Efficient Route to (2R)-6-Hydroxy-2-methyl-dihydropyridin-3-ones, Key Intermediates for Piperidine Alkaloids Syntheses

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Abstract The efficient synthesis of (2R,6S)-6-hydroxy-2-methyl-1-tosyl-1,2-dihydropyridin-3(6H)-one 5 in five steps and 30 % overall yield is reported. This dihydropyridone constitutes versatile chiral building block repetitively used in the synthesis of various piperidine alkaloids and may serve as key template for the construction of synthetic libraries of bioactive derivatives and analogues of the piperidine alkaloids.

Keywords Pyridones, Piperidine Alkaloids, Azasugars, Glucal

1. Introduction

Multifunctionalized piperidine alkaloids (including azasugars) constitute a distinct class of natural compounds widely found in living systems[1] that exhibit a wide range of biological activities, as a result of their ability to mimic carbohydrate substrates in a plethora of enzymatic processes [2,3]. These activities include glycosidase inhibition[4], tumour growth inhibition[5] and anti-HIV behaviour[6], making those particularly attractive synthetic targets.

Thus, an intense research effort has been devoted for the development of methodologies and synthetic strategies for the efficient approach of these compounds and their derivatives[7-10]. Among the various synthetic routes developed for their efficient access, the use of dihydropyridones as advanced intermediates –prior to their conversion to piperidines– constitutes a well reviewed important synthetic strategy[11,12] that has been a long term objective of our research group [12 and references therein]. In this respect, a series of synthetic methods including the microwave-assisted synthesis, regioselective nucleophilic addition to pyridinium salts, incorporation of boronate esters to dihydropyridones, have been reported during the last 5 years as concise routes for the preparation of dihydropyridone derivatives[13-15].

Herein we report the efficient transformation of the commercially available 3,4-di-O-acetyl-6-deoxy-L-glucal 1 to (2R, 6S)-2-methyl-dihydropyridone 5, which accounts as the key intermediate for the synthesis of many bioactive natural piperidine alkaloids, such as the molecules of (−)-Cassine, (−)-Spectaline, (−)-Carnavaline, Prosafrine and (−)-Prosafrinine. The literature reports implicating the derivatives of L-glucal in synthetic endeavours are limited and mainly refer to their transformation to L-ristosamine and L-epi-daunosamine glycosides[16].

Figure 1. Piperidine alkaloids approached through the synthesis of key intermediate dihydropyridone 5

2. Chemistry

Our synthetic route substrate is the commercially available molecule of 3,4-di-O-acetyl-6-deoxy-L-glucal, which in acidic environment (0.002 M H₂SO₄ solution) by reaction with HgSO₄ was efficiently converted to the optically active furfural 2, in accordance to a previously reported method [17]. The displacement of the secondary hydroxy group with the azide moiety, with the simultaneous inversion of its configuration, was performed in high enantiomeric excess (>98%) by treating the compound 2 with DBU in toluene and DPPA. The enantiomeric excess of azide 3 was determined after the hydrogenation of the molecule for 50 min over 10% Pd/C catalyst and 1 bar pressure[18]. The mixture was filtered over Celite® and the resulting amine was in situ derivatized with (−)-menthyl chloroformate, in the presence of
Et$_3$N. The enantiomeric ratio was determined by reversed-phase HPLC [Kromasil 100-5, C-18, H$_2$O/MeOH/CH$_3$CN gradient elution from 45:35:20 to 0:20:80, flow = 1.1 mL/min, UV detection at 238 nm]; $t_R$ major 49.2 min (97%); and $t_R$ minor 50.1 min (3%).

Scheme 1. Reagents and Conditions (a) DPPA, DBU, toluene, 0 °C; (b) H$_2$, Pd/C, EtOAc; (c) TsCl, Et$_3$N, CH$_2$Cl$_2$; (d) m-CPBA, CH$_2$Cl$_2$

On the other hand, the hydrogenation of 3 over Pd/C and subsequent in situ tosylation of the resulting amine afforded the (R)-N-furfurylsulfonamide 4. Finally, the oxidative cyclization of compound 4, using a modified version of the standard aza-Achmatowich rearrangement conditions, provided the target dihydropyridone 5.

The diastereomeric purity of the product was revealed by $^1$H-NMR and HPLC, since the presence of the other diastereoisomer was not detected, while the stereochirality of the newly formed stereocenter was determined by 2D-NOESY spectroscopic analysis (the absolute configuration of C-2 derived from the starting material). Thus, the clear strong cross peak observed between the protons on C-2 and C-6 confirms their cis pseudo-diaxial conformation (Figure 2).

Finally, the observed value of optical rotation of this compound [(α]$_{22}^D$ = -24.4) constitutes an additional proof of the assigned configuration, since its enantiomer displays the opposite sign [(α]$_{22}^D$ = +24.9).

3. Experimental Part

Air- and/or moisture sensitive reactions were carried out under argon atmosphere in flame-dried glassware. Solvents were distilled from the appropriate drying agents prior to use. All starting materials were purchased from Aldrich (analytical reagent grades) and used without further purification. All reactions were monitored by thin-layer chromatography using TLC sheets coated with silica gel 60 F254 (Merck); spots were visualized with UV light or by treatment with. Products were purified by flash chromatography on Merck silica gel 60 (230-400 mesh ASTM). Melting points (uncorrected); Büchi melting point apparatus. FT-IR: Nicolet Magna 750, series II. Samples were recorded as KBr pellets, unless otherwise stated. $^1$H NMR spectra were recorded on a Bruker DRX-400 (400 MHz) spectrometer, in the indicated solvents. Chemical shifts are referenced to internal TMS.

HPLC measurements were performed using an Agilent 1100 series instrument equipped with a variable UV wavelength detector and coupled to HP ChemStation utilizing the manufacturer’s 5.01 software package.

(S)-1-(furan-2-yl)ethanol, 2: 0.37 g (2.84 mmol) Of 3,4-di-O-acetyl-6-deoxy-L-glucal 1 were stirred at room temperature in an aqueous solution of H$_2$SO$_4$ (0.002 M) in the presence of 0.017 g (0.057 mmol) of HgSO$_4$. The reaction was completed after 3 h of stirring (revealed by TLC). Then the reaction mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were extracted with 30 mL of a saturated solution of NH$_4$Cl. The organic phase was separated, dried over MgSO$_4$ and concentrated under reduced pressure to give 0.33 g of compound 2 as a colourless oil (76% yield), which was further used without any additional purification.

$^1$H NMR (400 MHz) CDCl$_3$ δH: 1.56 (d, J = 6.5 Hz, 3H, C-CH$_3$), 4.88 (q, J = 13.1, 6.5 Hz, 1H, H-1), 6.25 (d, J = 3.1 Hz, 1H, H-3’), 6.35 (m, 1H, H-4’), 7.35 (s, 1H, H-5’).

(R)-2-(1-azidoethyl)furan, 3: To an ice-cold stirred solution of 50 mg (0.38 mmol) of furanylethanol and 0.1 mL (0.47 mmol) DPPA in 1 mL of anhydrous toluene 0.068 mL (0.47 mmol) DBU were added dropwise. The resulting biphasic system was stirred at this temperature for 2 h and at room temperature for additional 20 hours. After revealing the end of the reaction (TLC), the reaction mixture was washed successively with H$_2$O (2 × 1 mL) and aqueous HCl (5%, 1 mL). The organic layer was dried with MgSO$_4$ and concentrated under reduced pressure. The oily residue was
flash chromatographed using hexane/EtOAc 95:5 as eluent to provide 38 mg of furan 3 as a colourless oil (70% yield).

1H NMR (400 MHz) CDCl3 δ 1.45 (d, J = 7 Hz, 3H, C-CH3), 2.41 (s, 3H, ArCH3), 4.5 (m, 1H, H-1), 4.8 (m, 1H, NH), 5.99 (d, J = 3.2 Hz, 1H, H-5), 7.67 (m, 5H, ArH).

(R)-N-(1-(furan-2-yl)ethyl)-4-methylbenzenesulfonamide, 4: 60 mg (0.44 mmol) of (R)-2-(1-azidoethyl)furane 3 in 10 mL EtOAc were hydrogenated at atmospheric pressure using as catalyst 10% w/w Pd/C (0.04 g). After 1.5 h of stirring the reaction was completed and the solution was filtered through celite. The filtrate was dried over MgSO4 and concentrated under reduced pressure to provide an oily residue. Then, 3 mL CH2Cl2 and 0.12 mL Et3N (0.9 mmol) were added, cooled to 0 °C and 0.07 g (0.49 mmol) of benzoyl-chloride were added gradually under stirring. After completion of the addition, the reaction temperature was maintained at 0 °C for 10 min and then allowed to proceed at room temperature and stirred for additional 3 h. Then, the reaction mixture was quenched with saturated solution of NaHCO3 and brine was added. The organic phase was separated, dried over MgSO4 and concentrated under reduced pressure. The resulting yellow solid was flash chromatographed using as eluent hexane/EtOAc 8.5:1.5, providing 77 mg of sulphonamide 4 (yield, 67%), which recrystallizes as white crystals from Et2O/hexane.

1H NMR (400 MHz) CDCl3 δ 1.45 (d, J = 7 Hz, 3H, C-CH3), 2.46 (s, 3H, ArCH3), 4.5 (m, 1H, H-2), 4.9 (br, 1H, OH), 6.1 (m, 1H, H-6), 6.24 (d, J = 10.2 Hz, 1H, H-4), 7.09 (m, J = 10.2, 4.9 Hz, 1H, H-5), 7.3–7.8 (m, 4H, ArH).

4. Conclusions

The commercially available L-glucal substrate provided efficiently the molecule of dihydropyridin-3(6H)-one in five steps and satisfactory overall yield (30.3%). This compound can serve as crucial key intermediate for the efficient syntheses of various bioactive natural piperidine alkaloids.

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