A STEREOSELECTIVE SYNTHESIS OF (±)-CORYNANTHEAL

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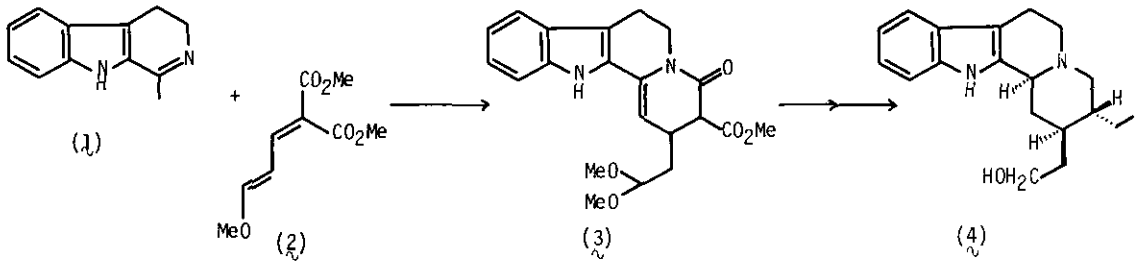
Abstract —— A stereoselective synthesis of (±)-corynantheal (10) was achieved via novel epimerization at C_3 position of an indolo[2,3-a]-quinolizine and the corresponding lactam by Adams catalyst. This synthesis constitutes a formal total synthesis of (±)-corynantheine (11) and (±)-ajmalicine (12).

Recently we reported a stereoselective total synthesis of (±)-dihydrocorynantheol (4)[1] through the indolo[2,3-a]quinolizine (3) which was prepared by enamine annelation[2] using 3,4-dihydro-1-methyl-β-carboline (1) and dimethyl 3-methoxy-allylidenemalonate (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 C_3 position with Adams catalyst.



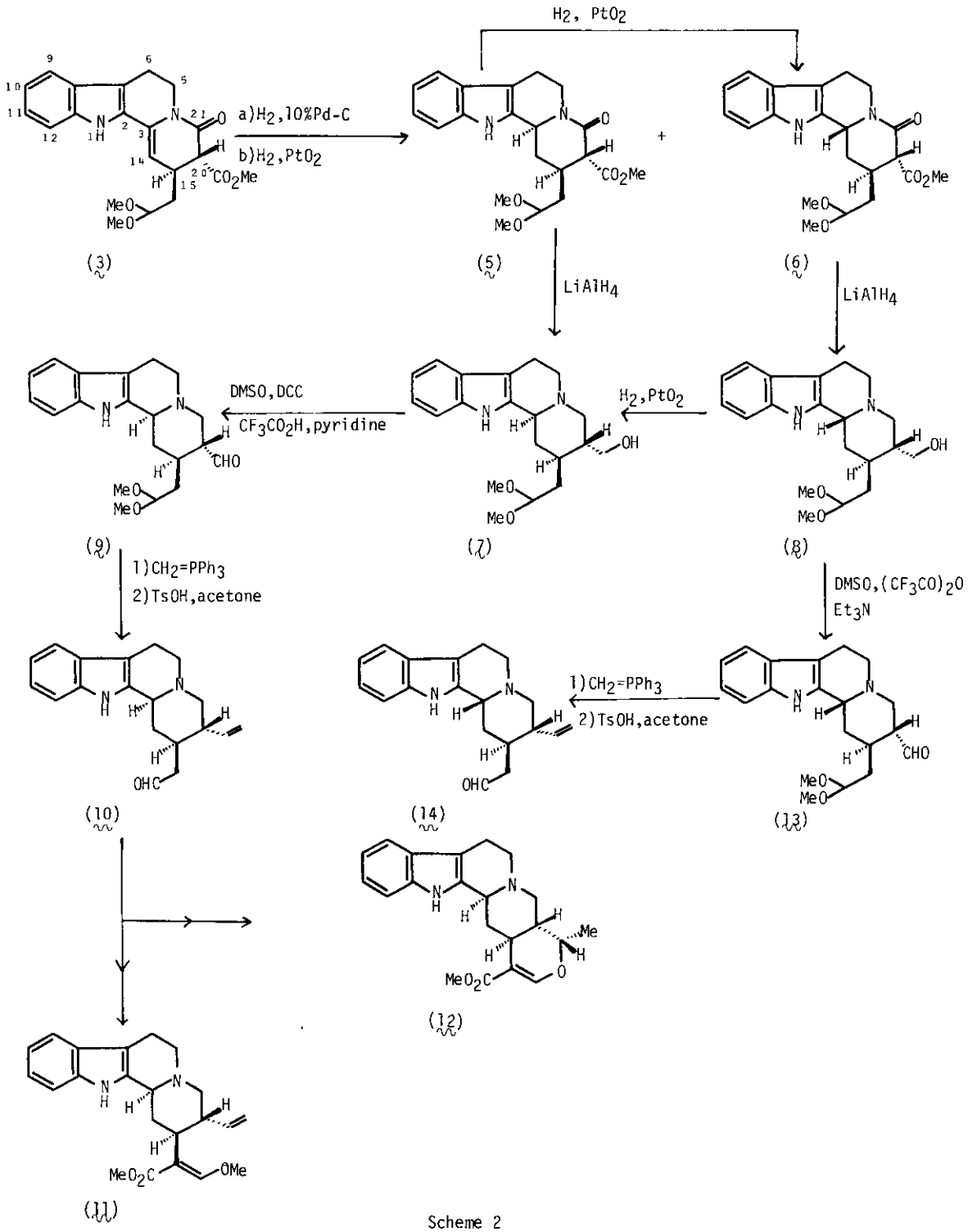
(1) (2) (3) (4)

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) [$\delta(CDCl_3)$ 3.26 and 3.35 (each 3H, each s, 2 x OMe) and 3.73 (3H, s, CO_2Me)] and (6) [mp 209 ~ 210°, $\delta(CDCl_3)$ 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 dimethylformamide[2] 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 C_{15} and C_{20} 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°, 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 C_1 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 (6) 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 (±)-corynantheal (10) as follows. The alcohol (7) was oxidized to the aldehyde (9) in 84.6 % yield using dimethyl sulphoxide, dicyclohexylcarbodiimide, trifluoroacetic acid and pyridine.[4] Wittig reaction of 9 using methyltriphenylphosphonium bromide and n-butyl lithium, followed by deprotection using p-toluenesuphonic acid in acetone, furnished (±)-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.


H2, PtO2
a)H2,10%Pd-C
b)H2,PtO2
LiAlH4
LiAlH4
DMSO,DCC
CF3CO2H,pyridine
H2,PtO2
1)CH2=PPh3
2)TsOH,acetone
DMSO,(CF3CO)2O
Et3N
1)CH2=PPh3
2)TsOH,acetone
(3)
(5)
(6)
(7)
(8)
(9)
(10)
(11)
(12)
(13)
(14)

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 procedure[4] 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 C_3 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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