A NEW STEREOSELECTIVE SYNTHESIS OF (±)-DEOXYASPIDODISPERMINE

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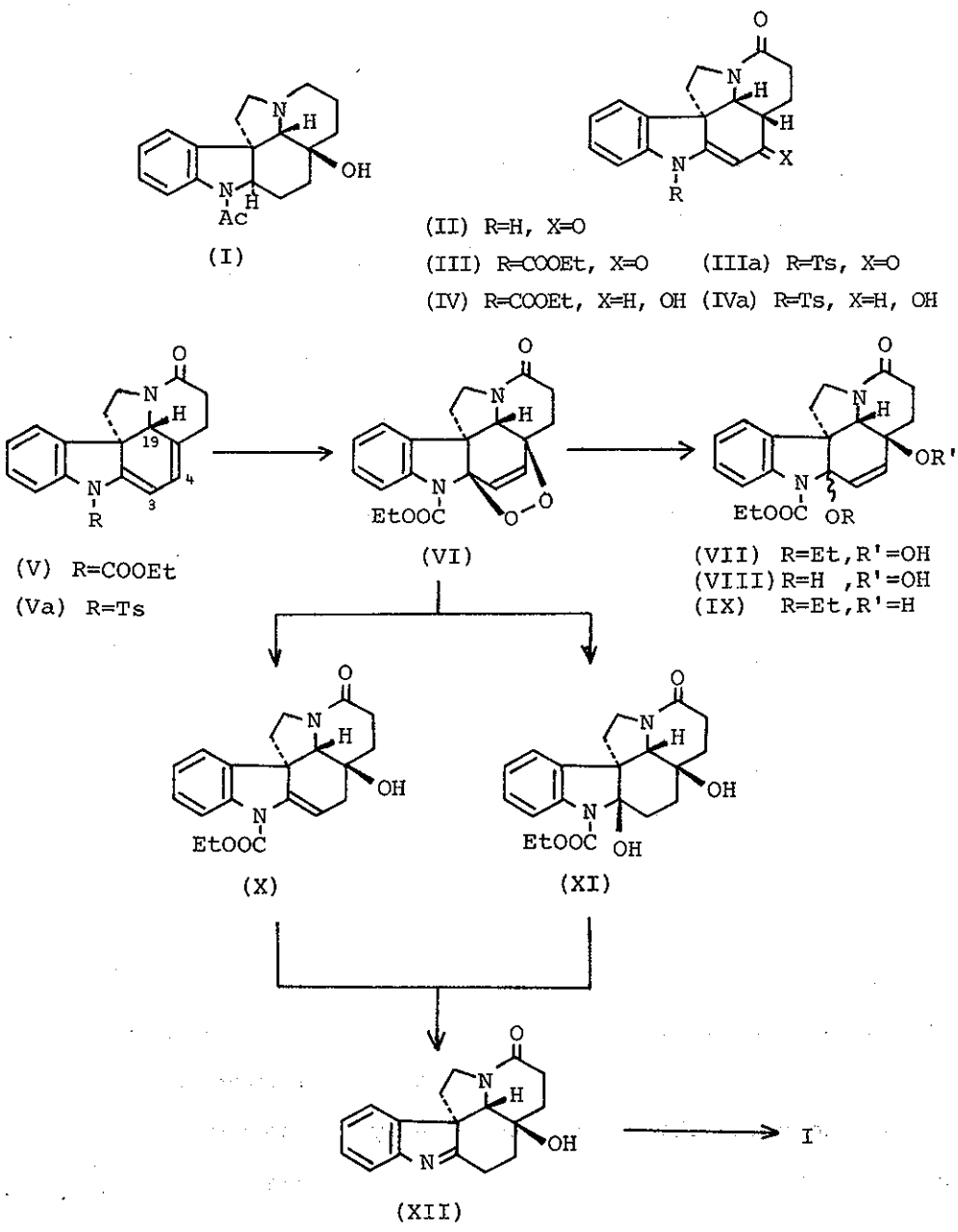
A new stereoselective total synthesis of (±)-deoxyaspidodispermine(I) was achieved; the feature of the present synthesis was to involve the *photosensitized oxygenation* of the diene(V) by singlet oxygen, exclusively furnishing the cyclic peroxide adduct(VI) of β-orientation, which might be regarded as a biomimetic process subsequent to Djerassi's work on the removal of the angular ethyl group of *Aspidosperma* alkaloids.

The total synthesis of the alkaloid (±)-deoxyaspidodispermine (I) has been already reported from this laboratory[1] to establish the unique structure proposed by Djerassi.[2] In the present communication, we report the exclusively stereoselective synthesis of the same alkaloid through the cyclic peroxide adduct(VI) generated by action of singlet oxygen as a dienophile to the diene(V), since this type of the strained diene(Va) turned out to be readily obtained from the compound(IIIa) and react with the


(I)
(II) R=H, X=O
(III) R=COOEt, X=O
(IIIa) R=Ts, X=O
(IV) R=COOEt, X=H, OH
(IVa) R=Ts, X=H, OH
(V) R=COOEt
(Va) R=Ts
(VI)
(VII) R=Et,R'=OH
(VIII) R=H ,R'=OH
(IX) R=Et,R'=H
(X)
(XI)
(XII)
I

Scheme 1

dienophile to afford a single product having the new two-carbon unit in *cis* configuration to C_{19}-H, which finally attained the total synthesis of (±)-aspidofractinine.[3]

The versatile intermediate(II, mp 247-249°)[4a] for this series of synthetic works,[4] was reacted with sodium hydride and ethyl chloroformate in DMF at room temperature to provide the carbamate[III, mp 177-179°, M^+352, IR(Nujol) ν 1722 and 1650 cm^{-1}; NMR($CDCl_3$) δ1.49(3H, t, J=7Hz, $OCH_2\underline{CH}_3$), 4.34(1H, d, J=9Hz, C_{19}-$\underline{H}$), 4.50(2H, q, J=7Hz, OCH_2CH_3), 6.67(1H, s, C_3-$\underline{H}$), 7.1~7.6(3H, m,aromatic $\underline{H}$) and 7.99(1H, b-d, J=8Hz, C_{17}-$\underline{H}$); 76.5% yield], which was reduced with sodium borohydride in EtOH-THF(1:1) at room temperature to furnish the allyl alcohol [IV, mp 225-227°, M^+354, IR(Nujol) ν 3340(OH), 1710 and 1635 cm^{-1}; 94.5% yield]. The diene[V, mp 183-186°, M^+336, IR(Nujol) ν 1710 and 1660 cm^{-1}; NMR($CDCl_3$) δ 5.83(1H, b-d, J=6Hz, C_4-$\underline{H}$) and 6.28(1H,b-d, J=6Hz, C_3-$\underline{H}$)] was obtained in 81% yield by dehydration of the above alcohol(IV) on treatment with phosphorus tribromide and pyridine in a similar manner with the tosylate (IVa).[3]

The diene(V) was converted into the cyclic peroxide adduct, [VI, colorless resin, M^+368, IR(Nujol) ν 1722 and 1640 cm^{-1}; NMR($CDCl_3$) δ 6.41(1H, d, J=9Hz, C_4-$\underline{H}$) and 7.20(1H, d, J=9Hz, C_3-$\underline{H}$), ca. 100% yield], whose peroxide bridge should be oriented in *cis* configuration to C_{19}-H,[5] by passing oxygen into its ethanolic solution in the presence of eosine as a sensitizer in the sun light. Although the β-oriented peroxide adduct(VI) is

a rather stable compound which does not change at all on exposure to air at room temperature, it was warmed with ethanol at 40-50° to provide the hydroperoxide(VII, mp 193-195°, M^+414, IR(Nujol) 3200, 1700 and 1630 cm^{-1}; 65.5% yield) and the other compound(VIII, mp 227-230°, M^+386, IR($CHCl_3$) ν 3200, 1700 and 1615 cm^{-1}; 15.3% yield) after separation on preparative tlc over alumina. The former(VII) was reduced by merely refluxing with ethanol for 30 min to give the hydroxy derivative(IX, mp 244-245°, M^+398, IR(Nujol) ν 3260, 1708 and 1615 cm^{-1}). The cyclic peroxide(VI) was submitted to the hydrogenation with Adams' catalyst in ethanol under 4-4.5 kg/cm^2 pressure of hydrogen to afford the diol(XI, mp 234-235°, M^+372; IR(Nujol) ν 3480, 3305, 1685 and 1607 cm^{-1}; 84.5% yield) as a single product. On hydrogenation with the same catalyst under 4.9 kg/cm^2 pressure of hydrogen in ethyl acetate, however, the compound (VI) provided two products, the above diol(XI, 54.8% yield) and the ene-ol[X, mp 209-210°, M^+354; IR(Nujol) ν 3300, 1713 and 1638 cm^{-1}; NMR($CDCl_3$) δ6.24(1H, d-d, J=7.5Hz and 4.2Hz, C_3-H); 27.8% yield].[6] The compound(X) was refluxed with 10% aqueous solution of sodium hydroxide mixed with methanol(1:1) for 2 hr to give the indolenine(XII, mp 257-260°, M^+282; IR(Nujol) ν 3250 and 1628 cm^{-1}; UV λ_{max}^{EtOH} 216, 220 and 263 nm, λ_{min}^{EtOH} 218.5 and 239 nm; 50.2% yield), which was also obtained in 43% yield from XI in a similar manner.

The indolenine(XII) was reduced with lithium aluminum hydride in THF to give the corresponding indoline, which

without purification was acetylated with acetic anhydride in pyridine at room temperature to give (±)-deoxyaspidodispermine(I) as a colorless resin[MS(m/e) 312(M^+, 66%), 311(38%), 294(16%), 284(4%), 266(9%), 246(8%), 178(9%), 144(10%), 140 (29%), 130(11%), 126(7%) and 112(100%); NMR($CDCl_3$, 100 MHz) δ 2.26(3H, s, N-$COC\underline{H}_3$), 4.04(1H, d-d, J=5Hz and 6Hz, C_2-$\underline{H}$), 6.9 ~ 7.25(3H, m, aromatic $\underline{H}$) and 8.06(1H, d, J=8Hz, C_{17}-$\underline{H}$); UV λ_{max}^{EtOH} 253, 260(sh), 281 and 290 nm; IR($CHCl_3$) ν 3580, 3450 and 1640 cm^{-1}; picrate, mp 253-255°(dec.)]. The spectra [IR($CHCl_3$), UV and NMR] of the synthetic specimen were identical with those of the natural alkaloid. The identity of both samples was further confirmed by comparison of the behaviors on tlc over silica gel and alumina.

Thus, the later stage in the present synthesis of the unique alkaloid(I) may be deemed as a biomimetic process subsequent to Djerassi's elegant presentation on the removal of the angular ethyl group of *Aspidosperma* alkaloids.[7] (See Scheme 3).

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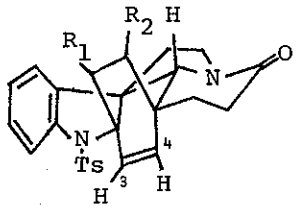
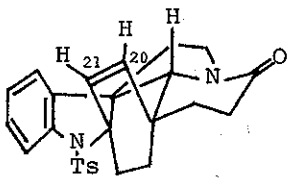


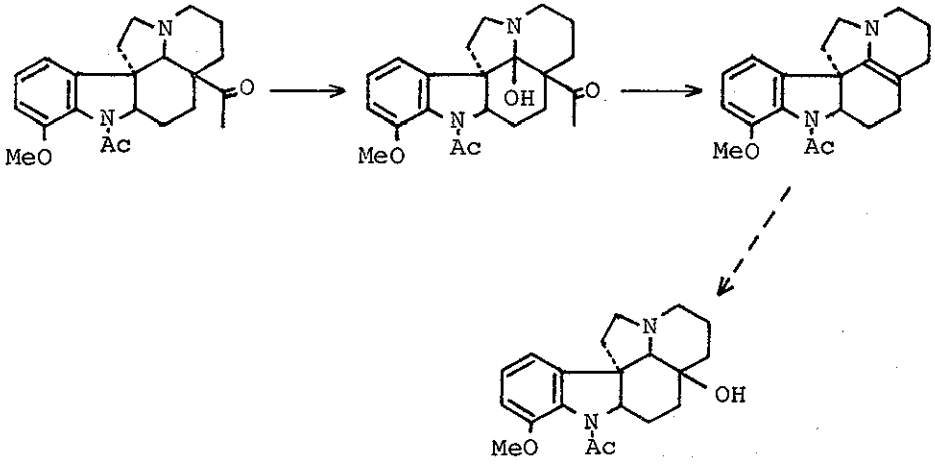
(i)



(ii)

R_1	R_2				
CN	H	C_3-H	7.10～7.12 ppm	C_{20}-H	5.78 ppm
NO_2	H	C_4-H	6.14～6.24 ppm	C_{21}-H	5.98 ppm
CO-O-CO					

Scheme 2



Scheme 3

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5 The stereochemistry of the structure(VI) was assigned mainly due to the chemical shifts of C_3-H and C_4-H, which were compared with the signals of vinyl protons in the (i) and (ii) types of compounds. The signals of C_{20}-H and C_{21}-H in the latter(ii) are in the higher magnetic field than C_3-H and C_4-H of the formers(i). (See Scheme 2).

6 It seemed to be a surprising fact that the ene-ol(X) was obtained on hydrogenation of XI in ethyl acetate. The possibility of generation of the ene-ol(X) through the diol (XI) was excluded by the experiment that the diol(XI) was submitted to hydrogenation in ethyl acetate under the same condition to give no trace of X.

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