# STEREOSELECTIVE SYNTHESIS OF (±)-DEETHYLASPIDOSPERMIDINE

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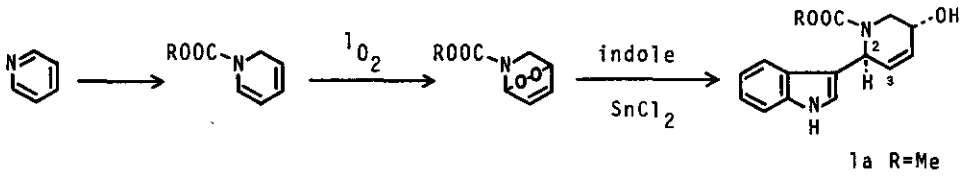
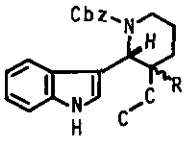
*Abstract*: Conjugate addition of various carbanions to the enones 2 afforded 2,3-*trans* substituted piperidinones 3. (±)-Deethylaspidospermidine (12a) was synthesized from 1b via 5b, 7, and 11a in the stereoselective manner.

In the previous communication,[1] we reported a novel reaction producing 1 by connection of indole with endoperoxides derived from 1,2-dihydropyridines. The compounds 1 might serve as starting materials for the synthesis of aspidosperma type of alkaloids, and for this purpose, we studied the introduction of carbon side chains at the 3 position of the piperidine ring. Then, our effort was concentrated to find out reaction conditions for construction of the framework C by way of A and B. In this paper, we wish to describe a stereoselective synthesis of (±)-deethylaspidospermidine[2] (12a)=C (R=H), the simplest model of the aspidosperma alkaloids.

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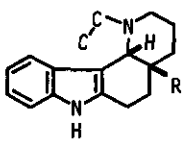
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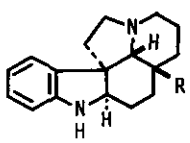
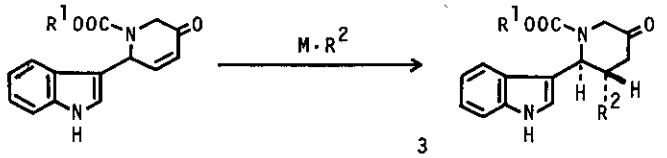
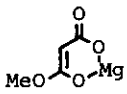
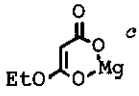

C

The compounds 1 were oxidized with Collins' reagent to enones 2 in 57% (R=Me) and 61% (R=PhCH$_2$) yields. Conjugate addition of various kinds of organometallic reagents to 2 was investigated to give stereoselective addition products 3 in fair

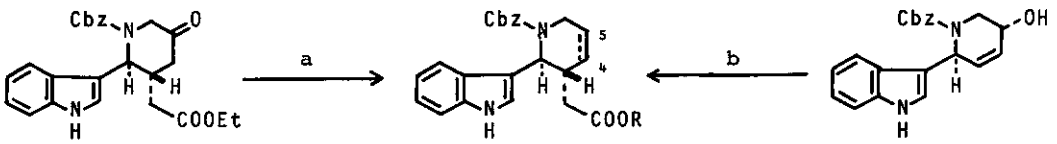
to good yields as shown in the following Table. The *trans* nature of the stereochemical relationship between 3-indolyl group and the newly introduced substituents was confirmed by correlation of the representative 3a with the structure definite compound 5a, obtained from 1b by modified Claisen rearrangement (Chart 1). In the $^1$H-nmr spectra of 3, coupling constant between H-2 and H-3 was observed to be in the range of 3-5 Hz and this fact suggested that both bulky substituents of 3 were situated in the *trans* diaxial orientation, when one assumed the piperidinone ring to be in the chair form. This phenomenon coincided well with the description in the literature[3] that the substituent α to the nitrogen in the N-acylpiperidine system prefered the axial configuration in order to release the steric congestion between N-acyl group and the α-substituent.




2 3

| $R^1$ | M·$R^2$ | Solv. | React. Temp. | Yield (%) | $J_{2,3}$ of H-2 (Hz) |
|---|---|---|---|---|---|
| Me | EtMgBr, n-$Bu_3$P·CuI [a] | ether | r.t. | 40 | |
| Me | Li<COOEt, COOEt | THF | 0° | 82.5 | 4 |
| Me | Li<SePh, COOEt, n-$Bu_3$P·CuI | THF | -78° | 88 | 3 |
| $PhCH_2$ | Li<COOMe, COOMe | ether | -30° | 80 | 4 |
| $PhCH_2$ | Li<SePh, COOMe [b] | THF | -78°→r.t. | 72 | |
| $PhCH_2$ | Li<SePh, COOEt, n-$Bu_3$P·CuI | THF | -78° | 80 | |
| $PhCH_2$ |  | DMF | 65-70° | $R^2$=$CH_2$COOMe 36 | 5 |
| $PhCH_2$ |  [c] | DMF | 65-70° | $R^2$=$CH_2$COOEt 3a 40 | 5 |

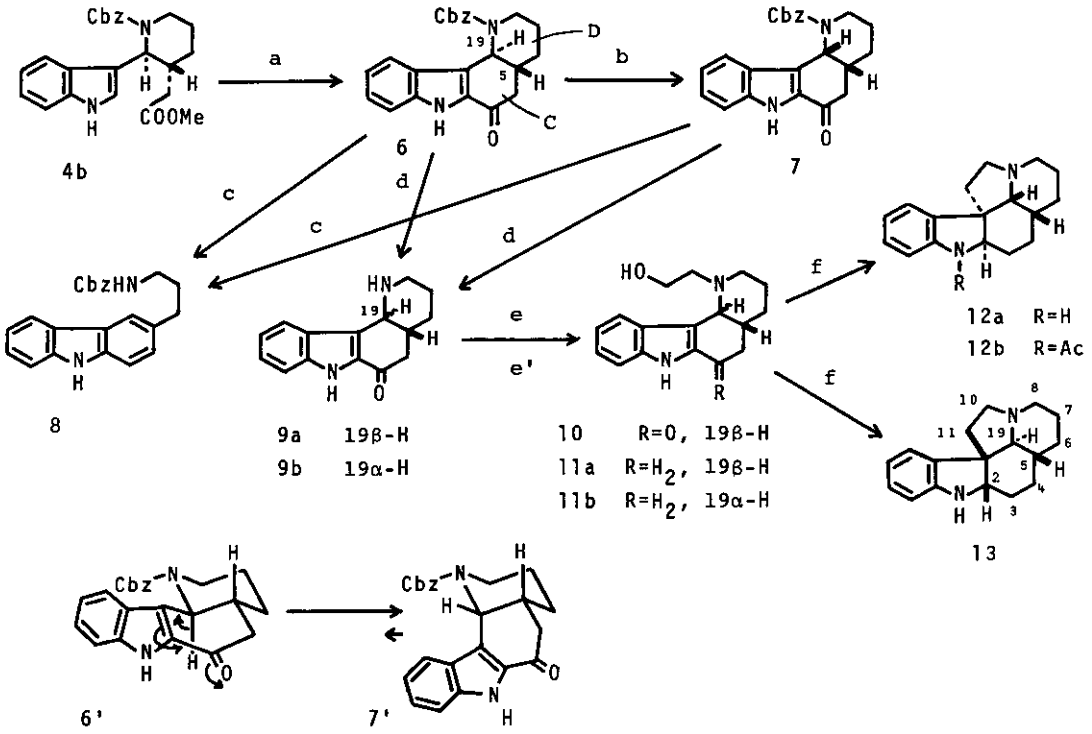
*a*. H.O. House, W.L. Respess, and G.M. Whitesides, *J. Org. Chem.*, 31, 3128 (1966).
*b*. J. Luchetti and A. Krief, *Tetrahedron Lett.*, 2697 (1978).
*c*. J.E. McMurry, W.A. Andrus, and J.H. Musser, *Synth. Commun.*, 8, 53 (1978).



3a 4a R=Et 5a $\Delta^{4,5}$, R=Et
4b R=Me 5b $\Delta^{4,5}$, R=Me
1b

a. (i) $NaBH_4$, MeOH, 0°. (ii) MsCl, $Et_3N$, $CH_2Cl_2$, 0°. (iii) DBU, xylene, reflux. (iv) $H_2$, $PtO_2$, DME. 3a→4a: 8% overall yield.
b. (i) $MeC(OR)_3$, $Me_3CCOOH$, reflux. 1b→5a: 38%; 1b→5b: 54%. (ii) $H_2$, $PtO_2$, DME. 5a→4a: 68%; 5b→4b: 67%.

Chart 1



8 9a 19β-H 9b 19α-H 10 R=O, 19β-H 11a R=$H_2$, 19β-H 11b R=$H_2$, 19α-H 12a R=H 12b R=Ac 13



6' 7'

a. (i) 2% NaOH, MeOH-$H_2O$, reflux. (ii) $(F_3CCO)_2O$, $CH_2Cl_2$, r.t. 42%.
b. t-BuOK, DMSO, 70-80°. 64.5%.
c. (i) $NaBH_4$, MeOH, r.t. (ii) 2% HCl, $Me_2CO$-$H_2O$, r.t. 6→8: 56%; 7→8: 61%.
d. $H_2$, 10% Pd-C, 95% EtOH-DME, r.t. 7→9a: 88%; 6→9b: 82%.
e. (i)  , MeOH, r.t. 9a→10: 80%. (ii) $LiAlH_4$, dioxane, reflux. 10→11a: 86%.
e'. (i) $LiAlH_4$, dioxane, reflux. (ii) , MeOH, r.t. 9b→11b: 53.5%.
f. (i) MsCl, $K_2CO_3$, $CH_2Cl_2$, r.t. (ii) t-BuOK, DMSO or DMF, r.t. (iii) $LiAlH_4$, THF, r.t. 11a→12a: 26%; 11b→13: 32%.

Chart 2

As 4b was readily available from 1b via 5b, the carboxylic acid derived from 4b was used for the study on the C ring formation (Chart 2). Trifluoroacetic anhydride was only a reagent for successful cyclization to afford 6,[4] mp 204.5-206° [IR (KBr) $cm^{-1}$: 3320, 1660; UV (95% EtOH) nm (ε): 236 (12,900), 309 (20,000)], whose UV absorption spectrum was characteristic of a partial structure of 2-acyl-3-alkylindole.[5] When 6 was warmed with t-BuOK in DMSO at 70-80° for 42 hr, a new compound 7,[4] mp 216-218° [IR (KBr) $cm^{-1}$: 3325, 1700, 1660; UV (95% EtOH) nm (ε): 236 (13,600), 309 (21,200)],was produced in 64.5% yield as the sole isolable compound. Judging from elementary analysis, fragmentation pattern of MS, and absorption data of IR and UV spectra, 7 was considered to be isomeric with 6, and degradation experiment leading to the common carbazole derivative 8 from both 7 and 6 suggested that no skeletal change took place during the treatment with t-BuOK.

$^1H$ NMR spectra of 6 and 7 provided the structural assignment of 7. The coupling constant between H-5 and H-19 was observed by inspection of H-19 of 6 and 7, which appeared at 4.49 δ (d, J=10.5 Hz) and 6.13 δ (J=4.5 Hz). The other pair of $J_{5,19}$ was observed in the spectra of 9b,[4] mp 217-219° [IR (KBr) $cm^{-1}$: 3275, 1645; $^1H$ NMR ($CDCl_3$-$CD_3OD$) δ: 3.99 (d, J=9 Hz, H-19)] and 9a,[4] mp 212-213.5° [IR (KBr) $cm^{-1}$: 3310, 1642; $^1H$ NMR ($CDCl_3$) δ: 4.40 (d, J=3 Hz, H-19)], prepared from 6 and 7 by removal of the N-protecting group. Large coupling constant values of 6 and 9b implied that the stereochemistry on the piperidine ring system remained to be *trans* during the C ring formation reaction,[6] whereas 7 and 9a were supposed to be C/D *cis* derivatives, judging from the small $J_{5,19}$ values. Again, the conformational requirement of the α axial substituent at the N-acylpiperidine system would be a main factor for transformation of 6 into 7 by base treatment, as illustrated by the formulas 6'→7'.

Structural confirmation of 7 was achieved by synthesis of (±)-deethylaspidospermidine (12a) from 9a. Two-carbon unit was easily attached to the nitrogen by using ethylene oxide to give 10,[4] mp 159-160.5°, and the ketone group was removed by reduction with $LiAlH_4$. Construction of the aspidosperma skeleton was carried out by t-BuOK treatment[7] of the mesylate derived from 11a,[4] mp 115-117°, followed by reduction of the resulting indolenine derivative with $LiAlH_4$ to yield 12a, which was acetylated to 12b, picrate[4] (MeOH): mp 205-208.5°, for the purpose of identification [IR ($CHCl_3$), $^1H$ NMR spectra] with the known material.[8]

The corresponding C/D *trans* compound 13,[4,9] mp 105-106° (MeOH), picrate[4] (MeOH): mp 222-226° [MS *m/z*: 254 ($M^+$), 253, 226, 162, 141, 96; $^1H$ NMR (200 MHz,

$CDCl_3$) δ: 2.30 (d, J=10 Hz, H-19), 2.80-3.25 (m, 4H, 2×$NCH_2$), 3.81 (dd, J=4, 3 Hz, H-2), 6.59-7.27 (m, 4H, arom. H); IR ($CHCl_3$) $cm^{-1}$: 1610] was synthesized from 9b in the analogous fashion. Comparison of the above data with those[10] in the literature[9] suggested the possible identity of 13 with the Wenkert's material.

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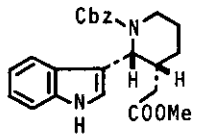
## REFERENCES AND NOTES

1. M. Natsume, Y. Sekine, M. Ogawa, H. Soyagimi, and Y. Kitagawa, *Tetrahedron Lett.*, 3473 (1979).
2. Y. Honma, T. Ohnuma, and Y. Ban, *Heterocycles*, 5, 47 (1976).
3. (a) F. Johson, *Chem. Rev.*, 68, 388 (1968). (b) J. Quick, C. Modello, M. Humora, and T. Brennen, *J. Org. Chem.*, 43, 2705 (1978). (c) M. Natsume and M. Ogawa, *Heterocycles*, 14, 169 (1980).
4. Satisfactory results of elementary analysis (C, H, N) were obtained for these compounds.
5. (a) R.T. Brown and J.A. Joule, "Comprehensive Organic Chemistry," Vol. 4 ed. by D. Barton and W.D. Ollis, Pergamon Press, 1979, p. 415. (b) F.E. Ziegler and G.B. Bennett, *J. Am. Chem. Soc.*, 95, 7458 (1973).
6. The carboxylic acid from the *cis* compound j gave 6 by treatment with $(F_3CCO)_2O$ in 36% yield. M. Natsume and I. Utsunomiya, unpublished result.



j

7. *cf.* (a) H.-P. Husson, C. Thal, and P. Potier, *Chem. Commun.*, 480 (1970). (b) F.E. Ziegler and E.B. Spitzer, *J. Am. Chem. Soc.*, 92, 3492 (1970). (c) E. Wenkert, *J. Nat. Prod.*, 43, 235 (1980).
8. Y. Ban, T. Ohnuma, M. Nagai, Y. Senda, and T. Oishi, *Tetrahedron Lett.*, 5023 (1972).
9. E. Wenkert, J.S. Bindra, and B. Chauncy, *Synth. Commun.*, 2, 285 (1972).
10. Mp 102-104° (MeOH). MS *m/z*: 254, 226, 130, 96. $^1H$ NMR (220 MHz, $CDCl_3$) δ: 2.25 (d, J=10 Hz), 2.7-3.2 (m, 4H), 3.79 (dd, J=4, 3 Hz), 6.5-7.3 (m, 4H).

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