

A TOTAL SYNTHESIS OF ( $\pm$ )-CORYDAINE FROM COPTISINE

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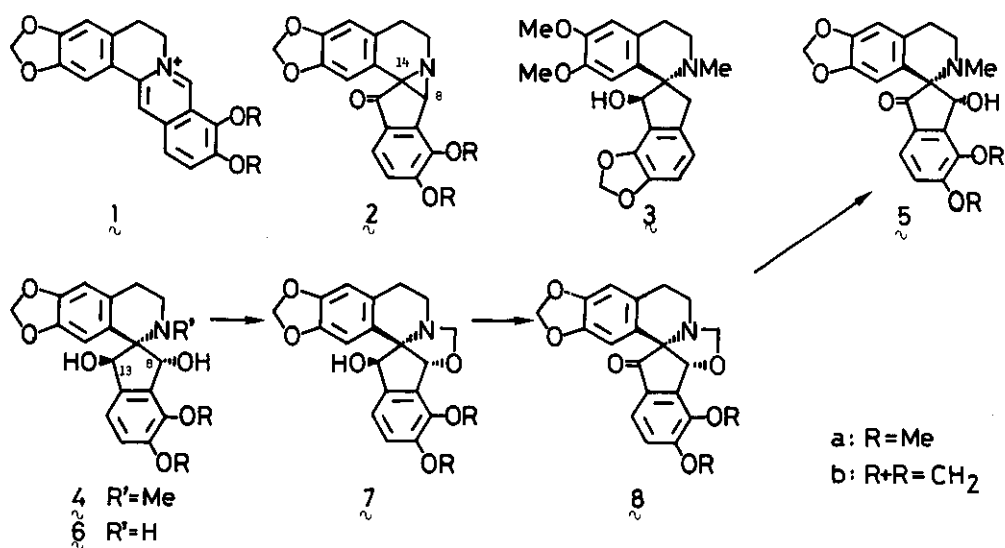
*Abstract*— Regioselective protection of C<sub>8</sub>-hydroxy of the spiro-diol (6b) derived from coptisine (1b), followed by oxidation of C<sub>13</sub>-hydroxy afforded the keto-oxazolidine (8b) which was treated with sodium cyanoborohydride to provide ( $\pm$ )-corydaine (5b) in an excellent yield.

We have recently reported an efficient and simple method<sup>1</sup> 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 ( $\pm$ )-fumaricine (3)<sup>2</sup> and ( $\pm$ )-ochrobirine (4b).<sup>3</sup> This communication presents a further application to the new synthesis of corydaine (5b)<sup>4</sup> from its biogenetic precursor,<sup>5</sup> a protoberberine alkaloid coptisine (1b), though the total synthesis of 5b has already been achieved by two groups.<sup>6</sup>

Treatment of the spirobenzylisoquinoline (6a),<sup>3</sup> derived from berberine (1a), with 37% formaldehyde in methanol at room temperature effected regioselective and simultaneous protection of the C<sub>8</sub>-hydroxyl and the amino group to afford the oxazolidine [7a, 94%, mp 183-184°C, IR  $\nu_{\text{cm}}^{-1}$ : 3450 (OH),  $m/e$ : 383 ( $M^+$ ),  $\delta$ : 4.64, 4.58 (2H, AB-q,  $J=7$ , NCH<sub>2</sub>O)]. Oxidation of 7a with silver carbonate on celite in refluxing benzene afforded the keto-oxazolidine [8a, 93%, mp 225.5-226°C, IR  $\nu_{\text{cm}}^{-1}$ : 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<sup>6b</sup> provided corydaine analogue [1a, 96%, mp 167.5-168.5°C (lit.<sup>6a</sup> mp 164-165°C), IR  $\nu_{\text{cm}}^{-1}$ : 3250 (OH), 1700 (CO),  $m/e$ : 383 ( $M^+$ ),  $\delta$ : 5.05 (1H, s, C<sub>8</sub>-H), 2.32 (3H, s, NCH<sub>3</sub>)].

A similar procedure was applied to the transformation of the spiro-diol (6b),<sup>3</sup> 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  $\text{vcm}^{-1}$ : 3425 (OH),  $m/e$ : 367 ( $M^+$ ),  $\delta$ : 4.68, 4.58 (2H, AB-q,  $J=7$ ,  $\text{NCH}_2\text{O}$ ). Oxidation of **7b** with silver carbonate on celite provided the keto-oxazolidine [**8b**, 96%, mp 252-253°C, IR  $\text{vcm}^{-1}$ : 1720 (CO),  $m/e$ : 365 ( $M^+$ )]. This was treated with sodium cyanoborohydride in methanol to produce ( $\pm$ )-corydaine [**5b**, 81%, mp 142-143°C (lit. mp 127-129°C, <sup>6a</sup> mp 127-128°C<sup>6b</sup>), IR  $\text{vcm}^{-1}$ : 3250 (OH), 1705 (CO),  $m/e$ : 367 ( $M^+$ ),  $\delta$ : 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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