STEREOSELECTIVE SYNTHESES OF (±)-18-DEOXYPALUSTRINE AND (±)-18-DEOXY-13-EPIPALUSTRINE

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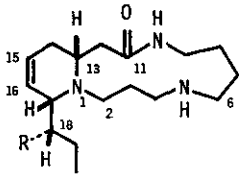
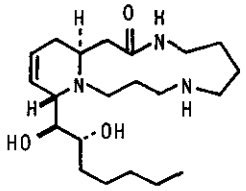
Abstract— Total syntheses of the title compounds (4 and 5) were achieved in a regio- and stereoselective fashion via 13, 15, 17, 18, 22, and 34, starting from the compound (8) obtained by the $SnCl_2$ effected reaction of an *endo*-peroxide derived from 7. Treatment of an amino-aldehyde derivative such as 23 in a basic condition furnished the preferential conversion of 2,6-*cis*-dialkylpiperidines into 2,6-*trans* derivatives through retro Michael intermediates.

Palustrine (1)[1] (isolated from *Equisetum palustre* L.), cannabisativine (2)[2] and anhydrocannabisativine (3)[3] (from *Cannabis sativa* L.) are special type of macrocyclic spermidine alkaloids,[4] one of the polyamine functions being incorporated into a 2,6-disubstituted tetrahydropyridine ring.



1 R=OH
4 R=H



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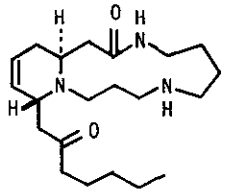

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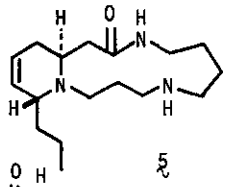

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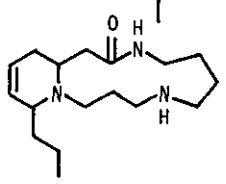

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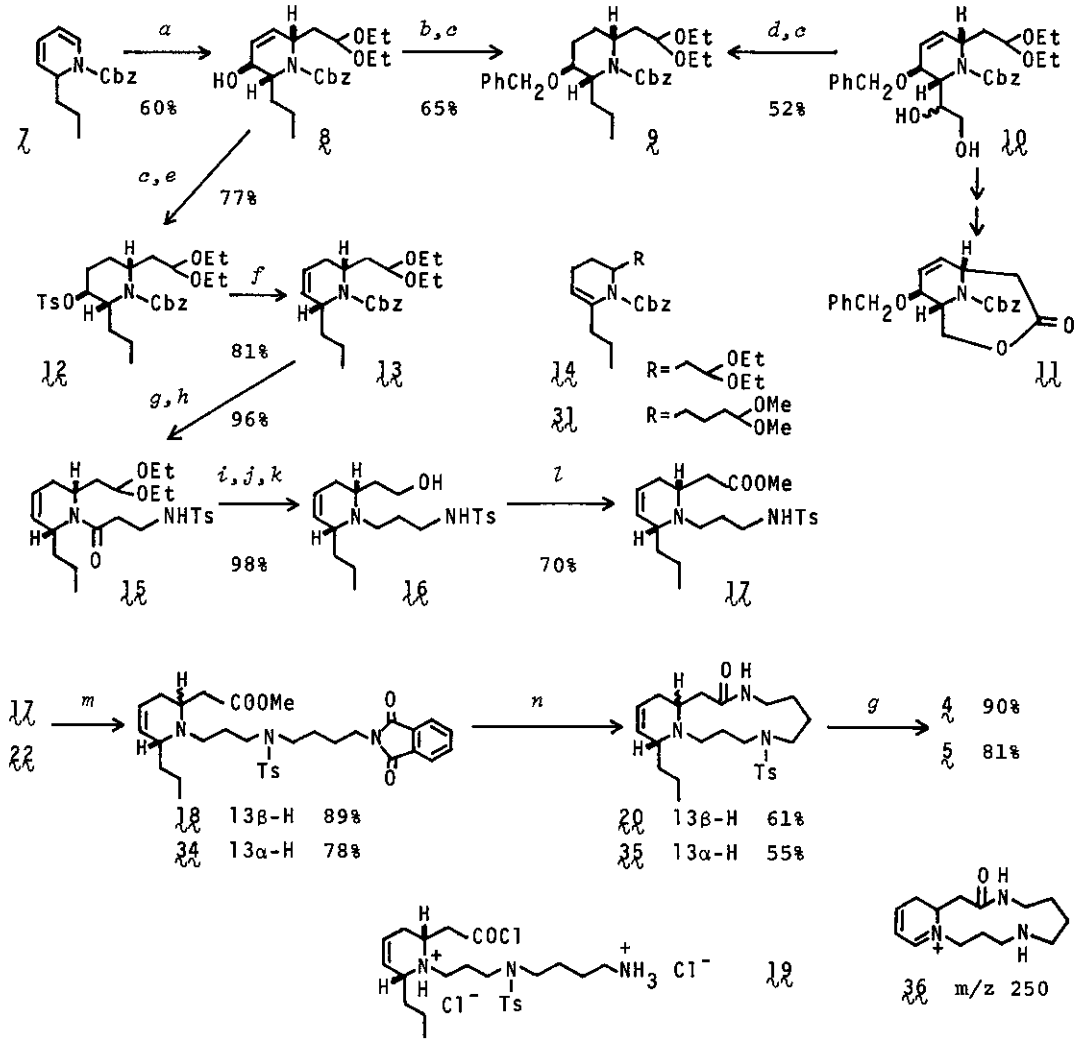
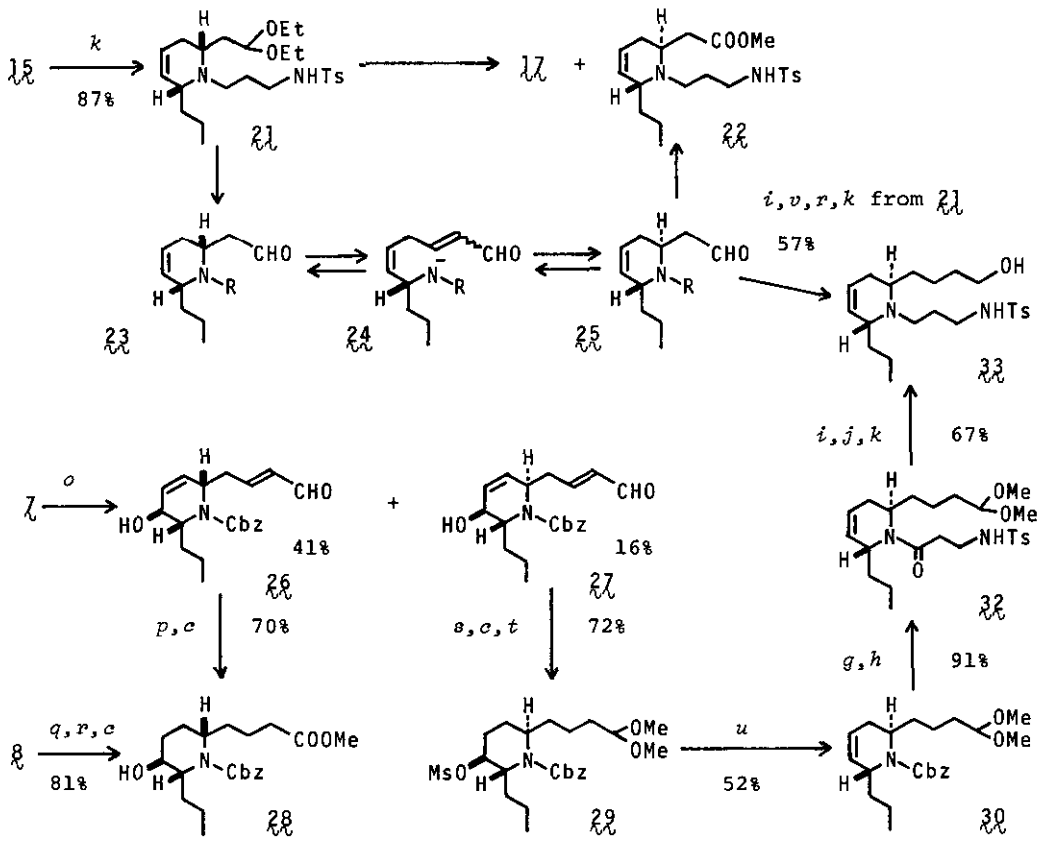
For the synthesis of these alkaloids in a regio- and stereoselective manner, several difficulties were anticipated to be overcome.[5] Especially, common problems such as (i) the construction of 2,6-*cis*- or 2,6-*trans*-dialkylated piperidine moiety having a double bond in a particular position, (ii) the formation of a thirteen-

membered lactam ring, and (iii) the stereo-controlled introduction of hydroxyl group into the alkyl side chain, required preliminary studies in order to establish suitable reactions involving new methodologies. As the result of the investigation related to the first two problems, we succeeded in the syntheses of (±)-18-deoxypalustrine (4) and (±)-18-deoxy-13-epipalustrine (5) in connection with a minor alkaloid P_3 of *Equisetum palustre*, whose structure was briefly reported to be 6 mainly from a mass spectral evidence.[6]



Starting material for the present synthesis was 8, obtained as a single product by photooxygenation of 7 [prepared from pyridine with propylmagnesium bromide and benzyl chloroformate in 66% yield], followed by the $SnCl_2$ mediated reaction with ethyl vinyl ether.[7] The 2,6-*cis* disubstituted structure of 8 was readily deter-



a: i) $^1O_2$; ii) , $SnCl_2$; iii) EtOH. *b*: NaH, THF-HMPA (4:1), r.t. and then $PhCH_2Cl$, r.t. *c*: H_2, Pt, DME. *d*: i) $NaIO_4$, MeOH-H_2O (4:1), r.t.; ii) Ph_3P=CHMe, THF, -25°. *e*: TsCl, Py, r.t. *f*: DBU-PhMe (1:1), 100°C (bath temp.). *g*: Na, liq. NH_3-THF. *h*: TsNH  COCl, K_2CO_3, PhH-PhMe-H_2O (3:1:3), 0°C→r.t. *i*: 10% aq. HCl-DME (1:1), 0°C→r.t. *j*: $NaBH_4$, MeOH, 0°C→r.t. *k*: $LiAlH_4$, THF, reflux. *l*: i) Jones reagent, Me_2CO, 0°C; ii) CH_2N_2 in Et_2O, MeOH, 0°C. *m*: *N*-(4-bromo-1-butyl)-phthalimide, K_2CO_3, DMF, r.t. *n*: i) 80% NH_2NH_2, EtOH, r.t.; ii) $Ba(OH)_2$, MeOH-H_2O (2:1), r.t.; iii) HCl salt; iv) $SOCl_2$, abs. CH_2Cl_2, 0°C→r.t.; v) K_2CO_3, abs. MeCN, r.t. *o*: i) $^1O_2$; ii)  OTMS, $SnCl_2$. *p*: NaCN, HOAc, MnO_2, MeOH, r.t. *q*: 10% aq. HCl-DME (1:3), r.t. *r*: Ph_3P=CHCOOMe, CH_2Cl_2, r.t. *s*: $CH(OMe)_3$, NH_4Cl, MeOH, r.t. *t*: MsCl, Py, 0°C→r.t. *u*: DBU, 70-80°C. *v*: K_2CO_3, MeOH, 0°C.

mined by interrelation with 10, whose stereochemistry was rigorously proved by formation of the lactone derivative (11).[8]

Introduction of the double bond at the desired position required a careful selection of a reaction condition in order to minimize the production of a by-product (14) and the best result (13 from 8 in 62% yield) was obtained by treatment of the tosylate (12) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in the condition

described in the Chart, accompanied by a formation of 14 in only 1% yield. The protecting group of the nitrogen in 13 was cleaved and then an aminoalkyl substituent had to be attached. We planned at first that this process was carried out simply by way of an acylated compound (15), followed by reduction to *N*-alkyl side chain. However, some precaution was necessary in advance of the $LiAlH_4$ reduction, otherwise contamination of 2,6-*trans* derivatives was unavoidable as discussed in detail later. Protected acetaldehyde substituent of 15 was once converted to the ethanol side chain, and the subsequent reduction of the amide function afforded exclusively 16, which was further oxidized to an ester (17) in 66% yield from 13. The ester (17) was condensed with *N*-(4-bromo-1-butyl)phthalimide[9] to construct the spermidine moiety and the amino acid derived from 18 was subjected to a macrocyclic lactam formation. Satisfactory result was obtained when a solution of the hydrochloride of amino acid chloride (19) in anhydrous acetonitrile was added slowly using motor-driven syringe into a suspension of well-ground dried K_2CO_3 in anhydrous acetonitrile in a high dilution condition. Reductive cleavage of the tosyl group completed a total synthesis of (±)-18-deoxypalustrine (4), [dihydrochloride, mp 199-202°C (MeOH-Et_2O)], in 49% yield from 17 (20% overall yield from the starting material (8).

The compound (15) was reduced with $LiAlH_4$ beforehand, and the successive treatment of 21 with an acid [10% aqueous HCl-dimethoxyethane (DME) (1:1), room temp.], Jones reagent and CH_2N_2 in Et_2O afforded the afore-mentioned compound (17) in 73% yield, accompanied by production in 6% yield of an epimeric compound (22), which exhibited the identical mass spectrum with 17. This finding suggested that an original *cis* amino-aldehyde (23) was in the equilibrium with a *trans* species (25) by way of the retro Michael intermediate (24). When one could shift the equilibrium to the right-hand side in a high yield, this reaction provided a practical method for preparation of 2,6-*trans*-dialkylpiperidines, hitherto inaccessible compounds in a stereoselective manner.[10] Treatment of 23 with K_2CO_3 in MeOH (saturated solution at 0°C) for a few hours was found to be a suitable condition for this purpose, and insertion of this treatment after the acid hydrolysis in the above transformation from 21 enabled the yield of 22 to enhance to 80% with formation of 17 in 2% yield. For the equilibration between a pair of the esters (17 and 22), much more drastic condition (NaOMe in MeOH at reflux temp.) was necessary, so that no epimerization was observed during transformation from 18 into 20 as far as the acid derivatives were treated with alkali at room temperature. *N*-Acyl

derivatives such as 15 were stable in either acidic or alkaline medium and this phenomenon was utilized for the stereoselective synthesis of 17 from 15, which produced no *trans* derivative during deacetalization process.

Structural proof of the intermediary (25) was performed as follows. A pair of compounds (26 and 27) were prepared as reported previously.[11] As a major product (26) was correlated with the 2,6-*cis* derivative (8) *via* 28, structure of a minor product was expressed as 27 on the basis of other instances.[7,8,11] A key compound (33) was synthesized from 27 by application of series of conventional steps, during which the methanesulfonate (29) was superior to the corresponding tosylate for the DBU treatment, but the yield of 30 was not so good as compared with the case of 13, along with the formation of 31 in 5% yield. Transformation of 25 into 33 was readily achieved by elongation of two carbon unit, and identity of 33 from both ways provided the evidence that 22 possessed the structure of 2,6-*trans* side chains.

The compound (22) was finally converted to (±)-18-deoxy-13-epipalustrine (5), mp 131-132°C (Me_2CO-Et_2O), in 35% yield (17% overall yield from 8) by the same procedure as described above. Structure of the final products (4 and 5) was verified by comparison of their mass spectra (both were almost identical) with that of palustrine, whose characteristic fragment pattern below m/z: 250 was superimposable with that of 4 or 5, because molecular ions generated the common ion (36) by facile elimination of the alkyl side chain in all cases. Identification of alkaloid P_3 with either 4 or 5, however, must await further investigation in the future.[12]

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12. Professor Eugster imformed us that mass spectra of 4 and 5 were almost superimposable with those of alkaloid P_3, but the latter showed additional fragment peaks due to the presence of contaminations, which disturbed the idetification by infrared absorption spectral comparison.

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