

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

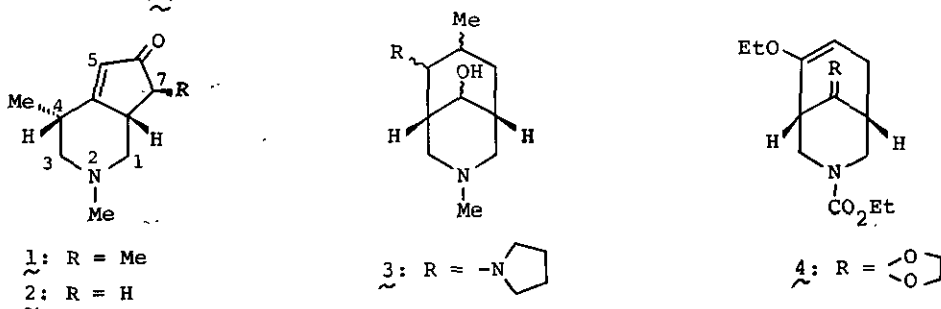
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Abstract — A stereoselective synthesis of (±)-7-demethyl-tecomanine (2) via a 3-azabicyclo[3.3.1]nonane precursor (4) which has the same configuration at the 3,5-position on the piperidine ring as that for tecomanine (1) is described.

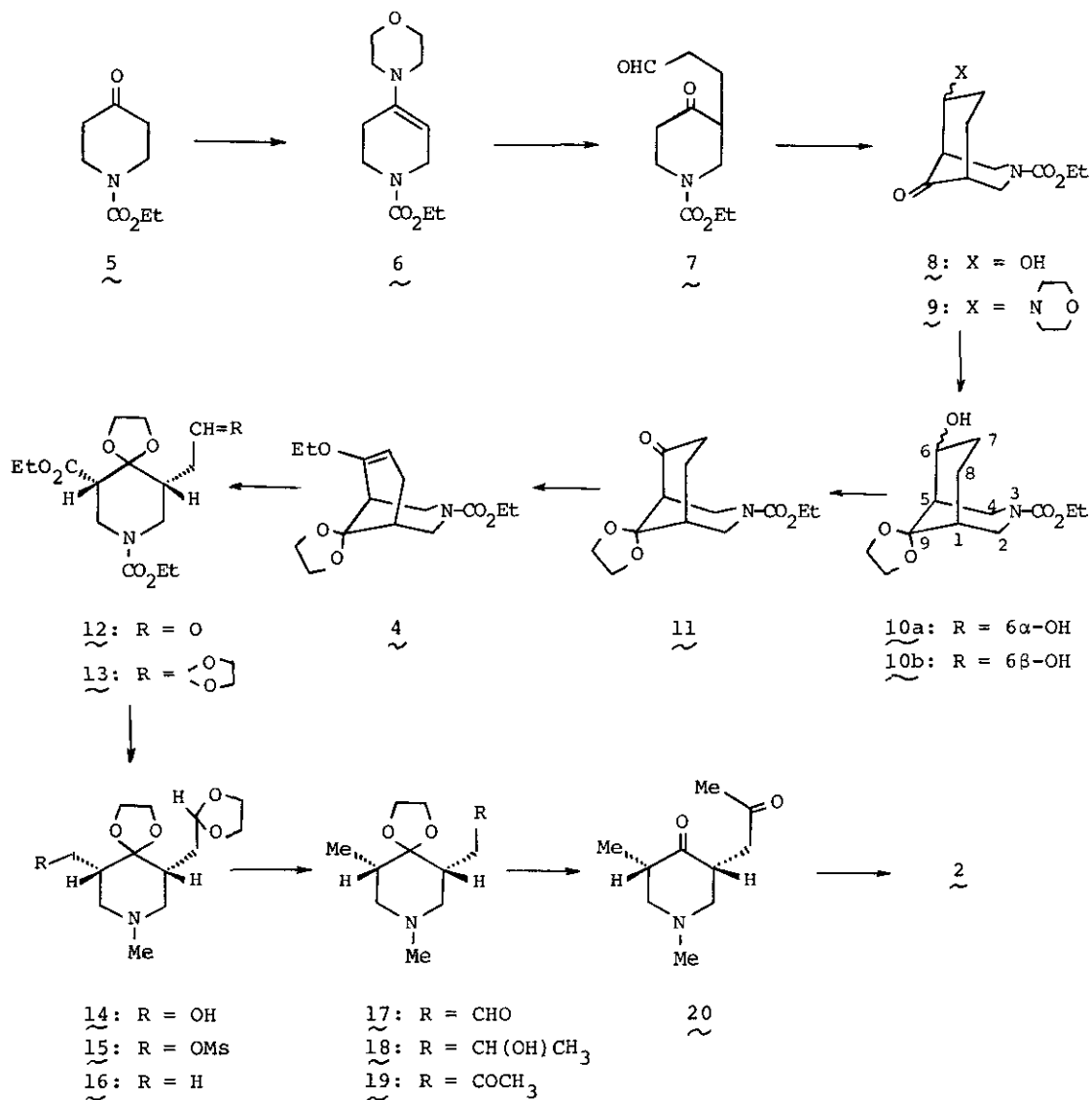
Tecomanine, isolated from *Tecoma stans* Juss. in 1963, is an alkaloid having the hydroactinidine skeleton as shown in 1,<sup>1</sup> and its salts display a powerful hypoglycemic activity.<sup>2</sup> In spite of its simple framework, no achievement of total synthesis of 1 has been described, owing probably to its complex stereochemistry. On the other hand, Takeuchi and co-workers<sup>3</sup> 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).



The  $\alpha, \alpha'$ -annulation of cyclohexanones with acrolein<sup>4</sup> was utilized as an initial step of our approach. The morpholine enamine (6) of 1-ethoxycarbonyl-4-piperidone<sup>5</sup> (5) was treated with acrolein in benzene at 0-5° followed by hydrolysis to

give a keto aldehyde [7;  $\nu(\text{film})$ :  $2720\text{ cm}^{-1}$ ], which was cyclized by the action of 3N hydrochloric acid in acetone to afford the 3-azabicyclo[3.3.1]nonanol [8; bp  $155\text{-}160^\circ$  (0.05 mmHg);  $\nu(\text{CHCl}_3)$ :  $3360\text{ cm}^{-1}$ ] as a mixture of diastereomers in 46% yield from 5.<sup>6</sup> Ketalization of 8 under the usual condition yielded two isomeric ketals, 10a [mp  $102\text{-}104.5^\circ$ ;  $\delta^7$ : 3.99(4H, s,  $\text{OCH}_2\text{CH}_2\text{O}$ )] and 10b [bp  $141\text{-}145^\circ$  (0.005 mmHg);  $\delta$ : 4.06(4H, m,  $\text{OCH}_2\text{CH}_2\text{O}$ )], in 87% total yield.<sup>8</sup> Oxidation of a mixture of 10a and 10b with pyridinium chlorochromate (PCC)<sup>9</sup> in dichloromethane in the presence of sodium acetate afforded a ketone [11; bp  $136^\circ$  (0.005 mmHg); 90% yield], whose enol ether [4; bp  $122\text{-}125^\circ$  (0.007 mmHg); 81% Yield;  $\delta$ : 4.61(1H, t,  $J = 3\text{ Hz}$ ,  $\text{CH}=\text{C}-\text{OEt}$ )] was ozonized in ethyl acetate at  $-78^\circ$  followed by treatment with zinc/acetic acid to afford an aldehyde [12;  $\nu(\text{film})$ :  $2730$  and  $1720\text{ cm}^{-1}$ ]. Its acetal [13; mp  $107\text{-}109^\circ$ ; 54% yield from 12;  $\delta$ : 4.91(1H, t,  $J = 4.6\text{ Hz}$ ,  $\text{O} \begin{array}{c} \diagup \text{O} \\ \diagdown \text{H} \end{array}$ )] was reduced with lithium aluminum hydride (LAH) in ether to yield an amino alcohol [14; mp  $113\text{-}114^\circ$ ; 73% yield;  $\delta$ : 2.28(3H, s,  $\text{N}-\text{CH}_3$ )]. Replacement of the hydroxyl group by hydrogen was effected via its mesylate [15; mp  $193\text{-}194^\circ$ ] by the action of sodium iodide/zinc in boiling 1,2-dimethoxyethane<sup>10</sup> to give the 3-methylpiperidine system [16; oil;  $\delta$ : 0.83(3H, d,  $J = 6.4\text{ Hz}$ ,  $\text{CH}-\text{CH}_3$ ); the picrolonate: mp  $197.5\text{-}199^\circ$ ] in 54% overall yield from 14. Mild hydrolysis of 16 with 1N hydrochloric acid at room temperature afforded an aldehyde [17; oil; 88% yield;  $\nu(\text{film})$ :  $1735\text{ cm}^{-1}$ ;  $\delta$ : 9.8(1H, d-d,  $J = 4$  and  $2\text{ Hz}$ , CHO), 0.84(3H, d,  $J = 6.1\text{ Hz}$ ,  $\text{CH}-\text{CH}_3$ );  $M^+$ : 213}], which was then subjected to the Grignard reaction with methylmagnesium iodide in ether to yield a carbinol [18; oil; 80% yield;  $\delta$ : 1.13(3H, d,  $J = 6\text{ Hz}$ ,  $\text{CH}(\text{OH})-\text{CH}_3$ ), 0.81(3H, d,  $J = 6\text{ Hz}$ ,  $\text{CH}-\text{CH}_3$ ). The PCC oxidation of 18 afforded a ketone [19; oil; 68% yield;  $\delta$ : 2.13(3H, s,  $\text{COCH}_3$ ), 0.82(3H, d,  $J = 5.9\text{ Hz}$ ,  $\text{CH}-\text{CH}_3$ )]. Complete hydrolysis of 19 by refluxing in 3N hydrochloric acid afforded diketone 20 [oil; 53% yield;  $\delta$ : 2.34(3H; s,  $\text{N}-\text{CH}_3$ ), 2.19(3H, s,  $\text{COCH}_3$ ), 0.98(3H, d,  $J = 6.7\text{ Hz}$ ,  $\text{CH}-\text{CH}_3$ )], which was shown to be identical with a specimen prepared by the method of Jones and co-workers.<sup>11</sup> Finally, the intramolecular aldol condensation<sup>12</sup> of 20 was effected by its treatment with potassium carbonate in boiling ethanol to afford the desired enone ( $\pm$ )-7-demethyltecomanine (2) in 16.5% yield. Its spectral features well agreed with the reported ones of tecomanine.<sup>1</sup> As for the approach according to a 'two-dimensional' design,<sup>12</sup> the N-methoxycarbonyl diketone was found to cyclize into the pyridinone 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<sup>13</sup> as a key intermediate is in progress.

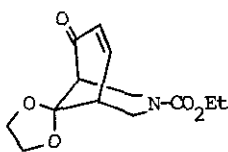


## NOTES AND REFERENCES

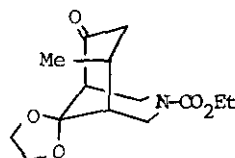
- 1) G. Jones, H.M. Fales, and W.C. Wildman, *Tetrahedron Lett.*, 1963, 397; E.M. Dickinson and G. Jones, *Tetrahedron*, 1969, 25, 1523; G. Ferguson and W.C. Marsh, *J. Chem. Soc. Perkin II*, 1975, 1124.
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- 3) S. Takeuchi, T. Fukano, C. Dohi, and Y. Inoue, *Japanese J. Pharmacol.*, 1971,

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- 4) cf. G. Stork and H.K. Landesman, J. Am. Chem. Soc., 1956, 78, 5129; A.C. Cope, D.L. Nealy, P. Scheiner, and G. Wood, ibid., 1965, 87, 3130; J.P. Schaefer, J.C. Lark, C.A. Flegal, and L.M. Honig, J. Org. Chem., 1967, 32, 1372; V. Dressler and K. Bodendorf, Tetrahedron Lett., 1967, 4243; Z. Horii, T. Imanishi, S. Kim, and I. Ninomiya, Chem. Pharm. Bull., 1968, 16, 2107; R.D. Allan, B.G. Cordiner, and R.J. Wells, Tetrahedron Lett., 1968, 6055.
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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 <sup>1</sup>H-NMR spectra were measured for the CDCl<sub>3</sub> 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  $\alpha,\beta$ -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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