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THE TOTAL SYNTHESIS OF (±)-ASPIDOFRACTININE[1a]

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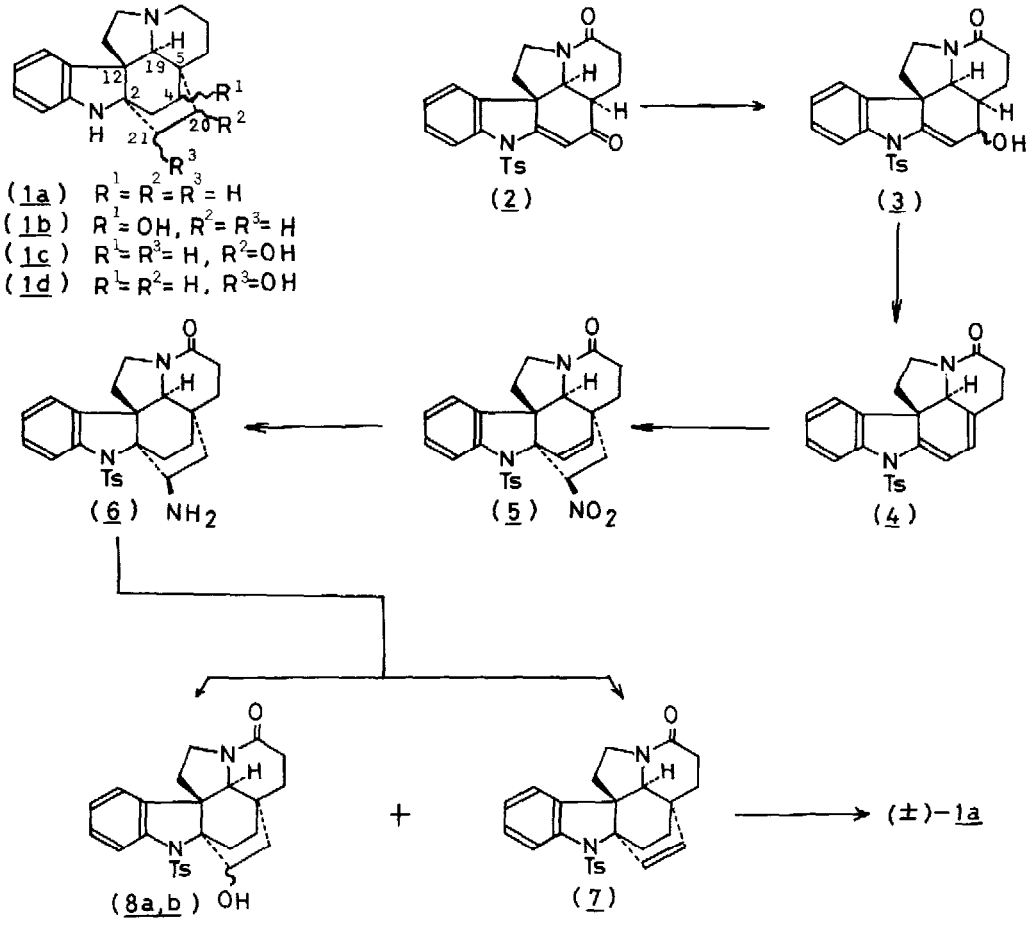
(-)-Aspidofractinine(1a)[2] is a most important alkaloid constituting the fundamental skeleton of more than twenty members in the pleiocarpine series.[3] The structure of this alkaloid(1a) was elucidated on the basis of spectral data, particularly mass spectrometry, combined with exquisite chemical intercorrelations with (-)-kopsine,[4] (-)-pleiocarpine[4] and (-)-minovincine.[5] The extraordinary cage structure(1a) of this group of alkaloids with quaternary centers at C-2, C-5 and C-12 is not susceptible to usual chemical reactions, that had prevented the synthetic approaches for many years. We describe the first total synthesis of the hexacyclic aspidosperma alkaloid, (±)-aspidofractinine(1a), from our versatile precursor(2), which has been utilized for the syntheses of (±)-deoxyaspidodispermine,[6a] (±)-4-hydroxyaspidofractinine(1b),[6b] (±)-1-acetylaspidoalbidine[6c] and (±)-1-acetylaspidospermidine.[6d]

Although (±)-4-hydroxyaspidofractinine(1b) had been synthesized through the novel two-fold Michael cyclization of the above precursor(2) with methyl vinyl sulfone, it could not be transformed to the entitled alkaloid(1a). Therefore, an alternative route was adopted to involve an effective cycloaddition of nitroethylene[7] to the crowded diene system(4) which was readily available from the above intermediate(2).

The compound(2) of known stereochemistry,[6,8] was converted into the hydroxy derivative(3, mp 219-221°, yield 87%)[9] by reduction with sodium borohydride in ethanol-tetrahydrofuran(1:1) at room temperature. The product(3) was dehydrated with anhydrous pyridine and phosphorus tribromide in benzene at room temperature to furnish the diene(4, mp 228-231°, yield 74%).



The diene(4) was subjected to the Diels-Alder reaction with nitroethylene[10] by stirring the mixture in methylene chloride in a current of nitrogen at room temperature overnight to stereoselectively afford a single product(5, mp 267-269°, yield 80%).[11] Since attempts for conversion of the foregoing nitro compound(5) to the corresponding ketone were unsuccessful, it was submitted to hydrogenation with Adams' catalyst under 5.3 atmospheric pressure of hydrogen to furnish the amino derivative(6, mp 132-134°, yield 90%), which was reacted with sodium nitrite in aqueous acetic acid at 55-60° for 5 hr. The crude product was separated into three compounds, (7, mp 249-250°, yield 43.2%), (8a,

mp >300°, yield 33%) and (8b, mp 288-291°, yield 6.8%), by chromatography on alumina.

The stereochemistry of the products(5,6,7 and 8) was verified by the subsequent conversion of the product(8a) into 21-hydroxyaspidofractinine(1d, colorless resin) by reduction with lithium aluminum hydride in 1,2-dimethoxyethane at reflux for 3 hr. The product(1d) demonstrated the fragmentation patterns[m/e: 296(M^+), 252(M-44), 158, 140 and 109(100%)], which should be characteristic of the compound with the hydroxyl substituent at C-20 or C-21, but neither at C-3 nor C-4, since it is well known that retro-Diels-Alder type fragmentation at the C(5)-C(20) and C(2)—C(21) bonds *cis* to C(19)-H are common for alkaloids of the refractine class.[2b] Thus, the intermediates (5, 6, 7 and 8) could be delineated by the respective formulas described herein.[11] The major product(7) was reduced with lithium aluminum hydride in 1,2-dimethoxyethane at reflux for 3 hr to afford a colorless resin, which without further purification was hydrogenated over platinum in ethyl acetate under an atmospheric pressure of hydrogen to give (±)-aspidofractinine(1a) as colorless resin[IR $\nu_{max}(CCl_4)$: 3360(NH), 2920, 2850(CH), 1609(indoline) cm^{-1}. UV λ_{max}(EtOH): 243, 292 nm. λ_{min}(EtOH): 226, 269 nm. MS(m/e): 280(M^+), 252, 158, 144, 130, 124 and 109(100%).[2] The infrared(CCl_4), ultraviolet and mass spectra were identical with those of the natural alkaloid,(-)-aspidofractinine (1a), in every respect.[12]

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References and Notes

1) a) This work was presented at the 5th International Congress of Heterocyclic Chemistry which was held at Ljubljana, Yugoslavia, on July 17, 1975. b) The present address: The Institute of Physical and Chemical Research, Wako-shi, Saitama-ken, 351 Japan.

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product from *Pleiocarpa tubicina* STAPF[2a] or *Aspidosperma refractum* MART.[2b] in an amorphous form[2b] or as colorless presims, mp 101-102°, $[\alpha]_D$ -20°($CHCl_3$).[2a]

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9) The ir, uv, mass and nmr spectra were in agreement with the structures assigned to all of the crystalline intermediates(3~8), on which satisfactory elemental analyses were obtained.

10) Ranganathan et al. conducted the cycloaddition of nitroethylene as a ketene equivalent with 5-methoxymethylcyclopentadiene to attain the one step preparation of prostaglandin intermediates. [S. Ranganathan, D. Ranganathan and A. K. Mehrotra, J. Am. Chem. Soc., 96, 5261 (1974)].

11) The mechanistic considerations and Alder's rule of the cycloaddition of nitroethylene to the diene(4) could reach the conclusion that the structure(5) should be allocated to the addition product. The X-ray studies on the compound(8b) carried out by Mr. T. Date, Analystical Center, Tanabe Seiyaku Co., Ltd., are in progress to preliminarily agree with the above conclusion. We are grateful to him for his cooperation.

12) The physical properties of the natural (-)-aspidofractinine are: IR[2a] $\nu_{max}(CCl_4)$ 3350(NH), 1612(idnoline) cm^{-1}; UV[2a] λ_{max}(EtOH) 241(log ε 3.83), 291(log ε 3.46) nm, λ_{min}226(log ε 3.70), 267(log ε 3.09) nm; Mass spectrum(m/e): 280(M^+), 252, 158, 144, 130, 124 and 109.[2b]