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Synthesis of (*R*)- and (*S*)-3-(*tert*-butyldimethylsilyloxy)-1-pyrroline *N*-oxides — chiral nitrones for synthesis of biologically active pyrrolidine derivative, Geissman-Waiss lactone

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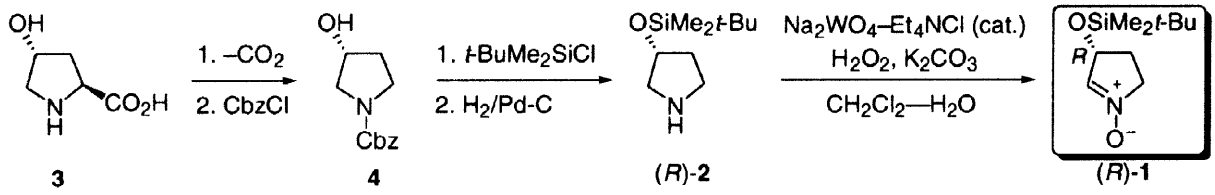
Abstract

Tungstate-catalyzed oxidation of *O*-*tert*-butyldimethylsilyl (*O*-TBDMS) protected (*R*)-3-hydroxypyrrolidine ((*R*)-**2**), derived from *trans*-4-hydroxy-L-proline, gave *O*-TBDMS protected (*R*)-3-hydroxy-1-pyrroline *N*-oxide ((*R*)-**1**), which is a new chiral precursor for the synthesis of Geissman-Waiss lactone. The enantiomeric nitrone (*S*)-**1** was also prepared by the oxidation of (*S*)-**2** derived from L-malic acid.

Keywords: Oxidation; Nitrones; Asymmetric synthesis; Biologically active compounds

Nitrones are highly valuable synthetic intermediates for the construction of nitrogen heterocycles [1]. Optically active five-membered cyclic nitrones [2] are of particular importance in view of synthesis of biologically active pyrrolizidine and indolizidine alkaloids [3] and antibiotics [4]. In this paper we describe selective synthesis of (*R*)- and (*S*)-3-(*tert*-butyldimethylsilyloxy)-1-pyrroline *N*-oxides ((*R*)-**1** and (*S*)-**1**) by the Na_2WO_4-catalyzed oxidation of the corresponding secondary amines [5] and the application to the synthesis of Geissman-Waiss lactone.

(*R*)-3-(*tert*-Butyldimethylsilyloxy)pyrrolidine ((*R*)-**2**) was prepared by decarboxylation of *trans*-4-hydroxy-L-proline (**3**) followed by protection and hydrogenolysis of **4** (71% overall yield). Treatment of (*R*)-**2** with a 30% aqueous H_2O_2 (2.2 equiv) in the presence of Na_2WO_4 (5 mol%) and Bu_4NCl (5 mol%) in CH_2Cl_2–H_2O at 0 °C for 4 h gave a mixture of (*R*)-**1** and (*R*)-4-(*tert*-butyldimethylsilyloxy)-1-pyrroline *N*-oxides ((*R*)-**5**) in 70% yield (**1**:**5** = 6.8:1). Upon column chromatography (SiO_2) the enantiomerically pure (*R*)-**1** was isolated readily as a crystalline solid in 61% yield (mp 73.8–75.5 °C; $[\alpha]^{28}_D$ +55.9 (*c* 1.14, MeOH)). It is noteworthy that the regioisomeric nitrone (*R*)-**5** can be prepared selectively by decarboxylative oxidation of *trans*-4-(*tert*-butyldimethylsilyloxy)-L-proline [6]. Therefore, we are now in a position to be able to prepare either (*R*)-**1** or (*R*)-**5**.



3 **4** (*R*)-**2** (*R*)-**1**

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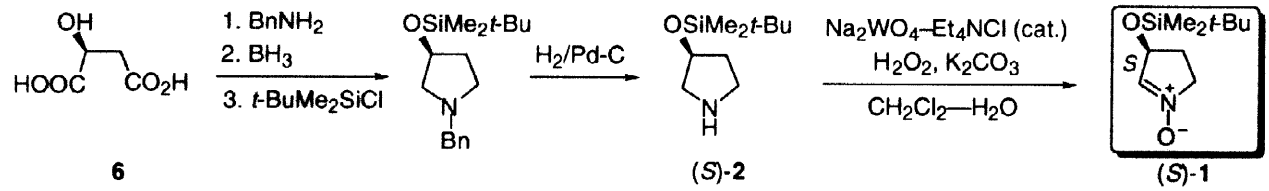
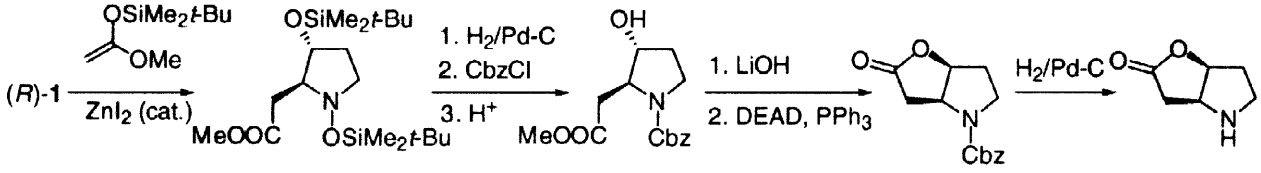
The regioselective synthesis of nitrone (*S*)-**1** can be performed selectively on a preparative scale. The precursor of optically active pyrrolidine (*S*)-**2** was prepared from L-malic acid (**6**) in four steps in 54% overall yield. Similar treatment of (*S*)-**2** with H_2O_2 in the presence of Na_2WO_4 (5 mol%) under phase-transfer conditions followed by column chromatographic separation gave enantiomerically pure (*S*)-**1** (mp 74.2–75.3 °C; $[\alpha]^{28}_D$ –55.7 (*c* 1.10, MeOH)) in 59% isolated yield.



6 (*S*)-**2** (*S*)-**1**

Optically active nitrones (*R*)-**1**, (*S*)-**1**, and (*R*)-**5** thus obtained are especially useful for the preparation of optically active pyrrolidine alkaloids. As an example, we want to show here the synthesis of Geissman-Waiss lactone **7** [7], which is an important intermediate for synthesis of necine bases (pyrrolizidine alkaloids) such as retronecine and platynecine [8]. The ZnI_2-promoted addition of *O*-(*tert*-butyldimethylsilyl)-*O*-methyl ketene acetal to nitrone (*R*)-**1** in CH_2Cl_2 at –70 °C for 30 min gave a mixture of *trans*- and *cis*-**8** in a ratio of 9:1 in 99% yield. Hydrogenolysis of **8**, protection with CbzCl, and deprotection with a diluted HCl solution gave *trans*-**9** (91%, $[\alpha]^{26}_D$ +2.0 (*c* 1.21, MeOH)) and lactone (-)-**10** (6%), which was derived from acid-catalyzed lactonization of *cis*-**9**. Saponification of pure *trans*-**9** and subsequent lactonization with PPh_3 and diethyl azodicarboxylate (DEAD) afforded (+)-**10** ($[\alpha]^{28}_D$ +109.2 (*c* 1.10, MeOH)) in 96% yield. Catalytic hydrogenation of (+)-**10** under hydrogen (1 atm) gave the Geissman-Waiss lactone **7** in 91% isolated yield (79% yield from (*R*)-**1**). Its hydrochloride (mp 185–187 °C, $[\alpha]^{28}_D$ –46.4 (*c* 1.43, MeOH); lit. mp 182–184 °C, $[\alpha]_D$ +45.6 (*c* 0.3, MeOH)) had physical properties identical with those reported [8a].



8 **9** (+)-**10** **7**

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