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Practical synthesis of both enantiomers of protected 4-oxopipecolic acid

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Abstract—A new synthesis of both enantiomers of protected 4-oxopipecolic acid was achieved in six steps via 1,3-dipolar cycloaddition of *C*-ethoxycarbonyl *N*-(1*R*)-phenylethylnitrone to but-3-en-1-ol.

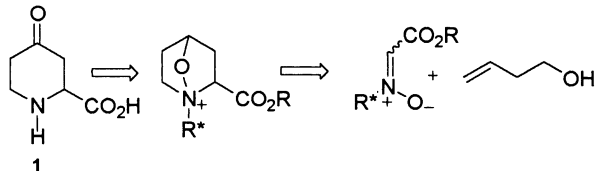
1. Introduction

The (2*S*) enantiomer of 4-oxopipecolic acid (**1**) is a rare non-proteinogenic amino acid present in some biologically important cyclic peptides with antibiotic activity belonging to the virginiamycin family.[1] Owing to its use as a building block in the syntheses of cyclopeptides, as an intermediate in the preparation of *N*-methyl-D-aspartate (NMDA) receptor antagonists,[2] and as a precursor of 4-hydroxypipecolic acid[3,6f] (a naturally occurring imino acid isolated from some Acacia species in 1955[4]), **1** has attracted a great deal of synthetic attention leading to sixteen syntheses since its isolation in 1959 from Staphylomycin.[5] However, only a few of the reported syntheses satisfy the enantio-controlled construction of the 4-oxopipecolic skeleton, and do not involve the oxidation of the corresponding enantiopure 4-hydroxypipecolic derivative.[3b,6] We have recently reported the preparation of the (2*S*)-4-oxopipecolic acid via a domino process having as a key step the diastereoselective cycloaddition of a *N*-glycosylnitrone to methylenecyclopropane followed by the thermal rearrangement of the adduct.[3b] Continuing our study on the synthesis of amino acids and derivatives employing chiral nitrones, we investigated the use of *C*-ethoxycarbonyl-*N*-(1*R*)-phenylethylnitrone in the cycloaddition with but-3-en-1-ol as a route to produce (2*S*) and (2*R*) protected 4-oxopipecolic acids (Scheme 1).

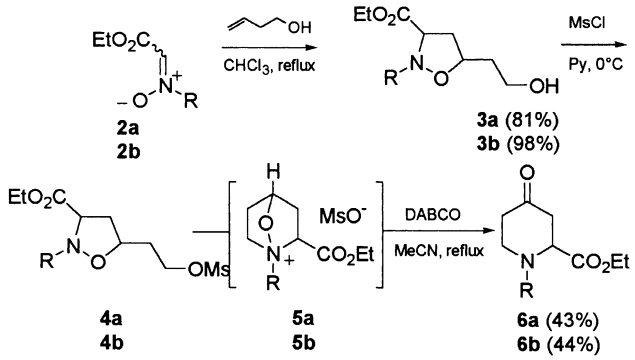
2. Results and discussion

The approach was first attempted with racemic intermediates (Scheme 2, R=Bn). The nitrone **2a** was prepared by condensation of *N*-benzylhydroxylamine and ethyl glyoxylate, readily available from diethyl tartrate,[7] according to the literature.[8]

Nitrone **2a** was found to be a 1:1 mixture of *E*/*Z* isomers by ^{1}H NMR analysis. Cycloaddition of the nitrone **2a** to but-3-en-1-ol gave 1:1 mixture of the *cis* and *trans* adducts **3a** in 80% combined yield. Since both of them converge into product **6a** the next step of the synthesis was carried out with the above mixture and no attempt was made to isolate the individual compounds. Upon treatment with MsCl in pyridine, the adducts **3a** gave the corresponding mesylates



Scheme 1.



Scheme 2.

Keywords: amino acid; cycloaddition; rearrangement; oxopipecolic acid; nitrone.

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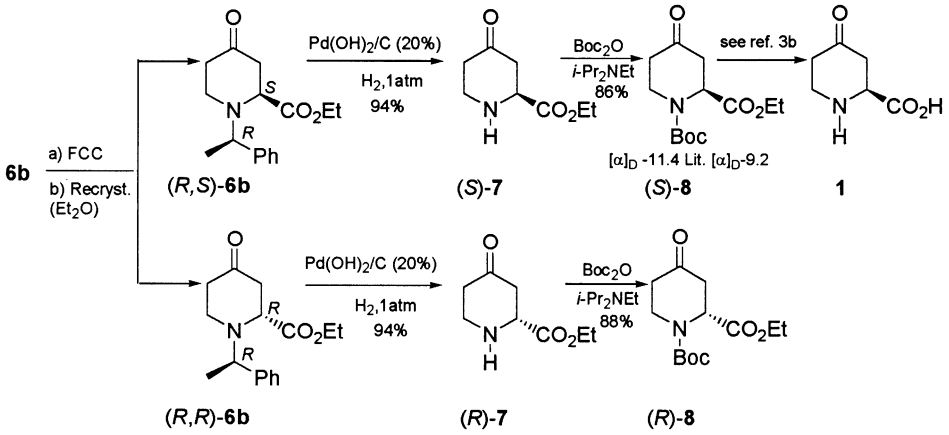

Scheme 3.

4a which could not be isolated because they undergo intramolecular nucleophilic displacement to give salts **5a**. The extraction of the bridgehead proton, according to a procedure investigated on similar salts,[9] by DABCO in refluxing MeCN was followed by the cleavage of the N–O bond,[10] to afford the racemic oxopipecolic ester **6a**. The synthetic strategy described above was successfully applied to the synthesis of (2*R*) and (2*S*)-4-oxopipecolic acid derivatives using a nitrone which contains the chiral information at the *N*-substituent (Scheme 2).

A large-scale preparation of nitrone **2b** was performed by condensation of ethylglyoxylate and (*R*)-(+)-*N*-phenylethylhydroxylamine, readily prepared in high yield from (*R*)-(+)-phenylethylamine.[11] Cycloaddition of nitrone **2b** to but-3-en-1-ol in refluxing $CHCl_3$ gave an equimolecular mixture of four diastereomeric adducts **3b** in 98% combined yield. The scale up of the synthesis was brought to the synthesis of 65 g of adducts in one batch. The mixture of isomers **3b** was mesylated and no attempt was made to separate the diastereoisomers. Treatment of the mixture of mesylates **4b** in refluxing MeCN in the presence of DABCO gave the compounds (*R*,*S*)-**6b** and (*R*,*R*)-**6b**, epimers at C(2), in nearly 1:1 ratio and 44% overall yield (Scheme 2).

The separation of diastereomeric compounds (*R*,*S*)-**6b** and (*R*,*R*)-**6b** was easily undertaken either by silica gel chromatography or by repeated crystallization from Et_2O. If the direct crystallization failed occasionally a preliminary chromatographic purification on a short pad of silica gel was necessary.

The stereochemical assignment of the diastereoisomers (*R*,*S*)-**6b** and (*R*,*R*)-**6b** was done by chemical correlation to the known product *N*-Boc-4-oxopipecolic acid ethyl ester as outlined in Scheme 3. Hydrogenolysis of (*R*,*S*)-**6b** in the presence $Pd(OH)_2$ afforded the *N*-deprotected compound (*S*)-**7**. Then, treatment with Boc_2O and *i*-Pr_2NEt afforded the *N*-Boc-4-oxopipecolic acid ethyl ester (*S*)-**8** with $[\alpha]_D^{25}=-11.4$ (c=0.94, $CHCl_3$) in agreement to the previously reported value in the literature ($[\alpha]_D^{23}=-9.2$, (c=0.91, $CHCl_3$)).[3b] The same procedure on diastereomeric (*R*,*R*)-**6b** gave the enantiomeric protected oxopipecolic acid (*R*)-**8** in similar yield.

In summary a practical, multigram scale, six step synthesis of both enantiomers of 4-oxopipecolic acid ethyl ester, has been achieved in very good overall yield (20% for each, including the synthesis of nitrone **2b**) starting from inexpensive commercial materials.

3. Experimental

3.1. General

Melting points are uncorrected. Chromatographic separations (FCC) were performed on silica gel; R_f values refer to TLC carried out on 25-mm silica gel plates (Merck F254), with the same eluent indicated for the column chromatography. ^1H and ^{13}C NMR spectra were recorded at 200 and 50.33 MHz, respectively, unless otherwise stated. Mass spectra were carried out in EI at 70 eV ionizing voltage.

The (*R*)-(+)-*N*-phenylethylhydroxylamine oxalate was prepared on a multigram scale as previously reported starting from (*R*)-(+)-phenylethylamine.[12]

3.1.1. *N*-Benzyl-*C*-ethoxycarbonylnitrone (*E*/*Z*) (2a). The title compound was prepared as previously reported starting from ethyl glyoxylate and *N*-benzylhydroxylamine.[13]

White solid. mp 83–85°C (Lit.[13] 84.0–85.6°C). ^1H NMR ($CDCl_3$) δ 7.44–7.36 (m, 5H), 7.16 (*E*) and 7.09 (*Z*) (s, 1H), 5.68 (*E*) and 4.96 (*Z*) (s, 2H), 4.38–4.17 (m, 2H), 1.35–1.23 (m, 3H).

3.1.2. *cis* and *trans* 2-Benzyl-5-(2-hydroxy-ethyl)-isoxazolidine-3-carboxylic acid ethyl ester (3a). A solution of nitrone **2a** (1.64 g, 7.9 mmol) and but-3-en-1-ol (0.82 ml, 9.5 mmol) in $CHCl_3$ (10 mL) was heated to reflux for 6 h. The solvent was evaporated and the residue purified by FCC (EtOAc–Petroleum ether 7:9, R_f 0.15 and 0.18) to give adducts **3a** (1.6 g, 6.4 mmol) in 81% yield. Clear oil. 1:1 Mixture of isomers. ^1H NMR ($CDCl_3$) δ 7.42–7.20 (m, 5H), 4.50–4.00 (m, 4H), 3.80–3.44 (m, 3H), 2.80–2.52 (m, 1H), 2.24–2.05 (m, 1H), 2.00–1.64 (m, 3H), 1.31–1.18 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 170.8, 170.5, 136.1, 136.0, 129.2,

128.2, 128.1, 127.4, 76.1, 75.4, 66.5, 66.3, 62.2, 61.4, 61.2, 61.1, 38.6, 37.8, 36.6, 36.4, 14.1. IR ($CDCl_3$) 3090, 2982, 1740 cm^{-1}. MS *m/z* (%) 279 (M^+, <1), 206 (9), 91 (100). Anal. Calcd for $C_{15}H_{21}NO_4$ (279.33): C, 64.50; H, 7.58; N, 5.01. Found: C, 64.47; H, 7.61; N, 5.29.

3.1.3. *N*-Benzyl-4-oxo-piperidine-2-carboxylic acid ethyl ester (6a). MsCl (0.4 ml, 5.2 mmol) was added dropwise to a solution of isoxazolidines **3a** (0.726 g, 2.60 mmol) in pyridine (18 mL) at 0°C. The mixture was stirred at the same temperature for 4 h then filtered. The solvent was removed in vacuo and the solid residue was used without any purification in the next step. ^1H NMR ($CDCl_3$) δ 7.60–7.22 (m, 5H), 6.00–5.80 and 5.60–5.42 (m, 1H), 5.42–5.20 (m, 1H), 4.42–4.00 (m, 2H+2H), 3.64 (s, 2H), 3.60–3.40 (m, 1H), 2.81 (s, 3H), 2.75–2.40 (m, 2H), 2.30–2.00 (m, 1H), 1.40–1.22 (t, *J*=7.4 Hz, 3H).

A solution of crude **5a** and DABCO (0.941 g, 8.4 mmol) in freshly distilled MeCN (5 mL) was heated at 75°C for 1 h. The reaction mixture was filtered and the solvent was evaporated under reduced pressure. The residue oil was dissolved in Et_2O (30 mL) and then washed with water. The organic phase was dried over Na_2SO_4 and the solvent was evaporated to give crude **6a**. Purification by FCC (CH_2Cl_2–MeOH=100:1, R_f=0.32) afforded 0.292 g of **6a** as a dark oil (yield 43%). ^1H NMR ($CDCl_3$) δ 7.44–7.16 (m, 5H), 4.19 (q, *J*=6.8 Hz, 2H), 4.02 (m, 1H), 3.78 (s, 2H), 3.10–2.94 (m, 2H), 2.94–2.86 (m, 2H), 2.60–2.50 (m, 1H), 2.50–2.46 (m, 1H), 1.27 (t, *J*=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 206.6 (s), 170.6 (s), 137.8 (s), 128.7 (d), 128.3 (d), 127.3 (d), 61.7 (d), 60.7 (t), 58.9 (t), 47.3 (t), 42.7 (t), 40.1 (t), 14.2 (q). IR ($CDCl_3$) 3080, 3040, 2979, 2930, 1722 cm^{-1}. MS *m/z* (%) 261 (M^+, <1), 188 (M^+-CO_2Et, 81), 91 (100). Anal. Calcd for $C_{15}H_{19}NO_3$ (261.32): C, 68.94; H, 7.33; N, 5.36. Found: C, 68.66; H, 7.61; N, 5.29.

3.1.4. *N*-[(1*R*)-Phenylethyl]-*C*-ethoxycarbonylnitrone (*E*/*Z*) (2b). TEA (52.2 mL, 373 mmol) was added dropwise to an ice cooled mixture of *N*-(1*R*)-phenylethylhydroxylamine oxalate (64.9 g, 285 mmol) and ethyl glyoxylate (35.0 g, 342 mmol) in CH_2Cl_2 (360 mL) after which the whole was stirred at 0°C for 16 h. The reaction mixture was washed with H_2O (3×300 mL) and then the organic phase dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. Two recrystallization from Et_2O afforded an analytical sample of **3** (53.1 g, 84%).

White solid. mp 79–80°C. $[\alpha]_D^{25}$=+93.0 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (3:2 mixture of isomers) major isomer 7.59–7.26 (m, 5H), 7.14 (s, 1H), 5.09 (q, *J*=7.0 Hz, 1H), 4.26–4.12 (m, 2H), 1.80 (d, *J*=7.0 Hz, 3H), 1.32–1.21 (m, 3H) minor isomer 7.59–7.26 (m, 5H), 7.13 (s, 1H), 7.03 (q, *J*=7.0 Hz, 1H), 4.26–4.12 (m, 2H), 1.71 (d, *J*=7.0 Hz, 3H), 1.32–1.21(m, 3H). ^{13}C NMR ($CDCl_3$) δ 160.8 (s), 160.1 (s), 138.4 (s), 137.2 (s), 129.2 (d), 128.8 (d), 128.6 (d), 128.4 (d), 127.6 (d), 127.3 (d), 126.5 (d), 123.9 (d), 77.8 (d), 68.3 (d), 61.3 (t), 60.9 (t), 19.3 (q), 19.1 (q), 14.2 (q). IR ($CDCl_3$) 1721, 1543 cm^{-1}. MS *m/z* (%): 204 (9), 176(4), 130(5), 105 (100), 77(43). Anal. Calcd for $C_{12}H_{15}NO_3$ (221.25): C, 65.14; H, 6.83; N, 6.33. Found C, 65.38; H, 6.77; N, 6.37.

3.1.5. *cis* and *trans* (1′*R*)-2-[1′-Phenylethyl]-5-(2-hydroxyethyl)-isoxazolidine-3-carboxylic acid ethyl ester (3b). A solution of nitrone **2b** (50 g, 226 mmol) and but-3-en-1-ol (23.3 ml, 271 mmol) in $CHCl_3$ (300 mL) was heated to reflux for 18 h. The solvent and the excess of but-3-en-1-ol were evaporated in vacuo to give adducts **3b** (65 g, 270 mmol) in 98% yield and sufficiently pure to be used directly in the next step.

Mixture of isomers. ^1H NMR ($CDCl_3$) δ 7.40–7.18 (m, 5H), 4.48–3.40 (m, 7H), 2.64–1.60 (m, 5H), 1.58–1.38 (m, 3H), 1.36–1.00 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 171.6 (s), 171.5 (s), 141.7 (s), 141.4 (s), 141.2 (s), 140.8 (s), 128.3 (d), 128.1 (d), 128.0 (d), 127.9 (d), 127.8 (d), 127.7 (d), 127.6 (d), 127.5 (d), 127.2 (d), 76.4 (d), 75.2 (d), 75.0 (d), 67.9 (d), 65.1 (d), 64.8 (d), 64.5 (d), 63.6 (d), 61.1 (t), 60.9 (t), 60.8 (t), 60.4 (t), 59.9 (t), 39.2 (t), 37.3 (t), 36.9 (t), 36.1 (t), 36.0 (t), 21.8 (q), 21.4 (q), 20.7 (q), 20.3 (q), 14.0 (q), 13.8 (q). MS *m/z* (%) 293 (M^+, <1), 220 (M^+-CO_2Et, 4), 116 (27), 105 (100), 77 (20). IR ($CDCl_3$) 3476, 2981, 1725 cm^{-1}. Anal. Calcd for $C_{16}H_{23}NO_4$ (293.36): C, 65.51; H, 7.90; N, 4.77. Found: C, 65.84; H, 7.66; N, 4.54.

3.1.6. (1′*R*, 2*S*)-1-[1′-Phenylethyl]-4-oxo-piperidine-2-carboxylic acid ethyl ester [(*R*,*S*)-6b] and (1′*R*, 2*R*)-1-[1′-Phenylethyl]-4-oxo-piperidine-2-carboxylic acid ethyl ester [(*R*,*R*)-6b]. MsCl (10.0 ml, 129 mmol) was added dropwise to a solution of isoxazolidines **3b** (15.4 g, 52.5 mmol) in pyridine (170 mL) cooled to 0°C. The mixture was stirred at the same temperature for 4 h and then filtered. The solvent was removed in vacuo and the solid residue was used as crude in the next step.

A solution of crude **4b** and DABCO (13.9 g, 124 mmol) in freshly distilled MeCN (140 mL) was heated at 75°C for 1 h. The reaction mixture was filtered and the solvent was evaporated under reduced pressure. The residue oil was subjected to chromatographic purification over a short pad of silica gel (AcOEt–Petroleum ether 1:7). The first fraction (R_f=0.24) containing (*R*,*S*)-**6b** was followed by a second fraction containing (*R*,*S*)-**6b** and (*R*,*R*)-**6b** in nearly equimolecular ratio and a third fraction containing (*R*,*R*)-**6b** (R_f=0.18). The intermediate fraction was subjected to diastereomeric separation by repeated crystallization from Et_2O to give pure (*R*,*S*)-**6b** (3.29 g) and (*R*,*R*)-**6b** (3.08 g) in 44% combined yield).

(*R*,*S*)-**6b** white solid. mp 99–100°C R_f=0.24. $[\alpha]_D^{25}$=−8.4 (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.48–7.22 (m, 5H), 4.30–4.14 (m, 3H), 3.88 (q, *J*=6.6 Hz, 1H), 2.94–2.82 (m, 2H), 2.80–2.56 (m, 2H), 2.50–2.22 (m, 2H), 1.45 (d, *J*=6.6 Hz, 3H), 1.31 (t, *J*=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 207.2 (s), 171.2 (s), 145.0 (s), 128.5 (d, 2 C), 127.1 (d, 2 C), 126.9 (d), 61.4 (d), 60.8 (t), 58.5 (d), 45.0 (t), 43.1 (t), 40.5 (t), 20.4 (q), 14.3 (q). MS *m/z* (%): 202 (M^+-CO_2Et, 7), 105 (100), 98 (21), 79 (16), 77 (20). IR ($CDCl_3$) 1716 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_3$ (275.34): C, 69.79; H, 7.69; N, 5.09. Found: C, 69.37; H, 7.81; N, 5.21.

(*R*,*R*)-**6b** Clear oil. R_f=0.18. $[\alpha]_D^{25}$=+77.9 (*c* 0.8, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.42–7.20 (m, 5H), 4.28–4.10 (m, 2H), 4.00 (q, *J*=6.6 Hz, 1H), 3.76–3.66 (m, 1H), 3.32–3.18 (m, 1H), 3.16–3.00 (m, 1H), 2.72–2.28 (m, 4H), 1.43 (d, *J*=6.6 Hz, 3H), 1.29 (t, *J*=7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ

207.1 (s), 171.3 (s), 143.8 (s), 128.4 (d, 2C), 127.3 (d, 2C), 126.9 (d), 60.8(d), 60.7 (t), 59.9 (d), 45.0 (t), 43.1 (t), 40.5 (t), 21.4 (q), 14.9 (q). MS *m/z* (%): 202 (M^+-CO_2Et, 9), 105 (100), 98 (29), 79 (19), 77 (23). IR ($CDCl_3$) 1718 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_3$ (275.34): C, 69.79; H, 7.69; N, 5.09. Found: C, 69.60; H, 7.78; N, 5.47.

3.1.7. (2*S*)-4-Oxo-piperidine-2-carboxylic acid ethyl ester [(*S*)-7]. The *N*-phenylethylamine (*R,S*)-**6b** (70 mg, 0.25 mmol) was dissolved in EtOH (2 mL), $Pd(OH)_2$/C (20%) (10 mg) was added and the apparatus flushed three times with H_2. The reaction mixture was hydrogenated under atmospheric pressure at room temperature for 24 h filtered through a pad of Celite (3×2 ml of EtOH rinse) and then concentrated under reduced pressure to obtain the amine (*S*)-**7** (40 mg, 94%) that was sufficiently pure to be used in the next step without purification.

Clear oil. $[\alpha]_D^{25}=-27.5$ (*c* 0.9, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 4.21 (q, *J*=7.1 Hz, 2H), 3.68 (dd, *J*=4.2 and 10.0 Hz, 1H), 3.44–3.32 (m, 1H), 3.02–2.88 (m, 1H), 2.73–2.61 (m, 1H), 2.58–2.38 (m, 3H), 1.27 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 206.8 (s), 171.5 (s), 61.4 (t), 58.5 (d), 44.5 (t), 44.2 (t), 42.2 (t), 14.1 (q). IR ($CDCl_3$) 3154, 2983, 2965, 2937, 1722, 1378 cm^{-1}. Anal. Calcd for $C_8H_{13}NO_3$ (171.20): C, 56.13; H, 7.65; N, 8.18. Found: C, 56.24; H, 7.36; N, 8.44.

3.1.8. (2*S*)-*N*-*tert*-Butoxycarbonyl-4-oxo-piperidine-2-carboxylic acid ethyl ester [(*S*)-8]. Boc_2O (23 mg, 0.10 mmol) was added portionwise to a solution of amine (*S*)-**7** (18 mg, 0.10 mmol) and DIEA (0.017 mL, 0.10 mmol) in CH_2Cl_2–EtOH 4:1 (1 mL). The mixture was stirred at room temperature for 3 days and then concentrated under reduced pressure. The residue was partitioned between Et_2O–CH_2Cl_2 2:1 and 10% $NaHSO_4$. The aqueous layer was extracted with Et_2O–CH_2Cl_2 2:1. The solvent was evaporated and the residue purified by FCC on silica gel (CH_2Cl_2–MeOH 30:1, R_f 0.29) to give (*S*)-**8** (24 mg, 0.089 mmol) in 86% yield.

Clear oil. $[\alpha]_D^{25}=-11.4$, (*c* 0.94, $CHCl_3$) (Lit.[3b] $[\alpha]_D^{23}=+9.2$, *c* 0.91, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 5.05 and 4.80 (m, 1H, two conformers), 4.16 (q, *J*=7.4 Hz, 2H), 4.02 (dt, *J*=14.0 and 5.8 Hz, 1H), 3.64 (m, 1H), 2.80 (m, 2H), 2.54 (m, 2H), 1.48 (s, 9H), 1.26 (t, *J*=7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 205.9 (s), 171.1 (s), 146.7 (s), 81.1 (s), 61.7 (t), 54.8 and 54.1 (d, two conformers), 41.1 (t), 40.46 and 39.33 (t, two conformers), 39.7 (t), 28.2 (q, 3 C), 14.1 (q). MS *m/z* (%) 215 (1), 198 (16), 170 (24), 142 (61), 98 (100), 57 (100). Anal. Calcd for $C_{13}H_{21}NO_5$ (271.31): C, 57.57; H, 7.80; N, 5.16%. Found: C, 57.96; H, 7.54; N, 4.62%.

3.1.9. (2*R*)-4-Oxo-piperidine-2-carboxylic acid ethyl ester [(*R*)-7]. $[\alpha]_D^{25}=+25.8$ (*c* 0.94, $CHCl_3$). Spectral and analytical properties identical with (*S*)-**7**.

3.1.10. (2*R*)-*N*-*tert*-Butoxycarbonyl-4-oxo-piperidine-2-carboxylic acid ethyl ester [(*R*)-8]. $[\alpha]_D^{25}=+10.8$, (*c* 0.92, $CHCl_3$). Spectral and analytical properties identical with (*S*)-**8**.

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