Synthetic Approaches to Cularines [1]. III. Nucleophilic Addition and Substitution

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Attempts to induce the formation of the dibenzoxepine ring of cularine compounds by generating an electron-deficient system in ring C of an 8-hydroxybenzylisoquinoline met with failure. Attack by C-8 phenol on a "*p*-quinone methide" intermediate afforded benzofurans **16**, which it has been suggested are intermediates in the biogenesis of quettamines. Among the nucleophilic substitution reactions tried, only that based on a phenoxide attack on a benzyne intermediate (generated by dimsyl sodium treatment of a 2'-bromo-8-hydroxybenzylisoquinoline) afforded the dibenzoxepine nucleus of tetradehydrocularines **25** and **27**. Competing *N*-attack afforded the indolizine skeleton present in **24** and **26**. From compounds **25** and **27**, the corresponding cularines, cularimines and oxocularines were obtained.

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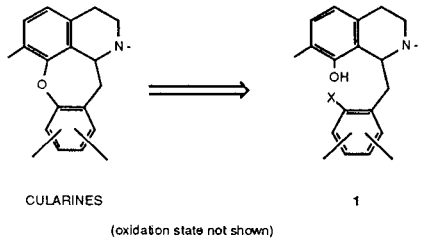
In the previous articles of this series [1] we have reported some of our efforts towards the synthesis of the expanding group of cularine alkaloids [4]. Consideration of the retrosynthetic disconnection of the diaryl ether bond to give a benzylisoquinoline unit (Figure I) led us to attempt two further approaches: I, phenol attack on an electron-deficient hexadienone (or similar) sytem, and II, nucleophilic aromatic substitution, each of which requires an appropriate precursor **1**.

Figure I



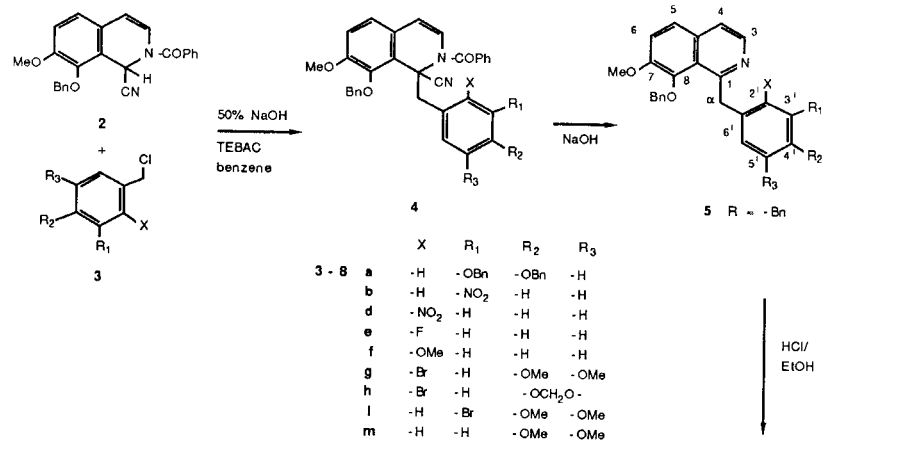
Type I Ring Closure.

Marino and Schwartz [5a] have recently shown that diphenyl selenoxide is a useful and very promising selective oxidant of catechols. A proposed "orthoquinone" intermediate is apparently trapped by a second monophenolic ring (not oxidized by the reagent) to produce a triphenolic biphenyl aporphine system. The obvious extension of this work was to trap the proposed "orthoquinone" intermediate with a phenol so as to generate a diaryl ether bond. It was hoped that this would provide an interesting entry to the cularine skeleton. Accordingly, *O*-benzyl protected triphenolic benzylisquinoline **5a** was synthesized by the Reissert compound approach described previously [1a] and then deprotected to produce the triphenol **9a**. Treatment of **5a** with methyl iodide followed by sodium borohydride reduction and final deprotection yielded tetrahydrobenzylisoquinoline **8a**. However, although treatment of **8a** or **9a** with diphenyl selenoxide [5b] in methanol yielded diphenyl selenide, the expected cularine was not found, even after diazomethane treatment. The cause of this failure may perhaps by attributed to the absence of *N*-protection [5c], but the readily prepared quaternary salt **10a** also failed to convert to a cularine structure on treatment with diphenyl selenoxide.

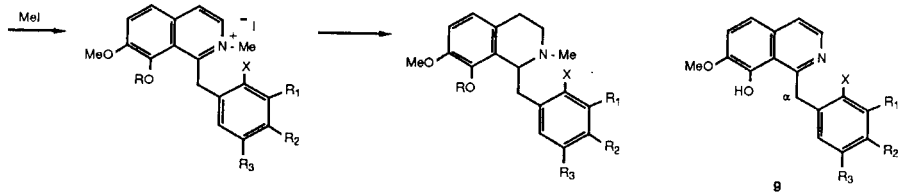
It then occurred to us that trapping an intermediate "quinone methide" by 1,4-addition (path a, Figure III) of a phenol group at C-8 might also provide the target molecule(s). The competing 1,6-addition (path b, Figure III) was thought to be reversible, and that the 1,4-addition process would afford the major product. Accordingly, on the basis of our previous experience of the demethylation of related compounds [6] (see Figure III), we selected the α-hydroxytetrahydrobenzylisoquinoline **11** and the α-hydroxybenzylisoquinoline **12** (or its aromatic *O*-benzyl ether derivatives) as models for acidic treatment.

Tetrahydrobenzylisoquinoline **15** (Figure IV) was prepared by the procedure described previously [1b], which involves the condensation [7] of Reissert compound **2** with the corresponding benzaldehyde to give benzoate **13** which is easily hydrolysed to alcohol **14**. Once prepared, tetrahydrobenzylisoquinoline **15** was treated with trifluoracetic acid [8a] for 24 hours. In the resulting mixture, the major product (30% yield) was not the expected cularine, as was shown by the absence of the characteristic H_1-dd signal from its ^{1}H-nmr spectrum. Instead, the presence of a doublet at 5.34 ppm (J = 10.4 Hz) and a molecular ion at m/e 327 (100%) in its ms clearly suggested the *trans*-dihydrofuran isoquinoline structure **16a**. The 5'-benzyl analogue **16b** (16% yield) was also isolated from the reaction mixture as was deduced from its ^{1}H-nmr spectrum, which

Figure II



		X	R_1	R_2	R_3
3 - 8	a	-H	-OBn	-OBn	-H
	b	-H	$-NO_2$	-H	-H
	d	$-NO_2$	-H	-H	-H
	e	-F	-H	-H	-H
	f	-OMe	-H	-H	-H
	g	-Br	-H	-OMe	-OMe
	h	-Br	-H	$-OCH_2O-$	
	l	-H	-Br	-OMe	-OMe
	m	-H	-H	-OMe	-OMe

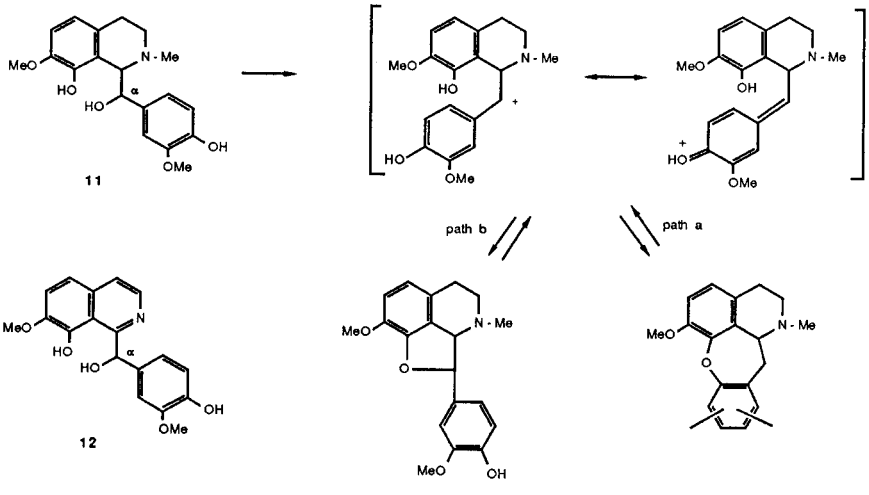


	R	X	R_1	R_2	R_3
6a	-Bn	-H	-OBn	-OBn	-H
6b	-Bn	-H	$-NO_2$	-H	-H
6c	-Bn	-Bn	-H	-OMe	-OMe
10a	-H	-H	-H	-OH	-H
10g	-H	-H	-H	-OMe	-OMe

	R	X	R_1	R_2	R_3
7a	-Bn	-H	-OBn	-OBn	-H
7b	-Bn	-H	$-NO_2$	-H	-H
7c	-Bn	-H	-H	-O Me	-OMe
8a	-H	-H	-OH	-OH	-H
8b	-H	-H	$-NO_2$	-H	-H
8c	-H	-H	$-NH_2$	-H	-H
8g	-H	-Br	-H	-OMe	-OMe
8m	-H	-H	-H	-OMe	-OMe

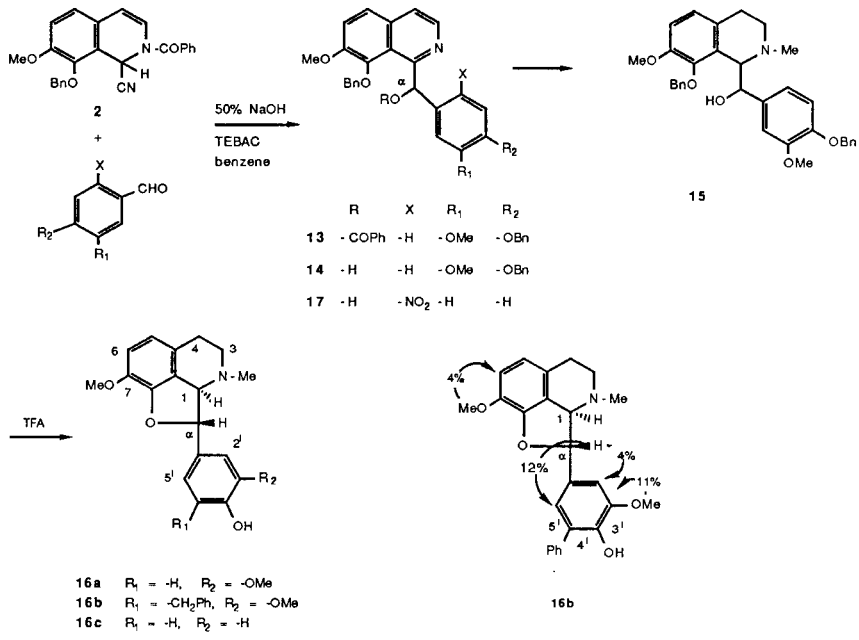
	X	R_1	R_2	R_3
a	-H	-OH	-OH	-H
b	-H	$-NO_2$	-H	-H
c	-H	$-NH_2$	-H	-H
d	$-NO_2$	-H	-H	-H
g	-Br	-H	-OMe	-OMe
h	-Br	-H	$-OCH_2O-$	
l	-H	-Br	-OMe	-OMe

Figure III



showed (together with the characteristic signals of the *trans* dihydrofuran skeleton) an aromatic ABq system with J = 1.8 Hz, attributable to the meta protons located at C_6 and $C_{2'}$ (see the set of NOE experiments depicted in the figure **16b**). The substitution group at position $C_{5'}$ was deduced to be a benzyl group with the $-CH_2-$ protons appearing at 3.97 and 4.05 ppm (ABq, J = 10.5 Hz) and the aromatic unit at 7.16-7.25 ppm as complex signal. The ms (M^+, 417) and the ^{13}C-nmr spectrum corroborated this hypothesis. This compound must be formed by the C-to-O re-

Figure IV



arrangement process observed [8b] in the acid deprotection of *O*-benzyltyrosine and related compounds in solid-state peptide synthesis, and which can be avoided by addition of methyl thioanisole to the reaciton mixture [8c].

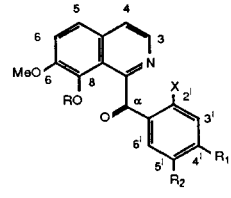
At the time the above experiment was being done, Shamma and Chattopadhyay [9] published an identical procedure for the synthesis of **16c**, which they proposed as an intermediate in the biosynthesis of the recenly isolated quettamines [10,2b], methyl chlorides of compounds like **16c**. By obtaining a single product with the *trans* configuration between C_1 and C_α they demonstrated the diastereoselectivity of the *O*-attack, which we also observed. In the same studies [9], it was found that under acid conditions (trifluoracetic acid or gaseous hydrogen bromide and zinc), compounds like **12** (see Figure III) lose their benzyl hydroxy group, and we therefore discontinued our efforts in this direction.

We next looked into the possibility of phenol-trapping an intermediate "iminium benzenium" [11] ion generated by zinc-trifluoromethanesulphonic acid reduction of a nitroarene [11]. This would lead to readily used amino-functionalized cularine. To this end we prepared the nitrotetrahydrobenzylisoquinoline **8b** (see Figure II) by the usual method [1a]. Once again, however, our expectations were frustrated. Reaction of **8b** with purified zinc [12] in a mixture of trifluoracetic acid-trifluoromethanesulphonic acid gave a 70% yield of aminotetrahydrobenzylisoquinoline **8c**, and an analogous result was obtained when nitrobenzylisoquinoline **9b** was subjected to the same process, aminobenzylisoquinoline **9c** being the only product isolated (see Figure II).

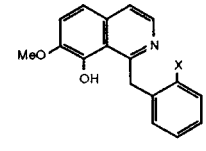
Type II Ring Closure.

At the outset we hoped to achieve the desired cyclization by any of the numerous reactions of nucleophilic aromatic substitution [13]. In particular we wanted a simple, direct means of reaching the oxocularine skeleton. Consequently, we planned the formation of the dihydrodibenzoxepine ring by cyclization of precursor **19** (see Figure V). Nitrobenzylisoquinoline **5d** (see Figure II) was easily made, but resisted all attempts at direct oxidation at its benzylic position (selenium dioxide, potassium dichromate). However, generation of the corresponding anion (sodium hydride/dimethylformamide), and subsequent treatment with oxygen yielded a 1:1 mixture of alcohol **17** (see Figure IV) and ketone **18d** (see Figure V) from which

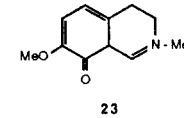
Figure V



	R	X	R_1	R_2
18d	-Bn	$-NO_2$	-H	-H
18e	-Bn	-F	-H	-H
18f	-Bn	-OMe	-H	-H
19d	-H	$-NO_2$	-H	-H
19f	-H	-OMe	-H	-H
19g	-H	-Br	-OMe	-OMe
19j	-H	-H	-OMe	-OMe
19k	-Me	-H	-OMe	-OMe
19l	-H	-H	-OMe	-OH
20	-Buty	-OMe	-H	-H



21 X = - NH_2
22 X = - $N_2^+ BF_4^-$



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benzoylisoquinoline **18d** was isolated in 80% yield by treatment with pyridinium dichromate in methylene chloride [14].

Regrettably, treatment of **19d** with sodium hydride in hexamethylphosphoramide [15] at room temperature yielded unaltered starting material, and on heating led to a complex mixture of products. Furthermore, attempts to make use of the greater readiness of fluoride as leaving group by an approach *via* fluorobenzoylisoquinoline **18e** had to be abandoned due to the enormous difficulty of oxidizine precursor **5e** (see Figure II).

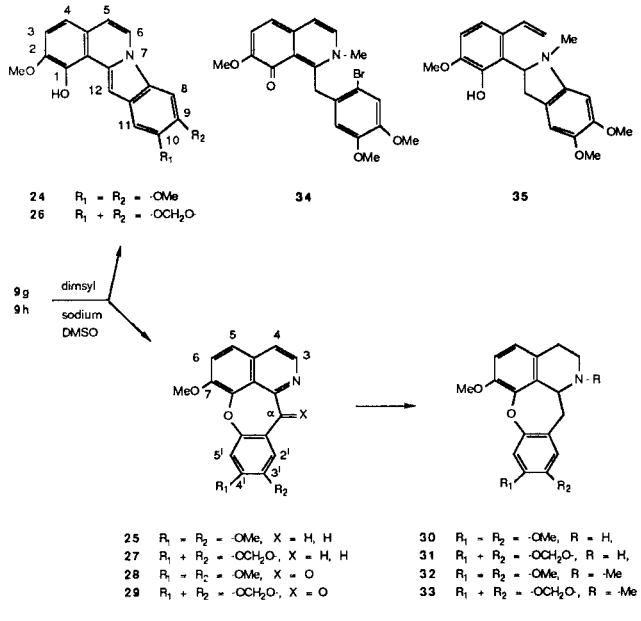
The -OMe, being a poorer leaving group than fluoride or nitrite, has been shown to be an efficient substituent for achieving the formation of the xanthone skeleton starting from a phenolic benzophenone [16]. We therefore prepared benzoylisoquinoline **18f** by selenium dioxide oxidation [17] of precursor **5f** (see Figure II). Under the conditions found to be suitable for xanthone formation (pyridine/tetrabutylammonium hydroxide/reflux) [16], **19f** yielded a single non-phenolic product easily identified as **20** (see Figure V). Quaternary ammonium salts are known to be cleaved by nucleophiles such as sulfides [18,19], boron and aluminium hydrides [20,21] and others, but we know of only one reference their cleavage by oxygen nucleophiles [22].

In an attempt to reproduce the phenoxidediazonization (S_N1) reaction [23a], we next prepared diazonium salt **22** by diazotation [23b] of aminobenzylisoquinoline **21** (itself obtained by catalytic hydrogenation of nitro compound **5d**). However, when we subjected the arenediazonium salt **22** to the conditions suggested (addition over refluxing dimethylformamide) [24], a complex mixture of coloured products was obtained.

Although much less common, photoinduced aromatic substitution [25] seemed to us the obvious alternative to the above ground state reactions. Irradiation of a Pyrex-filtered solution of the sodium phenoxide [26] of **8g** (generated with sodium hydride in acetonitrile) brought about the smooth disappearance of starting material, but led to a mixture of unsought products. Irradiation of phenolic compound **8g** (see Figure II) in acetonitrile on the other hand brought about homolytic rupture to produce the known [1a] compound **23**, though in low yield. Irradiation of phenoxide **8g** under $S_{RN}1$ [27-31] conditions (with photochemical stimulation) [31] led to its debromination as the major pathway, which confirms that phenoxide ions are unreactive in $S_{RN}1$ conditions [29], contrary to what has previously been suggested [30].

After the above series of failures, we were finally successful in using the intramolecular trapping of a benzyne to generate the desired cularine skeleton. Bromobenzylisoquinolines **9g** and **9h** (see Figure II) were subjected to the action of dimsyl sodium [32], and in both cases we obtained two major products (**24** and **25** from **9g**, and **26** and **27** from **9h**), which originated from competing nitrogen and oxygen attacks on the intermediate benzyne (see Figure VI). As expected, the tetradehydrocularines thus obtained (**25** and **27**) were found to be easily oxidized by air or Fremy's salt, yielding the natural oxocularines **28** (oxocularine) [33] and **29** (oxocompostelline) [33]. Catalytic hydrogenation of **25** and **27** produced cularimine **30** and non-natural *O*-methyl-*N*-norcularicine **31** respectively; and methyl iodide treatment of **25** and **27**, followed by sodium borohydride reduction, produced cularine **32** [34] and *O*-methylcularicine **33** [35,1b] in good yield. However, the reaction of 3'-bromobenzylisoquinoline **9i** (see Figure II) with dimsyl sodium under identical conditions as used for **9g** and **9h** led to the formation of the unstable benzoylisoquinoline **19j** (see Figure V) as the major product (40% yield). Its structure was confirmed by independent synthesis of its *O*-methyl derivative **19k** starting from the described **19l** [1a].

Figure VI



The obvious protection of the isoquinoline **9g** as quaternary *N*-methiodide did not solve the problem of *N*-competition, because of the formation of the violet compound **34** in basic medium. Furthermore, blocking the benzylic position by starting with benzoylisoquinoline **19g** (see Figure V) did not give the desired oxocularine, but instead a complex mixture of unsought products. Finally, the *N*-attack was also the only process observed when tetrahydrobenzylisoquinoline **8g** (see Figure II) was subjected to dimsyl sodium as above, the major product (38% yield) being the Hofmann degradation product indole **35**.

EXPERIMENTAL

Materials and Techniques.

Please refer to the Materials and Techniques portion of the first paper in this series [1a].

Proton magnetic resonance spectra were recorded on a Varian CFT-20 or a Bruker WM-250 spectrometers. Carbon-13 spectra were recorded at 62.89 MHz on a Bruker WM-250 spectrometer. Carbon multiplicities were assigned by INEPT techniques [36].

Dimethylformamide, dimethyl sulfoxide and hexamethylphosphoramide were dried from calcium hydride, distilled under reduced pressure and stored over 4A molecular sieves. Methanol was dried by distillation from magnesium.

Photolyses were carried out with medium pressure mercury vapor arc lamps (Hanovia, 250 watts).

General procedures for the synthesis of compounds **4-9** and **18-19** have been described in part I of this series [1a]. Reaction conditions, yields, recrystallization solvents and spectroscopic data for these compounds are given below. Phenolic compounds generally proved to be highly unstable and their elemental analysis could sometimes not be carried out.

8-Benzyloxy-*N*-benzoyl-1-(3',4'-dibenzyloxybenzyl)-1,2-dihydro-7-methoxyisoqunoline-1-carbonitrile (**4a**).

From 1.1 molar equivalents of benzyl chloride **3a** per mole of Reissert compound **2** and stirring for 6 hours, compound **4a** was obtained in 96% yield, mp 154-156° (ethanol); ^{1}H-nmr: 3.68 (d, J = 13.7 Hz, 1H, -CH$_a$Ar), 3.92 (s, 3H, -OMe), 4.27 (d, J = 13.7 Hz, 1H, -CH$_b$Ar), 4.72 (s, 2H, -OCH$_2$Ph), 4.98 (d, J = 8.1 Hz, 1H, H$_4$), 5.02 (s, 2H, -OCH$_2$Ph), 5.46-5.50 (m, 2H, -OCH$_2$Ph), 5.94-7.72 (m, 17H, ArH); ms: m/e (%) 698 (M$^+$, 1), 476 (19), 266 (16), 131 (80), 105 (80) and 91 (100).

Anal. Calcd. for $C_{46}H_{38}N_2O_5$: C, 79.08; H, 5.42; N, 4.01. Found: C, 78.68; H, 5.50; N, 3.97.

8-Benzyloxy-*N*-benzoyl-1-(3'-nitrobenzyl)-1,2-dihydro-7-methoxyisoquinoline-1-carbonitrile (**4b**).

From 1.3 molar equivalents of **3b** per mole of Reissert compound **2** and 2 hours stirring, **4b** was obtained in 98% yield, mp 210-212° (ethanol); ^{1}H-nmr: 3.84 and 4.48 (ABq, J = 13.7 Hz, 2H, -CH$_2$Ar), 3.98 (s, 3H, -OMe), 4.92 and 6.03 (ABq, J = 8.0 Hz, 2H, H$_4$ and H$_5$), 5.51 (s, 2H, -OCH$_2$Ph), 6.55 and 6.95 (ABq, J = 8.3 Hz, 2H, H$_6$ and H$_5$), 7.10-7.93 (m, 14H, ArH); ms: m/e (%) 399 (25), 131 (15), 105 (69) and 91 (100).

Anal. Calcd. for $C_{32}H_{25}N_3O_5$: C, 72.31; H, 4.70; N, 7.90. Found: C, 72.19; H, 4.64; N, 7.65.

8-Benzyloxy-*N*-benzoyl-1-(2'-nitrobenzyl)-1,2-dihydro-7-methoxyisoquinoline-1-carbonitrile (**4d**).

From 1.2 molar equivalents of **3d** per mole of Reissert compound **2** and 2 hours stirring, compound **4d** was obtained in 87% yield as an oil which could not be crystallized, and was hydrolysed to **5d**. The data for compound **4d** follow: ^{1}H-nmr: 3.92 (s, 3H, -OMe), 4.09 and 4.68 (ABq, J = 13.9 Hz, 2H, -CH$_2$Ar), 5.04 and 6.05 (ABq, J = 8.0 Hz, 2H, H$_4$ and H$_5$), 5.50 (s, 2H, -CCH$_2$Ph), 6.52 (d, J = 8.4 Hz, 1H, H$_6$), 6.71-7.72 (m, 15H, ArH); ms: m/e (%) 279 (5), 105 (70), 92 (100) and 77 (58).

8-Benzyloxy-*N*-benzoyl-1-(2'-fluorobenzyl)-1,2-dihydro-7-methoxyisoquinoline-1-carbonitrile (**4e**).

From 1 molar equivalent of benzyl chloride **3e** per mole of Reissert compound **2** and 8 hours stirring compound **4e** was obtained in 86% yield, mp 183-185° (ethanol); ^{1}H-nmr: 3.63 and 4.61 (ABq, J = 13.7 Hz, 2H, -CH$_2$Ar), 3.93 (s, 3H, -OMe), 4.93 and 6.13 (ABq, J = 7.9 Hz, 2H, H$_4$ and H$_5$), 6.44-7.74 (m, 16H, ArH); ms: m/e (%) 146 (5), 132 (6), 105 (47), 91 (100) and 77 (45).

Anal. Calcd. for $C_{32}H_{25}FN_2O_3$: C, 76.19; H, 4.96; N, 5.55. Found: C, 76.01; H, 4.95; N, 5.66.

8-Benzyloxy-*N*-benzoyl-1-(2'-methoxybenzyl)-1,2-dihydro-7-methoxyisoquinoline-1-carbonitrile (**4f**).

From 1.1 molar equivalents of benzyl chloride **3f** per mole of Reissert compound **2** and 8 hours stirring, compound **4f** was obtained. Like **4d**, it was hydrolysed to **5f** without isolation.

8-Benzyloxy-*N*-benzoyl-1-(3'-bromo-4',5'-dimethoxybenzyl)-1,2-dihydro-7-methoxyisoquinoline-1-carbonitrile (**4i**).

From 1.1 molar equivalents of benzyl chloride **3i** per mole of Reissert compound **2** and 3 hours stirring compound **4i** was obtained in 88% yield, mp 156-158° (ethanol); ^{1}H-nmr: 3.46, 3.73 and 3.94 (ss, each 3H, 3 × -OMe), 3.69 and 4.28 (ABq, J = 13.5 Hz, 2H, -CH$_2$Ar), 5.00 and 6.95 (ABq, J = 8.1 Hz, 2H, H$_4$ and H$_5$), 5.49 (m, 2H, -OCH$_2$Ph), 6.03-6.64 (m, 5H, ArH), 7.35-7.74 (m, 10H, ArH); ms: m/e (%) 404 and 402 (22), 395 (33), 231 and 229 (13), 131 (21) and 91 (100).

Anal. Calcd. for $C_{34}H_{29}BrN_2O_5$: C, 65.28; H, 4.48; N, 4.64. Found: C, 65.35; H, 4.55; N, 4.67.

8-Benzyloxy-1-(3',4'-dibenzyloxybenzyl)-7-methoxyisoquinoline (**5a**).

Compound **5a** was obtained in quantitative yield, mp 119-121° (ethanol). Its hydrochloride melted at 171-173° and could be analyzed; ^{1}H-nmr: 3.95 (s, 3H, -OMe), 4.73, 4.83, 4.87 and 5.03 (ss, each 2H, 4 × -CH$_2$Ar), 6.72-7.55 (m, 21H, ArH), 8.34 (d, J = 5.6 Hz, 1H, H$_3$); ms: m/e (%) 567 (M$^+$, 2), 476 (14), 386 (10), 97 (13), 92 (25) and 91 (100).

Anal. Calcd. for $C_{38}H_{34}ClNO_4$: C, 75.76; H, 5.63; N, 2.32. Found: C, 75.83; H, 5.69; N, 1.96.

8-Benzyloxy-1-(3'-nitrobenzyl)-7-methoxyisoquinoline (**5b**).

Compound **5b** was obtained in quantitative yield; mp 68-70° (ethanol); ^{1}H-nmr: 3.89 (s, 3H, -OMe), 4.80 and 5.00 (ss, each 2H, 2 × -CH$_2$Ar), 7.11-7.82 (m, 12H, ArH), 8.27 (d, J = 5.6 Hz, 1H, H$_3$); ms: m/e (%) 400 (M$^+$, 67), 309 (28), 263 (27), 220 (29), 212 (32) and 91 (100).

Anal. Calcd. for $C_{24}H_{20}N_2O_4$: C, 72.00; H, 5.00; N, 7.00. Found: C, 71.91; H, 5.03; N, 6.91.

8-Benzyloxy-1-(2'-nitrobenzyl)-7-methoxyisoquinoline (**5d**).

The general procedure [1a] gave an 80% yield. A better method was as follows [37]. A mixture of 0.17 g (0.32 mmole) of **4d**, 5 ml of methanol and 3 ml of Triton B (40% in water) was magnetically stirred for 24 hours at room temperature under an inert gas. After evaporation to a small volume (2 ml), water (30 ml) and methylene chloride (30 ml) were added. The aqueous layer was extraced with methylene chloride (3 × 40 ml) and the dried extracts (sodium sulfate) were concentrated under vacuum, affording **5d** (0.12 g, 94% yield) as a crystalline solid, mp 126-128° (ethanol); ^{1}H-nmr: 3.99 (s, 3H, -OMe), 5.14 and 5.22 (ss, each 2H, 2 × -CH$_2$Ar), 6.98 (dd, J_{AX} = 6.5 Hz, J_{BX} = 2.5 Hz, 1H, ArH), 7.26-7.94 (m, 11H, ArH), 8.14 (d, J = 5.7 Hz, 1H, H$_3$); ms: m/e (%) 400 (M$^+$, 43), 354 (66), 309 (80), 292 (83), 263 (100), 219 (94), 190 (91) and 91 (94).

Anal. Calcd. for $C_{24}H_{20}N_2O_4$: C, 72.00; H, 5.00; N, 7.00. Found: C, 71.60; H, 5.00; N, 7.00.

8-Benzyloxy-1-(2'-fluorobenzyl)-7-methoxyisoquinoline (**5e**).

Compound **5e** was obtained in quantitative yield. It crystallized as the hydrochloride, mp 156-158° dec. The data for **5e** is as follows; ^{1}H-nmr: 3.94 (s, 3H, -OMe), 4.90 and 5.02 (ss, each 2H, 2 × -CH$_2$Ar), 6.84-7.55 (m, 12H, ArH), 8.30 (d, J = 5.6 Hz, 1H, H$_3$); ms: m/e (%) 373 (M$^+$ 52), 282 (80), 267 (100), 184 (46) and 91 (75).

Anal. Calcd. for $C_{24}H_{21}ClFNO_2$: C, 70.32; H, 5.12; N, 3.41. Found: C, 70.56; H, 5.19; N, 3.01.

8-Benzyloxy-1-(2'-methoxybenzyl)-7-methoxyisoquinoline (**5f**).

Compound **5f** was obtained in 70% yield, mp 106-108° (ethanol); ^{1}H-nmr: 3.57 and 3.92 (s, each 3H, 2 × -OMe), 4.85 (s, 4H, 2 × -CH$_2$Ar), 6.59-7.56 (m, 12H, ArH), 8.33 (d, J = 5.6 Hz, 1H, H$_3$); ms: m/e (%) 385 (M$^+$, 0.5), 354 (42), 264 (20), 121 (20) and 91 (100).

Anal. Calcd. for $C_{25}H_{23}NO_3$: C, 77.92; H, 5.97; N, 3.63. Found: C, 77.42; H, 6.15; N, 3.30.

8-Benzyloxy-1-(3'-bromo-4',5'-dimethoxybenzyl)-7-methoxyisoquinoline (**5i**).

Compound **5i** was obtained in quantitative yield. It crystallized as the hydrochloride, mp 183-185°. The data for **5i** is as follows ^{1}H-nmr: 3.52, 3.73 and 3.96 (ss, each 3H, 3 × -OMe), 4.77 and 5.02 (ss, each 2H, 2 × -CH_2Ar), 6.55 (broad s, 1H, H_3), 6.70 (d, J = 1.8 Hz, 1H, H_6), 7.39-7.56 (m, 8H, ArH), 8.36 (d, J = 5.7 Hz, 1H, H_1); ms: m/e (%) 494 and 492 (M^+, 1), 404 and 402 (6), 92 (10) and 91 (100).

Anal. Calcd. for $C_{26}H_{25}BrClNO_4$: C, 58.81; H, 4.71; N, 2.64. Found: C, 58.92; H, 4.96; N, 2.17.

8-Benzyloxy-1-(3',4'-dibenzyloxybenzyl)-7-methoxy-*N*-methylisoquinolinium Iodide (**6a**).

Treatment of **5a** with methyl iodide for 18 hours afforded in 82% yield compound **6a**, mp 132-134° (acetone); ^{1}H-nmr: 4.06 (s, 3H, -OMe), 4.38 (s, 3H, -N^+-Me), 4.89, 4.93, 5.10 and 5.23 (ss, each 2H, 4 × -CH_2Ar), 7.11-7.97 (m, 20H, ArH), 8.21 and 8.71 (ABq, J = 6.9 Hz, 2H, H_4 and H_3); ms: m/e (%) 490 (19), 477 (23), 386 (43), 355 (42), 265 (100), 92 (71) and 91 (72).

Anal. Calcd. for $C_{39}H_{36}INO_4$: C, 66.00; H, 5.07; N, 1.97. Found: C, 65.95; H, 5.07; N, 1.60.

8-Benzyloxy-1-(3'-nitrobenzyl)-7-methoxy-*N*-methylisoquinolinium Iodide (**6b**).

Treatment of **5b** as above afforded in 90% yield compound **6b**, mp 163-165° (acetone); ^{1}H-nmr: 4.07 (s, 3H, -OMe), 4.48 (s, 3H, -N^+-Me), 5.22 and 5.44 (ss, each 2H, 2 × -CH_2Ar), 7.04-8.02 (m, 11H, ArH), 8.19 and 8.56 (ABq, J = 6.8 Hz, 2H, H_4 and H_3); ms: m/e (%) 414 (44), 400 (34), 310 (65), 142 (100), 127 (68) and 91 (70).

Anal. Calcd. for $C_{25}H_{23}IN_2O_4$: C, 55.35; H, 4.24; N, 5.16. Found: C, 55.57; H, 4.32; N, 4.91.

8-Benzyloxy-1-(3',4'-dibenzyloxybenzyl)-1,2,3,4-tetrahydro-7-methoxy-*N*-methylisoquinoline (**7a**).

Compound **7a** was obtained in quantitative yield as an oily product; ^{1}H-nmr: 2.15 (s, 3H, -NMe), 2.26-2.88 (m, 6H, 3 × -CH_2-), 3.89 (s, 3H, -OMe), 4.95, 5.03, 5.11 and 5.12 (ss, each 2H, 4 × -CH_2Ar), 6.67-7.36 (m, 20H, ArH).

8-Benzyloxy-1-(3'-nitrobenzyl)-1,2,3,4-tetrahydro-7-methoxy-*N*-methylisoquinoline (**7b**).

Compound **7b** was obtained in quantitative yield, mp 95-97° (ethanol-water); ^{1}H-nmr: 2.13 (s, 3H, -NMe), 2.19-3.84 (m, 7H, -CH-), 3.91 (s, 3H, -OMe), 4.93 and 5.26 (ABq, J = 11.1 Hz, 2H, -OCH_2Ph), 6.83-8.02 (m, 11H, ArH); ms: m/e (%) 418 (M^+, 0.5), 282 (100), 191 (63), 190 (39), 162 (18) and 91 (48).

Anal. Calcd. for $C_{25}H_{26}N_2O_4$: C, 71.77; H, 6.22; N, 6.69. Found: C, 71.76; H, 6.40; N, 6.37.

1,2,3,4-Tetrahydro-1-(3',4'-dihydrobenzyl)-7-methoxy-*N*-methylisoquinolin-8-ol (**8a**).

This compound was prepared from **7a** by catalytic hydrogenation; 0.1 g of 10% Pd/C was added to a solution of 0.3 g (0.6 mmole) of **7a** in 30 ml of ethanol and 0.2 ml of concentrated hydrochloric acid and the mixture was hydrogenated at room temperature and atmospheric pressure until the uptake of hydrogen ceased. The solution was filtered and evaporated to dryness to give a syrup which was used immediately; ^{1}H-nmr (deuteriochloroform + perdeuteriomethanol): 2.35 (s, 3H, -NMe), 2.67-3.30 (m, 6H, 3 × -CH_2-), 3.87 (s, 3H, -OMe), 4.21 (dd, J_{AX} = 8.4 Hz, J_{BX} = 3.4 Hz, 1H, H_1), 6.48-6.85 (m, 5H, ArH); ms: m/e (%) 315 (M^+, 3), 314 (9), 313 (33), 312 (26), 297 (31) and 192 (100).

1,2,3,4-Tetrahydro-1-(3'-nitrobenzyl)-7-methoxy-*N*-methylisoquinolin-8-ol (**8b**).

Application of the standard procedure [1a] to **7b** afforded in quantitative yield compound **8b**, mp 106-108° (ethanol); ^{1}H-nmr: 2.37 (s, 3H, -NMe), 2.43-3.31 (m, 6H, 3 × -CH_2-), 3.88 (s, 3H, -OMe), 4.04 (dd, J_{AX} = 7.6 Hz, J_{BX} = 4.2 Hz, 1H, H_1), 6.55-8.08 (m, 6H, ArH); ms: m/e (%) 328 (M^+, 0.5), 193 (12), 192 (100), 177 (17).

Anal. Calcd. for $C_{18}H_{20}N_2O_4$: C, 65.85; H, 6.09; N, 8.53. Found: C, 65.32; H, 6.05; N, 8.56.

1,2,3,4-Tetrahydro-1-(2'-bromo-4',5'-dimethoxybenzyl)-7-methoxy-*N*-methylisoquinolin-8-ol (**8g**).

See part II of this series [1b].

1-(3',4'-Dihydroxybenzyl)-7-methoxyisoquinolin-8-ol (**9a**).

Compound **9a** was obtained in quantitative yield, mp 216-218° (acetone-hexane); ^{1}H-nmr (deuteriochloroform + perdeuteriomethanol): 3.94 (s, 3H, -OMe), 4.79 (s, 2H, -CH_2Ar), 6.56-6.60 (m, 3H, ArH), 7.33 and 7.55 (ABq, J = 8.8 Hz, 2H, H_6 and H_5), 7.49 and 8.07 (ABq, J = 5.8 Hz, 2H, H_4 and H_3); ms: m/e (%) 297 (M^+, 100), 296 (27), 280 (32), 277 (65), 89 (45) and 77 (77).

1-(3'-Nitrobenzyl)-7-methoxyisoquinolin-8-ol (**9b**).

Compound **9b** was obtained in quantative yield, mp 108-110° (ethanol-dichloromethane); ^{1}H-nmr: 3.98 (s, 3H, -OMe), 5.00 (s, 2H, -CH_2Ar), 6.90 (broad s, 1H, -OH), 7.47-8.17 (m, 6H, ArH), 8.31 (d, J = 5.8 Hz, 1H, H_3); ms: m/e (%) 310 (M^+, 100), 309 (55), 293 (39), 263 (28), 220 (33) and 191 (19).

1-(2'-Bromo-4',5'-dimethoxybenzyl)-7-methoxyisoquinolin-8-ol (**9g**).

Described in part II of this series [1b].

1-(2'-Bromo-4',5'-methylenedioxybenzyl)-7-methoxyisoquinolin-8-ol (**9h**).

Compound **5h** [1b] afforded in 90% yield, compound **9h**, mp 161-163° (ethanol-dichloromethane); ^{1}H-nmr: 3.98 (s, 3H, -OMe), 4.89 (s, 2H, -CH_2Ar), 5.85 (s, 2H, -OCH_2O-), 6.24 (s, 1H, H_3), 7.05 (s, 1H, H_6), 7.39 (m, 3H, ArH), 8.29 (d, J = 5.7 Hz, 1H, H_3); ms: m/e (%) 388 and 386 (M^+-1, 0.5), 310 (49), 309 (88), 308 (100), 307 (59), 293 (79) and 264 (51).

Anal. Calcd. for $C_{18}H_{14}BrNO_4$: C, 55.67; H, 3.60; N, 3.60. Found: C, 55.42; H, 3.71; N, 3.21.

1-(3'-Bromo-4',5'-dimethoxybenzyl)-7-methoxyisoquinolin-8-ol (**9i**).

Compound **9i** was obtaind in 93% yield, mp 200-201° (ethanol); ^{1}H-nmr: 3.76, 3.77 and 3.99 (ss, each 3H, 3 × -OMe), 4.85 (s, 2H, -CH_2Ar), 6.88 (d, J = 1.2 Hz, 1H, H_6), 7.05 (d, J = 1.3 Hz, 1H, H_2), 7.39 (broad s, 2H, ArH), 7.43 and 8.31 (ABq, J = 5.8 Hz, 2H, H_4 and H_3); ms: m/e (%) 405 and 403 (M^+, 100), 390 (62), 388 (64), 372 (29), 266 (28), 162 (30) and 86 (48).

Anal. Calcd. for $C_{19}H_{18}BrNO_4$: C, 56.43; H, 4.45; N, 3.46. Found: C, 56.15; H, 4.70; N, 3.13.

8-Benzyloxy-1-(2'-nitrobenzoyl)-7-methoxyisoquinoline (**18d**).

To a suspension of 0.011 g (0.37 mmole) of 80% sodium hydride in 2 ml of anhydrous dimethylformamide stirred under inert gas at room temperature was added dropwise, through a septum, a solution of 0.1 g (0.25 mmole) of **5d** dissolved in 2 ml of anhydrous dimethylformamide. The intense blue solution was stirred for 5 minutes prior to the bubbling of oxygen through it for 3 hours, during which time the colour turned to pale yellow. Ethanol (3 drops) was added to destroy excess hydride, and the solvent was removed. The residue was taken into methylene chloride (20 ml) and washed with water (2 × 30 ml) and brine (20 ml). The dried (sodium sulfate) extracts were evaporated to dryness to give a residue which was taken into anhydrous methylene chloride (1 ml) and stirred with pyridinium dichromate (1.5 molar equivalents) for 30 hours under inert gas. Work-up as desribed elsewhere [1b] afforded a solid which crystallized from ethanol, mp 169-171°, 80% yield; ir: 1690 (-CO) cm^{-1};

^{1}H-nmr: 3.99 (s, 3H, -OMe), 5.18 (s, 2H, -CH_2Ar), 7.11-7.68 (m, 12H, ArH), 8.35 (d, J = 5.7 Hz, 1H, H_3); ms: m/e (%) 414 (M^+, 39), 250 (12), 105 (15), 104 (16), 92 (39) and 91 (100).

Anal. Calcd. for $C_{24}H_{18}N_2O_5$: C, 69.56; H, 4.34; N, 6.76. Found: C, 69.61; H, 4.46; N, 6.36.

8-Benzyloxy-1-(2'-methoxybenzoyl)-7-methoxyisoquinoline (**18f**).

The general selenium dioxide oxidation method [17,1b] was used. Compound **18f** was obtained in 95% yield, mp 137-139° (ethanol); ir: 1660 (-CO) cm^{-1}; ^{1}H-nmr: 3.19 and 3.95 (ss, each 3H, 2 × -OMe), 5.00 (s, 2H,

-CH_2Ar), 6.71-7.60 (m, 11H, ArH), 7.96 (dd, J_{AX} = 7.7 Hz, J_{BX} = 1.8 Hz, 1H, $H_{6'}$), 8.33 (d, J = 5.8 Hz, 1H, H_3); ms: m/e (%) 399 (M^+, 32), 198 (30), 135 (97), 92 (62), 91 (100) and 77 (85).

Anal. Calcd. for $C_{25}H_{21}NO_5$: C, 75.18; H, 5.26; N, 3.51. Found: C, 74.80; H, 5.37; N, 3.53.

1-(2'-Nitrobenzoyl)-7-methoxyisoquinolin-8-ol (**19d**).

Acidic debenzylation of **18d** afforded in 78% yield compound **19d**, mp 166-168° (dichloromethane): ^{1}H-nmr: 4.06 (s, 3H, -OMe), 7.40 (d, J = 8.8 Hz, H_6), 7.51-8.16 (m, 7H, ArH), 10.57 (broad s, 1H, -OH); ms: m/e (%) 324 (M^+, 95), 309 (15), 279 (45), 278 (100), 264 (32), 235 (55) and 234 (23).

Anal. Calcd. for $C_{17}H_{12}N_2O_5$: C, 62.96; H, 3.70; N, 8.64. Found: C, 62.92; H, 3.68; N, 8.29.

1-(2'-Methoxybenzoyl)-7-methoxyisoquinolin-8-ol (**19f**).

Acidic debenzylation of **18f** afforded in 95% yield compound **19f**, mp 176-178° (methanol); ir: 1660 (-CO) cm^{-1}; ^{1}H-nmr: 3.33 and 3.97 (ss, each 3H, 2 × -OMe), 6.76-7.58 (m, 6H, ArH), 8.05 (dd, J_{AX} = 7.6 Hz, J_{BX} = 1.8 Hz, 1H, $H_{6'}$), 8.29 (d, J = 5.8 Hz, 1H, H_3); ms: m/e (%) 309 (M^+, 37), 278 (29), 135 (49), 130 (16), 92 (45) and 78 (100).

Anal. Calcd. for $C_{18}H_{15}NO_4$: C, 69.90; H, 4.85; N, 4.53. Found: C, 69.70; H, 4.93; N, 4.41.

8-Benzyloxy-1-(α-benzoyloxy-4'-benzyloxy-3'-methoxybenzyl)-7-methoxyisoquinoline (**13**).

This compound was synthesized by the general procedure [1b] using an excess of 1.1 molar equivalent of 4-benzyloxy-3-methoxybenzaldehyde. A stirring time of 3 hours was needed. Compound **13** was obtained in 91% yield, mp 156-158° (ethanol); ir: 1695 cm^{-1}; ^{1}H-nmr: 3.55 and 3.98 (ss, each 3H, 2 × -OMe), 5.05 (s, 2H, $-OCH_2Ph$), 5.09 and 5.38 (Abq, J = 10.3 Hz, 2H, $-OCH_2Ph$), 6.69-8.25 (m, 22H, ArH + -CHα-), 8.37 (d, J = 5.6 Hz, 1H, H_3); ms: m/e (%) 400 (5), 122 (73), 106 (10), 105 (100) and 91 (23).

Anal. Calcd. for $C_{39}H_{33}NO_6$: C, 76.59; H, 5.40; N, 2.29. Found: C, 76.38; H, 5.45; N, 2.28.

8-Benzyloxy-1-(4'-benzyloxy-α-hydroxy-3'-methoxybenzyl)-7-methoxyisoquinoline (**14**).

Treatment of **13** under standard basic conditions [1b] afforded quantitatively compound **14** as an oil whose hydrochloride melted at 216-218°; ^{1}H-nmr: 3.50 and 3.84 (ss, each 3H, 2 × -OMe), 4.73 and 4.98 (ABq, J = 11.0 Hz, 2H, $-OCH_2Ph$), 4.98 (s, 2H, $-CH_2Ph$), 6.20 (dd, J_{AX} = 8.3 Hz, J_{BX} = 1.8 Hz, 1H, $H_{6'}$), 6.55 (d, J = 8.3 Hz, 1H, $H_{5'}$), 6.71-7.72 (m, 15H, ArH + -CHα-), 8.33 (d, J = 5.6 Hz, 1H, H_3); ms: m/e (%) 507 (M^+, 0.5), 400 (6), 174 (5), 91 (100) and 65 (17).

8-Benzyloxy-1-(4'-benzyloxy-α-hydroxy-3'-methoxybenzyl)-1,2,3,4-tetrahydro-7-methoxy-*N*-methylisoquinoline (**15**).

A solution of alcohol **14** (1.56 g, 3.07 mmoles) in 20 ml of acetonitrile and 10 ml of methyl iodide was gently refluxed for 12 hours with periodic additions of methyl iodide until tlc showed that no starting material remained. Solvent was removed under vacuum (T < 40°) and the resulting oil, which could not be crystallized, was used without further purification in the next step. Reduction with sodium borohydride under described conditions [1a] afforded an oil which was purified by silica gel column chromatography. The oily product with the highest R_f was the expected compound, **15**, total yield, 31%; ^{1}H-nmr: 2.21 (s, 3H, -NMe), 2.44-3.30 (m, 4H, 2 × $-CH_2$-), 3.52 and 3.89 (ss, each 3H, 2 × -OMe), 5.04-5.19 (m, 2H, $-OCH_2Ph$), 6.28-7.34 (m, 16H, ArH + -CHα-).

Acidic Treatment of **15**.

A solution of alcohol **15** (0.33 g, 0.57 mmole) in 10 ml of trifluoroacetic acid was magnetically stirred for 24 hours under inert gas at room temperature. Solvent was removed under vacuum with no heating and the residue was partitioned between saturated sodium bicarbonate solution (25 ml) and ethyl acetate (25 ml). The aqueous layer was extracted with ethyl acetate (3 × 25 ml), and the dried (sodium sulfate) extracts were evaporated to dryness. The residue so obtained was subjected to column chromatography.

The main product (lowest R_f value), 0.056 g (30% yield), was identified as dihydrofuran **16a**, mp 172-174° (methanol); ^{1}H-nmr: 2.14 (s, 3H, -NMe), 2.35-3.09 (m, 4H, 2 × $-CH_2$-), 3.81 (dd, $J_{1-\alpha'}$ = 10.5 Hz, J_{1-3} = 1.0 Hz, 1H, H_1), 3.85 and 3.88 (ss, each 3H, 2 × -OMe), 5.37 (d, $J_{1-\alpha}$ = 10.5 Hz, 1H, H_α), 6.68 and 6.77 (ABq, J = 8.2 Hz, 2H, H_6 and H_5), 6.87, 7.05 and 7.11 (ABX, $J_{5'-6'}$ = 8.2 Hz, $J_{2'-6'}$ = 1.9 Hz, 3H, $H_{5'}$, $H_{6'}$ and $H_{2'}$ respectively); ^{13}C-nmr: 26.02 (t), 43.82 (q), 55.56 (t), 55.81 (q), 56.49 (q), 71.72 (d), 94.98 (d), 110.34 (d), 114.28 (d), 114.42 (d), 120.02 (d), 121.62 (d), 124.54 (s), 128.24 (s), 130.38 (s), 142.17 (s), 145.14 (s), 146.54 (s) and 146.79 (s); ms: m/e (%) 327 (M^+, 100), 326 (54), 204 (92), 175 (60), 174 (92) and 154 (92).

Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.72; H, 6.42; N, 4.28. Found: C, 69.25; H, 6.82; N, 4.19.

The product with the highest R_f value (0.04 g, 16% yield) was identified as the 5'-benzyl derivative **16b**, mp 178-180° (methanol); ^{1}H-nmr: 2.09 (s, 3H, -NMe), 2.40-3.10 (m, 4H, 2 × $-CH_2$-), 3.73 and 5.28 (ABq, J = 10.5 Hz, 2H, H_1 and Hα respectively), 3.84 and 3.90 (ss, each 3H, 2 × -OMe at C_7 and $C_{3'}$ respectively), 3.97 and 4.05 (ABq, J = 15.0 Hz, 2H, $-CH_2Ph$), 5.82 (broad s, 1H, -OH), 6.67 and 6.77 (ABq, J = 8.4 Hz, 2H, H_5 and H_6 respectively), 6.89 and 7.02 (ABq, J = 1.8 Hz, 2H, $H_{2'}$ and $H_{6'}$), 7.16-7.25 (m, 5H, ArH); ^{13}C-nmr: 26.21 (t), 35.42 (t), 43.95 (q), 55.67 (t), 56.09 (q), 56.57 (q), 71.74 (d), 95.39 (d), 108.20 (d), 114.24 (d), 120.06 (d), 123.35 (d), 124.66 (s), 125.96 (d), 126.28 (s), 128.31 (2 × d), 128.48 (s), 128.84 (2 × d), 128.96 (s), 129.75 (s), 140.56 (s), 142.27 (s), 144.24 (s) and 146.56 (s); ms: m/e (%) 417 (M^+, 46), 402 (4), 204 (33), 174 (100), 146 (22), 145 (52) and 91 (24).

Anal. Calcd. for $C_{26}H_{27}NO_4$: C, 74.82; H, 6.47; N, 3.35. Found: C, 74.39; H, 6.80; N, 3.78.

Zinc-Trifluoromethanesulphonic Acid Treatment of **8b** and **9b**.

To a solution of **8b** (0.95 g, 2.89 mmoles) in 7.6 ml of trifluoromethanesulphonic acid (30 molar equivalents) and 6.6 ml of trifluoracetic acid (30 molar equivalents) stirred under inert gas at -5° (ice bath), 3.79 g of purified [12] zinc (20 molar equivalents) was added in three portions over 3 hours with efficient stirring. The mixture was poured into cold saturated ammonium chloride solution and neutralized with solid sodium bicarbonate prior to methylene chloride extraction (5 × 100 ml). The dried (sodium sulfate) extracts were evaporated to dryness and the main product was isolated by silicagel column chromatography as a highly hygroscopic solid (0.67 g, 79% yield) that could not be crystallized; ^{1}H-nmr: 2.35 (s, 3H, -NMe), 2.38-3.30 (m, 6H, 3 × $-CH_2$-), 3.60-3.80 (broad, 2H, $-NH_2$), 3.87 (s, 3H, -OMe), 4.14 (dd, J_{AX} = 8.4 Hz, J_{BX} = 3.6 Hz, 1H, H_1), 6.45-7.15 (m, 6H, ArH); ms: m/e (%) 298 (M^+, 2), 297 (6), 194 (32), 193 (84), 192 (100) and 191 (60).

The same procedure applied to **9b** afforded in 96% yield compound **9c** as an unstable solid, mp 86-88° (ethanol); ^{1}H-nmr: 3.88 (s, 3H, -OMe), 4.84 (s, 2H, $-CH_2Ar$), 6.37-7.07 (m, 4H, ArH), 7.31 (m, 3H, ArH), 8.28 (d, J = 5.8 Hz, 1H, H_3); ms: m/e (%) 280 (M^+, 100), 279 (22), 265 (25), 264 (18) and 262 (45).

Synthesis of the *O*-Butyl Derivative (**20**).

A solution of 0.1 g (0.32 mmole) of benzoylisoquinoline **19** in 3 ml of pyridine:water:tetrabutylammonium hydroxide (8:6:1 v/v) was refluxed for 24 hours under inert gas. Solvent was removed and the residue was taken into methylene chloride (30 ml) and washed with water (3 × 10 ml), 10% cupric sulfate (2 × 20 ml) and water again (10 ml). The dried (sodium sulfate) extracts were evaporated to dryness and the final residue was chromatographed on a silica-gel preparative plate. Together with starting **19** (0.05 g), 0.04 g (35% yield) of a product easily identified as **20** was obtained and crystallized from ethanol, mp 119-121°; ir: 1670 cm^{-1}; ^{1}H-nmr: 0.77-1.46 (m, 7H, CH_3-CH_2-CH_2-), 3.23 and 3.93 (ss, each 3H, 2 × -OMe), 3.93 (t, J = 5.5 Hz, 2H, $-CH_2O$-), 6.78-7.56 (m, 6H, ArH), 8.15 (dd, J_{AX} = 7.7 Hz, J_{BX} = 1.9 Hz, 1H, $H_{6'}$), 8.29 (d, J = 5.8 Hz, 1H, H_3); ms: m/e (%) 365 (M^+, 22), 334 (22), 294 (35), 278 (35) and 135 (100).

Anal. Calcd. for $C_{22}H_{23}NO_4$: C, 72.32; H, 6.30; N, 3.83. Found: C, 72.33; H, 6.37; N, 4.31.

1-(2'-Aminobenzyl)-7-methoxyisoquinolin-8-ol (**21**).

A solution of 0.2 g (0.5 mmole) of **5d** in 10 ml of ethanol and 0.1 ml of concentrated hydrochloric acid containing 0.03 g of 10% Pd/C was hydrogenated at room temperature and pressure until the uptake of hydrogen ceased. The catalyst was filtered off and the solvent was evaporated *in vacuo*. The residue was taken into methylene chloride (50 ml) and washed with saturated sodium bicarbonate solution (25 ml). The dried (sodium sulfate) extracts were evaporated to dryness to give a crystalline solid which was recrystallized from ethanol, mp 172-174°, 92% yield; ^{1}H-nmr: 4.00 (s, 3H, -OMe), 4.87 (s, 2H, -CH_2-), 6.61-7.47 (m, 7H, ArH), 8.21 (d, J = 5.6 Hz, 1H, H_3); ms: m/e (%) 280 (M^+, 60), 265 (50), 264 (100) and 249 (26).

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.85; H, 5.71; N, 10.00. Found: C, 72.93; H, 5.83; N, 9.94.

Synthesis [23b] and Thermolysis of 1-(2'-Diazobenzyl Tetrafluoroborate)-7-methoxyisoquinolin-8-ol (**22**).

Fluoroboric acid (0.25 ml of 48%), (0.55 mmole, 1.35 molar equivalent) were added to a suspension of 0.115 g (0.41 mmole) of **21** in 5 ml of 2-propanol stirred in an ice-water bath, complete solution of **21** being achieved. Isoamyl nitrite (0.2 ml) was added dropwise to the resulting solution and stirring at 0-5° was maintained for a further 30 minutes. Addition of ether (15 ml) caused the precipitation of a red solid which was carefully washed with ether (3 × 20 ml). The solid obtained (0.13 g, 84% yield) melted between 70° and 80°, and since it proved to be rather unstable, was used without further purification. A solution of this compound in anhydrous dimethylformamide was added dropwise under inert gas to refluxing dimethylformamide and refluxing continued for 5 hours. Evaporation to dryness afforded a complex mixture of coloured compounds (tlc) which were not separated.

Photochemical Irradiation of **8g**.

A degassed solution of **8g** (0.1 g, 0.237 mmole) in 15 ml of anhydrous acetonitrile in a Pyrex irradiation vessel was subjected to external irradiation for 8 hours. Solvent was removed under vacuum and the residue was purified was purified by preparative silica gel plate chromatography. The main product (0.005 g, 12% yield) was identified [1a] as **23**, mp 155-157° (ethanol).

Photochemical-$S_{RN}1$ Reaction of **8g** [31].

This photochemical experiment was carried out [31] using an external light source in a standard Pyrex reaction flask positioned adjacent to the reaction vessel, a three-necked flask equipped with a dry-ice condenser and a three-way stopcock connected to nitrogen and ammonia lines. The reaction mixture (0.1 g of **8g**, 0.237 mmole and 0.007 g of 80% sodium hydride, 0.24 mmole) was placed under inert gas, and then gaseous ammonia was passed into the system and condensed at the dry-ice condensor until the desired level was attained (15 ml). The reaction flask was isolated and irradiation commenced, the flask being washed at frequent intervals with a stream of ethyl alcohol to minimize the accumulation of frost-ice on the outer surface. After irradiation for 2 hours under reflux, excess aqueous ammonium chloride was added portionwise and the ammonia was allowed to evaporate. The residue was extracted with methylene chloride (3 × 30 ml), dried (sodium sulfate) and evaporated to dryness. Chromatography of the resulting material afforded 0.048 g (60% yield) of 1,2,3,4-tetrahydro-1-(3',4'-dimethoxybenzyl)-7-methoxy-*N*-methylisoquinolin-8-ol (**8m**) [1a].

General Procedure for the Benzyne Intermediate Reactions.

The relevant phenolic compound (0.13 mmole in 1 ml of anhydrous dimethyl sulfoxide) was added dropwise (20 minutes) under inert gas and at 40° to dimsyl sodium [32] freshly prepared from 1.42 mmoles of 80% sodium hydride and 0.5 ml of anhydrous dimethyl sulfoxide. The resulting intense red solution was stirred for a further 3 hours before being poured into ice-water, basified with ammonium chloride and extracted with methylene chloride (4 × 25 ml). The organic extracts were washed with water (3 × 25 ml), dried (sodium sulfate) and evaporated to dryness. The residue was purified by silica gel column chromatography.

Reaction of **9g** with Dimsyl Sodium [33].

From 0.5 g (1.23 mmoles) of **9g**, a mixture of 0.21 g (53% yield) of dibenzo[*b*,*g*]indolizine (**24**) and 0.1 g (25% yield) of dehydrocularine **25** was obtained. Compound **24** had mp 201-203° (methanol); ^{1}H-nmr: 3.98 (s, 6H, 2 × -OMe), 4.00 (s, 3H, -OMe), 6.97 and 7.08 (ABq, J = 9.0 Hz, 2H, H_3 and H_4), 7.21 (s, 1H, H_{11}), 7.25 (s, 1H, H_8), 7.56 (s, 1H, H_{12}), 6.54 and 7.80 (ABq, J = 7.4 Hz, 2H, H_5 and H_6); ms: m/e (%) 323 (M^+, 100), 308 (92) and 264 (27).

Anal. Calcd. for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.21; H, 5.32; N, 4.31.

Compound **25** had mp 131-133° (ether-petroleum ether) (lit [34] 133°); ^{1}H-nmr: 3.84, 3.85 and 4.09 (ss, each 3H, 3 × -OMe), 4.60 (s, 2H, -CH_2-), 6.77 and 6.94 (ABq, J = 9.0 Hz, 2H, H_6 and H_5), 7.50 (s, 2H, $H_{2'}$ and $H_{5'}$), 7.39 and 8.15 (ABq, J = 5.8 Hz, 2H, H_4 and H_3); ms: m/e (%) 323 (M^+, 100), 308 (28), 293 (10), 280 (11) and 264 (14).

Reaction of **9h** with Dimsyl Sodium [33].

From 0.5 g (1.288 mmoles) of **9h**, a mixture of 0.26 g (65% yield) of dibenzo[*b*,*g*]indolizine **26** and 0.08 g (20% yield) of dehydrocularine **27** was obtained.

Compound **26** had mp 250-252° (methanol); ^{1}H-nmr: 4.00 (s, 3H, -OMe), 6.00 (s, 2H, -OCH_2O-), 6.43 (broad s, 1H, -OH), 6.56 and 7.75 (ABq, J = 7.5 Hz, 2H, H_5 and H_6), 6.94 and 7.11 (ABq, J = 9.0 Hz, 2H, H_3 and H_4), 7.19 (s, 2H, H_8 and H_{11}), 7.54 (s, 1H, H_{12}); ms: m/e (%) 307 (M^+, 100), 292 (30), 289 (29), 264 (55) and 206 (18).

Anal. Calcd. for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.26; N, 4.56. Found: C, 69.85; H, 4.16; N, 4.23.

Compound **27** had mp 154-156° (methylene chloride-petroleum ether); ^{1}H-nmr: 4.07 (s, 3H, -OMe), 4.56 (s, 2H, -CH_2-), 5.89 (s, 2H, -OCH_2O-), 6.77 and 6.94 (ABq, J = 9.0 Hz, 2H, H_6 and H_5), 7.49 (s, 2H, $H_{2'}$ and $H_{5'}$), 7.38 and 8.16 (ABq, J = 5.8 Hz, 2H, H_4 and H_3); ms: m/e (%), 307 (M^+, 100), 292 (20), 264 (17) and 262 (24).

Anal. Calcd. for $C_{18}H_{13}NO_4$: 307.0845. Found: (hrms): 307.0849.

Reaction of **9i** with Dimsyl Sodium.

From 0.1 g (0.234 mmole) of **9i** and after 2 hours reaction, we obtained 0.035 g (40% yield) of an unstable solid, mp 170-172° (ethanol), identified as **19j**; ^{1}H-nmr: 3.88 (s, 3H, -OMe), 3.93 (s, 6H, 2 × -OMe), 6.61-7.71 (m, 6H, ArH), 8.40 (d, J = 5.7 Hz, 1H, H_3); ^{1}H-nmr (deuteriochloroform + deuteriotrifluoroacetic acid): 3.87 (s, 6H, 2 × -OMe), 4.02 (s, 3H, -OMe), 6.72, 6.84 and 7.56 (ABX, J_{AX} = 8.9 Hz, J_{BX} = 1.2 Hz, 3H, $H_{5'}$, $H_{6'}$ and $H_{2'}$ respectively), 7.73 and 7.89 (ABq, J = 9.0 Hz, 2H, H_6 and H_5), 8.13 and 8.30 (ABq, J = 6.6 Hz, 2H, H_4 and H_3); ms: m/e (%) 339 (M^+, 100), 324 (14), 165 (90), 158 (24), 138 (80) and 130 (46).

Methylation of **19j** with ethereal diazomethane afforded, in quantitative yield, 1-(3',4'-dimethoxybenzoyl)-7,8-dimethoxyisoquinoline **19k**, mp 112-114° (ether); ir: 1675 cm^{-1}; ^{1}H-nmr: 3.68, 3.89, 3.93 and 3.95 (ss, each 3H, 4 × -OMe), 6.76 (d, J = 8.4 Hz, 1H, $H_{5'}$), 7.09 (dd, J_{AX} = 8.4 Hz, J_{BX} = 1.9 Hz, 1H, $H_{6'}$), 7.33-7.72 (m, 4H, ArH), 8.44 (d, J = 5.8 Hz, 1H, H_3); ms: m/e (%) 353 (M^+, 64), 338 (12), 324 (55), 185 (100), 166 (85) and 163 (85).

Anal. Calcd. for $C_{20}H_{29}NO_5$: C, 67.99; H, 5.38; N, 3.97. Found: C, 67.70; H, 5.54; N, 3.70.

Synthesis of Oxocularine (**28**).

A solution of 0.1 g of Fremy's salt in 3 ml of aqueous 4% sodium carbanate was added to a magnetically stirred solution of base **25** (0.02 g, 0.062 mmole) in 1 ml of methanol at room temperature. Stirring was maintained for 5 hours until the starting material had all disappeared. Water (30 ml) was added and the aqueous solution was extracted with methylene chloride (3 × 15 ml). The dried (sodium sulfate) extracts were evaporated to dryness to give a yellow solid which crystallized from ethanol, mp 197-199° (lit [33] 198-199°), 85% yield; ir: 1670 cm^{-1}; uv (ethanol): λ max 256, 294 sh and 404; uv (acidic ethanol): λ max 266, 406 and 480 nm; ^{1}H-nmr: 3.89, 3.98 and 4.13 (ss, each 3H, 3 × -OMe), 6.94 (s, 1H, $H_{5'}$), 7.24 (s, 1H, $H_{2'}$), 7.58 and 7.75 (ABq, J = 9.0 Hz, 2H, H_6 and H_5), 7.74 and 8.68 (ABq, J = 5.8 Hz, 2H, H_4 and H_3); ms: m/e (%) 337 (M^+, 100), 322 (8), 309 (12) and 294 (83).

Synthesis of Cularimine (**30**).

A solution of **25** (0.045 g, 0.14 mmole) in methanol (15 ml) containing 3 drops of concentrated hydrochloric acid was hydrogenated in the presence of Adams' catalyst (0.032 g). Filtration and removal of the solvent *in vacuo* gave a brown oil which was dissolved in water (20 ml), basified with 10% sodium carbonate solution and extracted with methylene chloride (3 × 20 ml). The dried (sodium sulfate) extracts were chromatographed on a preparative silica gel plate, giving 0.02 g (45% yield) of an oil which crystallized on mixing with ether, mp 100-102° (lit [34] 106-107°).

Synthesis of Cularine (**32**).

A solution of **25** (0.05 g, 0.154 mmole) in 1 ml of methyl iodide was kept at room temperature under inert gas for 24 hours. The solvent was removed and the residue dissolved in methanol (15 ml) containing several drops of water. Addition of sodium borohydride (0.1 g) in small portions with stirring caused the total disappearance of the yellow colour. After stirring for a further 2 hours, the solvent was removed *in vacuo* and the residue was taken into water (20 ml) and extracted with methylene chloride (3 × 15 ml). The dried (sodium sulfate) extracts gave a solid which crystallized from ethanol, mp 130-132° (lit [38] 125-126° from ether).

Synthesis of Oxocompostelline (**29**).

Application of the same procedure as above to **27** gave a yellow solid which crystallized from methanol, mp 256-258° (lit [33] 259°); and was identified as oxocompostelline **29**; ir: 1670 cm^{-1}; ^{1}H-nmr: 4.08 (s, 3H, -OMe), 5.99 (s, 2H, -OCH_2O-), 6.90 (s, 1H, H_5), 7.11 (s, 1H, H_2), 7.53 and 7.71 (ABq, J = 9.0 Hz, 2H, H_6 and H_5), 7.69 and 8.63 (ABq, J = 5.7 Hz, 2H, H_4 and H_3); ms: m/e (%) 321 (M^+, 72), 306 (5), 278 (100) and 293 (5).

Synthesis of *O*-Methyl-*N*-norcularicine (**31**).

A solution of base **27** (0.035 g, 0.014 mmole) in 12 ml of ethanol containing 0.025 g of Adams' catalyst and two drops of glacial acetic acid was hydrogenated at room temperature and pressure for two hours. The catalyst was filtered off and the solution was hydrogenated again with 0.025 g of fresh platinum oxide for 15 hours until tlc showed the complete disappearance of the starting material. Work-up as above afforded a crystalline residue (0.015 g, 43% yield) of **31**, mp 150-152° (ethanol). Due to the rapid oxidation of **31** to **29**, no elemental analysis could be obtained; ^{1}H-nmr: 2.61-3.18 (m, 6H, 3 × -CH_2-), 3.85 (s, 3H, -OMe), 4.64 (broad t, 1H, H_1), 5.87 and 5.89 (m, 2H, -OCH_2O-), 6.52-6.93 (m, 4H, ArH); ms: m/e (%) 311 (M^+, 100), 294 (33), 281 (22), 161 (20) and 160 (15).

Synthesis of *O*-Methylcularicine (**33**).

Reaction conditions and yields were similar to those of the conversion of **25** into cularine **32**. The final product was identified as *O*-methylcularicine **33** [35] by direct comparison with the same product as obtained in the Ullmann reaction [1b].

Reaction of **8g** with Dimsyl Sodium.

From 0.2 g (0.474 mmole) of **8g** the unstable stirene **35** (0.061 g, 38% yield) was obtained and crystallized from ether-petroleum ether, mp 148-150°; ^{1}H-nmr: 2.70 (s, 3H, -NMe), 2.97-3.76 (m, 2H, -CH_2-), 3.84 (s, 3H, -OMe), 3.89 (s, 6H, 2 × -OMe), 4.52 (dd, J_{AX} = 12.3 Hz, J_{BX} = 8.5 Hz, 1H, -CH-N), 5.21 (dd, J_{ax} = 10.9 Hz, J_{ab} = 1.3 Hz, 1H, H_a-C=CHR), 5.46 (dd, J_{bx} = 17.1 Hz, J_{ab} = 1.3 Hz, 1H, H_b-C=CH-R), 6.43 (s, 1H, ArH), 6.68 (m, 4H, ArH); ^{13}C-nmr: 35.75 (q), 37.22 (t), 55.89 (q), 56.30 (q), 56.76 (q), 70.44 (d), 97.51 (d), 109.52 (d), 111.13 (d), 115.90 (d), 117.36 (t), 120.81 (s), 121.83 (s), 130.72 (s), 133.94 (d), 144.52 (s), 144.95 (s), 146.48 (s), 148.40 (s) and 149.31 (s), ms: m/e (%) 341 (M^+, 76), 339 (35), 326 (100) and 324 (22).

Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.38; H, 6.74; N, 4.10. Found: C, 69.87; H, 6.65; N, 3.96.

Acidic Debenzylation of Methiodide **6g**. Synthesis of **34**.

Classical debenzylation of 0.15 g (0.25 mmole) of **6g** afforded quantitatively a deep violet solid which crystallized from benzene-petroleum ether, mp 132-134° dec and was identified as **34**; ir: 1635, 3200-3700 cm^{-1}; uv (ethanol): λ max 236 sh, 268, 360 and 526; uv (acidified ethanol): λ max 236 sh, 260, 290 sh, 320 sh and 430 nm; ^{1}H-nmr: 3.52, 3.82 and 3.84 (ss, each 3H, 3 × -OMe), 3.64 (s, 3H, -NMe), 5.52 (s, 2H, -CH_2-), 6.34 and 7.12 (ABq, J = 7.7 Hz, 2H, H_4 and H_3), 6.46 (s, 1H, ArH), 6.81-7.10 (m, 3H, ArH); ^{1}H-nmr (deuteriochloroform + deuteriotrifluoroacetic acid): 3.47, 3.86 and 4.11 (ss, each 3H, 3 × -OMe), 4.24 (s, 3H, -N^+-Me), 5.29 (broad s, 2H, -CH_2-), 6.08 (s, 1H, ArH), 7.16-8.03 (m, 5H, ArH); ms: m/e (%) 433 and 431 (M^+ + 14, 9), 419 (8), 418 (8), 417 (18), 338 (47), 337 (100), 324 (70) and 322 (80).

Anal. Calcd. for $C_{20}H_{20}BrNO_4 \cdot \times H_2O$: C, 55.04; H, 5.04; N, 3.21. Found: C, 55.26; H, 4.52; N, 3.31.

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REFERENCES AND NOTES

[1a] See Part I of this series; [b] See Part II of this series. A preliminary communication of this work has already been published, see ref [33].

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[3] Present address: Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Málaga, Spain.

[4a] L. Castedo, "The Chemistry and Pharmacology of Cularine Alkaloids" in "The Chemistry and Pharmacology of Isoquinoline Alkaloids", Phillipson, *et al.*, ed, Springer-Verlag, Berlin Heidelberg, 1985, pp 102-125; [b] B. Gözler and M. Shamma, *J. Nat. Prod.*, **47**, 753 (1984).

[5a] J. P. Marino and A. Schwartz, *Tetrahedron Letters*, 3253 (1979); [b] H. J. Reich and S. K. Shah, *J. Am. Chem. Soc.*, **97**, 3250 (1975); [c] Tertiary amines are known to be converted to the corresponding *N*-oxides with diphenyl selenoxide, M. Poje and K. Balenovic, *Bull. Sci., Cons. Acad. Sci. Arts RSF Yougosl., Sect. A*, **20**, 1 (1975); *Chem. Abstr.*, **83**, 43558u (1975).

[6a] L. Castedo, J. M. Saá, R. Suau and M. C. Villaverde, *Heterocycles*, **9**, 659 (1978); [b] L. Castedo, A. Rodríguez de Lera, J. M. Saá, R. Suau and M. C. Villaverde, *Heterocycles*, **14**, 1135 (1980).

[7] F. D. Popp, *Adv. Heterocyclic Chem.*, **24**, 187 (1979).

[8a] Trifluoroacetic acid is known to produce debenzylation in 10 hours; E. Kotani and S. Tobinaga, *Tetrahedron Letters*, 4759, (1973); [b] Y. Kiso, H. Isawa, K. Kitagawa and T. Akita, *Chem. Pharm. Bull.*, **26**, 2562 (1978); [c] B. W. Erickson and R. B. Merrifield, *J. Am. Chem. Soc.*, **95**, 3750 (1973).

[9] S. Chattopadhyay and M. Shamma, *Heterocycles*, **19**, 697 (1982).

[10] M. H. Abu Zarga, G. A. Miana and M. Shamma, *Tetrahedron Letters*, **22**, 541 (1981).

[11] T. Ohta, R. Machida, K. Takeda, Y. Endo, K. Shudo and T. Okamoto, *J. Am. Chem Soc.*, **102**, 6385 (1980) and references cited therein. We are indebted to Professor Koichi Shudo for providing us with experimental details of this reaction.

[12] R. L. Shriner and F. W. Newman, *Org. Synth. Coll* Vol **3**, 73 (1955).

[13] F. Pietra, *Quart. Rev.*, **23**, 504 (1969).

[14] E. J. Corey and G. Schmidt, *Tetrahedron Letters*, 399 (1979).

[15] N. Kornblum, L. Cheng, R. C. Kerber, M. M. Kestner, B. N. Newton, H. W. Pinnick, R. G. Smith and P. A. Wade, *J. Org. Chem.*, **41**, 1560 (1976).

[16] A. J. Quillinan and F. Scheinmann, *J. Chem. Soc., Perkin Trans. 1*, 1329 (1973).

[17] K. C. Agrawal, P. D. Mooney and A. C. Sartorelli, *J. Med. Chem.*, **19**, 970 (1976).

[18] R. O. Hutchins and F. J. Dux, *J. Org. Chem.*, **38**, 1961 (1973).

[19] M. Shamma, N. C. Deno and J. F. Remar, *Tetrahedron Letters*, 1375 (1966).

[20] M. P. Cooke, Jr., and R. M. Parlman, *J. Org. Chem.*, **40**, 531

(1975).

[21] A. C. Cope, E. Ciganek, C. J. Fleckenstein and M. A. P. Meisinger, *J. Am. Chem. Soc.*, **82**, 4651 (1960).

[22] K. Williams and B. Halpern, *Aust. J. Chem.*, **28**, 2065 (1975); see also C. Paradisi, U. Quintily and G. Scorrano, *J. Org. Chem.*, **48**, 3022 (1983).

[23a] C. G. Swain, J. E. Sheats and K. G. Harbison, *J. Am. Chem. Soc.*, **97**, 783 (1975); [b] S. H. Pines, R. M. Purick, R. A. Reamer and G. Gal, *J. Org. Chem.*, **43**, 1337 (1978).

[24] H. Zollinger, *Angew. Chem., Int. Ed. Engl.*, **17**, 141 (1978).

[25] C. Parkanyi, *Pure Appl. Chem.*, **55**, 331 (1983).

[26] M. A. Fox, *Chem. Rev.*, 257 (1979).

[27a] J. K. Kim and J. F. Bunnett, *J. Am. Chem. Soc.*, **92**, 7463 (1970); [b] J. F. Bunnett, *Acc. Chem. Res.*, **11**, 413 (1978).

[28] S. Hoz and J. F. Bunnett, *J. Am. Chem. Soc.*, **99**, 4690 (1977).

[29] R. A. Rossi and A. B. Pierini, *J. Org. Chem.*, **45**, 2914 (1980).

[30] S. Rajan and P. Sridaran, *Tetrahedron Letters*, 2177 (1977).

[31] M. F. Semmelhack and T. Bargar, *J. Am. Chem. Soc.*, **102**, 7765 (1980).

[32] E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1345 (1965).

[33] J. M. Boente, L. Castedo, A. Rodríguez de Lera, J. M. Saá, R. Suau and M. C. Vidal, *Tetrahedron Letters*, **24**, 2295 (1983).

[34] T. Kametani and K. Fukumoto, *J. Chem. Soc.*, 4289 (1963).

[35] G. Blaschke and G. Scriba, *Z. Naturforsch.*, **38c**, 670 (1983); *ibid., Phytochemistry*, **24**, 585 (1985).

[36] R. Benn and H. Günther, *Angew. Chem., Int. Ed. Engl.*, **22**, 350 (1983).

[37] M. P. Cava and I. Noguchi, *J. Org. Chem.*, **38**, 60 (1973).

[38] T. Kametani, K. Fukumoto and M. Fujihara, *J. Chem. Soc., Chem. Commun.*, 352 (1971); *ibid., Bioorg. Chem.*, **1**, 40 (1971).