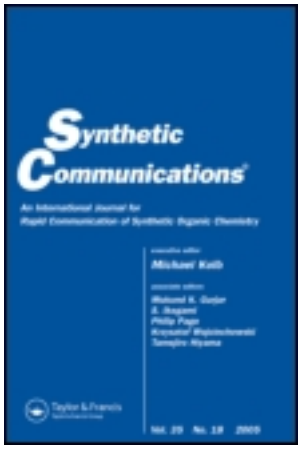

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Expedient Synthesis of cis- and trans-3-Aminocyclobutanecarboxylic Acids

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EXPEDIENT SYNTHESIS OF *CIS*- AND *TRANS*-3-AMINOCYCLOBUTANECARBOXYLIC ACIDS

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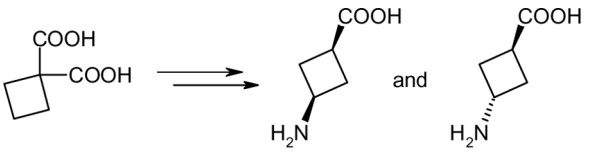
GRAPHICAL ABSTRACT



Abstract *An expedient approach to* cis- *and* trans-*3-aminocyclobutanecarboxylic acids was developed starting from 1,1-cyclobutanedicarboxylic acid. Stereochemistry of the title compounds was established by nuclear Overhauser effect spectroscopy experiments.*

Keywords Amino acids; conformational restriction; cyclobutanes; drug design; GABA analogs

INTRODUCTION

Conformationally restricted amino acids have been shown to be efficient scaffolds in modern drug design.[1] The restriction is often achieved by the use of small rings; small-ring-derived amino acids have attracted much attention in recent decades, partially because of their occurrence in nature. In particular, a number of cyclobutane-derived analogs of natural amino acids, either isolated from living organisms or synthesized in the laboratory, were described in the literature.[1,2]

In this work, we report our results on the synthesis of 3-aminocyclobutanecarboxylic acid **1**, which is the simplest achiral cyclic conformationally restricted γ-aminobutyric acid analog (Figure 1). γ-Aminobutyric acid (GABA) **2** is the chief inhibitory neurotransmitter in the mammalian central nervous system.[3] A number of drugs are aimed at GABA receptors as their biological targets, and hence it is not surprising that many γ-aminobutyric acid analogs were reported in the literature.[4] Despite the fact that both isomers of **1** showed only moderate or poor activity on

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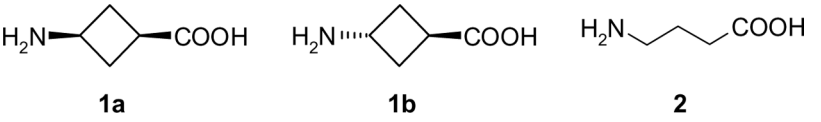
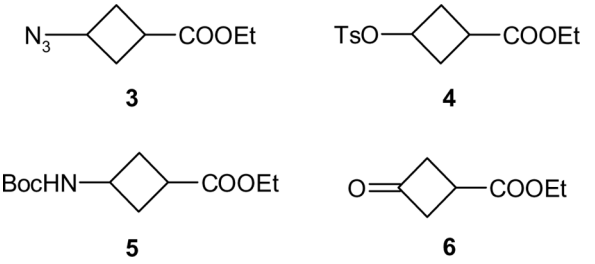


1a 1b 2

Figure 1. γ-Amino acids **1** and **2**.



3 4 5 6

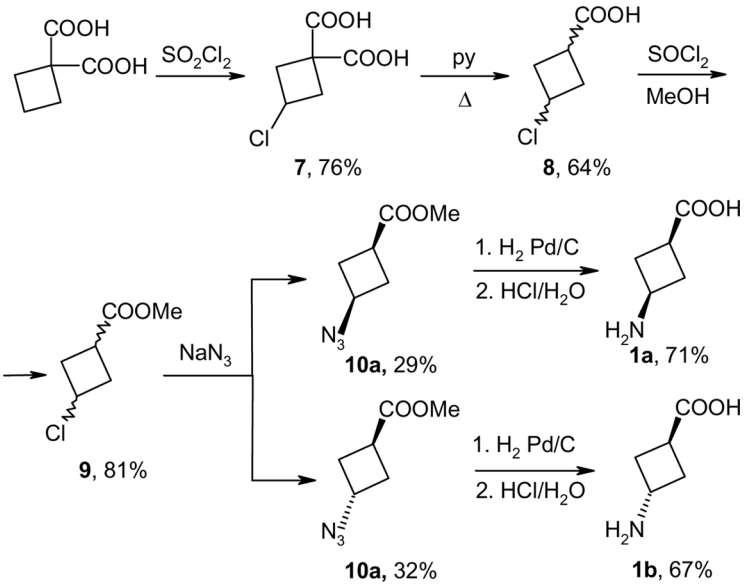
Figure 2. Key intermediates in the syntheses of **1** reported previously.

GABA receptors,[5–7] they are promising building blocks for drug discovery. For example, recently both isomers of amino acid **1** were used in the design of cholesteryl ester transfer protein (CETP) inhibitors,[8] sphingosine 1-phosphate receptor S1P1/Edg1 agonists,[9] and phosphodiesterase PDE4 inhibitors.[10]

Several syntheses of amino acid **1** were reported in the literature. In particular, compound **1** was prepared as a mixture of stereoisomers in nine steps starting from epibromohydrine, azide **3** being the key intermediate (Figure 2). Pure *cis*-isomer **1a** was obtained by tedious crystallization of the mixture; isolation of the *trans*-isomer **1b** required transformation of **1** to the corresponding methyl ester of its *N*-carboxybenzyl derivative.[5] In another approach, a mixture of isomers **1a** and **1b** was prepared from epichlorohydrine in nine steps via tosylate **4**; ion-exchange chromatography was used to separate the diastereomers of the title amino acid.[6] Recently, a method for the synthesis of both *cis*- and *trans*-isomers of *Boc*-aminoester **5** was reported;[10] it commenced from the keto ester **6**. Column chromatography was used to separate diastereomers. The main disadvantage of the latter approach is that the starting compound **6** is not easily available. Finally, multistep methods for the stereoselective synthesis of *cis*-isomer **1a** were described in the literature.[5,6]

RESULTS AND DISCUSSION

All the previous methods for the preparation of amino acid **1** relied on the construction of 1,3-disubstituted cyclobutane core as one of the key steps in the synthesis. In our approach to the synthesis of **1**, the functional group at C-3 atom of cyclobutane ring was introduced *after* the construction of cyclobutane ring (Scheme 1). 1,1-Cyclobutanedicarboxylic acid (which is readily available from commercial sources) was chlorinated to give 1,1,3-trisubstituted cyclobutane **7**.[11] Compound **7** was decarboxylated to afford 3-chlorocyclobutanecarboxylic acid **8** as a mixture of diastereomers. Esterification of **8** followed by reaction with sodium



Scheme 1. Synthesis of amino acids **1a** and **1b**.

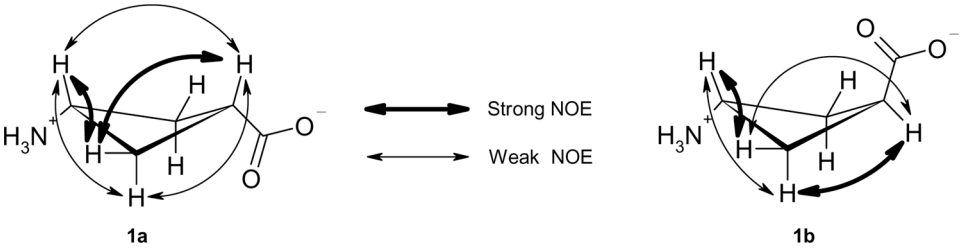


Figure 3. NOESY correlations in the spectra of *cis*- and *trans*-3-aminocyclobutanecarboxylic acids **1a** and **1b**.

azide led to the azido esters **10a** and **10b**, which were easily separated by column chromatography ($R_f = 0.39$ and 0.50, respectively). Both compounds **10a** and **10b** were transformed to the corresponding amino acids **1a** and **1b** by a hydrogenation–hydrolysis sequence. The assignment of the stereochemistry of **2a** and 2**b** was done using nuclear Overhauser effect spectroscopy (NOESY) experiments (Fig. 3).

In conclusion, an expedient synthesis of both isomers of 3-aminocyclobutanecarboxylic acid **1** was developed. The high efficiency (six steps, 16% total yield) of the synthesis permits multigram preparation of the title amino acids.

EXPERIMENTAL

Solvents were purified according to the standard procedures. All starting materials were purchased from Acros, Merck, and Fluka. Analytical thin-layer

chromatography (TLC) was done using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H, ^{13}C NMR, and all two-dimentional NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 499.9 MHz for ^{1}H, 124.9 MHz for ^{13}C). Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS; ^{1}H, ^{13}C) as an internal standard. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument [chemical ionization (CI)] and Agilent 5890 series II 5972 gas chromatography–mass spectrometry (GCMS) instrument [electron impact ionization (EI)]. Elemental analyses were performed on Elementar Vario MICRO Cube CHNS/O analyzer.

3-Chlorocyclobutanecarboxylic Acid (8)

3-Chlorocyclobutane-1,1-dicarboxylic acid (22.6 g, 0.127 mol)[11] was dissolved in pyridine (250 mL), and the solution was refluxed for 18 h. After cooling, most of the solvent was removed in vacuo, and water (200 mL) was added to the residue, followed by 6 N HCl, to adjust the pH to 2. The resulting mixture was extracted with dichloromethane (DCM, 2×150 mL). The combined organic phases were washed with brine, dried over sodium sulfate, and evaporated at reduced pressure to afford a mixture of *cis*- and *trans*-3-chlorocyclobutanecarboxylic acids **8** (10.9 g, 0.081 mol, 64%), which was pure enough for the next step. For spectral and physical data, see Ref.[12]

Methyl 3-Chlorocyclobutanecarboxylate (9)

3-Chlorocyclobutanecarboxylic acid **8** (10.9 g, 0.081 mol) was dissolved in DCM (100 mL), and thionyl chloride (7.1, 0.097 mol) was added carefully. The resulting mixture was refluxed for 1 h. The volatiles were removed in vacuum, and methanol (100 mL) was added to the residue. The solution was refluxed for 1 h, then cooled and evaporated. The residue was distilled under reduced pressure (bp 52–53 °C/2 mmHg) to give an equimolar mixture of *cis*- and *trans*-methyl 3-chlorocyclobutanecarboxylates as colorless liquids (9.8 g, 0.066 mol, 81%). For spectral and physical data, see Ref.[12]

cis- and *trans*-Methyl 3-azidocyclobutanecarboxylates (10a and 10b)

Methyl 3-chlorocyclobutanecarboxylate **9** (5.6 g, 0.038 mol) was dissolved in dimethylformamide (60 mL), and sodium azide (5.9 g, 0.091 mol) was added. The resulting mixture was stirred at 100 °C for 75 h. After cooling, water (80 mL) was added, and the resulting mixture was extracted with DCM (2×50 mL). The combined organic phases were washed with brine, dried over sodium sulfate, and evaporated in vacuum. The residue was subjected to flash column chromatography to afford methyl *trans*-3-azidocyclobutanecarboxylate **10b** (1.87 g, 0.012 mol, 32%, eluted first) and *cis*-3-azidocyclobutanecarboxylate **10a** (1.70 g, 0.011 mol, 29%, eluted next) as pure colorless liquids. **10a**: MS (m/z, EI): 124 (M^{+}–OCH_3), 113 (M^{+}–N_3), 99, 87, 68, 59, 41 ($COOCH_3^{+}$). Anal. calcd. for $C_6H_9N_3O_2$: C 46.45, H 5.85, N 27.08, found C 46.71, H 6.08, N 26.99; ^{1}H NMR ($CDCl_3$), δ: 3.75 (quint,

J = 8.0 Hz, 1H, 3-C*H*), 3.66 (s, 3H, COOCH_3), 2.78 (quint, *J* = 8.8 Hz, 1H, 1-C*H*), 2.49–2.55 (m, 2H, 2- and 4-CH*H*), 2.30–2.36 (m, 2H, 2- and 4-C*H*H); ^{13}C NMR ($CDCl_3$), δ: 174.0 (*C*OOCH$_3$), 52.0, 50.8, 32.6, 30.6. **10b**: MS (*m*/*z*, EI): 124 (M^+–OCH_3), 113 (M^+–N_3), 99, 87, 68, 59, 41 ($COOCH_3^+$). Anal. calcd. for $C_6H_9N_3O_2$: C 46.45, H 5.85, N 27.08, found C 46.28, H 5.87, N 27.24; ^{1}H NMR ($CDCl_3$), δ: 4.14 (quint, J = 7.8 Hz, 1H, 3-C*H*), 3.68 (s, 3H, COOCH_3); 3.07–3.13 (m, 1H, 1-C*H*), 2.53–2.58 (m, 2H, 2- and 4-CH*H*), 2.29–2.34 (m, 2H, 2- and 4-C*H*H); ^{13}C NMR ($CDCl_3$), δ: 175.4 (*C*OOCH$_3$), 51.9, 49.4, 32.7, 32.1.

cis-3-Aminocyclobutanecarboxylic acid (1a)

Azide **10a** (0.30 g, 1.9 mmol) was dissolved in methanol (5 mL); then 6 N HCl (2 mL) and 10% palladium on charcoal were added to the solution. The resulting mixture was stirred under 1 bar of hydrogen for 3 h, then the catalyst was filtered off, and the solvent was removed under reduced pressure. The residue was dissolved in 6 N HCl (5 mL) and refluxed upon stirring for 1 h, then evaporated in vacuum. The residue was purified by ion-exchange chromatography (Amberlite® IR-120(plus) ion-exchange resin, 3.5% aqueous ammonia as an eluent) to give *cis*-3-aminocyclobutanecarboxylic acid **1a** (0.16 g, 1.4 mmol, 71%) as white powder: mp > 250 °C (dec.); Anal. calcd. for $C_5H_9NO_2$: C 52.16, H 7.88, N 12.17, found C 51.93, H 7.96, N 12.01; ^{1}H NMR (D_2O), δ: 3.66 (quint, *J* = 8.0 Hz, 1H, 3-C*H*), 2.80 (quint, *J* = 9.0 Hz, 1H, 1-C*H*), 2.49–2.54 (m, 2H, 2- and 4-C*H*H), 2.12–2.18 (m, 2H, 2- and 4-C*H*H); ^{13}C NMR (D_2O), δ: 182.7 (*C*OO$^-$), 41.2 (3-*C*H), 33.9, 31.1.

trans-3-Aminocyclobutanecarboxylic acid (1b)

Compound **1b** was obtained from azide **10b** analogously to the *cis*-isomer in 67% (0.17 g) yield as white solid: mp > 250 °C (dec.). Anal. calcd. for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17; found C, 52.42; H, 8.10; N, 11.92. ^{1}H NMR (D_2O), δ: 3.84 (quint, *J* = 8.0 Hz, 1H, 3-C*H*), 3.06 (tt, *J* = 10.3 Hz and 5.1 Hz, 1H, 1-C*H*), 2.47–2.53 (m, 2H, 2- and 4-C*H*H), 2.30–2.36 (m, 2H, 2- and 4-C*H*H); ^{13}C NMR (D_2O), δ: 183.3 (*C*OO$^-$), 44.0 (3-*C*H), 35.2, 30.2.

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