N-Bridgehead Polycyclic Compounds by Sequential Rearrangement-Annulation of Isoxazoline-5-spirocyclopropanes. 6.[1] A General Synthetic Method for 5,6-Dihydro-7(8*H*)- and 2,3,5,6-Tetrahydro-7(1*H*)-indolizinones

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The thermal rearrangement-annulation of isoxazoline-5-spirocyclopropanes **4a-e** substituted with a chain bearing a carbonyl group affords, in one step, 5,6-dihydro-7(8*H*)-indolizinones **5a-e**. The rearrangement-annulation of isoxazoline-5-spirocyclopropanes **4f-h** substituted with a chlorine on the side chain affords, also in one step, 2,3,5,6-tetrahydro-7(1*H*)-indolizinones **5f-h**. When the cyclopropane ring is fused to a cyclohexane, or when a cyclohexanone is present in the side chain of isoxazoline **4**, the process leads to N-bridgehead tricyclic compounds. Short rection times, mild reaction conditions, complete regioselectivity, and good stereoselectivity are the valuable features of this strategy.

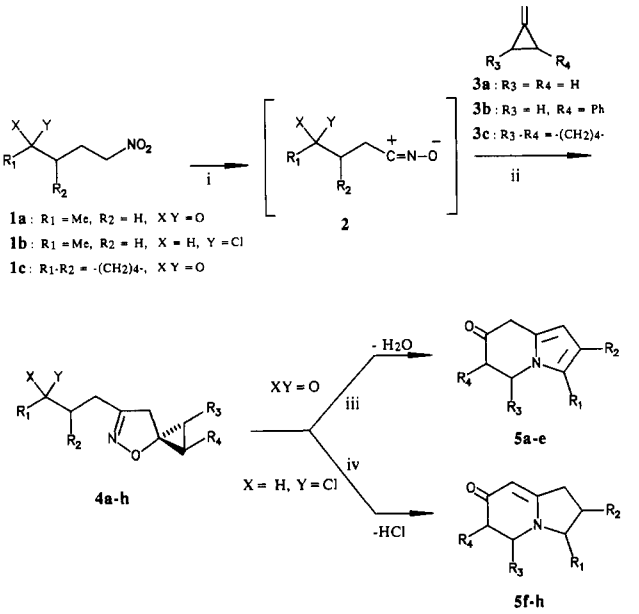
Indolizine skeletons with different degrees of unsaturation are found in many families of alkaloids in the animal and vegetable kingdoms and are important targets in organic synthesis.[2] Consequently, considerable effort has been addressed to the design of general synthetic methods for this class of compounds.[2] Recently, we described the stereoselective synthesis of 3,5-disubstituted hexahydro-7-indolizinones by thermal rearrangement of the corresponding tetrahydroisoxazole-5-spirocyclopropanes.[1] Using a similar strategy, we synthesized 2,3,5,6-tetrahydro-7-(1*H*)-indolizinone and 1,2,5,6-tetrahydroindolizin-3,7-dione by thermal rearrangement of dihydroisoxazole-5-spirocyclopropanes having a side chain bearing a primary halide or an ester suitable for ring closure on the N-atom of the rearranged product.[3] We now report a general method for the synthesis of 5,6-dihydro-7(8*H*)-indolizinones and 2,3,5,6-tetrahydro-7(1*H*)-indolizinones by thermal rearrangement of isoxazoline-5-spirocyclopropanes containing, as an appropriate functionality for the annulation, either a carbonyl or a secondary chloride group.

Results and Discussion

Nitrile oxides **2a-c** were prepared in situ from the corresponding primary nitro compounds **1a-c** according to the Mukaiyama method[4] and were allowed to react with an excess of methylenecyclopropanes **3a-c** at room temperature for 60 h (Scheme I). Eight isoxazoline-5-spirocyclopropanes **4a-h** (Scheme I and Table I) were prepared in yields ranging from 41 to 72%. The cycloadditions were highly regioselective for the formation of the 5-spiro isomers. Indeed, the other regioisomer was seldom detected by GC-MS or ^{1}H-NMR in the crude reaction mixture and only in quantities less than 5%.[5] Only the stereoisomer derived from the anti approach was formed when the cycloaddition was carried out on 1-methylene-2-phenylcyclopropane (**3b**) and methylenenorcarane (**3c**) (see isoxazolines **4b**, **4c**, **4e**, **4g**, and **4h**; Table I). The stereochemical outcome is in agreement with previously observed selectivities[6] and was determined by means of ^{1}H- and ^{13}C-NMR data (see Experimental Section).[7]

The thermal rearrangements of isoxazoline-5-spirocyclopropanes **4a-e**, which bear a carbonyl on the side chain, were carried out in refluxing mesitylene, and the rearrangements of isoxazoline-5-spirocyclopropanes **4f-h**, which bear a chlorine on the side chain, were carried out in refluxing DMF. In the latter case, solid potassium

Scheme I



i : 2 eq PhNCO, NEt_3 cat, Et_2O.
ii : 25°C, 60 h. Yields of isolated products: 41-72%.
iii : Mesitylene, 165 °C, 0.5-2 h.
iv : 1 eq K_2CO_3, DMF, 153 °C, 0.5-2.5 h.

(1) Part 5: Cordero, F. M.; Brandi, A.; Querci, C.; Goti, A.; De Sarlo, F.; Guarna, A. *J. Org. Chem.* **1990**, *55*, 1762-1767.

(2) Reviews: (a) Howard, A. S.; Michael, J. P. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 26, Chapter 3. (b) Herbert, R. B. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1985; Vol. 3, Chapter 6, pp 241-274. (c) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1987; Vol. 5, Chapter 1, pp 1-54.

(3) Goti, A.; Brandi, A.; Danza, G.; Guarna, A.; Donati, D.; De Sarlo, F. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1253-1258.

(4) Mukaiyama T.; Hoshino T. *J. Am. Chem. Soc.* **1960**, *82*, 5339-5342.

(5) The 4- and 5-spiro regioisomers are well differentiated by their ^{1}H-NMR spectra. The chemical shifts of the methylene protons of the isoxazoline ring are in the range δ 4.5-4.0 ppm for the former compounds and in the range δ 3.0-2.5 ppm for the latter. For convenience, here and throughout the text, the regioisomers are named with reference to the numbering of the isoxazoline nucleus.

(6) Guarna, A.; Brandi, A.; De Sarlo, F.; Goti, A.; Pericciuoli, F. *J. Org. Chem.* **1988**, *53*, 2426-2429.

(7) All compounds possessing stereogenic centers are racemic. Isoxazolines **4e** and **4g** are mixtures of diastereoisomers.

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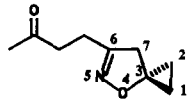
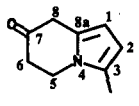
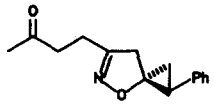
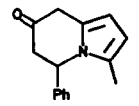
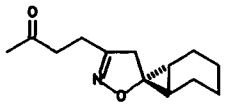
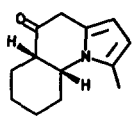
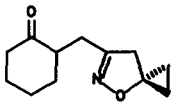
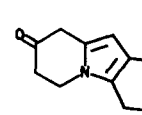
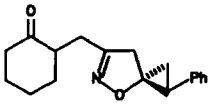
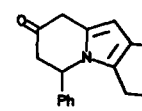
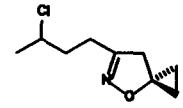
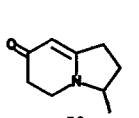
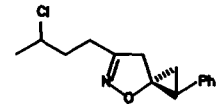
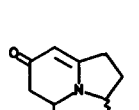
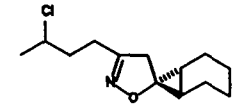
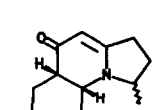
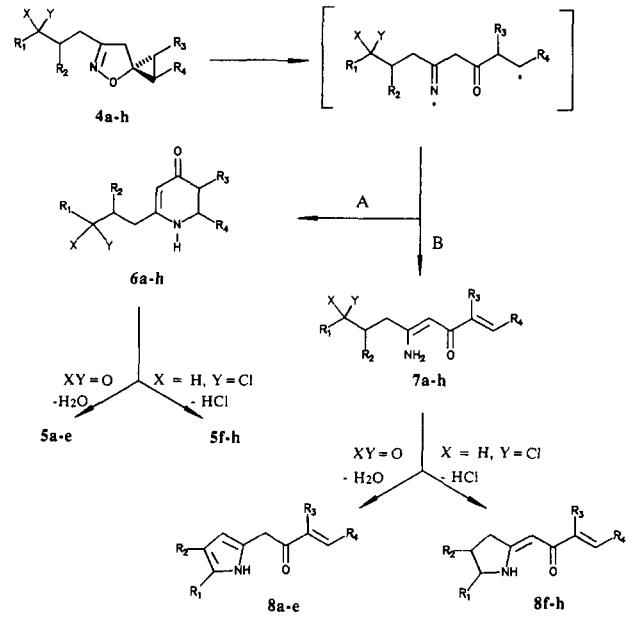
Table I. Thermal Rearrangement-Annulation of Isoxazoline-5-spirocyclopropanes 4a-h to Indolizinones 5a-h

entry	isoxazoline	reaction time	indolizinone (yield,[a] %)
1	 4a	2h[b]	 5a (32) (70)[c]
2	 4b	0.5h[b]	 5b (64)
3	 4c	0.75h[b]	 5c (47)
4	 4d	1.5h[b]	 5d (36) (57)[c]
5	 4e	0.5h[b]	 5e (52) (77)[c]
6	 4f	2.5h[d]	 5f (65)
7	 4g	0.5h[d]	 5g (48) (cis:trans =1 : 1.5)[e]
8	 4h	1.5h[d]	 5h (60) (cis:trans =1: 1.5)[e]

[a] Yield of isolated compounds. [b] Mesitylene, reflux. [c] Yield determined on the crude reaction mixture by ^{1}H-NMR. [d] 1 equiv K_2CO_3, DMF, reflux. [e] Diastereomeric ratio determined on the crude reaction mixture by ^{1}H-NMR.

Scheme II



Compounds 4-8	R_1	R_2	R_3	R_4	X	Y
a	Me	H	H	H	O	
b	Me	H	H	Ph	O	
c	Me	H	-$(CH_2)_4$-		O	
d	-$(CH_2)_4$-		H	H	O	
e	-$(CH_2)_4$-		H	Ph	O	
f	Me	H	H	H	H	Cl
g	Me	H	H	Ph	H	Cl
h	Me	H	-$(CH_2)_4$-		H	Cl

carbonate was added to facilitate the annulation and to neutralize the hydrogen chloride eliminated.[3]

The thermolysis of isoxazolines 4 produced indolizinones 5 directly. The process consists of the homolytic cleavage of the N–O bond of the isoxazoline 4 and subsequent cyclopropane ring cleavage (Scheme II). There are two possible reaction paths for the diradical intermediate generated by the ring cleavage. The radical could cyclize to dihydropyridone 6 (Scheme II, path A) or form open-chain vinyl enamino ketone 7 (Scheme II, path B).[6] Subsequent nucleophilic attack of the nitrogen atom of 6 or 7 at the electrophilic site on the side chain produced the observed product 5 or 8, respectively. As further evidence for the proposed reaction sequence, in some cases, isolated products 6 and 7 could be converted to cyclized compounds 5 and 8, respectively, when submitted to the conditions of the rearrangement. Another observation consistent with the proposed scheme is that, under the same reaction conditions, the isolated enaminones 7 and 8 are not converted to indolizinones 5.

Compared with the rate of the rearrangement of 3-phenylisoxazoline-5-spirocyclopropane,[8] the reaction rates of 4 were greatly increased by the presence of substituents on the side chain. The substituted carbon on the side chain may interact with the isoxazoline nitrogen, thus increasing the polarization of the N–O bond and making

(8) This isoxazoline rearranged completely in 10 h in a refluxing mesitylene solution, affording a 1:1.1 mixture of 5,6-dihydro-2-phenyl-4-pyridone and 1-amino-1-phenylpenta-1,4-dien-3-one.[6]

the cleavage easier. Furthermore, the presence of substituents on the cyclopropane ring facilitates the rearrangement, presumably by stabilizing the radical intermediate (cf. the reaction times of entries 1 and 2, 4 and 5, or 6 and 7, Table I). In all the cases, rearrangement to a dihydropyridone followed by annulation was the prevalent process. This process offers a valuable route for the synthesis of complex nitrogen-bridgehead polycyclic compounds. The structure and the sequence of fused rings depend on the type of substituents on the side chain and the cyclopropane ring.

The thermal rearrangements of oxo-substituted isoxazolines **4a–e** afforded **5a–b** and **5c–e**, the bicyclic and tricyclic N-bridgehead compounds, respectively, and minor amounts of the corresponding byproducts **8**. The presence of typical pyrrole signals in the ^{1}H- and ^{13}C-NMR spectra allowed an easy assignment of the structures. Although NMR yields of compounds from the crude reaction mixtures were always good, yields of isolated compounds were only moderate. In fact, the final pyrrole compounds were rather unstable and darkened rapidly in the air.[9]

The thermal rearrangements of isoxazolines **4f–h**, which were chloro-substituted in the side chain, afforded indolizin-7-ones **5f–h** (see Table I) characterized by the presence of a carbon–carbon double bond conjugated with a carbonyl in the 6-membered ring. The isolated yields of indolizinones **5f–h** were generally higher (48–65%) than those of compounds **5a–e**. Among the byproducts, open-chain products **7** and **8**, derived from the reaction pathway B, were obtained in variable amounts (Scheme II). Compound **7f** could be converted to pyrroline derivative **8f** by further heating (1 h) in dimethylformamide with potassium carbonate, but conversion of **8f** to **5f** failed.

When a phenyl group was present on the cyclopropane ring of isoxazolines **4** (entries 2, 5, and 7, Table I), the cleavage of the cyclopropane ring occurred selectively to give only the more stable secondary radical (Scheme II).[6] The process, therefore, was completely regioselective for all the reaction products **5–8**. The assignments of the structures of the regioisomers were supported by correlation of the ^{1}H- and ^{13}C-NMR spectra with those of the corresponding unsubstituted products.

Because of the presence of the phenyl group, the rearrangement of **4g** gave two diastereomeric 3-methyl-5-phenylindolizinones (**5g**) with modest selectivity (cis to trans, 1:1.5). The stereochemical assignments were made on the basis of the ^{1}H-NMR spectra of the two isomers. The methyl group of the cis isomer is shielded with respect to that of the trans isomer by the nearby phenyl group (δ 0.81 ppm vs δ 1.00 ppm). In the trans isomer, the proton on C-3 experiences the same shielding (δ 3.80 ppm for the cis isomer vs δ 3.59 ppm for the trans isomer).[10]

The isoxazolines containing a cyclopropane cis-fused to a cyclohexane (**4c** and **4h**) or a cyclohexanone in the side chain (**4d** and **4e**) afforded, in a single step, the N-bridgehead tricyclic compounds **5c**, **5h**, **5d**, and **5e**, respectively.

Isoxazolines **4c** and **4h** gave selectively pyrrolo[1,2-*a*]-quinolinones **5c** and **5h**, respectively, having the cis junction of the two six-membered rings (compound **5h** was obtained as a 1:1.5 C3–C5 cis/trans mixture). The presence of the cis fusion was determined on the basis of the vicinal coupling constants between the protons on the two bridgehead carbon atoms. The values (5.6 Hz for **5c**; 6.1 Hz and 5.5 Hz for the two isomers of **5h**) are consistent with the values reported for other cis-fused hydroquinolines.[11]

The relative stereochemistry of the minor and major isomers of octahydroquinolinone **5h** was assigned as C3–C5 cis and C3–C5 trans, respectively, on the basis of NOE experiments. Upon irradiation of the proton on C-5, the methyl signal of both isomers experienced an NOE effect; however, the NOE effect was 2-fold for the major isomer. This observation was consistent with the molecular models of the two isomers and was confirmed by molecular mechanics calculations.[12] Indeed, the distance between the proton on C-5 and the methyl group is significantly lower in the most stable conformation of the trans isomer than in that of the cis isomer.

The stereochemistry of the final products depends on two different annulation processes. In the ring closure of the diradical intermediate, predominant axial attack of the N$^\bullet$ radical on the cyclohexyl CH$^\bullet$ radical gives the cis-fused product. Similar high diastereoselectivity has been observed previously in analogous processes[6] and can be explained by the tendency to minimize torsional strain effects when low steric requirements do not prevent axial attack.[13] In contrast, the subsequent annulation reaction of pyridone **6** by nucleophilic displacement of the chloride ion proceeds with low selectivity, producing only a slight stereoisomeric excess in favor of the trans diasteroisomers of both **5g** and **5h**.

Conclusions

Several features make this rearrangement–annulation strategy feasible for, and of general applicability to, the synthesis of complex molecules containing N-bridgehead polycyclic systems. The starting materials, nitro compounds **1** and methylenecyclopropanes **3**, are readily available and easily functionalized, and they give the final products in only two steps. The introduction of different substituents at positions 2, 3, 5, and 6 of the indolizinone nucleus is possible simply by the functionalization of the two cycloaddition partners. The same strategy is applicable to the synthesis of dihydro- and tetrahydroindolizinones. The rearrangement requires short reaction times and mild reaction conditions and affords the indolizinones with complete regioselectivity, good stereoselectivity, and fair yields.

Application of this strategy to the total synthesis of 19-nor-10-azasteroids is under study.[14]

Experimental Section

The assignment of the ^{13}C-NMR signals of isoxazolines **4a–h** and indolizinones **5a–h** refer to the numbering for **4a** and **5a**, respectively, reported in Table I. 5-Nitro-2-pentanone (**1a**),[15] 2-chloro-5-nitropentane (**1b**),[16] and 2-(2-nitroethyl)cyclohexanone (**1c**)[17] were prepared by literature procedures. Methylenecyclopropane (**3a**) was purchased from Fluka. 1-Methylene-2-phenylcyclopropane (**3b**) and 7-methylenenorcarane (**3c**) were prepared by literature procedures.[18]

(9) Jefford, C. W.; Johncock, W. *Helv. Chem. Acta* **1983**, *66*, 2666–2671.

(10) X-ray studies confirming the structural assignment will be published separately.

(11) (a) Overman, L. E.; Freerks, R. L. *J. Org. Chem.* **1981**, *46*, 2833–2835. (b) Hart, D. J. *J Org. Chem.* **1981**, *46*, 367–373.

(12) PC-MODEL program by Serena Software.

(13) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1971**, 383–386.

(14) Belle, C.; Guarna, A.; Cardelli, A. *Tetrahedron Lett.* **1991**, *32*, 6395–6398.

(15) Shechter, H.; Ley, D. E.; Zeldin, L. *J. Am. Chem. Soc.* **1952**, *74*, 3664–3668.

(16) Korsakova, I. S.; Ivanov, A. I.; Sadikov, R. A.; *Izv. Uyssh. Uchlebn. Zaved., Khim. Khim. Teknol.* **1974**, *17*, 1174–1177; *Chem. Abstr.* **1975**, *82*, 3710k.

(17) Trave, R.; Bianchetti, G. *Atti Accad. Nazl. Lincei Rend.* **1960**, *28*, 814–823. *Chem. Abstr.* **1962**, *56*, 339c.

Isoxazoline-5-spirocyclopropanes 4a–h. General Procedure. Methylenecyclopropane (1.2–2.5 equiv) was transferred into a 0.25 M solution of nitro compound **1a–c** (1 equiv) in anhydrous Et_2O at –60 °C containing phenyl isocyanate (2 equiv) and anhydrous NEt_3 (0.1–0.2 equiv). The mixture was left at 0 °C for 1 h and then at rt for 60 h. The reaction mixture was filtered, the clear solution concentrated in vacuo, and the residue chromatographed by flash column chromatography to give the isoxazoline-5-spirocyclopropanes **4a–h**.

6-(3-Oxobutyl)-4-oxa-5-azaspiro[2.4]hept-5-ene (4a). 1a (2.4 g, 18.5 mmol), **3a** (1.9 g, 35.2 mmol); eluent AcOEt/light petroleum ether (1:1); **4a** (1.98 g, 63%).

4a: colorless solid; mp 35–36 °C (light petroleum ether); R_f 0.35; MS m/z (rel intensity) 167 (M^+, 12), 43 (100); ^{13}C-NMR δ 206.4 (s, C=O), 158.2 (s, C-6), 64.6 (s, C-3), 42.3 (t, C-7), 38.8 (t), 29.5 (t), 22.0 (q), 11.1 (t, 2 C, C-1 and C-2); ^{1}H-NMR δ 2.97 (s, 2 H), 2.81 (t, J = 7.0 Hz, 2 H), 2.58 (t, J = 7.0 Hz, 2 H), 2.17 (s, 3 H), 1.08 (m, 2 H), 0.68 (m, 2 H); IR ($CDCl_3$) 1723 cm^{-1}. Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.88; H, 7.99; N, 8.13.

The 4-spiro regioisomer (5%) was detected by ^{1}H-NMR and MS analysis of the crude reaction mixture: MS m/z (rel intensity) 167 (M^+, 14), 43 (100); ^{1}H-NMR δ 4.23 (s, 2 H), 2.88 (t, J = 7.0 Hz, 2 H), 2.58 (t, J = 7.0 Hz, 2 H), 1.10 (m, 2 H), 0.90 (m, 2 H).

6-(3-Oxobutyl)-1-phenyl-4-oxa-5-azaspiro[2.4]hept-5-ene (4b). 1a (1 g, 7.63 mmol), **3b** (1.19 g, 9.16 mmol); eluent AcOEt/light petroleum ether (1:2); **4b** (0.95 g, 51%), 4-spiro regioisomer (5 mg, 0.3%).

4b:[19] white solid, mp 54–55 °C; R_f 0.32; ^{13}C-NMR δ 206.1 (s, C=O), 157.9 (s, C-6), 136.7 (s), 128.1 (d, 2 C), 127.0 (d, 2 C), 125.9 (d), 69.9 (s, C-3), 38.7 (t, C-7), 38.4 (t), 29.4 (t), 27.2 (q), 21.9 (d, C-1), 15.9 (t, C-2); ^{1}H-NMR δ 7.35–7.15 (m, 3 H), 7.00 (m, 2 H), 2.81 and 2.64 (AB system, J = 17.8 Hz, 2 H), 2.75 (m, 2 H), 2.55–2.45 (m, 3 H), 2.14 (s, 3 H), 1.65 (dd, J = 11.0, 7.0 Hz, 1 H), 1.18 (t, J = 7.0 Hz, 1 H); IR ($CDCl_3$) 1715 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.83; H, 7.22; N, 5.46.

4-Spiro regioisomer: R_f 0.2; ^{1}H-NMR δ 7.35–7.20 (m, 3 H), 7.03 (d, J = 6.6 Hz, 2 H), 4.11 and 3.87 (AB system, J = 8.0 Hz, 2 H), 2.90 (t, J = 6.8 Hz, 2 H), 2.59 (dd, J = 9.3, 7.0 Hz, 1 H), 2.24 (dt, J = 3.1, 6.9 Hz, 2 H), 2.20 (s, 3 H), 1.63 (dd, J = 9.3, 6.2 Hz, 1 H), 1.32 (dd, J = 7.0, 6.2 Hz, 1 H).

3-(3-Oxobutyl)spiro[bicyclo[4.1.0]heptane-7,5′-(4′*H*)-isoxazole] (4c). 1a (1 g, 7.63 mmol), **3c** (0.99 g, 9.16 mmol); eluent $CHCl_3$/MeOH (40:1); **4c** (0.714 g, 42%).

4c: white solid; mp 37–38 °C; R_f 0.35; MS m/z (rel intensity) 221 (M^+, 10), 43 (100); ^{13}C-NMR δ 206.4 (s, C=O), 157.4 (s, C-6), 71.0 (s, C-3), 39.0 (t), 35.1 (t, C-7), 29.7 (t), 22.2 (q), 20.8 (t), 17.8 (t), 15.8 (d, 2C, C-1 and C-2); ^{1}H-NMR δ 2.83 (s, 2 H), 2.82 (t, J = 6.7 Hz, 2 H), 2.59 (t, J = 6.7 Hz, 2 H), 2.18 (s, 3 H), 1.80 (m, 2 H), 1.36 (m, 2 H), 1.32 (m, 2 H), 1.16 (m, 2 H), 1.00 (m, 2 H); IR ($CDCl_3$) 1714 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.39; H, 8.80; N, 6.23.

6-[(2-Oxocyclohexyl)methyl]-4-oxa-5-azaspiro[2.4]hept-5-ene (4d). 1c (5 g, 29.2 mmol), **3a** (4 g, 74 mmol); eluent AcOEt/light petroleum ether (1:2); **4d** (4.375 g, 72%).

4d: colorless solid; mp 45–47 °C; R_f 0.42; MS m/z (rel intensity) 207 (M^+, 67), 55 (100); ^{13}C-NMR δ 211.1 (s, C=O), 158.1 (s, C-6), 64.6 (s, C-3), 47.9 (d), 42.8 (t, C-7), 41.7 (t), 34.0 (t), 27.9 (t), 27.7 (t), 24.9 (t), 11.4 (t, C-1 or C-2), 11.2 (t, C-1 or C-2); ^{1}H-NMR δ 3.03 and 2.94 (AB system, J = 17.0 Hz, 2 H), 2.82 (m, 1 H), 2.76 (m, 1 H), 2.39–2.25 (m, 3 H), 2.10 (m, 1 H), 1.87 (m, 1 H), 1.67 (m, 2 H), 1.39 (m, 2 H), 1.09 (m, 2 H), 0.68 (m, 2 H); IR ($CDCl_3$) 1715 cm^{-1}. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.67. Found: C, 69.83; H, 8.38; N, 6.65.

The 4-spiro regioisomer (5%) was detected by ^{1}H-NMR and MS analysis of the crude reaction mixture: MS m/z (rel intensity) 207 (M^+, 25), 41 (100); ^{1}H-NMR δ 4.23 (s, 2 H).

6-[(3-Oxocyclohexyl)methyl]-1-phenyl-4-oxa-5-azaspiro-[2.4]hept-5-ene (4e). 1c (0.95 g, 5.55 mmol), **3b** (0.91 g, 7.02 mmol); eluent AcOEt/light petroleum ether (30:70); **4e** (0.642 g, 41%), 1:1 mixture of two diastereoisomers.

4e:[19] oil; R_f 0.46; ^{13}C-NMR δ 210.8 and 210.7 (s, C=O), 157.9 (s, C-6), 136.8 (s), 128.2 (d, 2 C), 127.2 and 127.1 (d, 2 C), 126.0 (d), 69.9 and 69.8 (s, C-3), 47.8 and 47.6 (d), 38.8 and 38.6 (t, C-7), 33.7 (t), 27.7 (t), 27.6 (t), 27.4 (t), 24.8 (d, C-1), 15.8 and 15.6 (t, C-2); ^{1}H-NMR δ 7.35–7.10 (m, 3 H), 7.00 (m, 2 H), 2.88 (d, J = 17.7 Hz, 1 H), 2.80–2.48 (m, 3 H), 2.63 (d, J = 17.7 Hz, 1 H), 2.42–2.11 (m, 4 H), 2.05 (m, 1 H), 1.82 (m, 1 H), 1.67 (dd, J = 10.7, 7.0 Hz, 1 H), 1.74–1.50 (m, 2 H), 1.32 (m, 1 H), 1.19 (t, J = 7.0 Hz, 1 H); IR (neat) 1712 cm^{-1}. Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47; N, 4.94. Found: C, 75.94; H, 7.47; N, 4.58.

6-(3-Chlorobutyl)-4-oxa-5-azaspiro[2.4]hept-5-ene (4f). 1b (5.3 g, 35 mmol), **3a** (4 g, 74 mmol); eluent CH_2Cl_2/light petroleum ether (5:2); **4f** (4.02 g, 62%).

4f: oil; R_f 0.42; MS m/z (rel intensity) 187 (M^+, 3), 42 (100); ^{13}C-NMR δ 158.3 (s, C-6), 64.5 (s, C-3), 57.5 (d, CCl), 42.1 (t, C-7), 36.0 (t), 25.4 (t), 24.9 (q), 11.2 (t, 2C, C-1 and C-2); ^{1}H-NMR δ 4.10 (ddq, J = 9.0, 4.0, 6.5 Hz, 1 H), 2.98 (s, 2 H), 2.62–2.41 (m, 2 H), 2.04 (m, 1 H), 1.97 (m, 1 H), 1.52 (d, J = 6.5 Hz, 3 H), 1.10 (m, 2 H), 0.70 (m, 2 H); IR (neat) 3080, 1610 cm^{-1}. Anal. Calcd for $C_9H_{14}ClNO$: C, 57.60; H, 7.52; N, 7.46. Found: C, 57.92; H, 7.91; N, 7.48.

By ^{1}H-NMR and MS analysis of the crude reaction mixture a small amount (5%) of the 4-spiro regioisomer was detected: MS m/z (rel intensity) 187 (M^+, 55), 83 (100); ^{1}H-NMR δ 4.24 (s, 2 H).

6-(3-Chlorobutyl)-1-phenyl-4-oxa-5-azaspiro[2.4]hept-5-ene (4g). 1b (1 g, 6.62 mmol), **3b** (1.03 g, 7.95 mmol); eluent AcOEt/light petroleum ether (1:5); **4g** (1.19 g, 68%), 1:1 mixture of two diastereoisomers.

4g:[19] oil; R_f 0.46; ^{13}C-NMR δ 158.0 (s, C-6), 136.8 (s), 128.2 (d, 2 C), 127.1 (d, 2 C), 126.0 (d), 69.9 (s, C-3), 57.4 (d, CCl), 38.3 (t, C-7), 35.9 (t), 27.3 (t), 25.3 (q), 24.9 (d, C-1), 15.9 (t, C-2); ^{1}H-NMR δ 7.35–7.15 (m, 3 H), 7.03 (d, J = 6.9 Hz, 2 H), 4.05 (m, 1 H), 2.82 and 2.65 (AB system, J = 17.7 Hz, 2 H), 2.60–2.40 (m, 3 H), 2.05–1.80 (m, 2 H), 1.70 (m, 1 H), 1.50 and 1.49 (d, J = 6.6 Hz, 3 H), 1.21 (m, 1 H); IR (neat) 3062, 3028, 1604 cm^{-1}. Anal. Calcd for $C_{15}H_{18}ClNO$: C, 68.31; H, 6.88; N, 5.31. Found: C, 67.89; H, 6.95; N, 5.03.

3′-(3-Chlorobutyl)spiro[bicyclo[4.1.0]heptane-7,5′-(4′*H*)-isoxazole] (4h). 1b (1 g, 6.6 mmol), **3c** (0.86 g, 7.95 mmol); eluent $CHCl_3$/hexane (5:2); **4h** (0.845 g, 53%).

4h: colorless solid; mp 69–70 °C; R_f 0.38; MS m/z (rel intensity) 241 (M^+, 1), 42 (100); ^{13}C-NMR δ 157.5 (s, C-6), 70.9 (s, C-3), 57.7 (d, CCl), 36.2 (t), 35.0 (t, C-7), 25.7 (t), 25.1 (q), 21.0 (t, 2 C), 18.0 (t, 2 C), 16.0 (d, 2 C, C-1 and C-2); ^{1}H-NMR δ 4.12 (m, 1 H), 2.83 (s, 2 H), 2.55 (m, 2 H), 2.10 (m, 1 H), 1.99 (m, 1 H), 1.90–1.75 (m, 2 H), 1.54 (d, J = 6.5 Hz, 3 H), 1.37 (m, 2 H), 1.34 (m, 2 H), 1.20 (m, 2 H), 1.00 (m, 2 H); IR ($CDCl_3$) 1603 cm^{-1}. Anal. Calcd for $C_{13}H_{20}ClNO$: C, 64.59; H, 8.34; N, 5.79. Found: C, 64.66; H, 8.34; N, 5.60.

Rearrangement of Isoxazoline-5-spirocyclopropanes 4a–h. General Procedure. Solutions of isoxazolines **4a–e** (0.05 M in anhydrous mesitylene) or isoxazolines **4f–h** (0.05 M in anhydrous DMF containing 1 equiv of K_2CO_3) were refluxed for 0.5–2.5 h. The reactions were monitored by GLC and TLC. The solvent was removed under vacuum, and the oily residue was chromatographed by flash column chromatography.

3-Methyl-5,6-dihydro-7(8*H*)-indolizinone (5a). 4a (1.2 g, 7.18 mmol); eluent CH_2Cl_2; **4a** (0.34 g, 32%).

5a: yellow solid; mp 68–69 °C; R_f 0.38; MS m/z (rel intensity) 149 (M^+, 66), 120 (100); ^{13}C-NMR δ 205.8 (s, C-7), 126.6 (s, C-3), 123.6 (s, C-8a), 106.1 (d, C-2), 103.9 (d, C-1), 39.2 (t, C-8), 39.0 (t, 2C, C-5 and C-6), 11.4 (q, CH_3); ^{1}H-NMR δ 5.86 (dq, J = 3.3, 0.7 Hz, 1 H), 5.84 (dt, J = 3.3, 0.8 Hz, 1 H), 4.1 (t, J = 6.3 Hz, 2 H), 3.64 (d, J = 0.8 Hz, 2 H), 2.72 (t, J = 6.3 Hz, 2 H), 2.23 (d, J = 0.7 Hz, 3 H); IR ($CDCl_3$) 1725 cm^{-1}. Anal. Calcd for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.38. Found: C, 72.23; H, 7.34; N, 9.28.

3-Methyl-5-phenyl-5,6-dihydro-7(8*H*)-indolizinone (5b). 4b (0.5 g, 2.06 mmol); eluent CH_2Cl_2; **5b** (0.298 g, 64%), **8b** (0.036 g, 8%).

5b: yellow solid; mp 72–73 °C; R_f 0.47; MS m/z (rel intensity) 225 (M^+, 100), 104 (97), 94 (97); ^{13}C-NMR δ 205.0 (s, C-7), 140.2 (s), 128.9 (d, 2 C), 127.6 (d), 127.2 (s, C-3), 125.1 (d, 2 C), 124.0 (s, C-8a), 107.1 (d, C-2), 104.7 (d, C-1), 54.3 (d, C-5), 46.8 (t, C-6), 38.9 (t, C-8), 11.4 (q, CH_3); ^{1}H-NMR δ 7.40–7.20 (m, 3 H), 6.79

(18) Arora, S.; Binger, P. *Synthesis* **1974**, 801–803.

(19) The mass spectrum of the compound is not reported here since the compound rearranged completely to the corresponding indolizinone during the GC–MS analysis.

(d, J = 7.0 Hz, 2 H), 5.99 and 5.97 (AB system, J = 3.4 Hz, 2 H), 5.66 (dd, J = 6.5, 1.9 Hz, 1 H), 3.74 and 3.49 (AB system, J = 21.5 Hz, 2 H), 3.23 (dd, J = 15.8, 6.5 Hz, 1 H), 3.07 (dd, J = 15.8, 1.9 Hz, 1 H), 2.15 (s, 3 H); IR ($CDCl_3$) 1725 cm^{-1}. Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.36; H, 6.73; N, 6.04.

8b: R_f 0.33; ^{1}H-NMR δ 8.38 (s, 1 H), 7.65 (d, J = 16.0 Hz, 1 H), 7.56–7.35 (m, 5 H), 6.80 (d, J = 16.0 Hz, 1 H), 5.93 (m, 1 H), 5.80 (m, 1 H), 3.93 (s, 2 H), 2.26 (s, 3 H).

1-Methyl-5a,6,7,8,9,9a-hexahydro-5(4*H*)-pyrrolo[1,2-*a*]quinolinone (5c). **4c** (0.221 g, 1 mmol); eluent AcOEt/light petroleum ether (1:10); **5c** (0.095 g, 47%), **8c** (0.052 g, 26%).

5c: colorless solid; mp 78–79 °C; R_f 0.35; MS m/z (rel intensity) 203 (M^+, 99), 94 (100); ^{13}C-NMR δ 207.5 (s, C-7), 126.1 (s, C-3), 123.1 (s, C-8a), 106.3 (d, C-2), 103.7 (d, C-1), 53.8 (d, C-5), 48.6 (d, C-6), 38.2 (t, C-8), 32.5 (t), 24.8 (t, 2 C), 21.2 (t), 11.4 (q, CH_3); ^{1}H-NMR δ 5.86 and 5.80 (AB system, J = 3.1 Hz, 2 H), 4.23 (ddd, J = 12.0, 5.6, 4.0, 1 H), 3.71 and 3.58 (AB system, J = 22.2 Hz, 2 H), 2.83 (br s, 1 H), 2.53 (m, 1 H), 2.26 (s, 3 H), 1.97 (m, 1 H), 1.78 (m, 1 H), 1.55 (m, 1 H), 1.45–1.20 (m, 4 H); IR ($CDCl_3$) 1721 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 77.08; H, 8.75; N, 6.53.

8c: colorless solid; mp 48–49 °C; R_f 0.2; MS m/z (rel intensity) 203 (M^+, 14), 94 (100); ^{13}C-NMR δ 199.9 (s), 141.6 (d), 138.6 (s), 127.5 (s), 123.2 (s), 106.7 (d), 105.5 (d), 35.3 (t), 26.1 (t), 23.0 (t), 21.7 (t) 21.3 (t), 12.9 (q); ^{1}H-NMR δ 8.40 (br s, 1 H), 7.05 (br s, 1 H), 5.80 and 5.74 (AB system, J = 2.5 Hz, 2 H), 3.89 (s, 2 H), 2.30–2.15 (m, 4 H), 2.22 (s, 3 H), 1.65–1.50 (m, 4 H); IR ($CDCl_3$) 3455, 1654 cm^{-1}.

1,2,3,4,6,7-Hexahydro-8(9*H*)-pyrido[1,2-*a*]indolone (5d). **4d** (1.045 g, 5.05 mmol); eluent CH_2Cl_2; **5d** (0.347 g, 36%).

5d: colorless solid; mp 61–63 °C; R_f 0.28; MS m/z (rel intensity) 189 (M^+, 42), 133 (100); ^{13}C-NMR δ 206.2 (s, C-7), 126.6 (s, C-3), 123.5 (s, C-8a), 117.5 (s, C-2), 103.7 (d, C-1), 39.3 (t, C-8), 39.1 (t, C-5), 39.0 (t, C-6), 23.5 (t), 23.1 (t), 22.8 (t), 21.2 (t); ^{1}H-NMR δ 5.74 (s, 1 H), 4.05 (t, J = 6.3 Hz, 2 H), 3.64 (s, 2 H), 2.72 (t, J = 6.3 Hz, 2 H), 2.50 (m, 4 H), 1.83 (m, 2 H), 1.74 (m, 2 H); IR ($CDCl_3$) 1720 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.55; H, 8.04; N, 7.38.

1,2,3,4,6,7-Hexahydro-6-phenyl-8(9*H*)-pyrido[1,2-*a*]indolone (5e). **4e** (0.283 g, 1 mmol); eluent $CHCl_3$/light petroleum ether (5:1); **5e** (0.137 g, 52%).

5e: colorless solid; mp 140–141 °C; R_f 0.4; MS m/z (rel intensity) 265 (M^+, 79), 209 (100); ^{13}C-NMR δ 205.2 (s, C-7), 140.7 (s), 128.8 (d, 2C), 127.5 (d), 126.5 (s, C-3), 125.1 (d, 2 C), 123.1 (s, C-8a), 118.1 (s, C-2), 104.2 (d, C-1), 54.0 (d, C-5), 46.9 (t, C-6), 38.9 (t, C-8), 23.5 (t), 23.1 (t), 23.0 (t), 21.1 (t); ^{1}H-NMR δ 7.35–7.25 (m, 3 H), 6.80 (m, 2 H), 5.84 (s, 1 H), 5.57 (dd, J = 6.5, 1.9 Hz, 1 H), 3.72 and 3.50 (AB system, J = 21.5 Hz, 2 H), 3.20 (dd, J = 15.6, 6.5 Hz, 1 H), 3.00 (dd, J = 15.6, 1.9 Hz, 1 H), 2.55–2.45 (m, 3 H), 2.25 (m, 1 H), 1.80–1.65 (m, 4 H); IR ($CDCl_3$) 1721 cm^{-1}. Anal. Calcd for $C_{18}H_{19}NO$: C, 81.48; H, 7.22; N, 5.28. Found: C, 81.15; H, 7.03; N, 5.20.

Compound **8e** (17%) was detected by ^{1}H-NMR analysis of the crude reaction mixture: ^{1}H-NMR δ 7.62 (d, J = 16.0 Hz, 1 H), 6.80 (d, J = 16.0 Hz, 1 H), 5.80 (s, 1 H), 3.90 (s, 2 H).

3-Methyl-2,3,5,6-tetrahydro-7(1*H*)-indolizinone (5f). **4f** (2.3 g, 12.3 mmol); eluent CH_2Cl_2/MeOH (10:1); **5f** (1.21 g, 65%), and 0.66 g of a mixture of **7f** (15%) and **8f** (17%). Compound **7f** was converted to **8f** by heating in DMF with 1 equiv of K_2CO_3 for 1 h.

5f:[20] oil; R_f 0.43; MS m/z (rel intensity) 151 (M^+, 60), 136 (100); ^{13}C-NMR δ 190.6 (s, C-7), 169.0 (s, C-8a), 93.0 (d, C-8), 59.4 (d, C-3), 42.5 (t, C-5), 34.8 (t, C-6), 30.0 (t, C-1), 29.3 (t, C-2), 18.3 (q, CH_3); ^{1}H-NMR δ 4.94 (s, 1 H), 3.54 (sextet, J = 6.6 Hz, 1 H), 3.50 (dt, J = 12.0, 6.6 Hz, 1 H), 3.24 (dt, J = 6.6, 12.0 Hz, 1 H), 2.68 (ddd, J = 17.4, 9.0, 4.8 Hz, 1 H), 2.57 (dt, J = 17.4, 8.7 Hz, 1 H), 2.50 (ddd, J = 16.5, 11.7, 6.6 Hz, 1 H), 2.41 (dt, J = 16.5, 6.6 Hz, 1 H), 2.19 (dddd, J = 12.6, 8.8, 6.9, 4.9 Hz, 1 H), 1.61 (dddd, J = 12.6, 9.0, 8.1, 6.9 Hz, 1 H), 1.23 (d, J = 6.3 Hz, 3 H); IR (neat) 1620 cm^{-1}.

8f: oil; R_f 0.7; MS m/z (rel intensity) 151 (M^+, 74), 150 (60), 124 (100); ^{13}C-NMR δ 185.9 (s), 168.4 (s), 137.7 (d), 122.1 (t), 89.2 (d), 55.7 (d), 32.3 (t), 29.3 (t), 21.2 (q); ^{1}H-NMR δ 10.20 (br s, 1 H), 6.30 (dd, J = 17.3, 10.2 Hz, 1 H), 6.09 (dd, J = 17.3, 2.0 Hz, 1 H), 5.43 (dd, J = 10.2, 2.0 Hz, 1 H), 5.14 (s, 1 H), 3.97 (m, 1 H), 2.65 (m, 2 H), 2.15 (m, 1 H), 1.55 (m, 1 H), 1.24 (d, J = 6.3 Hz, 3 H); IR (neat) 3283 (br), 1597, 1527 cm^{-1}.

7f: oil; R_f 0.7; MS m/z (rel inetensity) 124 ($M^+ - CH_3CHCl^\bullet$, 93), 55 (100); ^{13}C-NMR δ 187.8 (s), 165.8 (s), 137.7 (d), 123.3 (t), 94.4 (d); 57.3 (d), 38.4 (t), 33.5 (t), 25.1 (q); ^{1}H-NMR δ 6.30 (dd, J = 17.3, 10.2 Hz, 1 H), 6.06 (dd, J = 17.3, 1.9 Hz, 1 H), 5.46 (dd, J = 10.2, 1.9 Hz, 1 H), 5.14 (s, 1 H), 3.95 (m, 1 H), 2.40 (m, 1 H), 2.25 (m, 1 H), 1.91 (m, 2 H), 1.48 (d, J = 6.5 Hz, 3 H).

3-Methyl-5-phenyl-2,3,5,6-tetrahydro-7(1*H*)-indolizinone (5g). **4g** (0.5 g, 1.9 mmol); eluent acetone; *trans*-**5g** (0.112 g, 26%), *cis*-**5g**, (0.095 g, 22%).

***trans*-5g**: colorless solid; mp 114–115 °C; R_f 0.75; MS m/z (rel intensity) 227 (M^+, 53), 108 (100); ^{13}C-NMR δ 189.4 (s, C-7), 168.0 (s, C-8a), 138.9 (s), 128.8 (d, 2 C), 127.9 (d), 126.6 (d, 2 C), 93.3 (d, C-8), 57.5 (d, C-5), 56.9 (d, C-3), 43.4 (t, C-6), 30.3 (t, C-1), 28.5 (t, C-2), 17.5 (q, CH_3); ^{1}H-NMR δ 7.35–7.15 (m, 5 H), 5.03 (s, 1 H), 4.63 (t, J = 7.9 Hz, 1 H), 3.59 (dquintet, J = 4.4, 6.3 Hz, 1 H), 2.85–2.65 (m, 2 H), 2.79 (dd, J = 16.4, 7.0, Hz, 1 H), 2.61 (dd, J = 16.4, 8.8 Hz, 1 H), 2.15 (dq, J = 12.7, 7.8 Hz, 1 H), 1.63 (dddd, J = 12.7, 8.0, 5.6, 4.4 Hz, 1 H), 1.00 (d, J = 6.4 Hz, 3 H); IR ($CDCl_3$) 1630, 1568 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.52; H, 7.82; N, 6.28.

***cis*-5g**: colorless solid; mp 85–86 °C; R_f 0.63; MS m/z (rel intensity) 227 (M^+, 59), 108 (100); ^{13}C-NMR δ 189.9 (s, C-7), 168.6 (s, C-8a), 140.7 (s), 128.5 (d, 2 C), 127.8 (d), 126.6 (d, 2 C), 92.8 (d, C-8), 60.5 (d, C-5), 58.6 (d, C-3), 43.0 (t, C-6), 30.4 (t, C-1), 30.2 (t, C-2), 20.2 (q, CH_3); ^{1}H-NMR δ 7.30 (s, 5 H), 5.03 (s, 1 H), 4.61 (t, J = 6.8 Hz, 1 H), 3.80 (sextet, J = 6.5 Hz, 1 H), 2.92 (dd, J = 16.3, 7.5 Hz, 1 H), 2.89 (ddd, J = 17.0, 8.8, 6.7 Hz, 1 H), 2.66 (ddd, J = 17.0, 9.1, 7.1 Hz, 1 H), 2.59 (dd, J = 16.3, 6.2 Hz, 1 H), 2.25 (dddd, J = 12.6, 8.8, 7.3, 6.4 Hz, 1 H), 1.65 (ddt, J = 12.6, 9.1, 6.5 Hz, 1 H), 0.81 (d, J = 6.4 Hz, 3 H); IR ($CDCl_3$) 1624, 1567 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.33; H, 7.69; N, 6.24.

By ^{1}H-NMR analysis of the crude reaction mixture, enaminones **7g** (3%) and **8g** (5%) were detected.

7g: ^{1}H-NMR δ 4.00 (m, 1 H), 1.42 (d, J = 6.5 Hz, 3 H).

8g: ^{1}H-NMR δ 7.5 (m, 1 H), 6.68 (d, J = 18.0 Hz, 1 H), 5.25 (s, 1 H), 1.28 (d, J = 6.5 Hz, 3 H).

1-Methyl-2,3,5a,6,7,8,9,9a-octahydro-5(1*H*)-pyrrolo[1,2-*a*]quinolinone (5h). **4h** (0.241 g, 1 mmol); eluent CH_2Cl_2/MeOH (20:1); **5h**, 1:1.5 mixture of cis and trans isomers (*Rf* 0.28, 0.123 g, 60%), and **7h** + **8h** (1:2 mixture, R_f 0.5, 0.080 g). Further chromatographic separation (eluent AcOEt) of the *cis*–*trans*-**5h** mixture gave pure *trans*-**5h** (R_f 0.42, 0.065 g, 32%) and *cis*-**5h** (R_f 0.38, 0.04 g, 20%).

***trans*-5h**:[20] oil; MS m/z (rel intensity) 205 (M^+, 93), 150 (100); ^{13}C-NMR δ 192.8 (s, C-7), 166.6 (s, C-8a), 91.9 (d, C-8), 56.0 (d, C-3), 53.6 (d, C-5), 43.8 (d, C-6), 30.2 (t, C-1), 29.9 (t, C-2), 24.6 (t), 23.4 (t), 23.0 (t, 2 C), 18.2 (q, CH_3); ^{1}H-NMR δ 4.95 (s, 1 H), 3.78 (sextet, J = 6.3 Hz, 1 H), 3.59 (ddd, J = 8.6, 5.5, 3.4 Hz, 1 H), 2.68 (ddd, J = 16.2, 8.6, 6.5 Hz, 1 H), 2.55 (ddd, J = 16.2, 8.8, 6.6 Hz, 1 H), 2.55–2.45 (m, 1 H), 2.25-2.10 (m, 1 H), 2.14 (ddt, J = 12.5, 8.9, 6.7 Hz, 1 H), 1.80–1.10 (m, 8 H), 1.19 (d, J = 6.3 Hz, 3 H); IR (neat) 1567 cm^{-1}.

***cis*-5h**:[20] oil; MS m/z (rel intensity) 205 (M^+, 100), 150 (98); ^{13}C-NMR δ 191.4 (s, C-7), 165.4 (s, C-8a), 91.1 (d, C-8), 59.0 (d, C-3), 55.2 (d, C-5), 43.7 (d, C-6), 30.1 (t, 2C, C-1 and C-2), 25.9 (t), 24.7 (t), 24.3 (t), 22.1 (t), 20.1 (q, CH_3); ^{1}H-NMR δ 4.92 (s, 1 H), 3.87 (sextet, J = 6.5 Hz, 1 H), 3.53 (ddd, J = 10.6, 6.1, 4.1 Hz, 1 H), 2.75–2.65 (m, 1 H), 2.70 (ddd, J = 17.0, 9.4, 6.6 Hz, 1 H), 2.54 (ddd, J = 17.0, 8.8, 6.5 Hz, 1 H), 2.45–2.35 (m, 1 H), 2.21 (dddd, J = 12.7, 8.6, 7.5, 6.6 Hz, 1 H), 1.92 (m, 1 H), 1.70 (m, 1 H), 1.58 (ddt, J = 12.5, 9.5, 6.1 Hz, 1 H), 1.57–1.20 (m, 5 H), 1.28 (d, J = 6.5 Hz, 3 H); IR (neat) 1560 cm^{-1}.

7h: MS m/z (rel intensity) 205 (M^+ - HCl, 100), 176 (75); ^{13}C-NMR δ 191.5 (s), 164.0 (s), 139.3 (s), 132.9 (d), 90.6 (d), 59.5 (d), 38.6 (t), 33.8 (t), 25.6 (t), 25.2 (q), 23.9 (t), 22.2 (t), 21.7 (t); ^{1}H-NMR δ 6.64 (m, 1 H), 5.38 (s, 1 H), 3.95 (m, 1 H), 1.51 (d, J = 6.5 Hz, 3 H).

8h: MS m/z (rel intensity) 205 (M^+, 69), 176 (100); ^{13}C-NMR δ 189.5 (s), 167.2 (s), 139.0 (s), 131.7 (d), 85.2 (d), 55.4 (d), 32.5 (t), 29.5 (t), 25.6 (t), 24.1 (t), 22.4 (t), 21.8 (t), 21.4 (q); ^{1}H-NMR

(20) The compound retains water, and attempts to remove the water with strong drying agents under vacuum failed.

δ 6.64 (m, 1 H), 5.34 (s, 1 H), 1.23 (d, J = 6.3 Hz, 3 H).

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Registry No. **1a**, 22020-87-7; **1b**, 141345-97-3; **1c**, 141345-98-4; **3a**, 6142-73-0; **3b**, 124571-36-4; **3c**, 54211-14-2; **4a**, 141345-99-5; **4a** 4-spiro regioisomer, 141346-01-2; **4b**, 141346-00-1; **4b** 4-spiro regioisomer, 141346-02-3; **4c**, 141346-03-4; **4d**, 141346-04-5; **4d** 4-spiro regioisomer, 141346-05-6; **4e** (isomer 1), 141346-06-7; **4e** (isomer 2), 141434-12-0; **4f**, 141346-07-8; **4f** 4-spiro regioisomer, 141346-08-9; **4g** (isomer 1), 141346-09-0; **4g** (isomer 2), 141434-13-1; **4h**, 141346-10-3; **5a**, 141346-11-4; **5b**, 141346-12-5; **5c**, 141346-13-6; **5d**, 141346-14-7; **5e**, 141346-15-8; **5f**, 141346-16-9; *trans*-**5g**, 141346-17-0; *cis*-**5g**, 141346-18-1; *trans*-**5h**, 141346-19-2; *cis*-**5h**, 141434-14-2; **7f**, 141346-20-5; **7g**, 141346-21-6; **7h**, 141346-22-7; **8b**, 141346-23-8; **8c**, 141346-24-9; **8e**, 141346-25-0; **8f**, 141346-26-1; **8g**, 141346-27-2; **8h**, 141346-28-3.

Supplementary Material Available: ^{1}H- and ^{13}C-NMR spectra for compounds **5f**, *trans*-**5h**, and *cis*-**5h** (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Asymmetric Synthesis. 26.[1] An Expeditious Enantioselective Synthesis of the Defense Alkaloids (−)-Euphococcinine and (−)-Adaline via the *CN*(*R*,*S*) Method

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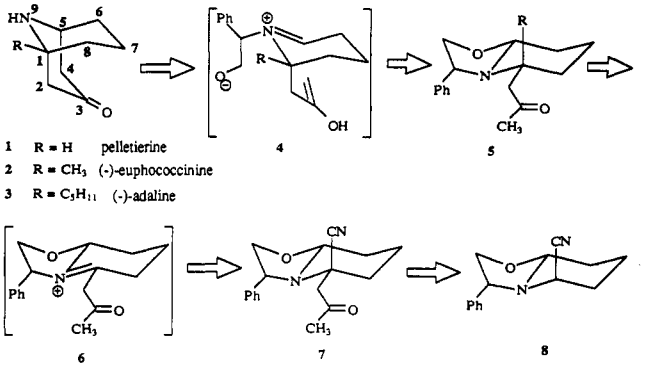
The unnatural enantiomer (−)-euphococcinine (**2**) and the natural enantiomer of (−)-adaline (**3**), two homotropane alkaloids, were each prepared in three steps from chiral (−)-2-cyano-6-oxazolopiperidine synthon **8** by the *CN*(*R*,*S*) method. The key steps of these syntheses are the formation of a chiral quaternary center α to the piperidine nitrogen with complete stereocontrol and a subsequent intramolecular Mannich reaction. The previously unknown absolute configuration of natural (+)-euphococcinine was deduced from the synthesis of its enantiomer (−)-**2**.

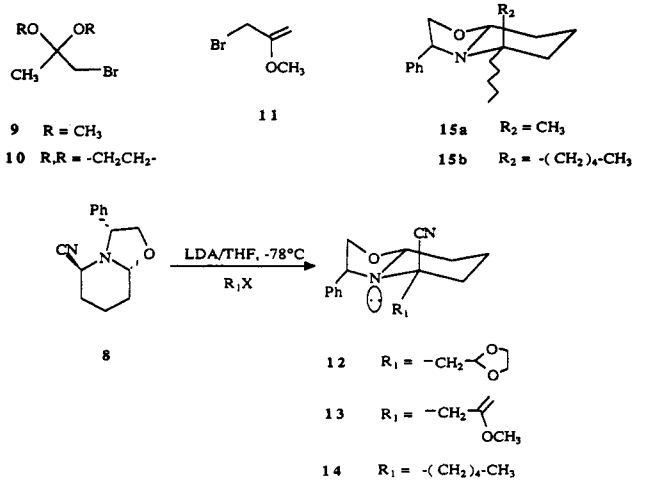
(+)-Euphococcinine (**2**) has been found in both the vegetable and the animal kingdoms. It was first isolated from *Euphorbia atoto*[2] and has also been found in the defense secretion of ladybugs *Cryptolaenus montrouzieri*[3a] and *Epilachna varivestis*.[3b] A pentyl analog, (−)-adaline (**3**), was also isolated from secretion of the ladybugs *Cryptolaenus montrouzieri*[3a] and *Adalia bipunctata*.[4] These alkaloids were found to exhibit repulsive activity against different insects. The absolute configuration of (−)-adaline has been determined to be 1*R*, 5*S*.[5] It is proposed that the absolute configuration of (+)-euphococcinine is 1*S*, 5*R*,[6] but this has yet to be proved.

In this paper we wish to report a new application of the established *CN*(*R*,*S*) method[7] to the enantioselective synthesis of **2** and **3**[6,8] from synthon **8**.[9] As depicted retrosynthetically in Scheme I, the strategy used involved stepwise introduction of an acetone equivalent and an alkyl chain in regio- and stereocontrolled manner. We show here that the Lewis acid TBDMSOTf is a very efficient agent for the selective formation of the appropriate iminium **6** from **7**, allowing formation of the quaternary center.

Scheme I



Scheme II



Results

Although several electrophilic equivalents of the acetonyl

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