Straightforward Synthesis of 1-Amino-2,2-dialkylcyclopropanecarboxylic Acids via Selective Saponification of 2,2-Dialkylcyclopropane-1,1-dicarboxylic Esters and Curtius Rearrangement

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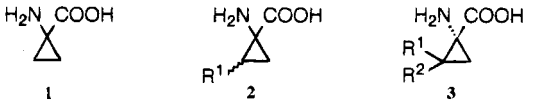
Selective monosaponification of dimethyl 2,2-dialkylcyclopropane-1,1-dicarboxylic esters afforded the corresponding 2,2-dialkyl-1-(methoxycarbonyl)cyclopropane-1-carboxylic acids, which were rearranged with diphenyl phosphoroazidate via a modified Curtius-type reaction to give methyl 2,2-dialkyl-1-[*N*-(alkoxycarbonyl)amino]cyclopropanecarboxylic esters. Selective deprotection of the carbamate or methyl cyclopropanecarboxylic ester was worked out, giving rise to a whole variety of ACC analogues. Straightforward ways to 1-amino-2,2-dialkylcyclopropanecarboxylic acids (2,2-dialkyl-ACC's) were developed.

Introduction

The synthesis of ring substituted 1-aminocyclopropanecarboxylic acids has attracted widespread attention in recent years. This interest stems from the potential applications of these derivatives of 1-aminocyclopropanecarboxylic acid **1** (ACC) in agrochemistry and the pharmaceutical field (Chart 1).

ACC is the biochemical precursor of the phytohormone ethylene in plant material[1] and, as a consequence, ACC analogues are potential plant growth regulators. Some monoalkylated ACC analogues **2** are inhibitors of ethylene production.[2–5] Other derivatives displayed an inhibitory effect on senescence in cut flowers.[6] The detailed mechanistic studies with 2-alkyl-1-aminocyclopropanecarboxylic acids **2** provided an insight in the steric requirements of the active center for ethylene production.[2,3,7] ACC analogues, also referred to as 2,3-methanoamino acids, cyclopropane amino acids or cyclopropylogues, are a unique class of conformationally constrained amino acids, which can be used to probe the effect of the orientation of side chains on peptide secondary structures and to produce peptide analogues resistant to proteolytic cleavage.[8–10] Cyclopropane-containing peptides have been shown to exhibit irreversible inhibition of carboxypeptidase A.[11,12] Substituted ACC analogues illustrate the importance of stereochemistry.[13]

Chart 1



1 2 3

Several entries into ring substituted ACC analogues have been developed in recent years, mainly based on strategies involving (1) double alkylation of glycine equivalents with a 1,2-dielectrophile, (2) cyclopropanation of dehydroamino acids or unsaturated oxazolones, (3) ring closure of halogenated imines, or (4) elaboration of suitably substituted epoxides.[8,14–16] The majority of synthetic efforts have been in the field of 2-alkyl-1-aminocyclopropanecarboxylic acids **2**.[8,15] A number of 2,2-dialkyl-1-aminocyclopropanecarboxylic acids **3** have been synthesized by 1,3-dehydrohalogenation of suitably substituted imine or amine precursors,[16–21] by cyclopropanation of α-functionalized-α,β-unsaturated esters[22–24] and by a Strecker-type reaction of cyclopropanone adducts.[25] 2,3-Disubstituted and 2,2,3-trisubstituted ACC derivatives have been synthesized by cyclopropanation of functionalized olefins or epoxides.[26–29] In this paper, the selective saponification of one of the ester function-

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(1) Yang, S. F. in *Plant Nitrogen Metabolism,* Chapter 8, Ed. Poulton, J. E., Romeo, J. T. and Conn, E. E., Plenum Press: New York, 1989.
(2) Pirrung, M. C.; McGeehan, G. M. *Angew. Chem.* **1985**, *97*, 1074.
(3) Pirrung, M. C.; McGeehan, G. M. *J. Org. Chem.* **1986**, *51*, 2103.
(4) Switzer, F. L.; Van Halbeek, H.; Holt, E. M.; Stammer, C. H.; Saktveit, M. E., Jr. *Tetrahedron* **1989**, *45*, 6091.
(5) Stammer, C. H., U. S. US 4,954,158 (Cl. 71-76; A01N43/38), 04 Sep 1990, US Appl. 523,080, 16 Aug 1983; *Chem. Abstr.* **1991**, *114*, 143132.
(6) Toshima, H.; Niwayama, Y.; Nagata, H.; Greulich, F.; Ichihara, A. *Biosci. Biotech. Biochem.* **1993**, *57*, 1394.
(7) Hoffman, N. E.; Yang, S. F.; Ichihara, A.; Sakamura, S. *Plant Physiol.* **1982**, *70*, 195.
(8) Stammer, C. H. *Tetrahedron* **1990**, *46*, 2231 and references cited therein.
(9) Burgess, K.; Ho, K.-K. *Tetrahedron Lett.* **1992**, *33*, 5677.
(10) Mendel, D.; Ellman, J.; Schultz, P. G. *J. Am. Chem. Soc.* **1993**, *115*, 4359.
(11) Ner, S. K.; Suckling, C. J.; Bell, A. R.; Wrigglesworth, R. *J. Chem. Soc., Chem. Commun.* **1987**, 480.
(12) Kemp, A.; Tedford, M. C.; Suckling, C. J. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 557.
(13) Campbell, M. M.; Horwell, D. C.; Mahon, M. F.; Pritchard, M. C.; Walford, S. P. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 667.
(14) Williams, R. M.; Fegley, G. J. *J. Am. Chem. Soc.* **1991**, *113*, 8796.
(15) Alami, A.; Calmes, M.; Daunis, J.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1993**, 5–24 and references cited therein.
(16) De Kimpe, N.; Sulmon, P.; Brunet, P. *J. Org. Chem.* **1990**, *55*, 5777.
(17) De Kimpe, N.; Sulmon, P.; Brunet, P.; Lambein, F.; Schamp, N. *Tetrahedron Lett.* **1989**, *30*, 1863.
(18) De Kimpe, N.; Sulmon, P.; Schamp, N. *Tetrahedron Lett.* **1989**, *30*, 5029.
(19) De Kimpe, N.; Sulmon, P.; Boeykens, M. *Tetrahedron* **1991**, *47*, 3389.
(20) De Kimpe, N.; Sulmon, P.; Stevens, C. *Tetrahedron* **1991**, *47*, 4723.
(21) Easton, C. J.; Tan, E. W.; Ward, C. M. *Aust. J. Chem.* **1992**, *45*, 395.
(22) Srivastava, V. P.; Roberts, M.; Holmes, T.; Stammer, C. H. *J. Org. Chem.* **1989**, *54*, 5866.
(23) Kirihata, M.; Sakamoto, A.; Ichimoto, I.; Ueda, H.; Honma, M. *Agric. Biol. Chem.* **1990**, *54*, 1845.
(24) Schöllkopf, U.; Harms, R.; Hoppe, D. *Liebigs Ann. Chem.* **1973**, 611.
(25) Fadel, A. *Synlett.* **1993**, 503.

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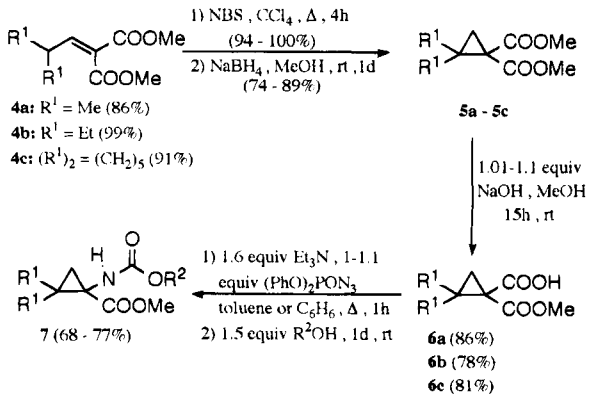
Scheme 1



alities of 2,2-dialkylcyclopropane-1,1-dicarboxylic esters **7** will be evaluated and coupled to a modified Curtius reaction in order to have a ready access to *gem* dialkyl-ACC analogues **3**. The Curtius reaction of monalkylated cyclopropane-1,1-dicarboxylic esters has been utilized for the synthesis of monoalkyl-ACC derivatives.[15,30-36] In these cases monohydrazides, acylazides and mixted anhydrides have been used as intermediates[15] and it has been shown that the initial hydrolysis of the diester to the monoester is not always selective.[32] In the present paper a highly selective saponification and a very efficient Curtius modification using diphenyl phosphoroazidate leading to 2,2-dialkyl-ACC derivatives **3** in a short and convenient synthetic way is disclosed.

Results and Discussion

Dimethyl 2,2-dialkylcyclopropane-1,1-dicarboxylic esters **5a–c** were prepared from alkylidenemalonates **4** by allylic bromination with *N*-bromosuccinimide in carbon tetrachloride under reflux and subsequent Michael induced ring closure (MIRC Reaction) of the allylic bromide with sodium borohydride in methanol at room temperature (Scheme 1).[37] The selective hydrolysis of one ester functionality of cyclopropane-1,1-dicarboxylic esters **5** was achieved by using sodium hydroxide in methanol at room temperature overnight. The cyclopropanecarboxylic acids **6** were obtained in 78–86% yield. The generation of the α-amino acid moiety from **6** requires a Curtius-type rearrangement. The modified Curtius rearrangement using diphenyl phosphoroazidate (DPPA)[38,39] proceeds in one step under more or less neutral and non-oxidative reaction conditions.[40] Through this procedure, competitive reactions under classical Schmidt or Hofmann rearrangement conditions, such as ring opening of the cyclopropane skeleton and/or partial or complete hydrolysis of the ester function, are eliminated. The Curtius-type reaction was executed with a slight excess of diphenyl phosphoroazidate in toluene or benzene in the presence of triethylamine. The formation of an intermediate isocyanate **11** allows a simple variation of the resulting carbamate type. In this way methyl, ethyl and benzyl carbamates **7** were prepared in 68–77% yield (Table 1). t-Butyl carbamates **7** (R^2 = t-Bu) could not be prepared in this way. As will be shown further, methyl and ethyl carbamates **7** behave similarly. Full details on all carbamates **9** are disclosed in the supplementary material. The advantage of the preparation of these carbamates stems from the flexibility with which partial or complete deprotection of the amino and/or carboxylic ester group can be performed. In this way, several other ACC analogues become accessible, e.g., *N*-alkoxycarbonyl α-amino acids **8**, α-amino carboxylic esters **10**, and the free amino acids **9**. Carbamates are stable under relatively mild alkaline reaction conditions,[31,41,42] which explains the selective hydrolysis of the cyclopropanecarboxylic esters **7** into N-(alkoxycarbonyl) α-amino acids **8** with 1 N sodium hydroxide in methanol under reflux for a short time (Scheme 2). Alternatively, 1 N sodium hydroxide in aqueous ethanol can be used with success as well (**8b** : 85%). Trimethylsilyl iodide in chloroform at 60 °C selectively cleaved the carbamate ester group giving rise to methyl 1-amino-2,2-dialkylcyclopropanecarboxylic esters **10** (Table 2). Trimethylsilyl iodide, generated in situ from trimethylsilyl chloride and sodium iodide in acetonitrile under reflux, was less effective (2–3 equiv each Me_3SiCl/NaI, Δ, 1–2 days) as it always resulted in incomplete hydrolysis of the carbamate esters **7ba** and **7bb**. Both the latter ACC analogues **10** and the N-alkoxycarbonyl α-amino acids **8** could be converted into the free α-amino acids under acidic conditions. The hydrolysis of 1-aminocyclopropanecarboxylic esters **10** was accomplished with excess 2 N hydrogen chloride under reflux overnight, while the carbamate **8ab** was hydrolyzed using 25% hydrogen bromide in acetic acid at room temperature, both affording 1-amino-2,2-dialkylcyclopropanecarboxylic acids **9**. To a minor extent (5%), the use of 25% hydrogen bromide in acetic acid also resulted in ring opening of the dimethyl derivative **9a** into the corresponding γ-hydroxy-α-amino acid. This phenomenon was already previously observed with higher substituted gem. dialkyl-ACC analogues.[16,17] A more direct deprotection of the carbamate esters **7** to afford the free α-amino acids **9** under more forcing alkaline reaction conditions is also possible. As an example, the carbamate ester **7cb** was hydrolyzed into the free α-amino acid **9c** by excess 6 N sodium hydroxide under reflux for 15h (86%). Full details about the conversion of carbamates into ACC analogues **8**, **9** and **10** are given in the supplementary material.

If the free α-amino acid **9** is the target molecule, then the carbamate ester **7** is an unnecessary intermediate.

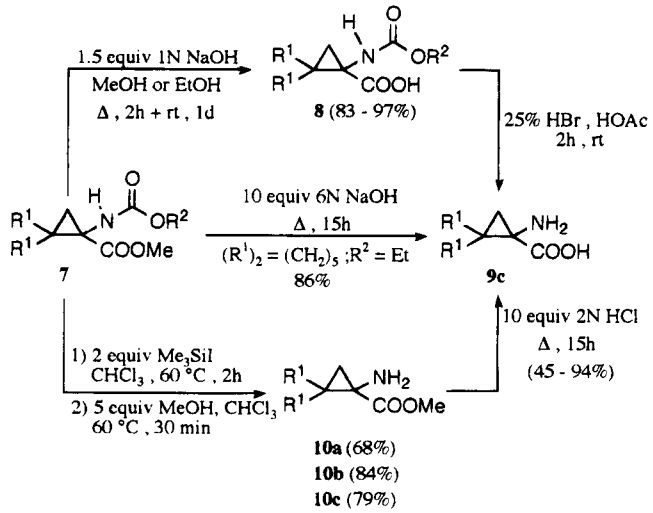
(26) Schöllkopf, U.; Hupfeld, B.; Gull, R. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 754.
(27) Schöllkopf, U.; Hauptreif, M.; Dippel, J.; Nieger, M.; Egert, E. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 192.
(28) Lalitha, N.; Bhalerao, U. T.; Iyengar, D. S. *J. Org. Chem.* **1992**, *57*, 6684.
(29) Lalitha, N.; Iyengar, D. S.; Bhalerao, U. T. *J. Org. Chem.* **1989**, *54*, 1771.
(30) Koskinen, A. M. P.; Munoz, L. *J. Org. Chem.* **1993**, *58*, 879.
(31) Baldwin, J.; Adlington, R.; Rawlings, B. *Tetrahedron Lett.* **1985**, *26*, 481.
(32) Mapelli, C.; Turocy, G.; Switzer, F.; Stammer, C. H. *J. Org. Chem.* **1989**, *54*, 145.
(33) Dappen, M.; Pellicciari, R.; Natalini, B.; Monahan, J.; Chiorri, C.; Cordi, A. *J. Med. Chem.* **1991**, *34*, 161.
(34) Izquierdo, M.; Arenal, I.; Bernabé, M.; Alvarez, F. *Tetrahedron* **1985**, *41*, 215.
(35) Wheeler, T.; Ray, J. *Synth. Commun.* **1988**, *18*, 141.
(36) Ichihara, A.; Shiraishi, K.; Sakamura, S. *Tetrahedron Lett.* **1977**, 269.
(37) (a) Verhé, R.; De Kimpe, N.; De Buyck, L.; Courtheyn, D.; Schamp, N. *Bull. Soc. Chim. Belg.* **1978**, *87*, 215. (b) Verhé, R.; De Kimpe, N.; De Buyck, L.; Courtheyn, D.; Schamp, N. *Synthesis* **1978**, *530*.
(38) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.
(39) Yamada, S.; Ninomiya, K.; Shioiri, T. *Tetrahedron Lett.* **1973**, 2343.
(40) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151.
(41) Strazewski, P.; Tamm, C. *Synthesis* **1987**, 298.
(42) Wheeler, T. N.; Ray, J. *J. Org. Chem.* **1987**, *52*, 4875.

Table 1. Synthesis of 1-(Methoxycarbonyl)cyclopropanecarboxylic Acids 6 and Methyl [*N*-(Alkoxycarbonyl)amino]cyclopropanecarboxylic Esters 7

	malonate 5	saponification of 5	yield 6 (%)	physical constants 6	Curtius reaction of 6	alcohol used (1.5 equiv rt, 20h)	carbamate[a] 7	yield 7 (%)	physical constants bp (°C/mmHg)	mp (°C)	R_f
a	R^1 = Me	1.01 equiv of 1 N NaOH/MeOH, rt, 15 h	86	R_f = 0.54[b]	1.1 equiv of DPPA, 1.6 equiv of Et_3N, toluene, Δ, 1 h	EtOH	**7ab**	68	85–105/0.03	49	
b	R^1 = Et	1.01 equiv of 1 N NaOH/MeOH, rt, 24 h	78	73 °C	1 equiv of DPPA, 1 equiv of Et_3N, benzene, Δ, 2 h	MeOH	**7ba**	68	77/0.07	56	
						EtOH	**7bb**	77	78–80/0.02		
						BzOH	**7bc**	74	135–38/0.04	63	
c	$(R^1)_2$ = $(CH_2)_5$	1.01 equiv of 1 N NaOH/MeOH, rt, 15 h	81	R_f(MeOH) = 0.62	1.1 equiv of DPPA, 1.6 equiv of Et_3N, toluene, Δ, 1 h	MeOH	**7ca**	74		100[c]	
						EtOH BzOH	**7cb**	77	125–126/0.03	45	$CHCl_3$/Hex (90/10) = 0.23
							7cc	68		77	Et_2O/C_5H_{12} (20/80) = 0.09

[a] The first letter indicatds the substitution pattern of the cyclopropane ring (**a**: R^1 = Me; **b**: R^1 = Et; **c**: $(R^1)_2 = (CH_2)_5$) while the second letter designates the alcohol part of the carbamate (**a**: Me; **b**: Et; **c**: benzyl). [b] Purified by flash chromatography on RP_{18} eluting with a $CHCl_3$/MeOH 95/5 solvent mixture. [c] Recrystallized from EtOAc/Hex (50/50) at −20 °C.

Scheme 2



In principle, α-amino acid esters **10** are directly accessible via the Curtius reaction of cyclopropanecarboxylic acids **6** and subsequent reaction of the intermediate isocyanate **11** with water and final decarboxylation of the carbamic acid (Scheme 3). However, when cyclopropanecarboxylic acid **6c** was rearranged with DPPA in benzene the resulting intermediate isocyanate **11** $[(R^1)_2 = (CH_2)_5]$ reacted with water (1.5 or 10 equiv) in benzene under reflux to afford the ureide **12** in 84% yield. The formation of the urea derivative **12** can be avoided by desactivation of α-amino ester **10**, once formed, as the hydrochloride. Treatment of the in situ prepared isocyanate **11** (R^1 = Me, Et) with 8 N hydrogen chloride at 60 °C for 30 min gave the α-amino esters **10a** and **10b** in 53–64% yield. Prolonging the same hydrolytic procedure for a period of 1h under reflux provided a direct access to α-amino acids **9a** and **9b** in pure form but in lower yield (48–54%) than the above mentioned conversions. Trapping of the intermediate isocyanate **11** $[(R^1)_2 = (CH_2)_5]$ or α-amino ester **10c** with Me_3SiOH or 2 N HCl, respectively, does not work and in both cases yields the ureide **12**.

Experimental Section

^{1}H NMR spectra were recorded at 60 MHz, 270 MHz, 360 MHz, and 500 MHz. ^{13}C NMR spectra were obtained at 67.8 MHz, 90 MHz, and 125 MHz. IR spectra were measured as a liquid film between NaCl or as a KBr pellet. Mass spectra were recorded at 70 eV, either by the direct inlet mode or via GC-MS coupling. GC analyses were performed using a capillary column (fused silica, RSL 200, 20 m length, id 0.530 mm, He carrier gas). Flash chromatography was performed using Merck Kieselgel 60 (0.04–0.063 mm) and different solvent combinations, determined via initial tlc analysis (Merck Kieselgel 60 F_{254}, precoated). Melting points were measured on a Kofler Hotbench (Reichert Jung).

Synthesis of Dimethyl 2,2-Dialkylcyclopropanecarboxylic Esters 5. Knoevenagel condensation of aldehydes with dimethyl malonate in benzene in the presence of piperidine acetate gave dimethyl alkylidenemalonates **4**, which were brominated with NBS and subsequently ring closed with sodium borohydride in methanol to afford dimethyl 2,2-dialkylcyclopropanecarboxylic esters.[37]

Selective Monosaponification of Dimethyl 2,2-Dialkylcyclopropane-1,1-dicarboxylic Esters 5. The preparation of 2,2-diethyl-1-(methoxycarbonyl)cyclopropane-1-carboxylic acid (**6b**) is representative.

To a solution of dimethyl 2,2-diethylcyclopropane-1,1-dicarboxylic ester (**5b**) (52.97 g, 0.247 mol) in MeOH (250 mL) was added NaOH (250 mL, 1 N). After stirring for 24h at room temperature methanol was evaporated *in vacuo*. The residual water layer was extracted with ether (3 × 100 mL), acidified by means of a saturated $KHSO_4$ solution and extracted with EtOAc (4 × 150 mL). The combined extracts were dried ($MgSO_4$) and evaporated to give **6b** as a white solid. Yield 38.50 g (78%). The product can be used without further purification. Recrystallization can be performed in a EtOAc/hexane mixture (90/10, −20 °C), mp 73 °C. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.93 and 0.94 (6H, 2xt, J = 7.45 Hz), 1.28–1.43 (1H, m), 1.52–1.77 (5H, m), 3.79 (3H, s), 9.95 (1H, br s). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 10.46, 10.51, 22.53, 23.90, 26.23, 39.41, 43.29, 52.88, 171.64, 172.00. IR (KBr, cm^{-1}) ν_{OH} invisible, ν_{COOMe} = 1735, ν_{COOH} = 1685. MS (70 eV) *m/z* (rel. int.) 200 (1, M^+), 182 (7), 168 (6), 156 (8), 151 (22), 150 (100), 139 (12), 135 (20), 131 (6), 123 (10), 122 (29), 121 (42), 118 (13), 113 (32), 107 (24), 90 (21), 96 (6), 95 (20), 94 (19), 93 (9), 87 (13), 83 (27), 82 (68), 79 (42), 67 (42), 59 (25), 55 (89), 53 (29), 45 (21), 41 (79), 40 (11). Anal. Calcd (Found) for **6b** $C_{10}H_{16}O_4$: C, 59.98; H, 8.05 (C, 59.87; H, 8.14).

For compound **6a** acidification was performed using 2 N HCl.

Cyclopropanecarboxylic acids **6a** and **6c** were prepared in an analogous way (see Table 1 and supplementary material).

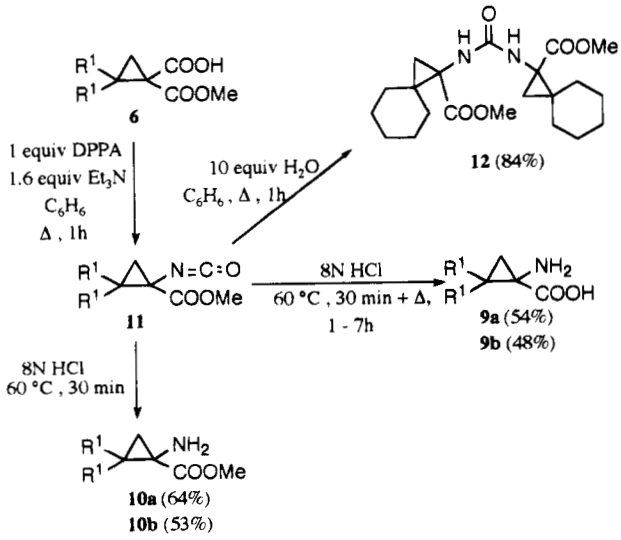
Preparation of Methyl 2,2-Dialkyl-1-(*N*-(alkoxycarbonyl)amino)cyclopropanecarboxylic Esters 7. The procedure for methyl 2,2-diethyl-1-(*N*-(methoxycarbonyl)amino)-cyclopropanecarboxylic ester **7ba** (R^1 = Et; R^2 = Me) is representative. To a solution of monoester **6b** (12.01 g, 60 mmol) and triethylamine (6.13 g, 60 mmol) in benzene (60 mL) was added DPPA (16.51 g, 60 mmol) at rt. After stirring for

Table 2. Synthesis of (*N*-(Alkoxycarbonyl)amino)cyclopropanecarboxylic Acids 8 and α-Amino Esters 10

	carbamate ester	saponification	product yield (%)	mp (recrystallized from)	dealkoxycarbonylation	product yield (%)	physical data
7ab	R^1 = Me R^2 = Et	1.5 equiv of 1 N NaOH/MeOH, Δ, 2 H + rt, 1 d	**8ab**[a] (97)	126 °C (EtOAc/Hex 2/1)	1. 2 equiv of Me_3SiI, $CHCl_3$, 60 °C, 2 h 2. 5 equiv of MeOH, $CHCl_3$, 60 °C, 30 min	**10a** (68)	**10a**.HCl[a] sublimates at 135 °C
7ba	R^1 = Et R^2 = Me	1.5 equiv of 1 N NaOH/EtOH, Δ, 2 h + rt, 20 h	**8ba** (85)	133 °C (EtOAc)	1. 2 equiv of Me_3SiI, $CHCl_3$, 60 °C, 2.5 h 2. 5 equiv of MeOH, $CHCl_3$, 60 °C, 40 min	**10b** (84)	R_f Et_2O/C_5H_{12} 4/6 = 0.18[a]
7ca	$(R^1)_2 = (CH_2)_5$ R^2 = Me	1.5 equiv of 1 N NaOH/MeOH, Δ, 2 h + rt, 1 d	**8ca** (87)	183 °C (EtOAc)			
7cb	$(R^1)_2 = (CH_2)_5$ R^2 = Et	1.5 equiv of 1 N NaOH/MeOH, Δ, 2 h + rt, 1 d	**8cb** (83)	174 °C (EtOAc)	1. 2 equiv of Me_3SiI, $CHCl_3$, 60 °C, 2 h 2. 5 equiv of MeOH, $CHCl_3$, 60 °C, 30 min	**10c** (79)	bp 59–64 °C/ 0.035 mmHg[b] **10c**.HCl sublimates at 118 °C

[a] See also ref 43. [b] Partial decomposition during distillation.

Scheme 3



2 h at reflux temperature, methanol (2.88 g, 90 mmol) was added and the mixture was stirred for 15h at rt. It was washed twice with a citric acid solution (50 mL, 10%) and twice with a $NaHCO_3$ solution (50 mL, 10%). The remaining benzene layer was dried ($MgSO_4$) and evaporated which resulted in the crude carbamate as a viscous syrup. Yield 9.31 g (68%). Purification of the crude product by flash chromatography on silica gel (Et_2O/pentane 4/10, R_f = 0.34) or distillation afforded **7ba** as white crystals, mp 56 °C, bp 77.5–78 °C/0.07 mmHg. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.82 and 0.97 (6H, 2xt, J = 7.42 Hz), 1.35–1.80 (6H, m), 3.68 (3H, s), 3.71 (3H, s), 5.44 (1H, br s). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 10.42, 10.75, 21.46, 23.43, 27.69, 38.35, 43.70, 52.40, 157.34, 172.36. IR (KBr, cm^{-1}) ν_{NH} = 3325, ν_{COOMe} = 1725, ν_{NHCO} = 1710. MS (70 eV) *m/z* (rel. int.) 229 (M^+, 9), 200 (2), 198 (18), 197 (100), 183 (7), 182 (65), 170 (17), 169 (9), 168 (65), 165 (7), 159 (7), 154 (19), 150 (5), 140 (16), 136 (42), 128 (11), 127 (29), 122 (14), 110 (39), 108 (12), 100 (6), 96 (9), 95 (15), 94 (26), 93 (8), 88 (5), 84 (5), 83 (8), 82 (13), 81 (5), 80 (5), 79 (12), 76 (14), 70 (9), 69 (14), 68 (7), 67 (10), 59 (23), 56 (18), 55 (42), 54 (6), 53 (9), 44 (14), 43 (12), 42 (23), 41 (35), 40 (32). Anal. Calcd (Found) for **7ba** $C_{11}H_{19}O_4N$: C, 57.63; H, 8.35; N, 6.11 (C, 57.74; H, 8.46; N, 6.05).

(*N*-(Alkoxycarbonyl)amino)cyclopropanecarboxylic esters **7ab**, **7bb**, **7bc**, **7ca**, **7cb**, and **7cc** were prepared in an analogous way (see Table 1 and supplementary material).

Preparation of 2,2-dialkyl-1-(*N*-(alkoxycarbonyl)amino)cyclopropane-1-carboxylic acids 8. A typical procedure is the preparation of 2,2-diethyl-1-(*N*-(methoxycarbonyl)amino)cyclopropane-1-carboxylic acid **8ba** (R^1 = Et; R^2 = Me). To a solution of **7ba** (0.69 g, 3 mmol) in ethanol (4.5 mL) was added NaOH (4.5 mL, 1 N) and the mixture was refluxed for 2 h, followed by another 20 h at rt. The excess of ethanol was evaporated and the residue dissolved in H_2O (5 mL). After extraction with ether (3 × 10 mL) in order to remove organic impurities, the aqueous layer is acidified (pH = 2) by adding a saturated $KHSO_4$ solution or HCl (2 N). Extraction of the aqueous phase with EtOAc (3 × 10 mL), drying of the organic extracts ($MgSO_4$) and evaporation *in vacuo* yielded 0.55 g (86%) crude product. This ACC analogue was purified by recrystallization from EtOAc, mp 133 °C. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.26 Hz), 0.97 (3H, t, J = 7.42 Hz), 1.34–1.76 (6H, m), 3.71 (3H, s), 5.41 (1H, br s). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 10.44, 10.75, 21.42, 23.50, 27.92, 39.37, 43.58, 52.60, 157.97, 176.80. IR (KBr, cm^{-1}) ν_{NH} = 3305, ν_{OH} = 3400–2500, $\nu_{COOH+COOMe}$ = 1720–1690. MS (70 eV) *m/z* (rel. int.) 215 (M^+, 7), 197 (86), 182 (89), 168 (78), 156 (9), 155 (5), 154 (35), 150 (8), 149 (8), 146 (8), 145 (8), 141 (20), 140 (32), 138 (18), 136 (49), 129 (9), 128 (22), 127 (18), 122 (19), 115 (5), 114 (7), 113 (11), 112 (8), 111 (13), 110 (85), 108 (19), 101 (9), 100 (14), 97 (10), 96 (16), 95 (22), 94 (51), 93 (12), 88 (9), 84 (8), 83 (20), 82 (35), 81 (15), 80 (11), 79 (22), 77 (9), 76 (27), 71 (13), 70 (30), 69 (32), 68 (16), 67 (22), 59 (46), 57 (19), 56 (35), 55 (100), 54 (14), 53 (22), 45 (44), 44 (16), 43 (43), 42 (73), 41 (97), 40 (16). Anal. Calcd (Found) for **8ba** $C_{10}H_{17}O_4N$: C, 55.78; H, 7.96; N, 6.51 (C, 55.60; H, 7.85; N, 6.42).

(*N*-(Alkoxycarbonyl)amino)cyclopropanecarboxylic acids **8ab**, **8ca** and **8cb** were prepared in an analogous way (see Table 2 and supplementary material).

Preparation of Methyl 1-Amino-2,2-dialkylcyclopropanecarboxylic Esters 10. A typical procedure is the preparation of methyl 1-amino-2,2-diethylcyclopropanecarboxylic ester **10b**. To a solution of **7ba** (2.46 g, 11 mmol) in $CHCl_3$ (10 mL) was added trimethylsilyl iodide and the mixture was stirred for 2.5h at 60 °C. After cooling, MeOH (1.76 g, 55 mmol) was added and heating (60 °C) was continued for another 40 min. The reaction mixture was concentrated *in vacuo* and the residu dissolved in a NaOH solution (10 mL, 0.5 N). Extraction with CH_2Cl_2 (3 × 10 mL), drying ($MgSO_4$) and evaporation of the solvent afforded 1.58 g (84%) of compound **10b**. Purification was performed by means of flash chromatography R_f Et_2O/C_5H_{12} 4/6 = 0.18. α-Amino esters **10a** and **10b** were prepared in the same way (see Table 2). Spectroscopic data for α-aminoesters **10a** and **10b** are listed in ref 43. Spectroscopic data for amino ester **10c** are additional.

Methyl 1-Aminospiro[2.5]octane carboxylic Ester (10c). Bp 59–64 °C/0.035 mmHg. The product decomposed partially during distillation. This amino ester was stored as its hydrochloride salt which sublimates at 118 °C. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.69 and 1.35 (2H, AX, J = 4.64 Hz), 1.2–1.8 (10H, m), 1.7–1.9 (2H, br s), 3.71 (3H, s). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 25.73, 26.09, 26.36, 26.70, 30.19, 31.02, 34.70, 44.35,

(43) Boeykens, M.; De Kimpe, N.; Abbaspour Tehrani, K. *J. Org. Chem.* **1994**, in press.

51.88, 175.35. IR (NaCl, cm $^{-1}$) ν_{NH2} = 3390, ν_{COOMe} = 1728. MS (70 eV) *m/z* (rel. int.) 183 (M^+, 9), 168 (14), 151 (29), 124 (32), 123 (21), 122 (20), 108 (18), 102 (23), 101 (100), 95 (12), 94 (14), 91 (5), 88 (5), 82 (8), 81 (36), 80 (18), 79 (14), 71 (27), 68 (8), 67 (19), 55 (14), 54 (13), 53 (11), 44 (11), 43 (29), 42 (43), 41 (25), 40 (20). Anal. Calcd (Found) for **10c** $C_{10}H_{17}O_2N$: C, 65.53; H, 9.36; N, 7.65 (C, 65.49; H, 9.51; N, 7.51).

Curtius Rearrangement of 2,2-Dialkyl-1-(methoxycarbonyl)cyclopropane-1-carboxylic Acids 6 Followed by Acidic Hydrolysis. Typical procedure: to a solution of 2,2-diethyl-1-(methoxycarbonyl)cyclopropane-1-carboxylic acid **6b** (0.50 g, 2.5 mmol) and triethylamine (0.26 g, 2.5 mmol) in benzene (3 mL) was added DPPA (0.69 g, 2.5 mmol). The mixture was refluxed during 2h and the solvent was evaporated *in vacuo*. The isocyanate obtained can be used as such in the next step.

Route A: Preparation of methyl 1-amino-2,2-diethylcyclopropanecarboxylic ester (**10b**). An 8 N HCl solution (5 mL) was added to the isocyanate and the mixture was heated during 40 min (60 °C) while CO_2 evolution was observed. To make the aqueous mixture alkaline some NaOH pellets were added. Extraction with CH_2Cl_2 (3 × 10 mL) and drying ($MgSO_4$) of the combined organics afforded the crude compound **10b** after evaporating the solvent *in vacuo*. Yield 0.25 g (58%). Purification was executed by flash chromatography on silica gel (Et_2O/n-pentane 4/6, R_f = 0.18). α-Amino ester **10a** was prepared in an analogous way (see Table 3 in Suppl. Material Section).

Route B: Preparation of 1-amino-2,2-diethylcyclopropanecarboxylic acid **9b**. After heating the mixture of the isocyanate and 8 N HCl solution (5 mL, 60 °C), further reflux was continued for 7h. After extraction of the acid reaction mixture with CH_2Cl_2 (10−5−5 mL), the aqueous layer was basified with NaOH pellets and extracted again with CH_2Cl_2 (10−5−5 mL). Then the aqueous layer was concentrated in vacuo and acidified with HCl. This acid solution was purified by means of a Dowex 50 × 8 cation exchange resin and 5% NH_4OH as eluens : R_f n-BuOH/AcOH/H_2O 4/1/1 = 0.55. Yield 0.38 g (48%). The product was recrystallized from MeOH at rt : mp = 233.5 °C. Full spectroscopic data of α-amino acids **9a** and **9b** are listed in reference 16. α-Amino acid **9a** was prepared in an analogous way (see Table 3 in supplementary material).

Total Alkaline Hydrolysis of Methyl 1-(*N*-(ethoxycarbonyl)amino)spiro[2.5]octanecarboxylic Ester (7cb). A mixture of methyl 1-(*N*-(ethoxycarbonyl)amino)spiro[2.5]-octanecarboxylic ester (**7cb**) (0.51 g, 2 mmol) and 6 N NaOH (3.3 mL) is heated at reflux temperature for a period of 15 h. The resulting white suspension is then acidified with 2 N HCl and chromatographed over Dowex 50 × 8 (H^+) ion exchange resin eluting with water, followed by 5% NH_3. After checking the different fractions by TLC (n-BuOH/H_2O/AcOH 4/1/1, R_f = 0.52, R_f = **9c**.HCl = 0.58), the fractions containing the amino acid are collected and the solvent evaporated *in vacuo* to obtain pure 1-aminospiro[2.5]octane-1-carboxylic acid **9c**. Sublimation point = 139 °C. Yield 0.25 g (86%).

1-Aminospiro[2.5]octanecarboxylic Acid (9c). ^{1}H NMR (270 MHz, D_2O) δ 1.23 and 1.57 (2H, AX, J = 6.92 Hz), 1.3−1.7 (10H, m). ^{13}C NMR (67.8 MHz, D_2O) δ 22.64, 23.85, 24.04, 24.31, 27.87, 29.40, 32.70, 170.62. IR (KBr, cm^{-1}) : ν_{NH3}+ = 2200−3600, ν_{COOH} = 1708. MS (70 eV) *m/z* (rel. int.) 170 (M^+ + 1,1), 169 (M^+, 5), 151 (4), 124 (7), 123 (5), 108 (5), 100 (3), 94 (4), 93 (4), 88 (35), 87 (100), 82 (4), 81 (8), 80 (6), 79 (4), 70 (4), 69 (4), 68 (4), 67 (15), 55 (6), 54 (10), 53 (5), 42 (21), 41 (22). Anal. Calcd (Found) for **9c** $C_9H_{15}O_2N$: C, 63.86; H, 8.94; N, 8.28 (C, 64.02; H, 8.81; N, 8.13).

Acid Hydrolysis of Methyl 1-Aminospiro[2.5]octanecarboxylic Ester (10c). Acid hydrolysis of methyl 1-aminospiro[2.5]octanecarboxylic ester **10c** was performed in the same way as previously described for compounds **10a** and **10b**.[43] The reaction was monitored by tlc (n-BuOH/ H_2O/AcOH 4/1/1, R_f **9c.HCl** = 0.58). After evaporation, ^{1}H NMR analysis showed 4% of the starting material still remaining. Purification with Dowex 50 × 8 (H^+), using 5% NH_3 as eluens, afforded 0.79 g (94%) of the free amino acid **9c**, R_f n-BuOH/AcOH/H_2O 4/1/1 = 0.52.

Preparation, Physical, and Spectroscopic Data of *N,N'*-Bis[1-(methoxycarbonyl)spiro[2.5]oct-1-yl]urea (12). See Scheme 3 and supplementary material.

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Supplementary Material Available: Full spectroscopic data (^{1}H NMR, ^{13}C NMR, IR and MS) and physical data for compounds **6a**, **6c**, **7ab**, **7bb**, **7bc**, **7ca**, **7cc**, **8ca**, **8cb** and **12** and experimental details for **12** (6 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 ordening information.