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Non-thiazolidinedione antihyperglycaemic agents. Part 4: Synthesis of (±)-, (*R*)-(+)- and (*S*)-(−)-enantiomers of 2-oxy-3-arylpropanoic acids †

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Abstract

The synthesis of a new series of potent 2-oxy-3-arylpropanoic acid antihyperglycaemic agents in both racemic and non-racemic form is described. Resolution of racemic acids **1** is accomplished via amide formation with either (*S*)-2-phenylglycinol or (*S*)-4-benzyloxazolidin-2-one as complementary resolving agents.

1. Introduction

Non-insulin-dependent diabetes mellitus (NIDDM) is a complex metabolic disorder characterised by insulin resistance in the liver and peripheral tissues.[2] NIDDM affects up to 5% of the population of most western industrialised nations. Improvement of glycaemic control via reduction of peripheral tissue insulin resistance has long been recognised as pivotal to the development of an effective long-term therapy for the disease.[3] Thiazolidine-2,4-dione insulin sensitisers,[4] such as Rezulin (troglitazone)[5] and our own Phase-III clinical drug Avandia (rosiglitazone, BRL-49653),[6] are members of a new family of drugs used for the treatment of chronic NIDDM. Recent evidence suggests that compounds of this class exert their antidiabetic activity via activation of a nuclear hormone receptor PPARγ (peroxisomal proliferator-activated receptor γ).[7]

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† For the previous paper in this series, see Haigh et al.[1]

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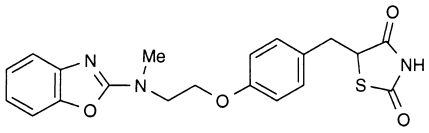
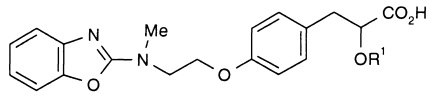


BRL 48482



1 **a**, R^1 = Et, **d**, R^1 = CH_2Ph,
b, R^1 = CH_2CF_3, **e**, R^1 = *m*-$C_6H_4CF_3$,
c, R^1 = CH_2CH_2OMe, **f**, R^1 = Me

In the first paper of this series[8] we reported on the preliminary results of additional structure–activity studies on BRL 48482 (a compound equipotent to BRL 49653),[6] in which the 5-benzylthiazolidine-2,4-dione moiety of the former agent was replaced by a series of racemic 2-oxy-3-arylcarboxylic acids **1**. In an initial examination of the enantioselectivity of PPARγ binding and antidiabetic potency of these compounds,[1] we recently described an enzymic resolution approach to the synthesis of the (*R*)-(+)- and (*S*)-(−)-enantiomers of the 2-methoxy-acid **1f**, together with an alternative preparation of the enantiomers of the 2-benzyloxy-analogues **1d**. In order to undertake a more thorough examination of the impact of chirality in this area[9] we subsequently required larger quantities of both enantiomers of the key lead compounds for in vivo biological evaluation. This paper describes a new synthesis of racemic 2-alkoxy(aryloxy)-3-arylpropanoic acids **1a**–**e** and the preparation of their enantiomers by two complementary resolution methodologies.

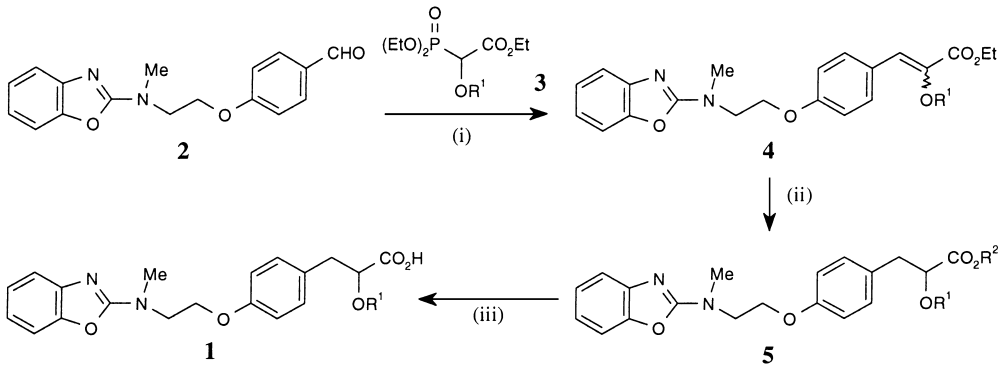
2. Results and discussion

2.1. Synthesis of racemic 2-oxy-3-arylpropanoic acids

The racemic acids **1a**–**e**, chosen for the present resolution studies, were prepared according to Scheme 1. The Wadsworth–Emmons reaction of the appropriate alkoxy(aryloxy)phosphonoacetate **3** (prepared from triethyl diazophosphonoacetate and the alcohol in the presence of rhodium acetate)[10,11] with aldehyde **2**[6] afforded mixtures of geometric isomers of 2-oxy-3-arylpropenoates **4**. In agreement with an earlier report[11a] the alkoxy compounds **4a**–**d** were predominantly isolated as the *Z*-isomer (Table 1), although the ratio varied according to the substituent.[12,13] As expected,[11b] the *m*-trifluoromethylphenoxy-analogue **4e** was isolated as a 1:1 mixture of isomers. Reduction of **4** either by catalytic hydrogenation over palladium charcoal (for **4a**,**b**), or by dissolving magnesium metal in methanol solution[14] gave esters **5**. In the latter reaction, products **5c**–**e** were isolated as the methyl esters following in situ transesterification. Hydrolysis of **5** subsequently afforded the desired acids **1a**–**e** (Table 1).

2.2. Chemical resolution of 2-oxy-3-arylpropanoic acids

Resolution of racemic α-functionalised carboxylic acids has classically been achieved via formation and fractional crystallisation of salts of a chiral amine.[15] However, in view of the unpredictability of the method and difficulties we had previously encountered in the choice of a suitable amine to resolve closely related thiazolidine-2,4-dione analogues,[16] this approach was deemed unattractive. Alternative approaches to the resolution of functionalised carboxylic acids have included kinetic[17] and dynamic kinetic[18] resolution and the formation and chromatographic separation[19] of diastereoisomeric esters by reaction of the acid with a suitable chiral alcohol.[20] Unfortunately, attempts to resolve racemic acids



Scheme 1. For definition of substituents R^1 and R^2 see Table 1. Reagents: (i) NaH, THF then **2**. (ii) Either (A) H_2, 10% Pd–C, EtOH, or (B) Mg, MeOH. (iii) NaOH, MeOH

Table 1
Synthesis of racemic acids

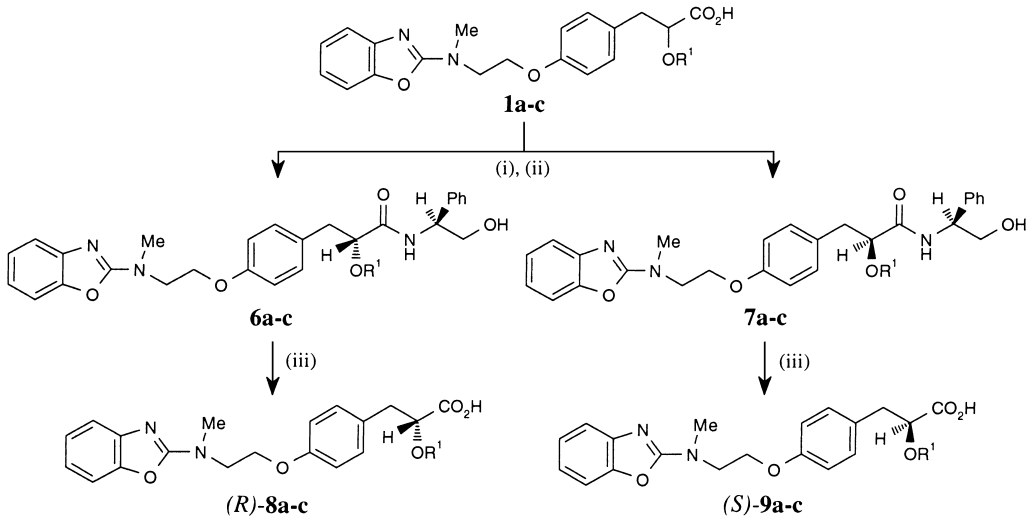
Substituent R^1		Olefin 4		(±)-Ester 5			(±)-Acid 1
		Yield (%)	E:Z ratio	Method[a]	R^2	Yield (%)	Yield (%)
a	Et	71	38:62	A	Et	73	50
b	CH_2CF_3	88	43:57	A	Et	97	93
c	CH_2CH_2OMe	60	24:76	B	Me[b]	37	92
d	CH_2Ph	68	41:59	B	Me[b]	84	91
e	*m*-$C_6H_4CF_3$	94	50:50	B	Me[b]	78	89

[a]Reduction method (A): H_2, 10% Pd-C, ethanol; (B): Magnesium, methanol.
[b]Methyl ester formed by *in-situ* transesterification.

1 via formation of diastereoisomeric esters of (*S*)-1-phenylethanol or of (*R*)-pantolactone[20d] afforded chromatographically inseparable mixtures.

In an extension of this concept, the formation and separation of diastereoisomeric amides has also been used for the resolution of racemic acids[21] and Helmchen[22] has shown 2-phenylglycinol to be a particularly useful amine in this context. Reaction of the acid chlorides derived from **1a–c** with (*S*)-2-phenylglycinol afforded amides which were easily separated by silica gel chromatography to give the individual[2*R*,*N*(1*S*)]-diastereoisomers **6a–c** (faster eluting isomer) and [2*S*,*N*(1*S*)]-diastereoisomers **7a–c** (slower eluting isomer), respectively, in excellent diastereoisomeric excess (often >98%; Scheme 2; Table 2). Subsequent acid hydrolysis afforded the corresponding (*R*)- and (*S*)-enantiomers **8a–c** and **9a–c**, respectively, in good enantiomeric excess (88–96%), although in only modest chemical yield (Table 2). However, the diastereoisomeric amides derived from acids **1d** or **1e** and either (*S*)-2-phenylglycinol or (*S*)-alaninol were inseparable by chromatography.

The use of various chiral oxazolidin-2-ones in the formation and separation of diastereoisomeric imide derivatives of racemic carboxylic acids has recently been reported.[23] However, to our knowledge, only a single example of the resolution of an α-oxyacid in this manner has been recorded.[23a] Consequently, we decided to examine the suitability of the Evans chiral auxiliary (*S*)-4-benzyloxazolidin-2-one **10** for the resolution of the racemic acids **1d** and **1e**. Auxiliary **10** was acylated by the acid chlorides derived from



Scheme 2. Resolution of (±)-**1** via (*S*)-2-phenylglycinol. Reagents: (i) $(COCl)_2$, benzene. (ii) (*S*)-2-Phenylglycinol, NEt_3, CH_2Cl_2. (iii) 1 M H_2SO_4, aq. dioxan

Table 2
Resolution of (±)-**1** via (*S*)-2-phenylglycinol

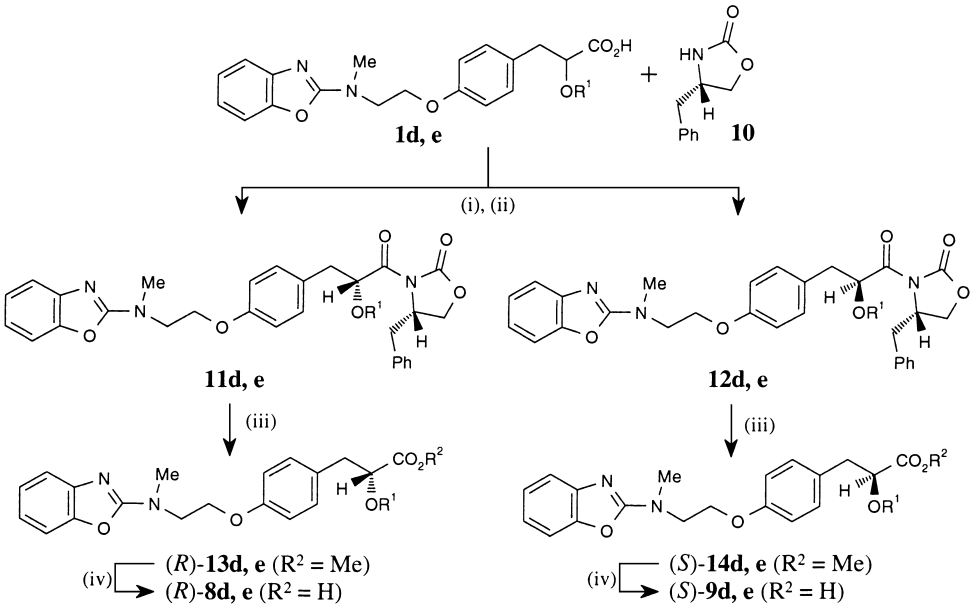
Substituent R^1		Diastereoisomeric Amides[a]				Enantiomeric Acids			
		6		**7**		(*R*)-**8**		(*S*)-**9**	
		Yield (%)[b]	d.e. (%)	Yield (%)[b]	d.e. (%)	Yield (%)	e.e. (%)	Yield (%)	e.e. (%)
a	Et	32	98.4	33	100	37	93.2	38	93.6
b	CH_2CF_3	32	100	34	99	51	96.6	48	95.2
c	CH_2CH_2OMe	44	90.8	27	92.6	60	94.0	43	88.0[c]

[a]Diastereoisomer **6** was the first-eluted isomer in each case.
[b]Maximum yield 50%.
[c]E.e. improved to 94% by repeated crystallisation of the (*S*)-1-phenylethylamine salt.

1d and **1e** in a standard manner.[24] The resulting diastereoisomeric acyloxazolidinones **11d**,**e** and **12d**,**e** (faster and slower eluting isomers, respectively) were readily separable by chromatography (Scheme 3; Table 3). Subsequent cleavage of the auxiliary by treatment with sodium methoxide,[25] followed by acid hydrolysis of the resulting esters **13** and **14** afforded the desired enantiomeric acids **8d**,**e** and **9d**,**e**. It is of note that diastereoisomer separation was not possible when acids **1a** and **1b** were employed in this sequence; hence it would appear that (*S*)-2-phenylglycinol and (*S*)-4-benzyloxazolidin-2-one are complementary in their suitability for the resolution of 2-oxycarboxylic acids of this type.

2.3. Determination of absolute configuration

Following Helmchen's proposal of a conformational model for the determination of chromatographic elution order[21a] and determination of absolute stereochemistry[21a,b,d] of the pair of diastereoisomeric



Scheme 3. Resolution of (±)-**1** via (*S*)-4-benzyloxazolidin-2-one. Reagents: (i) **1**, $(COCl)_2$, benzene. (ii) **10**, *n*-BuLi, THF, then add acid chloride. (iii) 1.1 equiv. NaOMe, MeOH. (iv) 2 M HCl, dioxan

Table 3
Resolution of (±)-**1** via (*S*)-4-benzyloxazolidin-2-one

Substituent R^1		Diastereoisomeric Imides[a]				Enantiomeric Acids			
		11		12		(*R*)-8		(*S*)-9	
		Yield (%)[b]	d.e. (%)	Yield (%)[b]	d.e. (%)	Yield (%)[c]	e.e. (%)	Yield (%)[c]	e.e. (%)
d	CH_2Ph	24	97.8	17	89.8	55	96	54	88
e	*m*-$C_6H_4CF_3$	28	100	19	97.2	75	98	73	98

[a]Diastereoisomer **11** was the first-eluted isomer in each case.
[b]Max. yield 50%.
[c]Overall yield from imide

amides formed by the reaction of a racemic carboxylic acid with a chiral amine (or vice versa), the generality of this model for predicting stereochemistry has been firmly established.[26] Thus, inspection of the conformational models and 'extended Newman projections' (arrowed) for (*R*,*S*)- and (*S*,*S*)-diastereoisomers **6** and **7**, Figs. 1 and 2, respectively, suggested that the methylene protons of the $ArCH_2-$ group in **7** should be shielded relative to **6** by the phenyl ring of the auxiliary.[21a] Comparison of the ^1H NMR spectra for **6a**–**c** and **7a**–**c** showed a consistent upfield shift of these protons in **7** ($-0.05 \leq \Delta\delta \leq -0.15$ ppm). However, the protons directly attached to the stereogenic centre of the acid moiety showed no ^1H NMR diastereoisomeric shifts. Figs. 1 and 2 also predicted that the (*R*,*S*)-diastereoisomer **6** should be the chromatographically earlier eluting isomer, since the bulky phenyl and aryl groups occupy opposite sides of the plane of the amide group.[21a] In each case, diastereoisomer **6** was indeed the chromatographically earlier eluting isomer. Together, these data thus supported the assignment of the stereochemistry of **6**

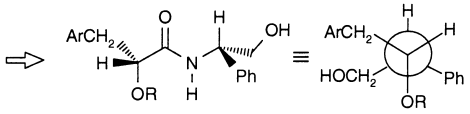


Figure 1. (*R*,*S*)-Diastereoisomer **6**

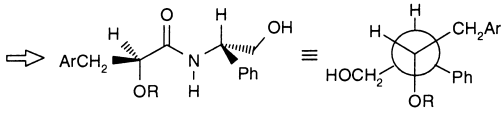


Figure 2. (*S*,*S*)-Diastereoisomer **7**

and **7** and hence of the corresponding enantiomeric acids **8a**–**c** and **9a**–**c**. Independent proof of absolute stereochemistry was subsequently provided by correlation of **8a**–**c** and **9a**–**c** with the enantiomers of **1d** and **1f**, whose stereochemistry had been unambiguously determined by X-ray crystallography.[1]

Similar observations were also noted with the diastereoisomers **11d**,**e** and **12d**,**e**. In each case, (*R*,*S*)-diastereoisomer **11** was the faster eluting. The protons attached to the two stereogenic centres in **11** and **12** were also found to show diagnostic shift differences in the ^{1}H NMR spectra. Diastereoisomer **11** consistently showed an upfield shift for the proton on the stereogenic centre in the acid moiety[‡] and a downfield shift for the proton on the stereogenic centre in the auxiliary, relative to **12**.

3. Conclusion

Synthesis of a new series of potent, racemic, 2-oxy-3-arylpropanoic acid antihyperglycaemic agents **1** has been reported. Resolution of acids **1** was achieved by the complementary utilisation of either (*S*)-2-phenylglycinol or (*S*)-4-benzyloxazolidin-2-one as resolving agents. Use of the latter auxiliary represents an extension to the versatility of this oxazolidin-2-one in synthesis. The absolute stereochemistry of acids **8** and **9** was inferred by literature analogy based on chromatographic elution order and ^{1}H NMR chemical shift differences between the diastereoisomeric amide intermediates and was substantiated by correlation to earlier X-ray studies.

Biological evaluation of the enantiomeric acids **8** and **9** demonstrated the greater potency of the (*S*)-enantiomer **9** and will be reported elsewhere. However, a de novo enantioselective aldol synthesis of **9a**–**e** is the subject of the following paper.[27]

4. Experimental

4.1. General experimental details

Mass spectroscopy was conducted using electron impact (EI), chemical ionisation (CI), with ammonia as the reagent gas, or fast atom bombardment (FAB) in a 3-nitrobenzyl alcohol–sodium acetate (NOBA–Na) matrix. Compounds characterised by high resolution mass measurement were homogeneous by TLC. ^{1}H NMR spectra were recorded at 270 or 400 MHz in $CDCl_3$ solution. Chemical shifts are given

[‡] The ^{1}H NMR signal for the proton on the stereogenic centre in the acid moiety is particularly diagnostic. $\Delta\delta$ ($\delta_{\mathbf{11}}$–$\delta_{\mathbf{12}}$) for C*H*OR^1 is −0.12 ppm and −0.16 ppm for **11d**/**12d** (R^1=CH_2Ph) and **11e**/**12e** (R^1=*m*-$C_6H_4CF_3$), respectively. Similar shifts were observed for the (inseparable) diastereoisomers corresponding to **11a**/**12a** (R^1=Et, $\Delta\delta$=−0.14 ppm) and **11b**/**12b** (R^1=CH_2CF_3, $\Delta\delta$=−0.12 ppm).

in δ (ppm) relative to TMS and coupling constants *J* are given in hertz. $[\alpha]_D^{25}$ values are given in deg cm^2 g^{-1}. Dry solvents refer to the use of Aldrich Sure-Seal™ dried solvents. All organic solutions obtained from aqueous extractions were dried over $MgSO_4$. Chromatography refers to flash chromatography on silica gel.

4.2. HPLC conditions

Diastereoisomeric amides **6a**,**c** and **7a**,**c** were resolved on a Zorbax Octyl column using MeOH:0.05 M NH_4OAc (pH 4.5, 70:30 v/v) as eluent. Amides **6b** and **7b** were resolved on the same column using MeOH:0.1 M NH_4OAc (pH 4.5, 65:35 v/v). Diastereoisomeric imides **11** and **12** were separated on a Lichrosorb Si60 column using hexane:ethyl acetate (70:30 v/v) as eluent. Chiral esters **13d** and **14d** were resolved on a Chiralcel OD column using hexane:Pr^{i}OH (95:5 v/v) and for esters **13e** and **14e**, a Chiralpak AD column using hexane:EtOH (90:10 v/v) as eluent was employed. Chiral acids **8a**,**d** and **9a**,**d** were separated on a Chiralpak AD column using hexane:Pr^{i}OH (92:8 v/v) containing CF_3CO_2H (0.05% v/v) as eluent; for acids **8b** and **9b**, hexane:EtOH (96.5:3.5 v/v) containing CF_3CO_2H (0.05% v/v) was used and for acids **8c** and **9c**, hexane:EtOH (90:10 v/v) containing CF_3CO_2H (0.05% v/v) was used. Acids **8e** and **9e** were resolved on a Chiralcel OJ column using hexane:EtOH (85:15 v/v) containing CF_3CO_2H (0.05% v/v) as eluent. Solvent flow rate was 1 mL min^{-1} throughout and detection wavelength was either 220, 245 or 250 nm.

4.3. General procedure for preparation of 2-alkoxy(aryloxy)phosphonoacetates *3*

4.3.1. Ethyl 2-(2,2,2-trifluoroethoxy)-2-diethylphosphonoacetate *3b*

A mixture of ethyl 2-diazo-2-diethylphosphonoacetate (3.75 g, 0.015 mol), 2,2,2-trifluoroethanol (2.19 mL, 0.03 mol) and rhodium(II) acetate dimer (66 mg, 1 mol%) in benzene (40 mL) was heated at reflux for 18 h. After removal of solvent under reduced pressure, the residual oil was chromatographed with ethyl acetate:diethyl ether (2.5:97.5) as eluent to give the product as a clear oil (3.66 g, 76%); (found M^+ (EI) 322.0795. $C_{10}H_{18}F_3PO_6$ requires *M* 322.0793); ν_{max} (film)/cm^{-1} 1745 (CO) and 1260 [PO(OEt)$_2$]; δ_H (270 MHz, $CDCl_3$) 1.30–1.40 (9H, m, 3×CH_3), 3.95 (1H, m, OC*H*HCF$_3$), 4.10–4.40 (7H, m, OCH*H*CF$_3$ and 3×CH_2) and 4.51 (1H, d, $^2J_{PH}$ 18.7, POCH); *m/z* (CI) 340 [$(M+NH_4)^+$, 100%], 323 [$(M+H)^+$, 12] and 258 (9).

4.3.2. Ethyl 2-(2-methoxyethoxy)-2-diethylphosphonoacetate *3c*

Similarly prepared. An oil, 66%; (found M^+ (EI) 298.1181. $C_{11}H_{23}PO_7$ requires *M* 298.1181); δ_H (270 MHz, $CDCl_3$) 1.32 (9H, m, 3×CH_2CH_3), 3.35 (3H, s, OMe), 3.59 (2H, t, *J* 4.5, CH_2OMe), 3.80 (2H, m, OCH_2CH_2OMe), 4.20 (6H, m, 3×CH_2CH_3) and 4.47 (1H, d, $^2J_{PH}$ 18.9, POCH).

4.3.3. Ethyl 2-benzyloxy-2-diethylphosphonoacetate *3d*

Similarly prepared. An oil, 56%; (found $(M+H)^+$ (CI) 331.1308. $C_{15}H_{23}PO_6$ requires *M* 331.1311); δ_H (270 MHz, $CDCl_3$) 1.30 (9H, m, 3×OCH_2CH_3), 4.20 (6H, 3×OCH_2CH_3), 4.35 (1H, d, $^2J_{PH}$ 18.9, POCH), 4.58 (1H, d, *J* 11.8, OC*H*HPh), 4.82 (1H, d, *J* 11.8, OCH*H*Ph) and 7.28 (5H, m, Ph).

4.4. General procedure for olefination of aldehyde **2**

4.4.1. Ethyl (E/Z)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propenoate **4b**

Sodium hydride (60% dispersion in oil, 250 mg, 6.2×10^{-3} mol, 1.1 equiv.) was added to a solution of phosphonate **3b** (1.819 g, 5.6×10^{-3} mol) in dry THF (5 mL) at 0°C under an atmosphere of argon. After stirring at 0°C for 10 min, a solution of aldehyde **2** (1.670 g, 1 equiv.) in dry THF (5 mL) was added and the mixture allowed to warm to ambient temperature and stirred for 3.5 h. Water (30 mL) was added, the mixture was extracted with ethyl acetate (×3) and the combined extracts washed with brine then dried and evaporated to dryness to afford an oil. This was chromatographed using ethyl acetate:hexane (gradient, 10:90 to 50:50) as eluent to afford a 43:57 *E*:*Z* mixture of geometric isomers of the title compound as a wax (2.278 g, 88%); (found $(M+H)^+$ (FAB) 465. $C_{23}H_{23}F_3N_2O_5$ requires *M* 465); ν_{max} (film)/cm^{-1} 1712 (CO); δ_H (270 MHz, $CDCl_3$) geometric isomerism causes doubling of most peaks, 1.17, 1.36 (combined, 3H, t, *J* 7.1, isomers of OCH_2CH_3), 3.35, 3.36 (combined, 3H, s, NMe), 3.95 (2H, m, OCH_2CH_2N), 4.10–4.40 (6H, m, 3×OCH_2), 6.48 (0.43H, s, *E*-olefinic H) and 6.80–7.70 (8.57H, m, *Z*-olefinic H and ArH); *m/z* (FAB) 487 [$(M+Na)^+$, 10%], 465 [$(M+H)^+$, 100], 419 (4), 316 (16) and 175 (61).

4.4.2. Ethyl (E/Z)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-ethoxypropenoate **4a**

Similarly prepared. A gum, 71%; 38:62 *E*:*Z* mixture of geometric isomers; (found M^+ (EI) 410.1840. $C_{23}H_{26}N_2O_5$ requires *M* 410.1842); δ_H (270 MHz, $CDCl_3$) geometric isomerism causes doubling of most peaks, 1.13 (0.38×3H, t, *J* 7.1, $CO_2CH_2CH_3$, *E*-isomer), 1.25–1.45 (3H+0.62×3H, m, OCH_2CH_3 and $CO_2CH_2CH_3$, *Z*-isomer), 3.34 (3H, s, NMe), 3.95–4.40 (8H, m, 3×OCH_2 and NCH_2), 6.06 (0.32H, s, *E*-olefinic H) and 6.80–7.80 (8.62H, m, *Z*-olefinic H and aryl-H).

4.4.3. Ethyl (E/Z)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)-propenoate **4c**

Similarly prepared. A gum, 60%; 24:76 *E*:*Z* mixture of geometric isomers; (found M^+ (EI) 440.1948. $C_{24}H_{28}N_2O_6$ requires *M* 440.1948); δ_H (270 MHz, $CDCl_3$) geometric isomerism causes doubling of most peaks, 1.12, 1.35 (combined, 3H, t, *J* 7.1, isomers of OCH_2CH_3), 3.35–3.45 (combined, 6H, m, isomeric NMe and OMe), 3.67, 3.72 (combined, 2H, m, OCH_2CH_2OMe), 3.90–4.35 (8H, m, 3×OCH_2 and NCH_2), 6.15 (0.24H, s, *E*-olefinic H) and 6.80–7.80 (8.76H, m, *Z*-olefinic H and ArH).

4.4.4. Ethyl (E/Z)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-benzyloxypropenoate **4d**

Similarly prepared. A gum, 68%; 41:59 *E*:*Z* mixture of geometric isomers. These were partially resolved by silica gel chromatography using ethyl acetate:dichloromethane (2:98) as an eluent to afford initially the *Z*-isomer *Z*-**4d**: (found M^+ (EI) 472.1996. $C_{28}H_{28}N_2O_5$ requires *M* 472.1996); δ_H (270 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1, OCH_2CH_3), 3.34 (3H, s, NMe), 3.95 (2H, t, *J* 5.2, NCH_2), 4.30 (4H, m, 2×OCH_2), 4.93 (2H, s, CH_2Ph), 6.83 (2H, d, *J* 8.9, aryl 3-H and 5-H) and 6.95–7.75 (12H, m, aryl-H and *Z*-olefinic H); followed by the *E*-isomer *E*-**4d**: δ_H (270 MHz, $CDCl_3$) 1.15 (3H, t, *J* 7.2, OCH_2CH_3), 3.34 (3H, s, NMe), 3.94 (2H, t, *J* 5.3, NCH_2), 4.16 (2H, q, *J* 7.2 OCH_2CH_3), 4.25 (2H, t, *J* 5.3 OCH_2), 4.94 (2H, s, CH_2Ph), 6.19 (1H, s, *E*-olefinic H) and 6.78–7.45 (13H, m, aryl-H).

*4.4.5. Ethyl (*E/Z*)-3-[4-[2-[*N*-(2-benzoxazolyl)-*N*-methylamino]ethoxy]phenyl]-2-(3-trifluoromethylphenoxy)propenoate* ***4e***

Similarly prepared. A gum, 94%; 50:50 *E*:*Z* mixture of geometric isomers; (found M^+ (EI) 526.1712. $C_{28}H_{25}N_2O_5$ requires *M* 526.1716); δ_H (270 MHz, $CDCl_3$) geometric isomerism causes doubling of most peaks, 1.05, 1.18 (combined, 3H, t, *J* 7.1, isomers of OCH_2CH_3), 3.32, 3.35 (combined, 3H, s, NMe), 3.96 (2H, m, NCH_2), 4.05–4.35 (4H, m, 2×OCH_2) and 6.80–7.70 (13H, m, aryl-H and olefinic H).

4.5. Reduction of alkene ***4****, Method A*

*4.5.1. Ethyl 3-[4-[2-[*N*-(2-benzoxazolyl)-*N*-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoate* ***5b*** *(R^2=Et)*

A mixture of alkene **4b** (2.240 g, 4.83×10^{-3} mol), 10% palladium on charcoal (220 mg) and ethanol (30 mL) was shaken under an atmosphere of hydrogen at 30 p.s.i. and ambient temperature. After 5 h, the catalyst was removed by filtration and solvent removed in vacuo to give the product as an oil (2.201 g, 98%), which was used without further purification; (found M^+ (EI) 466.1715. $C_{23}H_{25}F_3N_2O_5$ requires *M* 466.1716); ν_{max} (film)/cm^{-1} 1744 (CO); δ_H (270 MHz, $CDCl_3$) 1.24 (3H, t, *J* 7.2, OCH_2CH_3), 3.00 (2H, m, $ArCH_2CH$), 3.34 (3H, s, NMe), 3.65 (1H, m, $OCHHCF_3$), 3.94 (2H, t, *J* 5.2, NCH_2), 3.97 (1H, m, $OCHHCF_3$), 4.10–4.30 (5H, m, 2×OCH_2 and $ArCH_2CH$), 6.80 (2H, d, *J* 8.8, phenyl-3H and 5H) and 6.95–7.40 (6H, m, ArH); *m/z* (FAB) 489 [$(M+Na)^+$, 17%], 467 [$(M+H)^+$, 100], 175 (52) 161 (18) and 148 (58).

*4.5.2. Ethyl 3-[4-[2-[*N*-(2-benzoxazolyl)-*N*-methylamino]ethoxy]phenyl]-2-ethoxypropanoate* ***5a*** *(R^2=Et)*

Similarly prepared. A gum, 73%; (found $(M+H)^+$ (CI) 413.2070. $C_{23}H_{28}N_2O_5$ requires *M* 413.2077); δ_H (270 MHz, $CDCl_3$) 1.15 (3H, t, *J* 6.9, OCH_2CH_3), 1.22 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 2.95 (2H, m, $ArCH_2CH$), 3.30 (1H, m, $OCHHCH_3$), 3.34 (3H, s, NMe), 3.60 (1H, m, $OCHHCH_3$), 3.93 (3H, m, $ArCH_2CH$ and NCH_2), 4.17 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 4.24 (2H, t, *J* 5.2, OCH_2), 6.80 (2H, d, *J* 8.8, aryl 3-H and 5-H) and 6.95–7.40 (6H, m, aryl H).

4.6. Reduction of alkene ***4****, Method B*

*4.6.1. Methyl 3-[4-[2-[*N*-(2-benzoxazolyl)-*N*-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoate* ***5c*** *(R^2=Me)*

A mixture of alkene **4c** (1.36 g, 3 mmol), magnesium (0.5 g, 20 mmol) iodine (ca. 10 mg) and methanol (80 mL) was warmed gently (hairdryer) with stirring until evolution of hydrogen commenced. An additional portion of magnesium (3.5 g, 140 mmol) was added and the mixture stirred at room temperature (temperature regulated by immersion in a cold water bath) for 23 h then concentrated. The residue was suspended in water (500 mL) and concentrated hydrochloric acid was added to give a final pH of 2, once all the solid had dissolved. The mixture was extracted with ethyl acetate (3×500 mL) and the combined organic solutions washed with brine (500 mL), dried and evaporated. The residue was chromatographed using ethyl acetate:dichloromethane (gradient, 5:95 to 10:90) as eluent to afford **5c** (R^2=Me), a colourless gum, 0.476 g, 37%; (found $(M+H)^+$ (CI) 428.1946. $C_{23}H_{28}N_2O_6$ requires *M* 428.1948); ν_{max} (film)/cm^{-1} 1748 (CO); δ_H (270 MHz, $CDCl_3$) 2.95 (2H, m, $ArCH_2CH$), 3.29 (3H, s, OMe), 3.35 (3H, s, NMe), 3.47 (3H, m, $OCHHCH_2OMe$), 3.69 (4H, m, CO_2Me and $OCHHCH_2OMe$),

3.93 (2H, t, *J* 5.2, NCH_2), 4.06 (1H, t, *J* 5.8, $ArCH_2CH$), 4.24 (2H, t, *J* 5.2, OCH_2), 6.80 (2H, d, *J* 8.8, aryl 3-H and 5-H) and 6.95–7.40 (6H, m, aryl H); *m/z* (CI) 429 [$(M+H)^+$, 100%], 175 (15) and 148 (10).

*4.6.2. Methyl 3-[4-[2-[*N*-(2-benzoxazolyl)*-N*-methylamino]ethoxy]phenyl]-2-benzyloxypropanoate* ***5d*** *(R^2=Me)*

Similarly prepared. A gum, 84%; (found M^+ (EI) 460.2000. $C_{27}H_{28}N_2O_5$ requires *M* 460.1999); δ_H (270 MHz, $CDCl_3$) 2.98 (2H, m, $ArCH_2CH$), 3.35 (3H, s, NMe), 3.69 (3H, s, OMe), 3.94 (2H, t, *J* 5.2, NCH_2), 4.10 (1H, dd, *J* 7.7 and 5.5, $ArCH_2CH$), 4.24 (2H, t, *J* 5.2, OCH_2), 4.35 (1H, d, *J* 11.9, OCHHPh), 4.64 (1H, d, *J* 11.9, OCHHPh), 6.79 (2H, d, *J* 8.8, aryl 3-H and 5-H) and 6.95–7.40 (11H, m, aryl-H).

*4.6.3. Methyl 3-[4-[2-[*N*-(2-benzoxazolyl)*-N*-methylamino]ethoxy]phenyl]-2-(3-trifluoromethylphenoxy)propanoate* ***5e***

Similarly prepared. (R^2=Me), a gum, 78%; (found M^+ (EI) 514.1717. $C_{27}H_{25}F_3N_2O_5$ requires *M* 514.1716); δ_H (270 MHz, $CDCl_3$) 3.18 (2H, d, *J* 6.4, $ArCH_2CH$), 3.33 (3H, s, NMe), 3.71 (3H, s, OMe), 3.93 (2H, t, *J* 5.2, NCH_2), 4.23 (2H, t, *J* 5.2, OCH_2), 4.77 (1H, t, *J* 6.4, $ArCH_2CH$), 6.83 (2H, d, *J* 8.8, aryl 3-H and 5-H) and 6.90–7.35 (10H, m, aryl-H).

4.7. Alkaline hydrolysis of esters ***5***

*4.7.1. (±)-3-[4-[2-[*N*-(2-Benzoxazolyl)*-N*-methylamino]ethoxy]phenyl]-2-ethoxypropanoic acid* ***1a***

Aqueous sodium hydroxide hydrolysis of **5a** afforded acid **1a** as a white solid (50%), m.p. 109–110°C; (found C, 65.6; H, 6.3; N, 7.4%; M^+ (EI) 384.1686. $C_{21}H_{24}N_2O_5$ requires C, 65.6; H, 6.3; N, 7.3%; *M* 384.1685); ν_{max} (KBr)/cm^{-1} 3000–2500 (COOH), 1710 (CO); δ_H (270 MHz, $CDCl_3$) 1.18 (3H, t, *J* 6.9, OCH_2CH_3), 2.95 (1H, dd, *J* 14.0 and 7.2, ArCHHCH), 3.05 (1H, dd, *J* 14.0 and 5.0, ArCHHCH), 3.32 (3H, s, NMe), 3.45 (1H, m, OCHHCH$_3$), 3.60 (1H, m, OCHHCH$_3$), 3.91 (2H, t, *J* 5.0, NCH_2), 4.04 (1H, dd, *J* 7.2 and 5.0, $ArCH_2CH$), 4.18 (2H, t, *J* 5.0, OCH_2), 5.00 (1H, br, exchanges with D_2O, CO_2H), 6.79 (2H, d, *J* 8.8, aryl 3-H and 5-H) and 6.95–7.40 (6H, m, aryl-H); *m/z* (EI) 384 (M^+, 9%), 311 (40), 175 (100), 161 (72) and 148 (100).

*4.7.2. (±)-3-[4-[2-[*N*-(2-Benzoxazolyl)*-N*-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)-propanoic acid* ***1b***

Similarly prepared. A solid, 93%; m.p. 116–117°C; (found C, 57.4; H, 4.9; N, 6.4%; M^+ (EI) 438.1403. $C_{21}H_{21}F_3N_2O_5$ requires C, 57.5; H, 4.8; N, 6.4%; *M* 438.1403); δ_H (270 MHz, $CDCl_3$) 3.11 (2H, m, $ArCH_2CH$), 3.29 (3H, s, NMe), 3.76 (1H, m, OCHHCF$_3$), 3.85 (2H, m, NCH_2), 4.02 (2H, m, OCH_2CH_2N), 4.10 (1H, m, OCHHCF$_3$), 4.24 (1H, m, $ArCH_2CH$), 6.75 (2H, d, *J* 8.8, phenyl 3-H and 5-H), 6.95–7.40 (6H, m, ArH) and 8.75 (1H, br, exchanges with D_2O, COOH).

*4.7.3. (±)-3-[4-[2-[*N*-(2-Benzoxazolyl)*-N*-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)-propanoic acid* ***1c***

Similarly prepared. A solid, 92%; m.p. 87–89°C; (found C, 63.8; H, 6.5; N, 7.05%; M^+ (EI) 414.1791. $C_{21}H_{26}N_2O_6$ requires C, 63.8; H, 6.3; N, 6.8%; *M* 414.1791); δ_H (270 MHz, $CDCl_3$) 2.91 (1H, dd, *J* 14.3 and 8.5, ArCHHCH), 3.14 (1H, dd, *J* 14.3 and 3.8, ArCHHCH), 3.33 (3H, s, NMe), 3.38 (3H, s, OMe), 3.40–3.70 (5H, m, reduces to 4H on exchange with D_2O, COOH and OCH_2CH_2OMe), 3.93 (2H, t, *J* 5.2, NCH_2), 4.05 (1H, dd, *J* 8.5 and 3.8, $ArCH_2CH$), 4.21 (2H, t, *J* 5.2, OCH_2), 6.80 (2H, d, *J* 8.6, aryl 3-H and 5-H) and 6.96–7.40 (6H, m, aryl-H).

*4.7.4. (±)-3-[4-[2-[*N*-(2-Benzoxazolyl)*-N*-methylamino]ethoxy]phenyl]-2-benzyloxypropanoic acid* ***1d***

Similarly prepared. A foam, 91%; (found M^+ (EI) 446.1843. $C_{26}H_{26}N_2O_5$ requires *M* 446.1842); δ_H (270 MHz, $CDCl_3$) 3.05 (2H, m, ArC*H*$_2$CH), 3.31 (3H, s, NMe), 3.90 (2H, t, *J* 5.4, NC*H*$_2$), 4.15 (3H, m, ArCH$_2$C*H* and OC*H*$_2$CH$_2$N), 4.45 (1H, d, *J* 11.5, PhC*H*HO), 4.70 (1H, d, *J* 11.5, PhCH*H*O), 6.70–7.40 (13H, m, aryl-H) and 7.50 (1H, br, exchanges with D_2O, COOH).

*4.7.5. (±)-3-[4-[2-[*N*-(2-Benzoxazolyl)*-N*-methylamino]ethoxy]phenyl]-2-(3-trifluoromethylphenoxy)-propanoic acid* ***1e***

Similarly prepared. A solid, 89%; m.p. 168–169°C; (found C, 62.4; H, 4.6; N, 5.7%; M^+ (EI) 428.1946. $C_{26}H_{23}F_3N_2O_5$ requires C, 62.4; H, 4.6; N, 5.6%; *M* 428.1948); δ_H (270 MHz, $CDCl_3$) 3.25 (5H, m, ArCH$_2$ and NMe), 3.83 (2H, t, *J* 4.9, NC*H*$_2$), 4.00 (1H, br, exchanges with D2O, COOH), 4.04 (2H, t, *J* 4.9, OCH$_2$), 4.86 (1H, t, *J* 6.0, ArCH$_2$C*H*), 6.77 (2H, d, *J* 8.5, aryl 3-H and 5-H) and 6.95–7.40 (10H, m, aryl-H).

4.8. General procedure for reaction of racemic ***1a–c*** *with (*S*)-2-phenylglycinol. Preparation of diastereoisomeric α-ethoxyamides* ***6a*** *and* ***7a***

Oxalyl chloride (3.4 mL, 39 mmol) was added dropwise to a solution of ethoxyacid **1a** (2.96 g, 7.7 mmol) in dry benzene (100 mL). The resulting mixture was heated at reflux for 2 h, cooled and evaporated in vacuo to afford the acid chloride. This was dissolved in dry dichloromethane (150 mL) and the solution added, over 5 min, to an ice-cooled solution of (*S*)-2-phenylglycinol (1.056 g, 7.7 mmol) and triethylamine (2.2 mL, 15.4 mmol) in dichloromethane (150 mL) under argon. The mixture was allowed to warm to ambient temperature and stirred for an additional 16 h before being evaporated. The residue was chromatographed using isohexane:ethyl acetate (gradient, 25:75 to 0:100) as eluent to afford firstly the [2*R*,*N*(1*S*)]-diastereoisomeric amide **6a**, followed by the [2*S*,*N*(1*S*)]-diastereoisomer **7a**.

*4.8.1. [2*R,N*(1*S*)]-3-[4-[2-[*N*-(2-benzoxazolyl)*-N*-methylamino]ethoxy]phenyl]-2-ethoxy*-N*-(2-hydroxy-1-phenylethyl)propanamide* ***6a***

A colourless gum (1.222 g, 32%); (found $(M+H)^+$ (CI) 504.2491. $C_{29}H_{33}N_3O_5$ requires *M* 504.2499); $[\alpha]_D^{25}$ +21 (*c* 1.15 in $CHCl_3$); d.e. 98.4% by HPLC; ν_{max} (film)/cm^{-1} 3420 (NH) and 1645 (CO); δ_H (270 MHz, $CDCl_3$) 1.12 (3H, t, *J* 7.0, OCH$_2$*Me*), 2.65 (1H, br, exchanges with D_2O, OH), 2.94 (1H, dd, *J* 14.1 and 6.3, ArC*H*HCH), 3.10 (1H, dd, *J* 14.1 and 3.8, ArCH*H*CH), 3.33 (3H, s, NMe), 3.50 (2H, m, OC*H*$_2$Me), 3.65 (2H, m, C*H*$_2$OH), 3.93 (2H, t, *J* 5.3, NC*H*$_2$), 3.95 (1H, dd, *J* 6.3 and 3.8, ArCH$_2$C*H*), 4.25 (2H, t, *J* 5.3, OC*H*$_2$CH$_2$N), 4.95 (1H, m, PhC*H*N) and 6.80–7.40 (14H, m, reduces to 13H on exchange with D_2O, aryl-H and NH); *m/z* (CI) 504 [$(M+H)^+$, 100%], 486 (5), 440 (10) and 412 (3).

*4.8.2. [2*S,N*(1*S*)]-3-[4-[2-[*N*-(2-Benzoxazolyl)*-N*-methylamino]ethoxy]phenyl]-2-ethoxy*-N*-(2-hydroxy-1-phenylethyl)propanamide* ***7a***

A colourless gum (1.278 g, 33%); (found $(M+H)^+$ (CI) 504.2486. $C_{29}H_{33}N_3O_5$ requires *M* 504.2499); $[\alpha]_D^{25}$ −19 (*c* 1.25 in $CHCl_3$); d.e. 100% by HPLC; ν_{max} (film)/cm^{-1} 3420 (NH) and 1645 (CO); δ_H (270 MHz, $CDCl_3$) 1.16 (3H, t, *J* 7.0, OCH$_2$*Me*), 2.60 (1H, br, exchanges with D_2O, OH), 2.86 (1H, dd, *J* 14.2 and 6.8, ArC*H*HCH), 3.05 (1H, dd, *J* 14.2 and 3.7, ArCH*H*CH), 3.35 (3H, s, NMe), 3.55 (2H, m, OC*H*$_2$Me), 3.83 (2H, m, C*H*$_2$OH), 3.95 (3H, m, NC*H*$_2$ and ArCH$_2$C*H*), 4.21 (2H, t, *J* 5.2, OC*H*$_2$CH$_2$N), 4.97 (1H, m, PhC*H*N) and 6.80–7.40 (14H, m, reduces to 13H on exchange with D_2O, aryl-H and NH); *m/z* (CI) 504 [$(M+H)^+$, 100%] and 486 (5).

*4.8.3. [2*R,N*(1*S*)]-3-[4-[2-[*N*-(2-Benzoxazolyl)*-N*-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)*-N*-(2-hydroxy-1-phenylethyl)propanamide* ***6b***

Similarly prepared. A foam, 32%; (found M^+ (EI) 557.2136. $C_{29}H_{30}F_3N_3O_5$ requires *M* 557.2138); $[\alpha]_D^{25}$ +39 (*c* 0.35 in MeOH); d.e. 100% by HPLC; δ_H (270 MHz, $CDCl_3$) 2.40 (1H, br, exchanges with D_2O, OH), 3.00 (1H, dd, *J* 13.5 and 6.9, ArC*H*HCH), 3.18 (1H, dd, *J* 13.5 and 3.6, ArCH*H*CH), 3.33 (3H, s, NMe), 3.60–3.85 (4H, m, OCH_2CF_3 and CH_2OH), 3.94 (2H, t, *J* 5.2, NCH_2CH_2O), 4.11 (1H, dd, *J* 6.9 and 3.6, $ArCH_2CH$), 4.26 (2H, t, *J* 5.2, NCH_2CH_2O), 5.00 (1H, m, PhC*H*), 6.83 (2H, d, *J* 8.8, aryl 3-H and 5-H) and 6.90–7.40 (12H, m, aryl-H and NH).

*4.8.4. [2*S,N*(1*S*)]-3-[4-[2-[*N*-(2-Benzoxazolyl)*-N*-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)*-N*-(2-hydroxy-1-phenylethyl)propanamide* ***7b***

Similarly prepared. A foam, 34%; (found M^+ (EI) 557.2136. $C_{29}H_{30}F_3N_3O_5$ requires *M* 557.2138); $[\alpha]_D^{25}$ +14 (*c* 0.50 in MeOH); d.e. 99% by HPLC; δ_H (400 MHz, $CDCl_3$) 2.30 (1H, br, exchanges with D_2O, OH), 2.90 (1H, dd, *J* 14.4 and 7.3, ArC*H*HCH), 3.13 (1H, dd, *J* 14.4 and 3.6, ArCH*H*CH), 3.36 (3H, s, NMe), 3.70–3.87 (2H, m, OCH_2CF_3), 3.84 (2H, d, *J* 5.0, CH_2OH), 3.95 (2H, t, *J* 5.2, NCH_2CH_2O), 4.12 (1H, dd, *J* 7.3 and 3.6, $ArCH_2CH$), 4.22 (2H, t, *J* 5.2, NCH_2CH_2O), 5.01 (1H, m, PhC*H*), 6.75 (2H, d, *J* 8.7, aryl 3-H and 5-H) and 6.95–7.40 (12H, m, aryl-H and NH).

*4.8.5. [2*R,N*(1*S*)]-3-[4-[2-[*N*-(2-Benzoxazolyl)*-N*-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)-N-(2-hydroxy-1-phenylethyl)propanamide* ***6c***

Similarly prepared. A gum, 44%; (found M^+ (EI) 533.2526. $C_{30}H_{35}N_3O_6$ requires *M* 533.2526); $[\alpha]_D^{25}$ +34 (*c* 1.7 in $CHCl_3$); d.e. 90.8% by HPLC; δ_H (400 MHz, $CDCl_3$) 2.86 (1H, br, exchanges with D_2O, OH), 2.92 (1H, dd, *J* 14.2 and 7.8, ArC*H*HCH), 3.11 (3H, s, OMe), 3.17 (1H, dd, *J* 14.2 and 3.3, ArCH*H*CH), 3.34 (3H, s, NMe), 3.35 (1H, m, OC*H*HCH_2OMe), 3.47 (2H, m, OCH_2CH_2OMe), 3.55 (1H, m, OCH*H*CH_2OMe), 3.70 (2H, m, CH_2OH), 3.94 (2H, t, *J* 5.3, NCH_2), 3.95 (1H, dd, *J* 7.8 and 3.3, $ArCH_2CH$), 4.26 (2H, t, *J* 5.3, NCH_2CH_2O), 4.96 (1H, m, PhC*H*), 6.83 (2H, d, *J* 8.7, aryl 3-H and 5-H), 6.95–7.35 (11H, m, aryl-H) and 7.57 (1H, br, exchanges with D_2O, NH).

*4.8.6. [2*S,N*(1*S*)]-3-[4-[2-[*N*-(2-Benzoxazolyl)*-N*-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)-N-(2-hydroxy-1-phenylethyl)propanamide* ***7c***

Similarly prepared. A gum, 27%; (found M^+ (EI) 533.2526. $C_{30}H_{35}N_3O_6$ requires *M* 533.2526); $[\alpha]_D^{25}$ −33 (*c* 1.1 in $CHCl_3$); d.e. 92.6% by HPLC; δ_H (400 MHz, $CDCl_3$) 2.81 (1H, dd, *J* 14.3 and 8.3, ArC*H*HCH), 3.07 (1H, dd, *J* 14.3 and 3.2, ArCH*H*CH), 3.30 (1H, br, exchanges with D_2O, OH), 3.35 (3H, s, OMe), 3.36 (3H, s, NMe), 3.48–3.65 (4H, m, OCH_2CH_2OMe), 3.71 (1H, dd, *J* 11.8 and 7.5, NCHPhC*H*HOH), 3.82 (1H, dd, *J* 11.8 and 4.0, NCHPhCH*H*OH), 3.93 (2H, t, *J* 5.3, NCH_2), 3.94 (1H, dd, *J* 8.3 and 3.2, $ArCH_2CH$), 4.22 (2H, t, *J* 5.3, NCH_2CH_2O), 5.05 (1H, m, PhC*H*), 6.85 (2H, d, *J* 8.7, aryl 3-H and 5-H), 6.95–7.35 (11H, m, aryl-H) and 7.54 (1H, br, exchanges with D_2O, NH).

4.9. General procedure for reaction of racemic ***1d*** *and* ***1e*** *with (*S*)-4-benzyloxazolidin-2-one. Preparation of diastereoisomeric 3-(trifluoromethyl)phenoxyacyloxazolidin-2-ones* ***11e*** *and* ***12e***

Oxalyl chloride (2.62 mL) was added dropwise to a solution of the acid **1e** (3.0 g, 6.0 mmol) in dry benzene (120 mL). The mixture was heated at reflux for 2.5 h, cooled and evaporated in vacuo. Repeated re-evaporation from dry THF afforded the crude acid chloride, a gum.

A solution of *n*-butyllithium (1.6 M in hexane, 7.5 mL, 12.0 mmol) was added dropwise, over 10 min, to a −70°C solution of (*S*)-4-benzyloxazolidin-2-one (2.12 g, 6.0 mmol) in dry THF (50 mL) under

argon. The mixture was stirred at −70°C for an additional 10 min prior to the addition, over 10 min, of a solution of the acid chloride (above) in dry THF (100 mL). Stirring was continued at −70°C for 1 h and the mixture was then allowed to warm to room temperature overnight (20 h), then concentrated. The residue was diluted with water (500 mL), extracted with ethyl acetate (3×500 mL) and the combined ethyl acetate solutions washed with water (500 mL) and brine (500 mL), dried and evaporated. Chromatography using ethyl acetate:isohexane (30:70) as eluent afforded firstly the [3(2*R*),4*S*]-diastereoisomer **11e**, followed by the [3(2*S*),4*S*]-diastereoisomer **12e**.

*4.9.1. [3(2*R*),4*S*]-3-[3-[4-[2-[*N*-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-[3-(trifluoromethyl)phenoxy]propanoyl]-4-benzyloxazolidin-2-one* ***11e***

A white foam (1.08 g, 28%); (found $(M+H)^+$ (CI) 660.2319. $C_{36}H_{32}F_3N_3O_6$ requires *M* 660.2322); $[\alpha]_D^{25}$ +29 (*c* 1.00 in $CHCl_3$); d.e. 100% by HPLC; ν_{max} (KBr)/cm^{-1} 1780, 1710 and 1645 (CO); δ_H (400 MHz, $CDCl_3$) 2.72 (1H, dd, *J* 13.5 and 9.6, PhC*H*HCH), 3.11 (1H, dd, *J* 14.0 and 8.9, ArC*H*HCH), 3.23 (1H, dd, *J* 13.5 and 3.3, PhCH*H*CH), 3.26 (1H, dd, *J* 14.0 and 3.2, ArCH*H*CH), 3.32 (3H, s, NMe), 3.92 (2H, t, *J* 5.3, NCH_2), 4.23 (2H, t, *J* 5.3, OCH_2CH_2N), 4.25 (1H, dd, *J* 9.0 and 3.5, oxazolidinone 5a-H), 4.31 (1H, t, *J* 9.0, oxazolidinone 5b-H), 4.71 (1H, m, oxazolidinone 4-H), 5.97 (1H, dd, *J* 8.9 and 3.3, $ArCH_2CH$), 6.83 (2H, d, *J* 8.7, aryl 3-H and 5-H), 6.92 (1H, dd, *J* 8.3 and 2.6, CF_3-phenoxy 6-H) and 6.99–7.36 (14H, m, aryl-H); *m/z* (CI) 660 [$(M+H)^+$, 100%], 500 (9), 483 (4), 371 (5), 325 (7), 297 (7) and 195 (85).

*4.9.2. [3(2*S*),4*S*]-3-[3-[4-[2-[*N*-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-[3-(trifluoromethyl)phenoxy]propanoyl]-4-benzyloxazolidin-2-one* ***12e***

A white foam (0.73 g, 19%); (found $(M+H)^+$ (CI) 660.2319. $C_{36}H_{32}F_3N_3O_6$ requires *M* 660.2322); $[\alpha]_D^{25}$ +62 (*c* 1.01 in $CHCl_3$); d.e. 97.2% by HPLC; ν_{max} (KBr)/cm^{-1} 1780, 1710 and 1640 (CO); δ_H (400 MHz, $CDCl_3$) 2.73 (1H, dd, *J* 13.5 and 9.5, PhC*H*HCH), 3.18 (2H, d, *J* 6.6, $ArCH_2CH$), 3.18 (1H, dd, *J* 13.5 and 3.3, PhCH*H*CH), 3.32 (3H, s, NMe), 3.92 (2H, t, *J* 5.3, NCH_2), 4.02 (1H, dd, *J* 9.1 and 7.7, oxazolidinone 5a-H), 4.15 (1H, dd, *J* 9.1 and 2.4, oxazolidinone 5b-H), 4.23 (2H, t, *J* 5.3, OCH_2CH_2N), 4.52 (1H, m, oxazolidinone 4-H), 6.13 (1H, t, *J* 6.6, $ArCH_2CH$), 6.82 (2H, d, *J* 8.7, aryl 3-H and 5-H) and 6.95–7.40 (15H, m, aryl-H); *m/z* (CI) 660 [$(M+H)^+$, 100%], 500 (15), 297 (4) and 195 (92).

*4.9.3. [3(2*R*),4*S*]-3-[3-[4-[2-[*N*-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-benzyloxypropanoyl]-4-benzyloxazolidin-2-one* ***11d***

Similarly prepared. A foam, 24%; (found M^+ (EI) 605.2525. $C_{36}H_{35}N_3O_6$ requires *M* 605.2526); $[\alpha]_D^{25}$ +32 (*c* 1.09 in $CHCl_3$); d.e. 97.8% by HPLC; δ_H (270 MHz, $CDCl_3$) 2.66 (1H, dd, *J* 13.2 and 9.3, PhC*H*HCH), 2.80–3.20 (3H, m, $ArCH_2$ and PhCH*H*CH), 3.34 (3H, s, NMe), 3.94 (2H, t, *J* 5.5, NCH_2), 4.10–4.30 (4H, m, OCH_2CH_2N and oxazolinone 5-H_2), 4.38 (1H, d, *J* 11.6, PhC*H*HO), 4.51 (1H, d, *J* 11.6, PhCH*H*O), 4.55 (1H, m, oxazolidinone 4-H), 5.21 (1H, dd, *J* 9.3 and 3.8, $ArCH_2CH$), 6.81 (2H, d, *J* 8.8, aryl 3-H and 5-H) and 6.95–7.40 (16H, m, aryl-H).

*4.9.4. [3(2*S*),4*S*]-3-[3-[4-[2-[*N*-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-benzyloxypropanoyl]-4-benzyloxazolidin-2-one* ***12d***

Similarly prepared. A gum, 17%; (found M^+ (EI) 605.2525. $C_{36}H_{35}N_3O_6$ requires *M* 605.2526); $[\alpha]_D^{25}$ +39 (*c* 1.02 in $CHCl_3$); d.e. 89.8% by HPLC; δ_H (400 MHz, $CDCl_3$) 2.66 (1H, dd, *J* 13.5 and 9.5, PhC*H*HCH), 2.92 (1H, dd, *J* 13.6 and 8.3, ArC*H*HCH), 3.00 (1H, dd, *J* 13.6 and 4.8, ArCH*H*CH), 3.17 (1H, dd, *J* 13.5 and 3.3, PhCH*H*CH), 3.33 (3H, s, NMe), 3.93 (2H, t, *J* 5.3, NCH_2), 4.04 (1H, m, oxazolidinone 5a-H), 4.10 (1H, m, oxazolidinone 5b-H), 4.24 (2H, t, *J* 5.3, OCH_2CH_2N), 4.43 (1H, d, *J*

11.7, PhC*H*HO), 4.51 (1H, m, oxazolidinone 4-H), 4.53 (1H, d, *J* 11.7, PhCH*H*O), 5.33 (1H, dd, *J* 8.3 and 4.8, $ArCH_2CH$), 6.80 (2H, d, *J* 8.6, aryl 3-H and 5-H) and 6.95–7.40 (16H, m, aryl-H).

*4.10. General procedure for hydrolysis of diastereoisomeric amides **6** and **7***

*4.10.1. (*R*)-(+)-3-[4-[2-[*N*-(2-benzoxazolyl)-*N*-methylamino]ethoxy]phenyl-2-ethoxypropanoic acid **8a***

A solution of amide **6a** (1.137 g, 2.3 mmol), sulphuric acid (1.0 M, 23 mL), water (46 mL) and dioxan (46 mL) was heated at 90°C for 48 h, cooled, diluted with water (300 mL) and the pH adjusted to 2.5 by addition of saturated aqueous sodium bicarbonate solution. The mixture was extracted with ethyl acetate (3×250 mL) and the combined organic solutions washed with water (500 mL) and brine (500 mL), dried and evaporated. The residue was chromatographed with methanol:dichloromethane (gradient, 1.5:98.5 to 3.5:96.5) as eluent to afford acid **8a**, (0.324 g, 37%), a foam, spectroscopically identical with racemate **1a**; (found M^+ (EI) 384.1687. $C_{21}H_{24}N_2O_5$ requires *M* 384.1685); $[\alpha]_D^{25}$ +15 (*c* 0.90 in MeOH); e.e. 93.2% by HPLC.

*4.10.2. (*S*)-(−)-3-[4-[2-[*N*-(2-Benzoxazolyl)-*N*-methylamino]ethoxy]phenyl-2-ethoxypropanoic acid **9a***

Similarly prepared. A foam, 38%; (found M^+ (EI) 384.1684. $C_{21}H_{24}N_2O_5$ requires *M* 384.1685); $[\alpha]_D^{25}$ −16 (*c* 1.08 in MeOH); e.e. 93.6% by HPLC; otherwise identical with racemate **1a**.

*4.10.3. (*R*)-(+)-3-[4-[2-[*N*-(2-Benzoxazolyl)-*N*-methylamino]ethoxy]phenyl-2-(2,2,2-trifluoroethoxy)-propanoic acid **8b***

Similarly prepared. A solid, 51%; m.p. 115°C; (found C, 57.8; H, 4.7; N, 6.7%; M^+ (EI) 438.1403. $C_{21}H_{21}F_3N_2O_5$ requires C, 57.5; H, 4.8; N, 6.4%; *M* 438.1403); $[\alpha]_D^{25}$ +24 (*c* 0.31 in $CHCl_3$); e.e. 96.6% by HPLC; otherwise identical with racemate **1b**.

*4.10.4. (*S*)-(−)-3-[4-[2-[*N*-(2-Benzoxazolyl)-*N*-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)-propanoic acid **9b***

Similarly prepared. A solid, 48%; m.p. 116–117°C; (found C, 57.9; H, 4.7; N, 6.8%; M^+ (EI) 438.1403. $C_{21}H_{21}F_3N_2O_5$ requires C, 57.5; H, 4.8; N, 6.4%; *M* 438.1403); $[\alpha]_D^{25}$ −25 (*c* 0.24 in $CHCl_3$); e.e. 95.2% by HPLC; otherwise identical with racemate **1b**.

*4.10.5. (*R*)-(+)-3-[4-[2-[*N*-(2-Benzoxazolyl)-*N*-methylamino]ethoxy]phenyl]-2-(2-methoxyeth-oxy)propanoic acid **8c***

Similarly prepared. A foam, 60%; (found M^+ (EI) 414.1791. $C_{22}H_{26}N_2O_6$ requires *M* 414.1791); $[\alpha]_D^{25}$ +28 (*c* 0.63 in $CHCl_3$); e.e. 94% by HPLC; otherwise identical with racemate **1c**.

*4.10.6. (*S*)-(−)-3-[4-[2-[*N*-(2-Benzoxazolyl)-*N*-methylamino]ethoxy]phenyl]-2-(2-methoxyeth-oxy)propanoic acid **9c***

Similarly prepared. A foam, 43%; e.e. 88% by HPLC. Repeated crystallisation of the (*S*)-(−)-1-phenylethylamine salt subsequently afforded acid **9c**, a foam; (found C, 63.6; H, 6.4; N, 6.8%; M^+ (EI) 414.1791. $C_{22}H_{26}N_2O_6$ requires C, 63.8; H, 6.3; N, 6.8%; *M* 414.1791); $[\alpha]_D^{25}$ −28 (*c* 0.63 in $CHCl_3$); e.e. 94% by HPLC; otherwise identical with racemate **1c**.

4.11. General procedure for recovery of chiral α-oxyacids **8d**,**e** and **9d**,**e** from diastereoisomeric acyloxazolidin-2-ones **11** and **12**

4.11.1. (R)-(+)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-[3-(trifluoromethyl)-phenoxy]propanoic acid **8e**

A freshly prepared solution of sodium methoxide in methanol [sodium hydride (60% dispersion in oil, 0.064 g, 1.6 mmol) dissolved in methanol (2.5 mL)] was added to a 0°C solution of imide **11e** (0.940 g, 1.4 mmol) in methanol (30 mL). The mixture was stirred at 0°C for 13 min, then quenched by the addition of dilute hydrochloric acid (2.0 M, 0.7 mL, 1.4 mmol) and concentrated in vacuo. The residue was suspended in water (100 mL) and extracted with ethyl acetate (3×200 mL). The combined ethyl acetate solutions were washed with brine, dried and evaporated. Chromatography using ethyl acetate:dichloromethane (3:97) as eluent afforded the ester **13e** (0.586 g, 81%), a gum, spectroscopically identical with racemate **5e**; (found M^+ (EI) 514.1717. $C_{27}H_{25}F_3N_2O_5$ requires *M* 514.1716); $[\alpha]_D^{25}$ +12 (*c* 1.33 in $CHCl_3$); e.e. 97% by HPLC.

A solution of ester **13e** (0.543 g, 1.1 mmol), dilute hydrochloric acid (2.0 M, 55 mL) and dioxan (55 mL) was heated at 90°C for 6.5 h then concentrated in vacuo. The residue was suspended in brine (150 mL) and sufficient aqueous sodium hydroxide solution (2.5 M) was added until the solution was at pH 1.5. The mixture was extracted with ethyl acetate (3×300 mL) and the combined ethyl acetate solutions dried and evaporated to afford the crude acid **8e**, a solid (0.511 g, 93%), spectroscopically identical with racemate **1e**. A sample of this material was recrystallised form dichloromethane–hexane to afford an analytical sample, m.p. 151–152°C; (found C, 62.0; H, 4.5; N, 5.4%; M^+ (EI) 500.1568. $C_{26}H_{23}F_3N_2O_5$ requires C, 62.4; H, 4.6; N, 5.6%; M 500.1559); $[\alpha]_D^{25}$ +8 (*c* 0.7 in MeOH); e.e. 98% by HPLC.

4.11.2. (S)-(−)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-[3-(trifluoromethyl)-phenoxy]propanoic acid **9e**

Similarly prepared. Methyl ester **14e**: a gum, 86%; $[\alpha]_D^{25}$ −12 (*c* 1.2 in $CHCl_3$); e.e. 96.4% by HPLC. Acid **9e**: a solid, 85%; m.p. 149–151°C; (found C, 62.3; H, 4.6; N, 5.5%. $C_{26}H_{23}F_3N_2O_5$ requires C, 62.4; H, 4.6; N, 5.6); $[\alpha]_D^{25}$ −7 (*c* 1.09 in MeOH); e.e. 98% by HPLC; otherwise identical with racemate **1e**.

4.11.3. (R)-(+)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-benzyloxypropanoic acid **8d**

Similarly prepared. Methyl ester **13d**: a gum, 80%; (found M^+ (EI) 460.2000. $C_{27}H_{28}N_2O_5$ requires M 460.1999); $[\alpha]_D^{25}$ +31 (*c* 0.4 in $CHCl_3$); e.e. 96% by HPLC. Acid **8d**: a foam, 68%; $[\alpha]_D^{25}$ +24 (*c* 1.00 in $CHCl_3$); e.e. 96% by HPLC; otherwise identical with racemate **1d**.

4.11.4. (S)-(−)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-benzyloxypropanoic acid **9d**

Methyl ester **14d**: a gum, 75%; $[\alpha]_D^{25}$ −34 (*c* 0.55 in $CHCl_3$); e.e. 88% by HPLC. Acid **9d**: a foam, 71%; $[\alpha]_D^{25}$ −27 (*c* 1.46 in $CHCl_3$); e.e. 88% by HPLC; otherwise identical with racemate **1d**.

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