Synthesis of 1-Amino-2,2-dialkylcyclopropanecarboxylic Acids via Base-Induced Cyclization of γ-Chloro-α-imino Esters

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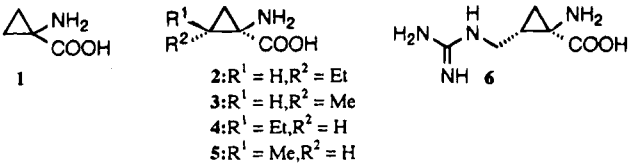
β-Chloro ketones were oxidatively transformed into α-keto carboxylic esters and condensed with primary amines in the presence of titanium(IV) chloride. Base-induced cyclization of the resulting γ-chloro-α-imino esters, incorporating suitable N-substituents, led directly to 1-amino-2,2-dialkylcyclopropanecarboxylic ester derivatives via a 1,5-dehydrochlorination process. Syntheses of different N- and/or carboxyl-protected geminally (*gem*) dialkylated cyclopropane amino acids were developed, while access to the free α-amino acids is also given. The methodology used was further extended by reduction of the γ-chloro-α-imino esters to functionalized γ-chloro-α-amino esters, prior to ring closure, affording *N*-alkyl-*gem*-dialkyl-1-aminocyclopropanecarboxylic acid derivatives.

Introduction

Cyclopropaneamino acids (∇-AA), also referred to as cyclopropylogs, methanologs, or 2,3-methano α-amino acids, constitute a peculiar class of strained alicyclic amino acids which are of considerable interest due to their natural occurrence, structural characteristic features, and diverse physiological activities. 1-Aminocyclopropanecarboxylic acid (**1**, ACC, Chart 1) has been designated as the immediate biochemical precursor of the phytohormone ethylene by means of tracer studies of methionine metabolism.[1] The ACC congeners coronamic acid (**2**) and norcoronamic acid (**3**), phytotoxins produced by the phytopathogenic Pseudomonas species, were shown to induce chlorosis in Italian ryegrass (chocolate spot disease) and hypertrophy in potato tissue.[2,3] The guanidine-containing ∇-AA carnosadine **6** is a constituent of the red algae Grateloupia carnosa.[4] Recently, N-methylated norcoranamic acid was identified in the cyclic peptide portion of the newly discovered DNA-intercalating antibiotics of the quinomycin family, isolated from Streptomyces braegensis subsp. japonicus.[5] Synthetic ∇-AA have been found to exert physiological activities of diverse nature, and several of them have been patented as plant growth regulating compounds, abscission agents for fruits and leaves, and fungicides.[6] Concomitantly, ∇-AA attracted the attention in peptide chemistry because the 2,3-methano moiety imposes steric constraints

Chart 1



1 **2**:R¹ = H,R² = Et **3**:R¹ = H,R² = Me **4**:R¹ = Et,R² = H **5**:R¹ = Me,R² = H **6**

in which substituents at the β-position are fixed in space with reference to the carboxyl and amino function—as in α,β-dehydroamino acids—yet retaining chirality. The latter research led to the synthesis of peptide mimetics resistant to proteolytic cleavage.[7,8a] Given the physiological importance of ACC (**1**) and its derivatives as well as the potential importance of ∇-AA in general, several methodologies have been developed for their synthesis.[8]

Allocoronamic acid (**4**)[9,10] and especially allonorcoronamic acid (**5**)[11] behave as competitive inhibitors of the ethylene-forming enzyme. Linked to a pyridine moiety 2,2-dimethyl-ACC exerts herbicidal activity and is useful for the control of a variety of plants.[12] Therefore, our attention was focused on the synthesis of geminally dialkylated 1-aminocyclopropanecarboxylic acids as potential plant growth regulating compounds. Thus far, only in a few minor cases has it been possible to extrapolate known methods for the synthesis of ACC (**1**) and its monoalkylated derivatives to *gem* dialkylated

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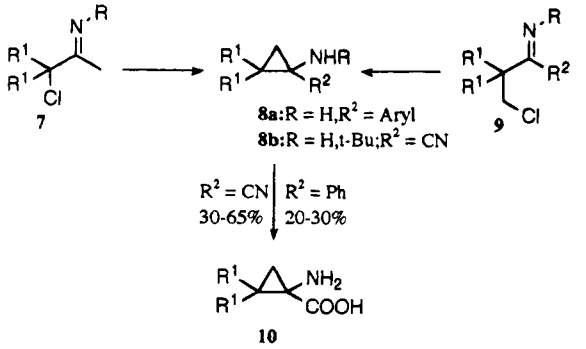
Scheme 1



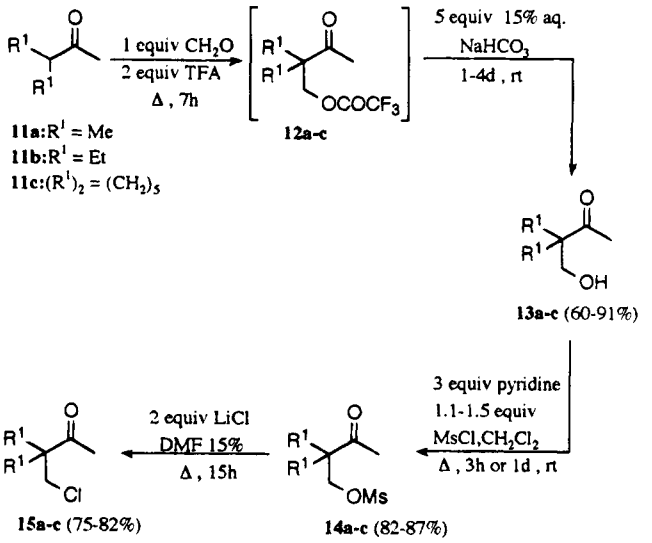
analogues. At present, the desired ACC analogues can be obtained starting from α- or β-halogenated imines **7**[6a,13] and **9**[14] (Scheme 1), via cycloaddition reactions to protected methyleneglycine (dehydroalanine) derivatives[7a] or 3,3-dialkylisocyanoacrylates[15] and base-induced ring closure of *N*-phthaloyl-γ-bromoleucine methyl ester.[16] Very recently, the synthesis of chiral 1-amino-2,2-dimethylcyclopropanecarboxylic acid (diMe-ACC) was reported.[15b,17] On the basis of our ongoing investigation on the synthesis and reactivity of functionalized imines,[6,13,14] we would like to report an improved synthesis of the title compounds on a preparative scale.

Results and Discussion

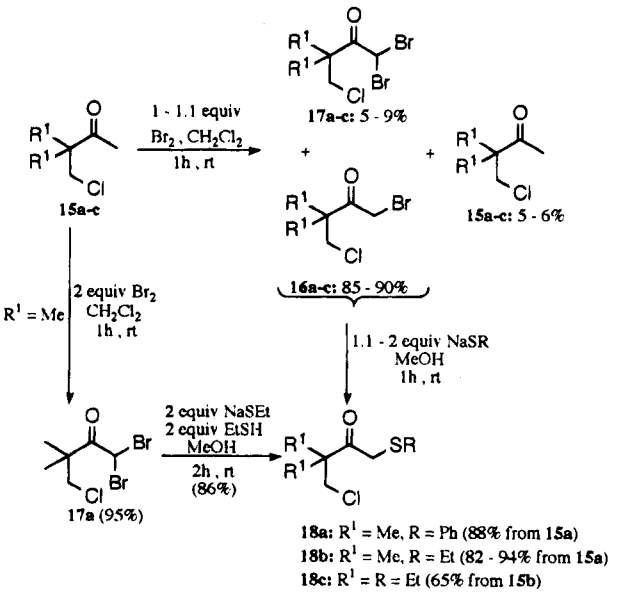
The formation of 2,2-dialkylcyclopropane amino acids **10** (Scheme 1) from the cyclopropylamines **8a** or the tertiary α-aminonitrile **8b** by oxidation ($RuO_2/NaIO_4$) or hydrolysis (12 N HCl/Δ/3 d), respectively, is not possible without side reactions such as ring opening of the cyclopropane skeleton.[6a,14] Therefore, a strategy was developed for the incorporation of an ester functionality (or chemical equivalent), easily hydrolyzable to the corresponding acid, prior to ring closure.

The synthesis of the β-chloro ketones **15**, as previously described, was not suitable to perform on a 1 mol scale.[18] Several modifications in different steps of the reaction sequence were introduced to overcome scale-up problems (Scheme 2). These modifications consisted of (a) trifluoroacetoxymethylation of ketones **11** and subsequent alkaline hydrolysis of the intermediate β-(trifluoroacetoxy) ketone **12**, (b) activation of the alcohol moiety as a mesylate function (previously the less convenient tosylate was used), and (c) substitution of the resulting mesylate **14** using LiCl in DMF. The experimental conditions for the alkaline hydrolysis of the intermediate β-(trifluoroacetoxy) ketone (see Experimental Section) were crucial to obtain good yields, especially for the dimethyl derivative **13a**. Because of the fact that β-hydroxy ketone **13a** is partially water soluble, the amount of water used for hydrolysis was minimized and the extraction procedure adjusted. The replacement of TsCl by MsCl imparted two major advantages. All three mesylates can be easily purified by vacuum distillation to remove the small excess of MsCl used. Second, the substitution reaction with LiCl in DMF proceeds much more smoothly with the mesylates than with the corresponding tosylates. In the same step, pyridine was replaced by CH_2Cl_2 as solvent.

Scheme 2



Scheme 3



In the next stage the β-chloro ketones **15a,b** were oxidatively transformed into the γ-chloro-α-keto esters **23**. As expected, a selective monobromination of an acetyl moiety as present in the β-chloro ketones **15** is difficult to achieve.[19] This lack of selectivity leads to the presence of small amounts of α′,α′-dibromo ketone **17** and starting material, unreacted or obtained by disproportionation of the resulting α′-monobromo ketone **16** (Scheme 3). These side reactions cannot be circumvented by

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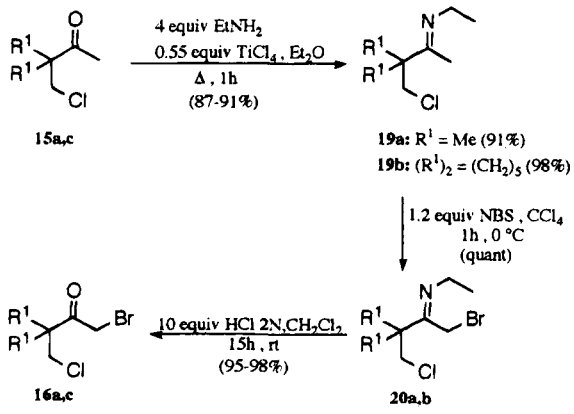
Scheme 4



slowly adding the substrate and reagent to the solvent in a simultaneous and equable way. Therefore, the reaction mixture was used as such in the following step. Both side products, however, did not pose any major drawback for further transformations. The β-chloro ketones **15a,b** could be removed easily in the following step by evaporation *in vacuo* (35 °C/0.1 mmHg). In the reaction with sodium thiolates, both the α′,α′-dibromo ketones **17** and the α′-monobromo ketones **16** yielded the monosulfenylated ketones **18**. Results obtained for this reaction will be reported elsewhere. This fact was used to obtain a selective α-monosulfenylation of the β-chloro ketone **15a** on a preparative scale (0.5 mol) without any loss of starting material. The β-chloro ketone **15a** reacts smoothly with 2 equiv of bromine at room temperature to afford the α′,α′-dibromo ketone **17a**. Reaction of **17a** with sodium ethylthiolate then solely gives rise to the monosulfenylated ketone **18b**. During the course of this investigation sodium phenylthiolate was used only in preliminary experiments to facilitate spectroscopic analysis. On a preparative scale, it was replaced by sodium ethylthiolate. The diethyl disulfide thus formed was removed with the β -chloro ketones **15** (*vide supra*).

Though not requisite in this context, a method was developed allowing a selective α-monobromination of the β-chloro ketones **15** (Scheme 4). For this purpose, the corresponding *N*-ethylimine **19** is treated with NBS under controlled reaction conditions (CCl_4/ 0 °C/1 h) followed by aqueous hydrolysis of the α′-bromo-β-chloro ketimine **20**. A selective monobromination of a methyl ketimine is not so evident but in this case probably is influenced by the bulky substituent at the other side of the imino group. The selectivity, together with the excellent yields of imination, bromination, and hydrolysis, compares favorably with the direct bromination of β-chloro ketones **15**.

The chlorination at the α′-position of *S*-alkyl or *S*-aryl β-keto sulfides **18** using sulfuryl chloride proceeds very smoothly (Scheme 5). The increase in acidity of the protons α to the carbonyl imparted by the sulfur substituent accounts for this observation.[20] For the *S*-ethyl derivative **18b**, a third chloro atom could be introduced by applying somewhat more strenuous conditions. In some preliminary solvolysis reactions, **21a** mainly yielded mixtures out of which a major component could be isolated and/or identified in some cases (Scheme 5, Table 1). Reaction with Na_2CO_3 (all reactions were run in alcoholic medium) selectively replaced both chloro atoms to afford the dialkoxy sulfide **22a**. In the presence of $HgCl_2$ and Ag_2CO_3 all substituents at the α′-position were removed, generating the keto ester **23a** and/or ortho ester **24a**. In basic alcoholic medium the β-chloro ester **25** was the sole product from an iodoform type of reaction. The reaction conditions were then optimized for compounds **21b–d** (Scheme 5, Table 1). With the appropriate number of equivalents of Ag_2CO_3, the ortho esters **24** were obtained in moderate to high yield and in *quasi* pure form. Hydrolysis of the latter finally led to the desired α-keto esters **23**. Hydrolysis could be executed *in situ* on treating **21b–d** with $Hg(OAc)_2$ as a consequence of the somewhat more acidic conditions created during the course of this reaction. In the presence of Na_2CO_3 a varying mixture of dialkoxy sulfide **22b**, α-keto ester **23a**, and the ortho ester **24a** was isolated. The former was also present in each case when a stoichiometric "shortage" of metal ions in the Ag^+- and Hg^{2+}-ion assisted alcoholysis was applied. Initially, the sulfide **22b** was never isolated as such, but always as its rearrangement product **27** by preparative GC. The on-column conditions on GC analysis enable this rare form of neighboring group participation resulting in a 1,4-migration of the sulfur substituent and concomittant loss of MeCl. This phenomenon was shown unambiguously for in one case **22b** could be isolated as the sole product, distilled, and then rearranged almost completely into the α-keto ester **27** on preparative GC. During this investigation a report describing a closely related transformation urged us to disclose some of our results in a preliminary form.[21]

From the γ-chloro-α-keto esters **23** some straightforward transformations were elaborated. Imination with primary amines in the presence of stoichiometric quantities of $TiCl_4$ proceeded very smoothly, even at room temperature, showing that the electronic effect of the ester moiety overrules steric hindrance of the substituent on the opposite side of the carbonyl group (Scheme 6, Table 1). With the *N*-benzylimines, a stage was reached which *a priori* was postulated as the synthetic basis for the synthesis of a variety of the desired geminally dialkylated ACC analogues **10** (Table 1). The formation of the cyclopropane amino acid moiety from *N*-benzylimines **28a,d** was accomplished conveniently by a base-induced ring closure (Scheme 6). Initial deprotonation at the benzylic methylene group leads to a 2-azaallylic anion. The anion then cyclizes through an intramolecular nucleophilic substitution of the neopentylic chloro atom, resulting in a 1,5-dehydrochlorination. The intramolecular substitution reaction could be performed either with a nucleophilic (NaOMe/MeOH) or a less nucleophilic base (KO-t-Bu/THF). The *N*-benzylidene-α-amino esters **29**, thus formed, are themselves dialkylated analogues of compounds facilitating abscission of fruits and leaves. The synthesis of *N*-benzylidene-α-amino esters **29** on a multigram scale (up to 19 g) allowed for the further development of various N- and/or carbonyl-protected *gem* dialkylated ACC derivatives. First, amino esters **29** were fully deprotected by treatment with excess aqueous acid at reflux (10 equiv of 2N HCl) to provide the title compounds **10**. Not a trace of ring-opening product could be detected under these conditions. As a result, the free amino acids could be isolated in high yields and purity. The latter is in sharp contrast with the very difficult acidic hydrolysis of 1-aminocyclopropanecarbonitriles and 1-(*N*-benzylideneamino)cyclopro-

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Table 1. Synthesis of α-Keto Esters 23, Ortho Esters 24, and α-Amino Esters 28

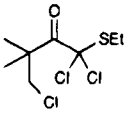
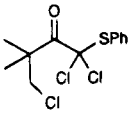
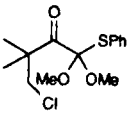
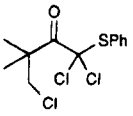
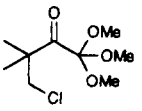
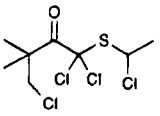
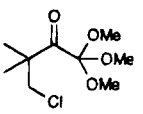
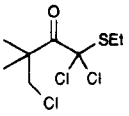
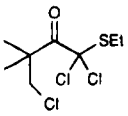
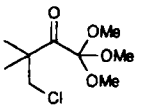
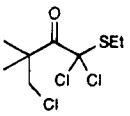
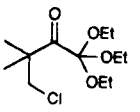
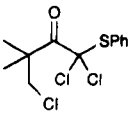
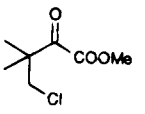
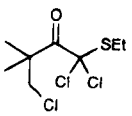
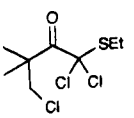
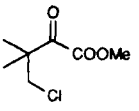
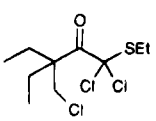
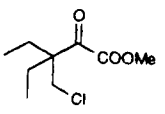
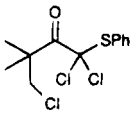
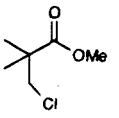
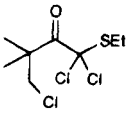
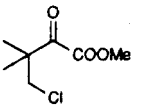
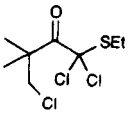
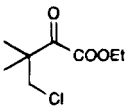
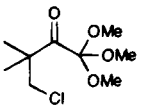
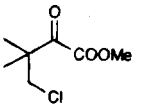
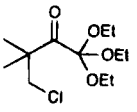
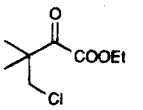
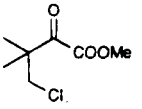
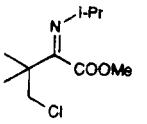
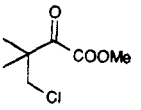
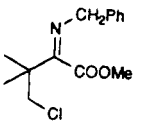
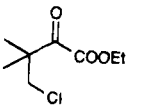
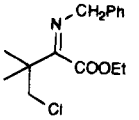
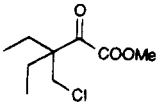
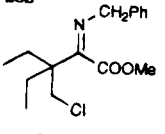
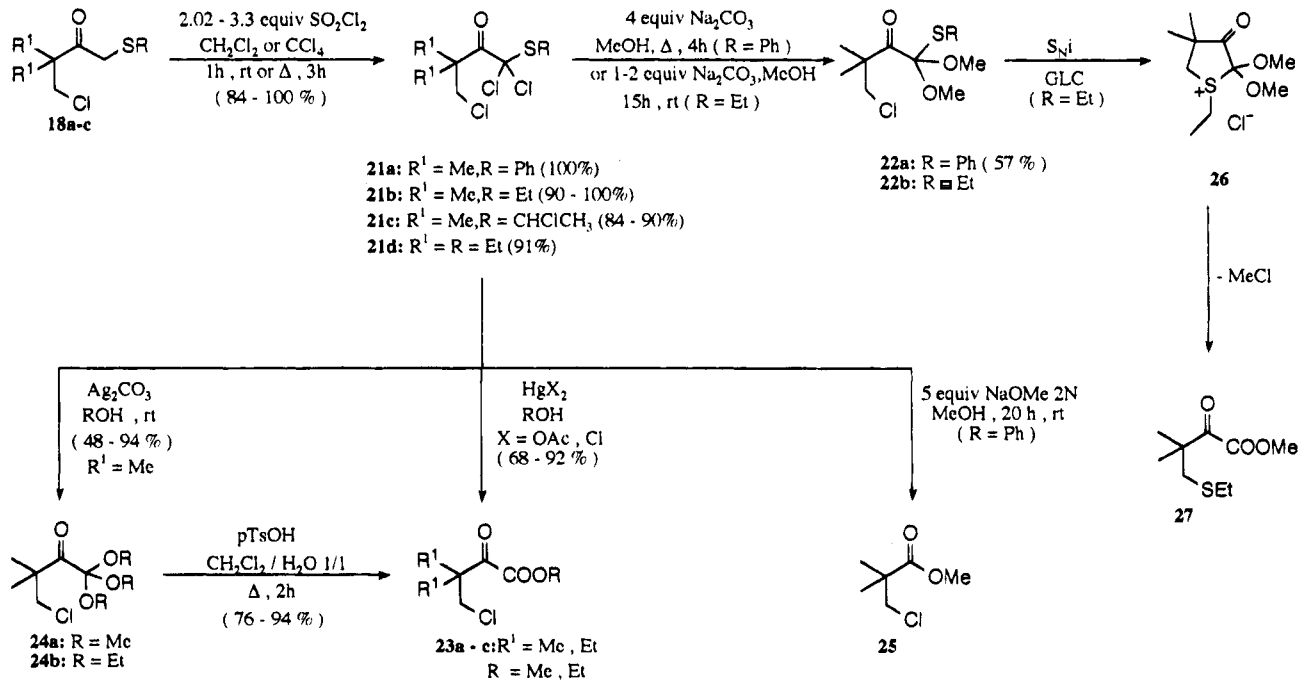
Entry	Substrate	Reaction Conditions	Reaction[a] Product	Yield (%)
1	 **21b**	1 or 2 equiv Na_2CO_3 MeOH, 15h, rt	52 - 100 % **22b** 0 - 48 % **24a**	63-87
2	 **21a**	4 equiv Na_2CO_3 MeOH, Δ, 4h	 **22a**	57
3	 **21a**	1 equiv Ag_2CO_3 MeOH, 20h, rt	 **24a**	48[b,c]
4	 **21c**	3 equiv Ag_2CO_3 MeOH, 17h, rt	 **24a**	50-60
5	 **21b**	1 equiv Ag_2CO_3 MeOH, 15h, rt	14 % **22b** 69 % **23a** 17 % **24a**	78
6	 **21b**	1.5 equiv Ag_2CO_3 MeOH, 15h, rt	 **24a**	94[c]
7	 **21b**	1.5 equiv Ag_2CO_3 EtOH, 15h, rt	 **24b**	68[c]
8	 **21a**	1 equiv $HgCl_2$ MeOH, 20h, rt	 **23a**	53[c]
9	 **21b**	1 equiv $Hg(OAc)_2$ MeOH, 15h, rt	6 % **22b** 94 % **23a**	82
10	 **21b**	1.2 equiv $Hg(OAc)_2$ MeOH, 3d, rt	 **23a**	70-87
11	 **21d**	1.2 equiv $Hg(OAc)_2$ MeOH, 15h, rt	 **23c**	90[d]

Table 1 (Continued)

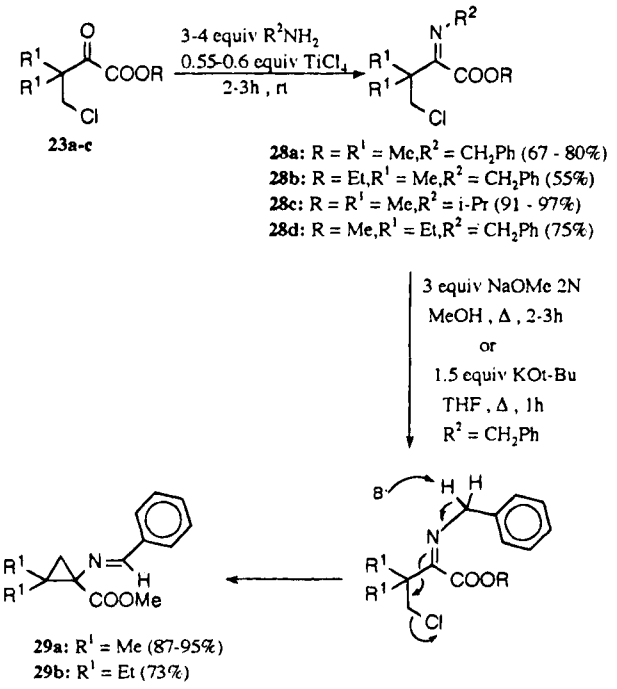
Entry	Substrate	Reaction Conditions	Reaction[a] Product	Yield (%)
12	 **21a**	5 equiv NaOMe2N MeOH, 20h, rt	 **25**	73[c]
13	 **21b**	1) 1.5 equiv Ag_2CO_3 MeOH, on, rt 2) 0.2 equiv pTsOH.aq CH_2Cl_2/H_2O, Δ, 2h	 **23a**	94-98
14	 **21b**	1.2 equiv $Hg(OAc)_2$ EtOH, 3d, rt	 **23b**	68[e]
15	 **24a**	0.1 equiv pTsOH.aq acetone/H_2O 4/1	 **23a**	77[f]
16	 **24b**	0.2 equiv pTsOH.aq CH_2Cl_2/H_2O 1/1 Δ, 2h	 **23b**	86
17	 **23a**	4 equiv i-$PrNH_2$ 0.6 equiv $TiCl_4$, Et_2O, 3h, rt	 **28c**	91-97
18	 **23a**	3 equiv $BnNH_2$ 0.55 equiv $TiCl_4$, Et_2O, 2h, rt	 **28a**	67-80[g]
19	 **23b**	3 equiv $BnNH_2$ 0.6 equiv $TiCl_4$, Et_2O, 3h, rt	 **28b**	55
20	 **23c**	3 equiv $BnNH_2$ 0.6 equiv $TiCl_4$, Et_2O, 3h, rt	 **28d**	75

[a]Ratios, if reported,were determined by GC and ^1H NMR.
[b]Purification was performed by flash chromatography. Elution with pentane removed diphenyldisulfide. Rf pentane/Et_2O (95/5) = 0.45.
[c]An analytically pure sample was obtained by preparative GC.
[d]Bp 40-42°C/0.07 mmHg.
[e]Bp 43-46°C/0.075 mmHg.
[f]Bp 31-34°C/0.075 mmHg.
[g]Bp 100-104°C/0.02 mmHg.

Scheme 5



Scheme 6



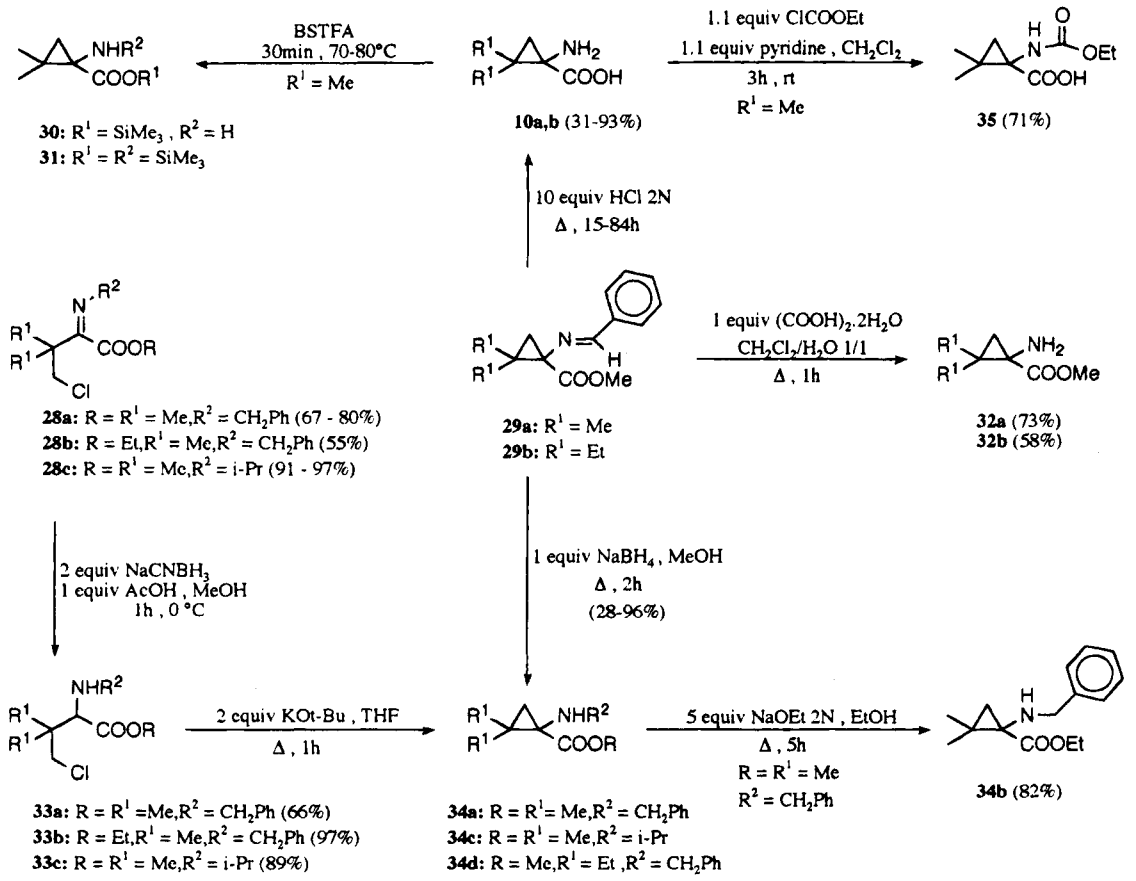
panecarbonitriles, which are all complicated by side reactions because of the comparitively long reaction times. The amino acids **10** were silylated prior to GC–MS analysis by heating them at 70–80 °C in BSTFA as reagent and solvent until all material dissolved (about 30 min), giving rise to the mono- and disilylated amino acids **30** and **31**. Second, an aqueous solution of oxalic acid and CH_2Cl_2 as cosolvent selectively cleaved the carbon–nitrogen double bond giving access to the α-amino esters **32**. The same aldimine double bond could also be reduced with sodium borohydride in methanol under reflux, giving access to the N-benzylated α-amino esters **34a** and **34d**. Furthermore, it was also possible to direct the methodology toward N-alkylated 2,2-dialkyl-1-aminocyclopropanecarboxylic acids **34**. This was accomplished by reduction of the α-imino esters **28a–c** to α-amino esters **33** with $NaCNBH_3$ in methanol in the presence of 1 equiv of acetic acid, prior to base treatment (Scheme 7, Table 2). Reaction of the functionalized intermediate γ-chloro-α-amino esters **33** with KO-t-Bu in THF exclusively afforded the *N*-alkyl-α-aminocyclopropanecarboxylic esters **34** through 1,3-dehydrochlorination. Other transformations include the N-alkoxycarbonylation of the free α-amino acid **10a** and the transesterification of the amino ester **34a**. Alkoxycarbonylation of the free amino acid **10a** was executed using ethyl chloroformate in dichloromethane in the presence of pyridine. Recrystallization from a EtOAc/hexane 2/1 mixture afforded the *N*-(ethoxycarbonyl)amino acid **35** in pure form. The functionalization of the amino function with suitable chloroformates, i.e., with a lipophilic and easily hydrolyzable ester moiety, can have important applications. When administered, the lipophilic character is apt to improve uptake by plant material compared with the highly hydrophilic free amino acid.[22] Once taken up in the plant the carbamate can be deprotected by hydrolysis to the free amino acid. By the same rationale the transesterification of the α-amino ester **33a** was performed. On treatment of the α-amino ester **33a** with 1 N NaOEt in EtOH under reflux for a period of 5 h the substrate is transesterified completely.

Conclusions

Starting from γ-chloro-α-imino esters **28**, a wide variety of N- and/or carboxyl-derivatized geminally dialkylated ACC analogues has been synthesized (Chart 2). The methodology used thereby opens up routes to virtually any combination of N and/or carboxyl protection possibly desired. In view of any applications, be it as potential plant growth regulating compounds or for the incorporation in biologically active peptides, the access

(22) Fukuto, T. R. In *Pesticide Synthesis Through Rational Approaches, Chapter 6, Prepesticides*; Magee, P. S., Kohn, C. K., Menn, J. J., Eds.; ACS Symposium Semi 255; American Chemical Society: Washington D.C., 1984.

Scheme 7



to structurally divergent substrates is a requisite for the development of structure–activity relationships.

Experimental Section

^{1}H NMR spectra were recorded at 60 MHz, 270 MHz, 360 MHz, and 500 MHz. ^{13}C NMR spectra were recorded at 20 MHz, 67.8 MHz, and 90 MHz. Mass spectra were obtained on a mass spectrometer (70 eV) using direct inlet or GC–MS coupling (RSL 200, 20 m glass capillary column, i.d. 0.53 mm, He carrier gas). Gas chromatographic analyses were performed with glass columns (RSL 150, 20 m, i.d. 0.53 mm, He carrier gas and 1.5 m, 5–10% SE-30, Chromosorb W 60–80, H_2 carrier gas). Flash chromatography was executed with Merck Kieselgel 60 (0.04–0.063 mm) using solvent combinations determined via initial TLC analysis with Merck Kieselgel $60F_{254}$ plates (precoated). Melting points were measured on a Kofler-type hotbench.

Hydroxymethylation of Ketones 11. The synthesis of 4-hydroxy-3,3-dimethyl-2-butanone (**13a**) is representative. A mixture of 3-methyl-2-butanone (**11a**) (86 g, 1 mol), paraformaldehyde (30 g, 1 mol), and TFA (228 g, 2 mol) was heated at reflux for 7 h (the reaction can be monitored by ^{1}H NMR) and then poured into 15% $NaHCO_3$ (5 mol, 2.8 L). The resulting suspension was stirred at room temperature for 1 d and extracted with CH_2Cl_2 (8 × 200 mL). The combined organic extracts was dried ($MgSO_4$) and evaporated to afford 106 g (91%) of relatively pure β-hydroxy ketone **13a** which could be used as such in the following step or distilled prior to further use, bp 65 °C/15 mmHg. In the case of 3-ethyl-2-pentanone (**13b**) and cyclohexyl methyl ketone **13c**, 15% Na_2CO_3 (5 equiv/rt/4 d) was used for the alkaline hydrolysis. Spectroscopic and physical data for β-hydroxy ketones **13a,c** have been reported earlier,[18] data for compound **13b** are additional (see also the supplementary material).

Mesylation of β-hydroxy Ketones 13. The synthesis of 4-(mesyloxy)-3,3-dimethyl-2-butanone (**14a**) is representative. To a solution of 4-hydroxy-3,3-dimethyl-2-butanone (**13a**) (104.4 g, 0.9 mol) in CH_2Cl_2 (700 mL) was added pyridine (213.3 g, 2.7 mol) and MsCl (113.35 g, 0.99 mol). The mixture was stirred at room temperature for a period of 1 d during which time a white precipitate was formed. The resulting suspension was filtered, the filtrate washed with 2 N HCl (225 mL, 0.45 mol), and the water layer extracted two additional times with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated and the residue distilled to give 152 g (87%) of pure β-(mesyloxy) ketone **14a** as a colorless liquid: bp 113 °C/0.02 mmHg; ^{1}H NMR δ (270 MHz, $CDCl_3$) 1.23 (6H, s), 2.20 (3H, s), 3.04 (3H, s), 4.20 (2H, s); ^{13}C NMR δ (67.8 MHz, $CDCl_3$) 21.35, 25.35, 36.77, 47.60, 74.73, 210.29; IR (NaCl, cm^{-1}) $\nu_{C=O}$ = 1710; MS (70 eV) *m/z* (rel int) no M^+, 138 (5), 99 (1), 98 (9), 97 (1), 83 (3), 79 (8), 73 (3), 71 (1), 57 (5), 56 (65), 55 (21), 44 (7), 43 (100), 41 (18), 40 (79). Anal. Calcd (Found) for **14a** $C_7H_{14}O_4S$: C, 43.28; H, 7.26 (C, 43.39; H, 7.38).

For β-hydroxy ketone **13b**, 1.5 equiv MsCl was used together with 3 equiv of pyridine in CH_2Cl_2 as solvent. The mixture was refluxed for 3 h.

3-Ethyl-3-(mesyloxy)methyl-2-pentanone (14b). Bp 107–110 °C/0.05mmHg (see also the supplementary material).

1-Acetyl-1-((mesyloxy)methyl)cyclohexane (14c). Purification was performed by distillation or recrystallization from Et_2O/pentane 1/1 at room temperature, bp 118–122 °C/0.01 mmHg, mp 39 °C (see also supplementary material).

Chlorination of β-(Mesyloxy) Ketones 14. The chlorination of 4-(mesyloxy)-3,3-dimethyl-2-butanone (**14a**) is representative. To a warmed (60 °C) solution of 4-(mesyloxy)-3,3-dimethyl-2-butanone (**14a**) (151.3 g, 0.78 mol) in DMF (1 L) was added slowly and under vigorous stirring LiCl (66.2 g, 1.56 mol). Stirring was then continued under reflux for 15 h. After this period, the reaction mixture was cooled, poured into 12 N HCl (1 L), and extracted with CCl_4 (4 × 400 mL). The combined organic extracts were washed with 12 N HCl (500 mL), dried ($MgSO_4$), and distilled under atmospheric pressure. The residue was distilled further *in vacuo* to afford 86 g (82%) of pure β-chloro ketone **15a**, bp 60–65 °C/13 mmHg. Spec-

Table 2. Synthesis of γ-Chloro-α-amino Esters 33 and Geminally Dialkylated 1-Aminocyclopropanecarboxylic Acid Derivatives 29, 34, 32, 35, and 10

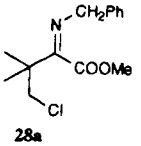
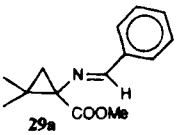
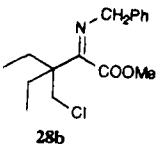
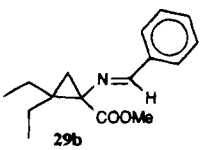
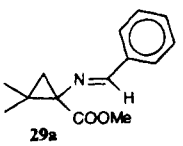
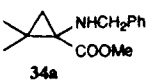
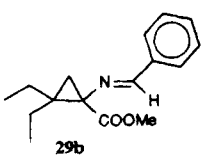
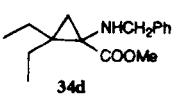
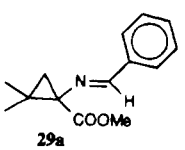
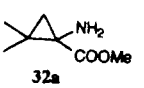
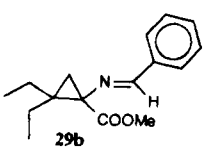
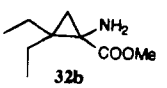
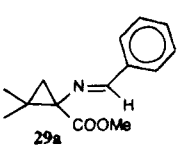
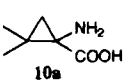
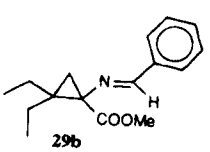
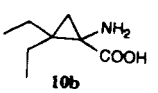
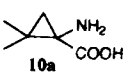
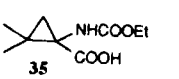
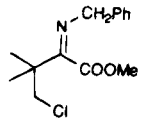
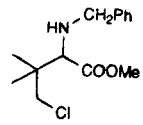
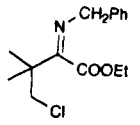
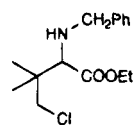
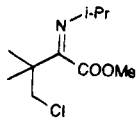
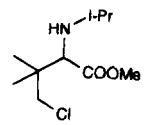
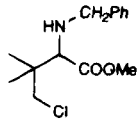
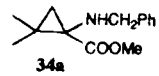
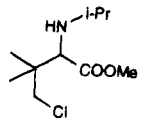
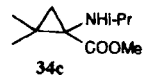
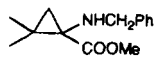
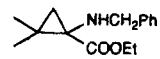
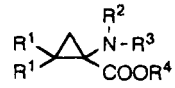
Entry	Substrate	Reaction Conditions	Reaction Product	Yield (%)	Physical Data
1	 **28a**	3 equiv NaOMe 2N, MeOH, Δ, 2h or KOtBu 1.5 eq THF, Δ, 1h	 **29a**	95-96 87	bp 78-81°C/ 0.05mmHg ibid.
2	 **28b**	3 equiv NaOMe 2N, MeOH, Δ, 3h	 **29b**	73	bp 106-107°C/ 0.09 mmHg
3	 **29a**	1 mol equiv $NaBH_4$, MeOH, Δ, 2h	 **34a**	96	
4	 **29b**	1 mol equiv $NaBH_4$, MeOH, Δ, 2h	 **34d**	28	
5	 **29a**	1 equiv $(COOH)_2.2H_2O$, CH_2Cl_2/H_2O 1/1, Δ, 1h	 **32a**	73-81	**32a**.HCl mp 135°C (subl.)
6	 **29b**	1 equiv $(COOH)_2.2H_2O$, CH_2Cl_2/H_2O 1/1, Δ, 2.5h	 **32b**	58	
7	 **29a**	1) 10 equiv HCl 2N, Δ, 15h 2) Dowex 50x8 (purification)	 **10a**	93	R_f = 0.49 n-BuOH/AcOH/ H_2O : 4/1/1 mp = 257°C[a] **10a**.HCl 243.5°C[b]
8	 **29b**	10 equiv HCl 2N Δ, 84h	 **10b**	31	R_f = 0.55 n-BuOH/AcOH/ H_2O : 4/1/1, Recrystallized from MeOH, rt : mp 233.2°C[c]
9	 **10a**	1.1 equiv ClCOOEt, 1.1 equiv py, CH_2Cl_2, 3h, rt	 **35**	71	Recrystallized from EtOAc/ Hex 2/1, -20°C mp 126°C

Table 2 (Continued)

Entry	Substrate	Reaction Conditions	Reaction Product	Yield (%)	Physical Data
10	 **28a**	2 mol equiv $NaCNBH_3$, MeOH, 1 equiv AcOH, 1h, 0°C	 **33a**	66	R_f = 0.75 Et_2O/pentane : 1/1
11	 **28b**	2 mol equiv $NaCNBH_3$, MeOH, 1 equiv AcOH, 1h, 0°C	 **33b**	97	R_f = 0.50 Et_2O/pentane : 1/9
12	 **28c**	2 equiv $NaCNBH_3$, MeOH, 1 equiv AcOH, 1h, 0°C	 **33c**	89	R_f = 0.56 Et_2O/pentane : 1/9
13	 **33a**	2 equiv KOt-Bu, THF Δ, 1h	 **34a**	78	
14	 **33c**	2 equiv KOt-Bu, THF, Δ, 1h	 **34c**	85	bp 63-65°C/ 12 mmHg
15	 **34a**	5 equiv NaOEt 2N, EtOH, Δ, 5h	 **34b**	82	R_f = 0.87 Et_2O/pentane (1/1)

[a] Lit. mp > 260°C[6a], Lit. decomp. 202-203°C[15b]
[b] Lit. mp > 220-222°C[7a], mp 218-219 and 219-220°C[17b]
[c] Lit. mp > 260°C[6a]

Chart 2



R^1 = Me, Et or $(R^1)_2$ = $(CH_2)_5$
R^2 = H
R^3 = H,i-Pr,CH_2Ph ,COOEt
R^2-R^3 = CHC_6H_5
R^4 = H,Me,Et

troscopic and physical data for compounds **15a,c** were reported earlier; data for β-chloro ketone **15b** are additional.[18]

3-(Chloromethyl)-3-ethyl-2-pentanone (15b): bp 85–90.5 °C/13 mmHg (see also the supplementary material).

Monobromination of β-Chloro Ketones 15. The bromination of 4-chloro-3,3-dimethyl-2-butanone (**15a**) is representative. To a solution of 4-chloro-3,3-dimethyl-2-butanone (**15a**) (26.80 g, 0.2 mol) in CH_2Cl_2 (300 mL) was added dropwise bromine (32.00 g, 0.2 mol), dissolved in the same solvent (50 mL). After complete addition the reaction mixture was stirred for 1 additional hour, washed with 1 N $NaHCO_3$ until neutral or slightly alkaline and saturated $NaHSO_3$ until colorless. The organic phase was dried ($MgSO_4$), filtered, and evaporated *in vacuo* to yield a mixture of 1-bromo-4-chloro-3,3-dimethyl-2-butanone (**16a**) (86%), 1,1-dibromo-4-chloro-3,3-dimethyl-2-butanone (**17a**) (8%), and starting material **15a** (6%). The resulting mixture was used as such in the next step. Bromination of 1-acetyl-1-(chloromethyl)cyclohexane (**15c**) under the same conditions gave rise to a reaction mixture consisting of 1-(bromoacetyl)-1-(chloromethyl)cyclohexane (**16c**) as the major compound (80%) next to 1-(dibromoacetyl)-1-(chloromethyl)-cyclohexane (**17c**) (12%) and starting material **15c** (8%). Bromination of 3-(chloromethyl)-3-ethyl-2-pentanone (**15b**) was performed using 1.1 equiv of Br_2 and gave rise to a mixture containing 1-bromo-3-(chloromethyl)-3-ethyl-2-pentanone (**16b**) (70–76%), 1,1-dibromo-3-(chloromethyl)-3-ethyl-2-pentanone (**17b**) (19–26%), and starting β-chloro ketone **15b** (4–5%). Full spectroscopic data of α′-bromo ketone **16a** are listed further. Full spectroscopic data for compound **16c** are listed in the supplementary material.

1-Bromo-3-(chloromethyl)-3-ethyl-2-pentanone (16b): ^1H NMR δ (60 MHz, CCl_4) 0.83 (6H, t, J = 7.4 Hz), 1.4–2.1 (4H, m), 3.70 (2H, s), 4.05 (2H, s).

Imination of β-Chloro Ketones 15. The imination of 4-chloro-3,3-dimethyl-2-butanone (**15a**) is representative. To an ice-cooled solution of 4-chloro-3,3-dimethyl-2-butanone (**15a**) (40.2 g, 0.3 mol) and ethylamine (54 g, 1.2 mol) in Et_2O (700 mL) was added dropwise $TiCl_4$ (31.35 g, 0.165 mol), dissolved in pentane (30 mL). After complete addition, the ice bath was removed and the reaction mixture stirred for 1 hour at reflux. After this period, the resulting suspension was

cooled and poured into 1 N NaOH (600 mL). The organic layer was separated and the water layer extracted two times with Et_2O (150 mL). The combined organic extracts were dried (K_2CO_3), filtered, and evaporated to yield 44.2 g (91%) of *N*-(4-chloro-3,3-dimethyl-2-butylidene)ethylamine (**19a**) which was used as such in the next step (purity >95%; ^1H NMR). Distillation led to substantial loss by decomposition: bp 41–43 °C/0.01 mmHg; ^1H NMR δ (60 MHz, $CDCl_3$) 1.15 (6H, s), 1.15 (3H, t, J = 7.2 Hz), 1.77 (3H, 7, J = 1 Hz), 3.22 (2H, qxq, J_1 = 7.2 Hz, J_2 = 1 Hz), 3.60 (2H, s); ^{13}C NMR δ (20 MHz, C_6D_6) 12.63, 16.06, 23.70, 44.82, 45.53, 54.52, 170.16; IR (NaCl, cm^{-1}) $\nu_{C=N}$ = 1651; MS (70 eV) *m/z* (rel int) 160/2 ($M^+ - 1$, 0.4), 146/8 (1), 126 (29), 125 (4), 112 (2), 110 (2), 91 (2), 70 (92), 69 (6), 58 (4), 56 (8), 55 (6), 42 (100), 41 (17), 40 (13). Anal. Calcd (Found) for **19a** $C_8H_{16}ClN$: N,8.66 (N, 8.78).

1-(1-(*N*-ethylimino)ethyl)-1-(chloromethyl)cyclohexane (19b). Starting from 1-acetyl-1-(chloromethyl)cyclohexane (**15c**) (4.10 g, 23.5 mmol), 1-(1-(*N*-ethylimino)ethyl)-1-(chloromethyl)cyclohexane (**19b**) (4.63 g, 98%) was obtained, bp 88–89 °C/2 mmHg. In an attempt to distill the β-chloro imine **19b**, partial hydrolysis occurred, bp 88–89 °C/2 mmHg (see also the supplementary material).

Bromination of β-chloro imines 19. The bromination of *N*-(4-chloro-3,3-dimethyl-2-butylidene)ethylamine (**19a**) is representative. To an ice-cooled solution of *N*-(4-chloro-3,3-dimethyl-2-butylidene)ethylamine (**19a**) (8.06 g, 0.05 mol) in CCl_4 (100 mL) was added NBS (10.68 g, 0.06 mol). The reaction mixture was stirred for 1 h at 0 °C, filtered, and evaporated to afford 10.22 g (96%) of *N*-(1-bromo-4-chloro-3,3-dimethyl-2-butylidene)ethylamine (**20a**) which was used as such for subsequent aqueous hydrolysis: ^1H NMR δ (60 MHz, $CDCl_3$) 1.28 (3H, t, J = 7 Hz), 1.33 (6H, s), 3.52 (2H, q, J = 7 Hz), 3.66 (2H, s), 3.83 (2H, s); ^{13}C NMR δ (67.8 MHz, $CDCl_3$) 15.67, 17.13, 24.24, 44.91, 45.79, 54.52, 167.33; IR (NaCl, cm^{-1}) $\nu_{C=N}$ = 1641; MS (70 eV) *m/z* (rel int) no M^+, 204/6 (8), 196 (3), 148/50 (40), 148/8 (17), 120/2 (34), 118 (6), 110 (6), 104 (3), 97 (6), 96 (6), 91/3 (10), 82 (6), 76 (6), 70 (18), 69 (21), 68 (10), 67 (8), 65 (4), 58 (5), 57 (4), 56 (75), 55 (33), 54 (8), 53 (9), 51 (4), 49 (5), 44 (13), 42 (45), 41 (100), 40 (23). For spectroscopic data for compound **20b**, see the supplementary material.

Hydrolysis of α′-Bromo-β-Chloro Imines 20. The hydrolysis of *N*-(1-bromo-4-chloro-3,3-dimethyl-2-butylidene)-ethylamine (**20a**) is representative. A solution of *N*-(1-bromo-4-chloro-3,3-dimethyl-2-butylidene)ethylamine (**20a**) (0.24 g, 1 mmol) in CH_2Cl_2 (5 mL) and 2 N HCl (5 mL) was stirred vigorously for 17 h. The organic layer was separated and the aqueous layer extracted two times with CH_2Cl_2 (5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to afford 0.21 g (98%) of 1-bromo-4-chloro-3,3-dimethyl-2-butanone (**16a**) which was used as such in the next step (purity >95%; ^1H NMR); ^1H NMR δ (270 MHz, $CDCl_3$) 1.36 (6H, s), 3.64 (2H, s), 4.22 (2H, s); ^{13}C NMR δ (67.8 MHz, $CDCl_3$) 23.13, 32.79, 49.16, 51.57; IR (NaCl, cm^{-1}) $\nu_{C=O}$ = 1726; MS (70 eV) *m/z* (rel int) 212/4/6 (M^+, 1), 119/21 (34), 91/3 (85), 65 (5), 63 (13), 57 (4), 56 (91), 55 (100), 53 (6), 51 (3), 49 (5), 44 (4), 43 (6), 42 (13), 41 (36), 40 (53).

1-(Bromoacetyl)-1-(chloromethyl)cyclohexane (16c). Purification was performed by recrystallization from pentane at −20 °C: mp 46 °C (see also the supplementary material).

Sulfenylation of α′-Bromo-β-chloro Ketones 16. The sulfenylation of 1-bromo-4-chloro-3,3-dimethyl-2-butanone (**16a**) is representative and is an extension of the above-described bromination of 4-chloro-3,3-dimethyl-2-butanone (**15a**). To an ice-cooled solution of 2 N NaOMe (110 mL, 0.22 mol) in methanol was added ethanethiol (14.88 g, 0.24 mol), followed after some 5 min by the dropwise addition of the brominated reaction mixture. During addition a white precipitate was formed. After complete addition the ice bath was removed and the reaction mixture stirred for 1 h at room temperature. The resulting suspension was then poured into water (300 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$), filtered, and evaporated. The diethyl disulfide and the remaining α-chloro ketone **15a** were removed by warming the residue *in vacuo* (35 °C/0.02 mmHg) while monitoring by capillary GC, thus giving 36.54 g (94%) of *quasi* pure (97%) 4-chloro-1-(ethylthio)-3,3-dimethyl-2-butanone (**18b**): ^1H NMR δ (270 MHz, $CDCl_3$) 1.25 (3H, t, J = 7.59 Hz), 1.33 (6H, s), 2.56 (2H, q, J = 7.59 Hz), 3.46 (2H, s), 3.64 (2H, s); ^{13}C NMR δ (67.8 MHz, $CDCl_3$) 14.09, 23.34, 25.95, 36.77, 48.97, 52.06, 206.81; IR (NaCl) $\nu_{C=O}$ = 1705; MS (70 eV) *m/z* (rel int) 194/6 (M^+, 32), 159 (14), 138/40 (6), 134/6 (9), 119/21 (17), 110/12 (10), 91/3 (68), 85 (100), 56 (12), 55 (32), 49 (7), 47 (24), 44 (11), 41 (14).

For the sulfenylation of α′-bromo ketone **16b**, prepared as described above, 2 equiv of NaSEt was used. Full spectroscopic data of compounds **18a** and **18c** are mentioned in the supplementary material.

Dibromination of β-Chloro Ketone 15a. In a well-ventilated hood bromine (160 g, 1 mol), dissolved in dichloromethane (100 mL), was added dropwise to a solution of β-chloro ketone **15a** (67 g, 0.5 mol) in the same solvent (600 mL). After complete addition, the reaction mixture was stirred for 1 additional hour, washed with 1 N $NaHCO_3$ (until neutral or slightly alkaline), followed by 0.5 N $NaHSO_3$ (until colorless). The organic phase was dried, filtered, and evaporated to afford 139 g (95%) of the α′,α-dibromo ketone **17a** as a pale yellow crystalline solid. The product recrystallized easily and quantitatively from pentane at −20 °C: mp 38 °C; ^1H NMR δ (270 MHz, $CDCl_3$) 1.46 (6H, s), 3.64 (2H, s), 6.36 (1H, s); ^{13}C NMR δ (67.8 MHz, $CDCl_3$), 23.52, 37.92, 49.02, 198.76; IR (KBr, cm^{-1}) $\nu_{C=O}$ = 1722; MS (70 eV) *m/z* (rel int) no M^+, 199/201/203 (1), 171/173/175 (2), 119/121 (5), 91/93 (100), 65 (4), 63 (11), 56 (10), 55 (87), 53 (5), 41 (17). Anal. Calcd (Found) for $C_6H_9Br_2ClO$ **17a**: C, 24.65; H, 3.10 (C, 24.53; H, 3.01).

Sulfenylation of 1,1-Dibromo-4-chloro-3,3-dimethyl-2-butanone (17a). The sulfenylation of ketone **17a** was performed in the same way as described for 1-bromo-4-chloro-3,3-dimethyl-2-butanone (**16a**). From 139 g of α′,α′-dibromo ketone **17a** was obtained pure (>97%) 81 g (82%, including the bromination step) of 4-chloro-1-(ethylthio)-3,3-dimethyl-2-butanone **18b**.

Chlorination of α′-Sulfenylated β-Chloro Ketones 18. The synthesis of chlorinated sulfides **21c** and **21d** by chlorination of the α′-sulfenylated β-chloro ketones **18b,c** was performed in the same way as previously described for compounds **21a,b**.[21] Full spectroscopic data of compounds **21c** and **21d** are mentioned in the supplementary material.

Silver Ion Induced Solvolysis of α′,α′,β-Trichloro Ketones 21b and 21c. The synthesis of 4-chloro-1,1,1-trimethoxy-3,3-dimethyl-2-butanone (**24a**) is representative. To an ice-cooled suspension of Ag_2CO_3 (41.1 g, 0.15 mol) in methanol was added dropwise 1,1,4-trichloro-1-(ethylthio)-3,3-dimethyl-2-butanone (**21b**) (26.3 g, 0.1 mol) at such a rate as to ensure a smooth reaction. When the addition was completed the ice bath was removed and the reaction mixture stirred for 15 h at ambient temperature. The mixture was then filtered, evaporated, poured into 2 N NaOH (500 mL), and extracted with dichloromethane (3 × 150 mL). The combined organic extracts, which contain suspended particles, were filtered over a filter paper, dried ($MgSO_4$), and evaporated *in vacuo* to afford 21 g (94%) of 4-chloro-1,1,1-trimethoxy-3,3-dimethyl-2-butanone (**24a**) (purity >96%, GC). Filtration of the reaction mixture prior to workup is necessary to avoid the formation of emulsions. An analytically pure sample was obtained by preparative GC: ^1H NMR δ (60 MHz, $CDCl_3$) 1.31 (6H, s), 3.30 (9H, s), 3.79 (2H, s); ^{13}C NMR δ (20 MHz, $CDCl_3$) 23.07, 48.52, 50.35, 52.34, 111.90, 201.62; IR (NaCl, cm^{-1}) $\nu_{C=O}$ = 1722; MS (70 eV) *m/z* (rel int) no M^+, 193/5 (26), 138/40 (6), 119/21 (7), 105 (100), 91/3 (33), 89 (3), 87 (4), 75 (7), 61 (8), 59 (24), 55 (25), 50 (3), 47 (3), 45 (9), 44 (3), 41 (6). Full spectroscopic data of compound **24b** are mentioned in the supplementary material.

Aqueous Acid Hydrolysis of 1,1,1-Trialkoxy-4-chloro-3,3-dimethyl-2-butanones 24. To a solution of 4-chloro-1,1,1-trimethoxy-3,3-dimethyl-2-butanone (**24a**) (17.96 g, 0.08 mol) in a biphase system of CH_2Cl_2 and water (180 mL each) was added p-TsOH (aq) (3.04 g, 0.016 mol). The reaction mixture was refluxed for 2 h, cooled, and neutralized with a 10% $NaHCO_3$ solution. The organic phase was separated and the aqueous layer extracted two times with dichloromethane

(75 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated *in vacuo* to yield 13.4 g (94%) of **23a**. Full spectroscopic data of γ-chloro-α-keto ester **23a** are listed in ref 21.

Ethyl 4-chloro-3,3-dimethyl-2-oxobutanoate (23b): bp 43–46 °C/0.075 mmHg (see also the supplementary material).

Mercuric Ion Induced Solvolysis of α′,α′,β-Trichloro Ketones 21. The Hg^{2+}-ion assisted solvolysis of α′,α′,β-trichloro ketones **21b–d** was performed in the same way as previously described.[21]

Methyl 3-(chloromethyl)-3-ethyl-2-oxopentanoate (23c): bp 40–42 °C/0.07 mmHg; ^1H NMR δ (60 MHz, $CDCl_3$) 0.83 (6H, t, J = 7.3 Hz), 1.8–2.1 (4H, m), 3.83 (2H, s), 3.90 (3H, s); IR (NaCl, cm^{-1}) $\nu_{CO+COOMe}$ = 1725 and 1710; MS (70 eV) *m/z* (rel int) 206/8 (M^+, 4), 171 (0.5), 147/9 (27), 119/21 (65), 84 (8), 83 (100), 77 (8), 69 (5), 67 (3), 59 (8), 57 (13), 56 (5), 55 (76), 54 (2), 53 (7), 51 (2), 49 (2), 44 (4), 43 (27), 42 (2), 41 (27). Anal. Calcd (Found) for **23c** $C_9H_{15}ClO_3$: C, 52.30; H, 7.32 (C, 52.34; H, 7.42).

Solvolysis of α,α-Dichloro Sulfides 21a,b in the Presence of Sodium Carbonate. The solvolysis of 1,1,4-trichloro-1-(ethylthio)-3,3-dimethyl-2-butanone (**21b**) is representative. To an ice-cooled suspension of Na_2CO_3 (1.06 g, 0.01 mol) in MeOH (26 mL) was added 1,1,4-trichloro-1-(ethylthio)-3,3-dimethyl-2-butanone (**18b**) (2.63 g, 0.01 mol). During addition a white precipitate was formed. The ice bath was removed and the reaction mixture stirred for 15 h at ambient temperature. The resulting suspension was then poured into water (150 mL), extracted three times with CH_2Cl_2 (30 mL), dried ($MgSO_4$), and evaporated to yield 2.22 g (87%) of *quasi* pure 4-chloro-1-(ethylthio)-1,1-dimethoxy-3,3-dimethyl-2-butanone (**22b**). The product was stable on distillation (bp 65–70 °C/0.05 mmHg) and was rearranged into γ-sulfenylated α-keto ester **27** by preparative GC.

4-Chloro-1-(ethylthio)-1,1-dimethoxy-3,3-dimethyl-2-butanone (22b): ^1H NMR δ (60 MHz, CCl_4) 1.18 (3H, t, J = 7.5 Hz), 1.34 (6H, s), 2.52 (2H, q, J = 7.5 Hz), 3.38 (6H, s), 3.76 (2H, s); IR (NaCl, cm^{-1}) $\nu_{C=O}$ = 1702; MS (70 eV) *m/z* (rel int) no M^+, 233/5 (3), 193/5 (13), 135 (100), 119/21 (9), 107 (12), 91/3 (40), 89 (6), 76 (10), 75 (32), 63 (8), 61 (13), 59 (16), 56 (7), 55 (48), 48 (8), 47 (17), 45 (5), 41 (10), 40 (7).

Methyl 4-(ethylthio)-3,3-dimethyl-2-oxobutanoate (27): ^1H NMR δ (60 MHz, $CDCl_3$) 1.24 (3H, t, J = 7.4 Hz), 1.34 (6H, s), 2.55 (2H, q, J = 7.4 Hz), 2.93 (2H, s), 3.88 (3H, s); IR (NaCl, cm^{-1}) $\nu_{C=O+COOMe}$ = 1720 + 1735; MS (70 eV) *m/z* (rel int) 204 (M^+, 8), 176 (4), 149 (3), 143 (7), 121 (19), 117 (38), 89 (7), 86 (7), 84 (9), 83 (16), 77 (4), 76 (4), 75 (91), 63 (10), 61 (19), 59 (19), 57 (4), 56 (13), 55 (100), 51 (7), 49 (12), 47 (20), 45 (6), 44 (31), 43 (10), 42 (2), 41 (24).

Full spectroscopic data of compound **22a** are mentioned in the supplementary material.

Imination of γ-chloro-α-keto Esters 23. The imination of methyl 4-chloro-3,3-dimethyl-2-oxobutanoate (**23a**) is representative. To an ice-cooled solution of methyl 4-chloro-3,3-dimethyl-2-butanoate (**23a**) (21.36 g, 0.12 mol) and isopropylamine (28.32 g, 0.48 mol) in diethyl ether (300 mL) was added dropwise $TiCl_4$ (12.54 g, 0.066 mol), dissolved in pentane (15 mL). After complete addition, the ice bath was removed and the reaction mixture stirred for 2 h at room temperature. After this period, the resulting suspension was cooled and poured into 1 N NaOH (300 mL). The organic layer was separated and the water layer extracted two times with ether (100 mL). The combined organic extracts were dried (K_2CO_3), filtered, and evaporated to yield 25.61 g (97%) of methyl 4-chloro-2-(*N*-isopropylimino)-3,3-dimethylbutanoate (**28c**) which was used as such in the next step: ^1H NMR δ (60 MHz, $CDCl_3$) 1.13 (6H, d, J = 6.1 Hz), 1.25 (6H, s), 3.39 (1H, septet, J = 6.1 Hz), 3.71 (2H, s), 3.85 (3H, s); ^{13}C NMR δ (90 MHz, $CDCl_3$) 23.57, 23.64, 42.03, 51.21, 53.07, 55.61, 163.60, 165.93; IR (NaCl, cm^{-1}) $\nu_{C=O}$ = 1733, $\nu_{C=N}$ = 1653; MS (70 eV) *m/z* (rel int) 219/21 (M^+, 1), 184 (1), 170 (4), 160/2 (21), 128 (3), 118/20 (100), 110 (3), 91/3 (46), 86 (2), 83 (2), 82 (10), 73 (6), 70 (1), 69 (4), 68 (7), 67 (2), 66 (1), 65 (2), 63 (2), 59 (21), 56 (12), 55 (46), 54 (4), 53 (3), 49 (1), 44 (2), 43 (11), 42 (14), 41 (39).

For the preparation of α-(*N*-benzylimino) esters **28a**, **28b**, and **28d** the reaction mixture was filtered over a glass filter prior to alkaline aqueous workup.

Methyl 2-(*N*-benzylimino)-4-chloro-3,3-dimethylbutanoate (28a): bp 100–104 °C/0.02 mmHg; ^1H NMR δ (60 MHz, $CDCl_3$) 1.31 (6H, s), 3.75 (2H, s), 3.84 (3H, s), 4.58 (2H, s), 7.38 (5H, s); ^{13}C NMR δ (90 MHz, $CDCl_3$) 23.69, 42.90, 51.50, 52.82, 58.27, 126.98, 127.64, 128.45, 138.70, 165.55, 167.52; IR (NaCl, cm^{-1}) $\nu_{C=O}$ = 1771, $\nu_{C=N}$ = 1681; MS (70 eV) *m/z* (rel int) 267/9 (M^+, 1), 218 (3), 208/10 (1), 207 (1), 158 (1), 91 (100), 90 (2), 89 (2), 65 (8), 63 (1), 59 (1), 55 (1), 51 (1), 44 (3). Anal. Calcd (Found) for **28a** $C_{14}H_{18}ClNO_2$: C, 62.80; H, 6.78; N, 5.23 (C, 62.74; H, 6.86; N, 5.31).

Methyl 2-(*N*-benzylimino)-3-(chloromethyl)-3-ethylpentanoate (28d): ^1H NMR δ (60 MHz, $CDCl_3$) 0.85 (6H, t, J = 7.3 Hz), 1.5–2.0 (4H, m), 3.78 (2H, s), 3.88 (3H, s), 4.52 (2H, s), 7.33 (5H, s); ^{13}C NMR δ (90 MHz, $CDCl_3$) 7.92, 26.81, 46.35, 49.09, 51.53, 58.24, 126.97, 127.64, 128.41, 138.78, 165.33, 166.66; IR (NaCl, cm^{-1}) $\nu_{C=N+C=O}$ = 1635–1750; MS (70 eV) *m/z* (rel int) 295/7 (M^+, 2), 266/8 (1.5), 260 (3), 246 (1.5), 236/8 (4), 232 (4), 191 (4), 186 (1), 176 (0.5), 117 (1), 106 (1), 91 (100), 92 (9), 77 (0.8), 69 (0.8), 65 (7), 59 (0.6), 55 (2), 49 (0.8), 44 (3), 41 (2), 40 (33).

Full spectroscopic data of compound **28b** are mentioned in the supplementary material.

Base-Induced Cyclization of γ-Chloro-α-Imino Esters 28. Procedure a. NaOMe as Base. The base-induced cyclization of methyl 2-(*N*-benzylimino)-4-chloro-3,3-dimethylbutanoate (**28a**) is representative. To a solution of 2 N NaOMe in MeOH (87 mL) was added methyl 2-(*N*-benzylimino)-4-chloro-3,3-dimethylbutanoate (**28a**) (23.2 g, 0.087 mol). The reaction mixture was stirred for 2 h at reflux temperature during which time a white precipitate was formed. The resulting suspension was poured into water (500 mL) and extracted three times with CH_2Cl_2 (120 mL). The combined organic extracts were washed with brine (100 mL), dried (K_2CO_3), and evaporated to afford 19 g (95%) of *quasi* pure methyl 1-(*N*-benzylideneamino)-3,3-dimethylcyclopropanecarboxylic ester (**29a**): yield after distillation 19 g (95%), bp 78–81 °C/0.05 mmHg; ^1H NMR δ (60 MHz, C_6D_6) 1.22 and 1.25 (2 × 3H, 2 × s), 1.19 and 1.81 (2H, AB, J = 4.9 Hz), 3.48 (3H, s), 7.1–7.4 (3H, m), 7.6–8.0 (2H, m), 8.57 (1H, s); ^{13}C NMR δ (90 MHz, $CDCl_3$) 20.91, 21.10, 26.02, 28.31, 51.96, 57.72, 128.17, 128.67, 130.84, 136.33, 162.31, 171.12; IR (NaCl, cm^{-1}) $\nu_{C=O}$ = 1725, $\nu_{C=N}$ = 1640; MS (70 eV) *m/z* (rel int) 231 (M^+, 59), 216 (100), 200 (7), 199 (8), 190 (4), 188 (4), 184 (15), 175 (7), 172 (53), 171 (29), 170 (27), 157 (7), 156 (28), 155 (4), 154 (7), 145 (5), 144 (10), 143 (78), 131 (13), 130 (48), 129 (8), 128 (5), 121 (7), 118 (7), 117 (27), 116 (44), 115 (7), 105 (8), 104 (17), 103 (12), 91 (31), 90 (89), 89 (55), 77 (8), 73 (9), 72 (7), 68 (5), 67 (3), 65 (5), 63 (7), 59 (20), 44 (27). Anal. Calcd (Found) for **29a** $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06 (C, 72.73; H, 7.47; N, 6.11).

Methyl 1-(*N*-benzylideneamino)-2,2-diethylcyclopropane-1-carboxylic ester (29b): bp 106–107 °C/0.09 mmHg; ^1H NMR δ (270 MHz, $CDCl_3$) 0.92 and 0.94 (6H, 2 × t, J = 7.43 Hz), 1.17 and 1.59 (2H, 2 × d, AB, J = 5.28 Hz), 1.41–1.70 (4H, m), 3.76 (3H, s), 7.39–7.43 (3H, m), 7.73–7.77 (2H, m), 8.34 (1H, s); ^{13}C NMR δ (67.8 MHz, $CDCl_3$) 10.46, 10.62, 22.73, 23.32, 25.28, 37.97, 52.02, 58.45, 128.10, 128.57, 130.74, 136.46, 162.01, 171.26; IR (NaCl, cm^{-1}) $\nu_{C=O}$ = 1728, $\nu_{C=N}$ = 1640; MS (70 eV) *m/z* (rel int) 259 (M^+, 14), 244 (6), 230 (100), 200 (19), 198 (23), 190 (7), 184 (7), 177 (14), 175 (7), 174 (7), 170 (27), 168 (10), 155 (6), 146 (9), 145 (7), 144 (6), 143 (40), 132 (6), 131 (9), 130 (26), 129 (7), 128 (4), 121 (7), 118 (17), 117 (39), 116 (29), 106 (13), 105 (10), 104 (10), 103 (19), 91 (61), 90 (56), 89 (37), 77 (14), 65 (6), 59 (14), 55 (14), 44 (20), 43 (7), 42 (4), 41 (21). Anal. Calcd (Found) for **29b** $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40 (C, 74.18; H, 8.21; N, 5.31).

Procedure b. KO-t-Bu as Base. To a solution of methyl 2-(*N*-benzylimino)-4-chloro-3,3-dimethylbutanoate (**28a**) (0.267 g, 1 mmol) in THF (8 mL) was added KO-t-Bu (0.17 g, 1.5 mmol). The reaction mixture was stirred for 1 h at reflux, poured into 1 N NaOH (10 mL), and extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried (K_2CO_3), filtered, and evaporated to afford 0.2 g (87%) of 1-(*N*-benzylideneamino)-3,3-dimethylcyclopropanecarboxylic ester (**29a**).

Hydrolysis of 2,2-Dialkyl-1-(*N*-benzylideneamino)cyclopropane-1-carboxylic Esters 29 with Oxalic Acid. The hydrolysis of methyl 1-(*N*-benzylideneamino)-3,3-dimethylcyclopropanecarboxylic ester (**29a**) is representative. To a solution of $(COOH)_2{\cdot}2aq$ (12.6 g, 0.1 mol) in water (100 mL) was added methyl 1-(*N*-benzylideneamino)-3,3-dimethylcyclopropanecarboxylic ester (**29a**) (11.55 g, 0.05 mol), dissolved in CH_2Cl_2 (100 mL). The biphasic liquid system was stirred vigorously for 1 h at reflux and neutralized with $NaHCO_3$. The organic layer was separated and the aqueous layer extracted four times additionally with CH_2Cl_2 (30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to yield 5.22 g (73%) of pure methyl 1-amino-2,2-dimethylcyclopropanecarboxylic ester (**32a**): ^{1}H NMR δ (60 MHz, CCl_4) 0.70 and 1.40 (2H, 2 × d, AB, J = 4.1 Hz), 1.15 and 1.30 (2 × 3H, 2 × s), 1.81 (2H, s), 3.73 (3H, s); ^{13}C NMR δ (90 MHz, $CDCl_3$) 20.40, 20.97, 27.31, 28.21, 44.30, 51.82, 175.35; IR (NaCl, cm^{-1}) ν_{NH2} = 3385, $\nu_{C=O}$ = 1720; MS (70 eV) *m/z* (rel int) 143 (M^+, 13), 128 (100), 111 (100), 110 (16), 96 (55), 84 (45), 83 (83), 82 (62), 68 (83), 67 (13), 59 (11), 57 (19), 56 (15), 55 (22), 44 (47), 43 (24), 42 (53), 41 (60).

In order to store the free α-amino ester it was converted into the corresponding hydrochloride by adding a saturated solution of dry gaseous HCl in Et_2O to a solution of the amino ester in the same solvent: sublimes at 135 °C; ^{1}H NMR δ (270 MHz, D_2O, CH_3CN = 2.00) 1.20 and 1.29 (2 × 3H, 2 × s), 1.29 and 1.63 (2 × 1H, 2 × d, AX, J = 6.84 Hz), 3.78 (3H, s); ^{13}C NMR δ (67.8 MHz, D_2O, CH_3CN = 0.00) 18.06, 18.89, 24.28, 25.86, 41.74, 52.51, 169.11; IR (NaCl, cm^{-1}) ν_{NH2} = 2500−3200, $\nu_{C=O}$ = 1742. Anal. Calcd (Found) for **32a**·HCl $C_7H_{14}ClNO_2$: C, 46.80; H, 7.86; N, 7.80 (C, 46.89; H, 7.81; N, 7.73).

Methyl 1-Amino-2,2-diethylcyclopropanecarboxylic Ester (32b). Purification was performed by means of flash chromatography R_f Et_2O/pentane 4/6 = 0.18. The amino ester hydrochloride was prepared in the same way as described above: mp = 145 °C; ^{1}H NMR δ (500 MHz, $CDCl_3$) 0.81 (3H, t, J = 7.43 Hz), 0.94 (3H, t, J = 7.45 Hz), 0.67 and 1.32 (2H, 2 × d, AB, J = 4.71 Hz), 1.42 and 1.48 (2H, d × d × q, J = 7.31 Hz, J_{gem} = 14.74 Hz), 1.64 and 1.71 (2H, d × d × q, J = 7.28 Hz, J_{gem} = 14.69 Hz), 1.78 (2H, br s), 3.71 (3H, s); ^{13}C NMR δ (125 MHz, $CDCl_3$) 10.71, 10.98, 22.17, 22.28, 26.64, 37.58, 44.92, 51.93, 175.50; IR (NaCl, cm^{-1}) ν_{NH2} = 3390, ν_{CO} = 1725; MS (70 eV) *m/z* (rel int) 171 (M^+, 7), 156 (6), 143 (6), 142 (73), 139 (15), 124 (3), 112 (15), 110 (93), 102 (5), 101 (40), 96 (11), 95 (7), 82 (100), 71 (21), 70 (8), 69 (25), 68 (7), 67 (13), 59 (5), 56 (13), 55 (43), 54 (8), 53 (9), 44 (6), 43 (47), 42 (73), 41 (53), 40 (4). Anal. Calcd (Found) for **32b**·HCl $C_9H_{18}ClNO_2$: H, 6.74 (N, 6.70).

Hydrolysis of 2,2-Dialkyl-1-(*N*-benzylideneamino)cyclopropane-1-carboxylic Esters 29 with HCl. The hydrolysis of methyl 1-(*N*-benzylideneamino)-3,3-dimethylcyclopropanecarboxylic ester (**29a**) is representative. To an aqueous solution of 2 N HCl (150 mL) was added 1-(*N*-benzylideneamino)-3,3-dimethylcyclopropanecarboxylic ester (**29a**) (6.93 g, 0.03 mol), and the resulting emulsion was stirred at reflux temperature for 15 h. Evaporation of the solvent *in vacuo* then yielded the amino acid hydrochloride in pure form. Yield 4.95 g (100%). The free amino acid **10a** was obtained by ion-exchange chromatography on Dowex 50 × 8 (H^+) (100 g) eluting with water followed by 5% aqueous NH_4OH (TLC, silica gel, n-BuOH/AcOH/H_2O 4/1/1, R_f = 0.49): yield 3.57 g (93%). Full spectroscopic data of α-amino acids **10** are listed in ref 9a. The free amino acid **10a** was recrystallized from MeOH in a recrystallization chamber with saturated Et_2O atmosphere: mp 257 °C (lit.[6a] mp > 260 °C; lit.[15b] mp 202−203 °C). The amino acid hydrochloride was recrystallized from MeOH/Et_2O, mp 243.5 °C (lit.[7a] mp 220−222 °C; lit.[17b] mp 218−219 °C and 219−220 °C).

Reaction of 1-Amino-2,2-dimethylcyclopropanecarboxylic Acid (10a) with Ethyl Chloroformate. Alkoxycarbonylation of 1-amino-2,2-dimethylcyclopropanecarboxylic acid (**10a**) was performed in the same way as previously described.[9a] Starting from 0.26 g (2 mmol) of **10a**, 0.9 g (71%) 1-(*N*-(ethoxycarbonyl)amino)-2,2-dimethylcyclopropanecarboxylic acid (**35**) was obtained after recrystallization from a EtOAc/hexane (2/1) solvent mixture at −20 °C: mp 126 °C; ^{1}H NMR δ (60 MHz, $CDCl_3$) 1.03 and 1.71 (2 × 1H, 2 × d, AB, J = 5.4 Hz), 1.25 (3H, t, J = 7.0 Hz), 1.28 (6H, s), 4.20 (2H, q, J = 7.0 Hz), 5.2−6.1 (1H, br s), 10.8−11.2 (1H, br s); ^{13}C NMR 14.47, 19.68, 22.01, 29.04, 29.24, 42.96, 61.40, 157.54, 176.92; IR (KBr, cm^{-1}) ν_{NH} = 3300, ν_{OH} = 2300−3500, $\nu_{COOH+COOEt}$ = 1645 and 1685−1715; MS (70 eV) *m/z* (rel int) 201 (M^+, 2), 183 (38), 155 (43), 154 (11), 137 (11), 128 (20), 110 (21), 96 (11), 83 (15), 82 (100), 68 (18), 59 (10), 57 (13), 56 (19), 55 (18), 45 (9), 44 (20), 43 (23), 42 (20), 41 (33), 40 (71). Anal. Calcd (Found) for **35** $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96 (C, 53.68; H, 7.55; N, 6.90).

Reduction of 2,2-Dialkyl-1-(*N*-benzylideneamino)cyclopropane-1-carboxylic Esters 29. The reduction of methyl 1-(*N*-benzylideneamino)-3,3-dimethylcyclopropanecarboxylic ester (**29a**) is representative. To a solution of methyl 1-(*N*-benzylideneamino)-3,3-dimethylcyclopropanecarboxylic ester (**29a**) (0.924 g, 4 mmol) in methanol (10 mL) was added $NaBH_4$ (0.152 g, 4 mmol). The reaction mixture was stirred for 2 h at reflux temperature, poured into water (60 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$) and evaporated to afford 0.9 g (96%, purity > 97% GC) of methyl 1-(*N*-benzylamino)-2,2-dimethylcyclopropanecarboxylic ester **34a**: ^{1}H NMR δ (60 MHz, $CDCl_3$) 0.70 and 1.36 (2H, 2 × d, AB, J = 4.5 Hz), 1.12 (3H, s), 1.33 (3H, s), 2.22 (1H, br s), 3.70 (3H, s), 3.78 (2H, br s), 7.35 (5H, s); ^{13}C NMR δ (90 MHz, $CDCl_3$) 20.50, 21.34, 26.20, 28.32, 50.30, 51.62, 51.85, 126.62, 128.16, 128.23, 140.60, 174.45; IR (NaCl, cm^{-1}) ν_{NH} = 3340, $\nu_{C=O}$ = 1725; MS (70 eV) *m/z* (rel int) no M^+, 233 (3), 218 (3), 190 (26), 158 (4), 142 (11), 131 (3), 130 (8), 110 (8), 103 (4), 91 (100), 82 (18), 73 (3), 65 (11), 59 (4), 57 (3), 56 (4), 55 (6), 44 (9), 42 (7), 41 (9).

Methyl 1-(*N*-benzylamino)-2,2-diethylcyclopropanecarboxylic Ester (34d): ^{1}H NMR δ (60 MHz, $CDCl_3$) 0.82 (6H, 2 × t, J = 7.3 Hz), 0.68 and 1.31 (2H, 2 × d, AB, J = 2.4 Hz), 1.3−2.0 (4H, m), 2.1 (1H, br s), 3.72 (3H, s), 3.74 (2H, br s), 7.37 (5H, s); ^{13}C NMR δ (90 MHz, $CDCl_3$) 10.57, 11.01, 22.39, 22.70, 24.74, 38.65, 51.74, 51.83, 126.82, 128.17, 128.24, 140.78, 174.69; IR (NaCl, cm^{-1}) ν_{NH} = 3340, ν_{CO} = 1725; MS (70 eV) *m/z* (rel int) 261 (M^+, 3), 246 (1), 232 (4), 202 (6), 190 (20), 172 (5), 170 (8), 138 (4), 132 (3), 131 (3), 130 (7), 110 (13), 91 (100), 84 (2), 83 (2), 82 (2), 69 (4), 65 (9), 55 (6), 49 (2), 45 (0.7), 44 (2), 43 (3), 42 (3), 41 (9), 40 (11).

Transesterification of Methyl 1-(*N*-Benzylamino)-2,2-dimethylcyclopropanecarboxylic Ester (34a). To a solution of 1 N NaOEt in EtOH (15 mL) was added methyl 1-(*N*-benzylamino)-2,2-dimethylcyclopropanecarboxylic ester (**34a**) (0.70 g, 3 mmol). The reaction mixture was stirred at reflux for 5 h, poured into water (50 mL), and extracted three times with CH_2Cl_2 (20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to afford 0.61 g (82%) of ethyl 1-(*N*-benzylamino)-2,2-dimethylcyclopropanecarboxylic ester (**34b**). Purification was performed by means of flash chromatography, R_f Et_2O/C_5H_{12} 1/1 = 0.87: ^{1}H NMR δ (60 MHz, $CDCl_3$) 0.69 (1H, d, J = 4.4 Hz), other part of AB-system of the methylene group covered at δ = ~1.3, 1.12, and 1.33 (2 × H, 2 × s), 1.27 (3H, t, J = 6.9 Hz), 2.23 (1H, br s), 3.71 and 3.82 (2 × 1H, 2xd, AB, J_{gem} = 13 Hz), 4.17 (2H, q, J = 6.9 Hz), 7.30 (5H, br s); ^{13}C NMR δ (90 MHz, $CDCl_3$) 14.50, 20.47, 21.36, 26.00, 28.17, 50.25, 51.84, 60.57, 126.82, 128.19, 128.23, 140.65, 173.89; MS (70 eV) *m/z* (rel int) 247 (M^+, 3), 232 (1), 218 (4), 204 (12), 174 (3), 173 (2), 158 (3), 156 (4), 132 (1), 131 (2), 130 (5), 128 (2), 117 (2), 110 (4), 106 (1), 105 (1), 103 (2), 92 (9), 91 (100), 90 (2), 89 (2), 83 (1), 82 (8), 79 (1), 77 (1), 74 (1), 68 (1), 66 (1), 65 (9), 59 (2), 58 (1), 57 (2), 56 (4), 55 (3), 53 (1), 51 (1), 45 (1), 44 (5), 43 (3), 42 (3), 41 (7). Anal. Calcd (Found) for **34b** $C_{15}H_{21}NO_2$: N, 5.66 (N, 5.61).

Reduction of γ-Chloro-α-imino Esters 28. The reduction of methyl 4-chloro-2-(*N*-isopropylimino)-3,3-dimethylbutanoate (**28c**) is representative. To an ice-cooled solution of methyl 4-chloro-2-(*N*-isopropylimino)-3,3-dimethylbutanoate (**28c**) (2.19 g, 0.01 mol) in methanol (30 mL) was added $NaCNBH_3$ (1.24 g, 0.02 mol), followed by 98% AcOH (0.06 g, 0.01 mol). The reaction mixture was stirred for 1 h at 0 °C and then poured into water and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to yield 1.97 g (89%) of methyl 4-chloro-2-(*N*-

isopropylamino)-3,3-dimethylbutanoate (**33c**). Purification was performed by means of flash chromatography, R_f Et_2O/pentane 1/9 = 0.56: ^1H NMR δ (60 MHz, $CDCl_3$) 0.98 (6H, s), 1.00 and 1.03 (2 × 3H, 2 × d, J = 6.2 Hz), 2.67 (1H, septet, J = 6.2 Hz), 3.37 (1H, s), 3.36 and 3.86 (2 × 1H, AB, J = 10.4 Hz), 3.78 (3H, s), 1.5–1.9 (1H, br s); ^{13}C NMR δ (90 MHz, $CDCl_3$) 175.38, 62.83, 53.67, 51.53, 48.17, 38.68, 23.00, 20.55; IR (NaCl, cm^{-1}) ν_{NH} = 3325, $\nu_{C=O}$ = 1735; MS (70 eV) m/z (rel int) no M^+, 206/8 (1, −Me), 185 (1), 172 (2), 170 (2), 162/4 (19), 146/8 (3), 130 (100), 126 (8), 120/2 (16), 112 (3), 103 (2), 98 (3), 88 (81), 84 (9), 83 (2), 82 (2), 72 (2), 71 (6), 70 (13), 69 (3), 68 (2), 67 (3), 60 (2), 59 (4), 58 (3), 57 (2), 56 (10), 55 (7), 54 (1), 53 (1), 49 (1), 45 (1), 44 (8), 43 (23), 42 (8), 41 (16), 40 (11). Anal. Calcd (Found) for **33c** $C_{10}H_{20}ClNO_2$: C, 54.17; H, 9.09; N, 6.32 (C, 54.21; H, 9.01; N, 6.34).

Methyl 2-(*N*-benzylamino)-4-chloro-3,3-dimethylbutanoate (33a): ^1H NMR δ (270 MHz, $CDCl_3$) 0.97 and 0.99 (2 × 3H, 2 × s), 1.46 (1H, br s), 3.29 (1H, s), 3.36 and 3.79 (2 × 1H, 2 × d, AX, J = 10.50 Hz), 3.70 (3H, s), 3.59 and 3.75 (2 × 1H, 2 × d, AB, J = 12.96 Hz); ^{13}C NMR δ (67.8 MHz, $CDCl_3$) 175.06, 139.78, 128.79, 128.28, 127.37, 65.21, 53.82, 53.14, 51.41, 38.90, 22.91, 20.39; IR (NaCl, cm^{-1}) ν_{NH} = 3325, $\nu_{C=O}$ = 1730; MS (70 eV) m/z (rel int) no M^+, 233 (1), 210 (1), 178 (6), 174 (11), 119 (8), 118 (5), 117 (6), 106 (2), 105 (2), 92 (9), 91 (100), 90 (2), 89 (2), 83 (2), 82 (2). 65 (11), 56 (5), 55 (3), 44 (2), 42 (3), 41 (6), 40 (18). Anal. Calcd (Found) for **33a** $C_{14}H_{20}ClNO_2$: N, 5.19 (N, 5.26).

Ethyl 2-(*N*-benzylamino)-4-chloro-3,3-dimethylbutanoate (33b): ^1H NMR δ (500 MHz, $CDCl_3$) 0.97 and 1.00 (2 × 3H, 2 × s), 1.28 (3H, t, J = 7.16 Hz), 3.26 (1H, s), 3.36 and 3.79 (2H, AX, J = 10.50 Hz), 3.60 and 3.75 (2H, AB, J = 12.86 Hz), 4.18 (2H, d × q, J_1 = 2.89 Hz, J_2 = 7.16 Hz), 7.2–7.35 (5H, m); ^{13}C NMR δ (125 MHz, $CDCl_3$) 174.40, 139.82, 128.46, 128.31, 127.14, 65.27, 60.57, 53.89, 53.14, 38.96, 22.96, 20.65, 14.39; IR (NaCl, cm^{-1}) ν_{NH} = 3330, $\nu_{C=O}$ = 1725; MS (70 eV) m/z (rel int) 283/5 (M^+, 2), 210/2 (3), 192 (8), 174 (23), 120 (2), 119 (8), 118 (8), 117 (8), 106 (2), 105 (4), 92 (9), 91 (100), 65 (8), 56 (7), 55 (3), 51 (2), 49 (2), 45 (3), 44 (15), 43 (5), 42 (6), 41 (6), 40 (100). Anal. Calcd (Found) for **33b** $C_{15}H_{22}ClNO_2$: N, 4.94 (N, 4.82).

Base-Induced Cyclization of γ-chloro-α-amino Esters 33. The reaction of methyl 4-chloro-2-(*N*-isopropylamino)-3,3-dimethylbutanoate (**33c**) with KO-t-Bu is representative. To a solution of methyl 4-chloro-2-(*N*-isopropylamino)-3,3-dimethylbutanoate (**33c**) (1.36 g, 6.15 mmol) in THF (20 mL) was added KO-t-Bu (1.38 g, 12.3 mmol). The reaction mixture was stirred for 1 h at reflux temperature, poured into water (40 mL), and extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to afford 0.97 g (85%) of methyl 1-(*N*-isopropylamino)-2,2-dimethylcyclopropanecarboxylic ester (**34c**). Purification was performed by distillation; bp 63–65 °C/12 mmHg; ^1H NMR δ (60 MHz, $CDCl_3$) 1.02 (6H, d, J = 6.6 Hz), 1.05 and 1.25 (2 × 3H, 2 × s), 0.74 and 1.40 (2 × 1H, AB, J = 4.8 Hz), 1.90 (1H, br s), 2.92 (1H, septet, J = 6.6 Hz), 3.76 (3H, s); ^{13}C NMR δ (90 MHz, $CDCl_3$) 174.96, 51.49, 48.78, 47.86, 26.17, 25.51, 24.03, 23.00, 20.91, 20.60; IR (NaCl, cm^{-1}) ν_{NH} = 3330, $\nu_{C=O}$ = 1725; MS (70 eV) m/z (rel int) 186 (M^+ + 1, 2), 185 (M^+, 9), 171 (3), 170 (21), 143 (8), 142 (100), 138 (2), 129 (2), 128 (22), 126 (10), 125 (4), 124 (4), 114 (4), 111 (4), 110 (52), 97 (3), 96 (21), 94 (2), 88 (4), 87 (2), 86 (4), 85 (3), 84 (43), 83 (10), 82 (65), 77 (2), 73 (8), 70 (6), 69 (4), 68 (30), 67 (5), 60 (3), 59 (12), 58 (6), 57 (18), 56 (17), 55 (20), 54 (3), 53 (3), 51 (2), 49 (4), 44 (6), 43 (48), 42 (43), 41 (48). Anal. Calcd (Found) for **34c** $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56 (C, 64.81; H, 10.25; N, 7.62).

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Supplementary Material Available: Full spectroscopic data (^1H NMR, ^{13}C NMR, IR, and MS) for compounds **13b**, **14b**, **c**, **15b**, **16c**, **18a**, **c**, **19b**, **20b**, **21c**, **d**, **22a**, **23b**, **24b**, and **28b** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.