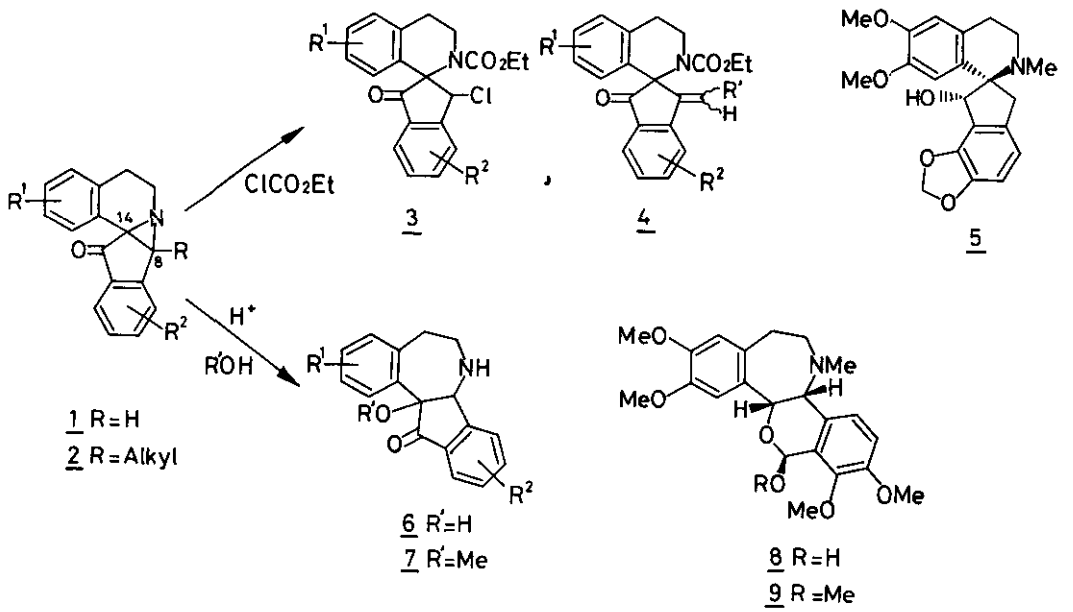
SIMPLE CONVERSION OF 8-ALKYL-8,14-CYCLOBERBINES TO SPIROBENZYL-ISOQUINOLINES BY REGIOSELECTIVE C-N BOND CLEAVAGE

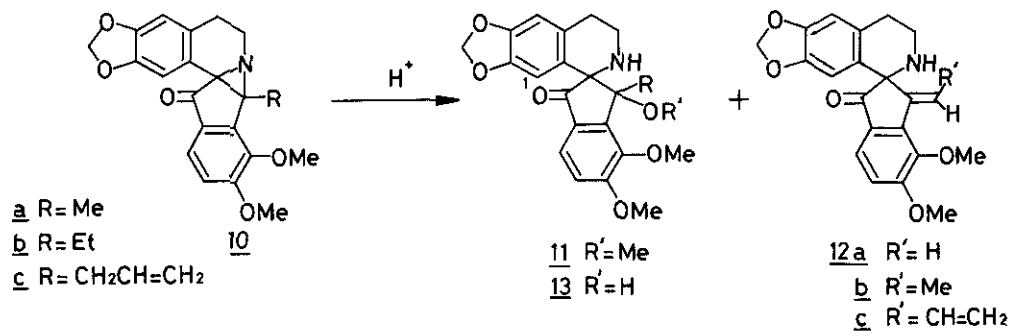
Miyoji Hanaoka,* Shun-ichiro Sakurai, Yuko Sato, and Chisato Mukai
Faculty of Pharmaceutical Sciences, Kanazawa University
Takara-machi, Kanazawa 920, Japan

Abstract—— On acidic treatment the 8-alkyl-8,14-cycloberbines (10) were converted easily to the spirobenzylisoquinolines (11, 12, or 13) in good yields. Reduction of 10 gave stereoselectively the diastereoisomeric alcohols (14 or 15) depending on the reagents, $NaBH_4$ or $LiAlH(OBu^t)_3$, respectively. The both alcohols afforded also corresponding spirobenzylisoquinolines with acids.

Previously, we developed a novel method for a synthesis of the *N*-substituted spirobenzylisoquinolines (3 or 4) from the 8,14-cycloberbines (1 or 2) through regio-



selective C_8-N bond cleavage by treatment with ethyl chloroformate[1] and reported a synthesis of (±)-fumaricine (5),[2] a spirobenzylisoquinoline alkaloid, utilizing this method. On the other hand, we have recently demonstrated an efficient conversion of 1 into the benzindenoazepines (6 or 7)[3,4,5] through alternate regioselective C_{14}-N bond cleavage by treatment with acids and its application to a synthesis of (±)-*cis*-alpinigenine (8) and (±)-*cis*-alpinine (9),[4] rhoeadine alkaloids. This communication describes a simple synthesis of *N*-unsubstituted 8-alkylspirobenzylisoquinolines *from* 8-alkyl-8,14-cycloberbines by acidic treatment. The 8-methyl-8,14-cycloberbine (10a)[1] was stirred in methanol in the presence of trifluoroacetic acid at room temperature (Method I) for 3.5 h afforded the spirobenzylisoquinoline [11a; 76%; mp 190-191°C; *m/e* 397 (M^+); ν 3350, 1710; δ 7.66, 7.12 (2H, AB-q, *J*=8.5), 6.58 (1H, s), 5.81, 5.77 (2H, AB-q, *J*=1.4), 5.75 (1H, s, H-1), 4.02, 3.90, 3.13, 1.56 (3H x 4, s)]. Similar treatment of the 8-ethyl- and 8-allyl-8,14-cycloberbines (10b[1] and 10c[6]) gave the methoxyspirobenzylisoquinolines, 11b (83%) and 11c (56%), along with the unsaturated spirobenzylisoquinolines, 12b (12%) and 12c (31%), respectively. On the other hand, upon being heated with



a R=Me
b R=Et
c R=CH2CH=CH2

10

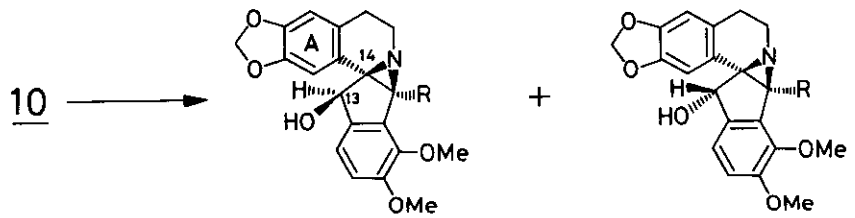
11 R'=Me
13 R'=H

12a R'=H
b R'=Me
c R'=CH=CH2

10% hydrochloric acid at 70-80°C (Method II) for 2 h, the 8-alkyl-8,14-cycloberbines (10a, 10b, and 10c) furnished the hydroxyspirobenzylisoquinolines, 13a [74%; mp 173-174°C; *m/e* 383 (M^+); ν 3300, 1700; δ 7.61, 7.07 (2H, AB-q, *J*=8.5), 6.58 (1H, s), 5.94 (1H, s, H-1), 5.84, 5.80 (2H, AB-q, *J*=1.5), 4.00, 3.98, 1.64 (3H x 3, s)], 13b (80%), and 13c (56%), accompanied with the unsaturated spirobenzylisoquinolines, 12a [21%; mp 152-153°C; *m/e* 365 (M^+); ν 3400, 1700, 1640; δ 7.61, 7.05 (2H, AB-q, *J*=8.5), 6.60 (1H, s), 6.38 (1H, s, $=\!\!<^{H}_{H}$), 6.12 (1H, s, H-1), 5.85, 5.81 (2H, AB-q, *J*=1.2), 5.38 (1H, s, $=\!\!<^{H}_{H}$), 3.99, 3.94 (3H x 2, s)], 12b (17%), and 12c (33%),

respectively. In consonance with the spirobenzylisoquinoline skeleton, all these products revealed the signals due to H-1 at higher field (5.75-6.21 ppm)[7] in their PMR spectra. And the Z-configuration of 12b and 12c was confirmed by the lower chemical shift [7.04 (12b) and 7.41 (12c)] of the vinylic proton depicted in 12.[8] Contrary to the previous results on the 8,14-cycloberbine (1) giving exclusively the benzindenoazepines (6 or 7), the introduction of 8-alkyl substituents to cycloberbines changed completely the regioselectivity in C-N bond cleavage of the aziridine ring presumably because of the enhanced stability of the intermediate carbocation at C_8 to spiro compounds in comparison with that at C_{14} to benzindenoazepines.

Reduction of 10a with $NaBH_4$ in methanol yielded the two diastereoisomeric alcohols, 14a and 15a in 71 and 13% yields, respectively, whereas that with $LiAlH(OBu^t)_3$ in tetrahydrofuran gave 14a and 15a in 14 and 77% yields, respectively. As the signal due to H-13 of 14a appeared at lower field (δ 5.21 ppm) than that of 15a (δ 4.77 ppm) by deshielding effect of the aromatic ring A,[9,10] the relative stereochemistry of C_{13}-OH and C_{14}-N in 14a is *cis* and that in 15a, *trans*. The similar results were obtained in the reduction of 10b and 10c, and summarized in Table I



14 15

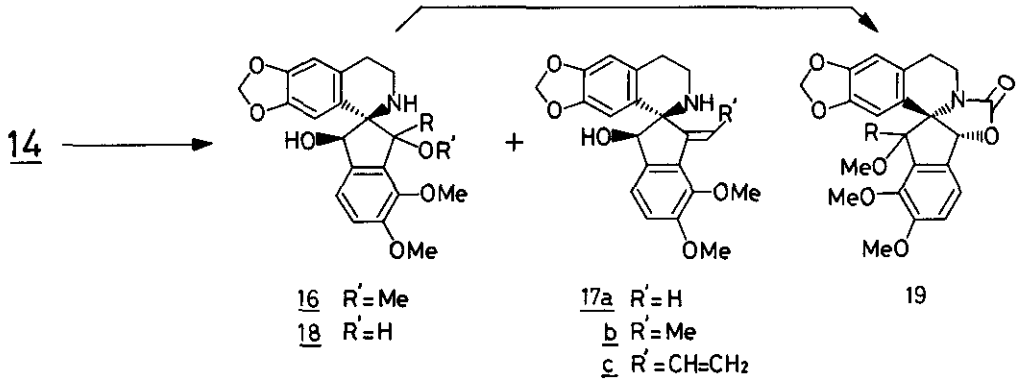
Table I Reduction of the 8,14-Cycloberbines (10) with $NaBH_4$ (A) or $LiAlH(OBu^t)_3$ (B)

Cycloberbine	R	Reagent	Yield(%) 14	Yield(%) 15	Product Ratio 14:15	H-13 Chemical Shift(δ) 14	H-13 Chemical Shift(δ) 15
10a	Me	A	71	13	5.5:1.0	5.21	4.77
		B	14	77	1.0:5.5		
10b	Et	A	88	9	9.5:1.0	5.22	4.74
		B	12	88	1.0:7.5		
10c	CH_2-CH=CH_2	A	80	12	6.5:1.0	5.05	4.68
		B	13	85	1.0:6.5		
10d*	H	A	95	0	1.0:0.0	5.63	4.84
		B	14	67	1.0:5.0		

* The results have already been reported.[9,10]

The above reverse stereoselectivity depending on the reagents would be well interpreted by the assumption that $NaBH_4$ attacks the carbonyl mainly from its less-hindered side, whereas $LiAlH(OBu^t)_3$ at first forms predominantly a complex with the nitrogen of the aziridine ring and then the hydride of the complex attacks intramolecularly the carbonyl from the same side of the nitrogen.

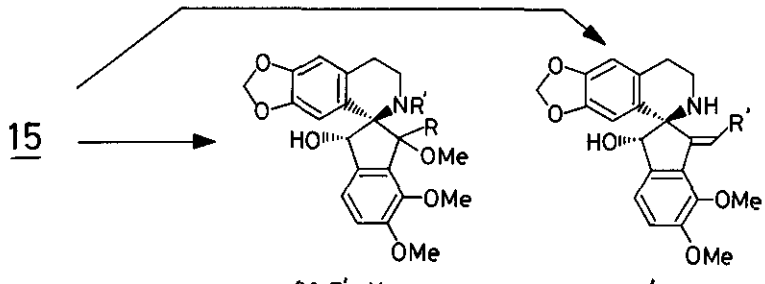
Acidic cleavage of the 13-hydroxycycloberbines (14 and 15) was next investigated. On treatment with the Method I the *cis*-alcohols (14a and 14b) gave the methoxyspirobenzylisoquinolines, 16a (71%) and 16b (83%), respectively, while the alcohol (14c) afforded 16c (60%) along with the unsaturated spiro compound (17c; 16%). Similarly, treatment of 14a, 14b, and 14c with the Method II furnished the dihydroxy spiro derivatives, 18a (45%), 18b (25%), and 18c (49%), accompanied with 17a (36%), 17b (54%), and 17c (22%), respectively. On the other hand, the *trans*-alcohols (15a, 15b, and 15c) gave the methoxyspiro compounds, 20a (70%), 20b (68%), and 20c (64%), with the Method I and the unsaturated spiro compounds, 21a (79%), 21b (70%), and 21c (74%), with the Method II, respectively. Again the 13-hydroxy-



16 R'=Me
18 R'=H

17a R'=H
b R'=Me
c R'=CH=CH$_2$

19



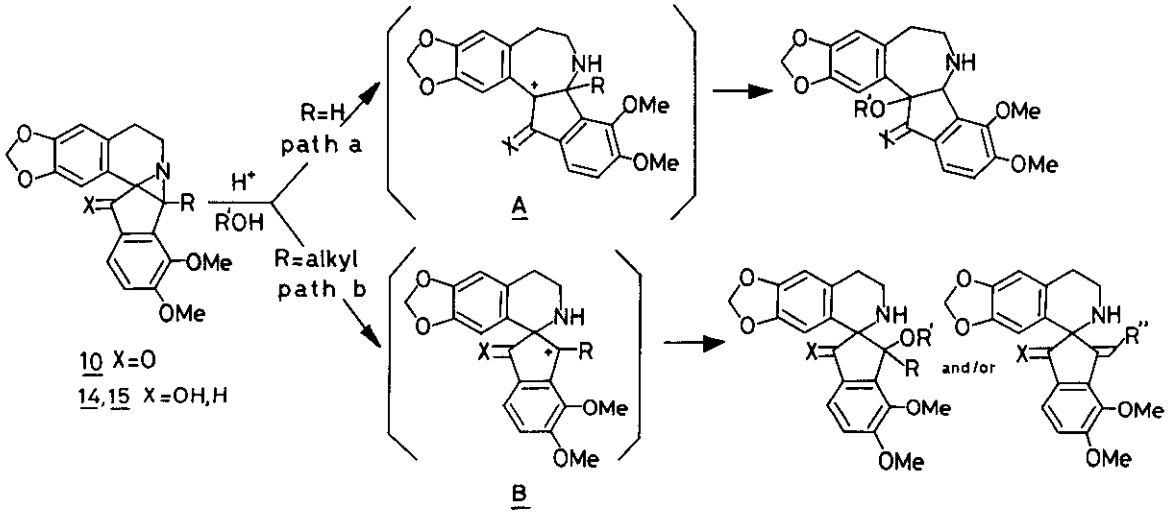
20 R'= H
22 R'= CO_2Et

21a R'=H
b R'=Me
c R'=CH=CH$_2$

cycloberbines (14 and 15) afforded exclusively spirobenzylisoquinolines and none of benzindenoazepines could be detected.

On treatment with ethyl chloroformate the methoxyspiro compounds (16a, 16b, and 16c) derived from 14 afforded the oxazolidinones (19a, 19b, and 19c), respectively, while the methoxyspiro compounds (20a, 20b, and 20c) derived from 15 were led to the carbamates (22a, 22b, and 22c), respectively. These results established unambiguously the aforementioned stereochemistry of the *cis*- and *trans*-alcohols (14 and 15).

The regioselectivity in acidic C-N bond cleavage of cycloberbines would depend on the relative stability between the intermediate carbocation A and B to benzindeno-azepines and spirobenzylisoquinolines, respectively, as shown below.



Thus 8-alkyl-8,14-cycloberbines were found to afford easily spirobenzylisoquinolines by acidic treatment and this simple transformation would be of value particularly in terms of providing *N*-unsubstituted spirobenzylisoquinolines which could lead to various modified derivatives.

REFERENCES AND FOOTNOTES

1) M. Hanaoka, S. Yasuda, K. Nagami, K. Okajima, and T. Imanishi, *Tetrahedron Letters*, 1979, 3749.

2) M. Hanaoka, S. Yasuda, Y. Hirai, K. Nagami, and T. Imanishi, *Heterocycles*, 1980, 14, 1455.

3) M. Hanaoka, M. Inoue, K. Nagami, Y. Shimada, and S. Yasuda, *Heterocycles*, 1982, 19, 313.

4) M. Hanaoka, M. Inoue, S. Sakurai, Y. Shimada, and S. Yasuda, *Chem. Pharm. Bull.*, 1982, 30, 1110.

5) *cf.* N. Murugesan, G. Blaskó, R.D. Minard, and M. Shamma, *Tetrahedron Letters*, 1981, 22, 3131; G. Blaskó, V. Elango, N. Murugesan, and M. Shamma, *Chem. Commun.*, 1981, 1246.

6) The compound (10) was prepared from berberine by the following reaction sequence; i) CH_2=$CHCH_2MgBr$ ii) mCPBA iii) hν.[1)]

7) R.M. Preisner and M. Shamma, *J. Natural Products*, 1980, 43, 305.

8) The vinylic proton of (Z)-*N*-methyl derivative of 12b resonated at 7.00 ppm.[1)]

9) M. Hanaoka, M. Inoue, M. Takahashi, and S. Yasuda, *Heterocycles*, 1982, 19, 31.

10) M. Hanaoka, S. Sakurai, T. Ohshima, S. Yasuda, and C. Mukai, *Chem. Pharm. Bull.*, in press.

Received, 6th August, 1982