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Effective Strategy for the Preparation of Indolocarbazole Aglycons and Glycosides: Total Synthesis of Tjipanazoles B, D, E, and I

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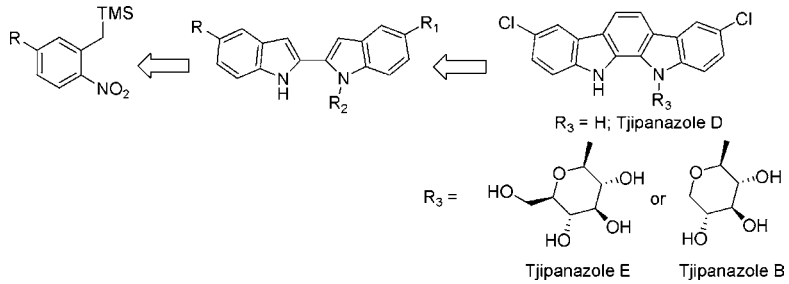
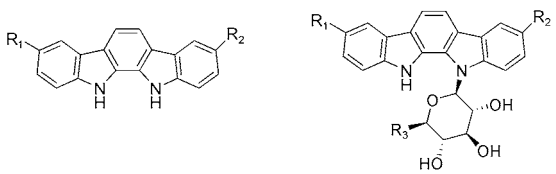
ABSTRACT



An effective strategy has been developed for the rapid and efficient preparation of *ortho*-nitrostyrenes, which can be converted to unsymmetrical 2,2′-biindoles. A unique condensation of these 2,2′-biindoles with (dimethylamino)-acetaldehyde diethyl acetal affords the indolocarbazole ring system of the tjipanazole aglycon alkaloids in three synthetic steps and good to excellent overall yield. The first total synthesis of the tjipanazole glycoside alkaloids B and E is also discussed.

The indolo[2,3-*a*]carbazole ring system constitutes the core skeleton of a family of structurally unique natural products possessing a wide range of biological activity.[1] Indolocarbazole glycosides with either one or two glycosidic linkages have been shown to be potent inhibitors of protein kinase C and topoisomerases and exhibit excellent antitumor activity.[1,2] The aglycons have been shown to be potent and selective inhibitors of human cytomegalovirus.[3] The selectivity and potency of many of the indolocarbazoles depends on the substituents about the aglycon as well as the nature of the carbohydrate moiety. To fully define biological profiles, a strategy is required to allow rapid access to functionalized aglycones and effective methods for glycosidation. These are formidable challenges for organic synthesis since the aromatic substituents are displayed in an unsymmetrical manner.



1 R_1 = H, R_2 = Cl: tjipanazole I
2 R_1 = Cl, R_2 = Cl: tjipanazole D
3 R_1 = Cl, R_2 = Cl, R_3 = H: tjipanazole B
4 R_1 = Cl, R_2 = Cl, R_3 = CH_2OH: tjipanazole E
5 R_1 = Cl, R_2 = H, R_3 = H: tjipanazole F1
6 R_1 = H, R_2 = Cl, R_3 = H: tjipanazole F2

The indolocarbazole alkaloids isolated from *Tolypothrix tjipanasensis* contain both chlorine and glycosidic (*β*-D-

(1) For leading references, see: (a) Bergman, J.; Janosik, T.; Wahlström, N. *Adv. Heterocycl. Chem.* **2001**, *80*, 1. (b) Pindur, U.; Kim, Y.-S. *Curr. Med. Chem.* **1999**, *6*, 29. (c) Bergman, J. *Stud. Nat. Prod. Chem., A* **1988**, *1*, 3. (d) Steglich, W. *Fortschr. Chem. Org. Naturst.* **1987**, *51*, 216. (e) Gribble, G. W.; Berthel, S. J. *Stud. Nat. Prod. Chem.* **1993**, *12*, 365. (f) Prudhomme, M. *Curr. Pharm. Design* **1997**, *3*, 265.

(2) (a) Tamaoki, T.; Nomoto, H.; Takahishi, I.; Kato, Y.; Morimoto, M.; Tomita, F. *Biochem. Biophy. Res. Commun.* **1986**, *135*, 397. (b) Omura, S.; Sasaki, Y.; Iwai, T.; Takashima, H. *J. Antibiot.* **1995**, *48*, 535.

(3) Slater, M. J.; Cockerill, S.; Baxter, R.; Bonser, R. W.; Gohil, K.; Gowrie, C.; Robinson, J. E.; Littler, E.; Parry, N.; Randall, R.; Snowden, W. *Bioorg. Med. Chem.* **1999**, *7*, 1067.

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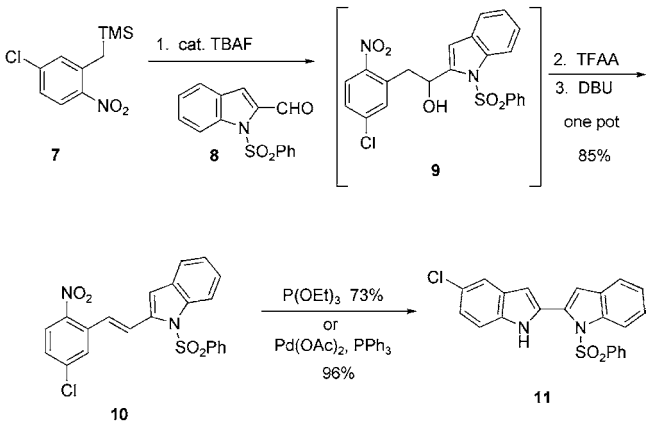
glucosyl, β-D-deoxygulosyl, β-L-rhamnosyl, or β-D-xylosyl) substituents on the polyaromatic core.[4] The aglycon tjipanazoles (**1**, **2**) and the glycosidic tjipanazoles (**3**−**6**) are natural products. While approaches exist for the synthesis of some tjipanazole alkaloids,[3,4] many of the tjipanazole natural products have eluded synthesis. Synthetic methods that provide rapid assembly of the indole ring and tolerate a wide range of functional groups leading to increasing molecular complexity are important synthetic tools. Our general approach to the indolocarbazoles was inspired by the unique versatility of nitrobenzenes, which are able to serve as both electrophilic and nucleophilic partners. Reductive cyclization of a suitably substituted *ortho*-nitrostyrene would give access to unsymmetrical 2,2′-biindoles and with appropriate elaboration would lead to indolocarbazole aglycons. In this Letter, we report our preliminary findings in this area.

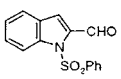
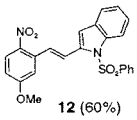
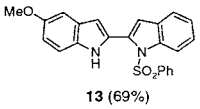
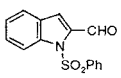
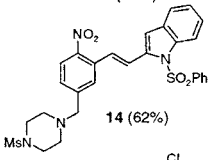
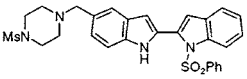
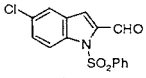
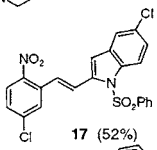
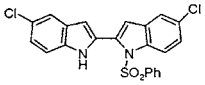
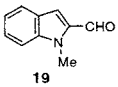
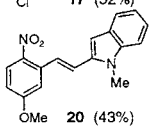
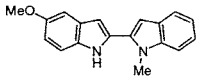
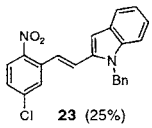
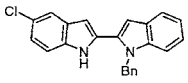
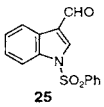
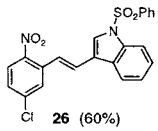
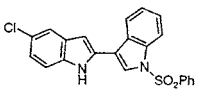
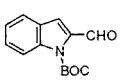
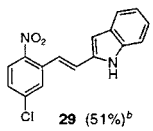
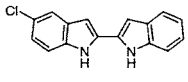
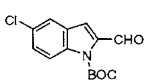
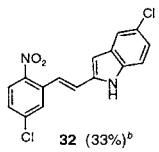
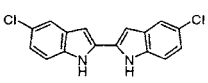
Our first challenge was preparation of the *ortho*-nitrostyrenes. Reaction of TMS-nitro compound **7**[5] and indole carboxaldehyde **8** with a catalytic amount of tetrabutylammonium fluoride (TBAF) afforded the desired alcohol **9** (Scheme 1).[6] Direct addition of TFAA to the reaction mixture

Scheme 1



was followed by elimination of the corresponding trifluoroacetate with DBU at 60 °C and afforded *trans*-nitrostyrene **10** in 85% overall yield. Reductive cyclization of **10** under the classic Cadogan/Sundberg conditions [$P(OEt)_3$] gave biindole **11** in 73% yield.[7−9] Alternatively, palladium-catalyzed reductive cyclization of **10** using Söderberg conditions[10] gave biindole **11** in 96% yield. The reaction sequence was general and gave access to a diverse array of both

Table 1. Preparation of Nitrostyrenes and Biindoles

aldehyde	styrene (% yield)[a]	biindole (% yield)[a]
 **8**	 **12** (60%)	 **13** (69%)
 **8**	 **14** (62%)	 **15** (63%)
 **16**	 **17** (52%)	 **18** (44%)
 **19**	 **20** (43%)	 **21** (84%)
 **22**	 **23** (25%)	 **24** (94%)
 **25**	 **26** (60%)	 **27** (71%)
 **28**	 **29** (51%)[b]	 **30** (68%)
 **31**	 **32** (33%)[b]	 **33** (68%)

[a] Isolated yields determined by flash chromatography on silica gel. [b] BOC group was cleaved under the reaction conditions.

symmetrical and unsymmetrical nitrostyrenes and biindoles in modest to excellent yield for each synthetic step (Table 1).

Preparation of the indolocarbazole ring system of the tjipanazoles from 2,2′-biindoles appears to be unprecendented.[9,11] An operationally trivial procedure for the incorporation of the two-carbon fragment of the indolocarbazole ring with the correct oxidation state involved condensation with (dimethylamino)-acetaldehyde diethyl acetal in acetic acid (Scheme 2).[12] For example, tjipanazoles I and D were obtained in 79 and 71% yields from biindoles **30** and **33**, respectively. In similar fashion, the indolocarbazole **34** was

(4) Bonjouklian, R.; Smitka, T. A.; Doolin, L. E.; Molloy, R. M.; Debono, M.; Shaffer, S. A.; Moore, R. E.; Stewart, J. B.; Patterson, G. M. L. *Tetrahedron* **1991**, *47*, 7739.

(5) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Todesco, R. E. *J. Org. Chem.* **1986**, *51*, 3694.

(6) Bartoli, B.; Bosco, M.; Caretti, D.; Dalpozzo, R.; Todesco, R. E. *J. Org. Chem.* **1987**, *52*, 4381.

(7) (a) Cadogan, J. I. G.; Cameron-Wood, M. *Proc. Chem. Soc.* **1962**, 361. (b) Cadogan, J. I. G.; Mackie, R. K.; Todd, M. J. *J. Chem. Soc., Chem. Commun.* **1966**, 491.

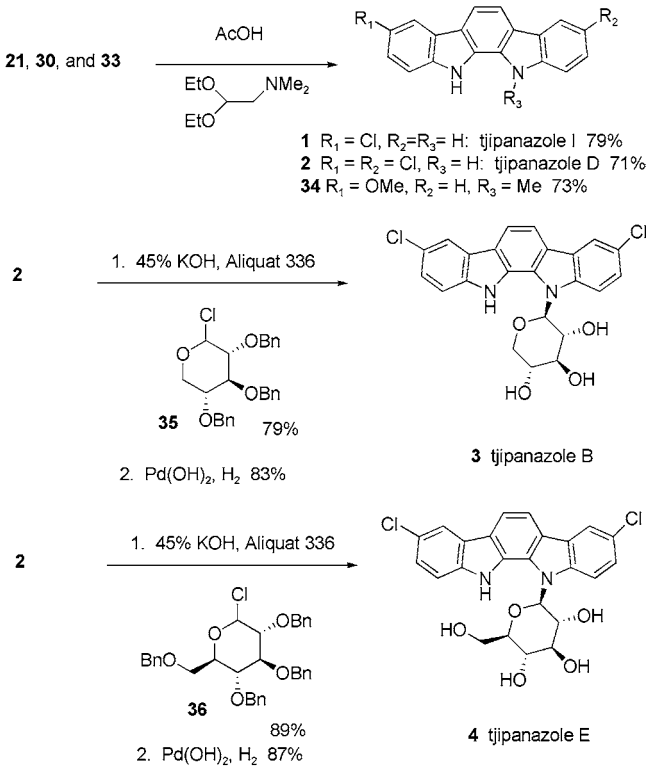
(8) Sundberg, R. J. *J. Org. Chem.* **1965**, *30*, 3604.

(9) Merlic, C. A.; You, Y.; McInnes, D. M.; Zechman, A. L.; Miller, M. M.; Deng, Q. *Tetrahedron* **2001**, *57*, 5199.

(10) Söderberg, B. C.; Shiver, J. A. *J. Org. Chem.* **1997**, *62*, 5838.

(11) For the synthesis of substituted indolocarbazoles from 2,2′-biindoles, see: (a) Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1995**, *117*, 10413. (b) Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J.; Pflum, D. A.; Petsch, D. T. *J. Am. Chem. Soc.* **1997**, *119*, 9641.

Scheme 2



formed in 73% yield from biindole **21**. This synthetic strategy is particularly noteworthy since it gives access to unsymmetrical indolocarbazole aglycons in just three synthetic operations.

The installation of the carbohydrate moiety of the tjipanazoles and other indolocarbazole glycosides presents significant challenges due to low yields (<10%), control of anomeric stereochemistry, and control of regiochemistry.[4,13a] Although this problem has been partially solved by the glycosylation of 2,2′-indolylindolines,[13] a general approach employing the direct glycosylation of the indolocarbazole nitrogen of the tjipanazoles would be advantageous. To this end, we examined the synthesis of the symmetrical tjipanazole alkaloids tjipanazole B (**3**) and E (**4**) from indolocarbazole **2**.

Inspired by previous reports from these laboratories, reaction of **2** with α-D-xylopyranosyl chloride **35**[14] in a biphasic mixture of MTBE and 45% aqueous KOH and Aliquat 336 gave protected tjipanazole B as single anomer in 79% isolated yield.[15] Hydrogenation over $Pd(OH)_2$ gave tjipanazole B (**3**) in 83% isolated yield. The synthesis of tjipanazole E was also accomplished by reaction of **2** with α-D-glycolopyranosyl chloride **36**[15] to give the protected glycoside in 89% yield. Hydrogenation over $Pd(OH)_2$ gave tjipanazole E (**4**) in 87% yield. The spectroscopic and optical properties of synthetic **3** and **4** were in full agreement with the reported values.[4]

The sequence demonstrated in the *xylo*- and *gluco*-series should lend itself to the preparation of a variety of other glycosidic linkages.

In conclusion, we have established a rapid, practical, and efficient method for the preparation of unsymmetrical 2,2′-biindoles from *o*-nitrostyrenes, which can be elaborated to indolocarbazole aglycons or indolopyrrolocarbazoles[16] in three synthetic steps. Hallmarks of the sequence include a general biindole synthesis, a novel elaboration to the indolocarbazole aglycons, and a high-yielding, stereoselective glycosidation of an indolocarbazole aglycon. This strategy allowed for the first reported total synthesis of tjipanazoles B and E. A full account of related studies in these laboratories will be forthcoming.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035418R

(12) Janosik, T.; Bergman, J. *Tetrahedron* **1999**, *55*, 2371.

(13) (a) Gilbert, E. J.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 5500. (b) Gilbert, E. J.; Ziller, J. W.; Van Vranken, D. L. *Tetrahedron* **1997**, *53*, 16553. (c) Gilbert, E. J.; Chisholm, J. D.; Van Vranken, D. L. *J. Org. Chem.* **1999**, *55*, 2371.

(14) Iversen, T.; Bundle, D. R. *Carbohydr. Res.* **1982**, *103*, 29.

(15) Akao, A.; Hiraga, S.; Iida, T.; Kamatani, A.; Kawasaki, M.; Mase, T.; Nemoto, T.; Satake, N.; Weissman, S. A.; Tschaen, D. M.; Rossen, K.; Petrillo, D.; Reamer, R. A.; Volante, R. P. *Tetrahedron* **2001**, *57*, 8917.

(16) Preliminary studies reveal that the arcyriaflavin class of natural products are also accessible using this approach; see Supporting Information. For the synthesis of related compounds, see: Zhu, G.; Conner, S. E.; Zhou, X.; Shih, C.; Li, T.; Anderson, B. D.; Brooks, H. B.; Cambell, R. M.; Considine, E.; Dempsey, J. A.; Faul, M. M.; Ogg, C.; Patel, B.; Schultz, R. M.; Spencer, C. D.; Teicher, B.; Watkins, S. A. *J. Med. Chem.* **2003**, *46*, 2027.