Intramolecular Cyclopropanation: Stereospecific Synthesis of (*E*)- and (*Z*)-1-Aminocyclopropane-1-carboxylic Acids

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Received February 18, 1992 (Revised Manuscript Received November 12, 1992)

tert-Butyl-substituted allyl malonates, prepared in two steps from malonic acid, are diazotized in high yields. The diazomalonates **7** undergo a stereospecific copper(I)-catalyzed cyclopropanation to give 1-(*tert*-butoxycarbonyl)-3-oxa-2-oxobicyclo[3.1.0]hexanes **8** which can be converted to the protected (*E*)- or (*Z*)-1-aminocyclopropane-1-carboxylic acids **10** or **15** via Curtius- or Hoffmann-type rearrangements, respectively. The sequences are short (six steps from malonic acid) and proceed with good overall yields (20–40% overall from malonic acid). The free amino acids **12** and **18** can be liberated in two steps.

Introduction

Cyclopropane derivatives occupy an important role in synthetic organic chemistry.[1] Their structural and reactivity features have found widespread applications in the synthesis of several natural products.[2] Recently, they have also gained increased interest in the rapidly expanding field of conformationally constrained amino acid analogue synthesis[3] and as mechanistic probes in biochemical studies.[4] Furthermore, perhaps the best known example of their use, insecticidal pyrethrins are derivatives of cyclopropanoid chrysanthemic acid.[5] Several attractive natural products also contain the cyclopropane moiety, such as the unsubstituted 1-aminocyclopropane-1-carboxylic acid **1**, coronamic acid **2**, coronatine **3**, and carnosadine **4**.[6]

Substituted 1-aminocyclopropane-1-carboxylic acids (ACC's) especially have been the focus of several research efforts, and the synthetic approaches have been reviewed.[7] These approaches include (Scheme I) the following: (a) tandem alkylation of glycine equivalents with 1,2-dielectrophiles;[8] (b) dimethylsulfoxonium methylide or diazoalkane mediated cyclopropanation of dehydroamino acids or unsaturated malonic acid derivatives, followed by Curtius-type rearrangement;[7,9] and (c) cyclopropanation of an unsaturated oxazolone with diazomethane.[10]

The synthesis of ACC's generally provides a significant challenge, especially in controlling the relative stereochemistry around the cyclopropane ring. Although recent literature provides a wealth of examples related to solving the problem of absolute stereochemical control,[11] that of the relative stereochemistry has largely remained elusive, and the applications of catalytic asymmetric synthesis to the synthesis of ACC's are still lacking. Intramolecular

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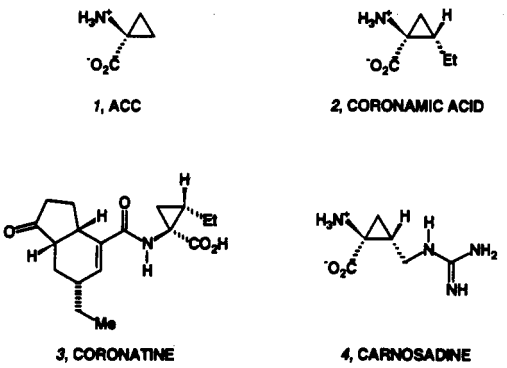
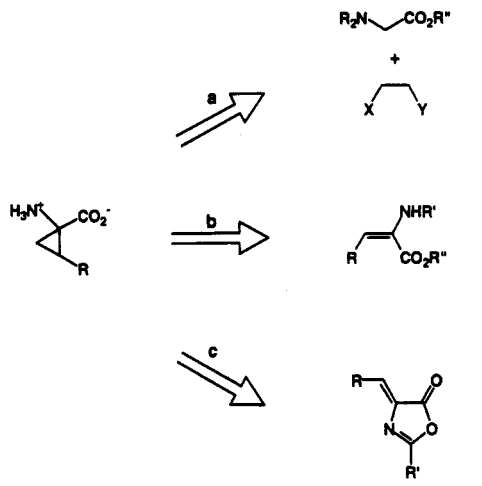
Chart I

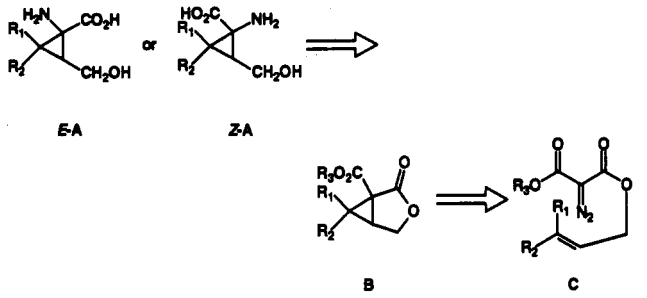


Scheme I



cyclopropanations[12] of olefins are known to allow stereospecific formation of the desired products,[13] and we were attracted to the possibility of using this approach to solve the question of relative stereochemistry around the ring.[14]

Scheme II



We now wish to disclose our findings on the efficient intramolecular cyclopropanation reaction and synthesis of the diastereomers of several substituted methanohomoserines by Curtius- or Hoffmann-type rearrangements of the cyclopropane-1,1-dicarboxylic acids. The key to the successful evolution of a general method for the synthesis of the diastereomeric 1-aminocyclopropane-1-carboxylic acids lies in the efficient differentiation of the two carboxyl groups and chemo- and regiospecific rearrangements of the two intermediate acids from a single advanced intermediate.

Results and Discussion

Both the *E* and *Z* isomers of the 1-aminocyclopropane-1-carboxylic acids A can, in principle, be synthesized from the cyclopropanolactones B (Scheme II). This would require specific cleavage of either the ester or lactone moiety at will, followed by selective methods for functional group interchange to effect the transformation of the acid equivalents to an amine equivalent. It was envisaged that the *tert*-butyl group could be cleaved in the presence of the γ-lactone at will, whereas literature precedent suggested that nucleophilic opening of the lactone would leave the *tert*-butyl ester unchanged.[8c,15]

The synthesis of the cyclopropanolactone B can be performed with complete stereocontrol employing intramolecular cheletropic [1 + 2] addition of a carbenoid onto the olefin C. Thus, the stereochemistry of the olefin (*E* or *Z*) will be relayed into the stereochemistry around the incipient cyclopropane ring.

In the first stage, we needed an efficient and general synthesis of *tert*-butyl-substituted allyl diazomalonates **6a–d** (Scheme III). *tert*-Butyl malonate **5** was efficiently synthesized by a modification of a literature procedure,[16] whereby diethyl malonate was first converted to the potassium salt of monomethyl malonate and the salt was esterified with *tert*-butyl alcohol with pyridine, DCC, and DMAP.[17] Cleavage of the methyl ester (LiOH, THF–H_2O (5:1)) followed by acidification gave the desired **5** in 80% overall yield. An alternative more direct monoesterification of malonic acid could be effected with 2-methyl-2-propanol, DCC, DMAP, and pyridine to give an easily separable mixture of malonic acid mono- and di-*tert*-butyl esters, where the desired monoester **5** predominated (60% yield). The diester could be hydrolyzed to the monoester,[18] thus raising the overall efficiency. The allyl esters **6a–d** were then prepared using standard esterification conditions.[17]

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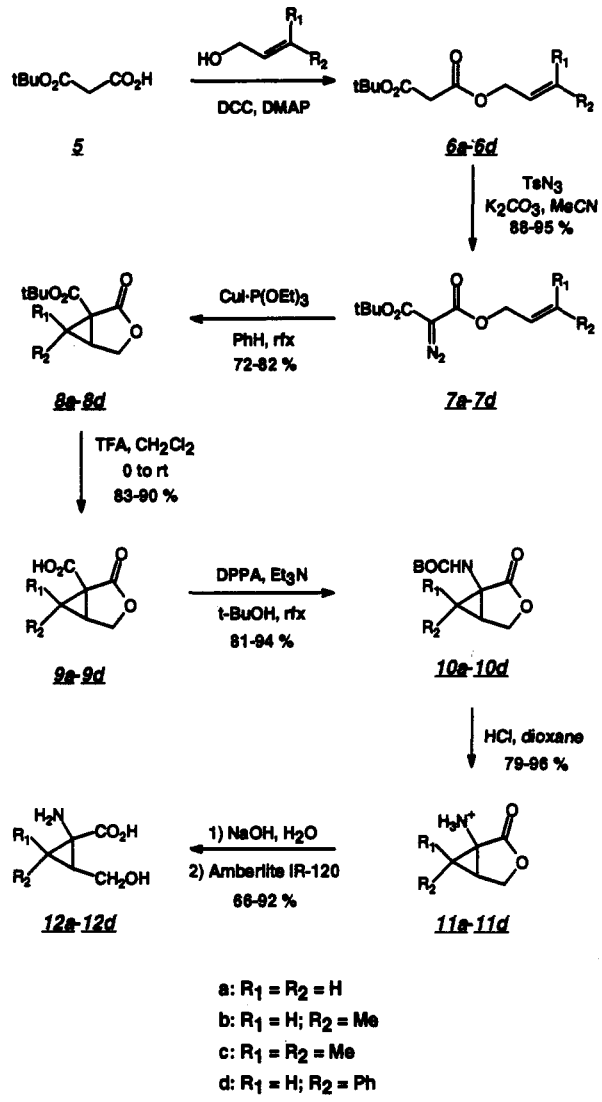
Scheme III. *E*-Selective ACC Synthesis



a: $R_1 = R_2 = H$
b: $R_1 = H$; $R_2 = Me$
c: $R_1 = R_2 = Me$
d: $R_1 = H$; $R_2 = Ph$

We have previously reported on an efficient diazotransfer reaction, which allowed easy transformation of a number of malonates to the corresponding diazomalonates under mild conditions.[19] Using the same protocol, treatment of the malonates **6a–d** with anhydrous potassium carbonate and *p*-toluenesulfonyl azide in acetonitrile at 0 °C or room temperature gave the corresponding diazo compounds **7a–d** in high yields. The low molecular weight diazomalonates are surprisingly stable compounds; they can be distilled at low pressures (avoiding temperatures higher than 100 °C), and they are stable at rt in the presence of air for several months. Compound **7b** was prepared using commercial but-2-en-1-ol, which is an approximately 6:1 mixture of the *E* and *Z* isomers. No attempt was made to separate the two crotyl esters **6b** or the diazomalonates **7b**, since the two diastereomeric products could be easily separated by column chromatography at the cyclized stage **8b**.

The diazo malonates **7a–d** were then subjected to cyclopropanation using a variety of copper salts.[20,21] Among the different copper(I) and -(II) salts tried for cyclopropanation, copper(I) iodide gave the highest yields of cyclopropanes. All the copper(II) salts were able to promote decomposition of the diazomalonates, but no cyclopropanes were produced. Instead, dimerization of the carbenoid species was the main reaction pathway. When cuprous bromide was used, cyclopropane production was accompanied with the formation of several byproducts. Finally, we found the most reliable catalyst to be the complex between copper(I)iodide and triethyl phoshite. The lowest temperature used for the cyclopropanations was 105–110 °C. Thus, a high-boiling solvent (toluene) gave cyclopropanes **8a–d** in 72–82% yield.

Differentiation and subsequent transformation of either carboxyl group was then our next task. The cleavage of the *tert*-butyl ester was selectively effected under standard hydrolysis conditions (trifluoroacetic acid in dichloromethane at 0 °C or rt) to give the *E* acid **9a–d** in high yield. Compounds **9a–d** could be treated, without further purification, with diphenylphosphoryl azide (DPPA) and triethylamine in refluxing 2-methyl-2-propanol to give the Curtius rearrangement products **10a–d**.[22]

Treatment of the BOC-amino lactones **10a–d** with HCl in dioxane resulted in clean cleavage of the BOC group to give, after freeze drying, the highly hygroscopic hydrochloride salts **11a–d** in 79–96% yield. Opening the lactone proved to be easier than expected: an equimolar solution of sodium hydroxide in water at room temperature resulted in complete conversion of the starting material to the products **12a–d**, which were purified by ion-exchange chromatography. The free amino acids **12a–d** are quite stable; the lactone is not re-formed even on standing in neutral aqueous solution for several days.

In order to have access to the isomeric *Z* series (Scheme IV), the lactone ring in **8a–d** was selectively cleaved in the presence of the *tert*-butyl ester.[8c] Thus, treatment of **8a–d** with saturated methanolic ammonia at room temperature gave the amide alcohols **13a–d** in 92–98% yields. It is worth noting that **8c** behaves very differently in this reaction, requiring a much prolonged reaction time. This is obviously due to the steric shielding effect of the *cis*-methyl and the *tert*-butyl ester groups. It is also interesting to note that the *tert*-butyl ester moiety remains unchanged even after several days of treatment with methanolic ammonia. Although previous work has suggested that protection of the alcohol moiety as the corresponding acetate would be acceptable for further transformations,[8c] we needed an alternative protecting strategy. Thus, *tert*-butyl dimethylsilyl (TBS) ether protection was chosen. Introduction of the protecting group was conducted under standard conditions to give the siloxy amides **14** in 94–98% yields.[23]

Conversion of the amides **14a–d** to the (*Z*)-ACC derivatives **15a–d** was achieved by means of Hoffmann reaction.[24] Of the various modifications examined (including bisacetoxy iodosobenzene), the classical version employing lead tetraacetate turned out to be the most reliable one. Thus, treatment of **14a,b** with lead tetraacetate in refluxing 2-methyl-2-propanol gave moderate to good yields (75 and 77%, respectively) of the desired ACC derivatives **15a,b**. It is interesting to note at this stage that the derivatives

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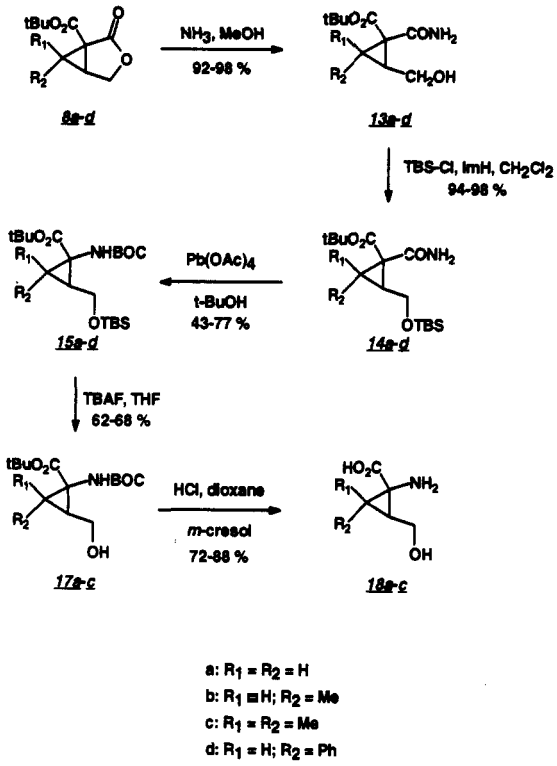
Scheme IV. Z-Selective ACC Synthesis



14c and **14d** behaved differently under these conditions. Compound **14c** led to a nearly 1:1 mixture of two products, the desired cyclopropane derivative **15c** (43%), and a rearrangement product **16c** (30%). The phenyl derivative **14d** led to exclusive formation of the rearranged product **16d** in 76% yield.

The products **16c,d** exhibited spectral data inconsistent with cyclopropane-containing compounds. Examination of the ^1H and ^{13}C NMR, both 1D and especially 2D (COSY, XHCORR and COLOC), and mass spectral data led us to the conclusion that the compounds had the rearranged structures **16c** and **16d** with the cyclopropane ring opened. In these rearranged structures, one bond (C(1)–C(3), Figure 1) is broken oxidatively.

The final stages of the synthesis of the (*Z*)-ACC's **18a–c** consisted of cleavage of the silyl protecting group which was effected with tetrabutylammonium fluoride in THF in moderate yields. The simultaneous cleavage of the *tert*-butyl ester and *tert*-butyl carbamate could be achieved using the relatively mild conditions of HCl in dioxane. Whereas the cleavage of a BOC protecting group does not require the presence of a phenol (*m*-cresol turned out to be optimal in this case) to scavenge the *tert*-butyl cation, the cleavage of a *tert*-butyl ester does.

Conclusions

We have shown that intramolecular cyclopropanation gives an efficient access to multiply-substituted cyclopropanoids, and these materials can be transformed, with complete relative stereocontrol, into 1-amino-1-cyclopropane carboxylic acids in high overall yields. Developments toward a catalytic asymmetric version of this methodology will be reported in due course, as well as our findings concerning the exploitation of the rearrangement reactions in the synthesis of cyclopentanoid structures.

Experimental Section

General. All air-moisture-sensitive reactions were performed under a positive atmosphere of Ar. Toluene and pyridine were dried by distillation from metallic Na. Diethyl ether was dried by distillation from $LiAlH_4$. 2-Methyl-2-propanol and acetonitrile were distilled from CaH_2 prior to use. Methanol was distilled from magnesium methoxide. Dichloromethane was distilled from P_2O_5 and stored over 4-Å molecular sieves. Triethylamine (TEA) was distilled from CaH_2 and stored over 4-Å molecular sieves. Trifluoroacetic acid (TFA) was distilled from P_2O_5 and stored under Ar. Diphenyl phosphorazidate (DPPA) was distilled under vacuum prior to use. Lead tetraacetate (LTA) was recrystallized from boiling acetic acid, washed with anhydrous diethyl ether, dried under high vacuum for 1 day, and stored in a desiccator in the dark at 5 °C. All other reagents were used as obtained from commercial suppliers. Reactions were monitored by thin-layer chromatography on precoated aluminum-backed plates (Merck silica gel 60 F_{254}). The chromatograms were visualized by UV light and staining with phosphomolybdic acid (PMA), *p*-anisaldehyde–acetic acid–sulfuric acid, or hydroxylamine–ferric chloride. After extractive workup, the organic solutions were dried and subjected to flash column chromatography (FC) over silica gel (Merck silica gel 60, 230–400 mesh).[25] Melting ranges for solids were recorded in capillary tubes, and are reported uncorrected. IR data are given in cm^{-1}.

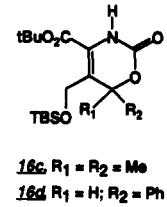


Figure 1. Structures of **16c,d**.

General Procedure for the Diazotization. The appropriate malonic ester **6** was dissolved in anhyd acetonitrile (ca. 2 mL per mmol). A solution of tosyl azide (100 mol %) in acetonitrile (ca. 1 mL per mmol) and solid anhyd potassium carbonate (100 mol %) were added. The flask was fitted with a balloon filled with Ar, and the mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure, and the slurry was redissolved in ether. The organic phase was washed twice with 10% aqueous potassium carbonate and concentrated under reduced pressure. The solid residue was cracked with a mixture of ether–hexanes (1:5), transferred to a sintered glass filter, and washed with the same mixture. The solvent was evaporated, and the product was purified either by distillation or by column chromatography.

Allyl *tert*-Butyl Diazomalonate (7a). Yield: 93%. Bp 75–77 °C (0.05 mmHg). IR (neat): 2150, 1760, 1730, 1695. ^1H-NMR ($CDCl_3$/TMS) δ: 1.51 (s, 9 H), 4.70 (d, 2 H, J = 5.6 Hz), 5.24 (dd, 1 H, J = 1.1, 10.4 Hz), 5.35 (dd, 1 H, J = 1.4, 7.2 Hz), 5.94 (m, 1 H). ^{13}C-NMR ($CDCl_3$) δ: 27.88 (CH_3, *t*Bu), 65.44 (CH_2), 82.73 (C, *t*Bu), 118.38 (=CH_2), 131.39 (=CH), 159.36 (C=O), 160.76 (C=O). HRMS: m/z calcd for $C_{10}H_{14}N_2O_4$ 226.0954, found 226.0961.

2-Butenyl *tert*-Butyl Diazomalonate (7b). Commercial but-2-en-1-ol (Aldrich) is a ca. 6:1 mixture of the *E* and *Z* isomers which were not separated. This is reflected in the product mixture and all subsequent products. Data for the major (from (*E*)-butenol) component are given. Yield: 88%. Bp: 85–90 °C (0.05 mmHg). IR (neat): 2150, 1755, 1735, 1695. ^1H-NMR ($CDCl_3$/TMS) δ: 1.51 (s, 9 H), 1.71 (dd, 3 H, J = 1.0, 6.4 Hz), 4.64 (dt, 1 H, J = 1.0, 6.5 Hz), 5.61 (m, 1 H), 5.83 (m, 1 H). ^{13}C-NMR ($CDCl_3$) δ: 17.71 (CH_3), 28.17 (CH_3, *t*Bu), 65.95 (CH_2), 82.97 (C, *t*Bu), 124.64 (=CH), 132.03 (=CH), 159.78 (C=O), 161.31 (C=O). HRMS: m/z calcd for $C_{11}H_{16}N_2O_4$ 240.1110, found 240.1113.

3-Methyl-2-butenyl *tert*-Butyl Diazomalonate (7c). Yield: 93%. Bp 90–95 °C (0.05 mmHg). IR (neat): 2150, 1760, 1740, 1695. ^1H-NMR ($CDCl_3$/TMS) δ: 1.51 (s, 9 H), 1.72 (s, 3 H), 1.75 (s, 3 H), 4.72 (d, 2 H, J = 7.2 Hz), 5.36 (dd, 1 H, J = 1.2,

(25) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

7.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 18.01 (CH_3), 25.71 (CH_3), 28.18 (CH_3, *t*Bu), 62.17 (CH_2), 82.92 (C, *t*Bu), 118.21 (=CH), 139.57 (=C), 159.86 (C=O), 161.45 (C=O). HRMS: *m/z* calcd for $C_{12}H_{18}N_2O_4$ 254.1267, found 254.1247.

Cinnamyl *tert*-Butyl Diazomalonate (7d). Yield: 95%. Thick yellow oil. IR (neat): 2150, 1750, 1730, 1690. ^{1}H-NMR ($CDCl_3$/TMS) δ: 1.52 (s, 9 H), 4.88 (dd, 2 H, *J* = 1.0, 6.5 Hz), 6.31 (dt, 1 H, *J* = 6.5, 16.9 Hz), 6.68 (d, 1 H, *J* = 16.9 Hz), 7.25–7.40 (m, 5 H). ^{13}C-NMR ($CDCl_3$) δ: 22.17 (CH_3, *t*Bu), 65.82 (CH_2), 83.03 (C, *t*Bu), 122.57 (CH=), 126.62 (Ar-CH), 128.13 (Ar-CH), 128.54 (Ar-CH), 134.89 (CH=), 135.97 (Ar-C), 159.70 (C=O), 161.29 (C=O). HRMS: *m/z* calcd for $C_{16}H_{18}N_2O_4$ 302.1267, found 302.1282.

General Procedure for the Cyclopropanation. The diazomalonate **7** was dissolved in toluene (ca. 12 mL per mmol). The complex CuI·P(OEt)$_3$ (1 mol %) was added at room temperature, and the flask was fitted with an Ar balloon. The flask was then placed in an oil bath at 100–120 °C. The starting yellowish clear solution became cloudy after a few minutes (presumably the copper complex dissociates). After being stirred overnight, the solution was concentrated under reduced pressure and the residue chromatographed on a silica gel column with CH_2Cl_2–ether (95:5) as eluent.

1-(*tert*-Butoxycarbonyl)-3-oxabicyclo[3.1.0]hexane (8a). Yield: 76%. Mp: 73–74 °C (from hexane). IR (neat): 1790, 1725. ^{1}H-NMR ($CDCl_3$/TMS) δ: 1.31 (t, 1 H, *J* = 5.0 Hz), 1.49 (s, 9 H), 2.00 (dd, 1 H, *J* = 4.7, 8.0 Hz), 2.67 (m, 1 H), 4.16 (d, 1 H, *J* = 9.4 Hz), 4.36 (dd, 1 H, *J* = 4.8, 9.4 Hz). ^{13}C-NMR ($CDCl_3$) δ: 20.32 (CH_2), 27.41 (CH), 27.88 (CH_3, *t*Bu), 29.91 (C), 66.82 (CH_2), 82.70 (C, *t*Bu), 165.50 (C=O), 170.67 (C=O). MS (EI): *m/z* (relative intensity) 183 (9, M − 15), 143 (36), 125 (53), 83 (64), 69 (100). HRMS: *m/z* calcd for $C_{10}H_{14}O_4$ 198.0892, found 198.0896.

1-(*tert*-Butoxycarbonyl)-2-oxo-3-oxa-6-methylbicyclo[3.1.0]-hexane (8b). 6:1 mixture of isomers (data for the major isomer, which could be separated at this stage by chromatography). Yield: 74%. IR (neat): 1785. 1725. ^{1}H-NMR ($CDCl_3$/TMS) δ: 1.33 (d, 3 H, *J* = 6.2 Hz), 1.51 (s, 9 H), 1.64 (m, 1 H), 2.48 (t, 1 H, *J* = 5.0 Hz), 4.16 (d, 1 H, *J* = 9.3 Hz), 4.30 (dd, 1 H, *J* = 4.7, 9.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 11.75 (CH_3), 27.93 (CH_3, *t*Bu), 28.74 (CH), 30.57 (CH), 35.37 (C), 66.93 (CH_2), 82.62 (C, *t*Bu), 164.11 (C=O), 171.00 (C=O). MS (EI): *m/z* (relative intensity) 197 (8, M − 15), 157 (64), 139 (100), 122 (50), 111 (76), 83 (47). HRMS: *m/z* calcd for $C_{10}H_{13}NO_4$ (M − 15) 197.0814, found 197.0809.

1-(*tert*-Butoxycarbonyl)-2-oxo-3-oxa-6,6-dimethylbicyclo-[3.1.0]hexane (8c). Yield: 72%. Mp: 77–78 °C. IR (neat): 1785, 1725. ^{1}H-NMR ($CDCl_3$/TMS) δ: 1.26 (s, 3 H), 1.31 (s, 3 H), 1.51 (s, 9 H), 2.47 (d, 1 H, *J* = 5.5 Hz), 4.08 (d, 1 H, *J* = 9.9 Hz), 4.38 (dd, 1 H, *J* = 5.5, 9.8 Hz). ^{13}C-NMR ($CDCl_3$) δ: 15.88 (CH_3), 21.07 (CH_3), 28.03 (CH_3, *t*Bu), 30.91 (C), 34.43 (CH), 41.65 (C), 64.49 (CH_2), 82.64 (C, *t*Bu), 164.67 (C=O), 170.15 (C=O). MS (EI): *m/z* (relative intensity) 211 (7, M − 15), 170 (47), 153 (48), 129 (27), 112 (53), 83 (100). HRMS: *m/z* calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1204.

1-(*tert*-Butoxycarbonyl)-2-oxo-3-oxa-6-phenylbicyclo[3.1.0]-hexane (8d). Yield: 82%. Mp: 141–142 °C (EtOAc–hexanes). IR (neat): 1785, 1720. ^{1}H-NMR ($CDCl_3$/TMS) δ: 1.12 (s, 9 H), 2.85 (d, 1 H, *J* = 5.4 Hz), 3.24 (t, 1 H, *J* = 5.1 Hz), 4.33 (d, 1 H, *J* = 9.3 Hz), 4.48 (dd, 1 H, *J* = 4.8, 9.3 Hz), 7.26–7.35 (m, 5 H). ^{13}C-NMR ($CDCl_3$) δ: 26.91 (CH), 27.42 (CH_3, *t*Bu), 36.90 (CH), 37.95 (C), 67.06 (CH_2), 82.52 (C, *t*Bu), 128.02 (Ar-CH), 128.33 (Ar-CH), 128.89 (Ar-CH), 132.09 (Ar-C), 162.29 (C=O), 170.33 (C=O). MS (EI): *m/z* (relative intensity) 259 (3, M − 15), 218 (40), 201 (39), 171 (69), 129 (100), 115 (97). HRMS: *m/z* calcd for $C_{16}H_{18}O_4$ 274.1205, found 274.1207.

General Procedure for the Preparation of Acids 9. The ester **8** (2.5 mmol) was dissolved in CH_2Cl_2 (10 mL). TFA (12.6 mmol) was added at 0 °C and the solution stirred while warming to rt. The evolution of the reaction was followed by TLC. When no starting material was found (ca. 5 h) the solution was concentrated under reduced pressure and the clear residue was chromatographed (EtOAc:hexanes = 1:1 or EtOAc:hexanes = 2:1) or, if used without purification in the next reaction, dried under high vacuum for several hours. The oil obtained slowly crystallized.

1-Carboxy-2-oxo-3-oxabicyclo[3.1.0]hexane (9a). Yield: 90%. Mp: 77–78 °C. IR (KBr): 3600–2400, 1775, 1720. ^{1}H-NMR ($CDCl_3$/TMS) δ: 1.55 (t, 1 H, *J* = 5.2 Hz), 2.15 (dd, 1 H, *J* = 7.1, 8.1 Hz), 2.97 (m, 1 H), 4.28 (d, 1 H, *J* = 9.5 Hz), 4.46 (dd, 1 H, *J* = 4.8, 9.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 22.50 (CH_2), 28.20 (CH), 29.13 (C), 67.90 (CH_2), 169.93 (C=O), 172.78 (C=O). MS (EI): *m/z* (relative intensity) 142 (5, M$^+$), 125 (11), 112 (11), 98 (100), 83 (60), 69 (99). HRMS: *m/z* calcd for $C_6H_6O_4$ 142.0266, found 142.0279.

1-Carboxy-6-methyl-2-oxo-3-oxabicyclo[3.1.0]hexane (9b). Yield: 83%. Mp: 137–138 °C. IR (KBr): 3600–2400, 1770, 1685. ^{1}H-NMR (MeOD/TMS) δ: 1.33 (d, 3 H, *J* = 5.7 Hz), 1.73 (t, 1 H, *J* = 5.3 Hz), 2.59 (br s, 1 H), 4.19 (d, 1 H, *J* = 8.5 Hz), 4.30 (br d, 1 H, 4.0 Hz). ^{13}C-NMR (MeOD) δ: 12.17 (CH_3), 30.79 (CH), 32.79 (CH), 35.99 (C), 68.96 (CH_2), 168.46 (C=O), 174.31 (C=O). MS (EI): *m/z* (relative intensity) 157 (6, M + 1), 138 (20), 112 (46), 97 (57), 83 (100). HRMS: *m/z* calcd for $C_7H_8O_4$ 156.0423, found 156.0424.

1-Carboxy-6,6-dimethyl-2-oxo-3-oxabicyclo[3.1.0]hexane (9c). Yield: 86%. Mp: 76–78 °C. IR (KBr): 3600–2400, 1760, 1690. ^{1}H-NMR (MeOD/TMS) δ: 1.15 (s, 3 H, Me), 1.24 (s, 3 H, Me), 2.52 (dd, 1 H, *J* = 4.7, 5.4 Hz), 4.08 (dd, 1 H, *J* = 0.7, 10.0 Hz), 4.33 (dd, 1 H, *J* = 5.4, 10.0 Hz). ^{13}C-NMR (MeOD) δ: 16.00 (CH_3), 21.44 (CH_3), 32.82 (C), 36.57 (CH), 42.29 (C), 66.37 (CH_2), 168.73 (C=O), 173.18 (C=O). MS (EI): *m/z* (relative intensity) 171 (13, M + 1), 152 (100), 137 (43), 129 (70), 111 (69), 83 (36). HRMS: *m/z* calcd for $C_8H_{10}O_4$ 170.0579, found 170.0591.

1-Carboxy-6-phenyl-2-oxo-3-oxabicyclo[3.1.0]hexane (9d). Yield: 90%. Mp: 174–175 °C (EtOAc–hexanes). IR (KBr): 3500–2200, 1770, 1695. ^{1}H-NMR (MeOD/TMS) δ: 2.98 (d, 1 H, *J* = 5.6 Hz), 3.39 (t, 1 H, *J* = 5.1 Hz), 4.36 (d, 1 H, *J* = 9.3 Hz), 4.48 (dd, 1 H, *J* = 4.8, 9.3 Hz), 7.26–7.31 (m, 5 H). ^{13}C-NMR (MeOD) δ: 29.06 (CH), 38.86 (CH), 39.04 (C), 69.04 (CH_2), 128.86 (Ar-CH), 129.30 (Ar-CH), 130.03 (Ar-CH), 134.07 (Ar-C), 166.87 (C=O), 173.37 (C=O). MS (EI): *m/z* (relative intensity) 218 (26, M$^+$), 200 (16), 171 (64), 129 (100), 115 (89). HRMS: *m/z* calcd for $C_{12}H_{10}O_4$ 218.0579, found 218.0578.

General Procedure for the Preparation of 1-[(*tert*-Butoxycarbonyl)amino]-2-oxo-3-oxabicyclo[3.1.0]hexanes 10. To a stirred solution of **9** (4 mmol) in 2-methyl-2-propanol (10 mL) were added TEA (100 mol %) and DPPA (100 mol %), and the solution was refluxed overnight under Ar. The reaction mixture was then cooled and poured into a saturated aqueous solution of sodium bicarbonate and extracted twice with ethyl acetate. The organic phase was washed with brine, dried with solid anhyd magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel with EtOAc–hexanes (1:1) affording the protected aminolactones **10**.

1-[(*tert*-Butoxycarbonyl)amino]-2-oxo-3-oxabicyclo[3.1.0]-hexane (10a). Yield: 94%. Mp: 153–154 °C. IR (KBr): 3330, 1785, 1685, 1515. ^{1}H-NMR (MeOD/TMS) δ: 1.17 (br t, 1 H, *J* = 5.0 Hz), 1.44 (s, 9 H), 1.54 (m, 1 H), 2.32 (m, 1 H), 4.14 (br d, 1 H, *J* = 9.4 Hz), 4.39 and 4.47 (dd, 1 H, *J* = 4.8, 10.2 Hz). ^{13}C-NMR (MeOD) δ: 18.60 (CH_2), 25.17 (CH), 28.59 (CH_3, *t*Bu), 39.26 (C), 69.56 (CH_2), 81.22 (C), 158.18 (C=O), 177.01 (C=O). MS (EI): *m/z* (relative intensity) 157 (10, M − 56), 140 (10), 113 (36), 68 (100). HRMS: *m/z* calcd for $C_6H_7NO_4$ (M − 56) 157.0375, found 157.0410.

1-[(*tert*-Butoxycarbonyl)amino]-6-methyl-2-oxo-3-oxabicyclo[3.1.0]hexane (10b). Yield: 94%. Mp: 158–159 °C. IR (KBr): 3270, 1765, 1710. ^{1}H-NMR (MeOD/TMS) δ: 1.19 (m, 3 H), 1.37 (m, 1 H), 1.42 (s, 9 H), 1.99 (t, 1 H, *J* = 4.5 Hz), 4.15 (d, 1 H, *J* = 9.2 Hz), 4.27–4.42 (m, 1 H, *J* = 4.8, 9.2 Hz). ^{13}C-NMR (MeOD) δ: 12.14 (CH_3), 25.71 (CH), 28.61 (CH_3, *t*Bu), 30.98 (CH), 42.27 (C), 69.67 (CH_2), 81.15 (C, *t*Bu), 158.62 (C=O), 177.62 (C=O). MS (EI): *m/z* (relative intensity) 228 (9, M + 1), 172 (100), 154 (13), 127 (48), 99 (63), 82 (80). HRMS: *m/z* calcd for $C_{11}H_{17}NO_4$ 227.1158, found 227.1189.

1-[(*tert*-Butoxycarbonyl)amino]-6,6-dimethyl-2-oxo-3-oxabicyclo[3.1.0]hexane (10c). Yield: 91%. Mp: 134–135 °C. IR (KBr) 3270, 1770, 1705. ^{1}H-NMR (MeOD/TMS) δ: 1.10 (s, 3 H), 1.22 (br s, 3 H), 1.42 (s, 9 H), 2.03 (d, 1 H, *J* = 5.2 Hz), 4.12 (d, 1 H, *J* = 10.0 Hz), 4.40–4.52 (m, 1 H, *J* = 5.4, 9.8 Hz). ^{13}C-NMR (MeOD) δ: 15.21 (CH_3), 21.41 (CH_3), 28.00 (C), 28.70 (CH_3, *t*Bu), 35.47 (CH), 48.63 (C), 66.75 (CH_2), 81.08 (C, *t*Bu), 158.46

(C=O), 176.70 (C=O). MS (EI): *m/z* (relative intensity) 225 (8, M - 16), 185 (100), 168 (19), 141 (27), 126 (85). HRMS: *m/z* calcd for $C_{11}H_{15}NO_4$ (M - 16) 225.1001, found 225.1012.

1-[(*tert*-Butoxycarbonyl)amino]-6-phenyl-2-oxo-3-oxabicyclo[3.1.0]hexane (10d). Yield: 81%. Mp: 157–158 °C. IR (KBr): 3260, 1770, 1700. ^{1}H-NMR (MeOD/TMS) δ: 1.34 (s, 9 H), 2.61 (d, 1 H, *J* = 5.0 Hz), 2.86–2.95 (m, 1 H, *J* = 4.8 Hz), 4.32 (d, 1 H, *J* = 9.4 Hz), 4.47–4.78 (m, 1 H, *J* = 4.8, 9.2 Hz), 7.16–7.33 (m, 5 H). ^{13}C-NMR (MeOD) δ: 28.50 (CH_3, *t*Bu), 29.23 (CH), 35.07 (CH), 46.40 (C), 69.73 (CH_2), 81.15 (C, *t*Bu), 128.35 (Ar-CH), 129.32 (Ar-CH), 129.42 (Ar-CH), 134.25 (Ar-C), 158.17 (C=O), 176.63 (C=O). MS (EI): *m/z* (relative intensity) 274 (2, M - 15), 233 (65), 216 (20), 189 (100), 172 (37), 144 (56), 115 (63). HRMS: *m/z* calcd for $C_{12}H_{11}NO_4$ (M - 56) 233.0688, found 233.0686.

General Procedure for the Deprotection of BOC Aminolactones 10. To a solution of the BOC aminolactone **10** in dioxane (2 mL/mmol) was added a solution of HCl in dioxane (5.5 M, 2 mL/mmol). The solution was stirred until no starting material was detected by TLC (EtOAc–petroleum ether (1:1), visualized with ninhydrin). The solvent was removed under reduced pressure and the solid crushed and washed with ether several times. The product **11** was collected by filtration and dried. In all cases the product was pure enough for next reaction.

1-Amino-2-oxo-3-oxabicyclo[3.1.0]hexane Hydrochloride (11a). Yield: 90%. Mp: 163–165 °C dec. IR (KBr): 3380, 1760, 980, 760. ^{1}H-NMR (D_2O/HOD) δ: 1.47 (t, 1 H, *J* = 5.7 Hz), 1.83 (bt, 1 H, *J* = 7.9 Hz), 2.91 (m, 1 H), 4.30 (d, 1 H, 9.7 Hz), 4.53 (dd, 1 H, *J* = 4.7 and 9.7 Hz). ^{13}C-NMR (D_2O/TMS_2O) δ: 15.21 (CH_2), 21.56 (CH), 37.05 (C), 69.73 (CH_2), 173.22 (C=O). MS (EI): *m/z* (relative intensity) 113 (28, M^+), 85 (62), 68 (100). HRMS: *m/z* calcd for $C_5H_7NO_2$ 113.0477, found 113.0480.

1-Amino-6-methyl-2-oxo-3-oxabicyclo[3.1.0]hexane Hydrochloride (11b). Yield: 79%. Mp: 125–127 °C dec. IR (KBr): 3380, 1770, 975, 760. ^{1}H-NMR (D_2O/HOD) δ: 1.27 (d, 3 H, *J* = 6.4 Hz), 1.98 (m, 1 H), 2.59 (bt, 1 H, *J* = 4.6 Hz), 4.31 (d, 1 H, *J* = 9.6 Hz), 4.47 (dd, 1 H, *J* = 4.6 and 9.6 Hz). ^{13}C-NMR (D_2O/TMS_2O) δ: 9.65 (CH_3), 22.26 (CH), 27.23 (CH), 40.80 (C), 69.90 (CH_2), 173.72 (C=O). MS (EI): *m/z* (relative intensity) 127 (30, M^+), 112 (43), 99 (49), 82 (54), 72 (100). HSMS: *m/z* calcd for $C_6H_9NO_2$ 127.0633, found 127.0604.

1-Amino-6,6-dimethyl-2-oxo-3-oxabicyclo[3.1.0]hexane Hydrochloride (11c). Yield: 81%. Mp: 152–154 °C dec. IR (KBr): 3390, 1775, 1758, 980, 780. ^{1}H-NMR (D_2O/HOD) δ: 1.17 (s, 3 H), 1.35 (s, 3 H), 2.64 (d, 1 H, *J* = 5.3 Hz), 4.33 (d, 1 H, *J* = 10.3 Hz), 4.60 (dd, 1 H, *J* = 5.2 Hz and 10.3 Hz). ^{13}C-NMR (D_2O/TMS_2O) δ: 13.53 (CH_3), 19.08 (CH_3), 25.68 (C), 32.38 (CH), 46.27 (C), 67.27 (CH_2), 173.43 (C=O). MS (EI): *m/z* (relative intensity) 141 (14, M^+), 126 (100), 113 (9), 99 (68). HRMS: *m/z* calcd for $C_7H_{11}NO_2$: 141.0790, found 141.0780.

1-Amino-6-phenyl-2-oxo-3-oxabicyclo[3.1.0]hexane Hydrochloride (11d). Yield: 96%. Mp: 135–137 °C. IR (KBr): 3400, 1770, 1005, 760. ^{1}H-NMR (D_2O/HOD) δ: 3.05 (d, 1 H, *J* = 5.0 Hz), 3.45 (t, 1 H, *J* = 4.9 Hz), 4.49 (d, 1 H, *J* = 9.6 Hz), 4.68 (dd, 1 H, *J* = 4.8 and 9.6 Hz), 7.34–7.46 (m, 5 H). ^{13}C-NMR (D_2O/TMS_2O) δ: 24.51 (CH), 31.33 (CH), 41.91 (C), 69.96 (CH_2), 128.80 (Ar-CH), 128.97 (Ar-CH), 129.05 (Ar-CH), 129.29 (Ar-C), 172.85 (C=O). MS (EI): *m/z* (relative intensity) 189 (22, M^+), 144 (43), 130 (77), 98 (100). HRMS: *m/z* calcd for $C_{11}H_{11}NO_2$ 189.0790, found 189.0780.

General Procedure for the Opening of the Lactone 11 To Give the (*E*)-ACC's 12. To a solution of the amino lactone hydrochloride **11** in water (2 mL/mmol) was added aqueous sodium hydroxide (2.5 M, 2 mL/mmol). The solution was stirred at room temperature for 4–6 h. The mixture was poured into an ion-exchange resin column (Amberlite IR-120, Fluka, acidic form, 5 × 1 cm) and eluted initially with water. The product was eluted with ammonia (2 M, 80 mL). Ammonia was removed for a few minutes in a rotary evaporator at room temperature, and the remaining solution was freeze-dried.

(*E*)-1-Amino-2-(hydroxymethyl)cyclopropane-1-carboxylic Acid (12a). Yield: 72%. Mp: 215–218 °C dec. IR (KBr): 3100, 1620, 1030, 950. ^{1}H-NMR (D_2O/HOD) δ: 1.28–145 (m, 2 H), 1.77 (m, 1 H), 3.69–3.87 (m, 2 H). ^{13}C-NMR (D_2O/TMS_2O) δ: 15.06 (CH_2), 26.31 (CH), 39.83 (C), 59.54 (CH_2), 173.22 (C=O). HRMS: *m/z* calcd for $C_5H_9NO_3$ 131.0582, found 131.0600.

(*E*)-1-Amino-2-(hydroxymethyl)-3-methylcyclopropane-1-carboxylic Acid (12b). Yield: 83%. Mp: 208–211 °C dec. IR (KBr): 3230, 1610, 1040, 950. ^{1}H-NMR (D_2O/HOD) δ: 1.21 (d, 3 H, *J* = 6.5 Hz), 1.47 (q, 1 H, *J* = 7.2 Hz), 1.78 (m, 1 H), 3.68–3.94 (m, 2 H). ^{13}C-NMR (D_2O/TMS_2O) δ: 10.90 (CH_3), 21.51 (CH), 33.57 (CH), 42.86 (C), 58.41 (CH_2), 173.33 (C=O). FABMS (glycerol), *m/z* 146 (M + 1). HRMS: *m/z* calcd for $C_6H_{11}NO_3$ 145.0739, found 145.0764.

(*E*)-1-Amino-2-(hydroxymethyl)-3,3-dimethylcyclopropane-1-carboxylic Acid (12c). Yield: 92%. Mp: 194–196 °C dec. IR (KBr): 3200, 1600, 1040, 950. ^{1}H-NMR (D_2O/HOD) δ: 1.20 (s, 3 H), 1.27 (s, 3 H), 1.33 (bt, 1 H), 3.92 (d, 1 H, *J* = 7.3 Hz). ^{13}C-NMR (D_2O/TMS_2O) δ: 14.93 (CH_3), 20.98 (CH_3), 25.26 (C), 36.01 (CH), 46.81 (C), 57.37 (CH_2), 174.68 (C=O). FABMS (glycerol): *m/z* 160 (M + 1). HRMS: *m/z* calcd for $C_7H_{13}NO_3$ 159.0895, found 159.0874.

(*E*)-1-Amino-2-(hydroxymethyl)-3-phenylcyclopropane-1-carboxylic Acid (12d). Yield: 66%. Mp: 184–186 °C dec. IR (KBr): 3200, 1630, 1035, 690. ^{1}H-NMR (D_2O/HOD) δ: 2.26 (q, 1 H, *J* = 7.1 Hz), 3.19 (d, 1 H, *J* = 8.2 Hz), 3.93–4.06 (m, 2 H), 7.30–7.47 (m, 5 H). ^{13}C-NMR (D_2O/TMS_2O) δ: 30.29 (CH), 31.62 (CH), 43.33 (C), 58.10 (CH_2), 127.86 (Ar-CH), 128.59 (Ar-CH), 128.99 (Ar-CH), 132.09 (Ar-C), 171.82 (C=O). FABMS (glycerol): *m/z* 208 (M + 1). HRMS: *m/z* calcd for $C_{11}H_{13}NO_3$ 207.0895, found 207.0930.

General Procedure for the Preparation of Amides 13. The lactone **8** was dissolved in methanol (ca. 4 mL per mmol), and methanol saturated with ammonia (5.8 M, ca. 2 mL per mmol) was added. The solution was stirred at room temperature and monitored by TLC. After consumption of the starting material the mixture was stirred for a further time (total time indicated). The solvent was evaporated under reduced pressure and the amide **13** was used in the next reaction without further purification.

1-(*tert*-Butoxycarbonyl)-2-(hydroxymethyl)cyclopropanecarboxamide (13a). Time: 6 h. Yield: 98%. Mp: 70–74 °C. IR (KBr): 3600–3100, 1715, 1680, 1570. ^{1}H-NMR ($CDCl_3$/TMS) δ: 1.45 (s, 9 H), 1.64 (dd, 1 H, *J* = 4.2, 9.5 Hz), 1.71 (dd, 1 H, *J* = 4.3, 7.8 Hz), 2.12 (m, 1 H), 3.02 (br s, 1 H, OH), 3.65 (br dd, 1 H, *J* = 8.8, 11.8 Hz), 3.90 (br dd, 1 H, *J* = 4.1, 12.2 Hz), 6.56 (br s, 1 H, NH), 8.17 (br s, 1 H, NH). ^{13}C-NMR ($CDCl_3$) δ: 19.18 (CH_2), 27.71 (CH_3, *t*Bu), 32.80 (C), 34.11 (CH), 59.65 (CH_2), 82.23 (C, *t*Bu), 170.76 (C=O), 170.89 (C=O). MS (EI): *m/z* (relative intensity) 216 (4, M + 1), 159 (39), 142 (30), 116 (32), 103 (100). HRMS: *m/z* calcd for $C_{10}H_{17}NO_4$ 215.1158, found 215.1162.

1-(*tert*-Butoxycarbonyl)-2-(hydroxymethyl)-3-methylcyclopropanecarboxamide (13b). Time: 8 h. Yield: 97%. Colorless oil. IR (neat): 3600–3150, 1725, 1675, 1615. ^{1}H-NMR ($CDCl_3$/TMS) δ: 1.22 (d, 3 H, *J* = 6.3 Hz), 1.48 (s, 9 H), 2.00 (m, 1 H), 2.17 (m, 1 H), 3.05 (br s, 1 H, OH), 3.57 (dd, 1 H, *J* = 8.7, 12.3 Hz), 3.94 (dd, 1 H, *J* = 4.2, 12.2 Hz), 6.17 (br s, 1 H, NH), 7.37 (br s, 1 H, NH). ^{13}C-NMR ($CDCl_3$) δ: 12.47 (CH_3), 27.66 (CH), 28.02 (CH_3, *t*Bu), 37.22 (CH), 39.45 (C), 60.20 (CH_2), 82.71 (C, *t*Bu), 169.11 (C=O), 171.77 (C=O). MS (EI): *m/z* (relative intensity) 230 (9, M + 1), 174 (38), 156 (28), 142 (100), 103 (62). HRMS: *m/z* calcd for $C_{11}H_{19}NO_4$ 229.1314, found 229.1298.

1-(*tert*-Butoxycarbonyl)-2-(hydroxymethyl)-3,3-dimethylcyclopropanecarboxamide (13c). Time: 7 days. Yield: 92%. Mp: 131–133 °C. IR (neat): 3350, 3180, 1715, 1675, 1630. ^{1}H-NMR ($CDCl_3$/TMS) δ: 1.21 (s, 6 H), 1.48 (s, 9 H), 2.11 (dd, 1 H, *J* = 6.4, 10.3 Hz), 3.69 (br t, 1 H, *J* = 11.2 Hz), 3.93 (m, 1 H), 6.06 (br s, 1 H, NH), 7.04 (br s, 1 H, NH). ^{13}C-NMR ($CDCl_3$) δ: 17.95 (CH_3), 22.48 (CH_3), 27.94 (CH_3, *t*Bu), 31.16 (C), 36.55 (CH), 43.98 (C), 59.06 (CH_2), 82.75 (C, *t*Bu), 168.58 (C=O), 170.41 (C=O). MS (EI): *m/z* (relative intensity) 230 (5, M - 13), 212 (18), 187 (5), 170 (9), 156 (100), 139 (77), 122 (23). HRMS: *m/z* calcd for $C_{12}H_{21}NO_4$ 243.1471, found 243.1479.

1-(*tert*-Butoxycarbonyl)-2-(hydroxymethyl)-3-phenylcyclopropanecarboxamide (13d). Time: 8 h. Yield: 98%. Mp: 154–156 °C. IR (neat): 3600–3150, 1700, 1675, 1605. ^{1}H-NMR ($CDCl_3$/TMS) δ: 1.01 (s, 9 H), 2.99 (m, 1 H), 3.46 (d, 1 H, *J* = 8.5 Hz), 3.63 (br s, 1 H, OH), 3.98 (m, 1 H), 4.14 (m, 1 H), 6.20 (br s, 1 H, NH), 7.27 (m, 5 H), 8.05 (br s, 1 H). ^{13}C-NMR ($CDCl_3$) δ: 27.27 (CH_3, *t*Bu), 35.00 (CH), 38.27 (CH), ca. 40 (C), 59.64 (CH_2), 82.69 (C, *t*Bu), 127.28 (Ar-CH), 128.09 (Ar-CH), 129.36 (Ar-CH), 135.23 (Ar-C), 168.45 (C=O), 171.54 (C=O). MS (EI):

m/z (relative intensity) 260 (52, M - 31), 218 (7), 204 (100), 170 (20), 115 (37). HRMS: *m/z* calcd for $C_{16}H_{20}O_3$ (M - 31) 260.1412, found 260.1412.

General Procedure for the Protection of Amides 13. The alcohol **13** (ca. 1 mmol) was dissolved in dry CH_2Cl_2 (10 mL per mmol) together with *tert*-butyldimethylchlorosilane (110 mol %) and imidazole (110 mol %). The flask was fitted with an Ar balloon, and the mixture was stirred overnight at room temperature. The solution was washed with saturated aqueous sodium bicarbonate (2 × 10 mL) and brine (10 mL). The organic phase was dried with anhyd magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by FC yielding the silyl ethers **14**. The yields given refer to overall yields from the lactones **8**.

1-(*tert*-Butoxycarbonyl)-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]cyclopropanecarboxamide (14a). Colorless oil. Yield: 94%. IR (neat): 3520–3150, 1720, 1675, 1575, 1265. ^{1}H-NMR ($CDCl_3$/TMS) δ: 0.04 (s, 3 H), 0.06 (s, 3 H), 0.88 (s, 9 H), 1.45 (s, 9 H), 1.62 (dd, 1 H, *J* = 4.2, 9.5 Hz), 1.68 (dd, 1 H, *J* = 4.2, 7.9 Hz), 2.00 (m, 1 H), 3.66 (dd, 1 H, *J* = 8.2, 11.3 Hz), 3.88 (dd, 1 H, *J* = 5.7, 11.3 Hz), 6.36 (br s, 1 H, NH), 8.06 (br s, 1 H, NH). ^{13}C-NMR ($CDCl_3$) δ: -5.51 (CH_3), -5.45 (CH_3), 18.01 (C, *t*Bu), 18.78 (CH_2), 25.66 (CH_3, *t*Bu), 27.66 (CH_3, *t*Bu), 32.48 (C), 34.38 (CH), 60.88 (CH_2), 81.81 (C, *t*Bu), 169.24 (C=O), 171.05 (C=O). MS (EI): *m/z* (relative intensity) 330 (6, M + 1), 274 (9), 256 (7), 216 (85), 198 (10), 172 (100), 142 (18). HRMS: *m/z* calcd for $C_{16}H_{31}NO_4Si$ 329.2022, found 329.2040.

1-(*tert*-Butoxycarbonyl)-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3-methylcyclopropanecarboxamide (14b). Yield: 95%. Mp: 138–139 °C. IR (neat): 3520–3160, 1720, 1670, 1625, 1260. ^{1}H-NMR ($CDCl_3$/TMS) δ: 0.04 (s, 3 H), 0.06 (s, 3 H), 0.88 (s, 9 H), 1.22 (d, 3 H, *J* = 6.0 Hz), 1.48 (s, 9 H), 1.94–2.06 (m, 2 H), 3.56 (dd, 1 H, *J* = 7.8, 11.3 Hz), 3.90 (dd, 1 H, *J* = 5.4, 11.3 Hz), 5.72 (br s, 1 H, NH), 6.96 (br s, 1 H, NH). ^{13}C-NMR ($CDCl_3$) δ: -5.32 (CH_3), -5.24 (CH_3), 12.39 (CH_3), 18.15 (C), 25.81 (CH_3, *t*Bu), 26.96 (CH), 28.06 (CH_3, *t*Bu), 37.44 (CH), 39.54 (C), 61.54 (CH_2), 82.20 (C), 169.35 (C=O), 169.97 (C=O). MS (EI): *m/z* (relative intensity) 344 (2, M + 1), 286 (6), 270 (5), 230 (100), 212 (49), 186 (26), 142 (14). HRMS: *m/z* calcd for $C_{17}H_{33}NO_4Si$ 343.2179, found 343.2166.

1-(*tert*-Butoxycarbonyl)-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3,3-dimethylcyclopropanecarboxamide (14c). Yield: 98%. Mp: 73–74 °C. IR (neat): 3550–3100, 1720, 1680, 1610, 1260. ^{1}H-NMR ($CDCl_3$/TMS) δ: 0.08 (s, 3 H), 0.10 (s, 3 H), 0.90 (s, 9 H), 1.20 (s, 3 H), 1.25 (s, 3 H), 1.47 (s, 9 H), 1.88 (dd, 1 H, *J* = 6.9, 8.5 Hz), 3.79 (dd, 1 H, *J* = 8.6, 11.8 Hz), 4.04 (dd, 1 H, *J* = 6.9, 11.8 Hz), 5.74 (br s, 1 H, NH), 7.18 (br s, 1 H, NH). ^{13}C-NMR ($CDCl_3$) δ: -5.29 (CH_3), -5.17 (CH_3), 18.06 (C), 18.17 (CH_3), 22.01 (CH_3), 25.77 (CH_3, *t*Bu), 27.93 (CH_3, *t*Bu), 29.89 (C), 37.06 (CH), 43.88 (C), 60.23 (CH_2), 81.96 (C), 168.76 (C=O), 198.99 (C=O). MS (EI): *m/z* (relative intensity) 358 (5, M + 1), 300 (12), 284 (14), 244 (73), 226 (40), 212 (20), 171 (40), 156 (100). HRMS: *m/z* calcd for $C_{18}H_{35}NO_4Si$ 357.2335, found 357.2324.

1-(*tert*-Butoxycarbonyl)-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3-phenylcyclopropanecarboxamide (14d). Yield: 97%. Mp: 85–86 °C. IR (neat): 3520–3160, 1710, 1660, 1600, 1260. ^{1}H-NMR ($CDCl_3$/TMS) δ: 0.09 (s, 3 H), 0.10 (s, 3 H), 0.92 (s, 9 H), 1.01 (s, 9 H), 2.81 (m, 1 H), 3.46 (d, 1 H, *J* = 8.5 Hz), 3.89 (dd, 1 H, *J* = 7.2, 11.2 Hz), 4.08 (dd, 1 H, *J* = 6.3, 11.2 Hz), 5.78 (br s, 1 H, NH), 7.21–7.30 (m, 5 H), 7.52 (br s, 1 H, NH). ^{13}C-NMR ($CDCl_3$) δ: -5.25 (CH_3), -5.15 (CH), 18.24 (C), 25.88 (CH_3, *t*Bu), 27.34 (CH_3, *t*Bu), 35.64 (CH), 38.09 (CH), 40.13 (C), 60.85 (CH_2), 82.21 (C), 127.00 (Ar-CH), 128.02 (Ar-CH), 129.41 (Ar-CH), 135.86 (Ar-C), 168.89 (C=O), 169.53 (C=O). MS (EI): *m/z* (relative intensity) 406 (1, M + 1), 348 (12), 332 (8), 292 (100), 274 (44), 260 (49) 204 (96), 172 (25). HRMS: *m/z* calcd for $C_{16}H_{22}NO_4$ (M - 113) 292.1549, found 292.1526.

General Procedure for the Preparation of the Protected Amino Acids 15. The protected amide **14** was dissolved in dry *t*-BuOH (20 mL per mmol) with a few drops of anhyd pyridine and fitted with a balloon filled with Ar. LTA (220 mol %) was added, and the reaction mixture was heated with stirring under smooth reflux until no starting material was detected by TLC (ca. 1 h). After heating for a further hour, the mixture was poured into diethyl ether and washed twice with saturated aqueous sodium bicarbonate and once with brine. The organic phase was dried with anhyd magnesium sulfate and concentrated under reduced pressure. The residue was purified by FC yielding **15**.

1-(*tert*-Butoxycarbonyl)-1-[(*tert*-butoxycarbonyl)amino]-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]cyclopropane (15a). Colorless oil. Yield: 75%. IR (neat): 3440, 3370, 1725, 1260. ^{1}H-NMR ($CDCl_3$/TMS) δ: 0.07 (s, 6 H), 0.90 (s, 9 H), 1.06 (m, 1 H), 1.44 (s, 9 H), 1.46 (s, 9 H), 1.71 (m, 1 H), 1.84 (m, 1 H), 3.50 (m, 1 H), 3.96 (m, 1 H), 5.29 (br s, 1 H, NH). ^{13}C-NMR ($CDCl_3$) δ: -5.38 (CH_3), -5.23 (CH_3), 18.07 (C), 21.34 (CH_2), 25.76 (CH_3, *t*Bu), 27.88 (CH_3, *t*Bu), 28.21 (CH_3, *t*Bu), 29.01 (CH), 38.44 (C), 62.87 (CH_2), 79.34 (C), 80.95 (C), 156.30 (C=O), 171.82 (C=O). MS (EI): *m/z* (relative intensity) 402 (1, M + 1), 358 (9), 328 (8), 317 (9), 302 (14), 289 (83), 272 (37), 244 (35), 232 (98), 214 (43), 202 (27), 188 (63), 170 (34), 157 (24), 142 (32), 117 (42), 75 (100). HRMS: *m/z* calcd for $C_{17}H_{32}NO_5Si$ (M - 43) 358.2080, found 358.2050.

1-(*tert*-Butoxycarbonyl)-1-[(*tert*-butoxycarbonyl)amino]-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3-methylcyclopropane (15b). Yield: 77%. Mp: 82–83 °C. IR (neat): 3440, 3380, 1725, 1260. ^{1}H-NMR ($CDCl_3$/TMS) δ: 0.06 (s, 6 H), 0.89 (s, 9 H), 1.26–1.33 (m, 4 H), 1.45 (s, 18 H), 1.83 (m, 1 H), 3.56 (m, 1 H), 3.84 (m, 1 H), 5.15 (br s, 1 H, NH). ^{13}C-NMR ($CDCl_3$) δ: -5.26 (CH_3), -5.16 (CH_3), 11.86 (CH_3), 18.13 (C), 25.83 (CH_3, *t*Bu), 28.09 (CH_3, *t*Bu), 28.30 (CH_3, *t*Bu), 30.22 (CH), 35.27 (CH), 42.75 (C), 62.73 (CH_2), 79.26 (C), 81.05 (C), 156.38 (C=O), 170.40 (C=O). MS (EI): *m/z* (relative intensity) 416 (1, M + 1), 359 (4), 303 (100), 286 (28), 246 (94), 228 (44), 202 (47), 184 (26), 171 (25), 156 (46), 126 (28), 113 (54), 75 (79). HRMS: *m/z* calcd for $C_{15}H_{29}NO_5$ (M - 112) 303.2076, found 303.2046.

1-(*tert*-Butoxycarbonyl)-1-[(*tert*-butoxycarbonyl)amino]-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3,3-dimethylcyclopropane (15c). Colorless oil. Yield: 43%. IR (neat): 3430, 1720, 1715, 1255. ^{1}H-NMR ($CDCl_3$/TMS) δ: 0.04 (s, 3 H), 0.05 (s, 3 H), 0.88 (s, 9 H), 1.19 (s, 3 H), 1.25 (s, 3 H), 1.44 (br s, 18 H), 1.96 (t, 1 H, *J* = 7.9 Hz), 3.56 (br dd, 1 H, *J* = 9.1, 10.9 Hz), 3.87 (dd, 1 H, *J* = 7.3, 11.3 Hz), 4.98 (br s, 1 H, NH). ^{13}C-NMR ($CDCl_3$) δ: -5.25 (CH_3), -5.15 (CH_3), 16.64 (CH_3), 18.12 (C), 21.37 (CH_3), 25.84 (CH_3, *t*Bu), 28.06 (CH_3, *t*Bu), 28.23 (CH_3, *t*Bu), 35.84 (CH), 45.89 (C), 59.30 (CH_2), 79.36 (C), 80.91 (C), 156.38 (C=O), 170.57 (C=O). MS (EI): *m/z* (relative intensity) 430 (2, M + 1), 374 (4), 317 (61), 300 (11), 260 (33), 242 (10), 216 (11), 185 (43), 172 (79), 128 (63), 75 (100). HRMS: *m/z* calcd for $C_{16}H_{31}NO_5$ (M - 112) 317.2202, found 317.2227.

In addition, a slightly more polar byproduct **16c** was obtained. Yield: 30%. Mp: 57–58 °C. IR (neat): 3400, 3310, 1760, 1740, 1250. ^{1}H-NMR ($CDCl_3$/TMS) δ: 0.09 (s, 6 H), 0.89 (s, 9 H), 1.45 (s, 9 H), 1.57 (s, 6 H), 4.73 (s, 2 H), 4.34 (br s, 1 H, NH). ^{13}C-NMR ($CDCl_3$) δ: -5.65 (2 × CH_3), 18.20 (C), 25.81 (CH_3, *t*Bu), 25.90 (2 × CH_3), 28.03 (CH_3, *t*Bu), 58.36 (CH_2), 81.28 (C), 86.54 (C), 119.53 (C), 149.67 (C), 152.13 (C=O), 169.00 (C=O). MS (CI, isobutane): *m/z* (relative intensity) 428 (6, M + 56), 372 (14, M^+), 316 (100). HRMS: *m/z* calcd for $C_{14}H_{25}NO_5Si$ (M - 56) 315.1502, found 315.1491.

Rearrangement of the Phenyl Derivative 14d. The amide **14d** (140 mg, 0.34 mmol) was refluxed in *t*-BuOH (10 mL) together with LTA (330 mg, 0.75 mmol) and a few drops of pyridine. After workup the residue was chromatographed with CH_2Cl_2. The product **16d** (110 mg, 0.26 mmol) was obtained as a colorless oil which solidified on standing. Yield: 76%. IR (neat): 3410, 3330, 1790–1730, 1250. ^{1}H-NMR ($CDCl_3$/TMS) δ: 0.11 (s, 3 H), 0.18 (s, 3 H), 1.08 (s, 9 H), 1.74 (s, 9 H), 4.56 (d, 1 H, *J* = 15.2 Hz), 5.08 (d, 1 H, *J* = 15.2 Hz), 6.29 (s, 1 H), 6.78 (br s, 1 H, NH), 7.51–7.63 (m, 5 H). ^{13}C-NMR ($CDCl_3$) δ: -5.90 (CH_3), -5.87 (CH_3), 18.10 (C), 25.73 (CH_3, *t*Bu), 28.05 (CH_3, *t*Bu), 58.69 (CH_2), 81.63 (C), 82.93 (CH), 119.99 (C), 127.55 (2 Ar-CH), 128.78 (2 Ar-CH), 129.32 (Ar-CH), 134.64 (Ar-C), 144.63 (C), 152.17 (C=O), 170.18 (C=O). MS (EI): *m/z* (relative intensity) 418 (3, M - 1), 364 (6), 306 (44), 262 (100), 216 (22), 170 (7), 115 (16), 75 (46). HRMS: *m/z* calcd for $C_{16}H_{20}NO_5$ (M - 113) 306.1342, found 306.1357.

General Procedure for the Cleavage of the Silyl Protecting Group of Amino Acids 15. To a THF solution of the fully protected amino acid **15** (5 mL/mmol) was added a 2-fold excess of tetrabutyl ammonium hydroxide (Aldrich, 1.0 M in THF). The solution was stirred at room temperature until no starting material was detected by TLC (EtOAc–hexanes (1:9),

ninhydrin) and then stirred for a further 1 h. The solvent was concentrated in a rotary evaporator and the residue redissolved in EtOAc and washed consecutively with 20% citric acid (10 mL), saturated aqueous sodium bicarbonate (10 mL), and brine (10 mL). The organic solution was dried and chromatographed (FC) on silica gel with EtOAc–hexanes (1:4, 1:3.5, 1:3, and 1:1). The alcohol **17** was obtained as a colorless residue which crystallized in the rotary evaporator.

1-(*tert*-Butoxycarbonyl)-1-[(*tert*-butoxycarbonyl)amino]-2-(hydroxymethyl)cyclopropane (17a). Yield: 68%. Mp: 107 °C (EtOAc–hexanes). IR (KBr): 3350, 3200, 1715, 1685. ^{1}H-NMR ($CDCl_3$/TMS) δ: 0.7 (q, 1 H, J = 5.0 and 7.4 Hz), 1.44 (s, 9 H), 1.47 (s, 9 H), 2.21 (bq, 1 H, J = 9.8 Hz), 3.18 (t, 1 H, J = 11.1 Hz), 3.77–3.97 (m, 2 H), 5.09 (bs, 1 H). ^{13}C-NMR ($CDCl_3$) δ: 18.76 (CH_2), 27.96 (CH_3, *t*Bu), 28.21 (CH_3, *t*Bu), 30.58 (CH), 38.87 (C), 61.58 (CH_2), 80.94 (C), 81.61 (C), 158.11 (C=O), 171.19 (C=O). FABMS (glycerol): m/z (relative intensity) 288 (4, M + 1), 232 (8), 176 (46), 69 (100). HRMS: m/z calcd for $C_{14}H_{26}NO_5$ (M + 1) 288.1811, found 288.1857.

1-(*tert*-Butoxycarbonyl)-1-[(*tert*-butoxycarbonyl)amino]-2-(hydroxymethyl)-3-methylcyclopropane (17b). Yield: 62%. Mp: 140–141 °C (EtOAc–hexanes). IR (KBr): 3320, 3230, 1715, 1675. ^{1}H-NMR ($CDCl_3$/TMS) δ: 1.12 (m, 1 H), 1.19 (d, 3 H, J = 5.5 Hz), 1.47 (s, 18 H), 2.16 (m, 1 H), 3.18 (t, 1 H, J = 11.7 Hz), 3.94 (dd, 1 H, J = 3.4 and 12.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 11.31 (CH_3), 26.53 (CH), 28.08 (CH_3, *t*Bu), 28.20 (CH_3, *t*Bu), 36.20 (CH), 43.53 (C), 61.59 (CH_2), 80.86 (C), 81.56 (C), 158.16 (C=O), 169.60 (C=O). FABMS (glycerol): m/z 302 (6, M + 1), 246 (14), 190 (70), 57 (100). HRMS: m/z calcd for $C_{15}H_{28}NO_5$ (M + 1) 302.1968, found 302.1990.

1-(*tert*-Butoxycarbonyl)-1-[(*tert*-butoxycarbonyl)amino]-2-(hydroxymethyl)-3,3-dimethylcyclopropane (17c). Yield: 66%. Mp: 157 °C (sublimes). IR (KBr): 3380, 3260, 1720, 1685. ^{1}H-NMR ($CDCl_3$/TMS) δ: 1.10 (s, 3 H), 1.20 (s, 3 H), 1.45 (s, 9 H), 1.47 (s, 9 H), 2.14 (dd, 1 H, J = 3.1 and 10.5 Hz), 3.35 (bt, 1 H, J = 11.1 Hz), 3.79 (dd, 1 H, J = 3.3 and 11.9 Hz) and 5.03 (bs, 1 H). ^{13}C-NMR ($CDCl_3$) δ: 16.50 (CH_3), 21.17 (CH_3), 28.05 (CH_3, *t*Bu), 28.22 (CH_3, *t*Bu), 28.75 (C), 37.07 (CH), 45.72 (C), 58.38 (CH_2), 80.88 (C), 81.34 (C), 158.51 (C=O) and 170.04 (C=O). HRMS: m/z calcd for $C_{16}H_{30}NO_5$ (M + 1) 316.2124, found 316.2178.

General Procedure for the Cleavage of the *tert*-Butyl Groups To Give the (*Z*)-ACC's 18. To a solution of the *N*-BOC ACC *tert*-butyl ester **17** in dioxane (5 mL/mmol) was added a solution of HCl in dioxane (5.5 M, 5 mL/mmol) and *m*-cresol (3 mL/mmol). After the solution was stirred overnight at rt, the solvent was concentrated in a rotary evaporator at rt and the residue was dried for 12–24 in high vacuum. The residue was treated with ether until a solid appeared. The solid was crushed, washed, and filtered. The hygroscopic filtrate was immediately dissolved in water, basified until pH 12 with sodium hydroxide, and purified in an Amberlite IR-120 column as described for **12**.

(*Z*)-1-Amino-2-(hydroxymethyl)cyclopropane-1-carboxylic Acid (18a). Yield: 76%. Mp: >340 °C. IR (KBr): 3300, 1610, 1020. ^{1}H-NMR (D_2O/HOD) δ: 1.15 (t, 1 H, J = 6.7 Hz), 1.47 (dd, 1 H, J = 6.1 and 9.6 Hz), 1.87 (m, 1 H), 3.74 (dd, 1 H, J = 6.8 and 12.2 Hz), 3.96 (dd, 1 H, J = 4.9 and 12.2 Hz). ^{13}C-NMR (D_2O/TMS_2O) δ: 12.89 (CH_2), 22.24 (CH), 37.03 (C), 56.30 (CH_2), 173.69 (C=O). HRMS: m/z calcd for $C_5H_9NO_3$ 131.0582, found 131.0605.

(*Z*)-1-Amino-2-(hydroxymethyl)-3-methylcyclopropane-1-carboxylic Acid (18b). Yield: 88%. Mp: >340 °C. IR (KBr): 3300, 1580, 1020. ^{1}H-NMR (D_2O/HOD) δ: 1.09 (bs, 4 H), 1.64 and 1.91 (2 × bs, 1 H), 3.43 (dd, J = 9.0 and 11.6 Hz), 3.67 (dd, J = 7.8 and 11.7), 3.71 (dd) and 3.81 (dd, J = 6.5 and 11.7). ^{13}C-NMR (D_2O/TMS_2O) δ: 11.23 (CH_3), 25.49 (CH), 31.09 (CH), 45.51 (C), 60.16 (CH_2), 179.15 (C=O). HRMS: m/z calcd for $C_6H_{11}NO_3$ 145.0739, found 145.0746.

(*Z*)-1-Amino-2-(hydroxymethyl)-3,3-dimethylcyclopropane-1-carboxylic Acid (18c). Yield: 72%. Mp: >340 °C. IR (KBr): 3320, 1590, 1030. ^{1}H-NMR (D_2O/HOD) δ: 1.09 (bs, 7 H), 3.58 (d, J = 7.0 Hz), 3.69 (br d, J = 7.0 Hz). ^{13}C-NMR (D_2O/TMS_2O) δ: 14.57 (CH_3), 20.96 (CH_3), 25.38 (C), 33.63 (CH), 47.55 (C), 58.31 (CH_2), 173.30 (C=O). FABMS (glycerol): m/e 160 (M + 1).

Acknowledgment. Financial support from the Nuffield Foundation (U.K.) is gratefully acknowledged. L.M. graciously thanks the Ministry of Education (MEC), Spain, for a post-doctoral fellowship. We also thank Professor Ricardo Riguera, Universidad de Santiago de Compostela, Spain, and Mrs. Päivi Joensuu for the mass spectra and Mrs. Leena Maihkila for technical assistance.

Supplementary Material Available: ^{1}H NMR spectra of compounds 7–18 (43 pages). This information 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.