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Cycloaddition Reactions of Carbohydrate Derivatives. Part III.[1] A New Route to Swainsonine Analogs.

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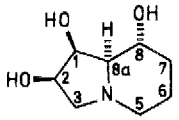
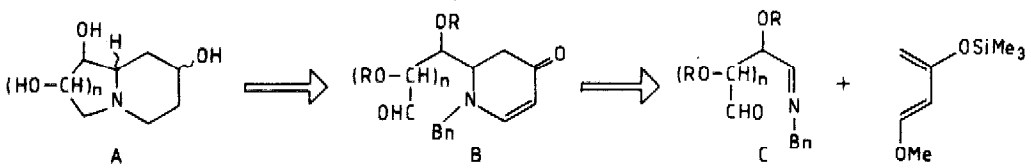
Abstract: Swainsonine analogs 10 and 12 have been synthesized from D- and L-arabinose, respectively, using cyclocondensation of azomethines with Danishefsky's diene followed by stereoselective carbonyl and double bond reduction of the resulting pyridones, chain shortening and ring closure by reductive amination.

Swainsonine ((1*S*,2*R*,8*R*,8a*R*)-1,2,8-trihydroxyindolizidine) (**1**) was isolated from the plant *Swainsona canescens*[2], from the fungus *Rhizoctonia leguminicola*.[3]. Its potent α-mannosidase inhibitory[4], immunomodulant[5], antimetastatic[6] properties stimulated an intensive synthetic research activity[7]. Modification of stereocenters of **1**, i.e. preparation of its analogs is of considerable importance for the elucidation of structure-biological activity relationships[8,9]. This latter aim has motivated our synthetic effort to elaborate a versatile method for the preparation of polyhydroxylated indolizidines and related ring systems. This paper is a preliminary account of that work.



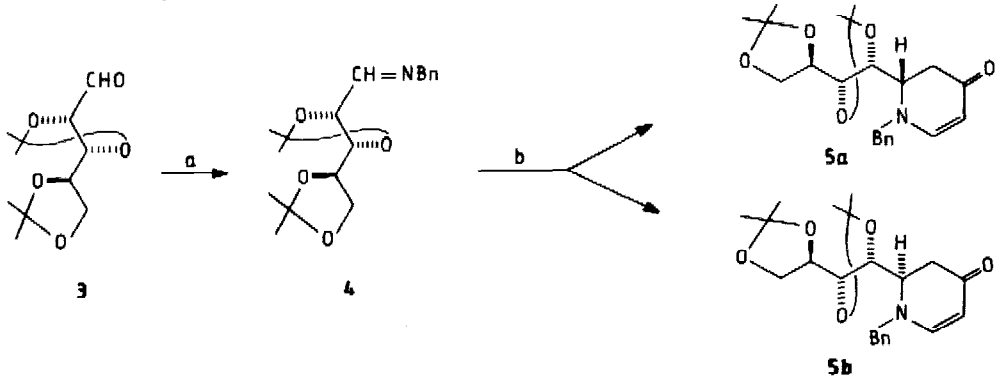
1

Polyhydroxylated structural analogs of **1** (**A**) can be deduced retrosynthetically from 5,6-dihydro-γ-pyridones **B**. The heterocyclic ring can be prepared with the method of Kerwin and Danishefsky[10] using cyclocondensation of azomethines with diene **2** as shown recently for chiral compounds [11,12]. In our case a sugar aldehyde has been used to prepare the azomethine **C**.



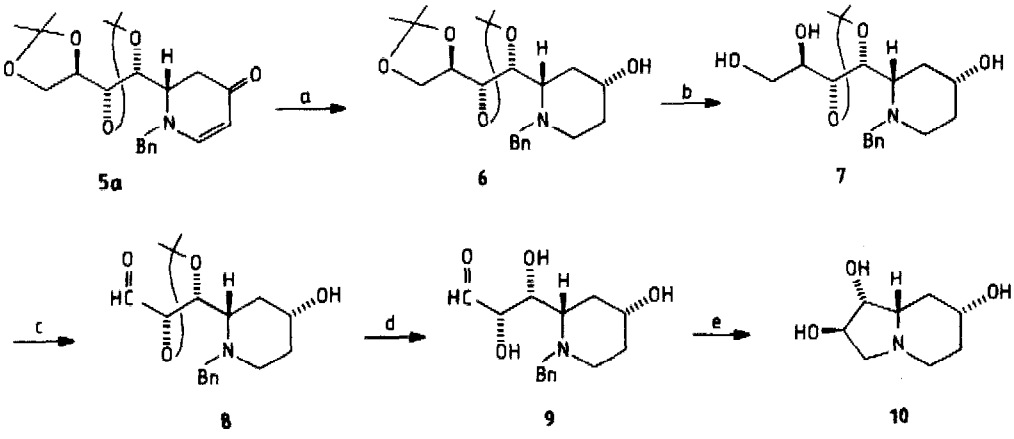
n = 1, 2, 3; R = protective group

Schiff base **4** has been prepared from the aldehydo-D-arabinose derivative **3**[13] with benzylamine in dry benzene. Without isolation, **4** was allowed to react with **2** in dry dioxane in the presence of zinc chloride at room temperature to afford a mixture of diastereomers **5a** and **5b**[14], readily separated by chromatography. A moderate diastereoselection was observed in favour of **5a** the product ratio being 4.7:1. In view of free rotation in the side chain the configuration of new chirality center in the product **5a** had to be established by X-ray crystallography[15].



(a) $BnNH_2$, benzene, rt, 30 min; (b) **2**, $ZnCl_2$, dioxane, rt, 1h, 79% (for a-b).

Treated with sodium tetrahydridoborate in dry ethanol, **5a** afforded, by way of simultaneous reduction of the C-C double bond and the keto function, a single diastereomer **6**. The complete diastereoselection in this reduction can be attributed to the shielding of one side of the dihydropyridone ring by the bulky side chain. The *cis* relationship in the new hydroxy group and the side chain was ascertained by an X-ray crystallographic study[15] of the enantiomer of **6** prepared from L-arabinose.



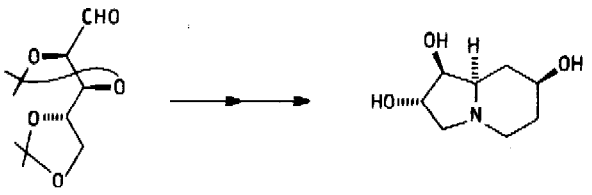
(a) $NaBH_4$, EtOH, rt, 14h, 99%; (b) $AcOH/H_2O$, 55°C, 10h, 84%; (c) $Pb(OAc)_4$, benzene, rt, 10 min;
(d) TFA/H_2O, rt, 10h; (e) $H_2/Pd(C)$, AcOH, rt, 16h, 54% (for c-e).

The terminal isopropylidene protective group of **6** was removed by partial hydrolysis in 75% acetic acid at 55° to afford **7**. Glycol-cleaving oxidation of the latter with lead(IV) acetate in dry benzene gave aldehyde **8**. Hydrolysis of the dioxolane ring in **8**

with trifluoroacetic acid at room temperature furnished **9** which was subjected to palladium catalyzed hydrogenolysis. Removal of *N*-benzyl protecting group and subsequent intramolecular reductive amination of the formyl group in this step led to the formation of **10**.

Configurations of stereocenters as well as the conformation of **10** were deduced from NOE measurements. NOE enhancements between various protons are represented by arrows.

By the same sequence of transformations **12** has been prepared from L-arabinose derivative **11**.



11 **12**

Compounds **10** and **12** are the first swainsonine analogs having a hydroxy substituent at C-7 and not at C-8 as in **1**. **10** and **12** have two stereocenters with different configurations with respect to the natural product. **10** competitively inhibits *Lupinus luteus* α-mannosidase (K_i = 4.2 x 10^{-4} mols) and **12** showed β-glucosidase inhibition against sweet almond enzyme (K_i = 4.0 x 10^{-4} mols).

Utilization of this cycloaddition route to other polyhydroxylated nitrogen bases and biological evaluation of the products are under way.

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14. All new compounds have been characterized by elemental analysis and/or spectroscopic methods. Selected physical data: **5a**: m.p. 75-78°, $[\alpha]_D$ = -215 (c = 1.3, $CHCl_3$). MS: *m/z* = 388 (M^+ + 1). **5b**: oil, $[\alpha]_D$ = +37 (c = 1.6, $CHCl_3$). **6**: m.p. 95-97°, $[\alpha]_D$ = +35 (c = 1.2, $CHCl_3$). MS: *m/z* = 392 (M^+ + 1). **7**: m.p. 39-45°, $[\alpha]_D$ = -41 (c = 1.2, $CHCl_3$). MS: *m/z* = 352 (M^+ + 1). **8**: $[\alpha]_D$ = -33 (c = 1.1, $CHCl_3$). MS: *m/z* = 320 (M^+ + 1). **9**: Has not been purified. MS: *m/z* = 280 (M^+ + 1). **10**: $[\alpha]_D$ = +11 (c = 1.0, MeOH). MS: *m/z* = 174 (M^+ + 1). ^{1}H NMR: δ (D_2O-DCl, pH = 2): 4.38 (dd, 1H, H-2, $J_{2,3}$ = 6.5 Hz, $J_{2,3}$ = 3.2 Hz), 4.20 (d, 1H, H-1, $J_{1,8a}$ = 2.9 Hz), 4.09 (m, 1H, H-7), 4.04 (dd, 1H, H-3, $J_{3,3}$ = 13.0 Hz), 3.70 (ddd, 1H, H-5eq, $J_{5ax,5eq}$ = 12.9 Hz, $J_{5eq,6eq}$ = 2.1 Hz, $J_{5eq,6ax}$ = 4.7 Hz), 3.51 (ddd, 1H, H-8a, $J_{8ax,8a}$ = 12.5 Hz, $J_{8eq,8a}$ = 2.7 Hz), 3.17 (m, 1H, H-5ax, $J_{5ax,6ax}$ = 13.0 Hz), 2.91 (m, 1H, H-3), 2.34 (m, 1H, H-8eq), 2.24 (m, 1H, H-6eq), 1.79 (m, 1H, H-6ax), 1.67 (m, 1H, H-8ax).

The enantiomers of **5-9** as well as **12** gave satisfactory physical data and elemental analyses.

15. The detailed X-ray data will be published later.

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