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SYNTHETIC APPROACHES TO EUDISTOMINS. PART 1. SYNTHESIS OF 1-AMINO-3-THIAINDOLO [2,3-a] QUINOLIZIDINE

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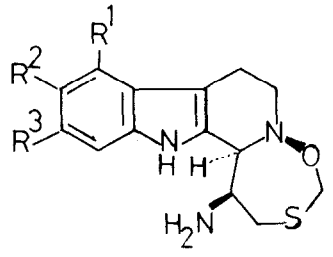
Summary : The optically active 1-amino-3-thiaindoloquinolizidine **8** was synthesized by rearrangement of the ß-carboline **6** which was obtained by the Bischler-Napieralski reaction of the thioamide **4b** followed by $NaBH_4$ reduction, whereas the isomer **7** gave the pentacycle **9**.

Eudistomins C, E, K, and L (**1**) have been isolated from the colonial tunicate Eudistoma olivaceum and reported to show a potent antiviral activity towards Herpes simplex virus type 1.[1] These marine natural products have a unique ring system which is not found in natural products previously and is possibly derived from tryptamine and cysteine.

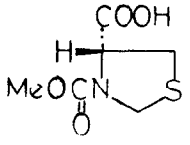
We now report a synthesis of the 1-amino-3-thiaindoloquinolizidine **8** which may be a possible precursor for the synthesis of the eudistomin ring system, involving the ring transformation process of 1-(4-thiazolidinyl)-ß-carboline **6**

The N-methoxycarbonylthiazolidinecarboxylic acid **2**[2], readily obtained from L-cysteine, was condensed with tryptamine by use of DCC in methylene chloride to give the amide **4a** [98% yield; amorphous; $[\alpha]_D^{17}$ -97°(c 0.38, MeOH); ν_{max} (KBr) 1690, 1650, 1530 cm^{-1}; δ[3] 3.17 (1H, m, S-CH), 3.40 (1H, m, S-CH), 4.16 (1H, d, J = 9 Hz, N-CH-S), 4.60 (1H, d, J = 9 Hz, N-CH-S), 4.71 (1H, br, CO-CH)]. Bischler-Napieralski (B.-N.) reaction of **4a** with phosphorous oxychloride in boiling benzene followed by reduction with sodium borohydride gave two ß-carbolines **6** and **7** via **5** [**6**: more polar isomer; 63%; mp 177-178°C[4]; ν_{max} (KBr) 3340, 1690cm^{-1}; m/z 317 (M^+); δ 2.97 (1H, dd, J = 6,12 Hz, S-CH), 3.23 (1H, dd, J = 7,12 Hz, S-CH), 4.28 (1H, d, J = 10 Hz, N-CH-S), 4.60 (2H, br, C_1-H), 5.00 (1H, d, J = 10 Hz, N-CH-S). **7**: less polar isomer; 20%; mp 182-182.5°C; m/z 317 (M^+); δ 4.40 (1H, d, J = 10 Hz, N-CH-S), 4.51 (1H, br, N-CH), 4.70 (1H, m, CON-CH), 4.89 (1H, d, J = 10 Hz, N-CH-S)]. Both **6** and **7**, however, were racemic, indicating that racemization had occurred during the B.-N. reaction.

When refluxed in trifluoroacetic acid for 3 h, the more polar isomer **6** slowly isomerized to **7** (50%), probably via protonation of the indole ring. However, when **6** was refluxed in aqueous acetic acid for 42 h,[5] a ring transformation occurred to give the 3-thiaindoloquinolizidine **8** [40%; mp 225°C (dec.); ν_{max} (KBr) 1690, 1515 cm^{-1}; m/z 317 (M^+); δ 2.72 (2H, m, N-CH_2),



1a (C) R^1=H, R^2=OH, R^3=Br
b (E) R^1=Br, R^2=OH, R^3=H
c (K) R^1=R^2=H, R^3=Br
d (L) R^1=R^3=H, R^2=Br



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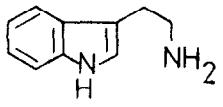

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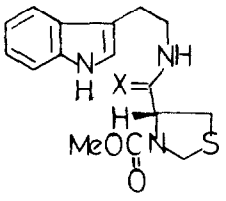
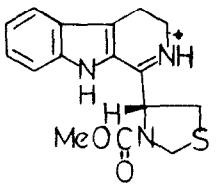


4 a, X=O
b, X=S



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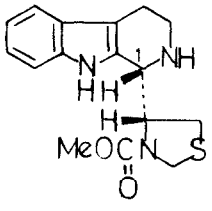

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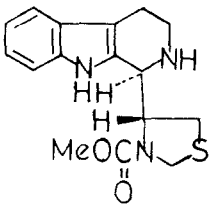

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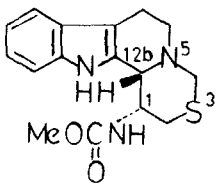
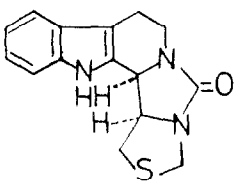


8



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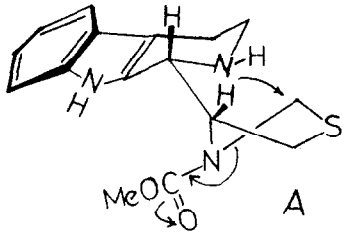
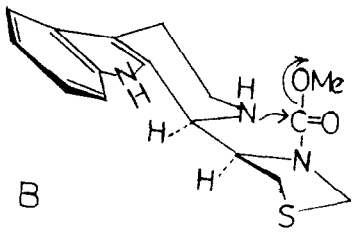


A



B

2.89 (1H, dd, J = 3,14 Hz, S-CH), 3.00 (2H, m, Ind-CH_2), 3.18 (1H, dd, J = 2, 14 Hz, S-CH), 3.51 (3H, s, OCH_3), 3.64 (1H, d, J = 1 Hz, Ind-CH-N), 3.73 (1H, dd, J = 2,12 Hz, N-CH-S), 3.86 (1H, d, J = 12 Hz, N-CH-S), 4.53 (1H, m, CON-CH), 5.86 (1H, d, J = 9 Hz, NH, exchangeable), 8.33 (1H, br, Ind-NH, exchangeable)]. On the other hand, a similar treatment of 7 in boiling aqueous acetic acid gave the pentacyclic compound 9 [33%; mp 260-261°C; ν_{max} (KBr) 1690 cm^{-1}; m/z 285 (M^+); δ 2.27 (1H, t-like, J = 11 Hz, S-CH), 2.67 (1H, dd, J = 6,11 Hz, S-CH), 2.85 (2H, m, Ind-CH_2), 3.15 (1H, m, N-CH), 4.16 (1H, d, J = 9 Hz, N-CH-S), 4.20 (1H, m, N-CH), 5.08 (1H, d, J = 9Hz, N-CH-S), 5.27 (1H, d, J = 7 Hz, Ind-CH-N)], and 8 was not obtained. The stereochemistry of 8 was confirmed by X-ray analysis[6] as shown in Figure 1. Consequently, the stereochemistry of 6 and 7 was deduced as depicted. Model studies suggest that 8 and 9 most likely arose from the conformers A and B, respectively, as shown in the chart. In order to obtain the optically active 8, we utilized the modified Bischler-Napieralski ring closure of the thioamide developed by Oh-ishi's group.[8] The reaction of the amide 4a with Lawesson's reagent in toluene proceeded well to give the corresponding thioamide (-)-4b [87%; amorphous; $[\alpha]_D^{17}$ -140°(c 0.28, MeOH); m/z 349 (M^+); δ 3.34 (1H, m, S-CH), 3.56 (1H, m, S-CH), 3.96 (2H, m, N-CH_2), 4.05 (1H, d, J = 9 Hz, N-CH-S), 4.54 (1H, d, J = 9 Hz, N-CH-S), 5.03 (1H, m, CON-CH)]. Treatment of the thioamide with benzyl bromide in boiling methylene chloride gave the 3,4-dihydro-ß-carboline 5, which was readily reduced with sodium borohydride to give two diastereo-isomeric optically active tetrahydro-ß-carbolines (-)-6 [44%; $[\alpha]_D^{21}$ -134°(c 0.30, MeOH)] and (-)-7 [19%; $[\alpha]_D^{21}$ -95°(c 0.32, MeOH)]. High optical purity of 6 was confirmed by a chiral shift reagent.[9]

Reflux of (-)-6 in aqueous acetic acid gave the optically acitve 8 [mp 204°C (dec.); 25%; $[\alpha]_D^{22}$ +133°(c 0.20, MeOH)] whose spectral data were identical with those of 8.[9]

Transformation of 8 to the basic ring system of eudistomins is now in progress.

Acknowledgements Financial support from The Ministry of Education, Science and Culture, Japan, in the form of a Grant-in-Aid for Scientific Research, is greatly appreciated.

References and Notes

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2. 2 : 98%; ν_{max} (neat) 3500-2500, 1700 cm^{-1}; δ 3.31 (2H, , SCH), 3.77 (3H, s, OMe), 4.60 (2H, m, N-CH-S), 4.90 (1H, m, N-CH), 9.06 (1H, br, COOH, exchangeable). The compound 2 was obtained by the reaction of methyl chlorofomate with thiazolidine-4-carboxylic acid in the presence of NaOH,

which was prepared by the reported method : S. Ratner, and H. T. Clarke, J. AM. Chem. Soc., 59, 200 (1937).

3. All the ^{1}H-NMR spectra were recorded in $CDCl_3$.
4. All the crystalline compounds except **9** gave satisfactory elemental analyses.
5. A trace amount of **7** and **9** was detected on TLC.
6. Crystal data for **8**: Large monoclinic crystals were obtained by crystallization from ethyl acetate-hexane solution.

$C_{16}H_{19}N_3O_2S$: space group P $2_1/N$; a = 10.967(3), b = 8.708(2), c = 17.290(6) A°, ß = 102.37°, U = 1612.8A°^{3}, Dc = 1.31 gcm^{-3}, Z = 4.

Lattice constants and intensity data were measured using graphite monochromated Cu-Kα radiation on a RIGAKU AFC-5 diffractiometer. A total of 2919 unique reflections with $F(\theta) > \delta(F\theta)$ were obtained using the $\omega < 30 < \omega - 2\theta$ scanning method with a 2θ scan speed of 4° min^{-1} to 2θ = 155°, R = 0.134. The structure was solved by the UNICS-III system (Library of Computer of Tokyo University) based on the direct method.[7)]

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8. A. Ishida, T. Nakamura, K. Irie, and T. Oh-ishi, Chem. Pharm. Bull., 33, 3237 (1985).
9. The ^{1}H-NMR spectrum using the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato)europium(III)] derivative showed the absence of the other enantiomer.

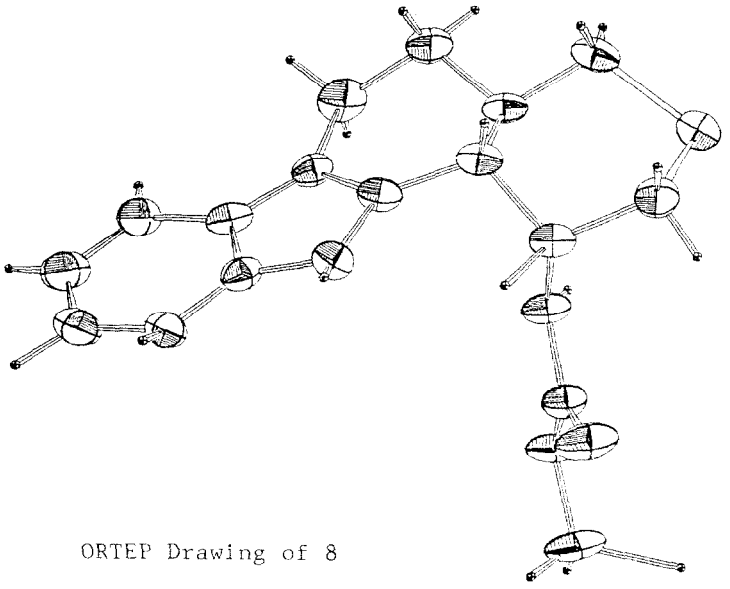

Figure 1 ORTEP Drawing of 8

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