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Synthesis of the first deprotected indigo N-glycosides (blue sugars) by reductive glycosylation of dehydroindigo

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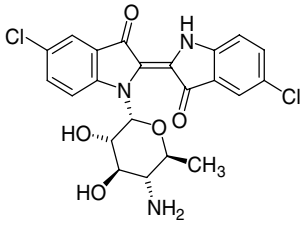
Abstract—The first deprotected indigo N-glycosides (blue sugars) have been prepared by reaction of dehydroindigo with in situ generated rhamnosyl, glucosyl and mannosyl iodide.

Glycosylated indole derivatives, such as the prominent indolo[2,3-*a*]carbazole glycosides staurosporine, K-252d, rebeccamycin and the tjipanazoles,[1,2] represent promising anticancer agents.[3] Furthermore, several indirubine derivatives (isomeric to corresponding indigo derivatives) show anti-proliferative activity.[4] In this case also the parental compound, the indirubine itself, is active. A few years ago, Laatsch and co-workers reported the isolation of the first N-glycosides of indigo derivatives—the akashines A, B and C (Fig. 1). [5] In contrast to pharmacologically inactive parent indigo, the akashines show a considerable activity against various human tumour cell lines. The akashines represent the first indigo derivatives isolated from nature so far, except from the well-known purpur (6,6′-dibromoindigo) and from two other brominated indigos. Recently, we have reported the first synthesis of an indigo glycoside—a pivaloyl protected rhamnoside—by O-glycosylation of *N*-benzylindigo and subsequent rearrangement of the O- into the desired N-glycoside.[6] However, the success of the key step of this approach, the O→N rearrangement, proved to be severely dependent on the type of carbohydrate moiety and protective groups. In fact, the application of this strategy to glycosyl donors other than rhamnosyl, and to protective groups other than pivaloyl proved to be unsuccessful so far. In addition, all attempts to remove the pivaloyl protective groups failed. Herein, we report what is, to the best of our knowledge, the first synthesis of deprotected indigo N-glycosides. The synthesis was achieved based on a new synthetic strategy—the addition of a glycosyl iodide to dehydroindigo. Notably, this strategy allows the mono-glycosylation of indigo without the need of a nitrogen protective group.



Akashine A

Figure 1. Akashine A isolated from terrestric *Streptomyces*.

Dehydroindigo (**3**)[7] was prepared in high yield by reaction of indigo (**1**) with $KMnO_4$ in the presence of acetic acid (to give diacetate **2**), and subsequent base mediated elimination of acetic acid (Scheme 1). The addition of hydrogen halides,[8] phenols and thiols[9] to dehydroindigo has been previously studied. Treatment of **3** with hydrogen iodide (HI) afforded indigo (**1**). The formation of the

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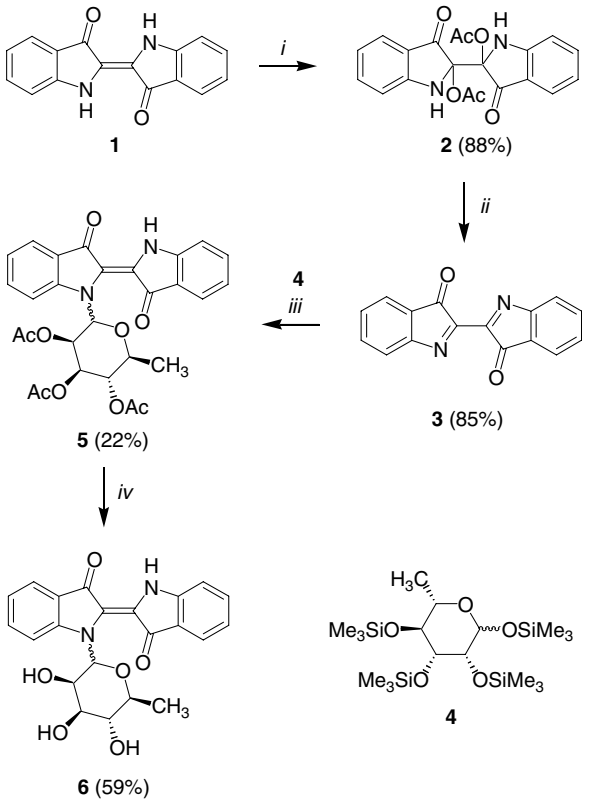

Scheme 1. Synthesis of indigo glycoside **6**. Reagents and conditions: (i) $KMnO_4$, AcOH, high-power-stirring (12,000 rot/min), 20 °C, 3–4 h; (ii) pyridine/toluene = 1:2, 70 °C, 1 h; (iii) (a) **4**, CH_2Cl_2; (b) Me_3SiI, 20 °C, 30 min; (c) **3**, 0 °C, 30 min; (d) *n*-PrSH, 0 → 20 °C, 1 h; (e) Ac_2O/pyridine = 3:1, KHF_2, 70 °C, 3 h; (iv) NaO-*t*-Bu (15 mol %), MeOH, 20 °C, 4 h.

latter can be explained by initial formation of 2,2′-diiodo-2,2′-bis(indolin-3-one), analogously to the addition of HCl to **3**, and subsequent extrusion of iodine. Based on this observation, we developed the synthesis of indigoglycoside **5**. The reaction of dehydroindigo (**3**) with TMS protected L-rhamnosyl iodide—generated in situ by conversion of tetra-*O*-trimethylsilyl-L-rhamnopyranose (**4**) with TMSI—and subsequent acetolysis (Ac_2O/pyridine/KHF_2) afforded the *N*-(2,3,4-tri-*O*-acetyl-L-rhamnosyl)indigo **5** (α/β = 2:1).[10] An analytically pure sample of the α anomer was isolated by repeated crystallisation from MeOH. The yield of the glycosylation reaction is relatively low, due to loss of material during chromatography and formation of side-products (bis-glycosylation and desilylation). Treatment of a MeOH solution of **5** with NaO-*t*-Bu (5–15 mol %) afforded the desired deprotected indigo glycoside **6** (α/β = 2:1).[11] The use of catalytic amounts of NaO-*t*-Bu proved to be important, since employment of stoichiometric amounts or the use of other reagents (e.g., K_2CO_3, MeOH) resulted in decomposition.

The formation of **5** can be explained by addition of TMS protected L-rhamnosyl iodide (generated in situ by treatment of the rhamnose derivative **4** with Me_3SiI) to dehydroindigo, addition of *n*PrSH, extrusion of iodine and dipropyl disulfide and subsequent acetolysis (by addition of acetic anhydride, pyridine and KHF_2). The replacement of the TMS by acetyl groups proved to be important for practical reasons (stability during chromatography). The relatively low yield of the product after the reaction sequence is mainly due to side reactions of the dehydroindigo in the addition step. A possible N′-acetylation of the glycosylated indigo during the acetolysis can be extensively suppressed by tuning the Ac_2O/pyridine ratio. Higher ratios cause less formation of N′-acetylated by-product (violet colour on TLC), but result in other side reactions.

The structures of **5α** and **5β** were proved by spectroscopic methods (Fig. 2). The NMR signals were assigned by DEPT and two-dimensional ^1H, ^1H COSY, ^1H, ^1H NOESY and ^1H, ^{13}C correlation spectra (HSQC, HMBC) recorded with a Bruker AVANCE 500. Indigoglycoside **5α**, which was measured both as the pure anomer (α/β > 98:2) and as the anomeric mixture (α/β = 2:1), resides as an N-glycoside containing a α-rhamnosyl moiety which possesses a $^4C_1$ conformation. The structure was independently confirmed by crystal structure analysis (Fig. 3).[12] The conformation of the sugar moiety of **5β** was determined to be $^1C_4$. NOE-correlations between the protons H-15 and H-17, and H-15 and H-19 clearly indicate this conformation.

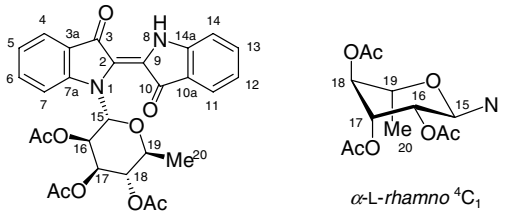

Figure 2. Structure of **5α**.

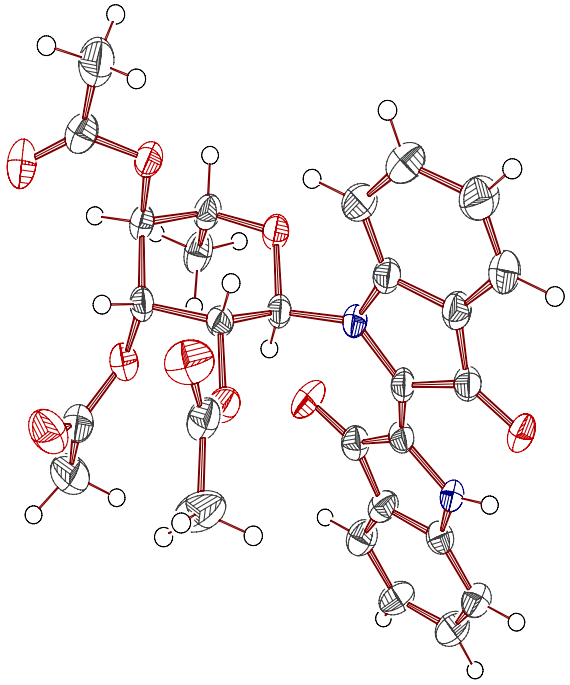

Figure 3. Crystal structure of **5α**.