A Synthesis of Optically Active *cis* and *trans* 2-(5-Hydroxypiperidin-2-yl)acetates

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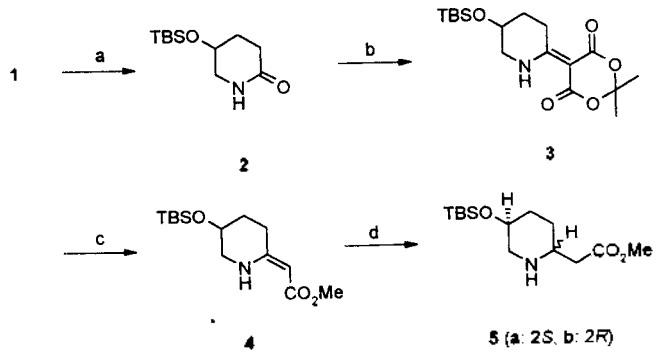
In dealing with stereochemical issues in the synthesis of antitumor agent DKP 593A, isolated from the soil microorganism *Steptomyces griseoluteus*,[1] the stereochemistry of 2,5-disubstituted piperidines should be controlled. Many of them are found as biologically active compounds in nature, such as streptolutin and pseudoconhydrine.[2]

2-(5-Hydroxypiperidin-2-yl)acetate would be a common intermediate in the preparation of hydroxyhomopipecollic acid and pseudoconhydrine.[3] In this paper, we would like to report a synthesis of *cis* and *trans* 2-[5-(*t*-butyldimethylsilyloxy)piperidin-2-yl]acetates from (*S*)-5-hydroxy-2-oxopiperidine (**1**) which was readily available from L-glutamic acid.[4]

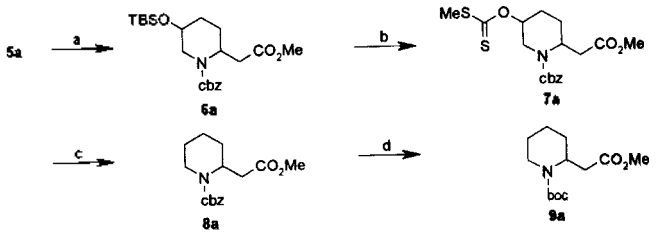
Hydroxy group of **1** was protected by *t*-butyldimethylsilyl group to give silyloxy lactam **2**. The lactam **2** was treated with trimethyloxonium tetrafluoroborate and the resulting imino methyl ether was condensed with Meldrum's acid to afford adduct **3**. The resulting adduct was reacted with NaOMe in MeOH at refluxing temperature to give conjugated ester **4**.[5] Herdeis and coworkers also prepared the corresponding ethyl ester of compound **4** from an intermediate in the preparation of (*S*)-5-hydroxy-2-oxopiperidine (**1**), while we are preparing this manuscript.[3c] In the preparation of **4**, yield and the number of steps are almost same in both methods.

Reduction of **4** gave a mixture of *cis* and *trans* ester **5** which was separated by columm chromatography (Scheme 1). The ratio of the *cis* to *trans* isomer was about 20 : 1 by hydrogenation on 10% Pd/C,[3c] and 4 : 6 by $NaBH_3CN$. Herdeis also prepared a derivative of **5** using different method from **1**, which gave the mixture of *trans* and *cis* isomers in a ratio of 3 : 1.[3a]

On the other hand, the adduct **3** was reacted with $NaBH_4$ and then the resulting mixture was treated with 6 N HCl at 110 °C to give a mixture of *cis* and *trans* 5-hydroxyhomopipecolic acids.[3b] The stereochemistry of the *cis* and *trans* isomers could be assingned by ^1H NMR, and indirectly confirmed by comparision with the optical rotation of a known compound.[8]



Scheme 1. [a] *t*-$BuMe_2SiCl$, imidazole. [b] i) Me_3OBF_4, ii) Meldrum's acid, Et_3N. [c] NaOMe, MeOH, △. [d] H_2, 10% Pd/C, 3 atm.



Scheme 2. [a] cbz-Cl, Et_3N. [b] i) 6 N HCl, ii) NaH, CS_2, MeI. [c] AIBN, $(nBu)_3SnH$, xylene, △. [d] $(Boc)_2O$, H_2, 10% Pd/C.

The isomer, which has a lower R_f value on TLC (5% $MeOH/CH_2Cl_2$), was reacted with benzyl chloroformate[3c] and then treated with 6 N HCl to give desilylated alcohol. Removal of the alcohol moiety was done by a sequence; *i.e.* conversion of the alcohol to xanthate **7a** and cleavage of the xanthate with AIBN and $(nBu)_3SnH$.[6] The resulting methyl 2-(*N*-benzyloxylcarbonyl)piperidineacetate (**8**)[7] was hydrogenated on 10% Pd/C in the presence of di-*t*-butylcarbonate to give methyl 2-(*N*-*t*-butyloxycarbonyl)piperidineacetate [**9**, $[\alpha]^{20}_D = -8.1$ (c 0.1, $CHCl_3$)], which could be assigned S form in comparison with the reported specific rotation [lit.[8] $[\alpha]^{20}_D = -8.3$ (c 0.54, $CHCl_3$)]. In consequence, the stereochemistry of the isomer was *cis* because both substituents on the piperidine ring have *S* configuration (Scheme 2). This result is consistent with X-ray analysis.[3b]

Using this methodology, 2-alkylpiperidines such as coniine and hygrine could be synthesized as an optically active form.[2]

In conclusion, 2-(5-hydroxy)piperidineacetate can be synthesized *via* Meldrum's acid adduct. Control of the *trans* stereochemistry is currently in progress and the diastereoselective reaction on the side chain will be also studied for the synthesis of streptolutin.[9]

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9. **Experiment**. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 (200 MHz) spectrometer in $CDCl_3$. Chemical shifts for ^{1}H and ^{13}C NMR spectra were reference to TMS and measured with respect to the residual protons in $CDCl_3$. Melting points were measured on a Yamato MP-21 and were uncorrected. Elemental analysis were performed by OCRC at Sogang University in Seoul, Korea.

(5*S*)-*t*-Butyldimethylsilyloxy-2-oxopiperidine (2); mp 46-47 °C. ^{1}H NMR δ 0.04 (s, 6H, Si-Me), 0.85 (s, 9H, t-Bu), 1.80-2.00 (m, 2H, H_4), 2.22-2.39 (m, 1H, H_{3a}), 2.48-2.68 (m, 1H, H_{3e}), 3.12-3.26 (m, 1H, H_{6a}), 3.33-3.45 (m, 1H, H_{6e}), 4.07 (m, 1H, H_{3e}), 6.50 (bs, 1H, N-H). ^{13}C NMR δ −6.64, 16.2, 23.9, 25.7, 27.1, 47.5, 62.3, 170.7. Anal. Calcd for $C_{11}H_{23}NO_2Si$: C, 57.64; H, 10.04; N, 6.11. Found; C, 57.36; H, 10.72; N, 6.10.

2,2-Dimethyl-5-[2-(5*S*)-(*t*-butyldimethylsilyloxy) piperidin-2-ylidene]-1,3-dioxane-4,6-dione (3). Meldrum's Acid adduct 3; mp 125-126 °C. ^{1}H NMR δ 0.05 (s, 6H, Si-Me), 0.84 (s, 9H, t-Bu), 1.64 (S, 6H, Me), 1.76-1.91 (m, 2H, H_4). 3.23-3.86 (m, 4H, H_3, H_6), 4.11 (m, 1H, H_{5a}), 11.5 (bs, 1H, N-H); ^{13}C NMR δ −4.8, 18.0, 25.7, 25.8, 26.4, 26.8, 49.3, 62.6, 83.1, 102.3, 162.3, 167.5, 173.7. Anal. Calcd for $C_{17}H_{29}NO_5Si$: C, 57.43; H, 8.22; N, 3.94. Found; C, 57.56; H, 8.22; N, 3.85.

Methyl 2-[(5*S*)-5-(*t*-butyldimethylsilyloxy)piperidin-2-ylidene]acetate (4).[3c] ^{1}H NMR δ 0.05, 0.07 (s, 6H, Si-Me), 0.88 (s, 9H, t-Bu), 1.58-1.78 (m, 1H, H_{4a}), 1.78-1.93 (m, 1H, H_{4e}), 2.20-2.40 (m, 1H, H_{3a}), 2.50-2.70 (m, 1H, H_{3e}), 3.02-3.16 (m, 1H, H_{6a}), 3.34-3.48 (m, 1H, H_{6e}), 3.62 (s, 3H, OMe), 3.97-4.10 (m, 1H, H_{5a}), 4.41 (s, 1H, Olefin-H), 8.61 (bs, 1H, N-H). ^{13}C NMR δ −6.60, 16.2, 23.9, 24.4, 27.1, 46.7, 48.1, 63.5, 78.1, 160.2, 169.3.

Methyl 2-[(2*S*, 5*S*)-5-(*t*-butyldimethylsilyloxy)piperidin-2-yl]acetate (5a); ^{1}H NMR δ 0.00, 0.05 (s, 6H, Si-Me), 0.82 (s, 9H, t-Bu), 1.35-1.93 (m, 4H, H_3, H_4), 2.20-2.40 (m, 2H, H), 2.64-3.00 (m, 3H, H_6, N-H), 3.64 (S, 3H, OMe), 3.68 (m, 1H, H_{5e}). ^{13}C NMR δ −6.68, 16.3, 24.0, 25.2, 29.8, 39.6, 49.7, 50.9, 51.3, 63.0, 170.8.

Methyl 2-[(2*R*, 5*S*)-5-(*t*-butyldimethylsilyloxy)piperidin-2-yl]acetate (5b); ^{1}H NMR δ 0.03 (s, 6H, Si-Me), 0.86 (s, 9H, t-Bu), 1.14-1.48 (m, 2H, H_4), 1.86-2.00 (m, 2H, H_3), 2.24-2.56 (m, 3H, H_{6a}, H), 2.76-2.92 (m, 1H, H_{2a}), 3.02-3.14 (m, 1H, H_{6e}), 3.50-3.68 (m, 1H, H_{5a}), 3.68 (s, 3H, OMe). ^{13}C NMR δ −6.46, 16.4, 24.1, 29.6, 32.6, 38.9, 49.8, 50.7, 52.4, 67.1, 171.1.

Xanthate 7a; ^{1}H NMR δ 1.70-1.92 (m, 2H, H_3), 2.05-2.23 (m, 2H, H_4), 2.55 (s, 3H, SMe), 2.50-2.76 (m, 2H, H_a), 2.92 (dd, J_{gem}=13 Hz, J_{vic}=10.8 Hz, 1H, H_{6a}), 3.61 (s, 3H, OMe), 4.39-4.57 (m, 1H, H_{6e}), 5.14 (s, 2H, benzyl), 5.36-5.55 (m, 1H, H_{5a}), 7.34 (bs, 5H, phenyl). ^{13}C NMR δ 17.4, 22.9, 24.7, 33.2, 40.2, 45.8, 50.0, 65.8, 75.4, 126.2, 126.4, 126.8, 134.8, 153.4, 169.4, 213.3.