First Synthesis of *N*-Indigoglycosides – Analogues of Cancerostatic Akashines

Martin Hein,*[a] Dirk Michalik,[b] Peter Langer*[a,b]

[a] Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany
Fax +49(381)4986412; E-mail: peter.langer@uni-rostock.de

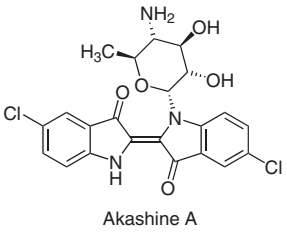
[b] Leibniz-Institut für Organische Katalyse an der Universität Rostock e.V. (IfOK), Albert-Einstein-Str. 29a, 18059 Rostock, Germany

Received 9 October 2005

Dedicated to Professor Steven V. Ley, FRS, on the occasion of his 60th birthday

Abstract: The first and surprisingly simple synthesis of *N*-indigoglycosides has been accomplished based on glycosylation of *N*-benzylindigo with tri-*O*-pivaloyl-α-L-rhamnosyl trichloroacetimidate and subsequent rearrangement of the *O*- into the *N*-glycoside. *N*-Indigoglycosides are of considerable pharmacological relevance and occur in cancerostatic natural akashines.

Key words: indigo, *N*-heterocycles, rearrangements, regioselectivity

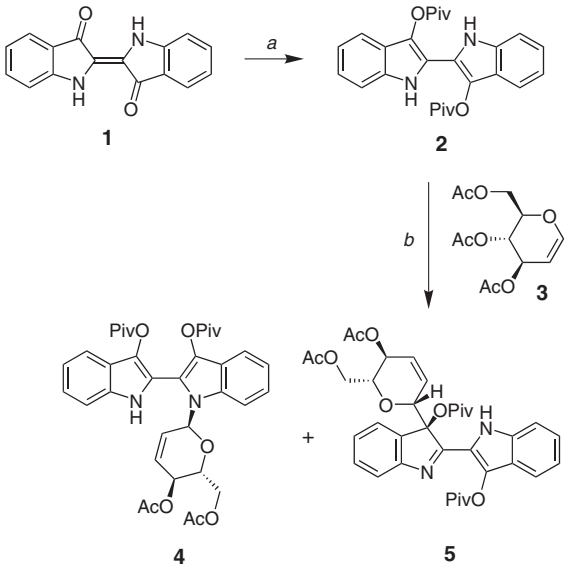


Akashine A

Figure 1 Akashine A isolated from terrestric *Streptomyces*

Heterocyclic *N*-glycosides are of considerable pharmacological relevance and occur in a number of unusual natural products. For example, indolo[2,3-*a*]carbazole glycosides, including the natural products staurosporine, K-252d, rebeccamycin, and the tjipanazoles,[1,2] represent promising anticancer agents; for example, rebeccamycin induces a topoisomerase I mediated DNA cleavage.[3] Synthetically available indigo and 6,6′-dibromoindigo (purpur) represent well-known dyes which have been used for a long time; they possess many technical applications and are of considerable theoretical interest.[4] Indigo has been isolated from many plants and fungi.[5] Until recently, only three *natural* derivatives of indigo – the well-known purpur (isolated from purpur snail)[6a] and two other brominated indigos[6b] – were known. In 2002, Laatsch et al. reported the isolation of akashine A, B and C from terrestric *Streptomyces* (Figure 1).[7] Besides the indigo moiety, the akashines contain a *N*-glycosidic 4-amino-4,6-didesoxyglucose (akashine A) or a 4-acetamido-4,6-didesoxyglucose moiety (akashine B). They exhibit a considerable activity against various human tumor cell lines, in contrast to pharmacologically inactive indigo. Herein, we report what is, to the best of our knowledge, the first synthetic approach to *N*-indigoglycosides.

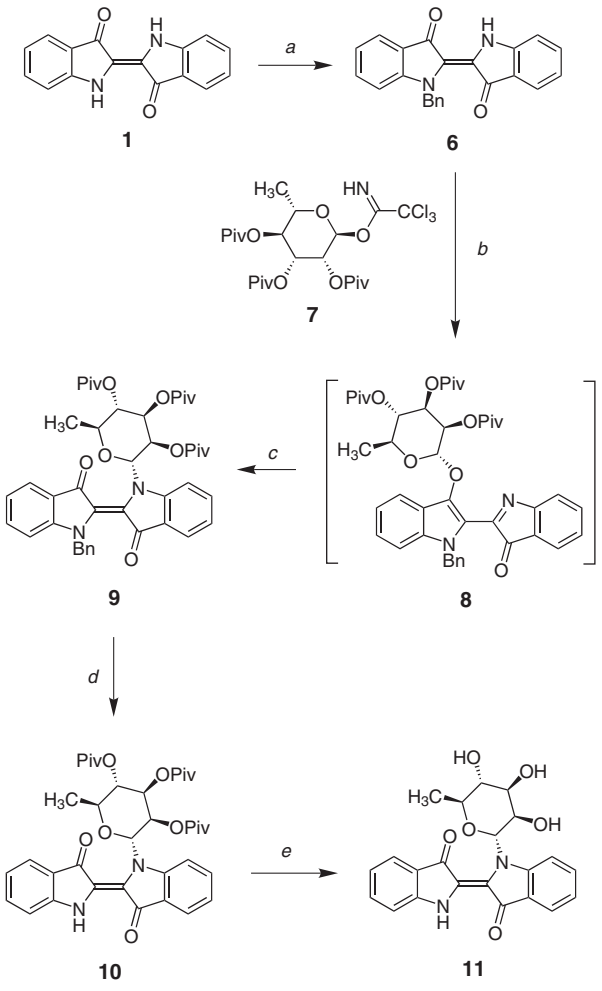
The synthesis of heterocyclic *N*-glycosides is not straightforward in many cases. For example, Van Vranken et al. reported that the direct glycosylation of fully unsaturated bis-indoles failed; eventually, the glycosylation of 2,2′-indolylindolines and subsequent oxidation led to the desired product.[8] In fact, our initial attempts to prepare *N*-indigoglycosides were unsuccessful: the direct acid-mediated glycosylation of indigo failed, due to the low solubility of the latter in nearly all solvents. An alternative strategy relied on the glycosylation of glycine derivatives, intramolecular acylation, to give a glycosylated indoxyl, and subsequent oxidative dimerization. This approach again failed, due to deglycosylation during the formation of the indoxyl moiety. Our third approach took advantage from the higher solubility of di-*O*-pivaloylleukoindigo (**2**), readily available from indigo (**1**), in organic solvents (Scheme 1). The glycosylation of **2** using a variety of conditions and substrates was studied: the $BF_3{\cdot}OEt_2$-mediated reaction of **2** with tri-*O*-acetylglucal (**3**) resulted in formation of a separable mixture of the *N*- and *C*-glycosylated indigos **4** and **5** in low yield. The anomeric configuration in the glycosides was proved to be α (**4**) and β (**5**), respectively.



Scheme 1 Glycosylation reaction of *O*-pivaloylleukoindigo (**2**). *Reagents and conditions*: *a*) 1) $Na_2S_2O_4$, NaOH, H_2O, 50 °C, 20 min; 2) PivCl, –10 → 0 °C, 45%; *b*) $BF_3{\cdot}OEt_2$, 4Å MS, CH_2Cl_2, –10 → 20 °C, 8 h.

SYNTHESIS 2005, No. 20, pp 3531–3534
Advanced online publication: 24.11.2005
DOI: 10.1055/s-2005-918489; Art ID: C19205SS

Our final and successful strategy is depicted in Scheme 2. *N*-Benzylindigo (**6**), which shows a good solubility in many organic solvents, was prepared by reaction of **1** with sodium hydride and benzyl bromide in DMF.[9] The TMSOTf-mediated reaction of **6** with tri-*O*-pivaloyl-α-L-rhamnosyl trichloroacetimidate (**7**)[10] afforded the *O*-indigoglycoside **8** (4Å MS, CH_2Cl_2, –20 °C, 1.5 h). Interestingly, extension of the reaction time (20 °C, 8–12 h) resulted in the rearrangement of **8** into the desired *N*-indigoglycoside **9**. Further extension of the reaction time or elevated temperature resulted in a dramatic decrease in yield, due to side reactions. Besides using **6** as starting material, the O → N rearrangement – which is, to the best of our knowledge, unprecedented so far – represents the key step of our synthesis. Hydrogenation of **9** resulted in discharge of the colour indicating reduction of the indigo moiety rather than debenzylation. However, we observed that an NMR solution of **9** slowly underwent oxidative debenzylation in the presence of air.[11] In fact, by stirring an AcOH solution of **9** in an oxygen atmosphere (2 h, 100 °C) resulted in complete debenzylation and formation of *N*-indigoglycoside **10** in high yield. The cleavage of the pivaloyl groups is under current investigation.



Scheme 2 Synthesis of *N*-indigoglycosides. *Reagents and conditions*: *a*) 1) NaH (1.0 equiv), DMF, 20 °C, 1 h; 2) BnBr (1.2 equiv), 20 °C, 1 h, 30%; *b*) TMSOTf, 4Å MS, CH_2Cl_2, –20 °C, 1.5 h; *c*) TMSOTf, 4Å MS, CH_2Cl_2, 20 °C, 8–12 h, 35% (based on **7**); *d*) O_2, AcOH, 100 °C, 2 h, 90%; *e*) under investigation.

The structures of the indigoglycosides were investigated by NMR spectroscopy. For example, it has been confirmed that **9** again exists as an *N*-glycoside containing an α-rhamnose moiety. The NMR signals of **4**, **5**, and **9** were assigned by DEPT and two-dimensional ^{1}H,^{1}H-COSY, ^{1}H,^{1}H-NOESY and ^{1}H,^{13}C correlation spectra (HSQC, HMBC) recorded with a Bruker Avance 500 spectrometer. For example, in the HMBC spectrum of **9** cross peaks were found for C-14a with H-11,13,CH_2; C-7a with H-4,6,15; C-10a with H-12; C-3a with H-5. In the NOESY spectrum cross peaks were found for H-20 with H-15,18,19; H-14 with H-13,CH_2(b); and H-7 with H-16. The NMR results confirm the suggested structure given in Figure 2. Interestingly, the rhamnose possesses a $^4C_1$ conformation which is supported by $^3J_{15,16}$ = 9.8 Hz, $^3J_{18,19}$ = <1.0 Hz, and by an NOE between H-15 and H-20.

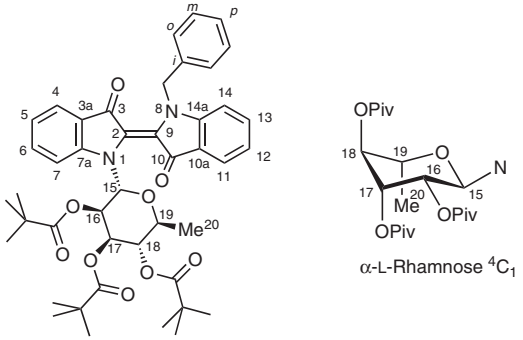


Figure 2 Structure elucidation of *N*-indigoglycoside **9**

In conclusion, we have reported the first and surprisingly simple synthesis of *N*-indigoglycosides. Our approach relies on, firstly, the glycosylation of *N*-benzylindigo with tri-*O*-pivaloyl-α-L-rhamnosyl trichloroacetimidate and, secondly, on the unprecedented rearrangement of the *O*- into the desired *N*-glycoside; this rearrangement possesses considerable synthetic value. We believe that the strategy outlined herein will be applicable to the synthesis of a wide range of pharmacologically relevant *N*-indigoglycosides including akashine A, B and C. These studies are currently in progress in our laboratory.

The ^{1}H NMR (500.13 MHz) and ^{13}C NMR (125.8 MHz) spectra were recorded on a Bruker A 500 spectrometer in C_6D_6 as solvent. Calibration of spectra was carried out on the solvent signals (C_6D_6: ^{1}H NMR, δ = 7.15; ^{13}C NMR, δ = 128.0).

Di-*O*-pivaloylleukoindigo (2)

Under an inert gas, indigo (**1**; 1 g, 3.81 mmol) was suspended in aq NaOH solution (10 mL) containing NaOH (1.52 g, 38.1 mmol). To the solution was added $Na_2S_2O_4$ (1.00 g, 5.74 mmol) and the mixture was stirred at 40–50 °C until all indigo had been dissolved (15–20 min). Subsequently, the mixture was cooled to –10 °C and pivaloyl chloride (1.5 mL, 12.2 mmol) was added in small portions. After the addition of each portion, the mixture was allowed to warm to 0 °C; and before adding the next portion the solution was cooled to

–10 °C. The addition was stopped when a sample of the mixture did not change its colour to blue on exposure to air. H_2O was added to the solution to give a precipitate; the latter was collected by filtration, washed with H_2O and MeOH and crystallized from a mixture of THF and MeOH to give **2** as a colorless solid; yield: 740 mg (45%).

Reaction of Di-*O*-pivaloylleukoindigo (2) with Tri-*O*-acetyl-D-glucal (3)

Under argon, compound **2** (200 mg, 0.462 mmol) was suspended in anhyd CH_2Cl_2 (2 mL), containing 4Å molecular sieves (100 mg). Subsequently, glucal **3** (123 mg, 0.452 mmol) was added and the mixture was cooled to –10 °C. After addition of $BF_3{\cdot}OEt_2$ (30 µL, 0.239 mmol), the mixture was allowed to warm to 20 °C and was stirred for 8 h. To the solution was added a sat. aq solution of $NaHCO_3$ (5 mL). The aqueous and the organic layer were separated and the latter was washed with H_2O (5 mL) and brine (5 mL). The organic layer was dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The products **4** and **5** were isolated by repeated column chromatography (silica gel, *n*-heptane–EtOAc, 4:1) as colorless and yellow oils, respectively.

Leukoindigo-*N*-glycoside (4)

For the numbering of atoms in **4**, see Figure 3.

^{1}H NMR (500.13 MHz, C_6D_6): δ = 9.47 (br s, 1 H, NH), 7.87 (m, 1 H, H-7), 7.79 (d, 1 H, $^3J_{13,14}$ = 8.2 Hz, H-14), 7.70 (d, 1 H, $^3J_{11,12}$ = 8.0 Hz, H-11), 7.61 (m, 1 H, H-4), 7.26 (ddd, 1 H, $^3J_{13,14}$ = 8.2 Hz, $^3J_{12,13}$ = 7.2 Hz, $^4J_{11,13}$ = 1.2 Hz, H-13), 7.18 (ddd, 1 H, $^3J_{11,12}$ = 8.0 Hz, $^3J_{12,13}$ = 7.2 Hz, $^4J_{12,14}$ = 1.0 Hz, H-12), 7.13–7.08 (m, 2 H, H-5,6), 5.97 ('q', 1 H, $^3J_{15,16}$ = 2.5 Hz, $^4J_{15,17}$ = $^5J_{15,18}$ = 2.0 Hz, H-15), 5.70 (dt, 1 H, $^3J_{16,17}$ = 10.2 Hz, $^4J_{15,17}$ = $^3J_{17,18}$ = 2.0 Hz, H-17), 5.60 (ddd, 1 H, $^3J_{16,17}$ = 10.2 Hz, $^3J_{15,16}$ = 2.5 Hz, $^4J_{16,18}$ = 2.0 Hz, H-16), 5.35 (d'q', 1 H, $^3J_{18,19}$ = 8.8 Hz, $^3J_{17,18}$ = $^4J_{16,18}$ = $^5J_{15,18}$ = 2.0 Hz, H-18), 4.21 (dd, 1 H, ^2J = 12.5 Hz, $^3J_{19,20b}$ = 2.5 Hz, H-20b), 3.88 (ddd, 1 H, $^3J_{18,19}$ = 8.8 Hz, $^3J_{19,20a}$ = 3.8 Hz, $^3J_{19,20b}$ = 2.5 Hz, H-19), 3.61 (dd, 1 H, ^2J = 12.5 Hz, $^3J_{19,20a}$ = 3.8 Hz, H-20a), 1.59 (s, 3 H, $OCOCH_3$), 1.64 (s, 3 H, $OCOCH_3$), 1.39 [s, 9 H, $OCOC(CH_3)_3$], 1.24 [s, 9 H, $OCOC(CH_3)_3$].

^{13}C NMR (125.8 MHz, C_6D_6): δ = 176.6 (C=O, Piv), 176.1 (C=O, Piv), 171.3 (C=O, Ac), 169.4 (C=O, Ac), 136.3 (C-7a), 135.6 (C-14a), 131.7 (C-10), 131.0 (C-3), 130.2 (C-17), 127.8 (C-16), 123.9 (C-13), 123.7 (C-6), 122.9 (C-2), 121.35 and 121.28 (C-3a and C-10a), 121.0 (C-5), 120.5 (C-12), 118.5 (C-4), 117.9 (C-11), 115.7 (C-9), 113.0 (C-7), 112.9 (C-14), 78.5 (C-15), 71.1 (C-19), 64.8 (C-18), 61.2 (C-20), 39.3 [$OCOC(CH_3)_3$], 39.2 [$OCOC(CH_3)_3$], 27.4 [$OCOC(CH_3)_3$], 27.2 [$OCOC(CH_3)_3$] 20.4 ($OCOCH_3$), 20.3 ($OCOCH_3$).

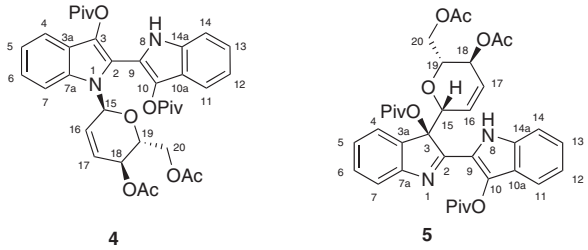


Figure 3

Leukoindigo-*C*-glycoside (5)

For the numbering of atoms in **5**, see Figure 3.

^{1}H NMR (500.13 MHz, C_6D_6): δ = 10.11 (br s, 1 H, NH), 7.80 (d, 1 H, $^3J_{13,14}$ = 8.2 Hz, H-14), 7.68 (d, 1 H, $^3J_{11,12}$ = 8.2 Hz, H-11), 7.55 (d, 1 H, $^3J_{6,7}$ = 7.5 Hz, H-7), 7.31 (br d, 1 H, $^3J_{4,5}$ = 7.5 Hz, H-4), 7.24 (ddd, 1 H, $^3J_{13,14}$ = 8.2 Hz, $^3J_{12,13}$ = 7.0 Hz, $^4J_{11,13}$ = 1.2 Hz, H-13), 7.14 (d't', 1 H, $^3J_{5,6}$ = $^3J_{6,7}$ = 7.5 Hz, $^4J_{4,6}$ = 1.2 Hz, H-6), 7.07 (ddd, 1 H, $^3J_{11,12}$ = 8.2 Hz, $^3J_{12,13}$ = 7.0 Hz, $^4J_{12,14}$ = 1.0 Hz, H-12), 6.95 (d't', 1 H, $^3J_{4,5}$ = $^3J_{5,6}$ = 7.5 Hz, $^4J_{5,7}$ = 1.2 Hz, H-5), 5.33 (dt, 1 H, $^3J_{16,17}$ = 10.5 Hz, $^4J_{15,17}$ = $^3J_{17,18}$ = 2.2 Hz, H-17), 5.04 ('q', 1 H, $^3J_{15,16}$ = 2.8 Hz, $^4J_{15,17}$ = 2.2 Hz, $^5J_{15,18}$ = 1.8 Hz, H-15), 4.81–4.37 (m, 2 H, H-16,18), 4.71 (dd, 1 H, ^2J = 12.5 Hz, $^3J_{19,20b}$ = 8.2 Hz, H-20b), 3.73 (dd, 1 H, ^2J = 12.5 Hz, $^3J_{19,20a}$ = 2.0 Hz, H-20a), 3.63 (ddd, 1 H, $^3J_{18,19}$ = 9.0 Hz, $^3J_{19,20b}$ = 8.2 Hz, $^3J_{19,20a}$ = 2.0 Hz, H-19), 1.79 (s, 3 H, $OCOCH_3$), 1.54 [s, 9 H, $OCOC(CH_3)_3$] 1.39 (s, 3 H, $OCOCH_3$), 1.01 [s, 9 H, $OCOC(CH_3)_3$].

^{13}C NMR (125.8 MHz, C_6D_6): δ = 175.4 (C=O, Piv), 175.3 (C=O, Piv), 170.7 (C=O, Ac), 168.9 (C=O, Ac), 167.9 (C-2), 156.8 (C-7a), 135.7 (C-14a), 134.2 and 134.0 (C-3a and C-10), 131.1 (C-6), 129.5 (C-17), 126.1 (C-5), 125.5 (C-16), 125.0 (C-13), 122.8 (C-4), 122.3 (C-10a), 121.5 (C-7), 120.9 (C-12), 120.7 (C-9), 119.2 (C-11), 112.9 (C-14), 92.1 (C-3), 76.6 (C-15, C-19), 64.7 (C-18), 63.1 (C-20), 39.4 [$OCOC(CH_3)_3$], 39.1 [$OCOC(CH_3)_3$], 27.8 [$OCOC(CH_3)_3$], 27.0 [$OCOC(CH_3)_3$], 20.7 ($OCOCH_3$), 20.1 ($OCOCH_3$).

Indigo-*N*-glycoside 9

N-Benzylindigo (**6**; 100 mg, 0.284 mmol) and 2,3,4-tri-*O*-pivaloyl-L-rhamnopyranosyl trichloroacetimidate (**7**; 155 mg, 0.276 mmol) were dissolved in anhyd CH_2Cl_2 (2 mL), containing molecular sieves (4 Å, 200 mg), under argon. The mixture was cooled to –20 °C and TMSOTf (20 µL, 0.111 mmol) was added. After stirring for a short time, a red-violet spot was detected by TLC indicating the formation of **8**. After stirring for 1.5 h, the mixture was warmed to 20 °C and stirred for 8–12 h. During this time the red-violet spot vanished while the intensity of a blue spot due to **6** increased and a new, more polar green spot of **9** appeared. To the solution was added a sat. aq solution of $NaHCO_3$ (5 mL). The aqueous and the organic layer were separated and the latter was washed with H_2O (5 mL) and brine (5 mL). The organic layer was dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-heptane–EtOAc, 4:1) to give **9** as a deep green solid; yield: 73 mg (35%).

^{1}H NMR (500.13 MHz, C_6D_6): δ = 8.05 (d, 1 H, $^3J_{6,7}$ = 8.2 Hz, H-7), 7.72 (d, 1 H, $^3J_{4,5}$ = 7.5 Hz, H-4), 7.70 (d, 1 H, $^3J_{11,12}$ = 7.5 Hz, H-11), 7.22 ('t', 1 H, $^3J_{6,7}$ = 8.2 Hz, $^3J_{5,6}$ = 7.5 Hz, H-6), 7.05–6.94 (m, 5 H, C_6H_5), 6.77 ('t', 1 H, $^3J_{13,14}$ = 8.2 Hz, $^3J_{12,13}$ = 7.5 Hz, H-13), 6.70 ('t', 1 H, $^3J_{4,5}$ = $^3J_{5,6}$ = 7.5 Hz, H-5), 6.51 ('t', 1 H, $^3J_{11,12}$ = $^3J_{12,13}$ = 7.5 Hz, H-12), 6.38 (d, 1 H, $^3J_{13,14}$ = 8.2 Hz, H-14), 6.41 (d, 1 H, $^3J_{15,16}$ = 9.8 Hz, H-15), 6.15 (dd, 1 H, $^3J_{15,16}$ = 9.8 Hz, $^3J_{16,17}$ = 3.2 Hz, H-16), 5.90 ('t', 1 H, $^3J_{17,18}$ = 3.8 Hz, $^3J_{16,17}$ = 3.2 Hz, H-17), 5.57 [d, 1 H, ^2J = 7.5 Hz, CH_2(a)], 5.47 [d, 1 H, ^2J = 7.5 Hz, CH_2(b)], 5.02 (d, 1 H, $^3J_{17,18}$ = 3.8 Hz, H-18), 4.50 (q, 1 H, $^3J_{19,20}$ = 7.5 Hz, H-19), 1.90 (d, 3 H, $^3J_{19,20}$ = 7.5 Hz, H-20), 1.25 [s, 9 H, $OCOC(CH_3)_3$], 0.98 [s, 9 H, $OCOC(CH_3)_3$], 0.73 [s, 9 H, $OCOC(CH_3)_3$].

^{13}C NMR (125.8 MHz, C_6D_6): δ = 185.5 and 185.1 (C-3 and C-10), 176.5, 176.3, 176.0 (3 C=O, Piv), 152.7 (C-14a), 150.8 (C-7a), 137.6 (C_i, Ph), 135.0 (C-13), 134.7 (C-6), 128.8 (CH_m, Ph), 128.4 and 125.2 (C-2 and C-9), 127.2 (CH_p, Ph), 126.7 (CH_o, Ph), 124.24 and 124.17 (C-4 and C-11), 123.9 (C-3a), 122.7 (C-5), 122.1 (C-10a), 121.4 (C-12), 116.5 (C-7), 112.8 (C-14), 82.4 (C-15), 74.6 (C-19), 72.3 (C-18), 69.1 (C-17), 66.6 (C-16), 54.0 (CH_2), 38.9, 38.7, 38.5 [3 $OCOC(CH_3)_3$] 27.1, 27.0, 26.9 [3 $OCOC(CH_3)_3$], 16.4 (C-20).

MS (CI, isobutene): *m*/*z* = 750 (M^-, 100).

HRMS (ESI): *m*/*z* calcd for $C_{44}H_{51}N_2O_9$ ([M + H]$^+$): 751.35946; found: 751.35893.

Acknowledgment

This work was supported by the state of Mecklenburg-Vorpommern (Landesforschungsschwerpunkt 'Neue Wirkstoffe und Screening-verfahren').

References

(1) Review: Gribble, G.; Berthel, S. *Studies in Natural Products Chemistry*, Vol. 12; Elsevier Science Publishers: New York, **1993**, 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 of staurosporin (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) (a) Xia, Z.; Zenk, M. H. *Phytochemistry* **1992**, *31*, 2695. (b) Schweppe, H. *Handbuch der Naturfarben*; Ecomed: Landsberg/Lech, **1993**, 282–318.
(5) (a) Miles, P. G.; Lund, H.; Raper, J. R. *Arch. Biochem. Biophys.* **1956**, *62*, 1. (b) Hosoe, T.; Nozawa, K.; Kawahara, N.; Fukushima, K.; Nishimura, K.; Miyaji, M.; Kawai, K. *Mycopathologia* **1999**, *146*, 9. (c) Falanghe, H.; Bobbio, P. A. *Arch. Biochem. Biophys.* **1962**, *96*, 430. (d) Laatsch, H.; Ludwig-Köhn, H. *Liebigs Ann. Chem.* **1986**, 1847.
(6) (a) Friedländer, P. *Justus Liebigs Ann. Chem.* **1906**, *351*, 390. (b) Higa, T.; Scheuer, P. J. *Heterocycles* **1976**, *4*, 227.
(7) Maskey, R. P.; Grün-Wollny, I.; Fiebig, H. H.; Laatsch, H. *Angew. Chem. Int. Ed.* **2002**, *41*, 597; *Angew. Chem.* **2002**, *114*, 623.
(8) (a) Chisholm, J. D.; Van Vranken, D. L. *J. Org. Chem.* **1995**, *60*, 6672. (b) Gilbert, E. J.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 5500.
(9) Meng, J.-B.; Li, P.; He, Y.-Z.; Xu, L.-L.; Wang, Y.-M. *Gaodeng Xuexiao Huaxue Xuebao* **2001**, *22*, 63; *Chem. Abstr.* **2002**, *137*, 179362.
(10) Li, B.; Yu, B.; Hui, Y.; Li, M.; Han, X.; Fung, K.-P. *Carbohydr. Res.* **2001**, *331*, 1.
(11) Pummerer, R.; Meininger, F. *Liebigs Ann. Chem.* **1954**, *590*, 173.