Simple and Efficient Procedure for a Multigram Synthesis of Both *trans*- and *cis*-1-Amino-2-(trifluoromethyl)cyclopropane-1-carboxylic Acid

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Abstract: A simple and efficient procedure for the multigram synthesis of both (±)-*trans*- and (±)-*cis*-1-amino-2-(trifluoromethyl)cyclopropane-1-carboxylic acid was developed. The key step of the synthesis is the addition of 1-diazo-2,2,2-trifluoroethane to methyl 2-[(*tert*-butoxycarbonyl)amino]acrylate, followed by thermal decomposition of the resulting pyrazoline. Gram quantities of *trans*- and *cis*-1-amino-2-(trifluoromethyl)cyclopropane-1-carboxylic acid were easily prepared from L-serine in one synthetic run.

Key words: fluorine, alkenes, amino acids, catalysts, diazo compounds

1-Aminocyclopropane-1-carboxylic acid (Acc, Figure 1) is a natural compound isolated first from cider apples and perry pears.[1] Since its identification as the intermediate in the biosynthesis of ethylene,[2] Acc has been of considerable interest to biologists and chemists alike.[3] Moreover, in recent years Acc has attracted much attention in medicinal chemistry as a valuable building block.[4] In addition, derivatives of Acc have been used as enzyme inhibitors and biosynthetic and mechanistic probes.[5] On the other hand, introduction of fluorine-containing substituents into Acc could advantageously modify its properties by changing the chemical stability and electronic effects.[6] Little is, however, known to date on the fluorinated analogues of Acc.[7] Therefore, in the present work we wish to report a simple and efficient procedure for the practical multigram synthesis of trifluoromethyl-substituted analogues of Acc: isomeric amino acids **1a** and **1b** (Figure 1).

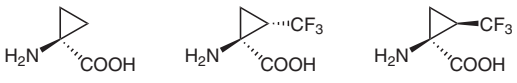
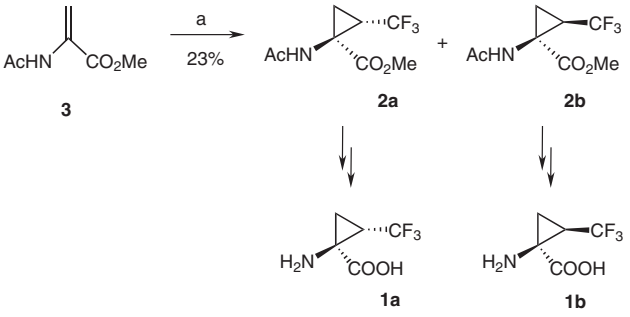


Figure 1 1-Aminocyclopropane-1-carboxylic acid (Acc) and its trifluoromethyl-substituted analogues **1a** and **1b**

Several syntheses of **1a** and **1b** have been described in the literature. In 2000, Uneyama et al. reported the first stereoselective approach to optically active **1a** and **1b**, but on a milligram scale only (50 mg of **1a**, 5 steps, 20% overall yield; 5 mg of Boc-**1b**, 6 steps, 5% overall yield).[7b,c] In addition, several steps of the abovementioned synthesis included the use of butyllithium, sodium hydride, and sodium hexamethyldisilazide, which require great caution, thereby making the scale-up procedure rather unlikely. In 2003, another strategy to (±)-**1a** was described.[7d] However, in that publication neither detailed experimental details, nor the scale of the synthesis was given. Recently, we reported a new approach to both (±)-**1a** and (±)-**1b** (Scheme 1).[7e]



Scheme 1 *Reagents and conditions*: (a) $Rh_2(OAc)_4$, CF_3CHN_2 (5 equiv), CH_2Cl_2.

However, the isomers **2a/2b** were obtained in milligram quantities, with the key transformation **3**→**2a/2b** performed with a yield of only 23%.[7e] Moreover, this procedure required the use of rather expensive dirhodium(II) tetraacetate (Scheme 1). Therefore, as reported here, we have optimized the abovementioned strategy in order to easily obtain both (±)-**1a** and (±)-**1b** in multigram quantities from L-serine without use of rhodium reagents.

Since the dirhodium(II) tetraacetate mediated addition of 1-diazo-2,2,2-trifluoroethane to alkene **3** led to **2a/2b** in very poor yield (Scheme 1),[7e] a 'pyrazoline strategy'[4a,7a,8] was attempted next (Scheme 2). Indeed, 1-diazo-2,2,2-trifluoroethane reacted smoothly with **3** at room temperature to form pyrazoline **4**, which was thermally decomposed to afford an isomeric mixture of **2a** and **2b** in an overall yield of 86%.

However, although isomers **2a** and **2b** were previously separated by flash column chromatography on the milligram scale, separation of gram quantities of **2a/2b** turned

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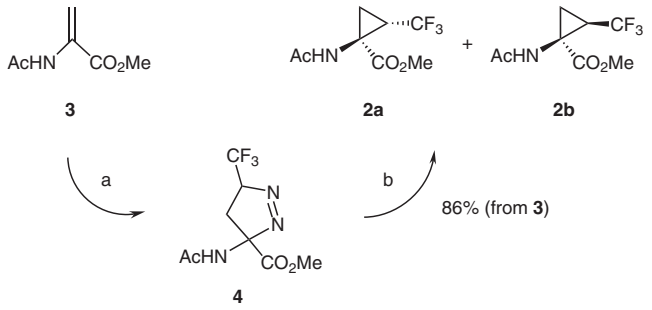
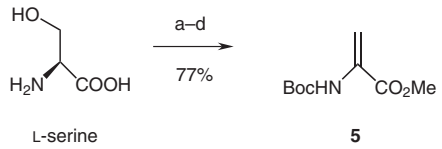


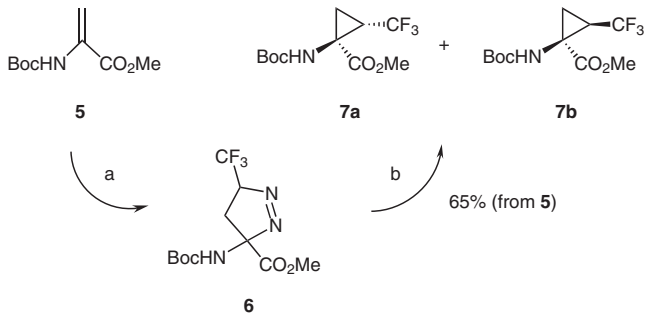
Scheme 2 *Reagents and conditions*: (a) CF_3CHN_2 (5 equiv), CH_2Cl_2; (b) 70 °C, 1 h.

out to be completely ineffective, because of a too small difference in their retention factors (R_f; see the experimental section). To facilitate a practical separation of the diastereomers, we replaced the acetyl residue in **2a/2b** with the much bulkier N-protecting group *tert*-butoxycarbonyl. The corresponding starting compound **5** was easily obtained from L-serine in 77% yield by following literature procedures[9] (Scheme 3).



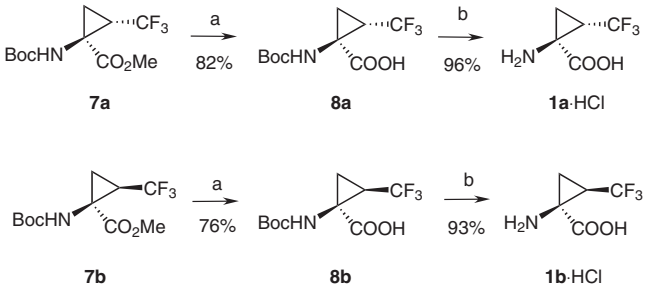
Scheme 3 *Reagents and conditions*: (a) $SOCl_2$, MeOH, 20 h, r.t.; (b) Boc_2O (1.2 equiv), Et_3N (2.5 equiv), CH_2Cl_2, r.t., 3 h; (c) Boc_2O (2.2 equiv), DMAP (0.1 equiv), MeCN, r.t., 12 h; (d) TFA (1.5 equiv), CH_2Cl_2, r.t., 12 h.

Next, the reaction of alkene **5** with 1-diazo-2,2,2-trifluoroethane to form pyrazoline **6** was carried out (Scheme 4). Subsequently, thermal decomposition of **6** afforded the mixture **7a/7b** (4:1) in 65% yield. Separation of ca. 45 g of **7a/7b** was easily performed by flash column chromatography, since the retention factors of isomers **7a/7b** indeed had a larger difference than those of the cyclopropanes **2a/2b** (see the experimental section).



Scheme 4 *Reagents and conditions*: (a) CF_3CHN_2 (5 equiv), CH_2Cl_2; (b) 70 °C, 1 h.

Finally, basic hydrolysis of the methoxycarbonyl group, followed by a standard acidic cleavage of the *tert*-butoxycarbonyl group afforded the final amino acids **1a** (19 g) and **1b** (5 g) (Scheme 5).



Scheme 5 *Reagents and conditions*: (a) 1. LiOH (4 equiv), MeOH, 2 h; 2. HCl; (b) HCl, 65 °C, 2 h.

The stereoconfiguration of the amino acids thus obtained was determined by NOESY experiments of compound **8b** (Figure 2).[10]

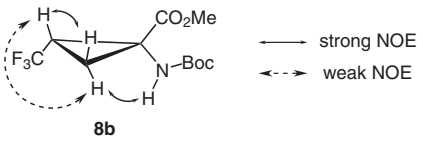


Figure 2 Determination of the stereochemistry of **8b** by H,H-NOESY experiments

In conclusion, we have developed a simple and efficient procedure for the multigram synthesis of both (±)-*trans*- and (±)-*cis*-1-amino-2-(trifluoromethyl)cyclopropane-1-carboxylic acids (**1a/1b**). Thus, **1a** (19 g) and **1b** (5 g) were easily synthesized from L-serine in one synthetic run.

Solvents were purified according to standard procedures. Alkenes **3**[11] and **5**[9] were synthesized from L-serine by following procedures described in the literature. All other materials were purchased from Aldrich and Enamine. Melting points are uncorrected. Analytical TLC was perfomed on Polychrom SI F_{254} plates. Column chromatography was performed on Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H-, ^{13}C-, and ^{19}F NMR spectra were recorded either on a Varian Unity Plus 400 spectrometer (at 400.4, 100.7, and 376.7 Hz, respectively) or on a Bruker Avance 500 spectrometer (at 499.9 MHz, 124.9, and 470.3 MHz, respectively). Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F) as internal standards. IR spectra were obtained on a Hewlett Packard UR 20 spectrometer. Mass spectra by the CI method were recorded on an Agilent 1100 LCMSD SL instrument.

Methyl 3-(Acetylamino)-5-(trifluoromethyl)-4,5-dihydro-3*H*-pyrazole-3-carboxylate (4)

A soln of CF_3CHN_2·HCl (116 g, 1.68 mol, 5 equiv) in H_2O (150 mL) was slowly added (~5–7 h) to a stirred mixture of a soln of $NaNO_2$ (227 g, 1.68 mol, 5 equiv) in H_2O (300 mL) and dodecane (200 mL). Upon addition, the CF_3CHN_2 that had formed was gradually blown off by an inert gas through a drying tube ($MgSO_4$) into a vessel containing a stirring soln of **3** (48 g, 335 mmol, 1 equiv) in CH_2Cl_2 (200 mL). After the addition had been completed, the solvent was gently removed on a rotary evaporator in vacuum at r.t.; this gave crude **4**.

Yield: 84 g (100%); white solid; mp >40 °C (dec).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (br s, 1 H, N*H*), 5.82 (m, 1 H, C*H*CF_3), 3.87 (s, 3 H, OCH_3), 2.25 (dd, *J* = 13.5, 10.0 Hz, 1 H, CH_2), 2.09 (dd, *J* = 13.5, 7.0 Hz, 1 H, CH_2), 2.05 (s, 3 H, CH_3CO).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.46 (s, COO), 167.57 (s, CONH), 123.61 (q, ^1J(C,F) = 278.8 Hz, CF_3), 102.82 (s, NH*C*CO), 93.10 (q, ^2J(C,F) = 28.8 Hz, *C*HCF_3), 54.44 (s, OCH_3), 25.70 (s, CH_2), 23.44 (s, *C*H_3CO).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –72.09 (s, CF_3).

MS (CI): *m*/*z* = 226 [M – N_2 + 1]$^+$.

Methyl 1-(Acetylamino)-2-(trifluoromethyl)cyclopropane-1-carboxylate (2a/2b)

After the CH_2Cl_2 had been completely removed during the isolation of **4** (see the previous step), the temperature of the water bath was increased to 50–70 °C; this led to exothermic evolution of N_2. After **4** had been heated at 70 °C for 1 h, the reaction was completed to form cyclopropanes **2a/2b**.

Although small quantities (mg scale) of **2a/2b** had been separated by flash column chromatography,[7e] the difference between the R_f values of **2a** and **2b** was too small to make separation feasible for gram quantities of **2a/2b** [R_f difference <0.05; R_f = ~0.4 (CH_2Cl_2–MeOH, 5:1)].

Total yield: 65 g (86%); oil.

LC-MS (CI): *m*/*z* = 226 (2 peaks) [M + 1]$^+$.

Methyl 3-[(*tert*-Butoxycarbonyl)amino]-5-(trifluoromethyl)-4,5-dihydro-3*H*-pyrazole-3-carboxylate (6)

Crude **6** was obtained from alkene **5** (46 g, 229 mmol) analogously to the synthesis of **4** from alkene **3**. It was immediately used in the next step without purification.

White solid; mp >40 °C (dec).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.48 (br s, 1 H, N*H*), 5.79 (m, 1 H, C*H*CF_3), 3.86 (s, 3 H, OCH_3), 2.24 (dd, *J* = 13.5, 9.0 Hz, 1 H, CH_2), 2.13 (dd, *J* = 13.5, 7.0 Hz, 1 H, CH_2), 1.39 (s, 9 H, (CH_3)$_3$C).

MS (CI): *m*/*z* = 284 [M – N_2 + 1]$^+$.

(±)-Methyl Cyclopropanecarboxylates 7a and 7b

The crude mixture **7a/7b** was obtained from pyrazoline **6** (71 g, 229 mmol) by the same procedure applied for preparing **2a/2b** from **4**. To remove impurities of the alkenes that had formed, the crude **7a/7b** mixture was dissolved in CH_2Cl_2 (700 mL), triturated with 10% aq $KMnO_4$ (1 L), washed with H_2O (1 L), dried over $MgSO_4$, and evaporated. The diastereomeric mixture **7a/7b** (~45 g) was separated by flash column chromatography (silica gel, hexane–EtOAc, 10:1). For an efficient separation of the whole quantity of **7a/7b**, ~1 kg silica gel was used. The isomer **7a** (51% from **5**) eluted first (R_f = 0.4). Further elution afforded isomer **7b** (R_f = 0.3) (14% from **5**).

(±)-Methyl (1*S*,2*R*)-1-[(*tert*-Butoxycarbonyl)amino]-2-(trifluoromethyl)cyclopropane-1-carboxylate (7a)

Yield: 33 g (51% from **5**); R_f = 0.4 (hexane–EtOAc, 10:1; white solid; mp 53–54 °C.

IR (KBr): 1730 (br, $\nu_{C=O}$) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.33 (br s, 1 H, N*H*), 3.75 (s, 3 H, OCH_3), 2.18 (m, 2 H, CH_2), 1.61 (m, 1 H, C*H*CF_3), 1.43 (s, 9 H, (CH_3)$_3$C).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.79 (s, *C*OOMe), 155.36 (s, NCO), 125.13 (q, ^1J(C,F) = 269.1 Hz, CF_3), 80.92 (s, O*C*(CH$_3$)$_3$), 52.84 (s, OCH_3), 38.74 (s, N*C*COOH), 31.33 (br s, *C*HCF_3), 28.16 (s, OC(*C*H$_3$)$_3$), 18.72 (s, CH_2).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –61.48 (br s, CF_3).

MS (CI): *m*/*z* = 284 [M + 1]$^+$.

(±)-Methyl (1*S*,2*S*)-1-[(*tert*-Butoxycarbonyl)amino]-2-(trifluoromethyl)cyclopropane-1-carboxylate (7b)

Yield: 9 g (14% from **5**); white solid; R_f = 0.3; mp 53–54 °C.

IR (KBr): 1737 ($\nu_{C=O}$, CO_2Me), 1695 ($\nu_{C=O}$, NHBoc) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.10 (br s, 1 H, N*H*), 3.75 (s, 3 H, OCH_3), 2.45 (m, 1 H, C*H*CF_3), 1.96 (m, 1 H, C*H*H), 1.79 (m, 1 H, CH*H*), 1.43 (s, 9 H, (CH_3)$_3$C).

^{13}C NMR (125 MHz, DMSO-d_6): δ (rotamers) = 167.44 (s, *C*OOMe), 156.03 (s, NCO), 126.23 (q, ^1J(C,F) = 272.3 Hz, CF_3), 79.22 (s, O*C*(CH$_3$)$_3$), 53.14 (s, OCH_3), 37.86 (s, N*C*COOH), 28.52, 28.17 (2 s, OC(*C*H$_3$)$_3$), 25.85 (^2J(C,F) = 36.5 Hz, *C*HCF_3), 16.95 (s, CH_2).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –49.04 (d, ^3J(F, H) = 4.7 Hz, CF_3).

MS (CI): *m*/*z* = 284 [M + 1]$^+$.

(±)-(1*S*,2*R*)-1-[(*tert*-Butoxycarbonyl)amino]-2-(trifluoromethyl)cyclopropane-1-carboxylic acid (8a)

LiOH·H_2O (20 g, 476 mmol, 4 equiv) was slowly added to a stirring soln of **7a** (34 g, 117 mmol, 1 equiv) in MeOH–THF (3:4, 1.4 L). The mixture was then stirred for 3 h at r.t. and evaporated to produce a yellowish solid. The mixture thus formed was dissolved in H_2O (~500 mL) and extracted with CH_2Cl_2 (3 × 70 mL). The organic phase was discarded and the aqueous phase was acidified to pH 4 by use of aq HCl. The thus formed suspension was extracted again with EtOAc (3 × 100 mL). The organic phase was separated, dried over Na_2SO_4, and evaporated to produce **8a**.

Yield: 26 g (82%); white solid; mp 152–153 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.19 (m, 2 H, CH_2), 1.62 (m, 1 H, C*H*CF_3), 1.46 (s, 9 H, (CH_3)$_3$C).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 171.70 (s, *C*OOMe), 156.22 (s, NCO), 125.42 (q, ^1J(C,F) = 272.9 Hz, CF_3), 79.02 (s, O*C*(CH$_3$)$_3$), 38.47 (s, N*C*COOH), 29.53 (q, ^2J(C,F) = 37.7 Hz, *C*HCF_3), 28.59 (s, OC(*C*H$_3$)$_3$), 18.71 (s, CH_2).

^{19}F NMR (470 MHz, DMSO-d_6): δ = –62.39 (br s, CF_3).

MS (CI): *m*/*z* = 270 [M + 1]$^+$.

(±)-(1*S*,2*S*)-1-[(*tert*-Butoxycarbonyl)amino]-2-(trifluoromethyl)cyclopropane-1-carboxylic acid (8b)

Compound **8b** was obtained from **7b** (9 g, 32 mmol) by an analogous method to that used to obtain **8a** from **7a**.

Yield: 6.5 g (76%); white solid; mp 157–158 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.14 (N*H*), 2.50 (br s, 1 H, C*H*CF_3), 2.00 (br s, 1 H, C*H*H), 1.80 (br s, 1 H, CH*H*), 1.46 (s, 9 H, (CH_3)$_3$C).

^{13}C NMR (125 MHz, DMSO-d_6): δ (rotamers) = 171.90, 171.68 (2 s, *C*OOMe), 156.00, 155.33 (2 s, NCO), 125.35 (q, ^1J(C,F) = 271.6 Hz, CF_3), 78.93 (s, O*C*(CH$_3$)$_3$), 38.55, 37.66 (2 s, N*C*COOH), 28.56, 28.19 (2 s, OC(*C*H$_3$)$_3$), 25.62 (q, ^2J(C,F) = 32.7 Hz, *C*HCF_3), 16.79 (s, CH_2).

^{19}F NMR (470 MHz, DMSO-d_6): δ = –61.48 (br s, CF_3).

MS (CI): *m*/*z* = 270 [M + 1]$^+$.

(±)-(1*S*,2*R*)-1-Carboxy-2-(trifluoromethyl)cyclopropylammonium Chloride (1a)

An 8 N aq soln of HCl (45 mL) was added to a soln of **8a** (26 g, 96 mmol) in THF (200 mL). The stirred mixture was heated for 2 h at 65 °C. After cooling to r.t., the reaction mixture was washed with

EtOAc (3 × 70 mL). The organic phase was discarded, and the aqueous phase was evaporated in vacuum; this produced **1a**·HCl.

Yield: 19 g (96%); white solid; mp >200 °C.

^{1}H NMR (500 MHz, D_2O): δ = 2.57 (m, 1 H, C*H*CF_3), 2.11 (t, *J* = 8.0 Hz, 1 H, C*H*H), 1.35 (tq, *J* = 9.0, 1.5 Hz, 1 H, CH*H*).

^{13}C NMR (125 MHz, D_2O): δ = 168.38 (s, COOH), 123.55 (q, ^1J(C,F) = 271.3 Hz, CF_3), 37.74 (q, ^3J(C,F) = 2.5 Hz, N*C*COOH), 27.75 (q, ^2J(C,F) = 40.0 Hz, *C*HCF_3), 15.46 (q, ^3J(C,F) = 2.5 Hz, CH_2).

^{19}F NMR (470 MHz, D_2O): δ = –60.82 (d, ^3J(F,H) = 9.4 Hz, CF_3).

MS (CI): *m*/*z* = 170 $[M - Cl]^+$.

(±)-(1*S*,2*S*)-1-Carboxy-2-(trifluoromethyl)cyclopropylammonium Chloride (1b)

Compound **1b**·HCl was obtained from **8b** (6.5 g, 24 mmol) by an analogous method to that used to obtain **1a**·HCl from **8a**.

Yield: 4.6 g (93%); white solid; mp 157–158 °C.

^{1}H NMR (500 MHz, D_2O): δ = 2.77 (m, 1 H, C*H*CF_3), 1.93 (t, *J* = 8.0 Hz, 1 H, C*H*H), 1.83 (t, *J* = 8.0 Hz, 1 H, CH*H*).

^{13}C NMR (125 MHz, D_2O): δ = 169.90 (s, COOH), 124.10 (q, ^1J(C,F) = 272.9 Hz, CF_3), 37.13 (s, N*C*COOH), 24.75 (q, ^2J(C,F) = 37.7 Hz, *C*HCF_3), 15.02 (q, ^3J(C,F) = 1.3 Hz, CH_2).

^{19}F NMR (470 MHz, D_2O): δ = –60.47 (d, ^3J(F, H) = 9.3 Hz, CF_3).

MS (CI): *m*/*z* = 170 $[M - Cl]^+$.

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