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Preparation of (*R*)-(1-adamantyl)glycine and (*R*)-2-(1-adamantyl)-2-aminoethanol: a combination of cobalt-mediated β-ketoester alkylation and enzyme-based aminoalcohol resolution

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Abstract

Alkylation of the cobalt(II) complex of ethyl acetoacetate with 1-bromoadamantane affords ethyl 2-(1-adamantyl)acetoacetate, which was converted into *rac*-(1-adamantyl)glycine **1** and *rac*-2-(1-adamantyl)-2-aminoethanol **7**. This was separated into enantiomers by means of vinyl acetate in the presence of *Pseudomonas cepacea*. Configuration *R* was assigned to the enantiomerically pure aminoalcohol (*R*)-**7** on the basis of X-ray diffraction data. Further oxidation of *N*-protected aminoalcohol (*R*)-**8** afforded enantiomerically pure amino acid (*R*)-**1**.

1. Introduction

The preparation of α-amino acids in enantiomerically pure form is a topic of high interest.[1–4] In particular, substituted glycines featuring bulky substituents confer decreased conformational mobility to artificial peptides rendering them useful for studying peptide–receptor interactions.[5–7] *tert*-Leucine (*t*-butylglycine) has been the object of an intense investigation and a review has been published on its preparations and uses.[8] In sharp contrast little is known on (1-adamantyl)glycines (*R*)-**1** and (*S*)-**1** (Scheme 1). Racemic **1** was mentioned for the first time in a difficult accessible document.[9] Later, Belokon et al. reported the resolution of the racemic methyl ester by a diastereoisomeric salt formation with (−)-dibenzoyltartaric acid. Isolation of a pure salt (17%) and further transformations gave dextrorotatory (as hydrochloride) **1**, shown

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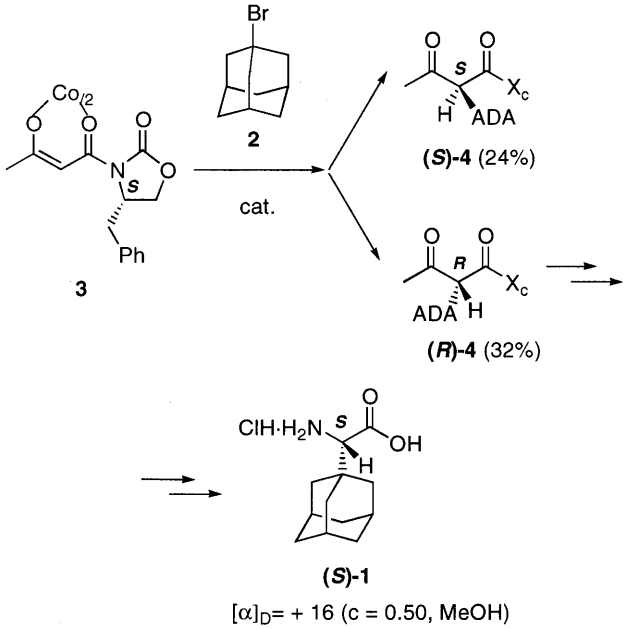
to be of (*S*)-configuration by examination of the CD spectra of transition metal complexes of the Schiff bases of (*S*)-**1** and other amino acids with an enantiomerically pure acetophenone derivative.[10]



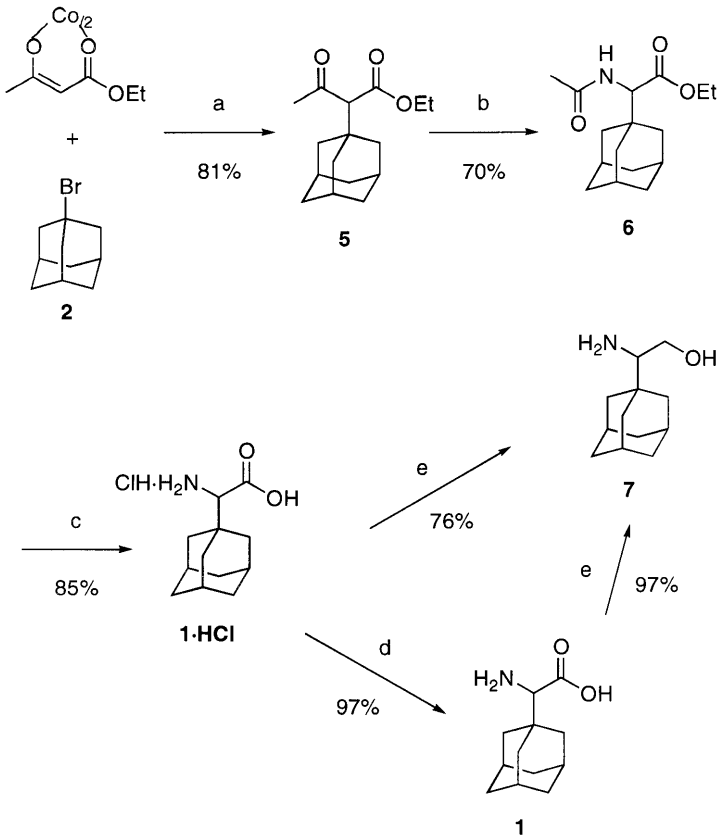
Scheme 1. Preparation of (*S*)-**1** according to Ref. 11

Later, some of us reported the preparation of (*S*)-**1** by the method in Scheme 1.[11] Reaction of 1-bromoadamantane **2** with the cobalt(II) complex **3**, featuring Evans oxazolidinone, afforded a mixture of both diastereomeric alkylation products (*R*)-**4** and (*S*)-**4**. The severe experimental conditions (140°C) resulted in a low diastereomeric excess of (*R*)-**4**. In fact the chiral auxiliary worked more as a resolution agent rather than as a real chiral auxiliary. Diastereoisomers **4** were separated by column chromatography and (*R*)-**4** was converted into (*S*)-**1** by Schmidt rearrangement and hydrolysis.[11] Alkylation of transition metal [mainly Co(II) and Cu(II) complexes of β-dicarbonyl compounds] is performed in neutral media permitting introduction of carbon radical precursors of stabilized free radicals.[12]

Therefore, we planned a different and more versatile approach, consisting of the preparation of racemic **1**, reduction to the corresponding racemic 2-(1-adamantyl)-2-aminoethanol **7**, enzymatic resolution of aminoalcohol **7** and reoxidation to enantiomerically pure **1**. This strategy offers the added bonus of permitting the preparation of **7** in enantiomerically pure form. Enantiomerically pure aminoalcohols are important intermediates for the elaboration of chiral ligands for transition metals, affording complexes useful in asymmetric catalysis.[13–15] Moreover, enzymatic resolution of 1,2-aminoalcohols has been carried out through an enzymatic aminolysis reaction.[16] However, better results are obtained by a transesterification reaction following prior *N*-protection of the amino group.[17] Recently, different 1,2-aminoalcohols have been resolved with very good enantioselectivities by enzymatic transesterification reaction of the corresponding carbamates using *Pseudomonas cepacia* lipase (PSL) and vinyl acetate as acyl donor.[18]

2. Results and discussion

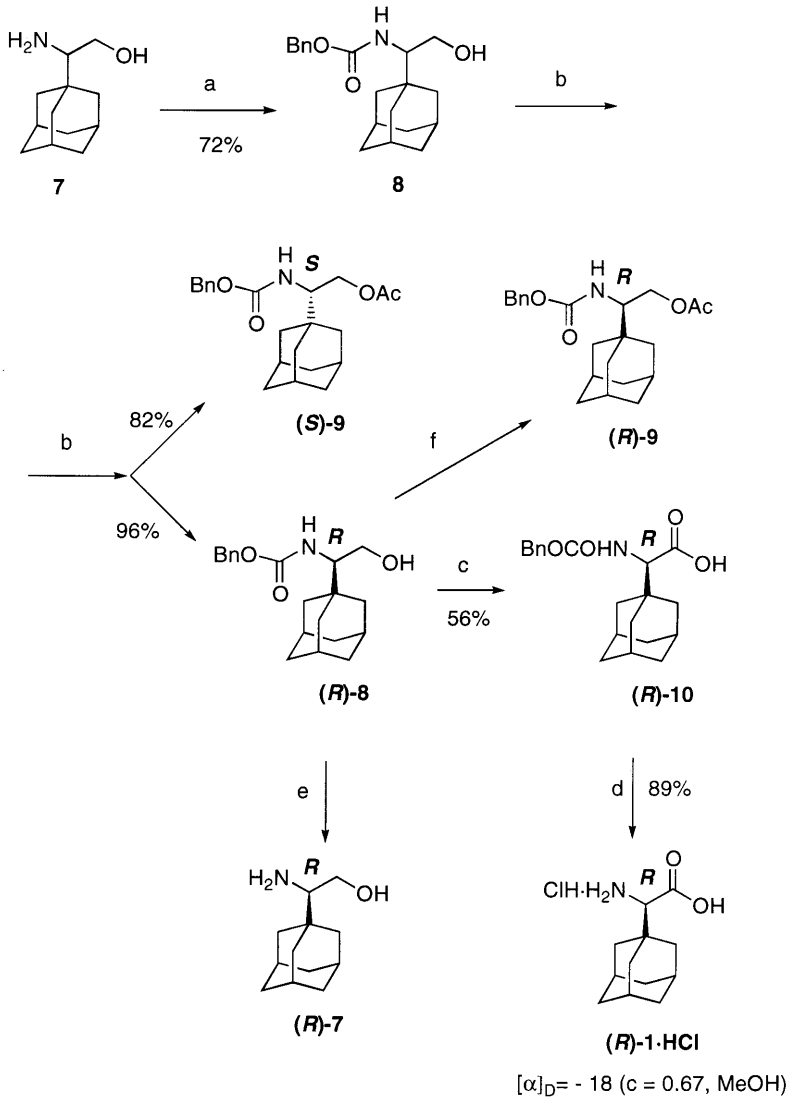
The chemistry leading to the racemic compounds was successful (Scheme 2). Reaction of the cobalt(II) complex of ethyl acetoacetate with 1-bromoadamantane, **2**, gave adamantylketoester **5**. Schmidt rearrangement in DME[19] gave the amino acid derivative **6** which was treated with HCl to afford racemic **1**·HCl. The free amino acid was obtained by the standard method by treating with propylene oxide in ethanol. Reduction from both **1** or its hydrochloride is best achieved by reaction with sodium borohydride and iodine in THF.[20]



Scheme 2. Key: (a) $CoCl_2(PPh_3)_2$, $LaBr_3{\cdot}6H_2O$, $HCCl_3$, 140°C; (b) $3NaN_3$, $MeSO_3H$, dimethoxyethane, rt; (c) refluxing 7 M HCl; (d) propylene oxide, ethanol; (e) $NaBH_4$, I_2, THF, 0°C to rt

For the preparation of enantiomerically pure aminoalcohol **7** we have adopted the same strategy used for the resolution of other aminoalcohols.[18] Thus, compound **7** was conveniently protected and the resolution of its *N*-Cbz derivative **8** was carried out in *tert*-butyl methyl ether (TBME) at 40°C, using *Pseudomonas cepacia* lipase (PSL) as biocatalyst and vinyl acetate as the acyl donor (Scheme 3).

The enzyme reacted faster with the (*S*)-enantiomer of carbamate **8**, yielding the *O*-acetyl derivative (*S*)-**9** and the unreacted carbamate (*R*)-**8**. The enantiomeric ratio (*E*)[21] measured by means of the *ee*(s) and *ee*(p) was 59. This *E* value allowed us to obtain the remaining substrate with an *ee*>99% by stopping the reaction at a conversion value of 54% or higher. In order to obtain the absolute configuration, the optically active aminoalcohol (*R*)-**7** was converted into



Scheme 3. Key: (a) $PhCH_2OCOCl$, Na_2CO_3, H_2O–THF; (b) *Pseudomonas cepacea*, vinyl acetate, CH_3-O–*t*-Bu; (c) $RuCl_3 \cdot 2H_2O$, $NaIO_4$, water–tetrachloromethane–acetonitrile; (d) i. H_2 (2 atm), 10% Pd–C, methanol; ii. 7 M HCl; (e) H_2, 15% Pd–C, methanol; (f) DMAP, CH_2Cl_2, Ac_2O, Pyr

the perchlorate salt. The resulting (*R*)-**7**·$HClO_4$ was crystallized from a chloroform/methanol mixture for X-ray analysis.

On the other hand, oxidation of enantiomerically pure (*R*)-**8** with ruthenium(III) chloride and sodium periodate afforded *N*-Cbz protected amino acid (*R*)-**10** (Scheme 3), which upon hydrogenolysis and further treatment with 7 M HCl afforded (*R*)-(1-adamantyl)glycine hydrochloride, (*R*)-**1**·HCl, featuring a specific rotation of opposite sign compared with that previously described for the (*S*)-enantiomer.[11]

3. Experimental

3.1. Ethyl 2-(1-adamantyl)acetoacetate **5**

An improved procedure[22] was followed. A mixture of Co(II) complex of ethyl acetoacetate (1.526 g, 4.2 mmol), 1-bromoadamantane (2.012 g, 9.4 mmol), cobalt(II) chloride bis-triphenylphosphine (0.315 g, 0.5 mmol), lanthanum(III) bromide hexahydrate (0.215 g, 0.50 mmol) and chloroform (4 ml) was heated at 140°C in a closed glass reactor for 44 h (GLC monitoring). The cooled reaction mixture was partitioned between dichloromethane and 1N HCl. The organic phase was dried with sodium sulfate and evaporated. The residue was purified through a column of silica gel with hexanes–diethyl ether (98:2) as eluent to afford (0.891 g, 81%) as an oil: bp 125°C/0.4 mmHg (lit.[22] bp 170–175°C/4 mmHg); IR (film) 2907, 2851, 1729 (br) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 1.28 (t, $J=7.3$ Hz, 3H), 1.68–1.99 (12H), 2.23 (s, 3H), 3.20 (3H), 4.17 (q, $J=7.3$ Hz, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 14.0, 28.4, 31.8, 36.5, 39.8, 60.4, 69.5, 168.3, 202.7; MS (m/z) 264 (M^+, 1), 135 (100).

3.2. Ethyl N-acetyl-2-(1-adamantyl)glycinate **6**

Methanesulfonic acid (67 ml) was added into a magnetically stirred solution of **5** (14.842 g, 56.0 mmol) in dimethoxyethane (80 ml) maintained at −30°C (acetonitrile–liquid nitrogen bath). After 5 min sodium azide (11.364 g, 174.8 mmol) was added in three portions. The mixture was stirred for 15 min at −30°C and left to reach room temperature until evolution of gases ceased. Then more dimethoxyethane (20 ml) and finally aqueous ammonia were added until pH 8–9 was reached. The mixture was partially evaporated and the solution was extracted with dichloromethane. The organic phase was washed with water, dried, and evaporated. The residue was passed through a column of silica gel with mixtures of hexanes–ethyl acetate (v/v 8:1 to 1:3). Starting material **5** (0.940 g) and amidoester **6** (10.950 g, 70%) were obtained. Compound **6**: mp 111–113°C (hexanes–ethyl acetate); IR (KBr) 3269, 2926, 2902, 2851, 1734, 1648 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 1.30 (t, $J=7.3$ Hz, 3H), 1.53–1.73 (12H), 2.00 (s, 3H), 2.05 (s, 3H), 4.19 (q, $J=7.3$ Hz, 2H), 4.34 (d, $J=9.5$ Hz, 1H). ^{13}C NMR (62.5 Mz, $CDCl_3$): δ 14.0, 23.3, 28.2, 36.7, 38.7, 60.6, 60.9, 169.7, 171.3; MS (m/z) 279 (M^+, 1), 135 (100). Anal. calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 69.16 and 68.96; H, 8.90 and 8.80; N, 4.89 and 4.90.

3.3. rac-2-(1-Adamantyl)glycine hydrochloride **1**·HCl

A stirred mixture of amidoester **6** (10.935 g, 39.0 mmol) and 7 M hydrochloric acid (300 ml) was refluxed for 12 h. The mixture was filtered at room temperature and the solid was washed with cold 7 M HCl, with diethyl ether, and dried to afford **1**·HCl (8.129 g, 85%), mp 238–241°C (dec) (lit.[11] mp (*S*-isomer) 236–240°C (dec)); IR (KBr) 3555, 3484, 3025–2451 (br), 1737 cm^{-1}. ^1H NMR (250 MHz, methanol-D_4): δ 1.50–1.71 (12H), 1.93 (3H), 3.40 (s, 1H). ^{13}C NMR (62.5 MHz, methanol-D_4): δ 29.6, 35.7, 37.3, 39.3, 63.5, 170.4.

3.4. rac-2-(1-Adamantyl)glycine **1**

Propylene oxide (40 ml) was added to a solution of **1**·HCl (2.619 g, 11.0 mmol) in absolute ethanol (70 ml). The mixture was stirred at room temperature for 48 h, a white precipitate being formed. The solid was filtered, washed with absolute ethanol to afford free amino acid **1** (2.165

g, 97%), mp 287–288°C (ethanol); IR (KBr) 3081, 2906, 2850, 1649, 1627 cm^{-1}. ^1H NMR (250 MHz, methanol-D_4): δ 1.59–1.75 (12H), 1.95 (3H), 3.03 (s, 1H).

3.5. rac-*2-(1-Adamantyl)-2-aminoethanol* **7**

Amino acid **1** (4.541 g, 22.0 mmol) was added into a stirred suspension of sodium borohydride (2.512 g, 66.0 mmol) in anhydrous THF (55 ml) under argon atmosphere. The stirred mixture was cooled at 0°C and then a solution of iodine (6.230 g, 25.0 mmol) in anhydrous THF (30 ml) was added dropwise during 20 min. When the evolution of gas ceased the mixture was heated to reflux for 16 h. After cooling, methanol was added until transparency and stirring was continued for an additional 30 min. Solvents were evaporated and the pasty residue was dissolved into 20% aqueous sodium hydroxide and the alkaline solution was stirred for 4 h and then extracted with dichloromethane (4×50 ml). The organic extracts were dried and evaporated to afford aminoalcohol **7** (4.168 g, 97%), mp 97–98°C (dichloromethane); IR (KBr) 3444, 3369, 2905, 2850 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 1.25–1.75 (15H ($6CH_2$+NH_2+OH)), 1.99 (3H), 2.32 (dd, $J=10.2$ and 3.7 Hz, 1H), 3.24 (t, $J=10.2$ Hz, 1H), 3.70 (dd, $J=10.2$ and 3.7 Hz, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 28.3, 35.1, 37.2, 38.6, 61.2, 62.1; MS (m/z) 196 (M^+, 1), 164 (100). Aminoalcohol **7** reacted with one equivalent of phenylisocyanate in toluene at room temperature to afford the phenylurea, *N*-(1-adamantyl)-2-hydroxyethyl-*N′*-phenylurea, mp 189–190°C; IR (KBr) 3341, 2905, 2849, 1652 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 1.59–1.70 (12H), 1.90 (3H), 3.37 (dd, $J=7.3$ and 2.9 Hz, 1H), 3.45 (dd, $J=11.0$ and 7.3 Hz, 1H), 3.72 (dd, $J=11.0$ and 2.9 Hz, 1H), 6.86 (dt, $J=7.3$ and 1.5 Hz, 1H), 7.14 (t, $J=7.3$ Hz, 2H), 7.27 (apparent d, $J=11.0$ Hz, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 28.8, 36.7, 37.6, 39.7, 59.7, 60.9, 118.2, 121.6, 129.6, 141.8, 156.4; MS (m/z) 315 (M^+, 1), 283 (23), 164 (77), 135 (42), 93 (100). Anal. calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91. Found: C, 72.38 and 72.33; H, 8.18 and 8.13; N, 8.60 and 8.83.

3.6. rac-N-*(Benzyloxycarbonyl)-2-(1-adamantyl)-2-aminoethanol* ***8***

Benzyl chloroformate (0.95 ml, 6.7 mmol) was added via syringe into a stirred mixture of aminoalcohol **7** (0.989 g, 5.1 mmol) and sodium carbonate (0.683 g, 6.4 mmol) in the solvent system water (10 ml)–THF (3 ml) maintained at 0°C. The mixture was stirred at room temperature for 18 h (TLC monitoring) and then partitioned between dichloromethane and water. The organic phase was dried and evaporated to afford a white solid which was passed through a column of silica gel with hexanes–ethyl acetate (v/v 2:1) to afford **8** (1.198 g, 72%), mp 125–127°C; IR (KBr) 3377, 3239, 2901, 2849, 1695 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 1.52–1.73 (12H), 1.89 (s, 1H (OH)), 1.98 (3H), 3.40 (m, 1H), 3.57 (dd, $J=10.6$ and 8.5 Hz, 1H), 3.86 (dd, $J=10.6$ and 2.0 Hz, 1H), 4.90 (d, $J=9.1$ Hz, 1H), 5.12 (s, 2H), 7.34–7.39 (m, 5H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 28.2, 35.7, 36.9, 38.9, 61.2, 61.9, 67.0, 128.1, 128.5, 136.4, 157.6; MS (m/z) 254 (46), 135 (44), 91 (100). Anal. calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 73.09 and 73.02; H, 8.04 and 8.11; N, 4.09 and 4.00.

3.7. *Enzymatic resolution of compound* ***8****. Preparation of* (R)-N-*(benzyloxycarbonyl)-2-(1-adamantyl)-2-aminoethanol* (R)-***8*** *and* (S)-N-*(benzyloxycarbonyl)-2-(1-adamantyl)-2-aminoethanol acetate* (S)-***9***

Vinyl acetate (2 mmol) and 1 mmol of carbamate **8** were added to a suspension of

Pseudomonas cepacia lipase (PSL, from Amano Pharmaceuticals Co.) (320 mg) in *tert*-butyl methyl ether (3 ml) under nitrogen. The mixture was shaken at 40°C and 200 rpm during 24 hours. The enzyme was then filtered off and washed with dichloromethane (2×10 ml) and the organic solvents were evaporated off. The crude residue was subjected to column chromatography, with hexane–ethyl acetate (v/v 2:1) as eluent.

*3.8. (*S*)-*N*-(Benzyloxycarbonyl)-2-(1-adamantyl)-2-aminoethanol acetate (*S*)-**9***

The above described procedure gave 96% of (*S*)-**9** as a white solid, mp 75–77°C; IR (KBr) 3337, 1718, 1544, 1232 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.59–1.70 (m, 12H), 1.98 (br s, 6H), 3.60 (m, 1H), 4.17 (m, 2H), 4.79 (d, $J=9.7$ Hz, 1H), 5.12 (apparent q, 2H), 7.27–7.40 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7, 28.0, 32.7, 36.6, 38.7, 58.5, 62.8, 66.6, 127.6, 127.9, 128.1, 128.3, 136.4, 156.5; 171. 1; MS (m/z) 371 (100), 135 (100), 298 (80). $[\alpha]_D^{23}=-3.38$ ($c=0.59$, $CHCl_3$). Determination of ee for (*S*)-**9**, 84% by chiral HPLC (Chiralcel OD), hexane–propan-2-ol (90:10 v/v); in isochratic conditions (flux 0.8 ml min^{-1}) and the λ was 210 nm. The retention times of the enantiomers were 8.77 min for (*R*)-**9** and 10.55 min for (*S*)-**9**.

*3.9. (*R*)-*N*-(Benzyloxycarbonyl)-2-(1-adamantyl)-2-aminoethanol (*R*)-**8***

The above described procedure gave 82% of (*R*)-**8** as a white solid, mp 114–116°C; $[\alpha]_D^{23}=-3.86$ ($c=0.75$, $CHCl_3$). Determination of ee for (*R*)-**8**, >99% by chiral HPLC after derivatization to the known ester (*R*)-**9**. The retention time of the enantiomer (*R*)-**8** was 8.77 min; *R*s, 2.06.

*3.10. (*R*)-2-(1-Adamantyl)-2-aminoethanol (*R*)-**7**·$HClO_4$*

A solution of (*R*)-**8** (0.170 g, 0.52 mmol) in absolute methanol (3 ml) was hydrogenated in the presence of 15% Pd/C (0.026 g) at room temperature for 12 h. The mixture was filtered (Celite) and washed with methanol. Then, perchloric acid (0.050 ml, 0.83 mmol) was added and the mixture was stirred for 5 min. The solvent was evaporated to afford (*R*)-**7**·$HClO_4$, mp 233–235°C; $[\alpha]_D^{23}=-15.6$ ($c=0.68$, methanol).

*3.11. (*R*)-*N*-(Benzyloxycarbonyl)-2-(1-adamantyl)glycine (*R*)-**10***

Ruthenium(III) chloride dihydrate (0.009 g, 3.7×10^{-2} mol) was added into a stirred mixture of carbamate (*R*)-**8** (0.328 g, 1.0 mmol), sodium periodate (0.905 g, 4.2 mmol), tetrachloromethane (2 ml), acetonitrile (2 ml), and water (3 ml). The mixture darkened immediately. It was stirred overnight at room temperature, then dichloromethane was added and the organic layer separated, dried, and evaporated to give a residue which was dissolved in diethyl ether. The ether solution was passed through Celite and evaporated. The residue was chromatographed through a column of silica gel with mixtures of hexanes–ethyl acetate of increasing polarity to afford (*R*)-**10** (0.193 g, 56%), mp 184–186°C (hexanes–ethyl acetate); IR (KBr) 3402, 2910, 2852, 1728, 1696 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 1.63–1.72 (12H), 2.00 (3H), 4.09 (d, $J=9.6$ Hz, 1H), 5.11 (s, 2H), 5.38 (d, $J=9.6$ Hz, 1H (NH)), 7.34–7.36 (m, 5H), 10.31 (br s, 1H (COOH)). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 28.2, 36.3, 36.5, 38.5, 62.9, 67.2, 128.2, 128.5, 136.4, 156.6, 176.1; $[\alpha]_D=-14$ ($c=0.85$, chloroform).

3.12. (R)-2-(1-Adamantyl)glycine hydrochloride (R)-1·HCl

A solution of (*R*)-**10** (0.182 g, 0.5 mmol) in methanol (10 ml) was hydrogenated overnight at 2 atmospheres under stirring in the presence of 10% Pd–C. Then, 7 M HCl was added and the mixture was stirred for 10 min, then filtered through Celite, and the Celite eluted with more methanol. The solvent was evaporated to afford (*R*)-**1**·HCl (0.120 g, 92%), mp 237–241°C (dec); $[\alpha]_D = -18$ ($c = 0.67$, methanol) (lit.[11] $[\alpha]_D$ (*S*-isomer) $= +16$ ($c = 0.50$, methanol)).

3.13. X-Ray of (R)-7·$HClO_4$

Colourless crystal, size 0.3×0.2×0.1 mm. Throughout the experiment Cu Kα radiation was used with a graphite crystal monochromator on an Nonius KappaCCD single-crystal diffractometer ($\lambda = 1.54178$ Å). Data collection[23] was divided in 4 ω-scans with a total amount of 414 frames, each one 1° width and being exposed during 12 s. Data were scaled and merged together and cell refined over 15479 reflections[24] with a final $R_{int} = 0.066$ resulting in 1477 'unique' reflections in the *hkl* range (–25, 0, 0) and (27, 8, 9) ($2.72 < \theta < 50.45$). The space group was determined to be $P2_12_12$ from systematic absences and structure determination.

The structure was solved by Patterson methods using DIRDIF.[25] Initial isotropic and further anisotropic least-squares refinement, using SHELX97,[26] converged to a final $R = 0.051$ and WR2 = 0.110 for 847 'observed' reflections and $R = 0.099$ an WR2 = 0.132 for all data. Empirical absorption correction[27] was made with minimum and maximum transmission factor of 0.205 and 1.000. All non-hydrogen atoms except C34 were anisotropically refined. Hydrogen atoms were geometrically placed. The function minimised was $\Sigma w(F_o - F_c)^2$, $w = 1/[\sigma^2(F_o^2) + (0.0786P)^2]$ with $\sigma(F_o^2)$ from counting statistics and $P = (\max(F_o^2, O) + 2*F_c^2)/3$. The maximum shift to e.s.d. ratio in the last full-matrix least-squares cycle was 0.014 and the final difference Fourier map showed no peaks higher than 0.25 e Å^{-3} nor deeper than –0.23 e Å^{-3}. Absolute configuration was checked refining Flack parameter[28] $\chi = -0.02(5)$. The ORTEP type diagram was obtained using EUCLID package.[29]

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