73.4 (CH_2), 71.3 (CH_2), 70.8 (d, J=2.5Hz, CH_3). m/e 211 (M^+), 163, 122, 108, 107, 91 (100%).

3-Benzyloxy-1,2-propanediol[6]

Methyl 3-benzyloxy-2-hydroxypropionate (crude from above) was dissolved in dry ether (10ml) and lithium aluminium hydride (200mg) was added. The mixture was stirred at room temperature overnight and then poured into water (20ml). Concentrated sulphuric acid was added dropwise until all the aluminate had dissolved. The aquoes layer was then extracted with dichloromethane (3 x 20ml) and these extracts were combined with the ether layer, dried and evaporated to give a pale yellow oil which was distilled (bulb to bulb,

95-105°, 0.2 torr) to give a colourless oil, 93mg, 28% over three steps from potassium cyanide. δ7.40 (5H, m, ArH), 4.54 (2H, s, $ArCH_2$), 3.88 (1H, m, CHOH), 3.60 (4H, m, CH_2O), 2.33 (2H, bs, OH). ^{13}C δ137.7 ($\underline{C}CH_2O$), 127-129 (Ar), 73.4 (CH_2), 71.6 (CH_2), 70.8 (CHOH), 63.9 (CH_2OH). ν3420 (s,b), 3020 (m), 2940 (m), 2880 (m), 1603 (w). m/e 182 (M^+), 179, 163, 149, 107, 91 (100%).

(1-^{13}C)-3-Benzyloxy-1,2-propanediol (6)

As above, using (1-^{13}C)-methyl 3-benzyloxy-2-hydroxypropionate. δ7.4 (5H, m, Ar), 4.54 (2H, s, $ArCH_2$), 3.0-4.5 (5H, m, CH_2OH, CHOH). ^{13}C δ137.7 ($\underline{C}CH_2O$), 127-129 (Ar), 73.4 (CH_2), 71.6 (CH_2), 70.8 (d, J=64Hz, CH_2), 63.9 (strong CH_2OH). m/e 183 (M^+), 164, 149, 133, 107, 91 (100%).

Glycerol

3-Benzyloxy-1,3-propanediol (91mg) was dissolved in Analar methanol (10ml) and glacial acetic acid (5 drops) and 10% palladium on charcoal (9 mg) were added. The mixture was hydrogenolysed until hydrogen uptake ceased (12 hours) and then filtered through celite. The solution was evaporated and the residue distilled (130-135°, 0.4 torr, bulb to bulb) to give glycerol (35mg, 78%). δ (CD_3OD) 3.77 (m). ^{13}C δ76.86 (CHOH), 64.49 (CH_2OH).

(1-^{13}C)-Glycerol (7)

As above, using (1-^{13}C)-3-benzyloxypropanediol. δ3.77 (3H, m), 3.62 (1H, dd, J=142 Hz, 6 Hz), 3.64 (1H, dd, J=142 Hz, 6Hz), no further coupling was observed at this field strength. ^{13}C δ76.86 (weak, d, J=41 Hz, CHOH), 64.49 (strong, CH_2OH).

REFERENCES

1. Barber J. and Retey J., to be published.

2. Doerschuk A.P., J. Amer. Chem. Soc., 73, 821, (1951).

3. Gidez L.I. and Karnovsky M.L., J. Amer. Chem. Soc., 74, 2413, (1952).

4. Parham W.E. and Reiff H.E., J. Amer. Chem. Soc., 77, 6391, (1955).

5. Rigby W., J. Chem. Soc., 1907, (1950).

6. Fairbourne A., Gibson G.P. and Stephens D.W., J. Chem. Soc., 445, (1931).