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Synthesis of racemic and enantiopure 3,4-methanonipecotic acid

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ABSTRACT

The synthesis of both racemic and enantiomerically pure (1*R*,6*S*)-3,4-methanonipecotic acid, a cyclopropane-containing β-amino acid, which is a valuable building block for drug discovery, is described. The synthetic scheme commences from natural (*S*)-malic acid and allows for the preparation of the title compound in 12 steps in 28% overall yield. A novel approach to the racemic 3,4-methanonipecotic acid, which relies on a Simmons–Smith cyclopropanation as the key step, was also developed. In this case, the product was obtained in 8 steps and 38% total yield.

1. Introduction

Natural products provide us a boundless pool of ideas for design; many examples of the successful application of this concept can be found in the literature.[1] Non-proteinogenic amino acids exhibit a class of natural products that are rarely found in higher organisms but are widespread in bacteria and plants. The functions of these amino acids vary significantly, and in many cases are yet to be established. Cyclopropane amino acids represent a special subtype of non-proteinogenic natural amino acids that are embodied in coronamic acid **1** (*Pseudomonas corona-facience*), carnosadine **2** (*Grateloupia carmosa*), cleonine **3** (*Streptomyces verticillus*), *trans*-3,4-methanoglutamic acid **4** (*Blighia unuugata*) and 3,4-methanoproline **5** (*Aesculus parviflora*) (Fig. 1).[2] The latter compound is an example of bicyclic cyclopropane-containing amino acids which are also incorporated (as a part of polycyclic systems) into the molecules of lenticellarines **6**–**8** (*Dysoxylum lenticellare*).[3]

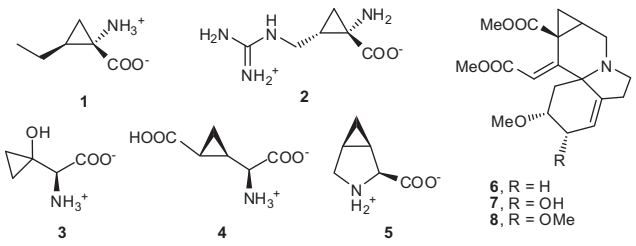

Figure 1. Naturally occurring cyclopropane amino acids and their derivatives.

The idea of bicyclic cyclopropane amino acids has previously been applied to the design of tailor-made α- and γ-amino acids, that is, proline analogues **9**[4] and **10**[5] and 3,4-methanoisonipecotic acid **11** (Fig. 2).[6] This concept was also used in the synthesis of β-proline analogues **12**,[7] **13**,[8] and **14**.[9] β-Amino acids have been shown to exhibit an intrinsic conformational behavior when incorporated into β-peptides; on the other hand, β-amino acid derivatives are often characterized by potent biological activity.[10] In particular, nipecotic acid **15** reveals GABA reuptake inhibitor activity;[11] the oligomers of **15** appear to adopt a regular secondary structure which is not stabilized by hydrogen bonds.[12]

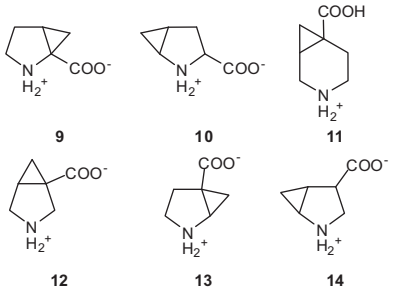

Figure 2. Synthetic bicyclic cyclopropane α- and γ-amino acids.

If the concept described above is applied to the molecule of amino acid **15**, structures **16**–**19** are generated (Fig. 3). Recently, the synthesis of the racemic compound **17** was described (Scheme 1).[13] The key step of this seven-step reaction sequence

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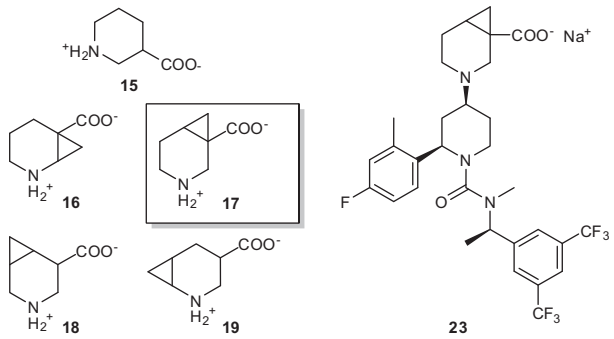
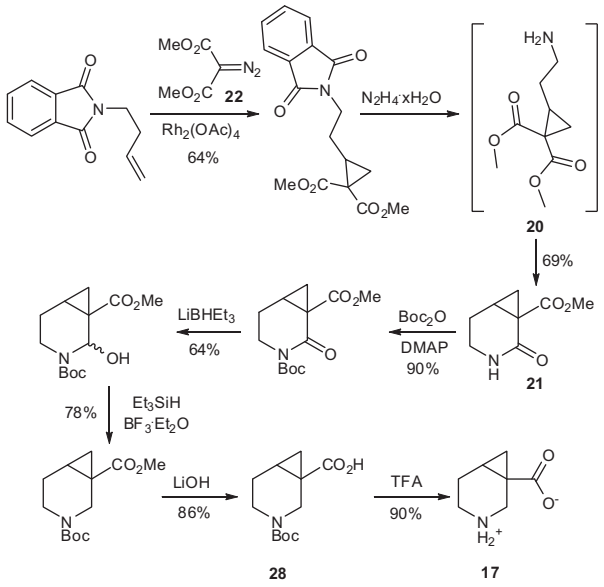


Figure 3. Nipecotic acid **15**, its cyclopropane-containing methanologues and biologically active derivative of **17**.



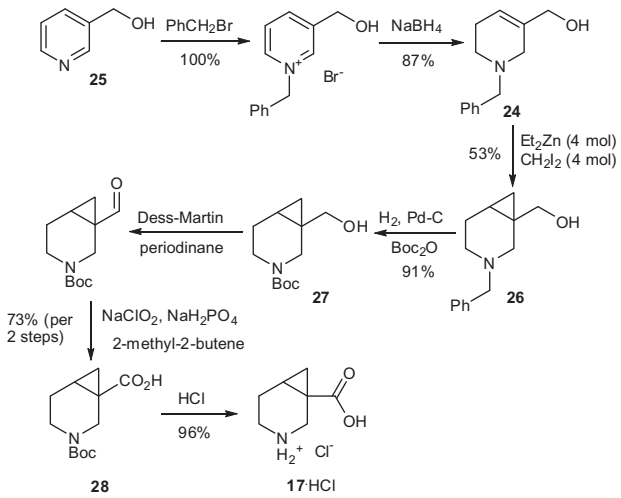
Scheme 1. Literature synthesis of racemic compound **17**.

included intramolecular cyclization of the in situ generated amino ester **20** to give bicyclic lactone **21**. This method involved the use of explosive and shock sensitive diazomalonate **22** in refluxing chlorobenzene in the first step, which might limit scaling up of the synthesis.

It was found that a derivative of amino acid **17**, compound **23**, was found to be a subnanomolar neurokinin NK1 receptor antagonist ($pK_i = 9.8$) (Fig. 3).[14] This result demonstrates the utility of compound **17** as a building block for medicinal chemistry. Herein we report a novel approach to racemic amino acid **17**, as well as synthesis of its enantiomerically pure (1*R*,6*S*)-isomer.

2. Results and discussion

Our approach to the synthesis of racemic **17** relied on a Simmons–Smith cyclopropanation of the known amino alcohol **24**, prepared in two steps from the readily available 3-pyridinylmethanol **25** (Scheme 2).[15] It should be noted that previous work stated that the cyclopropanation of analogues of **24** under various conditions was unsuccessful.[13] We have found that reaction of **24** with a 4-fold excess of diethylzinc–diiodomethane system gave the expected product **26** in 53% yield. This reaction was performed successfully on a 100 g scale. After changing the



Scheme 2. Our synthesis of racemic amino acid **17**.

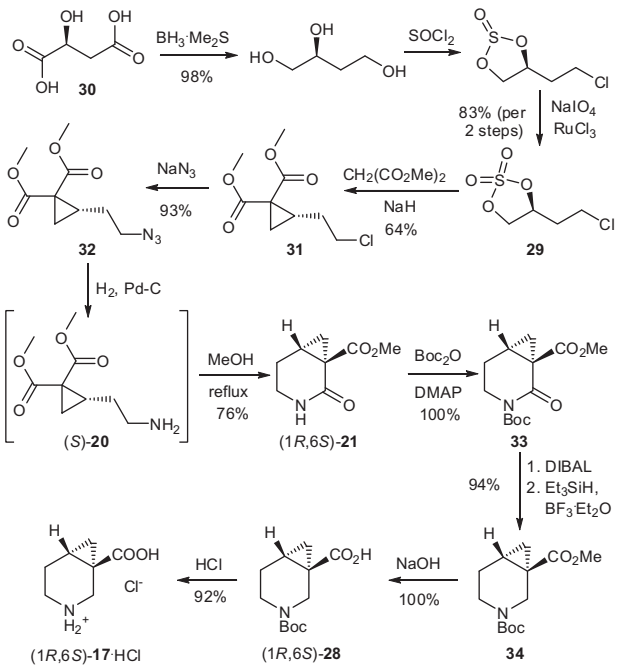
protecting group, alcohol **27** was subjected to a two-step oxidation sequence (first with Dess–Martin periodinane, then using Pinnick reaction) to give the Boc derivative **28**. Removal of the protecting group in the molecule of **28** using a modified known procedure[13] allowed amino acid **17** to be obtained as the hydrochloride.

For the preparation of enantiomerically pure amino acid **17**, we used a strategy similar to that described for the preparation of racemic **17**.[13] However, for the preparation of enantiomerically pure amino ester **20**, the known enantiopure chloride **29** was taken, which was previously used in the syntheses of cyclopropane-containing amino acids, such as 2,3-methanoproline **9**.[16] Compound **29** can be prepared from natural (*S*)-malic acid **30** in three steps (Scheme 3). The reaction of **29** with diethyl malonate and NaH gave the cyclopropane derivative **31**. In turn, the reaction of **29** with NaN_3 in CH_3CN led to the formation of azide **31**. Catalytic hydrogenation of **31** was accompanied by partial cyclization, to give a mixture of (*S*)-**20** and (1*R*,6*S*)-**21**. To complete the cyclization of (*R*)-**20**, this mixture was refluxed in methanol. Finally, the bicyclic lactone (1*R*,6*S*)-**21** was transformed into enantiomerically pure (1*R*,6*S*)-**17** (as the hydrochloride) in five steps analogous to those shown in Scheme 1 for the racemate. It should be noted that in our hands, the reduction of lactam **33** with $LiBHEt_3$ under the reaction conditions described for the racemate[13] did not give reproducible results. An alternative procedure involving the use of DIBAL as the reducing agent[17] was employed instead, which gave excellent results.

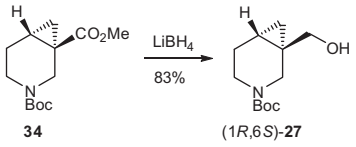
To prove the enantiomeric purity of the product, ester **34** was reduced with $LiBH_4$ to give alcohol (1*R*,6*S*)-**27** (Scheme 4). Both racemic and enantiopure samples of **27** were analyzed by chiral stationary phase HPLC; the enantiomeric excess of (1*R*,6*S*)-**27** was found to be 91.5%.

3. Conclusion

A novel approach to racemic 3,4-methanonipecotic acid was developed. An eight-step reaction sequence involving a Simmons–Smith cyclopropanation as the key step allowed the title compound to be obtained in 38% overall yield. An approach to enantiomerically pure (1*R*,6*S*)-3,4-methanonipecotic acid has also been described. In this case, the target product was obtained in 12 steps and 28% overall yield from natural (*S*)-malic acid.



Scheme 3. Synthesis of enantiomerically pure amino acid (1*S*,6*R*)-**17**.



Scheme 4.

4. Experimental

4.1. General

Solvents were purified according to standard procedures. Alcohol **24**[15] and chloride **29**[16] were prepared using reported procedures. All other starting materials were purchased from Acros, Merck, Fluka, and UkrOrgSyntez. 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 the 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)]. Flash chromatography was performed using Combiflash Companion chromatograph with 12 g or 40 g RediSep column. Chiral stationary phase HPLC analyses of **27** were performed on an Agilent 1100/1200 instrument, Chiralpak IA 250 mm × 4.6 mm column, Hexanes–*i*-PrOH (95:5) as eluent, 0.6 mL/min, 2 μL injection volume, 25 °C, detection at 215 nm.

4.2. (3-Benzyl-3-azabicyclo[4.1.0]heptan-1-yl)methanol 26

A solution of CH_2I_2 (536 g, 2.00 mol) in CH_2Cl_2 (500 mL) was added dropwise to a solution of Et_2Zn (1 M in Hexanes, 2 L, 2.00 mol) in CH_2Cl_2 (500 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h, after which a solution of alcohol **24** (101.6 g, 0.500 mol) in CH_2Cl_2 (1 L) was added dropwise at −10 to 0 °C. The resulting mixture was stirred at 0 °C for 2 h then warmed to rt overnight with stirring and cooled again to 0 °C. Next, 2 M aq HCl (1.5 L) was added dropwise with external cooling and stirring (CAUTION! Highly exothermic reaction and violent gas evolution). The organic phase was separated and extracted with 2 M aq HCl (2 × 300 mL). The combined aqueous phases were made alkaline (pH = 12–14) with 40% aq KOH upon external cooling. The product was extracted with CH_2Cl_2 (4 × 450 mL). The combined organic extracts were dried over Na_2SO_4, and evaporated to dryness to give the product **26**. 57.6 g (53%). Colorless oil. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.17; H, 9.06; N, 6.29. MS (CI): 218 (MH^+). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.15 (m, 5H), 3.49 (d, J = 13.3 Hz, 1H), 3.43 (d, J = 13.3 Hz, 1H), 3.40 (s, 2H), 2.76 (d, J = 11.2 Hz, 1H), 2.72 (br s, 1H), 2.68 (d, J = 11.2 Hz, 1H), 2.27–2.18 (m, 1H), 2.16–2.09 (m, 1H), 2.02–1.93 (m, 1H), 1.82–1.68 (m, 1H), 0.89 (dd, J = 13.4, 7.9 Hz, 1H), 0.65–0.58 (m, 1H), 0.53 (dd, J = 9.1, 4.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4 (*C*), 128.8 (*CH*), 128.1 (*CH*), 126.8 (*CH*), 70.4 (CH_2), 62.6 (CH_2), 55.4 (CH_2), 49.4 (CH_2), 23.6 (CH_2), 23.1 (CH_2), 15.1 (CH_2), 13.8 (*CH*).

4.3. *tert*-Butyl 1-(hydroxymethyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate 27

To a solution of alcohol **26** (21.7 g, 0.100 mol) in MeOH (300 mL), 10% Pd-C (8 g) was added under an argon atmosphere, followed by Boc_2O (32.7 g, 0.250 mol). The mixture was hydrogenated at 50 °C and 70 bar for 48 h. The catalyst was filtered off, and the filtrate was evaporated to dryness to give product **27**. Yield 20.7 g (91%). Colorless oil. Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.19; H, 8.94; N, 6.46. MS (CI): 228 (MH^+). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.86–3.65 (br m, 1H), 3.63–3.19 (br m, 4H), 3.01 (br s, 1H), 2.15 (br s, 1H), 1.93 (dt, J = 12.5, 5.7 Hz, 1H), 1.66 (s, 1H), 1.44 (s, 9H), 1.03–0.90 (m, 1H), 0.66–0.58 (m, 1H), 0.37 (t, J = 5.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.9 (*C*=O), 79.2 (*C*), 69.0 (CH_2), 44.3 and 44.0 (CH_2), 40.8 and 39.6 (CH_2), 28.0 (CH_3), 22.1 (*C*), 21.8 (CH_2), 14.1 (CH_2), 13.4 (*CH*).

4.4. 3-(*tert*-Butoxycarbonyl)-3-azabicyclo[4.1.0]heptane-1-carboxylic acid 28

A mixture of alcohol **27** (20.2 g, 92.9 mmol) and Dess–Martin periodinane (47.3 g, 0.111 mol) in CH_2Cl_2 (500 mL) was refluxed overnight, then cooled and diluted with hexanes (170 mL). The precipitate was filtered off, and the filtrates were evaporated to dryness. The crude aldehyde obtained was used in the next step without further purification. Next, it was dissolved in acetone (300 mL), and H_2O (300 mL), Na_2HPO_4 (66.8 g, 0.557 mol), 2-methyl-2-butene (26.1 g, 0.372 mol), and $NaClO_2$ (80%, 31.5 g, 0.279 mol) were added. The mixture was stirred vigorously for 24 h. Most of the acetone was removed in vacuo, and the residue was extracted with CH_2Cl_2 (4 × 150 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated in vacuo. The residue was triturated with 10% aq K_2CO_3 (300 mL). The resulting mixture was washed with CH_2Cl_2 (3 × 100 mL). The aqueous phase was acidified with 10% aq citric acid to pH = 1–3 and extracted with CH_2Cl_2 (4 × 150 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated in vacuo to give product **28**.

Yield 16.4 g (73% per two steps). Colorless oil. For other spectroscopic and physical data, see Ref. 13.

4.5. 3-Azabicyclo[4.1.0]heptane-1-carboxylic acid, hydrochloride 17·HCl

Saturated HCl in dioxane (75 mL) was added to a solution of **28** (5.08 g, 21.2 mmol) in EtOAc (150 mL). The mixture was stirred overnight and evaporated in vacuo. The residue was triturated with acetone and filtered. The solid was dried in vacuo to give the hydrochloride of **17** as a white solid. Yield 4.60 g (96%). Colorless solid. Mp >200°C (dec.). Anal. Calcd for $C_7H_{12}ClNO_2$: C, 47.33; H, 6.81; Cl, 19.96; N, 7.89. Found: C, 47.53; H, 7.13; Cl, 19.60; N, 8.06. ^{1}H NMR (500 MHz, D_2O) δ 4.18 (d, J = 14.0 Hz, 1H), 3.14–3.04 (m, 1H), 2.97 (d, J = 14.0 Hz, 1H), 2.63 (td, J = 12.4, 3.9 Hz, 1H), 2.22–2.09 (m, 1H), 1.91 (d, J = 14.8 Hz, 1H), 1.81 (dd, J = 15.0, 7.9 Hz, 1H), 1.57 (dd, J = 9.3, 5.2 Hz, 1H), 1.06–0.97 (m, 1H). ^{13}C NMR (126 MHz, D_2O) δ 176.2 (*C*=O), 42.7 (*C*H$_2$), 37.8 (*C*H$_2$), 20.9 (*C*H$_2$), 19.6 (*C*H), 18.5 (*C*), 18.3 (*C*H$_2$).

4.6. (*R*)-Dimethyl 2-(2-chloroethyl)cyclopropane-1,1-dicarboxylate 31

Chloride **29** (23.6 g, 0.126 mol) and dimethyl malonate (15.1 mL, 0.133 mol) were dissolved in absolute toluene (400 mL) under argon. Lithium *tert*-butoxide (21.2 g, 0.265 mol) was added to the reaction mixture in portions at 0 °C. The mixture was stirred at room temperature overnight and then quenched with 20% aq NH_4Cl (25 mL). After 15 min, H_2O (200 mL) was added, and the phases were separated. The aqueous phase was washed with toluene (200 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated. The crude mixture was purified by fractional distillation at 1.4 mbar to give diester **31** as a colorless liquid. Yield 17.7 g (64%). Bp 81–82 °C (1.4 mbar). $[\alpha]_D^{22} = -30.5$ (c 1.0, $CHCl_3$). Anal. Calcd for $C_9H_{13}ClO_4$: C, 48.99; H, 5.94; Cl, 16.07. Found: C, 49.36; H, 5.61; Cl, 16.23. MS (EI): 220/222 (M^+). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.73 (s, 3H), 3.58 (t, J = 6.6 Hz, 2H), 2.10–2.02 (m, 1H), 1.96–1.87 (m, 1H), 1.76–1.68 (m, 1H), 1.50–1.41 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 168.0, 52.3, 52.2, 42.9, 33.0, 31.4, 25.4, 20.2.

4.7. (*S*)-Dimethyl 2-(2-azidoethyl)cyclopropane-1,1-dicarboxylate 32

Diester **31** (17.7 g, 80.2 mmol) was dissolved in CH_3CN (160 mL) and H_2O (40 mL). Sodium azide (7.82 g, 120 mmol), sodium iodide (60 mg, 0.4 mmol), and tetrabutylammonium bromide (260 mg, 0.8 mmol) were added. The resulting mixture was refluxed until the reaction was completed (monitored by NMR, ca. 6 d). After cooling to rt, the mixture was diluted with H_2O (250 mL) and extracted with *tert*-butyl methyl ether (2 × 200 mL). The combined extracts were dried over Na_2SO_4 and evaporated to give **32** as a colorless liquid which was used without further purification. Yield 16.9 g (93%). $[\alpha]_D^{22} = -61.1$ (c 1.0, $CHCl_3$). Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.24; H, 5.63; N, 18.27. MS (EI): 199 (M^+-N_2), 140, 108. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (s, 3H), 3.67 (s, 3H), 3.32 (t, J = 6.6 Hz, 2H), 1.95–1.86 (m, 1H), 1.65 (td, J = 12.9, 6.3 Hz, 1H), 1.48 (td, J = 14.0, 6.9 Hz, 1H), 1.44–1.38 (m, 1H), 1.38–1.33 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8 (*C*=O), 167.9 (*C*=O), 52.24 (*C*H$_3$), 52.17 (*C*H$_3$), 50.1 (*C*H$_2$), 33.2 (*C*), 27.8 (*C*H$_2$), 25.1 (*C*H), 20.2 (*C*H$_2$).

4.8. (1*R*,6*S*)-Methyl 2-oxo-3-azabicyclo[4.1.0]heptane-1-carboxylate (1*R*,6*S*)-21

The crude azide **31** (5.80 g, 25.5 mmol) was dissolved in MeOH (400 mL) (*the dilution is critical!*) and 10% Pd on charcoal (5.0 g) was added. Hydrogen was bubbled through this mixture under vigorous stirring at rt until the starting material has disappeared (monitored by TLC; ca. 3 h). The suspension was filtered, and the filtrate was diluted with additional MeOH (400 mL). The solution was refluxed for 16 h and then evaporated in vacuo to give crude (1*R*,6*S*)-**21** as a white solid, which was used without further purification. An analytical sample was obtained by recrystallization from diethyl ether/methanol mixture. Yield 3.29 g (76%). White solid. Mp 132–134 °C. $[\alpha]_D^{22} = -35.8$ (c 1.0, $CHCl_3$). For other spectroscopic and physical data, see Ref. 13.

4.9. (1*R*,6*S*)-3-*tert*-Butyl 1-methyl 2-oxo-3-azabicyclo[4.1.0]heptane-1,3-dicarboxylate 33

4-(Dimethylamino)pyridine (1.36 g, 11.1 mmol) was added to a solution of lactam (1*R*,6*S*)-**21** (3.76 g, 22.2 mmol) in CH_3CN (60 mL). Next, a solution of Boc_2O (7.27 g, 33.3 mmol) in CH_3CN (20 mL) was added over 2 h. The mixture was stirred at rt overnight and evaporated. The residue was dissolved in EtOAc (150 mL), washed with 10% aq citric acid to pH ca. 4 and H_2O, then dried over Na_2SO_4 and evaporated. The pure product **33** was obtained after chromatography (Hex/EtOAc (2:1) as eluent, R_f = 0.37). Yield 5.98 g (quant.). Yellowish oil, which crystallized upon standing. Mp 43–44 °C. $[\alpha]_D^{22} = -6.0$ (c 1.0, $CHCl_3$). For other spectroscopic and physical data, see Ref. 13.

4.10. (1*R*,6*S*)-3-*tert*-Butyl 1-methyl 3-azabicyclo[4.1.0]heptane-1,3-dicarboxylate 34

A solution of DIBAL (0.7 M in toluene, 16.2 mL, 11.3 mmol) was added dropwise to the solution of the imide **32** (2.66 g, 9.9 mmol) in THF (50 mL) at −80 °C under argon atmosphere. This mixture was stirred at −80 °C for 1 h, and saturated aq NH_4Cl (5 mL) was added. The suspension obtained was allowed to warm to rt, stirred for 30 min, and then filtered. The solid residue was washed thoroughly with THF (3 × 50 mL), and the combined filtrates were evaporated to give a crude mixture of diastereomeric hemiamidals (2.73 g), which was used without further purification.

A solution of hemiamidals (2.73 g) and triethylsilane (1.58 mL, 9.9 mmol) in CH_2Cl_2 (80 mL) was cooled to −80 °C under an argon atmosphere, and $BF_3{\cdot}Et_2O$ (1.22 mL, 9.9 mmol) was added. This mixture was stirred at the same temperature for 30 min. The second portion of triethylsilane (1.58 mL, 9.9 mmol) and then—$BF_3{\cdot}Et_2O$ (1.22 mL, 9.9 mmol) were added. The resulting solution was stirred for 1.5 h and then quenched with saturated aq $NaHCO_3$ (100 mL). This mixture was stirred vigorously at rt for 20 min, and the phases were separated. The aqueous layer was washed with CH_2Cl_2 (50 mL). The combined extracts were dried over Na_2SO_4, evaporated, and dried in vacuo to give product **34**. Yield 2.36 g (94%). Colorless oil. $[\alpha]_D^{22} = -61.9$ (c 1.0, $CHCl_3$). For other spectroscopic and physical data, see Ref. 13.

4.11. (1*R*,6*S*)-3-(*tert*-Butoxycarbonyl)-3-azabicyclo[4.1.0]heptane-1-carboxylic acid (1*R*,6*S*)-28

At first, aq NaOH (2 M, 9 mL, 18.0 mmol) was added to a solution of (1*R*,6*S*)-3-*tert*-butyl 1-methyl 3-azabicyclo[4.1.0]heptane-1,3-dicarboxylate **34** (2.30 g, 9.0 mmol) in MeOH (50 mL). The resulting mixture was stirred at rt overnight and evaporated. The residue was dissolved in H_2O (50 mL), washed with Et_2O (30 mL), acidified by the addition of 1 M aq $NaHSO_4$ to pH = 3 and extracted with $CHCl_3$ (2 × 50 mL). Extracts was dried over Na_2SO_4 and evaporated to give the product (1*R*,6*S*)-**28** as colorless solid. Yield 2.16 g (100%). Mp 96–97 °C. $[\alpha]_D^{22} = -57.2$ (c 1.0, $CHCl_3$). For other spectroscopic and physical data, see Ref. 13.

4.12. (1*R*,6*S*)-3-Azabicyclo[4.1.0]heptane-1-carboxylic acid, hydrochloride (1*R*,6*S*)-17·HCl

(1*R*,6*S*)-**17**·HCl was obtained following the procedure for the racemate. Yield 770 mg (92%). Mp 208–212°C (dec.). $[\alpha]_D^{22}$ = −38.8 (*c* 1.0, H_2O). Other spectroscopic and physical data were consistent with that obtained for the racemate.

4.13. *tert*-Butyl 1-(hydroxymethyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate (1*R*,6*S*)-27

To a solution of ester **34** (200 mg, 0.78 mmol) in THF (8 mL), $LiBH_4$ (51 mg, 2.34 mmol) was added at 0 °C. The reaction mixture was stirred at rt overnight, and then quenched carefully with MeOH (5 mL). The reaction mixture was evaporated in vacuo to dryness, diluted with 10% aq K_2CO_3 (30 mL), and extracted with CH_2Cl_2 (5 × 30 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo to give the product (1*R*,6*S*)-**27**. Yield 147 mg (83%). An analytical sample was obtained using flash chromatography (gradient Hexanes–EtOAc as eluent). Colorless oil. Other spectroscopic and physical data were consistent with that obtained for the racemate.

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