Highly Diastereoselective Construction of Substituted Pyrrolidines: Formal Synthesis of (–)-Bulgecinine[1]

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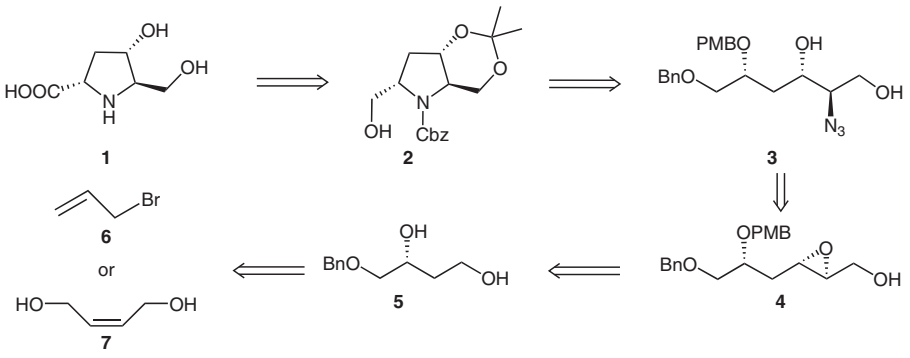
Abstract: A highly diastereoselective synthesis of substituted pyrrolidines has been achieved starting from nonchiral molecule, allyl bromide, or *cis*-but-2-ene-1,4-diol. The method involves the asymmetric epoxidation and *endo*-mode epoxide opening with azide nucleophile as the key steps. The method has been applied for the formal synthesis of (–)-bulgecinine.

Key words: substituted pyrrolidine, (–)-bulgecinine, diastereoselective synthesis, asymmetric epoxidation, *endo*-mode epoxide opening

Substituted pyrrolidines are important bioactive natural products. Many of these compounds are known to possess various impressive biological properties including antifungal, antibacterial, and hypotensive activities.[2] (–)-Bulgecinine (**1**), a tetrasubstitued pyrrolidine, is a core constituent of the glycosides, bulgecinine A, B, and C derived from *Pseudomonas* sp.[3] These glycosides exhibit interesting synergistic antibacterial activity. In continuation of our work[4] on the stereoselective synthesis of natural products we report here a highly diastereoselective construction of substituted pyrrolidines and the application of the method for the formal synthesis of (–)-bulgecinine (**1**). Previously, some methods have been reported[5] for the synthesis of **1**. However, the present method constitutes a novel approach for the synthesis of this pyrrolidine derivative.

The retrosynthetic analysis (Scheme 1) revealed that the compound **1** can be prepared from the intermediate **2**[5e] which can be obtained from the azide **3** generated from the epoxide **4**. This epoxide **4** in turn can be synthesized from the alcohol **5** prepared from allyl bromide (**6**) or *cis*-but-2-ene-1,4-diol (**7**). Thus this synthetic approach constitutes the preparation of (–)-bulgecinine (**1**) starting from nonchiral molecules. Allyl bromide (**6**) or *cis*-but-2-ene-1,4 diol (**7**) was initially converted into the allyl alcohol **8** following the reported methods.[6] This allyl alcohol **8** was subjected to Sharpless asymmetric epoxidation[7] to produce the epoxide **9** (Scheme 2). The regioselective reduction of the epoxide **9** with Red-Al[8] afforded the alcohol **5**. The primary hydroxy group of **5** was protected as TBS ether and the secondary hydroxy group as PMB ether to form the product **10**. The TBS ether group of the latter was again deprotected to generate the primary alcohol **11**. This alcohol was subsequently converted into an aldehyde under Swern oxidation conditions, and the resulting aldehyde was subjected to two-carbon homologation using ethoxy carboxymethylene triphenylphosphorane in CH_2Cl_2 to furnish the (*E*)-α,β-unsaturated ester **12** in high yield. The ester group of **12** was reduced with DIBAL-H to generate the allylic alcohol **13** which underwent asymmetric epoxidation to give the epoxide **4**. This epoxide was then purified, and the pure compound was subjected to a highly efficient C-2 selective azide substitution reaction using NaN_3-$(MeO)_3B$ system[9] to form the diol **3**. The reaction proceeded via an intramolecular boron chelate through a novel *endo*-mode epoxide opening.[9] The minor 1,2-diol that resulted from C-3 opening was removed by treatment of the reaction mixture with $NaIO_4$ followed by purification over chromatography. The 1,3-diol group of **3** was protected as acetonide, and the PMB ether group



Scheme 1

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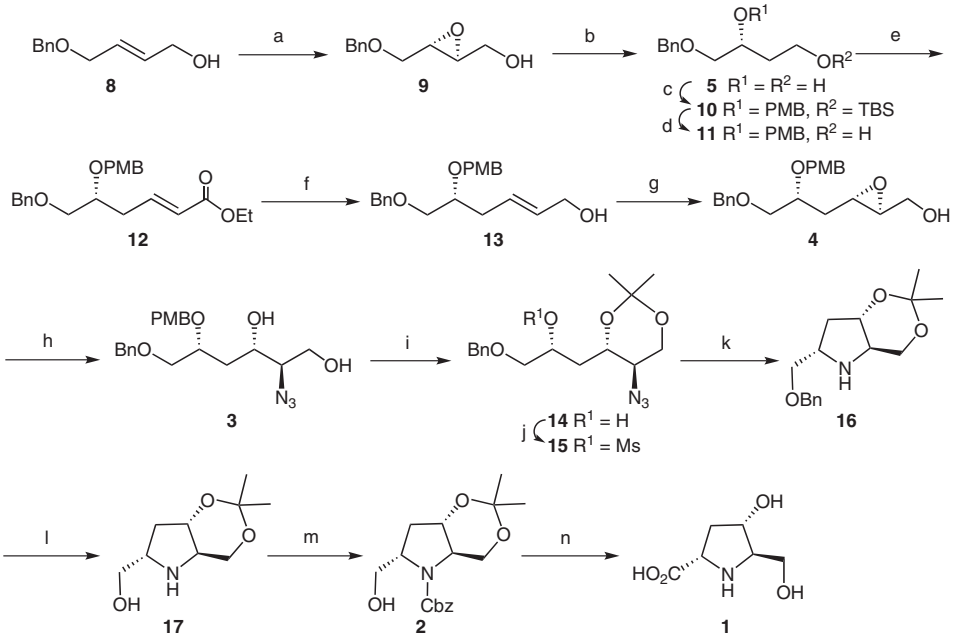

Scheme 2 *Reagents and conditions*: (a) Ti(*i*-OPr)$_4$ (0.2 equiv), (+)-DIPT (0.3 equiv), TBHP (2.5 equiv), CH_2Cl_2, –20 °C, 12 h, 82%; (b) Red Al, THF, 0 °C to r.t., 12 h, 98%; (c) 1. TBSCl, imidazole, r.t., 12 h, 94%; 2. PMBBr, NaH, THF, 0 °C to r.t., 3.5 h, 93%; (d) PTSA, MeOH, r.t., 94%; (e) 1. IBX, DMSO, CH_2Cl_2, 0 °C to r.t., 3 h; 2. $PPh_3CHCOOEt$, CH_2Cl_2, r.t., 2 h, 86% (in two steps); (f) DIBAL-H, CH_2Cl_2, –78 °C to –10 °C, 0.5 h, 84%; (g) Ti(*i*-OPr)$_4$ (0.2 equiv), (+)-DIPT (0.3 equiv), TBHP (2.5 equiv), CH_2Cl_2, –20 °C, 20 h, 80%; (h) NaN_3, $(MeO)_3B$, DMF, 90 °C, 3.5 h, 85%; (i) 1. 2,2 DMP, PTSA, CH_2Cl_2, r.t., 4 h, 71%; 2. DDQ, CH_2Cl_2–H_2O, r.t., 5 h, 90%; (j) $MeSO_2Cl$, *i*-Pr_2NH, 0 °C to r.t., 4.5 h; (k) indium powder, NH_4Cl, Et_3N, MeOH, reflux, 6 h, 89% (in the last two steps); (l) Pd/C, MeOH, r.t., 5 h, 86%; (m) CbzCl, EtOAc, $NaHCO_3$, 0 °C, 1 h, 78%; (n) ref. 5e.

was deprotected with DDQ in CH_2Cl_2–H_2O to give the azido alcohol **14**. The hydroxy functionality of **14** was converted into its mesylate using methanesulfonyl chloride and diisopropylamine to afford **15**. The mesylate compound **15** was directly treated with indium powder and NH_4Cl in MeOH to produce the substituted pyrrolidine **16**. The latter was hydrogenated using catalytic amount of Pd/C in MeOH to generate the amino alcohol **17** which was subsequently reacted with benzyl chloroformate and saturated $NaHCO_3$ in EtOAc to afford the *N*-Cbz protected alcohol **2** in good yield. Compound **2** could be converted into (–)-bulgecinine (**1**) following the method reported earlier.[5e] The structures of all the products of the present synthesis were confirmed from their spectral (IR, ^{1}H NMR, ^{13}C NMR, and MS) and analytical data.[10]

In conclusion, we have developed a highly diastereoselective synthesis of substituted pyrrolidines starting from nonchiral molecules involving asymmetric epoxidation and *endo*-mode epoxide opening with azide nucleophile as the key steps. We have also demonstrated the application of this method for the synthesis of (–)-bulgecinine. The major steps of this synthesis included simple protection–deprotection strategies.

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(10) **Spectral and Analytical Data of Selected Compounds**

(3-{3-(Benzyloxy)-2-[(4-methoxybenzyl)oxy]propyl}-oxiran-2-yl)methanol (4)

$[\alpha]_D^{25}$ –16.8 (*c* 0.9, $CHCl_3$). IR (KBr): ν_{max} = 3449, 1455, 1375, 1248 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.16 (7 H, m), 6.81 (2 H, d, *J* = 8.0 Hz), 4.65–4.43 (4 H, m), 3.79 (3 H, s), 3.74–3.63 (2 H, m), 3.62–3.42 (3 H, m), 2.99 (1 H, m), 2.82 (1 H, m), 1.92–1.73 (2 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.3, 139.2, 13 2.3, 129.3, 128.8, 128.0, 121.9, 116.0, 73.2, 71.4, 70.7, 70.5, 70.3, 61.2, 56.3, 49.3, 30.7. ESI-MS: *m/z* = 358 $[M]^+$. Anal. Calcd (%) for $C_{21}H_{26}O_5$: C, 70.39; H, 7.26. Found: C, 70.41; H, 7.21.

2-Azido-6-(benzyloxy)-5-(4-methoxybenzyloxy)hexane-1,3-diol (3)

IR (KBr): ν_{max} = 3390, 2103 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.38–7.16 (7 H, m), 6.81 (2 H, d, *J* = 8.0 Hz), 4.65–4.44 (4 H, m), 4.07 (1 H, m), 3.85 (1 H, m), 3.78 (3 H, s), 3.56–3.47 (4 H, m), 2.09 (1 H, m), 1.99–1.78 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 137.8, 129.5, 128.5, 127.7, 126.7, 116.0, 73.2, 72.8, 70.1, 66.1, 65.5, 62.6, 55.9, 29.8. ESI-MS: *m/z* = 401 $[M]^+$. Anal. Calcd (%) for $C_{21}H_{27}N_3O_5$: C, 62.84; H, 6.73. Found: C, 62.80; H, 6.75.

(4a*R*,6*S*,7a*S*)-6-(Benzyloxymethyl)-2,2-dimethyl-hexahydro[1,3]dioxino[5,4-*b*]pyrrole (16)

$[\alpha]_D^{25}$ +31.3 (*c* 1.7, $CHCl_3$). IR (KBr): ν_{max} = 3385, 1600, 1490, 1279 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.20 (5 H, m), 4.53 (2 H, s), 4.22 (1 H, m), 4.08 (1 H, m), 3.47 (1 H, m), 3.33 (1 H, m), 2.93–2.74 (3 H, m), 2.30 (1 H, m), 1.97–1.71 (2 H, m), 1.48 (6 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.8, 129.3, 128.5, 127.8, 100.9, 81.8, 72.6, 72.2, 70.0, 54.0, 36.7, 27.7. ESI-MS: *m/z* = 277 $[M]^+$. Anal. Calcd (%) for $C_{16}H_{23}NO_3$: C, 69.31; H, 8.30. Found: C, 69.33; H, 8.27.

(4a*R*,6*S*,7a*S*)-Benzyl 6-Hydroxymethyl)-2,2-dimethyl-tetrahydro[1,3]dioxino[5,4-*b*]pyrrole-5(6*H*)-carboxylate (2)

$[\alpha]_D^{25}$ –55.4 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.13 (5 H, m), 5.05 (2 H, s), 4.40 (1 H, m), 4.24–4.00 (2 H, m), 3.96–3.65 (4 H, m), 3.07 (1 H, m), 2.63 (1 H, br s), 2.25 (1 H, m), 1.47 (6 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.8, 135.5, 129.0, 128.7, 128.5, 127.8, 100.1, 72.0, 68.5, 67.0, 66.2, 61.1, 58.6, 31.4, 29.5, 19.8. ESI-MS: *m/z* = 321 $[M]^+$. Anal. Calcd (%) for $C_{17}H_{23}NO_5$: C, 63.55; H, 7.17. Found: C, 63.51; H, 7.12.