A New Synthesis of Alkaloid (*S*)-3-Hydroxypiperidin-2-one and Its *O*-TBS Protected Derivative

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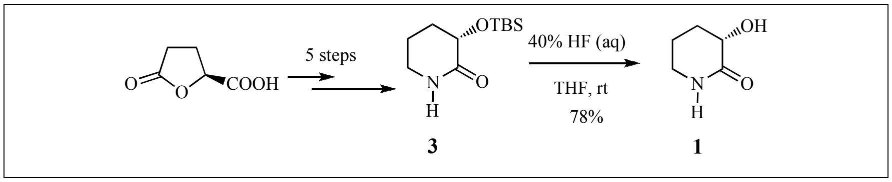

From the known lactone (*S*)-**4,** easily derived from L-glutamic acid, a scalable approach to chiral building block *O*-silylated 3-hydroxypiperidin-2-one **3** and alkaloid **1** was achieved in five and six-steps respectively. The key steps are a chemoselective amidation of lactone-ester **5** and a one-pot reductive borane-decomplexation, *N*-debenzylation and cyclization.

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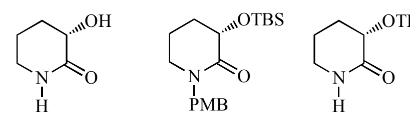
(*S*)-3-Hydroxypiperidin-2-one (**1**) is an alkaloid recently isolated from two coccinellid beetles *Harmonia axyridis* and *Aiolocaria hexaspilota* [1]. Before its isolation from natural sources, several syntheses of enantio-enriched **1** and its derivatives have been reported [2]. Recently, we have reported an approach to *N*,*O*-diprotected (*S*)-3-hydroxypiperidin-2-one **2** starting from (*S*)-glutamic acid [3]. In a project aimed at the development of a synthetic methodology for bioactive piperidines [4], we needed a scalable approach to *N*-unprotected *O*-protected 3-hydroxypiperidin-2-one **3**. In view of the modest yield for the oxidative cleavage of PMB group from **2**, we needed to develop an alternative approach and now report a scalable and shorter synthesis of **3** and (*S*)-3-hydroxypiperidin-2-one (**1**).

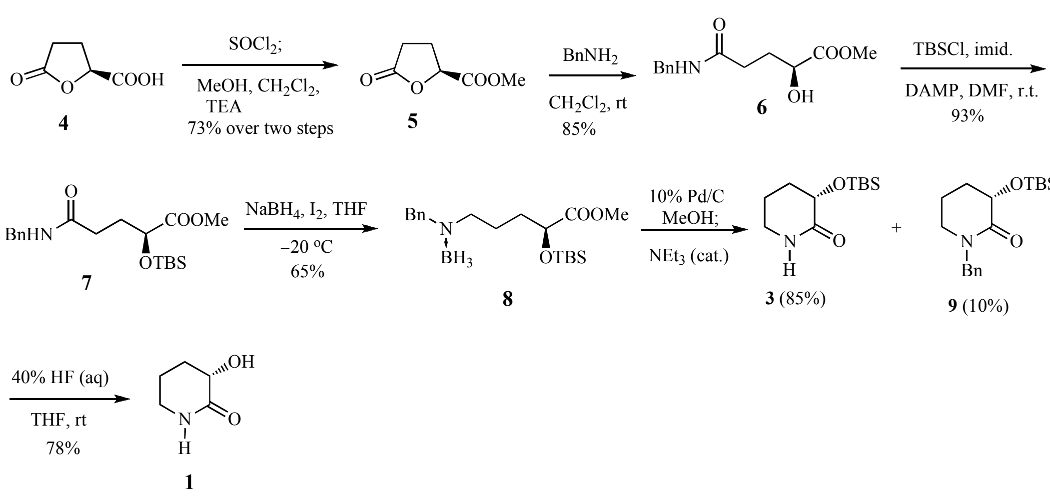
The synthesis started from the known lactone (*S*)-**4**, easily available from (*S*)-glutamic acid *via* a one-pot transformation [5]. Esterification by treating **4** with DCC



1 **2** **3**

in methanol gave the desired lactone-ester **5** in only moderate yields (50%-60%), which was improved to 73% *via* the classical two-step procedure ($SOCl_2$; MeOH, CH_2Cl_2, NEt_3, −20 °C). Selective lactone aminolysis of **5** was achieved by treating with benzylamine at rt for 48 hours, which gave **6** in 85% yield. The hydroxyl group in **6** was then protected (TBSCl, imid., DMAP, DMF, rt, 3 h) to give **7** in 93% yield. Chemoselective reduction of the amide group with borane dimethyl sulfide complex (BH_3•SMe_2) at −20 °C gave the reduced product as an *N*-borane complex **8** in about 65% yield. A more economical variation constituted in using $NaBH_4/I_2$ as a source of diborane [6], which afforded **8** in 65% yield. Attempt to

Scheme 1



cleave the benzyl group under catalytic transfer hydrogenation conditions (HCOOH, MeOH, 10% Pd/C) was unsuccessful. To our delight, using the method reported recently by Couturier *et al.* [7] (10% Pd/C, MeOH, rt, 4 days; then NEt_3 (cat., 12 h) provided, in one-pot, 3-silyloxypiperidin-2-one **3** in 85% yield, alongside with about 10% of *N*-benzyl piperidine-2-one **9**. In this reaction, a catalytic amount of NEt_3 was used to enhance the *in situ* cyclization. To synthesize **1**, **3** was treated with an aqueous solution of 40% HF, which afforded the alkaloid **1** in 78% yield. The synthetic **1** showed identical physical and spectral data with those reported.

In summary, a scalable approach to *O*-silylated 3-hydroxypiperidin-2-one **3** and alkaloid **1** was achieved in five and six-steps respectively from **4**. The use of **3** as a chiral building block in the asymmetric synthesis of 2-substituted piperidin-3-ols is in progress in these laboratories and will be reported in due course.

EXPERIMENTAL

Melting points were determined on a Yanaco MP-500 micromelting point apparatus and are uncorrected. Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer using film KBr pellet technique. ^1H nmr spectra were recorded in $CDCl_3$ on a Bruker Avance DPX 400 MHz or a Varian unity +500 NMR spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded by a Bruker Dalton Esquire 3000 plus liquid chromatography–mass spectrum (direct injection). Optical rotations were measured with a Perkin–Elmer 341 automatic polarimeter. Flash column chromatography was carried out with silica gel (300–400 mesh). THF was distilled over sodium. Dichloromethane was distilled over P_2O_5.

Methyl (*S*)-5-oxo-tetrahydrofuran-2-carboxylate (5). Thionyl chloride (21.9 mL, 35.7 g, 300 mmol) was added to **4** (13.9 g, 107 mmol) at room temperature. The mixture was refluxed for 4 hours followed by stirred at room temperature for 12 hours. The excess $SOCl_2$ was removed under reduced pressure. The residue was resolved in CH_2Cl_2 (140 mL). To the resulting mixture was added dropwise, at –20 °C, a mixture of MeOH (4.0 mL, 100 mmol) and Et_3N (16.6 mL, 120 mmol). The reaction mixture was warmed to room temperature and stirred for 12 hours. The reaction was quenched with water (80 mL). The resulting mixture was extracted with CH_2Cl_2 (6×30mL). The organic phases were washed with brine (30 mL×2), dried over anhydrous Na_2SO_4 and filtered. After concentrated in vacuum, the residue was purified by flash chromatography (EtOAc/PE 1/2) to afford **5** (11.3 g, 73% overall yield from **4**) as a colorless oil. $[\alpha]^{20}_D$ = 14.5 (*c* 1.1, MeOH) [lit.: for (*S*)-**5**: $[\alpha]^{20}_D$ = 14.9 (*c* 1.1, MeOH) [8a], $[\alpha]^{25}_D$ = 15.8 (*c* 0.65, MeOH) [8b]; ir: 2959, 1786, 1744, 1632, 1440, 1375, 1329, 1225, 1175, 1107, 1069 cm^{-1}; ^1H nmr: δ 2.19-2.27 (m, 1H, H-3), 2.41-2.56 (m, 3H, H-3, H-4), 3.72 (s, 3H, OCH_3), 4.68 (dd, *J* = 4.5, 8.0 Hz, 1H, H-2) ppm; ^{13}C nmr: δ 25.3, 26.3, 52.2, 75.3, 170.0, 175.8 ppm; ms: *m/z* 167.2 (M+Na$^+$), 162 (M$^+$+H_2O).

Methyl (*S*)-5-(benzylamino)-2-hydroxy-5-oxopentanoate (6). To a solution of **5** (8.58 g, 59.6 mmol) in 60 mL CH_2Cl_2 was added $BnNH_2$ (6.39 g, 59.6 mmol). The mixture was stirred at room temperature for 48 hours, then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (EtOAc/PE 2:1) to afford **6** (12.7 g , 85%) as white crystals. mp 52-54 ° C (EtOAc/PE 1:1); $[\alpha]^{20}_D$ = –4.6 (*c* 1.0, $CHCl_3$); ir: 3405, 3032, 2953, 1739, 1642, 1548, 1454, 1217, 1110, 1030 cm^{-1}; ^1H nmr: δ 1.90 (m, 1H, H-3), 2.11-2.176 (m, 1H, H-3), 2.25-2.36 (m, 2H, H-4), 3.53 (br s, 1H, OH), 3.69 (s, 3H, OCH_3), 4.17 (dd, J = 3.5, 7.5 Hz, 1H, H-2), 4.33 (d, J = 13.2 Hz, 1H, Ph-CH_2), 4.34 (d, J = 13.2 Hz, 1H, Ph-CH_2), 5.98 (br s, 1H, NH), 7.18-7.26 (m, 5H, Ph-H) ppm; ^{13}C nmr: δ 29.7, 32.0, 43.7, 52.5, 69.9, 127.5, 127.8, 128.7, 138.1, 172.2, 175.0 ppm; ms: *m/z* 274 (M+Na$^+$), 252 (M+H$^+$). *Anal.* Calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.43; H, 6.92; N, 5.39.

Methyl (*S*)-5-(benzylamino)-2-(*tert*-butyldimethylsilyloxy)-5-oxopentanoate (7). Under a nitrogen atmosphere, a mixture of **6** (4.23 g, 16.8 mmol), imidazole (2.87 g, 42.1 mmol), TBSCl (4.57 g, 30.3 mmol) and DMAP (100 mg) in DMF (40 mL) was stirred at room temperature for 3 hours. The reaction was quenched with water (160 mL). The aqueous layer was extracted with ether (5×30 mL). The combined organic phases were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. After concentrated in vacuum, the residue was purified by flash chromatography on silica gel (EtOAc/PE 1/5) to afford **7** (5.72 g, 93%) as a yellow oil. $[\alpha]^{20}_D$ = –17.8 (*c* 1.0, $CHCl_3$) ; ir: 3295, 3065, 2952, 2930, 2857, 1756, 1650, 1548, 1435, 1258, 1132 cm^{-1}; ^1H nmr: δ 0.03 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 1.98-2.05 (m, 1H, H-3), 2.09-2.16 (m, 1H, H-3), 2.27 (dd, J = 5.0, 15.0 Hz, 1H, H-4), 2.34 (dd, J = 8.5, 15.0 Hz, 1H, H-4), 3.69 (s, 3H, $COOCH_3$), 4.30 (dd, J = 5.0, 6.5 Hz, 1H, H-2), 4.37 (d, J = 15.0 Hz, 1H, $PhCH_2$), 4.41 (d, J = 15.0 Hz, 1H, $PhCH_2$), 6.12 (br s, 1H, NH), 7.24-7.32 (m, 5H, Ph-H) ppm; ^{13}C nmr: δ –5.3, –4.9, 18.2, 25.6, 25.8, 30.6, 31.5, 43.6, 51.7, 71.2, 127.4, 127.8, 128.6, 138.3, 171.9, 173.7 ppm; ms: *m/z* 366 (M+H$^+$), 388 (M+Na$^+$); *Anal.* Calcd. for $C_{19}H_{31}NO_4Si$: C, 62.43; H, 8.55; N, 3.83. Found: C, 62.36; H, 8.46; N, 3.70.

Methyl (*S*)-5-(benzylamino)-2-(*tert*-butyldi-methylsilyloxy) pentanoate borane complex (8). To a mixture of **7** (5.64 g, 15.4 mmol), $NaBH_4$ (1.05 g, 27.8 mmol) in anhydrous THF (75 mL) was added, under a nitrogen atmosphere and at –20 °C, a solution of I_2 (3.53 g, 13.9 mmol) in anhydrous THF (30 mL). The resulting mixture was stirred at room temperature for 8 hours. After dilution with ethyl acetate (75 mL) at –20 °C, the reaction was quenched with water (30 mL). The aqueous layer was extracted with ethyl acetate (3×30 mL); the combined organic phases were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. After concentrated in vacuum, the residue was purified by flash chromatography on silica gel (EtOAc/PE 1/15) to afford **8** (3.63 g, 65%) as a colorless oil, which is a mixture of two diastereoisomers in a ratio of 6: 4 as determined by ^1H nmr integration. Major diastereomer: $[\alpha]^{20}_D$ = –16.9 (*c* 1.0, $CHCl_3$); ir: 3202, 3031, 2953, 2930, 2856, 2374, 2320, 2274, 1755, 1738, 1456, 1252, 1168, 1139 cm^{-1}; ^1H nmr: δ 0.01 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.52-1.94 (m, 7H, BH_3, H-3, H-4), 2.60-2.67 (m, 2H, H-5), 3.52 (br s, 1H, NH), 3.65 (d, J = 13.5 Hz, 1H, $PhCH_2$), 3.69 (s, 3H, $COOCH_3$), 4.10-4.13 (m, 1H, H-2), 4.20 (d, J = 13.5, 1H, $PhCH_2$), 7.26-7.39 (m, 5H, Ph-H) ppm; ^1H nmr (minor diastereoisomer): δ 0.01 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.52-1.94 (m, 7H, BH_3, H-3, H-4), 2.67-2.76 (m, 2H, H-5), 3.45 (br s, 1H, NH), 3.62 (d, J = 13.5 Hz, 1H, $PhCH_2$), 3.68 (s, 3H, $COOCH_3$), 4.13-4.15 (m, 1H, H-2), 4.20 (d, J = 13.5, 1H, $PhCH_2$), 7.26-7.39 (m, 5H, Ph-H) ppm; ^{13}C nmr (mixture of two diastereoisomers): δ –5.6, –5.3, –4.9, 18.2, 21.9, 25.6, 25.8, 32.2, 51.7, 51.9, 52.0, 52.7, 52.9, 59.7, 71.5, 128.7, 129.0, 129.4, 134.1, 173.6 ppm; ms: *m/z* 383 (M^++H_2O); *Anal.* Calcd. for $C_{19}H_{36}BNO_3Si$: C, 62.45; H, 9.93; N, 3.83. Found: C, 62.22; H, 9.88; N, 3.79.

(*S*)-3-(*tert*-Butyldimethylsilyloxy) piperidin-2-one (3). To a mixture of **8** (2.95 g, 8.07 mmol) and 10% Pd/C (1.12 g) was added methanol (30 mL). The reaction vessel was quickly sealed and stirred at r.t. for 4 days. To the resulting mixture was added Et_3N (0.1 mL, 0.72 mmol) and stirred for 12 hours. The resulting mixture was filtered through Celite and washed with methanol. After concentrated in vacuum, the residue was purified by flash chromatography on silica gel (EtOAc/PE 1/5) to afford **3** (1.57 g, 85%), along sides with about 10% of *N*-benzyl piperidin-2-one **9** (317 mg, 10%). **3**: colorless oil. $[\alpha]^{20}_D$ = –36.6 (*c* 1.0, $CHCl_3$); ir: 3223, 3097, 2951, 2929, 2855, 1679, 1471, 1333, 1251, 1146, 1107, 1032 cm^{-1}; ^1H nmr: δ 0.14 (s, 3H, $SiCH_3$), 0.16 (s, 3H, $SiCH_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 1.70-1.76 (m, 1H, H-4), 1.80-1.88 (m, 1H, H-4), 1.94-2.02 (m, 2H, H-5), 3.21-3.25 (m, 1H, H-6), 3.27-3.32 (m, 1H, H-6), 4.07 (dd, J = 4.0, 7.5 Hz, 1H, H-3), 5.78 (br s, 1H, CONH) ppm; ^{13}C nmr: δ –5.5, –4.6, 18.2, 19.3, 25.8, 30.7, 42.0, 69.0, 172.5 ppm; ms: *m/z* 230 ($M+H^+$); *Anal.* Calcd. for $C_{11}H_{23}NO_2Si$: C, 57.59; H, 10.11; N, 6.11. Found: C, 57.87; H, 10.03; N, 5.88.

(*S*)-3-Hydroxypiperidin-2-one (1). To a solution of **3** (92 mg, 0.40 mmol) in acetonitrile (2 mL) was added a solution of 40% aqueous HF (0.13 mL). The mixture was stirred at r.t. for 6 hours. After cooled to 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL), diluted with water (3 mL) and extracted with ethyl acetate (6 × 5 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and filtered. After concentrated in vacuum, the residue was purified by flash chromatography on silica gel (EtOAc/MeOH 10/1) to afford **1** (36 mg, 78%) as white crystals. mp 144-146 °C (EtOAc); $[\alpha]^{20}_D$ = –11.2 (*c* 1.0, CH_3OH) lit. [2f]: for (*R*)-**1**: $[\alpha]^{20}_D$ = +6.0 (*c* 1.0, $CHCl_3$)]; ir: 3307, 3205, 2957, 2939, 2868, 1656, 1319, 1095 cm^{-1}; ^1H nmr: δ 1.69-1.78 (m, 1H, H-4), 1.82-1.92 (m, 1H, H-4), 1.93-2.02 (m, 1H, H-5), 2.27-2.33 (m, 1H, H-5), 3.29-3.39 (m, 2H, H-6), 3.66 (br s, 1H, OH), 4.05 (dd, J = 7.7, 13.8 Hz, 1H, H-3), 5.99 (br s, 1H, NH) ppm; ^{13}C nmr: δ 20.6, 28.4, 42.4, 67.7, 174.4 ppm; ms: *m/z* 116 ($M+H^+$), 138 ($M+Na^+$).

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