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Synthesis of Bicyclic Tertiary α-Amino Acids

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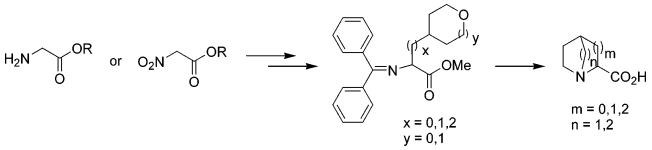


Novel bicyclic α-amino acids, *exo* and *endo*-1-azabicyclo-[2.2.1]heptane-2-carboxylic acid, 1-azabicyclo[2.2.1]heptane-7-carboxylic acid, and 1-azabicyclo[3.2.2]nonane-2-carboxylic acid have been readily synthesized for the generation of neuronal nicotinic receptor ligands. Alkylation of glycine-derived Schiff bases or nitroacetates with cyclic ether electrophiles, followed by acid-induced ring opening and cyclization in NH_4OH, allowed for the preparation of substantial quantities of the three tertiary bicyclic α-amino acids.

Non-natural α-amino acids have been the subject of much synthetic effort, primarily as a result of their usefulness as intermediates in the synthesis of polypeptides, natural products, and pharmaceutical agents.[1−4] For these applications considerable effort has focused upon multicomponent syntheses of amino acids.[5] To further our research program at Targacept, we required a robust synthesis of bicyclic tertiary α-amino acids **1**−**3** (Figure 1).[6] These amino acids were anticipated to be key intermediates in the synthesis of neuronal nicotinic receptor (NNR) ligands. Upon further review of the literature, it was

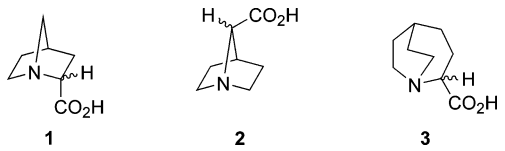
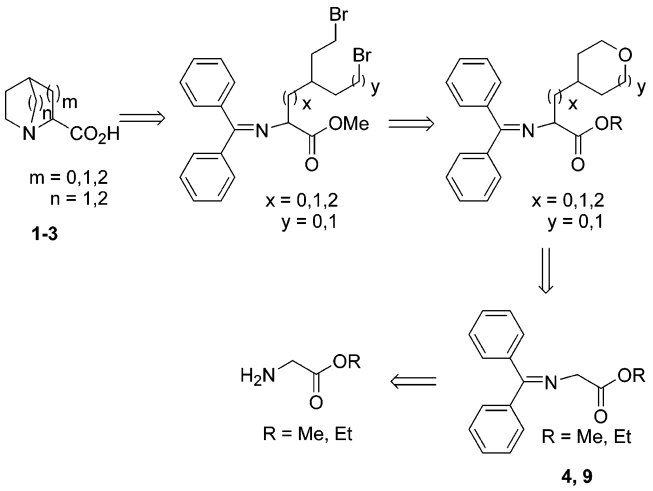


FIGURE 1. Bicyclic α-amino acids.

evident that there was a lack of synthetic methodology available for their synthesis. Diels−Alder reactions with α,β-didehydroalaninate and cyclopentadiene in the presence of chiral Lewis acids have given rise to 2-aminonorbornane-2-carboxylic acids enantioselectively.[7] Several 1-carboxy-7-azabicyclo[2.2.1]heptane amino acids, from L-glutamic acid through an enantiomerically pure proline analog, have also been described.[8] However, neither of these approaches were suitable for synthesizing amino acids **1**−**3**.

SCHEME 1. Retrosynthetic Analysis of Bicyclic α-Amino Acids



Retrosynthetic analysis (Scheme 1) of tertiary α-amino acids **1**−**3** indicates that they could be synthesized via an acid (HBr) induced ring opening of tetrahydrofuran or tetrahydropyran rings and subsequent cyclization in NH_4OH. Alkylation of Schiff bases **4** and **9**, an approach that has been used successfully by others in the synthesis of various non-natural α-amino acids,[9,10] will give the desired substituted tetrahydrofuran and tetrahydropyran rings. Schiff bases **4** and **9** are in turn synthesized from readily available *N*-methyl or ethyl glycine. This note details the racemic synthesis of novel bicyclic α-amino acids **1**−**3**.

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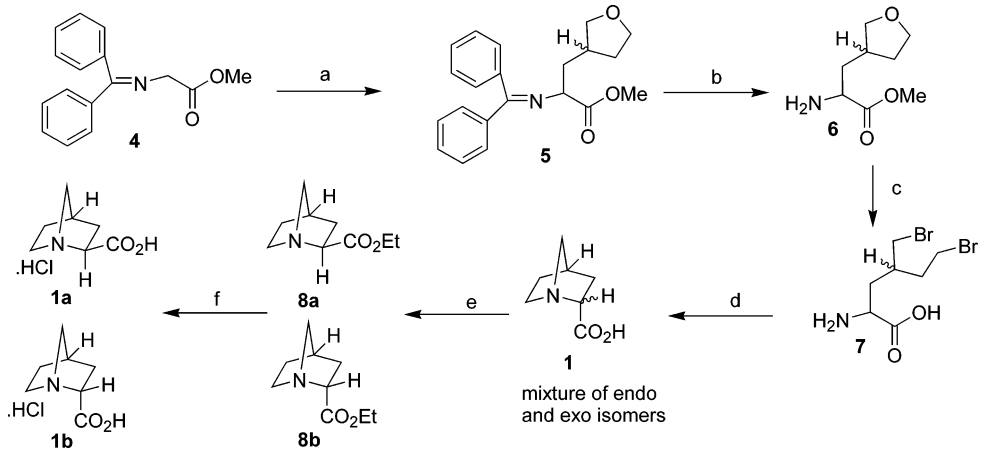
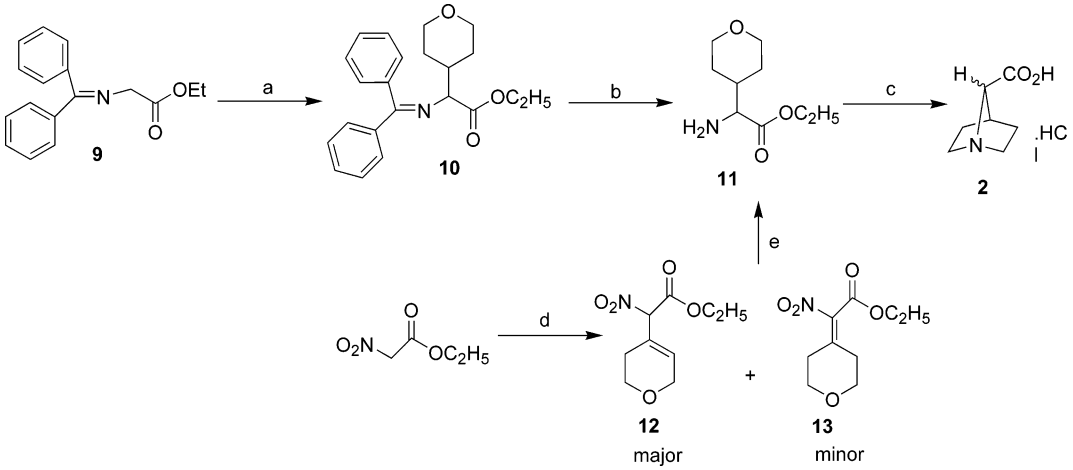
SCHEME 2. Synthesis of 1-Azabicyclo[2.2.1]heptane-2-carboxylic Acid[a]



[a] Reagents and conditions: (a) KO^{t}Bu, 3-iodomethyltetrahydrofuran, DMF/toluene (1:1), 25 °C, (b) (i) 2 N HCl, (ii) $NaHCO_3$, (c) 48% HBr, $HBr_{(g)}$, 120 °C sealed tube, 8 h, (d) NH_4OH, 60 °C, (e) EtOH, concd H_2SO_4, reflux, 8 h, and (f) (i) $NaHCO_3$, (ii) concd HCl.

SCHEME 3. Synthesis of 1-Azabicyclo[2.2.1]heptane-7-carboxylic Acid[a]



[a] Reagents and conditions: (a) LDA, 4-iodotetrahydropyran, THF, −78 °C, (b) (i) 2 N HCl, (ii) $NaHCO_3$, (c) (i) 48% HBr, $HBr_{(g)}$, 120 °C sealed tube, 8 h, (ii) NH_4OH, 60 °C, (iii) H_2SO_4, EtOH, reflux, (iv) concd HCl, reflux, (d) tetrahydropyran-4-one, $TiCl_4$, *N*-methylmorpholine, THF, 0 °C, and (e) H_2, EtOH, Raney Ni.

A number of groups have described the alkylation of benzophenone imine glycine enolates.[9,11] O'Donnell et al. pioneered use of ester analogue **4** for glycine ester alkylation under remarkably mild conditions.[9] Subsequently, other workers have employed related glycine amide benzophenone imines[12] or bis(methylthio)methylene imines[13] for similar alkylations. In our work, we found that when the electrophile tetrahydro-3-iodomethylfuran,[14] a primary iodide, was used, the alkylated imine **5** was obtained in accordance with the observations of O'Donnell and Wojciechowski,[15] and subsequent hydrolysis with 2 N HCl gave amino acid ester **6** (68% from **4**). Bicyclic tertiary α-amino acid **1** was obtained in 90% yield from **6** via a sealed tube reaction with HBr at 120 °C for 8 h followed by treatment with NH_4OH at 60 °C for 4 h (Scheme 2).

Determination of *exo*- and *endo*-isomers was based upon the chemical shift and coupling constants for H atoms attached to C-2 and C-3 in the bicyclic system. We have proposed that the hydrogen attached to C-2 for *exo*-isomer **8a** will be shielded to a greater extent than that for *endo*-isomer **8b**. Esterification of bicyclic amino acid **1** allowed for the separation of *exo*- and *endo*-isomers **8a** and **8b**. Assignment of their ^{1}H NMR spectra allowed us to designate **8a** (*C*2-H, δ 3.15−3.20, dtd, J = 6.6 Hz, 1H) as *exo* and **8b** (*C*2-H, δ 3.67−3.73, dddd, J = 5.2, 10.6 Hz, 1H) as *endo*. Saponification of **8a** and **8b** with $NaHCO_3$ gave amino acids **1a** and **1b** as racemic mixtures.

Alkylation of benzophenone imines **4** and **9** with KO^{t}Bu failed to yield product when the electrophile tetrahydro-4*H*-pyran-4-iodide, a secondary iodide, was used (Scheme 3). However, deprotonation of benzophenone imine **9** with LDA at −78 °C gave the desired alkylated product **10**, albeit in low yield (22%), and hydrolysis with 2 N HCl gave amino acid ester **11**. An alternative approach to **11** was to use highly acidic nitroacetates in Lehnert's modification of the Knoevenagel

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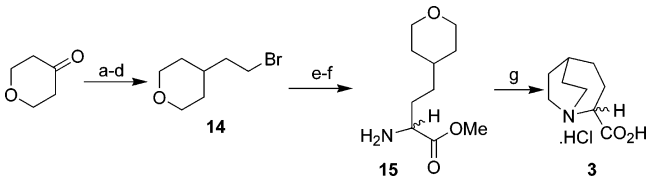
SCHEME 4. Synthesis of 1-Azabicyclo[3.2.2]nonane-2-carboxylic Acid[a]



[a] Reagents and conditions: (a) NaH, $(EtO)_2POCH_2CO_2Et$, benzene, 25 °C, (b) H_2, EtOH, Pd/C, (c) $LiAlH_4$, THF, 0 °C, (d) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, (ii) LiBr, acetone, reflux, (e) **4**, KO^{t}Bu, DMF/toluene (1:1), 0 °C, (f) (i) 2 N HCl, (ii) $NaHCO_3$, and (g) (i) 48% HBr, $HBr_{(g)}$, 120 °C sealed tube, 8 h, (ii) NH_4OH, 60 °C, (iii) H_2SO_4, EtOH, reflux, (iv) concd HCl, reflux.

condensation, employing $TiCl_4$ in the presence of *N*-methylmorpholine in THF.[10] With use of these conditions, tertrahydropyran-4-one and ethyl nitroacetate gave a mixture of isomers **12** (nonconjugated, major) and **13** (conjugated, minor) that were not separated (70%). Hydrogenation of this mixture of isomers with Raney Ni gave amino acid ethyl ester **11** in quantitative yield. Bicyclic tertiary α-amino acid **2** was obtained in 90% yield, in racemic form, as the HCl salt from **11** via a sealed tube reaction with a 48% solution of HBr saturated with $HBr_{(g)}$, followed by cyclization in NH_4OH, esterification to the ethyl ester, and subsequent hydrolysis with concd HCl. This procedure removed ammonium or hydrobromide salts.

Bicyclic α-amino acid **3** (racemic mixture) was synthesized in nine steps from tetrahydropyran-4-one (Scheme 4). Alkylation of imine **4** with 4-(2-bromoethyl)tetrahydropyran[16] **14** gave **15** in good yield (70%). Sealed tube reaction with HBr opened the pyran ring to the dibromo intermediate which was cyclized in NH_4OH, esterified to the ethyl ester, and subsequently hydrolyzed with concd HCl to give the desired amino acid **3** (85%).

In conclusion, the syntheses of three non-natural bicyclic α-amino acids have been accomplished from readily available starting materials. Currently, we are investigating the nonracemic synthesis of these tertiary bicyclic α-amino acids, and the results of these efforts will be reported in due course. We will also report the transformation of these amino acids into biologically active NNR ligands.

Experimental Section

General Experimental Procedures. See the Supporting Information.

General Procedure for the Synthesis of Bicyclic α-Amino Acids: *exo*-1-Azabicyclo[2.2.1]heptane-2-carboxylic Acid (1a), *endo*-1-Azabicyclo[2.2.1]heptane-2-carboxylic Acid (1b), 1-Azabicyclo-[2.2.1]heptane-7-carboxylic Acid (2), and 1-Azabicyclo[3.2.2]-nonane-2-carboxylic Acid (3). α-Substituted amino acid ester is taken up in 48% aq HBr. HBr gas was passed through the solution until full saturation. The contents were heated at 110−120 °C for 8 h in a sealed tube. The contents were taken up in a round-bottom flask and the acid was removed in vacuo by azeotroping with EtOH. The resultant solid was dissolved in 28% NH_4OH (∼10 mL for each 1 g) and heated at 60 °C for 4 h. The solid obtained after removal of NH_4OH was taken up in EtOH to which concd H_2SO_4 was added and heated at reflux for 8 h. The reaction mixture was cooled, basified with saturated aq $NaHCO_3$ solution, and extracted with $CHCl_3$ (4 × 10 mL). Combined organic extracts were dried over Na_2SO_4 and filtered and solvent was removed in vacuo. Ethyl ester was heated at reflux with concd HCl to give the hydrochloride salt.

(a) *exo*-1-Azabicyclo[2.2.1]heptane-2-carboxylic Acid (1a). ^{1}H NMR (300 MHz, D_2O) δ 4.13−4.18 (t, J = 15.6 Hz, 1H), 3.26−3.32 (m, 1H), 3.13−3.22 (m, 3H), 2.89 (br s, 1H), 1.98−2.14 (m, 3H), 1.63−1.66 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 171.5, 64.8, 58.9, 52.4, 35.1, 33.4, 26.2. Anal. Calcd for $C_7H_{11}NO_2$·HCl: C, 47.33; H, 6.81; N, 7.89; Cl, 19.96. Found: C, 47.28; H, 6.87; N, 7.78; Cl, 19.82.

(b) *endo*-1-Azabicyclo[2.2.1]heptane-2-carboxylic Acid (1b). ^{1}H NMR (300 MHz, D_2O) δ 4.43−4.50 (dddd, J = 20.8 Hz, 1H), 3.42−3.56 (m, 1H), 3.32−3.34 (m, 1H), 3.27−3.30 (br d, J = 9.3 Hz, 1H), 3.18−3.21 (br d, J = 9.3 Hz, 1H), 2.90−2.93 (t, J = 8.8 Hz, 1H), 2.24−2.36 (m, 1H), 1.94−2.06 (m, 1H), 1.76−1.83 (dddd, J = 21.0 Hz, 1H), 1.59−1.69 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 169.8, 64.8, 60.7, 49.0, 36.4, 29.5, 27.5. Anal. Calcd for $C_7H_{11}NO_2$·HCl: C, 47.33; H, 6.81; N, 7.89; Cl, 19.96. Found: C, 46.87; H, 6.84; N, 7.82; Cl, 20.04.

(c) 1-Azabicyclo[2.2.1]heptane-7-carboxylic Acid (2). Crystallized from IPA and ether as a light brown solid (961 mg, 85%). m.p. = turned brown at 231 °C and melted at 254 °C. ^{1}H NMR (300 MHz, D_2O) δ 4.15−4.16 (d, J = 1.2 Hz, 1H), 3.56−3.67 (m, 1H), 3.24−3.36 (m, 1H), 3.04−3.16 (m, 2H), 2.92−2.97 (t, J = 8.1 Hz, 1H), 2.01−2.14 (m, 1H), 1.84−1.97 (m, 1H), 1.59−1.76 (m, 2H); ^{13}C NMR (75 MHz, D_2O) δ 168.8, 71.4, 53.4, 51.6, 37.8, 27.2, 26.5; MS (FD) m/z 142 (M + H). Anal. Calcd for $C_7H_{11}NO_2$·HCl: C, 47.33; H, 6.81; N, 7.89; Cl, 19.96. Found: C, 47.07; H, 6.73; N, 7.92; Cl, 19.76.

(d) 1-Azabicyclo[3.2.2]nonane-2-carboxylic Acid (3). ^{1}H NMR (300 MHz, D_2O) δ 4.11−4.17 (dd, J = 16.6 Hz, 1H), 3.19−3.42 (m, 4H), 2.19−2.30 (m, 2H), 1.78−2.08 (m, 6H), 1.58−1.72 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 171.9, 67.5, 49.1, 44.1, 32.3, 24.6, 24.4, 23.6, 20.5. Anal. Calcd for $C_8H_{13}NO_2$·HCl: C, 50.14; H, 7.36; N, 7.31; Cl, 18.50. Found: C, 52.37; H, 9.00; N, 6.63; Cl, 17.42.

Supporting Information Available: Experimental details, synthetic methods for starting material preparation, characterization data, and ^{1}H NMR and ^{13}C NMR spectra of compounds **1a**, **1b**, **2**, and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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