ORGANIC LETTERS

2006
Vol. 8, No. 11
2353−2356

A Concise Stereoselective Synthesis of Preussin, 3-*epi*-Preussin, and Analogues

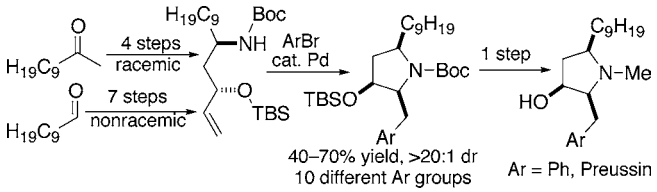
Myra Beaudoin Bertrand and John P. Wolfe*

Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan, 48109-1055

jpwolfe@umich.edu

Received March 15, 2006

ABSTRACT



A new stereoselective synthesis of the antifungal and antitumor agents Preussin and 3-*epi*-Preussin via a Pd-catalyzed carboamination of a protected amino alcohol is described. The key transformation leads to simultaneous formation of the N–C2 bond and the C1′–aryl bond, and allows installation of the aryl group one step from the end of the sequence. This strategy permits the facile construction of a variety of preussin analogues bearing different aromatic groups.

The natural product preussin (**1**) was first isolated in 1988 by Schwartz and co-workers from the fermentation extracts of *Preussia sp*. and *Aspergillus ochraceus*.[1] Initial screens revealed that this compound had significant antifungal activity,[1,2] and more recent work has demonstrated that preussin induces apoptosis in a number of human cancer cell lines and is a potent (IC_{50} = 500 nm) inhibitor of cyclin-E kinase.[3] Preussin has also shown antiviral activity, and is believed to inhibit −1 ribosomal frameshifting of RNA-based viruses.[4] Interestingly, all eight stereoisomers of preussin exhibit biological activity.[5]

Owing to its interesting biological properties, preussin has been a popular target for total synthesis, and has been prepared via 22 different routes ranging from 5 steps to over 23 steps.[6−9] However, the large majority of these syntheses employ phenylalanine as the source of the C1′-phenyl group, and most other routes also install this group early in the synthetic sequence.[7,10] Thus, the previously described syntheses of preussin are generally not well suited to the rapid generation of preussin analogues that differ in the nature of the aryl substituent. A concise approach to this molecule that involves the installation of the aryl group near the end of

(1) Schwartz, R. E.; Liesch, J.; Hensens, O.; Zitano, L.; Honeycutt, S.; Garrity, G.; Fromtling, R. A.; Onishi, J.; Monaghan, R. *J. Antibiot.* **1988**, *41*, 1774.

(2) (a) Johnson, J. H.; Phillipson, D. W.; Kahle, A. D. *J. Antibiot.* **1989**, *42*, 1184. (b) Kasahara, K.; Yoshida, M.; Eishima, J.; Takesako, K.; Beppu, T.; Horinouchi, S. *J. Antibiot.* **1997**, *50*, 267.

(3) Achenbach, T. V.; Slater, P. E.; Brummerhop, H.; Bach, T.; Müller, R. *Antimicrob. Agents Chemother.* **2000**, *44*, 2794.

(4) Kinzy, T. G.; Harger, J. W.; Carr-Schmid, A.; Kwon, J.; Shastry, M.; Justice, M.; Dinman, J. D. *Virology* **2002**, *300*, 60.

(5) Okue, M.; Watanabe, H.; Kasahara, K.; Yoshida, M.; Horinouchi, S.; Kitahara, T. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 1093.

(6) Kitahara has described a nonstereoselective route that affords all eight stereoisomers of preussin in a two-step sequence. The isomers were separated by preparative chiral HPLC. See ref 5.

(7) For a recent review, see: Basler, B.; Brandes, S.; Spiegel, A.; Bach, T. *Top. Curr. Chem.* **2005**, *243*, 1.

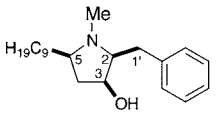
(8) For early synthetic studies see: (a) Shimazaki, M.; Okazaki, F.; Nakajima, F.; Ishikawa, T.; Ohta, A. *Heterocycles* **1993**, *36*, 1823. (b) McGrane, P. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1993**, *115*, 11485. (c) Overhand, M.; Hecht, S. M. *J. Org. Chem.* **1994**, *59*, 4721. (d) Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241.

(9) For recent syntheses, see: (a) Canova, S.; Bellosta, V.; Cossy, J. *Synlett* **2004**, 1811. (b) Davis, F. A.; Deng, J. *Tetrahedron* **2004**, *60*, 5111. (c) Raghavan, S.; Rasheed, M. A. *Tetrahedron* **2003**, *59*, 10307. (d) Huang, P.-Q.; Wu, T.-J.; Ruan, Y.-P. *Org. Lett.* **2003**, *5*, 4341. (e) Dikshit, D. K.; Goswami, L. N.; Singh, V. S. *Synlett* **2003**, 1737.

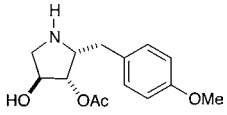
(10) Two strategies allow installation of the aryl moiety within 1−3 steps of the final target. Davis generated the C-2 benzyl group as the final step via reaction of lithium diphenyl cuprate with a pyrrolidinylmethyl iodide (40% yield, single diastereomer; 10 steps total, 9% overall yield). Bach employed a Paternò−Büchi reaction of benzaldehyde with a dihydropyrrole (4:1 dr, 53% yield after separation of diastereomers) followed by a two-step deprotection sequence to generate the benzyl substituent (39% over 3 steps; 9 steps total, 11% overall yield). See: (a) Reference 9b. (b) Bach, T.; Brummerhop, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 3400.

10.1021/ol0606435 CCC: $33.50
Published on Web 04/27/2006

the synthetic route would be of value for the straightforward construction of preussin derivatives, particularly if the arene could be incorporated in a manner that would permit synthesis of functionalized and/or heteroaryl analogues from readily available precursors.



Preussin (**1**)

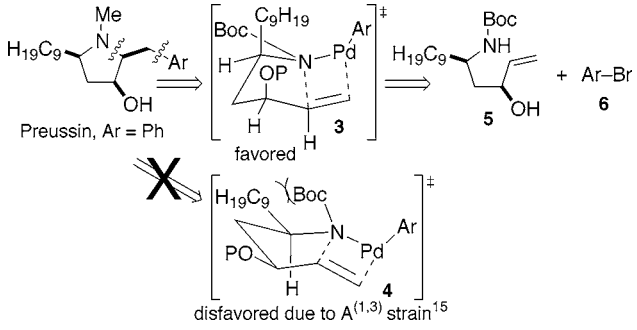


Anisomycin (**2**)

Due to the limitations of existing synthetic routes, very little work has been conducted on the synthesis and study of preussin analogues.[11] However, limited studies on the effect of arene substitution on the activity of the related alkaloid anisomycin (**2**) have been performed that demonstrate the nature of the C1′−aryl group has a profound effect on biological activity.[12,13] For example, an anisomycin analogue bearing a phenyl group in place of the *p*-methoxyphenyl moiety showed 40-fold less cytotoxic potency than **2** against a human KB cell line.[13] Thus, a synthetic route to preussin that allows facile modification of the arene moiety may be of significant biological interest.

In this Letter we describe a new strategy for the stereoselective synthesis of preussin via the Pd-catalyzed carboamination[14] of a protected amino alcohol. The key disconnection is a retrosynthetic cleavage of both the N−C2 bond and C1′−aryl bond to yield starting amino alcohol **5** and aryl bromide **6** (Scheme 1). This strategy has two

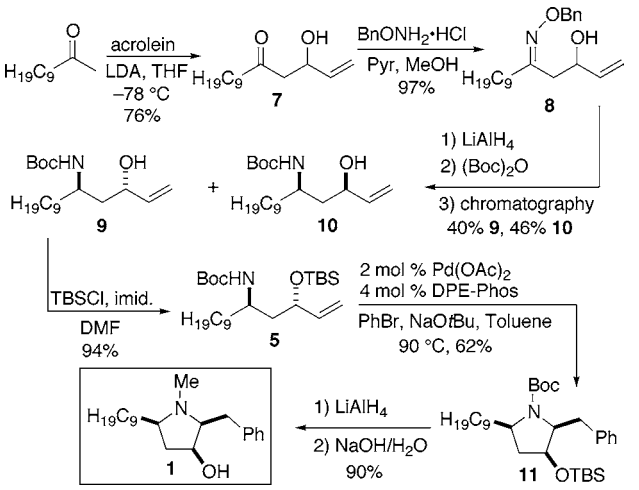
Scheme 1. Key Disconnection and Stereocontrol



significant implications for the construction of the molecule. It allows the installation of a variety of different functionalized arenes one step from the end of the sequence, which permits the facile construction of a number of preussin analogues. It also allows control of the relative stereochemistry at C2 through use of $A^{(1,3)}$-strain[15] in conjunction with a favorable eclipsed orientation of the Pd−N and alkene C−C bonds during the stereochemistry determining step of the carboamination,[14] which promotes cyclization through transition state **3** in which the C-3 oxygen substituent is oriented in a pseudoaxial position.

To probe the feasibility of the key Pd-catalyzed carboamination reaction, our initial studies focused on the development of a synthesis of (±)-preussin. As outlined in Scheme 2, aldol reaction between commercially available 2-undecanone and acrolein provided keto-alcohol **7** in 76% yield. Conversion of **7** to the *O*-benzyl oxime **8** proceeded smoothly, and was followed by a one-pot sequence of $LiAlH_4$ reduction and Boc-protection to provide an 86% yield of a 1:1.2 mixture of readily separable amino alcohol diastereomers **9** and **10**. Although stereoselective reductions of β-hydroxy oxime ethers have been previously described,[16] we elected to employ nonselective conditions to allow access to both *syn*- and *anti*-amino alcohol substrates for the Pd-catalyzed cyclization reactions, which ultimately provide two different biologically active pyrrolidine derivatives (**1** and **14**).

Scheme 2. Synthesis of (±)-Preussin



TBS protection of *anti*-amino alcohol **9** provided **5**, the substrate for the key Pd-catalyzed carboamination reaction. In the event, treatment of **5** with bromobenzene and NaO*t*Bu in the presence of catalytic $Pd(OAc)_2$/dpe-phos[17] provided pyrrolidine **11** in 62% isolated yield with >20:1 diastereo-

(11) To date, no analogues of preussin have been prepared that are modified on the aromatic ring. Bach has reported the synthesis of two analogues that differ in the nature of the C5 alkyl chain, and four analogues that differ in the nature of the C-3 substituent have been described in the patent literature. See: (a) Bach, T.; Brummerhop, H.; Harms, K. *Chem. Eur. J.* **2000**, *6*, 3838. (b) Suzuki, K.; Miike, N.; Kawamoto, E. Jpn. Kokai. Tokkyo Koho 2003277357, 2003.

(12) Hall, S. S.; Loebenberg, D.; Schumacher, D. P. *J. Med. Chem.* **1983**, *26*, 469.

(13) Schwardt, O.; Veith, U.; Gaspard, C.; Jäger, V. *Synthesis* **1999**, 1473.

(14) (a) Ney, J. E.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3605. (b) Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 8644. (c) Bertrand, M. B.; Wolfe, J. P. *Tetrahedron* **2005**, *61*, 6447. (d) Yang, Q.; Ney, J. E.; Wolfe, J. P. *Org. Lett.* **2005**, *7*, 2575.

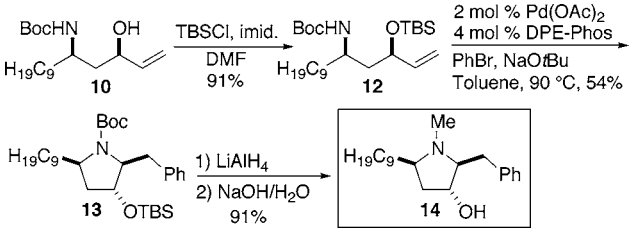
(15) For a discussion of allylic strain related to the partial double bond character between the nitrogen atom and the carbonyl carbon in α-substituted amides and carbamates see: (a) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841. (b) Hart, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 397. (c) Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547. (d) Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Heterocycles* **1987**, *26*, 2805.

(16) Narasaka, K.; Ukaji, Y.; Yamazaki, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 525.

selectivity. As noted above, the desired stereoisomer most likely arises from transition state **3** (Scheme 1) in which the C_9 chain is oriented in a pseudoaxial position to minimize $A^{(1,3)}$-strain between this substituent and the *N*-Boc group.[15] Although the C3-OTBS group is also pseudoaxial, the energetic cost of this conformation is lower than that of the $A^{(1,3)}$-strain in transition state **4** in which both the C_9 chain and the OTBS group are equatorial. One-pot reduction and deprotection of **11** afforded (±)-preussin (**1**) in 90% yield as a single diastereomer. This six-step sequence proceeded with an overall yield of 15% from 2-undecanone.

The *syn*-amino alcohol **10** was converted to (±)-3-*epi*-preussin (**14**)[8a,d] by using a sequence of reactions analogous to that described above (Scheme 3). The stereoselectivity of

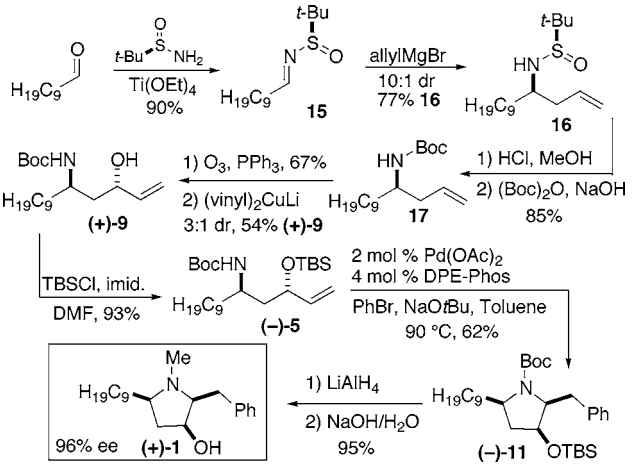
Scheme 3. Synthesis of (±)-3-*epi*-Preussin



the Pd-catalyzed cyclization of **12** was high, although the chemical yield obtained in the reaction of the syn-diastereomer **12** (54%) was slightly lower than that achieved for the reaction of the anti-isomer **5** (62%). This route provided the desired pyrrolidine **14** as a single isomer in an overall yield of 15%. Thus, the strategy described herein provides straightforward access to both racemic preussin diastereomers in comparable yields and stereoselectivities.[18]

Having demonstrated the feasibility of Pd-catalyzed carboamination for the construction of preussin, we turned our attention toward the development of an asymmetric synthesis of the naturally occurring (+)-enantiomer. As shown in Scheme 4, addition of allylmagnesium bromide to enantiopure sulfinylimine **15** under Ellman's conditions[19] afforded **16**, which was isolated in 77% yield as a single diastereomer upon purification.[20] Cleavage of the chiral auxiliary and protection of the resulting primary amine afforded **17** in 85% yield. Ozonolysis of **17** (67%) followed by vinylcuprate addition[21] to the resulting *β*-amino aldehyde **18** generated (+)-**9** with 3:1 diastereoselectivity; the desired pure anti-diastereomer was obtained in 54% yield after chromatographic separation. The remaining three steps proceeded with similar yields and selectivities to those obtained from the

Scheme 4. Synthesis of (+)-Preussin



racemic route, and provided (+)-preussin {$[\alpha]^{23}_D$ +21.2 (*c* 1.0, $CHCl_3$) [lit.[2] $[\alpha]^{25}_D$ +22.0 (*c* 1.0, $CHCl_3$)]} with an overall yield of 12% in nine steps from commercially available decanal.

To demonstrate the amenability of this strategy toward the synthesis of differentially arylated preussin analogues, Pd-catalyzed reactions of **5** and **12** were conducted with a variety of different aryl bromide coupling partners. To illustrate the utility of this method for the rapid generation of useful quantities of analogues the Pd/dpe-phos catalyst was employed for all substrate combinations. However, previous studies indicate that other ligands may provide superior results for certain aryl bromide coupling partners.[14c] Thus, the yields obtained in these transformations are not optimized on a case-by-case basis. As shown in Table 1, the cyclization reactions proceed in moderate to good yields for a variety of different aryl bromides including substrates that are electron-rich (entries 3 and 4),[22] electron poor (entries 1−2, 5−6, 9, and 12), or sterically hindered (entry 8). Several functional groups are tolerated, and heterocyclic aryl bromides can also be employed (entries 10 and 11). In most cases examined, the cyclizations of *anti*-amino alcohol derivative **5** proceeded in higher yield than the analogous reactions of *syn*-amino alcohol derivative **12**. In all cases the reactions proceeded with >20:1 diastereoselectivity as judged by ^1H and ^{13}C NMR analysis.

To illustrate that the *N*-Boc-*O*-TBS-preussin analogues could be converted to *N*-methyl-3-hydroxy-2-(arylmethyl)-pyrrolidines that are closely related to the natural product, a subset of the products shown in Table 1 were deprotected in a 1−2 step sequence. As shown in Table 2, deprotection was effected by using $LiAlH_4$ followed by treatment with aqueous base or TBAF for products bearing unreactive aromatic functionality. Alternatively, deprotection was also achieved through one-pot Boc cleavage and reductive ami-

(17) Dpe-phos = bis(2-diphenylphosphinophenyl) ether.

(18) The (−)-B-chlorodiisopinocampheylborane-mediated asymmetric aldol reaction between 2-undecanone and acrolein provided **7** in 78% yield and 48% ee, using Paterson's conditions. See: Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663.

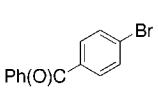
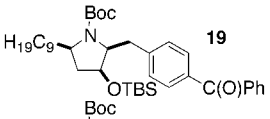
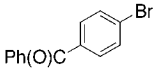
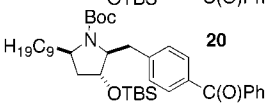
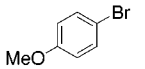
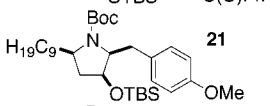
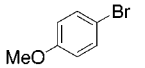
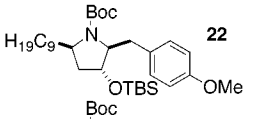
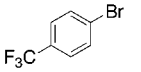
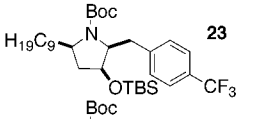
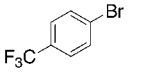
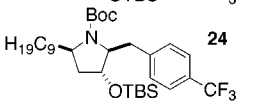
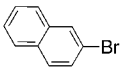
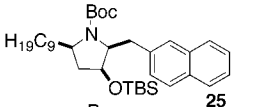
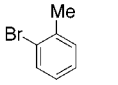
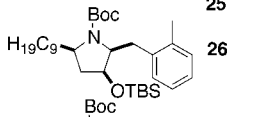
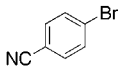
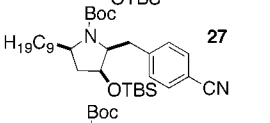
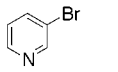
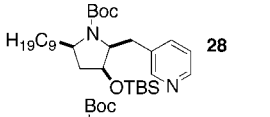
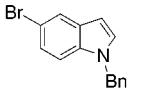
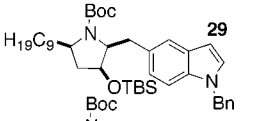
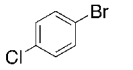
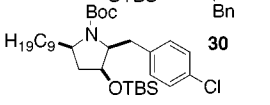
(19) Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883.

(20) The crude reaction mixture was judged to contain a 10:1 mixture of diastereomers by ^1H NMR analysis.

(21) Toujas, J.-L.; Toupet, L.; Vaultier, M. *Tetrahedron* **2000**, *56*, 2665.

(22) Use of high-purity starting material (>97% by NMR and GC) was essential to obtain high yields in reactions of electron-rich aryl bromides. Use of starting material with trace (ca 5%) impurities led to catalyst deactivation and formation of complex mixtures of products with these substrate combinations.

Table 1. Synthesis of *N*-Boc-*O*-TBS-Preussin Analogues[a]

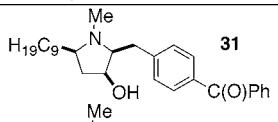
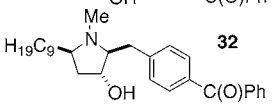
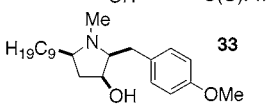
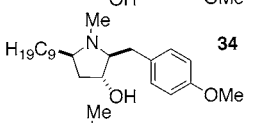
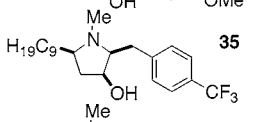
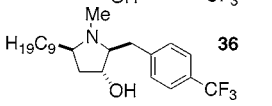
entry	substrate	ArBr	product	yield (%)
1	**5**		 **19**	70
2	**12**		 **20**	65
3	**5**		 **21**	52
4	**12**		 **22**	49
5	**5**		 **23**	69
6	**12**		 **24**	52
7	**5**		 **25**	69
8	**5**		 **26**	57
9	**5**		 **27**	62
10	**5**		 **28**	54
11	**5**		 **29**	40
12	**5**		 **30**	70

[a] Reagents and conditions: 1.0 equiv ofsubstrate, 1.2 equiv of ArBr, 2.3 equiv of NaO*t*Bu, 2 mol % of $Pd(OAc)_2$, 4 mol % of dpe-phos, toluene, 90 °C.

nation with formic acid/formaldehyde followed by treatment with TBAF. The latter conditions tolerate functional groups (e.g., ketones, trifluoromethyl substituents) that would be reduced by $LiAlH_4$. Both deprotection protocols provided the desired products in excellent yields.

In conclusion, we have developed concise, stereoselective routes to (+)-preussin, (±)-preussin, and (±)-3-*epi*-preussin.

Table 2. Deprotection of *N*-Boc-*O*-TBS-Preussin Analogues[a]

entry	substrate	method	product	yield (%)
1	**19**	B	 **31**	83
2	**20**	B	 **32**	84
3	**21**	A	 **33**	85
4	**22**	A	 **34**	89
5	**23**	B	 **35**	80
6	**24**	B	 **36**	81

[a] Reagents and conditions: Method A: (i) $LiAlH_4$, THF, 60 °C; (ii) H_2O or TBAF. Method B: (i) HCO_2H, HCHO; (ii) TBAF, THF.

These routes feature a new strategy for the synthesis of 2-benzylpyrrolidine alkaloids that allows the construction of both the C2−N and the C1′−Ar bonds in a single step near the end of the synthetic sequence. This strategy allows the facile synthesis of differentially arylated preussin analogues, and provides straightforward access to derivatives that could not be easily and rapidly prepared with previously developed routes. This strategy is potentially applicable to other members of this class of natural products; further studies in this area are currently underway.

Acknowledgment. This research was supported by the NIH-NIGMS (GM 071650) and the University of Michigan. J.P.W. thanks the Camille and Henry Dreyfus Foundation for a New Faculty Award, Research Corporation for an Innovation Award, and Eli Lilly for a Grantee Award. Additional unrestricted support was provided by Amgen, Eli Lilly, and 3M.

Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^1H and ^{13}C spectra for all compounds reported in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0606435