Rearrangement of Isoxazoline-5-spiro Derivatives. 2. Synthesis and Rearrangement of Tetrahydroisoxazole-5-spirocyclopropanes. Preparation of Precursors of Quinolizine, Isoquinoline, and Indole Alkaloids[1]

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Tetrahydroisoxazole-5-spirocyclopropanes **3**, prepared by cycloaddition of nitrones **1** to methylenecyclopropane (**2**), have been converted by thermolysis into heterocyclic ketones **5** of the piperidine or indolizine or quinolizine series, according to the structure of the starting nitrone. The enaminones **6** are obtained as side products, as a result of 1,5 H-transfer on the assumed intermediates **7**. This procedure has been applied to the preparation of precursors of drugs and alkaloids of the quinolizine or indole group. Thus, the ketones **10** and **11**, related to the natural heterocyclic alcohols lasubine I and lasubine II, the ketone **17**, precursor of yohimbine and of other natural indole alkaloids, and the ketone **22**, intermediate for the synthesis of drugs related to emetine, have been obtained by the present method.

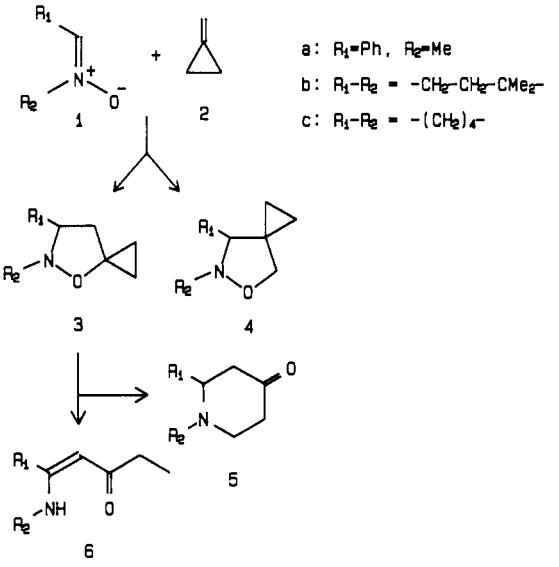
The thermolytic rearrangement of isoxazoline-5-spiro cyclopropanes to 5,6-dihydropyridone derivatives, reported in the accompanying paper,[1] can be extended to isoxazolidine-5-spiro cyclopropanes.[2] These intermediates are accessible by cycloadditions analogous to those reported in the preceding paper, with nitrones as 1,3-dipoles instead of nitrile oxides. Their thermolysis is even easier, and the adducts derived from cyclic nitrones will eventually lead to N-bridgehead polycyclic compounds of interest in numerous alkaloids.[2]

Results and Discussion

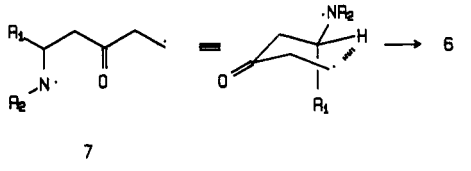
Nitrone Cycloadditions to Methylenecyclopropane; Rearrangement of the Adducts 3. The cycloadditions, carried out at 60 °C for 2 days in a sealed tube, give good yields (69–86%) of mixtures of the two regioisomers **3** and **4** (Scheme I). The 5-spiro regioisomers **3** are predominant (65–90%) but the relative amounts of the minor regioisomers **4** are considerably higher than those produced in the corresponding cycloadditions of nitrile oxides.[1] The regioisomers **3** and **4** can be separated only in part by flash column chromatography, but isolation of compounds **4** is possible after the rearrangement (see below). Structure assignments of the regioisomeric pairs rest upon the shielding effect of the cyclopropane ring (^{13}C NMR: the isoxazolidine C4 appears at δ 45.1 in **3a** and at 31.4 in **4a**; the C5 at 61.6 in **3a** and at 73.8 in **4a**) and on the chemical shift of the isoxazolidine methylene (^1H NMR: δ 2.75 and 2.38 in **3a**, 4.03 and 3.83 in **4a**). Analogous behavior allows the other pairs of regioisomers to be identified.

The rearrangement of the cycloadducts **3**, carried out by FVT as already reported,[1,2] leads to mixtures of tetrahydropyridones **5** and enaminones **6** that are rather unstable volatile compounds. When rearrangements are carried out on mixtures of both regioisomers **3** and **4**, the same products are obtained, besides the unchanged regioisomers **4**. In solution (refluxing toluene) the rearrangement gives lower yields of **5**. The isomers **5** and **6** are easily distinguished on the basis of the carbonyl spectral data ($\nu_{C=O}$ 1725–1735 cm^{-1} for **5**, 1620 cm^{-1} for **6**; ^{13}C δ 208–210 for **5**, 198–199 for **6**); only one isomer **6** is identified in each case and is assigned the depicted structure, in agreement with the observed NMR chemical shift of the olefinic proton (δ 4.9–5.0).[3]

Scheme I



Scheme II



In the rearrangement of isoxazoline-5-spirocyclopropanes, we assumed that diradical intermediates were responsible for either cyclization to dihydropyridones or H-shift to vinylenaminones (see Scheme II of ref 1). In the present case (Scheme II), a similar intermediate (**7**) can account for the observed formation of both the tetrahydropyridones **5** (by recyclization) and the enaminones **6** (via a different H-shift). Intramolecular H-shifts must be invoked in order to explain the enaminone production in the gaseous FVT conditions. The relative amounts of the isomers actually produced also depend on intermole-

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(1) Part 1: Guarna, A.; Brandi, A.; De Sarlo, F.; Goti A.; Pericciuoli, F. *J. Org. Chem.*, preceding paper in this issue.
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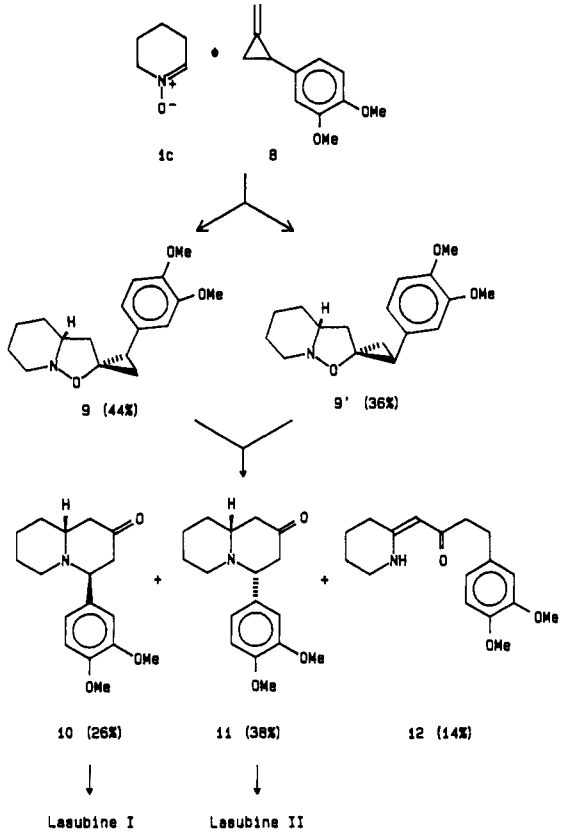
Scheme III



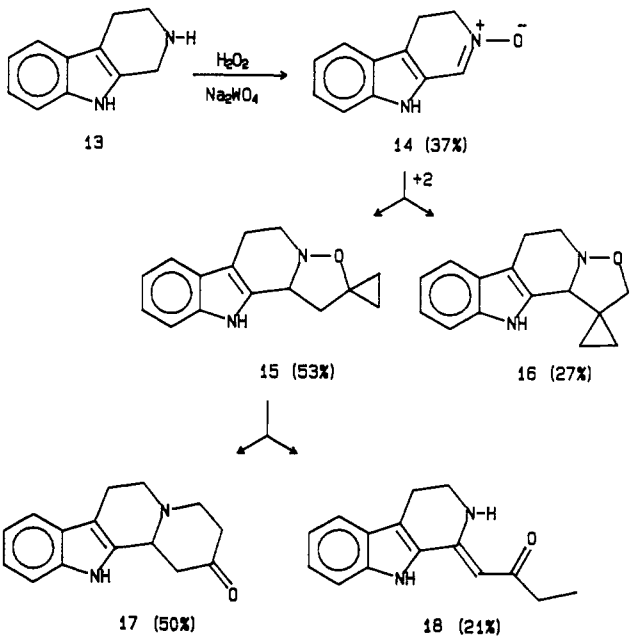
cular H-transfers (when the rearrangements are carried out in a condensed phase, possibly due to radical solvation) and on further cyclization to dihydropyridones, possible only from the vinylenaminones (Scheme II of ref 1) by intramolecular Michael addition.

Key Intermediates toward Quinolizine, Isoquinoline, and Indole Alkaloids. The availability of the above direct synthesis of indolizine or quinolizine derivatives prompted us to apply this procedure to the preparation of natural product intermediates containing those heterocyclic moieties.

Lasubine. The two isomeric alkaloids lasubine I and lasubine II have been prepared by diastereoselective reduction of the corresponding ketones **10**[4] and **11**.[5] A retrosynthetic analysis shows that the ketones **10** and **11** are expected to be the rearrangement products of the intermediate adduct **9** between the nitrone **1c** and the substituted methylenecyclopropane **8** (Scheme III).

We prepared compound **8** according to Binger's procedure,[6] by reaction of 3,4-dimethoxystyrene with the carbene MeCCl, generated in situ, followed by dehydrochlorination: however, the cyclopropanation step fails, unless an excess of ethylidene chloride and BuLi is used in the presence of additional lithium bromide.[7] The successive cycloaddition is highly regioselective (>95%), affording a mixture of only two isomers, both with 5-spiroisoxazolidine structures, as supported by the chemical shift of the isoxazolidine methylene: ^{1}H NMR δ 2.63–2.06, m; ^{13}C NMR δ 36.76 (major isomer) and 36.61 (minor isomer). Among the four possible diastereoisomers, only those with the aryl group trans to the isoxazole oxygen (**9** and **9'**) are produced, as a result of the more favorable "anti" transition states.[8] This diastereoselectivity is immaterial, as chirality at the cyclopropane ring is lost during the rearrangement.[1] By thermolysis of the adducts **9** and **9'**, the two expected ketones **10** and **11** are obtained, along with a minor amount of the enaminone **12**, analogous to **6**. After chromatographic separation of the three isomers (the yields refer to isolated products), the major ketone was identified as the trans isomer (**11**) and the minor as the cis (**10**) by comparison with the literature data.[4] On the whole, the method is straightforward in comparison with those previously reported;[9] moreover, it appears to be complementary with the alternative procedure,[4] which predominantly produces the ketone **10**, precursor of lasubine I.

Scheme IV



Indole Alkaloids. The interest in ketone **17** as an intermediate for the synthesis of some indole alkaloids of the yohimbine[10] and reserpine types[11] has prompted various preparative procedures.[12-15] The method here described provides another access to the ketone **17** by cycloaddition of the nitrone **14** to methylenecyclopropane (**2**) and rearrangement of the 5-spiro adduct **15** (Scheme IV). To this end, the nitrone **14** has been prepared by oxidation of tetrahydro-β-carboline (**13**) as recently reported[16] and then reacted with methylenecyclopropane in a sealed tube. The two regioisomers **15** and **16** are obtained in a 2:1 molar ratio and high overall yield. In refluxing mesitylene the adduct **15** is converted in 4 h into a mixture of the expected products **17** and **18**: the physical properties of the ketone **17** are in agreement with the literature data.[12,13]

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Isoquinoline Alkaloids. Hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizin-2-one (**22**) has received much attention in recent years as an useful intermediate for the synthesis of drugs related to emetine.[17,18] The starting nitrone **19** has been obtained from tetrahydro-6,7-dimethoxyisoquinoline by the same procedure employed for the nitrone **14**. Cycloaddition of **19** to methylenecyclopropane (**2**) (Scheme V) gives mainly the adduct **20**, which in turn rearranges thermally to the expected quinolizinone **22**, along with a minor amount of the isomeric enaminone **23**.

Experimental Section

Instruments and procedures were as in the preceding paper.[1] In addition, mass spectra by direct inlet were recorded on a MAT 111 and exact mass measurements were performed with a VG 70-70 EQ mass spectrometer, at an ionization potential of 70 eV.

Methylenecyclopropane (2) was purchased from Fluka.

2-(3,4-Dimethoxyphenyl)methylenecyclopropane (8). 1-Chloro-1-methyl-2-(3,4-dimethoxyphenyl)cyclopropane has been obtained by a procedure reported for a similar compound,[6] modified as follows. A solution of dimethoxystyrene (2.54 g, 15.5 mmol) in anhydrous diethyl ether (30 mL) containing LiBr (4 g, 45 mmol) was cooled at −40 °C. After addition of 1,1-dichloroethane (1.3 mL, 12.4 mmol), a 1.6 M solution of BuLi (7.7 mL, 12.3 mmol) was added dropwise to the stirred mixture, during 20 min. The addition of 1,1-dichloroethane and BuLi was repeated in the same manner eight times: GC control indicated that 60% of the employed dimethoxystyrene had been converted into the product. Treatment with water was followed by ether extraction, drying over Na_2SO_4, and removal of solvent and unreacted dimethoxystyrene. The residue was dissolved again in diethyl ether, passed over silica gel, and concentrated: the crude mixture of diastereoisomers [MS: *m/e* (rel intensity) 226 (17), 191 (100), 160 (48); ^{1}H NMR: 7.02–6.40 (m, 3 H), 4.50 (m, 1 H), 3.93 (s, 6 H), 1.88 (s, 3 H), 1.78–1.12 (m, 2 H)] was directly employed in the next step.

A solution of *t*-BuOK (757 mg, 6.5 mmol) in DMSO was added dropwise at 90 °C to a stirred solution of the above intermediate (1.48 g, 6.5 mmol) in DMSO (1 mL). After 2 h of heating, the solution was cooled, treated with water, and extracted with light petroleum ether. Solvents were removed in vacuo from the dried (Na_2SO_4) organic layer to give the product **8** (0.95 g, 5 mmol, yield 77%).

8. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.91; H, 7.57. MS: *m/e* (rel intensity) 190 (**8**$^{\bullet+}$, 8), 159 (100). ^{1}H NMR: 6.90–6.70 (m, 3 H), 5.78–5.60 (m, 2 H), 3.92 (s, 6 H), 2.65 (m, 1 H), 1.75 (m, 1 H), 1.21 (m, 1 H). ^{13}C NMR: 148.8 s, 147.2 s, 135.5 s, 134.2 s, 118.3 d, 111.2 d, 109.7 d, 104.3 t, 55.8 q, 55.6 q, 19.6 d, 14.1 t. IR (CCl_4): 3060, 3000, 2960, 2910, 2840, 1610, 1595, 1470, 1250 cm^{-1}.

Nitrones 1. Known procedures were followed for the preparation of the nitrones **1a**,[19] **1b**,[20] and **1c**.[21] 3,4-Dihydro-β-carboline 2-oxide (**14**) and 3,4-dihydro-6,7-dimethoxyisoquinoline *N*-oxide (**19**) have been obtained by oxidation of the corresponding cyclic amines with H_2O_2 and Na_2WO_4, as recently reported.[16]

4,9-Dihydro-3*H*-pyrido[3,4-*b*]indole 2-Oxide or 3,4-Dihydro-β-carboline 2-Oxide (14). 1,2,3,4-Tetrahydro-β-carboline[22] (219 mg, 1.27 mmol) in anhydrous methanol (15 mL) was added with Na_2WO_4 hydrate (50 mg, 0.15 mmol) and then treated in the cold (0 °C) with 36% aqueous H_2O_2 (0.4 mL, 2.54 mmol). Stirring was continued for 2 h at 0 °C and for 1 h at room temperature, then aqueous $NaHSO_3$ was added, and the solution was extracted with methylene chloride (6 × 15 mL). The organic layer was dried (Na_2SO_4) and concentrated and the residue column-chromatographed (eluant: methylene chloride + ethyl acetate + methanol, 3:2:1) to give the nitrone **14**, R_f 0.45, 92 mg (37%).

14, yellow crystals, from ligroin, mp 195–196 °C. Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.24; H, 5.33; N, 14.39. MS (direct inlet) *m/e* (rel intensity) 186 (**14**$^{\bullet+}$, 100), 170 (23), 169 (42), 168 (31), 158 (20), 143 (20). ^{1}H NMR: 10.50 (br s, 1 H), 7.95 (s, 1 H), 7.15 (m, 4 H), 4.10 (t, J = 9, 2 H), 2.95 (t, J = 9, 2 H). ^{13}C NMR: 138.2 s, 128.9 d, 127.4 s, 124.9 s, 123.6 d, 120.4 d, 118.8 d, 112.0 d, 108.3 s, 59.4 t, 20.0 t. IR ($CDCl_3$): 1150 cm^{-1}.

3,4-Dihydro-6,7-dimethoxyisoquinoline *N*-Oxide (19). 1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinoline (53 mmol) in methanol (60 mL) was treated, as described for the nitrone **14**, with Na_2WO_4 hydrate (700 mg, 2.12 mmol) and with 36% aqueous H_2O_2 (11.3 mL, 116.6 mmol). Workup as above (eluant for chromatography: methylene chloride + methanol, 1:1) gave the crude nitrone **19** (6.52 g), recrystallized 3.57 g (32.5%).

19, from methylene chloride + light petroleum ether, mp 188–190 °C (lit.[23] mp 189–191 °C). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.59; H, 6.41; N, 6.74. MS (direct inlet): *m/e* (rel intensity) 207 (**19**$^{\bullet+}$, 100), 192 (31), 191 (21), 176 (10), 133 (19). ^{1}H NMR in agreement with the reported[24] values: 7.76 (s, 1 H), 6.77 (s, 1 H), 6.69 (s, 1 H), 4.08 (t, J = 8, 2 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.10 (t, J = 8, 2 H). ^{13}C NMR: 149.7 s, 148.0 s, 133.85 d, 123.0 s, 120.4 s, 110.3 d, 108.35 d, 57.1 t, 55.7 q (2 C), 27.1 t. IR (CH_2Cl_2): 1520, 1285, 1170, 1125 cm^{-1}.

Cycloadditions to methylenecyclopropane were carried out in sealed tubes at 60 °C without solvent, unless indicated.

5-Methyl-6-phenyl-4-oxa-5-azaspiro[2.4]heptane (3a) and 6-Methyl-7-phenyl-5-oxa-6-azaspiro[2.4]heptane (4a). The nitrone **1a** (675 mg, 5 mmol) and excess methylenecyclopropane (**2**, 54 mg) were maintained at 60 °C for 2 days, and then the mixture was passed over a pad of silica gel, washed with diethyl ether, and concentrated: crude oil, 784 mg, containing **3a** and **4a** in molar ratio 2.3:1 (GC). Attempted separation by column chromatography was incomplete, giving only some enriched **3a**; **4a** was isolated after rearrangement of the mixture (see below).

3a: HRMS calcd for $C_{12}H_{15}NO$ 189.1153, found (GC inlet) 189.1115. MS: *m/e* (rel intensity) 189 (**3a**$^{\bullet+}$, 14), 160 (40), 132 (100), 118 (83), 104 (66). ^{1}H NMR: 7.55–7.25 (m, 5 H), 3.84 (t, J = 9, 1 H), 2.75 (dd, J_{gem} = 13, J = 9, 1 H), 2.63 (s, 3 H), 2.38 (dd, J_{gem} = 13, J = 9, 1 H), 1.28–0.45 (m, 4 H). ^{13}C NMR: 139.5 s, 128.2 d (2 C), 127.3 d (3 C), 73.8 d, 61.6 s, 45.1 t, 43.5 q, 12.1 t, 9.5 t.

4a: HRMS calcd for $C_{12}H_{15}NO$ 189.1153, found (GC inlet) 189.1168. MS: *m/e* (rel intensity) 189 (**4a**$^{\bullet+}$, 43), 160 (25), 144 (60), 129 (100). ^{1}H NMR: 7.45–7.20 (m, 5 H), 4.03 (d, J_{gem} = 7.5, 1 H), 3.83 (d, J_{gem} = 7.5, 1 H), 3.55 (s, 1 H), 2.65 (s, 3 H), 0.90–0.15 (m, 4 H). ^{13}C NMR: 136.7 s, 128.3 d (2 C), 127.9 d (2 C), 127.3 d, 77.9 s, 73.8 t, 43.5 q, 31.4 s, 9.6 t, 8.7 t. IR (CCl_4): 3080, 3040, 3010, 2970, 2930, 2880, 2860, 1610, 1500, 1460, 1030 cm^{-1}.

Rearrangement of 3a: 1-Methyl-2-phenylpiperidin-4-one (5a) and 1-(Methylamino)-1-phenylpent-1-en-3-one (6a). A mixture of the adducts **3a** (133 mg, 0.71 mmol) and **4a** (59 mg) was submitted to flash vacuum thermolysis (FVT) by leading the vapors (0.15 Torr, 80–120 °C) into a quartz tube heated at 400 °C and then in a cold trap. The collected products **5a**, **6a**, and unchanged **4a** (overall 155 mg, relative amount 40:8:52, by GC) were column-chromatographed (eluant: methylene chloride + diethyl ether, 5:1) to give **5a**, R_f 0.24, 61 mg (46%, based on **3a**) and a mixture (78 mg) of **4a**, R_f 0.46, and **6a**, R_f 0.63. Separation by bulb-to-bulb distillation gave **4a** (37 mg) and **6a** (19 mg, 14%, based on **3a**).

5a: HRMS calcd for $C_{12}H_{15}NO$ 189.1153, found (direct inlet) 189.1152. MS: *m/e* (rel intensity) 189 (**5a**$^{\bullet+}$, 60), 188 (32), 146 (42), 118 (100). ^{1}H NMR: 7.35 (s, 5 H), 3.25 (m, 2 H), 3.10–2.35 (m, 5 H), 2.20 (s, 3 H). ^{13}C NMR: 207.9 s, 142.0 s, 128.7 d (2 C), 127.6 d, 127.1 d (2 C), 69.7 d, 55.5 t, 49.6 t, 42.8 q, 41.5 t. IR ($CDCl_3$): 3040, 3000, 2970, 2940, 2860, 2800, 1730, 1610, 1500, 1460, 1375 cm^{-1}.

6a: HRMS calcd for $C_{12}H_{15}NO$ 189.1153, found (direct inlet) 189.1152. MS: *m/e* (rel intensity) 189 (**6a**$^{\bullet+}$, 20), 160 (100), 118

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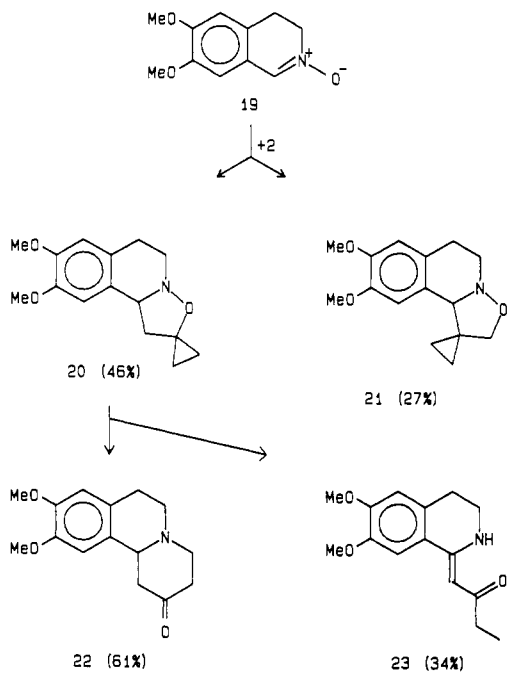
Scheme V



(19). ^{1}H NMR: 10.80 (s, 1 H), 7.42 (m, 5 H), 5.00 (s, 1 H), 2.83 (d, J = 5.4, 3 H), 2.33 (q, J = 7.5, 2 H), 1.11 (t, J = 7.5, 3 H). ^{13}C NMR: 199.4 s, 165.9 s, 129.1 s, 128.2 d (2 C), 127.5 d (3 C), 95.3 d, 34.9 q, 31.1 t, 9.8 q. IR ($CDCl_3$): 1620, 1580 cm^{-1}.

Hexahydro-6′,6′-dimethylspiro[cyclopropane-1,2′-pyrrolo[1,2-*b*]isoxazole] (3b) and Hexahydro-6′,6′-dimethylspiro[cyclopropane-1,3′-pyrrolo[1,2-*b*]isoxazole] (4b). The nitrone **1b** (565 mg, 5 mmol) afforded, by the same procedure described for **1a**, a crude oil, 720 mg, containing **3b** and **4b** in molar ratio 1.8:1 (GC). Attempted separation failed; the mixture was submitted to FVT, and then **4b** was isolated (see below).

3b: HRMS calcd for $C_{10}H_{17}NO$ 167.1309, found (GC inlet) 167.1295. MS: m/e (rel intensity) 167 (**3b**$^{\bullet+}$, 17), 152 (57), 111 (20), 110 (33), 96 (100). ^{1}H NMR: 4.08 (m, 1 H), 2.60 (dd, J_{gem} = 11, J = 8, 1 H), 2.38–1.40 (m, 5 H), 1.25 (s, 3 H), 1.05 (s, 3 H), 1.00–0.65 (m, 4 H). ^{13}C NMR: 67.9 s, 65.0 d, 61.3 s, 43.0 t, 35.7 t, 32.1 t, 26.4 q, 23.9 q, 11.2 t, 9.0 t.

4b: HRMS calcd for $C_{10}H_{17}NO$ 167.1309, found (GC inlet) 167.1246. MS: m/e (rel intensity) 167 (**4b**$^{\bullet+}$, 32), 152 (100), 138 (27), 81 (60). ^{1}H NMR: 3.85 (d, J_{gem} = 7, 1 H), 3.65 (d, J_{gem} = 7, 1 H), 3.32 (m, 1 H), 2.15–1.40 (m, 4 H), 1.45 (s, 3 H), 1.05 (s, 3 H), 0.80–0.45 (m, 4 H). ^{13}C NMR: 73.1 t, 71.0 d, 68.7 s, 35.8 t, 31.5 s, 29.8 t, 27.0 q, 23.7 q, 13.2 t, 6.8 t. IR ($CDCl_3$): 3080, 2970, 2940, 2865, 1460, 1370, 1250, 1150, 1020 cm^{-1}.

Rearrangement of 3b: Octahydro-3,3-dimethylindolizin-7-one (5b) and 2-(2-Oxobutylidene)-5,5-dimethyltetrahydropyrrole (6b). The rearrangement was carried out by FVT, as reported above, from a mixture of **3b** (167 mg, 1 mmol) and **4b** (101 mg) evaporated at 0.3 Torr and 70 °C. The products **5b** and **6b** were collected with unchanged **4b** (overall 206 mg, relative amount 50:20:30, by GC) and then column-chromatographed (eluant: methylene chloride + methanol, 15:1) to give **5b**, R_f 0.36, 93 mg (54%, based on **3b**) and a mixture (78 mg) of **4b**, R_f 0.50, and **6b**, R_f 0.58. Separation by bulb-to-bulb distillation gave **4b** (20 mg) and **6b** (28 mg, 17%, based on **3b**).

5b: HRMS calcd for $C_{10}H_{17}NO$ 167.1309, found (direct inlet) 167.1284. MS: m/e (rel intensity) 167 (**5b**$^{\bullet+}$, 4), 152 (100), 110 (4), 82 (24). ^{1}H NMR: 3.75 (m, 1 H), 3.15–1.04 (m, 10 H), 1.20 (s, 3 H), 0.93 (s, 3 H). ^{13}C NMR: 209.7 s, 60.4 d, 59.3 s, 48.6 t, 42.6 t, 41.1 t, 38.6 t, 28.8 t, 27.7 q, 19.8 q. IR (CCl_4): 2970, 2930, 2870, 2800, 2700 and 2660 (Bohlmann bands), 1725, 1470, 1385, 1315, 1240, 1190 cm^{-1}.

6b: HRMS calcd for $C_{10}H_{17}NO$ 167.1309, found (direct inlet) 167.1287. MS: m/e (rel intensity) 167 (**6b**$^{\bullet+}$, 24), 138 (100), 110 (19), 96 (27). ^{1}H NMR: 10.50 (br s, 1 H), 5.05 (s, 1 H), 2.72 (t, J = 7.6, 2 H), 2.30 (q, J = 8, 2 H), 1.78 (t, J = 7.6, 2 H), 1.35 (s, 6 H), 1.15 (t, J = 8, 3 H). ^{13}C NMR: 196.6 s, 165.3 s, 87.8 d, 62.1 s, 35.5 t, 34.4 t, 31.7 t, 28.4 q (2 C), 9.8 q. IR ($CDCl_3$): 1620, 1535 cm^{-1}.

Hexahydrospiro[cyclopropane-1,2′-[2*H*]isoxazolo[2,3-*a*]pyridine] (3c) and Hexahydrospiro[cyclopropane-1,3′-[2*H*]isoxazolo[2,3-*a*]pyridine] (4c). The nitrone **1c**, prepared from 10 mmol of its precursor *N*-hydroxypiperidine, was dissolved in dichloromethane (0.5 mL) and treated with methylenecyclopropane (15 mmol) as described for **1a**. The mixture was then worked up as above to give a crude oil, 1.062 g, containing **3c** and **4c** in molar ratio 9:1 (GC). Owing to the small amount, the adduct **4c** was not isolated, even after the rearrangement. Pure **3c** could not be obtained, as rearrangement occurred in part even at room temperature.

3c: HRMS calcd for $C_9H_{15}NO$ 153.1153, found (GC inlet) 153.1111. MS: m/e (rel intensity) 153 (**3c**$^{\bullet+}$, 31), 124 (21), 96 (73), 82 (46), 55 (100). ^{1}H NMR: 3.86–2.70 (m, 3 H), 2.70–1.12 (m, 8 H), 1.12–0.28 (m, 4 H). ^{13}C NMR: 68.4 d, 61.1 s, 55.1 t, 41.1 t, 29.1 t, 24.4 t, 23.5 t, 13.4 t, 9.3 t. IR (CCl_4): 3100, 3010, 2960, 2870, 2840, 1460, 1350, 1235, 1120, 1005 cm^{-1}.

4c: HRMS calcd for $C_9H_{15}NO$ 153.1153, found (GC inlet) 153.1116. MS: m/e (rel intensity) 153 (**4c**$^{\bullet+}$, 45), 152 (32), 136 (18), 124 (100), 82 (15). ^{13}C NMR: 72.9 t, 62.4 t, 50.1 t, 37.4 t, 12.7 t, 8.9 t; no other signals were identified.

Rearrangement of 3c: Octahydroquinolizin-2-one (5c) and 2-(2′-Oxobutylidene)piperidine (6c). The rearrangement was carried out by FVT, as reported above, on a mixture of **3c** (174 mg, 1.14 mmol) and **4c** evaporated at 0.15 Torr and 40–50 °C. The products **5c** and **6c** were collected with unchanged **4c** (overall 146 mg, relative amount 58:26:16, by GC) and then column-chromatographed (eluant: methylene chloride + methanol, 10:1) to give **5c**, R_f 0.34, 63 mg (38%, based on **3c**), and a mixture (64 mg) of **4c**, R_f 0.61, and **6c**, R_f 0.64, in molar ratio 1:3 (^{1}H NMR).

5c: HRMS calcd for $C_9H_{15}NO$ 153.1153, found (direct inlet) 153.1114. MS: m/e (rel intensity) 153 (**5c**$^{\bullet+}$, 56), 152 (18), 110 (52), 83 (100), 55 (80). ^{1}H NMR: 3.20–2.90 (m, 2 H), 2.90–1.95 (m, 7 H), 1.90–1.15 (m, 6 H). ^{13}C NMR: 208.4 s, 61.6 d, 55.25 t, 55.13 t, 48.0 t, 41.2 t, 33.5 t, 25.4 t, 23.1 t. IR ($CDCl_3$): 2950, 2860, 2810, 2770 and 2700 and 2670 (Bohlmann bands), 1735, 1470, 1375, 1295, 1165, 1110 cm^{-1}.

6c: HRMS calcd for $C_9H_{15}NO$ 153.1153, found (direct inlet) 153.1116. MS: m/e (rel intensity) 153 (**6c**$^{\bullet+}$, 20), 124 (100), 82 (19). ^{1}H NMR: 11.20 (br s, 1 H), 4.90 (s, 1 H), 3.38 (m, 2 H), 2.30 (q, J = 7.5, 2 H), 2.60–2.00 (m, 2 H), 1.88–1.32 (m, 4 H), 1.08 (t, J = 7.5, 3 H). ^{13}C NMR: 198.0 s, 164.0 s, 92.2 d, 40.7 t, 34.6 t, 28.3 t, 22.2 t, 19.2 t, 10.3 q. IR ($CDCl_3$): 1615, 1560 cm^{-1}.

Cycloaddition of 1c and 8: Hexahydro-2-(3,4-dimethoxyphenyl)spiro[cyclopropane-1,2′-[2*H*]isoxazolo[2,3-*a*]pyridine] (9 and 9′). The nitrone **1c**, prepared from 8 mmol of its precursor *N*-hydroxypiperidine, was dissolved in dichloromethane (0.5 mL) and treated with 2-(3,4-dimethoxyphenyl)-methylenecyclopropane (**8**, 5 mmol) at room temperature for 4 days (until **8** was no longer detected by GC). The solvent was removed and the residue column chromatographed (eluant: diethyl ether) to give a mixture of the adducts **9** and **9′**, R_f 0.33 (1.156 g, molar ratio 1.2:1). Traces of the other regioisomers were detected by GC-MS and ^{13}C NMR.

9 and **9′** mixture: oil. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.43; H, 8.10; N, 4.93. In an attempt to obtain the MS by GC inlet, only the rearranged products were detected. ^{1}H NMR: 7.08–6.60 (m, 3 H), 3.98 (s, 6 H), 3.78–3.40 (m, 1 H), 2.65–2.06 (m, 2 H), 2.06–0.70 (m, 11 H). ^{13}C NMR (major isomer): 148.43 s, 146.95 s, 130.59 s, 118.42 d, 111.09 d, 110.82 d, 67.77 d, 66.31 s, 55.46 q (2 C), 55.23 t, 36.76 t, 28.90 t, 28.07 d, 24.32 t, 23.33 t, 18.31 t; (minor isomer): 148.31 s, 146.80 s, 130.85 s, 118.71 d, 111.50 d, 110.68 d, 68.46 d, 65.85 s, 55.46 q (2 C), 54.99 t, 36.61 t, 28.90 t, 28.07 d, 24.46 t, 23.33 t, 14.49 t. IR ($CDCl_3$): 3060, 3010, 2940, 2860, 2840, 1610, 1590, 1520, 1460, 1250, 1140, 1020 cm^{-1}.

Regioisomers of 9. MS: m/e (rel intensity) 289 (M$^{\bullet+}$, 10), 272 (20), 151 (20), 138 (18), 124 (28), 100 (100).

Rearrangement of the Cycloadducts 9 and 9′: 4-(3,4-Dimethoxyphenyl)octahydro-[2*H*]quinolizin-2-one (*cis*-10 and *trans*-11) and 2-[2′-Oxo-4′-(3,4-dimethoxyphenyl)butylidene]piperidine (12). A solution of the mixture of the cycloadducts **9** and **9′** (0.45 g, 1.56 mmol) in mesitylene (40 mL) was refluxed for 4 h and then the solvent was removed in vacuo. The

residue was column-chromatographed (eluant: diethyl ether) to give **11**, R_f 0.28, 121 mg (38%); **12**, R_f 0.17, 65 mg (14%); and **10**, R_f 0.09, 119 mg (26%).

10 (cis isomer), yellow oil. MS: *m/e* (rel intensity) 289 (**10**$^{\bullet+}$, 5), 206 (14), 175 (27), 164 (100). ^{1}H NMR (close to the reported values):[4] 6.70–6.50 (m, 3 H), 4.22 (dd, J = 6, 4.5, 1 H), 3.87 (s, 6 H), 2.96–1.92 (m, 7 H), 1.68–1.00 (m, 6 H). ^{13}C NMR: 209.08 s, 148.59 s, 148.34 s, 130.94 s, 120.78 d, 111.56 d, 110.48 d, 63.60 d, 55.75 q, 55.68 q, 54.31 d, 51.10 t, 47.23 t, 46.55 t, 31.47 t, 23.61 t, 23.12 t. IR ($CDCl_3$): 1700 cm^{-1}.

11 (trans isomer), mp 83–84 °C, as reported.[4] MS: identical with that of **10**, in agreement with a previous report.[24] ^{1}H NMR (one additional signal reported):[4] 7.01 (s, 1 H), 6.94 (s, 2 H), 4.13 (s, 3 H), 3.98 (s, 3 H), 3.23 (dd, J = 11, 3.6, 1 H), 2.85–2.20 (m, 6 H), 2.00–1.12 (m, 7 H). ^{13}C NMR: 207.35 s, 149.09 s, 148.08 s, 134.92 s, 119.22 d, 110.84 d, 109.54 d, 69.64 d, 62.12 d, 55.67 q, 55.58 q, 52.47 t, 50.55 t, 48.41 t, 34.04 t, 25.54 t, 23.89 t. IR (CCl_4): 2790 and 2750 (Bohlmann bands), 1730 cm^{-1}.

12, red crystals, mp 56–57 °C. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.42; H, 8.33; N, 4.56. MS: *m/e* (rel intensity) 289 (**12**$^{\bullet+}$, 10), 151 (12), 124 (100), 97 (99). ^{1}H NMR: 11.10 (br s, 1 H), 6.85 (s, 3 H), 4.95 (s, 1 H), 3.95 (s, 6 H), 3.45 (m, 2 H), 3.00–2.75 (m, 2 H), 2.70–2.12 (m, 4 H), 2.05–1.55 (m, 4 H). ^{13}C NMR: 195.56 s, 164.25 s, 148.57 s, 146.93 s, 134.75 s, 119.87 d, 111.64 d, 111.09 d, 92.84 d, 55.74 q, 55.59 q, 43.46 t, 40.78 t, 31.79 t, 28.27 t, 22.10 t, 19.14 t. IR ($CDCl_3$): 1610, 1555 cm^{-1}.

3,4-Dihydro-β-carboline 2-Oxide (14) and Methylenecyclopropane (2): Cycloadducts 15 and 16. The nitrone **14** (748 mg, 4 mmol) was heated at 70 °C with an excess of **2** (702 mg, 13 mmol) in a sealed tube for 2 days. The mixture was passed over a pad of silica gel, and washed with methylene chloride (120 mL) to remove impurities and then with ethyl acetate (250 mL). Concentration of the acetate solution gave the products **15** and **16** in molar ratio 2:1 (^{1}H NMR) as a viscous oil, 769 mg. Attempted chromatographic separation failed; however, by treating the oil with a little chloroform, pure **15** was isolated (200 mg), while **16** was obtained after rearrangement of the mixture (see below).

15, mp 178–179 °C. Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.02; H, 6.42; N, 11.48. In an attempt to obtain the MS by GC inlet, only the rearranged products were detected. ^{1}H NMR (300 MHz): 8.00 (br s, 1 H), 7.55 (m, 1 H), 7.39–7.06 (m, 3 H), 4.82 (t, J = 7.5, 1 H), 3.72–3.52 (m, 1 H), 3.43–3.29 (m, 1 H), 2.92 (t, J = 6, 2 H), 2.68 (dd, J_{gem} = 11, J = 8, 1 H), 2.42 (dd, J_{gem} = 11, J = 7, 1 H), 0.98 (m, 2 H), 0.68 (m, 2 H). ^{13}C NMR: 136.51 s, 132.52 s, 126.28 s, 121.67 d, 119.46 d, 118.19 d, 110.89 d, 107.59 s, 63.43 s, 59.75 d, 49.36 t, 40.63 t, 19.31 t, 12.30 t, 9.05 t. IR (KBr): 3400, 3140, 3060, 2940, 2850, 1450, 1325, 1225 cm^{-1}.

16, light-brown crystals, from ligroin, mp 167–169 °C. Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.20; H, 6.79; N, 11.76. MS: *m/e* (rel intensity) 240 (**16**$^{\bullet+}$, 54), 239 (100), 197 (32), 156 (49). ^{1}H NMR: 8.20 (br s, 1 H), 7.70–7.43 (m, 1 H), 7.37–7.03 (m, 3 H), 4.60 (s, 1 H), 4.12 (s, 2 H), 3.70–3.20 (m, 2 H), 3.12–2.70 (m, 2 H), 1.08–0.37 (m, 4 H). ^{13}C NMR: 136.64 s, 129.37 s, 126.28 s, 121.65 d, 119.39 d, 118.17 d, 110.91 d, 108.60 s, 74.53 t, 63.25 d, 49.21 t, 28.57 s, 20.16 t, 10.52 t, 6.43 t. IR (KBr): 3400, 3160, 3060, 2960, 2920, 2860, 1455, 1360, 1250 cm^{-1}.

Rearrangement of the Cycloadduct 15: 3,4,6,7,12,12b-Hexahydroindolo[2,3-*a*]quinolizin-2(1*H*)-one (17) and 1,2,3,4-Tetrahydro-1-(2-oxobutylidene)-9*H*-pyrido[3,4-*b*]indole (18). A hot solution of the cycloadduct **15** (140 mg, 0.58 mmol) in mesitylene (15 mL) was refluxed 4 h, then the solvent was removed in vacuo. The residue was column-chromatographed (eluant: light petroleum ether + ethyl acetate, 1:1) to give **18**, R_f 0.35, 29 mg (21%), and **17**, R_f 0.15, 70 mg (50%). The same reaction, carried out on a mixture of the cycloadducts **15** and **16**, allowed the regioisomer **16** to be isolated, R_f 0.29.

17, pale yellow crystals, mp 180–181 °C (lit.[13] mp 181–182 °C). MS: *m/e* (rel intensity) 240 (**17**$^{\bullet+}$, 23), 225 (33), 182 (14), 171 (100). ^{1}H NMR (in agreement with available data):[15] 8.15 (br s, 1 H), 7.60–7.00 (m, 4 H), 3.60 (br d, J = 12, 1 H), 3.40–2.30 (m, 10 H). ^{13}C NMR: 207.9 s, 136.2 s, 133.1 s, 126.75 s, 121.6 d, 119.3 d, 118.0 d, 111.0 d, 108.1 s, 58.3 d, 54.0 t, 51.6 t, 45.4 t, 41.4 t, 21.6 t. IR ($CDCl_3$): 3480, 3400, 3060, 2965, 2930, 2860, 2815 and 2765 and 2700 (Bohlmann bands), 1730, 1470, 1350, 1150 cm^{-1}.

18, brown waxy solid. MS: *m/e* (rel intensity) 240 (**18**$^{\bullet+}$, 25), 211 (100), 154 (11). ^{1}H NMR: 10.30 (br s, 1 H), 9.05 (br s, 1 H), 7.78–7.02 (m, 4 H), 5.40 (s, 1 H), 3.60 (m, 2 H), 2.98 (m, 2 H), 2.40 (q, J = 7, 2 H), 1.20 (t, J = 7, 3 H). ^{13}C NMR: 199.9 s, 150.8 s, 137.4 s, 127.5 s, 125.95 s, 124.8 d, 120.3 d, 119.5 d, 116.9 s, 111.6 d, 87.8 d, 40.0 t, 35.3 t, 20.3 t, 10.1 q. IR ($CDCl_3$): 3480, 1630, 1615, 1570, 1535 cm^{-1}.

3,4-Dihydro-6,7-dimethoxyisoquinoline *N*-Oxide (19) and Methylenecyclopropane (2): Cycloadducts 20 and 21. The nitrone **19** (528 mg, 2.55 mmol) in methylene chloride (0.6 mL) was heated at 45 °C with an excess of **2** (338 mg, 6.2 mmol) in a sealed tube for 3 days. The mixture was passed over a pad of silica gel and washed with ethyl acetate to give, after solvent removal, a mixture of the adducts **20** and **21** in molar ratio 1.7:1 (488 mg, 73%). Attempted separation failed; the isomer **21** was isolated after rearrangement of the mixture (see below).

20, spectral data obtained from a mixture with the isomer **21**. ^{1}H NMR: 6.73 (s, 1 H), 6.70 (s, 1 H), 4.80 (t, J = 9, 1 H). ^{13}C NMR: 147.50 s (2 C), 127.42 s, 124.92 s, 110.61 d, 109. 57 d, 62.87 d, 62.78 s, 55.67 q (2 C), 48.34 t, 42.72 t, 27.07 t, 12.04 t, 8.64 t.

21, mp 75–76 °C, from light petroleum ether. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.28; H, 7.71; N, 5.16. MS (direct inlet): *m/e* (rel intensity) 261 (**21**$^{\bullet+}$, 47), 260 (37), 246 (100), 232 (17), 218 (10), 207 (16). ^{1}H NMR (300 MHz): 6.61 (s, 1 H), 6.25 (s, 1 H), 4.45 (s, 1 H), 4.13 and 4.01 (doublets, AB system, J_{gem} = 7, 2 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 3.40, 3.23, 3.08, 2.80, 0.79, 0.67, 0.41 and 0.24 (series of multiplets, 1 H each). ^{13}C NMR: 148.01 s, 147.22 s, 125.88 s, 123.51 s, 111.03 d, 108.75 d, 74.28 t, 65.20 d, 55.81 q, 55.64 q, 48.28 t, 28.67 t, 28.47 s, 11.15 t, 4.35 t. IR (CCl_4): 3080, 3005, 2960, 2940, 2910, 2840, 2820, 1460, 1355, 1255, 1120 cm^{-1}.

Rearrangement of the Cycloadduct 20: Hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizin-2-one (22) and 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2-oxobutylidene)quinoline (23). A solution of the mixture of the cycloadducts **20** (191 mg) and **21** (113 mg) in mesitylene (23 mL) was refluxed for 2.5 h. The solution was then column-chromatographed (eluant: light petroleum ether, in order to remove mesitylene, then ethyl acetate); a fraction with R_f 0.53–0.48, 130 mg, containing unchanged **21** and the enaminone **23** in 1:1 molar ratio, was followed by the product **22**, R_f 0.28, 117 mg (61%). From the mixture of **21** and **23**, only pure **21** could be isolated by repeated chromatography.

22, mp 152–154 °C. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.40; H, 7.04; N, 5.82. MS (direct inlet): *m/e* (rel intensity) 261 (**22**$^{\bullet+}$, 32), 260 (56), 218 (11), 191 (16), 149 (100). ^{1}H NMR (300 MHz): 6.59 (s, 1 H), 6.51 (s, 1 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 3.45 (dd, J = 12, 3, 1 H), 3.23 (m, 1 H), 3.07 (m, 2 H), 2.85 (dt, J_{gem} = 15, J = 3, 1 H), 2.77–2.33 (m, 6 H). ^{13}C NMR: 208.54 s, 147.69 s, 147.41 s, 128.41 s, 126.04 s, 111.36 d, 107.69 d, 61.37 d, 55.83 q, 55.75 q, 54.62 t, 50.63 t, 47.43 t, 40.96 t, 29.18 t. IR (CCl_4): 3000, 2960, 2940, 2910, 2800 and 2760 (Bohlmann bands), 1730, 1470, 1360, 1260, 1160 cm^{-1}.

23, spectral data obtained from a mixture with the isomer **21**. ^{1}H NMR: 11.25 (br s, 1 H), 7.10 (s, 1 H), 6.62 (s, 1 H), 5.45 (s, 1 H), 3.85 (s, 6 H), 3.37 (m, 2 H), 2.72 (m, 2 H), 2.28 (q, J = 8, 2 H), 1.05 (t, J = 8, 3 H). ^{13}C NMR: 198.95 s, 156.9 s, 151.3 s, 147.75 s, 130.4 s, 121.1 s, 110.6 d, 108.2 d, 88.0 d, 56.0 q, 55.8 q, 38.4 t, 35.2 t, 27.9 t, 10.3 q. IR (CCl_4): 1615, 1515 cm^{-1}.

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Registry No. **1a**, 3376-23-6; **1b**, 3317-61-1; **1c**, 34418-91-2; **2**, 6142-73-0; **3a**, 106051-09-6; **3b**, 106051-11-0; **3c**, 106051-13-2; **4a**, 106051-10-9; **4b**, 106051-12-1; **4c**, 106051-14-3; **5a**, 91640-05-0; **5b**, 106051-16-5; **5c**, 23581-42-2; **6a**, 106051-15-4; **6b**, 106051-17-6; **6c**, 106051-18-7; **8**, 112840-38-7; **9**, 112840-39-8; **9′**, 112924-59-1; **10**, 112840-40-1; **11**, 71593-15-2; **12**, 112840-41-2; **14**, 112863-43-1; **15**, 112840-42-3; **16**, 112863-44-2; **17**, 1217-82-9; **18**, 112840-43-4; **19**, 84122-10-1; **20**, 112840-44-5; **21**, 112840-45-6; **22**, 841-95-2; **23**, 112840-46-7; $MeCHCl_2$, 75-34-3; dimethoxystyrene, 6380-23-0; 1-chloro-1-methyl-2-(3,4-dimethoxyphenyl)cyclopropane, 112840-47-8; 1,2,3,4-tetrahydro-β-carboline, 16502-01-5; 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline, 1745-07-9.