Gram-Scale Synthesis of 3,5-Methanonipecotic Acid, a Nonchiral Bicyclic β-Amino Acid

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Abstract: A scalable synthesis was developed of 3,5-methanonipecotic acid (3-azabicyclo[3.1.1]heptane-1-carboxylic acid), a rare example of a conformationally constrained nonchiral β-amino acid, potentially useful in peptide engineering and peptidomimetic drug design. A retrosynthetic strategy based on disconnections exclusively within the symmetry planes of the target and the intermediate molecules was found to be useful and might deliver expedite syntheses in other similar cases.

Key words: amino acids, bicyclic compounds, heterocycles, conformation

The field of β-amino acids and β-peptides has generated much interest in recent years.[1] Such compounds are widespread in nature, because many bacteria, fungi, and plants incorporate β-amino acids to ensure their survival in competition with other organisms.[2] Because β-amino acids derivatives are often characterized by potent biological and physiological activities, they are potentially useful as lead structures for the development of new drugs.[3] Furthermore, these compounds have been shown to possess considerable stability against a wide range of proteolytic enzymes.[3b]

The incorporation of β-amino acids in the design of peptidomimetics and β-peptides was a pivotal development in this field, because β-peptides have been shown to adopt intrinsic secondary structures.[4] Interesting parallels and contrasts in the folding behaviors of α- and β-peptides have been demonstrated.[1,5] As a result, the use of β-amino acid oligomers might permit testing of basic assumptions about the forces that are responsible for the molecular structures of biological macromolecules such as proteins.

β-Amino acids with restricted molecular flexibility are of particular interest. Conformational restriction has been repeatedly used as a tool in model studies on peptides, proteins, and other biologically relevant molecules.[7] Conformationally restricted β-amino acids have been successfully used to stabilize particular secondary structures of β-peptides, such as the 14-helix,[8] 12-helix,[9] and 10-helix,[10] as well as hairpins and reverse turns.[11,12] For a β-peptide to adopt one of these secondary structures, the constituent residues must adopt the required torsional angles (Figure 1; ϕ, θ, ψ, and ω).

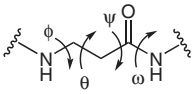

Figure 1 Torsional angles in a β-peptide, defined according to Banerjee and Balaram[6]

Conformational restriction allows the values of the θ-angle or both the θ- and ϕ-angles to be fixed. The latter case occurs in residues of amino acids containing an endocyclic backbone nitrogen atom, for example pyrrolidine-3-carboxylic acid (**1**) or nipecotic acid (**2**) (Figure 2). This constraint on the θ-angle prevents β-peptides containing residues of **1** or **2** from adopting any helical conformation. A sequence consisting of an (*R*)-nipecotic acid residue and an (*S*)-nipecotic residue has been shown to induce a reverse-turn structure, characterized by a twelve-membered hydrogen-bonded ring.[10] Amino acids **1** and **2** are also useful in medicinal chemistry; in particular, nipecotic acid (**1**) and its derivatives are widely used as inhibitors of both glial and neuronal uptake of γ-aminobutyric acid.[13]

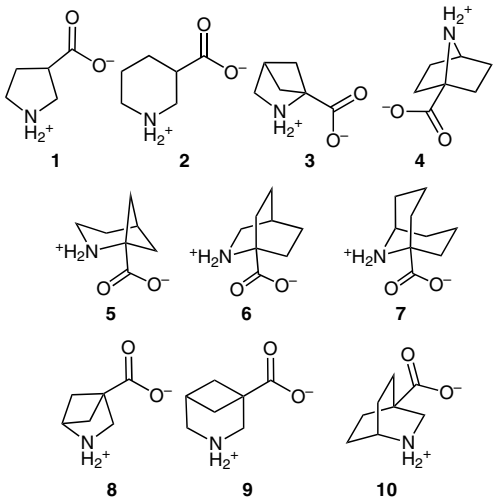

Figure 2 Conformationally constrained amino acids

A promising approach to the design of conformationally rigid amino acids relies on symmetrization of the parent cyclic molecules[14] (such as **1** or **2**) by introducing an appropriate polymethylene bridge to form a rigid bicyclic structure containing a plane of symmetry. For example, the application of this concept to a proline molecule af-

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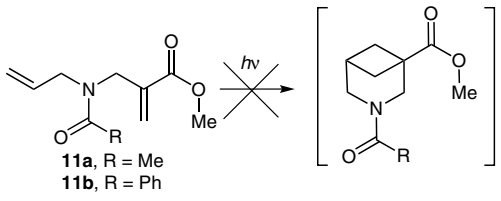
fords the amino acids 2,4-methanoproline (**3**)[15] and 2,5-ethanoproline (**4**) (Figure 2).[16] This approach has also been used in the design of the pipecolic acid analogues **5**–**7**.[17] Note that all the amino acids **3**–**7** are nonchiral, which leads to distinctive conformational behavior of peptides containing these residues.[18] Furthermore, these compounds are promising three-dimensional building blocks, potential useful in drug discovery.[19] In this respect, the lack of chirality of the compounds can be advantageous because chiral compounds are more costly to synthesize and to analyze, and because of the increasing stringency of regulatory guidelines on submissions for chiral drugs that have been adopted in many countries.

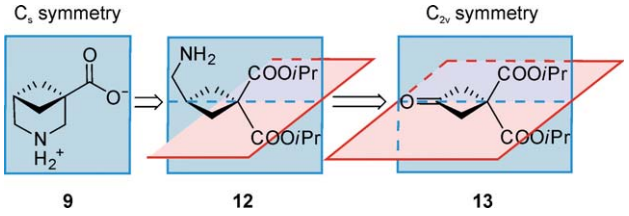
Application of the design concept discussed above to molecules **1** and **2** generates a family of nonchiral bicyclic β-amino acids **8**–**10**. Analysis of molecular models showed that the conformational rigidity of **8**–**10** restricts large values of both the ϕ- and θ-torsion angles in molecules of model peptides; these define antiperiplanar conformations around the corresponding bonds of the peptide backbone, a combination rarely encountered in known peptides containing β-amino acid residues.[5] Here we report a scalable and practical synthesis of a first representative of this family: 3,5-methanonipecotic acid (**9**; 3-azabicyclo-[3.1.1]heptane-1-carboxylic acid).

Although several approaches to the synthesis of 3-azabicyclo[3.1.1]heptane derivatives have been reported in the literature,[20] none of these was considered to be amendable to the synthesis of amino acid **9**. Our initial retrosynthetic analysis of **9** relied on a photochemical intramolecular [2 + 2] cycloaddition of the corresponding dienes **11** (Scheme 1), in an approach analogous to that reported previously for the preparation of 2,4-methanoproline derivatives.[15a,15b,21] However, neither **11a** nor **11b** gave any traces of the expected products; instead, the dienes underwent polymerization. Therefore we shifted our attention to sequential construction of the rings in the molecule of **9**. Our revised retrosynthetic strategy relied on the disconnections of the bicyclic system of **9** (C_s symmetry) exclusively within the symmetry plane, leading to the amine **12** (Scheme 2) and, subsequently, to the ketone **13** (C_{2v} symmetry) described previously by our group.[22] This strategy ensures that the key intermediates in the synthesis will possess planes of symmetry, thereby eliminating any problems with separating and isolating stereoisomers.



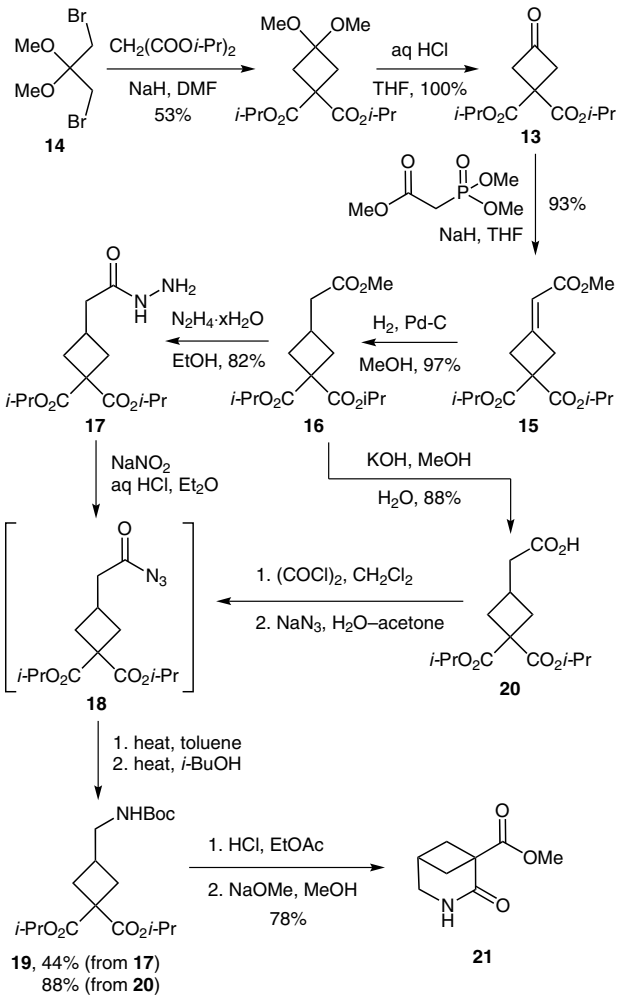
Scheme 1

Ketone **13** was obtained in two steps and 53% overall yield from dibromide **14**[23] (Scheme 3; for experimental details, see Supporting Information). The carbon chain in



Scheme 2

diester **13** was elongated by a Horner–Wadsworth–Emmons olefination to give triester **15** in 93% yield.[24] Catalytic reduction of **15** proceeded smoothly to give the saturated triester **16** (97%).[25]



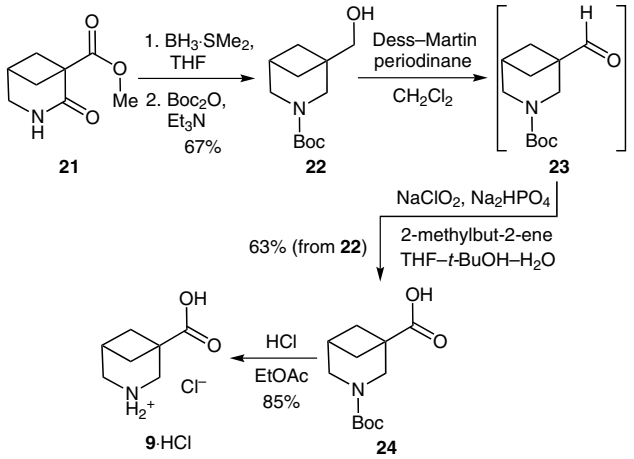
Scheme 3

Note that the methyl and isopropyl ester functions in **16** differ significantly in their reactivity, a feature necessary for achieving regioselectivity in subsequent steps of the synthesis. The reaction of triester **16** with hydrazine hydrate gave hydrazide **17** in 82% yield. This was converted into the acyl azide **18**, which was not isolated. Curtius rearrangement of **18** and subsequent trapping with *tert*-butanol gave carbamate **19**. Unfortunately, the yield of **19** (44% from **17**) was moderate, which might limit the scal-

ability of the method. We therefore subjected triester **16** to selective hydrolysis to give the carboxylic acid **20** in 88% yield;[26] this was transformed into azide **18** via the corresponding acid chloride. Again, **18** was not isolated, but was converted into carbamate **19** (88% from **20**) by using the reaction sequence described above. In this case, carbamate **19** was sufficiently pure to be used in the next step without further purification.[27]

Deprotection of **19** with hydrogen chloride in ethyl acetate gave amine **12** as its hydrochloride; this was not isolated, but instead was subjected to the key step of the synthesis, intramolecular amide formation, which proceeded smoothly upon action of sodium methoxide in refluxing methanol. Under these conditions, simultaneous transesterification occurred, and the bicyclic lactam **21** was isolated in 78% yield.[28]

An attempted selective reduction of the amide moiety in **21** with borane–dimethyl sulfide complex was unsuccessful. The corresponding amino alcohol formed instead, and was isolated as its protected derivative **22** in 67% yield (Scheme 4).[29] Treatment of alcohol **22** with ruthenium(III) chloride–sodium periodate was accompanied by oxidation of the bicyclic skeleton. We therefore adopted a two-step procedure, namely, reaction of alcohol **22** with Dess–Martin periodinane followed by Pinnick oxidation of an intermediate aldehyde **23**. This gave the carboxylic acid **24** (63% from **22**).[30] Finally, deprotection of **24** gave the required amino acid **9**, isolated in 85% yield as its hydrochloride.[31]



Scheme 4

In conclusion, we have developed an approach to the synthesis of 3,5-methanonipecotic acid, a novel nonchiral bicyclic β-amino acid. The compound was obtained in 17 steps and 10% overall yield from readily available 1,3-dibromo-2,2-dimethoxypropane. Note that the final product was obtained on a gram scale in a single run.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(24) **Diisopropyl 3-(2-Methoxy-2-oxoethylidene)cyclobutane-1,1-dicarboxylate (15)**
Colorless oil; R_f = 0.49 (hexanes–EtOAc, 5:1). IR (neat): 1718, 1626, 1625, 1101, 1082 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.69 (t, *J* = 2.0 Hz, 1 H), 5.05 (sept, *J* = 6.2 Hz, 2 H), 3.67 (s, 3 H), 3.58 (d, *J* = 2.0 Hz, 2 H), 3.30 (s, 2 H), 1.22 (d, *J* = 6.2 Hz, 12 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.3 (C), 166.3 (C), 157.7 (C), 114.7 (CH), 69.4 (CH), 51.2 (CH_3), 49.9 (C), 41.2 (CH_2), 39.1 (CH_2), 21.6 (CH_3). MS (CI): *m/z* = 299 [M + H]$^+$. Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.18; H, 7.64.

(25) **Diisopropyl 3-(2-Methoxy-2-oxoethyl)cyclobutane-1,1-dicarboxylate (16)**
Colorless oil; R_f = 0.46 (hexanes–EtOAc, 5:1). IR (neat): 1720, 1265, 1164, 1097 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.03 (sept, *J* = 6.2 Hz, 1 H), 4.99 (sept, *J* = 6.2 Hz, 1 H), 3.61 (s, 3 H), 2.63–2.73 (m, 3 H), 2.42 (d, *J* = 6.7 Hz, 2 H), 2.18–2.24 (m, 2 H), 1.20 (d, *J* = 6.2 Hz, 6 H), 1.18 (d, *J* = 6.2 Hz, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4 (C), 171.24 (C), 171.18 (C), 68.9 (CH), 68.8 (CH), 51.4 (CH_3), 49.8 (C), 40.4 (CH_2), 34.3 (CH_2), 25.9 (CH), 21.6 (CH_3). MS (CI): *m/z* = 301 [M + H]$^+$. Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 59.67: H, 7.89.

(26) **[3,3-Bis(isopropoxycarbonyl)cyclobutyl]acetic Acid (20)**
Colorless solid; mp 80–82 °C; R_f = 0.65 (hexanes–EtOAc, 1:2). IR (KBr): 2987, 1724, 1705 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.38 (very br s, 1 H), 5.06 (sept, *J* = 6.1 Hz, 1 H), 5.02 (sept, *J* = 6.1 Hz, 1 H), 2.67–2.77 (m, 3 H), 2.48 (d, *J* = 6.5 Hz, 2 H), 2.22–2.27 (m, 2 H), 1.22 (d, *J* = 6.1 Hz, 6 H), 1.21 (d, *J* = 6.1 Hz, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.0, 171.28, 171.25, 69.00, 68.96, 49.9, 40.3, 34.3, 25.6, 21.6. MS (CI): *m/z* = 287 [M + H]$^+$. Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H 7.74. Found: C, 58.95; H, 7.98.

(27) **Diisopropyl 3-{[(*tert*-Butoxycarbonyl)amino]methyl}-cyclobutane-1,1-dicarboxylate (19)**
Colorless oil. R_f = 0.26 (hexanes–EtOAc, 5:1). IR (neat): 3365, 1712, 1525 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.04 (sept, *J* = 6.1 Hz, 1 H), 5.01 (sept, *J* = 6.1 Hz, 1 H), 4.61 (br s, 1 H), 3.18 (d, *J* = 5.9 Hz, 0.5 H), 3.12 (br s, 1.5 H), 2.45–2.58 (m, 3 H), 2.18–2.23 (m, 2 H), 1.41 (s, 9 H), 1.21 (d, *J* = 6.1 Hz, 6 H), 1.20 (d, *J* = 6.1 Hz, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.4, 171.1, 156.1, 79.3, 68.93, 68.86, 49.5, 45.2, 32.0, 29.4, 28.5, 21.6. MS (ESI): *m/z* = 358 [M + H]$^+$. Anal. Calcd for $C_{18}H_{31}NO_6$: C, 60.48; H, 8.74; N, 3.92. Found: C, 60.70; H, 8.46; N, 4.12.

(28) **Methyl 2-Oxo-3-azabicyclo[3.1.1]heptane-1-carboxylate (21)**
White crystals; mp 115–116 °C. IR (KBr): 3220 [ν(N–H)], 1741 [ν(C=O)], 1676 cm^{-1} [ν(C=O)].
^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.61 (br s, 1 H), 3.60 (s, 3 H), 3.29 (s, 2 H), 2.53–2.57 (m, 1 H), 2.35–2.42 (m, 2 H), 1.79–1.85 (m, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 172.6 (C), 170.9 (C), 51.5 (C), 51.4 (CH_3), 44.8 (CH_2), 32.7 (CH_2), 27.6 (CH). MS (CI): *m/z* = 170 [M + H]$^+$. Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.53; H, 6.58; N, 8.52.

(29) ***tert*-Butyl 1-(Hydroxymethyl)-3-azabicyclo[3.1.1]-heptane-3-carboxylate (22)**
White crystals; mp 97–98 °C. IR (KBr): 3449, 3448, 1666, 1408, 1176 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.50 (br s, 2 H), 3.47 (s, 2 H), 3.42 (s, 2 H), 2.45 (br s, 0.5 H), 2.38 (br s, 0.5 H), 1.90 (br s, 2 H), 1.80 (br s, 1 H), 1.47 (s, 9 H), 1.34 (br s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.5 (C), 79.4 (C), 67.8 and 67.4 (CH_2), 52.2 and 51.8 (CH_2), 50.2 and 49.8 (CH_2), 42.7 (C), 32.6 and 32.4 (CH_2), 28.71 (CH_3), 28.67 (CH). MS (CI): *m/z* = 228 [M + H]$^+$. Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.08; H, 9.14; N, 6.48.

(30) **3-(*tert*-Butoxycarbonyl)-3-azabicyclo[3.1.1]heptane-1-carboxylic Acid (24)**
White crystals; mp 172–174 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.38 (br s, 1 H), 3.65 (s, 0.8 H), 3.62 (s, 1.2 H), 3.47 (s, 1.2 H), 3.44 (s, 0.8 H), 2.32–2.41 (m, 3 H), 1.53–1.55 (m, 2 H), 1.42 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.5 and 178.1 (C), 156.32 and 156.30 (C), 80.1 and 80.0 (C), 49.9 and 49.6 (CH_2), 49.3 and 48.8 (CH_2), 44.1 (C), 34.33 and 34.28 (CH_2), 28.7 (CH_3), 28.6 (CH). MS (ESI): *m/z* = 242 [M + H]$^+$. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.80. Found: C, 59.48; H, 8.27; N, 5.53.

(31) **3-Azabicyclo[3.1.1]heptane-1-carboxylic Acid Hydrochloride (9·HCl)**
White crystals; mp >250 °C (dec.). IR (KBr): 3423, 2987 (br), 1724, 1592, 1398 cm^{-1}. ^{1}H NMR (500 MHz, D_2O): δ = 3.69 (s, 2 H), 3.53 (s, 2 H), 2.60–2.68 (m, 2 H), 2.57–2.61 (m, 1 H), 1.82–1.87 (m, 2 H). ^{13}C NMR (125 MHz, D_2O): δ = 175.7 (C), 47.2 (CH_2), 46.7 (CH_2), 43.9 (C), 33.3 (CH_2), 28.1 (CH). Anal. Calcd for $C_8H_{12}ClNO_4$: C, 43.35; H, 5.46; Cl, 16.00; N, 6.32. Found: C, 43.62; H, 5.09; Cl, 16.25; N, 6.39.

