Available online at www.sciencedirect.com
ScienceDirect
Journal of Fluorine Chemistry 128 (2007) 535–539
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/fluor

Synthesis of 3-deoxy-3,3-difluoro-D-ribohexose from *gem*-difluorohomoallyl alcohol

Xiu-Hua Xu [a], Zheng-Wei You [a], Xingang Zhang [a], Feng-Ling Qing [a,b,*]

[a] *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Science, 354 Fenglin Lu, Shanghai 200032, China*

[b] *College of Chemistry and Chemistry Engineering, Donghua University, 2999 North Renmin Lu, Shanghai 201620, China*

Received 10 January 2007; accepted 18 January 2007
Available online 23 January 2007

Abstract

A novel synthetic route to 3-deoxy-3,3-difluoro-D-ribohexose **1** has been developed. Dihydroxidation of *gem*-difluorohomoallyl alcohol followed by several steps of protection and deprotection gave key intermediate **9**. Oxidation of 1,5-diol **9** with 2 equiv. trichloroisocyanuric acid and catalytic TEMPO gave lactone **10**. Reduction of **10** with DIBAL-H followed by deprotections afforded the target molecule **1**.
© 2007 Elsevier B.V. All rights reserved.

Keywords: Fluorosugars; *Gem*-Difluoromethylenated compounds; Building block

1. Introduction

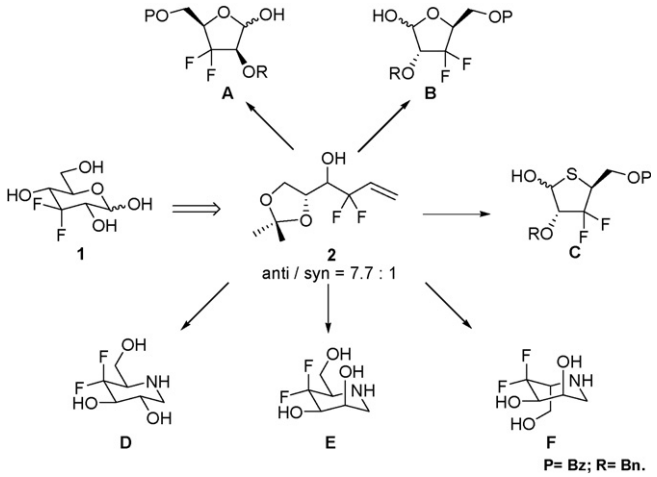
The interest of fluorinated analogues of natural substances is increasing continuously, because the incorporation of fluorine atom(s) or fluoroalkyl groups may greatly modify the chemical properties and biological activities of those molecules [1]. Among these fluorinated analogues of natural products, fluorinated carbohydrates (fluorosugars) have recently attracted more and more attentions from organic chemists and pharmaceutists [2]. Fluorosugars can retain much of the reactivity of natural saccharides while lacking the ability to enter into critical hydrogen bonding interactions with nucleic acids or proteins. Although monofluorinated [3] and trifluoromethylated sugars [4] have been well studied, only a few *gem*-difluoromethylenated sugars have been reported, which is probably due to the shortcomings of existing synthetic methods. 2-Deoxy-2,2-difluorinated sugars were obtained either by electrophilic fluorination of 2-fluoroglycals [5] and by reaction of carbonyl groups with DAST [6]. The difluorination at the 4-keto- and 3-keto-groups with DAST for synthesis of the corresponding 4-deoxy-4,4-difluorinated [7] and 3-deoxy-4,4-difluorinated [8] sugars have been described. The difluorinations of keto groups of carbohydrates have been well-documented complications arising from neighbouring group participation, group migration and elimination reactions [9]. Therefore, the development of efficient and practical route to *gem*-difluorinated sugars was anticipated. Percy and co-workers have reported the synthesis of 4-deoxy-4,4-difluoroglycosides from *gem*-difluoromethylene-containing building block using ring-closing metathesis as the key step [10]. Recently, our group has developed a practical route to *gem*-difluorinated homoallyl alcohol **2**. Staring from *gem*-difluoromethylene-containing building block **2**, several *gem*-difluorinated sugars such as 3-deoxy-3,3-difluoro-D-arabinofuranose **A** [11], 3-deoxy-3,3-difluoro-L-ribofuranose **B** [12], *gem*-difluorinated thiofuranose **C** [13] and *gem*-difluorinated azasugars **D–F** [14] were synthesized (Scheme 1). Herein, we wish to describe preparation of 3-deoxy-3,3-difluoro-D-ribohexose **1** from *gem*-difluorohomoallyl alcohol **2**.

2. Results and discussion

The building block *gem*-difluorohomoallyl alcohol **2** was prepared by the coupling of *gem*-difluoroallylindium, in situ generated from 3-bromo-3,3-difluoropropene **4** and indium in DMF, with 1-(*R*)-glyceraldehyde acetonide **3** [11] (Scheme 2). Compound **2** can be made on a 50 g scale in our group. The ratio

* Corresponding author at: Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Science, 354 Fenglin Lu, Shanghai 200032, China. Tel.: +86 21 54925187; fax: +86 21 64166128.
E-mail address: flq@mail.sioc.ac.cn (F.-L. Qing).

0022-1139/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2007.01.007

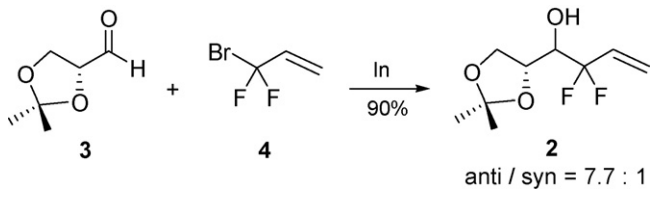


Scheme 1.

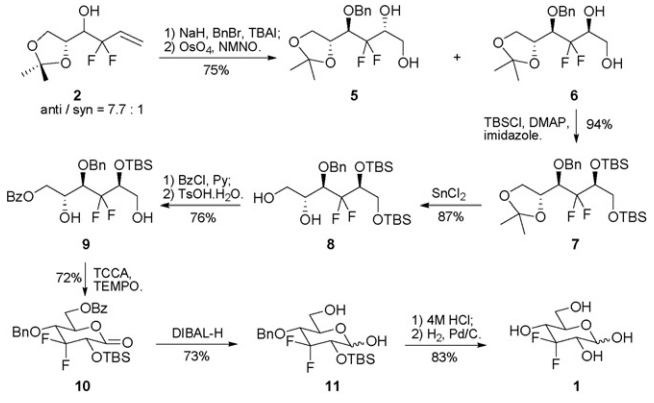
of *anti*/*syn* compound **2** is 7.7:1 determined by ^{19}F NMR. The difluoromethylene group of *anti*-**2** appeared at a higher field than that of *syn*-**2**. Notably, the *anti*-**2** isomer is our desired compound.

With *gem*-difluorohomoallyl alcohol **2** in hand, 3-deoxy-3,3-difluoro-D-ribohexose **1** was synthesized in a straightforward fashion (Scheme 3). Utilizing the kinetic resolution method and optimized reaction condition, benzylation of the *gem*-difluorohomoallyl alcohol **2** was easily accomplished by treatment with sodium hydride (0.8 equiv.) and catalytic TBAI, followed by benzyl bromide. The desired single *anti*-isomer was afforded in 78% yield. Then, the Os-catalyzed dihydroxylation of the resulting benzyl ether gave the mixture of diol compounds **5** and **6** in 95% yield and in 1:1 ratio, which could be easily separated by column chromatography. The two hydroxyl groups of diol **6** were protected to the *tert*-butyldimethylsilyl ether form and the desired compound **7** was provided in 94% yield. Deprotection of the acetonide moiety was achieved in a chemoselective manner by using $SnCl_2$ as the promoter to give diol **8** in 87% yield [15]. The beneficial effect of $SnCl_2$ was cleavage of the acetonide moiety without interference with the TBDMS and benzyl groups, which were easily cleaved under Lewis acids such as BCl_3. Selective benzoylation of the primary hydroxyl group of diol **8** followed by selective removal of the primary TBS group gave 1,5-diol **9** in 76% yield.

Recently, Giacomelli and co-workers described the chemoselective oxidation of primary alcohol to aldehyde without no overoxidation to carboxylic acids at room temperature using trichloroisocyanuric acid in the presence



Scheme 2.



Scheme 3.

of catalytic TEMPO [16]. We were interested in extending Giacomelli's reaction condition to compound **9**. It was expected that the primary hydroxyl group of **9** was oxidized to aldehyde followed by the subsequent cyclization to give the desired lactol. Initially, when compound **9** was oxidized with 1.0 equiv. of trichloroisocyanuric acid in the presence of catalytic TEMPO in CH_2Cl_2, the byproduct lactone **10** was formed even the oxidation was carried out at −5 °C. This result showed that compound **9** was overoxidized under Giacomelli's reaction condition. To obtain the single lactone **10**, the oxidation of **9** with 2.0 equiv. of trichloroisocyanuric acid and catalytic TEMPO was carried out. We were pleased to find that the single product **10** was isolated in 72% yield. Treatment of lactone **10** with DIBAL-H allowed efficient reduction of the lactone as well as removal of the benzoyl group to give 4-*O*-benzyl-2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3,3-difluoro-D-ribohexose **11** in 73% yield as a 4:1 mixture of anomers determined by ^{19}F NMR. Finally, compound **11** was deprotected by treatment with 4 M HCl and followed by hydrogenation in the presence of Pd/C to furnish the target molecule 3-deoxy-3,3-difluoro-D-ribohexose **1** in 83% yield as a 4:1 mixture of anomers.

In summary, a novel *gem*-difluorinated sugar 3-deoxy-3,3-difluoro-D-ribohexose **1** has been synthesized from *gem*-difluoromethylene-containing building block **2**. The method was divergent and stereocontrolled and could be easily expanded to synthesize other similar *gem*-difluorinated sugars.

3. Experimental

3.1. General

All reagents were used as received from commercial sources, unless specified otherwise, or prepared as described in the literature. Reactions requiring anhydrous conditions were performed in vacuum flame-dried glassware under nitrogen atmosphere. NMR spectra were recorded on either 300 MHz (^1H NMR), 75 MHz (^{13}C NMR) or 282 MHz (^{19}F NMR, $FCCl_3$ as outside standard and low field is positive). Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hz.

Download English Version:

https://daneshyari.com/en/article/1315101

Download Persian Version:

https://daneshyari.com/article/1315101

Daneshyari.com