^1H and ^2H Nuclear Magnetic Resonance Determination of the Enantiomeric Purity and Absolute Configuration of α-Deuteriated Primary Carboxylic Acids, Alcohols, and Amines

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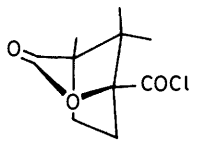
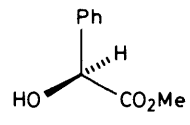
The enantiomeric composition and absolute configuration of α-deuteriated primary carboxylic acids may be accurately determined by ^1H and ^2H nuclear magnetic resonance analysis of the corresponding esters of (*S*)-methyl 2-hydroxy-2-phenylethanoate (2). Similar methods with (*S*)-2-acetoxy-2-phenylethanoic acid (3) and (−)-camphanoyl chloride (1) as chiral reagents have enabled the enantiomeric purity of α-deuteriated primary alcohols and primary amines to be assayed. These chiral reagents may also be used to determine the enantiomeric composition of chiral secondary acids, alcohols, and amines.

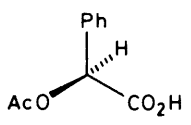
As a result of the growing interest in stereoisomerism apparent in many branches of biochemistry, chemistry, and pharmacology, there is a need for more accurate and versatile methods for determining the enantiomeric purity and absolute configuration of chiral molecules. Considerable progress has been made in the development of chiral stationary phases for the chromatographic separation of enantiomers,[1-5] but such methods are not applicable for compounds which owe their chirality to isotopic substitution. The analysis of these compounds is of particular importance for determining the steric course of enzymatic and microbiological conversions [6-8] and in the elucidation of biosynthetic pathways.[9,10] The classical approach is to use chiroptical methods [11] which are rendered difficult because of the low rotations and weak c.d. spectra involved. Following the initial studies of Mislow,[12] various n.m.r. techniques have been employed for the determination of enantiomeric purity, using chiral solvating agents,[13] chiral lanthanide shift reagents,[14] and chiral derivatising agents.[15] Although α-deuteriated benzyl alcohols may be directly assayed by n.m.r. with chiral shift reagents,[16] this method is not generally applicable and chiral derivatising agents have proved to be more useful. Gerlach introduced (−)-camphanoyl chloride (1) as such a chiral derivatising agent and found that n.m.r. analysis of camphanate esters of chiral α-deuteriated primary alcohols in the presence of an achiral shift reagent facilitated the estimation of the enantiomeric purity of the chiral alcohol.[17] Schwab, for example has recently used Gerlach's method to elucidate the stereochemistry of an enzymatic Baeyer–Villiger reaction using ^2H n.m.r.[6] The approach described here, involves the use of the cheap, chiral derivatising agents (2) and (3) [derived from (*S*)-mandelic acid] for estimating the enantiomeric purity of chiral α-deuteriated acids and alcohols respectively by ^1H and ^2H n.m.r. analysis of the corresponding esters. Furthermore, (1) may be used as a chiral derivatizing agent for α-deuteriated primary amines by n.m.r. analysis of the corresponding amides in the absence of added shift reagent.



(1)



(2)



(3)

Results and Discussion

The basis of the n.m.r. method involves conversion of a mixture of enantiomers $\bar{X}$ and X into a diastereoisomeric mixture XY and $\bar{X}$Y by reaction with an enantiomerically pure, chiral reagent Y under non-racemising conditions. The diastereomeric ratio XY : $\bar{X}$Y will then be equal to the enantiomeric ratio X : $\bar{X}$ and may be determined by direct integration of anisochronous resonances in the n.m.r. spectrum of the diastereoisomeric mixture. Reaction of (3) with (*R*)-[1-^2H]-butan-1-ol [18] promoted by dicyclohexylcarbodi-imide in the presence of 4-dimethylaminopyridine [19] in dichloromethane at −10 °C gave the ester (4a) which was purified by preparative t.l.c. The ^1H n.m.r. spectrum of this ester in [$^2H_6$]benzene is shown in Figure 1, together with the spectrum of the unlabelled ester (4b) prepared from achiral butan-1-ol. The geminal α-methylene protons of the unlabelled ester are 0.09 p.p.m. anisochronous and are coupled to each other (J 10.6 Hz) and to the adjacent methylene protons giving the symmetrical twelve-line multiplet. The chiral α-deuteriated ester (4a) gave a simple triplet, broadened by coupling to the geminal deuterium (J_{HD} 1.6 Hz). As the absolute configuration of the α-deuteriated butan-1-ol was known,[18] the prochirality of the geminal methylene protons in (4b) was established, the *pro-R* hydrogen resonating to high field of the *pro-S*. The observation of no significant loss of deuterium in the ^1H n.m.r. spectrum of (4a) indicates a similarly small extent of racemisation (<0.05%) during derivatisation. Esters (4c—e) were prepared in a similar manner and exhibited anisochronous α-methylene protons, the non-equivalence varying between 0.09 and 0.12 p.p.m. (Table 1). For purposes of comparison, the ethyl ester of Mosher's acid,[20] 2-methoxy-2-phenyl-2-(trifluoromethyl)ethanoic acid (5) gives a ^1H n.m.r. spectrum in which the diastereotopic CH_2 protons are only 0.03 p.p.m. chemical shift non-equivalent.

Reaction of primary carboxylic acids RCH_2CO_2H with (*S*)-methyl 2-hydroxy-2-phenylethanoate (2) in dichloromethane at −10 °C (using dicyclohexylcarbodi-imide and 4-dimethylaminopyridine) gave the corresponding esters (6a—e) which were purified by distillation or chromatography on silica. The chemical shift differences for the diastereoisotopic geminal methylene protons were typically of the order of 0.12 p.p.m. in [$^2H_6$]benzene (Table 1). Using authentic samples of (2*S*)-[2,3-$^2H_2$]propanoic acid,[21] (2*S*,3*R*)-[2,3-$^2H_2$]-3-phenylpropanoic acid,[22] (2*R*,3*R*)-[2,3-$^2H_2$]butanoic acid,* and (2*R*,3*R*)-[2,3-$^2H_2$]-4-methylpentanoic acid,† the corresponding man-

* (2*R*,3*R*)-[2,3-$^2H_2$]sodium butanoate; $[\alpha]^{20}_{365}$ −1.89°.[21]
† Prepared by reduction of 4-methylpentenoic acid in D_2O (with P. Anaerobius); $[\alpha]^{20}_{365}$ −1.64°; supplied by Professor H. Simon.

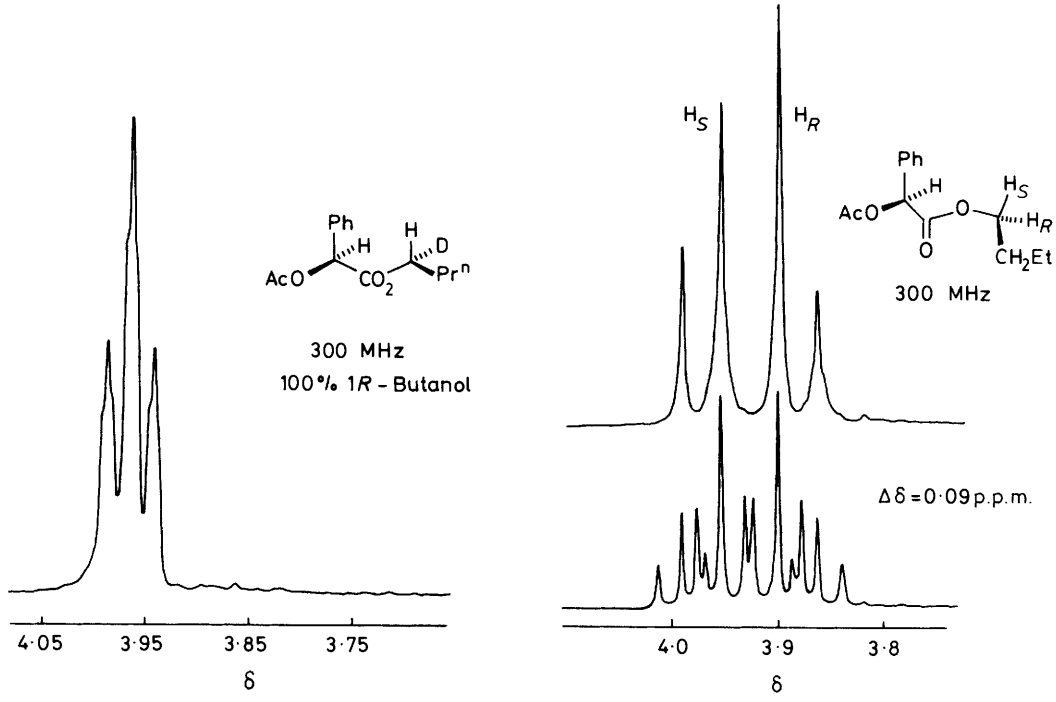
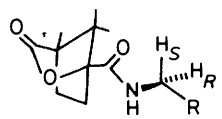
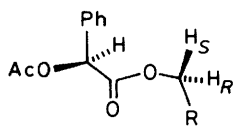
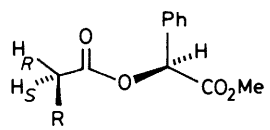


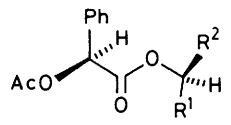
Figure 1. 300 MHz ^{1}H N.m.r. spectrum of (4a and b); the upper spectrum was recorded with irradiation of the adjacent methylene group

Table 1. ^{1}H N.m.r. data for chiral derivatives of primary acids, amines, and alcohols

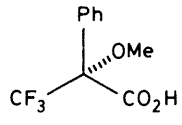
Compound		Chemical shifts (p.p.m.) [b]			
		δ_{H_R}	δ_{H_S}	$\Delta\delta_{H_R,S}$	$J_{H_RH_S}$/Hz
	(7a)	2.89	3.04	0.15	17.5
	(7b)	2.91	3.12	0.21	14.3
	(7c)	2.95	3.11	0.16	13.6
	(7d)	4.12	4.25	0.13	14.8
	(4b)	3.86	3.95	0.09	10.6
	(4c)	3.85	3.97	0.12	11.8
	(4d)	3.80	3.87	0.07	10.5
	(4e)	4.85	4.96	0.11	15.0
	(5) [a]	3.89	3.92	0.03	11.2
	(6a)	2.53	2.41	0.12	17.5
	(6b)	2.19	2.07	0.12	15.7
	(6c)	2.32	2.21	0.11	15.6
	(6d)	3.54	3.46	0.08	15.3
	(6e)	2.56	2.43	0.13	16.8

[a] Ethyl ester of Mosher's acid (5). [b] Spectra recorded in [$^2H_6$]benzene solution at 298 K.

delate esters of (2) were prepared. ^{1}H N.m.r. spectra of these esters revealed that the *pro-S* hydrogen consistently resonates to high field of the *pro-R*. Such consistency enabled the absolute configuration of α-monodeuteriated primary carboxylic acids to be assigned by this n.m.r. method. The enantiomeric purity of the chiral α-deuteriated acids may also be determined using ^{2}H n.m.r.[23] With the mandelate ester derived from achiral [2,3-$^2H_2$]propanoic acid, for example, two cleanly separated singlets were observed at δ 2.53 and 2.41 p.p.m. in a 1 : 1 ratio (for efficient resolution of these resonances, ^{2}H n.m.r. at frequencies of at least 38.5 MHz is desirable with broad-band proton decoupling). Figure 2 shows the ^{1}H and ^{2}H n.m.r. spectra of the mandelate ester of (2*R*,3*R*)-[2,3-$^2H_2$]-4-methylpentanoic acid, together with the ^{1}H n.m.r. spectrum of (6c) for comparison. The original sample of the labelled acid was contaminated by a small

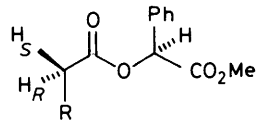


(4)



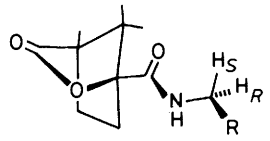
(5)

a; R^1 = ^2H, R^2 = Pr^n
b; R^1 = H, R^2 = Pr^n
c; R^1 = H, R^2 = Me
d; R^1 = H, R^2 = Et
e; R^1 = H, R^2 = Ph



(6)

a; R = Me
b; R = Et
c; R = CH_2CHMe_2
d; R = Ph
e; R = CH_2Ph



(7)

a; R = Me
b; R = Et
c; R = Pr^n
d; R = Ph

amount of acid where C-2 H/^{2}H exchange had occurred,* so that the ^{1}H n.m.r. spectrum did not allow direct integration of H_R and H_S to establish the enantiomeric purity of the sample. That the purity of the unexchanged compound is >99.5% 2*R* is clearly demonstrated in the ^{2}H n.m.r. spectrum (Figure 2).

Reaction of (1*S*,4*R*)-camphanoyl chloride with various primary amines in the presence of triethylamine at 0 °C in dichloromethane gave the corresponding amides (7a—d). The chemical shift non-equivalence of the geminal CH_2 protons in benzene varied between 0.13 and 0.21 p.p.m. (Table 1). Chiral amides were also prepared from (2*S*)-[2-^{2}H]ethylamine † and (2*S*,3*S*)-[2,3-$^2H_2$]propylamine ‡ and ^{1}H n.m.r. analysis revealed that in each case the *pro-S* hydrogen resonates to low field of the *pro-R*. The configuration about the rotationally hindered amide bond is presumably *Z* rather than *E* and efforts to determine the *Z* : *E* ratio for (7a) by variable temperature (10—50 °C) n.m.r. measurements revealed a broadening of the NH proton with increasing temperature ($\omega_{\frac{1}{2}}$ 18 at 10, 30 Hz at 50 °C) accompanied by a small decrease in chemical shift non-equivalence for H_R and H_S (Δδ 0.16 at 10, 0.125 p.p.m. at 50 °C). *Z* to *E* interconversion is very slow on the n.m.r. timescale in this solvent at room temperature.

A sample of [2,3-$^2H_2$]ethylamine prepared by addition of deuterium to *N*-vinylacetamide using a chiral biphosphine-rhodium catalyst,[24] followed by acidic hydrolysis, was assayed using this method. ^{1}H and ^{2}H n.m.r. spectra of the derived amide and of (7a) are shown in Figure 3. The ^{1}H n.m.r. spectrum of (7a) recorded at 300 MHz reveals the *pro-R* and *pro-S* hydrogens to be 0.15 p.p.m. anisochronous, and

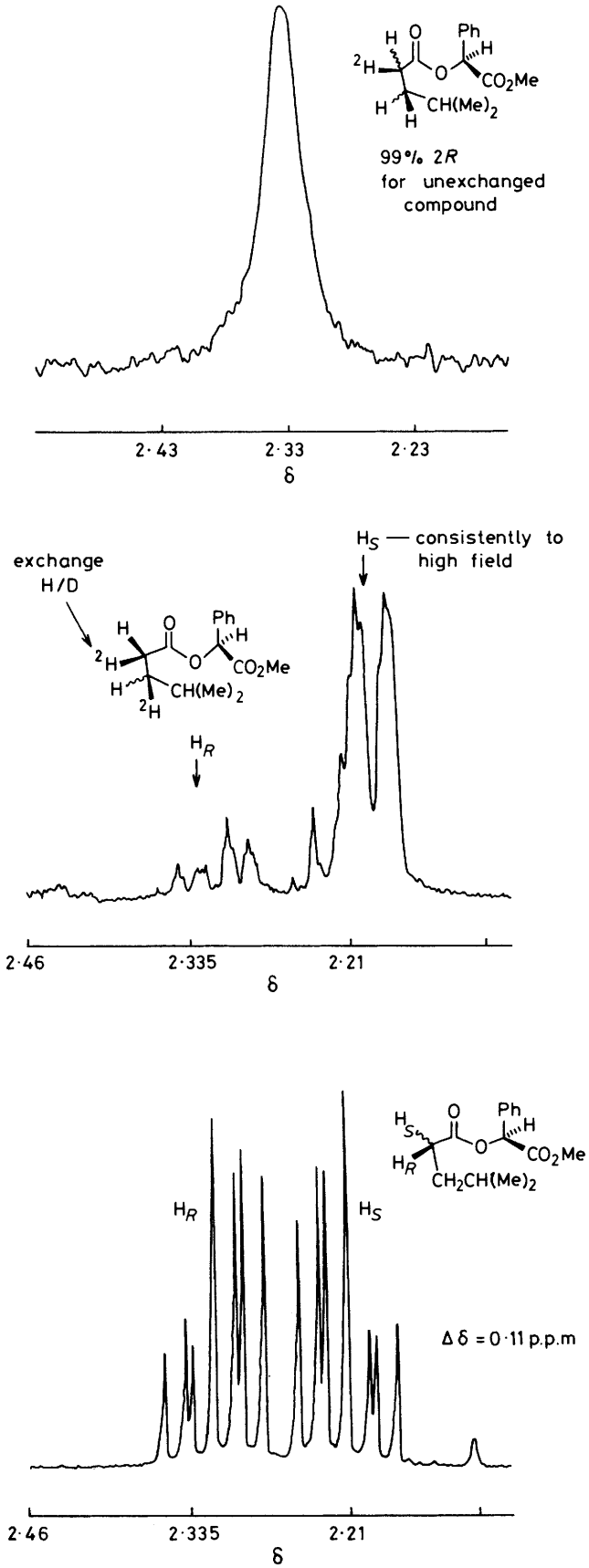


Figure 2. Lower spectrum, 400 MHz ^{1}H n.m.r. of (6c) in [$^2H_6$]benzene; centre, 400 MHz ^{1}H n.m.r. spectrum of labelled ester; upper, 6.4 MHz ^{2}H n.m.r. spectrum of labelled ester in benzene

* The ratio of 2-^{2}H : 3-^{2}H as determined by ^{2}H n.m.r. was constant for the acid and the derived chiral ester.

† Prepared by Schmidt degradation of (2*S*)-[2,3-$^2H_2$]propanoic acid.[21]

‡ A sample from Professor H. Simon; full details of the spectral analysis of chirally labelled materials will be reported (H. Gunther, D. Parker, and H. Simon, unpublished data).

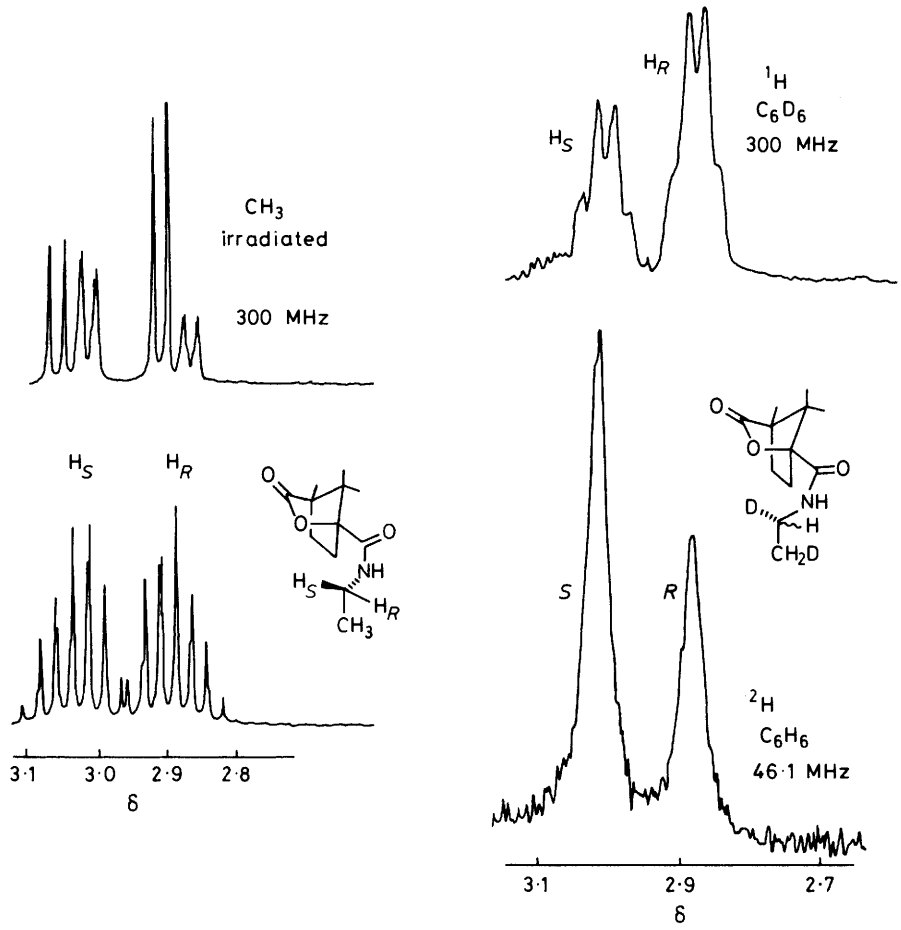
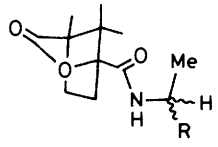
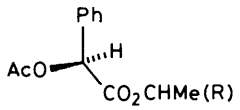
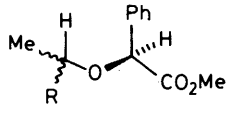


Figure 3. 300 MHz ^1H N.m.r. spectrum of (7a) (upper trace was recorded with irradiation of the adjacent methyl group) and of labelled amide

Table 2. ^1H Chemical shift differences for diastereoisotopic nuclei in chiral derivatives

Compound	R	Chemical shift differences (p.p.m.) [a] ΔδC–Me	ΔδC–H [c]	ΔδC–H [b]
	Me	0.04		
	Ph	0.05	0.05	
	Me	0.16		
	Ph	0.12	0.02	0.04
	Me	0.12		
	Ph	0.09	0.07	0.04
	$PhCH_2$	0.12		0.045

[a] Spectra recorded in [$^2H_6$]benzene at 298 K. [b] C–H of mandelate moiety. [c] CH of chiral acid, alcohol, or amine. [d] Less than 0.01 p.p.m.

these are coupled both to each other (J 17.5 Hz), to the adjacent methyl group and to the amide proton to generate the observed 32 line pattern. Integration of the separated *pro-R* and *pro-S* resonances of the ^1H and ^2H n.m.r. spectra of the chirally labelled material gives a direct measure of enantiomeric composition.

Compounds (1)—(3) may also be used as chiral derivatising agents for secondary amines, acids, and alcohols. The observed diastereoisotopic non-equivalences for various derived amides and esters are given in Table 2. The magnitude of the observed non-equivalences enables enantiomeric composition to be directly determined by integration of the separated resonances. When compounds (1)—(3) were reacted with several racemic, amines, acids, and alcohols and the reaction stopped before completion, the ratio of diastereoisomers was observed to be 50 : 50 (±2%) as determined by n.m.r. integration, indicating that no significant asymmetric induction had occurred during derivatisation.

In summary, (1)—(3) are useful chiral derivatising agents which are cheap and readily available in pure form.* They facilitate estimation of the enantiomeric purity of chiral α-deuteriated primary amines, acids, and alcohols by examination of the ^1H and ^2H n.m.r. spectra of the chiral derivatives. In the case of chiral esters of primary α-deuteriated carboxylic acids with (2), the *pro-S* hydrogen resonates consistently to high field of the *pro-R* enabling absolute configuration to be assigned. Using (3) as a chiral reagent for α-deuteriated primary alcohols, it would seem likely that the *pro-R* hydrogen will also consistently resonate to high field of the *pro-S*. Preliminary experiments have indicated that this is also the case for chiral amides of primary α-deuteriated amines with (1). In principle, the accuracy of these n.m.r. methods is limited by the homogeneity of the superconducting magnet used which controls the observed signal : noise ratio.† Application of ^3H n.m.r. may also be envisaged in conjunction with the described methods for assaying the enantiomeric composition of suitable chirally labelled α-tritiated acids, alcohols, and amines.[25]

Experimental

M.p.s were determined on a Reichert–Kofler block and are uncorrected. ^1H N.m.r. spectra were obtained on either a Bruker WH300 (300.13 MHz), a Bruker SY200, or a Bruker WH400 (400.12 MHz) instrument. Chemical shifts of anisochronous geminal methylene protons were determined by irradiating the adjacent methyl or methylene group with minimal decoupling power and then assigning the AB chemical shifts using the relation $\delta_A - \delta_B = (\nu_4 - \nu_1)(\nu_3 - \nu_2)$ (ν_1 at higher field than ν_4). ^2H N.m.r. spectra were recorded on a Bruker WH300 (46.1 MHz) or a Bruker WH400 (61.4 MHz) instrument and chemical shifts were referenced against internal [$^2H_6$]benzene. Mass spectra were determined on a V.G. Micromass 16F spectrometer or on a Varian MS9. Microanalyses were performed by Dr. F. B. Strauss (University of Oxford) and by M. Cocks (University of Durham). I.r. spectra were recorded using a Perkin-Elmer 257 spectrometer or a Beckman IR-12 spectrophotometer. Optical rotations were recorded using a Perkin-Elmer 141 polarimeter. Representative procedures for preparation of chiral esters and amides are given below.

(S)-*Methyl* 2-*Acetoxy*-2-*phenylethanoate*.—To a solution of propanoic acid (148 mg, 2.0 mmol) and 4-dimethylaminopyridine (5.0 mg), in dichloromethane (10 cm^3) at −10 °C was added (*S*)-methyl 2-hydroxy-2-phenylethanoate (2) (332 mg, 2.0 mmol) and dicyclohexylcarbodi-imide (412 mg, 2.0 mmol) and the mixture was stirred (3 h). After filtration of the precipitated urea, solvent was removed under reduced pressure and the residue taken up in dichloromethane (4 cm^3) and filtered again. Removal of solvent under reduced pressure gave a liquid which was distilled ‡ (bath temperature 100 °C; 0.1 mmHg §) (200 mg, 90%); $[\alpha]_D^{20}$ −137.2° (*c* 1.2, $CHCl_3$) {lit.[26] $[\alpha]_D^{20}$ −135.5° (*c* 1.0, $CHCl_3$}, $\delta_H(C_6D_6)$ 7.50—7.20 (5 H, m, ArH), 6.09 (1 H, s, CHO), 3.17 (3 H, s, OMe), 2.53 (1 H, dq, H_R), 2.41 (1 H, dq, $J_{H_RH_S}$ 17.5, J_{vic} 7.5 Hz, H_S), and 1.22 (3 H, t, Me), *m/e* 222, 190, 166, 105, and 71.

(1S,4R)-(−)-*Ethylcamphanamide* {(1S,4R)-N-*Ethyl*-(3-*oxo*-4,7,7-*trimethyl*-2-*oxabicyclo*[2.2.1]*heptane*-1-*carboxamide*) (7a).—To a suspension of ethylamine hydrobromide (126 mg, 1.0 mmol) in dry dichloromethane (5 cm_3) was added triethylamine (150 mg, 1.5 mmol) and (−)-camphanoyl chloride (238 mg, 1.1 mmol) and the mixture was stirred at 0 °C (3 h). The solution was poured into dilute aqueous sodium hydroxide solution (0.5M; 20 cm^3) and extracted with dichloromethane (3 × 10 cm^3), washed with water (2 × 10 cm^3), dried ($MgSO_4$), filtered, and solvent removed under reduced pressure to give a solid which was sublimed (bath temperature 70 °C; 0.09 mmHg) to give needles (200 mg, 89%), m.p. 92—93° (Found: C, 64.1; H, 8.3; N, 6.2. $C_{12}H_{19}NO_3$ requires C, 64.0; H, 8.45; N, 6.2%); $\delta_H(C_6D_6)$ 6.15br (1 H, s, NHCO), 3.04 (1 H, ddq, H_S), 2.89 (1 H, ddq, $J_{H_RH_S}$ 17.5, J_{vic} 6.0 Hz, H_R), 2.32 (1 H, m), 1.58 (1 H, m), 1.24 (1 H, m), 1.18 (1 H, m), 0.85, 0.84 (6 H, s + s, CMe_2), 0.71 (3 H, s, OCCMe), and 0.70 (3 H, t, CH_2Me); *m/e* 225, 178, 154, 115, 109, and 83; $[\alpha]_D^{20}$ −42.6° (*c* 0.44, $CHCl_3$).

(S)-*Butyl* 2-*Acetoxy*-2-*phenylethanoate*.—To a solution of (*S*)-2-acetoxy-2-phenylethanoic acid (194 mg, 1.0 mmol) and 4-dimethylaminopyridine (5.0 mg) in dry dichloromethane (10 cm^3) at −10 °C, was added butan-1-ol (111 mg, 1.5 mmol) and dicyclohexylcarbodi-imide (206 mg, 1.0 mmol) and the mixture stirred (6 h). After filtration of the precipitated urea, solvent was removed under reduced pressure, and the residue was purified by preparative t.l.c. on silica gel (Merck 60 $PF_{254,366}$) eluting with ethyl acetate–hexane (1 : 2), to give a liquid (220 mg, 88%) (Found: C, 67.1; H, 7.35. $C_{14}H_{18}O_4$ requires C, 67.2; H, 7.2%); $\delta_H(C_6D_6)$ 7.54—7.51 (2 H, m, *ortho*-ArH), 7.09—6.99 (3 H, m, ArH), 6.06 (1 H, s, CHO), 3.95 (1 H, dt, H_S), 3.86 (1 H, dt, $J_{H_RH_S}$ 10.6 Hz, H_R), 1.75 (3 H, s, OMe), 1.20 (2 H, m, OCH_2CH_2), 1.01 (2 H, m, CH_2Me), and 0.62 (3 H, t, $MeCH_2$); *m/e* 250, 207, 174, 149, 107, and 74. Spectral and analytical data for compounds (4c—e), (6b—e), (7b—d), and (8a—g) are given in Supplementary Publication No. SUP 23462 (6 pp.).¶

Acknowledgements

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* (1*S*,4*R*)-(−)-Camphanoyl chloride is available from Fluka, $[\alpha]^{20}_{546}$ −24.1° (*c* 2.5, CCl_4). (*S*)-Mandelic acid for preparation of (2) and (3) is available from Aldrich and was recrystallised to constant rotation before use, $[\alpha]^{20}_{589}$ +155.0° (*c* 2.1, H_2O).

† Bruker WH400; signal : noise 760 (^1H, 90° single pulse, 1% ethylbenzene).

‡ In the case of labelled material purification was effected by preparative t.l.c. on silica gel (ethyl acetate–hexane 1 : 2).

§ 1 mmHg = 13.6 × 9.8 Pa.

¶ For details of Supplementary Publications see Notice to Authors No. 7 in *J. Chem. Soc., Perkin Trans. 2*, 1981, Index Issue.

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