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A practical route to enantiopure 3-hydroxy-pyrrolidines: application to a straightforward synthesis of (−)-bulgecinine

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Abstract

A practical synthesis of enantiopure substituted 3-hydroxy-pyrrolidines is reported. In four steps, starting from commercially available amino acids as chiral educts, this method allows for an efficient preparation of a variety of 3-hydroxy-pyrrolidines, as well as 3-hydroxy-piperidines and azepanes. Application of this methodology for a straightforward asymmetric synthesis of (−)-bulgecinine is also described.

The 3-hydroxy-pyrrolidine subunit is found in a wide range of naturally occurring alkaloids and biologically active molecules.[1] For example, a substituted pyrrolidinol nucleus can be found in detoxin A_1 **1**, a natural chemical detoxification agent (Fig. 1).[2] Other interesting hydroxylated pyrrolidines include retronicine (**2**, a pyrrolizidine necine base),[3] bulgecin C **3**,[4] the cyclopeptide alkaloid paliurine E **4**[5] and pharmaceuticals such as the antihypertensive Barnidipine **5** (Fig. 1).[6] 3-Hydroxy-pyrrolidines are also commonly used as intermediates for the preparation of a variety of drugs[7] and now clearly appear as most useful chiral ligands and promoters in organocatalysis.[8]

Due to growing interest for this scaffold, a number of synthetic approaches to the stereoselective synthesis of 3-hydroxy-pyrrolidine and its derivatives have been developed.[9] They include intramolecular displacement of a leaving group by an amine,[10] amidomercuration or haloamidation reactions,[11] asymmetric hydroboration of 3-pyrroline derivatives,[12] reduction of lactams obtained by condensation of amines with malic acid,[13] nitroalkenes [4+2] cycloaddition,[14] enzymatic hydroxylation,[15] reaction

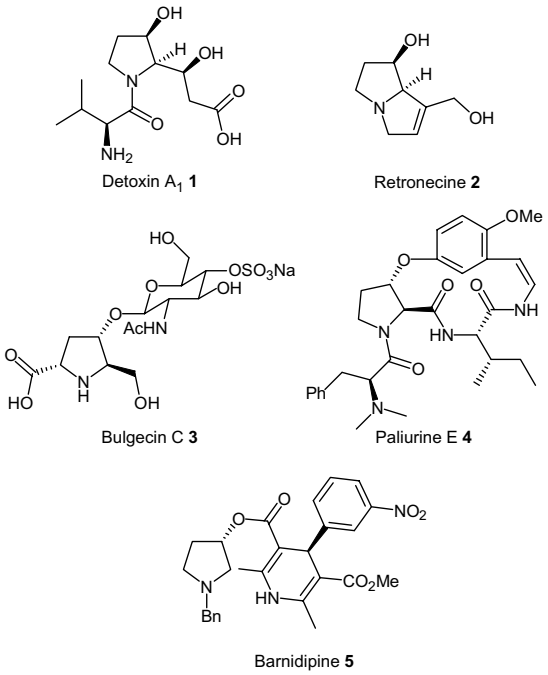

Fig. 1. Natural products and drugs featuring a 3-hydroxy-pyrrolidine subunit.

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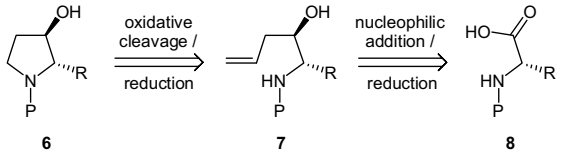


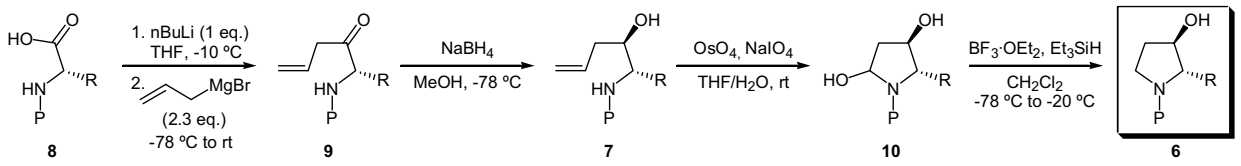
Scheme 1. Four-step synthesis of 3-hydroxy-pyrrolidines from amino acids.

of epoxysulfonamides with sulfoxonium ylides[16] or cyclization of α-lithio-carbamates.[17]

In connection with our interest in the total synthesis of various cyclopeptide alkaloids,[18] we considered the possibility of a short synthesis of 2-substituted 3-hydroxy-pyrrolidines **6** starting from inexpensive, commercially available protected amino acids **8** (Scheme 1).

Indeed, a nucleophilic addition/substrate-controlled diastereoselective reduction sequence from **8** would allow for the installation of the oxygenated stereocenter[19] in **7**. A two-step cyclization from **7**[20] would next be used to form the pyrrolidine ring in **6**. Recently, we successfully applied

Table 1
Asymmetric synthesis of 3-hydroxy-pyrrolidines from amino acids



Entry	Starting amino acid **8**	Amino alcohol **7**	Yield (addition/reduction)[a] (%)	dr[b]	Hydroxy-pyrrolidine **6**	Yield (oxidative cleavage/reduction)[a] (%)	Overall yield from amino acid **8**[a] (%)
1	**8a** *N*-Cbz-Ala	**7a**	82[c]	77:23	**6a**	70[c]	57[c]
2	**8b** *N*-Boc-Phe	**7b**	86	92:8	**6b**	70	60
3	**8c** *N*-Boc-Leu	**7c**	58	90:10	**6c**	35	20
4	**8d** *N*-Boc-Nle	**7d**	64	89:11	**6d**	31	20
5	**8e** *N*-Boc-Phg	**7e**	72	91:9	**6e**	52	20
6	**8f** *N*-Boc-Ser(OTBS)	**7f**	96	>95:5	**6f**	72	69

[a] Yield of isolated, pure product.
[b] Determined by ^{1}H NMR analysis of crude reaction mixtures.
[c] Obtained as an inseparable 77:23 mixture of isomer at the C3 stereocenter.

this straightforward sequence to a gram scale four-step synthesis of the hydroxy-pyrrolidine core of the cyclopeptide alkaloid paliurine F[18a] starting form D-serine. We now report on the generalization of this method starting from other amino acids as well as its application for an efficient asymmetric synthesis of (−)-bulgecinine.

To evaluate the scope of this methodology, a set of six natural and non-natural aminoacids **8a–f** was selected for this study (Table 1). These aminoacids were firstly subjected to the non epimerizing Rapoport's modification of the Tegner reaction:[21] deprotonation of the acid with 1 equiv of butyllithium followed by the addition of 2 equiv of allylmagnesium bromide cleanly afforded the corresponding unconjugated ketones **9** in good yields. To avoid conjugation of the double bond and to install the oxygenated stereocenters, these ketones were immediately reduced with sodium borohydride in methanol at −78 °C to give aminoalcohols **7** with useful levels of diastereoselectivity (Table 1, dr ranging from 77:23 to 95:5, minor diastereoisomer separated when needed by column chromatography). The configuration of the newly created stereocenter was secured through stereochemistry assessment of the final hydroxy-pyrrolidines **6** (see below) and the observed diastereoselectivity most certainly arises from chelation with the carbamate in **9**.[19]

Formation of the pyrrolidine ring was finally initiated by oxidative cleavage of the double bond in amino-alkenes **7**. Spontaneous cyclization of the intermediate amino-aldehydes followed by reduction of the resulting protected aminals **10** using boron trifluoride and triethylsilane[22] ultimately gave the desired hydroxy-pyrrolidines **6** in moderate to good yields (Table 1).

As can be seen from results in Table 1, enantiopure 3-pyrrolidinols **6** could be obtained in overall yields ranging from 20% to 69%, in four steps only, using substrate-controlled diastereoselective reactions from readily available amino acids **8**. An interesting feature resides in the possibility of formation of both antipode of each heterocycle since L- and D-amino acid are all commercially available: an example of synthesis starting from an unnatural D-amino acid (*N*-Boc, *O*-TBS-D-serine **8f**) can be found in entry 6.

Before moving on to further developments and application of our synthetic route to 2-substituted-3-hydroxy-pyrrolidines, it was necessary to unambiguously ascertain their relative configuration. Therefore, NOE experiments were performed on a representative set of 3-pyrrolidinols **6**. Results from these experiments are shown in Figure 2 and clearly confirm the 2,3-trans relative configurations.

Formation of higher homochiral ring systems (i.e., 3-hydroxy-piperidines and 3-hydroxy-azepanes) using a similar strategy was next investigated. To this end, 1-amino-hex-5-ene and 1-amino-hept-6-ene derivatives **12a** and **12b** were prepared from *N*-Cbz-phenylalanine **11** (Scheme 2). In contrast with the reaction of amino acid derivatives with allylmagnesium bromide, the use of a modified Tegner reaction failed to give the corresponding ketones when **11** was reacted with less reactive but-3-enyl-

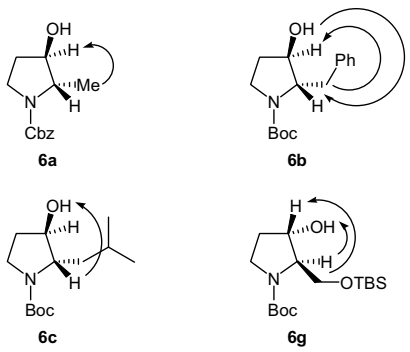
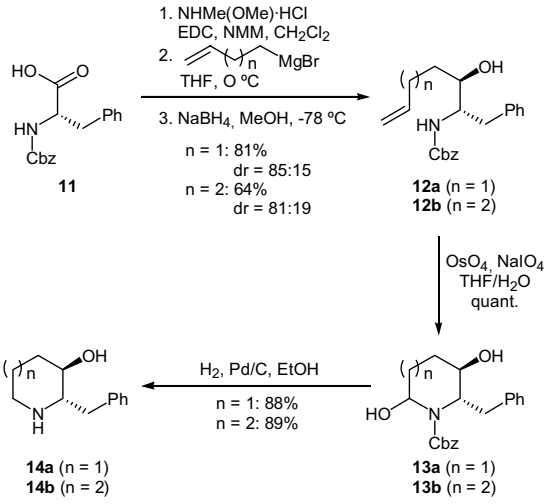


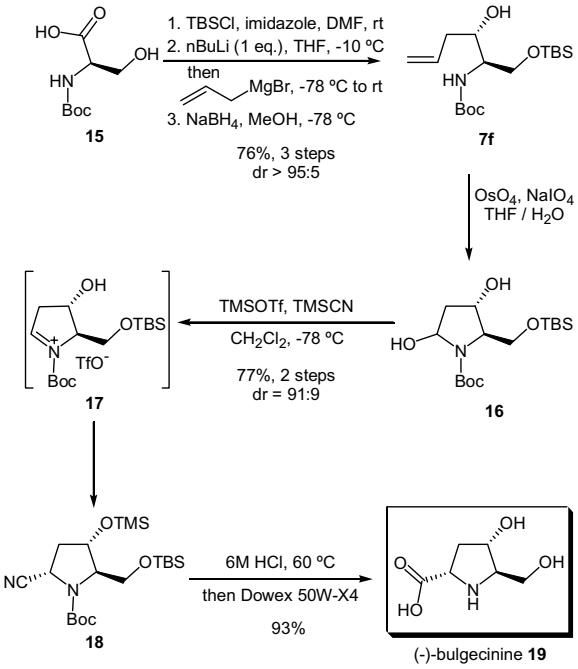
Fig. 2. Assignment of relative stereochemistries of 3-hydroxy-pyrrolidines through NOE experiments.

or pent-4-enyl-magnesium bromide. To overcome this problem, the Weinreb amide derivative of **11** was first prepared and then reacted with Grignard reagents. Using this two-step sequence, the corresponding ketones were obtained in excellent yields and finally reduced to **12a** and **12b** with sodium borohydride (Scheme 2).

Having useful quantities of amino-alkenes **12a** and **12b** in hand, we next focused on their cyclization to piperidine and azepane ring systems, respectively. In a similar fashion, **12a** and **12b** were treated with catalytic osmium tetroxide and sodium periodate and cleanly gave the corresponding cyclized products **13a** and **13b** in quantitative yields. In this case, the reaction of protected hemiaminals **13a** and **13b** with triethylsilane and boron trifluoride failed to cleanly give the corresponding deoxygenated heterocycles, which was attributed to the easier formation of cyclic enamide derivatives (and their subsequent oligomerization), a side reaction that could hardly happen with five-membered ring compounds. This problem could however be easily overcome by using a hydrogenation reaction for the reduction step: after reduction and concomitant deprotection, enantiopure 3-hydroxy-piperidine **14a** and azepane **14b** were obtained in excellent yields. These results show that



Scheme 2. Formation of 3-hydroxy-piperidines and 3-hydroxy-azepanes.



Scheme 3. Six-step asymmetric synthesis of (−)-bulgecinine from D-serine.

pyrrolidines as well as higher ring systems can be easily obtained in few steps from amino acids (Scheme 2).

We finally wanted to address the efficiency of our reaction sequence for the synthesis of trisubstituted hydroxypyrrolidines. With this goal in mind, (−)-bulgecinine **19** was chosen as target since it possesses the desired pyrrolidine core.[4c] This molecule, which is a common constituent of *Pseudomonas* sp. derived glycopeptides (bulgecins A, B and C), has drawn considerable interest since 24 asymmetric total (or formal) syntheses have, to date, been reported (number of steps ranging from 7 to 20 and overall yields from 3% to 37%).[23] This molecule therefore appeared as a good candidate, firstly to further put at test the synthetic utility of our route and secondly to evaluate whether trisubstituted pyrrolidines could be formed with useful level of selectivity using a slight modification of our method.

The beginning of our synthesis closely follows the one we recently reported for the synthesis of the 3-hydroxy-pyrrolidine core of the cyclopeptide alkaloid paliurine F.[18a] Commercially available *N*-Boc-D-serine **15** was chosen as the starting point of the synthesis (Scheme 3). Its treatment with excess TBSCl in DMF followed by acidic workup allowed for a clean protection of the alcohol. As detailed previously (Table 1, entry 6), a Tegner reaction–reduction sequence provided the desired protected amino-diol **7f** as a single diastereoisomer. Next, formation of the pyrrolidine ring was initiated by oxidative cleavage of the double bond. Spontaneous cyclization of the intermediate amino-aldehyde gave the protected aminal **16** (Scheme 3).

Acyl-iminium ion intermediate **17** was then formed by activation of the hydroxyl group in **16** with TMSOTf, and trapped with TMSCN[23h] to cleanly afford 5-cyano-pyrrolidine **18**. Compound **18** was obtained in good yield (77% over two steps) and diastereoselectivity (dr = 91:9). It should be noted here that a concomitant protection of the hydroxyl group as its TMS ether was observed during the reaction, a protection that however had no effect on our synthesis since final acidic cleavage of the TBS ether and nitrile hydrolysis would with no doubt simultaneously cleave this extra protecting group. Interestingly, we were able to reach a quite high level of diastereoselectivity during the addition of the cyanide ion onto iminium **17**. This might arise from two synergistic effects: steric hindrance of the protected hydroxymethyl substituent at C2 and assistance of the free hydroxyl for the delivery of the cyanide ion.

To complete the synthesis, amino-nitrile **18** was transformed into (−)-bulgecinine hydrochloride[4c,23b,24] by treatment in 6 M HCl at 60 °C. Purification of this hydrochloride using Dowex 50W-X4 sulfonic acid ion exchange resin then gave synthetic (−)-bulgecinine **19** which exhibited physical, spectroscopic and spectrometric characteristics (^{1}H NMR, ^{13}C NMR, IR, $[\alpha]_D$ and MS) identical to those reported for natural and synthetic products.[4c,23,25] Using the six-step asymmetric synthesis depicted in Scheme 3, synthetic bulgecinine was therefore obtained in 54% overall yield, with a limited use of protecting groups.

In summary, we have developed a practical asymmetric synthesis of 2-substituted 3-hydroxy-pyrrolidines. Starting from commercially available amino acids as chiral educts, this method allows for an efficient preparation of a variety of 3-hydroxypyrrolidines in only four steps. This method has also been used for the preparation of trisubstituted 3-pyrrolidinols and has been successfully applied to a straightforward asymmetric synthesis of (−)-bulgecinine. Further applications of this methodology are under investigation and will be reported in due time.

Acknowledgments

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24. *Bulgecinine hydrochloride* (−)-**19**·**HCl**: $[\alpha]_D^{20}$ +12 (*c* 1, 1 M HCl); ^{1}H NMR (300 MHz, D_2O): δ 4.56 (dd, $J = 8.8$, 5.2 Hz, 1H), 4.40 (br s, 1H), 3.69–3.89 (m, 3H), 2.59–2.69 (m, 1H), 2.28–2.33 (m, 1H); ^{13}C NMR (75 MHz, D_2O): δ 171.7, 70.5, 67.6, 58.3, 58.0, 36.2.
25. (−)-*Bulgecinine* (−)-**19**: Mp: 180–185 °C; $[\alpha]_D^{20}$ −12 (*c* 1, 1 M HCl); ^{1}H NMR (300 MHz, D_2O): δ 4.30 (app. q, $J = 4.6$ Hz, 1H), 4.13 (dd, $J = 8.8$, 6.6 Hz, 1H), 3.81 (dd, $J = 14.4$, 6.8 Hz, 1H), 3.61–3.69 (m, 2H), 2.58 (ddd, $J = 14.0$, 9.0, 5.9 Hz, 1H), 2.08 (app. dt, $J = 14.0$, 5.5 Hz, 1H); ^{13}C NMR (75 MHz, D_2O): δ 174.4, 71.4, 67.4, 60.1, 58.9, 37.3; ESIHRMS *m*/*z* calcd for $C_6H_{11}NNaO_4$ $[M+Na]^+$ 184.0575, found 184.0586.