A New and Convenient Preparation of 1-Aminocyclopropanecarboxylic Acid from Acrolein

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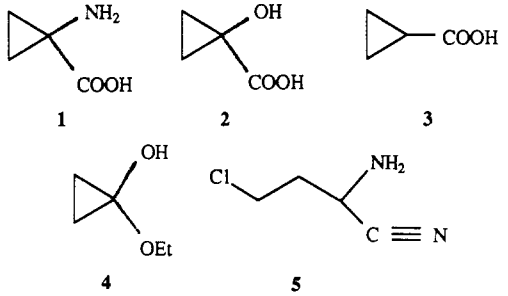
Cyclopropanecarboxylic acid **3** and cyclopropanone hemiacetal **4** have been tested as possible convenient precursors of the α-aminocyclopropanecarboxylic acid (**1**), an immediate biosynthetic source of ethylene, the phytohormone which regulates plant growth. While acid **3** was aminated only in low yield and hemiacetal **4** did not submit to the Strecker synthesis, the benzophenone imine of 2-amino-4-chlorobutyronitrile **5**, readily available from acrolein, did undergo quantitative base-induced cyclization smoothly under various conditions.

Present in the tissue of many plants,[1] 1-aminocyclopropanecarboxylic acid (ACC, **1**) is biosynthesized from (*S*)-adenosylmethionine under the catalytic influence of a pyridoxal 5′-phosphate linked enzyme (ACC synthase).[2] It is the immediate biosynthetic precursor of ethylene, the phytohormone that initiates and regulates many aspects of plant growth, including germination, inhibition, senescence, ripening of fruits, and is engaged in the metabolism of plants.[3] Rigorous demonstrations of this biosynthetic pathway have been established by ACC production upon incubation of (*S*)-adenosylmethionine with the crude synthase obtained from ripe tomatoes[4] and by ethylene production on addition of ACC to soybean leaves[5] or to apple slices.[6,7] Another biological transformation of ACC is cleavage into α-ketobutyrate and ammonia carried out by certain bacteria;[8] thus, ACC deaminase has been isolated from *Pseudomonas* growing on ACC as the sole nitrogen source.[9] Recently, cyclopropane-containing peptides synthesized from the coupling of the benzamides of ACC with phenylalanine and proline methyl esters have been shown to exhibit irreversible inhibition of carboxypeptidase.[10]

The physiological importance of ACC (**1**) and its derivatives has motivated the initiation of several research programs aimed at the synthesis of these challenging three-membered ring amino acids. Among the various approaches reported are those involving: (a) Curtius rearrangement of 1-phenyl-, 1-(hydroxymethyl)-, or 1-carboxycyclopropanecarboxylic acids;[11,12] (b) cyclopropanation of benzylidene oxazolone, 2-azido-2-alkenoates, or α-ethylenic α-amino acids by diazomethane or sulfoxonium;[13,14] (c) cyclopropanation of olefins by an aminocarboxycarbene;[15] (d) cycloalkylation of glycine derivatives by 1,2-dibromoethane;[7,14] (e) enzymatic or base-induced cyclization of methionine derivatives;[14,16-18] (f) α-halo imines cyanation.[19]

Most of the starting materials used are not readily available or are quite expensive. Furthermore, the sequences are often lengthy, the reported yields of ACC (**1**) are frequently low, and these syntheses suffer from some drawbacks inconsistent with successful large-scale preparations. Thus an efficient route to 1-aminocyclopropanecarboxylic acid (ACC, **1**) and its derivatives became an imperative in light of the increased interest in amino acids containing a cyclopropane ring. To this end, we have investigated the suitability of cyclopropanecarboxylic acid **3**, cyclopropanone hemiacetal **4**, and 2-amino-4-chlorobutyronitrile **5** as candidate synthons, and report herein the results of our inquiry which opened a new, simple, and convenient way to the desired ACC (**1**) from acrolein.



1-Hydroxycyclopropanecarboxylic acid (**2**), available in two steps from succinic esters,[20,21] is a very useful building block for the elaboration of various frameworks with composite functional groups.[22] Unfortunately, direct or

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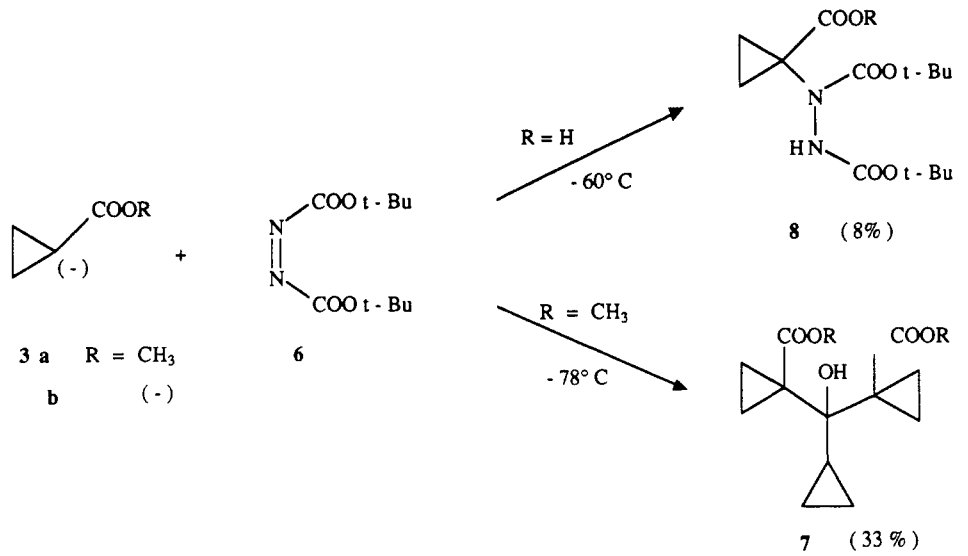
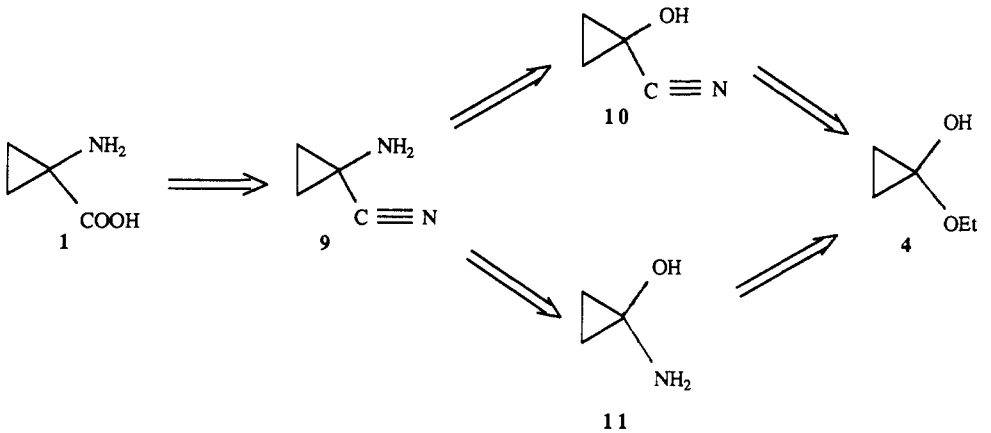
Scheme I



Scheme II



indirect aminodehydroxylations[23,24] (i.e., direct transformation **2** → **1**), involve an S_N1 process and an intermediate carbocation which is precluded in the case of a three-membered ring bearing an adjacent electron-withdrawing group, such as the carboxylic acid group of α-hydroxy acid **2**. (For the S_N1' formation of cyclopropylcation stabilized by electron-donating α-substituents, see ref 25). On the other hand, succinonitrile derivatives underwent sodium-induced cleavage of nitriles and olefin conversion rather than cyclization in analogy to succinates[26] and thus are not able to directly provide the expected 1-aminocyclopropanecarboxylic acid (**1**). Therefore, it appears that α-hydroxycyclopropanecarboxylic acid (**2**) cannot be considered as a potential precursor of ACC, **1**.

1. Amination of Cyclopropanecarboxylic Acid (3). The methyl ester of acid **3**, a cheap and commercially available three-membered ring, was deprotonated by lithium diisopropylamide (LDA) in THF at -78 °C to give, after quenching with Me_3SiCl, a mixture of *O*- and *C*-trimethylsilyl derivatives in 10 and 40% yields, respectively.[27] Deprotonation of its substituted derivatives with LDA followed by reactions of the resulting enolates with carbonyl compounds had been reported to yield α-alkylated cyclopropylcarboxylates in yields up to 78%.[28] Thus, one might envision that straightforward route to **1** could be the C α-amination of the carbanion **3a** with electrophilic agents.

Recently, di-*tert*-butylazodicarboxylate (TBAD, **6**) was proposed as an attractive, stable and commercially available synthetic equivalent of $[NH_2]^+$; its reactions with ester enolates are reported to occur smoothly at -78 °C with good yields and high diastereoselectivities.[29] However, addition of 1 equiv of TBAD to a solution of **3a** prepared in THF at -78 °C, performed under various conditions, led only to the diester **7** in 33% yield, the product of self-condensation of the anion **3a**.[30] The dianion **3b** (R = (-)), prepared upon treatment of the acid **3** with 2 equiv of LDA,[31] was known to undergo self-con-

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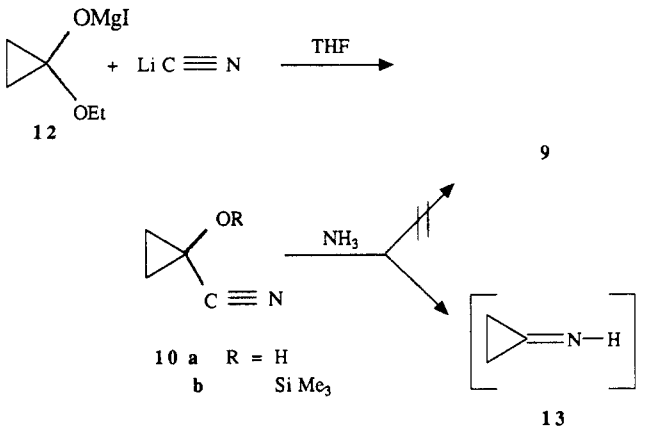
densation at a higher temperature (50 °C);[32] in fact, its reaction with TBAD (6) at −60 °C provided the expected 1-hydrazinocyclopropanecarboxylic acid 8, which was isolated by liquid chromatography on silica gel in only 8% yield (Scheme I).

Lithium enolates of (2,6-di-*tert*-butyl-4-methylphenyl)- and (2,4,6-tri-*tert*-butylphenyl)cyclopropanecarboxylates have been α-nitrated with isopentylnitrate in 60–70% yields; it has been reported however, that reduction of the NO_2 group with $Zn/AcOH/Ac_2O$ gave *N*-acetyl-2-aminobutanoic acid from ring opening, exclusively.[33]

2. Amination and Cyanation of the Cyclopropanone Hemiacetal, 4. Examination of the retrosynthetic scheme for the preparation of the amino acid **1**, led to the conclusion that cyclopropanone hemiacetal (or 1-ethoxycyclopropanol, **4**) should be considered as a possible precursor for ACC, **1**.

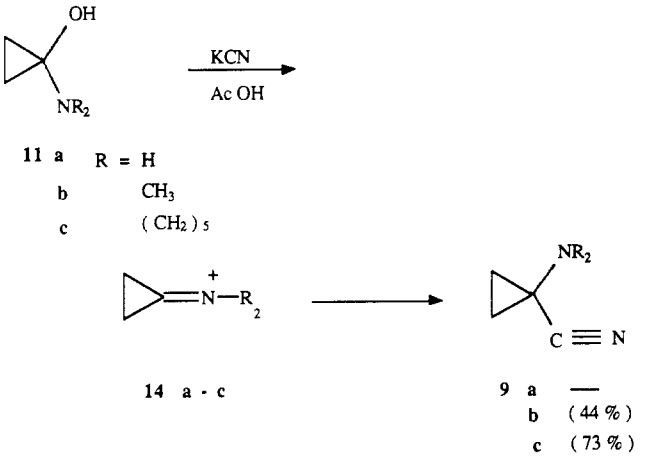
Effectively, the amino acid **1** derives from the amino nitrile **9**, which could, a priori, be obtained either from the cyclopropanone cyanohydrin **10** or from the 1-aminocyclopropanol **11**, following a well known classical pathway (i.e. Strecker synthesis) (Scheme II); both cyclopropanols **10** and **11** are prepared from the hemiacetal **4**. The 1-ethoxycyclopropanol (**4**) (readily available from the sodium induced cyclization of ethyl 3-chloropropionate in the presence of Me_3SiCl, followed by simple methanolysis[34]) recently became the substrate of choice in a number of useful chemical transformations leading to homologous rings.[22,35]

We have previously reported that the addition of lithium cyanide to the magnesium salt **12**, obtained upon treatment of the hemiacetal **4** with 1 equiv of CH_3MgI, provided the cyclopropanone cyanohydrin **10a** in 75% yield.[36a] (For



a recent preparation of cyanohydrin **10a** from 1-hydroxycyclopropanecarboxylic acid, **2**, see ref 36b.) α-Amino nitriles, which provide important intermediates for the preparation of amino acids, are usually available from the reaction of ammonia (or amines) with cyanohydrins; this synthesis has recently been improved upon by allowing trimethylsiloxy nitriles to react with various amines in methanol. From aliphatic or aromatic aldehydes, the corresponding α-amino nitriles were obtained in high yields (83–99%), while ketones led either to amino nitriles in lower yields (50% from cyclohexanone) or to ketimines (70% from benzophenone).[38] Addition of cyclopropanone cyanohydrin **10a** (or of its silylated derivative **10b**)[37] to a saturated solution of methanolic ammonia, and heating the mixture at 40 °C for 2–16 h did not provide the expected α-amino nitrile **9**, as indicated in both the IR and ^1H NMR spectra of the crude product by disappearance of the nitrile vibration ($\gamma_{C\equiv N}$ (CCl_4): 2240 cm^{-1} for **10a,b**) and of the protons of the cyclopropane ring ($\delta(CDCl_4)$: 1.20 ppm for **10a,b**), respectively. Furthermore, addition of gaseous HCl gave a white solid (mp 109–110 °C) with spectroscopic and analytical data different from those recorded for the chlorohydrate of amino nitrile **9** (obtained from acrolein, vide infra) instead indicating the presence of polymeric compounds. Likely, the cyclopropylketimine **13** was formed and rapidly polymerized, as does the parent cyclopropanone.[39]

Otherwise, it has been reported that the hydroxy group of 1-(dimethylamino)cyclopropanol **11b**, prepared by addition of a 10-fold excess of dimethylamine to cyclopropanone, is easily displaced by all common nucleophiles. Thus, addition of acetic acid at 0 °C to an aqueous solution of amino alcohol **11b** and KCN gave 1-cyano-1-(dimethylamino)cyclopropane (**9b**) in 44% yield.[40]



Similarly, 1-hydroxy-1-piperidinocyclopropane, **11c**, readily available from β-chloropropionyl chloride, was treated with KCN in the presence of aqueous acetic acid to give the nitrile **9c** in 73% yield.[41] The mechanism of such displacements was discussed in terms of an S_N1 type reaction involving the cyclopropyliminium ions **14b,c** as intermediates. Thus, 1-aminocyclopropanol, **11a**, the active moiety of coprine (N^5-(1-hydroxycyclopropyl)-L-glutamine), which is an in vivo inhibitor of liver aldehyde dehydrogenase (ALDH),[42] might also appear to be a convenient precursor of the amino acid **1** (see Scheme II). It has been reported that reaction of cyclopropanone with ammonia and quenching with HCl gave a low yield of the chlorohydrate of amino alcohol **11a**, which was alternatively obtained by HCl hydrolysis of 1-ethoxycyclopropyl isocyanate or *tert*-butyl *N*-(1-ethoxycyclopropyl)carbamate.[43]

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Scheme III

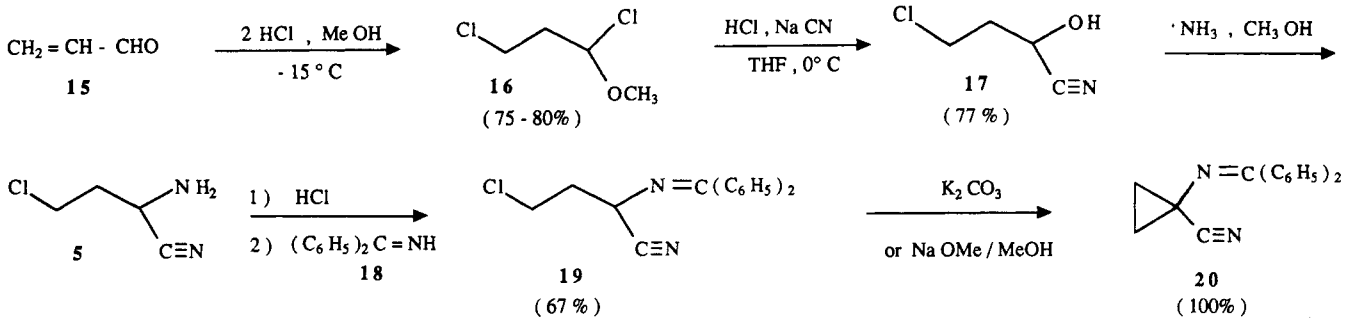

Table I. Base-Induced Cyclization of the Benzophenone Imine of 2-Amino-4-chlorobutronitrile, 19

entry	base	solvent	temp, °C	time, h	convn, % (yield, %)
1	Cs_2CO_3	DMF	18	24	100 (100)
2	Cs_2CO_3	DMF	40	2.5	100 (100)
3	K_2CO_3	DMF	40	3	100 (100)
4	KOH	DMSO	18	2	100 (93)
5	NaOMe	MeOH	18	24	100 (95)
6	aqueous NaOH 50% (Bu_4N^+, SO_4H^-)	anisole	18	24	100 (95)
7	NEt_3	DMF	18	4 days	25.5
8	-	-	50	21.5	50
9	HCO_3Na	MeOH (or THF)	20–40	48	0

Surprisingly, hemiacetal **4** did not react with liquid ammonia but underwent nucleophilic addition of sodium amide in ammonia to provide a 37:62 mixture of propionamide and 1-aminocyclopropanol. Quenching by HCl of the reaction product did not give the chlorohydrate of amino alcohol **11a**; moreover, one-pot successive addition of KCN, acetic acid, and HCl did not lead to the expected chlorohydrate of α-aminocyanocyclopropane, **9a**. Although cyclopropyliminium **14a** has been transiently considered as an enzyme inhibitor,[44] the 1-aminocyclopropanol **11a**, in contrast to its N-substituted derivatives **11b,c**, appears considerably too labile to undergo CN substitution.

3. Preparation and Cyclization of the 2-Amino-4-chlorobutyronitrile, 5. In light of the fact that the readily available cyclopropane derivatives **2–4** did not provide efficient precursors of ACC, **1**, we next turned our attention to the 2-amino-4-chlorobutyronitrile (**5**), which, on base-induced cyclization, could readily provide the amino nitrile **9**. As far as we know, the preparation of **5** had not been reported previously.

Cheap and commercially available acrolein **15** underwent addition of 2 equiv of HCl in methanol at −15 °C to provide 1,3-dichloro-1-methoxypropane, **16**, in 75–80% yield.[45] Hydrolysis of the dichloro ether **16** in the presence of sodium cyanide at 0 °C gave the stable 2-chloropropionaldehyde cyanohydrin **17**,[46] which was isolated by distillation (bp 82 °C/0.6 mm) in 77% yield (Scheme III). Addition of the cyanohydrin **17** to a saturated solution of methanolic ammonia[47] and heating the mixture at 40 °C for 3 h gave, after removal of ammonia and methanol under reduced pressure, the 2-amino-4-chlorobutyronitrile, **5**, which was isolated by bubbling gaseous HCl through an etheral solution to provide the chlorohydrate of **5** as a white fine powder, in 73% yield. A suspension of this salt in methylene chloride was treated with benzophenone imine **18**[48] (readily available either from the addition of benzonitrile to benzylmagnesium bromide[49] or from the reaction of α-(trimethylsiloxy-α,α-diphenylacetonitrile with methanolic ammonia[47b]) to yield 4-chloro-2-[(diphenylmethylene)amino]butyronitrile, **19** (92%), as a crystalline white solid (mp 89 °C ether–hexane). This benzophenone Schiff base derivative **19** is then able to undergo facile cyclization into the 1-[(diphenylmethylene)amino]-1-cyclopropanecarbonitrile **20** under various basic conditions. In DMF solution **19** was totally cyclized into cyclopropanenitrile **20** by 1.1 equiv of cesium or potassium carbonate at 18 and 40 °C within 24 or 3 h, respectively (see Table I, entries 1–3). It was also totally cyclized at 18 °C either by 1.5 equiv of powdered KOH in DMSO (entry 4) or by 1.5 equiv of sodium methylate in MeOH (entry 5); under phase-transfer catalysis (anisole, 50% aqueous NaOH, Bu_4N^+, SO_4H^-) cyclization of **19** occurred completely within 24 h, as shown by TLC, (entry 6). After the usual workup, aminocyclopropanecarbonitrile **20** was obtained in yields greater than 95%. Triethylamine in DMF induced the cyclization smoothly: 25% within 4 days at 18 °C and 50% within 21.5 h at 50 °C (entries 7, 8); sodium bicarbonate in either MeOH or THF was ineffective (Table I).

The aminocyclopropanecarbonitrile **20**, previously obtained from a glycine derivative and 1,2-dibromoethane under phase-transfer catalysis,[7c] can be readily converted into ACC, **1**. Effectively, 1 N hydrochloric acid hydrolysis of **20** gave the chlorohydrate of 1-aminocyclopropanecarbonitrile, **9**, while further hydrolysis with 6 N HCl at reflux led, after treatment with either K_2CO_3 in MeOH, propylene oxide, or an anion exchange resin (Duolite A7), to the 1-aminocyclopropanecarboxylic acid (ACC, **1**) in 98% yield.

Conclusion

Commercially or readily synthetically available cyclopropane derivatives **2–4** did not provide effective synthons for the challenging preparation of 1-aminocyclopropanecarboxylic acid (ACC, **1**) and its derivatives; in particular,

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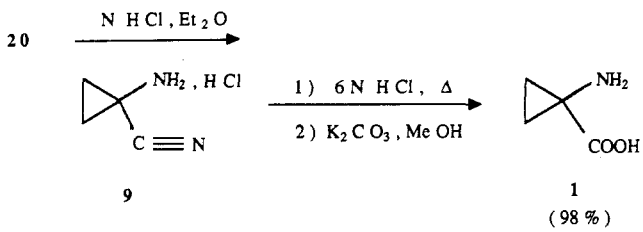

9 1 (98 %)

the cyclopropanone hemiacetal 4,[35] which is so well suited to nucleophilic substitutions, was not able to conveniently undergo the Strecker synthesis. The most suitable route to ACC, 1 appeared to be the base-induced cyclization of the benzophenone imine of an α-aminobutyronitrile γ-substituted by a chlorine leaving group, such as 5, which was readily prepared for the first time from acrolein. The syntheses of other cyclic amino acids, e.g., optically acitve substituted derivatives of ACC, 1 are under current investigation.

Experimental Section

1-Hydroxycyclopropanecarboxylic acid (2)[21] and cyclopropanone hemiacetal (4)[34] were prepared as previously reported. Cyclopropanecarboxylic acid (3) and acrolein (5) are commercially available (Aldrich).

Reaction of Methyl Cyclopropanecarboxylate with TBAD. A solution of 4.2 mL (30 mmol) of diisopropylamine in 15 mL of anhydrous THF was treated at −78 °C with 20 mL of a 1.5 N solution of *n*-BuLi; the mixture was stirred for 15 min, after which 2 g (20 mmol) of methyl cyclopropanecarboxylate was added dropwise and the mixture was stirred for 2 h at −78 °C. To the resulting enolate **3a** were added 5.52 g (1.2 equiv) of di-*tert*-butylazodicarboxylate (TBAD) in 30 mL of THF. The reaction mixture was stirred at −78 °C for 10 min, quenched by addition of 3 g (2.5 equiv) of acetic acid, and allowed to warm to room temperature. The mixture was then poured into 60 mL of iced water and extracted with 2 × 100 mL of ether. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Chromatography of the residue on silica gel (ether/hexane, 15/85) gave, besides unidentified polar material (R_f = 0.1) and 0.5 g of TBAD (R_f = 0.58), 2.77 g (33%) of the tricyclopropyl hydroxy diesters 7 (R_f = 0.4): ^{1}H NMR (200 MHz) ($CDCl_3$) δ 0.2 (m, 2 H), 0.42 (m, 2 H), 0.9 (m, 2 H), 1.15 (m, 2 H), 1.30 (m, H), 1.45 (m, 2 H), 3.60 (s, 6 H), 4.05 (d, 1 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 0.83 (t, CH_2), 11.20 (t, CH_2), 13.90 (s, C), 32.35 (s, C), 51.59 (q, CH_3), 69.58 (s, C), 174.59 (s, $COOCH_3$); IR (CCl_4) (cm^{-1}) 3460 (γ(OH)), 3100 (γ(C–H(cyclopropane))), 1735 (γ(C=O)); MS *m/e* (rel int) 231 (1.1), 174 (22), 130 (18), 57 (100), 43 (40). Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.52. Found: C, 63.01; H, 7.13 (lack of nitrogen).

Reaction of Cyclopropanecarboxylic Acid (3) with TBAD. A solution of 2.37 g (23.74 mmol) of diisopropylamine in 30 mL of THF was treated at −20 °C with 1.5 equiv of *n*-BuLi for 30 min. Then 1 g (11.62 mmol) of cyclopropanecarboxylic acid (3) was added, and the mixture was stirred for 10 min and cooled to −78 °C. To the resulting dianion was added 3.21 g (1.2 equiv) of TBAD, and the mixture was stirred for 20 min at 60 °C, quenched with 4 mL (69.8 mmol) of acetic acid, stirred at −60 °C for 15 min, and finally allowed to warm to room temperature. The mixture was poured into 50 mL of water and extracted with 2 × 50 mL of ether; the organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give 4.3 g of crude product. Flash chromatography of the residue (CH_2Cl_2–Et_2O, 5/95) gave 290 mg (8%) of the 1-(*N*,*N*′-di-*tert*-butylhydrazino)cyclopropanecarboxylic acid, 8 (R = H): ^{1}H NMR δ 0.90 (m, 2 H), 1.07 (m, 2 H), 1.47 (s, 18 H), 6.30 (broad s, 1 H, NH); IR (cm^{-1}) 3600–3000 (γ(OH)), 1695 (γ(COOH)). Anal. Calcd. for $C_{14}H_{24}O_6N_2$: C, 53.15; H, 7.65; N, 8.85. Found: C, 52.95; H, 7.31; N, 8.76.

Reaction of Cyclopropanone Cyanohydrin 10 with Methanolic Ammonia. To 20 mL of methanol saturated with gaseous ammonia was added 0.900 g (10.7 mmol) of cyclopropanone cyanohydrin **10** (prepared from hemiacetal 4 and lithium cyanide as reported[36a]), and the mixture was heated at 40 °C for 2 h. Removal of ammonia and methanol under reduced pressure gave 0.65 g of a residue. ^{1}H NMR spectra of the crude product showed the disappearance of the cyclopropanic protons of **10** at δ 1.20 ppm and new signals at δ 1.50, 3.50, and 3.70 ppm ($CDCl_3$). Addition of anhydrous HCl to the residue gave a white solid, which was isolated by filtration (mp 109–110 °C) and showed, in its elemental analysis, a nitrogen deficiency (N, 9.26%) relative to the expected nitrogen composition (N, 23.62%) for the chlorohydrate of amino nitrile **9** (vide infra).

Reaction of Cyclopropanone Hemiacetal (4) with Sodium Amide. Addition of 1 g (9.8 mmol) of cyclopropanone hemiacetal (4) to 20 mL of liquid ammonia and slow evaporation of NH_3 overnight restored the unchanged hemiacetal 4.

To 20 mL of liquid ammonia at −30 °C was added 0.225 g (9.8 mmol) of sodium, and to the blue solution a catalytic amount of $(NO_3)_3Fe$ was added. To the gray suspension of sodium amide in NH_3 was added dropwise a solution of 1 g (9.8 mmol) of hemiacetal 4 in 3 mL of ether; ammonia was then allowed to evaporate overnight. To the residue were added 50 mL of ether and 5 mL of saturated aqueous NH_4Cl. After the mixture was stirred for 10 min, the organic phase was decanted, washed with brine, and dried over Na_2SO_4 to give a 37:63 mixture of propionamide [200 MHz NMR (ppm) δ 1.15 (t, 3 H, J = 7.9 Hz), 2.25 (q, 2 H), 0.9 (m, 2 H), 1.15 (m, 2 H), 1.30 (m, H), 1.45 (m, 2 H), 3.60 (s, 6 H), 4.05 (d, 1 H, J = 7 Hz, J = 7.9 Hz), 2.80 (broad s, 2 H)] and of 1-aminocyclopropanol **11a** [δ ($CDCl_3$) 1.20 (s, 4 H), 4.8 (m, 2 H)] which appeared unstable on purification. Bubbling gaseous HCl through a solution of the crude mixture in ether provided a white solid whose ^{1}H NMR spectra [200 MHz, NMR δ (D_2O) 1.05 (m, 2 H) and 1.20 (m, 2 H)] are not consistent with reported data [δ (D_2O) 1.20 (s, 4 H) for hydrochloride **11a**[44]].

One-Pot Successive Reaction of Cyclopropanone Hemicetal (4) with Sodium Amide and Potassium Cyanide. To the reaction product of 1 g (9.8 mmol) of hemiacetal 4 with NH_2Na (1 equiv) in 20 mL of ammonia was added at 0 °C, after removal of NH_3 under reduced pressure, a solution of 6.38 g (1 equiv) of KCN in 5 mL of water and 1.2 g (2 equiv) of acetic acid. The mixture was stirred overnight at room temperature. Extraction with ether gave 0.426 mg of a mixture of four unidentified compounds (TLC) among which the expected amino nitrile **9a** was absent (from NMR, IR, and mass spectra).

1,3-Dichloro-1-methoxypropane (16). A solution of 56 g (1 mol) of freshly distilled acrolein on $CuSO_4$ and 42 g (1 mol) of methanol was cooled to −20 °C (external dry ice/acetone bath); then dry gaseous HCl was bubbled through the solution at a rate such that the temperature of the solution was kept below −15 °C to avoid the formation of 3-chloro-4,1-dimethoxypropane.[45] When 73 g (2 equiv) of HCl were absorbed, the solution was transferred to a separating funnel, and water was eliminated by decantation. The organic phase was dried over $CaCl_2$, concentrated under reduced pressure, and distilled through a 30-cm Vigreux column to yield 107.2 g (75%) of pure 1,3-dichloro-1-methoxypropane (16) (bp 47 °C/12 mm): ^{1}H NMR (200 MHz) ($CDCl_3$) δ 2.45 (m, 2 H), 3.55 (s, 3 H), 3.70 (t, 2 H, J = 6.4 Hz), 5.65 (t, 1 H, J = 5.52 Hz); MS *m/e* (rel int) 143 (M^+, 0.1), 109 (M − Cl, 31), 107 (M − Cl, 100), 79 (61), 75 (100), 71 (57), 45 (37), 41 (22). (Note: A sample of dichloro ether **16** was kept at −20 °C, unaltered for months.)

4-Chloro-2-hydroxybutyronitrile (17). To a mixture of 27 mL of 4 N HCl (108 mmol) and 41 mL of THF at 0 °C were added simultaneously and slowly in small portions 27.6 g (193 mmol) of dichloro ether **16** and 11.34 g (230 mmol) of sodium cyanide. After stirring at 0 °C for 10 min, the aqueous mixture was extracted by ether (3 × 100 mL); the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, and the residue was distilled to yield 17.6 g (77%) of 4-chloro-2-hydroxybutyronitrile (5) (bp 82 °C/0.6 mm): ^{1}H NMR (200 MHz) ($CDCl_3$) δ 2.30 (m, 2 H), 3.73 (m, 3 H), 4.78 (dd, 1 H, J = 5.41 and 8.14 Hz); ^{13}C NMR ($CDCl_3$) δ 36.94 (CH_2), 39.16 (CH_2), 57.77 (CH), 119.72 (CN); IR (CCl_4) (cm^{-1}) 3400 (γ(OH)), 2220 (γ(C≡N)); MS *m/e* (rel int) 103 (s), 101 (14, M − 18), 83 (25, M − HCl), 65 (46), 63 (100); CIMS (rel int) 139 (67, MNH_4), 137 (100, MNH_4).

2-Amino-4-chlorobutyronitrile (5) (and Its Chlorohydrate). Ammonia was bubbled through 30 mL of methanol until the end of the exothermic reaction, 5 g (42 mmol) of the cyanohydrin **17** was added and the reaction mixture was stirred at 40 °C for 3 h. After evaporation of the ammonia and methanol,

most of the residue was dissolved in 80 mL of ether leaving 0.8 g of insoluble (but soluble in water) material. Removal of ether from an aliquot gave 2-amino-4-chlorobutyronitrile (**5**): ^{1}H NMR (200 MHz) ($CDCl_3$) δ 1.8 (m, 2 H), 2.25 (m, 2 H), 3.70 (m, 2 H), 3.95 (t, 1 H, J = 7.31 Hz). An equivalent of gaseous dry HCl (1.53 g, 42 mmol) was bubbled through the etheral solution cooled at 0 °C; removal of ether under reduced pressure gave 4.75 g (73%) of the corresponding chlorohydrate as a white powdered crude product: ^{1}H NMR (200 MHz) (DMSO-d_3) δ 2.00 (m, 2 H), 3.70 (m, 2 H), 3.90 (dd, 1 H, J = 6.7 and 7 Hz), 9.50 (m, 3 H).

4-Chloro-2-[(diphenylmethylene)amino]butyronitrile (19). To a stirred suspension of 5.42 g (35 mmol) of the crude chlorohydrate of **5** in 50 mL of methylene chloride was added 7 g (39 mmol) of benzophenone imine **18**.[49] After 10 min the chlorohydrate was completely dissolved, and NH_4Cl was formed and precipitated as a byproduct. TLC of an aliquot showed the formation of a single product. After stirring for 24 h at room temperature, the mixture was filtered to remove NH_4Cl and concentrated on a rotary evaporator. Flash chromatography gave 9 g (92%) of 4-chloro-2-[(diphenylmethylene)amino]butyronitrile (**19**), which was recrystallized from ether–hexane as a white crystalline compound, mp 89 °C: ^{1}H NMR (200 MHz) ($CDCl_3$) δ 2.35 (m, 2 H), 3.60 (m, 2 H), 4.40 (dd, 1 H, J = 8 and 5.48 Hz), 7.40 (m, 10 H); IR (CCl_4) (cm^{-1}) 2240 (γ(C≡N)). Anal. Calcd for $C_{17}H_{15}NCl$:C, 72.21; H, 5.30; N, 9.91; Cl, 12.56. Found: C, 72.21; H, 5.25; N, 9.63; Cl, 12.27.

1-[(Diphenylmethylene)amino]cyclopropanecarbonitrile (20). (a) Cyclization by Cesium Carbonate at 20 °C. A solution of 4 g (14.15 mmol) of the chloro imine **19** in 50 mL of dimethylformamide (DMF) containing 5.075 g (1.1 equiv) of Cs_2CO_3 was stirred at 20 °C for 24 h. TLC of an aliquot showed formation of a single product. Then, the mixture was filtered, and DMF was removed on a rotary evaporator. The residue was dissolved in 50 mL of ether, and the organic phase washed with 3 × 10 mL of water, dried over Na_2SO_4, and evaporated to dryness to give 3.48 g (100%) of pure 1-[(diphenylmethylene)amino]-cyclopropanecarbonitrile, **20**: ^{1}H NMR (200 MHz) ($CDCl_3$) δ 1.65 (s, 4 H), 7.50 (m, 10 H). Recrystallization from ether–hexane gave a white crystalline compound, mp 81 °C (lit.[50] mp 77–80 °C). Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.91; H, 5.73; N, 11.37. Found: C, 82.99; H, 5.79; N, 11.28.

(b) Cyclization by Cesium Carbonate at 40 °C. A solution of 307 mg (1.08 mmol) of chloro imine **19** in 2 mL of DMF containing 330 mg (1.1 equiv) of Cs_2CO_3 was stirred at 40 °C. After 5 min, formation of the expected compound **20** was monitored by TLC; the cyclization was completed within 2 h. After cooling at room temperature, workup as above gave 267 mg (100%) of pure cyclopropanecarbonitrile **20**, as shown by TLC and ^{1}H NMR analyses.

(c) Cyclization by Potassium Carbonate at 40 °C. A solution of 226 mg (0.8 mmol) of chloro imine **19** in 3 mL of DMF containing 122 mg (1.1 equiv) of K_2CO_3 was stirred at 40 °C. As monitored by TLC the reaction was completed within 3 h. Workup as above yielded 196 mg (100%) of pure cyclopropanenitrile **20** (TLC, ^{1}H NMR).

(d) Cyclization by Potassium Hydroxide in Dimethyl Sulfoxide at 18 °C. A solution of 186 mg (0.66 mmol) of chloro imine **19** in dimethyl sulfoxide (DMSO) containing 55.2 mg (1.5 equiv) of freshly pulverized potassium hydroxide was stirred at 18 °C; the reaction was completed within 2 h as monitored by TLC. The mixture was poured into 15 mL of water, and the aqueous phase was extracted with 3 × 5 mL of pentane. The organic phase was washed with 3 × 3 mL of water, dried over Na_2SO_4, and concentrated on a rotary evaporator to yield 154 mg (93%) of pure cyclopropanenitrile **20** (^{1}H NMR).

(e) Cyclization by Sodium Methylene in Methanol at 18 °C. The chloro imine **19** is not soluble in pure methanol; thus, to 2 mL of MeOH was added 17 mg (0.74 mmol) of sodium, and after total dissolution of the metal, 150 mg (0.53 mmol) of chloro imine **19** were added. The mixture was stirred at 18 °C for 24 h, and MeOH was removed under reduced pressure. The residue was dissolved in 10 mL of ether, and the organic phase was neutralized with dilute HCl, dried over Na_2SO_4, and concentrated on a rotary evaporator to yield 124 mg (95%) of pure cyclopropanenitrile **20** (TLC ^{1}H NMR).

(f) Cyclization by Phase-Transfer Catalysis at 18 °C. A mixture of 1 mL of anisole, 0.8 mL (10 mmol) of 50% aqueous NaOH containing 54 mg (0.1 mmol) of tetrabutylammonium bisulfate, and 282 mg (1 mmol) of chloro imine **19** was stirred at 18 °C for 24 h. TLC showed complete cyclization; then 5 mL of ether was added, the organic phase was washed with 3 × 2 mL of half-saturated NaCl aqueous solution, dried over $MgSO_4$, and concentrated on a rotary evaporator to remove ether and anisole (bp 155 °C). The residue 230 mg (95%) is the pure cyclopropanenitrile **20** (TLC, ^{1}H NMR).

(g) Cyclization by Triethylamine in DMF. At 18 °C. A solution of 146 mg (0.52 mmol) of chloro imine **19** in 1.5 mL of DMF containing 78.1 mg (0.77 mmol) of triethylamine was stirred at 18 °C for 4 days; after workup, NMR of the residue showed the formation of 25.5% of cyclopropanenitrile **20**.

At 50 °C. A solution of 120 mg (0.45 mmol) of chloro imine **19** in 1 mL of DMF containing 64 mg (0.62 mmol) of NEt_3 was stirred at 50 °C for 21.5 h. After workup, ^{1}H NMR analysis of the residue showed the formation of 50% of cyclopropanenitrile **20**.

(h) Use of Sodium Bicarbonate in MeOH and THF. A mixture of 282 mg (1 mmol) of chloro imine **19** and 2 mL of methanol containing 1.5 equiv of $NaHCO_3$ was stirred at 18 °C for 48 h; TLC and ^{1}H NMR analyses showed the starting compound **19** unrearranged. Then, MeOH was removed under reduced pressure and 2 mL of THF was added. The mixture was stirred at 18 °C for 4 days, TLC and ^{1}H NMR analyses showed formation of unidentified byproducts.

1-Amino-cyclopropanenitrile Chlorohydrate (9). A mixture of 2 g (8.13 mmol) of cyclopropanenitrile **20**, 20 mL of ether, and 40 mL of 1 N HCl was stirred at 18 °C for 15 h. The aqueous phase, isolated by decantation, was washed with 2 × 10 mL of ether, concentrated on a rotary evaporator, and dried in high vacuum to yield 0.96 g (100%) of 1-aminocyclopropanenitrile chlorohydrate **9**: mp 170–172 °C; ^{1}H NMR (DMSO-d_6) δ 1.55 (s, 4 H), 8.50 (m, 3 H); IR (KBr) (cm^{-1}) 2950 (NH_2) and 2150 (γ-(C≡N)). Anal. Calcd for $C_4H_7N_2Cl$: C, 40.50; H, 5.92; N, 23.62; Cl, 29.95. Found: C, 40.76; H, 6.00; N, 23.57; Cl, 29.91.

1-Aminocyclopropanecarboxylic Acid (1). A mixture of 2 g (8.13 mmol) of cyclopropanenitrile **20**, 20 mL of ether and 40 mL of 1 N HCl was stirred at 18 °C for 24 h. The decanted aqueous phase was washed with 2 × 10 mL of ether, and 34 mL of concentrated HCl was added. The solution was refluxed for 4 h, and water was then removed on a rotary evaporator. The residue was dissolved in 10 mL of water and concentrated under reduced pressure; this process was conducted twice in order to eliminate completely any HCl. Twice again, the residue was dissolved in 10 mL of methanol, concentrated under reduced pressure in order to remove water, and finally dried under high vacuum (0.05 mm) to yield 1.08 g (98%) of pure 1-aminocyclopropanecarboxylic acid chlorohydrate: ^{1}H NMR (200 MHz) (D_2O) δ 1.15–1.55 (m, 4 H), 4.60 (m, 3 H).

A solution of this chlorohydrate (360 mg) in 10 mL of CH_3OH, containing 400 mg (1.1 equiv) of K_2CO_3, was stirred at 20 °C for 48 h. After filtration, MeOH was removed under reduced pressure, and the residue was recrystallized from a mixture of NH_4OH–EtOH to yield 252 mg (98%) of pure 1-amino-cyclopropanecarboxylic acid (ACC, **1**): mp 240 °C (lit.[18] mp 240–241 °C); ^{1}H NMR (200 MHz) (DMSO-d_6) δ 0.80 (m, 2 H), 1.10 (m, 2 H), 4.0 (broad s, 3 H). Anal. Calcd for $C_4H_7NO_2$: C, 47.52; H, 6.98; N, 13.86. Found: C, 47.28; H, 7.10; N, 13.98.

Otherwise, a solution of the chlorohydrate of **1** in water was passed through a weakly basic anion exchange resin (Duolite A7) to yield, after removal of water and drying under high vacuum, pure ACC, **1** (NMR).

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