Chemical Transformation of Protoberberines. XV.[1] A Novel and Efficient Method for the Introduction of Alkyl Groups on the C-13 Position in the Protoberberine Skeleton[2]

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The Wittig reaction of 8,14-cycloberbin-13-ones (4), derived from the corresponding protoberberine alkaloids (2), with methylenetriphenylphosphorane afforded 13-methylene-8,14-cycloberbines (5). Irradiation of 5 with a 100 W high pressure mercury lamp effected photochemically-induced electrocyclic fission of the aziridine ring to yield 13-methylberberine (1a), dehydrocorydaline (1b), and corysamine (1c) in high yield. Introduction of ethyl and propyl groups on the C-13 position in 2 was also conveniently achieved *via* photochemical reaction of the corresponding alkylidene derivatives (8 and 9, respectively).

Keywords Wittig reaction; 8,14-cycloberbin-13-one; irradiation; 13-methylprotoberberine; (±)-thalictricavine; (±)-corydaline; (±)-tetrahydrocorysamine

In connection with our program aiming at a biomimetic synthesis of corydalic acid methyl ester,[3] a representative 3-arylisoquinoline alkaloid,[4,5] we required 13-methylprotoberberine (**1c**) as a starting material for our strategy. Although 13-methylprotoberberines (**1**) had been prepared by conventional means,[6-11] the direct introduction of a methyl group on the C-13 position in the protoberberine skeleton attracted us because of the ready availability of the starting protoberberines (**2**). There are two methods[12,13] available to date for the introduction of methyl and other alkyl groups on the C-13 position in **2**. The first procedure[12] involves exposure of **2** to acetone in the presence of base, followed by treatment with alkylating reagents in a sealed tube. One of the principal drawbacks to this method is concomitant formation of the starting protoberberines (**2**) and/or of *N*-alkylated compounds, removal of which is not always easy since these undesired quaternary bases have chemical properties similar to those of **1**. Furthermore, the yields are generally unsatisfactory. The second procedure[13] is based on the reaction of the 7,8-dihydro derivative of **2** with formaldehyde in acetic acid. This condition is much milder than the first one and affords **1a** in a moderate yield. This sequence, however, lacks generality because it cannot be applied to the introduction of substituents other than a methyl group. The dihydro derivative of **2a** actually did not react with acetaldehyde at all under the same conditions.

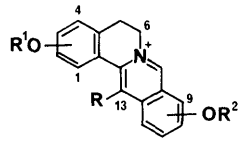
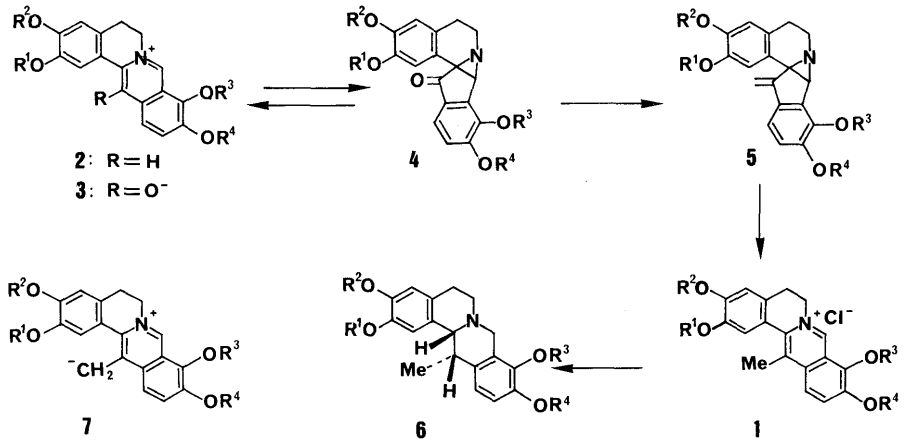


Fig. 1

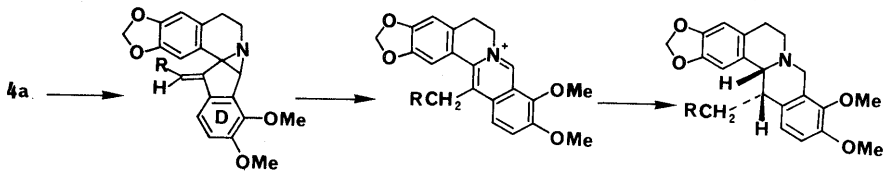
Early studies[14] from this laboratory demonstrated an efficient reversible photochemical valence bond isomerization between berberinephenolbetaines (**3**) and the 8,14-cycloberbin-13-ones (**4**). We now envisioned that the Wittig reaction of the 8,14-cycloberbin-13-ones (**4**) with proper phosphoranes should give the corresponding alkylidene derivatives without difficulty, and the latter would in turn undergo the photochemically induced aziridine cleavage[15,16] to produce the 13-alkylprotoberberines. In addition, this conversion could be expected to be irreversible in a protic solvent because the resulting anion on the 13-alkyl group in **7** would be protonated immediately by the solvent. The successful execution of our plan is detailed below.

8,14-Cycloberbin-13-one (**4a**),[14a,b] easily synthesized from berberine (**2a**) by three steps *via* **3a**, was treated with methylenetriphenylphosphorane[17] in refluxing dry tetrahydrofuran (THF) to give the exomethylene derivative (**5a**) in 95% yield. The structure of **5a** was elucidated from its spectral data (see Experimental). On irradiation with a



a: $R^1+R^2=CH_2$, $R^3=R^4=Me$ b: $R^1=R^2=R^3=R^4=Me$ c: $R^1+R^2=R^3+R^4=CH_2$

Chart 1



8: R=Me
9: R=Et

10: R=Me
11: R=Et

12: R=Me
13: R=Et

Chart 2

100 W high pressure mercury lamp through a Pyrex filter in a stream of nitrogen in aqueous ethanol at −20 °C, 13-methylene-8,14-cycloberbine (**5a**) underwent photochemically induced electrocyclic reaction of the vinylaziridine ring in a disrotatory manner[15,16] to produce 13-methylberberine chloride (**1a**) in 80% yield after exposure to hydrogen chloride. The structure of **1a** was apparent from the diagnostic signals at δ 9.94 (1H, s) and 2.94 (3H, s) due to the C-8 proton and C-13 methyl protons in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum. The synthetic 13-methylberberine chloride (**1a**) was identical with an authentic sample[12f] by comparison of their spectra. When irradiation was carried out with a 20 W low pressure mercury lamp instead of a high pressure lamp, 13-methylberberine (**1a**) was also obtained, but the yield was somewhat lower (57%). On the other hand, **5a** was stable in refluxing aqueous ethanol for a prolonged period without any irradiation and could be recovered completely. This result is in accord with our prediction that the thermal disconnection of the vinylaziridine ring in **5a** cannot be attained because of the extremely strained intermediate which would result from conrotatory rotation of the four electron system.[15,16] Similar treatment of **4b** and **4c**, accessible from palmatine (**2b**)[14c] and coptisine (**2c**),[14d] with methylenetriphenylphosphorane in refluxing dry THF afforded the corresponding 13-methylene-8,14-cycloberbines (**5b** and **5c**) in 97 and 94% yields, respectively. The exomethylene compounds (**5b** and **5c**) were subsequently irradiated under the same conditions as for **5a** to furnish dehydrocorydaline (**1b**) and corysamine (**1c**) in 85 and 86% yields, respectively. The synthetic **1b** and **1c** were found to be identical with natural and authentic specimens,[12b] respectively. The 13-methylprotoberberines (**1**) were reduced with sodium borohydride[12] ($NaBH_4$) to yield the corresponding (±)-thalictricavine (**6a**, 95%), (±)-corydaline (**6b**, 97%), and (±)-tetrahydrocorysamine (**6c**, 94%).

Our endeavor was next concentrated on the introduction of bulkier ethyl and propyl groups on the C-13 position in the protoberberine skeleton in order to make sure that the newly developed photochemical sequence has generality. The Wittig reaction of **4a** with ethylidenetriphenylphosphorane[18] or triphenylpropylidenephosphorane[19] in dry refluxing THF provided (*Z*)-13-ethylidene-8,14-cycloberbine (**8**, 96%) or (*Z*)-13-propylidene-8,14-cycloberbine (**9**, 92%) respectively, as a single stereoisomer. The stereochemistry of **8** and **9** was determined by careful consideration of the ^{1}H-NMR spectra. The vinylic protons in **5a** appeared at δ 5.77 and 5.16 ppm. This large difference in chemical shift between the two vinylic protons may be attributed mainly to the diamagnetic anisotropic effect of the benzene ring (ring D). Each vinylic proton in **8** and **9** resonated at δ 6.19 and 6.08 ppm, both of which are in good agreement with the chemical shift value of the lower field vinylic proton (δ 5.77 ppm) rather than that of the higher field vinylic proton (δ 5.16 ppm) in **5a**. Therefore, the stereochemistry of **8** and **9** could be established as (*Z*). This stereochemical assignment was further supported by examination of molecular models, which indicated that no characteristic steric repulsion of the alkylidene group with other functions would be expected in the (*Z*)-isomer, while a serious nonbonded interaction between the alkyl substituent of the alkylidene group and the C-12 proton on the benzene ring (ring D) should occur in the (*E*)-isomer. Exclusive formation of the (*Z*)-isomer should reflect a large energy difference between the (*Z*)- and (*E*)-isomers.

13-Ethylidene- and 13-propylidene-8,14-cycloberbines (**8** and **9**), thus obtained, were transformed into 13-ethyl and 13-propylberberine (**10**[12d,f] and **11**[12f]) in 42 and 86% yields, respectively, by similar photolysis. Unfortunately no improvement of the yield for **10** was realized after several attempts under various conditions. It is not obvious why only the ethylidene derivative (**8**) gave a rather low yield compared to the other cases. The structures of **10** and **11** were easily elucidated from their spectral evidence (see Experimental). Reduction of **10** and **11** afforded the corresponding tetrahydro derivatives (**12** and **13**) in 85 and 82% yields, respectively. It is noteworthy that our new method provides the desired 13-methylprotoberberines without any contamination with the starting protoberberine (**2**) and/or other inseparable quaternary bases.

In summary, we have succeeded in an efficient introduction of alkyl groups on the C-13 position in the protoberberine skeleton through the Wittig reaction of a versatile intermediate, 8,14-cycloberbin-13-one, followed by photochemical collapse of the aziridine ring. This procedure provides a general method for the synthesis of 13-methylprotoberberine alkaloids, since berberine (**2a**) is commercially available and is easily converted into palmatine (**2b**)[14c] and coptisine (**2c**)[14d] in two steps.

Experimental

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were measured with a JASCO A-102 spectrometer, mass spectra (MS) with a Hitachi M-80 mass spectrometer, ultraviolet (UV) spectra with a Hitachi 323 spectrometer in MeOH, and ^{1}H-NMR spectra with a JEOL FX-100 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard unless otherwise stated. Irradiation was carried out with a 100 W high pressure mercury lamp with a Pyrex filter (Riko Kagaku, Co.) or a 20 W low pressure mercury lamp (Eikosha Co.). Organic extracts were dried over anhydrous sodium sulfate.

9,10-Dimethoxy-13-methylene-2,3-methylenedioxy-8,14-cycloberbine (5a) A solution of *n*-BuLi in hexane (1.8 ml, 2.88 mmol) was added dropwise to a solution of methyltriphenylphosphonium bromide (900 mg, 2.52

mmol) in dry THF (25 ml) in a stream of argon at room temperature. After stirring for 1 h at the same temperature, a solution of **4a** (590 mg, 1.68 mmol) in dry THF (20 ml) was added dropwise to the resulting methylenetriphenylphosphorane in THF and the reaction mixture was heated under reflux for 15 min. Water was added to the reaction mixture and the THF layer was separated. The THF layer was dried and concentrated to dryness. Chromatography of the residue on alumina with methylene dichloride gave **5a** (558 mg, 95%), mp 175—176 °C (MeOH). IR ($CHCl_3$): 1640 cm^{-1}. UV λ_{max} (log ε): 231 (sh, 4.39), 258 (4.20), 276 (4.26). ^{1}H-NMR δ: 7.25, 6.82 (ABq, J=8.3 Hz, 2H), 7.05, 6.65 (s each, 2H), 5.96, 5.92 (ABq, J=1.5 Hz, 2H), 5.77 (s, 1H), 5.16 (s, 1H), 3.94, 3.87 (s each, 6H), 3.68 (s, 1H), 3.60—2.37 (m, 4H), MS m/z (relative intensity, %): 349 (M^+, 100), 348 (67), 304 (24). *Anal.* Calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.16; H, 5.37; N, 3.90.

2,3,9,10-Tetramethoxy-13-methylene-8,14-cycloberbine (5b) 8,14-Cycloberbin-13-one (**4b**) (250 mg, 0.68 mmol) was treated with methylenetriphenylphosphorane [prepared from methyltriphenylphosphonium bromide (400 mg, 1.12 mmol) and *n*-BuLi in hexane (0.8 ml, 1.28 mmol)] in dry THF (40 ml) as described for **5a** to afford **5b** (240 mg, 97%), mp 164—165 °C (AcOEt). IR ($CHCl_3$) 1640 cm^{-1}. UV λ_{max} (log ε): 241 (sh, 4.39), 276 (4.29). ^{1}H-NMR δ: 7.27, 6.83 (ABq, J=8.5 Hz, 2H), 7.10, 6.69 (s each, 2H), 5.78 (s, 1H), 5.21 (s, 1H), 3.95, 3.90, 3.88, 3.84 (s each, 12H), 3.71 (s, 1H), 3.59—2.45 (m, 4H). MS m/z (relative intensity, %): 365 (M^+, 100), 350 (44), 334 (16), 322 (14). *Anal.* Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.08; H, 6.25; N, 3.73.

13-Methylene-2,3:9,10-bis(methylenedioxy)-8,14-cycloberbine (5c) 8,14-Cycloberbin-13-one (**4c**) (260 mg, 0.78 mmol) was treated with methylenetriphenylphosphorane [prepared from methyltriphenylphosphonium bromide (440 mg, 1.23 mmol) and *n*-BuLi in hexane (1.0 ml, 1.60 mmol)] in dry THF (40 ml) as described for **5a** to afford **5c** (242 mg, 94%), mp 173—174 °C (MeOH). IR ($CHCl_3$): 1655 cm^{-1}. UV λ_{max} (log ε): 239 (sh, 4.39), 291 (4.19), 319 (sh, 3.57). ^{1}H-NMR δ: 7.09, 6.73 (ABq, J=8.0 Hz, 2H), 7.02, 6.64 (s each, 2H), 6.00, 5.96 (ABq, J=1.2 Hz, 2H), 5.95, 5.92 (ABq, J=1.2 Hz, 2H), 5.76 (s, 1H), 5.15 (s, 1H), 3.54 (s, 1H), 3.52—2.33 (m, 4H). MS m/z (relative intensity, %) 333 (M^+, 100), 304 (10), 275 (17). *Anal.* Calcd for $C_{20}H_{15}NO_4$: C, 72.06; H, 4.54; N, 4.20. Found: C, 72.17; H, 4.41; N, 3.90.

(*Z*)-13-Ethylidene-9,10-dimethoxy-2,3-methylenedioxy-8,14-cycloberbine (8) 8,14-Cycloberbin-13-one (**4a**) (101 mg, 0.29 mmol) was treated with ethylidenetriphenylphosphorane [prepared from ethyltriphenylphosphonium bromide (150 mg, 0.40 mmol) and *n*-BuLi in hexane (0.4 ml, 0.64 mmol)] in dry THF (20 ml) as described for **5a** to provide **8** (100 mg, 96%), mp 181—182 °C (MeOH). UV λ_{max} (log ε): 254 (4.22), 274 (4.28). ^{1}H-NMR δ: 7.11, 6.78 (ABq, J=8.3 Hz, 2H), 6.93, 6.63 (s each, 2H), 6.19 (q, J=7.5 Hz, 1H), 5.94, 5.90 (ABq, J=1.5 Hz, 2H), 3.94, 3.85 (s each, 6H), 3.50 (s, 1H), 3.74—2.36 (m, 4H), 1.58 (d, J=7.5 Hz, 3H). MS m/z (relative intensity, %): 363 (M^+, 100), 318 (9). *Anal.* Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.64; H, 5.74; N, 3.71.

(*Z*)-9,10-Dimethoxy-2,3-methylenedioxy-13-propylidene-8,14-cycloberbine (9) 8,14-Cycloberbin-13-one (**4a**) (96 mg, 0.27 mmol) was treated with triphenylpropylidenephosphorane [prepared from triphenylpropylphosphonium bromide (170 mg, 0.44 mmol) and *n*-BuLi in hexane (0.4 ml, 0.64 mmol)] in dry THF (20 ml) according to the procedure described for **5a** to provide **9** (95 mg, 92%), mp 175—176 °C (MeOH). UV λ_{max} (log ε): 231 (sh, 4.59), 285 (4.39). ^{1}H-NMR δ: 7.13, 6.78 (ABq, J=8.5 Hz, 2H), 6.39, 6.63 (s each, 2H), 6.08 (t, J=7.5 Hz, 1H), 5.91, 5.87 (ABq, J=1.5 Hz, 2H), 3.94, 3.85 (s each, 6H), 3.74—2.35 (m, 4H), 3.48 (s, 1H), 1.95 (quin, J=7.5 Hz, 2H), 0.94 (t, J=7.5 Hz, 3H). MS m/z (relative intensity,%): 377 (M^+, 100), 362 (18), 332 (9). *Anal.* Calcd for $C_{23}H_{23}NO_4$: C, 73.17; H, 6.14; N, 3.91. Found: C, 73.13; H, 6.05; N, 3.57.

13-Methylberberine Chloride (1a) A solution of **5a** (104 mg, 0.30 mmol) in aqueous ethanol [H_2O (5 ml) and EtOH (50 ml)] was irradiated with a 100 W high pressure mercury lamp through a Pyrex filter in a stream of nitrogen for 1 h at −20 °C. The reaction mixture was saturated with hydrogen chloride and allowed to stand at room temperature overnight, and then concentrated to give a residual solid, which was recrystallized from isopropyl alcohol to furnish **1a** (92 mg, 80%), mp 187—189 °C (dec.) [lit.[20] mp 185—187 °C (dec.)]. UV λ_{max} (log ε): 231 (4.45), 265 (4.48), 342 (4.34), 420 (3.77). ^{1}H-NMR [$(CD_3)_2SO$] δ: 9.94 (s, 1H), 8.20 (s, 2H), 7.47, 7.15 (s each, 2H), 6.18 (s, 2H), 4.85 (t, J=5 Hz, 2H), 4.11, 4.10 (s each, 6H), 3.13 (t, J=5 Hz, 2H), 2.94 (s, 3H). *Anal.* Calcd for $C_{21}H_{20}ClNO_4 \cdot 3/2H_2O$: C, 61.09; H, 5.62; N, 3.39. Found: C, 61.24; H, 5.41; N, 3.02.

Irradiation of **5a** (95 mg, 0.27 mmol) in aqueous ethanol [H_2O (8 ml) and EtOH (42 ml)] with a 20 W low pressure mercury lamp in a stream of nitrogen for 3 h at −20 °C yielded **1a** (60 mg, 57%) after treatment with hydrogen chloride.

Dehydrocorydaline Chloride (1b) The methylene derivative (**5b**) (88 mg, 0.24 mmol) was irradiated with a 100 W high pressure mercury lamp in aqueous ethanol (55 ml) at −20 °C as described for **1a** to give **1b** (82 mg, 85%), mp 162—163 °C (iso-PrOH) [lit.[21] mp 191—193 °C (dec.)]. UV λ_{max} (log ε): 231 (4.36), 266 (4.23), 341 (4.36), 423 (3.75). ^{1}H-NMR [$(CD_3)_2SO$] δ: 9.93 (s, 1H), 8.20 (s, 2H), 7.39, 7.18 (s each, 2H), 4.88 (t, J=5.4 Hz, 2H), 4.11, 4.10, 3.90, 3.86 (s each, 12H), 3.16 (t, J=5.4 Hz, 2H), 2.99 (s, 3H). *Anal.* Calcd for $C_{22}H_{24}ClNO_4 \cdot 1/2H_2O$: C, 64.30; H, 6.13; N, 3.41. Found; C, 64.25; H, 6.21; N, 3.12.

Corysamine Chloride (1c) The methylene derivative (**5c**) (75 mg, 0.23 mmol) was irradiated with a 100 W high pressure mercury lamp in aqueous ethanol (55 ml) at −20 °C as described for **1a** to give **1c** (71 mg, 86%), mp 210—211 °C (EtOH) [lit.[22] mp 230 °C (dec.)]. UV λ_{max} (log ε): 232 (4.24), 242 (sh, 4.18), 269 (4.19), 343 (4.14), 445 (3.48). ^{1}H-NMR [$(CD_3)_2SO$] δ: 9.99 (s, 1H), 8.04, 7.99 (ABq, J=9.3 Hz, 2H), 7.44, 7.13 (s each, 2H), 6.55, 6.17 (s each, 4H), 4.80 (t, J=4.9 Hz, 2H), 3.12 (t, J=4.9 Hz, 2H), 2.92 (s, 3H). *Anal.* Calcd for $C_{20}H_{16}ClNO_4 \cdot 5/3H_2O$: C, 60.07; H, 4.87; N, 3.50. Found: C, 59.94; H, 4.83; N, 3.52.

13-Ethylberberine Chloride (10) The ethylidene derivative (**8**) (201 mg, 0.55 mmol) was irradiated with a 100 W high pressure mercury lamp in aqueous ethanol (250 ml) at −20 °C as described for **1a** to give **10** (94 mg, 42%), mp 235—240 °C (dec.) (iso-PrOH). UV λ_{max} (log ε): 213 (4.44), 265 (4.48), 342 (4.34), 421 (3.79). ^{1}H-NMR [$(CD_3)_2SO$] δ: 9.93 (s, 1H), 8.22 (s, 2H), 7.29, 7.16 (s each, 2H), 6.19 (s, 2H), 4.83 (t, J=5 Hz, 2H), 4.11 (s, 6H), 3.54—2.98 (m, 4H), 1.48 (t, J=7.5 Hz, 3H). *Anal.* Calcd for $C_{22}H_{22}ClNO_4 \cdot 5/3H_2O$: C, 61.46; H, 5.94; N, 3.26. Found: C, 61.11; H, 5.57; N, 3.05.

13-Propylberberine Chloride (11) The propylidene derivative (**9**) (210 mg, 0.56 mmol) was irradiated with a 100 W high pressure mercury lamp in aqueous ethanol (250 ml) at −20 °C as described for **1a** to give **11** (199 mg, 86%), mp 215—217 °C (iso-PrOH). UV λ_{max} (log ε): 232 (4.41), 265 (4.43), 343 (4.30), 421 (3.74). ^{1}H-NMR [$(CD_3)_2SO$] δ: 9.92 (s, 1H), 8.21 (s, 2H), 7.26, 7.16 (s each, 2H), 6.20 (s, 2H), 4.82 (t, J=5.9 Hz, 2H), 4.11 (s, 6H), 3.45—2.97, 2.04—1.55 (m, 6H), 1.01 (t, J=6.4 Hz, 3H). *Anal.* Calcd for $C_{23}H_{24}ClNO_4 \cdot 1/3H_2O$: C, 65.79; H, 5.92; N, 3.33. Found: C, 66.06; H, 5.80; N, 3.20.

(±)-Thalictricavine (6a) $NaBH_4$ (100 mg, 2.62 mmol) was added portionwise to a stirred solution of **1a** (75 mg, 0.19 mmol) in ethanol (10 ml) at room temperature and the reaction mixture was heated under reflux for 1 h. After evaporation of ethanol, water was added to the residue and the mixture was extracted with methylene dichloride. The organic solution was washed with water and brine, dried, and concentrated to give a residue, which was chromatographed on alumina with methylene dichloride to afford **5a** (64 mg, 94%), mp 209—210 °C (MeOH) (lit.[11d] mp 211.5—212.5 °C). IR ($CHCl_3$): 2850, 2800, 2750 cm^{-1}. UV λ_{max} (log ε): 230 (sh, 4.15), 286 (3.78), 291 (3.80). ^{1}H-NMR δ: 6.88, 6.82 (ABq, J=8.5 Hz, 2H), 6.67, 6.57 (s each, 2H), 5.92, 5.90 (ABq, J=1.5 Hz, 2H), 4.19, 3.49 (ABq, J=16 Hz, 2H), 3.85 (s, 6H), 3.66 (br s, 1H), 3.28—2.41 (m, 5H), 0.95 (d, J=6.8 Hz, 3H). MS m/z (relative intensity, %): 353 (M^+, 24), 178 (100), 163 (24). *Anal.* Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.34; H, 6.55; N, 3.98.

(±)-Corydaline (6b) Reduction of **1b** (107 mg, 0.23 mmol) with $NaBH_4$ (100 mg, 2.62 mmol) in ethanol as described for **6a** afforded **6b** (84 mg, 97%), mp 135—136 °C (MeOH) (lit.[12b] mp 135—136 °C). IR ($CHCl_3$): 2850, 2750 cm^{-1}. UV λ_{max} (log ε): 229 (sh, 4.26), 283 (3.76). ^{1}H-NMR δ: 6.91, 6.83 (ABq, J=8.5 Hz, 2H), 6.69, 6.61 (s each, 2H), 4.21, 3.51 (ABq, J=16 Hz, 2H), 3.88, 3.86 (s each, 12H), 3.70 (d, J=2.7 Hz, 1H), 3.32—2.43 (m, 5H), 0.95 (d, J=6.8 Hz, 3H). MS m/z (relative intensity, %): 369 (M^+, 35), 178 (100), 163 (17). *Anal.* Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.52; H, 7.43; N, 3.72.

(±)-Tetrahydrocorysamine (6c) Reduction of **1c** (50 mg, 0.14 mmol) with $NaBH_4$ (100 mg, 2.26 mmol) in ethanol as described for **6a** afforded **6c** (43 mg, 94%), mp 207—209 °C (MeOH) (lit.[23] mp 210—211 °C). IR ($CHCl_3$): 2830, 2780 cm^{-1}. UV λ_{max} (log ε): 234 (sh, 4.01), 290 (3.93). ^{1}H-NMR δ: 6.70, 6.66 (ABq, J=8.3 Hz, 2H), 6.68, 6.57 (s each, 2H), 5.95, 5.92 (ABq, J=1.5 Hz, 2H), 5.92, 5.91 (ABq, J=1.5 Hz, 2H), 4.05, 3.48 (ABq, J=15 Hz, 2H), 3.70 (d, J=2.5 Hz, 1H), 3.36—2.41 (m, 5H), 0.94 (d, J=6.8 Hz, 3H). MS m/z (relative intensity, %): 337 (M^+, 25), 162 (100). *Anal.* Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 70.69; H, 5.58; N, 4.14.

13-Ethyltetrahydroberberine (12) Reduction of **10** (24 mg, 0.06 mmol) with $NaBH_4$ (50 mg, 1.31 mmol) in ethanol as described for **6a** gave **12** (18 mg, 85%), mp 135—136 °C (aqueous MeOH) (lit.[12d] mp 135—136 °C).

IR ($CHCl_3$): 2800, 2750 cm^{-1}. UV λ_{max} (log ε): 230 (4.10), 286 (3.92). ^{1}H-NMR δ: 6.88, 6.80 (ABq, J=8.3 Hz, 2H), 6.69, 6.58 (s each, 2H), 5.93, 5.91 (ABq, J=1.5 Hz, 2H), 4.24, 3.51 (ABq, J=16 Hz, 2H), 3.86 (s, 6H), 3.69 (br s, 1H), 3.24—2.36 (m, 5H), 1.52—1.16 (m, 2H), 0.80 (t, J=7.5 Hz, 3H). MS m/z (relative intensity, %): 367 (M^+, 33), 192 (100), 177 (13). *Anal.* Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.65; H, 6.89; N, 3.78.

13-Propyltetrahydroberberine (13) Reduction of **11** (29 mg, 0.07 mmol) with $NaBH_4$ (30 mg, 0.79 mmol) in ethanol as described for **6a** gave **13** (22 mg, 82%). IR ($CHCl_3$): 2850, 2800, 2750 cm^{-1}. ^{1}H-NMR δ: 6.86, 6.79 (ABq, J=8.3 Hz, 2H), 6.68, 6.59 (s each, 2H), 5.94, 5.91 (ABq, J=1.5 Hz, 2H), 4.24, 3.51 (ABq, J=16 Hz, 2H), 3.86 (s, 6H), 3.67 (br s, 1H), 3.28—2.40 (m, 5H), 1.41—1.00 (m, 4H), 0.74 (t, J=6 Hz, 3H). MS m/z (relative intensity, %): 381 (M^+, 43), 338 (12), 206 (100), 191 (27), 175 (16). High resolution MS Calcd for $C_{23}H_{27}NO_4$: 381.1939. Found: 381.1950.

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