New Approaches to 6-Oxoisoaporphine and Tetrahydroisoquinoline Derivatives

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2,3-Dihydro-6-hydroxy-5-methoxy-7*H*-dibenzo[*de*,*h*]quinolin-7-one, 6-hydroxy-5-methoxy-7*H*-dibenzo[*de*,*h*]quinolin-7-one, and 2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)benzyl benzoate, easily available by a *Bischler–Napieralski* cyclization, were used as starting materials to afford 6-oxoisoaporphine and 2,3-dimethoxy-5,6,8,12b-tetrahydroisoindolo[1,2-*a*]isoquinoline as the main products. However, the catalytic hydrogenation of the benzyl benzoate derivative afforded, under mild conditions, 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(2-methylphenyl)isoquinoline.

Introduction. – Oxoisoaporphines (=7*H*-dibenzo[*de*,*h*]quinolin-7-ones) are a family of oxoisoquinoline-derived alkaloids that have been isolated from *Menispermum dauricum* DC. (Menispermaceae) as the sole known natural source [1]. In traditional chinese medicine, these isoquinoline alkaloids, present in small quantities in rhizomes of the plants, have been used as analgesic, antipyretic, and with some cytotoxic activity [2–4], whilst the isolation and reactivity studies are difficult to be carried out. However, compounds with the same skeleton, known as azabenzanthrones, had been synthesized earlier due to their possible photo- and electrochemical properties [5] and as dyes [6]. Later, the synthesis of 7*H*-dibenzo[*de*,*h*]quinolin-7-one derivatives through the cyclization of *N*-(2-phenylethyl)phthalimides afforded a new way to these compounds [7]. In addition, some authors reported the synthesis of 2,3-dihydro-oxoisoaporphine derivatives by cyclization of 3-{[(*β*-(dialkoxyaryl)ethyl]-amino}phthalides with polyphosphoric acid (PPA) [8]. Later, study of the synthesis and reactivity of these alkaloids with different substitution patterns on their isoquinoline skeleton led to several derivatives by means of metals and catalytic hydrogenation [9]. In this sense, the reactivity of some oxoisoaporphine derivatives with PtO_2 showed an unexpected keto–enol tautomerism and a later formation of the C=O group at C(6), without evidence of a partial or complete hydrogenation of the aromatic system.

On the other hand, the major availability of this type of oxoisoaporphines allowed studying its photoreduction, affording the unexpected formation of 1-(diethylamino)-

butadiene, when triethylamine Et_3N was used as the electron donor under anaerobic conditions [10].

Therefore, a further understanding of the reactivity of these compounds and the possibility to obtain them by means of convenient synthetic routes will help us to study their pharmacology and possible therapeutic use.

Here, we report the electrophilic behavior of 2,3-dihydro-6-hydroxy-5-methoxy- and 6-hydroxy-5-methoxy-7*H*-dibenzo[*de*,*h*]quinolin-7-one (**1** and **2**, resp.) in the presence of reducing agents, and the synthesis of 2-(3,4-dihydro-6,7-dimethoxyisoquinolin-1-yl)benzyl benzoate (**3**) by a *Bischler–Napieralski* (*BN*) condensation between homoveratrylamine (HV) and 2-(chlorocarbonyl)benzyl benzoate. The latter has been used as a novel starting material for diverse studies of intramolecular cyclizations under acidic conditions. Thus, 5-methoxy-6*H*-dibenzo[*de*,*h*]quinolin-6-one (**4**), 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(2-methylphenyl)isoquinoline (**6**), and 5,6,8,12b-tetrahydro-2,3-dimethoxyisoindolo[1,2-*a*]isoquinoline (**7**) were isolated in good yields as the main products.

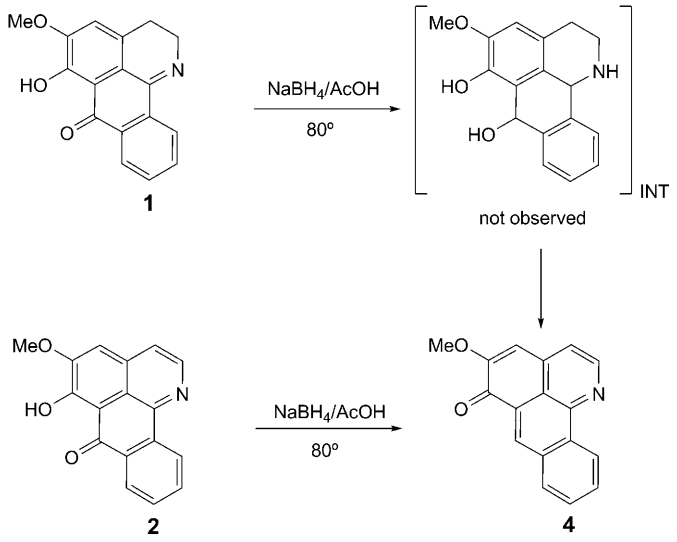
Results and Discussion. – In agreement with the catalytic hydrogenation of 2,3-dihydro- and oxoisoaporphine derivatives [9], treatment of 6-hydroxy-5-methoxy-7*H*-dibenzo[*de*,*h*]quinolin-7-one (**2**) with PtO_2 in AcOH afforded **4** as the main product in a poor yield. Despite the use of other catalysts and solvents, such as Pd/C and toluene, respectively, the mentioned oxoisoaporphine was not generated, and the starting material was recovered. It is possible that 2,3-dihydro-6-hydroxy-5-methoxyoxoisoaporphine (**1**) and its aromatic derivative **2**, when treated with reducing reagents as hydride donors, could form a major proportion of **4** using solvents of different polarity.

Thus, **1** and **2** were treated with $LiAlH_4$ and $NaBH_4$ in solvents such as MeOH, EtOH, and THF from room temperature up to reflux. Nevertheless, there was no reaction, leading to the formation of the secondary amine and/or alcohol, observed (^{1}H-NMR spectroscopy of the crude reaction mixture), and the starting material was entirely recovered. Although the use of $NaBH_4$ in AcOH at room temperature afforded the same result, surprisingly **4** was generated in high yield without evidence of a possible carbinolamine intermediate (INT) from **1**, when the temperature of the solution of **1** and **2** was raised to 80° (*Scheme 1*).

These experimental findings indicated that, prior to hydride uptake, obviously, protonation of the C=O group at C(7) has to take place, leading to an intermediate with two OH groups at C(6) and C(7). The formation of a C=O group at C(6) and the concomitant generation of the aromatic system on ring *C* are rapid steps without allowing demethylation of the MeO group.

On the other hand, the search for synthetic templates that generate the oxoisoaporphine skeleton of **4**, has led us to study the synthesis of 1-benzylisoquinoline systems that, substituted with a (benzoyloxy)methyl moiety at C(2′), could generate **4** by an acid-catalyzed intramolecular cyclization easily and without the formation of side products. The use of acidic conditions will allow us to study the reaction rate and regioselectivity that, according to the influence of electron-donating substituents such as MeO on ring *B* of the 1-benzylisoquinoline skeleton, would steer the formation of 2,3-dihydro-7*H*-dibenzo[*de*,*h*]quinoline (**C**), which, for a later oxidation of ring *A*, would afford the oxoisoaporphine derivatives.

Scheme 1. *Synthesis of 5-Methoxy-6*H*-dibenzo[*de,h*]quinolin-6-one* (**4**) *from Oxoisoaporphines* **1** *and* **2**



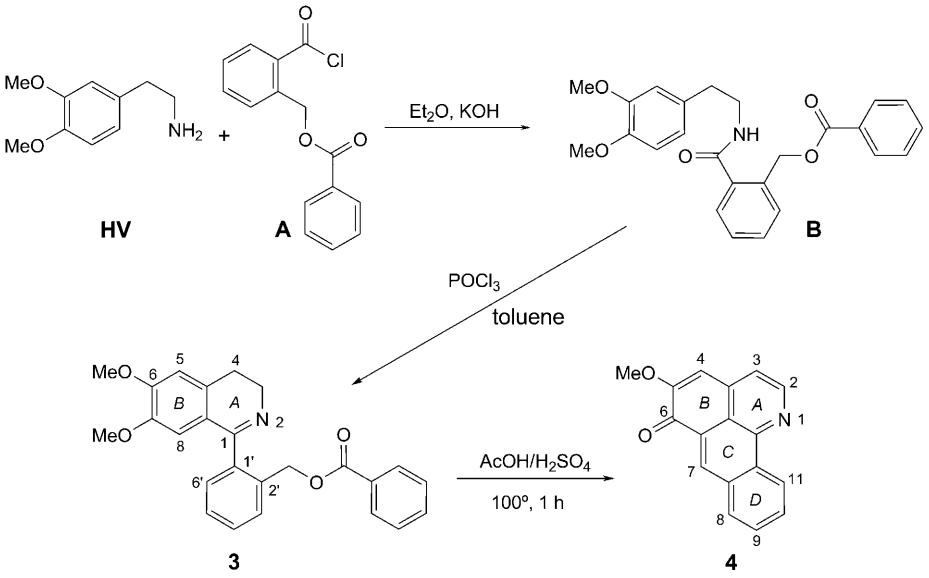
In this sense, the synthesis of 2-(3,4-dihydro-6,7-dimethoxyisoquinolin-1-yl)benzyl benzoate (**3**) was carried out by condensation of the commercially available 2-(chlorocarbonyl)benzyl benzoate (**A**) and 2-(3,4-dimethoxyphenyl)ethylamine (homoveratrylamine; **HV**). The isolated 2-({[2-(3,4-dimethoxyphenyl)ethyl]amino}carbonyl)benzyl benzoate (**B**) was, without purification, treated under the conditions of the *Bischler–Napieralski* reaction to give the desired product in excellent yield.

Thus, **3** was treated under acidic conditions to allow the cyclization at C(8) of the 1-benzylisoquinoline skeleton to afford the required oxoisoaporphine (*Scheme 2*). However, treatment of **3** by warming a sample with CF_3COOH (TFA) and polyphosphoric acid (PPA) between 80–100° did not give the expected result, and the starting material was recovered. Finally, by using a 5 : 1 mixture of $AcOH/H_2SO_4$, it was possible to obtain a compound that, purified by column chromatography on silica gel, turned out to be **4**. This result was confirmed by NMR spectroscopy [11] and now also by an X-ray diffraction analysis (*Scheme 2*).

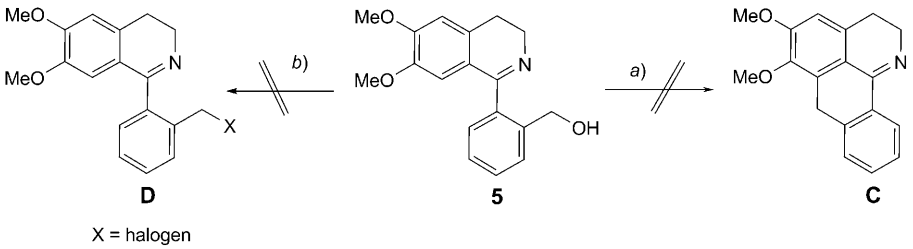
In agreement with these results, the formation of the oxoisoaporphine derivative **4** would be the result of a previous demethylation of MeO–C(7) of the 1-benzylisoquinoline skeleton of **3**, probably due to steric hindrance with regard to MeO–C(6) and concomitant oxidation of the ring *A*. Thereafter, the oxidation of HO–C(7) would regenerate the C=O group, which becomes the driving force for the cyclization and the formation of ring *C* of the oxoisoaporphine. This type of mechanism has been described for the synthesis of other oxoisoaporphine derivatives with a variable number of MeO groups at the quinoline framework [12].

To confirm the reactivity of the intermediate **3** under acidic conditions, the cyclization of the corresponding benzylic alcohol was studied. Thus, the benzyl benzoate **3** was hydrolyzed in MeOH with K_2CO_3 to give [2-(3,4-dihydro-6,7-dimethoxyisoquinolin-1-yl)phenyl]methanol (**5**) in good yield (*Scheme 3*). Its cycliza-

Scheme 2. *Synthesis of 2-(3,4-Dihydro-6,7-dimethoxyisoquinolin-1-yl)benzyl Benzoate* (**3**) *and 5-Methoxy-6*H*-dibenzo[*de,h*]quinolin-6-one* (**4**)



Scheme 3. *Reactivity of* **5** *under Acidic Conditions and with Halogen Reagents*



a) CF_3COOH (TFA) or polyphosphoric acid (PPA) $AcOH/H_2SO_4$, 100°, 1 h. *b*) $MeSO_3H$/NaI/MeCN or 1*H*-imidazole/I_2/PPh_3 THF or CBr_4/PPh_3/CH_2Cl_2.

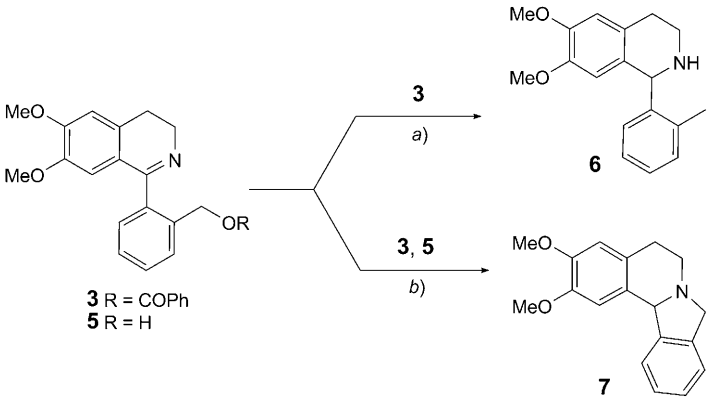
tion was tried in $AcOH/H_2SO_4$, TFA, and PPA under the same temperatures mentioned previously. However, **5** was recovered without evidence (^{1}H-NMR) of the formation of 5,6-dimethoxy-2,3-dihydro-7*H*-dibenzo[*de*,*h*]quinoline (**C**) or of the oxoisoaporphine **4**.

The lack of the reactivity of the benzylic CH_2OH group in **5**, to afford by acid cyclization the oxoisoaporphine **4**, can be explained partly by the stability of the leaving group. In case of **3**, benzoic acid, in contrast to H_2O, is a better leaving group for the intramolecular cyclization between C(8) and the benzylic C-atom. Therefore, we tried to replace the benzylic OH group of **5** by a better leaving group such as halogen for the intramolecular cyclization. In the literature, there is a wide spectrum of synthetic possibilities for the conversion of benzylic alcohols to the corresponding halogenides

[13]. Indeed, we studied three different routes using $MeSO_3H$/NaI/MeCN [14], 1*H*-imidazole/I_2/PPh_3/THF [15], and CBr_4/PPh_3/CH_2Cl_2 [16]. However, with none of them we achieved a replacement of the OH group leading to the formation of the halogenated derivative (**D**). Solely the starting material and various polar products, which are difficult to separate were recovered.

In view of this dilemma of reactivity, a synthetic route was studied to obtain the secondary amine from **3** without affecting the 2-[(benzoyloxy)methyl] group so that, as soon as the quaternary salt is formed under acidic conditions, we could carry out the same cyclization that afforded **4**, but maintaining the tetrahydroisoquinoline system. Thus, **3** was hydrogenated in EtOH with Pd/C. Unexpectedly, 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(2-methylphenyl)isoquinoline (**6**) was formed quantitatively under these conditions (*Scheme 4*).

Scheme 4. *Conversion of the Intermediate* **3** *and* **5** *into 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2-methylphenyl)isoquinoline* (**6**), *and 5,6,8,12b-Tetrahydro-2,3-dimethoxyisoindolo[1,2-a]isoquinoline* (**7**) *under Hydrogenation and Reducing Conditions*



a) H_2/Pd-C/EtOH. *b*) $NaBH_4$/MeOH.

Finally, based on these new and unexpected results, the reactivity of the dihydroisoquinoline intermediates **3** and **5** was studied with regard to the reduction with $NaBH_4$/MeOH and thereby obtaining **C** and later the oxoisoaporphine. However, in both cases, 5,6,8,12b-tetrahydro-2,3-dimethoxyisoindolo[1,2-*a*]isoquinoline (**7**) was formed in high yield as the main product (*Scheme 4*; see also [17] for further information).

*Crystal Structure of 5-Methoxy-6*H*-dibenzo[*de,h*]quinolin-6-one* (**4**). The compound was recrystallized from MeOH to afford crystals suitable for X-ray diffraction studies. Compound **4** crystallizes in the centro-symmetric space group $P2_1/c$ with one molecule per asymmetric unit. The ORTEP [18] view of the molecule, with the atomic numbering scheme, is given in the *Figure*.

The molecule of **4** is largely planar with the MeO group almost coplanar with the aromatic ring *B*. The bond length of the C=O group at C(6) [C(1)–O(1a)] of 1.224 Å is similar to that of the studied oxoisoaporphine derivatives [19].

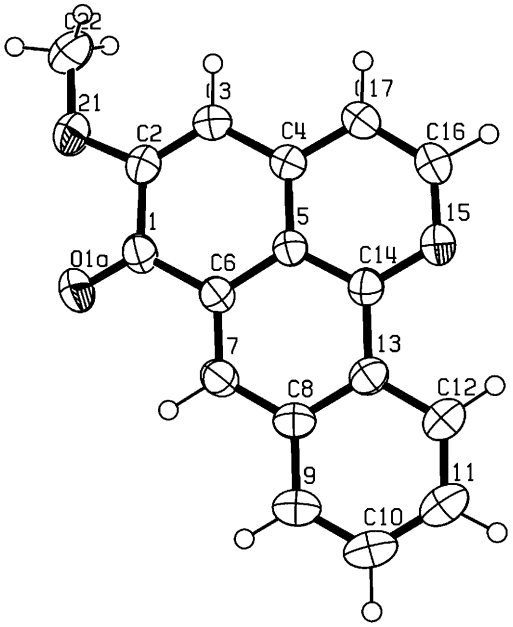


Figure. *ORTEP* [18] *drawing of the molecular structure of* **4** *indicating atom numbering.* Thermal ellipsoids represent 50% probabilities.

Conclusions. – It is noteworthy to emphasize that the reaction of the 2,3-dihydro-6-hydroxy-5-methoxy- and 6-hydroxy-5-methoxy-7*H*-dibenzo[*de,h*]quinolin-7-one (**1** and **2**, resp.) with reducing agents such as $NaBH_4$, as well as the use of **3** and **5** as intermediates for the formation of 6-oxoisoaporphine **4** and some isoquinoline derivatives, allowed us to determine the experimental conditions under which oxoisoaporphine compounds, which are not accessible under reductive and acidic intramolecular cyclization conditions, are generated. These findings could be used and applied to other alkaloids as oxoaporphines or similar imino-quinones to obtain other quinone derivatives as main products.

Experimental Part

General. The commercial reagents were used without purification. The utilized solvents were dried by means of distillation under N_2 or Ar, using the following reagents: Na/benzophenone, for Et_2O, toluene, and THF; and CaH_2 for MeOH, EtOH, CH_2Cl_2, and MeCN. The catalytic hydrogenation was carried out in a *Parr* shaker hydrogenator using 100-ml bottles. The purification and separation of the products were carried out by means of low-pressure column chromatography (CC), using silica gel *60* (SiO_2; 230–400 mesh; *Merck*). M.p.: *Kofler Reichert–Jung Galen III* apparatus; uncorrected. IR Spectra: *Perkin–Elmer Paragon 1000 FT-IR* spectrometer at the University of Santiago de Compostela. The ^{1}H- and ^{13}C-NMR spectra: at r.t., with a *Bruker AMX 300* MHz spectrometer at 300 MHz (^{1}H) and 75.5 MHz (^{13}C); $CDCl_3$, unless otherwise specified, as solvent containing TMS as an internal standard. HR-MS: *Micromass Autospec-Q* spectrometer. Elemental analyses: *Fisons EA 1108* analyzer with sulfanilamide and coal for the calibration.

2-(3,4-Dihydro-6,7-dimethoxyisoquinolin-1-yl)benzyl benzoate (**3**). To a stirred soln. of *2-(3,4-dimethoxyphenylethyl)amine* (**HV**; 2.0 ml, 17 mmol) in cold Et_2O (150 ml) was added dropwise a 10% aq. soln. of KOH (250 ml) at 0–5°. Then, *2-(chlorocarbonyl)benzyl benzoate* (**A**; 4.6 g, 17 mmol) was slowly added during 15 min. The formed precipitate was filtered off and dissolved in CH_2Cl_2. The CH_2Cl_2 layer was washed with 10% aq. HCl and H_2O, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue by CC ($CHCl_3$/20% MeOH) gave 6.9 g (98%) of the respective *2-({[2-(3,4-dimethoxyphenyl)ethyl]amino}carbonyl)benzyl benzoate* (**B**), recrystallized from cyclohexane as white needles.

Compound **B** (6.2 g, 14 mmol) was heated with $POCl_3$ (30 ml) in dry toluene (30 ml) at 120° for 3 h. The solvent and the excess reagent were removed by evaporation *in vacuo*, and the residue was decomposed by adding MeOH and 10% aq. HCl. The acidic soln. was washed once with Et_2O, made alkaline with 10% aq. NH_4OH, and extracted with CH_2Cl_2. The extract was washed with H_2O, dried, and the solvent was evaporated. The residue was purified by CC ($CHCl_3$/20% MeOH). Recrystallization from cyclohexane gave 4.6 g (78%) of **3** as light green needles.

Data of **B**. M.p. 99–100°. IR (KBr): 1719 (C=O), 1636 (C=O). ^{1}H-NMR: 2.88 (*t*, *J* = 7.1, CH_2); 3.72 (*t*, *J* = 6.6, CH_2); 3.83 (*s*, MeO); 3.84 (*s*, MeO); 5.51 (*s*, CH_2); 6.77–6.80 (*m*, 3 arom. H); 7.44–7.48 (*m*, 7 arom. H); 8.04 (*d*, *J* = 7.2, 2 arom. H). ^{13}C-NMR: 31.2 (CH_2); 41.4 (CH_2); 56.1 (MeO); 56.1 (MeO); 64.8 (CH_2); 111.7 (CH); 112.2 (CH); 121.0 (CH); 127.7 (C); 127.8 (CH); 128.7 (CH); 128.8 (2 CH); 129.5 (CH); 130.0 (CH); 130.3 (C); 130.7 (CH); 131.1 (C); 131.6 (C); 133.5 (CH); 136.4 (CH); 149.4 (C–O); 151.4 (C–O); 166.6 (C=O); 167.7 (C=O). Anal. calc. for $C_{25}H_{25}NO_5$: C 71.58, H 6.01, N 3.34; found: C 71.43, H 5.68, N 3.29.

Data of **3**. M.p. 121–123°. IR (KBr): 1715 (C=O). ^{1}H-NMR: 2.73 (*t*, *J* = 7.63, CH_2); 3.56 (*s*, MeO); 3.84 (*t*, *J* = 7.80, CH_2); 3.90 (*s*, MeO); 5.39 (*s*, CH_2); 6.47 (*s*, 1 arom. H); 6.68 (*s*, 1 arom. H); 7.32–7.35 (*m*, 3 arom. H); 7.46–7.49 (*m*, 3 arom. H); 7.58–7.60 (*m*, 1 arom. H); 7.86–7.89 (*m*, 2 arom. H). ^{13}C-NMR: 25.5 (CH_2); 47.6 (CH_2); 55.9 (2 MeO); 64.7 (CH_2); 110.2 (CH); 111.0 (CH); 122.3 (C); 128.1 (C); 128.1 (2 CH); 128.6 (C); 128.9 (CH); 129.4 (CH); 129.4 (2 CH); 129.8 (C); 131.3 (C); 132.8 (CH); 134.4 (CH); 139.0 (CH); 147.3 (C–O); 151.1 (C–O); 166.0 (C); 166.3 (C=O). HR-EI-MS: 401.16168 ($C_{25}H_{23}NO_4$; calc. 401.4664). Anal. calc. for $C_{25}H_{23}NO_4$: C 74.80, H 5.77, N 3.49; found: C 74.62, H 5.77, N 3.41.

*5-Methoxy-6*H*-dibenzo*[de,h]*quinolin-6-one* (**4**) [9]. To a soln. of **3** (1.0 g, 2.49 mmol) in AcOH (30 ml) was added dropwise 97% H_2SO_4 soln. (10 ml), and the soln. was heated with stirring at 100° for 1 h. Then, the org. residue was diluted with H_2O, neutralized with NH_4OH, and extracted with CH_2Cl_2. The extracts were then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by CC (hexane/AcOEt 1:4 (*v*/*v*)), and then recrystallized from MeOH to afford **4** (147 mg, 22%). Brownish-yellow needles.

Synthesis of **4** *from* **1**. To a soln. of **1** (152 mg, 0.57 mmol) in AcOH (20 ml) was added $NaBH_4$ (110 mg, 2.90 mmol) with stirring at 80° for 1 h. After cooling, the mixture was poured into ice-water (100 ml), the pH was adjusted with NH_4OH, the mixture was extracted with CH_2Cl_2, dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. The residue was purified by CC (hexane/AcOEt (5%)) to give 83 mg (59%) of **4**.

Synthesis of **4** *from* **2**. To a soln. of **2** (200 mg, 0.70 mmol) in AcOH (30 ml) was added $NaBH_4$ (200 mg, 5.30 mmol) with stirring at 80° for 1 h. After cooling, the mixture was poured into ice-water (100 ml), the pH was adjusted with NH_4OH, the mixture was extracted with CH_2Cl_2, dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. The residue was purified by CC (hexane/AcOEt 1:4 (*v*/*v*)) to give 162 mg (86%) of **4**.

X-Ray Crystal-Structure Analysis of Compound **4**[1]). Data were collected on an *Enraf–Nonius TURBOCAD4*, using Cu radiation (λ 1.54184) and were corrected for polarization effects. The structure was solved by direct methods using SIR-97 [20] and refined using SHELXL-97 [21] within the WinGX suite of programs [22]. Non-H-atoms were refined anisotropically, and H-atoms were identified from the

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[1]) CCDC-643378 contains the supplementary crystallographic data of **4**. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif, or by e-mail: deposit@ccdc.cam.ac.uk, or by contacting the *Cambridge Crystallographic Data Centre*, 12, Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336033.

difference map and allowed to refine freely. The crystal data and refinement parameters are summarized in the *Table*.

Table. *Crystallographic Data of* **4**

Empirical formula	$C_{17}H_{11}NO_2$
Formula weight	261.27
Crystal dimensions	$0.44 \times 0.15 \times 0.12$ mm^3
Temp.	293(2) K
Crystal system	monoclinic
Space group	$P2_1/c$
Wavelength	1.54184 Å
Unit cell parameters	
a [Å]	12.7085(6)
b [Å]	13.0859(9)
c [Å]	7.4080(5)
β [°]	92.174(4)
V [Å^3]	1231.08(13)
Z	4
$F(000)$	544
D_x	1.410 g cm^{-3}
$\mu(\mathrm{Mo}K_\alpha)$	0.753 mm^{-1}
θ Range for data collection	3.48 to 74.87°.
Index ranges	$-15 \le h \le 15$, $-16 \le k \le 0$, $0 \le l \le 9$
Reflections collected	2729
Independent reflections	2526 [$R_{int} = 0.0170$]
Completeness to $\theta = 74.87°$	99.8%
Absorption correction	Ψ-scan
Max. and min. transmission	0.9151 and 0.7330
Refinement method	Full-matrix least-squares on F^2
Data; restraints; parameters	2526; 0; 226
Goodness-of-fit on F^2	1.028
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0391$, $wR2 = 0.1076$
R indices (all data)	$R1 = 0.0624$, $wR2 = 0.1182$
Extinction coefficient	0.0022(4)
Largest diff. peak and hole	0.265 and -0.141 e Å^{-3}

[2-(3,4-Dihydro-6,7-dimethoxyisoquinolin-1-yl)phenyl]methanol (**5**). To a stirred soln. of **3** (1.0 g, 2.51 mmol) in MeOH (30 ml) was added K_2CO_3 (550 mg, 3.97 mmol) at r.t., and stirring was continued for 2 h. The mixture was poured into ice-water (100 ml), the pH was adjusted with glacial AcOH, and the mixture was extracted with CH_2Cl_2, dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. The residue was purified by recrystallization from hexane to give **5** (560 mg, 75%). Yellow needles.

Data of **5**. M.p. 129–132°. IR (KBr): 3154 (OH). ^{1}H-NMR: 2.75 (*t*, J = 7.4, CH_2); 3.70 (*s*, MeO); 3.85–3.87 (*m*, CH_2); 3.95 (*s*, MeO); 4.5 (*s*, CH_2); 6.65 (*s*, 1 arom. H); 6.80 (*s*, 1 arom. H); 7.35–7.40 (*m*, 4 arom. H). ^{13}C-NMR: 26.1 (CH_2); 47.2 (CH_2); 56.4 (MeO); 56.5 (MeO); 65.0 (CH_2); 110.6 (CH); 112.3 (CH); 127.3 (2 CH); 129.9 (2 CH); 130.1 (C); 130.5 (C); 131.3 (C); 132.9 (C); 141.9 (C–O); 147.6 (C–O); 166.1 (C). HR-EI-MS: 297.13763 ($C_{18}H_{19}NO_3^+$; calc. 297.3570). Anal. calc. for $C_{18}H_{19}NO_3$: C 72.71, H 6.44, N 4.71; found: C 72.22, H 6.44, N 4.59.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2-methylphenyl)isoquinoline (**6**). A soln. of **3** (2.6 g, 6.53 mmol) in EtOH (100 ml) was hydrogenated at r.t. in the presence of 10% Pd/C (400 mg) for 24 h at 60 psi. The suspension was filtered, and the filtrate was diluted with H_2O (100 ml), made alkaline with 10% aq. NH_4OH, and extracted with $CHCl_3$. The extracted materials were dried (Na_2SO_4), and the

solvent was evaporated. The residual crude product was purified by CC ($CHCl_3$/10% MeOH) to give **6** (1.8 g, 100%). Brownish amorphous solid.

For further characterization, **6** was transformed into the HCl salt. Thus, 670 mg of **6**·HCl (2.36 mmol) were dissolved in 50 ml of hot i-PrOH, and 37% HCl (0.2 ml) was added. The resulting product was precipitated with EtO_2 to give **6**·HCl (268 mg, 35%). White needles.

Data of **6**. M.p. 264° (dec.). ^{1}H-NMR ((D_6)DMSO): 2.55 (*s*, Me); 3.01–3.03 (*m*, 1 H of CH_2); 3.33–3.36 (*m*, 3 H of 2 CH_2); 3.47 (*s*, MeO); 3.77 (*s*, MeO); 5.78 (*s*, CH); 6.15 (*s*, 1 arom. H); 6.88 (*s*, 1 arom. H); 7.05 (*d*, $J = 7.7$, 1 arom. H); 7.22–7.24 (*m*, 1 arom. H); 7.32–7.35 (*m*, 2 arom. H). ^{13}C-NMR ((D_6)DMSO): 19.8 (Me); 24.9 (CH_2); 39.1 (CH_2); 54.6 (CH); 55.9 (2 MeO); 111.0 (CH); 111.9 (CH); 124.4 (C); 125.5 (C); 126.7 (CH); 129.5 (CH); 130.4 (CH); 131.2 (CH); 136.0 (C); 138.2 (C); 148.0 (C–O); 148.9 (C–O).

*5,6,8,12b-Tetrahydro-2,3-dimethoxyisoindolo[1,2-*a*]isoquinoline* (**7**). Treatment of a suspension of **5** (910 mg, 3.06 mmol) in MeOH (60 ml) with an excess of $NaBH_4$ (5 g) in an ice-water bath resulted in effervescence and dissolution of the material. The soln. was diluted with H_2O (100 ml), and its pH was adjusted to 8–9 with aq. AcOH. Finally, the mixture was extracted with CH_2Cl_2, the residue was dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. The residue was purified by CC (CH_2Cl_2/5% MeOH) to give **7** (780 mg, 90%). Brownish amorphous solid.

Synthesis of **7** *from* **3**. The addition of an excess of $NaBH_4$ (5 g) to a suspension of **3** (752 mg, 1.87 mmol) in MeOH (60 ml), kept in an ice-water bath, resulted in effervescence and dissolution of the material. The soln. was diluted with H_2O (100 ml), and its pH was adjusted to 8–9 with aq. AcOH. Finally, the mixture was extracted with CH_2Cl_2, the residue was dried (Na_2SO_4), and the solvent evaporated *in vacuo*. The residue was purified by CC (CH_2Cl_2/5% MeOH) to give **7** (480 mg, 91%). Brownish amorphous solid.

Data of **7**. M.p. 138–140°. ^{1}H-NMR: 2.76–2.79 (*m*, 1 H of CH_2); 3.01–3.17 (*m*, 3 H of 2 CH_2); 3.61 (*s*, MeO); 3.87 (*s*, MeO); 4.30–4.35 (*m*, CH_2); 5.30 (*s*, CH); 6.22 (*s*, 1 arom. H); 6.65 (*s*, 1 arom. H); 7.10–7.13 (*m*, 1 arom. H); 7.28–7.33 (*m*, 3 arom. H). ^{13}C-NMR: 28.1 (2 CH_2); 55.82 (2 MeO); 64.4 (CH); 110.0 (CH); 111.4 (CH); 127.1 (CH); 127.6 (CH); 128.0 (CH); 128.3 (CH); 130.8 (C); 131.0 (C); 141.4 (C); 141.5 (C); 147.4 (C–O); 147.9 (C–O).

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