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Practical Synthesis of Optically Active Bicyclic Oxazolidinylpiperidines, Chiral Building Blocks for Preparing 1-Deoxyazasugars, from Serine

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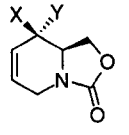
Abstract

Optically active bicyclic oxazolidinylpiperidines **1a**, **1b**, **1c** and **1d**, known chiral building blocks for preparing 1-deoxyazasugars, were synthesized in high overall yield from D-serine by a method wherein the titanium(II)-mediated intramolecular nucleophilic acyl substitution and $FeCl_3$-mediated ring enlargement of bicyclic cyclopropanols are the key reactions.

Keywords: titanium and compounds; amino sugars; amino acids and derivatives; cyclohexenones

Recently, azasugars have attracted much interest because of their importance as glycosidase inhibitors [1]. Among them, 1-deoxyazasugars, which are rather stable compared with the fragile original azasugars, have received special attention due to their therapeutic potential [2]. Development of an efficient and practical synthesis of these 1-deoxyazasugars, therefore, has been a continuing research subject [3].

Optically active bicyclic oxazolidinylpiperidines **1** were recently introduced as a versatile chiral building block for synthesizing 1-deoxyazasugars. Ciufolini prepared **1** starting from a racemic furylglycine derivative through kinetic resolution by enantioselective hydrolysis with papain [4] while Katsumura prepared it starting from optically active glycidol [5]. In spite of the elegance, both methods suffer from several disadvantages in application to large-scale production such as rather low overall yield and/or inclusion of steps which require an expensive reagent and/or very low reaction temperature. We report here a highly practical entry to **1**.



1a ; X = OH, Y = H
1b ; X = H, Y = OH
1c ; X = H, Y = OCH_2Ph
1d ; X = H, Y = OTBS

We previously reported the highly practical synthesis of optically active pyrrolidine derivative **3** from serine according to the procedure shown in Scheme 1. Thus, serine was converted into **2** in good overall yield by conventional reaction sequences, which was then treated with a Ti(O-*i*-Pr)4/2*i*-PrMgCl reagent to afford, after hydrolysis, **3** in excellent yield [6]. We have now found that **3** can be readily converted into 3-piperidinone **5**. As illustrated in Scheme 1, the reaction of **3** with $FeCl_3$ in Et_2O afforded the ring expansion

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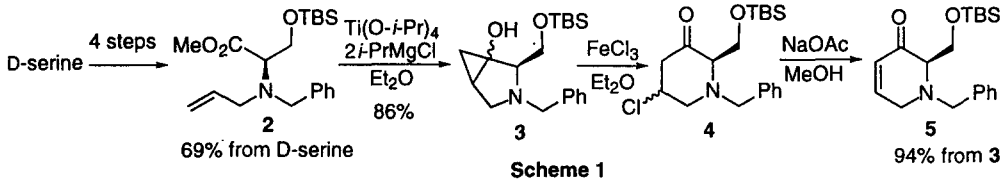
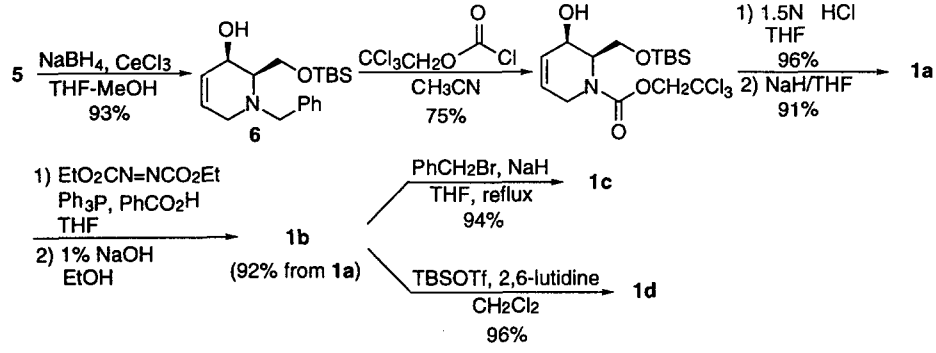
product **4**, which was treated in turn, without purification, with AcONa in MeOH to provide **5** in 94% overall yield from **3**. Although the FeCl3-mediated ring expansion reaction of bicyclic cyclopropanols to the corresponding 2-cycloalkenones developed by Ito and Saegusa [7] has been widely used, however, it should be noted that, to the best of our knowledge, our present work exemplifies the first application of the reaction to *N*-heterocyclic compounds. The compound **5** has been found to be an efficient precursor of **1**.



Scheme 1

The conversion of **5** into **1** was carried out according to the procedure shown in Scheme 2. The reduction of **5** with NaBH4-CeCl3 in THF-MeOH furnished **6** as the sole product in 93% yield. The stereochemistry of **6** thus obtained was speculated by ^{1}H NMR analysis at this stage, and finally was confirmed by converting it to **1**. The conversion of **6** to **1a** [5] was readily accomplished in good overall yield by conventional reaction sequences which involve the replacement of the *N*-benzyl protecting group to a trichloroethoxycarbonyl group, cleavage of the silyl protecting group and cyclization by treatment with NaH in THF. The yield of **1a** from **6** was 61%; thus, the overall yield to **1a** from D-serine was 34%. Inversion of the hydroxyl group in **1a** was readily carried out by the Mitsunobu reaction to provide **1b** [4,5] in 92% yield. Protection of the hydroxyl group of **1b** with benzyl or TBS group to furnish the corresponding **1c** [4] or **1d** [5,8], respectively.



Scheme 2

References and Notes

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[8] The ^{1}H NMR data and $[\alpha]_D$ value of **1d** thus obtained were well coincident with those reported in the literature [5] ; $[\alpha]_D^{25}$ +25.8 (*c* 0.50, $CHCl_3$) [lit. $[\alpha]_D^{23}$ +26.0 (*c* 1.00, $CHCl_3$)].