Stereochemistry of the Deamination of Spiropentylamine

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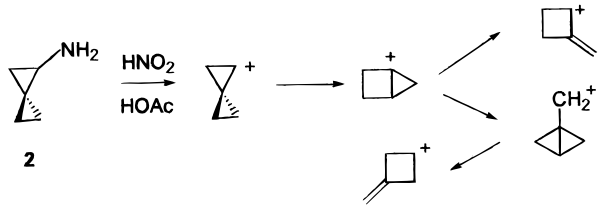
The stereochemistry of the deamination of (−)-spiropentylamine in acetic acid has been studied, and it was found that one of the major products, (−)-spiropentyl acetate, was formed with essentially complete inversion of configuration. This suggests that it is formed via an S_N2 displacement on the spiropentyldiazonium ion. The stereochemistry was established by the conversion of (−)-spiropentanecarboxylic acid to (−)-spiropentylamine via a Curtius rearrangement that proceeds with retention of configuration. The (−) acid also was converted to spiropentyl methyl ketone with methyllithium and then to (+)-spiropentyl acetate via the Baeyer−Villiger reaction that also results in retention of configuration. The deamination of *N*-nitroso-*N*-spiropentyl urea was studied in methanol, and spiropentyl methyl ether was a major product. Similarly, the reaction in water led to spiropentanol. The latter reactions also lead to 2-methoxymethyl- or 2-hydroxymethyl-1,3-butadiene, respectively, corresponding to the alternative mode of reaction via a cyclopropyl cation−allyl cation rearrangement.

Introduction

The spiropentyl cation is unusual in that it is both a cyclopropyl cation and a cyclopropylcarbinyl cation. We have been interested in the behavior of this ion, and we have carried out both an experimental and a theoretical study. The spiropentyl system has received previous study. Applequist examined the solvolysis of spiropentyl chloride (**1**) and found 2-methylenebut-3-en-1-ol as the product.[1] It corresponds to ring opening as a cyclopropyl cation.

1

The nitrous acid deamination of spiropentylamine (**2**) in aqueous solution was found to give 2- and 3-methylenecyclobutanols in a 1:5 ratio.[2] A later study confirmed these results and also found a small amount of 1-vinylcyclopropanol.[3] When carried out in acetic acid solution, the reaction has been reported to give spiropentyl acetate, 2-methylenecyclobutyl acetate, and 3-methylenecyclobutyl acetate in a 5:1:5 ratio.[4] The rearranged products are formed via a cyclopropylcarbinyl−cyclobutyl rearrangement.



2

The formation of spiropentyl acetate is interesting in that the loss of nitrogen from the intermediate diazonium ion would lead to the spiropentyl cation, which would be expected to quickly rearrange.[5] Our calculations have found the cation to be a transition state,[6] and if this is correct, the acetate could not be formed from the ion. Another possibility would be an S_N2 reaction with the spiropentyldiazonium ion, which would lead to the acetate with complete inversion of configuration. To examine this question, we have carried out the deamination of optically active spiropentylamine.

Resolution of Spiropentanecarboxylic Acid

Monosubstituted spiropentyl derivatives have not previously been resolved. Spiropentanecarboxylic acid (**3**) appeared to be the best compound for a resolution because it could easily be converted to both spiropentylamine (**2**) and spiropentyl acetate (**4**) by reactions that are known to give complete retention of configuration. It was conveniently prepared by the rhodium-catalyzed addition of ethyl diazoacetate to methylenecyclopropane followed by hydrolysis.[7] An attempt to effect an enantioselective addition using a chiral rhodium catalyst[8] was unsuccessful.

Resolution of the acid by using brucine proceeded rather slowly, and (−)-α-phenylethylamine proved to be a superior resolving agent. The maximum rotation achieved via fractional crystallization was $[\alpha]_D = -172.7°$. It was found that the two diastereomeric amides formed from racemic **3** and the above amine had slightly different GC retention times and gave two bands of equal intensity. When resolved **3** with the above optical rotation was converted to the amide, a GC analysis of the latter without prior purification indicated that the enantiomeric

(1) Applequist, D. E.; Bernett, W. A. *Tetrahedron Lett.* **1968**, 3005. Landgrebe, J. A.; Applequist, D. E. *J. Am. Chem. Soc.* **1964**, *86*, 1536.
(2) Applequist, D. E.; Fanta, G. F. *J. Am. Chem. Soc.* **1960**, *82*, 6393.
(3) Konzelman, L. M.; Conley, R. T. *J. Org. Chem.* **1968**, *33*, 3828.
(4) Gajewski, J. J.; Chang, M. J. *J. Org. Chem.* **1978**, *43*, 765.
(5) Compare Streitwieser, A. *J. Org. Chem.* **1957**, *22*, 861.
(6) Wiberg, K. B.; Shobe, D. *J. Org. Chem.* **1999**, *64*, 7768.
(7) de Meijere, A.; Kozhushkov, S. I.; Spaeth, T.; Zefirov, N. S. *J. Org. Chem.* **1993**, *58*, 502.
(8) Doyle, M. P.; Protopopova, M.; Muller, P.; Ene, D.; Shapiro, E. A. *J. Am. Chem. Soc.* **1994**, *116*, 8492.

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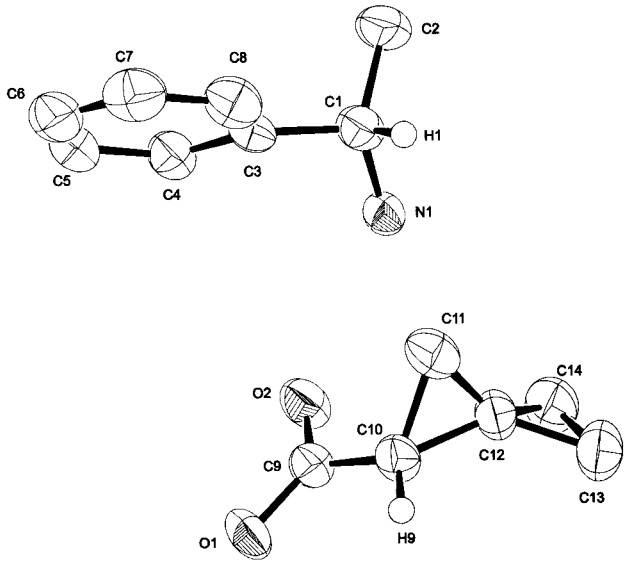


Figure 1. ORTEP representation of (*S*)-α-methylbenzylammonium (*R*)-spiropentanecarboxylate.

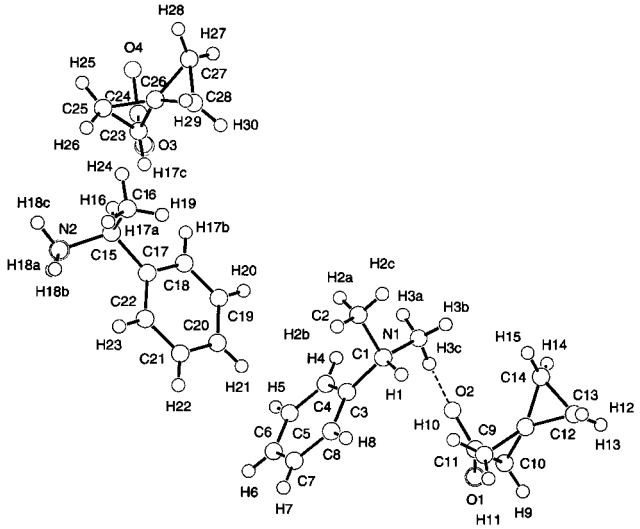


Figure 2. Crystal structure of (*S*)-α-methylbenzylammonium (*R*)-spiropentanecarboxylate showing the NH_3^+ or CO_2^- hydrogen bond.

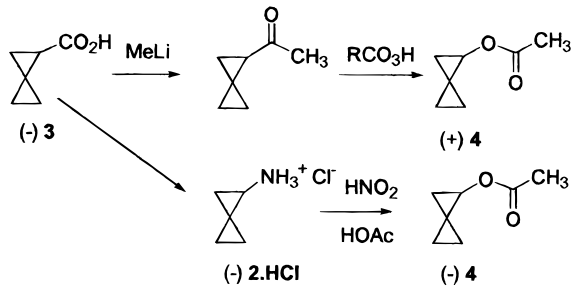
purity was 95.5%. Thus, the maximum rotation of **3** is $[\alpha]_D = 190°$.

The phenylethylamine salt (**5**) formed well-developed crystals which were suitable for an X-ray crystallographic study. The structure is shown in Figure 1. The amine component has structurally similar methyl and ammonium groups at the chiral center. The assignment shown in the figure leads to the smaller *R* value, and also has a short N···O nonbonded distance characteristic of a hydrogen bond (Figure 2). The (−) resolving agent has the *S* configuration, and the structure indicates that (−)-**3** has the *R* configuration.

The acid (**3**) was converted to **2** via the Curtius reaction (Scheme 1), and it was isolated as the amine hydrochloride. The rearrangement is known to proceed via retention of configuration.[9] The (+) acid with $[\alpha]^{25}_D = +64.2°$ gave the amine hydrochloride with $[\alpha]^{25}_D = +21.1°$ The acid with $[\alpha]^{25}_D = -113.3°$ also was converted to the

(9) Jones, L. W.; Wallis, E. S. *J. Am. Chem. Soc.* **1926**, *48*, 169.

Scheme 1



methyl ketone using methyllithium, and the latter was subjected to a Baeyer−Villiger oxidation using the urea−hydrogen peroxide complex and trifluoroacetic anhydride[10] giving (**4**) having $[\alpha]^{25}_D = +27.0°$. This reaction is known to proceed with retention of configuration.[11] These data indicate that the (−)-(*R*) acid, the (−)-(*R*) amine, and the (+)-(*R*) acetate have the same arrangement of the groups about the stereocenters. The maximum rotations of (*R*)-**3**, (*R*)-**2**·HCl, and (*R*)-**4** are −190°, −62.4°, and 45.3°, respectively.

Deamination of Spiropentylamine in Acetic Acid Solution

Treatment of the chiral amine hydrochloride with nitrous acid in acetic acid led to a mixture of 2-methylenecyclobutyl acetate, 3-methylenecyclobutyl acetate, and spiropentyl acetate in a 1:3:2 ratio. Starting with an acid having $[\alpha]_D = -116.2°$, the acetate was isolated by preparative GC, giving a mixture of spiropentyl acetate (95.5%) and achiral 3-acetoxymethylenecyclobutene. When corrected for the latter, it had a rotation of −26.1°, which corresponds to 94% inversion of configuration. In view of the difficulty in isolating pure **4** from the deamination reaction, it is reasonable to conclude that the reaction proceeded with complete inversion of configuration.[12]

Although nitrous acid deaminations of some chiral amines do lead to inverted acetates as products, complete inversion is not found,[13] suggesting that in these cases the acetate may be formed by reaction of the intermediate carbocation with the solvent. In view of the computational results that indicate the spiropentyl cation to be a transition state and the observation of complete inversion of configuration, it is reasonable to propose that the acetate is formed by an S_N2 displacement on the spiropentyldiazonium ion.

Deamination of Spiropentylamine in Methanol Solution

Is the formation of spiropentyl acetate a consequence of carrying out the deamination reaction in a medium with a low dielectric constant, which forces all ions to exist as ion pairs or higher aggregates? It is possible to examine this question by studying the deamination of

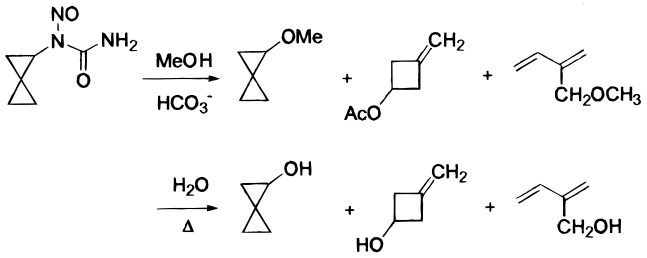
(10) Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett* **1990**, 533.

(11) Mislow, K.; Brenner, J. *J. Am. Chem. Soc.* **1953**, *75*, 2318.

(12) It is possible that some loss of configuration may result from reversible deprotonation of the diazonium ion forming an achiral diazoalkane: Kirmse, W.; Wächterhäuser, G. *Liebigs Ann. Chem.* **1967**, *707*, 44.

(13) As an example, the deamination of (+)-2-butylamine in acetic acid gave 30% inversion: Kirmse, W.; Banart, K.; Bunce, M.; Gassen, K.-R.; Kurnianto, A. W. *Recl. Trav. Chim. Pays Bas* **1986**, *195*, 272.

Scheme 2



the corresponding nitrosourea in methanol by using base catalysis. Here, the products from the *N*-nitroso-*N*-spiropentyl urea (**5**) were spiropentyl methyl ether (41%), 3-methoxy-1-methylenecyclobutane (28%), and 2-methoxymethyl-1,3-butadiene (31%) (Scheme 2). The formation of methoxymethylbutadiene indicates an intermediate position of this reaction between the solvolysis of spiropentyl chloride and the deamination of spiropentylamine hydrochloride in acetic acid.

The deamination also was carried out by heating **5** in water. Here the products were spiropentanol (32%), 2-hydroxymethylbuta-1,3-diene (31%), and 3-hydroxy-1-methylenecyclobutane (41%) (Scheme 2). The butadiene derivatives formed in these reactions result from a cyclopropyl cation type ring opening, which is the course followed in the solvolysis of spiropentyl chloride.[1]

The stereochemistry of the reactions of the nitrosourea was not studied because it is known that diazonium ions and diazoalkanes are interconverted under basic conditions,[12] which would lead to racemization.

Summary

The deamination of spiropentylamine in acetic acid solution leads to the formation of spiropentyl acetate with essentially complete inversion of configuration. The deamination of the corresponding *N*-nitrosourea in basic methanol leads to spiropentyl methyl ether as a major product, and the reaction in water leads to spiropentanol. All of these reactions probably proceed via an S_N2 displacement on spiropentyldiazonium ion. This indicates that ion pairs are not necessary to obtain the displacement reaction and also suggests that this diazonium ion has a longer lifetime than most aliphatic diazonium ions so that it has time to react via an S_N2 pathway. It is also interesting to note that, in addition to unrearranged spiropentyl derivatives, the deamination in acetic acid solution leads only to cyclopropylcarbinyl−cyclobutyl cation type rearrangements, whereas the reaction in methanol or water also leads to a cyclopropyl cation rearrangement product. The latter product is also found in the solvolysis of spiropentyl derivatives.[1]

It should be noted that S_N2 reactions at cyclopropane rings have previously been observed. The reaction of 2-methylcyclopropyl trifluoromethanesulfonate with tributyl-hexadecylphosphonium azide in an apropic solvent was found to give complete inversion of configuration.[14] However, an S_N1 reaction leading to an allyl cation is more commonly observed.[5]

Experimental Section

General Information. FT NMR spectra were taken in $CDCl_3$ and FT IR spectra were taken in CCl_4. Analytical GC measurements were performed with a gas chromatograph connected to an integrator. The capillary column used was a 50 m × 0.2 μm i.d. column coated with a 0.33 μm layer of cross-linked methyl silicone. Preparative gas chromatography was performed using a 4 ft × 1/4 in. column fitted with 20% Carbowax 20M on Chromosorb P (80/100 mesh). Boiling and melting points are uncorrected. Polarimetric analysis was performed using a 1 dm cell.

Deamination of Spiropentylamine Hydrochloride. To a 15 mL round-bottomed flask was added 0.31 g of spiropentylamine hydrochloride[4] (2.6 mmol) in 4 mL of glacial acetic acid. Over a period of 45 min, 0.21 g of $NaNO_2$ (3.1 mmol) was added in small portions. Stirring was continued for another 2 h. The solution was extracted with pentane, and the combined organic extracts were washed with saturated $NaHCO_3$ until the washings were basic. The organic extract was dried over anhydrous Na_2CO_3 and concentrated in vacuo. Analysis of the product mixture by analytical GC (T_0 = 40 °C, t_{init} = 30 min, r = 15°/min, T_f = 250 °C) showed the presence of three reaction products. Since TLC analysis showed that column chromatography would not separate the solution into its different components, another approach was taken. The solution was dissolved in 10 mL of CH_2Cl_2 and placed in a three-necked round-bottomed flask equipped with gas inlet and magnetic stirrer. The flask was placed in a dry ice/acetone bath, and ozone was bubbled through the solution until the solution turned light blue. The solution was purged with oxygen for 20 min, then 2 mL of dimethyl sulfide was added, and the solution was stirred overnight. The dry ice/acetone bath was not removed but was allowed to warm to room temperature overnight. The solution was extracted with 20 mL of $NaHSO_3$, washed with water, and dried over anhydrous $NaHCO_3$. Concentration of the liquid in vacuo yielded a yellow oil. Two of the compounds were isolated using microchromatography on silica gel. The column was prerun with solvent (10% ethyl acetate in pentane) before it was charged with the product mixture. The first fraction isolated contained spiropentyl acetate (R_f = 0.74), and the second fraction was 3-acetoxy-1-methylenecyclobutanone[15] (R_f = 0.015), which is the product of the ozonolysis of 3-acetoxy-1-methylenecyclobutane. The third component, 2-acetoxy-1-methylenecyclobutane, was identified by comparison of the GC trace with that of an authentic sample. Spiropentyl acetate (t_R = 11.9 min, 32%), 3-acetoxy-1-methylenecyclobutane (t_R = 12.3 min, 50%), and 2-acetoxy-1-methylenecyclobutane (t_R = 12.4 min, 16%) were formed.

Optical Resolution of Spiropentanecarboxylic Acid with (*S*)-(−)-α-Methylbenzylamine. Spiropentanecarboxylic acid (5.0 g, 44.6 mmol) was dissolved in 20 mL of ethyl acetate in a 50 mL Erlenmeyer flask, and 5.4 g of (*S*)-(−)-α-methylbenzylamine (44.6 mmol) was added. The solution became warm when the amine was added to the acid. The solution was heated to boiling on a hot plate and was allowed to cool to room temperature. Crystallization was achieved only after cooling the solution to −60 °C and scratching the walls of the Erlenmeyer flask with a spatula. The solution was allowed to crystallize over a period of 10 h. The white crystals were collected by removing the liquid by pipet. Fractional recrystallization and acidic hydrolysis of the salt yielded optically active spiropentanecarboxylic acid with $[\alpha]^{25}_D = -172.7°$ (c = 0.035 g/mL, methanol), mp 120−121 °C. IR (KBr): 1650 cm^{-1}. ^1H NMR (C_6D_6): 0.6 (m, 2H, CH_2), 0.83 (m, 2H, CH_2), 0.97 (dd, 1H, J = 7.5,3.3), 1.3 (d, 3H, J = 6.6, CH_3), 1.42 (m, 1H, CH), 1.85 (dd, 1H, J = 7.5,3.9, C*H*CO_2), 3.92 (q, 1H, J = 6.6, C*H*CH_3), 5.5 (bs, 3H, NH_3), 7.0 (m, 1H, CH aromatic), 7.1 (m, 2H, aromatic), 7.2 (d, 2H, aromatic). ^{13}C NMR (C_6D_6): 5.59(t), 6.56(t), 14.5(t), 17.64(s), 22.6(q), 22.66(d), 50.95(d), 126.7(d), 128.5(d), 142.5(s), 179.6(s). Anal. Calcd for $C_{14}H_{19}NO_2$: C 72.07, H 8.21, N 6.00. Found: C 71.95, H 8.33, N 6.04.

After 6-fold fractional recrystallization of the above salt, a small sample of the crystals (approximately 0.2 g) was dissolved in 10 mL of ethyl acetate in a 15 mL Erlenmeyer flask,

(14) Banert, K. *Chem. Ber.* **1985**, *118*, 1564.

(15) Tenud, L.; Meilmann, M.; Dallwigk, E. *Helv. Chim. Acta* **1977**, *60*, 975.

heated to boiling for 5 min, and allowed to cool to room temperature. The clear liquid was transferred to a small vial and covered with perforated Parafilm. After a period of 36 h rod-shaped clear crystals had formed which could be used for the X-ray structure determination

Deamination of Chiral Spiropentylamine Hydrochloride. To a 15 mL round-bottomed flask was added 0.261 g of chiral spiropentylamine hydrochloride (4.5 mmol) (derived from **3** having $[\alpha]^{25}_D = -116.2°$) in 4 mL of glacial acetic acid. Over a period of 45 min, 0.31 g of $NaNO_2$ (4.5 mmol) was added in small portions. Stirring was continued for another 2 h. The solution was extracted with pentane, and the combined organic extracts were washed with saturated $NaHCO_3$ until the washings were basic. The organic extract was dried over anhydrous Na_2CO_3 and concentrated *in vacuo*. Analysis of the product mixture by analytical GC (T_0 = 40 °C, t_{init} = 30 min, r = 15°/min, T_f = 250 °C) showed that spiropentyl acetate, 3-acetoxy-1-methylenecyclobutane, and 2-acetoxy-1-methylenecyclobutane were formed in a 1.6:2.8:1 ratio.

For this run ozonolysis was not performed, because only a small amount of amine was deaminated and loss of product was to be avoided. Instead, preparative GC was used for the separation of the liquid into its components (T_{col} = 110 °C, T_{inj} = 120 °C, T_{det} = 140 °C). Two fractions were collected; one containing a mixture of spiropentyl acetate (90.5%) and 3-acetoxy-1-methylenecyclobutane was collected after 8.15 min and another fraction containing spiropentyl acetate (11%), 3-acetoxy-1-methylenecyclobutane (76%), and a third component, 2-acetoxy-1-methylenecyclobutane (12%), was collected after 8.40 min. ^{1}H NMR spectra were recorded for two fractions, and the integration of the peaks was compared with the analytical GC data. GC assignments and NMR spectra agreed well. The optical rotation measured for the first fraction was $[\alpha]^{25}_D = -23.46°$ (c = 4.9 mg/mL, methanol). Because the impurity was known and is achiral, this value could be corrected, giving $[\alpha]^{25}_D = -26.1°$.

Spiropentyl Methyl Ketone. In a 100 mL three-neck round-bottomed flask equipped with magnetic stirring bar were placed 3.4 g of spiropentanecarboxylic acid (30 mmol) and 50 mL of anhydrous ether. The flask was placed in an ice/salt bath at 0 °C, and methyllithium (1.4 M in ether, 42.7 mL, 59.9 mmol) was added slowly over a period of 1 h. A white precipitate formed during this process. After the addition was complete, the white slurry was stirred for an additional 1 h at room temperature. The lithium salt was hydrolyzed by slowly adding the slurry to a cold, vigorously stirred solution of dilute HCl. The two layers were separated, and the aqueous layer was extracted with three 10 mL portions of ether. The combined ether extracts were washed with saturated $NaHCO_3$ and saturated NaCl, dried over anhydrous Na_2SO_4, and evaporated in vacuo to yield a yellow oil (2.9 g, 87%). The high-resolution MS data showed a molecular ion peak at m/z 109.0651 instead of 110.0732. The analysis did not change after isolating the compound by preparative GC, and no obvious explanation can be given as to the origin of the hydrogen atom loss. The low combustion analysis value for carbon may be due to the presence of the quaternary spiro carbon atom, which can lead to incomplete combustion. IR (CCl_4): 1704(s) cm^{-1}. ^{1}H NMR: 0.8−1.10 (m, 4H, CH_2), 1.42 (dd, 1H, J = 7.5, 3.6), 1.53 (t, 1H, J = 4.5, 3.6), 2.08 (s, 3H), 2.22 (dd, J = 7.5, 4.5). ^{13}C NMR: 5.46(t), 6.69(t), 16.58(t), 20.26(s), 28.28(d), 29.73(q), 208.56(s). HRMS(EI): calcd for C_7H_9O 109.0653, found 109.0651. Anal. Calcd for $C_7H_{10}O$: C 76.33, H 9.15. Found: C 75.51, H 9.10.

Spiropentyl Acetate. In a 50 mL round-bottomed flask were placed 0.85 g of spiropentyl methyl ketone (7.7 mmol), 7.6 g of urea·H_2O_2 complex (15.4 mmol), 10 g of Na_2HPO_4 (70.4 mmol), and 30 mL of dry CH_2Cl_2. Trifluoroacetic anhydride (3 mL, 20 mmol) was added dropwise over a period of 30 min. The reaction solution warmed during this period, and a reflux condenser had to be attached. After the addition was completed, the solution was heated to reflux for another 3 h. The solution was allowed to cool to room temperature, and 20 mL of water was added. The layers were separated, and the aqueous layer extracted with two 10 mL portions of CH_2Cl_2. The combined organic extracts were extracted with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo to yield a yellow oil (0.54 g, 56%). The acetate could be further purified by flash column chromatography on silica gel (R_f = 0.47; ether:pentane 1:8). The NMR spectrum agreed with that reported in the literature.[4]

Synthesis of Chiral Spiropentyl Acetate. The conversion of chiral **3** ($[\alpha]^{25}_D = -113.3°$) to the methyl ketone was carried out as described above, and the latter was converted to the acetate. The acetate could be further purified by flash column chromatography on silica gel (R_f = 0.47; ether:pentane 1:8), $[\alpha]^{25}_D = +27.7°$ (c = 0.02 g/ mL, methanol).

***N*-(*S*)-(−)-(α-Methylbenzyl)spiropentanecarboxamide.** To a 50 mL round-bottomed flask cooled in an ice bath was added 0.3 mL of spiropentanecarboxylic acid (2.7 mmol) in 10 mL CH_2Cl_2. Oxalyl chloride (0.3 mL, 3.5 mmol) was added dropwise via syringe over a period of 30 min. After the addition was complete the solution was stirred for another 0.5 h at 0 °C and 0.5 h at room temperature. The solution was cooled to 0 °C, and 1.5 mL of (*S*)-(−)-α-methylbenzylamine (11.6 mmol) dissolved in 2 mL CH_2Cl_2 was added slowly over a period of 40 min. The solution was stirred for 2 h at room temperature. After the addition of 30 mL of ether the solution was washed with 20 mL of water, two 10 mL portions of 1 M phosphoric acid, 10 mL of a saturated $NaHCO_3$ solution, and 10 mL of brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Chromatography on silica gel with 3:1 ether/pentane afforded 0.44 g of a white powder (77% yield, R_f = 0.44, mp 94−97 °C). IR (KBr): 1676(s), 1540(m), 1494(s) cm^{-1}. ^{1}H NMR (C_6D_6): 0.56 (m, 2H, CH_2), 0.76−0.69 (m, 3H, CH_2, CH), 1.15 (d, 3H, CH_3), 1.39 (m, 1H, CH), 1.50 (t, 0.5H, CH, J = 3.6), 1.54 (t, 0.5H, CH, J = 3.6), 5.4 (bs, 1H, NH), 6.9−7.2 (m, 5H, C_6H_5) ppm. ^{13}C NMR (C_6D_6): 5.25-(t), 6.34(t), 13.4(t), 16.9(s), 21.7(q), 22.2(d), 48.3(d), 126.2(d), 126.3(d), 126.9(d), 127.7(s), 170.5(s). MS(CI): 216.2. HRMS-(CI): calcd for $C_{14}H_{18}NO$ (MH^+) 216.1388, found 216.1386. Anal. Calcd for $C_{14}H_{17}NO$: C 78.1, H 7.96, N 6.51. Found: C 77.01, H 7.97, N 6.39.

Determination of %ee by GC Analysis of *N*-(*S*)-(−)-(α-Methylbenzyl)spiropentanecarboxamide. Gas chromatographic analysis of the racemic and chiral samples of *N*-(*S*)-(−)-(α-methylbenzyl)spiropentanecarboxamide was performed with analytical GC (T_{init} = 120 °C, T_f = 250, t = 15 min, r = 10 °/min). For the two diastereomers two peaks appeared in the GC trace at t_R = 24.05 min and t_R = 24.25 min. For the racemic sample the integrations of the two peaks indicated a 1:1 ratio. The integrations for the chiral sample ($[\alpha]^{25}_D = -172.73°$) were 2.96 and 62.95, respectively, indicating 95.5% optical purity of the sample. With the X-ray structure it was determined that negatively rotating acid has the (*R*) configuration, which leads to the assignment of *N*-(*S*)-(−)-α-methylbenzyl)-(*R*)-(−)-spiropentanecarboxamide for the chiral sample (mp 129−131 °C). The maximum optical rotation of spiropentanecarboxylic acid is determined to be $[\alpha]^{25}_D = -190°$.

***N*-Spiropentyl Urea.** Spiropentanecarboxylic acid (0.99 g, 8.8 mmol) was added to 10 mL of distilled water in a 50 mL round-bottomed flask equipped with a pressure-equalizing addition funnel and magnetic stirrer, and sufficient acetone was added to dissolve the acid in the water. The flask was placed in a 0 °C ice/salt bath, and 1.46 mL of triethylamine (10.6 mmol) in 10 mL of acetone was added. After the addition was completed 1.1 mL of ethyl chloroformate (13.6 mmol) in 10 mL acetone was added slowly over a period of 30 min. Stirring continued for 30 min at 0 °C, after which a solution of 0.88 g of sodium azide (15.8 mmol) in 10 mL of distilled water was added dropwise. After stirring at 0 °C for 1 h, the solution became cloudy and was poured into 100 mL of distilled water. The solution was concentrated in vacuo, and the aqueous solution was extracted with 3 × 10 mL of ether. The combined ether extracts were washed with saturated $NaHCO_3$ solution to eliminate any unreacted acid and dried over anhydrous Na_2SO_4, and the solvent was carefully removed in vacuo. The presence of the acyl azide was confirmed by IR spectroscopy (ν = 2130 and 1739 cm^{-1}). The acyl azide was used without further purification.

Spiropentanecarbonyl azide was added to 30 mL of dry toluene in a 50 mL round-bottomed flask equipped with a reflux condenser. The liquid was heated to reflux for 5 h until the evolution of gas stopped. The solution then was cooled to room temperature. IR spectroscopic analysis confirmed the conversion to spiropentane isocyanate (ν = 2200 cm^{-1}). The solution was cooled in an ice bath, and ammonia (gas) was bubbled through the solution for 40 min. A white precipitate formed. The solution was allowed to stand for an additional 1 h in the refrigerator, after which time the precipitate was collected by vacuum filtration in a Buchner funnel. The solid was washed with cold toluene, dried, recrystallized from ethyl acetate, collected, and dried in vacuo to yield a white powder (0.18 g, 16% yield, mp 149−151 °C). IR (KBr): 1661, 1538, 1311 cm^{-1}. ^{1}H NMR (CD_3OD): 0.63 (m, 2H, CH_2), 0.80 (m, 2H, CH_2), 1.047 (t, 2H, J = 5.5, CH_2), 2.67 (m, 1H, J = 3.5, C*H*NH). ^{13}C NMR (CD_3OD): 3.45(t), 6.83(t), 15.09(t), 15.97(s), 28.68(d), 163(s). HRMS (CI): calc for $C_6H_{11}NO_2$ (MH^+) 127.0871, found 127.0871. Anal. Calcd for $C_6H_{10}NO_2$: C 57.12, H 7.99, N 22.21. Found: C 57.40, H 7.93, 22.01.

***N*-Nitroso-*N*-spiropentyl Urea.** A 50 mL round-bottomed flask was placed in an ice/salt bath and equipped with a magnetic stirrer. To the flask were added 0.22 g of *N*-(spiropentyl) urea (1.39 mmol) and 3 mL of a 7:3 mixture of acetic acid and acetic anhydride. $NaNO_2$ (0.15 g, 2.2 mmol) was dissolved in 3 mL of water and added to the solution via syringe pump over a period of 1 h. To the solution was added 30 mL of ice water, and the solution was stirred for an additional 1 h in the ice bath. A yellow precipitate formed during this time. The solution was placed in the refrigerator overnight. The crystals were collected by vacuum filtration, washed with ice water, and dried in vacuo. After recrystallization (ethyl acetate/petrol ether 1:1) 0.17 g of pure *N*-nitroso-*N*-spiropentyl urea (81% yield) was collected (mp 87−89 °C, dec). IR (KBr): 1715, 1507 cm^{-1}. ^{1}H NMR (CD_3OD): 0.64−0.74 (m, 2H), 0.85 (m, 1H), 1.08 (m, 2H), 1.52 (t, 1H, J = 6.6), 2.7 (dd, 1H, J = 6.6, 7.8). ^{13}C NMR (CD_3OD): 3.97(t), 5.27(t), 13.35(t), 16.36(s), 29.4(d), 156.0(s). HRMS(CI): calcd for $C_6H_{10}N_3O_2$ (MH^+) 156.0773, found 156.0772. Anal. Calcd for $C_6H_9N_3O_2$: C 46.45, H 5.85, N 27.08. Found: C 46.56, H 5.84, N 27.01.

Deamination of *N*-Nitroso-*N*-spiropentyl Urea in Water. A 10 mL round-bottomed flask equipped with magnetic stirrer containing 4 mL of distilled water and 0.52 g of *N*-nitroso-*N*-spiropentyl urea (3.4 mmol) was heated to 100 °C. The decomposition of the nitrosourea was accompanied by vigorous gas evolution (colorless gas). The solution was allowed to cool to room temperature, the aqueous solution was extracted with 3 × 10 mL portions of CH_2Cl_2, and the combined organic extracts were dried over anhydrous Na_2SO_4. The solvent was removed in vacuo, and a GC/MS analysis was performed. The analysis revealed that three major compounds had been formed. The MS data of the three compounds indicated the formation of three alcohol derivatives with identical mass (*m*/*z* 84). Analysis of the mixture by ^{1}H NMR spectroscopy provided enough information to identify the compounds as 3-hydroxy-1-methylenecyclobutane (δ 2.65 m, 2H, CH_2; 3.0 m, 2H, CH_2; 4.9 m, 1H, C*H*OH; 4.15 m, 2H, =CH_2), spiropentanol[16] (δ 0.69−0.85, m, 4H, CH_2; 1.0, t, 2H, CH_2; 3.85, dd, 1H, C*H*OH), and 2-hydroxymethyl-1,3-butadiene[17] (δ 4.4, s, 2H, CH_2OH; 5.15−5.4, m, 4H, =CH_2; 6.4, 1H, dd, =CH). GC analysis (analytical GC, T_0 = 50 °C) showed the product distribution to be 27% 2-hydroxymethyl-1,3-butadiene (t_R = 15.6 min), 41% 3-hydroxy-1-methylenecyclobutane (t_R = 16.1 min), and 32% spiropentanol (t_R = 16.3 min).

Deamination of *N*-nitroso-*N*-spiropentyl Urea in Methanol. To a solution of 0.79 g of $NaHCO_3$ (9.5 mmol) in 2 mL of methanol in a 5 mL round-bottomed flask was added a solution of 0.74 g of *N*-nitroso-*N*-spiropentyl urea (4.8 mmol) in 2 mL of methanol. The solution was stirred for 2 h during which time the solution changed color from yellow to clear. The solution was poured into 20 mL of water and extracted with 3 × 10 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2CO_3 and concentrated to 2 mL by distillation through a 20 cm steel-packed distillation column. The concentrated solution was purified by preparative GC (column A, T_{inj} = 120 °C, T_{det} = 150 °C, T_{col} = 100 °C, t_R = 3.3 min). NMR analysis of the collected sample shows three individual compounds, 1-methoxyspiropentane, 1-methoxy-3-methylenecyclobutane,[18] and 2-methoxymethyl-1,3-butadiene.[19] GC analysis (analytical GC, T_0 = 40 °C) showed the product distribution to be 31% 2-methoxymethyl-1,3-buta-diene (t_R = 3.26 min), 41% 3-methoxy-1-methylenecyclobutane (t_R = 3.4 min), and 32% 1-methoxyspiropentane (t_R = 3.7 min).

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Supporting Information Available: X-ray crystallographic data for (*S*)-α-phenylethylammonium (*R*)-spiropentanecarboxylate, **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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