Studies on the Synthesis of Aza Analogues of Illudins by Cycloadditions to Highly Strained Methylenecyclopropanes

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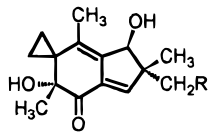
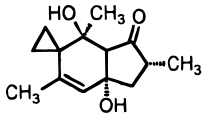
A series of 3-spirocyclopropane-tetrahydropyrid-4-ones has been synthesized by the method consisting of nitrone cycloaddition to bicyclopropylidene and thermal rearrangement of the adducts. Regioisomeric 5-spirocyclopropanetetrahydropyrid-4-ones and 5-spirocyclopropanedihydropyrid-4-ones were instead obtained by cycloaddition of nitrones and nitrile oxides, respectively, to methylenespiropentane, followed by thermal rearrangement. Methylenedispiro[2.0.2.1]heptane gave, in turn, 5,6-bis(spirocyclopropane)dihydropyrid-4-ones. The new compounds were prepared as simple aza analogues of the cytotoxic natural products illudins and ptaquiloside in order to study their activity in cleaving a DNA plasmid. The activities shown by several of the compounds are moderate, but from a comparative qualitative analysis of the results a useful structure−activity relationship for this new class of compounds could be derived.

Introduction

The release of strain energy associated with the cleavage of a cyclopropane ring in an organic molecule is able to bring about multiform transformations the selectivity of which depends on the nature and pattern of substituents on the cyclopropane ring and at the adjacent positions. A cyclopropyl group is known to stabilize a positive charge in the α position,[1] yet cyclopropylmethyl cations tend to undergo a stereoselective ring enlargement to a cyclobutyl cation[2] or ring opening to a homoallyl cation to yield, in the presence of an appropriate nucleophile, the corresponding substitution products.[3] The enhanced reactivity of a cyclopropane ring toward ring opening has been attributed to the peculiar nature of the bonding in a carbocyclic three-membered ring, and it has been extensively investigated by mechanistically oriented organic chemists and also utilized in organic synthesis.[4] In developing synthetic strategies based on this reactivity of a cyclopropane ring researchers did nothing more than copying what nature does. In fact, regarding the tendency of an acceptor-activated cyclopropane moiety to undergo ring opening upon nucleophilic attack, several natural products containing a cyclopropane ring exhibit their biological activity through a process of opening resulting in an alkylation of a nucleophilic substrate, e.g., an enzyme. Among these are compounds such as the illudins (**1**)[5−7] and ptaquiloside (**2**),[8] three extremely cytotoxic sesquiterpenes isolated from mushrooms and bracken fern, respectively.[5−8]



1 **a** Illudin S (R = OH)
b Illudin M (R = H)



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The potent carcinogenic activity of these natural compounds has been ascribed to their alkylating ability toward DNA due to their strained spiro[2.5]octene moieties with a tertiary hydroxy group in the α-position of the spirocyclopropane ring that creates a high tendency to concomitant aromatization of the six-membered ring.[7,8] The extreme general cytotoxicity of these compounds has hampered their development as an anticancer drug for a long time, until a synthetic derivative of illudins has

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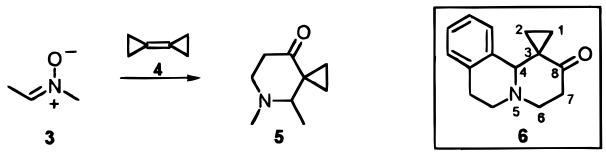
Scheme 1



been found recently, which is now in clinical trial. This new synthetic derivative maintains the potent antineoplastic activity of the natural products **1** and at the same time has a drastically reduced cytotoxicity.[9] This result provided additional incentive to prepare a number of simpler analogues of illudins,[10] in this context aza analogues, which might display DNA alkylating properties due to their 5-azaspiro[2.5]octanone moieties with an electrophilic carbonyl group α to the spirocyclopropane ring, a feature that might make the six-membered ring prone to aromatization.

Thus, 5-azaspiro[2.5]octan-8-ones **5** that are easily obtained by a straightforward sequential cycloaddition−rearrangement process from nitrones **3** and bicyclopropylidene (BCP) (**4**) (Scheme 1)[11] appeared to be excellent candidates to furnish a biological activity similar to that of the illudins **1**. In fact, the benzoannelated spirocyclopropane-1,1′-quinolizidine-2′-one **6** showed a good activity at micromolar concentration in cleaving a DNA plasmid.[12] This very preliminary result demonstrated also that the aromatization of the ring is not essential for the bioactivity, being only involved in determining the potency of the activity against DNA. To be able to derive at least a first approximation of a structure−activity relationship of this new class of compounds as a basis for the construction of a candidate for more advanced pharmacological tests, it was necessary to synthesize a larger series of these simple aza analogues of the illudin skeleton with some structural variations. The logic structural changes appeared to be as follows: (i) the introduction of substituents on the lead compound **6**; (ii) the position of the spirocyclopropane ring on the skeleton; and (iii) the introduction of unsaturation in the six-membered ring spirofused with the cyclopropane moiety. In this paper, we report the synthesis of new spirocyclopropane-annelated aza heterocycles by 1,3-dipolar cycloaddition of various nitrones and nitrile oxides to bicyclopropylidene (BCP) (**4**) as well as methylenespiropentane (MSP) (**7**) and 7-methylenedispiro[2.0.2.1]heptane (MDH) (**8**).[13,14]

The collected biological activities of the newly synthesized compounds in terms of their ability to cleave a supercoiled DNA plasmid leads to at least a first approximation of the structure−activity relationship for these aza analogues of the illudin skeleton.

Preparative Results and Discussion

The sequence of 1,3-dipolar cycloaddition and thermal rearrangement of the adducts involving nitrones **9**, **12**, **15**, and **18** as 1,3-dipoles and BCP **4**[11] was applied to afford α-spirocyclopropane-annelated piperidones **11**, **14**, **17**, and **19** with high selectivity and in good yields except for nitrone **9** (see Table 1).

In comparison to **6**, compounds **11**, **14**, **17**, and **19** contain a variety of structural modifications. The two methoxy groups on the aromatic ring of the tetrahydroisoquinoline moiety in **11** were introduced in order to induce some electronic interactions with the DNA plasmid. The extended flat part in **14** compared to a tetrahydroisoquinoline moiety could possibly improve the intercalation between DNA bases.[12] Compounds **17** and **19**, which more closely resemble "aza analogues" of the natural illudin skeleton, were obtained from the hydroxylated enantiomerically pure nitrones **15** and **18**, synthesized from L-malic and D-tartaric acid, respectively.[15]

The structural assignments of new products were made on the basis of ^{1}H and ^{13}C NMR spectra. Adducts **10**, **13**, and **16** show characteristic signals for the cyclopropane protons (δ 0−1), the corresponding carbons (δ 3−11), and the proton bound to C3 of the isoxazolidine ring (singlet at δ 4.78 and 4.89 for **10** and **13**, respectively, doublet at δ 3.33, J = 6 Hz for **16**). The thermal rearrangement products show the characteristic carbonyl group signals (δ 209.2, 207.8, 208.9, and 208.9 for **11**, **14**, **17**, and **19**, respectively), the signals of the four protons on the cyclopropane ring with two protons shifted over 1.00 ppm by the carbonyl anisotropy, and the methine proton α to the nitrogen (singlets at δ 4.19 and 4.13 in **11** and **14**, respectively, doublet at δ 2.64 and 2.82 with J = 8.2 and 6 Hz for **17** and **19**, respectively).

Cycloadditions to MSP **7** and MDH **8** of nitrones and nitrile oxides, recently reported,[13] established the possibility to synthesize isomeric compounds bearing the spiroannelated cyclopropane ring at a different position of the tetrahydropyridine ring, and even a second spiroannelated cyclopropane ring. With nitrones, this process suffers from a low selectivity, as regioisomeric compounds **II** can form in the cycloaddition step and isomeric enaminones **IV** in the rearrangement (Scheme 2).[13] The result is a general decrease in yields of isolated products.

The cycloadducts of nitrones **15**, **22**, and **25** to MSP **7** and MDH **8** and the products of their subsequent thermal rearrangement are summarized in Table 2, yet only the 5-spirocyclopropane adducts of type **I** and the cyclic ketones of type **III** are listed. In each case, the reactions were performed both in the typical "two-step" process and in the more convenient "one-pot" version, i.e., heating mixtures of the starting materials directly under the conditions under which the thermal rearrangement of the primary adducts occurs (125−163 °C). The cycloadditions were carried out under relatively mild conditions (40 or 60 °C). Because of the low thermal stability of the

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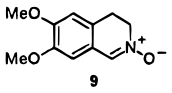
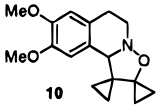
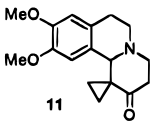
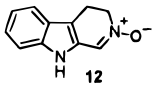
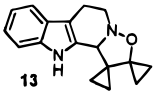
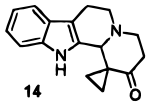
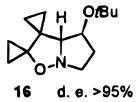
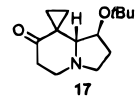
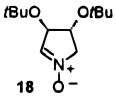
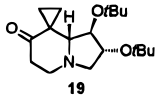
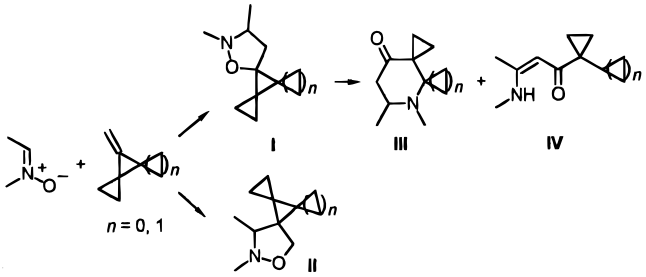
Table 1. Cycloadditions of Nitrones 9, 12, 15, and 18 to Bicyclopropylidene (4) and Thermal Rearrangement of the Adducts

Nitrone	Reaction Conditions[a]	Cycloadduct	Yield (%)	Reaction Conditions[b]	Product	Rearrang. Yield (%)	Yield of "one pot" reaction (calc. for two steps) (%)
 9	CH_2Cl_2 45 °C 5 d	 10	32	$C_6H_4Me_2$ 125 °C 2 d	 11	67	31 (21)
 12	C_6H_6 60 °C 24 h	 13	72	$C_6H_4Me_2$ 125 °C 2 d	 14	60	65 (43)
 15	C_6H_6 60 °C 2 d	 16 d. e. >95%	80	$C_6H_4Me_2$ 120 °C 8 h	 17	80	64 (64)
 18	—	—		$C_6H_4Me_2$ 120 °C 16 h	 19	—	62 (–)

[a] For the cycloaddition step. [b] For the rearrangement step and the "one pot" reaction.

Scheme 2



5-spirocyclopropane derivatives, prolonged reaction times instead of higher reaction temperatures were more appropriate to obtain the cycloadducts in good yields. An increase of the temperature reduces the required reaction times but also brings about partial or total rearrangements of the cycloadducts. In every instance, the cycloaddition step led to a complex mixture of 5-spiro- and 4-spirocyclopropaneisoxazolidines, which could not be completely separated by flash chromatography on silica gel. Thus, spectral data for the 5-spirocyclopropane isomers refer to enriched fractions obtained after repeated chromatographic purification. 4-Spirocyclopropane isomers were also collected after chromatographic separation of the mixtures of rearrangement products.

Product mixtures from methylenespiropentane (**7**) are particularly complex because of the stereogenicity of C-5 (isoxazolidine numbering), which causes diastereomers to occur. Because of the symmetrical substitution at the central cyclopropane ring in 7-methylenedispiro[2.0.2.1]-heptane (**8**), the number of stereoisomeric products is smaller. For this reason, in the ^{1}H NMR spectrum of **28**, obtained from **8** and **25**, characteristic signals for both 4- and 5-spirocyclopropane regioisomers could be observed (triplet at δ 4.70 with J = 8.8 Hz for the bridgehead proton in the 5-spirocyclopropane regioisomer; AB system at δ 4.06 and 3.99 with J = 7.5 Hz for the methylene group adjacent to the oxygen and singlet at δ 4.55 for the bridgehead proton in the 4-spirocyclopropane isomer).

The thermal rearrangements were performed by heating solutions of mixtures of 5-spirocyclopropane and the corresponding 4-spirocyclopropane regioisomers in a high-boiling aromatic solvent at an adequate temperature (Table 2). As expected,[16] only the 5-spirocyclopropane derivatives **20**, **23**, **26**, and **28** underwent the thermal rearrangement process and gave, in all four cases, mixtures of α-spirocyclopropane piperidones **21**, **24**, **27**, and **29**, the open-chain enaminone compounds of type **IV**, and the unreacted 4-spirocyclopropane adducts of type **II**. As previously observed,[13] the spirocyclopropane ring opening occurs with high regio- and chemoselectivity. The structural assignment for **21**, **24**, and **27** was based on the observation of the characteristic signals for the piperidone carbonyl group (^{13}C NMR δ 208.1, 208.1, and 208.5 for **21**, **24**, and **27**, respectively) and for the cyclopropane moiety (four distinguishable proton signals between δ 1.70 and 0.50 in the ^{1}H NMR spectrum). The position of the cyclopropane ring on piperidones **21**, **24**, and **27**, which allows us to elucidate the regiocontrol in the ring-opening process,[13] is confirmed by the observation of signals of AB systems for isolated methylene protons α to the nitrogen in the ^{1}H NMR spectra (δ 2.80 and 2.57, J = 11.4 Hz, for **21**, δ 2.90 and 2.52, J = 12.2 Hz, for **24**). The analogous signal for **27** was not easily detectable, as the ^{1}H NMR spectrum was highly complex, but in the ^{13}C NMR spectrum a reasonable signal for the corresponding carbon was found (δ 62.4 , $-$N$-$CH$_2-$). The thermal rearrangement of **28** was carried out with the mixture of regioisomers, under conditions that allowed the additional cyclopropane rings to survive both in the final structures **29** and in the open-chain isomer. The structural assignment for **29** is based on the observation of the characteristic signal for the carbonyl group (δ 208.1) and the bridgehead proton (dd at δ 4.62 with J = 11.4; 4.9 Hz). The open-chain isomers, as described in the Experimental Section, show typical signals for the intramolecular hydrogen bonded NH,[17] for the olefinic proton, for the isolated methyl groups, and for the conjugated carbonyl group.

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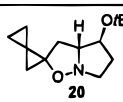
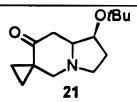
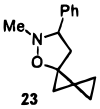
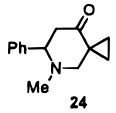
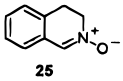
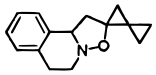
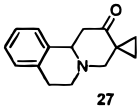
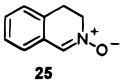
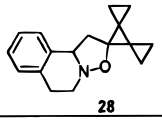
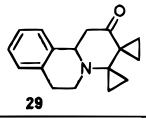
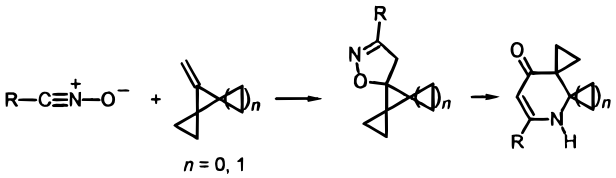
Table 2. Cycloadditions of Nitrones 15, 22, and 25 to Methylenespiropentane (MSP) (7) and 7-Methylenedispiro[2.0.2.1]heptane (MDH) (8) and Thermal Rearrangements of the Adducts

Nitrone	Alkene	Reaction Conditions[a]	Cycloadduct	Yield[b] (%)	Reaction Conditions[c]	Product	Rearrang. Yield (%)	Yield of "one pot" reaction (calc. for two steps) (%)
 **15**	7	C_6H_6 40 °C 28 d	 **20**	57	$C_6H_4Me_2$ 125 °C 6 h	 **21**	40	22 (22)
 **22**	7	C_6H_6 60 °C 57 d	 **23**	48	$C_6H_4Cl_2$ 160 °C 8 h	 **24**	40	28 (19)
 **25**	7	C_6H_6 60 °C 4 d	 **26**	44	$C_6H_3Me_3$ 160 °C 2 h	 **27**	32	29 (13)
 **25**	8	C_6H_6 60 °C 4 d	 **28**	51	$C_6H_3Me_3$ 160 °C 3 h	 **29**	34	19 (17)

[a] For the cycloaddition step. [b] Calculated from NMR integration of regioisomeric mixtures. [c] For the rearrangement step and the "one pot" reaction.

Scheme 3



Higher chemoselectivities were achieved with nitrile oxides in the same sequence of 1,3-dipolar cycloaddition/thermal rearrangement (Scheme 3). The results are summarized in Table 3.

The cycloaddition of benzonitrile oxide **30**, slowly generated in situ at room temperature from the corresponding hydroximoyl chloride,[18] to MSP **7** afforded the 5-spiropentaneisoxazoline **31** in 64% yield, with high regioselectivity, while the stable mesitonitrile oxide **33** gave the corresponding adduct **34** in quantitative yield. Analogous 5-dispiroheptane-annelated isoxazolines **39** and **41** were obtained with MDH **8**. Nitrile oxide **36**, slowly generated in situ from methyl 4-nitrobutyrate according to Mukaiyama's method,[19] gave with **7** at 50 °C in benzene the isoxazoline **37** in 44% yield.

The spectroscopic characterization of adducts **31**, **34**, **37**, **39**, and **41** is based on the observation of signals for the methylene groups in the isoxazoline rings [AB systems at δ 3.47 and 3.32 (J = 17.2 Hz), 3.25 and 3.12 (J = 17.6 Hz), 3.02 and 2.90 (J = 17.5 Hz) for **31**, **34**, and **37**, respectively, singlets at δ 3.36 and 3.14 for **39**, **41**, respectively.

Compared to BCP **4**,[11] MSP **7** showed higher reactivity toward nitrile oxides, as becomes apparent from the milder conditions required for the reaction of **7** with the stable nitrile oxide **33** and the considerable decrease of furoxan and other side products[11] with the unstable nitrile oxide **30**.

Isoxazolines **31**, **34**, and **37** also underwent the thermal rearrangement more readily than their counterparts from BCP **4**[11] and provided pyridones **32**, **35**, and **38**, with a retained spirocyclopropane ring (Table 3). With compound **37**, the thermal rearrangement and subsequent cyclization both occurred under the same conditions (DMF, NaCl, H_2O, 150 °C, 4 h) in a one-pot operation.[20,21]

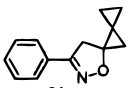
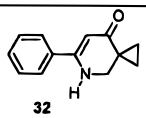
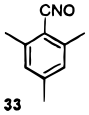
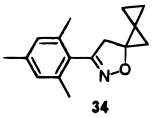
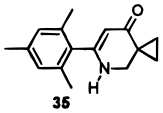
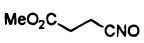
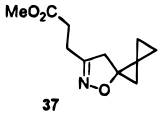
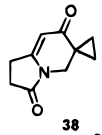
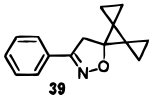
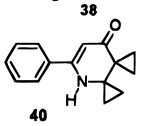
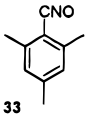
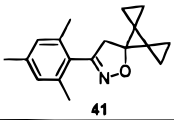
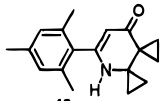
The structural assignments are based on the observation of the characteristic signals in the NMR spectra for the α,β-unsaturated carbonyl system (^{13}C NMR δ 194.3, 193.3, and 192.9 for the carbonyl group in **32**, **35**, and **38**, respectively; doublet at δ 5.48, J = 1.7 Hz, and 5.02, J = 1.5 Hz, for **32** and **35**, respectively, triplet at δ 5.42, J = 1.3 Hz, for **38**, for the olefinic proton) and the methylene group adjacent to the nitrogen (doublet at δ 3.55, J = 2.4 Hz, and δ 3.52, J = 2.2 Hz, for **32** and **35**, respectively; singlet at δ 3.68 for **38**). In the ^{13}C NMR spectrum of **38**, the signal for the lactam C=O at δ 175.0 is also diagnostic. The rearrangement products **40** and **42** showed typical signals for conjugated carbonyl groups (δ 193.2 and 192.7 respectively) and olefinic protons (doublets at δ 5.58, J = 1.5 Hz, and δ 5.04, J = 1.7 Hz, respectively).

The cycloaddition−thermal rearrangement sequence with MSP **7** provides a complementary access to spirocyclopropanated heterocycles with respect to the one starting from BCP **4** (Scheme 4). The process leads to piperidones bearing the cyclopropane ring spirofused either in position 3 (from BCP) or in position 5 (from MSP). With nitrile oxides as dipoles and MSP **7** the overall transformation affords spirocyclopropanated pyridones, which are not accessible from BCP.[11] It is interesting to note the different reactivities of the dipoles toward dipolarophiles **4** and **7**. To have a quantitative estimate of the relative reactivities of **4** and **7** two competition experiments were set up (Scheme 5).

In each experiment, 0.3 M solutions of the dipole in $CDCl_3$ were treated with an equimolar mixture of BCP **4** and MSP **7** (1.5 equiv each) and heated at 60 °C, until the dipole had been consumed. The progress of each reaction was followed by ^{1}H NMR, and it was clearly shown that nitrile oxide **33** was at least four times more reactive toward MSP **7** than BCP **4** ($k_{MSP}/k_{BCP} > 4$). The opposite behavior was observed for the nitrone **25**. BCP **4** reacted

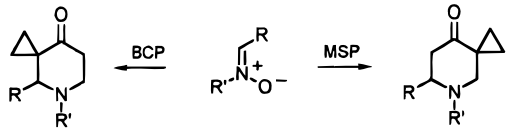
(18) Corsico Coda, A.; Tacconi, G. *Gazz. Chim. Ital.* **1984**, *114*, 131.
(19) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.
(20) Goti, A.; Brandi, A.; Danza, G.; Guarna, A.; Donati, F.; De Sarlo, F. *J. Chem. Soc., Perkin Trans.1* **1989**, 1253.
(21) Krapcho, A. P. *Synthesis* **1982**, 805 and 893.

Table 3. Cycloadditions of Nitrile Oxides 30, 33, and 36 to MSP 7 and MDH 8 and Thermal Rearrangements of the Adducts

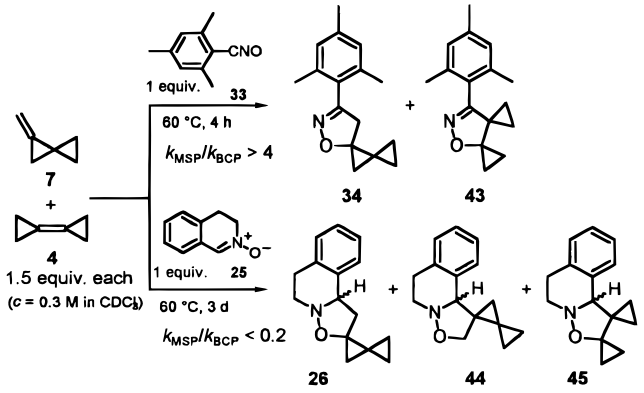
Nitrile oxide	Alkene	Reaction Conditions[a]	Cycloadduct	Yield (%)	Reaction Conditions[b]	Product	Yield (%)
 **30**	7	C_6H_6 25 °C 16 h	 **31**	64	$C_6H_4Cl_2$ 160 °C 14 h	 **32**	70
 **33**	7	C_6H_6 60 °C 4 h	 **34**	95	$C_6H_3Me_3$ 165 °C 4 h	 **35**	92
 **36**	7	C_6H_6 55 °C 10 h	 **37**	44	DMF, NaCl, H_2O 155 °C, 4 h	 **38**	66
 **30**	8	C_6H_6 25 °C 16 h	 **39**	54	$C_6H_4Cl_2$ 160 °C 9 h	 **40**	53
 **33**	8	C_6H_6 60 °C 4 h	 **41**	93	$C_6H_4Cl_2$ 160 °C 5 h	 **42**	73

[a] For the cycloaddition step. [b] For the rearrangement step.

Scheme 4



Scheme 5



much faster (k_{MSP}/k_{BCP} < 0.2) with **25** than MSP **7**, the latter producing a mixture of regioisomers **26** and **44**.

A simple FMO analysis is not able to explain the higher reactivity of **4** compared to **7** toward nitrones.[22] A tentative explanation must invoke steric factors which intervene at transition states of cycloadditions. The increased reactivity of MSP **7** toward nitrile oxides could be explained with the decreased steric hindrance compared to BCP **4** at least for the formation of a C−C bond by attack at the terminal methylene group. The higher regioselectivity observed for this reaction is in full agreement with this analysis. Cycloadditions of nitrile oxides to dipolarophiles are known, in fact, to have a transition state in which the incipient C−C bond is shorter than the O−C bond.[23] In contrast, in cycloadditions to nitrones, a nucleophilic attack is invoked and the incipient O−C bond is shorter than the C−C bond at the transition state.[24] Steric factors must play a less important role with nitrones.[25] The higher reactivity of BCP **4** might, then, be explained with the higher strain of BCP **4** compared to MSP **7**, which is exemplified by the fact that BCP **4**, under thermal conditions (≥150 °C), rearranges to MSP **7**,[26] however, reversibly. [26e]

Tests of DNA-Cleavage Activity. It has recently been proven that α-spirocyclopropanated piperidinones can be considered an interesting new class of DNA-cleaving agents.[12] Some of their structural features resemble those of the illudins and ptaquiloside, natural compounds with a strong cytotoxic activity. Most presumably, it is the alkylating property of the spirocyclopropane ring adjacent to the electrophilic carbonyl group acting on the DNA chain with its nucleophilic functionalities that is responsible for the biological activity of these compounds. In total, the DNA-cleaving activity of compounds **11**, **14**, **27**, **32**, **38**, **40**, and **46**−**48** was tested in order to study the effect of structural modifications on α-spirocyclopropanated piperidinones, like compound **6**, which was the most active of the first series of

(22) Ab initio STO 3G calculations for the FM orbitals of nitrone **22**, BCP **4**, and MSP **7** were performed and showed that the dominant interaction was the LUMO (dipole)−HOMO (dipolarophile) for both alkenes, but the corresponding Δ*E* values were not significantly different.

(23) (a) Sustmann, R.; Sicking, W. *Chem. Ber.* **1987**, *120*, 1471. (b) McAlduff, E. J.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1978**, *100*, 105.

(24) Leroy, G.; Nguyen, M. T.; Sana, M. *Tetrahedron* **1978**, *34*, 2459.

(25) For a recent computational study of nitrone and nitrile oxide cycloadditions, see: Cossío, F. P.; Morao, I.; Jiao, H.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1999**, *121*, 6737 and references therein.

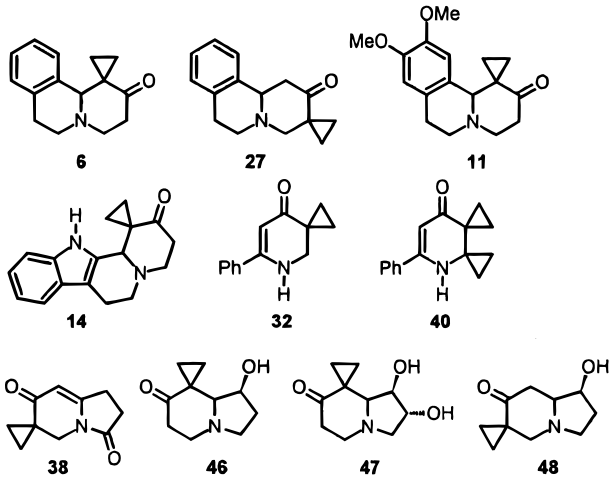
(26) (a) Le Perchec, P.; Conia, J.-M. *Tetrahedron Lett.* **1970**, 1587. (b) de Meijere, A.; Erden, I.; Weber, W.; Kaufmann, D. *J. Org. Chem.* **1988**, *53*, 152. (c) Beckhaus, H.-D.; Rüchardt, C.; Kozhushkov, S. I.; Belov, V. N.; Verevkin, S. P.; de Meijere, A. *J. Am. Chem. Soc.* **1995**, *117*, 11854. (d) Kozhushkov, S. I.; de Meijere, A. In *Houben-Weyl, Carbocyclic Three-Membered Ring Compounds*; de Meijere, A., Ed.; Thieme: Stuttgart, 1996; Vol. E17b, p 1695. (e) Faber, D.; Walsh, R.; de Meijere, A. Manuscript in preparation. Faber, D. Dissertation, Universität Göttingen, 1996.

Table 4. Cleaving Activity of Various Piperidinones and Pyridinones on pUC18 (or pUC19)[12]

27 **32** **38** **40** **48**	**11** **47**	**6** **14** **46**
> 250x[a]	100x[a]	50–25x[a,12]

[a] Concentration limit of piperidones (>250, 100, 50−25[12] times the nucleotide concentration) to observe the activity.

previously tested products.[12] Compounds **46**−**48** were easily obtained in high yields by deprotection of the *tert*-butyl ether moieties in the indolizidinones **17**, **19**, and **21**, respectively, with trifluoroacetic acid.



The DNA-cleaving activity was detected by the topological change of plasmid pUC18 (2686 pairs of bases): the circular supercoiled form I can be converted into the nicked form II and into the linear form III, as any kind of cut acts on one or both of the DNA strands. The comparison with the activity of compound **6** allowed a qualitative analysis of the activity of all the compounds (see the Experimental Section and the Supporting Information).

None of the compounds was able to produce form III DNA, which was formed only in the Hind III solution. Only compounds **11**, **14**, **46**, and **47** proved to be able to produce a partial relaxation of form I DNA into form II DNA, whereas compounds **27**, **32**, **38**, **40**, and **48** left the plasmide intact. Albeit few compounds were active and none was found more active than the ketone **6**, the comparative analysis of activity and structures of various compounds gave interesting information (Table 4).

The activity of compound **6** was matched by compounds **14** and **46** and only approached by compounds **11** and **47**. Compounds **11** and **14**, in fact, closely resemble **6** and confirm the importance of an annelated aromatic ring, which is probably responsible for a more efficient interaction with the DNA. However, the presence of functionality like the MeO groups and the indole nitrogen appears not to contribute to the activity. Compound **46** (and **47**) lacks an aromatic ring moiety but shows comparable activity. This must be due to the fact that **46** and **47** much more closely resemble the illudine structure. The lack of activity of all the other compounds opens up some insights into the structure−activity relationship. Particularly striking is the lack of activity of compounds **27** and **48**, which are isomers of **6** and **46**. As the two pairs are different only in the spirocyclopropane ring position, this must play a key role in the activity. An explanation cannot be given currently. The lack of activity of compounds **32**, **38**, and **40** might have to do with a reduced reactivity of the spirocyclopropane ring caused by the adjacent enaminone moiety, which has a reduced electrophilicity at its C=O group. Compound **46** remained to be one of the most active ones even when the activity tests were repeated under UV light irradiation, whereas compounds **14** and **6** lost much of their activity.

Conclusions

The ability of α-spirocyclopropane-annelated tetrahydropyridones to provoke cleavage in a supercoiled DNA plasmid has been confirmed in the present work. Although the activity shown by these compounds is only moderate, it is sufficient to entitle these compounds as a class of aza analogues of natural compounds such as illudins or ptaquiloside possessing a similar spirocyclopropane functionality responsible for their potent cytotoxic activity. Due to the high cytotoxicity of the natural products, the synthesis of nonnatural analogues has been suggested and carried out with success since one of these products is already in clinical study.[9] The aza analogues reported in this study represent a new promising class of compounds that are easily accessible and offer themselves for further structural modifications. The present study has allowed us to draw a preliminary picture of the structure−activity relationship for these compounds that will be of great utility toward the design of new and more potent analogues.

Experimental Section

All reactions were carried out under nitrogen or in screw-capped Sovirel tubes, and the solvents were appropriately dried before use. R_f values refer to TLC on 0.25 mm silica gel plates (Merck F_{254}) obtained using the same eluent as in the column chromatographies. NMR spectra were recorded with $CDCl_3$ as solvent. IR spectra were recorded in $CDCl_3$ solution. Mass spectra were recorded at 70 eV by GC inlet or by direct inlet for the thermally labile cycloadducts.

8′,9′-Dimethoxydispiro[cyclopropane-1,1′-(1,5,6,10b-tetrahydro-2*H*-isoxazolo[3,2-*a*]isoquinoline)-2′,1″-cyclopropane] (10). A solution of **4** (240 mg, 3.00 mmol) and **9** (400 mg, 1.93 mmol) in dichloromethane (2 mL) was stirred at 45 °C for 5 days. The solvent was removed in vacuo, and the crude material was purified by flash chromatography on silica gel (ethyl acetate−light petroleum ether 3:1 as eluent) to give **10** (R_f 0.39, 176 mg, 0.61 mmol, 32%).

10: ^{1}H NMR δ 6.65 (s, 1 H), 6.32 (s, 1 H), 4.78 (s, 1 H), 3.86 (s, 3 H), 3.83 (s, 3 H), 3.60 (td, J = 10.7, 4.1 Hz, 1 H), 3.25 (ddd, J = 10.6, 5.0, 3.4 Hz, 1 H), 3.04 (ddd, J = 16.0, 11.0, 5.1 Hz, 1 H), 2.78 (dt, J = 16.0, 3.5 Hz, 1 H), 0.95−0.86 (m, 2 H), 0.65−0.56 (m, 1 H), 0.46−0.40 (m, 1 H), 0.33−0.12 (m, 4 H); ^{13}C NMR δ 148.0 (s), 147.2 (s), 126.5 (s), 124.1 (s), 111.0 (d), 108.7 (d), 67.2 (s), 66.6 (d), 55.9 (q), 55.7 (q), 49.8 (t), 30.3 (s), 28.4 (t), 8.3 (t), 8.0 (t), 7.8 (t), 3.3 (t); MS *m*/*z* 287 (M^+, 26), 286 (37), 272 (30), 258 (77), 190 (100), 176 (91), 164 (74); IR 3028, 3004, 2974, 1613, 1540, 1519, 1466 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.82; H, 7.52; N, 4.94.

Dispiro[cyclopropane-1,1′-(1,2,5,6,11,11b-hexahydroisoxazolo[3,2-*a*]-*β*-carboline)-2′,1″-cyclopropane] (13). A solution of **4** (65 mg, 0.81 mmol) and **12** (100 mg, 0.54 mmol) in benzene (0.5 mL) was stirred at 60 °C for 24 h. The solvent was removed in vacuo, and the crude material was purified by flash chromatography on silica gel (dichloromethane−ethyl acetate 2:1 as eluent) to give **13** (R_f 0.50, 103 mg, 0.39 mmol, 72%).

13: mp 162−165 °C; ^{1}H NMR δ 7.60 (br s, 1 H), 7.53 (m, 1 H), 7.32 (m, 1 H), 7.15 (m, 2 H), 4.89 (s, 1 H), 3.78−3.62 (m, 1

H), 3.46−3.38 (m, 1 H), 2.99−2.93 (m, 2 H), 0.98−0.83 (m, 2 H), 0.76−0.62 (m, 1 H), 0.60−0.40 (m, 2 H), 0.39−0.26 (m, 3 H); ^{13}C NMR δ 137.3 (s), 130.2 (s), 126.9 (s), 122.3 (d), 120.0 (d), 118.8 (d), 111.7 (d), 109.5 (s), 68.6 (s), 64.9 (d), 51.0 (t), 30.9 (s), 20.9 (t), 9.2 (t), 8.7 (t), 7.66 (t), 5.4 (t). MS *m*/*z* 266 (M^+, 52), 265 (50), 197 (48), 182 (38), 169 (49), 91 (100); IR 3489, 3029, 2940, 1468, 1452 cm^{-1}. Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.33; H, 6.96; N, 10.59.

(3′a*R*,4′*S*)-4′-*tert*-Butoxydispiro[cyclopropane-1,2′-(hexahydropyrrolo[1,2-*b*]isoxazole)-3′,1″-cyclopropane] (16). A solution of **4** (120 mg, 1.5 mmol) and **15** (157 mg, 1 mmol) in benzene (1 mL) was heated in a screw-capped Sovirel tube at 60 °C for 2 d. The solvent was removed in vacuo, and the crude material was purified by flash chromatography on silica gel (eluent diethyl ether) to give **16** (190 mg, 0.8 mmol, 80%).

16: R_f 0.33; $[\alpha]^{25}_D$ +13.2 (*c* 0.34, $CHCl_3$); ^{1}H NMR δ 4.11 (dt, J = 6.0; 3.9 Hz, 1 H), 3.46−3.26 (m, 2 H), 3.33 (d, J = 6 Hz, 1 H), 2.27−2.12 (m, 1 H), 1.72−1.58 (m, 1 H), 1.15 (s, 9 H), 0.91−0.42 (m, 6 H), 0.19−0.04 (m, 2 H); ^{13}C NMR δ 79.2 (d), 76.0 (d), 73.8 (s), 65.9 (s), 56.3 (t), 34.1 (t), 30.8 (s), 28.6 (q, 3 C), 11.3 (t), 10.2 (t), 3.8 (t), 3.7 (t); MS *m*/*z* 237 (M^+, 20), 180 (36), 153 (78), 152 (89), 57 (100). Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.80; H, 9.70; N, 5.58.

Thermal Rearrangement of Adducts 10, **13**, and **16: General Procedure.** A solution of **10**, **13**, and **16** in xylenes was heated in a screw-cap sealed Sovirel tube at the temperature and time indicated in Table 1. After the solution was cooled to room temperature, the solvent was removed by elution with light petroleum ether through a short pad of silica gel. Compounds **11**, **14**, and **17** were then eluted with the appropriate solvent.

9′,10′-Dimethoxyspiro[cyclopropane-1,1′-(1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin)]-2′-one (11). 10 (134 mg, 0.47 mmol), xylenes (8 mL). **11** (90 mg, 67%): R_f 0.44 (ethyl acetate−methanol 2:1); mp 132−134 °C; ^{1}H NMR δ 6.60 (s, 1 H), 6.52 (s, 1 H), 4.19 (s, 1 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 3.56−3.24 (m, 3 H), 3.10−2.83 (m, 3 H), 2.65 (ddd, J = 16.4, 9.3, 6.8 Hz; 1 H), 2.45 (dt, J = 16.4, 4.8 Hz, 1 H), 1.42−1.30 (m, 1 H), 1.05−0.97 (m, 1 H), 0.90−0.86 (m, 1 H), 0.79−0.50 (m, 1 H); ^{13}C NMR δ 209.2 (s), 148.4 (s), 147.0 (s), 127.5 (s), 125.6 (s), 112.1 (d), 111.2 (d), 61.7 (d), 56.4 (q), 56.3 (q), 50.4 (t), 45.8 (t), 36.3 (t), 31.9 (s), 27.8 (t), 16.0 (t), 10.6 (t); MS *m*/*z* 287 (M^+, 27), 286 (59), 218 (100); IR 3010, 2939, 1688, 1607, 1506, 1454 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.71; H, 7.43; N, 4.68.

Spiro[cyclopropane-1,1′-(1,2,3,4,5,6,7,12,12b-octahydropyrido[2,1-*a*]-*β*-carbolin)]-2′-one (14). 13 (56 mg, 0.21 mmol), xylenes (2 mL). **14** (33 mg, 60%): R_f 0.55 (ethyl acetate−methanol 5:1); mp 222−224 °C; ^{1}H NMR δ 7.87 (bs, 1 H), 7.50 (d, J = 8.4 Hz, 1 H), 7.35−7.08 (m, 3 H), 4.13 (s, 1 H), 3.48−2.98 (m, 5 H), 2.80−2.62 (m, 2 H), 2.45 (dt, J = 16.1, 5.2 Hz, 1 H), 1.77−1.62 (m, 1 H), 1.26−0.86 (m, 3 H); ^{13}C NMR δ 207.8 (s), 136.2 (s), 132.1 (s), 126.7 (s), 122.5 (d), 120.2 (d), 118.8 (d), 111.6 (d), 108.7 (s), 62.0 (d), 50.5 (t), 47.4 (t), 38.9 (t), 31.8 (s), 19.1 (t), 16.6 (t), 12.0 (t); MS *m*/*z* 266 (M^+, 86), 265 (54), 197 (85), 182 (75), 169 (100), 167 (51); IR 3469, 3059, 2985, 2926, 1702, 1441, 1429 cm^{-1}. Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.12; H, 7.18; N, 10.25.

(1′*S*,8a′*R*)-1′-*tert*-Butoxyspiro(cyclopropane-1,8′octahydroindolizin)-7′-one (17). 16 (237 mg, 1 mmol), xylenes (1 mL). **17** (190 mg, 80%): R_f 0.21 (diethyl ether-acetone 2:1); $[\alpha]^{25}_D$ +113.0 (*c* 0.95, $CHCl_3$); ^{1}H NMR δ 3.76 (td, J = 8.2, 4.3 Hz, 1 H), 3.25−3.14 (m, 1 H), 3.08 (td, J = 8.9, 2.5 Hz, 1 H), 2.69−2.42 (m, 4 H), 2.64 (d, J = 8.2 Hz, 1 H), 2.20 (dq, J = 13.5, 8.6 Hz, 1 H), 1.66 (dddd, J = 13.5, 9.0, 4.3, 2.5 Hz, 1 H), 1.49 (m, 1 H), 1.20 (m, 1 H), 1.16 (s, 9 H), 1.02 (m, 1 H), 0.87−0.72 (m, 1 H); ^{13}C NMR δ 208.9 (s), 74.0 (s), 73.5 (d), 69.3 (d), 52.9 (t), 50.1 (t), 38.6 (t), 33.4 (t), 31.5 (s), 28.7 (q, 3 C), 16.3 (t), 11.4 (t); MS *m*/*z* 237 (M^+, 2), 180 (100); IR 3010, 2978, 2812, 1688, 1336 cm^{-1}. Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.66; H, 9.76; N, 6.29.

One-Pot Reactions of Nitrones 9, 12, 15, and 18 with BCP 4 To Yield 11, 14, 17, and 19. General Procedure. A solution of BCP **4** and the nitrone in xylenes was heated in a screw-capped Sovirel tube for the appropriate time. The reaction mixture was purified by flash chromatography on silica gel.

11: 4 (78 mg, 0.97 mmol), **9** (150 mg, 0.65 mmol), xylenes (4 mL), 125 °C for 2 d, eluent ethyl acetate−methanol + 1% NH_4OH 5:1, 58 mg, 31%.

14: 4 (49 mg, 0.61 mmol), **12** (76 mg, 0.41 mmol), xylenes (5 mL), 125 °C for 2 d, eluent ethyl acetate−methanol 5:1, 71 mg, 65%.

17: 4 (382 mg, 4.77 mmol), **15** (500 mg, 3.18 mmol), xylenes (5 mL), 120 °C for 8 h, eluent diethyl ether−acetone 2:1, 482 mg, 64%.

(1′*R*,2′*R*,8a′*R*)-1′,2′-Di-*tert*-butoxyspiro(cyclopropane-1,8′octahydroindolizin)-7′-one (19). BCP **4** (63 mg, 0.79 mmol), **18** (121 mg, 0.53 mmol), xylenes (1 mL), 120 °C for 16 h, eluent ethyl acetate/methanol + 1% NH_4OH 20:1 (R_f 0.42), 101 mg, 62%: $[\alpha]^{25}_D$ −17.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 3.92 (dt, J = 5.5, 2.5 Hz, 1 H), 3.65 (dd, J = 6.2, 2.5 Hz, 1 H), 3.25−3.15 (m, 1 H), 3.08 (dd, J = 10.4, 2.2 Hz, 1 H), 2.95−2.76 (m, 2 H), 2.82 (d, J = 6 Hz, 1 H), 2.69 (dd, J = 11.3, 6 Hz, 1 H), 2.48−2.34 (m, 1 H), 1.44−1.22 (m, 2 H), 1.21 (s, 9 H), 1.20 (s, 9 H), 1.09−0.88 (m, 2 H); ^{13}C NMR δ 208.9 (s), 82.1 (d), 78.3 (d), 74.5 (s), 74.0 (s), 68.7 (d), 60.4 (t), 49.1 (t), 37.5 (t), 30.4 (s), 29.0 (q, 3 C), 28.9 (q, 3 C), 16.1 (t), 12.7 (t); MS *m*/*z* 309 (M^+, 1), 252 (84), 196 (40), 137 (27), 57 (100). Anal. Calcd for $C_{18}H_{31}NO_3$: C, 69.87; H, 10.10; N, 4.53. Found: C, 69.83; H, 10.20; N, 4.76.

Cycloaddition of Nitrone 15, 22, and 25 to MSP 7 and MDH 8. General Procedure. A solution of nitrones (0.7−3.5 mmol) and MSP **7** or MDH **8** (1.2−1.5 equiv) in benzene (1−5 mL) was heated in a screw-capped Sovirel tube. After the solution was cooled to room temperature, the solvent was removed in vacuo, and the crude product was purified by flash chromatography on silica gel to give a mixture of two 5-spirocyclopropane-annelated adducts and the corresponding two 4-spirocyclopropanated derivatives as an oil. Attempts to separate the regioisomers by chromatography failed, and only enriched fractions were obtained. Enriched fractions of the 4-spirocyclopropane-annelated adducts could also be obtained after thermal rearrangement.

(3a″*R*,4″*S*)-4″-*tert*-Butoxydispiro[cyclopropane-1,1′-cyclopropane-2,2″-(hexahydropyrrole[1,2-*b*]isoxazole)] (20) and (3a″*R*,4″*S*)-4″-*tert*-butoxydispiro[cyclopropane-1,1′-cyclopropane-2,3″-(hexahydropyrrole[1,2-*b*]isoxazole)]: 40 °C for 28 d, 2.3:1 ratio, eluent diethyl ether, 258 mg, 1.09 mmol, 83%.

20. Two inseparable diastereoisomers: R_f 0.37; ^{1}H NMR (one isomer) δ 4.06 (dt, J = 6.7, 4.1 Hz, 1 H), 3.59−3.52 (m, 1 H), 3.34 (dd, J = 7.6, 6.2 Hz, 2 H), 2.54 (dd, J = 12.5, 8.5 Hz, 1 H), 2.27 (dq, J = 12.9, 7.5 Hz, 1 H), 2.12 (dd, J = 12.5, 2.9 Hz, 1 H), 1.70 (m, 1 H), 1.31−1.27 (m, 1 H), 1.19 (s, 9 H), 1.06−1.00 (m, 1 H), 0.95−0.84 (m, 2 H), 0.82−0.66 (m, 2 H); ^{13}C NMR (one isomer) δ 77.9 (d), 73.7 (d), 73.5 (s), 65.6 (s), 55.7 (t), 38.4 (t), 33.7 (t), 28.5 (q, 3 C), 17.2 (t), 15.0 (s), 6.1 (t), 5.5 (t), (the other isomer) 78.1 (d), 74.0 (d), 73.8 (s), 66.3 (s), 55.2 (t), 39.1 (t), 33.4 (t), 28.6 (q, 3 C), 17.8 (t), 15.8 (s), 6.4 (t, 2 C); MS *m*/*z* 237 (M^+, 2), 236 (2), 180 (48), 96 (33), 84 (33), 57 (100). Anal. Calcd for $C_{14}H_{23}NO_2$ (mixture of regioisomers): C, 70.85; H, 9.77; N, 5.90. Found: C, 71.01; H, 9.78; N, 5.48.

4-Spirocyclopropanated Regioisomer. Two inseparable diastereoisomers: R_f 0.34; ^{1}H NMR (the only discernible signals are reported) (one isomer) δ 4.12 (dt, J = 6.6; 3.3 Hz, CHO-*t*-Bu), [3.87 (d, J = 8.0 Hz, 1 H), 3.62 (d, J = 8.0 Hz, 1 H), CH_2O], 1.18 (s, 9 H), (the other isomer) δ [3.82 (d, J = 8.0 Hz, 1 H), 3.65 (d, J = 8.0 Hz, 1 H), CH_2O], 1.14 (s, 9 H); ^{13}C NMR (one isomer) δ 78.5 (d), 76.9 (d), 73.8 (s), 71.6 (t), 55.4 (t), 40.1 (s), 34.1 (t), 28.6 (q, 3 C), 19.3 (s), 12.5 (t), 5.7 (t), 5.2 (t), (the other isomer) δ 76.7 (d), 76.3 (s), 73.1 (t), 72.1 (d), 55.3 (t), 33.9 (s), 33.7 (t), 28.4 (q, 3 C), 16.9 (s), 16.4 (t), 7.0 (t), 3.7 (t); MS *m*/*z* 237 (M^+, 6), 180 (100), 152 (28).

2″-Methyl-3″-phenyldispiro(cyclopropane-1,1′-cyclopropane-2,5″-isoxazolidine) (23) and 2″-methyl-3″-phen-

yldispiro(cyclopropane-1,1′-cyclopropane-2,4″-isoxazolidine): 60 °C for 57 d, 2.5:1 ratio, eluent ethyl acetate/light petroleum ether 1:3, 110 mg, 0.51 mmol, 68%.

23: ^{1}H NMR δ 7.43−7.22 (m, 5 H), 3.64 (t, J = 8.6 Hz, 1 H), 2.83−2.60 (m, 2 H), 2.59 (s, 3 H), 1.50−0.70 (m, 6 H); ^{13}C NMR δ (only discernible signals) 74.03 (d), 66.8 (s), 46.8 (t), 43.8 (q); MS m/z 215 (M^+, 4), 160 (29), 118 (28), 91 (100). Anal. Calcd for $C_{14}H_{17}NO$ (mixture of regioisomers): C, 78.10; H, 7.96; N, 6.51. Found: C, 77.92; H, 7.94; N, 6.48.

4-Spirocyclopropanated regioisomer: ^{1}H NMR δ 7.30−7.20 (m, 5 H), 4.20 (d, J = 7.7 Hz, 1 H), 3.83 (d, J = 7.7 Hz, 1 H), 3.34 (s, 1 H), 2.63 (s, 3 H), 1.10−0.92 (m, 2 H), 0.88−0.70 (m, 3 H), 0.50 (m, 1 H); ^{13}C NMR δ 139.8 (s), 128.8 (d, 2 C), 128.3 (d, 2 C), 127.8 (d), 76.7 (d), 72.5 (t), 43.6 (q), 35.8 (s), 17.5 (s), 14.0 (t), 5.7 (t), 4.0 (t); MS m/z 215 (M^+, 48), 170 (27), 169 (44), 155 (59), 141 (70), 129 (57), 128 (51), 118 (49), 115 (84), 91 (100), 77 (86).

Dispiro[cyclopropane-1,1′-cyclopropane-2,2″-(1,5,6,-10b-tetrahydro-2*H*-isoxazolo[3,2-*a*]isoquinoline)] (26) and dispiro[cyclopropane-1,1′-cyclopropane-2,1″-(1,5,6,10b-tetrahydro-2*H*-isoxazolo[3,2-*a*]isoquinoline)] (44): 60 °C for 4 d, 4:1 ratio, eluent diethyl ether/hexane 1:1, 429 mg, 1.89 mmol, 54%.

26. Two inseparable diastereoisomers: R_f 0.51; ^{1}H NMR (one isomer) δ 7.22−7.08 (m, 4 H), 4.84 (t, J = 8.9 Hz, 1 H), 3.34 (dt, J = 10.1, 4.2 Hz, 1 H), 3.19−2.62 (m, 4 H), 2.24 (dd, J = 12.3, 8.9 Hz, 1 H), 1.40−0.54 (m, 6 H), (the other isomer) δ 7.22−7.08 (m, 4 H), 4.80 (t, J = 8.9 Hz, 1 H), 3.50 (dt, J = 10.7, 3.7 Hz, 1 H), 3.19−2.62 (m, 4 H), 2.48 (dd, J = 12.3, 8.9 Hz, 1 H), 1.40−0.54 (m, 6 H); ^{13}C NMR (one isomer) δ 136.3 (s), 133.1 (s), 128.1 (d), 127.2 (d), 126.4 (d), 126.2 (d), 67.5 (s), 63.6 (d), 48.3 (t), 41.2 (t), 28.1 (t), 18.1 (s), 14.9 (t), 7.5 (t), 5.7 (t), (the other isomer) δ 136.1 (s), 132.9 (s), 128.1 (d), 127.2 (d), 126.4 (d), 126.2 (d), 66.7 (s), 63.8 (d), 48.5 (t), 41.5 t, 28.4 (t), 26.8 (t), 19.0 (t), 14.4 (s), 5.8 (t); MS m/z 227 (M^+, 25), 226 (29), 198 (27), 172 (42), 147 (56), 130 (100), 96 (65); IR 3064, 3021, 2999, 2961, 1536, 1493, 1472 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO$ (mixture of regioisomers): C, 79.26; H, 7.54; N, 6.16. Found: C, 79.03; H, 7.67; N, 6.17.

44. Two inseparable diastereoisomers: R_f 0.52; ^{1}H NMR δ 7.20−7.08 (m, 2 H), 7.05−6.92 (m, 2 H), 4.73 (s, 1 H, one isomer), 4.37 (s, 1 H, the other isomer), 4.35 and 4.26 (AB system, J = 7.5 Hz, 2 H, one isomer), 3.96 and 3.93 (AB system, J = 7.2 Hz, 2 H, the other isomer), 3.45−2.40 (m, 4 H), 1.38 to −0.23 (m, 6 H); ^{13}C NMR (one isomer) δ 133.6−125.8 (aromatic ring), 72.7 (t), 65.1 (d), 47.8 (t), 33.7 (s), 29.2 (t), 15.3 (t), 13.8 (s), 6.3 (t), 4.6 (t); MS m/z 227 (M^+, 26), 226 (10), 196 (29), 167 (32), 147 (95), 132 (58), 130 (100), 128 (43), 117 (30), 115 (56), 103 (36), 91 (31), 77 (53).

Trispiro[cyclopropane-1,1′-cyclopropane-1,2″-cyclopropane-1,3‴-(1,5,6,10b-tetrahydro-2*H*-isoxazolo-[3,2-*a*]isoquinoline)] (28) and Trispiro[cyclopropane-1,1′-cyclopropane-2,1″-cyclopropane-3,3‴-3,3a,8,9-tetrahydro-(2*H*)-isoquinoline[2,1-*b*]isoxazole]: 60 °C for 4 d, 6:1 ratio, eluent diethyl ether/hexane 1:1, 108 mg, 0.43 mmol, 60%.

28: R_f 0.25; ^{1}H NMR δ 7.20−7.10 (m, 4 H), 4.70 (t, J = 8.8 Hz, 1 H), 3.28−3.04 (m, 2 H), 2.99−2.68 (m, 3 H), 2.28 (dd, J = 12.5, 8.8 Hz, 1 H), 1.22−1.12 (m, 1 H), 0.97−0.80 (m, 4 H), 0.77−0.66 (m, 1 H), 0.65−0.55 (m, 2 H); ^{13}C NMR δ 136.1 (s), 132.9 (s), 128.2 (d), 127.3 (d), 126.5 (d), 126.2 (d), 70.3 (s), 63.4 (d), 48.4 (t), 39.6 (t), 28.2 (t), 21.4 (s), 17.9 (s), 7.1 (t), 5.4 (t, 2 C overlapped), 5.1 (t); MS m/z 253 (M^+, 30), 252 (31), 238 (26), 147 (66), 145 (52), 144 (47), 132 (45), 130 (100), 79 (74).

4-Spirocyclopropanated regioisomer: ^{1}H NMR δ 7.20−7.10 (m, 4 H), 4.55 (s, 1 H), 4.06 and 3.99 (AB system, J = 7.5 Hz, 2 H), 3.42−2.58 (m, 4 H), 1.28 (m, 1 H), 1.01−0.80 (m, 2 H), 0.77−0.25 (m, 4 H), −0.23 (m, 1 H); MS m/z 253 (M^+, 36), 252 (19), 238 (100), 130 (67), 115 (60).

Thermal Rearrangement of Cycloadducts 20, 23, 26, and 28. General Procedure. A solution of cycloadducts (0.40−0.80 mmol) (contaminated with the corresponding inseparable 4-spirocyclopropanated regioisomers) in the appropriate solvent (see Table 2) was heated in a screw-capped Sovirel tube. After the solution was cooled to room temperature, the solvent was removed by elution with petroleum ether through a column of silica gel. The mixture was then flash chromatographed (eluent diethyl ether) to give mixtures of unreacted 4-spirocyclopropanated isomers (if present) along with the isomeric enaminones and pure tetrahydropyridones as the most polar fraction.

Thermal rearrangement of the adduct 20: xylenes, 125 °C for 6 h.

(1′*S*,8a′*R*)-1′-*tert*-Butoxyspiro(cyclopropane-1,6′-octahydroindolizin)-7′-one (21): 43 mg, 40%; R_f 0.18; $[\alpha]^{25}_D$ +21.4 (c 0.22, $CHCl_3$); ^{1}H NMR δ 3.86 (m, 1 H), 3.08 (td, J = 8.6; 2.2 Hz, 1 H), 2.82−2.70 (m, 1 H), 2.80 (d, J = 11.4 Hz, 1 H), 2.57 (d, J = 11.4 Hz, 1 H), 2.55−2.24 (m, 4 H), 1.78−1.67 (m, 1 H), 1.66−1.54 (m, 1 H), 1.17 (s, 9 H), 1.05−1.00 (m, 1 H), 0.96−0.82 (m, 1 H), 0.62−0.48 (m, 1 H); ^{13}C NMR δ 208.1 (s), 77.3 (d), 73.5 (s) 67.9 (d), 59.3 (t), 52.8 (t), 43.5 (t), 33.2 (t), 28.4 (q, 3 C), 27.8 (s), 23.7 (t), 11.9 (t); MS m/z 237 (M^+, 5), 180 (100), 137 (14), 112 (22). Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.47; H, 9.77; N, 6.36.

Enaminone: 46% (calculated by NMR integration); R_f 0.32; ^{1}H NMR δ 9.58 (br s, 1 H), 5.38 (s, 1 H), 4.57 (t, J = 7.8 Hz, 1 H), 3.64−3.25 (m, 2 H), 2.24 (m, 1 H), 1.86 (dq, J = 12.5, 8.3 Hz, 1 H), 1.34 (s, 3 H), 1.27 (s, 9 H), 1.15 (dd, J = 7.3, 4.1 Hz, 2 H), 0.55 (dd, J = 7.3, 4.1 Hz, 2 H); ^{13}C NMR δ 199.8 (s), 166.6 (s), 85.2 (d), 74.4 (s), 73.6 (d), 44.4 (t), 32.2 (t), 28.3 (q, 3 C), 23.7 (s), 20.5 (q), 17.4 (t), 17.2 (t); MS m/z 237 (M^+, 32), 181 (43), 180 (54), 126 (100), 108 (81).

Thermal rearrangement of the adduct 23: dichlorobenzene, 160 °C for 8 h.

1′-Methyl-6′-phenylspiro(cyclopropane-1,3′-piperidin)-4′-one (24): 25 mg, 40%; R_f 0.39; ^{1}H NMR δ 7.34−7.28 (m, 5 H), 3.44 (dd, J = 10.0, 4.8 Hz, 1 H), 2.90 (d, J = 12.2 Hz, 1 H), 2.76 (dd, J = 17.2, 10.0 Hz, 1 H), 2.63 (dd, J = 17.2, 4.8 Hz, 1 H), 2.52 (d, J = 12.2 Hz, 1 H), 2.07 (s, 3 H), 1.58 (m, 1 H), 1.13−1.02 (m, 1 H), 1.00−0.94 (m, 1 H), 0.66−0.58 (m, 1 H); ^{13}C NMR δ 208.1 (s), 141.7 (s), 128.6 (d, 2 C), 127.6 (d), 127.4 (d, 2 C), 68.4 (d), 62.5 (t), 47.5 (t), 43.1 (q), 28.5 (s), 22.0 (t), 12.2 (t); MS (m/z) 215 (M^+, 70), 214 (28), 138 (100), 118 (33); IR 3062, 3030, 2951, 1701, 1603, 1494, 1453, 1384 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.95; H, 8.03; N, 6.54.

Enaminone: 29 mg, 46%; R_f 0.65; ^{1}H NMR δ 10.90 (br s, 1 H), 7.46−7.30 (m, 5 H), 5.23 (s, 1 H), 2.80 (d, J = 5.3 Hz, 3 H), 1.31 (s, 3 H), 1.20 (dd, J = 6.4; 3.5 Hz, 2 H), 0.59 (dd, J = 6.4; 3.5 Hz, 2 H); ^{13}C NMR δ 199.3 (s), 165.6 (s), 135.4 (s), 129.0 (d), 128.2 (d, 2 C), 127.5 (d, 2 C), 92.2 (d), 31.0 (q), 23.8 (s), 20.5 (q), 17.5 (t, 2 C); MS m/z 215 (M^+, 33), 214 (8), 160 (100); IR 3061, 2997, 2957, 1599, 1572, 1527, 1484, 1335 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.12; H, 7.99; N, 6.50.

Thermal rearrangement of the adduct 26: mesitylene, 160 °C for 2 h.

Spiro[cyclopropane-1,3′-(1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin)]-2′-one (27): 44 mg, 32%; R_f 0.40; ^{1}H NMR δ 7.19−7.08 (m, 4 H), 3.80 (dd, J = 11.8, 3.4 Hz, 1 H), 3.29−3.00 (m, 4 H), 2.79 (m, 1 H), 2.70−2.46 (m, 3 H), 1.71−1.61 (m, 1 H), 1.14−1.07 (m, 1 H), 1.06−0.95 (m, 1 H), 0.69−0.61 (m, 1 H); ^{13}C NMR δ 208.5 (s), 136.8 (s), 133.8 (s), 128.9 (d), 126.4 (d), 126.1 (d), 124.9 (d), 62.4 (t), 60.9 (d), 50.9 (t), 45.8 (t), 29.3 (t), 28.3 (s), 24.1 (t), 12.1 (t); MS m/z 227 (M^+, 93), 226 (100), 212 (21), 184 (26), 131 (25), 130 (52). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.18; H, 7.68; N, 6.05.

Enaminone: 59 mg, 43%; R_f 0.52; ^{1}H NMR δ 11.40 (br s, 1 H), 7.71 (d, J = 7.8 Hz, 1 H), 7.42−7.26 (m, 2 H), 7.20 (d, J = 7.3 Hz, 1 H), 5.84 (s, 1 H), 3.43 (td, J = 6.5, 3.4 Hz, 2 H), 2.89 (t, J = 6.5 Hz, 2 H), 1.42 (s, 3 H), 1.23 (dd, J = 6.3; 3.5 Hz, 2 H), 0.61 (dd, J = 6.4; 3.5, 2 H); ^{13}C NMR δ 199.4 (s), 156.5 (s), 136.7 (s), 130.6 (d), 129.5 (s), 128.1 (d), 127.3 (d), 125.2 (d), 85.8 (d), 38.3 (t), 28.4 (t), 24.0 (s), 20.8 (q), 17.5 (t, 2 C); MS m/z 227 (M^+, 79), 226 (25), 172 (86), 147 (100), 130 (39). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.41; H, 7.76; N, 6.36.

Thermal rearrangement of the adduct 28: mesitylene, 160 °C for 3 h.

Dispiro[cyclopropane-1,3′-(1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline)-4′,1″-cyclopropan]-2′-one (29): 58 mg, 34%; R_f 0.71; ^{1}H NMR δ 7.20−7.11 (m, 3 H), 7.08−7.00 (m, 1 H), 4.62 (dd, J = 11.4; 4.9 Hz, 1 H), 3.52−3.40 (m, 1 H), 3.12−2.95 (m, 2 H), 2.88−2.73 (m, 2 H), 2.65 (dd, J = 17.5; 4.9 Hz, 1 H), 1.49 (m, 1 H), 1.00 (m, 1 H), 0.97−0.78 (m, 2 H), 0.70−0.54 (m, 2 H), 0.26 (m, 1 H), 0.06 (m, 1 H); ^{13}C NMR δ 208.1 (s), 139.4 (s), 136.1 (s), 129.3 (d), 126.5 (d), 126.4 (d), 125.8 (d), 56.3 (d), 44.8 (s), 42.1 (t), 41.8 (t), 29.7 (t), 29.4 (s), 19.5 (t), 16.6 (t), 8.1 (t), 5.8 (t); MS *m*/*z* 253 (M^+, 46), 238 (68), 134 (84), 133 (100), 105 (61), 84 (69). Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.30; H, 7.88; N, 6.00.

Enaminone: 55% (calculated by NMR integration); R_f 0.52; ^{1}H NMR δ 11.39 (br s, 1 H), 7.77 (d, J = 7.4 Hz, 1 H), 7.46−7.32 (m, 2 H), 7.20 (d, J = 7.4 Hz, 1 H), 6.39 (s, 1 H), 3.45 (td, J = 6.5, 3.4 Hz, 2 H), 2.91 (t, J = 6.5 Hz, 2 H), 1.51 (m, 1 H), 1.09 (dd, J = 6.6, 3.5 Hz, 2 H), 0.57 (m, 2 H), 0.49 (dd, J = 6.6, 3.5 Hz, 2 H), 0.15 (m, 2 H); ^{13}C NMR δ 199.2 (s), 156.2 (s), 144.7 (s), 131.1 (d), 130.6 (s), 129.6 (d), 128.1 (d), 127.9 (d), 97.2 (d), 38.3 (t), 29.7 (s), 28.4 (t), 13.4 (t, 2 C), 12.7 (d), 3.3 (t, 2 C); MS *m*/*z* 253 (M^+, 80), 172 (37), 147 (100).

One-Pot Reactions of Nitrones 15, 22, and 25 with MSP 7 and MDH 8 To Yield 21, 24, 27, and 29. General Procedure. A solution of **7** (or **8**) and the nitrone in the solvent appropriate for the rearrangement was heated in a Sovirel tube for the appropriate time. Isolation of the products was carried out by chromatography on silica gel, first removing the solvent by elution with petroleum ether followed by diethyl ether.

21: 7 (244 mg, 3.05 mmol), **15** (319 mg, 2.03 mmol), xylenes (4 mL), 125 °C for 6 h, 108 mg, 22%.

24: 7 (147 mg, 1.83 mmol), **22** (166 mg, 1.23 mmol), *o*-dichlorobenzene (10 mL), 160 °C for 8 h, 75 mg, 28%.

27: 7 (76 mg, 0.95 mmol), **25** (93 mg, 0.63 mmol), mesitylene (4 mL), 160 °C for 2 h, 42 mg, 29%.

29: 8 (128 mg, 1.21 mmol), **25** (118 mg, 0.80 mmol), mesitylene (8 mL), 160 °C for 3 h, 38 mg, 19%.

Cycloaddition of Nitrile Oxide 30 to MSP 7. A solution of benzohydroximoyl chloride[17] in benzene (0.35 M, 4 mL) was added dropwise over 4 h to a stirred mixture of **7** (94 mg, 1.17 mmol) and $NaHCO_3$ (118 mg, 1.40 mmol) in benzene (2 mL). After being stirred at room temperature for 12 h, the salts were filtered over Celite, the solvent was removed in vacuo, and the crude mixture was purified by flash chromatography on silica gel (diethyl ether−hexane 1:1) to give **31** (150 mg, 64%).

7-Phenyl-5-oxa-6-azadispiro[2.0.4.1]non-6-ene (31): R_f 0.51; ^{1}H NMR δ 7.70−7.64 (m, 2 H), 7.43−7.39 (m, 3 H), 3.47 and 3.32 (AB system, J = 17.2 Hz, 2 H), 1.60 (d, J = 5.9 Hz, 1 H), 1.18 (d, J = 5.9 Hz, 1 H), 1.12−1.08 (m, 2 H), 0.90−0.84 (m, 2 H); ^{13}C NMR δ 156.7 (s), 130.0 (d), 129.0 (s), 128.6 (d, 2 C), 126.4 (d, 2 C), 70.2 (s), 38.4 (t), 18.2 (t), 17.2 (s), 6.4 (t), 6.0 (t); MS *m*/*z* 199 (M^+, 64), 198 (87), 170 (31), 144 (52), 117 (89), 103 (43), 96 (62), 78 (63), 77 (100). Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.20; H, 6.54; N, 7.46.

Cycloaddition of Nitrile Oxide 33 to MSP 7. A stirred solution of **7** (50 mg, 0.62 mmol) and **33** (84 mg, 0.52 mmol) in 1 mL of benzene was heated at 60 °C for 4 h. After being cooled at room temperature, the solvent was removed in vacuo, and the crude mixture was filtered through a short pad of silica gel (diethyl ether−hexane 1:1 as eluent) to provide **34 (**121 mg, 95%).

7-(2,4,6-Trimethylphenyl)-5-oxa-6-azadispiro[2.0.4.1]-non-6-ene (34): R_f 0.56; ^{1}H NMR δ 6.90 (s, 2 H), 3.25 and 3.12 (AB system, J = 17.6 Hz, 2 H), 2.29 (s, 3 H), 2.25 (s, 6 H), 1.61 (d, J = 5.6 Hz, 1 H), 1.17 (d, J = 5.8 Hz, 1 H), 1.13 (m, 2 H), 0.90−0.82 (m, 2 H); ^{13}C NMR δ 158.2 (s), 138.7 (s), 136.4 (s, 2 C), 128.3 (d, 2 C), 126.9 (s), 69.2 (s), 42.1 (t), 21.0 (q), 19.6 (q, 2 C), 17.6 (t), 17.2 (s), 6.3 (t), 6.1 (t); MS *m*/*z* 241 (M^+, 12), 240 (8), 226 (16), 198 (30), 158 (55), 91 (16), 59 (100). Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.30; H, 8.02; N, 6.12.

Cycloaddition of Nitrile Oxide 36 to MSP 7. A benzene (3 mL) solution of **7** (240 mg, 3.0 mmol) and phenyl isocyanate (943 mg, 7.9 mmol) was heated at 55 °C, and a benzene solution (3 mL) of methyl 4-nitrobutyrate (529 mg, 3.6 mmol) and triethylamine (0.15 mL, 1 mmol) was added over 10 h. After being cooled to room temperature, the mixture was filtered over Celite, the solvent removed in vacuo, and the crude mixture purified by flash chromatography on silica gel (eluent diethyl ether−light petroleum ether 1:2) to provide **37** (273 mg, 44%).

5-Oxa-6-azadispiro[2.0.4.1]non-6-ene-7-propanoic acid methyl ester (37): R_f 0.11; ^{1}H NMR δ 3.67 (s, 3 H), 3.02 and 2.90 (AB system, J = 17.5 Hz, 2 H), 2.64 (br s, 4 H), 1.44 (d, J = 5.9 Hz, 1 H), 1.03−0.97 (m, 3 H), 0.85−0.71 (m, 2 H); ^{13}C NMR: δ 172.6 (s), 157.7 (s), 69.0 (s), 51.7 (q), 40.8 (t), 30.1 (t), 23.6 (t), 18.0 (t), 16.7 (s), 6.1 (t), 5.8 (t); MS *m*/*z* 209 (M^+, 2), 127 (16), 111 (32), 97 (44), 85 (70), 71 (88), 57 (100).

Cycloaddition of Nitrile Oxide 30 to MDH 8. A benzene solution of benzohydroximoyl chloride[17] (0.35 M, 2.5 mL) was added dropwise over 4 h to a stirred mixture of **8** (71 mg, 0.67 mmol) and $NaHCO_3$ (73 mg, 0.87 mmol) in benzene (1 mL). The mixture was stirred at room temperature for 12 h, the salts were filtered over Celite, the solvent was removed in vacuo, and the crude mixture was purified by flash cromatography on silica gel (diethyl ether−hexane 1:4) to provide **39** (82 mg, 54%).

10-Phenyl-8-oxa-9-azatrispiro[2.0.2.0.4.0]undec-9-ene (39): R_f 0.35; ^{1}H NMR δ 7.72−7.63 (m, 2 H), 7.49−7.35 (m, 3 H), 3.36 (s, 2 H), 1.29−1.12 (m, 2 H), 1.08−0.86 (m, 4 H), 0.81−0.53 (m, 2 H); ^{13}C NMR δ 156.6 (s), 129.9 (d), 128.6 (s), 128.3 (d, 2 C), 126.4 (d, 2 C), 73.1 (s), 36.7 (t), 20.8 (s, 2 C), 6.1 (t, 2 C), 5.5 (t, 2 C); MS *m*/*z* 225 (M^+, 5), 224 (14), 196 (17), 178 (100), 119 (24), 117 (51), 105 (61), 79 (71), 77 (70). Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.61; H, 7.07; N, 6.54.

Cycloaddition of Nitrile Oxide 33 to MDH 8. A benzene (1 mL) solution of **8** (128 mg, 1.2 mmol) and **33** (161 mg, 1 mmol) was heated at 60 °C for 4 h. The solvent was removed in vacuo, and the crude mixture was filtered over a short pad of silica gel (diethyl ether−hexane 1:2) to provide **41** (249 mg, 93%).

10-(2,4,6-Trimethylphenyl)-8-oxa-9-azatrispiro-[2.0.2.0.4.0]undec-9-ene (41): R_f 0.45; ^{1}H NMR δ 6.89 (s, 2 H), 3.14 (s, 2 H), 2.28 (s, 3 H), 2.20 (s, 6 H), 1.29−1.16 (m, 2 H), 1.00−0.88 (m, 4 H), 0.78−0.68 (m, 2 H); ^{13}C NMR δ 158.0 (s), 138.6 (s), 136.4 (s, 2 C), 128.3 (d, 2 C), 127.0 (s), 72.2 (s), 44.5 (t), 21.0 (q), 20.6 (s, 2 C), 19.5 (q, 2 C), 6.0 (t, 2 C), 5.5 (t, 2 C); MS *m*/*z* 267 (M^+, 5), 266 (8), 252 (10), 224 (30), 159 (84), 158 (66), 144 (32), 127 (100). Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.71; H, 8.34; N, 5.59.

Thermal Rearrangement of the Adduct 31. A solution of **31** (210 mg, 1.05 mmol) in *o*-dichlorobenzene (6 mL) was heated in a screw-capped Sovirel tube at 160 °C for 14 h. After being cooled to room temperature, the mixture was filtered over a short pad of silica gel eluting first with petroleum ether to remove the solvent and then with diethyl ether to give **32** (146 mg, 70%).

6-Phenyl-5-azaspiro[2.5]oct-6-en-8-one (32): R_f 0.16; ^{1}H NMR δ 7.61−7.55 (m, 2 H), 7.50−7.40 (m, 3 H), 5.48 (d, J = 1.7 Hz, 1 H), 5.30 (br s, 1 H), 3.55 (d, J = 2.4 Hz, 2 H), 1.28 (dd, J = 6.5, 3.9 Hz, 2 H), 0.69 (dd, J = 6.5, 3.9 Hz, 2 H); ^{13}C NMR: δ 194.3 (s), 161.2 (s), 136.1 (s), 130.8 (d), 128.9 (d, 2 C), 126.2 (d, 2 C), 99.2 (d), 49.6 (t), 24.0 (s), 13.8 (t, 2 C); MS *m*/*z* 199 (M^+, 100), 198 (87), 170 (10), 156 (20), 143 (40). Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.01; H, 6.83; N, 7.15.

Thermal Rearrangement of the Adduct 34. A mesitylene solution (13 mL) of **34** (133 mg, 0.55 mmol) was refluxed for 4 h. After the solution was cooled to room temperature, analytically pure **35**, in part, precipitated from the mesitylene solution and was collected and washed several times with hexane (yield 110 mg). More **35** (13 mg) was obtained by chromatography of the mother solution. Total yield 123 mg (92%).

6-(2,4,6-Trimethylphenyl)-5-azaspiro[2.5]oct-6-en-8-one (35): R_f 0.28; ^{1}H NMR δ 6.84 (s, 2 H), 5.02 (d, J = 1.5 Hz, 1 H), 4.77 (br s, 1 H), 3.52 (d, J = 2.2 Hz, 2 H), 2.28 (s, 9 H), 1.30 (dd, J = 6.6, 3.9 Hz, 2 H), 0.69 (dd, J = 6.6, 3.9 Hz, 2 H);

^{13}C NMR δ 193.3 (s), 162.6 (s), 138.4 (s), 135.0 (s, 2 C), 133.3 (s), 128.1 (d, 2 C), 101.2 (d), 57.9 (t), 27.8 (s), 21.0 (q), 19.1 (q, 2 C), 13.4 (t, 2 C); MS *m/z* 241 (M^+, 100), 198 (80), 184 (67). Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.61; H, 7.93; N, 6.00.

Thermal Rearrangement of the Adduct 37. A dimethylformamide (4 mL) solution of **37** (106 mg, 0.51 mmol) containing NaCl (30 mg) and H_2O (0.05 mL) was refluxed for 4 h. After being cooled to room temperature, the solvent was removed in vacuo and the crude mixture purified by flash chromatography on silica gel (acetone as eluent) to provide **38** (59 mg, 66%).

Spiro[cyclopropane-1,6′-(1,2,3,5,6,7-hexahydroindolizine)]-3′,7′-dione (38): pale yellow solid; mp 125−127 °C; R_f 0.66; ^{1}H NMR δ 5.42 (t, J = 1.3 Hz, 1 H), 3.68 (s, 2 H), 2.95−2.88 (m, 2 H), 2.65−2.57 (m, 2 H), 1.27 (dd, J = 6.8, 3.9 Hz, 2 H), 0.71 (dd, J = 6.8; 3.9 Hz, 2 H); ^{13}C NMR δ 192.9 (s), 175.0 (s), 160.7 (s), 103.0 (d), 45.5 (t), 28.0 (t), 23.6 (t), 22.8 (s), 15.4 (t, 2 C); MS *m/z* 177 (M^+, 58), 176 (100), 149 (14), 148 (28), 84 (32). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.90; H, 6.46; N, 7.67.

Thermal Rearrangement of Adducts 39 and 41. General Procedure. A solution of **39** or **41** in *o*-dichlorobenzene (5×10^{-2} M) was heated in a screw-capped Sovirel tube at 160 °C for the time indicated in Table 3. After being cooled to room temperature, the solution was filtered over a short pad of silica gel, eluting first with hexane in order to remove the aromatic solvent and then with the appropriate solvent to give **40** and **42**.

5-Phenyl-4-azadispiro[2.0.2.4]dec-5-en-7-one (40): eluent diethyl ether-methanol 10:1, R_f 0.50, yield 53%; ^{1}H NMR δ 7.58−7.45 (m, 2 H), 7.45−7.37 (m, 3 H), 5.58 (d, J = 1.5 Hz, 1 H), 5.02 (br s, 1 H), 1.19 (dd, J = 6.8, 4.0 Hz, 2 H), 0.78−0.67 (m, 4 H), 0.52 (dd, J = 6.8, 4.0 Hz, 2 H); ^{13}C NMR δ 193.2 (s), 160.4 (s), 135.5 (s), 131.3 (d), 128.9 (d, 2 C), 126.4 (d, 2 C), 99.7 (d), 38.1 (s), 30.9 (s), 11.5 (t, 2 C), 11.4 (t, 2 C); MS *m/z* 225 (M^+, 26), 224 (100), 210 (30). Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.10; H, 7.00; N, 6.30.

5-(2,4,6-Trimethylphenyl)-4-azadispiro[2.0.2.4]dec-5-en-7-one (42): eluent diethyl ether, R_f 0.32, yield 73%; ^{1}H NMR δ 6.85 (s, 2 H), 5.04 (d, J = 1.7 Hz, 1 H), 4.78 (br s, 1 H), 2.26 (s, 9 H), 1.18 (dd, J = 6.8; 4.0 Hz, 2 H), 0.66 (m, 4 H), 0.52 (dd, J = 6.8; 4.0 Hz, 2 H); ^{13}C NMR δ 192.7 (s), 161.6 (s), 138.5 (s), 135.3 (s, 2 C), 133.0 (s), 128.1 (d, 2 C), 101.0 (d), 38.4 (s), 28.3 (s), 21.0 (q), 19.1 (q, 2 C), 10.6 (t, 2 C), 10.5 (t, 2 C); MS *m/z* 267 (M^+, 29), 266 (100), 252 (33). Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.48; H, 8.10; N, 5.53.

Competition Experiments. A 0.3 M solution of mesitonitrile oxide (**33**) in $CDCl_3$ was treated with an equimolar mixture of BCP **4** and MSP **7** (1.5 equiv each) and heated at 60 °C for 4 h, until the nitrile oxide had been consumed as monitored by ^{1}H NMR. Integration of characteristic signals of the adducts to BCP[11b] and to MSP gave a 4:1 ratio of **34** over **43**.

A 0.3 M solution of tetrahydroisoquinoline *N*-oxide (**25**) in $CDCl_3$ was treated with an equimolar mixture of BCP **4** and MSP **7** (1.5 equiv each) and heated at 60 °C for 3 days, until the nitrone had been consumed as monitored by ^{1}H NMR. Integration of characteristic signals of the adducts to BCP[11b] and regioisomeric adducts **26** and **44** to MSP (formed in 4:1 ratio, respectively) gave a 4:1 ratio of **45** over **26** + **44**.

Deprotection of Ketones 17, 19, and 21. General Procedure. A solution of *tert*-butoxy ketones **17**, **19**, and **21** (1 mmol) in trifluoroacetic acid (2.3 mL, 30 mmol) was stirred at room temperature for 2 h. The TFA was removed under reduced pressure and the residue dissolved in methanol and passed through a column of Amberlyst 26. The methanol was then removed in vacuo, and the crude mixture was filtered over a short pad of silica gel, eluting with ethyl acetate−methanol 4:1 + 1% NH_4OH, to provide the hydroxyketones.

(1′*S*,8a′*R*)-1′-Hydroxyspiro(cyclopropane-1,8′-octahydroindolizin)-7′-one (46): R_f 0.28; $[\alpha]^{25}_D$ +97.8 (*c* 0.50, MeOH); yield 84%; ^{1}H NMR δ 3.92 (ddd, J = 8.5, 6.8, 4.2 Hz, 1 H), 3.34 (br s, 1 H), 3.32−3.18 (m, 1 H), 3.10 (td, J = 8.8, 2.9 Hz, 1 H), 2.81−2.41 (m, 4 H), 2.74 (d, J = 6.8 Hz, 1 H), 2.33 (dq, J = 13.4, 8.5 Hz, 1 H), 1.69 (dddd, J = 13.4, 8.8, 4.2, 3.1 Hz, 1 H), 1.58−1.49 (m, 1 H), 1.34−1.17 (m, 1 H), 0.88 (m, 2 H); ^{13}C NMR δ 208.8 (s), 72.8 (d), 71.2 (d), 52.3 (t), 49.7 (t), 38.3 (t), 33.8 (t), 30.9 (s), 16.0 (t), 11.8 (t); MS *m/z* 181 (M^+, 12), 180 (50), 163 (67), 162 (42), 137 (100), 136 (40), 84 (55). Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 65.96; H, 8.45; N, 7.47.

(1′*R*,2′*R*,8a′*R*)-1′,2′-Dihydroxyspiro(cyclopropane-1,8′-octahydroindolizin)-7′-one (47): R_f = 0.22; $[\alpha]^{23}_D$ +43.6 (*c* 0.50, MeOH); yield 83%; ^{1}H NMR δ 4.68 (br s, 2 H), 4.06 (dd, J = 4.4, 3.0 Hz, 1 H), 3.68 (dd, J = 8.0, 3.0 Hz, 1 H), 3.43 (m, 1 H), 3.00 (d, J = 11.0 Hz, 1 H), 2.80−2.40 (m, 4 H), 2.72 (d, J = 8.0 Hz, 1 H), 1.57−1.43 (m, 1 H), 1.38−1.16 (m, 1 H), 0.92 (m, 2 H); ^{13}C NMR δ 208.2 (s), 81.4 (d), 78.2 (d), 69.2 (d), 60.6 (t), 50.0 (t), 38.0 (t), 31.0 (s), 16.3 (t), 12.11 (t); MS *m/z* 197 (M^+, 23), 196 (91), 180 (28), 137 (100), 136 (71), 124 (51), 109 (43). Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.48; H, 7.89; N, 7.60.

(1′*S*,8a′*R*)-1′-hydroxyspiro(cyclopropane-1,6′-octahydroindolizin)-7′-one (48): R_f = 0.27; $[\alpha]^{26}_D$ +25.9 (*c* 0.56, MeOH); yield 93%; ^{1}H NMR δ 4.06 (ddd, J = 8.6, 6.2, 4.5 Hz, 1 H), 3.06 (td, J = 8.5, 2.8 Hz, 1 H), 2.90 (br s, 1 H), 2.82 (dd, J = 11.4, 1.4 Hz, 1 H), 2.78 (dd, J = 15.4, 2.6 Hz, 1 H), 2.60−2.27 (m, 4 H), 2.59 (d, J = 11.4 Hz, 1 H), 1.72 (dddd, J = 12.8, 8.3, 4.4, 2.6 Hz, 1 H), 1.56 (ddd, J = 9.5, 6.8, 4.0 Hz, 1 H), 1.00 (dddd, J = 9.5, 7.0, 3.3, 1.4 Hz, 1 H), 0.87 (ddd, J = 9.3, 6.8, 3.3 Hz, 1 H), 0.60 (ddd, J = 9.3, 7.0, 4.0 Hz, 1 H); ^{13}C NMR δ 208.5 (s), 77.0 (d), 69.2 (d), 58.5 (t), 52.1 (t), 43.1 (t), 32.8 (t), 27.6 (s), 23.6 (t), 12.6 (t); MS *m/z* 181 (M^+, 22), 180 (54), 137 (100), 108 (38). Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.04; H, 8.66; N, 7.83.

Tests of DNA-Cleavage Activity. Reaction mixtures containing pUC18-DNA (42 μM nucleotide concentration), 8 mM TRIS-borate buffer (pH 7.5), 0.4 mM EDTA, and 17% of 0.00, 2.10, 4.20, and 10.50 mM solutions in acetonitrile (final concentrations 0, 50, 100, and 250 times the nucleotide concentration) of compounds **11**, **14**, **27**, **32**, **38**, **40**, and **46**−**48**, and of compound **6** for comparison, were incubated at 37 °C for 18 h. Another buffered pUC18 solution was incubated under the same conditions with the restriction enzyme Hind III, which is able to produce the topological change to form III. After incubation, the mixtures were analyzed by electrophoresis (1 h, 70 V) on agarose gel. Reaction mixtures containing pUC18-DNA (42 μM nucleotide concentration), 8 mM TRIS-borate buffer (pH 7.5), 0.4 mM EDTA, and 17% of 0.00, 2.10, 4.20, 10.50 mM solutions in acetonitrile (final concentrations 0, 50, 100, and 250 times the nucleotide concentration) of compounds **6**, **14**, **32**, **38**, **40**, and **46** were also incubated under UV irradiation (25 μW/cm^2) for 2 h. Longer UV exposure times resulted in damage for the DNA double helix, while no damage was observed on the α-spirocyclopropane piperidinones.

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Supporting Information Available: Electrophoresis pUC18 plasmidic DNA reacted with compounds **6**, **11**, **14**, **46**, **47**, and **48**. This material is available free of charge via the Internet at http://pubs.acs.org.

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