Available online at www.sciencedirect.com
SCIENCE DIRECT®
Carbohydrate Research 338 (2003) 2825–2833
CARBOHYDRATE RESEARCH
www.elsevier.com/locate/carres

Utilization of nosylepimines of 1,6-anhydro-β-D-hexopyranoses for the preparation of halogenated aminosaccharides

Jiří Kroutil,[a,*] Jindřich Karban,[b] Miloš Buděšínský[c]

[a] *Department of Organic Chemistry, Charles University, 128 43 Prague 2, Czech Republic*
[b] *Institute of Chemical Process Fundamentals, Academy of Sciences of the Czech Republic, 160 00 Prague 6, Czech Republic*
[c] *Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, 166 10 Prague 6, Czech Republic*

Received 12 March 2003; accepted 10 July 2003

Abstract

The aziridine ring cleavage of *N*-nosylepimines **3** and **7** having D-*allo* and D-*manno* configurations with halides led regioselectively to *N*-*o*-nitrobenzenesulfonylated 2-halo-3-amino- and 3-halo-2-amino-2,3-dideoxy derivatives of 1,6-anhydro-β-D-glucopyranose **8**–**14** in 59–81% yields. Removal of *o*-nitrobenzenesulfonyl protecting group with benzenethiol afforded aminosaccharides, which were converted into more stable hydrochlorides **15**–**18**.

Keywords: Ring opening reactions; Stereospecific synthesis; NMR data; Aziridines; Nitrobenzenesulfonamides

1. Introduction

Halogenated carbohydrates are known as reactive intermediates involved in the syntheses of complex saccharides (as in reductive dehalogenations,[1–3] glycosidations[4–6]) and as key components of bioactive molecules, in which halogen atoms modify their biochemical and pharmacological properties (as in antibiotics,[1,7–9] enzyme[10–13] or virus[14–16] inhibitors, anticancer chemotherapeutics[17–19]). Fluoro carbohydrates[20,21] (such as 2-deoxy-2-fluoro-D-glucose[22]) are their most important representatives, but other halogens have also been incorporated[23–25] into the sugar molecule. The introduction of a halogen atom into carbohydrate molecule can be accomplished by various methods: nucleophilic displacement[1,23–26] and the cleavage of an oxirane[27–30] and an aziridine[31,32] ring are the most common. We have recently[33] found that *N*-tosylepimines of 1,6-anhydro-β-D-hexopyranoses react with halides by *trans*-diaxial cleavage and have elaborated experimental conditions for aziridine ring cleavage with chloride, bromide, and iodide anions, resulting in regioselective formation of a single isomer of the corresponding sulfonamide. A crucial step in preparing of halogenated amino sugars is the *N*-deprotection of such amides. As the *N*-tosyl group is difficult to cleave,[34,35] we switched to the *o*-nitrobenzenesulfonyl activating group, exploiting its capability for smooth deprotection.[36–40] Here we present aziridine ring cleavage of *N*-*o*-nitrobenzenesulfonylated epimino derivatives (nosylepimines) of 1,6-anhydro-β-D-hexopyranoses with halide (F, Cl, Br, I) anions and subsequent *N*-deprotection of the resultant sulfonamides with benzenethiol.

2. Results and discussion

The nosylepimines **3** and **7** were prepared by sodium borohydride reduction of vicinal azidotosylates **1** and **4** and subsequent sulfonylation using *o*-nitrobenzenesulfonyl chloride in a triethylamine–tetrahydrofuran mixture at −30 °C. The low temperature was necessary to achieve high yields of *N*-*o*-nitrobenzenesulfonylated epimines (cf. Refs. 37,40). The reduction of azidotosylates with $NaBH_4$ gave a better yield of aziridine **2** than

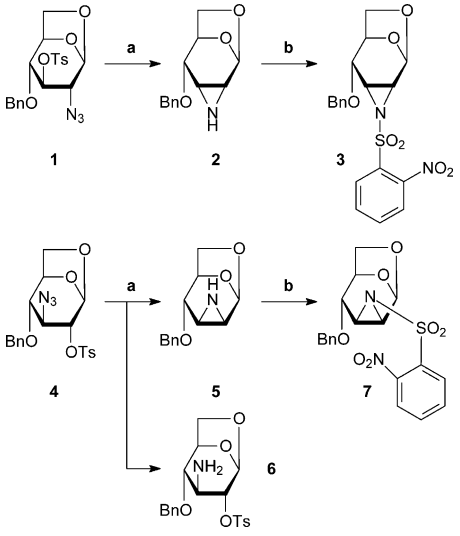
* Corresponding author.
E-mail addresses: kroutil@natur.cuni.cz (J. Kroutil), karban@icpf.cas.cz (J. Karban), milos.budesinsky@uochb.cas.cz (M. Buděšínský).

0008-6215/03/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2003.07.003

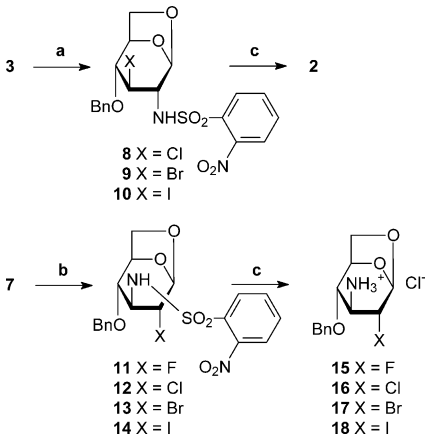
the $LiAlH_4$ reduction used previously[41] (73 vs 59%). In the preparation of epimine **5**, the $NaBH_4$ reduction gave 56% of the D-*manno*-epimine **5** together with 13% of aminotosylate **6** (Scheme 1).

Epimino derivatives **3** and **7** were treated with halides under four reaction conditions (Scheme 2) according to the reactivity of their aziridine rings towards the particular halide.

The D-*allo*-epimino derivative **3** was more reactive and yielded 3-halo-2-amino-2,3-dideoxy derivatives **8**–**10** under the action of concentrated hydrochloric, hydrobromic and hydroiodic acids in methanol at 50 °C (method **A**). Yields were good (66–74%) after recrystallization. The corresponding fluoro derivative was not obtained because of complete decomposition of the epimine **3** under all conditions used (see later). The D-*manno* epimine **7** was more resistant and prolonged heating with HX acids caused only decomposition, and no cleavage products were formed. For successful cleavage, harsher conditions previously reported[33] had to be applied (methods **B**, **C**). Thereafter, the chloro, bromo, and iodo derivatives **12**, **13**, and **14** were formed in 81, 77, and 78% yields, respectively. The introduction of fluorine was still more difficult. The reaction of epimino derivative **7** with neat tetrabutylammonium hydrogen difluoride[42] at 100 °C (method **D**) was found to be the best method, but the fluoro derivative **11** was formed in only modest 59% yield. The yield of **11** depended markedly on the reaction temperature—18% at 80 °C, 59% at 100 °C, and 21% at 200 °C, probably because of competitive decomposition of nosylepimine **7** (cf. Ref. 43). Other reagents examined led either to the recovery of starting material (diethylaminosulfur trifluoride, Olah reagent—pyridinium polyhydrogenfluoride—in wide range of reaction temperatures, from −20 °C up to 80 °C), or to complete



Scheme 1. (a) 1. $NaBH_4$–THF, rt; 2. MeOH, reflux; (b) *o*-NO_2-C_6H_4-SO_2Cl–Et_3N–THF, −30 °C.



Scheme 2. (a) Method **A**: HX–MeOH–H_2O, 50 °C; (b) Method **B**: LiCl+NH_4Cl–Me_2SO, 110 °C; Method **C**: Bu_4NX+NH_4X–toluene, reflux; Method **D**: neat Bu_4NHF_2, 100 °C; (c) 1. PhSH+K_2CO_3–acetone–H_2O, rt; 2. HCl–Et_2O.

decomposition (anhydrous Bu_4NF in acetonitrile, KHF_2 under PTC conditions with dicyclohexano-18-crown-6 in toluene) or yielded only small amount of fluoro derivative **11** (reaction with molten KHF_2 at 240 °C, 33–38%). Tetrabutylammonium hydrogen difluoride has already been reported[44,45] to be an efficient fluorinating reagent, but not until now for the aziridine-ring opening. All cleavage products prepared had the D-*gluco* configuration as predicted by the Fürst–Plattner rule[46] (*trans*-diaxial aziridine-ring opening). No diequatorial isomers were detected in the reaction mixtures.

Halonosylamides **8**–**14** were treated with benzenethiol under alkaline (potassium carbonate) conditions to cleave the *N*-*o*-nitrobenzenesulfonyl group. Derivatives **8**–**10**, after *N*-deprotection in situ, cyclized to yield only the free D-*allo*-epimine **2**. On the other hand, derivatives **11**–**14** readily afforded the corresponding haloaminosaccharides, which were isolated as their hydrochlorides **15**–**18**. Yields were remarkably high, 87–97.5%. This distinctive behavior is due to the rather slow formation of the epimine having the 2,3-*endo*-oriented aziridine ring (cf. Ref. 33) and corresponds with the reactivity of 2-, 3-, and 4-*O*-tosyl derivatives of 1,6-anhydro-β-D-glucopyranose towards alkali-mediated formation of oxirane rings.[47]

The structure of epimino derivatives **3** and **7**, halonosylamides **8**–**14**, and haloamino hydrochlorides **15**–**18** was determined by ^1H and ^{13}C NMR spectroscopy (for NMR data see Tables 1–3). Assignment of protons and carbon atoms was achieved using correlated homonuclear 2D-COSY and heteronuclear ^1H, ^{13}C-2D-HMQC spectra. The presence of the aziridine ring in compounds **3** and **7** is manifested by the upfield shift of their carbon atoms in positions 2 and 3 ($\delta \approx 36$–45 ppm) and characteristic vicinal interproton coupling $J_{2,3} \approx 6.5$–7.0 Hz. The long-range $J_{H,H}$ couplings, typical for compounds having the D-*gluco* configuration

Table 1
Proton chemical shifts (ppm) of compounds **3**, **7**–**14** ($CDCl_3$) and **15**–**18** (CD_3SOCD_3)

Comp.	H-1	H-2	H-3	H-4	H-5	H-6endo	H-6exo	OCH_2	$-C_6H_5$	NH	NBs[a]
3	5.81 um	3.35 dd	3.57 m	3.54 dd	4.48 m	3.68 dd	3.92 dd	4.90 d 4.72 d	7.30–7.40 m	–	8.32 m (H-6'), 7.69–7.81 m (H-3',4',5')
7	5.76 d	3.63 dd	3.35 dd	3.73 bs	4.52 m	3.59 dd	3.64 dd	4.86 d 4.74 d	7.30–7.42 m	–	8.24 m (H-6'), 7.76–7.84 m (H-3',4',5')
8	5.36 t	3.92 dm	3.88 p	3.53 m	4.57 m	4.25 dd	3.73 dd	4.60 d 4.49 d	7.27–7.38 m	6.22 d	8.16 m (H-6'), 7.72–7.81 m (H-3',4',5')
9	5.38 t	4.03 dm	3.88 p	3.65 m	4.56 m	4.34 dd	3.75 dd	4.60 d 4.45 d	7.27–7.37 m	6.23 d	8.16 m (H-6'), 7.72–7.82 m (H-3',4',5')
10	5.42 t	4.07 um	3.97 p	3.74 m	4.55 m	4.44 dd	3.78 dd	4.58 d 4.41 d	7.25–7.37 m	6.27 bd	8.17 m (H-6'), 7.73–7.82 m (H-3',4',5')
11	5.53 m	4.09 dm	3.89 m	3.49 m	4.58 dt	4.00 dd	3.72 ddd	4.76 d 4.67 d	7.32–7.41 m	5.91 bd	8.07 dd (H-3') 7.88 dd (H-6') 7.75 dt (H-5') 7.72 dt (H-4')
12	5.49 q	3.52 dd	4.03 dm	3.52 m	4.59 m	4.06 dd	3.75 dd	4.81 d 4.66 d	7.32–7.43 m	6.11 d	8.08 m (H-6'), 7.75–7.89 m (H-3',4',5')
13	5.55 q	3.54 dd	4.15 dm	3.54 m	4.60 m	4.09 dd	3.75 dd	4.83 d 4.65 d	7.44 m 7.38 m 7.33 m	6.15 bd	8.10 m (H-6'), 7.75–7.89 m (H-3',4',5')
14	5.60 um	3.64 m	4.19 dm	3.58 m	4.59 m	4.14 dd	3.72 dd	4.86 d 4.64 d	7.46 m 7.39 m 7.33 m	6.25 d	8.10 m (H-6'), 7.77–7.90 m (H-3',4',5')
15	5.59 d	4.59 bdd	3.23 dt	3.69 dd	4.83 bd	3.89 dd	3.61 dd	4.71 d 4.61 d	7.44 m 7.37 m 7.31 m	8.79 bs (NH_3^+)	–
16	5.58 d	4.14 dd	3.31 bt	3.75 dd	4.82 m	4.02 dd	3.64 dd	4.67 d 4.64 d	7.43 m 7.37 m 7.31 m	8.80 bs (NH_3^+)	–
17	5.68 d	4.17 dd	3.47 um	3.75 dd	4.81 bd	4.07 dd	3.63 dd	4.69 d 4.65 d	7.43 m 7.37 m 7.31 m	8.76 bs (NH_3^+)	–
18	5.73 d	4.14 dm	3.59 um	3.77 m	4.77 bd	4.14 dd	3.60 dd	4.67 s (2H)	7.44 m 7.37 m 7.30 m	8.64 bs (NH_3^+)	–

[a] – NBs denotes *o*-nitrobenzenesulfonyl.

Table 2
Proton coupling constants (Hz) of compounds **3**, **7**–**14** ($CDCl_3$) and **15**–**18** (CD_3SOCD_3)

Comp. [a]	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6en}$	$J_{5,6ex}$	$J_{6en,6ex}$	J_{gem} (OBn)	$J_{NH,2}$ or $J_{NH,3}$	$J_{1,3}$	$J_{2,4}$	$J_{3,5}$
3 [a,b]	1.2	6.6	5.6	0.9	2.2	6.8	8.2	12.0	–	0.65	~0	1.2
7 [a,b]	3.9	7.0	~0	0.9	2.0	6.7	7.5	12.0	–	~0	~0	1.7
8 [a,f]	2.0	1.8	1.4	1.9	0.9	5.6	7.9	12.1	10.2	1.4	1.3	1.5
9 [a,g]	2.1	1.7	1.5	1.7	0.8	5.5	8.0	12.0	10.1	1.5	1.3	1.5
10 [a,h]	2.3	1.7	1.5	1.6	0.8	5.4	8.0	12.0	*	1.4	1.2	1.5
11 [i]	2.0	2.2	1.85	1.6	0.7	5.1	8.1	12.5	8.4	1.1	1.0	1.4
12 [a,c]	1.2	1.85	1.85	2.2	0.7	5.2	8.2	12.4	8.8	1.15	*	1.5
13 [a,d]	1.3	1.7	1.6	2.4	0.7	5.2	8.1	12.4	8.9	1.1	*	1.5
14 [a,e]	1.8	1.3	1.5	1.9	0.7	5.2	8.1	12.4	8.8	1.0	1.3	1.5
15 [j]	0.6	5.2	5.6	0.7	1.0	5.4	8.2	11.3	–	~0	~0	~0
16	1.0	5.1	4.7	1.0	0.9	5.4	8.3	11.4	–	~0	~0	~0
17	1.1	4.4	4.0	1.1	0.9	5.3	8.4	11.4	–	~0	~0	~0
18	1.2	3.0	3.0	1.0	0.7	5.2	8.6	*	–	~0	0.9	~0

Additional coupling constants (Hz):
[a] $J_{1,5} \leq 0.3$; $J_{1,6en} \sim J_{1,6ex} \leq 0.2$;
[b] $J_{1,4} \leq 0.3$;
[c] $J_{1,4} = 1.1$;
[d] $J_{1,4} = 1.0$;
[e] $J_{1,4} = 0.8$; $J_{2,5} = 0.6$;
[f] $J_{1,4} = 0.7$;
[g] $J_{1,4} = 0.6$;
[h] $J_{1,4} = 0.7$.
[i] $J_{1,4} = 0.7$, $J_{1,F} = 1.6$, $J_{2,F} = 46.1$, $J_{3,F} = 18.0$, $J_{4,F} = 0.8$, $J_{6ex,F} = 1.2$;
[j] $J_{1,F} = 9.0$, $J_{2,F} = 48.7$, $J_{3,F} = 24.0$;
* Value of parameter could not be determined.

(mainly for H-1) were identified by selective homodecoupling experiments with compounds **8**–**14**. These compounds also showed small vicinal couplings $J_{1,2}$, $J_{2,3}$, $J_{3,4}$ and $J_{4,5}$ in the range (1.3–2.4 Hz) typical for 1,6-anhydro-β-D-glucopyranoses adopting the $^1C_4$ form. The character of the halogen atom has practically no effect on vicinal $J_{H,H}$ values in the series of halonosylamides **8**–**10** (having a halogen atom in position 3) and a very small effect in the series of halonosylamides **11**–**14** having the halogen atom in position 2. On the other hand, the series of haloamino hydrochlorides **15**–**18** show generally higher values of $J_{2,3}$ and $J_{3,4}$, indicating a significant population of the boat form ($B_{O,3}$) of the tetrahydropyrane ring in a conformational equilibrium (Scheme 3).

When using the reference values $J_{2,3} \approx J_{3,4} = 1.7$ Hz for the $^1C_4$-form and $J_{2,3} \approx J_{3,4} = 8.8$ Hz for the $B_{O,3}$ (calculated for 3-amino-1,6-anhydro-3-deoxy-β-D-glucopyranose by Grindley et al.[48]), we can observe a decreasing population of the $B_{O,3}$ boat form with decreasing electronegativity (together with increasing van der Waals radius and soft character, cf. Ref. 48) of the corresponding halogen atom: ≈55% (for the fluoro derivative **15**), ≈42% for the chloro derivative **16**, ≈32% for the bromo derivative **17**, and ≈18% for the iodo derivative **18**. The observed $J_{3,4}$ values in **15**–**18** were used for the calculation since the $J_{2,3}$ values are influenced also by the character of the halogen atom. Switching the halogen substituent from fluorine to iodine, the corresponding boat $B_{O,3}$ conformation becomes less polar and unfavorable in such polar solvents as dimethyl sulfoxide (cf. Ref. 48). This corresponds with 3-amino-1,6-anhydro-3-deoxy-β-D-hexopyranose hydrochloride, which was found to exist mainly in the $B_{O,3}$ conformation (90% in dimethyl sulfoxide solution[49]). The significant population of the boat conformation in other derivatives of 3-amino-1,6-anhydro-3-deoxy-β-D-hexopyranose has been reported earlier.[50]

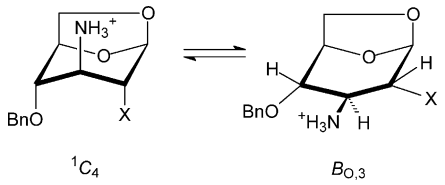
3. Conclusion

Methods for effective aziridine ring-opening of *o*-nitrobenzenesulfonylepimines of 1,6-anhydro-β-D-hexopyranoses with halogen-derived nucleophiles are reported. The smooth *N*-deprotection of the cleavage products using benzenethiol is also demonstrated.

Table 3
^{13}C NMR data of compounds **3**, **7**–**14** ($CDCl_3$) and **15**–**18** (CD_3SOCD_3)

Comp.	C-1	C-2	C-3	C-4	C-5	C-6	Other carbons
3	96.30	40.61	36.34	70.38	75.57	65.72	OBn: 70.09 (OCH_2), 137.14 (C-1′), 127.98 (C-2′,6′), 128.50 (C-3′,5′), 127.97 (C-4′); Nbs: 132.27 (C-1′), 148.32 (C-2′), 124.61 (C-3′), 132.74 (C-4′), 134.58 (C-5′), 131.87 (C-6′)
7	95.86	44.85	36.61	72.49	72.72	65.63	OBn: 71.92 (OCH_2), 137.08 (C-1′), 127.92 (C-2′,6′), 128.59 (C-3′,5′), 128.10 (C-4′); Nbs: 132.16 (C-1′), 148.27 (C-2′), 124.90 (C-3′), 132.63 (C-4′), 134.58 (C-5′), 131.12 (C-6′)
8	100.70	56.24	52.69	76.76	74.05	65.55	OBn: 71.59 (OCH_2), 136.46 (C-1′), 127.97 (C-2′,6′), 128.64 (C-3′,5′), 128.30 (C-4′); Nbs: 134.70 (C-1′), 147.61 (C-2′), 125.49 (C-3′), 133.13 (C-4′), 133.82 (C-5′), 130.19 (C-6′)
9	100.85	56.65	40.61	76.90	74.46	65.86	OBn: 71.59 (OCH_2), 136.46 (C-1′), 128.01 (C-2′,6′), 128.66 (C-3′,5′), 128.32 (C-4′); Nbs: 134.69 (C-1′), 147.62 (C-2′), 125.49 (C-3′), 133.14 (C-4′), 133.83 (C-5′), 130.24 (C-6′)
10	101.11	58.09	12.85	77.92	75.01	66.42	OBn: 71.442 (OCH_2), 136.51 (C-1′), 128.03 (C-2′,6′), 128.66 (C-3′,5′), 128.31 (C-4′); Nbs: 134.73 (C-1′), 147.61 (C-2′), 125.49 (C-3′), 133.18 (C-4′), 133.82 (C-5′), 130.22 (C-6′)
11[a]	98.72 d (26.9)	86.45 d (190.4)	52.75 d (27.4)	75.39	76.06	65.74	OBn: 71.41 (OCH_2), 137.26 (C-1′), 128.02 (C-2′,6′), 128.59 (C-3′,5′), 128.08 (C-4′); Nbs: 133.50 (C-1′), 147.81 (C-2′), 125.59 (C-3′), 133.16 (C-4′), 134.02 (C-5′), 130.90 (C-6′)
12	101.32	54.25	55.03	76.42	75.55	66.00	OBn: 71.28 (OCH_2), 137.21 (C-1′), 128.05 (C-2′,4′,6′), 128.57 (C-3′,5′); Nbs: 133.58 (C-1′), 147.81 (C-2′), 125.58 (C-3′), 133.18 (C-4′), 134.10 (C-5′), 130.77 (C-6′)
13	101.48	43.57	54.88	76.55	75.55	66.06	OBn: 71.17 (OCH_2), 137.18 (C-1′), 128.08 (C-2′,6′), 128.56 (C-3′,5′), 128.04 (C-4′); Nbs: 133.55 (C-1′), 147.82 (C-2′), 125.60 (C-3′), 133.22 (C-4′), 134.14 (C-5′), 130.79 (C-6′)
14	102.79	19.41	55.53	76.81	75.47	66.21	OBn: 70.96 (OCH_2), 137.14 (C-1′), 128.13 (C-2′,6′), 128.55 (C-3′,5′), 128.03 (C-4′); Nbs: 133.54 (C-1′), 147.82 (C-2′), 125.62 (C-3′), 133.30 (C-4′), 134.17 (C-5′), 130.77 (C-6′)
15[a]	98.93 d (32.2)	89.06 d (180.7)	51.76 d (27.3)	76.05 d (7.8)	74.26	66.46	OBn: 70.84 (OCH_2), 137.85 (C-1′), 128.25 (C-2′,6′), 128.42 (C-3′,5′), 127.92 (C-4′)
16	101.46	55.64	53.76	74.31	76.46	66.35	OBn: 70.86 (OCH_2), 137.93 (C-1′), 128.14 (C-2′,6′), 128.41 (C-3′,5′), 127.86 (C-4′)
17	101.50	45.58	53.58	74.19	76.40	66.28	OBn: 70.82 (OCH_2), 137.97 (C-1′), 128.06 (C-2′,6′), 128.40 (C-3′,5′), 127.82 (C-4′)
18	102.64	20.98	53.94	73.90	75.91	66.16	OBn: 70.76 (OCH_2), 138.04 (C-1′), 127.87 (C-2′,6′), 128.40 (C-3′,5′), 127.76 (C-4′)

[a] $J_{C,F}$/Hz shown in parentheses.



Scheme 3.

4. Experimental

4.1. General methods

Melting points were determined on a Boëtius melting-point microapparatus and are uncorrected. The optical rotations were measured on an Autopol III (Rudolph Research, Flanders, NJ) polarimeter at 23 °C. The ^{1}H and ^{13}C NMR spectra were measured on a Varian Unity-500 (^{1}H at 500 MHz and ^{13}C at 125.7 MHz) instrument in $CDCl_3$ (ref.: Me_4Si for ^{1}H and the chloroform signal at δ 77.0 ppm for ^{13}C) at 25 °C. The ^{1}H–^{1}H-COSY and ^{1}H–^{13}C-HMQC techniques were used for the structural assignments. TLC was carried out on Merck DC Alufolien with Kieselgel F_{254} with the following solvent systems: S_1, 3:2 hexane–EtOAc; S_2, 1:1 hexane–EtOAc; S_3, 3:1 hexane–EtOAc. TLC plates were visualized by UV detection at 254 nm and by anisaldehyde solution in H_2SO_4. Column chromatography was performed on silica gel 60 Merck (70–230 mesh ASTM) with hexane–EtOAc gradient elution. The solvents were evaporated on a vacuum rotary evaporator at 40 °C (unless stated otherwise). Light petroleum (PE) refers to the 40–60 °C fraction. *o*-Nitrobenzenesulfonyl chloride (purity 97%) was purchased from Fluka. Bu_4NHF_2 was prepared according to Ref. 42. Reactions were carried out under Ar atmosphere. The ^{1}H NMR spectral parameters are given in Tables 1 and 2, and those of ^{13}C NMR spectra in Table 3.

4.2. Preparation of epimines 3 and 7

4.2.1. General procedure. To a solution of an azidotosylate ($\sim$6 mmol) in anhyd THF (30 mL) was added $NaBH_4$ (2 equiv) and the suspension was stirred at rt. After consumption of the starting azidotosylate (TLC in S_1), MeOH (5 mL) was carefully added dropwise under cooling with an ice-water bath. The mixture was refluxed for the given time, cooled to rt and evaporated under diminished pressure to give a solid residue. The residue was extracted with CH_2Cl_2 (3×10 mL), the combined extracts were stirred with anhyd Na_2SO_4 and charcoal, filtered, and evaporated. The resulting oil was chromatographed on silica gel (50 g) with EtOAc to give pure compounds (free epimines **2**, **5** and aminotosylate **6**). In the next step, a solution of *o*-nitrobenzenesulfonyl chloride (1.5 equiv) in THF (10 mL) was gradually added to the solution of free epimine (**2**, **5**, $\sim$4 mmol) and Et_3N (1.5 equiv) in THF (15 mL) under cooling to -30 °C in a solid CO_2–EtOH bath. The stirring was continued for an additional hour, allowing the temperature rise to -10 °C. The mixture was poured onto crushed ice (200 g) and extracted with CH_2Cl_2 (3×30 mL). The organic layers were washed with 5% HCl, 10% $NaHCO_3$ and water. After drying over anhyd Na_2SO_4 and evaporation of the solvent, the residue was crystallized (EtOAc–Et_2O–PE) to afford nosylepimines **3** and **7**.

4.2.2. 1,6-Anhydro-4-*O*-benzyl-2,3-dideoxy-2,3-(*N*-*o*-nitrobenzenesulfonylepimino)-β-D-allopyranose (3). Prepared from 1,6-anhydro-2-azido-4-*O*-benzyl-2-deoxy-3-*O*-tosyl-β-D-glucopyranose (**1**,[41] 2.55 g, 5.9 mmol) according to the general procedure (6 h reflux). Yield 1.19 g (66%); mp 59–62 °C; $[\alpha]_D$ $-21.5°$ (*c* 0.21, $CHCl_3$). Anal. Calcd for $C_{19}H_{18}N_2O_7S$: C, 54.54; H, 4.34; N, 6.70; S, 7.66. Found: C, 54.25; H, 4.49; N, 6.46; S, 7.66.

4.2.3. 1,6-Anhydro-4-*O*-benzyl-2,3-dideoxy-2,3-(*N*-*o*-nitrobenzenesulfonylepimino)-β-D-mannopyranose (7). Prepared from 1,6-anhydro-3-azido-4-*O*-benzyl-3-deoxy-2-*O*-tosyl-β-D-glucopyranose (**4**, [51] 2.55 g, 5.9 mmol) according to the general procedure (32 h reflux). Yield 1 g (72%); mp 148–149 °C; $[\alpha]_D$ $-75°$ (*c* 0.30, $CHCl_3$). Anal. Calcd for $C_{19}H_{18}N_2O_7S$: C, 54.54; H, 4.34; N, 6.70; S, 7.66. Found: C, 54.35; H, 4.42; N, 6.52; S, 7.54. In addition, 3-amino-1,6-anhydro-4-*O*-benzyl-3-deoxy-2-*O*-tosyl-β-D-glucopyranose (**6**) was isolated. Yield 309 mg (13%); mp 71–72 °C, lit.[51] 70–72 °C; $[\alpha]_D$ $-35°$ (*c* 0.44, $CHCl_3$), lit.[51] $-32°$C.

4.3. Reaction of epimine 3 with HCl, HBr and HI

4.3.1. General procedure. Epimine **3** (100 mg, 0.24 mmol) was dissolved in MeOH (5 mL) and HCl (1.05 mL, 35% wt. solution in water, 12 mmol), HBr (1.4 mL, 46% wt. solution in water, 12 mmol) or HI (0.7 mL, 57% wt. solution in water, 5 mmol) was added. The resulting solution was heated at 50 °C until TLC (S_1) showed no starting material (32 h). After cooling to rt the mixture was poured onto crushed ice (50 g) and the precipitated halo derivative (**8**–**10**) was collected and air-dried. The recrystallization (Et_2O–PE) afforded pure compound.

4.3.2. 1,6-Anhydro-4-*O*-benzyl-3-chloro-2,3-dideoxy-2-(*N*-*o*-nitrobenzenesulfonylamino)-β-D-glucopyranose (8). Yield 71 mg (66%); mp 117–118 °C; $[\alpha]_D$ $-40°$ (*c* 0.18, $CHCl_3$). Anal. Calcd for $C_{19}H_{19}ClN_2O_7S$: C, 50.17; H, 4.21; Cl, 7.79; N, 6.16; S, 7.05. Found: C, 50.16; H, 4.28;Cl, 7.88; N, 6.03; S, 7.07.

4.3.3. 1,6-Anhydro-4-*O*-benzyl-3-bromo-2,3-dideoxy-2-(*N*-*o*-nitrobenzenesulfonylamino)-β-D-glucopyranose (9). Yield 79 mg (66%); mp 141–142 °C; $[\alpha]_D$ −47° (*c* 0.31, $CHCl_3$). Anal. Calcd for $C_{19}H_{19}BrN_2O_7S$: C, 45.70; H, 3.84; Br, 16.00; N, 5.61; S, 6.42. Found: C, 45.56; H, 3.87; Br, 16.08; N, 5.42; S, 6.42.

4.3.4. 1,6-Anhydro-4-*O*-benzyl-2,3-dideoxy-3-iodo-2-(*N*-*o*-nitrobenzenesulfonylamino)-β-D-glucopyranose (10). Yield 96 mg (74%); mp 147–148 °C; $[\alpha]_D$ −56° (*c* 0.36, $CHCl_3$). Anal. Calcd for $C_{19}H_{19}IN_2O_7S$: C, 41.77; H, 3.51; I, 23.23; N, 5.13; S, 5.87. Found: C, 41.65; H, 3.52; I, 23.36; N, 4.93; S, 5.97.

4.4. Reaction of epimine 7 with chloride

4.4.1. Preparation of 1,6-anhydro-4-*O*-benzyl-2-chloro-2,3-dideoxy-3-(*N*-*o*-nitrobenzenesulfonylamino)-β-D-glucopyranose (12). Epimine **7** (314 mg, 0.75 mmol), anhyd LiCl (318 mg, 7.5 mmol), anhyd NH_4Cl (401 mg, 7.5 mmol) and Me_2SO (5 mL) were mixed and heated at 110 °C. The reaction was monitored by TLC (S_1) and stopped after 1 h. The mixture was cooled to rt and poured onto crushed ice. Extraction by CH_2Cl_2 (3 × 20 mL) afforded a solution that was passed through a short column of silica gel (2 g) to remove polar impurities. The effluent was further concentrated to dryness and the residue crystallized (MeOH–Et_2O–PE). Yield 275 mg (81%); mp 124–125 °C; $[\alpha]_D$ −34° (*c* 0.31, $CHCl_3$). Anal. Calcd for $C_{19}H_{19}ClN_2O_7S$: C, 50.17; H, 4.21; Cl, 7.79; N, 6.16; S, 7.05. Found: C, 50.04; H, 4.26; Cl, 7.82; N, 5.97; S, 6.93.

4.5. Reaction of epimine 7 with bromide and iodide

4.5.1. General procedure. A mixture of epimine **7** (314 mg, 0.75 mmol), thoroughly pulverized Bu_4NBr (484 mg, 1.5 mmol), and NH_4Br (294 mg, 3 mmol) or Bu_4NI (554 mg, 1.5 mmol) and NH_4I (435 mg, 3 mmol) in toluene (15 mL) was heated under reflux (the temperature of a silicone oil bath was maintained at 160 °C) with exclusion of water. The reaction was monitored by TLC (S_1) and stopped if no progress was detected (50 and 35 min, respectively). The brown-colored suspension was evaporated to dryness and the solid residue was partitioned between water (30 mL) and CH_2Cl_2 (30 mL). The aqueous layer was extracted twice with CH_2Cl_2 (total 30 mL) and the combined organic layer was washed with water and dried with Na_2SO_4. The CH_2Cl_2 solution was evaporated and the residue chromatographed on silica gel (40–50 g, S_2 solvent) to purify the bromo or iodo derivatives. The halo derivatives obtained were further recrystallized (EtOAc–Et_2O–PE) to afford pure compounds **13**–**14**.

4.5.2. 1,6-Anhydro-4-*O*-benzyl-2-bromo-2,3-dideoxy-3-(*N*-*o*-nitrobenzenesulfonylamino)-β-D-glucopyranose (13). Yield 291 mg (77%); mp 103–104 °C; $[\alpha]_D$ −21° (*c* 0.25, $CHCl_3$). Anal. Calcd for $C_{19}H_{19}BrN_2O_7S$: C, 45.70; H, 3.84; Br, 16.00; N, 5.61; S, 6.42. Found: C, 45.49; H, 3.83; Br, 15.91; N, 5.40; S, 6.49.

4.5.3. 1,6-Anhydro-4-*O*-benzyl-2,3-dideoxy-2-iodo-3-(*N*-*o*-nitrobenzenesulfonylamino)-β-D-glucopyranose (14). Yield 322 mg (78%); mp 145–146 °C; $[\alpha]_D$ −2° (*c* 0.36, $CHCl_3$). Anal. Calcd for $C_{19}H_{19}IN_2O_7S$: C, 41.77; H, 3.51; I, 23.23; N, 5.13; S, 5.87. Found: C, 41.69; H, 3.55; I, 23.27; N, 5.07; S, 5.97.

4.6. Reaction of epimine 7 with fluoride

4.6.1. Preparation of 1,6-anhydro-4-*O*-benzyl-2,3-dideoxy-2-fluoro-3-(*N*-*o*-nitrobenzenesulfonylamino)-β-D-glucopyranose (11).

4.6.1.1. Reaction with KHF_2. Epimine **7** (56 mg, 0.13 mmol) and potassium hydrogen difluoride (630 mg) were mixed and thoroughly pulverized. The mixture was placed in a Pyrex test-tube (10 mL volume) and another portion of pulverized KHF_2 (380 mg) was added without mixing. The test-tube was quickly heated to 240 °C in a silicone oil bath, where the mixture melted and the temperature was maintained for 15 min. The dark brown mixture was further cooled to rt and triturated with CH_2Cl_2 (40 mL). After filtration and evaporation of CH_2Cl_2, the residue was chromatographed on silica gel (12 g, S_2) to afford the pure fluoro derivative **11**. Yield 22 mg (38%, EtOAc–Et_2O–PE); mp 181–182 °C; $[\alpha]_D$ −80° (*c* 0.2, $CHCl_3$). Anal. Calcd for $C_{19}H_{19}FN_2O_7S$: C, 52.05; H, 4.37; F, 4.33; N, 6.39; S, 7.31. Found: C, 51.96; H, 4.60; F, 4.34; N, 6.17; S, 7.41.

4.6.1.2. Reaction with Bu_4NHF_2 at various temperatures. Epimine **7** (42 mg, 0.1 mmol) and tetrabutylammonium hydrogendifluoride (280 mg, 1 mmol) were mixed and being heated with stirring at given temperature until the epimine disappeared (monitored by TLC in S_1). After cooling to rt, the mixture was diluted with EtOAc (1 mL) and the solution chromatographed on silica gel (20 g, S_2) to afford pure fluoro derivative **11**. For 80 °C (4 h heating)—yield 8 mg (18%), for 100 °C (30 min heating)—26 mg (59%), and for 200 °C (2.5 min heating)—9.1 mg (21%). The prepared samples were identical with compound **11** described already.

4.7. Deprotection with benzenethiol

4.7.1. General procedure. The halo derivative (**11**–**14**), anhyd K_2CO_3, anhydrous acetone (5 mL), benzenethiol, and water (0.5 mL) were mixed and stirred at rt until the starting halo derivative disappeared (30–40 min). The

yellow suspension was filtered through a pad of celite, celite washed with EtOH (40 mL), and the combined filtrates were concentrated to a yellow oil. The oil was chromatographed on silica gel (20 g, EtOAc–EtOH, gradient elution) to afford the free amine. The amine was dissolved in EtOH (1 mL) and a 1.4 M HCl solution in Et_2O (1 mL) was added to precipitate the corresponding hydrochloride (**15**–**18**). The solid was filtered off and dried in a vacuum desiccator over P_2O_5. Analytical samples were further recrystallized (EtOH–Et_2O).

4.7.2. 3-Amino-1,6-anhydro-4-*O*-benzyl-2,3-dideoxy-2-fluoro-β-D-glucopyranose hydrochloride (15). Prepared from **11** (126 mg, 0.287 mmol), K_2CO_3 (396 mg, 2.86 mmol) and benzenethiol (90 μL, 0.88 mmol). Yield 81 mg (97.5%); mp 210–213 °C (dec); $[\alpha]_D$ −63° (*c* 0.14, water). Anal. Calcd for $C_{13}H_{17}ClFNO_3$: C, 53.89; H, 5.91; Cl, 12.24; F, 6.56; N, 4.83. Found: C, 53.67; H, 5.92; F, 6.78; Cl, 12.51; N, 4.66.

4.7.3. 3-Amino-1,6-anhydro-4-*O*-benzyl-2-chloro-2,3-dideoxy-β-D-glucopyranose hydrochloride (16). Prepared from **12** (222 mg, 0.49 mmol), K_2CO_3 (670 mg, 4.8 mmol) and benzenethiol (150 μL, 1.5 mmol). Yield 137 mg (92%); mp 200–203 °C (dec); $[\alpha]_D$ −26.5° (*c* 0.3, water). Anal. Calcd for $C_{13}H_{17}Cl_2NO_3$: C, 51.00; H, 5.60; Cl, 23.16; N, 4.57. Found: C, 49.64; H, 5.91; Cl, 22.88; N, 4.29.

4.7.4. 3-Amino-1,6-anhydro-4-*O*-benzyl-2-bromo-2,3-dideoxy-β-D-glucopyranose hydrochloride (17). Prepared from **13** (195 mg, 0.39 mmol), K_2CO_3 (540 mg, 3.9 mmol) and benzenethiol (120 μL, 1.17 mmol). Yield 132 mg (96%); mp 195–197 °C (dec); $[\alpha]_D$ −10° (*c* 0.25, water). Anal. Calcd for $C_{13}H_{17}BrClNO_3$: C, 44.53; H, 4.89; Br, 22.79; Cl, 10.11; N, 3.99. Found: C, 44.71; H, 5.23; Br, 22.76; Cl, 10.14; N, 4.00.

4.7.5. 3-Amino-1,6-anhydro-4-*O*-benzyl-2,3-dideoxy-2-iodo-β-D-glucopyranose hydrochloride (18). Prepared from **14** (250 mg, 0.46 mmol), K_2CO_3 (630 mg, 4.6 mmol) and benzenethiol (140 μL, 1.4 mmol). Yield 159 mg (87%); mp 173–174.5 °C (dec); $[\alpha]_D$ +17.5° (*c* 0.33, water). Anal. Calcd for $C_{13}H_{17}ClINO_3$: C, 39.27; H, 4.31; Cl, 8.92; I, 31.91; N, 3.52. Found: C, 39.05; H, 4.61; Cl, 9.16; I, 31.82; N, 3.66.

Acknowledgements

The authors are grateful for the financial support of the Grant Agency of the Czech Republic (grant No. 203/01/0862) and the Ministry of Education, Youth and Sports of the Czech Republic (MSM 113100001).

References

1. Baer, H. H.; Mateo, F. H.; Siemsen, L. *Carbohydr. Res.* **1990**, *195*, 225–245.
2. Horton, D.; Priebe, W.; Sznaidman, M. L. *J. Org. Chem.* **1993**, *58*, 1821–1826.
3. Fürstner, A.; Baumgartner, J.; Jumbam, D. N. *J. Chem. Soc., Perkin Trans. 1* **1993**, 131–138.
4. Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503–1531.
5. Toshima, K. *Carbohydr. Res.* **2000**, *327*, 15–26.
6. Jona, H.; Mandai, H.; Chavasiri, W.; Takeuchi, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 291–309.
7. Baer, H. H.; Jaworska-Sobiesiak, A. *Carbohydr. Res.* **1985**, *140*, 201–214.
8. Shitara, T.; Umemura, E.; Tsuchiya, T.; Matsuno, T. *Carbohydr. Res.* **1995**, *276*, 75–89.
9. Takahashi, Y.; Ueda, C.; Tsuchiya, T.; Kobayashi, Y. *Carbohydr. Res.* **1993**, *249*, 57–76.
10. Barlow, J. N.; Blanchard, J. S. *Carbohydr. Res.* **2000**, *328*, 473–480.
11. Chapeau, M.-C.; Frey, P. A. *J. Org. Chem.* **1994**, *59*, 6994–6998.
12. Gebler, J. C.; Aebersold, R.; Withers, S. G. *J. Biol. Chem.* **1992**, *267*, 11126–11130.
13. Howard, S.; He, S.-M.; Withers, S. G. *J. Biol. Chem.* **1998**, *273*, 2067–2072.
14. Yao, G.-Q.; Liu, S.-H.; Chou, E.; Kukhanova, M.; Chu, C. K.; Cheng, Y.-C. *Biochem. Pharmacol.* **1996**, *51*, 941–947.
15. Liaw, Y.-C.; Gao, Y. G.; Marquez, V. E.; Wang, A. H. J. *Nucleic Acids Res.* **1992**, *20*, 459–465.
16. Kong, X. B.; Vidal, P.; Tong, W. P.; Chiang, J.; Gloff, C. A.; Chou, T. C. *Antimicrob. Agents Chemother.* **1992**, *36*, 1472–1477.
17. Parker, W. B.; Shaddix, S. C.; Rose, L. M.; Shewach, D. S.; Hertel, L. W.; Secrist, J. A.; Montgomery, J. A.; Bennett, L. L. *Mol. Pharmacol.* **1999**, *55*, 515–520.
18. Parker, W. B.; Shaddix, S. C.; Chang, C. H.; White, E. L.; Rose, L. M.; Brockman, R. W.; Shortnacy, A. T.; Montgomery, J. A.; Secrist, J. A.; Bennett, L. L. *Cancer Res.* **1991**, *51*, 2386–2394.
19. Shafiee, M.; Griffon, J. F.; Gosselin, G.; Cambi, A.; Vincenzetti, S.; Vita, A.; Eriksson, S.; Imbach, J. L.; Maury, G. *Biochem. Pharmacol.* **1998**, *56*, 1237–1242.
20. Dax, K.; Albert, M.; Ortner, J.; Paul, B. J. *Curr. Org. Chem.* **1999**, *3*, 287–307.
21. Tsuchiya, T. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 91–277.
22. Pacák, J.; Černý, M. *Mol. Imag. Biol.* **2002**, *4*, 352–354.
23. Li, T.; Zeng, Z.; Estevez, V. A.; Baldenius, K. U.; Nicolaou, K. C.; Joyce, G. F. *J. Am. Chem. Soc.* **1994**, *116*, 3709–3715.
24. Hadfield, A. F.; Hough, L.; Richardson, A. C. *Carbohydr. Res.* **1980**, *80*, 123–130.
25. Maradufu, A.; Perlin, A. S. *Carbohydr. Res.* **1974**, *32*, 261–277.
26. Mikhailopulo, I. A.; Sivets, G. G. *Helv. Chim. Acta* **1999**, *82*, 2052–2065.

27. Cirelli, A. F.; Mohn, H.; Thiem, J. *Carbohydr. Res.* **1997**, *303*, 417–422.
28. Nikitenko, A. A.; Arshava, B. M.; Mikerin, I. E.; Raifeld, Y. E.; Lee, V. J.; Lang, S. A. *Tetrahedron Lett.* **1992**, *33*, 7087–7088.
29. Černý, M.; Staněk, J. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 23–177.
30. Černý, M. In *Frontiers in Biomedicine and Biotechnology. Levoglucosenone and Levoglucosans, Chemistry and Applications*; Witzcak, Z. J., Ed.; ATL Press: New York, 1994; pp 121–146.
31. Giudicelli, M.-B.; Thomé, M.-A.; Picq, D.; Anker, D. *Carbohydr. Res.* **1993**, *249*, 19–37.
32. Baptistella, L. H. B.; Marsaioli, A. J.; de Souza Filho, J. D.; de Oliveira, G. G.; de Oliveira, A. B.; Dessinges, A.; Castillon, S.; Olesker, A.; Thang, T. T.; Lukacs, G. *Carbohydr. Res.* **1985**, *140*, 51–59.
33. Kroutil, J.; Trnka, T.; Buděšínský, M.; Černý, M. *Eur. J. Org. Chem.* **2002**, 2449–2459.
34. Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, 1994.
35. Greene, T. W.; Nuts, P. G. M. *Protective Groups in Organic Synthesis*; 3rd ed; Wiley: New York, 1999.
36. Mao, H.; Joly, G. J.; Peeters, K.; Hoornaert, G. J.; Compernolle, F. *Tetrahedron* **2001**, *57*, 6955–6967.
37. Maligres, P. E.; See, M. M.; Askin, D.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 5253–5256.
38. Farràs, J.; Ginesta, X.; Sutton, P. W.; Taltavull, J.; Egeler, F.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron* **2001**, *57*, 7665–7674.
39. Fujiwara, A.; Kan, T.; Fukuyama, T. *Synlett* **2000**, 1667–1669.
40. Favre-Réguillon, A.; Segat-Dioury, F.; Nait-Bouda, L.; Cosma, C.; Siaugue, J.-M.; Foos, J.; Guy, A. *Synlett* **2000**, 868–870.
41. Karban, J.; Buděšínský, M.; Černý, M.; Trnka, T. *Collect. Czech. Chem. Commun.* **2001**, *66*, 799–819.
42. Landini, D.; Molinari, H.; Penso, M.; Rampoldi, A. *Synthesis* **1988**, 953–955.
43. Kroutil, J.; Karban, J.; Trnka, T.; Buděšínský, M.; Černý, M. *Collect. Czech. Chem. Commun.* **2002**, *67*, 1805–1819.
44. Albanese, D.; Landini, D.; Maia, A.; Penso, M. *J. Mol. Catal. A Chem.* **1999**, *150*, 113–131.
45. Bosch, P.; Camps, F.; Chamorro, E.; Gasol, V.; Guerrero, A. *Tetrahedron Lett.* **1987**, *28*, 4733–4736.
46. Fürst, A.; Plattner, P.A. In *12th Internat. Congr. Pure & Appl. Chem.* Abstract of Papers, New York, 1951; p. 409.
47. Černý, M.; Staněk, J.; Pacák, J. *Collect. Czech. Chem. Commun.* **1969**, *34*, 849–856.
48. Grindley, T. B.; Cude, A.; Kralovic, J.; Thangasara, R. *Frontiers in Biomedicine and Biotechnology. Levoglucosenone and Levoglucosans, Chemistry and Applications*; ATL press: New York, 1994; pp 147–164.
49. Trnka, T.; Černý, M.; Buděšínský, M.; Pacák, J. *Collect. Czech. Chem. Commun.* **1975**, *40*, 3038–3045.
50. Krečmerová, M.; Černý, M.; Buděšínský, M.; Holý, A. *Collect. Czech. Chem. Commun.* **1989**, *54*, 2753–2766.
51. Černý, M.; Elbert, T.; Pacák, J. *Collect. Czech. Chem. Commun.* **1974**, *39*, 1752–1767.