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An Efficient and Highly Stereocontrolled Route to Bulgecinine Hydrochloride

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(−)-Bulgecinine is a nonproteinogenic amino acid component present in bulgecins A, B, and C, antibiotic glycopeptides derived from *Pseudomonas acidophila* and *Pseudomonas mesoacidophila*. In combination with β-lactam antibiotics, bulgecins exihibit a unique synergistic antibacterial activity against various Gram-negative microorganisms. Utilizing D-serine as a chiral template and employing a highly regio- and stereoselective intramolecular amidomercuration-oxidation protocol in the key pyrrolidine ring forming step, an efficient total synthetic route to enantiopure bulgecinine is reported herein.

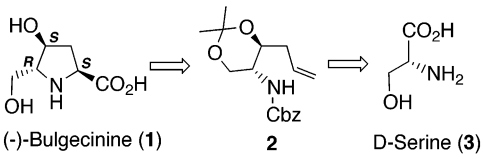
Introduction

(2*S*,4*S*,5*R*)-(−)-Bulgecinine (**1**) is a common constituent of *Pseudomonas* sp. derived glycopeptides, bulgecins A, B, and C.[1] Structurally, the aglycon bulgecinine can be considered to be a proline analogue with additional hydroxy and hydroxymethylene substituents at the 4- and 5-positions of the pyrrolidine ring, respectively. Interestingly, despite lacking antibacterial activity on their own, bulgecins were found to sensitize various Gram-negative bacteria toward β-lactam antibiotics, resulting in more efficient inhibition of bacterial growth at lowered drug concentrations. This unique synergistic antibacterial activity and the unusual amino acid core of bulgecinine have attracted considerable attention as targets of total synthesis[2] and biological studies.[1,3] Although several total syntheses of (−)-bulgecinine have been reported in the literature,[2] many of these methods suffer from lack of efficiency and poor stereoselectivity in key bond-forming reactions. Consequently, development of new strategies and approaches to address the above challenges continues to be a worthwhile research goal.

In continuation of our efforts toward stereoselective synthesis of bioactive molecules, utilizing amino acids as chiral template,[4] we report herein an efficient route to enantiopure (−)-bulgecinine, starting from the readily available amino acid D-serine. Our retrosynthetic strategy is outlined in Scheme 1.

The key transformations in the proposed strategy will involve (i) chelation-controlled reduction of a chiral allylic ketone intermediate toward stereoselective formation of the C4 secondary hydroxy group and (ii) an intramolecular amidomercuration-oxidation protocol to construct the pivotal pyrrolidine core of the target molecule.

SCHEME 1



Results and Discussion

As per a literature procedure, D-serine was converted to the corresponding *N*,*O*-acetonide-protected Weinreb

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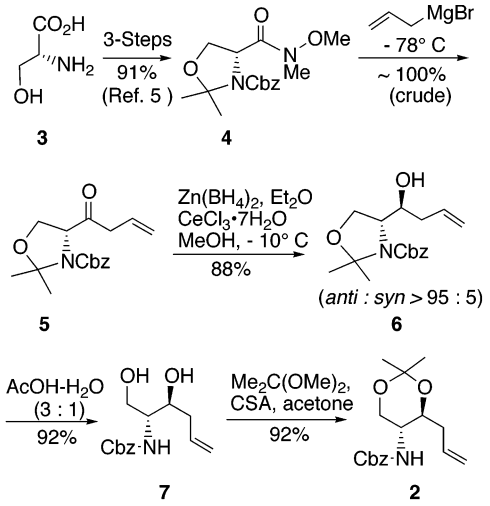
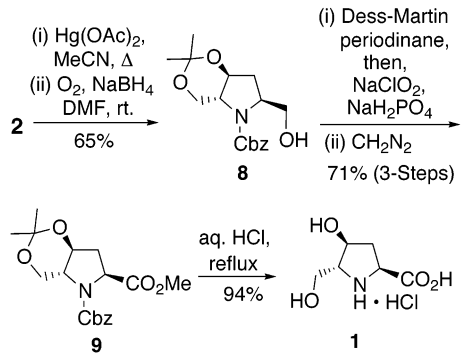
SCHEME 2



amide derivative **4** (Scheme 2) in 91% overall yield.[5] Reaction of the amide **4** with freshly prepared allylmagnesium bromide cleanly afforded the corresponding allyl ketone **5** in quantitative yield. It was, however, observed that prolonged storage or attempted column chromatographic purification of **5** resulted in partial isomerization of the terminal olefin to the corresponding α,*β*-unsaturated ketone derivative. Subsequently, instead of purification, the crude ketone **5** was directly subjected to the next reaction. Thus, the neighboring NCbz group assisted chelation-controlled reduction[4b,6] of the keto carbonyl with $Zn(BH_4)_2$ in the presence of $CeCl_3 \cdot 7H_2O$ resulted in the required 1,2-*anti* amino alcohol derivative **6** with excellent stereocontrol (*anti*/*syn* > 95/5 by HPLC) and high overall yield. Deprotection of the *N*,*O*-acetonide linkage of **6** and reprotection of the resulting 1,3-diol **7** uneventfully afforded the corresponding *O*,*O*-acetonide derivative **2**.

Electrophile-initiated cyclization of *δ*-alkenylamines, amides, and carbamates has proven to be a useful route for the formation of a substituted pyrrolidine structural framework.[7] Considerable efforts have been expended to study the stereochemical aspects of the above type of cyclization, with particular emphasis on processes leading to stereoselective formation of either *cis*- or *trans*-2,5-disubstituted pyrrolidines.[8] It has thus been found that mercury(II) ion assisted cyclization of *δ*-alkenylamine derivatives leads to the formation of 2,5-substituted pyrrolidine derivatives with good *trans*-selectivity.[8,9]

SCHEME 3



In light of the above studies, we reasoned that extension of the above amidomercuration protocol to the aminodiol derivative **2**, containing a *δ*-alkenyl-carbamate moiety, could conveniently lead to the corresponding 2,5-*trans*-substituted pyrrolidine derivative required for our present synthesis. To our pleasant surprise, treatment of **2** with $Hg(OAc)_2$ in refluxing acetonitrile resulted in the formation of a single product. Subsequent workup under standard conditions[10] and oxidative demercuration of the organomercury adduct in the presence of molecular oxygen[11] afforded the trisubstituted pyrrolidine derivative **8** (Scheme 3) in good overall yield. At this stage, stereochemistry at the newly created center was tentatively assigned on the basis of the expected *trans*-2,5-substitution pattern, as precedented for similar cyclizations.[8] The structural and stereochemical integrity of product **8** was further ascertained by NMR (^1H and ^{13}C), mass spectroscopy, and HPLC analysis. Gratifyingly, conclusive confirmation of the stereochemistry as assigned could be obtained from X-ray crystallographic studies of **9**, a downstream product obtained from 8 (vide infra).

High stereoselectivity during the above pyrrolidine ring forming reaction can be rationalized by invoking preferential formation of a chairlike transition state intermediate (Figure 1), with energetically favorable equatorial substituents, leading to the observed product.[8h]

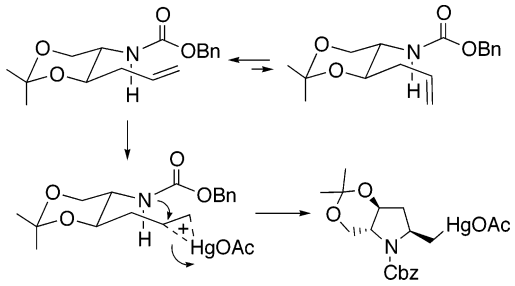


FIGURE 1. Energetically favorable chairlike transition state, leading to the observed stereoselective formation of **8**.

The strategically functionalized key pyrrolidine derivative **8** (Scheme 3) was next subjected to a standard mild oxidation sequence toward conversion of the free primary

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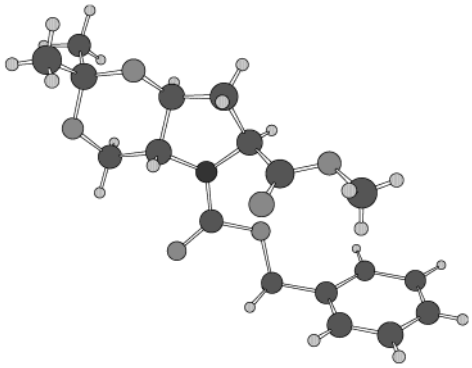

FIGURE 2. Ball and stick model of pyrrolidine **9** (adapted from the X-ray crystallographic structure).

hydroxy group to carboxylic acid and its subsequent esterification with diazomethane, to form the fully protected bulgecinine derivative **9** as a colorless crystalline solid. The esterification of the intermediate carboxylic acid in the above sequence was found to facilitate purification and characterization of the resulting carboxylate derivative. X-ray crystallographic analysis of the ester **9** (Figure 2) also conclusively proved the assigned structure and absolute configuration across the pyrrolidine core.

Finally, a one-pot, simultaneous global deprotection in refluxing aqueous hydrochloric acid culminated in an efficient and highly stereoselective total synthesis of the hydrochloride salt of natural bulgecinine **1** (Scheme 3).[12] The spectral and analytical data of **1** were found to be in good agreement with the assigned structure {$[\alpha]^{25}_D$ +11.71(*c* 0.65, 1 N HCl); lit.[1b] $[\alpha]_D$ +12.4 (*c* 0.95 N HCl)}.

In conclusion, starting from D-serine and utilizing a highly regio- and stereoselective intramolecular amidomercuration protocol in the key pyrrolidine ring forming step, we have developed an efficient route to enantiopure natural (−)-bulgecinine. The present synthesis compares well with the reported methods and offers an attractive alternative approach to the title compound. Furthermore, as chiral nonracemic pyrrolidines are common structural subunits found in many natural and nonnatural compounds of structural and biomedical importance, the strategy and the approach described above can also be easily extended toward accessing variously functionalized pyrrolidine cores with potential applications in chemistry and biology.

Experimental Section

1-[(4*R*)-3-*N*-Benzyloxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl]-but-3-en-1-one (5). To a cooled (−78 °C) solution of the D-serine-derived Weinreb amide **4**[5] (28.4 g, 88.2 mmol) in THF (300 mL) was added dropwise a solution of allylmagnesium bromide [prepared from Mg (8.5 g, 354 mmol) and allylbromide (17 mL, 194 mmol) in Et_2O (180 mL)] over a period of 1.5 h. After completion of the addition, the reaction was stirred at the same temperature for another 2 h and then quenched by careful addition of a saturated aqueous solution of NH_4Cl (150 mL). The resulting solution was allowed to come to room temperature, the layers were separated, and the aqueous layer was extracted with EtOAc (2 × 150 mL). The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give the allyl ketone **5** as a yellow oil, which was used as such without further purification: ^{1}H NMR (crude) (400 MHz, $CDCl_3$, rotameric mixture) δ 1.50−1.74 (4s, 6H), 3.15 and 3.32 (2d, J = 6.8 Hz, 2H), 3.94−3.97 (m, 1H), 4.14−4.19 (m 1H), 4.47 and 4.49 (2dd, J = 2.69 and 7.46 Hz, 2H), 5.00−5.19 (m, 4H), 5.73−5.98 (m, 1H), 7.28−7.36 (m, 5H).

(1*S*)-1-[(4*R*)-3-*N*-Benzyloxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl]-but-3-en-1-ol (6). To a solution of the allyl ketone **5** (13 g, 42.9 mmol) in MeOH (300 mL) was added $CeCl_3 \cdot 7H_2O$ (5.4 g, 104 mmol) in one portion, and the resulting solution was cooled to −10 °C (NaCl−ice bath) with continuous stirring. A $Zn(BH_4)_2$ solution (0.189 M in Et_2O, 550 mL, 104 mmol) was then added dropwise to the reaction mixture (1.5 h), and stirring was continued at the same temperature for another 1 h. The reaction was quenched by slow addition of saturated aqueous $NaHCO_3$ solution (100 mL), allowed to attain room temperature, and then filtered through a sintered glass funnel. The residual solid was washed thoroughly with EtOAc, the organic layer was separated from the filtrate, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Purification of the crude residue by flash chromatography (hexane/EtOAc = 4:1 to 3:1) yielded the amino alcohol **6** as a colorless oil (12 g, 88%): $[\alpha]^{25}_D$ +16.8 (*c* 1.01, $CHCl_3$); IR (NaCl) 3462, 1695 cm^{-1}; ^{1}H NMR (125.7 MHz, $CDCl_3$, rotameric mixture) δ 1.27−1.60 (4s, 6H), 2.02−2.40 (m, 2H), 3.14 (br s, 1H, exchangeable with D_2O), 3.86−4.23 (m, 4H), 4.99−5.37 (m, 4H), 5.66−6.0 (m, 1H), 7.38 (s, 5H); ^{13}C NMR (125.7 MHz, $CDCl_3$ rotameric mixture) δ 22.9, 24.5, 26.3, 26.6, 30.8, 37.9, 38.7, 60.6, 62.0, 64.0, 64.3, 66.8, 67.5, 70.9, 71.2, 94.4, 117.5, 117.7, 126.8, 127.2, 128.0, 128.1, 128.3, 128.5, 134.5, 134.9, 135.9, 154.2, 152.5; FABMS calcd for $C_{17}H_{23}NO_4$ *m*/*z* $(M + H)^+$ 306.2, found 306.2. HPLC: Iprosil 120-5 Si 5.0 μm, 20% EtOAc/hexane, 1 mL/min, 254 nm, t_R major isomer (*anti*) = 17.29 min (> 95%), t_R minor isomer (syn) = 17.97 min.

(2*R*,3*S*)-2-(Benzyloxycarbonyl)amino-hex-5-ene-1,3-diol (7). The amino alcohol **6** (3.0 g, 9.84 mmol) was dissolved in a mixture of AcOH/H_2O (3:1, 30 mL) and stirred at room temperature overnight. Excess solvent was removed in vacuo, and the residual product was purified by flash chromatography (hexane/EtOAc = 7:3), affording the amino diol **7** as a white solid (2.4 g, 92%): mp 96−98 °C; $[\alpha]^{25}_D$ −12.0 (*c* 0.83, $CHCl_3$); IR (NaCl) 3305, 1688 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33−2.45 (m, 4H, 2H exchangeable with D_2O), 3.67−3.68 (m, 1H), 3.79−3.81 (m, 1H), 3.89−3.92 (m, 1H), 4.05−4.08 (m, 1H), 5.12−5.21 (m, 4H), 5.67 (br d, J = 6.6 Hz, 1H), 5.82−5.94 (m, 1H), 7.34−7.40 (m, 5H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 38.8, 54.8, 62.1, 66.9, 72.5, 118.6, 118.8, 128.0, 128.1, 128.5, 133.9, 136.2, 156.4; FABMS calcd for $C_{14}H_{19}NO_4$ *m*/*z* $(M + H)^+$ 266.1, found 266.1.

(4*S*,5*R*)-5-(Benzyloxycarbonyl)amino-2,2-dimethyl-4-(2-propenyl)-1,3-dioxane (2). The amino diol **7** (1.8 g, 6.79 mmol) was dissolved in a mixture of acetone (45 mL) and 2,2-dimethoxypropane (14 mL), a catalytic amount of camphor sulfonic acid (30 mg) was added to it, and the resulting solution was stirred at room temperature for 2 h. The reaction was quenched by addition of NEt_3 (4.5 mL), and the solvent was removed in vacuo to give the crude product. Purification by flash chromatography (hexane/EtOAc = 3:1) yielded the dioxane **2** as a white solid (1.9 g, 92%): mp 56−58 °C; $[\alpha]^{25}_D$ −28.0 (*c* 0.95, $CHCl_3$); IR (NaCl) 3314, 1694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, rotameric mixture) δ 1.41 (s, 3H), 1.45 (s, 3H), 2.21−2.46 (m, 2H), 3.55−3.73 (m, 3H), 3.93−4.00 (m, 2H), 4.68 (br s, 1H), 5.08−5.18 (m, 4H), 5.81−5.91 (m, 1H), 7.35−7.40 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.4, 28.4, 37.4, 50.0, 63.6, 67.4, 72.1, 72.6, 99.3, 117.5, 128.6, 128.7, 129.0,

(12) The results of this study have been reported: Khalaf, J. K.; Datta, A. Stereoselective total synthesis of (−)-bulgecinine. *Abstracts of Papers*, 226th National Meeting of the American Chemical Society, New York, 2003; American Chemical Society: Washington, DC, 2003; ORGN 611.

134.4, 136.6, 156.1; FABMS calcd for $C_{17}H_{23}NO_4$ *m*/*z* $(M + H)^+$ 306.2, found 306.2.

(4a*R*,6*S*,7a*S*)-5-*N*-(Benzyloxycarbonyl)-2,2-dimethyl-6-hydroxymethyl-hexahydro-[1,3]-dioxino[5,4-*b*]pyrrole (8). (Step 1) To a stirred solution of the alkenyl carbamate **2** (1.86 g, 6.1 mmol) in CH_3CN (50 mL) was added mercuric(II) acetate (4.86 g, 15.3 mmol), and the mixture was refluxed for 1 h. The reaction was cooled to room temperature and diluted by addition of EtOAc (20 mL) and brine (20 mL). The resulting biphasic mixture was stirred at room temperature for 1.5 h and filtered to remove the precipitated inorganic byproduct. The organic layer was separated from the filtrate, the aqueous layer was extracted with EtOAc (3 × 50 mL), the combined organic extract was dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo to give a white foamy solid, which was used as such for the subsequent reaction. (Step 2) Through a well-stirred solution of $NaBH_4$ (0.228 g, 6.0 mmol) in DMF (125 mL) at room temperature was bubbled oxygen (O_2) gas for 1 h. To this mixture was added dropwise (2 h) a DMF solution (125 mL) of the white foamy product (2.56 g), obtained as above, with continuous bubbling of O_2. After stirring for a further 2 h, the reaction mixture was filtered through Celite, the residue was washed thoroughly with EtOAc (4 × 75 mL), and the filtrate was concentrated under vacuum. Purification of the crude residue by flash chromatography (hexane/EtOAc = 1:1) yielded the bicyclic pyrrolidine **8** as a colorless oil (1.27 g, 65% overall): $[\alpha]^{25}_D$ − 55.4 (*c* 1.0, $CHCl_3$); IR (NaCl) 3454, 1699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotameric mixture) δ 1.44 (s, 3H), 1.48 (s, 3H), 2.31−2.33 (m, 1H), 3.09−3.11 (m, 1H), 3.67−3.95 (m, 4H), 4.01−4.16 (m, 2H), 4.26−4.35 (d, J = 6.6 Hz, 1H, exchangeable with D_2O), 4.40−4.47 (m, 1H), 5.13 (br s, 2H), 7.35−7.41 (m, 5H); ^{13}C NMR (125.7 MHz, $CDCl_3$, rotameric mixture) δ 19.4, 29.1, 31.6, 58.7, 61.4, 66.0, 66.5, 67.8, 72.0, 100.1, 128.1. 128.2, 128.3, 128.4, 128.6, 135.5, 156.6; FABMS calcd for $C_{17}H_{23}NO_5$ *m*/*z* $(M + H)^+$ 322.6, found 322.1. HPLC: Iprosil, 120-5 Si 5.0 μm, 20% EtOAc/hexane, 1 mL/min, 254 nm, t_R = 19.63 min.

Methyl (4a*R*,6*S*,7a*S*)-5-*N*-(Benzyloxycarbonyl)-2,2-dimethyl-hexahydro-[1,3]-dioxino[5,4-*b*]pyrrol-6-carboxylate (9). (Step 1) Dess−Martin periodinane (1.11 g, 2.59 mmol) dissolved in CH_2Cl_2 (10 mL) was added to an ice-cooled solution of the pyrrolidino methanol **8** (0.694 g, 2.16 mmol) in CH_2Cl_2 (22 mL), and the reaction mixture was stirred at the same temperature for another 30 min. The reaction was then allowed to attain room temperature and stirred for another 2 h. The reaction was quenched by addition of a solution of 60 mL of saturated $NaHCO_3$ containing 3 g of $Na_2S_2O_3$. The layers were separated, the aqueous layer was extracted with EtOAc (3 × 100 mL), and the combined organic extract was washed sequentially with 50 mL each of saturated aqueous $NaHCO_3$, H_2O, and brine. Drying over anhydrous Na_2SO_4 and removal of solvent under vacuum resulted in a colorless oily residue, which was used directly for the subsequent reaction. (Step 2) The product (0.683 g) as obtained above was dissolved in *tert*-butyl alcohol (67 mL) followed by addition of a solution of 2-methyl-2-butene (48 mL, 95.0 mmol, 2 M in THF). To the resulting mixture at room temperature was added dropwise a solution of $NaClO_2$ (1.76 g, 19.44 mmol) and NaH_2PO_4 (1.81 g, 15.12 mmol) in H_2O (27 mL). The reaction mixture was stirred at room temperature for 30 min and partitioned with 20 mL of H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 60 mL). The combined organic extract was dried over anhydrous Na_2SO_4, and the solvent was removed in a vacuum to give a colorless viscous oil which was used as such for the subsequent esterfication. (Step 3) [**CAUTION**: Diazomethane is an explosive and a highly toxic gas. Explosions may occur if the substance is dry and undiluted. All operations involving diazomethane should be carried out in an efficient fumehood following appropriate precautions]. To an ice-cooled biphasic solution of KOH (5 g) in H_2O (15 mL) and ether (80 mL) was added *N*-methyl-*N*′-nitro-*N*-nitrosoguanindine (MNNG, 1.5 g) in one lot. The organic layer turned bright yellow. The ethereal layer was decanted into an ice-cooled Erlenmeyer flask containing KOH pellets. The aqueous layer was washed with ether (3 × 25 mL), and the ethereal layers were combined. The diazomethane (CH_2N_2) thus prepared was added to a stirred solution of the crude acid (0.728 g in 10 mL of ether), as obtained in step 2, and the mixture was stirred for 30 min. Excess CH_2N_2 was removed by bubbling nitrogen into the reaction mixture for 15 min, followed by removal of solvent under vacuum to yield the crude product. Purification by flash chromatography (hexane/EtOAc = 9:1) afforded the pyrrolidine carboxylate **9** as a white crystalline solid (CH_2Cl_2/hexane) (0.528 g, 71% overall): mp 97−99 °C; $[\alpha]^{25}_D$ −88.9 (*c* 1.00, $CHCl_3$); IR (NaCl) 1748, 1712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotameric mixture) δ 1.44, 1.47 and 1.51 (3s, 6H), 1.78−1.82 (dd, J = 2.2 and 11.4 Hz, 1H), 2.56−2.65 (m, 1H), 3.27−3.37 (m, 1H), 3.55 and 3.78 (2s, 3H), 3.72−3.76 (m, 1H), 3.89−4.03 (2t, J = 10.6 Hz, 1H), 4.34−4.38 (dd, J = 8.8 and 18.0 Hz, 1H), 4.45−4.48 and 4.74−4.78 (2dd, J = 4.3 and 10.6 Hz, 1H), 4.96−5.18 (m, 2H), 7.31−7.38 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$, rotameric mixture) δ 19.8, 19.9, 29.5, 29.6, 33.2, 33.8, 52.6, 52.9, 56.8, 56.9, 57.2, 66.1, 66.5, 67.5, 68.0, 72.5, 72.8, 100.8, 101.0, 128.5, 128.6, 128.7, 128.7, 128.9, 129.0, 136.2, 136.4, 154.5, 155.4, 172.6, 172.7; FABMS calcd for $C_{18}H_{23}NO_6$ *m*/*z* $(M + H)^+$ 350.1, found 350.1.

(2*S*,4*S*,5*R*)-Bulgecinine Hydrochloride (1). The fully protected *N*-Cbz-bulgecinine methyl ester acetonide (**9**) (0.070 g, 0.2 mmol) was taken in 6 N HCl (7 mL) and refluxed for 5 h. The reaction mixture was cooled to room temperature and extracted once with 10 mL of CH_2Cl_2 to remove any organic soluble impurities. The aqueous layer was then concentrated in a rotary evaporator to remove the volatiles and the excess solvent. The residual oily product was kept under high vacuum overnight, affording bulgecinine hydrochloride (**1**) as a light yellow viscous solid (0.037 g, 94%): $[\alpha]^{25}_D$ +11.71(*c* 0.65, 1 N HCl) {lit.[1b] $[\alpha]_D$ + 12.4 (*c* 0.95 N HCl)}; ^1H NMR (400 MHz, D_2O) δ 2.15−2.23 (m, 1H), 2.48−2.58 (m, 1H), 3.57−3.80 (m, 3H), 4.27−4.32 (m, 1H), 4.40−4.48 (m, 1H); ^{13}C NMR (100.6 MHz, D_2O) δ 36.5, 58.4, 58.6, 68.0, 70.8, 172.0; FABMS calcd for $C_6H_{12}ClNO_4$ *m*/*z* $(M + H)^+$ 198.62, found 162.1 (MH^+ − HCl).

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Supporting Information Available: General experimental details and copies of ^1H and ^{13}C NMR spectra for compounds **1**, **2**, and **5**−**9** and the X-ray crystallographic details for compound **9** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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