Tetrahedron Letters No. 19, pp 1605 - 1608, 1976. Pergamon Press. Printed in Great Britain.

A NEW ENTRY INTO CINCHONA ALKALOIDS VIA A BIOMIMETIC PATHWAY

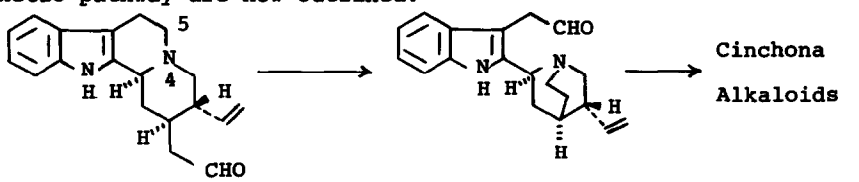
Shun-ichi Yamada*, Kazuo Murato, and Takayuki Shioiri

Faculty of Pharmaceutical Sciences, University of Tokyo,

Hongo, Bunkyo-ku, Tokyo 113, Japan

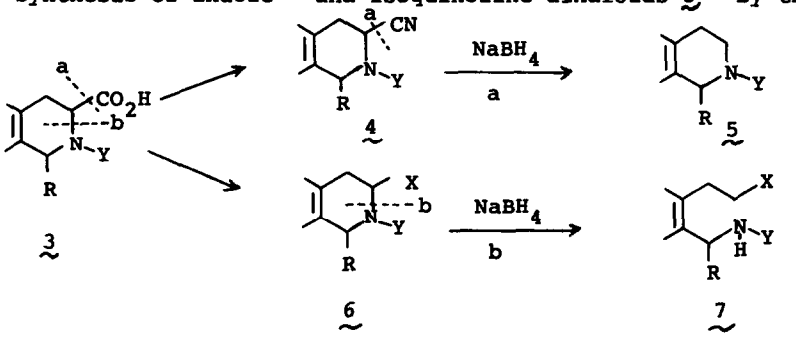
(Received in Japan 13 March 1976; received in UK for publication 29 March 1976)

Recent biosynthetic experiments on Cinchona alkaloids[1] have suggested that the bond-cleavage reaction between positions 4 and 5 of corynantheal 1 will afford cinchonaminal 2, a key intermediate leading to Cinchona alkaloids. Model experiments which may promise the bond-cleavage reaction according to the biosynthetic pathway are now outlined.



1 2

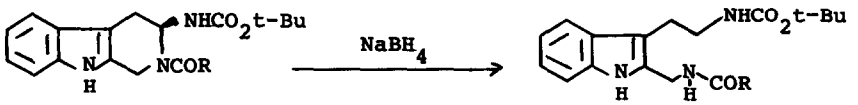
We have already disclosed[2] that laboratory simulation of decarboxylative processes of α-amino acids 3 (cleavage a) may be achieved by reduction of α-amino nitriles 4 with sodium borohydride, and we succeeded a biogenetic-type, asymmetric synthesis of indole[2a] and isoquinoline alkaloids 5[2b] by this new method.[3]



3 4 5 6 7

If the electron-withdrawing substituent, CN function, in 4 could be replaced with substituents containing electron-donating properties (X in 6) and further the electron-withdrawing group could be attached at N(Y in 6), reductive fission b with sodium borohydride might occur as shown above. We chose $NHCO_2t$-Bu or OH as the function X and CO as the function Y.

(S)-tert-Butyl 2-benzyloxycarbonyl-1,2,3,4-tetrahydro-β-carboline-3-carbamate 8a[4], mp 193-194°, $[\alpha]_D^{26}$+67°(C=0.54, $CHCl_3$), prepared from (S)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid[5] by Nb-benzyloxycarbonylation[6] followed by the modified Curtius reaction[7] with diphenyl phosphorazidate in the presence of triethylamine in tert-butyl alcohol, was refluxed with a large excess of sodium borohydride in ethanol-dioxane(4:1). The reductive cleavage(6→7) occurred in an expected way in 89% yield, but its nmr spectrum revealed that 2-benzyloxycarbonyl function in 8a was replaced with ethoxycarbonyl one in the product 9a, mp 148-148.5°[8]. The acetyl analog 8b[9], mp 193-195°(dec), $[\alpha]_D^{20}$+42.5°(C=0.31, MeOH), was also reduced with sodium borohydride in refluxing ethanol-dioxane(3:1) to give the expected ring-cleavage product 9b, mp 176.5-177.5°, in 90% yield.

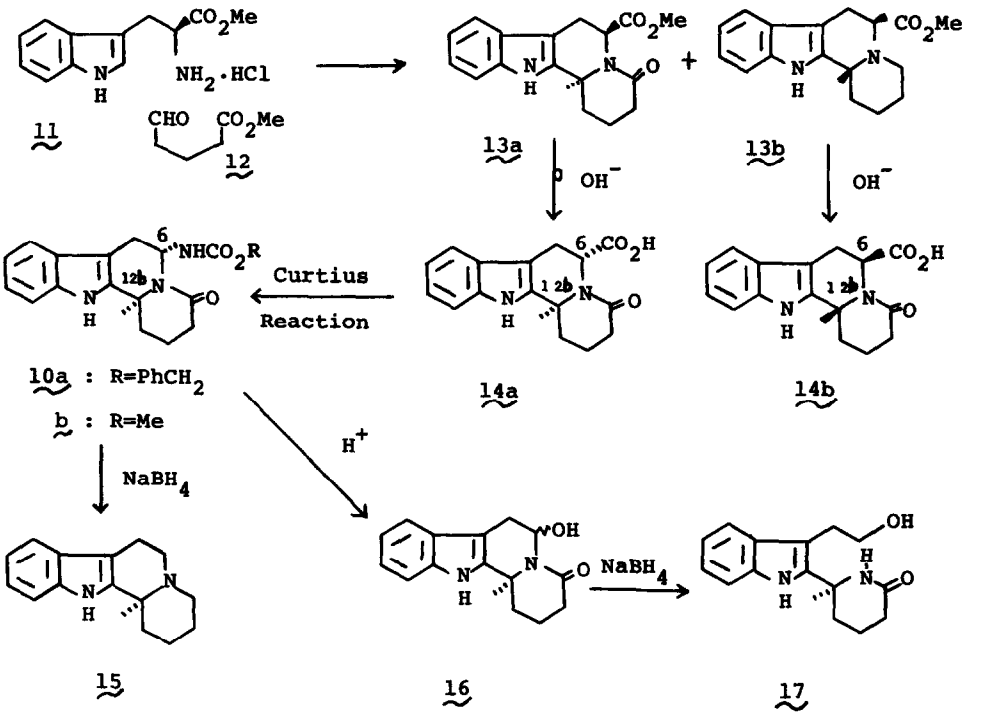


8a : R=$PhCH_2O$
b : R=Me

9a : R=EtO
b : R=Me

On the basis of these encouraging results, we further investigated the synthesis and reductive cleavage of the tetracyclic analog 10. The biogenetic-type, asymmetric Pictet-Spengler reaction[2] of L-tryptophan methyl ester hydrochloride 11 with methyl 4-formylbutyrate 12 in refluxing aqueous methanol afforded a diastereoisomeric mixture of 13a (12% yield), mp 228-229°, $[\alpha]_D^{20}$-103°(C=1.0, MeOH), and 13b(34% yield), mp 181-182°, $[\alpha]_D^{20}$+189°(C=1.0, MeOH).[10] Both esters 13a and 13b were saponified with 2N sodium hydroxide to give the antipodal carboxylic acids 14a, mp 181-185°(dec), $[\alpha]_D^{20}$-245°(C=0.2, MeOH), and 14b, mp 181-185°(dec), $[\alpha]_D^{20}$+249°(C=0.2, MeOH), since epimerization at C-6

occurred in the former case. The Curtius reaction of 14a in benzyl alcohol and methanol afforded benzyl and methyl carbamates 10a and 10b, respectively. Surprisingly, however, the reduction of the benzyl carbamate 10a with sodium borohydride in refluxing ethanol did not yield the expected ring-cleavage product similar to 9. Instead, the known[2a] (-)-indoloquinolizidine 15, mp 148-150°, $[\alpha]_D^{20}$ -82° (C=0.15, MeOH), was obtained in 45% yield. Similar treatment of the benzyl carbamate derived from 14b also resulted in the anomalous reduction to give (+)-isomer of 15. A series of the processes confirmed the absolute configuration at C-12b of 10 and 14[2a]. Thus, the carbamate function was transformed into hydroxyl by the treatment of 10a or 10b with hot aqueous acetone containing hydrochloric acid, giving the hydroxy lactam 16, mp 180-183°, $[\alpha]_D^{20}$ -157° (C=0.37, MeOH), in 23 or 35% yield. Sodium borohydride reduction of 16 in aqueous methanol afforded the desired ring-cleavage product 17, mp 64-65°



$[\alpha]_D^{20}$-18.5°(C=0.4, MeOH), in 90% yield.

Extension of the novel reductive process to the biomimetic synthesis of Cinchona alkaloids is now under way.

REFERENCES AND NOTES

1 A. R. Battersby and R. J. Parry, Chem. Comm., 1971, 30 and 31.

2 a) H. Akimoto, K. Okamura, M. Yui, T. Shioiri, M. Kuramoto, Y. Kikugawa, and S. Yamada, Chem. Pharm. Bull., 22, 2614(1974). b) M. Konda, T. Shioiri, and S. Yamada, Chem. Pharm. Bull., 23, 1025 and 1063(1975).

3 Sodium in liquid ammonia may serve as a substitute for sodium borohydride, S. Yamada, K. Tomioka, and K. Koga, Tetra. Lett., 1976, 57 and 61.

4 All new compounds gave satisfactory elemental analyses and spectroscopic (ir, nmr, mass) data.

5 A. Brossi, A. Focella, and S. Teitel, J. Med. Chem., 16, 419(1973).

6 (S)-2-Benzyloxycarbonyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid[4], mp 177-179°(dec), $[\alpha]_D^{20}$ + 59°(C=1.0, $CHCl_3$).

7 T. Shioiri, K. Ninomiya, and S. Yamada, J. Am. Chem. Soc., 94, 6203(1972); K. Ninomiya, T. Shioiri, and S. Yamada, Tetrahedron, 30, 2151(1974).

8 A probable mechanism of the replacement will be reported elsewhere.

9 Prepared from (S)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid[5] by Nb-acetylation(Nb-acetyl derivative: mp 211-215°(dec), $[\alpha]_D^{20}$ + 145°(C=1.0, MeOH)), followed by the modified Curtius reaction.[7]

10 R. T. Brown, C. L. Chapple, and G. K. Lee, Chem. Comm., 1972, 1007, obtained a lactam, mp 176°, $[\alpha]_D$ + 198°($CHCl_3$), by the Pictet-Spengler reaction of L-tryptophan methyl ester with α-oxoadipic acid in acetic acid.