Cyclopropyl Building Blocks in Organic Synthesis, 51[+]

An Easy Access to 1-Azaspiropentane-2-carboxamides – The First Derivatives of a New Type of Amino Acids

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Dedicated to Professor Murray Goodman on the occasion of his 70th birthday

Keywords: Amino acids / Azaspiropentanes / Heterocycles / Peptides / Strained molecules

Azaspiropentanecarboxamides **10** and **12** are formed with remarkable ease in two steps in a one-pot operation from methyl 2-chloro-2-cyclopropylideneacetate (**4**) by addition of a primary amine in tetrahydrofuran and subsequent treatment with sodium hydride/triethylamine in the presence of another equivalent of a primary amine or ammonia. Achievable yields of the amides **10**, **12** were moderate to good (27–59%, 12–48%), while the corresponding esters **9** could only be obtained in poor yields (4–14%). The new α-amino acid amides are surprisingly stable, and they can be incorporated into small peptides as demonstrated with the preparation of the glycine **13e** and the spirocyclopropaneoxazoline derivative **14e**.

Introduction

Quite a variety of unusual amino acids including at least 26 with a cyclopropyl group have been found in nature, and many of them exhibit special biological activities.[1][2] In addition, cyclopropyl group containing homologs of other natural amino acids are attracting an ever increasing interest as potential enzyme inhibitors[3] and conformationally restricted building blocks for peptidomimetics.[4] A wide range of biological activities has been uncovered for such unnatural amino acid analogs and small peptides containing them.[5][6] The most highly strained amino acid occurring naturally, (*S*)-2-azabicyclo[2.1.0]pentane-3-carboxylic acid (**1**), has a remarkable antimicrobial activity.[7] Neither the isomeric 1-azaspiropentane-2-carboxylic acid (**2**), nor any of its derivatives have yet been described; in fact, only relatively few azaspiropentane derivatives have been reported so far.[8] In addition to its structural particularity, **2** and its derivatives should be of interest in view of their potential biological activity due to the aziridine subunit,[9] which in **2** is especially strained and should therefore be more reactive than simple aziridines due to the spiro-linked cyclopropane ring. In fact, azaspiropentanes show interesting alkylating activity even in weakly acidic media.[8b,8d] The amino acid **2** must also be viewed as a spirocyclopropane derivative of aziridinecarboxylic acid (**3**),[10] which has been applied in interesting peptidomimetics.[10c] We have now uncovered a rather facile formation of 1-azaspiropentane-2-carboxylic acid derivatives from methyl 2-chloro-2-cyclopropylideneacetate (**4**),[11] which has previously been described as a versatile and highly reactive small-ring building block for various types of compounds.[12]

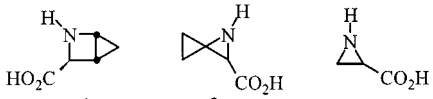

Figure 1. Three unusually strained small-ring α-amino acids

Results and Discussion

The Michael adduct **6a**-Bn of dibenzylamine (**5a**-Bn) to the reactive acrylate **4** can be prepared in tetrahydrofuran (THF) solution as a stable compound, but it cleanly rearranges when heated in dimethylformamide (DMF) at 80 °C for 48 h to yield the 2-dibenzylaminocyclobutene-1-carboxylate **8a**-Bn.[13] This rearrangement probably involves a cationic azaspiropentane intermediate **7a**-Bn (Scheme 1), it is facilitated by polar solvents and elevated temperatures. The Michael adduct **6a**-H of benzylamine (**5a**-H) to **4** can also be prepared in THF solution, but the isolated product **6a**-H turned out to be rather unstable even at −20 °C and to rapidly rearrange to 2-benzylaminocyclobutenecarboxylate **8a**-H. The latter was also obtained di-

[+] Part 50: V. N. Belov, C. Funke, T. Labahn, M. Es-Sayed, A. de Meijere, *Eur. J. Org. Chem*. **1999**, 1345−1356. − Part 49: M. Brandl, S. I. Kozhushkov, D. S. Yufit, J. A. K. Howard, A. de Meijere, *Eur. J. Org. Chem*. **1998**, 2785−2795.

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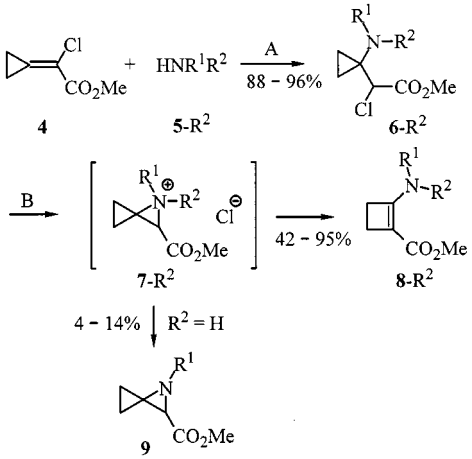
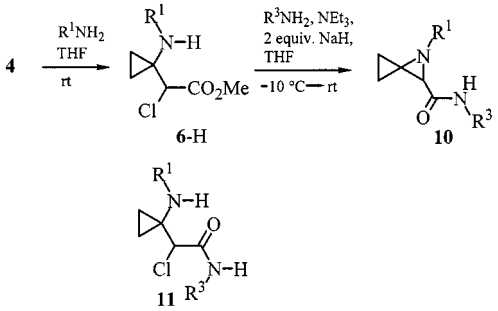
  1434−193X/99/0909−2017 $ 17.50+.50/0

rectly upon treatment of **4** with benzylamine in DMF at room temperature. When the adduct **6b**-H was treated in methanol (MeOH) solution with triethylamine, the expected ring-enlargement product, the cyclobutene **8b**-H, was accompanied by a small amount of the methyl azaspiropentanecarboxylate **9b**. Under these conditions, **6a**-H and **6c**-H gave the azaspiropentane derivatives **9a** and **9c** as the only isolable products (14 and 13%, respectively) (Table 1).[14] Apart from the very low yields, the isolated methyl esters **9**-R were unstable at room temperature and underwent decomposition when stored for a couple of hours. However, in an attempt to improve the yield of the aziridine-ring-closed product from **6a**-H by using a second equivalent of benzylamine (**5a**-H) to possibly transform the ester function into a potentially more stable amide,[15] and also adding triethylamine as well as two equivalents of sodium hydride, the *N*-benzyl-1-azaspiropentane-2-carboxylic acid *N*-benzylamide **10aa** was obtained in 59% yield as the only isolable product (Scheme 2). This compound, a colorless solid (m.p. 36 °C), turned out to be remarkably stable with no detectable decomposition even after long-term storage at room temperature. A variety of analogous *N*-arylalkyl-1-azaspiropentane-2-carboxylic acid *N*-(arylalkyl)amides **10** was prepared by the same protocol with various combinations of (arylalkyl)amines **5a**–**d**-H applied in sequence. Virtually no diastereoselectivity was observed with enantiomerically pure (*S*)-α-phenylethylamine **5d**-H (see Table 2).



Scheme 1. Synthesis of methyl cyclobutenecarboxylates **8** and methyl azaspiropentanecarboxylates **9**; for details see Table 1



Scheme 2. Synthesis of 1-azaspiropentane-2-carboxylic acid alkylamides **10**; for details see Table 2

The ring closure to the azaspiropentane most likely occurs at the stage of the β-amino-α-chloro esters **6**-H to first yield the methyl azaspiropentanecarboxylates **9**, which subsequently react with the second equivalent of the amine to the more stable amides **10**. However, an attempt to transform **9a** into **10aa** by treatment with benzylamine under the optimized conditions for the conversion of **6a**-H to **10aa** only led to decomposition of **9a**. Alternatively, the β-amino esters **6**-H might first be transformed to the amides **11** with subsequent γ-dehydrochlorination into the final products **10**.

Apparently, the stability of these azaspiropentane derivatives is greatly enhanced by the arylalkyl substituents on the ring nitrogen atom. All attempts to remove the *N*-benzyl group from the skeleton of **10aa** led to complete destruction of the system. However, the *N*-arylalkyl group on the carboxamide group is not essential. Treatment of **6a**-H in THF solution with gaseous ammonia in the presence of triethylamine and sodium hydride gave the primary *N*-benzyl-1-azaspiropentane-2-carboxamide **12a**. Analogously, the *N*-(2′-phenylethyl)-1-azaspiropentane-2-carboxamide **12e** was obtained along this route, but in lower yield. Probably, the stability of the compounds **12** depends on the bulk of the substituent on the ring nitrogen atom.

The *N*-benzylazaspiropentanecarboxamide **12a** could be crystallized from ethanol and characterized by X-ray crystallography.[16] This represents the first crystal structure analysis of any azaspiropentane derivative.

The nitrogen atom in the aziridine ring of **12a** is pyramidal, the average of the C–N distances is 1.465 Å and the

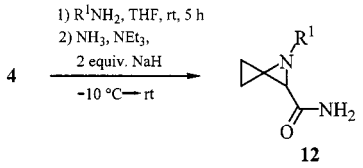
Table 1. Methyl cyclobutenecarboxylates **8** and methyl azaspiropentanecarboxylates **9** from methyl 2-chloro-2-cyclopropylideneacetate (**4**); see Scheme 1

R^1R^2NH **5**-R^2	R^1	R^2	Conditions A	Conditions B	Product **8**-R^2	Yield **8**-R^2 (%)	Product **9**	Yield **9** (%)
5a-Bn	Bn	Bn	THF, r.t., 24 h	DMF, 80°C, 48 h	**8a**-Bn	95	–	–
5a-H	Bn	H	DMF, r.t., 1 h	DMF, r.t., 48 h	**8a**-H	51[a]	**9a**	0
5b-H	CH_2CO_2tBu	H	THF, r.t., 3 h	MeOH, NEt_3, r.t., 9 d	**8b**-H	42[a]	**9b**[b]	4[a]
5a-H	Bn	H	THF, r.t., 30 min	MeOH, NEt_3, r.t., 24 h	**8a**-H	0	**9a**[b]	14

[a] Overall yield in two steps. – [b] Slow decomposition at room temp.

Table 2. 1-Azaspiropentane-2-carboxylic acid alkylamides **10** from **4** and amines **5**-H

R^1NH_2 **5**-H	R^1	R^3NH_2 **5**-H	R^3	Time [h]	Product **10**	Yield (%)	d. r.
5a-H	Bn	**5a**-H	Bn	48	**10aa**	59	–
5c-H	4-$MeOC_6H_4CH_2$	**5c**-H	4-$MeOC_6H_4CH_2$	36	**10cc**	27	–
5a-H	Bn	**5c**-H	4-$MeOC_6H_4CH_2$	18	**10ac**	47	–
5a-H	Bn	**5d**-H	(*S*)-$C_6H_5C(CH_3)H$	48	**10ad**	47	1.1:1
5d-H	(*S*)-$C_6H_5C(CH_3)H$	**5a**-H	Bn	36	**10da**	36	1.6:1



Scheme 3. Synthesis of 1-azaspiropentane-2-carboxamides **12**; for details see Table 3

Table 3. 1-Azaspiropentane-2-carboxamides **12** from **4**, amines **5**-H and ammonia

RNH_2 **5**-H	R	Time [h]	Product **12**	Yield (%)
5a-H	Bn	24	**12a**	48
5e-H	$C_6H_5C_2H_4$	50	**12e**	33

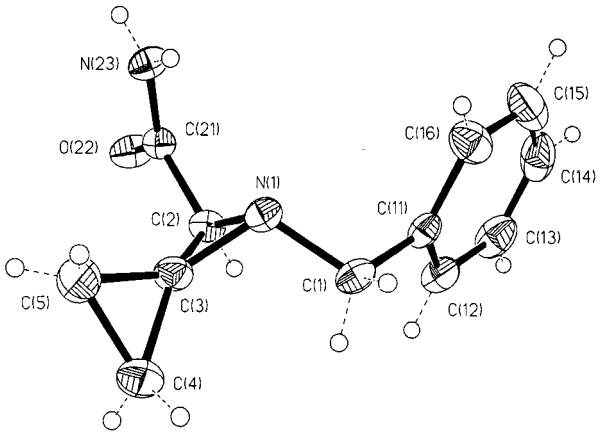
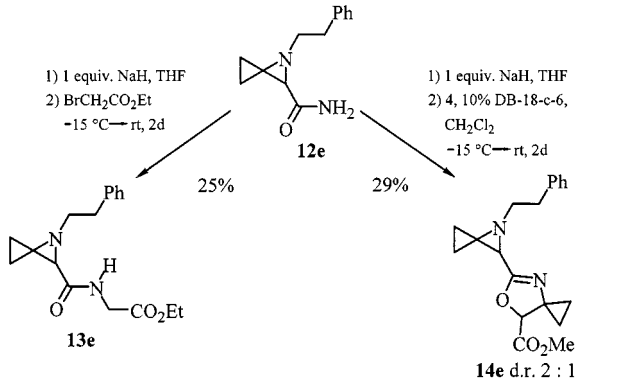


Figure 2. Structure of **12a** in the crystal, showing 50% probability displacement ellipsoids; of the two independent molecules in the asymmetric unit only one is shown for clarity[16]

C−C distances are 1.471(3) and 1.467(3) Å for the two independent molecules in the asymmetric unit. The C−C distances in the spirofused cyclopropane ring show the typical alternation as in spiropentane[17] and [3]rotane[18] with a shorter proximal [1.463(3)] and a longer distal [1.532(3) Å] bond. The angle between the plane of the aziridine ring and the plane of the cyclopropane ring is 88.4(1)° and 87.6(1)° for the two independent molecules in the asymmetric unit.

In recent years, the simple aziridinecarboxylic acid (**3**) has been incorporated into small peptides, and this, in some cases, has led to remarkable biological activities.[10c] In order to prove the feasibility, the first basic attempts for the incorporation of the novel azaspiropentanecarboxamides into simple peptides were made. Indeed, after deprotonation of the amide function in **12e** by treatment with sodium hydride, a nucleophilic substitution on ethyl bromoacetate could be achieved to give the azaspiropentylcarbonylglycine ester **13e**. Reaction of the deprotonated **12e** with **4** did not give the expected Michael adduct, which would also be a simple dipeptide, but rather the azaspiropentyloxazoline **14e** as the only isolated product. The latter consists of *N*-(2-phenylethyl)-1-azaspiropentane-2-carboxylic acid and the unnatural cyclopropane analog of the amino acid isoserine. Further investigations on this new oxazoline-forming reaction will be published separately.[19]



Scheme 4. Transformation of the amide **12e** to the dipeptide **13e** and the oxazoline **14e**

Conclusion

An easy access to 1-azaspiropentane-2-carboxamides and the corresponding esters, derivatives of a new class of amino acids, starting from the Michael acceptor **4**, has been developed. The structure of amide **12a** was verified by X-ray crystallography, the first X-ray structure of any azaspiropentane. The amides **10** and **12** are stable at room temperature, and those with a primary amide group can easily be incorporated into small peptides. Biological testing of the glycine derivative **13e** and the spirocyclopropaneoxazoline **14e** is currently in progress.

Experimental Section

General: The used chemicals are commercially available except for methyl 2-chloro-2-cyclopropylideneacetate (**4**),[20] which was prepared by a literature method.[11] All reactions were performed under anhydrous conditions and N_2. Solvents were distilled under N_2

from sodium benzophenone (THF) or CaH_2 (DMF, NEt_3, CH_2Cl_2). All other reagents and solvents were purified when necessary by standard procedures. − Reactions were monitored by thin-layer chromatography on silica gel plates (Macherey−Nagel SIL G/UV_{254}). The chromatograms were visualized by UV light and by staining with Merck ninhydrin spray reagent. Silica gel 60 (I, 0.063−0.200 mm, 230−400 mesh) obtained from Merck, silica gel 60 (II, 0.004−0.063 mm, 230−400 mesh, "flash") obtained from Macherey−Nagel, and aluminum oxide [III, neutral, activation grade 2 (4%)] obtained from ICN were used for column chromatography. Eluting solvents were distilled before use. When silica gel was utilized, the column material was deactivated with 3% NEt_3, and the eluents contained 3% NEt_3. − NMR spectra were recorded with a Bruker AM 250 instrument at 250 MHz (^{1}H) and at 62.9 MHz (^{13}C) in $CDCl_3$. Chemical shifts δ are reported in ppm relative to C*H*Cl_3 (^{1}H, δ = 7.26) and *C*DCl_3 (^{13}C, δ = 77.0) as internal standard; *c*Pr = cyclopropyl; *c*Bu = cyclobutyl. − Melting points are uncorrected.

Methyl 2-Dibenzylaminocyclobutene-1-carboxylate (8a-Bn): A solution of **6a**-Bn[21] (800 mg, 2.33 mmol) in DMF (20 mL) was heated for 48 h at 80 °C. After cooling to room temp., H_2O (30 mL) and NEt_3 (10 mL) were added. The mixture was extracted with Et_2O (3 × 50 mL), the organic layers were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel [I, 30 g, light petroleum ether (LP)/Et_2O, 10:1] to give **8a**-Bn (680 mg, 95%) as a colorless solid which crystallized from Et_2O at −20 °C. − M.p. 65 °C; R_f = 0.16 (LP/Et_2O, 10:1). − IR (KBr): $\tilde{\nu}$ = 2929 cm^{-1} (C−H), 2858 (C−H), 1734 (C=O), 1667 (C=C), 1593, 1449, 1424, 1365, 1351, 1275, 1218, 1114, 1077, 1059, 1028, 955, 754, 701, 627, 473. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.45−2.51 (m, 2 H, C_2H_4), 2.57−2.63 (m, 2 H, C_2H_4), 3.66 (s, 3 H, OCH_3), 4.60 (d, ^2J = 14.3 Hz, 2 H, $PhCH_2$), 4.70 (d, ^2J = 14.5 Hz, 2 H, $PhCH_2$), 7.13−7.41 (m, 10 H, Ph). − ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 20.97 (−, C_2H_4), 27.73 (−, C_2H_4), 50.28 (+, OCH_3), 51.57 (−, CH_2), 90.43 (C_{quat}, C-2), 127.22 (+, Ph), 127.43 (+, Ph), 128.36 (+, Ph), 137.27 (C_{quat}, Ph), 157.58 (C_{quat}, C1), 163.62 (C_{quat}, CO_2Me). − MS (70 eV, EI); *m/z* (%): 307 (56) [M^+], 276 (18) [M^+ − OMe], 248 (7) [M^+ − CO_2Me], 216 (42) [M^+ − $PhCH_2$], 184 (58), 156 (11), 91 (100) [$PhCH_2^+$]. − $C_{20}H_{21}NO_2$ (307.4): calcd. C 78.15, H 6.89, N 4.55; found C 78.22, H 6.92, N 4.68.

Methyl 2-Benzylaminocyclobutene-1-carboxylate (8a-H): To a solution of **4** (500 mg, 3.41 mmol) in DMF (10 mL) was added **5a**-H (370 mg, 3.45 mmol), and the solution was stirred for 48 h at room temp. After addition of H_2O (50 mL) and NEt_3 (10 mL), the mixture was worked up as in the preceding procedure. Column chromatography on silica gel (I, 15 g, LP/Et_2O, 2:1−1:1) gave **8a**-H as a colorless solid which crystallized from Et_2O at −20 °C. − M.p. 63 °C; R_f = 0.17 (LP/Et_2O, 1:1). − IR (KBr): $\tilde{\nu}$ = 3327 cm^{-1} (N−H), 2928 (C−H), 2863 (C−H), 1741 (C=O), 1620 (C=C), 1456, 1354, 1293, 1242, 1220, 1187, 1133, 1100, 1077, 1032, 967, 936, 763, 738, 697, 601, 522, 457. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.45−2.48 (m, 2 H, C_2H_4), 2.53−2.56 (m, 2 H, C_2H_4), 3.66 (s, 3 H, OCH_3), 4.33 (d, ^3J = 6.4 Hz, 2 H, $PhCH_2$), 5.88 (br. s, 1 H, NH), 7.29−7.39 (m, 5 H, Ph). − ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 21.52 (−, C_2H_4), 26.68 (−, C_2H_4), 47.51 (−, CH_2), 50.02 (+, OCH_3), 92.29 (C_{quat}, C-2), 126.94 (+, Ph), 127.45 (+, Ph) 128.65 (+, Ph), 138.60 (C_{quat}, Ph), 158.34 (C_{quat}, C1), 164.59 (C_{quat}, *C*O_2Me). − MS (70 eV); *m/z* (%): 217 (36) [M^+], 186 (16) [M^+ − OMe], 158 (17) [M^+ − CO_2Me], 91 (100) [$PhCH_2^+$], 65 (10); $C_{13}H_{15}NO_2$ (217.3): calcd. C 71.87, H 6.96, N 6.45; found C 71.74, H 6.89, N 6.41.

Methyl 2-Chloro-2-[1-(*tert*-butoxycarbonylmethylamino)cyclopropyl]acetate (6b-H): To a solution of **4** (395 mg, 2.69 mmol) in THF (10 mL) was added **5b**-H (362 mg, 2.76 mmol). After having stirred the mixture for 3 h at room temp., the solvent was removed in vacuo, and the residue was purified by column chromatography (I, 20 g, LP/Et_2O, 4:1−1:1) to give **6b**-H (679 mg, 91%) as a colorless liquid. − R_f = 0.44 (LP/Et_2O, 1:1). − IR (neat): $\tilde{\nu}$ = 3275 cm^{-1} (N−H), 2980 (C−H), 2955 (C−H), 1740 (C=O), 1677 (C=O), 1527, 1437, 1395, 1370, 1254, 1157, 1018, 934, 886, 844, 802, 750. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.70−0.80 (m, 1 H, *c*Pr−H), 0.84−1.04 (m, 3 H, *c*Pr−H), 1.44 [s, 9 H, $C(CH_3)_3$], 2.24 (br. s, 1 H, NH), 3.39 (d, ^2J = 17.4 Hz, A-part of an AB system, 1 H, NCH_2), 3.50 (d, ^2J = 17.4 Hz, B-part of an AB system, 1 H, NCH_2), 3.79 (s, 3 H, CO_2CH_3), 4.18 (s, 1 H, 2-H). − ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 14.80 (−, *c*Pr−C), 15.52 (−, *c*Pr−C), 28.01 [+, $C(CH_3)_3$], 41.71 (C_{quat}, *c*Pr−C), 48.98 (−, NCH_2), 52.96 (+, OCH_3), 63.93 (+, C-2), 81.20 [C_{quat}, $C(CH_3)_3$], 168.69 (C_{quat}, CO_2R), 171.63 (C_{quat}, CO_2R). − MS (70 eV, EI); *m/z* (%): 279/277 (2/5) [M^+], 242 (1) [M^+ − Cl], 223/221 (4/11) [M^+ − C_4H_8], 192/190 (2/5) [M^+ − C_4H_8 − CH_3O], 186 (100) [M^+ − Cl − C_4H_8], 178/176 (10/32) [M^+ − $CO_2C(CH_3)_3$], 154 (38) [M^+ − Cl − C_4H_8 − CH_4O], 57 (12) [$C_4H_9^+$]. − HRMS [M^+]; *m/z* calculated for $C_{12}H_{20}ClNO_4$: 277.1081; found 277.1080.

Methyl 2-(*tert*-Butoxycarbonylmethylamino)cyclobutene-1-carboxylate (8b-H): To a solution of **4** (500 mg, 3.41 mmol) in THF (15 mL) was added **5b**-H (447 mg, 3.41 mmol). After the mixture had been stirred for 3 h, the solvent was evaporated in vacuo. The crude yellow liquid of **6b**-H was dissolved in MeOH (8 mL), and NEt_3 (5.0 mL, 35.9 mmol) was added. The solution was stirred for 9 d, then concentrated in vacuo. To the residue were added H_2O (2 mL) and Et_2O (10 mL). After separation of the two phases, the water layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried with Na_2SO_4, then the solution was concentrated to 5 mL. After storing at −20 °C **8b**-H (248 mg, 1.03 mmol) crystallized as a colorless solid. − M.p. 96 °C; R_f = 0.27 (LP/Et_2O, 1:1). − IR (KBr): $\tilde{\nu}$ = 3392 cm^{-1} (N−H), 2974 (C−H), 2948 (C−H), 2927 (C−H), 1744 (C=O), 1675 (C=O), 1631 (C=C), 1470, 1393, 1305, 1230, 1187, 1159, 1122, 1039, 849, 764. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.46 [s, 9 H, $C(CH_3)_3$], 2.42−2.45 (m, 4 H, C_2H_4), 3.64 (s, 3 H, CO_2CH_3), 3.78−3.93 (m, 2 H, NCH_2), 5.63 (br. s, 1 H, NH). − ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 21.48 (−, *c*Bu−C), 26.43 (−, *c*Bu−C), 27.95 [+, $C(CH_3)_3$], 45.77 (−, NCH_2), 50.20 (+, CO_2CH_3), 82.29 [C_{quat}, $C(CH_3)_3$], 93.64 (C_{quat}, C1), 157.13 (C_{quat}, C-2), 164.35 (C_{quat}, CO_2R), 169.12 (C_{quat}, CO_2R). − MS (DCI); *m/z* (%): 483 (100) [2 × M + H^+], 259 (6) [M + NH_4^+], 242 (81) [M + H^+]. − $C_{12}H_{19}NO_4$ (241.3): calcd. C 59.73, H 7.94, N 5.81; found C 59.67, H 7.97, N 5.82. − From the mother liquor, the solvent was evaporated, and the remaining substance was chromatographed on silica gel (I, 45 g, LP/Et_2O, 2:1−1:2) to give additional 101 mg of **8b**-H (total yield: 42%). − In a second fraction as a colorless liquid methyl *N*-(*tert*-butoxycarbonylmethyl)-1-azaspiropentane-2-carboxylate (**9b**) (30 mg, 4%) was isolated. − R_f = 0.13 (LP/Et_2O, 1:1). − IR (neat): $\tilde{\nu}$ = 2973 cm^{-1} (C−H), 2915 (C−H), 1731 (C=O), 1683 (C=O), 1438, 1393, 1340, 1290, 1156, 1041, 963, 849, 759, 618. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.83−0.91 (m, 1 H, *c*Pr−H), 0.93−1.22 (m, 3 H, *c*Pr−H), 1.43 [s, 9 H, $C(CH_3)_3$], 2.56 (s, 1 H, 2-H), 3.03 (d, ^2J = 16.1 Hz, A-part of an AB system, 1 H, NCH_2), 3.32 (d, ^2J = 16.1 Hz, B-part of an AB system, 1 H, NCH_2), 3.75 (s, 3 H, CO_2CH_3). − ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 1.99 (−, *c*Pr−C), 3.54 (−, *c*Pr−C), 27.95 [+, $C(CH_3)_3$], 43.82 (+, C-2), 45.14 (C_{quat}, C-3), 52.32 (+, CO_2CH_3), 58.97 (−, NCH_2), 81.58 [C_{quat}, $C(CH_3)_3$], 168.52 (C_{quat}, CO_2R),

170.45 (C_{quat}, CO_2R). − MS (70 eV, EI): *m/z* (%): 241 (23) [M^+], 226 (42) [$M^+ - CH_3$], 210 (5) [$M^+ - OCH_3$], 185 (26) [$M^+ - C_4H_8$], 170 (35) [$M^+ - C_4H_8 - CH_3$], 154 (5) [$M^+ - C_4H_8 - OCH_3$], 140 (48) [$M^+ - CO_2C(CH_3)_3$], 126 (45) [$M^+ - C_4H_8 - CO_2CH_3$], 98 (20) [$M^+ - C_4H_8 - CO_2CH_3 - CO$], 74 (33) [$C_3H_6O_2^+$], 57 (100) [$C_4H_9^+$]. − MS (DCI); *m/z* (%): 500 (7) [$2 \times M + NH_4^+$], 483 (100) [$2 \times M + H^+$], 276 (10) [$M + NH_3 + NH_4^+$], 259 (100) [$M + NH_4^+$], 242 (63) [$M + H^+$]. − HRMS [M^+]; *m/z* calculated for $C_{12}H_{19}NO_4$: 241.1314; found 241.1314. − In a third fraction 73 mg (8%) of **6b**-H could be recovered.

Methyl *N*-Aryl-1-azaspiropentane-2-carboxylates (9). − General Procedure (GP1): To a solution of **4** (0.71 mmol) in THF (10 mL) was added an amine **5**-H (0.71 mmol). After stirring for 30 min at room temp., the solution was concentrated in vacuo. The residue was purified by column filtration through silica gel (I, *n*-pentane/Et_2O, 3:1). The isolated amine adduct **6**-H was immediately dissolved in MeOH, and NEt_3 (1.0 mL, 7.2 mmol) was added. After the solution had been stirred at room temp., the solvent was removed in vacuo, and the residue was purified by column chromatography to give product **9**.

Methyl *N*-Benzyl-1-azaspiropentane-2-carboxylate (9a): Reaction of **4** (104 mg, 0.71 mmol) with **5a**-H (76 mg, 0.71 mmol) according to GP1 gave **6a**-H (168 mg, 93%) as a colorless liquid. Stirring of **6a**-H (160 mg, 0.63 mmol) in MeOH (6 mL) in the presence of NEt_3 (1.0 mL, 7.2 mmol) for 24 h, followed by workup as described above, furnished after column chromatography on aluminum oxide (III, 30 g, Et_2O) as a colorless liquid **9a** (20 mg, 14%). − $R_f = 0.36$ (*n*-pentane/Et_2O, 1:1). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.84−1.25 (m, 4 H, *c*Pr−H), 2.59 (s, 1 H, 2-H), 3.52 (d, ^2J = 13.9 Hz, A-part of an AB system, 1 H, $PhCH_2$), 3.73 (s, 3 H, OCH_3), 3.78 (d, ^2J = 13.8 Hz, B-part of an AB system, 1 H, $PhCH_2$), 7.24−7.33 (m, 5 H, Ph). − ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 1.94 (−, *c*Pr−C), 3.53 (−, *c*Pr−C), 43.56 (+, C-2), 45.83 (C_{quat}, C-3), 52.26 (+, OCH_3), 61.23 (−, CH_2Ph), 127.09 (+, Ph), 127.66 (+, Ph), 128.39 (+, Ph), 138.09 (C_{quat}, Ph). − MS (70 eV, EI); *m/z* (%): 217 (1) [M^+], 202 (2) [$M^+ - CH_3$], 186 (6) [$M^+ - OCH_3$], 158 (7) [$M^+ - CO_2CH_3$], 129 (6), 126 (5) [$M^+ - PhCH_2$], 91 (100) [$PhCH_2^+$]. HRMS (M^+); *m/z* calculated for $C_{13}H_{15}NO_2$: 217.1102; found 217.1102. − In a second fraction 20 mg (26%) of **5a**-H could be recovered.

***N*-Alkyl-1-azaspiropentane-2-carboxylic Acid Alkylamides and *N*-Arylmethyl-1-azaspiropentane-2-carboxylic Acid Arylmethylamides (10). − General Procedure (GP2):** To a solution of **4** (500 mg, 3.41 mmol) in THF (20 mL) was added an amine **5**-H (3.41 mmol). The mixture was stirred at room temp. overnight, then cooled to −10 °C, before NEt_3 (2 mL), a second equivalent of an amine **5**-H (3.41 mmol) and NaH (270 mg, 6.75 mmol, 60% suspension in mineral oil) were added. The resulting suspension was allowed to warm to room temp. and stirred (for the exact time, see the particular example). Workup: **Method A:** To the resulting orange mixture were added MeOH (5 mL) and silica gel (5 g). The solvent was evaporated, and the remaining solid was chromatographed on silica gel. **Method B:** To the resulting suspension was added H_2O (50 mL), and the mixture was extracted with Et_2O (3 × 30 mL). The organic layers were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel. The product resulting from both methods was recrystallized, if possible, from Et_2O at −20 °C.

***N*-Benzyl-1-azaspiropentane-2-carboxylic Acid Benzylamide (10aa):** A solution of **4** (500 mg, 3.41 mmol) in THF (20 mL) was treated with **5a**-H (730 mg, 6.81 mmol) according to GP2, and the mixture was stirred for 48 h. Workup was carried out according to method A. Column chromatography on silica gel (I, 30 g, LP/Et_2O, 1:1−1:2, CH_2Cl_2/MeOH 10:1) gave **10aa** (590 mg, 59%) which crystallized as a colorless solid. − M.p. 36 °C; $R_f = 0.55$ (Et_2O). − IR (KBr): $\tilde{\nu}$ = 3307 cm^{-1}, (N−H), 3062 (C−H), 3031 (C−H), 2928 (C−H), 1663 (C=O), 1526, 1496, 1454, 1266, 1155, 1077, 1029, 737, 700, 668, 458. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.84−1.03 (m, 2 H, *c*Pr−H), 1.05−1.19 (m, 2 H, *c*Pr−H), 2.66 (s, 1 H, CHN), 3.56 (d, ^2J = 13.8 Hz, A-part of an AB system, 1 H, $PhCH_2$), 3.67 (d, ^2J = 13.8 Hz, B-part of an AB system, 1 H, $PhCH_2$), 4.40 (dd, ^3J = 4.8, ^2J = 14.5 Hz, A-part of an ABX system, 1 H, $PhCH_2$), 4.48 (dd, B-part of an ABX system, ^3J = 4.8, ^2J = 14.5 Hz, 1 H, $PhCH_2$), 7.13−7.35 (m, 11 H, Ph, CONH). − ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 2.04 (−, *c*Pr−C), 2.95 (−, *c*Pr−C), 42.59 (−, $PhCH_2$), 45.07 (C_{quat}, C-3), 45.83 (+, C-2), 60.20 (−, $PhCH_2$), 127.16 (+, Ph), 127.23 (+, Ph), 127.54 (+, Ph), 127.58 (+, Ph), 128.46 (+, Ph), 128.54 (+, Ph), 138.38 (C_{quat}, Ph), 138.47 (C_{quat}, Ph), 169.84 (C_{quat}, C=O). − MS (70 eV, EI); *m/z* (%): 292 (< 1) [M^+], 291 (< 1) [$M^+ - H$], 235 (1), 201 (3) [$M^+ - PhCH_2$], 186 (11) [$M^+ - PhCH_2NH$], 159 (19) [$M^+ - PhCH_2NCO$], 106 (7) [$PhCH_2NH^+$], 105 (7) [$PhCHNH^+$], 91 (100) [$PhCH_2^+$]. − $C_{19}H_{20}N_2O$ (292.4): calcd. C 78.06, H 6.89, N 9.58; found C 77.97, H 6.91, N 9.61.

***N*-(*p*-Methoxybenzyl)-1-azaspiropentane-2-carboxylic Acid *p*-Methoxybenzylamide (10cc):** A solution of **4** (500 mg, 3.41 mmol) in THF (20 mL) was treated with **5c**-H (940 mg, 6.85 mmol) according to GP2, and the mixture was stirred for 36 h. Workup was carried out according to method B. Column chromatography on silica gel (I, 30 g, LP/Et_2O, 1:1 − Et_2O) gave **10cc** (320 mg, 22%) which crystallized as a colorless solid. − M.p. 87 °C; $R_f = 0.42$ (Et_2O). − IR (KBr): $\tilde{\nu}$ = 3261 cm^{-1} (N−H), 3060 (C−H), 3006 (C−H), 2957 (C−H), 2836 (C−H), 1651 (C=O), 1614, 1585, 1513, 1456, 1360, 1301, 1254, 1174, 1032, 831, 805, 734, 583, 513. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.80−0.93 (m, 2 H, *c*Pr−H), 1.04−1.23 (m, 2 H, *c*Pr−H), 2.61 (s, 1 H, 2-H), 3.47 (d, ^2J = 13.4 Hz, A-part of an AB system, 1 H, $PhCH_2$), 3.60 (d, ^2J = 13.4 Hz, B-part of an AB system, 1 H, $PhCH_2$), 3.79 (s, 6 H, $PhOCH_3$), 4.31 (dd, ^3J = 6.1, ^2J = 14.9 Hz, A-part of an ABX system, 1 H, $PhCH_2$), 4.40 (dd, ^3J = 6.1, ^2J = 14.9 Hz, B-part of an ABX system, 1 H, $PhCH_2$), 6.83 (d, ^3J = 8.6 Hz, 4 H, Ph), 7.00 (br. s, 1 H, NH), 7.09−7.19 (m, 4 H, Ph). − ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 1.98 (−, *c*Pr−C), 2.86 (−, *c*Pr−C), 42.07 (−, $PhCH_2$), 44.92 (+, OCH_3), 45.82 (C_{quat}, *c*Pr−C), 5.20 (+, OCH_3), 55.21 (+, C-2), 59.67 (−, $PhCH_2$), 113.81 (+, Ph), 113.88 (+, Ph), 128.57 (+, Ph), 128.79 (+, Ph), 130.41 (C_{quat}, Ph), 130.43 (C_{quat}, Ph), 158.71 (C_{quat}, Ph), 158.79 (C_{quat}, Ph), 169.82 (C_{quat}, CONH). − MS (70 eV, EI): *m/z* (%): 352 (< 1) [M^+], 247 (2), 136 (19) [$MeOPhCH_2NH^+$], 121 (100) [$MeOPhCH_2^+$]; $C_{21}H_{24}N_2O_3$ (352.4): calcd. C 71.57, H 6.86; found C 71.42, H 6.92.

***N*-Benzyl-1-azaspiropentane-2-carboxylic Acid *p*-Methoxybenzylamide (10ac):** A solution of **4** (3.00 g, 20.5 mmol) in THF (20 mL) was treated first with **5a**-H (2.20 g, 20.5 mmol) and then with **5c**-H (2.80 g, 20.4 mmol) according to GP2, and the mixture was stirred for 18 h. Workup was carried out according to method A. Column chromatography on silica gel (I, 30 g, LP/Et_2O, 1:1 − Et_2O) gave **10ac** (3.10 g, 47%) which crystallized as a colorless solid. − M.p. 79 °C; $R_f = 0.43$ (Et_2O). − IR (KBr): $\tilde{\nu}$ = 3297 cm^{-1} (N−H), 3028 (C−H), 3003 (C−H), 2957 (C−H), 2936 (C−H), 2874 (C−H), 2835 (C−H), 1664 (C=O), 1587, 1516, 1451, 1356, 1305, 1254, 1161, 1117, 1037, 1008, 811, 737, 699, 625, 574, 518, 455. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.81−0.97 (m, 2 H, *c*Pr−H), 1.05−1.19 (m, 2 H, *c*Pr−H), 2.64 (s, 1 H, 2-H), 3.57 (d, ^2J = 13.8 Hz, A-part of an AB system, 1 H, $PhCH_2$), 3.66 (d, ^2J =

13.8 Hz, B-part of an AB system, 1 H, $PhCH_2$), 3.79 (s, 3 H, $PhOCH_3$), 4.29−4.45 (m, 2 H, $PhCH_2$), 6.84 (d, ^3J = 8.6 Hz, 2 H, Ph), 7.03 (br. s, 1 H, NH), 7.13 (d, ^3J = 8.6 Hz, 2 H, Ph), 7.24−7.35 (m, 5 H, Ph). − ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 1.96 (−, *c*Pr−C), 2.84 (−, *c*Pr−C), 42.07 (−, $PhCH_2$), 45.03 (+, OCH_3), 45.82 (C_{quat}, *c*Pr−C), 55.23 (+, C-2), 60.20 (−, $PhCH_2$), 113.92 (+, Ph), 127.12 (+, Ph), 127.49 (+, Ph), 128.42 (+, Ph), 128.59 (+, Ph), 130.45 (C_{quat}, Ph), 138.33 (C_{quat}, Ph), 158.77 (C_{quat}, Ph), 169.69 (C_{quat}, CONH). − MS (70 eV, EI): *m/z* (%): 322 (2) [M^+], 231 (1) [$M^+ - PhCH_2$], 203 (4) [$M^+ - PhCH_2 - C_2H_4$], 186 (11) [$M^+ - MeOPhCH_2NH$], 159 (20), 136 (44) [$MeOPhCH_2NH^+$], 121 (51) [$MeOPhCH_2^+$], 91 (100) [$PhCH_2^+$]. − $C_{20}H_{22}N_2O_2$ (322.4): calcd. C 74.51, H 6.88; found C 74.40, H 6.88.

***N*-Benzyl-1-azaspiropentane-2-carboxylic Acid (*S*)-Phenylethylamide (10ad):** A solution of **4** (1.00 g, 6.82 mmol) in THF (20 mL) was treated first with **5a**-H (740 mg, 6.90 mmol) and then with **5d**-H (840 mg, 6.93 mmol) according to GP2, and the mixture was stirred for 48 h. Workup was carried out according to method B. Column chromatography on silica gel (I, 30 g, LP/Et_2O, 2:1−1:1) gave **10ad** (986 mg, 47%) as a colorless liquid which consisted of two diastereomers in a ratio of 1.1:1. − R_f = 0.17 (LP/Et_2O, 1:1). − IR (neat): $\tilde{\nu}$ = 3379 cm^{-1} (N−H), 3062 (C−H), 3030 (C−H), 2973 (C−H), 2927 (C−H), 2868 (C−H), 1669 (C=O), 1526, 1496, 1454, 1361, 1266, 1210, 1155, 1132, 1100, 1076, 1029, 972, 737, 701. − Major isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.73−1.19 (m, 4 H, *c*Pr−H), 1.46 (d, ^3J = 7.0 Hz, 3 H, CH_3), 2.60 (s, 1 H, 2-H), 3.43 (d, ^2J = 13.9 Hz, A-part of an AB system, 1 H, $PhCH_2$), 3.51 (d, ^3J = 13.9 Hz, B-part of an AB system, 1 H, $PhCH_2$), 5.02−5.19 (m, 1 H, PhCH), 7.08 (br. s, 1 H, NH), 7.12−7.47 (m, 10 H, Ph). − ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 1.67 (−, *c*Pr−C), 2.50 (−, *c*Pr−C), 21.85 (+, CH_3), 44.69 (+, C-2), 45.53 (C_{quat}, *c*Pr−C), 47.54 (+, *C*HCH_3), 58.81 (−, $PhCH_2$), 125.60 (+, Ph), 126.85 (+, Ph), 126.98 (+, Ph), 127.30 (+, Ph), 128.20 (+, Ph), 128.29 (+, Ph), 138.08 (C_{quat}, Ph), 142.92 (C_{quat}, Ph), 168.68 (C_{quat}, CONH). − Minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.73−1.19 (m, 4 H, *c*Pr−H), 1.48 (d, ^3J = 7.0 Hz, 3 H, CH_3), 2.62 (s, 1 H, 2-H), 3.70 (d, ^2J = 13.9 Hz, A-part of an AB system, 1 H, $PhCH_2$), 3.76 (d, ^2J = 13.9 Hz, B-part of an AB system, 1 H, $PhCH_2$), 5.02−5.19 (m, 1 H, PhCH), 7.08 (br. s, 1 H, NH), 7.12−7.47 (m, 10 H, Ph). − ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 1.85 (−, *c*Pr−C), 2.62 (−, *c*Pr−C), 21.99 (+, CH_3), 44.73 (+, C-2), 45.53 (C_{quat}, *c*Pr−C), 47.57 (+, *C*HCH_3), 58.88 (−, $PhCH_2$), 126.82 (+, Ph), 126.91 (+, Ph), 127.17 (+, Ph), 127.30 (+, Ph), 128.20 (+, Ph), 128.29 (+, Ph), 138.17 (C_{quat}, Ph), 143.22 (C_{quat}, Ph), 168.78 (C_{quat}, CONH). − MS (70 eV, EI); *m/z* (%): 306 (< 1) [M^+], 235 (7), 186 (18) [$M^+ - PhCHCH_3NH$], 159 (23), 120 (18) [$PhCHCH_3NH^+$], 105 (39) [$PhCHCH_3^+$], 91 (100) [$PhCH_2^+$]. − $C_{20}H_{22}N_2O$ (306.4): calcd. C 78.40, H 7.24, N 9.14; found C 78.78, H 7.08, N 8.99.

***N*-(*S*)-Phenylethyl-1-azaspiropentane-2-carboxylic Acid Benzylamide (10da):** A solution of **4** (500 mg, 3.41 mmol) in THF (20 mL) was treated first with **5d**-H (420 mg, 3.47 mmol) and then with **5a**-H (370 mg, 3.45 mmol) according to GP2, and the mixture was stirred for 36 h. Workup was carried out according to method B. Column chromatography on silica gel (I, 15 g, LP/Et_2O, 1:1 − Et_2O) gave **10da** (371 mg, 36%) as a colorless liquid consisting of two diastereomers in a ratio of 1.6:1. − R_f = 0.24 (LP/Et_2O, 1:1). − IR (neat): $\tilde{\nu}$ = 3384 cm^{-1} (N−H), 3054 (C−H), 2985 (C−H), 1670 (C=O), 1526, 1496, 1454, 1420, 1265, 1155, 1076, 1029, 896, 745, 704. − Major isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.70−1.44 (m, 4 H, *c*Pr−H), 1.46 (d, ^3J = 7.4 Hz, 3 H, CH_3), 2.70 (s, 1 H, 2-H), 3.02−3.20 (m, 1 H, PhCH), 4.24−4.68 (m, 2 H, $PhCH_2$), 7.04−7.45 (m, 11 H, Ph, NH). − Minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.70−1.44 (m, 4 H, *c*Pr−H), 1.27 (d, ^3J = 7.4 Hz, 3 H, CH_3), 2.49 (s, 1 H, 2-H), 3.02−3.20 (m, 1 H, PhCH), 5.10−5.23 (m, 2 H, $PhCH_2$), 7.04−7.43 (m, 11 H, Ph, NH). − MS (70 eV, EI); *m/z* (%): 306 (7) [M^+], 202 (17), 162 (18), 105 (100) [$PhCHCH_3^+$], 91 (43) [$PhCH_2^+$], 86 (39).

***N*-Alkyl-1-azaspiropentane-2-carboxylic Acid Amides and *N*-Arylmethyl-1-azaspiropentane-2-carboxylic Acid Amides (12). − General Procedure (GP3):** A solution of **4** (500 mg, 3.41 mmol) and an amine **5**-H (3.45 mmol) in THF (20 mL) was stirred at room temp. for 5 h. The mixture was saturated with gaseous ammonia at −10 °C, after which NEt_3 (2 mL) and NaH (280 mg, 7.00 mmol, 60% suspension in mineral oil) were added. The resulting suspension was allowed to warm to room temp. and stirred (for the exact time, see the particular example). MeOH (5 mL) and silica gel (5 g) were added. The solvents were evaporated and the remaining solid was chromatographed on silica gel. The product was recrystallized from Et_2O at −20 °C.

***N*-Benzyl-1-azaspiropentane-2-carboxamide (12a):** A solution of **4** (500 mg, 3.41 mmol) in THF (20 mL) was first treated with **5a**-H (370 mg, 3.45 mmol) and subsequently with ammonia according to GP3. The mixture was stirred for 24 h and then worked up. Column chromatography on silica gel (I, 30 g, LP/Et_2O, 1:1 − Et_2O) gave **12a** (330 mg, 48%), which crystallized as a colorless solid. − M.p. 135 °C, R_f = 0.15 (Et_2O). − IR (KBr): $\tilde{\nu}$ = 3370 cm^{-1} (N−H), 3144 (N−H), 2861 (C−H), 1683 (C=O), 1610, 1429, 1407, 1357, 1153, 1092, 1016, 915, 755, 725, 698, 667, 638, 513. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.83−0.98 (m, 2 H, *c*Pr−H), 1.03−1.14 (m, 2 H, *c*Pr−H), 2.54 (s, 1 H, 2-H), 3.59 (d, ^2J = 11.4 Hz, A-part of an AB system, 1 H, $PhCH_2$), 3.68 (d, ^2J = 11.4 Hz, B-part of an AB system, 1 H, $PhCH_2$), 6.48 (br. s, 1 H, NH), 6.59 (br. s, 1 H, NH), 7.20−7.38 (m, 5 H, Ph). − ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 2.05 (−, *c*Pr−C), 2.88 (−, *c*Pr−C), 44.71 (+, C-2), 45.76 (C_{quat}, *c*Pr−C), 60.10 (−, $PhCH_2$), 126.96 (+, Ph), 127.30 (+, Ph), 128.28 (+, Ph), 138.21 (C_{quat}, Ph), 173.22 (C_{quat}, $CONH_2$). − MS (70 eV, EI); *m/z* (%): 201 (1) [M^+ − H], 185 (9) [$M^+ - NH_3$], 157 (10) [$M^+ - NH_3 - C_2H_4$], 91 (100) [$PhCH_2^+$], 77 (2) [Ph^+], 65 (11). − $C_{12}H_{14}N_2O$ (202.3): calcd. C 71.27, H 6.98; found C 71.22, H 7.07.

***N*-(2′-Phenylethyl)-1-azaspiropentane-2-carboxamide (12e):** A solution of **4** (2.00 g, 13.6 mmol) in THF (70 mL) was treated with **5g**-H (1.65 g, 13.6 mmol) and then with ammonia according to GP3. The mixture was stirred for 50 h and then worked up. Column chromatography on silica gel (I, 40 g, Et_2O/EtOAc, 1:1−1:2) gave **12e** (985 mg, 33%), which crystallized as a colorless solid. − M.p. 71 °C; R_f = 0.25 (Et_2O/EtOAc, 1:1). − IR (KBr): $\tilde{\nu}$ = 3425 cm^{-1} (N−H), 3177 (N−H), 3080 (C−H), 3030 (C−H), 3002 (C−H), 2943 (C−H), 2932 (C−H), 2846 (C−H), 1657 (C=O), 1602, 1496, 1454, 1402, 1151, 1111, 1092, 749, 700, 646. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.77−0.86 (m, 3 H, *c*Pr−H), 0.88−1.05 (m, 1 H, *c*Pr−H), 2.32 (s, 1 H, 2-H), 2.58−2.86 (m, 4 H, CH_2), 5.87 (br. s, 1 H, NH_2), 6.48 (br. s, 1 H, NH_2), 7.17−7.32 (m, 5 H, Ph). − ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 1.92 (−, *c*Pr−C), 2.98 (−, *c*Pr−C), 36.17 (−, $PhCH_2$), 44.78 (+, C-2), 45.62 (C_{quat}, C-3), 58.30 (−, NCH_2), 126.26 (+, Ph), 128.36 (+, Ph), 128.69 (+, Ph), 139.56 (C_{quat}, Ph), 173.34 (C_{quat}, $CONH_2$). − MS (70 eV, EI): *m/z* (%): 217 (1) [M^+ + H], 216 (1) [M^+], 215 (1) [M^+ − H], 199 (2) [$M^+ - NH_3$], 172 (3) [$M^+ - CONH_2$], 145 (3) [$M^+ + H - CONH_2 - C_2H_4$], 125 (31), 112 (30) [$M^+ + H - PhC_2H_4$], 105 (100) [$PhC_2H_4^+$], 91 (15) [$PhCH_2^+$], 77 (18) [$Ph^+$], 65 (4) [$C_5H_5^+$]. − $C_{13}H_{16}N_2O$ (216.3): calcd. C 72.19, H 7.46, N 12.95; found C 72.37, H 7.46, N 12.96.

***N*-(2′-Phenylethyl)-1-azaspiropentane-2-carboxylic Acid Ethoxycarbonylmethylamide (13e):** To a solution of **12e** (232 mg, 1.07 mmol) in THF (10 mL) was added NaH (44 mg, 1.10 mmol, 60% suspension in mineral oil) at −15 °C. The mixture was stirred for 8 h at room temp., then cooled to −15 °C and ethyl bromoacetate (198 mg, 1.19 mmol) was added dropwise. After the mixture had been stirred for 43 h at room temp., EtOH (1 mL) was added and the solvent was evaporated in vacuo. Purification of the residue by flash chromatography (I, 40 g, LP/EtOAc, 4:3 − EtOAc) gave **13e** (83 mg, 25%) as a colorless oil. − R_f = 0.19 (LP/EtOAc, 4:3). − IR (neat): $\tilde{\nu}$ = 3383 cm^{-1} (N−H), 3063 (C−H), 3025 (C−H), 2980 (C−H), 2932 (C−H), 2847 (C−H), 1750 (C=O), 1675 (C=O), 1522, 1496, 1453, 1409, 1375, 1354, 1195, 1156, 1028, 752, 701, 518. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.76−1.04 (m, 4 H, *c*Pr−H), 1.26 (t, ^3J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 2.37 (s, 1 H, 2-H), 2.58−2.84 (m, 4 H, NC_2H_4Ph), 3.85−4.07 (m, 2 H, NCH_2CO_2Et), 4.19 (q, ^3J = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 7.09−7.29 (m, 6 H, Ph, NH). − ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 1.76 (−, *c*Pr−C), 2.95 (−, *c*Pr−C), 14.11 (+, CH_3), 36.23 (−, $PhCH_2$), 40.65 (−, NCH_2CO_2Et), 44.76 (+, C-2), 45.64 (C_{quat}, C-3), 58.33 (−, NCH_2), 61.30 (−, OCH_2), 126.25 (+, Ph), 128.35 (+, Ph), 128.76 (+, Ph), 139.59 (C_{quat}, Ph), 169.58 (C_{quat}, CONH), 170.49 (C_{quat}, CO_2Et). − MS (70 eV, EI); *m/z* (%): 303 (1) [M^+ + H], 302 (1) [M^+], 257 (4) [M^+ − OC_2H_5], 212 (5) [M^+ + H − $PhCH_2$], 211 (43) [M^+ − $PhCH_2$], 198 (18) [M^+ + H − PhC_2H_4], 172 (7), 137 (4), 105 (100) [$PhC_2H_4^+$]. − HRMS [M^+]; *m/z* calculated for $C_{17}H_{22}N_2O_3$: 302.1630; found 302.1630. − In a second fraction 52 mg (22%) **12e** could be recovered.

Methyl 5-[*N*-(2′′-Phenylethyl)-1-azaspiropent-2′-yl]4-aza-6-oxaspiro[2.4]hept-4-ene-7-carboxylate (14e): To a solution of **12e** (297 mg, 1.37 mmol) in THF (5 mL) was added NaH (55 mg, 1.37 mmol, 60% suspension in mineral oil) at −15 °C. The mixture was stirred for 6 h at room temp. and then cooled to −15 °C after diluting with CH_2Cl_2 (5 mL). Now a solution of **4** (221 mg, 1.51 mmol) and dibenzo-18-crown-6 (72 mg, 0.20 mmol) in CH_2Cl_2 (10 mL) was added dropwise. After stirring for 2 d at room temp., ice-cold water (20 mL) was added and the phases were separated. The water layer was extracted with CH_2Cl_2 (3 × 30 mL), and the organic layers were washed with saturated NaCl solution. The solvent was evaporated and flash chromatography of the residue (II, 40 g, LP/EtOAc, 3:4−1:4) gave **14e** (129 mg, 29%) as a slightly yellow liquid which consisted of two diastereomers in a ratio of 2:1. − R_f = 0.20 (LP/EtOAc, 4:3). − IR (neat): $\tilde{\nu}$ = 3062 cm^{-1} (C−H), 3025 (C−H), 3003 (C−H), 2951 (C−H), 2845 (C−H), 1762 (C=O), 1738 (C=O), 1662 (C=N), 1583, 1496, 1453, 1437, 1415, 1355, 1286, 1202, 1178, 1161, 1055, 1023, 750, 700. − Major isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.76−0.95 (m, 3 H, *c*Pr−H), 0.96−1.17 (m, 3 H, *c*Pr−H), 1.18−1.25 (m, 2 H, *c*Pr−H), 2.55 (s, 1 H, 2′-H), 2.58−2.95 (m, 4 H, 2 CH_2), 3.72 (s, 3 H, OCH_3), 4.77 (s, 1 H, $CHCO_2Me$), 7.10−7.29 (m, 5 H, Ph). − ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 1.40 (−, *c*Pr−C), 3.79 (−, *c*Pr−C), 9.82 (−, *c*Pr−C), 14.48 (−, *c*Pr−C), 36.30 (−, $PhCH_2$), 40.06 (+, C-2′), 44.51 (C_{quat}, C-3′), 51.98 (+, CO_2CH_3), 52.76 (C_{quat}, C-3), 59.88 (−, NCH_2), 79.51 (+, $CHCO_2Me$), 126.07 (+, Ph), 128.31 (+, Ph), 128.64 (+, Ph), 139.49 (C_{quat}, Ph), 164.72 (C_{quat}, C=N), 169.13 (C_{quat}, CO_2Me). − Minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.73−0.95 (m, 3 H, *c*Pr−H), 0.96−1.17 (m, 3 H, *c*Pr−H), 1.18−1.25 (m, 2 H, *c*Pr−H), 2.43 (s, 1 H, 2′-H), 2.58−2.95 (m, 4 H, 2 CH_2), 3.77 (s, 3 H, OCH_3), 4.73 (s, 1 H, $CHCO_2Me$), 7.10−7.29 (m, 5 H, Ph). − ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 1.40 (−, *c*Pr−C), 3.37 (−, *c*Pr−C), 9.93 (−, *c*Pr−C), 14.37 (−, *c*Pr−C), 36.18 (−, $PhCH_2$), 40.06 (+, C-2′), 44.21 (C_{quat}, C-3′), 52.18 (+, CO_2CH_3), 52.76 (C_{quat}, C-3), 59.77 (−, NCH_2), 79.61 (+, $CHCO_2Me$), 126.14 (+, Ph), 128.48 (+, Ph), 128.72 (+, Ph), 139.58 (C_{quat}, Ph), 164.82 (C_{quat}, C=N), 169.06 (C_{quat}, CO_2Me). − MS (70 eV, EI): *m/z* (%): 327 (3) [M^+ + H], 326 (3) [M^+], 325 (2) [M^+ − H], 298 (13) [M^+ − C_2H_4], 283 (3) [M^+ − C_3H_7], 235 (23) [M^+ − $PhCH_2$], 221 (8) [M^+ − PhC_2H_4], 205 (10) [M^+ − $NH_2C_2H_4Ph$], 105 (100) [$PhC_2H_4^+$], 91 (100) [$PhCH_2^+$]. − HRMS [M^+]; *m/z* calculated for $C_{19}H_{22}N_2O_3$: 326.1630; found 326.1630. − In a second fraction 83 mg (28%) of **12e** could be recovered.

Acknowledgments

This work was supported by the Deutsche Forschungsgemeinschaft (SFB 416, Project A3) and the Fonds der Chemischen Industrie. We are grateful to the companies BASF, Bayer, Degussa, Hoechst and Hüls AG for generous gifts of chemicals. M. T. B. thanks the European Community for a postdoctoral fellowship (N. ERBCHBGCT 940731).

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[15] Unsubstituted aziridinecarboxamide has been found to be a reasonably stable compound, cf.: K. Jähnisch, E. Schmitz, E. Gründemann, *J. Prakt. Chem*. **1979**, *321*, 712−720.

[16] Crystallographic data for **9**: Data were collected at −140°C using a Siemens-Stoe Huber four-circle diffractometer equipped with a SMART CCD area detector, with Mo-K_α radiation (λ = 0.71073 Å). The sample-to-detector distance was set to be 5 cm. Reflexions were collected by means of a φ-scan rotation (step width 0.5°), with an exposure time of 15 s/frame. Structure was solved by direct methods (SHELXS-96: G.M. Sheldrick, *Acta Crystallogr., Sect. A* **1990**, *46*, 467) and refined versus F^2 by the least-squares method with all data (SHELXL-96: *Program for Crystal Structure Refinement*, University of Göttingen, **1996**). Single crystal obtained from ethanol, colorless, space group $P\bar{1}$; $Z = 4$, $a = 7.7561(16)$ Å, $b = 9.6162(19)$ Å, $c = 16.034(3)$ Å, $\alpha = 80.08(3)$, $\beta = 82.21(3)$, $\gamma = 68.15(3)°$; $\gamma = 1090.1(4)$ Å^3; $\rho_{calcd.} = 1.232$ Mg/m^3. 11169 reflexions, 3112 unique observed [$I > 2\sigma(I)$], were measured. The non-hydrogen atoms were refined anisotropically. All hydrogen atoms were refined on calculated positions by using a riding method. $R1 = 0.0391$, $wR2 = 0.1047$ (all data) for 272 parameters. Goodness-of-fit on $F^2 = 1.031$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100381. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: int. code + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk).

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[19] M. Tamm, M. Nötzel, A. de Meijere, *J. Org. Chem.*, submitted.

[20] The immediate precursor to methyl 2-chloro-2-cyclopropylideneacetate (**4**), 1-chloro-1-(trichlorovinyl)cyclopropane[11] is commercially available from Merck KGaA, Frankfurter Str. 250, D-64293 Darmstadt, Germany.

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Received January 22, 1999
[O99029]