Cyclopropyl Building Blocks for Organic Synthesis, 49[◇]

Convenient Preparation of α-Amino Acids with Bicyclopropylidene and Other Methylenecyclopropane Moieties

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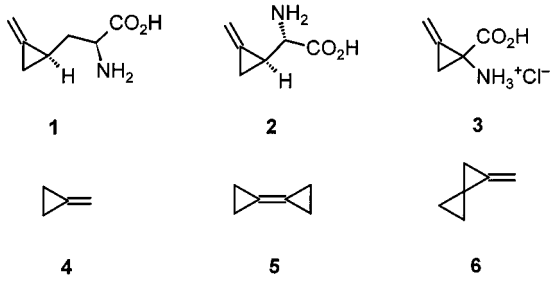
Racemic bicyclopropylidenyl- (*rac*-**11**) and methylenespiropentyl- (*rac*-**17**) substituted alanines have been synthesized by iodination of bicyclopropylidenyl- and methylenespiropentylmethanols **7**, **13**, nucleophilic substitution of the iodine in **8**, **14** with the enolate of ethyl α-(diphenylmethyleneamino)acetate (O'Donnell's glycine equivalent) and deprotection of **9**, **15** in 24 and 18% overall yield, respectively. *N*-Methylbicyclopropylidenylalanine *rac*-**22**, was obtained from the Michael adduct of (bicyclopropylidenyl)magnesium bromide **18** to enamine **19** and deprotection of the carbamate **20** (23% overall yield). Racemic (1-amino-2-methylenespiropentane)- (**37**), (1-amino-2-methylenecyclopropane)- (**3**), and (1-aminobicyclopropylidene)carboxylic acid (**39**) were prepared as hydrochlorides by *tert*-butoxycarbonylation of the lithiated methylenespiropentane (**6**), methylenecyclopropane (**4**), or bicyclopropylidene (**5**) intermediates with di-*tert*-butyl pyrocarbonate (Boc_2O), repeated lithiation of the *tert*-butyl esters **29**, **30**, and **33** with LDA and subsequent carboxylation, Curtius degradation of the half esters **31**, **32**, and **34** followed by deprotection in 11, 45, and 4% overall yields, respectively. Compound **37** was also prepared from bicyclopropylidene (**5**) following the same procedure, but with rearrangement in the last but one step, in 19% overall yield. An attempted Hofmann degradation of the bicyclopropylidenecarboxamido ester **40** with NBS failed and gave only bromohydrin **44** (27%), but with bis(acetoxy)iodobenzene provided carbamate **46a,b** in 76 amd 79% yield, respectively. Along this route with subsequent deprotection of **46b**, the amino acid **39** could be prepared in up to 10% overall yield from bicyclopropylidene.

Most of the known naturally occurring amino acids containing a cyclopropyl group[1] and their nonnatural analogs exhibit interesting biological activities[1][2][3]. No wonder that a number of synthetically oriented groups around the world have invested a considerable amount of work into the development of feasible syntheses of such amino acids[4]. Two particularly interesting specimen in this group of natural products are 3-(2-methylenecyclopropyl)alanine (**1**), so-called hypoglycine A[5], occurring in unripe ackee plums, and 2-(2-methylenecyclopropyl)glycine (**2**) which has been isolated from lychee fruits[6], because both show a strong hypoglycemic effect. The irreversible inactivation of ACC deaminase caused by the action of 1-amino-2-methylenecyclopropane-1-carboxylate (methylene-ACC) (**3**) has also recently been reported[7]. Most likely these enzyme inhibitory effects of **1**−**3** are associated with the presence of the reactive methylenecyclopropane unit in these molecules[8][9]. Since the more highly strained cyclopropanated analogs of methylenecyclopropane (**4**), the unique tetrasubstituted alkene bicyclopropylidene (**5**)[10], as well as methylenespiropentane (**6**) are even more reactive than methylenecyclopropane (**4**), it is to be expected that analogs of the amino acids **1**−**3** containing bicyclopropylidenyl and methylenespiropentyl moieties would also exhibit biological activities. We therefore engaged ourselves in a program to prepare the whole series of such amino acids.



1 **2** **3**

4 **5** **6**

The most straightforward synthetic approach to the alanine derivatives containing a bicyclopropylidenyl (*rac*-**11**) and a methylenespiropentyl (*rac*-**17**) residue is essentially

[◇] Part 47: C. M. Williams, V. Chaplinski, A. de Meijere, *Tetrahedron Lett*. **1998**, *39*, 7695−7698; Part 48: C. Zorn, A. Goti, A. Brandi, K. Johnsen, M. Noltemeyer, S. I. Kozhushkov, A. de Meijere, *J. Org. Chem.*, in press.

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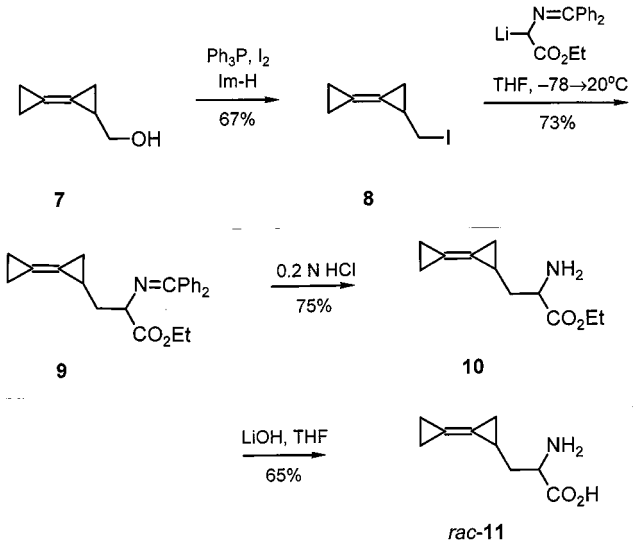
analogous to one that was recently used[5a] for the preparation of hypoglycine A (**1**). The starting materials bicyclopropylidenylmethanol (**7**)[11] and methylenespiropentylmethanol (**13**) were prepared from the parent hydrocarbons **5** and **6**, respectively, by deprotonation with butyllithium and subsequent reaction with an appropriate C_1 electrophile, as it has been reported for methylenecyclopropane (**4**)[10][12] and bicyclopropylidene (**5**)[13] (Schemes 1, 2). Direct deprotonation of methylenespiropentane (**6**) had never been probed before, yet treatment of **6** with butyllithium in THF solution at 0°C and subsequently with carbon dioxide gave 2-methylenespiropentanecarboxylic acid (**12**) in 65% yield, and **12** could easily be reduced to the primary alcohol **13**. The iodomethyl derivatives **8** and **14** were obtained from the corresponding alcohols **7**[14] and **13** by treatment with the triphenylphosphane-iodine-imidazole reagent[15] in 67 and 88% yield, respectively. The nucleophilic substitution on these primary iodides **8**, **14** with the lithium enolate of ethyl α-(diphenylmethyleneamino)acetate (O′Donnell′s glycine equivalent[16]) provided the protected alanine derivatives **9**, **15** in 73 and 85% yield, respectively. Deprotection of **9** and **15** in two steps led to the racemic free amino acids *rac*-**11** and *rac*-**17**, respectively, as 1.3:1 and 5:1 mixtures of diastereomers (Schemes 1, 2).

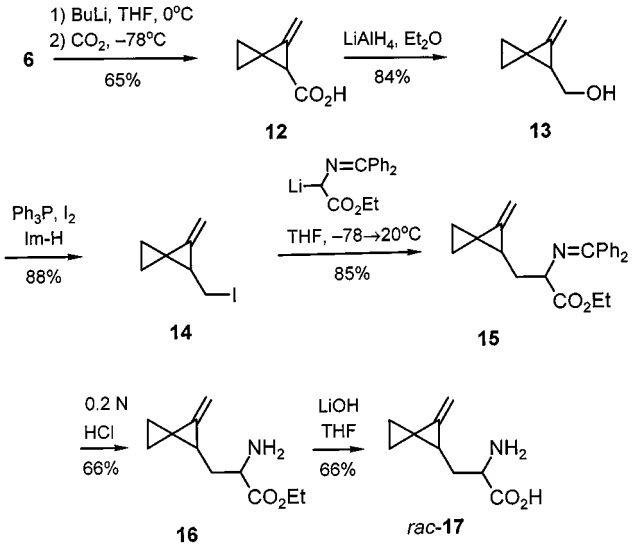
Scheme 1



The overall yields of *rac*-**11** and *rac*-**17** starting from the corresponding hydrocarbons **5** and **6** were 24 and 18%, respectively.

The *N*-methyl derivative *rac*-**22** of the amino acid *rac*-**11** could more easily be obtained by addition of bicyclopropylidenylmagnesium bromide **18** prepared from bicyclopropylidenyllithium by metal exchange with magnesium bromide, across the double bond of the Boc-protected α-(methylamino)acrylate **19**[17] under CuI catalysis[18] (Scheme 3) to the Boc-protected ester **20** as a 1.1:1 mixture of diastereomers. The α-(Boc-amino)acrylate without the methyl group at the nitrogen as in **19** did not react with **18** in the same way. At ambient temperature, each diastereomer of **20** exists as a 1:1 mixture of rotamers. ^{13}C-NMR measure-

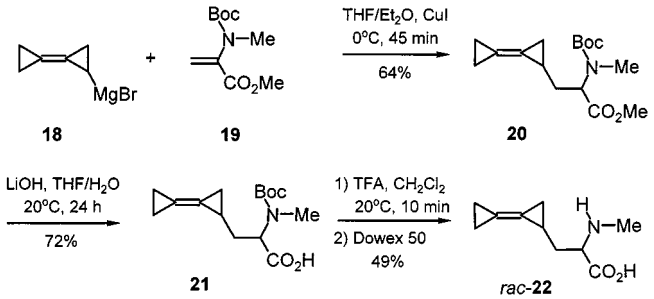
Scheme 2



ments of **20** in $C_2D_2Cl_4$ solution at elevated temperatures indicate a dynamic behavior with a strong temperature dependence of the carbon signals. Upon raising the temperature, fast exchange was observed for the signals of the quaternary carbon atom and the *N*-methyl groups already at +35°C; the coalescence of the signals of the *N*-CH carbons was observed at +75°C which corresponds to an estimated rotational barrier of $\Delta G^{\neq} = 17.1$ kcal mol^{-1}. All of the carbon signals were completely sharp only at +115°C and, upon cooling, the whole exchange phenomenon returned to the initial state[19][20].

Deprotection of **20** was easily achieved to give free amino acid *rac*-**22** in 23% overall yield as a 1.8:1 mixture of diastereomers.

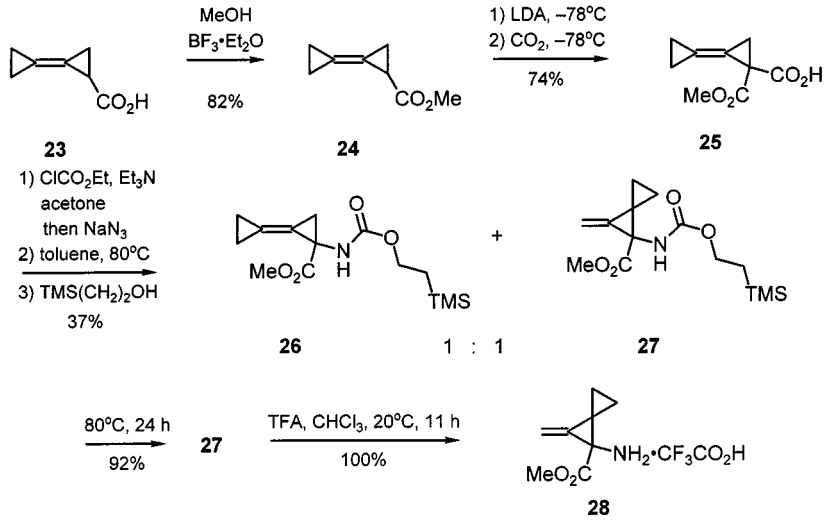
Scheme 3



Since the enolates of methylenecyclopropanecarboxylates[21] in contrast to the enolates of cyclopropanecarboxylates[22] can be generated and electrophilically substituted without complications, it appeared most straightforward to prepare the bicyclopropylidene and methylenespiropentane analogs of 1-amino-2-methylenecyclopropanecarboxylic acid **3** by Curtius degradation of appropriate 1,1-dicarboxylic acid half esters. Accordingly, in a first attempt, 1-methoxycarbonyl-bicyclopropylidene-1-carboxylic acid (**25**) was prepared by carboxylation of the lithium enolate generated from methyl bicyclopropylidene-1-carboxylate (**24**) with LDA. This acid **25** was converted to the azide

adopting established methodology[23], and the azide heated in toluene (80°C, 0.5 h). Surprisingly, the Curtius degradation under these conditions was accompanied by the well-known bicyclopropylidene to methylenespiropentane rearrangement[24] and gave, after quenching with trimethylsilylethanol, a 1:1 mixture of the bicyclopropylidene **26** and the methylenespiropentane carbamate **27** (Scheme 4). Extended heating of this mixture in benzene brought this rearrangement to completion and gave the carbamate **27** as a single product. Compound **27** appeared to be inert towards reagents commonly used for the removal of the 2-trimethylsilylethoxy group such as tetrabutylammonium fluoride[25a][25b] (50°C, 30 min), but reacted with trifluoroacetic acid[25c] to give the protected amino ester hydrotrifluoroacetate **28**. However, all attempts to prepare the corresponding completely deprotected amino acid only led to polymeric materials (cf.[26]).

Scheme 4



In order to permit deprotection in a single operation under milder conditions (cf. e.g.[27]), the combination of a *tert*-butyl ester and *N*-*tert*-butoxycarbonyl groups were considered. Esterification of bicyclopropylidenecarboxylic acid **23** with *tert*-butyl alcohol in the presence of dicyclohexylcarbodiimide (DCC) and 4-pyrrolidinopyridine[28] led to only 30% of the ester **33**. A far better approach to the *tert*-butyl ester **33** was achieved by treating the lithiated hydrocarbon **5** with di-*tert*-butyl pyrocarbonate (Boc_2O)[29] to give the corresponding ester **33** in 66% yield. With the same sequence, methylenecyclopropane (**4**) could be converted to the *tert*-butyl carboxylate **30** in 75% yield, but methylenespiropentane (**6**) gave the corresponding carboxylate in only 28% yield. This is probably due to steric interactions between the incoming electrophile and the spirocyclopropane moiety adjacent to the reacting center in the lithiated alkene **6** (cf.[30]). All three *tert*-butyl carboxylates **29**, **30**, and **33** could be deprotonated with lithium diisopropylamide and the resulting enolates carboxylated to the corresponding dicarboxylic acid mono-*tert*-butyl esters **31**, **32**, and **34**, respectively, in high yields (Scheme 5).

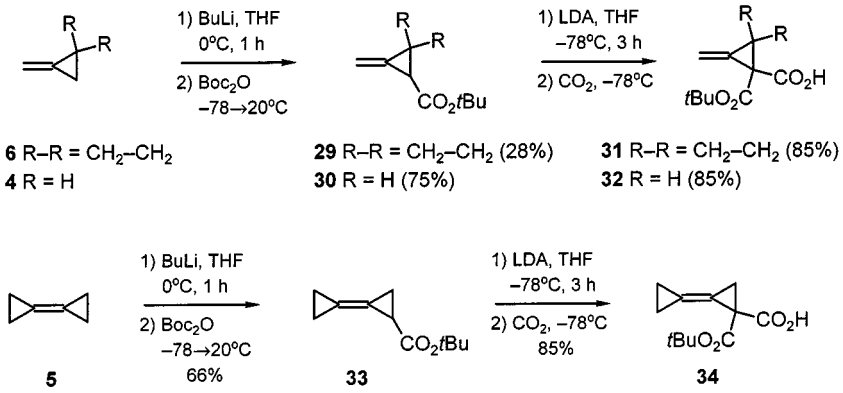
With the availability of the half esters **31** and **32** the protected amino acids **35** and **36** could easily be prepared applying the Jamada[31] modification for the Curtius degradation in *tert*-butyl alcohol (Scheme 6) with diphenylphosphoryl azide (DPPA)[32]. Again, the bicyclopropylidenecarboxylic acid azide derived from **34** upon the necessary extended heating (83°C, 12 h) led to the methylenespiropentane carbamate **35** as a single product (45% yield).

Photochemically induced Curtius degradation has also been reported[33]. The first attempt, in which the azide from the acid **34** was irradiated in *t*BuOH/toluene solution in a quartz tube with 150-W medium-pressure mercury lamp at 0°C for 3 h, did give the carbamate **38**, albeit in low yield (14%). Better conditions have not yet been found, e.g. no carbamate **38** was formed upon irradiation of the acid azide in hexane/*t*BuOH solution with pyrex-filtered light at 0°C.

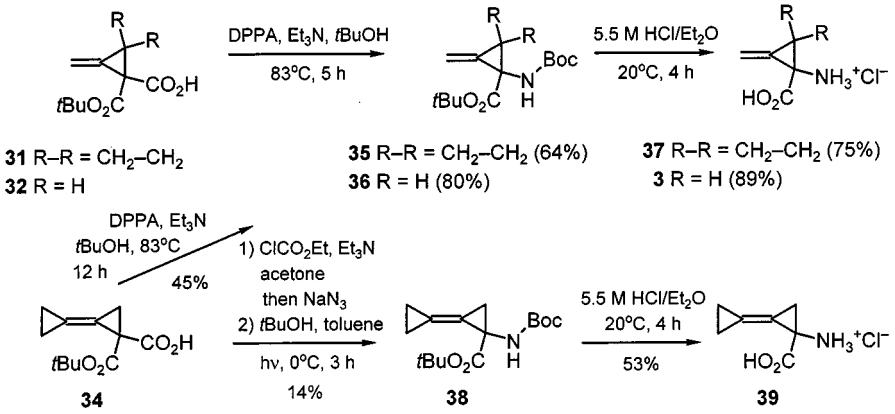
Both protecting groups could easily be removed from compounds **35**, **36**, and **38** by stirring them with a 5.5 M HCl solution in Et_2O at ambient temperature for 4 h. The precipitates which could be collected by simple filtration were the analytically pure hydrochlorides **3**, **37**, and **39**. Starting from methylenecyclopropane (**4**), amino acid **3** was thus prepared in four steps in 45% overall yield, i.e. far more efficiently than along the previously reported route with ten steps and 23% overall yield[7]. The aminomethylenespiropentanecarboxylic acid **37** was obtained in 19% overall yield starting from bicyclopropylidene (**5**) and 11% starting from methylenespiropentane (**6**). Only in the case of the aminobicyclopropylidenecarboxylic acid **39**, the overall yield was just 4% because of the poor efficiency of the photochemical Curtius degradation step.

In an attempt to improve the preparation of the bicyclopropylidene amino acid **39**, the possible Hofmann degradation of the amide **40**[34] under mild conditions was prob-

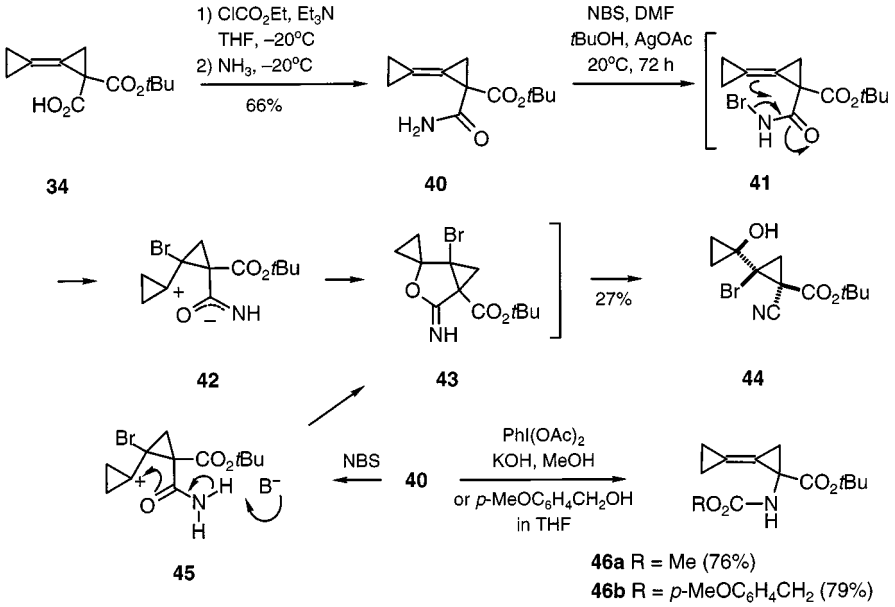
Scheme 5



Scheme 6



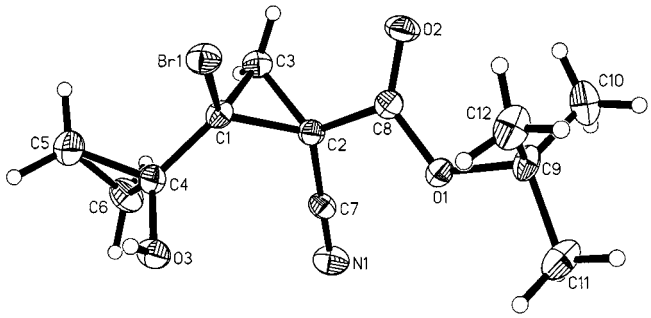
Scheme 7



ed. However, when the amide **40** was treated with *N*-bromosuccinimide in DMF/*t*BuOH mixture in the presence of silver acetate[35], no Hofmann degradation product, but only *tert*-butyl (*Z*)-1-bromo-1-(1-hydroxycyclopropyl)-2-cyanocyclopropane-2-carboxylate (**44**) was isolated in low yield (27%) (Scheme 7). Its structure was unequivocally established by X-ray crystal structure analysis (Figure 1). Mechanistically, formation of **44** can be rationalized by fragmentation of an intermediate bicyclic spirocyclopropanedihydrofuranoneimine **43**, which might have been formed via in-

tramolecular electrophilic bromine transposition from nitrogen to carbon in the typical *N*-bromocarboxamide intermediate and subsequent ring closure. Alternatively, an electrophilic intermolecular bromine transfer from NBS[36] to **40** could have produced the stabilized cyclopropyl cation intermediate **45**[37] which would end up as **44** after first cyclizing to **43**. It is an open question, why only oxygen and not nitrogen would attack at the cationic center in **42** or **45** to close the five-membered heterocycle.

Figure 1. Structure of *tert*-butyl (*Z*)-1-bromo-1-(1-hydroxycyclopropyl)-2-cyanocyclopropane-2-carboxylate (**44**) in the crystal



Under conditions which have recently been applied for the Hofmann degradation of another sensitive substrate[38], i.e. treatment of the amido ester **40** with bis(acetoxy)iodobenzene in a methanolic solution of potassium hydroxide, the carbamate **46a** was obtained in 76% yield (Scheme 7). Unfortunately, all attempts to cleave the methyl carbamate **46a**, even by treatment with lithium propylmercaptide[39] in HMPT, failed, and the analogous transformation of **40** in a solution of potassium *tert*-butoxide in a *t*BuOH/THF mixture gave only traces of the corresponding *tert*-butyl carbamate **38** which can be cleaved under acidic conditions. However, the *p*-methoxybenzyl carbamate **46b** which could be obtained in 79% yield by performing the transformation of **40** in a *p*-methoxybenzyl alcohol solution of potassium hydroxide, could cleanly be deprotected by treatment with 5.5 N hydrochloric acid in ether to give the amino acid hydrochloride **39** in 29% yield. The overall yield of **39** from **40** can be raised to 28% if the carbamate **46b** is not isolated.

In conclusion, bicyclopropylidenyl- (*rac*-**11**) and methylenespiropentylalanines (*rac*-**17**) as analogs of hypoglycine A (**1**) as well as bicyclopropylidene and methylenespiropentane analogs of 2-methylene-1-aminocyclopropanecarboxylic acid **3** can easily be obtained in racemic form along the described routes. With bicyclopropylidenecarboxylic acid (**23**) readily available in enantiomerically pure form by classical resolution[40], the enantiomerically pure alanine derivative **11** and possibly also **17** should be accessible by the same strategies (cf.[5a]). Unfortunately, the enolate of ethyl bicyclopropylidenecarboxylate is not configurationally stable (cf.[41]), and consequently complete racemization of the optically active ethyl ester of acid **23** was observed upon deprotonation with lithium diisopropylamide and subsequent carboxylation. Therefore, resolution of the half esters **31**, **32**, and **34** would be an appropriate approach to enantiomerically pure amino acids **3**, **37**, and **39**.

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Experimental Section

^{1}H- and ^{13}C-NMR spectra: at 250 (^{1}H), and 62.9 MHz [^{13}C, additional DEPT (Distortionless Enhancement by Polarization Transfer)] on a Bruker AM 250 instrument in $CDCl_3$ soln, if not otherwise specified, $CHCl_3/CDCl_3$ as internal reference. − High-temperature ^{13}C NMR: at 75.5 MHz on a Varian Unity 300 instrument in $C_2D_2Cl_4$, $C_2HDCl_4/C_2D_2Cl_4$ as internal reference. − FT-IR: Bruker IFS 66, measured as KBr pellets, or oils between NaCl plates. − MS (EI) and MS (HR-EI): Finnigan MAT 95 spectrometer (70 eV). MS (HR-EI): preselected ion peak matching at R >> 10000 to be within ±2 ppm of the exact masses. − CI-MS: with NH_3. − M.p.: Büchi 510 capillary melting point apparatus, uncorrected. − TLC: Macherey-Nagel precoated sheets, 0.25 mm Sil G/UV_{254}. − Column chromatography: Merck silica gel, grade 60, 230−400 mesh.

Starting Materials: Anhydrous *tert*-butyl alcohol was obtained by distillation from sodium *tert*-butoxide and anhydrous acetone by distillation from anhydrous potassium carbonate. Anhydrous diethyl ether and THF were obtained by distillation from sodium benzophenone ketyl. Other water-free solvents were prepared according to common methods[42]. Compounds **5**[43], **6**[44], **19**[17], DPPA[32] and bis(acetoxy)iodobenzene[45] were prepared according to published procedures. All other chemicals were used as commercially available. Organic extracts were dried over $MgSO_4$.

Crystal Structure Determination: The appropriate crystals of **44** had been obtained by slow evaporation of a dilute solution in hexane/diethyl ether. The light-yellow translucent plate-like crystal (0.52 × 0.26 × 0.03 mm) was chosen for the single-crystal X-ray analysis. At 120(1) K the crystal of **44** ($C_{12}H_{16}BrNO_3$, M = 302.17) is orthorhombic, space group $Pca2_1$, a = 12.0366(2), b = 10.6170(2), c = 10.7646(2); V = 1375.6(1), F(000) = 616, Z = 4, D_c = 1.459 Mg/m^{-3}, μ = 2.985 mm^{-1} (Mo-K_α, λ = 0.71073 Å). 13625 reflections (1.90 ≤ θ ≤ 30.4°) were collected on a Siemens SMART-CCD diffractometer (ω-scan, 0.3°/frame) yielding 3780 unique data (R_{merg} = 0.048). The structure was solved by direct methods and refined by full-matrix least squares on F^2 for all data using SHELXL software. All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms were located on the difference map and refined isotropically. Final w$R_2(F^2)$ = 0.0615 for all data (218 refined parameters), conventional $R(F)$ = 0.0305 for 3125 reflections with $I \geq 2\sigma$, GOF = 1.013. The absolute configuration was determined by refinement of Flack's parameter [x = 0.022(8)][46].

(2-Methylenespiropentane-1-carboxylic Acid (**12**): *n*BuLi (50 mmol, 19.5 ml of a 2.57 M solution in hexane) and methylenespiropentane (**6**) (4.01 g, 50 mmol) were mixed in THF (100 ml) at −78°C. After stirring at 0°C for 1 h, the solution was cooled to −78°C, and an excess of powdered dry ice was added in one portion. The mixture was allowed to warm to 20°C and extracted with ice-cold 2 N NaOH solution (50 ml). The aqueous phase was washed with Et_2O (50 ml), acidified to pH 2 with 12 N HCl solution at 5°C and extracted with Et_2O (4 × 40 ml). The combined organic phases were dried and concentrated under reduced pressure to give

4.06 g (65%) of the acid **12** as an oil. − ^{1}H NMR ($CDCl_3$): δ = 1.25−1.39 (m, 4 H, Cpr), 2.44 (br. s, 1 H, Cpr), 5.27 (d, *J* = 2.1 Hz, 1 H, =CH_2), 5.42 (d, *J* = 1.1 Hz, 1 H, =CH_2), 10.95 (s, 1 H, OH). − ^{13}C NMR ($CDCl_3$): δ = 10.31, 11.68, 100.31 (CH_2), 24.17 (CH), 18.95, 134.53, 178.84 (C). − MS (CI), *m/z* (%): 142 (45) [M^+ + NH_4], 125 (100) [M^+ + H].

(2-Methylenespiropentyl)methanol (**13**)[14]: A solution of compound **12** (4.00 g, 32.2 mmol) in Et_2O (15 ml) was added dropwise to a suspension of $LiAlH_4$ (1.01 g, 26.6 mmol) in Et_2O (100 ml). After 2 h under reflux, quenching with Na_2SO_4 sat. solution and the usual work-up, 3.00 g (84%) of **13** was obtained. − ^{1}H NMR ($CDCl_3$): δ = 0.92−1.13 (m, 2 H, Cpr), 1.14−1.22 (m, 2 H, Cpr), 1.93 (br. t, *J* = 6.5 Hz, 1 H, Cpr), 2.55 (br. s, 1 H, OH), 3.53−3.68 (m, 2 H, OCH_2), 5.11 (d, *J* = 1.9 Hz, 1 H, =CH_2), 5.32 (br. s, 1 H, =CH_2). − ^{13}C NMR ($CDCl_3$): δ = 7.57, 9.75, 64.60, 99.18 (CH_2), 22.61 (CH), 15.39, 138.90 (C).

Preparation of Iodides. General Procedure (GP) 1: Iodine (5.07 g, 20 mmol) was added in small portions over a period of 30 min to an efficiently cooled (0°C) solution of the appropriate alcohol (10.1 mmol), Ph_3P (4.71 g, 18 mmol), and imidazole (1.29 g, 18.9 mmol) in a mixture of anhydrous MeCN (20 ml) and Et_2O (30 ml). Stirring was continued for 2 h at 0°C, and the reaction mixture was diluted with Et_2O (150 ml) and washed with 20% $Na_2S_2O_3$ solution (2 × 100 ml), brine (100 ml), dried, and concentrated under reduced pressure. The residue was thoroughly extracted with hexane (100 ml) by vigorous stirring for 1 h in the dark, filtered and concentrated under reduced pressure. The residue was used immediately without further purification or stored at −78°C. Chromatographic purification led to the product of practically the same quality but in essentially lower yield.

(Iodomethyl)bicyclopropylidene (**8**): From (bicyclopropylidenyl)methanol (**7**)[11] (1.110 g, 10.1 mmol), 1.481 g (67%) of iodide **8** was obtained according to GP1. − ^{1}H NMR ($CDCl_3$): δ = 0.97−1.04 (m, 1 H, Cpr), 1.15−1.26 (m, 4 H, Cpr), 1.57−1.64 (m, 1 H, Cpr), 2.02−2.08 (m, 1 H, Cpr), 3.07 (dd, *J* = 8.9, 9.7 Hz, 1 H, CH_2I), 3.39 (dd, *J* = 6.4, 9.7 Hz, 1 H, CH_2I). − ^{13}C NMR ($CDCl_3$): δ = 2.91, 3.45, 10.79, 14.38 (CH_2), 20.01 (CH), 111.78, 117.23 (C).

1-Iodomethyl-2-methylenespiropentane (**14**): From (2-methylenespiropentyl)methanol (**13**) (3.00 g, 27.2 mmol), I_2 (13.28 g, 52.3 mmol), Ph_3P (12.34 g, 47.0 mmol), and imidazole (3.37 g, 49.5 mmol), 5.24 g (88%) of iodide **14** was obtained according to GP1. − ^{1}H NMR ($CDCl_3$): δ = 0.87−0.94 (m, 1 H, Cpr), 1.09−1.17 (m, 1 H, Cpr), 1.20−1.29 (m, 1 H, Cpr), 1.41−1.48 (m, 1 H, Cpr), 2.14−2.21 (m, 1 H, Cpr), 3.07 (dd, *J* = 6.1, 9.4 Hz, 1 H, CH_2I), 3.37 (dd, *J* = 9.4, 9.4 Hz, 1 H, CH_2I), 5.06 (d, *J* = 2.0 Hz, 1 H, = CH_2), 5.39 (br. s, 1 H, =CH_2). − ^{13}C NMR ($CDCl_3$): δ = 6.15, 9.04, 10.75, 98.68 (CH_2), 23.30 (CH), 19.52, 141.43 (C). − MS (CI), *m/z* (%): 255 (100) [M^+ + NH_4 + NH_3].

Coupling of Iodides **8**, **14** *with Ethyl N-(Diphenylmethylene)glycinate. General Procedure (GP) 2*: To a stirred solution of lithium diisopropylamide (LDA), prepared from *n*BuLi (7 mmol, 2.93 ml of a 2.39 M solution in hexane) and diisopropylamine (0.721 g, 1.00 ml, 7.13 mmol) in anhydrous THF (40 ml), a solution of ethyl *N*-(diphenylmethylene)glycinate[16] (1.800 g, 6.73 mmol) in THF (10 ml) was added dropwise at −78°C over a period of 1 h. After stirring for an additional 1 h at this temp., a solution of iodide (6.73 mmol) in THF (10 ml) was added to the suspension of the lithio compound at the same temperature within 15 min. The mixture was stirred for 24 h at −78°C, then allowed to warm to 20°C over a period of 48 h and poured into ice-cold water (100 ml). After extraction with diethyl ether (3 × 100 ml), the combined organic layers were washed with H_2O (2 × 100 ml), brine (100 ml), dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel deactivated with triethylamine (60 g of silica gel, 3 × 25 cm column, hexane/EtOAc, 3:1).

Ethyl β-Bicyclopropylidenyl-N-(diphenylmethylene)-d,l-alaninate (**9**): From iodide **8** (1.481 g, 6.73 mmol), 1.774 g (73%) of compound **9** was obtained according to GP2 as a 1.3:1 mixture of diastereomers (oil), R_f = 0.48. − IR: ṽ = 3055 cm^{-1}, 2979, 1738, 1623, 1446, 1378, 1180, 1073, 696. − ^{1}H NMR ($CDCl_3$): δ = 0.65−1.17 (m, 4 H, Cpr), 1.19−1.22 (m, 5 H, Cpr, CH_3), 1.38−1.48 (m, 1 H, Cpr), 1.88−1.97 (m, 2 H, CH_2), 4.10−4.18 (m, 3 H, CH, OCH_2), 7.14−7.57 (m, 10 H, 2 Ph). − ^{13}C NMR ($CDCl_3$, major diastereomer): δ = 14.21 (CH_3), 2.63, 2.96, 9.78, 37.27, 60.81 (CH_2), 13.03, 65.92, 127.92, 128.00, 128.25, 128.38, 128.45, 128.51, 128.61, 128.82, 130.04, 130.27 (CH), 110.18, 114.84, 136.51, 139.57, 170.36, 172.11 (C). − ^{13}C NMR ($CDCl_3$, minor diastereomer): δ = 2.84, 2.96, 9.87, 37.44, 60.87 (CH_2), 13.16, 66.01 (CH), 110.56, 114.97 (C), the other signals coincide with those of the major diastereomer. − MS (CI), *m/z* (%): 360 (100) [M^+ + H]. − $C_{24}H_{25}NO_2$ (359.5): calcd. C 80.20, H 7.01; found C 80.05, H 7.00.

Ethyl N-Diphenylmethylene-β-(2-methylenespiropentyl)-d,l-alaninate (**15**): From iodide **14** (3.476 g, 15.8 mmol), *n*BuLi (15.8 mmol, 6.61 ml of a 2.39 M solution in hexane), *i*Pr_2NH (1.660 g, 2.30 ml, 16.4 mmol), and ethyl *N*-(diphenylmethylene)glycinate (4.237 g, 15.8 mmol), 4.810 g (85%) of compound **15** was obtained according to GP2 after column chromatography (175 g of deactivated silica gel, 7 × 20 cm column) as a 3:1 mixture of diastereomers (oil), R_f = 0.53. − IR: ṽ = 3063 cm^{-1}, 2990, 1738, 1623, 1446, 1277, 1179, 1030, 875, 697. − ^{1}H NMR ($CDCl_3$): δ = 0.82−1.06 (m, 3 H, Cpr), 1.18−1.29 (m, 4 H, Cpr, CH_3), 1.61−1.66 (m, 1 H, Cpr), 2.01−2.13 (m, 2 H, CH_2), 4.13−4.24 (m, 3 H, CH, OCH_2), [4.94 (d, *J* = 1.8 Hz, 1 H, =CH_2), 4.99 (s, 1 H, CH_2), minor diastereomer], [5.03 (d, *J* = 1.8 Hz, 1 H, =CH_2), 5.15 (s, 1 H, CH_2), major diastereomer], 7.19−7.71 (m, 10 H, 2 Ph). − ^{13}C NMR ($CDCl_3$, major diastereomer): δ = 14.00 (CH_3), 7.31, 10.00, 35.76, 60.57, 98.33 (CH_2), 17.39, 65.17, 127.27, 127.63, 127.81, 128.05, 128.23, 128.43, 128.55, 128.62, 130.09, 132.18 (CH), 15.84, 136.16, 139.26, 141.18, 169.93, 171.76 (C). − ^{13}C NMR ($CDCl_3$, minor diastereomer): δ = 7.73, 10.12, 35.49, 98.02 (CH_2), 17.52, 65.59 (CH), 16.04, 170.08 (C), the other signals coincide with those of the major diastereomer. − MS (CI), *m/z* (%): 360 (100) [M^+ + H]. − $C_{24}H_{25}NO_2$ (359.5): calcd. C 80.20, H 7.01; found C 77.89, H 7.10.

Deprotection of Alaninates **9**, **15**. *General Procedure (GP) 3*: The suspension of protected alaninate **9** or **15** (1 mmol) in 0.2 N HCl solution (200 ml) was intensively stirred for 72 h at room temp. in the dark and then washed with Et_2O (3 × 80 ml). The water layer was brought to pH 8 with conc. NH_4OH solution and extracted with Et_2O (3 × 80 ml). The combined organic layers were dried and concentrated under reduced pressure to give ethyl alaninates **10**, **16** as oils. The latter were dissolved in a THF/H_2O mixture (3:1, 40 ml) and vigorously stirred at room temp. for 24 h with LiOH (1 equiv.). The mixture was concentrated under reduced pressure and brought to pH 2 with 0.2 N HCl solution. Subsequent concentration of the solution, filtration through a Dowex-50 (3 × 20 cm column, eluent 0.9 N NH_4OH), repeated concentration and recrystallization from *n*PrOH/H_2O (0°C, 48 h) gave amino acids **11**, **17** as colorless crystals.

Ethyl β-(Bicyclopropylidenyl)-d,l-alaninate (**10**): From imine **9** (1.774 g, 4.94 mmol), 0.723 g (75%) of compound **10** was obtained according to GP3 as a 1.4:1 mixture of diastereomers. − IR: ṽ =

3381 cm^{-1}, 2978, 1734, 1445, 1368, 1190, 1027. – ^1H NMR ($CDCl_3$): δ = 0.87–0.90 (m, 1 H, Cpr), 1.15 (br. s, 4 H, Cpr), 1.23 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.35–1.37 (m, 1 H, Cpr), 1.52–1.62 (m, 1 H, Cpr), 1.79–1.91 (m, 2 H, CH_2), 3.52–3.57 (m, 1 H, CH), [4.13 (q, *J* = 7.1 Hz, 2 H, OCH_2), minor diastereomer], [4.15 (q, *J* = 7.1 Hz, 2 H, OCH_2), major diastereomer]. – ^{13}C NMR ($CDCl_3$, major diastereomer): δ = 14.07 (CH_3), 2.53, 2.83, 9.41, 37.75, 60.68 (CH_2), 11.95, 54.52 (CH), 110.72, 114.31, 175.48 (C). – ^{13}C NMR ($CDCl_3$, minor diastereomer): δ = 2.62, 9.64, 38.34 (CH_2), 12.88, 54.83 (CH), 114.50 (C), the other signals coincide with those of the major diastereomer.

Ethyl β-(2-Methylenespiropentyl)-d,l-alaninate (**16**): From imine **15** (3.200 g, 8.9 mmol), 1.148 g (66%) of compound **16** was obtained according to GP3 as a 5:1 mixture of diastereomers. – IR: $\tilde{\nu}$ = 3383 cm^{-1}, 2990, 1734, 1616, 1446, 1379, 1189, 1031, 847. – ^1H NMR ($CDCl_3$, major diastereomer): δ = 0.78–0.91 (m, 1 H, Cpr), 0.93–1.12 (m, 3 H, Cpr), 1.19 (t, *J* = 7.8 Hz, 3 H, CH_3), 1.50–1.69 (m, 1 H, Cpr), 1.71–1.89 (m, 2 H, CH_2), 3.45–3.49 (m, 1 H, CH), 4.01–4.14 (m, 2 H, OCH_2), 5.01 (d, *J* = 2.0 Hz, 1 H, $=CH_2$), 5.22 (br. s, 1 H, CH_2). – ^{13}C NMR ($CDCl_3$, major diastereomer): δ = 13.90 (CH_3), 7.45, 10.01, 36.86, 60.44, 98.49 (CH_2), 16.99, 54.01 (CH), 15.94, 140.85, 175.59 (C).

β-Bicyclopropylidenyl-d,l-alanine (**11**): From ester **10** (0.723 g, 3.7 mmol), 0.403 g (65%) of compound **11** was obtained according to GP3 as a 1.3:1 mixture of diastereomers, m. p. 234°C (dec.). – IR: $\tilde{\nu}$ = 3440 cm^{-1}, 2978, 1653, 1582, 1413, 1346, 1319, 1153, 929. – ^1H NMR (D_2O): δ = 0.75–0.85 (m, 1 H, Cpr), 1.00 (br. s, 4 H, Cpr), 1.24–1.44 (m, 1 H, Cpr), 1.49–1.63 (m, 2 H, CH_2), 1.86–2.02 (m, 1 H, Cpr), 3.59–3.64 (m, 1 H, CH). – ^{13}C NMR (D_2O, major diastereomer): δ = 3.48, 3.83, 10.19, 35.11 (CH_2), 12.39, 56.49 (CH), 113.28, 114.83, 175.80 (C). – ^{13}C NMR (D_2O, minor diastereomer): δ = 3.63, 3.94, 10.70, 35.45 (CH_2), 13.11, 56.62 (CH), 113.28, 114.98, 175.80 (C). – MS (CI), *m/z* (%): 185 (40) [$M^+ + NH_4$], 168 (100) [$M^+ + H$]. – $C_9H_{13}NO_2$ (167.2): calcd. C 64.64, H 7.84, N 8.38; found C 64.78, H 7.94, N 8.48.

β-(2-Methylenespiropentyl)-d,l-alanine (**17**): From ester **16** (1.148 g, 5.9 mmol), 0.653 g (66%) of compound **17** was obtained according to GP3 as a 5:1 mixture of diastereomers, m. p. 220°C (dec.). – IR: $\tilde{\nu}$ = 3400 cm^{-1}, 3070, 2995, 2956, 1619, 1593, 1499, 1411, 1324, 1289, 878. – ^1H NMR (D_2O): δ = 0.65–1.10 (m, 4 H, Cpr), 1.50–1.63 (m, 2 H, CH_2), 1.86–1.92 (m, 1 H, Cpr), 3.54–3.56 (m, 1 H, CH), 4.99 (br. s, 1 H, $=CH_2$), 5.16 (br. s, 1 H, CH_2). – ^{13}C NMR (D_2O, major diastereomer): δ = 8.14, 10.75, 33.81, 99.85 (CH_2), 16.75, 55.51 (CH), 16.64, 141.78, 175.24 (C). – MS (CI), *m/z* (%): 185 (35) [$M^+ + NH_4$], 168 (100) [$M^+ + H$]. – $C_9H_{13}NO_2$ (167.2): calcd. C 64.64, H 7.84, N 8.38; found C 64.53, H 7.84, N 8.33.

Methyl N-Methyl-N-tert-butoxycarbonyl-β-(bicyclopropylidenyl)-d,l-alaninate (**20**): *n*BuLi (44.66 mmol, 30.8 ml of a 1.45 M solution in hexane) and bicyclopropylidene (**5**) (3.570 g, 4.18 ml, 44.6 mmol) were mixed in THF (100 ml) at −78°C. After stirring at 0°C for 1 h, the solution was cooled to −78°C, and a solution of anhydrous $MgBr_2$ freshly prepared from Mg (1.087 g, 44.71 mmol) and 1,2-dibromoethane (8.398 g, 3.85 ml, 44.7 mmol) in Et_2O (30 ml) was added in one portion. The resulting solution was allowed to warm to room temp. and, after additional stirring at this temp. for 20 min, recooled again to −78°C. CuI (430 mg, 2.26 mmol) and anhydrous benzene (40 ml) were added, and the mixture was allowed to warm to 0°C and then stirred for 10 min at this temp. A solution of protected enamine **19** (4.811 g, 22.35 mmol) in Et_2O (20 ml) was added over a period of 20 min at the same temp. After additional stirring for 45 min, the mixture was poured into ice-cold sat. NH_4Cl solution (200 ml) and extracted with Et_2O (2 × 100 ml). The combined organic phases were dried and concentrated under reduced pressure. Column chromatography (100 g of silica gel, 40 × 4 cm column, hexane/Et_2O 4:1) gave 4.208 g (64%) of **20** as a 1.1:1 mixture of diastereomers (oil), R_f = 0.42. – IR: $\tilde{\nu}$ = 2977 cm^{-1}, 1745, 1699, 1480, 1435, 1391, 1367, 1323, 1152, 870, 774. – ^1H NMR: δ = 0.75–0.88 (m, 1 H, Cpr), 1.06–1.12 (m, 4 H, Cpr), 1.18–1.45 (m, 1 H, Cpr), [1.33 (s, major diastereomer), 1.37 (s, minor diastereomer) (9 H, 3 CH_3)], [1.58–1.70 (m), 1.73–1.87 (m), 1.92–2.04 (m) (3 H, CH_2, Cpr)], [2.72 (s), 2.77 (s), 2.79 (s), 2.88 (s) (3 H, NCH_3)], 3.60 (s, 3 H, OCH_3), [4.16 (dd, *J* = 10.6, 4.2 Hz), 4.36 (dd, *J* = 9.1, 5.8 Hz), 4.59 (dd, *J* = 10.1, 5.2 Hz), 4.76 (dd, *J* = 9.0, 5.8 Hz) (1 H, CH)]. – ^{13}C NMR ($C_2D_2Cl_4$, 115°C, major diastereomer): δ = 28.17 (3 CH_3), 31.38, 51.28 (CH_3), 2.48, 2.87, 9.48, 32.86 (CH_2), 13.29, 59.35 (CH), 79.62, 110.74, 114.94, 155.43, 171.80 (C). – ^{13}C NMR ($C_2D_2Cl_4$, 115°C, minor diastereomer): δ = 28.19 (3 CH_3), 32.13, 51.28 (CH_3), 2.54, 2.90, 9.67, 32.13 (CH_2), 13.22, 59.97 (CH), 79.65, 110.69, 114.61, 155.51, 171.76 (C). – MS (HR-EI): 295.1783 ($C_{16}H_{25}NO_4$, calcd. 295.1783). – $C_{16}H_{25}NO_4$ (295.4): calcd. C 65.06, H 8.53; found C 65.36, H 8.75.

N-Methyl-N-tert-butoxycarbonyl-β-bicyclopropylidenyl-d,l-alanine (**21**): The ester **20** (4.014 g, 13.58 mmol) was treated with $LiOH·H_2O$ (570 mg, 13.59 mmol) in a THF/H_2O mixture (3:1, 160 ml) according to GP3, but after the acidification the water phase was extracted with EtOAc (3 × 50 ml), the combined organic layers were dried and concentrated. Compound **21** (2.735 g, 72%) was obtained as a 1.3:1 mixture of diastereomers after column chromatography (50 g of silica gel, 15 × 3 cm column, hexane/EtOAc, 1:1), R_f = 0.29, m. p. 25°C. – IR: $\tilde{\nu}$ = 3550 cm^{-1}, 2979, 1695, 1480, 1392, 1154, 738. – ^1H NMR: δ = 0.80–0.92 (m, 1 H, Cpr), 1.05–1.18 (m, 4 H, Cpr), 1.19–1.29 (m, 1 H, Cpr), [1.43 (s, major diastereomer), 1.45 (s, minor diastereomer) (9 H, 3 CH_3)], 1.50–2.08 (m, 3 H, CH_2, Cpr), [2.77 (s), 2.83 (s), 2.88 (s), 2.97 (s) (3 H, NCH_3)], [4.32 (m), 4.49 (m), 4.63 (m), 4.82 (m) (1 H, CH)], 9.76 (br. s, 1 H, OH). – ^{13}C NMR: δ = 28.30 (3 CH_3), 31.14, 31.51, 32.25, 32.68 (CH_3), 2.60, 2.73, 2.89, 3.15, 9.47, 10.03, 32.00, 32.66, 33.23 (CH_2), 9.47, 10.03, 58.64, 59.74, 59.90, 60.89 (CH), 80.42, 80.55, 80.73, 110.70, 110.72, 113.91, 114.40, 155.39, 156.25, 176.81, 176.92, 177.17 (C). The other carbon signals of four rotamers are indistinguishable. – MS (CI), *m/z* (%): 299 (100) [$M^+ + NH_4$], 277 (72), 255 (28), 238 (28), 188 (52), 149 (60). – MS (HR-EI): 281.1627 ($C_{15}H_{23}NO_4$, calcd. 281.1627).

N-Methyl-β-bicyclopropylidenyl-d,l-alanine (**22**): A solution of the protected amino acid **21** (2.735 g, 9.7 mmol) in anhydrous dichloromethane (30 ml) was treated with CF_3COOH (50 ml) at room temperature for 10 min. The dark solution was concentrated under reduced pressure, taken up with water (5 ml) and filtered through Dowex-50 (3 × 20 cm column, eluent 0.9 N NH_4OH). Repeated concentration gave amino acid **22** (0.867 g, 49%) as a colorless powder as a 1.8:1 mixture of diastereomers. The analytical sample was recrystallized from acetone/H_2O, m. p. 190°C (decomp.). – IR: $\tilde{\nu}$ = 3419 cm^{-1}, 2957, 2859, 1586, 1471, 1398, 1315, 1141, 1072, 959, 842, 668. – ^1H NMR (D_2O): δ = 0.50–0.61 (m, 1 H, Cpr, major diastereomer), 0.61–0.82 (m, 1 H, Cpr, minor diastereomer), 0.95 (br. s, 4 H, Cpr, major diastereomer), 1.04 (br. s, 4 H, Cpr, minor diastereomer), 1.15–1.41 (m, 2 H, Cpr), 1.50–1.91 (m, 2 H, CH_2), 2.50 (s, 3 H, NCH_3), 3.20–3.49 (m, 1 H, CH). – ^{13}C NMR (D_2O, major diastereomer): δ = 33.04 (CH_3), 3.27, 3.61, 10.28, 34.00 (CH_2), 12.14, 64.84 (CH), 113.03, 114.22, 174.37 (C). – ^{13}C NMR (D_2O, minor diastereomer): δ = 34.28 (CH_3), 3.29, 3.58, 10.28, 34.23 (CH_2), 11.75, 65.00 (CH), 113.00, 114.42, 176.98 (C). – MS (CI), *m/z* (%): 199 (10) [$M^+ + NH_4$], 182 (40) [$M^+ + H$],

160 (100), 138 (38), 114 (42). − $C_{10}H_{15}NO_2$ (181.2): calcd. C 66.27, H 8.34, N 7.73; found C 64.69, H 8.19, N 7.95.

Methyl Bicyclopropylidenecarboxylate (**24**): The acid **23**[13] (4.93 g, 39.7 mmol) was treated with $BF_3 \cdot Et_2O$ (4 ml) in anhydrous MeOH (50 ml) to give the ester **24** (4.560 g, 82%) according to the protocol of Kadaba[47], b. p. 30°C (0.1 Torr). − ^{1}H NMR: δ = 1.10−1.28 (m, 4 H, Cpr), 1.65−1.75 (m, 1 H, Cpr), 1.77−1.95 (m, 1 H, Cpr), 2.27−2.38 (m, 1 H, Cpr), 3.66 (s, 3 H, CH_3). − ^{13}C NMR: δ = 51.74 (CH_3), 3.38, 3.59, 11.83 (CH_2), 18.06 (CH), 110.79, 112.56, 173.02 (C).

Preparation of tert-Butyl Methylenecyclopropanecarboxylates **29**, **30**, *and* **33**. *General Procedure (GP) 4:* *n*BuLi (71.9 mmol, 25.4 ml of a 2.83 M solution in hexane) and methylenespiropentanes **4**, **5,** or **6** (72 mmol) were mixed in THF (100 ml) at −78°C. After stirring at 0°C for 1 h, the solution was transferred by cannula into the precooled (−78°C) solution of di-*tert*-butyl pyrocarbonate (15.0 g, 68.7 mmol) over a period of 30 min. After the additional stirring for 30 min at this temp., the mixture was allowed to warm to 20°C and then poured into ice-cold water. The aqueous phase was extracted with Et_2O (2 × 50 ml), the combined organic phases were washed with brine (100 ml), dried, concentrated under reduced pressure, and distilled under reduced pressure.

tert-Butyl 2-Methylenespiropentane-1-carboxylate (**29**): From methylenespiropentane (**6**) (5.770 g, 72 mmol), 3.579 g (28%) of the ester **29** was obtained according to GP4, b. p. 49−51°C (0.6 Torr). − ^{1}H NMR: δ = 1.25−1.33 (m, 4 H, Cpr), 1.42 (s, 9 H, 3 CH_3), 2.35 (br. s, 1 H, Cpr), 5.20 (d, *J* = 2.3 Hz, 1 H, =CH_2), 5.37 (br. s, 1 H, =CH_2). − ^{13}C NMR: δ = 28.12 (3 CH_3), 9.94, 11.32, 99.54 (CH_2), 25.19 (CH), 17.87, 80.42, 135.33, 171.22 (C). − MS (CI), *m/z* (%): 215 (32) [$M^+ + NH_4 + NH_3$], 198 (100) [$M^+ + NH_4$].

tert-Butyl 2-Methylenecyclopropane-1-carboxylate (**30**): From methylenecyclopropane (**4**) (1.623 g, 1.91 ml, 30 mmol), *n*BuLi (24 mmol, 15.6 ml of a 1.54 M solution in hexane), and di-*tert*-butyl pyrocarbonate (5.0 g, 22.9 mmol), 2.632 g (75%) of the ester **30** was obtained according to GP4, b. p. 45−47°C (6 Torr). − IR: $\tilde{\nu}$ = 2981 cm^{-1}, 2934, 1717, 1479, 1457, 1393, 1369, 1345, 1305, 1257, 1206, 1155, 1109, 1084, 1021, 965, 910, 844, 809, 734, 649. − ^{1}H NMR: δ = 1.42 (s, 9 H, 3 CH_3), 1.50 (dddd, *J* = 9.1, 8.5, 2.7, 2.3 Hz, 1 H, Cpr), 1.71 (dddd, *J* = 9.1, 4.8, 2.7, 2.2 Hz, 1 H, Cpr), 2.14 (dddd, *J* = 8.5, 2.8, 2.4, 1.7 Hz, 1 H, Cpr), 5.44−5.48 (m, 2 H, =CH_2). − ^{13}C NMR: δ = 27.93 (3 CH_3), 11.00, 103.98 (CH_2), 19.02 (CH), 80.50, 130.54, 171.13 (C). − MS (CI), *m/z* (%): 189 (8) [$M^+ + NH_4 + NH_3$], 172 (100) [$M^+ + NH_4$], 155 (12) [$M^+ + H$].

tert-Butyl Bicyclopropylidenecarboxylate (**33**): 1) From bicyclopropylidene (**5**) (5.770 g, 6.76 ml, 72 mmol), 8.556 g (66%) of the ester **33** was obtained according to GP4, b. p. 59°C (0.6 Torr). − IR: $\tilde{\nu}$ = 2980 cm^{-1}, 1725, 1368, 1244, 1149, 1071, 845. − ^{1}H NMR: δ = 1.05−1.22 (m, 4 H, Cpr), 1.40 (s, 9 H, 3 CH_3), 1.57−1.65 (m, 1 H, Cpr), 1.76−1.79 (m, 1 H, Cpr), 2.19−2.24 (m, 1 H, Cpr). − ^{13}C NMR: δ = 27.96 (3 CH_3), 3.18, 3.43, 11.27 (CH_2), 19.19 (CH), 80.40, 111.19, 111.68, 171.70 (C). − MS (CI), *m/z* (%): 215 (100) [$M^+ + NH_4 + NH_3$], 198 (90) [$M^+ + NH_4$].

2) A mixture of the acid **23**[13] (11.175 g, 90 mmol), dicyclohexylcarbodiimide (DCC) (20.425 g, 99 mmol), *tert*-butanol (7.338 g, 9.78 ml, 99 mmol), and 4-pyrrolidinopyridine (10 mmol, 1.482 g) in anhydrous Et_2O (250 ml) was intensively stirred at ambient temp. for 24 h and then filtered. The ethereal solution was washed with water (3 × 150 ml), 5% solution of acetic acid (3 × 150 ml) and again with water (3 × 150 ml), dried, concentrated under reduced pressure, and distilled in vacuum to give 4.930 g (30%) of the ester **33**.

Preparation of 1-Alkoxycarbonylmethylenecyclopropane-1-carboxylic Acids **25**, **31**, **32** *and* **34**. *General Procedure (GP) 5:* To a stirred solution of lithium diisopropylamide (LDA), prepared from *n*BuLi (52.4 mmol) and diisopropylamine (55 mmol) in anhydrous THF (150 ml), a solution of the ester **24**, **29**, **30**, or **33** (50 mmol) in THF (50 ml) was added dropwise at −78°C over a period of 1 h. After additional stirring for 3 h at this temp., an excess of powdered dry ice was added in one portion. The mixture was allowed to warm to 20°C, concentrated under reduced pressure and extracted with ice-cold 2 N NaOH solution (100 ml). The aqueous phase was washed with Et_2O (100 ml), acidified to pH 2 with 12 N HCl solution at 5°C, and extracted with Et_2O (4 × 100 ml). The combined organic phases were dried and concentrated under reduced pressure.

1-Methoxycarbonylbicyclopropylidene-1-carboxylic Acid (**25**): From methyl bicyclopropylidenecarboxylate (**24**) (7.735 g, 56.0 mmol), *n*BuLi (59.1 mmol, 23 ml of a 2.57 M solution in hexane), and *i*Pr_2NH (5.99 g, 8.30 ml, 59.2 mmol), 8.29 g (81%) of the acid **25** was obtained according to GP5 as an oil. Column chromatography (120 g of silica gel, 40 × 4 cm column, Et_2O) gave 7.60 g (74%) of **25** of essentially the same quality, R_f = 0.52. − IR: $\tilde{\nu}$ = 3481 cm^{-1}, 2956, 1735, 1439, 1309, 1248, 1127, 915, 733. − ^{1}H NMR: δ = 1.17−1.42 (m, 4 H, Cpr), 2.55−2.69 (m, 2 H, Cpr), 3.74 (s, 3 H, OCH_3), 11.11 (br. s, 1 H, OH). − ^{13}C NMR: δ = 53.27 (CH_3), 3.90, 4.55, 21.70 (CH_2), 29.94, 112.82, 114.43, 169.49, 173.85 (C). − MS (CI), *m/z* (%): 200 (100) [$M^+ + NH_4$].

1-tert-Butoxycarbonylbicyclopropylidene-1-carboxylic Acid (**34**): From *tert*-butyl bicyclopropylidenecarboxylate (**33**) (8.416 g, 46.7 mmol), *n*BuLi (50.0 mmol, 30.5 ml of a 1.64 M solution in hexane), and *i*Pr_2NH (5.363 g, 7.43 ml, 53 mmol), 8.945 g (85%) of the acid **34** was obtained according to GP5 as an oil. − IR: $\tilde{\nu}$ = 3438 cm^{-1}, 2978, 2932, 1728, 1424, 1370, 1257, 1166, 1135, 843, 740, 542. − ^{1}H NMR: δ = 1.35−1.43 (m, 4 H, Cpr), 1.40 (s, 9 H, 3 CH_3), 2.49 (dt, *J* = 8.3, 2.5 Hz, 1 H, Cpr), 2.66 (dt, *J* = 8.3, 2.5 Hz, 1 H, Cpr), 10.90 (br. s, 1 H, OH). − ^{13}C NMR: δ = 27.66 (3 CH_3), 3.75, 4.59, 21.50 (CH_2), 30.42, 84.53, 111.58, 115.43, 169.64, 173.48 (C). − MS (CI), *m/z* (%): 466 (100) [$2M^+ + NH_4$], 242 (38) [$M^+ + NH_4$], 186 (18) [$M^+ + NH_4 - H - C_4H_9$].

1-tert-Butoxycarbonyl-2-methylenespiropentane-1-carboxylic Acid (**31**): From *tert*-butyl 2-methylenespiropentane-1-carboxylate (**29**) (3.556 g, 19.7 mmol), *n*BuLi (20.7 mmol, 7.33 ml of a 2.83 M solution in hexane), and *i*Pr_2NH (2.196 g, 3.04 ml, 21.7 mmol), 3.751 g (85%) of the acid **31** was obtained according to GP5 as an oil. − ^{1}H NMR: δ = 1.33−1.48 (m, 4 H, Cpr), 1.42 (s, 9 H, 3 CH_3), 5.26 (s, 1 H, =CH_2), 5.41 (s, 1 H, =CH_2), 9.41 (br. s, 1 H, OH). − ^{13}C NMR: δ = 27.71 (3 CH_3), 12.51, 12.78, 99.65 (CH_2), 27.03, 35.22, 83.91, 135.54, 170.28, 174.03 (C).

1-tert-Butoxycarbonyl-2-methylenecyclopropane-1-carboxylic Acid (**32**): From *tert*-butyl 2-methylenecyclopropane-1-carboxylate (**30**) (5.313 g, 34.5 mmol), *n*BuLi (35.7 mmol, 23.2 ml of a 1.54 M solution in hexane), and *i*Pr_2NH (3.785 g, 4.90 ml, 37.4 mmol), 5.826 g (85%) of the acid **32** was obtained according to GP5, m. p. 54−56°C (hexane). − IR: $\tilde{\nu}$ = 3400 cm^{-1}, 2982, 1731, 1695, 1457, 1423, 1392, 1371, 1303, 1259, 1174, 1127, 1093, 917, 860, 737. − ^{1}H NMR: δ = 1.46 (s, 9 H, 3 CH_3), 2.43 (dt, *J* = 9.0, 2.8 Hz, 1 H, Cpr), 2.62 (dt, *J* = 9.0, 2.8 Hz, 1 H, Cpr), 5.54 (m, 1 H, =CH_2), 5.56 (m, 1 H, =CH_2), 11.82 (br. s, 1 H, OH). − ^{13}C NMR: δ = 27.50 (3 CH_3), 21.20, 103.40 (CH_2), 30.03, 84.88, 133.14, 169.20, 172.77. − $C_{10}H_{14}O_4$ (198.2): calcd. C 60.59, H 7.12; found C 60.35, H 7.11.

Curtius Degradation, General Procedure (GP) 6: Variant A: A solution of acid **31**, **32** or **34** (31.6 mmol), diphenylphosphoryl az-

ide (DPPA) (32 mmol), and Et_3N (32.3 mmol) in anhydrous *t*BuOH (80 ml) was heated under reflux for a period of 5 h. After cooling, the solution was concentrated under reduced pressure, taken up with Et_2O (200 ml), washed with 5% citric acid solution (200 ml), 5% $NaHCO_3$ solution (2 × 100 ml), brine (100 ml), dried, and concentrated under reduced pressure. The product was purified by column chromatography on silica gel, eluent hexane/EtOAc, 4:1.

Variant B: To a stirred solution of the monoester **25** or **34** (40 mmol) in anhydrous acetone (150 ml), Et_3N (51.1 mmol) was added dropwise at −5°C. After additional stirring for 15 min at this temp., a solution of ethyl chloroformate (64.9 mmol) in acetone (40 ml) was added over a period of 1 h, and the resulting mixture was stirred for 1.5 h at this temp. Then a solution of NaN_3 (68 mmol) in H_2O (18 ml) was added over a period of 1 h. The mixture was stirred for 1.5 h at 0°C, poured into ice-cold water (600 ml) and extracted with diethyl ether (5 × 800 ml). The combined ethereal solutions were washed with ice-cold water (200 ml) and dried at 0°C overnight. After concentration under reduced pressure at 0°C, the residue was treated as indicated below.

tert-Butyl 2-Methylene-1-(N-tert-butoxycarbonylamino)-spiropentane-1-carboxylate (**35**): 1) From the acid **31** (3.750 g, 16.7 mmol), DPPA (4.597 g, 3.60 ml, 16.7 mmol), and Et_3N (1.706 g, 2.35 ml, 16.86 mmol), carbamate **35** (3.163 g, 64%) was obtained according to GP6A after column chromatography (100 g of silica gel, 20 × 4 cm column), R_f = 0.34. − IR: $\tilde{\nu}$ = 3338 cm^{-1}, 2978, 2932, 1717, 1590, 1490, 1457, 1392, 1367, 1302, 1163, 1093, 1049, 1025, 967, 881, 850, 834, 784, 689, 599. − ^{1}H NMR: δ = 1.13−1.19 (m, 4 H, Cpr), 1.36 (s, 18 H, 6 CH_3), 5.12 (br. s, 1 H, $=CH_2$), 5.45 (br. s, 2 H, NH and $=CH_2$). − ^{13}C NMR: δ = 27.77, 27.95 (3 CH_3), 11.02, 12.49, 99.86 (CH_2), 24.83, 40.23, 79.51, 80.78, 149.61, 155.79, 169.71 (C). − MS (CI), *m/z* (%): 313 (90) [$M^+ + NH_4$], 296 (59) [$M^+ + H$], 293 (100) [$M^+ - 2H$].

2) From the acid **34** (2.668 g, 11.9 mmol), DPPA (3.269 g, 2.56 ml, 11.9 mmol), and Et_3N (1.212 g, 1.67 ml, 12 mmol), carbamate **35** (1.593 g, 45%) was obtained according to GP6A (but after 12 h reflux) after column chromatography (50 g of silica gel, 20 × 3 cm column).

tert-Butyl 2-Methylene-1-(N-tert-butoxycarbonylamino)cyclopropane-1-carboxylate (**36**): From the acid **32** (5.824 g, 29.38 mmol), DPPA (8.045 g, 6.30 ml, 29.2 mmol), and Et_3N (2.998 g, 4.13 ml, 29.63 mmol), carbamate **36** (6.347 g, 80%) was obtained according to GP6A after column chromatography (125 g of silica gel, 20 × 4 cm column), R_f = 0.40. − IR: $\tilde{\nu}$ = 3348 cm^{-1}, 2933, 1591, 1457, 1097, 1059, 1026, 1011, 967, 910, 850, 783, 689, 647. − ^{1}H NMR: δ = 1.37 (s, 9 H, 3 CH_3), 1.39 (s, 9 H, 3 CH_3), 1.64 (dt, *J* = 9.8, 1 Hz, 1 H, Cpr), 2.34 (dt, *J* = 9.8, 1 Hz, 1 H, Cpr), 5.31 (s, 1 H, NH), 5.45 (t, *J* = 1 Hz, 1 H, $=CH_2$), 5.63 (t, *J* = 1 Hz, 1 H, $=CH_2$). − ^{13}C NMR: δ = 27.73, 28.12 (3 CH_3), 20.28, 105.12 (CH_2), 36.17, 79.60, 81.26, 125.97, 155.69, 169.82 (C). − MS (CI), *m/z* (%): 287 (100) [$M^+ + NH_4$], 270 (92) [$M^+ + H$], 269 (20) [M^+], 268 (35) [$M^+ - H$], 231 (90).

tert-Butyl 1-(N-tert-Butoxycarbonylamino)bicyclopropylidene-1-carboxylate (**38**): A solution of the acid azide, prepared from the acid **34** (1.725 g, 7.69 mmol), Et_3N (1.002 g, 1.38 ml, 9.9 mmol), ethyl chloroformate (1.0 g, 0.88 ml, 9.2 mmol), and NaN_3 (0.815 g, 12.54 mmol) according to GP6B, in a mixture of anhydrous toluene and *tert*-butanol (25 + 25 ml), was irradiated in a quartz tube with a 150 wt medium pressure mercury lamp at 0°C for 3 h. After additional stirring for 48 h at ambient temp., the mixture was concentrated under reduced pressure. Column chromatography (50 g of silica gel, 15 × 4 cm column, hexane/EtOAc, 4:1) gave 313 mg (14%) of carbamate **38** as an oil, R_f = 0.33. − ^{1}H NMR: δ = 1.13−1.18 (m, 4 H, Cpr), 1.33 (s, 9 H, 3 CH_3), 1.35 (s, 9 H, 3 CH_3), 1.65 (d, *J* = 10.1 Hz, 1 H, Cpr), 2.35 (d, *J* = 10.1 Hz, 1 H, Cpr), 5.30 (br. s, 1 H, NH). − ^{13}C NMR: δ = 27.68, 28.03 (3 CH_3), 3.11, 3.53, 20.42 (CH_2), 36.51, 79.35, 80.91, 113.07, 114.66, 155.48, 170.03 (C).

Methyl 2-Methylene-1-[N-(2-trimethylsilylethoxy)carbonylamino]spiropentane-1-carboxylate (**27**): A solution of the acid azide, prepared from the acid **25** (7.60 g, 41.7 mmol), Et_3N (5.393 g, 7.43 ml, 53.3 mmol), ethyl chloroformate (7.347 g, 6.47 ml, 67.7 mmol), and NaN_3 (4.61 g, 70.9 mmol) according to GP6B, was heated in toluene (150 ml) at 80°C for 0.5 h. After cooling to 20°C, 2-(trimethylsilyl)ethanol (6.0 ml, 41.9 mmol) was added dropwise, and the mixture was stirred at this temp. for 24 h. Concentration under reduced pressure and column chromatography (200 g of silica gel, 15 × 7 cm column, hexane/Et_2O, 1:1) gave 4.62 g (37%) of a nonseparable 1:1 mixture (^{1}H NMR) of the two isomeric compounds **26** and **27**, R_f = 0.41. The crude yield before column chromatography was 68%. This mixture was taken up with benzene (80 ml), the solution then heated under reflux for 24 h and concentrated under reduced pressure to give 4.25 g (92%) of **27** as an oil. − IR: $\tilde{\nu}$ = 3258 cm^{-1}, 2954, 1740, 1734, 1437, 1333, 1066. − ^{1}H NMR: δ = 0.02 [s, 9 H, $Si(CH_3)_3$], 0.03 (t, *J* = 6 Hz, 2 H, $SiCH_2$), 1.01−1.22 (m, 1 H, Cpr), 1.24−1.26 (m, 1 H, Cpr), 1.42−1.46 (m, 1 H, Cpr), 1.57−1.78 (m, 1 H, Cpr), 3.71 (s, 3 H, OCH_3), 4.11−4.19 (m, 2 H, OCH_2), 5.28 (s, 1 H, $=CH_2$), 5.40 (s, 1 H, NH), 5.60 (s, 1 H, $=CH_2$). − ^{13}C NMR: δ = −1.57 (3 CH_3), 52.43 (CH_3), 11.34, 12.90, 17.54, 63.50, 100.92 (CH_2), 25.44, 39.84, 136.79, 156.96, 171.51 (C). − MS (CI), *m/z* (%): 315 (35) [$M^+ + NH_4$], 298 (100) [$M^+ + H$]. − $C_{14}H_{23}NO_4Si$ (297.4): calcd. C 56.54, H 7.79; found C 56.59, H 7.72.

N-(1-Methoxycarbonyl-2-methylenespiropentyl)ammonium Trifluoroacetate (**28**): A solution of the carbamate **27** (100 mg, 0.34 mmol) in a mixture of $CHCl_3$ (1 ml) and CF_3COOH (0.60 ml, 7.8 mmol) was stirred at 20°C for 11 h. After concentration of the solution under reduced pressure and drying of the residue under vacuum (20°C/1 h/1 Torr), 88 mg (100%) of the amino ester hydrotrifluoroacetate **28** was obtained. − IR: $\tilde{\nu}$ = 2966 cm^{-1}, 2668, 1729, 1664, 1603, 1516, 1444, 1426, 1323, 1210, 1176, 1136, 890, 835, 799, 722. − ^{1}H NMR (D_2O): δ = 1.33 (br. s, 2 H, Cpr), 1.39 (br. s, 2 H, Cpr), 3.59 (s, 3 H, OCH_3), 5.35 (s, 1 H, $=CH_2$), 5.55 (s, 1 H, $=CH_2$). − ^{13}C NMR (D_2O): δ = 54.93 (CH_3), 13.16, 13.74, 106.01 (CH_2), 25.44, 40.50, 117.56 (J_{CF} = 288 Hz), 132.04, 164.11 (J_{CF} = 36 Hz), 171.27 (C). − MS (CI), *m/z* (%): 171 (40) [$M^+ + NH_4$], 154 (100) [$M^+ + H$].

Deprotection of Protected Amino Acids **35**, **36**, **38**. *General Procedure (GP) 7:* The solution of protected amino acid **35**, **36**, or **38** (5 mmol) in 5.5 N HCl solution in Et_2O (20 ml) was intensively stirred for 4 h at room temp. in the dark. The precipitate formed was filtered, washed with Et_2O (40 ml) and dried in a vacuum desiccator over P_4O_{10} overnight.

1-Amino-2-methylenecyclopropane-1-carboxylate Hydrochloride (**3**): From the compound **36** (3.234 g, 12 mmol), 1.60 g (89%) of the amino acid hydrochloride **3** was obtained according to GP7, m. p. 179°C (expl. dec.). − IR: $\tilde{\nu}$ = 3250 cm^{-1}, 2967, 2594, 2538, 2440, 1728, 1577, 1499, 1420, 1385, 1278, 1173, 927, 895, 841, 743, 538. − ^{1}H NMR (D_2O): δ = 1.92 (dt, *J* = 11.8, 2.8 Hz, 1 H, Cpr), 2.20 (dt, *J* = 11.8, 1.8 Hz, 1 H, Cpr), 5.64 (br. s, 1 H, $=CH_2$), 5.73 (br. s, 1 H, $=CH_2$). − ^{13}C NMR (D_2O): δ = 18.83, 111.34 (CH_2), 35.70, 128.49, 172.56 (C). − $C_5H_8ClNO_2$ (149.6): calcd. C 40.15, H 5.39, N 9.37; found C 40.28, H 5.61, N 9.30.

1-Amino-2-methylenespiropentane-1-carboxylate Hydrochloride (**37**): From the compound **35** (2.087 g, 7.1 mmol), 0.935 g (75%) of

the amino acid hydrochloride **37** was obtained according to GP7, m. p. 190°C (expl. dec.). – IR: $\tilde{\nu}$ = 3500 cm^{-1}, 2994, 2719, 2636, 1733, 1576, 1477, 1409, 1253, 1153, 909, 830, 592. – ^1H NMR (D_2O): δ = 1.31 (br. s, 2 H, Cpr), 1.39 (br. s, 2 H, Cpr), 5.33 (br. s, 1 H, $=CH_2$), 5.55 (br. s, 1 H, $=CH_2$). – ^{13}C NMR (D_2O): δ = 13.19, 13.83, 105.96 (CH_2), 23.77, 40.44, 132.41, 172.80 (C). – $C_7H_{10}ClNO_2$ (175.6): calcd. C 47.88, H 5.74, N 7.98; found C 47.99, H 5.99, N 7.39.

1-Aminobicyclopropylidene-1-carboxylate Hydrochloride (**39**): From the compound **38** (313 mg, 1.06 mmol), 99 mg (53%) of the amino acid hydrochloride **39** was obtained according to GP7, m. p. 187–188°C (dec.). – IR: $\tilde{\nu}$ = 3500 cm^{-1}, 2976, 2675, 1725, 1493, 1400, 1191, 1143, 912, 808. – ^1H NMR (D_2O): δ = 1.18 (br. s, 4 H, Cpr), 1.96 (d, *J* = 9.3 Hz, 1 H, Cpr), 2.26 (d, *J* = 9.3 Hz, 1 H, Cpr). – ^{13}C NMR (D_2O): δ = 4.62, 4.68, 19.06 (CH_2), 36.38, 109.40, 122.08, 173.40 (C). – $C_7H_{10}ClNO_2$ (175.6): calcd. C 47.88, H 5.74, N 7.98; found C 47.62, H 5.77, N 7.93.

1-tert-Butoxycarbonylbicyclopropylidene-1-carboxamide (**40**): To a stirred solution of the monoester **34** (3.630 g, 16.19 mmol) in anhydrous THF (60 ml), Et_3N (2.429 g, 3.35 ml, 24 mmol) was added dropwise at −20°C. After additional stirring for 10 min at this temp., ethyl chloroformate (2.022 g, 1.78 ml, 18.62 mmol) was added over a period of 0.5 h, and the resulting mixture was stirred for 0.5 h at this temp. Then an aqueous NH_3 solution (51.4 mmol, 3.7 ml of 13.89 M solution) was added in one portion. The mixture was allowed to warm to room temp., concentrated under reduced pressure, diluted with 0.5 M Na_2CO_3 solution (80 ml) and extracted with EtOAc (3 × 200 ml). The combined organic solutions were washed with 0.5 M Na_2CO_3 solution (2 × 80 ml), 0.1 M HCl solution (3 × 80 ml), again with 0.5 M Na_2CO_3 solution (100 ml), and dried. After concentration under reduced pressure, the residue was recrystallized from hexane/Et_2O (1:1) to give 1.829 g of **40**. The mother liquor, after concentration, was purified by column chromatography (80 g of silica gel, 15 × 4 cm column, Et_2O, R_f = 0.40) to give additionally 558 mg of the product. The total yield of **40** was 2.387 g (66%), m. p. 98–100°C. – IR: $\tilde{\nu}$ = 3394 cm^{-1}, 3191, 2984, 2974, 1711, 1674, 1572, 1396, 1367, 1304, 1137, 1107, 942, 845, 641. – ^1H NMR: δ = 1.14–1.36 (m, 4 H, Cpr), 1.38 (s, 9 H, 3 CH_3), 2.39 (dt, *J* = 7.8, 2.5 Hz, 1 H, Cpr), 2.62 (dt, *J* = 7.8, 2.6 Hz, 1 H, Cpr), 6.02 (br. s, 2 H, NH_2). – ^{13}C NMR: δ = 27.79 (3 CH_3), 3.42, 4.15, 19.67 (CH_2), 32.10, 82.08, 110.17, 116.03, 170.05, 170.34 (C). – $C_{12}H_{17}NO_3$ (223.3): calcd. C 64.55, H 7.68; found C 64.77, H 7.85.

tert-Butyl (Z)-1-Bromo-1-(1-hydroxycyclopropyl)-2-cyanocyclopropane-2-carboxylate (**44**): Under argon atmosphere, to the stirred solution of amide **40** (558 mg, 2.5 mmol), AgOAc (494 mg, 2.96 mmol), and *tert*-butanol (5.559 g, 7.17 ml, 75 mmol) in anhydrous DMF (13 ml), a solution of *N*-bromosuccinimide (585 mg, 3.29 mmol) in DMF (6 ml) was added dropwise at 20°C over a period of 40 min. After the additional stirring for 3 d at ambient temp., the mixture was concentrated under reduced pressure, taken up with EtOAc (300 ml), washed with water (2 × 40 ml), 0.1 M HCl solution (2 × 40 ml), 5% $NaHCO_3$ solution (2 × 40 ml), and dried. After concentration under reduced pressure, the residue was purified by column chromatography (50 g of silica gel, 15 × 3 cm column, hexane/EtOAc, 4:1, R_f = 0.27) to give 202 mg (27%) of the bromide **44**, m. p. 147–149°C (dec.). – ^1H NMR: δ = 0.79–0.93 (m, 1 H, Cpr), 0.95–1.02 (m, 1 H, Cpr), 1.08–1.17 (m, 1 H, Cpr), 1.33–1.48 (m, 1 H, Cpr), 1.53 (s, 9 H, 3 CH_3), 1.69 (d, *J* = 7.8 Hz, 1 H, Cpr), 2.20 (d, *J* = 7.8 Hz, 1 H, Cpr), 3.10 (br. s, 1 H, OH). – ^{13}C NMR: δ = 27.81 (3 CH_3), 16.32, 18.00, 26.65 (CH_2), 27.32, 48.27, 59.76, 85.23, 115.72, 161.67 (C).

tert-Butyl 1-(N-Methoxycarbonylamino)bicyclopropylidene-1-carboxylate (**46**): Amido ester **40** (200 mg, 0.90 mmol) and then bis(acetoxy)iodobenzene (286 mg, 0.89 mmol) were added to a stirred solution of KOH (90 mg, 1.6 mmol) in anhydrous MeOH (8 ml) at 0°C. The reaction mixture was progressively warmed up to room temp. and, after additional stirring for 1.5 h at this temp., concentrated under reduced pressure. The residue was diluted with water (10 ml) and CH_2Cl_2 (5 ml), extracted with CH_2Cl_2 (3 × 5 ml) and, after drying of the combined organic phases and concentration, purified by column chromatography (50 g of silica gel, 15 × 3 cm column, hexane/Et_2O, 1:1, R_f = 0.39) to give 173 mg (76%) of the carbamate **46**, m. p. 60–62°C. – IR: $\tilde{\nu}$ = 3330 cm^{-1}, 2981, 1723, 1517, 1456, 1315, 1250, 1158, 1092, 1070, 732. – ^1H NMR: δ = 1.18 (br. s, 4 H, Cpr), 1.37 (s, 9 H, 3 CH_3), 1.81 (br. s, 1 H, Cpr), 2.41 (br. s, 1 H, Cpr), 3.62 (s, 3 H, CH_3), 5.45 (br. s, 1 H, NH). – ^{13}C NMR: δ = 27.77 (3 CH_3), 52.09 (CH_3), 3.29, 3.43, 20.75 (CH_2), 36.78, 81.27, 113.65, 114.47, 156.91, 170.08 (C). – MS (CI), *m/z* (%): 271 (90) [$M^+ + NH_4$], 254 (38) [$M^+ + H$], 215 (100) [$M^+ + NH_4 - C_4H_8$]. – $C_{13}H_{19}NO_4$ (253.3): calcd. C 61.64, H 7.56; found C 61.53, H 7.84.

tert-Butyl 1-(N-p-Methoxybenzylcarbonylamino)bicyclopropylidene-1-carboxylate (**46b**): Amido ester **40** (1.40 g, 6.30 mmol) and then bis(acetoxy)iodobenzene (2.10 g, 6.53 mmol) were added to a stirred solution of KOH (1.06 g, 18.90 mmol) and *p*-methoxybenzyl alcohol (2.60 g, 2.35 ml, 18.82 mmol) in anhydrous THF (20 ml) at −20°C. The reaction mixture was stirred for an additional 3 h at 5–8°C, then poured into ice-cold water (100 ml), extracted with CH_2Cl_2 (3 × 10 ml), the combined extracts washed with brine (1 × 10 ml), dried, concentrated, and the residue purified by column chromatography (50 g of silica gel, 15 × 3 cm column, hexane/Et_2O 1:1, R_f = 0.34) to give 1.80 g (79%) of carbamate **46b**. – ^1H NMR: δ = 1.14–1.22 (m, 4 H, Cpr), 1.35 (s, 9 H, 3 CH_3), 1.82 (m, 1 H, Cpr), 2.42 (m, 1 H, Cpr), 3.75 (s, 3 H, OCH_3), 5.00 (br. s, 2 H, OCH_2), 5.53 (s, 1 H, NH), 6.82 (d, *J* = 8.9 Hz, 2 H, Ph), 7.26 (d, *J* = 8.9 Hz, 2 H, Ph). – ^{13}C NMR: δ = 27.83 (3 CH_3), 55.20 (CH_3), 3.39, 3.50, 20.90, 66.63 (CH_2), 113.74, 130.08 (2 CH), 31.52, 81.44, 114.24, 114.52, 137.38, 159.43, 159.44, 170.07 (C). – MS (CI), *m/z* (%): 736 (30) [2 $M^+ + NH_4$], 377 (100) [$M^+ + NH_4$].

After the deprotection of the carbamate **46b** according to GP7, 252 mg (29%) of amino acid hydrochloride **39** was obtained. By deprotecting the crude carbamate **46b** without isolation, the hydrochloride **39** was obtained in 28% overall yield from the amido ester **40**.

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