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New Synthetic Protocols for the Preparation of Unsymmetrical Bisindoles

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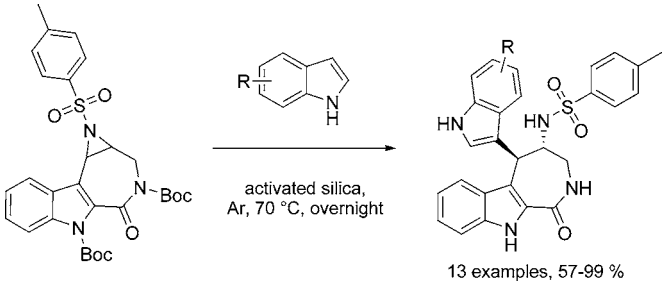
ABSTRACT



Novel unsymmetrical bisindoles were synthesized by a solvent-free C−C bond-formation reaction under mild conditions. Starting from aziridines or hydroxyl precursors, indoles have been used as C-nucleophiles to form new pharmacologically interesting bisindoles via an electrophilic aromatic substitution pathway in good to excellent yields.

During the last two decades, protein kinases were found to be involved in essential regulatory cellular functions such as gene expression, cellular proliferation, differentiation, membrane transport, and apoptosis.[1] Staurosporine (**1**), a bisindole, has been found as one of the first kinase inhibitors in nanomolar concentrations.[2] In addition, various small molecular kinase inhibitors are known.[3] Among them, Hymenialdisine (HMD) (**2**)[4] and annulated derivatives **3**[5] (Figure 1) have been found to inhibit a number of different kinases very selectively. Additionally, compounds **2** and **3** prevent the production of cytokines.[6]

We have been interested in the application of catalytic reactions for the synthesis of potential pharmaceuticals for some time.[7] As a starting point for the development of new bioactive kinase inhibitors, we decided to prepare a small

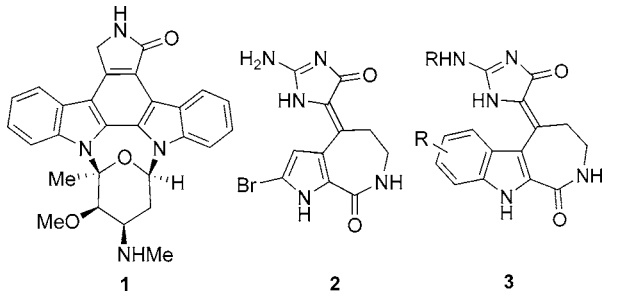


Figure 1. Structures of Staurosporine (**1**), Hymenialdisine (HMD) (**2**), and HMD analogues **3**.

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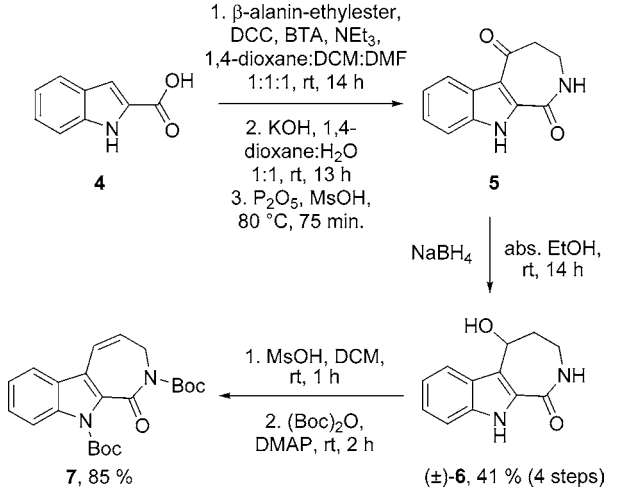
compound library of unsymmetrical bisindoles. As a part of this project, we developed a solvent-free, efficient, and easy to handle diversification strategy for annulated HMD-type bisindoles via a C−C bond-formation reaction on activated silica under mild reaction conditions starting from aziridines or hydroxyl compounds.

In the past, different synthetic strategies have been developed for the synthesis of the pyrrolo[2,3-*c*]azepine motif of HMD. The first total synthesis of HMD (**2**) was published by Annoura;[8] later, Horne introduced another synthetic strategy.[9] Recently, a new total synthesis was introduced by Papeo.[10] Annulated HMD derivatives usually were prepared via the azepino[3,4-*b*]indole-1,5-dione (**5**) intermediate or the corresponding alcohol (±)-**6** and subsequent attachment of the imidazole heterocycle.[5] Azepino-indole **5** is usually synthesized via intramolecular cyclization reactions with $MsOH/P_2O_5$.[11] Also, protocols employing ring-closing metathesis[12] and polyphosphoric acid[13] were introduced so far.

It has been shown that the kinase inhibiting activities of annulated HMDs **3** vary very much when other heterocycles instead of imidazole are introduced.[5] Hence, we aimed to develop a general and easy manageable preparation of unsymmetrical HMD-type bisindoles. On the basis of our experience on oxidation methods,[14] we planned to use different oxidation reactions as a toolbox for diversity-oriented synthesis.[15] Until now, relatively little use has been made applying oxidation methodologies for this purpose. The starting material **7** was synthesized in a one-pot elimination−protection procedure from (±)-**6** (Scheme 1).[5] Boc-protecting

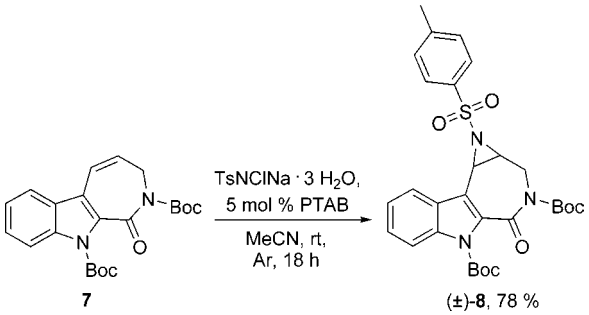
Scheme 1. Synthesis of Intermediates (±)-**6** and **7**



groups were introduced to obtain a more stable and storable alkene, which smoothly reacts in the subsequent aziridination reaction.

Although initial exploratory experiments employing standard epoxidation methods such as *m*-CPBA or MTO[16] were not successful, we turned our interest to the aziridination of olefin **7**.[17] It is well documented that *N*-arylsulfonylaziridines react with C, O, S, N, halogen, or hydrogen nucleophiles[18] in the presence of a base, an acid, or a Lewis acid. In general, it should be possible to perform these reactions highly regio- and stereoselectively.[19] For aziridination of olefins, a number of different metal-catalyzed nitrene transfer methods with copper, rhodium, ruthenium, iron, cobalt, manganese, silver, and gold catalysts were described.[20] With respect to synthetic application, we decided to perform the bromine-catalyzed aziridination developed by Sharpless and co-workers because this protocol does not require an excess of olefin (Scheme 2).[21]

Scheme 2. Bromine-Catalyzed Aziridination of **7**



To our delight, the aziridination of **7** proceeded smoothly to give (±)-**8** in good yield (78%). In contrast to the reported literature conditions, the reaction is favorably carried out

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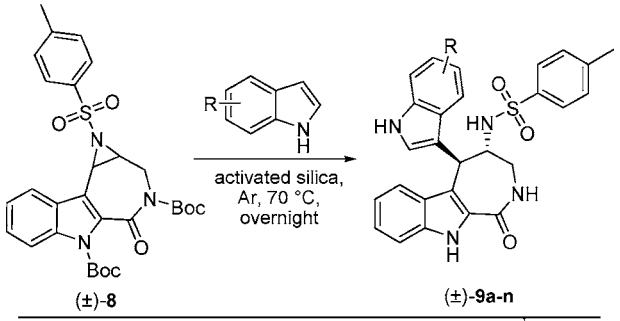
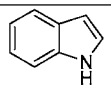
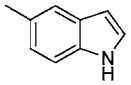
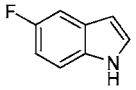
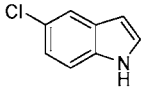
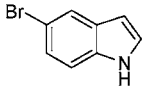
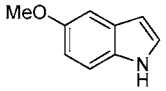
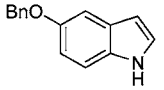
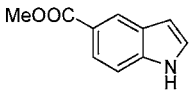
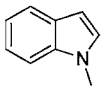
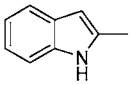
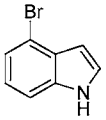
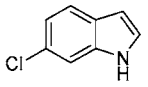
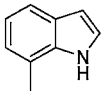
(19) For a review, see: Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247−258.

Table 1. Ring-Opening Reactions of (±)-**8**[a]



(±)-**8** (±)-**9a-n**

entry	substrate	product	yield[b] [%]
1		(±)-**9a**	93
2		(±)-**9b**	81
3		(±)-**9c**	99
4		(±)-**9d**	57
5		(±)-**9e**	84
6		(±)-**9f**	93
7		(±)-**9g**	72
8		(±)-**9h**	67
9		(±)-**9i**	86
10		(±)-**9k**	96
11		(±)-**9l**	70
12		(±)-**9m**	85
13		(±)-**9n**	76

[a] Reaction conditions: aziridine (±)-**8** (113 mg, 0.20 mmol), indole derivative (2.00 mmol), activated silica (0.040−0.063 mm, 429 mg), 70 °C, Ar, overnight. [b] Isolated yield.

employing an understoichiometric amount of chloramine-T trihydrate (1 equiv) in the presence of only 5 mol % of phenyltrimethylammonium tribromide (PTAB) and 2 equiv of **7** to reduce side products such as the brominated olefin and the ring-opening product of the formed aziridine with the amide salt.[22] Next, we attempted the direct arylation of various indoles using (±)-**8** as the key building block in the presence of acidic heterogeneous catalysts such as clay[23] or silica.[24] The arylations took place highly regioselectively at the benzylic position of (±)-**8** applying Hudlicky's protocol of solvent-free conditions on silica (Table 1).[24a] All reactions ran overnight at 70 °C and yielded the ring-opening product in good to excellent yields.

The crystal structure of product (±)-**9f** clearly showed that the reaction yielded a trans ring-opening product (Figure 2).[25]

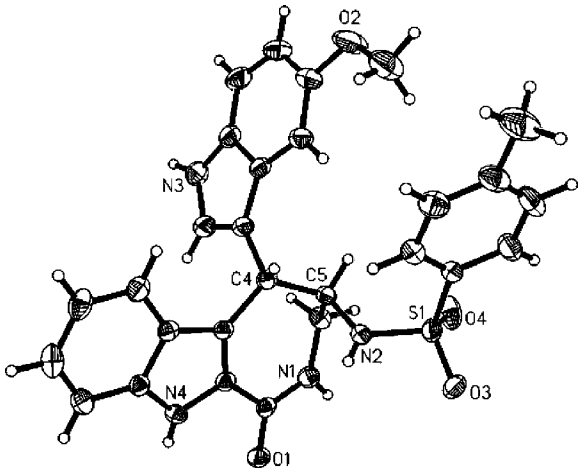


Figure 2. Molecular structure of (±)-**9f**. The thermal ellipsoids correspond to 30% probability.[25]

Functional groups such as alkyl, halide, alkoxy, and ester groups were tolerated by the mild reaction conditions. However, nitro- and cyano-substituted indoles did not react well in this protocol. In the case of 5,6-dimethylindole, we obtained an unseparable 70:30 mixture of two different

(20) (a) For an overview, see: Möβner, C.; Bolm, C. Catalyzed Asymmetric Aziridinations. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 389−402. (b) For a review, see: Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905−2919. (c) For recent developments with Au and Ag, see: Li, Z.; Ding, X.; He, C. *J. Org. Chem.* **2006**, *71*, 5876−5880. Cui, Y.; He, C. *J. Am. Chem. Soc.* **2003**, *125*, 16202−16203.

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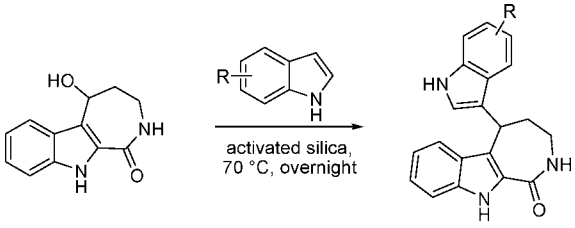
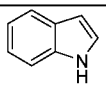
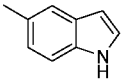
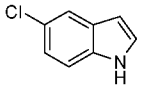
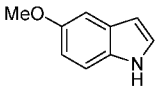
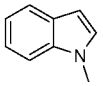
(25) X-ray crystallographic study of **9f**: data were collected with a STOE-IPDS diffractometer using graphite-monochromated Mo Kα radiation. The structure was solved by direct methods [SIR2004: Burla, M. C.; Caliandro, R.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; De Caro, L.; Giacovazzo, C.; Polidori, G.; Spagna, R. *J. Appl. Cryst.* **2005**, *38*, 381−389] and refined by full-matrix least-squares techniques against F^2 [Sheldrick, G. M. *SHELXL-97*; University of Göttingen: Germany, 1997.] XP (BRUKER AXS) was used for a structural representation. Space group $P2_1/c$, monoclinic, $a = 13.641(3)$, $b = 16.424(3)$, $c = 12.005(2)$ Å, $b = 94.29(3)°$, $V = 2682.1(9)$ Å^3, $Z = 4$, $r_{calcd} = 1.354$ g/cm^{-3}, 28 216 reflections measured, 4732 were independent of symmetry, of which 2669 were observed ($I > 2s(I)$), R1 = 0.042, wR^2 (all data) = 0.090, 367 parameters.

Table 2. Formation of Bisindoles (±)-**10a**−**e** from (±)-**6**[a]



(±)-**6** (±)-**10a-e**

entry	substrate	product	yield[b] [%]
1		(±)-**10a**	91
2		(±)-**10b**	52
3		(±)-**10c**	64
4		(±)-**10d**	53
5		(±)-**10e**	56

[a] Reaction conditions: alcohol (±)-**6** (100 mg, 0.462 mmol), indole derivative (4.62 mmol), activated silica (0.040−0.063 mm, 800 mg), 70 °C, overnight. [b] Isolated yield.

regioisomers likely caused by the electron-rich aromatic system of the substrate.

In all cases, the functionalization took place in the 3-position of the employed indoles, which is in agreement with an electrophilic aromatic substitution mechanism. Interestingly, both nitrogen atoms were deprotected in situ giving products (±)-**9a**−**n** directly. This desired parallel reaction avoids any other further deprotection steps.

For direct comparison in biological screenings, we also prepared the analogues (±)-**10a**−**e** without the tosylamide side chain. Under similar reaction conditions, the hydroxyl compound (±)-**6** yielded the corresponding bisindoles (±)-**10a**−**e** in moderate to good yields (Table 2). Presumably, a carbocation is formed in situ at the benzylic position, which reacted afterwards in an electrophilic aromatic substitution pathway with the various indoles. Also a reaction following Horne's azafulvenium ion pathway seems possible.[9a] To the best of our knowledge, this is the first direct benzylation of indoles at the 3-position with a hydroxyl precursor under solvent-free reaction conditions.[26]

In summary, we have developed new synthetic protocols for the preparation of unsymmetrical bisindoles. The ring-opening arylation of the aziridine or the direct arylation of the hydroxyl precursor proceeds highly regio- and stereoselectively with various indoles solvent free on solid support. This reaction enables an easily manageable and fast diversification pathway for a number of unsymmetrical bisindoles and pharmaceutically interesting HMD derivatives.

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Supporting Information Available: Experimental procedures, characterization of all compounds, and crystallographic data of (±)-**9f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) For a similar reaction employing α-amino sulfones, see: Ballini, R.; Palmieri, A.; Petrini, M.; Torregiani, E. *Org. Lett.* **2006**, *8*, 4093−4096.