Syntheses of *O*-Methylasparvenone-Derived Serotonin-Receptor Antagonists

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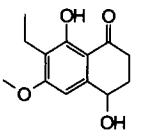
Based on *O*-methylasparvenone (**1**), a N-free $5HT_{2C}$ antagonist with moderate affinity ($pK_i = 6.7$), derivatives bearing dimethylamino (**7**), (dimethylamino)methyl (**17**, **18**, **21**, and **22**), and aminomethyl substituents (**26**) in place of the benzylic OH group of **1** as well as pyrrolidine- (**33**) and piperidine-fused derivatives (**29**, **43**, and **45**) were synthesized. In contrast to the lead structure **1**, these new ligands were active *in vivo* in the rat. The tricycles **33** and **45** display high affinities for the $5HT_{2C}$ receptor ($pK_i = 8$).

1. Introduction. – Serotonin (5HT) receptor antagonists which bind preferentially to the $5HT_{2C}$ receptor are receiving increasing attention. Agents from diverse chemical classes such as pyridylureas [1], indolonaphthyridines [2], and benzenesulfonamido-substituted valerophenones [3] have been reported to bind with high affinity to the $5HT_{2C}$ receptor. Potential therapeutic targets of $5HT_{2C}$ receptor antagonists include anxiety, migraine, sleep disorders, and other diseases [4], and for a mixed $5HT_{2C}/5HT_{2B}$ receptor antagonist, *Kennett et al.* report anxiolytic-like effects in animal models [5].

We have identified the natural product *O*-methylasparvenone (**1**) as an antagonist at the $5HT_{2C}$ receptor binding site [6]. This N-free ligand binds with moderate affinity ($pK_i = 6.7$) and fully antagonizes the 5HT-induced phosphoinositol turnover *in vitro*. Due to the insolubility of the compound in bio-compatible solvents, however, **1** could not be evaluated in an *in vivo* model of $5HT_{2C}$ receptor function, the antagonism of mCPP-induced penile erections in rats [7]. Our goal was to synthesize H_2O-soluble derivatives of **1** by the incorporation of a basic N-atom and to study them *in vivo*. In contrast to a prodrug approach, the synthesis of such derivatives was considered to be a means to find new antagonists with improved affinity as well as solubility.

We envisaged replacing the benzylic OH group of the lead structure **1** by dimethylamino and (dimethylamino)methyl substituents since this position seems to tolerate variations without affecting the affinity to the receptor [6]. Other variations concern the size and the nature of the saturated ring. We describe derivatives with five- and six-membered-ring ketones, γ-lactams, and pyrrolidine- and piperidine-fused ring systems.



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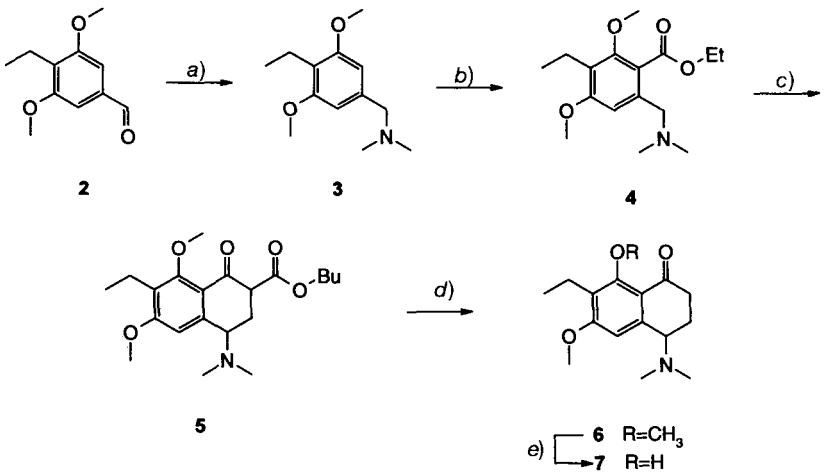
2. Syntheses. – 2.1. *Bicyclic Derivatives.* The (dimethylamino)-substituted derivative **7** was prepared as shown in *Scheme 1*. Reductive amination of the known aldehyde **2** [8] followed by metalation of **3** with butyllithium and reaction with ethyl chloroformate (= ethyl carbonochloridate) yielded the amino ester **4** (61% overall). The cyclization was performed *via* a tandem *Michael-Dieckmann* reaction of the anion of **4** with acrylate [9] affording a mixture of diastereoisomers of the bicyclic β-keto esters **5** (*ca.* 1:1). Ester hydrolysis and decarboxylation followed by selective ether cleavage of **6** with BBr_3 gave **7**, the dimethylamino analog of **1**.

Scheme 1



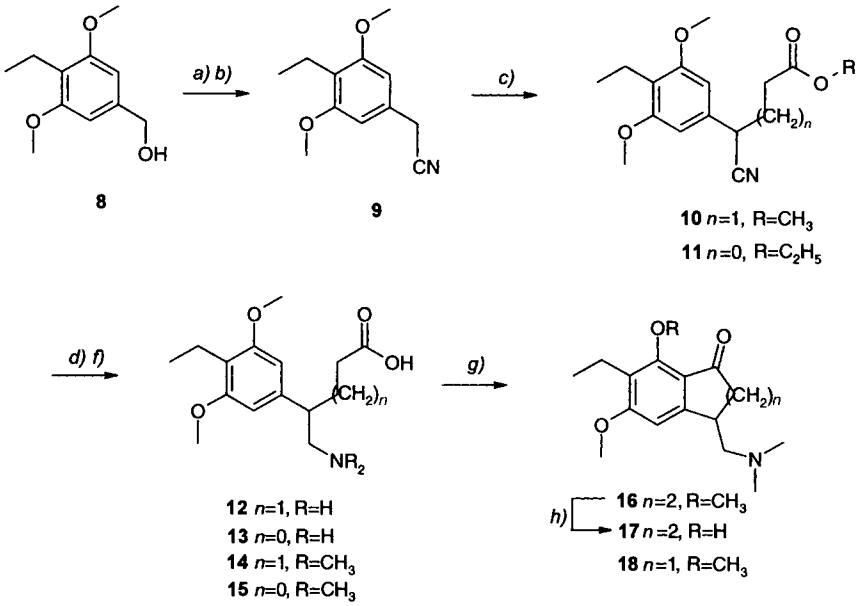
2 **3** **4** **5**

a) DMF, HCOOH; 75%. *b*) BuLi, ClCOOEt, 82%. *c*) LDA, H_2C=CHCOOBu. *d*) HCl; 38%. *e*) BBr_3; 64%.

The syntheses of (dimethylamino)methyl derivatives **17** and **18** are outlined in *Scheme 2*. Benzyl alcohol **8** [6] was transformed to the nitrile **9** in 78% yield by treatment with $SOCl_2$ and subsequent reaction with NaCN in DMSO. Alkylation of the benzeneacetonitrile **9** was carried out with NaH and 3-bromopropanoate or bromoacetate to give either **10** or **11** in low yield (13–17%), together with unreacted starting material. The ω-amino acids **12** and **13** were prepared by ester hydrolysis and hydrogenation. Reductive methylation afforded the ω-(dimethylamino) acids **14** and **15**, the precursors to the bicyclic ketones **16** and **18** which were accessible through intramolecular *Friedel-Crafts* acylation with trifluoroacetic anhydride in trifluoroacetic acid [10] in 32–40% overall yield. Treatment of **16** with BBr_3 yielded the phenol **17**, whereas all attempts to selectively cleave the methyl-ether moiety of **18** failed.

Derivatives of five-membered lactones are readily available. Thus, lactones **21** and **22** were synthesized by aminoalkylation of the phthalides **19** and **20** [6] with lithium diisopropylamide (LDA) and *Eschenmoser*'s salt (*Scheme 3*) in 39 and 27% yield, respectively. Being compatible with the lactone group, the primary amine **26** was synthesized by nitroaldol condensation of the hydroxyphthalide **24** with nitromethane and hydrogenation of the (nitromethyl)phthalide **25**. The precursor **24** was accessible in three steps from aldehyde **2**. Bromination of **2** followed by acetalization yielded **23** in 89% yield which was cyclized with CO_2 after Br/Li exchange and acidic workup.

Scheme 2



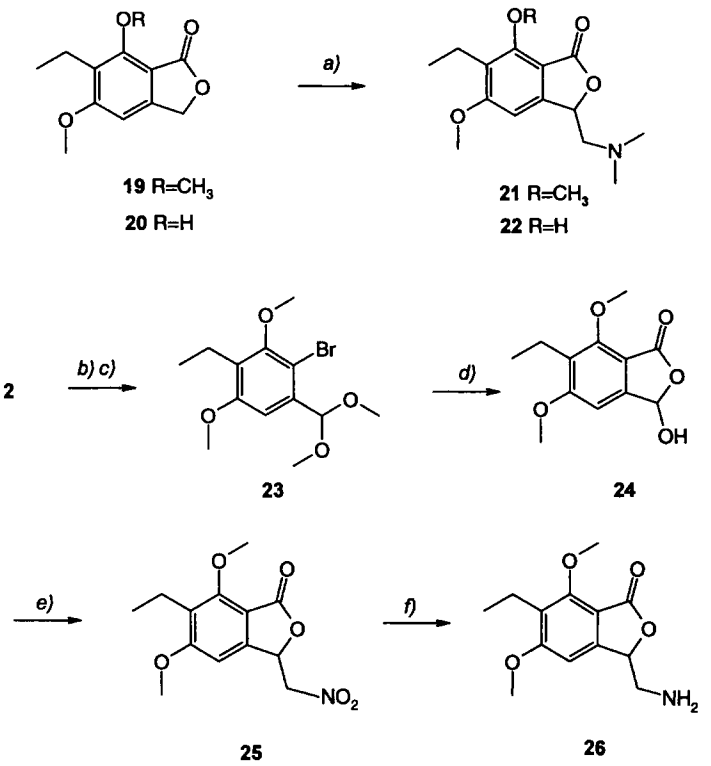
a) $SOCl_2$. *b*) NaCN, DMSO; 87%. *c*) NaH, $Br(CH_2)_nCH_2COOR$; 13–17%. *d*) NaOH. *e*) *Raney*-Ni, H_2. *f*) HCHO, $NaCNBH_3$. *g*) CF_3COOH, $(CF_3CO)_2O$; 71–78%. *h*) BBr_3; 66%.

2.2. *Tricyclic Derivatives.* The syntheses of rigidified structures with an aminomethyl group are the subject of *Schemes 4–6*. The tetrahydroisoquinoline derivative **29** (*Scheme 4*) was prepared from amino acid **12**. Cyclization with formaldehyde and subsequent reaction with formaldehyde and cyanoborohydride yielded **27** in 53% yield. Hydrolysis of the ester followed by intramolecular *Friedel-Crafts* reaction produced the tricycle **28** (67%) which gave **29** upon treatment with BBr_3.

The synthesis of the pyrrolidine-fused compound **33** is summarized in *Scheme 5*. Nitrile **11** was hydrogenated over *Raney*-Ni to give the pyrrolidinone **30**. Alkylation with MeI in the presence of NaH led to **31**. Enolate formation with LDA and subsequent reaction with bromoacetate gave **32** as a mixture of diastereoisomeric esters (*trans*/*cis* ≈ 95:5, based on the integral ratios of the NMR signals of the *tert*-butyl ester; *trans*-configuration of the major component according to $J(3,4) = 17.5$ Hz). Reduction of the amide with borane and cyclization with polyphosphoric acid (PPA) afforded exclusively the *cis*-configured phenol **33** (evidenced by $J(3a,9b) = 7$ Hz), representing the thermodynamically more stable ring system [11].

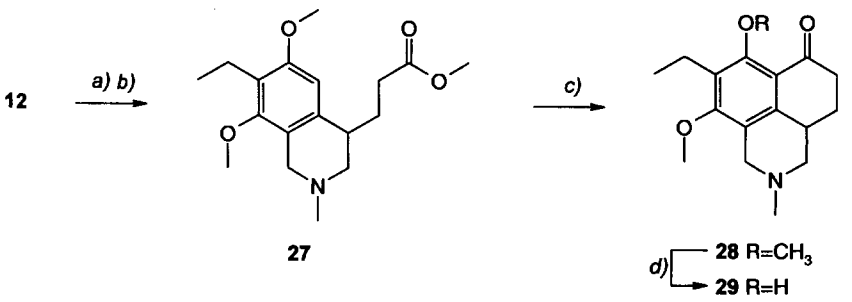
The homologous *cis*- and *trans*-compounds **43** and **45**, respectively, were obtained according to *Scheme 6*. Following the procedure by *Ogura et al.* [12] using methyl (methylthio)methyl sulfoxide, aldehyde **2** was transformed *via* **34** into phenylacetate **35** in 65% yield. Treatment of **35** with paraformaldehyde in the presence of K_2CO_3 [13] led to acrylate **36** (67%). *Michael* addition of ethyl 3-(methylamino)propanoate [14] to **36** gave the precursor **37** to the piperidone **38** which was formed upon treatment with NaH followed by hydrolysis and decarboxylation with HCl [15]. The subsequent conversion of **38** into the octahydrobenz[*h*]isoquinolinones **43** and **45** was accomplished by a known

Scheme 3



a) LDA, $H_2C{=}NMe_2I$. *b*) Br_2, CCl_4. *c*) $HC(OMe)_3$; 89%. *d*) BuLi, CO_2; 64%. *e*) $MeNO_2$, KOH; 70%. *f*) Pd/C, H_2; 55%.

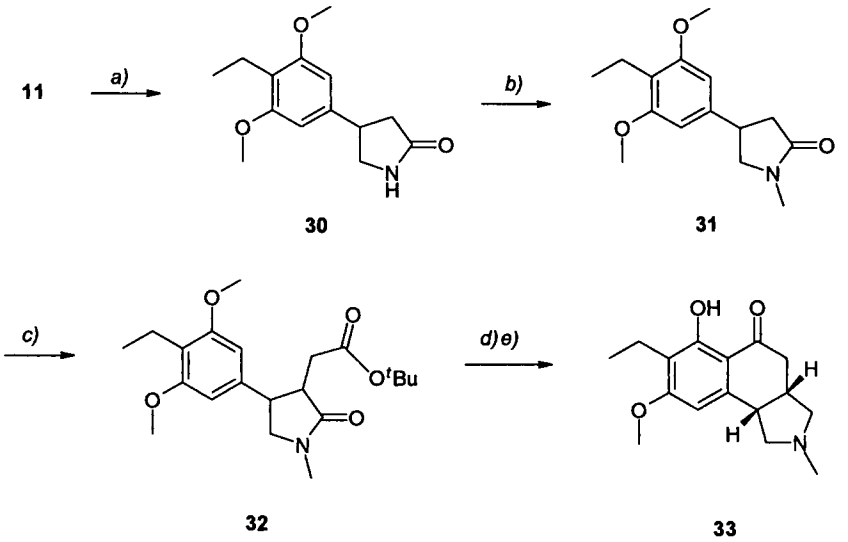
Scheme 4



a) HCHO. *b*) HCHO, $NaCNBH_3$; 53%. *c*) CF_3COOH, $(CF_3CO)_2O$; 67%. *d*) BBr_3; 63%.

route described by *Bastian* and *Ebnöther* [16]. *Horner-Emmons* reaction produced the (*E*)-alkene **39** in 85% yield. The geometry of the double bond was assigned by means of NOE measurements (irradiation at 5.34 ppm (olefinic proton) NOE's at the aromatic protons (6%) and the benzylic proton (2.3%)). Hydrogenation of **39** gave a mixture

Scheme 5



a) *Raney*-Ni, H_2; 47%. *b*) NaH, MeI; 86%. *c*) LDA, $BrCH_2COO^tBu$; 43%. *d*) $B_2H_6 \cdot THF$. *e*) PPA; 97%.

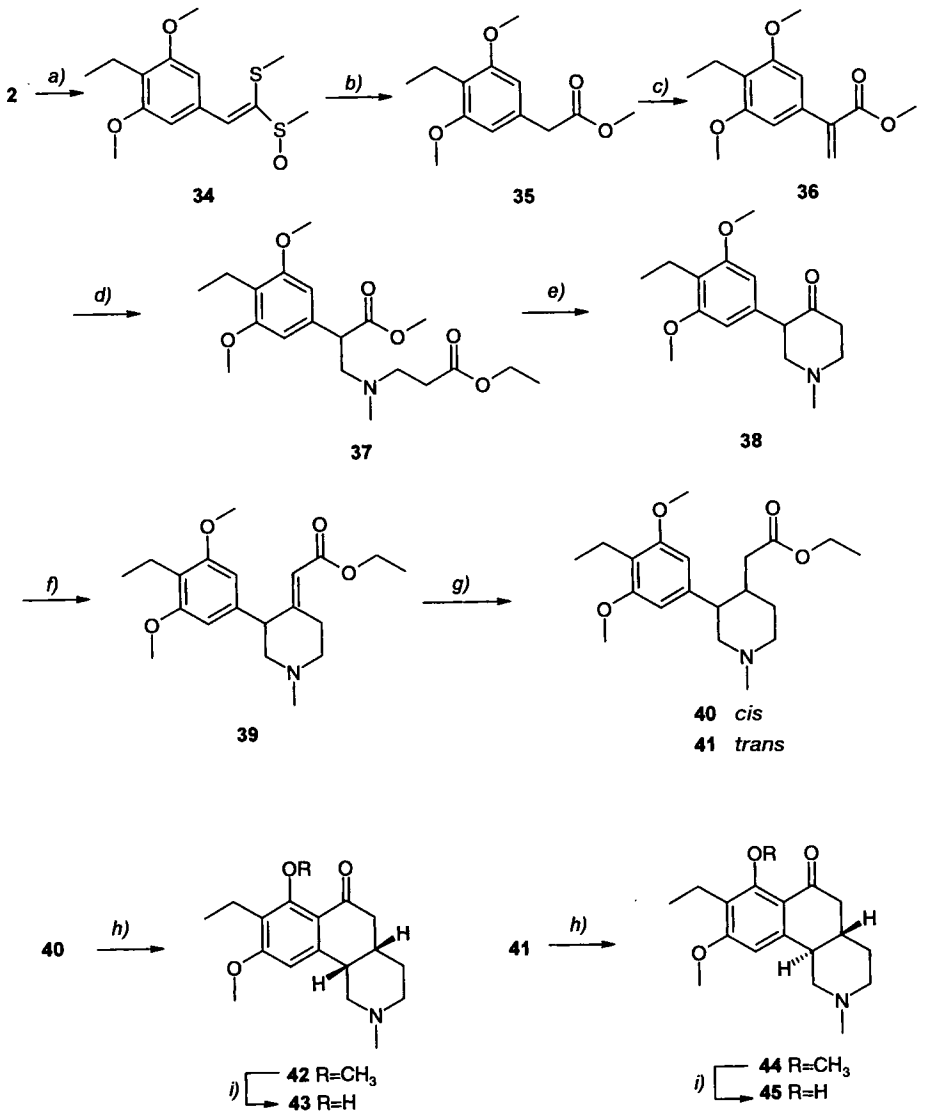
40/**41** (*cis*/*trans ca.* 80:20). The *trans*-configuration of **41** was derived from NMR data. The benzylic proton at 2.51 ppm shows two axial (J = 10 Hz each) and one equatorial (J = 4 Hz) coupling. This can only be rationalized with an equatorial, thus *trans*, relationship between the aromatic ring and the ester side chain on the piperidine ring. Finally, by treating each isomer with PPA, the corresponding *cis*- (**42**) and *trans*-fused (**44**) piperidine ring systems were formed. Selective phenol-ether cleavage with BBr_3 yielded the *O*-methylasparvenone analogs **43** and **45**[1]).

3. Pharmacology. – The affinities of the compounds for the human $5HT_{2C}$ receptors were assessed in 3T3 cells stably expressing the recombinant $5HT_{2C}$ receptors using [^{3}H]-5HT as the radioligand [6][17] (*cf. Table*). Replacement of the benzylic OH group by a dimethylamino substituent results in reduced affinity of compound **7**. The (dimethylamino)methyl analog **17** displays similar affinity as *O*-methylasparvenone (**1**), whereas the pK_i of the corresponding methyl ether **16** is lower. For the phthalide derivatives, the opposite is the case. The methyl ether **21** has a somewhat higher affinity than the phenol **22**. The primary amine **26** is a high-affinity ligand with a pK_i of 7.4.

Particularly interesting are the rigidified tricyclic compounds. The isoquinolines **28** and **29** show only low affinity, whereas ring closure to C(3) of the asparvenone skeleton leads to a sharp increase in binding affinity to the $5HT_{2C}$ receptor; the pyrrolidine derivative **33** displays a pK_i of 8.0. In the series of the piperidine-fused compounds, the *trans*-stereoisomers **44** and **45** bind with higher affinity to the $5HT_{2C}$ receptor than the corresponding *cis*-derivatives **42** and **43**. Again the pK_i values of the methyl ethers are inferior to those of the phenols.

[1]) The *trans*-configuration of **45** was confirmed by X-ray analysis.

Scheme 6



a) $MeSCH_2SOMe$, *Triton B*, 69%. *b*) HCl, MeOH; 94%. *c*) Paraformaldehyde, K_2CO_3, Bu_4NI; 67%. *d*) $MeNHCH_2CH_2COOEt$; 59%. *e*) NaH, HCl; 88%. *f*) NaH, $(MeO)_2POCH_2COOEt$; 85%. *g*) Pd/C, H_2; 98%. *h*) PPA; 61–68%. *i*) BBr_3; 67–94%.

In addition, the ligands were functionally characterized *in vitro* in the phosphoinositol turnover model of $5HT_{2C}$ receptor activation in the choroid plexus of the rat under the previously described conditions [6]. With the exception of the partial agonist **26**, the compounds display no intrinsic activity.

As expected, the new ligands were soluble in physiological saline. The compounds with sufficient affinity ($pK_i \geq 6.3$) as well as the dimethylamino analog **7** were tested *in*

Table. *$5HT_{2C}$ Receptor Binding Affinity* (pK_i) *and* in vivo *Inhibition of $5HT_{2C}$ Receptor-Mediated Function* (mCPP-induced penile erections)

	pK_i ($5HT_{2C}$)	ID_{50} [mg/kg *sc*]		pK_i ($5HT_{2C}$)	ID_{50} [mg/kg *sc*]
1	6.7	inact.	**28**	5.8	n.t.
7	6.0	30	**29**	6.2	n.t.
16	6.2	n.t.	**33**	8.0	5.3
17	6.5	30	**42**	5.9	n.t.
18	6.6	9.5	**43**	6.5	inact.
21	6.3	2.2	**44**	7.5	1.3
22	6.1	n.t.	**45**	8.0	2.5
26	7.4	1			

vivo. Indeed, $5HT_{2C}$ receptor-mediated penile erections (induced with mCPP) [7] were antagonized by the compounds in a dose range of ID_{50} of 2.5–30 mg/kg given subcutaneously. The tricycles **33** and **45** which displayed high affinity for the $5HT_{2C}$ receptor were also administered orally and were found to be active ($ID_{50} \approx 9.7$ and 100 mg/kg, resp.)

The pharmacological profiles of several pyridiylureas which exhibit $5HT_{2C}$ receptor antagonism are described in the literature [1][18][19]. The $5HT_{2C}$ receptor antagonism was demonstrated *in vivo* through reversal of mCPP-induced hypolocomotion in rats. In view of the recent evidence that activation of the $5HT_{2C}$ receptors in rats elicits penile erection [20], the reversal of mCPP-induced penile erection in rats by *O*-methylasparvenone derivatives in the present experiment provides clear evidence for potent $5HT_{2C}$ receptor antagonism *in vivo*.

Experimental Part

General. All laboratory glassware was dried at 130° and purged with dry Ar. Tetrahydrofuran was distilled from sodium benzophenone ketyl (sodium diphenylketyl) and then transferred *via* syringe. Melting points: *Büchi-530* apparatus, capillary tubes; uncorrected. Column chromatography (CC): silica gel (230–400 mesh; *Merck*), 0.3–1.0 bar pressure. IR Spectra: *Nicolet-7199*-FT-IR in cm^{-1}. ^{1}H-NMR Spectra: *Bruker-AC-250* (250 MHz); δ values in ppm rel. to internal $SiMe_4$, coupling constants J in Hz. MS: *MS*9, updated with a *Finnigan* MAT data system *SS 200*; *m/z* (rel.%).

4-Ethyl-3,5-dimethoxy-N,N-*dimethylbenzenemethanamine* (**3**). To a soln. of **2** [8] (7.4 g, 39 mmol) in DMF (20 ml) and formic acid (2 ml), H_2O (0.4 ml) was added, and the mixture was heated under reflux overnight. After cooling, Et_2O was added and the mixture extracted with 1N aq. HCl (150 ml). The aq. layer was basified with 2N NaOH and extracted with Et_2O. The org. layer was dried (Na_2SO_4) and evaporated. The crude material was purified by bulb-to-bulb distillation yielding **3** (6.4 g, 75.3%). Colorless oil. B.p. 150°, 0.3 mbar. ^{1}H-NMR ($CDCl_3$): 1.07 (*t*, J = 7.5, 3 H); 2.25 (*s*, 6 H); 2.63 (*q*, J = 7.5, 2 H); 3.37 (*s*, 2 H); 3.81 (*s*, 6 H); 6.49 (*s*, 2 H). MS: 223 (M^+), 180 ([$M - CH_2NCH_3$]$^+$). Anal. calc. for $C_{13}H_{21}NO_2$ (223.30): C 69.92, H 9.48, N 6.27; found: C 69.90, H 9.55, N 6.27.

Ethyl 6-[(Dimethylamino)methyl]-3-ethyl-2,6-dimethoxybenzoate (**4**). To a soln. of **3** (2.23 g, 10 mmol) in Et_2O (50 ml) was added 1.6N BuLi (7.5 ml) at 0°. The mixture was stirred for 2 h at r.t. and then cooled to 0°. A soln. of ethyl carbonochloridate (1.14 ml, 12 mmol) in Et_2O (10 ml) was added and after 12 h at r.t. the mixture was quenched with H_2O (10 ml). The org. layer was dried (Na_2SO_4) and evaporated. The residue was subjected to CC (silica gel, AcOEt): **4** (2.4 g, 82%). Yellow oil. IR (film): 1725, 1601, 1456. ^{1}H-NMR ($CDCl_3$): 1.13 (*t*, J = 7.5, 3 H); 1.37 (*t*, J = 7.5, 3 H); 2.19 (*s*, 6 H); 2.63 (*q*, J = 7.5, 2 H); 3.39 (*s*, 2 H); 3.79 (*s*, 3 H); 3.83 (*s*, 3 H); 4.35 (*q*, J = 7.5, 2 H); 6.66 (*s*, 1 H). MS: 295 (M^+), 280 ([M – Me]$^+$), 266 ([$M - C_2H_5$]$^+$), 234 ([M – Me – EtOH]$^+$).

The fumarate was prepared in Et_2O by treatment of **4** with fumaric acid. M.p. 141–143°. Anal. calc. for $C_{16}H_{25}NO_4 \cdot C_4H_4O_4$ (411.45): C 58.38, H 7.10, N 3.40; found: C 58.25, H 7.17, N 3.47.

(RS)-4-(Dimethylamino)-7-ethyl-3,4-dihydro-6,8-dimethoxynaphthalen-1(2H)-one (**6**). To a soln. of freshly prepared LDA (9 mmol) in THF/hexane 9:1 (45 ml), **4** (2.4 g, 8 mmol) was added at −75°. After stirring for 75 min at −75°, butyl acrylate (1.3 ml, 9 mmol) was added. The mixture was stirred at −75° for 1 h, warmed to −40°, and stirred for an additional 15 h at −40°. The reaction was quenched with AcOH (1.6 ml), and after the addition of H_2O (400 ml) and 28% NaOH soln. (16 ml), the mixture was extracted with AcOEt. The org. layer was dried (Na_2SO_4) and evaporated. The residue was purified by CC (silica gel, AcOEt): 1.2 g of *butyl (2RS,4RS)- and (2RS,4SR)-4-(dimethylamino)-7-ethyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-oxonaphthalene-2-carboxylate* (*ca.* 1:1; **5**) as a yellow oil. A soln. of **5** in EtOH (30 ml) and 1M aq. Na_2CO_3 (30 ml) was stirred for 3 d at r.t., and after the addition of 25% HCl soln. (15 ml), for another 2 d. The soln. was basified with Na_2CO_3 and extracted with AcOEt. The org. layer was dried (Na_2SO_4) and evaporated and the residue purified by CC (silica gel, AcOEt): **6** (330 mg, 38%). Yellow oil. IR (film): 1737, 1588, 1455. ^{1}H-NMR ($CDCl_3$): 1.11 (*t*, *J* = 7.4, 3 H); 2.10 (*m*, 2 H); 2.28 (*s*, 6 H); 2.45 (*ddd*, *J* = 17.1, 9.7, 5.4, 1 H); 2.65 (*q*, *J* = 7.4, 2 H); 2.79 (*ddd*, *J* = 17.1, 6.3, 4.8, 1 H); 3.57 (*dd*, *J* = 8.5, 3.7, 1 H); 3.79 (*s*, 3 H); 3.89 (*s*, 3 H); 6.99 (*s*, 1 H). MS: 277 (M^+), 248 ($[M - Et]^+$), 233 ($[M - Me_2N]^+$).

(RS)-4-(Dimethylamino)-7-ethyl-3,4-dihydro-8-hydroxy-6-methoxynaphthalen-1(2H)-one (**7**). To a soln. of **6** (190 mg, 0.7 mmol) in CH_2Cl_2 (7 ml), 0.07M HCl in Et_2O (20 ml) was added, and then the solvent was removed. The hydrochloride was again dissolved in CH_2Cl_2 (14 ml), and 1M boron tribromide in CH_2Cl_2 (0.7 ml) was added at −75°. After 5 min, the cooling bath was removed, and the mixture was warmed to r.t. and stirred at r.t. for 1 h. The reaction was quenched with H_2O (13 ml), CH_2Cl_2 removed, and the residue heated under reflux for 45 min. The mixture was extracted with AcOEt (3 × 10 ml) and the org. layer washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The residue was purified by CC (silica gel, AcOEt). 140 mg (78%) of **7**. The fumarate was prepared in Et_2O by treatment with fumaric acid: M.p. 156–158° (dec.). ^{1}H-NMR ((D$_6$)DMSO): 1.01 (*t*, *J* = 7.5, 3 H); 1.95 (*m*, 1 H); 2.09 (*m*, 1 H); 2.27 (*s*, 6 H); 2.53 (*q*, *J* = 7.5, 2 H); 2.67 (*m*, 2 H); 3.77 (*dd*, *J* = 9.7, 3.6, 1 H); 3.87 (*s*, 3 H); 6.62 (*s*, 1 H). MS: 263 (M^+), 220 ($[M - CH_2NMe]^+$), 219 ($[M - NMe_2]^+$). Anal. calc. for $C_{15}H_{21}NO \cdot C_4H_4O_4$ (411.45): C 60.15, H 6.64, N 3.69; found: C 59.94, H 6.69, N 3.66.

4-Ethyl-3,5-dimethoxybenzeneacetonitrile (**9**). To a stirred soln. of **8** [6] (15.1 g, 76.7 mmol) in pyridine (7 ml) at 0°, thionyl chloride (7.25 ml, 99.7 mmol) was added dropwise within 10 min. The mixture was then heated to 80° for 20 min, poured into ice-water (150 ml), and extracted with Et_2O (3 × 300 ml). The combined org. layers were washed (2 × 150 ml H_2O), dried ($MgSO_4$), and evaporated. The residue (14.8 g, 69.1 mmol) was taken up in DMSO (45 ml) and added dropwise to a stirred mixture of NaCN (3.72 g, 76.0 mmol) at 120°. After 10 min, the mixture was poured into ice-water (150 ml) and extracted with Et_2O (3 × 300 ml). The combined org. layers were washed with H_2O (2 × 150 ml), dried ($MgSO_4$), and evaporated. The crude material was purified by CC (silica gel, hexane/AcOEt 3:1): **9** (11.1 g, 78%). Pale-brown solid. M.p. 103–104°. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.05 (*t*, *J* = 7.5, 3 H); 2.63 (*q*, *J* = 7.5, 2 H); 3.72 (*s*, 2 H); 3.82 (*s*, 6 H); 6.47 (*s*, 2 H). MS: 205 (M^+), 190 ($[M - Me]^+$), 130. Anal. calc. for $C_{12}H_{15}NO_2$ (205.25): C 70.22, H 7.37; found: C 69.99, H 7.25.

Methyl (RS)-γ-Cyano-4-ethyl-3,5-dimethoxybenzenebutanoate (**10**). To a stirred and cooled (0°) soln. of **9** (8.60 g, 41.9 mmol) in DMF (60 ml), NaH (60% in oil; 1.84 g, 46.1 mmol) was added. The soln. was stirred at r.t. for 30 min and cooled again to 0°. A soln. of methyl 3-bromopropanoate (5.08 ml, 46.1 mmol) in DMF (40 ml) was added dropwise. The mixture was stirred at 0° for 30 min and for additional 4 h at r.t., poured into ice-water (150 ml), and extracted with Et_2O (3 × 200 ml). The combined org. layers were washed with H_2O (2 × 150 ml), dried ($MgSO_4$), and evaporated. The crude material was purified by CC (silica gel, toluene/AcOEt 19:1): **9** (5.11 g, 59%) and **10** (1.57 g, 13%). **10**: Pale yellow oil. ^{1}H-NMR ($CDCl_3$): 1.05 (*t*, *J* = 7.5, 3 H); 2.23 (*q*, *J* = 7.5, 2 H); 2.44–2.57 (*m*, 2 H); 2.63 (*q*, *J* = 7.5, 2 H); 3.70 (*s*, 3 H); 3.83 (*s*, 6 H); 3.92 (*t*, *J* = 7.5, 1 H); 6.48 (*s*, 2 H).

(RS)-γ-(Aminomethyl)-4-ethyl-3,5-dimethoxybenzenebutanoic Acid (**12**). A soln. of **10** (1.55 g, 5.32 mmol) in MeOH (40 ml) and 1N NaOH (20 ml) was stirred at r.t. for 1 h, poured into H_2O (100 ml), and extracted with AcOEt (2 × 100 ml). To the aq. layer was added 1N HCl (30 ml), and it was extracted with AcOEt (2 × 100 ml). The combined org. layers were washed with brine (100 ml), dried ($MgSO_4$), and evaporated. The residue was taken up in MeOH (30 ml) and 28% NH_4OH soln. (2 ml), and hydrogenated over *Raney*-Ni for 15 h. The catalyst was filtered off and washed with MeOH (50 ml). The org. layer was evaporated: **12** (1.04 g, 69%). White solid. M.p. 160°. ^{1}H-NMR (CD_3OD): 1.00 (*t*, *J* = 7.5, 3 H); 1.76–2.19 (*m*, 4 H); 2.59 (*q*, *J* = 7.5, 2 H); 2.89 (br. *s*, 1 H); 3.04–3.25 (*m*, 2 H); 3.82 (*s*, 6 H); 6.49 (*s*, 2 H). MS: 280 ($[M - H]^-$).

(RS)-γ-[(Dimethylamino)methyl]-4-ethyl-3,5-dimethoxybenzenebutanoic Acid (**14**). To a stirred soln. of **12** (500 mg, 1.78 mmol) and formaldehyde (1.3 ml) in MeOH (10 ml) was added sodium cyanoborohydride (262 mg, 3.55 mmol), and stirring was continued for 1 h. The mixture was evaporated and the residue purified by CC (silica gel, CH_2Cl_2/MeOH/NH_4OH 1:1:0.01): **14** (349 mg, 63%). Colorless oil. ^{1}H-NMR ($CDCl_3$): 1.04 (*t*, *J* = 7.5,

3 H); 1.74–1.89 (*m*, 1 H); 1.97–2.18 (*m*, 3 H); 2.30 (*s*, 6 H); 2.42–2.65 (*m*, 1 H); 2.66 (*q*, *J* = 7.5, 2 H); 2.76–2.86 (*m*, 1 H); 3.75 (*s*, 6 H); 6.31 (*s*, 2 H).

(RS)-4-[(Dimethylamino)methyl]-7-ethyl-3,4-dihydro-6,8-dimethoxynaphthalen-1(2H)-one Fumarate (1:1) (**16** · $C_6H_4O_4$). To a cooled (0°) and stirred soln. of **14** (250 mg, 0.81 mmol) in CF_3COOH (3.5 ml) was added $(CF_3CO)_2O$ (0.35 ml). The mixture was stirred at r.t. for 3 h, poured into ice-water (50 ml), neutralized with $NaHCO_3$, and extracted with CH_2Cl_2 (2 × 50 ml). The combined org. layers were dried ($MgSO_4$) and evaporated to yield 225 mg of a colorless oil. To a stirred soln. of the crude base (70 mg, 0.24 mmol) in EtOH (1 ml) was added fumaric acid (27.9 mg, 0.24 mmol) and hexane (10 ml). The mixture was stirred at r.t. for 15 h, and the solid was subsequently filtered off to give **16** · $C_4H_4O_4$ (69 mg, 71%). White crystals. M.p. 187°. ^{1}H-NMR ((D$_6$)DMSO): 1.02 (*t*, *J* = 7, 3 H); 1.91–2.14 (*m*, 2 H); 2.31 (*s*, 6 H); 2.32–2.74 (*m*, 6 H); 3.07–3.14 (*m*, 1 H); 3.64 (*s*, 3 H); 3.87 (*s*, 3 H); 6.59 (*s*, 2 H); 6.81 (*s*, 1 H). MS: 292 ([*M* + H]$^+$). Anal. calc. for $C_{17}H_{25}NO_3 \cdot C_4H_4O_4$ (407.46): C 61.90, H 7.17, N 3.44; found: C 61.67, H 7.24, N 3.41.

(RS)-4-[(Dimethylamino)methyl]-7-ethyl-3,4-dihydro-8-hydroxy-6-methoxynaphthalen-1(2H)-one Fumarate (1:1.5) (**17** · 1.5 $C_6H_4O_4$). A soln. of **16** (154 mg, 0.53 mmol of the base) in 2.3N MeOHHCl (5 ml) was evaporated. The hydrochloride of **16** was dissolved in CH_2Cl_2 (15 ml) and the stirred soln. cooled to −78°. A soln. of BBr_3 in CH_2Cl_2 (0.58 ml, 0.58 mmol) was added dropwise, and stirring was continued for 1.5 h at r.t. The mixture was then poured into ice-sat. $NaHCO_3$ soln. (50 ml) and extracted with CH_2Cl_2 (2 × 50 ml). The combined org. layers were washed with brine (50 ml), dried ($MgSO_4$), and evaporated: 128 mg of a pale green oil. To a stirred soln. of crude **17** (128 mg, 0.46 mmol) in EtOH (1 ml), fumaric acid (53.5 mg, 0.46 mmol) and hexane (10 ml) were added. The mixture was stirred at r.t. for 3 h, and the solid was subsequently filtered off: **17** · 1.5 $C_6H_4O_4$ (137 mg, 66%). White crystals. M.p. 177°. ^{1}H-NMR ((D$_6$)DMSO): 1.00 (*t*, *J* = 7, 3 H); 2.01–2.11 (*m*, 2 H); 2.35 (*s*, 6 H); 2.37–2.58 (*m*, 4 H); 2.71–2.86 (*m*, 2 H); 3.07–3.14 (*m*, 1 H); 3.88 (*s*, 3 H); 6.60 (*s*, 3 H); 6.61 (*s*, 1 H); 13.10 (*s*, 1 H). MS: 278 ([*M* + H]$^+$). Anal. calc. for $C_{16}H_{23}NO_3 \cdot 1.5\ C_4H_4O_4$ (451.472): C 58.53, H 6.47, N 3.10; found: C 58.50, H 6.52, N 2.87.

Ethyl (RS)-β-Cyano-4-ethyl-3,5-dimethoxybenzenepropanoate (**11**). Alkylation of **9** (2.05 g, 10.0 mmol) in DMF (40 ml) using NaH (60% in oil; 0.44 g, 11.0 mmol) and ethyl bromoacetate (1.21 ml, 11.0 mmol), as described for **10**, yielded **9** (1.15 g, 56%) and **11** (0.50 g, 17%). **11**: Pale brown oil. ^{1}H-NMR ($CDCl_3$): 1.05 (*t*, *J* = 7.5, 3 H); 1.27 (*t*, *J* = 7, 3 H); 2.62 (*q*, *J* = 7.5, 2 H); 2.83 (*dd*, *J* = 16, 6, 2 H); 3.01 (*dd*, *J* = 16, 7, 1 H); 3.82 (*s*, 6 H); 4.19 (*q*, *J* = 7.5, 2 H); 4.24 (*dd*, *J* = 7, 6, 2 H); 6.50 (*s*, 2 H).

(RS)-β-[(Dimethylamino)methyl]-4-ethyl-3,5-dimethoxybenzenepropanoic Acid (**15**). Hydrolysis of **11** (0.50 g, 1.72 mmol) in a mixture of MeOH (10 ml) and 1N NaOH (5 ml), hydrogenation over *Raney*-Ni in 2.5N NH_3MeOH (25 ml), and reductive amination with formaldehyde (1 ml) and sodium cyanoborohydride (186 mg, 2.52 mmol), as described for **14**, gave **15** (263 mg, 52%). White foam. ^{1}H-NMR ((D$_6$)DMSO): 0.96 (*t*, *J* = 7.5, 3 H); 2.26 (*s*, 6 H); 2.31–2.54 (*m*, 4 H); 2.63 (*dd*, *J* = 12.5, 9.5, 1 H); 2.76 (*dd*, *J* = 17.5, 6.5, 1 H); 3.11–3.24 (*m*, 1 H); 3.74 (*s*, 6 H); 6.49 (*s*, 2 H).

(RS)-3-[(Dimethylamino)methyl]-6-ethyl-2,3-dihydro-5,7-dimethoxy-1H-inden-1-one Fumarate (1:1) (**18**). Reaction of **15** (263 mg, 0.89 mmol) in CF_3COOH acid (3 ml) and $(CF_3CO)_2O$ (0.3 ml) and crystallization of the base (212 mg, 0.76 mmol) with fumaric acid (88.7 mg, 0.76 mmol) in EtOH (1 ml) and Et_2O (15 ml), as described for **16**, yielded **18** (272 mg, 78%). White crystals. M.p. 212°. ^{1}H-NMR ((D$_6$)DMSO): 1.01 (*t*, *J* = 7.5, 3 H); 2.36 (*s*, 6 H); 2.37–2.52 (*m*, 2 H); 2.53 (*q*, *J* = 7.5, 2 H); 2.74 (*dd*, *J* = 18.5, 5.5, 1 H); 2.91 (*dd*, *J* = 12.5, 4.5, 1 H); 3.39–3.52 (*m*, 1 H); 3.83 (*s*, 3 H); 3.90 (*s*, 3 H); 6.60 (*s*, 2 H); 6.99 (*s*, 1 H). MS: 277 (M^+), 58 ($C_3H_8N^+$). Anal. calc. for $C_{16}H_{23}NO_3 \cdot C_4H_4O_4$ (393.43): C 61.06, H 6.92, N 3.56; found: C 61.06, H 6.92, N 3.38.

(RS)-3-[(Dimethylamino)methyl]-6-ethyl-5,7-dimethoxyisobenzofuran-1(3H)-one (**21**). To a soln. of freshly prepared LDA (2.2 mmol) in THF/hexane 9:1 (12 ml), **16** [6] (444 mg, 2 mmol) was added at −75°. After stirring for 75 min at −75°, *N*,*N*-dimethylmethylenimmonium chlorid (196 mg, 2.1 mmol) was added. The mixture was stirred at −75° for 4 h, and the reaction was quenched with H_2O (1 ml). Then the mixture was diluted with Et_2O (50 ml) and extracted with brine (20 ml). The org. layer was dried (Na_2SO_4) and evaporated. The residue was purified by CC (silica gel, AcOEt, then AcOEt/MeOH 4:1): **21** (219 mg, 39%). Colorless oil. The fumarate **21** · $C_6H_4O_4$ was prepared in Et_2O/MeOH by treatment with fumaric acid. M.p. 148–151° (dec.). ^{1}H-NMR ((D$_6$)DMSO): 1.03 (*t*, *J* = 7.3, 3 H); 2.31 (*s*, 6 H); 2.59 (*q*, *J* = 7.3, 2 H); 2.97 (*dd*, *J* = 13.7, 3.2, 1 H); 3.90 (*s*, 3 H); 3.94 (*s*, 3 H); 5.54 (*dd*, *J* = 7.5, 3.2, 1 H); 6.60 (*s*, 1 H). Anal. calc. for $C_{15}H_{21}NO_4 \cdot C_4H_4O_4 \cdot CH_3OH$ (369.41): C 58.52, H 7.40, N 3.77; found: C 58.27, H 7.20, N 3.89.

3-[(Dimethylamino)methyl]-6-ethyl-7-hydroxy-5-methoxyisobenzofuran-(3H)-one (**22**). Using the preceding procedure, LDA (20 mmol) was reacted with **20** [6] (1.84 g, 8.8 mmol) and *N*,*N*-dimethylmethylenimmonium-chloride (1.83 g, 20 mmol): 627 mg (27.4%) of **22**. The fumarate **22** · 0.5 $C_4H_4O_4$ was prepared in Et_2O/MeOH by treatment with fumaric acid. M.p. 183–184°. IR (KBr): 1764, 1621. ^{1}H-NMR ((D$_6$)DMSO): 0.99 (*t*, *J* = 7.5,

3 H); 2.31 (*s*, 6 H); 2.57 (*q*, *J* = 7.5, 2 H); 2.96 (*dd*, *J* = 13.6, 3, 1 H); 3.87 (*s*, 3 H); 5.53 (*dd*, *J* = 8, 3, 1 H); 6.60 (*s*, 1 H). Anal. calc. for $C_{15}H_{21}NO_4 \cdot 0.5\ C_4H_4O_4$ (323.34): C 59.43, H 6.55, N 4.33; found: C 59.22, H 6.50, N 3.99.

2-Bromo-4-ethyl-3,5-dimethoxybenzaldehyde Dimethyl Acetal (**23**). To a soln. of **2** [8] (5 g, 25.7 mmol) in CCl_4 was added a soln. of Br_2 (1.32 ml, 25.7 mmol) in CCl_4 (20 ml) at 0°. After stirring overnight, the solvent was removed, the residue dissolved in trimethyl orthoformate (35 ml) and MeOH (35 ml), and NH_4Cl (70 mg) added. The mixture was refluxed for 2 h and then evaporated. After the extraction with H_2O and Et_2O, the org. phase was dried (Na_2SO_4) and evaporated: **23** (7.3 g, 89%). Yellow oil. ^{1}H-NMR ($CDCl_3$): 1.13 (*t*, *J* = 7.5, 3 H); 2.69 (*q*, *J* = 7.5, 2 H); 3.42 (*s*, 6 H); 3.81 (*s*, 3 H); 3.83 (*s*, 3 H); 5.54 (*s*, 1 H); 6.93 (*s*, 1 H). MS: 320 (M^+), 287, 289 ($[M - MeO]^+$).

(RS)-6-Ethyl-3-hydroxy-5,7-dimethoxyisobenzofuran-1(3H)-one (**24**). To a soln. of **23** (2.18 g, 6.8 mmol) in THF (70 ml), 1.6N BuLi (8.5 ml) was added at –76°. After stirring for 90 min at –76°, a stream of CO_2 was passed through the red soln. for 1 h, followed by the addition of 1N HCl (34 ml). The resultant yellow soln. was diluted with H_2O (300 ml) and the org. layer evaporated. The residue was dissolved in dioxane (30 ml) and 25% HCl soln. (5 ml) and stirred for 24 h. After the addition of H_2O, the mixture was extracted with Et_2O, the org. layer dried (Na_2SO_4) and evaporated, and the residue purified by CC (toluene, toluene/AcOEt 4:1, and then AcOEt). To the solid product, hexane/Et_2O 1:1 (40 ml) was added, and the crystals of **24** were isolated: 1 g (64%). IR (KBr): 3389, 1768, 1742, 1605. ^{1}H-NMR ($CDCl_3$): 1.07 (*t*, *J* = 7.5, 3 H); 2.67 (*q*, *J* = 7.5, 2 H); 3.93 (*s*, 3 H); 4.06 (*s*, 3 H); 6.45 (*s*, 1 H); 6.82 (*s*, 1 H). MS: 238 (M^+), 220 ($[M - H_2O]^+$), 192 ($[M - H_2O - CO]^+$).

(RS)-6-Ethyl-3-(nitromethyl)-5,7-dimethoxyisobenzofuran-1(3H)-one (**25**). To a soln. of **24** (476 mg, 2 mmol) and nitromethane (0.12 ml, 2.2 mmol) in EtOH (10 ml), a soln. of KOH (600 mg, 50%) in EtOH (1.2 ml) was added at 0°, and the suspension was left overnight in the refrigerator. After the addition of AcOH (100 ml, 10% aq.), the soln. was stirred at r.t. for 4 d. The crystalline precipitate was collected by filtration: 395 mg (70%) of **25**. M.p. 118–119°. IR: 1744, 1599, 1557. ^{1}H-NMR ($CDCl_3$): 1.09 (*t*, *J* = 7.5, 3 H); 3.92 (*s*, 3 H); 4.08 (*s*, 3 H); 4.72 (*m*, 2 H); 5.98 (*dd*, *J* = 7.2, 5, 1 H); 6.60 (*s*, 1 H). MS: 2.81 (M^+), 235 ($[M - NO_2]^+$), 221 ($[M - CH_2NO_2]^+$), 217 ($[M - NO_2 - H_2O]^+$). Anal. calc. for $C_{13}H_{15}NO_6$ (281.20): C 55.52, H 5.38, N 4.98; found: C 55.46, H 5.14, N 4.96.

(RS)-3-(Aminomethyl)-6-ethyl-5,7-dimethoxyisobenzofuran-1(3H)-one (**26**). A suspension of **25** (241 mg, 0.85 mmol) in EtOH (17 ml) and 1N HCl (0.9 ml) was hydrogenated over 10% Pd/C (60 mg) at 60°. After 24 h, the catalyst was filtered off and the solvent evaporated to give white crystals of **26** which were recrystallized from EtOH: 121 mg (55%). M.p. 206–207°. IR: 3439, 2969, 1748, 1602. ^{1}H-NMR ((D$_6$)DMSO): 1.03 (*t*, *J* = 7.5, 3 H); 2.61 (*q*, *J* = 7.5, 2 H); 3.14 (*dd*, *J* = 13.7, 8.3, 1 H); 3.65 (*dd*, *J* = 13.7, 2.7, 1 H); 3.92 (*s*, 3 H); 3.96 (*s*, 3 H); 5.70 (*dd*, *J* = 8.3, 2.7, 1 H); 7.20 (*s*, 1 H); 8.39 (*s*, 3 H). MS: 252 (M^+), 234 ($[M - H_2O]^+$). Anal. calc. for $C_{13}H_{17}NO_4 \cdot HCl$ (287.70): C 54.26, H 6.31, N 4.87; found: C 54.14, H 6.22, N 4.89.

Methyl (RS)-7-Ethyl-1,2,3,4-tetrahydro-6,8-dimethoxy-2-methylisoquinoline-4-propanoate (**27**). To a stirred suspension of **12** (0.87 g, 3.09 mmol) in MeOH (20 ml), formaldehyde (0.73 ml) was added at r.t. The mixture was stirred at r.t. for 15 min and then heated to 50°. After 45 min, conc. HCl soln. (3.57 ml) was added dropwise, and stirring was continued for 30 min at 50°. The mixture was poured into a cooled, sat. NaOAc soln. (80 ml) and extracted with AcOEt (3 × 100 ml). The combined org. layers were washed with brine (2 × 70 ml), dried ($MgSO_4$), and evaporated. The residue was subsequently dissolved in MeOH (20 ml). While stirring, formaldehyde (3 ml) and sodium cyanoborohydride (485 mg, 7.73 mmol) were added, and stirring was continued for 15 h. The mixture was poured into ice-brine (70 ml) and extracted with AcOEt (2 × 100 ml). The combined org. layers were washed with brine (2 × 70 ml), dried ($MgSO_4$), and evaporated. The residue was purified by CC (silica gel, CH_2Cl_2/MeOH 49:1): **27** (530 mg, 53%). Pale yellow oil. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.13 (*t*, *J* = 7.5, 3 H); 1.91–2.22 (*m*, 2 H); 2.39 (*d*, *J* = 8.5, 2 H); 2.44 (*s*, 3 H); 3.45–2.61 (*m*, 2 H); 2.62 (*q*, *J* = 7.5, 2 H); 2.81–2.94 (*m*, 1 H); 3.38 (*d*, *J* = 15.5, 1 H); 3.63 (*d*, *J* = 15.5, 1 H); 3.68 (*s*, 3 H); 3.72 (*s*, 3 H); 3.80 (*s*, 3 H); 6.52 (*s*, 1 H). MS: 322 ($[M + H]^+$).

(RS)-8-Ethyl-1,2,3,3a,4,5-hexahydro-7,9-dimethoxy-2-methyl-6H-benz[de]isoquinolin-6-one Hydrochloride (**28** · HCl).To a stirred soln. of **27** (530 mg, 1.65 mmol) in MeOH (10 ml) 1N NaOH (5 ml) was added at r.t., and stirring was continued for 2 h. The mixture was cooled to 0° and, after the addition of 1N HCl (5 ml), evaporated. The residue was purified by CC (silica gel, CH_2Cl_2/MeOH/AcOH/H_2O 80:20:3:3) to give a white foam which was dissolved in CF_3COOH (10 ml). To the stirred and cooled (0°) soln. was added $(CF_3CO)_2O$ (2 ml), and stirring was continued at r.t. for 16 h. The mixture was poured into ice-water (60 ml), neutralized with $NaHCO_3$, and extracted with CH_2Cl_2 (2 × 50 ml). The combined org. layers were washed with brine (50 ml), dried ($MgSO_4$), and evaporated, and the residue was purified by CC (silica gel, CH_2Cl_2/MeOH/NH_4OH 20:1:0.1) to yield 325 mg (68%) of a colorless oil. A part of the base (125 mg, 0.43 mmol) was subsequently dissolved in 2.3N HCl/MeOH

(5 ml), the soln. evaporated, and the residue crystallized with Et_2O: **28** · HCl (94 mg, 67%). Pale-pink, very hygroscopic solid. ^{1}H-NMR ($CDCl_3$): 1.18 (*t*, *J* = 7.5, 3 H); 1.58–1.82 (*m*, 2 H); 2.07–2.24 (*m*, 1 H); 2.56–2.91 (*m*, 5 H); 3.02 (*s*, 3 H); 3.56–3.72 (*m*, 1 H); 3.82 (*s*, 3 H); 3.83 (*s*, 3 H); 3.83–3.99 (*m*, 1 H); 4.52–4.72 (*m*, 1 H). MS: 289 (M^+), 288 ([M – H]$^+$), 246 ([M – C_3H_6]$^+$), 231. HR-MS: 289.1666 (M^+, $C_{17}H_{23}NO_3^+$; calc. 289.1677).

*(*RS*)-8-Ethyl-1,2,3,3,3a,4,5-hexahydro-7-hydroxy-9-methoxy-2-methyl-6*H*-benz[*de*]isoquinolin-6-one-Hydrochloride* (**29** · HCl). To a stirred and cooled (–78°) soln. of **28** (194 mg, 0.67 mmol) was added dropwise a soln. of BBr_3 in CH_2Cl_2 (0.58 ml, 0.58 mmol), and stirring was continued for 2 h at r.t. The mixture was then poured into ice-sat. $NaHCO_3$ soln. (30 ml) and extracted with CH_2Cl_2 (3 × 50 ml). The combined org. layers were washed with brine (50 ml), dried ($MgSO_4$), and evaporated: 170 mg of an orange oil. The crude base was purified by CC (silica gel, CH_2Cl_2/MeOH 19:1), subsequently dissolved in 2.3N HCl/MeOH (5 ml), the soln. evaporated, and the residue crystallized with Et_2O: **29** · HCl (131 mg, 63%). Pale yellow, very hygroscopic solid. ^{1}H-NMR ($CDCl_3$): 1.19 (*t*, *J* = 7.5, 3 H); 1.57–1.81 (*m*, 2 H); 2.08–2.24 (*m*, 1 H); 2.58–2.89 (*m*, 5 H); 3.02 (*s*, 3 H); 3.58–3.72 (*m*, 1 H); 3.76–3.99 (*m*, 1 H); 3.84 (*s*, 3 H); 4.51–4.68 (*m*, 1 H); 13.02 (*s*, 1 H). MS: 275 (M^+), 274 ([M – H]$^+$), 232 ([M – C_3H_6]$^+$), 217. HR-MS: 275.1500 (M^+, $C_{16}H_{21}NO_3^+$, calc. 275.1521).

*(*RS*)-4-(4-Ethyl-3,5-dimethoxyphenyl)pyrrolidin-2-one* (**30**). For 21 h, **11** (1.10 g, 3.78 mmol) in 2.5N/MeOH (50 ml) was hydrogenated over *Raney*-Ni. The catalyst was filtered off and washed with MeOH (50 ml). The org. layer was evaporated and the residue purified by CC (silica gel, CH_2Cl_2/MeOH 49:1): **30** (0.44 g, 47%) as a pale-yellow solid. M.p. 156°. ^{1}H-NMR ($CDCl_3$): 1.06 (*t*, *J* = 7.5, 3 H); 2.52 (*dd*, *J* = 16.5, 8.5, 1 H); 2.63 (*q*, *J* = 7.5, 1 H); 2.74 (*dd*, *J* = 17.5, 8.5, 1 H); 3.44 (*t*, *J* = 7, 1 H); 3.68 (*quint.*, *J* = 7, 1 H); 3.79 (*t*, *J* = 7, 1 H); 3.82 (*s*, 6 H); 5.95 (br., 1 H); 6.42 (*s*, 2 H). MS: 249 (M^+), 234 ([M – Me]$^+$), 192, 177 ([$C_{11}H_{13}O_2$]$^+$). Anal. calc. for $C_{14}H_{19}NO_3$ (249.31): C 67.45, H 7.68, N 5.62; found: C 67.29, H 7.72, N 5.51.

*(*RS*)-4-(4-Ethyl-3,5-dimethoxyphenyl)-1-methylpyrrolidin-2-one* (**31**). To a stirred suspension of **30** (2.21 g, 8.87 mmol) in THF (90 ml) and DMF (1 ml) NaH (60% in oil; 0.78 g, 19.5 mmol) was added at r.t. The mixture was stirred for 1 h, MeI (0.88 ml, 26.6 mmol) added, and stirring continued for 16 h. The mixture was poured into ice-water (70 ml) and extracted with AcOEt (2 × 120 ml). The combined org. layers were washed with brine (2 × 70 ml), dried ($MgSO_4$), and evaporated. The crude material was purified by CC (silica gel, CH_2Cl_2/MeOH 39:1); **31** (2.02 g, 86%). Pale-brown solid. M.p. 167°. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.06 (*t*, *J* = 7.5, 3 H); 2.57 (*dd*, *J* = 16.5, 8.5, 1 H); 2.62 (*q*, *J* = 7.5, 1 H); 2.81 (*dd*, *J* = 17.5, 8.5, 1 H); 2.92 (*s*, 3 H); 3.41 (*t*, *J* = 7, 1 H); 3.56 (*quint.*, *J* = 7, 1 H); 3.73 (*t*, *J* = 7, 1 H); 3.81 (*s*, 6 H); 6.39 (*s*, 2 H). MS: 263 (M^+), 248 ([M – Me]$^+$), 192, 177 ([$C_{11}H_{13}O_2$]$^+$). Anal. calc. for $C_{15}H_{21}NO_3$ (263.33): C 68.42, H 8.04, N 5.32; found: C 68.38, H 7.92, N 5.37.

tert-*Butyl (3*RS*,4*RS*)-4-(4-Ethyl-3,5-dimethoxyphenyl)-1-methyl-2-oxopyrrolidine-3-acetate* (**32**). To a stirred and cooled (–70°) soln. of **31** (2.0 g, 7.6 mmol) in THF (20 ml), a freshly prepared soln. of LDA (9.5 mmol) in THF (20 ml) was added dropwise. After 30 min, a soln. of *tert*-butyl bromoacetate (1.23 ml, 8.35 mmol) in THF (20 ml) was added dropwise, and stirring was continued for 22 h during which the mixture reached r.t. The mixture was poured into ice-water (150 ml) and extracted with AcOEt (2 × 200 ml). The combined org. layers were washed with brine (100 ml), dried ($MgSO_4$), and evaporated. The crude material was purified by CC (silica gel, AcOEt): **31** (0.54 g, 27%) and **32** (1.23 g, 43%). Pale-yellow oil. NMR ($CDCl_3$): 1.04 (*t*, *J* = 7.5, 3 H); 1.29 (*s*, 9 H); 2.41 (*dd*, *J* = 16, 7.5, 1 H); 2.61 (*q*, *J* = 7.5, 2 H); 2.71 (*dd*, *J* = 16, 4.5, 1 H); 2.93 (*s*, 3 H); 2.94–3.05 (*m*, 1 H); 3.25 (*dd*, *J* = 17.5, 7, 1 H); 3.39 (*t*, *J* = 7, 1 H); 3.60 (*t*, *J* = 7, 1 H); 3.81 (*s*, 6 H); 6.41 (*s*, 2 H). MS: 377 (M^+), 321 ([M – C_4H_8]$^+$), 304 ([M – C_4H_9O]$^+$), 262 ([M – C_5H_9O]$^+$).

*(3a*RS*,9b*RS*)-*cis*-7-Ethyl-1,2,3,3a,4,9b-hexahydro-6-hydroxy-8-methoxy-2-methyl-5*H*-benz[*e*]isoindol-5-one Fumarate (1:1)* (**33** · $C_4H_4O_4$). To a stirred soln. of **32** (1.23 g, 3.26 mmol) in THF (20 ml), 1M borane in THF (32.6 ml, 32.6 mmol) was added at r.t. The mixture was then boiled under reflux for 7 h, subsequently cooled to 0°, and mixed with MeOH (10 ml). Evaporation and purification of the residue by CC (silica gel, AcOEt) yielded a colorless oil which was mixed with PPA (11 g) and while stirring heated to 120° for 75 min. The mixture was poured into 3N NaOH (50 ml), neutralized by the addition of NaOAc, and extracted with CH_2Cl_2 (3 × 100 ml). The combined org. layers were washed with brine (70 ml), dried ($MgSO_4$), and evaporated. The residue was purified by CC (silica gel, CH_2Cl_2/MeOH/NH_4OH 20:1:0.1) to yield a colorless oil (0.4 g, 44%). To a stirred soln. of the base (0.4 g, 1.45 mmol) in EtOH (0.5 ml), fumaric acid (168 mg, 1.45 mmol) and Et_2O (50 ml) were added. The mixture was stirred at r.t. for 17 h and the solid subsequently filtered of: **33** · $C_4H_4O_4$ (550 mg, 97%). White crystals. M.p. 195°. ^{1}H-NMR ((D$_6$)DMSO): 1.00 (*t*, *J* = 7.5, 3 H); 2.36–2.48 (*m*, 1 H); 2.53 (*q*, *J* = 7.5, 2 H); 2.68 (*s*, 3 H); 2.70 (*dd*, *J* = 18, 12.5, 1 H); 2.80 (*dd*, *J* = 12.5, 4.5, 1 H); 2.92 (*t*, *J* = 10.5, 1 H); 3.11 (*t*, *J* = 10.5, 1 H); 3.19–3.31 (*m*, 2 H); 3.71 (*dd*, *J* = 9.5, 7, 1 H); 3.89 (*s*, 3 H); 6.36 (*s*, 1 H); 6.52 (*s*, 2 H); 13.00 (*s*, 1 H). MS: 275 (M^+), 57 ($C_3H_7N^+$). Anal. calc. for $C_{16}H_{21}NO_3 \cdot C_4H_4O_4$ (391.42): C 61.37, H 6.44, N 3.58; found: C 61.09, H 6.51, N 3.60.

(E,RS)-2-Ethyl-5-[2-(methylsulfinyl)-2-(methylthio)ethenyl]-1,3-dimethoxybenzene (**34**). To a soln. of **2** (126.5 g, 651.2 mmol) and methyl (methylthio)methyl sulfoxide (80.89 g, 651.2 mmol) in THF (300 ml), 40% benzyltrimethylammonium hydroxide (*Triton B*) soln. in MeOH (130 ml) was added, and the resulting mixture was refluxed for 5 h. After addition of CH_2Cl_2 (300 ml), the mixture was washed with 0.5M H_2SO_4 (200 ml). The org. layer was dried ($MgSO_4$) and evaporated. The residue was purified by CC (silica gel, AcOEt/hexane 1:1): **34** (134.6 g, 69%). Colorless oil. An anal. sample was crystallized with hexane to give colorless plates. M.p. 82–83°. IR ($CHCl_3$): 1601, 1572, 1415, 1235, 1141, 1061. ^{1}H-NMR ($CDCl_3$): 1.08 (*t*, *J* = 7, 3 H); 2.36 (*s*, 3 H); 2.67 (*q*, *J* = 7, 2 H); 2.76 (*s*, 3 H); 3.84 (*s*, 6 H); 7.20 (*s*, 2 H); 7.56 (*s*, 1 H). MS: 300 (M^+), 237 ([M – SOMe]$^+$). Anal. calc. for $C_{14}H_{20}S_2O$ (300.43): C 55.97, H 6.71, S 21.34; found: C 55.79, H 6.61, S 21.26.

Methyl 4-Ethyl-3,5-dimethoxybenzeneacetate (**35**). A soln. of **34** (134.6 g, 448 mmol) in MeOH (200 ml) was added to sat. HCl in MeOH (400 ml) and stirred for 4 h at 50°. After evaporation, the residue was dissolved in CH_2Cl_2 (300 ml) and washed with sat. $NaHCO_3$ soln. (2 × 200 ml). The org. layer was dried ($MgSO_4$), filtered, and evaporated. The orange residue was purified by CC (silica gel, AcOEt/hexane 1:9): **35** (100.5 g, 94%). Colorless oil. An anal. sample was crystallized with hexane to give colorless plates. M.p. 40–41°. IR (KBr): 1745, 1729, 1589, 1238, 1141. ^{1}H-NMR ($CDCl_3$): 1.05 (*t*, *J* = 7, 3 H); 2.62 (*q*, *J* = 7, 2 H); 3.57 (*s*, 2 H); 3.70 (*s*, 3 H); 3.80 (*s*, 3 H); 6.45 (*s*, 2 H). MS: 238 (M^+), 223 ([M – Me]$^+$). Anal. calc. for $C_{13}H_{18}O_4$ (238.28): C 65.53, H 7.61; found C 65.10, H 7.58.

Methyl 4-Ethyl-3,5-dimethoxy-α-methylidenebenzeneacetate (**36**). A soln. of **35** (100 g, 420 mmol), paraformaldehyde (18.9 g, 630 mmol) K_2CO_3 (92.8 g, 672 mmol), and Bu_4NI (3.1 g, 8.4 mmol) in toluene (200 ml) was heated for 6 h at 80°. After addition of H_2O (150 ml), the aq. layer was washed with toluene (2 × 120 ml), the combined org. layer dried ($MgSO_4$) and evaporated, and the residue purified by CC (silica gel, CH_2Cl_2/hexane 1:2): **36** (70.5 g, 67%). Colorless oil. IR (film): 1726, 1604, 1578, 1278, 1238, 1139. ^{1}H-NMR ($CDCl_3$): 1.07 (*t*, *J* = 7, 3 H); 2.64 (*q*, *J* = 7, 2 H); 3.82 (*s*, 6 H); 3.83 (*s*, 3 H); 5.89 (*d*, *J* = 0.5, 1 H); 6.32 (*d*, *J* = 0.5, 1 H); 6.58 (*s*, 2 H). MS: 250 (M^+), 235 ([M – Me]$^+$).

Methyl (RS)-α-{[(3-Ethoxy-3-oxopropyl)methylamino]methyl}-4-ethyl-3,5-dimethoxybenzeneacetate (**37**). A soln. of **36** (78.4 g, 313 mmol) and ethyl 3-(methylamino)propanoate [13] (47.7 g, 364 mmol) was stirred for 48 h at r.t. CC (silica gel, AcOEt/hexane 1:1) of the mixture and crystallization with hexane yielded **37** (71.1 g, 59%). Colorless plates. M.p. 74–75°. IR (KBr): 1744, 1727, 1132, 1048, 1029. ^{1}H-NMR ($CDCl_3$): 1.04 (*t*, *J* = 7, 3 H); 1.25 (*t*, *J* = 7, 3 H); 2.30 (*s*, 3 H); 2.42–2.55 (*m*, 3 H); 2.60 (*q*, *J* = 7, 2 H); 2.70 (*ddd*, *J* = 12, 7.5, 6); 2.84 (*ddd*, *J* = 12, 7.5, 7.5, 1 H); 3.20 (*dd*, *J* = 12, 10, 1 H); 3.67 (*s*, 3 H); 3.75 (*dd*, *J* = 10, 4.5, 1 H); 3.81 (*s*, 6 H); 4.12 (*q*, *J* = 7, 2 H); 6.47 (*s*, 2 H). MS: 382.4 ([M + H]$^+$), 223. Anal. calc. for $C_{20}H_{31}NO_6$ (381.47): C 62.97, H 8.19, N 3.67; found: C 62.96, H 7.92, N 3.60.

(RS)-3-(4-Ethyl-3,5-dimethoxyphenyl)-1-methylpiperidin-4-one (**38**). A soln. of **37** (53.51 g, 140 mmol) in toluene (150 ml) was added to a suspension of NaH (60% in oil; 10.65 g, 266.3 mmol) in toluene (150 ml) at 80°. After heating for 15 h at 120°, the soln. was cooled to r.t. and the pH adjusted to 1 with 6N HCl. The toluene phase was extracted with 6N HCl (1 × 150 ml). The acidic phase was heated under reflux for 20 h and then cooled down and the pH adjusted to pH 14 with 28% NaOH soln. The aq. layer was washed with CH_2Cl_2 (3 × 250 ml). The combined org. layers were washed with H_2O (1 × 300 ml) and brine (1 × 300 ml), dried ($MgSO_4$), and evaporated. The residue was purified by CC (silica gel, CH_2Cl_2/MeOH 19:1) and crystallized from hexane: **38** (34.5 g, 88%). Light-yellow needles. M.p. 84–85°. IR (KBr): 1717, 1609, 1586, 1137. ^{1}H-NMR ($CDCl_3$): 1.05 (*t*, *J* = 7, 3 H); 2.44 (*s*, 3 H); 2.50–2.81 (*m*, 4 H); 2.64 (*q*, *J* = 7, 2 H); 2.96–3.09 (*m*, 1 H); 3.14 (*ddd*, *J* = 12, 6, 2.5, 1 H); 3.77 (*dd*, *J* = 10, 6, 1 H); 3.79 (*s*, 6 H); 6.40 (*s*, 2 H). MS: 277 (M^+), 260 ([M – OH]$^+$), 192, 177. Anal. calc. for $C_{16}H_{23}NO_3$ (277.36): C 69.29, H 8.36, N 5.05; found: C 69.09, H 8.51, N 4.86.

Ethyl (RS,E)-[3-(4-Ethyl-3,5-dimethoxyphenyl)-1-methylpiperidin-4-ylidene]acetate (**39**). To a suspension of NaH (60% in oil; 1.44 g, 36 mmol) in THF (160 ml) was added a soln. of ethyl (dimethoxyphosphinyl)acetate (8.21 g, 39.6 mmol; 95%) in THF (30 ml) at 0°. After 10 min at 0°, a soln. of **38** (5.0 g, 18 mmol) in THF (70 ml) was added at 0°. After the addition was complete, the cooling bath was removed and the mixture heated at 50° for 1 h. After addition of Et_2O (250 ml) and H_2O (250 ml), the org. layer was washed with H_2O (1 × 200 ml), dried ($MgSO_4$), and evaporated to give a light-yellow oil which was purified by CC (silica gel, CH_2Cl_2/MeOH 19:1). The product was crystallized with hexane **39** (5.36 g, 85%). Colorless needles. M.p. 93.5–94.5°. IR (KBr): 1711, 1644, 1584, 1456, 1420, 1237. ^{1}H-NMR ($CDCl_3$): 1.08 (*t*, *J* = 7, 3 H); 1.23 (*t*, *J* = 7, 3 H); 2.26 (*ddd*, *J* = 12, 12, 4, 1 H); 2.34 (*s*, 3 H); 2.48–2.59 (*m*, 2 H); 2.50 (*q*, *J* = 7, 2 H); 2.91–3.09 (*m*, 2 H); 3.58 (*m*, 2 H); 3.58 (*dd*, *J* = 12, 4, 1 H); 3.75 (*ddd*, *J* = 12, 4, 4, 1 H); 3.79 (*s*, 6 H); 4.10 (*q*, *J* = 7, 2 H); 5.34 (br. *s*, 1 H); 6.38 (*s*, 2 H). MS: 348 ([M + H]$^+$). Anal. calc. for $C_{20}H_{29}NO_4$ (347.45): C 69.14, H 8.41, N 4.03; found: C 68.88, H 8.45, N 3.82.

(RS,4RS)- and (3RS,4SR)-Ethyl 3-(4-Ethyl-3,5-dimethoxyphenyl)-1-methylpiperidine-4-acetate (**40** and **41**). A soln. of **39** (4.4 g, 12.7 mmol) in EtOH (150 ml) in the presence of 5% Pd/C (500 mg) was stirred under H_2 for

12 h. After filtration of the catalyst through a pad of *Celite*, the soln. was evaporated and the residue purified by CC (silica gel, CH_2Cl_2/MeOH/NH_4OH 200:10:1): **40** (3.38 g, 77%) and **41** (0.924 g, 21%) as colorless oils.

Data of **40**: ^{1}H-NMR ($CDCl_3$): 1.06 (*t*, *J* = 7, 3 H); 1.19 (*t*, *J* = 7, 3 H); 1.58–1.91 (*m*, 2 H); 2.03–2.24 (*m*, 2 H); 2.32 (*s*, 3 H); 2.60 (*q*, *J* = 7, 2 H); 2.57–2.71 (*m*, 2 H); 3.02–3.17 (*m*, 1 H); 3.79 (*s*, 6 H); 4.03 (*q*, *J* = 7, 2 H); 6.53 (br. *s*, 1 H). MS: 349 (M^+).

The fumarate of **40** was prepared in Et_2O by treatment with fumaric acid. M.p. 128.0–129.5°. Anal. calc. for $C_{20}H_{31}NO_4 \cdot C_4H_4O_4$ (465.54): C 61.92, H 7.58, N 3.01; found: C 61.66, H 7.47, N 2.70.

Data of **41**: ^{1}H-NMR ($CDCl_3$): 1.05 (*t*, *J* = 7, 3 H); 1.18 (*t*, *J* = 7, 3 H); 1.47 (*dddd*, *J* = 12, 12, 12, 4, 1 H); 1.86–2.16 (*m*, 5 H); 2.28 (*dd*, *J* = 14, 4, 1 H); 2.30 (*s*, 3 H); 2.51 (*ddd*, *J* = 10, 10, 4, 1 H); 2.60 (*q*, *J* = 7, 2 H); 2.86–3.04 (*m*, 2 H); 3.82 (*s*, 6 H); 4.04, 4.06 (2*q*, *J* = 7, 2 H); 6.35 (*s*, 1 H). MS: 349 (M^+).

The fumarate of **41** was prepared in Et_2O by treatment with fumaric acid. M.p. 175–176°. Anal. calc. for $C_{20}H_{31}NO \cdot C_4H_4O_4$ (465.54): C 61.92, H 7.58, N 3.01; found: C 61.67, H 7.58, N 3.05.

*(4a*RS,*10b*RS*)-8-Ethyl-2,3,4,4a,5,10b-hexahydro-7,9-dimethoxy-2-methylbenz[*h*]isoquinolin-6(1*H*)-one* (**42**). A soln. of **40** (1.9 g, 5.4 mmol) in toluene (120 ml) was added to a mixture of PPA (22 g) and toluene (10 ml) at 120° and stirred for 1 h at 120°. The soln. was then cooled to 80° and added to H_2O (100 ml) and the pH adjusted to 12 with 28% NaOH soln. The soln. was extracted with AcOEt (3 × 100 ml), dried (Na_2SO_4), and evaporated. CC (silica gel, CH_2Cl_2/MeOH/NH_4OH 110:10:1) of the residue yielded **42** (1.0 g, 61%). Colorless oil. ^{1}H-NMR ($CDCl_3$): 1.09 (*t*, *J* = 7, 3 H); 1.60 (*dddd*, *J* = 14, 4, 4, 4, 1 H); 1.89–2.11 (*m*, 1 H); 2.19–2.48 (*m*, 3 H); 2.32 (*s*, 3 H); 2.51–2.80 (*m*, 4 H); 2.63 (*q*, *J* = 7, 2 H); 3.16 (*ddd*, *J* = 12, 4, 4, 1 H); 3.77 (*s*, 3 H); 3.87 (*s*, 3 H); 6.54 (*s*, 2 H). MS: 303 (M^+), 275.

The fumarate of **42** was prepared in Et_2O by treatment with fumaric acid. M.p. 199–201.5°. Anal. calc. for $C_{18}H_{25}NO_3 \cdot C_4H_4O_4$ (419.48): C 62.21, H 6.71, N 3.45; found: C 62.62, H 6.91, N 3.01.

*(4a*RS,*10b*RS*)-8-Ethyl-2,3,4,4a,5,10b-hexahydro-7-hydroxy-9-methoxy-2-methylbenz[*h*]isoquinoline-6(1*H*)-one* (**43**). To a soln. of **42** (1.22 g, 3.6 mmol) in CH_2Cl_2 (100 ml), 1M BBr_3 in CH_2Cl_2 (4.4 ml) was added at −78°, and the resulting soln. was stirred for 15 min. The cooling bath was removed, and when the temp. reached r.t., the soln. was poured into an ice-cooled sat. $NaHCO_3$ soln. (60 ml) and extracted with CH_2Cl_2 (3 × 100 ml). The combined org. layers were dried (Na_2SO_4) and evaporated. CC (silica gel, CH_2Cl_2/MeOH/NH_4OH 110:10:1) of the residue yielded 0.90 g (94%) of **43**. Colorless oil. ^{1}H-NMR ($CDCl_3$): 1.07 (*t*, *J* = 7, 3 H); 1.65 (*dddd*, *J* = 12, 4, 4, 4, 1 H); 1.88–2.11 (*m*, 1 H); 2.19–2.79 (*m*, 6 H); 2.32 (*s*, 3 H); 2.62 (*q*, *J* = 7, 2 H); 2.96 (*tm*, *J* = 12, 1 H); 3.16 (*ddd*, *J* = 12, 4, 4, 1 H); 3.87 (*s*, 3 H); 6.32 (*s*, 1 H); 12.92 (*s*, 1 H). MS: 290 ($[M + H]^+$).

The fumarate of **43** was prepared from the EtOH soln. by treatment with fumaric acid. M.p. 221–223°. Anal. calc. for $C_{18}H_{25}NO_3 \cdot C_4H_4O_4$ (419.48): C 62.21, H 6.71, N 3.45; found: C 62.00, H 6.47, N 3.21.

*(4a*RS,*10b*SR*)-8-Ethyl-2,3,4,4a,5,10b-hexahydro-7,9-dimethoxy-2-methylbenzo[*h*]isoquinolin-6(1*H*)-one* (**44**). As described for **42**, with **41** (19.9 g, 41.5 mmol), toluene (120 ml), PPA (140 g), and toluene (50 ml), 3 h. Workup with H_2O (500 ml), 28% NaOH soln., and AcOEt (3 × 300 ml) and CC yielded **44** (8.64 g, 68%). Colorless oil. ^{1}H-NMR ($CDCl_3$): 1.10 (*t*, *J* = 7, 3 H); 1.51–1.84 (*m*, 3 H); 1.97 (*dd*, *J* = 12, 12, 1 H); 2.05 (*ddd*, *J* = 12, 12, 4, 1 H); 2.36 (*dd*, *J* = 16, 12, 1 H); 2.43 (*s*, 3 H); 2.65 (*q*, *J* = 7, 2 H); 2.70 (*dd*, *J* = 16, 4, 1 H); 2.75 (*ddd*, *J* = 12, 12, 4, 1 H); 2.94 (*dm*, *J* = 12, 1 H); 3.54 (*dd*, *J* = 12, 4, 1 H); 3.78 (*s*, 3 H); 3.90 (*s*, 3 H); 6.52 (*s*, 2 H). MS: 304 ($[M + H]^+$).

The fumarate of **44** was prepared in Et_2O by treatment with fumaric acid. M.p. 194–195.5°. Anal. calc. for $C_{18}H_{25}NO_3 \cdot C_4H_4O_4$ (419.48): C 62.21, H 6.71, N 3.45; found: C 61.80, H 6.74, N 3.21.

*(4a*RS,*10b*SR*)-8-Ethyl-2,3,4,4a,5,10b-hexahydro-7-hydroxy-9-methoxy-2-methylbenzo[*h*]isoquinolin-6(1*H*)-one* (**45**). As described for **43**, with **44** · HCl (4.41 g, 13 mmol), CH_2Cl_2 (280 ml), and 1M BBr_3 in CH_2Cl_2 (15.4 ml). Workup with sat. $NaHCO_3$ soln. (200 ml) and CH_2Cl_2 (3 × 250 ml) and CC yielded **45** (2.50 g, 67%). Colorless oil. ^{1}H-NMR ($CDCl_3$): 1.08 (*t*, *J* = 7, 3 H); 1.60 (*dd*, *J* = 12, 4, 1 H); 1.67–1.88 (*m*, 2 H); 1.97 (*dd*, *J* = 12, 12, 1 H); 2.03 (*ddd*, *J* = 12, 12, 4, 1 H); 2.40 (*dd*, *J* = 16, 12, 1 H); 2.43 (*s*, 3 H); 2.63 (*q*, *J* = 7, 2 H); 2.67 (*dd*, *J* = 12, 4, 1 H); 2.75 (*ddd*, *J* = 12, 12, 4, 1 H); 2.96 (*dm*, *J* = 12, 1 H); 3.53 (*dd*, *J* = 12, 4, 1 H); 3.90 (*s*, 3 H); 6.26 (*s*, 1 H); 13.12 (*s*, 1 H). MS: 289 (M^+).

The fumarate of **45** was prepared in Et_2O by treatment with fumaric acid. M.p. 201–203°. Anal. calc. for $C_{18}H_{25}NO_3 \cdot C_4H_4O_4$ (419.48): C 62.21, H 6.71, N 3.54; found: C 61.87, H 6.50, N 3.18.

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