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Synthesis of (R)- and (S)-3-(*tert*-butyldimethylsilyloxy)-1pyrroline 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. @ 1998 Elsevier Science Ltd. All rights reserved.

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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 Na₂WO₄-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 H₂O₂ (2.2 equiv) in the presence of Na₂WO₄ (5 mol%) and Bu₄NCl (5 mol%) in CH₂Cl₂-H₂O 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 (SiO₂) 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.



The regional selective 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 H₂O₂ in the presence of Na₂WO₄ (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.



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 ZnI₂-promoted addition of O-(tert-butyldimethylsilyl)-O-methyl ketene acetal to nitrone (R)-1 in CH₂Cl₂ 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%, $[\alpha]^{26}$ +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 PPh₃ 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, $[\alpha]^{28}$ –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].



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