# Synthetic Approaches to Cularines. II [1]. Ullmann Condensation.



Angel Rodríguez de Lera, Rafael Suau [2] and Luis Castedo*

Departamento de Química Orgánica de la Facultad de Química y
Sección de Alcaloides del CSIC, Santiago de Compostela, Spain

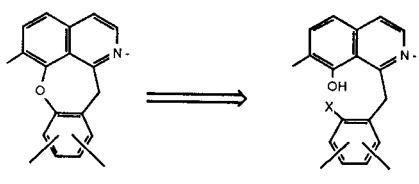
Received October 18, 1985

The first total syntheses of *O*-methylcularicine **9b** and sarcocapnine **9c** are described together with a new synthesis of cularine **9a** using the Ullmann condensation reaction of the appropriate 2'-bromo-8-hydroxytetrahydrobenzylisoquinoline formed by phase-transfer alkylation of Reissert compound **2**. When this strategy was combined with the lead tetraacetate treatment of the tetrahydrobenzylisoquinoline it yielded 4-hydroxycularines, from which highly oxidized members of the family can be obtained. This is exemplified by the first synthesis of 4-hydroxysarcocapnine **19** and its transformation to the 3,4-dioxoisocularine yagonine **20**, rearrangement of which afforded the aristoisocularine aristoyagonine **21**.

*J. Heterocyclic Chem.*, **24**, 313 (1987).

The recent enlargement of the cularine group of isoquinoline alkaloids [3] with new members exhibiting a variety of substitution patterns [4] and oxidation states [4,5] has created a need for new synthetic approaches. In our previous report [1] we described a simple and regioselective entry to cularines which is based on the phenolic oxidative coupling of **1**, which is probably a biogenetic precursor. In the present article we report our results in this field using the more "classical" Ullmann condensation [6].

Figure I




CULARINES 1

(oxidation state not shown)

Although the mechanism of Ullmann condensation is unclear [6], recent research [7] points to the initial formation of an ArOCu intermediate which couples with the organic halide Ar'X to give the product ArOAr'. However, the reaction course for the ArOCu intermediate is not established, both a radical reaction [8a] and a nucleophilic aromatic substitution [8b] having been proposed for the reaction mechanism, although other experiments [8c] do not agree with either hypothesis.

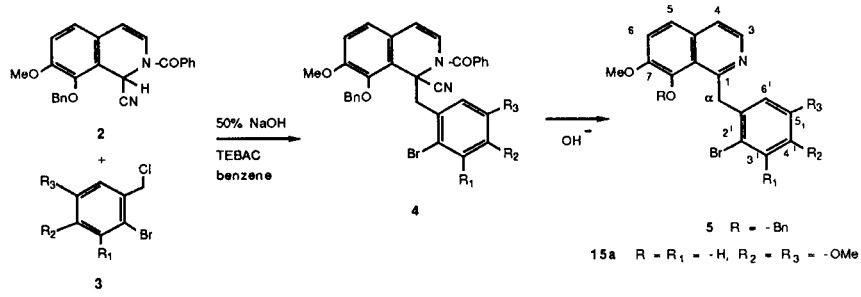
The Ullmann condensation has repeatedly been used [9] in the field of cularine synthesis, mainly to form the diaryl ether bridge in the final step. Although this generally occurs in good yield, it was not taken full advantage of by early syntheses, in which the tetrahydrobenzylisoquinoline intermediate was synthesized by the Bischler-Napieralski [10] or the Pictet-Spengler [11] methods, which afford low yields and require protection-deprotection steps [10-12] in order to orient the isoquinoline nucleus cyclization step in the correct direction. These problems can be circumvented by using the well-established Reissert approach [13] to the benzylisoquinoline compounds, which consists in the condensation of a Reissert compound (in this case **2**) with bromobenzyl chlorides **3** under phase-transfer conditions. Further manipulation of the isoquinoline nucleus according to Figure II [1] afforded 8-hydroxytetrahydrobenzylisoquinolines **8**, all the steps giving good to excellent yields which compare well with those achieved by the recently described [14] electrochemical reduction of immonium salts to construct the benzylisoquinoline linkage.

By heating a mixture of **8a**, anhydrous potassium carbonate and cupric oxide in pyridine we obtained cularine **9a** in 91% yield. Analogous treatment of **8b** and **8c** produced an 83% yield of *O*-methylcularicine **9b** [15] and an 86% yield of the isocularine sarcocapnine **9c** [4a], the first total synthesis in each case.

Attempts to extend the above strategy to the oxocularine compounds met with unforeseen difficulties. Oxidation of benzylisoquinoline **5a** with selenium dioxide failed, and we resorted to the direct introduction of the oxygen function in the benzyl position [16] by means of the alkylation of the Reissert compound with 2-bromoveratraldehyde **10** [17]. The alcohol **12** derived from the benzoate **11** was oxidized to **13** by using pyridinium dichromate in methylene chloride [18], and deprotection of **13** gave the sensitive phenol **14**, which was subjected to Ullmann condensation without purification. However, we were unable to detect any oxocularine in the resulting complex mixture, and the same disapppointing result was obtained with the phenolic benzylisoquinoline **15a** (see Figure II).

The synthesis of other oxidized members of the cularine group was achieved by applying the Ullmann reaction to an oxygenated tetrahydrobenzylisoquinoline precursor, such as **17**. This was obtained by lead tetraacetate oxida-

Figure II




3-8 a $R_1$ = -H, $R_2$ = $R_3$ = -OMe
b $R_1$ = -H, $R_2$ + $R_3$ = $-OCH_2O-$
c $R_1$ = $R_2$ = -OMe, $R_3$ = -H

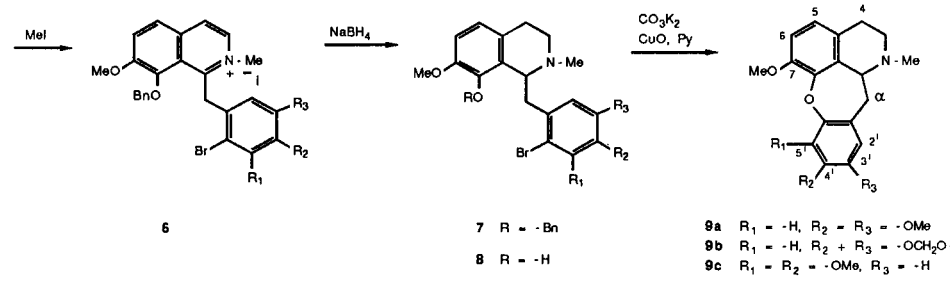



Figure III

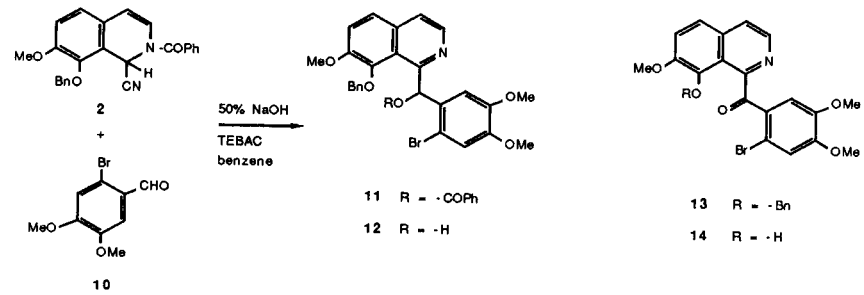
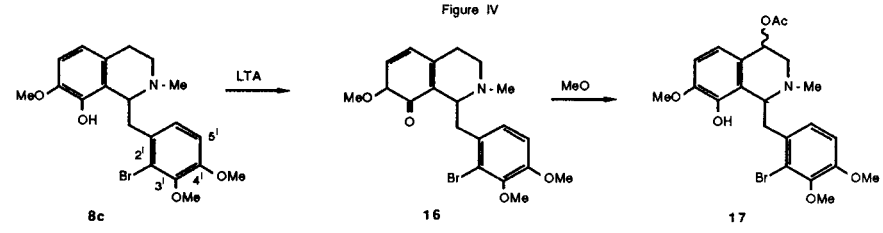



Figure IV



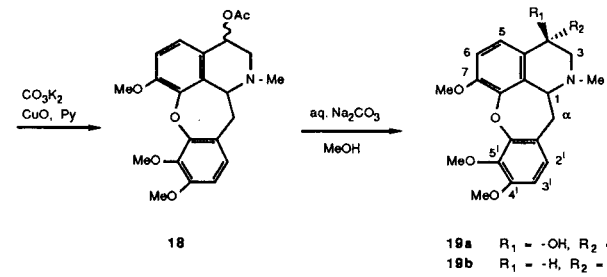
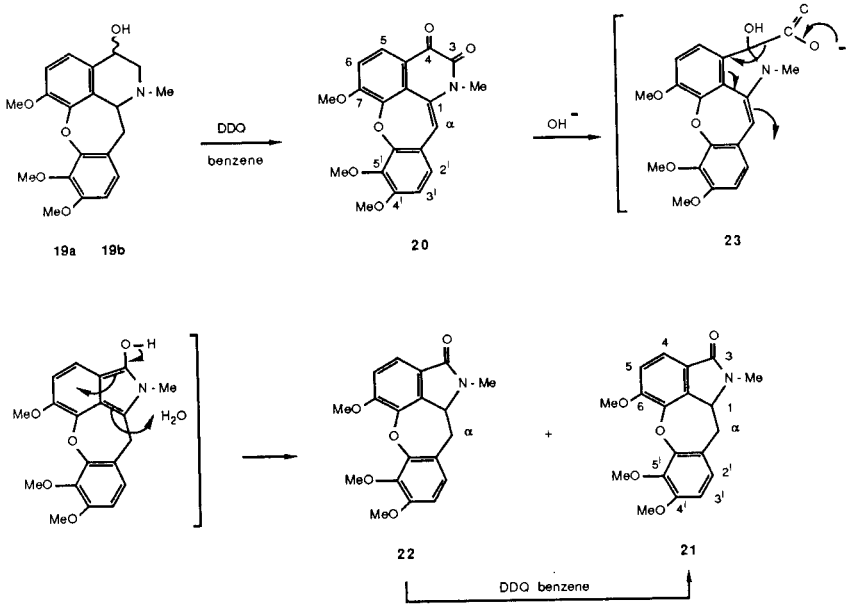



Figure V




tion of **8c** to give *o*-quinol acetate **16**, which after two successive [3,3]-sigmatropic rearrangements [19] afforded a 1:9 mixture of epimeric 4-acetoxyl derivatives (83% yield).

After Ullmann cyclization followed by basic hydrolysis, a 92% yield of a similarly inseparable mixture of epimeric 4-hydroxysarcocapnine **19a,b** was obtained. We have shown [5a] by nmr experiments that the main epimer **19b** has *anti*-stereochemistry between H-1 and H-4 and that natural 4-hydroxysarcocapnine [5a] isolated from *Sarcocapnos enneaphylla* (L.) D. C. is the *syn* epimer **19a**.

Oxidation of **19** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (as reported for the preparation of oxoaporphines) [20] afforded a 40% yield of yagonine **20** [5b], the first known member of the 3,4-dioxoisocularine subgroup. Further benzylic acid-type rearrangement of **20** with barium hydroxide or sodium hydroxide in methanol (also observed in the dioxoaporphine alkaloids) [20] afforded a mixture of the first member of the aristoisocularine subgroup aristoyagonine **21** [5b] in 7% yield and, in 56% yield, the colorless 1,$\alpha$-dihydro derivative **22**, which was reoxidized to aristoyagonine in almost quantitative yield with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. The mechanism of the decarbonylation reaction must therefore be different from that of the dioxoaporphines, in which only the oxidized product is isolated. Furthermore, we have not seen replacement of any methoxyl group when the rearrangement was carried out with sodium hydroxide in ethanol, as occurs at C-8 in dioxoaporphines [20]. In the present case, the mechanism seems likely to involve the formation of the intermediate **23** (which has been isolated in the alkaline treatment of analogous systems) [21] and its decarboxylation by two successive protonations of the dibenzoxepine nucleus. In the dioxoaporphine skeleton this type of mechanism would bring about the loss of the aromatic character of its phenanthrene unit.

## EXPERIMENTAL

### Materials and Techniques.

Please refer to the Materials and Techniques portion of the previous paper.

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 [22].

Pyridine was dried by refluxing with solid potassium hydroxide for 8 hours followed by distillation.

### General Procedures for the Conversion of **3** to **8**.

Benzyl chlorides **3** were prepared as usual from the corresponding commercial aldehydes by bromination [17], sodium borohydride reduction [23] and treatment with thionyl chloride [23].

Compounds **4-8** were synthesized by the procedure described in the previous article [1] for the condensation of Reissert compounds with benzyl chlorides and further elaboration of the tetrahydrobenzylisoquinoline nucleus. Reaction conditions, yields, recrystallization solvents and spectroscopic data are listed below.

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

From 1.1 mole-equivalents of **3a** per mole of the Reissert compound **2** and with 8 hours of stirring, compound **4a** was obtained in 72% yield, mp 164-166° (ethanol); $^1$H-nmr: 3.58 (s, 3H, -OMe), 3.67 (d, J = 14.0 Hz, -CH$_a$Ar), 3.73 and 3.89 (ss, each 3H, 2 × -OMe), 4.51 (d, J = 14.0 Hz, -CH$_b$Ar), 5.08 (d, J = 7.9 Hz, 1H, H$_4$), 5.54 (s, 2H, -OCH$_2$Ar), 6.05-7.72 (m, 15H, ArH); ms: m/e (%) 625 (M$^+$, 0.5), 519 (6), 414 (23), 395 (26), 323 (38), 105 (73), 91 (100).

*Anal.* Calcd. for $C_{34}H_{29}BrN_2O_5$: C, 65.28; H, 4.64; N, 4.48. Found: C, 64.89; H, 4.57; N, 4.30.

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

From 1.3 mole-equivalents of **3b** per mole of the Reissert compound **2** and with 2.5 hours of stirring, compound **4b** was obtained in 98% yield, mp 196-198° (ethanol); $^1$H-nmr: 3.67 (d, J = 14.0 Hz, 1H, -CH$_a$Ar), 3.90 (s, 3H, -OMe), 4.41 (d, J = 14.0 Hz, 1H, -CH$_b$Ar), 5.16 (d, J = 7.9 Hz, 1H, H$_4$), 5.79 (s, 2H, -OCH$_2$O-), 6.10-7.97 (m, 15H, ArH); ms: m/e (%) 503 (5); 412 (19), 399 (27), 398 (100), 308 (42), 307 (89), 264 (41), 105 (63), 91 (63).

*Anal.* Calcd. for $C_{33}H_{25}BrN_2O_5$: C, 65.02; H, 4.10; N, 4.59. Found: C, 64.82; H, 4.01; N, 4.45.

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

From 1.1 mole-equivalents of **3c** per mole of Reissert compound **2** and with 24 hours of stirring compound **4c** was obtained in 87% yield, mp 181-183° (methanol); $^1$H-nmr: 3.67, 3.72 and 3.91 (ss, each 3H, 3 × -OMe), 3.75 (d, J = 14.0 Hz, 1H, -CH$_a$Ar), 4.48 (d, J = 14.0 Hz, 1H, -CH$_b$Ar), 5.08 (d, J = 7.9 Hz, 1H, H$_4$), 5.46 (d, J = 10.5 Hz, -OCH$_A$Ph), 5.57 (d, J = 10.5 Hz, -OCH$_B$Ph), 6.16 (d, J = 7.9 Hz, 1H, H$_3$), 6.39 and 6.40 (ABq, J = 8.6 Hz, 2H, H$_5$ and H$_6$), 6.55 and 6.90 (ABq, J = 8.3 Hz, 2H, H$_{5'}$ and H$_{6'}$); ms: m/e (%) 414 (16), 404 (4), 402 (4), 323 (10), 308 (9), 131 (42), 105 (100), 91 (36), 77 (44).

*Anal.* Calcd. for $C_{34}H_{29}BrN_2O_5$: C, 65.28; H, 4.64; N, 4.48. Found: C, 65.59; H, 4.62; N, 4.63.

8-Benzyloxy-1-(2'-bromo-4',5'-dimethoxybenzyl)-7-methoxyisoquinoline (**5a**).

Compound **5a** was obtained in quantitative yield, mp 150-152° (ethanol); $^1$H-nmr: 3.59, 3.83 and 3.97 (ss, each 3H, 3 × -OMe), 4.89 and 5.05 (ss, each 2H, 2 × -CH$_2$Ar), 6.35 (s, 1H, H$_3$), 6.99 (s, 1H, H$_6$), 7.35-7.57 (m, 8H, ArH), 8.30 (d, J = 5.6 Hz, H$_3$); ms: m/e (%) 494 (M$^+$, 0.5), 415 (27), 414 (80), 325 (30), 324 (85), 308 (42), 165 (14) and 91 (100).

*Anal.* Calcd. for $C_{26}H_{24}BrNO_4$: C, 63.15; H, 4.85; N, 2.83. Found: C, 63.46; H, 4.83; N, 2.69.

8-Benzyloxy-1-(2'-bromo-4',5'-methylenedioxybenyzl)-7-methoxyisoquinoline (**5b**).

Compound **5b** was obtained in 95% yield, mp 101-103° (methanol); $^1$H-nmr: 3.95 (s, 3H, -OMe), 4.84 and 5.04 (ss, each 2H, 2 × -CH$_2$Ar), 5.86 (s, 2H, -OCH$_2$O-), 6.22 (s, 1H, H$_3$), 6.97 (s, 1H, H$_6$), 7.34-7.57 (m, 8H, ArH), 8.31 (d, J = 5.5 Hz, 1H, H$_3$); ms: m/e (%) 399 (23), 398 (100), 308 (31), 307 (67), 264 (30) and 91 (58).

*Anal.* Calcd. for $C_{25}H_{20}BrNO_4$): C, 62.76; H, 4.18; N, 2.92. Found: C, 62.49; H, 4.27; N, 2.54.

8-Benzyloxy-1-(2'-bromo-3',4'-dimethoxybenzyl)-7-methoxyisoquinoline (**5c**).

Compound **5c** was obtained in quantitative yield, mp 126-128° (methanol); $^1$H-nmr: 3.80, 3.81 and 3.98 (ss, each 3H, 3 × -OMe), 4.91 and 5.00 (ss, each 2H, 2 × -CH$_2$Ar), 6.40 and 6.68 (ABq, J = 8.5 Hz, H$_{5'}$ and H$_{6'}$), 7.26-7.66 (m, 8H, ArH), 8.33 (d, J = 5.6 Hz, H$_3$); ms: m/e (%) 495 and 493 (M$^+$, 1.3), 4.14 (28), 404 (11), 402 (11), 323 (24), 308 (25) and 91 (100).

*Anal.* Calcd. for $C_{26}H_{24}BrNO_4$: C, 63.15; H, 4.85; N, 2.83. Found: C, 63.20; H, 4.81; N, 2.43.

8-Benzyloxy-1-(2'-bromo-4',5'-dimethoxybenzyl)-7-methoxy-*N*-methylisoquinolinium Iodide (**6a**).

Treatment of **5a** in acetone with methyl iodide for 48 hours afforded in quantitative yield compound **6a** as a syrup which could not be crystallized; $^1$H-nmr: 3.55, 3.84 and 4.09 (ss, each 3H, 3 × -OMe), 4.44 (s, 3H, -N$^+$-Me), 5.12 and 5.21 (ss, each 2H, 2 × -CH$_2$Ar), 6.00 (s, 1H, H$_3$), 6.98 (s, 1H, H$_6$), 7.00-8.10 (m, 7H, ArH), 8.37 and 8.98 (ABq, J = 6.8 Hz, 2H, H$_4$ and H$_3$); ms: m/e (%) 428 (9), 414 (6), 338 (33), 324 (100), 142 (92), 127 (75), 92 (22), 91 (35).

8-Benzyloxy-1-(2'-bromo-4',5'-methylenedioxybenzyl)-7-methoxy-*N*-methylisoquinolinium Iodide (**6b**).

Treatment of **5b** with methyl iodide for 24 hours afforded in 97% yield compound **6b**, mp 182-184° (ethanol); $^1$H-nmr: 4.10 (s, 3H, -OMe), 4.42 (s, 3H, -N$^+$-Me), 5.16 (s, 4H, 2 × -CH$_2$Ar), 5.85 (s, 1H, H$_3$), 5.92 (s, 2H, -OCH$_2$O-), 6.96-8.37 (m, 9H, ArH), 9.03 (d, J = 6.7 Hz, 1H, H$_3$); ms: m/e (%) 398 (93), 397 (100), 383 (29), 382 (37), 308 (64), 215 (39), 213 (39), 91 (42).

*Anal.* Calcd. for $C_{26}H_{23}BrINO_4$: C, 50.32; H, 3.71; N, 2.25. Found: C, 50.60; H, 3.80; N, 2.51.

8-Benzyloxy-1-(2'-bromo-3',4'-dimethoxybenzyl)-7-methoxy-*N*-methylisoquinolinium Iodide (**6c**).

Treatment of **5c** with methyl iodide for 48 hours afforded in 88% yield compound **6c**, mp 170-172° (methanol); $^1$H-nmr: 3.82, 3.83 and 4.09 (ss, each 3H, 3 × -OMe), 4.43 (s, 3H, -N$^+$-Me), 4.99 and 5.16 (ss, each 2H, 2 × -CH$_2$Ar), 6.23 and 6.73 (ABq, J = 8.5 Hz, 2H, H$_{5'}$ and H$_{6'}$), 7.10-7.30 (m, 5H, ArH), 7.96 and 8.07 (ABq, J = 9.1 Hz, 2H, H$_5$ and H$_6$), 8.37 and 9.05 (ABq, J = 6.8 Hz, 2H, H$_4$ and H$_3$); ms: m/e (%) 510 and 508 (29), 495 and 493 (10), 428 (43), 427 (29), 413 (62), 412 (100), 397 (67), 334 (62), 231 (43), 229 (43).

*Anal.* Calcd. for $C_{27}H_{27}BrINO_4$: C, 50.94; H, 4.24; N, 2.20. Found: C, 50.81; H, 4.34; N, 1.75.

8-Benzyloxy-1-(2'-bromo-4',5'-dimethoxybenzyl)-1,2,3,4-tetrahydro-7-methoxy-*N*-methylisoquinoline (**7a**).

Compound **7a** was obtained in quantitative yield as an oily product; its picrate melted at 182-184°; $^1$H-nmr: 2.22 (s, 3H, -NMe), 2.58-3.08 (m, 6H, 3 × -CH$_2$-), 3.56, 3.82 and 3.86 (ss, each 3H, -OMe), 4.96 and 5.16 (ABq, J = 11.2 Hz, 2H, -OCH$_2$Ph), 6.56 (s, 1H, H$_3$), 6.83 (s, 2H, ArH), 6.91-7.38 (m, 6H, ArH).

8-Benzyloxy-1-(2'-bromo-4',5'-methylenedioxybenzyl)-1,2,3,4-tetrahydro-7-methoxy-*N*-methylisoquinoline (**7b**).

Compound **7b** was obtained in quantitative yield as an oily product; its picrate melted at 146-148°; $^1$H-nmr: 2.15 (s, 3H, -NMe), 2.25-3.19 (m, 6H, 3 × -CH$_2$-), 3.86 (s, 3H, -OMe), 4.94 and 5.18 (ABq, J = 11.2 Hz, 2H, -OCH$_2$Ph), 5.88 (s, 2H, -OCH$_2$O-), 6.55-7.43 (m, 9H, ArH).

8-Benzyloxy-1-(2'-bromo-3',4'-dimethoxybenzyl)-1,2,3,4-tetrahydro-7-methoxy-*N*-methylisoquinoline (**7c**).

Compound **7c** was obtained in quantitative yield as an oily product; $^1$H-nmr: 2.15 (s, 3H, -NMe), 2.40-3.40 (m, 6H, 3 × -CH$_2$-), 3.79, 3.82 and 3.87 (ss, each 3H, 3 × -OMe), 4.04 (dd, $J_{AX}$ = 9.0 Hz, $J_{BX}$ = 5.1 Hz, 1H, H$_1$), 4.98 and 5.15 (ABq, J = 11.2 Hz, 2H, -OCH$_2$Ph), 6.70-7.38 (m, 9H, ArH).

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

Compound **8a** was obtained in quantitative yield; mp 110-112° (ethanol); $^1$H-nmr: 2.40 (s, 3H, -NMe), 2.50-3.30 (m, 6H, 3 × -CH$_2$-), 3.77, 3.83 and 3.84 (ss, each 3H, 3 × -OMe), 4.20 (broad t, J = 6.6 Hz, 1H, H$_1$), 6.60-6.97 (m, 4H, ArH); ms: m/e (%) 421 (M$^+$-1, 3), 419 (M$^+$-1, 3), 231 (51), 229 (52), 192 (100), 191 (58), 190 (61), 177 (73).

*Anal.* Calcd. for $C_{20}H_{24}BrNO_4$: C, 56.87; H, 5.68; N, 3.31. Found: C, 56.94; H, 5.92; N, 2.87.

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

Compound **8b** was obtained in quantitative yield, mp 157-159° (ethanol); $^1$H-nmr: 2.36 (s, 3H, -NMe), 2.51-3.09 (m, 6H, 3 × -CH$_2$-), 3.86 (s, 3H, -OMe), 4.18 (broad t, $J_{AX}$ = 6.9 Hz, $J_{BX}$ = 6.5 Hz, 1H, H$_1$), 5.93 (s, 2H, -OCH$_2$O-), 6.59-6.96 (m, 4H, ArH); ms: m/e (%) 406 and 404 (M$^+$-1, 2), 282 (17), 215 (33), 213 (33), 193 (60), 192 (100), 190 (56), 177 (81), 176 (31).

*Anal.* Calcd. for $C_{19}H_{20}BrNO_4$: C, 56.15; H, 4.92; N, 3.45. Found: C, 55.71; H, 4.89; N, 3.22.

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

Compound **8c** was obtained in 86% yield, mp 130-132° (ethanol); $^1$H-nmr: 2.39 (s, 3H, -NMe), 2.40-3.40 (m, 6H, 3 × -$CH_2$-), 3.84, 3.86 and 3.87 (ss, each 3H, 3 × -OMe), 4.29 (broad t, J = 7.0 Hz, 1H, $H_1$), 6.64 and 6.75 (ABq, J = 8.2 Hz, 2H, ArH), 6.84 and 7.11 (ABq, J = 8.3 Hz, 2H, ArH); ms: m/e (%) 423 and 421 ($M^+$, 6), 231 (11), 229 (11), 192 (100), 177 (41).

*Anal.* Calcd. for $C_{20}H_{24}BrNO_4$: C, 56.87; H, 5.68; N, 3.31. Found: C, 56.81; H, 5.81; N, 2.93.

General Procedure for the Ullmann Condensation Reaction.

A mixture of 1.52 mmoles of the appropriate phenolic benzylisoquinoline, 20 ml of anhydrous pyridine and 11.45 mmoles of anhydrous potassium carbonate was heated to 135° under inert gas and 5.51 mmoles of purified cupric oxide [24] added. The resulting mixture was heated to 160° with efficient stirring under inert gas for the time indicated. After cooling, the solution was filtered through Celite, which was washed thoroughly with methylene chloride. Solvent was removed under vacuum and the residue was taken into methylene chloride (75 ml) and washed with water (3 × 50 ml), 10% cupric sulfate (3 × 50 ml) and water again (50 ml). The dried (sodium sulfate) extracts were purified by silica gel column chromatography.

Ullmann Cyclization of **8a**. Synthesis of Cularine **9a**.

The above conditions (5 hours) afforded a 91% yield of a compound which crystallized from ethanol, mp 130-132° (lit [25] 125-126° from ether) and was identified as cularine **9a** by direct comparison with the natural product.

Ullmann Cyclization of **8b**. Synthesis of *O*-Methylcularicine **9b**.

The reaction time was 5 hours, and the product obtained in 83% yield crystallized as hydrochloride, mp 263-265° (lit [26] 267° for the hydrochloride of a sample obtained by diazomethane methylation of cularicine) and was identified as *O*-methylcularicine **9b**; $^1$H-nmr: 2.57 (s, 3H, -NMe), 2.63-3.17 (m, 6H, 3 × -$CH_2$-), 3.83 (s, 3H, -OMe), 4.42 (dd, $J_{AX}$ = 11.55 Hz, $J_{BX}$ = 4.4 Hz, 1H, $H_1$), 5.84 and 5.89 (ABq, J = 1.3 Hz, -$OCH_2O$-), 6.47 (s, 1H, $H_5$), 6.72 (d, J = 8.4 Hz, $H_6$), 6.81-6.93 (m, 2H, ArH); ms: m/e (%) 325 ($M^+$, 100), 310 (18), 308 (45), 294 (23), 192 (59).

*Anal.* Calcd. for $C_{19}H_{20}ClNO_4$: C, 63.07; H, 5.53; N, 3.87. Found: C, 63.35; H, 5.53; N, 4.24.

Ullmann Cyclization of **8c**. Synthesis of Sarcocapnine **9c**.

The reaction time was 3.5 hours. The product obtained in 86% yield crystallized as hydrochloride, mp 210-212° (lit [4a] 213°) and was identified as sarcocapnine **9c** by direct comparison with a natural specimen.

8-Benzyloxy-1-(2'-bromo-α-benzoyloxy-4',5'-dimethoxybenzyl)-7-methoxyisoquinoline (**11**).

This was synthesized by the same procedure as **4** using 1.2 mole equivalent of 2-bromoveratraldehyde **10** [17] per mole of Reissert compound **3**. A reaction time of 5 hours was needed. The final product crystallized from ethanol, mp 131-133°, 92% yield; ir: 1715 (CO) $cm^{-1}$; $^1$H-nmr: 3.49, 3.83 and 3.85 (ss, each 3H, 3 × -OMe), 4.86 and 5.27 (ABq, J = 11.3 Hz, 2H, -$OCH_2Ph$), 6.38 (s, 1H, $H_{3'}$), 6.99 (s, 1H, $H_{6'}$), 7.21-8.12 (m, 13H, ArH), 8.30 (s, 1H, -CHα-), 8.40 (d, J = 5.7 Hz, 1H, $H_3$); ms: m/e (%) 534 (1), 414 (6), 323 (9), 122 (25), 105 (70), 91 (100).

*Anal.* Calcd. for $C_{33}H_{28}BrNO_6$: C, 64.49; H, 4.56; N, 2.28. Found: C, 64.78; H, 4.69; N, 2.28.

8-Benzyloxy-1-(2'-bromo-α-hydroxy-4',5'-dimethoxybenzyl)-7-methoxyisoquinoline (**12**).

The procedure was the same as for **5**. Compound **12** was obtained in quantitative yield; its hydrochloride melted at 196-198° (ethanol); $^1$H-nmr: 3.38, 3.81 and 3.82 (ss, each 3H, 3 × -OMe), 4.81 and 5.22 (ABq, J = 11.4 Hz, 2H, -$OCH_2Ph$), 5.90 (s, 1H, $H_{3'}$), 6.98-7.58 (m, 10H, ArH + -$CH_{\alpha'}$-), 8.36 (d, J = 5.6 Hz, $H_3$); ms: m/e (%) 511 and 509 ($M^+$, 0.5), 430 (3), 174 (3), 132 (3), 92 (7), 91 (100).

*Anal.* Calcd. for $C_{26}H_{25}BrClNO_5$: C, 57.09; H, 4.57; N, 2.56. Found: C, 57.54; H, 4.63; N, 2.20.

8-Benzyloxy-1-(2'-bromo-4',5'-dimethoxybenzoyl)-7-methoxyisoquinoline (**13**).

To a solution of **12** (0.5 mmole) in 1.5 ml of anhydrous methylene chloride under inert gas were added 0.75 mmole (1.5 mole equivalents) of pyridinium dichromate [18] and the resulting mixture was magnetically stirred for 48 hours until tlc showed that no starting material remained. The reaction mixture was filtered through Celite, which was washed with methylene chloride (6 × 20 ml). The organic solution was extracted with 10% cupric sulfate (2 × 15 ml) and water (20 ml), dried (sodium sulfate) and evaporated to dryness, giving a residue which crystallized from ethanol, mp 137-139°, 88% yield; ir: 1652 (CO), $cm^{-1}$; $^1$H-nmr: 3.73, 3.87 and 3.97 (ss, each 3H, 3 × -OMe), 5.12 (s, 2H, -$OCH_2Ph$), 6.92 (s, 1H, $H_{3'}$), 7.19-7.65 (m, 9H, ArH), 8.38 (d, J = 5.7 Hz, 1H, $H_3$); ms: m/e (%) 509 and 507 ($M^+$, 30), 408 (60), 338 (44), 337 (74), 308 (83), 306 (83), 294 (100) and 91 (54).

*Anal.* Calcd. for $C_{26}H_{22}BrNO_5$: C, 61.41; H, 4.33; N, 2.75. Found: C, 61.24; H, 4.28; N, 2.92.

1-(2'-Bromo-4',5'-dimethoxybenzoyl)-7-methoxyisoquinolin-8-ol (**14**).

The general method for acid deprotection was employed to transform **13** into **14**, which proved to be unstable and was used immediately; $^1$H-nmr: 3.91 (s, 6H, 2 × -OMe), 4.01 (s, 3H, -OMe), 7.04-7.66 (m, 5H, ArH), 8.35 (d, J = 5.7 Hz, 1H, $H_3$); ms: m/e (%) 419 and 417 ($M^+$, 6), 339 (31), 338 (100), 322 (10), 280 (9), 243 (6).

1-(2'-Bromo-4',5'-dimethoxybenzyl)-7-methoxyisoquinolin-8-ol (**15a**).

The same procedure as used in the synthesis of **8** was employed. Compound **15a** was obtained in quantitative yield, mp 183-185° (ethanol); $^1$H-nmr: 3.55, 3.83 and 3.98 (ss, each 3H, 3 × -OMe), 4.94 (s, 2H, -$CH_2Ph$), 6.35 and 7.07 (ss, 2H, $H_{3'}$ and $H_{6'}$), 7.39-7.46 (m, 3H, ArH), 8.29 (d, J = 5.7 Hz, 1H, $H_3$); ms: m/e (%) 404 and 402 ($M^+$-1, 0.5), 326 (23), 325 (81), 324 (100), 311 (45), 310 (62), 294 (58), and 162 (36).

4-Acetoxy-1,2,3,4-tetrahydro-1-(2'-bromo-3',4'-dimethoxybenzyl)-8-methoxy-*N*-methylisoquinolin-8-ol (**17**).

To a solution of **8c** (1.06 g, 2.51 mmoles) in 15 ml of anhydrous methylene chloride stirred at 0° under inert gas, 1.33 g of 90% lead tetraacetate (0.027 mmole), 1.1 mole equivalents) was added in one portion and the mixture was vigorously stirred for 1 minute before being poured into ice-water and neutralized with sodium bicarbonate. Extraction with methylene chloride (4 × 50 ml), drying of organic extracts (sodium sulfate) and final evaporation (T < 30°) to a small volume (*ca.* 50 ml) afforded a brown solution. This was further stirred under inert gas at rt for 12 hours. Evaporation to dryness and silica gel column chromatography of the residue gave 1 g of an unstable solid (83% yield) which was used immediately; $^1$H-nmr: 2.06 (s, 3H, -OAc), 2.45 (s, 3H, -NMe), 2.90-3.80 (m, 4H, 2 × -$CH_2$-), 4.52 (dd, $J_{AX}$ = 9.3 Hz, $J_{BX}$ = 4.2 Hz, 1H, $H_1$), 5.82 (d, J = 3.1 Hz, 1H, $H_4$), 6.80 and 6.88 (ABq, J = 8.5 Hz, 2H, ArH), 6.81 and 7.10 (ABq, J = 8.5 Hz, 2H, ArH); ms: m/e (%) 481 and 479 ($M^+$, 1.3), 422 and 420 (15), 250 (100), 190 (54), 175 (40).

Ullmann Condensation of **17**.

By the general procedure, with 3.5 hours at 165°. After silica gel column chromatography, a 92% yield of **18** was obtained and crystallized from acetone, mp 146-148°; $^1$H-nmr: 2.13 (s, 3H, -OAc), 2.64 (s, 3H, -NMe), 3.85 (s, 3H, $C_{4'}$ -OMe), 3.87 (s, 3H, $C_7$OMe), 4.05 (s, 3H, $C_{5'}$ -OMe), 2.89 (dd, $J_{3\beta\text{-}4}$ = 2.9 Hz, 1H, $H_{3\beta}$), 3.24 (dd, $J_{3\alpha\text{-}3}$ = 13.5 Hz, $J_{3\alpha\text{-}4}$ = 3.5 Hz, 1H, $H_{3\alpha}$), 2.95, 3.22 and 4.69 (ABX, $J_{1\text{-}\alpha\beta}$ = 12.3 Hz, $J_{1\text{-}\alpha\alpha}$ = 3.1 Hz, $J_{\alpha\alpha\text{-}\alpha\beta}$ = 15.5 Hz, 3H, $H_{\alpha\beta}$, $H_{\alpha\alpha}$ and $H_1$, respectively), 5.90 (broad t, J = 3.0 Hz, 1H, $H_4$), 6.61 and 6.76 (ABq, J = 8.7 Hz, 2H, $H_{3'}$ and $H_{2'}$), 6.85 and 7.17 (ABq, J = 8.6 Hz, 2H, $H_6$ and $H_5$) (main epimer); ms m/e (%) 399 ($M^+$, 100), 374 (8), 340 (14), 339 (29), 338 (37), 324 (74), 308 (31), 306 (29), 296 (26), 174 (63), 172 (37).

*Anal.* Calcd. for $C_{22}H_{25}NO_6$: C, 66.16; H, 6.26; N, 3.51. Found: C, 65.89; H, 6.28; N, 3.16.

Hydrolysis of **18**. Synthesis of 4-Hydroxysarcocapnine **19** [5a].

To a solution of 0.23 g (0.576 mmole) of **18** in 10 ml of methanol and 3 ml of water was added 0.2 g of solid sodium carbonate. The mixture was stirred at room temperature for 2 hours, diluted with water (15 ml), saturated with solid ammonium chloride and extracted into methylene chloride (5 × 25 ml). The extracts were dried (sodium sulfate) and evaporated to dryness to give 0.2 g of epimeric 4-hydroxysarcocapnines **19** in quantitative yield. The main epimer **19b** crystallized from ethanol, mp 146-147°; $^1$H-nmr: 2.61 (s, 3H, -NMe), 3.85, 3.87 and 4.05 (ss, each 3H, 3 × -OMe at $C_{4'}$, $C_7$ and $C_{5'}$), 2.79 (dd, $J_{3\beta\text{-}4}$ = 3.3 Hz, 1H, $H_{3\beta}$), 3.14 (dd, $J_{3\alpha\text{-}3\beta}$ = 12.3 Hz, $J_{3\alpha\text{-}4}$ = 2.8 Hz, 1H, $H_{3\alpha}$), 2.90, 3.22 and 4.60 (ABX, $J_{1\text{-}\alpha\beta}$ = 12.6 Hz, $J_{1\text{-}\alpha\alpha}$ = 3.1 Hz, $J_{\alpha\alpha\text{-}\alpha\beta}$ = 15.6 Hz, 3H, $H_{\alpha,\beta}$, $H_{\alpha\alpha}$ and $H_1$ respectively), 6.60 and 6.75 (ABq, J = 8.7 Hz, 2H, $H_{3'}$ and $H_{2'}$), 6.86 and 7.22 (ABq, J = 8.5 Hz, 2H, $H_6$ and $H_5$); ms: m/e (%) 357 ($M^+$, 100), 342 (52), 324 (40), 314 (18); 311 (18), 278 (20), 277 (40), 142 (62), 140 (26). The minor epimer, **19a**, was identified as 4-hydroxysarcocapnine by comparison with a natural specimen [5a].

DDQ Oxidation of (±)-4-Hydroxysarcocapnine **19**. Synthesis of Yagonine (**20**).

To a deoxygenated solution of **19** (0.28 g, 0.784 mmole) in dry benzene (80 ml), 0.45 g (1.96 mmoles, 2.5 mole equivalents) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone were added in one portion and the mixture was refluxed under an inert atmosphere for two hours. The residue after evaporation was loaded into a basic alumina (Act III) column and eluted with methylene chloride to afford 0.11 g (41% yield) of a red solid which crystallized from methanol as red needles, mp 237-239° (lit [5b] 226-227° from ethanol); ir: 1680 (CO) cm$^{-1}$; $^1$H-nmr: 3.66 (s, 3H, -NMe), 3.90, 4.07 and 4.09 (ss, each 3H, 3 × -OMe at $C_{4'}$, $C_7$ and $C_{5'}$ respectively), 6.62 (s, 1H, $H_\alpha$), 6.76 and 6.90 (ABq, J = 8.7 Hz, 2H, $H_{3'}$ and $H_{2'}$), 7.20 and 8.06 (ABq, J = 8.7 Hz, 2H, $H_6$ and $H_5$); $^{13}$C-nmr: 175.24 (s, -CO), 156.96 (s, -CO), 156.76 (s), 155.33 (s), 149.30 (s), 141.98 (s), 133.48 (s), 130.03 (s), 126.83 (d), 124.26 (d), 122.29 (s), 121.82 (s), 118.59 (d), 113.94 (d), 108.95 (d), 61.61 (q), 56.47 (q), 56.22 (q) and 32.92 (q); ms: m/e (%) 367 ($M^+$, 20), 366 (100), 338 (55), 323 (57), 308 (13), 280 (25).

Synthesis of Aristoyagonine (**21**).

Two g of barium hydroxide was added in one portion to a suspension of 0.03 g (0.0817 mmole) of **20** in 15 ml of anhydrous methanol at rt. After stirring for a further 2 hours, the solvent was removed and water (50 ml) and methylene chloride were added. The aqueous layer was extracted with methylene chloride (2 × 25 ml) and the dried (sodium sulfate) extracts were evaporated to dryness, giving a yellow residue which was chromatographed on a preparative silica gel plate.

The minor product (higher $R_f$ value) was a bright yellow solid (0.002 g, 7% yield) which was identified as aristoyagonine **21** and crystallized from methanol, mp 165-166° (lit [5b] 165-166°); ir: 1680 and 1700 cm$^{-1}$; $^1$H-nmr: 3.25 (s, 3H, -NMe), 3.86, 3.94 and 3.96 (ss, each 3H, -OMe at $C_{4'}$, $C_{5'}$ and $C_6$ respectively), 5.76 (s, 1H, Hα), 6.55 and 6.64 (ABq, J = 8.6 Hz, 2H, $H_{3'}$ and $H_{2'}$), 6.95 and 7.36 (ABq, J = 8.7 Hz, 2H, $H_5$ and $H_4$); $^{13}$C-nmr: 166.13 (s, -CO), 154.94 (s), 152.14 (s), 148.05 (s), 141.87 (s), 141.48 (s), 135.42 (s), 127.47 (s), 125.79 (d), 122.03 (s), 121.62 (s), 118.80 (d), 115.03 (d), 108.21 (d), 107.94 (d), 61.19 (q), 56.70 (q), 56.07 (q) and 25.49 (q); ms: m/e (%) 339 ($M^+$, 100), 324 (30), 309 (7), 296 (10), 281 (17), 253 (12), 238 (27).

The major product (lesser $R_f$ value) proved to be a colorless solid (0.015 g, 56% yield) which crystallized from methanol, mp 162-164° and was identified as 1,α-dihydroaristoyagonine **22**; ir: 1680 (-CO) cm$^{-1}$; $^1$H-nmr: 3.17 (s, 3H, -NMe), 2.86, 3.39 and 4.52 (ABX, $J_{1\text{-}\alpha\beta}$ = 11.3 Hz, $J_{1\text{-}\alpha\alpha}$ = 2.7 Hz, $J_{\alpha\alpha\text{-}\alpha\beta}$ = 13.6 Hz, 3H, $H_{\alpha\beta}$, $H_{\alpha\alpha}$ and $H_1$ respectively), 3.89, 4.00 and 4.03 (ss, each 3H, 3 × -OMe), 6.67 and 6.89 (ABq, J = 8.6 Hz, 2H, $H_{3'}$ and $H_{2'}$), 7.05 and 7.52 (ABq, J = 8.1 Hz, 2H, $H_5$ and $H_4$); $^{13}$C-nmr: 168.02 (s, -CO), 153.08 (s), 152.30 (s), 148.66 (s), 140.76 (s), 139.37 (s), 133.15 (s), 126.10 (d), 124.57 (s), 118.41 (d), 117.42 (s), 112.69 (d), 107.31 (d), 61.10 (q), 59.91 (d), 56.68 (q), 56.29 (q), 37.54 (t), and 27.19 (q); ms: m/e (%) 341 ($M^+$, 100), 326 (28), 310 (44), 189 (28), 176 (26), 167 (36).

*Anal.* Calcd. for $C_{19}H_{19}NO_5$: C, 66.86; H, 5.57; N, 4.10. Found: C, 66.61; H, 5.76; N, 3.86.

DDQ Oxidation of **22** to **21**.

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (0.024 g, 0.1 mmole, 2.4 mole equivalents) was added to a solution of 0.015 g (0.044 mmole) of **22** in 2 ml of deoxygenated benzene and the mixture was heated for 24 hours at 100° under inert gas. Work-up as above afforded 0.014 g (94% yield) of aristoyagonine **21**.

Acknowledgements

We thank the Comisión Asesora (CAICYT) for its financial support.

## REFERENCES AND NOTES

[1] See Part I of this series; part of this work has already been published in preliminary communications, see ref [5].

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

[3a] L. Castedo, "The Chemistry and Pharmacology of Cularine Alkaloids" in "The Chemistry and Pharmacology of Isoquinoline Alkaloids", Phillipson *et al.*, eds, Springer-Verlag, Berlin Heidelberg, 1985, pp. 102-125; [b] B. Gözler and M. Shamma, *J. Nat. Prod.*, **47**, 753 (1984).

[4a] M. J. Campello, L. Castedo, J. M. Saá, R. Suau and M. C. Vidal, *Tetrahedron Letters*, **23**, 239 (1982); [b] S. Firdous, A. J. Freyer, M. Shamma and A. Urzúa, *J. Am. Chem. Soc.*, **106**, 6099 (1984).

[5a] L. Castedo, D. Domínguez, A. R. de Lera and E. Tojo, *Tetrahedron Letters*, **25**, 4573 (1984); [b] M. J. Campello (in part), L. Castedo, D. Domínguez, A. Rodríguez de Lera, J. M. Saá, R. Suau, E. Tojo and M. C. Vidal, *Tetrahedron Letters*, **25**, 5933 (1984).

[6] A. A. Moroz and M. S. Shvartberg, *Russ. Chem. Rev. (Engl. Transl.)*, **43**, 679 (1974).

[7] T. Yamamoto and Y. Kurata, *Can. J. Chem.*, **61**, 86 (1983).

[8a] G. W. Whitesides, J. S. Sadowski and J. Lilburn, *J. Am. Chem. Soc.*, **96**, 2829 (1974); [b] H. Weingarten, *J. Org. Chem.*, **29**, 977 and 3624 (1964); see also J. Knabe and W. Weirch, *Arch. Pharm.*, **316**, 624 (1983); [c] S. Tokita, N. Hirakawa, T. Masaaki and H. Nishi, *Saitama Daigaku Kiyo Kogakuku*, **13**, 32 (1979); *Chem. Abstr.*, **95**, 144955g (1981).

[9a] M. Shamma, "The Isoquinoline Alkaloids", Academic Press, NY, 1972, Chapter 6; [b] M. Shamma and J. L. Moniot, in "Isoquinoline Alkaloid Research, 1972-1977", Plenum Press, NY, 1978, Chapter 7.

[10a] H. Hsu, T. Kikuchi, S. Aoyagi and H. Iida, *Yakugaku Zasshi*, **92**, 1030 (1972); *Chem. Abstr.*, **77**, 140365n (1972); [b] H. Iida, T. Kikuchi, S. Tanaka and M. Shinbo, *Yakugaku Zasshi*, **89**, 1169 (1969); *Chem. Abstr.*, **72**, 3338p (1970).

[11] T. Kametani, K. Fukumoto and M. Fujihara, *Chem. Pharm. Bull.*, **20**, 1800 (1972).

[12] S. Ishiwata, T. Fujii, N. Miyagi, Y. Satoh and K. Itakura, *Chem. Pharm. Bull.*, **18**, 1850 (1970).

[13] A. H. Jackson, G. Stewart, G. A. Charnock and J. A. Martin, *J. Chem. Soc., Perkin Trans. 1*, 1911 (1974).

[14] T. Shono, T. Miyamoto, M. Mizukami and H. Hamaguchi, *Tetrahedron Letters*, **22**, 2385 (1981).

[15] This compound has recently been isolated from *Corydalis claviculata* (L.) D. C., G. Blaschke and G. Scriba, *Z. Naturforsch.*, **38c**, 670 (1983); *ibid., Phytochemistry*, **24**, 585 (1985).

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

[17] L. Small and S. G. Turnbull, *J. Am. Chem. Soc.*, **59**, 1541 (1937).

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

[19] H. Hara, H. Shinoki, O. Hoshino and B. Umezawa, *Heterocycles*, **20**, 2149 (1983).

[20] L. Castedo, R. Suau and A. Mouriño, *Tetrahedron Letters*, 501 (1976).

[21] P. A. S. Smith and R. O. Kan, *J. Am. Chem. Soc.*, **83**, 2580 (1961).

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

[23] I. Baxter, L. T. Allan and G. A. Swan, *J. Chem. Soc.*, 3645 (1965).

[24] G. Brauer, "Preparative Inorganic Chemistry", 2nd Ed, F. E. Verlag-Stuttgart, 1965, Vol **2**, p 1012.

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

[26] R. H. F. Manske, *Can. J. Chem.*, **43**, 989 (1965).