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APPLICATION OF THE NEW ACYLATING AGENTS [PhS(O)-CH=C(OMe)Cl AND $PhSO_2$-CH=C(OMe)Cl] TO THE SYNTHESIS OF INDOLE ALKALOIDS. A TOTAL SYNTHESIS OF (±)-ASPIDOFRACTININE

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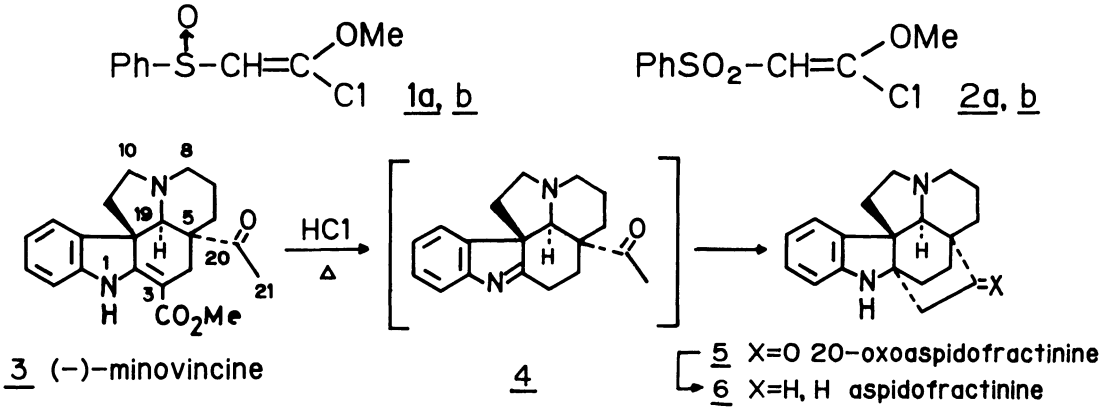
The new acylating agents [PhS(O)-CH=C(OMe)Cl and the corresponding sulfone] were proved to be useful for indroduction of an acetyl group into the α-position of the carbonyl group by means of two-carbon Michael acceptors, which was successfully applied to a total synthesis of (±)-aspidofractinine.

It was previously demonstrated by us that two-carbon Michael acceptors such as 1 and 2 are synthetically useful as a synthon equivalent to an acetyl cation,[1] for introduction of an acetyl group into angular position in decalone derivatives. We now report that these reagents are effective even for introduction of an acetyl group into the very sterically hindered α-position of the ketone, thus achieving a total synthesis of the entitled alkaloids from our versatile intermediate.

There are a number of aspidosperma alkaloids possessing a substituent with oxygen at C-20 position, typified with minovincine (3).[2] Acidic degradation of 3 afforded 20-oxoaspidofractinine (5)[3] through cyclization via intermediate 4[4] which would be formed by hydrolysis and decarboxylation of 3. Thus, C-20 oxygenated compounds should be expected as the potential precursors for not only alkaloids of C-20 oxygenated skeleton but also a variety of aspidosperma alkaloids.[5]



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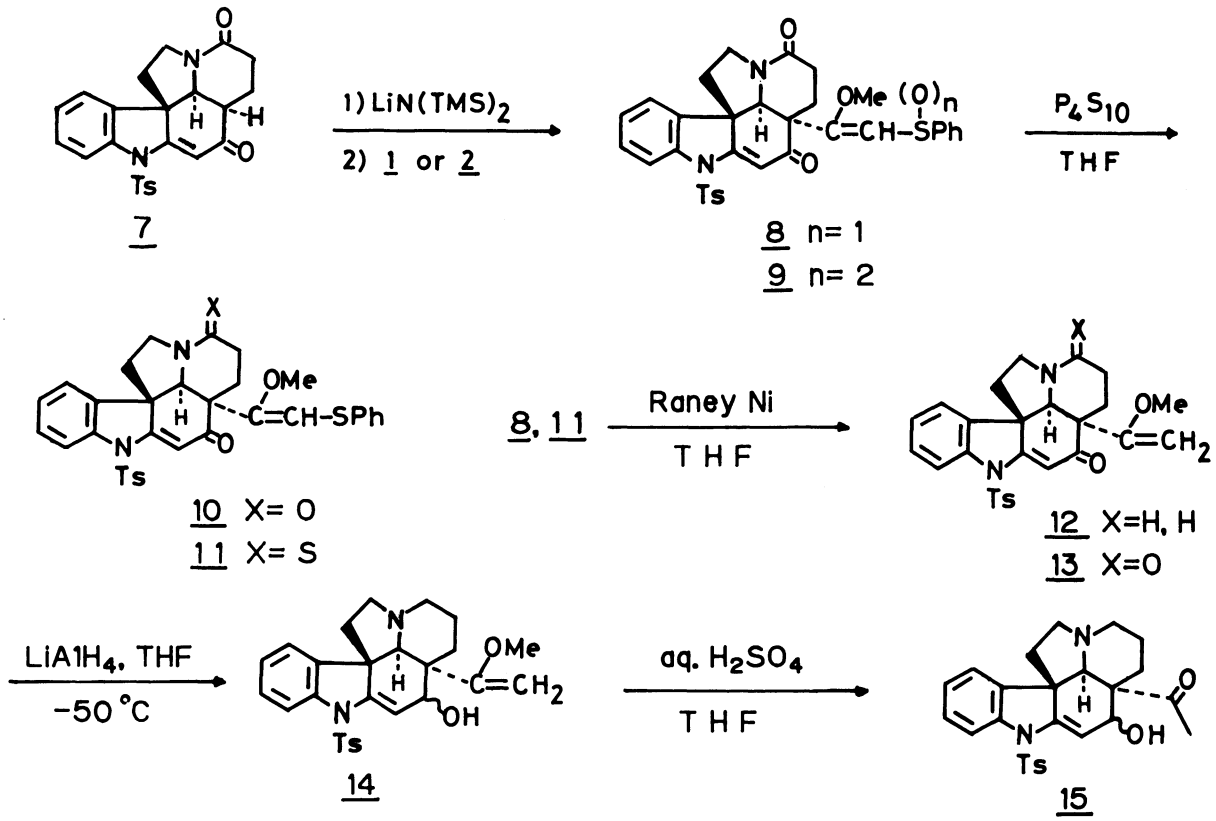
Compound 7[6] was subjected to the Michael condensation with chloromethoxyvinyl sulfoxide 1a[7] in THF using lithium hexamethyldisilazide as a base at -50 °C to afford Michael adduct 8[8,9] in 60% yield, whereas the condensation with the isomeric sulfoxide 1b resulted in a poor yield under the same conditions. The oxidation of 8 with MCPBA gave quantitatively sulfone 9, also directly obtained by condensation of 2a with 7. Since manupilation of the side chain in sulfone 9 was troublesome, sulfoxide 8 was used for further transformations. Treatment of adduct 8 with P_4S_{10} in refluxing THF was accompanied by reduction of the sulfoxide to yield thiolactam sulfide 11 along with a small amount of lactam sulfide 10. Under these conditions, the latter was quantitatively converted into 11, then the total yield reached 78%. Desulfurization of 11 was carried out by treatment with Raney nickel in refluxing THF to produce enol ether 12 in 67% yield. A similar treatment of lactam 8 afforded enol ether 13 in 74% yield, remaining the lactam carbonyl group intact. The enol ether moiety in these compounds was sufficiently stable to even silica-gel column chromatography, unless exposured to acidic media.

The NMR spectrum in compound 12 showed two characteristic vinyl protons at δ 3.33 and 3.58 as AB quartet pattern (J= 3.2 Hz), and a methoxyl group at δ 2.46. These protons reasonate at the higher magnetic field due to the anisotropic effect of the aromatic ring. Compound 12 was reduced with $LiAlH_4$ in THF at -50 °C to yield alcohol 14, then treated with aq. H_2SO_4 to afford a single keto alcohol 15 in 86% yield. Although the hydride reduction would proceed in a stereospecific manner, the stereochemistry of the hydroxyl group was not clear.



7

8 n= 1
9 n= 2

10 X= O
11 X= S

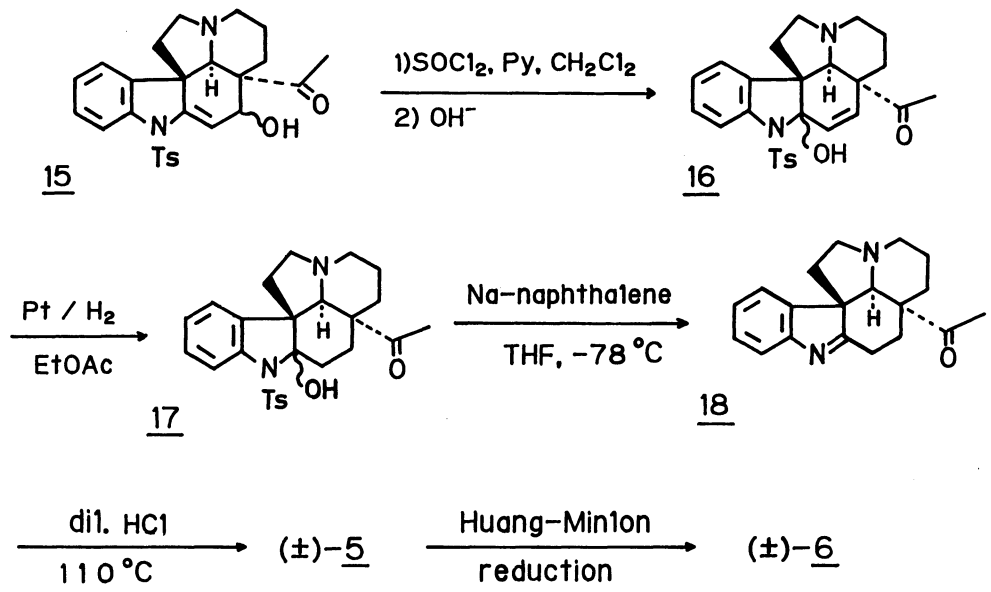
12 X=H, H
13 X=O

14

15

Then the removal of the C-4 hydroxyl group was investigated. Attempted radical deoxygenation via the corresponding thionoester[10] was unsuccessful. The halogenation of the alcohol by usual methods proceeded in a complicated manner to give only a considerable amount of polar products as well as on the tosylation and mesylation. However, when compound 15 was reacted with thionyl chlolide in CH_2Cl_2 in the presence of pyridine at -50 °C for 30 min, then treated with aq. $NaHCO_3$, an isomeric alcohol 16 was obtained in 53% yield instead of the desired chlorinated compound. Subsequently, compound 16 was hydrogenated over platinum in EtOAc at 1 atm to give the saturated alcohol 17 in a nearly quantitative yield. It was expected that the deprotection of the tosyl group in 17 would furnish the corresponding indolenine, since similar transformations have been performed for the compound having N-ethoxycarbonyl-2-hydroxy moiety on heating in a methanolic alkaline solution.[6a] Therefore, compound 17 was reacted with sodium naphthalenide in THF at -78 °C to give an unstable indolenine 18 in 50% yield. The UV spectrum revealed a typical indolenine absorption at 265 nm, and the absence of the tosyl and hydroxyl group was also shown by NMR, IR, and Mass spectra.

Aspidofractinine (6) is a very important alkaloid constituting the fundamental skeleton of more than twenty members of the pleiocarpine series.[2] The first total synthesis has been accomplished in this laboratory,[6b] through the Diels-Alder reaction[11] of nitroethylene with the diene compound derived from 7. Keto indolenine 18 corresponds to the compound 4, which was postulated as an intermediate in the formation of 20-oxoaspidofractinine (5) by acidic degradation of 3. Thus, treatment of indolenine 18 with dil. HCl at 110 °C for 1.5 h proceeded smoothly to give desired product 5 in 90% yield. The IR, UV, and mass spectra were identical with those of the natural alkaloid (5).[3b] Finally, ketone 5 was subjected to the Huang-Minlon reduction to afford (±)-aspidofractinine (6) in 74% yield. It was identical with our previously synthesized sample in all respects.



This work demonstrated that both compounds 12 and 13 with a functionalized substituent at angular position could serve as useful intermediates for the total synthesis of a variety of indole alkaloids. Further studies are now in progress.

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8) Addition of Michael acceptors to the precursor 7 has also been reported; Y. Ban, T. Ohnuma, and T. Oishi, Tetrahedron Lett., 1975, 727; T. Ohnuma, N. Hata, H. Fujiwara, and Y. Ban, J. Org. Chem., 47, 4713 (1982).
9) All new compounds were characterized by IR, NMR, UV, and Mass spectra. The selected spectral data are as follows; 8 IR($CHCl_3$) 1660, 1640, 1030 cm^{-1}; NMR ($CDCl_3$) δ 2.33(3H, s), 3.35(3H, s), 4.52(1H, s), 5.44(1H, s), 6.43(1H, s), 12 NMR($CDCl_3$) δ 2.36(3H, s), 2.46(3H, s), 3.20(1H, s), 3.33(1H, d, J=3.2 Hz), 3.58(1H, d, J=3.2 Hz), 6.28(1H, s); MS(m/z) 476(M^+), 321, 152(bp), 16 IR ($CHCl_3$) 3430, 3300, 1700 cm^{-1}; NMR($CDCl_3$) δ 1.58(3H, s), 2.37(3H, s), 3.00(1H, d, J=1.8 Hz), 5.80(1H, dd, J=10.3, 1.8 Hz), 6.54(1H, d, J=10.3 Hz); MS(m/z) 464(M^+), 421(bp) 18 IR($CHCl_3$) 1695, 1660, 1580 cm^{-1}; NMR($CDCl_3$) δ 1.70(3H, s); MS(m/z) 294(M^+), 293, 251(bp), 43; exact mass 294.1740, Calcd for $C_{19}H_{20}N_2O$, 294.1733.
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