Kinetic Resolution of 1,2-Diols with D-Camphorquinone; Preparation of (*R*)-(Chloromethyl)oxirane

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Acid-catalysed reaction of D-camphorquinone with racemic 1,2-diols (*e.g.* 3-chloropropane-1,2-diol) under kinetically controlled conditions yields a predominant diastereoisomeric acetal, that can be easily converted into an optically pure epoxide.

(*R*)- and (*S*)-(Chloromethyl)oxirane ['epichlorohydrins' (**1a**) and (**1b**), respectively] are valuable starting materials for the preparation of optically active compounds. Both have been prepared by rather lengthy routes from D-mannitol.[1] Because *rac.*-3-chloropropane-1,2-diol is a cheap starting material, we have sought to prepare either epoxide (**1a**) or (**1b**) by kinetic resolution[2] of this diol, *via* a derivative that can be converted directly into the epoxide.

In principle, the reaction of a racemic 1,2-diol ($RCHOH\text{-}CH_2OH$) with one enantiomer of a chiral ketone (R^1COR^2) will generate four diastereoisomeric products (**2a**)—(**2d**), two from each enantiomer of the diol. The interactions between R and R^1, and between R and R^2, will govern the proportion of each diastereoisomer under conditions of both kinetic and thermodynamic control. Clearly one diastereoisomer must predominate to permit its efficient separation, ideally by direct crystallisation.

Reaction of either (*R*)- or (*S*)-propane-1,2-diol[3] with D-camphor in refluxing benzene or toluene containing toluene-*p*-sulphonic acid catalyst gave *ca.* 1:1 mixtures of

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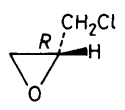
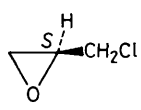

(1a)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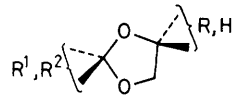
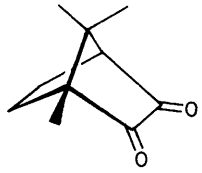

(2a)-(2d)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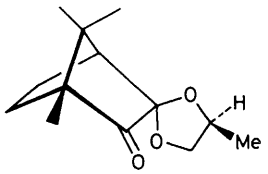
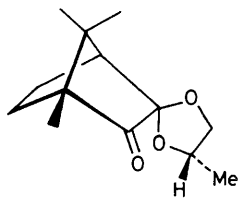

(4a)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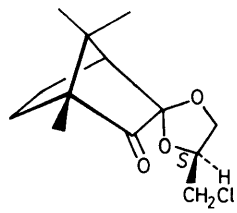
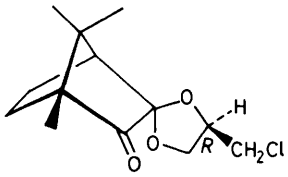

(5a)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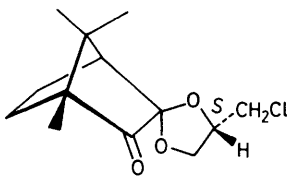
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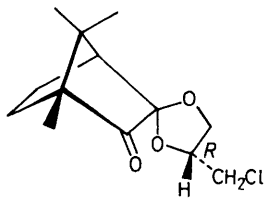
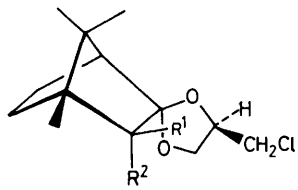

(5d)


(6a) R^1 = H, R^2 = OH
(6b) R^1 = OH, R^2 = H

diastereoisomeric acetals. Corey treated D-(−)-butane-2,3-diol with *rac.*-camphor and separated the derived acetals by g.l.c.[4] However, acid-catalysed reaction of (*S*)-propane-1,2-diol with D-camphorquinone[5] (**3**) in refluxing benzene gave a 4:1 mixture of diastereoisomeric acetals (**4a**) and (**4b**), from which the predominant one could be easily crystallised, m.p. 35—37 °C. When this acetal was heated in toluene (105 °C; 96 h) it yielded a 2:3 ratio of (**4a**) and (**4b**). Likewise, the acid-catalysed reaction of (*R*)-propane-1,2-diol with D-camphorquinone in refluxing benzene gave a 4:3 mixture of the corresponding diastereoisomeric acetals. We suggest that the acetals produced in refluxing benzene are products of kinetic control, whereas equilibrium mixtures are obtained at 105 °C in toluene.

We have found that an excess of *rac.*-3-chloropropane-1,2-diol reacts with D-camphorquinone (**3**) in refluxing benzene containing a catalytic quantity of toluene-*p*-sulphonic acid‡ to give a kinetically controlled mixture of the diastereoisomers (**5a**)—(**5d**) in yields of 27, 45, 17, and 12%, respectively, determined by h.p.l.c. The major diastereoisomer could be readily separated by fractional crystallisation (from 40/60 petroleum spirit), and all four diastereoisomers were completely separated in one pass through a preparative h.p.l.c. column [Whatman Partisil M20: 10/50 (50 cm × 22 mm i.d.), elution with 2% (v/v) ethyl acetate in hexane]. When acetal (**5b**) was heated in toluene (103 °C; 96 h) containing a catalytic quantity of toluene-*p*-sulphonic acid it equilibrated with the acetal (**5d**) (ratio 1:1 at equilibrium). Thus the acetals (**5b**) and (**5d**) have the same chirality at C bearing a chloromethyl group. The structural assignments made for acetals (**5a**)—(**5d**) are additionally based on careful analysis of their 400 MHz ^{1}H n.m.r. spectra.

The acetal (**5b**) is a source of (*R*)-3-chloropropane-1,2-diol and (*R*)-(chloromethyl)oxirane. The acetal was not readily hydrolysed, but after reduction ($NaBH_4$ in ethanol) to give the alcohols (**6a**) and (**6b**), (*R*)-3-chloropropane-1,2-diol {55% based on starting acetal, $[\alpha]_D^{19}$ −7.4° (*c* 1 in water), lit.[6] $[\alpha]_D^{20}$ +7.3° (*c* 1 in water) for the (*S*)-isomer} was liberated on treatment of the mixture of alcohols with 2 M HCl in methanol (3 h reflux).

Treatment of the acetal (**5b**) with 48% HBr in acetic acid[3] (60 °C; 5 h) gave a mixture of camphorquinone and (*S*)-2-acetoxy-1-bromo-3-chloropropane. This mixture was treated with 1.2 M sodium ethane-1,2-diolate in ethane-1,2-diol (1 mol. equiv. of $NaOCH_2CH_2OH$) to give (*R*)-(chloromethyl)oxirane (**1a**) that was distilled directly from the reaction mixture: 58% based on acetal (**5b**). The epoxide (**1a**) was chemically and optically pure by ^{1}H n.m.r. spectroscopy {no enantiomer detected after addition of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(−)-camphorato]europium(III)} and gave $[\alpha]_D^{24}$ −33° (*c* 1.5 in MeOH), comparable with the highest literature values[1] [−34.3° for (*R*)-isomer, +33° (*c* 1.126 in MeOH) for (*S*)-isomer].

The method described is convenient for the preparation of optically active epoxides from readily available racemic diols, when alternative methods (*e.g.* Sharpless epoxidation;[7] derivation from the 'chiral pool'[8]) are not directly applicable.

‡ Acetal (**5b**): a stirred solution of D-camphorquinone[4] (0.6 mol), *rac.*-3-chloropropane-1,2-diol (2.86 mol), and toluene-*p*-sulphonic acid (0.052 mol) in benzene (1 750 cm^3) was boiled for 18 h in a flask connected to a Dean–Stark apparatus. The solvent was removed (rotary evaporator) to give a yellow liquid that was suspended in water (1 000 cm^3). The resulting aqueous mixture was extracted with 40/60 petroleum spirit (3 × 500 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated to yield a yellow oil. This was dissolved in petrol–ethyl acetate (7:1) and was filtered through silica gel to give a colourless oily mixture of acetals (**5a**)—(**5d**). The mixture crystallised on standing and was recrystallised repeatedly from 40/60 petroleum spirit to afford acetal (**5b**) as a colourless crystalline solid (9.4%), m.p. 75.5—76.5 °C (starts to sublime at 61 °C), $[\alpha]_D^{22}$ + 90° (*c* 2 in CCl_4).

New compounds gave spectroscopic (^{1}H and ^{13}C n.m.r.; electron impact mass; i.r.) and analytical data in accord with the assigned structure.

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