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A NEW SYNTHESIS OF (±)-VINDOROSINE

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The pentacyclic compound (15) was stereoselectively synthesized in the racemic form using indole and acetylpyridine as starting materials according to the synthetic route shown in Chart 2. This constitutes a new formal synthesis of (±)-vindorosine (16).

KEYWORDS ——— vindorosine synthesis; aspidosperma alkaloid synthesis; indole alkaloid; 1-acyl-5-alkyl-1,2-dihydropyridine; oxygenative nucleophile introduction reaction

It is wellknown that the reduction of 3-alkylpyridines (1) with $NaBH_4$ in the presence of ClCOOR' produces exclusively 3-alkyl-1,2-dihydropyridine derivatives (2).[1,2] We have now devised a direct preparation of 5-alkyl-1,2-dihydropyridine derivative (4) in 58% yield by reduction of 3-(2-methyl-1,3-dioxolan-2-yl)pyridine (3) using a bulky reducing reagent, $NaAl(MeOCH_2CH_2O)_2H_2$ with $PhCH_2OCOCl$ in THF, accompanied by a mixture of other dihydropyridines in 16% yield. The methyldioxolanyl group is an essential side chain for this purpose, since 3-(1-benzyloxyethyl)-pyridine (1, R=CHMe-OCH_2Ph) afforded an unsatisfactory result. The compound (4) was submitted to our oxygenative nucleophile introduction reaction[3] (sensitized photooxygenation of 4, followed by $SnCl_2$-mediated ring-opening reaction of the endoperoxide in the presence of indole) to form readily a crystalline compound (5) in 57% yield. With this knowledge in hand, we planned a synthesis of the aspidosperma class of indole alkaloids envisaging a novel type of ring closure reaction (i → ii → iii) which consists of two successive carbon-carbon bond formations on the indole ring, furnishing a new methodology for the construction of the aspidosperma skeleton.

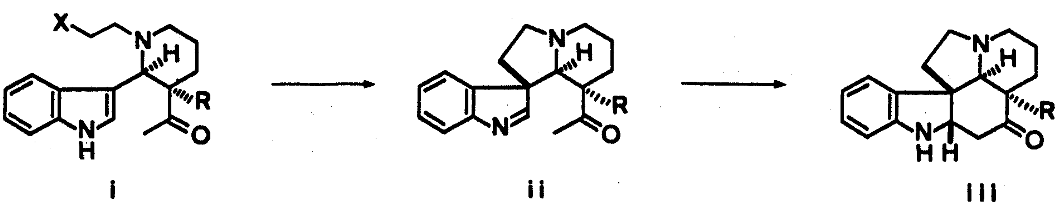
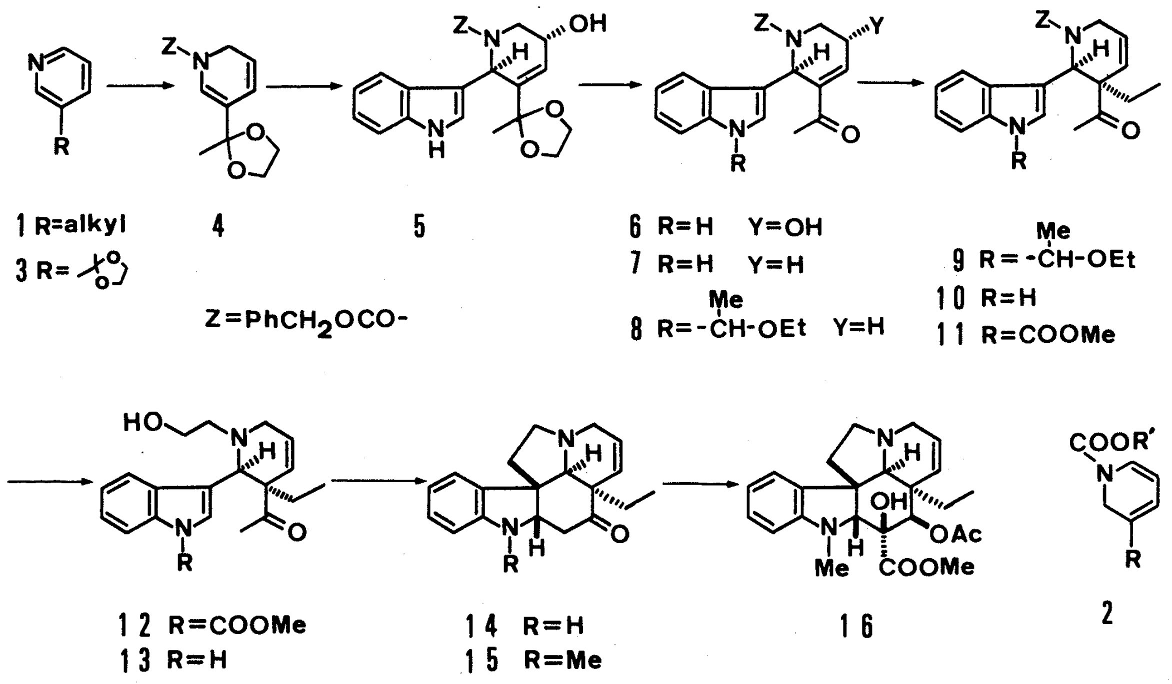


Chart 1

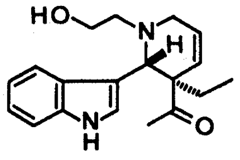
The ethylene ketal group in 5 was hydrolyzed at first in 93% yield to 6 which was converted to its methanesulfonate and hydrogenated over Pd-C in MeOH in the presence of Et_3N. Removal of the secondary hydroxyl group in 6 was achieved in 93.5% yield to afford 7 without affecting the double bond, the ketone function, and the *N*-protecting group by adding a small amount of Et$_3$N. The indole nitrogen of 7 was once protected by an acid catalyzed reaction with ethyl vinyl ether to give 8 in 85% yield and this was heated with EtI in the presence of *tert*-BuOK in a 6:1 mixture of benzene and *tert*-BuOH at 90-100°C for 5 min. A single product (9) obtained in 63% yield was hydrolyzed smoothly by warming in a mixture of HOAc-MeOH-H$_2$O (2:1:1) to produce the compound (10) in 84% yield. Its structure was deduced from its ^{1}H NMR spectrum [δ (CDCl$_3$, 70°C): 0.82 (3H, t, J=7.5 Hz, CH$_2$C$\underline{H}_3$); 1.86 (3H, s, COC$\underline{H}_3$); 1.72-2.23 (2H, m, C$\underline{H}_2$CH$_3$); 3.27 (1H, ddd, J=18, 2, 2 Hz) and 4.35



3 → 4: PhCH$_2$OCOCl, NaAl(MeOCH$_2$CH$_2$O)$_2$H$_2$, THF, -70°C, 30 min, 58%.
4 → 5: i) O$_2$, $h\nu$ (500 W halogen lamp), methylene blue, CH$_2$Cl$_2$, -60°C, 30 min; ii) indole, SnCl$_2$ in EtOAc, -60 → 5°C, 2 h, 57%.
5 → 6: *ca.* 2% HCl in MeOH-H$_2$O (5:1), r.t., 10 min, 93%.
6 → 7: i) MsCl, Et$_3$N, CH$_2$Cl$_2$, 0°C, 15 min; ii) H$_2$, 10% Pd-C, Et$_3$N, MeOH, r.t., 1.5 h, 93.5%.
7 → 8: CH$_2$=CH·OEt, TsOH, CH$_2$Cl$_2$, 0°C, 10 min, 85%.
8 → 9: EtI, t-BuOK, PhH-t-BuOH, 90–100°C, 5 min, 63%.
9 → 10: HOAc-MeOH-H$_2$O (2:1:1), 90°C, 1.5 h, 84%.
10 → 11: ClCOOMe, (Me$_3$Si)$_2$NK, THF, -80 – -70°C, 20 min, 67%.
11 → 12: i) H$_2$, 10% Pd-C, *ca.* 4% HCl in MeOH-H$_2$O (9:1), 10 min; ii) ethylene oxide, MeOH, r.t., 38 h, 71%.
12 → 13: 0.4% NaOH in MeOH, r.t., 15.5 h, 85%.
13 → 14: i) MsCl, K$_2$CO$_3$, CH$_2$Cl$_2$, r.t., 14 h; ii) (Me$_3$Si)$_2$NK, THF, -70°C → r.t., 1 h, 60%.
14 → 15: 37% CH$_2$O-H$_2$O, NaBH$_3$CN, HOAc, MeCN, r.t., 15 min, 75%.

Chart 2

(1H, br d, J=18 Hz)(N-C$\underline{H}_2$-CH=); 5.25 (2H, br s, COOC$\underline{H}_2$Ph); 5.78 (1H, br d, J=10.5 Hz, N-CH$_2$-C$\underline{H}$=CH-); 6.17 (1H, br s, indolyl-C$\underline{H}$-N); 6.67 (1H, d, J=10.5 Hz, N-CH$_2$-CH=C$\underline{H}$-)].[4)] The N-protecting group of 10 was cleaved by catalytic hydrogenation over Pd-C in MeOH and the subsequent treatment of the secondary amine with ethylene oxide in MeOH gave rise to the production of three compounds, 13, 17, and 18 in 53%, 20%, and 10% yields, respectively. Contrary to the unchanged character of 13 and 17 by heating, the secondary amine (19) is thermally very unstable and the formation of 20 due to the equilibrium by way of 21 is inevitable, judging from the production of 17, even when the above two-step operation was carried out in the same MeOH solution without isolation of the secondary amines.



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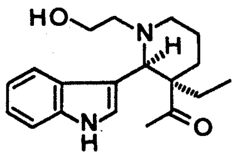

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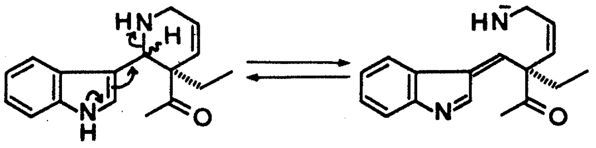

19 α-H
20 β-H

21

Therefore, the indole nitrogen was protected by an electron-withdrawing group, and the compound (11) obtained by reaction with ClCOOMe in the presence of $(Me_3Si)_2NK$ in THF was subjected to the rapid hydrogenation over Pd-C in an acidic medium, followed by treatment with ethylene oxide. Compound (12) was prepared in 71% yield, accompanied by formation of the corresponding dihydro derivative in 6% yield. Mild alkaline hydrolysis of 12 afforded 13 in 85% yield. The requisite ring closure described in Chart 1 was realized in a single operation by treating the methanesulfonate of 13 with $(Me_3Si)_2NK$ in THF at -70°C at first and then at room temperature for 1 h. The desired compound (14) was obtained in 60% yield, and 14 was methylated with CH_2O and $NaBH_3CN$ to afford in 75% yield the compound (15), whose identity with Büchi's sample[5)] was confirmed by admixture and comparison of the IR spectra (KBr). As this was converted to (±)-vindorosine (16) in four steps,[5)] the present work constitutes a formal synthesis of (±)-16.[6)]

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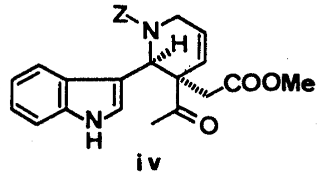
4) Stereochemistry of the ethyl side chain was confirmed as shown by correlation of 10 with the Claisen rearrangement product (iv) of 6. Details will be reported later.



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