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Chemical Transformation of Protoberberines. V.[1] Photochemical Valence Isomerization of Berberinephenolbetaines to 8,14-Cycloberbines, Versatile Aziridine Derivatives for a Novel and Efficient Entry to Spirobenzylisoquinolines and Benzindenoazepines[2]

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Irradiation of berberinephenolbetaine (**12a**) and its 8-alkyl derivatives (**12b**—**e**) readily effected valence isomerization to afford the corresponding novel 8,14-cycloberbines (**13a**—**e**) in high yields. On treatment with ethyl chloroformate, the 8,14-cycloberbines (**13a**, **13b**, and **13c**) were efficiently converted to the spirobenzylisoquinolines (**14**, **15**, and **16**—**18**, respectively) *via* regioselective C_8–N bond cleavage. The 8,14-cycloberbine (**13a**), on treatment with methyl iodide, provided the benzindenoazepine (**21**) through regioselective C_{14}–N bond cleavage, whereas 8-methyl- and 8-ethyl-8,14-cycloberbine (**13b** and **13c**) gave 8-methylidene- and (*Z*)-8-ethylidene-spirobenzylisoquinoline (**22** and **23**), respectively. Irradiation of 8-methoxyberberinephenolbetaine (**26**) directly afforded the spirobenzylisoquinoline (**31**) having a ketone and a ketal on the five-membered ring. The product (**31**) was converted easily to a variety of spirobenzylisoquinolines such as the diketone (**36**), the hydroxy-ketal (**38**), and the keto-alcohol derivatives (**41** and **42**) in excellent yields.

Keywords——photochemical valence isomerization; berberinephenolbetaine; 8,14-cycloberbine; regioselective ring cleavage; spirobenzylisoquinoline; benzindenoazepine; ethyl chloroformate; methyl iodide

Among numerous successful transformations of protoberberine and related alkaloids,[3] several conversions involving an 8,14-cycloberbine as a mechanistic intermediate have been reported;[4] *e.g.* the conversions *via* the 8,14-cycloberbines (**1** and **2**) as shown in Chart 1. A unique and interesting feature of these intermediates attracted our attention: as an 8,14-cycloberbine possesses a reactive aziridine ring in its molecule, it can be converted to a spirobenzylisoquinoline, a benzindenoazepine, or a protoberberine through regioselective C_8–N, C_{14}–N, or C_8–C_{14} bond cleavage, respectively (Chart 2). A synthesis of an 8,14-cycloberbine, therefore, seems to represent a promising new route to protoberberine and related alkaloids, although isolation of such a cycloberbine has not so far been reported. This paper presents a convenient synthesis of 8,14-cycloberbines and a simple conversion of cycloberbines to spirobenzylisoquinolines and benzindenoazepines.

Photochemical valence isomerization of a six-membered ring to a bicyclo[3.1.0]hexane ring has been observed in the following cases: pyrylium oxide (**3**)—epoxyindenone (**4**),[5] isoquinolinium betaine (**5**)—indanoaziridine (**6**),[6] and isoquinolinium imide (**7**)—indanoaziridine (**8**).[7] Irradiation of pyridinium betaine (**9**) afforded a 6% yield of a valence-isomerized aziridine derivative, 6-azabicyclo[3.1.0]hexene (**10**) in addition to dimeric products[8] (Chart 3). We accordingly investigated the photochemical valence isomerization of ber berinephenolbetaines for the synthesis of 8,14-cycloberbines.

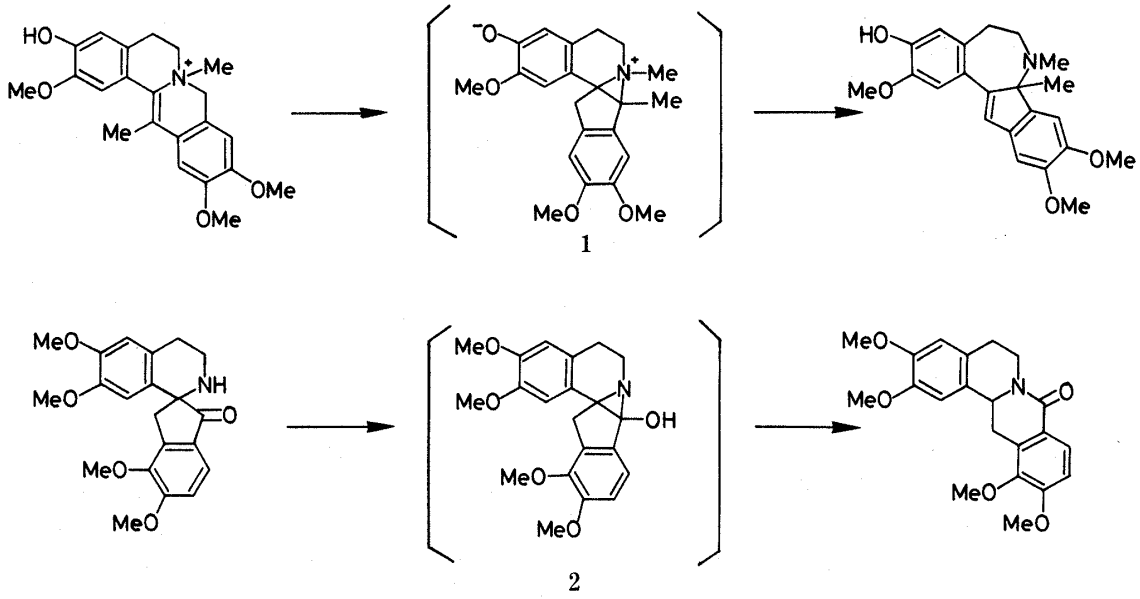


Chart 1

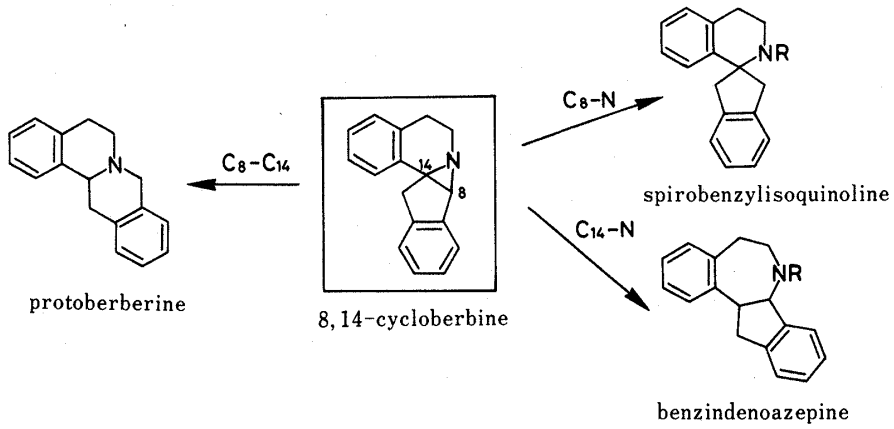


Chart 2

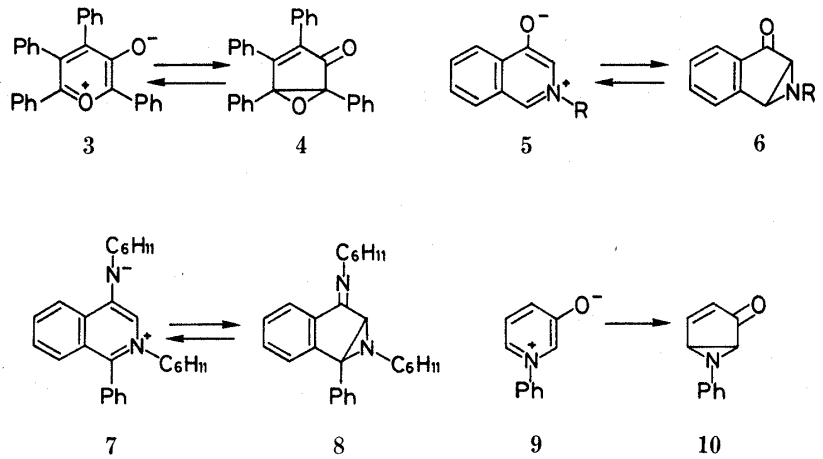
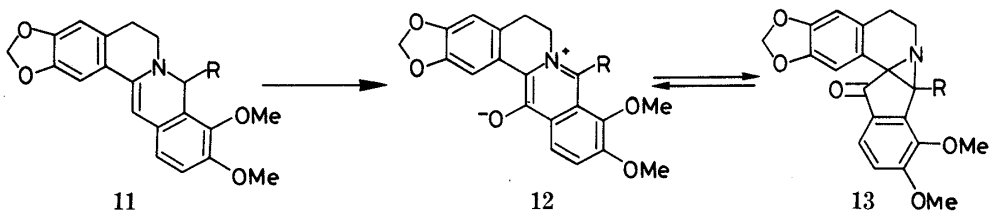


Chart 3

The precursors, berberinephenolbetaine (**12a**)[9] and its 8-alkylphenolbetaines (**12b—e**), required for valence isomerization were prepared by oxidation of dihydroberberine (**11a**) and its 8-alkyl derivatives (**11b—e**)[10] with *m*-chloroperbenzoic acid.[11] A solution of the betaine



a:R=H, b:R=Me, c:R=Et, d:R=$CH_2C_6H_5$, e:R=$CH_2CH=CH_2$

Chart 4

(**12a**) in methanol was irradiated through a Pyrex filter in a stream of nitrogen to afford the 8,14-cycloberbine (**13a**) in 70% yield. The structure of **13a** was assigned by analysis of its spectral data: a parent peak at *m/e* 351 in the mass spectrum, a carbonyl band at 1715 cm^{-1} in the infrared (IR) spectrum, and a singlet due to H-8[12] at 4.00 ppm in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum. The presence of an aziridine ring in the 8,14-cycloberbine (**13a**) was further confirmed by the ^{13}C-NMR spectrum, which revealed C-8 and C-14 signals at 40.98 and 49.55 ppm as a doublet and a singlet, respectively. This product is unexpectedly stable because conrotatory opening of the aziridine ring is thermally disallowed in this ring system, but the colorless spot of the product (**13a**) on a thin-layer chromatography plate turned orange on irradiation at 254 nm. In fact, on irradiation without the filter the product (**13a**) reverted to the starting orange-colored betaine (**12a**) in 55% yield through photochemically allowed disrotatory ring opening. The existence of a photoequilibrium[5-7] between the 8,14-cycloberbine (**13a**) and the betaine (**12a**) was thus confirmed.

Similarly, the betaines (**12b—e**) were efficiently converted to the corresponding 8,14-cycloberbines (**13b—e**) (see Experimental). The present smooth photochemical valence isomerization was remarkable in terms of a high yield in comparison with the previous example[8] probably because of the stability of the products due to conjugation with the aromatic ring. Thus, the 8,14-cycloberbines, previously reported only as hypothetical reaction intermediates,[4] were actually isolated as crystalline compounds.

With the novel 8,14-cycloberbines in hand, the next operation undertaken was a regioselective C–N bond cleavage to spirobenzylisoquinolines and/or benzindenoazepines, the latter of which could also be transformed to related alkaloids such as rhoeadine[4a,13] and protopine alkaloids.[14]

Heating of the 8,14-cycloberbine (**13a**) in benzene with ethyl chloroformate effected regioselective C_8–N bond cleavage to furnish the spirobenzylisoquinoline (**14**)[15] in 70% yield. The product, *m/e* 461, 459 (M^+, 1:3), showed bands at 1720 (CO) and 1675 cm^{-1} (NCO) in the IR spectrum, and its ^{1}H-NMR spectrum was consistent with the expected structure, showing a high-field singlet due to H-1 at 6.06 ppm (diagnostic of a spirobenzylisoquinoline skeleton).[16] Upon similar treatment of the 8,14-cycloberbine (**13b**) with ethyl chloroformate, C_8–N bond cleavage occurred, accompanied with dehydrochlorination to give quantitatively the methylidene-spiroisoquinoline (**15**), the vinylic protons of which appeared as singlets at 6.28 and 5.44 ppm in the ^{1}H-NMR spectrum. Similar treatment of the 8,14-cycloberbine (**13c**) afforded the (*Z*)- and (*E*)-ethylidene-spiroisoquinoline (**16** and **17**) as well as the oxazolidinone (**18**) in a *ca.* 3:2:2 ratio. The *Z*-configuration of the ethylidene product (**16**) was confirmed by comparison of the chemical shifts of the vinylic methyl signal (1.69 ppm) and the vinylic proton signal (7.09 ppm) with those of the corresponding signals (2.14 and 5.91 ppm) of the isomer (**17**). The structure of the oxazolidinone (**18**) was well supported by the appearance of the band at 1745 cm^{-1} in its IR spectrum.

The regioselective C_8–N bond fission of the 8,14-cycloberbine (**13a**) was also accomplished by exposure to acetyl chloride, resulting in a 52% yield of the *N*-acetyl derivative (**19**).

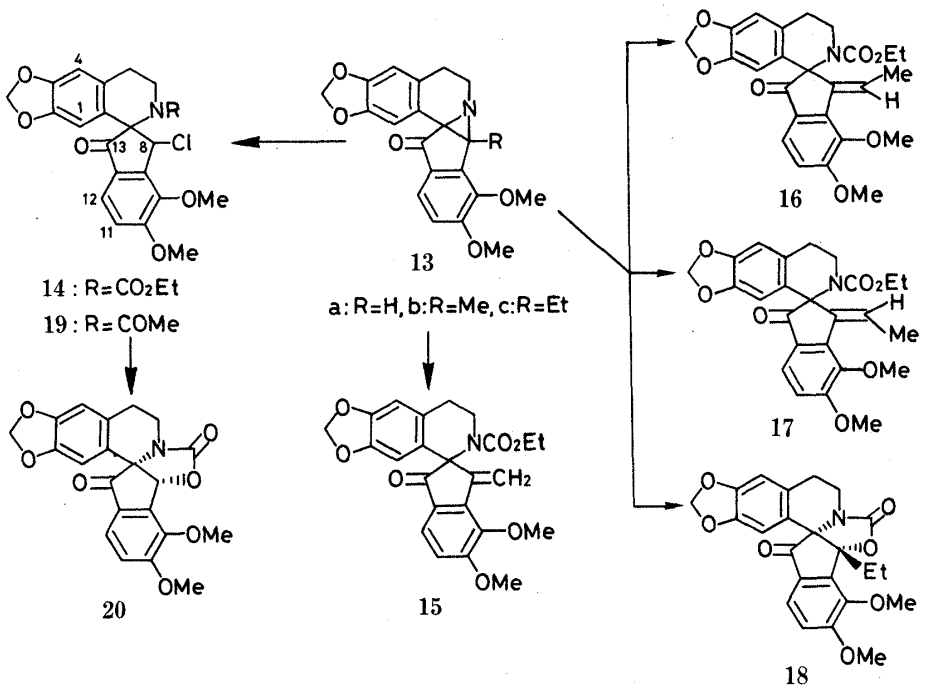


Chart 5

The spiroisoquinoline (**14**) was further treated with silver nitrate in aqueous acetone to give the oxazolidinone (**20**) in 71% yield.

N-Methylation of the 8,14-cycloberbine (**13a**) with methyl iodide in methanol produced the benzindenoazepine (**21**) in 60% yield. The product, *m/e* 397 (M^+), showed a carbonyl band at 1705 cm^{-1} in the IR spectrum, and singlets at 7.37, 4.68, 3.37, and 2.49 ppm attributable to H-1, H-8, aliphatic *O*-methyl, and *N*-methyl, respectively, in the ^{1}H-NMR spectrum. These data indicated that the product (**21**) has a benzindenoazepine skeleton instead of a spirobenzylisoquinoline skeleton, but the stereochemistry of **21** remained undetermined. The product must be obtained through *N*-methylation followed by regioselective C_{14}–N bond cleavage and concomitant substitution with methanol at C_{14}.[17]

On the other hand, upon treatment with methyl iodide, the 8,14-cycloberbines (**13b** and **13c**) underwent both *N*-methylation and the Hofmann elimination to afford the methylidene- and ethylidene-spiroisoquinoline (**22** and **23**), respectively, in 72 and 66% yields. The spiroisoquinoline structure of **22** and **23** was established by the presence of a high-field singlet[16] due to H-1 at 6.06 and 6.07 ppm, respectively. The *Z*-configuration of **23** was confirmed by the low and high chemical shifts of the vinylic proton (7.00 ppm) and the vinylic methyl (1.67 ppm) signals, respectively (*cf.* the corresponding signals of **16** and **17**). The exclusive formation of the *Z*-isomer can be explained on the basis that there exists a severe steric interaction between the *C*-methyl and the methoxyl group in the conformer leading to the *E*-isomer in the elimination of the possible intermediate (**24**). In the previous reaction of the 8,14-cycloberbine (**13c**) with ethyl chloroformate, however, there is no great energy difference between the conformer leading to the *Z*-isomer and that leading to the *E*-isomer in the elimination of the intermediate (**25**), resulting in formation of both the *Z*- and *E*-isomer (**16** and **17**).

Thus, the three possible regioselective bond cleavages of the 8,14-cycloberbines shown in Chart 2 were realized in practice. The present ready photochemical valence isomerization of the berberinephenolbetaines to the unique 8,14-cycloberbines provides a novel and efficient entry to a variety of related alkaloids such as spirobenzylisoquinoline, benzindenoazepine,

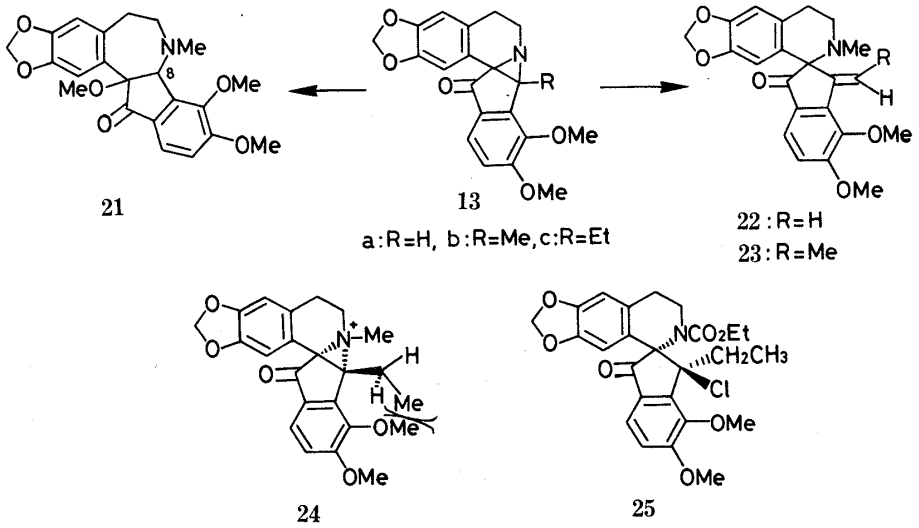


Chart 6

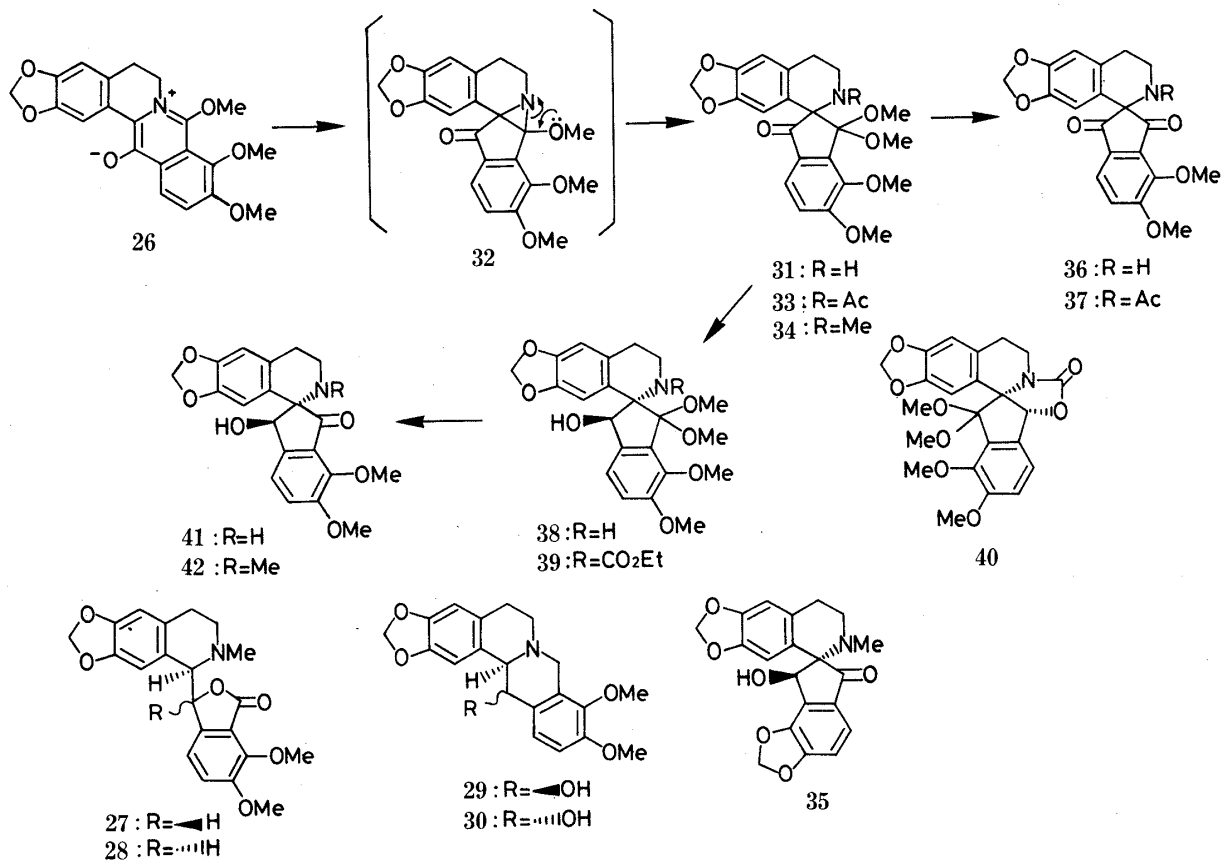


Chart 7

rhoeadine, and protopine alkaloids, from protoberberine alkaloids.

Next, the above conversion involving photochemical valence isomerization was applied to 8-methoxyberberinephenolbetaine (**26**),[18,19] the key intermediate for the synthesis of (±)-α- and β-hydrastine (**27** and **28**) as well as (±)-ophiocarpine (**29**) and (±)-epiophiocarpine (**30**). Irradiation of the betaine (**26**) directly afforded the spirobenzylisoquinoline (**31**) in 74% yield instead of the 8,14-cycloberbine (**32**). The product, *m/e* 413 (M^+), showed a carbonyl band at 1710 cm^{-1} in the IR spectrum and the characteristic high-field singlet due to H-1 at

6.26 ppm in its ^{1}H-NMR spectrum. The presence of a secondary amino group in the product was proved by its conversion to the *N*-acetyl (**33**) and the *N*-methyl (**34**) derivatives. The formation of the spiro compound (**31**) can be interpreted as follows. Irradiation of the betaine (**26**) effects valence isomerization to give the 8,14-cycloberbine (**32**); however, this cycloberbine having the methoxyl group at C-8 is so labile that it decomposes immediately to the spiro compound (**31**) through the substitution with methanol.

Since the product (**31**) has a carbonyl and a ketal group on the five-membered ring, it is possible to transform it into any desired type of spirobenzylisoquinoline alkaloids,[16] including those with two different substituents on the five-membered ring such as sibiricine (**35**). As a model examination, some functional group interconversions of the product (**31**) were investigated. Upon treatment with 10% hydrochloric acid, the spiro compound (**31**) produced a 77% yield of the diketone (**36**), acetylation of which gave the *N*-acetyl derivative (**37**) in 83% yield. Sodium borohydride reduction of **31** afforded quantitatively the hydroxy-ketal (**38**) as a single stereoisomer. The *trans* relationship between the nitrogen and the hydroxyl group was supported by its conversion to the urethane (**39**) instead of the oxazolidinone (**40**), the former of which exhibited a urethane band at 1680 cm^{-1} in the IR spectrum. Deketalization of the hydroxy-ketal (**38**) with 10% hydrochloric acid furnished quantitatively the keto-alcohol (**41**), which was methylated with formaldehyde–formic acid to give an 87% yield of the *N*-methyl derivative (**42**) having the same stereochemistry as that of sibiricine (**35**).

Photochemical valence isomerization of 8-methoxyberberinephenolbetaine (**26**) thus provided in one operation the spirobenzylisoquinoline (**31**) possessing two oxygenated substituents on the five-membered ring. This procedure offers a simple and convenient method for the synthesis of a variety of spirobenzylisoquinoline alkaloids.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography was carried out with silica gel (Kieselgel 60, 70—230 mesh, Merck) and alumina (Aluminiumoxid 90, Aktivitätsstufe II-III, 70—230 mesh, Merck). Preparative thin-layer chromatography (p-TLC) was performed on alumina (Aluminiumoxid GF_{254} Typ 60/E, Merck), and silica gel (Kieselgel GF_{254} Typ 60, Merck). 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, and ^{1}H-NMR and ^{13}C-NMR spectra with a JEOL FX-100 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. Irradiation was carried out with a 100 W high-pressure mercury lamp with a Pyrex filter (Riko Kagaku Co.) unless otherwise stated.

General Procedure for the Synthesis of Berberinephenolbetaines——A solution of *m*-chloroperbenzoic acid (15 mmol) in CH_2Cl_2 (80 ml) was added dropwise to a stirred solution of a dihydroberberine (**11**, 10 mmol) in CH_2Cl_2 (350 ml) at −25——30 °C in a stream of nitrogen for 15 min and the mixture was stirred for a further 1 h at the same temperature. Then the reaction temperature was raised to 0 °C, and finely powdered Na_2SO_3 (2.5 g) was added to the reaction solution. The mixture was stirred vigorously at room temperature for 1 h. The inorganic precipitate was filtered off and the filtrate was concentrated to dryness. The residue was chromatographed on alumina with CH_2Cl_2 and CH_2Cl_2–MeOH (50 : 1). The fraction eluted with CH_2Cl_2–MeOH gave the betaine (**12**). In the case of the betaine (**12a**), the above filtrate was concentrated to the volume of *ca.* 30 ml. MeOH (50 ml) was added to the residue and the precipitate was collected by filtration to afford the betaine (**12a**).

Berberinephenolbetaine (12a)——Yield: 70%. Orange prisms, mp 260—262 °C (MeOH). UV λ_{max}^{MeOH} nm (log ε): 236 (4.48), 258 sh (4.24), 312 (4.05), 365 (4.02), 444 (4.16). The product was identical with an authentic sample[9] (IR spectral comparison and TLC).

8-Methylberberinephenolbetaine (12b)——Yield: 47%. Orange needles, mp 165—166.5 °C (MeOH). ^{1}H-NMR δ: 8.74 (1H, s, C_1–H), 8.38, 7.29 (2H, AB-q, J=9 Hz, C_{12}– and C_{11}–H), 6.46 (1H, s, C_4–H), 5,86 (2H, s, OCH_2O), 4.41 (2H, t, J=6 Hz, C_6–H), 3.95, 3.81 (each 3H, s, $OCH_3 \times 2$), 3.40 (CH_3OH), 3.01 (C_8–CH_3), 2.83 (2H, t, J=6 Hz, C_5–H). UV λ_{max}^{MeOH} nm (log ε): 237.5 (4.53), 258.5 sh (4.30), 315.5 (4.08), 371 (4.05), 456 (4.18). MS *m/e*: 365 (M^+). *Anal.* Calcd for $C_{21}H_{19}NO_5 \cdot MeOH$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.58; H, 5.61; N, 3.78.

8-Ethylberberinephenolbetaine (12c)——Yield: 52%. Orange needles, mp 151—154 °C (MeOH). ^{1}H-NMR δ: 8.73

(1H, s, C_1–H), 8.41, 7.28 (2H, AB-q, J=9 Hz, C_{12}– and C_{11}–H), 6.49 (1H, s, C_4–H), 5.88 (2H, s, OCH_2O), 4.45 (2H, t, J=6 Hz, C_6–H), 3.97, 3.93 (each 3H, s, $OCH_3 \times 2$), 3.43 (CH_3OH), 2.87 (2H, t, J=6 Hz, C_5–H), 1.06 (3H, t, J=7 Hz, $CH_2\underline{CH_3}$). UV λ_{max}^{MeOH} nm (log ε): 240 (4.46), 261.5 sh (4.24), 312.5 (4.02), 370 (3.99), 458 (4.14). MS *m/e*: 379 (M^+). *Anal.* Calcd for $C_{22}H_{21}NO_5 \cdot MeOH$: C, 67.14; H, 6.12; N, 3.40. Found: C, 67.35: H, 5.97; N, 3.37.

8-Benzylberberinephenolbetaine (12d)——Yield: 47%. Orange needles, mp 169—172 °C (AcOEt). ^{1}H-NMR δ: 8.89 (1H, s, C_1–H), 8.56, 7.41 (2H, AB-q, J=9 Hz, C_{12}– and C_{11}–H), 7.3—7.0 (5H, m, Ar-H), 6.57 (1H, s, C_4–H), 5.95 (2H, s, OCH_2O), 5.00 (2H, br s, CH_2Ph), 4.37 (2H, t, J=6 Hz, C_6–H), 3.97, 3.45 (each 3H, s, $OCH_3 \times 2$), 2.76 (2H, t, J=6 Hz, C_5–H). UV λ_{max}^{MeOH} nm (log ε): 240.5 (4.53), 261.5 sh (4.34), 323 (4.09), 373 (4.08), 461 (4.26). MS *m/e*: 441 (M^+). *Anal.* Calcd for $C_{27}H_{23}NO_5$: C, 73.48; H, 5.15; N, 3.09. Found: C, 73.45; H, 5.25; N, 3.17.

8-Allylberberinephenolbetaine (12e)——Yield: 63%. Orange needles, mp 154—156 °C (AcOEt). ^{1}H-NMR δ: 8.63 (1H, s, C_1–H), 8.30, 7.20 (2H, AB-q, J=10 Hz, C_{12}– and C_{11}–H), 6.42 (1H, s, C_4–H), 6.28—5.77 (1H, m, $\underset{H}{}\!\!>\!\!=$), 5.80 (2H, s, OCH_2O), 5.34—4.83 (2H, m, $=\!\!<^{H}_{H}$), 3.90, 3.70 (each 3H, s, $OCH_3 \times 2$). MS *m/e*: 391 (M^+). *Anal.* Calcd for $C_{23}H_{21}NO_5$: C, 70.57; H, 5.41; N, 3.58. Found: C, 70.55; H, 5.40; N, 3.34.

General Procedure for Irradiation of Berberinephenolbetaines to 8,14-Cycloberbines——A solution of a berberinephenolbetaine (**12**, 0.4 mmol) in MeOH (100 ml) was irradiated at room temperature in a stream of nitrogen for 20—120 min. The solvent was evaporated off and the residue was chromatographed on silica gel with C_6H_6–AcOEt (4:1) to afford the corresponding 8,14-cycloberbine (**13**).

9,10-Dimethoxy-2,3-methylenedioxy-8,14-cycloberbin-13-one (13a)——Irradiation time: 50 min. Yield: 70%. Colorless scales, mp 182—183 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715 (C=O). ^{1}H-NMR δ: 7.56, 6.91 (2H, AB-q, J=8.5 Hz, C_{12}– and C_{11}–H), 7.31 (1H, s, C_1–H), 6.64 (1H, s, C_4–H), 5.92 (2H, s, OCH_2O), 4.00 (1H, s, C_8–H), 3.97, 3.93 (each 3H, s, $OCH_3 \times 2$). ^{13}C-NMR δ: 196.97 (s), 157.40 (s), 146.48 (s), 145.31 (s), 141.43 (s), 129.51 (s), 128.28 (s), 126.81 (s), 122.06 (d), 120.47 (s), 112.19 (d), 108.79 (d), 108.50 (d), 100.92 (t), 61.47 (q), 56.30 (q), 49.55 (s), 46.21 (t), 40.98 (d), 26.18 (t). MS *m/e*: 351 (M^+). *Anal.* Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.48; H, 4.87; N, 4.23.

9,10-Dimethoxy-8-methyl-2,3-methylenedioxy-8,14-cycloberbin-13-one (13b)——Irradiation time: 30 min. Yield: 85%. Colorless prisms, mp 176—178 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (C=O). ^{1}H-NMR δ: 7.53, 6.90 (2H, AB-q, J=8 Hz, C_{12}– and C_{11}–H), 6.67 (2H, s, C_1– and C_4–H), 5.94, 5.93 (2H, AB-q, J=1.5 Hz, OCH_2O), 3.93 (6H, s, $OCH_3 \times 2$), 1.65 (3H, s, C_8–CH_3). ^{13}C-NMR δ: 200.09 (s), 158.22 (s), 147.25 (s), 146.54 (s), 146.25 (s), 145.49 (s), 131.28 (s), 128.69 (s), 121.82 (d), 119.36 (s), 112.02 (d), 109.26 (d), 108.14 (d), 100.92 (t), 61.06 (q), 56.24 (1), 53.78 (s), 51.31 (s), 45.32 (t), 28.42 (t), 9.45 (q). MS *m/e*: 365 (M^+). *Anal.* Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 68.84; H, 5.15; N, 4.12.

8-Ethyl-9,10-dimethoxy-2,3-methylenedioxy-8,14-cycloberbin-13-one (13c)——Irradiation time: 60 min. Yield: 77%. Colorless prisms, mp 179—181 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (C=O). ^{1}H-NMR δ: 7.53, 6.81 (2H, AB-q, J=8 Hz, C_{12}– and C_{11}–H), 6.60 (2H, s, C_1– and C_4–H), 5.87 (2H, s, OCH_2O), 3.89 (6H, s, $OCH_3 \times 2$), 1.00 (3H, t, J=7 Hz, $CH_2\underline{CH_3}$). MS *m/e*: 379 (M^+). *Anal.* Calcd for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.38; H, 5.45; N, 3.93.

8-Benzyl-9,10-dimethoxy-2,3-methylenedioxy-8,14-cycloberbin-13-one (13d)——Irradiation time: 120 min. Yield: 37%. Colorless plates, mp 178.5—180 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (C=O). ^{1}H-NMR δ: 7.42, 6.75 (2H, AB-q, J=8.5 Hz, C_{12}– and C_{11}–H), 6.98 (5H, s, Ar-H), 6.57, 6.53 (each 1H, s, C_1– and C_4–H), 5.80 (2H, s, OCH_2O), 4.00 (2H, s, CH_2Ph), 3.75, 3.55 (each 3H, s, $OCH_3 \times 2$). MS *m/e*: 441 (M^+). *Anal.* Calcd for $C_{27}H_{23}NO_5$: C, 73.45; H, 5.25; N, 3.17. Found: C, 73.34; H, 5.24; N, 3.23.

8-Allyl-9,10-dimethoxy-2,3-methylenedioxy-8,14-cycloberbin-13-one (13e)——Irradiation time: 20 min. Yield: 82%. Colorless needles, mp 185—186 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (C=O). ^{1}H-NMR δ: 7.54, 6.92 (2H, AB-q, J=9 Hz, C_{12}– and C_{11}–H), 6.66 (2H, s, C_1– and C_4–H), 5.94, 5.89 (2H, AB-q, J=1 Hz, OCH_2O), 5.91—5.61 (1H, m, $\underset{H}{}\!\!>\!\!=$), 5.13—4.87 (2H, m, $=\!\!<^{H}_{H}$), 3.95, 3.93 (each 3H, s, $OCH_3 \times 2$). MS *m/e*: 391 (M^+). *Anal.* Calcd for $C_{23}H_{21}NO_5$: C, 70.56; H, 5.41; N, 3.58. Found: C, 70.39; H, 5.39; N, 3.58.

Isomerization of the 8,14-Cycloberbine (13a) to Berberinephenolbetaine (12a)——A solution of the cycloberbine (**13a**, 51.5 mg) in MeOH (150 ml) was irradiated with a 200 W high pressure mercury lamp (Toshiba) without a Pyrex filter in a stream of nitrogen at room temperature for 20 min. The solvent was evaporated off and the residue was chromatographed on alumina with $CHCl_3$–MeOH (50:1) to give the betaine (**12a**, 31 mg, 55%) as orange prisms, mp 260—262 °C (MeOH); this product was identical with an authentic specimen (IR spectral comparison and TLC).

Ethyl 8-Chloro-9,10-dimethoxy-2,3-methylenedioxy-13-oxonorochotensane-7-carboxylate (14)[20]——A solution of the cycloberbine (**13a**, 57.5 mg) and ethyl chloroformate (150 mg) in benzene (10 ml) was heated with stirring at 80 °C for 1 h. The solvent was evaporated off and the residue was chromatographed on p-TLC (SiO_2) with C_6H_6–AcOEt (4:1) to give the spirobenzylisoquinoline (**14**, 52.8 mg, 70%) as colorless prisms, mp 192—195 °C (EtOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (C=O), 1675 (NCO). ^{1}H-NMR δ: 7.53, 7.03 (2H, AB-q, J=8.5 Hz, C_{12}– and C_{11}–H), 6.55 (1H, s, C_4–H), 6.06 (1H, s, C_1–H), 5.87 (1H, s, C_8–H), 5.79, 5.77 (2H, AB-q, J=1.5 Hz, OCH_2O), 3.94, 3.91 (each 3H, s,

$OCH_3 \times 2$), 1.4—1.0 (3H, m, CH_2CH_3). UV λ_{max}^{MeOH} nm (log ε): 234 (4.42), 289 (4.34). MS *m/e*: 461, 459 (M^+, 1:3). *Anal.* Calcd for $C_{23}H_{22}ClNO_7$: C, 60.07; H, 4.82; N, 3.05. Found: C, 59.85; H, 4.81; N, 3.25.

Ethyl 9,10-Dimethoxy-8-methylene-2,3-methylenedioxy-13-oxonorochotensane-7-carboxylate (15)——A solution of the cycloberbine (**13b**, 61.8 mg) and ethyl chloroformate (300 mg) in benzene (5 ml) was heated under reflux with stirring for 3 h. The solvent was evaporated off and the residue was chromatographed on alumina with $CHCl_3$ to give a pale brown amorphous solid (**15**, 75.8 mg, 100%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715 (C=O), 1685 (NCO). ^{1}H-NMR δ: 7.52, 7.02 (2H, AB-q, J=8.5 Hz, C_{12}– and C_{11}–H), 6.60 (1H, s, C_4–H), 6.28, 5.44 (each 1H, s, $=<^{H}_{H}$), 6.18 (1H, s, C_1–H), 5.78 (2H, m, OCH_2O), 3.92 (6H, s, $OCH_3 \times 2$), 1.4—0.7 (3H, m, CH_2CH_3). MS *m/e*: 437 (M^+). High resolution MS *m/e*: Calcd for $C_{24}H_{23}NO_7$: 437.152. Found: 437.150.

Reaction of the 8-Ethyl-8,14-cycloberbine (13c) with Ethyl Chloroformate——A solution of the cycloberbine (**13c**, 102.2 mg) and ethyl chloroformate (800 mg) in benzene (10 ml) was heated under reflux with stirring for 22 h. The solvent was evaporated off and the residue was chromatographed on silica gel with C_6H_6–AcOEt (4:1) to give an oily residue (110 mg), a part (46.1 mg) of which was further subjected to p-TLC (SiO_2) with Et_2O–hexane (4:1). The upper fraction afforded ethyl (*Z*)-8-ethylidene-9,10-dimethoxy-2,3-methylenedioxy-13-oxonorochotensane-7-carboxylate (**16**, 17.6 mg) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (C=O), 1685 (NCO). ^{1}H-NMR δ: 7.48, 6.95 (2H, AB-q, J=8.5 Hz, C_{12}– and C_{11}–H), 7.09 (1H, q, J=7.5 Hz, $=CHCH_3$), 6.65 (1H, s, C_4–H), 6.37 (1H, s, C_1–H), 5.86, 5.79 (2H, AB-q, J=1.5 Hz, OCH_2O), 3.97, 3.94 (each 3H, s, $OCH_3 \times 2$), 1.69 (3H, d, J=7.5 Hz, $=CHCH_3$). MS *m/e*: 451 (M^+), 378 (base peak). High resolution MS *m/e*: Calcd for $C_{25}H_{25}NO_7$: 451.163. Found: 451.164. The middle fraction afforded ethyl (*E*)-8-ethylidene-9,10-dimethoxy-2,3-methylenedioxy-13-oxonorochotensane-7-carboxylate (**17**, 11.2 mg) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (C=O), 1690 (NCO). ^{1}H-NMR δ: 7.61, 7.05 (2H, AB-q, J=8 Hz, C_{12}– and C_{11}–H), 6.62 (1H, s, C_4–H), 6.18 (1H, s, C_1–H), 5.91 (1H, q, J=7.5 Hz, $=CHCH_3$), 5.83, 5.78 (2H, AB-q, J=1.5 Hz, OCH_2O), 2.14 (3H, d, J=7.5 Hz, $=CHCH_3$). MS *m/e*: 451 (M^+), 378 (base peak). High resolution MS *m/e*: Calcd for $C_{25}H_{25}NO_7$: 451.163. Found: 451.163. The lower fraction afforded *rel*-(8*R*,14*R*)-8-ethyl-9,10-dimethoxy-2,3-methylenedioxy-13-oxonorochotensane-7,8-carbolactone (**18**, 11.9 mg) as colorless crystals. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1745 (NCO), 1715 (C=O). ^{1}H-NMR δ: 7.69, 7.20 (2H, AB-q, J=8.5 Hz, C_{12}– and C_{11}–H), 6.67 (1H, s, C_4–H), 6.12 (1H, s, C_1–H), 5.94, 5.89 (2H, AB-q, J=1.5 Hz, OCH_2O), 4.02, 3.97 (each 3H, s, $OCH_3 \times 2$), 0.60 (3H, t, J=7 Hz, CH_2CH_3). MS *m/e*: 423 (M^+), 364 (base peak). High resolution MS *m/e*: Calcd for $C_{23}H_{21}NO_7$: 423.132. Found: 423.132.

7-Acetyl-8-chloro-9,10-dimethoxy-2,3-methylenedioxynorochotensan-13-one (19)——A solution of the cycloberbine (**13a**, 546 mg) and acetyl chloride (500 mg) in benzene (35 ml) was heated at 55 °C with stirring for 3 h. The solvent was evaporated off and the residue was taken up in $CHCl_3$. The $CHCl_3$ layer was washed with aqueous K_2CO_3 and brine, then dried, and concentrated. The residue was chromatographed on alumina with CH_2Cl_2–MeOH (50:1) to afford the spiroisoquinoline (**19**, 351 mg, 52%) as colorless cubes, mp 239—241 °C (MeOH–$CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715 (C=O), 1660 (NCO). ^{1}H-NMR δ: 7.62, 7.12 (2H, AB-q, J=8.5 Hz, C_{12}– and C_{11}–H), 6.65 (1H, s, C_4–H), 6.14 (1H, s, C_1–H), 5.89, 5.85 (2H, AB-q, J=1.5 Hz, OCH_2O), 5.88 (1H, s, C_8–H), 3.98, 3.93 (each 3H, s, $OCH_3 \times 2$), 2.19 (3H, s, $COCH_3$). MS *m/e*: 431, 429 (M^+, 1:3). *Anal.* Calcd for $C_{22}H_{20}ClNO_6$: C, 61.47; H, 4.69; N, 3.26. Found: C, 61.31; H, 4.66; N, 3.29.

***rel*-(8*R*,14*R*)-9,10-Dimethoxy-2,3-methylenedioxy-13-oxonorochotensane-7,8-carbolactone (20)**——A mixture of the urethane (**14**, 52.8 mg) in acetone (2.5 ml) and silver nitrate (50 ml) in distilled water (2.5 ml) was heated under reflux with stirring for 20 h. The solvent was evaporated off and the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, and concentrated. The residue was chromatographed on p-TLC (Al_2O_3) with $CHCl_3$ to give the oxazolidinone (**20**, 32 mg, 71%) as colorless needles, mp 221—221.5 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750 (NCO), 1715 (C=O). ^{1}H-NMR δ: 7.54, 7.11 (2H, AB-q, J=9 Hz, C_{12}– and C_{11}–H), 6.55 (1H, s, C_4–H), 6.02 (1H, s, C_1–H), 5.80 (2H, s, OCH_2O), 5.76 (1H, s, C_8–H), 3.98 (6H, s, $OCH_3 \times 2$). UV λ_{max}^{MeOH} nm (log ε): 234 (4.40), 294 (4.35). MS *m/e*: 395 (M^+). *Anal.* Calcd for $C_{21}H_{17}NO_7$: C, 63.79; H, 4.33; N, 3.54. Found: C, 63.85; H, 4.23; N, 3.78.

5,6,7,8,13,14-Hexahydro-9,10,14-trimethoxy-7-methyl-2,3-methylenedioxybenz[*d*]indeno[1,2-*b*]azepin-13-one (21)[22]——A solution of the cycloberbine (**13a**, 105.3 mg) and MeI (2 ml) in MeOH (10 ml) and CH_2Cl_2 (5 ml) was kept standing at room temperature for 4 days. The solvents were evaporated off and the residue was chromatographed on alumina with C_6H_6–AcOEt (4:1) to give the benzindenoazepine (**21**, 70.9 mg, 60%) as colorless prisms, mp 193—194.5 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (C=O). ^{1}H-NMR δ: 7.61, 7.06 (2H, AB-q, J=8 Hz, C_{12}– and C_{11}–H), 7.37 (1H, s, C_1–H), 6.56 (1H, s, C_4–H), 5.95, 5.92 (2H, AB-q, J=1.5 Hz, OCH_2O), 4.68 (1H, s, C_8–H), 3.99, 3.94, 3.37 (each 3H, s, $OCH_3 \times 3$), 2.49 (3H, s, NCH_3). MS *m/e*: 397 (M^+). *Anal.* Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5,83; N, 3.52. Found: C, 66.53; H, 5.85; N, 3.41.

9,10-Dimethoxy-8-methylene-2,3-methylenedioxyochotensan-13-one (22)——A solution of the cycloberbine (**13b**, 117 mg) and MeI (300 mg) in acetone (10 ml) was kept standing at room temperature for 24 h. The solvent was evaporated off and the residue was chromatographed on alumina with CH_2Cl_2 to give the spiroisoquinoline (**22**, 88 mg, 72%) as pale yellow prisms, mp 166—168 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (C=O), 1640 (C=C). ^{1}H-NMR δ: 7.57, 7.06 (2H, AB-q, J=8.5 Hz, C_{12}– and C_{11}–H), 6.58 (1H, s, C_4–H), 6.45, 5.56 (each 1H, br s, $=<^{H}_{H}$), 6.06 (1H, s, C_1–H), 5.82, 5.80 (2H, AB-q, J=1.5 Hz, OCH_2O), 4.00, 3.96 (each 3H, s, $OCH_3 \times 2$), 2.28 (3H, s, N–CH_3). UV

λ_{max}^{MeOH} nm (log ε): 246 sh (4.48), 253 (4.52), 293 (4.27). MS *m/e*: 379 (M^+). *Anal.* Calcd for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.44; H, 5.44; N, 3.72.

(*Z*)-8-Ethylidene-9,10-dimethoxy-2,3-methylenedioxyochotensan-13-one (23)——A solution of the cycloberbine (**13c**, 77.8 mg) and MeI (300 mg) in acetone (5 ml) was kept standing at room temperature for 3 days. The solvent was evaporated off and the residue was chromatographed on alumina with $CHCl_3$ to give the spiroisoquinoline (**23**, 53.5 mg, 66%), as pale yellow prisms, mp 167—169 °C (hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1695 (C=O). ^{1}H-NMR δ: 7.42, 6.88 (2H, AB-q, J=8 Hz, C_{12}– and C_{11}–H), 7.00 (1H, q, J=7.5 Hz, =C<u>H</u>CH$_3$), 6.50 (1H, s, C_4–H), 6.07 (1H, s, C_1–H), 3.93, 3.87 (each 3H, s, OCH_3 × 2), 2.24 (3H, s, N–CH_3), 1.67 (3H, d, J=7.5 Hz, =CHC<u>H</u>$_3$). UV λ_{max}^{MeOH} nm (log ε): 249 sh (4.52), 257 (4.60), 294 (4.28). MS *m/e*: 393 (M^+). *Anal.* Calcd for $C_{23}H_{23}NO_5$: C, 70.21; H, 5.89; N, 3.56. Found: C, 70.25; H, 5.80; N, 3.67.

8,8,9,10-Tetramethoxy-2,3-methylenedioxynorochotensan-13-one (31)——A solution of the betaine (**26**, 416 mg) in MeOH (300 ml) was irradiated at room temperature in a stream of nitrogen for 40 min. The solvent was evaporated off and the residue was chromatographed on alumina with $CHCl_3$ to give the spiroisoquinoline (**31**, 333 mg, 74%) as pale yellow needles, mp 194—196 °C (isopropyl ether). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (C=O). ^{1}H-NMR δ: 7.60, 7.10 (2H, AB-q, J=8.5 Hz, C_{12}– and C_{11}–H), 6.59 (1H, s, C_4–H), 6.26 (1H, s, C_1–H), 5.84, 5.80 (2H, AB-q, J=1.5 Hz, OCH_2O), 4.00, 3.92, 3.35, 3.24 (each 3H, s, OCH_3 × 4). UV λ_{max}^{MeOH} nm (log ε): 230 (4.33), 289 (4.29). MS *m/e*: 413 (M^+). *Anal.* Calcd for $C_{22}H_{23}NO_7$: C, 63.91; H, 5.61; N, 3.39. Found: C, 63.90; H, 5.68; N, 3.56.

7-Acetyl-8,8,9,10-tetramethoxy-2,3-methylenedioxynorochotensan-13-one (33)——Acetic anhydride (3 ml) was added to a solution of the spiroisoquinoline (**31**, 60 mg) in pyridine (2 ml) and the reaction mixture was heated at 140 °C for 1 h, then cooled. The solvent was evaporated off and the residue was taken up in $CHCl_3$. The $CHCl_3$ solution was washed with a saturated $NaHCO_3$ solution and water. The organic layer was dried and concentrated. The residue was recrystallized from MeOH to give the *N*-acetyl derivative (**33**, 48 mg, 73%) as colorless needles, mp 283—284 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (C=O), 1645 (NCO). ^{1}H-NMR δ: 7.69, 7.11 (2H, AB-q, J=8 Hz, C_{12}– and C_{11}–H), 6.55 (1H, s, C_4–H), 6.06 (1H, s, C_1–H), 5.83, 5.80 (2H, AB-q, J=1.5 Hz, OCH_2O), 3.97, 3.87, 3.43, 2.92 (each 3H, s, OCH_3 × 4), 2.15 (3H, s, $COCH_3$). UV λ_{max}^{MeOH} nm (log ε): 226.5 (4.36), 286 (4.28). MS *m/e*: 455 (M^+). *Anal.* Calcd for $C_{24}H_{25}NO_8$: C, 63.29; H, 5.52; N, 3.08. Found: C, 63.49; H, 5.53; N, 3.16.

8,8,9,10-Tetramethoxy-2,3-methylenedioxyochotensan-13-one (34)——A solution of the spiroisoquinoline (**31**, 205 mg) and methyl iodide (1 ml) in tetrahydrofuran (20 ml) was stirred at room temperature for 10 h. The solvent was evaporated off and the residue was taken up in CH_2Cl_2. The CH_2Cl_2 solution was washed with aqueous K_2CO_3 and water, dried, and concentrated. The residue was chromatographed on alumina with CH_2Cl_2 to give the *N*-methyl derivative (**34**, 153 mg, 72%) as pale yellow needles, mp 121—123 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700 (C=O). ^{1}H-NMR δ: 7.67, 7.15 (2H, AB-q, J=8.5 Hz, C_{12}– and C_{11}–H), 6.54 (1H, s, C_4–H), 6.02 (1H, s, C_1–H), 5.86, 5.79 (2H, AB-q, J=1.5 Hz, OCH_2O), 4.01, 3.86, 3.46, 3.09 (each 3H, s, OCH_3 × 4), 2.50 (3H, s, N–CH_3). MS *m/e*: 427 (M^+). *Anal.* Calcd for $C_{23}H_{25}NO_7 \cdot 1/2MeOH$: C, 63.65; H, 6.14; N, 3.16. Found: C, 63.82; H, 6.15; N, 3.26.

9,10-Dimethoxy-2,3-methylenedioxynorochotensane-8,13-dione (36)——Hydrochloric acid (10%, 5 ml) was added to a solution of the spiroisoquinoline (**31**, 200 mg) in MeOH (3 ml) and the reaction mixture was heated at 95 °C for 3 h. The solvent was evaporated off and the residue was made alkaline with 10% NaOH and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, and concentrated. The residue was recrystallized from C_6H_6–hexane to give diketone (**36**, 136 mg, 77%) as pale yellow needles, mp 178—179 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1710 (C=O). ^{1}H-NMR δ: 7.82, 7.41 (2H, AB-q, J=8 Hz, C_{12}– and C_{11}–H), 6.64 (1H, s, C_4–H), 6.01 (1H, s, C_1–H), 5.81 (2H, s, OCH_2O), 4.10, 4.05 (each 3H, s, OCH_3 × 2), 3.48 (2H, t, J=6 Hz, N–C<u>H</u>$_2$CH$_2$), 2.82 (2H, t, J=6 Hz, N–CH$_2$C<u>H</u>$_2$). UV λ_{max}^{MeOH} nm (log ε): 247.5 (4.63), 291.5 (4.13), 334 (3.73). MS *m/e*: 367 (M^+). *Anal.* Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.41; H, 4.55; N, 3.86.

7-Acetyl-9,10-dimethoxy-2,3-methylenedioxynorochotensane-8,13-dione (37)——Acetic anhydride (2 ml) was added to a solution of the diketone (**36**, 50 mg) in pyridine (2 ml) and the reaction mixture was allowed to stand overnight at room temperature. The solvent was evaporated off and the residue was taken up in $CHCl_3$. The $CHCl_3$ solution was washed with a saturated $NaHCO_3$ solution and water, dried, and concentrated. The residue was recrystallized from MeOH to give the *N*-acetyl derivative (**37**, 46 mg, 83%) as pale yellow needles, mp 282—283 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1745, 1710 (C=O), 1640 (NCO). ^{1}H-NMR δ: 7.65, 7.23 (2H, AB-q, J=8 Hz, C_{12}– and C_{11}–H), 6.60 (1H, s, C_4–H), 6.06 (1H, s, C_1–H), 5.76 (2H, s, OCH_2O), 4.00, 3.96 (each 3H, s, OCH_3 × 2), 2.14 (3H, s, $COCH_3$). UV λ_{max}^{MeOH} nm (log ε): 248 (4.57), 292. 5 (4.11), 332.5 (3.69). MS *m/e*: 409 (M^+). *Anal.* Calcd for $C_{22}H_{19}NO_7$: C, 64.54; H, 4.68; N, 3.42. Found: C, 64.28; H, 4.63; N, 3.35.

***rel*-(13*R*,14*S*)-13-Hydroxy-8,8,9,10-tetramethoxy-2,3-methylenedioxynorochotensane (38)**——Sodium borohydride (100 mg) was added portionwise to a stirred solution of the spiroisoquinoline (**31**, 500 mg) in MeOH (75 ml) at room temperature and the reaction mixture was stirred for a further 1 h. The solvent was evaporated off and the residue was taken up in $CHCl_3$. The $CHCl_3$ solution was washed with water, dried, and concentrated. The residue was recrystallized from isopropyl ether to give the alcohol (**38**, 500 mg, 100%) as colorless scales, mp 188.5—189 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350 (OH and NH). ^{1}H-NMR δ: 7.16, 6.94 (2H, AB-q, J=8.5 Hz, C_{12}– and C_{11}–H), 6.60 (1H, s, C_4–H), 6.16 (1H, s, C_1–H), 5.84, 5.80 (2H, AB-q, J=1.5 Hz, OCH_2O), 4.89 (1H, s, C_{13}–H), 3.91, 3.86, 3.33, 3.19 (each 3H, s, OCH_3 × 4). UV λ_{max}^{MeOH} nm (log ε): 238 (4.10), 289 (3.82). MS *m/e*: 400 ($M^+ - 15$). *Anal.* Calcd for $C_{22}H_{25}NO_7$: C,

63.60; H, 6.07; N, 3.37. Found: C, 63.62; H, 6.14; N, 3.62.

Ethyl *rel*-(13*R*,14*S*)-13-Hydroxy-8,8,9,10-tetramethoxy-2,3-methylenedioxynorochotensane-7-carboxylate (39)——A solution of the alcohol (**38**, 210 mg), ethyl chloroformate (220 mg) and triethylamine (100 mg) in CH_2Cl_2 (10 ml) was stirred at room temperature for 12 h. Aqueous K_2CO_3 solution was added to the reaction mixture and the whole was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water, dreid, and concentrated. The residue was chromatographed on alumina with $CHCl_3$ to give the urethane (**39**, 220 mg, 85%) as colorless prisms, mp 186—187 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (OH), 1680 (NCO). ^{1}H-NMR δ: 7.34, 7.09 (2H, AB-q, J=8.5 Hz, C_{12}– and C_{11}–H), 6.55 (1H, s, C_4–H), 6.40 (1H, s, C_1–H), 5.78 (2H, s, OCH_2O), 5.70 (1H, s, C_{13}–H), 3.90, 3.88, 3.29, 3.28 (each 3H, s, OCH_3 × 4), 1.27 (3H, t, J=7 Hz, CH_2CH_3). MS *m/e*: 487 (M^+). *Anal.* Calcd for $C_{25}H_{29}NO_9$: C, 61.59; H, 6.00; N, 2.87. Found: C, 61.36; H, 5.73; N, 3.14.

***rel*-(13*R*,14*S*)-13-Hydroxy-9,10-dimethoxy-2,3-methylenedioxynorochotensan-8-one (41)**——Hydrochloric acid (10%, 20 ml) was added to a solution of the alcohol (**38**, 550 mg) in MeOH (10 ml) and the reaction mixture was heated at 100 °C for 2 h. After evaporation of the solvent, the residue was made alkaline with 10% NaOH and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, and concentrated. The residue was recrystallized from benzene to give the keto-alcohol (**41**, 490 mg, 100%) as colorless needles, mp 117—118.5 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350 (OH and NH), 1715 (C=O). ^{1}H-NMR δ: 7.38, 7.34 (2H, AB-q, J=8.5 Hz, C_{12}– and C_{11}–H), 6.64 (1H, s, C_4–H), 5.95 (1H, s, C_1–H), 5.84, 5.83 (2H, AB-q, J=1.5 Hz, OCH_2O), 5.19 (1H, s, C_{13}–H), 4.03, 3.94 (each 3H, s, OCH_3 × 2). UV λ_{max}^{MeOH} nm (log ε): 224 (4.47), 259.5 (4.05), 294 (3.74), 331.5 (3.57). MS *m/e*: 369 (M^+). *Anal.* Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.19; N, 3.79. Found: C, 65.31; H, 5.03; N, 3.64.

***rel*-(13*R*,14*S*)-13-Hydroxy-9,10-dimethoxy-2,3-methylenedioxyochotensan-8-one (42)**——Formaldehyde (37%, 3 ml) was added to a solution of the keto-alcohol (**41**, 160 mg) in formic acid (3 ml) and the reaction mixture was heated at 110—115 °C for 10 h, then cooled. Water was added to the reaction mixture, and the whole was made alkaline with saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, and concentrated. The residue was recrystallized from isopropyl alcohol to give the *N*-methyl derivative (**42**, 145 mg, 87%) as pale yellow plates, mp 183—184 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540 (OH), 1710 (C=O). ^{1}H-NMR δ: 7.50, 7.39 (2H, AB-q, J=8 Hz, C_{12}– and C_{11}–H), 6.67 (1H, s, C_4–H), 5.98 (1H, s, C_1–H), 5.87 (2H, s, OCH_2O), 5.38 (1H, s, C_{13}–H), 4.06, 3.98 (each 3H, s, OCH_3 × 2), 2.44 (3H, s, N–CH_3). UV λ_{max}^{MeOH} nm (log ε): 225 (4.50), 261.5 (4.05), 294 (3.72), 335 (3.49). MS *m/e*: 383 (M^+). *Anal.* Calcd for $C_{21}H_{21}NO_6$: C, 65.78; H, 5.52; N, 3.65. Found: C, 65.63; H, 5.47; N, 3.90.

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References and Notes

1) Part IV: M. Hanaoka, K. Nagami, M. Inoue, and S. Yasuda, *Chem. Pharm. Bull.*, **31**, 2685 (1983).
2) A part of this work was published in preliminary communications: M. Hanaoka, S. Yasuda, K. Nagami, K. Okajima, and T. Imanishi, *Tetrahedron Lett.*, **1979**, 3749; M. Hanaoka and C. Mukai, *Heterocycles*, **6**, 1981 (1977).
3) *a*) M. Shamma, "The Isoquinoline Alkaloids—Chemistry and Pharmacology," Academic Press, New York, 1972, pp. 268—417; *b*) M. Shamma and J. L. Moniot, "Isoquinoline Alkaloids Research 1972—1977," Plenum Press, New York, 1978, pp. 209—353.
4) *a*) protoberberine → benzindenoazepine: M. Shamma and J. F. Nugent, *Tetrahedron*, **29**, 1265 (1973); *b*) benzindenoazepine → spirobenzylisoquinoline and phthalideisoquinoline: T. Kametani, T. Ohsawa, S. Hirata, M. S. Premila, M. Ihara, and K. Fukumoto, *Chem. Pharm. Bull.*, **25**, 321 (1977); *c*) spirobenzylisoquinoline → protoberberine: D. Greenslade and R. Ramage, *Tetrahedron*, **33**, 927 (1977); *d*) spirobenzylisoquinoline → benzindenoazepine: H. Irie, S. Tani, and H. Yamane, *J. Chem. Soc., Perkin Trans. 1*, **1972**, 2986. This paper did not propose a reaction mechanism but the intermediacy of an 8,14-cycloberbine has been suggested.[4a)]
5) E. F. Ullman, *J. Am. Chem. Soc.*, **85**, 3529 (1963); J. M. Dunston and P. Yates, *Tetrahedron Lett.*, **1964**, 505.
6) P. E. Hansen and K. Undheim, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 305.
7) J. W. Lown and K. Matsumoto, *J. Org. Chem.*, **36**, 1405 (1971); *idem*, *Can. J. Chem.*, **49**, 3443 (1971).
8) N. Dennis, A. R. Katritzky, and H. Wilde, *J. Chem. Soc., Perkin Trans. 1*, **1976**, 2338.
9) T. Takemoto and Y. Kondo, *Yakugaku Zasshi*, **82**, 1413 (1962); Y. Kondo, J. Imai, and H. Inoue, *J. Chem. Soc., Perkin Trans. 1*, **1980**, 911; M. Hanaoka, C. Mukai, and Y. Arata, *Chem. Pharm. Bull.*, **31**, 947 (1983).
10) *a*) C. Tani and K. Ishibashi, *Yakugaku Zasshi*, **74**, 317 (1954); *b*) M. Freund and H. Commessmann, *Justus Liebigs Ann. Chem.*, **397**, 57 (1913); *c*) M. Freund and H. Beck, *Ber.*, **37**, 4673 (1904).
11) *Cf.* P. W. Jeffs and J. D. Scharver, *J. Org. Chem.*, **40**, 644 (1975).
12) The numbering of all the compounds described in this paper is in accord with that for the protoberberine and spirobenzylisoquinoline alkaloids.
13) K. Orito, R. H. Manske, and R. Rodrigo, *J. Am. Chem. Soc.*, **96**, 1944 (1974).

14) K. Orito, Y. Kurokawa, and M. Itoh, *Tetrahedron*, **36**, 617 (1980); K. Orito, S. Kudoh, K. Yamada, and M. Itoh, *Heterocycles*, **14**, 11 (1980).
15) Although the stereochemistry of the product (**14**) was not determined, the relationship between the nitrogen and the chlorine of **14** should be *trans via* an S_N2-type reaction.
16) R. M. Preisner and M. Shamma, *J. Natural Products*, **43**, 305 (1980).
17) The regioselective C_{14}–N bond cleavage is considered to be due to the S_N1-type nature of this reaction, which might be distinct from the S_N2-type reaction with ethyl chloroformate resulting in the C_8–N bond cleavage product (**14**).
18) J. L. Moniot and M. Shamma, *J. Am. Chem. Soc.*, **98**, 6714 (1976); *idem, J. Org. Chem.*, **44**, 4337 (1979).
19) M. Hanaoka, C. Mukai, and Y. Arata, *Heterocycles*, **6**, 895 (1977); *idem, Chem. Pharm. Bull.*, **31**, 947 (1983).
20) The compound (**14**) should be named ethyl 1,2,3,4-tetrahydro-4′,5′-dimethoxy-6,7-methylenedioxy-1′-oxo-isoquinoline-1-spiro-2′-indane-2-carboxylate, but all spirobenzylisoquinolines in this paper were numbered according to the spirobenzylisoquinoline alkaloid skeleton, ochotensane,[21] in order to follow the numbering system for the spirobenzylisoquinoline alkaloids.
21) M. Shamma, ref. 3*a*, p. 381.
22) The numbering of the benzindenoazepine (**21**) is in accord with that for spirobenzylisoquinolines.