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An enantiodivergent and formal synthesis of paroxetine enantiomers by asymmetric desymmetrization of 3-(4-fluorophenyl)glutaric anhydride with a chiral SuperQuat oxazolidin-2-one

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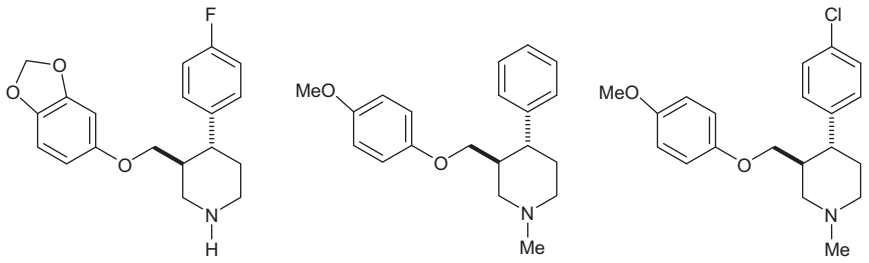
ABSTRACT

The asymmetric desymmetrization of 3-(4-fluorophenyl)glutaric anhydride **9** with lithiated chiral oxazolidin-2-one **8** has been studied. The desymmetrized product was formed with >90% de and converted into known intermediates for both (+)- and (−)-paroxetines.

1. Introduction

The piperidine ring system is widely found in biologically active natural products as well as in many synthetic drugs.[1,2] As a consequence, a considerable amount of synthetic effort has been made to develop the enantioselective syntheses of piperidine derivatives,[3–6] especially for 4-arylpiperidines such as paroxetine **1**, femoxetine **2** and Roche-1 **3** (Fig. 1).[7] (−)-Paroxetine **1** (Paxil®) is a *trans*-3,4-disubstituted piperidine and is a selective serotonin (5-hydroxy-tryptamine, 5-HT) reuptake inhibitor, which is used for the treatment of depression, anxiety, and panic disorders.[8] A large number of enantioselective synthetic methods have been reported[7,9–15] for (−)-**1** including resolutions, chiral auxiliaries, chiral bases, use of the chiral pool, enantioselective catalysis, and enzymatic asymmetrizations.

The asymmetric desymmetrization of symmetric anhydrides[16–19] has been a particular focus of interest because the enantioselective total synthesis of a number of classes of natural products has been achieved based on this reaction. Recently we introduced a general method for the desymmetrization of 3-substituted glutaric anhydrides[20,21] and *meso*-anhydrides[22] using lithiated chiral oxazolidin-2-ones **4–8** (Fig. 2) with varying and divergent diastereoselectivity depending upon the structure of the anhydrides, oxazolidin-2-ones and reaction conditions. Some of these intermediates have also been applied to the synthesis of hydroxylated pyrrolidine[23,24] and piperidine[25] based natural products. We were interested in the asymmetric synthesis of 4-arylpiperidine based bio-active molecules such as **1–3** based on the asymmetric desymmetrization of 3-aryl substituted glutaric anhydrides and chose paroxetine **1** as the target. Herein we report a strategy involving



1 paroxetine **2** femoxetine **3** Roche-1

Figure 1. Biologically active 4-arylpiperidines.

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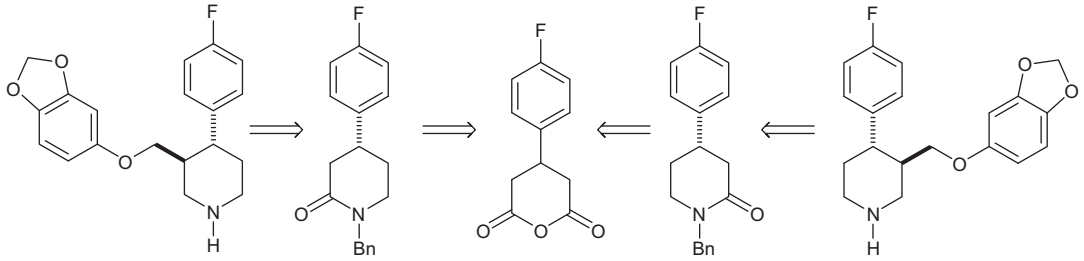


Scheme 1. Retrosynthetic analyses for paroxetine enantiomers.

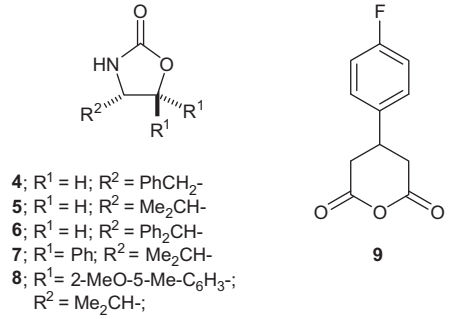
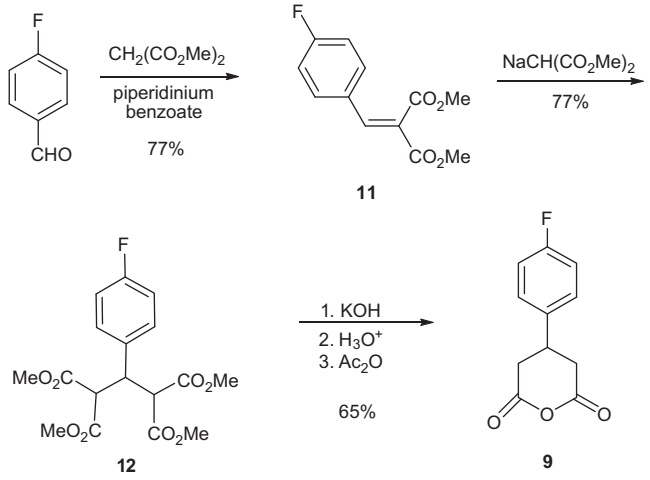


Figure 2. Structures of oxazolidin-2-ones **4–8** and anhydride **9**.

the asymmetric desymmetrization of 3-(4-fluorophenyl)glutaric anhydride **9** with a SuperQuat[26] oxazolidin-2-one **8** as the key step for the synthesis of piperidones (+)-**10** and (−)-**10** (Scheme 1), key intermediates for (−)-paroxetine **1** and its enantiomer (+)-**1**.



Scheme 2. Synthesis of anhydride **9**.

2. Results and discussion

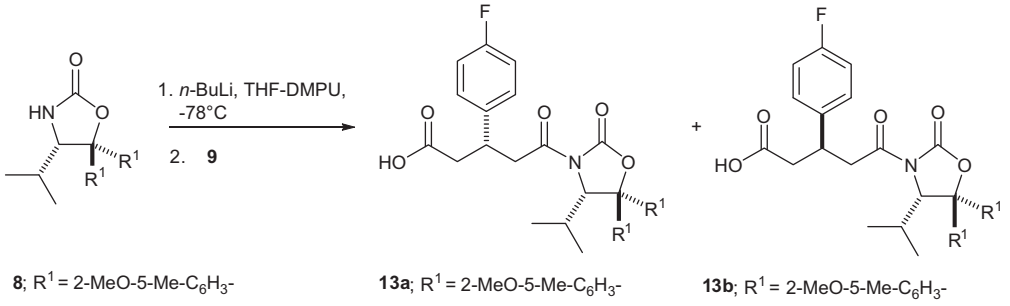
(−)-Paroxetine **1** has previously been synthesized by the asymmetric desymmetrization of 3-(4-fluorophenyl)glutaric anhydride **9** with (*S*)-methylbenzylamine.[27] Although this reported asymmetric desymmetrization selectivity was highly improved over Schwartz and Carter's[28] first published selectivity, the chiral amine was not recoverable due to its destruction during its removal. We have recently reported that (*S*)-valine-derived SuperQuat oxazolidin-2-one **8** is a good reagent for the asymmetric desymmetrization of 3-substituted glutaric[21] and other anhydrides.[22] There are certain advantages when using 5,5-disubstituted oxazolidin-2-ones, also known as SuperQuats. They have been used as chiral auxiliaries mainly to obviate problems such as purification of products by crystallization, and to limit endocyclic cleavage during removal, which is known to be problematic with Evans' oxazolidin-2-one.[29] It is also important to note the general importance of these auxiliary types, due to their superior exo cleavage,[30] conformational bias,[31] and versatility.[32] More recently, other research groups have used these auxiliaries and shown them to be excellent and versatile.

We prepared 4-isopropyl-5,5-diaryloxazolidin-2-one **8** from (*S*)-valine following the reported procedure.[21,33] Anhydride **9** was synthesized from 4-fluorobenzaldehyde as shown in Scheme 2. Dimethyl 4-fluorobenzylidene malonate **11**, the Knoevenagel condensation product of 4-fluorobenzaldehyde and dimethyl malonate, upon treatment with dimethyl malonate/NaOMe gave tetraester **12** (77%). This tetraester, upon hydrolysis and decarboxylation, gave the intermediate diacid, which when treated with acetic anhydride gave the anhydride **9** (65%).

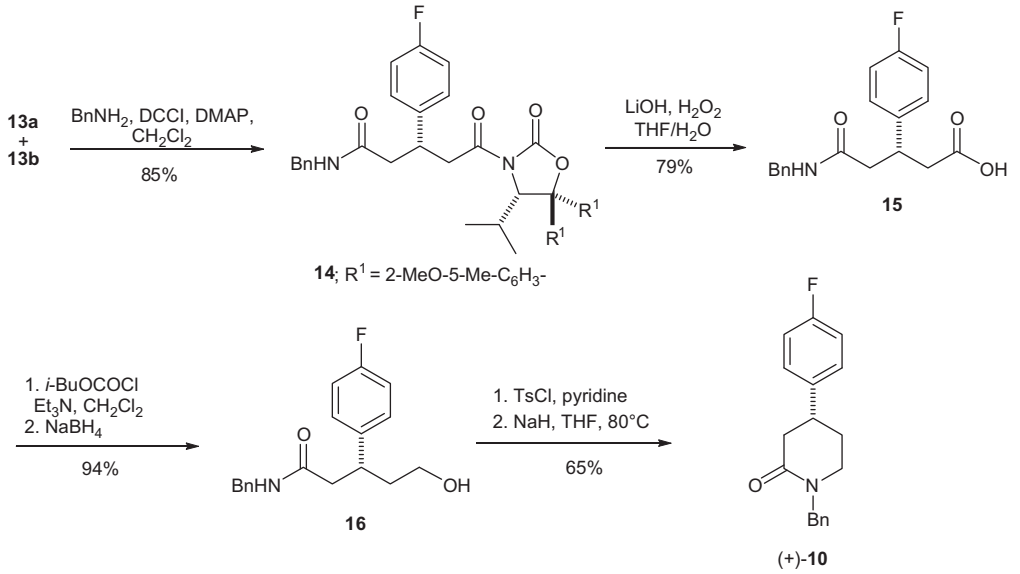
The lithiated oxazolidin-2-one **8** in THF was made using *n*-BuLi at 0 °C and reacted with anhydride **9** at −78 °C in THF-DMPU [DMPU = 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one] (4/1) to give a quantitative mixture of diastereoisomeric acids **13a** and **13b** in a ratio of 95:5[21] (estimated by ^{1}H NMR spectroscopy after diazomethane esterification) (Scheme 3).

For the synthesis of (−)-paroxetine **1**, the mixture of acids **13a** and **13b** obtained from the asymmetric desymmetrization experiment was converted into benzyl amide **14** (85%) after which oxazolidin-2-one **8** was removed using LiOH/H_2O_2 with 92% recovery of **8**. The resulting acid **15** (79%) was converted into alcohol **16** (94%) via mixed anhydride formation with isobutyl chloroformate followed by sodium borohydride reduction. The alcohol group was tosylated and subsequently subjected to known[27] cyclization conditions using NaH in THF to give the known piperidone (+)-**10**[34,35] (65%), from which (−)-paroxetine **1** has already been synthesized (Scheme 4).[35] In comparison to the literature value, the lower specific rotation value of **10** {$[\alpha]_D^{23} = +7.8$ (*c* 0.9, $CHCl_3$) lit.[34]: $[\alpha]_D^{21} = +34$ (*c* 1.09, $CHCl_3$) for a sample of 99% ee} surprised us. We checked the enantiomeric purity of **10** by HPLC using a chiral column (AD-H) and the enantiomeric excess was found to be ~9%. The experiment was repeated a few times wherein the specific rotation value of **10** varied between +7.8 to +16. This indicated that a significant amount of epimerization at the benzylic position had taken place during the process because we had started with an asymmetric desymmetrization product with a de ⩾90%.

We envisaged that epimerization of the benzylic centre could happen during the use of strong bases in the oxazolidin-2-one **8** removal with LiOH/H_2O_2 and/ or NaH-mediated cyclization of the tosylate derived from alcohol **16**. In order to determine in which step the epimerization took place, we reacted the mixture of acids **13a** and **13b**, obtained from the asymmetric desymmetrization experiment, with (*S*)-methylbenzylamine in the presence of DCCI to give the corresponding amide **17** (77%); the oxazolidin-2-one



Scheme 3. Desymmetrization of anhydride **9** with SuperQuat oxazolidin-2-one **8**.



Scheme 4. Synthesis of (+)-**10**, a key intermediate for (−)-paroxetine **1**.

8 was subsequently removed using $LiOH/H_2O_2$ to give the known acid **18** (91%) (Scheme 5).[27] The specific rotation of amide **18** {$[\alpha]_D^{26} = -74$ (*c* 1, MeOH); lit.[27]: $[\alpha]_D^{25} = -78$ (*c* 1, MeOH)} was in close agreement with the literature value, indicating that the oxazolidin-2-one removal took place without any epimerization thus confirming that NaH-mediated cyclization was the problematic step.

For the synthesis of (+)-paroxetine **1**, the mixture of diastereoisomeric acids **13a** and **13b**, obtained from the asymmetric desymmetrization of anhydride **9** with lithiated oxazolidin-2-one **8**, was converted into alcohol **19** (96%) by selective reduction of the carboxylic acid group to the alcohol using the borane–dimethyl sulphide complex in THF. Alcohol **19** was converted into the intermediate mesylate and subsequently reacted with benzylamine to give the known piperidone (−)-**10**[35] (78%) from which (+)-paroxetine **1** has already been synthesized (Scheme 6).[35] The enantiomeric purity of (−)-**10** has also been checked by HPLC using a chiral column (AD-H) and the enatiomeric excess was found to be 89%. During the process, oxazolidin-2-one **8** was also recovered (87% recovery).

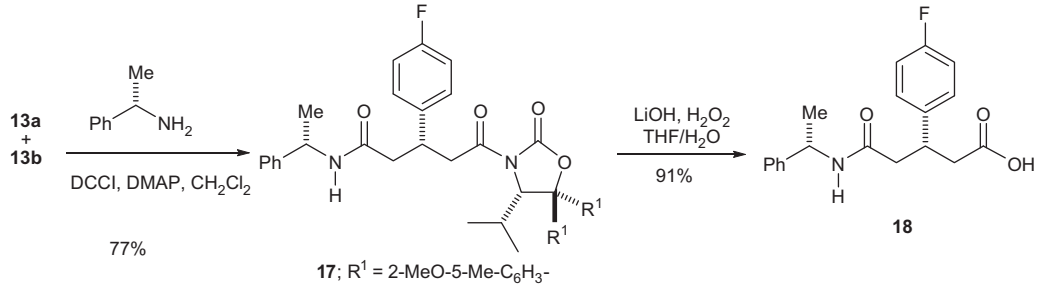
3. Conclusion

In conclusion, a highly stereoselective method for the preparation of key intermediates for the synthesis of paroxetine enantiomers has been described involving an asymmetric desymmetrization of 3-(4-fluorophenyl)glutaric anhydride with a lithiated chiral SuperQuat oxazolidin-2-one as the key step. The chiral reagent, SuperQuat oxazolidin-2-one is recoverable and recyclable. We have found for the first time that the benzylic stereogenic centre is prone to epimerization under drastic conditions, such as the use of NaH at elevated temperatures. Although NaH has frequently been used in the synthesis of paroxetine,, no one has encountered or reported an epimerization at the benzylic centre.

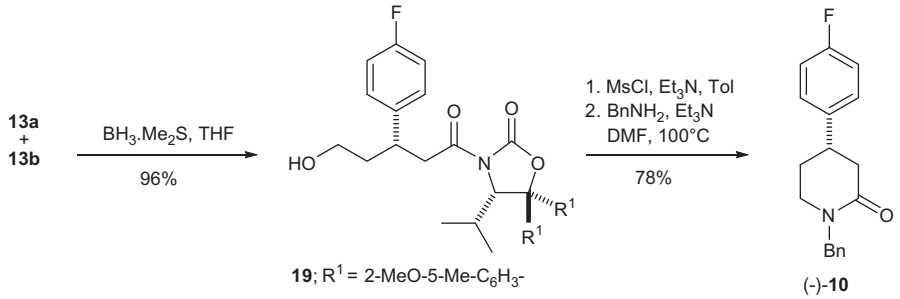
4. Experimental

4.1. General

All reactions were performed in oven-dried (120 °C) or flame-dried glass apparatus under dry N_2 or an argon atmosphere. Tetrahydrofuran (THF) was dried from sodium/benzophenone. *n*-BuLi (1.5 M in hexane) was purchased from Aldrich. Oxazolidin-2-one **8** was prepared following our published procedure.[21] Column chromatography was performed on silica gel (230–400 mesh). The ^1H NMR and ^{13}C NMR spectra were recorded with Bruker 200/300/500/700 MHz spectrometers. The spectra were referenced to residual chloroform (δ 7.25 ppm, ^1H; δ 77.00 ppm, ^{13}C). High resolution mass spectra (HRMS) were recorded with a Waters Micromass Q-TOF spectrometer (ESI, Ar). The IR spectra were recorded with a JASCO FT IR spectrophotometer in NaCl cells or in KBr discs. Peaks are reported in cm^{-1}. Melting points (Mp) were determined on a Fischer John's melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-360 polarimeter. Since



Scheme 5. Study of epimerization.



Scheme 6. Synthesis of (−)-**10**, a key intermediate for (+)-paroxetine **1**.

the 5,5-aryl groups in oxazolidin-2-one **8** are diastereotopic and magnetically non equivalent, some of the aromatic protons and carbons for these aryls are discernable by NMR. Similar NMR differences of the aryl groups were also observed for acylated oxazolidin-2-ones **13a, 14, 17** and **19** (vide infra).

4.2. Dimethyl-2-(4-fluorobenzylidine)malonate 11

A mixture of 4-fluorobenzaldehyde (12.7 mL, 120 mmol), dimethyl malonate (11.4 mL, 100 mmol) and piperidinium benzoate (6.2 g, 30 mmol) in benzene (120 mL) was refluxed (with Dean-Stark apparatus) for 24 h. The mixture was cooled and washed with water. The organic layer was dried over $MgSO_4$ and evaporated to give a crude residue, which was purified by distillation (125–140 °C/0.3 mmHg) to give **11** (18.2 g, 77%). R_f = 0.38 (hexane/ethyl acetate, 90/10); IR ($CHCl_3$ film) 2954, 1732, 1631, 1602, 1510, 1438 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.84 (s, 6H, CO_2CH_3), 7.02–7.11 (m, 2H, *Ar*), 7.38–7.45 (m, 2H, *Ar*), 7.72 (s, 1H, C*H*-4-F-Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ 52.6 (2C), 116.0 (d, *J* = 21.8 Hz, 2C), 125.1, 128.8 (d, *J* = 3.1 Hz), 131.4 (d, *J* = 8.7 Hz, 2C), 141.4, 163.8 (d, *J* = 251.2 Hz), 164.3, 166.9.

4.3. Tetramethyl-2-(4-fluorophenyl)propane-1,1,3,3-tetracarb oxylate 12

A solution of dimethyl malonate (9.7 mL, 85 mmol) in dry MeOH (10 mL) was added to a stirred solution of sodium methoxide [prepared using sodium (1.96 g, 85 mmol) in dry methanol] in dry MeOH (20 mL) at 0 °C under an argon atmosphere. After the addition was over, the mixture was stirred at room temperature for 30 min. A solution of malonate **11** (15 g, 63 mmol) in dry MeOH (20 mL) was added to the above mixture at 0 °C and the mixture was stirred at room temperature for 3 d. The solvent was evaporated and the residue was dissolved in ethyl acetate. The mixture was neutralized with dilute HCl and the organic layer was separated. The organic phase was washed with water, dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by recrystallization (hexane/ethyl acetate) to give white crystals of tetraester **12** (18 g, 77%). Mp 90–92 °C. R_f = 0.17 (hexane/ethyl acetate, 10/90); IR ($CHCl_3$ film) 3006, 2955, 2846, 1738, 1605, 1510, 1435 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.48 (s, 6H, 2 × CO_2Me), 3.68 (s, 6H, 2 × CO_2Me), 4.05–4.24 (m, 3H, 3 × CH), 6.89–6.99 (m, 2H, *Ar*), 7.22–7.31 (m, 2H, *Ar*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 43.2, 52.2 (2C), 52.6 (2C), 54.6 (2C), 114.9 (d, *J* = 21 Hz, 2C), 130.9 (d, *J* = 7 Hz, 2C), 133.0, 162.0 (d, *J* = 245 Hz), 167.6, 167.7, 168.0, 168.1.

4.4. 3-(4-Fluorophenyl)glutaric anhydride 9

Tetraester **12** (17 g, 45.9 mmol) was dissolved in a 10% KOH solution in ethanol/water (2/1) (170 mL) and heated at reflux for 3 h. The solvent was evaporated under reduced pressure and the residue was acidified with 10% aqueous sulphuric acid and refluxed for 6 h. The reaction mixture was saturated with sodium chloride and extracted with ethyl acetate (3 × 150 mL). The organic extract was dried (Na_2SO_4) and evaporated to give 3-(4-fluorophenyl)glutaric acid, which was purified by crystallization (7.1 g, 68%). Mp 146–147 °C (lit.[27] Mp 146–146.5 °C).

A solution of the diacid (7.1 g, 31 mmol) in acetic anhydride (15 mL) was heated at 100 C under nitrogen for 2.5 h. After cooling to room temperature, the excess acetic anhydride and acetic acid were removed under high vacuum. The residue was crystallized from ethyl acetate to give **9** (6.1 g, 95%). Mp 100–101 °C (lit.[27] Mp 99 °C). R_f = 0.6 (hexane/ethyl acetate, 60:40); ^1H NMR (200 MHz, $CDCl_3$) δ 2.83 (dd, *J* = 11.2, 17 Hz, 2H, 2 × CH_AH_BCO), 3.07 (dd, *J* = 4.4 Hz, 17.2 Hz, 2H, 2 × CH_AH_BCO), 3.35–3.50 (m, 1H, CH), 7.01–7.25 (m, 4H, *Ar*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 33.3, 37.0 (2C), 116.2 (d, *J* = 21.5 Hz, 2C), 127.9 (d, *J* = 8.1 Hz, 2C), 134.9 (d, *J* = 3 Hz), 162.1 (d, *J* = 245.6 Hz), 165.8 (2C).

4.5. (3′*R*,4*S*)-5,5-Di(2-methoxy-5-methylphenyl)-3-[3-(4-fluorophenyl)-4-methoxycarbonyl-1-oxobutyl]-4-isopropyloxazolidin-2-one 13a

n-Butyl lithium (1.8 mL, 1.5 M in hexane, 2.7 mmol) was slowly added to a suspension of oxazolidin-2-one **8** (922 mg, 2.5 mmol) in dry THF (12.5 mL) at 0 °C under an argon atmosphere until a clear

solution was obtained (30 min). The reaction mixture was cooled to −78 °C and dry DMPU (6 mL) was added followed by a solution of the anhydride **9** (562 mg, 2.7 mmol) in dry THF (12.5 mL). After 4 h at −78 °C, the reaction mixture was acidified with 5% citric acid solution and extracted with ethyl acetate. The extract was concentrated under reduced pressure and the residue was dissolved in benzene. The benzene solution was washed several times with water, dried over $MgSO_4$ and concentrated under reduced pressure to give crude **13a** (1.5 g, '100%') contaminated with about 5% of its diastereoisomer **13b** (vide infra). A small amount of the residue was treated with ethereal diazomethane and concentrated under reduced pressure. The ^{1}H NMR analysis of the resulting methyl ester indicated that the diastereoisomeric ratio was 95:5.

4.6. Data for the methyl ester of 13a

Mp 95–98 °C. $[\alpha]_D^{23} = -173.1$ (*c* 0.84, MeOH); R_f = 0.46 (hexane/ethyl acetate 85/15); IR (KBr) 1765, 1736, 1706, 1504 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.69 (d, *J* = 6.6 Hz, 3H, H_3CHCH_3), 0.88 (d, *J* = 6.6 Hz, 3H, CH_3CHCH_3), 1.55–1.72 (m, 1H, CH_3CHCH_3), 2.02 (s, 3H, ArCH_3), 2.34 (s, 3H, ArCH_3), 2.53 (dd, *J* = 8.2, 15.4 Hz, 1H, $CH_AH_BCO_2Me$), 2.65 (dd, *J* = 6.8, 15.4 Hz, 1H, $CH_AH_BCO_2Me$), 3.16 (dd, *J* = 5.6, 17.2 Hz, 1H, $NCOCH_AH_B$), 3.36 (dd, *J* = 9.2, 17.2 Hz, 1H, $NCOCH_AH_B$), 3.39 (s, 3H, ArOCH_3), 3.42 (s, 3H, ArOCH_3), 3.56 (s, 3H, CO_2CH_3), 3.66–3.84 (m, 1H, ArC*H*), 5.70 (d, *J* = 1.8 Hz, 1H, NC*H*), 6.59 (d, *J* = 8.2 Hz, 1H, Ar), 6.62 (d, *J* = 8.4 Hz, 1H, Ar), 6.79–7.04 (m, 5H, Ar), 7.09–7.16 (m, 2H, Ar), 7.65 (d, *J* = 2 Hz, 1H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.9, 20.4, 20.6, 22.4, 29.8, 36.8, 40.4, 41.0, 51.4, 55.3, 55.8, 62.0, 89.2, 111.0, 113.6, 115.1 (d, *J* = 21.1 Hz, 2C), 126.4, 127.3, 127.6, 128.5, 128.7, 128.8, 128.9 (2C), 129.1, 130.0, 138.3, 152.6, 153.5, 156.0, 161.4 (d, *J* = 243 Hz), 170.6, 171.8; ESI MS: *m*/*z* (%) = 592 (10) (M^++H), 548 (100); HRMS: Calcd for $C_{34}H_{39}NO_7F$ (M^++H) 592.2711. Found: 592.2715.

4.7. (3′*R*,4*S*)-5,5-Di(2-methoxy-5-methylphenyl)-3-[3-(4-fluorophenyl)-4-benzylcarbamoyl-1-oxobutyl]-4-isopropyloxazolidin-2-one 14

A solution of DCCI (495 mg, 2.4 mmol) in dry dichloromethane (5 mL) was added dropwise to a stirred solution of acid **13a** (1.15 g, 2 mmol), benzylamine (260 μL, 2.4 mmol) and DMAP (12 mg, 0.1 mmol) in dry dichloromethane (10 mL) under argon atmosphere at 0 °C. The resulting mixture was allowed to return to room temperature and stirred overnight. The mixture was filtered and the filtrate was evaporated. The resulting residue was dissolved in ethyl acetate, filtered and the filtrate was evaporated. This was done several times, after which the resulting residue was chromatographed to obtain pure amide **14** (1.13 g, 85%). R_f = 0.3 (hexane/ethyl acetate, 70/30); $[\alpha]_D^{23} = -192$ (*c* 0.5, $CHCl_3$); IR ($CHCl_3$ film) 3010, 2964, 2931, 1771, 1703, 1651, 1504, 1374 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.69 (d, *J* = 6.6 Hz, 3H, CH_3CHCH_3), 0.88 (d, *J* = 7.2 Hz, 3H, CH_3CHCH_3), 1.51–1.53 (m, 1H, CH_3CHCH_3), 2.01 (s, 3H, ArCH_3), 2.35 (s, 3H, ArCH_3), 2.30–2.40 (m, 1H, CH_AH_BCON) 2.57 (dd, *J* = 6.1, 14 Hz, 1H, CH_AH_BCONH), 3.19 (dd, *J* = 5.1, 17.1 Hz, 1H, CH_AH_BCON), 3.35–3.5 (m, 1H, CH_AH_B-CON), 3.39 (s, 3H, ArOCH_3), 3.42 (s, 3H, ArOCH_3), 3.79–3.90 (m, 1H, ArC*H*), 4.22 (dd, *J* = 5.2, 14.9 Hz, 1H, $PhCH_AH_BNH$), 4.39 (dd, *J* = 6, 14.7 Hz, 1H, $PhCH_AH_BNH$), 5.58 (s, broad, 1H, N*H*), 5.71 (s, 1H, NC*H*), 6.59–6.64 (m, 2H, Ar), 6.81–6.87 (m, 2H, Ar), 6.94–7.05 (m, 6H, Ar), 7.11–7.16 (m, 2H, Ar), 7.23–7.26 (m, 2H, Ar), 7.66 (s, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.0, 20.4, 20.6, 22.4, 29.8, 37.6, 40.4, 43.3, 44.1, 55.3, 55.9, 62.0, 89.3, 111.1, 113.8, 115.2 (d, *J* = 21 Hz, 2C), 126.5, 127.3, 127.4, 127.5 (3C), 127.7, 128.5 (2C), 128.6, 128.8, 128.9, 129.0, 129.2, 130.0, 138.0, 138.4, 152.7, 153.6, 156.1, 161.5 (d, *J* = 243 Hz), 170.4, 170.6; HRMS: Calcd for $C_{40}H_{44}FN_2O_6$ (M^++H) 667.3183. Found: 667.3201.

4.8. (*S*)-4-(Benzylcarbamoyl)-3-(4-fluorophenyl)butanoic acid 15

Hydrogen peroxide (420 μL, 30% v/v) was added to the solution of amide **14** (666 mg, 1 mmol) in THF (7.5 mL) and water (3 mL) at 0 °C. Lithium hydroxide (84 mg, 2 mmol) was then added and the mixture was stirred at 0 °C for 2 h. The mixture was allowed to return to room temperature and the solvent was evaporated. The residue was diluted with water and filtered. The filtrate was extracted with chloroform and the aqueous phase was acidified with aqueous sodium bisulphate solution. The aqueous phase was extracted with ethyl acetate, dried over $MgSO_4$ and evaporated to obtain acid **15** (250 mg, 79%). $[\alpha]_D^{23} = +1.8$ (*c* 1.1, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.75 (s, broad, 1H, CO_2H), 2.48 (dd, *J* = 8.1, 14 Hz, 1H, $COCH_AH_B$), 2.67 (dd, *J* = 5.4, 14 Hz, 1H, $COCH_AH_B$), 2.68 (dd, *J* = 7.2, 14 Hz, 1H, $COCH_AH_B$), 2.80 (dd, *J* = 7.5, 14 Hz, 1H, $COCH_AH_B$), 3.63–3.73 (m, 1H, ArC*H*), 4.27 (dd, *J* = 5.4, 14.7 Hz, 1H, CH_AH_BNHBn), 4.39 (dd, *J* = 6, 14.7 Hz, 1H, CH_AH_BNHBn), 5.62 (s, 1H, N*H*), 6.96–7.03 (m, 4H, Ar), 7.15–7.21 (m, 2H, Ar), 7.26 (s, broad, 3H, Ar); ^{13}C NMR (175 MHz, CD_3OD) δ 38.5 (d, *J* = 14.8 Hz), 40.3, 42.3, 42.4, 114.7 (d, *J* = 21 Hz, 2C), 126.6, 126.9 (2C), 127.9 (2C), 129.1 (2C), 138.3, 138.5, 161.7 (d, *J* = 242 Hz), 172.1, 173.9; HRMS: Calcd for $C_{18}H_{19}FNO_3$ (M^++H) 316.1349. Found: 316.1346. The chloroform extract was evaporated to give oxazolidin-2-one **8** (340 mg, 92%).

4.9. (*R*)-*N*-Benzyl-3-(4-fluorophenyl)-5-hydroxypentanamide 16

Isobutyl chloroformate (160 μL, 1.25 mmol) was added dropwise to a solution of acid **15** (315 mg, 1 mmol) and triethylamine (180 μL, 1.3 mmol) in dry THF (12 mL) at −78 °C. The solution was allowed to return to room temperature and stirred overnight. The mixture was filtered through a silica gel pad and washed with a small amount of THF. The filtrate was cooled on an ice-bath and sodium borohydride (122 mg, 3.2 mmol) was added to it followed by the dropwise addition of water (0.7 mL). The reaction mixture was stirred for 4 h and filtered through a Celite pad. After evaporation of the solvent, the aqueous layer was extracted several times with ethyl acetate. The organic extract was washed with brine, dried over magnesium sulphate and concentrated to obtain **16** (284 mg, 94%). R_f = 0.16 (hexane/ethyl acetate, 50/50); $[\alpha]_D^{23} = -12.5$ (*c* 0. 4, $CHCl_3$); IR ($CHCl_3$ film) 3437, 3018, 2927, 1658, 1510, 1216 cm^{-1}; ^{1}H NMR ($CDCl_3$, 700 MHz) δ 1.87–1.91 (m, 1H, $CH_AH_BCH_2OH$), 1.93–1.97 (m, 1H, $CH_AH_BCH_2OH$), 2.11 (s, broad, 1H, OH), 2.44 (dd, *J* = 8.4, 14 Hz, 1H, $COCH_AH_BCH$), 2.62 (dd, *J* = 5.6, 14 Hz, 1H, $COCH_AH_BCH$), 3.36–3.42 (m, 1H, ArC*H*), 3.50–3.55 (m, 1H, CH_AH_BOH), 3.56–3.62 (m, 1H, CH_AH_BOH), 4.27 (dd, *J* = 2.1, 14.7 Hz, 1H, $PhCH_AH_BNH$), 4.41 (dd, *J* = 6.3, 14.7 Hz, 1H, $PhCH_AH_BNH$), 5.68 (s, 1H, N*H*), 6.98–7.00 (m, 2H, Ar), 7.03 (d, *J* = 6.3 Hz, 2H, Ar), 7.16–7.21 (m, 2H, Ar), 7.25–7.20 (m, 3H, Ar); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 38.3, 38.9, 43.5, 44.0, 60.3, 115.5 (d, *J* = 21 Hz, 2C), 127.4, 127.5 (2C), 128.6 (2C), 128.8, 128.9, 137.9, 139.4, 161.6 (d, *J* = 243 Hz), 171.3; HRMS: Calcd for $C_{18}H_{21}FNO_2$ (M^++H) 302.1556. Found: 302.1555.

4.10. (*R*)-1-Benzyl-4-(4-fluorophenyl)piperidin-2-one (+)-10

4-Toluenesulphonyl chloride (109 mg, 0.57 mmol) was added to a solution of alcohol **16** (171 mg, 0.57 mmol) in dry pyridine (1 mL) at 0 °C. After 2 days at 0 °C, the reaction mixture was diluted with water and extracted with dichloromethane. The organic extract was washed with dilute HCl and water. The organic extract was dried over magnesium sulphate and concentrated under re-

duced pressure to give the intermediate tosylate. A solution of this tosylate (214 mg, 0.47 mmol) in dry THF (2.5 mL) was added to a suspension of NaH (16 mg, 0.66 mmol) at 0 °C under an argon atmosphere. The mixture was allowed to return to room temperature and stirred for 2 h. The reaction mixture was slowly cooled in an ice bath and quenched with methanol (1 mL). After evaporation of the solvent, the residue was diluted with ethyl acetate and then washed with brine. The organic layer was filtered through a silica gel pad. After the removal of solvent, the crude solid was recrystallized from ethyl acetate and hexanes to obtain (+)-**10** (86 mg, 65%). M. p. 65 °C. R_f = 0.56 (hexane/ethyl acetate, 40/60); $[\alpha]_D^{27} = +7.8$ (*c* 0.9, $CHCl_3$); lit.[34]: $[\alpha]_D^{21} = +34$ (*c* 1.09, $CHCl_3$) for a sample of 99% *ee*; IR ($CHCl_3$ film) 3009, 2932, 1632, 1511, 1495, 1454, 1217 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.82–1.94 (m, 1H, C*H*$_A$H$_B$CH$_2$N), 2.00–2.10 (m, 1H, CH$_A$*H*$_B$CH$_2$N), 2.55 (dd, *J* = 11.1, 17.4 Hz, 1H, COC*H*$_A$H$_B$CH), 2.82 (dd, *J* = 3.9, 17.4 Hz, 1H, COCH$_A$*H*$_B$CH), 3.00–3.10 (m, 1H, ArC*H*), 3.20–3.34 (m, 2H, NC*H*$_2$CH$_2$), 4.52 (d, *J* = 14.7 Hz, 1H, PhC*H*$_A$H$_B$N), 4.72 (d, *J* = 14.7 Hz, 1H, PhCH$_A$*H*$_B$N), 6.94–7.03 (m, 2H, Ar), 7.09–7.14 (m, 2H, Ar), 7.23–7.33 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 30.2, 37.9, 39.5, 46.1, 49.9, 115.4 (d, *J* = 21 Hz, 2C), 127.4, 127.8 (d, *J*, = 7 Hz, 2C), 128.1 (2 C), 128.5 (2 C), 136.9, 139.0, 161.5 (d, *J* = 244 Hz), 169.0; HPLC (AD-H, 95/5 hexane/isopropanol, flow: 1 mL/min, λ 210 nm) R_t 30.37 min (45.8%), R_t 32.49 min (54.2%).

4.11. (1″*S*,3′*R*,4*S*)-5,5-Di(2-methoxy-5-methylphenyl)-3-[3-(4-fluorophenyl)-4-(1-phenylethylcarbamoyl-1-oxobutyl]-4-isopropyloxazolidin-2-one 17

Amide **17** was prepared from acid **13a** (288 mg, 0.5 mmol) and (*S*)-phenylethylamine (85 μL, 0.65 mmol) following the procedure for the preparation of amide **14**. Yield 263 mg (77%). R_f = 0.35 (hexane/ethyl acetate, 70/30); IR ($CHCl_3$ film) 3019, 2927, 1770, 1657, 1504 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.68 (d, *J* = 6.6 Hz, 3H, C*H*$_3$CHCH$_3$), 0.86 (d, *J* = 6.9 Hz, 3H, CH$_3$CHC*H*$_3$), 1.24 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$), 1.60–1.70 (m, 1H, CH$_3$C*H*CH$_3$), 2.01 (s, 3H, ArC*H*$_3$), 2.29–2.35 (m, 1H, C*H*$_A$H$_B$CON), 2.35 (s, 3H, ArC*H*$_3$), 2.52 (dd, *J* = 6.0, 14.4 Hz, 1H, CH$_A$*H*$_B$CON), 3.16 (dd, *J* = 4.6 Hz, 17.2 Hz, 1H, C*H*$_A$H$_B$CONH), 3.33–3.45 (m, 1H, CH$_A$*H*$_B$CONH), 3.39 (s, 3H, ArOC*H*$_3$), 3.42 (s, 3H, ArOC*H*$_3$), 3.70–3.85 (m, 1H, ArC*H*), 4.93–5.05 (m, 1H, PhC*H*NH), 5.51 (d, *J* = 6.6 Hz, 1H, N*H*), 5.69 (s, 1H, NC*H*), 6.59–6.64 (m, 2H, Ar), 6.82–6.88 (m, 2H, Ar), 6.93–7.28 (m, 10H, Ar), 7.66 (s, 1H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.0, 20.5, 20.7, 21.7, 22.5, 29.9, 37.7, 40.5, 44.0, 48.6, 55.4, 55.8, 62.0, 89.4, 111.1, 113.7, 115.2 (d, *J* = 21 Hz, 2C), 126.1 (2C), 126.4, 127.2, 127.3, 127.6, 128.6 (4C), 129.0 (3C), 129.3, 130.1, 138.6, 143.3, 152.7, 153.8, 156.1, 161.5 (d, *J* = 244 Hz), 169.9, 170.6; HRMS: Calcd for $C_{41}H_{46}FN_2O_6$ (M^++H) 681.3340. Found: 681.3357.

4.12. (3*S*,1′*S*)-3-(4-Fluorophenyl)-5-oxo-5-(1′-phenylethylamino) pentanoic acid 18

Hydrogen peroxide (120 μL, 30% v/v) was added to a solution of amide **17** (185 mg, 0.27 mmol) in THF (2 mL) and water (0.3 mL) at 0 °C. Lithium hydroxide (23 mg, 0.54 mmol) was added and the mixture was stirred at 0 °C for 2 h. The mixture was allowed to return to room temperature and the solvent was evaporated. The residue was diluted with water and filtered. The filtrate was extracted with chloroform and the aqueous phase was acidified with aqueous sodium bisulphate solution. The aqueous phase was extracted with ethyl acetate, dried over $MgSO_4$ and evaporated to obtain acid **18** (80 mg, 91%). Mp 191–192 °C. $[\alpha]_D^{26} = -74$ (*c* 1, MeOH); lit.[27]: $[\alpha]_D^{25} = -78$ (*c* 1, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 2.46–2.72 (m, 4H, C*H*$_2$CHC*H*$_2$), 3.56–3.66 (m, 1H, ArC*H*), 4.83–4.93 (m, 1H, PhC*H*NH), 4.95 (s, 1H, N*H*), 6.98–7.04 (m, 2H, Ar), 7.22–7.33 (m, 7H, Ar); ^{13}C NMR (CD_3OD, 125 MHz) δ 20.7, 38.5, 40.0, 42.2, 48.4, 114.6 (d, *J* = 21 Hz, 2C), 125.7 (2C), 126.6, 128.0 (2C), 129.0 (d, *J* = 7 Hz, 2C), 138.5, 143.5, 161.7 (d, *J* = 242 Hz), 171.2, 173.8. The chloroform extract was evaporated to give oxazolidin-2-one **8** (86 mg, 86%).

4.13. (3′*R*,4*S*)-5,5-Di(2-methoxy-5-methylphenyl)-3-[3-(4-fluorophenyl)-5-hydroxypentyl]-4-isopropyloxazolidin-2-one 19

Borane dimethyl sulphide complex (95 μL, 1 mmol) was slowly added to a solution of acid **13a** (288 mg, 0.5 mmol) (obtained by desymmetrization of **9** with **8**) in dry THF (2.5 mL) at 0 °C. The mixture was allowed to return to room temperature and stirred for 30 min. The mixture was quenched with methanol (1 mL) and the solvent was evaporated. The residue was purified by column chromatography to obtain **19** (270 mg, 96%). R_f = 0.39 (hexane/ethyl acetate, 70/30); $[\alpha]_D^{26} = -152$ (*c* 0.84, $CHCl_3$); IR ($CHCl_3$ film) 3516 (br), 3017, 2961, 2926, 1771, 1700, 1606, 1503, 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.71 (d, *J* = 6.6 Hz, 3H, C*H*$_3$CHCH$_3$), 0.84 (d, *J* = 6.6 Hz, 3H, CH$_3$CHC*H*$_3$), 1.29 (s, broad, 1H, OH), 1.60–1.86 (m, 3H, CH$_3$C*H*CH$_3$, C*H*$_2$CH$_2$OH), 2.10 (s, 3H, ArC*H*$_3$), 2.35 (s, 3H, ArC*H*$_3$), 3.16–3.24 (m, 2H, C*H*$_2$CON), 3.40–3.50 (m, 2H, C*H*$_2$OH), 3.42 (s, 3H, ArOC*H*$_3$), 3.44 (s, 3H, ArOC*H*$_3$), 3.50–3.60 (m, 1H, ArC*H*), 5.73 (s, 1H, NC*H*), 6.60–6.66 (m, 2H, Ar), 6.86–6.92 (m, 2H, Ar), 6.96–7.05 (m, 3H, Ar), 7.12–7.16 (m, 2H, Ar), 7.67 (s, 1H, Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.0, 20.5, 20.6, 22.4, 29.8, 37.1, 39.8, 41.3, 55.4, 55.9, 60.2, 62.1, 89.3, 111.1, 113.8, 115.0, 115.1 (d, *J* = 21 Hz, 2C), 126.5, 127.4, 127.8, 128.6, 128.9, 129.0 (2C), 129.2, 130.0, 139.3, 152.7, 153.6, 156.1, 161.4 (d, *J* = 243 Hz), 171.3; HRMS: Calcd for $C_{33}H_{39}FNO_6$ (M^++H) 564.2761. Found: 564.2759.

4.14. (*S*)-1-Benzyl-4-(4-fluorophenyl)piperidin-2-one (−)-10

Methanesulphonyl chloride (35 μL, 0.46 mmol) was added to a stirred solution of alcohol **19** (173 mg, 0.3 mmol) and triethylamine (65 μL, 0.45 mmol) in dichloromethane (5 mL) at 0 °C. After 1 h at 0 °C, the reaction mixture was allowed to attain room temperature and quenched with water. The organic layer was washed with dilute HCl and then with water. The organic extract was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude mesylate. The mesylate was dissolved in dry DMF (0.5 mL) and triethylamine (65 μL, 0.46 mmol) was added followed by the addition of benzylamine (40 μL, 0.37 mmol). The resulting mixture was stirred at 90 °C for 4 h, cooled to room temperature and diluted with water. The reaction mixture was extracted with chloroform and the chloroform extract was washed with dilute HCl, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed to obtain pure lactam (−)-**10** (68 mg, 78%). R_f = 0.56 (hexane/ethyl acetate, 40/60). $[\alpha]_D^{25} = -30$ (*c* 0.4, $CHCl_3$). HPLC (AD-H, 95/5 hexane/isopropanol, flow: 1 mL/min, λ 210 nm) R_t 30.39 min (94.25%), R_t 32.68 min (5.75%).

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