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NEW STRATEGY FOR CHIRAL ALKALOID SYNTHESIS COMMENCING WITH A CARBOHYDRATE. SIMPLE SYNTHESIS OF (-)-ALLO-YOHIMBANE FROM LEVOGLUCOSENONE

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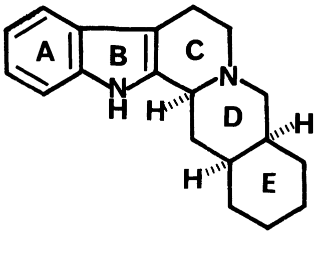
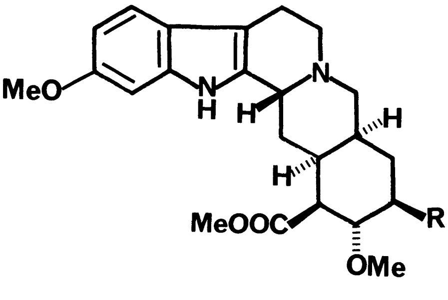
An optically active allo-yohimbane was synthesized in 12 steps from levoglucosenone. The key steps are Diels-Alder cycloaddition for the E-ring construction followed by eliminative Wolff-Kishner reduction and selective double cyclization in the D- and C-ring formation.

Synthesis of the optically active natural products from carbohydrates$^{1)}$ can provide chiral carbon-frameworks in short steps. We would like to describe a general method$^{1)}$ that constructs pentacyclic skeletons of alkaloids such as allo-yohimbane **1** and reserpine **2**: the carbohydrate-strategy summarized in Scheme 1 involving the key steps (1) initial Diels-Alder cycloaddition$^{2)}$ to afford the E-ring, (2) its further functionalization by a cleavage of the notoriously stable 1,6-anhydro pyranoside bridge under eliminative Wolff-Kishner reduction, (3) coupling with tryptamine by amidation, (4) cyclization of D-ring followed by the last cyclization of the C-ring.



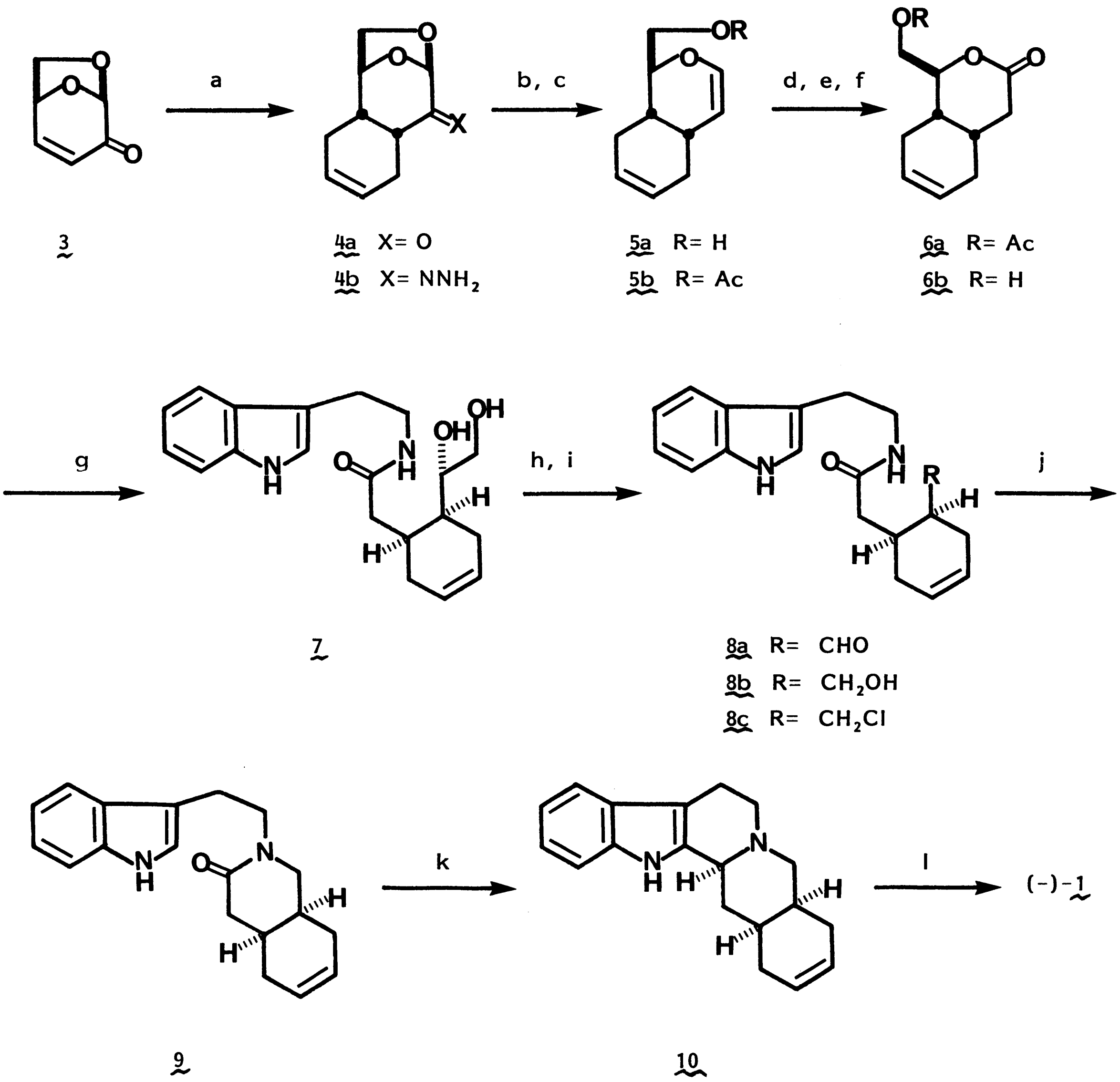
allo-yohimbane (**1**)



reserpine (**2**)

Levoglucosenone (1,6-anhydro-3,4-dideoxy- β -D-glycero-hex-3-enopyrano-2-ulose) **3** was chosen as the starting material, since **3** is readily obtained by pyrolysis of cellulose.$^{3)}$ It undergoes Diels-Alder cycloaddition with 1,3-butadiene (at 140 °C for 10 h) to afford the crystalline adduct **4a** (mp 66.0 °C) in 98% yield.[4] The ketone was reduced in two steps, first by treatment with NH_2NH_2-H_2O (5 equiv.) and Et_3N (1 equiv.) (in EtOH at 60 °C for 20 min) affording the hydrazone (**4b**) which was then treated with sodium hydride in DMSO at rt for 1.5 h to obtain the vinyl ether **5a** (PMR δ 4.68(1H, dd, J= 6, 4 Hz), 6.28(1H, dd, J= 6, 1.5 Hz); $[\alpha]_D$ $+38.6^\circ$ (c 1.00, $CHCl_3$)) in 93% overall yield. Such an eliminative Wolff-Kishner reduction undergoes at an ordinary temperature rather than at elevated ones and is recently reported by us.[5] Acetylation gave **5b** (PMR δ 2.08(3H, s), 4.08(1H, ddd, J= 6.5, 5.0, 4.0 Hz), 4.23(2H, ABX), 4.64(1H, dd, J= 6.0, 3.0 Hz); IR 1740 cm^{-1}) in 100% yield with acetic anhydride (3 equiv.) and pyridine (7 equiv.) in CH_2Cl_2 at rt for 4 h. The vinyl ether **5b** was hydrolyzed in a mixture of 1 mol dm^{-3} HCl and THF (1:5) at 50 °C for 2 h and the corresponding hemi-acetal was oxidized with Jones reagent at 0 °C for 5 min to give in 90% yield the lactone **6a** (mp 77.0 °C; $[\alpha]_D$ -58.6° (c 1.02, $CHCl_3$)). A large scale preparation afforded **6a** (16.7 g) in 63% overall yield in continuous 5 steps from **3** (15 g). The acetate **6a** was hydrolyzed with NaOMe (1.2 equiv.) in MeOH at rt for 5 min to give the alcohol **6b** (mp 65.0 °C; 86% yield; PMR δ 1.72-2.42(6H, m), 2.54(2H, ABX), 3.10-3.90(1H, brs, OH), 3.76(1H, dd, J= 12.5, 4.5 Hz), 3.86(1H, dd, J= 12.5, 3.0 Hz), 4.40(1H, brs), 5.66(2H, brs); IR 3600, 3400, 1725, 1655 cm^{-1}; $[\alpha]_D$ $+115.2^\circ$ (c 1.03, $CHCl_3$)).

The lactone **6b** was heated with tryptamine (2 equiv.) in a mixture of THF and ethyldiisopropylamine (6:1) to give **7** (IR 1645 cm^{-1}; $[\alpha]_D$ $+5.1^\circ$ (c 0.99, MeOH)) in 96% yield. The glycol **7** was cleaved by oxidation with HIO_4 (1.2 equiv.)[8] in a mixture of THF and water (3:1) at -20 °C for 1 min to yield the aldehyde **8a**. Reduction of **8a** with $NaBH_4$ in MeOH (rt, 5 min) gave the amide alcohol **8b** $[\alpha]_D$ -3.6° (c 1.00, $CHCl_3$)) in 93% overall yield from the diol **7**. The amide alcohol **8b** was chlorinated with triphenylphosphine (3 equiv.) and CCl_4 in a mixture of $CHCl_3$ and pyridine (2:1) at 55 °C to give the chloride **8c** ($[\alpha]_D$ -16.6° (c 1.05, $CHCl_3$)) in 51% yield (75% conversion yield). Since the amide chloride **8c** was not stable, it was quickly used for the following basic treatments with lithium bis-(trimethylsilyl)amide in THF at -78 °C. When the reaction temperature was raised gradually to rt, the lactam **9** was produced in 91% yield ($[\alpha]_D$ -16.5° (c 1.12, $CHCl_3$)). Final cyclization[6] was achieved in 73% yield by treatment with phosphorus oxychloride at 100 °C for 1.5 h and the reaction mixture was evaporated in vacuo; the residue being reduced with $NaBH_4$ in a mixture of MeOH and water (9:1)



Scheme 1.

a) 1,3-butadiene/140 °C, 10 h, b) NH_2NH_2-H_2O-Et_3N/EtOH/60 °C, 20 min then $NaCH_2SOCH_3$/DMSO, c) Ac_2O/Py, d) 1N HCl-THF (1:5)/50 °C, 2 h, e) Jones/0 °C, 5 min, f) NaOMe/MeOH, g) tryptamine/i-Pr_2EtN/THF, h) HIO_4, i) $NaBH_4$, j) Ph_3P-CCl_4/ $LiN(SiMe_3)_2$, k) $POCl_3$/100 °C 1.5 h then $NaBH_4$, l) H_2/Pd-C.

at pH >7 in an ice-bath to give 10 (PMR δ 1.60-2.08(6H, m), 2.30-3.06(8H, m), 3.20(1H, brs), 5.58(2H, brs), 7.08(2H, m), 7.24(1H, m), 7.44(1H, m), 7.68(1H, brs); CMR δ 21.9, 25.6, 31.2, 32.0, 32.1, 33.2, 53.1, 60.1, 60.5, 108.1, 110.5, 117.8, 119.9, 123.1, 125.9, 127.4, 135.3, 135.9; IR 3500, 2800, 2750 , 1460 cm^{-1}; $[\alpha]_D$ -57.9 (c 1.00, $CHCl_3$)). Hydrogenation of 10 with 10% Pd-C/H_2 in a mixture of MeOH and CH_2Cl_2 (1:1) afforded (-)-1 in 92% yield; 1 (double mp at 108 °C and at 157 °C; HCl-salt $[\alpha]_D$ -79.9° (c 0.38, EtOH)). The relative and absolute stereochemistry of 1 was confirmed by identifying the final product with the authentic data7) (allo-Yohinbane, mp 156 °C, $[\alpha]_D$ -79.2° (c 0.35 EtOH), -166.5° (c 0.4, pyridine), while 3-epi-allo-yohimbane $[\alpha]_D$ +190.4° (c 0.4, pyridine)) and PMR and CD spectra, all of which were identical with those reported values.7) The continuous studies on the alkaloid synthesis along this line will be reported.

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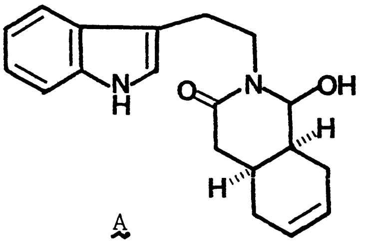
8) Incidentally, when neat 8a was kept at rt for 12 h, it was converted into the carbinolamide A (mp 141.0 °C).



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