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Synthesis of Stable Δ^4-Isoxazolines by 1,3-Dipolar Cycloaddition of 3,4-Dihydroisoquinoline *N*-Oxides with Alkynes and Their Rearrangement to Isoquinoline-Fused Pyrroles[1]

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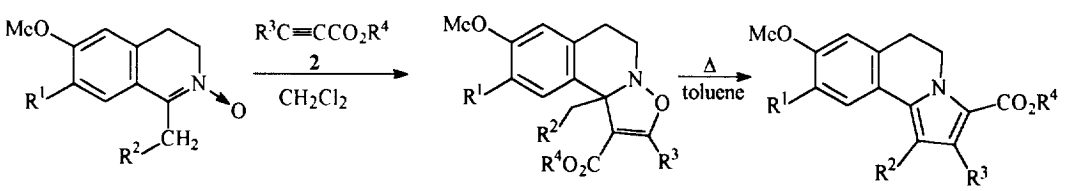
Abstracts: *Novel stable 4-substituted Δ^4-isoxazoline derivatives were obtained by cycloaddition reaction of isoquinoline N-oxides with alkynes. The thermal reaction of some 4-isoxazoline derivatives leading to isoquinoline-fused pyrroles was investigated and it was found that the pathway of the rearrangement to pyrroles is consistent with the way involving acylaziridine.*

The 1,3-dipolar cycloaddition reaction has attracted considerable attention as a convenient tool for constructing various five-membered heterocycles and synthesizing a wide variety of natural products.[2] Nitrones are well known to behave as 1,3-dipoles in cycloaddition reactions with alkynes, alkenes, isocyanates, isothiocyanates, thiocarbonyl compounds, phosphoranes, sulphenes, and sulphinyl compounds. It is well documented that nitrones react efficiently with alkynes to afford Δ^4-isoxazolines.[3] However, a number of the isoxazolines can not be isolable because they are unstable under the conditions at which they are formed.[4] The isoxazolines sometimes undergo interesting transformations, for example, a few of the rearrangement to pyrroles have been reported.[5] We are interested in the synthesis of fused pyrroles which would be hoped to have new bioactivity. In our preceding paper we reported that 3,4-dihydroisoquinoline *N*-oxides were successfully synthesized by *m*-CPBA oxidation of the corresponding 3,4-dihydroisoquinolines.[1] We wish to report herein the synthesis of stable Δ^4-isoxazolines and pyrrole derivatives fused to 3,4-dihydroisoquinoline skeletons based on the cycloaddition of 3,4-dihydroisoquinoline *N*-oxides with alkynes and the rearrangement as depicted in Scheme 1.



1 **3** **4**

Scheme 1

RESULTS AND DISCUSSION

Synthesis of Stable Δ^4-isoxazolines

Alkynes undergo facile thermal cycloaddition reactions with nitrones. In the case of unsymmetrical alkynes, the regioselectivity depends on whether the dominant interaction is between the HOMO of the nitrone and the LUMO of the acetylene or the nitrone LUMO and the acetylene HOMO.[6] It was known that a variety of nitrones react with methyl propiolate to provide the corresponding 4-substituted Δ^4-isoxazolines exclusively.[7] The present cycloaddition of 3,4-dihydroisoquinoline *N*-oxides (**1**) with alkynes (**2**) produced also stable 4-substituted Δ^4-isoxazolines (**3**) in 35-98 % yields at rt (20-25 °C) and these results are summarized in Table 1. The structures of these cycloadducts were confirmed by the spectral inspections. These compounds contain strong absorption in the carbon-carbon double bond stretching region ranging from 1603 to 1660 cm^{-1} due to the vinyl ether group. When alkynes (**2**) are unsymetrical terminal acetylenes, i.e. (**2**) ($\mathbf{R^3}$ = H) such as methyl propiolate and ethyl propiolate, the cycloaddition was regioselective, affording only 4-substituted isoxazolines **3a**, **3b** **3e**, **3f**, **3k**, and **3l**. The vinyl hydrogen at isoxazolines C-5 is strongly deshielded, appearing in the region of δ 7.25-7.32 ppm as a doublet peak (J = 1.8 Hz) due to a long range coupling with one of hydrogen at dihydroisoquinoline C-3 in ^{1}H NMR.

Table 1. Cycloadditions of 3,4-Dihydroisoquinoline *N*-Oxides with Alkynes[a]

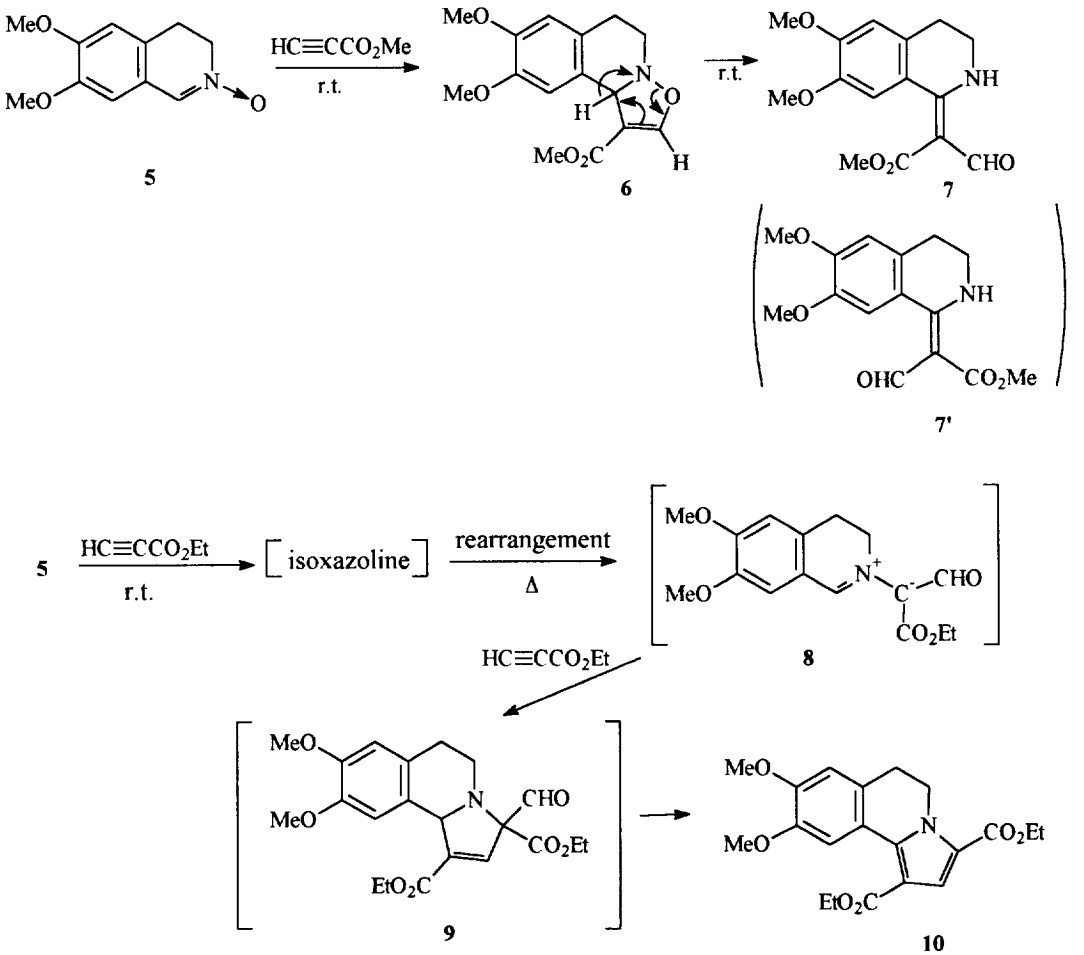
entry	$\mathbf{R^1}$	$\mathbf{R^2}$	$\mathbf{R^3}$	$\mathbf{R^4}$	Temp °C	Time hrs	Product	Yield %[b]	mp °C
1	OMe	H	H	Me	rt	7	**3a**	40	oil
2	OMe	H	H	Et	40	10	**3b**	68	oil
3	OMe	H	CO_2Me	Me	rt	1	**3c**	83	oil
4	OMe	H	CO_2Et	Et	rt	3	**3d**	55	oil
5	H	H	H	Me	rt	16	**3e**	69	oil
6	H	H	H	Et	rt	16	**3f**	68	oil
7	H	H	CO_2Me	Me	rt	2	**3g**	77	oil
8	H	H	CO_2Et	Et	rt	2	**3h**	49	oil
9	OMe	Me	CO_2Me	Me	rt	2	**3i**	60	138-139
10	OMe	Me	CO_2Et	Et	rt	2	**3j**	60	77-79
11	OMe	Ph	H	Me	rt	13	**3k**	74	43-45
12	OMe	Ph	H	Et	rt	13	**3l**	35	29-31
13	OMe	Ph	CO_2Me	Me	rt	4	**3m**	98	108-110

[a] All reactions were carried out in CH_2Cl_2 using 1.5 equiv. of alkynes.

[b] Isolated yields.

Furthermore, from the Table 1 we can observe that dimethyl (or diethyl) acetylenedicarboxylate was apparently more reactive than methyl (or ethyl) propiolate because the isoxazolines could be obtained with high yields in a shorter reaction time.

It was reported that the reaction of 3,4-dihydroisoquinoline *N*-oxide with methyl propiolate afforded the stable azomethine ylides through ring opening of ketoaziridine rearrangement from initial Δ^4-isoxazoline,[8] and 3,4-dihydro-6,7-dimethoxyisoquinoline *N*-oxide (**5**) was treated with ethyl propiolate (2.5 equiv.) in benzene at room temperature for 14 h, followed by heating under reflux for 3 h to give diethyl 5,6-dihydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline-1,3-dicarboxylate (**10**) via (**8**) and (**9**) (Scheme 2).[9] In the present cycloaddition product of (**5**) with methyl propiolate was isolable as relatively stable isoxazoline (**6**) which, however, isomerized ultimately to compound (**7**) on standing for one day at room temperature. The NOESY spectrum was consistent with the structure (**7**) rather than isomer (**7'**). These facts could be explained by two different pathways for the rearrangement of Δ^4-isoxazoline, initial cycloadduct such as (**6**) depending on the reaction conditions as depicted in Scheme 2.

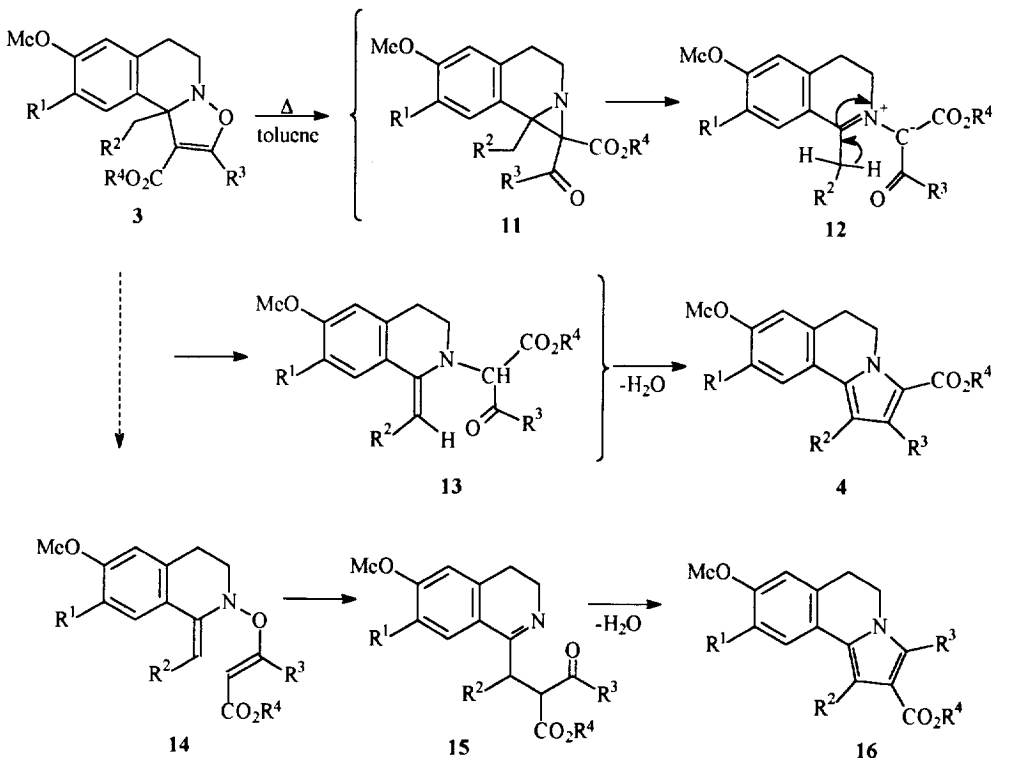


Scheme 2

Rearrangement of Isoxazolines (3) to 3,4-Dihydroisoquinoline-Fused Pyrroles (4)

It has been reported that the thermal conversion of 3-methyl-Δ^4-isoxazolines and 3-substituted-methylene-Δ^4-isoxazolines to pyrroles can be explained by two pathways, i.e., the hetero-Cope process involving enamine formation and the path involving acylaziridine.[5a,10] In the case of isoxazolines mentioned above, the rearrangement occurred cleanly by heating in toluene to give pyrroles (**4**) in the way of acylaziridine as shown Scheme 3. In general, a solution of isoxazoline (**3**) in dry toluene was heated in a sealed tube at 120-140 °C under an atmosphere of argon until the isoxazoline was converted completely (the reaction was monitored by TLC). Then the separation of product was carried out by preparative TLC. The results are summarized in Table 2.

The structure of the pyrroles (**4**) was confirmed by spectral inspections. In the case of **4a, 4b, 4e,** and **4f**, the ^{1}H NMR spectrum showed two doublet peaks at 7.01 ppm and 6.42 ppm with a coupling constant J = 4.0 Hz that were assignable to C_2-H and C_1-H protons, respectively. Furthermore, the ^{1}H NMR spectrum of **4k** showed a singlet peak at 7.01 ppm and multiplet peaks at 7.30-7.50 ppm due to C_2-H and C_1-Ph protons, respectively. The ^{1}H NMR spectrum of **4c, 4d, 4g** and **4h** also showed the C_1-H proton signal at 6.72-6.74 ppm. The hetero-Cope process would produce a different regioisomer (**16**), but this route was denied by the above structural assignment.



Scheme 3

Table 2. Rearrangement of Isoxazolines (**3**) to Pyrroles (**4**)[a]

entry	3	R^1	R^2	R^3	R^4	Temp °C	Time hrs	Product 4	Yield %[b]	mp °C
1	**3a**	OMe	H	H	Me	140	8	**4a**	96	106-108
2	**3b**	OMe	H	H	Et	140	3	**4b**	93	130-133
3	**3c**	OMe	H	CO_2Me	Me	140	12	**4c**	79	132-134
4	**3d**	OMe	H	CO_2Et	Et	120	3	**4d**	54	oil
5	**3e**	H	H	H	Me	130	1.5	**4e**	61	91-92
6	**3f**	H	H	H	Et	130	2.5	**4f**	87	72-73
7	**3g**	H	H	CO_2Me	Me	120	4	**4g**	70	115-116
8	**3h**	H	H	CO_2Et	Et	120	4	**4h**	75	113-114
9	**3i**	OMe	Me	CO_2Me	Me	120	7	**4i**	53	104-106
10	**3j**	OMe	Me	CO_2Et	Et	120	7	**4j**	42	oil
11	**3k**	OMe	Ph	H	Me	120	7	**4k**	42	137-138

[a] All reactions were carried out in a sealed tube using toluene solution under an atmosphere of argon.

[b] Isolated yields.

In conclusions, 4-substituted isoxazolines **3** were obtained by cycloadditions of 3,4-dihydroisoquinoline *N*-oxides **1** with alkynes **2**. The isoxazolines **3** were rearranged thermally to afford 3,4-dihydroisoquinoline-fused pyrroles **4** selectively via acylaziridine pathway.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The IR spectra of liquids were measured as films on sodium chloride plates and those of solids were measured in pressed potassium bromide discs on a JASCO FT/IR 5300 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on a Varian GEMINI 200 spectrometer at 200 and at 50 MHz, respectively. Chemical shifts are recorded in part per million (ppm) for samples in $CDCl_3$ solution with Me_4Si as internal standard. Coupling constants *J* are reported in Hz. Elemental analyses were carried out on a Perkin-Elmer 2400S elemental analyzer. Mass spectra (EI) were obtained using a JEOL JMS-AX505 HA mass spectrometer at 70 eV. The thin layer chromatography (TLC) was performed on Merck Kieselgel $60F_{254}$.

General Procedure for the Synthesis of Isoxazolines (3). A solution of 3,4-dihydroisoquinoline *N*-oxide (**1**) (0.2 mmol) and alkyne (**2**) (0.3 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for an appropriate time, while the reaction was monitored by TLC. After removal of the solvent under a reduced

pressure, separation of the residue with preparative TLC (silica gel) gave the products **3** (**a-m**). For the reaction conditions and yields, see Table 1.

Methyl 5,6-dihydro-8,9-dimethoxy-10b-methylisoxazolo[3,2-*a*]isoquinoline-1-carboxylate (3a). A colorless oil; R_f = 0.53 (EtOAc/Hexane, 2:1); IR (neat), ν (cm^{-1}) 1703, 1603, 1514, 1439, 1259, 1204, 1141, 1103, 1070, 999, 916, 875, 785, 769; ^1H NMR, δ 1.91 (s, 3H), 2.49 (ddd, 1H, *J* = 15.8, 3.4 and 3.0), 3.08 (ddd, 1H, *J* = 15.8, 11.2 and 4.0), 3.31(dddd, 1H, *J* = 14.2, 11.2, 3.4 and 1.8), 3.69 (s, 3H), 3.85 (ddd, 1H, *J* = 14.2, 4.0 and 3.0), 3.86 (s, 3H), 3.88 (s, 3H) , 6.55 (s, 1H), 7.31 (d, 1H, *J* = 1.8), 7.42 (s, 1H); ^{13}C NMR, δ 23.4, 27.5, 48.2, 51,2, 56.0, 56.2, 68.2, 111.0, 111.1, 115.2, 125.7, 131.1, 148.1, 148.2, 155.1, 165.0; MS, m/z (%) 305 (M^+, 12), 291 (27), 290 (100), 287 (21). *Anal* Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.90; H, 6.44; N, 4.23.

Ethyl 5,6-dihydro-8,9-dimethoxy-10b-methylisoxazolo[3,2-*a*]isoquinoline-1-carboxylate (3b). A colorless oil; R_f = 0.45 (EtOAc/Hexane, 1:1); IR (neat), ν (cm^{-1}) 1701, 1612, 1514, 1464, 1371, 1331, 1259, 1142, 1101, 1069, 999, 878, 772; ^1H NMR, δ 1.25 (t, 3H, *J* = 7.2), 1.91 (s, 3H), 2.48 (ddd, 1H, *J* = 15.8, 3.4 and 3.0), 3.08 (ddd, 1H, *J* = 15.8, 11.4 and 4.0), 3.31 (dddd, 1H, *J* = 14.2, 11.4, 3.4 and 1.8), 3.84 (ddd, 1H, *J* = 14.2, 4.0 and 3.0), 3.85 (s, 3H), 3.87 (s, 3H), 4.14 (q, 2H, *J* = 7.2), 6.55 (s, 1H), 7.31 (d, 1H, *J* = 1.8), 7.43 (s, 1H); ^{13}C NMR, δ 14.4, 23.3, 27.5, 48.1, 56.0, 56.1, 60.0, 68.1, 111.0, 111.1, 115.4, 125.7, 131.3, 148.1, 148.2, 154.9, 164.6; MS, m/z (%) 319 (M^+, 8), 305 (16), 304 (100), 301 (22), 276 (5). *Anal* Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 64.15; H, 6.64; N, 4.17.

Dimethyl 5,6-dihydro-8,9-dimethoxy-10b-methylisoxazolo[3,2-*a*]isoquinoline-1,2-dicarboxylate (3c). A pale yellowish oil; R_f = 0.45 (EtOAc/Hexane, 3:2); IR (neat), ν (cm^{-1}) 1749, 1717, 1641, 1610, 1516, 1439, 1074, 871, 785; ^1H NMR, δ 1.89 (s, 3H), 2.59-2.72 (m, 1H), 2.94-3.09 (m, 1H), 3.28-3.41 (m, 1H), 3.64-3.70 (m, 1H), 3.72 (s, 3H), 3.85 (s, 3H), 3.86 (s, 6H), 6.56 (s, 1H), 7.18 (s, 1H); ^{13}C NMR, δ 24.5, 27.9, 48.6, 52.1, 53.2, 56.0, 56.1, 71.2, 110.4, 111.1, 116.5, 126.1, 128.9, 148.2, 148.4, 151.1, 160.1, 164.1; MS, m/z (%) 363 (M^+, 7), 349 (17), 348 (100), 346 (8), 345 (40), 305 (10), 304 (32). *Anal* Calcd for $C_{18}H_{21}NO_7$: C, 59.50; H, 5.83; N, 3.85. Found: C, 59.65; H, 5.96; N, 3.57.

Diethyl 5,6-dihydro-8,9-dimethoxy-10b-methylisoxazolo[3,2-*a*]isoquinoline-1,2-dicarboxylate (3d). A colorless oil; R_f = 0.28 (EtOAc/Hexane, 1:1); IR (neat), ν (cm^{-1}) 1748, 1709, 1639, 1516, 1466, 1402, 1371, 1258, 1213, 1180, 1144, 1099, 1072, 1024, 964, 914, 862, 783; ^1H NMR, δ 1.28 (t, 3H, *J* = 7.0), 1.33 (t, 3H, *J* = 7.0), 1.89 (s, 3H), 2.56-2.69 (m, 1H), 2.95-3.11 (m, 1H), 3.26-3.40 (m, 1H), 3.67-3.80 (m, 1H), 3.86 (s, 6H), 4.16 (q, 2H, *J* = 7.0), 4.28 (q, 2H, *J* = 7.0), 6.56 (s, 1H), 7.22 (s, 1H); ^{13}C NMR, δ 14.0 (2C), 24.4, 27.9, 48.6, 56.0, 56.1, 61.0, 62.6, 71.0, 110.6, 111.1, 115.7, 126.2, 129.2, 148.2, 148.3, 151.7, 159.9, 163.7; MS, m/z (%) 376 (52), 373 (34), 229 (39), 203(100). *Anal* Calcd for $C_{20}H_{25}NO_7$: C, 61.37; H, 6.44; N, 3.58. Found: C, 61.44; H, 6.80; N, 3.31.

Methyl 5,6-dihydro-8-methoxy-10b-methylisoxazolo[3,2-*a*]isoquinoline-1-carboxylate (3e). A colorless oil; R_f = 0.44 (EtOAc/Hexane, 1:2); IR (neat), ν (cm^{-1}) 1711, 1615, 1501, 1437, 1343, 1259, 1246, 1154, 1094, 1034, 844, 816; ^1H NMR, δ 1.91 (s, 3H), 2.53 (dt, 1H, *J* = 14.8 and 3.2), 3.09 (ddd, 1H, *J* = 14.8, 11.6 and 3.8), 3.25 (dddd, 1H, *J* = 16.0, 11.6, 3.2 and 1.8), 3.67 (s, 3H), 3.78 (s, 3H), 3.83 (ddd, 1H, *J* = 16.0, 3.8 and 3.2), 6.60 (d, 1H, *J* = 2.8), 6.78 (dd, 1H, *J* = 8.8 and 2.8), 7.32 (d, 1H, *J* = 1.8), 7.70 (d, 1H, *J* = 8.8); ^{13}C NMR, δ 24.4, 27.8, 48.8, 51.1, 55.3, 68.3, 113.0, 113.3, 115.0, 129.5, 131.0, 135.9, 154.8, 158.6, 164.7; MS, m/z (%) 275 (M^+, 3), 261 (15), 260 (100), 257 (16). *Anal* Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.50; H, 6.21; N, 5.12.

Ethyl 5,6-dihydro-8-methoxy-10b-methylisoxazolo[3,2-*a*]isoquinoline-1-carboxylate (3f). A colorless oil; R_f = 0.49 (EtOAc/Hexane, 1:2); IR (neat), ν (cm^{-1}) 1703, 1615, 1501, 1445, 1372, 1333, 1259, 1246, 1149, 1093, 1034, 844, 816; ^1H NMR, δ 1.25 (t, 3H, *J* = 7.2), 1.91 (s, 3H), 2.52 (dt, 1H, *J* = 15.2 and 3.0), 3.11 (ddd, 1H, *J* = 15.2, 11.8 and 3.8), 3.24 (dddd, 1H, *J* = 14.0, 11.8, 3.0 and 1.8), 3.78 (s, 3H), 3.81(ddd, 1H, *J* = 14.0, 3.8 and 3.0), 4.13 (qd, 2H, *J* =7.2 and 3.2), 6.60 (d, 1H, *J* = 2.8), 6.78 (dd, 1H, *J* = 8.8 and 2.8), 7.32 (d, 1H, *J* = 1.8), 7.71 (d, 1H, *J* = 8.8); ^{13}C NMR, δ 14.3, 24.4, 27.9, 48.8, 55.3, 60.0, 68.3, 113.0, 113.3, 115.3, 129.6, 131.1, 135.9, 154.7, 158.6, 164.3; MS, m/z (%) 289 (M^+, 4), 275 (16), 274 (100), 271 (33), 246 (15). *Anal* Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.49; H, 6.67; N, 4.80.

Dimethyl 5,6-dihydro-8-methoxy-10b-methylisoxazolo[3,2-*a*]isoquinoline-1,2-dicarboxylate (3g). A colorless oil; R_f = 0.39 (EtOAc/Hexane, 1:2); IR (neat), ν (cm^{-1}) 1751, 1718, 1641, 1610, 1502, 1437, 1315, 1267, 1213, 1167, 1138, 1095, 1032, 1005, 910, 827, 785; ^1H NMR, δ 1.88 (s, 3H), 2.65-2.78 (m, 1H), 2.97-3.12 (m, 1H), 3.24-3.37 (m, 1H), 3.62-3.71 (m, 1H), 3.72 (s, 3H), 3.78 (s, 3H), 3.85 (s, 3H), 6.61 (d, 1H, *J* = 2.6), 6.75 (dd, 1H, *J* = 8.8 and 2.6), 7.47 (d, 1H, *J* = 8.8); ^{13}C NMR, δ 25.6, 28.2, 49.1, 52.0, 53.1, 55.4, 71.4, 113.2, 113.3, 116.6, 128.9, 129.0, 136.0, 150.7, 158.9, 160.1, 163.8; MS, m/z (%) 333 (M^+, 1), 318 (100). *Anal* Calcd for $C_{17}H_{19}NO_6$: C, 61.25; H, 5.75; N, 4.20. Found: C, 61.29; H, 5.88; N, 4.02.

Diethyl 5,6-dihydro-8-methoxy-10b-methylisoxazolo[3,2-*a*]isoquinoline-1,2-dicarboxylate (3h). A colorless oil; R_f = 0.47 (EtOAc/Hexane, 1:2); IR (neat), ν (cm^{-1}) 1747, 1711, 1641, 1610, 1500, 1466, 1446, 1371, 1309, 1178, 1094, 1031, 858, 818; ^1H NMR, δ 1.23 (t, 3H, *J* = 7.0), 1.33 (t, 3H, *J* = 7.0), 1.89 (s, 3H), 2.63-2.76 (m, 1H), 2.99-3.13 (m, 1H), 3.29-3.36 (m, 1H), 3.64-3.76 (m, 1H), 3.79 (s, 3H), 4.15 (qd, 2H, *J* = 7.0 and 1.2), 4.28 (q, 2H, *J* = 7.0), 6.61 (d, 1H, *J* = 2.6), 6.75 (dd, 1H, *J* = 8.8 and 2.6), 7.50 (d, 1H, *J* = 8.8); ^{13}C NMR, δ 14.0 (2C), 25.5, 28.2, 49.2, 55.4, 61.0, 62.6, 71.3, 113.1, 113.3, 116.0, 129.1, 129.2, 136.1, 151.2, 158.8, 159.9, 163.4; MS, m/z (%) 361 (M^+, 1), 346 (100), 343 (29). *Anal* Calcd for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41; N, 3.88. Found: C, 63.20; H, 6.38; N, 3.92.

Dimethyl 5,6-dihydro-8,9-dimethoxy-10b-ethylisoxazolo[3,2-*a*]isoquinoline-1,2-dicarboxylate (3i). A white solid, mp 138-139 °C; R_f = 0.43 (EtOAc/Hexane, 1:1); IR (KBr), ν (cm^{-1}) 1749, 1718, 1657, 1612, 1524, 1469, 1362, 1300, 1209, 1161, 1115, 1072, 1022, 960, 903, 885, 794; ^1H NMR, δ 0.89 (t, 3H, *J* = 7.2), 2.01-2.18 (m, 1H), 2.26-2.44 (m, 1H), 2.61-2.74 (m, 1H), 2.86-3.01 (m, 1H), 3.25-3.38 (m, 1H), 3.57-3.70 (m, 1H), 3.71 (s, 3H), 3.85 (s, 6H), 3.86 (s, 3H), 6.57 (s, 1H), 7.11 (s, 1H); ^{13}C NMR, δ 8.6, 25.0, 32.4, 49.6,

52.1, 53.1, 55.9, 56.1, 75.2, 110.3, 111.1, 115.8, 127.5, 127.6, 148.1, 148.3, 150.6, 160.1, 164.2; MS, m/z (%) 377 (M^+, 2), 349 (39), 348 (100), 320 (9), 319 (4), 318 (18), 305 (11), 290 (4), 288 (4), 286 (5), 258 (5). *Anal* Calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.30; H, 6.31; N, 3.71.

Diethyl 5,6-dihydro-8,9-dimethoxy-10b-ethylisoxazolo[3,2-*a*]isoquinoline-1,2-dicarboxylate (3j). A pale yellowish solid, mp 77-79 °C; R_f = 0.32 (EtOAc/Hexane, 1:1); IR (KBr), ν (cm^{-1}) 1741, 1711, 1651, 1521, 1462, 1369, 1263, 1207, 1157, 1076, 1024, 864, 792; ^{1}H NMR, δ 0.90 (t, 3H, *J* = 7.2), 1.23 (t, 3H, *J* = 7.2), 1.33 (t, 3H, *J* = 7.2), 2.10-2.19 (m, 1H), 2.28-2.46 (m, 1H), 2.59-2.72 (m, 1H), 2.88-3.02 (m, 1H), 3.24-3.37 (m, 1H), 3.60-3.71 (m, 1H), 3.85 (s, 3H), 3.86 (s, 3H), 4.14 (q, 2H, *J* = 7.2), 4.28 (q, 2H, *J* =7.2), 6.57 (s, 1H), 7.15 (s, 1H); ^{13}C NMR, δ 8.6, 14.0 (2C), 24.9, 32.4, 49.5, 55.9, 56.1, 61.0, 62.5, 75.0, 110.5, 111.0, 115.0, 127.6, 127.8, 148.1, 148.2, 151.1, 159.9, 163.8; MS, m/z (%) 405 (M^+, 1), 387 (5), 378 (3), 377 (19), 327 (100), 320 (4). *Anal* Calcd for $C_{21}H_{27}NO_7$: C, 62.21; H, 6.71; N, 3.45. Found: C, 62.19; H, 6.74; N, 3.43.

Methyl 5,6-dihydro-8,9-dimethoxy-10b-benzylisoxazolo[3,2-*a*]isoquinoline-1-carboxylate (3k). A pale yellowish solid, mp 43-45 °C; R_f = 0.48 (EtOAc/Hexane, 1:1); IR (KBr), ν (cm^{-1}) 1701, 1613, 1516, 1439, 1346, 1261, 1115, 781; ^{1}H NMR, δ 2.28 (dt, 1H, *J* = 15.6 and 3.4), 2.67 (dddd, 1H, *J* = 11.6, 11.2, 3.4 and 1.8), 2.91 (ddd, 1H, *J* = 15.6, 11.2 and 3.8), 3.51-3.58 (m, 1H), 3.61 (ddd, 1H, *J* = 11.6, 3.8 and 3.4), 3.70 (s, 3H), 3.75-3.82 (m, 1H), 3.85 (s, 3H), 3.96 (s, 3H), 6.49 (s, 1H), 7.07-7.18 (m, 5H), 7.26 (d, 1H, *J* = 1.8), 7.73 (s, 1H); ^{13}C NMR, δ 23.3, 45.4, 49.1, 52.3, 55.9, 56.2, 71.8, 111.1, 111.4, 114.3, 126.7, 127.2, 128.0 (2C), 129.5, 131.3 (2C), 137.1, 147.9, 148.1, 155.2, 165.1; MS, m/z (%) 363 (20), 290 (100). *Anal* Calcd for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.24; H, 6.10; N, 3.71.

Ethyl 5,6-dihydro-8,9-dimethoxy-10b-benzylisoxazolo[3,2-*a*]isoquinoline-1-carboxylate (3l). A pale yellowish solid, mp 29-31 °C; R_f = 0.39 (EtOAc/Hexane, 1:1); IR (KBr), ν (cm^{-1}) 1701, 1613, 1516, 1464, 1329, 1261, 1221, 1115, 873, 781; ^{1}H NMR, δ 1.26 (t, 3H, *J* = 7.2), 2.27 (ddd, 1H, *J* = 15.6, 3.6 and 3.0), 2.68 (dddd, 1H, *J* =16.0, 10.8, 3.6 and 1.8), 2.92 (ddd, 1H, *J* = 15.6, 10.8 and 4.0), 3.25-3.56 (m, 1H), 3.59 (ddd, 1H, *J* = 16.0, 4.0 and 3.0), 3.74-3.81 (m, 1H), 3.85 (s, 3H), 3.96 (s, 3H), 4.18 (q, 2H, *J* = 7.2), 6.49 (s, 1H), 7.08-7.19 (m, 5H), 7.25 (d, 1H, *J* = 1.8), 7.74 (s, 1H); ^{13}C NMR, δ 14.4, 23.3, 45.4, 49.0, 55.9, 56.3, 60.1, 71.8, 111.1, 111.4, 114.5, 126.7, 127.2, 128.0 (2C), 129.7, 131.3 (2C), 137.2, 147.9, 148.0, 155.0, 164.8; MS, m/z (%) 377 (26), 304 (100). *Anal* Calcd for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.82; H, 6.41; N, 3.57.

Dimethyl 5,6-dihydro-8,9-dimethoxy-10b-benzylisoxazolo[3,2-*a*]isoquinoline-1,2-dicarboxylate (3m). A pale yellowish solid, mp 108-110 °C; R_f = 0.39 (EtOAc/Hexane, 1:1); IR (KBr), ν (cm^{-1}) 1738, 1714, 1660, 1611, 1520, 1439, 1321, 1285, 1219, 1167, 1115, 1049, 866, 795; ^{1}H NMR, δ 2.32-2.45 (m, 1H), 2.70-2.96 (m, 2H), 3.38- 3.50 (m, 1H), 3.53-3.70 (m, 2H), 3.75 (s, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 3.93 (s, 3H), 6.46 (s, 1H), 7.10-7.15 (m, 5H), 7.38 (s, 1H); ^{13}C NMR, δ 24.9, 45.9, 49.5, 52.2, 53.1, 55.9, 56.2, 75.2, 110.6, 111.1, 116.0, 126.8, 127.1, 127.8, 127.9 (2C), 131.4 (2C), 136.3, 147.9, 148.4, 150.8, 159.9, 164.5; MS, m/z (%) 423 (2), 422 (9), 421 (32), 348 (100), 349 (20), 91 (3). *Anal* Calcd for $C_{24}H_{25}NO_7$: C, 65.59; H,

5.73; N, 3.19. Found: C, 65.62; H, 5.55; N, 3.19.

General Procedure for Thermal Rearrangement of (3) to Pyrroles (4) (a-k). A solution of (**3**) (0.1 mmol) in dry toluene (1 mL) was heated in a sealed tube at 120-140 °C for a period of time under an atmosphere of argon. After evaporation of the solvent under a reduced pressure, the product was separated on preparative TLC (silica gel) to give the pyrrole (**4**). For the reaction conditions and yields, see Table 2.

Methyl 5,6-dihydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (4a). A white solid, mp 106-108 °C; R_f = 0.43 (CH_2Cl_2); IR (KBr), ν (cm^{-1}) 1701, 1614, 1550, 1493, 1429, 1361, 1249, 1211, 1155, 1132, 1064, 1033, 1008, 856, 790, 760; ^{1}H NMR, δ 3.01 (t, 2H, *J* = 7.0), 3.83 (s, 3H), 3.91 (s, 3H), 3.93 (s, 3H), 4.61 (t, 2H, *J* = 7.0), 6.43 (d, 1H, *J* = 4.0), 6.74 (s, 1H), 7.01 (d, 1H, *J* =4.0), 7.05 (s, 1H); ^{13}C NMR, δ 28.6, 42.4, 51.2, 56.2, 56.3, 103.7, 107.2, 111.3, 118.8, 121.4, 121.7, 124.9, 136.8, 148.7, 149.2, 162.3; MS, m/z (%) 288 (16), 287 (M^+, 100), 272 (42), 273 (6), 212 (8), 185 (11), 127 (6). *Anal* Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.86; H, 6.12; N, 4.75.

Ethyl 5,6-dihydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (4b). A white solid, mp 130-133 °C; R_f = 0.55 (CH_2Cl_2); IR (KBr), ν (cm^{-1}) 1695, 1608, 1548, 1491, 1450, 1408, 1365, 1246, 1134, 1062, 1037, 937, 858, 792, 760; ^{1}H NMR, δ 1.37 (t, 3H, *J* = 7.2), 3.01 (t, 2H, *J* = 7.0), 3.91 (s, 3H), 3.93 (s, 3H), 4.30 (q, 2H, *J* = 7.2), 4.61 (t, 2H, *J* =7.0), 6.42 (d, 1H, *J* = 4.0), 6.74 (s, 1H), 7.02 (d, 1H, *J* = 4.0), 7.05 (s, 1H); ^{13}C NMR, δ 14.6, 28.7, 42.5, 56.2, 56.3, 59.9, 103.6, 107.2, 111.3, 118.7, 121.5, 122.1, 124.9, 136.7, 148.7, 149.2, 161.9; MS, m/z (%) 302 (19), 301 (M^+, 100), 287 (7), 286 (45), 273 (10), 258 (13), 185 (13). *Anal* Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.85; H, 6.44; N, 4.47.

Dimethyl 5,6-dihydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline-2,3-dicarboxylate (4c). A pale yellowish solid, mp 132-134 °C; R_f = 0.30 (EtOAc/Hexane, 1:1); IR (KBr), ν (cm^{-1}) 1715 (sh), 1696, 1613, 1563, 1489, 1372, 1242, 1134, 1032, 858, 791, 770; ^{1}H NMR, δ 3.02 (t, 2H, *J* = 6.6), 3.87 (s, 3H), 3.90 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 4.44 (t, 2H, *J* = 6.6), 6.73 (s, 1H), 6.76 (s, 1H), 7.04 (s, 1H); ^{13}C NMR, δ 28.4, 43.0, 52.0, 52.1, 56.2 (2C), 105.5, 107.0, 111.2, 120.6, 121.7, 123.1, 124.6, 134.1, 148.9, 149.4, 162.2, 165.7; MS, m/z (%) 346 (16), 345 (M^+, 100), 330 (28), 314 (11), 270 (9). *Anal* Calcd for $C_{18}H_{19}NO_6$: C, 62.60; H, 5.55; N, 4.06. Found: C, 62.65; H, 5.68; N, 3.86.

Diethyl 5,6-dihydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline-2,3-dicarboxylate (4d). A colorless oil; R_f = 0.23 (EtOAc/Hexane, 1:1); IR (neat), ν (cm^{-1}) 1720 (sh), 1699, 1612, 1560, 1518, 1489, 1441, 1412, 1379, 1337, 1263, 1238, 1213, 1136, 1063, 1034, 956, 918, 854, 772; ^{1}H NMR, δ 1.37 (t, 6H, *J* = 7.2) , 3.01 (t, 2H, *J* = 6.8), 3.91 (s, 3H), 3.92 (s, 3H), 4.31 (q, 2H, *J* = 7.2), 4.34 (q, 2H, *J* = 7.2), 4.44 (t, 2H, *J* = 6.8), 6.73 (s, 2H), 7.04 (s, 1H); ^{13}C NMR, δ 14.2, 14.4, 28.5, 42.9, 56.1, 56.2, 60.8, 61.2, 105.2, 107.0, 111.2, 120.7, 122.3, 123.0, 124.6, 134.0, 148.9, 149.4, 161.7, 165.6; MS, m/z (%) 373 (M^+, 100), 358 (15), 374 (19). *Anal* Calcd for $C_{20}H_{23}NO_6$: C, 64.32; H, 6.21; N, 3.75. Found: C, 64.38; H, 6.19; N, 3.70.

Methyl 5,6-dihydro-8-methoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (4e). A white solid, mp 91-92 °C; R_f = 0.43 (CH_2Cl_2); IR (KBr), ν (cm^{-1}) 1701, 1616, 1553, 1485, 1462, 1435, 1354, 1248, 1201, 1147, 1117, 1074, 1040, 924, 872, 818, 752; ^1H NMR, δ 3.05 (t, 2H, *J* = 6.8), 3.83 (s, 6H), 4.62 (t, 2H, *J* = 6.8), 6.43 (d, 1H, *J* = 4.0), 6.77 (d, 1H, *J* = 2.4), 6.80 (dd, 1H, *J* = 8.4 and 2.4), 7.00 (d, 1H, *J* = 4.0), 7.50 (d, 1H, *J* = 8.4); ^{13}C NMR, δ 29.4, 42.2, 51.2, 55.4, 103.6, 113.2, 113.5, 118.8, 121.4, 121.8, 125.5, 133.9, 136.8, 159.6, 162.3; MS, m/z (%) 257 (M^+, 100), 242 (55), 226 (11). *Anal* Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.09; H, 5.81; N, 5.50.

Ethyl 5,6-dihydro-8-methoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (4f). A white needles, mp 72-73°C; R_f = 0.42 (CH_2Cl_2); IR (KBr), ν (cm^{-1}) 1688, 1611, 1551, 1460, 1415, 1348, 1273, 1248, 1159, 1113, 1064, 1032, 826, 795, 756; ^1H NMR, δ 1.36 (t, 3H, *J* = 7.2), 3.05 (t, 2H, *J* = 6.8), 3.83 (s, 3H), 4.3 (q, 2H, *J* = 7.2), 4.62 (t, 2H, *J* = 6.8), 6.42 (d, 1H, *J* =4.0), 6.77 (d, 1H, *J* = 2.4), 6.82 (dd, 1H, *J* = 8.0 and 2.4), 7.01 (d, 1H, *J* = 4.0), 7.50 (d, 1H, *J* = 8.0); ^{13}C NMR, δ 14.6, 29.4, 42.2, 55.5, 59.9, 103.5, 113.2, 113.5, 118.7, 121.8, 121.9, 125.4, 133.9, 136.71, 159.6, 161.9; MS, m/z (%) 271 (M^+, 100), 243 (27), 228 (34). *Anal* Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.91; H, 6.31; N, 5.22.

Dimethyl 5,6-dihydro-8-methoxypyrrolo[2,1-*a*]isoquinoline-2,3-dicarboxylate (4g). A white solid, mp 115-116 °C; R_f = 0.20 (EtOAc/Hexane, 1:2); IR (KBr), ν (cm^{-1}) 1724, 1692, 1616, 1562, 1512, 1464, 1398, 1335, 1275, 1242, 1070, 972, 877, 814, 775; ^1H NMR, δ 3.06 (t, 2H, *J* = 6.8), 3.83 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 4.45 (t, 2H, *J* = 6.8), 6.74 (s, 1H), 6.77 (d, 1H, *J* = 2.4), 6.84 (dd, 1H, *J* = 8.4 and 2.4), 7.48 (d, 1H, *J* =8.4); ^{13}C NMR, δ 29.2, 42.7, 52.0, 52.1, 55.5, 105.4, 113.5, 113.6, 121.0, 122.0, 122.7, 125.5, 133.7, 134.2, 159.9, 162.1, 165.9; MS, m/z (%) 315 (M^+, 100), 284 (21), 282 (27). *Anal* Calcd for $C_{17}H_{17}NO_5$: C, 64.74; H, 5.44; N, 4.44. Found: C, 64.72; H, 5.49; N, 4.34.

Diethyl 5,6-dihydro-8-methoxypyrrolo[2,1-*a*]isoquinoline-2,3-dicarboxylate (4h). A white solid, mp 113-114 °C; R_f = 0.31 (EtOAc/Hexane, 1:2); IR (KBr), ν (cm^{-1}) 1722, 1692, 1615, 1561, 1462, 1421, 1379, 1333, 1312, 1244, 1217, 1182, 1153, 1065, 1033, 844, 825; ^1H NMR, δ 1.37 (t, 6H, *J* = 7.2), 3.05 (t, 2H, *J* = 6.6), 3.83 (s, 3H), 4.33 (q, 2H, *J* = 7.2), 4.35 (q, 2H, *J* = 7.2), 4.45 (t, 2H, *J* = 6.6), 6.72 (s, 1H), 6.77 (d, 1H, *J* = 2.4), 6.84 (dd, 1H, *J* = 8.4 and 2.4), 7.49 (d, 1H, *J* = 8.4); ^{13}C NMR, δ 14.2, 14.4, 29.2, 42.6, 55.6, 60.9, 61.1, 105.1, 113.4, 113.6, 121.1, 122.5, 122.6, 125.5, 133.7, 134.1, 159.8, 161.7, 165.8; MS, m/z (%) 343 (M^+, 100), 298 (11), 296 (12), 271 (15). *Anal* Calcd for $C_{19}H_{21}NO_5$: C, 66.44; H, 6.17; N, 4.08. Found: C, 66.23; H, 6.42; N, 4.04.

Dimethyl 5,6-dihydro-8,9-dimethoxy-1-methylpyrrolo[2,1-*a*]isoquinoline-2,3-dicarboxylate (4i). A white solid, mp 104-106 °C; R_f = 0.36 (EtOAc/Hexane, 1:1); IR (KBr), ν (cm^{-1}) 1721, 1693, 1611, 1551, 1485, 1445, 1267, 1233, 1148, 1059, 856, 801; ^1H NMR, δ 2.40 (s, 3H), 2.95 (t, 2H, *J* = 7.0), 3.84 (s, 3H), 3.89 (s, 3H), 3.92 (s, 6H), 4.47 (t, 2H, *J* = 7.0), 6.78 (s, 1H), 7.20 (s, 1H); ^{13}C NMR, δ 11.7, 29.3, 42.6, 51.9, 52.2, 56.2, 56.3, 108.8 (2C), 111.5 (2C), 115.2, 121.7, 123.9, 126.5, 148.4, 148.7, 161.7 (2C); MS, m/s (%) 359 (M^+, 100), 344 (13), 328 (14), 241 (26). *Anal* Calcd for $C_{19}H_{21}NO_6$: C, 63.49; H, 5.89; N, 3.90. Found:

C, 63.52; H, 5.81; N, 3.96.

Diethyl 5,6-dihydro-8,9-dimethoxy-1-methylpyrrolo[2,1-*a*]isoquinoline-2,3-dicarboxylate (4j). A colorless oil; R_f = 0.28 (EtOAc/Hexane, 1:1); IR (neat), ν (cm^{-1}) 1720 (sh), 1699, 1611, 1552, 1485, 1400, 1263, 1225, 1192, 1091, 858, 801; ^1H NMR, δ 1.34 (t, 3H, *J* = 7.2), 1.38 (t, 3H, *J* = 7.2), 2.40 (s, 3H), 2.95 (t, 2H, *J* = 6.8), 3.92 (s, 6H), 4.29 (q, 2H, *J* = 7.2), 4.35 (q, 2H, *J* = 7.2), 4.48 (t, 2H, *J* = 6.8), 6.78 (s, 1H), 7.19 (s, 1H); MS, m/z (%) 387 (M^+, 100), 341 (18), 312 (12), 241 (25). *Anal* Calcd for $C_{21}H_{25}NO_6$: C, 65.09; H, 6.51; N, 3.62. Found: C, 65.12; H, 6.48; N, 3.69.

Methyl 5,6-dihydro-8,9-dimethoxy-1-phenylpyrrolo[2,1-*a*]isoquinoline-3-carboxylate (4k). A pale yellowish solid, mp 137-138 °C; R_f = 0.45 (EtOAc/Hexane, 1:1); IR (KBr), ν (cm^{-1}) 1701, 1610, 1551, 1441, 1395, 1339, 1240, 1194, 1144, 1094, 1059, 866, 760; ^1H NMR, δ 3.03 (t, 2H, *J* = 6.8), 3.39 (s, 3H), 3.85 (s, 3H), 3.89 (s, 3H), 4.62 (t, 2H, *J* = 6.8), 6.74 (s, 1H), 6.80 (s, 1H), 7.01 (s, 1H), 7.30-7.50 (m, 5H); ^{13}C NMR, δ 29.2, 42.7, 51.3, 55.4, 56.1, 109.0, 111.1, 119.6, 120.7, 121.3, 122.2, 126.3, 127.2, 128.8 (2C), 129.9 (2C), 132.1, 137.0, 147.7, 148.7, 162.3; MS, m/z (%) 363 (M^+, 100), 348 (25), 288 (6), 261 (8). *Anal* Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.89; H, 5.73; N, 3.76.

Methyl 5,6-dihydro-8,9-dimethoxy-10b-*H*-isoxazolo[3,2-*a*]isoquinoline-1-carboxylate (6). This pale yellowish oil was obtained from (**5**) by the same way to above mentioned isoxazoline synthesis, yield 70%; R_f = 0.50 (EtOAc/Hexane, 2:1); IR (neat), ν (cm^{-1}) 1705, 1624, 1514, 1440, 1348, 1248, 1230, 1145, 1103, 1012, 866, 783; ^1H NMR, δ 2.41-2.50 (m, 1H), 2.92-3.08 (m, 1H), 3.09-3.23 (m, 1H), 3.70 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 3.89-4.00 (m, 1H), 5.71 (s, 1H), 6.60 (s, 1H), 7.22 (s, 1H), 7.34 (t, 1H, *J* = 2.0).

1-(1-Formyl-1-methoxycarbonyl)methylene-6,7-dimethoxytetrahydroisoquinoline (7). On standing (**6**) at room temperature for one day, a pale yellowish solid of (**7**) was obtained in 75% yield, mp 154-157 °C; R_f = 0.20 (EtOAc/Hexane, 4:1); IR (KBr), ν (cm^{-1}) 1690, 1589, 1518, 1474, 1406, 1346, 1311, 1265, 1140, 1107, 1043, 1016, 881, 785; ^1H NMR, δ 2.88 (t, 2H, *J* = 7.0), 3.46 (t, 2H, *J* = 7.0), 3.67 (s, 3H), 3.84 (s, 3H), 3.95 (s, 3H), 6.72 (s, 1H), 6.98 (s, 1H), 9.73 (s, 1H), 12.3 (brs, 1H), A positive NOE was observed between signals at δ 3.67 (COOMe) and 6.98 (aromatic 8-CH) in the NOESY spectrum; ^{13}C NMR, δ 27.5, 38.9, 51.1, 56.2 (2C), 98.7, 110.3, 113.8, 119.6, 132.2, 147.4, 153.1, 164.8, 170.2, 189.1; MS, m/z (%) 291 (M^+, 56), 276 (23), 260 (21), 232 (100). *Anal* Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.90; H, 5.81; N, 4.87.

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