PREPARATION OF 2-ARYL-4a,5-DIHYDRO-4*H*-[1,3,4]OXADIAZINO[4,5-*a*]INDOLES AS A [*a*]-FUSED INDOLE DERIVATIVES#

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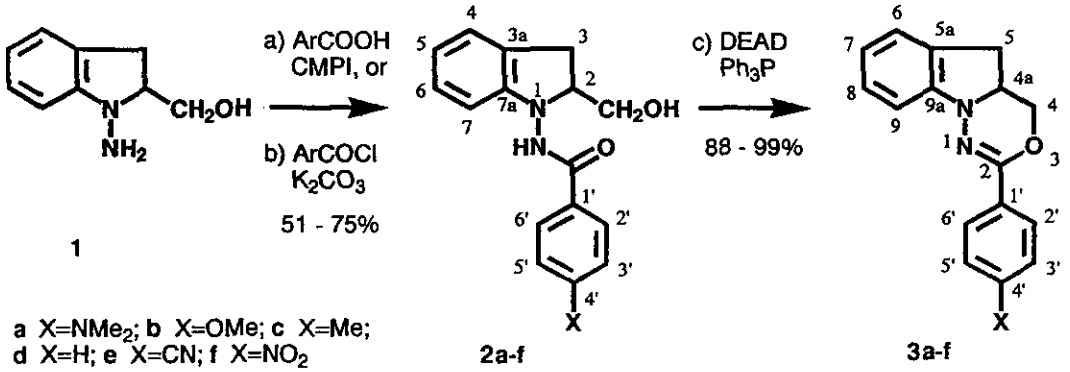
Abstract - The formation of 2-aryl-4a,5-dihydro-4*H*-[1,3,4]oxadiazino[4,5-*a*]indoles was effected by the intramolecular Mitsunobu reaction between primary hydroxy and NH-amide groups in excellent yield.

1,3,4-Oxadiazines have been known to have a variety of biological activities such as platelet aggregation inhibitory and anti-hypertensive effects,[1] and cardiotonic,[2] vasodilating,[3] antibacterial,[4] antiviral,[5] and acaricidal activities.[6] We have been studying the indole derivatives which are condensed indole ring with heterocycles at [*a*]-face of indole nucleus.[7] We became interested in combining 1,3,4-oxadiazine at [*a*]-face of indole ring, *i.e.*, the formation of novel [1,3,4]oxadiazino[4,5-*a*]indole derivatives, from the mind of exploring pharmaceutically useful compounds, and selected the title compounds as the first candidate for our purposes. There are a few reports concerning with the heterocyclic compounds having both indole and 1,3,4-oxadiazine rings linked by single bond[8] as well as the synthesis of

Dedicated to professor Alan R. Katritzky on the occasion of his 65th birthday



[1,3,5]oxadiazino[3,2-*a*]indole derivative,[9] but no reports have appeared so far about the title compounds. As a starting compound, we selected 1-amino-2-hydroxymethylindoline **(1)**[10] and converted it into *N*-acyl derivatives **(2)** either by the reaction with acid chloride (method a) or with free acid in the presence of 2-chloro-1-methylpyridinium iodide[CMPI][11] (method b) in the yields 51-75%. Their structures of the products **(2)** were unambiguously determined by the spectroscopic methods (Tables 1 and 2 for ^{1}H- and ^{13}C-nmr spectra).[12] In order to construct 1,3,4-oxadiazine nucleus, we adopted Mitsunobu reaction,[13] since Galeotti and coworkers had effectively prepared the oxazolines in clear fashion from *N*-(β-hydroxethyl)amides by this reaction.[14]

When triphenyphosphine was added into the solution of amido alcohols **(2)** and diethyl azodicarboxylate (DEAD) in dry THF, smooth reaction took place with slight heat evolution and gave the cyclized products **(3)** in excellent yields. On adding triphenylphosphine the color of reaction medium changed from orange to deep red, but faded away within a few minutes. Cyclization was fast and completed within five minutes on tlc analyses. The structures of 4a,5-dihydro-4*H*-[1,3,4]oxadiazinino[4,5-*a*]indole rings were supported from the ir spectra straightforward way by the observation of C=N absorptions which are characteristic for 5,6-dihydro-4*H*-[1,3,4]oxadiazines[15] and spread over from 1610 to 1595 cm^{-1} depending on electron attracting abilities of the substituents X on 2-phenyl group. The supports for the skeleton were also available from nmr spectra of the products **(3)** (Tables 3 and 4).[12] In ^{1}H-nmr spectra the

increase of electron attraction at X shifted the chemical shifts of 4a-H and 5-H_2 to the lower magnetic field, but in ^{13}C-nmr spectra the C-2 signals were moved to the considerably higher magnetic area (Δ 4.0 ppm) compared with the similar shifts of the amide **(2)** (Δ 1.7 ppm). These observations suggest the resonance participation of the nitrogen lone pair as shown in the structure **(3)**, which is strengthened by the presence of electron-attracting group at X. The strong bathochromic shifts observed at the longest absorption bands in uv-vis spectra are also attributed to the above resonance contribution. In the intramolecular cyclization of β-hydroxy carboxylic acids to β-lactones under Mitsunobu reaction, reactions usually proceeded by hydroxy group activation.[16] In the heavily crowded systems, on the other hand, the lactonizations have been known to occur by carboxyl group activation.[17] The observation of color change during cyclization implys amide group activation in our reaction.

EXPERIMENTALS

All melting points were determined with a hot stage apparatus Yanaco MP-3 and uncorrected. Infrared spectra (ir) were recorded as KBr pellet with Perkin-Elmer FT-IR 1720. ^{1}H- and ^{13}C-Nuclear magnetic resonance spectra (nmr) were measured with JEOL JNM-FT 200 and JNM-Alpha 400 in DMSO-d_6 or $CDCl_3$ containing tetramethylsilane as internal standard. Ultraviolet-visible spectra (uv-vis) were recorded with a Shimadzu UV-200S double beam spectrophotometer. Mass spectra (ms) were measured with Hitachi RMU-7MG and M-2500 mass spectrometers. Flash column chromatography were conducted with silica gel (Merck 9385).

1-(4-Dimethylaminobenzoylamino)-2-hydroxymethylindoline(2a).

(method b): Under nitrogen atmosphere, *p*-dimethylaminobenzoic acid (8.3 g, 50 mmol), triethylamine (15.2 g, 0.15 mol), and 2-chloro-1-methylpyridinium iodide[11] (25.5 g, 0.1 mol) were added into a solution of the amino alcohol **(1)** (8.1 g, 50 mmol) in dry THF (200 ml), and the resulting suspension was stirred for 2 h, then refluxed for 4 h. After concentrating the solution without heating under reduced

Table I ^{1}H-Nmr spectra (δ ppm) of 1-Acylamino-2-hydroxymethylindolines(**2**) in DMSO-d_6 [a]

	2a	**2b**	**2c**	**2d**	**2e**	**2f**
2-H	3.90, br s	3.93, br s	3.93, br s	3.95, br s	3.70, br s	3.97, br s
3-H	2.85, dd (15.7, 10.7)	2.84, dd (15.6, 10.5)	2.84, dd (15.5, 10.7)	2.85, dd (15.7, 10.5)	2.83, dd (15.6, 10.5)	2.84, dd (15.7, 10.5)
3-H	3.10, dd (15.7, 8.9)	3.12, dd (15.6, 8.9)	3.12, dd (15.5, 8.9)	3.14, dd (15.7, 8.9)	3.15, dd (15.6, 8.8)	3.16, dd (15.7, 8.7)
8-H_2	3.60, m	3.62, m	3.61, m	3.63, m	3.65, m	3.67, m
OH	4.58, t (6.1)	4.54, t (6.0)	4.54, t (5.8)	4.55, t (6.1)	4.56, t (5.4)	4.56, t (5.6)
NH	10.01, s	10.22, s	10.27, s	10.36, s	10.59, s	10.67, s
4-H	7.09, d (7.3)	7.10, d (7.1)	7.10, d (7.0)	7.11, d (6.9)	7.12, d (7.0)	7.13, d (7.3)
5-H	6.73, t (7.3)	6.74, t (7.2)	6.74, t (7.3)	6.75, t (7.0)	6.77, t (7.3)	6.78, t (7.3)
6-H	7.02, t (7.5)	7.03, t (7.9)	7.03, t (7.5)	7.04, t (7.4)	7.04, t (7.7)	7.05, t (7.5)
7-H	6.47, d (7.9)	6.50, d (7.6)	6.50, d (7.7)	6.53, d (7.6)	6.56, d (7.7)	6.58, d (8.0)
2', 6'-H_2	7.78, AB (9.2)	7.90, dt (8.9, 2.4)	7.86, d (7.6)	7.91, dt (7.3, 1.5)	8.05, AB (8.5)	8.14, AB (8.6)
3', 5'-H_2	6.73, AB (9.2)	7.04, dt (8.9, 2.4)	7.30, d (7.6)	7.51, tt (7.3, 1.5)	8.00, AB (8.5)	8.35, AB (8.6)
X-H	3.33, s NMe_2	3.83, s OCH_3	2.37, s CH_3	7.59, tt (7.5, 1.6)		

[a] Coupling constants (Hz) are shown in parentheses.

Table 2 ^{13}C-Nmr spectra (δ ppm) of 1-Acylamino-2-hydroxymethylindolines **(2)** in DMSO-d_6

	2a	**2b**	**2c**	**2d**	**2e**	**2f**
C-2	68.5	68.4	68.4	68.4	68.4	68.5
C-3	30.8	30.9	30.9	30.9	31.0	31.0
C-8	61.4	61.6	61.7	61.8	62.0	62.0
C-3a	126.8	126.9	126.9	126.9	127.0	127.02
C-4	124.4	124.4	124.4	124.4	124.5	124.5
C-5	119.4	119.6	119.7	119.7	120.0	120.1
C-6	126.9	126.9	126.9	126.9	127.0	126.98
C-7	108.4	108.6	108.6	108.7	108.9	108.9
C-7a	151.7	151.5	151.4	151.4	151.2	151.2
C=O	166.4	165.9	166.3	166.3	164.9	164.7
C-1'	118.8	124.8	129.9	132.8	136.9	138.6
C-2', 6'	128.7	129.2	127.4	127.3	128.2	128.9
C-3', 5'	110.8	113.7	128.9	128.4	132.5	123.6
C-4'	152.5	162.0	141.7	131.7	114.0	149.3
X	39.6	55.3	20.9		118.1	

pressure, the yellow residue was suspended in ethyl acetate (100 ml). The suspension was transferred into a separatory funnel and shaken well with water (200 ml). The organic layer was separated and the aqueous phase was extracted with ethyl acetate (2 X 100 ml). The combined organic extract was washed with brine (2 X 50 ml) and dried over anhydrous potassium carbonate. The solvent was removed in vacuo and yellow residue (32.2 g) was purified by flash column chromatography (dichloromethane-ethyl acetate 7 : 3) to give colorless crystalline **(2a)** (8.3g, 53%), mp 200-201°C (EtOH). Ir cm^{-1}: 3208, 1634(s), 1607, 1301, 756; uv-vis (95% EtOH) λmax (nm) (ε): 308 (31200), 234 (15200); ms m/z: 311(M^+, 40), 279(24), 164(84), 163(12), 148(100). Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.50. Found: C, 69.42; H, 6.84; N, 13.42.

1-(4-Methoxybenzoylamino)-2-hydroxymethylindoline (2b). - Typical procedure (method a): Amino alcohol **(1)** (6.7 g, 41 mmol), K_2CO_3 (8.3 g, 70 mmol) and water (10 ml) were added into CH_2Cl_2 (160 ml) in the atmosphere of nitrogen and the heterogeneous solution was stirred and cooled at -10°C for 30 min. Into this solution, a solution of 4-methoxybenzoyl chloride (7.7 g, 45 mmol) dissolved in CH_2Cl_2 (20 ml) was dropped for 20 min, then the reaction mixture was left stirring at room temperature for 24 h. After addition of aqueous 1M NaOH solution (100 ml) and CH_2Cl_2 (100 ml), the solution was stirred vigorously for 30 min, then organic layer was collected. The aqueous phase was extracted with CH_2Cl_2 (3 X 50 ml). The combined organic layer was worked up as described above and the crude residue (14.6 g) was purified similarly to give pale yellow prisms of **2b** (8.2g, 68%), mp 165-166°C (EtOH). Ir cm^{-1}: 3433, 3262, 1634(s), 1606, 1500, 1258, 1183, 752; uv-vis (95%EtOH) λmax(nm) (ε): 251 (24500); ms m/z: 298(M^+,7), 280(3), 267(13), 163(14), 151(14), 135(100). Anal. Calcd for $C_{17}H_{18}N_2O_3$:C, 68.44; H, 6.08; N, 9.39. Found: C, 68.43; H, 6.00; N, 9.30.

1-(4-Methylbenzoylamino)-2-hydroxymethylindoline (2c), (colorless

crystals, 51%. method a), mp 167-169°C (EtOH). Ir cm^{-1}: 3289, 3228, 1669(s), 1662, 1638, 747; uv-vis (95%EtOH) λmax(nm) (ε): 282 (3100), 242 (20600); ms m/z: 282(M^+, 11), 251(47), 163(33), 133(32), 119(100), 91(47). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.62; H, 6.46; N, 9.63.

1-Benzoylamino-2-hydroxymethylindoline (2d),[7e] (75%. method a), mp 168-169°C (EtOH).

1-(4-Cyanobenzoylamino)-2-hydroxymethylindoline (2e), (pale yellow crystals, 51%. method a), mp 153-155°C (EtOH). Ir cm^{-1}: 3335, 3197, 2234, 1665(s), 1482, 1266, 758; uv-vis (95% EtOH) λmax(nm) (ε): 282 (4100), 241 (26600); ms m/z: 293(M^+, 23), 262(63), 163(88), 135(61), 130(63), 116(100). Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.77; H, 5.12; N, 14.23.

1-(4-Nitrobenzoylamino)-2-hydroxymethylindoline (2f), (orange crystals, 53%. method a), mp 176-178°C (EtOH). Ir cm^{-1}: 3356, 3190, 1669(s), 1601, 1525, 1345, 851, 757; uv-vis (95% EtOH) λmax(nm) (ε): 246 (15400); ms m/z: 313(M^+, 21), 282(63), 163(76), 150(44), 133(60), 116(100). Anal. Calcd for $C_{16}H_{15}N_3O_4$: C, 61.33; H, 4.83; N, 13.41. Found: C, 61.04; H, 4.78; N, 13.37.

2-(4-Dimethylaminophenyl)-4a,5-dihydro-4*H*-[1,3,4]oxadiazino[4,5-*a*]-*indole* (3a). -Typical procedure: In nitrogen atmosphere, triphenyl phosphine (577 mg, 2.2 mmol) was added into a solution of amido alcohol **(2a)** (623 mg, 2 mmol) and DEAD (383 mg, 2.2 mmol) in dry THF (20 ml) by one portion. The color of the reaction medium changed from orange to pale brown immediately, but the color was faded away slowly. After stirring for 30 min, the solution was evaporated and the brown oily residue was separated by flash column chromatography (*n*-hexane - CH_2Cl_2 2-1 : 1), affording colorless crystalline

Table 3 ^{1}H-Nmr spectra (δ ppm) of 2-Aryl-4a,5-dihydro-4*H*-[1,3,4]oxadiazino[4,5-*a*]indoles **(3)** in $CDCl_3$ [a)]

	3a	3b	3c	3d	3e	3f
4-H	3.88, t (9.8)	3.89, t (9.8)	3.89, t (9.7)	3.91, t (9.8)	3.92, t (9.7)	3.96, t (9.7)
4-H	4.42, dd (9.8, 3.7)	4.45, dd (9.8, 3.7)	4.47, dd (9.7, 3.8)	4.49, dd (9.8, 3.8)	4.58, dd (9. 7, 3.9)	4.62, dd (9.8, 3.9)
4a-H	4.13, m*	4.15, m*	4.16, m*	4.18, m*	4.24, m*	4.28, m*
5-H	2.86, dd (16.0, 5.9)	2.87, dd (15.9, 5.9)	2.88, dd (15.9, 6.1)	2.89, dd (15.9, 6.1)	2.94, dd (16.1, 6.7)	2.97, dd (15.9, 7.0)
5-H	3.26, dd (16.0, 9.4)	3.27, dd (15.9, 9.4)	3.27, dd (15.9, 9.5)	3.27, dd (15.9, 9.5)	3.29, dd (16.1, 9.5)	3.31, dd (15.9, 9.5)
6-H	7.07, dd (7.0, 0.4)	7.08, d (7.4)	7.08, d (8.0)	7.09, dd (8.2, 0.8)	7.09-7.12, m	7.12, dd (7.1, 1.0)
7-H	6.75, td (7.2, 1.2)	6.77, td (7.3, 1.1)	6.77, td (7.3, 1.2)	6.78, t (7.2)	6.82, td (7.4, 1.1)	6.84, td (7.3, 1.1)
8-H	7.15, t (7.5)	7.18, t (7.7)	7.13-7.18, m	7.16, t (7.6)	7.19, t (7.6)	7.20, td (7.6, 0.8)
9-H	7.09, dd (7.4, 0.4)	7.09, d (7.1)	7.10, d (8.3)	7.11, d (7.8)	7.09-7.12, m	7.13, dd (7.4, 0.5)
2', 6'-H	7.75, dt (9.0, 2.5)	7.82, dt (9.1, 2.5)	7.77, dt (8.1, 1.8)	7.87-7.91 m	7.96, dt (8.2, 1.7)	8.01, dt (9.1, 2.1)
3', 5'-H	6.68, dt (9.0, 2.5)	6.88, dt (9.1, 2.5)	7.15-7.18, m	7.34-7.38, m	7.62, dt (8.2, 1.7)	8.20, dt (9.1, 2.1)
4'-X	2.98, s NMe_2	3.82, s OCH_3	2.36, s CH_3	7.34-7.38, m H		

a) Coupling constants (Hz) are cited in parentheses. Multiple splittings with asterisk * were analyzed to be dddd type with *J*=9.7-9.8, 9.4-9.5, 5.9-7.0, and 3.7-3.9 Hz.

Table 4 ^{13}C-Nmr spectra (δ ppm) of 2-Aryl-4a,5-dihydro-4*H*-[1,3,4]oxadiazino[4,5-*a*]indoles **(3)** in $CDCl_3$

	3a	3b	3c	3d	3e	3f
C-2	147.6	146.6	146.6	146.3	143.9	143.6
C-4	66.3	66.4	66.4	66.5	66.6	66.6
C-4a	56.1	56.0	56.0	56.0	55.9	55.9
C-5	30.6	30.5	30.5	30.5	30.4	30.5
C-5a	124.7	124.7	124.7	124.7	124.8	124.9
C-6	124.8	124.8	124.8	124.9	125.0	125.1
C-7	119.7	120.0	120.0	120.1	120.8	120.9
C-8	128.1	128.2	128.2	128.2	128.3	128.4
C-9	110.0	109.9	109.9	109.9	109.6	109.6
C-9a	149.5	149.1	149.0	148.8	147.8	147.6
C-1'	120.0	124.8	129.4	132.1	136.2	138.0
C-2', 6'	126.9	127.1	125.5	125.5	125.6	125.7
C-3', 5'	111.6	113.6	128.9	128.1	131.9	123.5
C-4'	151.3	160.7	139.4	129.3	112.0	147.8
X	40.3	55.3	21.4		118.9	

product **(3a)** (528 mg, 90%), mp 157-158°C (CH_2Cl_2-MeOH). Ir cm^{-1}: 1610,1602, 1485, 1362, 1192, 823, 744; uv-vis (95%EtOH) λmax(nm) (ε): 335 (17900); ms m/z: 293(M^+, 87), 148(100). Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.33. Found: C, 73.39; H, 6.45; N, 14.33.

2-(4-Methoxyphenyl)-4a,5-dihydro-4*H*-[1,3,4]oxadiazino[4,5-*a*]indole (3b), colorless needles (92%), mp 142-143°C (CH_2Cl_2-MeOH). Ir cm^{-1}: 1610(s), 1600, 1483, 1313, 1255, 1028, 848, 753; uv-vis (95%EtOH) λmax(nm) (ε): 329 (16300), 246 (13500); ms m/z: 280(M^+, 35), 140(8), 136(9), 135(100). Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.02; H, 5.70; N, 10.02.

2-(4-Methylphenyl)-4a,5-dihydro-4*H*-[1,3,4]oxadiazino[4,5-*a*]indole (3c), More than two equivalents of triphenylphosphine and DEAD (4.4 mmol) were used. Colorless crystals (88%), mp 125-126°C (CH_2Cl_2-MeOH). Ir cm^{-1}: 1605(s), 1515, 1479, 1264, 1078, 825, 757; uv-vis (95%EtOH) λmax(nm) (ε): 336 (15200), 229 (14100); ms m/z: 264(M^+, 100), 119(98), 91(22). Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.24; H, 6.10; N, 10.57.

2-Phenyl-4a,5-dihydro-4*H*-[1,3,4]oxadiazino[4,5-*a*]indole (3d), colorless needles (97%), mp 113-115°C (CH_2Cl_2-MeOH). Ir cm^{-1}: 1599(s), 1478, 1263, 1097, 778, 745, 696, 668; uv-vis (95%EtOH) λmax(nm) (ε): 339 (12500), 225 (12200); ms m/z: 250(M^+, 67), 105(100), 77(31). Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76,78; H, 5.64; N, 11.19. Found: C, 76.80; H, 5.68; N, 11.22.

2-(4-Cyanophenyl)-4a,5-dihydro-4*H*-[1,3,4]oxadiazino[4,5-*a*]indole(3e), yellow needles (96%), mp 138-139°C (CH_2Cl_2-MeOH). Ir cm^{-1}: 2226, 1603(s), 1584, 1480, 1262, 1104, 849, 753; uv-vis (95%EtOH) λmax(nm) (ε): 387(17400),309 (3900), 247 (16400); ms m/z: 275(M^+, 100), 130(62), 117(25), 102(16). Anal. Calcd for $C_{17}H_{13}N_3O$: C, 74.16; H, 4.76; N, 15.26. Found: C, 74.13; H,

4.67; N, 15.16

2-(4-Nitrophenyl)-4a,5-dihydro-4*H*-[1,3,4]oxadiazino[4,5-*a*]indole (3f), dark red orthorhombic crystals (99%), mp 176-177°C (CH_2Cl_2-MeOH). Ir cm^{-1}: 1595(s), 1560, 1508, 1479, 1344, 1262, 1107, 856, 763; uv-vis (95%EtOH) $\lambda max(nm)$ (ε): 431 (12700), 266 (14600); *ms m/z*: 295(M^+, 9), 293(68), 277(24), 150(54), 145(38), 118(27), 117(67), 115(100), 104(53), 102(69). Anal. Calcd for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 64.96; H, 4.43; N, 14.18.

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REFERENCES

1. Mitsui Toatsu Chemicals, Inc., *Jpn. Kokai Tokkyo Koho JP 59 84 62,578* (*Chem. Abstr.*, 1984, **101**, 72767g).
2. I. Sircar, M. H. Cain, and J. G. Topliss, *U. S. US 4,508,718* (*Chem. Abstr.*, 1985, **103**, 6373r).
3. H. O. Haikala, P. T. Nore, E. J. Honkanen, J. J. Pystynen, K. K. Lonnberg, A. M. Luiro, and A. K. Pippuri, *Eur. Pat. Appl. EP 383,449* (*Chem. Abstr.*, 1991, **114**, 81895t).
4. K. Suhasini, T. V. P. Rao, and V. Thirupathaiah, *Curr. Sci.*, 1983, **52**, 1133.
5. a) Y. G. Atanasova and A. G. Atanasov, *Dokl. Bolg. Akad. Nauk.*, 1990, **43**, 107(*Chem. Abstr.*, 1991, **115**, 21673e); b) *idem, ibid.*, 1991, **44**, 109 (*Chem. Abstr.*, 1992, **117**, 19954v).
6. M. A. Dekeyser, D. M. Borth, R. C. Moore, and A. Mishra, *J. Agric. Food Chem.*, 1991, **39**, 374.

7. a) H. Katayama, N. Takatsu, H. Kitano, and Y. Shimaya, *Chem. Pharm. Bull.*, 1990, **38**, 1129; b) J.-K. Shen and H. Katayama, *Chem. Lett.*, 1992, 451; c) H. Katayama, M. Sakurada, W. H. H. Herath, N. Takatsu, and J.-K. Shen, *Chem. Pharm. Bull.*, 1992, **40**, 2267; d) H. Katayama, N. Takatsu, M. Sakurada, and Y. Kawada, *Heterocycles*, 1993, **35**, 453; e) J.-K. Shen, H. Katayama, N. Takatsu, and I. Shiro, *J. Chem. Soc., Perkin Trans.* 1, **1993**, 2087.
8. a) A. Mertens, W.-G. Friebe, B. Mueller-Beckmann, W. Kampe, L. Kling, and W. von der Saal, *J. Med. Chem.*, 1990, **33**, 2870; b) M.-C. Forest, P. Lahouratate, M. Martin, G. Nadler, M. J. Quiniou, and R. G. Zimmermann, *J. Med. Chem.*, 1992, **35**, 163.
9. R. J. Gallaschun and R. C. Schnur, *J. Heterocycl. Chem.*, 1992, **29**, 369.
10. E. J. Corey, R. J. McCaully and H. S. Sachdev, *J. Am. Chem. Soc.*, 1970, **92**, 2476
11. E. Bald, K. Saigo, and T. Mukaiyama, *Chem. Lett.*, 1975, 1163.
12. All assignments for ^{1}H and ^{13}C signals were carried out by using ^{1}H-Homo-decoupling, ^{1}H-^{1}H COSY, ^{1}H-^{1}H long range COSY, ^{1}H-^{1}H NOESY, ^{1}H-^{13}C COSY, and ^{1}H-^{13}C long range COSY experiments.
13. a) O. Mitsunobu, *Synthesis*, 1981, 1; b) D. L. Hughes, *Org. Reactions*, 1992, **42**, 335.
14. N. Galeotti, C. Montagne, J. Poncet, and P. Jouin, *Tetrahedron Lett.*, 1992, **33**, 2807.
15. D. L. Trepanier, V. Sprancmanis, and K. G. Wiggs, *J. Org. Chem.*, 1964, **29**, 668.
16. a) J. S. Bajwa, and M. J. Miller, *J. Org. Chem.*, 1983, **48**, 1114; b) S. E. Ramer, R. N. Moore, and J. C. Vederas, *Can. J. Chem.*, 1986, **64**, 706.
17. a) J. Mulzer, G. Bruentrup, and A. Chucholowski, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 622; b) W. Adam, N. Narita, and Y. Nishizawa, *J. Am. Chem. Soc.*, 1984, **106**, 1843.

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