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

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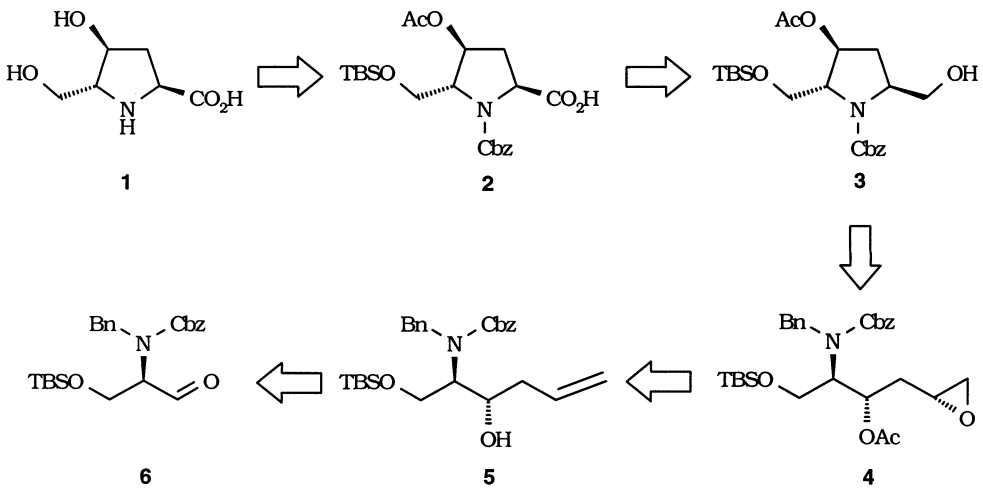
Abstract—*N*-Benzyl-*N*-carbobenzyloxy-*O*-*tert*-butyldimethylsilyl-D-serinal (**6**) was reacted under Barbier conditions with allyl bromide affording diastereoselectively (82:18) the *anti*-adduct **5**, which was subsequently transformed into (2*S*,4*S*,5*R*)-(−)-bulgecinine (**1**). © 2001 Elsevier Science Ltd. All rights reserved.

α-Amino aldehydes are synthetically useful chirons, readily available from naturally occurring α-amino acids.[1] In our recent studies, involving the synthesis of antibiotic amino sugars, we have shown that suitably protected α-amino aldehydes are versatile chirons.[2] For example, addition of allyltrimethylsilane to *N*-mono- and *N*,*N*-diprotected α-amino aldehydes offers an easy access to almost enantiomerically pure both *syn*- and *anti*-adducts,[3] which are readily transformed into natural products, such as 3-hydroxyproline,[4] 1,3-dideoxynojirimycin,[5] statine,[6] and preussin.[7]

Now we report a new application of our methodology to the stereoselective synthesis of (2*S*,4*S*,5*R*)-(−)-bulgecinine (**1**), an amino acid constituent of naturally occurring antibiotic glycopeptides called bulgecins, isolated from *Pseudomonas acidophila* and *Pseudomonas mesoacidophila*.[8] While bulgecins themselves show no



Scheme 1. Retrosynthetic analysis.

Keywords: asymmetric induction; amino aldehydes; allylation; epoxidation; cyclization; pyrrolidines.
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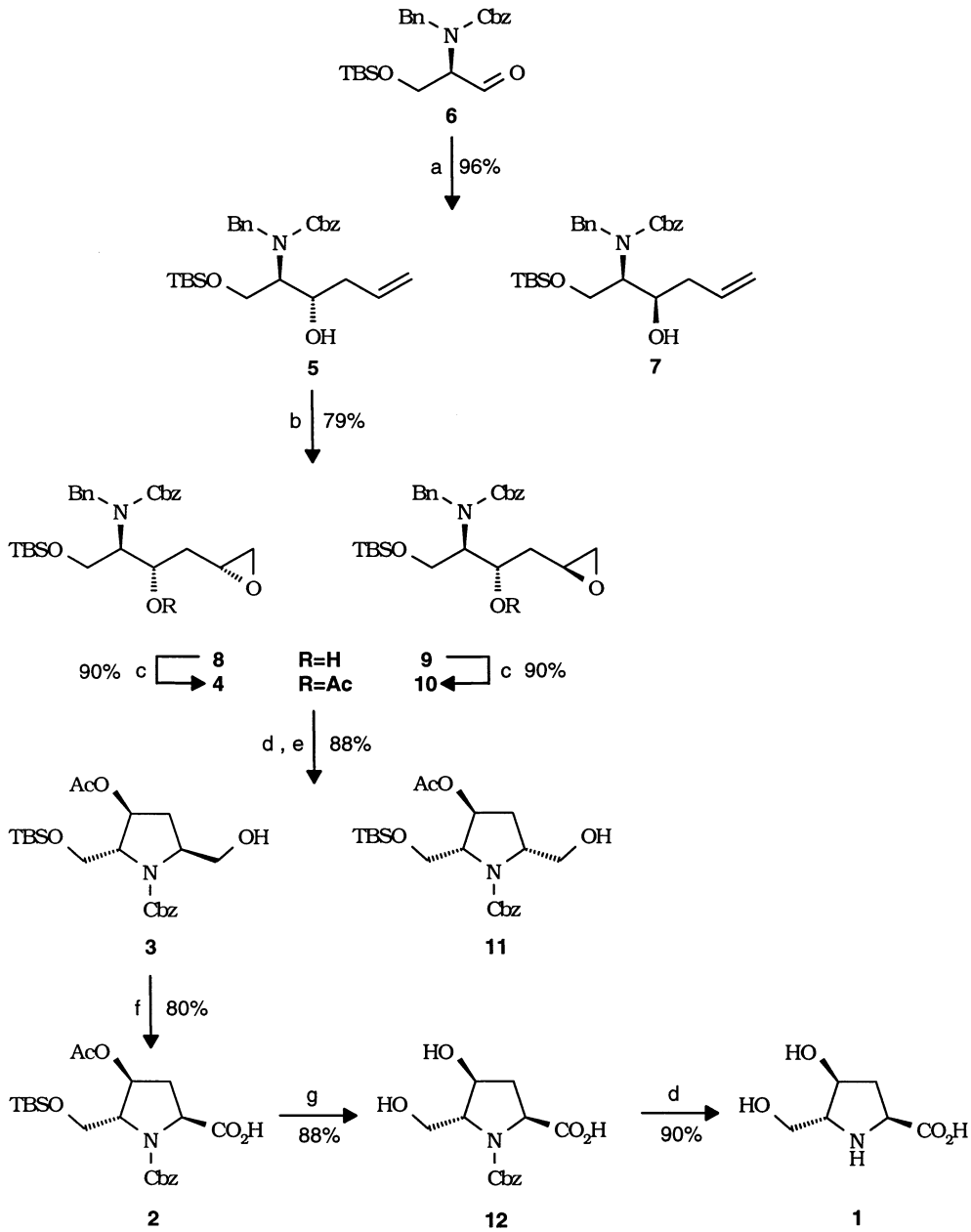
biological activity, they are synergists with some β-lactam antibiotics found in the above-mentioned culture broths. These properties make (–)-bulgecinine an attractive synthetic target.[9]

Retrosynthetic analysis, shown in Scheme 1, suggested that suitably protected D-serinal could serve as a starting material. On the basis of our earlier investigations we assumed the use of an *N*,*N*-diprotected derivative of D-serine.[5,10] Among several possible candidates we selected *N*-benzyl-*N*-carbobenzyloxy-*O*-*tert*-butyldimethylsilyl-D-serinal (**6**).[11]

Allyl addition to aldehyde **6**, carried out under Barbier conditions at room temperature, afforded diastereoselectively (5:7–82:18) the *anti*-adduct **5** in 96% yield (Scheme 2). Olefin **5**, obtained in pure form via column chromatography, was subjected to the vanadium-catalysed epoxidation reaction,[13] furnishing in 79% yield a chromatographically inseparable mixture of diastereoisomeric epoxides **8** (of *syn* relation between hydroxy and epoxy groups) and **9** (*anti*) in a ratio of 76:24. Protection of the secondary hydroxy group, with acetic anhydride in pyridine, afforded a still inseparable mixture of epoxides **4** and **10** in 90% overall yield. Hydrogenation of this mixture, on palladium-on-charcoal as a catalyst, caused deprotection of the amino group and subsequent cyclisation to afford a mixture of diastereoisomeric pyrrolidines, which after treatment with benzyl chloroformate (protection of the secondary amino group) was subjected to chromatographic separation giving two pure diastereoisomers **3**[14] and **11**[15] in



Scheme 2. Reagents and conditions: (a) AllBr, Zn, satd aq. NH_4Cl, THF, rt; (b) t-C_4H_9OOH, $VO(acac)_2$ cat., CH_2Cl_2, rt; (c) Ac_2O, Py, DMAP cat., rt; (d) H_2, 5% Pd/C, CH_3OH, rt; (e) $ClCO_2CH_2Ph$, CH_2Cl_2, satd aq. $NaHCO_3$, rt; (f) $NaIO_4$, $RuCl_3$ cat., CH_3CN–CCl_4–H_2O 2:2:3, 0°C; (g) 3 M aq. HCl, THF, reflux.

the same ratio as their precursors **8** and **9** (Scheme 2). The major diastereoisomer **3**, isolated in 65% yield (calculated from the mixture of epoxides **8** and **9**), was subjected to ruthenium-catalysed oxidation[16] furnishing protected (−)-bulgecinine (**2**) in 80% yield. Deprotection of both hydroxy groups by heating in a mixture of 3 M aqueous HCl with THF (2:3), followed by Pd/C hydrogenation of the benzyl carbamate, completed the synthesis of (2*S*,4*S*,5*R*)-(−)-bulgecinine (**1**) in 24% overall yield (calculated from **6**) with the correct stereochemistry. All analytical data, including $[\alpha]_D$ −13.5 (*c* 0.95, H_2O), are in agreement with those previously reported[8,9] (lit. $[\alpha]_D$ −13.1 (*c* 0.95, H_2O)).[8b]

It is noteworthy that **5** undergoes the $Al(Ot\text{-}C_4H_9)_3/t\text{-}C_4H_9OOH$ epoxidation with *anti*-selectivity (81:19), leading to compound **9** as the major diastereoisomer. This possibility provides selective access to diastereoisomer **11** and, as a consequence, to 2-*epi*-bulgecinine.

Acknowledgements

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11. The D-serine derivative **6** was obtained in 70% overall yield via the following route: D-serine methyl ester hydrochloride was treated with 1 equiv. of benzaldehyde and 1 equiv. of triethylamine in methanol, followed by in situ imine reduction with $NaBH_4$, giving *N*-benzyl-D-serine methyl ester. Its reaction with benzyl chloroformate afforded *N*-Bn-*N*-Cbz-D-serine methyl ester, then the hydroxy group was protected with TBSCl in DMF, followed by reduction of the ester moiety with $LiBH_4$ to give *N*-Bn-*N*-Cbz-*O*-TBS-D-serinol. Finally, oxidation of this amino alcohol using the TEMPO procedure[12] afforded the desired aldehyde **6**.
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14. Selected data: mp 64–66°C (AcOEt/hexane); $[\alpha]_D$ −38.6 (*c* 1.0, $CHCl_3$); ESIMS HR calcd for $(M+Na)^+$ ($C_{22}H_{35}NO_6NaSi$) 460.2126, found 460.2106; ^1H NMR (500 MHz, DMSO-d_6): 7.37–7.27 (m, 5H), 5.12 (d, J= 12.3 Hz, 0.5H), 5.11–5.01 (m, 2H), 4.96 (d, J=12.3 Hz, 0.5H), 4.73 (dt, $J_1=J_2=6.0$ Hz, $J_3=12.0$ Hz, 1H), 3.89–3.84 (m, 0.5H), 3.83–3.69 (m, 2.5H), 3.68–3.62 (m, 0.5H), 3.58–3.53 (m, 0.5H), 3.22–3.13 (m, 1H), 2.28–2.20 (m, 1H), 2.11–2.00 (m, 1H), 1.98 (s, 3H), 0.81 (s, 4.5H), 0.78 (s, 4.5H), −0.01 to −0.13 (m, 6H); ^{13}C NMR (125 MHz, DMSO-d_6): 170.23, 170.18, 153.94, 153.93, 137.18, 136.86, 128.88, 128.85, 128.54, 128.49, 128.32, 128.14, 77.03, 76.36, 66.69, 66.47, 66.31, 65.64, 62.39, 62.06, 61.57, 60.62, 60.12, 59.47, 32.60, 31.72, 26.09, 26.06, 21.46, 18.21, 18.17, −5.17, −5.28, −5.30.
15. Selected data: $[\alpha]_D$ −9.32 (*c* 1.0, $CHCl_3$); ESIMS HR calcd for $(M+Na)^+$ ($C_{22}H_{35}NO_6NaSi$) 460.2126, found 460.2157; ^1H NMR (500 MHz, DMSO-d_6): 7.37–7.27 (m, 5H), 5.16–4.99 (m, 3H), 4.71 (t, J=4.6 Hz, 1H), 3.90–3.76 (m, 2H), 3.68–3.60 (m, 1H), 3.54–3.38 (m, 3H), 2.29–2.13 (m, 1H), 1.99–1.93 (m, 1H), 1.97 (s, 3H), 0.86–0.77 (m, 9H), 0.04 to −0.10 (m, 6H); ^{13}C NMR (125 MHz, DMSO-d_6): 169.63, 154.41, 154.22, 136.60, 128.33, 127.80, 127.46, 74.34, 73.76, 66.11, 65.49, 65.17, 62.06, 61.72, 61.50, 60.88, 58.57, 57.90, 33.01, 32.04, 25.63, 20.83, 17.80, −5.63.
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