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Stereoselective synthesis of (−)-bulgecinine hydrochloride and its C-2 epimer from L-ascorbic acid☆

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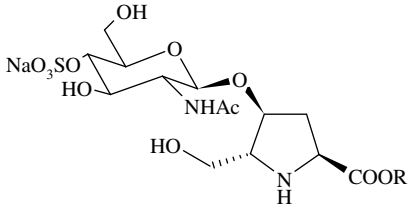
Abstract—An efficient strategy for the stereocontrolled synthesis of (−)-bulgecinine hydrochloride **1** was accomplished by utilizing a Wittig Horner olefination, stereoselective reduction of the double bond and intramolecular N-alkylation to furnish the target.

1. Introduction

The total synthesis of non-proteinogenic aminoacids is a challenging goal. This class of aminoacids has not only provided new insights into the secondary structures of oligopeptides[1] but also have been the constituents of several bioactive natural products viz., *Echinocandin B*,[2a] *Fosinopril*,[2b] *Prolinalin A* & *B*[2c] and *AG-7352*.[2d] The pyrrolidine ring, which contains the aminoacids has attracted more attention due to novel folding patterns.[3] Furthermore, proline and its analogues have proven to be excellent organocatalysts in asymmetric synthesis.[4]

Bulgecinine **1** is one such aminoacid, a constituent of antibiotic glycopeptides called bulgecins **2** and **3** (Fig. 1)



2 Bulgecin A: R = $NHCH_2CH_2SO_3H$
3 Bulgecin B: R = $NHCH_2CH_2COOH$

Figure 1.

isolated from *Pseudomonas acidophilia* and *Pseudomonas mesoacidophila*.[5] Interestingly, even though (−)-bulgecinines have limited antibacterial activity, these compounds contribute to cell wall changes in Gram-negative bacteria in association with β-lactam antibiotics. This cell wall change (bulge formation) allows the efficient killing of bacteria even at low concentrations of the antibiotic. This role of decreased concentration of the actual antibiotic has attracted the attention of researchers involved in the design and development of new class of antibiotics.

The stereochemical structure of (−)-bulgecinine **1** has been unequivocally confirmed by extensive spectroscopic and crystallographic studies and found to be (2*S*,4*S*,5*R*)-4-hydroxy-5-hydroxymethyl proline.[6] Due to its novel biological properties,[7] several groups have embarked onto the total synthesis of this scaffold and have reported successfully various strategies.[8]

In our efforts towards the development of new protocols[9] for the synthesis of a chiral pyrrolidine scaffold as a tool in probing biological properties and also for building 'organocatalysis',[10] we herein report a short and scaleable synthesis of this synthon. The retrosynthetic strategy is outlined in Scheme 1.

2. Results and discussion

The total synthesis of the (−)-bulgecinine hydrochloride salt began from commercially available L-ascorbic acid.

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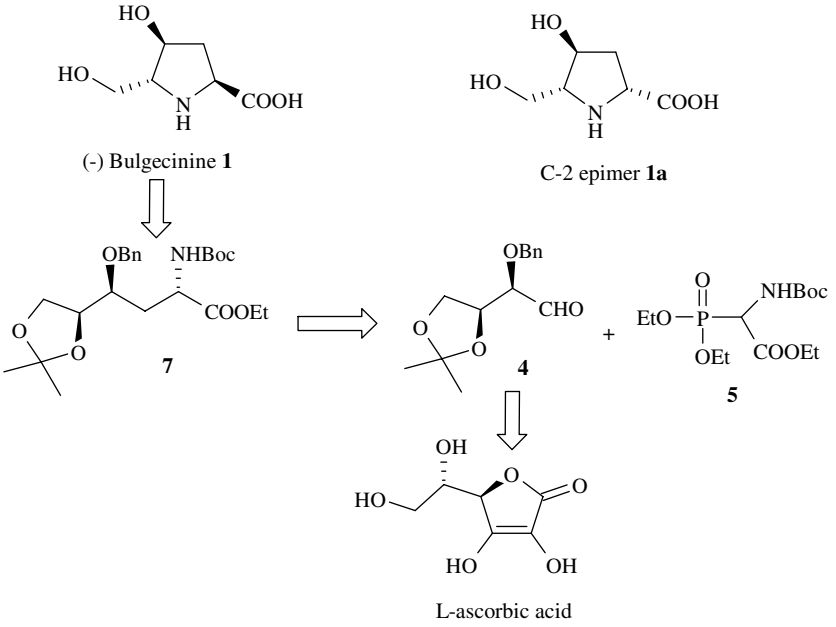
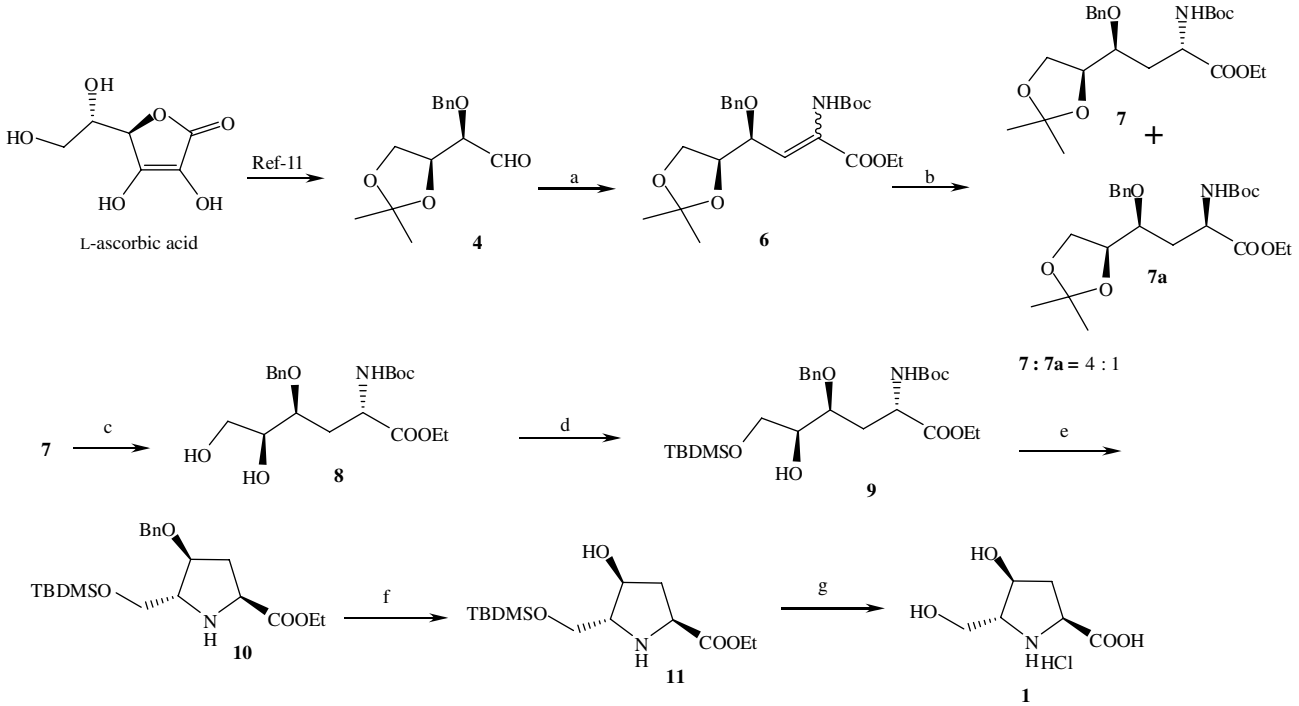


Scheme 1. Retrosynthesis.

The key compound, α-benzyloxy aldehyde **4** was prepared from known reactions.[11] This was quickly subjected to a Wittig–Horner reaction[12] with the phosphonate salt **5** generated from Boc-Glycine ethyl ester[13] to yield compound **6** as an inseparable mixture (6:4 ratio of *Z*/*E*) at −70 °C to rt in good yield. We attempted to synthesize the pure geometrical isomer of **6** using various conditions but were unsuccessful.[14] The inseparable mixture of compound **6** was subjected to controlled hydrogenation conditions using different solvents, such as ethanol (low yield and selectivity), dichloromethane (2:1 ratio of **7**:**7a**, 60% yield) and ethyl acetate[15] (4:1 ratio of **7**:**7a**, 74% yield). Based on these results, we carried out the hydrogenation of compound **6** in ethyl acetate and obtained a mixture, which was easily



Scheme 2. Reagents and conditions: (a) **5**, KOBu^t, CH_2Cl_2, −70 °C, 5 h, 82%; (b) 10% Pd/C, H_2, Na_2CO_3, EtOAc, 3 h, 74%; (c) PPTS, EtOH, 55 °C, 24 h, 80%; (d) TBDMSCl, imidazole, CH_2Cl_2, 6 h, 96%; (e) (i) MsCl, DIPEA, 2 h; (ii) 15% TFA in CH_2Cl_2, 3 h then $NaHCO_3$, overnight, 63% (two steps); (f) 10% Pd/C, H_2, EtOH, overnight, 90%; (g) 6 M HCl, 100 °C, 5 h, 85%.

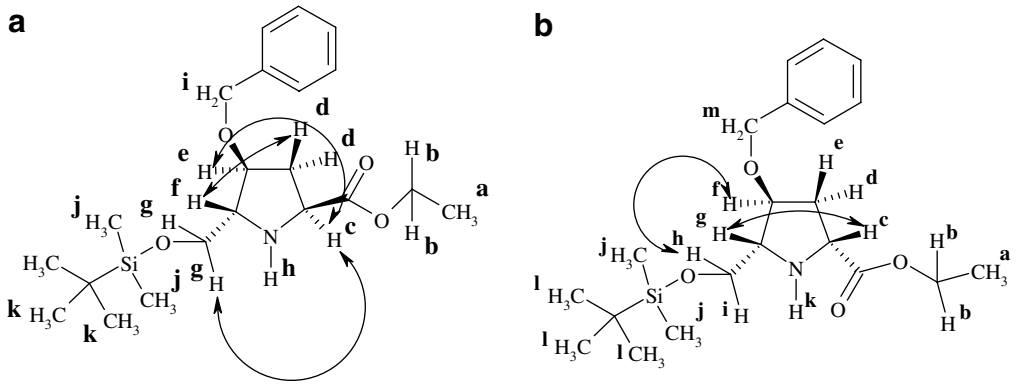


Figure 2. (a) Characteristic NOE's observed in compound **10**, (b) characteristic NOE's observed in compound **10a**.

separable by silica column chromatography. The diastereomers[16] were independently carried forward for the synthesis of (2*S*,4*S*,5*R*)- and (2*R*,4*S*,5*R*)-(−)-bulgecinine hydrochloride.

Diastereomer **7** on exposure to pyridinium *para* toluenesulfonate (PPTS) in ethanol furnished diol **8** in 80% yield, which on selective protection of the primary hydroxyl group with TBDMSCl and imidazole as base in methylene chloride afforded **9** in 96% yield. The secondary alcohol in **9** was mesylated, which on deblocking the *tert*-butyl carbonate group using 15% triflouroaceticacid in methylene chloride followed by basification with $NaHCO_3$ provided the pyrrolidine scaffold **10** in 63% yield (for two steps) (Scheme 2).

The structure and stereochemistry of compound **10** was assigned by one-dimensional ^1H, ^{13}C experiments and two-dimensional DQCOSY, NOESY experiments. The strong NOE cross peak between H_c–H_e, H_g–H_c and H_f–H_d supports the structure. Similarly, for compound **10a**, the NOE cross peak between H_c–H_g, and H_f–H_h supports the derived structure (Fig. 2).

Unmasking the hydroxy protecting groups in **10** was achieved first by exposure to Pd–C/H_2 followed by treatment with 6 M HCl at 100 °C to realize (2*S*,4*S*,5*R*)-(−)-bulgecinine hydrochloride **1**. The spectral data including optical rotations were in full agreement with the literature values {$[\alpha]_D^{25} = +11.6$ (*c* 0.75, 1 M HCl); lit.[6] $[\alpha]_D^{25} = +12.4$ (*c* 0.95, 1 M HCl)}.

The minor isomer **7a** under a series of similar reactions furnished diastereomer (2*R*,4*S*,5*R*)-(−)-bulgecinine **1a**.

3. Conclusion

In conclusion, a practical synthesis of natural (−)-bulgecinine and its C-2-epimer has been synthesized from commercially available L-ascorbic acid using standard laboratory chemicals. This route is amenable to both scale-up and analogue synthesis. Activity testing for the C-2 epimer is currently underway and will be published in future.

4. Experimental

4.1. General

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were recorded on Perkin–Elmer 683 spectrometer. Optical rotations were obtained on Jasco Dip 360 digital polarimeter. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or D_2O solution on a Varian Gemini 200, Brucker Avance 300, Varian Unity 400 or Inova Plus 500. Chemical shifts were reported in parts per million with respect to internal TMS. Coupling constants (*J*) are quoted in Hz. Mass spectra were obtained on an Agilent Technologies LC/MSD Trap SL.

4.1.1. *tert*-Butyl-(*S*)-1-(ethoxycarbonyl)-3-(benzyloxy)-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-1-enyl carbamate 6. To a stirred solution of potassium *tert*-butoxide (0.624 g, 5.57 mmol) in dry CH_2Cl_2 (20 mL), glycine phosponate **5** (1.620 g, 4.78 mmol) was added in dry CH_2Cl_2 (20 mL) under a nitrogen atmosphere at −78 °C. After 30 min, aldehyde **4** (1.000 g, 3.98 mmol) was slowly added to the reaction mixture in dry CH_2Cl_2 (10 mL) at −78 °C. The reaction mixture was warmed to room temperature and stirred for 5 h. Aqueous saturated NH_4Cl solution (20 mL) was added to the reaction mixture at 0 °C and stirred for 15 min. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (100 mL). The combined organic extracts were washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo to afford crude alkene **6** (1.421 g, 82%).

4.1.2. *tert*-Butyl-(1*S*,3*S*)-1-(ethoxycarbonyl)-3-(benzyloxy)-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]propyl carbamate 7. A mixture of alkene compound **6** (1.000 g, 2.29 mmol), Na_2CO_3 (0.731 g, 6.89 mmol) and 10% Pd/C (0.229 g, 2.29 mmol) in dry ethyl acetate (20 mL) was stirred under a hydrogen atmosphere pressure for 3 h. The reaction mixture was filtered through Celite and washed with ethyl acetate (3 × 10 mL). The filtrate was concentrated under vacuo and purified by column chromatography (hexane/EtOAc = 4:1) to afford the viscous oily compound **7** (0.743 g, 74%). $[\alpha]_D^{25} = -27.4$ (*c* 1.5, $CHCl_3$); IR (neat):

3421, 1700, 1637, 772 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.40–7.20 (m, 5H), 5.35–5.27 (m, 1H), 4.70 (d, $J = 11.2$ Hz, 1H), 4.54 (d, $J = 11.2$ Hz, 1H), 4.50–4.30 (m, 1H), 4.24–4.08 (m, 3H), 4.00–3.90 (m, 1H), 3.73–3.49 (m, 2H), 2.05–1.63 (m, 2H), 1.48–1.42 (m, 12H), 1.33–1.23 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.6, 155.5, 138.0, 128.4 (3C), 127.8 (2C), 109.5, 79.6, 77.3, 76.6, 73.5, 65.5, 61.3, 51.2, 32.4, 28.3 (3C), 26.4, 25.0, 14.1; ESIMS: m/z 460 $(M+Na)^+$; HRMS calcd for $C_{23}H_{36}NO_7$: 438.2495; found: 438.2491.

4.1.2.1. *tert*-Butyl-(1*R*,3*S*)-1-(ethoxycarbonyl)-3-(benzyloxy)-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]propyl carbamate 7a. $[\alpha]_D^{25} = -39.1$ (c 1.1, $CHCl_3$); IR (neat): 3425, 1703, 1642, 776 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.32–7.16 (m, 5H), 5.33–5.21 (m, 1H), 4.78 (d, $J = 11.4$ Hz, 1H), 4.40 (d, $J = 11.4$ Hz, 1H), 4.32–4.13 (m, 2H), 4.10–3.80 (m, 3H), 3.70–3.43 (m, 2H), 2.07–1.87 (m, 2H), 1.53–1.28 (m, 15H), 1.14 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.3, 155.2, 138.0, 128.3 (3C), 127.7 (2C), 109.6, 79.8, 77.5, 76.2, 72.8, 65.7, 61.2, 51.3, 32.7, 28.3 (3C), 26.4, 25.1, 14.0; ESIMS: m/z 460 $(M+Na)^+$; HRMS calcd for $C_{23}H_{36}NO_7$: 438.2495; found: 438.2489.

4.1.3. *tert*-Butyl-(1*S*,3*S*,4*S*)-1-(ethoxycarbonyl)-3-(benzyloxy)-4,5-dihydroxy pentyl carbamate 8. To a stirred solution of compound **7** (1.000 g, 2.28 mmol) in dry ethanol (20 mL), PPTS (0.250 g, 0.91 mmol) was added under a nitrogen atmosphere. The reaction mixture was slowly heated to 50–55 °C. After 12 h, PPTS (0.125 g, 0.41 mmol) was added to the reaction mixture and stirred at the same temperature for 12 h. Solid $NaHCO_3$ was added at 0 °C and stirred for 1 h. The reaction mixture was filtered and the solvent was removed in vacuo and extracted with CH_2Cl_2 (30 mL). The combined organic extracts were washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product purified by silica gel column chromatography (hexane/EtOAc = 1:1) to afford the compound **8** (0.726 g, 80%). $[\alpha]_D^{25} = -14.6$ (c 0.7, $CHCl_3$); IR (KBr): 3359, 3400, 1702, 1629, 1219, 1032, 771 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.40–7.24 (m, 5H), 5.47 (d, $J = 8.7$ Hz, 1H, NH), 4.58 (dd, $J = 10.8$ and 12.4 Hz, 2H), 4.37–4.39 (m, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 3.66–3.52 (m, 4H), 3.11 (br s, 1H, OH), 2.70 (br s, 1H, OH), 2.15–1.87 (m, 2H), 1.52 (s, 9H), 1.27 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.5, 155.4, 137.5, 128.3 (2C), 128.0 (2C), 127.8, 79.9, 76.4, 72.4, 72.2, 63.3, 61.3, 51.2, 32.9, 28.1 (3C), 13.9; ESIMS: m/z 420 $(M+Na)^+$; Anal. Calcd for $C_{20}H_{31}NO_7$: C, 60.44; H, 7.86; N, 3.52. Found: C, 60.57; H, 7.73; N, 3.64.

4.1.3.1. *tert*-Butyl-(1*R*,3*S*,4*S*)-1-(ethoxycarbonyl)-3-(benzyloxy)-4,5-dihydroxy pentyl carbamate 8a. $[\alpha]_D^{25} = -8.8$ (c 1.9, $CHCl_3$); IR (KBr): 3362, 3406, 1705, 1626, 1225, 1035, 777 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.37–7.25 (m, 5H), 5.38 (d, $J = 6.9$ Hz, 1H, NH), 4.51 (dd, $J = 11.1$ and 14.2 Hz, 2H), 4.34–4.26 (m, 1H), 4.06 (q, $J = 7.1$ Hz, 2H), 3.78–3.80 (m, 1H), 3.62–3.72 (m, 3H), 3.08 (br s, 1H, OH), 2.76 (br s, 1H, OH), 2.37–2.40 (m, 1H), 2.08–2.10 (m, 1H), 1.42 (s, 9H), 1.15 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.7, 155.8, 137.7, 128.7 (2C), 128.4 (2C), 127.6, 80.1, 76.8, 72.6, 72.4, 63.5, 61.7, 51.6, 33.1, 28.5 (3C), 14.1; ESIMS: m/z 420 $(M+Na)^+$; Anal. Calcd for $C_{20}H_{31}NO_7$: C, 60.44; H, 7.86; N, 3.52. Found: C, 60.51; H, 7.79; N, 3.58.

4.1.4. *tert*-Butyl-(1*S*,3*S*,4*S*)-1-(ethoxycarbonyl)-3-(benzyloxy)-4-hydroxy-5-(*tert*-butyl dimethyl silyloxy)-pentyl carbamate 9. To a stirred solution of diol **8** (1.000 g, 2.51 mmol) in dry CH_2Cl_2 (20 mL), imidazole (0.428 g, 6.62 mmol) and *tert*-butyl dimethyl silyl chloride (0.680 g, 4.53 mmol) were added at 0 °C and stirred for 6 h at room temperature. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (40 mL). The combined organic extracts were washed with water, brine and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and crude product was purified by column chromatography (hexane/EtOAc = 7:3) to afford compound **9** (1.233 g, 96%). $[\alpha]_D^{25} = -17.6$ (c 1.25, $CHCl_3$); IR (KBr): 3500, 3420, 1712, 1637, 1218, 1020, 772 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.30–7.28 (m, 5H), 5.34 (d, $J = 6.6$ Hz, 1H), 4.57 (s, 2H), 4.43–4.00 (m, 3H), 3.82–3.67 (m, 4H), 2.48 (s, 1H), 2.35–1.20 (m, 2H), 1.48 (s, 9H), 1.23 (t, $J = 7.1$ Hz, 3H), 0.95 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.6, 155.3, 137.9, 128.4 (2C), 128.1 (2C), 127.8, 76.1, 72.8, 72.5, 63.4, 61.2, 51.3, 33.0, 28.3 (3C), 25.9 (3C), 25.8, 18.2, 14.0, −5.4 (2C); ESIMS: m/z 534 $(M+H+Na)^+$; Anal. Calcd for $C_{26}H_{45}NO_7Si$: C, 61.03; H, 8.86; N, 2.74. Found: C, 61.11; H, 8.78; N, 2.86.

4.1.4.1. *tert*-Butyl-(1*R*,3*S*,4*S*)-1-(ethoxycarbonyl)-3-(benzyloxy)-4-hydroxy-5-(*tert*-butyl dimethyl silyloxy)-pentyl carbamate 9a. $[\alpha]_D^{25} = -18.2$ (c 1.25, $CHCl_3$); IR (KBr): 3502, 3425, 1708, 1639, 1223, 1022, 776 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.48–7.36 (m, 5H), 5.31 (dd, $J = 7.4$ Hz, 1H), 4.57–4.60 (m, 2H), 4.39–3.90 (m, 3H), 3.75–3.61 (m, 4H), 2.52 (s, 1H), 2.38–2.06 (m, 2H), 1.43 (s, 9H), 1.24 (t, $J = 7.2$ Hz, 3H), 0.89 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.8, 155.6, 138.0, 128.8, 128.7 (2C), 128.3 (2C), 127.8, 76.5, 73.0, 72.9, 63.6, 61.6, 51.9, 33.4, 28.4 (3C), 26.2 (3C), 27.6, 14.4, −5.8 (2C); ESIMS: m/z 534 $(M+H+Na)^+$; Anal. Calcd for $C_{26}H_{45}NO_7Si$: C, 61.03; H, 8.86; N, 2.74. Found: C, 61.06; H, 8.83; N, 2.78.

4.1.5. (2*S*,4*S*,5*R*)-Ethyl-4-(benzyloxy)-5-(*tert*-butyl dimethyl silyloxy methyl)pyrrolidine-2-carboxylate 10. To a stirred solution of alcohol **9** (1.000 g, 1.96 mmol) and DIPEA (0.75 mL, 4.31 mmol) in dry CH_2Cl_2 (20 mL) was slowly added a solution of methanesulfonyl chloride (0.210 mL, 2.77 mmol) in dry CH_2Cl_2 (5 mL) at −10 °C and stirred for 2 h at room temperature. The reaction mixture was extracted with CH_2Cl_2, washed with water, 1 M HCl (12 mL), brine and dried over anhydrous Na_2SO_4 and concentrated under *vacuum* to afford a colourless oily residue, which was used directly for the subsequent reaction.

To a stirred solution of the above mesylated product (0.800 g, 1.36 mmol) in dry CH_2Cl_2 (20 mL), TFA (2.4 mL) was added dropwise to the reaction mixture at 0 °C and slowly warmed to room temperature. After

completion of the reaction (by TLC analysis), excess TFA was removed in high vacuo and 30 mL of dry CH_2Cl_2 was added to the reaction mixture at 0 °C under nitrogen atmosphere. Solid $NaHCO_3$ was added to the reaction mixture and stirred overnight at room temperature. The reaction mixture was filtered and washed with CH_2Cl_2 (30 mL), the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (hexane/EtOAc = 4:1) to afford cyclized compound **10** (0.485 g, 63% for two steps): $[\alpha]_D^{25} = +5.4$ (*c* 1.3, $CHCl_3$); IR (neat): 3415, 1738, 1255, 1099, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.33–7.23 (m, 5H, Ar–H), 4.47 (s, 2H, H_i), 4.15 (q, $J = 7.0$ Hz, 2H, H_b), 3.93 (dt, $J = 2.2$ and 4.2 Hz, 1H, H_e), 3.82 (t, $J = 6.2$ Hz, 1H, H_c), 3.59 (dt, $J = 8.4$ and 5.0 Hz, 1H, H_f), 3.43 (m, 2H, H_g), 2.35 (br s, 1H, H_h), 2.27 (dd, $J = 4.2$, 6.2 Hz, 2H, H_d), 1.22 (t, $J = 7.0$ Hz, 3H, H_a), 0.88 (s, 9H, H_k), 0.04 (s, 6H, H_j); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.9, 138.3, 128.2 (2C), 127.3, 127.5 (2C), 79.9, 70.5, 64.8, 64.7, 61.0, 58.9, 34.9, 25.9 (3C), 18.2, 14.1, −5.4 (2C); ESIMS: *m*/*z* 394 $(M+H)^+$; HRMS calcd for $C_{21}H_{36}NO_4Si$ (M+H) 394.2413; found: 394.2422.

4.1.5.1. (2*R*,4*S*,5*R*)-Ethyl-4-(benzyloxy)-5-(*tert*-butyl dimethyl silyloxy methyl)pyrrolidine-2-carboxylate 10a. $[\alpha]_D^{25} = +21.6$ (*c* 1.8, $CHCl_3$); IR (neat): 3420, 1744, 1260, 1105, 778 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.35–7.28 (m, 5H, Ar–H), 4.51 (dq, $J = 11.7$, 9.5 Hz, 2H, H_m), 4.18 (q, $J = 7.0$ Hz, 2H, H_b), 3.97 (dt, $J = 1.9$ and 5.0 Hz, 2H, H_c and H_f), 3.68 (dd, $J = 4.2$ and 10.2 Hz, 1H, H_h), 3.61 (dd, $J = 5.4$ and 10.2 Hz, 1H, H_i), 3.25 (ddd, $J = 3.8$, 5.7 and 9.2 Hz, 1H, H_g), 2.24 (ddd $J = 2.9$, 7.3 and 10.2 Hz, 1H, Hd), 2.18 (br s, 1H, H_k), 1.94 (ddd, $J = 6.7$, 9.2 and 2.9 Hz, 1H, H_e), 1.27 (t, $J = 7.0$ Hz, 3H, H_a), 0.88 (s, 9H, H_l), 0.05 (s, 6H, H_j); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.9, 138.2, 128.4 (2C), 128.2, 127.6 (2C), 80.6, 71.2, 66.1, 63.2, 60.9, 58.9, 36.6, 25.8 (3C), 18.1, 14.1, −5.5 (2C); ESIMS: *m*/*z* 394 $(M+H)^+$; HRMS calcd for $C_{21}H_{36}NO_4Si$ (M+H) 394.2413; found: 394.2419.

4.1.6. (2*S*,4*S*,5*R*)-Ethyl 4-hydroxy-5-(*tert*-butyl dimethyl silyloxy methyl)pyrrolidine-2-carboxylate 11. A mixture of compound **10** (0.400 g, 1.01 mmol) and 10% Pd/C (0.300 g) in dry ethanol (20 mL) was stirred under a hydrogen atmosphere overnight. The reaction mixture was filtered through Celite and washed with ethanol (30 mL). The solvent was removed under reduced pressure and the crude product was purified by column chromatography (hexane/EtOAc = 7:3) to afford the pyrrolidine carboxylate **11** as an oily product (0.277 g, 90%): $[\alpha]_D^{25} = -8.1$ (*c* 0.9, $CHCl_3$); IR (KBr): 3315, 3300, 1726, 1219, 1054, 772 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.25–4.14 (m, 2H), 4.10–4.05 (m, 1H), 3.72 (dd, $J = 4.0$ and 8.8 Hz, 1H), 3.58 (dd, $J = 7.3$ and 12.1 Hz, 1H), 3.38 (dd, $J = 7.2$ and 9.9 Hz, 1H), 3.23–3.14 (m, 1H), 2.35 (s, 1H), 2.30–2.26 (m, 2H), 1.94–1.85 (m, 1H), 1.33 (t, $J = 7.1$ Hz, 3H), 0.83 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 175.8, 74.3, 67.0, 65.2, 61.2, 58.1, 37.8, 25.8 (3C), 18.2, 14.0, −5.5 (2C); ESIMS: *m*/*z* 304 $(M+H)^+$; HRMS calcd for $C_{14}H_{30}NO_4Si$: 304.1944. Found: 304.1930.

4.1.6.1. (2*R*,4*S*,5*R*)-Ethyl 4-hydroxy-5-(*tert*-butyl dimethyl silyloxy methyl)pyrrolidine-2-carboxylate 11a. $[\alpha]_D^{25} = +11.7$ (*c* 0.9, $CHCl_3$); IR (KBr): 3317, 3305, 1728, 1224, 1056, 777 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.23 (q, $J = 7.1$ Hz, 2H), 4.16–4.05 (m, 1H), 3.85–3.63 (m, 2H), 3.30–3.26 (m, 1H), 2.95–2.87 (m, 3H), 2.26–2.24 (m, 2H), 1.32 (t, $J = 7.1$ Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.7, 73.7, 67.8, 62.6, 61.7, 58.3, 38.5, 25.8 (3C), 18.1, 14.0, −5.6 (2C); ESIMS: *m*/*z* 304 $(M+H)^+$; HRMS calcd for $C_{14}H_{30}NO_4Si$: 304.1944; found: 304.1950.

4.1.7. (2*S*,4*S*,5*R*)-Bulgecinine hydrochloride 1. Compound **11** (0.200 g, 0.66 mmol) was taken up in 6 M HCl (15 mL) and refluxed for 5 h. The reaction mixture was cooled to room temperature and extracted once with 20 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, to afford bulgecinine hydrochloride **1** as a light yellow viscous solid (0.110 g, 85%): $[\alpha]_D^{25} = +11.6$ (*c* 0.75, 1 M HCl) {lit.[6] $[\alpha]_D^{25} = +12.4$ (*c* 0.95, 1 M HCl)}; ^1H NMR (200 MHz, D_2O): δ 4.44–4.37 (m, 1H), 4.35–4.27 (m, 1H), 3.81–3.58 (m, 3H), 2.61–2.47 (m, 1H), 2.24–2.13 (m, 1H); ^{13}C NMR (50 MHz, D_2O): δ 168.9, 67.4, 64.5, 55.3, 54.9, 33.1; ESIMS: *m*/*z* 197 $(M)^+$, 162 $(M+H-HCl)^+$; HRMS calcd for $C_6H_{12}NO_4Cl$ $(M)^+$ 197.6167; found: 197.6143.

4.1.7.1. (2*R*,4*S*,5*R*)-Bulgecinine hydrochloride 1a. $[\alpha]_D^{25} = +29.8$ (*c* 0.60, 1 M HCl); ^1H NMR (300 MHz, D_2O): δ 4.60–4.54 (m, 1H), 4.42–4.37 (m, 1H), 3.92–3.83 (m, 1H), 3.76–3.70 (m, 2H), 2.42–2.36 (m, 2H); ^{13}C NMR (75 MHz, D_2O): δ 172.9, 71.5, 68.6, 58.7, 36.7, 29.5; ESIMS: *m*/*z* 197 $(M)^+$, 162 $(M+H-HCl)^+$; HRMS calcd for $C_6H_{12}NO_4Cl$ $(M)^+$ 197.6167; found: 197.6032.

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