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3,10-Dimethoxyprotoberberines

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Protoberberines with the unusual 3,10-dimethoxy substitution are synthesized by photocyclization of *E*- and *Z*-1-ethylidene-1,2,3,4-tetrahydro-6-methoxy-2-(3-methoxybenzoyl)isoquinolines.

3,10-Dimethoxyprotoberberine

Protoberberine mit ungewöhnlicher 3,10-Dimethoxysubstitution werden durch Photocyclisierung von E- und Z-1-Ethyliden-1,2,3,4-tetrahydro-6-methoxy-2-(3-methoxybenzoyl)-isochinolinen hergestellt.

Commonly used methods such as *Mannich*- and *Bischler-Napieralski*-cyclizations could not be utilized in the synthesis of 10-oxygenated protoberberines1) due to lack of activation at the cyclization site. A first synthesis of 10-methoxyprotoberberines has recently been reported by *Mali* et al. using 7-methoxyisochroman-3-one2). However, this method is not suitable for the synthesis of 10-methoxy-8-oxoprotoberberines. Enamide photocyclizations have been widely used to synthesize protoberberines including optically active bases3). Because the enamides **10–12** can be prepared easily from dihydroisoquinolines we investigated photocyclization as a means of synthesizing unusually oxygenated protoberberines. The 3,4-dihydroisoquinolines **8** and **9** were prepared according to scheme 1.

Ninomiya et al. have prepared the enamides by refluxing a benzene solution of the pertinent 3,4-dihydroisoquinoline, triethylamine and the corresponding acid chloride4). In our hands, 1-ethyl-3,4-dihydro-6-methoxyisoquinoline **(8)** condensed with 3-methoxybenzoyl chloride in the presence of triethylamine in benzene readily at room temp. to give a mixture of the geometrical isomers **10** (Z isomer) and **11** (E isomer) which were separated by prep. tlc. These isomers were determined by comparison of chemical shifts of the olefinic and allylic methyl protons4). The olefin proton in the major Z isomer **10** absorbs at $\delta = 5.65$ ppm while that in the minor **E** isomer **11** resonates relatively upfield ($\delta = 5.10$ ppm) due to shielding by the carbonyl group. When 1-ethyl-3,4-dihydro-6-methoxy-3-methylisoquinoline **(9)** was condensed with 3-methoxybenzoyl chloride under similar conditions only the enamide **12** (**Z** isomer) was obtained in 80 % yield.

**) Dedicated to Prof. Dr. Maurice Shamma, The Pennsylvania State University (USA), on the occasion of his 60th birthday.

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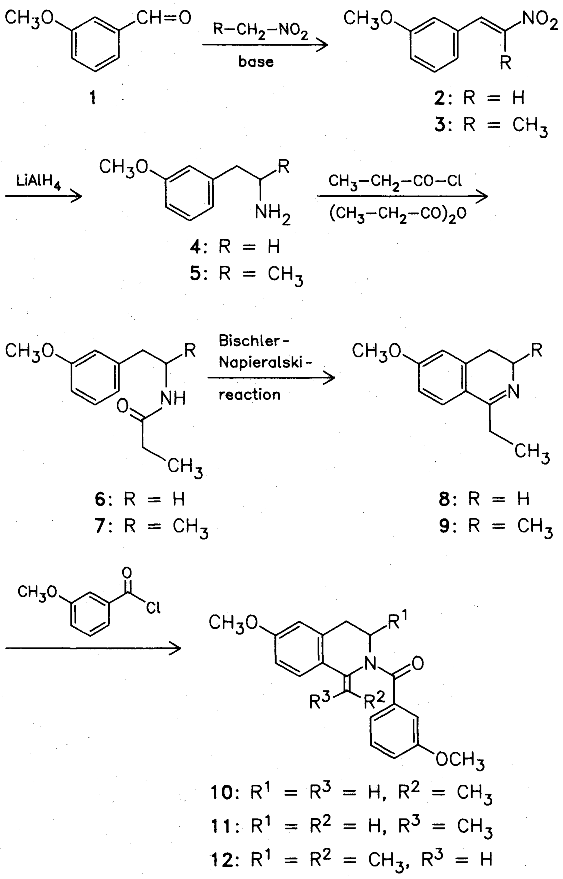
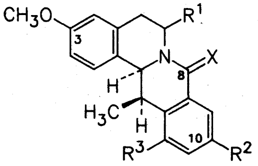
Scheme 1



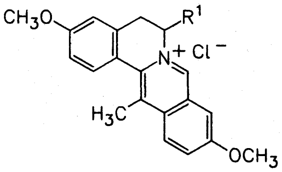
Upon irradiation of either of the enamides **10** or **11** in benzene under N_2 the same (inseparable) mixture of 8-oxo-protoberberines **13** and **14** was obtained in 36 % total yield. The IR-spectrum indicates the presence of 6-membered lactams (1645 and 1625 cm^{-1}). The diagnostic fragment in the mass spectrum is m/z = 162 (81 %, $C_{10}H_{12}NO^+$ and $C_{10}H_{10}O_2^+$, retro-Diels-Alder-fragmentation) helping to assign the structures **13** and **14** for the mixture.

$LiAlH_4$ reduction produced an easily separable mixture of 7,8,13,14-tetrahydro-3,10-dimethoxy-13-methylprotoberberine (**15**) and the 3,12-dimethoxy analogue **16** in 48 and 23 % yield, respectively. The 250 MHz ^1H-NMR-spectrum of **15** in $CDCl_3$ indicates the 3,10-disubstituted skeleton (two doublets at $\delta = 6.62$ ppm; $J_m = 2.5$ Hz and $\delta = 6.65$ ppm, $J_m = 2.6$ Hz). Moreover, the presence of *cis* hydrogens at C-13 and C-14 as well as the *trans* quinolizidine ring system in **15** is borne out by the chemical shift ($\delta = 0.93$ ppm) of the 13-methyl protons and the chemical shift difference (0.34 ppm) for the AB quartet of the C-8 protons[5-8]. The *Bohlmann* bands at 2770 and 2810 cm^{-1} in

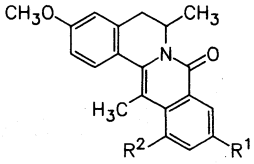
Scheme 2



13: $R^1 = R^3 = H$, $R^2 = OCH_3$, $X = O$
14: $R^1 = R^2 = H$, $R^3 = OCH_3$, $X = O$
15: $R^1 = R^3 = H$, $R^2 = OCH_3$, $X = H_2$
16: $R^1 = R^2 = H$, $R^3 = OCH_3$, $X = H_2$
18: $R^1 = CH_3$, $R^2 = OCH_3$, $R^3 = H$, $X = O$
19: $R^1 = CH_3$, $R^2 = H$, $R^3 = OCH_3$, $X = O$
22: $R^1 = CH_{3\text{equat.}}$, $R^2 = OCH_3$, $R^3 = H$, $X = H_2$
23: $R^1 = CH_{3\text{equat.}}$, $R^2 = H$, $R^3 = OCH_3$, $X = H_2$
25: $R^1 = CH_{3\text{axial}}$, $R^2 = OCH_3$, $R^3 = H$, $X = H_2$
26: $R^1 = CH_{3\text{axial}}$, $R^2 = H$, $R^3 = OCH_3$, $X = H_2$



17: $R^1 = H$
24: $R^1 = CH_3$



20: $R^1 = OCH_3$, $R^2 = H$
21: $R^1 = H$, $R^2 = OCH_3$

the IR-spectrum also support the *trans* quinolizidine ring junction[9, 10]. Similarly, the 250 MHz ^1H-NMR- and IR-spectra of **16** indicate the substitution pattern as well as the relative stereochemistry.

I_2-oxidation of **15** followed by ion exchange to the chloride form yielded the protoberberine **17** in 71 % yield. Its ^1H-NMR-spectrum in $CDCl_3$ and TFA exhibits the 13-methyl singlet at $\delta = 3.03$ ppm. The UV-spectrum (see Experim. Part) supports the protoberberine structure **17**. I_2-oxidation of the 3,12-dimethoxy analogue **16** did not yield any well defined product[11].

Irradiation of the benzene solution of the enamide **12** under N_2 yielded an inseparable mixture of the 8-oxo-tetrahydroprotoberberines **18** and **19** as well as the corresponding 8-oxo-6,7-dihydroprotoberberines **20** and **21** which were separated by prep. tlc.

$LiAlH_4$ reduction of a mixture of **18** and **19** afforded a separable mixture of 7,8,13,14-tetrahydro-3,10-dimethoxy-6,13-dimethylprotoberberine **(22)** and the 3,12-dimethoxy isomer **23** in 24 % yield each. The relative stereochemistry as well as the conformation of the *trans* quinolizidine ring system in **22** and **23** were assigned based on the 250 MHz ^1H-NMR- and IR-spectra. Additionally, the axial C-5 proton in **22** exhibits a doublet of doublets at $\delta = 2.79$ ppm with $J_{gem} = 15.6$ Hz and $J_{vic,aa} = 11.8$ Hz indicating an equatorial 6-methyl group. Similarly, the axial C-5 proton in **23** appears at $\delta = 2.81$ ppm (dd; $J_{gem} = 15$ Hz and $J_{vic,aa} = 11.5$ Hz).

Coincidentally, only **22** underwent I_2-oxidation to yield the protoberberine **24** while the 3,12-dimethoxy isomer **23** failed. In a separate set of experiments the 8-oxoprotoberberines **20** and **21** were reduced with $LiAlH_4$ followed by $NaBH_4$ to obtain **25** and **26** in 31 and 21 % yield, respectively. An interesting aspect of the 250 MHz ^1H-NMR-spectrum of **25** in $CDCl_3$ is the axial C-5 proton appearing as a doublet of doublets at $\delta = 3.23$ ppm ($J_{gem} = 15.2$ Hz and $J_{vic,ae} = 4.5$ Hz). This indicates an axial 6-methyl group in **25**. Similarly, coupling constants for the axial C-5 proton in **26** indicate the presence of axial 6-methyl. The relative stereochemistry at C-13 and C-14 and the *trans* quinolizidine conformation in **25** and **26** were deduced from the 250 MHz ^{1}H-NMR- and IR-spectra.

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Experimental Part

General remarks: m. ps. are uncorrected. – Elemental analysis: Microanalysis Laboratory, University of Regensburg. – UV-spectra: Uvikon 810 Kontron Spectrophotometer, MeOH. – IR-spectra: ($CHCl_3$, or KBr pellets if not mentioned otherwise): Beckman Acculab 3. – ^{1}H-NMR spectra (90 MHz, if not stated otherwise): Varian EM 390 or Bruker WM 250, TMS as intern. standard. – Mass spectra: Varian Mat CH 5; high resolution MS: Varian Mat 311A; formula of ions are established by h.r.

3-Methoxy-β-nitrostyrene (2)

10 g aldehyde **1**[12], 10 ml freshly distilled nitromethane and 4 g NH_4OAc in 40 ml glacial acetic acid were refluxed for 2 h; the mixture was poured into ice water with stirring; the precipitate was dried and recrystallized from ether, m. p. = 90°; Lit.[13] 91–92° (from EtOH); Yield: 13.3 g, 80 %.

β-(3-Methoxyphenyl)ethylamine (4)

3.88 g $LiAlH_4$ was added slowly to a suspension of 10.0 g **2** in 100 ml of ether kept in an ice bath. The temp. of the mixture should not exceed 20° by adjusting the rate of addition of $LiAlH_4$. After completion of the addition of $LiAlH_4$, the reaction mixture was allowed to come to room temp. and was refluxed for 90 min. The reaction mixture was cooled again to 0° and excess $LiAlH_4$ was destroyed by the successive addition of ethyl acetate (25 ml) and water. Usual work-up gave an oil which was purified by Kugelrohr-distillation (97–98°; $5 \cdot 10^{-2}$ mm); Lit[14]: b. p. 122–123°/7 mm. Yield: 6.3 g (75 %).

N-[β-(3-Methoxyphenyl)ethyl]propanamide (6)

3.06 g propionylchloride (2.9 ml) was added drop by drop to 5.0 g **4** in 3.5 ml of dry pyridine. After stirring for 2 h at room temp. the mixture was poured into 30 ml ice water, 30 ml 6 N HCl and 60 ml ether. The aqueous layer was extracted with CH_2Cl_2, the org. layers were dried (Na_2SO_4) and purified by CC (SiO_2, CH_2Cl_2) and Kugelrohr-distillation (97°; $5 \cdot 10^{-2}$ mm). Yield: 5.0 g (73 %) oil. – $C_{12}H_{17}NO_2$ (207.3) Calc. C 69.5 H 8.3 N 6.8 found C 69.0 H 8.33 N 7.0. – UV (MeOH): λ max (log ε) = 272 (3.30), 279 nm (3.27). – IR: 3450 (NH), 1650 cm^{-1} (CO). – ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.20 (t; 3H; CH_2-$C\underline{H}_3$), 2.10 (q; J = 7.5 Hz; 2H; $C\underline{H}_2$-CH_3) 2.65 (t; J = 7.5 Hz; 2H, Ph-$C\underline{H}_2$), 3.35 (m; 2H; $C\underline{H}_2$-NH), 3.75 (s; 3H; OCH_3), 5.75 [s (br.); 1H; NH], 6.60–7.05 (m; 4H, arom. H).

1-Ethyl-3,4-dihydro-6-methoxyisoquinoline (8)

2 g **6** were refluxed in 15 ml CH_3CN with 5 ml $POCl_3$ (freshly distilled) for 2 h under N_2. The mixture was cooled and the solvents removed under vacuum. The residue was taken up in CH_2Cl_2 and shaken with dil. NH_3 (2 × 30 ml) and water (1 × 30 ml). The org. layer was dried and evaporated under vacuum. The residue was subjected to Kugelrohr-distillation (135°, 10^{-2} mm). Yield: 0.73 g, 40 %, oil. – $C_{12}H_{15}NO$ (189.3) Calc. C 76.1 H 8.00 N 7.4 Found C 74.6*) H 7.88 N 7.3. – UV (MeOH): λ max (log ε) = 270 nm (4.03); –

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*) Various attempts to get better C-values failed.

(MeOH + HCl): λ max (log ε) = 316 (4.22), 235 nm (3.93). – IR: 1630 cm^{-1} (C=N). – ^1H-NMR ($CDCl_3$): δ (ppm) = 1.25 (t; J = 7.5 Hz; 3H, CH_2-$C\underline{H}_3$), 2.60 (q; J = 7.5 Hz; 2H; $C\underline{H}_2$-CH_3), 2.65 (t; J = 7.5 Hz; 2H; H-4), 3.60 (t; J = 7.5 Hz; 2H; H-3), 6.70–7.35 (m; 3H; arom. H).

1-(3-Methoxyphenyl)-2-nitropropene-2 (**3**)

A suspension of 10 g **1**, 4.1 g NaOAc (free of water), 3.4 g CH_3NH_2 × HCl and 5.3 g methylorthoformiate in 60 ml MeOH was boiled with 10.0 g nitroethane under reflux for 4 h. Pouring into 200 ml ice water leads to a precipitate which was crystallized from ether. Yield: 9.7 g (68 %), m. p. 45°; Lit.[15]: 46.5° (petrolether). – ^1H-NMR ($CDCl_3$): δ (ppm) = 2.40 (s; 3H, CH_3), 3.85 (s; 3H, OCH_3), 6.90–8.35 (m; 4H; arom. H), 7.95 (s; 1H, H-1).

1-(3-Methoxyphenyl)-2-aminopropane (**5**)

5 was prepared as described for **4**. Yield: 3.9 g (45 %), b. p. 96°, 5 · 10^{-2} mm (Kugelrohr); Lit.[16]: 124–126°, 11 mm. – ^1H-NMR-data correspond to those reported[17].

N-[α-Methyl-β-(3-methoxyphenyl)ethyl]propanamide (**7**)

7 was prepared analogously to **6**. – Yield: 5.1 g (75 %); oil, b. p. 96°, 5 · 10^{-2} mm (Kugelrohr). $C_{13}H_{19}NO_2$ (221.3); Calc. C 70.6 H 8.65 N 6.3 Found C 69.8*) H 8.70 N 6.5. – UV (MeOH): λ max (log ε) = 272 nm (3.30). – IR: 3300 (NH), 1650 cm^{-1} (CO). – ^1H-NMR ($CDCl_3$): δ (ppm) = 1.05–1.35 (m; 6H; CH_3), 2.10 (q; J = 8.0 Hz; 2H; $C\underline{H}_2$-CH_3), 2.65 (d; J = 8 Hz; 2H; Ph-$C\underline{H}_2$), 3.75 (s; 3H; OCH_3), 4.05–4.50 (m; 1H; $C\underline{H}$-NH), 5.35 [s (br.); 1H; NH], 6.60–7.05 (m; 4H, arom. H).

1-Ethyl-3,4-dihydro-6-methoxy-3-methylisoquinoline (**9**)

After drop by drop addition of 7.5 ml $POCl_3$ to 5.2 g **7** in 25 ml CH_3CN the mixture was refluxed for 3 h. After cooling and addition of 300 ml ice water the mixture was basified (NaOH) and extracted with ether. After evaporation of the dried org. layer the residue was purified first by CC (SiO_2, ethylacetate), then by Kugelrohr-distillation (125°, 10^{-2} Torr). Yield: 2.6 g, 55 %. – **9** could not be purified thoroughly on account of its instability and was further processed as such. – UV (MeOH): λ max (log ε) = 272 nm (4.06); – (MeOH + HCl): λ max (log ε) = 226 (4.00), 320 nm (4.22). – IR: 1630 cm^{-1} (C=N). – ^1H-NMR ($CDCl_3$): δ (ppm) = 1.05–1.35 (m; 6H; CH_3), 2.55–2.80 (m; 4H; $C\underline{H}_2$-CH_3/H-4), 3.40–3.70 (m; 1H; H-3), 3.75 (s; 3H, OCH_3), 6.80–7.45 (m; 3H; arom. H).

1-Ethylidene-1,2,3,4-tetrahydro-6-methoxy-2-(3-methoxybenzoyl)isoquinolines (**10** *and* **11**).

1.6 g (8.45 mmol) of 1-ethyl-3,4-dihydro-6-methoxyisoquinoline (**8**) in 10 ml dry benzene was mixed with 1.026 g (10.16 mmol) triethylamine and 1.443 g (8.46 mmol) 3-methoxybenzoyl chloride in 10 ml dry benzene. The mixture was stirred at r. t. for ½ h, then 50 ml benzene were added. The benzene suspension was washed with water (25 ml), 3N HCl (2 × 25 ml), water (25 ml), $NaHCO_3$ solution (2 × 25 ml), again with water (25 ml), dried (Na_2SO_4) and evaporated. The residue was separated by CC (SiO_2, CH_2Cl_2-MeOH). The fraction collected with 3 % MeOH–CH_2Cl_2 was pure enamide **10** (600 mg, 22 %). Later fractions were purified by prep.-tlc (SiO_2/Et_2O). The major band (R_f = 0.72) was collected to provide enamide **11** (100 mg, 4 %).

Enamide **10** could not be crystallized. – UV (MeOH): λ max (log ε) = 260 (4.18) and 210 nm (4.37). – IR ($CHCl_3$): 1625 cm^{-1} (C=O). – ^1H-NMR ($CDCl_3$): δ (ppm) = 1.30 (br. d, J = 7 Hz, 3H, $C\underline{H}_3CH=$), 2.6–3.4 (m; 3H, H-4, H-3), 3.70 and 3.80 (2 × s; 6H, OCH_3), 5.1 (br. s.; 1H, H-3), 5.65 (br. q.; 1H, $CH_3C\underline{H}=$), 6.60–7.50 (m; 7H, arom. H). – MS (70 eV): m/z = 323 (83, $M^{+\cdot}$), 308 (47), 294 (99), 188 (34, $C_{12}H_{14}NO^+$), 135 (100, $C_8H_7O_2^+$), 107 (66, $C_7H_7O^+$), 92 (36, $C_6H_4O^+$).

Enamide **11** also could not be crystallized. – UV (MeOH): λ max (log ε) = 251 (3.83) and 204 nm (4.24). – IR ($CHCl_3$): 1620 cm^{-1} (C=O). – ^1H-NMR ($CDCl_3$): δ (ppm) = 1.60 (d, J = 7 Hz; 3H, $C\underline{H}_3CH$=), 2.95 (t, J = 6 Hz; 2H, H-4), 3.75 and 3.85 (2 × s; 6H, OCH_3), 4.00 (t, J = 6 Hz; 2H, H-3), 5.10 (q, J = 7 Hz; 1 H, $CH_3C\underline{H}$=), 6.70–7.40 (m, 7H, arom. H). – MS (70 eV): m/z = 323 (21, $M^{+\cdot}$), 322 (16), 321 (19), 308 (12), 294 (19), 188 (20, $C_{12}H_{14}NO^+$), 173 (100, $C_{11}H_{11}NO^+$), 135 (84, $C_8H_7O_2^+$), 107 (30, $C_7H_7O^+$).

7,8,13,14-Tetrahydro-3,10-dimethoxy-13-methyl-8-oxoprotoberberine **(13)** *and 7,8,13,14-tetrahydro-3,12-dimethoxy-13-methyl-8-oxo-protoberberine* **(14)**.

The solution of enamide **10** (600 mg, 1.86 mmol) in 200 ml dry benzene was deoxygenated by passing N_2 through the solution for 45 min and then irradiated using a high pressure Hg lamp (Philips H.P.K.125 W) for 2 h under N_2. The products were purified by CC (SiO_2, CH_2Cl_2-MeOH and again SiO_2, Et_2O) to obtain an inseparable mixture of **13** and **14** (218 mg, 36 %). – UV: λ max (log ε) = 290 (3.53), 250 (3.85), 211 nm (4.42). – IR ($CHCl_3$): 1645 cm^{-1} (C=O). – MS (70 eV): m/z = 323 (100, $M^{+\cdot}$), 294 (28), 280 (32), 235 (21), 162 (81, $C_{10}H_{12}NO^+$ and $C_{10}H_{10}O_2^+$).

7,8,13,14-Tetrahydro-3,10-dimethoxy-13-methylprotoberberine **(15)** *and 7,8,13,14-tetrahydro-3,12-dimethoxy-13-methylprotoberberine* **(16)**.

A mixture of **13** and **14** (100 mg, 0.31 mmol) was reduced with $LiAlH_4$ (200 mg) in refluxing absol. THF (10 ml). After initial work-up the resulting mixture was separated by prep.-tlc (SiO_2, 25 % EtOAc in hexane) to yield the protoberberines **15** and **16**.

Major isomer **15** (R_f 0.56; 46 mg, 48 %): m. p. 136° (MeOH). – UV: λ max (log ε) = 287 (3.64), 278 (3.67), 208 nm (4.36). – IR: 2810, 2770 (*Bohlmann* bands) cm^{-1}. – ^1H-NMR (250 MHz, $CDCl_3$): δ (ppm) = 0.93 (d, J = 6.9 Hz; 3H, 13-CH_3), 3.26 (qd, J = 6.9 and 3.5 Hz; 1H, H-13), 3.75 (d, J = 3.5 Hz; 1H, H-14), 3.65 and 3.99 (AB, J = 15 Hz; 2H, H-8), 3.79 and 3.80 (2 × s; 6 H, OCH_3), 6.62 (d, J = 2.5 Hz; 1H, H-4), 6.65 (d, J = 2.6 Hz; 1H, H-9), 6.77 (dd, J_o = 9 Hz, J_m = 2.6 Hz, 1H, H-11), 6.79 (dd, J_o = 9 Hz, J_m = 2.5 Hz; 1H, H-2), 7.09 (d, J = 9 Hz; 1H, H-12), 7.13 (d, J = 9 Hz; 1H, H-1). – MS (70 eV): m/z = 309 (29, $M^{+\cdot}$), 294 (21), 162 (12, $C_{10}H_{12}NO^+$), 160 (8, $C_{10}H_{10}NO^+$), 148 (100, $C_{10}H_{12}O^+$). – $C_{20}H_{23}NO_2$ (309.4) calc. C 77.7 H 7.44 N 4.5 found C 77.4 H 7.41 N 4.5.

Minor isomer **16** (R_f 0.65; 22 mg, 23 %): m. p. (HCl salt): 180–183° (acetone). – UV (MeOH) λ max (log ε) = 285 (3.64), 278 (3.79), 208 nm (4.42). – IR: 2820, 2770 (*Bohlmann* bands) cm^{-1}. – ^1H-NMR (250 MHz, $CDCl_3$): δ (ppm) = 0.91 (d, J = 6.6 Hz; 3H, 13-CH_3), 3.65 and 4.04 (AB, J = 15 Hz; 2H, H-8), 3.80 and 3.85 (2 × s; 6H, OCH_3), 3.51 (qd, J = 6.6 and 3.5 Hz; 1H, H-13), 3.68 (br.; 1H, H-14), 6.65 (d, J = 2.6 Hz; 1H, H-4), 6.66 (d, J = 7.9 Hz; 1H, H-11), 6.75 (d, J = 7.9 Hz; 1H, H-9), 6.79 (dd, J_o = 8.6 Hz, J_m = 2.6 Hz; 1H, H-2), 7.13 (t, J = 7.9 Hz; 1H, H-10), 7.21 (d, J = 8.6 Hz; 1H, H-1). – MS (70 eV): m/z = 309 (100, $M^{+\cdot}$), 308 (51), 294 (59), 162 (26, $C_{10}H_{12}NO^+$), 160 (24, $C_{10}H_{10}NO^+$), 148 (66, $C_{10}H_{12}O^+$), 133 (95, $C_9H_9O^+$). – $C_{20}H_{24}NO_2 \cdot Cl \times 0.5\ H_2O$ (354.5) calc. C 67.7 H 7.05 found C 67.1 H 6.92.

3,10-Dimethoxy-13-methylprotoberberine Chloride **(17)**.

25 mg (0.08 mmol) of **15** in 10 ml EtOH was refluxed with 50 mg (0.39 mmol) I_2 for 16 h. The mixture was cooled, the solvent evaporated and excess I_2 decomposed by saturated $Na_2S_2O_3$ solution. The solid formed was washed with H_2O, dissolved in MeOH and the solution passed through chloride form of an anion exchange resin (*Merck*). The yellow solution was evaporated to obtain amorphous **17** (25 mg, 71 %). – UV (MeOH): λ max (log ε) = 393 (3.64), 320 (4.23), 274 (4.33), 243 (4.16), 228 nm (4.22). – ^1H-NMR ($CDCl_3$-TFA): δ (ppm) = 3.03 (s; 3H, 13-CH_3), 3.25 (br. t; 2H, H-5), 4.00 and 4.07 (2 × s; 6H, OCH_3), 4.78 (br. t; 2H, H-6), 7.07 (s; 1H, H-4), 7.13 (d, J = 9 Hz; 1H, H-2), 7.48 (s; 1H, H-9), 7.75 (d, J = 9 Hz; 1H, arom. H), 7.85 (d, J = 9 Hz; 1H, arom. H), 8.27 (d, J = 9 Hz; 1H, H-12), 9.23 (s; 1H, H-8).

1-Ethylidene-1,2,3,4-tetrahydro-6-methoxy-2-(3-methoxybenzoyl)-3-methylisoquinoline (**12**).

300 mg (1.48 mmol) of 1-ethyl-3,4-dihydro-6-methoxy-3-methylisoquinoline **(9)** was condensed with 252 mg (1.48 mmol) of 3-methoxybenzoyl chloride in benzene in the presence of 180 mg (1.78 mmol) Et_3N as described above. The crude product was purified by CC (SiO_2, CH_2Cl_2 + 2–4 % MeOH) to obtain the oily enamide **12** (400 mg, 80 %). – UV (MeOH): λ max (log ε) = 260 (4.30), 209 nm (4.51). – IR: 1620 cm^{-1} (C=O). – ^1H-NMR ($CDCl_3$): δ (ppm) = 1.20 (d, J = 7 Hz; 3H, $C\underline{H}_3CH{=}$), 2.62 (d, J = 16 Hz; 1H, H-4), 3.37 (dd, J = 16 Hz and 6 Hz; 1H, H-4), 3.65 and 3.80 (2 × s; 6H, OCH_3), 5.30 (mc; 1H, H-3), 5.75 (q, J = 7Hz; 1H, $CH_3C\underline{H}{=}$), 6.60–7.50 (m, 7H, arom. H).

Photocyclization of **12**.

1 g (2.97 mmol) **12** in 200 ml dry benzene was irradiated under N_2 for 2 h as described above. The crude product was subjected to CC (SiO_2, CH_2Cl_2/3 % MeOH). The major band consisted of the 8-oxoprotoberberines **18** and **19** (210 mg, 21 %). Later fractions were combined and subjected to prep. tlc (SiO_2, 50 % EtOAc-hexane). The lower band (R_f 0.59) yielded the 10-methoxy isomer **20** (85 mg, 8.5 %), the higher band (R_f 0.68) afforded the 12-methoxy isomer **21** (78 mg, 7.8 %).

18 and **19**. – UV (qual.): λ max = 310; 212 nm. – IR: 1635 cm^{-1} (C=O). – ^1H-NMR ($CDCl_3$): δ (ppm) = 0.9–1.20 (m, 6-CH_3, 13-CH_3), 3.83, 3.87 and 3.90 (3 × s; OCH_3), 4.82 (mc; H-6), 5.27 (mc; H-14), 6.70–7.80 (m; 6H, arom. H). – MS (70 eV): m/z = 337 (61, $M^{+\cdot}$), 336 (29), 335 (49), 322 (20), 320 (47), 235 (20), 176 (29, $C_{11}H_{14}NO^+$), 162 (94, $C_{10}H_{10}O_2^{\ +}$), 135 (100, $C_8H_7O_2^{\ +}$). – HR-MS: $C_{21}H_{23}NO_3$ calc. 337.16778 found 337.16692.

7,8-Dihydro-3,10-dimethoxy-6,13-dimethyl-8-oxoprotoberberine (**20**).

UV (MeOH): λ max (log ε) = 372 (sh, 3.70), 356 (sh, 3.84), 318 (4.18), 252 (sh, 4.46), 219 nm (4.46). – IR: 1635 cm^{-1} (C=O). – ^1H-NMR ($CDCl_3$): δ (ppm) = 1.05 (d, J = 7 Hz; 3H, 6-CH_3), 2.55 (s; 3H, 13-CH_3), 2.73 (dd, J = 15 and 2.5 Hz; 1H, H-5), 3.13 (dd, J = 15 and 5 Hz; 1H, H-5), 3.80 and 3.85 (2 × s; 6H, OCH_3), 5.50 (mc; 1H, H-6), 6.50–7.80 (m; 5H, arom. H), 8.00 (d, J = 3 Hz; 1H, H-9). – MS (70 eV): m/z = 335 (47, $M^{+\cdot}$), 320 (75), 305 (12), 277 (15), 135 (100, $C_8H_7O_2^{\ +}$). – HR-MS: $C_{21}H_{21}NO_3$ calc. 335.15213 found 335.15192.

7,8-Dihydro-3,12-dimethoxy-6,13-dimethyl-8-oxoprotoberberine (**21**).

UV (MeOH): λ max (log ε) = 375 (3.90), 359 (4.02), 343 (3.97), 325 (4.02), 255 (4.07), 215 nm (4.43). – IR: 1640 cm^{-1} (C=O). – ^1H-NMR ($CDCl_3$): δ (ppm) = 0.99 (d, J = 7 Hz; 3H, 6-CH_3), 2.68 (s; 3H, 13-CH_3), 3.07 (dd, J = 15 and 5 Hz; 1H, H-5), 3.85 and 3.88 (2 × s; 6H, OCH_3), 5.57 (mc; 1H, H-6), 6.77–7.77 (m; 5H, arom. H), 8.17 (dd, J_o = 8 Hz, J_m = 2 Hz; 1H, H-9). – MS (70 eV): m/z = 335 (100, $M^{+\cdot}$), 320 (78), 135 (16, $C_8H_7O_2^{\ +}$). – HR-MS: $C_{21}H_{21}NO_3$ calc. 335.15213 found 335.15238.

7,8,13,14-Tetrahydro-3,10-dimethoxy-6,13-dimethylprotoberberine (**22**) *and 7,8,13,14-tetrahydro-3,12-dimethoxy-6,13-dimethylprotoberberine* (**23**).

A mixture of **18** and **19** (100 mg, 0.30 mmol) was reduced with $LiAlH_4$ (200 mg) in refluxing absol. THF (10 ml). After initial work-up the resulting mixture was separated by prep.-tlc (SiO_2, 10 % EtOAc in hexane) to yield **22** and **23**.

22: (R_f 0.33, 23 mg, 24 %). – m. p. = 125° (MeOH). – UV (MeOH): λ max (log ε) = 286 (3.65), 278 (3.67), 208 nm (4.38). – IR: 2820, 2785 (*Bohlmann* bands) cm^{-1}. – ^1H-NMR (250 MHz, $CDCl_3$): δ (ppm) = 0.92 (d, J = 6.9 Hz; 3H, 13-CH_3), 1.31 (d, J = 6 Hz; 3H, 6-CH_3), 2.79 (dd, J_{gem} = 15.6 Hz, J_{vic} = 11.8 Hz; 1H, H-5 axial), 3.22 (qd, J = 6.9 Hz and 3 Hz; 1H, H-13), 3.44 and 4.27 (AB, J = 15 Hz; 2H, H-8), 3.79 and 3.80 (2 × s; 6H, OCH_3), 3.80 (d; J = 3 Hz, 1H, H-14), 6.60 (d, J = 2.6 Hz; 1H, H-4), 6.63 (d, J = 2.6 Hz; 1H, H-9), 6.76 (dd, J_o = 8.4 Hz, J_m = 2.6 Hz; 1H, H-11), 6.78 (dd, J_o = 8.4 Hz, J_m = 2.6

Hz; 1H, H-2), 7.09 (d, J = 8.4 Hz; 1H, arom. H), 7.11 (d, J = 8.4 Hz; 1H, arom. H). – MS (70 eV): m/z = 323 (27, $M^{+\cdot}$), 308 (15), 176 (10, $C_{11}H_{14}NO^+$), 174 (18, $C_{11}H_{12}NO^+$), 148 (100, $C_{10}H_{12}O^+$). – $C_{21}H_{25}NO_2$ (323.4) calc. C 78.0 H 7.74 found C 77.8 H 7.64.
23: (R_f 0.41, 23 mg, 24 %). – UV (MeOH): λ max (log ε) = 283 (3.65), 278 nm (3.80). – IR: 2820, 2795 (*Bohlmann* bands) cm^{-1}. – ^1H-NMR (250 MHz, $CDCl_3$): δ (ppm) = 0.91 (d, J = 6.6 Hz, 3H, 13-CH_3), 1.31 (d, J = 6 Hz; 3H, 6-CH_3), 2.81 (dd, J_{gem} = 15 Hz, J_{vic} = 11.5 Hz; 1H, H-5 axial), 3.45 and 4.31 (ABq, J = 15 Hz; 2H, H-8), 3.46 (qd, J = 6.6 Hz, 3 Hz; 1H, H-13), 3.73 (br; 1H, H-14), 3.80 and 3.85 (2 × s; 6H, OCH_3), 6.60 (d, J = 2.4 Hz; 1H, H-4), 6.71 (d, J = 8 Hz; 2H, arom. H), 6.78 (dd, J_o = 9 Hz, J_m = 2.2 Hz; 1H, H-2), 7.13 (t, J = 8 Hz; 1H, H-10), 7.19 (d, J = 9 Hz; 1H, arom. H). – MS (70 eV): m/z = 323 (88, $M^{+\cdot}$), 308 (35), 176 (26, $C_{11}H_{14}NO^+$), 174 (71, $C_{11}H_{12}NO^+$), 148 (59, $C_{10}H_{12}O^+$), 133 (100, $C_9H_9O^+$). – m. p. (HCl salt) = 215–217° (acetone). $C_{21}H_{26}NO_2 \cdot Cl \times 0.5\ H_2O$ (368.5) calc. C 68.4 H 7.33 N 3.8 found C 68.3 H 7.45 N 3.8.

3,10-Dimethoxy-6,13-dimethylprotoberberine Chloride (24).

25 mg (0.08 mmol) **22** in 10 ml EtOH was refluxed with 50 mg (0.39 mmol) I_2 for 16 h. Work-up and ion exchange as described above yielded the amorphous yellow solid **24** (25 mg, 72 %). – UV (MeOH): λ max (log ε) = 393 (3.69), 320 (4.29), 275 (4.40), 240 (4.27), 228 (4.32) nm. – ^1H-NMR ($CDCl_3$-TFA): δ (ppm) = 1.48 (d, J = 7 Hz; 3H, 6-CH_3), 3.07 (d; J = 15 Hz, 1H, H-5),3.05 (s; 3H, 13-CH_3), 3.60 (dd; J = 15 and 4 Hz, 1H, H-5), 4.02 and 4.07 (2 × s; 6H, OCH_3), 5.17 (mc; 1H, H-6), 7.07 (s; 1H, H-4), 7.15 (d, J = 9 Hz; 1H, H-2), 7.50 (d, J = 3 Hz; 1H, H-9), 7.77 (d, J = 9 Hz; 1H, H-1), 7.85 (dd, J_o = 9 Hz, J_m = 3 Hz; 1H, H-11), 8.27 (d, J = 9 Hz; 1H, H-12), 9.22 (s; 1H, H-8).

Reduction of **20** *to 7,8,13,14-tetrahydro-3,10-dimethoxy-6,13-dimethylprotoberberine* (25).

130 mg (0.39 mmol) of **20** was reduced with $LiAlH_4$ (250 mg) in refluxing absol. THF (25 ml) and the product further reduced with $NaBH_4$ (100 mg) in MeOH (25 ml). Work-up followed by prep. tlc (SiO_2, 10 % EtOAc in hexane) yielded **25** (R_f 0.32, oil, 40 mg, 31 %). – UV (MeOH): λ max (log ε) = 285 (3.66), 277 (3.74), 223 (4.31), 208 nm (4.31). – IR ($CHCl_3$): 2800, 2770 (*Bohlmann bands*) cm^{-1}. – ^1H-NMR (250 MHz, $CDCl_3$): δ (ppm) = 0.90 (d, J = 6.9 Hz; 3H, 13-CH_3), 0.95 (d, J = 6.2 Hz; 3H, 6-CH_3), 2.49 (dd, J_{gem} = 15.2 Hz, J_{vic} = 1.6 Hz; 1H, H-5 equatorial), 3.17 (qd, J = 6.9 and 3.2 Hz; 1H, H-13), 3.23 (dd, J_{gem} = 15.2 Hz, J_{vic} = 4.5 Hz; 1H, H-5 axial), 3.78 and 3.80 (2 × s; 6H, OCH_3), 3.90 (d, J = 3.2 Hz; 1H, H-14), 4.02 (d, J = 15 Hz; 1H, H-8), 6.61 (d, J = 2.6 Hz; 1H, H-4), 6.62 (d, J = 2.1 Hz; 1H, H-9), 6.75 (dd, J_o = 8.4 Hz, J_m = 2.6 Hz; 1H, H-2), 6.77 (dd, J_o = 8.4 Hz, J_m = 2.1 Hz; 1H, H-11), 7.06 (d, J = 8.4 Hz; 1H, arom. H), 7.09 (d, J = 8.4 Hz; 1H, arom. H). – MS (70 eV): m/z = 323 (22, $M^{+\cdot}$), 308 (11), 194 (27), 163 (100), 148 (78, $C_{10}H_{12}O^+$), 133 (31, $C_9H_9O^+$), 119 (25).

Reduction of **21** *to 7,8,13,14-tetrahydro-3,12-dimethoxy-6,13-dimethylprotoberberine* (26).

150 mg (0.45 mmol) of **21** was reduced with $LiAlH_4$ (250 mg) and $NaBH_4$ (100 mg) as described above. The product was subjected to prep. tlc (SiO_2, 10 % EtOAc in hexane). The major band (R_f 0.36) was collected to obtain amorphous **26** (30 mg, 21 %). – UV (MeOH): λ max (log ε) = 280 (3.41), 277 (3.58), 218 nm (4.15). – IR ($CHCl_3$): 2810, 2780 (*Bohlmann* bands) cm^{-1}. – ^1H-NMR (250 MHz, $CDCl_3$): δ (ppm) = 0.88 (d, J = 6.2 Hz; 3H, 13-CH_3), 0.95 (d, J = 6.1 Hz; 3H, 6-CH_3), 2.49 (dd, J = 15 and 1 Hz; 1H, H-5 equatorial), 3.30 (dd, J_{gem} = 15 Hz, J_{vic} = 4.7 Hz; 1H, H-5 axial), 3.80 and 3.84 (2 × s; 6H, OCH_3), 4.04 (d, J = 15.3 Hz; 1H, one of H-8), 6.63 (d, J = 2.2 Hz; 1H, H-4), 6.70 (d, J = 7.9 Hz; 2H, H-9 and H-11), 6.77 (dd, J_o = 8.7 Hz, J_m = 2.2 Hz; 1H, H-2), 7.12 (t, J = 7.9 Hz, 1H, H-10), 7.16 (d, J = 8.7 Hz; 1H, H-1). – MS (70 eV): m/z = 323 (87, $M^{+\cdot}$), 308 (48), 194 (25), 176 (34, $C_{11}H_{14}NO^+$), 174 (62, $C_{11}H_{12}NO^+$), 148 (84, $C_{10}H_{12}O^+$), 133 (100, $C_9H_9O^+$).

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