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Some novel homochiral derivatizing agents for the gas chromatographic analysis of enantiomeric secondary alcohols

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ABSTRACT

Some novel homochiral derivatizing agents for the determination of enantiomeric composition of chiral alcohols have been synthesised. The reactions of the reagents with alkan-2-ols and the gas chromatographic behaviour of the resulting diastereoisomeric derivatives have been examined. The most promising reagents are (*S*)-(+)-tetrahydro-5-oxo-2-furanmethyl chloromethyl ether, and (*S*)-(+)-2-methylcarboxypropyl chloromethyl ether. Despite having five bonds between chiral centres in their diastereoisomeric derivatives, resolution was readily achieved on common, conventional stationary phases.

INTRODUCTION

Chromatographic and electrophoretic methods for separating the enantiomers of chiral compounds depend on creating an asymmetric environment. This is achieved with (i) a homochiral derivatizing reagent, (ii) a homochiral stationary phase [1–5] or (iii) a mobile phase containing homochiral additives. Each of these approaches has both advantages and disadvantages. For gas chromatography and approach (i), many achiral derivatization agents, developed primarily to enhance the volatility of analytes, have been adapted for use as homochiral reagents so as to form diastereoisomers from enantiomers. The derivatization reaction most commonly employed in diastereoisomer formation involves the use of chiral acid chlorides. For example, homochiral acid chlorides include (+)-*trans*-chrysanthemoyl chloride which has enabled the quantification of enantiomers of pheromones [6], terpenes such as menthol [7] and triazole alcohols [8] and various amines (*e.g.*, amphetamine) [7] by gas chromatography (GC). Another, prepared from the cheap and readily available amino acid (*S*)-proline, is N-trifluoroacetyl-(*S*)-prolyl chloride. This reagent has been used widely for the separation of enantiomers of numerous alcohols and amines by GC [6,9–12] as well as by high-performance liquid chromatography [13,14]. Use of N-heptafluorobutyl-(*S*)-prolyl chloride has also been reported [15]. Conversely, homochiral alcohols that can be employed for the derivatization of enantiomers of acids (via their acid chlorides) for GC analysis include (−)-menthol [16–18], (+)-3-methyl-2-butanol [19, 20] and enantiomerically pure 2-alcohols [21–23]. Many other derivatization reactions applicable to the formation of diastereoisomers are known. Examples of homochiral reagents for these reactions are listed in several texts [24–26].

The advantages of homochiral derivatization are

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also several fold: (a) the reagents are usually obtained from cheap and readily available starting materials; (b) the separations can be achieved on conventional, relatively cheap achiral columns; (c) the order of elution of the diastereoisomeric products can be changed readily by using the optical antipode of the homochiral reagent; (d) different analogues of the homochiral reagents can be synthesised in order to enhance factors such as volatility of the reagent or to improve the sensitivity or selectivity of the analysis.

While GC analysis of diastereoisomers has produced some very good separations, the technique has several well known drawbacks such as: (i) the reagent used needs to be 100% optically pure; (ii) racemization of the reagent can occur under certain reaction conditions; (iii) kinetic resolution may occur (*i.e.*, one enantiomer may react more rapidly than its antipode with an asymmetric reagent), giving misleading results if the derivatization does not go to completion; (iv) where there are more than four bonds between the two chiral centres of the diastereoisomers unsatisfactory separations are said [1] to be produced; (v) different classes of analytes require different reagents (*i.e.*, many metho ds are specific to just onc class of compound); and (vi) an enantiomerically enriched sample of the analyte must be obtainable in order to determine the order of elution of the diastereoisomers (it does not always follow that the elution order will be the same for different homologues [27]). The work reported here seeks to overcome some of the disadvantages associated with the gas chromatographic determination of enantiomeric compositions following derivatization with a homochiral reagent.

The use of homochiral haloalkanes as derivatizing agents forming diastereoisomeric ethers from chiral alcohols

$$R^*OH + R{-}X \rightarrow R^*{-}O{-}R + HX \qquad (1)$$

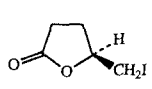
(where X = Cl, Br, I) has received little attention. For example, alcohols and related nucleophilic compounds react with simple haloalkanes under the mild, though basic, conditions of solid KOH in dimethyl sulphoxide (DMSO) [28]. This procedure would appear to be adaptable to chiral analysis. However, it was found [29] that, when more complex haloalkanes were employed (with β-branching to create a chiral centre), hydrolysis and/or dehydrohalogenation (elimination) predominated over the required substitution according to eqn. 1. Barluenga *et al.* [30,31] have effected the reaction in eqn. 1 under mild and neutral conditions. Mercury tetrafluoroborate in dichloromethane was utilized to enhance the reactivity of the haloalkane. We have applied this procedure to homochiral reagents as a means of derivatizing chiral alcohols prior to GC separation. The procedure has the advantage of being compatible with base-sensitive functions in the analyte or in the reagent.

If the reagent haloalkane molecule does not contain a C–H unit in the β-position, dehydrohalogenation is prevented from occurring. Chloromethyl ethers offer this feature:

$$R^*OH + R{-}OCH_2{-}Cl \xrightarrow[CHCl_3/\text{reflux}]{EtN^iPr_2} R^*{-}O{-}CH_2OR + HCl \qquad (2)$$

(where Et = ethyl and ^{i}Pr = isopropyl). In addition, these reagents are very reactive because the oxygen atom is able to stabilize the transition state and/or intermediate in the substitution reaction.

We have developed two derivatization procedures, one based on homochiral iodoalkanes **1** and **2**, the other on homochiral chloromethyl ethers **3**–



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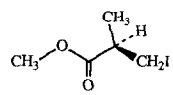

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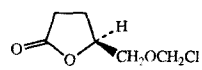

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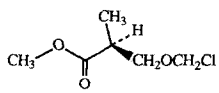

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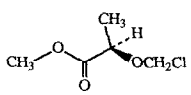

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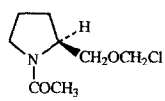

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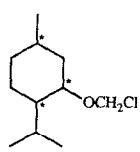


7 (* = chiral centres:1S,2R,5S)

7, for determining enantiomeric compositions of alcohols by GC. The efficiency of the methods is assessed by comparison with established derivatization schemes using homochiral acyl chlorides:

$$R^*OH + RCO{-}Cl \rightarrow R^*O{-}COR + HCl \quad (3)$$

An unexpected variation of resolution with the number of bonds between the chiral centers in the resulting diastereoisomeric ethers was observed and is also described herein.

EXPERIMENTAL

Apparatus and chemicals

The following gas chromatographs were used: (a) Carlo-Erba, GC6000 Vega Series 2 fitted with an on-column injector and flame ionization detector (250°C), the data being processed with a Milton Roy CI-10CB integrator; (b) Hewlett-Packard 5890 fitted with a split injector (275°C) and flame ionization detector (270°C), the data being processed with a Hewlett-Packard HP5895A work station. GC–mass spectrometry (MS) was effected with a Hewlett-Packard 5890 gas chromatograph coupled to a VG 20-250 quadrupole mass spectrometer in the electron ionization (EI) mode. Typically, the ion source was maintained at 200°C, the electron beam energy was 70 eV and the emission current 100–200 μA. Spectra were recorded repetitively every second. The various columns and temperature programmes used for GC are given in the legends to the figures and tables. Helium carrier gas inlet pressures were in the range 30–40 KPa.

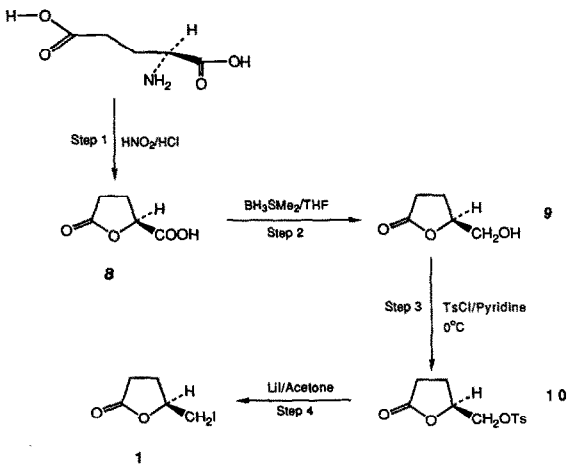


Fig. 1. Preparation of reagent **1**. Me = Methyl; Ts = tosyl.

Other instruments utilized during the preparation of the derivatizing agents: Jeol FX90Q FT NMR (90 MHz) for ^{13}C and ^{1}H NMR spectroscopy; Perkin-Elmer 1420 ratio recording spectrophotometer for infrared spectroscopy; a half-shadow polarimeter (Lippich type) for measuring optical rotations. Elemental analyses were performed by Medac, Brunel University, Uxbridge, UK.

All chemicals were purchased from either Aldrich or Sigma.

Synthesis of the homochiral derivatizing agents

Reagent ***1****: (S)-(−)-tetrahydro-5-oxo-2-furanmethyl iodide*

This compound was prepared according to Fig. 1 as follows [32–34]:

Step 1. A solution of sodium nitrite (126 g; 1.83 mol) in water (270 ml) was added dropwise to a mixture of (*S*)-(+)-glutamic acid (180 g; 1.22 mol) in water (480 ml) and concentrated (37%) hydrochloric acid solution (180 ml) at 0–5°C in a 2-l flask fitted with a mechanical strirrer. On addition, the stirred solution cleared and effervesced. After three hours stirring, the mixture was allowed to stand overnight at 0°C, then at room temperature for 5 h. The water was removed by freeze drying to yield a pale yellow oil and colourless fine crystals. Hot acetone was added (600 ml) until all the oil was dissolved, leaving a fine suspension of sodium chloride. This was filtered off and the filtrate was concentrated to 300 ml. Anhydrous magnesium sulphate was added and the mixture was allowed to stand overnight at 3°C. The solids were removed by filtration and the solvent was removed. The oily residue was taken up in ethyl acetate (500 ml), and any further insoluble material was removed by filtration. The solvent was removed and the residue was taken up in a minimum of warm ethyl acetate (200 ml). An equal volume of benzene was added and the mixture was allowed to crystallize in a freezer (after seeding). The crystalline product was filtered and washed with anhydrous diethyl ether. The combined filtrates were again seeded and cooled to give a further crop of crystals.

The total yield of acid **8** was 80 g (50%); m.p. 55°C (lit. 70–72°C [32]); $[\alpha]_D^{20}$ +14.6° (c = 2.0, C_2H_5OH)

(lit. +15.6°); IR: ν_{max} (nujol) 3600–2350 (OH_{STR}, acid[a]), 1765 ($C{=}O_{STR}$, lactone), 1720 ($C{=}O_{STR}$, acid), 1180 cm^{-1} ($C{-}O_{STR}$); NMR: δ_H ($C^2H_3O^2H$) 2.2–2.7 ($CH_2{-}CH_2$, m, 4H), 5.0 (CH, m, 1H) 5.4 ppm (OH, s, 1H); NMR: δ_c ($C^2H_3O^2H$) 28.5 and 29.5 ($CH_2{-}CH_2$), 79.0 (CH–O), 175.1 and 180.8 ppm (C=O lactone and acid).

Step 2. To a three-necked 500-ml round-bottomed flask, set up with a magnetic stirrer, septum, stopper and reflux condenser connected to an argon bubbler, was added acid **8** (21.6 g, 0.166 mol), followed by 140 ml of tetrahydrofuran (THF). After flushing the system with argon, a 2 *M* solution of borane methyl sulphide complex (95 ml, 0.19 mol) in THF was injected slowly (over 1 h). After 3 h stirring, the mixture was quenched by cautious addition of anhydrous methanol (60 ml). Most of the solvent was removed by rotary evaporation and a further portion of methanol (200 ml) was added then removed. Vacuum distillation (125–135°C/0.6 mmHg) yielded 16.7 g (87%) of alcohol **9** as a clear oil. $[\alpha]_D^{20}$ +25.5° (c = 2.0, C_2H_5OH) [lit. [32] $[\alpha]_D^{20}$ +29.6° (c = 0.4, C_2H_5OH)]. IR: ν_{max} (thin film) 3400 ($O{-}H_{STR}$), 1765 cm^{-1} ($C{=}O_{STR}$, lactone); NMR: δ_H (C^2HCl_3) 2.25 and 2.6 ($CH_2{-}CH_2$, m, 4H), 3.75 (CH_2–O, m, 2H), 4.1 (O–H, s, 1H), 4.6 ppm (CH, m, 1H); NMR: δ_C (C^2HCl_3) 23.0 (C–CH_2–C), 28.4 ($O_2C{-}CH_2{-}C$), 63.6 (O–CH–C), 80.9 (CH_2–OH), 178 ppm (C=O).

Step 3. *p*-Toluenesulphonyl chloride (tosyl chloride) (42 g, 0.22 mol) was added to a stirred solution of alcohol **9** (15 g, 0.13 mol) in dry pyridine (100 ml) at 0°C. After 30 min stirring the mixture was left to stand at 0°C for 22 h. The mixture was then filtered and the filtrate was poured into cold 5% sodium hydrogen carbonate solution (180 ml). The product was extracted into ethyl acetate (2 × 100 ml), and the combined extracts were washed with 5% sodium hydrogen carbonate solution (100 ml), water (100 ml) and brine (100 ml). After drying with anhydrous magnesium sulphate and filtering, the solvent was removed to yield an orange oil which was crystallized twice from benzene/hexane to yield 16.2 g (47%) of tosylate **10** as fine white needles. M.p. = 83°C (lit. = 85–87°C [32]). $[\alpha]_D^{20}$ +43° (c = 1, $CHCl_3$) [lit. [32] $[\alpha]_D^{20}$ +47° (c = 1.6, $CHCl_3$)]. IR: ν_{max} (KBr disc) 1760 ($C = O_{STR}$, lactone), 1355 (S=O), 1170 (S=O), 975 cm^{-1} (S–O–C); NMR: δ_H (C^2HCl_3) 2.0–2.6 (CH_2CH_2, m, 4H), 2.45 (CH_3, s, 3H), 4.15 (CH_2–O, dd, 2H), 4.65 (CH–O, m, 1H), 7.25 and 7.8 ppm (aromatic CH, 2 × d, 4H); NMR: δ_c (C^2HCl_3) 21.6 (CH_3), 23.4 and 27.8 ($CH_2{-}CH_2$), 69.9 (CH–O), 76.3 (CH_2–O), 127 and 130 (aromatic CH), 132.2 (C–CH_3), 145.3 (C–S), 175.9 ppm (C=O).

Step 4. Lithium iodide (24 g, 0.18 mol) was added to a solution of tosylate **10** (12 g, 0.044 mol) in acetone (150 ml). The mixture was stirred and heated under reflux for 5 h, when the reaction was seen to be complete by thin-layer chromatography (on silica plates using methanol or chloroform as solvent). The acetone was removed by rotary evaporation and the orange-brown residue was dissolved in water (20 ml). The product was extracted twice with ethyl acetate (15 ml), and the combined extracts were washed with sodium thiosulphate and brine solutions. After drying with anhydrous magnesium sulphate and filtering, the ethyl acetate was removed by rotary evaporation to yield 9.3 g (94%) of iodide **1** as a pale orange oil; $[\alpha]_D^{20}$ −15.4° (c = 1.75, $CHCl_3$); IR: ν_{max} (thin film) 1760 cm^{-1} ($C{=}O_{STR}$, lactone); NMR: δ_H (C^2HCl_3) 2-3 ($CH_2{-}CH_2$, m, 4H), 3.5 (CH–CH_2–I, d, 2H), 4.65 ppm (CH–O, m, 1H); NMR: δ_c ($C^2H_3O^2H$) 7.9 (CH_2–I), 28.0 and 28.8 ($CH_2{-}CH_2$), 78.4 (CH–O), 176.2 ppm (C=O).

Reagent 2: methyl (S)-(+)-3-iodo-2-methylpropanoate

This compound was prepared from methyl (*S*)-(+)-3-hydroxy-2-methylpropanoate **11** according to Fig. 2 by effecting steps 3 and 4 as above.

Thus, methyl (*S*)-(+)-3-hydroxy-2-methylpropanoate (1.534 g, 13 mmol), pyridine (10 ml) and tosyl chloride (4.2 g, 22 mmol) were used. The work-up, scaled accordingly, gave 2.4 g (68%) of compound **12** as a pale orange oil (pure by GC). Found: C, 52.88; H, 5.92 ($C_{12}H_{16}O_5S$ requires C, 52.93; H,

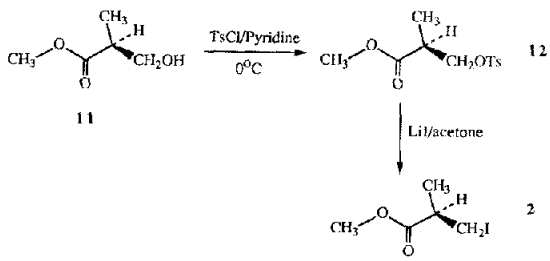


Fig. 2. Preparation of reagent **2**.

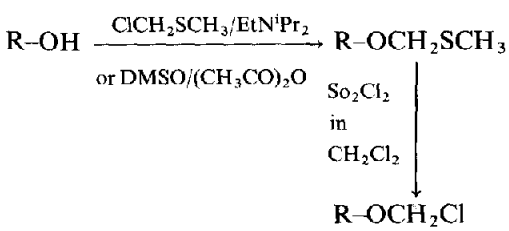
[a] STR = stretching.

5.92). $[\alpha]_D^{20}$ +9.0° (c = 2.0 CH_3OH); IR: ν_{max} (thin film) 1745 (C=O_{STR}, ester), 1600/1495 (aromatic C=C_{STR}), 1365 (S=O), 1210 [C(=O)–O–C_{STR}], 1180 (S=O), 975 (S–O–C), 750 (C–H_b)[a], 670 cm^{-1} (C=C_b); NMR: δ_H (C^2HCl_3) 1.15 (CH_3CH, d, 3H), 2.4 [aromatic group (Ar)–CH_3, s, 3H], 2.85 (CH, q, 1H), 3.6 (CH_3–O, s, 3H), 4.1 ($CHCH_2O$, 2H), 7.35 and 7.8 ppm (aromatic CHs, 2 × d, 4H); NMR: δ_C (C^2HCl_3) 13.6 (CH_3CH), 21.6 (Ar–CH_3), 39.2 (CH), 52.0 (CH_3O), 70.8 (CH_2O), 127.9 and 129.9 (aromatic CH), 132.8 (aromatic C–CH_3), 145.0 (aromatic C–S), 173.0 ppm (C=O); EI-MS: m/z 272 (8%, $M^{+\cdot}$), 241 (2%, $[M - CH_3O^{\cdot}]^+$), 187 (10%), 172 (12%, $TsOH^{+\cdot}$), 155 (80%, $CH_3(C_6H_4)\dot{S}O_2$), 117 (57%, $[M - CH_3(C_6H_4)SO_2^{\cdot}]^+$), 91 (100%, $C_7H_7^+$), 85 (30%, $CH_3OC\dot{O}{=}CH_2$) and 69 [20%, $O{=}C{=}C(CH_3)CH_2^+$].

The iodide **2** was prepared from tosylate **12** on a 5-mmol scale. Thus, lithium iodide (2.74 g, 20.5 mmol), tosylate **12** (1.35 g, 5 mmol) and acetone (20 ml) were used. The work-up, also scaled accordingly, gave 0.76 g (63%) of iodide **2** as a pale yellow liquid (pure by GC). Found: C, 26.68; H, 4.05 ($C_5H_9IO_2$ requires C, 26.34; H, 3.98). $[\alpha]_D^{20}$ +21° (c = 2.0, CH_3OH); IR: ν_{max} (thin film) 1740 (C=O_{STR}, ester), 1210 and 1160 cm^{-1} [C(=O)–O–C_{STR}]; NMR: δ_H (C^2HCl_3) 1.25 (CH_3–CH, d, 3H), 2.80 (CH, m, 1H), 3.3 (CH_2–I, m, 2H), 3.7 ppm (CH_3–O, s, 3H); NMR: δ_C (C^2HCl_3) 6.8 (CH_2–I), 18.1 (CH_3–CH), 42.2 (CH), 52.0 (CH_3–O), 173.7 ppm (C=O); EI-MS: m/z 228 (28%, $M^{+\cdot}$), 197 (8%, $[M - CH_3O^{\cdot}]^+$), 169 (26%, $[M - {}^{\cdot}COOCH_3]^+$), 127 (9%, I^+), 101 (100%, $[M - I^{\cdot}]^+$), 73 (20%), 59 (75%, $CH_3OC{\equiv}O^+$) and 41 (30%).

Reagents **3**–**7**: *chloromethyl ethers*

These reagents were prepared from the corresponding alcohol via their methylthiomethyl (MTM) ether derivatives:



[a] b = bending.

General synthesis of MTM ethers. To the homochiral alcohol (20 mmol) in ethanol-free chloroform (60 ml) was added diisopropylethylamine (12.9 g, 100 mmol) and chloromethyl methyl sulphide (5.8 g, 60 mmol) under an argon atmosphere. The mixture was refluxed for 3–4 h until the reaction mixture contained a maximun quantity of product (typically 60–70%) with respect to the starting material and by-products (as monitored by GC). The cooled reaction mixture was washed with 1 *M* hydrochloric acid (100 ml) and water (200 ml) then dried ($MgSO_4$). The solvent was removed and the product purified by distillation. The yields and analytical data were as follows.

(S)-(+)-Tetrahydro-5-oxo-2-furanmethyl methylthiomethyl ether. Prepared from (*S*)-(+)-tetrahydro-5-oxo-2-furanmethyl alcohol **9** (2.32 g, 20 mmol). Distillation (130°C/0.15 mmHg) afforded 1.625 g (46%) MTM ether as a pale yellow liquid. Found: C, 47.65; H, 7.01; S, 18.08 ($C_7H_{12}O_3S$ requires C, 47.71; H, 6.86; S, 18.18%). $[\alpha]_D^{20}$ +20° (c = 1.0, C_2H_5OH); IR: ν_{max} (thin film) 1780 (C=O_{STR}, lactone), 1180 (C(=O)–O–C_{STR}, ester), 1080 cm^{-1} (C–O–C_{STR}, ether); NMR: δ_H (C^2HCl_3) 2.0–2.7 (CH_2–CH_2, m, 4H), 2.15 (S–CH_3, s, 3H), 3.6 (CH_2–O, m, 2H), 4.6 ppm (O–CH_2–S, s, 2H and CH, m, 1H); NMR: δ_C (C^2HCl_3) 14.1 (S–CH_3), 24.3 (CH_2–CH_2–CH), 28.6 ($CH_2C{=}O$), 69.5 (O–CH), 75.9 (O–CH_2–S), 79.0 (CH_2–O), 177.6 ppm (C=O); EI-MS: m/z 176 (28%, $M^{+\cdot}$), 146 (43%, $[M - CH_2O]^{+\cdot}$), 129 (57%, $[M - CH_3S^{\cdot}]^+$), 114 (16%, $[M - CH_3SCH_3]^{+\cdot}$), 99 (100%, $[M - CH_3SCH_2O^{\cdot}]^+$), 85 (83%, $[M - {}^{\cdot}CH_2OCH_2SCH_3]^+$) and 61 (1%, $CH_2{=}\dot{S}CH_3$).

(S)(+)-2-Methylcarboxypropylmethylthiomethyl ether. Prepared from methyl (*S*)-(+)-3-hydroxy-2-methylpropanoate **11** (2.36 g, 20 mmol). Distillation (50–55°C/0.25 mmHg) afforded 0.9 g (25%) MTM ether as a clear liquid. Found: C, 47.14; H, 8.11; S, 17.89 ($C_7H_{14}O_3S$ requires C, 47.17; H, 7.92; S, 17.9%). $[\alpha]_D^{20}$ +27° (c = 0.6, CH_3OH); IR: ν_{max} (thin film) 1720 (C=O_{STR}, ester), 1190 (C(=O)–O–C_{STR}, ester), 1060 cm^{-1} (C–O–C_{STR}, ether); NMR: δ_H (C^2HCl_3) 1.1 (CH_3CH, d, 3H), 2.1 (S–CH_3, s, 3H), 2.7 (CH, m, 1H), 3.7 (CH_3OCO and CH_2–O, s and m, 5H), 4.6 ppm (O–CH_2–S, s, 2H); NMR: δ_C (C^2HCl_3) 13.73 (CH_3–CH), 14.02 (S–CH_3), 39.92 (CH), 51.76 (CH_3OCO), 69.74 (CH_2–O), 75.37 (O–CH_2–S), 175.1 ppm (C=O).

(S)-(−)-1-Methylcarboxyethyl methylthiomethyl ether. Prepared from (*S*)-(−)-methyl lactate (2.08 g, 20 mmol). Distillation (68°C/5.5 mmHg) afforded 1.29 g (40%) MTM ether as a clear liquid. Found: C, 43.84; H, 7.37; S, 19.28 ($C_6H_{12}O_3S$ requires C, 43.88; H, 7.37; S, 19.51%). $[\alpha]_D^{20}$ −158° (*c* = 2.0, $CHCl_3$); IR: ν_{max} (thin film) 1730 (C=O_{STR}, ester), 1200 (C(=O)–O–C_{STR}, ester), 1100 cm^{-1} (C–O–C_{STR}, ether); NMR: δ_H (C^2HCl_3) 1.4 (CH_3–CH, d, 3H), 2.15 (S–CH_3, s, 3H), 3.75 (CH_3–OCO, s, 3H), 4.35 (C*H*, q, 1H), 4.7 ppm (O–CH_2–S, s, 2H); NMR: δ_C (C^2HCl_3) 13.9 (S–CH_3), 18.4 (CH_3–CH), 51.9 (CH_3OCO), 71.1 (*C*H–O), 74.3 (O–CH_2–S), 173.3 ppm (*C*=O); EI-MS: *m/z* 117 (100%, $[M-CH_3S^{\bullet}]^+$), 89 (95%, $CH_3OCOCH{=}\dot{O}H$), 70 (30%), 61 (42%, $CH_2{=}\dot{S}CH_3$), 59 (49%, $^+COOCH_3$) and 45 (55%).

N-Acetyl-(S)-(−)-2-pyrrolidinemethyl methylthiomethyl ether. Prepared from N-acetyl-(*S*)-(−)-2-pyrrolidinemethanol (2.86 g, 20 mmol). Distillation (140°C/0.1 mmHg) afforded 1.04 g (26%) MTM ether as a pale yellow oil. $[\alpha]_D^{20}$ −80° (*c* = 0.35, C_2H_5OH); IR: ν_{max} (thin film) 1650 (C=O_{STR}, amide), 1420 (C–N_{STR}, amide), 1070 cm^{-1} (C–O–C_{STR}, ether); NMR: δ_H (C^2HCl_3) 1.6–2.1 (CH_2–CH_2, m, 4H), 2.05 (CH_3C=O, s, 3H), 2.15 (S–CH_3, s, 3H), 3.2–3.75 (CH_2–O and CH_2–N, m, 4H), 4.25 (C*H*, m, 1H), 4.6 ppm (O–CH_2–S, s, 2H); NMR: δ_C (C^2HCl_3) 14.0/14.39 (S–CH_3), 22.4 and 22.8/22.9 (CH_2–CH_2), 27.86/28.95 (CH_3C=O), 45.6/48.5 (CH_2–N), 56.1/57.6 and 68.1/69.1 (CH_2–O and *C*H–N), 75.6 (O–CH_2–S), 169.4 ppm (*C*=O); EI-MS: *m/z* 188 (1%, $[M-{}^{\bullet}CH_3]^+$), 156 (3%, $[M-CH_3S^{\bullet}]^+$), 142 (24%, $[M-{}^{\bullet}CH_2SCH_3]^+$), 127 (34%, $[M-CH_3SCH{=}O]^{+\bullet}$), 112 (40%, $[M-{}^{\bullet}CH_2OCH_2SCH_3]^+$), 100 (13%), 84 (16%), 70 (100%, $[M-(CH_2C{=}O+{}^{\bullet}CH_2OCH_2SCH_3)]^+$) and 61 (13%, $CH_2{=}\dot{S}CH_3$).

(1S, 2R, 5S)-(+)-Menthyl methylthiomethyl ether. This compound was prepared with a different, literature procedure [35]. To (1*S*, 2*R*, 5*S*)-(+)-menthol (1.872 g, 12 mmol) in a round-bottomed flask, was added DMSO (60 ml) and acetic anhydride (60 ml). The reaction was stirred at room temperature for 30 h (monitoring by GC) before pouring into water (200 ml). The product mixture was extracted into chloroform (100 ml), which was then washed 5 times with water (100 ml). After drying ($MgSO_4$), the solvent and acetic anhydride were removed by rotary evaporation. Applying a high vacuum and warming the flask removed the last traces of any remaining menthol to leave 2.15 g (78%) as a clear liquid. $[\alpha]_D^{20}$ +199° (*c* = 2.0, C_2H_5OH); IR: ν_{max} (thin film) 1050 cm^{-1} (C–O–C_{STR}, ether); NMR: δ_H (C^2HCl_3) 0.7–2.7 (CH_3, CH_2 and C*H*, 18H), 2.15 (S–CH_3, s, 3H), 3.5 (C*H*–O, dt, 1H), 4.6 ppm (O–CH_2–S, s, 2H); NMR: δ_C (C^2HCl_3) 12 signals observed as expected; diagnostic signals at 14.1 (SCH_3), 72.3 (*C*HO), 75.9 ppm (OCH_2S); EI-MS: *m/z* 216 (1.5%, $M^{+\bullet}$), 169 (18%, $[M-CH_3S^{\bullet}]^+$), 139 (24%, $[M-{}^{\bullet}CH_2OCH_2SCH_3]^+$), 111 (5%, $C_8H_{15}^+$), 97 (18%, $C_7H_{13}^+$), 83 (100%, $CH_2{=}CH{-}\dot{C}H{-}CH(CH_3)_2$), 69 (27%, $C_5H_9^+$), 61 (22%, $CH_2{=}\dot{S}CH_3$), 55 (25%, $C_4H_7^+$) and 41 (10%, $C_3H_5^+$).

General procedure for the preparation of chloromethyl ethers **3**–**7**. The chloromethyl ethers were prepared in small quantities from the corresponding MTM ethers when required. Sulphuryl chloride (0.34 g, 2.5 mmol) in dichloromethane (5 ml) was added dropwise to a stirred solution of the homochiral MTM ether (2.5 mmol) in dichloromethane (8 ml). A small amount of effervescence (SO_2) was observed on addition. After stirring for 30 min at room temperature, the solvent and methanesulphenyl chloride by-product were removed by rotary evaporation and high vacuum. The products were used in the derivatization reactions without further purification. Yields and analytical data are presented as follows.

(S)-(+)-Tetrahydro-5-oxo-2-furanmethyl chloromethyl ether **3**. Prepared from (*S*)-(+)-tetrahydro-5-oxo-2-furanmethyl MTM ether (0.44 g, 2.5 mmol). Yield: 0.39 g (95%) as a clear liquid. $[\alpha]_D^{20}$ +23° (*c* = 1.0, $CHCl_3$); IR: ν_{max} (thin film) 1780 (C=O_{STR}, lactone), 1180 (C(=O)–O–C_{STR}, ester), 1070 (C–O–C_{STR}, ether), 650 cm^{-1} (C–Cl_{STR}); NMR: δ_H (C^2HCl_3) 2.0–2.8 (CH_2–CH_2, m, 4H), 3.8 (CH_2–O, m, 2H), 4.65 (C*H*, m, 1H), 5.45 ppm (O–CH_2–S, s, 2H); NMR: δ_C (C^2HCl_3) 23.7 (CH_2–CH_2–CH), 28.2 (CH_2C=O), 69.2 (O–*C*H), 78.6 (CH_2–O), 95.4 (O–CH_2–Cl), 177.0 ppm (*C*=O); EI-MS: *m/z* 129 (7%, $[M-Cl^{\bullet}]^+$), 114 (7%, $[M-CH_3Cl]^{+\bullet}$), 99 (7%, $[M-ClCH_2O^{\bullet}]^+$), 85 (100%, $[M-{}^{\bullet}CH_2OCH_2Cl]^+$), 49/51 (6%, CH_2Cl^+) and 36/38 (4%, HCl^+).

(S)-(+)-2-Methylcarboxypropyl chloromethyl ether **4**. Prepared from (*S*)-(+)-2-methylcarboxypropyl MTM ether (0.44 g, 2.5 mmol). Yield: 0.39 g

(93%) as a pale yellow liquid. IR: ν_{max} (thin film) 1745 (C=O_{STR}, ester), 1200 (C(=O)–O–C_{STR}, ester), 1125 (C–O–C_{STR}, ether), 640 cm^{-1} (C–Cl_{STR}); NMR: δ_H (C^2HCl_3) 1.2 (CH_3CH, d, 3H), 2.7 (CH, m, 1H), 3.7 (CH_3–OCO and CH_2–O, s and d, 5H), 5.4 ppm (O–CH_2–Cl, s, 2H); NMR: δ_C (C^2HCl_3) 13.84/14.0 (CH_3–CH), 39.5/40.1 (CH), 51.78/51.9 (CH_3OCO), 69.7/71.9 (CH_2–O), 82.8 (O–CH_2–Cl), 175.1 ppm (C=O).

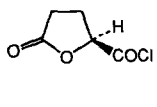
(S)-(−)-1-Methylcarboxyethyl chloromethyl ether ***5***. Prepared from (S)-(−)-1-methylcarboxyethyl MTM ether (0.41 g, 2.5 mmol). Yield: 0.36 g (95%) as a pale yellow liquid. Found: C, 39.49; H, 6.10 ($C_5H_9O_3Cl$ requires C, 39.36; H, 5.95%). $[\alpha]_D^{20}$ −129° (*c* = 1.0, $CHCl_3$); IR: ν_{max} (thin film) 1730 (C=O_{STR}, ester), 1200 (C(=O)–O–C_{STR}, ester), 1100 cm^{-1} (C–O–C_{STR}, ether); NMR: δ_H (C^2HCl_3) 1.45 (CH_3CH, d, 3H) 3.8 (CH_3–OCO, s, 3H), 4.45 (CH, q, 1H), 5.55 ppm (O–CH_2–Cl, s, 2H); NMR: δ_C (C^2HCl_3) 18.0 (CH_3–CH), 52.0 (CH_3OCO), 72.7 (CH–O), 80.8 (O–CH_2–Cl), 172 ppm (C=O).

N-Acetyl (S)-(−)-2-pyrrolidinemethyl chloromethyl ether ***6***. Prepared from N-acetyl-(S)-(−)-2-pyrrolidinemethyl MTM ether (0.51 g, 2.5 mmol). Yield: 0.46 g (97%) as a clear oil. IR: ν_{max} (thin film) 1640 (C=O_{STR}, amide), 1420 (C–N_{STR}, amide), 1040 (C–O–C_{STR}, ether), 640 cm^{-1} (C–Cl_{STR}); NMR: δ_H (C^2HCl_3) 1.8–2.2 (CH_2–CH_2, m, 4H), 2.2 (CH_3CO, s, 3H), 3.5 (CH_2–N, t, 2H), 3.75 (CH_2–O, d, 2H), 4.25 (CH, m, 1H), 5.4 ppm (O–CH_2–Cl, s, 2H); EI-MS: *m/z* 191/3 (1%, $M^{+\cdot}$), 156 (13%, $[M-Cl]^+$), 126 (28%, $[M-ClCH_2O^{\cdot}]^+$), 112 (95%, $[M-{}^{\cdot}CH_2OCH_2Cl]^+$), 70 (100%, $[M-(CH_2C{=}O+{}^{\cdot}CH_2OCH_2Cl)]^+$) and 36/38 (20%, HCl^+).

(1S, 2R, 5S)-(+)-Menthyl chloromethyl ether ***7***. Prepared from (1*S*,2*R*,5*S*)-(+)-menthyl MTM ether (0.54 g, 2.5 mmol). Yield: 0.47 g (91%) as a clear liquid. $[\alpha]_D^{20}$ +31° (*c* = 1.0, $CHCl_3$); IR: ν_{max} (thin film) 1115 (C–O–C_{STR}, ether), 640 cm^{-1} (C–Cl); NMR: δ_H (C^2HCl_3) 0.7–2.3 (CH_3, CH_2 and CH, 18H), 3.55 (CH–O, dt, 1H), 5.55 ppm (O–CH_2–Cl, s, 2H); NMR: δ_C (C^2HCl_3) 15–48 (9 signals from the menthyl unit), 78.97 (CH–O), 81.2 ppm (O–CH_2–Cl).

Reagents ***13*** *and* ***14****: acyl chlorides*

(S)-(+)-Tetrahydro-5-oxo-2-furancarbonyl chloride ***13***. Acid **8** (5 g; 0.038 mol) was heated with oxalyl chloride (6.71 ml; 0.077 mol) in dry benzene (10 ml) at 60–70°C for 5 h. Benzene and excess oxalyl chloride were removed under vacuum and the residual oil was distilled under vacuum (110–120°C/0.2 mmHg (lit. [36] 76–82°C/0.02 mmHg)) to yield 4.97 g (87%) of **13** as a clear oil; $[\alpha]_D^{20}$ +4.0° (*c* = 2, $CHCl_3$); IR: ν_{max} (thin film) 1800 (C=O_{STR}, lactone and acid chloride), 1170 and 1140 (C–O), 970 and 910 cm^{-1} (C–Cl); NMR: δ_H (C^2HCl_3) 2.3–2.8 (CH_2–CH_2, m, 4H), 5.1 ppm (CH, m, 1H); EI-MS: *m/z* 148/150 (1.2%, $M^{+\cdot}$), 85 (100%, $[M-{}^{\cdot}COCl]^+$), 36/38 (13%, HCl^+).



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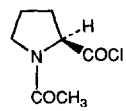

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N-Acetyl-(S)-(−)prolyl chloride ***14***. (S)-(−)-Proline (4 g; 0.035 mol) was dissolved in 2 *M* NaOH (15 ml). The stirred solution was cooled in ice while acetic anhydride (20 ml) was added dropwise. The reaction was left to stand for 18 h before acidifying with 2 *M* H_2SO_4. The product was extracted into chloroform (2 × 150 ml) which was then dried ($MgSO_4$). After filtering, the solvent was removed by rotary evaporation. Ethyl acetate (40 ml) was added to the residue and the white crystalline product was filtered then washed with cold ethyl acetate. The product was dried in an oven at 40°C yielding 3.61 g (66%) of N-acetyl-L-proline as a white solid. M.p. 116–118°C (lit. = 118°C [37]). $[\alpha]_D^{20}$ −101° (*c* = 2.0, H_2O) [commercial N-acetyl-L-proline $[\alpha]_D^{20}$ −100° (*c* = 2.0, H_2O)]. Lit. [37] $[\alpha]_D^{20}$ = −115° (*c* = 2.0, H_2O); IR: ν_{max} (KBr disc) 3600–2300 (O-H_{STR}, acid), 1720 (C=O_{STR}, acid) and 1600 cm^{-1} (C=O_{STR}, amide); NMR; δ_H (C^2HCl_3) 2.1 (CH_3CO, s, 3H), 1.8–2.3 (CH_2–CH_2, m, 4H), 3.5 (N–CH_2, m, 2H), 4.4 (CH, dt, 1H) and 8.5 ppm (COOH, s, 1H); NMR; δ_C (C^2HCl_3) 22.0/22.8 and 24.6 (CH_2–CH_2), 28.7 (CH_3CO), 46.6/48.3 (CH_2–N), 59.3/60.4 (CH), 171.7 and 173.6 ppm (C=O, acid and C=O, amide); EI-MS: *m/z* (probe) 157 (2%, $M^{+\cdot}$), 113 (28%), 112 (25%, $[M-{}^{\cdot}COOH]^+$), 85 (16%), 70 (100%, $[M-({}^{\cdot}COOH + CH_2CO)]^+$), 43 (63%, CH_3CO^+).

To a stirred solution of N-acetyl-(S)-(−)-proline

(1.56 g, 10 mmol) in dry, ethanol-free dichloromethane (40 ml) was added dropwise thionyl chloride (2.3 g, 20 mmol). The reaction was stirred for 1 h at room temperature before removing the solvent and excess thionyl chloride under vacuum. The N-acetyl-(S)-(−)-prolyl chloride product was a light orange viscous oil with a yield of 1.83 g (104%) indicating that some thionyl chloride was still present (trapped in the oil). IR: ν_{max} (thin film) 1798 (C=O_{STR}, acid chloride) and 1650 cm^{-1} (C=O_{STR}, amide); NMR: δ_H (C^2HCl_3) 1.8–2.4 (CH_2–CH_2, m, 4H), 2.15 (CH_3CO, s, 3H), 3.65 (–CH_2–N, dt, 2H) and 4.75 ppm (CH, t, 1H); NMR: δ_C 21.8/22.3 and 24.5 (CH_2–CH_2), 28.8/31.2 (CH_3CO), 47.0/48.0 (–CH_2–N), 67.3/69.1 (CH), 170.3 and 173.5 ppm (C=O, amide and C=O, acid chloride); EI-MS: *m/z* 139 (18%, $[M-HCl]^{+\bullet}$), 112 (48%, $[M-{}^{\bullet}COCl]^+$) 70 (100%, $[M-(CH_2CO+{}^{\bullet}COCl)]^+$), 43 (22%, CH_3CO^+) and 36/38 (3:1, 5%, HCl^+).

General derivatization procedures for the secondary alcohols

*Homochiral iodides **1** and **2** as reagents*

The $Hg(BF_4)_2$ reagent was prepared from yellow mercury(II) oxide according to a literature method [38]. A solution of alkan-2-ols (0.5 mmol) and the iodide (1 mmol) in dichloromethane (2 ml) were added to dry mercury(II) tetrafluoroborate (0.19 g; 0.5 mmol). The mixture was stirred for 2 h at room temperature before being treated with 3 *M* potassium hydroxide until basic [31,32]. The regenerated mercury(II) oxide was filtered off and the organic layer was separated and dried before undergoing GC and GC–MS analyses.

*Homochiral chloromethyl ethers **3**–**7** as reagents*

To a solution containing alkan-2-ols (0.125 mmol) in dichloromethane (0.5 ml) under an argon atmosphere was added diisopropylethylamine (80 mg, 0.62 mmol) and one of the chloromethyl ethers (0.377 mmol) in dichloromethane (0.5 ml). The mixture was allowed to react for 5 h before taking a sample (0.2 ml). The solvent was removed from the sample (argon gas) and the product was extracted from hydrochloric acid (2 ml of a 0.5 *M* solution) into ethyl acetate (1 ml). After washing with water and drying, the sample underwent GC–MS and/or GC analysis.

*Homochiral acyl chloride **13** as reagent*

Derivatizations with (*S*)-(+)-tetrahydro-5-oxo-2-furancarbonyl chloride followed a literature method [39]. The alkan-2-ol (0.14 mmol) was added to pyridine (80 μl) and the mixture was stirred and cooled to 0°C. A 2 *M* solution of acid chloride **13** in dichloromethane (100 μl; 0.2 mmol) was added and the reaction mixture was allowed to warm to room temperature. Two drops of 1 *M* hydrochloric acid solution was added followed by hexane (2 ml). The layers were separated and the organic phase was dried by passing through anhydrous magnesium sulphate. This solution was then analysed directly by GC and GC–MS. The mass spectrum for the product obtained from heptan-2-ol contained the following diagnostic ions: EI-MS: *m/z* 229 $[M+H]^+$, 213 $[M-{}^{\bullet}CH_3]^+$, 185 $[M-C_3H_7]^+$, 157 $[M-C_5H_{11}]^+$, 143 $[M-C_6H_{13}]^+$ and 85 $[M-{}^{\bullet}COOC_7H_{15}]^+$.

*Homochiral acyl chloride **14** as reagent*

To N-acetyl-(*S*)-(−)-prolyl chloride (0.35 g, 2 mmol) in toluene (15 ml) was added the alkan-2-ol mixture (27 mg, 0.25 mmol). The reaction was stirred at room temperature for 1 h. A 1-ml sample was taken and the solvent was removed. Ethyl acetate was added and the sample washed with water. This was dried ($MgSO_4$) and filtered, then analysed by GC and GC–MS.

RESULTS AND DISCUSSION

Extent of the derivatization reactions

The derivatization of alkan-2-ols [RCH(OH)-CH_3] with the homochiral chloromethyl ethers **3**–**7** and with the two acyl chlorides **13** and **14** proceeded rapidly, with little or none of the alkanol analytes remaining at the end of the stated reaction time. In the presence of mercury(II) tetrafluoroborate, the same alcohols reacted with the iodide reagents **1** and **2** to a much lesser extent. Even after extending the reaction time from 2 to 24 h, yields were typically 10% in our hands. Whilst GC separation of the resulting diastereoisomeric ethers was successful (see below), the low yield of this reaction undermines its application. Detection limits of the method would be poor and kinetic resolution could occur, leading to erroneous results.

TABLE I

SEPARATION FACTORS (α) AND RESOLUTION VALUES (R_s) FOR DIASTEREOISOMERIC DERIVATIVES OF OCTAN-2-OL

t_R = Retention time; NR = Not resolved; * = not sufficiently resolved to calculate R_s.

Derivatizing agent	t_R (min)	α	R_s
1[a]	10.02/10.22	1.021	1.57
2[b]	16.28/16.73	1.028	1.10
3[c]	19.41/19.76	1.019	1.36
4[d]	23.77/24.20	1.019	1.25
5[e]	17.50/17.71	1.012	*
6[f]	14.41/14.55	1.010	*
7[g]	13.37	NR	NR
13[h]	10.71	NR	NR
14[i]	12.20/12.90	1.060	1.73

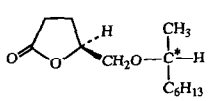
[a] BP-1, 12 m × 0.22 mm I.D. fused-silica column with 0.25 μm film thickness [80°C (2 min) to 220°C (at 10°C min^{-1})].
[b] BP-5, 12 m × 0.33 mm I.D. fused-silica column with 0.5 μm film thickness (isothermal 103°C). In this case the somewhat better separation factor of 1.036 was obtained with a BP-20 column (12 m × 0.32 mm I.D., 0.5 μm film thickness at 93°C).
[c] DB-1701, 30 m × 0.25 mm I.D. fused-silica column with 0.2 μm film thickness (isothermal 180°C).
[d] DB-1701 column as above[c] but isothermal 130°C.
[e] BP-5 as above[b] but isothermal 113°C.
[f] FFAP-CB 25 m × 0.32 mm I.D. fused-silica column with 0.3 μm film thickness (isothermal 200°C).
[g] BP-5 as above[b] but 120 to 220°C (at 5°C min^{-1}).
[h] The result shown is for the heptan-2-ol derivatives chromatographed on the BP-1 column[a]. Various temperature programs and columns were tried but separation was not achieved. The octan-2-ol derivatives have been reported to be inseparable on all but very polar columns [39].
[i] BP-5 column as above[b] but isothermal 170°C.

Separations of the diastereoisomeric derivatives

Undoubtedly, quantitative application of any of the reagents prepared in this study would require further purification to remove traces of the unwanted enantiomer. However, for the initial assessment of the efficiency of each "homochiral" reagent, the compounds were used without such purification. To illustrate results that are typical for alkan-2-ols, the case of octan-2-ol is described first.

The diastereoisomers produced from racemic octan-2-ol after derivatization with each of the various reagents were analysed by GC and/or by GC–MS. The results, giving both the separation factors (α) and resolutions (R_s), are summarized in Table I. In each case, the results shown are for separations obtained under conditions that were optimized in terms of stationary phase and column temperature.

Baseline separations were achieved for the ethers resulting from reaction of octan-2-ol with iodides **1** and **2**, and near-baseline separations resulted from derivatization with chloromethyl ethers **3** and **4**. Typical chromatograms are shown in Figs. 3 and 4b for the derivatives **15** and **16** arising from the furan-based reagents **1** and **3**, respectively. The elution order for the octan-2-ol diastereoisomeric derivatives was determined by separate analysis of commercially available, enantiomerically pure (*R*)- and (*S*)-octan-2-ols. MS confirmed the identity of the separated diastereoisomers. For each pair of diastereoisomers, **15** and **16**, the two EI spectra were virtually identical (Figs. 5 and 6, respectively).



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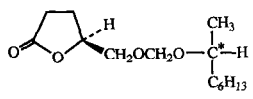

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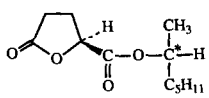

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It is noteworthy from Table I that the chloromethyl ether derived from menthol, **7**, failed to give a separation when reacted with alkan-2-ols, and that the lactate-derived reagent **5** and proline-based reagent **6** barely caused the resulting diastereoisomers to separate by GC. On the other hand, the proline-based acyl chloride, **14**, produced esters from racemic octan-2-ol that were well separated, whereas the furan-based acyl chloride, **13**, did not induce resolution of the corresponding diastereoisomeric esters, **17**, on the columns tested. This latter observation is in agreement with literature [39] that suggests that diastereoisomers produced from the reagent **13** only separate on very polar stationary phases. This behaviour of the diastereoisomeric esters, **17**, should be contrasted with that of the diastereoisomeric ethers, **15**, derived from reagent **1**. The ethers **15** are well separated even on a non-polar

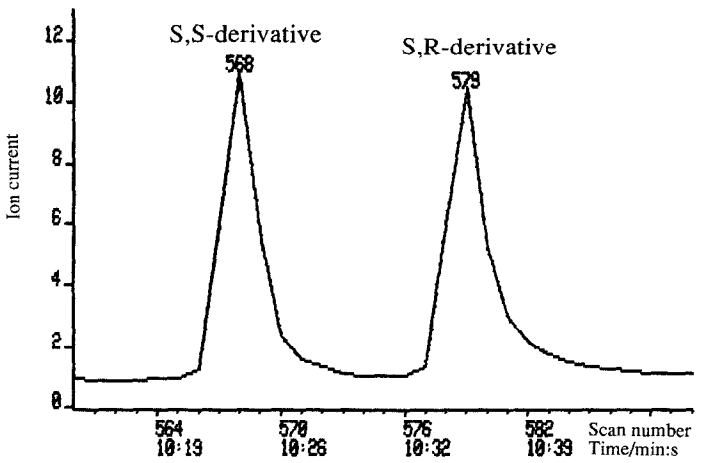
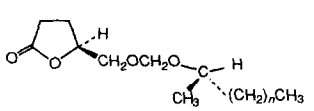


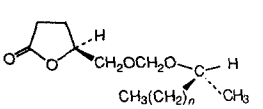
Fig. 3. Part of the total ion current chromatogram obtained by GC–MS after reacting reagent **1** with racemic octan-2-ol to give diastereoisomers **15**. The diastereoisomer from (*S*)-octan-2-ol eluted before that from the (*R*)-isomer. GC conditions: 12 m × 0.22 mm I.D. BP-1; film thickness, 0.25 μm; column temperature, 80–220°C at 10°C min^{-1}.

BP-1 column. Presumably, when the COO ester functionality of **17** is replaced by a CH_2O group in **15**, the reduction in polarity favours separation on less polar stationary phases.

These results are typical for a range of alkan-2-ols. It is instructive to examine the separation factors and resolutions across a range of alkan-2-ols following reaction with one of the homochiral derivatizing agents because it was generally observed that separation improved with increasing chain-length. For example, Table II shows the separations obtained for $CH_3(CH_2)_nCH(OH)CH_3$ (n = 2–5) after derivatization with chloromethyl ether **3** on a DB-1701 column at different temperatures, such that all five alkan-2-ol derivatives elute in the range 9.77–9.97 min. Notably, at a fixed retention time, the resolution (R_s) of the diastereoisomers increases markedly with increasing carbon chain length. The same trend, of slight increases in α and large increases in R_s with increasing chain length, was noted following derivatizations with acyl chloride reagent **14**, (+)-*trans*-chrysanthemoyl chloride [40] and chloromethyl ethers **4** and **5**. For example, at a constant retention time, the separation factors and resolutions of the diastereoisomeric (+)-*trans*-chrysanthemate esters [6] of racemic alkan-2-ols analysed on an SE-30 column (33 m × 0.25 mm) were: hexan-2-ol, α = 1.022, R_s = 0.79; heptan-2-ol, 1.036, 1.23; octan-2-ol, 1.041, 1.52 [40]. Such improvements in resolution with increasing carbon chain length may be rationalized by considering the structures of the compounds, say, **18**. It is assumed that the two hydrophobic chains in a given pair of diastereoisomers (*i.e.* the CH_3 and the $(CH_2)_nCH_3$ group) interact with the non-polar stationary phase and are involved in the chiral recognition mechanism. Then, the greater the dissimilarity of the two groups (*i.e.* as n increases), the more easily the stationary phase is able to differentiate them, and so the greater is the separation of the diastereoisomeric pair. Thus, when n = 0, structures **18a** and **18b** are identical molecules, but as n increases, the binding sites are increasingly able to differentiate a methyl group and a larger chain. This is reflected by the increase in the resolution values, as observed in Fig. 7, showing data from Table II in graphical form. The trend is most marked amongst the lower alkan-2-ol homologues. As the carbon chain length continues to increase, increasing n by one among the higher homologues gives little extra potential for molecular



18a



18b

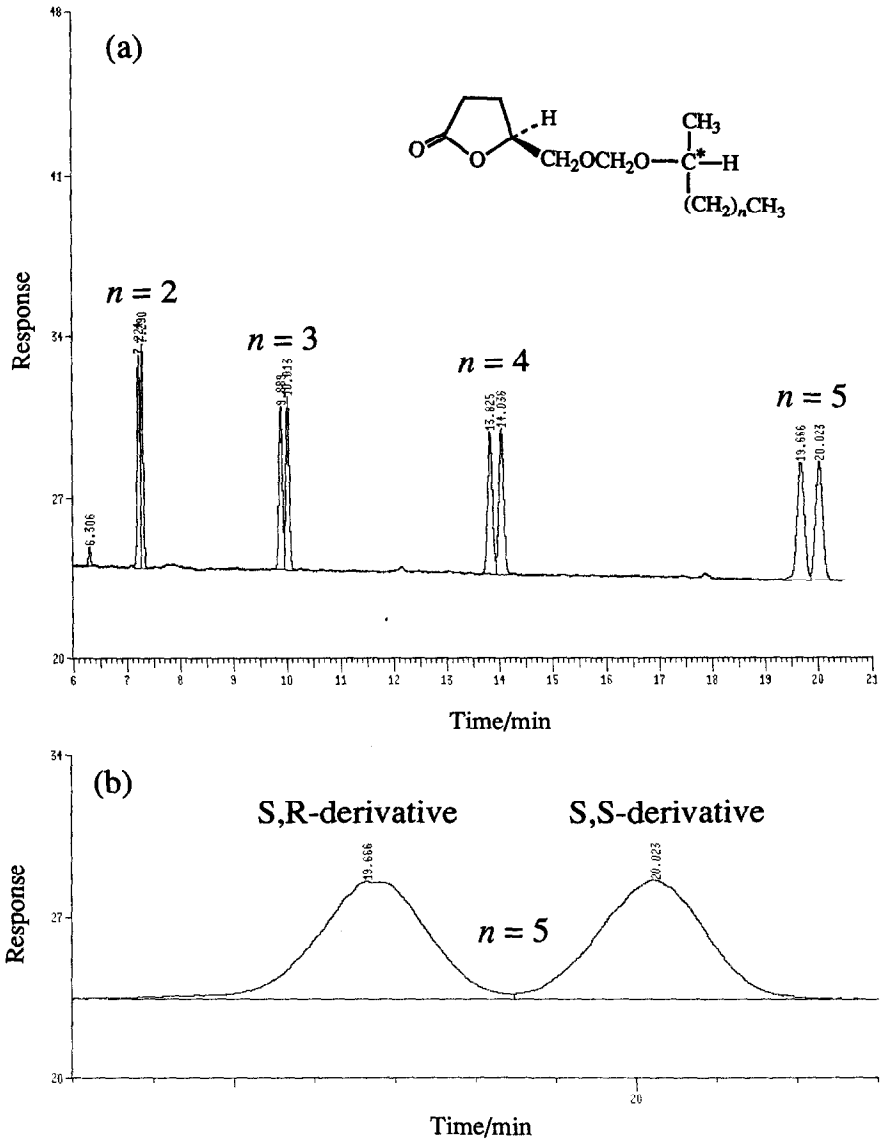


Fig. 4. (a) Chromatogram showing the GC resolution of a mixture of racemic pentan-2-ol, hexan-2-ol, heptan-2-ol and octan-2-ol after derivatization with chloromethyl ether **3**. (b) Close-up of the same chromatogram showing the separation of the enantiomers of octan-2-ol as diastereoisomeric derivatives, **16**. The diastereoisomer from (*R*)-octan-2-ol eluted before that from the (*S*)-isomer. GC conditions: 30 m × 0.25 mm I.D. DB-1701; film thickness, 0.25 μm; column temperature, 180°C.

recognition by the binding site. Hence, the resolution values would be expected to become almost constant with larger values of *n*. Accordingly, Fig. 7 shows a levelling off of the resolution values consistent with this hypothesis. The view that such diastereoisomers are separated most effectively when there is a large difference in size between the two hydrophobic chains receives strong support from the (+)-*trans*-chrysanthemate esters of heptan-2-ol and heptan-3-ol. On an SE-30 column, the R_s value for the diastereoisomeric derivatives of heptan-2-ol, where the stationary phase must differentiate C_1 and

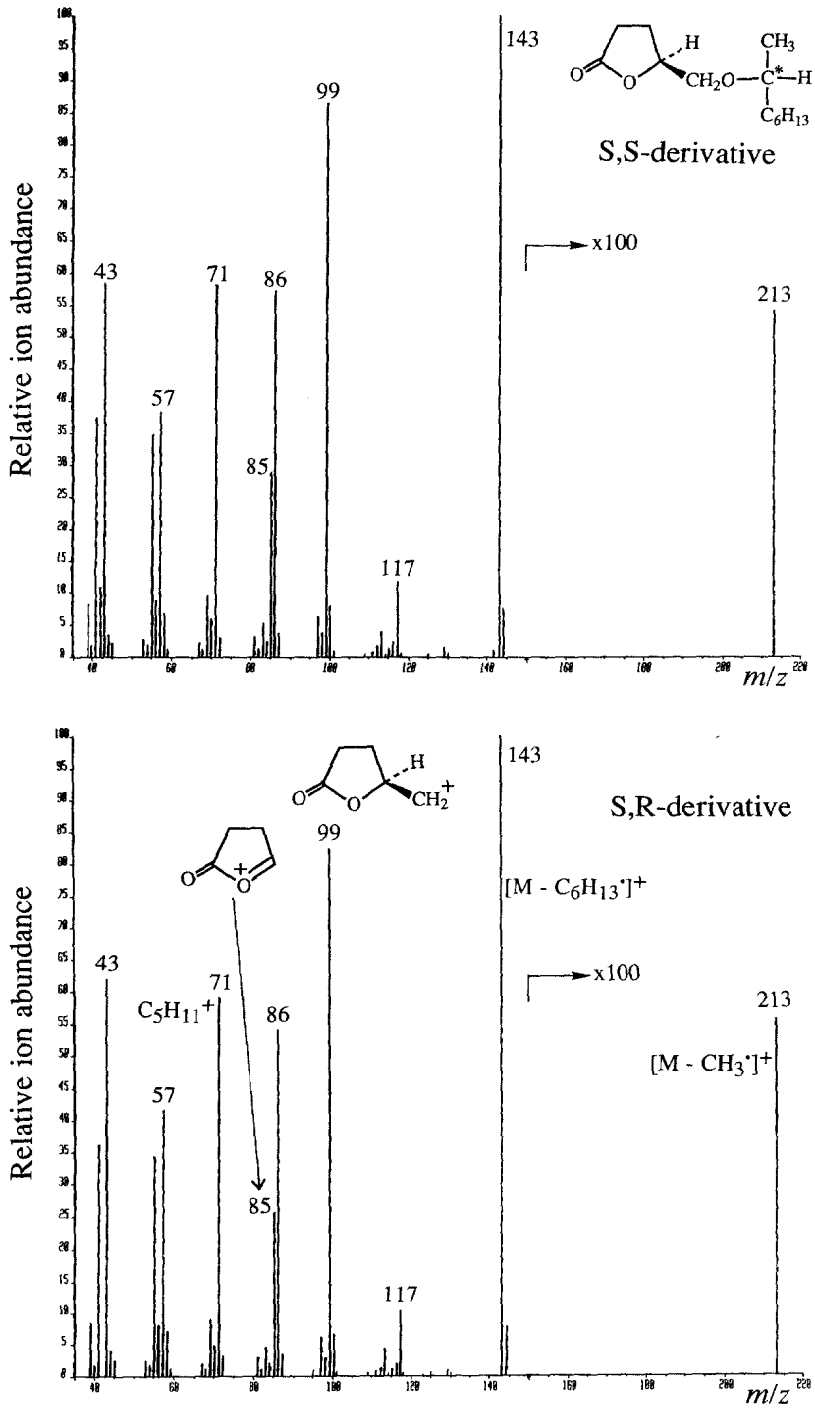


Fig. 5. EI Mass spectra of the resolved diastereoisomers from octan-2-ol, **15**. Top: *S,S*-isomer; bottom: *S,R*-isomer of derivative **15**.

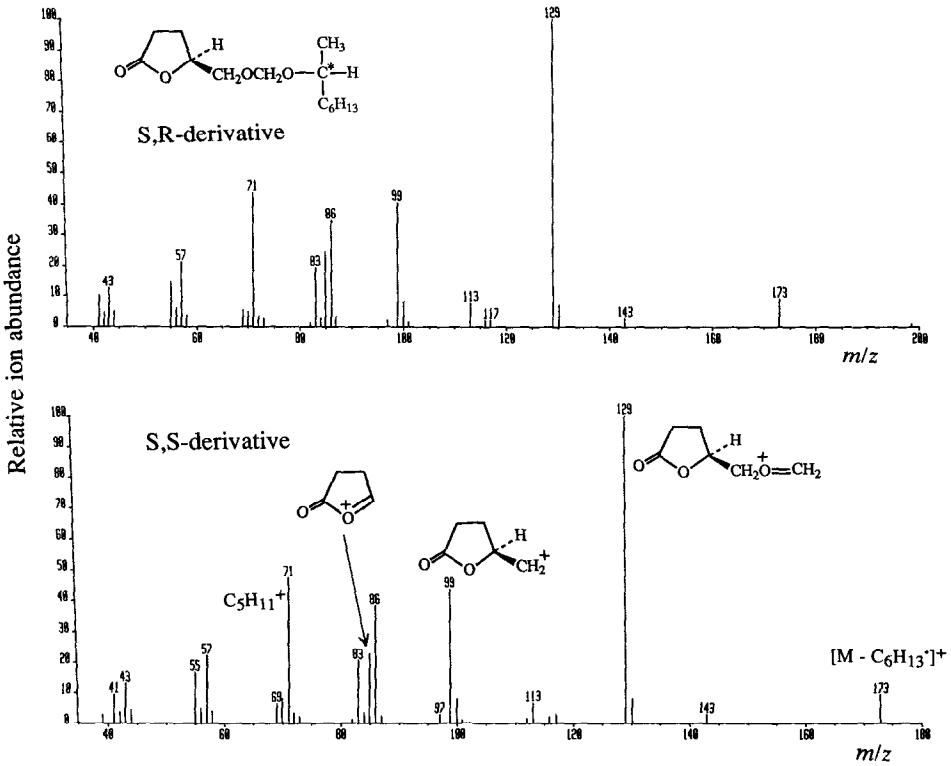
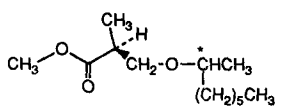


Fig. 6. EI Mass spectra of the resolved diastereoisomers from octan-2-ol, **16**. Top: *S,R*-isomer; bottom: *S,S*-isomer of derivative **16**.

C_5 chains, was measured to be 2.5 times greater than that of the heptan-3-ol derivatives, where the more demanding differentiation of C_2 and C_4 chains is required [40]. The dependence of separation factors on the relative bulk of side-chains in diastereoisomers has been noted previously (see, for example, ref. 41).

Another interesting trend becomes apparent when the octan-2-ol derivatives from reagents **2**, **5** and **4** are compared. The structures of the products (**19**, **20** and **21**, respectively) are similar except for the number of bonds between the chiral centre derived from the original analyte and that from the homochiral reagent in the resulting diastereoisomers. The number of bonds separating the chiral centres is 3, 4 and 5, respectively. Separation factors for these derivatives on a range of stationary phases are given in Table III. It would be expected that diastereoisomers with fewer bonds between chiral centres would be separated more efficiently. In fact, it has been assumed that diastereoisomers with 4 or more bonds between the chiral centres are indistinguishable by gas chromatography [1,3,42]. This concept is not compatible with the differences in the separation



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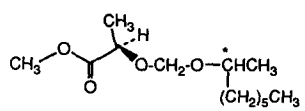

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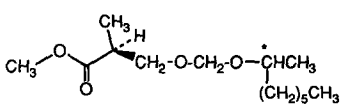

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TABLE II

RETENTION TIMES AND R_s VALUES FOR THE DIASTEREOISOMERIC DERIVATIVES **18** FOR A RANGE OF ALKAN-2-OLS FOLLOWING DERIVATIZATION WITH CHLOROMETHYL ETHER, **3**

These analyses were performed on a DB-1701 fused-silica column (30 m × 0.25 mm; 0.2 μm film thickness).

Alcohol	n	Oven temp. (isothermal, °C)	t_R (min)	R_s
2-Pentanol	2	170	9.77/9.88	0.77
2-Hexanol	3	180	9.77/9.90	0.93
2-Heptanol	4	190	9.84/9.97	1.00
2-Octanol	5	200	9.77/9.89	1.04

efficiencies shown in Table III. As expected, the best separations across the range of stationary phases were obtained for derivatives **19**, with three bonds between chiral centres, but the diastereoisomers with 5 bonds between chiral centres (**21**) were separated to a greater extent than those containing 4 bonds between the chiral centres (**20**). This result may be explained if it is assumed that interactions between the chiral centres are significant to the separation mechanism. This fits with the theory that generally the fewer bonds between the chiral centres, the closer their proximity, the greater their interactions and the greater is the separation of the diastereoisomers. However, if more distant chiral centres can be brought into close proximity by intramolecular interactions then separations could also be improved. In other words, chiral centres that have a large through-bond distance could take up conformations that bring them close through space. It is likely that the chiral centres of diastereoisomers **21**, with 5 bonds between them, can approach closer in space than the chiral centres of diastereoisomers **20**, with only 4 bonds between them. This may lead to stronger interactions in products **21** than in products **20**. However, the relevance of any such conformations at the high temperatures experienced in GC and in the presence of an interactive stationary phase are unclear.

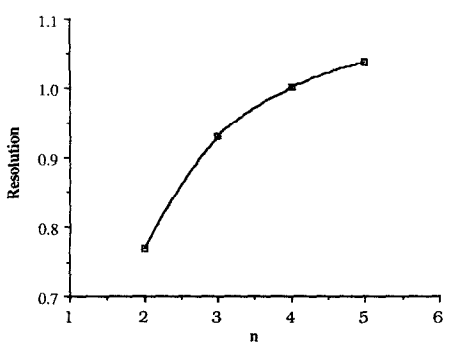

Fig. 7. The variation of GC resolution with carbon chain length for diastereoisomeric derivatives, **18**. See structures **18** for definition of n. When $n = 2$, the original analyte was pentan-2-ol; $n = 3$, hexan-2-ol; $n = 4$, heptan-2-ol; $n = 5$, octan-2-ol. The GC column used was coated with DB-1701, and the column temperature was adjusted in different analyses so that each had approximately the same retention time.

TABLE III

THE α VALUES FOR DIASTEREOISOMERS **19**, **20** AND **21** RESULTING FROM DERIVATIZATION OF OCTAN-2-OL WITH REAGENTS **2**, **5** AND **4**, RESPECTIVELY

Retention times (min) are given in parentheses, and the isothermal column temperatures on a range of different columns are also stated. NR = Not resolved.

Diastereoisomers	α		
	BP-1[a]	BR-5[b]	BP-20[c]
19	1.026 (18.15/18.62) 105°C	1.028 (16.28/16.73) 103°C	1.036 (18.72/19.40) 93°C
20	NR (19.25) 115°C	1.012 (17.50/17.71) 113°C	NR (17.38) 115°C
21	1.012 (15.86/16.06) 130°C	1.018 (16.79/17.09) 125°C	NR (19.45) 123°C

[a] 12.5 m × 0.32 mm, 1.0 μm film thickness.
[b] 12 m × 0.33 mm, 0.5 μm film thickness.
[c] 12 m × 0.32 mm, 0.5 μm film thickness.

CONCLUSIONS

Some new homochiral derivatizing agents have been prepared and initial investigations suggest that (*S*)-(−)-tetrahydro-5-oxo-2-furanmethyl iodide **1**, (*S*)-(+)-tetrahydro-5-oxo-2-furanmethyl chloromethyl ether **3**, and (S)-(+)-2-methylcarboxypropyl chloromethyl ether **4** are the most promising reagents. To be useful, conditions for the complete reaction of iodide **1** with nucleophilic analytes have

yet to be found. Chloromethyl ethers **3** and **4** are highly reactive electrophiles under very mild conditions so their reactions with alcohols go rapidly to completion, thus avoiding the potential effects of kinetic resolution. Being very reactive, these reagents may be applicable to a broad range of chiral nucleophilic analytes. When reacted with alkan-2-ols, the resulting diastereoisomers have five bonds between chiral centres. This could be considered a disadvantage, unlikely to allow resolution by GC [1,3,42]. However, good resolutions have been observed and these are superior to those achieved with diastereoisomers with similar structures but having four bonds between chiral centres.

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