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Synthesis of 6-methyl-8*H*-dibenzo[*a*,*g*]quinolizin-8-imines *via Reissert* compounds

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Abstract Alkylation of *Reissert* compounds derived from 3-methylisoquinolines with several 2-cyanobenzylbromides followed by hydrolytic cleavage provided the corresponding 1-benzyl-3-methylisoquinolines. Treatment of the latter with methylmagnesiumiodide caused cyclization to the title compounds rather than formation of 2-acetylbenzylisoquinolines.

Keywords Intramolecular cyclizations; 3-Methylisoquinoline *Reissert* compounds; Rearrangement of *Reissert* compounds.

Introduction

Coralyne (**IIIa**, 2,3,10,11-tetramethoxy-8-methyldibenzo[*a*,*g*]quinolizinium sulfoacetate or acetate, $X^- = HO_3SCH_2CO_2^-$ or $CH_3CO_2^-$) possesses the core of the protoberberine alkaloids, but it distinguishes itself from them in that it has not been isolated from natural sources, hitherto; thus, it is a purely synthetic member of this – probably most widespread – alkaloid group. The compound is well known firstly as the product of the ''coralyne reaction'' commonly used as a sensitve analytical detection of the alkaloid papaverine **Ia** in drug analytics. Thereby, the alkaloid is reacted with a mixture of sulfuric acid and acetic anhydride yielding coralyne sulfoacetate, which exhibits an intensive yellow green fluorescence in organic solvents and can be also isolated as bright yellow crystals [1, 2] (Fig. 1).

On the other hand, coralyne (**IIIa**) has received extensive attention because of its *DNA*-targeting properties [3].

As it has been reported, the formation of modified coralynes failed under certain structural conditions of the educt, *e.g.*, when starting from 3-methylpapaverine (**Ib**) to afford 6-methylcoralyne (**IIIb**) [4, 5] or from papaverine analogues without any donor function in the benzyl moiety as shown in the case of 1-benzyl-6,7-dimethoxyisoquinoline (**Ic**) to give 10,11-didemethoxy-coralyne (**IIIc**) [5, 6]. This has been explained by the steric hindrance of the 3-substituent to complete the cyclization to the corresponding coralyne analogue [5] or, in the latter cases, by the precluded generation of the crucial 6′-acetyl-intermediate **IIc** [5, 6]. Nevertheless the demethoxy-coralyne analogue **IIIc** was conveniently available using our strategy *via Reissert* compounds [7]. As well it was of interest wether our pathway would also be blocked by a substituent at C3 in the corresponding *Reissert* educts to give any 6-alkylprotoberberine analogues. In this paper we would like to report the results concerning these investigations.

Results and discussion

Educts

The required isoquinoline *Reissert* compounds **5** possessing an additional methyl group in the 3-posi-

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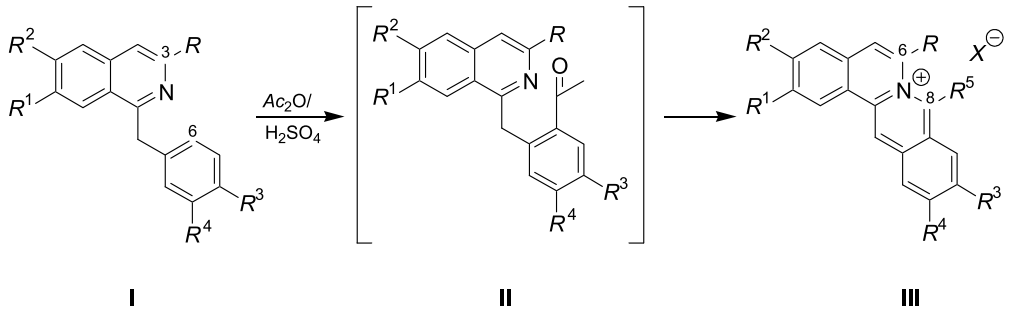
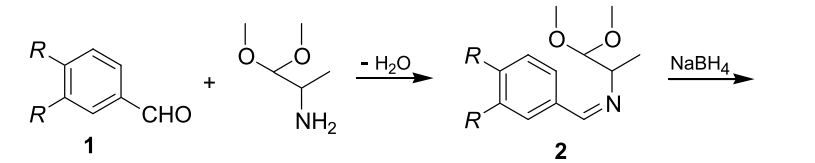


I, II, III	R	R^1	R^2	R^3	R^4	R^5
a	H	OMe	OMe	OMe	OMe	Me
b	Me	OMe	OMe	OMe	OMe	Me
c	H	OMe	OMe	H	H	Me
d	Me	H	H	H	H	Me

Fig. 1 Coralyne reaction



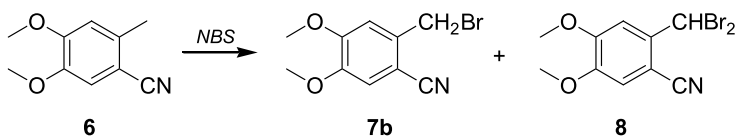
1, 2, 3, 4, 5	R	R^1
a	H	Ph
b	OMe	Ph
c	H	p-Tol

Scheme 1

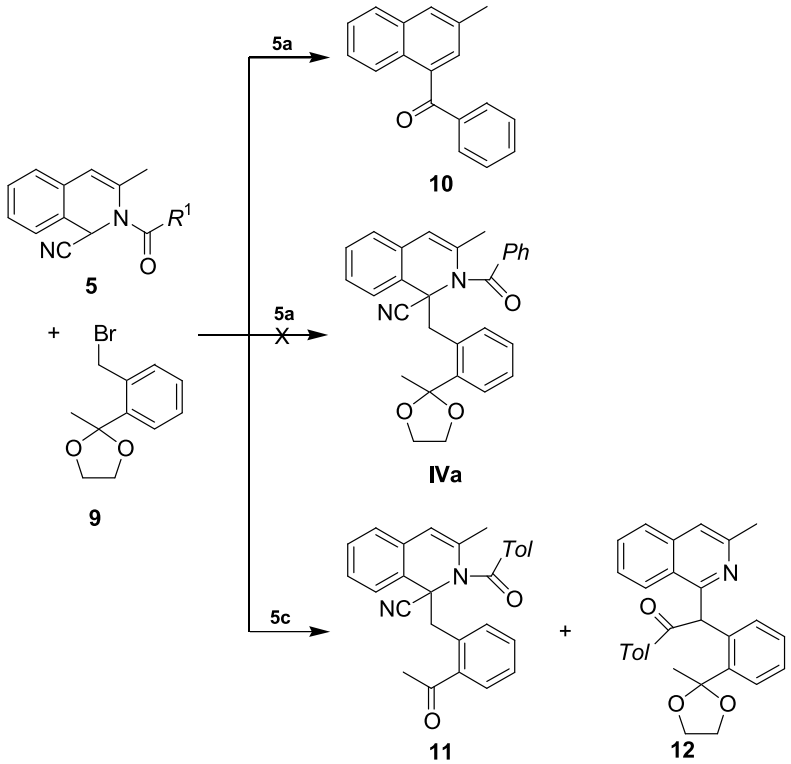
tion were prepared according to Scheme 1: Thus, the benzaldehydes **1** were reacted with α-aminopropionaldehyddimethylacetal affording the *Schiff* bases **2**, which were reduced with $NaBH_4$ yielding the amines **3**. These could be cyclized by chlorosulfuric acid immediately providing the 3-methylisoquinolines **4** in good total yields, which in turn could be transformed to the *Reissert* compounds **5** by our well established standard method. Since no procedure was available from literature the benzylbromide **7b** was prepared from 4,5-dimethoxy-2-methylbenzonitrile (**6**); besides **7b**, the dibromo-derivative **8** was also formed (see Scheme 2); the educt **6** in turn was available by an improved sequence according to Ref. [8] (see Experimental section).

Alkylation of the Reissert compounds 5

First, the *Reissert* compound **5a** was reacted with 2-(2-bromomethylphenyl)-2-methyl-[1,3]dioxolane (**9**) according to previous investigations [7], but instead of the expected alkylation product **IVa** 1-benzoyl-



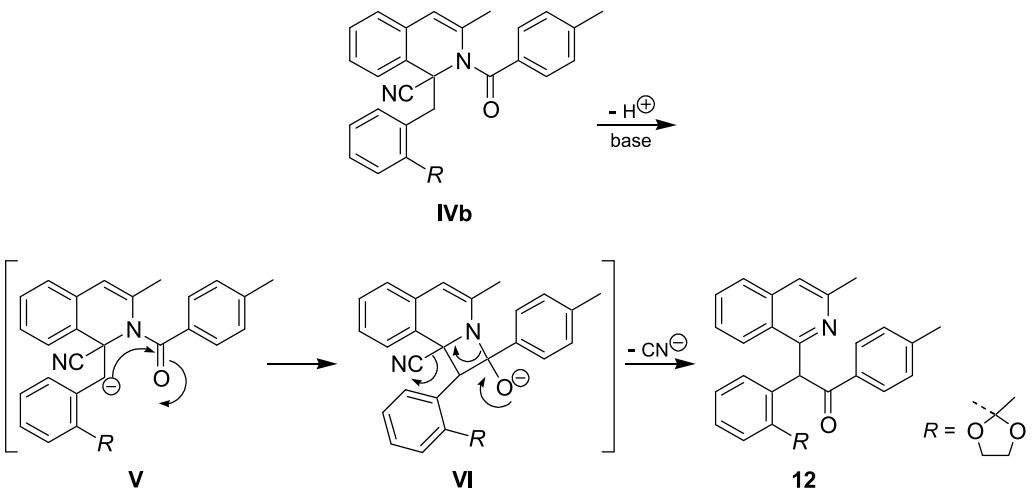
Scheme 2



Scheme 3

3-methylisoquinoline (**10**), a product of the well known rearrangement of *Reissert* compounds, was formed as the main product [9–11] (Scheme 3).

Since these rearrangements are repressed by donor substituents in the benzoyl moiety [10], consequently the alkylation was repeated with the *p*-toluoyl *Reissert* compound **5c** (Scheme 3) leading to a mixture of the benzylated product **11** and the ethanone derivative **12** emerged by rearrangement. Contrary to the previous work mentioned above the expected alkylation took place under a simultanous deprotection of the carbonyl group attached at the side chain, though both the reaction and workup had been accomplished under basic conditions (see Experimental section). In addition, the formation of the rearranged product **12** is noteworthy in that it has –

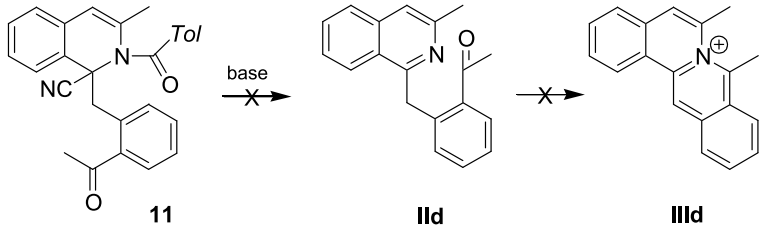


Scheme 4

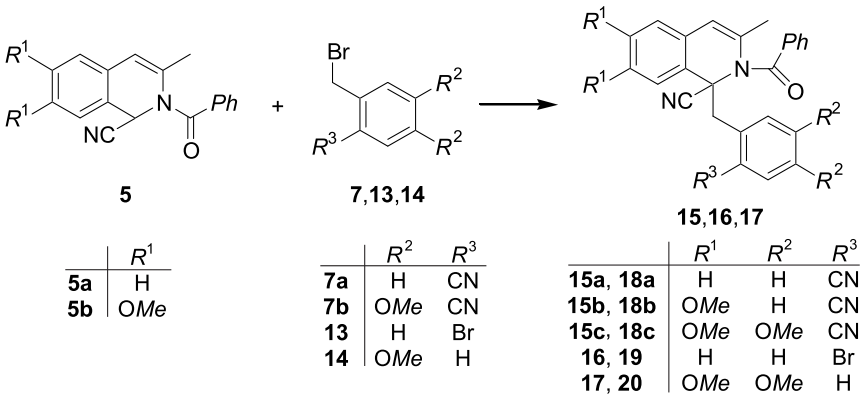
to the best of our knowledge – not yet been observed hitherto during an alkylation of an isoquinoline *Reissert* compound. It may be explained by assuming the generation of the expected, not isolated *Reissert* product **IVb** followed by the formation of its anion **V**, which would induce the rearrangement *via* the intermediate **VI** under expulsion of cyanide according to Scheme 4.

With the *Reissert* educt **11** in hand, our interest was focused to its conversion to the benzylisoquinoline **IId**, but despite all of our efforts the base induced cleavage of **11**, and hence its intended straight cyclization to the 6-methylcoralyne analogue **IIId** by improved methods used previously did not succeed (Scheme 5):

Obviously, the methyl group of the toluoyl moiety admittedly allowed the approach to the desired *Reissert* compound **11** but simultanously prevented the consecutive cleavage of the amide function by decreasing the reactivity of the carbonyl group; additionally, the steric interaction of the 3-methyl- and the amide function had to be taken in account. Comparable examples of *Reissert* compounds being uncleavable are – to the best of our knowledge – not reported in literature. Thus, the general question raised above concerning the preparation of 6-alkyl



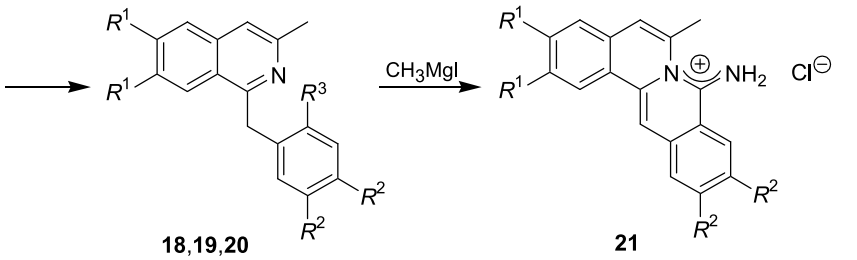
Scheme 5



	R^1
5a	H
5b	O*Me*

	R^2	R^3
7a	H	CN
7b	O*Me*	CN
13	H	Br
14	O*Me*	H

	R^1	R^2	R^3
15a, **18a**	H	H	CN
15b, **18b**	O*Me*	H	CN
15c, **18c**	O*Me*	O*Me*	CN
16, **19**	H	H	Br
17, **20**	O*Me*	O*Me*	H



	R^1	R^2	yield/%
21a	H	H	47
21b	O*Me*	H	69
21c	O*Me*	O*Me*	7

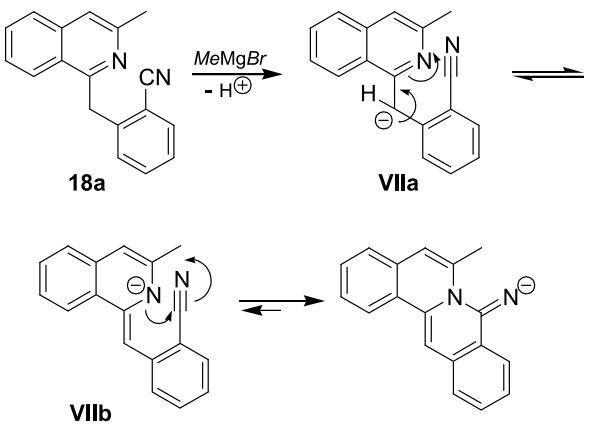
Scheme 6

coralynes *via* the *Reissert* pathway remained unresolved.

Meanwhile, it was of interest whether any other cyclizations of 3-methyl *Reissert* educts to protoberberine analogues other than coralynes could be achieved at all. Thus, *Reissert* compounds of the type **15** were found to be suitable educts for this purpose, possessing a cyano instead of a carbonyl group as the electrophilic reaction center. They could be cleaved affording the 1-benzylisoquinolines **18** in satisfying yields (51–77%). In contrast to previous results obtained with 3-unsubstituted educts [12, 13] the reaction exactly stopped at the stage mentioned, *i.e.*, no consecutive cyclizations to quinolizine derivatives **21** took place even though essentially stronger reaction conditions were needed. Additionally, bromobenzyl-3-methylisoquinoline **19** and 3-methylpapaverine **20** were prepared in the same way serving as valuable NMR references with respect to the products **18** (Scheme 6).

Finally, suitable conditions for the intended cyclization **18** → **21** were found during our attempts to transform the nitrile function of the educts **18** by *Grignard* reagents. Thus, treatment of the benzylisoquinolines **18** with methylmagnesium iodide cleanly afforded the 8-iminodibenzoquinolizines **21** instead of the expected acetyl compounds of the type **IId** (see Scheme 5). Obviously, the *Grignard* reagent acted as a base rather than as a nucleophile deprotonating **18** at the most C,H-acidic position [14] to provide the anions **VIIa** and **VIIb** according to Scheme 7.

In contrast, alcoholic KOH used as the approved base in previous related investigations failed to give the target compounds. A sterical influence of the 3-methyl group inhibiting the cyclization as reported in the case of 3-methylpapaverine (see above) could not be observed, though the yield of the product **21c** was low, but this has to be also associated with the decreased reactivity of the cyano group of the dimethoxylated benzyl moiety of the educt **18c**.



Scheme 7

The analytical characterization revealed several noteworthy properties of the new target compounds **21**. Thus, on determing the melting point or on temporary heating *e.g.*, **21b** to *ca.* 200°C under N_2, the deep yellow amorphous solid changed to colorless needles exhibiting the analytical data of the hydrochloride of the benzylisoquinoline educt **18b**. Obviously, the latter is the thermodynamically more stable structure isomer of the product. This thermal recleavage was also to be expected under the recording conditions of the mass spectra of the products **21**; this was really confirmed by the fragmentation patterns being nearly identical to those of the corresponding educts **18** (see Experimental section).

Furthermore, a signal of one proton as well as of one carbon atom were lacking in the NMR spectra of the amidinium salts **21** recorded in solvents with active deuterons, *e.g.*, in deuteriotrifluoroacetic acid. The comparison with those of the base of **21a** measured in $CDCl_3$ revealed that besides the protons of the 8-iminium group, the proton attached at C13 was also exchanged by deuterium. It is well known, that the deuteration of exchangeable C–H to C–D can result in a substantial diminution in the height of a carbon signal [15, 16] up to its full deletion as it is the case *e.g.*, of C2 in the enol form of ethyl benzoylacetate ($\delta = 87.40\,\text{ppm}/CDCl_3$) [17]. Thus, a signal applicable to C13 could not be observed in the spectra of the products **21** recorded in solvents with active deuterons. These visual differences caused by deuteration can be used as a simple aid to the assignment of ^{13}C NMR spectra [15]. Similarly, in the present case the chemical shifts of C13 and H13 could unambiguously assigned ($\delta = 97.34$, $6.78\,\text{ppm}/CDCl_3$; see Experimental section). In contrast, the revised NMR spectra of structural related 8-methyldibenzo[*a*,*g*]quinolizinium salts, *e.g.*, of coralyne analogues [13] and of coralyne (**IIIa**) itself [18], did not show a H,D-exchange at C13 and no diminution of the intensities of the signals concerned, in fact they exhibited the complete number of protons and carbon atoms. This is also true for 5,6-dihydrodibenzoquinolizines, *e.g.*, for berberine chloride (Fig. 2) measured in D_2O [19]. Due to lack-

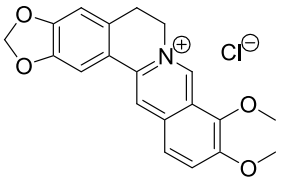
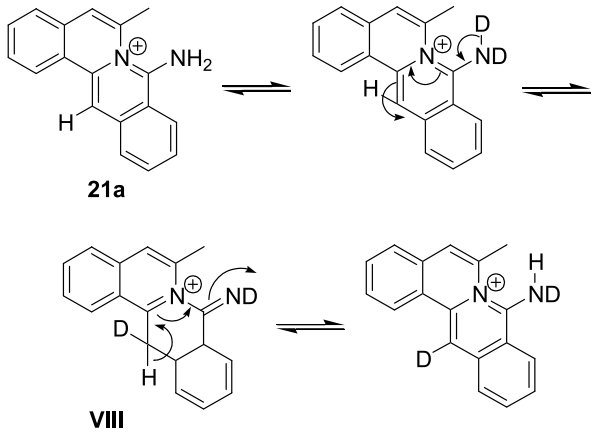


Fig. 2 Berberine chloride



Scheme 8

ing data in literature, the ^{13}C NMR spectrum of coralyne **IIIa** is included in the Experimental part. The easy H,D-exchange at C13 of the target compounds **21** was assumed to be favored by the presence of the (de)-protonable heteroatom at C8 *via* the tautomer **VIII** as indicated in Scheme 8.

Conclusions

The results presented show, that – in contrast to the coralyne reaction **Ia** → **IIIa**, which is known to be inhibited by a 3-methyl substituent in the educt **Ib** – the 1-benzylisoquinolines **18a**–**18c** related to the crucial intermediates **II** cyclize by means of methylmagnesium iodide yielding the target compounds **21a**–**21c** rather than the expected acetophenone derivatives of the type **II**. Moreover, the attempted alkylation of the *Reissert* compound **5a** with the dioxolane **9** preferentially provides the 1-benzoylisoquinoline **10** by a well known pathway. Finally, the same reaction with the *N*-toluoyl-*Reissert* educt **5c** reveals besides the expected alkylation product **11** an unprecedented rearrangement affording the toluylethanone derivative **12**. Further investigations on the scope of the cyclization of related 3-methylbenzylisoquinolines are in progress.

Experimental

Melting points are measured with a Büchi Melting Point B-545. IR: *Perkin Elmer* FT-IR Paragon 1000. NMR: Jeol GSX 400 (^1H: 400 MHz, ^{13}C: 100 MHz, $CDCl_3$, *TMS* as internal reference); MS (70 eV): Hewlett Packard MS-Engine. UV: *Perkin-Elmer* UV-Vis Lambda 20. Elemental analyses: Heraeus CHN-Rapid; the results were in good agreement with the calculated values. Thin layer chromatography (TLC): aluminium sheets Kieselgel 60 F_{254} (Merck), thickness of layer 0.2 mm. Flash chromatography (FC): ICN-SiliTech 32–36, 60 A. The following educts/compounds are commercial products: 3,4-dimethoxybenzaldehyde (**1b**), 3,4-dimethoxybenzylalkohol, 3,4-dimethoxytoluene, 1-bromo-2-bromomethylbenzene (**13**), 2-bromomethylbenzonitrile (**7a**) [12], and 2,2-dimethoxy-1-methylethylamin. 2-(2-Bromomethylphenyl)-2-methyl-[1,3]dioxolane (**9**) was prepared according to Ref. [7]. An improved procedure for 4-bromomethyl-1,2-dimethoxybenzene (**14**) [20] is given below.

*Coralyne sulfoacetate (**IIIa**)*
Synthesis according to Ref. [18]. ^{13}C NMR (F_3CCO_2D: $CDCl_3 = 1{:}1$): $\delta = 158.18, 154.68, 154.23, 152.95$ (4s, 4 arom C–O), 144.69, 136.82, 135.59, 125.53, 123.96 (5s), 123.80 (d, C-6), 123.22 (d, C-5), 121.56 (s), 117.32 (d, C-13), 109.21 (d, C-12), 106.01 (d, C-4), 105.73 (d, C-1), 104.06 (d, C-9), 57.73, 57.34, 57.26, 57.14 (4q, 4 OCH_3), 17.80 (q, C–CH_3) ppm.

*General procedure for the synthesis of the Schiff bases **2***
A mixture of the benzaldehyde **1** and 1,1-dimethoxy-2-propanamine (*Fluka*) in 200 cm^3 toluene was refluxed with H_2O separation by a *Dean-Stark* trap for 2 h. After evaporating the solvent *in vacuo* the residual oil was purified by distillation.

Benzylidene-(2,2-dimethoxy-1-methylethyl)amine
(**2a**, $C_{12}H_{17}NO_2$)
Benzaldehyde (**1a**) 21.75 cm^3 (215.1 mmol), 1,1-dimethoxy-2-propanamine 30.0 cm^3 (236.7 mmol). Yield 43.3 g (97%), colorless oil, bp 88–90°C/6 Pa; $n_D^{20} = 1.5173$; TLC ($CHCl_3$:*Me*OH:6*N* $NH_3 = 19{:}1{:}0.1$): $R_f = 0.70$ (educt: $R_f = 0.40$); MS (CI): m/z (%) = 208 ($M^{+\bullet} + 1$, 15), 176 (20), 120 (9), 88 (100); ^1H NMR ($CDCl_3$): $\delta = 8.20$ (s, N=CH), 7.67–7.65 (m, 2 arom H), 7.32–7.29 (m, 3 arom H), 4.30 (d, $J = 6.8$ Hz, O–CH–O), 3.44–3.38 (m, =N–CH–), 3.36, 3.28 (2s, 2OCH_3), 1.19 (d, $J = 6.8$ Hz, C–CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 160.98$ (N=CH), 136.24 (C-1′), 130.49 (C-4′), 128.41 (2C), 128.13 (2C), 107.30 (O–C–O), 68.35 (=N–C), 54.91, 54.47 (2OCH_3), 17.80 (–CH_3) ppm.

(3,4-Dimethoxy-benzylidene)-(2,2-dimethoxy-1-methylethyl)-amine (**2b**, $C_{14}H_{21}NO_4$)
3,4-Dimethoxybenzaldehyde **1b** 30.3 g (182.3 mmol), 1,1-dimethoxy-2-propanamine 24.0 cm^3 (200.6 mmol). Yield 46.8 g (96%), colorless oil, bp 129–131°C/10 Pa; mp 48–50°C; TLC ($CHCl_3$:*Me*OH:6*N* $NH_3 = 19{:}1{:}0.1$): $R_f = 0.90$ (educt: $R_f = 0.4$); MS (CI): m/z (%) = 268 ($M^{+\bullet} + 1$, 90), 236 (100), 192 (11), 130 (7); ^1H NMR ($CDCl_3$): $\delta = 8.27$ (s, N=CH), 7.49 (d, $J = 1.7$ Hz, 2′-H), 7.25 (dd, $J = 8.1/1.7$ Hz, 6′-H), 6.94 (d,

$J = 8.1$ Hz, 5′-H), 4.44 (d, $J = 6.8$ Hz, O–CH–O), 4.01, 3.98 (2s, 2*Ar*–OCH_3), 3.56–3.53 (m, =N–CH), 3.52, 3.44 (2s, 2*Alk*–OCH_3), 1.34 (d, $J = 6.4$ Hz, C–CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 160.55$ (N=CH), 151.28, 149.23 (C-4′, C-5′), 129.64 (C-1′), 123.02, 110.41, 109.12, 107.42 (O–C–O), 68.23 (=N–C), 55.98, 55.94 (2*Ar*–OCH_3), 54.86, 54.59 (2*Alk*–OCH_3), 17.98 (−CH_3) ppm.

General procedure for the synthesis of the benzylamines ***3***

To an ice cold solution of the *Schiff* base **2** in 150 cm^3 *Me*OH was added portionwise $NaBH_4$. The mixture was stirred under ice cooling for 1 h, thereafter at ambient temperatur for 2.5 h. After evaporating the solvent *in vacuo*, the residue was treated with 50 cm^3 CH_2Cl_2 and the mixture was washed with 100 cm^3 H_2O. The aqueous layer was extracted with 3×50 cm^3 CH_2Cl_2. The combined organic phases were washed with brine and dried (Na_2SO_4). After removing the solvent *in vacuo* the raw product was purified by distillation (**3a**) or used for the next step without further purification (**3b**).

Benzyl-(2,2-dimethoxy-1-methylethyl)amine
(**3a**, $C_{12}H_{19}NO_2$)

From 42.5 g **2a** (205 mmol), $NaBH_4$ 15.5 g (410 mmol). Yield 41.2 g (96%), colorless oil, bp 90–95°C/40 Pa; $n_D^{20} = 1.4941$; TLC ($CHCl_3$:*Me*OH:6 *N* NH_3 = 19:1: 0.1): $R_f = 0.50$ (educt: $R_f = 0.70$); IR (film): $\bar{\nu} = 3331$ (NH) cm^{-1}; MS (EI): m/z (%) = $M^{+\bullet}$ lacking, 178 (15), 134 (30), 91 (100); ^{1}H NMR ($CDCl_3$): $\delta = 7.31$ (like a d, 4 arom H), 7.25–7.20 (m, 1 arom H), 4.14 (d, $J = 6.0$ Hz, O–CH–O), 3.89, 3.69 (2d, AB-syst., $J = 12.8$, 13.2 Hz, N–CH_2), 3.37, 3.34 (2s, 2OCH_3), 2.86–2.80 (m, N–CH), 1.7 (br s, NH), 1.10 (d, $J = 6.4$ Hz, C–CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 140.54$ (C-1′), 128.40 (2C, C-2′/C-6′), 128.14 (2C, C-3′/C-5′), 126.86 (C-4′), 107.96 (O–C–O), 54.70, 54.50 (2OCH_3), 53.55 (N–CH), 51.21 (N–CH_2), 15.00 (C–*C*H_3) ppm.

(3,4-Dimethoxybenzyl)-(2,2-dimethoxy-1-methylethyl)amine
(**3b**, $C_{14}H_{23}NO_4$)

From 46.7 g **2b** (174.7 mmol), $NaBH_4$ 13.24 g (350 mmol). Yield 45.8 g (97%), viscous oily raw product; TLC ($CHCl_3$: *Me*OH:6 *N* NH_3 = 19:1:0.1): $R_f = 0.50$ (educt: $R_f = 0.90$); IR (film): $\bar{\nu} = 3330$ (NH) cm^{-1}; MS (CI): m/z (%) = 270 ($M^{+\bullet} + 1$, 100), 238 (30), 206 (40), 151 (30); ^{1}H NMR ($CDCl_3$): $\delta = 6.88$–6.80 (m, 3 arom H), 4.14 (d, $J = 6.4$ Hz, O–CH–O), 3.89, 3.86 (2s, 2*Ar*OCH_3), 3.86 (obscured), 3.64 (2d, AB-syst., $J = 12.8$ Hz, N–CH_2), 3.38, 3.35 (2s, 2*Alk*–OCH_3), 2.86–2.80 (m, N–CH), 1.84 (br s, NH), 1.10 (d, $J = 6.4$ Hz, C–CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 148.92$, 147.93, 133.14, 120.23, 111.37, 111.03, 107.88 (O–C–O), 55.89, 55.82 (2*Ar*OCH_3), 54.70, 54.54 (2*Alk*OCH_3), 53.47 (N–CH), 50.97 (N–CH_2), 14.98 (C–*C*H_3) ppm.

General procedure for the synthesis of the 3-methylisoquinolines ***4***

To CH_2Cl_2 cooled to −75°C was added dropwise $ClSO_3H$ followed under N_2 by a solution of the corresponding benzylamine **3** in CH_2Cl_2 cooled to the same temperature; the latter should not exceed −70°C. The mixture was stirred for 2 h at −70°C, then for 2 h at ambient temperature. After removing the solvent *in vacuo*, the dark brown solution was poured on ice. The mixture was washed twice with Et_2O, rendered alkaline by adding solid Na_2CO_3, and extracted twice with $CHCl_3$. The combined organic layers were concentrated to a smaller volume and then washed with brine. Finally, the solvent was removed *in vacuo*.

*3-Methylisoquinoline (****4a****)*

From 450 cm^3 CH_2Cl_2/145 cm^3 $ClSO_3H$, **3a** 41.2 g (196.8 mmol)/CH_2Cl_2 450 cm^3, ice 1 kg/Et_2O 2×100 cm^3, $CHCl_3$ 2×1000 cm^3. The residue (20.7 g) was purified by distillation. Yield 19.5 g (69%), bp 61–64°C/133 Pa; mp 63–64°C (Ref. [21]: 63–64°C); TLC (*n*-hexane:CH_2Cl_2:*Me*OH = 10:20:1): $R_f = 0.35$ (educt: $R_f = 0.55$); MS (EI): m/z (%) = 143 ($M^{+\bullet}$, 100), 129 (30), 115 (40), 100 (31); ^{1}H NMR: see Ref. [22]; ^{13}C NMR: see Ref. [23].

*6,7-Dimethoxy-3-methylisoquinoline (****4b****)*

From 170 cm^3 CH_2Cl_2/55 cm^3 $ClSO_3H$, **3b** 20.0 g (74.3 mmol)/CH_2Cl_2 170 cm^3, ice 400 g/Et_2O 2×50 cm^3, $CHCl_3$ 2×400 cm^3. The ginger residue (9.2 g) was crystallized from 30 cm^3 acetone; crystallization of the residue of the mother liquor from 10 cm^3 acetone afforded further product. Total yield: 7.59 g (50%), pale beige amorphous solid; mp 129–130°C (Ref. [21]: 130–131°C); TLC ($CHCl_3$:*Me*OH:6 *N* NH_3 = 19:1:0.1): $R_f = 0.30$ (educt: $R_f = 0.5$); MS (EI): m/z (%) = 203 ($M^{+\bullet}$, 100), 188 (30), 160 (40), 145 (13), 130 (13), 117 (16); ^{1}H NMR ($CDCl_3$): $\delta = 8.95$ (s, 1-H), 7.33 (s, 4-H), 7.15 (s, 8-H), 6.95 (5-H), 4.00 (s, 2OCH_3), 2.65 (s, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 153.03$ (C-6), 150.33, 149.65 (C-3, C-7), 149.34 (C-1), 133.34 (C-4a), 122.71 (C-8a), 117.46 (C-4), 105.17 (C-8), 104.02 (C-5), 56.02, 55.96 (2OCH_3), 24.05 (CH_3) ppm.

General procedure for the synthesis of the Reissert compounds ***5***

To an ice cold solution of the corresponding 3-methylisoquinoline **4** in CH_2Cl_2 was added a solution of KCN in H_2O under vigorous stirring. After 5 min the benzoyl chloride was added dropwise and stirring and cooling was continued for a certain time. The mixture was diluted with CH_2Cl_2, then the organic layer was washed three times with H_2O and once with brine, dried (Na_2SO_4) and evaporated *in vacuo*. After dissolving the yellow oily residue in boiling *Me*OH, the solution was chilled in an ice bath for 30 min and then immediately filtered. The mother liquor was filtered several times until no further product separated. The combined solids were washed with ice cold *Me*OH and dried *in vacuo*.

*2-Benzoyl-3-methyl-1,2-dihydroisoquinoline-1-carbonitrile (****5a****)*

From 5.0 g **4a** (34.9 mmol)/CH_2Cl_2 85 cm^3, KCN 8.15 g (125.2 mol)/H_2O 35 cm^3, benzoyl chloride 10.0 g (71.1 mmol), reaction time 1.5 h; CH_2Cl_2 100 cm^3, boiling *Me*OH 60 cm^3. Yield 6.41 g (67%), pale yellow crystals; mp 122–125°C (Ref. [24]: 127–128°C); TLC (*n*-hexane:CH_2Cl_2:*Me*OH = 20:10:1): $R_f = 0.40$ (educt: $R_f = 0.30$); IR (KBr): $\bar{\nu} = 2234$ (C≡N), 1665

(C=O) cm^{-1}; MS (CI): m/z (%) = 275 ($M^{+\bullet}$ + 1, 60), 248 (100), 144 (7), 105 (9); ^1H NMR ($CDCl_3$): δ = 7.56–7.52, 7.43–7.36, 7.24–7.21 (3m, 3 × 3 arom H), 6.53 (s, 1-H), 6.26 (s, 4-H), 1.80 (s, CH_3) ppm; ^{13}C NMR ($CDCl_3$): δ = 169.01 (C=O), 135.58, 135.25, 132.29, 131.46, 130.26, 128.99 (2C), 128.72 (2C), 128.19, 126.41, 126.01, 125.50, 117.07 (CN), 115.90 (C-4), 47.25 (C-1), 22.26 (CH_3) ppm.

2-Benzoyl-6,7-dimethoxy-3-methyl-1,2-dihydroisoquinoline-1-carbonitrile (**5b**, $C_{20}H_{18}N_2O_3$)

From 10.0 g **4b** (49.2 mmol)/CH_2Cl_2 120 cm^3, KCN 11.4 g (175 mmol)/H_2O 50 cm^3, benzoyl chloride 11.6 cm^3 (100 mmol), reaction time: 1.5 h, CH_2Cl_2 100 cm^3. Differing from the general procedure the raw product was crystallized from 160 cm^3 *Et*OAc and the residue of the evaporated mother liquor was crystallized from 40 cm^3 *Et*OAc. Total yield: 11.7 g (71%), colorless crystals; mp 171–173°C; TLC (*n*-hexane:CH_2Cl_2:*Me*OH = 20:10:1): R_f = 0.50 (educt: R_f = 0.30); IR (KBr): $\bar{\nu}$ = 1656 (C=O), (lacking C≡N) cm^{-1}; MS (EI): m/z (%) = 334 ($M^{+\bullet}$, 20), 229 (15), 203 (52), 160 (14), 131 (13), 105 (100); ^1H NMR ($CDCl_3$): δ = 7.57–7.51 (m, 3 arom H), 7.51–7.41 (m, 2 arom H), 6.82, 6.75, 6.49, 6.19 (4s, each 1H, 8-H, 5-H, 1-H, 4-H), 3.91, 3.89 (2s, each OCH_3), 1.77 (s, CH_3) ppm; ^{13}C NMR ($CDCl_3$): δ = 168.76 (C=O), 150.13 (C-6), 148.79 (C-7), 135.11 (C-3), 133.36 (C-1′), 131.93, 128.69 (2C), 128.42 (2C), 124.54 (C-4a), 118.40 (C-8a), 117.06 (C≡N), 115.58 (C-4), 108.87 (C-8), 108.30 (C-5), 56.18, 56.07 (each OCH_3), 46.76 (C-1), 21.80 (CH_3) ppm.

3-Methyl-2-(4-toluoyl)-1,2-dihydroisoquinoline-1-carbonitrile (***5c***)

From 1.65 g **4a** (11.5 mmol)/CH_2Cl_2 17 cm^3, KCN 2.7 g (41.5 mmol)/H_2O 11 cm^3, *p*-toluoyl chloride 6.1 cm^3 (38.8 mmol), reaction time: 2.5 h/ice cooling and 15 h/20°C; CH_2Cl_2 30 cm^3, boiling *Me*OH *ca.* 20 cm^3. Yield 2.47 g (75%), pale beige crystals; mp 116–117°C (Ref. [10]: 139–140, 128–129.5°C); TLC (*n*-hexane: CH_2Cl_2:*Me*OH = 20:20:1): R_f = 0.50 (educt: R_f = 0.30); IR (KBr): $\bar{\nu}$ = 1661 (C=O), (lacking C≡N) cm^{-1}; MS (EI): m/z (%) = 288 ($M^{+\bullet}$, 5), 119 (100); ^1H NMR: see Ref. [25]; ^{13}C NMR ($CDCl_3$): δ = 168.82 (C=O), 142.76 (C-4′), 135.57, 132.15, 131,29, 129.96, 129.37 (2C), 128.62 (2C), 126.18, 125.75 (2C), 125.18, 116.92 (CN), 115.36 (C-4), 47.11 (C-1), 22.02 (*Isoquin*-CH_3), 21.62 (*Tol*–CH_3) ppm.

2-Bromomethyl-4,5-dimethoxybenzonitrile (***7b***)

A) 1,2-Dimethoxy-4-methyl-5-nitrobenzene

To a solution of 18.4 g (121 mmol) 3,4-dimethoxytoluene in 90 cm^3 glacial acetic acid, cooled to 5–10°C, a mixture of 9 cm^3 (*ca.* 120 mmol) conc. HNO_3 and 50 cm^3 glacial acetic acid was added dropwise under stirring. After further stirring and cooling for 30 min the suspension was poured into 600 cm^3 H_2O. The dark red mixture was extracted with 2 × 500 cm^3 Et_2O. The combined yellow organic layers were washed with 2 × 400 cm^3 brine and evaporated *in vacuo*. The residue was taken up in 200 cm^3 CH_2Cl_2 and washed with 3 × 50 cm^3 of a saturated solution of $NaHCO_3$. Drying (Na_2SO_4) and removing the solvent afforded *ca.* 15 g of a moist yellowish solid, which was crystallized from 50 cm^3 *Me*OH. The product was washed with a small volume of petroleum ether and dried *in vacuo*. Yield 10.7 g (45%), pale yellow needles; mp 116–117°C (Ref. [26]: 119–120°C); TLC (*Et*OAc:*n*-hexane = 1:1): R_f = 0.80 (educt: R_f = 0.50); MS (EI): m/z (%) = 197 ($M^{+\bullet}$, 60), 180 (100), 152 (25), 136 (18), 121 (18); ^1H NMR ($CDCl_3$): δ = 7.57, 6.64 (2s, each 1 arom H), 3.89, 3.85 (2s, 2OCH_3), 2.54 (s, C–CH_3) ppm.

B) 4,5-Dimethoxy-2-methylaniline

A dark green mixture of 18.3 g (92.6 mmol) of the above nitro compound, 1.0 g *Adams* catalyst (PtO_2–H_2O), and 200 cm^3 *Et*OH was hydrogenated at ambient temperatur under normal pressure. After 2 h, 7.5 dm^3 (theory: 6.3 dm^3) H_2 were absorbed. The gray suspension was diluted with an adequate volume of *Me*OH to dissolve of some product. Now, the catalyst was centrifuged off, and the solvents were evaporated *in vacuo* with most 30°C. The residue was dried *in vacuo* at ambient temperatur. Yield 15.3 g (99%), pale beige solid; mp 106–107°C (Ref. [27]: 108°C); TLC (*Et*OAc:*n*-hexane = 1:1): R_f = 0.30 (educt: R_f = 0.80); IR (KBr): $\bar{\nu}$ = 3395 (NH) cm^{-1}; MS (EI): m/z (%) = 167 ($M^{+\bullet}$, 100), 152 (90), 124 (50), 109 (31); ^1H NMR: see Ref. [27].

C) 4,5-Dimethoxy-2-methyl-benzonitrile (***6***)

To a solution of 5.0 g (30 mmol) of the preceding aniline derivative in 50 cm^3 2*N* HCl cooled to 5°C was dropwise added a solution of 2.15 g $NaNO_2$ in 5 cm^3 H_2O. The mixture was stirred for 10 min under cooling and then adjusted to *pH* 7 with *ca.* 16 cm^3 conc. Na_2CO_3 (solution A). Generation of CuCN: To a solution of 9.38 g $CuSO_4$ and 2.44 g NaCl in 30 cm^3 hot H_2O was added a solution of 2.0 g $Na_2S_2O_5$ and 1.31 g NaOH in 15 cm^3 H_2O under N_2. After decantation the solid was repeatedly washed with 10 cm^3 portions of H_2O, until the supernatant was colorless. To the residue a mixture of 4.88 g NaCN, 7.5 cm^3 H_2O, and 5 cm^3 toluene was added followed by solution A (see above) under stirring and ice cooling. The mixture was stirred under cooling for 30 min, thereafter for 60 min at 20°C, and finally for 10 min at 80°C. After cooling to ambient temperatur the solids were removed by filtration. Then the deep red filtrate was saturated with NaCl and extracted with 3 × 300 cm^3 Et_2O. After concentrating the combined extracts the residue was purified by steam distillation. The distillate (*ca.* 1.5 dm^3) was saturated with NaCl and extracted with 4 × 300 cm^3 Et_2O. The combined organic phases were concentrated to a volume of 300 cm^3, washed with brine, and evaporated *in vacuo*. Yield 2.31 g (43%), beige crystals; mp 78–80°C (Ref. [28]: mp 79–80°C); TLC (*Et*OAc:*n*-hexane = 1:1): R_f = 0.80 (educt: R_f = 0.30); IR (KBr): $\bar{\nu}$ = 2215 (C≡N) cm^{-1}; MS (EI): m/z (%) = 177 ($M^{+\bullet}$, 100), 162 (40), 134 (15); ^1H NMR: see Ref. [28].

D) *2-Bromomethyl-4,5-dimethoxybenzonitrile* (**7b**, $C_{10}H_{10}BrNO_2$) *and 2-Dibromomethyl-4,5-dimethoxybenzonitrile* (**8**, $C_{10}H_9Br_2NO_2$)

A suspension of 770 mg (4.3 mmol) *N*-bromosuccinimide, 691 mg (3.9 mmol) **6** and 20 mg (0.08 mmol) dibenzoylperoxide in 20 cm^3 CCl_4 was refluxed for 3 h. After filtering off the solid, the filtrate was washed with a saturated solution of $NaHCO_3$ and brine, dried (Na_2SO_4) and

evaporated *in vacuo*. The products were separated by FC (*n*-hexane:*Et*O*Ac* = 3:1).

7b: Yield 658 mg (66%), colorless crystals; mr 122–125°C; TLC (see FC): $R_f = 0.40$; IR (KBr): $\bar{\nu} = 2224$ (C≡N), 582 (C–Br) cm^{-1}; MS (CI): m/z (%) = 257 ($M^{+\bullet}$, 20), 255 ($M^{+\bullet}$, 15), 176 (100); ^1H NMR ($CDCl_3$): $\delta = 7.05$ (s, 6-H), 7.00 (s, 3-H), 4.63 (s, CH_2), 3.96, 3.91 (2s, $2OCH_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 152.73$, 149.07 (C-3, C-4), 135.19 (C-2), 117.07 (C≡N), 114.03 (C-6), 112.57 (C-3), 103.70 (C-1), 56.21, 56.15 ($2OCH_3$), 29.89 (CH_2) ppm.

8: Yield 433 mg (33%), colorless crystals; mr 140–145°C; TLC (see FC): $R_f = 0.60$; IR (KBr): $\bar{\nu} = 2222$ (C≡N), 584 (C–Br) cm^{-1}; MS (EI): m/z (%) = 337, 335, 333 ($M^{+\bullet}$, 5–10), 256/254 (90/100), 206 (26), 176 (80); ^1H NMR ($CDCl_3$): $\delta = 7.44$ (s, 3-H), 6.99 (s, $CHBr_2$), 6.94 (s, 6-H), 4.03, 3.93 (2s, $2OCH_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 153.44$, 150.07 (C-4, C-5), 138.62 (C-2), 116.24 (C≡N), 112.49 (C-6), 111.94 (C-3), 99.58 (C-1), 56.44, 56.24 ($2OCH_3$), 36.03 ($CHBr_2$) ppm.

*4-Bromomethyl-1,2-dimethoxybenzene (**14**)*

To a solution of 1.0 (6 mmol) 3,4-dimethoxybenzylalkohol in 30 cm^3 Et_2O cooled with dry ice/acetone was dropwise added a mixture of 0.62 cm^3 (6.5 mmol) PBr_3 in 10 cm^3 Et_2O. After stirring for 1 h under cooling the mixture was allowed to come to ambient temperature and then poured on ice. The separated organic layer was washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. Yield 1.23 g (90%), colorless crystals quickly adopting a pale purple color cast; mp 56–58°C (Ref. [20]: 56°C); IR (KBr): $\bar{\nu} = 652$ (C–Br) cm^{-1}; MS (EI): m/z (%) = 232/230 ($M^{+\bullet}$, 2–5), 151 (100); ^1H NMR: see Ref. [20].

*General procedure for the synthesis of the alkylated Reissert compounds **15**, **16**, and **17***

To a mixture of the *Reissert* compound **5**, the corresponding benzylbromide, and cetrimoniumbromide (CTAB) or triethylbenzylammoniumchloride (TEBA) in toluene or benzene was added dropwise 50% KOH. The mixture protected against light was vigorously stirred for 24 h. Workup: Products being sparingly soluble in toluene precipitated and were filtered off and washed and/or recrystallized (method A) or alternatively, the reaction mixture was diluted with H_2O (300 cm^3) and *Et*O*Ac* (200 cm^3), then the aqueous phase was extracted with *Et*O*Ac*. The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*; residual toluene or benzene were removed by repeated evaporation with small volumes of CH_2Cl_2 (method B).

1-Benzoyl-3-methylisoquinoline (**10**, $C_{17}H_{13}NO$)

A mixture of 100 mg (0.36 mmol) **5a**, 250 mg (1 mmol) **9**, 90 mg TEBA (0.4 mmol), 0.2 cm^3 50% NaOH, and 1 cm^3 benzene was stirred for 3 h under ice cooling and thereafter poured into a mixture of 50 cm^3 *Et*O*Ac* and 50 cm^3 H_2O. The organic layer was washed with 2×100 cm^3 H_2O and dried (Na_2SO_4). After removing of the solvent *in vacuo* the residue was purified by FC (*n*-hexane:CH_2Cl_2:*Me*OH = 20:20:1). Yield 76 mg (85%), colorless crystals; mp 101–103°C (Ref. [29]: 103°C); IR (KBr): $\bar{\nu} = 1673$ (C=O) cm^{-1}; MS (EI): m/z (%) = 247 ($M^{+\bullet}$, 60), 246 (80), 218 (90), 105 (50); ^1H NMR ($CDCl_3$): $\delta = 8.07–8.04$, 7.97–7.94, 7.83–7.81, 7.69–7.58, 7.50–7.45 (each m, 1 + 2 + 1 + 3 + 3 H), 2.73 (s, CH_3) ppm.

1-(2-Acetylbenzyl)-3-methyl-2-(4-toluoyl)-1,2-dihydroisoquinoline-1-carbonitrile (**11**, $C_{28}H_{24}N_2O_2$) *and 2-[2-(2-methyl-[1,3]dioxolan-2-yl)-phenyl]-2-(3-methyl-isoquinolin-1-yl)-1-p-tolyl-ethanone* (**12**, $C_{29}H_{27}NO_3$)

From 580 mg (2 mmol) **5c**, **9** 1.6 g (6.2 mmol), TEBA 100 mg (0.44 mmol), benzene 1.5 cm^3, KOH 0.3 cm^3. Method B: the components were separated by repeated FC (*n*-hexane:CH_2Cl_2:*Me*OH = 20:10:1), followed by PTLC.

12 (1, fraction): Yield 75 mg (14%), colorless crystals; mp 208–212°C (*Me*OH); TLC (*n*-hexane:CH_2Cl_2:*Me*OH = 20:10:1): $R_f = 0.45$ (edcuct: $R_f = 0.50$); IR (KBr): $\bar{\nu} = 1670$ (C=O), 1039 (C–O dioxolane) cm^{-1}; MS (EI): m/z (%) = 437 ($M^{+\bullet}$, 15), 394 (35), 350 (60), 318 (15), 274 (65), 231 (20), 119 (100), 91 (65); ^1H NMR ($CDCl_3$): $\delta = 8.08$ (d, $J = 8.6$ Hz, 1 arom H), 7.70 (d, $J = 8.1$ Hz, 2 arom H), 7.64–7.60 (m, 2 arom H), 7.51–7.47 (m, 1 arom H), 7.42 (s, 1 arom H), 7.35–7.31 (m, 1 arom H), 7.26 (s, 1 arom H), 7.18–7.12 (m, 1 arom H), 7.04–7.01 (m, 3 arom H), 6.88 (d, $J = 7.7$ Hz, 1 arom H), 3.99–3.93, 3.79–3.74, 3.62–3.57 (3m, 1H, 2H, 1H, $2OCH_2$), 2.43 (s, *Isoquin*–CH_3), 2.24 (s, *Tol*–CH_3), 1.78 (s, *Dioxol*–CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 197.15$ (C=O), 159.03, 150.55, 142.15, 140.12, 137.60, 135.90, 135.75, 131.78, 129.61, 128.97 (2C), 128.35 (2C), 128.02, 126.96 (2C), 126.30 (2C), 125.09, 125.00, 117.72, 109.44 (C(O)O), 64.59, 64.28 ($2CH_2$–O), 55.14, 27.93 (*Dioxol*–CH_3), 24.12 (*Isoquin*–CH_3), 21.53 (*Tol*–CH_3) ppm.

11 (2, fraction): Yield 165 mg (20%), dark yellow oil; TLC (*n*-hexane:CH_2Cl_2: *Me*OH = 20:10:1): $R_f = 0.40$; IR (film): $\bar{\nu} = 2253$ (C≡N), 1683 (C=O), 1669 (C(O)N) cm^{-1}; MS (CI): m/z (%) = 421 ($M^{+\bullet} + 1$, 30), 394 (10), 276 (100), 119 (80); ^1H NMR ($CDCl_3$): $\delta = 7.61$ (br s, 2 arom H), 7.52–7.41 (m, 2 arom H), 7.34–7.19 (m, 4 arom H), 7.11–6.98 (m, 1 arom H), 6.78 (d, $J = 7.8$ Hz, 1 arom H), 5.98 (s, 4-H), 4.56–4.53, 3.74–3.71 (2d, AB-syst., each $J = 12.8$ Hz, CH_2), 2.39 (s, (*Tol*–CH_3), 2.01 (s, *Ac*–CH_3), 1.71 (s, *Isoquin*–CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 201.52$ (C=O), 170.02 (NHC=O), 143.45, 139.65, 134.14, 133.52, 132.70, 132.53, 131.02, 130.67, 129.44 (2C), 129.21 (2C), 129.06, 128.55, 127.63, 127.49, 127.36, 126.44, 124.29, 117.65, 111.96 (C-4), 64.17, 35.66 (CH_2), 28.88 (*Ac*–CH_3), 24.05 (*Isoquin*–CH_3), 21.65 (*Tol*–CH_3) ppm.

2-Benzoyl-1-(2-cyano-benzyl)-3-methyl-1,2-dihydroisoquinoline-1-carbonitrile (**15a**, $C_{26}H_{19}N_3O$)

From 1.0 g (3.6 mmol) **5a**, **7a** 920 mg (4.7 mmol), CTAB 50 mg (0.14 mmol), toluene 10 cm^3, KOH 3 cm^3. Method B: the raw product was crystallized from 30 cm^3 *Me*OH. Yield 1.12 g (81%), colorless crystals; mp 180–183°C; TLC (*n*-hexane:CH_2Cl_2:*Me*OH = 20:10:1): $R_f = 0.20$ (edcuct: $R_f = 0.40$); IR (KBr): $\bar{\nu} = 2228$ (C≡N), 1674 (C=O) cm^{-1}; MS (CI): m/z (%) = 390 ($M^{+\bullet} + 1$, 100), 363 (30), 259 (50), 105 (50); ^1H NMR ($CDCl_3$): $\delta = 7.65–7.63$ (m, 3 arom H), 7.53–7.45 (m, 2 arom H), 7.37–7.25 (m, 5 arom H), 7.06–7.04 (d, $J = 7.3$ Hz, 1 arom H), 6.97–6.93 (m, 1 arom H), 6.77–6.75 (d, $J = 7.7$ Hz, 1 arom H), 5.97 (s, 4-H), 3.84–3.80, 3.67–3.64

(2d, AB-syst., $J = 12.8/13.3$ Hz, *Ar*–CH_2), 1.63 (s, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 170.23$ (C=O), 136.49, 136.03, 133.29, 132.76, 132.39, 132.32, 132.16, 130.62, 129.69, 129.30 (2C), 128.74, 128.10 (2C), 126.93, 126.73, 124.97, 117.16, 116.47 (2C≡N), 114.47, 112.53, 63.47, 39.38 (CH_2), 24.02 (CH_3) ppm.

2-Benzoyl-1-(2-cyanobenzyl)-6,7-dimethoxy-3-methyl-1,2-dihydroisoquinoline-1-carbonitrile (**15b**, $C_{28}H_{23}N_3O_3$)
From 898 mg (2.7 mmol) **5b**, **7a** 683 mg (3.5 mmol), CTAB 74 mg (0.2 mmol), toluene 10 cm^3, KOH 3 cm^3. Method A: after consecutively washing with Et_2O, *Me*OH (2x), and Et_2O the product was dried *in vacuo* giving 842 mg; the mother liquor of the original reaction mixture provided further 61 mg. Total yield: 903 mg (74%) citreous crystals; mp 166–168°C; TLC (*n*-hexane:CH_2Cl_2:*Me*OH = 20:10:1): $R_f = 0.30$ (edcuct: $R_f = 0.40$); IR (KBr): $\bar{\nu} = 2226$ (C≡N), 1665 (C=O) cm^{-1}; MS (EI): m/z (%) = $M^{+\bullet}$ lacking, 422 (30), 405 (45), 394 (25), 345 (10), 317 (60), 105 (100); ^1H NMR ($CDCl_3$): $\delta = 7.72$–7.20 (m, 9 arom H), 6.56 (s, 5-H), 6.14 (s, 8-H), 5.92 (s, 4-H), 3.84 (s, OCH_3), 3.79–3.76, 3.68–3.65 (2d, AB-syst., each $J = 12.8$ Hz, CH_2), 3.40 (s, OCH_3), 1.62 (s, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 170.29$ (C=O), 149.81, 147.45, 136.80, 136.05, 132.72, 132.39, 132.34, 132.05, 131.37, 129.30 (2C), 128.72, 127.91 (2C), 124.11, 118.72, 117.45, 116.36, 114.86, 112.59, 110.36, 107.78, 63.36 (C-1), 55.95 (OCH_3), 55.71 (OCH_3), 39.14 (CH_2), 23.86 (CH_3) ppm.

2-Benzoyl-1-(2-cyano-4,5-dimethoxybenzyl)-6,7-dimethoxy-3-methyl-1,2-dihydroisoquinoline-1-carbonitrile
(**15c**, $C_{30}H_{27}N_3O_5$)
From 3.0 g (9.0 mmol) **5b**, **7b** 2.56 (10 mmol), CTAB 100 mg (0.27 mmol), toluene 20 cm^3, KOH 6 cm^3. Method B: the semi solid light brown raw product (*ca.* 5.8 g) was treated with 10 cm^3 hot *Me*OH affording 3.0 g (64%) yellow solid which was used for the next step without further purification. Repeating the treatment with the same solvent gave an analytical pure product, mp 155–157°C; TLC (*n*-hexane:CH_2Cl_2:*Me*OH = 20:10:1): $R_f = 0.30$ (edcuct: $R_f = 0.50$); IR (KBr): $\bar{\nu} = 2219$ (C≡N), 1668 (C=O) cm^{-1}; MS: a) EI: m/z (%) = $M^{+\bullet}$ lacking, 482 (50), 465 (50), 377 (100), 105 (50); b) CI: 510 ($M^{+\bullet} + 1$, 40), 483 (100), 379 (50), 333 (15), 229 (5), 105 (45); ^1H NMR ($CDCl_3$): $\delta = 7.67$ (br s, 2 arom H), 7.50–7.46 (m, 1 arom H), 7.38–7.34 (m, 2 arom H), 7.18 (s, 1 arom H), 6.73 (s, 1 arom H), 6.57 (s, 5-H), 6.23 (s, 8-H), 5.94 (s, 4-H), 3.93, 3.84, 3.77 (3s, 3OCH_3), 3.73–3.69, 3.59–3.56 (2d, AB-syst., $J =$ 12.8, 13.3 Hz, CH_2), 3.46 (s, OCH_3), 1.63 (s, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 170.21$ (C=O), 152.05, 149.81, 148.45, 147.45, 136.03, 132.71, 131.37, 131.00, 129.29 (2C), 128.72 (2C), 124.11, 118.97, 117.82, 116.76 (2C≡N), 114.33, 113.49, 112.64, 110.27, 107.72, 105.95, 63.38 (C-1), 56.32, 56.17, 55.93, 55.86 (4OCH_3), 39.00 (CH_2), 23.82 (CH_3) ppm.

2-Benzoyl-1-(2-bromobenzyl)-3-methyl-1,2-dihydroisoquinoline-1-carbonitrile (**16**, $C_{25}H_{19}BrN_2O$)
From 4.0 g (14.6 (mmol) **5a**, **13** 4.74 g (19.0 mmol), CTAB 100 mg (0.27 mmol), toluene 30 cm^3, KOH 6 cm^3. Method B: the raw product was crystallized from 40 cm^3 *Et*OAc and 4 cm^3 *Me*OH. Yield 4.6 g (71%), pale yellow crystals; mp 167–169°C; TLC (*n*-hexane:CH_2Cl_2:*Me*OH = 20:10:1): $R_f = 0.40$ (edcuct: $R_f = 0.40$); IR (KBr): $\bar{\nu} =$ (C≡N) lacking, 1674 (C=O), 1026 (C–Br) cm^{-1}; MS (CI): m/z (%) = 445/443 (each $M^{+\bullet} + 1$, each 100), 418/416 (each 40), 314/312 (each 50), 273 (22), 151 (19), 105 (100); ^1H NMR ($CDCl_3$): $\delta = 7.72$ (br s, 2 arom H), 7.55–7.51 (m, 1 arom H), 7.43–7.20 (m, 6 arom H), 7.10–7.03 (m, 3 arom H), 6.98–6.96 (m, 1 arom H), 5.92 (s, 4-H), 3.99–3.96, 3.67–3.64 (2d, AB-syst., $J = 13.3/12.8$ Hz, *Ar*–CH_2), 1.67 (s, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 170.19$ (C=O), 136.32, 133.58, 132.92, 132.66, 132.57, 130.70, 129.41, 129.30 (2C), 129.11, 128.75 (2C), 127.61, 127.32, 127.16, 127.05, 126.94, 126.88, 124.32, 117.67 (C≡N), 112.42, 63.68 (C-1), 40.42 (CH_2), 24.06 (CH_3) ppm.

2-Benzoyl-1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-3-methyl-1,2-dihydroisoquinoline-1-carbonitrile (**17**, $C_{29}H_{28}N_2O_5$)
From 1.0 g (3 mmol) **5b**, **14** 920 mg (4 mmol), CTAB 50 mg (0.14 mmol), toluene 10 cm^3, KOH 3 cm^3. Method A: Washing with 5 cm^3 H_2O and with 2×20 cm^3 Et_2O and drying *in vacuo* gave 978 mg of pale yellow raw product, which was crystallized from 20 cm^3 *Et*OAc/4 cm^3 *Me*OH. Repeated evaporation and crystallization of the residue of the mother liquor provided additional substance. Total yield: 724 mg (50%), pale yellow crystals; mp 154–156°C; TLC (*n*-hexane:CH_2Cl_2:*Me*OH = 20:10:1): $R_f = 0.40$ (edcuct: $R_f =$ 0.50); IR (KBr): $\bar{\nu} = 2224$ (C≡N), 1669 (C=O) cm^{-1}; MS: a) EI: m/z (%) = $M^{+\bullet}$ lacking, 457 (20), 465 (50), 352 (100), 338 (30), 320 (16), 228 (17), 105 (10); b) CI: 485 ($M^{+\bullet} + 1$, 2), 458 (40), 354 (20), 229 (100), 151 (10), 105 (20); ^1H NMR ($CDCl_3$): $\delta = 7.71$ (br s, 2 arom H), 7.55–7.51 (m, 1 arom H), 7.43–7.39 (m, 2 arom H), 6.69–6.67 (d, $J = 8.1$ Hz, 1 arom H), 6.61 (s, 1 arom H), 6.50 (s, 1 arom H), 6.46–6.41 (m, 2 arom H), 5.83 (s, 4-H), 3.91, 3.83, 3.73, 3.58 (4s, 4OCH_3), 3.50–3.46, 3.41–3.38 (2d, AB-syst., each $J = 12.8$ Hz, CH_2), 1.63 (s, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 170.03$ (C=O), 149.31, 148.34, 148.09, 147.34, 136.27, 132.50, 131.75, 129.18 (2C), 128.61, 128.44, 125.79, 123.36, 122.94, 120.49, 117.78 (C≡N), 114.00, 111.88, 111.35, 110.43, 107.01, 63.91 (C-1), 55.93, 55.82, 55.75, 55.62 (4OCH_3), 41.50 (CH_2), 23.80 (CH_3) ppm.

*General procedure for the synthesis of the 1-benzyl-3-methylisoquinolines **18**, **19**, and **20***
A mixture of the alkylated *Reissert* compound **15**, **16**, or **17**, KOH, and $FeSO_4$ in *Me*OH- or *Et*OH/H_2O was refluxed for 3 h. After removing the solids by filtration the solvent was evaporated *in vacuo*, and the yellow residue was partitioned between *Et*OAc and H_2O (each 300 cm^3). The aqueous layer was saturated with NaCl and extracted again with *Et*OAc. The combined organic phases were extracted five times with 2 *N* HCl, then the combined acidic extracts were rendered alkaline with 2 *N* NaOH and extracted with 3×100 cm^3 *Et*OAc. The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo*.

2-(3-Methyl-isoquinolin-1-ylmethyl)-benzonitrile
(**18a**, $C_{18}H_{14}N_2$)
From 1.0 g (2.6 mmol) **15a**, KOH 800 mg (14.3 mmol), $FeSO_4$ 500 mg (3.3 mmol), *Me*OH 100 cm^3, H_2O 5 cm^3. The tawny oily residue (589 mg) was used for the next step without further purification. An analytical pure sample was obtained

by FC (*n*-hexane:CH_2Cl_2:*Me*OH = 10:20:1). Yield 520 mg (77%), colorless oil; hydrochloride: mp 259°C; TLC (see FC): $R_f = 0.50$ (educt: 0.80); IR (film): $\bar{\nu} = 2222$ (C≡N) cm^{-1}; MS (EI): m/z (%) = 258 ($M^{+\bullet}$, 30), 257 ($M^{+\bullet} - 1$, 100), 232 (5), 195 (10), 167 (9), 149 (15), 115 (9); ^1H NMR ($CDCl_3$): $\delta = 8.00$ (d, $J = 8.6$ Hz, 8-H), 7.74–7.57 (3m, each 1H), 7.48–7.23 (3m, 2 + 1 + 1H), 7.10 (d, $J = 8.6$ Hz, 1H), 4.86 (s, CH_2), 2.69 (s, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 157.33$, 150.66, 143.27, 137.31, 132.72 (2C), 130.05, 129.53, 126.86, 126.77, 126.66, 126.57, 125.24, 118.27 (2C), 112.42, 39.70 (CH_2), 24.23 (CH_3) ppm.

2-(6,7-Dimethoxy-3-methylisoquinolin-1-ylmethyl)-benzonitrile (**18b**, $C_{18}H_{20}N_2O_2$)

A) From 2.48 g (5.5 mmol) **15b**, KOH 2 g (35.7 mmol), $FeSO_4$ 1.25 g (8.2 mmol), *Me*OH 250 cm^3, H_2O 13 cm^3. During the acidic extraction **18b** · HCl separated. Therefore the aqueous suspension was separated, rendered alkaline, and extracted with *Et*O*Ac*. The organic extracts were evaporated *in vacuo* and the light brown residue smelling according as vanillin was crystallized from 20 cm^3 *Me*OH. Yield 892 mg (51%), colorless crystals; mp 154–156°C; **18b** · HCl: mp 219–221°C; TLC (*n*-hexane:CH_2Cl_2:*Me*OH = 20:10:1): $R_f = 0.50$ (educt: 0.80); IR (KBr): $\bar{\nu} = 2222$ (C≡N) cm^{-1}; MS (EI): m/z (%) = 318 ($M^{+\bullet}$, 70), 317 (100), 303 (53), 259 (20), 135 (10); ^1H NMR ($CDCl_3$): $\delta = 7.67$–7.65 (m, 1 arom H), 7.41–7.24 (m, 5 arom H), 6.96 (s, 5-H), 4.78 (s, CH_2), 3.98, 3.96 (2s, $2OCH_3$), 2.67 (s, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 155.16$ (C-1), 152.69 (C-6), 149.69 (C-3), 149.41 (C-7), 143.34, 134.23 (C-4a), 132.88, 132.50, 129.77, 126.88, 120.83 (C-8a), 118.54 (C≡N), 117.37, 112.07, 104.77 (C-5), 103.40 (C-8), 56.27 (OCH_3), 55.98 (OCH_3), 39.92, 24.16 (CH_3) ppm.

B) From **21b** (see below): 42 mg (0.12 mmol) **21b** were heated to 200°C under N_2 for 1 min. From *ca.* 180°C decoloration of the educt began. After cooling to ambient temperature the solid was treated with a mixture of *Et*O*Ac* and 2 *N* NaOH (each 10 cm^3). The organic layer was separated, washed with brine, and dried with Na_2SO_4. After evaporating the solvent *in vacuo*, the residue was purified by FC (eluent see TLC under A). Mp, TLC and the spectroscopic data were identical to those given under A.

2-(6,7-Dimethoxy-3-methylisoquinolin-1-ylmethyl)-4,5-dimethoxybenzonitrile (**18c**, $C_{22}H_{22}N_2O_4$)

To a solution of 1.38 g (2.7 mmol) **15c** in 10 cm^3 *DMF* was added dropwise 2.8 cm^3 *Triton B* (40% benzyltrimethylammonium hydroxide in *Me*OH). After stirring for 15 h at ambient temperatur the red brown suspension formed was diluted with 300 cm^3 *Et*O*Ac* and 500 cm^3 H_2O. The yellow organic layer was extracted with 1 dm^3, thereafter with 2×200 cm^3 2 *N* HCl. The combined acidic phases were rendered alkaline with solid Na_2CO_3 and extracted with 3×200 cm^3 *Et*O*Ac*. After washing with brine and drying (Na_2SO_4) the organic extracts were evaporated *in vacuo* affording 1.3 g beige orange solid, which was recrystallized from 8 cm^3 *Et*O*Ac*. Crystallization of the residue of the mother liquor gave additional substance. Total yield: 752 mg (74%), pale yellow, fine needles; mp 169–171°C; TLC (CH_2Cl_2:*Me*OH = 20:1): $R_f = 0.60$ (educt: $R_f = 0.90$); IR (KBr): $\bar{\nu} = 2214$ (C≡N) cm^{-1}; MS (EI): m/z (%) = 378 ($M^{+\bullet}$, 90), 377 ($M^{+\bullet} - 1$, 100), 363 (50), 347 (20); ^1H NMR ($CDCl_3$): $\delta = 7.41$, 7.28 (2s, 8-H, 4-H), 7.02, 7.03 (2s, 3′-H, 6′-H), 6.96 (s, 5-H), 4.69 (s, CH_2), 4.04, 3.98, 3.85, 3.74 (4s, $4OCH_3$), 2.68 (s, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 155.63$ (C-1), 152.82, 152.76, 149.76, 149.19, 147.82, 137.84 (C-1′), 134.23 (C-4a), 120.79 (C-8a), 119.17 (C≡N), 117.30 (C-4), 113.35 (C-3′), 112.18 (C-6′), 104.74 (C-5), 103.53 (C-8), 102.85 (C-2′), 56.47, 56.13, 55.96, 55.85 ($4OCH_3$), 39.43 (CH_2), 24.20 (CH_3) ppm.

1-(2-Bromobenzyl)-3-methyl-isoquinoline (**19**, $C_{17}H_{14}BrN$)

From 720 mg (1.62 mmol) **16**, KOH 520 mg (9.3 mmol), $FeSO_4$ 320 mg (2.1 mmol), *Et*OH 70 cm^3, H_2O 3 cm^3. The yellow oily residue (482 mg) was purified by FC (*n*-hexane:CH_2Cl_2: *Me*OH = 10:20:1). Yield 387 mg (77%), pale yellow oil; HCl: mp 139–141°C; TLC (see FC): $R_f = 0.60$ (educt: 0.80); IR (film): $\bar{\nu} = 1024$ (C–Br) cm^{-1}; MS (CI): m/z (%) = 314/312 ($M^{+\bullet} + 1$, 100), 232 (20), 117 (20), 91 (42); ^1H NMR ($CDCl_3$): $\delta = 7.83$ (d, $J = 8.5$ Hz, 1 arom H), 7.64 (d, $J = 7.9$ Hz, 1 arom H), 7.52–7.47, 7.34–7.29, 6.96–6.91 (3m, each 2 arom H), 6.67–6.65 (m, 1 arom H), 4.65 (s, CH_2), 2.62 (s, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 157.01$ (C-1), 149.02 (C-3), 137.61 (C-4a), 135.76, 131.13, 128.59, 128.53, 126.38, 125.93, 125.35 (C-5), 125.06 (C-7), 124.37 (C-8), 124.13 (C-8a), 122.99, 116.77 (C-4), 41.48 (CH_2), 24.03 (CH_3) ppm.

1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3-methyl-isoquinoline (*3-Methylpapaverine* **20**)

From 100 mg (0.2 mmol) **17**, KOH 80 mg (1.4 mmol), $FeSO_4$ 50 mg (0.3 mmol), *Et*OH 10 cm^3, H_2O 0.5 cm^3, refluxing time: 1 h. The residue was crystallized from 0.5 cm^3 *Et*OH. Yield 51 mg (72%), colorless crystals; mp 132–134°C (Ref. [30]: 136°C); TLC (CH_2Cl_2:*Me*OH = 20:1): $R_f = 0.40$ (educt: $R_f = 0.70$); MS (EI): m/z (%) = 353 ($M^{+\bullet}$, 60), 338 (100), 322 (20); ^1H NMR ($CDCl_3$): $\delta = 7.27$ (s, 8-H), 7.26 (s, 4-H), 6.95 (s, 5-H), 6.84–6.73 (m, 3 arom H), 4.51 (s, CH_2), 3.97, 3.86, 3.81, 3.77 (4s, $4OCH_3$), 2.67 (s, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 157.24$ (C-1), 152.43 (C-6), 149.29 (C-7), 149.07 (C-3), 148.94 (C-3′), 147.44 (C-4′), 134.23 (C-4a), 132.42 (C-1′), 120.88 (C-8a), 120.43 (C-6′), 116.93 (C-4), 111.87 (C-2′), 111.12 (C-5′), 104.70 (C-5), 104.30 (C-8), 55.91, 55.83, 55.78 ($4OCH_3$), 42.32 (CH_2), 24.21 (CH_3) ppm.

General procedure for the synthesis of the dibenzoquinolizine derivatives ***21***

To a solution of the cyanobenzylisoquinoline **18** in anhydrous *THF* cooled by an ice bath was added a 1.6 *M* solution of methylmagnesiumbromide in Et_2O. Stirring and cooling was continued for 1 h, then further *Me*MgBr was added. The dark red solution was allowed to warm up to ambient temperature and stirred for additional 15 h. The mixture was diluted with *Me*OH, followed by 2 *N* HCl causing a deep yellow precipitate, which was filtered off and consecutively washed with acetone, H_2O, acetone, and $CHCl_3$ and dried *in vacuo*.

8-Amino-6-methyldibenzo[a,g]quinoliziniumchloride (**21a**, $C_{18}H_{15}ClN_2$)

From 100 mg (0.38 mmol) **18a**, *THF* 5 cm^3, CH_3MgBr 0.2/0.4 cm^3 (0.32/0.64 mmol), *Me*OH 1 cm^3, HCl 10 cm^3. Yield 54 mg (47%), deep yellow, amorphous solid; mr from 192°C (decompn.), 264–266°C (decompn., from *Me*OH,

several months); MS (EI): m/z (%) = 258 ($M^{+\bullet}$, 100), 257 ($M^{+\bullet} - 1$, 93), 232 (15), 149 (10), 128 (12), 115 (10); ^{1}H NMR (F_3CCO_2D): δ = 8.48–8.46, 8.35 (2m, 9-H, 1-H), 8.12–8.09 (m, 2H, 11-H, 12-H), 7.92–7.91 (m, 10-H), 7.72–7.67 (m, 3 arom H), 7.20 (s, 5-H), 2.81 (s, CH_3) ppm; ^{13}C NMR (F_3CCO_2D): δ = 156.31 (C=N), 138.97 (C-13a), 137.83 (C-11), 137.69 (C-4a), 133.84 (C-6), 133.80, 132.32, 132.03 (C-10), 130.73, 130.22, 129.58, 127.93 (C-12a), 126.84, 125.95 (C-1), 125.55 (C-9), 119.23 (C-8a), 22.55 (CH_3) ppm. Free base of **21a** ($C_{18}H_{14}N_2$): 230 mg (0.78 mmol) of the salt was stirred in a mixture of 2 *N* NaOH and $CHCl_3$. After usual workup the crude product was purified by FC (*Et*OAc:*n*-hexane:*Me*OH = 4:1:0.1). Yield 96 mg (47%), semi-solid yellow compound. MS (EI): m/z (%) = 258 ($M^{+\bullet}$, 100), 257 (70), 243 (14), 232 (15); ^{1}H NMR ($CDCl_3$): δ = 7.84 (d, J = 8.1 Hz, 9-H), 7.80 (d, J = 7.7 Hz, 1-H), 7.50 (m, 1 arom H), 7.44 (d, J = 7.5 Hz, 12-H), 7.39–7.29 (m, 3 arom H), 7.24 (d, J = 7.6 Hz, 4-H), 6.78 (s, 13-H), 6.14 (s, 5-H), 2.42 (s, CH_3) ppm; ^{13}C NMR ($CDCl_3$): δ = 159.69 (C=N), 137.97 (C-4a), 136.26, 133.47 (C-6), 131.05, 130.65, 129.30, 127.01, 126.85, 125.75, 125.44 (C-12), 125.35, 125.18 (C-4), 124.36 (C-9), 123.18 (C-1), 113.14 (C-5), 97.34 (C-13), 21.14 (CH_3) ppm. Bromide ($C_{18}H_{15}BrN_2$): Gaseous HBr was passed into a solution of the above base in acetone. The crystalline product was filtered off and dried. Mr: 244–260 (decompn.); UV ($c = 5.896 \times 10^{-5}$ mol dm^{-3}, *Me*OH): λ_{max} ($\varepsilon \times 10^{-3}$) = 407 (11.00), 381 (10.50) nm (mol^{-1} dm^3 cm).

8-Amino-2,3-dimethoxy-6-methyldibenzo[a,g]-quinoliziniumchloride (**21b**, $C_{20}H_{19}ClN_2O_2$)
From 500 mg (2.4 mmol) **18b**, *THF* 30 cm^3, CH_3MgBr 1.5/1.5 cm^3 (2.4/2.4 mmol), *Me*OH 5 cm^3, HCl 30 cm^3. Yield 380 mg (69%), yellow amorphous solid, from *ca.* 180°C up to 200°C converting to colorless needles; mr 218–230°C (decompn.); UV ($c = 5.636 \times 10^{-5}$ mol dm^{-3}, *Me*OH): λ_{max} ($\varepsilon \times 10^{-3}$) = 428 (11.75), 394 (13.49), 290 (28.18), 276–270 (30.20) nm (mol^{-1} dm^3 cm); MS (EI): m/z (%) = 318 ($M^{+\bullet}$, 80), 317 ($M^{+\bullet} - 1$, 100), 303 (60), 259 (20), 169 (16); ^{1}H NMR (F_3CCO_2D): δ = 8.45 (d, J = 8.6 Hz, 9-H), 8.14–8.05 (m, 2H, 11-H/12-H), 7.89–7.86 (m, 2H, 1-H/10-H), 7.21 (s, 2H, 5-H/4-H), 4.21, 4.13 (2s, 2OCH_3), 2.83 (s, CH_3) ppm; ^{13}C NMR (F_3CCO_2D): δ = 156.20, 154.25, 152.74, 138.69 (C-13a), 137.82 (C-4a), 137.68 (C-11), 133.35 (C-6), 131.73 (C-10), 130.2 (C-12), 126.63 (C-5), 126.23, 125.39, 121.26, 118.64 (C-8a), 110.77 (C-4), 108.20 (C-1), 58.19 (OCH_3), 57.91 (OCH_3), 22.63 (CH_3) ppm.

8-Amino-2,3,10,11-tetramethoxy-6-methyldibenzo[a,g]-quinoliziniumchloride (**21c**, $C_{22}H_{23}ClN_2O_4$)
From 100 mg (0.26 mmol) **18c**, *THF* 5 cm^3, CH_3MgBr 0.2/0.4 cm^3 (0.32/0.64 mmol), *Me*OH 1 cm^3, HCl 10 cm^3. Yield 7 mg (7%), yellow solid; mr 202–207°C (decompn.); UV ($c = 4.821 \times 10^{-5}$ mol dm^{-3}, *Me*OH): λ_{max} ($\varepsilon \times 10^{-3}$) = 434 (9.12), 389 (8.51), 312 (29.51), 290 (29.51) nm (mol^{-1} dm^3 cm); MS (CI): m/z (%) = 378 ($M^{+\bullet}$, 100), 363 (22), 149 (6); ^{1}H NMR (F_3CCO_2D): δ = 7.60, 7.51, 7.21 (3s, each 1H, 9-H, 1-H, 5-H), 6.95, 6.93 (2s, each 1H, 4-H, 12-H), 3.96 (s, 2OCH_3), 3.92, 3.86 (2s, 2OCH_3), 2.54 (s, CH_3) ppm; ^{13}C NMR (F_3CCO_2D): δ = 158.13 (C=N), 153.79, 153.68, 153.23, 152.35, 138.09 (C-13a), 135.49 (C-4a), 133.18 (C-6), 126.33 (C-5), 125.47 (C-12a), 122.10 (C-13b), 113.38 (C-12), 110.25 (C-8a), 108.37 (C-9), 107.54 (C-1), 104.47 (C-4), 58.17, 57.91, 57.75, 57.51 (4CO_3), 22.50 (CH_3) ppm.

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