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Epoxidation with Dioxiranes derived from 2-Fluoro-2-substituted-1-tetralones and -1-indanones.

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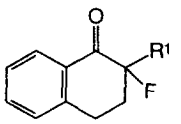
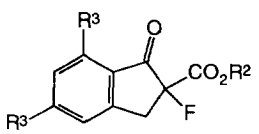
Abstract: Homochiral 2-fluoro-2-substituted-1-tetralones (**10a**, **10b**, **13**) and ethyl 2-fluoro-1-indanone-2-carboxylate (**16**) have been isolated. The dioxirane derivatives of these ketones have been prepared *in situ*, and have been shown to epoxidise alkenes but not enantioselectively. The dioxirane derivative of methyl 2,5,7-trifluoro-1-indanone-2-carboxylate (**18**) has been shown to be comparatively efficient in epoxidation.

In the last decade or so, dioxiranes (**3**) have been shown to be extremely versatile oxidants.[1] However, very few homochiral dioxiranes have been used and only low enantioselectivity has so far been reported.[2] In the course of our current research with dioxiranes,[3] we have looked at a new group of chiral dioxiranes generated *in situ* from 1-tetralones (**1**) and 1-indanones (**2**) substituted at the C-2 position with a fluorine and either an alkoxycarbonyl or a 2-hydroxyisopropyl group. To some extent these may be regarded as the cyclic equivalents of trifluoroacetophenone and related ring fluorinated acetophenones, which have been shown to generate a reactive dioxirane *in situ*.[4,5] It was thought that the planar aromatic ring might be important in directing the approach of a *trans*-alkene to the dioxirane, which is known[3a] to react in a spiro transition state. The synthesis and separation of the diastereomers and enantiomers of some 2-substituted-2-fluoro-1-tetralones (**1**) and -1-indanones (**2**) was therefore undertaken. The investigation of *in situ* dioxirane generation from the homochiral parent ketones and their potential in enantioselective alkene oxidation has also been conducted. The alkenes used were *trans*-stilbene (**4**), *trans*-β-methylstyrene (**5**) and 6-chloro-2,2-dimethyl-2H-1-benzopyran (**6**).



(1)



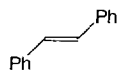
(2)

$R^1 = CO_2CH_3$; $C(CH_3)_2OH$; CO_2Men.

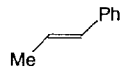
$R^2 = CH_2CH_3$; CH_3.

R^3 = H; F.

(3)



(4)



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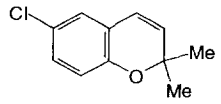


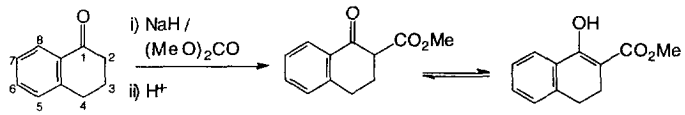
(6)

Synthesis of the 1-tetralone (1) and 1-indanone (2) derivatives

The synthesis of enantiomerically pure 2-hydroxy-2-substituted-1-tetralones[6] *via* oxidation of the enolates with enantiomerically pure (camphorylsulfonyl)oxaziridines, and the formation of homochiral 2,2-disubstituted-1-tetralols[7] *via* Grignard reactions with optically active (1-tetralone)-tricarbonyl chromium derivatives have been reported. Recently, the enantioselective reduction of racemic 2-alkoxycarbonyl-1-tetralones by chiral ruthenium(II) catalysts has been realised *via* kinetic resolution.[8] No work, however, has been reported which describes the separation of racemic mixtures of 2,2-disubstituted-1-tetralones. This paper describes the separation of the diastereomers of menthyl 2-fluoro-1-tetralone-2-carboxylate by chromatography, and the separation of enantiomers of 2,2-disubstituted-1-tetralones (**1**) and -1-indanones (**2**) *via* synthesis of their (*R*)-(+)-α-methylbenzylimine derivatives.

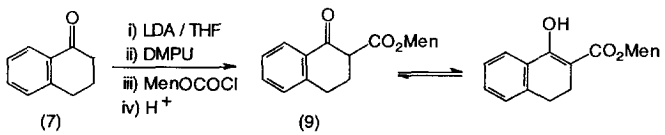
1) Synthesis of the 2,2-disubstituted-1-tetralones (1)

Several methods have been reported for the synthesis of 2-alkoxycarbonyl-1-tetralones and -1-indanones. These include the use of Mander's reagent[9] (methyl cyanoformate) and Stork[10] methodology, both of which alleviate the frequently encountered problem of O-acylation during attempted C-acylation of ketone enolates.[11] However, we found the most convenient synthesis of methyl 1-tetralone-2-carboxylate (**8**) was carried out using dimethyl carbonate and sodium hydride. Acylation *via* this method occurs quantitatively and exclusively at the carbon.

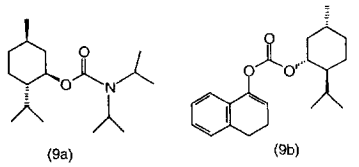


(7) (8)

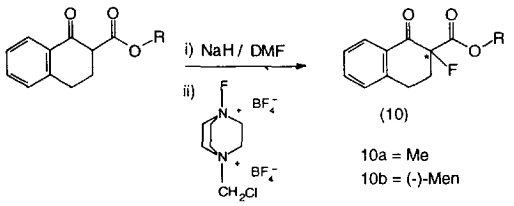
The menthyl ester (**9**) was synthesised using commercially available (-)-menthyl chloroformate, with lithium diisopropylamide. In the absence of DMPU or HMPA, no reaction was observed and although these reagents are known to encourage O-acylation, it was necessary to include one of them in the synthesis for any of the desired product to be observed. As expected, some O-acylated product (**9b**) was formed, along with the carbamate (**9a**).



(7) (9)



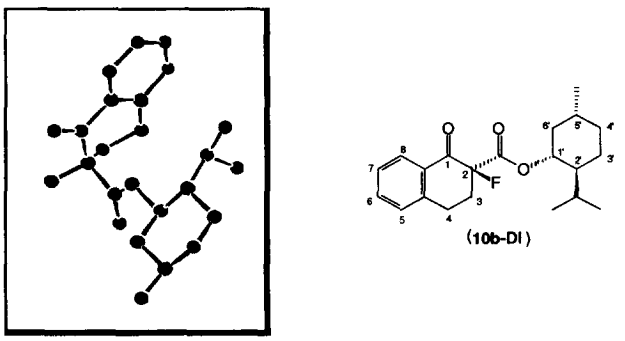
These compounds were then fluorinated using the commercially available electrophilic fluorinating reagent, N-fluoro-N'-chloromethyltriethylenediamine bis(tetrafluoroborate).[12]



2) Separation of diastereomers of (10b)

The diastereomers of (**10b**) were separated by flash chromatography to yield the homochiral tetralones. The less polar diastereomer (by tlc) was obtained as a solid. X-ray crystallography[13] revealed it to be (1'*R*,2'*R*,5'*R*)-(-)-menthyl 2*S*-fluoro-1-tetralone-2-carboxylate (**10b-DI**) and showed that the bulky ester residue was in an axial conformation (Figure 1).

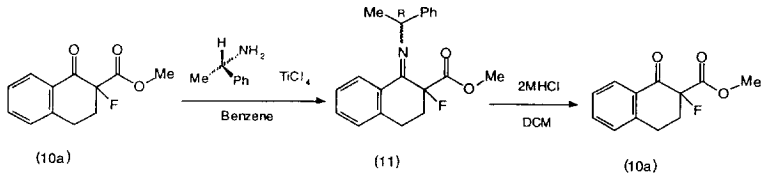
Figure 1: X-ray structure of (1'*R*,2'*R*,5'*R*)-(-)-menthyl 2*S*-fluoro-1-tetralone-2-carboxylate (**10b-DI**)



3) Separation of enantiomers of (10a) and (13) *via* an imine derivative

i) Ester derivative

Attempts to separate the enantiomers of (**10a**) *via* acetalisation,[14] using the optically active alcohol, (2*R*,4*R*)-(-)-pentanediol, were unsuccessful, even though several procedures were investigated.[15,16,17] The imine (**11**), derived from (*R*)-(+)-α-methylbenzylamine, was synthesised using titanium tetrachloride as catalyst.[18]

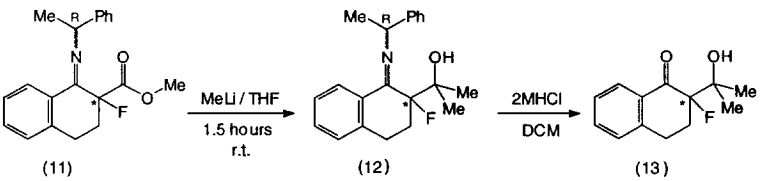


There are four possible diastereomers of (**11**). These are the *syn-* and *anti-* isomers of both the (*R,R*)- and the (*R,S*)-imine. On chromatographic separation of the diastereomers of (**11**), the *syn-* and *anti-* isomers of (*R,R*)-(**11**) eluted together, as did the *syn-* and *anti-* isomers of (*R,S*)-(**11**). This fact was determined using ^{1}H NMR spectroscopy, by treating the separated enantiomers of the deprotected ketone (**10a**) with the chiral shift reagent, Eu(hfc)$_3$.

The *syn-* and *anti-* isomers of the less polar diastereomer (**11-DI**) appeared as an oil, whereas those of the more polar diastereomer (**11-DII**) appeared as a solid. Only one signal (δ_H 3.33) was observed in the ^{1}H NMR spectrum for the OMe protons of the isomers in (**11-DI**). The signals for the OMe protons of the *anti-* and *syn-* isomers of (**11-DII**) appeared in the ^{1}H NMR at δ_H 3.87 and 3.83. It was noted that these latter *syn-* and *anti-* isomers partially interconverted on recrystallization from methanol. Hydrolysis of the imines (**11-DI**) and (**11-DII**) yielded the ketones (**10a-EI**) and (**10a-EII**), respectively. Chiral shift ^{1}H NMR spectroscopy studies showed that (**10a-EII**) had been isolated in >95% e.e. (no [**10a-EI**] apparently present) and (**10a-EI**) in 80% e.e.. The low e.e. in the latter case is due to incomplete separation of (**11-DI**) from (**11-DII**) by the chromatographic method used, and this was confirmed by the ^{1}H NMR spectrum of the less polar fraction.

ii) Tertiary alcohol derivative (13)

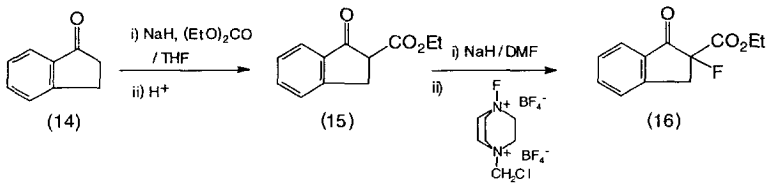
Synthesis of the hydroxyketone, 2-fluoro-2-(2-hydroxyisopropyl)-1-tetralone (**13**), *via* the imine (**11**) was attempted with methyllithium and methylmagnesium iodide using various reaction times and temperatures. The best yield, albeit low, was obtained using methyllithium, at 0°C and quenching after 1 - 1.5 hours. Flash chromatography of the reaction mixture containing the hydroxyimines (**12**) yielded the diastereomers (**12-DI**) and (**12-DII**) and recovered starting material (**11**). The diastereomers were deprotected with dilute acid to give the hydroxyketone enantiomers (**13-EI**) and (**13-EII**), respectively. The imines proved to be fairly stable to the acid, and required overnight stirring with 2M HCl for complete hydrolysis. Chiral shift ^{1}H NMR spectroscopy studies showed that (**13-EI**) had been isolated in >95% e.e. (2% of [**13-EII**])and that (**13-EII**) had been isolated in 90% e.e..



4) Synthesis of the ethyl 2-fluoro-1-indanone-2-carboxylate (16)

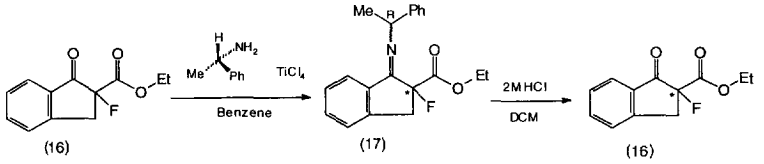
Ethyl 2-fluoro-1-indanone-2-carboxylate was synthesised from 1-indanone with diethyl carbonate and sodium hydride under the same conditions as used for the synthesis of methyl 1-tetralone-2-carboxylate (**10a**).

Fluorination was similarly carried out using N-fluoro-N'-chloromethyltriethylenediamine bis(tetrafluoroborate).



5) Separation of enantiomers of (16) *via* imine derivative (17)

The imines (**17**), derived from (*R*)-(+)-α-methylbenzylamine, were obtained by the method described for (**11**).[18]

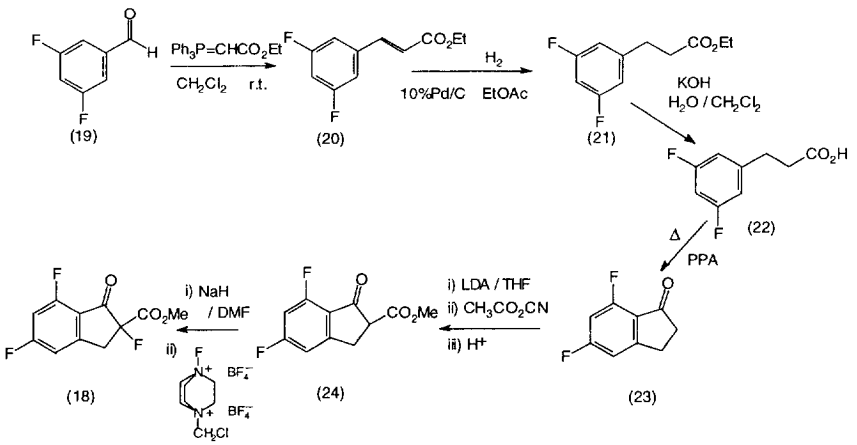


The isomers proved slightly more problematic to separate than those of the tetralone imine derivatives. All four isomers were visible by tlc. Two of the isomers could be crystallised out together from the diastereomeric mixture using ethanol. These were the fastest running and third fastest running compounds on the tlc plate. The less polar compound was the more abundant of the two isomers (**17-DI**) in the solid (ca. 9:1 by ^{1}H NMR spectroscopy). Removal of the imine group from these isomers (**17-DI**) yielded the ketone (**16-EI**), which was shown be one enantiomer (> 95% e.e.) by chiral shift ^{1}H NMR spectroscopy. The two isomers in the solid must therefore be the *syn-* and *anti-* isomers of either (*R,R*)-(**17**) or (*R,S*)-(**17**) isomer. The fraction containing the other isomers (**17-DII**) also contained a significant amount of (**17-DI**), hence the enantiomeric excess of the deprotected ketone (**16-EII**) was not determined.

6) Synthesis of methyl 2,5,7-trifluoro-1-indanone (18)

In order to further increase the activity of the dioxirane derivatives of the 2-acyl-2-fluoro-1-indanone, fluorine was incorporated into the aromatic ring. Previous work in this Department[5] has shown that fluorine positioned *ortho-* or *para-* to the carbonyl substituent increases the oxidising ability of the dioxirane derivative to a greater extent than if incorporated at a *meta-* position. 3,5-Difluorobenzaldehyde (**19**) was chosen as the starting ketone because the cyclization of the 3-(3,5-difluorophenyl)propionic acid (**22**), in a later step, produces only one product, the 5,7-difluoro-1-indanone (**23**), in which the fluorines are situated *ortho-* and *para-* to the carbonyl substituent.

Ethyl 3-(3,5-difluorophenyl)-2,3-dehydropropionate (**20**) was synthesised by two methods: i) from 3,5-difluorobenzaldehyde (**19**) and triethyl phosphonoacetate using the Wadsworth-Emmons Reaction,[19] ii) from 3,5-difluorobenzaldehyde (**19**) and (carbethoxymethylene)triphenylphosphorane using the Wittig Reaction.[20] The latter method proved to be much quicker and simpler.



The coupling constant (16 Hz) of the alkene (**20**) protons in the ^{1}H NMR spectrum confirmed the stereochemistry to be *trans*. Hydrogenation of (**20**) using 10% palladium on carbon catalyst, in ethyl acetate gave ethyl 3-(3,5-difluorophenyl)propionate (**21**), which was hydrolysed using potassium hydroxide in ethanol and water to give the acid (**22**).[21b] Cyclisation of (**22**), using polyphosphoric acid[21] and a reaction temperature of 45°C, gave the indanone (**23**). Acylation of the indanone (**23**), using sodium hydride and diethyl carbonate in THF, was attempted but provided only low yields, typically 5% or less. However, dropwise addition of the indanone (**23**) to LDA at -78°C, followed by the addition of Mander's reagent,[9] gave the required ester (**24**). Fluorination using the usual method produced the ethyl 2,5,7-trifluoro-1-indanone-2-carboxylate (**18**).

Use of the 1-tetralone (1) and 1-indanone (2) dioxirane derivatives in the oxidation of alkenes.

The dioxiranes were generated *in situ* from the tetralone and indanone derivatives. The concentration of ketone in the dichloromethane appears to have a dramatic effect on the rate of the reaction, therefore this was standardised using a 0.5 M solution of the ketone in the dichloromethane. Potassium peroxymonosulphate (Oxone®) was added in small portions. Reactions were monitored by ^{1}H NMR or GC analysis and sufficient Oxone® added until enough epoxide had been formed for chiral shift analysis to be performed. The reaction times of the experiments carried out, ranged from a few hours to several days.

The alkenes were first epoxidised using an isolated solution of dimethyldioxirane in acetone.[22] Chiral shift studies were then carried out on the resulting epoxides to determine the amount of chiral shift reagent, Eu(hfc)$_3$, required for baseline separation of either the methyl or methine signals of the enantiomers in the ^{1}H NMR spectrum. The enantiomeric ratio of the epoxide produced in each of the *in situ* reactions was then determined using these results as a standard.

Each of the alkenes were subjected to a blank run, in which no ketone was used in the reaction. After the addition of sixty equivalents of Oxone,® no epoxidation was noted for *trans*-stilbene (**4**) or the chromene (**6**), and only 1.5% epoxidation for *trans*-β-methylstyrene (**5**). From these results we can conclude that the dioxirane derived from the ketone is playing the major role in the alkene epoxidations.

Results of Epoxidations

No enantioselectivity was observed for the epoxidation reactions using the dioxirane derivatives of (**10a**) and (**10b**). It was thought that this may have been due to conformational mobility of the saturated ring in the tetralone system. The fact that, in the solid state, the ester residue prefers to take up the axial conformation supports this view (Figure 1).

By incorporating a hydroxy group *beta* to the ketone, it was hoped to confer some conformational stability to this ring system *via* hydrogen bonding to one of the oxygens in the dioxirane ring, and furthermore that such hydrogen bonding may encourage selective delivery of one of the dioxirane oxygens. The results that we obtained for the epoxidation of alkenes using the dioxirane derivative of such a ketone (**13**) did not show any improvement on our previous results.

From models of the 1-tetralones (**1**) and 1-indanones (**2**), it appeared that the 1-indanone (**2**) had less conformational flexibility than that of the 1-tetralone (**1**). We, therefore, hoped that with this more conformationally stable structure, the dioxirane derivative of the 1-indanone (**16**) would show some enantioselectivity in its epoxidation of alkenes. However, no enantioselectivity was observed.

Table 1 shows the general reactivity of the dioxirane derivatives of the ketones, i.e., in decreasing order of reactivity: (**18**), (**16**), (**10a**), (**10b**), (**13**). The result of the epoxidation reaction using the dioxirane derivative of methyl 2,5,7-trifluoro-1-indanone-2-carboxylate (**18**) confirms our previous findings, that incorporation of fluorine into the aromatic ring of arylalkyl ketones increases the reactivity of its dioxirane in alkene epoxidation.[5]

Table 1:

Ketone / Alkene	% Conversion of alkene to epoxide (Equivalents of Oxone used)					
	10a-EI	**10b-DII**	**10b-DI**	**13-EI**	**16-EI**	**18**
4	- -	14% (240)	19% (240)	- -	- -	- -
5	100% (120)	84% (120)	76 % (120)	98%+ (240)	98% (60)	100% (30)
6	- -	56% (180)	49% (180)	- -	- -	- -

Acknowledgements

We gratefully acknowledge SmithKline Beecham for their financial support. We also thank Professor R. Curci for his help and for allowing one of us (LW) a brief study period in his laboratory.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker 250 MHz NMR Spectrometer. ^{19}F NMR spectra were obtained on a 400 MHz NMR Spectrometer. IR spectra were recorded on a Nicolet 205 series FT-IR Spectrometer. Mass spectra were obtained on a Kratos MS80 Spectrometer with DS-55 data system. Column chromatography was carried out using the flash chromatography technique with Matrex Silica 60, 35-70

micron (Fisons Scientific Equipment) unless otherwise noted. Thin layer chromatography was carried out using aluminium sheet silica gel 60 F_{254}, 0.2 mm layer thickness (Merck) or aluminium sheet aluminium oxide 60 F_{254} neutral (type E), 0.2 mm layer thickness (Merck). The $[\alpha]_D$ values were measured using an Optical Activity Ltd. machine. Melting points were obtained on a Reichert Manual Melting Point Apparatus.

Methyl 1-tetralone-2-carboxylate (8)[23]

1-Tetralone (**7**) (2.50 g, 2.78 ml, 17.10 mmole) was added to a stirred suspension of sodium hydride (60% dispersion in oil, 0.821 g, 20.52 mmole) in dry dimethyl carbonate (19.50 g, 20 ml, 165 mmole), under an atmosphere of nitrogen.[24] The reaction mixture was heated for 15 minutes during which time a lilac and white solid formed. Further dry dimethyl carbonate (5 ml) was added *via* syringe. Tlc analysis of the solid showed no evidence of 1-tetralone. The solid was allowed to cool to room temperature, dissolved in hydrochloric acid (aqueous 2M, 50 ml) and extracted with ethyl acetate (4 x 50 ml). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield a brown oil (4.328 g). This crude product was purified by flash chromatography (silica with 9:1 light petroleum [b.p. 40 - 60°C] : ethyl acetate) to yield a colourless crystalline solid (**8**) (3.411 g, 98%); m.p. 61.5°C - 69.5°C; b.p. 200°C (2 mmHg); ν_{max} (neat) 2951 (C-H), 1745 (ester C=O), 1685 (α-aryl ketone C=O) 1650, 1648, 1620, 1600, 1570, 1453, 1441, 1363 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 12.41 (1 H, s, enol OH), 8.01 (1 H, d,d, *J* 7.8, 1.4 Hz, ketoester 8-H), 7.77 (1 H, d,d, *J* 7.0, 1.6 Hz), 7.45 - 7.13 (6 H, m, ketoester and enol 7-H, 6-H and 5-H, 3.78 (3 H, s, enol CH_3), 3.74 (3 H, s, ketoester CH_3), 3.01 - 2.91 (2 H, m, ketoester 4-H), 2.79 - 2.73 (2 H, s, enol 4-H), 2.63 - 2.08 (4 H, m, ketoester and enol 3-H); δ_C (62.5 MHz, $CDCl_3$) 192.9 (ketone 1-C), 173.0 and 170.6 (ketone and enol 2-CO_2Me), 165.0 (enol 1-C), 143.7 and 139.4 (ketone and enol 8a-C), 133.9 and 130.5 (ketone and enol 7-C), 131.6 and 129.9 (ketone and enol 4a-C), 128.8 and 127.7 (ketone and enol 6-C), 127.4 and 126.9 (ketone and enol 5-C), 126.5 and 124.3 (ketone and enol 8-C), 96.8 (enol 2-C), 54.4 (ketone 2-C), 52.3 and 51.6 (ketone and enol 2-CO_2CH_3), 27.7 and 27.6 (ketone and enol 4-C), 26.3 and 20.5 (ketone and enol 3-C).

L-Menthyl 1-tetralone-2-carboxylate (9)

To stirred diisopropylamine (0.977 g, 9.65 mmole) under argon, was added butyllithium (2.3M in hexane, 4.1 ml, 9.65 mmole) at -20°C. This immediately formed a clear gel, to which was added tetrahydrofuran (dry, 3 ml) and the resulting solution left to stir at -20°C for 30 minutes. The temperature was lowered then to -78°C and 1-tetralone (**7**) (1.200 g, 1.112 ml, 8.00 mmole) added. The flask was warmed to 0°C and stirred for one hour, after which time the temperature was lowered to -78°C and HMPA (1.44 g, 1.40 ml, 8.00 mmole) followed by L-menthyl chloroformate (2.11 g, 2.07 ml, 9.65 mmole) added. The reaction mixture was left to stir overnight at room temperature, then poured into a separating funnel containing distilled water (100 ml). The aqueous fraction was then extracted with dichloromethane. The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield a brown oil (4.289 g). This crude material was purified by flash chromatography (flash silica with 1:1 dichloromethane : light petroleum [b.p. 40 - 60°C] followed by 7:1 light petroleum [b.p. 40 - 60°C] : diethyl ether) to yield the desired material as a clear oil (1.100 g, 42%). Three products were produced in this reaction. These appeared (tlc analysis using silica with 1:1 dichloromethane : light petroleum [b.p. 40 - 60°C]) at R_f values of 0.75 (L-Menthyl 3,4-dihydronaphthalene-1-carbonic acid [**9b**]), 0.57 streaking (L-Menthyl 1-tetralone-2-carboxylate [**9**]), 0.57 (N,N-diisopropyl L-menthyl carbamate [**9a**]). Tlc analysis using silica with 7:1 light petroleum [b.p. 40 - 60°C] : diethyl ether gave

R_f values of 0.65 streaking (L-Menthyl 1-tetralone-2-carboxylate [**9**]) and 0.40 (N,N-diisopropyl L-menthyl carbamate [**9a**]).

L-Menthyl 1-tetralone-2-carboxylate (**9**): ν_{max} (neat) 2955 (aromatic C-H), 2932 (C-H), 2870 (saturated C-H), 1734 (ester C=O of ketoester), 1690 (α-aryl ketone C=O), 1643 (enol ester C=O), 1618 (enol ester C=O), 1570, 1455, 1389, 1268, 1213, 1085 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 12.60 (1 H, s, OH), 8.05 (1 H, d,d, *J* 7.7, 1.2 Hz, ketoester 8-H), 7.80 (1 H, d,d *J* 6.9, 1.7 Hz, enol ester 8-H), 7.47 (1 H, t,t, *J* 7.5, 1.4, ketoester 7-H), 7.35 -7.15 (5 H, m, enol ester 7-H, 6-H, 5-H, ketoester 6-H, 5-H), 4.89 - 4.79 (2 H, m, enol ester and ketoester C*H*-O-CO), 3.59 -3.55 (1 H, m, ketoester 2-H), 3.00 - 2.99 (2 H, m, ketoester 4-H), 2.81 (2 H, t, *J* 7.8 Hz, enol ester 4-H), 2.59 - 2.52 (4 H, m, enol ester and ketoester 3-H), 2.25 - 2.12 (2 H, m, menthyl C-H), 1.97 -1.83 (2 H, m, menthyl C-H), 1.73 - 1.24 (10 H, m, menthyl C-H), 1.20 - 0.69 (7 H, m, menthyl C-H), 0.94 - 0.90 (12 H, m, enol ester and ketoester CH_3 of *iso*-propyl group), 0.80 (6 H, d, *J* 7.0 Hz, enol ester and ketoester Me); δ_C (62.5 MHz, $CDCl_3$) 193.5 (ketone 1-C), 172.4 and 169.6 (ketone and enol 2-CO_2), 164.9 (enol 1-C), 143.6 and 139.3 (ketone and enol 8a-C), 133.7 and 130.1 (ketone and enol 7-C), 130.2 and 131.8 (ketone and enol 4a-C), 128.8 and 127.7 (ketone and enol 6-C), 127.4 and 126.9 (ketone and enol 5-C), 126.5 and 124.2 (ketone and enol 8-C), 97.3 (enol 2-C), 75.4 and 74.5 (ketone and enol 1'-C), 47.1 and 46.8 (ketone and enol 2'-C), 41.8 and 40.7 (ketone and enol 6'-C), 34.3 and 34.2 (ketone and enol 4'-C), 31.4 ($CCH(CH_3)_2$), 27.8 and 27.5 (ketone and enol 4-C), 26.6 (5'-C), 26.4 and 20.5 (ketone and enol 3-C), 23.7 (3'-C), 22.0 and 20.7 (2C, $CCH(CH_3)_2$), 16.7 (5-CCH_3); (Found: m/z 329.2117 ($MH^{+}\cdot$). $C_{11}H_{10}F_2O_2$ requires MH 329.2117).

N,N-diisopropyl L-menthyl carbamate (**9a**): ν_{max} (neat) 2956 (aromatic C-H), 2933 (C-H), 2871 (saturated C-H), 1686 (C=O), 1456, 1433, 1368, 1328, 1287, 1269 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 4.66 (1 H, t,t *J* 10.8, 4.3 Hz, CH-O-CO), 3.91 (2 H, broad s, NCH), 2.08 - 1.92 (2 H, m, menthyl C-H), 1.70 - 1.65 (2 H, m, menthyl C-H), 1.48 - 1.27 (2 H, m, menthyl C-H), 1.20 (12 H, d, *J* 6.8 Hz, $NCH(CH_3)_2$), 1.14 - 0.79 (3 H, m, menthyl C-H), 0.90 (6 H, d, *J* 6.9 Hz, $CCH(CH_3)_2$), 0.80 (3 H, d,d, *J* 6.9, 1.7 Hz, Me); δ_C (62.5 MHz, $CDCl_3$) 155.5 (OCON), 74.2 (1-C), 47.4 (2-C), 45.7 (2C, N*C*H), 41.6 (6-C), 34.5 (4-C), 34.5 and 34.3 ($CCH(CH_3)_2$), 26.2 (5'-C), 23.4 (3-C), 22.1 and 20.7 (2C, $CCH(CH_3)_2$), 21.0 (4C, $(CH_3)_2CHN$), 16.3 (5-CCH_3); (Found: m/z 283.2515 ($M^{+}\cdot$). $C_{17}H_{33}NO_2$ requires M 283.2511).

L-Menthyl 3,4-dihydronaphthalene-1-carbonic acid (**9b**): ν_{max} (neat) 2956 (aromatic C-H), 2933 (C-H), 2871 (saturated C-H), 1758 (C=O), 1733, 1456 (arene C-C), 1286, 1253, 1226, 1182, 1012 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.20 - 7.10 (4 H, m, ArH), 5.78 (1 H, t, *J* 4.7 Hz, 2-H), 4.56 (1 H, t,t, *J* 10.9, 4.4 Hz, CH-O-CO), 2.84 (2 H, t, *J* 7.9 Hz, 4-H), 2.46 - 2.38 (2 H, m, 3-H), 2.15 - 1.97 (2 H, m, menthyl C-H), 1.72 - 1.67 (1 H, m, menthyl C-H), 1.48 - 1.42 (1 H, m, menthyl C-H), 1.19 - 0.80 (5 H, m, menthyl C-H), 0.94 - 0.91 (6 H, m, CH_3 of *iso*-propyl group), 0.85 - 0.82 (3 H, m, Me); δ_C (62.5 MHz, $CDCl_3$) 153.2 (OCO_2), 146.1 (1-C), 136.4 (8a-C), 130.4 (4a-C), 128.2 (8-C), 128.0 (7-C), 127.5 (6-C), 120.5 (5-C), 115.0 (2-C), 79.2 (1'-C), 47.0 (2'-C), 40.6 (6'-C), 34.1 (4'-C), 31.4 ($CCH(CH_3)_2$), 27.4 (4-C), 26.5 (5'-C), 23.4 (3-C), 22.0 (3'-C), 22.0 and 20.7 (2C, $CCH(CH_3)_2$) 16.3 (5-CCH_3); (Found: m/z 328.2051 ($M^{+}\cdot$). $C_{21}H_{28}O_3$ requires M 328.2038).

Methyl 2-fluoro-1-tetralone-2-carboxylate (10a)

To a stirred suspension of sodium hydride (60% dispersion in oil, 0.098 g, 2.45 mmole) in DMF (2.5 ml), at 0°C, under nitrogen, was added methyl 1-tetralone-2-carboxylate (**8**) (0.500 g, 2.45 mmole) in DMF (2.5 ml). This was left to stir at 0°C for twenty minutes.[25] A solution of N-fluoro, N-chloromethyl

triethylenediamine bis(tetrafluoroborate (0.943 g, 2.13 mmole) in DMF (5 ml) was added to the above solution at -50°C. The reaction mixture was then allowed to slowly warm to room temperature and left to stir overnight. After this time, the reaction mixture was poured into a separating funnel containing diethyl ether (100 ml). This solution was washed with $NaHCO_3$ solution (10% aqueous, 100 ml) and NaCl solution (saturated aqueous, 100 ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow oil (0.775 g). Tlc analysis (9:1 light petroleum [b.p. 40 - 60°C] : ethyl acetate) of the crude reaction mixture showed the reaction to be complete after approximately five minutes (starting material: R_f 0.38, product: R_f 0.13). The crude product was then purified by flash chromatography (silica with 9:1 light petroleum [b.p. 40 - 60°C] : ethyl acetate, gradually moving to 4:1) followed by recrystallization from ethanol to give clear columnar-shaped crystals (**10a**) (0.334 g, 71%); m.p. 75°C; ν_{max} (neat) 2955 (aromatic C-H), 1766 (ester C=O), 1744, 1697 (ketone C=O), 1603, 1457 (arene C-C), 1438, 1312, 1281, 1228, 1199, 1088 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.06 (1 H, d,d, *J* 7.9, 1.3 Hz, 8-H), 7.55 (1 H, t,t, *J* 7.5, 1.5 Hz, 7-H), 7.40 - 7.28 (2 H, m, 5-H, 6-H), 3.62 (3 H, s, Me), 3.18 - 3.09 (2 H, m, 3-H), 2.77 - 2.52 (2 H, m, 4-H); δ_C (62.5 MHz, $CDCl_3$) 188.5 (d, *J* 18.8 Hz, 1-C), 167.7 (2-*C*O_2Me), 143.2 (8a-C), 134.7 (8-C), 130.5 (4a-C), 128.8 (7-C), 128.5 (6-C), 127.3 (5-C), 93.4 (d, *J* 201 Hz, 2-C), 53.1 (CH_3), 31.9 (d, *J* 22.5 Hz, 3-C), 24.8 (d, *J* 7.0 Hz, 4-C); (Found: m/z 222.0680 ($M^{+\cdot}$). C, 64.74; H, 4.93%. $C_{12}H_{11}FO_3$ requires M 222.0692. C, 64.86; H, 4.99%).

Menthyl 2-fluoro-1-tetralone-2-carboxylate (10b)

To a stirred suspension of sodium hydride (60% dispersion in oil, 0.091 g, 2.28 mmole) in DMF (1 ml), at 0°C and under nitrogen, was added menthyl 1-tetralone-2-carboxylate (**9**) (0.750 g, 2.28 mmole in DMF (4 ml). This was left to stir at 0°C for twenty minutes.[25] A solution of N-fluoro, N-chloromethyl triethylenediamine bis(tetrafluoroborate) (80% active ingredient, 0.879 g, 1.99 mmole) in DMF (5 ml) was then added dropwise to the above solution at -50°C. The solution was allowed to warm slowly to room temperature and left to stir for ten minutes, after which time the reaction appeared to be complete by tlc chromatography (silica with 20:1 light petroleum [b.p. 40 - 60°C] : ethyl acetate) (Starting material: R_f 0.80, product: R_f 0.61). The reaction mixture was poured into a separating funnel containing diethyl ether (100 ml). This solution was washed with $NaHCO_3$ solution (10% aqueous, 100 ml) and NaCl solution (saturated aqueous, 100 ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow oil (0.802 g). Column chromatography (silica with 1:1 dichloromethane : light petroleum [b.p. 40 - 60°C]) yielded a colourless oil (**10b**) (0.647 g, 94%).Separation of the diastereomers was carried out by flash chromatography using silica with 2:1 dichloromethane : light petroleum [b.p. 40 - 60°C]. The R_f values of the diastereomers, using this solvent system, were 0.49 (**10b-DI**) and 0.41 (**10b-DII**).

(1'*R*,2'*R*,5'*R*)-(-)-Menthyl 2*S*-fluoro-1-tetralone-2-carboxylate (**10b-DI**): m.p. 101°C; Optical rotation: $[\alpha]_D$ -61.5 (22°C, dichloromethane, 0.260 g/100 ml); ν_{max} (neat) 2956 C-H), 2931, 2871 (saturated C-H), 1759 (ester C=O), 1739, 1698 (ketone C=O), 1603, 1456, 1310, 1277, 1227, 1190 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.07 (1 H, d,d, *J* 7.8, 1.1 Hz, 8-H), 7.54 (1 H, t,t, *J* 7.5, 1.4 Hz, 7-H), 7.39 (1 H, t, *J* 7.3 Hz, 6-H), 7.27 (1 H, d, *J* 7.6 Hz, 5-H), 4.78 (1 H, t,t, *J* 10.9, 4.4 Hz, CO_2CH), 3.24 - 3.05 (2 H, m, 4-H), 2.76 - 2.51 (2 H, m, 3-H), 2.10 - 2.06 (1 H, m, 2'-H), 1.69 - 0.85 (8 H, m, 3'-H, 4'-H, 5'-H, 6'-H, C*H*i*P*r), 0.90 (3 H, d, *J* 6.5 Hz, 5'-Me), 0.77 (1 H, d, *J* 7.0 Hz, Me of *i*Pr), 0.69 (1 H, d, *J* 7.0 Hz, Me' of *i*Pr); δ_C (62.5 MHz, $CDCl_3$) 188.7 (d, *J* 15.1 Hz, 1-C), 167.0 (d, *J* 25.2 Hz, CO_2), 142.8 (8a-C), 134.4 (7-C), 130.8 (4a-C), 128.7 (6-C), 128.3 (5-C), 127.2 (8-C), 93.4 (d, *J* 193.5 Hz, 2-C), 77.0 (1'-C), 46.7 (2'-C), 40.2 (6'-C), 34.0 (3'-C), 31.7 (d,

J 21.9 Hz, 3-C), 31.4 (5'-C), 25.9 (*C*H*i*Pr), 25.0 (d, *J* 7.7 Hz, 4-C), 23.0 (4'-C), 21.9 (Me), 20.7 (Me'), 15.8 (Me"); δ_F (376.5 MHz, $CDCl_3$, ^1H decoupled, external reference CF_3CO_2H) -163.87; (Found: m/z 208 ($M^{+\cdot}$ -138). C, 72.56; H, 7.98%. $C_{21}H_{27}FO_3$ requires 208 (M -138). C, 72.81; H, 7.86%); **X-ray crystallographic data:**[13] Crystal (0.50 x 0.21 x 0.20 mm) grown from methanol, $C_{21}H_{27}FO_3$, monoclinic, space group $P2_1$, a =11.878(9), b = 12.694(7), c = 6.43(1) Å, β = 90.2(2)°, Z = 2, D_x = 1.186 gcm^{-3}, T = 293 K. MoK_α radiation (λ = 0.7169 Å), μ = 0.48 cm^{-1}. Stöe Stadi-2 diffractometer, 1857 reflections measured of which 1360 with F/σ(F)>5. Structure solved by direct methods and refined to a final R = 0.070, R_w = 0.070. All non-H atoms treated anisotropically. Phenyl and one methylene H atoms placed in calculated positions. Other H atoms found from difference map and not refined. The final maximum shift / error = 0.39, Δρ excursions -0.2 to 0.2.

(1'*R*,2'*R*,5'*R*)-(-)-Menthyl 2*R*-fluoro-1-tetralone-2-carboxylate (**10b-DII**): ν_{max} (neat) 2956 (aromatic C-H), 2930, 2871 (saturated C-H), 1760 (ester C=O), 1734, 1698 (ketone C=O), 1601, 1456, 1311, 1275, 1227, 1189 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.07 (1 H, d, *J* 7.8 Hz, 8-H), 7.55 (1 H, t, *J* 7.5 Hz, 7-H), 7.36 (1 H, t, *J* 7.5 Hz, 6-H), 7.29 (1 H, d, *J* 6.8 Hz, 5-H), 4.80 (1 H, t,t, *J* 10.9, 4.4 Hz, CO_2CH), 3.23 - 3.09 (2 H, m, 4-H), 2.73 - 2.53 (2 H, m, 3-H), 2.06 - 2.02 (1 H, m, 2'-H), 1.75 - 0.85 (8 H, m, 3'-H, 4'-H, 5'-H, 6'-H, C*H*i*Pr*), 0.89 (3 H, d, *J* 6.5 Hz, 5'-Me), 0.81 (3 H, d, *J* 7.0 Hz, Me of *i*Pr), 0.74 (3 H, d, *J* 7.0 Hz, Me' of *i*Pr); δ_C (62.5 MHz, $CDCl_3$)188.6 (d, *J* 15.1 Hz, 1-C), 167.0 (d, *J* 25.2 Hz, CO_2), 143.0 (8a-C), 134.4 (7-C), 130.9 (4a-C), 128.7 (6-C), 128.3 (5-C), 127.2 (8-C), 93.1 (d, *J* 193.8 Hz, 2-C), 77.0 (1'-C), 46.8 (2'-C), 40.5 (6'-C), 34.0 (3'-C), 32.0 (d, *J* 22.4 Hz, 3-C), 31.4 (5'-C), 25.9 (*C*H*i*Pr), 25.1 (d, *J* 7.7 Hz, 4-C), 23.2 (4'-C), 21.9 (Me), 20.8 (Me'), 16.0 (Me").

Methyl 2-fluoro-1-[(*R*)-(+)-α-methylbenzylimino]-tetralone-2-carboxylate (11)

To a solution of methyl 2-fluoro-1-tetralone-2-carboxylate (**10a**) (2.780 g, 12.510 mmole) and (*R*)-(+)-α-methylbenzylamine (4.548 g, 4.838 ml, 37.531 mmole) in dry benzene (100 ml), at 0-5°C, was added $TiCl_4$ (1.0M in dichloromethane, 6.88 ml, 6.881 mmole) dropwise, *via* syringe, under nitrogen.[18] The reaction was left to stir at 0-5°C for one hour, then allowed to warm to room temperature and left to stir for a further one hour. After this time, the reaction mixture was filtered and the filtrate concentrated *in vacuo* to yield a reddish white solid (still containing TiO_2). This material was purified by flash chromatography using alumina (basic, activated, Brockmann Type I, standard grade, 150 mesh) with 19:1 light petroleum [b.p. 40 - 60°C] : ethyl acetate. The solvent was removed *in vacuo* from the desired fractions to yield a sticky, pale yellow solid (3.651 g, 90%). Two spots were visible by tlc (silica with 7:3 light petroleum [b.p. 40 - 60°C] : diethyl ether) appearing at 0.53 and 0.45 (creamish yellow colour when visualised by anisaldehyde). Recrystallization from methanol yielded a white solid (diastereomer II). Further purification of the mother liquor using dry flash chromatography (tlc alumina, neutral, with light petroleum [b.p. 40 - 60°C]) and recrystallizations using methanol yielded the isolated diastereomers.

Diastereomer I (**11-DI**): colourless oil (0.196 g, 11%); ν_{max} (film) 2926 (aromatic C-H), 1758 (ester C=O), 1634, 1456, 1267, 1089 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.24 (1 H, d,d, *J* 6.5, 1.6 Hz, ArH), 7.42 -7.14 (8 H, m, ArH), 5.13 - 5.03 (1 H, m, NC*H*), 3.33 (3 H, s, OMe protons), 3.00 - 2.77 (2 H, m, 4-H), 2.48 - 2.15 (2 H, m, 3-H), 1.55 (3 H, d, *J* 6.2 Hz, CMe protons); δ_C (62.5 MHz, $CDCl_3$) 170.4 (d, *J* 26.1 Hz, *C*O_2Me), 154.2 (d, *J* 15.6 Hz, 1-C), 145.4 (4a-C), 139.1 (NCH[Me]*C*), 134.0 (d, *J* 3.9 Hz, 8a-C), 130.2, 128.2 (2 C), 127.5, 127.4, 127.1, 126.6, 126.2 (2 C), 91.1 (d, *J* 192.2 Hz, 2-C), 60.5 (d, *J* 3.4 Hz, CO_2CH_3), 52.4 (*N*CH), 34.6 (d, *J* 23.3 Hz, 3-C), 26.0 (CH*C*H_3), 24.8 (d, *J* 4.5 Hz, 4-C). Evidence of *syn*- and *anti*- isomers present

in the ^{13}C NMR spectrum. The aromatic tertiary carbons of the minor isomer are visible at δ_C 130.4, 128.8, 128.6, 126.9, 126.7, 126.0, 125.7. Also visible are δ_C 60.0 (CO_2CH_3), 52.3 (NCH), 31.4 (d, 3-C), 26.5 ($CHCH_3$), 25.1 (d, 4-C); (Found: m/z 325.1486 ($M^{+\cdot}$). $C_{20}H_{20}FNO_2$ requires M 325.14780).

Diastereomer II (**11-DII**): colourless crystalline solid (0.281 g, 16%); m.p. 101°C; ν_{max} (film) 2963 (aromatic C-H), 1761 (ester C=O), 1627, 1450, 1265, 1071 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.26 (1 H, d,d, *J* 6.7, 2.5 Hz, 6-H), 7.47 (2 H, d, *J* 7.2 Hz, ArH), 7.33 - 7.12 (6 H, m, ArH), 5.13 - 5.06 (1 H, m, NC*H*), 3.87* & 3.83 (1 H, singlets, OMe protons of *syn-* and *anti-* isomers), 2.91 - 2.85 (2 H, m, 4-H), 2.44 - 2.29 (2 H, m, 3-H), 1.60 & 1.42* (3 H, doublet & double doublet, *J* 6.4 & 6.3, 1.2 Hz, respectively, CMe protons); δ_C (62.5 MHz, $CDCl_3$) 170.7* (d, *J* 25.5 Hz, CO_2Me), 170.1 (d, *J* 27.1 Hz, CO_2Me), 159.2 (d, *J* 20.7 Hz, 1-C), 153.7* (d, *J* 15.7 Hz, 1-C), 145.9 (4a-C), 145.1* (4a-C), 142.4 (NCH[Me]*C*), 140.8* (NCH[Me]*C*), 138.1* (d, *J* 3.9 Hz, 8a-C), peaks of tertiary aromatic carbon of *syn-* and *anti-* isomers: 130.5, 130.1, 128.8, 128.7, 128.4, 128.5, 127.9, 127.8, 127.0, 126.8, 126.7, 126.2, 126.0, 125.9, 96.1 (d, *J* 188.8 Hz, 2-C), 90.7* (d, *J* 192.7 Hz, 2-C), 60.6* (d, *J* 4.4 Hz, CO_2CH_3), 59.7 (CO_2CH_3), 52.9* (NCH), 52.3 (NCH), 34.4* (d, *J* 23.4 Hz, 3-C), 32.0 (d, *J* 24.0 Hz, 3-C), 25.9 ($CHCH_3$), 25.4 (d, *J* 3.0 Hz, 4-C), 24.9 (d, *J* 5.8 Hz, 4-C), 23.9* ($CHCH_3$); (Found: m/z 325.1491 ($M^{+\cdot}$). $C_{20}H_{20}FNO_2$ requires M 325.1478). * Peaks of most abundant isomer.

Regeneration Of Methyl 2-fluoro-1-tetralone-2-carboxylate (10a-EI and 10a-EII)

A heterogeneous mixture of hydrochloric acid (aq. 2M, 15 ml) and methyl 2-fluoro-1-[(*R*)-(+)-α-methylbenzylimino]-tetralone-2-carboxylate (**11**) (0.218 g, 0.670 mmole) in dichloromethane (5 ml) was vigorously stirred for 1 hour at room temperature. After this time, no starting material was visible by tlc. The organic layer was isolated, diluted to 20 ml, washed with brine (saturated, 20 ml), dried (Na_2SO_4) and concentrated *in vacuo* to yield a colourless solid (0.147 g, 99%). This material was run through a silica column to give a colourless solid (**10a**) (0.143 g, 96%).

Removal of the imine from (**11-DII**) yielded the enantiomerically pure ketone (**10a-EII**), and deprotection of (**11-DI**) gave the other enantiomer (**10a-EI**). Both compounds had spectroscopic and physical data as previously described for (**10a**).

Chiral shift studies were carried out on the isolated enantiomers, using the chiral shift reagent $Eu(hfc)_3$. The proton NMR spectrum for (**10a-EII**) showed no splitting of peaks with the chiral shift reagent. On addition of a racemic mixture of the ketone to the NMR sample, splitting was observed. From this it can be deduced that the parent imine consists of the *syn-* and *anti-* isomers of the same diastereomer, either (*R,R*) or (*R,S*). NB. The $Eu(hfc)_3$ shifts the 6-H proton of (**10a-EII**) further downfield than that of (**10a-EI**). Baseline separation was observed for the most downfield proton with 2.7 equivalents of the chiral shift reagent.

2-Fluoro-2-(2-hydroxyisopropyl)-1-[(*R*)-(+)-α-methylbenzylimino]tetralone (12)

To a solution of the iminoester (**11**) (1.836 g, 5.643 mmole) in tetrahydrofuran (dry, 25 ml) was added methyllithium (1.5M in diethyl ether, 5.64 ml, 8.464 mmole) at 0°C under nitrogen. The reaction was allowed to stir at 0°C for 1.5 hours, after which time it was quenched with an aqueous solution of ammonium chloride (saturated, 50 ml). The resulting mixture was extracted with diethyl ether. The ethereal extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo* to yield a dark orange oil. This oil was subjected to flash chromatography (aluminium oxide, Brockmann Grade II, standard grade, ~150 mesh; 7 : 3 light

petroleum [b.p. 40 - 60°C] : ethyl acetate). This gave 0.399 g (22%) of the desired hydroxyimine diastereomers. This initial column afforded some separation of the diastereomers: the more polar diastereomer (**12-DI**) (0.093 g, 5%), the less polar diastereomer (**12-DII**) (0.152 g, 8%). Some staring material was recovered as a colourless oil (0.894 g, 49%).

Spectroscopic data for the more polar diastereomer (**12-DI**): Optical rotation $[\alpha]_D$ +37.0 (20°C, chloroform, 0.568 g/100 ml); ν_{max} (neat) 3354 (broad, OH), 2975, 2926, 1641, 1453, 1073, 1058, 964 cm^{-1}; δ_H (250MHz, $CDCl_3$) 7.51 - 7.15 (9 H, m, ArH), 6.20 (1 H, broad s, OH), 5.04 (1 H, q, *J* 6.4 Hz, NC*H*), 3.03 - 2.78 (2 H, m, 4-H), 2.47 - 2.15 (2 H, m, 3-H), 1.51 (3 H, s, C(OH)CH_3), 1.49 (3 H, d, *J* 3.4 Hz, NCCH_3), 1.38 (3 H, s, C(OH)CH_3"); δ_c (62.5 MHz, $CDCl_3$) 166.6 (d, 24.4 Hz, C=N), 145.1 (NCH[Me]*C*), 141.2 (8a-C), 130.3, 129.6 (4a-C), 128.7, 128.4, 127.8, 126.9, 126.1, 125.5, 96.9 (d, *J* 188.8 Hz, 2-C), 74.2 (d, *J* 24.4 Hz, COH), 60.2 (*C*HMe), 29.6 (d, *J* 23.9 Hz, 3-C), 25.9 (C[OH]CH_3), 25.5 (4-C), 25.5 (NCCH_3), 24.8 (C[OH]CH_3"); (Found: m/z 325.1836 ($M^{+\cdot}$). $C_{20}H_{20}FNO_2$ requires M 325.1842).

Spectroscopic data for the less polar diastereomer (**12-DII**): Optical rotation $[\alpha]_D$ +200.7 (20°C, chloroform, 0.304 g/100 ml); ν_{max} (neat) 3379 (broad, OH), 2976, 2940, 1455, 1367, 1072, 964 cm^{-1}; δ_H (250MHz, $CDCl_3$) 7.38 - 7.22 (9 H, m, ArH), 6.25 (1 H, broad s, OH), 5.03 (1 H, q, *J* 6.4 Hz, NC*H*), 3.04 - 2.66 (2 H, m, 4-H), 2.46 - 1.83 (2 H, m, 3-H), 1.58 (3 H, d, *J* 6.2 Hz, NCCH_3),1.43 (3 H, s, C(OH)CH_3), 1.13 (3 H, s, C(OH)CH_3"); δ_c (62.5 MHz, $CDCl_3$) 166.0 (d, 24.4 Hz, C=N), 145.1 (NCH[Me]*C*), 142.0 (8a-C), 130.4, 129.3 (4a-C), 128.8, 128.2, 128.0, 127.0, 126.0, 125.7, 96.8 (d, *J* 181.9 Hz, 2-C), 74.4 (d, *J* 23.4 Hz, COH), 61.0 (*C*HMe), 30.5 (d, *J* 23.8 Hz, 3-C), 26.2 (C[OH]CH_3), 25.7 (4-C), 25.7 (NCCH_3), 24.3 (C[OH]CH_3"); (Found: m/z 325.1828 ($M^{+\cdot}$). $C_{20}H_{20}FNO_2$ requires M 325.1842).

2-Fluoro-2-(2-hydroxyisopropyl)-1-tetralone (13-EI and 13-EII)

A heterogeneous solution of the hydroxyimine (**12-DI**) (0.301 g, 0.925 mmole) in dichloromethane (10 ml) and dilute hydrochloric acid (2M, 20 ml) was vigorously stirred for 20 hours. After this time no starting material was apparent by tlc analysis (7 :3 light petroleum [b.p. 40 - 60°C] : diethyl ether, starting material R_f 0.30 and product R_f 0.19). The aqueous layer was extracted with dichloromethane (2 x 50 ml). The organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to yield an orange oil. This was purified by flash chromatography (basic alumina, Brockmann Grade II with 7 : 3 light petroleum [b.p. 40 - 60°C] : diethyl ether) to yield the desired compound (**13-EI**) as a colourless solid; m.p. 74°C; Optical rotation: $[\alpha]_D$ -7.6 (25°C, chloroform, 0.724 g/100 ml); ν_{max} (film) 3781 (broad, OH, H-bonded), 2980 (Aryl C-H), 1684 (C=O), 1601, 1456 (Arene C-C) and 1229 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.01 (1 H, d,d, *J* 8.0, 1.0 Hz, 8-H), 7.52 (1 H, t,d, *J* 7.3, 1.3 Hz, 7-H), 7.34 (1 H, t, *J* 7.5 Hz, 6-H), 7.25 (1 H, d, *J* 7.6 Hz, 5-H), 3.54 (1 H, broad s, OH), 3.27 - 2.96 (2 H, m, 4-H), 2.58 - 2.21 (2 H, m, 3-H), 1.38 (3 H, s, Me), 1.37 (3 H, s, Me); δ_c (62.5 MHz, $CDCl_3$) 201.4 (1-C), 143.8 (8a-C), 134.2 (7-C), 132.0 (4a-C), 128.5 (6-C),128.2 (5-C), 126.9 (8-C), 95.3 (d, *J* 182.6 Hz, 2-C), 74.0 (d, *J* 22.6 Hz, *C*OH), 30.0 (d, *J* 22.8 Hz, 3-C), 25.8 (d, *J* 3.6 Hz, Me), 24.9 (d, *J* 7.8 Hz, 4-C), 24.1 (d, *J* 4.1 Hz, Me); (Found: m/z 222.1061 ($M^{+\cdot}$). $C_{11}H_{10}F_2O_2$ requires M 222.1056).

Ethyl 1-indanone-2-carboxylate (15)[23]

1-Indanone (**14**) (0.200 g, 1.51 mmole) in dry diethyl carbonate (distilled from sodium hydride, 5.5 ml, 45.4 mmole) was added, *via* syringe, to a stirred suspension of sodium hydride (0.073 g, 1.82 mmole) in dry diethyl carbonate (5.5 ml, 45.5 mmole).[24] The solution was heated to reflux for five minutes. During this time

a dark green solid was formed (note that on a larger scale using 2.00 g of 1-indanone (**14**), an exotherm was observed and no additional heat was required for the formation of this solid). Further diethyl carbonate (5 ml) was added. Tlc analysis of the solid (silica with 9:2 light petroleum [b.p. 40 - 60°C] : ethyl acetate) showed no evidence of any 1-indanone (**14**) (R_f 0.47), only the product (**15**) (R_f 0.56). The reaction mixture was heated to reflux for a further fifteen minutes, after which time it was allowed to cool to room temperature. The resultant solid was dissolved in HCl (aqueous 2M, 50 ml). The aqueous phase was extracted with ethyl acetate (4 x 50 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield a brown oil (0.611 g). The sample was purified by column chromatography (silica with 9:1 light petroleum [b.p. 40 - 60°C] : ethyl acetate) to yield a colourless oil (**15**) (0.265 g, 86%); ν_{max} (neat) 3009 (aromatic C-H), 1740 (ester C=O of ketoester), 1714 (a-aryl ketone C=O), 1650 (enol ester C=O), 1573, 1465 (arene C-C), 1370, 1258, 1208, 1187, 1153, 1093 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 12.5 (1H, broad s, OH), 7.74 - 7.32 (8H, m, ketoester and enol ArH), 4.74 - 4.12 (4H, m, ketoester and enol CH_2CH_3), 3.67 (1H, d,d, *J* 8.2, 4.1 Hz, 2-H), 3.68 - 3.29 (4H, m, ketoester and enol 3-H), 1.38 - 1.26 (6H, m, ketoester and enol CH_2CH_3); δ_C (62.5MHz, $CDCl_3$) 199.5 (ketoester 1-C), 169.1 (ketoester 2-CO_2Et), 153.7 (enol 1-C), 143.0 (ketoester 7a-C), 135.3 (ketoester 7-C), 135.2 (ketoester 3a-C), 129.3 (enol 7-C), 127.7 (ketoester 6-C), 126.8 (enol 6-C), 126.6 (ketone 5-C), 124.7 (enol 5-C), 124.4 (ketone 4-C), 120.5 (enol 4-C), 102.5 (enol 2-C), 61.5 (ketoester CH_2CH_3), 60.0 (enol CH_2CH_3), 53.3 (ketoester 2-C), 32.5 (enol 3-C), 30.3 (ketone 3-C), 14.4 (enol CH_2CH_3), 14.2 (ketoester CH_2CH_3).

Ethyl 2-fluoro-1-indanone-2-carboxylate (16)

To a stirred suspension of sodium hydride (60% dispersion in oil, 0.098 g, 2.45 mmole) in DMF (0.5 ml), at 0°C and under nitrogen, was added ethyl 1-indanone-2-carboxylate (**15**) (0.500 g, 2.45 mmole in DMF (2.5 ml). This was left to stir at 0°C for thirty minutes.[25] A solution of N-fluoro, N-chloromethyl triethylenediamine bis(tetrafluoroborate) (80% active ingredient, 0.986 g, 2.23 mmole) in DMF (5 ml) was then added dropwise to the above solution at -50°C. The solution was allowed to warm slowly to room temperature and left to stir for five minutes, after which time the reaction appeared to be complete by tlc chromatography (silica with 9:2 light petroleum [b.p. 40 - 60°C] : ethyl acetate) (Starting material: R_f 0.48 and 0.17, with streaking between; Product: R_f 0.30). The reaction was left to stir for a further twenty five minutes. After this time, the reaction mixture was poured into a separating funnel containing diethyl ether (100 ml). This solution was washed with $NaHCO_3$ solution (10% aqueous, 100 ml) and NaCl solution (saturated aqueous, 100 ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow oil (**16**) (0.635 g). The crude product was then purified by flash chromatography (silica with 9:1 light petroleum [b.p. 40 - 60°C] : ethyl acetate) to yield a very pale yellow oil (73%); ν_{max} (neat) 2986 (aromatic C-H), 1766 (ester C=O), 1728 (ketone C=O), 1608, 1467, 1298, 1216, 1193, 1074 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.82 (d, 1H, *J* 7.6 Hz, 7-H), 7.72 (t, 1H, *J* 7.6 Hz, 6-H), 7.54 - 7.47 (m, 2H, 5-H, 4-H), 4.27 (q, 2H, *J* 7.1 Hz, CH_2CH_3), 3.81 (d,d, 1H, *J* 17.7, 11.7 Hz, 3-H), 3.43 (d,d, 1H, *J* 23.4, 17.7 Hz, 3-H'), 1.24 (t, 3H, *J* 7.1 Hz, CH_3); δ_c (62.5 MHz, $CDCl_3$) 195.3 (d, *J* 17.5 Hz, 1-C), 167.3 (d, *J* 27.2 Hz, CO_2Et), 150.9 (d, *J* 3.2 Hz, 7a-C), 136.7, 133.3 (3a-C), 128.6, 126.6, 125.6, 94.5 (d, *J* 200.3 Hz, 2-C), 62.6 (CH_2CH_3), 38.3 (d, *J* 23.5 Hz, 3-C), 14.0 (CH_2CH_3); (Found: m/z 240.1035 ($M+NH_4^{+\cdot}$). $C_{12}H_{11}FO_3$ requires MNH_4 240.1036).

Ethyl 2-fluoro-1-[(*R*)-(+)-α-methylbenzylimino]-indanone-2-carboxylate (17)

To a stirring solution of ethyl 2-fluoro-1-indanone-2-carboxylate (**16**) (3.973 g, 17.88 mmole) and α-methylbenzylamine (6.500 g, 6.92 ml, 53.64 mmole) in benzene (dry, 100 ml) was added titanium tetrachloride (1.0M in dichloromethane, 9.83 ml, 9.83 mmole), at 0°C and under nitrogen. After one hour at 0°C, the reaction was allowed to warm to room temperature and left to stir for a further one hour. After this time, the benzene was removed *in vacuo*, dichloromethane (100 ml) was added, followed by diethyl ether (50 ml). The resulting suspension was filtered through glasswool. Solvent was removed *in vacuo* from the resulting filtrate, which was then purified by flash chromatography (basic alumina, Brockmann Grade I with 9 : 1 light petroleum [b.p. 40 - 60°C]). The imine diastereomers eluted together and were concentrated *in vacuo* to yield a colourless residue.

Diastereomer I (**17-DI**) colourless crystalline solid (1.334 g, 23%); m.p. 105°C; Optical rotation: $[\alpha]_D$ +13.6 (25°C, chloroform, 0.568 g/100 ml); ν_{max} (neat) 2981, 1756, 1659, 1190, 1062 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.93* (1 H, d, *J* 7.4 Hz, ArH), 7.77 (1 H, d, *J* 7.7 Hz, ArH), 7.44 - 7.19 (8 H from *syn-* and 8 H from *anti-* isomer, m, ArH), 5.42 (1 H, d,q, *J* 2.3, 6.5 Hz, NCH), 5.10* (1 H, d,q, *J* 2.2, 6.2 Hz, NCH), 4.47 - 4.22 (2 H, m, CH_2CH_3), 4.07 - 3.89* and 3.81 - 3.68* (2 H, 2 m, CH_2CH_3), 3.68 - 3.26 (2 H from *syn-* and 2 H from *anti-* isomer, m, 3-H), 1.60* (3 H, d, *J* 6.3 Hz, Me protons), 1.59 (3 H, d, *J* 6.4 Hz, Me protons), 1.30 (3 H, t, *J* 7.1 Hz, CH_2CH_3), 0.84* (3 H, t, *J* 7.2 Hz, CH_2CH_3); The isomers of this compound are in a ratio of 9 : 1. This proton spectrum was decoupled at the methyl group (CH_2CH_3) appearing at δ_H 0.82, causing the multiplets of the methylene protons (CH_2CH_3)at δ_H 4.07 - 3.89 and 3.81 - 3.68 to become doublets; δ_c (62.5 MHz, $CDCl_3$) 169.6* (d, *J* 28.7 Hz, CO_2Me), 162.4* (d, *J* 15.3 Hz, N=C), 146.4 (N-CH(CH_3)*C*), 145.3* (N-CH(CH_3)*C*), 143.7* (d, *J* 3.7 Hz, 7a-C), 137.6* (d, *J* 3.0 Hz, 3a-C), 132.2,* 128.7, 128.5,* 128.2,* 128.0, 127.7, 126.7,* 126.6, 126.2,* 125.1,* 123.6,* 94.3* (d, *J* 197.4 Hz, 2-C), 62.0* (CH_2CH_3), 61.7 (CH_2CH_3), 60.8* (NCH), 59.4 (NCH), 42.2* (d, *J* 25.4 Hz, 3-C), 39.6 (d, *J* 24.9 Hz, 3-C), 25.9* (Me carbon), 25.1 (Me carbon), 14.3 (CH_2CH_3), 13.3* (CH_2CH_3). NB. The quaternary and aromatic carbons of the minor isomer are not all visible in the carbon spectrum. Seven peaks are present for the aromatic CH carbons of the major isomer; only four peaks can be clearly identified for those of the minor isomer; (Found: m/z 325.147573 ($M^{+\cdot}$). C, 74.14; H, 6.41; N. 4.30%. $C_{20}H_{20}FNO_2$ requires M 325.147807. C, 73.81; H, 6.20; N, 4.31%). *Peaks of most abundant isomer.

Diastereomer II (**17-DII**): this contained approximately 20% of (**17-DI**). Identifiable peaks in the ^1H NMR spectrum are δ_H (250MHz, $CDCl_3$) 7.90* (1 H, d, *J* 7.9 Hz, ArH), 7.52 - 7.21 (8 H from *syn-* and 8 H from *anti-* isomer, m, ArH), 5.50 - 5.40 (1 H, NCH), 5.12* (1 H, d,q, *J* 2.2, 6.4 Hz, NCH), 4.41 - 4.26* (2 H, m, CH_2CH_3), 4.07 - 3.68 (2 H, 2 m, CH_2CH_3), 3.68 - 3.26 (2 H from *syn-* and 2 H from *anti-* isomer, m, 3-H), 1.68 (3 H, d, *J* 6.6 Hz, NCHCH_3), 1.49* (3 H, d, *J* 6.5 Hz, NCHCH_3), 1.32* (3 H, t, *J* 7.1 Hz, CH_2CH_3), 1.19 (3 H, t, *J* 7.2 Hz, CH_2CH_3).

Regeneration Of Ethyl 2-fluoro-1-indanone-2-carboxylate (16)

Ethyl 2-fluoro-1-[(*R*)-(+)-α-methylbenzylimino]-indanone-2-carboxylate (**17-DI**) (0.338 g, 1.038 mmole) was dissolved in dichloromethane (7.5 ml). To this was added 2M HCl (7.5 ml) and the solution vigorously stirred at room temperature for thirty six hours. The aqueous layer was then extracted with dichloromethane (3 x 100 ml). The organic extracts were dried (Na_2SO_4), and concentrated *in vacuo* to yield an orange oil (0.229 g, 99%). This oil was purified by flash chromatography (flash silica with 9 : 1 light

petroleum [b.p. 40 - 60°C] : diethyl ether) to yield a colourless solid (**16-EI**)(0.185 g, 80%); Optical rotation $[\alpha]_D$ -86.4 (25°C, chloroform, 0.428 g/100 ml). A further ~20% of the desired product was obtained, but in an impure form. Spectroscopic data as for racemic (**16**).

Removal of the imine from (**17-DI**) yielded the enantiomerically pure ketone (**16-EI**), and deprotection of (**17-DII**) gave the other enantiomer (**16-EII**). Both compounds had spectroscopic and physical data as previously described for the racemic material (**16**).

Chiral shift studies were carried out on the isolated enantiomers, using the chiral shift reagent $Eu(hfc)_3$. The proton NMR spectrum for (**16-EI**) showed no splitting of peaks with the chiral shift reagent. On addition of a racemic mixture of the ketone to the NMR sample, splitting was observed. From this it can be deduced that the parent imine consists of the *syn-* and *anti-* isomers of the same diastereomer, either (*R,R*) or (*R,S*). NB. The $Eu(hfc)_3$ shifts the 6-H proton of (**16-EI**) further up field than that of (**16-EII**). Baseline separation was observed for the most downfield proton with 2.7 equivalents of the chiral shift reagent.

Ethyl 3-(3,5-difluoro)-2,3-dehydropropionate (20)

To 3,5-difluorobenzaldehyde (**19**) (4.1134 g, 28.95 mmole) in dry dichloromethane (12 ml), under nitrogen and at room temperature, was carefully added (carboxymethylene)triphenylphosphorane (12.10 g, 34.74 mmole) in dry dichloromethane (12 ml). This produced an immediate exotherm. The reaction was left to cool to room temperature, after which time it appeared to have gone to completion by tlc. Tlc analysis was carried out using silica with 9:1 light petroleum [b.p. 40 - 60°C] : ethyl acetate, the product having an R_f value of 0.62 with this system. The dichloromethane was removed *in vacuo* to give a colourless solid. To this was added hexane (3 x 100 ml) and the mixture stirred for several minutes before the hexane was collected by filtration. The hexane fractions were concentrated *in vacuo* to yield an off-white solid (6.796 g). The product was purified by column chromatography (silica with 19:1 light petroleum [b.p. 40 - 60°C] : ethyl acetate) to give a colourless solid (**20**) (6.121 g, 99.7%); mpt. 38.5 - 39.0°C (recrystallized from light petroleum [b.p. 40 - 60°C]); ν_{max} (neat) 2985 (alkene C-H), 1716 (C=O), 1645, 1621, 1593 (α-carbonyl C=C), 1453 (arene C-C), 1440, 1311, 1280, 1181, 1121 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.57 (1 H, d, *J* 16.0 Hz [*trans*], C*H*CO_2), 7.03 (2 H, d,d, *J* 8.1, 1.9 Hz, C*H*CFCHCFC*H*), 6.87 - 6.78 (1 H, m, CFC*H*CF), 4.28 (2 H, q, *J* 7.2 Hz, CH_2CH_3), 1.34 (3 H, t, *J* 7.2 Hz, CH_2CH_3); (Found: m/z 212.0502 ($M^{+\cdot}$). $C_{11}H_{10}F_2O_2$ requires 212.0649).

Ethyl 3-(3,5-difluorophenyl)propionate (21)

To a round bottomed flask (250 ml) was added ethyl 3-(3,5-difluorophenyl)-2,3-dehydropropionate (**20**) (1.464 g, 6.90 mmole), 10% Pd/C (0.150 g), ethyl acetate (100 ml) and a magnetic stirrer. The flask was evacuated, then filled with hydrogen. This procedure was repeated six times to ensure an atmosphere of hydrogen. The solution was then left to stir overnight at room temperature. After this time, the reaction appeared to have gone to completion by tlc analysis (silica with 9:1 light petroleum [b.p. 40 - 60°C] : ethyl acetate) : The R_f value of the starting material was 0.61 and that of the product 0.54. The reaction mixture was filtered through Celite® to remove the palladium catalyst, then concentrated *in vacuo* to yield a clear liquid (1.461 g, 99%). This material was purified by column chromatography (silica with 19:1 light petroleum [b.p. 40 - 60°C] : ethyl acetate) to give a clear oil (**21**) (1.428 g, 97%); ν_{max} (neat) 3093 (aromatic C-H), 2984 (alkene C-H), 2938 (saturated C-H), 1736 (C=O), 1629, 1597, 1462 (arene C-C), 1376, 1186, 1161 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 6.76 (2 H, d,d, *J* 6.4, 2.1 Hz, CFC*H*CCH_2), 6.72 - 6.59 (1 H, m, CFC*H*CF), 4.14 (2 H, q,

J 7.0 Hz, CH_2CH_3), 2.93 (2 H, t, *J* 7.3 Hz, CH_2CO_2Et), 2.61 (2 H, t, *J* 7.3 Hz, $ArCH_2$), 1.24 (3 H, t, *J* 7.0 Hz, CH_2CH_3); δ_c (62.5 MHz, $CDCl_3$) 172.3 (CO_2), 162.9 (2 C, d,d, *J* 246.5, 12.7 Hz, C-F), 144.6 (t, *J* 9.2 Hz, $C[CH_2]_2CO_2Et$), 111.2 - 110.9 (2 C, m, $CFCHCCH_2$), 101.6 (t, *J* 25.3, CFCHCF), 60.5 (CH_2CH_3), 35.0 ($ArCH_2$), 30.5 (CH_2CO_2), 14.0 (CH_2CH_3); (Found: m/z 214.0812 ($M^{+\cdot}$). $C_{11}H_{12}F_2O_2$ requires 214.0805).

3-(3,5-Difluorophenyl)propionic acid (22)[21b]

Ethyl 3-(3,5-difluorophenyl)propionate (**21**) (0.700 g, 3.27 mmole) was dissolved in a mixture of ethanol (100 ml) and water (50 ml). To this was added potassium hydroxide (1.834 g, 32.68 mmole). The mixture was then heated to reflux for two hours with stirring. After this time, tlc analysis of the reaction mixture (silica with 9:1 light petroleum [b.p. 40 - 60°C] : ethyl acetate) showed baseline material only. The reaction was allowed to cool to room temperature, then the ethanol removed *in vacuo*. The aqueous fraction (diluted to 100 ml) was washed with dichloromethane (2 x 100 ml), acidified with hydrochloric acid (aqueous 2M) until a cloudy white suspension remained on shaking, then extracted with dichloromethane (3 x 100 ml). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield a pale yellow solid (**22**) (0.557 g, 92%). This was recrystallized from light petroleum [b.p. 40 - 60°C] to give a colourless crystalline solid (0.507 g, 84%); m.p. 59 - 60°C (lit[21b] m.p. 58 - 59°C from hexane); ν_{max} (neat) 3099, 3057, 2958 (CO_2H), 1703 (C=O), 1629, 1598, 1462, 1438, 1310, 1116 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 11.15 (1 H, broad s, CO_2H), 6.79 - 6.61 (3 H, m, ArH), 2.94 (2 H, t, *J* 7.6 Hz, $ArCH_2$), 2.68 (2 H, t, *J* 7.5 Hz, CH_2CO_2); δ_c (62.5 MHz, $CDCl_3$) 178.9 (CO_2H), 166.0 (2 C, d,d, *J* 246.6, 12.8 Hz, C-F), 143.8 (d, CFCHCF), 111.3 - 110.9 (2 C, m, $CFCHCCH_2$), 101.9 (t, *J* 24.9 Hz, CFCHCF), 34.8 ($ArCH_2$), 30.1 (d, *J* 1.7 Hz, CH_2CO_2); (Found: m/z 186.0461 ($M^{+\cdot}$). C, 57.97; H, 4.28%. $C_9H_8F_2O_2$ requires M 186.0492. C, 58.07; H, 4.33%).

5,7-Difluoro-1-indanone (23)[21b]

Polyphosphoric acid (6.0 g) was added to a round bottomed flask (25 ml), equipped with a magnetic stirrer and condenser. To this was added 3-(3,5-difluorophenyl)propionic acid (**22**) (0.314 g, 1.69 mmole).[21] The mixture was heated at 45°C for forty eight hours, with an attempt at stirring. After this time, the reaction mixture was allowed to cool to room temperature. Water (distilled, 100 ml) was mixed carefully with the reaction mixture to give a cloudy white suspension. This aqueous fraction was extracted with dichloromethane (3 x 100 ml). The organic extracts were reduced in volume, washed with sodium hydrogen carbonate solution (saturated, 3 x 100 ml), dried ($MgSO_4$), concentrated *in vacuo* and recrystallised from methanol to yield a colourless crystalline solid (**22**) (0.276 g, 97%); m.p. 81 - 81.5°C (lit[21b] m.p. 81 -82°C from hexane - chloroform); ν_{max} (neat) 3085 (aromatic C-H), 2925 (saturated C-H), 1711 (ester C=O of ketoester), 1679 (α-aryl ketone C=O), 1619 (enol ester C=O), 1593, 1439, 1326, 1208, 1124 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.96 (1 H, d,d, *J* 7.9, 1.8 Hz, 4-H), 6.74 (1 H, d,t, *J* 2.0, 9.2 Hz, 6-H), 3.15 (2 H, d,t, *J* 6.1, 0.5 Hz, 2-H), 2.75 - 2.72 (2 H, m, 3-H). No evidence of enol form in n.m.r.; δ_c (100 MHz, $CDCl_3$) 201.5 (d, J_{CF7} 2.0 Hz, 1-C), 167.8 (d,d, J_{CF5} 257.8 Hz, J_{CF7} 11.1 Hz, 5-C), 159.9 (d,d, J_{CF7} 266.6 Hz, J_{CF5} 14.1 Hz, 7-C), 159.4 (d,d, *J* 11.1, 4.0 Hz, 3a-C), 121.1 (d, 7a-C), 109.8 (d,d, J_{CF5} 22.14 Hz, J_{CF7} 5.0 Hz, 4-C), 103.8 (d,d, *J* 27.2, 23.1 Hz, 6-C), 37.2 (2-C), 26.4 (d, *J* 2.0 Hz, 3-C) Proton and carbon NMR spectra in agreement with the literature;[21b] (Found: m/z 168.0351 ($M^{+\cdot}$). C, 64.11; H, 3.52%. $C_9H_6F_2O$ requires M 168.0387. C, 64.28; H, 3.57%).

Methyl 5,7-difluoro-1-indanone-2-carboxylate (24)

To a stirred solution of LDA (0.892 ml, 1.78 mmole, 2.0M solution in heptane / tetrahydrofuran / ethylbenzene) in THF (dry, 2 ml) was added slowly dropwise (over forty five minutes), 5,7-difluoro-1-indanone (**23**) (0.200 g, 1.19 mmole) in THF (dry, 40 ml), at -78°C and under nitrogen. Stirring was continued for a further thirty minutes, after which time methylcyanoformate (0.111 g, 0.104 ml, 1.308 mmole) was added.[9] After stirring for half an hour at -78°C, the reaction mixture was allowed to warm to room temperature. After five minutes, at which time the reaction appeared to be complete by tlc, the reaction was poured into cold water (50 ml). The product was then extracted into diethyl ether (4 x 50 ml). The ethereal extracts were then dried (Na_2SO_4) and concentrated *in vacuo* to yield a brown solid (0.968 g). The crude material was purified by column chromatography (silica with 1:1 hexane : ethyl acetate) to give a colourless crystalline solid (**24**) (0.173 g, 64%); m.p. 94 - 95°C; ν_{max} (KBr disc) 3096 (aromatic C-H), 2934 (saturated C-H), 1735 (ester C=O of ketoester), 1700 (α-aryl ketone C=O), 1631 (ester C=O of ketoester),, 1593, 1444, 1222, 1123, 888 cm^{-1}; ν_{max} (neat), 3097, 3050, 2964, 2931, 1731, 1701, 1632 (medium-weak), 1595, 1124 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.99 (1 H, d,d, *J* 8.0, 0.8 Hz, keto 4-H [enol 4-H double doublet obscured underneath with the most downfield peak just visible at δ_H 7.01]), 6.78 (1 H, d,t, *J* 2.0, 9.0 Hz, keto 6-H [triplet of enol 6-H appears at δ_H 6.86]), 3.86 (3 H, s, enol OMe), 3.80 (3 H, s, keto OMe), 3.78 (1 H, d,d, *J* 8.4, 4.0 Hz, keto 2-H), 3.60 - 3.33 (2 H, ABX type system, keto 3-H [peaks of enol 3-H obscured]). Ratio of keto : enol tautomers is approximately 5 : 1; δ_c (100 MHz, $CDCl_3$) 193.8 (d, *J* 2.0 Hz, keto 1-C), 168.8 (keto *C*O_2Me), 168.0 (d,d *J* 260.6, 12.1 Hz, 5-C), 160.2 (d,d, *J* 268.6, 15.1 Hz, keto 7-C), 157.5 (d,d, *J* 12.1, 3.0 Hz, keto 7a-C), 147.3 (3a-C), 120.1 (enol 2-C), 109.6 (d,d, *J* 23.1, 4.0 Hz, keto 4-C), 108.7 (d, *J* 27.2 Hz, enol 4-C), 104.1 (d,d, *J* 27.2, 23.1, Hz, keto 6-C), 103.3 (d,d, *J* 27.2, 23.1 Hz, enol 6-C), 53.8 (keto OMe), 53.0 (keto 2-C), 33.2 (enol 3-C), 30.4 (d, *J* 2.0 Hz, keto 3-C), NB. Quaternary carbons of enol form not visible in spectrum; (Found: m/z 226 ($M^{+\cdot}$). C, 58.03; H, 3.49%. $C_{11}H_8F_2O_3$ requires C, 58.41; H, 3.57%).

Methyl 2,5,7-trifluoro-1-indanone-2-carboxylate (18)

To a stirred suspension of sodium hydride (80% dispersion in oil, 0.051 g, 1.703 mmole) in DMF (dry, 2 ml), at 0°C and under nitrogen, was added methyl 5,7-difluoro-1-indanone-2-carboxylate (**24**) (0.321 g, 1.419 mmole)in DMF (dry, 10 ml).[25] This was left to stir for twenty minutes at 0°C then the temperature was lowered to -50°C and the N-chloromethyl, N-fluoro ethylenediamine bis(tetrafluoroborate) (0.503 g, 1.419 mmole) added. The reaction was left to stir at -50°C for ten minutes then allowed to warm to room temperature. After stirring for one hour at room temperature, the reaction mixture was poured into a separating funnel containing diethyl ether (100 ml), washed with a saturated solution of sodium hydrogen carbonate (50 ml) and a saturated solution of sodium chloride (50 ml), dried (Na_2SO_4) and concentrated *in vacuo* to yield a pale yellow solid (0.489 g). This was purified by flash chromatography (silica with 3 : 1 light petroleum [b.p. 40 - 60°C] : ethyl acetate) to give a colourless solid (0.289 g, 83%); ν_{max} (KBr disc) 2968, 1764, 1733, 1620, 1602, 1415, 1327, 1229, 1213, 1126, 854 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.01 (1 H, d,d, *J* 7.6 0.8 Hz, 4-H), 6.85 (1 H, d,d, *J* 8.9, 1.9 Hz, 6-H), 3.84 (3 H, s, OMe), 3.79 (1 H, d,d, *J* 18.0, 11.4 Hz, 3-H), 3.43 (1 H, d,d, *J* 22.7, 18.0 Hz, 3-H); δ_c (100 MHz, $CDCl_3$) 169.6 (d,d, *J* 262.6, 12.1 Hz, 5-C), 167.2 (d, *J* 28.2 Hz, 7a-C), 161.0 (d,d, *J* 269.6, 13.1 Hz, 7-C), 154.4 (d, *J* 12.1 Hz, 3a-C), 110.1 (d,d, *J* 23.1, 4.0 Hz, 4-C), 105.2 (d,d, *J* 26.2, 22.1 Hz, 6-C), 94.9 (d, *J* 203.2 Hz, 2-C), 53.7 (OMe), 38.4 (d, *J* 24.1 Hz, 3-C); (Found: m/z 244.0348 ($M^{+\cdot}$). $C_{11}H_7F_3O_3$ requires 244.0347).

General Procedure for *in situ* Dioxirane Reactions

All apparatus was meticulously washed with EDTA.Na_2 solution,[26] followed by distilled acetone,[27] then dried before use. The assembled glassware was then covered in aluminium foil to help eliminate light.

To the reaction flask, at 0°C, was added phosphate buffer (25 ml),[28] dichloromethane (X ml, determined by the quantity of ketone used),[29] tetrabutylammonium hydrogen sulphate (~ 0.002 g), the alkene (1 equivalent) and the ketone (2 equivalents, 0.5 M concentration in the dichloromethane). The pH of the vigorously stirred solution was adjusted to between pH 7.0 and 7.5 by the addition of KOH solution.[30] Solid Oxone® (30 equivalents) was added over approximately half an hour, the pH being maintained between pH 7.0 and 7.5 throughout, by the addition of KOH solution.[30] The reaction was left to stir for a further four hours, then a sample taken for GC or ^{1}H NMR analysis. If the reaction had not gone to completion, a further portion of solid Oxone® (30 equivalents) was added, portionwise. The reaction left to stir for several hours, a GC or ^{1}H NMR analysis carried out, and if the epoxidation reaction was still incomplete, further solid Oxone® added. This was repeated until the either the reaction was complete, or, if the reaction was slow, until sufficient epoxide had been formed for chiral shift analysis to be performed. If the reaction needed to be left overnight, the stirring was stopped and then resumed the following morning.

The reaction mixture was then filtered through glasswool into a separating funnel. Dichloromethane (3 x 35 ml) was then used to rinse out the reaction flask and extract the aqueous phase. The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was analysed by GC and / or ^{1}H NMR spectroscopy. The epoxide and ketone were then isolated by flash chromatography.

For the reactions using the dioxirane derivatives of a homochiral ketone, the optical rotation of the isolated epoxide was determined and a ^{1}H NMR chiral shift experiment, using Eu(hfc)$_3$, carried out. The number of equivalents of chiral shift reagent needed for determination of enantiomer ratio were: *trans*-stilbene oxide : 0.05 equivalents; *trans*-β-methyl styrene oxide : 0.20 equivalents; 6-chloro-2,2-dimethyl-2H-1-benzopyran oxide : 0.15 equivalents

All chiral shift experiments revealed a 1 : 1 ratio of the epoxide enantiomers, consequently no optical rotation was seen in any of the cases.

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26. The EDTA.Na_2 solution was composed of 4 g EDTA.Na_2 in 2500 ml of distilled water. The EDTA.Na_2 was present to sequester any metal ions present in the reaction mixture.
27. The acetone was distilled from $KMnO_4$.
28. The phosphate buffer solution was made up using 20 g [85%] H_3PO_4 in 2000 ml of EDTA.Na_2 solution (*cf.* Ref. 26), made to pH 7.2 with NaOH (~29 g).
29. Dichloromethane was distilled from P_2O_5 before use.
30. The KOH solution was made up of 10% KOH in EDTA.Na_2 solution (*cf.* Ref. 26).

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