A FORMAL TOTAL SYNTHESIS OF (±)-DESERPIDINE

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Abstract ——— A formal total synthesis of (±)-deserpidine (11) was completed by preparing the known key intermediate (10) from harmalane (1) via the route involving reductive photocyclization of the enamide (2) and functionalization of the basic skeleton (6b) of the alkaloid.

Reserpine and related indole alkaloids such as deserpidine and raunescine have been prominently figured as the compounds of considerable medicinal importance during the past three decades largely due to their extensive use in the treatments of hypertension and mental disorders. Although total synthetic studies of these biologically active indole alkaloids have been reported up to date by several groups, first by Woodward[1], and recently by Pearlman[2], Wender[3], and Szántay[4], the establishment of a practically useful synthetic method of these alkaloids and their derivatives for their supply in large quantity has been regarded as urgent and important problem. Described herein is a new formal total synthesis of (±)-deserpidine according to the synthetic methodology developed previously[5] for the yohimbine synthesis involving reductive photocyclization of enamides and the following direct functionalization of a basic skeleton of the alkaloid. For the application of the previous route to the deserpidine synthesis, we picked the dimethoxy-substituted enamide (2) as a starting compound since it was expected that a selective cleavage of one of two adjacent methoxy groups in the photocyclized lactam (4) would give 18-methoxy-17-ketone (6) which would be suited for a regiocontrolled introduction of a methoxycarbonyl group into the 16-position, therefore giving to form the key intermediate (8), which would be readily converted into the alkaloid (11).

Reductive photocyclization[6] of the enamide (2), which was readily prepared from harmalane (1) and veratroyl chloride, proceeded smoothly to give a mixture of

two hydrogenated lactams (3)[7] and (4)[8] in 35 and 23 % yields respectively. Treatment of the dienol ether (4) with 10 % hydrochloric acid in methanol at room temperature for 30 min resulted in partial hydrolysis of either one of two enol ether groups giving a mixture of the 18-ketone (5a) and the 17-ketone (6a) in the ratio of 1 : 1 in 86 % combined yield. On the other hand, reduction of the lactam (4) with a large amount of lithium aluminum hydride followed by hydrolysis of an enol ether group under the same condition as above gave the desired 17-ketone (6b)[9] (47 %) as a major product along with the isomeric 18-ketone (5b)[10] (7 %).

As previously[5], we then investigated the introduction of a methoxycarbonyl group into the 16-position by using three types of electrophiles. Lithiation of the 17-ketone (6b) with lithium diisopropylamide (LDA)(2.3 eq.) in tetrahydrofuran at -78°C under the kinetically controlled condition followed by acylation with methyl chloroformate (2.3 eq.) afforded the O-acylated product (7) in 75 % yield, but none of the C-acylated product, whereas acylation of the corresponding magnesium enolate with the same acylating agent afforded the desired C-acylated product (8)[11] though only in 12 % yield. On the other hand, quenching of the lithium enolate by carbon dioxide followed by esterification of the resulting carboxylic acid with diazomethane afforded the C-acylated product (8) in 45 % yield and finally the quenching by methyl cyanoformate[12] improved the yield the C-acylated product (8) up to 64 % yield. Thus, the important intermediate (8), which is substituted at 16-, 17-, and 18-positions with respective functional groups, was prepared and then converted into the known intermediates[4] (9) and (10) as follows. Catalytic hydrogenation of the C-acylated product (8) over platinum dioxide in a hydrogen stream under an ordinary atmosphere in methanol afforded a mixture of the ketoester (9)[13] and the hydroxyester (10)[14] in 42 and 37 % yields respectively, which were readily separated by preparative t.l.c. and characterized from their spectral evidences. The ketoester (9) was then reduced with sodium borohydride to give the hydroxyester (10) which has been known[4] as a potent synthetic precursor for the synthesis of (±)-deserpidine (11). Direct comparisons of two esters (9) and (10) with respective authentic samples[4] unambiguously established their structures and completed a formal total synthesis of (±)-deserpidine (11).

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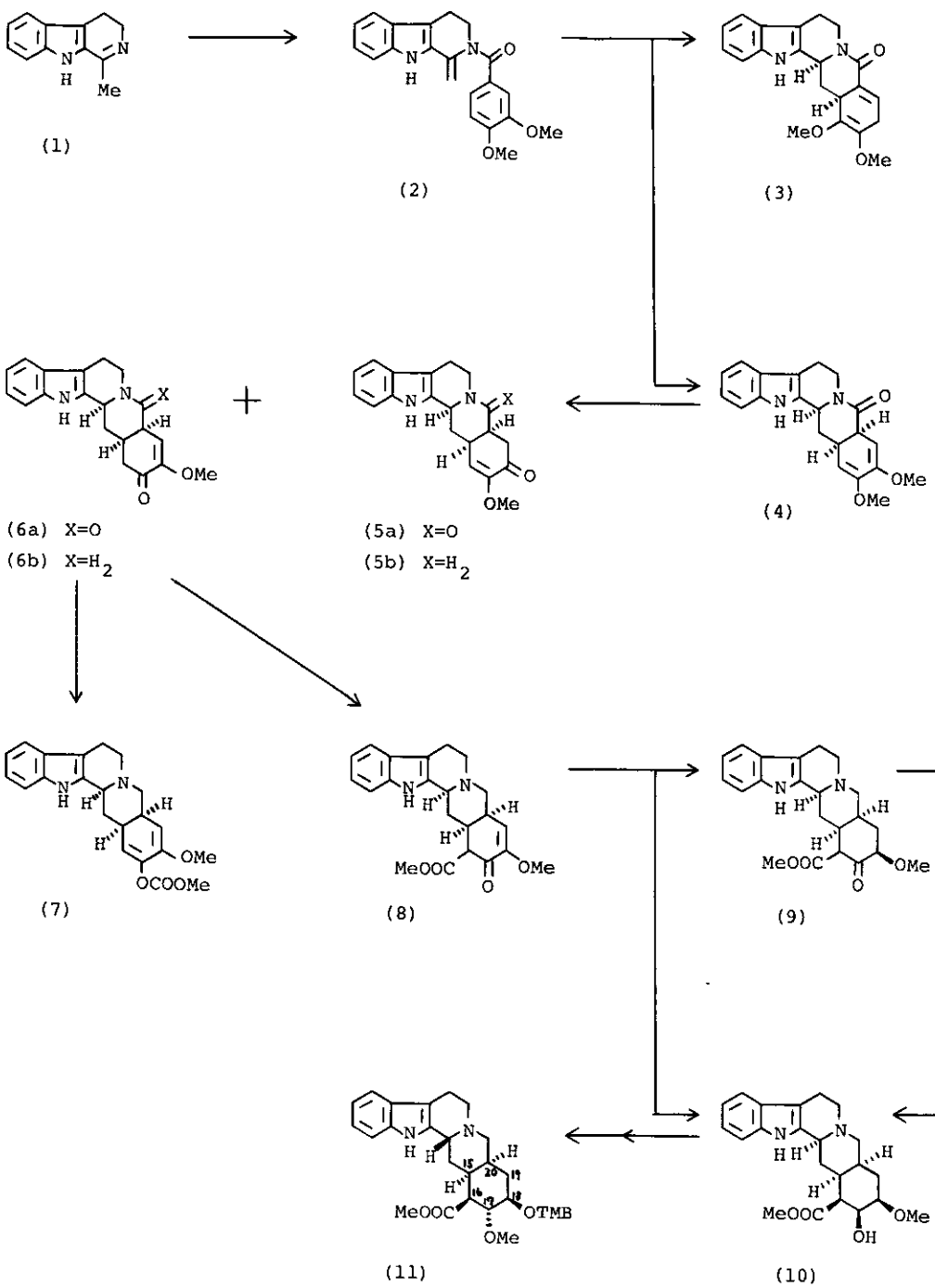
(1)
(2)
(3)
(4)
(5a) X=O
(5b) X=H2
(6a) X=O
(6b) X=H2
(7)
(8)
(9)
(10)
(11)
OMe
MeO
MeOOC
OCOOMe
OTMB
OH

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7 IR ($CHCl_3$) cm^{-1}: 3490, 1670, and 1610. NMR ($CDCl_3$) δ: 6.84 (1H, td, J= 3.5 and 2 Hz, 19-H), 3.76 and 3.63 (each 3H, s, OMe×2), and 3.40 (1H, m, 15-H).

8 IR ($CHCl_3$) cm^{-1}: 3490 and 1625. NMR ($CDCl_3$) δ: 4.79 (1H, d, J= 7 Hz, 16-H), 4.72 (1H, br.dd, J= 2 and 1 Hz, 19-H), 3.65 (1H, br.dd, J= 8 and 2 Hz, 20-H), and 3.62 and 3.57 (each 3H, s, OMe×2).

9 IR ($CHCl_3$) cm^{-1}: 3500, 1680, and 1625. NMR ($CDCl_3$)δ: 5.75 (1H, br.s, 19-H), 3.61 (3H, s, OMe), and 2.42 (1H, m, 20-H).

10 IR ($CHCl_3$) cm^{-1}: 3500, 1690, and 1630. NMR ($CDCl_3$)δ: 5.82 (1H, d, J= 6 Hz, 16-H), 3.57 (3H, s, OMe), and 3.13 (1H, dd, J= 18 and 15 Hz, 19ax-H).

11 IR ($CHCl_3$) cm^{-1}: 3500, 1740, 1695, 1630, and 1600. NMR ($CDCl_3$) δ: 12.35 (1/3H, s, enolic OH), 5.73 (2/3H, br.s, 19-H), 5.17 (1/3Hz, br.s, 19-H), 3.90 and 3.68 (each 1H, s, COOMe + OMe), and 3.77 and 3.65 (each 2H, s, COOMe + OMe).

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13 IR ($CHCl_3$) cm^{-1}: 3490, 1740 (sh), 1725, 1655, and 1610. NMR ($CDCl_3$) δ: 12.45 (1/2H, s, enolic OH), 4.19 (1/2H, dd, J= 12.5 and 6 Hz, 18-H), 4.14 (1/2H, dd, J= 10 and 7 Hz, 18-H), 3.90 and 3.80 (each 3/2H, s, COOMe), and 3.46 and 3.44 (each 3/2H, s, OMe).

14 IR ($CHCl_3$) cm^{-1}: 3550, 3490, and 1730. NMR ($CDCl_3$) δ: 4.55 (1H, t, J= 2.5 Hz, 17-H), 3.85 (3H, s, COOMe), 3.41 (3H, s, OMe), and 3.24 (1H, ddd, J= 12, 4.5, and 2.5 Hz, 18-H).

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