A New Route to Chiral Pyrrolidines *via* Radical Cyclisation; Enantioselective Synthesis of (+)-Bulgecinine

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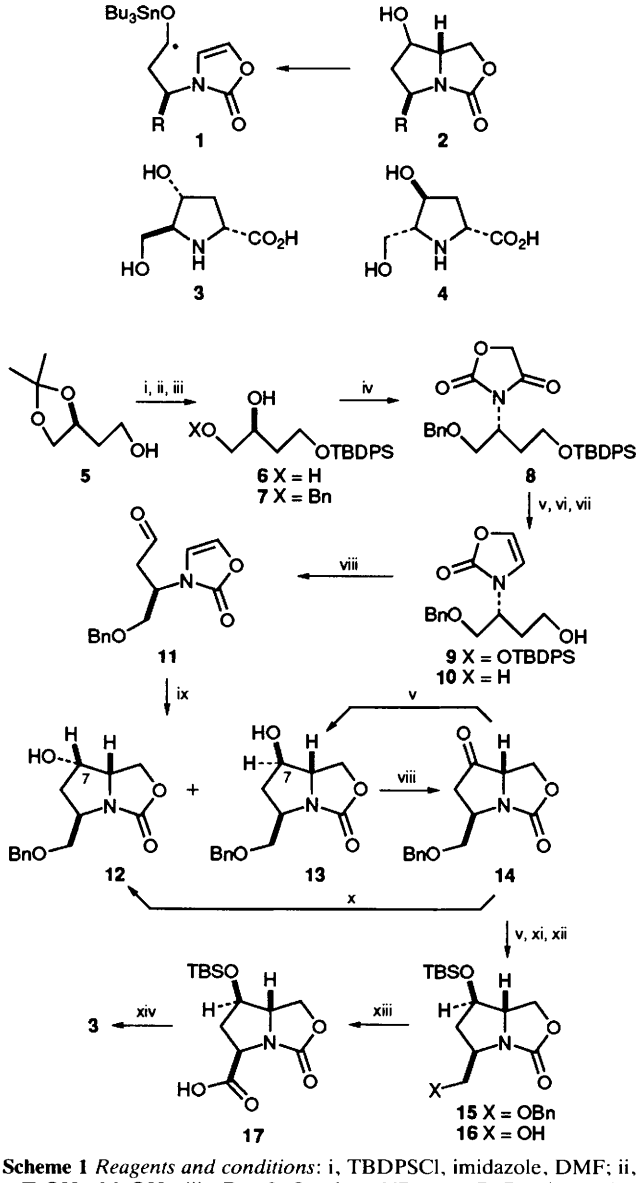
Reaction of the aldehyde **11** with tributyltin hydride in the presence of AIBN gave a mixture of **12** and **13**, which successfully led to (+)-bulgecinine **3**.

Cyclisation of *O*-stannyl ketyl, generated by treatment of aldehydes or ketones with tributyltin hydride, with alkenes has opened up a new synthetic methodology for synthesis of cycloalkanols.[1,2] We examined the cyclisation of the *O*-stannyl ketyl **1** by using $\Delta^{4,5}$-oxazolidinone as the radical acceptor to yield pyrrolooxazolidines **2**, which would be the effective synthon for 5-substituted 3-hydroxy-2-hydroxymethylpyrrolidines. The method was applied to a synthesis of (+)-bulgecinine **3**,[3] the enantiomer of natural (−)-bulgecinine **4**[4], a constituent amino acid of the glycopeptide bulgecins found in cultures of *Pseudomanas acidphila* and *Pseudomonas mesoacidphila*. Our synthetic procedure is given below (Scheme 1).



Scheme 1 *Reagents and conditions*: i, TBDPSCl, imidazole, DMF; ii, *p*-TsOH, MeOH; iii, Bu^n_2SnO, then NBu_4Br, BnBr; iv, PPh_3, $(Pr^iOCON{=})_2$, oxazolidine-2,4-dione; v, $NaBH_4$, MeOH; vi, MesCl, NEt_3, CH_2Cl_2; vii, NBu_4F, THF; viii, $(COCl)_2$, DMSO, NEt_3; ix, $SnHBu_3$, AIBN, benzene; x, K-Selectride; xi, TBSCl, imidazole, DMF; xii, 10% Pd–C, MeOH; xiii, $RuCl_3{\cdot}3H_2O$–$NaIO_4$; xiv, 10% NaOH–EtOH (TBDPS = *tert*-butyldiphenylsilyl, Mes = methanesulfonyl, TBS = *tert*-butyldimethylsilyl)

O-Silylation of the 1,2,4-triol acetonide **5**,[5] derived from (*S*)-malic acid, with TBDPSCl and imidazole, followed by ring cleavage of the acetonide with *p*-TsOH in methanol afforded the diol **6**. Selective benzylation of **6** at the primary hydroxy group was successfully achieved by treatment with Bu^n_2SnO[6] and successively with benzyl bromide in the presence of tetrabutylammonium bromide to give **7** in nearly quantitative yield. Condensation of **7** with oxazolidine-2,4-dione by Mitsunobu reaction provided **8**. Reduction of **8** with $NaBH_4$ followed by treatment with methanesulfonyl chloride in the presence of triethylamine gave **9** through spontaneous elimination of methanesulfonic acid. Desilylation of **9** with tetraethylammonium fluoride, followed by Swern oxidation of the resulting alcohol **10** safely afforded the aldehyde **11**, $[\alpha]_D$ +12.1 (*c* 1.3, $CHCl_3$), precursor for the formation of *O*-stannyl ketyl. Treatment of **11** with tributyltin hydride in the presence of AIBN (benzene reflux) afforded a diastereoisomeric mixture of **12**† and **13**‡ (1 : 1) in 86% yield (without diastereoselectivity at the C^7-position), which were separated by column chromatography. A particularly noteworthy feature was that the radical cyclisation proceeded with complete facial selectivity, and high *trans*-selectivity was observed regarding the relative configuration at the C^5 and C^{7a}-positions. The mixture of **12** and **13** was converted to the ketone **14**, $[\alpha]_D$ −84.6 (*c* 0.9, $CHCl_3$), by Swern oxidation. Stereospecific reduction of **14** was achieved by using $NaBH_4$ to give the 7β-ol (**13**), $[\alpha]_D$ +21.3 (*c* 1.1, $CHCl_3$), in 88% yield without formation of **12**. Both of the relative configurations of C^{7a}-H/C^7-H and C^{7a}-H/C^5-H in **13** were assigned to be *trans* by the study of ^{2}D NMR (NOESY) of **15**. On the other hand, reduction of **14** with K-selectride gave the 7α-ol (**12**) in 89% yield, $[\alpha]_D$ +6.5 (*c* 0.7, MeOH). Protection of hydroxyl group of **13** with TBS, followed by debenzylation of the *O*-silylation product **15**, $[\alpha]_D$ −8.4 (*c* 1.2, $CHCl_3$), by catalytic hydrogenolysis with 10% Pd–C in MeOH gave the alcohol **16** in 93% yield, mp 84–86 °C, $[\alpha]_D$ −30.6 (*c* 0.7, $CHCl_3$). Oxidation of **16** with $RuCl_3$–$NaIO_4$ afforded the carboxylic acid **17** in 92% yield, mp 61–63 °C, $[\alpha]_D$ −4.1 (*c* 1.2, $CHCl_3$). The oxazolidinone ring was subsequently cleaved with 10% NaOH–EtOH (reflux). The reaction mixture was, after washing with benzene, purified by ion exchange chromatography (Dowex 50, H^+ form) to afford (+)-bulgecinine in 75% yield, $[\alpha]_D$ +16.7 (*c* 0.42, H_2O), [lit.,[4b] $[\alpha]_D$ −15.6 (*c* 0.53, H_2O)], mp 187–192 °C, (lit.,[4b] mp 188–192 °C), the spectral data (MS, ^{1}H NMR) of which supported the product to be enantiomer of natural (−)-bulgecinine.

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Footnotes

† Compound **12**: ^{1}H NMR (400 MHz, *J* in Hz), δ 2.15–2.20 (m, 2H), 3.59 (dd, 1H, *J* = 4.0, 9.7), 3.65 (dd, 1H, *J* = 4.5, 9.7), 3.94 (dt, 1H, *J* = 3.5, 11.2), 4.18–4.22 (m, 1H), 4.24–4.28 (m, 1H), 4.43 (dd, 1H, *J* = 8.4, 8.9), 4.51 (dd, 1H, *J* = 3.4, 8.9), 4.54 (d, 1H, *J* = 11.6), 4.62 (d, 1H, *J* = 11.6), 7.25–7.39 (m, 5H).

‡ Compound **13**: ^{1}H NMR (400 MHz), δ 1.87 (dt, 1H, *J* = 4.7, 13.6), 2.39 (dt, 1H, *J* = 8.2, 13.6), 3.61 (dd, 1H, *J* = 3.3, 9.7), 3.72 (dd 1H,

J = 3.3, 9.7), 3.88 (dt, 1H, J = 4.7, 8.4), 4.03–4.11 (m, 1H), 4.12–4.16 (m, 1H), 4.21 (dd, 1H, J = 4.5, 9.1), 4.58 (dd, 1H, J = 8.8, 9.1), 4.56 (d, 1H, J = 11.6), 4.65 (d, 1H, J = 11.6), 7.29–7.34 (m, 5H).

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