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Non-thiazolidinedione antihyperglycaemic agents. Part 5: Asymmetric aldol synthesis of (*S*)-(−)-2-oxy-3-arylpropanoic acids †

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Abstract

Boron-mediated asymmetric aldol reactions of substituted benzaldehyde **5** with 2-oxyethanoyloxazolidinones **4a**–**e**, containing electron withdrawing, chelating, and bulky alkoxy and aryloxy groups, gave variable yields of *syn*-aldol adducts **6a**–**e** in high diastereoisomeric excess. Dehydroxylation of these adducts afforded **7a**–**e** in a sequence which complements the traditional Evans asymmetric alkylation strategy. Cleavage of the auxiliary from **7a**–**e** afforded antihyperglycaemic (*S*)-(−)-2-oxy-3-arylpropanoic acids **3a**–**e** in excellent enantiomeric excess.

1. Introduction

We have recently described[2] the discovery and potent antihyperglycaemic activity of a novel series of racemic 2-oxy-3-arylpropanoic acids **1**. These carboxylic acids were designed as non-heterocyclic analogues of thiazolidine-2,4-dione antihyperglycaemic agents currently being developed for the treatment of non-insulin-dependent diabetes mellitus (NIDDM).[3,4]

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

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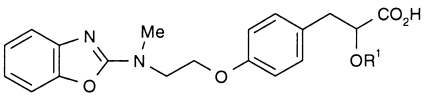
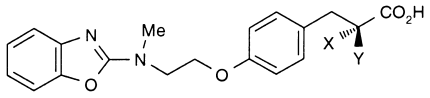


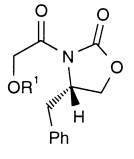


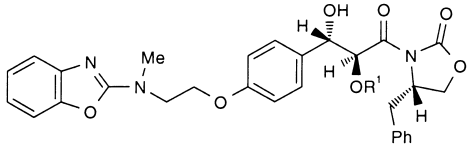
1 **a**, R^1 = Et, **d**, R^1 = CH_2Ph, (*R*)-(+)-**2**, X = OR^1, Y = H
b, R^1 = CH_2CF_3, **e**, R^1 = *m*-$C_6H_4CF_3$ (*S*)-(−)-**3**, X = H, Y = OR^1
c, R^1 = CH_2CH_2OMe,

In contrast to the thiazolidine-2,4-diones which undergo rapid racemisation in solution,[5] the individual enantiomers of acids **1a**–**e** retain their stereogenic integrity under a variety of conditions. It was important, therefore, to establish an efficient methodology for the synthesis of these enantiomers. In our preceding paper[1] we described the resolution of acids **1a**–**e** into their respective (*R*)- and (*S*)-enantiomers **2** and **3**. In subsequent biological evaluations, the (*S*)-enantiomers **3** clearly demonstrated greater potency than their (*R*)-antipodes, both at a molecular target (in vitro PPARγ binding)[6] and in an in vivo mouse model of antihyperglycaemic activity.[7,8] In order to establish further the full in vivo biological profile of **3**, a versatile route to multigram quantities of the drug candidates was required. In this paper we report the development of a robust, asymmetric aldol sequence suitable for the facile preparation of the required (*S*)-enantiomeric acids **3** in excellent enantiopurity.

2. Results and discussion

Development of the asymmetric aldol reaction[9] utilising chiral 3-acyloxazolidin-2-ones, pioneered by Evans[9a,10] and Heathcock,[9b,c,11] has made these reagents a first choice in the asymmetric synthesis of 2-alkyl-substituted carbonyl compounds and derivatives. Within the last decade, extensions of this methodology to encompass the preparation of chiral 2-alkoxycarbonyl compounds have also been reported.[12] However, despite the now widespread use of these reagents, the full scope of the reaction of 3-(2-oxyethanoyl)oxazolidin-2-ones **4** with bulkier aromatic aldehydes has not been explored.[12d,12m] Particularly important was the need to establish whether reagents carrying either electronegative (e.g. **4b**) or bulky (e.g. **4e**) alkoxy and aryloxy groups, or those containing an additional chelating functionality (e.g. **4c**) would compromise the diastereoselectivity of the reaction.[13]





4 **a**, R^1 = Et, **d**, R^1 = CH_2Ph, *anti*-**9**
b, R^1 = CH_2CF_3, **e**, R^1 = *m*-$C_6H_4CF_3$
c, R^1 = CH_2CH_2OMe,

The oxazolidin-2-ones **4a**–**e** were prepared by reaction of the anion of (*S*)-4-benzyloxazolidin-2-one (*n*-butyllithium, THF, −78°C) with appropriate acid chlorides and isolated in variable yield‡ following chromatography on silica gel (Table 1). Reaction of **4a**–**e** with the substituted benzaldehyde **5**[4] in dichloromethane under 'standard' aldol conditions (1.1 equiv. di-*n*-butylboron triflate, 1.2 equiv. triethylamine, −70°C → 0°C), followed by oxidative workup afforded moderate yields of the desired aldol

‡ With the exception of compound **4b**, the yields quoted for compounds **4** are those for unoptimised reactions. The yield of **4b** was optimised from 31% to 91% by utilising freshly distilled trifluoroethoxyethanoyl chloride. It is likely that similar increases in yield could be obtained for the other analogues.

Table 1
Asymmetric aldol synthesis of (*S*)-**3**. Yields and isomer purity data

Substituent R[1]		4	6			9	7		(*S*)-3	
		Yield (%)[a]	Yield (%)[b]	d.e. (%)[c]	J_{syn} (Hz)[d]	J_{anti} (Hz)[d]	Yield (%)	d.e. (%)[e]	Yield (%)[f]	e.e. (%)[g]
a	Et	32	45	96.0	4.95	6.90	83	>99.5	86	99.4
b	CH_2CF_3	91	67	95.4	4.80	7.80	95	>99.5	83	99.4
c	CH_2CH_2OMe	35	57	99.0	6.00	6.60	87	>99.5	67	99.8
d	CH_2Ph	52	52	94.0	4.90	8.30	66	>99.5	81	98.2
e	*m*-$C_6H_4CF_3$	73	31	90.4	5.40	7.40	64	>99.5	85	99.0

[a]With the exception of **4b**, these yields are unoptimised. See footnote in text.

[b]Chromatographed, isolated yield. A standard set of (unoptimised) reaction conditions were employed throughout and some unreacted imide **4** and aldehyde **5** were recovered in each case.

[c]The d.e. is calculated from ^{1}H NMR integrals of the C*H*OR[1] signals for purified aldol product **6**, comprising two diastereoisomers **6** (*syn*) and **9** (*anti*), see discussion.

[d]Coupling constant between C*H*OR[1] and C*H*OH protons in ^{1}H NMR spectrum.

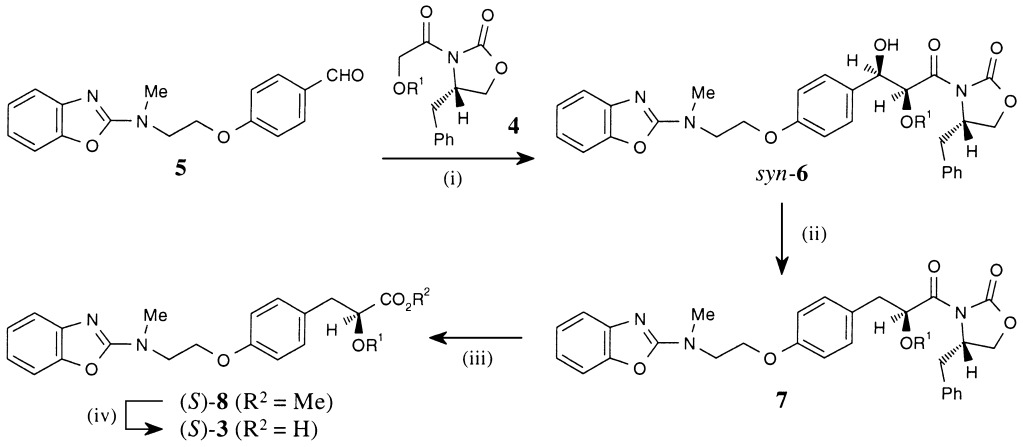
[e]Single diastereoisomer by ^{1}H NMR spectroscopy in each case. The improvement in d.e. observed in going from compound **6** to **7** is a consequence of removing the β-hydroxy group from the (inseparable) mixture of **6** and its β-epimer **9**. See note c above and also text of paper for a more thorough discussion of this point.

[f]Overall yield from **7**.

[g]The e.e. was measured by chiral HPLC.

product, together with the unreacted starting materials (Scheme 1). Inspection of the ^{1}H NMR spectrum of the crude reaction mixture in each case suggested the presence of the expected *syn*-[3(2*S*,3*R*),4*S*]-diastereoisomer **6** (~90–95% d.e.), accompanied by small quantities of two other diastereoisomers. Purification of the reaction mixture by chromatography on silica gel removed one of the minor isomers and allowed the isolation of an inseparable mixture of **6** (generally >94% d.e.) and the *anti*-[3(2*S*,3*S*),4*S*]-diastereoisomer **9** (Table 1). Assignment of the relative stereochemistry of **6** and **9** was based on literature precedent (**6**, J_{syn} 4.80–6.00 Hz; **9**, J_{anti} 6.60–8.30 Hz; Table 1) in combination with the subsequent chemistry and X-ray crystal structure determination (see below). In the case of oxazolidinone **4b**, this reaction has been conducted at a 0.1 mol scale with no reduction in yield or diastereoselectivity.

Inspection of Table 1 shows that, in comparison with 2-ethoxyethanoyloxazolidin-2-one **4a**, the electronegative trifluoroethoxy analogue **4b** does not affect the stereochemical outcome of the reaction.[13] However, the aryloxy analogue **4e** shows a small reduction in diastereoselectivity, with more of the *anti*-diastereoisomer **9** being produced. Assuming that the reaction proceeds via the normal 'Evans-*syn*' closed chair transition state, then reaction of the *si*-face of enolate **4e** with the *si*-face of aldehyde **5** brings the two bulky aryl groups into close proximity (Fig. 1). The resulting interaction may be sufficient to partially overcome the 1,3-diaxial interaction between the aldehyde and the oxazolidinone that normally precludes attack at the *re*-face of the aldehyde,[9b,c] thus accounting for the slight loss of stereocontrol at the resulting hydroxy centre in **6e**. Alternatively, Pridgen has recently suggested that formation of the *anti*-diastereoisomer in boron-mediated aldol reactions arises from a twist-boat transition state (Fig. 2) and that there is only a small energy difference between this and the chair transition state.[14] It is possible that a contribution from this transition state might also be involved in the production of the *anti*-diastereoisomer



Scheme 1. For definition of substituents R^1, see Table 1. Reagents: (i) 1.1 equiv. *n*-Bu_2BOTf, 1.2 equiv. NEt_3, CH_2Cl_2, −70°C → 0°C. (ii) Et_3SiH, CF_3CO_2H. (iii) 1.1 equiv. NaOMe, MeOH. (iv) 2.0 M HCl

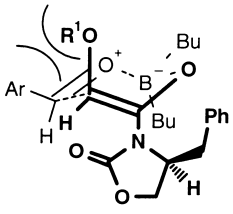


Figure 1. Chair transition state for attack at *si*-faces of both enolate **4** and aldehyde **5**, leading to *syn*-**6**

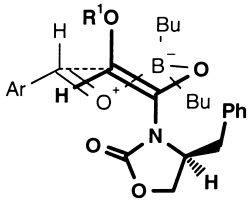


Figure 2. Twist-boat transition state for attack of *si*-face of enolate **4** and *re*-face of aldehyde **5**, leading to *anti*-**9**

9. The reduced chemical yield of aldol product **6e** may also be a reflection of these steric interactions. Interestingly, the (2-methoxyethoxy) analogue **4c** showed an increase in diastereoselectivity, although the reasons for this effect are not clear. It is notable, however, that both **6c** and **6e** display larger J_{syn}-coupling constants than the other aldol products, suggesting that the conformation of the molecular backbone is different in these two cases.

The yields of aldol products **6a**–**e** obtained in this manner were modest by comparison with those reported in the literature and so, in an attempt to optimise the product yield, a small study of the influence of temperature and reaction time was undertaken using 2-(2,2,2-trifluoroethoxy)ethanoyloxazolidinone **4b** as a substrate. In small-scale (1.5 mmol) experiments, reactions of **4b** and **5** under our standard conditions (1.1 equiv. *n*-Bu_2BOTf, 1.2 equiv. NEt_3, CH_2Cl_2, see Experimental for full details) afforded yields (~65%) and diastereoisomer ratios (~95% d.e.) comparable to the larger scale reactions, as determined from the 400 MHz ^1H NMR spectrum of the crude reaction mixture following oxidative workup. Attempts to improve the yield of **6b** by increasing the time for enolate formation, conducting the enolate formation at 0°C, or extending the reaction time for an additional period before quenching

Table 2
Aldol products. ^{1}H NMR data for diastereoisomers **6b**, **9b**, **10** and **11**

Isomer	Ratio[a]	δ_H (ppm)[b]	J (Hz)[c]	Assignment[d]
6b	1.0	5.48	4.80	Evans *syn*
9b	0.3	5.52	7.80	*anti*
10	3.6	5.44	3.43	Non-Evans *syn*
11	1.2	5.49	7.67	*anti*

[a]Reaction conducted with 1.1 eq. *n*-Bu_2BOTf, 1.2 eq. NEt_3 and 1.1 eq. $BF_3.Et_2O$. Ratio assessed from the 400 MHz ^{1}H NMR spectrum of crude product mixture.

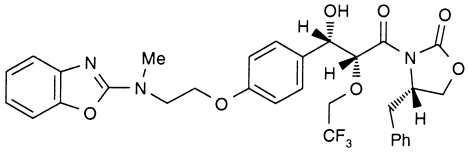
[b]Chemical shift of C*H*OCH_2CF_3 signal for each diastereoisomer.

[c]Coupling constant between C*H*OH and C*H*OCH_2CF_3 protons in ^{1}H NMR spectrum.

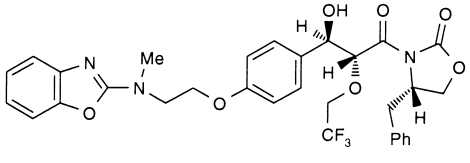
[d]Assignments based on literature predictions, confirmed by subsequent chemistry and crystallography.

had no effect on either the yield or d.e. of **6b**, whereas shortening the reaction time reduced the yield without affecting the diastereoisomer ratio.

These experiments suggest that the modest aldol product yield is attributable to incomplete enolate formation, and may be a consequence of using commercial di-*n*-butylboron triflate[15] rather than freshly prepared material. In an attempt to circumvent this problem, an experiment was conducted using a nominal 1.6 equiv. of the boron triflate and 1.6 equiv. of base. Under these conditions the yield was increased to 78% of **6b**, but diastereoselectivity was compromised (80% d.e.), consistent with an earlier report by Heathcock.[11] Finally, the effect of addition of 1.1 equiv. boron trifluoride etherate, a reagent reported to induce aldol reaction via an open transition state,[11] was also examined. The 400 MHz ^{1}H NMR spectrum of the crude product mixture from this experiment suggested the presence of all four possible diastereoisomers, in which the normal 'Evans' *syn*-[3(2*S*,3*R*),4*S*]-**6b** and the *anti*-[3(2*S*,3*S*),4*S*]-**9b** isomers were now accompanied by the 'non-Evans' *syn*-[3(2*R*,3*S*),4*S*]- and *anti*-[3(2*R*,3*R*),4*S*]-diastereoisomers **10** and **11** in a ratio of 1.0, 0.3, 3.6 and 1.2, respectively (Table 2). Assignment of stereochemistry to diastereoisomers **10** and **11** was based on literature precedent and was confirmed by subsequent chemistry (not discussed). Thus, in contrast to Heathcock's results,[11] boron trifluoride etherate was unsuccessful in promoting a clean *anti*-addition of trifluoroethoxyoxazolidinone **6b**. Instead, the results suggested that the reaction proceeds via a combination of different transition states in this particular case.



syn-**10**



anti-**11**

With the aldol products **6a–e** available, completion of the synthesis of chiral acids **3** was examined. Removal of the unwanted hydroxy group from **6** was readily accomplished by treatment with triethylsilane in trifluoroacetic acid.[16] Dehydroxylation product **7** was isolated as a single diastereoisomer (64–95% yield, >99.5% d.e., Table 1) in each case, as determined by ^{1}H NMR spectroscopy. The observed improvement in d.e. in going from **6** to **7** is a consequence of removal of the hydroxy group from the mixture of **6** and its accompanying, inseparable minor isomer **9** and thus confirms the stereochemical

assignment of **9** as epimeric to **6** at the hydroxy centre. The absolute configuration of **7b** was confirmed by X-ray crystal structure determination (Fig. 3), thereby corroborating the stereochemical assignment of **6** as consistent with literature predictions. In addition, compounds **7d** and **7e** prepared in this manner were found to be identical with the slower eluting diastereoisomers obtained when the racemic acids were resolved using the oxazolidinone auxiliary, thus confirming the stereochemical assignments detailed in our preceding paper.[1] The sequence of aldol and dehydroxylation reactions (**4** → **7**) described above represents an alternative approach to the conventional Evans asymmetric alkylation chemistry of acyloxazolidin-2-ones.[17,18]

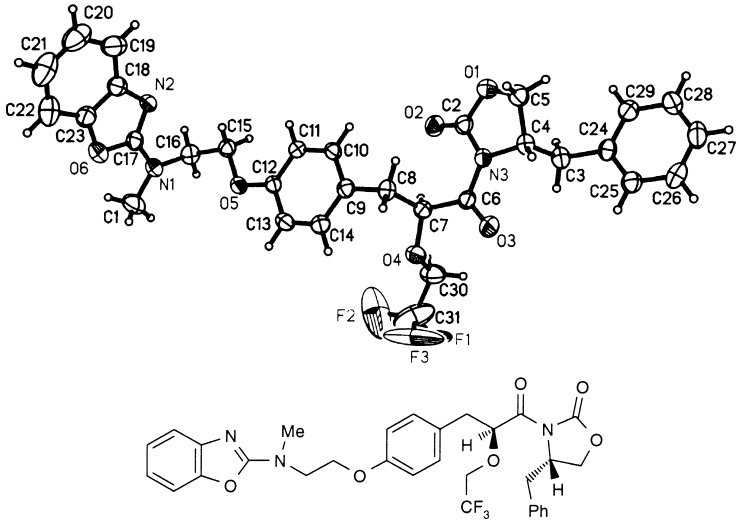


Figure 3. X-Ray crystal structure of compound **7b**

In order to avoid racemisation of the alkoxy stereocentre in **7**, cleavage of the auxiliary was initially accomplished by brief exposure to 1.1 equiv. of sodium methoxide[19] to afford esters **8a**–**e** (66–86% chromatographed, isolated yield; >99.4% e.e. throughout). Finally, acid hydrolysis of **8a**–**e** gave the desired (*S*)-(−)-acids **3a**–**e** in good yield and excellent enantiopurity (Table 1), spectroscopically identical to those produced by the resolution procedure detailed in the preceding paper.[1] In a subsequent modification to the cleavage step, it was found that **7b** could be cleaved by treatment with aqueous sodium hydroxide to afford **3b** directly in higher yield (95%), without any loss of enantiopurity (99.6% e.e.) in the resulting acid.[20] This modification was not examined with the other analogues **7a** and **7c**–**e**.

3. Conclusions

In this paper we have shown that 2-oxyethanoyloxazolidinones **4a**–**e**, bearing a range of electron withdrawing, chelating, and bulky alkoxy and aryloxy groups undergo boron-mediated asymmetric aldol reactions with substituted benzaldehyde **5** to afford *syn*-aldol adducts **6a**–**e** in variable yield, but with excellent stereocontrol (generally >94% d.e.) up to the 0.1 mol scale. Removal of the alcohol functionality from **6** afforded **7** as a single diastereoisomer, thereby confirming the identity of the minor diastereoisomer **9** derived from the aldol reaction. Sodium methoxide induced cleavage of the auxiliary, and acid hydrolysis of the resulting ester afforded the desired acids (*S*)-(−)-**3a**–**e** in excellent enantiomeric excess (generally >99% e.e.) and modest overall yield (17–53% from **4**) in sufficient quantities for biological evaluation. The absolute configuration of **7b**, and hence of acids **3**, was proved

by X-ray crystallography and confirmed the stereochemical assignments inferred in our preceding paper.[1] Chiral acids **3** are potent antihyperglycaemic agents, indicating that the (*S*)-2-oxy-3-arylpropanoate moiety provides an effective bioisosteric replacement for 5-benzylthiazolidine-2,4-dione in this class of compound.

4. Experimental

4.1. General experimental details

Mass spectroscopy was conducted using electron impact (EI), chemical ionisation (CI), with ammonia or methane 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 a $CDCl_3$ solution. Chemical shifts are given in δ (ppm) relative to TMS and coupling constants *J* are given in hertz. Values of $[\alpha]_D^{25}$ are given in deg cm^2 g^{-1}. Dry solvents refer to the use of Aldrich Sure-Seal™ dried solvents. Di-*n*-butylboron triflate was purchased from Aldrich as a 1.0 M solution in dichloromethane and each fresh bottle was titrated before use by means of a small-scale reaction between **4b** and **5**, to ensure consistency. All organic solutions obtained from aqueous extractions were dried over $MgSO_4$. Chromatography refers to flash chromatography on silica gel.

4.2. HPLC conditions

The enantiomeric excess of all chiral ester and acid samples was measured against the appropriate racemic standard.[1] Chiral esters **8a–c** and **8e** were assayed on a Chiralpak AD column, using hexane:ethanol (90:10 v/v) as the eluent for **8b**, **8c** and **8e**. For ester **8a**, hexane:Pr^{i}OH (97:3 v/v) was used. Chiral ester **8d** was assayed on a Chiralcel OD column using hexane:Pr^{i}OH (95:5 v/v). Chiral acids **3a**,**d** were resolved on a Chiralpak AD column using hexane:Pr^{i}OH (92:8 v/v) containing CF_3CO_2H (0.05% v/v) as an eluent; for acid **3b** hexane:EtOH (97:3 v/v) containing CF_3CO_2H (0.05% v/v) was used, and for acid **3c**, hexane:EtOH (90:10 v/v) containing CF_3CO_2H (0.05% v/v) was used. Acid **3e** was assayed on a Chiralcel OJ column using hexane:EtOH (85:15 v/v) containing CF_3CO_2H (0.05% v/v) as an eluent. Detection wavelength was either 220, 245 or 250 nm. The solvent flow rate was 1 mL min^{-1} except for ester **8b**, when a flow rate of 0.3 mL min^{-1} was used.

4.3. General procedure for preparation of 2-oxyacyloxazolidin-2-ones *4*

4.3.1. (*S*)-4-Benzyl-3-[2-(2,2,2-trifluoroethoxy)ethanoyl]oxazolidin-2-one *4b*

A solution of (*S*)-4-benzyloxazolidin-2-one (5.21 g, 29 mmol) in dry THF (60 mL) was cooled to −70°C under argon. *n*-Butyllithium (1.6 M solution in hexane, 18.4 mL, 32 mmol) was added over 10 min and the resulting mixture was stirred at −70°C for 20 min. A solution of (2,2,2-trifluoroethoxy)ethanoyl chloride[21] (5.19 g, 29 mmol) in dry THF (60 mL) was added over 10 min, the mixture was stirred at −70°C for a further 30 min, then allowed to warm to room temperature overnight. The reaction was quenched by addition of brine (20 mL) and concentrated in vacuo. The residue was diluted with brine (300 mL) and extracted with ethyl acetate (3×300 mL). The combined organic extracts were dried and evaporated, and then the residue chromatographed with dichloromethane as an eluent to give the imide **4b** as a clear oil (8.38 g, 91%); (found MH$^+$ (CI) 318.0934. $C_{14}H_{14}NO_4F_3$ requires *M* 318.0953); $[\alpha]_D^{25}$

+48 (*c* 2.55, $CHCl_3$); 100% e.e. by HPLC; ν_{max} (film)/cm^{-1} 1770 (CO) and 1705 (CO); δ_H (400 MHz, $CDCl_3$) 2.82 (1H, dd, *J* 13.4 and 9.5, PhC*H*H), 3.34 (1H, dd, *J* 13.4 and 3.4, PhCH*H*), 4.02 (2H, q, $^3J_{HF}$ 8.6, OCH_2CF_3), 4.30 (2H, m, oxazolidinone 5-H_2), 4.69 (1H, m, oxazolidinone 4-H), 4.84 (2H, s, OCH_2CO) and 7.15–7.40 (5H, m, aryl-H); *m/z* (CI) 335 [$(M+NH_4)^+$, 100%], 318 [$(M+H)^+$, 5] and 232 (10).

4.3.2. (S)-4-Benzyl-3-(2-ethoxyethanoyl)oxazolidin-2-one ***4a***

Similarly prepared. A gum, 32%; (found M^+ (EI) 263.1158. $C_{14}H_{17}NO_4$ requires *M* 263.1158); $[\alpha]_D^{25}$ +53 (*c* 1.62, $CHCl_3$); δ_H (270 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.2, Me), 2.82 (1H, dd, *J* 13.4 and 9.6, PhC*H*H), 3.33 (1H, dd, *J* 13.4 and 3.3, PhCH*H*), 3.65 (2H, q, *J* 7.2, OCH_2Me), 4.25 (2H, m, oxazolidinone 5-H_2), 4.70 (2H, ABq, *J* 2.5, OCH_2CO), 4.71 (1H, m, oxazolidinone 4-H) and 7.15–7.40 (5H, m, aryl-H).

4.3.3. (S)-4-Benzyl-3-[2-(2-methoxyethoxy)ethanoyl]oxazolidin-2-one ***4c***

Similarly prepared. A gum, 35%; (found M^+ (EI) 293.1263. $C_{15}H_{19}NO_5$ requires *M* 293.1264); $[\alpha]_D^{25}$ +50 (*c* 1.83, $CHCl_3$); δ_H (270 MHz, $CDCl_3$) 2.81 (1H, dd, *J* 13.5 and 9.6, PhC*H*H), 3.33 (1H, dd, *J* 13.5 and 3.3, PhCH*H*), 3.41 (3H, s, OMe), 3.63 (2H, t, *J* 5.3, OCH_2CH_2OMe), 3.78 (2H, t, *J* 5.3, OCH_2CH_2OMe), 4.25 (2H, m, oxazolidinone 5-H_2), 4.70 (1H, m, oxazolidinone 4-H), 4.74 (1H, d, *J* 17.9, OC*H*HCO), 4.76 (1H, d, *J* 17.9, OCH*H*CO) and 7.10–7.50 (5H, m, aryl-H).

4.3.4. (S)-4-Benzyl-3-(2-benzyloxyethanoyl)oxazolidin-2-one ***4d***

Similarly prepared. A solid, 52%; m.p. 67–69°C; (found C, 69.9; H, 5.9; N, 4.4%; M^+ (EI) 325.1314. $C_{19}H_{19}NO_4$ requires C, 70.1; H, 5.9; N, 4.3%; *M* 325.1314); $[\alpha]_D^{25}$ +56 (*c* 1.71, $CHCl_3$); δ_H (270 MHz, $CDCl_3$) 2.80 (1H, dd, *J* 13.5 and 9.4, PhC*H*H), 3.32 (1H, dd, *J* 13.5 and 3.3, PhCH*H*), 4.20 (2H, m, oxazolidinone 5-H_2), 4.70 (5H, m, oxazolidinone 4-H and CH_2OCH_2) and 7.10–7.50 (10H, m, aryl-H).

4.3.5. (S)-4-Benzyl-3-[2-(3-trifluoromethyl)phenoxyethanoyl]oxazolidin-2-one ***4e***

Similarly prepared. A gum, 73%; (found M^+ (EI) 379.1031. $C_{19}H_{16}F_3NO_4$ requires *M* 379.1032); $[\alpha]_D^{25}$ +62 (*c* 2.3, $CHCl_3$); δ_H (270 MHz, $CDCl_3$) 2.85 (1H, dd, *J* 13.5 and 9.4, PhC*H*H), 3.35 (1H, dd, *J* 13.5 and 3.3, PhCH*H*), 4.30 (2H, m, oxazolidinone 5-H_2), 4.70 (1H, m, oxazolidinone 4-H) 5.28 (2H, s, OCH_2CO) and 7.10–7.50 (9H, m, aryl-H).

4.4. General procedure for asymmetric aldol reaction of ***4***

4.4.1. [3(2S,3R),4S]-3-[3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-3-hydroxy-2-(2,2,2-trifluoroethoxy)propanoyl]-4-benzyloxazolidin-2-one ***6b***

(4*S*)-4-Benzyl-3-[2-(2,2,2-trifluoroethoxy)ethanoyl]oxazolidin-2-one **4b** (31.7 g, 0.1 mol) was dissolved in dry dichloromethane (300 mL) under argon and cooled to −78°C (internal temperature of solution). Triethylamine (16.72 mL, 0.12 mol) was added, followed by the slow addition, over approximately 10 min, of di-*n*-butylboron triflate (1.0 M solution in dichloromethane, 110 mL, 0.11 mol) such that the reaction temperature was kept below −70°C. The mixture was stirred at −78°C for 50 min, then the cooling bath was replaced with an ice bath and the mixture stirred at 0°C for an additional 50 min before being recooled to −78°C. A solution of 4-[2-[*N*-(2-benzoxazolyl)-*N*-methylamino]ethoxy]benzaldehyde **5** (29.6 g, 0.10 mol) in dry dichloromethane (220 mL), precooled to −50°C, was added over ca. 12 min, such that the reaction temperature was maintained below −70°C. The resulting mixture was stirred at −78°C for 30 min, then warmed from −78°C to 0°C over 60 min

along a linear gradient (warming rate ~1.3°C min^{-1}) and stirred at 0°C for a further 75 min. The reaction mixture was poured into a quenching solution of methanol (500 mL), pH 7 phosphate buffer (250 mL) and hydrogen peroxide (27.5% w/v, 110 mL) and stirred vigorously for 30 min. Water (4 L) was added and the aqueous solution was extracted with dichloromethane (3×1 L). The combined dichloromethane solutions were washed with water (2 L) and brine (2 L), dried and evaporated to afford a foam (60.18 g). ^{1}H NMR of this crude reaction mixture suggested a mixture of the desired aldol product (84% conversion, 3 diastereoisomers, comprising 95% major diastereoisomer) and starting materials. The crude mixture was chromatographed using ethyl acetate:dichloromethane (gradient 15:85 to 50:50) as an eluent to afford the aldol product **6b** as a foam (40.89 g, 67%); (found M^+ (EI) 613.2042. $C_{31}H_{30}F_3N_3O_7$ requires *M* 613.2036); $[\alpha]_D^{25}$ +45 (*c* 2.82, $CHCl_3$); two diastereoisomers, 95.4% d.e. by ^{1}H NMR; ν_{max} (KBr)/cm^{-1} 3432 (OH), 1780 (CO) and 1707 (CO); δ_H (400 MHz, $CDCl_3$) 2.75 (1H, dd, *J* 13.5 and 9.5, PhC*H*H), 2.90 (1H, d, *J* 6.1, exchanges with D_2O, OH), 3.25 (1H, dd, *J* 13.5 and 3.3, PhCH*H*), 3.34 (3H, s, NMe), 3.80–4.00 (5H, m, NCH_2, OCH_2CF_3 and oxazolidinone 5-H_a), 4.07 (1H, dd, *J* 9.0 and 2.0, oxazolidinone 5-H_b), 4.24 (2H, t, *J* 5.2, NCH_2CH_2O), 4.45 (1H, m, oxazolidinone 4-H), 4.99 (1H, apparent t, *J* 4.8, C*H*OH), 5.48 (1H, d, *J* 4.8, C*H*OCH_2CF_3), 6.85 (2H, d, *J* 8.8, aryl 3-H and 5-H) and 6.95–7.40 (11H, m, aryl-H); *m/z* (EI) 613 (M^+, 5%), 317 (23), 296 (51), 198 (22), 175 (24), 161 (82), 148 (100), 134 (27), 113 (66) and 91 (62).

*4.4.2. [3(2*S*,3*R*),4*S*]-3-[3-[4-[2-[*N*-(2-Benzoxazolyl)*-N*-methylamino]ethoxy]phenyl]-2-ethoxy-3-hydroxypropanoyl]-4-benzyloxazolidin-2-one* ***6a***

Similarly prepared. A foam, 45%; (found M^+ (EI) 559.2317. $C_{31}H_{33}N_3O_7$ requires *M* 559.2319); $[\alpha]_D^{25}$ +53 (*c* 2.5, $CHCl_3$); two diastereoisomers, 96% d.e. by ^{1}H NMR; δ_H (270 MHz, $CDCl_3$) 1.20 (3H, t, *J* 6.9, OCH_2CH_3), 2.75 (1H, dd, *J* 13.5 and 9.6, PhC*H*H), 3.15 (1H, br, exchanges with D_2O, OH), 3.29 (1H, dd, *J* 13.5 and 3.3, PhCH*H*), 3.32 (3H, s, NMe), 3.50 (1H, m, OC*H*HCH_3), 3.65 (1H, m, OCH*H*CH_3), 3.75 (1H, m, oxazolidinone 5-H_a), 3.92 (2H, t, *J* 5.3, NCH_2), 4.01 (1H, dd, *J* 9.1 and 1.9, oxazolidinone 5-H_b), 4.21 (2H, t, *J* 5.3, OCH_2CH_2), 4.40 (1H, m, oxazolidinone 4-H), 4.85 (1H, ~d, *J* 4.95, C*H*OH), 5.34 (1H, d, *J* 4.95, C*H*OEt) and 6.80–7.40 (13H, m, aryl-H).

*4.4.3. [3(2*S*,3*R*),4*S*]-3-[3-[4-[2-[*N*-(2-Benzoxazolyl)*-N*-methylamino]ethoxy]phenyl]-3-hydroxy-2-(2-methoxyethoxy)propanoyl]-4-benzyloxazolidin-2-one* ***6c***

Similarly prepared. A foam, 57%; (found $(M+H)^+$ (FAB) 590.2472. $C_{32}H_{35}N_3O_8$ requires *M* 590.2502); $[\alpha]_D^{25}$ +49 (*c* 1.14, $CHCl_3$); two diastereoisomers, 99% d.e. by ^{1}H NMR; δ_H (400 MHz, $CDCl_3$) 2.71 (1H, dd, *J* 13.3 and 9.7, PhC*H*H), 3.25 (1H, dd, *J* 13.3 and 3.2, PhCH*H*), 3.31 (3H, s, NMe), 3.35 (3H, s, OMe), 3.56 (2H, m, CH_2OMe), 3.72 (2H, m, oxazolidinone 5-H_a and OC*H*HCH_2OMe), 3.78 (1H, d, *J* 4.3, exchanges with D_2O, OH), 3.85–4.00 (4H, m, NCH_2, OCH*H*CH_2OMe and oxazolidinone 5-H_b), 4.22 (2H, t, *J* 5.2, OCH_2CH_2N), 4.31 (1H, m, oxazolidinone 4-H), 4.89 (1H, dd, *J* 6.0 and 4.3, C*H*OH), 5.42 (1H, d, *J* 6.0, C*H*OCH_2CH_2OMe) and 6.80–7.40 (13H, m, aryl-H).

*4.4.4. [3(2*S*,3*R*),4*S*]-3-[3-[4-[2-[*N*-(2-Benzoxazolyl)*-N*-methylamino]ethoxy]phenyl]-2-benzyloxy-3-hydroxypropanoyl]-4-benzyloxazolidin-2-one* ***6d***

Similarly prepared. A foam, 52%; (found M^+ (EI) 621.2474. $C_{36}H_{35}N_3O_7$ requires *M* 621.2475); $[\alpha]_D^{25}$ +58 (*c* 1.25, $CHCl_3$); two diastereoisomers, 94% d.e. by ^{1}H NMR; δ_H (400 MHz, $CDCl_3$) 2.56 (1H, dd, *J* 13.5 and 9.8, PhC*H*H), 3.05 (1H, br, exchanges with D_2O, OH), 3.05 (1H, dd, *J* 13.5 and 3.2, PhCH*H*), 3.32 (3H, s, NMe), 3.76 (1H, t, *J* 8.1, oxazolidinone 5-H_a), 3.95 (3H, m, NCH_2 and oxazolidinone 5-H_b), 4.24 (2H, t, *J* 5.3, OCH_2CH_2), 4.33 (1H, m, oxazolidinone 4-H), 4.57 (2H, s,

$PhCH_2O$), 4.90 (1H, t, *J* 4.9, C*H*OH), 5.43 (1H, d, *J* 4.9, C*H*OCH_2Ph), 6.83 (2H, d, *J* 8.8, aryl 3-H and 5-H) and 7.00–7.40 (16H, m, aryl-H).

*4.4.5. [3(2*S*,3*R*),4*S*]-3-[3-[4-[2-[*N*-(2-Benzoxazolyl)-*N*-methylamino]ethoxy]phenyl]-3-hydroxy-2-(3-trifluoromethyl)phenoxypropanoyl]-4-benzyloxazolidin-2-one **6e***

Similarly prepared. A foam, 31%; (found $(M+H)^+$ (CI) 676.2269. $C_{36}H_{32}F_3N_3O_7$ requires *M* 676.2271); $[\alpha]_D^{25}$ +74 (*c* 1.14, $CHCl_3$); two diastereoisomers, 90.4% d.e. by ^1H NMR; δ_H (400 MHz, $CDCl_3$) 2.68 (1H, dd, *J* 13.5 and 9.3, PhC*H*H), 3.05 (1H, dd, *J* 13.5 and 3.2, PhCH*H*), 3.11 (1H, d, *J* 5.1, exchanges with D_2O, OH), 3.31 (3H, s, NMe), 3.70 (1H, m, oxazolidinone 5-H_a), 3.92 (2H, m, NCH_2), 3.99 (1H, dd, *J* 9.0 and 1.9, oxazolidinone 5-H_b), 4.23 (2H, t, *J* 5.2, O*C*$H_2$$CH_2$), 4.31 (1H, m, oxazolidinone 4-H), 5.14 (1H, dd, *J* 5.4 and 5.1, C*H*OH), 6.23 (1H, d, *J* 5.4, C*H*OAr) and 6.80–7.40 (17H, m, aryl-H).

4.5. Aldol reaction in the presence of boron trifluoride etherate

This experiment was conducted on a 1.5 mmol scale in an identical manner to the aldol reaction described above, but with the addition of boron trifluoride etherate (1.65 mmol) immediately prior to the addition of the aldehyde. ^1H NMR (400 MHz, $CDCl_3$) of the crude reaction product following the standard oxidative workup suggested a mixture of starting materials and aldol products (69% conversion, four diastereoisomers, **6b**, **9b**, **10** and **11**; ratios 1.0, 0.3, 3.6 and 1.2, respectively). These were partially separated by chromatography, using ethyl acetate:dichloromethane (gradient, 10:90 to 15:85) as an eluent, and the 400 MHz ^1H NMR spectra of **10** and **11** were recorded. See Table 2 for comparison of the C*H*OH signals of all four diastereoisomers.

*4.6. General procedure for dehydroxylation of **6***

*4.6.1. [3(2*S*),4*S*]-3-[3-[4-[2-[*N*-(2-Benzoxazolyl)-*N*-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoyl]-4-benzyloxazolidin-2-one **7b***

Triethylsilane (120 mL, 0.75 mol) was added to a vigorously stirred, ice-cooled solution of [3 (2*S*, 3*R*), 4*S*]-3-[3-[4-[2-[*N*-(2-benzoxazolyl)-*N*-methylamino]ethoxy]phenyl]-3-hydroxy-2-(2,2,2-trifluoroethoxy)propanoyl]-4-benzyloxazolidin-2-one **6b** (46.23 g, 0.075 mol) in trifluoroacetic acid (650 mL). The mixture was stirred at 0°C for 1 h, then at room temperature for a further 60 h. The bulk of the solvent and residual triethylsilane was removed by rotary evaporation, firstly at 40 mmHg, and finally at ~5 mmHg. The residue was dissolved in dichloromethane (800 mL) and water (800 mL), then stirred vigorously during the cautious addition of solid sodium bicarbonate (~29 g) (frothing!) until the pH of the aqueous layer was pH 7. The layers were separated and the aqueous solution was extracted with dichloromethane (800 mL). The combined dichloromethane solutions were washed with water (600 mL), dried and evaporated. The residue was triturated with hot hexane and the resulting solid filtered off and dried under vacuum to afford the title compound **7b** (42.54 g, 95%). Recrystallisation from diethyl ether–hexane afforded an analytical sample, m.p. 107–109°C, a single diastereoisomer by 400 MHz ^1H NMR spectroscopy; (found C, 62.1; H, 4.9; N, 7.2%; M^+ (EI) 597.2089. $C_{31}H_{30}N_3O_6F_3$ requires C, 62.3; H, 5.1; N, 7.0%; *M* 597.2087); $[\alpha]_D^{25}$ +38 (*c* 1.51, $CHCl_3$); >99.5% d.e. by ^1H NMR; ν_{max} (KBr)/cm^{-1} 1775 (CO) and 1695 (CO); δ_H (400 MHz, $CDCl_3$) 2.82 [1H, dd, *J* 13.5 and 9.5, oxazolidinone 4-(C*H*HPh)], 2.96 (1H, dd, *J* 13.9 and 8.3, ArC*H*HCH), 3.04 (1H, dd, *J* 13.9 and 4.4, ArCH*H*CH), 3.32 [1H, dd, *J* 13.5 and 3.4, oxazolidinone 4-(CH*H*Ph)], 3.34 (3H, s, NMe), 3.70 (1H, m, O*C*HCF_3), 3.88 (1H, m, OCH*H*CF_3), 3.94 (2H, t, *J* 5.2, NCH_2), 4.12 (1H, m, oxazolidinone 5-H_a),

4.18 (1H, m, oxazolidinone 5-H_b), 4.25 (2H, t, *J* 5.2, NCH_2CH_2O), 4.57 (1H, m, oxazolidinone 4-H), 5.34 (1H, dd, *J* 8.3 and 4.4, $CHOCH_2CF_3$), 6.82 (2H, d, *J* 8.8, aryl 3-H and 5-H) and 7.00–7.35 (11H, m, aryl-H); *m/z* (CI, ammonia) 598 [$(M+H)^+$, 100%].

*4.6.2. [3(2*S*),4*S*]-3-[3-[4-[2-[*N*-(2-Benzoxazolyl)-*N*-methylamino]ethoxy]phenyl]-2-ethoxypropanoyl]-4-benzyloxazolidin-2-one* ***7a***

Similarly prepared. A foam, 83%; (found M^+ (EI) 543.2399. $C_{31}H_{33}N_3O_6$ requires *M* 543.2370); $[\alpha]_D^{25}$ +45 (*c* 1.03, $CHCl_3$); >99.5% d.e. by ^1H NMR; δ_H (270 MHz, $CDCl_3$) 1.16 (3H, t, *J* 6.9, OCH_2CH_3), 2.79 (1H, dd, *J* 13.5 and 9.6, PhC*H*H), 2.92 (2H, m, $ArCH_2CH$), 3.32 (1H, m, PhCH*H*), 3.33 (3H, s, NMe), 3.38 (1H, m, OC*H*HCH_3), 3.55 (1H, m, OCH*H*CH_3), 3.92 (2H, t, *J* 5.5, NCH_2), 4.08 (2H, m, oxazolidinone 5-H_2), 4.23 (2H, t, *J* 5.3, OCH_2CH_2), 4.55 (1H, m, oxazolidinone 4-H), 5.21 (1H, d, *J* 4.95, C*H*OEt) and 6.79–7.40 (13H, m, aryl-H).

*4.6.3. [3(2*S*),4*S*]-3-[3-[4-[2-[*N*-(2-Benzoxazolyl)-*N*-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoyl]-4-benzyloxazolidin-2-one* ***7c***

Similarly prepared. A gum, 87%; (found M^+ (EI) 573.2473. $C_{32}H_{35}N_3O_7$ requires *M* 573.2475); $[\alpha]_D^{25}$ +43 (*c* 1.78, $CHCl_3$); >99.5% d.e. by ^1H NMR; δ_H (400 MHz, $CDCl_3$) 2.76 (1H, dd, *J* 13.2 and 9.6, PhC*H*H), 2.94 (2H, m, $ArCH_2CH$), 3.30 (3H, s, NMe), 3.33 (4H, m, OMe and PhCH*H*), 3.40–3.70 (4H, m, OCH_2CH_2OMe), 3.93 (2H, t, *J* 5.3, NCH_2), 4.00 (1H, dd, *J* 7.1 and 5.3, oxazolidinone 5-H_a), 4.12 (1H, dd, *J* 7.1 and 2.5, oxazolidinone 5-H_b), 4.22 (2H, t, *J* 5.3, OCH_2CH_2N), 4.52 (1H, m, oxazolidinone 4-H), 5.31 (1H, dd, *J* 9.4 and 5.5, $CHOCH_2CH_2OMe$) and 6.79–7.40 (13H, m, aryl-H).

*4.6.4. [3(2*S*),4*S*]-3-[3-[4-[2-[*N*-(2-Benzoxazolyl)-*N*-methylamino]ethoxy]phenyl]-2-benzyloxypropanoyl]-4-benzyloxazolidin-2-one* ***7d***

Similarly prepared. A foam, 66%; (found M^+ (EI) 605.2525. $C_{36}H_{35}N_3O_6$ requires *M* 605.2526); $[\alpha]_D^{25}$ +40 (*c* 1.01, $CHCl_3$); >99.5% d.e. by ^1H NMR; 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 5-H_a), 4.10 (1H, m, oxazolidinone 5-H_b), 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).

*4.6.5. [3(2*S*),4*S*]-3-[3-[4-[2-[*N*-(2-Benzoxazolyl)-*N*-methylamino]ethoxy]phenyl]-2-(3-trifluoromethyl)phenoxypropanoyl]-4-benzyloxazolidin-2-one* ***7e***

Similarly prepared. A foam, 64%; sample slowly crystallised on standing, m.p. 98–100°C; (found C, 65.1; H, 4.8; N, 6.4%; $(M+H)^+$ (CI) 660.2319. $C_{36}H_{32}F_3N_3O_6$ requires C, 65.5; H, 4.9; N, 6.4%; *M* 660.2322); $[\alpha]_D^{25}$ +67 (*c* 1.23, $CHCl_3$); >99.5% d.e. by ^1H NMR; 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 5-H_a), 4.15 (1H, dd, *J* 9.1 and 2.4, oxazolidinone 5-H_b), 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).

4.7. General procedure for recovery of chiral α-oxyacids (S)-(±)-**3** from **7**

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

A solution of sodium methoxide [prepared from sodium hydride (60% dispersion in mineral oil, 138 mg, 3.41 mmol) and dissolved in dry methanol (3.5 mL)] was added to an ice-cooled and stirred suspension of [3(2*S*),4*S*]-3-[3-[4-[2-[*N*-(2-benzoxazolyl)-*N*-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoyl]-4-benzyloxazolidin-2-one **7b** (1.879 g, 3.10 mmol) in dry methanol (100 mL). The mixture was stirred at 0°C for 20 min then the reaction was quenched by the addition of dilute aqueous hydrochloric acid (2.0 M, 1.75 mL) and concentrated in vacuo. The residue was suspended in water (100 mL), extracted with ethyl acetate (3×200 mL) and the combined ethyl acetate solutions washed with brine (500 mL), dried and evaporated. The resulting gum was chromatographed using ethyl acetate:dichloromethane (4:96) as an eluent to afford ester **8b** as a gum (1.368 g, 97%); (found (EI) M^+ 452.1561. $C_{22}H_{23}N_2O_5F_3$ requires *M* 452.1559); $[\alpha]_D^{25}$ −17 (*c* 1.24, $CHCl_3$); >99.9% e.e. by HPLC.

A mixture of the ester **8b** (1.256 g, 2.8 mmol), aqueous hydrochloric acid (2.0 M, 50 mL) and dioxan (50 mL) was heated at reflux for 7 h, cooled and concentrated in vacuo. The residue was suspended in brine (200 mL) and extracted with ethyl acetate (3×300 mL). The combined ethyl acetate solutions were dried ($MgSO_4$) and evaporated to afford a waxy solid which was triturated with hexane to give the acid **3b** (1.011 g, 83%). Recrystallisation from dichloromethane:diethyl ether (25:75) afforded an analytical sample, m.p. 119–120°C; (found C, 57.25; H, 4.8; N, 6.3%; M^+ (EI) 438.1408. $C_{21}H_{21}F_3N_2O_5$ requires C, 57.5; H, 4.8; N, 6.4%; *M* 438.1403); $[\alpha]_D^{25}$ −32 (*c* 1.02, $CHCl_3$); 99.4% e.e. by HPLC; ν_{max} (Nujol)/cm^{-1} 3000–2300 (COOH) and 1718 (CO); δ_H (400 MHz, $CDCl_3$) 3.05 (1H, dd, *J* 14.4 and 7.3, ArC*H*HCH), 3.13 (1H, dd, *J* 14.4 and 4.6, ArCH*H*CH), 3.31 (3H, s, NMe), 3.72 (1H, m, OC*H*HCF$_3$), 3.89 (2H, m, NCH_2), 4.04–4.14 (3H, m, OCH*H*CF$_3$ and NCH_2CH_2O), 4.21 (1H, dd, *J* 7.3 and 4.6, C*H*OCH_2CF_3), 6.78 (2H, d, *J* 8.6, aryl 3-H and 5-H), 7.00–7.40 (6H, m, aryl-H) and 11.20 (1H, br, exchanges with D_2O, COOH); *m/z* (EI) 438 (M^+, 28%), 419 (2), 311 (21), 175 (41), 161 (41) and 148 (100).

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

Similarly prepared. Methyl ester **8a**: a gum, 86%; (found M^+ (EI) 398.1848. $C_{22}H_{26}N_2O_5$ requires *M* 398.1842); $[\alpha]_D^{25}$ −11 (*c* 1.11, $CHCl_3$); 99.6% e.e. by HPLC. Acid **3a**: a foam, 86%; (found M^+ (EI) 384.1684. $C_{21}H_{24}N_2O_5$ requires *M* 384.1685); $[\alpha]_D^{25}$ −19 (*c* 1.15, MeOH); e.e. 99.4% by HPLC; δ_H (270 MHz, $CDCl_3$) 1.17 (3H, t, *J* 7.0, Me), 2.95 (1H, dd, *J* 14.2 and 7.4, ArC*H*HCH), 3.06 (1H, dd, *J* 14.2 and 4.5, ArCH*H*CH), 3.34 (3H, s, NMe), 3.45 (1H, m, OC*H*HMe), 3.50 (1H, br, exchanges with D_2O, COOH), 3.58 (1H, m, OCH*H*Me), 3.92 (2H, t, *J* 5.3, NCH_2), 4.03 (1H, dd, *J* 7.4 and 4.5, $ArCH_2CH$), 4.22 (2H, t, *J* 5.3, OCH_2) and 6.79–7.40 (8H, m, aryl-H).

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

Similarly prepared. Methyl ester **8c**: a gum, 66%; (found M^+ (EI) 428.1947. $C_{23}H_{28}N_2O_6$ requires *M* 428.1948); $[\alpha]_D^{25}$ −12 (*c* 1.26, $CHCl_3$); >99.8% e.e. by HPLC. Acid **3c**: a gum, 67%; (found M^+ (EI) 414.1779. $C_{22}H_{26}N_2O_6$ requires *M* 414.1791); $[\alpha]_D^{25}$ −27 (*c* 0.73, $CHCl_3$); e.e. 99.8% by HPLC; δ_H (400 MHz, $CDCl_3$) 2.90 (1H, dd, *J* 14.3 and 8.8, ArC*H*HCH), 3.15 (1H, dd, *J* 14.3 and 2.4, ArCH*H*CH), 3.33 (3H, s, NMe), 3.37 (3H, s, OMe), 3.40–3.70 (5H, m, reduces to 4H on exchange with D_2O, COO*H* and OCH_2CH_2OMe), 3.93 (2H, t, *J* 5.3, NCH_2), 4.05 (1H, dd, *J* 8.8 and 2.4, $ArCH_2CH$), 4.21 (2H, t, *J* 5.3, OCH_2), 6.81 (2H, d, *J* 8.6, aryl 3-H and 5-H) and 6.95–7.40 (6H, m, aryl-H).

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

Similarly prepared. Methyl ester **8d**: a gum, 75%; (found M^+ (EI) 460.2000. $C_{27}H_{28}N_2O_5$ requires *M* 460.1999); $[\alpha]_D^{25}$ −34 (*c* 0.55, $CHCl_3$); >99.9% e.e. by HPLC. Acid **3d**: a foam, 81%; (found M^+ (EI) 446.1844. $C_{26}H_{26}N_2O_5$ requires *M* 446.1842); $[\alpha]_D^{25}$ −27 (*c* 1.46, $CHCl_3$); e.e. 98.2% by HPLC; δ_H (270 MHz, $CDCl_3$) 2.99 (1H, dd, *J* 14.0 and 7.1, ArC*H*HCH), 3.10 (1H, dd, *J* 14.0 and 4.7, ArCH*H*CH), 3.33 (3H, s, NMe), 3.95 (2H, m, NCH_2), 4.20 (3H, m, OCH_2CH_2 and $ArCH_2CH$), 4.25 (1H, br, exchanges with D_2O, CO_2H), 4.44 (1H, d, *J* 11.8, PhC*H*HO), 4.64 (1H, d, *J* 11.8, PhCH*H*O), 6.79 (2H, d, *J* 8.8, aryl 3-H and 5-H) and 7.00–7.40 (11H, m, aryl-H).

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

Similarly prepared. Methyl ester **8e**: a gum, 86%; (found M^+ (EI) 514.1717. $C_{27}H_{25}F_3N_2O_5$ requires *M* 514.1716); $[\alpha]_D^{25}$ −12 (*c* 1.2, $CHCl_3$); 99.6% e.e. by HPLC. Acid **3e**: a solid, 85%; m.p. 166–167°C; (found C, 62.3; H, 4.6; N, 5.5%; 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* 1.10, MeOH); e.e. 99% by HPLC; δ_H (270 MHz, $CDCl_3$) 3.25 (5H, m, $ArCH_2$ and NMe), 3.83 (2H, t, *J* 4.9, NCH_2), 4.00 (1H, br, exchanges with D_2O, COOH), 4.04 (2H, t, *J* 4.9, OCH_2), 4.86 (1H, t, *J* 6.0, $ArCH_2CH$), 6.77 (2H, d, *J* 8.5, aryl 3-H and 5-H) and 6.95–7.40 (10H, m, aryl-H).

*4.8. Sodium hydroxide hydrolysis of **7b***

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

An aqueous sodium hydroxide solution (2.5 M, 65 mL, 163 mmol) was added to a stirred solution of [3(2*S*),4*S*]-3-[3-[4-[2-[*N*-(2-benzoxazolyl)-*N*-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoyl]-4-benzyloxazolidin-2-one **7b** (42.5 g, 71 mmol) in THF (500 mL) and water (125 mL). After 20 min, the reaction was diluted with water (1 L) and washed with dichloromethane (3×700 mL) (this dichloromethane solution contained (*S*)-4-benzyloxazolidin-2-one which was recycled). The aqueous solution was acidified to pH 3.5 with dilute hydrochloric acid and re-extracted with dichloromethane (3×700 mL). The dichloromethane solution from the acid extraction was dried and evaporated to give a solid (29.7 g, 95%). Recrystallisation from dichloromethane:diethyl ether (25:75) afforded the acid **3b**, m.p. 119.5–120.5°C; (found C, 57.7; H, 4.7; N, 6.25%. $C_{21}H_{21}F_3N_2O_5$ requires C, 57.5; H, 4.8; N, 6.4%); $[\alpha]_D^{25}$ −31 (*c* 2.50, $CHCl_3$); 99.6% e.e. by HPLC; otherwise identical with that produced from ester **8b**.

*4.9. X-Ray crystallography of oxazolidinone **7b***

Oxazolidinone **7b** was recrystallised from a mixture of hexane and ethyl acetate to provide crystals suitable for study. Lattice parameters were determined from the setting angles of 25 reflections well distributed in reciprocal space measured on an Enraf Nonius CAD-4 diffractometer. Intensity data were collected on the diffractometer using graphite monochromated copper radiation and an ω–2θ variable speed scan technique. The structure was solved by direct methods using the SHELXS program and refined using the SHELXL-93 program. The trifluoromethyl moiety is disordered over two equally occupied orientations which were modelled as idealised CF_3 sites. Atomic positions for non-hydrogen

atoms were eventually refined with anisotropic displacement parameters. Hydrogen atoms were included in idealised positions riding on the atom to which they are attached.

Crystal data: $C_{31}H_{30}F_3N_3O_6$; M=597.58; T=223(2) K; λ=1.54178 Å; clear colourless needles; crystal size 0.50×0.10×0.10 mm; monoclinic; space group $P2_1$; unit cell dimensions a=4.6300(10) Å, b=11.852(2) Å, c=26.535(5) Å; β=90.27(2)°, V=1456.1(5) Å^3; Z=2; D_{calc}=1.363 Mg/m^3; μ=0.913 mm^{-1}; F(000)=624; θ range for data collection 1.66 to 62.96°; index ranges $0\leq h\leq 5$, $-13\leq k\leq 13$, $-30\leq l\leq 30$; reflections collected 6067; independent reflections 4732 (R_{int}=0.034); refinement method full-matrix least-squares on F^2; data:restraints:parameters 4732:37:413; goodness-of-fit on F^2 1.078; final R-indices: 4353 data; $I>2\sigma(I)$ $R1$=0.040, w$R2$=0.102, all data $R1$=0.046, w$R2$=0.106; absolute structure parameter 0.14(17); extinction coefficient 0.0028(4); largest diff. peak and hole 0.23 and −0.19 eÅ^{-3}.

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