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Expeditious synthesis of sulfoazetidine spiro-*C*-glycosides from ketose acetals

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Abstract—Pyranoid and furanoid spiro-*N*-mesyl azetidines, a new type of water-soluble spiro-*C*-nucleoside, have been prepared from easily available sugar spiroacetals (or glycosyl cyanides). The synthetic pathway involves opening of the acetalic ring with trimethylsilylcyanide, reduction, formation of an *N*,*O*-dimesylate, cyclization with sodium hydride in anhydrous DMF, and *O*-deprotection.

1. Introduction

The azetidine ring is an important target of synthetic organic chemistry due to the significant pharmaceutical activities of this four-membered heterocycle. Thus, the β-lactams are well-known antibiotics,[1] and take part in the structure of anticancer drugs;[2] and dihydroazetidines have been recently reported as probiotics.[3] *N*-Tosylazetidines have been used as masked dipoles in heterocyclization reactions.[4] The data on carbohydrate derivatives with azetidine rings are scarce; they are mainly on fused azetidines,[5] and in one case on alditol–azetidines biologically active as glycosidase inhibitors.[6] We have not found antecedents either on spiroazetidine sugar derivatives or on sugar *N*-sulfoazetidines. In this communication, we report the preparation of the water-soluble *N*-sulfospirosugarazetidines **6**, **12**, and **24**, as representative examples of azetidine spiro-*C*-glycosides.[7] The starting materials are the easily available pyranoid (**1**, **7**, and **13**) and furanoid (**18**) sugarspiroacetals with β-D-*ribo* (**1**, **18**) and β-D-*arabino* (**7**, **13**) configurations. The synthetic pathway involves a cyclization step to form the azetidine ring based on reported[8–10] preparations of simple monocyclic azetidines from 1,3 aminoalcohols.

2. Results and discussion

Treatment of the diisopropylidene acetal **1**[11] with trimethylsilyl cyanide, followed by *O*-desilylation with SiO_2 gave the β-D-ribohexulopyranosyl cyanide **2** in 81% yield (Scheme 1). The standard desilylation with tetrabutylammonium fluoride (TBAF)[12] was also attempted, but decomposition took place and the yield was very low. Reduction of **2** with lithium–aluminium hydride gave the non-isolated 1,3-aminohydroxy derivative, which was directly transformed into the sulfoamidoester **4** by reaction with mesyl chloride at rt. Basic treatment (NaH) of **4** in anhydrous DMF produced the spirosulfonamide **5**. Simultaneous removals of the isopropylidene and benzyl groups afforded the water-soluble sulfoazetidine spiro-*C*-nucleoside **6** in 40% overall yield from **1** (six steps).

The ^{13}C NMR spectrum of **2** presented a signal at 118.9 ppm for the cyano group, and the β-configuration for this compound was based on NOE experiments performed on **4**. The two mesyl groups of **4** resonated at 2.99, 2.97 (^{1}H), 40.5 and 37.6 (^{13}C) ppm and its 2D-NOESY spctrum showed strong NOE contacts between the CH_2NHMs and H-3 of the sugar ring confirming β configuration for this group, and consequently for the C≡N group of **2**. The signal for the resonance of the spiro carbon atom of **5** appeared at 72.0 ppm. The ^{13}C NMR spectrum of **6** showed the resonance for C-4 (anomeric carbon in the sugar ring) at 76.4 ppm, this being the sugar carbon atom resonating at lowest field, as in related *O*-unprotected pyranoid spiro-*C*-glycosides of different five-membered heterocycles.[13,14] The resonances for the mesyl group of **6** appeared at 2.93 (CH_3) and 33.9 (CH_3) ppm.

To obtain the *arabino*-spirosulfoazetidine **12** we have started (Scheme 1) from two differently O-protected D-fructose derivatives, the tri-*O*-benzyl spiroacetal **7**[15] and the 4,5-*O*-isopropylidenefructopyranosyl cyanide **14**, which was easily prepared[14] from the spiroacetal **13**.[16] The overall yield was better in the case of **7**. The opening of the spiroacetal ring of **7** to obtain **8** was performed with

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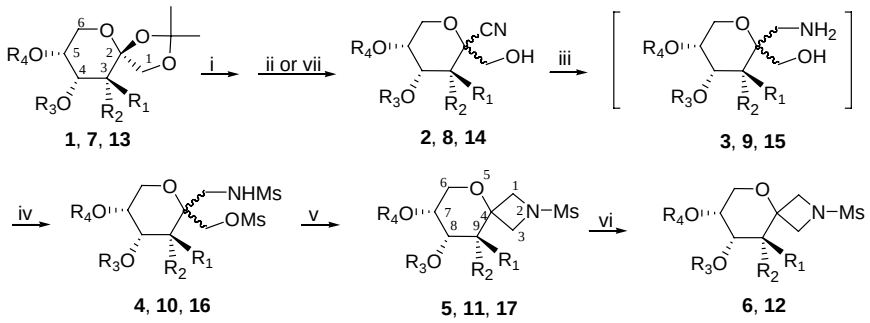

Compound	R_1	R_2	R_3	R_4	Anomers
1	H	OBn	CMe_2		β
2	H	OBn	CMe_2		β
3	H	OBn	CMe_2		β
4	H	OBn	CMe_2		β
5	H	OBn	CMe_2		–
6	H	OH	H	H	–
7	OBn	H	Bn	Bn	β
8	OBn	H	Bn	Bn	α:β
9	OBn	H	Bn	Bn	α:β
10	OBn	H	Bn	Bn	α:β
11	OBn	H	Bn	Bn	–
12	OH	H	H	H	–
13	OBn	H	CMe_2		β
14	OBn	H	CMe_2		β
15	OBn	H	CMe_2		β
16	OBn	H	CMe_2		β
17	OBn	H	CMe_2		–

Scheme 1. Reagents and conditions: (i) TMSCN, TfOTMS, CH_2Cl_2, −20 °C, 2.5 h; (ii) SiO_2, CH_2Cl_2, rt, 24 h; (iii) $LiAlH_4$, Et_2O, rt, 2.5 h; (iv) ClMs/Py, rt, 12 h; (v) NaH, DMF, 2.5 h; (vi) H_2, Pd/C; MeOH, AcOH, rt, 12 h; (vii) TBAF, CH_2Cl_2, rt, 0.5 h.

trimethylsilyl cyanide, but in this case, the use of TBAF was possible. Product **8** was a mixture of anomers (α/β ratio 1:3); the attack of the TMSCN took place preferably by the less hindered pathway to give the β anomer. The mixture was directly used in the next steps, as in both cases the same spiroazetidine is obtained. The ^{13}C NMR spectrum of **8** showed signals at 117.9 (α-anomer) and 116.2 ppm (β-anomer) for the C≡N group. The treatment of **8** and **14** with lithium–aluminium hydride (→ **9**, **15**) followed by reaction with mesyl chloride gave the pair of anomers **10** (β) and **10a** (α), as isolated products, and **16**, respectively.

Cyclization of **10** and **16** (→ **11**, **17**) followed by O-deprotection gave the target spiroazetidine **12** in high yield. The NMR data of **12** supported the proposed structure, being also C-4 the ring carbon atom whose resonance appeared at lowest field (75.7 ppm). The values of the coupling constants $J_{7,8}$ and $J_{8,9}$ (3.0 and 8.5 Hz, respectively) were indicative of *gauche* and antiperiplanar relationships, respectively, between the corresponding protons, and consequently the pyranoid ring of **12** is in the $^1C_4$ (numbering of the sugar ring) conformation in methanol (see Fig. 1).

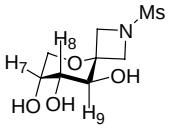

Figure 1. Conformation of compound **12**.

With the aim of preparing furanoid spiroazetidines we have started with the furanosyl cyanide **19**, which was easily prepared[17] from the furanoid spiroacetal **18**.[18] When the same reactions (Scheme 2) were performed on **19**, the sulfonamide spiro-*C*-glycoside **24** was obtained in 37% overall yield from **19**. In this case, the removal of the isopropylidene group was performed with MeOH/HCl (89% yield) and the *O*-debenzoylation with H_2/Pd/C in AcOEt (quantitative).

The key step is the cyclization (Scheme 3) by internal nucleophilic displacement of the mesyloxy group, to afford the spiroazetidine (**5**, **11**, **17**, and **23**). A preparation of *N*-mesylaminoglycosides through non-isolated *N*-mesylaziridines obtained by a related cyclization, has been recently communicated.[19]

In conclusion, we have developed a high yielding six-step synthesis of water-soluble pyranoid and furanoid spiro-*C*-glycosides derived of *N*-sulfoazetidines. The key step is the formation of the azetidine ring, which is promoted by NaH. The stereochemistry is defined by the starting sugar derivative and the reactions are experimentally easy.

3. Experimental

3.1. General methods

A Perkin-Elmer Model 141 MC polarimeter, 1-cm tubes, at 589 nm, was used for measurement of specific rotations.