hydrogen atoms were introduced at theoretical positions (*d* C-H = 1.00 Å) and assigned an isotropic thermal factor equivalent to that of the bonded carbon atoms, plus 10%. Convergence was reached at $R = 0.080$, $R_w = 0.129$ (with $R_w = \{\Sigma w(F_o - Fc)^2/\Sigma wF_o^2)^{1/2}$ and $w = 1/[\sigma^2(F_o) + 0.004\,901F_o^2]$). No residual was higher than 0.38 eÅ^{-3} in the final difference map.

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Supplementary Material Available: X-ray data for **14b** (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.

Rearrangement of Isoxazoline-5-spiro Derivatives. 8.[1] Selective Formation of Tetrahydropyridones from C,C-Disubstituted Nitrones

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The thermal rearrangement of isoxazolidines **3**, **7**, **9**, **17**, and **19** obtained by 1,3-dipolar cycloaddition of C,C-disubstituted nitrones and methylenecyclopropanes **1** and **6** has been studied. The lack of hydrogen at the C-3 position of the isoxazolidine ring leads selectively to azaheterocyclic ketones, structurally differentiated according to the starting dipoles and dipolarophiles. The process allows the "one-pot" synthesis of valuable perhydro pyridone, indolizinone, and pyrrolo[1,2-*a*]quinolinone ring systems with excellent overall yield and atom economy. A new entry to the functionalized 1-azaspiro[5.5]undecane **22** framework found in alkaloids of the histrionicotoxin family is also presented.

Introduction

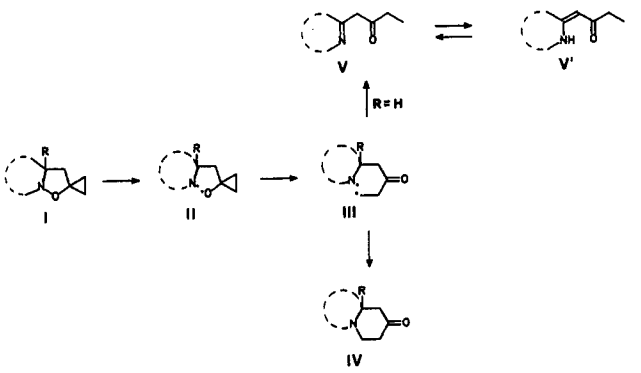
The thermal rearrangement of isoxazolidine-5-spirocyclopropanes has shown high versatility as a new method for the synthesis of azaheterocycles of pyridine, indolizine, and quinolizine type.[2] The method has been recently applied to the formal and total synthesis of alkaloids containing these skeletons.[3,4]

The mechanism proposed[2,5] for the process consists of a thermal homolytic cleavage of the N-O bond of the isoxazolidine **I** (Scheme I) obtained by 1,3-dipolar cycloaddition of a nitrone to methylenecyclopropane; the formed cyclopropyloxy diradical **II** then undergoes a rearrangement to the diradical **III** which cyclizes to the ketone **IV**.

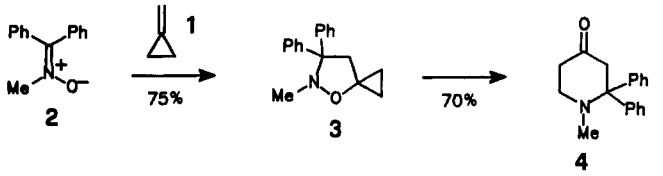
A serious drawback of the process is the possible transfer of the hydrogen α to nitrogen in the diradical **III** (R = H, Scheme I) to give the enaminone compounds **V'**. This side reaction invariably lowers the yield of cyclic ketones. The hydrogen abstraction might occur in an intermolecular fashion and possibly with participation of the solvent, but the intramolecular 1,5-hydrogen shift seems to be the most likely process. This is supported by the formation of enaminones in significant yields even under conditions of flash vacuum thermolysis (FVT).

If the proton on C-3 of isoxazolidine is replaced by a substituent (R ≠ H, Scheme I) this side reaction should be precluded, and cyclic ketones should form in higher yields. In the present study we report on the results obtained with structurally differentiated C-3 (isoxazolidine numbering) substituted isoxazolidines which substantiate our prediction.

Scheme I



Scheme II



Results and Discussion

C,C-Diphenyl-*N*-methylnitrone (**2**) reacted with **1** in a sealed tube to give the isoxazolidine **3** as the sole regioisomer in 75% yield (Scheme II). Upfield chemical shift for the isoxazolidine methylene (δ 3.08 ppm) is diagnostic for the assignment of the structure to **3**. The methylene of the 4-spirocyclopropane regioisomers usually resonate 1 ppm more downfield.[3,4] This high regioselectivity is unprecedented in the case of cycloadditions of nitrones to

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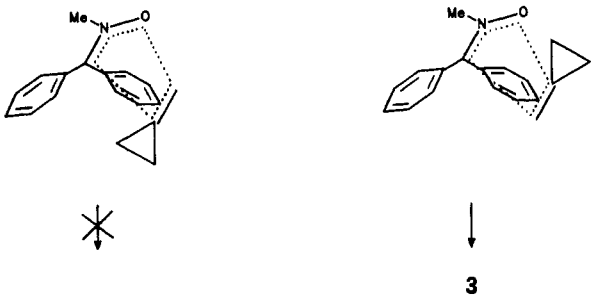
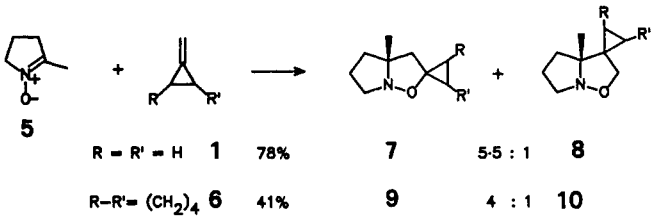


3

Figure 1. Transition-state structures for the cycloaddition leading to 4-spirocyclopropane and 5-spirocyclopropane regioisomers.

Scheme III



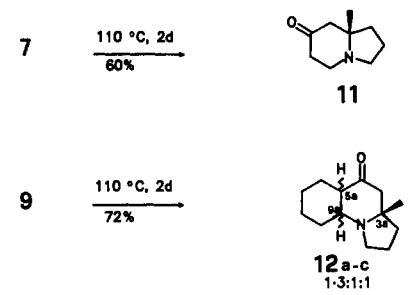
R = R' = H	1	78%	7	5·5 : 1	8
R–R' = $(CH_2)_4$	6	41%	9	4 : 1	10

methylenecyclopropanes,[2-4,6] and can be explained by considering that the transition state leading to **3** is considerably less crowded than the one leading to the 4-spirocyclopropane regioisomer (Figure 1).

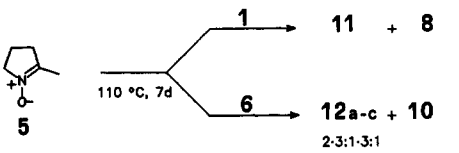
The isoxazolidine **3** gave exclusively the 1-methyl-2,2-diphenyltetrahydropyridin-4-one (**4**) in 70% yield when subjected to heating in refluxing toluene or to FVT conditions (400 °C (10^{-3} mmHg)) (Scheme II). No traces of other open chain isomers were observed in the crude mixture; decomposition products account for the lacking mass.

The cycloaddition of the methyl-substituted pyrroline *N*-oxide **5** to methylenecyclopropane (**1**) and methylenenorcarane (**6**) was also examined. In both cases the regioselectivity of the cycloaddition is lower (5.5:1 and 4:1 regioisomeric ratio for **7**:**8** and **9**:**10** respectively, Scheme III) than that of the nitrone **2**, but higher than that observed with analogous nitrones monosubstituted on carbon, i.e., *C*-phenyl-*N*-methylnitrone or 5,5-dimethylpyrroline *N*-oxide.[2-4] The steric hindrance of the substituent on the nitrone seems, therefore, to be effective in steering the regiochemistry of the cycloaddition as illustrated in Figure 1. In regard to the stereochemistry of isoxazolines **9** and **10**, it is assumed to be controlled by the attack of the nitrone on the convex face of the methylenenorcarane,[7] although it could be only tentatively assigned by NMR spectroscopy. The yields of the cycloadditions to **1** and **6** are rather different (78% and 41%, respectively, Scheme III) but difficult to compare because methylenecyclopropane (**1**) was always added in excess to the reaction mixture via cannula, whereas the more valuable methylenenorcarane (**6**) was used in nearly equimolar ratio. However, the methylenenorcarane (**6**) seems to be more sluggish as a dipolarophile because of steric hindrance, as previously observed.[7] The overall yield of the process was, however, partially balanced in the rearrangement step, since the isoxazolidine **7** gave the volatile indolizidinone **11** in 60% yield by heating for 2 days in refluxing toluene (Scheme IV), whereas the isoxazolidine **9**, under the same conditions, gave the pyrrolo[1,2-*a*]quinolinones **12a–c** in 72% yield. A discussion of the stereochemical outcome

Scheme IV



Scheme V



with respect to **12a–c** is presented below.

In both reactions no traces of open-chain rearrangement products were obvserved, which is a further confirmation of the selectivity conferred to the rearrangement by the substitution on the nitrone.

The lack of the undesired open-chain byproducts, which were usually found to be more abundant by carrying out the rearrangement in condensed phase or even in the cycloaddition step,[2-4] prompted us to carry out the cycloaddition and the rearrangement in "one pot". By heating a mixture of **5** and **1** in a sealed vial at 110 °C for 7 days the ketone **11** was obtained in 63% overall yield in addition to the regioisomer **8**, (13%) (Scheme V). Analogously, by heating a mixture of **5** and **6** in refluxing toluene for 7 days the tricyclic ketones **12a–c** were isolated in 41% yield along with 11% of the 4-spirocyclopropane regioisomer **10** (Scheme V). The convenience of the two-step "one-pot" reaction is evident from the higher yields of **11** and **12** compared to those calculated for the two-step "two-pot" processes (63% vs 47% for **11** and 41% vs 30% for **12**).

The stereochemical outcome of the rearrangement of the isoxazolidine **9** deserves some comments. The isoxazolidine **9** gave rise, in the two-pot process, to a mixture of three stereoisomers **12a–c** in a 1.3:1:1 ratio discerned in the crude mixture only by ^{1}H NMR of methyl group resonances (δ 0.96, 0.76, and 1.07 ppm for **12a**, **12b**, and **12c**, respectively). The three ketones were also obtained in the "one-pot" reaction, but with a different ratio (2.3:1.3:1, respectively). The major isomer **12a** has been tentatively assigned the trans {5a-H}-{9a-H} and cis {3a-methyl}-{5a-H} relationship on the basis of ^{1}H NMR spectra. Bridgehead protons 5a-H and 9a-H, which resonate at δ 0.25–2.10 (m) and δ 2.58 (dt, J = 3.3, 10.5 Hz) ppm, respectively, were assigned by COSY analysis, although their individual assignment remains tentative. Nevertheless, the 10.5-Hz coupling constant of the triplet is in accord with a trans relationship between the two protons. The shielded chemical shift for 9a-H proton α to nitrogen, moreover, indicates an antiperiplanar relationship between the proton and the nitrogen lone pair.[4,8] On the other hand, the ^{13}C chemical shift of the 3a methyl group (δ 20.14 ppm), if compared with that of the isomer **12b** (δ 14.11 ppm), indicates a cis relationship of the methyl group and the nitrogen lone pair in **12a**.

That the decomposition of the isomers **12b** and **12c** is the cause of the enrichment of isomer **12a** seems to be

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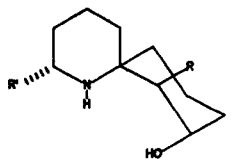
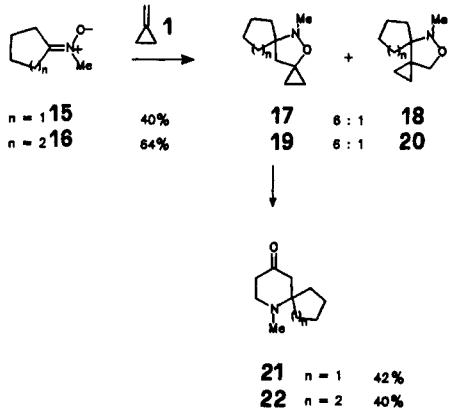


R=C_4H_3 R'=C_5H_5 **13**

R=C_4H_9 R'=C_5H_{11} **14**

Figure 2. Hystrionicotoxin (13) and perhydrohystrionicotoxin (14).

Scheme VI



excluded by the higher yield of rearrangement products in the "one-pot" reaction. On the other hand, the transformation of the isomer **12b** into **12a** was observed in a sample set apart for a long time at low temperature.[9] Several different processes are likely to occur in these molecules which are able to explain an isomerization towards the thermodynamically most stable compound. The enolization of 5a carbon is a possibility in these ketones which provide a strong basic site on the same molecule. But also retro-Mannich or retro-Michael processes can be effective to justify the overall transformation of the isomers **12b-c** into the isomer **12a** observed in one case.[9] The investigation of this equilibration process will be the object of further studies.

The present methodology can be easily applied to the synthesis of azaspiro[5.*n*] systems by simply starting from a nitrone derived from a cyclic ketone. The interesting neurotoxic activity of a family of alkaloids possessing the azaspiro[5.5]undecane skeleton,[10] mainly represented by hystrionicotoxin (13) and its perhydro derivative 14 (Figure 2),[11] prompted us to study the synthesis of the azaspiro-[5.5]undecane skeleton by our method.

Cyclopenta- and cyclohexanone derived nitrones **15** and **16** gave by cycloaddition with 1 regioisomeric mixtures of the isoxazolidines **17**, **18** and **19**, **20**, respectively, with the same ratio (6:1) between the two regioisomers (Scheme VI). The lower yield of the cycloadditions (40% for **15** and 64% for **16**), compared with the previous reaction, can be ascribed to the lower reactivity of the nitrones[12] and to the volatility of the spiroisoxazolidines **17–20**.

When subjected to FVT (400 °C (10^{-3} mmHg)), isoxazolidines **17** and **19** gave, respectively, 6-methyl-6-azaspiro[5.4]decan-9-one (**21**) and 1-methyl-1-azaspiro[5.5]-undecan-4-one (**22**) in 40% yield (Scheme VI). The ketones were the sole rearrangement products isolated after FVT. However, other volatile decomposition products were detected by GC–MS,[13] which accounts for the low yield of the rearrangement. In conclusion, we have demonstrated that the thermal rearrangement of 5-spirocyclopropane isoxazolidines affords only cyclic rearrangement products when two substituents are present on the C-3 (isoxazolidine numbering) of the isoxazolidine ring. The second substituent, moreover, positively influences the regioselectivity of the cycloaddition step, providing an increase in the overall yield of the process. The simple two-step and, practically, "one-pot" method allows the synthesis of valuable substituted monocyclic, bicyclic, and tricyclic azaheterocyclic ketones with a substantial atom economy. From the cyclohexanone-derived nitrone **16** it was possible to obtain the functionalized 1-azaspiro[5.5]-undecane framework which is found in the histrionicotoxin family of alkaloids. Further work aimed to the total synthesis of some representative of this alkaloid family is in progress in our group.

Experimental Section

All the reactions were carried out under inert atmosphere (N_2). R_f values were obtained from TLC analysis with the same solvent ratios reported for column chromatography. NMR spectra ($CDCl_3$ as solvent) were recorded on Varian Gemini (^{1}H, 200 MHz; ^{13}C, 50 MHz): notations s, d, t, q, m, and br designate singlet, doublet, triplet, quartet, multiplet, and broad, respectively. IR spectra were recorded on a Perkin-Elmer 881 spectrophotometer. Mass spectra were recorded at 70 eV by GC inlet on a 5790A-5970A Hewlett-Packard and by direct inlet on a Carlo Erba QMD 1000 instrument. Methylenecyclopropane (1) (commercially available from Aldrich or Fluka) was always added in 3–4-fold excess to the reaction mixture.

Cycloaddition of *C,C*-Diphenyl-*N*-methylnitrone (2) to 1: 5-Methyl-6,6-diphenyl-4-oxa-5-azaspiro[2.5]heptane (3). A solution of *C,C*-diphenyl-*N*-methylnitrone (**2**)[14] (633 mg, 3 mmol) and methylenecyclopropane (**1**) in excess in dry benzene (0.5 mL) was heated in a sealed tube at 80 °C for 2 days. The solvent was evaporated, and the crude reaction mixture was chromatographed on silica gel (eluant, ethyl acetate/*n*-pentane (1:5)) to give **3** (600 mg, 75%).

3. R_f = 0.61. Mp: 103–104 °C (from *n*-pentane). ^{1}H-NMR: δ 7.38–7.15 (m, 10 H), 3.08 (br s, 2 H), 2.43 (s, 3 H), 0.85 (s, 2 H), 0.55 (s, 2 H). ^{13}C-NMR: δ 143.85 s, 143.78 s, 127.73 s (8 C), 127.43 s, 126.42 s, 77.60 s, 62.14 s, 45.50 t, 41.11 q, 10.32 t (2 C). IR (KBr): 3064, 3004, 2973, 1596, 1447 cm^{-1}. MS: *m/z* (relative intensity) 265 ($M^{\cdot+}$, 7), 236 (11), 208 (25), 178 (18), 165 (29), 118 (100), 107 (27), 105 (32), 91 (27), 77 (66). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.21; N, 5.27. Found: C, 81.14; H, 7.18; N, 5.52.

Thermal Rearrangement of 3: Hexahydro-1-methyl-2,2-diphenylpyridin-4-one (4). A solution of the spiroisoxazolidine **3** (100 mg, 0.37 mmol) was heated at reflux (110 °C) in dry toluene (3 mL) for 1 day. Toluene was removed, and the crude reaction product was chromatographed on a short pad of silica gel (eluant, ethyl acetate/petroleum ether (1:5) first, then ethyl acetate/petroleum ether (1:1)). The more polar fractions gave **4** (85 mg, 85% R_f = 0.53) as a viscous oil. Thermal rearrangement carried out by FVT (400 °C (10^{-3} mmHg)) gave **4** in 70% yield.

4. ^{1}H-NMR: δ 7.38–7.09 (m, 10 H), 2.87 (s, 2 H), 2.68 (t, *J* = 6.3 Hz, 2 H), 2.44 (t, *J* = 5.8 Hz, 2 H), 2.21 (s, 3 H). ^{13}C NMR: δ 209.48 s, 143.03 s (2 C), 129.33 d (8 C), 127.96 d (2 C), 70.86 s, 52.99 t, 48.70 t, 40.08 t, 39.00 q. IR ($CDCl_3$): 1705 cm^{-1}. MS *m/z*

(9) In another rearrangement experiment, carried out once in a sealed vial at the same temperature and for the same time, the isomer **12a** was the only ketone obtained.

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(13) Cyclohexanone oxime was isolated in 20% yield from the rearrangement of **19**. A rationale for its formation is not apparent at the moment.

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(relative intensity) 265 ($M^{\bullet+}$, 29), 264 (50), 222 (30), 207 (37), 194 (44), 188 (76), 180 (37), 179 (34), 178 (47), 165 (42), 146 (38), 118 (64), 105 (24), 103 (42), 91 (29), 77 (100), 42 (29). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.21; N, 5.27. Found: C, 81.69; H, 7.05; N, 5.22.

Hexahydro-3'a-methylspiro[cyclopropane-1,2'-pyrrolo-[1,2-*b*]isoxazole] (7) and Hexahydro-3'a-methylspiro[cyclopropane-1,3'-pyrrolo[1,2-*b*]isoxazole] (8). A solution of 3,4-dihydro-5-methyl-2*H*-pyrrole 1-oxide (5)[15] (342 mg, 3.45 mmol) and methylenecyclopropane (1) in excess in dry benzene (1 mL) was heated at 80 °C in a sealed vial for 7 days. The oily residue obtained after concentration was chromatographed on a short pad of silica gel (eluant, ethyl acetate) to give a mixture of the cycloadducts 7 and 8 in a 5.5:1 ratio (441 mg, 78%). Attempts to separate the two isomers gave only mixtures enriched in either of the two components. Mixture of regioisomers. IR ($CDCl_3$): 2970, 2872, 1449, 1374, 1265 cm^{-1}. Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.86; N, 9.14. Found: C, 70.52; H, 10.00; N, 9.48.

7. ^1H NMR: δ 3.20–2.99 (m, 2 H), 2.24 (d, J = 11.9 Hz, 1 H), and 2.12 (d, J = 11.9 Hz, 1 H) (AB system), 2.13–1.36 (m, 4 H), 1.32 (s, 3 H), 0.95–0.48 (m, 4 H). ^{13}C NMR: δ 61.91 s, 56.27 t, 48.99 s, 38.48 t, 27.10 t, 24.29 t, 22.84 q, 9.88 t, 9.13 t. MS: m/z (relative intensity) 153 ($M^{\bullet+}$, 52), 138 (100), 124 (24), 108 (20), 94 (21), 67 (24), 55 (44).

8. ^1H NMR: δ 3.85 (d, J = 7.7 Hz, 1 H) and 3.76 (d, J = 7.7 Hz, 1 H), 3.37–3.11 (m, 2 H), 2.07–1.40 (m, 4 H), 0.98 (s, 3 H), 0.80–0.49 (m, 4 H). ^{13}C NMR: δ 73.94 t, 72.46 s, 55.82 t, 35.64 t, 33.60 s, 23.68 t, 22.88 q, 8.53 t, 8.18 t. MS: m/z (relative intensity) 153 ($M^{\bullet+}$, 27), 138 (66), 108 (20), 99 (26), 94 (25), 69 (29), 67 (40), 56 (31), 54 (68), 41 (100).

Thermal Rearrangement of 7: Octahydro-8a-methylindolizin-7-one (11). A solution of 7 (153 mg, 1 mmol) (containing 20 mg of the regioisomer 8) in dry toluene (10 mL) was heated at reflux (100 °C) for 2 days. The crude mixture after solvent removal was chromatographed on a short pad of silica gel (eluant, acetone) to give the unreacted regioisomer 8 and ketone 11 (R_f = 0.20, 92 mg, 60%).

11. ^1H NMR: δ 3.24–2.80 (m, 4 H), 2.65–2.37 (m, 2 H), 2.22–2.07 (m, 2 H), 1.97–1.65 (m, 4 H), 0.98 (s, 3 H). ^{13}C NMR: δ 210.35 s, 63.53 s, 50.20 t, 49.10 t, 44.32 t, 39.20 t, 37.17 t, 20.49 q, 20.41 t. IR ($CDCl_3$): 2969, 2825, 1708, 1266, 1191 cm^{-1}. MS: m/z (relative intensity) 153 ($M^{\bullet+}$, 50), 138 (91), 110 (36), 96 (100), 83 (21), 55 (37), 42 (48). Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.86; N, 9.14. Found: C, 70.86; H, 9.81; N, 8.99.

Synthesis and Thermal Rearrangement of 7: "One-Pot" Procedure. A solution of nitrone 5 (318 mg, 3.21 mmol) and methylenecyclopropane (1) in excess in dry toluene (1 mL) was heated in a sealed tube at 110 °C for 2 days. The crude mixture after solvent removal was flash chromatographed on silica gel (eluant, acetone) to give 8 (R_f = 0.47, 65 mg, 13%) and ketone 11 (R_f = 0.20, 311 mg, 63%).

Hexahydro-3a'-methylspiro[bicyclo[4.1.0]heptane-7,2'-pyrrolo[1,2-*b*]isoxazole] (9) and Hexahydro-3a'-methylspiro[bicyclo[4.1.0]heptane-7,3'-pyrrolo[1,2-*b*]isoxazole] (10). A solution of methylenenorcarane (6)[16] (477 mg, 4.42 mmol) and nitrone 5 (525 mg, 5.29 mmol) in dry toluene (0.5 mL) was maintained at 80 °C for 7 days. ^1H NMR monitoring of the crude reaction mixture after solvent removal showed the presence of regioisomers 9 and 10 in a 4:1 ratio, in addition to unreacted nitrone. Separation of the mixture by flash chromatography (eluant, ethyl acetate/petroleum ether (7:3)) gave the adducts 10 (R_f = 0.36, 64 mg, 7%) and 9 (R_f = 0.14, 310 mg, 34%). Nitrone 5 (198 mg) was recovered by washing the column with methanol.

9. ^1H NMR: δ 3.34–3.10 (m, 2 H), 2.01–1.60 (m, 4 H), 1.32 (s, 3 H), 1.48–0.71 (m, 12 H). ^{13}C NMR: δ 71.80 s, 69.44 s, 66.28 t, 40.75 t, 35.54 t, 29.65 t, 21.21 t, 18.30 q, 17.74 d, 12.81 d. IR ($CDCl_3$): 2967, 2933, 2871, 1447, 1372, 1185 cm^{-1}. MS: m/z (relative intensity) 207.20 ($M^{\bullet+}$, 18), 192.15 (100), 178.15 (35), 164.15 (87), 136.10 (15), 110.15 (24), 84.05 (37), 81.05 (26), 67.05 (13). Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.18; H, 10.56; N, 6.48.

10. ^1H NMR: δ 3.81 (d, J = 8 Hz, 1 H) and 3.76 (d, J = 8 Hz, 1 H) (AB system), 3.20–3.11 (m, 2 H), 0.89 (s, 2 H), 2.05–0.71 (m, 14 H). ^{13}C NMR: δ 74.58 s, 65.83 t, 54.81 t, 38.08 s, 34.18 t, 22.59 t, 21.95 t, 21.44 t, 21.24 t, 19.15 t, 13.64 d, 13.41 d. IR ($CDCl_3$): 2935, 2870, 2659, 1447, 1374, 1126 cm^{-1}. MS: m/z (relative intensity) 207 ($M^{\bullet+}$, 2), 192 (18), 100 (98), 79 (42), 67 (45), 55 (100). Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 74.89; H, 10.33; N, 6.64.

Thermal Rearrangement of 9: Perhydro-3a-methyl-5-oxo-4*H*-pyrrolo[1,2-*a*]quinoline (12a–c). A solution of 9 (207 mg, 1 mmol) in dry toluene (13 mL) was heated at reflux for 2 days. ^1H NMR monitoring of the crude mixture showed the presence of three isomeric ketones 12a–c in 1.3:1:1 ratio. Separation of the mixture by column chromatography (eluant, ethyl acetate/petroleum ether (7:3)) gave two fractions. The first contained pure ketone 12b (42 mg, 20%) and the second a mixture of isomers 12a and 12c in 1.3:1 ratio (108 mg, 52%). The isomer 12b, set apart in a refrigerator in a vial for several months, was found to be transformed quantitatively into the isomer 12a.

12a. ^1H NMR: δ 3.10–2.98 (m, 1 H), 2.88–2.76 (m, 1 H), 2.58 (dt, J = 3.3, 10.4 Hz, 1 H), 2.45 (br d, J = 12.7 Hz, 1 H), 2.25–2.10 (m, 1 H), 2.12 (d, J = 12.7 Hz, 1 H), 2.01–1.00 (m, 11 H), 0.96 (s, 3 H). ^{13}C NMR: δ 211.04 s, 64.77 s, 60.10 d, 50.32 t, 50.22 d, 45.08 t, 39.28 t, 32.65 t, 25.57 t, 25.25 t, 23.90 t, 20.48 q, 20.17 t. IR ($CHCl_3$): 2940, 2861, 2828, 170, 1448, 1375, 1330, 1247, 1206 cm^{-1}. MS: m/z (relative intensity) 207 ($M^{\bullet+}$, 14), 192 (71), 164 (52), 136 (10), 110 (44), 84 (100), 81 (63). Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.10; H, 10.58; N, 6.27.

12b. ^1H NMR: δ 3.03 (dt, J = 4, 8.9 Hz, 1 H), 2.81 (br q, J = 3 Hz, 1 H), 2.60 (d, J = 13 Hz, 1 H), 2.40–2.12 (m, 2 H), 2.21 (d, J = 13 Hz, 1 H), 2.1–0.9 (m, 12 H), 0.76 (s, 3 H). ^{13}C NMR: δ 214.98 s, 62.33 s, 52.72 d, 51.37 d, 51.08 t, 44.83 t, 39.17 t, 28.96 t, 25.92 t, 25.17 t, 20.08 t, 19.64 t, 14.11 q. IR ($CDCl_3$): 2966, 2939, 2859, 2814, 1693, 1445, 1323, 1251 cm^{-1}. MS: m/z (relative intensity) 207 ($M^{\bullet+}$, 18), 192 (100), 178 (14), 164 (68), 110 (22), 84 (36). Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.71; H, 10.66; N, 6.34.

12c. ^1H NMR: δ 3.32 (m, 1 H), 2.55 (d, J = 15 Hz, 1 H), 2.55–2.35 (m, 2 H), 2.33 (d, J = 15 Hz, 1 H), 2.10–0.90 (m, 13 H), 1.07 (s, 3 H). ^{13}C NMR: δ 213.00 s, 62.82 d, 59.86 s, 54.62 t, 50.78 d, 50.15 t, 41.06 t, 33.74 t, 32.79 t, 26.31 t, 25.51 q, 24.68 t, 23.66 t. MS: m/z (relative intensity) 207 ($M^{\bullet+}$, 16), 192 (100), 164 (48), 136 (7), 110 (10), 84 (34), 55 (32).

Synthesis and Thermal Rearrangement of 9: "One-Pot" Procedure. A solution of 7-methylenenorcarane (6) (433 mg, 4 mmol) and nitrone 5 (680 mg, 6.8 mmol) in dry toluene (20 mL) was heated at reflux for 7 days. ^1H NMR analysis of the crude mixture after concentration and filtration over a short pad of silica gel showed the presence of the regioisomer 10 and the mixture of ketones 12a–c in 2.3:1.3:1 ratio in addition to unreacted nitrone. The mixture was separated by column chromatography (eluant, ethyl acetate/petroleum ether (7:3)) to give four fractions: the first contained ketone 12b (89 mg, 11%), the second regioisomer 10 (89 mg, 11%), the third pure ketone 12a (65 mg, 8%), and the fourth a mixture of ketones 12a and 12c in 1.3:1 ratio (182 mg, 22%). Methanol washing contained unreacted nitrone 5 (400 mg).

Cycloaddition of *N*-Methylcyclopentylideneamine *N*-Oxide (15) to 1: 5-Methyl-4-oxa-5-azadispiro[2.2.4.1]undecane (17) and 6-Methyl-5-oxa-6-azadispiro[2.3.4.0]undecane (18). A solution of nitrone 15[14] (383 mg, 3 mmol) and methylenecyclopropane (1) in excess in dry benzene (0.5 mL) was heated in a sealed tube at 80 °C for 1 day. The oil obtained after concentration contained the two regioisomers 17 and 18 in a 6:1 ratio (from the ^1H NMR). The crude mixture was chromatographed on silica gel (eluant, ethyl acetate/petroleum ether(1:3)) to give an inseparable mixture of the regioisomers 17 and 18 (196 mg, 40% yield, R_f = 0.35) as a volatile oil. Mixture of regioisomers. IR ($CDCl_3$): 3084, 2967, 2876, 1446, 1374, 1344, 1221, 1120 cm^{-1}. Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.24; N, 8.37. Found: C, 71.83; H, 10.31; N, 8.67.

17. ^1H NMR: δ 2.67 (s, 3 H), 2.42–2.10 (m, 2 H), 1.95–1.46 (m, 8 H), 0.90 (br s, 2 H), 0.60 (br s, 2 H). ^{13}C NMR: δ 74.29 s, 62.57 s, 45.42 t, 41.08 q, 39.57 t (br), 32.86 t (br), 24.27 t (br), 23.88 t (br), 12.34 t (br), 9.42 t (br). MS: m/z (relative intensity) 167 ($M^{\bullet+}$, 6), 138 (12), 125 (11), 111 (17), 110 (17), 97 (14), 96 (18), 83 (24), 82 (22), 68 (100), 67 (44), 57 (35), 55 (76).

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18. ^{1}H NMR: δ 3.93 (br s, 1 H) and 3.90 (br s, 1 H) (isoxazolidine CH_2), 2.68 (s, 3 H), 2.07–1.40 (m, 8 H), 1.15–0.90 (m, 1 H), 0.88–0.70 (m, 1 H), 0.68–0.52 (m, 1 H), 0.50–0.35 (m, 1 H). ^{13}C NMR (only detected signals): δ 77.44 t, 31.31 t, 27.43 t, 25.66 t, 25.05 t. MS: *m/z* (relative intensity) 167 ($M^{\bullet+}$, 18), 138 (100), 121 (17), 108 (22), 93 (51), 79 (55), 68 (71), 67 (50), 55 (76).

Cycloaddition of *N*-Methylcyclohexylideneamine *N*-Oxide (16) to 1: 5-Methyl-4-oxa-5-azadispiro[2.2.5.1]dodecane (19) and 6-Methyl-5-oxa-6-azadispiro[2.3.5.0]dodecane (20). A solution of nitrone **16**[14] (470 mg, 3.07 mmol) and methylenecyclopropane (**1**) in excess in dry benzene (0.5 mL) was heated in a sealed tube at 80 °C for 1 day. The oil obtained after concentration contained the two regioisomers **19** and **20** in 6:1 ratio (from the ^{1}H NMR). The crude mixture was chromatographed on silica gel (eluant, ethyl acetate/petroleum ether (1:3)) to give fractions only enriched in either regioisomers **19** and **20** (362 mg, 64% yield, R_f = 0.46) as oils. Mixture of regioisomers. Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.72. Found: C, 73.16; H, 10.88; N, 7.58.

19. ^{1}H NMR: δ 2.66 (s, 3 H), 2.18 (s, 2 H), 1.68–1.27 (m, 10 H), 0.90 (s, 2 H), 0.57 (s, 2 H). ^{13}C NMR: δ 68.52 s, 61.42 s, 43.53 t, 38.60 q, 36.34 t (br), 31.47 t (br), 25.64 t, 23.39 t (2 C), 11.83 s (br), 9.22 s (br). IR ($CDCl_3$): 2938, 2861, 1447, 1346, 1093 cm^{-1}. MS: *m/z* (relative intensity) 181 ($M^{\bullet+}$, 6), 155 (25), 138 (45), 125 (12), 92 (37), 91 (100), 67 (22), 65 (52).

20. ^{1}H NMR: δ 3.96 (d, *J* = 6.5 Hz, 1 H) and 3.87 (d, *J* = 6.5 Hz, 1 H) (AB system), 1.97–0.35 (m, 14 H). MS: *m/z* (relative intensity) 181 ($M^{\bullet+}$, 12), 138 (100), 125 (15), 91 (14), 79 (31), 68 (30), 67 (28), 55 (49). IR ($CDCl_3$): 3075, 2998, 2936, 2859, 1441, 1356, 1156, 1063 cm^{-1}.

Thermal Rearrangement of 17: 6-Methyl-6-azaspiro[4.5]decan-9-one (21). The spiroisoxazolidine **17** (142 mg, 0.85 mmol) was subjected to FVT (400 °C (10^{-3} mmHg)) by vaporization at room temperature. The crude reaction product (80 mg) was chromatographed on a short pad of silica gel (eluant, ethyl acetate/petroleum ether (1:2) first, and then ethyl acetate/methanol (1:4)) to give **21** (60 mg, 42%) as a volatile oil.

21. R_f = 0.40 (EtOAc–MeOH (1:4)). ^{1}H NMR: δ 2.96 (t, *J* = 6.1 Hz, 2 H), 2.43 (s, 3 H), 2.39 (t, *J* = 6.2 Hz, 2 H), 2.35 (s, 2 H), 1.74–1.40 (m, 8 H). ^{13}C NMR: δ 209.58 s, 69.77 s, 51.70 t, 49.78 t, 38.95 t, 37.23 q, 35.21 t, 24.59 t. IR ($CDCl_3$): 1707 cm^{-1}. MS: *m/z* (relative intensity) 167 ($M^{\bullet+}$, 16), 138 (42), 125 (83), 110 (29), 97 (66), 96 (58), 82 (35), 69 (49), 68 (82), 55 (100). Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.24; N, 8.37. Found: C, 72.02; H, 10.41; N, 8.86.

Thermal Rearrangement of 19: 1-Methyl-1-azaspiro[5.5]undecan-4-one (22). The spiroisoxazolidine **19** (233 mg, 1.28 mmol) was subjected to FVT (400 °C (10^{-3} mmHg)) by vaporization at 50 °C. The collected crude mixture (204 mg) was chromatographed on a short pad of silica gel (eluant ethyl acetate/petroleum ether (1:4) first, and then ethyl acetate) to give **22** (92 mg, 40%) as a volatile oil.

22. R_f = 0.37 (MeOH/EtOAc/petroleum ether (1:1:2)) ^{1}H NMR: δ 3.09 (t, *J* = 6.2 Hz, 2 H), 2.45 (s, 3 H), 2.34 (t, *J* = 6.1 Hz, 2 H), 2.30 (s, 2 H), 1.61–1.35 (m, 10 H). ^{13}C NMR: δ 209.82 s, 60.34 s, 49.49 t, 47.38 t, 38.11 t, 35.59 q, 33.71 t, 25.62 t, 21.38 t. IR 1703 cm^{-1}. MS: *m/z* (relative intensity) 181 ($M^{\bullet+}$, 12), 139 (11), 138 (100), 125 (52), 97 (24), 96 (52), 69 (31), 68 (46), 55 (75). Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.72. Found: C, 72.56; H, 10.77; N, 7.46.

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C-Aryl Glycosides: Electrophile Initiated Cyclizations of 6-Aryl-5-hexen-2-ols

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An approach to the synthesis of C-aryl glycosides is described. Treatment of β-lactam **9** with *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS) afforded *trans*-2,6-disubstituted pyrans **11a** and **11b**. Treatment of **9** with phenylselenenyl chloride (PhSeCl) or *N*-(phenylselenenyl)phthalimide (N-PSP) gave **11c** and cis-2,6-disubstituted pyran **12c** in different ratios depending on the reaction conditions. Treatment of β-lactam **10** with NBS, NIS, PhSeCl, or N-PSP gave mixtures of pyrans **16** and **17**. Treatment of unsaturated alcohol **24a** with PhSeCl gave pyran **23a**. Conversion of **23a** to virenose analog **22**, a C-aryl glycoside related to the chrysomycins, was accomplished using a selenoxide elimination–osmium tetraoxide oxidation sequence.

Introduction

C-Aryl glycosides are a family of natural products of interest because of their structural complexity and biological properties.[1] A number of methods for the preparation of C-aryl glycosides have been reported. These can be placed in either of two broad categories: (1) grafting of an aryl group onto an available carbohydrate and (2) de novo synthesis of the aryl-containing carbohydrates. Methods belonging to the first category involve reactions between carbohydrate C-1 carbocation equivalents and aromatic nucleophiles,[2] addition of carbohydrate C-1 carbanions to aryl cation equivalents,[3] palladium-mediated coupling of glycals with aryl halides and stannanes,[4] and

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