

A STEREOSELECTIVE SYNTHESIS OF (±)-CORYNANTHEAL

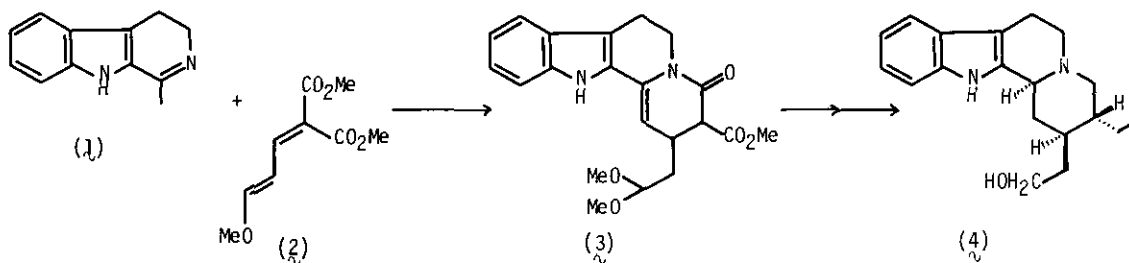
Tetsuji Kametani*, Naoaki Kanaya, and Masataka Ihara

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980,

Japan

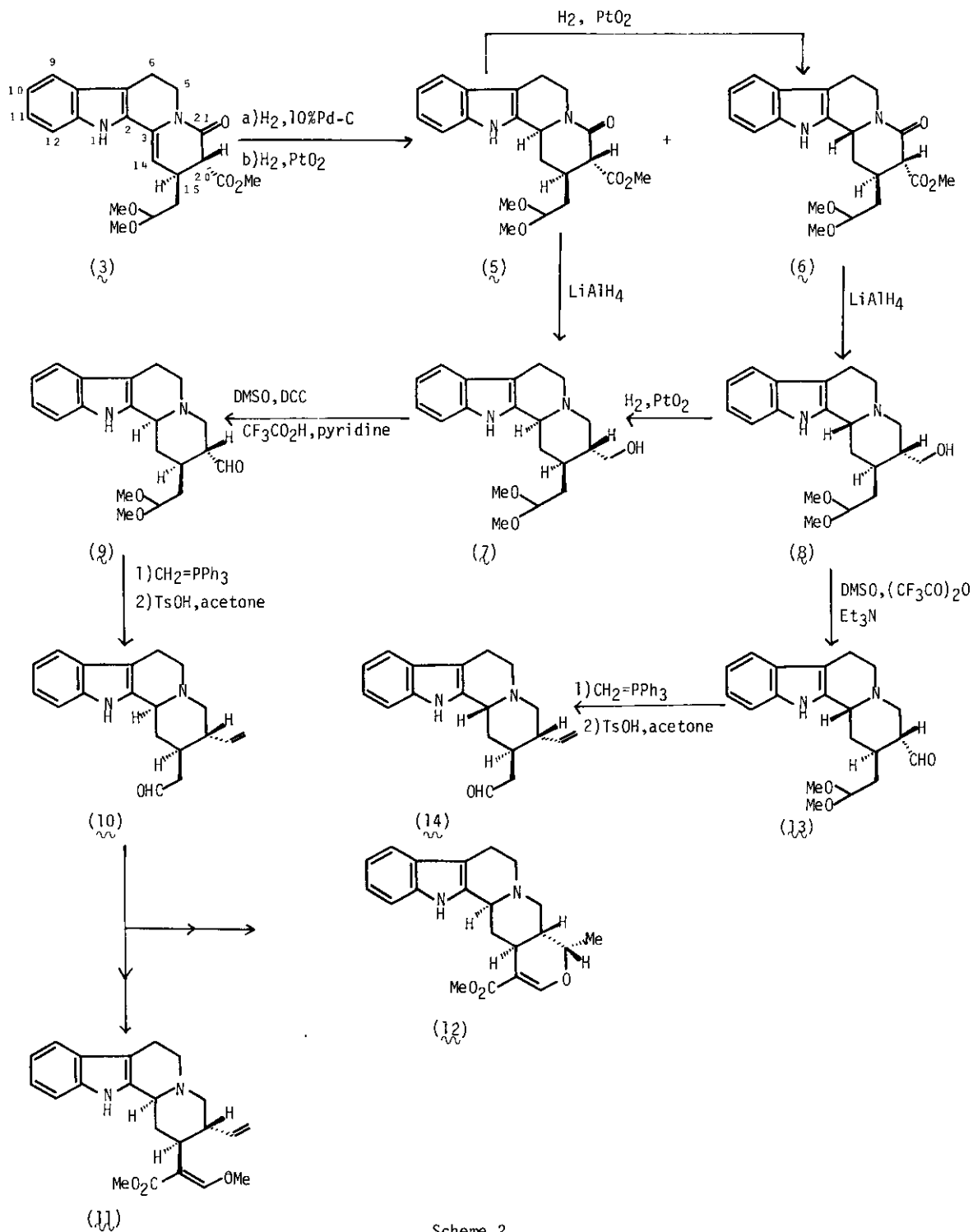
Abstract — A stereoselective synthesis of (±)-corynantheal (10) was achieved via novel epimerization at C₃ position of an indolo[2,3-a]quinolizine and the corresponding lactam by Adams catalyst. This synthesis constitutes a formal total synthesis of (±)-corynantheine (11) and (±)-ajmalicine (12).

Recently we reported a stereoselective total synthesis of (±)-dihydrocorynantheol (4)¹ through the indolo[2,3-a]quinolizine (3) which was prepared by enamine annelation² using 3,4-dihydro-1-methyl-β-carboline (1) and dimethyl 3-methoxyallylidene malonate (2). Transformation of the above intermediate (3) into other Corynanthé type alkaloids was further investigated. Here we wish to report a stereoselective synthesis of (±)-corynantheal (10) which is convertible into (±)-corynantheine (11) and (±)-ajmalicine (12) including a novel epimerization at C₃ position with Adams catalyst.



Scheme 1

The enamide (**3**) was completely reduced for 1 hr with 10 % palladium-charcoal or Adams catalyst in methanol under 2 atms of hydrogen producing two stereoisomers, (**5**) [$\delta(\text{CDCl}_3)$ 3.26 and 3.35 (each 3H, each s, 2 x OMe) and 3.73 (3H, s, CO_2Me)] and (**6**) [mp 209 ~ 210^o, $\delta(\text{CDCl}_3)$ 3.37 (6H, s, 2 x OMe) and 3.70 (3H, s, CO_2Me)]. However the ratio of two products depended on the catalysts. On the reaction using 10 % palladium-charcoal, **5** and **6** formed in the ratio of 1 : 1, while hydrogenation using Adams catalyst gave a mixture of **5** and **6** in the ratio of 9 : 20. Furthermore it was observed that the former (**5**) was slowly convertible into the latter (**6**) under the reduction conditions using Adams catalyst. Thus reduction of **3** with Adams catalyst for 60 hr under the same conditions as above gave **5** and **6** in the ratio of 1 : 30. Both compounds were not interchanged by the reaction with sodium hydride in dimethylformamide² and only starting materials were recovered. It was therefore assumed that both compounds (**5** and **6**) were stereoisomers at the angular position possessing trans-substituents at C₁₅ and C₂₀ positions. The lactam and ester groups of **5** and **6** were then reduced with lithium aluminium hydride. The amine (**7**), formed in 78.2 % from **5**, showed Bohlmann bands at 2900 ~ 2700 cm⁻¹ whereas the product (**8**), mp 189 ~ 190^o, obtained in 81.4 % yield from **6**, exhibited no trans-quinolizidine absorption. At this stage, the latter amine (**8**) was quantitatively converted into the former (**7**) by the reaction with Adams catalyst in methanol under 2 atms of hydrogen for 3 days. On the basis of the above observations, stereochemistries of **5** ~ **8** were determined as shown in Scheme 2. We had already found that the chirality at C₁ position of tetrahydroisoquinolines had been changed by treatment using Adams catalyst under hydrogen.³ It is noteworthy that in the case of lactams, the compound (**8**) having β -hydrogen predominantly formed in contrast with the case of amines. The alcohol (**7**), which was prepared as a sole product from **3** after treatment with Adams catalyst, was transformed into (\pm)-corynantheal (**10**) as follows. The alcohol (**7**) was oxidized to the aldehyde (**9**) in 84.6 % yield using dimethylsulphoxide, dicyclohexylcarbodiimide, trifluoroacetic acid and pyridine.⁴ Wittig reaction of **9** using methyltriphenylphosphonium bromide and *n*-butyl lithium, followed by deprotection using *p*-toluenesulphonic acid in acetone, furnished (\pm)-corynantheal (**10**) in 51 % yield, whose ir, nmr and mass spectra were consistent with the reported ones.⁵ Since corynantheal (**10**) had already been correlated to corynantheine (**11**) in three steps^{5,6,7} and ajmalicine (**12**) in four steps,^{5,8,9} formal total synthesis of the racemates of these alkaloids was accomplished.



Scheme 2

The stereoisomer (8) of the alcohol was also converted into the epimer (14) of (±)-corynantheal. Oxidation of the alcohol to the aldehyde (13) by the ordinary Moffatt procedure⁴ resulted in a poor yield probably due to the more hindered alcohol. The aldehyde (13) was synthesized in 78.2 % yield by the reaction with dimethyl sulphoxide, trifluoroacetic anhydride and triethylamine,¹⁰ and then transformed into the epimer (14) in 53.5 % yield under the same sequence as above. No Bohlmann bands were observed in the ir spectra of 13 and 14 and the hydrogen at C₃ position of 13 and 14 was resonated at 4.50 and 4.40 ppm, respectively.¹¹ These results also suggested the cis-quinolizidine form to these compounds (13 and 14) and confirmed the above assignment of the stereochemistry.

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