Tetrahedron Vol. 47, No. 32, pp. 6265-6274, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

A NEW AND CONVENIENT SYNTHESIS OF 1-AMINOCYCLOPROPANECARBOXYLIC ACID FROM CYCLOPROPANONE ACETAL.

Antoine FADEL

Laboratoire des Carbocycles, associé au CNRS, Institut de Chimie Moléculaire d'Orsay, Bât. 420
Université de Paris-Sud, 91405 ORSAY (FRANCE)

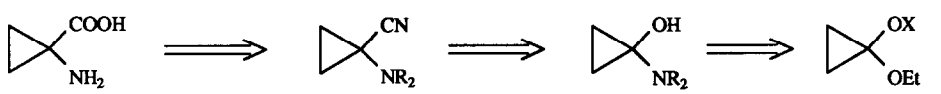
(*Received in Belgium* 16 *April* 1991)

Summary : *Cyclopropanone acetal* ***2a*** *undergoes the one-pot Strecker synthesis under sonication to provide the amino nitrile* ***8****, which after hydrolysis and catalytic hydrogenolysis, gives 1-aminocyclopropanecarboxylic acid (ACC,* ***1****) in good overall yield.*

The title amino acid 1-aminocyclopropanecarboxylic acid (ACC, **1**) which has been the subject of numerous syntheses in recent years, constitute a unique form of "conformationally constrained" amino acid which has been found in nature.[1] It has been shown that the amino acid ACC occurs naturally as the immediate biosynthetic precursor of the plant hormone ethylene,[2] the phytohormone that initiates and regulates many aspects of plant grouth [3] and also displays properties of pharmacological interest.[4]

Among the various strategies for the synthesis of ACC [5] are those involving : (a) Curtius rearrangement of 1-carboxycyclopropanecarboxylic acids and derivatives;[6] (b) cyclopropanation of α-ethylenic α-amino acids by diazomethane and derivatives;[7,8] (c) cyclopropanation of olefins by an aminocarboxycarbene;[9] (d) double alkylation of glycine anion equivalent by 1,2-dibromoethane;[8,10] (e) enzymatic or base induced cyclization of methionine derivatives;[8,10b,11] (f) α-haloimines cyanation;[12] (g) nitration of DBHA cyclopropanecarboxylate enolate;[13a] and (h) cyclization of aminochlorobutyronitrile.[13b] Many of the starting materials used in these processes are not readily available or are quite expensive. Furthermore, several of these syntheses suffer from some drawbacks inconsistent with successful large-scale preparation and the yields of ACC **1** are frequently low.

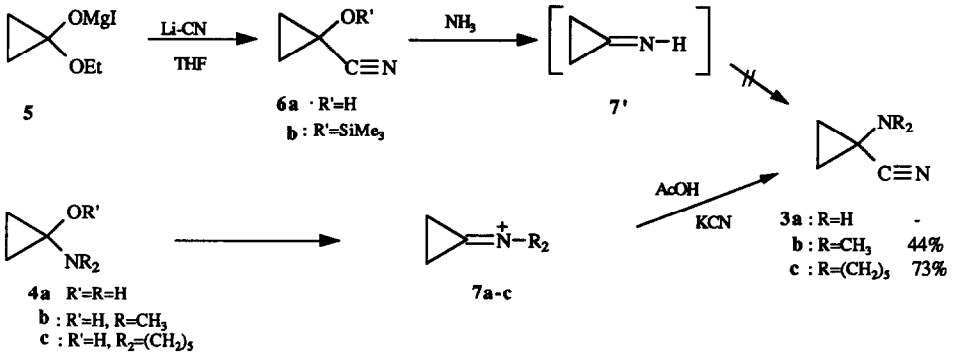
To develop an efficient route to 1-aminocyclopropanecarboxylic acid (ACC, **1**), the suitability of cyclopropanone hemiacetal as synthon has been investigated. This work offers a new, simple and convenient way to ACC from cyclopropanone hemiacetal **2b**.



1 **3** **4** **2a** : X= $SiMe_3$ **b** : X=H

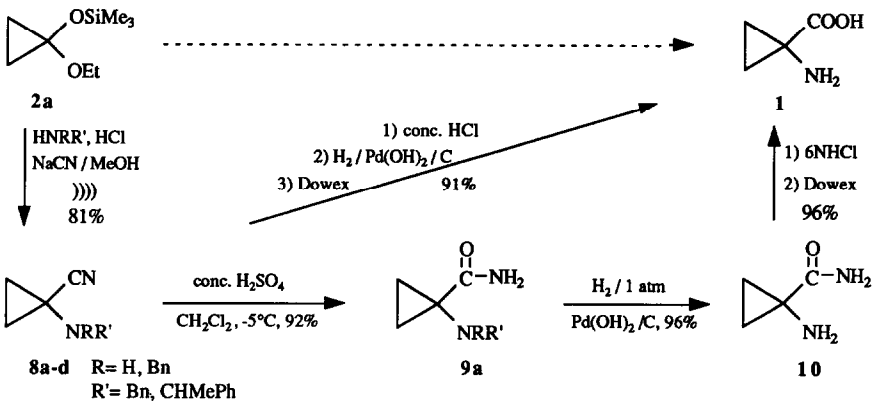
Retrosynthetically, ACC (**1**) is derived from the amino nitrile **3**, which could, in turn, be obtained from cyclopropanone hemiacetal **2b** via **4** following a well known classical pathway (i.e. Strecker synthesis).[14] The 1-ethoxycyclopropanol **2b** is readily prepared from the sodium induced cyclization of ethyl 3-chloropropionate in the presence of Me_3SiCl by sonication [15] at room temperature or in refluxing ether,[16] followed by simple methanolysis.[17]

It has been reported that the addition of cyclopropanone cyanohydrin **4a**, readily available from the magnesium salt **5**,[18] to a saturated solution of methanolic ammonia at 40°C did not provide the expected α-amino nitrile **3a** [13b] but polymeric compounds likely formed from the cyclopropylketimine **7'**. A similar situation is observed in the case of the parent cyclopropanones.[19]



It has been reported that the hydroxy group of 1-(dimethylamino)cyclopropanol **4b**, is easily displaced by common nucleophiles. Thus, addition of acetic acid at 0°C to an aqueous solution of amino alcohol **4b** and KCN gave 1-cyano-1-(dimethylamino)cyclopropane **3b** in 44% yield.[20] Similarly, 1-hydroxy-1-piperidinocyclopropane, **4c**, available from β-chloropropionyl chloride, was treated with KCN in the presence of aqueous acetic acid to give the amino nitrile **3c** in 73% yield.[21] Moreover 1-aminocyclopropanol, **4a**, an active moiety of coprine, which is an *in vivo* inhibitor of liver aldehyde dehydrogenase (ALDH) [22] did not give when treated with KCN in acetic acid and HCl, the expected chlorohydrate of α-aminocyanocyclopropane **3**.[13b]

Since the cyclopropanone derivatives **2** are readily available,[15] a ready synthesis of ACC could be via an aminocyanocyclopropane **8** obtained from **2a** by a Strecker reaction. Hydrolysis, deprotection and purification would then lead to ACC (Scheme 1). The realization of this synthesis is detailed below.



One-pot Strecker synthesis from cyclopropanone acetal **2a**

The mixture of cyclopropanone acetal **2a**, NaCN and amine undergoes Strecker reaction [23a] to form the aminocyanocyclopropane **8** under various conditions. Under sonication in MeOH with methylbenzyl amine

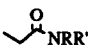
hydrochloride ((±)PhMeCHNH, HCl), **2a** gave the amino nitrile **8a** (81%, entry 1). Other conditions (method B : sonication in AcOH [23b] for 10 h or method C : heating at 40°C for 14 h) gave **8a** in slightly lower yield (entries 2 and 3). Moreover under sonication the Streaker reaction is cleaner and not contamined by intermediates or ring-opening by-products such as **6a**, **11** or **12** (Table 1).

Furthermore, the yield in the Strecker synthesis from **2a** changes, with the nature of amine hydrochloride decreasing from methylbenzylamine to dibenzylamine and benzylamine (81%, 30% and 25% , respectively; Table 1, entries 1, 4 and 6). Thus method A is the method of choice (Table 1, see entries 4 - 9).

However, when the Strecker reaction was carried out with ammonium chloride (R = R' = H) using the same conditions, the expected product **8d** was not obtained only traces of cyanohydrin **6a** were isolated from a polymerized mixture (entries 10 and 11), which agrees with the report by Salaün *et al* .[13b]

These, results are in agreement with the stability of the intermediates ammonium ion **7** which increases from ammonia (R = R' = H) to methylbenzylamine (R' = H, R = $CH(CH_3)Ph$) (Table 1, see entries 10, 6, 4 and 1) ; thus allowing nucleophilic reaction of NaCN instead of polymerization or ring-opening reaction.

Table 1[a]: Strecker synthesis with cyclopropanone acetal **2a**

entry	HNRR'	Method, NaCN reactions	T°C/time	 **8a-d**	 **11a-d**	 **12a-d**	**2b**
1	a : R' = H	A : HNRR'.HCl/MeOH	))))[b] 30h	81	5	1	0
2	R = CHMePh	B : HNRR'.HCl/AcOH	)))) 10h	70		5	1
3		C : HNRR'.HCl/MeOH	50°C 10h	62	10	5	2
4	b: R = R' = Bn	A : HNRR'.HCl/MeOH	)))) 24h	30		8	
5		C : HNRR'.HCl/MeOH	50°C 7d	22		10	
6	c: R' = H	A : HNRR'.HCl/MeOH	)))) 15h	25	10	30	
7	R = Bn	A' : HNRR'.HCl/MeOH.HCl	)))) 1h	0		80	
8		B : HNRR'/AcOH	)))) 16h	10		25	3
9		C : HNRR'.HCl/MeOH	60°C 16h	9	5	68	2
10	d: R = R' = H	B : NH_4Cl/AcOH.	)))) 7h			20	6[c]
11		C : NH_4Cl/MeOH.	40°C 3d			28	4[c]

a) All products are noted in chromatographed yield.b) Ultrasound reactions were carried out at 20 to 30°C.c) The product formed was cyclopropanonecyanohydrin **6a**.

Hydrolysis, deprotection and purification of ACC

The α-aminocyanocyclopropane **8a**, hydrolyzed with concentrated H_2SO_4 in CH_2Cl_2 at -5°C to 0°C for 10 h, afforded the amide **9a** in 92% yield after recrystallization, m.p. = 79°C.[24]

Subsequent hydrogenolysis of the previously obtained amide **9a** in the presence of catalytic amount of 20% $Pd(OH)_2$ on activated carbon (w/w : 15%) [25] in AcOH under hydrogen (1 atm) for 20 h gave, after crystallization, the free amino amide **10** in 96% yield, m.p. = 115.5°C. When the hydrogenolysis was carried out in the presence of 10% Pd/C (w/w : 15%) in EtOH under hydrogen : 2 atm (22h) or 3 atm (3 days), only 50% or

30% [26] of conversion was obtained, respectively. Moreover, in the presence of cat. PtO_2 in EtOH under 4 atm (22 h), the amide **9a** was converted into the free amino amide **10** with 10% yield accompanied by an unidentified solid.

Usual hydrolysis of amide **10** with 6N HCl at reflux (2 h) led after treatment with an ion-exchange resin (activated Dowex 50 WX.8.100) to 1-aminocyclopropanecarboxylic acid (ACC, **1**) in 96% yield of recrystallyzed product. m.p. 239°C (Lit.[11c] 240-241°C).

Direct hydrolysis of **8a** with concentrated HCl for 24 h gave quantitatively the corresponding acid intermediate [1-(methylbenzyl)aminocyclopropanecarboxylic acid, hydrochloride], which after treatment with 20% $Pd(OH)_2$ (50% : w/w) under hydrogen (1 atm.) for 30 h followed by ion-exchange (Dowex 50WX.8.100), furnished the 1-aminocyclopropanecarboxylic acid (ACC, **1**) in 91% overall yield form **8a**.

Conclusion

Cyclopropanone acetal **2a** [15] undergoes the Strecker synthesis facilitated by sonication and provides a useful synthesis of 1-aminocyclopropanecarboxylic acid (ACC, **1**) in 74% overall yield. The synthesis of other cyclic amino acids, e.g., optically active substituted derivatives of ACC, **1** are currently under investigation.[27]

Experimental Section

Melting points are uncorrected. The ^1H NMR data were obtained on a Bruker AC200 (200 MHz) and Bruker AM250 (250 MHz), the values are expressed in ppm downfield from tetramethylsilane in $CDCl_3$ and DMSO-d_6.^1H NMR chemical shifts in D_2O were referenced to HOD 4.8 ppm. Analytical thin layer chromatography (TLC) was performed on 250 µm silica gel (Merk), flash chromatography was performed with S.D.S. silica gel 60 (230-400 mesh). Sonications were carried out in a Sonoclean TK 52 (Bransonic) cleaning bath (60 KHz and 80 - 160 WL^{-1}). Unless otherwise noted all materials were obtained from commercial suppliers, cyclopropanone acetal **2a**, was prepared as previously reported.[15] Evaporation of solvent was accomplished under reduced pressure on a rotary evaporator.

General procedure of Strecker synthesis

Methods A and C : To a mixture of dried amine hydrochloride (45 mmol) (easily prepared from amine in $MeOH/SOCl_2$, after removal of solvent, the solid product was dried at 40°C/0.1 mm Hg for 2h), sodium cyanide (45 mmol) in methanol (20 mL) was added rapidily a solution of cyclopropanone acetal **2a** (30 mmol) containing a drop of TMSCl in methanol (5 mL). The reaction mixture was irradiated with ultrasound for 15 - 30 h (Method A) or stirred at 40° - 50°C for 14 h to 7 days (Method C). The reaction was monitored by TLC. K_2CO_3 (solid, amount) was added to the solution, the mixture was concentrated on a rotary evaporator, ether was added (30 mL),the mixture was filtered over celite and the precipitate was washed with ether (10 mL). The ethereal filtrates were concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane) to afford the pure aminocyanocyclopropane **8a-c** (9-81%), or used without further purification in the next step.

Method B : Following the modified procedure of Söllhuber *et al* ,[23b] to an ice cooled mixture of sodium cyanide (20 mmol), the suitable amine (15 mmol) and cyclopropanone acetal (10 mmol) were added glacial acetic acid (15 mL). The reaction mixture was irradiated with ultrasound for 7 - 16 h. The reaction was monitored by TLC. The solution was then poored into 10 g of ice, made basic (pH 8) with ammonium hydroxide or aqueous potassium carbonate. The reaction mixture was extracted with CH_2Cl_2 (4 x 50 mL) and the combined organic layers were dried over magnesium sulfate and evaporated under reduced pressure. The residue was used as above for the next step.

(±)-1-[(methylbenzyl)amino]cyclopropanecarbonitrile 8a

(a) Synthesis under sonication following Method A.

A mixture of (±)-methylbenzylamine hydrochloride (7 g, 45 mmol), NaCN (2.2 g, 45 mmol), 1-ethoxy-1-(trimethylsiloxy)cyclopropane **2a** [15] (5.22 g, 30 mmol) and a drop of TMSCl in MeOH (25 mL) was irradiated with ultrasound at 30°C for 30 h. Workup as described in Method A gave a crude oil (6 g) which was subjected to flash chromatography on silica gel (70 g, elution : EtOAc/hexane = 1/9) to afford beside (±)-1-[(methylbenzyl)amino]cyclopropanecarbonitrile **8a** (4.47 g as a colorless oil, 81%), 1-methoxy-1-[(methylbenzyl)amino]cyclopropane **11a** (285 mg, 5%) and N-(methylbenzyl)propionamide **12a** (55 mg, 1%).

8a : IR (neat) : 3320(γ_{NH}), 2212(γ_{CN}), 1605 and 1588 cm^{-1} ; ^{1}H NMR (250 MHz) ($CDCl_3$) δ: AA'BB' syst.[0.660 (A part, ddd, J = 9.7, 7.4 and 4.9 Hz, H cyclopropyl) ; 0.915 (A' part, ddd, 9.7, 7.4 and 4.9 Hz, H cyclopropyl) ; 1.038 (B' part, ddd, 9.7, 7.4 and 4.9 Hz, H cyclopropyl) ; 1.187 (B part, ddd, 9.7, 7.4 and 4.9 Hz, H cyclopropyl)], 1.40 (d, J = 6.5 Hz, CH_3), 2.2 (br.s, NH), 4.20 (q, J = 6.5 Hz, CH-N), 7.25 - 7.40 (m, 5H, Ph) ; ^{13}C NMR (50,29 MHz) ($CDCl_3$) δ : [arom. C : 144.06 (s), 128.09 (2d), 127.15 (d), 126.78 (2d)], 121.22 (s, CN), 56.61 (d, CH-N), 26.59 (s, C-CN), 23.13 (q, CH_3), 15.75 (t, CH_2 cyclopropyl), 15.66 (t, CH_2 cyclopropyl) ; M.S. m/e (rel. int.) : 186 (M^+, 1.14), 105 (CH_3-$C_7H_7^+$, 100), 106 (13), 77 (21), 79 (15), 51 (10). Anal. calcd. for $C_{12}H_{14}N_2$: C, 77.38 ; H, 7.58 ; N, 15.04. Found : C, 77.12 ; H, 7.52 ; N, 15.28.

11a : IR (neat) : 3330, 1605, 1585 cm^{-1} ; ^{1}H NMR (250 MHz) ($CDCl_3$) δ: AA'BB' syst.[0.487 (A part, ddd, J = 4.5, 6.4 and 10.5 Hz, H cyclopropyl) ; 0.656 (A' part, J = 4.5, 6.4 and 10.5 Hz, H cyclopropyl) ; 0.763 (B' part, ddd, J = 4.5, 6.4 and 10.5 Hz, H cyclopropyl) ; 0.860 (B part, ddd, J = 4.5, 6.4 and 10.5Hz, H cyclopropyl)], 1.40 (d, J = 6.5 Hz, CH_3), 2.65 (br.s, NH), 3.23 (s, OCH_3), 4.20 (q, CH-N), 7.20 - 7.40 (m, 5H, Ph) ; M.S. m/e (rel. int.) : 176 (M^+-15, 0.25), 105 (Me-$C_7H_7^+$, 100), 103 (11), 79 (16), 77 (17), 51 (9).

12a : 1.17 (t, J = 7.5 Hz), 1.50 (d, J = 6.8 Hz, CH_3-CH), 2.22 (q, J = 7.5 Hz, CH_2-CON), 5.16 (m, CH-N), 5.72 (m, NH), 7.33 (s, 5H, Ph).

b) Synthesis under sonication Method B.

A mixture of (±)-methylbenzylamine (1.8 g, 15 mmol), NaCN (0.98 g, 20 mmol) and 1-ethoxy-1-(trimethylsiloxy)cyclopropane **2a** (1.74 g, 10 mmol) in glacial AcOH (15 mL) was sonicated at 30°C for 10 h. Workup, as noted in Method B afforded after flash chromatography amino nitrile **8a** (1.29 g, 70%), amide **12a** (88 mg, 5%) and traces of starting material **2b** (< 2%).

Data of **8a**, **12a** and **2b** are identical with above.

c) Synthesis following Method C

Using the same mixture in Method A (see above) **2a** (5.22 g, 30 mmol), was heated at 50° for 14 h then workup as described in Method A furnished after chromatography amino nitrile **8a** (3.43 g, 62%), **11a** (565 mg, 10%), amide **12a** (265 mg, 5%) and starting material **2b** (6 mg, 2%). All data are identical with those noted above.

1-[(Dibenzyl)amino]cyclopropanecarbonitrile 8b

(a) Synthesis under sonication following Method A.

A mixture of dibenzylamine hydrochloride (10.5 g, 45 mmol), NaCN (2.2 g, 45 mmol) and 1-ethoxy-1-(trimethylsiloxy)cyclopropane **2a** (5.22 g, 30 mmol) in MeOH (25 mL) was sonicated at 30°C for 24 h. Workup as described in Method A and flash chromatography (EtOAc/hexane : 1/9) afforded 1-(dibenzylamino)cyclopropanecarbonitrile **8b** (2.36 g, 30%) as a colorless oil and N-dibenzylpropionamide **12b** (605 mg, 8%).

8b : IR (neat) : 2225(γ_{CN}), 1608 and 1590 cm^{-1} ; ^{1}H NMR (250 MHz) ($CDCl_3$) δ: 0.68 (AB syst.m, CH_2 cyclopropyl), 1.02 (AB syst. m, CH_2 cyclopropyl), 3.81 (s, $2CH_2$ benzyl), 7.31 (s, 10H, 2Ph) ; ^{13}C NMR

(50,29 MHz) ($CDCl_3$) δ : [12 arom. C : 137.63 (2s), 129.11 (4d), 128.17 (4d), 127.32 (2d)], 119.42 (s, CN), 57.90 (2t, CH_2 benzyl), 33.92 (s, C-CN), 16.41 (2t, $2CH_2$ cyclopropyl) ; M.S. m/e (rel. int.) : 262 (M^+, 0.7), 171 (M^+-Bn 73), 117 (7), 91 ($C_7H_7^+$, 100), 65 (24). Anal. calcld. for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68. Found : C, 82.42; H, 6.98; N, 10.81.

12b : ^1H NMR (250 MHz) ($CDCl_3$) δ: 1.25 (t, J = 7.5 Hz, CH_3), 2.47 (q, J = 7.5 Hz, CH_2-CON), 2 rotamers, 4.44 and 4.48 (s and s, $2CH_2$ benzyl), 7.5 - 7.2 (m, 10H, 2Ph).

b) Synthesis under sonication Method C.

A mixture of dibenzylamine hydrochloride (3.5 g, 15 mmol), NaCN (0.74 g, 15 mmol) and 1-ethoxy-1-(trimethylsiloxy)cyclopropane **2a** (1.74 g, 10 mmol) in MeOH (20 mL) was heated at 50°C for 7 days. Workup as described in Method A and flash chromatography (EtOAc/hexane : 1/9) gave amino nitrile **8b** (575 mg, 22%) and ring opening amide **12b** (250 mg, 10%). All data are identical with whose described above.

1-(Benzylamino)cyclopropanecarbonitrile 8c

(a) Synthesis under sonication following Method A.

A mixture of benzylamine hydrochloride (6.5 g, 45 mmol), NaCN (2.21 g, 45 mmol) and 1-ethoxy-1-(trimethylsiloxy)cyclopropane **2a** (5.22 g, 30 mmol) in MeOH (25 mL) was sonicated at 30°C for 15 h. Workup as described in Method A and flash chromatography (EtOAc/hexane : 1/9), gave 1-(benzylamino)cyclopropanecarbonitrile **8c** (1.3 g, 25%), 1-(benzylamino)-1-methoxycyclopropane **11c** (530 mg, 10%) as a colorless oil and N-benzylpropionamide **12c** (1.47 g, 30%).

8c : (IR (neat) : 3325(γ_{NH}), 2225(γ_{CN}), 1605 and 1585 cm^{-1} ; ^1H NMR (250 MHz) ($CDCl_3$) δ: 1.06 (m, CH_2 cyclopropyl), 1.21 (m, CH_2 cyclopropyl), 2.18 (broad m, NH), 2 rotamers 3.97 and 4.00 (s and s, CH_2 benzyl), 7.34 (s, 5H, 2Ph) ; M.S. m/e (rel. int.) : 173 (M^++1, 1.3), 172 (M^+, 6), 157 (7), 91 ($C_7H_7^+$, 100), 92 (13), 65 (15). Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.26. Found : C, 76.67; H, 7.05; N, 16.39.

11c (X = Me) : ^1H NMR (250 MHz) ($CDCl_3$) δ: 0.82 (m, CH_2 cyclopropyl), 0.90 (m, CH_2 cyclopropyl), 2.60 (br.s, NH), 3.32 (s, OCH_3), 3.98 (s, CH_2 benzyl), 7.60 - 7.20 (m, 5H, Ph).

12c: : ^1H NMR (250 MHz) ($CDCl_3$) δ: 1.19 (t, J = 7.5 Hz, CH_3), 2.25 (q, J = 7.5 Hz, CH_2), 2 rotamers 4.42 and 4.45 (s and s in 4:6 ratio, CH_2 benzyl), 5.25 and 5.94 (br.s and br.s in 4:6 ratio, NH), 7.15 - 7.45 (m, 5H, Ph).

a') Method A'.

Sonication of the same quantities and under the same conditions as above (Method A) but carried out in (MeOH/HCl) led exclusively after 1 h to the amide **12c** with 80% yield.

b) Synthesis under sonication Method B.

A mixture of benzylamine (1.6 g, 15 mmol), NaCN (0.98 g, 20 mmol) and 1-ethoxy-1-(trimethylsiloxy)cyclopropane **2a** (1.74 g, 10 mmol) in glacial AcOH (15 mL) was sonicated at 30°C for 16 h. Workup, afforded after flash chromatography 1-(benzylamino)cyclopropanecarbonitrile **8c** (175 mg, 10%), amide **12c** (410 mg, 25%) and traces of starting material **2b** (3%).
Data of all products were identical with those noted above.

c) Synthesis by heating Method C

A mixture of benzylamine hydrochloride (2.17 g, 15 mmol), NaCN (0.74 g, 15 mmol) and 1-ethoxy-1-(trimethylsiloxy)cyclopropane **2a** (1.74 g, 10 mmol) in MeOH (10 mL) was heated at 60°C for 16 h. Workup as described in Method A and flash chromatography (EtOAc/Hexane : 1/9), gave amino nitrile **8c** (155 mg, 9%), 1-(benzylamino)-1-methoxycyclopropane **11c** (88 mg, 5%), amide **12c** (1.11 g, 68%) and traces of starting material **2b** (2%). These products were identical as above.

Reactions of acetal 2a with NH_4Cl, sodium cyanide

(a) Sonication following Method B.

A mixture of ammonium chloride (800 mg, 15 mmol), NaCN (0.98 g, 20 mmol) and 1-ethoxy-1-(trimethylsiloxy)cyclopropane **2a** (1.74 g, 10 mmol) in glacial AcOH (15 mL) was sonicated at 30°C for 7 h. Workup, as described in Method B, led to polymeric mixture which after chromatography (eluant : MeOH/CH_2CH_2/hexane : 1/10/10), afforded cyclopropanone cyanohydrin **6a** (110 mg, 6%), propionamide **12d** (165 mg, 20%) and an unidentified product (20 mg) ^1H NMR (200 MHz) ($CDCl_3$) δ: 1.09 (m, 2H), 1.35 (m, 2H), 2.15 (br.s, 2H), 5.65 (br.s, 2H), 5.98 (br.s, 2H), 8.18 (d, 4H). The expected amino nitrile **8d** was absent (from NMR, IR and Mass spectra).

6a : IR (neat) : γ_{OH} : 3450, 3350, γ_{CN} : 2240 cm^{-1} ; ^1H NMR (200 MHz) ($CDCl_3$) δ: 1.20 (s, 4H), 4.78 (br.s, 0H) ; M.S. m/e (rel. int.) : 83 (23), 82 (50), 65 (31), 55 (58), 54 (100), according to the literature.[18]

12d : ^1H NMR (200 MHz) ($CDCl_3$) δ: 1.15 (t, J = 7.5 Hz, CH_3), 2.25 (q, J = 7.5 Hz, CH_2), 6.25 (br.s, H), 5.80 (br.s, H), according with reported *data* .[13b]

b) Synthesis by heating Method C.

A mixture of ammonium chloride (800 mg, 15 mmol), NaCN (0.98 g, 20 mmol) and 1-ethoxy-1-(trimethylsiloxy)cyclopropane **2a** (1.74 g, 10 mmol) in MeOH (15 mL) was heated at 40°C for 3 days. Workup, as above, afforded cyclopropanone cyanohydrin **6a** (75 mg, 4%), propionamide **12d** (230 mg, 28%) and an unidentified product (25 mg) as noted above. The expected amino nitrile **8d** was also absent (from NMR, IR and Mass spectra).

(±)-1-[(Methylbenzyl)amino]cyclopropanecarboxamide 9a

A solution of (±)-1-[(methylbenzyl)amino]cyclopropanecarbonitrile **8a** (1.86 g, 10 mmol) in CH_2CL_2 (20 mL) was cooled with an efficient cooling system to -5°C and concentrated sulphuric acid (14 mL) was added very slowly with efficient stirring at such a rate as to maintain the temperature of the reaction at or below O°C. The reaction mixture was allowed to worm to +5°C over a five hours period. After stirring the reaction mixture at +5°C for an additional 8 h. The aqueous layer separated, washed with CH_2Cl_2 (2 mL), then poured onto crushed ice (50 g), was slowly basified with NH_4OH. The mixture extracted with EtOAc (3 x 20 mL), dried over $MgSO_4$ and concentrated to give after crystallization from ether/hexane in two crops the title compound **9a** (1.875 g, 92%).[24] M.p. 79.0°C ; IR ($CDCl_3$) : 3450, 3330, 1675(γ_{CON}), 1600 cm^{-1} ; ^1H NMR (250 MHz) ($CDCl_3$) δ: 0.955 (AA' part of AA'BB' system, m, 2H cyclopropyl), 1.36 (d, J = 6.5 Hz, CH_3), 1.415 (BB' part of AA'BB' system, m, 2H cyclopropyl), 1.70 (br.s, H amine) ; 3.83 (q, J = 6.5 Hz, CH-N), 5.65 (br.s, H amide), 7.20 - 7.40 (m, 5H, Ph), 7.49 (br.s, H amide) ; ^{13}C NMR (50,29 MHz) ($CDCl_3$) δ : 178.62 (s, CON), [6 arom. C : 145.42 (s), 128.41 (2d), 127.09 (d), 126.34 (2d)], 56.34 (d, CH-N), 39.96 (s, C cyclopropyl), 23.56 (q, CH_3), 18.52 (t, CH_2 cyclopropyl), 14.24 (t, CH_2 cyclopropyl) ; M.S. m/e (rel. int.) : 206 (M^++2, 0.2), 205 (M^++1, 0.45), 204 (M^+, 0.3), 159 (M^+ -$CONH_2$, 15), 105 (Me $C_7H_7^+$, 100), 104 (13), 103 (15), 99 (21), 91 (12), 79 (27), 78 (14), 77 (48). Anal. calcd. for $C_{12}H_{16}N_2O$: C, 70.56 ; H, 7.90 ; N, 13.71. Found : C, 70.41 ; H, 7.82 ; N, 13.72.

1-Aminocyclopropanecarboxyamide 10

a) Hydrogenolysis in the presence of 20% $Pd(OH)_2$ on activated charcoal

A solution of amide **9a** (1.02 g, 5 mmol) in glacial acetic acid (20 mL) was hydrogenated in the presence of 20% palladium hydroxide on activated charcoal as catalyst (150 mg, w/w : 15%) at room temperature under hydrogen (1 atm) for 20 h. The resulting mixture was filtered and the solid washed with AcOH (3 x 5 mL). The combined washings were concentrated and the crude product was taken with $CHCl_3$ (20 mL), basified with aqueous $NaHCO_3$ solution to pH = 9 and extracted with $CHCl_3$ (3 x 20 mL). The organic layers dried, concentrated on rotary evaporator to afford after crystallization from CH_2Cl_2/Et_2O, the title free amine **10**

(480 mg, 96%). M.p. 115.5°C ; IR ($CDCl_3$) : γ_{NH} : 3390, 3200, γ_{CON} : 1650 cm^{-1} ; ^1H NMR (250 MHz) ($CDCl_3$) δ: 0.85 (m, like AB syst., 2H cyclopropyl), 1.46 (m, like AB syst., 2H cyclopropyl), 1.75 (s, 2H amine), 5.84 (br.s, H amide), 7.50 (br.s, H amide) ; ^{13}C NMR (50,29 MHz) ($CDCl_3$) δ : 178.84 (s, CON), 35.33 (s, C cyclopropyl), 19.48 (2t, $2CH_2$ cyclopropyl) ; M.S. m/e (rel. int.) : 100 (M^+,.21), 83 (78), 56 (71), 55 (M^+ -$CONH_3$, 100), 54 (53), 45 (25), 44 (35), 40 (32).

It is noteworthy that the same quantity of **9a** in the same conditions in the presence of 20% $Pd(OH)_2/C$ (650 mg) gave within 3 h the expected free amine **10** with 96% after crystallization.

b) Hydrogenolysis in the presence of 10% Pd/C in EtOH

A solution of amide **9a** (204 mg, 1 mmol) in EtOH (12 mL) was hydrogenated in the presence of 10% Pd/C as catalyst (30 mg, w/w : 15%) at room temperature under hydrogen (2 atm) in a parr-hydrogenation apparatus for 22 h. The resulting mixture was filtered through a celite pad and the solid washed with MeOH (3 x 5 mL). The combined washings concentrated, gave a crude product (155 mg) which indicated as shown in its ^1H NMR spectra that only 50% conversion in free amine **10** accompanied with 50% of starting material **9a**.

Moreover, when the crude amide **9a** (500 mg, 2 mmol) (obtained from the crude **8a** without purification contamined by the methylbenzylamine) in EtOH (20 mL) was hydrogenated in the presence of 10% Pd/C (75 mg, w/w : 15%) at room temperature under hydrogen (3 atm) for 3 days. The reaction was monitored by TLC indicated only 30% [26] of conversion into the free amine **10** and 70% of starting material **9a**.

c) Hydrogenolysis in the presence of PtO_2 in EtOH

A solution of amide **9a** (230 mg, 1 mmol) in EtOH (12 mL) was hydrogenated in the presence of PtO_2 as catalyst (10 mg, w/w : 5%) at room temperature under hydrogen (4 atm) for 22 h. Workup as described above and chromatography ($MeOH/CH_2Cl_2$: 1/3) gave amine **10** (10 mg, 10%) and recovered starting material (170 mg, 85%).

1-Aminocyclopropanecarboxylic acid (ACC, 1)

A mixture of 1-aminocyclopropanecarboxamide **10** (500 mg, 5 mmol) and 6N HCl (30 mL) was gently heated to reflux. The reaction was complete within 3 h as shown by TLC. The solution reaction cooled to room temperature,was extracted with ether (10 mL) to remove colored ether soluble material. The hydrochloric acid was evaporated to dryness under reduced pressure. The residue was diluted with water (10 mL) and applied to a Dowex 50WX.8.100 ion-exchange column in the activated form (NH_4^+). The column was washed with dist. water until neutral, and then the free amino acid was eluted with 1.3N aq. NH_3 (150 mL). The eluant was concentrated in vacuo. Complete removal of NH_3 was accomplished by redissolving the substance in H_2O and concentrating in a rotary evaporator. Finally, drying for 10 h (50°/0,1 mm Hg) provided pure 1-aminocyclopropanecarboxylic acid (ACC, **1**) (506 mg, quantitative yield). M.p. 235.2°C (Lit.[13b] m.p. 240°C, Lit.[13a] m.p. 237 - 238°C). Recrystallization from water-acetone furnished in two crops pure crystalline ACC, **1** (485 mg, 96%) : m.p. 239°C ; ^1H NMR (250 MHz) (D_2O) (HOD : 4.8 ppm) δ: 1.18 (m, 2H), 1.34 (m, 2H) (Lit.[13a] (90 MHz, D_2O), 1.15 (m, 2H), 1.30 (m, 2H)) ; ^1H NMR (200 MHz) (DMSO-d_6) δ: 0.75 (m, 2H), 0.98 (m, 2H) (Lit.[13b] in DMSO-d_6, 0.80 (m, 2H), 1.10 (m, 2H)), (Lit.[11c] DMSO-d_6, TMS, 0.65 - 0.95 (m, 2H), 0.95 - 1.20 (m, 2H), 2.65 - 5.4 (br.s, NH_3+). Anal. calcd. for $C_4H_7NO_2$: (101,065) : C, 47.50 ; H, 6.98 ; N, 13.86. Found : C, 47.39 ; H, 7.02 ; N, 13.84.

1-Aminocyclopropanecarboxylic acid 1 directly from 8a

A mixture of 1-aminocyclopropanecarbonitrile **8a** (272 mg, 2 mmol) and concentrated HCl (15 mL) was gently heated to reflux. The reaction was complete within 12 h as shown by TLC. The solution was evaporated to dryness and diluted with $CHCl_3$ (20 mL), filtered to remove NH_4Cl. The filtrate evaporated led to 1-(methylbenzylamino)cyclopropanecarboxylic acid hydrochloride (520 mg, quantitative yield) : m.p. : 99.5°C ; ^1H NMR (250 MHz) (D_2O) δ : 0.81 (m, H cyclopropyl), 1.24 (m, H cyclopropyl), 1.34 (m, H cyclopropyl), 1.40 (m, H cyclopropyl), 1.70 (d, J = 6.5 Hz, CH_3), 4.80 (s, 3H), 4.90 (q, J = 6.5 Hz, C<u>H</u>-N), 7.45 (s, 5H, Ph).

This crude amino acid hydrochloride was hydrogenolyzed without purification with 20% $Pd(OH)_2/C$ (200 mg, w/w : 40%) in glacial AcOH (15 mL) under H_2 (1 atm) at room temperature for 30 h. The resulting mixture was filtered and the solid washed with AcOH (3 x 5 mL). The combined washings were concentrated and the crude product was diluted with water (10 mL) and applied to a Dowex 50WX.8.100 ion-exchange column in the activated form (NH_4+). The column was washed with dist. water until neutral, and then the free amino acid was eluted with 1.3N aq.NH_3 (150 mL). The eluant was concentrated in vacuo as above to provide after crystallization in water/acetone pure 1-aminocyclopropanecarboxylic acid (ACC, **1**) (184 mg, 91%) : m.p. 239°C.

References and Notes

1) Fowden, L.; Lea, P.J.; Bell, E.A., "The Nonprotein Amino Acids of Plants", *Advances in Enzymology*, ed. by A. Meister, Wiley, New York, **1979**, pp 117 - 175.

2) Yang, S.F.; Hoffman, N.E. *Ann. Rev. Plant Physiol.* **1984**, *35*, 155.

3) Liberman, M. *Ann. Rev. Plant. Physiol.* **1979**, *30*, 533.

4) a) Ner, S.K.; Suckling, C.J.; Bell, A.R.; Wrigglesworth, R.*J. Chem. Soc. Chem. Commun.* **1987**, 480 ; b) Nadler, V.; Kloog, Y.; Sokolovsky, M. *Eur. J. Pharmacol.* **1988**, *157*, 115.

5) For a revue see : Stammer, C.H. *Tetrahedron* **1990**, *46*, 2231.

6) a) Hill, R.K.; Prakash, S.; Wiesendanger, R.; Angst, W.; Martinoni, B.; Arigoni, D.; Liu, H.; Walsh, C.T. *J. Am. Chem. Soc.* **1984**, *106*, 795; b) Izquierdo, M.L.; Arenal, J.; Bernabe, M.; Alvarez, F. *Tetrahedron* **1985**, *41*, 215 ; c) Baldwin, J.E.; Adlington, R.M.; Rawlings, B.J. *Tetrahedron Lett.* **1985**, *26*, 481 ; d) Wheeler, T.N.; Ray, J.A. *Synth. Commun.* **1988**, *18*, 141 ; e) Mapelli, C.; Turocy, G.; Switzer, F.L.; Stammer, C.H. *J. Org. Chem.* **1989**, *54*, 145.

7) a) King, S.W.; Riordan, J.M.; Holt, E.M.; Stammer, C.H. *J. Org. Chem.* **1982**, *47*, 3270 ; b) Hiyama, T., Kai, M. *Tetrahedron Lett.* **1982**, *23*, 2103 ; c) Elrod, L.F.; Holt, E.M.; Mapelli, C.; Stammer, C.H. *J. Chem. Soc., Chem. Commun.* **1988**, 252.

8) Schöllkopf, U.; Harms, R.; Hoppe, D. *Justus Liebigs Ann. Chem.* **1973**, 611. Pirrung, M.C.; Mc Geehan, G.M. *J. Org. Chem.* **1986**, *51*, 2103.

9) Schöllkopf, U.; Hauptreif, M.; Dippel, J.; Nieger, M.; Egert, E. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 192.

10) a) Adlington, R.M.; Aplin, R.T.; Baldwin, J.E.; Rawlings, B.J.; Osborne, D. *J. Chem. Soc., Chem. Commun.* **1982**, 1086 ; b) Prochazka, Z.; Budesinky, M.; Smolikova, J.; Troska, P.; Jost, K. *Collect. Czech. Chem. Commun.* **1982**, *47*, 2291 ; c) O'Donnell, M.J.; Bruder, W.A.; Eckrich, T.M.; Schullenberger, D.F.; Staten, G.S. *Synthesis* **1984**, 127.

11) a) Rich, D.H.; Tam, J.P. *Synthesis* **1978**, 46 ; b) Gallenkamp, B. Ger. off. 2.936,038 (Bayer), 1979 ; *Chem. Abstr.* **1981**, *95*, 97175 ; c) Strazewski, P.; Tamm, C. *Synthesis* **1987**, 298.

12) de Kimpe, N.; Sulmon, P.; Brunet, P.; Lambein, F.; Schamp, N. *Tetrahedron Lett.* **1989**, *30*, 1863.

13) a) Häner, R.; Seebach, D. Chimia **1985**, *39*, 356 ; b) Salaün, J.; Marguerite, J.; Karkour, B. *J. Org. Chem.* **1990**, *55*, 4276 and references cited therein.

14) Strecker amino acid synthesis (Strecker, A. *Liebigs Ann. Chem.***1850**, *75*, 27) is one of the most convenient experimental protocols for preparing amino acids on a preparative scale. See also : Williams R.M. "Synthesis of Optically Active α-Amino Acids", *Organic Chemistry Series*, ed. by Baldwin J.E.; Magnus P.D., Pergamon Press, Oxford **1989**, pp 208 - 229.

15) Fadel, A.; Canet, J.L.; Salaün, J. *Synlett* **1990**, 89.

16) Salaün, J.; Marguerite, J. *Org. Synth.* **1984**, *63*, 149.

17) **2a** stirred in MeOH with a drop of TMSCl at r.t. for 10 min. ; see also ref. 16.

18) a) Salaün, J.; Bennani, F.; Compain, J.C.; Fadel, A.; Ollivier, J. *J. Org. Chem.* **1980**, *45*, 4129 ; b) Cyanohydrin from 1-hydroxycyclopropanecarboxylic acid see : Hartmann, W. *Synthesis* **1989**, 272.

19) Turro, N.J.; Hammond, W.B. *J. Am. Chem. Soc.* **1966**, *88*, 3672. Schaafsma, S.E.; Steinberg, H.; De Boer, Th. J. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 1170.

20) Van Tilborg, W.J.M.; Steinberg, H.; De Boer, Th. J. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 290 ; *Synth. Commun.* **1973**, *3*, 1983.

21) Wasserman, H.H.; Dion, R.P. *Tetrahedron Lett.* **1982**, *23*, 1413.

22) Lindberg, P.; Bergamn, R.; Wickberg, B. *J. Chem. Soc., Chem. Commun.* **1975**, 946 ; Hellström, E.; Tottmar, O. *Biochem. Pharmcal.* **1982**, *31*, 3899 ; ibid, **1983**, *32*, 2181.

23) a) For asymmetric Strecker synthesis from cycloalkanones see : Weinges, K.; Blacholm, H. *Chem. Ber.* **1980**, *113*, 3098 and references cited therein; b) For Strecker synthesis using ultrasound irradiation see : Menéndez J.C.; Trigo, G.G.; Söllhuber, M.M. *Tetrahedron Lett.* **1986**, *27*, 3285.

24) The resulting crude **8a** can also be hydrolyzed without purification to afford after recrystallization the amide **9a** in 76.3% overall yield from the acetal **2a**.

25) With 65% w/w of 20% Pd/C; reaction for three hours was enough to convert totally the amide **9a** to free amino amide **10** with the same yield.

26) Crude amide **9a** containing methylbenzylamine was hydrogenated, although such amines were known to probably inhibit the palladium catalyst and thereby lower the yield of product; see Augustine, R.L., "Catalytic Hydrogenation", ed. by M. Dekker Inc., New York, **1966**, pp.23 - 35 and references cited therein.

27) Recently, after submission of this paper, was reported the use of an intermediate ammonium ion to the synthesis of cyclopropane β-amino acids; Mertin, A.; Thiemann, T.; Hanss, I.; de Meijere, A., *Synlett*, **1991**, 87.