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Chemical Transformation of Protoberberines. XIV.[1] Acid-Catalyzed Cleavage of 8-Alkyl-8,14-cycloberbines. A Simple Method for the Preparation of *N*-Unsubstituted Spirobenzylisoquinolines[2]

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On treatment with an acid, 8-alkyl-8,14-cycloberbines (**9**) afforded the *N*-unsubstituted spirobenzylisoquinolines (**10**, **11**, and **12**) through regioselective C_8–N bond cleavage in contrast to the 8-unsubstituted 8,14-cycloberbine (**9d**), which gave the benzindenoazepine (**19**, R=H) through regioselective C_{14}–N bond cleavage. Reduction of **9** with $NaBH_4$ or $LiAlH(OBu^t)_3$ yielded stereoselectively the alcohol (**20** or **21**, respectively) as the main product. Acidic treatment of the isomeric alcohols (**20** and **21**) effected regioselective C_8–N bond cleavage, resulting in the *N*-unsubstituted spirobenzylisoquinolines (**22**—**26**).

Keywords——8-alkyl-8,14-cycloberbine; spirobenzylisoquinoline; regioselective C–N bond cleavage; stereoselective reduction; hydrochloric acid; trifluoroacetic acid; lithium aluminum tri-*tert*-butoxyhydride; sodium borohydride; oxazolidinone; oxazolidine

Berberinephenolbetaines (**2**), derived from protoberberines (**1**) by successive lithium aluminum hydride reduction and oxidation with *m*-chloroperbenzoic acid, are susceptable to photo-induced valence isomerization to produce the unique 8,14-cycloberbines (**3**),[3] which were shown to be key intermediates in the formation of related alkaloids from **1**. For example, the spirobenzylisoquinolines (**4** and **5**) were obtained from **3** (R=H) and the 8-alkyl congeners (**3**, R=alkyl), respectively, through a regioselective C_8–N bond cleavage with ethyl chloroformate. This reaction has been successfully applied to a stereoselective synthesis of (±)-fumaricine (**6**).[4] On the other hand, **3** (R=H) underwent a regioselective C_{14}–N bond fission[5-7] to yield the benzindenoazepines (**7**) on exposure to acid. Benzindenoazepine and rhoeadine alkaloids such as *cis*-alpinigenine (**8**)[7] have been synthesized from **1** according to this method. Thus, it seemed to be of great interest to check whether acid treatment of **3** (R=alkyl) effects either C_8–N or C_{14}–N bond fission leading to spirobenzylisoquinolines or benzindenoazepines, respectively. This paper describes a simple method for the synthesis of *N*-unsubstituted spirobenzylisoquinolines.

The 8-methyl-8,14-cycloberbine (**9a**)[3] was heated in 10% hydrochloric acid at 70—80 °C (method I) for 2 h to furnish the 8-hydroxyspirobenzylisoquinoline (**10a**) accompanied with the unsaturated spirobenzylisoquinoline (**12a**) in 74 and 21% yields, respectively, through a C_8–N bond cleavage. The corresponding benzindenoazepine derived through a C_{14}–N bond fission could not be detected. Similar treatment of the 8-ethyl- and 8-allyl-8,14-cycloberbine (**9b** and **9c**)[3] also gave the 8-hydroxyspirobenzylisoquinolines (**10b**, 80% and **10c**, 56%) along with the unsaturated spirobenzylisoquinolines (**12b**, 17% and **12c**, 33%), respectively (Table I).

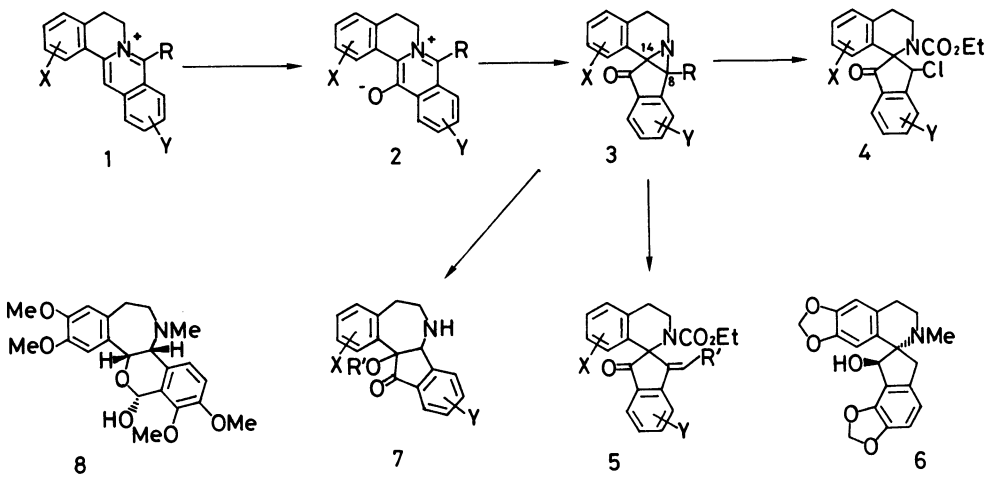

Chart 1

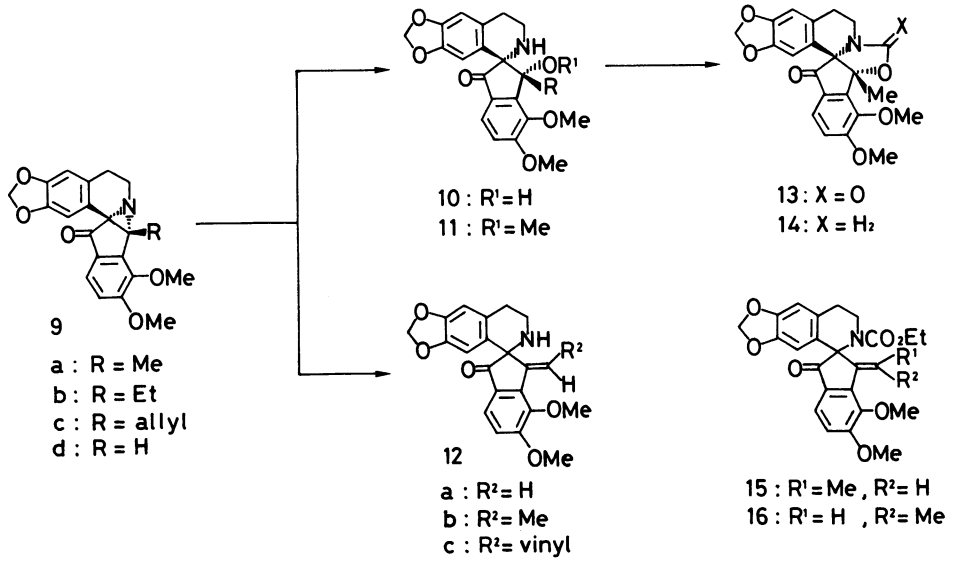

Chart 2

TABLE I. Solvolysis of 8,14-Cycloberbines (**9**)

Compd.	R	Method[a]	Product (yield, %)		
			10	**11**	**12**
9a	Me	I	74		21
9a	Me	II		76	
9b	Et	I	80		17
9b	Et	II		83	12
9c	Allyl	I	56		33
9c	Allyl	II		56	31

a) I, 10% HCl; II, CF_3CO_2H–MeOH.

The spirobenzylisoquinoline structures of these products were apparent from spectral data. The salient feature in the proton nuclear magnetic resonance (^{1}H-NMR) spectra of **10** and **12** is the H-1 signals, which appeared at relatively high field (5.94—6.21 ppm), characteristic of a spirobenzylisoquinoline skeleton.[8] In order to establish the stereochemistry of **10**, the methyl derivative (**10a**) was treated with ethyl chloroformate[4] or formaldehyde[9,10] resulting in the oxazolidinone (**13**, 63%) or the oxazolidine (**14**, 85%), respectively. Their structures were assigned from the spectral data, especially a characteristic band at 1740 cm^{-1} in the infrared (IR) spectrum of **13** and an AB quartet at 4.56 and 4.13 ppm due to the methylene of the oxazolidine ring in the ^{1}H-NMR spectrum of **14**. The *cis* relationship between C_{14}–N and the hydroxy group in **10a** was thus chemically determined. The *Z*-configuration of **12b** and **12c** was confirmed by the following features in the ^{1}H-NMR spectra. The *exo*-olefinic protons of **12b** and **12c** resonated at 7.04 and 7.41 ppm, respectively, and the downfield shift may be attributed to the deshielding effect of the benzene ring (ring D) as well as steric repulsion between the olefinic proton and the methoxy group at the C-9 position. This stereochemistry is well supported by the fact that the chemical shifts of the olefinic protons of **12b** and **12c** are similar to that of **15** (7.09 ppm) rather than that of **16** (5.91 ppm), both of which have established stereochemistry.[3]

When the cycloberbines (**9a**, **b**, and **c**) were stirred in methanol in the presence of a catalytic amount of trifluoroacetic acid at room temperature (method II) for 3.5 h, the 8-methoxyspirobenzylisoquinolines (**11a**, **b**, and **c**) were obtained in 76, 83, and 56% yields, respectively, together with the unsaturated spirobenzylisoquinolines (**12a**, **b**, and **c**) in 0, 12, and 31% yields, respectively. Upon treatment with *p*-toluenesulfonic acid instead of trifluoroacetic acid, **9b** similarly afforded **11b** and **12b** in 75 and 6% yields, respectively. The stereochemistry of **10b**, **10c**, and **11** is probably the same as that of **10a**, assuming an analogous attack of the solvent from the less-hindered side.

Thus, it appeared that acid treatment of the 8-alkyl-8,14-cycloberbines (**9**) effected exclusively C_8–N bond fission leading to the spirobenzylisoquinolines, and these results are contrary to that in the case of 8-unsubstituted 8,14-cycloberbine (**9d**), which gave the benzindenoazepine (**19**, R = H)[5-7] through a C_{14}–N bond cleavage. The introduction of an alkyl group at the C-8 position was found to alter dramatically the regioselectivity in C–N bond cleavage of the aziridine ring.

The above intriguing observation can presumably be interpreted as follows. An S_N1-type cleavage of the aziridine ring with acid produces the carbocation (**17** or **18**). The former cation, leading to the spirobenzylisoquinolines, might be more stable than the latter, leading to the benzindenoazepines, because the latter has a carbonyl group adjacent to the cation.

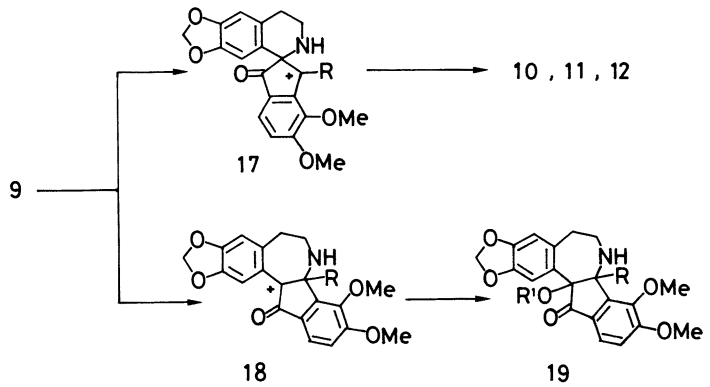

Chart 3

Consequently the reaction proceeded *via* the more stable carbocation (**17**) to the spirobenzylisoquinolines. In the case of the 8-unsubstituted 8,14-cycloberbine (**9d**), however, reaction would proceed *via* the tertiary carbocation (**18**, R=H) rather than the secondary carbocation (**17**, R=H). If this explanation is correct, the carbonyl group adjacent to the carbocation plays a crucial role in determining the reaction pathway. Therefore we next investigated the solvolysis of the 13-hydroxy-8,14-cycloberbines (**20** and **21**).

A solution of **9** in methanol was reduced with sodium borohydride ($NaBH_4$)[4] at room temperature to afford predominantly the alcohol (**20**) accompanied with the diastereoisomeric alcohol (**21**), whereas the latter was obtained as the main product when the reduction was carried out with lithium aluminum tri-*tert*-butoxyhydride [$LiAlH(OBu^t)_3$][11] in tetrahydro-

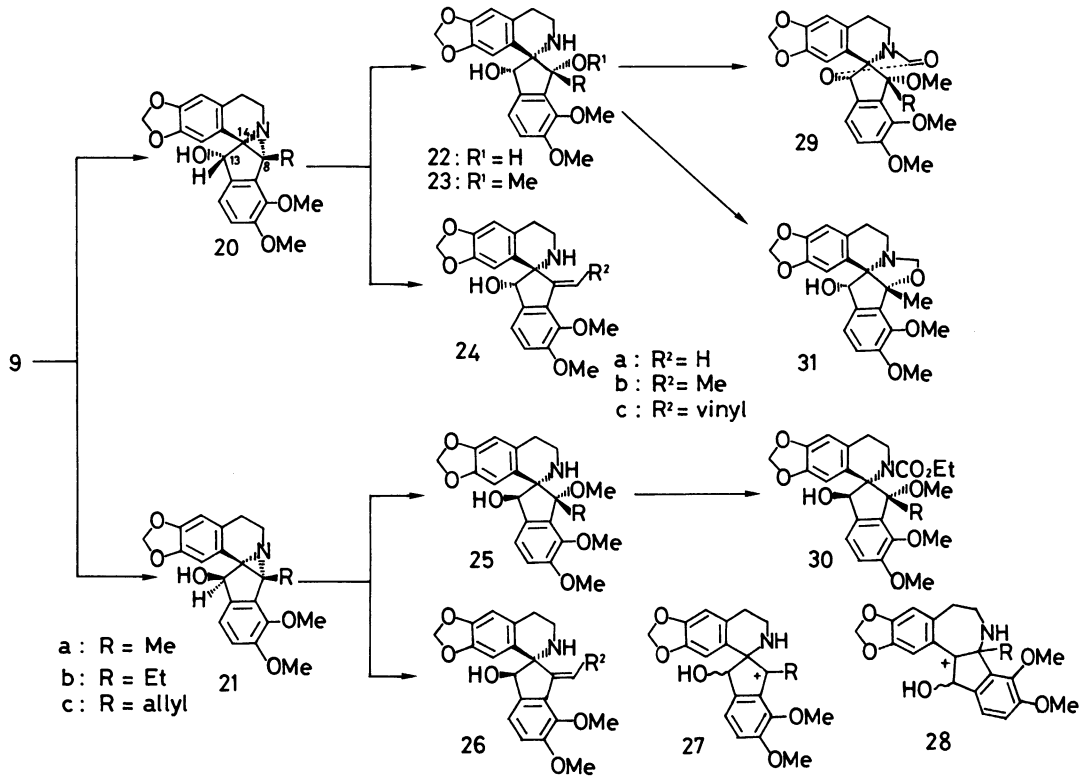

Chart 4

TABLE II. Reduction of 8,14-Cycloberbines (**9**)

Compd.	R	Reagent[a]	Product (**20**)		Product (**21**)		Product ratio (**20**/**21**)	Chemical shift difference[c]
			Yield (%)	H-13[b]	Yield (%)	H-13[b]		
9a	Me	A	71	5.21	13	4.77	5.5/1.0	0.44
9a	Me	B	14		77		1.0/5.5	
9b	Et	A	88	5.22	9	4.74	9.5/1.0	0.48
9b	Et	B	12		88		1.0/7.5	
9c	Allyl	A	80	5.20	12	4.68	6.5/1.0	0.52
9c	Allyl	B	13		85		1.0/6.5	

a) A, $NaBH_4$; B, $LiAlH(OBu^t)_3$. *b*) Chemical shift δ (ppm). *c*) $\Delta\delta$ (**20**−**21**).

furan (THF) at refluxing temperature. The results are summarized in Table II. The stereochemical relationship between the hydroxy group and the C_{14}–N bond in **20** and **21** was clarified from the ^{1}H-NMR spectral data. The C-13 proton signal of **20** appeared at lower field than that of **21**, in the range of 0.44—0.52 ppm, and the downfield shift may be ascribed to the deshielding effect of the benzene ring (ring A). Examination of a molecular model indicated that the C-13 proton of **20**, *cis* to ring A, lies on nearly the same plane as ring A and is strongly deshielded, whereas such a deshielding effect does not occur in **21**. Accordingly the relative stereochemistry of the C_{13}–OH and C_{14}–N bond in **20** is *cis* and that in **21**, *trans*.

The reverse stereoselectivity depending on the reducing agent used can be plausibly rationalized in terms of both steric hindrance and the reactivity of the reagents. In contrast to the case of $NaBH_4$ reduction, in which the hydride attacks the carbonyl group from the sterically less hindered side, producing the alcohol (**20**), less reactive $LiAlH(OBu^t)_3$, that does not react at all at room temperature, predominantly forms at first a complex with the nitrogen of the aziridine ring and then this complex reduces the carbonyl group intramolecularly from the same side as the nitrogen to provide the alcohol (**21**).

Acid cleavage of the 13-hydroxy-8,14-cycloberbines (**20** and **21**) was next investigated. The alcohols (**20** and **21**) were treated with 10% hydrochloric acid (method I) or trifluoroacetic acid in methanol (method II) as described for the reaction of the ketones (**9**) to afford exclusively the spirobenzylisoquinolines (**22**—**26**). The structures of these products were elucidated from spectral evidence, and the yields are summarized in Table III. Exclusive formation of spirobenzylisoquinolines in these reactions can be interpreted in terms of the intermediacy of the tertiary carbocation (**27**) which might still be more stable than the tertiary carbocation (**28**) destabilized by the inductive effect of the vicinal polar hydroxy group.

On treatment with ethyl chloroformate, 8-methoxyspirobenzylisoquinolines (**23**), derived from **20**, gave the oxazolidinones (**29**), which exhibited characteristic bands at 1730—1740 cm^{-1} in their IR spectra. On the other hand, the carbamates (**30**) were obtained on exposure of **25**, derived from **21**, to ethyl chloroformate. The carbamates (**30**) showed absorptions at 1670—1680 cm^{-1} in their IR spectra. These results confirmed unambiguously the aforementioned stereochemistry of the *cis*- and *trans*-alcohols (**20** and **21**). Treatment of **22a** with formaldehyde afforded the oxazolidine (**31**), which was identical with the product obtained from the reaction of **20a** with formaldehyde.[12] The formation of **31** established the

TABLE III. Solvolysis of 13-Hydroxy-8,14-cycloberbines (**20** and **21**)

Compd.	R	Method[a]	Product (yield, %)				
			22	**23**	**24**	**25**	**26**
20a	Me	I	45		36		
20a	Me	II		71			
20b	Et	I	25		54		
20b	Et	II		83			
20c	Allyl	I	49		22		
20c	Allyl	II		60	16		
21a	Me	I					79
21a	Me	II				70	
21b	Et	I					70
21b	Et	II				68	
21c	Allyl	I					74
21c	Allyl	II				64	

a) I, 10% HCl; II, CF_3CO_2H–MeOH.

TABLE IV. Physical and Spectral Data for Spirobenzylisoquinolines

Compd.	mp (°C) (Solvent)[a]	Formula	Analysis Calcd (Found) C	H	N	IR (cm^{-1}) ($CHCl_3$)	MS *m/z* (%)
10a	173—174 (B–H)	$C_{21}H_{21}NO_6$	65.78 (65.91)	5.52 (5.64)	3.65 (3.65)	3300, 1700[c]	383 (M^+, 100), 365 (44), 350 (37), 176 (62)
10b	163—164 (B–H)	$C_{22}H_{23}NO_6$	66.49 (66.61)	5.83 (5.77)	3.52 (3.46)	3300, 1700	397 (M^+, 100), 379 (45), 364 (47), 176 (65)
10c	157—159 (I)	$C_{23}H_{23}NO_6$	67.46 (67.66)	5.66 (5.69)	3.42 (3.70)	3450, 3300, 1705	409 (M^+, 72), 391 (38), 368 (100), 176 (35)
11a	190—191 (M)	$C_{22}H_{23}NO_6$	66.49 (66.23)	5.83 (5.84)	3.52 (3.47)	3350, 1710	397 (M^+, 100), 366 (73), 364 (30), 174 (16)
11b	143—144 (M)	$C_{23}H_{25}NO_6$	67.14 (66.91)	6.12 (5.92)	3.40 (3.51)	3400, 1700[c]	411 (M^+, 100), 380 (68), 378 (48)
11c	Amorphous	$C_{24}H_{25}NO_6$	423.1680[b] (423.1680)			1710, 1640	423 (M^+, 100), 392 (38), 382 (87), 367 (57), 352 (3)
12a	152—153 (B–H)	$C_{21}H_{19}NO_5$	69.03 (69.20)	5.24 (5.23)	3.83 (3.83)	3400, 1710	365 (M^+, 100), 336 (23), 320 (31), 306 (48), 290 (19), 149 (19)
12b	217—218 (B–H)	$C_{22}H_{21}NO_5$	69.64 (69.90)	5.58 (5.59)	3.69 (3.77)	3350, 1680[c]	379 (M^+, 100), 364 (45), 350 (59), 320 (43)
12c	213—214 (M)	$C_{23}H_{21}NO_5$	70.57 (70.42)	5.41 (5.43)	3.58 (3.56)	1700, 1630	391 (M^+, 100), 362 (50), 332 (22)
20a	189—190 (M)	$C_{21}H_{21}NO_5$	68.65 (68.46)	5.76 (5.78)	3.81 (3.77)	3550	367 (M^+, 47), 350 (45), 338 (21), 308 (100)
20b	197—198 (B–H)	$C_{22}H_{23}NO_5$	69.27 (69.24)	6.08 (6.01)	3.67 (3.88)	3300[c]	381 (M^+, 1.9), 364 (100), 334 (35), 320 (5.7)
20c	181—182.5 (B–H)	$C_{23}H_{23}NO_5$	70.21 (70.11)	5.89 (5.88)	3.56 (3.63)	3400, 1640	393 (M^+, 3.4), 376 (100), 360 (9.4), 346 (21), 330 (5.7)
21a	186—187 (I)	$C_{21}H_{21}NO_5$	68.65 (68.67)	5.76 (5.84)	3.81 (3.83)	3550	368 ($M^+ + 1$, 58),[d] 350 (100)
21b	167—168 (B–H)	$C_{22}H_{23}NO_5$	69.27 (69.23)	6.08 (6.08)	3.67 (3.57)	3600	381 (M^+, 2.3), 364 (100), 334 (21)
21c	197—198 (EA–H)	$C_{23}H_{23}NO_5$	70.21 (70.34)	5.89 (5.92)	3.56 (3.77)	3500, 3350, 1640	393 (M^+, 3.9), 376 (100), 360 (8.5), 346 (21), 344 (5.4), 330 (5.3)
22a	181.5—182.5 (B–H)	$C_{21}H_{23}NO_6$	65.44 (65.52)	6.02 (6.02)	3.63 (3.64)	3550, 3300	385 (M^+, 1.5), 367 (100), 352 (64), 338 (16), 308 (57)
22b	156—157 (M)	$C_{22}H_{25}NO_6$	66.15 (65.94)	6.31 (6.30)	3.51 (3.56)	3350	399 (M^+, 39), 381 (82), 176 (100)
22c	173.5—175 (M)	$C_{23}H_{25}NO_6$	67.14 (67.27)	6.12 (6.09)	3.40 (3.51)	3550, 3350, 1630	411 (M^+, 6.9), 393 (99), 364 (35), 352 (97), 189 (99), 176 (100)
23a	139—141 (I)	$C_{22}H_{25}NO_6$	66.15 (65.85)	6.31 (6.17)	3.51 (3.39)	3300	399 (M^+, 15), 367 (50), 352 (42), 338 (20), 308 (100), 176 (19)
23b	83—85 (M)	$C_{23}H_{27}NO_6 \cdot$ MeOH	64.70 (64.64)	7.01 (7.01)	3.14 (3.39)	3500, 3400[c]	413 (M^+, 14), 381 (84), 364 (24), 352 (100), 322 (93), 189 (18), 176 (37)
23c	62—64 (M)	$C_{24}H_{27}NO_6 \cdot$ MeOH	65.72 (66.05)	6.83 (6.84)	3.06 (3.09)	3350, 1640	425 (M^+, 15), 393 (35), 364 (18), 352 (100), 334 (16), 189 (51), 176 (35)
24a	192—194 (A)	$C_{21}H_{21}NO_5$	68.65 (68.54)	5.76 (5.82)	3.81 (3.96)	3300, 1635[c]	367 (M^+, 38), 338 (20), 308 (100)
24b	142—144 (A)	$C_{22}H_{23}NO_5 \cdot H_2O$	66.15 (66.28)	6.31 (6.36)	3.51 (3.55)	3350	381 (M^+, 100), 366 (40), 321 (68)
24c	186.5—188 (M–E)	$C_{23}H_{23}NO_5 \cdot$ 1/2 MeOH	68.73 (68.46)	6.15 (5.92)	3.42 (3.38)	3350, 1620	393 (M^+, 100), 364 (30), 352 (50), 334 (23), 189 (98), 176 (33)
25a	144.5—145.5 (I)	$C_{22}H_{25}NO_6 \cdot H_2O$	64.32 (64.61)	6.34 (6.19)	3.26 (3.50)	3550, 3300	399 (M^+, 13), 367 (47), 352 (41), 328 (21), 308 (100), 176 (18)
25b	139—140 (I)	$C_{23}H_{27}NO_6$	66.81 (66.77)	6.58 (6.52)	3.39 (3.28)	3550, 3350	413 (M^+, 13), 381 (70), 364 (15), 352 (96), 322 (100), 189 (18), 176 (40)

TABLE IV. (continued)

Compd.	mp (°C) (Solvent)[a]	Formula	Analysis Calcd (Found) C H N	IR (cm^{-1}) ($CHCl_3$)	MS *m/z* (%)
25c	143.5—145 (M–I)	$C_{24}H_{27}NO_6$	67.75 6.40 3.29 (67.47 6.51 3.29)	3550, 3350, 1660	425 (M^+, 11), 393 (79), 352 (100), 176 (29)
26a	Amorphous	$C_{21}H_{21}NO_5$	367.1418[b] (367.1423)	3550, 3300, 1635	367 (M^+, 49), 338 (21), 308 (100)
26b	98—100 (A)	$C_{22}H_{23}NO_5$	381.1574[b] (381.1600)	3550	381 (M^+, 100), 364 (45), 322 (76), 189 (26), 176 (25)
26c	97—99 (M)	$C_{23}H_{23}NO_5$	70.21 5.89 3.56 (70.09 5.75 3.69)	3550, 3300, 1625	393 (M^+, 2.6), 376 (100), 346 (68)

a) A, ethanol; B, benzene; E, ethyl ether; EA, ethyl acetate; H, hexane; I, isopropyl ether; M, methanol. *b*) High-resolution MS. *c*) KBr. *d*) Chemical ionization MS.

cis relationship between C_{14}–N and the hydroxy group at C-8 in **22a** and suggested the same stereochemistry at C-8 of the other products (**22**, **23**, and **25**), as depicted.

Thus, we have found that the 8-alkyl-8,14-cycloberbines (**9**) and their 13-hydroxy derivatives (**20** and **21**) undergo exclusive C_8–N bond cleavage on acid treatment to give the *N*-unsubstituted spirobenzylisoquinolines, which could be led to various modified derivatives by further elaboration. In combination with an easy preparation of the cycloberbines, this simple transformation reaction provides an efficient method for the synthesis of *N*-unsubstituted spirobenzylisoquinolines possessing substituents at C-8 and C-13 on the five-membered ring from protoberberines.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Alumina (Aluminiumoxid 90, Aktivitätsstufe II—III, 70—230 mesh, Merck) and silica gel (Kieselgel 60, 70—230 mesh, Merck) were used for column chromatography. Organic extracts were dried over anhydrous Na_2SO_4. IR spectra were measured with a JASCO A-102 spectrometer in $CHCl_3$ unless otherwise stated, mass spectrum (MS) with a Hitachi M-80 mass spectrometer, and ^{1}H-NMR spectra with a JEOL FX-100 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard unless otherwise stated.

General Procedure for Reaction of the 8-Alkyl-8,14-cycloberbines (9, 20, and 21) with 10% Hydrochloric Acid——A solution of the cycloberbine (**9**, **20**, or **21**; 1.2 mmol) in 10% hydrochloric acid (60 ml) was heated at 70—80 °C for 2 h. After cooling, the reaction mixture was made alkaline with solid potassium carbonate, and then extracted with methylene chloride. The extract was washed with water and brine, dried, and concentrated. Chromatography of the residue on silica gel with ethyl acetate–benzene (1 : 1) (in the case of **9**) or ethyl acetate (in the case of **20** and **21**) gave the products. The results and the physical data of the products are summarized in Tables I and III—V.

General Procedure for Reaction of the 8-Alkyl-8,14-cycloberbines (9, 20, and 21) with Trifluoroacetic Acid in Methanol——A solution of the cycloberbine (**9**, **20**, or **21**; 0.6 mmol) in methanol (10 ml) was stirred for 3.5 h in the presence of trifluoroacetic acid (2 drops) at room temperature. Methanol was evaporated off and the residue was made alkaline with 10% aq. potassium carbonate, and then extracted with methylene chloride. The extract was washed with water and brine, dried, and concentrated. Chromatography of the residue on alumina with methylene chloride–benzene (2 : 1) (in the case of **9**) or on silica gel with ethyl acetate (in the case of **20** and **21**) gave the products. The results and the physical data of the products are summarized in Tables I and III—V.

General Procedure for Reduction of 9 with $NaBH_4$——$NaBH_4$ (20 mmol) was added portionwise to a solution of **9** (4 mmol) in methanol (60 ml) and the reaction mixture was stirred for 1 h at room temperature. After evaporation of the methanol, water was added to the residue and the mixture was extracted with methylene chloride. The extract was washed with water and brine, dried, and concentrated. Chromatography of the residue on alumina with ethyl acetate–hexane (3 : 1) gave the alcohols (**20** and **21**). The results and the physical data of the products are summarized in Tables II, IV, and V.

General Procedure for Reduction of 9 with $LiAlH(OBu^t)_3$——$LiAlH(OBu^t)_3$ (10 mmol) was added to a solution of **9** (1 mmol) in dry THF (100 ml) and the reaction mixture was heated under reflux for 1 h, then allowed to cool. Water

TABLE V. ^{1}H-NMR Spectral Data for Spirobenzylisoquinolines

Compd.	Chemical shift (δ: ppm, J in Hz, $CDCl_3$)							
	H-1	H-4	H-11	H-12	H-13	OCH_2O	OMe	Others
10a	5.94 s	6.58 s	7.07 (AB-q, J=9)	7.61	—	5.84, 5.80 (AB-q, J=2)	4.00 s 3.98 s	1.64 s (3H)
10b	6.04 s	6.58 s	7.09 (AB-q, J=8)	7.59	—	5.86, 5.81 (AB-q, J=2)	3.99 s 3.96 s	1.92 q (2H, J=7) 0.72 t (3H, J=7)
10c	6.00 s	6.53 s	7.08 (AB-q, J=9)	7.60	—	5.83, 5.80 (AB-q, J=2)	4.00 s 3.98 s	4.92—4.36 m (2H)
11a	5.75 s	6.58 s	7.12 (AB-q, J=9)	7.66	—	5.81, 5.77 (AB-q, J=1)	4.02 s 3.90 s 3.13 s	1.56 s (3H)
11b	5.85 s	6.58 s	7.12 (AB-q, J=8)	7.62	—	5.83, 5.78 (AB-q, J=2)	4.01 s 3.91 s 3.09 s	1.87 q (2H, J=7) 0.85 t (3H, J=7)
11c	5.83 s	6.54 s	7.13 (AB-q, J=9)	7.64	—	5.80, 5.78 (AB-q, J=2)	4.02 s 3.93 s 3.09 s	6.16—5.72 m (1H) 5.04—4.55 m (2H)
12a	6.12 s	6.60 s	7.05 (AB-q, J=9)	7.61	—	5.85, 5.81 (AB-q, J=2)	3.99 s 3.94 s	6.38 s (1H) 5.38 s (1H)
12b	6.21 s	6.62 s	6.98 (AB-q, J=8)	7.57	—	5.86, 5.81 (AB-q, J=1)	3.98 s 3.90 s	7.04 q (1H, J=7) 1.63 d (3H, J=7)
12c	6.16 s	6.63 s	7.01 (AB-q, J=9)	7.57	—	5.84, 5.80 (AB-q, J=2)	3.98 s 3.94 s	7.41 d (1H, J=10) 6.72—6.31 m (1H) 5.43—5.12 m (2H)
20a	6.74 s	6.64 s	6.82 (AB-q, J=8)	7.09	5.21 br s	5.93 s	3.88 s 3.86 s	1.50 s (3H)
20b	6.78 s	6.65 s	6.87 (AB-q, J=8)	7.11	5.22 d[a] (J=12)	5.96, 5.94 (AB-q, J=2)	3.90 s 3.88 s	1.30 q (2H, J=7) 0.99 t (3H, J=7)
20c	6.74 s	6.64 s	6.84 (AB-q, J=8)	7.08	5.20 d[a] (J=12)	5.94, 5.92 (AB-q, J=1.5)	3.89 s 3.85 s	5.97—5.67 m (1H) 5.32—4.80 m (2H)
21a	7.00 s	6.67 s	6.81 (AB-q, J=9)	7.14	4.77 s	5.93, 5.91 (AB-q, J=2)	3.86 s 3.85 s	1.50 s (3H)
21b	7.07 s	6.68 s	6.86 (AB-q, J=8)	7.14	4.74 s	5.94, 5.92 (AB-q, J=2)	3.94 s 3.92 s	1.25 q (2H, J=9) 1.04 t (3H, J=9)
21c	7.03 s	6.67 s	6.82 (AB-q, J=9)	7.12	4.68 s	5.91, 5.89 (AB-q, J=2)	3.87 s 3.85 s	6.14—5.66 m (1H) 5.12—4.87 m (2H)
22a	5.93 s	6.55 s	6.96 (AB-q, J=8)	7.25	4.56 s	5.80 s	3.90 s 3.89 s	1.34 s (3H)
22b	6.24 s	6.58 s	6.97 (AB-q, J=8)	7.21	4.70 s	5.84, 5.83 (AB-q, J=1)	3.90 s (6H)	2.26 q (2H, J=8) 0.77 t (3H, J=8)
22c	6.12 s	6.54 s	6.98 (AB-q, J=9)	7.24	4.64 s	5.85, 5.82 (AB-q, J=2)	3.90 s (6H)	5.92—5.48 m (1H) 5.00—4.72 m (2H)
23a	5.80 s	6.55 s	7.02 (AB-q, J=9)	7.34	4.59 s	5.80 s	3.92 s 3.85 s 3.13 s	1.35 s (3H)
23b	5.90 s	6.53 s	7.02 (AB-q, J=8)	7.28	4.50 s	5.83, 5.82 (AB-q, J=2)	3.92 s 3.86 s 3.13 s	1.63 q (2H, J=7) 0.81 t (1H, J=7)
23c	5.87 s	6.49 s	7.04 (AB-q, J=9)	7.30	4.47 s	5.80, 5.79 (AB-q, J=2)	3.92 s 3.88 s 3.14 s	6.00—5.60 m (1H) 4.94—4.48 m (2H)
24a	6.06 s	6.56 s	6.95 (AB-q, J=9)	7.22	4.98 s	5.87, 5.86 (AB-q, J=1)	3.89 s 3.88 s	6.48 s (1H) 5.01 s (1H)
24b	6.44 s	6.55 s	6.89 (AB-q, J=8)	7.16	4.67 s	5.88, 5.85 (AB-q, J=1)	3.88 s 3.84 s	6.86 q (1H, J=8) 1.57 d (3H, J=8)

TABLE V. (continued)

Compd.	Chemical shift (δ: ppm, J in Hz, $CDCl_3$)							
	H-1	H-4	H-11	H-12	H-13	OCH_2O	OMe	Others
24c	6.41 s	6.57 s	6.92 (AB-q, J=8)	7.18	4.72 s	5.85, 5.84 (AB-q, J=1)	3.89 s (6H)	7.33 d (1H, J=12) 6.51—6.08 m (1H) 5.39—4.98 m (2H)
25a	5.74 s	6.58 s	6.96 (AB-q, J=9)	7.13	5.08 s	5.79, 5.78 (AB-q, J=2)	3.91 s 3.84 s 3.20 s	1.50 s (3H)
25b	5.80 s	6.60 s	6.98 (AB-q, J=8)	7.08	5.14 s	5.82, 5.79 (AB-q, J=2)	3.91 s 3.88 s 3.16 s	1.82 q (2H, J=7) 0.82 t (3H, J=7)
25c	5.79 s	6.58 s	6.99 (AB-q, J=8)	7.14	5.26 br s	5.84, 5.82 (AB-q, J=2)	3.92 s 3.90 s 3.22 s	6.12—5.82 m (1H) 5.04—4.56 m (2H)
26a	6.16 s	6.59 s	6.93 (AB-q, J=9)	7.17	4.93 s	5.86, 5.84 (AB-q, J=2)	3.89 s 3.88 s	6.41 s (1H) 5.17 s (1H)
26b	6.44 s	6.60 s	6.91 (AB-q, J=8)	7.15	4.91 s	5.86, 5.85 (AB-q, J=1)	3.89 s 3.84 s	6.85 q (1H, J=8) 1.50 d (3H, J=8)
26c	6.35 s	6.61 s	6.91 (AB-q, J=9)	7.16	4.93 s	5.85 s	3.89 s (6H)	7.30 d (1H, J=11) 6.50—6.16 m (1H) 5.36—4.92 m (2H)

a) Changed to s on addition of D_2O.

was added, and the precipitates were filtered off. The filtrate was concentrated to leave the residue, which was taken up in methylene chloride. The methylene chloride solution was washed with water and brine, dried, and concentrated. Chromatography of the residue on alumina with ethyl acetate–hexane (3 : 1) gave the alcohols (**20** and **21**). The results and the physical data of the products are summarized in Tables II, IV, and V.

General Procedure for Reaction of the Spirobenzylisoquinolines (10, 23, and 25) with Ethyl Chloroformate—A solution of the spirobenzylisoquinoline (**10a**, **23**, or **25**; 0.15 mmol) and ethyl chloroformate (0.75 mmol) in chloroform (5 ml) was refluxed for 5 h (in the case of **10a**, 26 h) in the presence of trimethylamine (0.75 mmol). After cooling, the solution was washed with 10% aq. potassium carbonate, water, and brine, dried, and concentrated. Chromatography of the residue on silica gel with ethyl acetate–benzene (1 : 2 or 1 : 3) gave the product.

rel-(8*R*,14*R*)-9,10-Dimethoxy-8-methyl-2,3-methylenedioxy-13-oxonorochotensane-7,8-carbolactone[13] (**13**): 63%. mp 234—236 °C (EtOH). IR ν_{max} cm^{-1}: 1740 (C=O), 1710 (C=O). ^{1}H-NMR δ: 7.90, 7.00 (2H, AB-q, J=8.5 Hz, H-12 and H-11), 6.67 (1H, s, H-4), 6.06 (1H, s, H-1), 5.92, 5.89 (2H, AB-q, J=1 Hz, OCH_2O), 4.02, 4.00 (each 3H, each s, OMe×2), 1.74 (3H, s, Me). MS *m/z* (%): 409 (M^+, 31), 365 (100), 350 (84), 320 (57), 306 (15). *Anal.* Calcd for $C_{22}H_{19}NO_7$: C, 64.54; H, 4.68; N, 3.42. Found: C, 64.75; H, 4.66; N, 3.31.

rel-(8*R*,13*S*,14*S*)-8,9,10-Trimethoxy-8-methyl-2,3-methylenedioxynorochotensane-7,13-carbolactone (**29a**): 78%. mp 151—153 °C (MeOH). IR ν_{max} cm^{-1}: 1740 (C=O). ^{1}H-NMR δ: 7.33, 7.06 (2H, AB-q, J=9 Hz, H-12 and H-11), 6.64 (1H, s, H-4), 5.99 (1H, s, H-1), 5.88 (2H, s, OCH_2O), 5.35 (1H, s, H-13), 3.94, 3.88, 3.16 (each 3H, each s, OMe×3), 1.40 (3H, s, Me). MS *m/z* (%): 425 (M^+, 36), 350 (100), 320 (13). High-resolution mass calcd for $C_{23}H_{23}NO_7$: 425.1473. Found: 425.1446.

rel-(8*R*,13*S*,14*S*)-8-Ethyl-8,9,10-trimethoxy-2,3-methylenedioxynorochotensane-7,13-carbolactone (**29b**): 79%. mp 145—147 °C (MeOH). IR ν_{max} cm^{-1}: 1730 (C=O). ^{1}H-NMR δ: 7.31, 6.97 (2H, AB-q, J=8 Hz, H-12 and H-11), 6.55 (1H, s, H-4), 5.81, 5.79 (2H, AB-q, J=2 Hz, OCH_2O), 5.77, 5.71 (each, 1H, each s, H-1 and H-13), 3.93, 3.87, 3.20 (each 3H, each s, OMe×3), 1.68 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 0.90 (3H, J=7 Hz, $CH_2C\underline{H}_3$). MS *m/z* (%): 439 (M^+, 5.6), 380 (19), 366 (61), 364 (100). *Anal.* Calcd for $C_{24}H_{25}NO_7 \cdot 1/2MeOH$: C, 64.60; H, 5.98; N, 3.07. Found: C, 64.83; H, 6.12; N, 3.00.

rel-(8*R*,13*S*,14*S*)-8-Allyl-8,9,10-trimethoxy-2,3-methylenedioxynorochotensane-7,13-carbolactone (**29c**): 82%. mp 195—198 °C (MeOH). IR ν_{max} cm^{-1}: 1730 (C=O). ^{1}H-NMR δ: 7.31, 7.10 (2H, AB-q, J=8 Hz, H-12 and H-11), 6.55 (1H, s, H-4), 6.01 (1H, s, H-1), 5.89, 5.88 (2H, AB-q, J=2 Hz, OCH_2O), 5.80—5.38 (1H, m, $\overset{H}{>}$=), 5.25 (1H, s, H-13), 5.02—4.70 (2H, m, =$\overset{H}{<}$), 3.95, 3.91, 3.16 (each 3H, each s, OMe×3). MS *m/z* (%): 451 (M^+, 30), 392 (29),

376 (26), 366 (100), 351 (29), 336 (37). *Anal.* Calcd for $C_{25}H_{25}NO_7$: C, 66.51; H, 5.58; N, 3.10. Found: C, 66.59; H, 5.56; N, 3.08.

rel-(8*R*,13*R*,14*S*)-7-Ethoxycarbonyl-13-hydroxy-8,9,10-trimethoxy-8-methyl-2,3-methylenedioxynorochotensane (**30a**): 61%. mp 169—170 °C (MeOH). IR ν_{max} cm^{-1}: 3450 (OH), 1670 (C=O). ^{1}H-NMR δ: 7.28, 7.06 (2H, AB-q, J=8 Hz, H-12 and H-11), 6.53 (1H, s, H-4), 6.40 (1H, s, H-1), 6.00 (1H, br s, H-13), 5.80 (2H, s, OCH_2O), 5.02 (1H, br s, OH), 4.15 (2H, q, J=7 Hz, CH_2CH_3). 3.90, 3.81, 3.16 (each 3H, each s, OMe×3), 1.44 (3H, s, Me), 1.30 (3H, t, J=7 Hz, CH_2CH_3). MS m/z (%): 439 (M^+ − MeOH, 100), 366 (30), 350 (21). *Anal.* Calcd for $C_{26}H_{29}NO_8$: C, 64.58; H, 6.05; N, 2.90. Found: C, 64.79; H, 6.11; N, 2.99.

rel-(8*R*,13*R*,14*S*)-7-Ethoxycarbonyl-8-ethyl-13-hydroxy-8,9,10-trimethoxy-2,3-methylenedioxynorochotensane (**30b**): 62%. mp 148—149 °C (MeOH). IR ν_{max} cm^{-1}: 3450 (OH), 1675 (C=O). ^{1}H-NMR δ: 7.31, 7.07 (2H, AB-q, J=8 Hz, H-12 and H-11), 6.53 (1H, s, H-4), 6.50 (1H, s, H-1), 5.97 (1H, d, J=4 Hz, H-13), 5.79 (2H, s, OCH_2O), 4.97 (1H, d, J=4 Hz, OH), 4.14 (2H, q, J=7 Hz, OCH_2CH_3), 3.90, 3.82, 3.11 (each 3H, each s, OMe×3), 1.29 (3H, t, J=7 Hz, OCH_2CH_3), 0.31 (3H, t, J=7 Hz, CH_2CH_3). MS m/z (%): 453 (M^+ − MeOH, 76), 435 (50), 380 (100), 335 (24), 248 (38). *Anal.* Calcd for $C_{26}H_{31}NO_8$: C, 64.31; H, 6.44; N, 2.89. Found: C, 64.57; H, 6.20; N, 3.00.

rel-(8*R*,13*R*,14*S*)-8-Allyl-7-ethoxycarbonyl-13-hydroxy-8,9,10-trimethoxy-2,3-methylenedioxynorochotensane (**30c**): 60%. mp 154—155 °C (MeOH). IR ν_{max} cm^{-1}: 3450 (OH), 1670 (C=O). ^{1}H-NMR δ: 7.31, 7.10 (2H, AB-q, J=7 Hz, H-12 and H-11), 6.52 (1H, s, H-4), 6.43 (1H, s, H-1), 5.99 (1H, d, J=4 Hz, H-13), 5.77 (2H, br s, OCH_2O), 5.52—5.06 (1H, m, $\overset{H}{\diagdown}\!=$), 5.00 (1H, d, J=4 Hz, OH), 4.50—4.09 (2H, m, $=\!\!<^{H}_{H}$), 4.16 (2H, q, J=7 Hz, CH_2CH_3), 3.90, 3.83, 3.13 (each 3H, each s, OMe×3), 1.32 (3H, t, J=7 Hz, CH_2CH_3). MS m/z: (%): 465 (M^+ − MeOH, 100), 392 (36), 352 (15), 336 (19), 248 (81). *Anal.* Calcd for $C_{27}H_{31}NO_8$: C, 65.18; H, 6.28; N, 2.82. Found: C, 65.23; H, 6.24; N, 2.98.

***rel*-(8*R*,14*R*)-8,7-Epoxymethano-9,10-dimethoxy-8-methyl-2,3-methylenedioxynorochotensan-13-one (14)**——Aqueous formaldehyde solution (38%, 3 ml) was added to a solution of **10a** (74 mg, 0.2 mmol) in MeOH (10 ml) and the mixture was refluxed for 30 min. The precipitate was collected by filtration and recrystallized from ethyl acetate to give **14** (61 mg, 85%). mp 256—258 °C. IR ν_{max} cm^{-1}: 1710 (C=O). ^{1}H-NMR δ: 7.64, 7.13 (2H, AB-q, J=8.5 Hz, H-12 and H-11), 6.64 (1H, s, H-4), 5.99 (1H, s, H-1), 5.89, 5.84 (2H, AB-q, J=1.5 Hz, OCH_2O), 4.56, 4.13 (2H, AB-q, J=8 Hz, NCH_2O), 4.00, 3.98 (each 3H, each s, OMe×2), 1.72 (3H, s, Me). MS m/z (%): 395 (M^+, 63), 366 (53), 352 (100), 324 (64). *Anal.* Calcd for $C_{22}H_{21}NO_6$: C, 66.84; H, 5.32; N, 3.54. Found: C, 66.47; H, 5.18; N, 3.56.

***rel*-(8*R*,13*S*,14*S*)-8,7-Epoxymethano-13-hydroxy-9,10-dimethoxy-8-methyl-2,3-methylenedioxynorochotensane (31)**——Aqueous formaldehyde solution (38%, 3 ml) was added to a solution of **22a** (70 mg, 0.2 mmol) in MeOH (10 ml), and the mixture was refluxed for 1 h and concentrated. The residue was made alkaline with sat. aq. potassium carbonate and extracted with methylene chloride. The extract was washed with water, dried, and concentrated. Chromatography of the residue on alumina with ethyl acetate–methylene chloride (1 : 4) gave **31** (60 mg, 83%). mp 153—155 °C (MeOH) (lit.[12] 155—157 °C). The product was identical with an authentic sample in IR and NMR spectra and thin-layer chromatographic behavior.

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