Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters 47 (2006) 5741–5745
Tetrahedron Letters

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

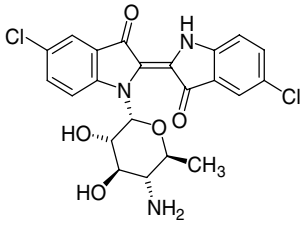
Martin Hein,[a,*] Nguyen Thi Bich Phuong,[a,b] Dirk Michalik,[c] Helmar Görls,[d] Michael Lalk[e] and Peter Langer[a,c,*]

[a]*Institut für Chemie, Universität Rostock, Albert-Einstein-Strasse 3a, D-18059 Rostock, Germany*
[b]*Institut für Biochemie, Universität Greifswald, Soldmannstr. 16, D-17487 Greifswald, Germany*
[c]*Leibniz-Institut für Katalyse e.Van der Universität Rostock, Albert-Einstein-Strasse 29a, D-18059 Rostock, Germany*
[d]*Institut für Anorganische und Analytische Chemie, Universität Jena, August-Bebel-Str. 2, D-07740 Jena, Germany*
[e]*Institut für Pharmazie, Universität Greifswald, Ludwig-Jahn-Str. 17, D-17487 Greifswald, Germany*

Received 26 January 2006; revised 24 May 2006; accepted 2 June 2006
Available online 22 June 2006

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.



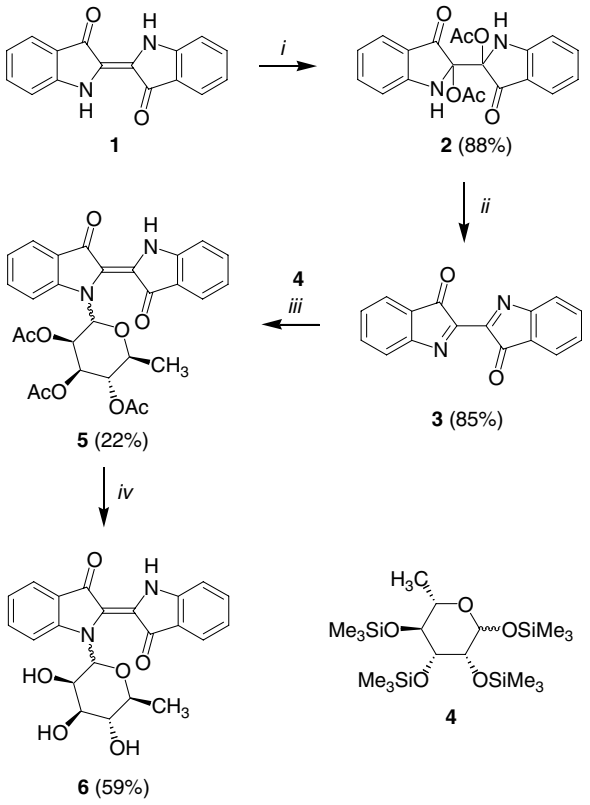
Akashine A

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

Keywords: Dehydroindigo; Indigo; *N*-Heterocycles; Regioselectivity.
* Corresponding authors. Tel.: +49 381 4986410; fax: +49 381 4986412 (P.L.); e-mail: peter.langer@uni-rostock.de

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.06.021



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.

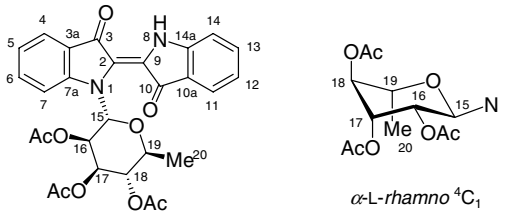


Figure 2. Structure of **5α**.

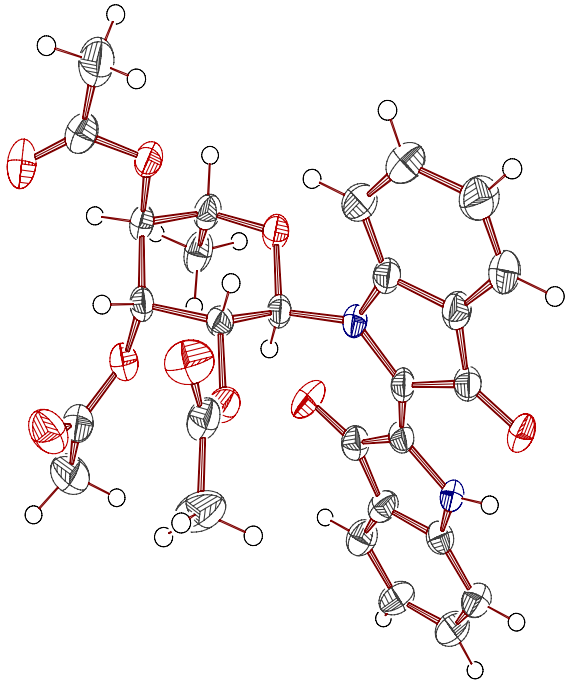
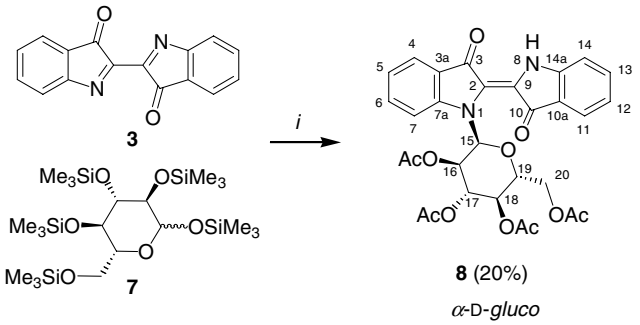


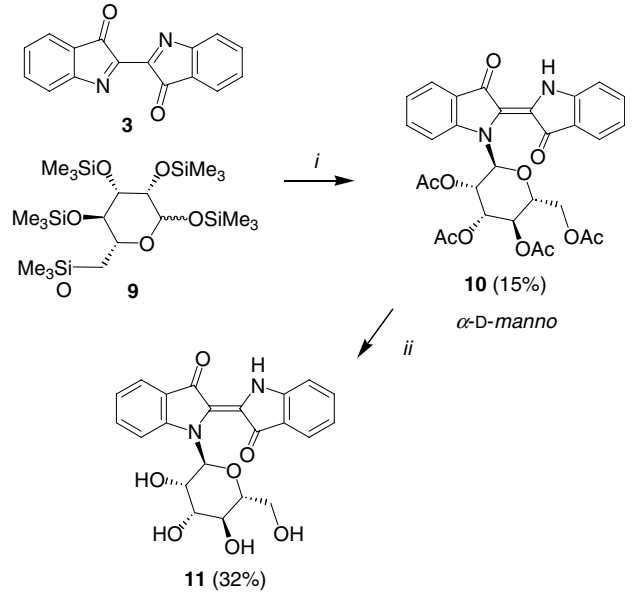
Figure 3. Crystal structure of **5α**.



Scheme 2. Synthesis of the acetylated *N*-(α-D-glucosyl)indigo **8**. Reagents and conditions: (i) (a) **7**, 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.

The reaction of **3** with TMS protected D-glucose **7**—carried out following the procedure given for the synthesis of **5**—afforded the desired anomerically pure *N*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)indigo **8** (Scheme 2).[13] The structure of **8** was established by NMR spectroscopy. In the NOESY, spectrum relevant cross peaks were found for H-15 with H-20a,b (confirming the α-configuration) and for H-15 with H-18 (confirming a boat-like conformation). Notably, the direct reaction of acetyl protected α-D-glucopyranosyl bromide with dehydroindigo was unsuccessful. The reaction of **3** with TMS protected D-mannose **9**, subsequent acetolysis and deprotection (NaO-*t*-Bu, 15 mol %) afforded the anomerically pure *N*-(α-D-mannopyranosyl)indigo **11** (Scheme 3). Like in the other cases, the indigo rest prefers an equatorial arrangement at the sugar, which is indicated by a large vicinal coupling of the sugar protons $^3J_{H\text{-}1,H\text{-}2} = 9.5$ Hz.

In conclusion, we have reported what are, to the best of our knowledge, the first syntheses of deprotected N-glycosides of indigo.



Scheme 3. Synthesis of *N*-(α-D-mannosyl)indigo **11**. Reagents and conditions: (i) (a) **9**, 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 (ii) NaO-*t*-Bu (15 mol %), MeOH, THF, 20 °C, 4 h.

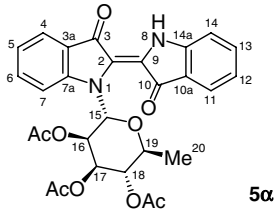
Acknowledgement

Financial support from the Ministry of Education of Vietnam (scholarship for T.B.P.N.) is gratefully acknowledged.

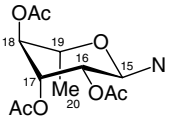
References and notes

1. Review: Gribble, G.; Berthel, S. In *Studies in Natural Products Chemistry*; Elsevier Science: New York, 1993; Vol. 12, pp 365–409.
2. Isolation of staurosporin: (a) Omura, S.; Iwai, Y.; Hirano, A.; Nakagawa, A.; Awaya, J.; Tsuchiya, H.; Takahashi, Y.; Masuma, R. *J. Antibiot.* **1977**, *30*, 275; synthesis: (b) Link, J. T.; Raghavan, S.; Gallant, M.; Danishefsky, S. J.; Chou, T. C.; Ballas, L. M. *J. Am. Chem. Soc.* **1996**, *118*, 2825.
3. Yamashita, Y.; Fujii, N.; Murkata, C.; Ashizawa, T.; Okabe, M.; Nakano, H. *Biochemistry* **1992**, *31*, 12069.
4. Moon, M. J.; Lee, S. K.; Lee, J.-W.; Song, W. K.; Kim, S. W.; Kim, J. I.; Cho, C.; Choi, S. J.; Kim, Y.-C. *Bioorg. Med. Chem.* **2006**, *14*, 237.
5. Maskey, R. P.; Grün-Wollny, I.; Fiebig, H. H.; Laatsch, H. *Angew. Chem.* **2002**, *114*, 623; *Angew. Chem., Int. Ed.* **2002**, *41*, 597.
6. Hein, M.; Michalik, D.; Langer, P. *Synthesis* **2005**, *20*, 3531.
7. Kalb, L. *Chem. Ber.* **1909**, *42*, 3642.
8. Kalb, L. *Chem. Ber.* **1912**, *45*, 2136.
9. Christophersen, C.; Waetjen, F.; Buchardt, O.; Anthoni, U. *Tetrahedron Lett.* **1977**, *20*, 1747.
10. *Synthesis of indigo glycoside* **5**: To a CH_2Cl_2 solution (8 mL) of 1,2,3,4-tetra-*O*-trimethylsilyl-L-rhamnopyranose (**4**) (925 mg, 2.04 mmol) was added iodotrimethylsilane (280 μL, 2.06 mmol) and the mixture was stirred for 30 min at 20 °C. The solution, now containing the glycosyl iodide, was cooled to 0 °C and dehydroindigo (531 mg, 2.04 mmol) was added. After stirring for 30–45 min at 0 °C, propanethiol (280 μL, 3.09 mmol) was added to the solution. The solution was warmed to 20 °C and was stirred for 1 h. The mixture was again cooled to 0 °C and a solution (8 mL) of $NaHCO_3$ and Na_2SO_3 (3.0 g of each per 100 mL of water) was added. Subsequently, 30–40 mL of cold ethyl acetate was added. The mixture was filtered and the aqueous and the organic layers were separated. The latter was washed with an aqueous solution of $NaHCO_3/Na_2SO_3$ (1 × 10 mL) and with brine (2 × 10 mL). The solution was dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was dissolved in a mixture of pyridine (2 mL) and acetic anhydride (6 mL). To the solution was added finely powdered KHF_2 (800 mg, 10.25 mmol) and the reaction mixture was stirred at 70 °C until one main spot of blue colour could be detected by TLC (2–3 h). The pyridine and acetic anhydride were removed by distillation under reduced pressure and the residue was purified by column chromatography (EtOAc/toluene = 1:5 → 1:2) to give **5** (198 mg, 22%, α/β = 2:1) as a blue solid. An analytically pure sample of the α anomer was isolated by repeated crystallisation from methanol.
Compound **5α**: ^{1}H NMR (500.13 MHz, $CDCl_3$): δ 10.87 (s, 1H, NH); 7.74 (dd, 1H, $^3J_{4,5} = 7.8$ Hz, $^4J_{4,6} = 1.5$ Hz, H-4); 7.72 (d, 1H, $^3J_{6,7} = 8.2$ Hz, H-7); 7.71 (br d, 1H, $^3J_{11,12} = 7.8$ Hz, H-11); 7.53 (ddd, 1H, $^3J_{6,7} = 8.2$ Hz, $^3J_{5,6} = 7.2$ Hz, $^4J_{4,6} = 1.5$ Hz, H-6); 7.48 (ddd, 1H, $^3J_{13,14} = 8.2$ Hz, $^3J_{12,13} = 7.3$ Hz, $^4J_{11,13} = 1.2$ Hz, H-13); 7.26 (d, 1H, $^3J_{15,16} = 9.8$ Hz, H-15); 7.10 ('t', 1H, $^3J_{4,5} =$

7.8 Hz, $^3J_{5,6} = 7.2$ Hz, H-5); 7.00 (d, 1H, $^3J_{13,14} = 8.2$ Hz, H-14); 6.96 ('t', 1H, $^3J_{11,12} = 7.8$ Hz, $^3J_{12,13} = 7.3$ Hz, H-12); 5.63 (dd, 1H, $^3J_{15,16} = 9.8$ Hz, $^3J_{16,17} = 3.5$ Hz, H-16); 5.44 (dt, 1H, $^3J_{16,17} = {}^3J_{17,18} = 3.5$ Hz, $^4J_{17,19} = 1.2$ Hz, H-17); 4.95 (dd, 1H, $^3J_{17,18} = 3.5$ Hz, $^3J_{18,19} = 1.2$ Hz, H-18); 4.45 (m, 1H, H-19); 2.23 (s, 3H, Ac); 2.15 (s, 3H, Ac); 1.86 (d, 3H, $^3J_{19,20} = 7.5$ Hz, H-20); 1.68 (s, 3H, Ac). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 189.2, 187.0 (C-3, C-10); 169.3, 169.3, 169.0 (3 Ac–CO); 151.7 (C-14a); 150.3 (C-7a); 136.4 (C-13); 135.6 (C-6); 126.0; 122.4 (C-2, C-9); 124.9 (C-11); 124.0 (C-4); 122.9 (C-3a); 122.2 (C-5); 120.9 (C-12); 119.9 (C-10a); 115.9 (C-7); 112.0 (C-14); 78.9 (C-15); 74.4 (C-19); 71.6 (C-18); 69.0 (C-17); 65.3 (C-16); 21.0, 20.7, 20.2 (3 Ac–Me); 16.3 (C-20). HRMS (NCI, $\alpha/\beta = 2{:}1$): *m/z* calcd for $C_{28}H_{26}N_2O_9$ ($[M]^-$): 534.1644; found: 534.1622.

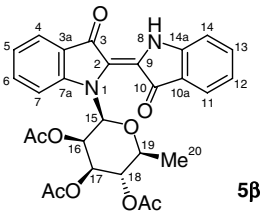


5α

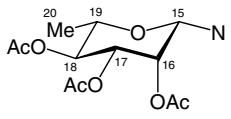


α-L-*rhamno* ^{4}**C**$_1$

Compound **5β**: ^{1}H NMR (500.13 MHz, $CDCl_3$) δ: 10.88 (s, 1H, NH); 7.83 (d, 1H, $^3J_{6,7} = 8.4$ Hz, H-7); 7.70–7.67 (m, 2H, H-4,11); 7.48–7.45 (m, 2H, H-6,13); 7.02 ('t', 1H, $^3J_{4,5} = {}^3J_{5,6} = 7.5$ Hz, H-5); 6.97 (d, 1H, $^3J_{13,14} = 8.2$ Hz, H-14); 6.94 ('t', 1H, $^3J_{11,12} = {}^3J_{12,13} = 7.5$ Hz, H-12); 6.79 (d, 1H, $^3J_{15,16} = 1.4$ Hz, H-15); 5.81 (dd, 1H, $^3J_{16,17} = 3.5$ Hz, $^3J_{15,16} = 1.4$ Hz, H-16); 5.46 (dt, 1H, $^3J_{17,18} = 10.0$ Hz, $^3J_{16,17} = 3.5$ Hz, H-17); 5.22 ('t', 1H, $^3J_{17,18} = 10.0$ Hz, $^3J_{18,19} = 9.8$ Hz, H-18); 3.88 (dq, 1H, $^3J_{18,19} = 9.8$ Hz, $^3J_{19,20} = 6.2$ Hz, H-19); 2.09 (s, 3H, Ac); 1.97 (s, 3H, Ac); 1.76 (s, 3H, Ac); 1.38 (d, 3H, $^3J_{19,20} = 6.2$ Hz, H-20). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ: 188.7, 187.7 (C-3, C-10); 170.1, 169.7, 169.6 (3 Ac–CO); 151.7 (C-14a); 150.7 (C-7a); 136.7 (C-13); 134.7 (C-6); 126.4; 121.1 (C-2, C-9); 125.2 (C-11); 123.4 (C-4); 122.0 (C-3a); 121.4 (C-5); 120.9 (C-12); 119.8 (C-10a); 117.6 (C-7); 111.9 (C-14); 85.5 (C-15); 73.4 (C-19); 71.5 (C-16); 70.8 (C-18); 70.7 (C-17); 20.7, 20.7, 20.5 (3 Ac–Me); 17.7 (C-20).

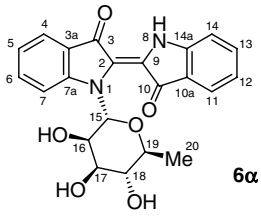


5β

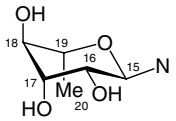


β-L-*rhamno* ^{1}**C**$_4$

11. *Synthesis of indigo glycoside* **6**: Acetylated indigo glycoside **5** (100 mg, 0.187 mmol, anomeric mixture) was dissolved in a mixture of THF (2 mL) and of MeOH (6 mL). To the solution was dropwise added a MeOH solution (1%) of sodium *tert*-butoxide and the rate of the deacetylation was adjusted (TLC-control, ca 5–15 mol %). After complete conversion (2–4 h), the mixture was cooled to 0 °C and silica gel was added (3.0 g). The solvent was removed by distillation at 30 °C under reduced pressure and the residue was purified by column chromatography (EtOAc/THF = 1:0 → 5:1) to give **6** (45 mg, 59%, $\alpha/\beta = 2{:}1$) as a blue solid.
Compound **6α**: ^{1}H NMR (500.13 MHz, DMSO) δ: 10.90 (s, 1H, NH); 7.82 (d, 1H, $^3J_{6,7} = 8.3$ Hz, H-7); 7.69 (dd, 1H, $^3J_{4,5} = 7.7$ Hz, $^4J_{4,6} = 1.4$ Hz, H-4); 7.62 (dd, 1H, $^3J_{11,12} = 7.5$ Hz, $^4J_{11,13} = 0.8$ Hz, H-11); 7.57 (ddd, 1H, $^3J_{6,7} = 8.3$ Hz, $^3J_{5,6} = 7.2$ Hz, $^4J_{4,6} = 1.4$ Hz, H-6); 7.51 (m, 1H, H-13); 7.37 (d, 1H, $^3J_{13,14} = 8.0$ Hz, H-14); 7.10 (d 't', 1H, $^3J_{4,5} = 7.7$ Hz, $^3J_{5,6} = 7.2$ Hz, $^4J_{5,7} = 0.8$ Hz, H-5); 6.94 (d 't', 1H, $^3J_{11,12} = {}^3J_{12,13} = 7.5$ Hz, $^4J_{12,14} = 0.8$ Hz, H-12); 6.28 (d, 1H, $^3J_{15,16} = 9.5$ Hz, H-15); 5.11 (d, 1H, $^3J_{18,OH} = 3.1$ Hz, $OH_{(18)}$); 4.93 (d, 1H, $^3J_{17,OH} = 3.5$ Hz, $OH_{(17)}$); 4.55 (d, 1H, $^3J_{16,OH} = 8.4$ Hz, $OH_{(16)}$); 4.20 ('q', 1H, H-19); 4.10 (d 't', 1H, $^3J_{15,16} = 9.5$ Hz, $^3J_{16,OH} = 8.4$ Hz, $^3J_{16,17} = 3.5$ Hz, H-16); 3.85 (m, 1H, H-17); 3.67 (br, 1H, H-18); 1.65 (d, 3H, $^3J_{19,20} = 7.3$ Hz, $Me_{(20)}$). ^{13}C NMR (125.8 MHz, DMSO) δ: 188.7 (C-3); 186.3 (C-10); 152.2 (C-14a); 151.5 (C-7a); 135.9 (C-13); 134.9 (C-6); 124.3 (C-9); 124.1 (C-11); 123.6 (C-2);123.3 (C-4); 122.9 (C-3a); 121.6 (C-5); 120.4 (C-12); 119.4 (C-10a); 117.1 (C-7); 113.2 (C-14); 81.9 (C-15); 75.9 (C-19); 72.7 (C-17); 72.0 (C-18); 64.0 (C-16); 17.1 (C-20). HRMS (EI, $\alpha/\beta = 2{:}1$): *m/z* calcd for $C_{22}H_{20}N_2O_6$ ($[M]^+$): 408.1316; found: 408.1300.

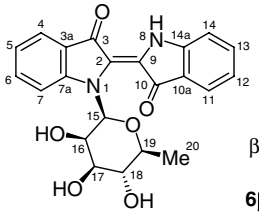


6α



α-L-*rhamno* ^{4}**C**$_1$

Compound **6β**: ^{1}H NMR (500.13 MHz, DMSO) δ: 11.00 (s, 1H, NH); 8.07 (d, 1H, $^3J_{6,7} = 8.5$ Hz, H-7); 7.58 (m, 2H, H-4,11); 7.52 (ddd, 1H, $^3J_{13,14} = 8.1$ Hz, $^3J_{12,13} = 7.2$ Hz, $^4J_{11,13} = 1.3$ Hz, H-13); 7.48 (ddd, 1H, $^3J_{6,7} = 8.5$ Hz, $^3J_{5,6} = 7.0$ Hz, $^4J_{4,6} = 1.5$ Hz, H-6); 7.36 (d, 1H, $^3J_{13,14} = 8.1$ Hz, H-14); 7.02 (ddd, 1H, $^3J_{4,5} = 7.7$ Hz, $^3J_{5,6} = 7.0$ Hz, $^4J_{5,7} = 0.8$ Hz, H-5); 6.95 ('dt', 1H, $^3J_{11,12} = {}^3J_{12,13} = 7.2$ Hz, $^4J_{12,14} = 0.8$ Hz, H-12); 5.86 (d, 1H, $^3J_{15,16} = 1.2$ Hz, H-15); 5.17 (d, 1H, $^3J_{16,OH} = 4.9$ Hz, $OH_{(16)}$); 4.85 (d, 1H, $^3J_{17,OH} = 5.4$ Hz, $OH_{(17)}$); 4.81 (d, 1H, $^3J_{18,OH} = 5.9$ Hz, $OH_{(18)}$); 4.47 (m, 1H, H-16); 3.55 (m, 1H, H-17); 3.33 (m, 1H, H-18); 3.31 (m, 1H, H-19); 1.19 (d, 3H, $^3J_{19,20} = 5.7$ Hz, $Me_{(20)}$). ^{13}C NMR (125.8 MHz, DMSO) δ: 188.4 (C-3); 187.1 (C-10); 152.1 (C-14a); 151.9 (C-7a); 136.5 (C-13); 134.5 (C-6); 125.1 (C-9); 124.3 (C-11); 123.1 (C-2); 122.3 (C-4); 121.4 (C-3a); 121.1 (C-5); 120.6 (C-12); 119.9 (C-7); 119.3 (C-10a); 113.3 (C-14); 88.1 (C-15); 75.3 (C-19); 73.4 (C-17); 72.8 (C-16); 71.9 (C-18); 18.3 (C-20).



β-L-*rhamno*

6β

12. CCDC-293346 contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; Fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk.
13. *Synthesis of indigo glycoside* **8**: The synthesis of **8** was carried out following the procedure given for the synthesis of **5**. Starting with **7** (454 mg, 0.84 mmol), **8** was isolated (100 mg, 20%) as a blue solid.

Compound **8**: ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 10.91$ (s, 1H, NH); 7.76 (br d, 1H, $^3J_{6,7} = 8.2$ Hz, H-7); 7.68 (br d, 1H, $^3J_{4,5} = 7.8$ Hz, H-4); 7.58 (br d, 1H, $^3J_{11,12} = 7.6$ Hz, H-11); 7.47 (ddd, 1H, $^3J_{6,7} = 8.2$ Hz, $^3J_{5,6} = 7.2$ Hz, $^4J_{4,6} = 1.3$ Hz, H-6); 7.44 (ddd, 1H, $^3J_{13,14} = 8.2$ Hz, $^3J_{12,13} = 7.3$ Hz, $^4J_{11,13} = 1.3$ Hz, H-13); 7.12 (d, 1H, $^3J_{15,16} = 2.7$ Hz, H-15); 7.02 ('dt', 1H, $^3J_{4,5} = 7.8$ Hz, $^3J_{5,6} = 7.2$ Hz, $^4J_{5,7} = 0.9$ Hz, H-5); 6.96 (br d, 1H, $^3J_{13,14} = 8.2$ Hz, H-14); 6.91 ('dt', 1H, $^3J_{11,12} = 7.6$ Hz, $^3J_{12,13} = 7.3$ Hz, $^4J_{12,14} = 0.9$ Hz, H-12); 5.67 ('t', 1H, $^3J_{16,17} = 3.0$ Hz, $^3J_{15,16} = 2.7$ Hz, H-16); 5.23 (ddd, 1H, $^3J_{17,18} = 4.5$ Hz, $^3J_{16,17} = 3.0$ Hz, $^4J_{17,19} = 0.6$ Hz, H-17); 5.09 ('dt', 1H, $^3J_{17,18} = 4.5$ Hz, $^3J_{18,19} = 4.0$ Hz, $^4J_{16,18} = 0.6$ Hz, H-18); 4.67 (dd, 1H, $^2J_{20a,20b} = 12.0$ Hz, $^3J_{19,20a} = 7.3$ Hz, H-20a); 4.48 ('ddt', 1H, $^3J_{19,20a} = 7.3$ Hz, $^3J_{19,20b} = 4.5$ Hz, $^3J_{18,19} = 4.0$ Hz, $^4J_{17,19} = 0.6$ Hz, H-19); 4.36 (dd, 1H, $^2J_{20a,20b} = 12.0$ Hz, $^3J_{19,20b} = 4.5$ Hz, H-20b); 2.27 (s, 3H, Ac); 2.16 (s, 3H, Ac); 2.01 (s, 3H, Ac); 1.68 (s, 3H, Ac).^{13}C NMR (125.8 MHz, $CDCl_3$): δ 188.9, 187.5 (C-3, C-10); 170.5, 169.4, 169.1, 168.8 (4 Ac–CO); 151.8 (C-14a); 150.5 (C-7a); 136.6 (C-13); 134.5 (C-6); 126.3; 121.5 (C-2, C-9); 124.9 (C-11); 123.5 (C-4); 122.9 (C-3a); 121.4 (C-5); 120.9 (C-12); 119.8 (C-10a); 117.3 (C-7); 112.0 (C-14); 80.6 (C-15); 74.0 (C-19); 69.7 (C-17); 69.4 (C-16); 65.1 (C-18); 61.5 (C-20); 20.9, 20.8, 20.7, 20.5 (4 Ac–Me). HRMS (EI): *m/z* calcd for $C_{30}H_{28}N_2O_{11}$ ($[M]^+$): 592.1688; found: 592.1682.