

186. Design and Synthesis of a Potential Dopamine D-1 Antagonist

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The diastereoselective synthesis of ($\pm$)-*trans-transoid*-7-bromo-8-hydroxy-1-methyl-1,2,3,4,4a,5,10,10a-octa-hydro-10-phenylbenzo[g]quinoline (**8**) is described, using an intramolecular *Diels-Alder* reaction and a reductive cyclisation for piperidine ring-formation as key steps. Compound **8** was prepared as a putative D-1 receptor antagonist which contains (2,2-diphenylethyl)amine as a partial structure.

Introduction. – Following the identification of dopamine (DA) as a neurotransmitter in the central nervous system, DA has become the most extensively investigated neurotransmitter in the nervous system [1]. DA is important in the modulation of many central, peripheral, and hormonal functions; substances that either mimic or antagonize the effects of DA at its receptors find application primarily in neurological, cardiovascular, and endocrinological diseases [2]. The major clinical application of central DA agonists is for the treatment of *Parkinson's* disease [3] and neuroendocrine disorders [4]. The principal clinical utility of DA antagonists is for treating schizophrenia, mania, delirium, severe agitation, and *Huntington's* disease [2] [5].

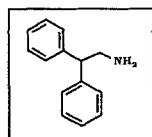
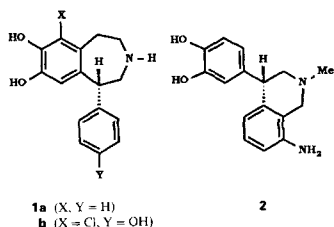
At present, it is accepted that there are two different subpopulations of DA receptors [6]. They have been termed D-1 and D-2²⁾; the D-1 receptor stimulates adenylate cyclase, whereas the D-2-receptor inhibits this enzyme [8]. So far, the D-1 receptor is better understood in the laboratory, whereas the D-2 receptor has received greater attention in the clinic [9]. The clinical use of D-2 agonists and antagonists may be accompanied by some very embarrassing side effects, such as emesis for agonists or acute extrapyramidal symptoms and tardive dyskinesia for antagonists [10]. It is hoped that the application of D-1 selective drugs might lead to a low liability for such severe side effects in humans. For this reason, much emphasis has recently been placed on the discovery of selective D-1 agonists and D-1 antagonists. The following compounds have been identified as selective agonists: **1a** (SK + F 38393) [11], **1b** (fenoldopam, SK + F 82526) [11], **2** (3',4'-dihydroxynomifensine) [12], **3** (CY 208-243) [13], and **4** [14]. The first selective and potent D-1 antagonist, **5a** (SCH 23390), was reported in 1983 [15]. Compound **5b** (SK + F 83566) [16] and **7** ((+)-butaclamol) [17] are equipotent with **5a**, **7** being a mixed D-1/D-2 antagonist. **6** [18] was described as a weak D-1 antagonist.

To devise strategies for the derivation of novel, selective, and more potent D-1 antagonists, the common structural features of these nine compounds were examined.

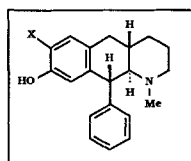
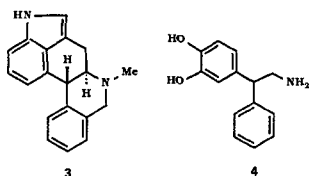
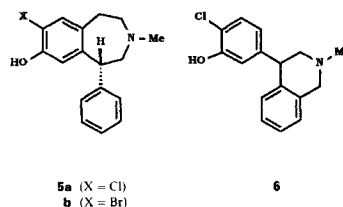
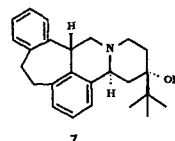
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²⁾ Goldberg and Kohli proposed that peripheral DA receptors can be subdivided into DA1 and DA2. In this paper, the term D-1 (D-2) implies also DA1 (DA2) [7].

D-1 Agonists (active enantiomers)

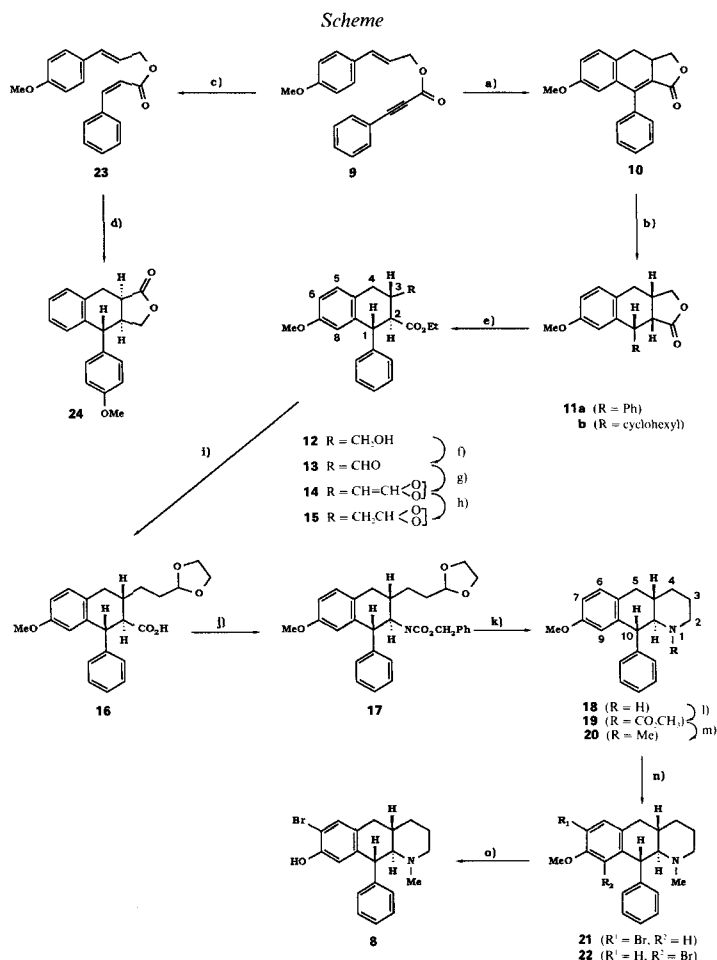
Proposed
D-1 Pharmacophore

D-1 Antagonists (active enantiomers)

Novel D-1 Antagonist?
8 (X = Cl or Br)

The constitutional requisites for D-1 receptor subtype discrimination appears to be a (2,2-diphenylethyl)amine moiety embedded in all these structures. Incorporation of this pharmacophore into a rigid *trans*-octahydrobenzo[*g*]quinoline system, introduction of an OH group and a halogen atom at C(8) and C(7), respectively (in accordance with **5a**, **5b**, and **6**), provides molecule **8**. Superposition of the aromatic centers and the N-atom of **8** with the corresponding centers in **5b**, **6**, and **7** revealed a reasonable fit [19] with **5b** (RMS = 0.429), and an excellent fit with **6** (RMS = 0.047) and **7** (RMS = 0.099). It was speculated on the basis of the above comparisons, that **8** might have potent D-1 antagonist activity. Compound **8** (X = Br) was, therefore, synthesized.

Chemistry. – Racemic **8** (X = Br) was synthesized as shown in the *Scheme*. (*E*)-4-Methoxycinnamyl phenylpropiolate **9** – obtained *via* esterification of (*E*)-4-methoxycinnamyl alcohol [20] with phenylpropionic acid, using DCC/DMAP in CH₂Cl₂ – was converted in 54% yield to lactone **10** by means of an intramolecular *Diels-Alder* reaction in refluxing Ac₂O [21]. Hydrogenation over *Raney*-Ni resulted in the formation of *cis-cisoid*-lactone **11a** contaminated with *ca.* 10% of the cyclohexyl by-product **11b**. Efforts to separate **11a** from **11b** by recrystallisation and chromatography were not successful. Therefore, it was attempted to obtain **11a** directly from (*Z*)-3-phenylacrylate **23**. However, when **23** was refluxed in DMF for 14 h, lactone **24** was isolated in 65% yield instead of the expected **11a**. Consequently, the crude mixture **11a/11b** was treated with NaOAc in refluxing EtOH for 48 h in order to effect lactone ring opening and epimerisation at C(2). The desired *trans,trans*-ester **12** could be isolated in pure form and 62% yield. The *all-trans* configuration of **12** was assigned on the basis of its ¹H-NMR spectrum. H–C(1) appears as a *doublet* at 4.33 ppm (*J* = 11 Hz) by *trans*-diaxial coupling with H–C(2); H–C(2) appears as a *triplet* at 2.8 ppm (*J* = 11 Hz) by *trans*-diaxial coupling with



a) Ac₂O, reflux, 6 h; b) EtOH, *Raney*-Ni, 60°, 120 atm, H₂; c) *Lindlar* cat., AcOEt, 1 atm H₂; d) DMF, reflux, 14 h; e) NaOAc, EtOH, reflux 48 h; f) *Swern* oxidation; g) (1,3-Dioxan-2-yl)(methyl)triphenylphosphonium bromide, DMF, *t*-BuOK; h) 5% Rh/C, MeOH, 1 atm H₂; i) EtOH, 4.55M NaOH, reflux 7 h; j) Diphenylphosphoryl azide, PhCH₂OH, Et₃N, toluene, reflux 48 h; k) EtOH, 1N HCl, reflux 45 min, then 10% Pd/C, EtOH/AcOEt 12:1, 1 atm H₂; l) ClCOOMe, Et₃N, toluene, 50°; m) LiAlH₄, THF, reflux; n) Br₂, OH, r.t.; o) Br₃B, CH₂Cl₂, -78° to r.t.

H–C(1) and H–C(3); H–C(3) shows a *multiplet* at 2.25–2.35 ppm. *Swern* oxidation [22] of **12** yielded the corresponding aldehyde **13** in quantitative yield. Chain elongation was effected by a *Wittig*-type reaction using (1,3-dioxan-2-yl)(methyl)triphenylphosphonium bromide [23], affording olefin **14**. Catalytic hydrogenation of the latter over Rh/C afforded saturated ester **15** which was saponified to acid **16** in the next step. Compound **16** underwent a *Curtius* rearrangement upon treatment with diphenylphosphoryl azide [24] followed by benzyl alcohol, yielding carbamate **17** in 73% yield. Evidence for the all-*trans* configuration of **17** was obtained from its ¹H-NMR spectrum: The large couplings (*J*(2,3) = 12 Hz; *J*(1,2) = 11 Hz) between H–C(2) and H–C(3), and H–C(2) and

H–C(1) showed them to be in a *trans*-diaxial relation to each other. H–C(1) appeared as a *doublet* at 4.06 ppm, H–C(2) as a *doublet of doublets* at 3.68 ppm, and H–C(3) as a *multiplet* at 1.98–2.01 ppm. Hydrolysis of acetal **17** followed by reductive cyclisation over Pd/C/H₂ in EtOH/HOAc afforded **18** in 73% yield. Compound **18** was *N*-methylated to **20** via reduction of the corresponding carbamate **19** with LiAlH₄. Bromination of **20** proceeded with good yield but proved to be nonselective, as the desired 7-bromo derivative **21** was formed in equal amounts with the 9-bromo derivative **22**. Originally, it was envisioned to synthesize the 7-chloro derivative of **8** (X = Cl), but treatment of **20** with SO₂Cl₂ or NCS resulted in the selective chlorination at the undesired position 9. Separation of the two bromo isomers **22** and **21**, followed by methyl-ether cleavage of the latter with Br₃B finally provided **8**. Preliminary pharmacological results showed (±)-**8** to be a very weak D-1 antagonist; further pharmacological details will be reported elsewhere.

We thank P. Candotti and H. Rumpel for their capable technical assistance in the synthetic work, H.R. Loosli, L. Oberer, M. Ponelle, and T. Zardin for interpretation of NMR spectra, C. Quiquerez for interpretation of MS, and Dr. R. Markstein for pharmacological testing. Thanks are also due to Dr. H. Braunschweiger for supply of ample quantities of lactone **10**, Dr. T.J. Petcher for encouragement and assistance with the manuscript, and to Dr. M. P. Seiler for interesting discussions.

Experimental Part

General. Silica gel 60 (Merck, 0.04–0.063 mm) was used for flash column chromatography (FCC). ¹H-NMR spectra were recorded on Bruker Spektrospin WH 360 (360 MHz) with TMS (0.00 ppm) as internal standard, J [Hz]. MS: AEI MS 30 or Varian MAT 212 spectrometer; *m/z* (% relative abundance).

(*E*)-4-Methoxycinnamyl Phenylpropiolate (**9**). DCC (30.1 g, 0.146 mol) was added to a soln. of phenylpropionic acid (21.3 g, 0.146 mol), 4-methoxycinnamyl alcohol (24 g, 0.146 mol), and DMAP (1.7 g, 14.6 mmol) in CH₂Cl₂ (400 ml). The mixture was stirred for 1 h at r.t., filtered, and evaporated. FCC of the residue over silica gel in CH₂Cl₂/hexane yielded **9** (32.4 g, 76%) as a pale yellow oil. ¹H-NMR (CDCl₃): 3.80 (s, MeO); 4.87 (*dd*, *J* = 7, 1, –CH₂–); 6.2 (*td*, *J* = 7, 16, =CH); 6.68 (*d*, *J* = 16, =CH); 6.82–6.88 (*m*, 2 H); 7.27–7.48 (*m*, 5 H); 7.58–7.6 (*m*, 2 H). MS: 292 (55, *M*⁺), 147 (70), 129 (100).

3a,4-Dihydro-7-methoxy-9-phenylnaphtho[2,3-*c*]furan-1(3H)-one (**10**). Ester **9** (48 g, 0.164 mol) was dissolved in Ac₂O (165 ml), the soln. degassed with Ar and refluxed for 6 h. The mixture was evaporated and the residue recrystallized from MeOH, yielding lactone **10** (26 g, 54%) as white crystals. M.p. 138–139°. ¹H-NMR (CDCl₃): 2.80 (*t*, *J* = 16, H_{ax}–C(4)); 3.02 (*dd*, *J* = 16, 6, H_{eq}–C(4)); 3.42 (*m*, H–C(3a)); 3.67 (s, MeO); 4.04 (*t*, *J* = 8, H–C(3)); 4.72 (*t*, *J* = 8, H–C(3)); 6.52 (*d*, *J* = 1.5, H–C(8)); 6.85 (*dd*, *J* = 1.5, 6, H–C(6)); 7.21 (*d*, *J* = 6, H–C(5)); 7.40–7.45 (*m*, 5 H). MS: 293 (100, [*M* + 1]⁺); 292 (*M*⁺, 30). Anal. calc. for C₁₉H₁₆O₃ (292.34): C 78.06, H 5.52; found: C 78.01, H 5.56.

cis-cisoid-3a,4,9,9a-Tetrahydro-7-methoxy-9-phenylnaphtho[2,3-*c*]furan-1(3H)-one (**11a**). Lactone **10** (10 g, 34 mmol) in EtOH (2 l) was heated for 15 h at 60° and 120 atm H₂ pressure in an autoclave over Raney-Ni (2 g). The soln. was filtered from the catalyst, evaporated, and the residue recrystallized from MeOH to afford **11a** (8.1 g, 81%), usually contaminated by ca. 10% **11b**. This mixture was used without further purification. M.p. 124–127°.

11a: ¹H-NMR (CDCl₃): 2.71 (*dd*, *J* = 16, 8, H_{eq}–C(4)); 3.02 (*dd*, *J* = 16, 10, H_{ax}–C(4)); 3.11–3.23 (*m*, H–C(3a), H–C(9a)); 3.38 (*t*, *J* = 8, H–C(3)); 3.76 (s, MeO); 4.38 (*t*, *J* = 8, H–C(3)); 4.58 (*d*, *J* = 5, 1H); 6.74 (*d*, *J* = 3, H–C(8)); 6.83 (*dd*, *J* = 8, 3, H–C(6)); 7.15–7.34 (*m*, 6 H). MS: 294 (100, *M*⁺), 249 (40), 218 (30), 209 (40), 179 (25).

Ethyl 1,2,3,4-Tetrahydro-*c*-3-(hydroxymethyl)-7-methoxy-*r*-1-phenylnaphthalene-*t*-2-carboxylate (**12**). Lactone **11a** (0.5 g, 1.7 mmol; contaminated with ca. 10% **11b**) and NaOAc (2.5 g, 30 mmol) were dissolved in EtOH (200 ml) and refluxed for 48 h. The mixture was evaporated, taken up in H₂O and extracted three times with CH₂Cl₂. The combined org. phases were dried, evaporated, and gave after FCC over silica gel in AcOEt/hexane crystalline **12** (0.36 g, 62%). M.p. 95–96°. ¹H-NMR (CDCl₃): 1.01 (*t*, *J* = 7, CH₃); 1.65 (br., *J* = 6, OH); 2.25–2.36 (*m*, H–C(3)); 2.80 (*t*, *J* = 11, H–C(2)); 2.92 (br. *s*, H–C(4)); 2.94 (br. *s*, H–C(4)); 3.60 (s, MeO); 3.68 (br. *t*, *J* = 5, CH₂OH); 3.98 (*dq*, *J* = 7, 2, O–CH₂); 4.33 (*d*, *J* = 11, H–C(1)); 6.23 (*d*, *J* = 3, H–C(8)); 6.71 (*dd*, *J* = 8, 3,

H–C(6)); 7.08 (*d*, *J* = 8, H–C(5)); 7.13–7.31 (*m*, 5 H). MS: 340 (40, M^+), 322 (20), 294 (25), 249 (100), 235 (90), 91 (90).

Ethyl c-3-Formyl-1,2,3,4-tetrahydro-7-methoxy-r-1-phenylnaphthalene-t-2-carboxylate (**13**). DMSO (10.2 ml, 144 mmol) in CH_2Cl_2 (180 ml) was slowly added at -60° to a soln. of oxalyl chloride (6.2 ml, 72 mmol) in CH_2Cl_2 (60 ml). After 15 min, **12** (20.3 g, 60 mmol), dissolved in CHCl_3 (180 ml), was introduced dropwise through a dropping funnel. The mixture was stirred for 30 min at -60° , Et_3 (39.2 ml, 0.28 mol) added and warmed up to 15° . After 1 h at 15° , H_2O was added and the mixture extracted with CH_2Cl_2 . The combined org. phases were dried, evaporated, and yielded crude **13** (20.3 g) as pale brown crystals, which were used in the next step without purification. MS: 338 (30 M^+), 320 (10), 264 (15), 235 (100), 86 (100).

Ethyl c-3-[2-(1,3-Dioxan-2-yl)ethyl]-1,2,3,4-tetrahydro-7-methoxy-r-1-phenylnaphthalene-t-2-carboxylate (**15**). (1,3-Dioxan-2-yl)(methyl)triphenylphosphonium bromide (47 g, 10 mmol) in DMF (470 ml) was treated with *t*-BuOK (12 g, 107 mmol) at r.t. for 15 min. Aldehyde **13** (17.3 g, 51 mmol) in DMF (125 ml) was added with stirring within 15 min. After 1.5 h at r.t., the red-orange mixture was poured on ice-water and extracted three times with Et_2O . The combined org. phases were dried, evaporated, and yielded 42 g of brownish crystals, which were purified by FCC over silica gel in AcOEt/hexane providing crystalline **14** (17 g, 82%) as a mixture of double bond isomers (m.p.: $100\text{--}123^\circ$). Compound **14** (17 g, 41.6 mmol) was hydrogenated at r.t. and 1 atm H_2 in MeOH (4.4 l) over 5% Rh/C (1.21 g). The theoretical amount of H_2 was consumed after 1 h; the catalyst filtered off and the residue evaporated. FCC over silica gel in AcOEt/hexane provided pure **15** (15.3 g, 89%). M.p. $79\text{--}80^\circ$. Overall yield from **13** to **15**: 73%. $^1\text{H-NMR}$ (CDCl_3): 0.98 (*t*, *J* = 7, CH_3); 1.33–1.47 (*m*, 1 H); 1.58–1.75 (*m*, 2 H); 1.81–1.92 (*m*, 1 H); 2.13–2.27 (*m*, H–C(3)); 2.61 (*dd*, *J* = 11, 14, $\text{H}_{\text{ax}}\text{--C}(4)$); 2.64 (*t*, *J* = 10, H–C(2)); 3.05 (*dd*, *J* = 5, 14, $\text{H}_{\text{eq}}\text{--C}(4)$); 3.60 (*s*, MeO); 3.82–4.01 (*m*, 3 CH_2O); 4.28 (*d*, *J* = 11, H–C(1)); 4.85 (*t*, *J* = 5, OCHO); 6.23 (*d*, *J* = 3, H–C(8)); 6.70 (*dd*, *J* = 7, 3, H–C(6)); 7.03 (*d*, *J* = 7, H–C(5)); 7.11–7.30 (*m*, 5 H). MS: 410 (10, M^+), 364 (60), 276 (50), 235 (55), 73 (100).

c-3-[2-(1,3-Dioxan-2-yl)ethyl]-1,2,3,4-tetrahydro-7-methoxy-r-1-phenylnaphthalene-t-2-carboxylic Acid (**16**). Ester **15** (17.9 g, 43.7 mmol) was dissolved in EtOH (400 ml), added to 4.55M NaOH (200 ml) and refluxed for 7 h. The solvent was evaporated, the residue taken up in H_2O , and washed with Et_2O . The aq. phase was acidified with 10% tartaric acid and extracted with CH_2Cl_2 . The combined org. phases were dried, evaporated, and gave **16** as white crystals. Recrystallisation from Et_2O /hexane provided pure **16** (14.9 g, 89%). M.p. $156\text{--}157^\circ$. $^1\text{H-NMR}$ (CDCl_3): 1.35–1.50 (*m*, 1 H); 1.63–1.78 (*m*, 2 H); 1.83–1.96 (*m*, 1 H); 2.11–2.26 (*m*, H–C(3)); 2.61 (*dd*, *J* = 11, 14, $\text{H}_{\text{ax}}\text{--C}(4)$); 2.64 (*t*, *J* = 11, H–C(2)); 3.02 (*dd*, *J* = 5, 14, $\text{H}_{\text{eq}}\text{--C}(4)$); 3.60 (*s*, MeO); 3.81–3.89 (*m*, CH_2O); 3.93–4.00 (*m*, CH_2O); 4.29 (*d*, *J* = 11, H–C(1)); 4.87 (*t*, *J* = 5, OCHO); 6.22 (*d*, *J* = 3, H–C(8)); 6.71 (*dd*, *J* = 7, 3, H–C(6)); 7.05 (*d*, *J* = 7, H–C(5)); 7.10–7.15 (*m*, 2 H); 7.20–7.30 (*m*, 3 H). MS: 382 (10, M^+), 364 (10), 336 (25), 320 (30), 275 (40), 235 (30), 73 (100).

Benzyl c-3-[2-(1,3-Dioxan-2-yl)ethyl]-1,2,3,4-tetrahydro-7-methoxy-r-1-phenylnaphthalene-t-2-carbamate (**17**). Acid **16** (4.5 g, 11.8 mmol), diphenylphosphoryl azide (3.2 g, 11.6 mmol) and Et_3 (1.8 ml, 12.9 mmol) were dissolved in toluene (150 ml) and heated at 100° for 1 h. The mixture was cooled to r.t. and PhCH_2OH (1.5 g, 13.9 mmol) in toluene (100 ml) added dropwise under stirring. After reflux for 24 h, another portion of PhCH_2OH (0.8 g, 7.4 mmol) in toluene (10 ml) was added and heating at 100° continued for 24 h. The mixture was evaporated; FCC over silica gel in AcOEt/hexane provided **17** (4.2 g, 73%). M.p. $152\text{--}153^\circ$. $^1\text{H-NMR}$ ($(\text{D}_6)\text{DMSO}$, 150°): 1.25–1.47 (*m*, 1 H); 1.53–1.68 (*m*, 1 H); 1.69–1.72 (*m*, 2 H); 1.98–2.01 (*m*, H–C(3)); 2.60 (*dd*, *J* = 16, 10, $\text{H}_{\text{ax}}\text{--C}(4)$); 2.93 (*dd*, *J* = 16, 5, $\text{H}_{\text{eq}}\text{--C}(4)$); 3.53 (*s*, MeO); 3.68 (*dd*, *J* = 11, 12, H–C(2)); 3.72–3.78 (*m*, CH_2O); 3.81–3.88 (*m*, CH_2O); 4.06 (*d*, *J* = 11, H–C(1)); 4.78–4.82 (*m*, OCHO); 4.83 (*d*, *J* = 14, 1 H, PhCH_2O); 4.88 (*d*, *J* = 15, 1 H, PhCH_2O); 6.13 (*d*, *J* = 3, H–C(8)); 6.48 (*br. d*, *J* = 11, NH); 6.65 (*dd*, *J* = 7, 3, H–C(6)); 7.03 (*d*, *J* = 7, H–C(5)); 7.10–7.30 (*m*, 10 H). MS: 487 (5, M^+), 379 (35), 336 (90), 248 (40), 209 (50), 108 (40), 91 (90), 73 (100).

*trans-transoid-1,2,3,4,4a,5,10,10a-Octahydro-8-methoxy-10-phenylbenzo[*g*]quinoline* (**18**). Acetal **17** (4.8 g, 9.85 mmol) was dissolved in hot EtOH (150 ml), 1N HCl (100 ml) added, and the mixture refluxed for 45 min. EtOH was evaporated, the residue taken up in ice-water and extracted three times with CH_2Cl_2 . The combined org. phases were evaporated and provided 5.3 g of the crude corresponding aldehyde, which was dissolved in EtOH/AcOH (250:20 ml) and hydrogenated over 10% Pd/C (600 mg), until the theoretical amount of H_2 was consumed (4.2 h). The catalyst was filtered off, the solvent evaporated, the residue taken up in ice-water, washed once with Et_2O , 1N NaOH added to pH 11, and extracted three times with Et_2O . The combined org. phases were dried, evaporated, and yielded crude **18** (3.1 g). FCC over silica gel in $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$ (conc.) yielded pure **18** (2.1 g, 73%). M.p. $> 285^\circ$ (MeOH). $^1\text{H-NMR}$ (CDCl_3): 1.10–1.21 (*m*, $\text{H}_{\text{ax}}\text{--C}(4)$); 1.63–1.70 (*m*, 2 H–C(3)); 1.71–1.84 (*m*, H–C(4a)); 1.92–2.01 (*m*, $\text{H}_{\text{eq}}\text{--C}(4)$); 2.45–2.55 (*m*, $\text{H}_{\text{ax}}\text{--C}(2)$); 2.61 (*dd*, *J* = 16, 12, $\text{H}_{\text{ax}}\text{--C}(5)$); 2.64 (*dd*, *J* = 11, H–C(10a)); 2.82 (*dd*, *J* = 16, 5, $\text{H}_{\text{eq}}\text{--C}(5)$); 2.95–3.01 (*m*, $\text{H}_{\text{eq}}\text{--C}(2)$); 3.58 (*s*, MeO); 3.82 (*d*, *J* = 11, H–C(10)); 6.17 (*d*, *J* = 3, H–C(9)); 6.68 (*dd*, *J* = 7, 3, H–C(7)); 7.01 (*d*, *J* = 7, H–C(6)); 7.20–7.38 (*m*, 5 H). MS:

293 (90, M^+), 210 (100), 209 (60), 179 (45), 91 (30). Anal. calc. for $C_{20}H_{23}NO$ (293.41): C 81.87, H 7.90, N 4.77; found: C 81.69, H 7.91, N 4.82.

trans-transoid-1,2,3,4,4a,5,10,10a-Octahydro-8-methoxy-1-methyl-10-phenylbenzo[*g*]quinoline (**20**). Methyl chloroformate (2.45 g, 26 mmol) in toluene (25 ml) was added under stirring at 50° to a soln. of **18** (2.93 g, 10 mmol) and Et_3 (4 g, 40 mmol) in toluene (100 ml). After 2.5 h, the mixture was poured on ice and washed first with 1N HCl then with H_2O . The org. phase was dried, evaporated, and purified by FCC over silica gel in AcOEt/hexane yielding crystalline **19** (2.3 g, 66%). Compound **19** (2.3 g, 6.55 mmol) in THF (50 ml) was added under stirring to a suspension of $LiAlH_4$ (750 mg, 19.65 mmol) in THF (20 ml). The mixture was refluxed for 30 min, excess $LiAlH_4$ destroyed by careful addition of conc. Na_2SO_4 at 0°, Et_2O added, the inorg. salts filtered off, and Et_2O evaporated, yielding crystalline **20** (1.95 g, 97%; 64% over two steps from **18** to **20**). 1H -NMR ($CDCl_3$): 1.20–1.34 (*m*, H_{ax} -C(4)); 1.56–1.65 (*m*, H-C(4a)); 1.71–1.86 (*m*, 2 H-C(3)); 1.95 (br. *d*, $J = 13$, H_{eq} -C(4)); 2.19 (*s*, CH_3N); 2.30 (*dt*, $J = 13$, 4, H_{ax} -C(2)); 2.61 (*dd*, $J = 9, 10$, H-C(10a)); 2.62 (*d*, $J = 7$, 2 H-C(5)); 2.90 (br. *d*, $J = 12$, H_{eq} -C(2)); 3.59 (*s*, MeO); 4.10 (*d*, $J = 9$, H-C(10)); 6.39 (*d*, $J = 4$, H-C(9)); 6.58 (*dd*, $J = 8, 4$, H-C(7)); 6.96 (*d*, $J = 8$, H-C(6)); 7.11–7.28 (*m*, 5 H). MS: 307 (70, M^+), 292 (35), 210 (100), 209 (90), 179 (60), 97 (75), 96 (65).

trans-transoid-7-Bromo-1,2,3,4,4a,5,10,10a-octahydro-8-methoxy-1-methyl-10-phenylbenzo[*g*]quinoline (**21**). Br_2 (1.44 g, 9 mmol) in AcOH (20 ml) was slowly added under stirring to **20** (920 mg, 3 mmol) in AcOH (35 ml) at r.t. After 2 h, AcOH was evaporated, 30% NaOH/ice added, and the residue extracted with CH_2Cl_2 . The org. phase was dried, the solvent evaporated, and the two isomers **21** and **22** separated by FCC over silica gel in AcOEt/hexane. Crystalline **22** (420 mg, 36%) was eluted first, followed by crystalline **21** (460 mg, 40%).

21: 1H -NMR ($CDCl_3$): 1.19–1.32 (*m*, H_{ax} -C(4)); 1.60 (br. *d*, $J = 13$, H_{eq} -C(3)); 1.70–1.83 (*m*, H_{ax} -C(3), H-C(4a)); 1.93 (br. *d*, $J = 13$, H_{eq} -C(4)); 2.19 (*s*, CH_3N); 2.29 (*dt*, $J = 13, 3$, H_{ax} -C(2)); 2.59 (*dd*, $J = 8, 9$, H-C(10a)); 2.61 (*d*, $J = 7$, 2 H-C(5)); 2.90 (br. *d*, $J = 13$, H_{eq} -C(2)); 3.60 (*s*, 3 H, MeO); 4.07 (*d*, $J = 8$, H-C(10)); 6.34 (*s*, H-C(9)); 7.12–7.30 (*m*, 6 H). MS: 388 (5), 387 (20), 386 (5, M^+), 385 (20), 307 (30), 210 (25), 209 (30), 97 (100), 96 (50).

22: 1H -NMR ($CDCl_3$): 1.18–1.29 (*m*, H_{ax} -C(4)); 1.48–1.61 (*m*, H_{eq} -C(3), H-C(4a)); 1.66–1.80 (*m*, H_{ax} -C(3)); 1.90 (br. *d*, $J = 13$, H_{eq} -C(4)); 2.22 (*dt*, $J = 12, 5$, H_{ax} -C(2)); 2.40 (*dd*, $J = 7, 8$, H-C(10a)); 2.43 (*s*, CH_3N); 2.58 (*dd*, $J = 17, 3$, H_{eq} -C(5)); 2.71 (*dd*, $J = 17, 13$, H_{ax} -C(5)); 2.93 (br. *d*, $J = 12$, H_{eq} -C(2)); 3.78 (*s*, MeO); 4.57 (*d*, $J = 7$, H-C(10)); 6.65 (*d*, $J = 8$, H-C(7)); 7.03–7.28 (*m*, 6 H). MS: 388 (10), 387 (40), 386 (15, M^+), 385 (40), 209 (25), 97 (95), 96 (100).

trans-transoid-7-Bromo-1,2,3,4,4a,5,10,10a-octahydro-8-hydroxy-1-methyl-10-phenylbenzo[*g*]quinoline (**8**). Bromide **21** (580 mg, 1.5 mmol) was dissolved in CH_2Cl_2 (200 ml) and cooled to –78°. Br_3B (1.5 ml, 15 mmol) in CH_2Cl_2 (65 ml) was added and stirring continued, while the mixture was gradually warmed up to r.t. (2 h) and kept at this temp. for 3 h. Excess Br_3B was destroyed by adding MeOH at –78° followed by conc. NH_3 ; after stirring for 30 min, the org. phase was separated and the aq. phase extracted with CH_2Cl_2 . The combined org. phases were dried, evaporated, and gave crude crystalline **8** (580 mg). FCC over silica gel in CH_2Cl_2 /MeOH/conc. NH_3 provided pure **8** (450 mg, 83%). M.p. 259–260° (EtOH). 1H -NMR ($(D_5)pyridine + CDCl_3$): 1.12–1.25 (*m*, H_{ax} -C(4)); 1.42 (br. *d*, $J = 13$, H_{eq} -C(3)); 1.64–1.78 (*m*, H-C(4a), H_{ax} -C(3)); 1.85 (br. *d*, $J = 12$, H_{eq} -C(4)); 2.13 (*s*, CH_3N); 2.28 (*dt*, $J = 13, 3$, H_{ax} -C(2)); 2.55 (br. *d*, $J = 8, 2$ H-C(5)); 2.63 (*dd*, $J = 9, 11$ H-C(10a)); 2.76 (br. *d*, $J = 12$, H_{eq} -C(2)); 3.97 (*d*, $J = 9$, H-C(10)); 6.48 (*s*, H-C(9)); 7.12–7.20 (*m*, 2 H); 7.23–7.30 (*m*, 4 H); 9.65 (br. *s*, OH). MS: 374 (5), 373 (25), 372 (5, M^+), 371 (30), 293 (2), 195 (10), 97 (100), 96 (45). Anal. calc. for $C_{20}H_{22}BrNO$ (372.31): C 64.52, H 5.96, Br 21.46, N 3.76, O 4.30; found: C 64.59, H 5.89, Br 21.64, N 3.74.

(*E*)-4-Methoxycinnamyl (*Z*)-3-Phenylacrylate (**23**). Ester **9** (1 g, 3.4 mmol) was hydrogenated at 1 atm in the presence of Lindlar catalyst (500 mg) in AcOEt (200 ml) containing quinoline (4 drops). After 1 equiv. of H_2 was consumed, the catalyst was filtered off, the solvent evaporated, and the residue chromatographed over silica gel in hexane/ CH_2Cl_2 , yielding crystalline **23** (680 mg, 68%). 1H -NMR ($CDCl_3$): 3.81 (*s*, MeO); 4.75 (*dd*, $J = 6, 1$, CH_2O); 5.98 (*d*, $J = 13$, =CHCO); 6.13 (*td*, $J = 16, 6$, =CHCH₂); 6.56 (*d*, $J = 16$, CH=CHCH₂); 6.85 (br. *d*, $J = 9$, 2 H *ortho* to MeO); 6.98 (*d*, $J = 13$, Ph-CH=); 7.28–7.38 (*m*, 5 H); 7.55–7.63 (*m*, 2 H). MS: 294 (20, M^+), 163 (20), 147 (80), 131 (100), 103 (40), 91 (25), 77 (30).

cis-transoid-3a,4,9,9a-Tetrahydro-4-(4-methoxyphenyl)naphtho[2,3-*c*]furan-1(3H)-one (**24**). Ester **23** (100 mg, 0.3 mmol) was dissolved in DMF (4 ml) and refluxed for 14 h under N_2 . DMF was evaporated, the residue recrystallized from MeOH yielding lactone **24** (65 mg, 65%). M.p. 193–194°. 1H -NMR ($CDCl_3$): 2.96 (*dd*, $J = 15, 6$, H-C(4)); 3.01–3.09 (*m*, H-C(2)); 3.1–3.18 (*m*, H-C(3)); 3.26 (*dd*, $J = 15, 6$, H-C(4)); 3.72 (*d*, $J = 10$, H-C(1)); 3.84 (*s*, MeO); 4.04 (*dd*, $J = 10$, CH_2O); 4.36 (*dd*, $J = 10$, and 6, CH_2O); 6.73 (*d*, $J = 7$, H-C(8)); 6.95 (br. *d*, $J = 8$, 2 H *ortho* to MeO); 7.12 (br. *d*, $J = 8$, 2 H *meta* to MeO, H-C(7)); 7.18–7.28 (*m*, 2 H). MS: 294 (85, M^+), 211 (60), 210 (90), 179 (100), 142 (50).

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