Cyclopropyl Building Blocks for Organic Synthesis, 53[+] Convenient Syntheses of Novel α- and β-Amino Acids with Spiropentyl Groups

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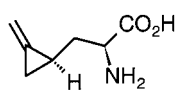
Keywords: Amino acids / Spiro compounds / Michael addition / Copper reagents / Curtius degradation

Racemic spiropentylglycine (**8**) has been synthesized by sodium borohydride reduction of benzyl (*E*/*Z*)-2-chloro-2-spiropentylideneacetate (**5**-Bn), nucleophilic substitution of the chlorine in the product **6** with azide and hydrogenolytic deprotection of the resulting **7** (overall yield 15%). An alternative approach to **8** consisted of the coupling of the higher-order cuprate **10**, generated by halogen-metal exchange from bromospiropentane (**9**), with the electrophilic glycine equivalent **11** followed by deprotection (overall yield 47%). Enantiomerically pure (1′-aminospiropentyl)acetic acid [(*R*)-**16**] (overall yield 16% from **5**-Me) and 1-aminospiropentanecarboxylic acid [(*R*)-**23**] (29% from **5**-Me) were obtained from the Michael adduct **14**-Me of (4*R*,5*S*)-4,5-diphenyloxazolidin-2-one (**13**) and methyl (*E*/*Z*)-2-chloro-2-spiropentylideneacetate (**5**-Me). Racemic 1-aminospiropentanecarboxylic acid (*R*/*S*-**23**) was prepared by rhodium-catalyzed addition of dimethyl diazomalonate to methylenecyclopropane and subsequent Curtius degradation of the halfester **28** via the azide **29** (overall yield 14%). Upon standing in aqueous solution, **23** underwent complete rearrangement to the new 1-amino-2-methylenecyclobutanecarboxylic acid (**24**). The interesting derivative of azabicyclo[3.1.0]hexane-1-carboxylate **34** with an annelated spiropentane moiety and a β-amino acid fragment was incidentally obtained in a one-step intermolecular domino reaction starting with the addition of lithium benzylamide to methyl 2-chloro-2-cyclopropylideneacetate (**32**, 41% yield).

Nature makes use of cyclopropyl groups, not the least as a source for the plant hormone ethylene, since the precursor of ethylene in green plants and their fruits is 1-aminocyclopropanecarboxylic acid (ACC) which is oxidatively degraded by the ethylene-forming enzyme (EFE).[1] Substituted ACC′s are generally inhibitors of EFE,[2] and most of the other more than two dozen known naturally occurring amino acids containing a cyclopropyl group as well as several of their analogs exhibit interesting biological activities.[3] It is not surprising 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 specimens 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] as both show a strong hypoglycemic effect.



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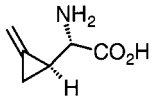

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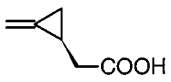

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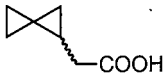

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Since three-membered rings have a number of chemical properties in common with a C=C bond,[7] it ought to be interesting to prepare the spiropentyl analogs of **1** and **2** and test their potential physiological activities. Such an anticipated similarity has been found between (spiropentyl)acetic acid (**4**)[8] and (methylenecyclopropyl)acetic acid (**3**), which is believed to play a crucial role in the biological action of hypoglycine A (**1**).[5] Apart from this, the highly strained spiropentyl unit, functionalized as an amino acid, might show biological effects in its own right. With this in mind, we have developed new methods to prepare different amino acids containing spiropentyl groups, two of them in enantiomerically pure form.

The key starting materials in most of these syntheses were methyl and benzyl (*E*/*Z*)-2-chloro-2-spiropentylideneacetate (*E*/*Z*)-**5**-Me[9a] and (*E*/*Z*)-**5**-Bn, respectively (Scheme 1).

[+] Part 52: C. Zorn, B. Anichini, A. Goti, A. Brandi, S. I. Kozhushkov, A. de Meijere, L. Citti, *J. Org. Chem.* **1999**, in press. Part 51: M. Tamm, M. Thutewohl, C. B. Ricker, M. T. Bes, A. de Meijere, *Eur. J. Org. Chem*. **1999**, 2017−2021.

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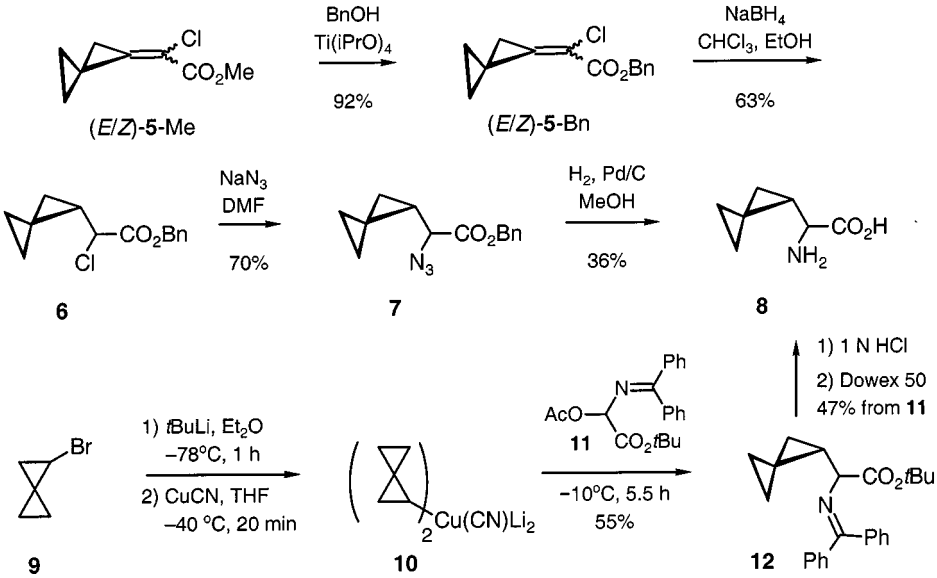
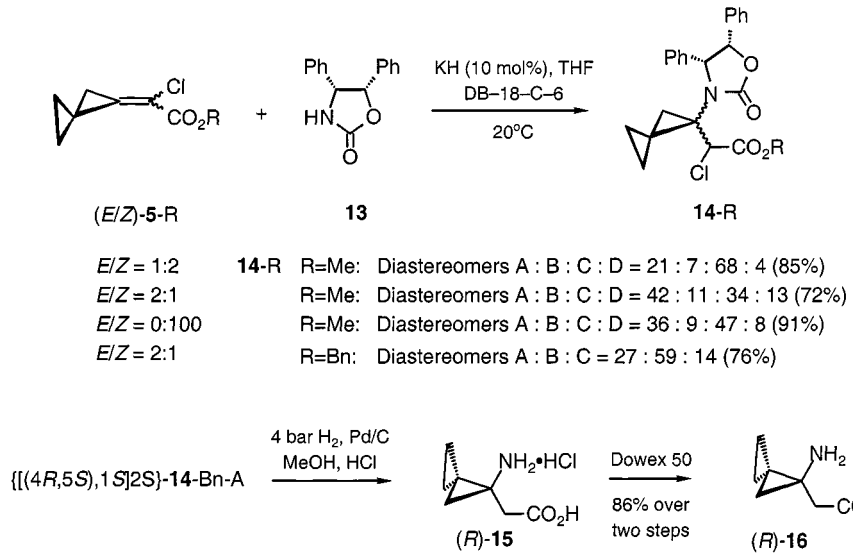
The previously described preparation of (*E*/*Z*)-**5**-Me[9b] was improved on. The first step, the addition of thermally ring-opened tetrachlorocyclopropene to methylenecyclopropane by using a 2.5-fold excess of tetrachlorocyclopropene, proceeded in 69% yield (compared to 39%). The second step gave a 70% yield by a modified procedure.[9a]

Transesterfication of (*E*/*Z*)-**5**-Me with benzyl alcohol with Ti(*i*PrO)$_4$ catalysis[10] gave the benzyl ester (*E*/*Z*)-**5**-Bn which can be more easily and selectively cleaved than the methyl ester, after appropriate transformations. Both esters (*E*/*Z*)-**5**-Me and (*E*/*Z*)-**5**-Bn were purified by column chromatography, and the initially formed 1:2 *E*/*Z* mixtures were separated into the two fractions each, namely 2:1 *E*/*Z* mixtures and the pure *Z*-diastereomers of **5**-Me and **5**-Bn. A complete separation of the two diastereomers could not be achieved. Reduction of benzyl 2-chloro-2-spiropentylideneacetate [(*E*/*Z*)-**5**-Bn] with sodium borohydride in a mixture of chloroform and 2-propanol gave the 2-chloro-2-spiropentyl acetate **6** as a 2:3 mixture of diastereomers. Subsequent nucleophilic substitution of chlorine with sodium azide in anhydrous dimethylformamide followed by hydrogenolytic reduction and deprotection of **7** yielded spiropentylglycine (**8**, Scheme 1).

In an attempt to improve the preparation of the spiropentylglycine (**8**), we have also examined the reaction of an electrophilic glycine equivalent − O′Donnells acetate **11**[11] − with a higher-order mixed cuprate of type $R_2Cu(CN)Li_2$[12] derived from bromospiropentane (**9**)[13] (prepared from 1,1-dibromospiropentane,[14] see Experimental Section) via halogen-metal exchange with *tert*-butyllithium followed by reaction with CuCN at −40°C. The higher-order cuprate **10** thus generated in the reaction with



Scheme 1



Scheme 2

11 yielded the spiropentylglycine derivative **12** (55%) as the only coupling product[15] (Scheme 1). Subsequent deprotection of **12** gave racemic spiropentylglycine **8** (mixture of both diastereomers) in 47% overall yield starting from acetate **11**.

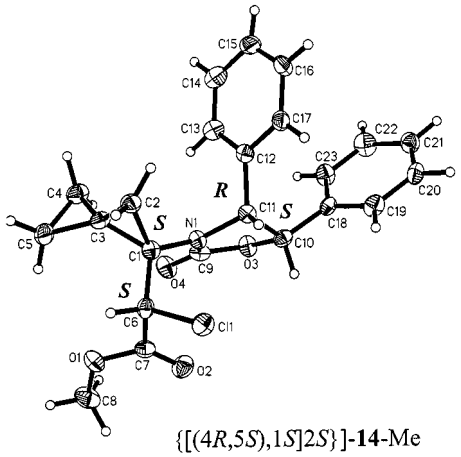
Even more so than the parent 2-chloro-2-cyclopropylideneacetate,[16] the spiropentylidene analogs (*E*/*Z*)-**5**-R are highly reactive Michael acceptors which, among other nucleophiles, readily add ammonia equivalents. For such substrates, (4*R*,5*S*)-4,5-diphenyloxazolidine-2-one (**13**) has been demonstrated to be a suitable chiral ammonia equivalent, allowing for good diastereoselectivities with respect to the stereogenic center α to the alkoxycarbonyl group.[17] Enantiomerically pure **13** is easily prepared from commercially available (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol,[17] and can readily be cleaved by catalytic hydrogenation over palladium on charcoal. A sub-stoichiometric amount (10 mol-%) of potassium hydride is necessary to generate a fraction of the potassium salt of **13** which has a sufficient nucleophilicity (Scheme 2).

Under these conditions, addition of **13** to the methyl ester (*E*/*Z*)-**5**-Me yielded a mixture of all four expected diastereomers **14**-Me, each of them enantiomerically pure, whereas the benzyl ester (*E*/*Z*)-**5**-Bn gave only three diastereomers **14**-Bn (ratio 27:59:14). The ratio of diastereomers **14**-Me is only slightly affected by the composition of the starting material **5**, but the *Z* diastereomer appears to be more reactive in this reaction (Scheme 2). All these diastereomers could be separated by column chromatography.

As the absolute configuration of the oxazolidinone **13** introduced into the adducts of type **14**-*R* is known, it ought to be possible to determine the absolute configuration of the resulting amino acids as well. Crystals of one diastereomer each of **14**-Me-A and **14**-Bn-A appropriate for X-ray crystal structure analyses were obtained by slow evaporation of dilute solutions in hexane/diethyl ether, and their absolute configurations were unequivocally established as {[(4*R*,5*S*),1*S*]2*S*}-**14**-Me and {[(4*R*,5*S*),1*S*]2*S*}-**14**-Bn (Figure 1).

The diastereomer {[(4*R*,5*S*),1*S*]2*S*}-**14**-Bn-A was hydrogenated over palladium on charcoal under 4 bar H_2 pressure in methanol containing hydrochloric acid to yield the hydrochloride (*R*)-**15** of the amino acid (*R*)-**16**. Ion exchange chromatography over Dowex 50 yielded 86% of enantiomerically pure (*R*)-(1′-aminospiropentyl)acetic acid [(*R*)-**16**] (Scheme 2) with an enantiomeric excess of 99%, as determined by gas chromatography on a chiral capillary column (6-TBDMS-2,3-dimethyl-β-CD).[19]

All attempts at a nucleophilic substitution of the chlorine in **14**-Me with azide by treatment with sodium azide under various conditions failed, just as was previously observed for other 2-chloro-2-(1′-diphenyloxazolidinylcyclopropyl)-acetates.[17] Therefore, the previously developed[17] two-step sequence was applied to convert **14**-Me into **18**-Me: reductive dehalogenation of **14**-Me (diastereomers C and D)[20] with zinc-copper couple in THF/H_2O to give the



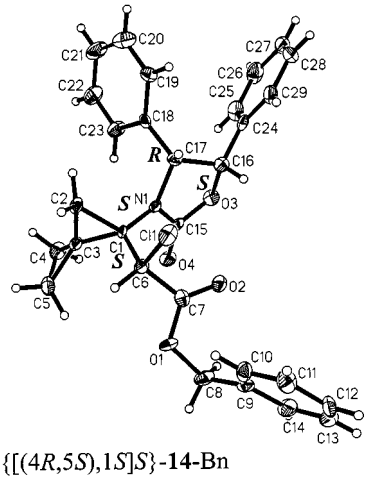
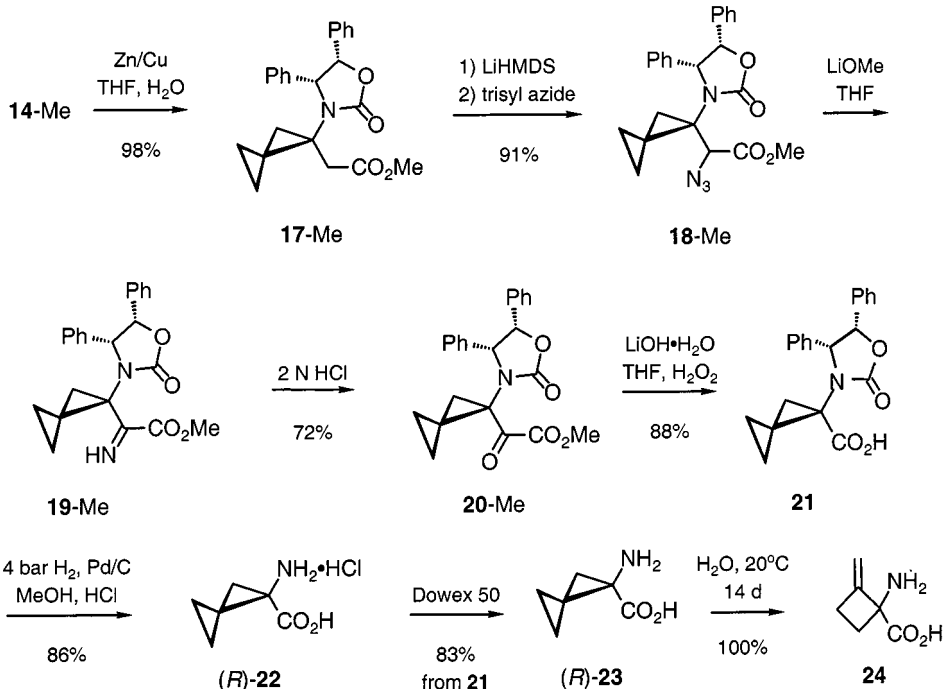


Figure 1. Structures of methyl {[(4*R*,5*S*),1*S*]2*S*}-2-chloro-2-[1-(2-oxo-4,5-diphenyl-3-oxazolidinonyl)spiropentyl]acetate {{[(4*R*,5*S*),1*S*]2*S*}-**14**-Me} and benzyl {[(4*R*,5*S*),1*S*]2*S*}-2-chloro-2-[1-(2-oxo-4,5-diphenyl-3-oxazolidinonyl)spiropentyl]acetate {{[(4*R*,5*S*),1*S*]2*S*}-**14**-Bn} in the crystal[18]

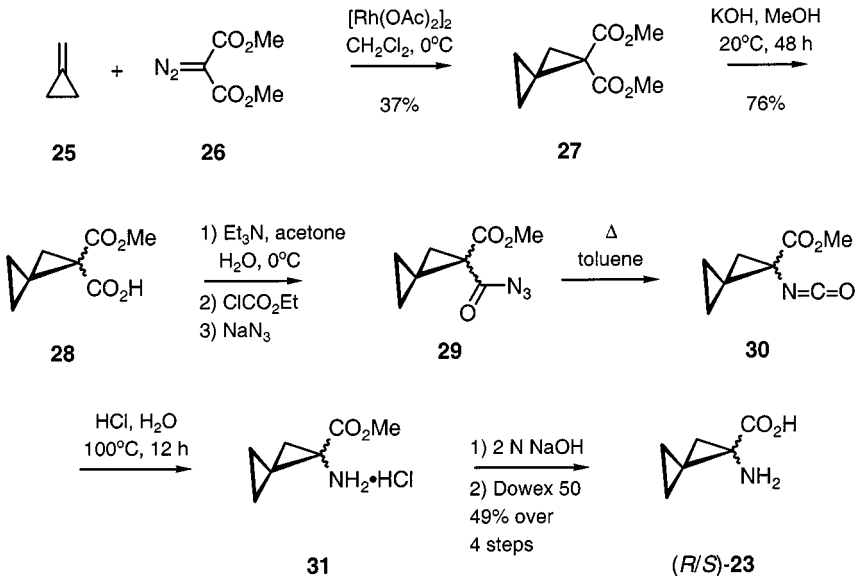
methyl spiropentyl acetate **17**-Me. Deprotonation of **17**-Me with LiHMDS and subsequent reaction of the enolate with trisyl azide (2,4,6-triisopropylbenzenesulfonyl azide) yielded two diastereomers of **18**-Me (91%) in a ratio of 1.6:1.[21] When NaHMDS was used as a base, the yield of **18**-Me was 71%, and the reaction was not consistently reproducible. The α-azido ester **18**-Me was converted into the α-keto ester **20**-Me by treatment with lithium methoxide. Finally, the latter was saponified and oxidatively decarboxylated by treatment with hydrogen peroxide in the presence of lithium hydroxide in THF/H_2O to give the protected amino acid **21**. The free amino acid **23** was obtained in enantiomerically pure form in reasonable yield (83% over the last two steps, 47% overall from **14**-Me) after hydrogenolytic cleavage of the oxazolidinone unit and ion-exchange chromatography over Dowex 50. Taking into account that this sequence of transformations applied to both diastereomers C and D of **14**-Me gave the same single enantiomer, and knowing the absolute configuration of diastereomer **14**-Me-A, the absolute configuration of the amino acid **23** can be derived to be (*R*)-**23**.



Scheme 3

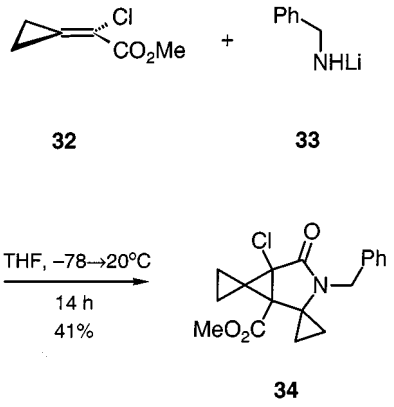
While the hydrochloride **22** appeared to be rather stable, the free acid **23** when left in an aqueous solution at room temperature slowly isomerized with loss of its optical activity to form new 1-amino-2-methylenecyclobutanecarboxylic acid **24**. The mechanism of this rearrangement remains speculative and should consist of the initial homo- or heterolytic cleavage of an activated distal bond followed by methylcyclopropyl-to-butenyl rearrangement and ring closure.

A simple access to racemic 1-aminospiropentanecarboxylic acid [(*R*/*S*)-**23**] was developed as well (Scheme 4). Rhodium(II)-catalyzed addition of dimethyl diazomalonate (**26**) to methylenecyclopropane (**25**) gave dimethyl spiropentane-1,1-dicarboxylate (**27**), albeit in moderate yield (37%). Selective saponification[22] of only one ester group led to the monoester **28** which was transformed into the carboxylic acid azide **29** by activation with ethyl chloroformate and subsequent reaction with sodium azide.[23] Rearrangement to the isocyanate **30** was carried out by heating a solution of **29** in anhydrous toluene until the evolution of nitrogen ceased. Treatment of **30** with aqueous hydrochloric acid at reflux yielded the amino ester hydrochloride **31** which



Scheme 4

was treated with sodium hydroxide at room temperature to give racemic 1-aminospiropentane-1-carboxylic acid [(*R*/*S*-**23**)] in a yield of 49% over the last four steps.



Scheme 5

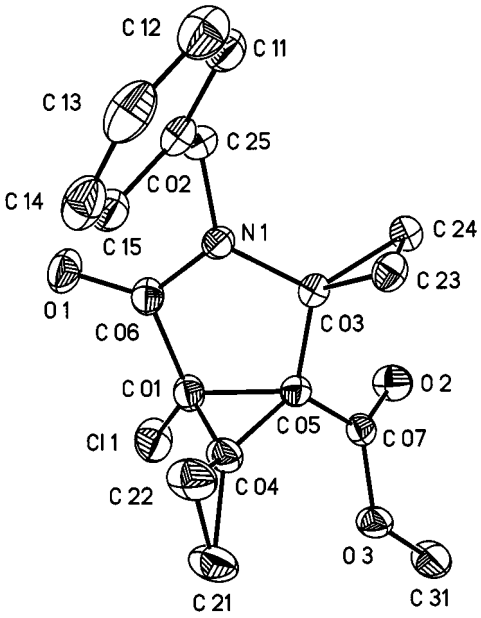


Figure 2. Structure of methyl 3-benzyl-5-chloro-4-oxo-2,6-bis(spirocyclopropyl)-3-azabicyclo[3.1.0]hexane-1-carboxylate (**34**) in the crystal[18]

Formation of the unique spiropentanecarboxylate **34** with a β-amino acid amide feature via the MIMIRC mechanism[24c] was observed when 2-chloro-2-cyclopropylideneacetate (**32**),[9] which had previously been described as a versatile and highly reactive small-ring building block for various types of compounds,[16,17,24] was treated with half an equivalent of lithium benzylamide (**33**) generated from benzylamine and butyllithium.

The structure of **34** was unequivocally established by an X-ray crystal structure analysis (Figure 2) after appropriate crystals had been obtained by slow evaporation of its dilute solution in hexane/Et_2O.

Experimental Section

^1H and ^{13}C NMR: at 250 (^1H) and 62.9 MHz [^{13}C, additional DEPT (Distortionless Enhancement by Polarization Transfer)] on Bruker AM 250 and Varian INOVA-500 instruments in $CDCl_3$ solution, unless otherwise specified, $CHCl_3$/$CDCl_3$ as internal reference. − FT-IR: Bruker IFS 66, measured as KBr pellets, 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. − GC: Siemens Sichromat 1−4. − Starting Materials: Compounds **5**-Me,[9a] **25**,[25] **26**[26] and **32**[9c] were prepared according to published procedures. All other chemicals were used as commercially available. Anhydrous methanol was obtained by distillation from magnesium methoxide. Anhydrous diethyl ether and THF were obtained by distillation from sodium benzophenone ketyl. Other water-free solvents were prepared by common methods.[27] Organic extracts were dried over $MgSO_4$. − Crystal Structure Determinations: Appropriate crystals of compounds **14**-Me, **14**-Bn and **34** were obtained by slow evaporation of their dilute solutions in hexane/Et_2O mixtures. The X-ray data for the compounds were collected on a Bruker SMART-1 K (**14**-Me, **14**-Bn) or a Siemens-Stoe AED2 (**34**) diffractometer with a CCD area detector using graphite monochromated Mo-K_α radiation for the compounds **14**-Me and **34**. The tiny colorless crystals of the compound **14**-Bn proved to be too small for conventional laboratory-based X-ray equipment. Therefore the experiment was performed using a synchrotron radiation of λ = 0.6785 Å at the Station 9.8 of the CLRC Daresbury Laboratory SRS. The structures were solved by direct methods and refined by the full-matrix least squares method on F^2. All non-hydrogen atoms were refined anisotropically, H atoms were located in a difference map and freely refined. Parameters of crystal data collection and structure refinement are presented in Table 1. The absolute configurations of compounds **14**-Me and **14**-Bn were assigned on the basis of the refinement of Flack parameters which are equal to 0.01(7) and 0.0(1), respectively, for the reported configurations and 0.9(1) for the inverted models of both molecules.

Molecular Structures of 14-Me, 14-Bn and 34: Selected bond lengths [Å] and angles [°] (for the atom numbering see Figures 1, 2; standard deviations are given in parentheses).

14-Me: Cl(1)−C(6) 1.805(3), O(3)−C(9) 1.369(3), O(3)−C(10) 1.460(3), O(4)−C(9) 1.212(3), N(1)−C(9) 1.360(3), N(1)−C(1) 1.442(3), N(1)−C(11) 1.468(3), C(1)−C(3) 1.491(4), C(1)−C(6) 1.509(4), C(1)−C(2) 1.534(4), C(2)−C(3) 1.486(4), C(3)−C(4) 1.482(4), C(3)−C(5) 1.480(4), C(4)−C(5) 1.530(4), C(6)−C(7) 1.527(4), C(10)−C(18) 1.499(4), C(10)−C(11) 1.551(4), C(11)−C(12) 1.516(4); C(9)−O(3)−C(10) 108.2(2), C(9)−N(1)−C(1) 123.1(2), C(9)−N(1)−C(11) 111.4(2), C(1)−N(1)−C(11) 125.5(2), N(1)−C(1)−C(3) 120.5(2), N(1)−C(1)−C(6) 114.9(2), C(3)−C(1)−C(6) 117.4(2), N(1)−C(1)−C(2) 117.6(2), C(3)−C(1)−C(2) 58.8(2), C(6)−C(1)−C(2) 116.1(2), C(3)−C(2)−C(1) 59.1(2), C(1)−C(6)−C(7) 114.3(2), C(1)−C(6)−Cl(1) 109.9(2), C(7)−C(6)−Cl(1) 108.7(2), N(1)−C(9)−O(3) 109.1(2), O(3)−C(10)−C(11) 102.9(2), N(1)−C(11)−C(10) 98.5(2).

14-Bn: Cl(1)−C(6) 1.817(6), O(3)−C(15) 1.354(7), O(3)−C(16) 1.483(6), O(4)−C(15) 1.208(7), N(1)−C(15) 1.358(7), N(1)−C(1) 1.426(7), N(1)−C(17) 1.482(7), C(1)−C(6) 1.486(7), C(1)−C(3) 1.498(7), C(1)−C(2) 1.539(7), C(2)−C(3) 1.486(7), C(3)−C(5) 1.472(8), C(3)−C(4) 1.471(8), C(4)−C(5) 1.526(8), C(6)−C(7) 1.527(8), C(16)−C(17) 1.523(8); C(15)−O(3)−C(16) 107.4(4), C(15)−N(1)−C(1) 123.5(5), C(15)−N(1)−C(17) 110.7(5), C(1)−N(1)−C(17) 125.1(4), N(1)−C(1)−C(6) 117.3(5), N(1)−C(1)−C(3)

118.7(5), C(6)−C(1)−C(3) 116.7(5), N(1)−C(1)−C(2) 117.1(5), C(6)−C(1)−C(2) 115.4(5), C(3)−C(1)−C(2) 58.5(3), C(1)−C(6)−C(7) 116.1(5), C(1)−C(6)−Cl(1) 111.4(4), C(7)−C(6)−Cl(1) 104.9(4), O(3)−C(15)−N(1) 109.9(5), O(3)−C(16)−C(17) 102.9(4), N(1)−C(17)−C(16) 99.4(4).

34: Cl(1)−C(01) 1.744(2), N(1)−C(03) 1.453(2), C(06)−C(01) 1.503(2), C(05)−C(01) 1.538(2), C(04)−C(01) 1.478(2), C(22)−C(21) 1.523(3), N(1)−C(06) 1.348(2), C(24)−C(23) 1.513(2), C(05)−C(04) 1.483(2), C(04)−C(21) 1.476(2), C(04)−C(22) 1.483(2), C(03)−C(23) 1.503(2); C(03)−C(24)−C(23) 59.9(1), C(04)−C(05)−C(07) 121.9(1), C(07)−C(05)−C(03) 120.8(1), C(07)−C(05)−C(01) 116.3(1), C(01)−C(04)−C(22) 135.4(2), C(01)−C(04)−C(05) 62.6(1), C(24)−C(03)−C(23) 60.6(1), C(24)−C(03)−C(05) 122.9(1), C(04)−C(01)−C(06) 115.7(1), C(06)−C(01)−C(05) 106.4(1), C(06)−C(01)−Cl(1) 117.6(1), C(04)−C(22)−C(21) 58.8(1).

Table 1. Crystal and data collection parameters for compounds **14**-Me, **14**-Bn, and **34**

Compound	**14**-Me	**14**-Bn	**34**
Formula	$C_{23}H_{22}ClNO_4$	$C_{29}H_{26}ClNO_4$	$C_{18}H_{18}ClNO_3$
Molecular mass	411.87	487.96	331.78
Crystal size [mm]	0.14×0.20×0.25	0.14×0.01×0.01	0.60×0.60×0.50
Crystal color	colorless	colorless	colorless
Space group	$P\,2_12_12_1$	$C\,2$	$P\,2_1/c$
a [Å]	11.888(1)	18.224(3)	12.073(2)
b [Å]	13.080(2)	6.359(1)	10.866(2)
c [Å]	13.373(1)	21.328(4)	13.638(3)
α [°]	90.0	90.0	90.0
β [°]	90.0	100.84(1)	113.27(3)
γ [°]	90.0	90.0	90.0
V [Å^3]	2079.5(1)	2427.5(4)	1643.7(6)
D [g cm^{-3}]	1.316	1.335	1.341
Z	4	4	4
Temperature [K]	100	150	133
F(000)	864	1024	696
Refl. collected	15669	6765	17528
Refl. independent	5760	4435	3351
[$F_o \geq 4\,\sigma(F)$]	3729	2792	2762
R	0.0567	0.0782	0.0511
R_w	0.107	0.1851	0.1095
μ [mm^{-1}]	0.213	0.194	0.247
Θ range measured [°]	2.2–30.4	2.2–25.0	2.6–26.4
No. of parameters refined	350	316	210
GOOF	1.094	0.967	1.100

Benzyl (2-Chloro-2-spiropentylidene)acetate (5-Bn): A mixture of methyl 2-chloro-2-spiropentylideneacetate (1.50 g, 8.7 mmol), Ti(*i*-PrO)$_4$ (0.52 mL, 1.77 mmol) and anhydrous benzyl alcohol (40 mL) was stirred under argon at 80−90°C for 21 h. The methanol formed was periodically collected in a cold trap (−78°C) under reduced pressure. After cooling, the reaction mixture was concentrated under reduced pressure and purified by chromatography (120 g of silica gel, 55 × 3 cm column, PE/*t*BuOMe, 10:1) to give 1.99 g (92%) of **5**-Bn as a 37:63 (^{1}H NMR) isomeric mixture, oil. − IR: $\tilde{\nu}$ = 3034 cm^{-1}, 3004, 2893, 1729 (C=O), 1587, 1465, 1377. − Minor isomer: R_f = 0.42; ^{1}H NMR: δ = 1.08−1.44 (m, 4 H, Cpr), 1.73 (s, 2 H, Cpr), 5.16 (s, 2 H, OCH_2), 7.3−7.5 (m, 5 H, Ph). − ^{13}C NMR: δ = 10.4, 10.8, 11.8, 67.8 (CH_2), 127.9, 128.2, 128.5, 128.6, 128.8 (CH), 17.3, 110.4, 135.3, 147.2, 162.2 (C). − Major isomer: R_f = 0.36; ^{1}H NMR: δ = 1.08−1.44 (m, 4 H, Cpr), 2.00 (s, 2 H, Cpr), 5.27 (s, 2 H, OCH_2), 7.3−7.5 (m, 5 H, Ph). − ^{13}C NMR: δ = 10.4, 10.8, 15.4, 67.4 (CH_2), 127.9, 128.2, 128.5, 128.6, 128.8 (CH), 14.3, 110.3, 135.8, 145.9, 161.9 (C). − MS (CI), *m*/*z* (%): 266 (47) [M + NH_4^+], 249 (26) [M + H^+], 213 (13) [M^+ − Cl], 108 (47) [$C_7H_8O^+$], 91 (100) [$C_7H_7^+$].

Benzyl (2-Chloro-2-spiropentyl)acetate (6): To a stirred mixture of the ester **5**-Bn (85 mg, 0.34 mmol) and silica gel (0.70 g) in a mixture of chloroform (5 mL) and EtOH (1.3 mL), was added under an atmosphere of argon $NaBH_4$ (64 mg, 1.69 mmol) in small portions at room temp. After 24 h of additional stirring at 20°C, the mixture was acidified with 2−3 drops of AcOH and filtered. The precipitate was washed with $CHCl_3$ (5 × 5 mL), the combined organic phases were washed with H_2O (5 mL) and the water layer was extracted with $CHCl_3$ (3 × 3 mL). The combined organic phases were dried, concentrated under reduced pressure and purified by chromatography (10 g of silica gel, 30 × 1.5 cm column, PE/*t*BuOMe, 10:1) to give 54 mg (63%) of **6** as a 2:3 (^{1}H NMR) mixture of diastereomers, an oil, R_f = 0.26. At a 4 mmol scale, the yield was only 45%. − IR: $\tilde{\nu}$ = 3002 cm^{-1}, 1747, 1456, 1378, 1289, 1160, 1004, 751, 689. − Minor isomer: ^{1}H NMR: δ = 0.60−1.29 (m, 6 H, Cpr), 1.78 (m, 1 H, Cpr), 3.99 (d, J = 10.5 Hz, 1 H, CHCl), 5.16 (s, 2 H, OCH_2), 7.29−7.43 (m, 5 H, Ph). − ^{13}C NMR: δ = 2.9, 6.1, 11.8, 67.9 (CH_2), 21.3, 62.0, 128.1, 128.3, 128.5, 128.6, 128.8 (CH), 15.5, 135.2, 168.9 (C). − Major isomer: ^{1}H NMR: δ = 0.60−1.29 (m, 6 H, Cpr), 1.78 (m, 1 H, Cpr), 3.88 (d, J = 10.3 Hz, 1 H, CHCl), 5.23 (s, 2 H, OCH_2), 7.29−7.43 (m, 5 H, Ph). − ^{13}C NMR: δ = 3.6, 5.5, 10.8, 67.5 (CH_2), 21.3, 61.8, 128.1, 128.3, 128.5, 128.6, 128.8 (CH), 16.5, 135.2, 168.9 (C). − MS (EI), *m*/*z* (%): 215 (4) [M^+ − Cl], 92 (8), 91 (100) [$C_7H_7^+$], 90 (7), 77 (5), 65 (7).

Benzyl (2-Azido-2-spiropentyl)acetate (7): Under an atmosphere of argon a mixture of the ester **6** (260 mg, 1.04 mmol) and sodium azide (270 mg, 4.15 mmol) in anhydrous DMF (5 mL) was stirred at 50°C for 42 h. After cooling, the mixture was diluted with H_2O (6 mL) and extracted with Et_2O (3 × 5 mL). The combined organic phases were washed with H_2O (2 × 4 mL), dried, concentrated under reduced pressure and purified by chromatography (15 g of silica gel, 30 × 1.5 cm column, PE/*t*BuOMe, 20:1) to give 187 mg (70%) of **7** as a 2:3 (^{1}H NMR) mixture of diastereomers, an oil, R_f = 0.35. − IR: $\tilde{\nu}$ = 3002 cm^{-1}, 2103, 1745, 1456, 1235, 1174, 1003, 751, 698. − Minor diastereomer: ^{1}H NMR: δ = 0.60−1.04 (m, 4 H, Cpr), 1.17 (m, 2 H, Cpr), 1.61 (m, 1 H, Cpr), 3.42 (d, J = 9.2 Hz, 1 H, CHN_3), 5.18 (d, J = 12.4 Hz, 2 H, OCH_2), 7.28−7.42 (m, 5 H, Ph). − ^{13}C NMR: δ = 4.0, 5.4, 11.4, 67.3 (CH_2), 18.8, 65.6, 128.2, 128.45, 128.5, 128.65, 128.7 (CH), 13.8, 135.3, 169.9 (C). − Major diastereomer: ^{1}H NMR: δ = 0.60−1.04 (m, 4 H, Cpr), 1.17 (m, 2 H, Cpr), 1.61 (m, 1 H, Cpr), 3.46 (d, J = 9.2 Hz, 1 H, CHN_3), 5.23 (s, 2 H, OCH_2), 7.28−7.42 (m, 5 H, Ph). − ^{13}C NMR: δ = 4.2, 6.0, 11.5, 67.4 (CH_2), 18.9, 65.9, 128.2, 128.45, 128.5, 128.65, 128.7 (CH), 14.7, 135.3, 169.9 (C). − MS (EI), *m*/*z* (%): 215 (2) [M^+ − N_3], 138 (6) [M^+ − N_2 − C_7H_7], 94 (4) [M^+ − N_2 − CO_2 − C_7H_7], 92 (17), 91 (100) [$C_7H_7^+$], 67 (38), 66 (14), 65 (26), 54 (18).

Spiropentyl Bromide 9: Tributyltin hydride (16.30 g, 15.1 mL, 56.0 mmol) was added dropwise to neat 1,1-dibromospiropentane[14] (12.0 g, 53.1 mmol). The temperature was maintained between 20 and 25°C with a water bath. After an additional 15 min of stirring, all the volatile material was distilled with a bulb-to-bulb distillation apparatus under reduced pressure (0.1 Torr) at 40°C oil-bath temperature to a trap cooled with acetone/dry ice. The contents of the cold trap were allowed to warm up to 20°C and distilled at atmospheric pressure to give 5.94 g (76%) of **9**, b.p. 118−120°C. − ^{1}H NMR: δ = 0.87−1.13 (m, 4 H, Cpr), 1.25 (dd, J = 5.5, 3.0 Hz,

1 H, Cpr), 1.52 (t, J = 5.5 Hz, 1 H, Cpr), 3.30 (dd, J = 5.5, 3.0 Hz, 1 H, CHBr). − ^{13}C NMR: δ = 7.32, 9.15, 16.40 (CH_2), 24.26 (CH), 16.85 (C). − MS (EI), *m/z* (%): 82 (5), 68 (5), 67 (100) [$C_5H_7^+$], 65 (15) [$C_5H_5^+$], 41 (25). − C_5H_7Br (147.0): calcd. C 40.85, H 4.80, Br 54.35; found C 41.05, H 4.84, Br 54.31.

***tert*-Butyl *N*-(diphenylmethylene)-α-spiropentylglycinate (12):** Spiropentyl bromide (**9**, 5.881 g, 40 mmol) in Et_2O (40 mL) was treated with *t*BuLi (80 mmol, 51.6 mL of a 1.55 M solution in pentane) at −78°C, and stirring was continued for an additional 1 h at this temp. The mixture was diluted with THF (100 mL), the solution was cooled to −110°C, and CuCN (1.791 g, 20 mmol) was added in one portion. The mixture was allowed to warm to −40°C and stirred for 20 min at this temp. until a clear solution had formed. After this, the reaction mixture was recooled to −78°C and transferred by cannula to a solution of **11** (4.67 g, 13.2 mmol) in THF (150 mL) at −10°C over a period of 1 h. The resulting mixture was stirred for 5.5 h at this temp., quenched at 0°C with a saturated NH_4Cl solution, and brought to pH 7−8 with 6 N NH_4OH solution. The aqueous phase was extracted with Et_2O (200 mL). The combined organic phases were dried and concentrated under reduced pressure. The residue was purified by column chromatography (200 g of silica gel, column 20 × 6 cm, hexane/Et_2O, 85:15) to give 2.63 g (55%) of **12** as a 3.3:1 mixture of diastereomers, an oil, R_f = 0.39, and *tert*-butyl *N*-(diphenylmethylene)glycinate[28] (0.95 g, 24%), R_f = 0.24. − **12**: IR: $\tilde{\nu}$ = 3061 cm^{-1}, 2978, 1733, 1624 (C=O), 392. − ^{1}H NMR: δ = 0.43 (t, J = 4.5 Hz, 1 H, Cpr), 0.52−0.58 (m, 1 H, Cpr), 0.70−0.75 (m, 2 H, Cpr), 0.80−0.86 (m, 1 H, Cpr), 0.95−1.0 (m, 1 H, Cpr), 1.80−1.95 (m, 1 H, Cpr), 7.19−7.44 (m, 8 H, Ph). Other signals: Major diastereomer: 1.44 (s, 9 H, 3 CH_3), 3.52 (d, J = 9.0 Hz, 1 H, CH), 7.67 (dd, J = 7.5, 1.5 Hz, 2 H, Ph). Minor diastereomer: 1.47 (s, 9 H, 3 CH_3), 3.59 (d, J = 8.2 Hz, 1 H, CH), 7.61 (dd, J = 6.5, 1.5 Hz, 2 H, Ph). − ^{13}C NMR: Major diastereomer: δ = 27.9 (3 CH_3), 4.0, 5.3, 11.0 (CH_2), 21.1, 69.9 (CH), 139.8 (2 C), 13.1, 80.6, 169.3, 170.9 (C). Minor diastereomer: δ = 28.0 (3 CH_3), 3.6, 5.9, 10.0 (CH_2), 21.5, 69.8 (CH), 136.6 (2 C), 14.0, 80.8, 169.4, 171.2 (C). The signals of the aromatic CH groups are in the region δ = 127.3−130.0 and indistinguishable. − MS (EI), *m/z* (%): 361 (0.3) [M^+], 304 (5) [$M^+ - C_4H_9$], 261 (20), 260 (100) [$M^+ - CO_2C_4H_9$], 182 (5), 166 (10) [CPh_2^+], 165 (19) [$CPh_2^+ - H$]. − MS (HR-EI): ($C_{24}H_{27}NO_2$) calcd. 361.2042; found 361.2041.

α-Spiropentylglycine (8): a) A solution of the ester **7** (140 mg, 0.54 mmol) in anhydrous MeOH (2 mL) was vigorously stirred in the presence of 10% Pd/C catalyst (50 mg) under a hydrogen atmosphere at 20°C for 3 h. The mixture was diluted with MeOH (60 mL) and filtered through Celite, then the Celite was washed with H_2O (60 mL). The combined MeOH/H_2O solution was concentrated under reduced pressure; the precipitate was washed with MeOH (1 mL) to give 28 mg (36%) of **8** as a 2:3 mixture of diastereomers.

b) An emulsion of the protected glycinate **12** (2.50 g, 6.92 mmol) in 1 N HCl solution (200 mL) was intensively stirred for 24 h at room temp. in the dark and then washed with Et_2O (3 × 80 mL). The aqueous layer was concentrated under reduced pressure to give α-spiropentylglycine hydrochloride (**8**·HCl, 1.134 g, 93%), as a 5.2:1 mixture of diastereomers, m.p. 216−219°C (decomp.). Major diastereomer: ^{1}H NMR (D_2O): δ = 0.58−0.68 (m, 3 H, Cpr), 0.75 (t, J = 4.6 Hz, 1 H, Cpr), 0.87 (dd, J = 5.6, 4.1 Hz, 1 H, Cpr), 1.00 (dd, J = 7.1, 5.6 Hz, 1 H, Cpr), 1.36 (ddd, J = 10.5, 7.1, 4.1 Hz, 1 H, Cpr), 3.44 (d, J = 10.5 Hz, 1 H, CH). − ^{13}C NMR (D_2O): δ = 5.9, 7.3, 13.2 (CH_2), 20.1, 59.4 (CH), 17.2, 174.0 (C). Minor diastereomer: ^{1}H NMR (D_2O): δ = 3.48 (d, J = 12.2 Hz, 1 H, CH), other signals are buried under the signals of the major diastereomer. − ^{13}C NMR (D_2O): δ = 5.7, 7.9, 13.1 (CH_2), 20.0, 58.8 (CH), 17.1, 174.2 (C). − $C_7H_{12}ClNO_2$ (177.6): calcd. C 47.33, H 6.81; found C 47.19, H 6.88. Subsequent filtration of an aqueous solution of **8**·HCl (1.09 g, 6.14 mmol in 15 mL of H_2O) through Dowex-50 (3 × 20 cm column, eluent 0.9 N NH_4OH) and repeated concentration gave the amino acid **8** (792 mg, 91%) as a colorless powder, 5:1 mixture of diastereomers. − ^{1}H NMR (D_2O): δ = 0.58−0.75 (m, 4 H, Cpr), 0.79−0.92 (m, 1 H, Cpr), 0.92−1.09 (m, 1 H, Cpr), 1.23−1.42 (m, 1 H, Cpr), 3.05−3.27 (m, 1 H, CH). − ^{13}C NMR (D_2O): Major diastereomer: δ = 5.8, 7.3, 12.9 (CH_2), 20.9, 61.2 (CH), 16.9, 177.0 (C). Minor diastereomer: δ = 5.5, 7.7, 13.1 (CH_2), 20.9, 60.7 (CH), 16.4, 177.2 (C). Analytical sample was recrystallized from water (0°C, 48 h) to give **8** as a single (major) diastereomer, slow decomp. at temperatures > 240°C, m.p. 263−265°C (decomp.). − IR: $\tilde{\nu}$ = 3440 cm^{-1}, 3001, 2630, 2102, 1606 (C=O), 1401, 1357, 1331. − ^{1}H NMR (D_2O): δ = 0.62 (br. s, 3 H, Cpr), 0.64 (t, J = 3.5 Hz, 1 H, Cpr), 0.87 (dd, J = 8.4, 7.3 Hz, 1 H, Cpr), 0.97 (dd, J = 7.3, 4.6 Hz, 1 H, Cpr), 1.29 (ddd, J = 9.5, 8.4, 4.6 Hz, 1 H, Cpr), 3.08 (d, J = 9.5 Hz, 1 H, CH). − MS (EI), *m/z* (%): 98 (74), 97 (100) [$M^+ - CO_2$], 96 (43), 82 (10), 81 (12) 80 (10) [$M^+ - NH_3 - CO_2$], 79 (14), 77 (19), 76 (21), 75 (16), 70 (25), 69 (33), 68 (19), 58 (28), 57 (39), 56 (19), 55 (13), 53 (10). − MS (HR-EI): 97.0885 ($C_7H_{11}NO_2 - CO_2$, calcd. 97.0891). − $C_7H_{11}NO_2$ (141.2): calcd. C 59.55, H 7.86; found C 59.33, H 7.69.

Benzyl (4*R*,5*S*)-2-Chloro-2-[1-(2-oxo-4,5-diphenyl-3-oxazolidinyl)-spiropentyl]acetate (14-Bn): To a stirred solution of (4*R*,5*S*)-4,5-diphenyloxazolidin-2-one (**13**, 2.41 g, 10.1 mmol) in anhydrous THF (280 mL), was added potassium hydride (200 mg, 5.0 mmol) in one portion at 20°C, and stirring was continued for 1.5 h at this temp. After addition of a catalytic quantity (30 mg) of dibenzo-18-crown-6, a solution of compound **5**-Bn (2.24 g, 9.0 mmol) in THF (20 mL) was slowly added at ambient temp. After additional stirring for 3 h at this temp., the mixture was quenched with brine (100 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic phases were dried, concentrated under reduced pressure and purified by chromatography (250 g of silica gel, 40 × 5 cm column, pentane/Et_2O, 3:1) to give 0.91 g (21%) of diastereomer A, 1.97 g (45%) of diastereomer B and 0.46 g (10%) of diastereomer C.

{[(4*R*,5*S*),1*S*]2*S*}-14-Bn-A: R_f = 0.57, m.p. 133°C, $[\alpha]_D^{25}$ = −46.8 (c = 1.25, $CHCl_3$). − IR: $\tilde{\nu}$ = 3006 cm^{-1}, 2920, 1760, 1740, 1480, 1415, 1325. − ^{1}H NMR: δ = 0.72 (m, 2 H, Cpr), 0.87 (d, J = 5.7 Hz, 1 H, Cpr), 0.95 (d, J = 5.7 Hz, 1 H, Cpr), 1.26 (d, J = 7.4 Hz, 1 H, Cpr), 1.68 (d, J = 7.4 Hz, 1 H, Cpr), 4.19 (s, 1 H, CHCl), 5.13 (m, 2 H, OCH_2), 5.39 (d, J = 7.6 Hz, 1 H, CHPh), 5.85 (d, J = 7.6 Hz, 1 H, CHPh), 6.55−6.91 (m, 3 H, Ph), 6.93−7.11 (m, 7 H, Ph), 7.20−7.33 (m, 3 H, Ph), 7.35−7.45 (m, 2 H, Ph). − ^{13}C NMR: δ = 6.0, 17.2, 26.1, 68.9 (CH_2), 65.2, 66.3, 81.2, 126.1, 127.7, 127.8, 128.0, 128.6, 129.2 (CH), 31.0, 43.0, 133.9, 134.9, 136.4, 159.8, 167.2 (C). − MS (EI), *m/z* (%): 487 (0.1) [M^+], 452 (95) [$M^+ - Cl$], 408 (8) [$M^+ - Cl - CO_2$], 304 (17), 91 (100) [$C_7H_7^+$]. − $C_{29}H_{26}ClNO_4$ (488.0): calcd. C 71.38, H 5.37, Cl 7.26, N 2.87; found C 71.47, H 5.25, Cl 7.21, N 2.91.

[(4*R*,5*S*)1*R*]-14-Bn-B: R_f = 0.37, m.p. 226°C, $[\alpha]_D^{25}$ = −9.6 (c = 1.11, $CHCl_3$). − IR: $\tilde{\nu}$ = 3045 cm^{-1}, 2930, 1755, 1400, 1220. − ^{1}H NMR: δ = 0.13 (m, 1 H, Cpr), 0.38 (m, 1 H, Cpr), 0.53 (m, 1 H, Cpr), 1.04 (m, 1 H, Cpr), 1.82 (d, J = 5.0 Hz, 1 H, Cpr), 1.95 (d, J = 5.0 Hz, 1 H, Cpr), 4.32 (s, 1 H, CHCl), 5.26 (d, J = 7.5 Hz, 1 H, CHPh), 5.27 (s, 2 H, OCH_2), 5.88 (d, J = 7.5 Hz, 1 H, CHPh), 6.50−6.80 (m, 2 H, Ph), 6.86−6.92 (m, 2 H, Ph), 7.02−7.08 (m, 6 H, Ph), 7.35−7.41 (m, 3 H, Ph), 7.48−7.53 (m, 2 H, Ph). − ^{13}C

NMR: δ = 4.6, 7.3, 21.9, 68.8 (CH_2), 64.9, 65.7, 81.1, 126.1, 127.0, 127.7, 127.9, 128.0, 128.6, 129.0 (CH), 21.2, 42.0, 133.8, 135.1, 137.1, 158.7, 167.2 (C). − MS (EI), *m/z* (%): 487 (0.1) [M^+], 452 (69) [$M^+ - Cl$], 408 (7) [$M^+ - Cl - CO_2$], 304 (18), 91 (100) [$C_7H_7^+$]. − $C_{29}H_{26}ClNO_4$ (488.0): calcd. C 71.38, H 5.37, Cl 7.26, N 2.87; found C 71.22, H 5.37, Cl 7.47, N 2.95.

[(4*R*,5*S*)1*R*]-14-Bn-C: R_f = 0.26, m.p. 102°C, $[\alpha]_D^{25}$ = −17.1 (*c* = 0.96, $CHCl_3$). − IR: $\tilde{\nu}$ = 3033 cm^{-1}, 2927, 1753, 1407, 1350. − ^1H NMR: δ = 0.26−0.67 (m, 3 H, Cpr), 1.08 (m, 1 H, Cpr), 1.47 (d, *J* = 6.0 Hz, 1 H, Cpr), 1.77 (d, *J* = 6.0 Hz, 1 H, Cpr), 4.48 (s, 1 H, CHCl), 4.89 (d, *J* = 7.5 Hz, 1 H, CHPh), 5.13 (d, *J* = 11.9 Hz, 1 H, OCH_2), 5.23 (d, *J* = 11.9 Hz, 1 H, OCH_2), 5.80 (d, *J* = 7.5 Hz, 1 H, CHPh), 6.79−6.84 (m, 2 H, Ph), 6.85−6.90 (m, 3 H, Ph), 7.00−7.06 (m, 4 H, Ph), 7.23−7.43 (m, 6 H, Ph). − ^{13}C NMR: δ = 6.0, 6.2, 20.9, 68.1 (CH_2), 63.4, 65.7, 81.1, 126.0, 126.9 127.59 127.64, 127.7, 127.9, 128.4, 128.6, 128.8 (CH), 23.2 42.5 133.9, 134.8, 136.3, 158.2, 167.2 (C). − MS (EI), *m/z* (%): 487 (1) [M^+], 452 (95) [$M^+ - Cl$], 408 (18) [$M^+ - Cl - CO_2$], 180 (57) [$C_{14}H_{12}^+$], 91 (100) [$C_7H_7^+$]. − $C_{29}H_{26}ClNO_4$ (488.0): calcd. C 71.38, H 5.37, Cl 7.26, N 2.87; found C 71.17, H 5.49, Cl 7.15, N 2.76.

Methyl (4*R*,5*S*)-2-Chloro-2-[1-(2-oxo-4,5-diphenyl-3-oxazolidinyl)-spiropentyl]acetate (14-Me): Under the conditions described above (except that the addition of **5**-Me was performed at −20°C), the reaction of **13** (2.36 g, 9.9 mmol) in anhydrous THF (250 mL), potassium hydride (160 mg, 4.0 mmol) and **5**-Me (1.55 g, 8.98 mmol) in THF (20 mL), resulted in diastereomer A (0.666 g, 18%), diastereomer B (0.221 g, 6%), diastereomer C (2.150 g, 58%) and diastereomer D (0.112 g, 3%) after column chromatography (pentane/Et_2O = 3:1).

{[(4*R*,5*S*),1*S*]2*S*}-14-Me-A: R_f = 0.29, m.p. 146°C, $[\alpha]_D^{25}$ = +53.2 (*c* = 0.97, $CHCl_3$). − IR: $\tilde{\nu}$ = 3015 cm^{-1}, 2986, 1750 (C=O), 1392, 1192, 1015. − ^1H NMR: δ = 0.68−0.82 (m, 2 H, Cpr), 0.74 (d, *J* = 6.0 Hz, 1 H, Cpr), 0.94 (d, *J* = 6.0 Hz, 1 H, Cpr), 1.33−1.45 (m, 1 H, Cpr), 1.62−1.74 (m, 1 H, Cpr), 3.72 (s, 3 H, OCH_3), 4.19 (s, 1 H, CHCl), 5.42 (d, *J* = 7.6 Hz, 1 H, CHPh), 5.92 (d, *J* = 7.6 Hz, 1 H, CHPh), 6.41−6.71 (m, 4 H, Ph), 6.71−7.05 (m, 6 H, Ph). − ^{13}C NMR: δ = 53.5 (CH_3), 5.7, 5.9, 17.2 (CH_2), 65.2, 66.1, 81.2, 126.0, 127.1, 127.65, 127.72 128.0 (CH), 26.1, 42.8, 133.9, 136.3, 157.9, 167.6 (C). − MS (EI), *m/z* (%): 411 (7) [M^+], 376 (60) [$M^+ - Cl$], 344 (7) [$M^+ - HCl - OCH_3$], 332 (13), 304 (18), 180 (100) [$C_{14}H_{12}^+$], 105 (67), 84 (84). − $C_{23}H_{22}ClNO_4$ (411.9): calcd. C 67.07, H 5.38, Cl 8.61, N 3.40; found C 67.01, H 5.45, Cl 8.71, N 3.41.

{[(4*R*,5*S*),1*S*]2*R*}-14-Me-B: R_f = 0.21, m.p. 173°C, $[\alpha]_D^{25}$ = −10.3 (*c* = 0.80, $CHCl_3$). − IR: $\tilde{\nu}$ = 3066 cm^{-1}, 3034, 2975, 1745, 1455, 1394, 1369. − ^1H NMR: δ = 0.70−0.86 (m, 2 H, Cpr), 0.92 (d, *J* = 5.9 Hz, 1 H, Cpr), 1.13−1.23 (m, 1 H, Cpr), 1.49 (d, *J* = 5.9 Hz, 1 H, Cpr), 1.52−1.64 (m, 1 H, Cpr), 3.77 (s, 3 H, OCH_3), 5.08 (s, 1 H, CHCl), 5.28 (d, *J* = 7.7 Hz, 1 H, CHPh), 5.98 (d, *J* = 7.7 Hz, 1 H, CHPh), 6.88−7.02 (m, 4 H, Ph), 7.02−7.17 (m, 6 H, Ph). − ^{13}C NMR: δ = 52.7 (CH_3), 5.7, 5.9, 13.2 (CH_2), 61.0, 66.4, 81.5, 126.1, 127.0, 127.8, 127.9, 128.0 (CH), 23.9, 42.0, 133.7, 136.2, 157.8, 167.5 (C). − MS (EI), *m/z* (%): 376 (60) [$M^+ - Cl$], 304 (17), 272 (15), 180 (100) [$C_{14}H_{12}^+$], 167 (33), 91 (28) [$C_7H_7^+$]. − $C_{23}H_{22}ClNO_4$ (411.9): calcd. C 67.07, H 5.38, Cl 8.61, N 3.40; found C 67.07, H 5.31, Cl 8.52, N 3.36.

[(4*R*,5*S*),1*R*]-14-Me-C: R_f = 0.19, m.p. 230°C, $[\alpha]_D^{25}$ = +22.1 (*c* = 0.95, $CHCl_3$). − IR: $\tilde{\nu}$ = 3036 cm^{-1}, 2899, 1758, 1652, 1558, 1458, 1278. − ^1H NMR: δ = 0.06−0.19 (m, 1 H, Cpr), 0.32−0.45 (m, 1 H, Cpr), 0.52−0.60 (m, 1 H, Cpr), 1.01−1.10 (m, 1 H, Cpr), 1.81 (d, *J* = 6.0 Hz, 1 H, Cpr), 1.96 (d, *J* = 6.0 Hz, 1 H, Cpr), 3.86 (s, 3 H, OCH_3), 4.28 (s, 1 H, CHCl), 5.34 (d, *J* = 7.6 Hz, 1 H, CHPh), 6.00 (d, *J* = 7.6 Hz, 1 H, CHPh), 6.65−6.82 (m, 2 H, Ph), 6.88−6.99 (m, 2 H, Ph), 7.02−7.12 (m, 6 H, Ph). − ^{13}C NMR: δ = 53.5 (CH_3), 4.4, 7.3, 22.1 (CH_2), 65.1, 65.7, 81.1, 126.1, 126.9, 127.7, 127.8, 127.9 (CH), 21.4, 41.9, 133.8, 137.0, 158.2, 167.7 (C). − MS (EI), *m/z* (%): 376 (43) [$M^+ - Cl$], 332 (11), 304 (16), 180 (100) [$C_{14}H_{12}^+$], 167 (37), 106 (17), 91 (26) [$C_7H_7^+$], 77 (18) [$C_6H_5^+$]. − $C_{23}H_{22}ClNO_4$ (411.9): calcd. C 67.07, H 5.38, N 3.40; found C 67.01, H 5.48, N 3.41.

[(4*R*,5*S*),1*R*]-14-Me-D: R_f = 0.16, m.p. 163°C, $[\alpha]_D^{25}$ = +4.7 (*c* = 0.51, $CHCl_3$). − IR: $\tilde{\nu}$ = 3010 cm^{-1}, 2895, 1757, 1455, 1395, 1371, 1320. − ^1H NMR: δ = 0.52 (m, 1 H, Cpr), 0.58−0.77 (m, 2 H, Cpr), 1.10−1.21 (m, 1 H, Cpr), 1.51 (d, *J* = 6.0 Hz, 1 H, Cpr), 1.77 (d, *J* = 6.0 Hz, 1 H, Cpr), 3.77 (s, 3 H, OCH_3), 4.56 (s, 1 H, CHCl), 5.03 (d, *J* = 7.5 Hz, 1 H, CHPh), 5.86 (d, *J* = 7.5 Hz, 1 H, CHPh), 6.82−6.99 (m, 4 H, Ph), 7.01−7.12 (m, 6 H, Ph). − ^{13}C NMR: δ = 53.1 (CH_3), 5.9, 6.3, 20.1 (CH_2), 62.8, 65.7, 81.2, 126.1, 127.6, 127.7, 127.9, 128.0 (CH), 22.6, 42.3, 133.9, 136.3, 158.4, 167.9 (C). − MS (EI), *m/z* (%): 382/380 (2/6) [$M^+ - OCH_3$], 376 (6) [$M^+ - Cl$], 344 (6) [$M^+ - HCl - OCH_3$], 332 (15), 304 (14), 180 (100) [$C_{14}H_{12}^+$], 167 (24), 77 (13) [$C_6H_5^+$]. − $C_{23}H_{22}ClNO_4$ (411.9): calcd. C 67.07, H 5.38, N 3.40; found C 67.02, H 5.51, N 3.38.

Methyl [(4*R*,5*S*)1*S*]-2-[1-(2-Oxo-4,5-diphenyl-3-oxazolidinyl)spiropentyl]acetate (17-Me): A solution of diastereomers C and D of compound **14**-Me (2.26 g, 5.49 mmol) in a mixture of THF (8 mL) and H_2O (2 mL) with freshly prepared zinc−copper couple (2.26 g) was kept in an ultrasonic bath at 60°C for 3 h. After cooling, the reaction mixture was filtered through Celite, then the Celite was washed with Et_2O (2 × 20 mL). The combined organic phases were dried, concentrated under reduced pressure and purified by chromatography (100 g of silica gel, 40 × 3 cm column, pentane/Et_2O, 2:1) to give 2.02 g (98%) of **17**-Me, R_f = 0.31, m.p. 114°C, $[\alpha]_D^{25}$ = −3.5 (*c* = 1.20, $CHCl_3$). − IR: $\tilde{\nu}$ = 3025 cm^{-1}, 2978, 1734, 1559, 1394, 1275. − ^1H NMR: δ = 0.54 (m, 2 H, Cpr), 0.91 (m, 2 H, Cpr), 1.22 (d, *J* = 5.5 Hz, 1 H, Cpr), 1.45 (d, *J* = 5.5 Hz, 1 H, Cpr), 2.41 (d, *J* = 16.1 Hz, 1 H, CH_2), 3.07 (d, *J* = 16.1 Hz, 1 H, CH_2), 3.56 (s, 3 H, OCH_3), 5.10 (d, *J* = 7.6 Hz, 1 H, CHPh), 5.79 (d, *J* = 7.6 Hz, 1 H, CHPh), 6.82−6.91 (m, 2 H, Ph), 6.91−7.03 (m, 2 H, Ph), 7.03−7.12 (m, 6 H, Ph). − ^{13}C NMR: δ = 51.3 (CH_3), 5.1, 6.7, 19.1, 39.9 (CH_2), 65.3, 80.9, 125.8, 127.2, 127.5, 127.6, 127.7 (CH), 21.1, 37.1, 134.1, 136.4, 157.9, 171.7 (C). − MS (EI), *m/z* (%): 377 (2) [M^+], 333 (23) [$M^+ - CO_2$], 304 (14), 274 (23), 180 (100) [$C_{14}H_{12}^+$], 165 (21), 105 (27), 78 (37). − $C_{23}H_{23}NO_4$ (377.4): calcd. C 73.19, H 6.14, N 3.71; found C 72.98, H 6.08, N 3.59.

Methyl [(4*R*,5*S*)-1*R*]-2-Azido-2-[1-(2-oxo-4,5-diphenyl-3-oxazolidinyl)spiropentyl]acetate (18-Me): A precooled (−78°C) solution of compound **17**-Me (230 mg, 0.61 mmol) in anhydrous THF (10 mL) was transferred by cannula under an atmosphere of argon into a precooled (−78°C) solution of LiHMDS (0.68 mmol, 0.5 mL of 1.35 M solution in THF) in THF (4 mL), and the mixture was stirred for an additional 1.5 h at the same temp. To this mixture, a precooled (−78°C) solution of 2,4,6-triisopropylbenzenesulfonyl azide (245 mg, 0.79 mmol) in THF (4 mL) was transferred by cannula and, after stirring for 3 min at this temp, the mixture was quenched with HOAc (160 μL, 2.80 mmol), immediately warmed-up in a water bath to 20°C and stirred at this temp. for a period of 3 h. After concentration under reduced pressure, the residue was taken up with Et_2O (100 mL), washed with a saturated $NaHCO_3$ solution (2 × 20 mL), then H_2O (20 mL), dried and concentrated under reduced pressure. Column chromatography (50 g of silica gel, 40 × 1.5 cm column, pentane/EtOAc/CH_2Cl_2, 4:1:1) gave 232 mg

(91%) of **18**-Me as a 1.6:1 mixture of diastereomers, R_f = 0.41 (isomer A) and 0.39 (isomer B). − IR: $\tilde{\nu}$ = 3064 cm^{-1}, 2973, 2109, 1756, 1498, 1455, 1436, 1388, 1365, 1203, 1118, 1080, 1016, 764, 699. − ^1H NMR (isomer A): δ = 0.36−0.46 (m, 1 H, Cpr), 0.54−0.62 (m, 1 H, Cpr), 0.66−0.78 (m, 1 H, Cpr), 0.94−1.12 (m, 1 H, Cpr), 1.81 (d, *J* = 6.0 Hz, 1 H, Cpr), 1.86 (d, *J* = 6.0 Hz, 1 H, Cpr), 3.93 (s, 3 H, OCH_3), 4.11 (s, 1 H, CHN_3), 5.22 (d, *J* = 7.6 Hz, 1 H, CHPh), 6.04 (d, *J* = 7.6 Hz, 1 H, CHPh), 6.87−6.98 (m, 2 H, Ph), 7.02−7.14 (m, 2 H, Ph), 7.15−7.23 (m, 6 H, Ph). − ^1H NMR (isomer B): δ = 0.56−0.62 (m, 1 H, Cpr), 0.71−0.77 (m, 1 H, Cpr), 0.81−0.89 (m, 1 H, Cpr), 1.06−1.18 (m, 1 H, Cpr), 1.50 (d, *J* = 6.0 Hz, 1 H, Cpr), 1.61 (d, *J* = 6.0 Hz, 1 H, Cpr), 3.75 (s, 3 H, OCH_3), 4.00 (s, 1 H, CHN_3), 4.82 (d, *J* = 7.6 Hz, 1 H, CHPh), 5.84 (d, *J* = 7.6 Hz, 1 H, CHPh), 6.77−6.85 (m, 2 H, Ph), 6.91−7.00 (m, 2 H, Ph), 7.04−7.13 (m, 6 H, Ph). − ^{13}C NMR (isomer A/isomer B): δ = 52.6/53.0 (CH_3), 5.7/5.5, 6.7/6.9, 21.1/20.4 (CH_2), 65.8/65.4, 66.7/67.4, 80.8/81.0, 126.0/127.2, 127.6/127.3, 127.67/127.72, 127.7/127.8, 127.9/128.1 (CH), 18.9/19.2, 41.5/40.0, 134.0/133.9, 135.9/136.6, 158.1/158.0, 168.1/168.8 (C). − MS (EI), *m/z* (%): 376 (18) [$M^+ - N_3$], 331 (13), 304 (18) [$M^+ - CO_2CH_3 - CHN_3$], 180 (100) [$C_{14}H_{12}^+$], 159 (52), 91 (60) [$C_7H_7^+$]. The ester **18**-Me was saponified to the corresponding acid **18**-H. − $C_{22}H_{20}N_4O_4$ (404.4): calcd. C 65.34, H 4.98; found C 65.45, H 5.05.

Methyl [(4*R*,5*S*)1*R*]-[1-(2-Oxo-4,5-diphenyl-3-oxazolidinyl)spiropentyl]glyoxylate (20-Me): To a stirred suspension of vacuum-dried lithium methoxide, freshly prepared from *n*BuLi (0.20 mmol, 85 μL of a 2.36 M solution in hexane) and anhydrous MeOH (20 μL), in anhydrous THF (5 mL), was added under an atmosphere of argon a solution of compound **18**-Me (158 mg, 0.38 mmol) in anhydrous THF (5 mL) at 20°C. The reaction mixture was stirred for 1.5 h at the same temp., then a 2 N solution of HCl (1.5 mL) was added, and stirring was continued for an additional 1.5 h. The mixture was diluted with water (5 mL) and extracted with Et_2O (3 × 10 mL); the combined organic phases were washed with a saturated $NaHCO_3$ solution (10 mL), dried and concentrated under reduced pressure to yield 106 mg (72%) of crude **20**-Me. Column chromatography (10 g of silica gel, 10 × 1 cm column, pentane/Et_2O, 1:1) gave 42 mg (28%) of analytically pure **20**-Me as colorless crystals, R_f = 0.21. − IR: $\tilde{\nu}$ = 3060 cm^{-1}, 3040, 2955, 2895, 1740, 1710, 1450, 1405. − ^1H NMR: δ = 0.62−0.72 (m, 1 H, Cpr), 0.73−082 (m, 1 H, Cpr), 0.83−0.93 (m, 1 H, Cpr), 0.94−1.04 (m, 1 H, Cpr), 1.95 (d, *J* = 5.3 Hz, 1 H, Cpr), 2.47 (d, *J* = 5.3 Hz, 1 H, Cpr), 3.82 (s, 3 H, OCH_3), 5.05 (d, *J* = 8.2 Hz, 1 H, CHPh), 5.96 (d, *J* = 8.2 Hz, 1 H, CHPh), 6.90−6.96 (m, 2 H, Ph), 6.96−7.03 (m, 2 H, Ph), 7.03−7.12 (m, 6 H, Ph). − ^{13}C NMR: δ = 52.8 (CH_3), 6.6, 6.8, 24.2 (CH_2), 65.2, 81.0, 126.2, 127.7, 127.8, 128.0, 128.1, 128.2 (CH), 27.3, 48.1, 134.3, 135.5, 158.5, 168.7, 192.0 (C). − MS (EI), *m/z* (%): 391 (37) [M^+], 332 (23) [$M^+ - CO_2CH_3$], 304 (33) [$M^+ - CO_2CH_3 - CO$], 288 (63), 260 (52), 180 (100) [$C_{14}H_{12}^+$], 167 (62). − MS (HR-EI): 391.1419 ($C_{23}H_{21}NO_5$, calcd. 391.1419). The crude **20**-Me was pure enough to be used in the next step.

[(4*R*,5*S*)1*R*]-1-(2-Oxo-4,5-diphenyl-3-oxazolidinyl)spiropentanecarboxylic Acid (21): To a stirred solution of the ester **20**-Me (101 mg, 0.26 mmol) in a mixture of THF (15 mL) and H_2O (5 mL) were added $LiOH·H_2O$ (26 mg, 0.62 mmol) and a 30% solution of H_2O_2 (0.27 mL, 2.6 mmol). After stirring for 3 h at room temp., the excess peroxide was destroyed with a small quantity of sodium pyrosulfite, then the reaction mixture was concentrated under reduced pressure, and the residue washed with Et_2O (3 × 5 mL). The aqueous layer was acidified with a 2 N solution of HCl to pH 2, the precipitate was filtered off, washed with Et_2O (10 mL), and dried to give 80 mg (88%) of **21**, m.p. 166°C, $[\alpha]_D^{25}$ = +40.6 (*c* = 2.40, MeOH). − IR: $\tilde{\nu}$ = 3630−3300 cm^{-1}, 3058, 1706, 1456, 1420. − ^1H NMR (CD_3OD): δ = 0.58−0.64 (m, 2 H, Cpr), 0.68−0.92 (m, 2 H, Cpr), 1.56 (d, *J* = 4.9 Hz, 1 H, Cpr), 1.65 (d, *J* = 4.9 Hz, 1 H, Cpr), 5.13 (d, *J* = 8.6 Hz, 1 H, CHPh), 5.84 (d, *J* = 8.6 Hz, 1 H, CHPh), 6.77−7.11 (m, 10 H, Ph). − ^{13}C NMR ([D_6]acetone): δ = 7.0, 7.5, 22.3 (CH_2), 65.5, 80.9, 127.0, 127.1, 127.9, 128.4, 128.5, 128.6 (CH), 25.0, 43.6, 132.7, 135.9, 167.8, 177.5 (C). − MS (EI), *m/z* (%): 349 (2) [M^+], 304 (8) [$M^+ - CO_2H$], 260 (17), 180 (100) [$C_{14}H_{12}^+$], 167 (24), 105 (42), 77 (35) [$C_6H_5^+$].

Deprotection of Amino Acids. − General Procedure (GP1): To a solution of the diphenyloxazolidinonyl-protected compound in MeOH, a 2 N solution of HCl (0.5 mL, 1 mmol), and 10% Pd/C were added, and the mixture was vigorously stirred under a hydrogen pressure of 4 bar for 4 h. The mixture was filtered and concentrated under reduced pressure, the residue was taken up with 2 N HCl solution (10 mL) and the mixture washed with Et_2O (3 × 10 mL) and then CH_2Cl_2 (2 × 10 mL). Subsequent concentration of the aqueous solution, filtration through Dowex 50 (3.0 g, 1 × 10 cm column, eluent 1.3 N solution of NH_4OH), repeated concentration and drying gave the free enantiomerically pure amino acid.

(*R*)-(+)-2-(1-Aminospiropentyl)acetic Acid [(*R*)-16]: From the ester **14**-Bn-A (300 mg, 0.61 mmol) in MeOH (5 mL), and 10% Pd/C (80 mg), enantiomerically pure amino acid (*R*)-**16** (74 mg, 86%) was obtained according to GP1 as colorless crystals, m.p. 128°C (dec.), $[\alpha]_D^{25}$ = +27.7 (*c* = 0.38, 1 N HCl). − IR: $\tilde{\nu}$ = 3450 cm^{-1}, 3000, 1580, 1400. − ^1H NMR (D_2O): δ = 0.66−0.89 (m, 4 H, Cpr), 1.01 (d, *J* = 6.3 Hz, 1 H, Cpr), 1.18 (d, *J* = 6.3 Hz, 1 H, Cpr), 2.26 (d, *J* = 17.3 Hz, 1 H, CH_2), 2.49 (d, *J* = 17.3 Hz, 1 H, CH_2). − ^{13}C NMR (D_2O): δ = 5.6, 5.7, 16.7, 40.8 (CH_2), 16.7, 37.0, 178.0 (C). − MS (CI), *m/z* (%): 159 (85) [M + NH_4^+], 142 (2) [M + H^+]. − MS (EI), *m/z* (%): 141 (18) [M^+], 140 (40) [M^+ − H], 126 (100) [$M^+ + H - NH_2$], 113 (33) [$M^+ - C_2H_4$], 112 (28) [$M^+ - H - C_2H_4$], 101 (42), 96 (80) [$M^+ - CO_2H$], 82 (76) [$M^+ - CH_2 - CO_2H$], 80 (50) [$M^+ - NH_2 - CO_2H$], 42 (100). − MS (HR-EI): 141.0789 ($C_7H_{11}NO_2$, calcd. 141.0789).

(*R*)-(−)-1-Aminospiropentanecarboxylic Acid [(*R*)-23]: From the protected amino acid **21** (63 mg, 0.18 mmol) in MeOH (10 mL), and 10% Pd/C (50 mg), the amino acid hydrochloride **22** (28 mg, 86%) was obtained according to GP1 after evaporation of the aqueous solution, m.p. 152°C, $[\alpha]_D^{25}$ = −79.2 (*c* = 0.90, H_2O). − IR: $\tilde{\nu}$ = 3417 cm^{-1}, 2960, 1700, 1635, 1559, 1506, 1456, 1384. − ^1H NMR (D_2O): δ = 0.68 (s, 4 H, Cpr), 1.49 (br. s, 2 H, Cpr). − MS (CI), *m/z* (%): 162 (38) [M − HCl + NH_3 + NH_4^+], 145 (100) [M − HCl + NH_4^+], 128 (46) [M + H^+]. − $C_6H_{10}ClNO_2·H_2O$ (181.63): calcd. C 39.68, H 6.67, N 7.71; found C 39.57, H 6.83, N 7.52. − After ion-exchange chromatography over Dowex 50, enantiomerically pure amino acid (*R*)-**23** (19 mg, 83%) was obtained as yellow crystals, m.p. 156°C (dec.), $[\alpha]_D^{25}$ = −45.7 (*c* = 0.80, H_2O). − IR: $\tilde{\nu}$ = 3550−2750 cm^{-1}, 1593, 1520, 1403. − ^1H NMR (D_2O): δ = 0.84 (m, 4 H, Cpr), 1.35 (d, *J* = 5.5 Hz, 1 H, Cpr), 1.60 (d, *J* = 5.5 Hz, 1 H, Cpr). − ^{13}C NMR (D_2O): δ = 6.3, 7.8, 19.3 (CH_2), 21.9, 41.7, 175.8 (C).

1-Amino-2-methylenecyclobutanecarboxylic Acid (24): The free amino acid **23** (19 mg, 0.15 mmol) when placed in contact with water underwent complete isomerization to **24** after 14 d at room temp. or after 24 h at 70°C, as determined by NMR measurement. − ^1H NMR (D_2O): δ = 2.05−2.13 (ddd, *J* = 12.4, 10.2, 8.5 Hz, 1 H, Cbu), 2.38−2.45 (ddd, *J* = 12.4, 9.8, 5.7 Hz, 1 H, Cbu), 2.63−2.70 (m, 2 H, Cbu), 4.92 (d, *J* = 1.4 Hz, 1 H, =CH_2), 4.99 (d, *J* = 1.4 Hz, 1 H, =CH_2). − ^{13}C NMR (D_2O): δ = 28.0, 28.3, 111.5 (CH_2), 65.3, 147.5, 175.9 (C).

Dimethyl Spiropentane-1,1-dicarboxylate (27): To a stirred solution of methylenecyclopropane (**25**, 1.06 g, 19.6 mmol) and $[Rh(OAc)_2]_2$ (88 mg, 0.19 mmol) in anhydrous CH_2Cl_2 (10 mL), was added dimethyl diazomalonate (**26**, 2.85 g, 18.0 mmol) at 0°C over a period of 8 h. After additional stirring at 20°C for 2 h, the mixture was concentrated under reduced pressure and purified by column chromatography (100 g of silica gel, 40 × 3 cm column, pentane/Et_2O, 10:1) to give 1.22 g (37%) of diester **27**, an oil, R_f = 0.34. − IR: $\tilde{\nu}$ = 2958 cm^{-1}, 1734, 1652, 1437, 1261. − ^1H NMR ($CDCl_3$): δ = 0.97 (s, 4 H, Cpr), 1.86 (s, 2 H, Cpr), 3.67 (s, 6 H, 2 CH_3). − ^{13}C NMR ($CDCl_3$): δ = 52.4 (2 CH_3), 6.3 (2 CH_2), 21.3 (CH_2), 169.3 (2 C), 25.1, 33.5 (C). − MS (EI), *m/z* (%): 184 (1) [M^+], 153 (24) [$M^+ - OCH_3$], 125 (100) [$M^+ - CO_2CH_3$], 94 (33) [$M^+ - OCH_3 - CO_2CH_3$], 66 (44) [$M^+ - 2\ CO_2CH_3$], 40 (37). − MS (HR-EI): 184.0735 ($C_9H_{12}O_4$, calcd. 184.0735).

1-(Methoxycarbonyl)spiropentane-1-carboxylic Acid (28): To a stirred solution of the diester **27** (1.22 g, 6.62 mmol) in MeOH (9 mL), was added a solution of KOH (517 mg, 9.21 mmol) in H_2O (3.3 mL). After additional stirring at 20°C for 48 h, the mixture was concentrated under reduced pressure, the residue was taken up with H_2O (10 mL), the mixture washed with Et_2O (2 × 20 mL), then acidified to pH 2 with 2 N HCl solution and extracted with Et_2O (3 × 30 mL). The combined organic phases were dried and concentrated under reduced pressure to give 0.86 g (76%) of **28**, m.p. 69°C. − IR: $\tilde{\nu}$ = 3481 cm^{-1}, 2958, 2802, 1765, 1448, 1351. − ^1H NMR ($CDCl_3$): δ = 1.11 (m, 4 H, Cpr), 2.25 (d, *J* = 3.5 Hz, 1 H, Cpr), 2.30 (d, *J* = 3.5 Hz, 1 H, Cpr), 3.82 (s, 3 H, CH_3), 11.99 (br. s, 1 H, OH). − ^{13}C NMR ($CDCl_3$): δ = 53.1 (CH_3), 7.2, 7.4, 25.2 (CH_2), 31.3, 31.7, 170.3, 175.2 (C). − MS (EI), *m/z* (%): 169 (5) [$M^+ - H$], 139 (36) [$M^+ - OCH_3$], 138 (63) [$M^+ - HOCH_3$], 125 (44) [$M^+ - CO_2H$], 111 (100) [$M^+ - CO_2CH_3$], 66 (77) [$M^+ - CO_2H - CO_2CH_3$].

***rac*-1-Aminospiropentanecarboxylic Acid [(*R*/*S*)-23]:** To a stirred solution of the acid **28** (350 mg, 2.06 mmol) in a 1:1 mixture of acetone and water (5 mL), a solution of Et_3N (244 mg, 2.41 mmol) in acetone (2.5 mL), and then a solution of ethyl chloroformate (300 mg, 2.76 mmol) in acetone (1.5 mL) were added dropwise at 0°C. After additional stirring for 1.5 h at this temp., a solution of NaN_3 (207 mg, 3.18 mmol) in H_2O (1.5 mL) was added dropwise at 0°C. The reaction mixture was stirred for a period of 4 h at this temp., poured into ice-cold water (10 mL), extracted with diethyl ether (3 × 10 mL), and the combined ethereal solutions were dried at 0°C for 24 h. After concentration under reduced pressure at 0°C, the residue was taken up with anhydrous toluene (5 mL), and the solution heated at 110°C for 30 min. After cooling and concentration under reduced pressure, the residue was suspended in 20% HCl solution (5 mL), refluxed with stirring for 12 h, cooled to 20°C and washed with Et_2O (2 × 10 mL). The resulting solution of the aminoester hydrochloride **31** was cooled to 0°C, brought to pH 10 with 2 N NaOH solution, stirred at 20°C for 4 h and acidified to pH 2 with 2 N HCl solution. Ion exchange chromatography over Dowex 50 according to GP1 gave 128 mg (49% over 4 steps) of racemic (*R*/*S*)-**23**, m.p. 160°C.

Methyl 3-Benzyl-5-chloro-4-oxo-3-azabicyclo[3.1.0]hexanedispiro-[2,1′:6,1″]cyclopropane-1-carboxylate (34): To a stirred solution of benzylamine (1.10 g, 10.3 mmol) in anhydrous THF (5 mL), *n*BuLi (12.3 mmol, 5.20 mL of a 2.36 M solution in hexane) was added dropwise at −78°C. After additional stirring for 30 min, a precooled (−78°C) solution of methyl 2-chloro-2-cyclopropylideneacetate (**32**) (3.00 g, 20.5 mmol) in anhydrous THF (20 mL) was transferred by cannula under an atmosphere of argon to this solution. The resulting mixture was allowed to warm to 20°C over a period of 14 h and then poured into ice-cold water (80 mL). The aqueous phase was extracted with CH_2Cl_2 (4 × 50 mL), the combined organic phases were dried and concentrated under reduced pressure. Column chromatography (30 g of silica gel, 10 × 3.5 cm column, hexane/Et_2O 2:1 to 1:1) gave 1.40 g (41%) of **34**, R_f = 0.37 (hexane/Et_2O 1:1), m.p. 96°C. − IR (KBr): $\tilde{\nu}$ = 1733 cm^{-1}, 1683, 1496, 1412, 1341, 1283. − ^1H NMR: δ = 0.63−1.40 (m, 8 H, Cpr), 3.72 (s, 3 H, OCH_3), 4.00 (d, *J* = 16.0 Hz, 1 H, CH_2), 4.46 (d, *J* = 16.0 Hz, 1 H, CH_2), 7.15−7.31 (m, 5 H, Ph). − ^{13}C NMR: δ = 52.2 (CH_3), 5.1, 5.49, 5.52, 7.4, 42.5 (CH_2), 126.9, 127.4, 128.6 (CH), 31.0, 38.7, 43.8, 53.0, 137.0, 165.9, 168.3 (C). − MS (EI), *m/z* (%): 333/331 (3/10) [M^+], 318/316 (7/20) [$M^+ - Me$], 302/300 [$M^+ - OMe$], 296 (13) [$M^+ - Cl$], 227/225 (17/45) [$M^+ - PhCH_2 - Me$], 189 (20), 114 (21), 106 (79) [$PhCH_2NH^+$], 91 (100) [$PhCH_2^+$], 77 (22) [Ph^+]. − $C_{18}H_{18}ClNO_3$ (331.8): calcd. C 65.16, H 5.47, Cl 10.68, N 4.22; found C 65.05, H 5.44, Cl 10.64, N 4.37.

Acknowledgments

This work was supported by the Deutsche Forschungsgemeinschaft (SFB 416, Project A3), the Fonds der Chemischen Industrie, and EPSRC (UK). We are grateful to the companies BASF AG, Bayer AG, Chemetall GmbH, Degussa AG, Hoechst AG, and Hüls AG for generous gifts of chemicals. The authors are grateful to CLRC Daresbury Laboratory SRS for the beamtime and the possibility to use the synchrotron facility, to Dr. S. J. Teat for his kind assistance in data collection for the compound **14**-Bn, to Dr. V. Sokolov, on leave from St. Petersburg State University at the Universität Göttingen, for his help in finding the correct systematic names for the new compounds, and to Dr. B. Knieriem for his careful reading of the manuscript.

[1] [1a] G. A. Rosenthal, *Plant Nonproteinogenic Amino and Imino Acids. Biological and Toxicological Properties*, Academic Press, New York, **1982**. − [1b] G. C. Barrett, *Chemistry and Biochemistry of the Amino Acids*, Chapman and Hall, New York, **1985**, pp. 64−95.

[2] [2a] M. C. Pirrung, G. M. McGeehan, *Angew. Chem.* **1985**, *97*, 1074−1075; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1044−1045. − [2b] R. E. Mitchell, M. C. Pirrung, G. M. McGeehan, *Phytochemistry* **1987**, *26*, 2695−2697.

[3] [3a] J. Salaün, M. S. Baird, *Curr. Med. Chem.* **1995**, *2*, 511−542. − [3b] C. H. Stammer, *Tetrahedron* **1990**, *46*, 2231−2254. − [3c] M. C. Pirrung, J. Cao, J. Chen, *J. Org. Chem.* **1995**, *60*, 5790−5794. − [3d] K. Burgess, D. Lim, K.-K. Ho, C.-Y. Ke, *J. Org. Chem.* **1994**, *59*, 2179−2185.

[4] For several recent communications see: [4a] J. Zindel, A. de Meijere, *J. Org. Chem.* **1995**, *60*, 2968−2973. − [4b] K. Burgess, C.-Y. Ke, *Synthesis* **1996**, 1463−1467. − [4c] A. Hercouet, B. Bessières, M. Le Corre, *Tetrahedron: Asymmetry* **1996**, *7*, 1267−1268. − [4d] G. Franzone, S. Carle, P. Dorizon, J. Ollivier, J. Salaün, *Synlett* **1996**, 1067−1070. − [4e] A. Hercouet, N. Godbert, M. Le Corre, *Tetrahedron: Asymmetry* **1998**, *9*, 2233−2234. − [4f] A. Fadel, A. Khesrani, *Tetrahedron: Asymmetry* **1998**, *9*, 305−320. − [4g] R. Chinchilla, L. R. Falvello, N. Galindo, C. Najera, *Tetrahedron: Asymmetry* **1998**, *9*, 2223−2227. − [4h] V. Atlan, S. Racouchot, M. Rubin, C. Bremer, J. Ollivier, A. de Meijere, J. Salaün, *Tetrahedron: Asymmetry* **1998**, *9*, 1131−1135.

[5] [5a] J. E. Baldwin, R. M. Adlington, D. Bebbington, A. T. Russell, *Tetrahedron* **1994**, *50*, 12015−12028, and ref. [2] therein. − [5b] M.-t. Lai, L.-d. Liu, H.-w. Liu, *J. Am. Chem. Soc.* **1991**, *113*, 7388−7397. − [5c] M.-t. Lai, H.-w. Liu, *J. Am. Chem. Soc.* **1992**, *114*, 3160−3162.

[6] N. Kurokawa, Y. Ohfune, *Tetrahedron Lett.* **1985**, *26*, 83−84, and references therein.

[7] [7a] A. de Meijere, *Angew. Chem.* **1979**, *91*, 867−884; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 809−826. − [7b] K. B. Wiberg in *Houben-Weyl, Vol. E 17a* (Ed.: A. de Meijere), Thieme, Stuttgart, **1997**, p. 1−27.

[8] J. M. Russo, W. A. Price, *J. Org. Chem*. **1993**, *58*, 3589−3590, and ref. [6] therein.
[9] [9a] L. Wessjohann, K. Giller, B. Zuck, L. Skattebøl, A. de Meijere, *J. Org. Chem*. **1993**, *58*, 6442−6450. For a general procedure for the preparation of 2-chloro-2-cyclopropylideneacetates see: [9b] T. Liese, S. Teichmann, A. de Meijere, *Synthesis* **1988**, 25−32; [9c] W. Weber, A. de Meijere, *Chem. Ber*. **1985**, *118*, 2450−2471; for the procedure to prepare methyl 2-chloro-2-cyclopropylideneacetate (**32**) see: [9d] T. Liese, F. Seyed-Mahdavi, A. de Meijere, *Org. Synth.* **1990**, *69*, 148−153.
[10] D. Seebach, E. Hungerbühler, R. Naef, P. Schnurrenberger, B. Weidmann, M. Züger, *Synthesis* **1982**, 138−141.
[11] [11a] M. J. O′Donnell, W. D. Bennett, R. L. Polt, *Tetrahedron Lett*. **1985**, *26*, 695−698. − [11b] M. J. O′Donnell, J.-B. Falmagne, *Tetrahedron Lett*. **1985**, *26*, 699−702. − [11c] M. J. O′Donnell, C. Zhou, A. Mi, N. Chen, J. A. Kyle, P. G. Andersson, *Tetrahedron Lett*. **1995**, *36*, 4205−4206. − [11d] M. J. O′Donnell, X. Yang, M. Li, *Tetrahedron Lett*. **1990**, *31*, 5135−5138. − [11e] M. J. O′Donnell, W. D. Bennett, *Tetrahedron* **1988**, *44*, 5389−5402. − [11f] M. J. O′Donnell, C. Zhou, N. Chen, *Tetrahedron: Asymmetry* **1996**, *7*, 621−624.
[12] [12a] B. H. Lipshutz, R. S. Wilhelm, J. Kozlowski, *Tetrahedron Lett*. **1982**, *23*, 3755−3758. − [12b] B. H. Lipshutz, D. A. Parker, J. A. Kozlowski, S. L. Nguyen, *Tetrahedron Lett*. **1984**, *25*, 5959−5962. − [12c] B. H. Lipshutz, M. Koerner, D. A. Parker, *Tetrahedron Lett*. **1987**, *28*, 945−948. − [12d] B. H. Lipshutz, *Synlett* **1990**, 119−128.
[13] [13a] R. Bloch, J. M. Denis, *Angew. Chem*. **1980**, *92*, 969−970; *Angew. Chem. Int. Ed. Engl*. **1980**, *19*, 928−929. − [13b] T. Späth, Dissertation, Universität Göttingen, **1995**.
[14] [14a] J. M. Denis, P. Le Perchec, J. M. Conia, *Tetrahedron* **1977**, *33*, 399−408. − [14b] K. A. Lukin, N. S. Zefirov, *Zh. Org. Khim*. **1987**, *23*, 2548−2552; *J. Org. Chem. USSR (Engl. Transl.)* **1987**, *23*, 2249−2252. − [14c] K. A. Lukin, A. A. Andrievskii, A. Yu. Masunova, N. S. Zefirov, *Dokl. Akad. Nauk SSSR Ser. Khim*. **1991**, *316*, 379−382; *Dokl. Chem. (Engl. Transl.)* **1991**, *316*, 19−21. − [14d] K. A. Lukin, N. S. Zefirov, D. S. Yufit, Yu. T. Struchkov, *Tetrahedron* **1992**, *48*, 9977−9984. − [14e] M. Borer, M. Neuenschwander, *Helv. Chim. Acta* **1997**, *80*, 2486−2501.
[15] This is in contrast to the behavior of (methylenecyclopropane)copper intermediates which undergo coupling with the electrophilic glycine equivalent only with concomitant opening of a cyclopropane ring. cf. S. I. Kozhushkov, M. Brandl, D. S. Yufit, R. Machinek, A. de Meijere, *Liebigs Ann.* **1997**, 2197−2204.
[16] [16a] L. Wessjohann, Dissertation, Universität Hamburg, **1990**. − [16b] N. Krass, Dissertation, Universität Hamburg, **1989**. − [16c] L. Wessjohann, N. Krass, D. Yu, A. de Meijere, *Chem. Ber*. **1992**, *125*, 867−882.
[17] [17a] M. Es-Sayed, C. Gratkowski, N. Krass, A. I. Meyers, A. de Meijere, *Synlett* **1992**, 962−964. − [17b] C. Gratkowski, N. Krass, A. I. Meyers, A. de Meijere, *Tetrahedron Lett*. **1993**, *34*, 289−292. − [17c] M. Es-Sayed, Dissertation, Universität Hamburg, **1992**.
[18] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + (1223)336-033, E-mail: teched@chemcrys.cam.ac.uk]. The deposition numbers are CCDC 118933 (**14**-Me), CCDC 118932 (**14**-Bn) and CCDC 118954 (**34**).
[19] W. A. König, *The Practice of Enantiomer Separation by Capillary Gas Chromatography*, Hüthig, Heidelberg, **1987**. We are grateful to Prof. Dr. W. A. König, Universität Hamburg, for his help in determining the enantiomeric purity of compound (*S*)-**16**.
[20] The isomers A and B did not react at all, neither with zinc−copper couple to remove the chlorine atom, nor with sodium azide to form a substitution product. The isomers C and D yielded a single diastereomer in the reductive dehalogenation which means that they should be enantiomers with respect to the stereogenic center C-2.
[21] The ratio of diastereomers obtained in this electrophilic azidation could be determined from the ^{1}H-NMR spectrum.
[22] P. E. Eaton, N. Nordari, J. Tsanaktsidis, S. P. Upadhyaya, *Synthesis* **1995**, 501−502.
[23] [23a] J. Weinstock, *J. Org. Chem*. **1961**, *26*, 3511. − [23b] H. Jendralla, *Chem. Ber*. **1980**, *113*, 3585−3596.
[24] Reviews: [24a] A. de Meijere, L. Wessjohann, *Synlett* **1990**, 20−32. − [24b] A. de Meijere in *New Aspects of Organic Chemistry II, Proceedings of the Fifth International Kyoto Conference on New Aspects of Organic Chemistry − IKCOC 5,* Kyoto Nov. 11−15 **1991**, (Ed.: Y. Ohshiro) Kodansha, Tokyo **1992**, pp. 181−213. − [24c] A. de Meijere, S. I. Kozhushkov, L. P. Hadjiarapoglou, *Top. Curr. Chem*. **1999**, *207*, 149−227.
[25] R. Köster, S. Arora, P. Binger, *Synthesis* **1971**, 322−323.
[26] M. Regitz, *Chem. Ber*. **1966**, *99*, 3128−3147.
[27] D. D. Perrin, W. L. F. Armarego, *Purification of Laboratory Chemicals*, Pergamon Press, New York, **1987**.
[28] M. J. O′Donnell, R. L. Polt, *J.Org.Chem*. **1982**, *47*, 2663−2666.

Received April 26, 1999
[O99235]