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Protoberberines from *Reissert*-Compounds. Part IX [1]. An Alternative Approach to Dibenzoquinolizine- and Isoquinonaphthyridin-13a-carboxylic Acids, a Novel Synthesis of Alangimarine[#]

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Summary. 3,4-Dihydroisoquinoline-*Reissert*-compounds were alkylated to 1-benzyl- and 1-picolyl-derivatives, which in turn could selectively be hydrolized yielding various carboxylic acids, among others certain amino acids related to 3′,4′-deoxynorlaudanosoline carboxylic acid (*DNLCA*). These on treating with ethanolic KOH underwent cyclization to dibenzoquinolizine- and isoquinonaphthyridine-13a-carboxylic acids. Alternatively this cyclization also could be achieved by a more convenient one-pot procedure starting from the same dihydro-*Reissert*-compounds. Thermal decarboxylation afforded among others the alangia alkaloids alangimarine and dihydroalangimarine.

Keywords. Alkaloids; Carboxylic acids; Cyclizations; Total synthesis.

Introduction

Starting from isoquinoline-*Reissert*-compounds we have previously synthesized partially hydrogenated dibenzoquinolizine-13a-carboxylic acids, which in turn were found to be very valuable precursors for the preparation of naturally occurring protoberberines [1, 2]. However, the application of this strategy to the synthesis of the corresponding 10-aza-analogues, the isoquinonaphthyridines, which represent the framework of the pharmacologically active alangia alkaloids, *e.g.* **24c** has failed. The expected intermediate oxazoloisoquinoline derivative indicating that

[#] Dedicated to Prof. *C. Herdeis*, Würzburg, on the occasion of his 60th birthday
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the intended reduction of the *Reissert* educt had occured, was not observed [3]. Furthermore, it has been also found, that, in contrast to dibenzoquinolizinones [4], the fully aromatic isoquinonaphthyridinone could not be reduced with complex hydrides to afford the hydrogenation pattern of the alangia alkaloids **24c** or **24b** [5].

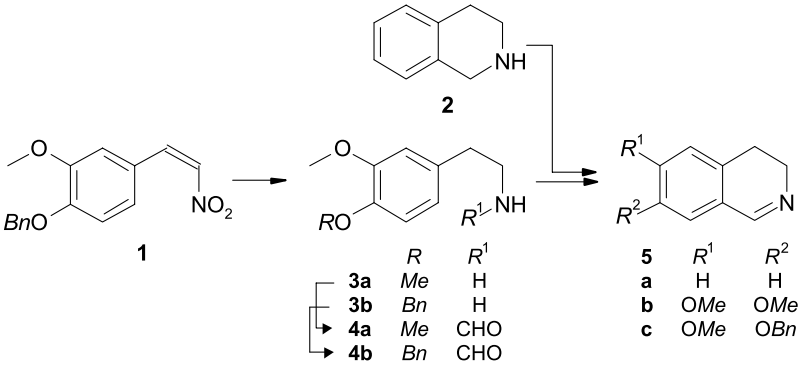
Therefore we envisaged that the reduction step required in our strategy should be avoided, if 3,4-dihydro-*Reissert*-compounds of type **7** would be employed as starting material. These are generally available from 3,4-dihydroisoquinolines **5** by the known standard procedures [6] and their alkylation at the C-1 position proceeds as readily as that of the classical *Reissert*-compounds [7, 8].

Results and Discussion

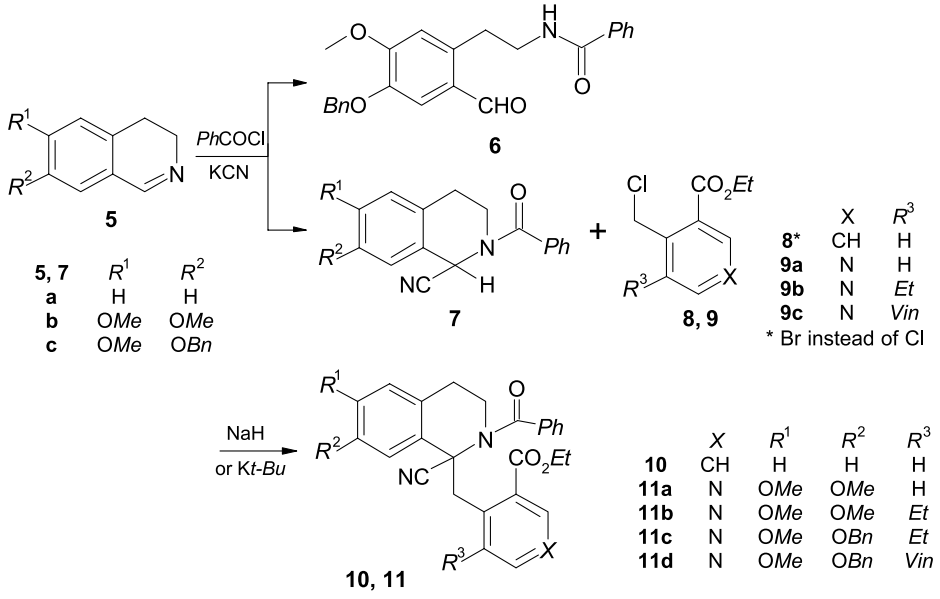
The 3,4-dihydroisoquinolines **5** were prepared by known but improved procedures according to Scheme 1 starting from 1,2,3,4-tetrahydroisoquinoline **2** or from the phenethylamines **3** *via* the formamides **4**. They could be reacted with benzoyl chloride and NaCN in the presence of $NaHCO_3$ [6] affording the expected dihydro-*Reissert*-compounds **7** in excellent yields. The formation of **6** as a possible side product reported [6] was detected in very small amounts only in the case of **7c** (see Scheme 2).

The sequential alkylation with the halogenides **8** and **9**, prepared according to Scheme 3, occured readily yielding the 1-benyzl- and 1-picolyl-dihydro-*Reissert* derivatives **10** and **11**. The reaction definitely stopped at this step. A further reaction leading to the tetracyclic isoquinonaphthyridinone previously reported [5], when classical *Reissert* compounds were employed as the educt, was not observed. In contrast, **10** and **11** were markedly more stable towards hydrolysis. An explanation may be that the complete aromatization cannot be achieved in the tetracyclic target compounds of the type **21** and **22** (see Scheme 6).

This gave rise to a more systematic investigation to elaborate suitable cyclization conditions using **11a** as educt. Thus it was hydrolyzed by ethanolic KOH to give **16**. On the other hand, more forced reaction conditions, *e.g.* KOH in monoethylene glycol, additionally caused elimination of HCN affording **17**. In contrast, dilute sulfuric acid selectively converted the angular nitrile group to the corresponding carboxylic acid **18**, and finally with concentrated phosphoric acid the



Scheme 1

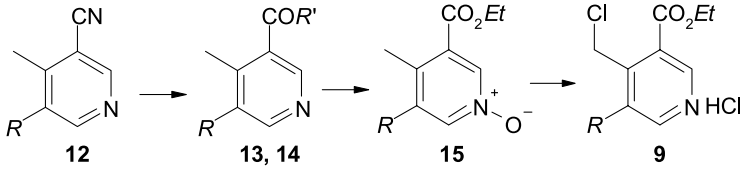


5, 7	R^1	R^2
a	H	H
b	OMe	OMe
c	OMe	OBn

	X	R^3
8*	CH	H
9a	N	H
9b	N	Et
9c	N	Vin

	X	R^1	R^2	R^3
10	CH	H	H	H
11a	N	OMe	OMe	H
11b	N	OMe	OMe	Et
11c	N	OMe	OBn	Et
11d	N	OMe	OBn	Vin

Scheme 2



	R'
13	NH_2
14	OEt

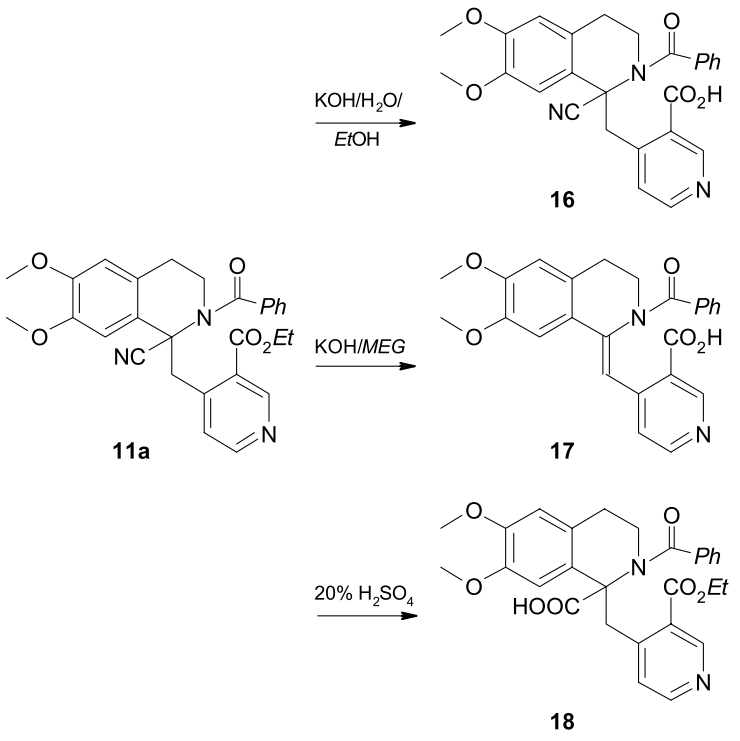
	R
9a, 12a, 13a, 14a, 15a	H
9b, 12b, 13b, 14b, 15b	Et
9c, 12c, 13c, 14c, 15c	Vin

Scheme 3

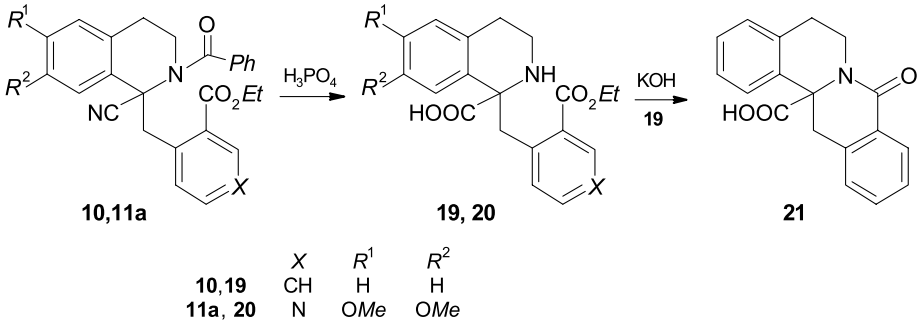
amino acids **19** and **20** were obtained from the educts **10** and **11a** under retention of the aromatic ester function (see Schemes 4 and 5). These new amino acids, being poorly soluble in the usual solvents, may be of biological interest due to their structural relationship to 3′,4′-deoxynorlaudanosoline carboxylic acid (*DNLCA*, **19**: R^1=R^2=OH, H instead of CO_2Et), which in turn is known to inhibit several enzymes, *e.g.* dihydropteridine reductase, tyrosine 3-monooxygenase, and dopamin-β-hydroxylase [9–11].

Concerning our present investigations the amino acids **19** and **20** obtained turned out to be suitable precursors for the intended cyclizations. Thus treatment of **19** with ethanolic potassium hydroxid solution afforded the oxoberbine-13a-carboxylic acid **21** in excellent yields, being identical with that prepared previously on an independent route (see Scheme 5) [1, 2].

The readily occurring cyclization of the amino acid **19** as well as its unequivocal formation in phosphoric acid prompted us to combine the two steps in an one-pot



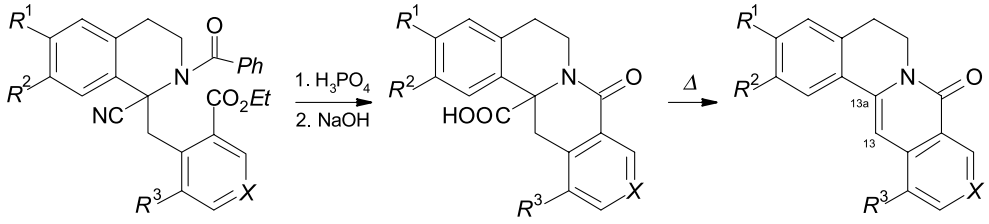
Scheme 4



Scheme 5

procedure. Thus in a model reaction the 1-alkylated dihydro-*Reissert*-compound **10** first was treated with phosphoric acid and then – without isolating **19** – was reacted with KOH. Indeed the berbinone carboxylic acid **21** was formed in 87% total yield meaning a 14% increase in comparison to the single steps (see Scheme 6).

In the same manner the 3,4-dihydro-*Reissert*-compounds **11a**, **11c**, and **11d** could be cyclized to the azalogue carboxylic acids **22a**, **22b**, and **22c**, whereby in the case of **11c** and **11d** the benzylic ether group was also cleaved to provide the corresponding phenols. Finally **21** and **22** underwent thermal decarboxylation



10, 11 **21, 22** **23, 24, 25**

	X	R^1	R^2	R^3
10	CH	H	H	H
11a	N	O*Me*	O*Me*	H
11c	N	O*Me*	O*Bn*	*Et*
11d	N	O*Me*	O*Bn*	*Vin*

	X	R^1	R^2	R^3
21, 23, 25*	CH	H	H	H
22a, 24a	N	O*Me*	O*Me*	H
22b, 24b	N	O*Me*	OH	*Et*
22c, 24c	N	O*Me*	OH	*Vin*

* **25**: 13,13a-dihydroderivative (= berbin-8-one)

Scheme 6

giving the alkaloids alangimarine (**24c**) and dihydroalangimarine (**24b**), whereas from the educt **21** the 13,13a-dihydro-product, berbin-8-one (**25**), was preferentially generated besides the corresponding *de*hydroderivative **23** [1, 2].

In conclusion, a novel route to partially hydrogenated 8-oxodibenzochinolizine-13a-carboxylic acids and the corresponding 10-aza analogues was designed starting from 1-substituted dihydro-*Reissert*-compounds. This method provides a convenient approach to the pharmacological attractive protoberberine- and alangia-alkaloids from easily accessible starting materials. Furthermore, certain intermediate amino acids related to 3′,4′-deoxynorlaudanosoline carboxylic acid, which is known as an enzyme inhibitor, are also available by this route. Further investigations concerning its applicability to natural product and drug synthesis are in progress in our laboratory.

Experimental

Melting points were measured with a *Reichert* hot-stage microscope. IR: Perkin Elmer FT-IR Paragon 1000 and Jasco FT-IR 410. UV/Vis: Jasco V-530. NMR: Jeol GSX 400 and Jeol GSX 500 (^{1}H: 400 and 500 MHz, ^{13}C: 100 and 125 MHz, $CDCl_3$, *TMS* as internal reference); MS (70 eV): Hewlett Packard MS-Engine. Elemental analyses: Heraeus CHN-Rapid and Elementar Vario EL; the results are in good agreement with the calculated values. Thin layer chromatography (TLC): Al sheets Kieselgel 60 F_{254} (Merck) and Al sheets Aluminiumoxid F_{254} (Fluka), each thickness of layer 0.2 mm. Preparative Layer Chromatography (=PLC): PSC-Fertigplatten Kieselgel 60 F_{254} (Merck), thickness of layer 1 mm. Flash chromatography (FC): ICN-Sili Tech 32-63, 60 A and Aluminumoxid Typ 507 C neutral 0.05–0.15 mm. Strongly basic ion-exchange resin: Amberlite IRA-400 (CI). **2** and **3a** are commercial products. **1**, **4a**, **8**, **9a**, and **12a** were prepared according to Refs. [12], [13], [2, 14], [15], and [16].

2-(4-Benzyloxy-3-methoxyphenyl)ethylamine (**3b**)

To a suspension of 19.0 g of $LiAlH_4$ (0.5 mol) in 500 cm^3 of dry Et_2O 25.8 g of 4-(benzyloxy)-3-methoxy-β-nitrostyrene (0.1 mol) (**1**) were added under stirring and refluxing by continuous extraction

in a *Soxhlet* apparatus for 30 h. Then to the mixture 10 cm^3 of H_2O, 20 cm^3 of 20% NaOH solution, and 37 cm^3 of H_2O were consecutively added under vigorous stirring, ice cooling, and N_2. After stirring for further 30 min, the mixture was filtered over kieselguhr. The organic layer was separated and the H_2O phase extracted with 3×200 cm^3 of Et_2O. The combined organic extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The remaining product was used without further purification. Yield: 20.6 g (80%) colourless oil, which solidified on storing in the refrigerator; mp 58°C (Ref. [17]: 60–62°C); TLC ($CHCl_3$:*Me*OH:25% NH_3 = 9:1:0.1): $R_f = 0.35$; ^{1}H NMR (400 MHz): $\delta = 7.47–7.25$ (m, 5 arom H), 6.81 (d, $J = 8.3$ Hz, 5-H), 6.74 (d, $J = 1.6$ Hz, 2-H), 6.67 (dd, $J = 1.6/8.3$ Hz, 6-H), 5.12 (s, aryl–CH_2O), 3.87 (s, CH_3O), 2.92 (t, $J = 6.8$ Hz, CH_2–N), 2.67 (t, $J = 6.8$ Hz, aryl–CH_2), 1.36 (s, NH_2) ppm.

N-[2-(4-Benzyloxy-3-methoxyphenyl)ethyl]formamide (**4b**)

A mixture of 20.0 g of **3b** (78 mmol) and 46.9 g of $HCOOCH_3$ (780 mmol) freshly distilled before use was stirred for 12 h at ambient temperature. After removing the volatile components *in vacuo*, a colourless, viscous oil remained, which was used for the next step without further purification. Yield: 22.3 g (100%) [18]; TLC (*n*-hexane:*Et*OA*c* = 3:1): $R_f = 0.68$; IR (film): $\bar{\nu} = 1665$ (C=O) cm^{-1}; MS (CI): m/z (%) = 286 ($M^{+\bullet} + 1$, 100); ^{1}H NMR (400 MHz): $\delta = 8.02$ (d, $J = 1.2$ Hz, N–CHO), 7.45–7.25 (m, 5 arom H), 6.80 (d, $J = 8.2$ Hz, 5-H), 6.72 (d, $J = 1.9$ Hz, 2-H), 6.64 (dd, $J = 8.2$, 2.0 Hz, 6-H), 6.06 (br s, NH), 5.09 (s, aryl–CH_2O), 3.83 (s, CH_3O), 3.46 (dd, $J = 13.3$, 7.0 Hz, CH_2–N), 2.72 (t, $J = 7.0$ Hz, aryl–CH_2) ppm; ^{13}C NMR (100 MHz): $\delta = 161.18$, 149.92, 147.02, 137.25, 131.77, 128.53, 128.50, 127.85, 127.32, 127.14, 120.71, 114.54, 112.62, 71.26, 56.06, 39.24, 35.13 ppm.

3,4-Dihydroisoquinoline (**5a**) *According to the General Procedure for the Dehydrogenation of Benzylamines* [19]

To a solution of 6.65 g of **2** (50 mmol) in 250 cm^3 of CH_2Cl_2 16.2 g of HgO and 19.1 g of I_2 (each 75 mmol) were added and the mixture was stirred for 1 h at ambient temperature. The solid was removed by a glass frit P4 and washed with 3×20 cm^3 of CH_2Cl_2. The combined filtrates were consecutively washed with 500 cm^3 of 5% $Na_2S_2O_3$ solution and 500 cm^3 of H_2O and dried (Na_2SO_4). After evaporating the solvent *in vacuo* the remaining product was used without further purification. An analytical sample was obtained by FC ($CHCl_3$:*Me*OH = 9:1). Yield: 6.4 g (98%) colourless oil; TLC ($CHCl_3$:*Me*OH:25% NH_3 = 9:1:0.1): $R_f = 0.52$; the ^{1}H NMR spectrum was in line with that reported in Ref. [20].

General Procedure for the Synthesis of 3,4-Dihydroisoquinolines ***5b*** *and* ***5c*** *by Bischler-Napieralski Cyclization*

A mixture of the formamide **4**, toluene, and freshly destilled $POCl_3$ was heated for 1 h at 85°C (temperature of the oil bath) and then reacted for additional 4 h at ambient temperature. After removing the excess $POCl_3$ *in vacuo*, the mixture was rendered alkaline with 2*N* NaOH under ice cooling and vigorous stirring and then was extracted with 3×50 cm^3 of $CHCl_3$. The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by FC ($CHCl_3$:*Me*OH:25% NH_3 = 9:1:0.1).

6,7-Dimethoxy-3,4-dihydroisoquinoline (**5b**)

From 5.0 g **4a** (19 mmol), 150 cm^3 toluene, 15 cm^3 $POCl_3$. Yield: 3.56 g (76%) pale yellow oil [13]; TLC (eluent see FC): $R_f = 0.43$; ^{1}H NMR (400 MHz): $\delta = 8.23$ (t, $J = 2.1$ Hz, 1-H), 6.81 and 6.67 (2s, 8-H and 5-H), 3.91 and 3.90 (2s, 2OCH_3), 3.76–3.70 and 2.72–2.63 (2m, 3-H_{ab} and 4-H_{ab}) ppm.

7-Benzyloxy-6-methoxy-3,4-dihydroisoquinoline (**5c**)

From 4.0 g **4b** (14 mmol), 150 cm^3 toluene, 10 cm^3 $POCl_3$. Yield: 3.21 g (86%) colourless oil, which solidified on storing in the refrigerator; mp 92°C, recrystallization of an analytical sample from *n*-hexane: mp 99–100°C (Ref. [21]: 101–101.5°C); TLC ($CHCl_3$:*Me*OH:25% NH_3 = 19:1:0.1): $R_f = 0.49$; MS (EI): m/z (%) = 267 ($M^{+\bullet}$, 22), 176 (17), 91 (100); ^{1}H NMR (400 MHz): $\delta = 8.15$ (t, $J = 2.2$ Hz, 1-H), 7.47–7.23 (m, 5 arom H), 6.83 and 6.68 (2s, 8-H and 5-H), 5.14 (s, aryl–OCH_2), 3.91 (s, OCH_3), 3.71 (dt, $J = 8.0$, 2.1 Hz, 3-H_{ab}), 2.67 (t, $J = 8.0$ Hz, 4-H_{ab}) ppm; ^{13}C NMR (100 MHz): $\delta = 159.71$, 152.17, 146.92, 136.80, 130.55, 128.61, 128.59, 127.99, 127.31, 127.01, 121.33, 113.42, 110.83, 71.34, 56.10, 47.11, 24.82 ppm.

General Procedure for the Synthesis of 3,4-Dihydroisoquinoline-Reissert-Compounds **7**

A solution of NaCN, adjusted to *pH* 8, was added to a mixture of **5**, $NaHCO_3$, and CH_2Cl_2 under ice cooling. Thereafter a solution of benzoyl chloride in CH_2Cl_2 was added dropwise during 30 min under vigorous stirring and further cooling. After stirring for additional 1.5 h at ambient temperature the mixture was diluted with 20 cm^3 of H_2O and extracted with 3×25 cm^3 of CH_2Cl_2. The combined organic extracts were consecutively washed with 20 cm^3 of 2*N* HCl, 20 cm^3 of 2*N* NaOH, and 2×20 cm^3 of H_2O, dried (Na_2SO_4), and filtered. After removing the solvent *in vacuo*, the residue was crystallized from 50 cm^3 of *Me*OH. The solid was collected by filtration and dried *in vacuo* at ambient temperature.

2-Benzoyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**7a**)

From 6.0 g **5a** (46 mmol), 150 cm^3 CH_2Cl_2, 13.3 g $NaHCO_3$ (158 mmol), 4.4 g NaCN (92 mmol)/20 cm^3 H_2O, 6.5 g C_6H_5COCl (69 mmol)/15 cm^3 CH_2Cl_2. Yield: 8.6 g (71%) colourless crystals; mp 113°C (Ref. [6]: 113–115°C); TLC (*n*-hexane:*Et*OAc = 1:1): $R_f = 0.45$; IR (KBr): $\bar{\nu} = 2238$ (CN), 1643 (C=O) cm^{-1}; MS (EI): m/z (%) = 262 ($M^{+\bullet}$, 57), 105 (100), 77 (65); ^{1}H NMR (400 MHz): $\delta = 7.59$–7.20 (m, 9 arom H), 6.46 (br s, 1-H), 4.23–3.90 and 3.72–3.36 (2 br s, 3-H_a and 3-H_b), 3.22–2.96 and 2.95–2.75 (2 m, 4-H_a and 4-H_b) ppm; ^{13}C NMR (100 MHz): $\delta = 170.99$, 133.90, 130.90, 129.55, 129.00, 128.81, 128.07, 127.48, 127.13 (5C), 117.78, 44.51, 43.29, 28.57 ppm.

2-Benzoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**7b**)

From 3.5 g **5b** (18 mmol), 100 cm^3 CH_2Cl_2, 5.3 g $NaHCO_3$ (63 mmol), 1.7 g NaCN (36 mmol)/10 cm^3 H_2O, 2.5 g C_6H_5COCl (27 mmol)/10 cm^3 CH_2Cl_2. Yield: 4.9 g (85%) colourless crystals; mp 205°C (Ref. [6]: 211–213°C); TLC (*n*-hexane:*Et*OAc = 1:1): $R_f = 0.36$; IR (KBr): $\bar{\nu} = 2230$ (C≡N), 1628 (C=O) cm^{-1}; MS (EI): m/z (%) = 322 ($M^{+\bullet}$, 100), 307 (24), 105 (76), 77 (68); ^{1}H NMR (400 MHz): $\delta = 7.57$–7.43 (m, 5 arom H), 6.83 (br s, 8-H), 6.66 (s, 5-H), 6.42 (br s, 1-H), 4.12–3.95 (br s, 3-H_a), 3.88 (s, 2OCH_3), 3.56 (br s, 3-H_b), 3.09–2.92 (m, 4-H_a), 2.74 (d, $J = 15.6$ Hz, 4-H_b) ppm; ^{13}C NMR (100 MHz): $\delta = 171.51$, 149.69, 148.71, 134.11, 130.97, 128.92 (2C), 127.27 (3C), 119.75, 118.03, 111.67, 109.50, 56.23, 56.11, 44.36, 43.45, 28.18 ppm.

2-Benzoyl-7-benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**7c**)

From 3.0 g **5c** (11 mmol), 80 cm^3 CH_2Cl_2, 3.2 g $NaHCO_3$ (38 mmol), 1.0 g NaCN (22 mmol)/8 cm^3 H_2O, 1.5 g C_6H_5COCl (17 mmol)/8 cm^3 CH_2Cl_2. Yield: 4.0 g (91%); mp 180°C (Ref. [22]: 178–180°C); TLC (*n*-hexane:*Et*OAc = 1:1): $R_f = 0.43$; IR (KBr): $\bar{\nu} = 2233$ w (C≡N), 1642 (C=O) cm^{-1}; MS (EI): m/z (%) = 398 ($M^{+\bullet}$, 54), 105 (100), 91 (96); ^{1}H NMR (400 MHz): $\delta = 7.54$–7.28 (m, 10 arom H), 6.85 (br s, 8-H), 6.67 (s, 5-H), 6.32 (br s, 1-H), 5.24–4.99 (m, OCH_2), 4.08–3.91 (br s,

3-H_a), 3.87 (s, OCH_3), 3.62–3.38 (br s, 3-H_b), 3.07–2.90 (m, 4-H_a), 2.73 (d, $J = 15.7$ Hz, 4-H_b) ppm; ^{13}C NMR (100 MHz): $\delta = 170.81$, 150.55, 147.89, 136.53, 134.20, 130.82, 128.83 (2C), 128.66 (2C), 128.13, 127.48 (3C), 127.18 (3C), 119.82, 117.82, 112.57, 112.42, 71.50, 56.19, 44.18, 28.11 ppm.

N-[2-(4-Benzyloxy-2-formyl-5-methoxyphenyl)ethyl]benzamide (**6**, $C_{24}H_{23}NO_4$)

Separation by FC ($CHCl_3$:*Me*OH = 95:5) from the crude product **7c** (see above). Yield: 86 mg (2%) colourless solid, mp 124°C; TLC (eluent see FC): $R_f = 0.43$; ^{1}H NMR (400 MHz): $\delta = 10.01$ (s, CHO), 7.74–7.68 (m, 2 arom H), 7.50–7.26 (m, 9 arom H), 6.81 (s, 1 arom H), 6.74–6.68 (like a t, NH), 5.16 (s, OCH_2), 3.89 (s, OCH_3), 3.71 (dd, $J = 12.7$, 7.0 Hz, N–CH_2), 3.31 (t, $J = 7.0$, aryl–CH_2) ppm.

5-Ethyl-4-methylnicotinonitrile (**12b**)

Preparation according to Ref. [23]. Yield: 11.3 g (86%) colourless oil; bp 118–122°C/9.0×10^2 Pa (Ref. [23]: 120°C/9.3×10^2 Pa); TLC (*n*-hexane:*Et*O*Ac* = 3:1): $R_f = 0.56$; IR (film): $\bar{\nu} = 2227$ (C≡N) cm^{-1}; MS (CI): m/z (%) = 147 ($M^{+\bullet} + 1$, 100); ^{1}H NMR (400 MHz): $\delta = 8.55$ and 8.43 (2s, 2-H and 6-H), 2.65 (q, $J = 7.7$ Hz, CH_2), 2.46 (s, ar-CH_3), 1.18 (t, $J = 7.7$ Hz, CH_3) ppm; ^{13}C NMR (100 MHz): $\delta = 152.37$, 150.66, 148.56, 138.38, 116.54, 111.06, 23.98, 17.11, 14.09 ppm.

4-Methyl-5-vinyl-nicotinonitrile (**12c**)

Preparation according to Ref. [24]. Yield: 6.6 g (52%) colourless oil; bp 96°C/2.7×10^2 Pa (Ref. [23]: 98°C/2.7×10^2 Pa) which solidified on storing in the refrigerator; TLC (*n*-hexane:*Et*O*Ac* = 3:1): $R_f = 0.34$; IR (film): $\bar{\nu} = 2229$ (C≡N) cm^{-1}; MS (EI): m/z (%) = 144 ($M^{+\bullet}$, 22), 117 (26), 94 (100), 86 (53), 84 (72); ^{1}H NMR (400 MHz): $\delta = 8.75$ and 8.69 (2s, 6-H and 2-H), 6.84 (dd, $J = 11.2$, 17.6 Hz, ar-CH), 5.78 and 5.57 (2d, $J = 17.6$ and 11.2 Hz, C=CH_2), 2.56 (s, CH_3) ppm; ^{13}C NMR (100 MHz): $\delta = 150.48$, 149.02, 146.34, 132.62, 129.37, 119.25, 115.14, 110.05, 16.51 ppm.

*General Procedure for the Preparation of Nicotinamides **13b** and **13c***

The ion-exchange resin was stored in 100 cm^3 of H_2O for 15 h, then transferred to a chromatography column and washed with *ca.* 1000 cm^3 of 6*N* NaOH, until no more Cl^- could be detected in the eluate. The resin was filtered off and washed with 2×100 cm^3 of H_2O. A suspension of the resin thus prepared and the nitrile **12** in H_2O was refluxed for 16 h. The resin was filtered off from the hot mixture and washed with 2×50 cm^3 of hot H_2O. The combined filtrates were evaporated *in vacuo* affording the solid product, which was used for the next step without further purification. An analytical sample was recrystallized from *Et*OH.

5-Ethyl-4-methylnicotinamide (**13b**, $C_9H_{12}N_2O$)

Ion-exchange resin 16.5 g, 11.1 g **12b** (76 mmol), 150 cm^3 H_2O; yield: 11.6 g (93%) colourless crystals; mp 154°C; TLC ($CHCl_3$:*Me*OH = 9:1): $R_f = 0.18$; IR (KBr): $\bar{\nu} = 1665$ (C=O) cm^{-1}; MS (EI): m/z (%) = 164 ($M^{+\bullet}$, 100), 148 (43), 147 (24), 120 (60); ^{1}H NMR (CD_3OD, 400 MHz): $\delta = 8.45$ and and 8.34 (2s, 2-H and 6-H), 4.95 (br s, NH_2), 2.75 (q, $J = 7.6$ Hz, ar-CH_2), 2.43 (s, ar-CH_3), 1.24 (t, $J = 7.6$ Hz, CH_3) ppm; ^{13}C NMR (CD_3OD, 100 MHz): $\delta = 172.83$, 150.44, 145.64, 145.16, 140.51, 134.78, 24.60, 15.52, 14.65 ppm.

4-Methyl-5-vinylnicotinamide (**13c**, $C_9H_{10}N_2O$)

Ion-exchange resin 8.5 g, 6.5 g **12c** (45 mmol), 100 cm^3 H_2O; yield: 6.5 g (89%) colourless crystals; mp 143°C; TLC ($CHCl_3$:*Me*OH = 9:1): $R_f = 0.19$; IR (KBr): $\bar{\nu} = 1667$ (C=O) cm^{-1}; MS (EI):

m/z (%) = 162 ($M^{+\bullet}$, 92), 144 (45), 118 (100), 91 (84), 65 (48); ^{1}H NMR (CD_3OD, 400 MHz): δ = 8.55 and 8.41 (2s, 6-H and 2-H), 6.95 (dd, J = 17.5, 11.0 Hz, ar-CH=), 5.75 and 5.51 (2d, J = 17.5 and 11.0 Hz, CH_2=), 5.37–4.84 (br s, NH_2), 2.42 (s, CH_3) ppm; ^{13}C NMR (CD_3OD, 100 MHz): δ = 170.38, 147.30, 145.12, 143.12, 134.28, 132.18, 131.14, 118.87, 15.55 ppm.

General Procedure for the Synthesis of Nicotinic Acid Ethyl Ester ***14b*** *and* ***14c***

A solution of the amide **13** in anhydrous *Et*OH was heated under reflux. Simultaneously a weak stream of dry HCl was passed into the mixture until no more NH_4Cl precipitated (*ca.* 5 h). Refluxing was continued for further 31 h. After evaporating the solvent *in vacuo*, the residue was triturated with 200 cm^3 of H_2O. The solution was rendered neutral with solid Na_2CO_3 and extracted with 3×100 cm^3 of Et_2O. The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The remaining product was used for the next step without further purification. An analytical sample was obtained by FC (*n*-hexane:*Et*O*Ac* = 3:1).

5-Ethyl-4-methylnicotinic Acid Ethyl Ester (**14b**)

From 11.5 g **13b** (70 mmol), 700 cm^3 *Et*OH. Yield: 12.6 g (93%) colourless liquid (Ref. [25]); TLC (*n*-hexane:*Et*O*Ac* = 3:1): R_f = 0.72; IR (film): $\bar{\nu}$ = 1721 (C=O) cm^{-1}; MS (EI): m/z (%) = 193 ($M^{+\bullet}$, 16), 165 (100), 150 (94), 120 (57); ^{1}H NMR (400 MHz): δ = 8.84 and 8.45 (2s, 2-H and 6-H), 4.39 (q, J = 7.1 Hz, OCH_2), 2.71 (q, J = 7.5 Hz, ar-CH_2), 2.54 (s, ar-CH_3), 1.41 (t, J = 7.1 Hz, OC–CH_3), 1.23 (t, J = 7.5 Hz, C–CH_3) ppm; ^{13}C NMR (100 MHz): δ = 166.92, 151.90, 148.99, 146.31, 138.42, 126.89, 61.30, 24.03, 15.65, 14.51, 14.29 ppm.

4-Methyl-5-vinylnicotinic Acid Ethyl Ester (**14c**, $C_{11}H_{13}NO_2$)

From 6.5 g **13c** (40 mmol), 500 cm^3 *Et*OH. Yield: 6.7 g (88%) colourless liquid; TLC (*n*-hexane: *Et*O*Ac* = 3:1): R_f = 0.84; IR (film): $\bar{\nu}$ = 1721 (C=O) cm^{-1}; MS (CI): m/z (%) = 192 ($M^{+\bullet}$ + 1, 34); ^{1}H NMR (400 MHz): δ = 8.86 and 8.63 (2s, 2-H and 6-H), 6.88 (dd, J = 17.4, 11.1 Hz, ar-CH=), 5.64 and 5.44 (2d, J = 17.4 and 11.1 Hz, CH_2=), 4.36 (q, J = 7.2 Hz, OCH_2), 2.52 (s, ar-CH_3), 1.37 (t, J = 7.2 Hz, OC–CH_3) ppm; ^{13}C NMR (100 MHz): δ = 166.61, 150.03, 149.71, 145.49, 134.38, 131.92, 126.68, 119.03, 61.32, 16.32, 14.26 ppm.

General Procedure for the Synthesis of the N-Oxides ***15b*** *and* ***15c***

A mixture of **14**, glacial acetic acid, and 30% H_2O_2 was heated for 3 h at 80°C (bath temperature) and, after addition of further 30% H_2O_2, for additional 12 h at 75°C. The solution was concentrated *in vacuo* to one half of its volume, then 20 cm^3 of H_2O were added and the remaining acetic acid was evaporated *in vacuo*. After triturating with 50 cm^3 of $CHCl_3$ the residue was neutralized with 30 cm^3 of a saturated $NaHCO_3$ solution. The $CHCl_3$ layer was separated and the aqueous phase was extracted with 6×20 cm^3 of $CHCl_3$ (TLC monitoring). After drying the combined organic extracts (Na_2SO_4) the solvent was removed *in vacuo*. The product was used for the next step without further purification. An analytical sample was obtained by FC ($CHCl_3$:*Me*OH = 9:1).

5-Ethyl-4-methyl-1-oxynicotinic Acid Ethyl Ester (**15b**, $C_{11}H_{15}NO_3$)

From 11.5 g **14b** (60 mmol), 50 cm^3 CH_3CO_2H, 5.0 + 2.5 cm^3 30% H_2O_2. Yield: 9.8 g (78%) pale yellow oil; TLC (eluent see FC): R_f = 0.36; IR (film): $\bar{\nu}$ = 1727 (C=O), 1306 (NO) cm^{-1}; MS (EI): m/z (%) = 209 ($M^{+\bullet}$, 15), 193 (92), 148 (100), 120 (82); ^{1}H NMR (CD_3OD, 400 MHz): δ = 8.52 and 8.27 (2s, 2-H and 6-H); 4.41 (q, J = 7.1 Hz, OCH_2), 2.78 (q, J = 7.6 Hz, ar-CH_2), 2.55 (s, ar-CH_3),

1.40 (t, $J = 7.1$ Hz, OC–CH_3), 1.26 (t, $J = 7.6$ Hz, C–CH_3) ppm; ^{13}C NMR (CD_3OD, 100 MHz): $\delta = 165.17$, 144.83, 142.33, 140.87, 138.44, 131.40, 63.30, 24.88, 15.53, 14.37, 13.86 ppm.

4-Methyl-1-oxy-5-vinylnicotinic Acid Ethyl Ester (**15c**, $C_{11}H_{13}NO_3$)

From 6.6 g **14c** (35 mmol), 25 cm^3 CH_3CO_2H, 2.5 + 1.25 cm^3 30% H_2O_2. The crude product was purified by FC ($CHCl_3$:*Me*OH = 9:1). Yield: 4.0 g (56%) pale yellow oil, which should be stored in the refrigerator under N_2 or immediately used in the next step. TLC (eluent see FC): $R_f = 0.38$; IR (film): $\bar{\nu} = 1725$ (C=O), 1304 (NO) cm^{-1}; MS (EI): m/z (%) = 207 ($M^{+\bullet}$, 100), 191 (44), 162 (89), 146 (51), 118 (85), 91 (63); ^{1}H NMR (400 MHz): $\delta = 8.59$ and 8.33 (2d, each $J = 2.1$ Hz, 2-H and 6-H), 6.81 (dd, $J = 17.4$, 11.0 Hz, ar-CH=), 5.70 and 5.58 (2d, $J = 17.4$ and 11.0 Hz, CH_2=), 4.39 (q, $J = 7.1$ Hz, OCH_2), 2.52 (s, ar-CH_3), 1.40 (t, $J = 7.1$ Hz, OC–CH_3) ppm; ^{13}C NMR (100 MHz): $\delta = 163.87$, 138.96, 138.27, 137.94, 136.64, 130.08, 129.48, 121.24, 62.14, 15.64, 14.12 ppm.

*General Procedure for the Synthesis of 4-Chloromethylnicotinic Acid Esters **9b**- and **9c**-HCl*

A solution of the *N*-oxide **15** and *p*-toluenesulfonyl chloride in dry dioxane was heated under reflux for 1.5 h. After cooling to ambient temperature the black mixture was diluted with 10% HCl, stirred for 15 min, and then washed with 5×20 cm^3 of *Et*$_2$O. After adding 30 cm^3 of ice-cold *Et*$_2$O the aqueous phase was cautiously neutralized with solid $NaHCO_3$. The unstable base was rapidly extracted with 3×20 cm^3 of ice-cold *Et*$_2$O. The combined extracts were dried (Na_2SO_4), stored in the refrigerator, and filtered. Thereafter a weak stream of dry HCl was passed into the filtrate under ice cooling until the precipitation of the reddish brown oil was complete (*ca.* 30–45 min). After evaporating the solvent *in vacuo* the residual product was immediately used in the next step.

4-Chloromethyl-3-ethoxycarbonyl-5-ethylpyridinium Hydrochloride (**9b**, $C_{11}H_{15}Cl_2NO_2$)

From 9.8 g **15b** (47 mmol), 18.3 g *p*-toluenesulfonyl chloride (94 mmol), 50 cm^3 dioxane, 50 cm^3 10% HCl. The crude oil was crystallized from 200 cm^3 of *Et*OA*c*, the crystals were washed with a small volume of the same solvent, and dried at ambient temperature *in vacuo*. Yield: 9.8 g (79%) pink solid; mp 45°C; TLC ($CHCl_3$:*Me*OH:25% NH_3 = 90:10:1): $R_f = 0.78$; IR (KBr): $\bar{\nu} = 1733$ (C=O) cm^{-1}; MS (EI): m/z (%) = 229 ($M^{+\bullet}$ − H, 11), 227 ($M^{+\bullet}$ − H, 37), 192 (23), 182 (42), 162 (100), 118 (99); ^{1}H NMR (CD_3OD, 400 MHz): $\delta = 9.18$ and 8.96 (2s, 2-H and 6-H), 4.92 (s, CH_2Cl), 4.52 (q, $J = 7.1$ Hz, OCH_2), 3.09 (q, $J = 7.6$ Hz, ar-CH_2), 1.46 (t, $J = 7.1$ Hz, OC–CH_3), 1.41 (t, J = C–CH_3) ppm; ^{13}C NMR (CD_3OD, 100 MHz): $\delta = 163.67$, 156.25, 145.47, 145.44, 143.21, 130.68, 64.31, 37.29, 24.09, 14.52, 14.28 ppm.

4-Chloromethyl-3-ethoxycarbonyl-5-vinylpyridinium Hydrochloride (**9c**, $C_{11}H_{13}Cl_2NO_2$)

From 4.0 g **15c** (19 mmol), 7.4 g *p*-toluenesulfonyl chloride (39 mmol), 30 cm^3 dioxane, 30 cm^3 10% HCl. The crude product was used for the next step without further purification. An analytical sample was obtained by FC ($CHCl_3$:*Me*OH:25% NH_3 = 90:10:1). Yield: 3.5 g (71%) pink oil; TLC (eluent see FC): $R_f = 0.74$; IR (film): $\bar{\nu} = 1730$ (C=O) cm^{-1}; MS (CI): m/z (%) = 228 ($M^{+\bullet}$ + 1, 42), 226 ($M^{+\bullet}$ + 1, 100), 190 (24), 162 (14); ^{1}H NMR (400 MHz): $\delta = 9.04$ and 8.82 (2s, 2-H and 6-H); 7.06 (dd, $J = 17.5$, 11.2 Hz, ar-CH=), 5.82 and 5.62 (2d, $J = 17.5$ and 11.2 Hz, CH_2=), 5.02 (s, CH_2Cl), 4.45 (q, $J = 7.1$ Hz, OCH_2), 1.44 (t, $J = 7.1$ Hz, C–CH_3) ppm; ^{13}C NMR (100 MHz): $\delta = 165.50$, 151.26, 150.87, 142.95, 134.04, 130.28, 124.95, 121.04, 61.89, 37.73, 14.17 ppm.

2-(2-Benzoyl-1-cyano-1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)benzoic Acid Ethyl Ester (**10**, $C_{27}H_{24}N_2O_3$)

Preparation according to Ref. [1], Meth. B, using **7a** and the following workup, The combined dry *Et*OA*c* extracts were evaporated *in vacuo* and the residue was crystallized from *Et*OH. The product was collected by filtration, washed with a small volume of ice-cold *Et*OH and dried at 60°C *in vacuo*. If the crystallization fails to occur and/or the mother liquor affords no more product, the solvent was removed *in vacuo* and the residue was purified by FC (*n*-hexane:*Et*OA*c* = 3:1).

From 8.0 g **7a** (30 mmol)/100 cm^3 dry *DMF*, 1.2 g 60% NaH (30 mmol), 7.5 g **8** (31 mmol)/10 cm^3 *DMF*, reaction time 1 h. Yield: 11.7 g (92%); mp 148°C (*Et*OH); TLC (*n*-hexane:*Et*OA*c* = 3:1): $R_f = 0.62$; IR (KBr): $\bar{\nu} = 2234$ (C≡N), 1716 (CO_2R), 1651 ($CONR_2$) cm^{-1}; MS (CI): m/z (%) = 425 ($M^{+\bullet} + 1$, 27), 263 (100), 236 (44); ^{1}H NMR (500 MHz): $\delta = 7.67$–7.63 and 7.54–7.50 (2m, 1 + 2 arom H), 7.49–7.44 (m, 5 arom H), 7.32 (ddd, $J = 8.0$, 6.7, 2.0 Hz, 1 arom H), 7.25 (dt, $J = 7.6$, 1.6 Hz, 6-H), 7.20 (dd, $J = 7.6$, 1.6 Hz, 8-H), 7.19–7.15 (m, 7-H), 7.06 (dd, $J = 7.6$, 0.5 Hz, 5-H), 4.65 and 4.35 (2d, each $J = 13.4$ Hz, each 1H, ar-CH_2), 4.00–3.85 (m, OCH_2), 3.68 and 3.35 (2ddd, $J = 12.9$, 5.0, 4.1 and 12.9, 10.4, 3.3 Hz, 3-H_{ab}), 2.64 (ddd, $J = 15.7$, 5.0, 3.3 Hz, 4-H_a), 2.33 (m, 4-H_b), 1.23 (t, $J = 7.1$ Hz, OC–CH_3) ppm; ^{13}C NMR (125 MHz): $\delta = 171.69$, 166.95, 136.03, 135.27, 134.72, 133.54, 132.14, 131.90, 131.29, 130.39, 130.23, 128.67 (2C), 128.49, 128.27, 127.97, 127.53, 127.05 (2C), 126.81, 119.28, 60.73, 60.03, 45.88, 40.06, 29.12, 13.92 ppm.

*General Procedure for the Synthesis of 1-Substituted 3,4-Dihydroisoquinoline-Reissert-Compounds **11***

To a solution of **7** in dry *DMF* K-*t*-OC_4H_9 was added at −56°C under N_2 and vigorous stirring. After stirring for additional 2 min a solution of **9** in *DMF* was added dropwise as slowly as the colour of the suspension disappeared at no time (*ca.* 15 min). Stirring was continued at −56°C for 30 min and thereafter for 15 min at ambient temperature. The suspension was cautiously poured into a mixture of 200 cm^3 of *Et*OA*c* and 800 cm^3 of H_2O and extracted with 4×200 cm^3 of *Et*OA*c*. The combined organic phases were dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The yellowish, semi-solid residue was purified by FC (*n*-hexane:*Et*OA*c* = 1:1) followed by recrystallization from *Me*OH.

4-(2-Benzoyl-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)nicotinic Acid Ethyl Ester (**11a**, $C_{28}H_{27}N_3O_5$)

From 3.0 g **7b** (9.3 mmol), 300 cm^3 dry *DMF*, 2.1 g K-*t*-OC_4H_9 (18.6 mmol), 1.9 g **9a** (9.4 mmol)/10 cm^3 *DMF*. Yield: 3.6 g (79%) colourless crystals; mp 160°C; TLC (*n*-hexane:*Et*OA*c* = 1:1): $R_f = 0.45$; IR (KBr): $\bar{\nu} = 2228$ (C≡N), 1721 (CO_2R), 1645 ($CONR_2$) cm^{-1}; MS (CI): m/z (%) = 486 ($M^{+\bullet} + 1$, 100), 321 (72); ^{1}H NMR (400 MHz): $\delta = 8.83$ (s, 1 arom H), 8.64 (d, $J = 5.0$ Hz, 1 arom H), 7.53–7.40 (m, 6 arom H), 6.51 and 6.50 (2s, 5-H and 8-H), 4.52 and 4.32 (2d, each $J = 12.6$ Hz, ar-CH_2), 3.99–3.90 (m, OCH_2), 3.83 and 3.63 (2s, 2OCH_3), 3.72 and 3.36 (2ddd, $J = 13.0$, 4.9, 4.2 and 13.0, 10.1, 3.3 Hz, 3-H_a and 3-H_b), 2.58 (ddd, $J = 15.8$, 4.9, 3.3 Hz, 4-H_a), 2.38 (m, 4-H_b), 1.21 (t, $J = 7.1$ Hz, CH_3) ppm; ^{13}C NMR (100 MHz): $\delta = 172.03$, 165.21, 151.65, 150.77, 149.13, 147.54, 144.41, 135.61, 130.75, 128.80 (2C), 128.04, 127.81, 127.59, 127.16 (2C), 122.78, 118.78, 111.14, 110.57, 61.26, 59.19, 55.93, 55.77, 45.90, 39.22, 28.80, 13.82 ppm.

4-(2-Benzoyl-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)-5-ethylnicotinic Acid Ethyl Ester (**11b**, $C_{30}H_{31}N_3O_5$)

From 1.0 g **7b** (3.1 mmol), 100 cm^3 dry *DMF*, 0.7 g K-*t*-OC_4H_9 (6.2 mmol), 0.7 g **9b** (2.7 mmol)/5 cm^3 *DMF*. Yield: 1.2 g (73%) colourless crystals; mp 164°C; TLC (*n*-hexane:*Et*OA*c* = 1:1): $R_f = 0.29$; IR (KBr): $\bar{\nu} = 2232$ (C≡N), 1703 (CO_2R), 1652 ($CONR_2$) cm^{-1}; MS (CI): m/z (%) = 542 ($M^{+\bullet} + 29$, 4),

514 ($M^{+\bullet}+1$, 100), 321 (100); ^{1}H NMR (−20°C, 400 MHz): $\delta = 8.74$ and 8.71 (2s, each 1 arom H), 7.63–7.47 (m, 5 arom H), 6.67 and 6.00 (2s, 5-H and 8-H), 4.53 and 4.44 (2d, each $J = 12.5$ Hz, ar-CH_2), 4.03–3.81 and 3.90 (br m and s, OCH_2 and OCH_3), 3.67–3.54 (m, 3-H_{ab}), 3.45 (s, OCH_3), 3.23–3.09 and 3.04–2.84 (2m, C–CH_2 and 4-H_{ab}), 1.33 and 1.24 (2 br t, each $J = 7.3$ Hz, OC–CH_3 and CH_3) ppm; ^{13}C NMR (100 MHz): $\delta = 172.15$, 165.97, 153.97, 149.24, 148.37, 147.07, 142.17, 141.68, 135.80, 130.79, 128.88 (2C), 128.64, 127.44, 127.20 (2C), 122.57, 118.70, 111.84, 110.58, 61.07, 59.22, 55.63, 45.87, 33.41, 29.02, 24.20, 16.18, 13.75 ppm.

4-(2-Benzoyl-7-benzyloxy-1-cyano-6-methoxy-1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)-5-ethylnicotinic Acid Ethyl Ester (**11c**, $C_{36}H_{35}N_3O_5$)

From 3.0 g **7c** (7.5 mmol), 300 cm^3 dry *DMF*, 1.7 g K-*t*-OC_4H_9 (15.0 mmol), 1.6 g **9b** (7.5 mmol)/10 cm^3 *DMF*. Yield: 3.1 g (70%) colourless crystals; mp 164°C; TLC (*n*-hexane:*Et*OAc = 1:2): $R_f = 0.57$; IR (KBr): $\bar{\nu} = 2225$ (C≡N), 1715 (CO_2R), 1640 ($CONR_2$) cm^{-1}; MS (CI): m/z (%) = 590 ($M^{+\bullet}+1$, 26), 397 (28), 74 (100); ^{1}H NMR (−20°C, 400 MHz): $\delta = 8.76$ and 8.73 (2s, each 1 arom H), 7.63–7.45 and 7.44–7.29 (2m, each 5 arom H), 6.68 and 6.12 (2s, 8-H and 5-H), 4.60 (s, ar-OCH_2-ar), 4.49 and 4.43 (2d, each $J = 12.8$ Hz, ar-CH_2), 4.03–3.79 and 3.88 (br m and s, OCH_2 and OCH_3), 3.71–3.50 (m, 3-H_{ab}), 3.20–2.77 (m, C–CH_2 and 4-H_{ab}), 1.33 (t, $J = 7.1$ Hz, OC–CH_3), 1.28 (t, $J = 7.4$ Hz, CH_3) ppm; ^{13}C NMR (100 MHz): $\delta = 172.19$, 166.18, 154.30, 149.29, 148.28, 146.11, 142.40, 141.37, 136.07, 135.61, 130.90, 128.95 (2C), 128.75 (2C), 128.55, 128.29, 127.94 (2C), 127.71, 127.28 (2C), 122.07, 118.40, 113.14, 110.49, 70.58, 61.28, 59.18, 55.95, 46.19, 33.69, 29.02, 24.25, 16.55, 13.75 ppm.

4-(2-Benzoyl-7-benzyloxy-1-cyano-6-methoxy-1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)-5-vinylnicotinic Acid Ethyl Ester (**11d**, $C_{36}H_{33}N_3O_5$)

From 1.5 g **7c** (3.8 mmol), 300 cm^3 dry *DMF*, 842 mg K-*t*-OC_4H_9 (7.5 mmol), 1.0 g **9c** (3.8 mmol)/10 cm^3 *DMF*. Yield: 1.3 g (61%) colourless crystals; mp 174°C; TLC (*n*-hexane:*Et*OAc = 1:1): $R_f = 0.39$; IR (KBr): $\bar{\nu} = 2219$ (C≡N), 1717 (CO_2R), 1639 ($CONR_2$) cm^{-1}; MS (CI): m/z (%) = 588 ($M^{+\bullet}+1$, 21), 397 (26), 192 (100); ^{1}H NMR (−20°C, 400 MHz): $\delta = 9.04$ and 8.77 (2s, each 1 arom H), 8.03 (dd, $J = 17.3$, 11.0 Hz, 1 arom H), 7.59–7.48 and 7.42–7.32 (2m, each 5 arom H), 6.69 and 6.31 (2s, 8-H and 5-H), 5.91 and 5.74 (2d, $J = 17.3$ and 11.0 Hz, CH_2=), 4.71–4.62 (m, ar-CH_2O-ar), 4.52 and 4.47 (2d, each $J = 12.9$ Hz, ar-CH_2), 4.05–3.95 (m, 3-H_a), 3.94–3.80 (m and s, OCH_2 and OCH_3), 3.74–3.63 (m, 3-H_b), 3.60–3.49 and 3.00–2.80 (2m, 4-H_{ab}), 1.29 (t, $J = 7.2$ Hz, CH_3) ppm; ^{13}C NMR (100 MHz): $\delta = 171.92$, 165.66, 150.55, 149.08 (2C), 146.01, 140.39, 136.08, 135.79, 135.26, 131.99, 130.67, 128.68 (2C), 128.53 (3C), 128.08, 127.69 (2C), 121.94, 120.13, 118.03, 112.72, 110.31, 70.36, 61.20, 58.65, 55.73, 45.94, 33.81, 28.73, 13.53 ppm.

4-(2-Benzoyl-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)nicotinic Acid (**16**, $C_{26}H_{23}N_3O_5$)

To a solution of 101 mg of **11a** (0.2 mmol) in 10 cm^3 of hot *Et*OH a solution of 42 mg KOH (0.6 mmol) in 0.5 cm^3 of H_2O was added. The mixture was refluxed for 2 h and then adjusted to *pH* = 6–7 with 2*N* HCl under ice-cooling. The colorless solid was filtered off, washed with 2×5 cm^3 of H_2O, and dried *in vacuo*. Yield: 87 mg (96%); mp 177°C; TLC ($CHCl_3$:*Me*OH = 9:1): $R_f = 0.24$; IR (KBr): $\bar{\nu} = 3300$–2800 (OH), 2218 (w, C≡N), 1711 (CO_2H), 1638 ($CONR_2$) cm^{-1}; MS (EI): m/z (%) = 412 ($M^{+\bullet} - CO_2$, 100), 397 (73), 105 (50), 77 (43); ^{1}H NMR (CD_3OD, 400 MHz): $\delta = 8.81$ (s, 2-H), 8.51 (d, $J = 5.1$ Hz, 6-H), 7.42 (m, 5 arom H), 7.31 (d, $J = 4.5$ Hz, 1 arom H), 6.55 and 6.51 (2s, each 1 arom H), 4.52 and 4.27 (2d, each $J = 12.6$ Hz, ar-CH_2), 3.79 (s, OCH_3), 3.62 (m, OCH_3 + 1H), 3.35

(ddd, $J = 13.5$, 9.8, 3.5 Hz, 1H), 2.57 and 2.37 (2ddd, $J = 15.7$, 4.9, 3.5 and 13.5, 9.8, 3.8 Hz, each 1H) ppm; ^{13}C NMR (CD_3OD, 100 MHz): $\delta = 173.95$, 168.95, 151.98, 151.61, 151.13, 149.10, 146.69, 137.02, 131.77, 130.01, 129.92 (2C), 129.63, 129.27, 127.97 (2C), 123.94, 120.01, 112.71, 112.57, 60.57, 56.49, 56.38, 47.01, 40.63, 29.32 ppm.

4-(2-Benzoyl-6,7-dimethoxy-3,4-dihydro-2H-isoquinolin-1-ylidenemethyl)nicotinic Acid (**17**, $C_{25}H_{22}N_2O_5$)

A mixture of 70 mg of **11a** (0.14 mmol), 23 mg of powdered KOH (0.4 mmol), and 10 cm^3 of monoethyleneglycol was refluxed for 3 h. The cold solution was diluted with 20 cm^3 of H_2O, and adjusted to $pH = 6$–7 with 2*N* HCl under ice-cooling. The solid was filtered off and after drying recrystallized from 10 cm^3 of *Et*OH. The colourless crystals were washed with a small volume of *Et*OH and dried *in vacuo*. Yield: 32 mg (62%); mp 199°C; TLC ($CHCl_3$:*Me*OH = 1:1): $R_f = 0.15$; ^{1}H NMR (400 MHz): $\delta = 9.16$ (s, 2-H), 8.71 (br s, 6-H), 7.74 (s, ar-CH=), 7.72 (d, $J = 5.1$ Hz, 5-H), 7.64–7.62 (m, 2 arom H), 7.36 (t, $J = 7.3$ Hz, 1 arom H), 7.28 (t, $J = 7.6$ Hz, 2 arom H), 6.83 and 6.80 (2s, each 1 arom H), 3.79 and 3.76 (2s, $2OCH_3$), 3.57 and 3.01 (2t, each $J = 7.8$ Hz, each 2H) ppm.

2-Benzoyl-1-(3-ethoxycarbonylpyridin-4-ylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid (**18**, $C_{28}H_{28}N_2O_7$)

A solution of 70 mg of **11a** (0.14 mmol) in 5 cm^3 of 20% H_2SO_4 was refluxed for 3 h and then adjusted to $pH = 7$ with NH_4OH under ice-cooling. The precipitated colourless solid was filtered off, washed with 2×5 cm^3 of H_2O, and dried *in vacuo*. Yield: 40 mg (56%); mp 232°C; TLC ($CHCl_3$:*Me*OH = 9:1): $R_f = 0.22$; IR (KBr): $\bar{\nu} = 3300$–2800 (OH), 1722 (CO_2R and CO_2H), 1636 ($CONR_2$) cm^{-1}; MS (CI): m/z (%) = 533 ($M^{+\bullet} + 29$, 7), 505 ($M^{+\bullet} + 1$, 52), 487 ($M^{+\bullet} - OH$, 57), 459 ($M^{+\bullet} - CO_2$, 54), 296 (84), 105 (100); ^{1}H NMR (CD_3OD, 400 MHz): $\delta = 8.61$ (s, heteroarom 2-H), 8.48 (d, $J = 5.1$ Hz, heteroarom 6-H), 7.51–7.47 (m, 5 arom H), 7.21 (d, $J = 5.1$ Hz, heteroarom 5-H), 7.12 and 6.58 (2s, 5-H and 8-H), 4.51 and 4.43 (2d, each $J = 13.3$ Hz, aryl–CH_2), 4.04 (dq, $J = 10.7$, 7.1 Hz, OCH_2), 3.87 and 3.81 (2s, $2OCH_3$), 3.40 and 2.89 (2ddd, $J = 11.3$, 8.0, 3.6 and 12.8, 7.2, 3.7 Hz, 3-H_{ab}), 2.52 and 1.77 (2ddd, $J = 11.3$, 7.2, 3.6 and 12.8, 8.0, 3.6 Hz, 4-H_{ab}), 1.23 (t, $J = 7.1$ Hz, CH_3) ppm.

*General Procedure for the Preparation of 1,2,3,4-Tetrahydroisoquinoline-1-carboxylic Acids **19** and **20***

85% H_3PO_4 was heated to 100°C (bath temperature) under stirring and then **10** or **11a** were added. Stirring was continued for additional 15 min causing sublimation of benzoic acid. The mixture was diluted with 10 cm^3 of ice/H_2O under ice-cooling and adjusted to $pH = 7$ with NH_4OH. Cooling was continued for 2–4 h causing a nearly colourless gelatinous precipitate, which was filtered off and dried *in vacuo*.

1-(2-Ethoxycarbonylbenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid (**19**, $C_{20}H_{21}NO_4$)

From 3.0 g **10** (7.1 mmol), 20 cm^3 H_3PO_4. Yield: 1.8 g (76%) colourless solid; mp 191°C; TLC (RP8, *Me*OH:H_2O = 1:1): $R_f = 0.54$; IR (KBr): $\bar{\nu} = 3411$ (NH), 3000–2600 (OH), 1714 (CO_2R), 1676 (CO_2H) cm^{-1}; MS (CI): m/z (%) = 340 ($M^{+\bullet} + 1$, 75), 322 (12), 294 (48), 248 (100); ^{1}H NMR (CD_3OD:F_3CCO_2D = 5:1, 400 MHz): $\delta = 7.97$ (dd, $J = 7.9$, 1.4 Hz, 1 arom H), 7.95–7.90 (m, 1 arom H), 7.61 and 7.53 (2dt, $J = 7.6$, 1.5 and 7.7, 1.1 Hz, each 1 arom H), 7.48 (dd, $J = 7.7$, 1.0 Hz, 1 arom H), 7.44–7.38 (m, 2 arom H), 7.34–7.28 (m, 1 arom H), 4.49–4.35 (m, OCH_2), 4.32 and 3.70 (2d, each $J = 14.4$ Hz, aryl–CH_2), 3.53–3.46 (m, 3-H_{ab}), 3.28–3.16 (m, 4-H_a), 3.10 (dt, $J = 17.3$, 4.2 Hz, 4-H_b), 1.41 (t, $J = 7.2$ Hz, CH_3) ppm; ^{13}C NMR (CD_3OD:F_3CCO_2D = 5:1, 100 MHz): $\delta = 172.28$, 171.57,

134.99, 134.36, 133.57, 133.49, 132.94, 132.50, 131.68, 130.49, 130.24, 129.99, 129.44, 128.86, 68.00, 63.94, 43.08, 41.45, 26.56, 14.10 ppm.

1-(3-Ethoxycarbonylpyridin-4-ylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid (**20**, $C_{21}H_{24}N_2O_6$)

From 1.5 g **11a** (3.1 mmol), 10 cm^3 H_3PO_4. Yield: 844 mg (68%) yellowish solid; mp 167–170°C; TLC (RP8, *Me*OH:H_2O = 1:1): R_f = 0.61; IR (KBr): $\bar{\nu}$ = 3421 (NH), 3000–2600 (OH), 1719 (CO_2R) cm^{-1}; MS (CI): m/z (%) = 309 ($M^{+\bullet}$ − OH, –CO, –OEt, 100), 236 ($M^{+\bullet}$ − C_7H_7, 79), 192 (65); ^{1}H NMR (F_3CCO_2D, 400 MHz): δ = 9.45 (s, heteroarom 2-H), 9.00 and 8.21 (2d, each J = 6.2 Hz, heteroarom 6-H and 5-H), 7.50 and 6.92 (2s, arom 8-H and 5-H), 4.68 (q, J = 7.2 Hz, OCH_2), 4.57 and 4.35 (2d, each J = 14.2 Hz, aryl–CH_2), 4.04 and 4.02 (2s, 2OCH_3), 3.86–3.74 and 3.61–3.51 (2m, 3-H_{ab}), 3.25–3.15 (m, 4-H_{ab}), 1.54 (t, J = 7.2 Hz, CH_3) ppm; ^{13}C NMR (F_3CCO_2D, 100 MHz): δ = 172.51, 167.95, 157.91, 152.90, 151.00, 146.46, 146.06, 134.47, 134.27, 128.76, 120.63, 114.51, 112.61, 69.17, 68.99, 58.23, 57.59, 44.03, 43.73, 26.96, 14.49 ppm.

8-Oxo-5,6,8,13-tetrahydrodibenzo[a,g]quinolizine-13a-carboxylic Acid (8-oxoberbine-13a-carboxylic Acid, **21***)*

*From **19***: To a solution of 4.0 g of KOH (71 mmol) in 40 cm^3 of 50% *Et*OH 1.7 g of **19** (5.0 mmol) were added and the mixture was refluxed for 2 h. After removing the *Et*OH *in vacuo*, the solution was acidified with conc. HCl under ice-cooling. The colourless solid was filtered off, dried *in vacuo* at ambient temperature, and crystallized from *Et*O*Ac*. Additional product could be obtained by concentrating the mother liquor. Yield: 1.4 g (96%); the analytical data are completely in line with those given in Ref. [2].

*General One-Pot Procedure for the Preparation of Oxocarboxylic Acids **21** and **22** from **10** and **11***

The educts **10** and **11** were added to 10 cm^3 of hot 85% H_3PO_4 (100°C bath temperature) under stirring. Heating and stirring was continued for 15 min causing sublimation of benzoic acid. The mixture was placed into an ice bath, diluted with 10 cm^3 of ice/H_2O, and stirred for additional 15 min. After rendering alkaline with 6*N* NaOH the mixture was heated to 80°C (bath temperature) under N_2 for 15 min. In the case of **21** conc. HCl was added under ice-cooling until a colourless precipitation occurred. Further workup was the same as already given (see above **21**). In the case of **22** the cold alkaline solution was justified to pH = 6–7 with 2*N* HCl and extracted with 10–12×30 cm^3 of *Et*O*Ac* until no more product was detected in the aqueous phase (TLC monitoring). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The residue was crystallized from the solvent indicated. The acids thus obtained were poorly soluble in Et_2O, $CHCl_3$, *Me*OH, acetone, *DMSO*, *DMF*, and H_2O). Chromatographical purification could be achieved only by PLC ($CHCl_3$:*Me*OH = 4:1), but this method was found to cause marked loss of the product.

8-Oxo-5,6,8,13-tetrahydrodibenzo[a,g]quinolizine-13a-carboxylic Acid (8-oxoberbine-13a-carboxylic Acid, **21***)*

From 1.0 g **10** (2.4 mmol). Yield: 670 mg (87%); analytical data are in line with those already given (see above).

2,3-Dimethoxy-8-oxo-5,6,13,13a-tetrahydro-8H-isoquino[2,1-b][2,7]naphthyridin-13a-carboxylic Acid (**22a**, $C_{19}H_{18}N_2O_5$)

From 1.1 g **11a** (2.1 mmol). The residue was crystallized from *Me*OH (4 days). Yield: 476 mg (64%) beige crystals; mp 211°C; TLC ($CHCl_3$:*Me*OH = 4:1): R_f = 0.16; IR (KBr): $\bar{\nu}$ = 3000–2600 (OH),

1716 (CO_2H), 1661 ($CONR_2$) cm^{-1}; MS (CI): m/z (%) = 355 ($M^{+\bullet}+1$, 3), 310 (100), 309 (61); ^1H NMR (CD_3OD, 400 MHz): $\delta = 9.00$ (s, 9-H), 8.53 (d, $J = 5.2$ Hz, 11-H), 7.51 (s, 1-H), 7.40 (d, $J = 5.2$ Hz, 12-H), 6.75 (s, 4-H), 4.81 (m, 6-H_a, superimposed by H_2O), 3.99 (d, $J = 16.0$ Hz, 13-H_a), 3.87 and 3.83 (2s, 2OCH_3), 3.55 (ddd, $J = 12.9$, 10.6, 5.3 Hz, 6-H_b), 3.02 (d, $J = 16.1$ Hz, 13-H_b), 2.95–1.81 (m, 5-H_{ab}) ppm; ^{13}C NMR (CD_3OD, 100 MHz): $\delta = 178.54$, 164.91, 152.11, 149.41, 149.26, 149.03, 148.94, 129.94, 128.25, 126.55, 123.85, 112.33, 111.32, 67.64, 56.60, 56.38, 42.25, 39.20, 29.38 ppm.

12-Ethyl-2-hydroxy-3-methoxy-8-oxo-5,6,13,13a-tetrahydro-8H-isoquino[2,1-b][2,7]naphthyridin-13a-carboxylic Acid (**22b**, $C_{20}H_{20}N_2O_5$)

From 1.1 g **11c** (1.7 mmol). The residue was crystallized from *Me*OH:H_2O = 9:1 (14 days). Yield: 384 mg (61%) beige crystals; mp 221°C; TLC ($CHCl_3$:*Me*OH = 4:1): $R_f = 0.20$; IR (KBr): $\bar{\nu} = 3000$–2600 (OH), 1709 (w, CO_2H), 1657 ($CONR_2$) cm^{-1}; MS (CI): m/z (%) = 397 ($M^{+\bullet}+29$, 9), 369 ($M^{+\bullet}+1$, 12), 325 (45), 324 (26), 323 (100); ^1H NMR F_3CCO_2D, 400 MHz): $\delta = 9.46$, 8.79, 7.45, and 6.95 (4s, 9-H, 11-H, 1-H, and 4-H), 5.12–5.03 (m, 6-H_a), 4.56 (d, $J = 17.6$ Hz, 13-H_a), 4.06 (s, OCH_3), 3.84–3.74 (m, 6-H_b), 3.49 (d, $J = 17.6$ Hz, 13-H_b), 3.29–3.01 (m, 5-H_{ab} and CH_2), 1.54 (t, $J = 7.5$ Hz, CH_3) ppm; ^{13}C NMR (F_3CCO_2D, 100 MHz): $\delta = 177.19$, 163–164, 158.43, 149.96, 145.75, 145.56, 143.78, 141.94, 130.14, 129.74, 124.62, 115.34, 115.08, 66.30, 57.49, 41.69, 39.24, 29.28, 25.06, 13.57 ppm.

2-Hydroxy-3-methoxy-8-oxo-12-vinyl-5,6,13,13a-tetrahydro-8H-isoquino[2,1-b][2,7]naphthyridin-13a-carboxylic Acid (**22c**, $C_{20}H_{18}N_2O_5$)

From 1.1 g **11d** (1.7 mmol). The residue was crystallized from *Me*OH (*ca.* 14 days). Yield: 398 mg (64%) pale yellow crystals; mp 212°C; TLC ($CHCl_3$:*Me*OH = 4:1): $R_f = 0.21$; IR ($CHCl_3$/film): $\bar{\nu} = 3418$ (aryl–OH), 3300–2700 (OH), 1726 (CO_2H), 1645 ($CONR_2$) cm^{-1}; MS: (FAB): m/z (%) = 367 ($M^{+\bullet}+1$, 23); (EI): m/z (%) = 322 ($M^{+\bullet}-CO_2$, 93), 307 (100), 305 (49), 293 (89), 176 (20); ^1H NMR (500 MHz; CD_3OD): $\delta = 8.93$, 8.67, and 7.32 (3s, 9-H, 11-H, 1-H), 7.02 (dd, $J = 11.3$, 11.4 Hz, vinyl–CH=), 6.75 (s, 4-H), 5.84 and 5.59 (2d, $J = 17.3$ and 11.3 Hz, vinyl–CH_2=), 4.82–4.76 (m, 6-H_a), 4.16 and 2.91 (2d, each $J = 16.5$ Hz, 13H_{ab}), 3.86 (s, OCH_3), 3.52–3.47 (m, 6-H_b), 2.88–2.82 (m, 5-H_{ab}) ppm; ^{13}C NMR (100 MHz; CD_3OD): $\delta = 177.70$, 165.20, 150.34, 148.63, 148.56, 146.40, 145.51, 133.22, 131.42, 128.88, 127.17, 126.03, 120.46, 114.33, 112.45, 66.45, 56.40, 39.75, 38.95, 29.35 ppm.

*General Procedure for the Decarboxylation of Compounds **21** and **22** According to Ref.* [1]

The crude products were purified by FC or PLC.

5,6,13,13a-Tetrahydro-8H-dibenzo[a,g]quinolizin-8-one (Berbin-8-one, **25***) and 5,6-Dihydro-8H-dibenzo[a,g]quinolizin-8-one* (**23**)

For preparation and analytical data see Ref. [1].

2,3-Dimethoxy-5,6-dihydro-8H-isoquino[2,1-b][2,7]naphthyridin-8-one (**24a**)

From 410 mg **22a** (1.2 mmol), reaction time 15 min, FC ($CHCl_3$:*Me*OH = 9:1). Yield: 228 mg (64%) yellow crystals; mp 161–165°C (*Me*OH, Ref. [26]: mp 169–170°C); TLC (eluent see FC): $R_f = 0.48$ (blue fluorescence, $\lambda_{em} = 365$ nm); IR (KBr): $\bar{\nu} = 1651$ ($CONR_2$) cm^{-1}; UV ($c = 3.243 \times 10^{-5}$ mol dm^{-3}, 0.1 *N* HCl in *Et*OH): λ_{max} ($\varepsilon \times 10^{-3}$) = 252 (23.34), 373 (26.46), 418

(33.33) nm ($mol^{-1}\,dm^3\,cm$); MS (EI): m/z (%) = 308 ($M^{+\bullet}$, 87), 293 (100); ^{1}H NMR: Data were in line with those published in Ref. [26]; ^{13}C NMR (100 MHz): δ = 161.45, 151.65, 150.29, 148.72, 148.67, 143.53, 142.72, 129.87, 121.10, 119.37, 119.19, 110.50, 108.31, 98.95, 56.32, 56.15, 39.60, 27.76 ppm.

12-Ethyl-2-hydroxy-3-methoxy-5,6-dihydro-8H-isoquino[2,1-b][2,7]naphthyridin-8-one (Dihydroalangimarine, **24b***)*

From 156 mg **22b** (0.4 mmol), reaction time 10 min, PLC ($CHCl_3$:*Me*OH = 9:1). Yield: 80 mg (61%) yellow crystals; mp 208–212°C (*Me*OH, Ref. [27]: mp 222°C); TLC (eluent see FC): R_f = 0.33 (blue fluorescence, λ_{em} = 365 nm); IR (KBr): $\bar{\nu}$ = 3421 (OH), 1657 ($CONR_2$) cm^{-1}; UV ($c = 3.7224\times10^{-5}$ mol dm^{-3}, 0.1 *N* HCl in *Et*OH): λ_{max} ($\varepsilon\times10^{-3}$) = 224 (32.24), 266 (18.91), 420 (34.92) nm ($mol^{-1}\,dm^3\,cm$); MS (EI): m/z (%) = 322 ($M^{+\bullet}$, 66), 307 (100), 292 (12); ^{1}H NMR: Data were in line with those published in Ref. [27]; ^{13}C NMR (100 MHz): δ = 161.73, 149.03, 148.12, 147.05, 146.92, 145.30, 143.05, 141.46, 129.01, 122.13, 119.14, 111.64, 109.96, 96.01, 56.20, 39.68, 27.83, 23.04, 14.62 ppm.

2-Hydroxy-3-methoxy-12-vinyl-5,6-dihydro-8H-isoquino[2,1-b][2,7]naphthyridin-8-one (Alangimarine, **24c***)*

From 333 mg **22c** (0.9 mmol), reaction time 15 min, FC ($CHCl_3$:*Me*OH = 9:1). Yield: 177 mg (61%) yellow crystals; mp 242–244°C (*Me*OH, Ref. [28]: mp 245–247°C); TLC (eluent see FC): R_f = 0.34 (blue fluorescent, λ_{em} = 365 nm); IR (KBr): $\bar{\nu}$ = 3508 (OH), 1655 ($CONR_2$) cm^{-1}; UV ($c = 2.4973\times10^{-5}$ mol dm^{-3}, *Et*OH): λ_{max} ($\varepsilon\times10^{-3}$) = 261 (19.77), 290 (10.69), 365 (25.26), 380 (21.96) nm ($mol^{-1}\,dm^3\,cm$); MS (EI): m/z (%) = 320 ($M^{+\bullet}$, 78), 305 (100), 290 (10); ^{1}H NMR: Data were in line with those published in Ref. [28]; ^{13}C NMR (125 MHz): δ = 160.85, 149.68 (2C), 148.09, 146.95, 144.27, 138.53, 129.50, 128.05, 126.91, 121.45, 118.56, 118.03, 110.59, 108.06, 95.33, 55.25, 38.71, 26.98 ppm.

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