A TOTAL SYNTHESIS OF (±)-CORYDAINE FROM COPTISINE

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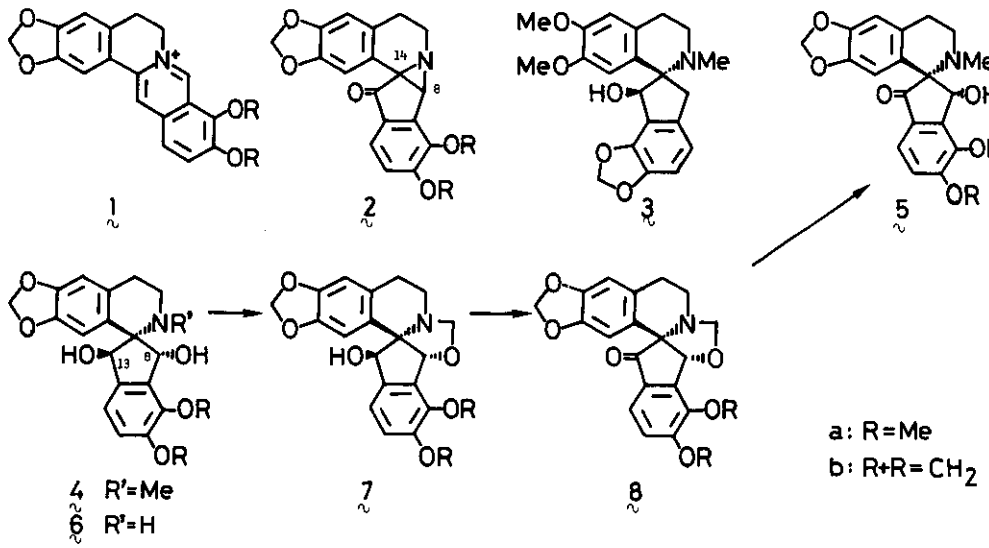
Abstract—— Regioselective protection of C_8-hydroxy of the spiro-diol (6b) derived from coptisine (1b), followed by oxidation of C_{13}-hydroxy afforded the keto-oxazolidine (8b) which was treated with sodium cyanoborohydride to provide (±)-corydaine (5b) in an excellent yield.

We have recently reported an efficient and simple method[1] for the preparation of a spirobenzylisoquinoline *via* an 8,14-cycloberbine (2a), derived from berberine (1a) and this method has successfully been applied to the synthesis of (±)-fumaricine (3)[2] and (±)-ochrobirine (4b).[3] This communication presents a further application to the new synthesis of corydaine (5b)[4] from its biogenetic precursor,[5] a protoberberine alkaloid coptisine (1b), though the total synthesis of 5b has already been achieved by two groups.[6]

Treatment of the spirobenzylisoquinoline (6a),[3] derived from berberine (1a), with 37% formaldehyde in methanol at room temperature effected regioselective and simultaneous protection of the C_8-hydroxyl and the amino group to afford the oxazolidine [7a, 94%, mp 183-184°C, IR νcm^{-1}: 3450 (OH), *m/e*: 383 (M^+), δ: 4.64, 4.58 (2H, ABq, *J*=7, NCH_2O)]. Oxidation of 7a with silver carbonate on celite in refluxing benzene afforded the keto-oxazolidine [8a, 93%, mp 225.5-226°C, IR νcm^{-1}: 1710 (CO), *m/e*: 381 (M^+)]. The oxidation with other reagents gave a rather lower yield: pyridinium dichromate (40%); Jones reagent (67%). Reductive cleavage of the oxazolidine ring of 8a with sodium cyanoborohydride in methanol[6b] provided corydaine analogue [1a, 96%, mp 167.5-168.5°C (lit.[6a] mp 164-165°C), IR νcm^{-1}: 3250 (OH), 1700 (CO), *m/e*: 383 (M^+), δ; 5.05 (1H, *s*, C_8-H), 2.32 (3H, *s*, NCH_3)].

A similar procedure was applied to the transformation of the spiro-diol (6b),[3] derived from coptisine (1b) *via* the cycloberbine (2b), into corydaine (5b). Protection of 6b with 37% formaldehyde afforded the oxazolidine [7b, 98%, mp 157-158°C,

IR νcm^{-1}: 3425 (OH), *m/e*: 367 (M^+), δ: 4.68, 4.58 (2H, AB-q, *J*=7, NCH_2O)]. Oxidation of 7b with silver carbonate on celite provided the keto-oxazolidine [8b, 96%, mp 252-253°C, IR νcm^{-1}: 1720 (CO), *m/e*: 365 (M^+)]. This was treated with sodium cyanoborohydride in methanol to produce (±)-corydaine [5b, 81%, mp 142-143°C (lit. mp 127-129°C,[6a] mp 127-128°C[6b]), IR νcm^{-1}: 3250 (OH), 1705 (CO), *m/e*: 367 (M^+), δ: 7.47, 7.01 (2H, AB-q, *J*=8), 6.58, 6.08 (each 1H, s), 6.23, 6.19 (2H, AB-q, *J*=1.5), 5.87, 5.85 (2H, AB-q, *J*=1.5), 5.04 (1H, s), 2.28 (3H, s)], which was identical with natural corydaine in IR, PMR, and TLC behavior. Thus, we accomplished the first total synthesis of corydaine from coptisine, a protoberberine alkaloid.



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