

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

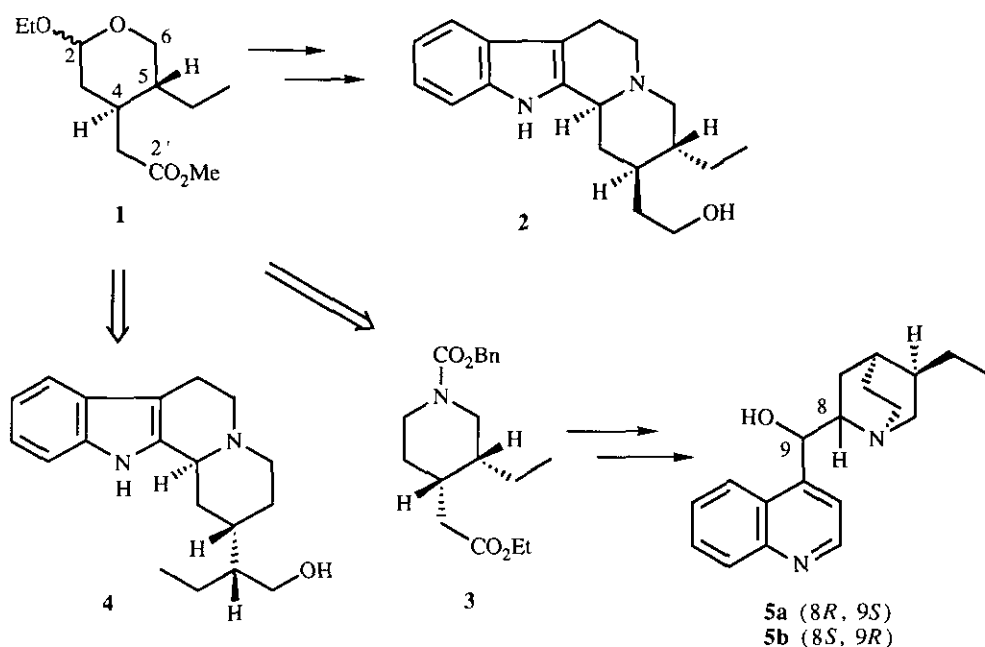
Nobuaki Taniguchi, Masataka Ihara, and Keiichiro Fukumoto*

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

Abstract--The epimeric mixture of the *trans*-substituted tetrahydro-
pyran 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**).

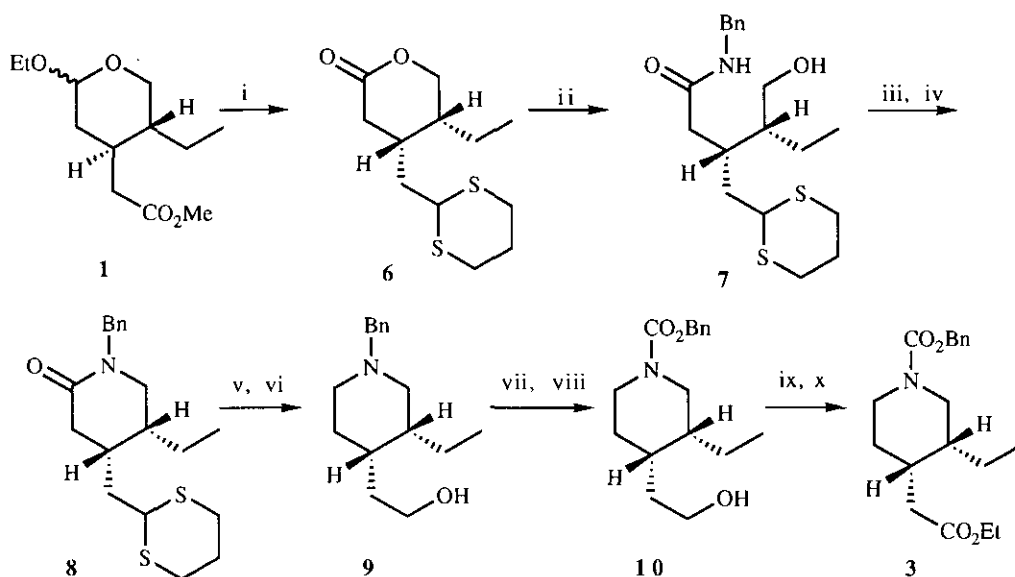
Recently, syntheses of *ipeacac* and *corynanthe* alkaloids such as dihydrocorynantheol (**2**) were achieved through the *trans*-substituted cyclic acetal (**1**), formed highly stereoselectively by radical cyclization.¹ In these cases, the *trans*-substituted piperidine rings were constructed by the 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.



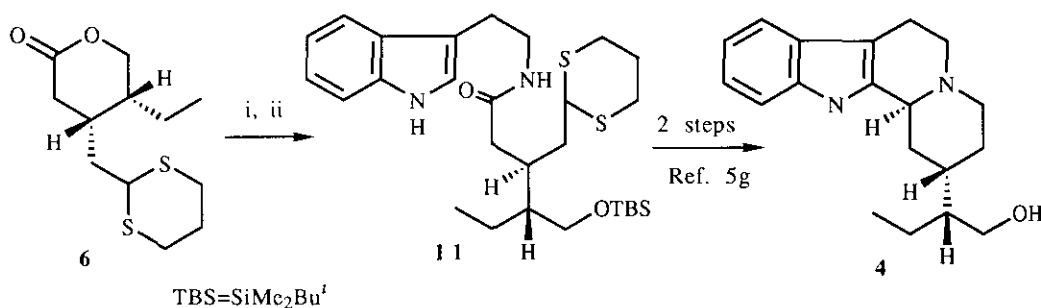
dihydroantirrhine (4), isolated from *Aspidosperma marcgravianum*,³ could be made by the connection of C2 and C2' through a nitrogen atom. Here we wish to report formal total syntheses of dihydrocinchonine (5a), dihydrocinchonidine (5b), and (±)-dihydroantirrhine (4) according to the above strategy.

The epimeric mixture of (±)-14 was first transformed into the *cis*-substituted lactone (6) in 99% yield by the treatment with 1,3-propanedithiol in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$. 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 sample² in all respects (ir, ^1H -nmr and tlc).



Reagents and conditions: i, 1, 3-propanedithiol, $\text{BF}_3 \cdot \text{Et}_2\text{O}$; 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 dihydroantirrhine (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 dihydroantirrhine (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).



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

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