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A TOTAL SYNTHESIS OF THE ALKALOID (±)-1-ACETYLASPIDOSPERMIDINE

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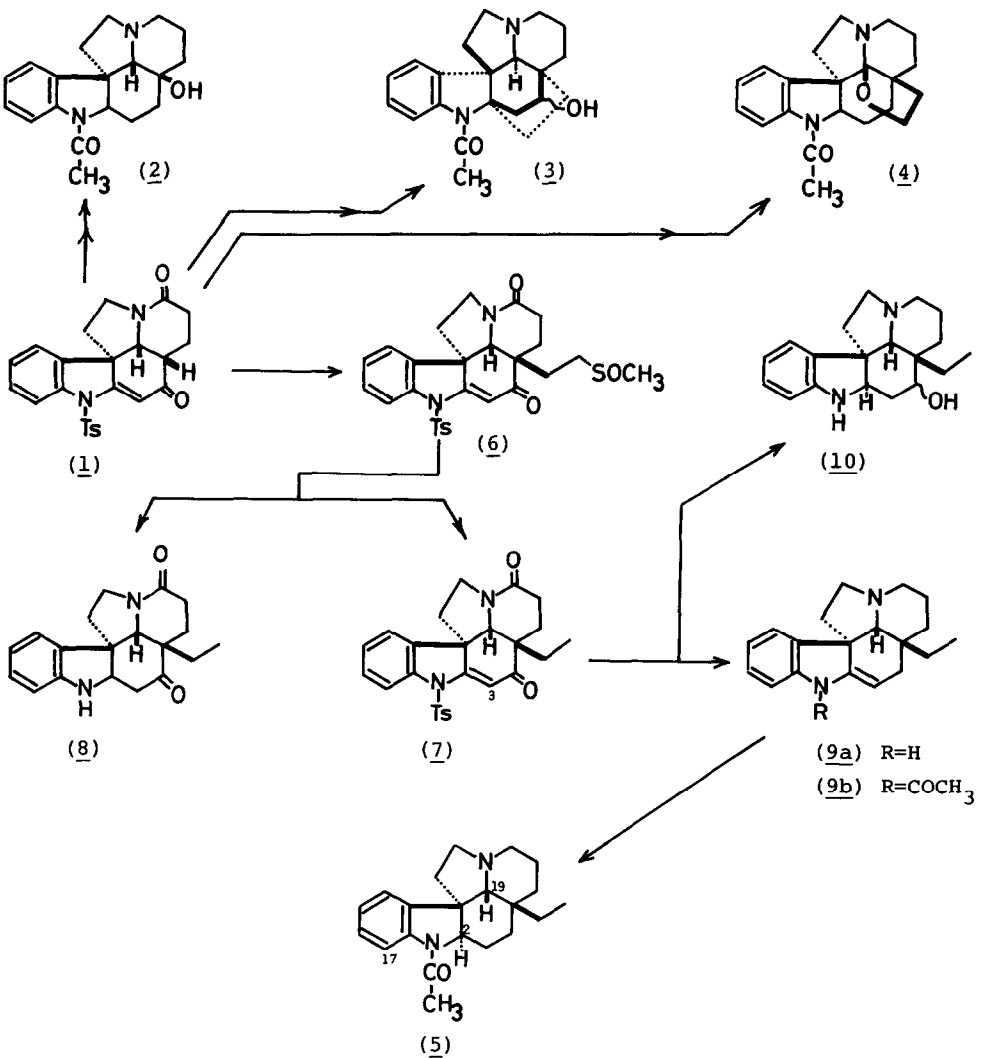
The direct oxygenation of the synthetic precursor(1) was successfully effected and followed by reduction, acetylation and hydrogenation to afford (±)-aspidodispermine(2), a unique member of *aspidosperma* alkaloids.[1] The Michael condensations of the same compound(1) with methyl vinyl sulfone and ketene thioacetal monoxide were reported to finally afford (±)-4-hydroxyaspidofractinine(3) and (±)-1-acetylaspidoalbidine(4), respectively.[2,3] Thus, this method was proved to be very effective on generally introducing the two carbon side chain into the position with an asterisk in the system of N-tosyl vinylogous amide[-N(Ts)-$\dot{C}$=CH-CO-$\dot{C}$H*-] by the Michael condensation, followed by elimination processes of the sulfur containing residue. In the present communication, this art has been applied to the condensation of 1 with methyl vinyl sulfoxide[4] and extended to a total synthesis of (±)-1-acetylaspidospermidine(5), which alkaloid was isolated from various *aspidosperma* species.[5,6]

The reason why methyl vinyl sulfoxide is used instead of the sulfone ($CH_3SO_2CH=CH_2$) in the present work, was due to the anticipation that the product(5) could be reduced much more easily than the corresponding sulfone and the single Michael condensation should proceed more predominantly than the two-fold reaction.[2] This assumption is substantially realized in the following.

The compound(1, mp 240-241°)[3] was reacted with methyl vinyl sulfoxide in the presence of the freshly prepared $LiN[CH(CH_3)_2]_2$(1.1 mol. equiv.) in tetrahydrofuran (at -20°∼-10° for 1 hr and -10°∼0° for further 1 hr, then at room temperature for 2 hr) to give the addition product[6, colorless needles, mp 212-213°, the elemental analyses met with $C_{27}H_{28}N_2O_5S_2$(MW=524)+H_2O; MS: m/e 460, 416 and 91(100%), the M^+ peak was not observed; NMR($CDCl_3$): δ2.41 & 2.46(3H, s & s,


(2)
(3)
(4)
(1)
(6)
(10)
(8)
(7)
(9a) R=H
(9b) R=COCH3
(5)

$SOC\underline{H}_3$), 2.40(3H, s, ar-$C\underline{H}_3$), 6.44 & 6.48(1H, s & s, C_3-$\underline{H}$) and 3.83(1H, s, C_{19}-$\underline{H}$); IR: ν_{max}^{nujol} 3440(hydrate water), 1650(C=O at C-4) and 1625(=N-CO-) cm^{-1}; 82% yield], which was submitted to desulfurization with Raney Ni[8] at 60° under stirring for 2.5 hr. The product was purified by chromatography on silica gel to give the two compounds[7, colorless needles, mp 175-178°[$C_{26}H_{26}N_2O_4S$(MW=462) + C_2H_5OH]; MS: m/e 462(M^+), 418, 337, 182(100%) and 91; NMR($CDCl_3$): δ0.50(3H, t, J=6 Hz, -$CH_2C\underline{H}_3$), 2.40(3H, s, ar-$C\underline{H}_3$), 3.78(1H, s, C_{19}-$\underline{H}$) and 6.46(1H, s, C_3-$\underline{H}$); IR: ν_{max}^{nujol} 1674, 1655 and 1625 cm^{-1}; 75% yield] and [8, colorless needles, mp 199-201°; MS: m/e 310(M^+), 157, 143 and 130; NMR($CDCl_3$): δ 0.57(3H, t, J=7 Hz, -$CH_2C\underline{H}_3$), the vinyl and ar-$C\underline{H}_3$ proton signals were not observed; IR: ν_{max}^{nujol} 3300(NH) and 1700(C=O at C-4) cm^{-1}; 10% yield]. The former product(7) was refluxed with $LiAlH_4$ in 1,2-dimethoxyethane for 4 hr to afford the olefinic compound(9a, colorless needles, mp 110-112°; MS: m/e 280(M^+), 150(100%) and 124; NMR($CDCl_3$): δ 0.64(3H, t, J=7 Hz, -$CH_2C\underline{H}_3$), 5.46(1H, singlet with a shoulder, C_3-$\underline{H}$); IR: ν_{max}^{nujol} 3300(NH), 2790-2770(Bohlmann's absorptions)[8] and 1598 cm^{-1}; ca. 50% yield] after separation by chromatography on silica gel from the hydroxy derivative[10, mp 151.5-153.5°; MS: m/e 298(M^+) and 124(100%); NMR ($CDCl_3$): δ 0.80(3H, t, J=7 Hz, -$CH_2C\underline{H}_3$); ca. 50% yield]. The olefinic derivative(9a) was acetylated with acetyl chloride in methylene chloride containing K_2CO_3 at room temperature under stirring for 4 hr to give the acetyl derivative (9b, colorless resin; MS: m/e 322(M^+) and 150(100%); NMR(CCl_4): δ 0.67(3H, t, J=7 Hz, -$CH_2C\underline{H}_3$), 2.25(3H, s, NH-CO-$C\underline{H}_3$), 5.57(1H, broad, C_3-$\underline{H}$), 6.80-7.40(3H, m, phenyl protons) and 7.92-8.22(1H, m, C_{17}-$\underline{H}$); IR: ν_{max}^{neat} 2850-2700(Bohlmann's absorptions) and 1650($NHCOCH_3$) cm^{-1}; 73% yield]. The hydrogenation of 9b in ethanol containing hydrochloric acid with Adams' catalyst at 4 atmospheric pressure of hydrogen gave (±)-1-acetylaspidospermidine(5, colorless resin; MS: m/e 324(M^+), 296, 152, 144, 130, 125 and 124(100%); NMR($CDCl_3$): δ 0.65(3H, t, J=7 Hz, -$CH_2C\underline{H}_3$), 2.28(3H, s, =N-CO-$C\underline{H}_3$), 4.08(1H, q, J=6 & 7 Hz, C_2-$\underline{H}$), 6.92-7.28(3H, m, phenyl protons) and 8.12(1H, d, J=8 Hz, C_{17}-$\underline{H}$); UV: λ_{max}^{EtOH} 255 nm, λ_{min}^{EtOH} 231, 283(infl.) and 291.5 nm; 50% yield]. These spectral data were in good agreement with those of the natural alkaloid.[5]

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