TOTAL SYNTHESIS OF (±)-19,20-DEHYDROYOHIMBINES

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Abstract —— The first total synthesis of three (±)-19,20-dehydroyohimbines (4), (5), and (6) was achieved according to the route involving regioselective acylation of 18,19-dehydroalloyohimbone (1) followed by selective migration of a double bond from the conjugated position to the unconjugated 19-20 position.

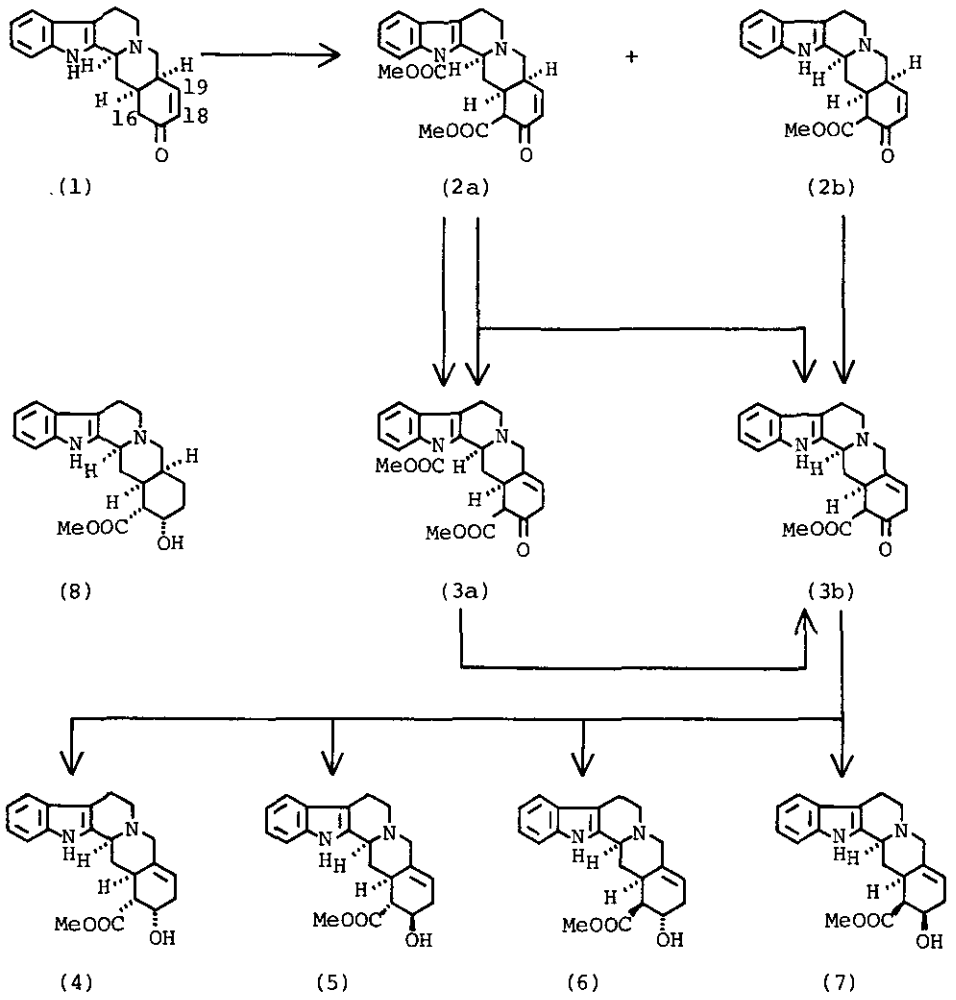
Among many yohimbine type of alkaloids[1], 19,20-dehydroyohimbines, namely 19-dehydroyohimbine , 19-dehydro-α-yohimbine , and 19-dehydro-β-yohimbine , were isolated as minor components from Aspidosperma pyricollum[2] and Aspidosperma oblongum[3] and their structures were characterized mainly from their spectral evidences. Their synthesis remained relatively untouched except a chemical conversion from secologanin[4]. Unique structures of these alkaloids particularly with a double bond at 19-20 position have drawn our interests that have recently been directed toward the development of a new strategy for the synthesis of yohimbine group of alkaloids[5,6] . Now we report the first synthesis of these dehydroyohimbines (4), (5), and (6) started from 18,19-dehydroalloyohimbone (1) which had been prepared in our synthesis of (±)-alloyohimbine[5].

In our previous paper[5] on the total synthesis of (±)-alloyohimbine, we described a selective acylation of the D/E-cis-enone (1) with methyl chloroformate via the route involving the magnesium enolate. The 16-acylated products, the ketoesters (2a) and (2b), were then reduced to furnish the alkaloid without isolating (2a)

and (2b). However, we now succeeded in the isolation of these ketoesters (2a) and (2b) from the acylation reaction employing a soft acylating agent, methyl cyanoformate[6] as follows. Lithiation of the enone (1) with lithium diisopropylamide (LDA) (2.3 eq.) in tetahydrofuran at -78°C under conditions of kinetic control followed by acylation with methyl cyanoformate (1.3 eq.) afforded the N,C-diacylated product (2a)[7] and the unstable C-acylated product (2b)[8] in 38% and 19% yields respectively. On the other hand, quenching the intermediary lithium enolate by an equimolar amount of methyl cyanoformate (2.3 eq.) to LDA afforded the N,C-diacylated product (2a) in 71% yield as a sole product.

Then we investigated the migration of a double bond at 18-19 position in the ketoesters (2a) and (2b) to the unconjugated 19-20 position under both acidic and alkaline conditions. As a result, probably because of the conformational stability of a planar 19,20-dehydroyohimbone skeleton over somewhat folded D/E-cis-18,19-dehydroalloyohimbone, the aimed migration was beautifully achieved under the condition of refluxing the N,C-diacylated compound (2a) in methanol in the presence of concentrated sulfuric acid. Thus, the desired N-acyl-19,20-dehydroyohimbinone (3a)[9] was obtained in 90% yield. On the other hand, treatment of the N,C-diacylated compound (2a) with potassium carbonate in methanol at 0°C gave a mixture of the N-acyl-19,20-dehydroyohimbinone (3a) and the N-deacylated 19,20-dehydroyohimbinone (3b)[2,10], of which the former (3a) was further converted into the latter (3b) under the same condition except the reaction temperature at 15°C. Alternatively, the 19,20-dehydroyohimbinone (3b) was prepared from the C-acylated compound (2b) by treatment with potassium carbonate in methanol at 0°C in 73% yield.

Finally, reduction of the ketoester (3b) with sodium borohydride in methanol at 0°C afforded four stereoisomeric hydroxyesters (4)[11], (5)[12], (6)[13], and (7)[14] in 10, 40, 20, and 10% yields respectively upon separation by p.l.c. Two hydroxyesters (5) and (6) were found to be identical with natural alkaloids, 19,20-dehydro-β-yohimbine[3], and 19,20-dehydro-α-yohimbine[3], respectively upon comparisons of their u.v., i.r., and n.m.r. spectra. The first hydroxyester (4) was deduced as 19,20-dehydroyohimbine[2] from its spectral data upon comparison with those reported[2], since direct comparison with natural alkaloid was not possible.



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7 IR ($CHCl_3$) cm^{-1}: 1735, 1680, 1660, 1620, and 1590. NMR ($CDCl_3$) δ : 11.94 (3/5H, br s, enolic OH), 6.95 (2/5H, dt, J=10 and 2Hz, 19-H), 6.34 (3/5H, dt, J=10 and 2Hz, 19-H), 6.07 (2/5H, dd, J=10 and 2.5Hz, 18-H), 5.99 (3/5H, dd, J=10 and 3Hz, 18-H), 4.08 (6/5H, s, NCOOMe), 4.04(9/5H, s, NCOOMe), 3.86 (9/5H, s, COOMe), and 3.76 (6/5H, s, COOMe).

8 IR ($CHCl_3$) cm^{-1}: 3490, 1735, 1680, 1620, and 1585. NMR ($CDCl_3$) δ : 11.98 (1/2H, br s, enolic OH), 6.93 (1/2H, dt, J=10.5 and 2Hz, 19-H), 6.36 (1/2H, dt, J=10 and 1.5Hz, 19-H), 6.07 (1/2H, dd, J=10.5 and 3Hz, 18-H), 6.00 (1/2H, dd, J=10 and 3Hz, 18-H), and 3.87 and 3.74 (each 3/2H, s, COOMe).

9 IR ($CHCl_3$) cm^{-1} : 1730, 1655, and 1620. NMR ($CDCl_3$) δ : 12.36 (1H, s, enolic OH), 5.49 (1H, br s, 19-H), 4.09 (3H, s, NCOOMe), and 3.86 (3H, s, COOMe).

10 IR ($CHCl_3$) cm^{-1} : 3500, 1740, 1680, 1660, and 1620. NMR ($CDCl_3$) δ : 12.40 (2/3H, s, enolic OH), 5.60 (1H, m, 19-H), 3.94 (2H, s, COOMe), and 3.90 (1H, s, COOMe).

11 IR ($CHCl_3$) cm^{-1} : 3500 and 1730. NMR ($CDCl_3$) δ : 5.58 (1H, br s, 19-H), 4.37 (1H, br s, 17-H), 3.84 (3H, s, COOMe), and 2.48 (1H, dd, J=10.5 and 1.5Hz, 16-H), UV (EtOH) nm: 228, 272, 284, and 291.

12 IR ($CHCl_3$) cm^{-1} : 3600, 3500, and 1720. NMR ($CDCl_3$) δ : 5.56 (1H, br d, J=5.5 Hz, 19-H), 4.08 (1H, td, J=10.5 and 5.5Hz, 17-H), 3.86 (3H, s, COOMe), and 2.44 (1H, t, J=10.5Hz, 16-H). UV (EtOH) nm: 228, 272, 284, and 291.

13 IR ($CHCl_3$) cm^{-1} : 3500 and 1720. NMR ($CDCl_3$) δ : 5.60 (1H, br s, 19-H), 4.31 (1H, td, J=5 and 3Hz, 17-H), 3.78 (3H, s, COOMe), and 3.00 (1H, dd, J=7 and 3Hz, 16-H). UV (EtOH) nm: 228, 272, 284, and 291.

14 IR ($CHCl_3$) cm^{-1} : 3500 and 1720. NMR ($CDCl_3$) δ : 5.74 (1H, br d, J=5Hz, 19-H) 4.32 (1H, m, 17-H), 3.76 (3H, s, COOMe), and 3.07 (1H, t, J=4Hz, 16-H).

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