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A method for determining the enantiomeric purity of profens

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ABSTRACT

A simple method for determining the enantiomeric purity of profens (based on the carbon skeleton of 2-phenylpropionic acid) is discussed. The enantiomeric purity of a given profen can be determined by stereospecific DCC self-coupling to give a statistical diastereoisomeric mixture of racemic and *meso*- anhydrides. The relative ratio of diastereoisomers formed can be related to the enantiomeric excess of the original carboxylic acid.

1. Introduction

Since 2004, we have been interested in the parallel kinetic resolution[1] of profen-based active esters,[2] such as pentafluorophenyl 2-phenylpropionate (*rac*)-**2**[3] [formed from the *N*,*N*′-dicyclohexylcarbodiimide (DCC) coupling of 2-phenylpropionic acid (*rac*)-**1** and pentafluorophenol in 92% yield] using a combination of *quasi*-enantiomeric oxazolidin-2-ones (*R*)-**3** and (*S*)-**4** (Scheme 1).[4] This process has been shown to be highly enantiomer selective leading to two separable oxazolidin-2-one adducts (*S*,*R*)-*syn*-**5** (in 53% yield with 96% de) and (*R*,*S*)-*syn*-**6** (in 50% yield with 96% de). Hydrolysis of both adducts (*S*,*R*)-*syn*-**5** and (*R*,*S*)-*syn*-**6** using LiOH–H_2O and H_2O_2 in THF/H_2O (3:1), gave the corresponding enantiomerically enriched 2-phenyl propionic acids (*S*)- and (*R*)-**1** in good yield with >98% ee and 96% ee, respectively (Scheme 1).

There are a variety of methods available for determining the enantiomeric purity of 2-phenylpropionic acid and related profens.[5] Chemical methods[6] have primarily been focussed on derivatisation[7] (with an enantiomerically pure reagent, such as an alcohol[8]) and thermodynamic salt formation (by the addition of an enantiomerically pure chiral ammonium salt[9]). Non-chemical methods, such as chiral HPLC[10] and/or NMR chiral shift reagents, have also been used extensively.[11]

2. Results and discussion

We have previously measured the enantiomeric purity of 2-phenylpropionic acid **1** through chemical derivatisation using enantiomerically pure 1-phenylethanol.[12] This procedure though successful has an obvious limitation in that the reaction needs to be driven to completion to ensure complete removal of both enantiomers of 2-phenylpropionic acid due to its inherent kinetic resolution.[13] We now report a synthetic extension to this approach by determining the enantiomeric purity of 2-phenylpropionic acid **1** and related profens using a stereospecific DCC coupling reaction to give a statistical mixture of two diastereoisomeric chiral and *meso*-anhydrides. The diastereoisomeric ratio of the anhydrides can be related to the enantiomeric purity of the original carboxylic acids. As the coupling is stereorandom there is no requirement for the reaction to be driven to completion. This concept is well documented[14] and has been used previously to enhance enantiomeric purity[15] and to determine the enantiomeric purity using chiral systems.[16] There are a limited number of reports[17] where a statistical resolution has been used to determine enantiomeric excess of alcohols and thiols using PCl_3[18,19] and $(PhO)_2PS_2H$.[20]

In an attempt to avoid this inherent rate difference, we became interested in developing an efficient and reliable derivatisation procedure for determining the enantiomeric excesses of 2-phenylpropionic acid (and related profens) which was independent of percentage conversion. For a diastereoselective coupling to have a minimal kinetic resolution, the stereochemical information [stereocentre(s)] present within the coupling reagent must to be positioned away from its reaction site in order to have no stereochemical discrimination. However, there is clearly a balance needed as for two non-isotopic diastereoisomeric products to be distinguishable (e.g., using traditional spectroscopic methods); the stereocentres need to be positioned near enough to one another in order for them to relay their stereochemical information.

For our method, we initially chose to investigate the self-coupling of 2-(4-isobutylphenyl)propionic acid **7** to give the corresponding anhydride **8** using a DCC coupling procedure as this would not require the use of an additional chiral auxiliary (Scheme 2). Treatment of 2-(4-isobutylphenyl)propionic acid (*rac*)-**7** with DCC (0.6 equiv) in CH_2Cl_2, gave an equimolar mixture of two inseparable diastereoisomeric anhydrides (*rac*)-*anti*- and *syn*-*meso*-**8** in 78% yield (Scheme 2). Formation of these anhydrides (*RS*,*RS*)-(*rac*)-*anti*- and (*SR*,*RS*)-*meso*-*syn*-**8** were stereo-unselective as both diastereoisomers were formed in a statistical and equimolar

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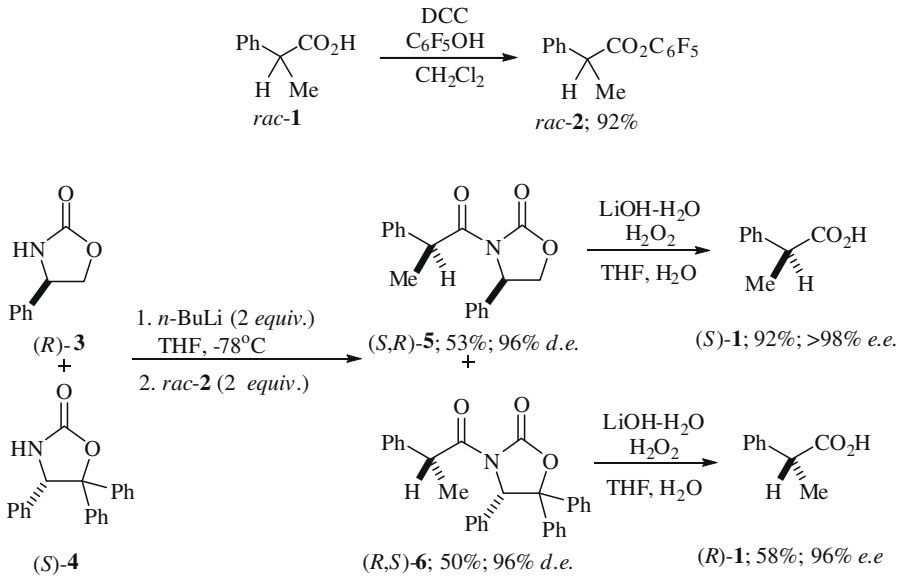
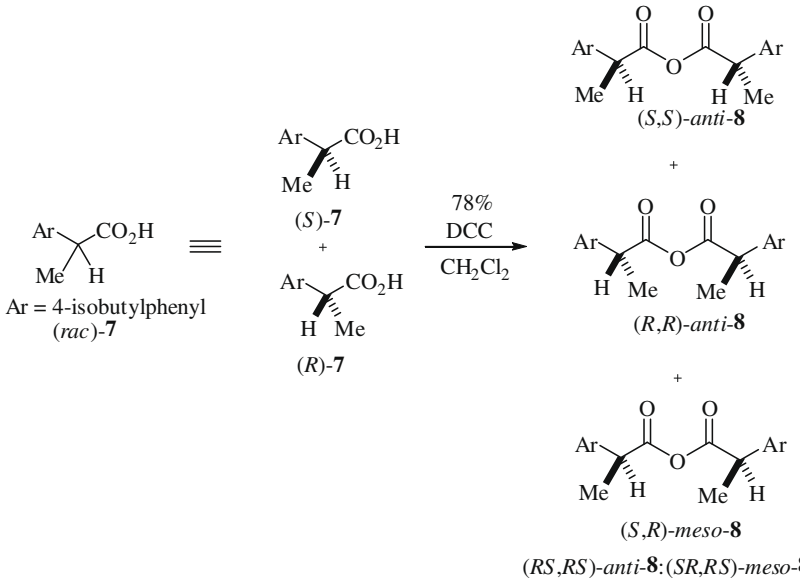


Scheme 1. Parallel kinetic resolution of active ester (*rac*)-**2** using *quasi*-enantiomeric oxazoldin-2-ones (*R*)-**3** and (*S*)-**4**.

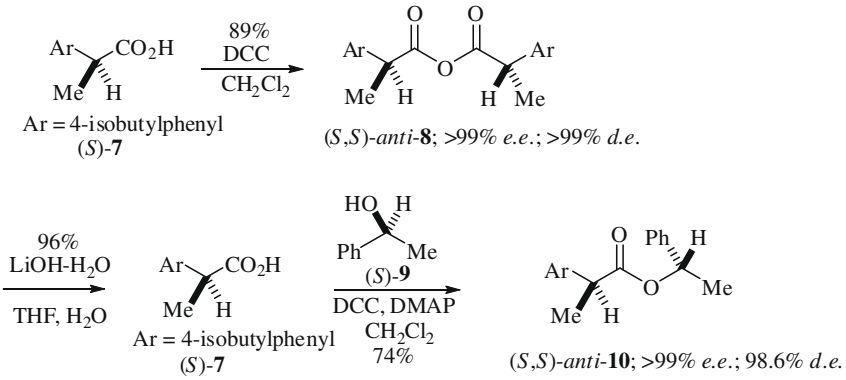


Scheme 2. Formation of anhydride **8** by stereorandom coupling of 2-(4-isobutylphenyl)propionic acid (*rac*)-**7**.

amount. This coupling procedure was also shown to be stereospecific as treatment of enantiomerically pure 2-(4-isobutylphenyl)propionic acid (*S*)-**7** under identical conditions gave a single diastereoisomeric anhydride (*S*,*S*)-*anti*-**8** in 89% yield with >99% diastereoisomeric excess.[22] The enantiomeric purity of this anhydride was established through simple hydrolysis [using LiOH–H_2O and H_2O_2 in THF/H_2O (3:1) to give (*S*)-**7** in 96% yield] and derivatisation of the resulting carboxylic acid with enantiomerically pure 1-phenylethanol (*S*)-**9** using a DMAP-mediated DCC coupling procedure to give the enantiomerically and diastereoisomerically pure ester (*S*,*S*)-*anti*-**10** in 74% yield (Scheme 3).

With this information at hand, we next investigated the accuracy and reliability of this method for determining enantiomeric purity for a series of scalemic mixtures of 2-(4-isobutylphenyl)propionic acid (*S*)-**7** (Table 1). DCC coupling of enantiomerically impure samples of 2-(4-isobutylphenyl)propionic acid (*S*)-**7** with 10% ee, 50% ee and 90% ee, gave inseparable mixtures of anhydrides (S^*,S^*)-*anti*-[21] and *meso*-**8** as the major stereoisomers with 2%, 26% and 82% diastereoisomeric excesses. These statistical levels of diastereoselectivity were found to be identical to their theoretical values. This procedure does appear to be reliable for determining the enantiomeric excesses of samples with moderate to high levels of enantiomeric purity (Tables 1 and 2). However, for samples with lower levels of enantiomeric purity (ca. 10% ee), the statistical levels of diastereoselectivity were near indistinguishable from a racemic sample by NMR spectroscopy (Tables 1 and 2).

We next probed the generality of this DCC coupling method for determining enantiomeric purity by screening a series of structurally related 2-aryl/phenyl-propionic acids (*R*)-**1**, (*S*)-**11**, (*S*)-**12** and (*S*)-**13**, and 2-phenylbutanoic acids (*S*)-**14** and (*R*)-**15** (Scheme 4). Under our standard conditions, the racemic carboxylic acids (*rac*)-**1** and (*rac*)-**11–15** were shown to give a stereo-unselective equimolar mixture of corresponding diastereoisomeric anhydrides (*rac*)-*anti*- and *meso*-**16–21** (Table 3). In comparison, the enantiomerically pure carboxylic acids (*R*)-**1**, (*S*)-**11–14** and (*R*)-**15**, gave stereospecifically the diastereoisomerically pure anhydrides



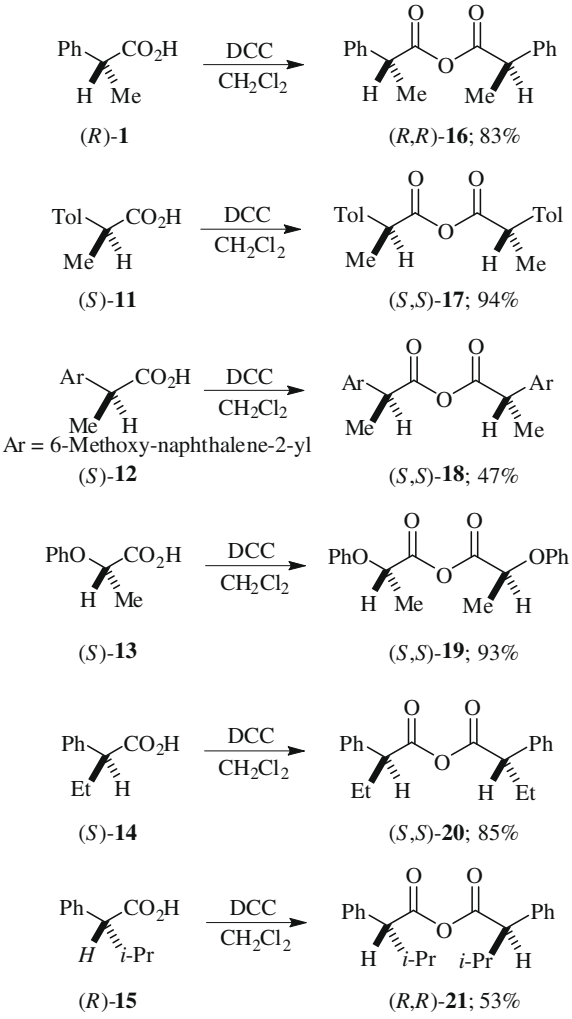
Scheme 3. Stereospecific formation of anhydride (*S*,*S*)-*anti*-**8** and ester (*S*,*S*)-*anti*-**10**.

Table 1
Statistical self-coupling of enantiomerically pure, scalemic and racemic 2-(4-isobutylphenyl)propionic acids

Carboxylic acid (*S*)-**7**; ee	100%	90%	50%	10%	0%
Anhydride (S^*,S^*)-**8**[21]:*meso*-**8**	100:0	91:9	63:37	51:49	50:50
de	100%	82%	26%	2%	0%
Yield	89%	89%	89%	85%	78%
Theoretical (statistical) ratio	100:0	90.5:9.5	62.5:37.5	50.5:49.5	50:50

Table 2
Theoretical (statistical) ratio of diastereoisomeric anhydrides formed through self-coupling of scalemic carboxylic acids

(*S*)-ee (%)	(S^*,S^*)-[21]	*meso*-	de (%)
98	98.02	1.98	96.04
96	96.08	3.92	92.16
94	94.18	5.82	88.36
92	92.32	7.68	84.64
90	90.50	9.50	81.00
88	88.72	11.28	77.44
86	86.98	13.02	73.96
84	85.28	14.72	70.56
82	83.63	16.38	67.26
80	82.00	18.00	64.00
78	80.42	19.58	60.84
76	78.88	21.12	57.76
74	77.38	22.62	54.76
72	75.92	24.08	51.84
70	74.50	25.50	49.00
60	68.00	32.00	36.00
50	62.50	37.50	25.00
40	58.00	42.00	16.00
32	55.12	44.88	10.24
26	53.18	46.12	7.06
20	52.00	48.00	4.00
14	50.98	49.02	1.96
10	50.50	49.50	1.00
6	50.18	49.82	0.36
2	50.02	49.98	0.04
0	50.00	50.00	0.00



Scheme 4. Stereospecific formation of *anti*-anhydrides (*R*,*R*)-**16**, (*S*,*S*)-**17**, (*S*,*S*)-**18**, (*S*,*S*)-**19**, (*S*,*S*)-**20** and (*R*,*R*)-**21** using DCC coupling.

(*R*,*R*)-**16**, (*S*,*S*)-**17**–**20** and (*R*,*R*)-**21** in excellent yield with high levels of enantiomeric and diastereoisomeric purity (Scheme 4). As this coupling procedure was found to be stereospecific and stereo-unselective; the relative amounts of both diastereoisomeric *anti*- and *meso*-anhydrides could be related to the enantiomeric purity of the parent carboxylic acid. To test this concept, we screened a series of scalemic samples of carboxylic acids (*R*)-**1**, (*S*)-**11**–**14** and (*R*)-**15** with 50% enantiomeric excess under our standard conditions, which gave predictably an inseparable diastereoisomeric mixture of anhydrides (R^*,R^*)-**16**, (S^*,S^*)-**17**–**20** and (R^*,R^*)-**21** in good yields with ~26% diastereoisomeric excesses, which were in close agreement with their theoretical value (25% de) (Table 2).[21]

More interestingly, as this coupling procedure was stereorandom, the diastereoselectivity was independent of the percentage conversion and the amount of (unreacted) carboxylic acid remaining. In order to test this, we chose to add a sub-stoichiometric amount of DCC (~0.1 equiv) to a solution of 2-(4-isobutylphenyl)propionic acid (*S*)-**7** with 90% ee in $CDCl_3$, which gave a

Table 3
Statistical self-coupling of enantiomerically pure, scalemic and racemic carboxylic acids **1** and **11–15**

Carboxylic acid	Anhydrides *anti*-:*meso*-		
ee→	100%	50%	0%
(*R*)-**1**	(*R*,*R*)-**16**	(*R**,*R**)-**16**[21]	*rac*-**16**
	100:0	63:37	50:50
	83%	99%	79%
(*S*)-**11**	(*S*,*S*)-**17**	(*S**,*S**)-**17**[21]	*rac*-**17**
	100:0	64:36	50:50
	94%	100%	100%
(*S*)-**12**	(*S*,*S*)-**18**	(*S**,*S**)-**18**[21]	*rac*-**18**
	100:0	63:37	50:50
	47%	51%	41%
(*S*)-**13**	(*S*,*S*)-**19**	(*S**,*S**)-**19**[21]	*rac*-**19**
	100:0	63:37	50:50
	93%	84%	97%
(*S*)-**14**	(*S*,*S*)-**20**	(*S**,*S**)-**20**[21]	*rac*-**20**
	100:0	63:37	50:50
	85%	73%	67%
(*R*)-**15**	(*R*,*R*)-**21**	(*R**,*R**)-**21**[21]	*rac*-**21**
	100:0	62:38	50:50
	53%	63%	45%

diastereoisomeric mixture of anhydrides (*S**,*S**)-[21] and *meso*-**8** in 18% conversion with 78% de (theoretical: ~20% conversion with 81% de) (determined by 400 MHz ^{1}H NMR spectroscopy). From this diastereoselectivity, the original enantiomeric excess of the parent 2-(4-isobutylphenyl)propionic acid (*S*)-**7** was found to be 89% ee Using ^{1}H NMR spectroscopy, this approach has also been shown to be useful for determining the enantiomeric purity of isotopically labelled carboxylic acids, such as (*R*)-[D_3]-**1** (Scheme 5).

3. Conclusion

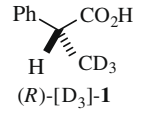
In conclusion, we have shown that the enantiomeric purity of 2-aryl/phenyl-propionic acids and 2-phenylbutanoic acids can be determined efficiently using a DCC-mediated self-condensation reaction. This procedure was shown to be stereospecific leading to the formation of an inseparable diastereoisomeric mixture of statistical chiral and *meso*-anhydrides. The enantiomeric purity of the parent carboxylic acid can be related to the relative ratio of diastereoisomers formed,[23] and re-isolated through base-mediated hydrolysis.

A typical NMR sample to determine enantiomeric excess. The appropriate carboxylic acid [e.g., (*S*)-**7**; 90% ee (20 mg, 97.1 μmol) was added to $CDCl_3$ (0.7 mL) and transferred to an NMR tube (100 mm). DCC (2 mg, 9.7 μmol) was added and the solution was allowed to stir for 2 min. The sample was analysed by ^{1}H NMR spectroscopy to give the anhydride (*S**,*S**)-[21] and *meso*-**8** in a relative 89:11 ratio. The percentage conversion for anhydride formation was 18%.

4. Experimental

4.1. General

All solvents were distilled before use. All reactions were carried out under nitrogen using oven-dried glassware. Flash column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). Thin layer chromatography (TLC) was carried out on commercially available pre-coated plates (Merck Kieselgel 60F_{254} silica). Proton and carbon NMR spectra were recorded on a Bruker 400 MHz Fourier transform spectrometer using an internal deuterium lock. Chemical shifts are quoted in parts per million downfield from tetramethylsilane. Carbon NMR spectra were recorded with broad proton decoupling. Infrared spectra were recorded on a Shimadzu 8300 FTIR spectrometer. Optical rotation was measured using an automatic AA-10 Optical Activity Ltd polAArimeter.



(*R*)-[D_3]-**1**

Scheme 5. 2-Phenyl-2-trideuteriomethylacetic acid (*R*)-[D_3]-**1**.

4.1.1. 2-(4-Isopropylphenyl)propionic anhydride (*S*,*S*)-8

N,*N*′-Dicyclohexylcarbodiimide (DCC) (60 mg, 0.29 mmol) was added to a solution of 2-(4-isopropylphenyl)propionic acid (*S*)-**7** (0.10 g, 0.48 mmol) in CH_2Cl_2 (5 mL) at room temperature. The solution was stirred for 2 h, and filtered (using CH_2Cl_2 as the eluent) to remove the *N*,*N*′-dicyclohexylurea, DCU). Water (10 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried (over $MgSO_4$) and evaporated under reduced pressure to give a residue. Pentane (10 mL) was added, and the resulting organic solution was filtered and evaporated under reduced pressure to give the 2-(4-isopropylphenyl)propionic anhydride (*S*,*S*)-**8** (85 mg, 89%) as a colourless oil; $[\alpha]_D^{20} = +60.8$ (*c* 3.6, $CHCl_3$); ν_{max} (film) cm^{-1} 1811 (C=O, asymm) and 1742 (C=O, symm); δ_H (400 MHz; $CDCl_3$) 7.08–7.02 (8H, m, 8 × CH; 2 × Ar), 3.66 (2H, q, *J* 7.2, 2 × ArC*H*CH_3), 2.45 (4H, d, *J* 7.3, 2 × CH_2Ar), 1.85 (2H, septet, *J* 6.7, 2 × C*H*$(CH_3)_2$), 1.41 (6H, d, *J* 7.2, 2 × ArCHC*H*$_3$) and 0.89 (12H, d, *J* 6.7, 2 × CH(C*H*$_3$)$_2$); δ_C (100 MHz; $CDCl_3$) 170.0[2] (2 × C=O), 141.0[2] (2 × *i*-C; 2 × Ar), 135.8[2] (2 × *i*-CCH_3; 2 × Ar), 129.5[4] and 127.3[4] (8 × CH; 2 × Ar), 46.0[2] (2 × ArCHCH$_3$), 45.0[2] (2 × CH_2Ar), 30.2[2] (2 × C*H*$(CH_3)_2$), 22.4[2] (2 × CH(C*H*$_3$)$_2$) and 17.7[2] (2 × ArCHC*H*$_3$); *m*/*z*: 206 (50%, $ArCHCO_2H^+$) and 161 (100, $ArCHCH_3^+$). (Found MNH_4^+, 412.2851; $C_{26}H_{38}NO_3$ required 412.2846; found $ArCHCO_2HNH_4^+$, 224.1645; $C_{13}H_{22}NO_2^+$ required 224.1645, and found isoureaH$^+$, 413.3160; $C_{26}H_{41}N_2O_2^+$ required 413.3165).

4.1.2. 2-Phenylpropionic anhydride (*R*,*R*)-16

In the same way as anhydride (*S*,*S*)-**8**, 2-phenylpropionic acid (*R*)-**1** (0.10 g, 0.67 mmol) and DCC (82 mg, 32 mmol) in CH_2Cl_2 (5 mL), gave after selective extraction with pentane, 2-phenylpropionic anhydride (*R*,*R*)-**16** (78 mg, 83%) as a colourless oil; $[\alpha]_D^{20} = -101.0$ (*c* 3.2, $CHCl_3$); ν_{max} (film) cm^{-1} 1812 (C=O, asymm) and 1742 (C=O, symm); δ_H (400 MHz; $CDCl_3$) 7.30–7.24 (6H, m, 6 × CH; 2 × Ph), 7.15–7.11 (4H, m, 4 × CH; 2 × Ph), 3.66 (2H, q, *J* 7.2, 2 × PhC*H*CH_3) and 1.43 (6H, d, *J* 7.2, 2 × PhCHC*H*$_3$); δ_C (100 MHz; $CDCl_3$) 169.7[2] (2 × C=O), 138.6[2] (2 × *i*-C; 2 × Ph), 128.8,[4] 127.6[4] and 127.5[2] (10 × CH; 2 × Ph), 46.4[2] (2 × PhCHCH$_3$) and 17.8[2] (2 × PhCHC*H*$_3$); *m*/*z*: 150 (20%, $ArCHCO_2H^+$) and 105 (100, $ArCHCH_3^+$) (Found MH^+, 283.2498; $C_{18}H_{19}O_3^+$ required 283.1328, and found isoureaH$^+$, 357.2544; $C_{22}H_{33}N_2O_2^+$ required 357.2536).

4.1.3. 2-(4-Methylphenyl)propionic anhydride (*S*,*S*)-17

In the same way as anhydride (*S*,*S*)-**8**, 2-(4-methylphenyl)propionic acid (*S*)-**11** (9 mg, 55 μmol) and DCC (7 mg, 33 μmol) in CH_2Cl_2 (2 mL), gave after selective extraction with pentane, 2-(4-methylphenyl)propionic anhydride (*S*,*S*)-**17** (8 mg, 94%) as a colourless oil; $[\alpha]_D^{20} = +83.8$ (*c* 1.6, $CHCl_3$); ν_{max} (film) cm^{-1} 1812 (C=O, asymm) and 1743 (C=O, symm); δ_H (400 MHz; $CDCl_3$) 7.06 (4H, dABq, *J* 7.9, 4 × CH; 2 × Ar), 7.01 (4H, dABq, *J* 7.9, 4 × CH; 2 × Ar), 3.63 (2H, q, *J* 7.2, 2 × ArC*H*CH_3), 2.31 (6H, s, 2 × CH_3Ar) and 1.41 (6H, d, *J* 7.2, 2 × ArCHC*H*$_3$); δ_C (100 MHz; $CDCl_3$) 169.9[2] (2 × C=O), 137.1[2] (2 × *i*-C; 2 × Ar), 135.6[2] (2 × *i*-CCH_3; 2 × Ar), 129.4[4] and 127.5[4] (8 × CH; 2 × Ar), 45.9[4] (2 × ArCHCH$_3$ and 2 × C*H*$_3$Ar) and 17.8[2] (2 × ArCHC*H*$_3$); *m*/*z:* 164 (40%, $ArCHCO_2H^+$)

and 119 (100, $ArCHCH_3^+$). (Found $M^+ + NH_3$, 327.0083; $C_{20}H_{25}NO_3^+$ required 327.1829; found isoureaH$^+$, 371.2694; $C_{23}H_{35}N_2O_2^+$ required 371.2693).

4.1.4. 2-(6-Methoxy-naphthalene-2-yl)propionic anhydride (*S*,*S*)-18

In the same way as anhydride (*S*,*S*)-**8**, 2-(6-methoxy-naphthalene-2-yl)propionic acid (*S*)-**12** (0.10 g, 0.43 mmol) and DCC (54 mg, 26 mmol) in CH_2Cl_2 (5 mL), gave after selective extraction with diethyl ether, 2-(6-methoxy-naphthalene-2-yl)propionic anhydride (*S*,*S*)-**18** (45 mg, 47%) as a colourless oil; $[\alpha]_D^{20} = +18.1$ (*c* 3.5, $CHCl_3$); ν_{max} (film) cm^{-1} 1812 (C=O, asymm) and 1743 (C=O, symm); δ_H (400 MHz; $CDCl_3$) 7.42 (2H, d, *J* 8.4, CH; 2 × Ar), 7.41 (2H, d, *J* 8.8, CH; 2 × Ar), 7.32 (2H, br s, CH; 2 × Ar), 7.06 (2H, dd, *J* 8.5 and 1.8, CH; 2 × Ar), 7.02 (2H, dd, *J* 8.8 and 2.5, CH; 2 × Ar), 6.95 (2H, d, *J* 2.5, CH; 2 × Ar), 3.85 (6H, s, 2 × OCH_3), 3.71 (2H, q, *J* 7.2, 2 × Ar*CH*CH_3) and 1.41 (6H, d, *J* 7.2, 2 × ArCH*CH*$_3$); δ_C (100.6 MHz; $CDCl_3$) 170.0[2] (2 × C=O), 157.7[2] (2 × *i*-CO; 2 × Ar), 133.7[2], 133.6[2] and 128.8[2] (6 × *i*-C; 2 × Ar), 129.2[2], 127.3[2], 126.3[2], 125.8[2], 119.0[2] and 105.5[2] (12 × CH; 2 × Ar), 55.3[2] (2 × OCH_3), 46.3[2] (2 × Ar*CH*CH_3) and 17.8[2] (2 × ArCH*CH*$_3$); (Found $ArCH^+$, 185.0963; $C_{13}H_{13}O^+$ required 185.09609; found $ArCHCONH_2–H^+$, 230.1180; $C_{14}H_{16}NO_2^+$ required 230.1175; found isoureaH$^+$, 437.2803; $C_{27}H_{37}N_2O_3^+$ required 437.2798).

4.1.5. 2-Phenoxypropionic anhydride (*S*,*S*)-19

In the same way as anhydride (*S*,*S*)-**8**, 2-phenoxypropionic acid (*S*)-**13** (34 mg, 0.20 mmol) and DCC (25 mg, 12 mmol) in CH_2Cl_2 (3 mL), gave after selective extraction with pentane, 2-phenoxypropionic anhydride (*S*,*S*)-**19** (30 mg, 93%) as a colourless oil; $[\alpha]_D^{20} = -50.0$ (*c* 6.0, $CHCl_3$); ν_{max} (film) cm^{-1} 1833 (C=O, asymm) and 1758 (C=O, symm); δ_H (400 MHz; $CDCl_3$) 7.18 (4H, t, *J* 7.6, 4 × CH; 2 × Ph), 6.93 (2H, t, *J* 7.6, 2 × CH; 2 × Ph), 6.75 (4H, d, *J* 7.6, 4 × CH; 2 × Ph), 4.71 (2H, q, *J* 7.0, 2 × PhC*H*CH_3) and 1.55 (6H, d, *J* 7.0, 2 × PhCHC*H*$_3$); δ_C (100 MHz; $CDCl_3$) 167.6[2] (2 × C=O), 157.0[2] (2 × *i*-CO; 2 × OPh), 129.6,[4] 122.1[2] and 115.1[4] (10 × CH; 2 × Ph), 72.6[2] (2 × PhOC*H*CH_3) and 17.9[2] (2 × PhOCHC*H*$_3$); *m*/*z*: 166 (50%, $PhOCHCH_3CO_2H^+$), 121 (90, $PhOCHMe^+$) and 94 (100, $PhOH^+$). (Found $PhOCHCO_2H–NH_4^+$, 184.0968; $C_9H_{14}NO_3^+$ required 184.0968; isoureaH$^+$, 373.2491; $C_{22}H_{33}N_2O_3^+$ required 373.2485).

4.1.6. 2-Phenylbutanoic anhydride (*S*,*S*)-20

In the same way as anhydride (*S*,*S*)-**8**, 2-phenylbutanoic acid (*S*)-**14** (0.10 g, 0.61 mmol) and DCC (75 mg, 0.37 mmol) in CH_2Cl_2 (5 mL), gave after selective extraction with pentane, 2-phenylbutanoic anhydride (*S*,*S*)-**20** (80 mg, 85%) as a colourless oil; $[\alpha]_D^{20} = +92.0$ (*c* 2.8, $CHCl_3$); ν_{max} (film) cm^{-1} 1812 (C=O, asymm) and 1742 (C=O, symm); δ_H (400 MHz; $CDCl_3$) 7.23–7.17 (6H, m, 6 × CH; 2 × Ph), 7.07–7.02 (4H, m, 4 × CH; 2 × Ph), 3.34 (2H, t, *J* 7.5, 2 × PhC*H*CH_2), 2.01–1.91 (2H, m, 2 × $CHCH_AH_BCH_3$), 1.72–1.61 (2H, m, 2 × $CHCH_AH_BCH_3$) and 0.76 (6H, t, *J* 7.5, 2 × CH_3); δ_C (100 MHz; $CDCl_3$) 169.2[2] (2 × C=O), 137.1[2] (2 × *i*-C; 2 × Ph), 128.7,[4] 128.1[4] and 127.5[2] (10 × CH; 2 × Ph), 54.0[2] (2 × PhCHCH$_2$), 25.8[2] (2 × PhCHCH$_2$) and 11.7[2] (2 × CH_3); *m*/*z*: 164 (20%, $PhCHEtCO_2H^+$), 119 (40, $PhCHEt^+$) and 91 (100, $PhCH_2^+$). (Found isoureaH$^+$, 371.2691; $C_{23}H_{35}N_2O_2^+$ required 371.2693).

4.1.7. 2-Phenyl-3-methylbutanoic anhydride (*R*,*R*)-21

In the same way as anhydride (*S*,*S*)-**8**, 2-phenyl-3-methylbutanoic acid (*R*)-**15** (28 mg, 0.16 mmol) and DCC (19 mg, 0.09 mmol) in CH_2Cl_2 (5 mL), gave after selective extraction with pentane, 2-phenyl-3-methylbutanoic anhydride (*R*,*R*)-**21** (14 mg, 53%) as a colourless oil; $[\alpha]_D^{20} = -31.1$ (*c* 4.6, $CHCl_3$); ν_{max} (film) cm^{-1} 1812 (C=O, asymm) and 1739 (C=O, symm); δ_H (400 MHz; $CDCl_3$) 7.26–7.21 (6H, m, 6 × CH; 2 × Ph), 7.15–7.11 (4H, m, 4 × CH; 2 × Ph), 3.10 (2H, d, *J* 10.2, 2 × PhC*H*CH), 2.28 (2H, double septet, *J* 10.2 and 6.5, 2 × $CH(CH_3)_2$), 0.94 (6H, d, *J* 6.5, 2 × $CH_3^ACHCH_3^B$) and 0.60 (6H, d, *J* 6.5, 2 × $CH_3^ACHCH_3^B$); δ_C (100 MHz; $CDCl_3$) 168.9[2] (2 × C=O), 136.4[2] (2 × *i*-C; 2 × Ph), 128.7,[4] 128.6[4] and 127.6[2] (10 × CH; 2 × Ph), 60.5[2] (2 × PhCHCH), 31.2[2] (2 × $CH(CH_3)_2$), 21.3[2] and 19.4[2] (4 × CH_3); *m*/*z*: 133 (100%, $ArCHCO_2H^+$) and 91 (60, $PhCH_2^+$) (Found $PhCH(i\text{-}Pr)CONH_2–H^+$, 178.1228; $C_{11}H_{16}NO^+$ required 178.1226; found isoureaH$^+$, 385.2857; $C_{24}H_{37}N_2O_2^+$ required 385.2849).

4.1.8. ^{1}H NMR assignment of configurations[21]

For (*S**,*S**)-*anti*-**8**, methyl doublet appears at 1.4344 ppm, for *meso*-**8**, Me doublet appears at 1.4198 ppm; $\Delta\delta = +0.0147$ ppm (5.88 Hz at 400 MHz).

For (*R**,*R**)-*anti*-**16**, methyl doublet appears at 1.4399 ppm, for *meso*-**16**, Me doublet appears at 1.4303 ppm; $\Delta\delta = +0.0097$ ppm (3.88 Hz at 400 MHz).

For (*R**,*R**)-*anti*-**17**, methyl doublet appears at 1.4170 ppm, for *meso*-**17**, Me doublet appears at 1.4115 ppm; $\Delta\delta = +0.0055$ ppm (2.2 Hz at 400 MHz).

For (*R**,*R**)-*anti*-**18**, methyl doublet appears at 1.4180 ppm, for *meso*-**18**, Me doublet appears at 1.4004 ppm; $\Delta\delta = +0.0176$ ppm (7.0 Hz at 400 MHz).

For (*R**,*R**)-*anti*-**19**, methyl doublet appears at 1.5460 ppm, for *meso*-**19**, Me doublet appears at 1.5197 ppm; $\Delta\delta = +0.0263$ ppm (10.5 Hz at 400 MHz).

For (*R**,*R**)-*anti*-20, methyl triplet appears at 0.8186 ppm, for *meso*-20, Me triplet appears at 0.8218 ppm; $\Delta\delta = -0.0032$ ppm (1.3 Hz at 400 MHz). For (*R**,*R**)-*anti*-20, the PhCH triplet appears at 3.4133 ppm, for *meso*-20, the PhCH triplet appears at 3.4316 ppm; $\Delta\delta = -0.0183$ ppm (7.32 Hz at 400 MHz).

For (*R**,*R**)-*anti*-**21**, the PhCH doublet appears at 3.0632 ppm, for *meso*-**21**, the PhCH doublet appears at 3.0854 ppm; $\Delta\delta = -0.0222$ ppm (8.9 Hz at 400 MHz).

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21. The configuration denotes the major enantiomer present in the non-racemic (scalemic) anhydride.
22. Partial racemisation of ibuprofen (*S*)-7 (~56% ee) occurred when using water soluble 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC) to give the corresponding anhydrides *anti*-8:*meso*-8 (ratio 65:35).
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