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O-(α-Phenylethyl)hydroxylamine as a 'chiral ammonia equivalent': synthesis and resolution of 5-oxopyrrolidine- and 6-oxopiperidine-3-carboxylic acids

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ABSTRACT

An approach to the synthesis and resolution of five- and six-membered lactams (i.e., 5-oxopyrrolidine- and 6-oxopiperidine-3-carboxylic acids) is described. The method relies on the one-pot Michael reaction—cyclization of itaconic acid or diethyl homoitaconate and enantiopure *O*-(α-phenylethyl) hydroxylamine as a 'chiral ammonia equivalent'. It is shown that this chiral auxiliary can be used for the separation of diastereomeric lactam products and then easily removed by catalytic hydrogenolysis.

1. Introduction

Functionalized five-[1] and six-membered[2] ring lactams (i.e., γ- and δ-lactams) are present in a large number of natural and non-natural biologically active compounds and are therefore of high interest in drug discovery. For example, derivatives of 5-oxopyrrolidine-3-carboxylic acid **1** and 6-oxopiperidine-3-carboxylic acid **2** were evaluated as inhibitors of tank-binding kinase 1 (TBK1),[3] autotaxin,[4] sodium-glucose linked transporter 1 (SGLT1),[5] or β-secretase 1 (BACE-1)[6] (Fig. 1). Since *C*-substituted γ- and δ-lactams are chiral compounds, their synthesis should preferably provide possibility to obtain pure enantiomers of the target products. In particular, there are several asymmetric or resolution-based approaches to the preparation of **1** or its derivatives reported in the literature. Most of them rely on the Michael reaction of itaconic acid or its derivatives **3** with an *N*-nucleophile (i.e., ammonia or its synthetic equivalent), which is accompanied/followed by the lactam ring formation (Scheme 1). To achieve enantiomer resolution, *N*-(α-phenylethyl)amine[7–12] and Evans oxazolidone[5,13] were used as the chiral auxiliaries, so that separation of diastereomeric derivatives **4** and **5** was performed at the corresponding steps of the synthesis. In the first case, the target product (*S*)-**1** (methyl ester) was obtained in 1.4% overall yield, mainly due to problems with removal of the chiral auxiliary.[7] The latter could be removed effectively only after reduction of the lactam moiety[9]—an experimental result which has been confirmed in our hands. In the second case, the method was more effective (48% overall yield)[5] but required two additional steps for installation and removal of the oxazolidone moiety, was very atom-inefficient, and finally, the procedures were described in a patent without detailed compound characterization.

Enzymatic resolution of esters **6** was also studied.[14] In the case of *N*-unsubstituted compound **6a**, only two-fold enantioselectivity was observed ($E = 2$), although the method was efficient for *N*-benzyl derivative **6b** ($E = 200$). Alternatively, enantiomers of **6b** were resolved using crystallization of its diastereomeric salts.[15] Nevertheless, removal of the benzyl protective group from the lactam moiety in the products obtained was not described; by analogy with **4** and according to other literature data,[16,17] it might be problematic.

Other methods for the synthesis of enantiopure derivatives of **1** included cyclization of the Cbz derivative **7** (prepared in six steps from common reagents) upon esterification with diazomethane and nitrogen deprotection,[7] as well as enantioselective hydrogenation of the lactam-based β-aminoacrylate **8** using a chiral rhodium (I) complex as a catalyst.[18]

Surprisingly, synthesis of enantiopure 6-oxopiperidine-3-carboxylic acid **2** has not been reported to date, although *N*-benzyl derivative **9** was prepared using the methods similar to those described above for **6b**.[18,19]

The main idea of this work was inspired by our previous synthesis of the racemic methyl ester **6a**, which commenced from itaconic

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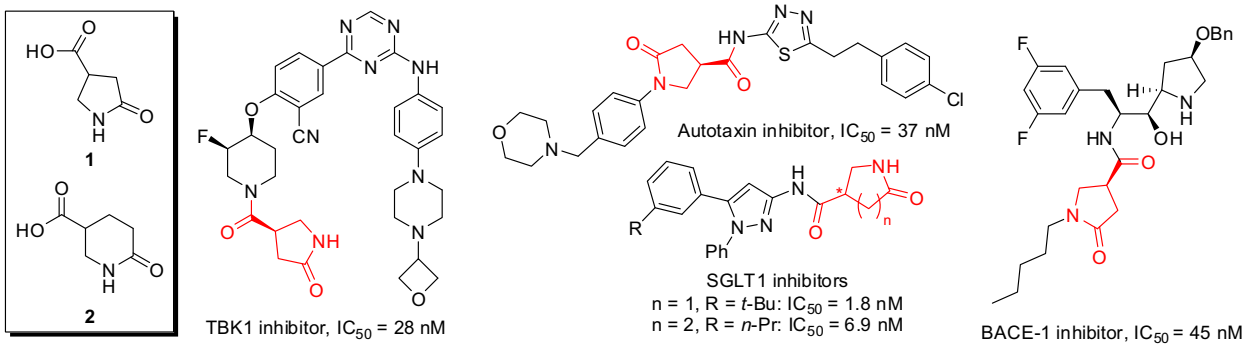
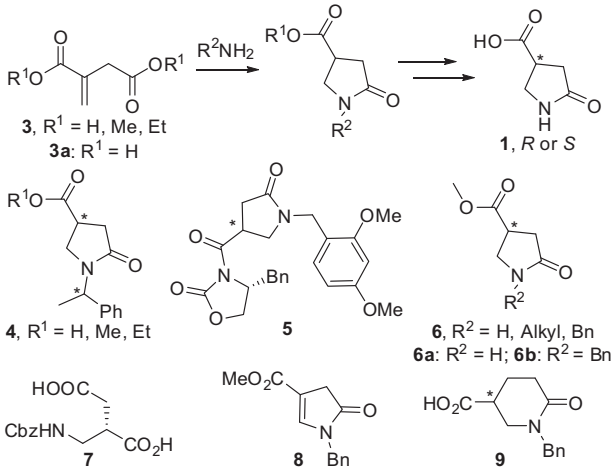
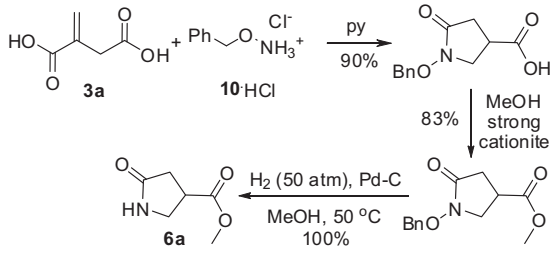


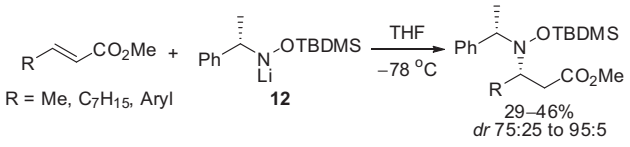
Figure 1. 5-Oxopyrrolidine-3-carboxylic acid **1**, 6-oxopiperidine-3-carboxylic acid **2** and some biologically active derivatives thereof.



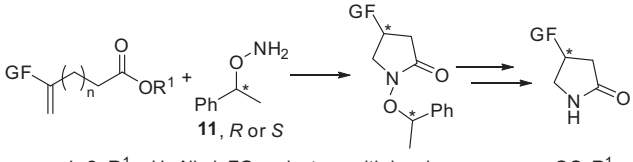
Scheme 1.



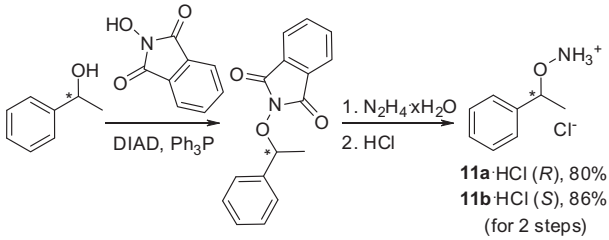
Scheme 2.



Scheme 3.



Scheme 4.



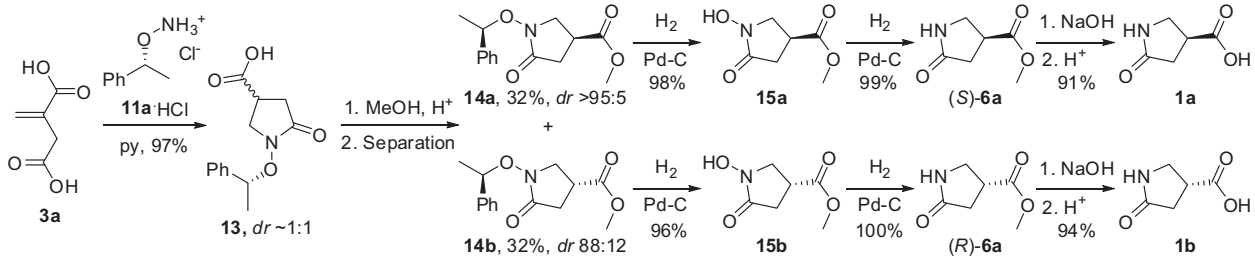
Scheme 5.

acid **3a** and used *O*-benzylhydroxylamine **10** as *N*-nucleophile (and ammonia synthetic equivalent) for the lactam formation (Scheme 2).[20] This method appeared to be so efficient that the target compound could be obtained on up to 100 g scale. We wondered if enantiopure five- and six-membered ring lactams could be obtained by a similar strategy using (*R*)- or (*S*)-*O*-(α-phenylethyl)hydroxylamine **11** as a 'chiral ammonia equivalent' for the Michael addition—cyclization step (Scheme 3). Notably, hydroxylamines **11** were used previously in diastereoselective addition of organometallic reagents to C=N double bonds.[21,22] Another related literature example includes stereoselective addition of lithium *N*-*tert*-butyldimethylsilyloxy-*N*-(α-methylbenzyl)amide (**12**) to α,β-unsaturated esters (Scheme 3).[23] In this work, we report implementation of similar strategy shown in the Scheme 4 for the synthesis of enantiopure **1** and **2**.

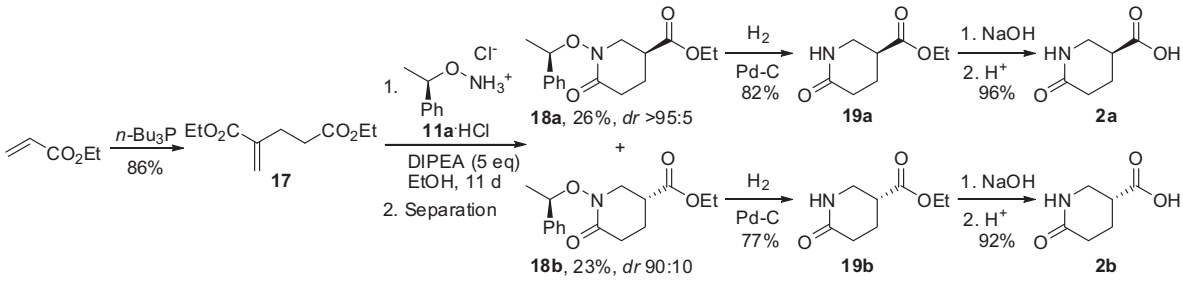
2. Results and discussion

Our synthesis of enantiopure **1** and **2** started with preparation of the chiral auxiliaries **11a**,**b** (Scheme 5). They were obtained using the known method, namely, Mitsunobu reaction of optically active (*R*)- or (*S*)-1-phenylethanols with *N*-hydroxysuccinimide, followed by removal of the phthalimide moiety by hydrazinolysis (80–86% overall yield).[21] The products **11a**,**b** were isolated as hydrochlorides.

Reaction of **11a**·HCl with itaconic acid **3** using conditions described previously for **10**·HCl (pyridine, reflux) proceeded smoothly and gave the product **13** as ca. 1:1 mixture of diastereomers (Scheme 6). It should be noted that the crystalline product **13** was isolated in excellent yield (97%) simply by evaporation of the solvent, addition of 2 M aq HCl and filtration. Unfortunately, all the attempts to separate the diastereomers of **13** were not successful. We have found, however, that chromatographic separation is possible for the corresponding methyl ester **14**. Therefore, **13** was esterified with methanol, and the product **14** thus obtained



Scheme 6.

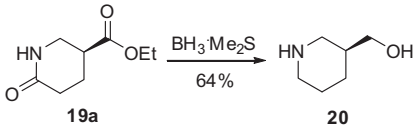


Scheme 7.

Table 1
Optimization of the reaction conditions between **17** and **11a**

#	Solvent	Base	Time, d	Yield of **18** (%)[d]
1	Pyridine	—[a]	4	0
2	Toluene	—[b]	4	0
3	MeOH	—[b]	9	0
4	EtOH	—[b]	4	0
5	—	—[c]	4	0
6	MeOH	Cs_2CO_3 (5 mol)[a]	4	0
7	MeCN	Cs_2CO_3 (5 mol)[a]	4	0
8	MeOH	DIPEA (2.5 mol)[a]	10	52
9	MeOH	DIPEA (5 mol)[a]	9	55
10	EtOH	DIPEA (5 mol)[a]	11	57

[a] **17** (1 mol), **11a**·HCl (1 mol), reflux.
[b] **17** (1 mol), **11a** (1 mol), reflux.
[c] **17** (1 mol), **11a** (1 mol), no solvent, 120 °C.
[d] Yield by ^{1}H NMR.



Scheme 8.

was subjected to preparative chromatography (hexanes–*t*-BuOMe (3:2) as eluent) to give diastereomers **14a** (32% yield, >95:5 *dr*) and **14b** (32% yield, 88:12 *dr*).

Removal of the chiral auxiliary in the products **14a**,**b** (H_2, Pd–C, 50 atm, 50 °C) started with cleavage of the C—O bond, so that intermediate hydroxamic acids **15a**,**b** could be isolated (96–98% yield). Further hydrogenolysis of **15a**,**b** gave the target enantiopure esters **6a** (96–97% yield from **14a**,**b**), which were subjected to alkaline hydrolysis (NaOH, MeOH–H_2O). The final products **1a** and **1b** were isolated in 91–94% yield after ion-exchange chromatography.

Synthesis of enantiopure carboxylic acids **2a**,**b** started with preparation of diethyl homoitaconate **17** using the known Rauhut–Currier reaction of ethyl acrylate (86% yield, Scheme 7).[24] Unfortunately, the product **17** did not give the target piperidone derivative **18** upon reaction with **11a**·HCl under the conditions described above (pyridine, reflux). Therefore, we performed screening of the reaction conditions for this transformation, and it was found that the best yield of the product **18** (57% by ^{1}H NMR, ca. 1:1 *dr*) is obtained when **17** and **11a**·HCl were refluxed in the presence of DIPEA (5 equiv) in EtOH for 11 d (Table 1). The crude product after reaction was subjected to preparative chromatography to give the target compounds **18a** (26% yield, >95:5 *dr*) and **18b** (23% yield, 90:10 *dr*). Hydrogenolysis of **18a**,**b** gave esters **19a**,**b** (77–82% yield), which were transformed into the target carboxylic acids **2a**,**b** (92–96% yield) by alkaline hydrolysis.

Table 2
Specific rotation values and chiral stationary phase HPLC analysis of the products **1a**,**b** and **2a**,**b**

Compound	$[\alpha]_D$	Column[a]	R_t, min	*Er*
1a	−26.7	Chirobiotic R®	6.9	96:4
1b	+20.1	Chirobiotic R®	6.4	86:14
2a	−21.0	Chirobiotic T®	16.7	96:4
2b	+18.4	Chirobiotic T®	15.4	92:8

[a] Eluent: MeOH–NH_4OH–AcOH (100:0.1:0.05), injection volume: 2.0 μL or 5.0 μL; eluent flow: 1 mL/min.

Absolute configurations of the products **1a** and **1b** were established by comparison of specific rotation values with the literature data.[5] In the case of **2a** and **2b**, transformation to the known compound **20** was used to assign the configuration (Scheme 8). To check enantiomeric excess of the final products obtained, they were analyzed using chiral stationary phase HPLC (Table 2).

3. Conclusions

The Michael reaction—cyclization of appropriate α,β-unsaturated carboxylic acids or their derivatives with *O*-(α-phenylethyl) hydroxylamine can be used for the synthesis of enantiopure lactams, which is demonstrated for 5-oxopyrrolidine- and 6-oxopiperidine-3-carboxylic acids. Although the reaction itself does not

provide diastereoselectivity, separation of diastereomers followed by removal of the chiral auxiliary can be used to obtain both enantiomers of the target products. Therefore, *O*-(α-phenylethyl)hydroxylamine can be considered as a 'chiral ammonia equivalent' in reactions with electrophilic substrates such as Michael addition, and in our opinion, this method can be extended to other synthetic sequences.

4. Experimental

4.1. General

The solvents were purified according to the standard procedures.[25] All the starting materials were purchased from Acros, Merck, Fluka, and Enamine Ltd. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 499.9 MHz for Protons and 124.9 MHz for Carbon-13) and Varian Unity Plus 400 spectrometer (at 400.4 MHz for protons and 100.7 MHz for Carbon-13). Chemical shifts are reported in ppm downfield from TMS as an internal standard. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, National Taras Shevchenko University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI), electrospray ionization (ESI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)). Preparative flash chromatography was performed using Combiflash Companion chromatograph with 12 g or 40 g RediSep column.

4.2. (*R*)-*O*-(α-Phenylethyl)hydroxylamine hydrochloride 11a·HCl

To a solution of (*S*)-1-phenylethanol (170 g, 1.39 mol) in THF (2.5 L), triphenylphosphine (438 g, 1.67 mol) was added at rt, followed by *N*-hydroxyphthalimide (272 g, 1.67 mol). To the resulting mixture, diisopropyl azodicarboxylate (338 g, 1.67 mol) was added at 0 °C. The mixture was stirred at rt overnight and evaporated in vacuo. The residue was dissolved in $CHCl_3$ (2.5 L) and MeOH (250 mL). Hydrazine hydrate (206 mL, 1.41 mol) was added. The mixture was stirred at rt overnight. The suspension was filtered, and the filtrate was evaporated in vacuo. The residue was dissolved in 2 M aq HCl (2 L), washed with CH_2Cl_2 (2 × 500 mL), neutralized to pH = 9 by addition of K_2CO_3 and extracted with CH_2Cl_2 (2 × 500 mL). The combined extracts were dried over Na_2SO_4 and evaporated in vacuo to give the product **11a** as a colorless liquid. To obtain the hydrochloride of **11a**, it was dissolved in THF (1 L). Saturated HCl in dioxane (1 L) was added, and the mixture was stirred at rt for 2 h. The suspension was filtered, and the precipitate was dried in vacuo to give the product **11a**·HCl as white crystals. Yield 155 g (80%). White crystals. Mp 128–130 °C. $[\alpha]_D^{20}$ = +123.0 (*c* 0.25, MeOH). Anal. Calcd for $C_8H_{12}ClNO$: C, 55.34; H, 6.97; N, 8.07; Cl, 20.42. Found: C, 55.31; H, 7.24; N, 7.88; Cl, 20.09. MS (CI): 138 (MH^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (s, 3H), 7.41 (br s, 5H), 5.29 (q, *J* = 6.2 Hz, 1H), 1.51 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 139.5, 129.4, 129.2, 127.4, 82.0, 21.2.

4.3. (S)-O-(α-Phenylethyl)hydroxylamine hydrochloride 11b·HCl

The product **11b**·HCl was obtained from (*R*)-1-phenylethanol using the procedure described above for **11a**·HCl. Yield 167 g (86%). White crystals. Mp 125–127 °C. $[\alpha]_D^{20}$ −125.0 (*c* 0.25, MeOH). Other physico-chemical and spectral data were identical to those of enantiomer **11a**·HCl.

4.4. 5-Oxo-1[(1*R*)-1-phenylethoxy]pyrrolidine-3-carboxylic acid 13

To a suspension of itaconic acid (**3a**) (38.0 g, 0.293 mol) in pyridine (210 mL), **11a**·HCl (51.0 g, 293 mol) was added. The resulting mixture was refluxed until the reaction was completed (monitored by ^{1}H NMR, ca. 16 h). After cooling to rt, the mixture was evaporated in vacuo. The residue was triturated with 2 M aq HCl (150 mL), the precipitate obtained was filtered and dried in vacuo to give **13** (70.8 g) as a brownish solid which was used in the next step without characterization.

4.5. Methyl (3*R*)-5-oxo-1[(1*S*)-1-phenylethoxy]pyrrolidine-3-carboxylate 14a and methyl (3*S*)-5-oxo-1[(1*S*)-1-phenylethoxy] pyrrolidine-3-carboxylate 14b

Strong cationite (KU-2) (17.8 g) was added to a stirred solution of acid **13** from the previous step (35.4 g, 0.142 mol) in absolute MeOH (180 mL). The mixture was refluxed for 1 d, filtered through silica gel (50 g), which was washed thoroughly with MeOH (100 mL). The filtrate was evaporated in vacuo to give a mixture of **14a** and **14b** (29.3 g). The diastereomers were separated by preparative flash chromatography (hexanes–*t*-BuOMe (3:2) as eluent).

14a: yield 9.25 g (32%). Brownish oil. $[\alpha]_D^{20}$ = +16.3 (*c* 0.25, MeOH). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.5; H, 6.50; N, 5.68. MS (CI): 264 (MH^+). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.51–7.18 (m, 5H), 5.17 (q, *J* = 6.4 Hz, 1H), 3.67 (s, 3H), 3.49 (t, *J* = 7.9 Hz, 1H), 3.10 (t, *J* = 8.6 Hz, 1H), 2.97–2.87 (m, 1H), 2.55 (t, *J* = 7.9 Hz, 2H), 1.59 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 169.7, 140.7, 128.7, 128.5, 127.2, 82.9, 52.5, 49.3, 33.6, 30.9, 20.5.

14b: yield 9.49 g (32%). Brownish oil. $[\alpha]_D^{20}$ = −144.3 (*c* 0.25, MeOH). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.98; H, 6.74; N, 5.15. MS (CI): 264 (MH^+). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.52–7.35 (m, 5H), 5.17 (q, *J* = 6.5 Hz, 1H), 3.61 (s, 3H), 3.50 (t, *J* = 8.8 Hz, 1H), 3.15 (dd, *J* = 8.9, 4.9 Hz, 1H), 3.05–2.97 (m, 1H), 2.64 (dd, *J* = 17.2, 5.6 Hz, 1H), 2.48 (dd, *J* = 17.3, 9.8 Hz, 1H), 1.59 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 169.4, 140.5, 128.6, 128.4, 127.3, 82.6, 52.4, 49.4, 33.5, 30.6, 20.4.

4.6. Methyl (3*R*)-1-hydroxy-5-oxopyrrolidine-3-carboxylate 15a

An autoclave was charged with **14a** (9.39 g, 36.7 mmol), 10% Pd–C (1.00 g) and THF (50 mL). The mixture was stirred vigorously at 50 atm of hydrogen and 50 °C for 24 h. The suspension was filtered, and the slurry of catalyst was washed with MeOH (2 × 25 mL). The filtrate was evaporated to dryness in vacuo to give the product **15a**. Yield 5.56 g (98%). Colorless oil. Anal. Calcd for $C_6H_9NO_4$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.26; H, 5.45; N, 8.66. MS (CI): 160 (MH^+). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.17 (s, 1H), 3.83 (s, *J* = 7.9 Hz, 2H), 3.73 (s, 3H), 3.29–3.20 (m, 1H), 2.71 (dd, *J* = 17.2, 7.0 Hz, 1H), 2.62 (dd, *J* = 17.2, 10.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 168.6, 52.6, 50.5, 33.3, 31.1.

4.7. Methyl (3*S*)-1-hydroxy-5-oxopyrrolidine-3-carboxylate 15b

The product **15b** was obtained from **14b** using the procedure described above for **15a**. Yield 4.37 g (96%). Colorless oil. Other physico-chemical and spectral data were identical to those of enantiomer **15a**.

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4.8. Methyl (3*S*)-5-oxopyrrolidine-3-carboxylate (*S*)-6a

An autoclave was charged with **14a** (9.39 g, 36.7 mmol), 10% Pd–C (1.00 g) and THF (50 mL). The mixture was stirred vigorously at 50 atm of hydrogen and 50 °C until the reaction was completed (monitored by ^{1}H NMR, ca. 96 h). The suspension was filtered, and the slurry of catalyst was washed with MeOH (2 × 25 mL). The filtrate was evaporated to dryness in vacuo to give the product **6a**. Yield 5.10 g (97%). Colorless oil. $[\alpha]_D^{20}$ = −9.6 (*c* 0.25, MeOH) (lit.[14] −7.3 (*c* 0.7, CH_3OH), *ee* 76%). Anal. Calcd for $C_6H_9NO_3$: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.52; H, 6.42; N, 9.70. MS (CI): 144 (MH^+). ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.80 (s, 1H), 3.74 (s, 3H), 3.67–3.61 (m, 2H), 3.40–3.29 (m, 1H), 2.67 (dd, *J* = 17.2, 7.7 Hz, 1H), 2.57 (dd, *J* = 17.2, 9.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.6, 173.1, 52.4, 44.4, 38.7, 33.1.

4.9. Methyl (3*R*)-5-oxopyrrolidine-3-carboxylate (*R*)-6a

The product (*R*)-**6a** was obtained from **15b** using the procedure described above for (*S*)-**6a**. Yield 4.03 g (96%). Colorless oil. $[\alpha]_D^{20}$ = +6.9 (*c* 0.25, MeOH). Other physico-chemical and spectral data were identical to those of enantiomer (*S*)-**6a**.

4.10. (3*S*)-5-Oxopyrrolidine-3-carboxylic acid 1a

Ester **6a** (5.10 g, 35.6 mmol) was dissolved in THF (30 mL) and H_2O (15 mL). Sodium hydroxide (1.42 g, 35.6 mmol) was added. The resulting mixture was stirred at rt for 1 h and evaporated in vacuo, filtered through strong cationite (KU-2, 35 g) and washed thoroughly with H_2O (20 mL). The filtrates were evaporated to dryness to give **1a**. Yield 4.20 g (91%). White solid. Mp 166–167 °C. $[\alpha]_D^{20}$ = −26.8 (*c* 0.25), *er* 96:4. Anal. Calcd for $C_5H_7NO_3$: C, 46.51; H, 5.46; N, 10.85. Found: C, 46.48; H, 5.39; N, 10.67. MS (CI): 130 (MH^+). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.56 (br s, 1H), 7.63 (s, 1H), 3.45 (t, *J* = 9.2 Hz, 1H), 3.37–3.30 (m, 1H), 3.29–3.17 (m, 1H), 2.41–2.23 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.6, 175.1, 44.2, 38.7, 33.5.

4.11. (3*R*)-5-Oxopyrrolidine-3-carboxylic acid 1b

The product **1b** was obtained from (*R*)-**6a** using the procedure described above for **1a**. Yield 3.51 g (94%). White crystals. Mp 149–153 °C (lit.[14] 147–149 °C). $[\alpha]_D^{20}$ = +20.1 (*c* 0.25, MeOH), *er* 86:14 (lit.[14] +10.2 (*c* 0.1, MeOH), *ee* 34%). Other physico-chemical and spectral data were identical to those of enantiomer **1a**.

4.12. Diethyl 2-methylenepentanedioate 17[24]

To ethyl acrylate **17** (100 g, 0.998 mol), tri-*n*-butylphosphine (20.2 g, 0.998 mmol) was added slowly under an argon atmosphere without external cooling (the addition rate was controlled so that the temperature was kept below 80 °C). After cooling to rt, the reaction mixture was distilled in vacuo. Yield 86.0 g (86%). Colorless liquid. Bp 95–96 °C/3 Torr (lit.[26] 92–94 °C/3 Torr). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.27; H, 8.02. MS (EI): 200 (M^+). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.19 (s, 1H), 5.59 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.65 (t, *J* = 7.4 Hz, 2H), 2.52 (t, *J* = 7.4 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 166.7, 139.2, 125.5, 60.7, 60.4, 33.2, 27.3, 14.2, 14.2.

4.13. Ethyl (3*R*)-6-oxo-1-[(1*R*)-1-phenylethoxy]piperidine-3-carboxylate 18a and ethyl (3*S*)-6-oxo-1-[(1*R*)-1-phenylethoxy] piperidine-3-carboxylate 18b

To a solution of diethyl 2-methylenepentanedioate **17** (6.19 g, 30.9 mmol) in EtOH (60 mL), **11a**·HCl (12.7 g, 92.7 mmol) was added at rt, followed by *N*,*N*-diisopropylethylamine (26.9 mL, 0.154 mmol). The resulting mixture was refluxed for 10 d and evaporated in vacuo. The residue was dissolved in *t*-BuOMe (100 mL), and the solution was washed with 2 M aq HCl (50 mL) to pH = 4. The organic phase was dried over Na_2SO_4 and evaporated in vacuo to give a mixture of **18a** and **18b**. The diastereomers were separated by preparative flash chromatography hexanes–*t*-BuOMe (3:2) as eluent).

18a: yield 1.19 g (26%). Colorless oil. $[\alpha]_D^{20}$ = −141.4 (*c* 0.25, MeOH). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.82; H, 7.15; N, 4.52. MS (CI): 292 (MH^+). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.24 (m, 5H), 5.20 (q, *J* = 6.4 Hz, 1H), 4.20–3.91 (m, 2H), 3.56 (dd, *J* = 11.4, 5.4 Hz, 1H), 3.24 (dd, *J* = 11.3, 8.7 Hz, 1H), 2.78–2.61 (m, 1H), 2.52 (dt, *J* = 17.3, 5.5 Hz, 1H), 2.42–2.28 (m, 1H), 2.00–1.89 (m, 1H), 1.80–1.65 (m, 1H), 1.54 (d, *J* = 6.5 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 166.9, 140.8, 128.5, 128.4, 127.3, 81.4, 61.1, 52.3, 39.7, 31.2, 23.3, 20.4, 14.0.

18b: yield 1.04 g (23%). Colorless oil. $[\alpha]_D^{20}$ = −153.2 (*c* 0.25, MeOH). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.95; H, 7; N, 4.54. MS (CI): 292 (MH^+). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.27 (m, 5H), 5.21 (q, *J* = 6.5 Hz, 1H), 4.17–3.93 (m, 2H), 3.64–3.51 (m, 1H), 3.14 (dd, *J* = 11.2, 5.1 Hz, 1H), 2.58–2.28 (m, 3H), 2.00–1.89 (m, 1H), 1.89–1.75 (m, 1H), 1.56 (d, *J* = 6.6 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 167.0, 140.7, 128.6, 128.6, 127.4, 81.4, 61.1, 52.3, 39.8, 31.3, 23.6, 20.0, 14.0.

4.14. Ethyl (3*R*)-6-oxopiperidine-3-carboxylate 19a

An autoclave was charged with **18a** (1.10 g, 3.77 mmol), 10% Pd–C (0.110 g) and THF (20 mL). The mixture was stirred vigorously at 50 atm of hydrogen and 50 °C until the reaction was completed (monitored by ^{1}H NMR, ca. 96 h). The suspension was filtered, and the slurry of catalyst was washed with MeOH (2 × 10 mL). The filtrate was evaporated to dryness in vacuo to give the product **19a**. Yield 0.523 g (82%). Colorless oil. $[\alpha]_D^{20}$ −27.5 (*c* 0.25, MeOH). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.12; H, 7.56; N, 8.46. MS (CI): 172 (MH^+). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.47 (d, *J* = 6.9 Hz, 2H), 2.80–2.65 (m, 1H), 2.50–2.27 (m, 2H), 2.16–2.05 (m, 1H), 2.03–1.89 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 171.8, 61.0, 43.2, 38.4, 29.8, 23.5, 14.1.

4.15. Ethyl (3*S*)-6-oxopiperidine-3-carboxylate 19b

The product **19b** was obtained from **18b** using the procedure described above for **19a**. Yield 0.499 g (77%). Colorless oil. $[\alpha]_D^{20}$ = +23.8 (*c* 0.25, MeOH). Other physico-chemical and spectral data were identical to those of enantiomer **19a**.

4.16. (3*R*)-6-Oxopiperidine-3-carboxylic acid 2a

Ester **19a** (0.291 g, 1.69 mmol) was dissolved in THF (10 mL) and H_2O (5 mL). Sodium hydroxide (0.700 g, 1.69 mmol) was added. The resulting mixture was stirred at rt for 1 h and filtered through strong cationite (KU-2, 5 g) and washed thoroughly with H_2O (10 mL). The filtrates were evaporated to dryness to give **2a**.

Yield 0.230 g (96%). Colorless solid. Mp 181–182 °C. $[\alpha]_D^{20}$ = −21.0 (*c* 1.0, MeOH). Anal. Calcd for $C_6H_9NO_3$: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.53; H, 6.11; N, 9.6. MS (CI): 144 (MH^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.43 (s, 1H), 3.32–3.16 (m, 2H), 2.73–2.58 (m, 1H), 2.21–2.09 (m, 2H), 2.01–1.88 (m, 1H), 1.86–1.72 (m, 1H), COO*H* is exchanged with HDO. ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.7, 170.2, 43.1, 38.3, 30.3, 23.8.

4.17. (3*S*)-6-Oxopiperidine-3-carboxylic acid 2b

The product **2b** was obtained from **19b** using the procedure described above for **19a**. Yield 0.222 g (92%). White crystals. Mp 184–185 °C. $[\alpha]_D^{20}$ = +18.4 (*c* 0.25, MeOH). Other physico-chemical and spectral data were identical to those of enantiomer **2a**.

4.18. (3*S*)-Piperidin-3-ylmethanol 20

To a solution of ester **19a** (0.200 g, 1.16 mmol) in THF (5 mL), BH_3·THF (0.3 mL, 2.92 mmol, 1 M in THF) was added at rt. The resulting mixture was refluxed for 2 d and then evaporated in vacuo. The residue was dissolved in MeOH (5 mL) and 4 M HCl in dioxane (5 mL). The mixture was refluxed overnight and evaporated in vacuo. The residue was dissolved in MeOH (10 mL), neutralized by addition of K_2CO_3 and evaporated in vacuo. The residue was dissolved in $CHCl_3$ (10 mL). The precipitate was filtered off, and the filtrate was evaporated in vacuo to give **20**. Yield 85.7 mg (64%). Yellowish oil. $[\alpha]_D^{20}$ = −7.4 (*c* 0.25, MeOH) (lit.[27] −8.4 (*c* 0.25, MeOH)). Other physico-chemical and spectral data were identical to those reported in the literature.[28]

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