SHORT PAPER

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Stereospecific oxygen rearrangement in the reduction of optically pure methyl mandelate to phenylethanol isomers†

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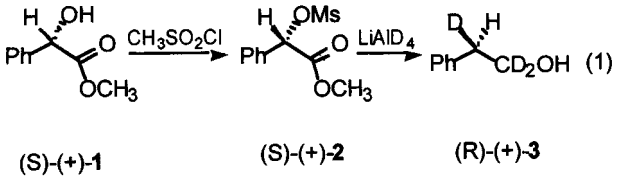
The reduction of methyl (S)-(+)-mandelate, **1**, produces the expected 2-phenylethanol, **3**, and the unexpected optically pure 1-phenylethanol, **6**, by a stereospecific oxygen atom metathesis; which occurs through a styrene oxide intermediate, whose concentration varies with solvent polarity.

Our continuing studies on stereoselective enzymatic reactions[1] required the synthesis of the enantiomerically pure substrate (R)-2-phenylethanol-1,1,2-d_3 (PhC*HDCD$_2$OH), **3**. Our simple, two step synthetic pathway shown below, (equation(1)), followed a slightly modified literature procedure.[2] However, after distillation (95 °C, 2 torr) of the reaction product **3**, the value of the measured optical rotation not only deviated substantially from that reported[3] in the literature ($[\alpha]^{25}_D$ +1.44), but also had a negative sign.

Surprised by this unexpected finding we studied the reaction further and we would like to propose the structure of an optically active minor product, as well as a mechanism that clarifies these unexpected results.



A careful GC analysis of the direct reduction of mesylate (S)-(+)-**2** with $LiAlD_4$ (equation (1)) showed that the desired product (R)-(+)-2-phenylethanol-1,1,2-d_3, **3**, was accompanied by another product of shorter retention time. This minor product was formed in 4–10% yield, depending on the reaction conditions. The optical rotation of the reaction mixture varied from $[\alpha]_D$ –1.6° to $[\alpha]_D$ +1.1°, depending on the purity of the sample. It appeared therefore that the product obtained by the above synthesis was contaminated by a small amount of strongly rotating material. By preparative GC we isolated the side product in pure form. This minor product was optically active, having a sign of rotation that was opposite of that of the major product (R)-(+)-**3**. ^{1}H-NMR, MS and GC analysis showed that the minor product was 1-phenylethanol-2,2,2-d_3, **6**. Comparison to an authentic sample prepared by the Grignard coupling of benzaldehyde and CD_3MgI, confirmed the structure of the compound. The optical rotation of the pure 1-phenylethanol-2,2,2-d_3, **6** [purified with a 20% Carbowax 20M (10′ × 3/8″) preparative column] was found to be $[\alpha]^{25}_D$ = –43.96° (c 26 g/100 ml, $CDCl_3$), a value that is similar to that reported[3] for the non-deuterated analogue (S)-(-)-1-phenylethanol, $[\alpha]^{25}_D$ = -44.1° (l 0.1 dm, neat). This result indicates that reduction of (S)-(+)-**1** through its mesylate derivative (S)-(+)-**2** affords, apart of the major (R)-(+)-**3** product, the (S)-(-)-1-phenylethanol-d_3 , **6,** stereospecifically. In a control experiment, a chiral capillary GC analysis of the reduction of 55% ee methyl (R)-(-)- O-mesyl-mandelate, **2**, (derived from mesylation of 55% ee methyl (R)-(-)-mandelate) with $LiAlH_4$, showed, apart from the signal that corresponds to the major 2-phenylethanol product, two additional signals in the ratio 75:25, that correspond to the two enantiomers of the 1-phenylethanol minor product. Assignment of the major signal (75%) to the (R)-(+) enantiomer and the minor (25%) to the (S)-(-) enantiomer of 1-phenylethanol was easily accomplished by chiral capillary GC and comparison of their retention times with those of the racemic mixture of 1-phenylethanol and that of authentic (S)-(-)-1-phenylethanol (92% ee, Sigma Co.), as shown in Fig. 1.

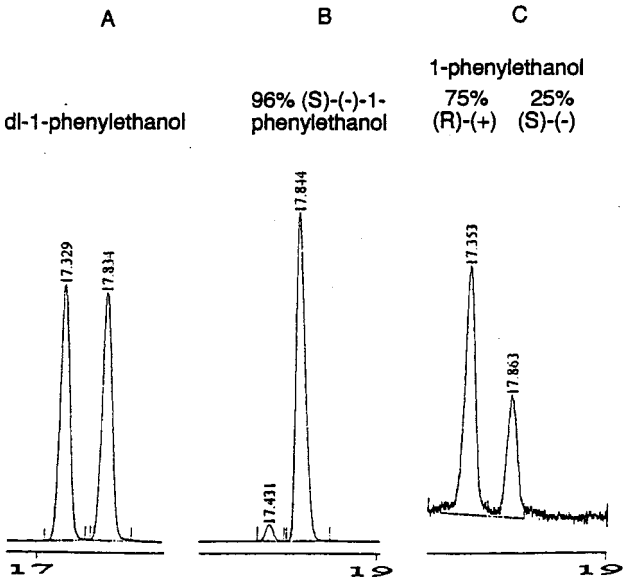


Fig. 1 Chiral capillary column GC analysis of **A**: racemic 1-phenylethanol; **B** commercially available 96% (S)-(-)-1-phenylethanol (Sigma Co.); **C**: minor reduction products (R)-(+)- and (S)-(-)-1-phenylethanol from 55% ee methyl (R)-(-)-mandelate.

These results further confirm the high stereoselectivity of the rearrangement of the oxygen during the reduction of **2** with $LiAlH_4$, since the enantiomeric ratio of the reduction products (S)-(-)- and (R)-(+)-1-phenylethanol-d_0 matches closely (50% ee) that of the initial enantiomeric purity (55% ee) of the starting methyl mandelate. We want to emphasize that the reduction of (R)-(-)-**1** affords (R)-(+)-1-phenylethanol-d_0 whereas that of the (S)-(+)-**1** enantiomer yields (S)-(-)-1-phenylethanol-d_0 Therefore, the optical purity of the starting material shows up in the enantiomeric ratio of the reduction products. It is interesting to note that, when a

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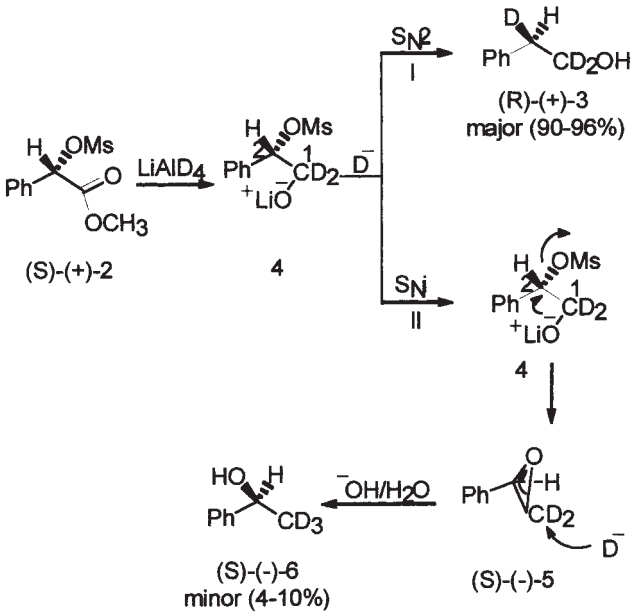
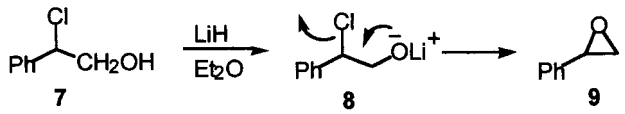
limited amount of the reducing agent $LiAlH_4$ is used, variable amounts of styrene oxide-depending on the solvent-are detected by GC analysis. For example, in THF or diethyl ether, 3–4% of styrene oxide was detected, whereas in diglyme, the amount of styrene oxide increased up to 11%. A mechanism consistent with these results is shown below.



Scheme 1

Two equivalents of D^- from $LiAlD_4$ are required to reduce the ester group and to form the polar intermediate **4** as the lithium salt. To this intermediate , an S_N2 nucleophilic attack of deuteride D^- on the C-2 carbon that bears the mesylate leaving group affords the major product (R)-(+)-**3**, with inversion of configuration (route I). However, this pathway competes with the intramolecular S_Ni attack of the negatively charged oxygen on the carbon bearing the mesylate leaving group, leading to the formation of intermediate **5** (route II). This pathway proceeds stereospecifically and produces enantiomerically pure styrene oxide of the (S) configuration as a stable intermediate. Subsequent opening of the styrene oxide[5] by deuteride produces the minor product (S)-(-)-**6** with overall inversion of configuration. Because of the change of substituent priority at the stereogenic centre in going from reactant **2**, to product **6**, the sign of configuration (S), remains the same. Because of the small specific rotation of 2-phenylethanol-1,1,2-d_3 ($[\alpha]^{25}_D$ +1.44 for the non-deuterated analogue), product (R)-(+)-**3**, and the large specific rotation of the 1-phenylethanol-2,2,2-d_3 {$[\alpha]^{25}_D = -43.96^o$ (c 26, $CDCl_3$)}, (S)-(-)-**6**, small quantities of enantiomerically pure 1-phenylethanol dramatically affect not only the value but also the sign of **3**. Therefore, the sign and the magnitude of the measured optical rotation of **3**, depend on the amount of the strongly rotating side product **6**. To further secure the above proposed mechanism, 2-chloro-2-phenylethanol, **7**, was treated with an equimolar amount of lithium hydride in ether. After solvent reflux for several hours, styrene oxide was formed as the only product.



This experiment shows that intermediate **8** undergoes, as expected, the same reaction as the structurally similar intermediate **4** (Scheme 1), and leads to the exclusive formation of styrene oxide **9**. In this case, however, the intermediate does not react further with the lithium hydride to produce 2-phenylethanol, because LiH is a weaker nucleophile than $LiAlH_4$, and chlorine is a poorer leaving group than mesylate.

In conclusion, we have shown that reduction of optically active methyl (S)-(+)-mandelate produces apart of the major product 2-phenylethanol, the (S)-(-) enantiomer of 1-phenylethanol, stereospecifically. However, the opposite enantiomer methyl (R)-(-)-mandelate produces also exclusively the (R)-(+) enantiomer of 1-phenylethanol, as the minor product. This interesting stereospecific oxygen rearrangement proceeds via the intermediacy of styrene oxide which subsequently leads to the minor product 1-phenylethanol, and is responsible for the ironic optical measurements of the major product (R)-2-phenylethanol-1,1,2-d_3 (PhC^*HDCD_2OH). These findings are useful for this and other structurally related reactions.

Experimental

Instrumentation and Materials: Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker MSL 300 MHz spectrometer and all data are reported in parts per million (δ) downfield from (Me_4Si). GC analyses were carried out on a Hewlett Packard 5890 series II Gas Chromatograph equipped with a chiral column (20% permethylated B-cyclodextrin, 30m × 0.25mm ID), and the preparative work on a Varian aerograph series 2700 equipped with a 20% Carbowax 20M (10′ × 3/8″) column. Mass spectra were recorded on a Hewlett Packard GC–MS (5971A MS detector). Rotations were recorded as neat liquids or as solutions by using 3.5 × 10 and 3.5 × 50mm cells with fixed end plates on a Jasco DIP-360 digital polarimeter. All reactions were performed under a dry nitrogen atmosphere in flame-dried glassware. THF and diethyl ether were freshly distilled from sodium/benzophenone under a dry nitrogen atmosphere.

Methyl (S)-(+)-mandelate: The standard method for esterification was followed. To a 150 ml flask , fitted with a drying tube and magnetic stirrer , were added 15 ml of methanol , 25 g (164 mmol) of (S)-(+)-mandelic acid, 98% ee, $[\alpha]^{25}_D$ –153°, (Aldrich Co.) and catalytic amounts of para-toluenesulfonic acid. The solution was stirred over a period of 10 hours and then poured into a saturated solution of sodium dicarbonate. The product was extracted several times with ether and the combined ether extracts were dried over $MgSO_4$. The solvent was removed by rotary evaporation to leave 22 g (80%) of the desired ester (m.p. 53–55 °C). $[\alpha]_D$ 172.4° (CH_3OH, c 7.0), 97.5% ee.[3] ^1H NMR ($CDCl_3$) δ 3.7 (s, 3H), 5.20 (s, 1H) , 7.42 (s, 5H).

Methyl (S)-(+)-O-mesyl-mandelate: The title compound was prepared according to the general procedure reported by Crossland and Servis.[6] To 150 ml CH_2Cl_2 were added 22g (132 mmol) of methyl (S)-(+)-mandelate, 14.96 g (148 mmol) of triethylamine, and 16.48 g (144 mmol) of methanesulfonyl chloride. The product was obtained in 96% yield (31 g) and recrystallized from a 1:1 dichloromethane/pentane solvent mixture, m.p. 115–117°C, $[\alpha]_D$ +133.6° (c 6.0, $CDCl_3$). ^1H NMR ($CDCl_3$) δ 3.11 (s, 3H), 3.83 (s, 3H), 6.06 (s, 1H), 7.59 (s, 5H).

(R)-(+)-1,1,2-trideuterio-2-phenylethanol: To 200 ml of dry THF, were added 4.19 g (100 mmol) of $LiAlD_4$ (Aldrich 99% D) and 26 g (106 mmol) of methyl (S)-(+)-O-mesylate of mandelate. The product was isolated in 80% (10.2 g) yield after distillation at 95 °C at 2 torr. GC analysis on 20% Carbowax 20 M (10′ × 3/8″) column showed that this product was a 9:1 mixture of 1,1,2-trideuterio-2-phenylethanol and 2,2,2-trideuterio-1-phenylethanol. The two optically active alcohols were isolated by using the same column. The alcohol with the shorter retention time that had an $[\alpha]_D$ –43.96° (c 26, $CDCl_3$) was the (S)-(-)-2,2,2-trideuterio-1-phenylethanol [lit $[\alpha]_D$ –44.1° (l 0.1 dm, neat) for the corresponding protio alcohol][3]. The second product, 1,1,2-trideuterio-2-phenylethanol (major isomer), had an $[\alpha]_D$ +0.42° after the first isolation by preparative GC. After the second purification through the same column, an $[\alpha]_D$ +1.13° (l 0.5 dm, neat) was obtained. The maximum rotation of (R)-(+)-1,1,2-trideuterio-2-phenylethanol that has been reported[3a] is $[\alpha]_D$ +1.44°. For identification purposes 2,2,2-trideuterio-1-phenylethanol was prepared by the Grignard reaction of CD_3MgI and benzaldehyde. Both this alcohol and the minor product showed identical MS and ^1H NMR spectra. ^1H NMR ($CDCl_3$) δ 1.84 (s, broad, –OH), 4.92 (s, broad, 1H), 7.28–7.40

(m, 5H). MS: *m/z* 125 (M+1), 107, 79, 77., ^{1}H NMR of (R)-(+)-1,1,2-trideuterio-2-phenylethanol (major product) ($CDCl_3$) δ 2.30 (s, –OH), 2.75 (s, broad, 1H), 7.25(s, 5H).

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