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The Application of [1]H Nuclear Magnetic Resonance Spectroscopy for the Determination of the Absolute Configuration of Chiral Carboxylic Acids

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Abstract: A modification of a model, described by Mosher, allows a correlation to be made between the absolute configuration of a range of simple chiral carboxylic acids with the corresponding nmr chemical shifts of their esters derived from (S)-methyl mandelate. Copyright © 1996 Elsevier Science Ltd

Introduction

Our interests in the synthesis of chiral carboxylic acids for micelle / liposome formation and their subsequent utility in the areas of drug delivery, enantiomeric resolution and as vectors for gene transfer into mammalian cells led us to investigate methods for determining not only the enantiomeric purity of compounds made but also their absolute stereochemical configuration. The applications of chiral derivatising agents (CDAs) for the determination of enantiomeric purity has been recently reviewed.[1] Of particular relevance to our investigations was the the use of nuclear magnetic resonance spectroscopy for the determination of the optical purity for a range of chiral alcohols and amines.[2] In this particular method a mixture of enantiomers was first converted into a mixture of diastereomers by reaction with a chiral reagent under non-racemizing conditions. The ratio of the diastereomers, as determined by measurement of the integrals of the corresponding proton nmr spectrum, was then equated to the ratio of the original enantiomeric mixture.

An empirical correlation was subsequently described relating the configuration and the nmr chemical shift for a range of mandelate, O-methyl mandelate and α–methoxy-α–trifluoromethylphenylacetate (MTPA) derivatives of alcohols and amines.[3] Additional evidence in support of this correlation has also been forthcoming from other laboratories.[4] Mosher additionally provided a useful conformational model to equate the nonequivalence between functional groups of the diastereomers. In the MTPA model both the carbinyl hydrogen

atom, derived from the alcohol functionality, and the α-trifluoromethyl group, derived from MTPA, are eclipsed with the carbonyl group, and lie in a common plane. The stereodifferentiation between the substituents R_1 and R_2 will thus depend upon their position, relative to the corresponding aromatic ring, with those protons that eclipse the aromatic ring experiencing an anisotropic shielding effect and will thus resonate upfield compared to the comparable protons of the diastereomer. According to the Mosher model, in the "Newman projection" of the preferred conformation in which the ester linkage is omitted (**Fig. 1a**), one group, R_2, eclipses the aromatic ring and the corresponding chemical shift will occur upfield compared to R_2 of the diastereomer which eclipses an OMe group. Likewise the proton, represented by R_1, eclipse the methoxy group and will thus resonate downfield compared to those protons (R_1) of the diastereomer which eclipse the aromatic ring. The versatility of this model has also been demonstrated by Trost [5] who investigated its applications with the O-methyl mandelate esters derived from a more diverse range of chiral alcohols (**Fig. 1b**).
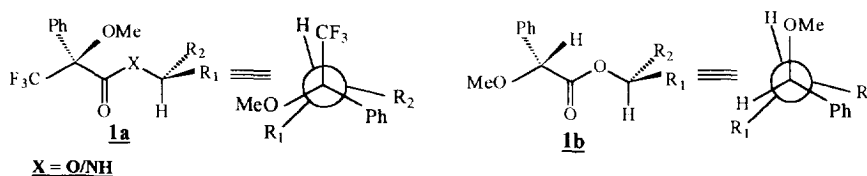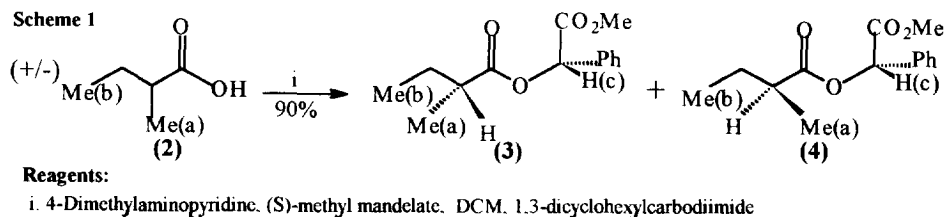

X = O/NH

Figure 1. To illustrate the preferred conformation of derivatives, the Mosher model describes an" extended Newman projection" in which the ester/amide linkage is omitted .

Results and Discussion

Although the use of S-methyl mandelate [6] for the determination of the absolute configuration of α–deuteriated primary carboxylic acids has been investigated,[7] few other examples of the use of this methodology in the determination of the absolute configuration of chiral carboxylic acids have appeared in the literature.[1]

The sense of nonequivalence for the derivatives of interest was readily demonstrated by analysis of the ^{1}H nmr of the diastereomeric esters (**3**) and (**4**) obtained from the treatment of a racemic mixture of 2-methylbutyric acid (**2**) with (S) - methyl mandelate under non-racemizing conditions (**Scheme 1**).

Scheme 1

Reagents:
  i. 4-Dimethylaminopyridine, (S)-methyl mandelate, DCM, 1,3-dicyclohexylcarbodiimide

Analysis of the ^{1}H nmr spectrum obtained from a mixture of the diastereomers (**3**) and (**4**) (**Fig. 2**) revealed that the signal attributed to the methyl groups, $Me_{(a)}$, appeared as a pair of doublets centred at chemical shifts of

δ 1.22 and δ 1.17 ppm, and a chemical shift difference (Δδ H_{R-S}) of 0.05 ppm, whereas the methyl groups, $Me_{(b)}$, appeared as a pair of triplets centred at a chemical shift of δ 0.97 and δ 0.89 ppm, with a corresponding chemical shift difference of 0.07 ppm.
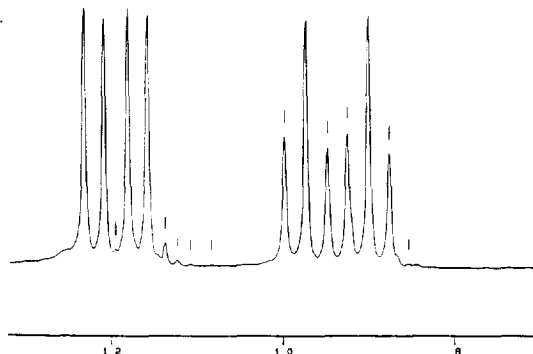

Figure 2. Part of the 300 MHz nmr spectrum of the diastereomeric esters derived from reaction of racemic 2-methylbutyric acid with (S)-methyl mandelate to show the nonequivalence of the methyl groups Me(a) and Me (b)

In order to determine which of the resonances were representative of the S-S isomer and which for the R-S isomer the esterification reaction was repeated with the acid component being enriched with an excess of either the (R) or of the (S) enantiomer.[8] The relevant regions of the ^{1}H nmr spectra are shown (**Fig. 3**) for the derivatives obtained by reaction of (+/-)-2-methylbutyric acid and (S)-methyl mandelate enriched with varying amounts of the (S)-acid.
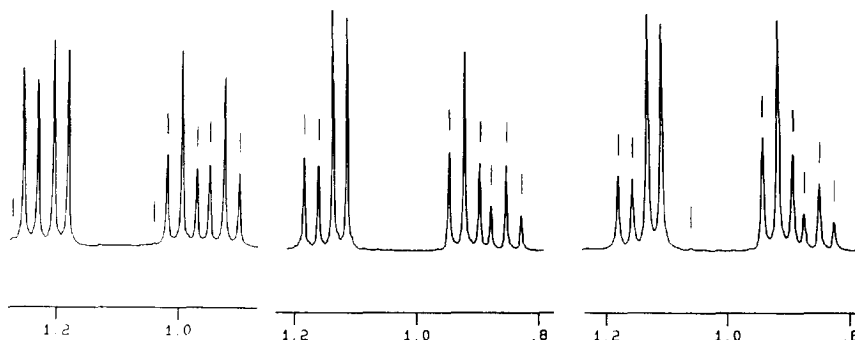

Figure 3. Part of the 300 MHz nmr spectrum of the esters derived from the reaction of racemic 2-methylbutyric acid with (S)-methyl mandelate enriched with 16%, 33% and 50% respectively of the (S)-acid.[9]

Although we did not anticipate any changes in chemical shift differences with increasing amounts of the enriching species the relationship was investigated.[9] Our results show that upon addition, of up to 50%, of the enriching species there was no significant change in the chemical shift differences (Δδ H_{RS}) for the nmr signals derived from $Me_{(a)}$, 0.05 ppm (15 Hz), and for $Me_{(b)}$, 0.07ppm (22Hz), thus illustrating the applicability of the methodology to our investigations.

From the spectra it can be seen that for the two sets of doublets, attributed to Me $_{(a)}$, the downfield signal is representative of the (R-S)-diastereomer whereas the upfield signal is representative of the (S-S)-diastereomer. A similar analysis for the resonances centred at δ 0.9 ppm, attributed to Me$_{(b)}$, may also be undertaken. Thus the downfield signal is representative of the (S-S)-diastereomer whereas the less intense upfield triplet must be representative of the (R-S)-diastereomer.

Having observed this pattern of nonequivalence between the two methyl groups (Me$_{(a)}$ and Me$_{(b)}$) in the diastereomeric esters we investigated the generality of this phenomenon with a range of chiral carboxylic acids. The synthesis of chiral acids, that were not commercially available, was achieved in high enantiomeric purity using Evans chiral oxazolidinone auxiliary **(5)** [10] shown in **(Scheme 2)** which illustrates its use in the synthesis of (R)-(-)-2-benzylpropionic acid **(8)**.

As expected the alkylating group always enters from the less shielded face of the enolate , that is, from

Scheme 2
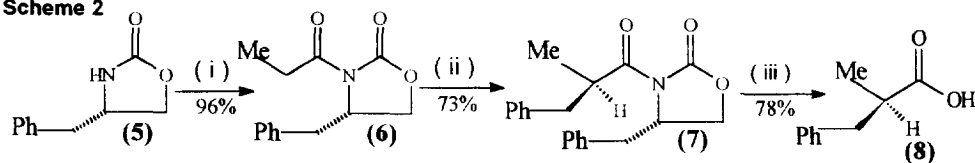
Reagents:
i. nBuLi, propionyl chloride, ii. LDA, benzyl bromide, iii. hydrogen peroxide, LiOH.

the side opposite to the bulky substituent of the chiral oxazolidinone auxiliary. Independent support for this was obtained by X-ray analysis[11] of the alkylated compound (7) **(Fig. 4)**
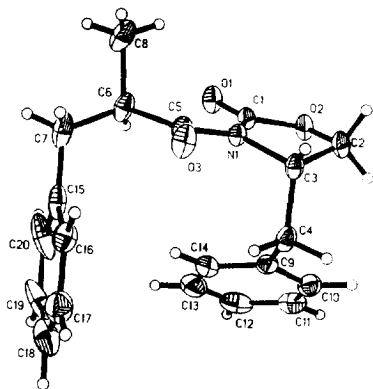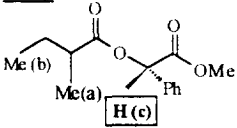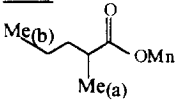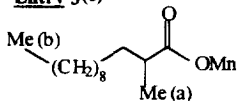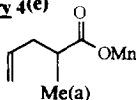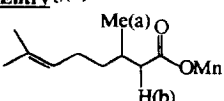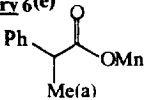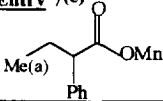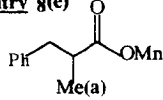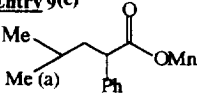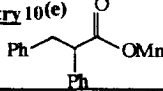

Figure 4.   Molecular structure of compound (7), displacement ellipsoids are shown at the 30% probability level.

The results and observations obtained from these enrichment experiments are shown in **(Table 1)** which show the chemical shift data, ($\Delta\delta$ H$_{RS}$), for both the (S-S)-isomer and the (R-S)- isomer, expressed on both ppm and in hertz (Hz). In addition, independent support for this correlation was obtained by analysis of the chemical shift differences from the proton nmr spectra obtained from the individual diastereomers.These were made using

TABLE 1	^{1}H NMR data for (S)-methyl mandelate derivatives of chiral carboxylic acids

Chemical shift data obtained from enrichment experiments [a]

Entry		S-S isomer		R-S isomer		Δδ H [b]	Δδ H [c]
Entry 1[d]	H(a)	1.19	U	1.24	D	0.05	15
	H(b)	0.99	D	0.92	U	0.07	22.0
	H(c)	5.92	U	5.94	D	0.015	4
Entry 2[e]	H(a)	1.20	U	1.25	D	0.05	15
	H(b)	0.94	D	0.90	U	0.05	14
	H(c)	5.92	U	5.93	D	0.013	4
Entry 3[e]	H(a)	1.20	U	1.24	D	0.04	8
	H(b)	0.88		0.88		0.00	0
	H(c)	5.92	U	5.93	D	0.02	5
Entry 4[e]	H(a)	1.20	U	1.26	D	0.06	16
	H(c)	5.93		5.93		0	0
Entry 5[d]	H(a)	1.001	U	1.008	D	0.008	2
	H(b)	2.51	D	2.45	U	0.06	17
	H(c)	5.93	U	5.94	D	0.006	2
Entry 6[e]	H(a)	1.53	U	1.61	D	0.08	24
	H(c)	5.94	D	5.92	U	0.013	4
Entry 7[e]	H(a)	0.98	U	1.05	D	0.07	20
	H(c)	6.02	D	5.98	U	0.04	11
Entry 8[e]	H(a)	1.19	U	1.27	D	0.08	24
	H(c)	5.93	D	5.90	U	0.03	10
Entry 9[e]	H(a)	0.91	U	0.96	D	0.05	16
	H(c)	5.91	D	5.87	U	0.04	12
Entry 10[e]	H(c)	5.86	U	5.88	D	0.02	6

NOTES : (a) In all cases, except where noted (S)- methyl mandelate was employed, and nmr were run on a Bruker AC-300MHz NMR Spectrometer. (b) Chemical shift differences were calculated by deducting the chemical shift of the downfield signal from the chemical shift of the upfield signal (expressed in ppm) . (c) As for (b) but expressed in hertz. (d) Sample was enriched with (S)-acid derivative by addition of 5 mg of of the (S)-acid to 30 mg of the racemic acid followed by esterification with (S)- methyl mandelate. (e) Sample enriched with (R)-acid derivative as described in (d). U - Upfield resonance. D - Downfield resonance, OMn = (S) - mandelate.

chiral auxiliary technology in order to synthesise the relevant enantiomeric carboxylic acid **(Scheme 2)**.

    From these data an interesting pattern emerges concerning the signals derived from the protons of substituents at the chiral centre of the acid moiety and from the methine proton (Hc) derived from the mandelate moiety. For each entry, the protons labelled Me $_{(a)}$ or H $_{(a)}$ of the (S-S) diastereomer resonate at a higher field compared to the comparable protons derived from the (R-S) diastereomer. This would suggest that there is a preferred conformation for these diastereomeric esters. For example **Fig. 5** shows the (S-S)-diastereomer derived from the esterification of (S)-2-methylbutyric acid with (S)-methyl mandelate **(4)**, and the corresponding Newman projections **(9-11)** of the staggered conformations. Conformation **(9)** clearly shows the methyl group in the vicinity of the aromatic ring whereas in the alternative conformation, **(10)**, both the ethyl and the methyl moieties would be under the anisotropic influence of the aromatic ring additionally steric factors would also suggest that this would be an inappropriate conformation. In conformation **(11)** the ethyl group and not the methyl group is in the vicinity of the aromatic ring.
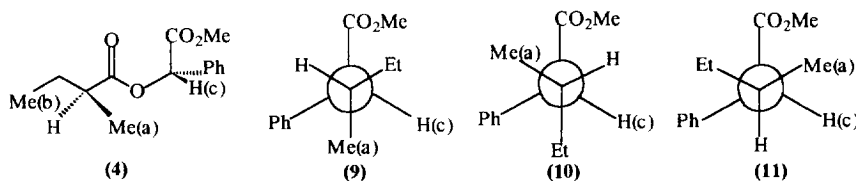

Figure 5 Conformational representations of ester (4)

    Although there are less examples shown, it can be observed that the protons labelled Me $_{(b)}$ or H$_{(b)}$, derived from the (S-S) diastereomer, consistently resonate downfield compared to the comparable protons derived from the (R-S) diastereomer. As one might expect, this effect appears to diminish with increasing length of the carbon chain (entry 3c, **Table 1**).

    For the proton derived from the mandelate moiety, labelled H$_{(c)}$ (entry 1 **table 1**), our results again show an interesting pattern. Thus for entries 1,2,3 & 5, where the acid substituent is an alkyl group, the proton H$_{(c)}$ derived from the (R-S) diastereomer consistently resonates downfield compared to the (S-S) diastereomer. In contrast when the acid substituent contained both an alkyl and either an aromatic or a benzyl substituent, entries 6 to 9, this observation was reversed with the proton H$_{(c)}$, derived from the (S-S) diastereomer, resonating downfield compared to the same proton derived from the (R-S) diastereomer. Interestingly when the acid substituents were both aromatic and benzyllic, entry 10, the pattern previously described was observed with the proton H$_{(c)}$, derived from the (R-S) diastereomer resonating downfield compared to the same proton derived from the (S-S) diastereomer. A possible explanation for these observations may be obtained by reference to the appropriate Newman Projections **(Fig. 6)** of entries 1 and 6, Table 1 which compares the spatial arrangement, around H$_{(c)}$, when the acid moiety has an alkyl **(9)** and an aromatic substituent **(12)**.
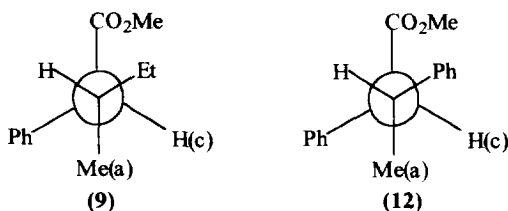
Figure 6 Newman projections of selected esters to show the spatial arrangements of both alkyl and aromatic carboxylic acid substituents.

Upon comparison of projection **(9)** with **(12)** it can be seen that the methine proton $H_{(c)}$ in **(9)** lies in the vicinity of adjacent alkyl groups (Me $_{(a)}$ and Et) and is not close to an aromatic ring. In contrast the corresponding proton $H_{(c)}$ in **(12)** lies in the vicinity of the aromatic ring derived from the acid moiety. This has the effect of shifting that signal downfield compared to the signal for the proton $H_{(c)}$ derived from the diastereomer.

The anisotropic effect of the aromatic ring, present in the mandelate moiety, upon the acid substituents, is offered as an explanation for the chemical shift differences observed between the diastereoisomers. Our results have shown that the presence of an aromatic or a benzyllic group at the chiral centre of the acid component has an influence upon the mandelate moiety, as seen by the changes in the chemical shift of the proton $H_{(c)}$ between the diastereoisomers suggesting a change in the general conformation, as proposed by Dale and Mosher, for these esters. Our investigations into this particular phenomenon are at the present time continuing.

The results and data obtained to date do, however, appear to support the fundamental correlation between the absolute stereochemical configuration and the nmr chemical shifts for this range of carboxylic acid derivatives. As a consequence to these results, it would appear that the mandelate esters derived from chiral acids do conform to the Dale and Mosher model although the corresponding stabilising hydrogen bonding interaction, as originally proposed, is absent.

From the results obtained it is possible to make the following observations:

i)   Significant chemical shift differences occur most consistently for α– chiral substituents,

       compare entry 1 $H_{(a)}$ Δ_δ (R-S) = 0.05 ppm, Δ_δ Hz = 15 for an α-substituent

       with   entry 5 $H_{(a)}$ Δ_δ (R-S) = 0.008 ppm , Δ_δ Hz = 2 for a β- chiral substituent.

ii)   As the carbon chain length of the acid moiety increases, the chemical shift differences decrease, consistent with a diminution in the anisotropic effect with distance.

       Entry   1 Me $_{(b)}$ Δ_δ (R-S) = 0.07 ppm (a 1,3- relationship to chiral centre)

       Entry   2 Me $_{(b)}$ Δ_δ (R-S) = 0.05 ppm (a 1,4- relationship to chiral centre)

       Entry   3 Me $_{(b)}$ Δ_δ (R-S) = 0.00 ppm (a 1,11-relationship to chiral centre)

iii)   The diastereomeric chemical shift difference observed for the carbinyl (methine) proton $H_{(c)}$ (derived from the mandelate moiety) was observed to be small. It was in the region 0.01-0.02 ppm for alkyl

substituents derived from the acid moiety, consistent with observations made by Mosher, however for the corresponding aromatic / benzyllic groups the chemical shift difference tended to be greater, up to 0.04ppm.

Conclusion

Thus in summary we have shown that the use of methyl mandelate esters derived from a range of carboxylic acids provides a method for the correlation of the ^{1}H nmr chemical shift differences between diastereomers to their absolute configuration.

Partial Experimental   General procedures detailed :

- **the synthesis of commercially unobtainable chiral carboxylic acids**

- **the synthesis of the corresponding racemic carboxylic acids**

- **the esterification reaction**

General. All melting points were determined using an Electrothermal digital melting point apparatus and are uncorrected. Measurements of optical rotations were performed with an AA10 automatic digital polarimeter. Mass spectra (MS) were obtained from a Hewlett Packard 5890 Trio 2 and a Hewlett Packard 5890 Gas Chromatograph with a 5971 series (mass select detector) mass spectrometer. Infrared (IR) spectral measurements were carried out using a Perkin Elmer Paragon 1000 FT-IR spectrophotometer. ^{1}H and ^{13}C-NMR spectra were obtained on a Bruker AC300 (300MHz) spectrometer. All resonances detailed are expressed in δ ppm using tetramethylsilane (TMS) in CDCl$_3$ as an internal standard. The following abbreviations were used when assigning resonances: singlet (s), doublet (d), triplet (t), quartet (q), and broad (br). Flash chromatography was performed on silica according to the method of Still [12] using 230-240 mesh silica and reagent grade solvents. Analytical t.l.c. was carried out on Macherey-Nagel SIL G-25 pre-coated plates with flourescent indicator UV$_{254}$ and visualised by shortwave ultraviolet irradiation, immersion in iodine vapours or by heating after immersion in aqueous potassium permanganate. All reactions were carried out under an atmosphere of nitrogen or argon.

* **Synthesis of (R)-(-)-2-benzylpropionic acid (8)**   (entry **8, Table 1**)

Step 1- Synthesis of (4S)-3- (propanoyl)-4-benzyl-2-oxazolidinone. (6)

To a stirred solution of (S)-(-)-4-benzyl-2-oxazolidinone (5) (1g, 5.64 mmol) in anhydrous tetrahydrofuran (10 ml) , under an atmosphere of nitrogen at -78 °C was added n-butyllithium (1.6M, 4.25ml, 6.77mmol) dropwise over a period of one hour. After this period propionyl chloride (0.55ml,6.2mmol) was added dropwise and left to stir until an ambient temperature had been reached. Analysis of the reaction mixture by tlc showed the presence of a new compound (Rf 0.56, ether/petroleum ether, 50:50). The reaction mixture was quenched by the careful addition of a saturated solution of ammonium chloride (25 ml) and the excess THF was removed *in vacuo.*

The residue reaction mixture was extracted with diethyl ether (3 x 20ml) and the combined organic extracts were dried over anhydrous magnesium sulphate, filtered and the solvent removed *in vacuo* to give a white crystalline solid which upon recrystallisation from hexane gave the desired compound 1.27g, 96%. mp. 41.2 °C; IR (KBr): v_{max}: 3030, 2980,1780, 1705, 1455, 1385, 1245, 1210,1080..cm^{-1}; ^{1}H-NMR (300MHz): 1.17-1.22 (3H, t, J=8Hz, CH$_3$), 2.73-2.81 (1H, dd, J= 10Hz, 14 Hz, CH), 2.91-2.98 (2H, q, J=8Hz, CH$_2$),3.28-3.33 (1H, dd, J=4 Hz, 14 Hz, CH), 4.15-4.23 (2H, m, CH$_2$), 4.64-4.70 (1H, m, CH), 7.19-7.36 (5H, m, aromatic). ^{13}C-NMR (75MHz): 8.30 (CH$_3$), 29.21 (CH$_2$), 37.93 (CH$_2$), 55.18 (CH$_2$), 66.22 (CH$_2$), 127.35-129.42 (CH-aromatic), 135.32 (C-R-aromatic), 153.53 (C=O), 174.10 (C=O); m/z: 233 (M$^+$), 142, 91, 51; Found: C, 66.91, H, 6.51, N, 5.98 Calc. for C$_{13}$H$_{15}$ NO$_3$ C, 66.95, H, 6.45, N, 6.01; [α] $_D^{20}$ +92.3 ° (c 1, CHCl$_3$), λ_{max} 259nm.

Step 2- Synthesis of (4S)-3- [(2R)-2-benzyl-propanoyl]-4-benzyl-2-oxazolidinone (7) :

To a stirred solution of (4S)-3-(propanoyl)-4-benzyl-2-oxazolidinone (6) (1g, 4.29mmol) in anhydrous THF (15ml), under an atmosphere of nitrogen at -78°C, was added dropwise lithium diisopropylamide (2M, 2.58ml, 5.15 mmol). The yellow solution was stirred and allowed to reach a temperature of -10°C whereupon benzyl bromide (2.2g, 1.53ml, 12.88mmol) was added and left to stir until the reaction mixture had reached an ambient temperature. Tlc analysis of the reaction mixture showed the presence of a new compound (Rf 0.71, ether/petrol 50:50) . The mixture was quenched by the careful addition of a saturated solution of ammonium chloride (20ml), THF was removed *in vacuo* and the aqueous phase extracted with diethyl ether (3 x 20 ml). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and the solvent removed *in vacuo* to provide a crude product. Purification by flash chromatography on silica (eluant - ether/hexane 50:50) gave the desired product as a crystalline compound (1g, 73%) mp. 92°C; IR (KBr) : v_{max} : 2980,1791, 1706, 1455, 1385, 1245 cm^{-1}; ^{1}H-NMR (300MHz): 1.19-1.21 (3H, d, J=7Hz, CH$_3$), 2.52-2.60 (1H, dd, J= 10Hz, 14 Hz, CH), 2.65-2.72 (1H,dd, J= 8Hz, 14 Hz, CH), 3.05-3.10 (1H, dd, J=4 Hz, 14 Hz, CH), 3.12-3.19 (1H, dd, J=8 Hz, 14 Hz), 4.08- 4.20 (3H, m, CH$_2$ & CH), 4.63-4.70 (IH,m,CH) , 7.04-7.07 (2H, m CH-aromatic), 7.17-7.32 (8H,m, CH- aromatic); ^{13}C-NMR (75MHz): 16.77 (CH$_3$), 37.68 (CH$_2$), 39.58 (CH), 39.90 (CH$_2$) 55.09 (CH), 65.88 (CH$_2$), 126.42-129.39 (C-H-aromatic), 135.17 & 139.20 (C-R aromatic), 153.07 (C=O), 176.55 (C=O); m/z: 323 (M$^+$), 147, 119, 91, 77, 65, 51, 41; Found: C, 73.76, H, 6.57, N, 5.29 Calc.for C$_{20}$H$_{21}$ NO$_3$ C, 74.30, H, 6.50, N, 4.33; [α] $_D^{20}$ +154.6° (c 1, CHCl$_3$); λ_{max} 259nm.

Step 3-Synthesis of (2R)-(-) 2-benzylpropionic acid (8):

To a stirred solution of (4S)-3-[(2R)-2-benzyl-propanoyl]-4-benzyl-2-oxazolidinone (7) (1g, 3.1mmol) in a THF/water mixture (4:1) (20ml) at 0°C was added, dropwise, an aqueous solution of hydrogen peroxide (7 ml of a 35% mixture) and lithium hydroxide (0.52g, 12.4 mmol) dissolved in distilled water (5ml). After an hour the organic solvent was removed *in vacuo* and the resulting aqueous phase was cooled in an ice bath and then acidified by the addition of aqueous hydrochloric acid (6M). The solution was then extracted with ethyl acetate (5 x 20ml), the combined organic phase was dried over anhydrous magnesium sulphate, filtered and the solvent removed *in vacuo* to afford a yellow oil. Purification by flash chromatography on silica eluted with an

ether/hexane mixture (50:50) gave the desired compound (0.4g, 78%) .IR (KBr) : v_{max} : 3420 (OH) 2940, 1693, cm^{-1}; ^{1}H-NMR (300MHz): 1.19-1.21 (3H, d, J=7Hz, CH$_3$), 2.66-2.73 (1H, dd, J= 8Hz, 14 Hz, CH), 2.86-2.97 (1H, m, CH), 3.07-3.13 (1H, dd, J=6 Hz, 14 Hz, CH), 7.20-7.34 (5H, m, aromatic), 11.46 (1H,b, OH), ^{13}C-NMR (75MHz): 16.51 (CH$_3$), 39.29 (CH$_2$), 41.28 (CH), 126.47-129.04 (C-H-aromatic), 182.68 (C=O); m/z: 164 (M$^+$), 100, 91; [α] $^{20}_{D}$ -23.1° (*c* 1, CHCl$_3$).

* Synthesis of (+/-)-2-benzylpropionic acid:

Step 1- Synthesis of diethyl-2-benzyl-methylmalonate:

To a cooled solution of sodium ethoxide, prepared from the dissolution of sodium metal (1.62g, 70.4 mmol) in dry ethanol (70ml) was added freshly distilled diethyl malonate (12.87g, 73.9 mmol) and left to stir for about thirty minutes whereupon benzyl bromide (12.04g, 8.4ml, 70.4 mmol) was added and the mixture heated to a reflux temperature for about two hours. After this period the mixture was cooled , residual ethanol was removed *in vacuo* and the residue partitioned between water and ether (3 x 20ml) . The combined organic layers were dried over anhydrous magnesium sulphate, filtered and the solvent removed *in vacuo* to afford the desired compound as an oil (13.2g, 71%). IR (NaCl disc) : v_{max} : 2980, 1740 cm^{-1}; ^{1}H-NMR (300MHz): 1.19-1.25 (6H, t, J=7Hz, 2 x CH$_3$), 1.33 (3H, s, CH$_3$) , 3.23 (2H, s, CH$_2$), 4.14-4.20 (4H, q, J= 7 Hz, CH$_2$), 7.08-7.33 (5H, m, aromatic); ^{13}C-NMR (75MHz): 13.99 (CH$_3$), 19.66 (CH$_3$) 41.09 (CH$_2$), 58.78 (C), 61.23 (CH$_2$), 126.86, 128.14 & 130.19 (C-H-aromatic), 136.22 (C-aromatic) 171.82 (C=O); m/z: 264 (M$^+$), 232, 205,149, 99, 77, 71, 43.

Step 2- Synthesis of (+/-)-2-benzylpropionic acid:

To a solution of potassium hydroxide (5g, 89.3 mmol,) dissolved in water (25ml) was cautiously added diethyl-2-benzyl-methylmalonate (5g, 18.9, mmol) as a vigorous reaction ensued. The reaction mixture was heated to a reflux temperature for about one hour after which the solution was diluted with water (25 ml). The remaining ethanol was removed *in vacuo* and the residue was cooled in ice whereupon concentrated sulphuric acid (5 ml) was added and the reaction mixture again heated to a reflux temperature. After about one hour the mixture was cooled to an ambient temperature and partitioned with diethyl ether (3 x 25 ml), the combined organic extracts were dried over anhydrous magnesium sulphate and the solvent removed *in vacuo* to afford an oil. Purification by flash chromatography on silica eluted with an ether/petrol mixture (50:50) gave the title compound (2.3g, 74.2%). IR (NaCl disc) : v_{max} : 3420 (OH) 2940, 1693 cm^{-1}; ^{1}H-NMR (300MHz): 1.18-1.20 (3H, d, J=7Hz, CH$_3$), 2.65-2.72 (1H, dd, J=8 Hz, 14 Hz, CH), 2.75-2.87 (1H, m, CH), 3.04-3.10 (IH, dd, J=6 Hz,14 Hz, CH) 4.2 (1H ,b, OH) 7.16-7.32 (5H, m, aromatic); ^{13}C-NMR (75MHz): 16.27 (CH$_3$), 39.96 (CH$_2$) 40.34 (CH), 125.78, 128.04 (aromatic) 182.68 (C=O); m/z: 164 (M$^+$), 130, 91.

** Typical procedure for the esterification reaction under non-racemizing conditions:

Synthesis of methyl-2-(2R-2-benzylpropanoyl)-2S-2-phenylethanoate:

To a stirred solution of (2R)-(-)-2-benzylpropionic acid (8) (0.20g, 1.22 mmol) in dichloromethane (15ml) at -10°C under an atmosphere of nitrogen was added 4-dimethylaminopyridine (7mg), followed by methyl (S)-(+)- mandelate (0.20g, 1.22 mmol) and 1.3-dicyclohexylcarbodiimide (0.25g 1.22 mmol). After three

hours tlc analysis showed the presence of a new compound (Rf 0.67) (ether/petrol 50:50). The suspension was filtered to remove the precipitated urea and the solvent removed *in vacuo* to afford the crude product. Purification by flash chromatography on silica eluted with an ether/hexane mixture (50:50) gave the desired ester as an oil (0.26g, 68%) IR (NaCl disc): v_{max} : 3114, 2940, 1760, 1740, 1630. 1350 & 1100 cm^{-1}; ^{1}H-NMR (300MHz): 1.25-1.28 (3H, d, J=7Hz, CH$_3$), 2.67-2.75 (1H, dd,J=8 Hz, 14 Hz, CH), 2.85-2.98 (1H, m, CH), 3.07-3.13 (1H, dd, J=6 Hz,14 Hz, CH) 3.72 (3H ,s, OMe) , 5.901 (1H,s, CH), 7.15-7.42 (10H, m, aromatic); ^{13}C-NMR (75MHz): 16.74 (CH$_3$), 39.96 (CH$_2$) 41.07 (CH), 52.59 (CH), 74.23 (OMe), 126.34- 129.17 (C-H aromatic), 135.01 and 139.06 (C-R aromatic) 169.33 (C=O), 175.46 (C=O) ; m/z: 312 (M$^+$), 286, 192, 91. $[\alpha]_D^{20}$ +168.3° (c 1,CHCl$_3$)

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8.   As the absolute configuration of the mandelate was known and the chiral acids were either readily available in either enantiomeric form (entries **5,6, & 7** [**Table 1**] , were synthesised in both enantiomeric forms (entries **3,4, 8, 9 10** [table 1] or the (R)-enantiomer only was synthesised (entries **1,2** [table 1]), the signals for the major component must be representative of either the R-S diastereomer or of the S-S diastereomer.

9.   The samples were prepared by addition of 5mg, 10mg and 15mg respectively of the (S)-acid to 30mg of the racemic acid. As well as investigating the effect of the concentration of chiral acid present during the enrichment experiments we have demonstrated that the chemical shift difference between resonances was not dependent upon the amount of sample present during the experiment. Routinely spectra were

carried out using a 2%- 3% solution of the sample in $CDCl_3$ (probe temperature of 23° C), analysis of the spectra obtained from 4%, 4.5% and 5% solutions (up to a two and a half fold increase of sample) showed that there was no concentration dependence upon the chemical shift difference..

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11.   **Crystal data:** $C_{20}H_{21}NO_3$, M = 323.38. Monoclinic. space group $P2_1$, a = 6.296(1), b = 14.927(2), c = 9.293(1)Å , ß = 104.95(1)°, V = 843.8(2) Å^3. Z = 2, Dc = 1.273 Mg m^{-3}. F(000) = 344, μ = 0.085 mm^{-3}, λ(Mo-K$_\alpha$) = 0.7107Å.

The crystal used for data collection was a colourless needle with the approximate dimensions 0.61 x 0.29 x 0.23mm. Unit cell parameters were determined by least squares refinement of the optimised setting angles of 26 reflections in the range $10 < 2\theta < 24°$. Intensity data for 1861 reflections were measured on a Siemens P4 diffractometer at 190K using an ω scan method. The reflections were corrected for Lorentz and polarisation effects to yield 1481 independent reflections (R_{int} = 0.0234). The structure was solved by direct methods using the program SHELTL-pc[1] and refined by full-matrix least squares on F^2 using the program SHELXL93[2]. All hydrogen atoms were included in calculated positions (C-H = 0.96Å) with refined isotropic displacement parameters. All non-hydrogen atoms were refined with anisotropic displacement parameters. Final cycles of refinement gave $R1$ = 0.0385, $wR2$ = 0.0951 for all data. $R1 = \Sigma||Fo| - |Fc||/\Sigma|Fo|$, $wR2 = [\Sigma w(Fo^2-Fc^2)^2/\Sigma w(Fo^2)^2]^{1/2}$, $w = 1/[\sigma^2(Fo^2) + (0.0483P)^2 + 0.09P]$ and $P = [max(Fo^2, 0) + 2Fc^2]/3$. The maximum and minimum electron densities in the final ΔF map were 0.13 and -0.14 e Å^{-3} respectively.

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