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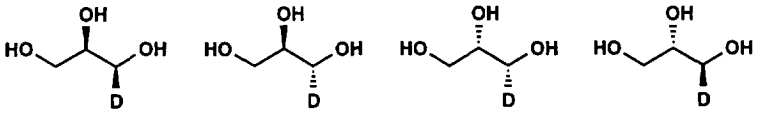
A short synthesis of (1*S*,2*R*)- and (1*R*,2*R*)-[1-^{2}H]-glycerols

Jens Nieschalk and David O'Hagan *
Department of Chemistry, University of Durham, Science Laboratories, South Road, Durham, DH1 3LE, UK

Abstract: A straightforward three step route to (1*S*,2*R*)- and (1*R*,2*R*)-[^{2}H]-glycerols **1a** and **1b** is reported. The key asymmetric step involves an AD-mix-β dihydroxylation on deuterium labelled *Z*- and *E*-allyl benzoates **4a** and **4b**. The route should facilitate the use of [^{2}H]-glycerols **1a–1d** in high enantiomeric purity (95%ee) in biosynthesis investigations. © 1997 Elsevier Science Ltd

Glycerol is a central intermediate in primary metabolism and is often efficiently incorporated into secondary metabolites. Accordingly isotopically labelled glycerols have been widely used in biosynthesis investigations.[1,2] Although glycerol is non chiral, substitution of each of its four hydroxymethylene hydrogens in turn by deuterium generates four unique stereoisomers **1a–d**. We required to prepare two of these stereoisomers (**1a** and **1b**) to extend a stereochemical investigation into the nature of C–F bond formation in the fluorometabolites produced by *Streptomyces cattleya*.[3]

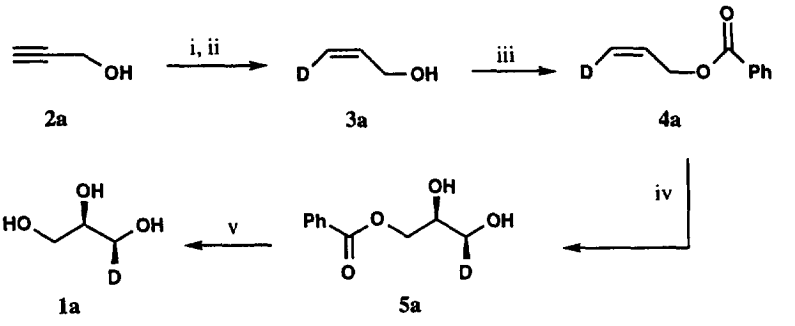


1a **1b** **1c** **1d**

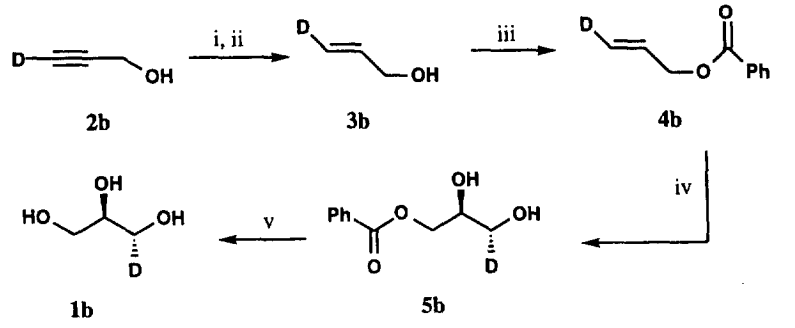
All of the four stereoisomers of [^{2}H]-glycerol **1a–d** have previously been prepared and characterised,[2,4–6] however the only reported syntheses of glycerols **1a** and **1b** are of poor enantiomeric excess (59%ee)[2] or involved eight steps[5] starting from D-glucose and provided glycerols **1a** and **1b** in a 8–41 mg-scale. The latter route required a stereospecific *trans* reduction of a carbohydrate templated propargylic alcohol, dihydroxylation with a chromatographic separation of diastereoisomers and then oxidative removal of the carbohydrate template. This route appeared unattractive at the outset, particularly as several hundred milligrams each of **1a** and **1b** were required for our purpose. In view of this we report the details of a shorter more efficient route to **1a** and **1b** which should find more general application (Schemes 1 and 2).

Propargylic alcohols are generally known to undergo stereoselective *trans* reduction on reaction with lithium aluminium hydride.[7] However, under certain circumstances *cis* reduction[8] can take place and hydride delivery can occur at the γ- as well as at the β-site[9,10] as revealed after a D_2O quench leading to 2- and 3-[^{2}H] allylic alcohols, respectively. Both *Z*- and *E*-[3-^{2}H] allyl alcohols (**3a** and **3b**) have been prepared by lithium aluminium hydride reduction of propargyl alcohol **2a** (or [3-^{2}H]-propargyl alcohol **2b** for **3b**) in diethyl ether and subsequent quenching with deuterium oxide (or water for **3b**).[10] In order to minimise the level of *cis* reduction tetrahydrofuran was employed instead of diethyl ether as the solvent.[8] Accordingly the route to **1b** was initiated from [3-^{2}H]-propargyl alcohol (**2b**) which was prepared by deprotonation of propargyl alcohol with n-butyllithium followed by a D_2O quench. This method is preferred to base catalysed exchange of the alkyne proton in D_2O/NaOD which proved to be low yielding and gave incomplete isotope incorporation. Reduction of propargyl alcohol **2b** with lithium aluminium hydride generated *E*-[3-^{2}H]-allyl alcohol (**3b**) as a single product. On the other hand reduction of **2a** followed by D_2O quench generated a more complex mixture. The

* Corresponding author. Email: David.O'Hagan@durham.ac.uk



Scheme 1. i) $LiAlH_4$, THF, r.t., 3 h; ii) D_2O; iii) PhCOCl, 30% NaOH, CH_2Cl_2, $Et_3BnN^+Cl^-$, 1 h, r.t., 40%; iv) AD-mix-β, t-BuOH/H_2O 1:1, 0°C, 4 h, 94%, 74%ee; v) NaOH (1 eq), H_2O, acetone, 55°C, 1 h, 64%.



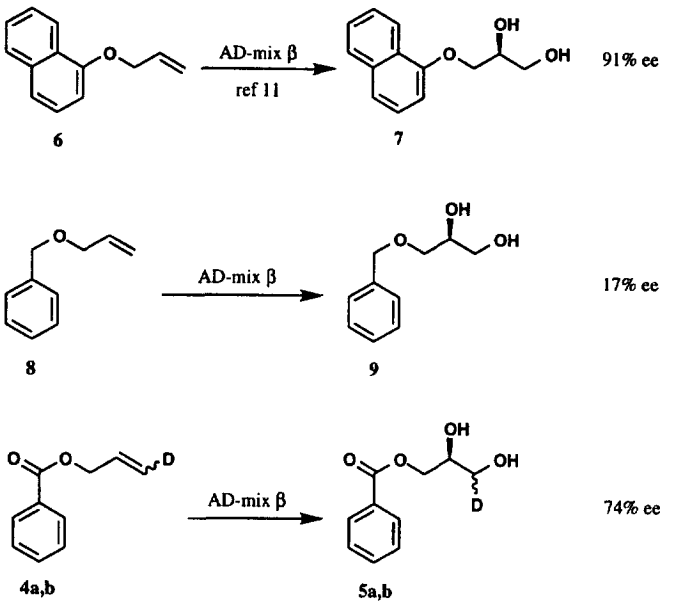
Scheme 2. i) $LiAlH_4$, THF, r.t., 3 h; ii) H_2O; iii) PhCOCl, 30% NaOH, CH_2Cl_2, $Et_3BnN^+Cl^-$, 1 h, r.t., 57%; iv) AD-mix-β, t-BuOH/H_2O 1:1, 0°C, 4 h, 93%, 74%ee; v) NaOH (1 eq), H_2O, acetone, 55°C, 1 h, 57%.

E/Z ratio although high was readily measured by ^2H NMR as 15:1 and the product also contained the [2-^{2}H]-allyl alcohol (15%), a result of some H^- attack at the terminal C-atom of the acetylene. This loss in regioselectivity is a limitation of the synthesis generating ultimately some [2-^{2}H]-glycerol in the sample of **1a**, however for most biosynthesis studies, this should not be a prohibitive problem provided the status of the sample is known prior to the feeding experiment.

The AD-mix asymmetric dihydroxylation[11] was explored to mediate asymmetric dihydroxylation of the labelled allyl alcohols. Previously allyl 1-naphthyl ether **6** has been established as a good substrate for the AD-mix-β reaction generating the resultant 1-(1-naphthyl) glycerol **7** in 91%ee[11] as shown in Scheme 3.

Despite the high enantiomeric excess there is no straightforward strategy for attaching allyl alcohol to naphthalene or for releasing glycerol from the resultant diol product. Therefore we investigated the allyl benzyl ether **8** and the allyl benzoate **4** as substrates for AD-mix-β dihydroxylation. Asymmetric dihydroxylation of **8** generated the glycerol **9** in only 17%ee. However the benzoate **4** proved to be the more satisfactory giving the protected glycerol **5** in 74%ee. Importantly this is a crystalline compound and the enantiomeric excess was readily increased to 95%ee after recrystallisation.

The allyl benzoates **4a** and **4b** were prepared by treatment of a dichloromethane solution of allyl alcohols **3a** and **3b** and benzoyl chloride with aqueous sodium hydroxide (30%) and triethylbenzylammonium chloride as a phase transfer catalyst.[12] The deuterium content of each sample was assessed at this stage by mass spectroscopy and shown to be 99.3% for **4a** and 77% for **4b**. We assume that some isotope exchange occurred during lithium aluminium hydride reduction of [3-^{2}H]-propargyl alcohol where hydride is acting as a base. Allyl benzoates **4a,b** were treated with AD-mix-β in 1:1 *t*-butyl alcohol/water at 0°C for 4 hours and gave the corresponding 1-benzoyl glycerols **5a,b** in



Scheme 3. Asymmetric AD-mix-β dihydroxylation reactions of allyl ethers **6**, **8** and ester **4**.

very good yield. The enantiomeric excess of 74%ee was evaluated from the ^{1}H NMR integral ratio of the *ortho* benzoate hydrogen atoms using Eu(hfbc)$_3$ as chiral shift reagent. This value was increased to 95%ee after recrystallisation as stated above. ^{1}H NMR analysis with the shift reagent and the specific rotations of **5a,b** were used to assess the enantiomeric excess, however melting point emerged also as a useful gauge. Since the melting point of the racemate (40–41°C for undeuterated **5**)[13] is lower than that of the enantiomerically pure material (60–61°C for undeuterated **5**[14]), an increase in the melting point correlates with enantiomeric purity. Alkaline hydrolysis of the glycerol benzoates with sodium hydroxide in 80% aqueous acetone[15] generated the deuterated glycerols **1a,b,** which were recovered efficiently by dissolution of the dried hydrolysis products with acetone, followed by chromatography.

The attractive features of the route are its efficiency in delivering milligram quantities of each of the stereoisomers **1a–1d** of glycerol in high enantiomeric excess. The preparative protocol is a three pot process and manipulations are kept to a minimum. Although only **1a** and **1b** were prepared during the study the remaining stereoisomers **1c** and **1d**, are accessible by replacing the AD-mix-β for the α catalyst. Sample **1a** contains **1b** (5.2%) and [2-^{2}H]-glycerol (15.4%) as a consequence of the *E*/*Z* ratio and regiospecificity of deuterium delivery after reduction. Also it is a limitation of the synthesis of **1b** (and also **1d**) that 23% of the isotope is lost to exchange, however this is not easily countered, and is an inherent problem in any route deploying this general strategy to labelled glycerol. The current method is a significant improvement on the previous route[5] to **1a** and **1b** and generates material of higher enantiomeric purity to a recent synthesis,[2] the details of which have yet to be reported.

Experimental

General

IR spectra were recorded on a Perkin–Elmer 257 Spectrometer. NMR spectra were obtained on Bruker AC-250 and Varian VXR 400S instruments in $CDCl_3$ or in D_2O. Chemical shifts are quoted relative to TMS (δ=0). Reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen, column chromatography was carried out over silica gel (Merck, Kieselgel 60, 230–400 mesh) and solvents were dried and distilled prior to use.

Z-[3-^{2}H]-(2-Propenyl) benzoate ***4a***

Propargyl alcohol (1 g, 17.8 mmol) was added dropwise at 0°C to a stirred solution of lithium aluminium hydride (0.88 g, 23.2 mmol) in THF (30 ml). After 3 h a mixture of THF (2 ml) and deuterium oxide (1 ml) was added carefully until hydrogen gas ceased to evolve. The mixture was filtered, the insoluble material washed with dichloromethane (50 ml) and the combined filtrate added to an aqueous sodium hydroxide solution (30%, 10 ml), which contained benzyltriethylammonium chloride (405 mg, 1.8 mmol). A solution of benzoyl chloride (3.5 g, 24.9 mmol) in dichloromethane (10 ml) was then added slowly with vigorous strirring. After 1 h water was added to dissolve precipitated material. The organic layer was separated and the aqueous phase extracted with dichloromethane. Washing of the combined organic layers with water until neutral and drying over magnesium sulphate gave the crude product after solvent removal. Purification by column chromatography (ethyl acetate/petroleum ether 1:8) gave **4a** (1.16 g, 40%) as a colourless oil. ^{1}H NMR ($CDCl_3$): 4.83 (d, J=5.3, 2H, CH_2), 5.28 (d, J=10.1, 1H, 3′-H *trans*), 6.00–6.07 (m, 1H, 2′-H), 7.44–7.48 (m, 2H, 3-H, 5-H), 7.53–7.61 (m,1H, 4-H), 8.05–8.09 (m, 2H, 2-H, 6-H). ^{2}H NMR ($CHCl_3$): 5.45 (s, 1D, 3′-D *cis*). ^{13}C NMR ($CDCl_3$): 65.4 (C-1′), 117.8 (t, J=23.7, C-3′), 128.3 (C-3, C-5), 129.6 (C-2, C-6), 130.1 (C-1), 132.1 (C-2′), 132.9 (C-4), 166.2 (CO_2Ph). IR (neat): 3061, 3033 (CH), 2941 (CH), 1721 (C=O), 1601 (C=C), 1451, 1273 (C-O), 1115, 711. MS (CI): 162 (0.43%), 163 (62.62%) M+, 99.3% D.

E-*[3-^{2}H]-Propenyl benzoate* ***4b***

A solution of propargyl alcohol (1g, 17.8 mmol) in THF was treated with n-butyllithium in hexanes (2.5 M, 16 ml, 40 mmol) at −78°C, and left to warm to room temperature. Deuterium oxide (1 g, 50 mmol) was added and the mixture was then dried over magnesium sulphate, filtered and concentrated by distilling off the solvents at through a vigreux column at atmospheric pressure. The remaining solution was slowly added to a solution of lithium aluminium hydride (0.88 g, 23.2 mmol) in THF (10 ml) at 0°C and was left to stir for 3 h at room temperature. After careful addition of a 2:1 water/THF mixture (3 ml) the crude *E*-[3-^{2}H]-allyl alcohol was benzoylated and purified as described above for **4a** to give **4b** (1.66 g, 57%) as a colourless oil. ^{1}H NMR ($CDCl_3$): 4.83 (d, J=5.5, 2H, CH_2), 5.40 (d, J=17.0, 1H, 3′-H*cis*), 6.04 (dt, J=5.5, J=17.0, 1H, 2′-H), 7.40–7.46 (m, 2H, 3-H, 5-H), 7.52–7.58 (m, 1H, 4-H), 8.06–8.09 (m, 2H, 2-H, 6-H). ^{2}H NMR ($CHCl_3$): 5.33 (s, 1D). ^{13}C NMR ($CDCl_3$): 65.4 (C-1′), 117.8 (t, J=12.2, C-3′), 128.3 (C-3, C-5), 129.5 (C-2, C-6), 130.1 (C-1), 132.1 (C-2′), 132.9 (C-4), 166.1 (CO_2Ph). IR (neat): 3062, 3038 (CH), 2948 (CH), 1721 (C=O), 1601 (C=C), 1451, 1270 (C–O), 1114, 710. MS (EI): 162 (0.69%), 163 (M^+, 2.33%), 77% D.

[3(S)-^{2}H]-2(R),3-Dihydroxypropyl benzoate ***5a***

To a mixture of tert-butyl alcohol (25 ml) and water (25 ml) was added AD-mix-β (7.43 g) with stirring. After cooling to 0°C allyl benzoate **4a** (0.865 g, 5.3 mmol) was added and the mixture stirred for 4 h at the same temperature. Sodium disulphite (8 g, 42 mmol) was added and the mixture allowed to warm to room temperature. Stirring was continued for 1 h and after addition of ethyl acetate the organic layer was separated. Further extraction (3 times) of the aqueous phase with ethyl acetate, drying of the combined organic extracts over magnesium sulphate and evaporation of the solvent under reduced pressure gave the crude product, which was purified by column chromatography (ethyl acetate/petroleum ether 2:1) to give **5a** (0.98 g, 94%) as a white crystalline solid. Recrystallisation from diethyl ether/petroleum ether increased the optical purity of **5a**. m.p. 61°C (undeuterated m.p. 60–61°C[14]). $[\alpha]_D$=+18.4 (*c* 2.5, EtOH), +15.2 (*c* 2, pyridine).[14] ^{1}H NMR ($CDCl_3$): 2.21 (br, 2H, OH), 3.76 (m, 1H, 3′-H), 4.05–4.11 (m,1H, 2′-H), 4.39 (dd, J=5.6, J=11.5, 1H, 1′-Ha), 4.47 (dd, J=4.9, J=11.6, 1H, 1′-Hb), 7.42–7.49 (m, 2H, 3-H, 5-H), 7.56–7.62 (m, 1H, 4-H), 8.03–8.07 (m, 2H, 2-H, 6-H). ^{2}H NMR ($CHCl_3$): 3.68 (s, 1D). ^{13}C NMR ($CDCl_3$): 63.1 (t, J=20.4, C-3′), 65.6 (C-2′), 70.2 (C-1′), 128.4 (C-3, C-5), 129.6 (C-1, C-2, C-6), 133.3 (C-4), 166.9 (C=O). IR (KBr): 3497 (OH), 3087, 3061, 3032 (CH), 2928, 2883 (CH), 1704 (C=O), 1599, 1584 (C=C), 1282 (C–O), 1132, 709; MS (CI): 198 (M^++H, 100%).

[3(R)-^{2}H]-2(R),3-Dihydroxypropyl benzoate ***5b***

5b (1.3 g, 93%) was obtained from allyl benzoate **4b** (1.16 g) as described above for **5a**. Recrystallisation afforded a material of m.p. 63°C (undeuterated 60–61°C[14]). $[\alpha]_D$=+17.2 (*c* 2.8, EtOH), +15.2 (*c* 2, pyridine).[14] ^{1}H NMR ($CDCl_3$): 2.33 (br, 1H, OH), 2.79(d, J=4.1, 1H, OH), 3.68 (br, 1H, 3′-H), 4.07 (br, 1H, 2′-H), 4.44 (dd, J=6.1, J=9.1, 2H, 1′-H), 7.42–7.48 (m, 2H, 3-H, 5-H), 7.56–7.61 (m, 1H, 4-H), 8.03–8.06(m, 2 H, 2-H, 6-H). ^{2}H NMR ($CHCl_3$): 3.77 (s, 1D). ^{13}C NMR ($CDCl_3$): 63.1 (t, J=19, C-3′), 65.6 (C-2′), 70.2 (C-1′), 128.3 (C-3, C-5), 129.6 (C-1, C-2, C-6), 133.2 (C-4), 166.9 (C=O); MS (CI): 198 (M^++H, 100%).

(1S,2R)-[1-^{2}H]-Glycerol ***1a***

1-Benzoyl glycerol **5a** (546 mg, 2.77 mmol) was dissolved in acetone (20 ml) and 0.5 N sodium hydroxide solution (5.6 ml, 2.8 mmol) was added. The mixture was heated to 55°C and kept at that temperature with stirring for 1 h. Solvents were evaporated under reduced pressure to dryness and the residual material suspended in dry acetone, and filtered. The inorganic material was washed with acetone and the combined extracts concentrated. Column chromatography (water/acetone 5:95) afforded glycerol **1a** (164 mg, 64%) as a viscous oil. ^{1}H NMR (D_2O, 400 MHz): 3.37 (m, 1H, 3-Ha), 3.45 (m, 2H, 1-Hb, 3-Hb), 3.59 (m, 1H, 2-H). ^{2}H NMR (H_2O): 3.50 (1D, 1-D) and 3.72 from 15% [2-$^2H_1$]-glycerol. ^{13}C NMR (D_2O): 66.5 (t, J=21.8, C-1), 66.9 (C-3), 76.4 (C-2).

(1R,2R)-[1-^{2}H]-Glycerol ***1b***

1b (144 mg, 57%) was obtained from **5b** (532 mg, 2.7 mmol) as described above. ^{1}H NMR (D_2O, 400 MHz): 3.38 (dd, J=6.6, J=11.8, 2H, 1-Ha, 3-Ha), 3.47 (dd, J=4.2, J=11.8, 1H, 3-Hb), 3.60 (m, 1H, 2-H). ^{2}H NMR (H_2O): 3.6 (1D, 1-D). ^{13}C NMR ($CDCl_3$): 64.6 (t, J=21.5, C-1), 64.9 (C-3), 74.5 (C-2).

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