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The Shortest Synthesis of Optically Active Geissman-Waiss Lactone, A Key Synthetic Intermediate for Necine Bases

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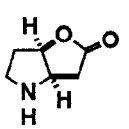
Abstract: A short synthesis of (+)-(1*R*,5*R*)-2-oxa-6-azabicyclo[3.3.0]octan-3-one (the Geissman-Waiss lactone, **1**) by palladium (II)-catalyzed intramolecular aminocarbonylation of (*R*)-*N*-benzyloxycarbonyl-3-hydroxy-4-pentenylamine (**4**) available from the Katsuki-Sharpless kinetic resolution of racemic **4** has been accomplished.

(+)-(1*R*,5*R*)-2-Oxa-6-azabicyclo[3.3.0]octan-3-one (the Geissman-Waiss lactone, **1**)[1] is an important intermediate in the synthesis of a number of necine bases (pyrrolizidine alkaloids), as exemplified by (+)-retronecine (**2**)[2] and (-)-platynecine (**3**).[2a] Due to a remarkably diverse range of biological activities such as antitumor and carcinogenic, hypotensive, antispasmodic, and antiinflammatory effects of this group of alkaloids,[3] this optically active bicyclic lactone **1** has more recently attracted considerable synthetic interest.[4] However, its preparation has required relatively lengthy sequences starting from *trans*-4-hydroxy-L-proline,[5] D-ribose,[6] D-erythorose,[7] L-malic acid,[8] *cis*-3-hydroxyproline,[9] or (*S*)-pyroglutamic acid[10] as chiral educts.[11] Accordingly, it seems difficult to gain a large amount of the material for practical use. Recent investigations in this laboratory have revealed that the chiral urethanes **4** and **5** serve as versatile, common chiral building blocks in the preparation of several biologically active nitrogen-containing compounds such as (-)-anisomycin, (-)-detoxinine, and 1-hydroxyindolizidines.[12] In this paper, we wish to disclose the shortest and most practical synthesis of the Geissman-Waiss lactone **1** by an intramolcular amidocarboxylation using optically active form of **4**.



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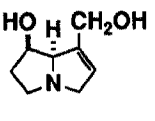

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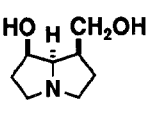

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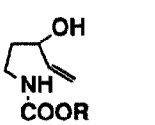
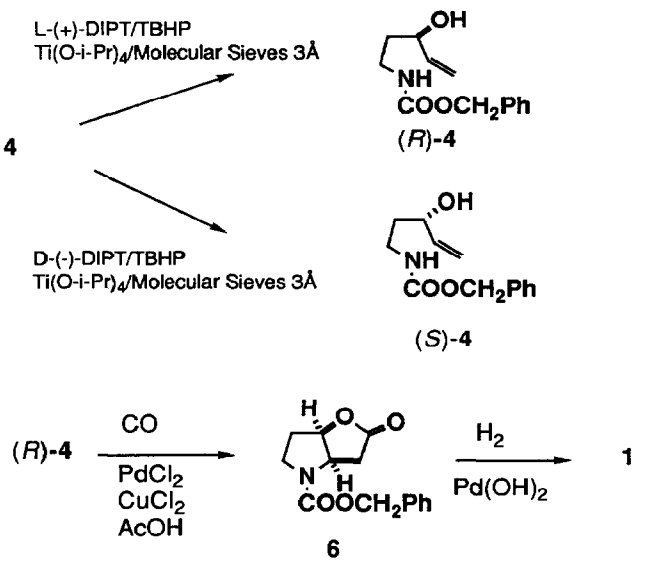


4 R=CH_2Ph
5 R=$C(CH_3)_3$

As part of our research objectives directed to development of an electrophile-mediated diastereoselective intramolecular aminocyclization induced by an allylic hydroxyl group,[13] we have developed a highly stereoselective amidomercuration of **4** and **5**.[12,14] Recently, an elegant palladium (II)-mediated bicyclization of *N*-toluenesulfonyl- or *N*-methoxycarbonyl-3-hydroxy-4-pentenylamine in racemic form has been reported by Tamaru.[15] Therefore, we examined this palladium (II)-catalyzed intramolecular aminocarbonylation capitalizing on an optically active form of the *N*-benzyloxycarbonyl protected urethane (**4**) , the group having several advantages such as facility of deprotection, stability to acidic conditions, and easy monitoring by UV detection.

Treatment of (*R*)-**4** available from kinetic resolution of the racemic **4** by Sharpless asymmetric oxidation[12], with palladium chloride under an atmosphere of carbon monoxide in acetic acid gave the lactone **6** {($[\alpha]_D^{26}$ -122.3 (*c* 4.7, $CHCl_3$), lit.[6] $[\alpha]_D$ -73.3 (*c* 0.45, $CHCl_3$)}, in 78% yield. Spectral data for **6** were identical with the values reported.[6] Hydrogenolysis of **6** under an atmosphere of hydrogen using $Pd(OH)_2$ as a catalyst in MeOH provided the Geissman-Waiss lactone **1** in quantitative yield. Its crystalline hydrochloride has physical properties {(mp 185-186 °C, $[\alpha]_D^{23}$ +45.75 (c 0.555, MeOH), lit.[6] mp 182-4 °C, $[\alpha]_D$ +45.6 (*c* 0.3, MeOH)} consistent with those reported. Similarly, the enantiomer of **1** was obtained in 75% overall yield from (*S*)-**4**. Among necine bases derived from the lactone **1**, (+)-retronecine has recently been transformed into other pyrrolizidines such as (+)-heliotridine[16] and (-)-supinidine.[17] Our work thus constitutes an enantiospecific avenue to these alkaloids.



In conclusion, we believe that the present synthesis of the optically active lactone **1** is substantially simpler and more effective than any previously described.

Experimental Section

Melting points were determined with a Yanaco micro melting point apparatus and are not corrected. Microanalyses were performed by Microanalysis Center of Toyama Medical & Pharmaceutical University. Infrared spectra (IR) were measured with a JASCO A 102 spectrophotometer. Proton magnetic resonance (^1H NMR) were recorded either at 60 MHz on a JEOL PMX-60 instrument or at 270 MHz on a JEOL-FX270 instrument with tetramethylsilane as an internal standard. Carbon-13 NMR spectra were determined on a Varian XL-200 instrument with tetramethylsilane as an internal standard unless otherwise specified. Mass spectra (MS) and high resolution mass spectra (HRMS) were measured on a JEOL JMS D-200. Optical rotations were measured on a JASCO DIP-140 instrument. Column chromatography was performed on silica gel (Fuji-Davision BW-200, or Merck 60 (No 9385) with a medium pressure apparatus. A solution of ethyl

acetate/hexane as eluant was used unless otherwise specified. The extracts were dried over Na_2SO_4 unless otherwise specified.

General Procedure for Sharpless Oxidation of the Racemic 4.

To a mixture of the racemic **4** (10 mmol) and MS (3A) (20 mmol%) in CH_2Cl_2 (88 mL) was added freshly distilled L-(+)- or D-(-)-DIPT (12 mmol). After being cooled to -20 °C, Ti(O-*i*-Pr)$_4$ (10 mmol) was added and then the resulting mixture was stirred for 30 min. TBHP (6 mmol, 3 M in 2,2,4-trimethylpentane) dried with MS (3A) was added to the mixture and then the resulting mixture was kept at -20 °C for 8 days. A solution of $FeSO_4.7H_2O$ (6 mmol) and citric acid (12 mmol) in H_2O (26 mL) was added to the reaction mixture at 0 °C. After being stirred at room temperature for 30 min, the MS was removed by filtration. The organic phase of the filtrate was separated and then the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic solvents were washed with brine (40 mL), dried, and evaporated. To a solution of the residue in ether (16 mL) was added a solution of NaOH (7.89 g) and NaCl (1.32 g) in H_2O (23.7 mL) at 0 °C and then the resulting mixture was vigorously stirred for 1 h. After addition of H_2O (5 mL), the organic phase was separated. The aqueous phase was extracted with ether (3 x 10 mL). The combined organic solvents were washed with brine, dried, and evaporated. The residue was chromatographed to yield optically active **4**.

(*R*)-*N*-Benzyloxycarbonyl-3-hydroxy-4-pentenylamine [(*R*)-4]. An oil; $[\alpha]_D^{25}$ -2.60 (*c* 1.08, $CHCl_3$); Enantiomeric excess was determined on the basis of ^{19}F NMR analysis for the corresponding (+)-α-methoxy-α-trifluorophenyl acetic ethyl ester, which indicated the optical purity to be 92%ee.IR (neat) 3350, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51-1.74 (m, 2 H), 3.13-3.35 (m, 2 H), 3.93-4.17 (m, 2 H), 5.04 (br s, 3 H), 5.15-5.21 (m, 2 H), 5.74-5.95 (m, 1 H), 7.25 (s, 5 H). HRMS calcd for $C_{13}H_{17}NO_3$ 235.1183, found 235.1206.

(*S*)-*N*-Benzyloxycarbonyl-3-hydroxy-4-pentenylamine [(*S*)-4].The chromatographic and spectral properties were identical with those of (*R*)-**4**. $[\alpha]_D^{25}$ +2.64 (*c* 2.975, $CHCl_3$).

(1*R*,5*R*)-Benzyl 3-Oxo-2-oxa-6-azabicyclo[3.3.0]octane-6-carboxylate (6). Under a CO balloon, a solution of (*R*)-**4** (580 mg, 2.56 mmol) in acetic acid (12.8 mL) was added to a mixture of $PdCl_2$ (45.5 mg, 0.256 mmol), $CuCl_2$ (1.04 g, 7.71 mmol), and NaOAc (632 mg, 7.71 mmol). After being stirred for 2 days at 23 °C, the mixture was filtered through Celite. The filtrate was evaporated to leave a residue, to which was added ethyl acetate. The solution was washed with aq. $NaHCO_3$, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel chromatography using a mixture of n-hexane/ethyl acetate (3:1) as an eluant to give (1*R*,5*R*)-**6** (500 mg, 78%) as an oil; $[\alpha]_D^{26}$ -122.3 (*c* 4.7, $CHCl_3$), IR (CH_2Cl_2) 1788, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.97-2.10 (m, 1 H), 2.32 (dd, *J*=6.1, 14.2 Hz, 1 H), 2.67-2.97 (m, 2 H), 3.43 (td, *J*=6.18, 11.2 Hz, 1 H), 3.76-3.91 (m, 1 H), 4.49-4.53 (m, 1 H), 5.07-5.19 (m, 3 H), 7.35 (s, 5 H). HRMS calcd. for $C_{14}H_{15}NO_4$ 261.1000, found 261.0994.

(1*S*,5*S*)-Benzyl 3-Oxo-2-oxa-6-azabicyclo[3.3.0]octane-6-carboxylate *ent*-(6) was prepared in 75% yield as described for the corresponding **6**. The chromatographic and spectral properties were identical with those of **6**. $[\alpha]_D^{24}$ +122.9 (*c* 1.42, $CHCl_3$).

(1*R*,5*R*)-2-Oxa-6-azabicyclo[3.3.0]octan-3-one Hydrochloride (1). A suspension of (*R*)-**4** (178 mg, 0.682 mmol) and $Pd(OH)_2$ (22.7 mg) in MeOH (2 mL) was stirred under an atmosphere of hydrogen for 1.5 h. After filtration, 5% hydrogen chloride methanol solution was added to the filtrate. The mixture was evaporated to give the hydrochloride salt of **1** (147 mg, 100%), as colorless crystals, mp 185-186 °C (dec) (recrystallized from ether/MeOH); $[\alpha]_D^{23}$ +45.75 (*c* 0.555, MeOH), lit.[5] mp 182-4 °C, $[\alpha]_D$ +45.6 (*c* 0.3,

MeOH); IR (KBr) 3540, 3417, 1775 cm^{-1}; ^1H NMR (D_2O) δ 2.29-2.45 (m, 2 H), 3.00 (dd, *J*=1.4, 19.8 Hz, 1 H), 3.32 (dd, *J*=8.79, 19.5 Hz, 1 H), 3.46 (td, *J*=6.6, 11.4 Hz, 1 H), 3.53-3.61 (m, 1 H), 4.66-4.83 (m, 1 H), 5.43 (br t, *J*=5.0 Hz, 1 H). Anal. Calcd for $C_6H_{10}ClNO_2$: C, 44.05; H, 6.16; N, 8.56. Found: C, 44.03; H, 6.16; N, 8.23.

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