Di- and Trispirocyclopropanated Tetrahydropyridinones[‡]

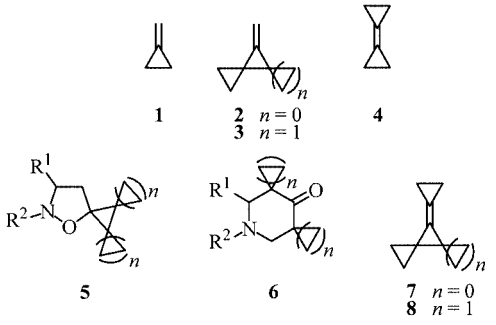
Martina Gensini,[a] Sergei I. Kozhushkov,[a] Daniel Frank,[a] Denis Vidović,[b] Alberto Brandi,*[c] and Armin de Meijere*[a]

Keywords: Bicyclopropylidene / Cycloaddition / Nitrones / Rearrangement / Spiro compounds

A variety of spirocyclopropane-annelated tetrahydropyridinones of types **14/15** and **18/19** have been prepared in good yields (68–80%) by means of 1,3-dipolar cycloadditions between nitrones **25**, **31**, and **34** and cyclopropylidenespiropentane (**7**) and 7-cyclopropylidenedispiro[2.0.2.1]heptane (**8**), with subsequent thermal rearrangement. While the overall reactions of nitrones **25** and **31** with 7-cyclopropylidenedispiro[2.0.2.1]heptane (**8**) occurred with the commonly observed regioselectivity (i.e., the initially formed cycloadducts of type **12/13** rearranged to give compounds **29**, **30**, and **33** as major products), the reactions of **31** and **34** with cyclopropylidenespiropentane (**7**) and of **34** with 7-cyclopropylidenedispiro[2.0.2.1]heptane (**8**) showed an opposite trend. Thermal rearrangement of compound **27** gave a mixture of pyridinone **29** and ring-opened product **30** (19 and 58% yields, respectively).

Introduction

Among the large variety of 1,3-dipolar cycloadditions between nitrones and alkenes, those to methylenecyclopropane (**1**)[1] and its spirocyclopropanated analogues **2**, **3**,[2] and bicyclopropylidene (**4**)[3] have been of special interest in the last 15 years. Nitrones cycloadd regioselectively to such alkenes of types **1**–**3**, mainly giving products of type **5**, in which the oxygen atom is directly attached to a cyclopropane moiety. These cycloadducts are prone to undergo a thermal rearrangement (so called Brandi–Guarna reaction[4]) to provide piperidinone derivatives of type **6** without and with annelated spirocyclopropane moieties.[2–5]



As aza analogues of the basic skeletons of the Illudin[6] and Ptaquilosin[7] sesquiterpenes, some of these compounds showed interesting biological activities in cleaving a DNA plasmid.[8] We have investigated the 1,3-dipolar cycloadditions of various nitrones to cyclopropylidenespiropentane (**7**) and 7-cyclopropylidenedispiro[2.0.2.1]heptane (**8**)[2b] and subsequent thermal rearrangement to test the influence of the presence of one and two additional spirocyclopropane moieties on bicyclopropylidene (**4**) upon the regioselectivity of these cycloadditions, and report our results here.

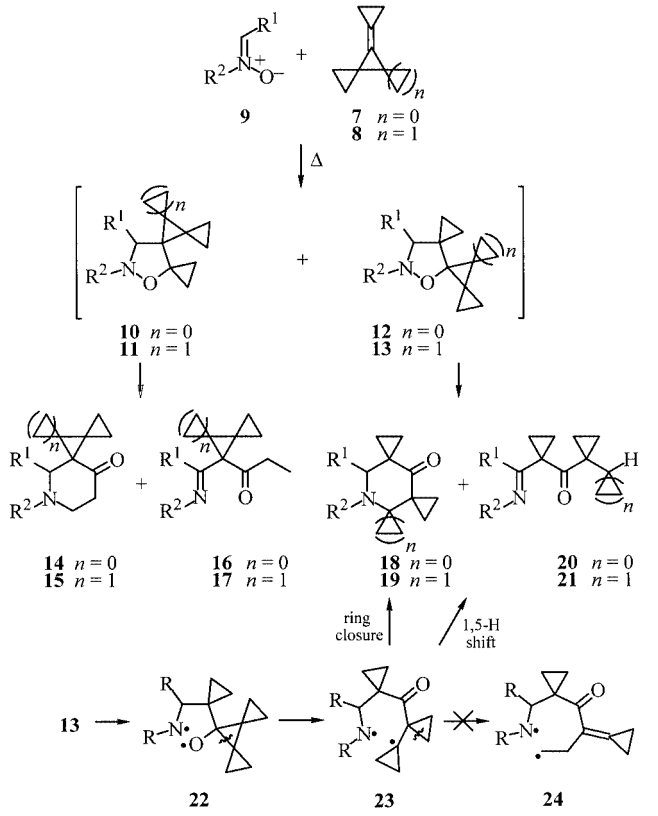
Results and Discussion

According to previous experience, the reaction between spirocyclopropanated bicyclopropylidenes **7** and **8** and nitrones of type **9** may yield products of types **14**–**21** (Scheme 1).

[‡] Cyclopropyl Building Blocks in Organic Synthesis, 91. Part 90: S. Wiedemann, D. Frank, H. Winsel, A. de Meijere, *Org. Lett.* **2003**, *5*, 753–755. Part 89: C. Liu, M. Tamm, M. W. Nötzel, A. de Meijere, J. K. Schilling, D. G. I. Kingston, *Tetrahedron Lett.* **2003**, *44*, 2049–2052.

[a] Institut für Organische Chemie der Georg-August-Universität Göttingen, Tammannstrasse 2, 37077 Göttingen, Germany
Fax: (internat.) + 49-551/399475
E-mail: Armin.deMeijere@chemie.uni-goettingen.de
[b] Institut für Anorganische Chemie der Georg-August-Universität Göttingen, Tammannstrasse 4, 37077 Göttingen, Germany
[c] Dipartimento di Chimica Organica "Ugo Schiff", and Centro di Studio sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni – CNR, Università degli Studi di Firenze, Polo Scientifico,
Via della Lastruccia 13, 50019 Sesto Fiorentino, Italy
Fax: (internat.) + 39-055/457-3572
E-mail: alberto.brandi@unifi.it

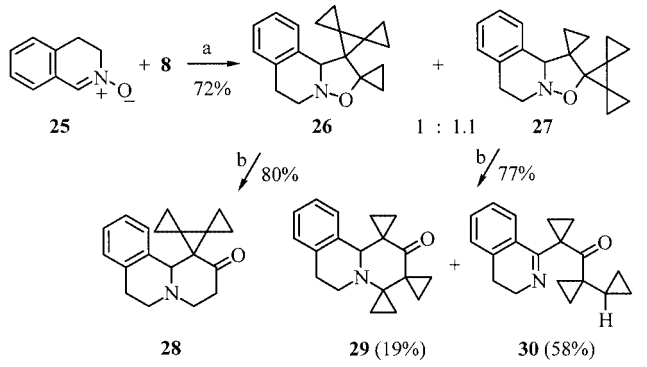
 DOI: 10.1002/ejoc.200200696



Scheme 1. Expected 1,3-dipolar cycloadditions between nitrones **9** and cyclopropylidenespiropentane (**7**) and 7-cyclopropylidenedispiro[2.0.2.1]heptane (**8**) and thermal rearrangement of the products

The first cycloaddition examined, that between the bicyclic nitrone **25** and 7-cyclopropylidenedispiro[2.0.2.1]heptane (**8**), proceeded at ambient temperature within 7 d and gave the cycloadducts **26** and **27** in a ratio of 1:1.2 (1:1.1 after chromatographic separation) (Scheme 2).

The slight predominance of **27** is in line with the previously published results for the methylenecyclopropanes **2** and **3** in relation to **1**,[8b] but the regioselectivity in this current case is lower than expected. Upon heating of the perspirocyclopropanated isoxazolidine **26** in *p*-xylene at 140 °C for 5 h, it rearranged cleanly (80% yield) to the pyridinone **28**, the structure of which was established by X-ray diffraction (Figure 1). The isomeric product **27** under these conditions gave a mixture of the trispirocyclopropanated benzoquinolizinone **29** and the noncyclized dihydroisoquinoline derivative **30** (77% yield, ratio 1:3). The latter product apparently arose through a 1,5-hydrogen shift of the hydrogen atom adjacent to the nitrogen atom in the intermediate diradical of type **23** (Scheme 1) (cf. refs.[9,10]). The one-pot reaction between the nitrone **25** and the bicyclopropylidene **8** (120 °C, 1 d) furnished a mixture of products **28**−**30**, from which **28** was isolated in 28% yield (Table 1). Unfortunately, compounds **29** and **30** could not be completely separated, and their yields were estimated from NMR spectra of enriched fractions as 11 and 32%, respectively. Spirocyclopropanated isoxazolidines of types **12** and **13** are known to undergo a sequence of highly chemo- and regioselective ring-openings.[11] The initially formed diradical intermediate of type **22** (Scheme 1), an oxygen analogue of a cyclopropylmethyl radical, immediately undergoes the well-known rapid rearrangement[12] to a homoallyl-type radical, forming a diradical **23**. This in turn intramolecularly recombines to give a trispirocyclopropanated skeleton of type **19**. A diradical of type **23** would also be capable of further rearrangement, to afford a diradical of type **24**, cyclization of which would form an azepinone derivative (cf. ref.[13]). No such product, however, was detected in the mixture originating from the rearrangement of isoxazolidine of type **13**. This indicates that intramolecular radical recombination in **23** is faster in this case than the cyclopropylmethyl-to-homoallyl radical ring-opening.[5b]



Scheme 2. a) C_6H_6, 20 °C, 7 d; b) *p*-xylene, 140 °C, 5 h

Further cycloadditions of nitrones **31** and **34** to bicyclopropylidene derivatives **7** and **8** with subsequent thermal

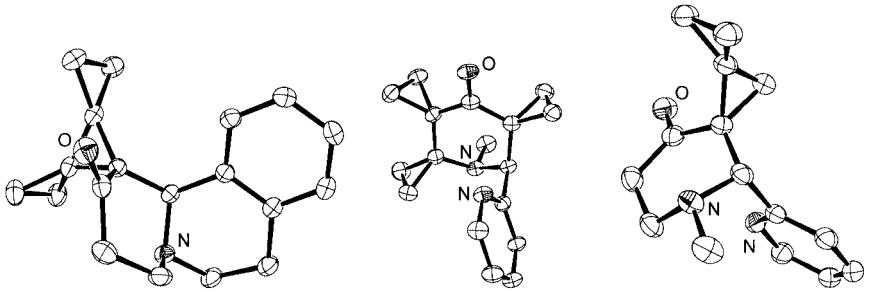
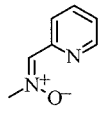
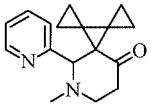
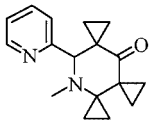
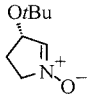
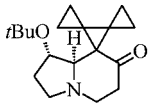
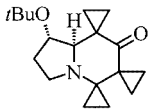
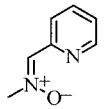
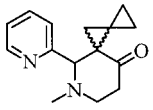
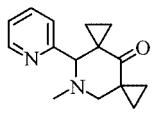
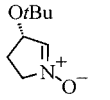
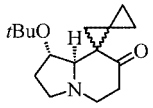
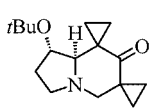


Figure 1. Molecular structures of compounds **28**, **33**, and *trans*-**37** in the crystal[15]

Table 1. One-pot 1,3-dipolar cycloaddition/thermal rearrangement transformations involving bicyclopropylidene derivatives **7** and **8**

Alkene	Nitrone	Products (Yield, %)	Total Yield (%)
8	**25**	**28** (28) + **29** (11) + **30** (32)	71
8	 **31**	 **32** (14) +  **33** (54) (ratio 1:3.8)	68
8	 **34**	 **35** (47) +  **36** (30) (ratio 1.6:1)	77
7	 **31**	 *cis*/*trans*-**37**[a] (52) ratio 1:1 +  **38** (20) (ratio 2.6:1)	72
7	 **34**	 *cis*/*trans*-**39**[a] (53) ratio 2:1 or 1:2 +  **40** (27) (ratio 2:1)	80

[a] The stereochemical designation relates to the sequence rules of Cahn, Ingold, and Prelog.

rearrangement were carried out as one-pot reactions in *o*-xylene at 120 °C for 1 d in order to increase the overall yields of the final products of types **14**−**21** and to avoid cycloreversions of the intermediate isoxazolidines.[14]

The products were obtained as mixtures of isomers, which were easily separated by chromatography on silica gel (Table 1). No open-chain isomers were observed from nitrones **31** and **34**. Products **37** and **39** were each obtained as mixtures of two diastereomers (ratios 1:1 and 2:1 or 1:2, respectively), due to the stereogenicity of C-3 in the piperidinone ring. In both cases the *cis* and *trans* isomers could be separated by chromatography. The diastereomer *trans*-**37** was obtained in crystalline form and identified by X-ray diffractometry (Figure 1); the *cis* and *trans* isomers of **39** could not be assigned. The molecular structure of **33** was also rigorously established by X-ray crystal structure analysis (Figure 1).

The previously observed regioselectivities in 1,3-dipolar cycloadditions between nitrones and methylenecyclopropane and its spirocyclopropanated analogues, predominantly forming isoxazolidines of type **5** in which the oxygen atom is attached to a cyclopropane ring, can be interpreted on the basis of both steric and electronic effects. The long-lasting controversial debate about whether 1,3-dipolar cycloadditions occur stepwise through diradical or dipolar intermediates,[16] or in a concerted fashion,[17] has now been settled in favor of a more or less concerted reaction mode.[18] The degree of concertedness undoubtedly depends on the nature and the pattern of substituents both on the 1,3-dipole and on the alkene substrate. The outcome of the nitrone cycloadditions to **7** and **8** is quite surprising: while the adducts of nitrones **25** and **31** to **8** are formed with the regioselectivity expected for steric reasons (Scheme 2 and Table 1), those of **34** to **8** and of **31** and **34** to **7** are formed with the reversed regioselectivity. Even the fact that the cycloadducts **26** and **27** are obtained in almost equal amounts from **25** and **8** is noteworthy, as the significant steric bulk of the dispiroheptyl moiety should also favor the formation of **27**, and the same arguments would also apply for the additions of **31** and **34** to cyclopropylidenespiropentane **7**. One can only speculate that electronic effects might favor the precursors to **35**, **37**, and **39**, respectively, yet the nature of these effects is not conceivable at this moment.

The high diastereoselectivities seen in the addition of the enantiomerically pure nitrone **34** to **7** and **8** are due to the *anti* approach of the alkenes towards the nitrone, which gives rise to the *cis* relationship of the *tert*-butoxy group and the bridgehead hydrogen atom in the final products **35**/**36** and **39**/**40**.

Conclusion

In conclusion, aside from the poorly understood influence of additional spirocyclopropane moieties on bicyclopropylidenes, as in **7** and **8**, upon the regioselectivity of nitrone 1,3-dipolar cycloadditions, these reactions and their subsequent thermal rearrangements allow one to prepare a variety of new tetrahydropyridinone derivatives with up to three spiroannelated cyclopropane rings in a simple way. It would be worth testing whether the increased number of spirocyclopropane units in these compounds affects the biological activity of such aza-heterocycles.[19]

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded at 250 (^{1}H), and 62.9 [^{13}C, additional DEPT (Distortionless Enhancement by Polarization Transfer)] MHz with a Bruker AM 250 instrument in $CDCl_3$ solution, $CHCl_3$/$CDCl_3$ as internal reference; δ in ppm, *J* in Hz. IR: Bruker IFS 66 (FT-IR) spectrophotometer, measured as KBr pellets, or oils between KBr plates. MS (EI): Finnigan MAT 95 spectrometer. Optical rotations: Perkin−Elmer 241 digital polarimeter, 1-dm cell. M.p.: Büchi 510 capillary melting point apparatus, uncorrected values. TLC: Macherey−Nagel precoated sheets, 0.25 mm Sil G/UV_{254}. Column chromatography: Merck silica gel, grade 60, 230−400 mesh. Starting materials: compounds **7** and **8**,[20] **25**,[21] **31**,[13] and **34**[22] were prepared by published procedures. Attempted elemental analysis to determine bulk purities for compounds **32**, **36**, *cis*/*trans*-**39**, and **40** all failed. However, these compounds were found to be at least ≥ 95% pure according to their ^{1}H and ^{13}C NMR spectra as well as by thin layer chromatography.

Tetraspiro[cyclopropane-1,1′-cyclopropane-2′,1′′-cyclopropane-3′,1′′′′-(1′′′′,5′′′′,6′′′′,10b′′′′-tetrahydro-2*H*-isoxazolo[3,2-*a*]iso-

quinoline)-2′′′′,1′′′-cyclopropane] (26) and Tetraspiro[cyclopropane-1,1′′′′-(1′′′′,5′′′′,6′′′′,10b′′′′-tetrahydro-2*H*-isoxazolo[3,2-*a*]-isoquinoline)-2′,1′′-cyclopropane-2′′,1′′′-cyclopropane-3′′,1′′′′-cyclopropane] (27): A solution of nitrone **25** (206 mg, 1.40 mmol) and bicyclopropylidene derivative **8** (231 mg, 1.75 mmol) in benzene (4 mL) was stirred at ambient temperature for 7 d. The solvent was removed, and the residue was purified by chromatography to yield 281 mg (72%) of a mixture of **26** and **27**. Compounds **26** and **27** were separated and obtained in a **26/27** ratio of 1:1.1.

Compound 26: 136 mg (35%) as a colorless solid, R_f (Et_2O/hexane, 1:1) = 0.55, m.p. 98−101 °C. ^{1}H NMR (250 MHz): δ = −0.39 to −0.31 (m, 1 H, *c*Pr), −0.02 to +0.12 (m, 1 H, *c*Pr), 0.26−0.34 (m, 1 H, *c*Pr), 0.58−0.91 (m, 7 H, *c*Pr), 1.05−1.09 (m, 2 H, *c*Pr), 2.77−2.84 (m, 1 H), 3.04−3.26 (m, 3 H), 4.84 (s, 1 H, CHN), 7.06−7.17 (m, 4 H) ppm. ^{13}C NMR (62.9 MHz): δ = 2.0 (CH_2, *c*Pr), 3.7 (CH_2, *c*Pr), 3.8 (CH_2, *c*Pr), 4.0 (CH_2, *c*Pr), 4.1 (CH_2, *c*Pr), 8.1 (CH_2, *c*Pr), 17.9 (C, *c*Pr), 18.6 (C, *c*Pr), 28.9 (CH_2), 33.8 (C, *c*Pr), 49.5 (CH_2), 66.4 (C, *c*Pr), 68.0 (CH, CHN), 125.4 (CH), 126.7 (CH), 127.6 (CH), 128.3 (CH), 132.6 (C), 133.8 (C) ppm. IR: $\tilde{\nu}$ = 3106 cm^{-1}, 2982, 2853, 1492, 1454, 1233. MS (EI): *m*/*z* (%) = 279 (53) [M$^+$], 278 (18) [M$^+$ − H], 250 (68), 222 (84), 130 (76), 91 (100). HRMS (EI): calcd. for $C_{19}H_{21}NO$ [M$^+$] 279.1623, found 279.1623. $C_{19}H_{21}NO$ (279.4): calcd. C 81.68, H 7.58; found C 81.63, H 7.33.

Compound 27: 145 mg (37%) as a colorless oil, R_f (Et_2O/hexane, 1:1) = 0.45. ^{1}H NMR (250 MHz): δ = −0.03 to +0.11 (m, 1 H, *c*Pr), 0.61−0.96 (m, 11 H, *c*Pr), 2.84−2.91 (m, 1 H), 3.08−3.22 (m, 3 H), 4.62 (s, 1 H, CHN), 6.79−6.82 (m, 1 H), 7.06−7.17 (m, 3 H) ppm. ^{13}C NMR (62.9 MHz): δ = 2.4 (CH_2, *c*Pr), 3.8 (CH_2, *c*Pr), 4.7 (CH_2, *c*Pr), 5.3 (CH_2, *c*Pr), 5.4 (CH_2, *c*Pr), 5.5 (CH_2, *c*Pr), 17.4 (C, *c*Pr), 18.8 (C, *c*Pr), 28.5 (CH_2), 29.9 (C, *c*Pr), 49.3 (CH_2), 67.6 (CH, CHN), 70.6 (C, *c*Pr), 125.9 (CH), 126.0 (CH), 127.1 (CH), 128.4 (CH), 131.9 (C), 132.6 (C) ppm. IR: $\tilde{\nu}$ = 3066 cm^{-1}, 2982, 2852, 1494, 1339, 1008. MS (EI): *m*/*z* (%) = 279 (48) [M$^+$], 278 (12) [M$^+$ − H], 250 (68), 222 (84), 91 (100). $C_{19}H_{21}NO$ (279.4): calcd. C 81.68, H 7.58, N 5.01; found C 81.60, H 7.74, N 5.16.

One-Pot 1,3-Dipolar Cycloaddition/Thermal Rearrangement. General Procedure (GP) 1: A solution of the respective nitrone (1.00 equiv., 610 μmol) and the alkene (1.25 equiv., 760 μmol) in *o*-xylene (4 mL) was heated at 120 °C for 1 d. The solvent was removed by filtration through a pad of silica gel, eluting first with petroleum ether then with methanol. The methanolic solution was concentrated, and the residue was purified by chromatography.

Trispiro[cyclopropane-1,1′-cyclopropane-3′,1′′-cyclopropane-2′,1′′′-(1′′′,3′′′,4′′′,6′′′,7′′′,11b′′′-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline)]-2′′′-one (28), Trispiro[triscyclopropane-1,1′′′:1′,3′′′:1′′,4′′′-(1′′′,3′′′,4′′′,6′′′,7′′′,11b′′′-hexahydro-2*H*-pyrido-[2,1-*a*]isoquinoline)]-2-one (29), and (1-Cyclopropylcyclopropyl)-[1-(3,4-dihydro-1-isoquinolinyl)cyclopropyl]methanone (30): A mixture of **28**, **29**, and **30** (298 mg, 71%) in a ratio of 2.7:1:3 was obtained from nitrone **25** (221 mg, 1.50 mmol) and bicyclopropylidene **8** (248 mg, 1.88 mmol) according to GP 1. Alternatively, compound **28** (20 mg, 80%) was prepared by heating isoxazolidine **26** (25 mg, 89 μmol) in *p*-xylene (1 mL) at 140 °C for 5 h, and a mixture of **29** and **30** (19 mg, 77%) was obtained from isoxazolidine **27** (25 mg, 89 μmol) in a ratio of 1:3, by the same procedure.

Compound 28: Colorless solid, R_f (EtOAc/hexane, 5:1) = 0.42, m.p. 122−124 °C. ^{1}H NMR (250 MHz): δ = 0.48−0.56 (m, 1 H, *c*Pr), 0.67−0.98 (m, 4 H, *c*Pr), 1.00−1.06 (m, 1 H, *c*Pr), 1.39−1.52 (m, 2 H, *c*Pr), 2.20−2.36 (m, 2 H), 2.67−3.09 (m, 5 H), 3.40−3.53 (m, 1 H), 4.04 (s, 1 H, CHN), 6.61 (d, *J* = 7.2 Hz, 1 H), 7.08−7.20 (m, 3 H) ppm. ^{13}C NMR (62.9 MHz): δ = 3.8 (CH_2, *c*Pr), 4.2 (CH_2, *c*Pr), 4.4 (CH_2, *c*Pr), 4.6 (CH_2, *c*Pr), 22.8 (C, *c*Pr), 24.6 (CH_2), 30.3 (C, *c*Pr), 37.7 (C, *c*Pr), 40.7 (CH_2), 46.0 (CH_2), 49.9 (CH_2), 64.4 (CH, CHN), 126.1 (CH), 126.7 (CH), 126.9 (CH), 128.6 (CH), 134.7 (C), 135.4 (C), 207.4 (C, C=O) ppm. IR: $\tilde{\nu}$ = 3093 cm^{-1}, 2983, 2865, 1713, 1485, 1263, 1121. MS (EI): *m*/*z* (%) = 279 (100) [M$^+$], 278 (48) [M$^+$ − H], 250 (25), 158 (83), 145 (40), 132 (37), 105 (23).

Mixture of 29 and 30 (1:3): Colorless oil, R_f (EtOAc/hexane, 5:1) = 0.29. ^{1}H NMR (250 MHz): δ = −0.38 to −0.32 (m, 1 H, *c*Pr of **29**), −0.18 to −0.12 (m, 2 H, *c*Pr of **30**), −0.02 to +0.04 (m, 1 H, *c*Pr of **29**), 0.22−1.53 (m, 21 H, *c*Pr), 2.69−2.74 (m, 2 H, 4-H of **30**), 3.06−3.24 (m, 4 H, 6′′′,7′′′-H of **29**), 3.63−3.69 (m, 2 H, 3-H of **30**), 4.82 (s, 1 H, CHN of **29**), 7.04−7.53 (m, 8 H) ppm. ^{13}C NMR (62.9 MHz): δ = 2.0 (CH_2, *c*Pr), 3.7 (CH_2, *c*Pr), 4.2 (CH_2, 3 C, *c*Pr), 8.1 (CH_2, *c*Pr), 11.9 (CH, *c*Pr of **29**), 14.3 (CH_2, 3 C, *c*Pr), 14.5 (CH_2, 3 C, *c*Pr), 17.8 (C, *c*Pr), 18.6 (C, *c*Pr), 25.8 (CH_2), 28.9 (CH_2), 33.1 (C, *c*Pr), 37.7 (C, *c*Pr), 47.1 (CH_2), 49.5 (CH_2), 66.4 (CH, CHN of **29**), 67.9 (C, *c*Pr), 125.4 (CH), 125.9 (CH), 126.7 (CH), 126.9 (CH), 127.4 (CH), 127.6 (CH), 128.3 (CH), 129.7 (C), 130.6 (CH), 132.5 (C), 133.8 (C), 137.5 (C), 165.2 (C, C=N of **30**), 207.4 (C, C=O) ppm. IR: $\tilde{\nu}$ = 3070 cm^{-1}, 3005, 2938, 2898, 1673, 1618, 1334, 1062, 1018. MS (EI): *m*/*z* (%) = 279 (16) [M$^+$], 278 (22) [M$^+$ − H], 250 (100), 222 (14), 170 (14), 115 (6). HRMS (EI): calcd. for $C_{19}H_{21}NO$ [M$^+$] 279.1623, found 279.1623. $C_{19}H_{21}NO$ (279.2): calcd. C 81.73, H 7.58; found C 81.83, H 7.75.

9-Methyl-8-(pyrid-2-yl)-9-azatrispiro[2.0.2^4.0.5^7]dodecan-12-one (32) and 12-Methyl-11-(pyrid-2-yl)-12-azatrispiro[2.0.2^4.1.2^8.2^3]dodecan-7-one (33): A mixture of **32** and **33** (110 mg, 68%) was obtained from nitrone **31** (82.3 mg, 604 μmol) and bicyclopropylidene **8** (100 mg, 756 μmol), according to GP 1. The products were separated by column chromatography and obtained in a ratio **32/33** of 1:3.8.

Compound 32: Yield 23 mg (14%) as a colorless oil, R_f (CH_2Cl_2/MeOH, 20:1) = 0.32. ^{1}H NMR (250 MHz): δ = −0.40 to −0.33 (m, 1 H, *c*Pr), 0.20−0.28 (m, 1 H, *c*Pr), 0.69−0.74 (m, 1 H, *c*Pr), 0.79−0.99 (m, 4 H, *c*Pr), 1.24−1.33 (m, 1 H, *c*Pr), 2.37 (s, 3 H, NMe), 2.45−2.71 (m, 3 H), 2.77−2.82 (m, 1 H), 3.88 (s, 1 H, CHN), 7.05 (d, *J* = 7.5 Hz, 1 H), 7.11−7.16 (m, 1 H), 7.57−7.64 (m, 1 H), 8.51−8.53 (m, 1 H) ppm. ^{13}C NMR (62.9 MHz): δ = 2.2 (CH_2, *c*Pr), 4.5 (CH_2, *c*Pr), 4.9 (CH_2, *c*Pr), 5.3 (CH_2, *c*Pr), 22.9 (C, *c*Pr), 33.5 (C, *c*Pr), 36.9 (C, *c*Pr), 39.5 (CH_2), 43.1 (CH_3, NMe), 46.8 (CH_2), 71.5 (CH, CHN), 121.8 (CH), 123.5 (CH), 135.4 (CH), 148.8 (CH), 157.0 (C), 207.4 (C, C=O) ppm. IR: $\tilde{\nu}$ = 3070 cm^{-1}, 2926, 2804, 1700, 1589, 1435, 1274. MS (EI): *m*/*z* (%) = 268 (24) [M$^+$], 267 (50) [M$^+$ − H], 253 (51), 226 (87), 212 (88), 190 (66), 184 (94), 182 (100), 168 (56), 154 (45), 106 (40), 79 (34). HRMS (EI): calcd. for $C_{17}H_{20}N_2O$ [M$^+$] 268.1576, found 268.1576.

Compound 33: Yield 87 mg (54%) as a colorless oil, R_f (CH_2Cl_2/MeOH, 20:1) = 0.49. ^{1}H NMR (250 MHz): δ = −0.49 to −0.43 (m, 1 H, *c*Pr), −0.17 to −0.09 (m, 1 H, *c*Pr), −0.04 to +0.16 (m, 2 H, *c*Pr), 0.28−0.47 (m, 2 H, *c*Pr), 0.95−1.02 (m, 1 H, *c*Pr), 1.12−1.30 (m, 3 H, *c*Pr), 1.45−1.53 (m, 1 H, *c*Pr), 1.73−1.81 (m, 1 H, *c*Pr), 2.93 (s, 3 H, NMe), 3.86 (s, 1 H, CHN), 7.13−7.18 (m, 1 H), 7.29−7.33 (m, 1 H), 7.61 (dt, *J* = 1.7, 7.7 Hz, 1 H), 8.64−8.71 (m, 1 H) ppm. ^{13}C NMR (62.9 MHz): δ = 6.4 (CH_2, *c*Pr), 7.6 (CH_2, *c*Pr), 10.7 (CH_2, *c*Pr), 17.6 (CH_2, *c*Pr), 22.9 (CH_2, *c*Pr), 25.7 (CH_2, *c*Pr), 25.9 (C, *c*Pr), 28.5 (C, *c*Pr), 41.1 (C, *c*Pr), 41.3 (CH_3, NMe), 73.2 (CH, CHN), 122.0 (CH), 135.7 (CH), 149.0 (CH), 158.0 (CH), 161.2 (C), 211.2 (C, C=O) ppm. IR: $\tilde{\nu}$ = 3068 cm^{-1}, 2924, 1700, 1579, 1430, 1270. MS (EI): *m*/*z* (%) = 268 (64) [M$^+$], 267 (58) [M$^+$ − H], 253 (47), 239 (90), 200 (22), 190 (100), 174

(17), 130 (33), 117 (14). HRMS (EI): calcd. for $C_{17}H_{20}N_2O$ [M^+] 268.1576, found 268.1576.

(1′′′*S*,8a′′′*R*)-1′′′-(*tert*-Butoxy)trispiro[cyclopropane-1,1′-cyclopropane-2′,1′′-cyclopropane-3′,8′′′-perhydroindolizin]-7′′′-one (35) and (1′′′*S*,8a′′′*R*)-1′′′-*tert*-Butoxytrispiro[triscyclopropane-1,5′′′:1′,6′′′:1′′,8′′′-perhydroindolizin]-7′′′-one (36): A mixture of **35** and **36** (136 mg, 77%) was obtained from nitrone **34** (96.0 mg, 610 μmol) and bicyclopropylidene **8** (100 mg, 756 μmol), according to GP 1. The products were separated by column chromatography and were obtained in a **35/36** ratio of 1.6:1.

Compound 35: Yield 83 mg (47%) as a colorless oil, R_f (CH_2Cl_2/MeOH, 20:1) = 0.28. $[\alpha]_D^{20}$ = +28.4 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (250 MHz): δ = 0.62−0.93 (m, 5 H, *c*Pr), 0.98−1.29 [m, 12 H, *c*Pr, $C(CH_3)_3$], 1.76−1.88 (m, 1 H, 2′′′-H), 1.96−2.11 (m, 1 H, 2′′′-H), 2.29−2.39 (m, 2 H, 6′′′-H), 2.61−2.72 (m, 2 H, 3′′′,5′′′-H), 2.82−2.90 (m, 2 H, 8a′′′,3′′′-H), 3.04−3.12 (m, 1 H, 5′′′-H), 4.27−4.33 (m, 1 H, 1′′′-H) ppm. ^{13}C NMR (62.9 MHz): δ = 4.1 (CH_2, *c*Pr), 5.5 (CH_2, *c*Pr), 6.0 (CH_2, *c*Pr), 6.9 (CH_2, *c*Pr), 23.7 (C, *c*Pr), 27.6 (C, *c*Pr), 29.2 [CH_3, 3 C, $C(CH_3)_3$], 34.5 (CH_2, C-2′′′), 38.2 (C, *c*Pr), 39.3 (CH_2, C-6′′′), 48.8 (CH_2, C-5′′′), 52.3 (CH_2, C-3′′′), 70.9 (CH, C-8a′′′), 72.9 (CH, C-1′′′), 73.6 [C, $C(CH_3)_3$], 208.3 (C, C=O) ppm. IR: ṽ = 3065 cm^{-1}, 2976, 2798, 1700, 1473, 1362, 1192, 1046. MS (EI): *m*/*z* (%) = 289 (3) [M^+], 232 (100) [$M^+ - C_4H_9$], 190 (5), 147 (5), 105 (6), 57 (14) [$C_4H_9^+$]. HRMS (EI): calcd. for $C_{18}H_{27}NO_2$ [M^+] 289.2042, found 289.2042. $C_{18}H_{27}NO_2$ (289.4): calcd. C 74.70, H 9.40, N 4.84; found C 74.62, H 9.23, N 4.55.

Compound 36: Yield 53 mg (30%) as a colorless oil, R_f (CH_2Cl_2/MeOH, 20:1) = 0.50. $[\alpha]_D^{20}$ = −96.0 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (250 MHz): δ = 0.10−0.19 (m, 1 H, *c*Pr), 0.49−0.57 (m, 1 H, *c*Pr), 0.61−0.70 (m, 1 H, *c*Pr), 0.81−0.90 (m, 4 H, *c*Pr), 1.03−1.30 [m, 13 H, *c*Pr, $C(CH_3)_3$], 1.42−1.46 (m, 1 H, *c*Pr), 1.58−1.73 (m, 1 H, 2′′′-H), 1.96−2.07 (m, 1 H, 2′′′-H), 2.85 (d, *J* = 6.8 Hz, 1 H, 8a′′′-H), 2.91−2.99 (m, 1 H, 3′′′-H), 3.11−3.21 (m, 1 H, 3′′′-H), 3.80−3.89 (m, 1 H, 1′′′-H) ppm. ^{13}C NMR (62.9 MHz): δ = 6.8 (CH_2, *c*Pr), 8.0 (CH_2, *c*Pr), 10.4 (CH_2, *c*Pr), 14.9 (CH_2, *c*Pr), 19.1 (CH_2, *c*Pr), 20.1 (CH_2, *c*Pr), 28.8 [CH_3, 3 C, $C(CH_3)_3$], 30.3 (C, *c*Pr), 30.9 (C, *c*Pr), 33.8 (CH_2, C-2′′′). 40.4 (C, *c*Pr), 47.8 (CH_2, C-3′′′), 69.9 (CH, C-8a′′′), 73.9 [C, $C(CH_3)_3$], 77.3 (CH, C-1′′′), 211.1 (C, C=O) ppm. IR: ṽ = 3067 cm^{-1}, 2973, 2929, 1700, 1457, 1363, 1088. MS (EI): *m*/*z* (%) = 289 (45) [M^+], 232 (98) [$M^+ - C_4H_9$], 204 (71), 100 (33), 57 (100) [$C_4H_9^+$]. HRMS (EI): calcd. for $C_{18}H_{27}NO_2$ [M^+] 289.2042, found 289.2042.

***cis*/*trans*-7-Methyl-6-(pyrid-2-yl)-7-azatrispiro[2.1.5^5]decan-10-one (*cis*/*trans*-37) and 5-Methyl-4-(pyrid-2-yl)-5-azadispiro[2.1.2.3^3]decan-10-one (38):** A mixture of *cis*/*trans*-**37** and **38** (129 mg, 72%) was obtained from nitrone **31** (100 mg, 734 μmol) and bicyclopropylidene **7** (98.0 mg, 923 μmol), according to GP 1. The products were separated by column chromatography and obtained in a *trans*-**37**/*cis*-**37/38** ratio of 1.3:1.3:1.

Compound *trans*-37: Yield 47 mg (26%) as a colorless oil, R_f (CH_2Cl_2/MeOH, 30:1) = 0.53. ^{1}H NMR (250 MHz): δ = 0.74−0.93 (m, 4 H, *c*Pr), 1.15−1.24 (m, 2 H, *c*Pr), 2.32 (s, 3 H, NMe), 2.38−2.44 (m, 1 H), 2.55−2.73 (m, 2 H), 2.89−2.99 (m, 1 H), 3.67 (s, 1 H, CHN), 7.10−7.19 (m, 2 H), 7.63 (dt, *J* = 1.8, 7.6 Hz, 1 H), 8.57−8.59 (m, 1 H) ppm. ^{13}C NMR (62.9 MHz): δ = 5.3 (CH_2, *c*Pr), 5.6 (CH_2, *c*Pr), 16.2 (CH_2, *c*Pr), 30.7 (C, *c*Pr), 36.3 (C, *c*Pr), 39.5 (CH_2), 43.4 (CH_3, NMe), 47.6 (CH_2), 72.3 (CH, CHN), 122.0 (CH), 123.4 (CH), 135.8 (CH), 149.0 (CH), 157.8 (C), 207.4 (C, C=O) ppm. IR: ṽ = 3068 cm^{-1}, 2925, 2850, 1700, 1588, 1435, 1276, 1064. MS (EI): *m*/*z* (%) = 242 (7) [M^+], 241 (17) [$M^+ - H$], 227 (22) [$M^+ - CH_3$], 212 (98), 185 (58), 164 (57) [$M^+ - C_5H_4N$], 158 (100), 124 (70), 78 (19) [$C_5H_4N^+$]. HRMS (EI): calcd. for $C_{15}H_{17}N_2O$ [$M^+ - H$] 241.1341, found 241.1341.

Compound *cis*-37: Yield 47 mg (26%) as a colorless oil, R_f (CH_2Cl_2/MeOH, 30:1) = 0.41. ^{1}H NMR (250 MHz): δ = 0.30−0.39 (m, 1 H, *c*Pr), 0.62−0.74 (m, 1 H, *c*Pr), 0.80−1.19 (m, 2 H, *c*Pr), 1.38−1.59 (m, 2 H, *c*Pr), 2.38 (s, 3 H, NMe), 2.50 (d, *J* = 10.0 Hz, 1 H), 2.97 (d, *J* = 10.0 Hz, 1 H), 3.40−3.49 (m, 1 H), 3.62 (d, *J* = 14.0 Hz, 1 H), 3.91 (s, 1 H, CHN), 7.12−7.20 (m, 2 H), 7.52−7.61 (m, 1 H), 8.55−8.62 (m, 1 H) ppm. ^{13}C NMR (62.9 MHz): δ = 12.4 (CH_2, *c*Pr), 15.1 (CH_2, *c*Pr), 23.0 (CH_2, *c*Pr), 27.1 (C, *c*Pr), 30.6 (C, *c*Pr), 43.8 (CH_3, NMe), 47.0 (CH_2), 57.2 (CH_2), 73.9 (CH, CHN), 123.4 (CH), 123.6 (CH), 135.8 (CH), 148.9 (CH), 157.9 (C), 207.9 (C, C=O) ppm. IR: ṽ = 3074 cm^{-1}, 3001, 2933, 1676, 1588, 1435, 1074. MS (EI): *m*/*z* (%) = 242 (16) [M^+], 227 (18) [$M^+ - CH_3$], 214 (100) [$M^+ - C_2H_4$], 172 (51), 164 (78) [$M^+ - C_5H_4N$], 136 (50), 78 (35) [$C_5H_4N^+$]. HRMS (EI): calcd. for $C_{15}H_{18}N_2O$ [M^+] 242.1419, found 242.1419. $C_{15}H_{18}N_2O$ (242.3): calcd. C 74.35, H 7.49; found C 74.46, H 7.45.

Compound 38: Yield 35 mg (20%) as a colorless oil, R_f (CH_2Cl_2/MeOH, 30:1) = 0.32. ^{1}H NMR (250 MHz): δ = 0.33−0.41 (m, 1 H, *c*Pr), 0.65−0.72 (m, 1 H, *c*Pr), 0.81−0.94 (m, 2 H, *c*Pr), 1.03−1.27 (m, 2 H, *c*Pr), 1.47−1.61 (m, 2 H, *c*Pr), 2.42 (s, 3 H, NMe), 2.53 (d, *J* = 12.4 Hz, 1 H), 2.98 (d, *J* = 12.4 Hz, 1 H), 3.62 (s, 1 H, CHN), 7.15−7.21 (m, 2 H), 7.66 (dt, *J* = 1.8, 7.7 Hz, 1 H), 8.57−8.60 (m, 1 H) ppm. ^{13}C NMR (62.9 MHz): δ = 12.5 (CH_2, *c*Pr), 15.2 (CH_2, *c*Pr), 22.5 (CH_2, *c*Pr), 23.1 (CH_2, *c*Pr), 29.6 (C, *c*Pr), 30.7 (C, *c*Pr), 43.8 (CH_3, NMe), 57.3 (CH_2), 74.0 (CH, CHN), 122.2 (CH), 123.5 (CH), 135.9 (CH), 149.0 (CH), 158.0 (C), 209.5 (C, C=O) ppm. IR: ṽ = 3079 cm^{-1}, 3001, 2925, 1675, 1589, 1436, 1387, 1073. MS (EI): *m*/*z* (%) = 242 (11) [M^+], 214 (100) [$M^+ - C_2H_4$], 185 (22), 172 (62), 164 (75) [$M^+ - C_5H_4N$], 136 (40), 78 (20) [$C_5H_4N^+$]. HRMS (EI): calcd. for $C_{15}H_{18}N_2O$ [M^+] 242.1419, found 242.1419. $C_{15}H_{18}N_2O$ (242.3): calcd. C 74.35, H 7.49, N 11.57; found C 74.19, H 7.68, N 11.71.

(1′′*S*,8′′*R*,8a′′*R* and 1′′*S*,8′′*S*,8a′′*R*)-1′′-*tert*-Butoxydispiro[cyclopropane-1,1′-cyclopropane-2′,8′′-perhydroindolizin]-7′′-one (*cis*/*trans*-39) and (1′′*S*,8a′′*R*)-1′′-*tert*-Butoxydispiro[biscyclopropane-1,6′′:1′,8′′-perhydroindolizin]-7′′-one (40): A mixture of *cis*/*trans*-**39** and **40** (134 mg, 80%) was obtained from nitrone **34** (100 mg, 636 μmol) and bicyclopropylidene **7** (81.0 mg, 763 μmol), according to GP 1. The products were separated by column chromatography and obtained in a *cis*- or *trans*-**39**/*cis*- or *trans*-**39/40** ratio of 1:2:1.5.

Compound *cis*- or *trans*-39: 29 mg (17%) as a colorless oil. R_f (CH_2Cl_2/MeOH, 30:1) = 0.27, $[\alpha]_D^{20}$ = −22.0 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (250 MHz): δ = 0.67−0.74 (m, 1 H, *c*Pr), 0.79−0.96 (m, 3 H, *c*Pr), 1.02−1.07 (m, 1 H, *c*Pr), 1.17 [s, 9 H, $C(CH_3)_3$], 1.62 (d, *J* = 3.8 Hz, 1 H), 1.66−1.77 (m, 1 H, *c*Pr), 1.86 (d, *J* = 3.9 Hz, 1 H), 2.13−2.31 (m, 2 H), 2.46−2.59 (m, 1 H), 2.66−2.76 (m, 2 H), 2.90−3.01 (m, 2 H), 3.87−3.97 (m, 1 H) ppm. ^{13}C NMR (62.9 MHz): δ = 5.7 (CH_2, *c*Pr), 6.0 (CH_2, *c*Pr), 16.6 (CH_2, *c*Pr), 27.7 (C, *c*Pr), 28.8 [CH_3, 3 C, $C(CH_3)_3$], 33.4 (CH_2), 35.0 (C, *c*Pr), 38.0 (CH_2), 47.6 (CH_2), 53.4 (CH_2), 69.2 (CH), 73.9 [C, $C(CH_3)_3$], 75.5 (CH), 208.5 (C, C=O) ppm. IR: ṽ = 3066 cm^{-1}, 2974, 1717, 1365, 1191, 1113. MS (EI): *m*/*z* (%) = 263 (3) [M^+], 240 (2), 206 (100) [$M^+ - C_4H_9$], 166 (15), 57 (10) [$C_4H_9^+$]. HRMS (EI): calcd. for $C_{16}H_{25}NO_2$ [M^+] 263.1885, found 263.1885.

Compound *trans*- or *cis*-39: 60 mg (36%) as a colorless oil, R_f (CH_2Cl_2/MeOH, 30:1) = 0.47, $[\alpha]_D^{20}$ = +35.4 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (250 MHz): δ = 0.47−0.53 (m, 1 H, *c*Pr), 0.65−0.73 (m, 1 H, *c*Pr), 1.03−1.11 (m, 1 H, *c*Pr), 1.18 [s, 9 H, $C(CH_3)_3$], 1.21−1.29

(m, 2 H, *c*Pr), 1.43 (d, J = 3.7 Hz, 1 H), 1.69−1.75 (m, 1 H, *c*Pr), 1.92 (d, J = 3.7 Hz, 1 H), 2.07−2.36 (m, 2 H), 2.40−2.54 (m, 2 H), 2.74 (d, J = 6.9 Hz, 1 H), 2.96−3.03 (m, 1 H), 3.14−3.22 (m, 1 H), 4.24 (dt, J = 3.0, 8.4 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz): δ = 3.6 (CH_2, *c*Pr), 6.9 (CH_2, *c*Pr), 13.4 (CH_2, *c*Pr), 25.1 (C, *c*Pr), 29.1 [CH_3, 3 C, C(*C*H_3)$_3$], 34.4 (CH_2), 35.9 (C, *c*Pr), 40.2 (CH_2), 50.6 (CH_2), 53.1 (CH_2), 71.3 (CH, 2 C), 74.2 [C, *C*(CH_3)$_3$], 209.5 (C, C=O) ppm. MS (EI): *m*/*z* (%) = 263 (1) [M^+], 206 (100) [$M^+ - C_4H_9$], 166 (8), 57 (6) [$C_4H_9^+$]. HRMS (EI): calcd. for $C_{16}H_{25}NO_2$ [M^+] 263.1885, found 263.1885.

Compound 40: 45 mg (27%) as a colorless oil, R_f (CH_2Cl_2/MeOH, 30:1) = 0.37, $[\alpha]_D^{20}$ = +12.0 (c = 1, $CHCl_3$). ^{1}H NMR (250 MHz): δ = 0.61−0.69 (m, 1 H, *c*Pr), 0.86−1.15 (m, 4 H, *c*Pr), 1.17 [s, 9 H, C(CH_3)$_3$], 1.19−1.54 (m, 3 H, *c*Pr), 1.62−1.73 (m, 1 H), 2.15−2.27 (m, 1 H), 2.42−2.53 (m, 1 H), 2.63 (d, J = 11.5 Hz, 1 H), 2.81 (d, J = 7.6 Hz, 1 H), 2.98 (d, J = 11.5 Hz, 1 H), 3.11 (dt, J = 2.6, 8.8 Hz, 1 H), 3.86 (dt, J = 4.5, 8.2 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz): δ = 13.4 (CH_2, *c*Pr), 13.9 (CH_2, *c*Pr), 17.3 (CH_2, *c*Pr), 24.7 (CH_2, *c*Pr), 27.3 (C, *c*Pr), 28.8 [CH_3, 3 C, C(*C*H_3)$_3$], 31.2 (C, *c*Pr), 33.2 (CH_2), 53.3 (CH_2), 59.6 (CH_2), 70.1 (CH), 74.2 (CH), 77.2 [C, *C*(CH_3)$_3$], 212.0 (C, C=O) ppm. IR: $\tilde{\nu}$ = 3062 cm^{-1}, 2973, 2803, 1700, 1457, 1364, 1192. MS (EI): *m*/*z* (%) = 263 (3) [M^+], 206 (100) [$M^+ - C_4H_9$], 190 (3), 163 (6), 57 (5) [$C_4H_9^+$]. HRMS (EI): calcd. for $C_{16}H_{25}NO_2$ [M^+] 263.1885, found 263.1885.

Acknowledgments

This work was supported by Bayer AG and the Fonds der Chemischen Industrie. The authors are grateful to the companies BASF AG, Bayer AG, Chemetall GmbH, and Degussa AG for generous gifts of chemicals. We are particularly grateful to Dr. B. Knieriem, Göttingen, for his careful reading of the final manuscript, Stefan Beußhausen for his assistance, and Federica Pisaneschi for the synthesis of nitrone **34**.

[1] Review: A. Brandi, A. Goti, *Chem. Rev.* **1998**, *98*, 589−636.
[2] Reviews: [2a] A. Goti, F. M. Cordero, A. Brandi, *Top. Curr. Chem.* **1996**, *178*, 1−97. [2b] A. de Meijere, S. I. Kozhushkov, *Chem. Rev.* **2000**, *100*, 93−142.
[3] [3a] A. de Meijere, S. I. Kozhushkov, A. F. Khlebnikov, *Top. Curr. Chem.* **2000**, *207*, 89−147. [3b] A. de Meijere, S. I. Kozhushkov, *Eur. J. Org. Chem.* **2000**, 3809−3822.
[4] A. Hassner, C. Stumer, "Organic Synthesis Based on Name Reactions", 2nd ed., *Tetrahedron Organic Chemistry Series, 22*, Pergamon, Oxford, UK, **2002**, p. 42.
[5] [5a] C. Zorn, A. Goti, A. Brandi, K. Johnsen, M. Noltemeyer, S. I. Kozhushkov, A. de Meijere, *J. Org. Chem.* **1999**, *64*, 755−763. [5b] B. Anichini, A. Goti, A. Brandi, S. I. Kozhushkov, A. de Meijere, *Chem. Commun.* **1997**, 261−262. [5c] A. Goti, B. Anichini, A. Brandi, S. I. Kozhushkov, C. Gratkowski, A. de Meijere, *J. Org. Chem.* **1996**, *61*, 1665−1672.
[6] [6a] M. J. Kelner, T. C. McMorris, W. T. Beck, J. M. Zamora, R. Taetle, *Cancer Res.* **1987**, *47*, 3186−3189. [6b] M. J. Kelner, T. C. McMorris, R. Taetle, *J. Natl. Cancer Inst.* **1990**, *82*, 1562−1565. [6c] T. C. McMorris, M. J. Kelner, W. Wang, L. A. Estes, M. A. Montoya, R. Taetle, *J. Org. Chem.* **1992**, *57*, 6876−6883.
[7] T. Kushida, M. Uesugi, Y. Sugiura, H. Kigoshi, H. Tanaka, J. Hirokawa, M. Ojika, K. Yamada, *J. Am. Chem. Soc.* **1994**, *116*, 479−486.
[8] [8a] A. Goti, B. Anichini, A. Brandi, A. de Meijere, L. Citti, S. Nevischi, *Tetrahedron Lett.* **1995**, *36*, 5811−5814. [8b] C. Zorn, B. Anichini, A. Goti, A. Brandi, S. I. Kozhushkov, A. de Meijere, L. Citti, *J. Org. Chem.* **1999**, *64*, 7846−7855.
[9] [9a] A. Brandi, F. M. Cordero, F. De Sarlo, A. Goti, A. Guarna, *Synlett* **1993**, 1−8. [9b] A. Brandi, S. Garro, A. Guarna, A. Goti, F. M. Cordero, F. De Sarlo, *J. Org. Chem.* **1988**, *53*, 2430−2434.
[10] F. M. Cordero, A. Brandi, C. Querci, A. Goti, F. De Sarlo, A. Guarna, *J. Org. Chem.* **1990**, *55*, 1762−1767.
[11] E. Ochoa, M. Mann, D. Sperling, J. Fabian, *Eur. J. Org. Chem.* **2001**, 4223−4231.
[12] [12a] D. C. Nonhebel, *Chem. Soc. Rev.* **1993**, 347−359. [12b] J. C. Walton, in *Methods of Organic Chemistry* (*Houben-Weyl*), vol. E17c ("Carbocyclic Three-Membered Ring Compounds") (Ed.: A. de Meijere), Thieme, Stuttgart, **1997**, pp. 2438−2525. [12c] S.-Y. Choi, M. Newcomb, *Tetrahedron* **1995**, *51*, 657−664. [12d] H. Venkatesan, M. M. Greenberg, *J. Org. Chem.* **1995**, *60*, 1053−1059. [12e] D. J. Hastings, A. C. Weedon, *J. Org. Chem.* **1991**, *56*, 6326−6331. [12f] D. Becker, N. Haddad, Y. Sahali, *Tetrahedron Lett.* **1989**, *30*, 2661−2664.
[13] For the synthesis of the corresponding spiro[cyclopropane-azepinones] see: A. de Meijere, M. von Seebach, S. I. Kozhushkov, R. Boese, D. Blaeser, S. Cicchi, T. Dimoulas, A. Brandi, *Eur. J. Org. Chem.* **2001**, 3789−3795.
[14] G. Bianchi, R. Gandolfi, *1,3-Dipolar Cycloaddition Chemistry*, vol. 2 (Ed.: A. Padwa), John Wiley & Sons, New York, **1984**, p. 451−542.
[15] CCDC-199272 (**28**), -199270 (**33**), and -199271 (*trans*-**37**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U. K.; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk]. [15a] G. M. Sheldrick, *Acta Crystallogr., Sect. A* **1990**, *46*, 467−473. [15b] G. M. Sheldrick, *SHELXL-93, program for crystal structure refinement*, University of Göttingen, **1993**.
[16] [16a] R. A. Firestone, *J. Org. Chem.* **1968**, *33*, 2285−2290. [16b] R. A. Firestone, *J. Org. Chem.* **1972**, *37*, 2181−2191. [16c] R. A. Firestone, *Tetrahedron* **1977**, *33*, 3009−3039.
[17] [17a] R. Huisgen, *J. Org. Chem.* **1968**, *33*, 2291−2297. [17b] R. Huisgen, *J. Org. Chem.* **1976**, *41*, 403−419. [17c] K. N. Houk, J. González, Y. Li, *Acc. Chem. Res.* **1995**, *28*, 81−90.
[18] [18a] C. Di Valentin, M. Freccero, R. Gandolfi, A. Rastelli, *J. Org. Chem.* **2000**, *65*, 6112−6120 and references cited therein. [18b] M. Carda, R. Portoles, J. Murga, S. Uriel, J. A. Marco, L. R. Domingo, R. J. Zaragoza, H. Roper, *J. Org. Chem.* **2000**, *65*, 7000−7009, and reference 8 cited therein.
[19] For a recent review on biologically active cyclopropane derivatives see: J. Salaün, *Top. Curr. Chem.* **2000**, *207*, 1−67.
[20] A. de Meijere, S. I. Kozhushkov, T. Späth, N. S. Zefirov, *J. Org. Chem.* **1993**, *58*, 502−505.
[21] S.-I. Murahashi, H. Mitsui, T. Shiota, T. Tsuda, S. Watanabe, *J. Org. Chem.* **1990**, *55*, 1736−1744.
[22] S. Cicchi, A. Goti, A. Brandi, *J. Org. Chem.* **1995**, *60*, 4743−4748.

Received December 12, 2002