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Stereoselective synthesis of azasugar thioglycosides

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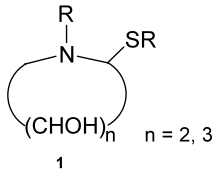
Abstract—Bicyclic (2-oxapyrrolizidines) and monocyclic (piperidine) azasugar ethyl thioglycosides, a new type of azasugar derivative, are stereoselectively prepared from suitable glycosylenamines, through anhydroazasugar derivatives.

The thioglycosides, a type of glycoside in which the anomeric oxygen atom has been substituted by a sulphur atom, are interesting compounds as the stability of the thioglycosidic linkage in enzymatic processes involving the corresponding *O*-glycosides has been reported,[1] and consequently, they are inhibitors of glycosidases.[2] The thioglycosides have also been used as chiral inductors in enzymatic syntheses.[3] At the same time, the azasugars (iminocyclitols), and among them polyhydroxylated-pyrrolizidines, belong to an important class of alkaloids having glycosidase- and glycosyltransferase-inhibitory properties.[4] They are useful, not only as biological tools for studying the biofunctions of oligosaccharides,[5] but also as potential drugs to treat a variety of carbohydrate-mediated diseases.[6–10]

Over the past decade, much interest has arisen in the preparation of iminocyclitols, in many cases, the control of the stereochemistry being an important problem.[11] The data on 2-thioalcoxy derivatives of iminocyclitols (**1**), that is azasugar thioglycosides, are very scarce, and limited to thioanalogues of the bicyclic alkaloids australine and castanospermine[12–14] having the sulphur atom in the ring.

In this communication, we report on the stereoselective preparation of bicyclic (**7**–**9**, **14**–**16**, **7a**) and monocyclic (**19**) azasugar ethyl thioglycosides, which can also be considered thioalkoxy alkaloid derivatives (Scheme 1). The starting materials are glycosylenamines with D-gluco (**2**), D-xylo (**3**),[15] L-rhamno (**10**),[15] and D-ribo (**17**),[16] configurations. The key intermediates are the anhydroazasugars **4**–**6**, **11**–**13**, and **18**, which were prepared through conventional strategies[17] using appropriate *O*-protecting groups.



1

Reaction of β-D-glucopyranosylenamine **2**[15] with *p*-methoxybenzaldehyde dimethyl acetal quantitatively gave the corresponding 4,6-*O*-*p*-methoxybenzylidene derivative, which was 2,3-di-*O*-benzoylated with benzoyl chloride/pyridine and reduced with sodium cyanoborohydride to have the partially *O*-protected glucosylenamine **20**. Successive treatments of **20** with mesyl chloride and sodium methoxide/DMF afforded the anhydroazasugar **4** in high yield. The 2,3-di-*O*-mesyl derivatives **5** and **6**[18] were prepared from the D-gluco (**2**) and D-xylo (**3**) pyranosylenamines, respectively.

Reaction of **4**–**6** with ethanethiol in dichloromethane in the presence of PTSA and at rt for 5 min produced the ethyl thioglycosides of azasugars **7**–**9**, respectively, in virtually quantitative yield. Scheme 2 shows the mechanism of formation of **7**–**9** taking **7** as example. *O*-Protonation of **4** with PTSA produced **21**, increasing the electrophilicity of the anomeric carbon. The attack of ethanethiol on **21** produces the ethylthiopyrrolidine **22**, which by internal cycloaddition of the OH on the carbon–carbon double bond gave the 2-oxapyrrolizidine **7**.[19] Compound **7** (98% yield) is formed as a pair of 5*R* and 5*S* diasteroisomers in a 1:4 ratio. NOE experiments performed on **7** (Fig. 1) confirmed the configuration of C-5 and C-3. The cycloaddition reaction was completely stereoselective (only the product with 3*R* configuration was formed) and the attack of the EtSH was 80% stereoselective.

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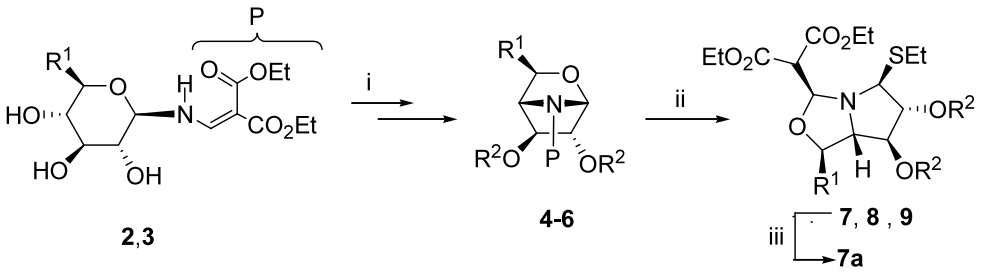
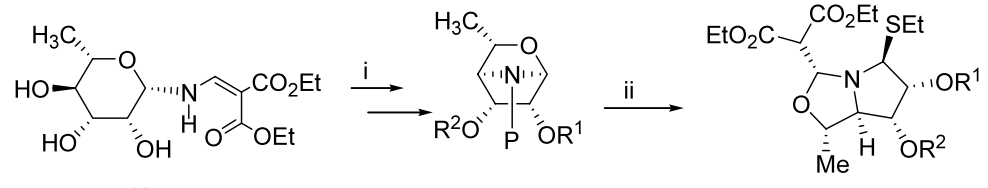
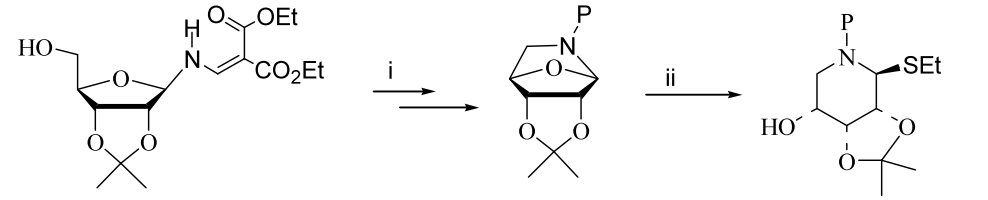


2,3 4-6



10 11-13 14-16

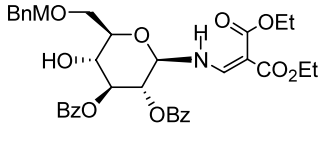


17 18 19

2	R^1 = CH_2OH; Conf. D-*gluco*
3	R^1 = H; Conf. D-*xylo*
4	R^1 = CH_2OMBn; R^2 = Bz; Conf. D-*galacto*
5	R^1 = CH_2OTr; R^2 = Ms; Conf. D-*galacto*
6	R^1 = H; R^2 = Ms; Conf. L-*arabino*
7	R^1 = CH_2OMBn; R^2 = Bz
7a	R^1 = CH_2OMBn; R^2 = H
8	R^1 = CH_2OH; R^2 = Ms
9	R^1 = H; R^2 = Ms

11	R^1, R^2 = $CH(C_6H_4OCH_3$-*p*); Conf. L-*talo*
12	R^1, R^2 = CMe_2; Conf. L-*talo*
13	R^1 = R^2 = Bz; Conf. L-*talo*
14	R^1 = R^2 = H
15	R^1, R^2 = CMe_2
16	R^1 = R^2 = Bz
17	Conf. D-*ribo*
18	Conf. D-*ribo*

Scheme 1. *Reagents and conditions*: (i) several steps depending on the protecting groups (see text); (ii) EtSH, CH_2Cl_2 (DMF for **19**), PTSA, rt, 5 min (60 min for **19**); (iii) NaOMe/MeOH.



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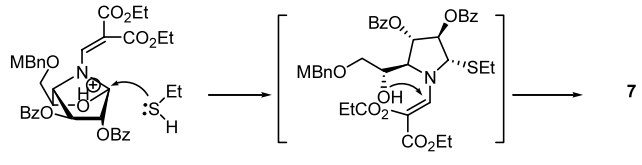
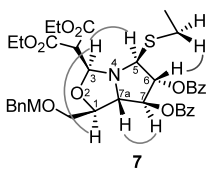


21 22

Scheme 2. Formation of **7**.

O-Debenzoylation of **7** with NaOMe quantitatively yielded the dihydroxythioethoxy-2-oxapyrrolizidine **7a**.[20]

The L-*talo*-anhydroazasugars **11**–**13** were prepared from L-rhamnopyranosylenamine (**10**).[15] The 2,3 selective *O*-acetalation with *p*-methoxybenzaldehyde dimethyl acetal, followed by *O*-mesylation (→**23**) and reaction with sodium methoxide, gave **11**. Compound **13** was obtained from **23** by removing the *p*-methoxybenzylidene group followed by *O*-benzoylation. A two-

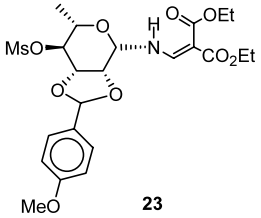


7

Figure 1. NOE experiments on **7**.

step transacetalation of **23** and reaction with sodium methoxide afforded the isopropylidene derivative **12**.

When compounds **11**–**13** were treated with ethanethiol, in a similar way to that commented above for **4**–**6**, the thioglycosides **14**–**16** were isolated. In the case of **11**, the ethanethiol remove the benzylidene group and the fully unprotected oxapyrrolizidine **14** was obtained. For **14**–**16** only the 3*R* stereoisomer was formed and the stereocontrol on the configuration of C-5 was lower than for **7**. In the case of **15** the isopropylidene group remained after the reaction with EtSH. For **14** and **16** the yields were 60 and 98%, whereas for **15** was only 50%, which suggest that the vicinal *O*-protection (isopropylidene ring) hinders the cyclisation. The stereochemistry of **14** was confirmed by NOE experiments.



23

Compound **18** was prepared from **17**[16] by successive treatments with mesyl chloride and sodium methoxide. Reaction of **18** with ethanethiol and PTSA in DMF yielded (90%) the azasugar thioglycoside **19**,[21] which was characterized in a similar way to **7**–**9**, **14**–**16**, and **7a**. The attack of EtSH was 100% stereoselective.

In conclusion, we have developed a method to prepare bicyclic and monocyclic azasugar ethyl thioglycosides from anhydroazasugars, which are easily obtained from glycosylenamines. The thioethoxy group is introduced through a highly stereoselective substitution. In the case of bicyclic compounds, 2-oxapyrrolizidines, the formation of the oxazolic ring is 100% stereoselective. The scope and limitations of the method are currently under study in our laboratory.

Acknowledgements

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18. For the preparation of compound **6** see reference 11d.
19. Selected spectroscopic data for (1*S*,3*S*,5*S*,6*R*,7*S*,7a*S*) 6,7-dibenzoyloxy-3-diethoxycarbonylmethyl-5-ethylthio-1-*p*-methoxybenzyloxymethyl-2-oxapyrrolizidine (**7**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (dd, 1H, $J_{5,6}=6.3$, $J_{6,7}=3.7$, H-6), 5.61 (d, 1H, $J_{3,CH}=8.8$, H-3), 5.34 (dd, 1H, $J_{7,7a}=1.8$, H-7), 4.35 (d, 1H, $J_{5,6}=6.3$, H-5), 4.33 (m, 1H, H-1), 3.80 (dd, 1H, $J_{1,7a}=8.0$, $J_{7,7a}=1.8$, H-7a), 3.78 [d, 1H, $CH(CO_2Et)_2$], 3.77–3.70 (m, 2H, H_2COMBn), 2.72, 2.66 (each dq, each 1H, $^2J_{H,H}=11.5$, $^3J_{H,H}=7.5$, SCH_2CH_3). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 95.2 (C-3), 80.8 (C-1), 80.4 (C-6), 79.0 (C-7), 72.1 (C-5), 69.6 (C-7a), 69.0 (H_2COMBn), 58.5 [$CH(CO_2Et)_2$], 22.3 (SCH_2CH_3). HRCIMS m/z obsd. 722.2608 calcd for $C_{38}H_{44}NO_{11}S$ 722.2635.
20. Selected spectroscopic data for (1*S*,3*S*,5*S*,6*R*,7*S*,7a*S*) 3-diethoxycarbonylmethyl-5-ethylthio-1-*p*-methoxybenzyloxymethyl-2-oxapyrrolizidine (**7a**). ^{1}H NMR (500 MHz, MeOD) δ 5.41 (d, 1H, $J_{3,CH}=8.5$, H-3), 4.35 (m, 1H, H-1), 4.20–4.15 (m, 3H, H-5, 6, 7), 4.10 (m, 1H, H-7a), 3.73 [d, 1H, $CH(CO_2Et)_2$], 2.65–2.55 (m, 2H, SCH_2CH_3). HRCIMS m/z obsd. 514.2112 calcd for $C_{24}H_{36}NO_9S$ 514.2111.
21. Selected spectroscopic data for (2*S*,3*R*,4*R*,5*R*) 1-diethoxycarbonylvinyl-2-ethylthio-5-hydroxy-3,4-*O*-isopropylidenepiperidine (**19**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 1H, HC=), 4.63 (d, 1H, $J_{2,3}=3.0$, H-2), 4.61 (m, 1H, H-5), 4.51 (dd, 1H, $J_{3,4}=7.7$, H-3), 4.40 [dd, 1H, $J_{4,5}=1.7$, H-4), 3.50 (dd, 1H, $J_{5,6a}=6.2$, $J_{6a,6b}=11.9$, H-6a), 3.07 (dd, 1H, $J_{5,6b}=11.0$, H-6b), 2.63, 2.61(each dq, each 1H, $^2J_{H,H}=13.0$, $^3J_{H,H}=7.5$, SCH_2CH_3). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 150.0 (HC=), 96.2 (=C), 76.2 (C-4), 72.9 (C-3), 68.9 (C-2), 63.4 (C-5), 46.3 (C-6), 25.7 (SCH_2CH_3). HREIMS m/z obsd. 403.1666 calcd for $C_{18}H_{29}NO_7S$ 403.1665.