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An efficient stereoselective synthesis of (2*S*,4*S*,5*R*)-(−)- and (2*R*,4*R*,5*S*)-(+)-bulgecinine

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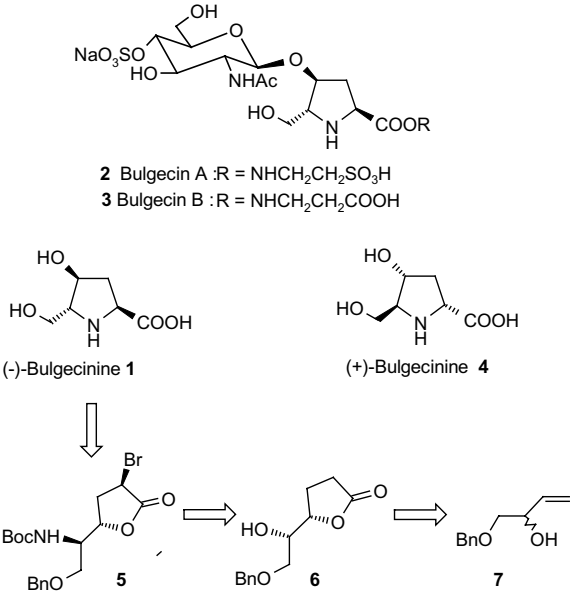
Abstract—A short synthetic route to (−)-and (+)-bulgecinine, the amino acid moiety of the bulgecins was achieved from the readily available nonchiral pool starting material *cis*-2-butene-1,4-diol in which a Claisen orthoester rearrangement and a Sharpless asymmetric dihydroxylation were used as the key steps.

Bulgecinine **1** is an amino acid constituent of naturally occurring antibiotic glycopeptides called bulgecins (**2**, **3**), isolated from *Pseudomonas acidophila* and *Pseudomonas mesoacidophila*[1] bulgecins although devoid of antibacterial activity, induce characteristic morphological changes, called bulge formation, in the cell wall of Gram-negative bacteria in co-operation with β-lactam antibiotics. As a result of bulge formation, the activity of these antibiotics is effectively enhanced and the bacteria are killed at lower β-lactam concentrations. The structure of (−)-bulgecinine **1** has been determined chemically and crystallographically to be (2*S*,4*S*,5*R*)-4-hydroxy-5-hydroxymethyl proline.[2]

As a consequence of their biological effects[3] and structural novelty, several total syntheses of (−)-bulgecinine have been reported in the literature.[4] Herein we describe our strategy involving a Sharpless asymmetric dihydroxylation approach for the synthesis of (−)- and (+)-bulgecinine. In connection with our current studies directed towards the construction of biologically active compounds from the versatile intermediate **6**,[5] we focused our attention on the stereoselective synthesis of (−)- and (+)-bulgecinine starting from the readily available nonchiral pool starting material *cis*-2-butene-1,4-diol.

The retrosynthetic analysis for our planned synthesis of (−)-bulgecinine is shown in Scheme 1. The bromolactone **5**, the precursor to bulgecinine, could be obtained from the hydroxylactone **6**, which in turn was obtained from the allyl alcohol **7**.



Scheme 1. Retrosynthetic analysis of **1**.

As outlined in Scheme 2, the enantiomerically pure hydroxylactone **6**, was obtained in four steps from *cis*-2-butene-1,4-diol **8**, in which a Claisen orthoester rearrangement and a Sharpless asymmetric dihydroxylation were used as the key steps to install the requisite chirality. Mesylation of the hydroxylactone **6** using MsCl and

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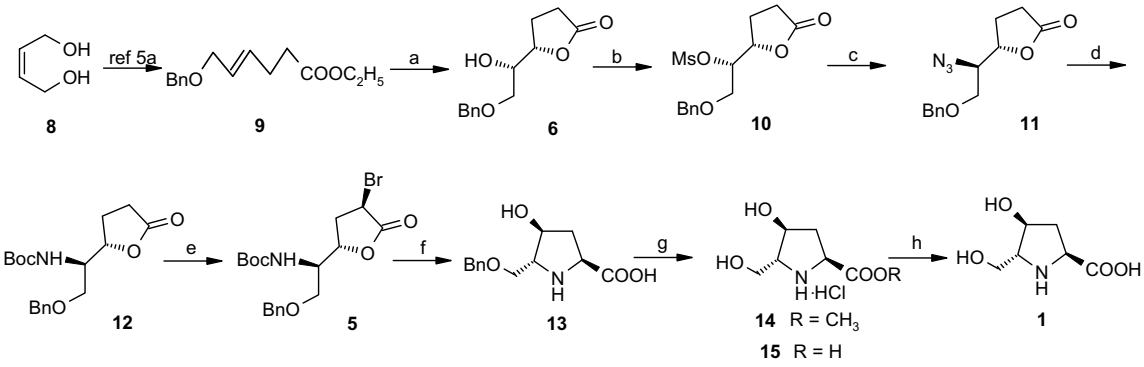

Scheme 2. Reagents and conditions: (a) AD-mix-α, $CH_3SO_2NH_2$, *t*-BuOH–H_2O (1/1), 24 h, 0 °C, 95%, 93% ee; (b) CH_3SO_2Cl, Et_3N, DMAP, DCM, 0 °C, 4 h, 92%; (c) NaN_3, DMF, 90 °C, 24 h, 89%; (d) H_2, 10% Pd–C, Et_3N, Boc_2O, EtOAc, rt, 2 h, 88%; (e) LiHMDS, TMSCl, Et_3N, NBS, THF, −78 °C, 2 h, 65%; (f) (i) CF_3COOH, DCM, 60 °C, 3 h, (ii) 0.1 N $Ba(OH)_2$, pH = 9, 3 h, (iii) dil HCl, Amberlite-IR-120, 24 h, (iv) 6 N NH_4OH (aq), 3 h; (g) 10% Pd–C, methanolic HCl, rt, 24 h; (h) 1 M NaOH, rt, 92% (over three steps).

Et_3N in the presence of a catalytic amount of DMAP gave the mesylated lactone **10**. Displacement of the mesylate with NaN_3 at 90 °C in DMF gave the azidolactone **11**. Catalytic hydrogenation of the azido lactone over 10% Pd–C in ethyl acetate in the presence of Boc_2O gave the Boc protected lactone **12**.

The challenging task in our synthesis was to introduce the bromine stereoselectively at C-2 of the lactone **12**. This was achieved using LiHMDS, Et_3N and NBS at −78 °C for 2 h. The major isomer **5** along with its diastereomer (9:1 ratio) was separated by silica gel column chromatography. The conditions developed by Oppolzer[6] were adapted to convert the major isomer (2*R*,4*S*,5*R*)-**5** into the (2*S*,4*S*,5*R*)-**13** using the following sequence of reactions. The lactone **5** was refluxed in DCM with 10 mol equiv of CF_3COOH for 3 h followed by evaporation of the solvent. The residue was then dissolved in 0.1 N $Ba(OH)_2$ and the mixture maintained at pH 9 for 3 h. Acidification to pH 1, stirring the aqueous solution with Amberlite-IR-120 ion-exchange resin for 24 h, filtration, washing the resin with distilled water (until it showed clear solution with $AgNO_3$ to test the complete removal of Cl^-), stirring the resin with 6 N aqueous NH_4OH solution for 3 h and filtration gave the benzyl protected (2*S*,4*S*,5*R*)-(−)-bulgecinine **13**. Removal of the benzyl protection was performed using Pd/C in methanolic HCl under normal hydrogen pressure and at room temperature to deliver a mixture of (−)-bulgecinine hydrochloride **15** and its methyl ester **14**. This mixture was subjected to basic hydrolysis using 1 M NaOH to deliver (−)-bulgecinine **1**.

Accordingly we also prepared (+)-bulgecinine **4** following the same sequence of reactions from the opposite enantiomer of hydroxylactone **6**, which was prepared from the γ,δ-unsaturated ester **9** using AD-mix-β. The physical and spectroscopic data of all the synthetic intermediates were in good agreement with the proposed structures and those of **1** and **4** are in good agreement with the literature data.[7]

In summary (+)-and (−)-bulgecinine were synthesized in an efficient overall yield of 43% in seven steps from the hydroxylactone **6**, which in turn was obtained from the readily available *cis*-2-butene-1,4-diol, as the common achiral precursor. The syntheses of other biologically active compounds from the versatile intermediate **6** are being investigated in our laboratory.

Acknowledgements

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7. All new compounds were characterized and gave satisfactory spectral data. Compound **6**: $[\alpha]_D^{24}$ + 40.59 (*c* 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ, ppm: 2.25 (2H, m), 2.48 (2H, m), 2.69 (1H, m), 3.59 (2H, m), 3.84 (1H, m), 4.57 (3H, m), 7.33 (5H, m). ^{13}C NMR (50 MHz) δ: 23.3, 28.1, 70.5, 71.6, 73.1, 79.9, 127.5, 128.1, 137.5, 177.7 ppm. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83%. Found: C, 65.99; H, 6.77%. Compound **10**: $[\alpha]_D^{24}$ + 8.31 (*c* 1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ, ppm: 2.26 (1H, m), 2.36 (1H, m), 2.46 (1H, ddd, *J* = 16.9, 10.1, 6.4 Hz), 2.67 (1H, ddd, *J* = 16.9, 9.6, 6.4 Hz), 3.06 (3H, s), 3.71 (1H, dd, *J* = 10.5, 3.6 Hz), 3.83 (1H, dd, *J* = 10.5, 7.3 Hz), 4.55 (2H, m), 4.68 (1H, ddd, *J* = 8.2, 5.5, 3.2 Hz), 4.80 (1H, m), 7.32 (5H, m). ^{13}C NMR (125 MHz) δ: 23.5, 27.3, 38.6, 66.9, 73.3, 77.5, 81.7, 127.7, 128.3, 136.9, 176.0 ppm. Anal. Calcd for $C_{14}H_{18}O_6S$; C, 53.49; H, 5.77; S, 10.2%. Found: C, 53.62; H, 5.86; S, 10.38%. Compound **11**: $[\alpha]_D^{24}$ − 15.83 (*c* 1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ, ppm: 2.12 (1H, m), 2.23 (1H, m), 2.44–2.59 (2H, m), 3.62 (1H, dd, *J* = 10.1, 6.4 Hz), 3.66 (1H, dd, *J* = 10.1, 4.6 Hz), 3.79 (1H, m), 4.55 (3H, m), 7.32 (5H, m). ^{13}C NMR (125 MHz) δ: 23.1, 27.6, 63.0, 68.9, 73.1, 77.6, 127.3, 128.2, 137.1, 175.7 ppm. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 59.77; H, 5.76; N, 16.08%. Found: C, 59.57; H, 5.84; N, 16.19%. Compound **12**: $[\alpha]_D^{24}$ + 1.87 (*c* 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ, ppm: 1.39 (9H, s), 2.15 (2H, m), 2.43 (2H, m), 3.50 (1H, dd, *J* = 9.4, 3.5 Hz), 3.68–3.80 (2H, m), 4.45–4.56 (3H, m), 5.10 (1H, d, *J* = 9.3 Hz), 7.28 (5H, m). ^{13}C NMR (125 MHz) δ: 24.4, 27.8, 28.1, 52.9, 68.8, 73.3, 78.5, 79.6, 127.5, 128.2, 137.5, 155.3, 176.2 ppm. Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.17%. Found: C, 64.38; H, 7.32; N, 4.08%. Compound **5**: $[\alpha]_D^{24}$ + 10.50 (*c* 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ, ppm: 1.36 (9H, s), 2.42 (1H, ddd, *J* = 8.2, 5.9, 2.3 Hz), 2.68 (1H, m), 3.52 (1H, dd, *J* = 9.8, 3.5 Hz), 3.80 (2H, m), 4.42 (1H, dd, *J* = 6.6, 2.3 Hz), 4.51 (2H, m), 4.78 (1H, m), 5.10 (1H, d, *J* = 9 Hz), 7.26 (5H, m). ^{13}C NMR (125 MHz) δ: 28.3, 36.8, 38.3, 52.8, 68.7, 73.5, 77.5, 80.0, 127.7, 128.4, 137.4, 155.3, 171.6 ppm. Anal. Calcd for $C_{18}H_{24}NO_5Br$; C, 52.18; H, 5.83; N, 3.37; Br, 19.28%. Found: C, 52.07; H, 5.97; N, 3.36; Br, 19.06%. Compound **13**: $[\alpha]_D^{24}$ − 8.09 (*c* 1, H_2O). ^1H NMR (500 MHz, D_2O) δ, ppm: 2.11 (1H, ddd, *J* = 14.1, 6.2, 4.3 Hz), 2.51 (1H, ddd, *J* = 14.1, 9.0, 5.8 Hz), 3.56–3.71 (3H, m), 4.06 (1H, dd, *J* = 9.0, 6.6 Hz), 4.23 (1H, m), 4.49 (2H, m), 7.32 (5H, m). ^{13}C NMR (125 MHz) δ: 36.2, 59.1, 64.8, 65.7, 70.6, 72.8, 128.0, 128.4, 136.7, 173.6 ppm. Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.81; N, 5.57%. Found: C, 62.02; H, 6.92; N, 5.49%. Compound **1**: $[\alpha]_D^{24}$ − 13.3 (*c* 0.9, H_2O). ^1H NMR (200 MHz, D_2O) δ, ppm: 2.11 (1H, ddd, *J* = 14.5, 6.3, 4.6 Hz), 2.58 (1H, ddd, *J* = 14.5, 9.0, 5.9 Hz), 3.56–3.71 (3H, m), 4.06 (1H, dd, *J* = 9.0, 6.6 Hz), 4.34 (1H, m), ^{13}C NMR (75 MHz) δ: 37.2, 59.2, 60.5, 66.2, 71.7, 174.7 ppm.