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

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(15.V.88)

The diastereoselective synthesis of (±)-*trans-transoid*-7-bromo-8-hydroxy-1-methyl-1,2,3,4,4a,5,10,10a-octahydro-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-2[2]); 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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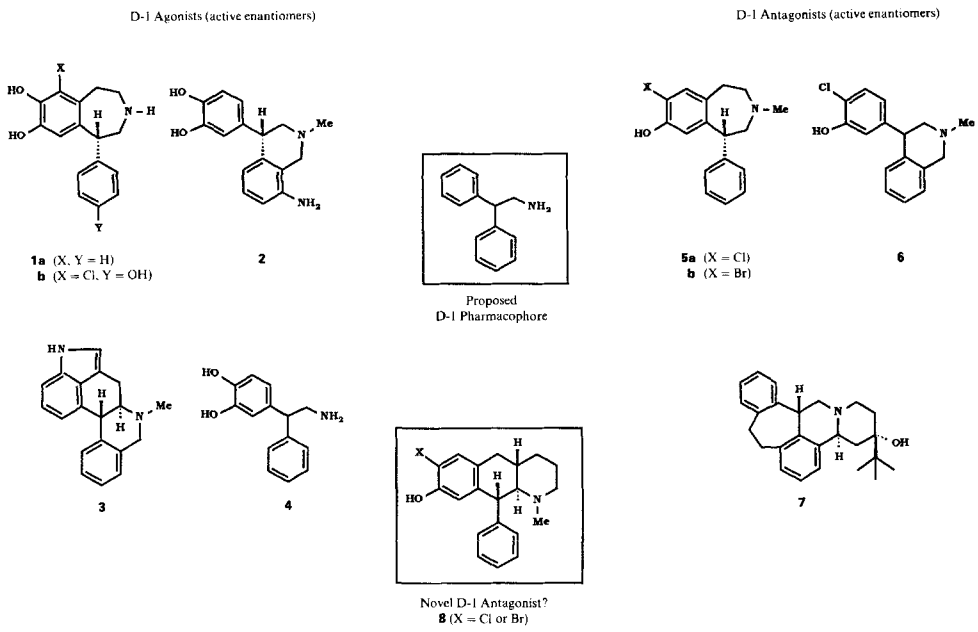
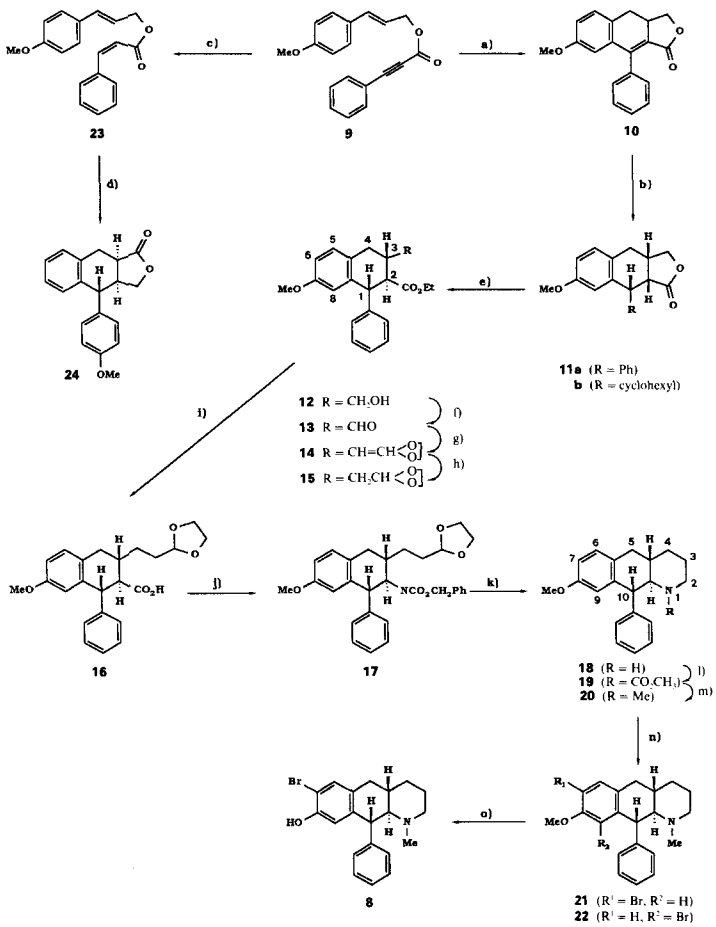
[2]) *Goldberg* and *Kohli* proposed that peripheral DA receptors can be subdivided into DA1 and DA2. In this paper, the term D-1 (D-2) implies also DA1 (DA2) [7].



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 phenylpropiolic acid, using DCC/DMAP in CH_2Cl_2 – was converted in 54% yield to lactone **10** by means of an intramolecular *Diels-Alder* reaction in refluxing Ac_2O [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 ^{1}H-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

Scheme



a) Ac_2O, reflux, 6 h; b) EtOH, *Raney*-Ni, 60°, 120 atm, H_2; c) *Lindlar* cat., AcOEt, 1 atm H_2; 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 H_2; i) EtOH, 4.55M NaOH, reflux 7 h; j) Diphenylphosphoryl azide, $PhCH_2OH$, Et_3N, toluene, reflux 48 h; k) EtOH, 1N HCl, reflux 45 min, then 10% Pd/C, EtOH/AcOEt 12:1, 1 atm H_2; l) ClCOOMe, Et_3N, toluene, 50°; m) $LiAlH_4$, THF, reflux; n) Br_2, OH, r.t.; o) Br_3B, CH_2Cl_2, −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 ^{1}H-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 $LiAlH_4$. 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 SO_2Cl_2 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 Br_3B 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). ^{1}H-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 phenylpropiolic acid (21.3 g, 0.146 mol), 4-methoxycinnamyl alcohol (24 g, 0.146 mol), and DMAP (1.7 g, 14.6 mmol) in CH_2Cl_2 (400 ml). The mixture was stirred for 1 h at r.t., filtered, and evaporated. FCC of the residue over silica gel in CH_2Cl_2/hexane yielded **9** (32.4 g, 76%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$): 3.80 (*s*, MeO); 4.87 (*dd*, *J* = 7, 1, $-CH_2-$); 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, $M^{+\cdot}$), 147 (70), 129 (100).

*3a,4-Dihydro-7-methoxy-9-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one* (**10**). Ester **9** (48 g, 0.164 mol) was dissolved in Ac_2O (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°. ^{1}H-NMR ($CDCl_3$): 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 ($M^{+\cdot}$, 30). Anal. calc. for $C_{19}H_{16}O_3$ (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(3*H*)-one* (**11a**). Lactone **10** (10 g, 34 mmol) in EtOH (2 l) was heated for 15 h at 60° and 120 atm H_2 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: ^{1}H-NMR ($CDCl_3$): 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, $M^{+\cdot}$), 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 H_2O and extracted three times with CH_2Cl_2. 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°. ^{1}H-NMR ($CDCl_3$): 1.01 (*t*, *J* = 7, CH_3); 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, CH_2OH); 3.98 (*dq*, *J* = 7, 2, $O-CH_2$); 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.: 100–123°). 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. 79–80°. Overall yield from **13** to **15**: 73%. ^{1}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, H_{ax}–C(4)); 2.64 (*t*, J = 10, H–C(2)); 3.05 (*dd*, J = 5, 14, H_{eq}–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. 156–157°. ^{1}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, H_{ax}–C(4)); 2.64 (*t*, J = 11, H–C(2)); 3.02 (*dd*, J = 5, 14, H_{eq}–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. 152–153°. ^{1}H-NMR ((D_6)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, H_{ax}–C(4)); 2.93 (*dd*, J = 16, 5, H_{eq}–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 CH_2Cl_2/MeOH/NH_3 (conc.) yielded pure **18** (2.1 g, 73%). M.p. > 285° (MeOH). ^{1}H-NMR ($CDCl_3$): 1.10–1.21 (*m*, H_{ax}–C(4)); 1.63–1.70 (*m*, 2 H–C(3)); 1.71–1.84 (*m*, H–C(4a)); 1.92–2.01 (*m*, H_{eq}–C(4)); 2.45–2.55 (*m*, H_{ax}–C(2)); 2.61 (*dd*, J = 16, 12, H_{ax}–C(5)); 2.64 (*dd*, J = 11, H–C(10a)); 2.82 (*dd*, J = 16, 5, H_{eq}–C(5)); 2.95–3.01 (*m*, H_{eq}–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**). ^{1}H-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: ^{1}H-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: ^{1}H-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). ^{1}H-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%). ^{1}H-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, =$CHCH_2$); 6.56 (*d*, *J* = 16, CH=$CHCH_2$); 6.85 (br. *d*, *J* = 9, 2 H *ortho* to MeO); 6.98 (*d*, *J* = 13, Ph–C*H*=); 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°. ^{1}H-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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