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BIOMIMETIC SYNTHESIS OF KOUMINE SKELETON: PARTIAL SYNTHESIS OF 11-METHOXYKOUMINE (GELSEMIUM-TYPE ALKALOID) FROM 18-HYDROXYGARDNERINE

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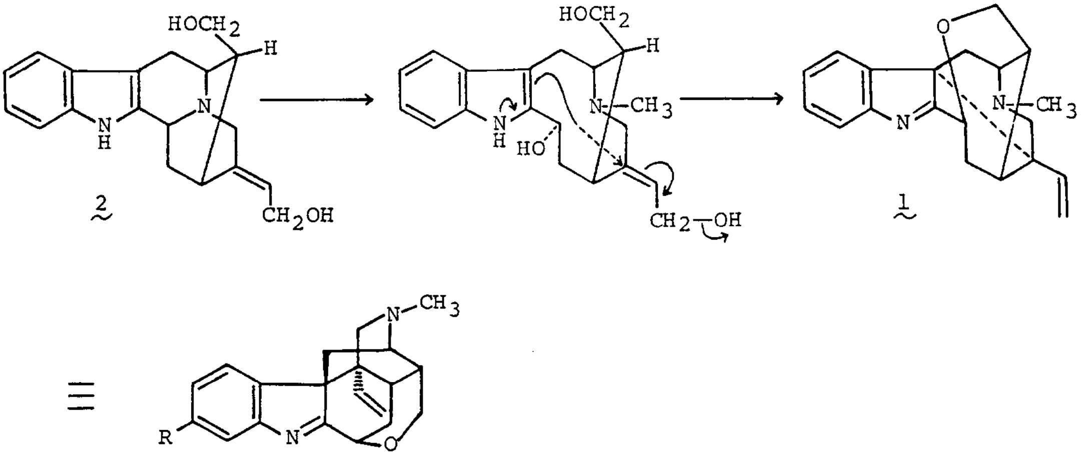
Summary: 11-Methoxykoumine (13) was derived from 18-hydroxygardnerine (4) through C-C intramolecular bond formation by Pd^0 catalysis between the indole part and allylic cation in an indole alkaloid. This is first example of the proof for the biogenetic route of koumine skeleton.

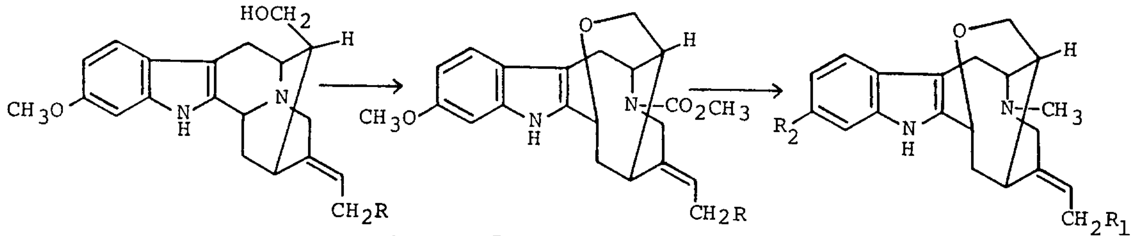
Koumine (1) is one of Gelsemium alkaloids (Loganiaceae), and its complicated indole alkaloid structure was recently determined by use of X-ray crystallography.1) Lounasmaa and Koskinen proposed the biosynthetic route of 1 from unnatural 18-hydroxy-desoxysarpagine (2) as shown in Chart 1.2)



R= H : koumine (1)
R= OCH_3 : 11-methoxykoumine (13)

Chart 1

18-Hydroxygardnerine (3) was isolated from leaves of <u>Gardneria nutans</u>3) (Loganiaceae) and also obtained as a $LiAlH_4$ reduction product of hydroxygardnutine.4) We report in this communication the biomimetic transformation of 3 to 11-methoxykoumine (13) along Lounasmaa's proposal but through a little defferent chemical route. We reported already the C/D ring opening reaction of gardnerine (4) with phenyl chlorocarbonate and 4 was converted to 11-methoxytsberpsychine (= Nb-methylapogardnerine) (6).5) This compound has not been found in nature, but closely related taberpsychine (7),6) a C/D ring opening ether alkaloid, is konwn.



R= OH : 3
R= H : 4

R = H : 5 , R = OCOCH$_3$: 9
R = OH : 8 , R = OCO$_2$CH$_3$: 10

R$_1$ = H, R$_2$ = OCH$_3$: 6
R$_1$ = R$_2$ = H : 7

Chart 2

Treatment of 18-hydroxygardnerine (3) with methyl chlorocarbonate (2.2 eq mol) and an excess Na_2CO_3 in aq-THF solution gave an amorphous Nb-carbomethoxy-apo-18-hydroxygardnerine (8)7) in 80% yield.

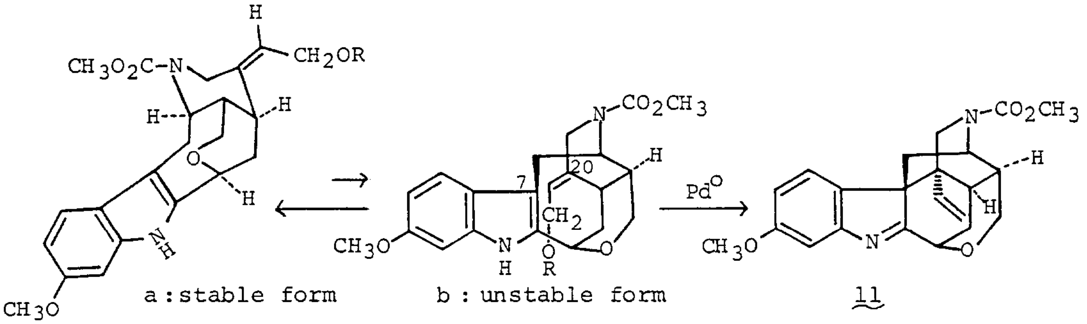


Chart 3

The bond distance between C-7 and C-20 in unstable form 8b shown in Chart 3 is less than 2.5Å from Büchi moleculer model examination. Allylation of β-position of indole by use of Pd^0 catalyst has been reported,8) and therefore 8b has possibility of C_7-C_{20} bond formation by above reaction. Allyl alcohol 8 was converted to acetate 9 9) and methoxy carbonate 10 10) by usual means. The acetate (9) was brought to indole anion with NaH in DMF solution and in the presence of triphenylphosphine, Pd(OAc)$_2$ was added to the DMF solution under Ar. After stirring for 4hr at 80-100°C, reaction mixture was treated with aq-NH$_4$Cl and ether. The residue from oraganic layer was purified by use of column chromatography. The ring closed compound 11 was obtained in 56% yield in an amorphous state which showed the UV spectrum characteristic to 11-methoxy-indolenine alkaloids4,11) and vinyl singnals on ^{1}H- and ^{13}C-NMR.12) Under the same condition carbonate 10 also gave rise to ring closed compound 11 in the 39% yield. Upon reduction with LiAlH$_4$ at rt, 11 was transformed solely into Nb-methlylindline derivative mp 166-168°C (12)13) which exhibited the UV spectrum of 11-methoxy-indoline type alkaloids.4,11) It was difficult to clarify stereochemistry of C-2 in 12 from NMR spectral analysis but this chiral centre disappeared in the next step. Oxidation of 12 with Pb(OAc)$_4$ gave rise to 11-methoxykoumine (13) (mp 126-127°C, colorless needles, in 78% yield).14)

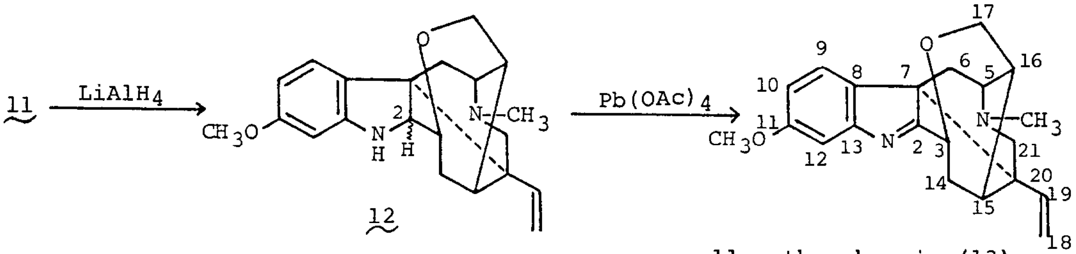


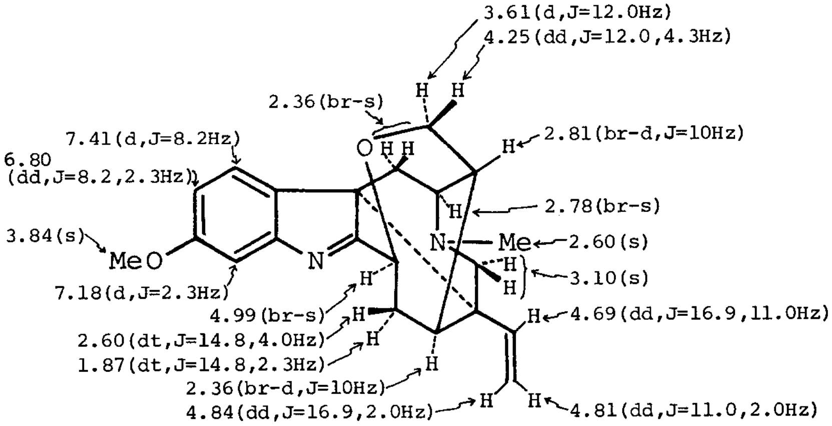
Chart 4

11-methoxykoumine(13)

By the comparison of ^{1}H- and ^{13}C-NMR spectra and CD spectra between partially synthesized 13 and natural koumine 1 which was isolated from Gelsemum elegantum in Thailand, the partially synthesized 13 is proved to have the same molecular skeleton and the same absolute configuration with koumine 1.

^{13}C- and ^{1}H-NMR Chemical Shifts and Assignments for 11-methoxykoumine (13) (in $CDCl_3$)

No.	(13)	
2	186.7	(s)
3	70.9	(d)
5	56.9	(d)
6	28.6	(t)*
7	57.4	(s)
8	135.5	(s)
9	123.2	(d)
10	112.0	(d)
11	160.1	(s)
12	106.7	(d)
13	156.2	(s)
14	25.3	(t)*
15	33.0	(d)**
16	38.8	(d)**
17	61.3	(t)
18	115.8	(t)
19	137.4	(d)
20	45.3	(s)
21	57.8	(t)
$N-CH_3$	42.6	(q)
$-OCH_3$	55.3	(q)



* Values may be interchanged.

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7) 8: Mass, Calcd. for $C_{22}H_{26}N_2O_5$, 398.1839, Found. 398.1831 (base paek). IR $\nu_{max}^{CHCl_3}$ 1670cm^{-1}($NCOOCH_3$); NMR (270MHz), $\delta_{ppm}^{CDCl_3}$ 5.63 (1H, m, C_{19}-H), 5.12 (1H, d, J=0.6Hz, C_3-H), 3.83 (3H, s, OCH_3), 3.75, 3.74 (3H, each s, $NCOOCH_3$).

8) W. E. Billups, R. S. Erbes and L. E. Reed, Synthetic commun., 10, 147 (1980).

9) 9: CH_3COCl/Py. in 77% yield, Mass, Calcd. for $C_{24}H_{28}N_2O_6$, 440.1945, Found. 440.1948 (base paek). $\nu_{CO}^{CHCl_3}$ cm^{-1}, 1730 ($OCOCH_3$), 1690 ($NCOOCH_3$); δ, 3.76, 3.75 (3H, each s, $NCOOCH_3$), 2.08 (3H, s, $OCOCH_3$).

10) 10: CH_3OCOCl/Py/DMAP; in 44% yield, Mass, 380 (100%), 456 (M^+, 24%), δ, 3.72 (6H, s, $OCOOCH_3$, $NCOOCH_3$).

11) S. Sakai, A. Kubo and J. Haginiwa, Tetrahedron Let., 19, 1485 (1969).

12) 11: Mass, Calcd. for $C_{22}H_{24}N_2O_4$, 380.1734, Found. 380.1720 (M^+, base peak), $\tilde{\nu}_{max}^{EtOH}$ nm 232, 276, 300 (sh), δ, 4.94, 4.91 (dd, J_1= 17.5Hz, J_2= 1Hz $C=C^{\diagup Ha}$), 4.88 (d, J= 10.6Hz, $C=C_{\diagdown Hb}$), 4.71 (dd, J_1= 17.5Hz, J_2= 10.6Hz, $-CH_c=C$). ^{13}C-NMR, δ, 186.0 (2), 70.8 (3), 49.1 (5), 33.8 (6), 56.6 (7), 134.7 (8), 123.1 (9), 112.3 (10), 160.3 (11), 106.9 (12), 156.1 (13), 25.0 (14), 34.0 (15), 39.2, 38.8 (2 signals, 16), 60.6 (17), 116.6, 116.3 (2 signals, 18), 136.4, 136.2 (2 signals, 19), 45.6 (20), 48.7 (21), 55.5 (OCH_3), 155.3, 52.6 ($NCOOCH_3$).

13) 12: colorless needles (acetone-hexane), in 67% yield, λ_{max}^{EtOH} nm (log ε), 297 (3.69), 240 (sh, 3.74), 210 (4.56). Calcd. for $C_{21}H_{26}N_2O_2$, C, 74.52; H, 7.74; N, 8.28; M^+, 338.1993, Found. C, 74.31; H, 7.75, N, 8.23; 338.1998 (M^+, base paek). δ, 2.47 (3H, s, N-CH_3), $/\alpha/_D^{19°}$ -28.0 (c=0.1, MeOH).

14) 13: λ_{max}^{MeOH} nm (log ε), 301 (sh, 3.27), 276 (3.50), 232 (4.40). Calcd. for $C_{21}H_{24}N_2O_2$, C, 74.97; H, 7.19; N, 8.33; M^+, 336.1836, Found, C, 74.78; H, 7.26; N, 8.24; 336.1836 (M^+, base peak); $/\alpha/_D^{16°}$ = -219 (c= 0.19, MeOH); CD, λ_{peak}^{MeOH} nm (Δε), 300 (0), 250 (-15.4), 241 (0), 232 (+13.3), 224 (+5.9), CD of koumine (1), 305 (0), 268 (-11.9), 234 (0), 222 (+21.6), 208 (0), 202 (-3.9).

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