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Synthesis of [^{14}C]-Labelled Glycidyl and Glycerol Ethers of Aliphatic and Aromatic Alcohols.

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SUMMARY

The synthesis of [^{14}C]-labelled glycidyl ethers and the corresponding glycerol ethers is described for the monofunctional compounds 1-dodecanol and *ortho*-cresol and the bifunctional compounds 4,4'-dihydroxy-3,3',5,5'-tetramethyl biphenyl and 1,6-hexanediol. The synthesis is based on reaction between the alcohol and [U-^{14}C]-epichlorohydrin (1). The aromatic compounds have been converted to the corresponding glycidyl ethers by using sodium hydroxide and the aliphatic compounds by using tin(IV) chloride as a catalyst. Thus radio-labelled glycidyl ethers were obtained in yields between 50-80%, with a chemical purity of > 92% and a radiochemical purity of > 95% by HPLC. The specific activities of the glycidyl ethers were approximately 0.2 mCi/mmol for the monofunctional compounds and approximately 0.4 mCi/mmol for the bifunctional compounds.

KEY WORDS

glycidyl ethers, diglycidyl ethers, glycerol ethers, isotopic labelling, ^{14}C

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INTRODUCTION

Glycidyl ethers (GEs) are widely used in industry as surface active agents, textile and dye auxiliaries, plasticizers and stabilisers for resins, additives for suspension polymerisation, and heat transfer agents (1). Besides their use in the chemical industry, they are also interesting as chemical intermediates, *e.g.* in the preparation of a new generation of drugs with cardiovascular activity (2).

A number of GEs are receiving regulatory attention to determine the need for classification and labelling. Some members of this class have been reported to show direct mutagenic properties in bacteria and, in a small number of examples, to cause tumours in animal studies. For example, phenyl glycidyl ether has been classified as a Group 2B carcinogen (*possibly carcinogenic to humans*) by IARC (3, 4). Because of their structural relationship to phenyl glycidyl ether other GEs are under scrutiny, although their metabolism may be very different. It is therefore of importance to generate mechanistic data of the overall toxicology of GEs, in order to permit appropriate ranking of this class of compounds. To study the molecular toxicology of GEs, chemically pure compounds are needed which are not readily available since nearly all commercially obtainable GEs are mixtures of various compounds. Ideally, the compounds would also contain a radio-label to simplify trace analysis and to allow the making of a mass balance.

The only commercial method for manufacturing low-molecular glycidyl derivatives based on aromatic alcohols is a proton-donor reaction with epichlorohydrin (ECH) (5). For instance, the commercial synthesis of *bis*-phenol A diglycidyl ether (BADGE, compound **4**, Fig. 2) is based on this process, in which ECH is reacted with diphenylol propane using sodium hydroxide as a catalyst, yielding at first a chlorohydrin which is simultaneously converted to the corresponding GE. Process conditions are crucial in order to obtain product with low contents of chlorine and prevent by-products of high molecular weight (6). Base-catalysed reaction of ECH with aliphatic alcohols yields crude product with low epoxy glycol contents and low product quality. A conventional

method that uses the commercially available tin(IV) chloride as the catalyst gives reasonable results in terms of epoxy glycol contents (7).

Based on the available synthetic routes for GEs, ECH was chosen as the source of radioactivity since [U-^{14}C]ECH (**1**) is available through custom synthesis and because all desired GEs and glycerol derivatives can be synthesised starting from ECH and the corresponding alcohols. Because the radio-labelled ECH is expensive, all syntheses of ^{14}C-labelled glycidyl ethers were performed on a small scale. As a result, the necessary excess of ECH for obtaining high product quality was optimised, a solvent was introduced in the syntheses, and the addition of base or Lewis acid was not performed under high dilution conditions.

METHODS AND MATERIALS

Chemicals

All solvents used were reagent grade and purchased from Merck. Demineralised water was used after further purification by ultrafiltration. *ortho*-Cresol, 1-dodecanol, 1,6-hexanediol, 4,4'-dihydroxy,3,3',5,5'-tetramethyl biphenyl, and sodium hydride (55% dispersion in kerosine) were purchased from Sigma-Aldrich (Zwijndrecht, The Netherlands). *Bis*-Phenol A diglycerol ether was obtained from the Shell International Chemicals B.V., Amsterdam, The Netherlands). Diphenylol propane (*bis*-phenol A) and epichlorohydrin were obtained from Shell Nederland Chemie B.V. (Pernis, The Netherlands).

Radiochemicals

[U-^{14}C]ECH (**1**) was custom-synthesised at ChemSyn Laboratories (Lot no. CSL-97-748-75-30) with a specific activity of 38.0 mCi/mmol and a radiochemical purity of greater than 98%. The total quantity of 10 mCi was diluted with non-labelled ECH (3.89 ml) to a specific activity of 0.2 mCi/mmol. This stock solution was used in the synthesis of GEs.

Identification of [^{14}C]Glycidyl ethers by GC-MS

The synthesised GEs were analysed by GC-MS using a HP5890 gas chromatograph coupled to a 5989B mass spectrometer (Hewlett Packard) on a 30 m × 0.25 mm (internal diameter) DB-5MS column (J&W Scientific) with a film thickness of 0.10 μm using the following temperature programme: 80°C for 1 min, ramp to 320°C at 15°/min, the temperature of 320°C was kept for 5 min. The column head pressure was kept at 60 kPa (constant flow mode). Scanned spectra are recorded in electron impact mode (EI) for structure information and in positive chemical ionisation mode (PCI) with ammonia/methane for molecular weight information. For EI mode the scan range was 20 to 400 amu, the interface temperature was 300°C and the source temperature 200°C. For PCI mode the scan range was 60 to 500 amu, the interface temperature was 300°C and the source temperature 200°C. Injections (1 μl using a HP 7673 autosampler) were made using a programmable temperature vaporiser (PTV) injector (Gerstel) in the 1:50 split mode.

Identification of [^{14}C]Glycidyl ethers by LC/MS

The synthesised GEs were analysed for purity using a HP 1050 liquid chromatograph, with UV detection (λ = 275 nm) and coupled to a Micromass Quattro quadrupole mass spectrometer, on a Waters NovaPak C18 3.9 × 150 mm column using 2 mM aqueous ammonium acetate (solvent A) and acetonitrile (solvent B) in the following gradient programme: starting with 75% (v/v) A + 25% (v/v) B and then via a linear gradient to 6% (v/v) A + 94% (v/v) B in 110 min followed by a linear gradient to 0% (v/v) A + 100% (v/v) B in 10 min. The flow rate was 3.0 ml/min (piston pump) and 10 μl aliquots were injected. Electrospray was used as the LC-MS interfacing and ionisation technique (positive ions). The scan range was 80-2000 amu with 0.5 scan/s.

Quantification and purification by HPLC

For quantification and purification of the synthesised products two HPLC systems were used. A HP 1100 liquid chromatograph equipped with a degasser, a variable

wavelength detector (λ = 275 nm) and an automated injector (Hewlett Packard) and a Ramona 2000 radio detector (Raytest) with a 500 µl solid scintillant flow cell was used for determination of purity and quantification (System A). Aliquots of 10 µl were injected on a 4.6 × 250 mm Beckman Ultrasphere ODS3 column and eluted with water (solvent A) and acetonitrile (solvent B) at 1.0 ml/min using the following gradients: starting with 75% (v/v) A + 25% (v/v) B and then via a linear gradient in 70 min to 20% (v/v) A + 80% (v/v) B, subsequently to 100% (v/v) B in 5 min via a linear gradient and after 10 min 100% (v/v) B back to ; B to 100% (v/v) + A to 0% (v/v) in 5 min via linear gradient; for 10 min gradient constant; B 75% (v/v) A + 25% (v/v) B in 5 min. For purification, a dual LC-10AT VP system was used (Shimadzu), equipped with a SPD-10A VP UV detector, a Ramona 2000 radio detector and a Shimadzu fraction collector (System B). Aliquots of 50 to 150 µl were injected onto a 10 × 250 mm stainless steel Nucleosil 120-7C18 column with a 10 × 50 mm Nucleosil 120-7C18 pre-column and eluted at a flow rate of 1.0 ml/min with water (solvent A) and acetonitrile (solvent B) using the following gradients: starting with 80% (v/v) A + 20% (v/v) B and then via a linear gradient to 100% (v/v) B in 16 min; after 50 min of 100% (v/v) B back to the starting conditions in 10 min via linear gradient.

EXPERIMENTAL

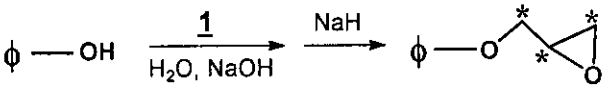
Epichlorohydrin has been classified as an anticipated human carcinogen (category 2). Its is recommended to do all handlings with this chemical in a well-ventilated hood and with the use of the appropriate personal protective equipment. All synthetic routes have been developed first for non-labelled materials. NMR data have been given for non-labelled compounds.

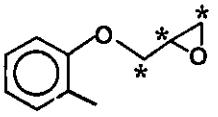
Reaction of Aromatic Alcohols with ECH (see Figure 1).

[^{14}C]-2-Methylphenyl glycidyl ether (2).

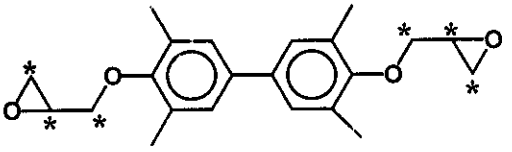
o-Cresol (254.8 mg; 2.34 mmol), [^{14}C-U] ECH (1; 0.2 mCi/mmol; 654.1 mg; 553 µl; 7.07 mmol), 2-propanol (425 mg; 7.07 mmol) and water (297 µl; 16.49 mmol)

Figure 1. Synthesis of [^{14}C]-labelled aromatic glycidyl ethers from [U-^{14}C]-epichlorohydrin (1)

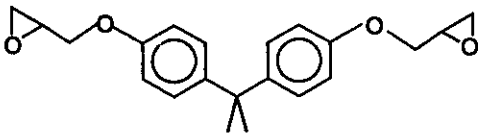




Compound 2: o-Cresyl glycidyl ether (*o*CGE)



Compound 3: Epikote YX4000



Compound 4: Bisphenol A diglycidyl ether (BADGE)

were mixed at room temperature and a catalytic amount of sodium hydroxide (19.8 µl of a 48% aqueous solution of NaOH; 0.46 mmol) was added. The reaction mixture was heated with water cooling and under a nitrogen atmosphere at 84°C for 25 min. Subsequently, sodium hydroxide (39.6 µ of a 48% solution) was added, followed by an equal amount (39.6 µl) 1.5 h later. Heating of the reaction mixture was continued for another 70 min. After cooling to room temperature, 10 ml ethyl acetate and 15 ml water were added to the reaction mixture and both layers were mixed vigorously with stirring. Both clear layers were separated and the organic layer was extracted twice

with 10 ml water. The combined water layers were extracted once with 15 ml ethyl acetate. The combined organic layers were dried with magnesium sulphate and concentrated by evaporation and the residue dissolved in 2.0 ml ethyl acetate. This solution was added, in 100 µl portions, to a stirred suspension of sodium hydride in 2.0 ml of hexane (55% oil dispersion; 103 mg; 2.36 mmol; kerosine removed by washing/ decanting with hexane). The resulting mixture was stirred for an additional 5 min after completion of addition and excess sodium hydride was destroyed by the careful addition of 10 ml water and 10 ml ethyl acetate. Both layers were mixed vigorously with stirring and separated. The organic layer was washed twice with 10 ml water and the combined water layers were extracted once with 10 ml ethyl acetate. The combined organic layers were concentrated by evaporation and the residue dissolved in 20 ml chloroform and washed twice with water (brought to pH 12-13 with sodium hydroxide), dried with magnesium sulphate and concentrated by evaporation. Compound **2** was purified by bulb-to-bulb distillation and the fraction was collected which boiled at 96°C/0.05 mm Hg. The overall yield was 231 mg (60%). Chemical purity by HPLC (UV-detection): 94% Radiochemical purity by HPLC (system A): 92%.

^{1}H-NMR ($CDCl_3$): δ 7.2-7.15 (m, 2H, ArH); δ 6.92-6.85 (m, 2H, ArH); δ 4.25 (dAB, J = 11.1, 4.3 Hz, 1H, $C\underline{H}_AH_BO$); δ 3.99 (dAB, J = 11.1, 5.4 Hz, 1H, $CH_A\underline{H}_BO$); δ 3.45-3.35 (m, 1H, C<u>H</u>-*epox*); δ 2.93 (dAB, J = 4.9, 4.2 Hz, 1H, $C\underline{H}_AH_BO$-*epox*); δ 2.80 (dAB, J = 4.9, 2.8 Hz, 1H, $CH_A\underline{H}_BO$-*epox*). ^{13}C-NMR ($CDCl_3$): δ [157.0 (s), 131.1 (d), 127.4 (s), 127.1 (d), 121.3 (d), 111.6 (d), Ar], δ 68.9 (t, OCH_2), δ 50.5 (d, CHO), δ 44.8 (t, CH_2O-*epox*), δ 16.3 (q, CH_3).

[^{14}C]-Diglycidyl ether of 4,4'-dihydroxy,3,3',5,5'-tetramethyl biphenyl (3)

4,4'-Dihydroxy,3,3',5,5'-tetramethyl biphenyl (226.7 mg; 0.94 mmol), [^{14}C-U]ECH (**1**; 0.2 mCi/ mmol; 520.2 mg; 440 µl; 5.62 mmol), 2-propanol (675.5 mg; 11.24 mmol), and water (337.5 mg; 18.75 mmol) were mixed in a round bottom flask at room temperature. A catalytic amount of sodium hydroxide (48% solution; 11.7 µl; 0.28 mmol) was added, a water cooler was adjusted, and the reaction mixture was placed in an oil-bath heated from room temperature to 78°C with a ramp of 5°C/min.

After 10 min, 20 min, 30 min, 40 min, 50 min, and 60 min, equal portions of sodium hydroxide (48% solution; 11.7 µl) were added. After the last addition the reaction mixture was stirred for an additional 20 min and worked up. After cooling the mixture to room temperature, 10 ml ethyl acetate and 10 ml water were added and the mixture stirred vigorously until both layers were clear. Two spatula tips of solid sodium chloride were added to promote separation of both layers and the organic layer was washed twice with 10 ml water, and the combined water layers once with 10 ml ethyl acetate. The combined organic layers were dried on magnesium sulphate, filtered, and evaporated under reduced pressure. The residue was dissolved in 2.0 ml ethyl acetate, and this solution was added, in 100 µl portions, to a stirred suspension of sodium hydride in 2.0 ml of n-hexane (55% oil dispersion; 82.0 mg; 1.88 mmol; kerosine removed by washing/decanting with n-hexane). The resulting mixture was stirred for an additional 5 min after completion of addition and excess sodium hydride was destroyed by the careful addition of 10 ml water and 10 ml ethyl acetate. The organic layer was separated and washed twice with 10 ml water and the combined water layers were extracted once with 10 ml ethyl acetate. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated by evaporation under reduced pressure. A coloured product was obtained as a thick oil. HPLC analysis (System A) showed that the product contained 70% of the desired diglycidyl ether. Purification by semi-preparative HPLC (system B) yielded 179 mg (54%) of compound **3**. Chemical purity: 97.3%; Radiochemical purity: >98% (HPLC system A).

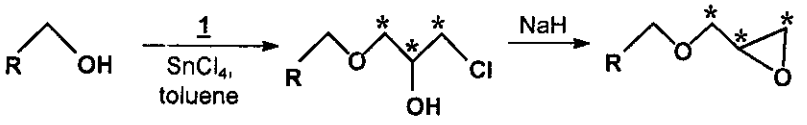
^{1}H-NMR ($CDCl_3$): δ 7.2 (s, 4H, ArH); δ 4.08 (dAB, 2H, J = 11.0 and 3.3 Hz, $C\underline{H}_AH_BO$); δ 3.79 (dAB, 2H, J = 11.0 and 5.9 Hz, $CH_A\underline{H}_BO$); δ 3.44-3.36 (m, 2H, $C\underline{H}O$-*epoxy*); δ 2.91 (dAB, 2H, J = 5.1 and 4.9 Hz, $C\underline{H}_AH_BO$-*epoxy*); δ 2.74 (dAB, 2H, J = 5.1 and 2.6 Hz, $CH_A\underline{H}_BO$-epoxy); δ 2.18 (s, 12H, CH_3). ^{13}C-NMR ($CDCl_3$):δ 155.3 (s, C_4), δ 137.0 (s, C_1), δ 131.2 (s, C_3), δ 127.8 (d, C_2), δ 73.5 (t, C_6), δ 50.8 (d, C_7), δ 44.7 (t, C_8), δ 16.5 (q, C_5). LC-MS (EI-mode): 354 m/e (M+1); retention time 43 min.

Reaction of Aliphatic Alcohols with ECH (see Figure 2).

[^{14}C]-Dodecyl glycidyl ether (5)

1-Dodecanol (314.3 mg; 1.69 mmol) was dissolved in 1.0 ml dry toluene under a nitrogen atmosphere and two drops of a 1.0 M tin(IV) chloride solution in *n*-heptane were added by syringe. The solution was stirred at 74°C in a vial with a water cooled condenser. A solution of [^{14}C-U] ECH (1; 0.2 mCi/mmol; 265 µl; 3.38 mmol) in 1.0 ml toluene was added by syringe over a period of 2 min and under a nitrogen atmosphere. The resulting mixture was stirred for 3 h at 90-93 °C and subsequently cooled to room temperature. The condenser was flushed with 2.0 ml toluene and the solution was concentrated by evaporation at reduced pressure. The residue was dissolved in 2.0 ml toluene and subsequently added by syringe in 100 µl portions to a stirred suspension of sodium hydride in 2.0 ml of *n*-hexane (55% oil-dispersion; 82 mg; 1.88 mmol; kerosene removed by washing/decanting with *n*-hexane) at room temperature. The resulting

Figure 2. Synthesis of [^{14}C]-labelled aliphatic glycidyl ethers from [U-^{14}C]-epichlorohydrin (1)



Compound 5: 1-Dodecyl glycidyl ether (C_{12}GE)

Compound 6: 1,6-Hexanediol diglycidyl ether (HDDGE)

mixture was stirred for an additional 5 min and excess sodium hydride was carefully destroyed by the addition of 10 ml water and 10 ml *n*-hexane. The mixture was stirred vigorously resulting in two clear layers which were separated. The organic layer was washed twice with 10 ml water and the combined water layers were extracted once with 10 ml *n*-hexane. The combined organic layers were dried with $MgSO_4$ and concentrated by evaporation at reduced pressure. The isolated crude product was purified by bulb-to-bulb distillation (boiling point 130°C at 0.02 mbar) yielding a colourless liquid. Yield after distillation: 266 mg, with a radio-purity of 85%. The product was further purified by HPLC (System B) to give compound **5** with a radiochemical purity of >98% as determined by HPLC (System A) and by GC-MS (CI mode). The overall yield was 56%.

^{1}H-NMR ($CDCl_3$): δ 3.71 (dAB, J = 11.6, 3.1 Hz, 1H, OCH_AH_BCH); δ 3.53-3.34 (m, 3H, CH_2CH_2O and OCH_AH_BCH); δ 3.19-3.10 (m, 1H, CHO-*epox*); δ 2.82 (dAB, J = 5.1, 5.0 Hz, 1H, OCH_AH_B-*epox*) and δ 2.80 (dAB, J = 5.1, 4.1 Hz, 1H, OCH_AH_B-*epox*); δ 1.6-1.5 (m, 2H, CH_2CH_2O); δ 1.4-1.15 (m, 18H, $(CH_2)_9$); δ 0.95 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): δ 71.6 (t, CH_2CH_2O); 71.4 (t, OCH_2CH); 50.8(d, CHO-*epox*); 44.2 (t, CH_2O-*epox*); [31.8 (t), 29.6 (t), 29.58 (t), 29.55 (t), 29.52 (t), 29.4 (t), 29.26 (t), 26.0 (t), 22.6 (t); alkyl]; 14.0 (q, C_1). MS (CI), m/e: 260 (MNH_4^+), 243 (MH^+); MS(EI), m/e: 197 (M - 45).

[^{14}C]-1,6-Hexane diglycidyl ether (6).

1,6-Hexanediol (733.4 mg; 3.20 mmol) was dissolved in 2.0 ml toluene and heated to 74°C. Tin(IV) chloride (3 drops of a 1.0 M solution in *n*-heptane; 0.06 mmol) was added, followed by the addition, over a period of 10 min, of a solution of [^{14}C-U] ECH (1; 0.2 mCi/mmol; 2.96 g; 32.0 mmol) dissolved in 1.5 ml toluene. The reaction mixture was heated at 90°C for 3 h. After cooling, the condenser was flushed with 2.0 ml toluene and the solution concentrated by evaporation at reduced pressure. The residue was dissolved in 2.0 ml toluene and subsequently added, in 100 µl portions, to a stirred suspension of sodium hydride in 2.0 ml of hexane (55% oil-dispersion; 279 mg; 6.39 mmol; kerosene removed by washing/decanting with hexane). After completion

of the addition, the mixture was stirred for an additional 5 minutes at room temperature and 10 ml water and 10 ml hexane were added. Both clear layers were stirred vigorously for 15 min and separated. The organic layers were washed twice with 15 ml water and the combined water layers were extracted once with 15 ml n-hexane. The combined organic layers were dried with magnesium sulphate and concentrated by evaporation. The residual oil was purified by bulb-to-bulb distillation and the product boiling at 161 °C/0.03 mm Hg was isolated as a clear liquid with a radio-purity of 70%. Compound 7 was further purified by HPLC (System B) to give a radio-chemical purity of >98% as determined by HPLC (System A) and GC/MS (CI-mode). The overall yield was 228 mg (31%).

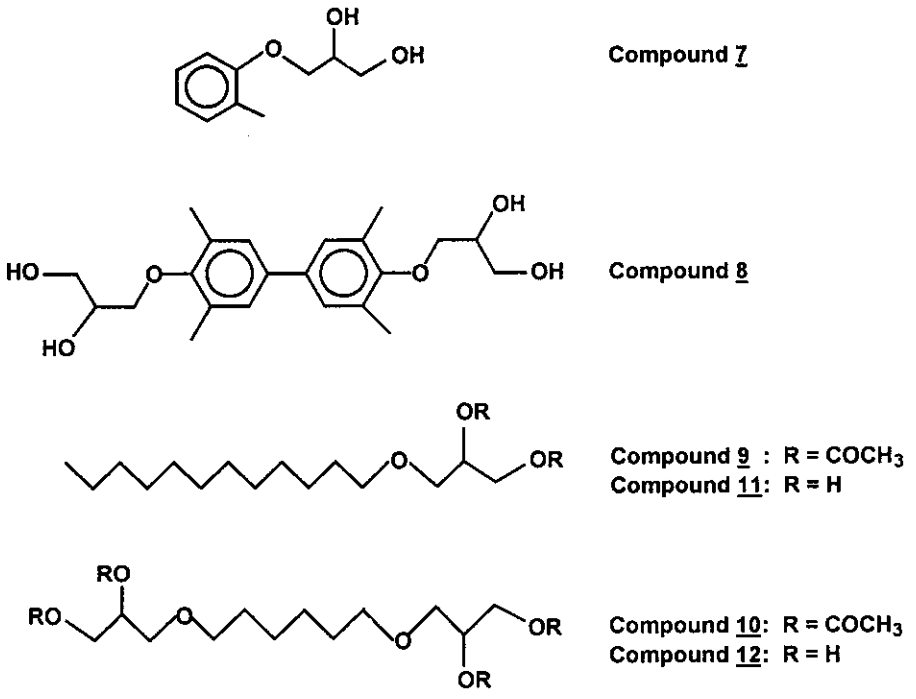
^{1}H-NMR ($CDCl_3$): δ 3.71 (dAB, 2H, J = 11.5 and 3.1 Hz, OCH_AH_BCH); δ 3.54-3.47 (m, 6H, OCH_AH_BCH and OCH_2-*alkyl*); δ 3.19-3.11 (m, 2H, C<u>H</u>-*epox*); δ 2.80 (dAB, 2H, CH_AH_B-*epox*, J = 4.1 and 5.1 Hz); δ 2.61 (dAB, 2H, J = 5.1 and 2.7 Hz, CH_AH_B-*epox*); δ 1.7-1.5 (m, 4H, -CH_2CH_2-); δ 1.4-1.25 (m, 4H, -CH_2CH_2-). ^{13}C-NMR ($CDCl_3$): δ 71.4 (CH_2CH_2O), δ 71.3 (CH_2CHO); δ 50.7 (C<u>H</u>O-*epox*), δ 44.1 (CH_2O-*epox*), δ 29.4 (CH_2), δ 25.7 (CH_2). MS (CI mode), m/e: 248 (MNH_4^+), 231 (MH^+); MS(EI mode), m/e: 140 (M - 2 × 45).

Synthesis of glycerol ethers (see Figure 3).

3-(2-Methylphenoxy)-1,2-propanediol (7)

Compound 2 (27 mg; 0.17 mmol) was dissolved in a mixture of acetic acid (0.47 ml; 8.23 mmol) and acetic anhydride (155 µl; 1.65 mmol) and heated in a closed vial at 100-110°C overnight. The mixture was subsequently concentrated by evaporation at reduced pressure at 45°C and re-dissolved in 1.3 ml 2-propanol and 1.3 water (1.3 ml). A solution of sodium hydroxide (132 mg; 3.3 mmol) in 0.2 ml water was added and the two-phase system was heated overnight at 85°C with vigorous stirring. The resulting mixture was acidified with 1.0 M aqueous hydrochloric acid to pH 1 and extracted

Figure 3. Synthesis of Aromatic and Aliphatic glycidol derivatives



twice with 10 ml ethyl acetate. The organic layer was dried and concentrated by evaporation. The residue was dissolved in diethyl ether and washed twice with saturated aqueous sodium bicarbonate solution. The organic layer was separated, dried and concentrated to give 20 mg of compound 7 as a solid. Purity according to HPLC (System A): 85%. The proton NMR of isolated material was identical to authentic, commercially available material (mephenesin).

^{1}H-NMR ($CDCl_3$): δ 7.2-7.1 and 6.95-6.8 (m, 2H, ArH); δ 4.2-4.1 (m, 1H, CHOH); δ 4.05 (d, 2H, J = 5.2 and 0.95 Hz, $OC\underline{H}_2$); δ 3.88 (dAB, J = 11.5 and 3.6 Hz, 1H, $C\underline{H}_AH_BOH$; δ 3.78 (dAB, J = 11.5 and 5.5 Hz, 1H, $CH_A\underline{H}_BOH$; δ 2.21 (s, 3H, CH_3).

3-{[4'-(2,3-Dihydroxypropoxy)-3,3',5,5'-tetramethyl[1,1'-biphenyl]-4-yl]oxy}-1,2-propanediol (8)

Compound **3** (50.01 mg; 0.14 mmol) was dissolved in glacial acetic acid (1.7 g; 28.3 mmol), acetic anhydride (0.33 g; 3.3 mmol) and heated at 100°C for 16 h. The mixture was concentrated by evaporation at reduced pressure, the residue dissolved in 1.0 ml 2-propanol and sodium hydroxide (203 mg; 5.1 mmol), dissolved in 1.0 ml water, was added. The mixture was stirred vigorously at 85°C for 7 h, cooled and acidified to pH 1 by the addition of 1.0 M hydrochloric acid. The mixture was subsequently extracted twice with 10 ml ethyl acetate. The combined organic layers were washed with 10 ml water and with 10 ml saturated aqueous sodium bicarbonate solution, dried with $MgSO_4$, and concentrated by evaporation at reduced pressure. Compound **8** was isolated as a white solid (41 mg; 82%) with a purity of 97% according to HPLC (system A).

^{1}H-NMR ($CDCl_3$): δ 7.18 (s, 4H, ArH), δ 4.07-3.96 (quint, 2H, J = 5.7 and 1.2 Hz, C<u>H</u>OH), δ 3.88 (dAB, 4H, J = 9.5 and 4.4 Hz, C<u>H$_A$H$_B$</u>OH, 3.80 (dAB, 4H, J = 9.5 and 6.0 Hz, CH$_A$<u>H$_B$</u>OH), δ 3.76 (dAB, 4H, J = 11.1 and 4.8 Hz, OC<u>H$_A$H$_B$</u>), 3.68 (dAB, 4H, J = 11.1 and 5.8 Hz, OCH$_A$<u>H$_B$</u>), δ 2.34 (s, 12H, CH_3). ^{13}C-NMR ($CDCl_3$): [δ 155.2 (s), 136.8 (s), 131.0 (s), 127.1 (d); Ar], δ 73.2 (t, OCH_2), δ 71.4 (d, CHOH), δ 63.2 (t, CH_2OH), δ 15.2 (q, CH_3).

3-(Dodecyloxy)-1,2-propanediol (11).

Compound **5** (201.4 mg;0.44 mmol) was dissolved in glacial acetic acid (1.23 g; 20.4 mmol) and acetic anhydride (0.25 g; 2.4 mmol) and heated at 100°C for 16 h. The mixture was concentrated by evaporation at reduced pressure and the residue was dissolved in 20.0 ml *n*-hexane. The solution was added drop-wise to a stirred suspension of sodium hydride (55% dispersion in oil; 266 mg; 6.1 mmol; pre-washed to remove kerosene). The reaction mixture was stirred at room temperature for 2 h and excess sodium hydride destroyed by the careful addition of 10 ml water. Both layers were stirred vigorously and the organic layer separated and washed with 10 ml water. The combined aqueous layers were extracted with 10 ml *n*-hexane. The combined organic

layers were dried with $MgSO_4$ and subsequently concentrated by evaporation under reduced pressure to give a slightly contaminated solid. The obtained product was purified by reversed phase HPLC (system B) to give **11** as a white solid (purity > 90% based on GC-MS) in an overall yield of 60%.

^{1}H-NMR ($CDCl_3/D_2O$): δ 3.92-3.81 (m, 1H, C**H**OH), 3.72 (dAB, J = 11.4 and 4.2 Hz, 1H, C**H**$_A$H$_B$-OH), 3.64 (dAB, J = 11.4 and 5.1 Hz, 1H, CH$_A$**H**$_B$OH), 3.57-3.44 (m, 4H, OC**H**$_2$CH and CH$_2$C**H**$_2$O), δ 1.6-1.4 (m, 2H, C**H**$_2$CH$_2$O), δ 1.35-1.1 (m, 18H, -(CH$_2$)$_9$-), δ 0.9-0.7 (t, J = 6.7 Hz, 3H, CH$_3$). ^{13}C-NMR ($CDCl_3$): δ 72.6 (t, O**C**H$_2$CH), 72.1 (t, CH$_2$**C**H$_2$O), 70.7 (d, CHOH), 64.4 (t, CH$_2$OH), 32.0, 29.7, 29.6, 29.4, 26.2, 22.8 (t, alkyl), 14.2 (q, CH$_3$). GC-MS (CI mode), m/e: 278 (MNH_4+), 261 (MH+).

3-{[6-(2,3-dihydroxypropoxy)hexyl]oxy}-1,2-propanediol (11)

Compound **6** (104 mg; 0.45 mmol) was mixed with 0.6 ml water in the presence of 1 µl trifluoroacetic acid. The flask was stoppered and the turbid mixture stirred vigorously overnight until homogeneous. Ten ml of ethyl acetate was added and the aqueous layer saturated by the addition of solid sodium chloride. After stirring for 0.5 h, the brine layer was extracted twice with 15 ml ethyl acetate. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to give 75 mg of compound **12** as a sticky colourless oil (63%).

^{1}H-NMR ($CDCl_3/D_2O$): δ 3.92-3.81 (m, 1H, C**H**OH), 3.72 (dAB, J = 11.4 and 4.2 Hz, 1H, C**H**$_A$H$_B$-OH), 3.64 (dAB, J = 11.4 and 5.1 Hz, 1H, CH$_A$**H**$_B$OH), 3.57-3.44 (m, 4H, OC**H**$_2$CH and CH$_2$C**H**$_2$O), δ 1.65-1.42 (m, 4H, C**H**$_2$CH$_2$O), 1.40-1.21 (m, 4H, -CH$_2$CH$_2$-). ^{13}C-NMR ($CDCl_3$): δ 72.5 (t, O**C**H2CH), 71.7 (t, O**C**H$_2$CH$_2$), 70.9 (d, **C**HOH), 64.3 (t, **C**H$_2$OH), 29.4 (t, OCH$_2$**C**H$_2$), 26.0 (t, CH$_2$**C**H$_2$).

RESULTS AND DISCUSSION

All optimisation experiments were performed with non-labelled epichlorohydrin (ECH). Reactions with ^{14}C-ECH were done under optimised conditions.

Reaction of aromatic alcohols with ECH.

At small scale (2 mmol) reasonable to good yields of the chlorohydrins as the addition products were obtained when 3 to 4 molar equivalents of ECH were used per hydroxyl unit. This excess of ECH gave good results for mono-functional alcohols (*o*-cresol) as well as for the bi-functional alcohols *bis*-phenol A (diphenylol propane) and 4,4'-dihydroxy-3,3',5,5'-tetramethyl biphenyl.

Sodium hydroxide is a good catalyst for the reaction between ECH and aromatic alcohol. Since chlorohydrins cyclise in the presence of sodium hydroxide to the corresponding GE, a slight excess of NaOH (1.05 molar equivalent) was used per hydroxyl unit in order to achieve complete consumption of the alcohol. Best results were obtained by keeping the concentration of NaOH low at all times during the reaction between aromatic alcohol and ECH, so that sodium hydroxide-catalysed side reactions are prevented. This was achieved by the addition of small portions of NaOH (1.05 molar equivalent in total) over a period of time.

According to HPLC analysis, complete conversion of chlorohydrins into the corresponding GEs could not be achieved by using NaOH. Recent work on the synthesis of radio-labelled glycidyl esters, which are closely related to GEs, showed clean and complete conversion when the corresponding chlorohydrin was reacted with sodium hydride as a base (8). This synthetic method also proved to be successful when applied in the synthesis of GEs. Thus, one equivalent of sodium hydroxide per hydroxyl function was used to ensure a high conversion to the alcohol, followed by the addition of one equivalent of sodium hydride per hydroxyl function in order to achieve complete conversion of the chlorohydrin to the corresponding GE. Small amounts of yellow-coloured material, most likely catechol adducts, which formed during sodium hydride addition could easily be extracted from the organic phase (ethyl acetate/*n*-hexane) with water prior to concentration by evaporation.

Reaction of Aliphatic Alcohols with ECH

Sodium hydroxide is too weak a base to deprotonate aliphatic alcohols in the addition reaction with ECH. The use of tin(IV) chloride as a catalyst resulted in almost complete and clean conversion of alcohol to the corresponding chlorohydrin.

For 1-dodecanol the use of two equivalents of ECH on alcohol resulted in complete conversion of alcohol (>95%, based on NMR). In the case of 1,6-hexanediol best results were obtained when an excess of 5 molar equivalents per hydroxyl group was used to obtain the corresponding di-functional chlorohydrin.

The conversion of aliphatic chlorohydrin into the corresponding glycidyl ether could be achieved using sodium hydride as a base. The use of ethyl acetate, which would be preferred for its polar properties, proved not to be the proper choice for this conversion. Impurities which were present in the GEs synthesised from 1-dodecanol and 1,6-hexanediol were most likely reaction products of ethyl acetate and unreacted aliphatic alcohol, yielding acetyloxy derivatives through trans-esterification under basic conditions. This would be in accordance with NMR analysis (^{13}C-NMR: δ 172 (s), δ 65 (t) and δ 18 (q) ppm and ^{1}H-NMR: δ 4.05 (t) ppm). Another possibility could be the reported re-arrangement of glycidyl moieties into alkoxy acetone moieties (9) which would give rise to ^{13}C-NMR absorptions close to those observed, but would not account for the observed triplet in the proton NMR at 4.05 ppm. Proof for the occurrence of trans-esterification during conversions of chlorohydrins was obtained by reacting 1,6-hexanediol with sodium hydride in ethyl acetate. NMR spectra from material thus obtained, matched those of the observed impurities exactly. Replacement of ethyl acetate as the solvent by toluene indeed resulted in clean conversion of aliphatic chlorohydrin to the corresponding GEs.

In the conversion of aromatic chlorohydrins to GEs with the use of sodium hydride, trans-esterification with ethyl acetate was not observed which may be due to the lower nucleophilicity of aromatic sodium alcoholates (10, 11).

Purification of [^{14}C]-Labelled Glycidyl Ethers

[^{14}C] 2-Methylphenyl glycidyl ether (2):

Distillation of the crude GE yielded product with a radiochemical purity of 94%. Analysis by HPLC showed that the main impurity in the material consisted of the radioactive glycerol derivative 7, formed by hydrolysis of the glycidyl moiety. Commercially available GE of *o*-cresol has a purity of 92% and contains 8% of its glycerol derivative. Semi-preparative HPLC-separation of products 2 and 7 can be achieved, but apart from the occurrence of spontaneous hydrolysis to some extent, isolation from aqueous mixtures is complex due to their relatively low boiling points and their water-solubility.

4,4'-dihydroxy,3,3',5,5'-tetramethyl biphenyl (3):

Earlier results obtained in the synthesis of the diglycidyl ether from *bis*-phenol A (BADGE, compound 4) indicated the complex kinetics in the addition reaction with ECH. Although reasonable high yields of the desired compound were obtained, extensive semi-preparative HPLC procedures were needed to isolate 4 with high purity. When 4,4'-dihydroxy,3,3',5,5'-tetramethyl biphenyl was reacted with ECH under similar conditions, the crude mixtures contained 30% of impurities and 70% of the desired GE. Most of the impurities were radiolabelled as well, since they containerd built-up products of radioactive ECH as a result of multiple additions. With the use of LC-MS analysis the retention time of diglycidyl ether 3 was determined and the product was subsequently isolated by semi-preparative HPLC in moderate yield and with a radio-purity of 97%.

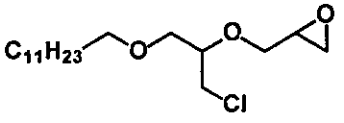
[^{14}C]-Dodecyl glycidyl ether (5) *and [^{14}C]-hexane-1,6-diglycidyl ether* (6):

Both compounds 5 and 6 (Fig. 2) were purified by Kugelrohr-distillation. According to HPLC with on line radio-detection both products had an initial radio-purity of

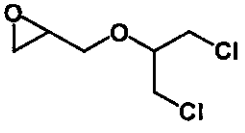
approximately 85% and contained UV- and radio-active impurities. Further purification was achieved by semi-preparative HPLC (system B) and the isolated products were analysed by GC-MS using electrospray and chemical ionisation.

According to GC-MS (EI mode), compound **5** was isolated with a radiochemical purity of >98% and positively identified as the desired compound based on the observation of ions at m/e 260 [MNH_4^+] and m/e 243 [MH^+]. The only radioactive impurity (< 2%) showed molecular ions at m/e 352 [MNH_4^+] and m/e 335 [MH^+] and contained one chlorine atom, strongly suggesting that this product results from a second addition of ECH to the initially formed chlorohydrin (Fig. 4).

Figure 4. Radioactive impurities identified in aliphatic glycidyl ethers 5 and 6



m/e 334



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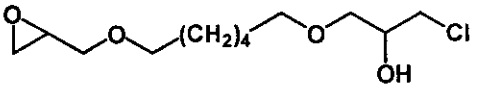

m/e 266

According to GC-MS (EI mode), compound **6** was isolated with a radiochemical purity of > 98% and positively identified as the desired compound based on the observation of ions at m/e 248 [MNH_4^+] and m/e 231 [MH^+]. Two radioactive impurities (both < 1%) were observed by GC-analysis. The first eluting impurity, with a retention time of 4.77 min, showed molecular ions at m/e 202 [MNH_4^+] and m/e 185 [MH^+] and contained two chlorine atoms. Based on an exact match of its mass spectrum with a fragmentation pattern available from the MassLib database this product was identified as the dichlorinated epoxide (depicted in Figure 4). The second impurity, with a retention time of 10.15 min, showed molecular ions at m/e 284 [$M\text{-}NH_4^+$] and m/e 267

[MH^+] and contained one chlorine atom. Based on these data this product most likely results from difunctionalised 1,6-hexane diol in which only one side of the chlorohydrin moieties has cyclised to the corresponding glycidyl moiety.

Synthesis of glycerol derivatives

Non-labelled GEs based on aromatic alcohols could be converted to the corresponding glycerol derivatives (α-glycols 7 and 8) in good yield and good purity, by opening the epoxide ring in refluxing acetic acid in the presence of acetic anhydride so that the hydroxyl functionality which results from ring-opening of the epoxide moiety of the GE is acetylated *in situ* and protected from undesired side-reactions. Hydrolysis of the acetyloxy functions with sodium hydroxide in water and extraction of product with a suitable organic solvent yielded the free alcohols quantitatively. In this way α-glycols of *o*-cresol (7) and 4,4'-dihydroxy,3,3',5,5'-tetramethyl biphenyl (8) were synthesised. HPLC and NMR data of 7 were identical to the data of commercially available material (Mephenesin, Aldrich). NMR spectra of compound 8 were similar to an authentic sample of *bis*-phenol A diglycerol ether. Products 7 and 8 could be further purified by HPLC (System A). This route was also used for the hydrolysis of radio-labelled GEs without optimisation.

Non-labelled GEs based on aliphatic alcohols could be ring-opened quantitatively to the corresponding acetylated glycerol derivatives 9 and 10, using acetic acid in the presence of acetic anhydride. However, hydrolysis of the acetyloxy-functions by sodium hydroxide in water/2-propanol resulted in poor recovery of the corresponding glycerol derivatives 11 and 12. Furthermore, we experienced difficulties in the isolation of α-glycol 11 from water/ethyl acetate mixtures, most likely due to its high water-solubility. We recently reported on the hydrolysis of trifluoro-acetylated, ring-opened, glycidyl esters in the presence of sodium hydride, yielding the corresponding α-glycols (8). It appeared that this method was also applicable to hydrolysis of GEs. Thus, when a solution of glycerol derivative 9 in hexane/toluene was treated with two equivalents of sodium hydride, the corresponding diol 11 could be isolated. Further purification by HPLC (System A) yielded α-glycol 11 as a white solid in a yield of 61% and a purity

of approximately 81% based on total ion mass-detection and NMR analysis. This method was, however, not successful in the hydrolysis of tetra-acetate **9** to give α-glycol **12**.

Recently, we found that glycidyl esters could successfully be hydrolysed in an inhomogeneous mixture with water using a catalytic amount of trifluoroacetic acid. When similar conditions were applied to diglycidyl ether **6**, clean conversion to α-glycol **12** was achieved in 63% yield. Recovery of desired material was achieved by salting out the product from the water layer and extraction with ethyl acetate. These methods were not optimised for the synthesis of radio-labelled, aliphatic α-glycols.

CONCLUSIONS

The synthesis of radio-labelled GEs from the corresponding alcohols and [U-^{14}C]epichlorohydrin is a general synthetic route that yields radio-labelled material in reasonable to good yields after purification by bulb-to-bulb distillation and/or semi-preparative HPLC. Typical radiochemical purities were in the range of 95% with specific activities of approximately 0.2 and 0.4 mCi/mmol for mono- and difunctional compounds, respectively.

Aromatic alcohols were reacted with epichlorohydrin and sodium hydroxide as a base to give mixtures of the corresponding chlorohydrin and glycidyl ether. Aliphatic alcohols were cleanly converted to the corresponding chlorohydrins in the presence of tin(IV) chloride as a catalyst. Aromatic and aliphatic chlorohydrins could be converted in high yield to the corresponding glycidyl ether *in situ* using sodium hydride as a base.

The epoxide moiety of aromatic glycidyl ethers was ring-opened with acetic acid/acetic anhydride and hydrolysed to the corresponding α-glycol derivatives with sodium hydroxide. Aliphatic glycidyl ethers were also ring-opened in mixtures of acetic acid/acetic anhydride. Hydrolysis to give the corresponding α-glycol derivatives gave the best results in mixtures with water and a catalytic amount of trifluoroacetic acid.

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