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A convenient large-scale chiral synthesis of protected 2-substituted 4-oxo-piperidine derivatives

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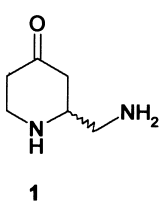
Abstract—A convenient large-scale chiral synthesis of protected 2-substituted-4-oxo-piperidine derivatives is described. Hetero Diels–Alder reaction between trifluoroacetic acid–boron trifluoride activated (1-phenyl-ethylimino)acetic acid ethyl ester and 2-trimethylsilyloxy-1,3-butadiene gave rise to a mixture of two diastereomers of 4-oxo-1-(1-phenyl-ethyl)-piperidine-2-carboxylic acid ethyl ester. Starting from (*S*)-1-phenyl-ethylamine pure adduct can be obtained by crystallization of the diastereomeric mixture. Reduction of the ester group gave rise to the corresponding hydroxymethyl analogue, which was subjected to further functional group transformations to yield the desired protected 2-aminomethyl-4-oxo-piperidine derivative without any racemization being observed.

1. Introduction

During work on our Protein Tyrosine Phosphatase inhibitor project[1] an efficient synthetic strategy for the preparation of protected 2-aminomethyl-4-oxo-piperidine (**1**) was required. Since the piperidine nucleus is found in a high number of natural products and biologically active compounds,[2] highly derivatized analogs thereof could also serve as templates for parallel synthesis of screening libraries. Furthermore, due to potential applications as intermediates in conformational modifiers for physiologically active peptides, such building blocks would be of significant interest. In particular, this area seems to be much less investigated relative to the corresponding proline analogs. To our knowledge no literature procedures for the synthesis of racemic or non-racemic 2-amino-methyl-4-oxo-piperidine derivatives have been described.



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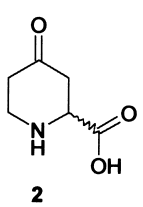

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Keywords: piperidinones; amino acids and derivatives; Diels–Alder reactions.

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2. Results and discussion

4-Oxopipecolic acid **2**, also an attractive building block, has attracted much attention since it was found to be a structural element in the cyclic peptidolactone antibiotic virginiamycin S_1.[3] A number of chiral[4] and achiral[5] procedures for the synthesis of 4-oxopipecolic acid derivatives have been reported. We found that one of the most promising procedures for large scale synthesis was the hetero Diels–Alder reaction between trifluoroacetic acid–boron trifluoride activated (1-phenyl-ethylimino)acetic acid ethyl ester and 2-trimethyl-silyloxy-1,3-butadiene reported by Abraham and Stella.[6] This procedure provides an easy entry to racemic 4-oxo-1-(1′-phenyl-ethyl)-piperidine-2-carboxylic acid ethyl ester with potential for subsequent chiral separation[7] and unlike other procedures involving Danishefsky's diene,[8] it does not require a reduction step in order to obtain the desired product.

In an initial attempt, benzylamine was used employing the protocol described by Abraham and Stella.[6] The resulting reaction mixture was impure and the work-up was difficult, due to the presence of an orange gummy material. Applying the same reaction conditions using either (*R*) or (*S*)-α-methylbenzylamine gave somewhat better results. We anticipated the gummy material may be a result of polymerized ethylglyoxalate from incomplete formation of the desired imine. Therefore we conducted an NMR study of commercial ethylglyoxalate (solution in toluene). The study showed that this was indeed the case, polymerized ethylglyoxalate was present and thus imine formation

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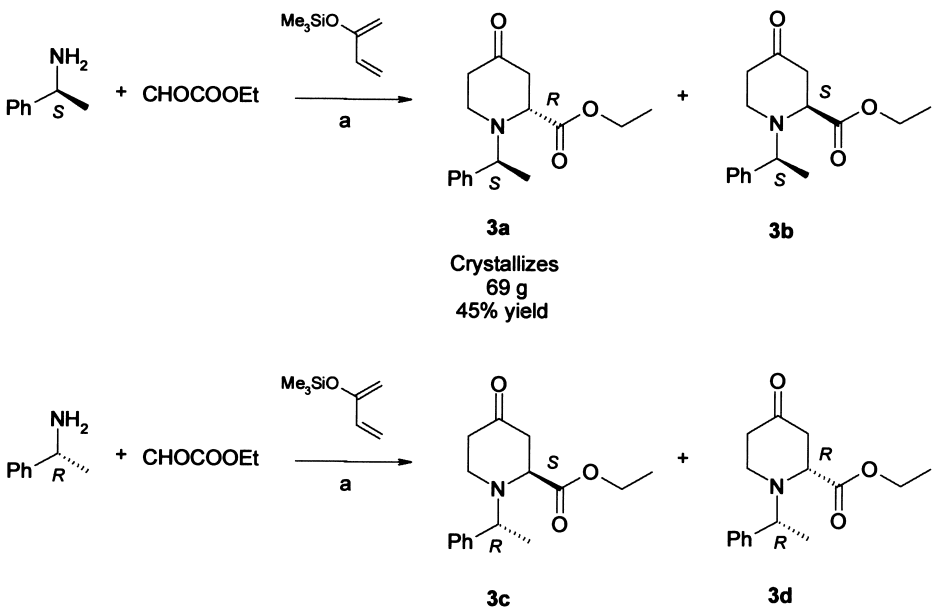


Scheme 1. (a) TFA, $BF_3{\cdot}OEt_2$, −78→−30°C.

would only proceed slowly with α-methylbenzylamine. However, when ethylglyoxalate was heated in a controlled fashion prior to reaction, imine formation with α-methylbenzylamine was much faster and cleaner, and the formation of polymerized ethylglyoxalate was suppressed to a level whereby a simple work-up yielded the crude product sufficiently pure to allow crystallization from hot heptane (Scheme 1).

Once the imine formation was optimized, (1-phenylethylimino)acetic acid ethyl ester prepared in situ was cooled to −78°C. Sequential addition of TFA, $BF_3{\cdot}Et_2O$ and 2-trimethylsilyloxy-butadiene followed by aqueous work up afforded a crude mixture of diastereoisomers as a pale orange oil. TLC (in toluene–EtOAc (9:2)) showed two main products (R_f: 0.45 and 0.38) and ^1H NMR spectroscopy revealed a distribution of 7:5 between the two diastereoisomers, respectively. On a small scale the two diastereoisomers could be separated chromatographically with difficulty, but for an efficient large scale synthesis chromatographic separation was not suitable. A filtration through a short pad of silica yielded a light yellow oil consisting of the two diastereoisomers. Addition of hot heptane to the mixture induced crystallization of the major diastereoisomer **3a**. Starting from *S*-(−)-α-methylbenzylamine a batch of 69 g of the pure diastereoisomer **3a** was prepared in 45% overall yield.

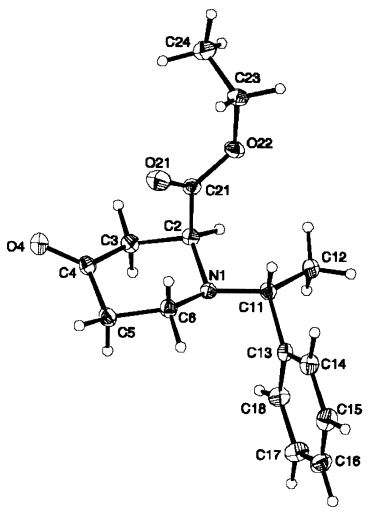


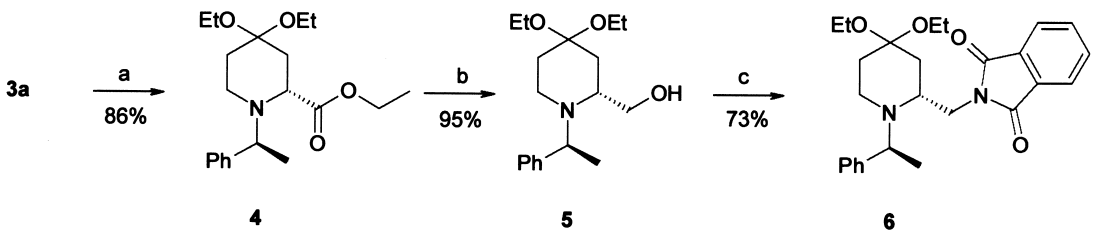
Figure 1. Molecular structure (ORTEP II)[9] of **3c** showing the absolute configuration and the atomic labeling. Displacement ellipsoids for non-hydrogen atoms are drawn at the 50% probability level. Hydrogen atoms are drawn at an arbitrary level.

Employing the other enantiomer, *R*-(+)-α-methylbenzylamine, the corresponding (1′*R*,2*S*)-4-oxo-1-(1′-phenylethyl)-piperidine-2-carboxylic acid ethyl ester **3c** could be crystallized by the same procedure.

X-Ray diffraction analysis was performed in order to establish the absolute configuration of compound **3c**. The configuration of carbon C2 (*S*) was determined relative to the known chiral center of carbon C11 (*R*). The molecule **3c** with the observed absolute configuration is shown in Fig. 1.

The observed geometry of the molecule is as expected with the piperidine ring adopting a chair conformation. The substituent on the nitrogen atom (N1) is observed in an equatorial position and the substituent on carbon atom C2 is observed in an axial position on the piperidine ring. The tertiary amine N1 is observed pyramidal.

In order to obtain the desired 2-aminomethyl moiety a reduction of the ester group in **3a** was necessary. Initial attempts of protecting ketone **3a** as the corresponding 1,3-dioxolane derivative using a variety of different reaction conditions only gave poor results. In an attempt using $BF_3{\cdot}OEt_2$, the main product was the acyclic di(2-hydroxyethyl) ketal. This prompted us to prepare the acyclic diethyl ketal **4** instead. Treatment of ketone **3a** with a mixture of triethyl orthoformate and ethanol in the presence of 1.5 equiv. of *p*-toluene sulfonic acid yielded ketal **4** in 86% yield after column chromatography (Scheme 2).[10]



Scheme 2. (a) TsOH, $(EtO)_3CH$, EtOH, 20°C, (b) $LiAlH_4$, Et_2O, reflux, (c) phthalimide, Ph_3P, DEAD, THF, 0°C.

Interestingly, if the diastereomeric mixture consisting of **3a** and **3b** was subjected to ketalization via this strategy the two diastereoisomers obtained could easily be separated by column chromatography in EtOAc–petroleum ether, 40–60°C (1:10).[11]

The ketal **4** was subjected to $LiAlH_4$ reduction in diethyl ether to give the hydroxymethyl analog **5** in 95% yield. The crude product could be used without further purification. Subsequent Mitsunobu[12] reaction with phthalimide, diethyl azadicarboxylate (DEAD) and triphenylphosphine yielded the phthalimide derivative **6** in 73% yield.

The ketal derivative of the protected amine **6** was smoothly deprotected with trifluoroacetic acid–water (9:1) at 0°C to give the ketone **7** in quantitative yield (Scheme 3).

Treatment of **6** with hydrazine hydrate in ethanol at room temperature yielded the free amine **8** in 75% yield. Since this derivative slowly decomposed, it was either used directly or converted to the corresponding stable Boc-protected analog **9**.

To exemplify the strategy, compound **8** was acylated with the intense UV-chromophore 4-biphenyl carboxylic acid by using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) and 1-hydroxy-7-azabenzotriazole (HOAt) as coupling reagents to give **10** in 81% yield (Scheme 3). Subsequent hydrogenolysis using Pd/C in a mixture of formic acid and methanol afforded the free amine **11** in 78% yield.

It is important to note that in all of the steps from **3a** to **9** no racemization was observed.

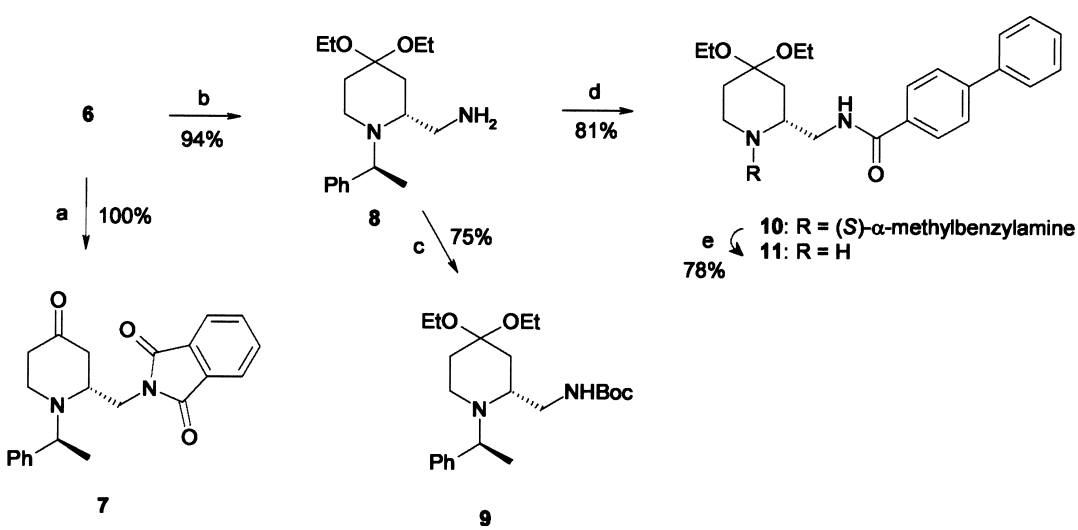
In summary, a practical large scale procedure for the synthesis of protected chiral 2-substituted-4-oxo-piperidine derivatives has been developed.

3. Experimental

3.1. General

Starting materials and reagents are commercially available and used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX300 or Bruker AMX400 instrument. Chemical shifts (δ given in ppm) are relative to TMS as internal standard. Multiplicities are indicated as s, singlet; d, doublet; t, triplet; dd, doublet of doublet; m, multiplet and coupling constants are quoted in Hertz (J values). Electrospray (ES) mass spectra and LCMS analyses were recorded on a PE Sciex API 3000 instrument with an HP1100 HPLC equipped with binary pump, column compartment, diode array detector, single quadrupole mass spectrometer detector and a C18 column (Waters Xterra MS C-18×3 mm).

3.1.1. (1′*S*,2*R*)-4-Oxo-1-(1′-phenyl-ethyl)-piperidine-2-carboxylic acid ethyl ester (3a). A 50% solution of ethylglyoxylate in toluene (117.6 mL, 0.57 mol) was refluxed for 30 min under nitrogen, then transferred to a 2 L three-necked round bottomed flask containing activated



Scheme 3. (a) TFA–H_2O (9:1), 20°C, (b) $NH_2NH_2{\cdot}H_2O$, EtOH, 20°C, (c) $(Boc)_2O$, aq. $NaHCO_3$–dioxane, 20°C, (d) 4-biphenylcarboxylic-acid, HOAt, EDC, DCM, 20°C, (e) Pd/C, HCOOH, EtOH, 20°C.

molecular sieves (3 Å, 125 g) in dry DCM (1 L) at 0°C. (*S*)-(−)-α-methylbenzylamine (71.7 mL, 0.57 mol) was added drop wise over 45 min, while the temperature was kept at 0°C. The mixture was stirred for 45 min and then cooled to −78°C. TFA (45.2 mL, 0.57 mol) was added over a period of 5 min. The mixture was stirred for an additional 5 min before $BF_3{\cdot}Et_2O$ (69.9 mL, 0.57 mol) was added over 5 min at −65°C. The reaction mixture was stirred for an additional 5 min before 2-(trimethylsiloxy)-1,3-butadiene (100 mL, 0.57 mol) was added over 10 min. After addition the temperature was allowed to rise to −30°C and the mixture was stirred at this temperature for 2 h. The cooling bath was removed and water (250 mL) was added drop wise with vigorous stirring over 10 min. The reaction mixture was stirred for 30 min before water (300 mL) was again added. Solid KH_2PO_4 was added until pH≈9. The phases were separated and the aqueous phase was extracted with DCM (3×300 mL). The combined organic phases were dried ($MgSO_4$) and the solvent removed in vacuo. The residue was dissolved in toluene (200 mL) and applied to the top of a 6 cm silica layer in a Buchner funnel (19 cm wide) and eluted with toluene–ethyl acetate (5:1) by application of vacuum. The fractions containing the desired compound as the main component (first band) were pooled and the solvent removed in vacuo, to give about 150 g of a pale orange oil. Heptane (300 mL) was added leading to solidification and the volatiles were removed in vacuo. Additional hot heptane (700 mL) was added to give a clear pale yellow heptane phase in addition to a small amount of an orange viscous oil on the glass surface. The heptane phase was filtered under vacuum and left at rt whereupon white crystals could be filtered off. The mother liquor was left in a refrigerator overnight (4°C) yielding pale orange crystals which after filtration was recrystallized from heptane (150 mL) to give a second crop of crystals. The crops were combined to give 69 g (45%) of **3a** as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.37 (m, 2H), 7.36–7.30 (m, 2H), 7.28–7.23 (m, 1H), 4.22–4.18 (m, 3H), 3.87 (q, 1H, *J*=7.0 Hz), 2.88–2.83 (m, 2H), 2.73–2.48 (m, 2H), 2.45–2.34 (m, 1H), 2.28–2.22 (m, 1H), 1.45 (d, 3H, *J*=7.0 Hz), 1.30 (t, 3H, *J*=7.0 Hz). ^{13}C NMR (75.47 MHz, $CDCl_3$): 207.28, 171.31, 145.06, 128.53, 127.20, 126.95, 61.35, 60.77, 58.43, 45.04, 43.03, 40.44, 20.45, 14.33. IR (KBr) 1727 cm^{-1}. LCMS: one peak, $[M+H]^+$=276. Calcd for $C_{16}H_{21}NO_3$ C, 69.79; H, 7.69; N, 5.09. Found C, 69.48; H, 7.82; N, 5.05.

For melting point determination a portion was recrystallized from 2-propanol to give small colorless needles. Mp 91–92°C (lit.[13] 99–100°C).

3.1.2. (1′*S*,2*R*)-4,4-Diethoxy-1-(1′-phenyl-ethyl)-piperidine-2-carboxylic acid ethyl ester (4). 3a (148 g, 0.54 mol) was dissolved in a mixture of EtOH (1.0 L) and $(EtO)_3CH$ (0.89 L, 5.38 mol) whereupon *p*-toluene sulfonic acid (153 g, 0.81 mol) was added and the reaction mixture was stirred for 16 h. The reaction mixture was neutralized with sodium bicarbonate (to pH ca. 7–8), and extracted with DCM (3×100 mL), dried with $MgSO_4$ and concentrated in vacuo. The title compound was purified by column chromatography (SiO_2, petrol ether–EtOAc 10:1) to give 12.0 g (86%) of **4** as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.38 (m, 2H), 7.34–7.15 (m, 3H), 4.23–4.05 (m, 3H), 3.79 (t, 1H, *J*=5.0 Hz), 3.50 (q, 2H, *J*=6.8 Hz), 3.38 (q, 2H, *J*=6.8 Hz), 2.80–2.70 (m, 1H), 2.43–2.29 (m, 2H), 1.99 (dd, 1H, *J*=13.6, 6.8 Hz), 1.75–1.55 (m, 2H), 1.32 (d, 3H, *J*=6.8 Hz), 1.25 (d, 3H, *J*=7.0 Hz), 1.19 (t, 3H, *J*=6.8 Hz), 1.12 (t, 3H, *J*=6.8 Hz). IR (KBr) 1738 cm^{-1}. LCMS: one peak, $[M+H]^+$=350. Calcd for $C_{20}H_{31}NO_4$ C, 68.74; H, 8.94; N, 4.01. Found C, 68.90; H, 9.27; N, 4.40.

3.1.3. (1′*S*,2*R*)-4,4-Diethoxy-1-(1′-phenyl-ethyl)-2-hydroxymethyl-piperidine (5). 4 (36.0 g, 0.103 mol) in dry Et_2O (150 mL) was added to a stirred suspension of $LiAlH_4$ (5.88 g, 0.155 mol) in dry Et_2O (300 mL) under N_2 at such a rate that the solution gently refluxed. The reaction mixture was stirred overnight, cooled to 0°C and EtOAc (30 mL) was added drop wise to destroy excess $LiAlH_4$ (*Caution*). After stirring for another 30 min, H_2O (12 mL) was added drop wise. After stirring for 10–15 min, the precipitate was filtered off using celite and the filter cage was washed with Et_2O (200 mL). The filtrate was washed with brine (100 mL) and dried ($MgSO_4$). The solvent was evaporated in vacuo affording 30 g (95%) of **5** as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.19 (m, 5H), 4.18 (q, 1H, *J*=6.8 Hz), 3.73–3.58 (m, 2H), 3.52–3.40 (m, 4H), 2.94–2.85 (m, 1H), 2.70–2.60 (m, 2H), 1.98–1.90 (m, 1H), 1.82–1.72 (m, 2H), 1.58–1.48 (m, 1H), 1.35 (d, 3H, *J*=6.8 Hz), 1.18 (t, 3H, *J*=6.8 Hz), 1.14 (t, 3H, *J*=6.8 Hz). IR (KBr) 3446, 1055 cm^{-1}. LCMS: one peak, $[M+H]^+$=308. Calcd for $C_{18}H_{29}NO_3{\cdot}1/2(H_2O)$ C, 68.32; H, 9.56; N, 4.43. Found C, 68.50; H, 9.61; N, 4.72.

3.1.4. (1′*S*,2*R*)-4,4-Diethoxy-1-(1′-phenyl-ethyl)-2-phthalimidomethyl-piperidine (6). To a suspension of **5** (65.35 g, 0.21 mol), triphenylphosphine (61.30 g, 0.23 mol) and phthalimide (34.4 g, 0.23 mol) in THF (700 mL) was cooled to 0°C and DEAD (36.84 mL, 0.23 mol) was added over a period of 90 min. The reaction mixture was stirred at 0°C for another 2 h before the solvent was removed in vacuo. The residue was dissolved in hot toluene–hexane (3:2) (650 mL) and cooled to 0°C on an ice bath. The precipitate was filtered off and washed with heptane. The filtrate was concentrated in vacuo and subjected to column chromatography in toluene–EtOAc–heptane 3:1:3. The solvent was evaporated in vacuo to produce a viscous oil. Upon addition of light petrol ether (500 mL), compound **6** crystallized to give 67.42 g (73%) of colorless crystals.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83–7.78 (m, 2H), 7.76–7.70 (m, 2H), 7.05–6.95 (m, 3H), 6.85–6.80 (m, 2H), 4.40 (dd, 1H, *J*=15.0, 10.0 Hz), 3.92 (q, 1H, *J*=7.0 Hz), 3.55–3.40 (m, 4H), 3.28 (dd, 1H, *J*=18.0, 4.5 Hz), 3.23–3.17 (m, 1H), 3.08–3.00 (m, 1H), 3.00–2.92 (m, 1H), 1.91 (dd, 1H, *J*=13.5, 4.5 Hz), 1.77–1.57 (m, 3H), 1.28–1.15 (m, 9H). IR (KBr) 1770, 1717 cm^{-1}. LCMS: one peak, $[M+H]^+$=437. Calcd for $C_{26}H_{32}N_2O_4$ C, 71.53; H, 7.39; N, 6.42. Found C, 71.48; H, 7.47; N, 6.43.

For melting point determination a sample was recrystallized from EtOH to give colorless needles. Mp 124–125°C.

3.1.5. (1′*S*,2*R*)-4-Oxo-1-(1′-phenyl-ethyl)-2-phthalimidomethyl-piperidine (7). 6 (90.37 g, 0.21 mol) was added to TFA–H_2O (9:1, 500 mL) pre-cooled to 0°C, and the reaction was stirred 3 h at 0°C. The solvent was removed in vacuo and the residue basified to pH 8 with a saturated solution of Na_2CO_3. The reaction mixture was extracted with EtOAc (3×200 mL) and dried ($MgSO_4$). After filtration the solvent was removed and the residue was dried in vacuo at 40°C for 2 d to yield 76.45 g (100%) of compound **7** as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85–7.80 (m, 2H), 7.78–7.70 (m, 2H), 7.15–7.07 (m, 3H), 7.20–6.95 (m, 2H), 4.00 (q, 1H, J=7.0 Hz), 3.95–3.85 (m, 1H), 3.65–3.55 (m, 1H), 3.50–3.30 (m, 3H), 2.70 (dd, 1H, J=14.0, 7.0 Hz), 2.55–2.44 (m, 1H), 2.29–2.15 (m, 2H), 1.38 (d, 3H, J=7.0 Hz). IR (KBr) 1712 cm^{-1}. LCMS: one peak, $[M+H]^+$=363. Calcd for $C_{22}H_{22}N_2O_3 \cdot 1/2(H_2O)$ C, 71.14; H, 6.24; N, 7.54. Found C, 71.02; H, 6.12; N, 7.57.

3.1.6. (1′*S*,2*R*)-4,4-Diethoxy-1-(1′-phenyl-ethyl)-2-aminomethyl-piperidine (8). A mixture of **6** (5.25 g, 12.0 mmol) and hydrazine hydrate (2.92 mL, 60 mmol) was stirred overnight in EtOH (100 mL) at rt. The solvent was removed in vacuo and the solid residue was extracted with Et_2O (3×50 mL). The Et_2O extracts were combined and the solvent was evaporated to yield 3.94 g (94%) of compound **8** as a colorless oil.

^{1}H NMR (300 MHz, DMSO-d_6): 7.44–7.38 (m, 2H), 7.33–7.25 (m, 2H), 7.23–7.17 (m, 1H), 4.20 (q, 1H, J=6.70 Hz), 3.45–3.28 (m, 2H), 2.82 (dd, 1H, J=12.0, 6.0 Hz), 2.65 (dd, 1H, J=12.0, 3.0 Hz), 2.60–2.48 (m, 1H), 2.35–2.2 (m, 2H), 1.90 (dt, 1H, J=13.2, 2.8 Hz), 1.73–1.63 (m, 1H), 1.59 (dd, 1H, J=13.2, 9.8 Hz), 1.27 (m, 1H), 1.22 (d, 3H, J=6.8 Hz), 1.10 (t, 3H, J=6.8 Hz), 1.07 (t, 3H, J=7.2 Hz). LCMS: one peak, $[M+H]^+$=307.

3.1.7. (1′*S*,2*R*)-4,4-Diethoxy-1-(1′-phenyl-ethyl)-2-tert-butyloxycarbonylaminomethyl-piperidine (9). 8 (1.96 g, 6.41 mmol) and di-*tert*-butyl dicarbonate (1.68 g, 7.69 mmol) was dissolved in a mixture of dioxane (30 mL) and sodium bicarbonate (15 mL, 5% in water). The reaction mixture was stirred 16 h at rt before the solvent was removed in vacuo. The residue was separated between DCM (30 mL) and water (50 mL). The organic phase was washed with water (50 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (SiO_2, toluene–EtOAc–heptane (3:1:3)) afforded 1.96 g (75%) of compound **9** as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 7.40–7.35 (m, 2H), 7.34–7.29 (m, 2H), 7.25–7.20 (m, 1H), 4.98 (m, 1H), 4.13 (q, 1H, J=7.0 Hz), 3.50–3.25 (m, 6H), 2.91–2.84 (m, 1H), 2.51–2.46 (m, 2H), 1.92 (d, 1H, J=13.0 Hz), 1.80–1.65 (m, 2H), 1.43 (s, 9H), 1.32 (d, 3H, J=7.0 Hz), 1.18 (t, 3H, J=7.0 Hz), 1.15 (t, 3H, J=7.0 Hz). IR (KBr) 1715 cm^{-1}. LCMS: one peak, $[M+H]^+$=407. Calcd for $C_{23}H_{38}N_2O_4$ C, 67.95; H, 9.42; N, 6.89. Found C, 68.00; H, 9.50; N, 7.00.

3.1.8. (1′*S*,2*R*)-Biphenyl-4-carboxylic acid [4,4-diethoxy-1-(1′-phenyl-ethyl)-(-piperidin-2-ylmethyl]-amide (10). To a solution of 4-biphenylcarboxylic acid (2.13 g, 0.011 mol) in DCM (50 mL) was added HOAt (1.47 g, 0.011 mol) and EDC (2.06 mg, 0.011 mol). The mixture was stirred for 20 min at rt before a solution of **8** (3.0 g, 0.01 mol) and DIPEA (1.84 mL, 0.011 mmol) in DCM (20 mL) was added. The reaction mixture was stirred at rt for 16 h.

The mixture was washed with aqueous $NaHCO_3$ (50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified using column chromatography (SiO_2, DCM–EtOAC (4:1)) to give 3.8 g (81%) of compound **10** as an amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82–7.78 (m, 2H), 7.68–7.60 (m, 4H), 7.52–7.45 (m, 2H), 7.42–7.35 (m, 2H), 7.32–7.18 (m, 4H), 6.77 (m, 1H), 4.19 (q, 1H, J=7.0 Hz), 3.73–3.57 (m, 2H), 3.48 (q, 4H, J=7.0 Hz), 3.10–3.00 (m, 1H), 2.68–2.62 (m, 2H), 2.05–2.00 (m, 1H), 1.87–1.72 (m, 2H), 1.62–1.52 (m, 2H), 1.48 (d, 3H, J=7.0 Hz), 1.22 (t, 3H, J=7.0 Hz), 1.80 (t, 3H, J=7.0 Hz). IR (KBr) 1684, 1644 cm^{-1}. LCMS: one peak, $[M+H]^+$=487. HRMS Calcd for ($C_{31}H_{38}N_2O_3$+H)=487.2961, Found 487.2972.

3.1.9. (2*R*)-Biphenyl-4-carboxylic acid [4,4-diethoxy-piperidin-2-ylmethyl]-amide (11). To a stirred solution of **10** (1.9 g) in EtOH (120 mL) was added formic acid (15 mL) and Pd/C (5%, dry) (500 mg). The mixture was stirred overnight under N_2, the Pd/C was filtered off and the volatiles evaporated in vacuo. The residue was dissolved in DCM (150 mL) and washed with saturated $NaHCO_3$ (2×150 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to afford 1.17 g (78%) of compound **11** as an amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89–7.83 (m, 2H), 7.68–7.58 (m, 4H), 7.50–7.43 (m, 2H), 7.42–7.36 (m, 1H), 6.80 (bt, 1H), 3.62–3.50 (m, 3H), 3.43 (q, 2H, J=7.0 Hz), 3.37–3.27 (m, 1H), 3.07–2.98 (m, 2H), 2.87–2.75 (m, 1H), 2.10–1.98 (m, 2H), 1.50–1.40 (m, 2H), 1.22–1.13 (m, 6H). IR (KBr) 1640 cm^{-1}. LCMS: one peak, $[M+H]^+$=383. Calcd for $C_{23}H_{30}N_2O_3 \cdot 1/3(H_2O)$ C, 71.11; H, 7.96; N, 7.21. Found C, 71.45; H, 7.95; N, 7.21.

3.2. Single crystal X-ray crystallographic analysis of compound 3c

X-Ray diffraction data was collected on an Enraf–Nonius CAD-4 diffractometer with $\omega/2\theta$ scan mode. Copper radiation was used (λ(Cu Kα)=1.5418 Å) with a graphite monochromator. The crystal was cooled with an Enraf–Nonius low-temperature device.

Suitable single crystals were obtained from a solution of **3c** in EtOAc–heptane. The crystal (0.47×0.23×0.04 mm^3) belonged to the orthorhombic crystal system, space group $P2_12_12_1$ with a=5.355(2), b=14.6290(10), c=18.867(13) Å, V=1478(1) Å^3, Z=4, T=122.0(5) K. D_{calc}=1.237 mg/m^3, μ(Cu Kα)=0.687 mm^{-1}, θ_{max}=74.90°, $-6 \le h \le 6$, $-18 \le k \le 18$, $-23 \le l \le 23$. Of the 9224 reflections collected 3044 were unique (R_{int}=0.025).

Data reduction was performed using the program DREADD.[13] Five standard reflections were measured

every 10^4 s and indicated a systematic decay in the intensity of 3.9% in the course of the data collection and the data was corrected for the decay.

The structure was solved by direct methods,[14] where all non-hydrogen atoms were located. Subsequent difference electron density maps reveal the positions of the hydrogen atoms.

Structure refinement was performed by full matrix least squares procedure based on F^2.[15] Atomic positions and anisotropic displacement parameters were refined for non-hydrogen atoms. The position of the hydrogen atoms were refined with fixed isotropic displacement parameters.

Final R=0.0298 and $wR(F^2)$=0.0766 for 2968 observed reflections ($I > 2\sigma(I)$) and 245 variables. $w=1/[\sigma^2(F_o^2)+(0.0427P)^2+0.2551P]$, $P=(F_o^2+2F_c^2)/3$. GooF=S=1.066. Structure refinement resulted in a Flack parameter[16] x=0.0(2) for the enantiomer, shown in Fig. 1. The parameter was refined using TWIN and BASF (0.15) in SHELXL97. Atomic scattering factors were used as implemented in SHELXL97, which were taken from International Tables for Crystallography.[17]

Crystallographic data (excluding structure factors) for the structure **3c** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 181005. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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