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1,6-DIHYDRO-3(2*H*)-PYRIDINONES AS SYNTHETIC INTERMEDIATES. TOTAL SYNTHESIS OF (±)-TECOMANINE

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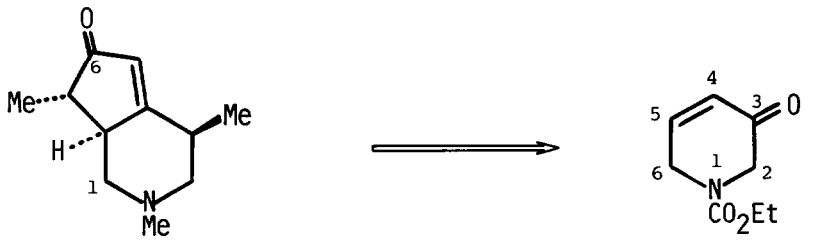
Summary: The first and stereoselective total synthesis of (±)-tecomanine (1) has been achieved from ethyl 1,6-dihydro-3(2*H*)-pyridinone-1-carboxylate (2) as a synthon.

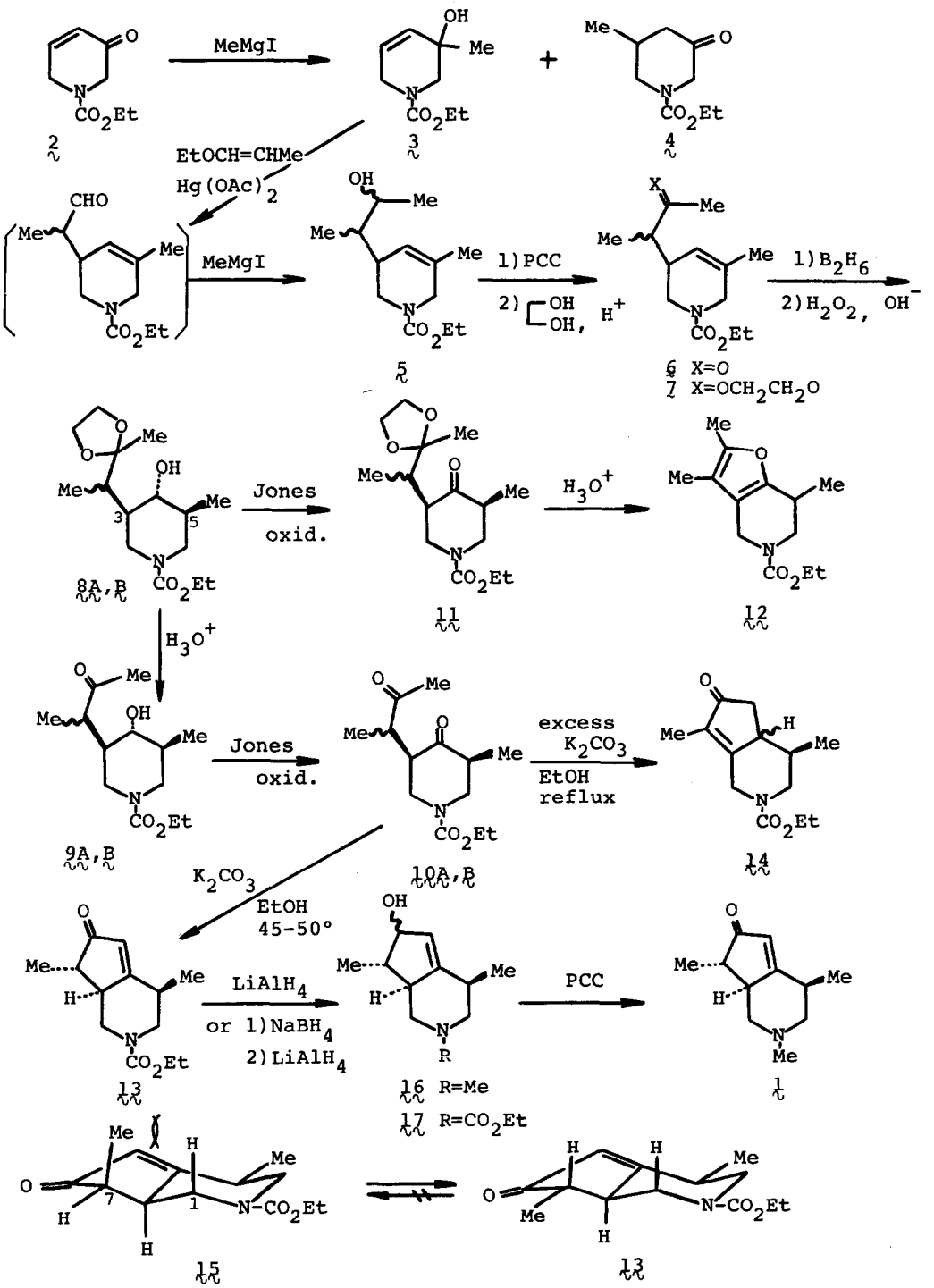
Tecomanine, a representative alkaloid isolated from *Tecoma stans* Juss.,[1] has a unique hexahydro-6*H*-2-pyrindin-6-one skeleton with three chiral centers as shown in structure 1[2] and its salts exhibit powerful hypoglycemic activities.[3] In spite of some efforts to synthesize the base (1),[4] no one has accomplished its final purpose to date.

Recently, we achieved formal syntheses of some indole alkaloids using a common starting material, ethyl 1,6-dihydro-3(2*H*)-pyridinone-1-carboxylate (2).[5] Now we wish to describe here the first and stereoselective total synthesis of (±)-tecomanine (1) starting from the same synthon.



1 2

Reaction of 2 with methylmagnesium iodide in ether at -5° gave the 1,2-adduct (3;[6a] 56%) along with a small amount of the 1,4-adduct (4; 7.7%). Heating of the former in ethyl propenyl ether[7] in the presence of mercuric acetate at 200° for 3 days, followed by methylation with methylmagnesium iodide, afforded the alcohol (5)[6b] in 51% yield. On oxidation with PCC[8] in methylene chloride the alcohol yielded the ketone (6;[6c] 72%) as a diastereoisomeric mixture, which was converted to the ketal (7; 92%) in the usual way. Hydroboration and oxidation of 7 afforded the two secondary alcohols (8A;[6d] 49% and 8B;[6e] 41%). The formation of only two diastereoisomers would be well interpreted by the highly stereoselective addition of borane to 7 from the opposite side of the


MeMgI
EtOCH=CHMe
Hg(OAc)2
MeMgI
1) PCC
2) OH, OH, H+
1) B2H6
2) H2O2, OH-
Jones oxid.
H3O+
Jones oxid.
H3O+
excess K2CO3
EtOH reflux
K2CO3
EtOH
45-50°
LiAlH4
or 1) NaBH4
2) LiAlH4
PCC

bulky substituent at the allylic position, therefore the alkyl substutuents at C-3 and C-5 in 8 could be *cis* with each other as depicted.[9] The *trans* relationship between C-3 and C-4 substituents would be supported from the fact that upon hydrolysis of 8A or 8B with a mineral acid the keto alcohol (9A or 9B) was obtained in an excellent yield (84 or 91% yield, respectively) without formation of any cyclic hemiacetals.

Jones oxidation of 9A or 9B gave the diketone (10A[6f] or 10B[6g]) in 76 or 86% yield, respectively. On the other hand, oxidation of 8 at first and the subsequent hydrolysis with 10% hydrochloric acid in boiling tetrahydrofuran afforded the furan (12)[6h] as a sole product *via* 10.[10]

The intramolecular condensation of 10A or 10B with excess potassium carbonate in boiling ethanol yielded none of the desired compound (13) but an exclusive formation of the more stable cyclopentenone isomer (14)[6i] in 29% (from 10A) or 23% (from 10B) yield.[11] On a short time treatment with a small amount of potassium carbonate in absolute ethanol under nitrogen at 45-50° both 10A and 10B gave regio- and stereoselectively the expected hexahydropyrindinone (13)[6j] in 87-88% yield. Under the condition employed the labile isomer (15) formed either from 10A or 10B seems to isomerize easily to the more stable and desired isomer (13) because of the severe steric interaction between C_7-methyl and C_1-hydrogen.

Careful reduction of 13 with lithium aluminum hydride in ether at room temperature gave a mixture of two isomeric alcohols (16)[6k] in 37% yield with a moderate amount of the undefined compounds. The same product (16) was also obtained *via* 17 in a rather low yield (28%) by sodium borohydride reduction of 13 and the subsequent lithium aluminum hydride reduction. Finally, PCC oxidation of 16 furnished (±)-tecomanine (1)[6l] in 16% yield. The synthetic (±)-tecomanine is proved to be identical with natural tecomanine by means of IR ($CHCl_3$), UV (MeOH), and PMR ($CDCl_3$) spectral comparisons.

Thus, the first total synthesis of (±)-tecomanine with a high stereoselectivity has been accomplished.

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6. All IR and PMR spectra were measured in $CHCl_3$ and $CDCl_3$ solutions, respectively. *a*) ν 3400, 1685, δ 1.29(3H,s), 3.29&3.69(2H,ABq,*J*=13), 3.75&4.09(2H, ABq-d,*J*=7,2), 5.40&5.70(2H,ABq-d,*J*=10,2); *b*) ν 3380, 1680, δ 1.16(3H,d,*J*=7), 1.68(3H,s), 5.47&5.63(4:1, total 1H, each m); *c*) ν 1705, 1680, δ 1.05&1.13 (2:3,total 3H,each d,*J*=6), 1.67(3H,s), 2.11&2.15(total 3H,each s), 5.37(1H,s); *d*) ν 3410, 1670, δ 0.94(3H,d,*J*=7), 1.01(3H,d,*J*=5.5), 1.31(3H,s), 3.93(4H,s); *e*) ν 3400, 1670, δ 1.01(3H,d,*J*=5), 1.02(3H,d,*J*=7), 1.34(3H,s), 3.97(4H,s); *f*) ν 1705, 1680, δ 0.99(3H,d,*J*=6), 1.08(3H,d,*J*=7), 2.31(3H,s); *g*) ν 1705, 1680, δ 1.03(3H,d,*J*=6.5), 1.22(3H,d,*J*=7.5), 2.23(3H,s); *h*) ν 1670. 1600, δ 1.18(3H, d,*J*=6.5), 1.85(3H,s), 2.17(3H,s), *m/e* 237(M^+), 136(base); *i*) ν 1720, 1680, δ 1.02(3H,d,*J*=6), 1.75(3H,m), 3.48&5.06(2H,ABq,*J*=15); *j*) ν 1695, 1680, 1615, δ 1.20(3H,d,*J*=4.5), 1.21(3H,d,*J*=7.5), 5.19(1H,s), *m/e* 237(M^+), 180(base); *k*) ν 3575, 2790, δ 1.06(3H,d,*J*=6.5), 1.17(3H,d,*J*=6.5), 2.31&2.25(total 3H,s), 4.41 (1H,broad s), 5.35&5.36(total 1H,s); *l*) ν 1690, 1620, 870, δ 1.16(3H,d,*J*=6.5), 1.19(3H,d,*J*=7.5), 2.35(3H,s), 5.86(1H,s); λ(MeOH) 225.5nm, *m/e* 179(M^+,base), its picrate: mp 184.5-185.5°(from EtOH).
7. Ethyl propenyl ether was prepared according to the method of F. Effenberger, P. Fisher, G. Prossel, and G. Kiefer, *Chem. Ber.*, 104, 1987 (1971). On the basis of its PMR spectrum the ether is a mixture of Z- and E-isomers in a ratio of 2.5:1.
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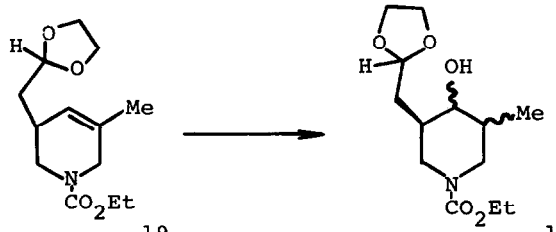
9. On the other hand, a mixture of *cis*- and *trans*-dialkylated alcohols (18) [δ 0.96&1.00(1:2, total 3H, each d, *J*=6, C_5-Me)] was obtained upon a similar treatment of the less bulky olefin (19), prepared from 3 by the reaction with ethyl vinyl ether and the subsequent acetalization.



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10. *cf.* R. Gaertner and R.G. Tonkyn, *J. Am. Chem. Soc.*, 73, 5872 (1951). *cf.* W.G. Dauben and D.J. Hart, *J. Org. Chem.*, 42, 3787 (1977); G. Stork, G. L. Nelson, F. Rouessac, and O. Gringore, *J. Am. Chem. Soc.*, 93, 3091 (1971).

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