Control of Dissymmetry in the Synthesis of (+)-Tjipanazole F2

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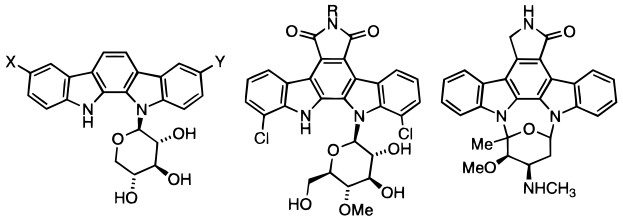
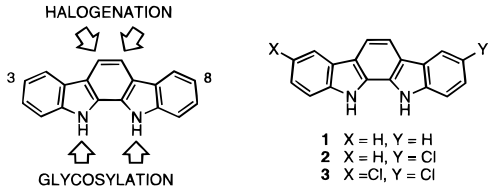
Indolo[2,3-a]carbazole glycosides with two aminal linkages (such as staurosporine and K252a) have been shown to be potent inhibitors of protein kinases.[1] In contrast, indolo[2,3-a]carbazole glycosides with only one glycosidic linkage are generally not potent inhibitors of protein kinases, but the recent finding that these antitumor antiobiotics (e.g., BMS 181176) can bind to DNA has led to renewed interest for this subclass of natural products.[2] Since sugars are often important determinants of DNA−drug binding interactions, an efficient synthetic strategy for the synthesis of indolo[2,3-a]carbazole glycosides with only one glycosidic bond would be valuable.[3−6] The groups of Clardy and Danishefsky have developed benchmark strategies for the synthesis of rebeccamycin[7,8] and staurosporine,[9] while



Wood has developed a decisive synthesis of K252a.[10−12] Here we present a complementary strategy for the synthesis of indolo-[2,3-a]carbazole glycosides which allows the introduction of halide and glycosidic substituents to a heterocyclic core without the use of protecting groups and with complete control of dissymmetry. This synthesis should be amenable to significant variation in the carbohydrate moiety since glycosylation of 2,2′-indolylindolines with unprotected sugars is a general reaction.[13]

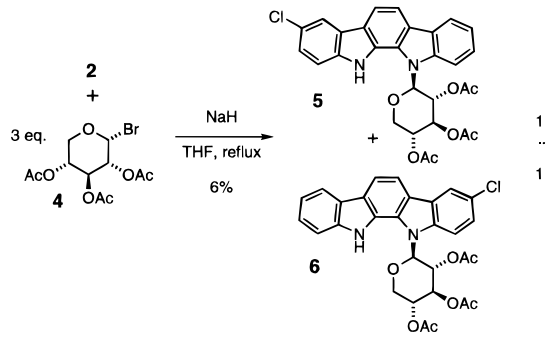
Many of the indolocarbazole glycosides isolated from *Tolypothrix tjipanasensis* possess both halogen and glycosidic (β-D-glucosyl, β-D-deoxygulosyl, β-L-rhamnosyl, or β-D-xylosyl) substituents on the polyaromatic core. Like staurosporine and K252a, the aglycons of tjipanazoles F1, F2, C1, C2, C3, and C4 are dissymmetric (X or Y = Cl), so the ability to coordinate the regiochemistry of glycosylation with the regiochemistry of halogenation is crucial for an efficient synthetic strategy.[14] In the synthesis of staurosporine, attempts to use the glycosyl substituent to direct the desymmetrization of the polyaromatic ring system have proven difficult.[9] For the synthesis of tjipanazole F1 and F2, regioselective chlorination of an indolo-[2,3-a]carbazole glycoside has little chance for success, since electrophilic reagents have been shown to attack at the central 5,6-ethylene bridge rather than the desired 3 or 8 position of the indolocarbazole.[15,16]

The introduction of the carbohydrate moiety presents three major problems: (i) yield, (ii) control of anomeric stereochemistry, and (iii) control of regioselectivity. Previous syntheses of tjipanazoles with symmetrical indolocarbazoles were accomplished by the glycosylation of the sodium salt of **1** and **3**



with an excess of the appropriately protected gluco-, rhamno-, and xylopyranosyl bromides, respectively.[14] While this process allowed control over the anomeric stereochemistry, the low reported yields (less than 2%) attest to the poor efficiency of indole glycosylation. Protected glycals have been added to **1** under acidic conditions to give 2-deoxyglycosides in yields ranging from 0−40%, but the capricious dimerization of glycals under these conditions is a significant problem.[17]

It may be possible to rely upon differential reactivity of the two indole nitrogens in the glycosylation of unsymmetrical indolo[2,3-a]carbazoles such as tjipanazole I (**2**). This strategy has been used in the synthesis of K252a to afford a 55% yield of the correct regioisomer.[12] Inspired by this success, we attempted the regioselective glycosylation of the monosodium salt of **2** with α-D-xylopyranosyl bromide **4** (eq 1) under kinetic conditions. This reaction gave a 6% yield of **5** and **6** as a



disappointing 1:1 mixture of the triacetates (53% recovered indolocarbazole). Conditions which have been successful in the synthesis of rebeccamycin (2 equiv of Ag_2O, 2 equiv of pyranosyl bromide, reflux) gave a 15% yield of glycosylation

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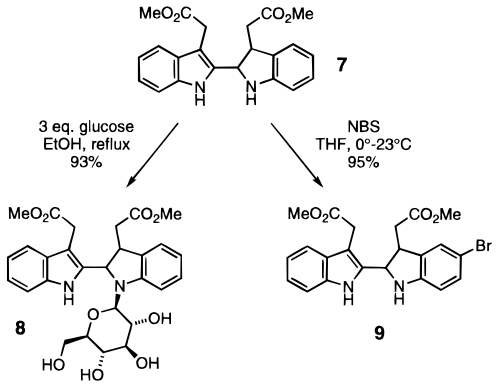
Scheme 1

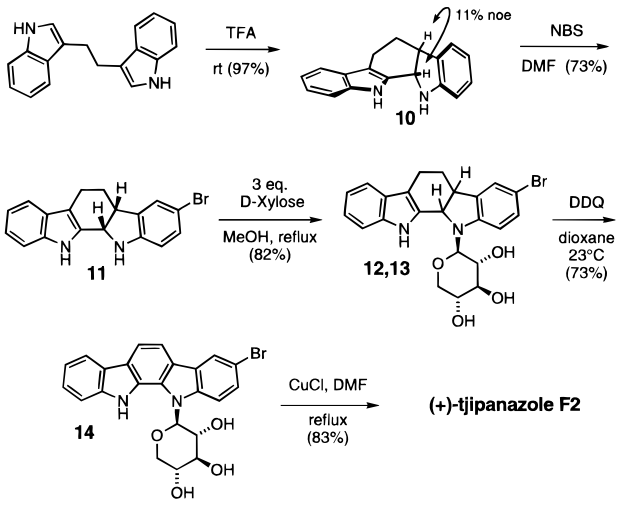


product as a 60:40 mixture of **5** and **6** (33% recovered indolocarbazole).[7] Clearly, a new approach to desymmetrization is needed.

Bergman has shown that intramolecular Mannich dimerization of indoles may be an effective approach for the synthesis of indolo[2,3-a]carbazoles.[18] We have demonstrated that 2,2′-indolylindolines such as **7** can be glycosylated in high yields using unprotected sugars such as D-glucose with complete control of anomeric stereochemistry (Scheme 1).[13] More importantly for the synthesis of the tjipanazoles, bromination of **7** by slow addition of NBS occurred selectively on the indoline ring in 95% yield.[19,20] These two patterns of reactivity set the stage for an efficient dissymmetric synthesis of indolo-[2,3-a]carbazole glycosides such as (+)-tjipanazole F2.

The synthesis of (+)-tjipanazole F2 is shown in Scheme 2. 1,2-Bis(3-indolyl)ethane was prepared in three steps from indole and oxalyl chloride.[21] Mannich cyclization in TFA afforded racemic **10** as a single diastereomer in 97% yield.[18,22] The stereochemistry of the ring fusion was determined to be cis on the basis of the 11% NOE between the hydrogens at the newly created stereogenic centers. All attempts to directly chlorinate **10** led to mixtures of **1** and starting material. In contrast, bromination proceeded in 73% yield to give **11** as the only bromination product. The racemic indoline **11** was glycosylated with 3 equiv of D-xylopyranose in methanol at reflux to afford **12** and **13** as a 1:1 mixture of diastereomers. The glycosylation

Scheme 2



is completely regioselective; only the indoline nitrogen was glycosylated. Interestingly, use of either anhydrous THF or anhydrous methanol in the glycosylation reaction led to unidentifiable products. The mixture of **12** and **13** was convergently oxidized with 2 equiv of DDQ to afford **14** in 60% yield for the two steps. The $J_{1,2}$ coupling constant of 8.8 Hz confirms that the anomeric configuration is β in **14**. Halogen exchange was effected with cuprous chloride to afford (+)-tjipanazole F2 ($[\alpha]_D = +20.3$) in 83% yield. This synthetic strategy is noteworthy for its brevity and lack of protecting groups.

In conclusion, we have completed the first synthesis of a dissymetric tjipanazole ((+)-tjipanazole F2) in five steps from 1,2-bis(3-indolyl)ethane. This synthesis allows the complete control of regiochemistry and anomeric stereochemistry without the use of protecting groups. The ease of variation in the carbohydrate partner also allows ready access to analogs for the study of conformational properties and DNA−indolocarbazole glycoside interactions; such studies are now in progress.

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Supporting Information Available: Experimental procedures and characterization data (5 pages). Ordering information is given on any current masthead page.

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