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Chemo-, Regio-, and Enantioselective Pd-Catalyzed Allylic Alkylation of Indolocarbazole Pro-aglycons

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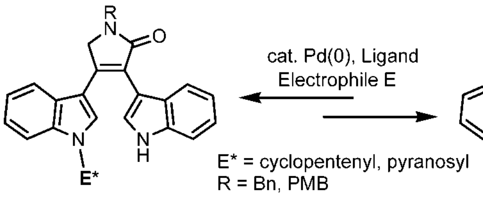
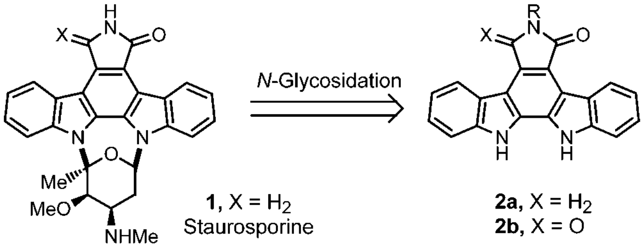
ABSTRACT



Monosubstituted isomerically pure indolopyrrolocarbazole precursors have been prepared via palladium-catalyzed asymmetric allylic alkylation methodology, employing both achiral cyclopentenyl electrophiles and chiral glycal derivatives. Chemoselective allylation of (bis)indole lactam pro-aglycon 3 allows access to *N*-distally substituted indolopyrrolocarbazole derivatives; glyoxamide precursor 14 provides entry into *N*-proximally substituted derivatives.

Members of the indolocarbazole family of natural products exhibit nanomolar PKC and topoisomerase inhibitory action.[1] Their remarkable biological activity and novel structure have captured the attention of synthetic chemists.[2] Since the initial total synthesis of staurosporine[3] **1** and of K-252a,[4] several syntheses of indolocarbazole natural products have appeared.[5−8] The vast majority of synthetic strategies involve *N*-glycosidation of activated sugars, such as bis-glycal derivatives, with aglycons **2a** or **2b** (Scheme 1). While the indolic nitrogens of **2a** are sterically equivalent, they are electronically unique owing to the inductive effects of the remote lactam carbonyl. Nevertheless, reported protocols for the glycosidation of **2a**

Scheme 1. Previous Synthetic Strategies



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[1] For reviews on studies related to their chemistry and biology, see: Gribble, G.; Berthel, S. *Studies in Natural Products Chemistry*; Elsevier Science Publishers: New York, 1993; Vol. 12, p 365. Sapi, J.; Massiot, G. *The Alkaloids*; Academic Press: New York, 1995; Vol. 47, p 173. Bergman, J. *Studies in Natural Products Chemistry*; Elsevier Science Publishers: New York, 1988; Vol. 1, p 3. Steglich, W. *Pure Appl. Chem.* **1989**, *61*, 281. For a review on the bioactivity of staurosporine, see: Omura, S.; Sasaki, Y.; Iwai, Y.; Takeshima, H. *J. Antibiot.* **1995**, *48*, 535.

[2] (a) Sarstedt, B.; Winterfeldt, E. *Heterocycles* **1983**, *20*, 469. (b) Hughes, I.; Nolan, W. P.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2475. (c) Moody, C. J.; Rahimtoola, K. F. *Chem. Soc., Chem. Commun.* **1990**, 1667. (d) Xie, G.; Lown, J. W. *Tetrahedron Lett.* **1994**, *35*, 5555.

[3] Link, J. T.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 552; Link, J. T.; Danishefsky, S. J. *Tetrahedron Lett.* **1994**, *35*, 9131. (c) Link, J. T.; Danishefsky, S. J. *Tetrahedron Lett.* **1994**, *35*, 9135. Link, J. T.; Raghavan, S.; Gallant, M.; Chou, T. C.; Ballas, L. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 2825.

[4] Wood, J.; Stolz, B. M.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1995**, *117*, 10413.

[5] Wood, J. L.; Petsch, D. T.; Stoltz, B. M.; Hawkins, E. M.; Elbaum, D.; Stover, D. R. *Synthesis* **1999**, 1529. Wood, J. L.; Stoltz, B. M.; Goodman, S. N.; Onwneme, K. *J. Am. Chem. Soc.* **1997**, *119*, 9652. Wood, J. L.; Stoltz, B. M.; Dietrich, H. J.; Pflum, D. A.; Petsch, D. T.. *J. Am. Chem. Soc.* **1997**, *119*, 9641. Wood, J. L.; Stoltz, B. M.; Goodman, S. N. *J. Am. Chem. Soc.* **1996**, *118*, 10656. Wood, J. L.; Stoltz, B. M.; Goodman, S. N.; Onwneme, K. *Tetrahedron Lett.* **1996**, *37*, 7335. (e) Stoltz, B. M.; Wood, J. L. *Tetrahedron Lett.* **1996**, *37*, 3925.

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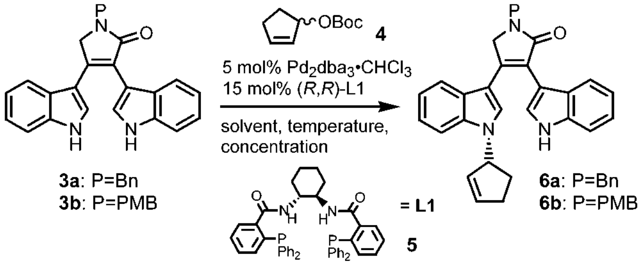
exhibit poor chemoselectivity. Similarly, desymmetrization of *N*-glycosidated imide **2b** affords mixtures of isomeric products. In this Letter, we disclose a highly chemoselective *N*-glycosidation of indolocarbazole pro-aglycons achieved on the basis of this electronic bias via Pd-catalyzed allylic alkylation.[9]

Our initial attempts at chemoselective *N*-glycosidation focused on aglycons **2a** and **2b**. While indole itself is a viable pro-nucleophile, it soon became apparent that **2a** and **2b** were not effective participants presumably owing to steric factors or bidentate complexation of palladium by the aglycon. Accordingly, the catalytic allylic alkylation of bis(indole) derivatives **3a** and **3b** in conjunction with cyclopentenyl carbonate **4** and chiral ligand **5**[10] was studied (Scheme 2).

Scheme 2. Asymmetric Allylic Alkylation of (Bis)indole Lactams **3a** and **3b** with Cyclopentenyl Carbonate **4**



Gratifyingly, catalytic allylation of **3a** afforded the single isomeric monoadduct **6a** in good yields.[11] Allylations conducted in THF gave products with poor levels of enantiomeric enrichment (entries 1 and 2). However, allylation performed in DCM gave products of high enantiomeric excess (entries 4 and 5). Remarkably, the products obtained in DCM were of the opposite stereochemical configuration to those obtained from THF. Overallylation in the case of **3b** was circumvented through slow addition of the electrophile over a 12 h period. In both cases, reactions conducted at lower temperatures gave products of higher enantiomeric excess. These results are summarized in Table 1.

Under the basic conditions of allylation, it was anticipated that the more acidic indolic nitrogen, i.e., the indolic nitrogen linearly conjugated and “distal” to the carbonyl function, would represent the preferred site of allylation. The structural assignment of the cyclopentenylated adduct was unambiguously established by high-field Overhauser enhancement and homo- and heteronuclear correlation and connectivity 2D NMR experiments (Figure 1).

Table 1. Asymmetric Allylic Alkylation of **3a** and **3b** with Cyclopentenyl Carbonate **4**

entry	pro-aglycon	solvent	cat. (%)	*T* (°C)	concn (mol/L)	yield (%)	ee (%)[a]
1	**3a**	THF	10	25	0.1	78	−22
2	**3a**	THF	10	−55	0.1	66	−30
3	**3a**	DCM	10	25	0.05	65	76
4	**3a**	DCM	10	−20	0.1	59	96
5	**3a**	DCM	10	−20	0.05	83	99
6	**3b**	DCM	5	25	0.06	61	83
7	**3b**	DCM	5	−20	0.06	75	99

[a] Enantionmeric excess determined by chiral stationary phase HPLC.

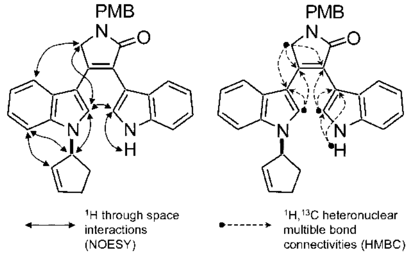


Figure 1. Selected, most indicative correlations.

Further support of the proposed structural assignment derives from consideration of the aggregation of **6b** in solution. In low dielectric media such as chloroform and toluene, the NMR spectra of **6b** are highly concentration dependent. However, in polar protic solvents, the NMR chemical shifts remain unchanged over a large concentration range. Conformational analyses[12] suggest the most stable conformation of **6b** to be one in which the non-alkylated indole NH and lactam carbonyl reside in syn-coplanar orientation. Thus, whereas the anticipated distal regioisomer may engage in a specific 2-fold self-association arising through the formation of hydrogen-bonded dimer, the alternate regioisomer should aggregate in nonspecific or polymeric fashion through single H-bonds (Figure 2).

Dilution experiments and mathematical treatments of the chemical shift values reveal the expected 2-fold self-assembly event.[13] The allylated adduct **6b** dimerizes in chloroform with

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(6) Gilbert, E. J.; Ziller, J. W.; VanVranken, D. L. *Tetrahedron* **1997**, *53*, 16553. Gilbert, E. J.; Vanvranken, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 5500.

(7) Eils, S.; Winterfeldt, E. *Synthesis* **1999**, 275. Riley, D. A.; Simpkins, N. S.; Moffat, D. *Tetrahedron Lett.* **1999**, *40*, 3929. Royer, H.; Joseph, D.; Prim, D.; Kirsch, G. *Synth. Commun.* **1998**, *28*, 1239. Ohkubo, M.; Nishimura, T.; Jona, H.; Honma, T.; Ito, S.; Morishima, H. *Tetrahedron* **1997**, *53*, 5937. Merlic, C. A.; McInnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 7661. Merlic, C. A.; McInnes, D. M.; You, Y. *Tetrahedron Lett.* **1997**, *38*, 6787.

(8) Kobayashi, Y.; Fujimoto, T.; Fukuyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 6501

(9) Trost, B. M.; VanVranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

(10) Trost, B. M.; Van Vranken, D. L. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 228.

(11) The good yields obtained in the cyclopentenylation reactions were found to be crucially dependent on careful oxygen exclusion from the reaction vessels.

(12) Systematic conformational searches were performed with the computer program CACHe Workstation Plus DGauss (Ver. 4.4), using molecular mechanics with augmented MM3 parameter sets. Subsequent geometric optimization using semiempirical PM3 potential functions.

(13) For the calculation of equilibrium constants, the computer program CHEM-EQUILI (Ver. 6.1) was employed. For a detailed description, see: Solov’ev, V. P.; Vnuk, E. A.; Strakhova, N. N.; Raevsky. O. A. *Thermodynamic of complexation of the macrocyclic polyethers with salts of alkali and alkaline-earth metals*; VINITI: Moscow, 1991.

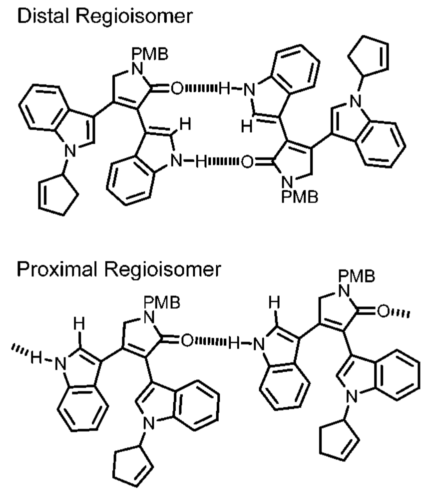
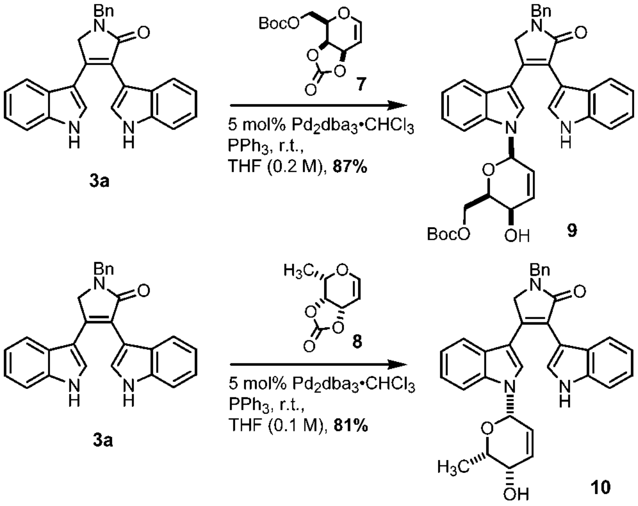


Figure 2. Different self-assembly modes of the two possible regioisomers of **6b**.

$K_{dim} = 10$ L•mol^{-1} and in toluene with $K_{dim} = 50$ L•mol^{-1}. In analogy to the cyclopentenylation of phthalimide[14a] and following our mnemonic for asymmetric induction in allylic allylations,[10,14b] the absolute configuration of the newly formed stereocenter is predicted to be *R* when *R,R*-**5** was employed.

We next explored the reaction of (bis)indole lactam **3a** with the galactose- and fucose-derived glycals **7** and **8**. Catalytic allylation utilizing these glycals afford monoadducts **9** and **10** as single regio-[15] and stereoisomers in high chemical yields (Scheme 3). On the basis of the aforementioned results, the site of allylation is anticipated to be the distal indolic nitrogen.

Scheme 3. Allylation of (Bis)indole Lactam **3a** with Sugar-Derived Electrophiles **7** and **8**



Oxidative cyclization of the cyclopentenyl adduct **6a** (DDQ)[16a] and the sugar-derived adducts (photolysis in the presence of I_2)[16b] afford the corresponding indolopyrrolocarbazoles **11**, **12**, and **13** in 87%, 86%, and 68% yields, respectively (Figure 3).

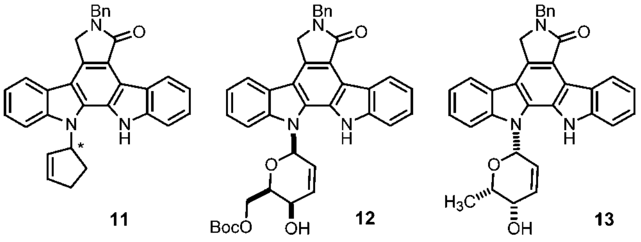
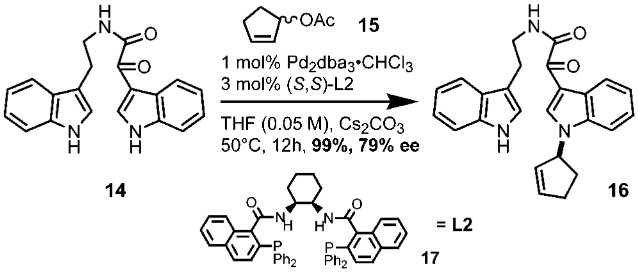


Figure 3. Oxidatively cyclized cyclopentenyl and sugar adducts **11**, **12**, and **13**.

Having achieved the chemoselective synthesis of monoalkylated indolopyrrolocarbazoles in which the indolic nitrogen *distal* to the carbonyl is functionalized, a method was sought for chemoselective functionalization of indolic nitrogen *proximal* to the lactam carbonyl. Toward this end, readily available glyoxamide **14** was employed as pronucleophile in the Pd-catalyzed allylation. As the site of alkylation should again be dictated by the site of greatest acidity, it was anticipated that the indolic nitrogen in conjugation with the dione would represent the preferred site of allylation. Exposure of **14** to allylic acetate **15** provides the monoallylated adduct **16** as a single constitutional isomer. Optimal enantioselectivities were observed upon use of binaphthyl ligand **17** (79% ee)[17] at low catalyst loadings. The structural assignment of **16** was established by X-ray crystallographic analysis[18] (Scheme 4).

Scheme 4. Allylation of Dione **14** with Cyclopentenyl Acetate **15**



In an effort directed toward the obtention of the sugar adducts, dione **14** was reacted with the sugar-derived

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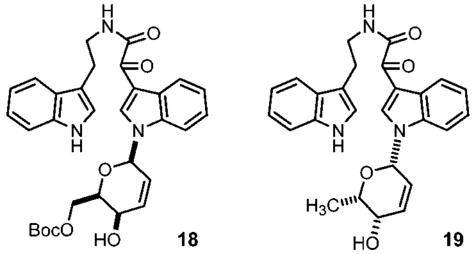
[14] (a) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089. (b) Trost, B. M.; Van Vranken, D. L.; Bingel, C. J. *J. Am. Chem. Soc.* **1992**, *114*, 9327.

[15] Exclusive nucleophilic attack on the π-allylpalladium complex terminus proximal to the oxygen of the pyran was supported by NMR chemical shift and coupling constant analyses.

[16] (a) Joyce, R.; Gainor, J.; Weinreb, S. M. *J. Org. Chem.* **1987**, *52*, 1177. (b) Link, J. T.; Raghaven, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 552.

[17] For precedence on the improvement of ee employing L2 instead of L1, see: Trost, B. M.; Schroeder, G. M. *J. Org. Chem.* **2000**, *65*, 1569.

electrophiles. Gratifyingly, the glycosidated regioisomerically pure adducts **18** and **19** could be obtained in 96% and 92% yields, respectively (Figure 4).[15]

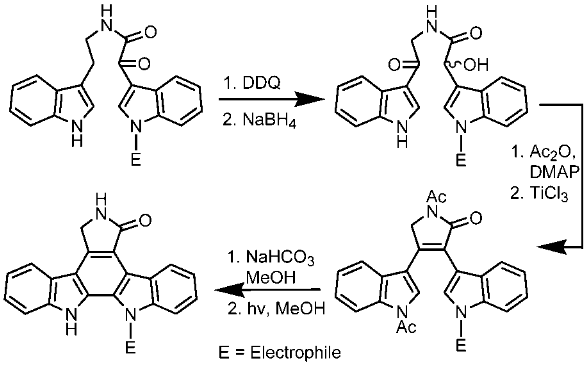


18 **19**

Figure 4. Glycosidated diones **18** and **19**.

Elaboration of **16** to the corresponding indolocarbazole finds close precedent in the literature,[2a] thus establishing a viable synthetic route to proximally substituted indolopyrrolocarbazoles (Scheme 5).

Scheme 5. Strategy for the Regiocontrolled Synthesis of Indolopyrrolocarbazoles Functionalized at the Nitrogen Proximal to the Carbonyl



In summary, Pd-catalyzed asymmetric allylation methodology has enabled a direct means of transforming indolopyrrolocarbazole precursors to isomerically pure monosubstituted adducts. Whereas the allylation of (bis)indole **3** provides adducts that may be transformed by distally substituted indolopyrrolocarbazoles, the allylation of glyoxamide **14** allows access to proximally substituted analogues. Notably, in the allylation of **14**, one of three nitrogens is chemoselectively allylated, thus circumventing the use of protecting groups. The utilization of these protocols for the preparation of isomerically pure monosubstituted indolopyrrolocarbazole natural products will be the topic of a forthcoming report.

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Supporting Information Available: Complete synthetic procedures for the preparation of all allylated products and their spectral data, 2D NMR structural elucidation and solution studies on self-assembly of **6b**, and X-ray crystallographic data pertaining to **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Structure factors available from author upon request.