Stereoselective Cycloadditions of Pyridinium or Isoquinolinium Methylides with Olefinic Dipolarophiles and Subsequent Cycloadditions of the Cycloadducts with Nitrile Oxides

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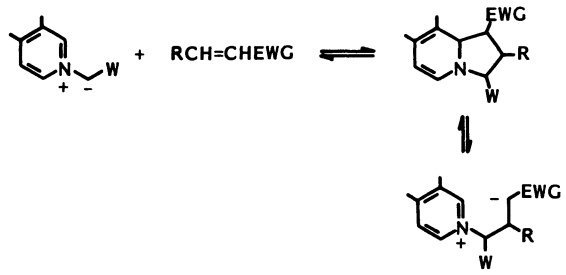
Pyridinium or isoquinolinium methylides undergo highly stereo- and regioselective cycloadditions with olefinic dipolarophiles to form unstable tetrahydroindolizine derivatives. One of the two double bonds existing in the dihydro heteroaromatic ring of the cycloadducts reacts with nitrile oxides, in the same flask, in stereo-, regio-, and periselective fashions to lead to stable isoxazole-fused tetrahydroindolizines in good yields.

Although the cycloadditions of heteroaromatic *N*-ylides such as pyridinium, quinolinium, isoquinolinium, pyridazinium, thiazolium, and triazolium methylides with electron-deficient olefins take place in a highly diastereoselective manner to give fused heterocycles which bear a nitrogen atom at the point of fusion,[1-13] the cycloadducts are not always thermally stable. This instability is mainly due to the loss of aromaticity of the heteroaromatic ring of ylides in the step of cycloaddition. The cycloadducts frequently undergo retro cycloaddition[1,2] or carbon–carbon bond cleavage into betaine intermediates,[2,14-16] both of which are encouraged by the recovery of aromaticity.

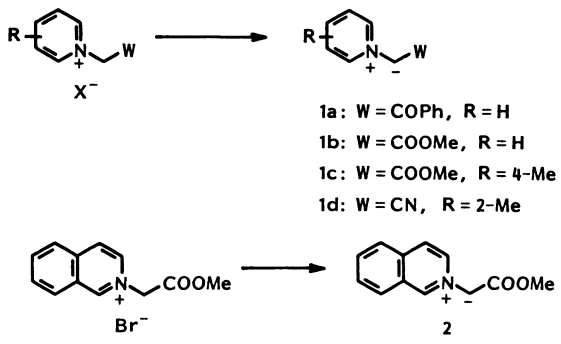


The cycloadducts derived from pyridinium methylides contain a fused dihydropyridine ring. Therefore, formal reduction of one of the two double bonds involved in the dihydropyridine skeleton should be effective for isolation of the cycloadducts as stable products. A cycloaddition and desilylation sequence of 4-silyloxypyridinium methylides is a successful example along this line.[17] In the present article, another method was applied for the formal reduction of these instability-causing double bonds: a cycloaddition method of such unstable cycloadducts with nitrile oxides.

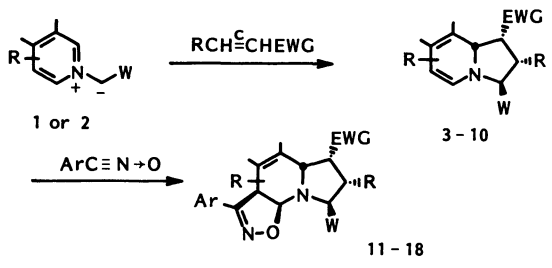
Results and Discussion

Pyridinium **1** and isoquinolinium methylides **2** were generated in situ from the corresponding pyridinium and isoquinolinium halides by treatment with triethylamine in dichloromethane and used for subsequent reactions without isolation (Scheme 1). More than two equivalent amounts of triethylamine were employed in general. One equivalent was for the ylide generation and the rest for the nitrile oxide generation which is to be carried out in the same flask as shown later.

These ylides **1** and **2** were first allowed to react with olefinic dipolarophiles to form diastereoselective cycloadducts **3**—**10**, though only **3** and **4** could be isolated and assigned as endo cycloadducts to the anti form of **1a** (Scheme 2 and Table 1).[1] The other cycloadducts **5**—**10** were too labile to be isolated, but their structures were readily deduced on the basis of the exclusive diastereoselectivity observed in the reaction of isoquinolinium phenacylide with unsymmetrical olefins such as methyl acrylate and acrylonitrile.[18] High regioselectivity (or periselec-



Scheme 1.



Scheme 2.

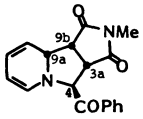
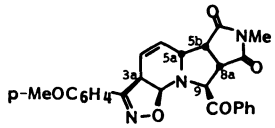
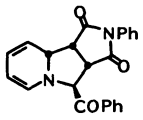
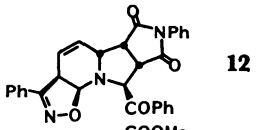
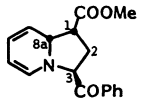
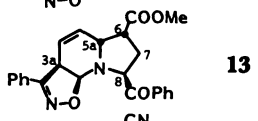
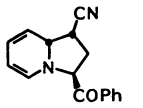
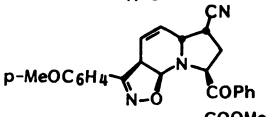
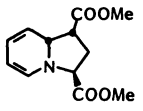
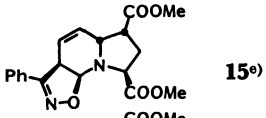
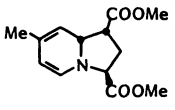
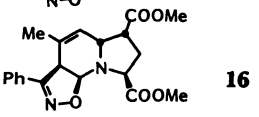
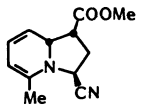
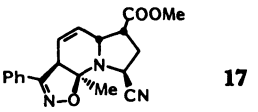
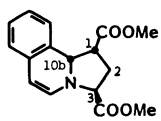
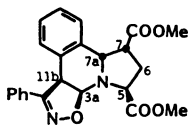
tivity) in favor of the 5-methyl derivative **9** is also consistent with the previously observed selectivity.[1]

The diastereoselective cycloadducts **3**—**10** formed in situ as thermally unstable products were next subjected to react with nitrile oxides (Scheme 2). Thus, *N*-(α-chloro-*p*-methoxybenzylidene)hydroxylamine was added to the reaction mixture which consisted of **3** and the remaining triethylamine. After 1 h at room temperature, nitrile oxide cycloadduct **11** was obtained as a single stereo- and regioisomer in an almost quantitative yield (based on the ylide precursor). Similar reactions of other unstable tetrahydroindolizines **4**—**7** with benzonitrile oxide or *p*-methoxybenzonitrile oxide gave also single isomers **12**—**15** of nitrile oxide cycloadducts (Scheme 2 and Table 1). Substitution on the fused dihydropyridine ring of **8**—**10** did not affect the cycloaddition with nitrile oxides, similar products **16**—**18** being produced.

It is clear that nitrile oxide cycloadducts **11**—**18** are all those formed through regioselective cycloaddition across the carbon-carbon double bond adjacent to the fused nitrogen. In every case, the newly formed methine carbon carrying an oxygen and a nitrogen substituent (10a-C in **11** and **12**, 9a-C in **13**—**17**, and 3a-C of **18**) appeared as low as 92—98 ppm, and the methine hydrogen on this carbon was observed around 5.8—6.0 ppm as a doublet.

Stereochemistry of the fused pyrrolidine ring of **11**—**18** should be the same with that of the initial cycloadducts **3**—**10**, respectively. Thus, the endo fusion of the maleimide ring and the exo configuration of 9-benzoyl of **11** were confirmed by the coupling constants J_{8a-9} and J_{5a-5b} (the same to **12**). The 6-endo (or 7-endo) and 8-exo (or 5-exo) substitution of **13**—**17** (or **18**) was assigned on the basis of the coupling patterns of **17** as well as the magnetic shielding of ester methyl at the 7-endo position of **18** (Fig. 1).

Table 1. Cycloaddition of Ylides **1** or **2** with Olefins and Then with Nitrile Oxides[a]

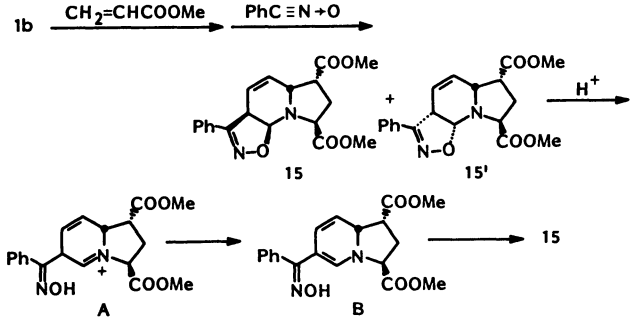
Ylide	Dipolarophile[b]	Cycloadduct	Nitrile oxide precursor[c]	Product	Yield/%[d]
1a	*N*-methylmaleimide rt, 10 min	 **3**	*p*-MeOC$_6$H$_4$C(Cl)=NOH, rt, 1 h	 **11**	97
1a	*N*-phenylmaleimide rt, 1 h	 **4**	PhC(Cl)=NOH, −85 °C, 1h	 **12**	96
1a	CH$_2$=CHCOOMe rt, 50 min	 **5**	PhC(Cl)=NOH, rt, 1 h	 **13**	45
1a	CH$_2$=CHCN rt, 20 min	 **6**	*p*-MeOC$_6$H$_4$C(Cl)=NOH, rt, 10 min	 **14**	55
1b	CH$_2$=CHCOOMe reflux, 1 h	 **7**	PhC(Cl)=NOH, reflux, 4 h	 **15**[e]	51
1c	CH$_2$=CHCOOMe reflux, 6 h	 **8**	PhC(Cl)=NOH, reflux, 3 h	 **16**	50
1d	CH$_2$=CHCOOMe reflux, 1 h	 **9**	PhC(Cl)=NOH, reflux, 5 h	 **17**	45
2	CH$_2$=CHCOOMe rt, 1 h	 **10**	PhC(Cl)=NOH, rt, 10 h	 **18**	62

a) All reactions were carried out in dichloromethane. b) One equivalent amounts of ylide precursor and dipolarophile were allowed to react in the presence of 2—4 equivalents of triethylamine. c) Nitrile oxide precursor was added at room temperature and the reactions were continued under the conditions shown in this table. d) Isolated yield based on ylide precursor. e) After treatment with a catalytic amount of trifluoroacetic acid.

Although stereochemistry of the fused isoxazoline ring of **11—18** could not be determined only by a spectroscopic analysis, these cycloadducts were tentatively assigned to have exo-fused isoxazolines on the basis of the following discussion: The reaction of stereoselective cycloadduct **7** with benzonitrile oxide provided, after chromatographic work-up over silica gel, a 1 : 1 mixture of two stereoisomers of nitrile oxide cycloadducts **15** and **15′**. When treated with a catalytic amount of trifluoroacetic acid in chloroform at room temperature, **15′** was converted into **15** in a quantitative yield. Thus, **15** and **15′** were assigned as thermodynamically controlled exo and kinetically controlled endo cycloadducts, respectively. Acid-catalyzed isomerization of **15′** into **15** was easily rationalized with a mechanism via iminium **A** and dienamine intermediate **B** (Scheme 3).

Experimental

General Methods. Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were taken with a JASCO A-702 spectrometer. ^{1}H NMR spectra were recorded on a Hitachi R-40 or a JEOL FX-100 instrument and ^{13}C NMR on a JEOL FX-100 spectrometer at 25.05 MHz. Chemical shifts are expressed in parts per million downfield from tetramethylsilane. Mass spectra were measured with a JEOL JMS-O1SG-2 spectrometer at 70 eV of ionization energy. Elemental analyses were performed on a Hitachi 026 CHN micro analyzer. Thin-layer chromatography (TLC) was accomplished on 0.2 mm precoated plates of silica gel 60 F-254 (Merck). Visualization was accomplished with ultraviolet light (254 and 365 nm) and iodine. Silica gel 60 (70—230 mesh or 230—400 mesh, Merck) or Wakogel C-200 (100—200 mesh) was used for preparative column chromatography. Micro vacuum distillation was performed with a Shibata GTO-250 R Kugelrohr distilling apparatus. Solvents were evaporated with a Tokyo Rikakikai rotary evaporator type V.



Scheme 3.

Ylide Precursors: The precursors for pyridinium methylides **1** and isoquinolinium methylide **2** were prepared from the reactions of substituted pyridines or isoquinoline with alkyl halides in dry acetone or dry ether at room temperature. The precursor salts precipitated were collected on a filter and washed with dry ether: 1-Phenacylpyridinium bromide:[19] Mp 204—206 °C; 96% (1 h in acetone). 1-(Methoxycarbonylmethyl) pyridinium chloride:[20] Mp 170—173 °C; 78% (24 h in acetone). 1-(Methoxycarbonylmethyl)-4-methylpyridinium bromide: Colorless prisms; mp 175—176 °C (decomp); 63% (54 h at 0 °C in ether); Found: C, 44.12; H, 4.95; N, 5.57%. Calcd for $C_9H_{12}NO_2Br$: C, 43.90; H, 4.88; N, 5.69%. 1-Cyanomethyl-2-methylpyridinium bromide: Colorless prisms; mp 194—197 °C (decomp); 49% (17 h in ether); Found: C, 44.90; H, 4.31; N, 12.96%. Calcd for $C_8H_9N_2Br$: C, 45.07; H, 4.23; N, 13.15%. 2-(Methoxycarbonylmethyl)isoquinolinium bromide:[21] Mp 158—160 °C; 62% (51 h in ether).

General One-pot Procedure for Cycloadditions of Ylides 1 or 2 with Olefins and Subsequent Cycloadditions of Cycloadducts 3—10 with Nitrile Oxides Leading to 11—18. An equimolar mixture of ylide precursor and olefin in dry dichloromethane (10—25 ml for 1 mmol of the precursor) was stirred in the presence of 2—4 equivalents of triethylamine at room temperature or under reflux (see Table 1). After the mixture was cooled to room temperature, 1 equivalent amount of an imidoyl chloride as nitrile oxide precursor was added. The mixture was allowed to react under the conditions listed in Table 1 and poured into ice water. The dichloromethane separated was dried over anhydrous magnesium sulfate and evaporated in vacuo. The residue was chromatographed over silica gel with hexane–ethylacetate (5-1 : 1) to give **11—18**. The yields are summarized in Table 1.

11: Colorless prisms (ethyl acetate–hexane); mp 210 °C; IR (KBr) 1770, 1700, and 1680 cm^{-1}; ^{1}H NMR (CD_3CN) δ=2.87 (3H, s, NMe), 3.42 (1 H, dd, J=7.6 and 0.8 Hz, 8a-H), 3.51 (1H, t, J=7.6 Hz, 5b-H), 3.77 (3H, s, p-MeO), 3.9—4.1 (1H, m, 3a-H), 4.2—4.3 (1H, m, 5a-H), 5.32 (1H, d,

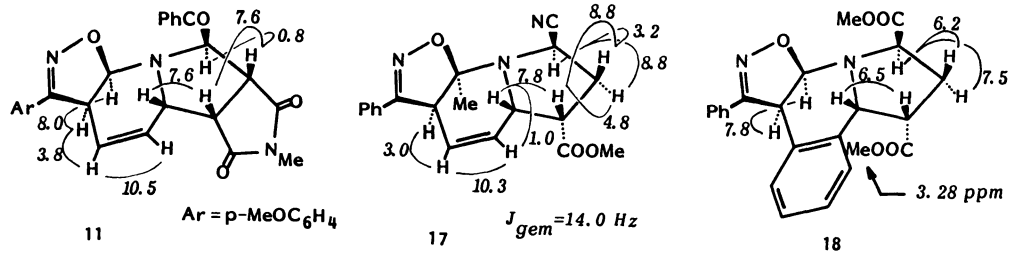


Fig. 1. Stereostructures of isooxazole-fused cycloadducts **11**, **17**, and **18** and their ^{1}H NMR spectral data.

J=0.8 Hz, 9-H), .5.67 (1 H, ddd, J=10.5, 3.8, and 2.5 Hz, 4-H), 5.85 (1H, d, J=8.0 Hz, 10a-H), 6.29 (1 H, br d, J=10.5 Hz, 5-H), 6.8—7.0 (2 H, m, Ar), 7.4—7.8 (5H, m, Ar), and 8.0—8.2 (2 H, m, Ar); ^{13}C NMR ($CDCl_3$) δ=25.35 (q, NMe), 44.71, 47.89 (each d, 5b- and 8a-C), 50.12 (d, 3a-C), 55.42 (q, *p*-MeO), 56.77 (d, 5a-C), 68.36 (d, 9-C), 92.71 (d, 10a-C), 114.48, 118.54 (each d), 121.42 (s), 124.54, 128.18, 129.13, 129.24, 134.01 (each d), 134.48, 159.89, 161.42 (each s), 175.89, 178.42 (each s, CON), and 195.43 (s, PhCO); MS *m/z* (rel intensity, %) 457 (M^+, 5), 353 (21), 352 (base peak), 240 (30), 203 (27), 196 (18), 105 (24), and 77 (23).

Found: C, 67.99; H, 5.14; N, 8.98%. Calcd for $C_{26}H_{23}N_3O_5$: C, 68.26; H, 5.07; N, 9.19%.

12: Colorless prisms (ethyl acetate–hexane); mp 238—240 °C (decomp); IR (KBr) 1780, 1713, 1687, 1595, 1387, and 1192 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.62 (1H, t, J=8.8 Hz, 5b-H), 3.95 (1H, dd, J=8.8 and 1.5 Hz, 8a-H), 3.8—4.0 (1H, m, 3a-H), 4.2—4.4 (1H, m, 5a-H), 5.53 (1H, d, J=1.5 Hz, 9-H), 5.62 (1H, dt, J=10.4, 2.8, and 2.8 Hz, 4-H), 5.83 (1H, d, J=6.8 Hz, 10a-H), 6.24 (1H, ddd, J=10.4, 3.2, and 2.3 Hz, 5-H), 7.2—7.7 (13 H, m, Ar), and 8.0—8.2 (2H, m, Ar); MS *m/z* (rel intensity, %) 384 (M^+—PhCO, 78), 291 (26), 105 (base peak), and 77 (71).

Found: C, 73.36; H, 4.90; N, 8.60%. Calcd for $C_{30}H_{23}N_3O_4$: C, 73.60; H, 4.74; N, 8.58%.

13: Pale yellow prisms (ethyl acetate–hexane); mp 174—175 °C; IR (KBr) 1740 and 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.0—2.4 (1H, m, one of 7-H), 2.5—3.0 (2H, m, the other of 7-H and 6-H), 3.67 (3H, s, COOMe), 3.7—4.0 (1H, m, 3a-H), 4.1—4.3 (1H, m, 5a-H), 5.01 (1H, dd, J=10.0 and 6.8 Hz, 8-H), 5.87 (1H, ddd, J=9.8, 4.0, and 2.8 Hz, 4-H), 5.92 (1H, d, J=8.0 Hz, 9a-H), 6.28 (1H, dt, J=9.8, 1.5, and 1.5 Hz, 5-H), 7.3—7.8 (8H, m, Ar), and 7.9—8.1 (2H, m, Ar); MS *m/z* (rel intensity, %) 402 (M^+, 1), 298 (19), 297 (base peak), 197 (40), 196 (49), 178 (37), 151 (48), 118 (22), 105 (21), 99 (32), and 77 (49).

HRMS Found: *m/z* 402.1597. Calcd for $C_{24}H_{22}N_2O_4$: M, 402.1580.

14: Colorless needles (ethyl acetate–hexane); mp 230 °C (decomp); IR (KBr) 2240, 1680, 1605, and 1515 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.36 (1H, ddd, J=13.6, 6.4, and 2.5 Hz, one of 7-H), 2.5—2.8 (1H, m, the other of 7-H), 3.26 (1H, ddd, J=8.2, 6.0, and 2.5 Hz, 6-H), 3.81 (3H, s, *p*-MeO), 3.8—4.1 (1H, m, 3a-H), 4.1—4.4 (1H, m, 5a-H), 4.90 (1H, dd, J=10.0 and 6.4 Hz, 8-H), 5.90 (1H, d, J=8.2 Hz, 9a-H), 5.8—6.3 (2H, m, 4- and 5-H), 6.8—7.0 (2H, m, Ar), 7.3—7.7 (5H, m, Ar), and 7.9—8.1 (2H, m, Ar); MS *m/z* (rel intensity, %) 399 (M^+, 4), 295 (20), 294 (base peak), 197 (25), 196 (28), and 77 (16).

Found: C, 72.41; H, 5.26; N, 10.38%. Calcd for $C_{24}H_{21}N_3O_3$: C, 72.16; H, 5.30; N, 10.52%.

15 and 15′: The above general procedure was applied to the reaction of **1b** with methyl acrylate and then with benzonitrile oxide to give a mixture of 3a,5a-trans isomer **15** and 3a,5a-cis isomer **15′** (51%, 1 : 1 by ^{1}H NMR) after chromatographic separation. When this mixture in deuteriochloroform was treated with a catalytic amount of trifluoroacetic acid at room temperature, **15′**was found to completely isomerize into **15** (^{1}H NMR). The isomer **15** was isolated by column chromatography over silica gel. **15**: Pale yellow prisms (diethyl ether); mp 116—117 °C; IR (KBr) 1753, 1730, and 1597 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.2—3.0 (3H, m, 6-H and 7-H), 3.6—3.9 (1H, m, 3a-H), 3.69, 3.75 (each 3H, s, COOMe), 4.12 (1H, dd, J=9.2 and 5.8Hz, 8-H), 4.1—4.3 (1H, m, 5a-H), 5.73 (1H, ddd, J=10.0, 4.4, and 2.3 Hz, 4-H), 6.02 (1H, d, J=9.0 Hz, 9a-H), 6.22 (1H, dt, J=10.0, 1.0, and 1.0 Hz, 5-H), 7.2—7.5 (3H, m, Ar), and 7.5—7.8 (2H, m, Ar); ^{13}C NMR ($CDCl_3$) δ=31.35 (t, 7-C), 44.42, 45.89 (each d, 3a- and 6-C), 52.18 (2×C, q, COOMe), 55.12 (d, 5a-C), 58.30 (d, 8-C), 91.95 (d,9a-C), 122.07, 126.79, 128.95 (each d), 129.48 (s), 130.18, 131.24 (each d), 158.60 (s, 3-C), and 172.93 (2×C, s, COOMe); MS *m/z* (rel intensity, %) 356 (M^+, 8), 237 (25), 236 (23), 222 (25), 151 (base peak), and 93 (17). Found: C, 63.84; H, 5.66; N, 7.81%. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.03; H, 5.66; N, 7.86%. **15′**: Available only as a mixture with its stereoisomer **15**. ^{1}H NMR ($CDCl_3$) δ=3.30 (1H, ddd, J=8.1, 7.0, and 4.8 Hz, 6-H), 3.64, 3.79 (each 3H, s, COOMe), and 4.08 (1H, dd, J=8.3 and 4.5 Hz, 8-H); ^{13}C NMR ($CDCl_3$) δ=29.77 (t, 7-C), 42.36, 46.12 (each d, 3a- and 6-C), 51.47, 52.24 (each q, COOMe), 53.89 (d, 5a-C), 61.83 (d, 8-C), 93.00 (d, 9a-C), 121.30, 126.60, 128.77, 129.24, 129.95, 158.37 (s, 3-C), 173.07, and 173.77 (each s, COOMe); MS *m/z* (rel intensity, %) 356 (M^+, 5) and 151 (base peak). HRMS Found: *m/z* 356.1353. Calcd for $C_{19}H_{20}N_2O_5$: M, 356. 1336.

16: Colorless viscous liquid; IR (neat) 1751, 1733, 1670, and 1647 cm^{-1}; ^{1}H NMR (CD_3CN) δ=1.50 (3H, br s, 4-Me), 2.2—2.8 (3H, m, 6- and 7-H), 3.63 (1H, m, 3a-H), 3.66, 3.69 (each 3H, s, COOMe), 3.98 (1H, dd, J=9.0 and 6.2 Hz, 8-H), 4.17 (1H, br d, J=8.5 Hz, 5a-H), 5.92 (1H, br s, 5-H), 5.95 (1H, d, J=8.1 Hz, 9a-H), 7.3—7.5 (3H, m, Ar), and 7.5—7.7 (2H, m, Ar); MS *m/z* (rel intensity, %) 370 (M^+, 6), 278 (16), 251 (53), 250 (31), 236 (20), 165 (base peak), 132 (33), 107 (72), and 76 (32).

HRMS Found: *m/z* 370.1529. Calcd for $C_{20}H_{22}N_2O_5$: M, 370.1529.

17: Colorless prisms (ethyl acetate–hexane), mp 122—124 °C; IR (KBr) 2250, 1751, 1741, and 1167 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.57 (3H, s, 9a-Me), 2.35 (1H, ddd, J=14.0, 8.8, and 3.2 Hz, 7-H_{exo}) 2.78 (1H, ddd, J=14.0, 8.8, and 4.8 Hz, 7-H_{endo}). 3.29 (1H, ddd, J=8.8, 7.8, and 4.8 Hz, 6-H), 3.66 (3H, s, COOMe), 3.70 (1H, m, 3a-H), 4.10 (1H, m, 5a-H), 4.47 (1H, dd, J=8.8 and 3.2 Hz, 8-H), 5.72 (1H, ddd, J=10.3, 3.0, and 2.0 Hz, 4-H), 5.97 (1H dt, J=10.3, 1.0, and 1.0 Hz, 5-H), 7.3—7.5 (3H, m, Ar), and 7.5—7.8 (2H, m, Ar); ^{13}C NMR ($CDCl_3$) δ=23.83 (q, 9a-Me), 32.24 (t, 7-C), 44.47, 45.89 (each d, 6- and 8-C) 50.24 (d, 3a-C),52.00 (q, COOMe), 55.30 (d, 5a-C), 98.36 (s, 9a-C), 120.13 (s, CN), 122.48, 126.54, 127.13, 129.07 (each d), 129.42 (s), 130.30 (d), 158.30 (s, 3-C), and 172.65 (s, COOMe); MS *m/z* (rel intensity, %) 337 (M^+, 8), 218 (35), 203 (23), 165 (13), 132 (base peak), and 92 (20).

Found: C, 67.51; H, 5.64; N, 12.20%. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46%.

18: Colorless solid; IR (KBr) 1730 cm^{-1}; ^{1}H NMR (CD_3CN) δ=2.2—2.6 (2H, m, 6-H), 3.28 (3H, s, 7-COOMe), 3.73 (3H, s, 5-COOMe), 3.4-3.7 (1H, m, 7-H), 4.17 (1H, dd, J=7.5 and 6.2 Hz, 5-H), 4.73 (1H, d, J=7.8 Hz, 11b-H), 4.83 (1H, d, J=6.5 Hz, 7a-H), 5.94 (1H, d, J=7.8 Hz, 3a-H), and 5.9—7.6 (9H, m, Ar); ^{1}H NMR ($CDCl_3$) δ=2.3—2.6 (2H, m, 6-H), 3.27 (3H, s, 7-COOMe), 3.75 (3H, s, 5-COOMe), 3.4—3.7 (1H, m, 7-H), 4.20 (1H, dd, J=7.0 and 6.0 Hz, 5-H), 4.50 (1H, d, J=9.0 Hz, 11b-H), 4.86 (1H, d, J=6.0 Hz, 7a-H), 5.90 (1H, d, J=9.0 Hz, 3a-H), and 6.8—7.6 (9H, m, Ar); MS *m/z* (rel intensity, %) 406 (M^+, 9) and 76 (base peak).

Found: C, 67.47; H, 5.35; N, 6.71%. Calcd for $C_{23}H_{22}N_2O_5$: C, 67.96; H, 5.46; N, 6.89%.

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