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An improved synthesis of enantiopure 2-azabicyclo[2.2.1]heptane-3-carboxylic acid

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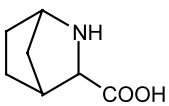
Abstract—A facile multigram scale preparation of (1*R*,3*S*,4*S*)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid via stereoselective synthesis of the corresponding α-amino ester hydrochloride is detailed. Hitherto applied protocols for the synthesis of this cyclic proline analogue involving a tedious chromatographic purification step could thus be considerably improved upon. The specific rotation of the α-amino acid reported in the literature has been revised.

1. Introduction

The bicyclic proline analogue, *exo*-2-azabicyclo-[2.2.1]heptane-3-carboxylic acid **1**, has received much interest in the field of peptide chemistry[1] and in the design of chiral ligands used in asymmetric catalysis.[2]



1

In general, the syntheses of **1** reported to date[1c,3] are based on the finding that chiral imines of the type **2** react with cyclopentadiene to give the [4+2]-cycloadduct **3** with high diastereoselectivity (Scheme 1).[4] As the groups of Mellor and Andersson have shown, (1*R*,3*S*,4*S*)-**3a** can be accessed by use of the enantiopure benzyl ester (*R*)-**2a** in the hetero-Diels–Alder reaction.[1c,3] Hydrogenation of the double bond and concomitant removal of the benzyl and phenylethyl groups by hydrogenolysis in the presence of Pd/C affords (1*R*,3*S*,4*S*)-**1**. The main disadvantage of this elegant one-pot approach is associated with the prior purification of the crude **3a** by tedious flash chromatography in order to obtain enantio- and diastereomerically pure (1*R*,3*S*,4*S*)-**3a**. Therefore, this method is limited to small-scale preparation.

In our current work we required larger quantities of enantiopure (1*R*,3*S*,4*S*)-**1** and its ester **5**. Although the asymmetric synthesis of the free amino ester of **5** utilizing **3b** as intermediate has been already reported by Andersson et al. the large-scale preparation of this compound is likewise hampered by the chromatographic purification of **3b**.[5]

Herein we report a short and facile pathway for the synthesis of the target compounds under the avoidance of flash chromatography. A crucial issue of our approach is based on the observation that catalytic hydrogenation of the double bond in **3b** can be achieved chemoselectively without significant hydrogenolysis of the exocyclic N–C bond when low loading of Pd/C is applied. Moreover, we found that hydrochloride (1*R*,3*S*,4*S*)-**4** is a readily crystallizing solid offering therefore the opportunity to isolate it directly after hydrogenation and subsequent acidification.

In our first trials we synthesized **3b** according to the original protocol of Stella and Abraham.[4a,b] Thus, imine (*R*)-**2b** was generated in situ from ethyl glyoxyl-

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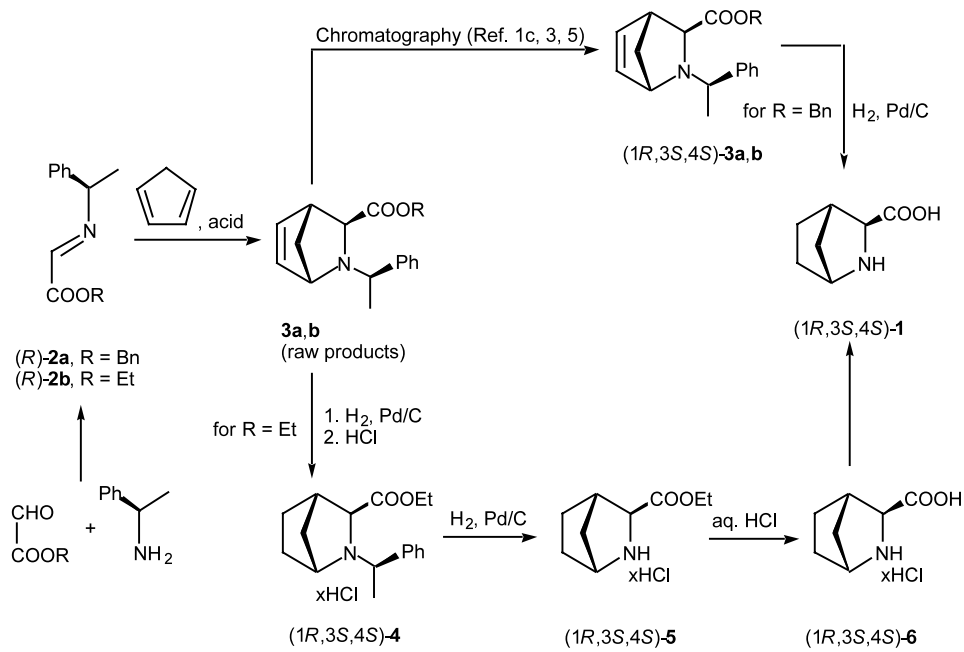


Scheme 1.

ate and (*R*)-phenylethylamine, followed by hetero-Diels–Alder reaction, which was accelerated by CF_3COOH and $BF_3{\cdot}Et_2O$ (method A) at low temperature (–60°C). The crude product **3b** was isolated and then hydrogenated in the presence of 5% Pd/C (0.3–0.4% by weight) at 50 bar H_2 pressure in EtOH. After separation of the catalyst an excess of concentrated HCl was added and the volatiles were evaporated. Finally, (1*R*,3*S*,4*S*)-**4** crystallized after trituration of the semi-solid hydrochloride with Et_2O/*i*-PrOH (5:1 mixture) and was isolated in an overall yield of 32%.

In order to improve the yield of the hydrochloride, in our next trials we isolated the pure imine (*R*)-**2b** prior to the hetero-Diels–Alder–reaction and reacted it with cyclopentadiene in the presence of CF_3COOH/$BF_3{\cdot}Et_2O$ in CH_2Cl_2 (–60°C, method B) and aqueous CF_3COOH in DMF (ambient temperature, method C),[6] respectively. The latter reaction has been reported to be similarly effective and stereoselective as the previous. The application of these procedures, followed by hydrogenation and salt formation gave hydrochloride (1*R*,3*S*,4*S*)-**4** with overall yields of 31 and 47%, respectively. Besides a good yield no polymeric side products were found by application of method C. Thus, it contrasted advantageously method B where the formation of polymeric impurities complicated isolation of the hydrochloride **4**.

Hydrogenolytic cleavage of the 1-phenylethyl group of the tertiary amine (1*R*,3*S*,4*S*)-**4** proceeded cleanly in the presence of Pd/C in ethanol at 15 bar H_2 pressure. Noteworthy is the fact that no side products which might be expected to arise in acidic media, were formed.[7] Hence, a facile access to the multigram preparation of α-amino acid ester (1*R*,3*S*,4*S*)-**5** was found. Hydrolysis of the ethyl ester (1*R*,3*S*,4*S*)-**5** with 5 M aqueous HCl gave quantitatively the hitherto unknown hydrochloride of α-amino acid (1*R*,3*S*,4*S*)-**6**. The free base (1*R*,3*S*,4*S*)-**1** was liberated by using Dowex 50×8 cation-exchange resin.

Surprisingly, we found that the specific rotation of our product (1*R*,3*S*,4*S*)-**1**, $[\alpha]_D^{22} = -1.2$ (*c* 1, H_2O), had the opposite sign and a different absolute value in comparison with that reported in the literature, $[\alpha]_D^{25} = +5.9$ (*c* 1, H_2O).[3] To confirm the correctness of our finding the enantiomeric α-amino acid (1*S*,3*R*,4*R*)-**1** was synthesised starting from (*S*)-1-phenylethylamine. The specific rotations of relevant enantiomeric intermediates and products compounds are given in Table 1. These data clearly show that specific rotations differ only in the sign but not in the absolute values.

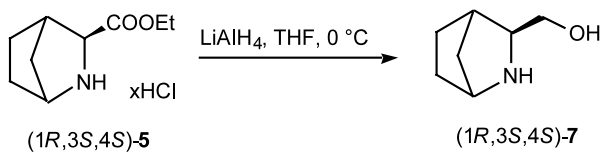
To obtain additional evidence that the configurations detailed in Scheme 1 are correct a sample of (1*R*,3*S*,4*S*)-**5** was transformed into the known amino alcohol (1*R*,3*S*,4*S*)-**7** according to Scheme 2.[5]

The specific rotation of (1*R*,3*S*,4*S*)-**7**, $[\alpha]_D^{24} = +59.9$ (*c* 1, $CHCl_3$), correlates with the specific rotation for its

Table 1. Comparison of specific rotations for enantiomeric amino acids **1** and intermediates

Compound	$[\alpha]_D^{22-25}$ (Solvent)[a]
(1*R*,3*S*,4*S*)-**5**	+16.2 (MeOH)
(1*S*,3*R*,4*R*)-**5**	−16.3 (MeOH)
(1*R*,3*S*,4*S*)-**6**	+22.3 (MeOH)
(1*S*,3*R*,4*R*)-**6**	−22.8 (MeOH)
(1*R*,3*S*,4*S*)-**1**	−1.2 (H_2O)
(1*S*,3*R*,4*R*)-**1**	+1.4 (H_2O)

[a] *c* 1.



(1*R*,3*S*,4*S*)-**5** (1*R*,3*S*,4*S*)-**7**

Scheme 2.

enantiomer (1*S*,3*R*,4*R*)-**7**, $[\alpha]_D^{26} = -62.9$ (*c* 1.03, $CHCl_3$) reported in the literature.[5]

2. Conclusion

In conclusion we have improved the stereoselective synthesis of α-amino ester hydrochloride (1*R*,3*S*,4*S*)-**5** and thus a fast and convenient access to enantiomeric 2-azabicyclo[2.2.1]heptane-3-carboxylic acids (1*R*,3*S*,4*S*)-**1** and (1*S*,3*R*,4*R*)-**1**, respectively, on multigram scale avoiding chromatographic purification is disclosed. The specific rotation of (1*R*,3*S*,4*S*)-**1** given in the literature is also revised.

3. Experimental

NMR spectra were recorded using a Bruker ARX 400. Chemical shifts (δ, in ppm) are given for ^1H NMR relative to TMS as internal standard and for ^{13}C NMR relative to residual solvent peaks (77.36 ppm for $CDCl_3$, and 49.86 for CD_3OD). Coupling constants (*J*) are given in Hz. The optical rotation was measured on a 'gyromat-HP' instrument (Fa. Dr. Kernchen). Melting points are corrected. Cyclopentadiene was obtained from its dimer by heating at 200°C. The monomer was received in a cooled flask and kept in dry ice. Ethyl glyoxylate was depolymerised by distillation in vacuum at 50 mbar (bath temperature 100°C) and used within a few hours.

3.1. Ethyl 2-[(*R*)-1-phenylethyl]iminoethanoate 2b

A cooled (0°C) solution of EtO_2CCHO (25.6 g, 0.25 mol) in Et_2O (150 mL) was treated by slow addition of (*R*)-1-phenylethylamine (30.5 g, 0.25 mol), followed by the addition of $MgSO_4$ (45 g, 0.38 mol). The reaction mixture was stirred overnight at ambient temperature, then the solids were filtered off and washed with Et_2O. The filtrate was concentrated and the residue was distilled in vacuo to give imine **2b** (41 g, 80%). Bp 95–98°C/0.05 mbar. ^1H NMR ($CDCl_3$), δ (ppm): 1.31 (3H, t, $J=7.0$, $\underline{CH_3}CH_2$), 1.59 (3H, d, $J=6.7$, $\underline{CH_3}CH$), 4.31 (2H, q, $J=7.0$, $\underline{CH_2}CH_3$), 4.58 (1H, q, $J=6.7$, $\underline{CH}CH_3$), 7.20–7.38 ($5H_{arom.}$, m), 7.72 (1H, s, CH=N). ^{13}C NMR ($CDCl_3$), δ (ppm): 14.2 (CH_3), 23.8 (CH_3), 61.8 (CH_2), 69.7 (CH), 128.7 (CH), 127.6 (CH), 126.9 (CH), 142.8 (C), 152.4 (CH), 163.3 (C).

3.2. Ethyl (1*R*,3*S*,4*S*)-2-[(*R*)-1-phenylethyl]-2-azabicyclo-[2.2.1]heptane-3-carboxylate hydrochloride 4

Method A. To a cooled (0°C) mixture of ethyl glyoxylate (25.6 g, 0.25 mol), molecular sieves (4 Å, 50 g) and CH_2Cl_2 (600 mL) (*R*)-phenylethylamine (30.5 g, 0.25 mol) was added slowly (30 min) with stirring. When the addition was complete the mixture was stirred for 1 h at the same temperature. The mixture was then cooled to −60°C and CF_3COOH (19.3 mL, 0.25 mol) and $BF_3{\cdot}Et_2O$ (31 mL, 0.25 mol) were added followed by freshly distilled cyclopentadiene (20 g, 0.25 mol). The resulting mixture was kept at −60°C for an additional 2 h (after 1 h the mixture solidified). The reaction mixture was allowed to warm to ambient temperature and left overnight then treated with aqueous $NaHCO_3$ (60 g in 500 mL of water). The layers were separated and the aqueous phase was additionally extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtrated and evaporated to give the crude product **3b** (62.4 g).

In a typical hydrogenation procedure the crude product (17 g) was hydrogenated over Pd/C (5%, 0.6 g) in abs. EtOH (10 mL) at 50 bar initial H_2 pressure. After the H_2 uptake had ceased (typically after 4 h) the mixture was filtered through Celite and the residue washed with abs. EtOH. To the filtrate, conc. HCl (7 mL) was added and then the mixture was evaporated. The procedure was repeated several times with fresh portions of EtOH until a semi-crystalline residue was formed. This was treated with a Et_2O/*i*-PrOH (5:1) mixture until crystals precipitated. The mixture was kept overnight in a freezer and then the mixture filtered. The solid collected was washed successively with an Et_2O/*i*-PrOH (5:1) mixture and Et_2O and dried to afford hydrochloride (1*R*,3*S*,4*S*)-**4** (7.3 g). When all of the starting material was hydrogenated the hydrochloride was isolated in an overall yield of 25.3 g (32.6%).

Method B. A solution of imine **2b** (15 g, 0.073 mol) in CH_2Cl_2 (100 mL) was cooled to −60°C and sequentially treated with CF_3COOH (5.7 mL, 0.074 mol), $BF_3{\cdot}Et_2O$ (9.3 mL, 0.073 mol) and cyclopentadiene (7.3 g, 0.11 mol). When the addition was complete the reaction mixture was stirred overnight at ambient temperature and poured into a solution of $NaHCO_3$ (20 g, 0.24 mol) in water (300 mL). The product was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to dryness. Hydrogenation of the crude product in the presence of Pd/C (5%, 0.7 g) in abs. EtOH (12 mL) under the conditions given above and subsequent treatment with conc. HCl (8 mL) afforded hydrochloride (1*R*,3*S*,4*S*)-**4** (7.1 g, 31.4%).

Method C. A solution of imine **2b** (15 g, 0.073 mol) in DMF (48 mL) was treated with CF_3COOH (5.7 mL, 0.074 mol), cyclopentadiene (9.7 g, 0.147 mol) and water (0.04 g, 2.2 mmol). The mixture was stirred at ambient temperature overnight, poured into aqueous $NaHCO_3$ (12.6 g, 0.15 mol) in water (300 mL). The product was extracted with Et_2O. The extract was washed with conc. $NaHCO_3$ solution and brine. After evaporation of the solvents the crude product was hydrogenated and pure material was isolated as described above yielding hydrochloride (1*R*,3*S*,4*S*)-**4** (10.7 g, 47%). An analytically pure sample was obtained by recrystallization from EtOH–Et_2O). Mp

203–205°C. $[\alpha]_D^{22} = -7.3$ (*c* 1, MeOH). ^{1}H NMR (CD_3OD), δ (ppm): 0.97 (3H, t, $J = 7.1$ Hz, $\underline{CH_3}CH_2$), 1.77 (2H, d, $J = 6.7$ Hz, $\underline{CH_3}CH$), 1.90–2.10 (5H, m), 2.22–2.36 (1H, m), 2.80 (1H, s), 3.80 (1H, s), 3.84–4.00 (2H, m, $\underline{CH_2}CH_3$), 4.56 (1H, s), 4.61 (1H, q, $J = 6.7$, $\underline{CH}CH_3$), 7.41–7.48 ($3H_{arom.}$, m), 7.63–7.71 ($2H_{arom.}$, m). ^{13}C NMR (CD_3OD), δ (ppm): 15.1 (CH_3), 19.7 (CH_3), 22.5 (CH_2), 29.2 (CH_2), 37.5 (CH_2), 43.9 (CH), 64.6 (CH), 64.8 (CH_2), 67.1 (CH), 72.3 (CH), 130.8 (CH), 131.1 (CH), 131.9 (CH), 137.4 (C), 169.9 (C). Anal. calcd for $C_{17}H_{24}ClNO_2$: C, 65.90; H, 7.81; N, 4.52. Found: C, 66.24; H, 7.62; N, 4.57%.

3.3. Ethyl (1*R*,3*S*,4*S*)-2-azabicyclo[2.2.1]heptane-3-carboxylate hydrochloride 5

In a typical experiment hydrochloride (1*R*,3*S*,4*S*)-**4** (17.7 g, 0.057 mol) were hydrogenated in the presence of 5% Pd/C (1.7 g) in abs. EtOH (20 mL) at 15 bar H_2 pressure. After 4 days the uptake of H_2 ceased and the mixture was filtered through Celite. The solids were washed with abs. EtOH. The combined washing solutions were evaporated and the residue was washed with Et_2O/EtOH, Et_2O and dried to give amino acid ester hydrochloride (1*R*,3*S*,4*S*)-**5** (11.1 g, 94.5%). An analytically pure sample was obtained by recrystallization from (EtOH–Et_2O). Mp 153–154°C; $[\alpha]_D^{22} = +16.2$ (*c* 1, MeOH). ^{1}H NMR (CD_3OD), δ (ppm): 1.36 (3H, t, $J = 7.1$, $\underline{CH_3}CH_2$), 1.67–1.80 (3H, m), 1.83–2.00 (3H, m), 3.01 (1H, s), 4.13 (1H, s), 4.22 (1H, s), 4.29–4.41 (2H, m, $\underline{CH_2}CH_3$). ^{13}C NMR (CD_3OD), δ (ppm): 15.2 (CH_3), 27.0 (CH_2), 28.5 (CH_2), 36.4 (CH_2), 42.7 (CH), 61.3 (CH), 64.8 (CH), 65.1 (CH_2), 170.7 (C). Anal. calcd for $C_9H_{15}ClNO_2$: C, 52.82; H, 7.39; N, 6.85. Found: C, 53.01; H, 7.63; N, 6.91%.

3.4. (1*R*,3*S*,4*S*)-2-Azabicyclo[2.2.1]heptane-3-carboxylic acid hydrochloride 6

A solution of hydrochloride **5** (1.3 g, 6.3 mmol) in aqueous HCl (6 M, 10 mL) was heated under reflux for 6 h. Evaporation to dryness and subsequent recrystallization of the residue from *i*-PrOH/Et_2O gave analytically pure material (0.95 g, 84.9%). Mp 237–238°C (dec.). $[\alpha]_D^{22} = +22.3$ (*c* 1, MeOH). ^{1}H NMR (CD_3OD), δ (ppm): 1.62–1.79 (3H, m), 1.83–1.97 (3H, m), 3.02 (1H, s), 4.05 (1H, s), 4.21 (1H, s). ^{13}C NMR (CD_3OD), δ (ppm): 27.1 (CH_2), 28.6 (CH_2), 36.32 (CH_2), 42.7 (CH), 61.2 (CH), 64.8 (CH), 172.0 (C). Anal. calcd for $C_7H_{12}ClNO_2$: C, 47.33; H, 6.81; N, 7.89. Found: C, 47.85; H, 6.66; N, 7.96%.

3.5. (1*R*,3*S*,4*S*)-2-Azabicyclo[2.2.1]heptane-3-carboxylic acid 1

Hydrochloride **6** (1.5 g, 8.4 mmol) was transformed into the free base using cation-exchange resin Dowex 50×8. After recrystallization from EtOH–Et_2O analytically pure product was obtained (1.1 g, 90%). Mp 230–235°C (dec.). $[\alpha]_D^{22} = -1.2$ (*c* 1, H_2O). ^{1}H NMR (CD_3OD), δ (ppm): 1.54–1.69 (2H, m), 1.70–1.93 (4H, m), 2.93 (1H, s), 3.59 (1H, s), 4.16 (1H, s). ^{13}C NMR (CD_3OD), δ (ppm): 27.4 (CH_2), 28.9 (CH_2), 36.0 (CH_2), 42.7 (CH), 60.3 (CH), 66.7 (CH), 174.1 (C). Anal. calcd for $C_7H_{11}NO_2 \times 0.25H_2O$: C, 57.72; H, 7.80; N, 9.62. Found: C, 57.91; H, 7.82; N, 9.56%. (After drying under vacuum at 80°C over P_2O_5 the elemental analysis was consistent with the non-hydrated amino acid, calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.86; N, 9.92. Found: C, 59.58; H, 7.77; N, 9.75%)

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