Annulated Diketopiperazines from Dipeptides or Schöllkopf Reagents via Tandem Cyclization−Intramolecular N-Arylation
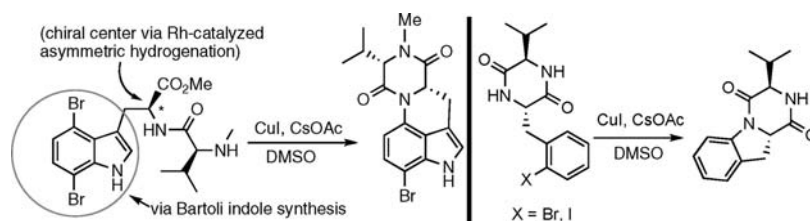
Hwan Jung Lim, Judith C. Gallucci, and T. V. RajanBabu*

Department of Chemistry, The Ohio State University, 100 W. 18th Avenue, Columbus, Ohio 43210

rajanbabu.1@osu.edu

ABSTRACT

Facile CuI-mediated N-arylation of diketopiperazine using the Fukuyama modification of the Ullmann−Goldberg reaction can be exploited in new approaches to enantiopure polycyclic diketopiperazines from easily assembled dipeptides or functionalized Schöllkopf reagents.

Several molecules containing a 2,5-diketopiperazine (**1**, DKP) moiety show promising biological activities which are helpful in treating human diseases (e.g., **2**, **3**; Figure 1).[1] However,
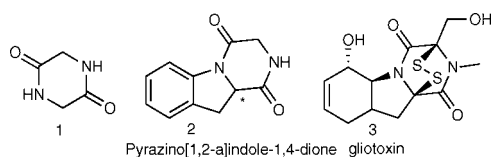

Figure 1. Diketopiperazines.

there is no general method for the synthesis of enantiopure pyrazino[1,2-*a*]indole-1,4-diones (**2**), which have potent immunosuppressive and antimicrobial activities. Reported nonstereoselective methods for this important pharmacophore

used a stepwise synthesis starting from indole 2-carboxylic acid derivatives.[2] Our studies in the area had its origin in an approach to lyngbyatoxin A, a potent PKC inhibitor, in which we planned to use a biosynthesis-inspired[3] N-arylation to construct the nine-membered lactam (Figure 2). While investigating the properties of a dipeptide precursor (**4**, X = Y = Br) for this intramolecular N-arylation, we have uncovered a number of potentially useful transformations that are relevant to the synthesis of functionalized diketopiperazines, and here we report the details of these investigations.

Our studies started with the assembly of the indolyldipeptide **13b** (Scheme 1).[4] The starting point for the synthesis is a one-step preparation of 4,7-dibromoindole **5** via the Bartoli protocol.[5] Reaction of **5** with POCl$_3$ and DMF gives the

(1) For recent reviews on the synthesis and biological activities of DKP, see: (a) Martins, M. B.; Carvalho, I. *Tetrahedron* **2007**, *63*, 9923. (b) Dinsmore, C. J.; Beshore, D. C. *Tetrahedron* **2002**, *58*, 3297.

(2) (a) Vigushin, D. M.; Brooke, G.; Willows, D.; Coombes, R. C.; Moody, C. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3661. For a Pd-catalyzed cyclization of an *N*-allyl derivative derived from indole-2-carboxylic acid, see: (b) Abbiati, G.; Beccalli, E.; Broggini, G.; Martinelli, M.; Paladino, G. *Synlett* **2006**, 73. (c) Attia, M. I.; Julius, J.; Witt-Enderby, P. A.; Zlotos, D. P. *Tetrahedron* **2007**, *63*, 754.
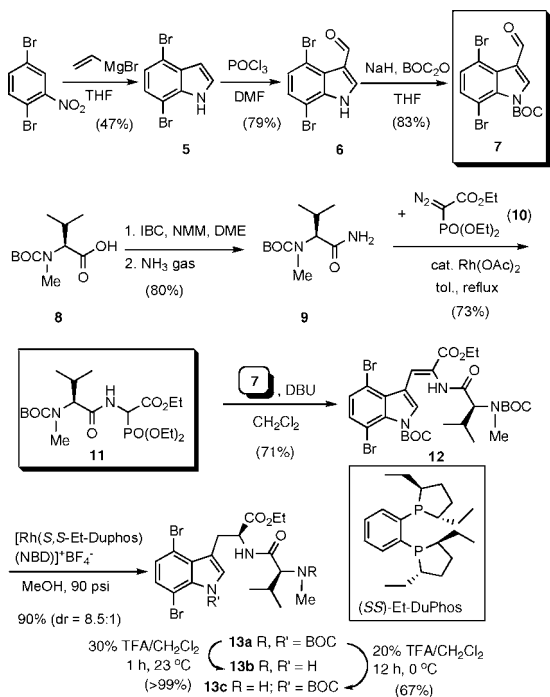
(3) Edwards, D. J.; Gerwick, W. H. *J. Am. Chem. Soc.* **2004**, *126*, 11432.

(4) See Supporting Information for experimental details and full characterization data for all new compounds including CIF for **14**.
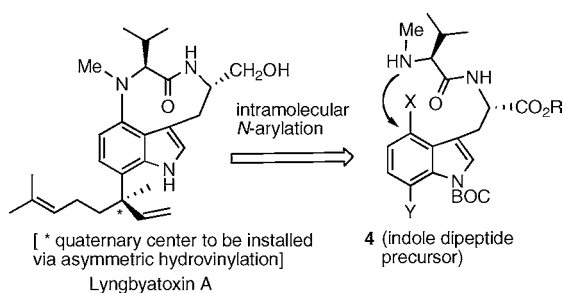
Figure 2. Lyngbyatoxin via asymmetric hydrovinylation and intramolecular N-arylation.

Scheme 1. Synthesis of Indolylpeptide for Cyclization

carboxaldehyde **6**, which after Boc-protection of the nitrogen is converted into the dehydroamino acid derivative **12** via a modified Horner–Emmons reaction using the phosphonate **11**.[6] Schmidt's phosphonate **11** was prepared by Rh-catalyzed carbene insertion into a N–H bond of the amide **9**.[7] The Horner–Emmons reaction of the aldehyde **7** with the phosphonate **11** under the prescribed procedure gives 71% of the pure (Z)-dehydrodipeptide **12** after column chroma-

tography. Installation of the additional chiral center in **12** turned out to be more challenging than we anticipated as even the best Rh catalysts give only modest diastereoselectivity in the asymmetric hydrogenation reaction. Selected results of Rh-catalyzed hydrogenation of **12** with various catalysts are reported in Table 1 in the Supporting Information.[4] Although various DIOP and bis-2,5-diphenylphosphinohexane ligands[8a] give excellent conversion at 90 psi of hydrogen in deoxygenated methanolic solution, the best result is obtained with [Rh(Et-DuPhos)(COD)]$^+$OTf^{-8b} as the precatalyst, which yields 8.5:1.0 dr of **13a**, which upon deprotection gave **13b**.

With the appropriately protected substrates **13b** and **13c** in hand, we first examined various intramolecular amination procedures to prepare the nine-membered lactam. Our initial attempts focused on Pd-catalyzed N-arylation reactions[9] of **13c**, under conditions remniscent of Buchwald's synthesis of dehydrobufotenine.[10] These experiments (Table 2, Supporting Information)[4] were uniformly unsuccessful and lead to no discernible products. Next we turned our attention to the Fukuyama modification[9f] of the Ullmann–Goldberg reaction, which he has used very effectively to prepare highly functionalized nitrogen heterocycles. Studies[4] of various substrates quickly revealed that the substrate **13b**, with both amines deprotected, is compatible with the standard conditions under which these cyclization reactions are run. However, none of the expected tricyclic compound (**15b**) is formed under a variety of conditions. Instead, a diketopiperazine derivative **14** is formed in acceptable yield (eq 1).

The structure of the tetracyclic diketopiperazine **14** has been unambiguously established by determination of the solid-state structure of a crystalline hydrate. Several features of this reaction are worthy of note: (i) under these conditions, only the 4-Br group undergoes displacement, leaving behind the 7-Br untouched; (ii) in the product isolated, there is no epimerization

(5) (a) Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989**, *30*, 2129. (b) Berthelot, A.; Piguel, S.; Le Dour, G.; Vidal, J. *J. Org. Chem.* **2003**, *68*, 9835.

(6) Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487.

(7) Buck, R. T.; Clarke, P. A.; Coe, D. M.; Drysdale, M. J.; Ferris, L.; Haigh, D.; Moody, C. J.; Pearson, N. D.; Swann, E. *Chem.—Eur. J.* **2000**, *6*, 2160.

(8) (a) Yan, Y.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 4137. (b) DuPhos ligands: Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125.

(9) For papers by leading researchers in the area, see: (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. For key references of Cu-mediated aminations, see: (c) Klapars, A.; Huang, X; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. (d) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (e) Tye, J. W.; Weng, Z.; Johns, A. M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 9971. (f) Kubo, T.; Katoh, C.; Yamada, K.; Okano, K.; Tokuyama, H.; Fukuyama, T. *Tetrahedron* **2008**, *64*, 11230. (g) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450. (h) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (i) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. For an especially valuable review that highlights the historical aspects of this crowded area and the relative synthetic advantages of the various methods, see: (j) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.

(10) Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 1028.

(11) (a) Yamada, K.; Kubo, T.; Tokuyama, H.; Fukuyama, T. *Synlett* **2002**, 231. (b) Okano, K.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 7136. (c) Yamada, K.; Kurokawa, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 6630.

at the two chiral centers, which is quite different from such a complication seen in intermolecular N-arylation of a diketopiperazine under the Buchwald conditions (CuI, *trans*-1,2-diaminocyclohexane, 110 °C, dioxane).[12]

The tetracyclic diketopiperazine, **14**, while it does not fill the need for our projected synthesis of lyngbyatoxin, nonetheless raises interesting questions about further utility of these compounds and the chemistry of its formation. For example, these compounds can be thought of as conformationally rigid congeners of indolactams, a class of compounds with significant biological activities.[13] Likewise, this chemistry, especially the tandem formation of a diketopiperazine and the N-arylation (not necessarily in that order) could provide access to novel structures from readily available precursors such as dipeptides. In addition, this route might facilitate the synthesis of a class of compounds known as mycenarubins,[14] which carry an epimerizable center next to the amide involved in the arylation.

Plausible routes to the formation of **14** from **13b** are shown in Scheme 2. It is conceivable that the expected medium

Scheme 2. Formation of **14** from **13b**
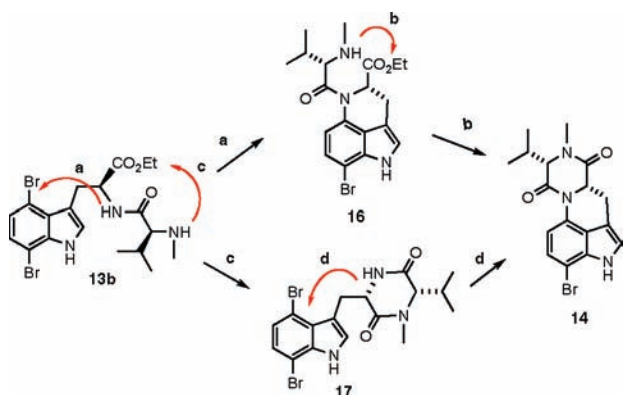
size ring formation (Figure 2) is kinetically unfavorable, and a more facile six-membered ring annulation (path a, Scheme 2) followed by cyclocondensation (path b) to give the DKP nucleus ensues. Alternatively, the dipeptide undergoes a base-mediated cyclization to a diketopiperazine (path c) followed by an intramolecular N-arylation (path d). If paths c/d are indeed followed, this might suggest that diketopiperazines prepared in situ from dipeptides could serve as broadly useful partners in N-arylation reactions.[15] To explore this possibility, we decided to examine the cyclization of two sets of simpler substrates, one derived from dipeptides, where we can explore the tandem reactions, and another, preformed diketopiperazines, where the direct N-arylation of these substrates can be studied.

(12) Beghyn, T.; Hounsou, C.; Deprez, B. P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 789.

(13) Kozikowski, A. P.; Shum, P. W.; Basu, A.; Lazo, J. S. *J. Med. Chem.* **1991**, *34*, 2420, and references cited therein.

(14) Peters, S.; Spiteller, P. *Eur. J. Org. Chem.* **2007**, 1571.

(15) For the use of diketopiperazines in intramolecular cyclization of 2-iodotryptophans, see: Coste, A.; Toumi, M.; Wright, K.; Razafimahaléo, V.; Couty, F.; Marrot, J.; Evano, G. *Org. Lett.* **2008**, *10*, 3841.

Scheme 3. Synthesis of 2-(2-Bromobenzyl)diketopiperazine Precursors
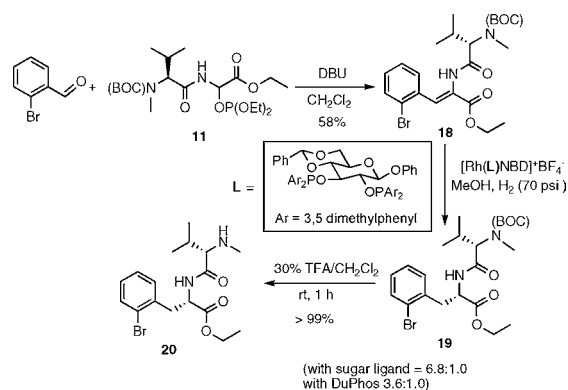
The dipeptide substrates were prepared (Scheme 3) following the scheme developed earlier for the synthesis of **13b** (Scheme 1). In this instance, for the hydrogenation of the dehydrodipeptide **18**, our D-glucose-derived 1,2-bis-diarylphosphinite-Rh complexes[16] (Table 3 in Supporting Information) gave the best results (dr = 6.8:1.0) for **19**.

Scheme 4. Synthesis of 2-(2-Halobenzyl)dipeptides via a Schöllkoff Reagent
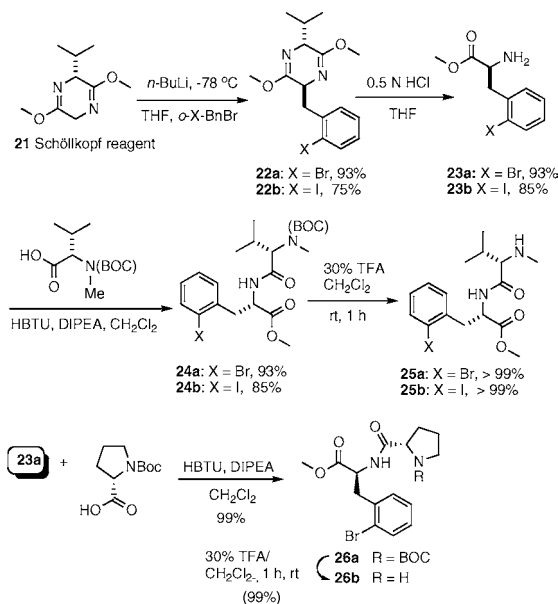
In a different approach, the desired dipeptides were also prepared via the Schöllkopf reagents (Scheme 4). The *ortho*-halophenylalanine derivatives **23a** and **23b** are very useful intermediates that could be used for the synthesis of a wide variety of dipeptide derivatives in enantiomerically pure

(16) (a) RajanBabu, T. V.; Ayers, T. A.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 4101. (b) RajanBabu, T. V.; Ayers, T. A.; Halliday, G. A.; You, K. K.; Calabrese, J. C. *J. Org. Chem.* **1997**, *62*, 6012.

form. Examples of Phe-Val (**25a**, **25b**) and Phe-Pro (**26b**) derivatives are illustrative. The dipeptides **19**, **20**, **25b**, and **26b** were subjected to the Cu-mediated cyclization reactions (Scheme 5), and the results are shown in Table 1. The Boc-

Scheme 5. Tandem Cycliztion and Intramolecular N-Arylation for the Formation of Diketopiperazines from Dipeptides

19: R = Boc, X = Br
20: R = H, X = Br
25b: R = H, X = I

26b   **29** (48%)   **30** (12%)
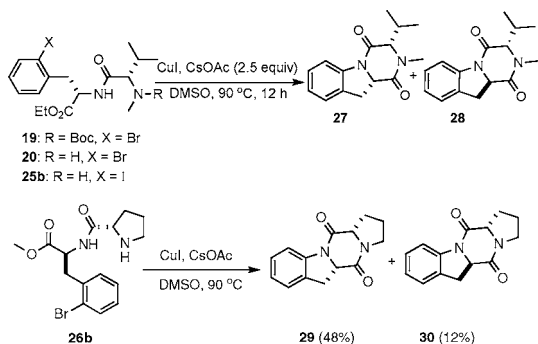
Table 1. Cu-Mediated Tandem Cyclization/N-Arylation

| no.	sm	conditions[a]	product yield[c](%)
1	**19**	CuI (1 equiv)	no cyclized product (**19** recovered)
2	**19**	CsOAc (2.5 equiv) only[b]	no cyclized product (**19** recovered, 23% racemization)
3	**20**	CuI (1 equiv)	**27/28** (59, 18)
4	**20**	CuI (0.1 equiv)	**27/28** (20, 69)
5	**25b**	CuI (1 equiv)	**27/28** (77, 8)
6	**25b**	CuI (0.1 equiv)	**27/28** (32, 61)
7	**26b**	CuI (1 equiv)	**29/30** (48, 12)

[a] Unless otherwise mentioned, all reactions used 2.5 equiv of CsOAc and heated to 90 °C for 12 h under N$_2$ in DMSO as a solvent. [b] Reaction temperature was 110 °C without CuI. [c] Isolated yields, and the extent of isomerization was determined by ^{1}H NMR.

protected substrate **19** under a variety of conditions *does not* undergo any cyclization (entries 1 and 2). With CsOAc alone, substantial isomerization of the starting material is observed (entry 2). Substrates in which both nitrogens of the dipeptide are free of any protecting group undergo the tandem cyclization/N-arylation (entries 3−7). The extent of epimerization seems to depend on the relative rates of the cyclization and epimerization. Thus, the arylbromide substrate **20** with a stoichiometric amount of CuI gives 59% of the diketopiperazine (**27**) with up to 18% isomerization (entry 3), while the same reaction under catalytic conditions (10 mol % of CuI) yields the isomerized product **28** as the major component (entry 4). Best results are seen by treating **25b** with 1 equiv of CuI and 2.5 equiv of CsOAc in DMSO at 90 °C, conditions under which 77% yield of the cyclic product **27** is obtained. Use of catalytic amounts of CuI leads to substantial epimerization to the more stable *trans*-2,5-dialkyl derivative (entry 6). The tandem cyclization−N-arylation appears to be quite general, and even a proline-derived dipeptide (**26b**) undergoes the reaction (entry 7). These results along with absence of cyclization in the N-protected derivative **19** (entry 1) suggest that the diketopiperazine

nitrogen is a significantly better nucleophile in N-arylation reactions. These observations are consistent with the facile cyclization of the indolyldipeptide **13b** (eq 1, Scheme 2), which prompted us to initiate this line of research.

The results described in the previous section raises the possibility that partially hydrolyzed Schöllkopf reagents could be used *directly* (without going through an intermediate amino acid) for the synthesis of diketopiperazine-annulated heterocycles, especially the 2,5-*trans* derivatives. An example of this seldom used strategy[17] is shown in Scheme 6. The

Scheme 6. Cu(I)-Catalyzed Annulation of Diketopiperazines

ent-**22a**: X = Br
ent-**22b**: X = I

31a: X = Br (90%)
31b: X = I (93%)
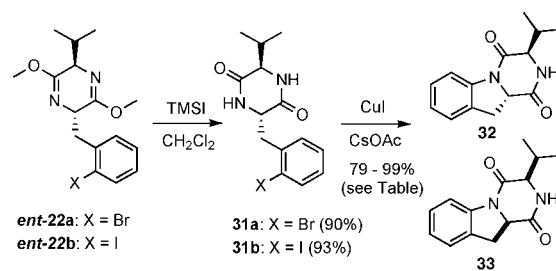
substrate	CuI (mol %)	yields (%) 32/33
31a	100	84/13
31a	10	79/16
31b	100	99/(-)
31b	10	95/<2

ortho-halobenzyl derivatives **22a** and **22b**, readily prepared from Schöllkopf reagents (Scheme 4), are partially hydolyzed to the diketopiperazines **31a** and **31b**. Intramolecular N-arylation of these substrates gives excellent yields of the annulated products **32** and **33**.

The iodo derivative **31b** is an especially good substrate showing no sign of epimerization under the stoichiometric CuI-mediated reactions. For characterization purposes, we converted **32** into *ent*-**28**, a compound that was prepared by the asymmetric hydrogenation/tandem cyclization/N-arylation route (Schemes 4 and 5).

In summary, in this work, we demonstrate that the facile CuI-mediated N-arylation of diketopiperazine can be exploited in new approaches to enantiopure bicyclic diketopiperazines from easily assembled dipeptides or functionalized Schöllkopf reagents.

Supporting Information Available: Experimental procedures for the synthesis of all new compounds and their full characterization including the CIF for **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100663Y

(17) For another notable example, see: Andrei, M.; Römming, C.; Undheim, K. *Tetrahedron: Asymmetry* **2004**, *15*, 1359.