Pergamon

Tetrahedron 54 (1998) 9023–9032

TETRAHEDRON

Three Complementary Methods Offering Access to 5-Substituted 1,2,3,4-Tetrahydroisoquinolines

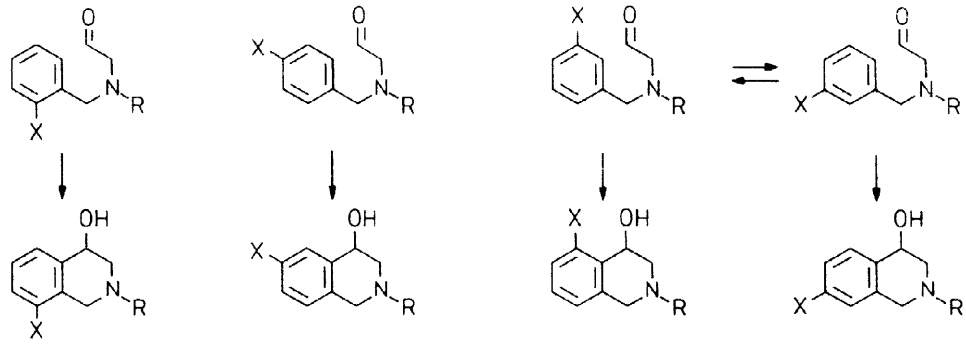
Manfred Schlosser *, Gyula Simig and Hervé Geneste

Institut de Chimie organique de l'Université
Bâtiment de Chimie (BCh), CH-1015 Lausanne-Dorigny, Switzerland

Received 31 March 1998; accepted 2 June 1998

Abstract: The scope and limitations of three independent, though related routes leading to 5-substituted tetrahydroisoquinolines are explored : the Pictet-Spengler type cyclization of *ortho*-substituted 2-phenylethylamines, the Pomeranz-Fritsch type cyclization of *meta*-substituted benzylamines and the electrophilic trapping of 5-lithiated 4-lithiooxytetrahydroquinolines. The introduction of the substituent relies in all three cases on a neighboring group assisted, site selective metalation step.

Pomeranz-Fritsch type cyclization of *ortho*- and *para*-substituted benzylamine derivatives opens the most convenient entry to 1,2,3,4-tetrahydroisoquinolines carrying substituents at the 8- and 6-position, respectively [1 - 3]. The outcome is less unequivocal when *meta*-substituted benzylamines are used as the starting materials since now mixtures are formed, in which the 7-isomer is generally the predominant component if it is not even formed exclusively [1 - 5]. In other words, the 5-isomers are the least accessible among the aromatically substituted isoquinolines.



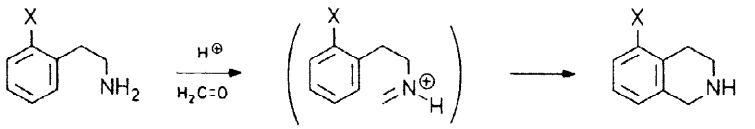
We present in the following three complementary methods that selectively lead to 5-substituted isoquinolines. All of them involve at some stage a neighboring group assisted, site specific hydrogen/lithium exchange ("metalation") at the aromatic ring.

The *first possibility* is to opt for a Pictet-Spengler or a Bischler-Napieralski rather than a Pomeranz-Fritsch type cyclization [1, 5]. This means, as the principal building block this time a 2-arylethylamine is required.

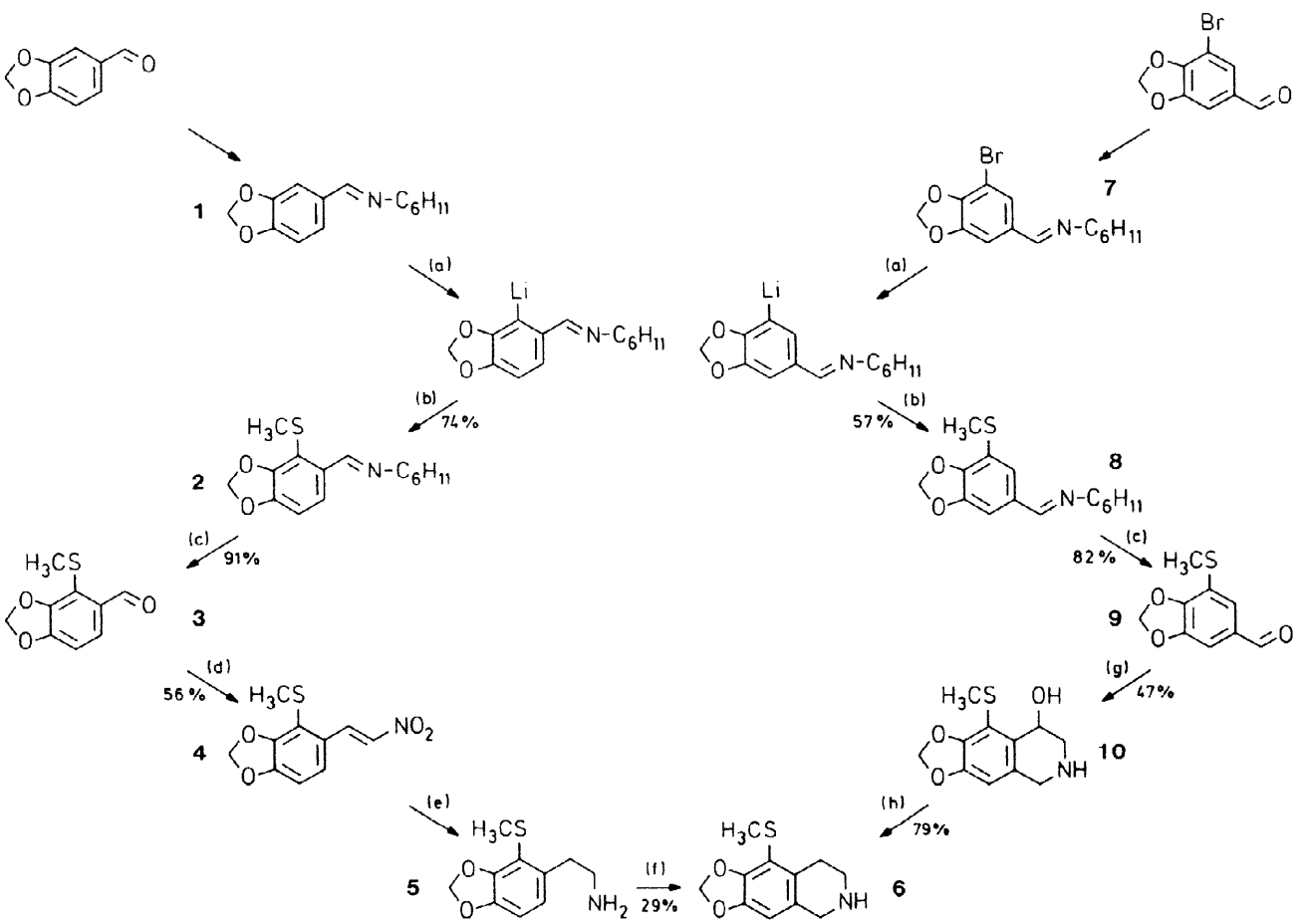
(Fax ++41 / 21 / 692 39 65)

PII: S0040-4020(98)00541-9

If a substituent is located at an *ortho*-position of the aryl ring, it will inevitably have to occupy the 5-position in the final isoquinolines.



To exemplify this approach we have prepared 2-(methylthio)piperonal **3** by consecutive reaction of *N*-(piperonylidene)cyclohexylamine **1** with butyllithium and dimethyl disulfide followed by acid hydrolysis of the resulting imine **2**. Aldehyde **3** was converted into the 2-arylethylamine **5** *via* the β-nitrostyrene **4** obtained by condensation with nitromethane under basic conditions and subsequent catalytic hydrogenation. Compound **5**, when treated with formaldehyde under acidic conditions, eventually afforded the tetrahydroisoquinoline **6**.

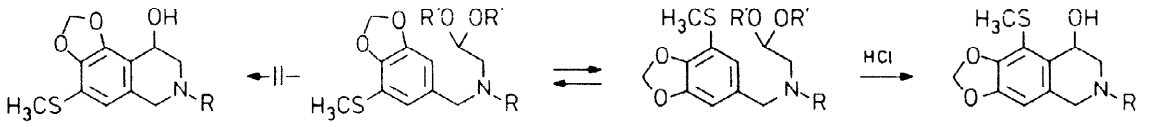


(a) LiC_4H_9; (b) H_3CSSCH_3; (c) 20% aq. HCl; (d) H_3CNO_2; (e) $LiAlH_4$, later H_2O; (f) CH_2O, later 20% aq. HCl; (g) $H_2NCH_2CH(OCH_3)_2$, later $NaBH_4$, finally 20% aq. HCl; (h) $NaBH_4$ and F_3CCOOH.

In general, 2-arylethylamines are less readily available than arylmethylamines (benzylic amines). Therefore, it was tempting to explore the *second possibility* of access to the isoquinoline **6** by starting with 5-bromopiperonal. The corresponding cyclohexylamine **7** was first submitted to a halogen/metal exchange performed with butyllithium in tetrahydrofuran and next allowed to react with dimethyl disulfide. The imine **8** thus obtained was hydrolyzed to set free aldehyde **9** which was condensed with 2,2-dimethoxyethylamine under

reductive conditions before being cyclized to give the 4-hydroxyisoquinoline **10**, the hydroxy group of which could be easily removed by hydrogenolysis.

The aminoacetal **11**, derived from 5-(methylthio)piperonal (**9**) by reductive amination, has two empty *ortho*-positions in which the side chain could "bite" thus giving rise to the actually formed isoquinoline **10** or its elusive regioisomer **12**. The high selectivity found in favor of product **10** is another manifestation of the pronounced *para*-directing effect [1 - 5] of alkoxy groups (here as part of a dioxolane ring) in electrophilic aromatic substitution reactions. The *N*-methyl aminoacetal **13**, obtained by reductive amination of aldehyde **9** with *N*-(2,2-diethoxyethyl)methylamine, shows the same kind of extreme regioselectivity, affording isoquinoline **14** (42%) as the sole isolated product.

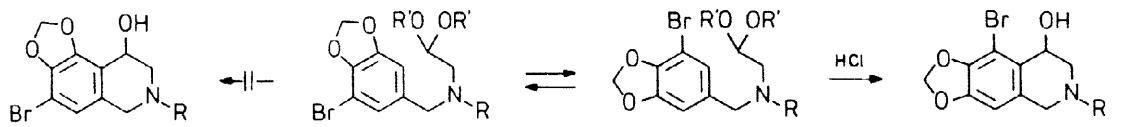


12
OR' = OCH_3, OC_2H_5

11: R = H
13: R = CH_3

10: R = H
14: R = CH_3

In the same way, 5-bromopiperonal was converted *via* the aminoacetals **15** and **17** into the 5-bromoisoquinolines **16** (51%) and **18** (49%). Evidently, neither alkylthio groups nor a bromine atom strongly bias the *ortho*/*para*-orientation of electrophilic aromatic substitution so that the alkoxy unit incorporated in the dioxonate ring can dictate the regiochemical course of the cyclization step.



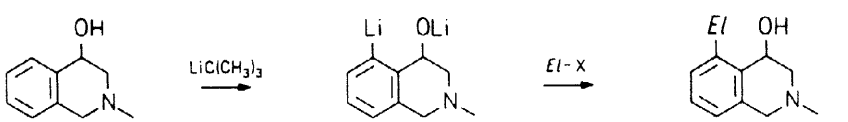
OR' = OCH_3, OC_2H_5

15: R = H
17: R = CH_3

16: R = H
18: R = CH_3

The 4-hydroxy group is a structural motif which is invariably associated with the Pomeranz-Fritsch method when performed according to the Bobbitt protocol [6 - 8]. It may or may not be subsequently removed by elimination or reduction. However, as long as present, it may be deprotonated and then exploited as a neighboring group directing the hydrogen/metal exchanging attack of an organolithium reagent to the nearby 5-position. The *third possibility* of introducing a substituent into the 5-position of isoquinolines is based on this concept. Numerous precedents [9 - 13] of lithium benzylalcoholate *ortho*-metalations and applications in the carbocyclic series (*e.g.*, the 5-lithiation of lithium 1,2,3,4-tetrahydro-1-naphtholate [12]) are known.

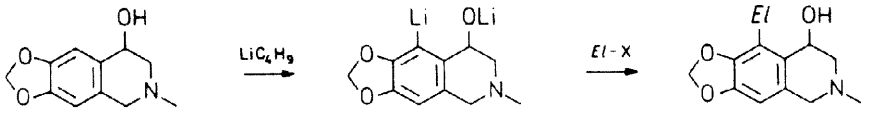
The lithiation of 4-hydroxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (**19**) did occur although it proceeded only sluggishly. An excess of *tert*-butyllithium in diethyl ether and prolonged reaction times (6 h at 25 °C) were required to achieve acceptable yields of the trapping products **20** - **22** (63%, 45% and 51%, respectively).



19

20: *El* = $(H_3C)_3Si$
21: *El* = I
22: *El* = O=CH

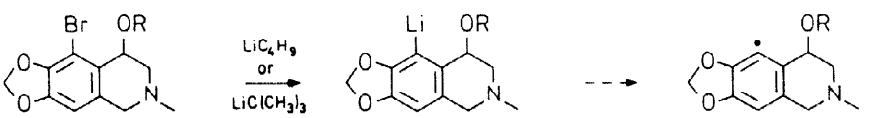
Against our expectation, the metalation was not much accelerated when we turned to the 1,3-dioxolo[4,5-*g*]-8-hydroxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (**23**) as the substrate. After treatment with excess butyllithium in tetrahydrofuran (again for 6 h at 25 °C) followed by interception with various electrophiles, the 5-substituted derivatives **24** - **26** were isolated in satisfactory yields (72%, 60% and 66%, respectively).



23

24: *El* = $(H_3C)_3Si$
25: *El* = I
26: *El* = H_3C

Since the 5-bromoisoquinoline **18** is so readily available, it was an obvious idea to submit it to consecutive *O*-lithiation and halogen/metal interconversion, thus generating the intermediate **27** instantaneously. Strange enough, only small amounts (0 - 20%) of 5-substituted derivatives where identified after trapping with a variety of electrophiles (deuterium oxide, methyl iodide, formaldehyde, *N,N*-dimethylformamide and carbon dioxide). The situation improved to some extent when the same reaction sequence was applied to the 4-methoxyisoquinoline **28**. Intermediate **29** was efficiently intercepted with heavy water (92% of deuterium incorporation), whereas the treatment with methyl iodide gave only about 15% of the expected product. Moreover, at least one third of the isoquinoline **28** was invariably lost by transformation into insoluble materials, presumably by concomitant base-promoted 1,8-elimination of methanol and subsequent dimerization of the resulting *o*-quinodimethane [14].



18: OR = OH
28: OR = OCH_3

27: OR = OLi
29: OR = OCH_3

30

Several factors which can compromise the outcome of the reactions appear to coincide. The flatness of the ring structures and aggregation make the intermediates **27** and **29** virtually insoluble and thus protect them against the action of electrophiles. At the same time, the oxygen functions in the vicinity of the organometallic bond may trigger a single electron transfer [15] from the latter to the electrophilic reagent, thus generating radicals **30** (OR = Li or OCH_3) which will seek and find stabilization by hydrogen atom abstraction from the solvent. No such complication is encountered with flexible precursors. For example, the 5-bromo substituted aminoacetal **17** undergoes the halogen/metal exchange with butyllithium and the subsequent electrophilic trapping almost quantitatively (*e.g.*, with dimethyl disulfide affording 83% of **14**).

EXPERIMENTAL PART

Starting materials were purchased from Fluka (CH-9470 Buchs) or Aldrich (D-89552 Steinheim), unless literature sources or details of the preparation are given. Solutions of butyllithium ("*n*-butyllithium") in hexane (1.5 M and "11.5 M", *i.e.* containing the organometallic reagent to the extent of 90%) were supplied by

CheMetall (D-60271 Frankfurt), potassium *tert*-butoxide by Callery (Pittsburgh, PA 15230). All commercial reagents were used without further purification.

Air and moisture sensitive compounds were stored in Schlenk tubes or Schlenk burettes. They were protected by and handled under an atmosphere of 99.995% pure nitrogen (glassware : Glasgerätebau Pfeifer, D-98711 Frauenwald).

Paraffinic or aromatic hydrocarbons (*e.g.*, hexane, benzene and toluene) were obtained anhydrous by careful azeotropic distillation. *Diethylether* and *tetrahydrofuran* were dried by distillation from sodium wire after the characteristic blue color of *in situ* generated sodium diphenyl ketyl [16] had been found to persist.

Ethereal extracts were dried with sodium sulfate. Before distillation of compounds prone to radical polymerization or sensitive to acids a spatula tip of *hydroquinone* or, respectively, *potassium carbonate* was added.

The temperature of dry ice methanol baths is consistently indicated -75 °C and "room temperature" (22 - 26 °C) as 25 °C. *Melting ranges* (mp) are reproducible after resolidification, unless stated otherwise ("dec."), and are corrected by using a calibration curve which was established with authentic standards. If no melting points are given, it means that all attempts to crystallize the liquid product have failed even at temperatures as low as -75 °C.

Silica gel (Merck Kieselgel 60) of 70 - 230 mesh (0.06 - 0.20 mm) particle size was used for *column chromatography*. The solid support was suspended in hexane and, when all air bubbles had escaped, was sluiced into the column. When the level of the liquid was still some 3 - 5 cm above the silica layer, the dry powder, obtained by adsorption of the crude product mixture on 15 - 20 g silica gel and subsequent evaporation of the solvent, was poured on top of the column.

Nuclear magnetic resonance spectra of hydrogen-1 and carbon-13 nuclei in deuterochloroform solution (unless stated otherwise) were recorded at 400 MHz, chemical shifts δ referring to the signal of tetramethylsilane. Coupling constants (*J*) are measured in Hz. Coupling patterns are abbreviated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets) and m (multiplet).

Mass spectra were obtained at 70 eV ionization potential maintaining a source temperature of 200 °C. The *m/e* ratios given for bromine-containing molecules or fragments thereof refer to the ^{81}Br isotopomers.

Elementary analyses were executed by the laboratory of I. Beetz, D-96301 Kronach. The expected numbers are calculated on the basis of atomic weights according to the 1986 IUPAC recommendations.

2-(Methylthio)piperonylidene-*N*-cyclohexylimine (2) : At -75 °C butyllithium (0.11 mol) in hexane (75 mL) and, 20 min later, dimethyl disulfide (13 mL, 14 g, 0.15 mol) were added to a solution of piperonylidene-*N*-cyclohexylimine [15] (**1**; 23 g, 0.10 mol) in tetrahydrofuran (0.20 L). The mixture was kept 2 h at 25 °C before it was poured into water (50 mL). The organic layer was washed with brine (25 mL), dried and evaporated. Recrystallization of the residue from methanol gave product **2** as a colorless solid; mp 102 - 103 °C; 20.6 g (74%). - ^{1}H-NMR : δ 8.85 (1 H, s), 7.59 (1 H, d, *J* 8.6), 6.80 (1 H, d, *J* 8.6), 6.06 (2 H, s), 3.15 (1 H, symm. m), 2.42 (3 H, s), 1.5 (10 H, m). - MS : 277 (3%, M^+), 262 (51%), 180 (100%). - Analysis : calc. for $C_{15}H_{19}NO_2S$ (277.38) C 64.95, H 6.90; found C 64.72, H 6.82%.

2-(Methylthio)piperonal (3) : Imine **2** (20.0 g, 72 mmol) was dissolved in dichloromethane (0.20 L). After addition of 10% hydrochloric acid, the mixture was vigorously stirred for 48 h. The organic layer was decanted, washed with a saturated aqueous solution (2 × 50 mL) of sodium carbonate and water (2 × 50 mL), dried and evaporated. The residue was triturated with hexanes (50 mL) and crystallized from methanol to afford product **3** as a colorless solid; mp 79 - 81 °C; 12.9 g (91%). - IR (KBr) : 1665 cm^{-1}, - ^{1}H-NMR : δ 10.39 (1 H, s), 7.55 (1 H, d, *J* 8.0), 6.83 (1 H, d, *J* 8.0), 6.14 (2 H, s), 2.52 (3 H, s). - MS : 196 (100%, M^+),

181 (48%), 167 (14%), 162 (14%), 149 (19%). - Analysis : calc. for $C_9H_8O_3S$ (196.22) C 55.09, H 4.11; found C 55.07, H 4.19%.

(*E*)-[2-(Methylthio)piperonylidene]nitromethane (4) : A mixture of aldehyde **3** (3.9 g, 20 mmol), nitromethane (5.4 mL, 6.1 g, 100 mmol), ammonium acetate (3.1 g, 40 mmol) and acetic acid (10 mL) was heated for 2 h under reflux before being kept 15 h in a refrigerator. The precipitate was collected by filtration under suction, washed with 50% aqueous ethanol and diethyl ether and recrystallized from ethanol to give the colorless solid **4**; mp 119 - 120 °C; 2.8 g (56%). - ^{1}H-NMR : δ 8.64 (1 H, d, *J* 14.2), 7.57 (1 H, d, *J* 14.2), 7.21 (1 H, d, *J* 8.2), 6.84 (1 H, d, *J* 8.2), 6.14 (2 H, s), 2.47 (3 H, s). - MS : 239 (4%, M^+), 193 (72%), 178 (100%). - Analysis : calc. for $C_{10}H_9NO_4S$ (239.24) C 50.20, H 3.79; found C 50.54, H 3.81%.

5,6,7,8-Tetrahydro-1-methylthio-1,3-dioxolo[4,5-*g*]isoquinoline (6) : A solution of the nitro compound **4** (2.4 g, 9.5 mmol) in tetrahydrofuran (20 mL) was added dropwise to a suspension of lithium aluminum hydride (1.4 g, 38 mmol) in tetrahydrofuran (20 mL). After 5 h of stirring at 25 °C, the mixture was poured into a saturated aqueous solution of sodium sulfate and extracted with diethyl ether (2 × 25 mL). The precipitate was removed by filtration and thoroughly extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with brine (2 × 25 mL) and evaporated. The oily residue, presumed to contain amine **5**, was treated with an 18% aqueous solution (6 mL) of formaldehyde (40 mmol) for 15 h at 25 °C. Then 20% hydrochloric acid (25 mmol) was added under stirring and the homogeneous mixture evaporated to dryness. Recrystallization from aqueous ethanol afforded the colorless hydrochloride of isoquinoline **6**; mp 255 - 256 °C (dec.); 0.71 g (29%). - ^{1}H-NMR (D_2O) : δ 6.73 (1 H, s), 6.04 (2 H, s), 4.30 (2 H, s), 3.54 (2 H, t, *J* 6.3), 3.15 (2 H, t, *J* 6.3), 2.40 (3 H, s). - MS : 223 (100%; M^+), 206 (22%), 193 (17%), 176 (28%), 161 (38%). - Analysis : calc. for $C_{11}H_{14}ClNO_2S$ (259.75) C 50.86, H 5.43; found C 51.00, H 5.34%.

Product **6** was also obtained by treatment of the hydroxyisoquinoline **10** (0.72 g, 3.0 mmol), described below, with sodium borohydride (0.23 g, 6.0 mmol) in a mixture of trifluoroacetic acid (2.0 mL) and dichloromethane (4.0 mL) for 16 h at 25 °C. The residue left behind upon evaporation to dryness was triturated with a 5% aqueous solution (10 mL) of sodium hydroxide and then collected by filtration. It was dissolved in ethanol (5 mL) and precipitated in diethyl ether (10 mL). Recrystallization from aqueous ethanol gave the hydrochloride of **6** as colorless needles; mp 255 - 256 °C (dec.); 0.62 g (79%).

***N*-(5-Bromopiperylidene)cyclohexylimine (7)** : A solution of 5-bromopiperonal [18] (34g, 0.15 mol; prepared from 5-bromo-3,4-dihydroxybenzaldehyde [19]) and cyclohexylamine (21 mL, 18 g, 0.18 mol) in toluene (0.25 mL) was heated under reflux for 2 h, while the water formed was continuously removed by means of a Dean-Stark separator. After evaporation of the solvent, the residue was crystallized from methanol; mp 94 - 95 °C (lit. [20] : mp 97.5 - 98.5 °C); 41 g (87%). - ^{1}H-NMR : δ 8.12 (1 H, s), 7.28 (1 H, d, *J* 1.3), 7.23 (1 H, d, *J* 1.3), 6.07 (2 H, s), 3.16 (1 H, symm. m), 1.5 (10 H, m). - MS : 311 (16%, M^+), 282 (13%), 280 (10%), 230 (51%), 45 (100%). - Analysis : calc. for $C_{14}H_{16}BrNO_2$ (310.19) C 54.21, H 5.20; found C 54.44, H 5.09%.

N-[5-(Methylthio)piperonylidene]cyclohexylamine (8) : At -75 °C, a solution (75 mL) of butyllithium (0.11 mol) in hexanes and, 20 min later, dimethyl disulfide (13 mL, 14 g, 0.15 mol) were added to bromoimine 7 (31 g, 0.10 mol) in tetrahydrofuran (0.20 L). The homogeneous mixture was kept 3 h at -75 °C before it was allowed to reach 25 °C. The residue obtained after washing with water (3 × 50 mL), drying and evaporation was triturated with hexanes (0.10 L) and crystallized from heptanes; mp 63 - 64 °C; 16 g (57%). - ^{1}H-NMR : δ 8.18 (1 H, s), 7.18 (1 H, d, *J* 1.3), 7.09 (1 H, s, *J* 1.3), 6.04 (2 H, s), 3.15 (1 H, symm. m), 2.51 (3 H, s), 1.5 (10 H, m). - MS : 177 (13%, M^+), 196 (20%), 195 (13%), 181 (8%), 45 (100%). - Analysis : calc. for $C_{15}H_{19}NO_2S$ (277.38) C 64.95, H 6.90; found C 65.01, H 6.82%.

5-(Methylthio)piperonal (9) : The imine **8** was hydrolyzed as described for the conversion of imine **2** into aldehyde **3** (see above); mp 80 - 81 °C (from methanol); 8.6 g (82%). - IR (KBr) : 1670 cm^{-1}. - ^{1}H-NMR : δ 9.83 (1 H, s), 7.36 (1 H, d, *J* 1.6), 7.19 (1 H, d, *J* 1.6), 6.14 (2 H, s), 2.55 (3 H, s). - MS : 196 (100%, M^+), 195 (54%), 151 (11%). - Analysis : calc. for $C_9H_8O_3S$ (196.22) C 5.09, H 4.11; found C 55.08, H 4.25%.

5,6,7,8-Tetrahydro-1-methylthio-1,3-dioxolo[4,5-*g*]isoquinolin-8-ol (10) : A suspension of aldehyde **9** (3.9 g, 20 mmol) and aminoacetaldehyde dimethyl acetal (2.4 mL, 2.3 g, 22 mmol) in methanol (20 mL) was stirred until a homogeneous solution had formed. The latter was cooled to 0 °C and sodium borohydride (0.38 g, 10 mmol) was dissolved in it. After 2 h at 25 °C, the solvent was evaporated and the residue taken up in 20% hydrochloric acid (0.10 L). The mixture was kept 16 h at 25 °C. Under cooling, a 40% aqueous solution (60 mL) of sodium hydroxide was added. Product **10** was extracted with dichloromethane (3 × 75 mL). The combined organic layers were dried and evaporated. Recrystallization of the residue from isopropanol gave a colorless powder; mp 159 - 161 °C; 2.2 g (47%). - ^{1}H-NMR (D_3CSOCD_3) : δ 6.54 (1 H, s), 6.01 (1 H, d, *J* 0.9), 5.98 (1 H, d, *J* 0.9), 4.76 (1 H, s, broad), 4.55 (1 H, s, broad), 3.75 (1 H, d, *J* 16.3), 3.60 (1 H, d, *J* 16.3), 3.23 (1 H, s, broad), 3.03 (1 H, d, *J* 13.3), 2.73 (1 H, dd, *J* 13.3, 2.5), 2.38 (3 H, s). - MS : 239 (26%, M^+), 219 (44%), 210 (35%), 204 (19%), 195 (32%), 45 (100%). - Analysis : calc. for $C_{11}H_{13}NO_3S$ (239.29) C 55.21, H 5.48; found C 55.46, H 5.13%.

5,6,7,8-Tetrahydro-6-methyl-1-methylthio-1,3-dioxolo[4,5-*g*]isoquinolin-8-ol (14) : A suspension of 5-(methylthio)piperonal (3.9 g, 20 mmol) in methanol (20 mL) and a 40% aqueous solution (3.5 mL) of methylamine (40 mmol) was stirred until a homogeneous solution had formed. Sodium borohydride (0.38 g, 10 mmol) was dissolved in this mixture. After 16 h at 25 °C, the solution was evaporated to dryness and water was added. The extract with dichloromethane (3 × 50 mL) was dried and evaporated. The residue was dissolved in ethanol (40 mL) and precipitated by addition of concentrated hydrochloric acid (2 mL) and diethyl ether (20 mL). - The crude hydrochloride was dissolved in a 20% aqueous solution (15 mL) of sodium hydroxide and extracted with ether (3 × 10 mL). After drying and evaporation of the combined organic layers, bromoacetaldehyde diethyl acetal (4.0 mL, 5.1 g, 25 mmol) and sodium hydrogen carbonate (5.0 g, 60 mmol) were added and the residue was heated for 6 h to 125 °C. The semisolid mixture was extracted with diethyl ether (3 × 10 mL). Evaporation of the filtrate afforded a yellowish oil. - This crude material (intermediate **13** according to nmr) was dissolved in 20% hydrochloric acid (0.10 L). After 16 h at 25 °C, the mixture was stirred with charcoal, filtered and made alkaline by addition of 40% aqueous sodium hydroxide (60 mL). Product **14** was extracted with dichloromethane (3 × 50 mL), dried and collected after evaporation of the solvent. Recrystallization from toluene gave a colorless solid; mp 115 - 116 °C; 2.2 g (42%). - ^{1}H-NMR (D_3CCN) : δ 6.37 (1 H, s), 6.01 (1 H, d, *J* 1.1), 5.96 (1 H, d, *J* 1.1), 4.72 (1 H, symm. m), 3.95 (1 H, s, broad), 3.44 (1 H, dd, *J* 14.8, 1.2), 2.95 (1 H, d, *J* 14.8), 2.90 (1 H, ddd, *J* 11.8, 2.0, 1.2), 2.39 (3 H, s), 2.30 (3 H, s), 2.29 (1 H, dd, *J* 11.8, 2.8). - MS : 253 (27%, M^+), 210 (31%), 45 (100%). - Analysis : calc. for $C_{12}H_{15}NO_3S$ (253.31) C 56.90, H 5.97; found C 57.10, H 5.84%.

N-Methylisoquinolinol **14** was independently prepared from the *N*-unsubstituted compound **10** (0.24 g, 1.0 mmol) to which 1% hydrochloric acid (3 mL) and a 36% aqueous solution (0.10 mL) of formaldehyde (1.3 mmol) were added. After 5 min of heating under reflux, sodium borohydride (50 mg, 2.3 mmol) and, 15 min later, a 40% aqueous solution (1 mL) of sodium hydroxide were added at 25 °C. The precipitate was collected and recrystallized from a 1 : 1 (v/v) mixture of ethyl acetate and hexanes; mp 115 - 116 °C; 0.17 g (67%).

The 1-bromoisoquinolinols **16** and **18** (see below) were prepared as described above for the 1-(methylthio)isoquinolinols **10** and **14**. However, some of the reactions were carried out on a considerably increased scale and some of the intermediate products (such as **17**) were isolated and characterized.

1-Bromo-5,6,7,8-tetrahydro-1,3-dioxolo[4,5-*g*]isoquinolin-8-ol (16) : As described above (see preparation of **10**), 5-bromopiperonal [18] (4.6 g, 20 mmol; prepared from 5-bromo-3,4-dihydroxybenzaldehyde [19]) was consecutively treated with aminoacetaldehyde dimethyl acetal (2.4 mL, 2.3 g, 22 mmol) in methanol (20 mL), sodium borohydride (0.38 g, 10 mmol) and 20% hydrochloric acid (0.10 L) to afford product **16**; mp 178 - 179 °C (from isopropanol); 2.8 g (51%). - ^{1}H-NMR : δ 6.45 (1 H, s), 6.01 (1 H, d, *J* 1.2), 6.00 (1 H, d, *J* 1.2), 4.68 (1 H, s, broad), 3.86 (2 H, symm. m), 3.37 (1 H, d, *J* 13.1), 2.90 (1 H, d, *J* 13.1), 2.39 (2 H, s, broad). - MS : 273 (8%, M^+), 244 (29%), 45 (100%). - Analysis : calc. for $C_{10}H_{10}BrNO_3$ (272.10) C 44.14, H 3.70; found C 44.37, H 3.78%.

1-Bromo-5,6,7,8-tetrahydro-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-8-ol (18) : As described above (see preparation of **10**), 5-bromopiperonal [18] (11.5 g, 50 mmol; prepared from 5-bromo-3,4-dihydroxybenz-

aldehyde [19]) was consecutively treated with methylamine (100 mmol) in 85% aqueous methanol (85 mL) and sodium borohydride (1.9 g, 50 mmol). ***N*-Methyl-5-bromopiperonylamine hydrochloride** precipitated from the acidified solution in ethanol upon addition of diethyl ether; mp 226 - 227 °C (from ethanol); 10.1 g (72%). - ^{1}H-NMR (D_2O) : 7.18 (1 H, d, *J* 1.7), 6.97 (1 H, d, *J* 1.7), 6.13 (2 H, s), 4.16 (2 H, s), 2.73 (3 H, s). - MS : 245 (51%, M^+), 244 (61%, $M^+ - 1$), 215 (100%). - Analysis : calc. for $C_9H_{11}BrClNO_2$ (280.55) C 38.53, H 3.95; found C 38.68, H 4.04%. - Reaction of the free amine, set free from the hydrochloride (5.6 g, 20 mmol) with a 40% aqueous solution of sodium hydroxide, with bromoacetaldehyde diethyl acetal (4.0 mL, 5.1 g, 25 mmol) in the presence of sodium hydrogen carbonate (5.0 g, 60 mmol) at 125 °C afforded the aminoacetal **17** which was purified by distillation; bp 130 - 135 °C/1 mmHg; n_D^{20} 1.5255; 4.7 g (65%). - ^{1}H-NMR : δ 6.95 (1 H, d, *J* 1.6), 6.82 (1 H, d, *J* 1.6), 6.03 (2 H, s), 4.63 (1 H, t, *J* 5.3), 3.65 (2 H, dq, *J* 9.7, 7.0), 3.53 (2 H, dq, *J* 9.2 7.0), 3.45 (2 H, s), 2.57 (2 H, d, *J* 5.3), 2.29 (3 H, s), 1.22 (6 H, t, *J* 7.0). - MS : 361 (1%, M^+), 215 (100%), 103 (60%). - Analysis : calc. for $C_{15}H_{22}BrNO_4$ (360.25) C 50.01, H 6.16; found C 50.08, H 6.09%. - Crude aminoacetal **17** [prepared from 0.10 mol of 5-(methylthio)piperonal] was isolated as described above (see preparation of **14**). Product **18** was obtained as a colorless solid, mp 134 - 135 °C; 13.9 (49% over-all [with respect to 5-(methylthio)piperonal]). - ^{1}H-NMR : δ 6.33 (1 H, s), 6.05 (1 H, d, *J* 1.5), 6.01 (1 H, d, *J* 1.5), 4.67 (1 H, s, broad), 4.00 (1 H, s, broad), 3.48 (1 H, d, *J* 14.8), 3.08 (1 H, dm, *J* 11.8), 3.02 (1 H, d, *J* 14.8), 2.40 (3 H, s), 2.34 (1 H, dd, *J* 11.8, 2.5). - MS : 287 (27%, M^+), 244 (36%, 45 (100%). - Analysis : calc. for $C_{11}H_{12}BrNO_3$ (286.12) C 46.18, H 4.23; found C 46.51, H 4.05%.

The same product was formed when the 1-bromoisoquinolinol **16** (0.27 g, 1.0 mmol) was simultaneously treated with formaldehyde and sodium borohydride in acidic aqueous medium (see above the alternative preparation of **14**, at the end of the paragraph dealing with this compound); mp 134 - 135 °C; 0.20 g (70%).

1,2,3,4-Tetrahydro-2-methyl-5-(trimethylsilyl)isoquinolin-4-ol (20) : 1,2,3,4-Tetrahydro-2-methyl-isoquinolin-4-ol [21] (**19**; 4.1 g, 25 mmol) was added to a solution of *tert*-butyllithium (75 mmol) in diethyl ether (0.15 L) and pentane (50 mL). After being stored 6 h at 25 °C, the mixture was treated with chlorotrimethylsilane (9.5 mL, 8.2 g, 75 mmol) at -25 °C. At 25 °C, it was neutralized with 5% sulfuric acid (approx. 0.10 L) and the aqueous phase extracted with diethyl ether (3 × 0.10 L). The combined organic layers were dried and evaporated. The residue was purified by distillation; mp -49 to -47 °C; bp 108 - 109 °C/0.4 mmHg; n_D^{20} 1.5090; 3.7 g (63%). The slightly orange colored oil was triturated with hydrogen chloride in ethanol. The initially amorphous solid was crystallized from methanol; mp 221 - 224 °C; 4.3 g (63%). - ^{1}H-NMR (D_3COD): δ 7.60 (1 H, d, *J* 7.3), 7.37 (1 H, t, *J* 7.6), 7.22 (1 H, d, *J* 7.3), 5.15 (1 H, t, *J* 2.4), 4.55 (1 H, d, *J* 15.7), 4.34 (1 H, d, *J* 15.7), 3.58 (2 H, s), 3.07 (3 H, s), 0.38 (9 H, s). - ^{13}C-NMR : δ 141.3 (1 C, s), 140.6 (1 C, s), 134.1 (1 C, s), 133.4 (1 C, d, *J* 156.7), 127.5 (1 C, d, *J* 156.1), 126.7 (1 C, d, *J* 157.4), 65.9 (1 C, d, *J* 144.7), 60.5 (1 C, t, *J* 133.8), 58.2 (1 C, t, *J* 133.8), 45.9 (1 C, q, *J* 133.8), 0.8 (3 C, q, *J* 119.4). - MS : 235 (28%, M^+), 234 (29%), 216 (47%), 202 (26%), 177 (100%). - Analysis : calc. for $C_{13}H_{22}ClNOSi$ (271.86) C 57.43, H 8.16; found C 57.45, H 8.22%.

1,2,3,4-Tetrahydro-5-iodo-2-methylisoquinolin-4-ol (21) : Using iodine (19 g, 75 mmol) instead of chlorotrimethylsilane, the hydrochloride of **21** was obtained; mp 199 - 201 °C (from ethanol); 4.8 g (59%). - ^{1}H-NMR (D_3COD) : δ 7.93 (1 H, d, *J* 7.8), 7.28 (1 H, d, *J* 7.8), 7.14 (1 H, t, 7.8), 5.07 (1 H, t, *J* 2.1), 4.54 (1 H, d, *J* 16.0), 4.33 (1 H, d, *J* 16.0), 3.71 (1 H, dt, *J* 12.7, 1.8), 3.53 (1 H, dd, *J* 12.7, 1.8), 3.10 (3 H, s). - MS : 188 (47%, M^+), 270 (100%), 245 (45%). - Analysis : calc. for $C_{10}H_{13}ClINO$ (325.57) C 36.89, H 4.02; found C 36.66, H 4.10%.

5-Formyl-1,2,3,4-tetrahydro-2-methylisoquinolin-4-ol (22) : Applying the same protocol as described for the preparation of product **20**, but replacing chlorotrimethylsilane by *N*,*N*-dimethylformamide (3.8, mL, 3.7 g, 50 mmol), the aldehyde **22** was formed, which was extracted from the ethereal solution with sodium bisulfate and, after decomposition of the adduct with an aqueous solution of sodium hydroxide, collected as a slightly ocherous colored amorphous solid; mp 106 - 108 °C (dec.) 2.45 g (51%). - ^{1}H-NMR : δ 10.20 (1 H, s), 7.76 (1 H, d, *J* 7.6), 7.43 (1 H, t, *J* 7.6), 7.32 (1 H, d, *J* 7.6), 5.16 (1 H, s, broad), 3.82 (1 H, d, *J* 15.3), 3.35 (1 H, d, *J* 15.3), 3.07 (1 H, ddd, *J* 12.1, 3.1, 1.3), 2.62 (1 H, d, *J* 12.1, 3.7), 2.48 (3 H, s). - MS : 192 (6%, $M^+ + 1$), 191 (5%, M^+), 190 (5%), 174 (16%), 119 (100%).

5,6,7,8-Tetrahydro-6-methyl-1-trimethylsilyl-1,3-dioxolo[4,5-*g*]isoquinolin-8-ol (24) : 5,6,7,8-Tetrahydro-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-8-ol [22] (23; 5.2 g, 25 mmol) was added to a solution of butyllithium (75 mmol) in tetrahydrofuran (0.10 L) and hexanes (50 mL). After 6 h at 25 °C, the mixture was treated with chlorotrimethylsilane (9.5 mL, 8.2 g, 75 mmol) and, 1 h later, neutralized with 5% sulfuric acid (approx. 0.10 L). Product **24** was isolated by extraction of the aqueous phase with diethyl ether (3 × 0.10 L), evaporation and distillation; bp 126 - 128 °C/0.4 mmHg; 5.0 g (72%). Trituration of the oil with a solution of hydrogen chloride in ethanol and recrystallization from methanol gave a colorless amorphous solid; mp 220 - 222 °C; 5.7 g (72%). - ^{1}H-NMR (D_3COD) : δ 6.68 (1 H, s), 5.94 (2 H, s), 5.04 (1 H, s, broad), 4.41 (1 H, d, *J* 15.2), 4.23 (1 H, d, *J* 15.2), 3.56 (1 H, d, *J* 12.7), 3.49 (1 H, d, *J* 12.7), 3.04 (3 H, s), 0.41 (9 H, s). - ^{13}C-NMR (D_3COD) : δ 154.8 (1 C, d, *J* 6.6), 148.2 (1 C, s), 131.7 (1 C, s), 123.2 (1 C, q, *J* 4.8), 120.9 (1 C, s), 107.6 (1 C, d, *J* 164.1), 101.9 (1 C, t, *J* 174.3), 64.2 (1 C, dd, *J* 146.6, 4.5), 59.9 (1 C, t, *J* 146.1), 56.4 (1 C, t, *J* 144.9), 44.1 (1 C, q, *J* 143.5), 1.0 (3 C, q, *J* 119.9). - MS : 279 (15%, M^+), 262 (31%, 221 (100%). - Analysis : calc. for $C_{14}H_{22}ClNO_3Si$ (315.87) C 53.24, H 7.02; found C 52.71, H 7.11%.

5,6,7,8-Tetrahydro-1-iodo-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-8-ol (25) : Using iodine (19 g, 75 mmol) instead of chlorotrimethylsilane, product **25** was obtained; mp 123 - 128 °C (dec.); 5.5 g (60%). - ^{1}H-NMR (D_3COD) : δ 6.70 (1 H, s), 6.07 (2 H, s), 5.0 (1 H, m), 4.43 (1 H, d, *J* 15.6), 4.22 (1 H, d, *J* 15.6), 3.66 (1 H, d, *J* 12.7), 3.48 (1 H, d, *J* 12.7), 3.07 (3 H, s). - MS : 333 (29%, M^+), 314 (27%), 290 (100%).

5,6,7,8-Tetrahydro-1,6-dimethyl-1,3-dioxolo[4,5-*g*]isoquinolin-8-ol (26) : Applying the same protocol as specified for the preparation of product **24**, but replacing chlorotrimethylsilane by methyl iodide (3.1 mL, 7.1 g, 50 mmol), derivative **26** was formed. It was isolated by extraction with diethyl ether and distillation. An orange-red colored oil (3.7 g) was collected and converted into the hydrochloride as described; mp 231 - 235 °C (dec.; from ethanol); 4.3 g (66%). - ^{1}H-NMR (D_3COD) : δ 6.55 (1 H, s), 5.97 (2 H, d, *J* 2.5), 5.02 (1 H, s, broad), 4.39 (1 H, *J* 15.6), 4.19 (1 H, d, *J* 15.6), 3.63 (1 H, d, *J* 12.8), 3.45 (1 H, d, *J* 12.8), 3.05 (3 H, s), 2.29 (3 H, s). - MS : 221 (9%, M^+), 202 (68%), 178 (30%), 162 (18%), 86 (100%). - Analysis : calc. for $C_{12}H_{16}ClNO_3$ (257.72) C 55.93, H 6.26; found C 56.08, H 5.98%.

1-Bromo-5,6,7,8-tetrahydro-8-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-8-ol (28) : A solution of the bromoisoquinol **18** (2.9 g, 10 mmol) in methanol (20 mL) containing a small quantity (2 mL) of concentrated hydrochloric acid was heated for 20 h under reflux. The hydrochloride of product **28** was precipitated by addition of diethyl ether (50 mL), collected by filtration and dissolved in water. A sufficient volume (approx. 1 mL) of a 40% aqueous solution of sodium hydroxide was added to make the solution slightly alcaline. Product **28** was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried and evaporated. The residue was triturated with hexanes and crystallized from heptanes; mp 103 - 104 °C; 1.6 g (53%). - ^{1}H-NMR : δ 6.47 (1 H, s), 6.01 (1 H, d, *J* 1.4), 6.00 (1 H, d, *J* 1.4), 4.25 (1 H, symm. m), 3.80 (1 H, d, *J* 14.7), 3.54 (3 H, s), 3.26 (1 H, dm, *J* 12.3), 3.13 (1 H, d, *J* 14.7), 2.48 (3 H, s), 2.27 (1 H, dd, *J* 12.3, 2.2). - MS : 301 (9%, M^+), 271 (36%), 258 (100%). - Analysis : calc. for $C_{12}H_{14}BrNO_3$ (300.15) C 48.02, H 4.70; found C 48.05, H 4.68%.

Acknowledgment: This work was financially supported by the Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung (grants 20-25'577-88 and 20-49'307-96), Bern.

REFERENCES

1. Andreae, S.; *Houben-Weyl : Methoden der organischen Chemie* (ed. : Kreher, R.P.), Vol. *E7a*, pp. 571 - 740, Thieme, Stuttgart, **1991**.
2. Simig, G.; Schlosser, M.; *ACH-Models in Chemistry* **1994**, *131*, 217 - 228.

3. Related cyclization reactions : Späth, E.; Brunner, O.; *Ber. Dtsch. Chem. Ges.* **1924**, *57*, 1243 - 1251; Leonard, N.J.; Herbrandson, H.F.; Van Heyningen, E.M.; *J. Am. Chem. Soc.* **1946**, *68*, 1279 - 1281; Price, C.C.; Jackson, W.G.; *J. Am. Chem. Soc.* **1946**, *68*, 1282 - 1283; Bradford, L.; Elliott, T.J.; Rowe, F.M.; *J. Chem. Soc.* **1947**, 437 - 445; Palmer, M.H.; *J. Chem. Soc.* **1962**, 3645 - 3652; Dey, A.S.; Joullié, M.M.; *J. Heterocycl. Chem.* **1965**, *2*, 113 - 119; Bajwa, G.S.; Joullié, M.M.; *J. Heterocycl. Chem.* **1972**, *9*, 1403 - 1405; Mävers, U.; Berruex, F.; Schlosser, M.; *Tetrahedron* **1996**, *52*, 3223 - 3228; Keller, H.; Schlosser, M.; *Tetrahedron* **1996**, *52*, 4637 - 4644.
4. Simig, G.; Schlosser, M.; *Tetrahedron Lett.* **1990**, *31*, 3125 - 3128.
5. Chemistry and bioactivity of isoquinolines : Grethe, G. (ed.); *Isoquinolines, Part One*, Wiley, New York, **1981**; Kathawala, F.G.; Coppola, G.M.; Schuster, H.F. (eds.); *Isoquinolines, Part Two*, Wiley, New York, **1990**.
6. Bobbitt, J.M.; Roy, D.N.; Marchand, A.; Allen, C.W.; *J. Org. Chem.* **1967**, *32*, 2225 - 2227; Bobbitt, J.M.; Sih, J.C.; *J. Org. Chem.* **1968**, 33, 856 - 858.
7. Bobbitt, J.M.; *Adv. Heterocycl. Chem.* **1973**, *15*, 99 - 136.
8. Simig, G.; Schlosser, M.; *Synlett* **1990**, 50 - 51.
9. Gilman, H.; Brown, G.E.; Webb, F.J.; Spatz, S.M.; *J. Am. Chem. Soc.* **1940**, *62*, 977 - 979; s.a. : Gilman, H.; Morton, J.W.; *Org. React.* **1954**, *8*, 258 - 304, spec. 282.
10. House, H.O.; Bare, T.M.; Hanners, W.E.; *J. Org. Chem.* **1969**, *34*, 2209 - 2217; House, H.O.; Strickland, R.C.; Zaiko, E.J.; *J. Org. Chem.* **1976**, *41*, 2401 - 2408.
11. Uemura, M.; Tokuyaman, S.; Sakan, T.; *Chem. Lett.* **1975**, 1195 - 1198.
12. Meyer, N.; Seebach, D.; *Angew. Chem.* **1978**, *90*, 553 - 554; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 521 - 522; *Chem. Ber.* **1980**, *113*, 1304 - 1319.
13. Orito, K.; Miyazawa, M.; Suginome, H.; *Tetrahedron* 1995, 51, 2489 - 2496.
14. Simig, G.; Schlosser, M.; *Tetrahedron Lett.* **1994**, *35*, 3081 - 3082.
15. For an analogy, see : Barlet, R.; *Tetrahedron Lett.* **1976**, *17*, 4171 - 4174.
16. Ziegler, K.; Crössmann, F.; Kleinert, H.; Schäfer, O.; *Liebigs Ann. Chem.* **1929**, *473*, 1 - 35, spec. 20; Metzger, H.; Müller, E.; in *Houben-Weyl : Methoden der organischen Chemie* (ed. Müller, E.), Thieme, Stuttgart, **1959**, *Vol. 1/2*, pp. 337 - 338.
17. Ziegler, F.E.; Fowler, K.W.; *J. Org. Chem.* **1976**, *41*, 1564 - 1566.
18. Tomita, M.; Aoyagi, Y.; *Chem. Pharm. Bull.* **1968**, *16*, 523 - 526.
19. Erne, M.; Ramirez, F.; *Helv. Chim. Acta* **1950**, *33*, 912 - 916.
20. Jacob, P.; Shulgin, A.T.; *Synth. Commun.* **1981**, *11*, 969 - 977.
21. Blagg, J.; Coote, S.J.; Davies, S.G.; Mobbs, B.E.; *J. Chem. Soc., Perkin Trans. 1* **1986**, 2257 - 2261.
22. Obtained by acid catalyzed cyclization [8] of *N*-2,2-diethoxyethyl-*N*-methylbenzylamine (prepared from piperonal, methylamine, sodium borohydride and bromoacetaldehyde diethyl acetal according to a general method [8]): mp 106 - 108 °C (dec.).