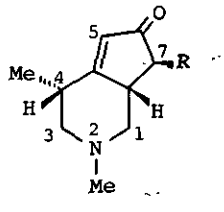
AN AZABICYCLO[3.3.1]NONANONE APPROACH TO TECOMA ALKALOIDS: A STEREOSELECTIVE SYNTHESIS OF (±)-7-DEMETHYLTECOMANINE

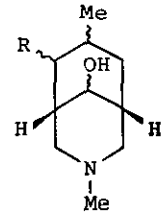
Takefumi Momose,* Masahiko Kinoshita, and Takeshi Imanishi†
Faculty of Pharmaceutical Sciences, Osaka University
Yamada-kami, Suita, Osaka 565, Japan

Abstract — A stereoselective synthesis of (±)-7-demethyltecomanine (2) via a 3-azabicyclo[3.3.1]nonane precursor (4) which has the same configuration at the 3,5-position on the piperidine ring as that for tecomanine (1) is described.

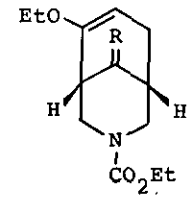
Tecomanine, isolated from Tecoma stans Juss. in 1963, is an alkaloid having the hydroactinidine skeleton as shown in 1,[1] and its salts display a powerful hypoglycemic activity.[2] In spite of its simple framework, no achievement of total synthesis of 1 has been described, owing probably to its complex stereochemistry. On the other hand, Takeuchi and co-workers[3] have reported a hypoglycemic effect of some 3-azabicyclo[3.3.1]nonane derivatives (3), whose stereochemistry concerning the piperidine ring system resembles that for the above alkaloid. We examined an attempt to convert the 3-azabicyclo[3.3.1]nonane system into the hydroactinidine skeleton. In this communication we wish to describe a stereoselective synthesis of (±)-7-demethyltecomanine (2) via the oxidative cleavage of an enol ether (4).



1: R = Me
2: R = H



3: R = -N

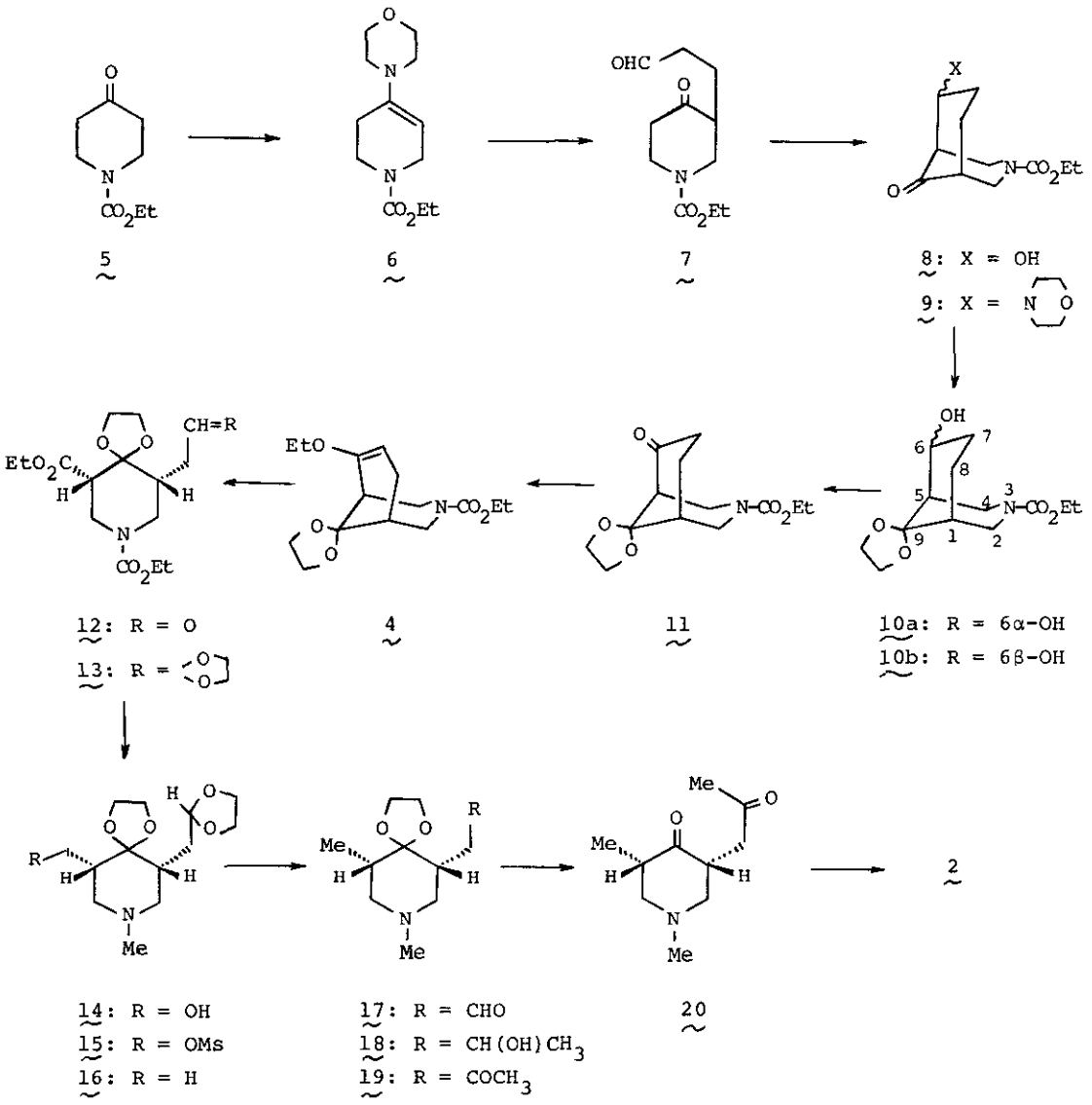


4: R = O,O

The α,α'-annelation of cyclohexanones with acrolein[4] was utilized as an initial step of our approach. The morpholine enamine (6) of 1-ethoxycarbonyl-4-piperidone[5] (5) was treated with acrolein in benzene at 0-5° followed by hydrolysis to

give a keto aldehyde [7; ν(film): 2720 cm^{-1}], which was cyclized by the action of 3N hydrochloric acid in acetone to afford the 3-azabicyclo[3.3.1]nonanol [8; bp 155-160°(0.05 mmHg); ν($CHCl_3$): 3360 cm^{-1}] as a mixture of diastereomers in 46% yield from 5.[6] Ketalization of 8 under the usual condition yielded two isomeric ketals, 10a[mp 102-104.5°; δ[7]: 3.99(4H, s, OCH_2CH_2O)] and 10b[bp 141-145°(0.005 mmHg); δ: 4.06(4H, m, OCH_2CH_2O)], in 87% total yield.[8] Oxidation of a mixture of 10a and 10b with pyridinium chlorochromate (PCC)[9] in dichloromethane in the presence of sodium acetate afforded a ketone [11; bp 136°(0.005 mmHg); 90% yield], whose enol ether [4; bp 122-125°(0.007 mmHg); 81% Yield; δ: 4.61(1H, t, J = 3 Hz, CH=C-OEt)] was ozonized in ethyl acetate at -78° followed by treatment with zinc/acetic acid to afford an aldehyde [12; ν(film): 2730 and 1720 cm^{-1}]. Its acetal [13; mp 107-109°; 54% yield from 12; δ: 4.91(1H, t, J = 4.6 Hz, )] was reduced with lithium aluminum hydride (LAH) in ether to yield an amino alcohol [14; mp 113-114°; 73% yield; δ: 2.28(3H, s, N-CH_3)]. Replacement of the hydroxyl group by hydrogen was effected via its mesylate [15; mp 193-194°] by the action of sodium iodide/zinc in boiling 1,2-dimethoxyethane[10] to give the 3-methylpiperidine system [16; oil; δ: 0.83(3H, d, J = 6.4 Hz, CH-C$\underline{H}_3$); the picrolonate: mp 197.5-199°] in 54% overall yield from 14. Mild hydrolysis of 16 with 1N hydrochloric acid at room temperature afforded an aldehyde [17; oil; 88% yield; ν(film): 1735 cm^{-1}; δ: 9.8(1H, d-d, J = 4 and 2 Hz, CHO), 0.84(3H, d, J = 6.1 Hz, CH-C$\underline{H}_3$); M^+: 213)], which was then subjected to the Grignard reaction with methylmagnesium iodide in ether to yield a carbinol [18; oil; 80% yield; δ: 1.13(3H, d, J = 6 Hz, CH(OH)-C$\underline{H}_3$), 0.81(3H, d, J = 6 Hz, CH-C$\underline{H}_3$). The PCC oxidation of 18 afforded a ketone [19; oil; 68% yield; δ: 2.13(3H, s, $COCH_3$), 0.82(3H, d, J = 5.9 Hz, CH-C$\underline{H}_3$)]. Complete hydrolysis of 19 by refluxing in 3N hydrochloric acid afforded diketone 20 [oil; 53% yield; δ: 2.34(3H; s, N-CH_3), 2.19(3H, s, $COCH_3$), 0.98 (3H, d, J = 6.7 Hz, CH-C$\underline{H}_3$)], which was shown to be identical with a specimen prepared by the method of Jones and co-wokers.[11] Finally, the intramolecular aldol condensation[12] of 20 was effected by its treatment with potassium carbonate in boiling ethanol to afford the desired enone (±)-7-demethyltecomanine (2) in 16.5% yield. Its spectral features well agreed with the reported ones of tecomanine.[1] As for the approach according to a 'two-dimensional' design,[12] the N-methoxycarbonyl diketone was found to cyclize into the pyrindinone system in 60% yield, and converted into 2 in a two-step sequence consisting of the initial reduction with LAH and subsequent PCC oxidation. A synthetic approach to tecomanine itself using an

appropriate 3-azabicyclo[3.3.1]nonane compound[13] as a key intermediate is in progress.



NOTES AND REFERENCES

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6) The annelation in boiling benzene afforded exclusively 9. During the course of this study, a similar annelation using the N-toluenesulfonyl analogue was reported by T.R. Bok and W.N. Speckamp, Tetrahedron, 1977, 33, 787.

7) All ^{1}H-NMR spectra were measured for the $CDCl_3$ solution with tetramethylsilane as an internal standard.

8) Ratio of 10a to 10b varied on the repeated runs, owing probably to fast isomerization of the hydroxyl orientation in 8 via the retrograde aldol reaction. See, ref. 6.

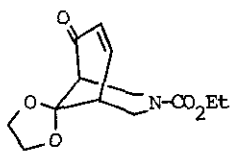
9) E.J. Corey and J.W. Suggs, Tetrahedron Lett.,1975, 2647.

10) Y. Fujimoto and T. Tatsuno, Tetrahedron Lett., 1976, 3325.

11) M. Alam, J.D. Baty, G. Jones, and C. Moore, J. Chem. Soc. (C), 1969, 1520.

12) G. Jones et al. have succeeded in cyclization of the N-benzylpiperidone derivative, but failed to cyclize 20; see ref. 11.

13) The α,β-unsaturated ketone (21) derived from 11 in a two-step sequence has been found to give exclusively the exo-methyl-ketone (22) by treatment with methylmagnesium iodide. This ketone (22) would serve as a key intermediate to our final goal.



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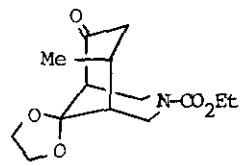

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†) Present address: Faculty of Pharmaceutical Sciences, Kanazawa University, 13-1 Takara-machi, Kanazawa 920, Japan.

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