Glycosylation of 2,2′-Indolylindolines

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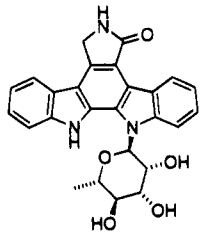
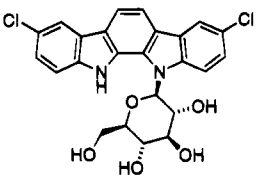
The indolo[2,3-*a*]carbazole glycosides are an important class of natural products which includes staurosporine, K-252d, and the tjipanazoles.[1] The sequence of dimerization/oxidation of 3-substituted indoles has been known since 1960 and was recently demonstrated as an approach to indolo[2,3-*a*]carbazole aglycons.[2,3] Prompted by this report, we now describe work on the glycosylation and oxidation of 2,2′-indolylindolines.



K-252d

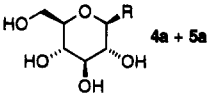
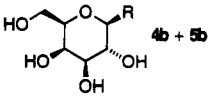
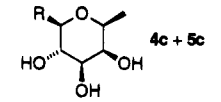
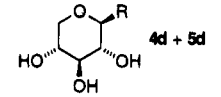
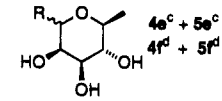


Tjipanazole E

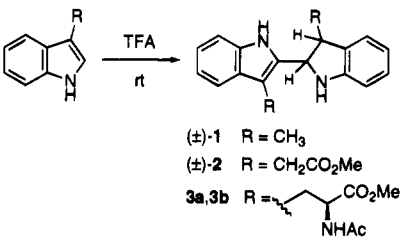
Many of the recent synthetic approaches toward the indolo[2,3-*a*]carbazole glycosides separately address the syntheses of the sugar and heterocyclic portions, leaving the glycosylation as the consummate step.[4] This strategy suffers from the lack of reactivity associated with indole nitrogens. Indolines, in contrast, are readily glycosylated, and so a strategy involving 2,2′-indolylindoline intermediates offers a dual solution to the problems of glycosylation and desymmetrization. Indolines can serve as glycosylation partners with simple, unprotected sugars.[5] We hoped to utilize this chemistry in a regioselective monoglycosylation of racemic 2,2′-indolylindolines.

The indolylindoline substrates were prepared by stirring the corresponding 3-substituted indoles in trifluoroacetic acid at room temperature.[6] Skatole dimer (±)-**1** is obtained in only 23% yield under these conditions due to the competitive formation of a trimeric product; however, indole-3-acetic acid methyl ester afforded racemic 2,2′-indolylindoline **2** as a single stereoisomer in 91% yield (eq 1). The stereochemistry of the substituents is assigned as trans based on mechanistic considerations.[7]

Table 1. Glycosylation of (±)-2

Entry	Sugar	Additive	Yield	Products
1	D-Glucose	b	93	 **4a + 5a**
2	D-Galactose	b	68	 **4b + 5b**
3	L-Fucose	a	95	 **4c + 5c**
4	D-Xylose	a	85	 **4d + 5d**
5	D-Ribose	b	-	complex mixture
6	L-Rhamnose	b	72	 **4e**[c] **+ 5e**[c] **4f**[d] **+ 5f**[d]

[a] No additive. [b] Three equiv of $(NH_4)_2SO_4$ added. [c] α anomers. [d] β anomers.



(1)

(±)-**1** R = CH_3

(±)-**2** R = CH_2CO_2Me

3a,3b R =

Attempts to glycosylate racemic **1** using 3,4,6-tri-*O*-acetyl-D-glucal and α-D-glucose pentaacetate under conditions of acid catalysis failed; however, reaction of (±)-**2** with 3 equiv of D-glucose in refluxing ethanol (42 h) afforded the glycosylated products **4a** and **5a** in a 1:1 ratio in 88% yield. Encouraged by the good results with D-glucose, we applied these conditions to other unprotected sugars. The results are summmarized in Table 1. The addition of ammonium sulfate was found to accelerate the reaction and, in some cases, to provide minor increases in yields (Table 1, entry 1).[8] When only 1 equiv of D-glucose is used, the yield of **4a** and **5a** falls from 93% to 72%. D-Ribose gave a complicated mixture of products which was probably due to the formation of both ribofuranose and ribopyranose products as well as

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(12) **3a** is the lower R_f isomer (ethyl acetate) from the dimerization of *N*-acetyl-L-tryptophan methyl ester in TFA.

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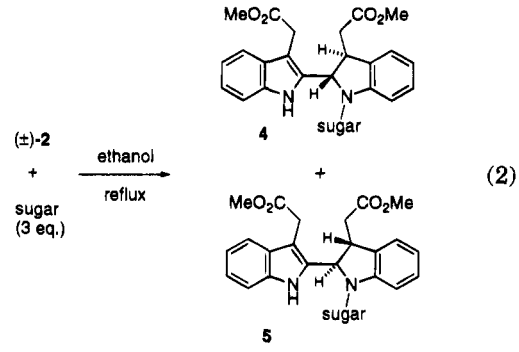
anomeric mixtures (Table 1, entry 5).[9] The glycosylation of (±)-**2** failed with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose. Products of Amadori rearrangements were not observed in any of these reactions.[10]



(2)

The 1.0:1.0 mixture of diastereomeric products **4/5** could be separated by reversed-phase HPLC using 50 mM triethylammonium acetate (pH 6.0)/acetonitrile, without detectable decomposition or isomerization. After prolonged (>1 week) storage in this buffer system, some decomposition was observed.

While the indole nitrogen is a potential site for glycosylation, the persistence of the indole N−H resonance at δ 9.0−9.6 in the ^{1}H NMR (CD_3CN) of the glycosidic products **4a**−**f** and **5a**−**f** provides confirmation that the indoline, and not the indole, is the site of glycosylation. It is common for glycosylamines to show no anomeric preference for axial substitution; consistent with this observation, the products of glycosylation with glucose, galactose, fucose, and xylose afford products with a β configuration (Table 1, entries 1−4).[11] This assignment is based on the diagnostic 8−10 Hz coupling constant (J_{12})which indicates equatorial substitution at positions 1 and 2 of the pyranose ring.[5d] In no case was it possible to unambiguously assign the diastereomeric stuctures **4** or **5** to the two glycosylation products. However, in any approach to indolocarbazole glycosides these two compounds will be convergently dehydrogenated to give the same 2,2′-bisindolyl-*N*-glycoside.

The excellent control of anomeric stereochemistry observed for entries 1−4 (Table 1) is not completely general. L-Rhamnose, which has an axial 2′ OH group, reacted with (±)-**2** to give a mixture of four products (**4e**, **5e**, **4f**, and **5f**) in 72% yield (Table 1, entry 6).[9] Only **4f** could be separated effectively by chromatography. The stereochemical assignment in **4f** is based upon the NOE's shown in Figure 1. Irradiation of the anomeric proton led to strong positive NOE's with the axial protons at the 3′ and 5′ positions of the pyranose ring, as well as the H-7 of the indoline ring.

Other 2,2′-indolylindolines can also be glycosylated.[12] Treatment of tryptophan dimer **3a** with 3 equiv of D-glucose and 3 equiv of $(NH_4)_2SO_4$ affords the expected β-glucoside **6** in 68% yield (eq 3). Only one isomer is formed in this reaction because the indolylindoline

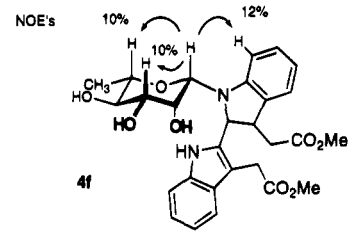
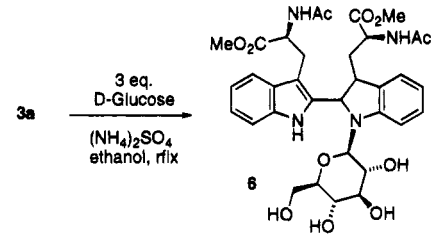


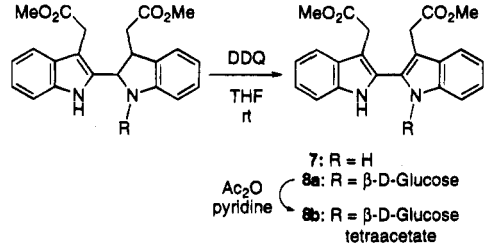
Figure 1. Intermolecular 1D NOE's in L-rhamnoside **4f**.

substrate is a single stereoisomer.



(3)

2,2′-Indolylindolines can be dehydrogenated to the corresponding 2,2′-bisindoles. Treatment of (±)-**2** with DDQ in dioxane over 5 min affords the bisindole **7** in 83% yield (eq 4).[13] The mixture of **4a** and **5a** is oxidized with



(4)

DDQ in THF over 12 h to give a single product, **8a**, in 88% yield (isolated as the pentaacetate **8b**).

The reactivity of simple indoles contrasts sharply with the 2,2′-indolylindolines. No products of glycosylation were detectable after either **7** or indole-3-acetic acid methyl ester was refluxed with D-glucose for 2 days in ethanol. The unreactive nature of these indoles supports the assigned regiochemistry (indoline vs indole) of the glycosylation products.

In conclusion, we have demonstrated an efficient, stereoselective synthesis of glycosylated indolylindolines and the subsequent oxidation to 2,2′-bisindole-*N*-glycosides. The chemistry is simple, and the nature of the starting materials (tryptophan, glucose, H^+) may be relevant to the biosynthetic pathways for formation of some of the indolo[2,3-*a*]carbazole natural products. Further applications of this chemistry are currently in progress.

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Supporting Information Available: Experimental procedures and characterization data (7 pages).

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