CONVERSION OF THE SYNTHETIC PRECURSOR FOR *IPECAC* AND *CORYNANTHE* ALKALOIDS INTO SYNTHETIC INTERMEDIATES OF QUININE ALKALOIDS AND (±)-DIHYDROANTIRHINE#

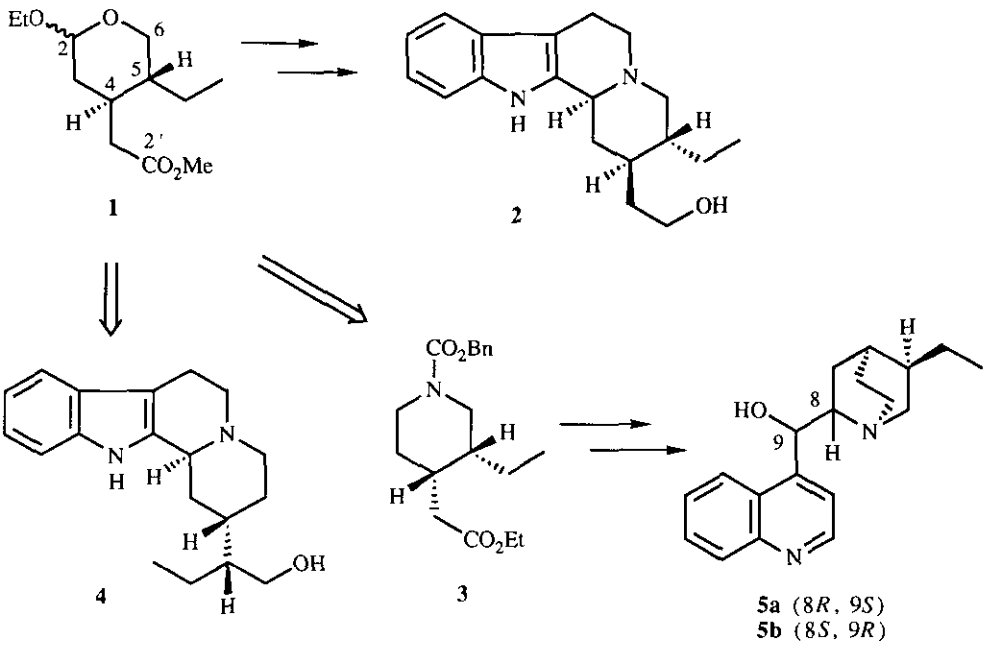
Nobuaki Taniguchi, Masataka Ihara, and Keiichiro Fukumoto*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Abstract--The epimeric mixture of the *trans*-substituted tetrahydropyran derivatives (**1**) was transformed to the *cis*-substituted lactone (**6**), which was converted into the piperidine (**3**), the synthetic intermediate of dihydrocinchonine (**5a**) and dihydrocinchonidine (**5b**), and the synthetic precursor (**11**) of (±)-dihydroantirhine (**4**).

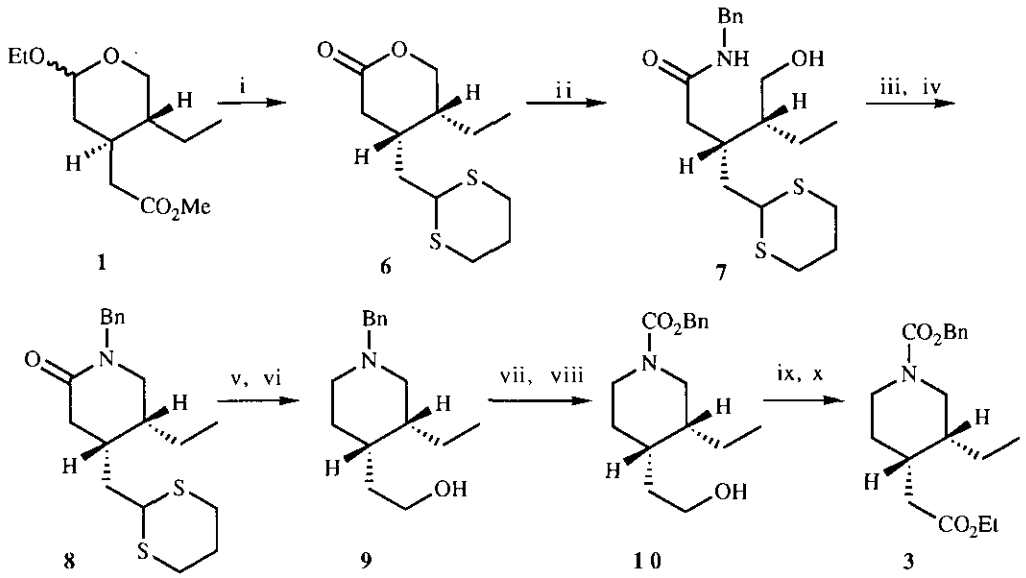
Recently, syntheses of *ipecac* and *corynanthe* alkaloids such as dihydrocorynantheol (**2**) were achieved through the *trans*-substituted cyclic acetal (**1**), formed highly stereoselectively by radical cyclization.[1] In these cases, the *trans*-substituted piperidine rings were constructed by the insertion of a nitrogen atom between the C2 and C6 positions of the key intermediate (**1**). It was considered that **1** was not only the useful precursor of *trans*-substituted piperidine derivatives but also the precursor of other types of substituted ones. For example, the *cis*-substituted piperidine derivative (**3**), which had been already converted into quinine alkaloids, dihydrocinchonine (**5a**) and dihydrocinchonidine (**5b**),[2] could be assembled by the insertion of a nitrogen atom between the C6 and C2' positions of **1**. On the other hand, the D ring of

This paper is dedicated to Emeritus Professor M. Hamana on the occasion of his 75th birthday.



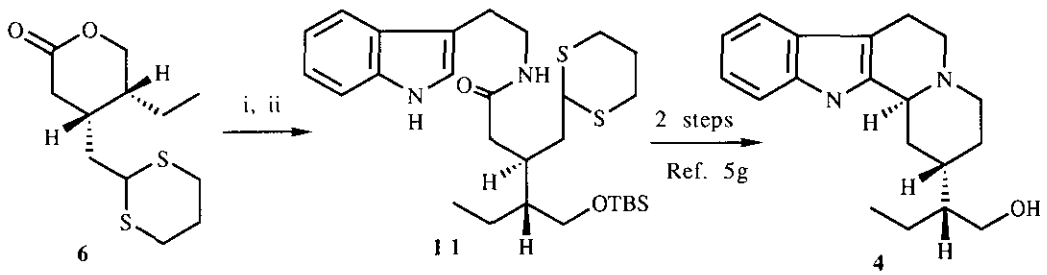
dihydroantirhine (**4**), isolated from *Aspidosperma marcgravianum*,[3] could be made by the connection of C2 and C2' through a nitrogen atom. Here we wish to report formal total syntheses of dihydrocinchonine (**5a**), dihydrocinchonidine (**5b**), and (±)-dihydroantirhine (**4**) according to the above strategy.

The epimeric mixture of (±)-**1**[4] was first transformed into the *cis*-substituted lactone (**6**) in 99% yield by the treatment with 1,3-propanedithiol in the presence of BF_3·Et_2O. Condensation of the lactone (**6**) with benzylamine afforded in quantitative yield the amide (**7**) which was treated with methanesulfonyl chloride. The formed mesylate was subjected to the base catalyzed cyclization in the presence of 18-crown-6 to give the *cis*-substituted lactam (**8**) in 67% overall yield for two steps. The resulting lactam (**8**) was converted into the *cis*-substituted piperidine (**9**) by the following sequences. Namely, deprotection of the thioacetal (**8**) with MeI, followed by reduction with $LiAlH_4$, gave **9** in 69% overall yield. Debenzylation of **9** and the subsequent selective protection of the secondary amino group afforded the alcohol (**10**) in 61% overall yield. Oxidation of **10** with Jones reagent, followed by esterification gave in 83% overall yield the ethyl ester (**3**), which was identical with the authentic sample[2] in all respects (ir, ^{1}H-nmr and tlc).



Reagents and conditions: i, 1, 3-propanedithiol, BF_3•Et_2O; ii, benzylamine, heat; iii, MsCl, Et_3N; iv, KH, 18-crown-6; v, MeI, $NaHCO_3$; vi, $LiAlH_4$; vii, 10% Pd-C, HCO_2NH_4, viii, $ClCO_2Bn$, $NaHCO_3$; ix, CrO_3, H_2SO_4, acetone; x, conc. H_2SO_4, EtOH.

For the purpose of the synthesis of dihydroantirhine (**4**),[3, 5] the lactone (**6**) and tryptamine were heated to give the amino alcohol, which was protected with *tert*-butyldimethylsilyl group to afford in 75% overall yield **11**, whose spectral data were identical with those of the authentic compound.[5g] Since **11** had been converted into dihydroantirhine (**4**) in two steps,[5g] the formal total synthesis was accomplished. Thus we realized the construction of three different types of substituted piperidine derivatives starting from the common key intermediate (**1**).



TBS=$SiMe_2Bu^t$

Reagents and conditions: i, tryptamine, heat; ii, TBSCl, Et_3N, DMAP.

ACNOWLEDGEMENT

We are indebted to Professor T. Suzuki of Akita University for supplying spectral data of the authentic specimen (**11**).

REFAENCES AND NOTES

1) M. Ihara, N. Taniguchi, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Chem. Commun.*, 1987, 1438; M. Ihara, K. Yasui, N. Taniguchi, K. Fukumoto, and T. Kametani, *Tetrahedron Lett.*, 1988, **29**, 4963; M. Ihara, K. Yasui, N. Taniguchi, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1469; M. Ihara, N. Taniguchi, K. Yasui, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2771.

2) M. Ihara, N. Taniguchi, K. Noguchi, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Chem. Commun.*, 1986, 573; *J. Chem. Soc., Perkin Trans. 1*, 1988, 1277.

3) G. M. T. Robert, A. Ahond, C. Poupat, P. Potier, and H. Jacquemin, *J. Nat. Prod.*, 1983, **46**, 649.

4) The epimeric mixture of **1** was synthesized starting from racemic 2-*tert*-butyldimethylsiloxymethylbutanol according to ref. 1.

5) Synthesis: a) S. R. Johns, J. A. Lamberton, and J. L. Occolowitz, *Aust. J. Chem.*, 1967, **20**, 1463; b) Y. K. Sawa and H. Matsumura, *Tetrahedron*, 1969, **25**, 5319; c) T. Kimura and Y. Ban, *Chem. Pham. Bull.*, 1969, **17**, 296; d) E. Wenkert, P. W. Sprague, and R. L. Webb, *J. Org. Chem.* 1973, **38**, 4305; e) L. Chevolot, H. P. Husson, and P. Potier, *Tetrahedron*, 1975, **31**, 2491; f) J. Ficini, A. Guingant, and J. d'Angelo, *J. Am. Chem. Soc.*, 1979, **101**, 1318; g) T. Kametani, T. Suzuki, E. Sato, M. Nishimura, and K. Unno, *J. Chem. Soc., Chem. Commun.*, 1982, 1201; h) M. Lounasmaa and R. Jokela, *Tetrahedron*, 1989, **45**, 7449.

Received, 6th December, 1991