Carbohydrate Research 345 (2010) 1088–1093

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

An unexpected rearrangement giving a new thiosubstituted carbohydrate

Agathe Martinez, Eric Hénon, Claire Coiffier, Aline Banchet, Dominique Harakat, Jean-Marc Nuzillard, Arnaud Haudrechy *

Institut de Chimie Moléculaire de Reims, UMR CNRS, Université de Reims, BP 1039, F-51687 REIMS Cedex, France

ARTICLE INFO

Article history:
Received 24 November 2009
Received in revised form 16 March 2010
Accepted 18 March 2010
Available online 21 March 2010

Keywords:
Thiosugars
Theoretical
Conformational bias
DFT
Transition state

ABSTRACT

A new thiosubstituted 'D-arabino'-type derivative was obtained from an open carbohydrate via a cascade of four consecutive transformations in a single reaction process. Molecular orbital computations were also performed to explain the stereochemical outcome of the reaction.

1. Introduction

During our studies toward the efficient synthesis of α-*C*-(alkynyl)-galactosides,[1,2] we identified an interesting side-product, the thiosugar **3** (Scheme 1).[3] This unexpected rearrangement, which occurred during the multigram scale-up synthesis of the epoxydithio compound **2**, was solely dependent on reaction conditions and can be explained by the cascade of reactions depicted in Scheme 1.

Intrigued by this unusual transformation, we anticipated that the same kind of reaction could be applied to a formal synthesis of salacinol **4**, a highly potent α-glucosidase inhibitor.[4,5]

As described by Ghavami et al.,[6] the four-carbon sulfated side chain could be easily introduced starting from the known sulfur derivative **5**. Furthermore, anomeric reduction of the thiobenzyl moiety can be performed in two steps ($Hg(OAc)_2$/AcOH followed by Et_3SiH/TMSOTf),[7] giving the well-known sulfur derivative **6** as an interesting target.[8] The followed strategy for the synthesis of compound **6** was directly inspired from our serendipitously discovered rearrangement.[3] Compared to our earlier work, two changes were made to precursor **1**. A TBS group was used in position 5 and the terminal aldehyde was protected as a dithiobenzyl acetal (compound **7**). It was expected that the thiobenzyl group in the final anomeric position would be easier to deprotect (Scheme 2).

2. Results and discussion

The alcohol derivative **11** was easily obtained after several straightforward reactions of the known D-arabinose derivative **8**.[9] The unstable compound **7** (not shown) was then formed by mesylation of **11** in quantitative yield and was used in the next step without further purification. Although the reaction was slow, direct treatment with TBAF at 0 °C cleanly gave a product in 65% yield. It was first speculated that compound **6** had been formed as expected (Scheme 3).

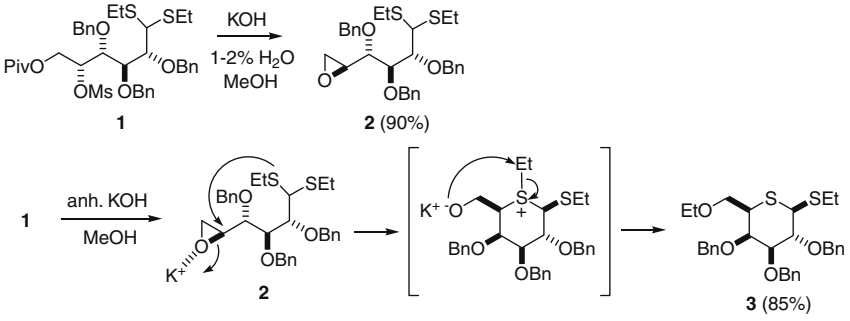
However, comparison of the ^{1}H NMR data (Table 1, see Scheme 3 for numbering) clearly showed that the isolated product was different from the known compound **6**.[8,10]

Moreover, supplementary COSY and HSQC experiments unambiguously showed that the signal for C-1 in our compound appeared at 80.8 ppm. This characteristic deshielding indicated that the anomeric position possessed one oxygen and one sulfur atom. An HMBC experiment confirmed the thioether function with a correlation between H-4 and a S*CH*$_2$Ph, and consequently a pyranose form for this compound. Finally, NOESY experiments showed that spatially, H-4 was closest to H-3 (and H-1 to H-2). This implied that the configuration at C-4 is *R*, and that the anomeric configuration is β. Consequently, the structure of the isolated compound was postulated to be that of **12**.

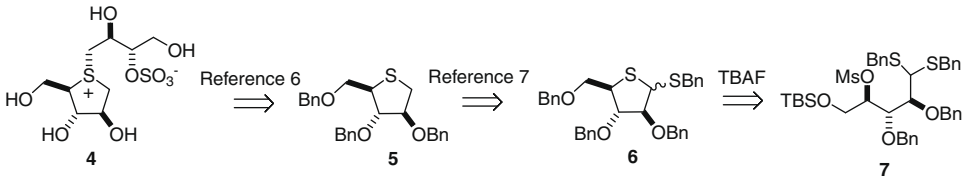
According to the cascade mechanism which had first been envisioned, it was thought that the formation of compound **12** followed an intra-S_N1 mechanism. Indeed, the direct attack of the intermediate alkoxide on the anomeric center via an intra-S_N2 mechanism is impossible because it is governed in this case by a 5-*endo*-Tet

* Corresponding author. Tel.: +33 (0)3 2691 3236; fax: +33 (0)3 2691 3166.
E-mail address: arnaud.haudrechy@univ-reims.fr (A. Haudrechy).

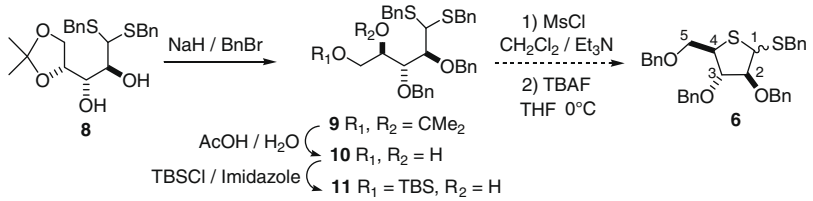
0008-6215/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2010.03.024



Scheme 1. Synthesis of thiosugar **3**.



Scheme 2. Salacinol **4** and target compound **6**.



Scheme 3. Synthesis of the alcohol derivative **11** and approach to salacinol.

process, forbidden by Baldwin's rules (Scheme 4).[11] The observation of an anomerically pure β-product could only result from the final ring-closure occurring on the *Re* face.

Molecular orbital computations were performed to better understand the stereochemical outcome of the reaction. Due to a prohibitive computational cost, the calculations in the present work were performed on a model system obtained by replacing all benzyl groups with methyl groups. According to the proposed mechanism for the formation of **12**, the final ring closing reaction involving the sulfonium cation **B** (Scheme 4) should lead to the two possible isomers of **12**, both adopting $^1C_4$ and $^4C_1$ chair conformations, respectively (Fig. 1).

We decided to first look at the energy levels of the different conformations. When considering destabilizing effects, a maximum number of equatorial groups should favor the **12α$_{eq}$** conformation, but the stabilizing anomeric effect is a good argument in favor of both the **12α$_{ax}$** and **12β$_{ax}$** conformations. We thus decided to calculate the energies of these final structures by carefully estimating the influence of several theoretical levels on the results (Table 2).

As can be seen in Table 2, comparison of PCM values with the gas-phase results indicates that there is no significant solvent effect on the relative energies (entries 1 and 2). This is not surprising owing to the small THF dielectric constant (7.58). The different theory levels used produced consistent results, except the MP2/AUG-cc-pVDZ method (entry 5) which indicated that the **12β$_{eq}$** conformer was less stable than the **12β$_{ax}$** one. CCSD(T) studies could not be achieved due to expensive computational calculations. It was clear however that the experimental β-stereochemistry of the anomeric carbon could not be explained from the relative stability of the final product **12**. Actually, the **12α$_{ax}$** isomer was predicted to be one of the more stable isomers but it was not observed experimentally.

Therefore, in order to explain the reaction selectivity, we examined the final ring-closure mechanism leading to **12**. Only the final formation of the O–C bond was studied. For the sake of simplicity, a B3LYP/6-31G* stretching energy profile was performed for all the possible final structures **12** to characterize the dissociative reaction pathway instead of the bonding one.

Table 1
Comparison of ^{1}H and ^{13}C NMR data of known **6** and the isolated compound **12**

δ in ppm (J in hertz)	**6**	**12**		**6**	**12**
H-1	4.36 (4.6)	4.77 (1.9)	C-1	**52.0**	**80.8**
H-2	4.20 (4.6)	3.42 (1.9, 3.5)	C-2	86.6	76.0
H-3	4.20 (5.0)	3.55 (3.5, 3.1)	C-3	84.9	76.6
H-4	3.47 (5.0, 7.2, 7.3)	3.17 (3.1, 4.7, 10.4)	C-4	47.4	42.7
H-5a	3.55 (7.2, 9.3)	3.63 (10.4, 11.0)	C-5	73.6	66.5
H-5b	3.85 (7.3, 9.3)	3.85 (4.7, 11.0)	SCH_2Ph	35.7	34.7 (C-1)–36.5 (C-4)
SCH_2Ph	3.87	3.80 (C-1)–3.71 (C-4)			