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A novel approach to 2,4-ethanoproline

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ABSTRACT

A novel approach to 2-azabicyclo[2.2.1]heptane-1-carboxylic acid (2,4-ethanoproline) is reported starting from (2*S*,4*R*)-4-hydroxyproline. The synthetic scheme consists of 10 steps and results in 22% total yield of the title compound. Enantiomeric purity of the product is checked by chiral stationary phase HPLC.

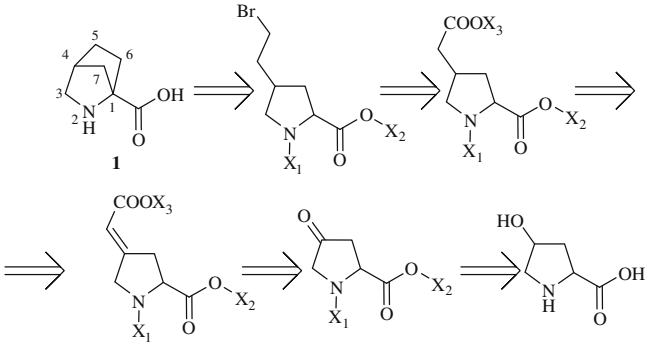
1. Introduction

Conformational restriction has been proven to be an efficient tool in various areas of organic and medicinal chemistry, particularly for drug design.[1] Synthesis of constrained and rigid amino acids has given rise to considerable interest in the last decade.[2] Among the numerous rigid amino acids synthesized, proline analogues are the most frequently encountered, due to the unique properties of this proteinogenic amino acid.[2,3]

Recently, we have reported the synthesis of 2-azabicyclo[2.2.1]heptane-1-carboxylic acid (2,4-ethanoproline) **1**, a rigid bicyclic proline analogue.[4] Despite the fact that the synthetic sequence was short (five steps), it resulted in only 2% total yield of the amino acid. Moreover, both enantiomers of **1** were formed in 1:1 ratio, therefore, tedious separation of diastereomeric derivatives was needed. Herein we wish to report an alternative and more practical approach to the synthesis of 2,4-ethanoproline.

2. Results and discussion

The key idea of the novel retrosynthetic scheme for 2,4-ethanoproline is a C1–C6 disconnection of the target molecule (Scheme 1). To the best of our knowledge, it is the first time this approach has been applied to the construction of 2-azabicyclo[2.2.1]heptane system. However, an analogous idea has been widely exploited for the synthesis of 7-azabicyclo[2.2.1]heptane derivatives.[5] Further retrosynthetic modification led us to 4-hydroxyproline as a starting material, both enantiomers of which are commercially available. The success of the approach depends critically on the choice of the protection groups X_1–X_3 (Scheme 1). It has been shown previously that Cbz N-protection is optimal for the base-induced cyclization step on formation of similar bicyclic cores.[5] To avoid the reductive cleavage of this protecting group during the hydrogenation of the double bond, a Boc group was decided to be used in the first steps of the synthesis, and then replaced by the Cbz protecting group. X_2 and X_3 protecting groups should be orthogonal, so methyl and *tert*-butyl groups (respectively) were chosen.



Scheme 1. Retrosynthetic analysis of 2,4-ethanoproline **1**.

The synthesis is outlined in Scheme 2. (2*S*,4*R*)-4-hydroxyproline was transformed into the protected derivative **3** by the procedures described previously.[6] Oxidation of **3** was performed with CrO_3-pyridine leading to the 4-oxoproline derivative **4**.[7] We have found that Wittig–Horner olefination of **4** using LHDMS as a base gives a better yield of **5** (85%, *E*/*Z* mixture) than Peterson olefination applied by Kondo et al. to synthesize an analogous compound.[8] Hydrogenation of **5** proceeded in a diastereoselective manner resulting in the formation of **6** (up to 84% de by NMR). Change of protecting group in **6** was accompanied by side chain carboxylic group deprotection necessary for the next steps and led to **7**.[9] Reduction of **7** via a mixed anhydride allowed alcohol **8** to be obtained. At this point of the synthesis, the relative configuration at the chiral centres of the molecule was assigned by NOESY measurements (correlation between 2-C*H* and 4-C*H* of pyrrolidine moiety was observed). Compound **8** was subjected to a Mitsunobu

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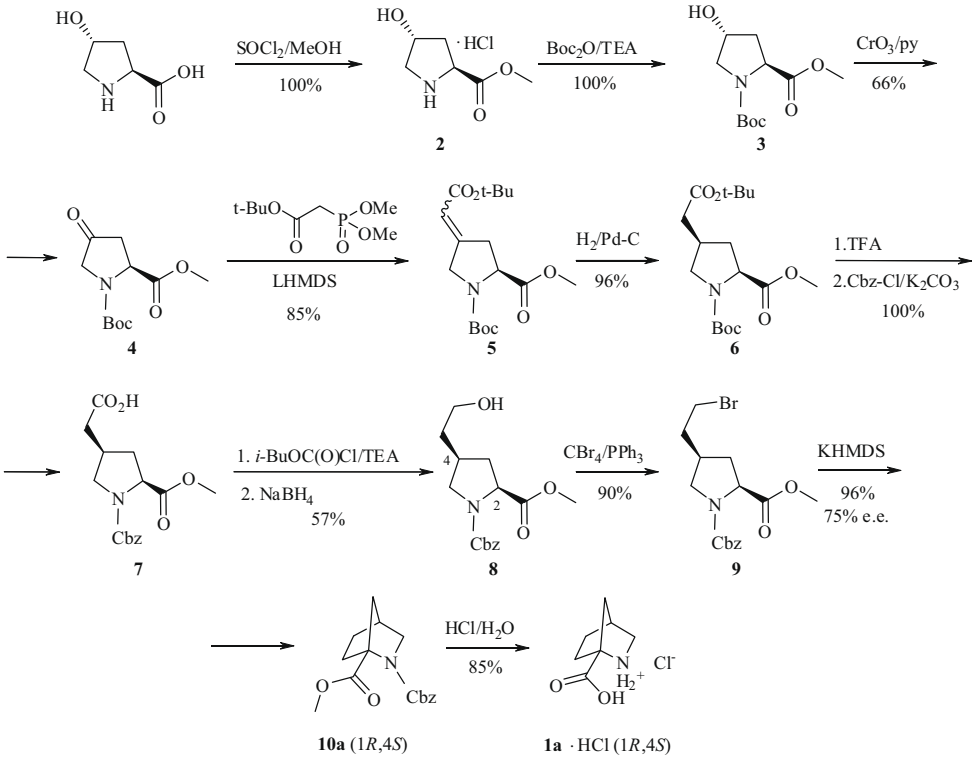

Scheme 2. Synthesis of 2,4-ethanoproline **1**.

reaction to give the bromide **9**. Cyclization of **9** induced by KHMDS resulted in an excellent yield of the desired 2,4-ethanoproline derivative **10a**, which was transformed into the amino acid **1a** (as the hydrochloride) by acidic hydrolysis.

To establish the enantiomeric purity of the product, compound **10a** was analyzed by chiral stationary phase HPLC. As the reference, we used a sample of a single enantiomer of 2,4-ethanoproline **1b** (1*S*,4*R*) with the known configuration obtained previously.[4] Standard methods were used to synthesize *N*-Cbz-protected methyl ester **10b** from this sample to compare with **10a**. It has been found that **10a** obtained by the novel method had moderate enantiomeric purity (75% ee) Nevertheless, good chromatographic separation of the enantiomers has been achieved at analytical scale.

It is interesting to note, that the synthetic approach to 2,4-ethanoproline described above is stereoselective, despite the fact, that both the stereogenic centres of the starting (2*S*,4*R*)-hydroxyproline were racemized at the corresponding steps. The stereoselectivity is ensured by sequential 1,3-induction of chirality during the synthesis, which is rather efficient in the conformationally restricted pyrrolidine core.

The synthesis allows the title compound to be obtained in 22% yield (10 steps, 75% ee) starting from 4-hydroxyproline. It should be noted that both enantiomers of 2,4-ethanoproline can be prepared, as both (2*S*,4*R*)- and (2*R*,4*S*)-4-hydroxyproline are commercially available.

3. Experimental

3.1. General

All reagents were purchased from the Aldrich Chemical Co. and were used without further purification. Solvents were dried, when necessary, by standard methods. The progress of the reactions was monitored by thin layer chromatography (TLC) on Merck 60 F240 precoated silica gel polyester plates, and products were visualized under UV light (254 nm), iodine vapour or ninhydrin chromatic reaction whichever was appropriate. Column chromatography was performed using Merck silica gel (40–60 μm). The solvents used as HPLC mobile phases were of chromoscan grade. IR spectra were registered on a Mattson Genesis FTIR spectrophotometer; ν_{max} is given for the main absorption bands. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity-300 or a Bruker ARX-300 instrument in $CDCl_3$, using the residual solvent signal as the internal standard; chemical shifts (δ) are given in parts per million and coupling constants (J) are given in hertz. Optical rotations were measured at room temperature using a PerkinElmer 241 Polarimeter-C in a 10-cm cell of 1-mL capacity. High-resolution mass spectra were obtained on a high-resolution VG-autospectrometer. HPLC was carried out using a Waters HPLC system equipped with a Waters 600-E pump and a Waters 991 photodiode array detector.

3.2. (*S*)-1-*tert*-Butoxycarbonyl-4-oxoproline methyl ester 4[7]

To a solution of pyridine (20 ml) in dichloromethane (50 ml), powdered chromium(VI) oxide (11.4 g) was slowly added upon stirring at 0 °C. The mixture was stirred for 0.5 h, and solution of 3.11 g of **3** in dichloromethane (40 ml) was added. The resulting mixture was stirred at ambient temperature overnight. The solution was decanted from the slurry formed, and the residue was washed thoroughly with dichloromethane. The combined organic phases were washed with saturated sodium bicarbonate, aqueous citric acid and brine, dried over magnesium sulfate and evaporated. The residue was chromatographed (hexane–ethyl acetate (1:1) as an eluent) to give 1.98 g (66%) of **4** as colourless oil. For spectral and physical data, see Ref. 7.

3.3. (*S*)-1-*tert*-Butyl 2-methyl 4-(2-*tert*-butoxy-2-oxoethylidene)-pyrrolidine-1,2-dicarboxylate 5

To a solution of *tert*-butyl *P*,*P*-dimethylphosphonoacetate (1.48 ml, 7.5 mmol) in absolute THF, 7.5 ml of 1.0 M LHMDS solu-

tion in THF was added under argon atmosphere upon stirring. The resulting mixture was stirred for 0.5 h, and then it was slowly added to a solution of 1.65 g of **4** in absolute THF at 0 °C. The mixture was stirred at 0 °C for 15 min, at ambient temperature for 45 min, and was then quenched with saturated aqueous ammonium chloride. THF was removed in vacuo, and the residue was diluted with water and extracted with ethyl acetate. The combined organic extracts were dried over magnesium sulfate and evaporated. The residue was passed through short silica gel column (hexane–ethyl acetate (2:1) as an eluent) to give 1.97 g (5.8 mmol, 85%) of **5** as yellowish oil. The compound is a mixture of *E/Z* isomers, both appearing as mixtures of *E/Z* rotamers at the amide bond. IR (cm^{-1}): 1750, 1707. HRMS (*m/z*): calcd for $C_{17}H_{27}NNaO_6$ 364.1730, found 364.1716. ^1H NMR ($CDCl_3$, δ): 5.70–5.78, 5.56–5.59 (2m, 1H, C=C*H*), 4.95–5.03, 4.42–4.62 (2m, 2H), 4.22–4.26 (m, 1H), 3.72 (br s, 3H, COOCH_3), 3.29–3.33, 2.98–3.16, 2.73–2.78 (3m, 2H), 1.41–1.48 (m, 18H, COOC(CH_3)$_3$). ^{13}C NMR ($CDCl_3$, δ): 173.1, 172.6, 168.8, 165.4, 165.4 and 165.0 (*C*O*t*-Bu), 155.7, 154.8, 154.4 and 153.8 (*C*OOMe), 136.5 and 136.4 (*C*=CH), 121.6, 121.4, 116.3 and 115.9 (C=*C*H), 80.7, 80.6, 80.5 and 80.2 (COO*C*(CH$_3$)$_3$), 66.8, 66.4, 59.3, 58.7, 57.5, 57.1, 52.4 and 52.3 (COO*C*H$_3$ and 2-*C*H), 55.3, 55.0, 52.0 and 50.9 (5-*C*H$_2$), 37.7, 37.0, 36.2 and 35.3 (3-*C*H$_2$), 28.5, 28.4, 28.2 and 28.1 (COOC(*C*H$_3$)$_3$).

3.4. (2*S*,4*R*)-1-*tert*-Butyl 2-methyl 4-(2-*tert*-butoxy-2-oxoethyl)-pyrrolidine-1,2-dicarboxylate 6

A mixture of 1.82 g of **5** dissolved in methanol and 0.18 g of 10% palladium on charcoal was stirred under atmospheric pressure of hydrogen for 1 h, and was then filtered over Celite and evaporated to dryness to give 96% yield of **6** as colourless oil. The de of the product **6** (as well as in the case of **7**–**9**) is 84% by NMR. For spectroscopic and physical data, see Ref. 8.

3.5. 2-((3*R*,5*S*)-1-(Benzyloxycarbonyl)-5-(methoxycarbonyl)-pyrrolidin-3-yl)acetic acid 7[9]

In a mixture of trifluoroacetic acid (25 ml) and dichloromethane (30 ml) 6.04 g (17.6 mmol) of **6** was dissolved and stirred for 1.5 h, and was then evaporated to dryness. The residue was dissolved in 50 ml of water, and 12.3 g of potassium carbonate was carefully added followed by 2.5 ml of Cbz-chloride at 0 °C upon stirring. The mixture was stirred for 5 h at ambient temperature, and was then washed with dichloromethane, acidified with 1 N hydrochloric acid to pH 1–2 and extracted with ethyl acetate. The combined organic extracts were dried over magnesium sulfate and were evaporated to give 5.62 g (100% yield) of **7** as colourless oil. Spectral data for the major (*cis*-) diastereomer are given. The compound is a mixture of *E/Z* rotamers at the amide bond. IR (cm^{-1}): 3150, 1738, 1728. HRMS (*m/z*): calcd for $C_{16}H_{18}NO_6$ (M−H) 320.1140, found 320.1128. ^1H NMR ($CDCl_3$, δ): 7.99 (br s, 1H, COO*H*), 7.28–7.37 (m, 5H, C$_6$*H*$_5$), 5.01–5.20 (m, 2H, OC*H*$_2$Ph), 4.37 (t, *J* = 8.0 Hz, 0.5H, 2-C*H*), 4.32 (t, *J* = 7.9 Hz, 0.5H, 2-C*H*), 3.92 (m, 1H, 5-C*H*$_2$), 3.75 (s, 1.5H, COOC*H*$_3$), 3.55 (s, 1.5H, COOC*H*$_3$), 3.19 (m, 1H, 5-C*H*$_2$), 2.58 (m, 2H, 3-C*H*$_2$ and 4-C*H*), 2.49 (C*H*$_2$COOH), 1.69 (m, 1H, 3-C*H*$_2$). ^{13}C NMR ($CDCl_3$, δ): 177.2 and 177.1, 173.2 and 173.1, 155.1 and 154.6 (*C*OOCH$_3$), 136.2 and 136.0 (*ipso*-*C*$_6$H$_5$), 128.6, 128.6, 128.3, 128.3, 128.2 and 128.1 (*o*-, *m*- and *p*-*C*$_6$H$_5$), 67.8, 59.1, 58.9, 52.6, 52.4, 52.2, 51.8, 36.9, 36.8, 36.6, 35.6, 34.5, 33.9.

3.6. (2*S*,4*R*)-1-Benzyl 2-methyl 4-(2-hydroxyethyl)pyrrolidine-1,2-dicarboxylate 8

To a solution of 4.76 g of **7** and 4.2 ml of triethylamine in dry THF (40 ml), 2.3 ml of isobutyl chloroformate was added dropwise upon stirring at −20 °C. The resulting mixture was stirred at −20 °C for 1 h, and a solution of 3.37 g of sodium borohydride in water (40 ml) was added carefully. The mixture was warmed to room temperature and stirred for 1 h, and was then quenched with saturated sodium bicarbonate. THF was removed in vacuo, and the residue was diluted with water and was extracted with ethyl acetate. The combined organic extracts were dried over magnesium sulfate and evaporated. The residue was chromatographed (ethyl acetate as an eluent) to give 2.54 g (57% yield) of **8** as colourless oil. Spectral data for the major (*cis*-) diastereomer are given. The compound is a mixture of *E/Z* rotamers at the amide bond. IR (cm^{-1}): 3466, 1747, 1705. HRMS (*m/z*): calcd for $C_{16}H_{21}NNaO_5$ (M+Na) 330.1312, found 330.1300. ^1H NMR ($CDCl_3$, δ):7.28–7.36 (m, 5H, C$_6$*H*$_5$), 5.17 (d, *J* = 12.4 Hz, 1H, C*H*$_2$Ph), 5.08 (d, *J* = 12.4 Hz, 0.5H, C*H*$_2$Ph), 5.00 (d, *J* = 12.3 Hz, 0.5H, C*H*$_2$Ph), 4.31 (dd, *J* = 8.7 Hz and 8.0 Hz, 0.5H, 2-C*H*), 4.28 (dd, *J* = 8.8 Hz and 7.9 Hz, 0.5H, 2-C*H*), 3.89 (dd, *J* = 10.4 Hz and 7.4 Hz, 0.5H, 5-C*H*$_2$), 3.82 (dd, *J* = 10.2 Hz and 7.6 Hz, 0.5H, 5-C*H*$_2$), 3.74 (s, 1.5H, COOC*H*$_3$), 3.64 (m, 2H, CH$_2$C*H*$_2$OH), 3.53 (s, 1.5H, COOC*H*$_3$), 3.11 (t, *J* = 10.2 Hz, 1H, 5-C*H*$_2$), 2.48 (m, 1H, 3-C*H*$_2$), 2.31 (m, 1H, 4-C*H*), 1.78 (br s, 1H, O*H*), 1.65 (m, 2H, C*H*$_2$CH$_2$OH), 1.61 (m, 1H, 3-C*H*$_2$). ^{13}C NMR ($CDCl_3$, δ): 173.4 and 173.3 (N*C*(O)OCH$_2$Ph), 154.8 and 154.2 (COOCH$_3$), 136.6 and 136.4 (*ipso*-*C*$_6$H$_5$), 128.5, 128.4, 128.1, 128.0, 127.9 (*o*-, *m*- and *p*-*C*$_6$H$_5$), 67.2 (OCH$_2$Ph), 61.1 (*C*H$_2$OH), 59.3 and 59.0 (COO*C*H$_3$), 52.5, 52.3, 52.2, 52.1, 37.2, 36.3, 35.8, 35.4, 35.3, 35.1.

3.7. (2*S*,4*R*)-1-Benzyl 2-methyl 4-(2-bromoethyl)pyrrolidine-1,2-dicarboxylate 9

To a solution of 1.20 g of **8** and 1.80 g of tetrabromomethane in 10 ml of absolute dichloromethane, a solution of 1.42 g of triphenylphosphine in dichloromethane was added dropwise under an argon atmosphere upon stirring at −10 °C. The resulting mixture was slowly warmed to room temperature over 4 h, and was then evaporated and chromatographed (hexane–ethyl acetate (2:1) as an eluent) to give 1.31 g (90%) of **9** as colourless oil. Spectral data for the major (*cis*-) diastereomer are given. The compound is a mixture of the rotamers at the amide bond. IR (cm^{-1}): 1748, 1708. HRMS (*m/z*): calcd for $C_{16}H_{20}BrNNaO_4$ (M+Na) 392.0468, found 392.0473. (M+2) isotope peak characteristic for bromine is present. ^1H NMR ($CDCl_3$, δ): 7.27–7.37 (m, 5H, C$_6$*H*$_5$), 5.18 (d, *J* = 12.4 Hz, 1H, OC*H*$_2$Ph), 5.09 (d, *J* = 12.3 Hz, 0.5H, OC*H*$_2$Ph), 5.01 (d, *J* = 12.4 Hz, 0.5H, OC*H*$_2$Ph), 4.34 (t, *J* = 8.1 Hz, 0.5H, 2-C*H*), 4.31 (t, *J* = 8.2 Hz, 0.5H, 2-C*H*), 3.91 (dd, *J* = 10.3 Hz and 7.3 Hz, 0.5 H, 5-C*H*$_2$), 3.83 (dd, *J* = 10.0 Hz and 7.5 Hz, 0.5H, 5-C*H*$_2$), 3.75 and 3.54 (2s, 3H, COOC*H*$_3$), 3.37 (m, 2H, C*H*$_2$Br), 3.13 (t, *J* = 9.9 Hz, 1H, 5-C*H*$_2$), 2.37–2.54 (m, 2H), 1.96 (m, 2H), 1.62 (m, 1H). ^{13}C NMR ($CDCl_3$, δ): 173.3 and 173.2 (N*C*(O)OCH$_2$Ph), 154.7 and 154.2 (COOCH$_3$), 136.6 and 136.5 (*ipso*-*C*$_6$H$_5$), 128.6, 128.5, 128.2, 128.2, 128.1, 128.0 (*o*-, *m*- and *p*-*C*$_6$H$_5$), 67.4, 67.3, 59.2 and 59.0 (COO*C*H$_3$), 52.5, 52.2, 51.9, 51.5, 37.2, 36.5, 35.5, 35.5, 31.3.

3.8. (1*R*,4*S*)-2-Benzyl 1-methyl 2-azabicyclo[2.2.1]heptane-1,2-dicarboxylate 10a

To a solution 0.95 g of **9** in freshly distilled absolute THF (10 ml), 6.4 ml of 0.5 M KHMDS in toluene was added slowly over 20 min under an argon atmosphere at −78 °C. The mixture was stirred under the following conditions: at −78 °C for 1 h, −78 °C to −40 °C for 1 h, at −40 °C for 2.5 h, −40 °C to rt for 1 h and at rt for 1 h, and was then cooled to 0 °C and quenched with saturated ammonium chloride. THF was removed in vacuo, and the residue was diluted with water and extracted with ethyl acetate. The combined organic extracts were dried over magnesium sulfate and evaporated. The residue was chromatographed (hexane–ethyl acetate (2:1) as an

eluent) to give 0.70 g (96% yield) of **10a** as a colourless oil. The compound is a mixture of the rotamers at the amide bond. $[\alpha]_D$ = +5.0 (*c* 0.034, $CHCl_3$). IR (cm^{-1}): 1744, 1704. HRMS (*m/z*): calcd for $C_{16}H_{19}NNaO_4$ (M+Na) 312.1206, found 312.1204. ^1H NMR ($CDCl_3$, δ): 7.26–7.37 (m, 5H, C_6H_5), 4.97–5.22 (m, 2H, OCH_2Ph), 3.80 and 3.39 (2s, 3H, $COOCH_3$), 3.53 (br s, 1H, *exo*-3-CH_2), 3.40 (d, *J* = 9.1 Hz, 0.5H, *endo*-3-CH_2), 3.30 (d, *J* = 9.3 Hz, 0.5H, *endo*-3-CH_2), 2.58 (s, 1H, 4-C*H*), 2.17 (td, *J* = 12.5 Hz and 5.2 Hz, 1H, *endo*-5-CH_2), 2.03 (m, 1H, 7-CH_2), 1.95–2.11 (m, 1H, 6-CH_2), 1.86 (tddd, *J* = 12.3 Hz, 6.9 Hz, 4.5 Hz and 1.4 Hz, 1H, *exo*-5-CH_2), 1.77 (d, *J* = 9.5 Hz, 7-CH_2), 1.51 (m, 1H, 6-CH_2). ^{13}C NMR ($CDCl_3$, δ): 176.2 and 171.6 (N*C*(O)OCH_2Ph), 154.8 ($COOCH_3$), 136.8 and 136.3 (*ipso*-C_6H_5), 128.5, 128.3, 128.2, 128.1, 128.0, 127.9 (*o*-, *m*- and *p*-C_6H_5), 69.6 and 69.4, 67.4 and 67.0, 55.9 and 55.1, 52.4 and 52.0, 44.6 and 43.6, 31.8 and 37.4, 32.3 and 31.4, 28.0 and 27.8.

3.9. (1*R*,4*S*)-2-Benzyl 1-methyl 2-azabicyclo[2.2.1]heptane-1,2-dicarboxylate 10b

To a solution of 0.11 g of **1b**[4] in absolute methanol (3 ml), 0.5 ml of thionyl chloride was added at 0 °C. The mixture was kept for 72 h (additional 0.5 ml of thionyl chloride was added after 24 h), and was then evaporated and dried in vacuo. The residue was dissolved in dichloromethane, and 0.28 ml of triethylamine was added upon stirring followed by 0.14 ml of Cbz-Cl at 0 °C. The resulting mixture was stirred for 24 h, and was then washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography (hexane–ethyl acetate (11:9) as an eluent) to give 0.16 g (69%) of **10b** as a colourless oil. $[\alpha]_D$ = −7.3 (*c* 0.012, $CHCl_3$). All the other spectral and physical data are the same as those in the case of compound **10a**.

3.10. (1*R*,4*S*)-2-Azabicyclo[2.2.1]heptane-1-carboxylic acid 1a

Compound **10a** (194 mg) was refluxed in 5 ml of 3 N hydrochloric acid for 14 h, and then washed with dichloromethane and evaporated to dryness to give 101 mg (85%) of **1a** hydrochloride as a white solid. Further purification of the product can be performed as described elsewhere.[4] For spectral and physical data, see Ref. 4.

3.11. HPLC analysis of 10a

HPLC analysis of **10a** was carried out by injections of 20 μL of 7 g/ml solution onto 150 × 4.6 mm ChiralPack IC® column using hexane–chloroform–2-propanol (85:5:10) as an eluent (flow rate: 1 mL/min) with UV monitoring performed at 248 nm. The capacity (k), selectivity (α) and resolution (R_s) factors are defined as follows: $k = (R_t - R_{t0})/R_{t0}$, $\alpha = k_1/k_2$, and $R_s = 1.18(R_{t2} - R_{t1})/(w_2 + w_1)$, where subscripts 1 and 2 refer to the first and second eluted enantiomers, w_1 and w_2 denote their half-height peak widths; R_{t1} and R_{t2} denote the retention times, and R_{t0} is the dead time. A sample of **10b** prepared from **1b** as described above was used as a reference.Resolution parameters: R_t(**10a**) = 17.5 min, R_t(**10b**) = 12.6 min, R_s = 5.4, α = 1.5. Ee = 75%.

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