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Conformationally Restricted Nonchiral Pipecolic Acid Analogues

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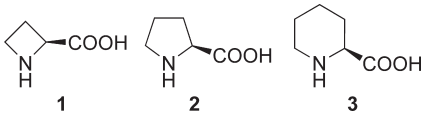
Practical syntheses of 2-azabicyclo[3.1.1]heptane-1-carboxylic (2,4-methanopipecolic), 2-azabicyclo [2.2.2]octane-1-carboxylic (2,5-ethanopipecolic), and 9-azabicyclo[3.3.1]nonane-1-carboxylic (2,6-propanopipecolic) acids are reported. The synthetic schemes are short (five, seven, and five steps, respectively) and result in reasonably high yields of the title compounds. The key step in the syntheses is the tandem Strecker reaction and intramolecular nucleophilic cyclization of ketones possessing a leaving group at the δ-position.

Introduction

Conformationally restricted amino acids (CRAAs) have been the subject of considerable interest in the past decade due to their importance for drug design. Incorporation of the CRAA in peptidomimetics can lead to improvement of their pharmacokinetic and pharmacodynamic characteristics.[1]

Most of the natural and unnatural CRAAs used for this purpose are cyclic; the presence of cycles in a molecule considerably restricts its conformational flexibility.[2] For example, three natural cyclic CRAAs, 2-azetidinecarboxylic acid (**1**), proline (**2**) and pipecolic acid (**3**), are frequently used either nonderivatized or as scaffolds in the design of conformationally restricted peptidomimetics.[2b,3]



It should be noted that compounds **1**−**3** and many of their non-natural analogues known to date are chiral. This property is very important for drug design: development of new drugs often requires the use of chiral building blocks. The fundamental reason behind this lies in the fact that almost all biological targets are chiral, and drug−receptor interaction requires strict matching of chirality. However, chirality also causes serious problems in drug design as a result of the cost of synthesis of chiral nonracemic compounds and their analysis and the strengthening of regulatory guidelines for submitting new drug applications in many countries. Therefore, the synthesis of novel nonchiral building blocks, including amino acids, capable of generating drug candidates has taken on increased importance.[4]

A design concept for bicyclic nonchiral α-amino acids consists of the incorporation of $-(CH_2)_n-$ bridges between the C(2) and C($n+3$) atoms of parent monocyclic scaffolds. For example, the proline nonchiral family includes the known 2,4-methanoproline **4**[5] and 7-azabicyclo[2.2.1]heptane-1-carboxylic acid **5**.[6] Recently, we used an analogous concept for a nonchiral analogue of α-aminoadipic acid, 7-azabicyclo [2.2.1]heptane-1,4-dicarboxylic acid **6**.[7]

Application of this design concept to the pipecolic acid scaffold **3** generates three less explored analogues, the nonchiral

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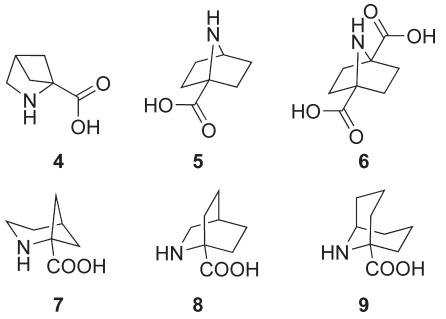
CRAAs **7**−**9**. Herein, we wish to report expedient syntheses of these compounds.



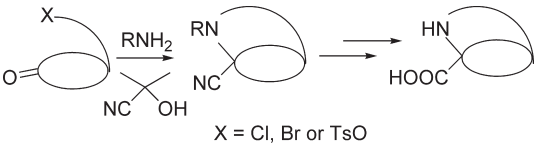
Results and Discussion

To the best of our knowledge, none of the compounds **7**−**9** are described in the open literature in the free form. Syntheses of *O*-benzyl[8a] and *N*-benzyl[8b] derivatives of 2-azabicyclo [2.2.2]octane-1-carboxylic acid (2,5-ethanopipecolic acid) have already been reported. The key transformation of the latter synthesis was the intramolecular cyclization of 1-aminocyclohexane-1,4-dicarboxylic acid dimethyl ester. Another synthesis of a 2,5-ethanopipecolic acid derivative (*N*-benzoyl-2-azabicyclo[2.2.2]octane-1-carboxylic acid methyl ester) through an intramolecular cyclization of methyl 1-(benzoylamino)-4-(mesyloxymethyl)cyclohexanecarboxylate has been published recently.[8c] Compounds with the core skeleton of **9** have also been described in the literature. They have been prepared by an intramolecular reductive radical cyclization of corresponding alkynes.[9]

In our syntheses of **7**−**9** we used a different approach, which had been recently developed by our group[10] and utilizes a tandem Strecker reaction−cyclization sequence followed by hydrolysis and deprotection, as shown in the Scheme 1. Advantages of this approach are generality, the simplicity of the synthetic procedures, short reaction paths, and good yields. As the final compounds are nonchiral, the synthetic strategy avoids the use of expensive chiral auxiliaries, reagents, or catalysts, as well as tedious separation of stereoisomers. Corresponding functionalized cyclic ketones can be easily synthesized from commercially available compounds.

Details of the syntheses are outlined in the Scheme 2. The functionalized ketone **12** was obtained from commercially available **10** by [2 + 2] cycloaddition of dichloroketene followed by reduction, utilizing the procedure described for an analogous compound.[11] Starting ketone **17** was synthesized from 2-trimethylsilyloxy-1,3-butadiene **14** by a method reported elsewhere.[12] Finally, ketone **21** was obtained as

SCHEME 1



described in the literature.[13] All these procedures are easy to scale up, thus allowing multigram quantities of the corresponding functionalized ketones to be obtained. Compounds **12**, **17**, and **21** smoothly underwent the Strecker reaction and cyclization in the presence of acetone cyanohydrin (ACH) and benzylamine, giving the aminonitriles **13**, **18**, and **22**. Their hydrolysis in aqueous HCl and deprotection by hydrogenolysis proceeded in reasonable yields. The overall yields for the syntheses were 14% (**7**, five steps), 14% (**8**, seven steps), and 15% (**9**, five steps), so the procedures can be used to obtain multigram quantities of the amino acids.

Conclusions

In summary, a set of nonchiral, conformationally restricted pipecolic acid analogues has been designed. An approach to their synthesis utilizing a tandem Strecker reaction−cyclization sequence has been developed. The procedure is a modification of a method previously reported by our group[10] and can be applied for the synthesis of other cyclic amino acids starting from corresponding functionalized ketones. These amino acids can be used as building blocks in the search for biologically active compounds and as model compounds in structural studies of peptides.

Experimental Section

2,2-Dichloro-3-(2-chloroethyl)cyclobutanone 11. Compound **10** (4.45 g, 49.1 mmol), Zn−Cu couple (3.51 g, 54 mmol), and dry ether (80 mL) were placed in a pre-dried three-necked flask under an argon atmosphere. A solution of trichloroacetyl chloride (5.75 mL, 51.5 mmol) and $POCl_3$ (4.81 mL, 51.5 mmol) in dry ether (40 mL) was added over a period of 30 min. The reaction mixture was refluxed for 1 day under argon, and the solution was filtered over Celite and washed with ether. The filtrate was evaporated to 60 mL and extracted with pentane (3×45 mL). The clear yellow upper solution was decanted from the brown residue into a separating funnel. The organic layer was washed with water (3 × 30 mL) and brine (1 × 30 mL) and dried over $MgSO_4$. Removal of the solvent in vacuo afforded crude **11** (6 g, 29.8 mmol) as a pale yellow oil (79.4% purity by GCMS), which was used in the next step without further purification: IR (cm^{-1}) 1815 (ν(C=O)); MS (*m*/*z*) 200(M^+), 158($M^+ - CH_2{=}C{=}O$), 122, 109; ^{1}H NMR ($CDCl_3$) δ 3.69 (m, 2H, CH_2CH_2Cl), 3.43 (dd, J = 17.2 and 9.2 Hz, 1H, 4-CH_2), 3.18 (m, 1H, 3-*CH*), 3.08 (dd, J = 17.4 and 9.3 Hz, 1H, 4-CH_2), 2.44 (m, 1H, CH_2CH_2Cl), 2.11 (m, 1H, CH_2CH_2Cl); ^{13}C NMR ($CDCl_3$) δ 191.9 (*C*=O), 88.7 (CCl_2), 47.9 (4-CH_2), 43.7 (3-*CH*), 42.2 (CH_2CH_2Cl), 34.1 (CH_2CH_2Cl).

3-(2-Chloroethyl)cyclobutanone 12. Zinc powder (10.5 g, 161 mmol) was added in small portions to a stirred solution of **11** (5 g, 24.8 mmol) in HOAc (50 mL) at 90 °C. The suspension was

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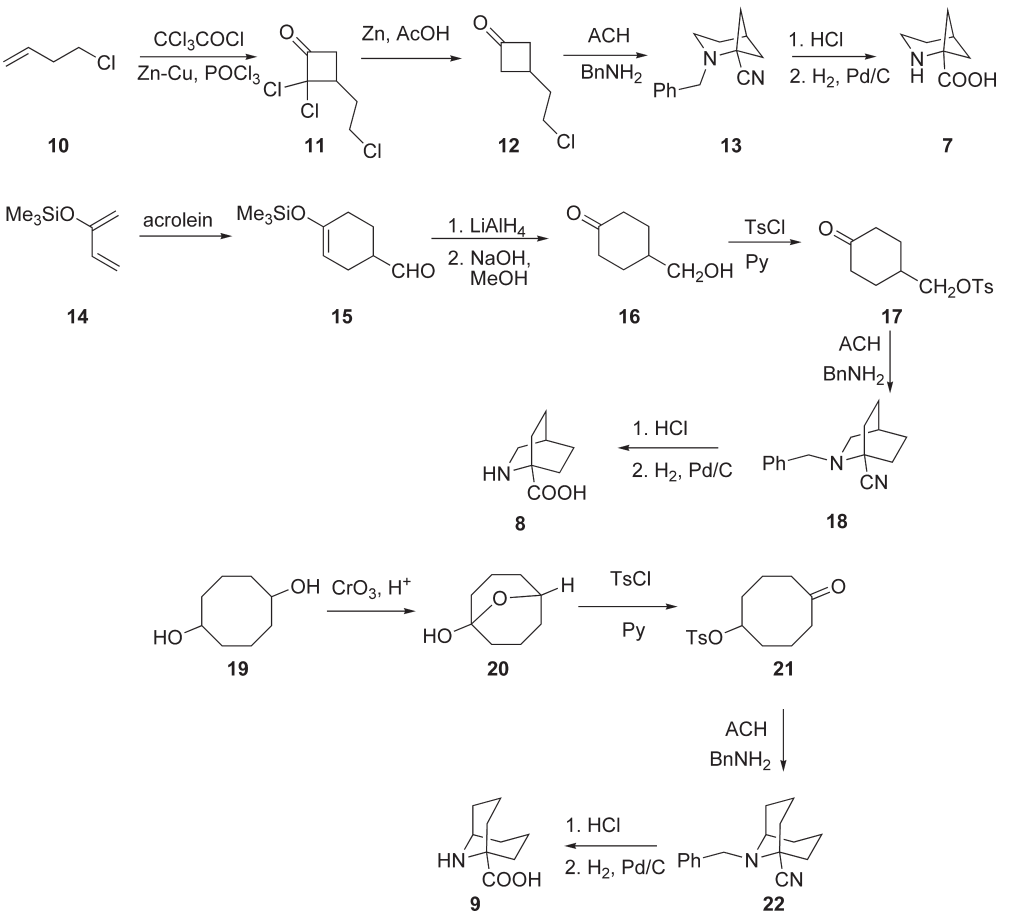
SCHEME 2. Synthesis of Amino Acids 7−9



heated at 90 °C for 2 h, cooled to rt, filtered over Celite, and washed with dichloromethane (100 mL). The resulting solution was washed with water (1×50 mL) and saturated $NaHCO_3$ solution until basic, dried over Na_2SO_4, and evaporated. Distillation of the crude product afforded **12** (2.58 g, 19.5 mmol, 79% yield) as a colorless oil: bp 98 °C/15 mmHg; IR (cm^{-1}) 1785 (ν(C=O)); MS (*m*/*z*) 132(M^+), 104, 55. Anal. Calcd for C_6H_9ClO: C 54.35, H 6.84, Cl 26.74. Found: C 54.72, H 6.79, Cl 26.83. ^{1}H NMR ($CDCl_3$) δ 3.57 (t, J = 6.5 Hz, 2H, CH_2Cl), 3.19−3.24 (m, 2H), 2.75−2.80 (m, 2H), 2.64 (sept, J = 7.5 Hz, 1H, 3-C*H*), 2.10 (q, J = 7.0 Hz, 2H, CH_2CH$_2$Cl); ^{13}C NMR ($CDCl_3$) δ 206.8 (*C*=O), 52.5 (*C*H_2), 43.3 (*C*H_2), 38.7 (*C*H_2), 21.8 (3-*C*H).

2-Benzyl-2-azabicyclo[3.1.1]heptane-1-carbonitrile 13. Acetone cyanohydrin (5.13 mL, 56.1 mmol) and benzylamine (2.06 mL, 18.9 mmol) were added to a solution of **12** (2.5 g, 18.9 mmol) in dry methanol (20 mL). The mixture was refluxed for 80 h, evaporated, diluted with 10% sodium hydroxide solution (25 mL), and extracted with ether. The combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed (hexane/ethylacetate/triethyamine (15:5:1) as an eluent) to give **13** (1.69 g, 7.96 mmol, 42%) as a white crystalline solid: mp 55−57 °C; IR (KBr, cm^{-1}) 2235 (ν(C≡N)); MS (*m*/*z*) 212(M^+), 184, 171, 91 ($C_7H_7^+$). Anal. Calcd for $C_{14}H_{16}N_2$: C 79.21, H 7.60, N 13.20. Found: C 79.05, H 7.57, N 12.98. ^{1}H NMR ($CDCl_3$) δ 7.38 (d, J = 7.1 Hz, 2H, *o*-C_6H_5), 7.34 (t, J = 7.1 Hz, 2H, *m*-C_6H_5), 7.27 (t, J = 7.0 Hz, 1H, *p*-C_6H_5), 3.87 (s, 2H, C$H_2C_6H_5$), 2.88 (t, J = 6.8 Hz, 2H, 3-CH_2), 2.52 (m, 1H, 5-C*H*), 2.44 (t, J = 6.8 Hz, 2H, 4-CH_2), 2.27 (dd, J = 7.3 and 2.2 Hz, 2H, 6- and 7-C*H*H), 1.93 (m, 2H, 6- and 7-CH*H*); ^{13}C NMR ($CDCl_3$) δ 139.0 (*ipso*-C_6H_5), 128.0 (*o*-C_6H_5), 128.8 (*m*-C_6H_5), 128.6 (*p*-C_6H_5), 120.5 (*C*N), 58.7 (1-*C*), 57.5 (*C*H$_2C_6H_5$), 43.0 (3-*C*H$_2$), 37.4 (6- and 7-*C*H$_2$), 31.5 (5-*C*H), 27.9 (4-*C*H$_2$).

2-Azabicyclo[3.1.1]heptane-1-carboxylic Acid 7. A solution of **13** (0.2 g, 0.9 mmol) in 6 N HCl (5 mL) was heated under reflux for 18 h. After evaporation of the solvent, the residue was dissolved in water and hydrogenated over 10% Pd/C at 70 bar and rt for 12 h. Evaporation of the solvent and purification by ion-exchange chromatography (Amberlite IR-120(plus) ion-exchange resin (20 g), 3.5% aqueous ammonia as an eluent) gave **7** (0.090 g, 0.6 mmol, 68%) as a white solid: mp 150 °C (dec); IR (KBr, cm^{-1}) 3394 ($\nu_{as}(NH_2^+)$), 3187 ($\nu_s(NH_2^+)$), 1686, 1639, and 1608 ($\delta(NH_2)$, $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$). Anal. Calcd for $C_7H_{11}NO_2$: C 59.56, H 7.85, N 9.92. Found: C 59.43, H 7.86, N 9.61. ^{1}H NMR (D_2O) δ 3.54 (t, J = 7.2 Hz, 2H, 3-CH_2), 2.64 (m, 3H, 5-C*H*, 6-C*H*H and 7-C*H*H), 2.14 (m, 2H, 4-CH$_2$), 1.92 (m, 2H, 6-CH*H* and 7-CH*H*); ^{13}C NMR (DMSO-d_6) δ 172.3 (*C*OOH), 65.1 (1-*C*), 36.7 (3-*C*H$_2$), 34.8 (6- and 7-*C*H$_2$), 29.2 (5-*C*H), 26.7 (4-CH$_2$).

2-benzyl-2-azabicyclo[2.2.2]octane-1-carbonitrile 18. Acetone cyanohydrin (32 mL, 0.354 mol) and benzylamine (12.9 mL, 0.118 mol) were added to a solution of **17** (33.3 g, 0.118 mol) in dry methanol (140 mL). The mixture was refluxed for 80 h, evaporated, diluted with 10% sodium hydroxide solution (150 mL), and extracted with ether. The combined extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was recrystallized from MeOH to give **18** (9.66 g, 0.043 mol, 36%) as a white crystalline solid: mp 96−98 °C; IR (KBr, cm^{-1}) 2235 (ν(C≡N)); MS (*m*/*z*) 226(M^+), 197, 91($C_7H_7^+$). Anal. Calcd for $C_{15}H_{18}N_2$: C 79.61, H 8.02, N 12.38. Found: C 79.36, H 7.79, N 12.43. ^{1}H NMR ($CDCl_3$)

δ 7.38 (d, $J = 7.1$ Hz, 2H, *o*-C_6H_5), 7.34 (t, $J = 7.4$ Hz, 2H, *m*-C_6H_5), 7.26 (t, $J = 7.0$ Hz, 1H, *p*-C_6H_5), 3.98 (s, 2H, $CH_2C_6H_5$), 2.64 (s, 2H, 3-CH_2), 2.40 (m, 2H, 6- and 7-CHH), 2.01 (td, $J = 12.1$ and 4.4 Hz, 2H, 6- and 7-CHH), 1.68 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 138.8 (*ipso*-C_6H_5), 129.0 (*o*-C_6H_5), 128.5 (*m*-C_6H_5), 127.3 (*p*-C_6H_5), 122.3 (CN), 59.1 ($CH_2C_6H_5$), 55.2 (3-CH_2), 52.6 (1-C), 30.4 (6- and 7-CH_2), 25.1 (4-CH), 24.3 (5- and 8-CH_2).

2-Azabicyclo[2.2.2]octane-1-carboxylic Acid 8. A solution of **18** (0.220 g, 1.0 mmol) in 6 N HCl (5 mL) was heated under reflux for 72 h. After evaporation of the solvent, the residue was dissolved in water and hydrogenated over 10% Pd/C at 70 bar and rt for 12 h. Removal of the solvent and purification by ion-exchange chromatography (Amberlite IR-120(plus) ion-exchange resin (20 g), 3.5% aqueous ammonia as an eluent) gave **8** (0.095 g, 0.6 mmol, 63%) as a white solid: mp 260 °C (dec); IR (KBr, cm^{-1}) 3361 ($\nu_{as}(NH_2^+)$), 3204 ($\nu_s(NH_2^+)$), 1653 and 1600 ($\delta(NH_2^+)$, $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$). Anal. Calcd for $C_8H_{13}NO_2$: C 61.91, H 8.44, N 9.03. Found: C 62.13% H 8.27, N 8.86. ^{1}H NMR (D_2O) δ 3.22 (s, 2H, 3-CH_2), 2.04 (td, $J =$ 13.1 and 5.2 Hz, 2H), 1.98 (s, 1H, 4-CH), 1.90 (m, 2H), 1.83 (m, 2H), 1.75 (m, 2H); ^{13}C NMR (D_2O) δ 177.7 (COOH), 58.2 (1-C), 45.8(3-CH_2), 25.9 (CH_2), 22.7 (CH_2), 22.3 (4-CH).

9-Benzyl-9-azabicyclo[3.3.1]nonane-1-carbonitrile 22. Acetone cyanohydrin (0.31 mL, 3.4 mmol) and benzylamine (0.13 mL, 1.19 mmol) were added to a solution of **21** (0.340 g, 1.15 mmol) in 1 mL of dry CH_3CN. The mixture was heated at 90 °C for 18 h with an air condenser to allow the solvent to evaporate gradually, cooled, diluted with 10% sodium hydroxide solution (5 mL), and extracted with ether (3 × 5 mL). The combined extracts were dried over $MgSO_4$ and evaporated under a reduced pressure to give crude **22** (0.190 g, 0.79 mmol, 69%), which was used in the next step without further purification. The analytical sample was obtained by flash chromatography (hexane/ethyl acetate (90:10 to 60:40 gradient) as an eluent, detection at 254 nm) as a white solid: mp 68−70 °C; IR (KBr, cm^{-1}) 2235 (ν(C≡N)); MS (*m*/*z*, CI) 241 (MH^+). Anal. Calcd for $C_{16}H_{20}N_2$: C 79.96, H 8.39, N 11.66. Found: C 79.64, H 7.98, N 11.40. ^{1}H NMR ($CDCl_3$) δ 7.38 (d, $J = 6.1$ Hz, 2H, *o*-C_6H_5), 7.32 (t, $J = 7.3$ Hz, 2H, *m*-C_6H_5), 7.25 (dd, $J = 6.7$ and 5.9 Hz, 1H, *p*-C_6H_5), 4.10 (s, 2H, $CH_2C_6H_5$), 2.79 (s, 1H, 5-CH), 2.40 (2m, 2H, 2- and 8-CHH), 2.10 (m, 2H, 3- and 7-CHH), 1.91−2.07 (m, 4H, 2- and 8-CH*H*, 4-and 6-CHH), 1.77 (m, 2H, 3- and 7-CH*H*), 1.40 (m, 2H, 4- and 6-CH*H*); ^{13}C NMR ($CDCl_3$) δ 139.2 (*ipso*-C_6H_5), 128.4 (CH), 128.3 (CH), 127.1 (CH), 123.2 (CN), 55.6 (1-C), 53.7 ($CH_2C_6H_5$), 47.2 (5-CH), 32.4 (2-CH_2), 25.0 (4-CH_2), 20.3 (3-CH_2).

9-Azabicyclo[3.3.1]nonane-1-carboxylic Acid 9. A solution of **22** (0.160 g, 0.67 mmol) in 6 N HCl (5 mL) was heated under reflux for 80 h. After evaporation of the solvent, the residue was dissolved in water and hydrogenated over 10% Pd/C at 70 bar and rt for 12 h. Evaporation of the solvent and purification by ion-exchange chromatography (Amberlite IR-120(plus) ion-exchange resin (20 g), 3.5% aqueous ammonia as an eluent) gave **9** (0.061 g, 0.36 mmol, 54%) as a white solid: mp 252 °C (dec); IR (KBr, cm^{-1}) 3378 ($\nu_{as}(NH_2^+)$), 3333 ($\nu_s(NH_2^+)$), 1642, 1617, and 1589 ($\delta(NH_2^+)$, $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$). Anal. Calcd for $C_9H_{15}NO_2$: C 63.88, H 8.93, N 8.28. Found: C 64.11, H 8.92, N 8.34. ^{1}H NMR (D_2O) δ 3.73 (s, 1H, 5-CH), 2.19 (m, 4H), 1.98 (m, 2H), 1.89 (m, 4H), 1.74 (m, 2H); ^{13}C NMR (D_2O) δ 178.3 (COOH), 59.4 (1-C), 48.7 (5-CH), 30.5 (CH_2), 26.1 (CH_2), 18.9 (3- and 7-CH_2).

Supporting Information Available: Copies of NMR spectra and LS-MS/GS-MS chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.