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First synthesis of oxa-analogous isoindigo-*N*-glycosides

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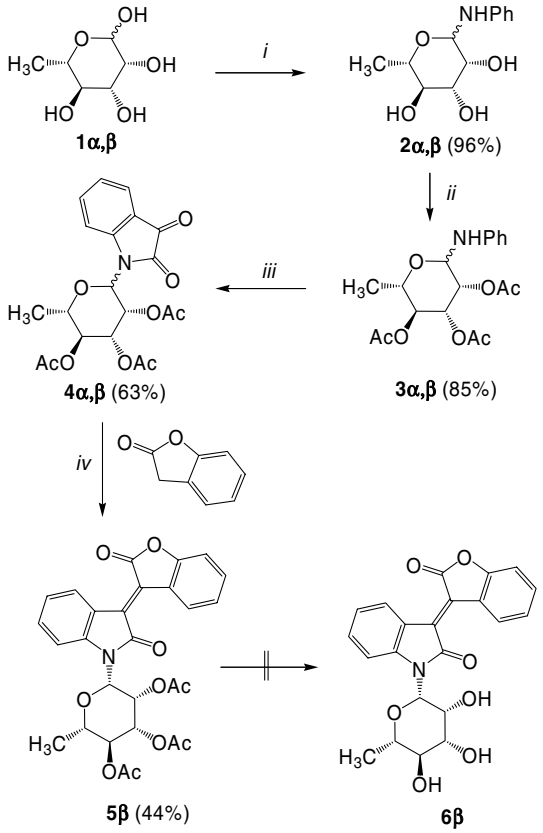
Abstract—Lactone-analogues of isoindigo-*N*-glycosides were prepared by condensation of *N*-glycosylisatines with 2-coumaranone and subsequent deprotection.

Glycosylated indoles are of remarkable pharmacological relevance. Prominent cancerostatic derivatives include, for example, the natural products staurosporine, K-252d, rebeccamycin and the tjipanazoles.[1,2] Indigo, indirubin and isoindigo contain a bis-indole framework and are found in a number of natural products. Recently, we reported[3] the synthesis of indigo-*N*-glycosides (blue sugars). This type of core structure is present in the akashines A–C which were isolated, by Laatsch and co-workers, from *Streptomyces* sp. GW48/1497.[4] In contrast to inactive parent indigo, the akashines show a remarkable cancerostatic activity against various human cancer cell lines. Indirubin, the red isomer of indigo, is the active ingredient of the traditional Chinese medicinal recipe *Danggui Longhui Wan* which has been used for the treatment of myelocytic leukaemia.[5] This substance and its substituted derivatives are potent inhibitors of several kinases such as GSK-3β and cyclin dependent kinases (CDK's).[6,7] Recently, we reported[8] the synthesis of indirubin-*N*-glycosides (red sugars) which exhibit a considerable anti-proliferative activity against various human cancer cell lines. Sassatelli et al. described the preparation of isoindigo-*N*-glycosides which also possess a considerable anti-proliferative activity and kinase inhibitory potency.[9] Noteworthy, both deprotected and protected isoindigo-*N*-glycosides are of pharmacological relevance. For example, the biological activity of so-called 'Natura', that is acetyl-protected β-D-xylopyranosyl-*N*-isoindigo, was reported to be higher than the activity of its deprotected analogue.[10,11] Herein, we report the



Scheme 1. Synthesis of acetyl-protected 3-[2′-coumaranon-3′-(*E*)-yl-idene]-1-(β-L-rhamnopyranosyl)oxindol **5β**. Reagents and conditions: (i) $PhNH_2$, EtOH, 20 °C, 12 h; (ii) Ac_2O, pyridine, 0→4 °C, 8–12 h; (iii) oxalyl chloride, $AlCl_3$, 55 °C, 1.5 h; (iv) AcOH, Ac_2O, NaOAc, 90 °C, 6 h.

Keywords: Oxa-analogous isoindigo-*N*-glycosides; Isoindigo analogues; 2-Coumaranone; *N*-Glycosylisatines; Carbohydrates; Aldol type condensation.
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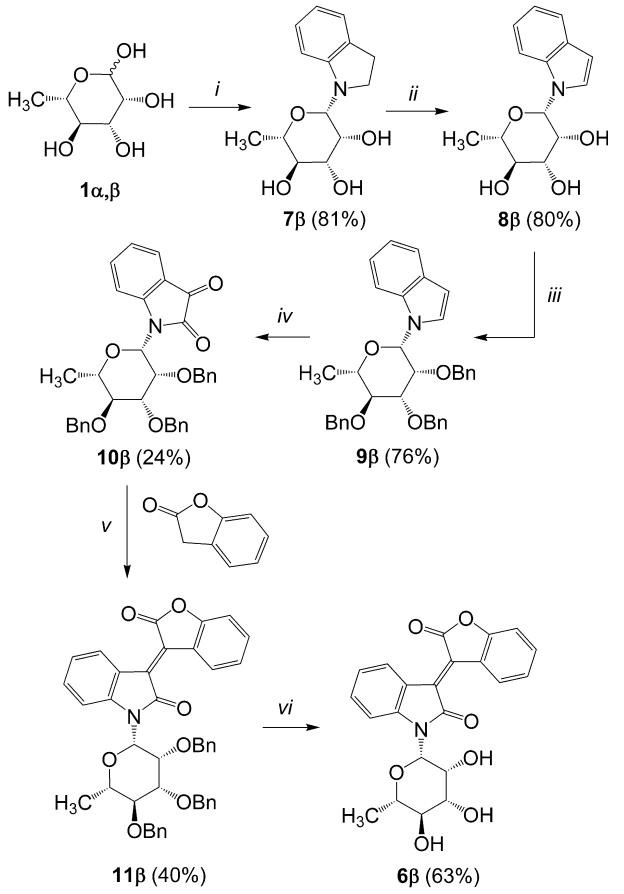

Scheme 2. Synthesis of deprotected 3-(2′-coumaranon-3′-(*E*)-ylidene)-1-(β-L-rhamnopyranosyl)oxindol **6β**. Reagents and conditions: (i) indoline, EtOH, 20 °C, 12 h; (ii) DDQ, dioxane, 20 °C, 12 h; (iii) NaH, BnBr, DMF, 0→4 °C, 12 h; (iv) CrO_3, acetone, AcOH, H_2O, 20 °C, 1.5 h; (v) AcOH, Ac_2O, NaOAc, 90 °C, 2 h; (vi) BBr_3, CH_2Cl_2, −78 °C, 2 h.

first synthesis of lactone-analogues of isoindigo-*N*-glycosides.

Acetyl-protected *N*-(α,β-L-rhamnopyranosyl)isatine **4α**, **β** was prepared from L-rhamnose as a separable mixture of anomers (Scheme 1).[12] The base-mediated reaction of **4** with 2-coumaranone (3*H*-benzofuran-2-one) proved to be unsuccessful, due to cleavage of the lactone moiety. The reaction of pure β-anomer **4β** with 2-coumaranone, in the presence of acetic acid, acetic anhydride and sodium acetate,[13] afforded the desired oxa-analogous isoindigo-*N*-glycoside **5β** in up to 44% yield. However, all attempts to remove the acetyl groups of **5β** failed, due to base-mediated cleavage of the lactone moiety.

The problem was solved by the use of the benzyl protective group (Scheme 2). The reaction of L-rhamnose with indoline afforded anomerically pure **7β** which was transformed into the indol-*N*-glycoside **8β** by dehydrogenation (DDQ). Benzylation and subsequent oxidation (CrO_3) afforded *N*-(β-L-rhamnopyranosyl)isatine **10β**. The condensation of **10β** with 2-coumaranone, following the conditions as described for **5β**, afforded the red coloured condensation product **11β** in 40% yield.[14] Treatment of the latter with BBr_3 resulted in formation of the desired deprotected oxa-analogous isoindigo-*N*-glycoside **6β** in up to 63% yield which was isolated as an orange to red solid.[14] The double bond between the coumaranone and the glycosylated oxindol part in the compounds **5β**, **11β** and **6β** was found to be (*E*)-configured. This is very likely because we observed downfield shifts for the proton resonances of H-4 and H-4′ (for the numbering see Ref. 14) of these compounds, which are comparable with those of the protons for similar (*E*)-configured isoindigo derivatives.[9b] Furthermore, we could obtain an X-ray structure analysis of a **5β**-analogous D-mannosyl derivative, which clearly shows the (*E*)-configuration of the double bond.

In conclusion, the first synthesis of lactone-analogues of isoindigo-*N*-glycosides has been reported. Our current studies suggest that the strategy outlined herein is rather general and can be successfully applied to the synthesis of a variety of derivatives containing different carbohydrate moieties. Noteworthy, it also proved to be possible to prepare oxa-analogous indirubin-*N*-glycosides by condensation of N-glycosylated isatines with 3-coumaranone.

Acknowledgement

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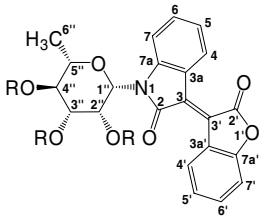
14. *Synthesis of oxa-analogous isoindigo-N-glycosides*: To a acetic acid/acetic anhydride (2:1) solution of the acetylated glycosyl isatine, 2-coumaranone (1.5 equiv) and sodium acetate (3.0–4.0 equiv) were added. The mixture was stirred at 90 °C upon completion of the reaction (tlc-control). The yellow colour of the solution changed to red. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel).



3-[2′-Coumaranon-3′-(E)-ylidene]-1-(2″,3″,4″-tri-O-acetyl-β-L-rhamnopyranosyl)oxindol (**5β**): reaction time: 6 h. Starting with **4β** (180 mg, 0.34 mmol), **5β** was isolated (44%, 100 mg) by column chromatography (*n*-heptane/EtOAc = 5:1 → 2:1) as an orange to red solid; R_f 0.64 (*n*-heptane/EtOAc = 1:3); mp = 101–103 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.11, 8.97 (2dd, $^4J_{4^*,6^*}$ = 1.1 Hz, $^3J_{4^*,5^*}$ = 8.3 Hz, 2H, H-4, H-4′); 7.54 (dd, $^4J_{5^*,7^*}$ = 1.1 Hz, $^3J_{6^*,7^*}$ = 8.1 Hz, 1H, H-7*); 7.45 (dt, $^4J_{4^*,6^*}$ = 1.3 Hz, $^3J_{5^*,6^*}$ = $^3J_{6^*,7^*}$ = 7.8 Hz, 1H, H-6*); 7.35 (dt, $^4J_{4^*,6^*}$ = 1.2 Hz, $^3J_{5^*,6^*}$ = $^3J_{6^*,7^*}$ = 7.7 Hz, 1H, H-6*); 7.19 ('dt', $^4J_{5^*,7^*}$ = 1.2 Hz,$^3J_{4^*,5^*}$ = $^3J_{5^*,6^*}$ = 7.8 Hz, 1H, H-5*); 7.12–7.02 (m, ^4J = 1.2 Hz, ^3J = 7.8 Hz, ^3J = 8.1 Hz, 1H, H-5*, H-7*); 5.98 (d, $^3J_{1'',2''}$ = 1.5 Hz, 1H, H-1″); 5.61 (dd, $^3J_{1'',2''}$ = 1.5 Hz, $^3J_{2'',3''}$ = 3.0 Hz, 1H, H-2″); 5.30–5.19 (m, $^3J_{2'',3''}$ = 3.1 Hz, $^3J_{3'',4''}$ = 10.2 Hz, 2H, H-3″, H-4″); 3.82–3.72 (m, $^3J_{4'',5''}$ = 9.2 Hz, $^3J_{5'',6''}$ = 6.1 Hz, 1H, H-5″); 2.10, 1.98, 1.85 (3s, 9H, 3 × C(O)CH_3); 1.37 (d, $^3J_{5'',6''}$ = 6.1 Hz, 3H, H-6″); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 169.7, 169.7 (3s, 3 × *C*(O)CH_3); 167.1, 166.4 (C-2, C-2′); 155.5 (C-7a′); 143.0 (C-7a); 133.9, 127.8 (C-3, C-3′); 133.9, 132.7 (C-6, C-6′); 129.8, 129.2 (C-4, C-4′); 124.1, 122.8 (C-5, C-5′); 122.9, 121.1 (C-3a, C-3a′); 113.4, 110.5 (C-7, C-7′); 80.6 (C-1″); 74.2 (C-5″); 70.6 (C-3″); 70.2 (C-2″); 70.1 (C-4″); 20.8, 20.8, 20.5 (3s, 3 × C(O)*C*H_3); 17.7 (C-6″). MS (EI, 70 eV): *m/z* (%) = 535 (16) [M^+], 273 (33) [sugar], 153 (100) [sugar-2HOAc]. HRMS (EI, 70 eV): calcd for $C_{28}H_{25}N_1O_{10}$ ([M^+]): 535.14730; found 535.14747.

3-[2′-Coumaranon-3′-(E)-ylidene]-1-(2″,3″,4″-tri-O-benzyl-β-L-rhamnopyranosyl)oxindol (**11β**): reaction time: 3 h. Starting with **10β** (300 mg, 0.53 mmol), **11β** was isolated (40%, 141 mg) by column chromatography (*n*-heptane/EtOAc = 15:1 → 8:1) as a red to brown syrup; R_f 0.47 (*n*-heptane/EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.02 (d, $^3J_{4^*,5^*}$ = 8.2 Hz, 1H, H-4*); 8.93 (d, $^3J_{4^*,5^*}$ = 8.0 Hz, 1H, H-4*); 7.60 (d, ^3J = 8.0 Hz, 1H, Heteroaryl); 7.46 (dt, ^4J = 1.1 Hz, ^3J = 7.8 Hz, 1H, Heteroaryl); 7.41–7.27 (m, 11H, Heteroaryl, Ph); 7.22–7.00 (m, 6H, Heteroaryl, Ph); 6.88–6.83 (m, 2H, Ph); 5.62 (d, $^3J_{1'',2''}$ = 1.1 Hz, 1H, H-1″); 5.00 (d, $^2J_{Ha,Hb}$ = 10.9 Hz,1H, CH_2Ph); 4.80, 4.75 (2d, $^2J_{Ha,Hb}$ = 11.5 Hz, 2H, CH_2Ph); 4.72 (d, $^2J_{Ha,Hb}$ = 10.9 Hz, 1H, CH_2Ph); 4.69 (d, $^2J_{Ha,Hb}$ = 11.4 Hz, 1H, CH_2Ph); 4.42 (d, $^2J_{Ha,Hb}$ = 11.4 Hz, 1H, CH_2Ph); 4.16 (m, 1H, H-2″); 3.83–3.72 (m, $^3J_{2'',3''}$ = 3.2 Hz, $^3J_{4'',5''}$ = 9.4 Hz, 2H, H-3″, H-4″); 3.55 (q, $^3J_{5'',6''}$ = 6.1 Hz, 1H, H-5″); 1.43 (d, $^3J_{5'',6''}$ = 6.1 Hz, 3H, H-6″); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2, 166.4 (C-2, C-2′); 155.3, 144.2 (C-7a′,C-7a); 138.2, 138.0, 137.0 (3s, 3C_{quart}-Ph); 135.1, 126.7 (C-3, C-3′); 133.4, 133.2 (2s, 2 × CH); 129.5, 128.8, 128.8, 128.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.1, 128.1, 128.0, 128.0, 127.8, 127.8, 127.7, 127.5 (17s, 15 × *C*H-Ph, 2 × CH); 123.9, 122.4 (2s, 2 × CH); 123.0, 121.0 (C-3a, C-3a′); 115.1, 110.4 (C-7, C-7′); 83.0, 82.4, 79.7, 75.6, 75.3 (C-1″, C-2″, C-3″, C-4″, C-5″); 75.4, 74.9, 72.6 (3s, 3 × CH_2Ph); 18.1 (C-6″). MS (EI, 70 eV): *m/z* (%) = 679 (1) [M^+], 259 (8), 181 (15), 91 (100). HRMS (EI, 70 eV): calcd for $C_{43}H_{37}NO_7$ ([M^+]): 679.25645; found 679.25552.

3-(2′-Coumaranon-3′-(E)-ylidene)-1-β-L-rhamnopyranosyl-oxindol (**6β**): To a cooled (−78 °C) CH_2Cl_2-solution (3 mL) of **11β** (130 mg, 0.19 mmol) was added BBr_3 (1 M solution in CH_2Cl_2, 2.85 mmol). After stirring for 2 h at −78 °C, an aqueous solution of sodium bicarbonate was added at −78 °C. The mixture was allowed to warm to 20 °C and was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc) to give **6β** (49 mg, 63%) as an orange to red solid; R_f 0.08 (EtOAc); mp 284–285 °C; ^{1}H NMR (250 MHz, DMSO): δ = 9.10, 8.80 (2d, $^4J_{4,5}$ = $^3J_{4',5'}$ = 8.1 Hz, 2H, H-4, H-4′); 7.65 (d, ^3J = 8.1 Hz, 1H, H-7*); 7.58, 7.37 (pt, ^3J = 7.8 Hz, 2H, H-6, H-6′); 7.32–7.02 (m, ^3J = 7.8 Hz, 2H, H-7*, H-5*); 7.03 (t, ^3J = 7.8 Hz, 1H, H-5*); 5.64 (s, 1H, H-1″); 5.15 (d, $^3J_{2'',OH}$ = 5.0 Hz, 1H, OH); 4.99 (d, $^3J_{4'',OH}$ = 4.8 Hz, 1H, OH); 4.87 (d, $^3J_{3'',OH}$ = 5.5 Hz, 1H, OH); 3.88 (m, $^3J_{2'',3''}$ = 3.4 Hz, 1H, H-2″); 3.50 (m, 1H, H-3″); 3.39, 3.36 (m,2H, H-4″, H-5″); 1.28 (d, $^3J_{5'',6''}$ = 5.0 Hz, 3H, H-6″); ^{13}C NMR (63 MHz, DMSO): δ = 167.0, 166.2 (C-2, C-2′); 155.1, 145.0 (C-7a, C-7a′); 134.5, 126.9 (C-3, C-3′); 134.1, 133.0 (C-6, C-6′); 129.3, 128.1 (C-4, C-4′); 124.0, 121.8 (C-5, C-5′); 122.9, 120.4 (C-3a, C-3a′); 115.5, 110.7 (C-7, C-7′); 82.7 (C-1″); 75.6, 71.5 (C-4″, C-5″); 73.2 (C-3″); 72.0 (C-2″); 18.2 (C-6″). MS (EI, 70 eV): *m/z* (%) = 409 (14) [M^+], 263 (100) [aglyconH], 235 (53), 132 (25). HRMS (EI, 70 eV): calcd for $C_{22}H_{19}NO_7$ ([M^+]): 409.11560; found 409.11583.

The asterisk indicates that it was not possible to distinguish between the both aromatic rings; for example, if a shift for H-4 is given, it can be either the one for H-4 or H-4′.