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Indolocarbazoles. 4. Synthetic Studies Towards Staurosporine and Tjipanazoles: Reactions of Indolocarbazole with Glycals.

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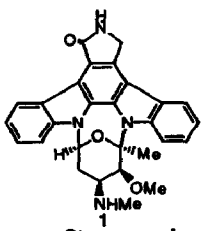
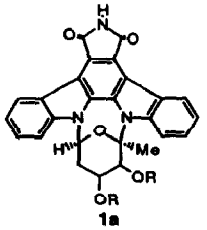
Abstract: In an attempt to construct the unique N,N'-bidentate glycosyl linkage found in the Staurosporine **1** class of natural products, the first example of an acid catalyzed 2,6-condensation of an activated pyran with indolocarbazole **4** is reported. In pursuit of the real system, a variety of glycals were reacted with indolocarbazole **4**. Formation of novel unexpected products (**B/C**) with 1,3-connections along with the expected product (**A**) and its' synthetic transformation to a potentially useful intermediate **24** are detailed.

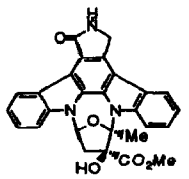
The Indolocarbazole natural products possess interesting biological activity and are the subject of a recent review article.[1] Noteworthy examples include the kinase inhibitors Staurosporine **1** and K252a **2**, and the antifungal Tjipanazoles **3**. As a part of our ongoing involvement[2] with synthesizing analogs of these natural products as anti-tumor agents[3] we wished to develop a general synthesis of pyranosylated indolocarbazoles especially with the two glycosyl bonds typical of **1**. After having failed to effect ring expansion on a synthetic K252a analog,[4] we were attracted to the potential of glycals as an entry into pyranosylated indolocarbazoles.



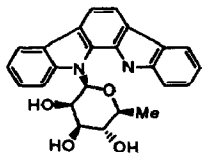
1
Staurosporine



1a
Analogs



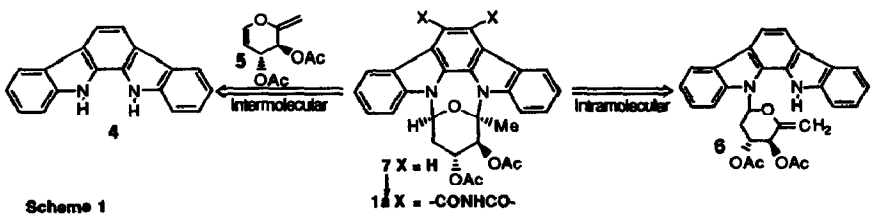
2
K 252a



3
Tjipanazole G-2

Several routes to the aglycones are known,[5] but the synthesis of the complete skeleton of staurosporine was only achieved very recently by Danishefsky et. al.[6] For our own studies, we chose to exploit the increased nucleophilicity of the parent heterocycle **4**, since we had established an efficient protocol for subsequently installing the crucial imide/lactam system (**7** -> **1a**).[2] Herein, we report the reactions of **4** with unsaturated sugars.

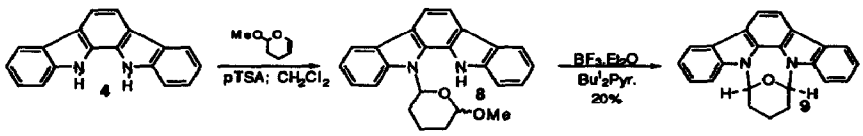
Reterosynthetically, the two related routes shown in Scheme 1 seemed attractive.



Scheme 1

Our initial exploration of the " intramolecular" route is shown in Scheme 2. The first glycosidic bond formed efficiently, providing **8** as an anomeric mixture. The clear equatorial preference for the heterocycle, evident from PMR, was reflected in the reluctance of the final closure. Under the indicated conditions, we were able to obtain a modest yield of **9**, the parent system of staurosporine.

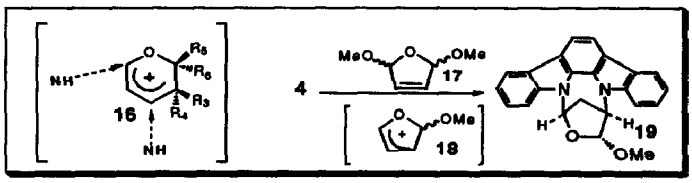
Scheme 2: Synthesis of staurosporine parent system.



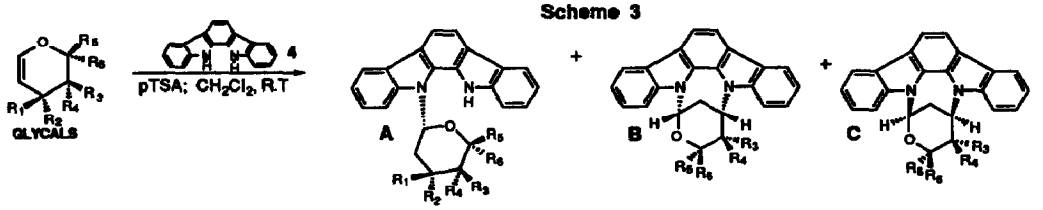
Recognizing that the glycal derived intermediates might be more stable, we proceeded to carry out our proposed intermolecular bis glycosidation. Bis enol ether **5** was synthesized in an efficient manner from tri-O-acetyl-D-glucal using a combination of literature procedures.[7,8] Remarkably bis enol diacetate **5** was very stable and was resistant to a number of glycosidation attempts with indolocarbazole under different lewis acid conditions.

We next turned our attention to the intramolecular strategy. The plan was to glycosidate indolocarbazole with tri-O-acetyl-D-glucal **10** and then unveil the second enol bond from the acetoxy methyl group of **10A** for electrophilic exo cyclization. Glycals normally react with nucleophiles to give either 2-deoxy glycosides by addition to the vinyl ether bond, or 2,3-dideoxy-hex-2-enopyranosides via the Ferrier rearrangement.[9] However, when indolocarbazole reacted with tri-O-acetyl-D-glucal in the presence of protic acid (PTSA) in methylene chloride at room temperature, the expected product was formed only in trace amounts. The major products were cyclic diasteroisomers **10B** and **10C**. Such anomalous C-3 substitutions on glycal systems are observed[10] only under high temperature conditions which promote sigmatropic or allylic rearrangement and such factors could not be invoked here. This prompted us to further elaborate this observation by treating indolocarbazole with other glycals[11] and the results are summarized in Scheme 3. The overall yields are unoptimised and are modest due to the capricious dimerization of these glycals[12] under the reaction conditions. Improvement was observed when the glycal was added by syringe pump over an extended period as a solution. The product distribution between the simple desired glycosidated product (**A**) and the unusual diasteroisomeric products (**B** + **C**)[13] is reversed in the case of arabinal and galactal acetates (entry **13** and **14**). A tentative explanation of our results could be a possible involvement of an allylic carbonium intermediate **16**[14] whose formation is inhibited by the cis orientation of the acetates at C-3 and C-4.

Similar observations were made when indolocarbazole reacted with 2,5-dimethoxy dihydrofuran **17**. The main product obtained was **19** via an analogus allylic carbonium intermediate **18**. The assignment of the products was derived unambiguously from the characteristic coupling constants and verified by the upfield shift of the acetate methyls syn to the indolocarbazole ring, due to anisotropy.[15]

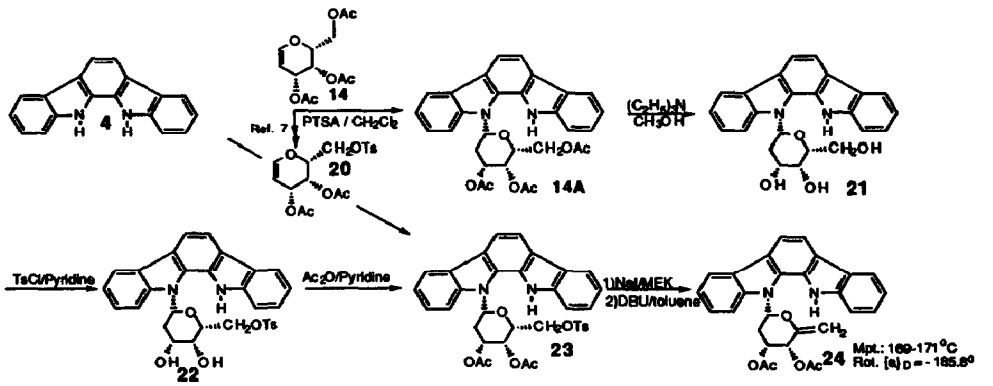


Scheme 3



# Glycal	R1	R2	R3	R4	R5	R6	A	B	C
10.Tri-O-acetyl-D-Glucal.	H	OAc	OAc	H	H	CH_2OAc	Yield: Trace amounts.	Yield:20% Rot.$[\alpha]_D$-73.4°	Yield:40% Rot$[\alpha]_D$+85.5°
11.3,4-di-O-Ac-6-deoxy L-Glucal.	OAc	H	H	OAc	CH_3	H	Yield:10%	Yield:15% Rot$[\alpha]_D$-97.6°	Yield: 7% Rot$[\alpha]_D$+73.6°
12.3-O-Ac- 4, 6-deoxy-(+,-)-Glucal.	OAc	H	H	H	CH_3	H			Yield: 15%
13.3,4-di-O-acetyl-D-Arabinal.	H	OAc	H	OAc	H	H	Yield: 30% Rot$[\alpha]_D$+154.2	Yield: 10%	Yield: 5%
14.Tri-O-Ac-D-Galactal.	H	OAc	H	OAc	H	CH_2OAc	Yield: 40% Rot.$[\alpha]_D$-95.3°	Yield: 7%	Yield: 4%

These observations restored our original plan of transforming an intermediate like **14A** to the exocyclic enol **24**. This was accomplished in five simple steps via **23**. **23** can also be obtained alternatively from readily accessible **20**.[7] Intermediate **21** can be viewed as an analog of *Tjipanazole* . Unfortunately all attempts to induce the desired electrophilic exo cyclization on **24** even with mild protic acids have resulted in fragmentation of the sugar portion, giving back the indolocarbazole **4**. Danishefsky et. al.[6] experienced similar frustration in their handling of analogus enolic intermediate. They had to resort to nucleophilic iodo cyclization followed by reduction, to realize a compound like **7**, in modest yield. Related considerations have forced us to seek alternatives and such refinements leading to the total synthesis of staurosporine are currently in progress and will be the subject of future publication.



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11. **3** was prepared by Lit. procedure: Danishefsky, S.; Kerwin, J. F. *J. Org. Chem.* **1982**, *47*, 1597. Other glycals are comercially available.
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13. Diasteroisomeric ratio (**B/C**) is affected by the acetoxy group at C-4 of the glycal; anti attack by the indolocarbazole N at C-3 is favored.
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15. All new compounds were characterized by ^{1}H-NMR,^{13}C-NMR, MS, and combustion analysis and/or high resolution MS. The chemical shifts of acetate methyl which are syn to the indolocarbazole appear at a higher field due to aniosotropy and they are highlighted where appropriate. **Selected Spectroscopic Data**: **5**:^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.06 (s, 3H), 2.09 (s, 3H), 4.68 (d, J = 1.5 Hz, 1H), 4.93 (d, J = 1.6 Hz, 1H), 5.11 (m, 2H), 5.42 (dd, J = 2.3, 2.6 Hz, 1H), 6.57 (dd, J = 5.2, 2.0 Hz, 1H). **9**:m.pt=224-227°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.66 (m, 2H), 2.2-2.5 (m, 4H), 6.69 (d, J = 3.8 Hz, 2H), 7.3-7.5 (m, 6H), 7.92 (s, 2H), 8.19 (d, J = 7.8 Hz, 2H). **10B**: m.pt.=135-137°C; Rot.$[\alpha]_D$ -73.4° (c=0.134, MeOH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.74 (s, 3H), **2.05** (s, 3H), 2.98 (ddd, J = 15.08, 2.3, 1.0 Hz, 1H), 3.3 (ddd, J = 15.08, 5.95, 5.95 Hz, 1H), 3.8 (dd, J = 12.5, 2.18 Hz, 1H), 4.05 (ddd, J = 10.67, 3.17, 2.18 Hz, 1H), 4.3 (dd, J = 12.5, 3.17, 1H), 5.46 (dd, J = 10.67, 4.46 Hz, 1H), 5.58 (ddd, J = 5.95, 4.46, 2.3 Hz, 1H), 6.6 (d, J = 5.95 Hz, 1H), 7.3-8.2 (m, 10H). **10C**: m.pt.=220-222°C; Rot.$[\alpha]_D$ + 85.5° (c=0.55, MeOH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ **1.58** (s, 3H), 2.3 (s, 3H), 2.9 (appt. d, J = 15.3 Hz, 1H), 3.37 (ddd, J = 15.26, 6.16, 6.16 Hz, 1H), 3.59 (dd, J = 11.88, 6.88 Hz, 1H), 3.65 (dd, J = 11.88, 6.88 Hz, 1H), 4.25 (ddd, J = 6.88, 6.88, 3.05), 5.14 (m, 1H), 5.27 (m, 1H), 6.58 (d, J = 6.16 Hz, 1H), 7.3-8.2 (m, 10H). **11B**: m.pt.=256-258°C; Rot.$[\alpha]_D$ -97.6° (c=0.125,$CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ **0.8** (d, J = 7.5 Hz, 1H), 2.28 (s, 3H), 2.87 (br. d, J = 15.3 Hz, 1H), 3.36 (ddd, J = 15.3, 6.1, 6.1 Hz, 1H), 4.18 (m, 1H), 5.13 (m, 2H), 6.58 (d, J = 6.1 Hz, 1H), 7.3-8.2 (m, 10H). **11C**: m.pt.= 278-280°C; Rot.$[\alpha]_D$ +73.6° (c=0.14,$CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.2 (d, J = 6.1 Hz, 3H), **1.76** (s, 3H), 2.96 (ddd, J = 15.06, 5.93, 1.22 Hz, 1H), 3.26 (ddd, J = 15.06, 5.93, 5.93 Hz, 1H), 3.96 (m, 1H), 5.14 (dd, J = 10.3, 4.35 Hz, 1H), 5.52 (ddd, J = 10.3, 5.93, 1.22 Hz, 1H), 6.52 (d, J = 5.93, 1H), 7.2-8.2 (m, 10H). **13A**: m.pt.=151-153°C; Rot.$[\alpha]_D$ +154.2° (c=0.184,$CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.88 (m, 1H), 1.91 (s, 3H), 2.36 (s, 3H), 2.56 (ddd, J = 11.8, 11.8, 10.8 Hz, 1H), 4.23 (appt. d, J = 13.1 Hz, 1H), 4.66 (appt. d, J = 13.1 Hz, 1H), 5.35 (appt. dd, J = 11.8, 4.0 Hz, 1H), 5.6 (br. S, 1H), 6.02 (dd, J = 10.8, 2.0 Hz, 1H), 7.2-8.2 (m, 10H), 9.8 (s, 1H, NH). **14A**: m.pt.=202-204°C; Rot.$[\alpha]_D$ -95.3° (c=0.286,$CHCl_3$);^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.9 (m, 1H), 1.94 (s, 3H), 2.06 (s, 3H), 2.36 (s, 3H), 2.56 (ddd, J = 12.5, 12.5, 11.29 Hz, 1H),4.42 (dt, J = 6.5, 1.05 Hz, 1H), 4.53 (m, 2H), 5.35 (ddd, J = 12.2, 4.88, 3.05Hz, 1H), 5.64 (d, J = 3.05Hz, 1H), 6.11 (dd, J = 11.29, 2.14 Hz, 1H), 7.2-8.2 (m, 10H), 9.78 (s, 1H, NH). **19**: m.pt: 221-223°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.75 (d, J = 13.8 Hz, 1H), 3.42 (s, 3H), 3.46 (m, 1H), 4.92 (s, 1H), 5.40 (d, J = 6.8 Hz, 1H), 6.94 (d, J = 7.3 Hz, 1H), 7.3-8.2 (m, 10H). **21**: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.9 (m, 1H), 2.5 (m, 1H), 3.7 (m, 2H), 3.93 (br. t, J = 6.2 Hz, 1H), 4.04 (br. s, 1H), 4.14 (br. m, 1H), 4.83 (t, J = 5.6 Hz, 1H, D_2O exch.), 5.18 (d, J = 5.25, 1H, D_2O exch.), 6.44 (dd, J = 11.3, 2.8 Hz, 1H), 6.53 (d, J = 3.05 Hz, 1H, D_2O exch.),7.2-8.2 (m, 10H), 11.56 (s, 1H, NH, D_2O exch.). **24**: m.pt.=169-171°C; Rot.$[\alpha]_D$ -185.8° (c=0.12,$CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.94 (s, 3H), 1.97 (m, 1H), 2.32 (s, 3H), 2.76 (ddd, J = 11.36, 11.3, 10.84 Hz, 1H), 5.14 (d, J = 1.4 Hz, 1H), 5.27 (br. S, 1H), 5.37 (ddd, J = 10.84, 4.66, 3.12), 6.01 (d, J = 3.12 Hz, 1H), 6.2 (dd, J = 11.36, 2.36 Hz), 7.2-8.2 (m, 10H), 9.45 (s, 1H, NH).

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