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Synthesis of 7-Substituted Dehydronoraporphines, with some Biogenetic Considerations

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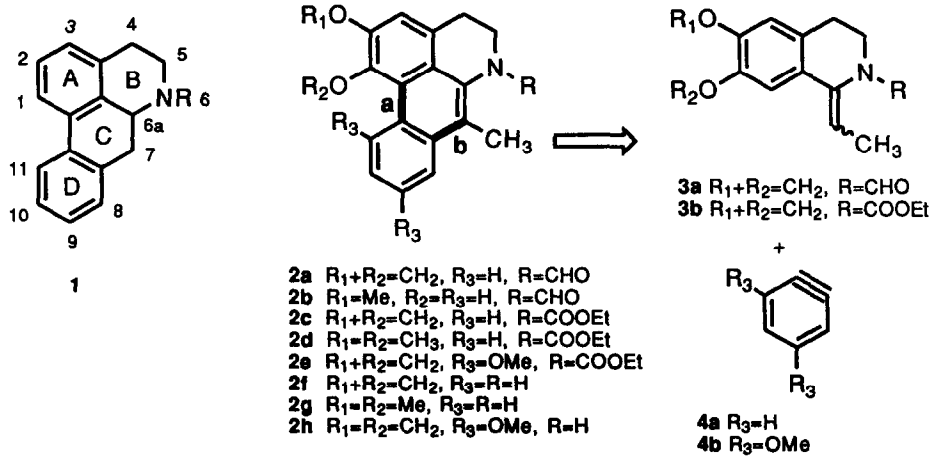
Abstract: N-protected 7-methyl-6a,7-dehydronoraporphines were synthesized by the intermolecular benzyne cycloaddition approach. During basic hydrolysis of the N-protecting group, oxidation of these compounds by oxygen led to guacoline and other 7-hydroxy-7-methyl-6,6a-dehydronoraporphines in what may be a biomimetic process.

The aporphinoids are a group of isoquinoline alkaloids characterized by the structure **1**; more than 300 are known.[1] A subgroup of these alkaloids of growing importance comprises the 7-substituted aporphinoids, a great number of which have been isolated in recent years.[2] Since these are largely minor alkaloids, the quantities isolated have been very small, so that dubious spectroscopic characterization have often been reported and their pharmacology and biogenesis remain unknown. If larger amounts of these compounds were made available, the paucity of reliable data regarding them could be redressed.

Although synthetic routes to a variety of aporphinoids are known,[3] we considered that for convenient synthesis of a range of examples, a more convergent procedure would be necessary.



1

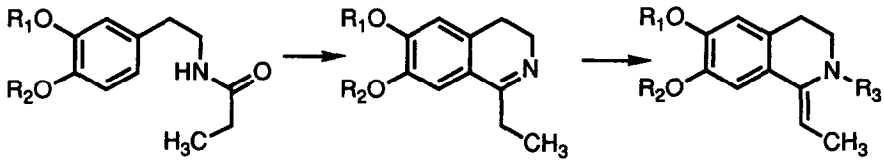
2a $R_1+R_2=CH_2$, $R_3=H$, R=CHO
2b $R_1=Me$, $R_2=R_3=H$, R=CHO
2c $R_1+R_2=CH_2$, $R_3=H$, R=COOEt
2d $R_1=R_2=CH_3$, $R_3=H$, R=COOEt
2e $R_1+R_2=CH_2$, $R_3=OMe$, R=COOEt
2f $R_1+R_2=CH_2$, $R_3=R=H$
2g $R_1=R_2=Me$, $R_3=R=H$
2h $R_1=R_2=CH_2$, $R_3=OMe$, R=H

Figure 1

The intermolecular benzyne cycloaddition (IBC) approach is a simple and convergent method that has proved to be useful for the synthesis of protoberberines[4], benzophenanthridines[5] and aporphinoids such as dehydroaporphines[6], noraporphines[6], 7-oxoaporphines[6] and 4,5-dioxoaporphines[6]. In this work we applied the IBC approach to the synthesis of 7-substituted aporphinoids.[7]

Structures **2a** and **2b** (Fig. 1), respectively attributed to the alkaloids trichoguattine (from *Guatteria trichostemonn*)[8] and duguespixine (from *Duguetia spixiana*)[9], were our initial synthetic targets because we had observed some discrepancies between the reported spectroscopic data and those of related compounds. For example, the UV spectra of trichoguattine and duguespixine (λ_{max} = 430 nm) are quite different from that of 6-ethoxycarbonyl-7-methyl-6a,7-dehydronornuciferine (**2d** ; λ_{max} = 370 nm)[7]; and in the ^{1}H NMR spectrum of trichoguattine the signal attributed to the C7 methyl group is at 3.3 ppm (s, 3H) while that of the 7-methyl group of **2d** is at 2.50 ppm.[7]

Our synthetic strategy for 7-substituted dehydronoraporphines **2** was based on a simple two-bond disconnection of bonds **a** and **b** to give as synthons 1-ethylideneisoquinolines **3** and arynes **4** (Fig.1).

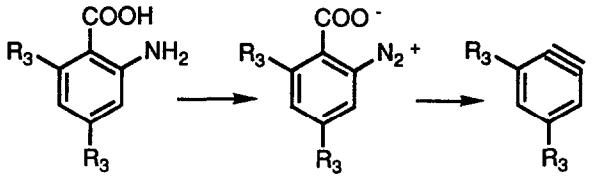


5a R_1+R_2=CH_2
5b R_1=R_2=CH_3

6a R_1+R_2=CH_2
6b R_1=R_2=CH_3

3a R_1+R_2=CH_2, R=CHO
3b R_1+R_2=CH_2, R=COOEt

Scheme 1



7a R_3=H
7b R_3=OMe

8a R_3=H
8b R_3=OMe

4a R_3=H
4b R_3=OMe

Scheme 2

The 1-ethylideneisoquinoline **3a** was prepared from 3,4-methylenedioxyphenethylamine by acylation with propionyl chloride to **5a**, Bischler-Napieralski cyclization to **6a**, and N-formylation with acetic formic anhydride (Scheme 1). For the generation of benzyne (**4a**) we chose the method based on thermal decomposition of preformed benzenediazonium-2-carboxylate (**8a**), which was obtained by aprotic diazotization of anthranilic acid (**7a**)[10](Scheme 2). The key step involved addition of a suspension of **8a** to a refluxing solution of compound **3a** in 1,2-dimethoxyethane (DME) or 1,2-dichloroethane. Work-up and

chromatographic purification afforded the dehydronoraporphine **2a** as minor product (16%), easily recognized by the characteristic ^1H NMR signal of H_{11} at ca 9 ppm (m, 1H), and a major product which was identified as the dibenzindolizine **9** (Fig.2).

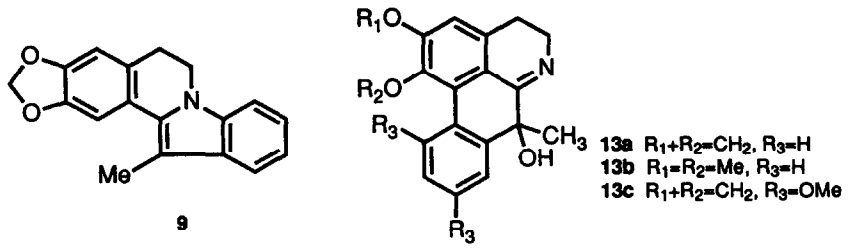
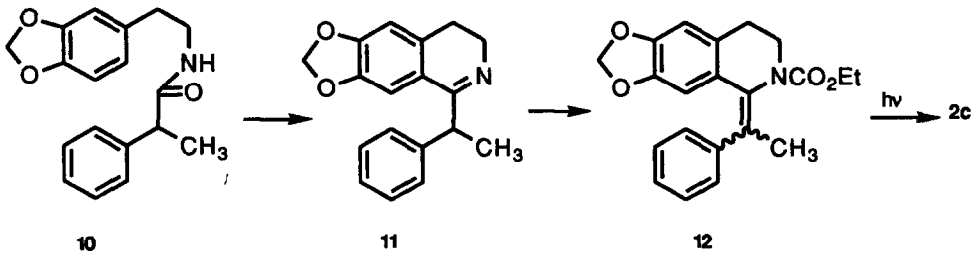


Figure 2

The dehydronoraporphine obtained shows ^1H NMR signals at 9.09 (m, 1H) and 2.64 ppm (s, 3H), UV absorption bands at λ_{max} 253, 288, 325, 357 and 376 nm, and a molecular ion peak at 305 (M^+, 100%) in the mass spectrum, all of which are in keeping with the structure **2a** (Fig.1), but very different from the corresponding values previously reported for trichoguattine.[8] Furthermore, comparison of our synthetic material with an authentic sample of trichoguattine by chromatography showed those to be different compounds. To establish definitively the structure of our product, we devised a photochemical synthesis of 7-substituted dehydronoraporphine **2a** (Scheme 3). The key step in this procedure is photochemical cyclization of stilbenoid **12**.



Scheme 3

Amide **10** was obtained by acylation of 3,4-methylenedioxyphenethylamine with 2-phenylpropionyl chloride, and after Bischler-Napieralski cyclization to **11** and N-protection of this with ethyl chloroformate, afforded **12**. Cyclization of this enamide by irradiation with a mercury lamp yielded phenanthrene **2c**. The nitrogen protecting group was removed by refluxing a solution of **2c** in ethanolic KOH, under argon atmosphere (Procedure A), which led to the desired amine **2f** in 78% yield and a minor product. N-formylation of **2f** by treatment with acetic-formic anhydride afforded a compound which was identical to the synthetic **2a** previously obtained through the IBC approach (92% yield). The minor product obtained in the

deprotection step shows the following spectroscopic features : the ^1H NMR signals corresponding to H_{11} (8.17-8.21 ppm) and CH_3-7 (1.49 ppm) indicate that these positions are more shielded than in **2f** (8.89-9.03 and 2.40 ppm, respectively) ; a molecular ion peak at m/z 293 in the LRM-Spectrum; λ_{max} at 258, 310, 354 and 368 in the UV spectrum. These data are in keeping with the aporphinoid structure **13a** (Fig. 2), which presumably results from oxidation of dehydronoraporphine **2f** by oxygen present in the reaction medium. Compound **13a** was also formed when N-formyl derivative **2a** was treated with more thoroughly deoxygenated ethanolic solution of KOH (Procedure B), this time in 52% yield.

To confirm the influence of oxygen concentration on the yield of the 7-hydroxy derivatives, we carried out hydrolysis of **2d**[7] with each of the KOH solutions above (Procedures A and B, the latter with the lower oxygen concentration; see Experimental). Using procedure A, we isolated **2g** and **13b** from the reaction mixture in approximate mole ratio 1:4 and 52% overall yield, and with the solution of lower oxygen concentration (Procedure B), we isolated **2g** and **13b** in approximate mole ratio 4:1 and 100% overall yield.

We then turned our attention to synthesis of guacoline (**13c**, Fig. 2) a 7-hydroxy-7-methyl-dehydronoraporphine recently isolated from *Guatteria discolor* [11] by the IBC approach. 2-Carboxy-benzenediazonium hydrochloride (**8b**.HCl), obtained by diazotization of anthranilic acid **7b** in EtOH/HCl, undergoes thermal decomposition to give 3,5-dimethoxybenzyne (**4b**). Thus, slow addition of a suspension of **8b**.HCl to a refluxing 1,2-dichloroethane solution of **3b** afforded, following work-up and chromatographic purification, the adduct **2e** in 37% yield. Treatment of this with concentrated ethanolic KOH (Procedure A) gave **13c** in 57% yield, with no **2h** being detected. **13c** showed the same spectroscopic data as natural guacoline.[11]

Remarkably, in some cases both 7-hydroxy-7-methylnoraporphines and 7-methyldehydroaporphines have been isolated from a single species of the *Guatteria* genus. Biogenesis of 7-hydroxy-7-methylnoraporphines is thought to include enzymic oxidation of the corresponding N-methyl-7-methyldehydroaporphines. However on the basis of our results, we believe that dehydronoraporphines should not be ruled out as intermediates in the biogenesis of 7-hydroxy-7-methylnoraporphinoids.

Regardless of these biogenetic aspects, optimization of this oxidation procedure may well open a new route to the 7-hydroxy-7-methylnoraporphinoids.

In conclusion, a) natural trichoguattine is not identical with the synthetic product obtained by synthesis using the IBC approach; the structure of this compound structure was unequivocally stablished and therefore that of trichoguattine and some related alkaloids should be revised b) The IBC approach is regioselective when a 3-methoxy benzyne was used c) 7-Methyl-6,6a-dehydronoraporphines are easily oxidized by oxygen in what may be a biomimetic process.

ACKNOWLEDGEMENTS

Financial support from the DGICYT (Project No PB87-0663-C02-01) is gratefully acknowledged. We thank Prof. A. Cavé for sending us a sample of natural trichoguattine and spectra of guacoline.

EXPERIMENTAL PROCEDURES

General Procedures. All melting points were determined on a Büchi apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in a Bruker (250 MHz) spectrometer with $CDCl_3$ as solvent and internal standard Me_4Si . IR spectra were of samples in KBr pellets and were recorded in a Pye-Unicam 1100 spectrometer; UV-visible spectra were run in a Pye-Unicam 1700 instrument; low and high resolution mass spectra were recorded on Hewlett-Packard and Kratos MS 50 instruments, respectively, both operating both at 70 eV; elemental analysis was performed by a Perkin Elmer instrument. Chloroform was purified by distillation from CaH_2. Acetonitrile was distilled from P_2O_5; ethanol was dried by refluxing with magnesium; and degased ethanolic KOH solutions were prepared under Ar by addition of KOH to refluxing EtOH.

N-(3,4-methylenedioxy-β-phenethyl)propionamide (5a). Propionyl chloride (5.56 mL, 68 mmol) in dry $CHCl_3$ (22 mL) was added dropwise to a cooled (0°C), stirred solution of 3,4-methylenedioxy-β-phenethyl)amine[12] (9.63 g, 58.3 mmol) and pyridine (15 mL, 187 mmol) in dry $CHCl_3$ (30 mL). After addition was completed, stirring was continued for 2.5 h. at r.t. The reaction mixture was washed with 10% $NaHCO_3$, 10% HCl, and finally with water until neutral, and the organic solution was dried over Na_2SO_4. Evaporation *in vacuo* afforded amide **5a** as a brown solid (81% yield). Mp 68 °C (AcOEt/hexane). IR (KBr) : 3310, 1750 cm^{-1}. ^1H NMR : 1.27 (t, J= 7.6 Hz, 3H), 2.18 (c, J= 7.6 Hz, 2H), 2.74 (t, J= 6.9 Hz, 2H), 3.48 (c, J=6.8 Hz, 2H), 5.48 (bs, 1H), 5.94 (s, 2H), 6.68 (m, 3H). LRMS m/z (%) : 221 (M^+, 100). Anal. calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found : C, 64.90; H, 7.01; N, 6.55.

1-Ethyl-6,7-methylenedioxy-3,4-dihydroisoquinoline (6a). $POCl_3$ (7.63 g, 49.9 mmol) was added to a refluxing solution of N-(3,4-methylenedioxyphenethyl)propionamide (**5a**, 5.00 g, 22.6 mmol) in acetonitrile (53 mL), and the mixture was refluxed for 1.5 h. The reaction mixture was evaporated *in vacuo* and the residue was treated with 10% NaOH, extracted with dichloromethane, and the organic phase was dried over Na_2SO_4. Evaporation of the solvent afforded **6a** as a brown oil (81% yield), which was crystallized from ether-petroleum ether. Mp 75-77 °C . UV (MeOH) λ_{max} : 228, 310 nm. IR (KBr) : 3000-2800 cm^{-1}. ^1H NMR : 1.43 (t, J= 7.5 Hz, 3H), 2.02 (t, J= 7.7 Hz, 2H), 3.16 (c, J= 7.5 Hz, 2H), 3.88 (m, 2H), 6.16 (s, 2H), 6.84 (s, 1H), 7.18 (s, 1H). LRMS m/z (%) : 203 (M^+, 100). HRMS calcd. for $C_{12}H_{13}NO_2$: 203.0946. Found: 203.0925.

1-Ethylidene-2-formyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (3a). Acetic formic anhydride (26.5 mL) and anhydrous sodium acetate (3.21 g, 37.8 mol) were added to 1-ethyl-6,7-methylenedioxy-3,4-dihydroisoquinoline (**6a**, 2 g, 9.85 mmol) and the mixture was stirred for 15 min at 0 °C and then 2 h at r.t. The reaction mixture was poured into crushed ice and the aqueous solution extracted with dichloromethane. The organic phase was dried and the solvent evaporated under reduced pressure to give the formamide (1.82 g, 76%) as a mixture of E and Z isomers. Crystallization from MeOH yielded the major isomer **3a** as a pure white crystalline solid. Mp 144-6 °C. UV (MeOH) λ_{max} : 230, 264, 312 nm. IR (KBr) : 1665 cm^{-1}. ^1H NMR : 1.87 (d, J=7.1 Hz, 3H), 2.81 (t, J=6.1 Hz, 2H), 3.85 (t, J=6.1 Hz, 2H), 5.94 (s, 2H), 5.98 (c, J=7.1 Hz, 1H), 6.55 (s, 1H), 7.01 (s, 1H), 8.22 (s, 1H). LRMS m/z (%) : 231 (M+, 24), 202 (100), 173 (11). HRMS calcd. for $C_{13}H_{13}NO_3$: 231.0895. Found : 231.0897.

2-Ethoxycarbonyl-1-ethylidene-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (3b). A solution of 1-ethyl-6,7-methylenedioxy-3,4-dihydroisoquinoline (**6a**, 0.425 g, 2.94 mmol) in dry toluene (10 mL) was refluxed under an argon atmosphere in a Dean-Stark apparatus (additional dry toluene was periodically added). Diethyl pyrocarbonate (0.613 g, 3.78 mmol) was added to the mixture and stirred at 50°C for 15 min. The solvent was evaporated *in vacuo* and the residue purified by flash chromatography on silica gel (dichloromethane), or aluminium oxide (ether-hexane 3:2), to afford **3b** as a pale yellow solid (68% yield). Mp 72-73 °C (EtOH). UV (MeOH) λ_{max} : 222, 264, 310 nm. IR (KBr) : 1690, 1650 cm^{-1}. ^1H NMR : 1.14-1.23 (m, 3H), 1.72 (d, J= 7.0 Hz, 3H), 2.83-2.94 (m, 2H), 3.42 (m, 2H), 4.06 (m, 2H), 5.30 (bs, 1H), 6.02 (s, 2H), 7.14 (s, 1H), 7.23 (s, 1H). LRMS m/z (%) : 275 (M^+, 23), 246 (100). HRMS calcd. for $C_{15}H_{17}NO_4$: 275.1158. Found : 275.1149. Anal. calcd. for $C_{15}H_{17}NO_4$ (%) : C, 65.44; H, 6.22; N, 5.09. Found : C, 65.07; H, 6.69; N, 5.19.

Benzenediazonium-2-carboxylate (8a).[10] To a cooled (0°C), stirred solution of anthranilic acid (**7a**) in dry DME containing a catalytic amount of trichloroacetic acid, a solution of excess isoamyl nitrite was added over 1-2 min. Stirring was continued at 0°C for 15 min, and then at r.t. for 90 min, and then the heterogeneous mixture resulting was diluted with DME. The supernatant was discarded (the use of a syringe fitted with a length of teflon tubing is recommended; never with a normal metal needle!). **Caution : Benzenediazonium-2-carboxylate when dry detonates violently on being scraped or heated.** Washing with DME was repeated several times until the washings were neutral. The brownish precipitate resulting, which should always remain soaked with solvent, was then transfered by syringe with teflon tubing (see above) and added slowly to a refluxing solution of the 1-alkylideneisoquinoline in DME (See next reaction).

IBC synthesis of N-formyl-7-methyl-6a,7-dehydroanonaine (2a). A suspension of benzenediazonium 2-carboxylate (**8a**), prepared from anthranilic acid (**7a**, 2.06 g, 15 mmol) and isoamyl nitrite (2.82 mg, 24 mmol), was added carefully from a syringe fitted with teflon tubing (see above), to a refluxing solution of formamide **3a** (0.6 g, 2.6 mmol). At the end of the addition the reaction was refluxed for an additional hour and then the solvent was evaporated and the residue taken up in dichloromethane. Following column chromatography 7-methyl-N-formyl-6a,7-dehydroanonaine (**2a**, 126 mg, 16%) and dibenzindolizine **9** (188 mg, 26%) were obtained.

7-Methyl-N-formyl-6a,7-dehydroanonaine (**2a**) (yellow crystals). Mp 197-9 °C (MeOH). UV (MeOH) λ_{max} : 254, 288, 340 nm. IR (KBr) : 1680 cm^{-1}. ^1H NMR : 2.64 (s, 3H), 3.16 (m, 2H), 3.70-4.30 (m, 2H), 6.23 (s, 2H), 7.00 (s, 1H), 7.55-7.70 (m, 2H), 7.97-8.01 (m, 1H), 8.37 (s, 1H), 9.07 ppm (m, 1H). ^{13}C NMR (DEPT): 15.2 (CH_3), 30.5 (CH_2), 39.3 (CH_2), 101.3 (CH_2), 109.4 (CH), 116.2 (C), 120.3 (C), 124.6 (CH), 126.1 (CH), 126.5 (C), 127.3 (CH), 131.4 (C), 132.5 (C), 142.2 (C), 145.6 (C), 164.0 ppm (CHO). LRMS m/z (%) : 305 (M^+, 100), 276 (41), 262 (17), 218 (13), 189 (17), 108 (9). HRMS calcd. for $C_{19}H_{15}NO_3$: 305.1052. Found : 305.1059. Anal. calcd. for $C_{19}H_{15}NO_3.1/2H_2O$: C, 72.45; H, 5.20; N, 4.59. Found : C, 72.60 H, 5.13; N, 4.46.

Dibenzindolizine **9** (pale yellow crystals). Mp 178-180 °C (MeOH). UV (MeOH) λ_{max} : 238, 262, 270, 333, 348 nm. IR (KBr) : 1470 cm^{-1}. ^1H NMR : 2.58 (s, 3H), 3.01 (t, J=6.3 Hz, 2H), 4.15 (t, J=6.3 Hz, 2H), 5.96 (s, 2H), 6.76 (s, 1H), 7.09-7.25 (m, 3H), 7.34 (s, 1H), 7.56-7.59 ppm (m, 1H). LRMS m/z (%)

: 277 (M^+, 100), 218 (17), 217 (19), 138.5 (M^{++}, 15). Anal. calcd. for $C_{18}H_{15}NO_2$: C, 77.99; H, 5.41; N, 5.05. Found : C, 77.68; H, 5.45; N, 5.14.

IBC synthesis of N-ethoxycarbonyl-7-methyl-6a,7-dehydroanonaine (2c). Benzenediazonium 2-carboxylate (**8a**), prepared from anthranilic acid (**7a**, 0.334 g, 2.44 mmol) and isoamyl nitrite (0.389 g, 2.32 mmol), was added as above to a refluxing solution of 2-ethoxycarbonyl-1-ethylidene-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline **3b** (0.118 g, 0.429 mmol). Work-up afforded **2c** as a yellow solid (56% yield). Mp 155°C (MeOH). UV (MeOH) λ_{max} : 252, 288, 318, 358, 376 nm. IR (KBr) : 1650-1700 cm^{-1}. ^1H NMR : 1.19-1.27 (m, 3H), 2.52 (s, 3H), 2.89-2.95 (m, 2H), 4.02-4.15 (m, 2H), 4.25-4.32 (m, 2H), 6.20 (s, 2H), 7.03 (s, 1H), 7.53-7.65 (m, 2H), 8.03-8.07 (m, 1H), 9.08-9.12 (m, 1H). Anal. calcd. for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found : C, 71.94; H, 5.31; N, 3.84.

IBC synthesis of N-ethoxycarbonyl-9,11-dimethoxy-7-methyl-6a,7-dehydroanonaine (2e). Concentrated HCl (1.8 mL) was added dropwise to a cooled (0°C) suspension of anthranilic acid **7b**[13] (1.107 g, mmol) in EtOH so giving a precipitate. Isoamyl nitrite (1.118 g, 9.56 mmol) was added and the mixture was stirred at 0°C until the precipitate redissolved. After stirring at 0 °C for 45 min ether (20 mL) was added and the mixture was stirred for a further 30 min. The precipitate of **8b**.HCl which formed was collected and washed with ether until washings were neutral, and was then suspended in 1,2-dichloroethane (the precautions described above should be taken).

A suspension of 3,5-dimethoxybenzenediazonium 2-carboxylate (**8b**) was added in portions to a refluxing solution of alkylideneisoquinoline **3b** in 1,2-dichloroethane and propylene oxide. At the end of the addition (2h) the solution was refluxed for a further 2h. Work up as above afforded 77 mg of **2e** as a yellow solid (27% or 37% based on unrecovered starting material). Mp 131-132°C (MeOH). UV (MeOH) λ_{max} : 264, 294 nm. IR (KBr) : 1700 cm^{-1}. ^1H NMR : 1.25 (s, 3H), 2.40 (s, 3H), 2.89 (m, 1H), 3.30-3.55 (m, 2H), 3.70-3.40 (m, 1H), 3.97 (s, 3H), 3.99 (s, 3H), 4.20-4.30 (m, 1H), 4.70-4.85 (m, 1H), 6.00 (s, 1H), 6.12 (s, 1H), 6.70 (s, 1H), 6.92-6.96 ppm (m, 2H). ^{13}C NMR : 14.4, 15.3, 18.1, 30.6, 44.3, 55.6, 56.0, 58.0, 61.7, 97.8, 98.3, 99.9, 108.3, 121.0, 124.0, 126.1, 132.1, 133.4, 135.7, 142.0, 145.0, 156.6, 158.7. Anal. calcd. for $C_{23}H_{23}NO_6.1/3H_2O$: C, 66.24; H, 5.79; N, 3.63. Found : C, 66.59; H, 5.54; N, 3.28.

Hydrolysis of N-protecting groups. Procedure A. Potassium hydroxide was dissolved in dry EtOH by heating under Ar. After cooling to r.t. the substrate was added and the mixture was refluxed until the hydrolysis was complete (TLC monitoring). Evaporation of the solvent under reduced pressure yielded a residue, which was dissolved in dichloromethane and purified by chromatography.

Procedure B. Dry EtOH was refluxed under Ar for 1 h. Potassium hydroxide was added and the mixture was refluxed (under Ar) until the KOH dissolved. The solution was cooled to r.t. and the substrate was added. The reaction was monitored and worked-up as above.

Hydrolysis of N-formyl-7-methyl-6a,7-dehydronornuciferine (2a). Procedure B. Reaction of **2a** (8 mg, 0.026 mmol) and KOH (152 mg, 2.72 mmol) in EtOH (0.8 mL) afforded **13a** as a yellow oil (4 mg, 52% yield). This was crystallized from MeOH to give a yellow powder. Mp. 165 °C (MeOH). UV (EtOH) λ_{max} : 257, 310 (sh), 354, 368 nm. IR (KBr) : 3400, 1600 cm^{-1}. ^1H NMR : 1.49 (s, 3H), 2.64-2.76 (m, 2H), 3.18-3.33 (m, 2H), 4.02 (m, 1H), 6.19 (s, 1H), 6.20 (s., 1H), 6.68 (s, 1H), 7.33-7.39 (m, 2H), 7.82-7.85 (m, 1H), 8.17-8.21 ppm (m, 1H).

Hydrolysis of N-ethoxycarbonyl-7-methyl-6a,7-dehydroanonaine (2c). Procedure A. Reaction of **2c** (250 mg, 0.7 mmol) and KOH (4g, 71.4 mmol) in EtOH afforded **13a** (38 mg, 18%) and 7-methyl-6a,7-dehydroanonaine (**2f**, 156 mg, 78%), which was used for the next reaction without further purification . ^{1}H NMR : 2.40 (s, 3H), 3.20 (t, J= 6 Hz, 2H), 3.5 (t, J= 6.1 Hz, 2H), 4.5 (m, 1H), 6.20 (s, 2H), 6.97 (s, 2H), 6.97 (s, 1H), 7.35-7.53 (m, 2H), 7.83-7.86 (m, 1H), 8.89-9.03 ppm (m, 1H). LRMS m/z (%): 278 ($M+1^+$, 26), 277 (M^+, 80), 276 (75).

From potassium hydroxyde (4g, 71.4 mmol) in dry EtOH and N-ethoxycarbonyl-7-methyl-6a,7-dehydroanonaine (**2c**, 250 mg, 0.7 mmol) was obtained the deprotected compound **2f** (156 mg, 78%), used for the next reaction without further purification .

Hydrolysis of N-ethoxycarbonyl-7-methyl-6a,7-dehydronornuciferine (2d). Procedure A. Reaction of **2d**[7] (60 mg, 0.164 mmol) and KOH (940 mg, 1.59 mol) in EtOH (4.7 mL) afforded 7-hydroxyaporphinoid **13b** (41%) and **2g** (11%). **Procedure B.** Reaction of **2d**[9] (100 mg, 0.274 mmol), KOH (1.6 g, 28.57 mmol) in EtOH (8.5 mL) afforded nordehydroaporphine **2g** (64 mg, 79%) and 7-hydroxyaporphinoid **13b** (18 mg, 21%).

13b (38 mg, 18%, yellow pulver). Mp. 127-129 °C (MeOH). UV (EtOH) λ_{max} : 232, 260, 296 nm. IR (KBr) : 3400 cm^{-1}. ^{1}H NMR : 1.53 (s, 3H), 2.72-2.85 (m, 2H), 3.24-3.32 (m, 1H), 3.80 (s, 3H), 3.98 (s, 3H), 4.06-4.13 (s, 1H), 6.75 (s, 1H), 7.34-7.42 (m, 2H), 7.85-7.89 (m, 1H), 8.54-8.58 ppm (m, 1H). ^{13}C NMR : 29.6, 33.4, 45.7, 56.0, 60.0, 72.4, 110.2, 115.8, 124.6, 126.4, 127.6, 128.0, 128.4, 128.8, 134.3, 143.0, 145.8, 156.8, 170.6 ppm. LRMS m/z (%) : 309 (M^+, 100). HRMS calcd. for $C_{19}H_{19}NO_3$: 309.1365. Found : 309.1373. Anal. calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found : C, 73.44; H, 6.08; N, 4.17.

Hydrolysis of N-ethoxycarbonyl-9,11-dimethoxy-7-methyl-6a,7-dehydro-anonaine (2e). Procedure A. Reaction of **2e** (85 mg, 0.21 mmol) and KOH (1.212 g, 21.6 mmol) in EtOH (7 mL) afforded (after 30 h) the aporphinoid (±)-guacoline[11] (**13c**, 42 mg, 57%). Mp. 74-76 °C (MeOH).

Photochemical synthesis of N-ethoxycarbonyl-7-methyl-6a,7-dehydroanonaine (2c).

α-Methyl-N-(3,4-methylenedioxy-β-phenethyl) propionamide (10). A solution of 2-phenylpropionyl chloride[14] (5.1 g, 0.03 mol) in dry chloroform (20 mL) was added dropwise to a cooled (0°C), stirred solution of 3,4-methylenedioxy-β-phenethylamine[12] (5 g, 0.03 mmol) in triethylamine (6 g, 0.06 mol). After addition was complete the solution was stirred for a further 2 h at r.t. The reaction mixture was washed with 10% $NaHCO_3$, 5% HCl and water and the organic phase was separated and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was crystallized from ethyl acetate to give brown crystals of **10** (8.25 g, 92%). Mp 68-70 °C. IR (KBr) : 1660 cm^{-1}. ^{1}H NMR : 1.50 (d, J=7.2 Hz, 3H), 2.57-2.62 (t, J=6.7 Hz, 2H), 3.39-3.51 (m, 3H), 5.3 (m, 1H), 5.9 (s, 2H), 6.37-6.65 (m, 3H), 7.20-7.32 ppm (m, 5H).

1-(α-Methylbenzyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (11). $POCl_3$ (2.8 g, 1.7 mL, 18 mmol) was added dropwise to a stirred solution of amide **10** (2.5 g, 8.4 mmol) in dry CH_3CN, and the solution was refluxed for 2 h. The solvent was evaporated in vacuo and the residue was dissolved in dichloromethane, washed with 5% NaOH (3 x 15 mL), dried over Na_2SO_4 and concentrated to an oil (**11**, 2.3 g, 98%) of imine, as which was used for the next reaction without further purification. ^{1}H NMR : 1.51 (d,

J=6.9 Hz, 3H), 2.60 (t, J=7.4 Hz, 2H), 3.69-3.80 (m, 2H), 4.23 (c, J=6.9 Hz, 1H), 5.87 (d, J= Hz, 2H), 6.60 (s, 1H), 6.88 (s, 1H), 7.16-7.28 ppm (m, 5H) .

N-Ethoxycarbonyl-1-(α-methylbenzylidene)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (12). Ethyl chloroformate (1.78 g, 16 mmol) was slowly added to a cooled (0°C) solution of imine **11** (2 g, 7.2 mmol) and potassium carbonate (2.3 g, 16 mmol) in chloroform (30 mL). The mixture was stirred at 0 °C for 30 min and then for 2 h at r.t. Solids were filtered out and the filtrate was washed with 10% HCl (2 x 10 mL), dried and concentrated under reduced pressure. The residue was purified by column chromatography (dichloromethane), to give carbamathe **12** as an oil (1.87 g, 75%) which crystallized from EtOH as pale yellow crystals. Mp 121-123 °C (EtOH). IR (KBr) : 1690 cm^{-1}. ^1H NMR : 1.30 (t, J=7.1 Hz, 3H), 2.07 (s, 3H), 2.75-3.00 (m, 2H), 3.40-3.59 (m, 2H),4.10 (m, 2H), 5.79 (s, 2H), 6.02 (s, 1H), 6.57 (s, 1H), 7.19-7.32 ppm (m, 5H). LRMS m/z (%) : 351 (M^+, 86), 322 (43), 278 (100), 263 (57), 164 (35). Anal. calcd for $C_{21}H_{21}NO_4$: C, 71.79; H, 5.98; N, 3.98. Found : C, 71.42; H, 5.74; N, 4.14.

N-Ethoxycarbonyl-7-methyl-6a,7-dehydroanonaine (2c). In a vycor reactor a solution of **12** (640 mg, 1.83 mmol), iodine (187 mg, 7.3 mmol) and cupric acetate (366 mg) in dry EtOH (400 mL) and under Ar was irradiated (450 w medium-pressure mercury lamp) for 18 h. The ethanol was evaporated and the residue was dissolved in dichloromethane, which was then washed with water, dried over over Na_2SO_4, concentrated and purified by column chromatography to yield N-ethoxycarbonyl-7-methyldehydroanonaine (**2c**, 340 mg, 53%). Mp. 154-156 °C (MeOH). UV (MeOH) λ_{max} : 258, 310, 354, 368 nm. IR (KBr) : 1660 cm^{-1}. ^1H NMR : 1.22 (m, 3H), 2.52 (s, 3H), 2.93 (m, 1H), 3.31-3.40 (m, 2H), 4.01 (m, 1H), 4.21 (m, 1H), 4.75 (m, 1H), 6.22 (s, 2H), 7.03 (s, 1H), 7.56-7.67 (m, 2H), 8.04 (dd, 1H, J_1= 7.4 Hz, J_2= 1.8 Hz), 9.09 ppm (dd, 1H, J_1= 7.4 Hz, J_2= 1.8 Hz). ^{13}C NMR : 14.5, 15.1, 30.4, 44.4, 61.9, 100.9, 109.1, 116.1, 121.0, 124.4, 124.7, 125.5, 126.8, 126.9, 127.2, 127.3, 131.5, 132.5, 142.0, 144.8 ppm. LRMS m/z (%) : 349 (M^+, 100), 321 (20), 303 (24), 278 (92), 73 (15). Anal. calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48 N, 4.01. Found : C, 71.94; H, 5.31; N, 3.84.

N-Formyl-7-methyl-6a,7-dehydroanonaine (2a). Compound **2f** (100 mg, 0.36 mmol) was stirred with acetic-formic anhydride in the presence of anhydrous sodium acetate (117 mg, 1.6 mmol) for 10 min at 0 °C, and then for 30 min at r.t. The reaction mixture was poured onto crushed ice and the aqueous phase was extracted with dichloromethane. The organic extracts were dried over Na_2SO_4 and concentrated to dryness, to give compound **2a** (102 mg, 92%) identical to that previously obtained by the IBC approach.

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