ORGANIC LETTERS

2010
Vol. 12, No. 18
4034−4037

A Concise and Stereoselective Synthesis of Hydroxypyrrolidines: Rapid Synthesis of (+)-Preussin

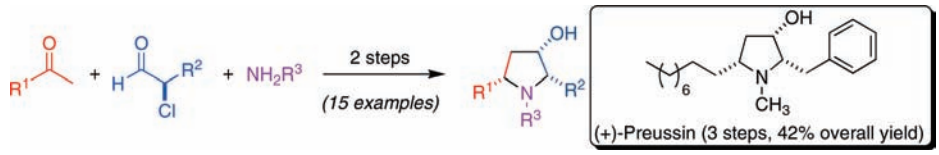
Jason A. Draper and Robert Britton*

Department of Chemistry, Simon Fraser University, Burnaby, British Columbia V5A 1S6, Canada

rbritton@sfu.ca

Received July 14, 2010

ABSTRACT



A convergent and stereoselective synthesis of 2,5-disubstituted 3-hydroxypyrrolidines has been developed that involves reductive annulation of *β*-iminochlorohydrins, which are readily available from *β*-ketochlorohydrins, and provides rapid access to a variety of 2,5-*syn*-pyrrolidines. Application of this process to the concise (three-step) synthesis of the fungal metabolite (+)-preussin and analogues of this substance is reported.

A number of biologically active alkaloids incorporate an oxygenated pyrrolidine as a key skeletal feature.[1] For example, the pyrrolizidine (e.g., hyacinthacine A_4 (**1**))[2] alkaloids possess a dihydroxypyrrolidine core and exhibit inhibitory activity toward various carbohydrate processing enzymes,[3] and the 3-hydroxypyrrolidine salinosporamide C (**2**)[4] is biogenetically related to the potent 20S proteasome inhibitor salinosporamide A.[5] In addition, preussin (**3**), which was originally isolated from a liquid fermentation broth of *Aspergillus ochraceus*,[6,7] displays broad spectrum antifungal activity[7] and has shown growth-inhibitory and cytotoxic effects on human cancer cells.[8] Despite the varied and potentially useful biological activities attributed to these and other pyrrolidine alkaloids, defining a concise, general, and

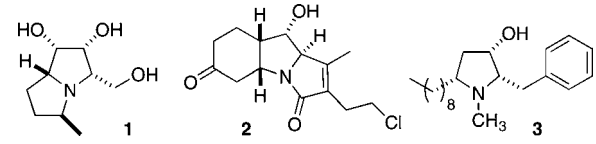


Figure 1. Hydroxypyrrolidine-containing natural products hyacinthacine A_4 (**1**), salinosporamide C (**2**), and preussin (**3**).

stereoselective strategy for their synthesis remains a significant challenge.[9] Thus, while at least 25 strategically unique syntheses of preussin (**3**) have been reported,[10−12] owing to their overall length (up to 22 steps) and/or reliance on amino acids or carbohydrates as starting materials, many of these synthetic routes are not well suited for the production of

(1) (a) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 191. (b) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773. (c) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435.

(2) Yamashita, T.; Yasuda, K.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J.; Asano, N. *J. Nat. Prod.* **2002**, *65*, 1875.

(3) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265.

(4) Williams, P. G.; Buchanan, G. O.; Feling, R. H.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *J. Org. Chem.* **2005**, *70*, 6196.

(5) Feling, R.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 355.

(6) For the original isolation of preussin, see: 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.

(7) For the relative and absolute stereochemical assignment of preussin, see: Johnson, J. H.; Phillipson, D. W.; Kahle, A. D. *J. Antibiot.* **1989**, *42*, 1184.

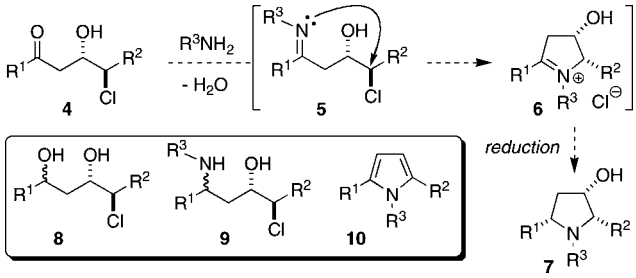
(8) Achenbach, T. V.; Slater, E. P.; Brummerhop, H.; Bach, T.; Müller, R. *Antimicrob. Agents Chemother.* **2000**, *44*, 2794.

(9) For reviews on pyrrolidine, pyrrolizidine, and indolizidine syntheses, see: (a) Stocker, B. L.; Dangerfield, E. M.; Win-Mason, A. L.; Haslett, G. W.; Timmer, M. S. M. *Eur. J. Org. Chem.* **2010**, 1615. (b) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571. (c) Huang, P.-Q. *Synlett* **2006**, 1133. (d) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693. (e) Yoda, H. *Curr. Org. Chem.* **2002**, *6*, 223. (f) Pichon, M.; Figadere, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927.

10.1021/ol101631e
Published on Web 08/20/2010

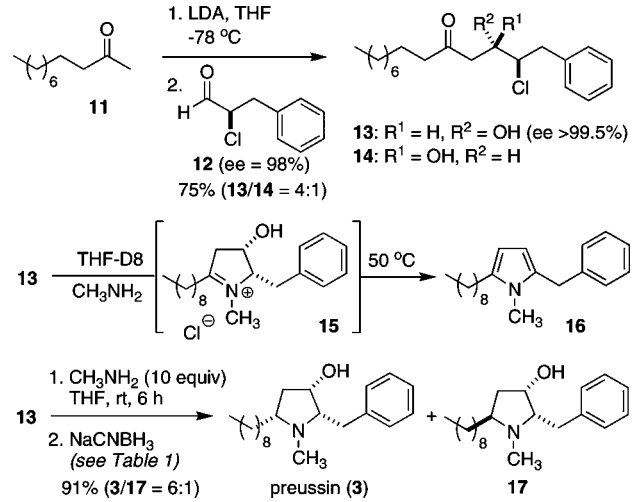
structural analogues or related natural products. As notable exceptions, Wolfe[12c] and Davis[12a] have recently reported 9- and 10-step syntheses of preussin in which late-stage introduction of the phenyl ring via Pd-catalyzed carboamination[12c] or Horner−Wadsworth−Emmons[12a] reactions facilitates the synthesis of derivatives of preussin with variously functionalized aromatic rings. Herein, we describe a concise and stereoselective synthesis of 3-hydroxypyrrolidines that provides rapid access to preussin (**3**) and analogues of this substance and should be adaptable for the production of other structurally related alkaloids (e.g., **1** and **2**).

Scheme 1. Strategy for Hydroxypyrrolidine Synthesis



As outlined in Scheme 1, our synthetic strategy centered on the reductive amination of β-ketochlorohydrins,[13] which are readily available from the lithium aldol reaction of a methyl ketone and an α-chloroaldehyde.[14] Thus, it was anticipated that reaction of a primary amine with a β-ketochlorohydrin (e.g., **4**) would afford a transient imine (e.g., **5**),[15] the subsequent cyclization of which would lead to a pyrrolinium intermediate (e.g., **6**)[16] and, following reduction, the desired 2,5-disubstituted-3-hydroxypyrrolidine in a *one-pot* process. Presumably, the diastereochemical outcome of the pyrrolinium reduction would be governed by the substituent at C2, affording *all-syn* pyrrolidines (e.g., **7**) from 1,2-*anti*-chlorohydrins.[17] Despite the apparent simplicity of this route, we were cognizant of the potential side products (see inset, Scheme 1) derived from reduction of the intermediate β-keto- or iminochlorohydrins and/or dehydration/isomerization of the pyrrolinium **6**. Thus, our initial efforts focused on the avoidance of these byproducts and optimization of this general strategy for the selective production of the 3-hydroxypyrrolidine (+)-preussin (**3**).

Scheme 2. Enantioselective Synthesis of (+)-Preussin (**3**)



As detailed in Scheme 2, treatment of the lithium enolate derived from 2-undecanone (**11**) with (2*R*)-2-chlorohydrocinnamaldehyde (**12**)[14,18] (Scheme 2) afforded a mixture of the diastereomeric chlorohydrins **13** and **14** (dr = 4:1).[19] The relatively low level of stereocontrol in the aldol reaction was attributed to the β-phenyl substituent in the α-chloroaldehyde **12**,[20] as lithium aldol reactions of both linear or branched aliphatic α-chloroaldehydes typically provide the corresponding *anti*-chlorohydrins with diastereomeric ratios in excess of 10:1.[13] Notwithstanding, with optically enriched[19] β-ketochlorohydrin **13** in hand, a number of experiments were carried out to assess the viability of the imine formation/cyclization/reduction strategy. For example, treatment of the β-ketochlorohydrin **13** with methylamine in THF-D8 resulted

(10) For early syntheses of preussin, see: (a) Pak, C. S.; Lee, G. H. *J. Org. Chem.* **1991**, *56*, 1128. (b) Shimazaki, M.; Okazaki, F.; Nakajima, F.; Ishikawa, T.; Ohta, A. *Heterocycles* **1993**, *36*, 1823. (c) McGrane, P. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1993**, *115*, 11485. (d) Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241. (e) Overhand, M.; Hecht, S. H. *J. Org. Chem.* **1994**, *59*, 4721.

(11) For a comprehensive review of preussin syntheses up to June 2003, see: Basler, B.; Brandes, S.; Speigel, A.; Bach, T. *Top. Curr. Chem.* **2005**, *243*, 1.

(12) For recent syntheses of preussin, see: (a) Davis, F. D.; Zhang, J.; Qiu, H.; Wu, Y. *Org. Lett.* **2008**, *10*, 1433. (b) Gogoi, N.; Boruwa, J.; Barua, N. C. *Eur. J. Org. Chem.* **2006**, 1722. (c) Bertrand, M. B.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2353. (d) Davis, F. A.; Deng, J. *Tetrahedron* **2004**, *60*, 5111. (e) Canova, S.; Bellosta, V.; Cossy, J. *Synlett* **2004**, 1811. (f) Okue, M.; Watanabe, H.; Kasahara, K.; Yoshida, M.; Horinouchi, S.; Kitahara, T. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 1093.

(13) Kang, B.; Mowat, J.; Pinter, T.; Britton, R. *Org. Lett.* **2009**, *11*, 1717. (b) Kang, B.; Chang, S.; Decker, S.; Britton, R. *Org. Lett.* **2010**, *12*, 1716.

(14) For the asymmetric α-chlorination of aldehydes, see: (a) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108. (b) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790. (c) Amatore, M.; Beeson, T. D.; Brown, S. P.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5121.

(15) Our anticipation that imine formation (i.e., **4** → **5**) would occur preferentially over direct chloride displacement was predicated by the fact that (3*S*,4*R*)-3-chloro-1-phenyl-4-octanol failed to react with methylamine in THF after 24 h at rt.

(16) For the intramolecular displacement of a *primary* alkyl chloride by an imine, see: (a) De Kimpe, N.; D'Hondt, L.; Stanoeva, E. *Tetrahedron Lett.* **1991**, *32*, 3879. (b) Maeda, K.; Yamamoto, Y.; Tomimoto, K.; Mase, T. *Synlett* **2001**, 1808. (c) Tehrani, K. K.; D'hooghe, M.; De Kimpe, N. *Tetrahedron* **2003**, *59*, 3099. (d) Breuning, M.; Steiner, M.; Mehler, C.; Paasche, A.; Hein, D. *J. Org. Chem.* **2009**, *74*, 1407. (e) Reddy, L. R.; Prashad, M. *Chem. Commun.* **2010**, *46*, 222.

(17) For the reduction of related pyrrolinium species see refs 10c, e and 11. Brenneman, J. B.; Martin, S. F. *Org. Lett.* **2004**, *6*, 1329.

(18) The α-chloroaldehyde **12** was prepared following the procedure reported by MacMillan and coworkers in ref 14c in 98% ee. The optical purity of **12** was determined by chiral HPLC analysis (see the Supporting Information) following conversion to the β-ketochlorohydrin **13**.

(19) The β-ketochlorohydrins **13** and **14** decomposed to varying degrees when purified by silica gel flash chromatography. Consequently, both compounds were ultimately purified by recrystalization from hexanes. Notably, the optical purity of the recrystallized β-ketochlorohydrin **13** was >99.5% ee as determined by chiral HPLC analysis.

in complete conversion to the corresponding *N*-methylimine after 6 h, as observed by ^{1}H and ^{13}C NMR spectroscopy. While the pyrrolinium intermediate **15** was not detected in these experiments, after extended periods of time (>6 h) or at elevated temperatures, conversion to the corresponding *N*-methylpyrrole **16** was observed, indicating the *N*-methylimine (or enamine) is a competent precursor to the desired pyrrolinium **15**. These observations proved crucial to the eventual success of this strategy, as the addition of reducing agents prior to imine formation (i.e., 6 h) resulted in the undesirable production of diols and amino chlorohydrins[21] (e.g., see **8** and **9** (Scheme 1)), while further delaying the reduction led to increased amounts of pyrrole **16**. As indicated in Table 1, however, addition of reducing agents

Table 1. Reductive Amination of β-Ketochlorohydrin **13**[a]

entry	reducing agent	yield[b]	**3**:**17**[c]
1	$NaBH_4$	50%	1:1
2	DIBAL-H	<5%	1:1
3	$NaBH(OAc)_3$	69%	1:1
4	$Me_4NBH(OAc)_3$	80%	3:1
5	H_2, Pd/C	23%	6:1
6	$NaCNBH_3$	91%	6:1

[a] General procedure: a 0.1 M solution of **13** and CH_3NH_2 (10 equiv) in THF was stirred at rt for 6 h followed by addition of reducing agent. [b] Combined isolated yield of **3** and **17**. [c] Determined by analysis of ^{1}H NMR spectra recorded on the crude reaction product following treatment with TFA.

after complete imine formation provided the diastereomeric hydroxypyrrolidines **3** and **17**.[22] For example, when the intermediate imine was treated with $NaBH_4$ or $NaBH(OAc)_3$ (entries 1 and 3), a 1:1 mixture of preussin (**3**) and 5-*epi*-preussin (**17**) was produced in good yield. While the diastereoselectivity and yield of this process was improved through the use of $Me_4NBH(OAc)_3$, the optimal reducing agent proved to be $NaCNBH_3$ (entry 6), which afforded a 6:1 mixture of hydroxypyrrolidines from which (+)-preussin (**3**) was isolated in 78% yield.[23] The spectral data (^{1}H, ^{13}C NMR, IR, HRMS)[24] derived from synthetic preussin was in complete agreement with that reported for the natural product. Notably, this three-step synthesis of preussin (**3**) compares well with those reported in the literature and presents new opportunities for the production of structural analogues with potentially improved pharmaceutical properties, work that is ongoing in our laboratory.

(20) Low levels of diastereocontrol have also been reported for the addition of methyl ketone derived lithium enolates to α-benzyloxyhydrocinnamaldehyde. See: Evans, D. A.; Cee, V. J.; Siska, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 9433.

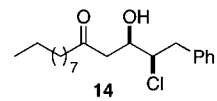
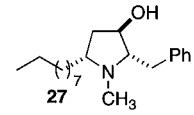
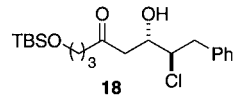
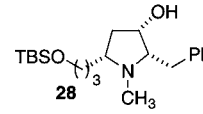
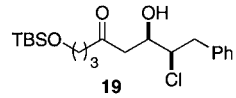
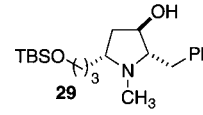
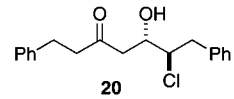
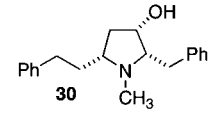
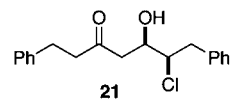
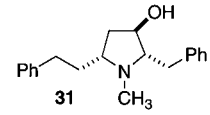
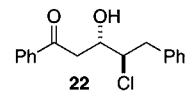
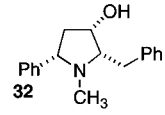
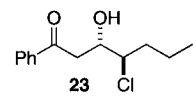
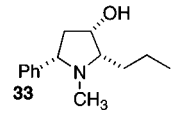
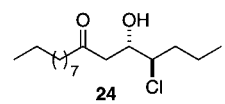
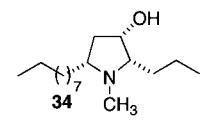
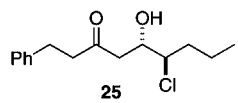
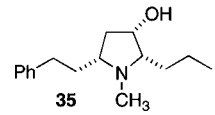
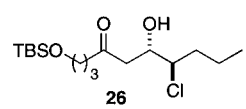
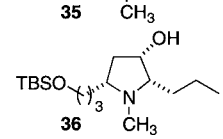
(21) Treatment of the β-ketochlorohydrin **13** with $MeNH_2$ and $NaBH(OAc)_3$ in THF provided a 2:1 mixture of diastereomeric aminochlorohydrins and none of the desired 3-hydroxypyrrolidine.

(22) The ^{1}H NMR spectral data derived from 5-*epi*-preussin (**17**) differed from that reported for this substance in refs 10b and 12f, which were also inconsistent. For characterization purposes, 5-*epi*-preussin (**17**) was treated with an excess amount of TFA, which produced a 1:1 mixture of diastereomeric ammonium salts prior to NMR spectroscopic analysis. See the Supporting Information for details.

(23) Reductive amination of the TBS-protected β-ketochlorohydrin (i.e., **13**: R^1 = H, R^2 = OTBS) employing the conditions described in entry 6 (Table 1) afforded a 2.3:1 mixture of 3-silyloxypyrrolidines. Treatment of this mixture with TBAF in THF afforded a 2.3:1 mixture of **3**:**17**.

In order to explore the scope and limitations of this hydroxypyrrolidine synthesis, a variety of readily available β-ketochlorohydrins[13,25] were treated with methylamine in THF followed, after 6 h, by the addition of $NaCNBH_3$ (Table 2). In general, these reactions provided the corresponding

Table 2. Stereoselective Synthesis of 3-Hydroxypyrrolidines[a]

entry	chlorohydrin	pyrrolidine	yield[b] (dr)[c]
1	 **14**	 **27**	68% (9:1)
2	 **18**	 **28**	55% (ND[d])
3	 **19**	 **29**	67% (6:1)
4	 **20**	 **30**	53% (12:1)
5	 **21**	 **31**	68% (9:1)
6	 **22**	 **32**	<15%
7	 **23**	 **33**	<15%
8	 **24**	 **34**	50% (14:1)
9	 **25**	 **35**	69% (9:1)
10	 **26**	 **36**	59% (6:1)

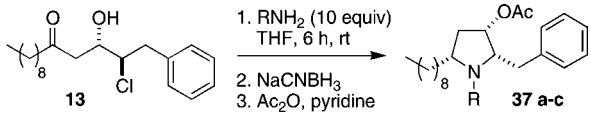
[a] General procedure: A solution of the chlorohydrin and CH_3NH_2 (10 equiv) in THF was stirred at rt for 6 h followed by the addition of $NaCNBH_3$. [b] Isolated yield of major diastereomer. [c] Determined by analysis of ^{1}H NMR spectra recorded on the crude reaction product in CD_3OD with excess TFA. [d] The minor, C5-epimer was not observed in ^{1}H NMR spectra recorded on the crude reaction product.

2,5-disubstituted 3-hydroxypyrrolidines in good to excellent yield. Notably, while the characterization of C2-benzyl-substituted pyrrolidines (e.g., **3** and **27**−**31**) by NMR spectroscopy did not present significant challenges, interpretation of ^{1}H and ^{13}C NMR spectroscopic data acquired

on the C2-alkyl analogues of these substances proved difficult. In particular, the ^{1}H NMR spectra of these later compounds were characterized by broad signals, and the chemical shifts of diagnostic protons (e.g., *N*-CH_3, H-2, H-3, and H-5) varied with concentration and source of deuterio solvent.[22] Consequently, the NMR spectroscopic characterization of these substances, including NOE analysis, was carried out on the corresponding TFA salts, which exhibited sharp resonances and reproducible spectroscopic data. As indicated in Table 2, the diastereoselectivity of these reactions was comparable to or better than that observed during the production of preussin (**3**) (dr = 6:1, Scheme 2) and 2,3-*anti* pyrrolidines could also be accessed from the corresponding *syn*-configured β-ketochlorohydrins[26] (e.g., entries 1, 3, and 5). For example, when the optimized conditions were employed, reaction of the β-ketochlorohydrin **14** with methylamine afforded 3-*epi*-preussin (**27**), an equipotent analogue of the natural product preussin (**3**),[12f] in excellent isolated yield. In all cases, reduction of the pyrrolinium intermediate occurred preferentially from the face opposite the substituent at C2, affording 2,5-*syn* pyrrolidines **27**−**36** as the major products. As an apparent limitation to this methodology, the optimized reaction conditions failed to provide significant quantities of the desired 3-hydroxypyrrolidines **32** and **33** from the phenylketones **22** and **23**, respectively. Allowing less time for pyrrolinium formation and/or lowering the reaction temperature offered little improvement on these results and in both cases the major byproduct was the corresponding pyrrole.

Finally, the reductive amination of ketochlorohydrin **13** with amines other than methylamine was briefly investigated (Table 3), and the versatility of this hydroxypyrrolidine

Table 3. Reductive Amination of β-Ketochlorohydrin **13**[a]



entry	R	pyrrolidine	yield[b] (dr)[c]
1	allyl	**37a**	60% (1.3:1)
2	benzyl	**37b**	37% (1.3:1)
3	*n*-heptyl	**37c**	30% (8:1)

[a] General procedure: A solution of the chlorohydrin **13** and amine (10 equiv) in THF was stirred at rt for 6 h followed by the addition of $NaCNBH_3$. [b] Combined isolated yield of both diastereomers. [c] Determined by analysis of ^{1}H NMR spectra recorded on the crude reaction product.

synthesis was demonstrated in the synthesis of *N*-functionalized analogues of preussin. Thus, treatment of the β-ketochlorohydrin **13** with allyl-, benzyl-, and *n*-heptylamine followed by $NaCNBH_3$ afforded the corresponding *N*-allyl-, *N*-benzyl-, and *N*-alkylpyrrolidines in modest to good yield. Acetylation of the crude mixtures of hydroxypyrrolidines proved necessary for both chromatographic purification and characterization purposes. Contrary to the reductive aminations with methylamine (Table 2) and heptylamine (Table 3, entry 3), the reactions involving allyl- and benzylamine afforded almost equal amounts of diastereomeric pyrrolidines. In these cases (entries 1 and 2), nonselective reduction[27] of the intermediate β-hydroxy imine may precede pyrrolidine formation. Notwithstanding, together with the results presented in Table 2, a wide variety of 3-hydroxypyrrolidines, functionalized at N1, C2, and C5, are now readily available in three steps (i.e., aldehyde chlorination, aldol coupling, reductive amination) from methyl ketones and aliphatic aldehydes, both of which are commonly available starting materials.

In summary, we have developed a straightforward and convergent synthesis of 2,5-disubstituted 3-hydroxy-pyrrolidines that involves treating readily available β-ketochlorohydrins with a primary amine followed by $NaCNBH_3$, all at room temperature. Notably, this operationally straightforward and protecting group-free process is selective for the production of 2,5-*syn*-pyrrolidines. The efficiency of this process was demonstrated in a short (three step, 42% overall yield) synthesis of the natural product (+)-preussin (**3**) as well as a number of analogues of this substance. The application of this methodology to the synthesis of more structurally complex hydroxypyrrolidine-containing natural products (e.g., **1** and **2**, Figure 1) is currently underway in our laboratory, and the results of these efforts will be reported in due course.

Acknowledgment. This research was supported by NSERC-Canada (R.B.) and the Province of BC through the ministry of Advanced Education (J.A.D.).

Supporting Information Available: Characterization data and detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101631E

(24) The specific rotation for (+)-preussin (**3**) ($[\alpha]_D$ = +19.0, *c* 0.6, $CHCl_3$) was consistent with that reported for the natural product in ref 7 ($[\alpha]_D$ = +22.0, *c* 1.0, $CHCl_3$).

(25) For the preparation, characterization, and stereochemical assignment of all compounds, see the Supporting Information.

(26) These compounds were produced as the minor diastereomeric products of the aldol reactions involving 2-chloro-3-phenylpropanal.

(27) For an example of a nonselective reductive amination of a β-hydroxyketone, see: Enders, D.; Palecek, J.; Grondal, C. *Chem. Commun.* **2006**, 655.