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3,10-Dimethoxyprotoberberines

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Protoberberines with the unusual 3,10-dimethoxy substitution are synthesized by photocyclization of Eand 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 Eund 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 (È 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 N₂ 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.

LiAlH₄ 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 CDCl₃ 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 protons⁵⁻⁸⁾. The *Bohlmann* bands at 2770 and 2810 cm⁻¹ in Scheme 2



13: $R^1 = R^3 = H$, $R^2 = OCH_3$, X = O14: $R^1 = R^2 = H$, $R^3 = OCH_3$, X = O15: $R^1 = R^3 = H$, $R^2 = OCH_3$, $X = H_2$ 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 = O19: $R^1 = CH_3$, $R^2 = H$, $R^3 = OCH_3$, $X = H_2$ 23: $R^1 = CH_{3equat.}$, $R^2 = OCH_3$, $R^3 = H$, $X = H_2$ 25: $R^1 = CH_{3equat.}$, $R^2 = H$, $R^3 = OCH_3$, $X = H_2$ 25: $R^1 = CH_{3equat.}$, $R^2 = H$, $R^3 = OCH_3$, $X = H_2$ 26: $R^1 = CH_{3axial}$, $R^2 = H$, $R^3 = OCH_3$, $X = H_2$



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



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.

I₂-oxidation of 15 followed by ion exchange to the chloride form yielded the protoberberine 17 in 71 % yield. Its ¹H-NMR-spectrum in CDCl₃ and TFA exhibits the 13methyl singlet at $\delta = 3.03$ ppm. The UV-spectrum (see Experim. Part) supports the protoberberine structure 17. I₂-oxidation of the 3,12-dimethoxy analogue 16 did not yield any well defined product¹¹).

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.

LiAlH₄ 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 LiAlH₄ followed by NaBH₄ to obtain 25 and 26 in 31 and 21 % yield, respectively. An interesting aspect of the 250 MHz ¹H-NMRspectrum of 25 in CDCl₃ is the axial C-5 proton appearing as a doublet of doublets at δ = 3.23 ppm (J_{gen} = 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 ¹H-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: (CHCl₃, or KBr pellets if not mentioned otherwise): Beckman Acculab 3. – ¹H-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 1¹²), 10 ml freshly distilled nitromethane and 4 g NH₄OAc 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 LiAlH₄ 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 LiAlH₄. After completion of the addition of LiAlH₄, 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 LiAlH₄ 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); Lit¹⁴): b. p. 122–123°/7 mm. Yield: 6.3 g (75 %).

$N-[\beta-(3-Methoxyphenyl)ethyl]propanamide$ (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 (Na₂SO₄) and purified by CC (SiO₂, 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). – ¹H-NMR (CDCl₃): δ (ppm) = 1.20 (t; 3H; CH₂-CH₃), 2.10 (q; J = 7.5 Hz; 2H; CH₂-CH₃) 2.65 (t; J = 7.5 Hz; 2H, Ph-CH₂), 3.35 (m; 2H; CH₂-NH), 3.75 (s; 3H; OCH₃), 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 CH₃CN with 5 ml POCl₃ (freshly distilled) for 2 h under N₂. The mixture was cooled and the solvents removed under vacuum. The residue was taken up in CH₂Cl₂ and shaken with dil. NH₃ (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. – C₁₂H₁₅NO (189.3) Calc. C 76.1 H 8.00 N 7.4 Found C 74.6°) H 7.88 N 7.3. – UV (MeOH): $\lambda \max (\log \varepsilon) = 270 \operatorname{nm} (4.03)$; –

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

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

A suspension of 10 g 1, 4.1 g NaOAc (free of water), 3.4 g $CH_3NH_2 \times HCl$ 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 (CDCl₃): δ (ppm) = 2.40 (s; 3H, CH₃), 3.85 (s; 3H, OCH₃), 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°, $5 \cdot 10^{-2}$ mm (Kugelrohr); Lit.¹⁶): 124–126°, 11 mm. – ¹H-NMR-data correspond to those reported¹⁷).

$N-[a-Methyl-\beta-(3-methoxyphenyl)ethyl]propanamide (7)$

7 was prepared analogously to 6. – Yield: 5.1 g (75 %); oil, b. p. 96°, $5 \cdot 10^{-2}$ mm (Kugelrohr). C₁₃H₁₉NO₂ (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 (CDCl₃): δ (ppm) = 1.05–1.35 (m; 6H; CH₃), 2.10 (q; J = 8.0 Hz; 2H; CH₂–CH₃), 2.65 (d; J = 8 Hz; 2H; Ph–CH₂), 3.75 (s; 3H; OCH₃), 4.05–4.50 (m; 1H; CH–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 POCl₃ to 5.2 g 7 in 25 ml CH₃CN 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 (SiO₂, 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). – 1R: 1630 cm⁻¹ (C=N). – ¹H-NMR (CDCl₃): δ (ppm) = 1.05–1.35 (m; 6H; CH₃), 2.55–2.80 (m; 4H; CH₂–CH₃/H-4), 3.40–3.70 (m; 1H; H-3), 3.75 (s; 3H, OCH₃), 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 $\frac{1}{2}$ h, then 50 ml benzene were added. The benzene suspension was washed with water (25 ml), 3N HCl (2 × 25 ml), water (25 ml), NaHCO₃ solution (2 × 25 ml), again with water (25 ml), dried (Na₂SO₄) and evaporated. The residue was separated by CC (SiO₂, CH₂Cl₂-MeOH). The fraction collected with 3 % MeOH–CH₂Cl₂ was pure enamide 10 (600 mg, 22 %). Later fractions were purified by prep.-tlc (SiO₂/Et₂O). The major band (R_f == 0.72) was collected to provide enamide 11 (100 mg, 4 %).

Enamide 10 could not be crystallized. – UV (MeOH): $\lambda \max(\log \varepsilon) = 260$ (4.18) and 210 nm (4.37). – IR (CHCl₃): 1625 cm⁻¹ (C=O). – ¹H-NMR (CDCl₃): δ (ppm) = 1.30 (br. d, J = 7 Hz, 3H, CH₃CH=), 2.6–3.4 (m; 3H, H-4, H-3), 3.70 and 3.80 (2 × s; 6H, OCH₃), 5.1 (br. s.; 1H, H-3), 5.65 (br. q.; 1H, CH₃CH=), 6.60–7.50 (m; 7H, arom. H). – MS (70 eV): m/z = 323 (83, M⁺⁻), 308 (47), 294 (99), 188 (34, C₁₂H₁₄NO⁺), 135 (100, C₈H₇O₂⁺), 107 (66, C₇H₇O⁺), 92 (36, C₆H₄O⁺).

Enamide 11 also could not be crystallized. – UV (MeOH): $\lambda \max(\log \varepsilon) = 251(3.83) \operatorname{and} 204 \operatorname{nm} (4.24)$. – IR (CHCl₃): 1620 cm⁻¹ (C=O). – ¹H-NMR (CDCl₃): δ (ppm) = 1.60 (d, J = 7 Hz; 3H, CH₃CH=), 2.95 (t, J = 6 Hz; 2H, H-4), 3.75 and 3.85 (2 × s; 6H, OCH₃), 4.00 (t, J = 6 Hz; 2H, H-3), 5.10 (q, J = 7 Hz; 1 H, CH₃CH=), 6.70–7.40 (m, 7H, arom. H). – MS (70 eV): m/z = 323 (21, M⁺⁺), 322 (16), 321 (19), 308 (12), 294 (19), 188 (20, C₁₂H₁₄NO⁺), 173 (100, C₁₁H₁₁NO⁺), 135 (84, C₈H₇O₂⁺), 107 (30, C₇H₇O⁺).

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 N₂ 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 N₂. The products were purified by CC (SiO₂, CH₂Cl₂-MeOH and again SiO₂, Et₂O) 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 (CHCl₃): 1645 cm⁻¹ (C=O). – MS (70 eV): m/z = 323 (100, M^{+.}), 294 (28), 280 (32), 235 (21), 162 (81, C₁₀H₁₂NO⁺ and C₁₀H₁₀O₂⁺).

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 (SiO₂, 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, CDCl₃): δ (ppm) = 0.93 (d, J = 6.9 Hz; 3H, 13-CH₃), 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, OCH₃), 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^{+.}), 294 (21), 162 (12, C₁₀H₁₂NO⁺), 160 (8, C₁₀H₁₀NO⁺), 148 (100, C₁₀H₁₂O⁺). – C₂₀H₂₃NO₂ (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_c 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, CDCl₃): δ (ppm) = 0.91 (d, J = 6.6 Hz; 3H, 13-CH₃), 3.65 and 4.04 (AB, J = 15 Hz; 2H, H-8), 3.80 and 3.85 (2 × s; 6H, OCH₃), 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, J₀ = 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⁺⁺), 308 (51), 294 (59), 162 (26, C₁₀H₁₂NO⁺), 160 (24, C₁₀H₁₀NO⁺), 148 (66, C₁₀H₁₂O⁺), 133 (95, C₉H₉O⁺). – C₂₀H₂₄NO₂ · Cl × 0.5 H₂O (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) I₂ for 16 h. The mixture was cooled, the solvent evaporated and excess I₂ decomposed by saturated Na₂S₂O₃ solution. The solid formed was washed with H₂O, 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 (CDCl₃-TFA): δ (ppm) = 3.03 (s; 3H, 13-CH₃), 3.25 (br. t; 2H, H-5), 4.00 and 4.07 (2 × s; 6H, OCH₃), 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) Et₃N as described above. The crude product was purified by CC (SiO₂, CH₂Cl₂ + 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 (CDCl₃): δ (ppm) = 1.20 (d, J = 7 Hz; 3H, CH₃CH=), 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, OCH₃), 5.30 (mc; 1H, H-3), 5.75 (q, J = 7Hz; 1H, CH₃CH=), 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 (SiO₂, CH₂Cl₂/3 % MeOH). The major band consisted of the 8-oxoprotoberberines 18 and 19 (210 mg, 21 %). Later fractions were combined and subjected to prep. tlc (SiO₂, 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.): $\lambda \max = 310$; 212 nm. – IR: 1635 cm⁻¹ (C=O). – ¹H-NMR (CDCl₃): δ (ppm) = 0.9–1.20 (m, 6-CH₃, 13-CH₃), 3.83, 3.87 and 3.90 (3 × s; OCH₃), 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⁺⁺), 336 (29), 335 (49), 322 (20), 320 (47), 235 (20), 176 (29, C₁₁H₁₄NO⁺), 162 (94, C₁₀H₁₀O₂⁺), 135 (100, C₈H₇O₂⁺). – HR-MS: C₂₁H₂₃NO₃ 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 (CDCl₃): δ (ppm) = 1.05 (d, J = 7 Hz; 3H, 6-CH₃), 2.55 (s; 3H, 13-CH₃), 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, OCH₃), 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⁺⁺), 320 (75), 305 (12), 277 (15), 135 (100, C₈H₇O₂+). – HR-MS: C₂₁H₂₁NO₃ calc. 335.15213 found 335.15192.

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

UV (MeOH): $\lambda \max (\log \epsilon) = 375 (3.90), 359 (4.02), 343 (3.97), 325 (4.02), 255 (4.07), 215 nm (4.43). - IR: 1640 cm⁻¹ (C=O). - ¹H-NMR (CDCl₃): <math>\delta$ (ppm) = 0.99 (d, J = 7 Hz; 3H, 6-CH₃), 2.68 (s; 3H, 13-CH₃), 3.07 (dd, J = 15 and 5 Hz; 1H, H-5), 3.85 and 3.88 (2 × s; 6H, OCH₃), 5.57 (mc; 1H, H-6), 6.77-7.77 (m; 5H, arom. H), 8.17 (dd, J₀ = 8 Hz, J_m = 2 Hz; 1H, H-9). - MS (70 eV): m/z = 335 (100, M^{+.}), 320 (78), 135 (16, C₈H₂O₃⁺). - HR-MS: C₂₁H₂₁NO₃ calc. 335.15213 found 335.15238.

7,8,13,14-Tetrahydro-3,10-dimethoxy-6,13-dimethylprotoberberine (22) and 7,8,13,14-tetrahydro-3,12dimethoxy-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 (SiO₂, 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, CDCl₃): δ (ppm) = 0.92 (d, J = 6.9 Hz; 3H, 13-CH₃), 1.31 (d, J = 6 Hz; 3H, 6-CH₃), 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, OCH₃), 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⁺⁺), 308 (15), 176 (10, $C_{11}H_{14}NO^+$), 174 (18, $C_{11}H_{12}NO^+$), 148 (100, $C_{10}H_{12}O^+$). – $C_{21}H_{22}NO_{23}$ (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, CDCl₃): δ (ppm) = 0.91 (d, J = 6.6 Hz, 3H, 13-CH₃), 1.31 (d, J = 6 Hz; 3H, 6-CH₃), 2.81 (dd, J_{gen} = 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, OCH₃), 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^{+.}), 308 (35), 176 (26, C₁₁H₁₄NO⁺), 174 (71, C₁₁H₁₂NO⁺), 148 (59, C₁₀H₁₂O⁺), 133 (100, C₉H₉O⁺). – m. p. (HCl salt) = 215–217° (acetone). C₂₁H₂₆NO₂ · Cl × 0.5 H₂O (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 (CDCI₃-TFA): δ (ppm) = 1.48 (d, J = 7 Hz; 3H, 6-CH₃), 3.07 (d; J = 15 Hz, 1H, H-5), 3.05 (s; 3H, 13-CH₃), 3.60 (dd; J = 15 and 4 Hz, 1H, H-5), 4.02 and 4.07 (2 × s; 6H, OCH₃), 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, J₀ = 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 LiAlH₄ (250 mg) in refluxing absol. THF (25 ml) and the product further reduced with NaBH₄ (100 mg) in MeOH (25 ml). Work-up followed by prep. tlc (SiO₂, 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 (CHCl₃): 2800, 2770 (*Bohlmann bands*) cm⁻¹. – ¹H-NMR (250 MHz, CDCl₃): δ (ppm) = 0.90 (d, J = 6.9 Hz; 3H, 13-CH₃), 0.95 (d, J = 6.2 Hz; 3H, 6-CH₃), 2.49 (dd, J_{gen} = 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_{gen} = 15.2 Hz, J_{vic} = 4.5 Hz; 1H, H-5 exial), 3.78 and 3.80 (2 × s; 6H, OCH₃), 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⁺⁺), 308 (11), 194 (27), 163 (100), 148 (78, C₁₀H₁₂O⁺), 133 (31, C₉H₉O⁺), 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 LiAlH₄ (250 mg) and NaBH₄ (100 mg) as described above. The product was subjected to prep. tlc (SiO₂, 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 (CHCl₃): 2810, 2780 (*Bohlmann* bands) cm⁻¹. – ¹H-NMR (250 MHz, CDCl₃): δ (ppm) = 0.88 (d, J = 6.2 Hz; 3H, 13-CH₃), 0.95 (d, J = 6.1 Hz; 3H, 6-CH₃), 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, OCH₃), 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⁺⁺), 308 (48), 194 (25), 176 (34, C₁₁H₁₄NO⁺), 174 (62, C₁₁H₁₂NO⁺), 148 (84, C₁₀H₁₂O⁺), 133 (100, C₉H₉O⁺).

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[Ph 284]