Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 603–615

Anhydroazasugars as key intermediates in the stereocontrolled preparation of azasugars and their ethyl thioglycosides

José Fuentes,* Francisco J. Sayago, José M. Illangua, Consolación Gasch, Manuel Angulo and M. Ángeles Pradera

Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, Apartado 553, E-41071 Sevilla, Spain

Received 12 September 2003; revised 19 December 2003; accepted 5 January 2004

Abstract—Bicyclic azasugar thioglycosides, a new type of azasugar and alkaloid derivative, are stereoselectively prepared from easily available glycosylenamines (D-gluco and L-rhamno configurations), via 1,4-anhydroazasugar derivatives. Polyhydroxylated pyrrolidines (nonreducing pyrrolidine azasugars) are also prepared by reduction with sodium cyanoborohydride of the same 1,4-anhydroazasugars. The stereochemical assignments of the new stereogenic centres are based on NMR experiments, including a study of the interproton distances from quantitative treatment of NOE data and molecular modeling.

1. Introduction

The stereocontrolled preparation of highly functionalized molecules, as natural and pharmaceutically important products, is currently a challenge in organic chemistry.[1] In these syntheses, key compounds with defined stereogenic properties are frequently generated, to be later transformed into the desired target. Among such intermediates are carbohydrate derivatives because they have numerous stereogenic centres and, due to their conformational properties, can be used in highly stereoselective reactions.[2] During the last few years, we have described 1,4-anhydroazasugars[3] and 1,6-anhydroazasugars,[4] which are easily prepared from inexpensive glycosylamines, and have been used, as versatile intermediates, in the stereocontrolled preparation of 4-aminosugars,[3] of seven-membered iminocyclitols[4] and of *N*-vinyl derivatives of O-protected hydroxypyrrolidines.[3]

At the same time, the wide range of physiological and pathological processes controlled by glycosidases has stimulated the isolation from natural sources and the syntheses of specific inhibitors of such enzymes.[5] Among these inhibitors are azasugars (for instance polyhydroxylated pyrrolidines and pyrrolizidines, which can be considered as alkaloid derivatives mimicking the structure of monosaccharides[6]), and thioglycosides, a type of glycoside in which the anomeric oxygen atom has been substituted by a sulfur atom.[7] The thioglycosides have also been used as chiral inductors in enzymatic syntheses.[8] As a consequence of their enzyme-inhibitory activity, both types of compounds have been tested as potential drugs to treat a variety of carbohydrate-mediated diseases.[9,10]

The bibliographic data on iminocyclitol derivatives having a thioalkoxy group on the pseudoanomeric carbon atom, that is azasugar thioglycosides, are very scarce, and limited to thioanalogues of the indolizidine alkaloid castanospermine having the sulfur atom taking part in the five-membered ring.[11]

Continuing our work on the chemistry of anhydroazasugars,[3,4] herein we present the preparation of the D-*galacto* **6** and L-*talo* **18** and **23** derivatives from readily available glycosylenamines **1** and **13**, and their use, as key intermediates, in the stereoselective synthesis of the dihydroxypyrrolidines **8** and **20**, and of the azasugar ethyl thioglycosides, or thioalkoxy alkaloid derivatives, **11**, **12**, **24** and **25**. The imino-D-galactitol **9** is an inhibitor of *E. coli K12* UDP-Gal mutase and micobacterial galactan biosynthesis,[12] and several multistep and/or low overall yielding syntheses of this compounds have been reported. One of these synthesis[12] starts from an aldolactone, and uses a strategy involving the formation of the pyrrolidine ring by reaction of benzylamine with a 1,4-di-*O*-mesyl acyclic D-glucose derivative. Other syntheses start from sugar acetals,[13]

* Corresponding author. Tel.: +34-954557150; fax: +34-954624960; e-mail: jfuentes@us.es

0957-4166/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2004.01.003

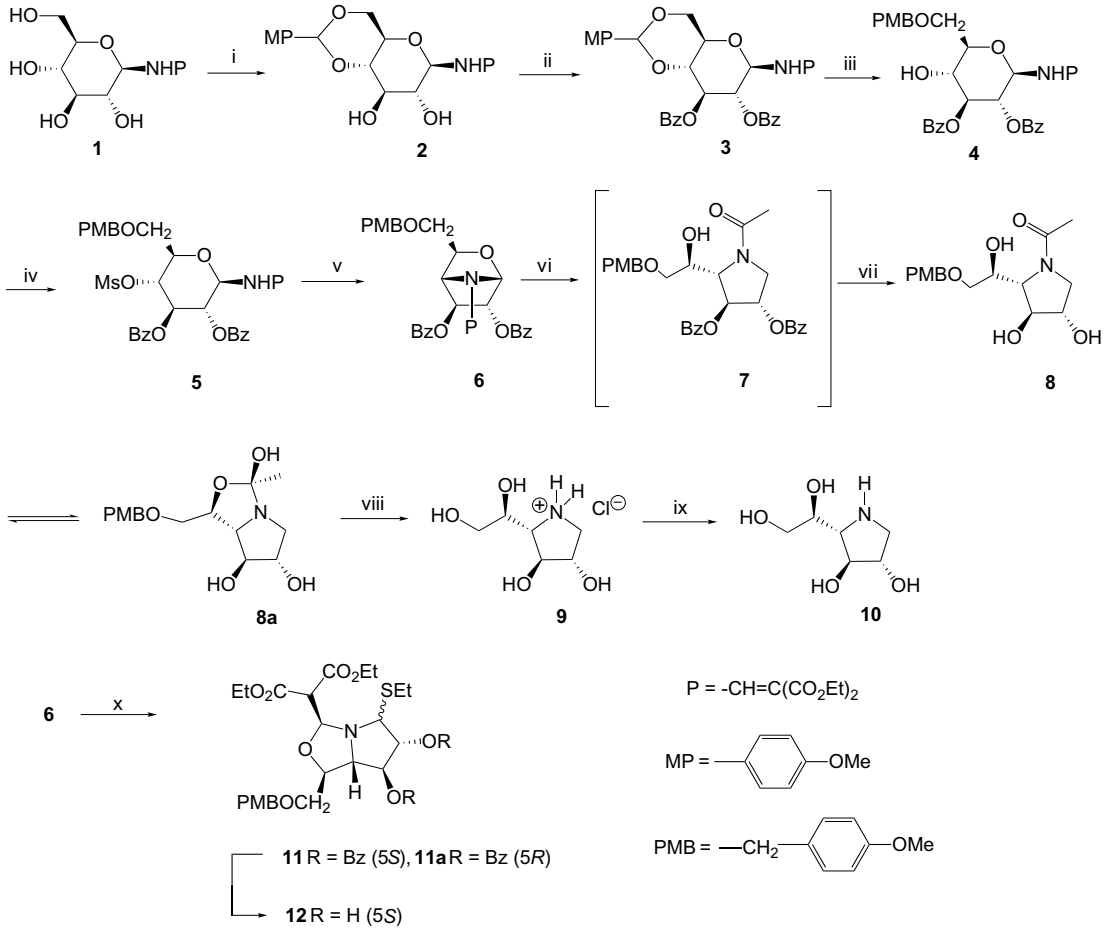
α-glycosides,[14] pyrrole-1-nitrones,[15] and glucose dithioacetal.[16] The hydroxypyrrolidine **22** has not been previously reported, although the hydrochloride of its enantiomer has been prepared[17] from a lactam. Our previous results on azasugar thioglycosides have been recently communicated.[18]

2. Results and discussion

2.1. Synthesis and structure

The preparation of the anhydroazasugars was based on the capacity of the diethoxycarbonylvinyl group to stabilize an amide ion[3,4] and to produce internal S_N2 reactions in suitably substituted sugar derivatives. The starting material for **6** (Scheme 1) was the β-D-glucopyranosylenamine **1**,[19] which by reaction with anisaldehyde dimethyl acetal produced the 4,6-*O*-*p*-methoxybenzylidene acetal **2**. Di-O-benzoylation of **2** (→**3**), followed by reduction with sodium cyanoborohydride gave the partially O-protected glucosylenamine **4**, which by successive reactions with mesyl chloride (→**5**) and sodium methoxide produced the anhydroazasugar **6** in high yield. Treatment of **6** with sodium cyanoborohydride in acetic acid caused N-deprotection, reduction of the anomeric carbon and N-acetylation with formation of the pyrrolidine derivative **7**, which was not purified and characterized only by FABMS. In situ treatment of **7** with a catalytic amount of sodium methoxide afforded **8** in 77% yield from **6**. The NMR data in methanol-d_4 of **8** showed the presence of the 2-oxapyrrolizidine **8a** (minor product), coming from the internal addition of the OH on the carbonyl group. Compound **8a** was not isolated and is in equilibrium, in the NMR tube, with **8**. Its ^{13}C NMR data are included in the Experimental section. Simultaneous N- and O-deprotection of **8** with 1 M HCl in methanol yielded (95%) the target iminocyclitol **10**, whose NMR data as ammonium hydrochloride **9** and as the free base were consistent with those previously reported.[12] The overall yield of the sequence **1**–**10** is 23.1%.

The structures of compounds **2**–**6** and **8** were based on analytical and spectroscopic data (see Tables 1 and 2, and experimental). For stereochemical assignments see Section 2.2. The benzoylation of the HO-2 and HO-3 in **3**, and the mesylation of HO-4 in **5** were evident from the deshielding in the resonances of H-2, H-3 and H-4,



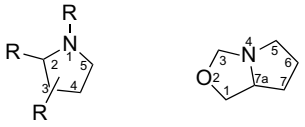
Scheme 1. Reagents and conditions: (i) anisaldehyde dimethyl acetal, DMF/PTSA, 50 °C/20 mmHg, 1 h; (ii) ClBz/Py, rt, 24 h; (iii) $NaBH_3CN$/AcOH, rt, 2.5 h; (iv) ClMs/Py, rt, 24 h; (v) NaOMe/DMF, 45 °C/20 mmHg, 15 min; (vi) $NaBH_3CN$/AcOH, rt, 24 h; (vii) NaOMe (catalytic)/MeOH, rt, 6 h; (viii) MeOH/HCl, 65 °C, 1 h; (ix) Dowex 50w8x; (x) EtSH/Cl_2CH_2/PTSA, rt, 15 min; (xi) NaOMe (catalytic)/MeOH, rt, 4 h.

Table 1. Selected NMR spectroscopic data (δ, ppm; J, Hz) for compounds **2**–**6**, **14**–**18** and **23** at 500 MHz

	Sugar ring							Enamino moiety			
	δH-1	$\delta J_{1,2}$	δH-2	δH-3	δH-4	δC-1	δC-4	δNH	$\delta=CH$	$\delta=CH$	$\delta=C$
2[a]	4.68t	8.6	3.29m	3.46m	3.40t	88.6	80.2	9.13dd	8.04d	158.1	91.3
3[b]	4.84t	8.9	5.52t	5.89t	3.93t	87.8	78.4	9.37dd	7.98d	157.4	94.9
4[c]	5.23t	9.1	5.41t	5.68t	4.05m	87.3	69.4	9.30dd	8.15d	158.5	94.7
5[b]	4.74t	9.3	5.44t	5.84t	5.17t	87.4	74.2	9.28dd	7.96d	157.1	95.1
6[b]	5.83d	2.2	5.14m	5.11d	4.76s	88.1	65.1	—	7.69s	145.9	100.1
14[b]	4.76dd	2.0	4.27dd	4.39dd	3.54t	84.7	71.3	9.42dd	8.04d	158.0	93.8
15[b]	4.79dd	1.5	4.37dd	4.60dd	4.51dd	84.6	79.9	9.42dd	8.02d	157.7	94.5
16[b]	4.61dd	<0.5	4.11br s	3.78dd	4.47t	85.8	82.0	9.52dd	8.04d	158.0	93.7
17[b]	5.01dd	1.2	5.90dd	5.51dd	4.90t	84.8	77.9	9.45dd	8.07d	156.9	94.6
18[b]	5.58br s	<0.5	5.37dd	5.31d	4.67br s	89.6	65.6	—	7.69s	146.3	98.9
23[b]	5.36br s	<0.5		4.44m		89.1	66.3	—	7.79s	146.5	99.5

[a] In DMSO-d_6.
[b] In $CDCl_3$.
[c] In $(CD_3)_2CO$.

Table 2. Selected NMR δ values (ppm) for pyrrolidines **8**, **20**, and pyrrolizidines **11**, **11a**, **12**, **24**, **24a**, **25** and **25a** at 500 MHz

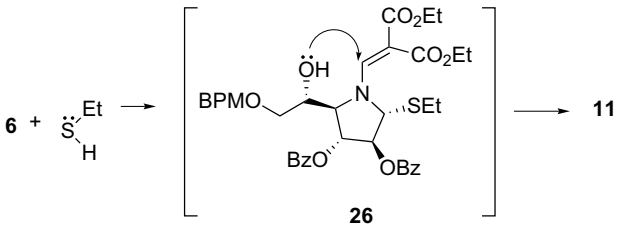


8, **20** **11**, **11a**, **12**, **24**, **24a**, **25**, **25a**

	Heterocyclic moiety										Aglycone	
	H-1	H-2	H-3	H-5	H-7a	C-1	C-2	C-3	C-5	C-7a	NC=O	CH_2	CH_2
8[a]	—	4.13–4.10	4.15	3.87 3.42	—	—	67.5	79.0	55.5	—	172.8	—	—
20[b]	—	3.90	3.96	3.61 3.38	—	—	69.4	74.7	56.4	—	173.8	—	—
11[a]	4.33	—	5.61	4.35	3.80	80.8	—	95.2	72.4	69.0	—	2.74 2.67	22.3
11a[a]	4.17	—	5.82	4.92	3.62	82.6	—	91.5	72.1	65.8	—	2.65 2.54	28.1
12[b]	4.35	—	5.41	4.20–4.15	4.10	79.8	—	95.8	72.0	70.9	—	2.65 2.55	22.0
24[b]	3.67	—	5.56	4.29	3.09	79.1	—	90.3	74.9	74.4	—	2.67	27.7
24a[b]	3.65	—	5.26	4.43	3.27	77.4	—	96.4	76.2	75.0	—	2.58 2.57	25.1
25[a]	4.51	—	5.68	4.51	3.48	79.6	—	90.5	72.6	72.6	—	2.78	27.5
25a[a]	3.97	—	5.35	4.72	3.53	78.2	—	96.2	72.5	72.8	—	2.63	25.2

[a] In $CDCl_3$.
[b] In CD_3OD.

when they were compared with the same signals in the parent compounds **2**, and **4**. The ^{1}H NMR spectrum of **6** had no signal for NH, and showed a singlet (7.69 ppm) for the HC= of the enamino moiety (=$CHNR_2$) instead of the doublet (=CHNHR) of the parent compounds **2**–**5**. The signal for H-1 was downfield shifted, whereas the resonances for H-4 and C-4 were 0.41 and 9.1 ppm, respectively, upfield shifted as corresponds to the substitution of an ester group by an enamino group.[3] The formation of **6** involves a strong change in the conformation of the sugar ring, which produces important changes in the values of all the ring coupling constants, these values being in agreement with that expected for the $B^{1,4}$ conformation. The monocyclic structure of **8** is supported on its ^{13}C NMR signals at δ 22.7 (N–COCH_3) and 172.8 (N–$COCH_3$) ppm, which are in agreement with the presence of an *N*-acetyl group.[20] The ^{13}C NMR signal for C-3 of **8a** appeared at 114.7 ppm as



Scheme 2. Formation of **11**.

corresponds to a carbon atom simultaneously bonded to two oxygens and one nitrogen.[21]

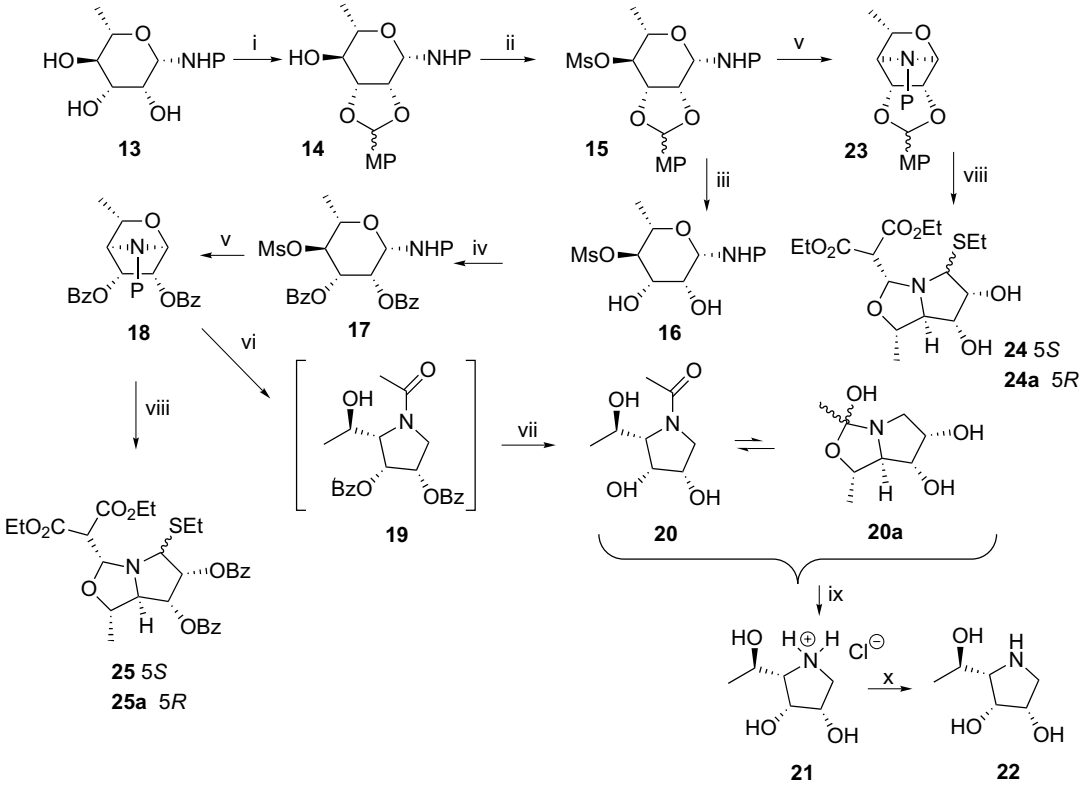
Reaction of **6** with ethanethiol in dichloromethane in the presence of *p*-toluensulphonic acid (PTSA) at rt for 15 min produced a diastereoisomeric mixture of the ethyl thioglycosides of azasugars **11** (3*S*,5*S*) and **11a** (3*S*,5*R*) in virtually quantitative yield, the **11**/**11a** ratio being 4:1. In the formation of **11** and **11a** (similarly for the formation of **24** and **25**) the attack of ethanethiol takes place preferably on the opposite side of the bulky OBz group producing the 5*S* ethylthiopyrrolidine **26** as major intermediate compound (Scheme 2). The stereoselectivity of the addition step in **26** is 100%, the bicyclic compound **11** being produced only with the 3*S* configuration.

The chemical shift (72.4 ppm) for the resonance of C-5 in **11** was in agreement with the presence of the sulfur atom. This resonance undergoes an upfield shift of 16 ppm with respect to that for the same atom (C-1) in **6**. The ethylthio group was also evident from the MS data and from the resonances of H-1, and S–CH_2 (Table 2). The NMR spectra of **11** showed no signals for the vinyl group, and the chemical shift values for the resonances of H-3 (5.61 ppm) and C-3 (95.2 ppm) were in the range expected for a CH group simultaneously joined to oxygen and nitrogen atoms. The structural data for **11a** were similar, the main difference between **11** and **11a** being the value for the chemical shift of H-5 (4.35 ppm for **11** and 4.92 ppm for **11a**). For stereochemical assigments see NOE study in Section 2.2.

Conventional deacylation[4] of **11** with NaOMe/MeOH afforded **12** in 70% yield.

Reaction of β-L-rhamnopyranosylenamine **13**[19] with anisaldehyde dimethyl acetal gave the di-O-protected derivative **14**, which was O-mesylated to have **15** (Scheme 3). The acetal group was removed with ethanethiol, under transacetalation conditions,[22] giving **16**. The treatment of **16** with benzoyl chloride (→**17**) followed by reaction with sodium methoxide in DMF produced the anhydroazasugar derivative **18**, which by reduction with sodium cyanoborohydride in acetic acid gave the *N*-acetyl pyrrolidine **18**, which was no isolated, and in situ de-O-benzoylated to have **20**. As in the case of **8**, the NMR data of **20** showed that this compound in methanol-d_4 is in equilibrium with the oxapyrrolizidine **20a**. N-Deprotection of **20** with 1 M HCl in methanol gave the pyrrolidine hydrochloride **21**, not previously reported. Its ^{1}H NMR data coincided with that reported for its enantiomer.[17] Treatment of **21** with resin Dowex 50W 8x produces the free base **22**. The overall yield for the transformations **13**–**22** is 31.4%.

The structural data for compounds **14**–**17** (Table 1) were similar to those discussed above for **2**–**5**. The NMR spectra of the 1,4-anhydroazasugars **18** and **23** showed the same strong changes with respect to the data for **17**



Scheme 3. Reagents and conditions: (i) anisaldehyde dimethyl acetal, DMF/PTSA, rt/20 mmHg, 1 h; (ii) ClMs/Py, rt, 24 h; (iii) EtSH/Cl_2CH_2/PTSA, rt, 4 h; (iv) ClBz/Py, rt, 24 h; (v) NaOMe/DMF, 45 °C/20 mmHg, 15 min; (vi) $NaBH_3CN$/AcOH, rt, 2.5 h; (vii) NaOMe/MeOH, rt, 4 h; (viii) EtSH/Cl_2CH_2/PTSA, rt, 15 min; (ix) MeOH/HCl, 65 °C, 1 h; (x) Dowex 50w8x.

and **15**, respectively, as in the case of **6**, and also the vicinal coupling constants were indicative of the $B^{1,4}$ conformation.

The pyrrolidine structure of **20** was evident from the ^{13}C NMR resonances at 22.4 (CH_3) and 173.8 (CO) ppm for the *N*-acetyl group. In this case, the NMR data showed that the bicyclic compound **20a** exists in the equilibrium in a 9:1 (**20/20a**) ratio. The resonance for C-3 in **20a** appears at 114.7 ppm.

Treatment of **23** with ethanethiol in the aforementioned conditions gave, after column chromatography, the O-unprotected ethyl thioglycosides **24** (5*S*, 49% yield) and **24a** (5*R*, 21% yield).

The best way to prepare the di-*O*-benzoyl derivatives **25** and **25a**, useful for the NMR study discussed in Section 2.2, was the reaction of **18** with ethanethiol. This reaction was virtually quantitative, **25** and **25a** were isolated products, and the **25/25a** ratio was 7:3. The attack of the EtSH on **18** and **23**, to give **25**, **25a**, and **24**, **24a**, respectively, also occurs mainly in *trans* relationship with respect to the substituent on C-2 of the sugar ring, with formation of the 5*S* thioglycoside as major compound. The internal addition was 100% stereoselective as in the case of **11**. Benzoylation of **24** with benzoylchloride and pyridine gave **25**. The structural data of **24**, **24a**, **25** and **25a** are included in Table 2 and Experimental section. For stereochemical assignments, see Section 2.2.

2.2. Stereochemical study

Assignment of proton and carbon resonances of **8**, **11**, **11a**, **25** and **25a** was helped by COSY, 1D TOCSY and HMQC experiments. Proton–proton coupling constants were directly measured from the ^1H NMR spectra. For the determination of the configuration of the two new stereogenic carbon atoms C-3 and C-5, one- and two-dimensional NOESY experiments were carried out. NMR analysis of **11** and **11a** was performed on a sample containing a mixture (4:1) of both compounds. Although these spectra were complex on account of the presence of two different set of signals, the assignment of all resonances, as well as the NOESY study, were possible for both diastereoisomers.

The values of the coupling constants $^3J_{1,7a}$ and $^3J_{3,CH}$ for the pairs of compounds **25/25a** and **11/11a** showed that the corresponding torsion angles are very similar for the members of each pair, and therefore it could be expected that the main structural differences between these compounds are located in another part of the molecule. For **25** the small value of $^3J_{5,6}$ (less than 1 Hz) indicates a dihedral angle close to 90° between this pair of nuclei. This could be interpreted as an indication of a *trans* relative disposition of H-5 and H-6, since it is difficult to consider a stable conformation of the pyrrolidine ring compatible with such a small *J* value for a *cis* geometry. Furthermore, the observation in the NOESY experiments of a contact between H-6 and the methylene group of the SEt linked to C-5 supports an *S* configuration for this stereogenic centre.

On the other hand, this enhancement is absent in the 1D NOESY spectrum of **25a**, indicating a possible change in the configuration of C-5 (*R* configuration) with respect to the former. The observation of the weak NOE interactions H-5/H-7a for **25** or H-5/H-1 and H-5/H-7 for **25a** also agreed with these assignments. Analogously, similar NOE contacts observed for the SEt group in the NOESY spectra of compounds **11** and **11a** suggest that these compounds also differ in the configuration of C-5 (5*S* for **11** and 5*R* for **11a**).

With the configuration of C-5 already assigned, the analysis of the NOE contact between H-5 and H-3 seems to be a good indication of the configuration at C-3. Nevertheless, a simple determination of the NOE intensities showed no great differences between these compounds for this interaction, probably due to differences in their conformations. For **25** and **25a**, the evidence for the assignment of the configuration at C-3 came from the weak interactions observed for H-3. Thus, a medium-intensity NOE contact with H-1 in both compounds clearly indicates a *R* configuration for C-3. Furthermore, a weak contact between H-3 and the methylene of the SEt group in **25** (not observed for **25a**) confirms the proposed configurations. In agreement with this assignment is the presence of a weak contact between the C*H*$(COOEt)_2$ and the methyl group linked to C-1, which can be considered as exclusive of the *R* configuration. For **11** and **11a**, no such a clear indications for the configuration at C-3 could be detected in the NOESY spectra. Only the trivial NOE contacts with H-5 and C*H*$(COOEt)_2$ were observed. Furthermore, the high overlapping in the spectral region where C*H*$(COOEt)_2$ is located made it very difficult to extract reliable information for this pair of diastereoisomers.

To address the problem of the stereochemistry at the C-3 centre in **11** and **11a** we decided to go further into the spectroscopic analysis and obtain interproton distances from a quantitative treatment of the NOE data, and compare them with those obtained for the energy optimized conformations resulting from the study by molecular modeling of the four possible diastereoisomers (3*R*,5*R*; 3*S*,5*S*; 3*R*,5*S* and 3*S*,5*R*). The same study was also applied to **25**, in order to check this approach in a similar compound whose asymmetric centres have been previously assigned.

The longitudinal cross-relaxation rate constants (σ^{NOE}) were obtained from the NOE build-up curves (1D NOESY for **25** and 2D NOESY for **11** and **11a**) as described in the Experimental part. Providing that the interaction between two protons with a known distance (r_{ref}) can be clearly identified in the NOESY spectra, and assuming a rigid isotropic hydrodynamic behaviour of the molecule in solution, it is possible to extract unknown distances (r_{ij}) by comparing the longitudinal cross-relaxation rate constants (σ_{ij} and σ_{ref}) according to

$$r_{ij} = r_{\mathrm{ref}}(\sigma_{\mathrm{ref}}/\sigma_{ij})^{1/6}.$$

Thus, for the evaluation of all the interproton distances, the *ortho–meta* interaction in the aromatic moiety was used as a reference with a value of 2.48 Å.

For those peaks of compound **25** in which the overlapping of signals prevented the use of selective experiments, a modified equation was used to calculate distances using the values of the normalized integral volumes V_{ref} and V_{ij}:

$$r_{ij} = r_{\mathrm{ref}}(V_{\mathrm{ref}}/V_{ij})^{1/6},$$

where the normalized integral volumes were measured in a 2D NOESY experiment with a mixing time of 300 ms (appropriate mixing time for this approximation in the light of the NOE build-up curves). For the well-resolved signals, it was also possible to estimate distances using the initial slope in the build-up curves (1D NOESY experiments), and compare them with those obtained from the analysis of the 2D NOESY spectrum, and a good match was found (differences lower than 0.08 Å). For compounds **11** and **11a**, the interproton distances were deduced from the 2D NOESY spectra.

Since no stereospecific assignment was available for the two protons of the methylene group of the SEt moiety and no correction[23] was applied, the estimated distances between these protons and H-6 or H-3 (data not shown) were considered from a qualitative point of view as a mere indication of the proximity between these parts of the molecule. These distances showed that the SEt group lies closer to H-3 in compound **11a** than in **11**, suggesting an *S* configuration for C-3 in both compounds.

Theoretical distances were measured from the energetically favourable conformations obtained by molecular mechanics calculations with MM2 force field. Experimental and theoretical values are shown in Table 3. The listed values for the H3/H5 distance clearly indicate that only one configuration for C-3 is in fair agreement between experimental and theoretical data, supporting the proposed configurations (3*S* for **11** and **11a** and 3*R* for **25**). In addition, the H5/H6 distance shows a better match for the diastereoisomers with the proposed configurations for C-5 (5*S* for **11** and **25** and 5*R* for **11a**).

For compound **8**, a series of 1D NOESY spectra (mixing time of 400 ms), with selective excitation of the well-resolved signals, together with a 2D NOESY spectrum (mixing time of 300 ms) were performed. All these spectra showed the presence of EXSY peaks coming from the hydroxyl groups and from a minor compound present in the sample, which could be attributed to the bicyclic compound **8a**, although no further spectroscopic information could be obtained for this compound. The concomitant presence of NOE and exchange peaks made difficult in some cases the extraction of the desired information for this compound. In this case, the use of a longer mixing time (1 s) clearly improved the situation. Under these conditions, the NOESY spectra showed clear NOE contacts between the methyl group of the *N*-acetyl moiety and the protons H-5a and H-5b indicating a major participation of a *Z* conformation of the N–CO bond. Taking into account this geometry and the high stereoselectivity observed in the case of the enamino group (compounds **11** and **11a**), we would expect the cycloaddition of the OH to the carbonyl group to give exclusively the *R* configuration for C-3 in **8a**.

3. Conclusion

1,4-Anhydroazasugars, which can be easily obtained from inexpensive glycosylenamines, are suitable intermediates to prepare stereoselectively two types of azasugar derivatives. (a) The reduction with sodium cyanoborohydride leads to *N*-acetyl polyhydroxypyrrolidines, with one methylene group adjacent to the nitrogen atom. (b) Reaction with ethanethiol gives azasugar thioglycosides with structure of 3-oxapyrrolizidines with a thioalkoxy group in the pseudoanomeric position. In both cases, the overall yields are high. For azasugars the method is an alternative to other described methods, and azasugar thioglycosides constitute a new class of glycoside. The only limitation is the necessary *trans* relationship between the enamino and the mesyloxy groups in the formation of the 1,4-anhydroazasugar.

Table 3. Experimental and theoretical interproton distances (Å) for **11**, **11a** and **25**

Proton pair	Experimental		Theoretical			
	11	**11a**	3*S*,5*S*	3*R*,5*S*	3*S*,5*R*	3*R*,5*R*
H1–H7	2.17	2.24	2.35	2.44	2.20	2.19
H3–H5	2.25	2.61	2.17	3.64	2.77	3.76
H5–H6	3.01	2.11	2.76	2.79	2.37	2.39
H6–H7	2.55	2.89	2.79	2.79	3.09	3.10
	25		3*R*,5*S*	3*S*,5*S*	3*R*,5*R*	3*S*,5*R*
H1–H7	2.22		2.38	2.21	2.32	2.31
H3–H5	2.78		2.98	3.75	2.41	3.50
H5–H6	2.64		2.72	2.70	2.49	2.41
H6–H7	2.40		2.50	2.46	2.43	2.48

4. Experimental

4.1. General methods

Melting points were determined with a Gallenkamp apparatus and are uncorrected. A Perkin–Elmer Model 141 MC polarimeter, 1-cm tubes, and solutions in CH_2Cl_2, at 589 nm, were used for measurement of specific rotations. IR spectra were recorded for KBr discs on a Bomen Michelson MB-120 FTIR spectrophotometer. Mass spectra (EI, CI and FAB) were recorded with a Kratos MS-80RFA or a Micromass AutoSpecQ instrument with a resolution of 1000 or 60,000 (10% valley definition). For the FAB spectra, ions were produced by a beam of xenon atoms (6–7 keV), using 3-nitrobenzyl alcohol or thioglycerol as matrix and NaI as salt. TLC was performed on silica gel HF_{254}, with detection by UV light or charring with H_2SO_4. Silica gel 60 (Merck, 70–230 and 230–400 mesh) was used for preparative chromatography.

NMR experiments were recorded on a Bruker AMX 500 (500.13 MHz for ^1H and 125.75 MHz for ^{13}C) or a Bruker AMX 300 spectrometer (300.15 MHz for ^1H and 75.50 MHz for ^{13}C). Sample concentrations were typically in the range 10–15 mg per 0.5 mL of $CDCl_3$. Chemical shifts are given in ppm, using the TMS as reference. ^1H and ^{13}C assignments were confirmed by 2D conventional experiments. For the stereochemical study, a 5 mm inverse detection probe operating at 303 K was used. Selective inversion 1D experiments were performed by using the DANTE-Z module[24] ($n = 300$, $\tau = 125\,\mu s$, $\theta = 0.3°$). In 1D TOCSY experiments, WALTZ16 was used for the 150 ms isotropic mixing time ($\pi/2$ pulse width of 49 μs).[25] For the 1D NOESY experiments, mixing times of 100, 200, 300 and 600 ms were used for **25**, and 400 ms for **8**, **11** and **25a**. Typically, for all the 2D experiments, a spectral width of 5300 Hz in the ^1H dimension and 27,000 Hz in the ^{13}C dimension were used. The 2D homonuclear COSY was performed using a standard pulse sequence. The data matrix of 1024×256 used in this experiment was zero-filled to 512 data points in the indirect dimension and multiplied by sine-bell functions in both dimensions. The 2D heteronuclear one bond proton–carbon correlation experiment was collected using the HMQC sequence with BIRD filter (null time for this filter of 400 ms). A total of 256 increments were collected with 16 transients per increment (data matrix of 256×1024 points), using a 1 s relaxation delay and a delay corresponding to a J value of 145 Hz. ^{13}C decoupling was achieved using the GARP scheme. The 2D NOESY experiments were obtained with mixing times of 300 ms and 1 s for **8**, 200, 300, 400, and 600 ms for **11** and **11a**, and 300 ms for **25**. Sixty-four scans of 1024 points were accumulated for 256 t_1-increments, using a recycle delay of 2 s. The TPPI-States procedure was used for frequency discrimination in the indirect dimension.[26] Prior to Fourier transformation, an expansion of the data by zero-filling to 2048×1024 was performed, and shifted sine-bell window functions were applied in both dimensions.

For all the studied compounds, the NOESY cross peaks were positive. 1D and 2D NOESY peak intensities were evaluated with the XWINNMR program (Bruker). Normalized integrals were obtained by division of the measured integrals by the auto-peak value. The same integration regions were used for all mixing times. If the two peaks in the NOESY spectra for any pair of protons were well isolated, the average normalized integral was used; otherwise only one peak was considered. NOE build-up curves were obtained from the normalized integrals at different mixing times, and the cross-relaxation rates were calculated as the initial slope by linear least-squares fitting of the measured points, assuming the isolated spin-pair approximation (ISPA).[27] The good linearity observed in the build-up curves ($R > 0.99$ in all cases), within the range of mixing-time values used, warranted the applicability of such approximation.

All the stereoisomers were modeled using the MM2 force field as implemented in CS Chem3D Ultra® software (CambridgeSoft).

4.2. Preparation of compounds 2 and 14

A solution of the corresponding compounds[19] **1** and **13** (51.5 mmol), 4-methoxybenzaldehyde dimethyl acetal (14.0 g, 76.8 mmol) and PTSA (97 mg, 0.48 mmol) in DMF (50 mL) was rotated under aspirator pressure (20 mmHg) at 50 °C for 25 h. The solution was poured onto a stirred mixture of ice (50 g), and satd aq $NaHCO_3$ (100 mL). The solid residue was filtered off, washed successively with light petroleum and water, and dried. The residue was crystallized from ethanol.

4.2.1. *N*-(2,2-Diethoxycarbonylvinyl)-4,6-*O*-(4-methoxybenzylidene)-β-D-glucopyranosylamine, 2. Yield 91%; mp 134–136 °C (ethanol); $[\alpha]_D^{21} = +20$ (c 0.7, CH_2Cl_2); FABMS m/z 490 [$(M+Na)^+$]; IR 3484, 3260, 2978, 2930, 2878, 1701, 1649, 1607, 1383, 1248, 1101, 1013, 797 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.13 (dd, 1H, $J_{NH,1} = 8.6$, $J_{NH,HC=} = 13.8$, NH), 8.04 (d, 1H, HC=), 7.35–6.91 (m, 4H, Ar), 5.67 (d, 1H, $J_{2,OH} = 5.8$, O*H*–H-2), 5.52 (s, 1H, OCHO), 5.46 (d, 1H, $J_{3,OH} = 5.0$, O*H*–H-3), 4.68 (t, 1H, $J_{1,2} = 8.6$, H-1), 4.17 (m, 1H, H-5), 4.13 (q, 2H, $J_{H,H} = 7.1$, CH_2CH_3), 4.07 (q, 2H, CH_2CH_3), 3.74 (s, 3H, CH_3O), 3.65 (t, 1H, $J_{5,6a} = J_{6a,6b} = 10.1$, H-6a), 3.49 (m, 1H, H-6b), 3.46 (m, 1H, H-3), 3.40 (t, 1H, $J_{3,4} = J_{4,5} = 9.3$, H-4), 3.29 (m, 1H, H-2), 1.20, (m, 6H, $2CH_2CH_3$); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 167.4 (CO chelated), 164.8 (CO free), 159.5–113.3 (Ar), 158.1 (HC=), 100.6 (OCHO), 91.3 (=C), 88.6 (C-1), 80.2 (C-4), 73.6 (C-2), 73.1 (C-3), 67.9 (C-6), 67.6 (C-5), 59.3, 59.1 ($2CH_2CH_3$), 55.1 (OCH_3), 14.3, 14.2 ($2CH_2CH_3$); Anal. Calcd for $C_{22}H_{29}NO_{10}$: C, 56.52; H, 6.25; N, 3.00. Found: C, 56.26; H, 6.27; N, 2.84.

4.2.2. *N*-(2,2-Diethoxycarbonylvinyl)-2,3-*O*-(4-methoxybenzylidene)-β-L-rhamnopyranosylamine, 14. Yield 98%; mp 174–176 °C (ethanol); $[\alpha]_D^{25} = +27$ (c 0.9, CH_2Cl_2);

FABMS m/z 474 [(M+Na)$^+$]; IR 3476, 2976, 2915, 1707, 1601, 1379, 1250, 1094, 804 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (dd, 1H, $J_{NH,1} = 9.0$, $J_{NH,HC=} = 14.0$, NH), 8.04 (d, 1H, HC=), 7.36–6.87 (m, 4H, Ar), 6.10 (s, 1H, OCHO), 4.76 (dd, 1H, $J_{1,2} = 2.0$, H-1), 4.39 (dd, 1H, $J_{3,4} = 7.0$, H-3), 4.27 (dd, 1 H, $J_{2,3} = 5.5$, H-2), 4.18 (m, 4H, 2CH_2CH$_3$), 3.79 (s, 3H, CH_3O), 3.54 (t, 1H, $J_{4,5} = 7.0$, H-4), 3.41 (m, 1H, H-5), 1.35 (d, 3H, $J_{5,6} = 6.5$, H-6), 1.26 (m, 6H, 2CH$_2$CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 167.5 (CO chelated), 165.9 (CO free), 158.0 (HC=), 160.5–114.0 (Ar), 103.7 (OCHO), 93.8 (=C), 84.7 (C-1), 80.7 (C-3), 73.9 (C-2), 72.4 (C-5), 71.3 (C-4), 60.1, 60.0 (2CH$_2$CH$_3$), 55.3 (OCH_3), 17.6 (C-6), 14.3, 14.2 (2CH$_2$$CH_3$); Anal. Calcd for $C_{22}H_{29}NO_9$: C, 58.53; H, 6.47; N, 3.10. Found: C, 58.35; H, 6.41; N, 3.17.

4.3. Preparation of compounds 3 and 17

Into a stirred solution of the corresponding compound **2**, **16** (5.6 mmol) in dry pyridine (13.8 mL), at 0 °C, benzoyl chloride (22.4 mmol) was dropped. The solution was stirred at rt for 24 h, then poured into ice–water and extracted with CH_2Cl_2. The combined extracts were washed with 1 M H_2SO_4, satd aq $NaHCO_3$, and water, dried ($MgSO_4$) and evaporated to dryness. The residue was purified by column chromatography.

4.3.1. 2,3-Di-*O*-benzoyl-*N*-(2,2-diethoxycarbonylvinyl)-4,6-*O*-(4-methoxybenzylidene)-β-D-glucopyranosylamine, 3. Column chromatography CH_2Cl_2. Yield 91%; amorphous solid; $[\alpha]_D^{23} = -36$ (c 0.9, CH_2Cl_2); CIMS m/z 676 [(M+H)$^+$]; IR 3069, 2982, 2944, 2903, 1730, 1663, 1613, 1267, 1101, 712 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.37 (dd, 1H, $J_{NH,1} = 8.9$, $J_{NH,HC=} = 13.2$, NH), 7.98 (d, 1H, HC=), 7.95–6.83 (m, 14H, Ar), 5.89 (t, 1H, $J_{2,3} = J_{3,4} = 9.6$, H-3), 5.53 (s, 1H, OCHO), 5.52 (t, 1H, $J_{1,2} = 8.9$, H-2), 4.84 (t, 1H, H-1), 4.40 (dd, 1H, $J_{5,6a} = 4.1$, $J_{6a,6b} = 9.9$, H-6a), 4.26 (m, 2H, CH_2CH$_3$), 4.14 (m, 2H, CH_2CH$_3$), 3.93 (t, 1H, $J_{4,5} = 9.3$, H-4), 3.82 (t, 1H, $J_{5,6b} = 9.9$, H-6b), 3.79 (m, 1H, H-5), 3.77 (s, 3H, CH_3O), 1.33, and 1.25, (each t, each 3H, 2CH$_2$CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 167.5 (CO chelated), 165.5 (CO free), 165.3 (2CO), 160.1–113.5 (Ar), 157.4 (HC=), 101.5 (OCHO), 94.9 (=C), 87.8 (C-1), 78.4 (C-4), 71.9 (C-3), 71.8 (C-2), 68.7 (C-6), 68.3 (C-5), 60.3, 60.2 (2CH$_2$CH$_3$), 55.2 (OCH_3), 14.3, 14.2 (2CH$_2$$CH_3$); Anal. Calcd for $C_{36}H_{37}NO_{12}$: C, 63.99; H, 5.52; N, 2.07. Found: C, 63.66; H, 5.40; N, 2.32.

4.3.2. 2,3-Di-*O*-benzoyl-*N*-(2,2-diethoxycarbonylvinyl)-4-*O*-mesyl-β-L-rhamnopyranosylamine, 17. Column chromatography CH_2Cl_2, and CH_2Cl_2/MeOH, 60:1. Yield 88%; amorphous solid; $[\alpha]_D^{26} = +14$ (c 0.9, CH_2Cl_2); FABMS m/z 642 [(M+Na)$^+$]; IR 3291, 2984, 2940, 1736, 1661, 1609, 1269, 1082, 843, 712 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.45 (dd, 1H, $J_{NH,1} = 8.8$, $J_{NH,HC=} =$ 13.2, NH), 8.07 (d, 1H, HC=), 8.05–7.34 (m, 10H, Ar), 5.90 (dd, 1H, $J_{1,2} = 1.2$, $J_{2,3} = 3.4$, H-2), 5.51 (dd, 1H, $J_{3,4} = 9.8$, H-3), 5.01 (dd, 1H, H-1), 4.90 (t, 1H, $J_{4,5} = 9.8$, H-4), 4.17, 4.07 (each m, each 2H, 2CH_2CH$_3$), 3.85 (m, 1H, H-5), 2.85 (s, 3H, CH_3SO_2), 1.56 (d, 3H, $J_{5,6} = 6.2$, H-6), 1.28, and 1.17, (each t, each 3H, $J_{H,H} = 7.1$, 2CH$_2$CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 167.7 (CO chelated), 165.6 (CO free), 165.5, 165.2 (2CO), 156.9 (HC=), 134.0–128.6 (Ar), 94.6 (=C), 84.8 (C-1), 77.9 (C-4), 71.5 (C-3), 72.6 (C-5), 70.4 (C-2), 60.2, 60.1 (2CH$_2$CH$_3$), 39.1 (SO_2CH_3), 18.0 (C-6), 14.4, 14.2 (2CH$_2$$CH_3$); HRCIMS m/z obsd 620.1778, calcd for $C_{29}H_{34}NO_{12}S$ 620.1802. Anal. Calcd for $C_{29}H_{33}NO_{12}S$: C, 56.21; H, 5.37; N, 2.26. Found: C, 56.19; H, 5.41; N, 2.28.

4.4. 2,3-Di-*O*-benzoyl-*N*-(2,2-diethoxycarbonylvinyl)-6-*O*-(4-methoxybenzyl)-β-D-glucopyranosylamine, 4

A solution of **3** (434 mg, 0.64 mmol) in acetic acid (8.68 mL), was treated with $NaBH_3CN$ (135 mg, 2.04 mmol), stirred for 2.5 h at rt and controlled by TLC (CH_2Cl_2/MeOH, 100:1). The mixture was added to ice–water and extracted with CH_2Cl_2. The organic layer was separated, washed with satd aq $NaHCO_3$, and water, dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified by column chromatography (CH_2Cl_2). Yield 68% as amorphous solid; $[\alpha]_D^{22} = -10$ (c 0.5, CH_2Cl_2); FABMS m/z 700 [(M+Na)$^+$]; IR 3464, 3072, 2905, 1724, 1669, 1607, 1382, 1265, 1101, 712 cm^{-1}; ^{1}H NMR (500 MHz, [$(CD_3)_2CO$]) δ 9.30 (dd, 1H, $J_{NH,1} = 9.1$, $J_{NH,HC=} = 13.4$, NH), 8.15 (d, 1H, HC=), 7.95–6.87 (m, 14H, Ar), 5.68 (t, 1H, $J_{2,3} = J_{3,4} = 9.1$, H-3), 5.41 (t, 1H, $J_{1,2} = 9.1$, H-2), 5.23 (t, 1H, H-1), 5.09 (d, 1H, $J_{4,OH} = 5.6$, OH–H-4), 4.52 (m, 2H, CH_2OPMB), 4.15, 4.13 (each m, each 2H, CH_2CH$_3$), 4.05 (m, 1H, H-4), 3.92 (ddd, 1H, $J_{4,5} = 9.8$, $J_{5,6a} = 1.9$, $J_{5,6b} = 5.3$, H-5), 3.89 (dd, 1H, $J_{6a,6b} = 11.0$, H-6a), 3.79 (m, 1H, H-6b), 3.78 (s, 3H, CH_3O), 1.22, 1.17 (each t, each 3H, $J_{H,H} = 8.6$, 2CH$_2$CH_3); ^{13}C NMR (125.7 MHz, [$(CD_3)_2CO$]) δ 168.4 (CO chelated), 166.3, 166.2, 165.3 (3CO), 158.5 (HC=), 134.4–114.4 (Ar), 94.7(=C), 87.3 (C-1), 78.7 (C-5), 77.0 (C-3), 73.6 (CH$_2$OPMB), 72.9 (C-2), 69.4 (C-4), 64.4 (C-6), 60.3, 60.1 (2CH$_2$CH$_3$), 55.5 (OCH_3), 14.3 (2CH$_2$$CH_3$); Anal. Calcd for $C_{36}H_{39}NO_{12}$: C, 63.80; H, 5.80; N, 2.07. Found: C, 63.52; H, 5.73; N, 1.98.

4.5. Preparation of compounds 5 and 15

Into a cooled (0 °C) stirred solution of the corresponding compounds **4** and **14** (0.894 mmol) in pyridine (3.1 mL) under argon, mesyl chloride (326 μL, 4.11 mmol) was dropped. The mixture was stirred at rt for 24 h and the reaction was controlled by TLC (CH_2Cl_2/MeOH, 100:1). The solution was poured into ice–water and extracted with CH_2Cl_2; the organic layer was separated, washed with 1 M sulfuric acid, satd aq $NaHCO_3$, and water, dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was purified by column chromatography (CH_2Cl_2).

4.5.1. 2,3-Di-*O*-benzoyl-*N*-(2,2-diethoxycarbonylvinyl)-4-*O*-mesyl-6-*O*-(4-methoxybenzyl)-β-D-glucopyranosylamine, 5. Amorphous solid. Yield 85%; $[\alpha]_D^{28} = 0$ (c 1.0,

CH_2Cl_2); FABMS m/z 778 [(M+Na)$^+$]; IR 3285, 2978, 2907, 2872, 1726, 1663, 1611, 1362, 1265, 1098, 957, 829, 712 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 9.28 (dd, 1H, $J_{NH,1} = 9.3$, $J_{NH,HC=} = 13.2$, NH), 7.96 (d, 1H, HC=), 7.96–6.89 (m, 14H, Ar), 5.84 (t, 1H, $J_{2,3} = J_{3,4} = 9.3$, H-3), 5.44 (t, 1H, $J_{1,2} = 9.3$, H-2), 5.17 (t, 1H, $J_{4,5} = 9.3$, H-4), 4.74 (t, 1H, H-1), 4.57, 4.53 (each d, each 1H, $J_{H,H} = 11.3$, CH_2OPMB), 4.26 (m, 2H, CH_2CH$_3$), 4.15 (q, 2H, $^3J_{H,H} = 7.1$, CH_2CH$_3$), 3.89–3.85 (m, 2H, H-5, H-6a), 3.81 (s, 3H, CH_3O), 3.76 (dd, 1H, $J_{5,6b} = 4.0$, $J_{6a,6b} = 11.4$, H-6b), 2.82 (s, 3H, Ms), 1.32, 1.25 (each t, each 3H, $J_{H,H} = 7.0$, 2CH$_2$CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 167.2 (CO chelated), 165.6, 165.4, 165.3 (CO), 159.4–113.5 (Ar), 157.1 (HC=), 95.1 (=C), 87.4 (C-1), 75.4 (C-5), 74.2 (C-4), 73.5 (*C*H$_2$OPMB), 72.4 (C-3), 71.1 (C-2), 67.4 (C-6), 60.3, 60.0 (2CH$_2$CH$_3$), 55.2 (OCH_3), 38.8 (Ms), 14.3, 14.2 (2CH$_2$CH$_3$); Anal. Calcd for $C_{37}H_{41}NO_{14}S$: C, 58.80; H, 5.47; N, 1.85. Found: C, 58.47; H, 5.50; N, 1.75.

4.5.2. *N*-(2,2-Diethoxycarbonylvinyl)-4-*O*-mesyl-2,3-*O*-(4-methoxybenzylidene)-β-L-rhamnopyranosylamine, 15.

Yield 93%; mp 150–152 °C (ethanol); $[\alpha]_D^{24} = +39$ (c 0.9, CH_2Cl_2); CIMS m/z 530 [(M+1)$^+$]; IR 3290, 2986, 2940, 1697, 1653, 1597, 1346, 1252, 1177, 847 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (dd, 1H, $J_{NH,1} = 9.0$, $J_{NH,HC=} = 13.5$, NH), 8.02 (d, 1H, HC=), 7.35–6.88 (m, 4H, Ar), 6.21 (s, 1H, OCHO), 4.79 (dd, 1H, $J_{1,2} = 1.5$, H-1), 4.60 (dd, 1H, $J_{2,3} = 5.5$, $J_{3,4} = 7.0$, H-3), 4.51 (dd, 1H, $J_{4,5} = 9.0$, H-4), 4.37 (dd, 1H, H-2), 4.19 (m, 4H, 2CH_2CH$_3$), 3.80 (s, 3H, CH_3O), 3.59 (m, 1H, H-5), 3.16 (s, 3H, Ms), 1.42 (d, 3H, $J_{5,6} = 6.0$, H-6), 1.27, 1.26 (each t, each 3H, $J_{H,H} = 7.0$, 2CH$_2$CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 167.5, 165.7 (2CO), 160.7–113.9 (Ar), 157.7 (HC=), 104.0 (OCHO), 94.5 (=C), 84.6 (C-1), 79.9 (C-4), 78.0 (C-3), 74.2 (C-2), 70.5 (C-5), 60.2, 60.1 (2*C*H$_2$CH$_3$), 55.3 (OCH_3), 39.2 (Ms), 17.5 (C-6), 14.3, 14.2 (2CH$_2$*C*H$_3$); Anal. Calcd for $C_{23}H_{31}NO_{11}S$: C, 52.17; H, 5.90; N, 2.65. Found: C, 51.94; H, 5.81; N, 3.00.

4.6. Preparation of compounds 6, 18 and 23

To a stirred solution of the corresponding mesyl compounds **5**, **17** and **15** (0.24 mmol) in DMF (3.2 mL) at 40 °C and 20 mmHg, sodium methoxide (14 mg, 0.24 mmol) was added. The reaction was stirred for 15 min, and controlled by TLC (CH_2Cl_2/MeOH 100:1). The mixture was poured into ice–water and extracted with CH_2Cl_2. The organic layer was separated, washed with water, dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified as described.

4.6.1. 1,4-Anhydro-2,3-di-*O*-benzoyl-*N*-(2,2-diethoxy-carbonylvinyl)-6-*O*-(4-methoxybenzyl)-β-D-glucopyranosylamine 6.

Column chromatography (CH_2Cl_2). Amorphous solid. Yield 66%; $[\alpha]_D^{23} = +49$ (c 0.5, CH_2Cl_2); FABMS m/z 682 [(M+Na)$^+$]; IR 3063, 2980, 2866, 1723, 1609, 1381, 1265, 1099, 714 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08–6.86 (m, 14H, Ar), 7.69 (s, 1H, HC=), 5.83 (d, 1H, $J_{1,2} = 2.2$, H-1), 5.14 (m, 1H, H-2), 5.11 (d, 1H, $J_{2,3} = 1.0$, $J_{3,4} = 0$, H-3), 4.76 (s, 1H, $J_{4,5} = 0$, H-4), 4.49, 4.44 (each d, each 1H, $J_{H,H} = 11.6$, CH_2OPMB), 4.06 (dd, 1H, $J_{5,6a} = 5.5$, $J_{5,6b} = 7.3$, H-5), 4.19 (m, 4H, CH_2CH$_3$), 3.79 (s, 3H, CH_3O), 3.47 (dd, 1H, $J_{6a,6b} = 10.1$, H-6a), 3.33 (dd, 1H, H-6b), 1.27, 1.20 (each t, each 3H, $J_{H,H} = 7.2$, 2CH$_2$CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 166.0, 165.9, 165.8, 165.6 (4CO), 159.3–113.8 (Ar), 145.9 (HC=), 100.1 (=C), 88.1 (C-1), 79.9 (C-2), 76.9 (C-3), 75.3 (C-5), 73.2 (*C*H$_2$O), 68.9 (C-6), 65.1 (C-4), 60.9, 60.5 (2*C*H$_2$CH$_3$), 55.2 (OCH_3), 14.2, and 14.0 (2CH$_2$*C*H$_3$); Anal. Calcd for $C_{36}H_{37}NO_{11}$: C, 65.54; H, 5.65; N, 2.12. Found: C, 65.34; H, 5.56; N, 2.26.

4.6.2. 1,4-Anhydro-2,3-di-*O*-benzoyl-*N*-(2,2-diethoxy-carbonylvinyl)-β-L-rhamnopyranosylamine 18.

Column chromatography AcOEt/hexane 1:4. Amorphous solid. Yield 60%; $[\alpha]_D^{24} = +22$ (c 0.9, CH_2Cl_2); CIMS m/z 524 [(M+H)$^+$]; IR 3063, 2991, 1736, 1609, 1458, 1370, 1283, 1029, 714 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88–7.22 (m, 10H, Ar), 7.69 (s, 1H, HC=), 5.58 (br s, 1H, H-1), 5.37 (d, 1H, $J_{2,3} = 6.0$, H-2), 5.31 (d, 1H, H-3), 4.67 (br s, 1H, $J_{4,5} = 0$, H-4), 4.18 (m, 4H, 2CH_2CH$_3$), 4.05 (m, 1H, H-5), 1.26 (d, 1H, $J_{5,6} = 6.0$, H-6), 1.25, 1.13 (each t, each 3H, $J_{H,H} = 7.0$, 2CH$_2$CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) 166.5 (2CO), 165.6, 165.2, (2CO), 146.3 (HC=), 133.9–128.3 (Ar), 98.9 (=C), 89.6 (C-1), 74.1 (C-2), 73.5 (C-5), 73.4 (C-3), 65.6 (C-4), 60.9, 60.6 (2*C*H$_2$CH$_3$), 19.6 (C-6), 14.4, 14.1 (2CH$_2$*C*H$_3$); HRCIMS m/z obsd 524.1917, calcd for $C_{28}H_{30}NO_9$ 524.1921.

4.6.3. 1,4-Anhydro-*N*-(2,2-diethoxycarbonylvinyl)-2,3-*O*-(4-methoxybenzylidene)-β-L-rhamnopyranosylamine, 23.

Column chromatography (AcOEt/hexane 1:4). Yield 93%; $[\alpha]_D^{28} = -53$ (c 1.0, CH_2Cl_2); EIMS m/z 433 [M$^+$]; IR 3079, 2991, 2896, 1712, 1609, 1379, 1275, 1077, 838 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), 7.79 (s, 1H, HC=), 7.29–6.82 (m, 4H, Ar), 6.10 (s, 1H, OCHO), 5.36 (s, 1H, H-1), 4.44 (m, 3H, H-2, H-3, H-4), 4.28, 4.20 (each m, each 2H, 2CH_2CH$_3$), 3.77 (s, 3H, CH_3O), 3.67 (m, 1H, H-5), 1.30, 1.27 (each t, each 3H, $J_{H,H} = 7.3$, 2CH$_2$CH_3), 1.12 (d, 1H, $J_{5,6} = 6.0$, H-6); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 166.6, 166.4 (2CO), 160.6–113.9 (Ar), 146.5 (HC=), 107.0 (OCHO), 99.5 (=C), 89.8 (C-1), 80.4 (C-2), 79.9 (C-3), 71.7 (C-5), 66.3 (C-4), 61.1, 60.7 (2*C*H$_2$CH$_3$), 55.4 (OCH_3), 19.3 (C-6), 14.4, 14.2 (2CH$_2$*C*H$_3$); HREIMS m/z obsd 433.1739, calcd for $C_{22}H_{27}NO_8$ 433.1737.

4.7. Preparation of compounds 8 and 20

To a solution of the corresponding 1,4-anhydroglycopyranosylamines **6** and **18** (0.083 mmol) in acetic acid (0.9 mL), $NaBH_3CN$ (18.2 mg, 0.28 mmol) was added. The solution was stirred for 24 h at rt and controlled by TLC (CH_2Cl_2/MeOH, 70:1). The mixture was added to ice-saturated aqueous sodium hydrogencarbonate and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered, and evaporated to dryness. To a solution of the residue (0.083 mmol) in anhydrous

methanol (16 mL) at rt, 1 M NaOMe in methanol (53 μL) was added. The process was controlled by TLC until total deacylation of the starting material was achieved. After 4 h the reaction mixture was neutralized with acid resin Amberlite IR-120(H^+), filtered, and the solvent was evaporated under reduced pressure. The residue was purified as described. When **8** and **20** were dissolved in methanol-d_4 to obtain the NMR spectra the equilibria **8**, **8a** and **20**, **20a** (see Discussion) were produced.

4.7.1. (2*S*,3*S*,4*S*,1′*R*)-1-Acetyl-3,4-dihydroxy-2-(1′-hydroxy-2′-*p*-methoxybenzyloxy)ethylpyrrolidine, 8. Column chromatography CH_2Cl_2/MeOH 15:1. Yield 77%; $[\alpha]_D^{30} = +47$ (*c* 1.0, CH_{2cc} Cl_2); EIMS *m*/*z* 325 [M^+]; IR 3309, 2936, 2856, 1625, 1521, 1371, 1251, 1124, 850 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25–6.86 (m, 4H, Ar), 4.50, 4.46 (each d, each 1H, $J_{H,H} = 11.5$, CH_2Ph), 4.15 (br s, 1H, H-3), 4.13–4.10 (m, 2H, H-2, 4), 4.03 (m, 1H, H-1′), 3.87 (dd, 1H, $J_{4,5a} = 6.0$, $J_{5a,5b} = 11.5$, H-5a), 3.79 (s, 3H, OCH_3), 3.67 (dd, 1H, $J_{1',2'a} = 4.5$, $J_{2'a,2'b} = 10.5$, H-2′a), 3.50 (dd, 1H, $J_{1,2'b} = 7.0$, H-2′b), 3.42 (dd, 1H, $J_{4,5b} = 2.5$, H-5b), 2.07 (s, 3H, CH_3). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 172.8 (N–CO), 159.6–114.0 (Ar), 79.0 (C-3), 75.4 (C-4), 73.4 (H_2COMP), 73.3 (C-1′), 72.5 (C-2′), 67.5 (C-2), 55.5 (C-5), 55.4 (OCH_3), 22.7 (CH_3). HREIMS *m*/*z* obsd 325.1523, calcd for $C_{16}H_{23}NO_6$ 325.1525.

4.7.2. (1*R*,3*R*,*S*,6*R*,7*S*,7a*S*)-3,6,7-trihydroxy-1-*p*-methoxybenzyloxymethyl-2-oxapyrrolizidine 8a. ^{13}C NMR (125.7 MHz, MeOD) δ 160.9–114.7 (6C, Ar), 114.6 (C-3), 79.7 (C-7), 76.0 (C-6), 74.1 (CH_2PhOMe), 72.9 (CH_2O), 70.6 (C-1), 70.2 (C-7a), 55.7 (OMe), 54.0 (C-5), 22.4 (CH_3–C).

4.7.3. (2*R*,3*S*,4*R*,1′*S*)-1-Acetyl-3,4-dihydroxy-2-(1′-hydroxy)ethylpyrrolidine, 20. Column chromatography CH_2Cl_2/MeOH 15:1. Yield 75%; CIMS *m*/*z* 190 [(M+H)$^+$]; IR 3309, 2964, 2933, 1722, 1645, 1479, 1261, 1093 cm^{-1}; ^1H NMR (300 MHz, MeOD) δ 4.22 (ddd, 1H, $J_{3,4} = 2.4$, $J_{4,5a} = 6.3$, $J_{4,5b} = 4.8$, H-4), 4.12 (m, 1H, H-1′), 3.96 (dd, 1H, $J_{2,3} = 4.5$, H-3), 3.90 (dd, 1H, $J_{2,1'} = 8.2$, H-2), 3.61 (dd, 1H, $J_{5a,5b} = 10.8$, H-5a), 3.38 (dd, 1H, H-5b), 2.07 (s, 3H, $COCH_3$), 1.14 (d, 3H, CH_3–CHOH) ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 173.8 ($COCH_3$), 74.7 (C-3), 71.4 (C-4), 73.3 (C-1), 70.2 (C-1′), 69.4 (C-2), 56.4 (C-5), 22.4 ($COCH_3$), 20.4 (2′). HRCIMS *m*/*z* obsd 190.1089, calcd for $C_8H_{16}NO_4$ 190.1079.

4.7.4. (1*R*,3*R*,*S*,6*R*,7*R*,7a*R*)-3,6,7-trihydroxy-1-methyl-2-oxapyrrolizidine 20a. ^{13}C NMR (125.7 MHz, MeOD) δ 114.7 (C-3), 74.8 (C-7), 73.1 (C-6), 70.8 (C-1), 69.1 (C-7a), 51.4 (C-5), 22.4 (CH_3–CO_2N), 20.4 (CH_3–CO).

4.8. *N*-(2,2-Diethoxycarbonylvinyl)-4-*O*-mesyl-β-L-rhamnopyranosylamine 16

To a solution of **15** (400 mg, 0.756 mmol) in dry CH_2Cl_2 (9.6 mL), ethanethiol (560 μL, 7.56 mmol), and PTSA (catalytic amount) were added. The reaction mixture was stirred for 4 h at rt and controlled by TLC (CH_2Cl_2/MeOH 15:1), neutralized with basic resin Amberlite IRA-400(OH^-), filtered, and the solvent was evaporated to dryness. The residue was purified by column chromatography (CH_2Cl_2, CH_2Cl_2/MeOH, 30:1) and gave **16** as amorphous solid. Yield 96%; $[\alpha]_D^{24} = -45$ (*c* 1.0, CH_2Cl_2); FABMS *m*/*z* 434 [(M+Na)$^+$];)$^+$]; IR 3488, 3298, 2984, 2876, 1723, 1649, 1597, 1344, 1252, 1071, 855, 801 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.52 (dd, 1H, $J_{NH,1} = 9.0$, $J_{NH,HC=} = 13.5$, NH), 8.04 (d, 1H, HC=), 4.61 (d, 1H, H-1), 4.47 (t, 1H, $J_{4,5} = J_{3,4} = 9.5$, H-4), 4.18 (m, 4H, $2CH_2CH_3$), 4.11 (br s, 1H, H-2), 3.78 (dd, 1H, $J_{2,3} = 2.5$, H-3), 3.53 (dq, 1H, $J_{5,6} = 6.0$, H-5), 3.17 (s, 3H, CH_3SO_2), 1.36 (d, 1H, H-6), 1.29, 1.26 (each t, each 3H, $J_{H,H} = 7.0$, $2CH_2CH_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 168.3, 166.1 (2CO), 158.0 (HC=), 93.7 (=C), 85.8 (C-1), 82.0 (C-4), 72.0 (C-3), 71.5 (C-5), 70.9 (C-2), 60.5, 60.3 ($2CH_2CH_3$), 38.9 (SO_2CH_3), 17.6 (C-6), 14.4, 14.3 ($2CH_2CH_3$); HREIMS *m*/*z* obsd 412.1281, calcd for $C_{15}H_{26}NO_{10}S$ 412.1277.

4.9. Preparation of compounds 9 and 21

To a solution of the corresponding compounds **8** and **20** (0.283 mmol) in methanol (7.5 mL), HCl 12 N (600 μL) was added. The mixture was stirred at 65 °C for 1 h, and then the solvent was evaporated under reduced pressure. Compound **9** had the same spectroscopic data previously reported.[12] The ^1H NMR data of compound **21** coincided with those reported[17] for its enantiomer.

4.10. Preparation of compounds 10 and 22

A solution of the corresponding compounds **9** and **21** (0.283) was treated in a chromatographic column with ion-exchange Dowex® 50W-XS resin NH_4^+ form (4 g). The column was eluted first with methanol, after with water, and then with a NH_4OH solution. The fractions containing the product were concentrated to dryness. The NMR data of compound **10** coincided with those reported.[12]

4.10.1. (2*R*,3*R*,4*S*,1′*S*)-3,4-dihydroxy-2-(1′-hydroxy)-ethylpyrrolidine, 22. Amorphous solid. Yield 72% from **18**; $[\alpha]_D^{23} = +27$ (*c* 1.5, EtOH); CIMS *m*/*z* 148 [(M+H)$^+$]; IR 3352, 2930, 2933, 1623, 1548 cm^{-1}; ^1H NMR (500 MHz, MeOD) δ 4.02 (m, 1 H, H-4), 3.81 (m, 2H, H-1′, H-3), 3.14 (dd, 1H, $J_{4,5a} = 5.5$, $J_{5a,5b} = 11.5$, H-5a), 2.81 (dd, 1H, $J_{4,5b} = 4.0$, H-5b), 2.80 (m, 1H, H-2), 1.24 (d, 3H, $J_{1',CH3}$, CH_3–CHOH). ^{13}C NMR (125.7 MHz, MeOD) δ 74.9 (C-3), 72.8 (C-4), 69.0 (C-2), 66.8 (C-1′), 52.1 (C-5), 21.3 (CH). HRCIMS *m*/*z* obsd 148.0972, calcd for $C_6H_{14}NO_3$ 148.0974.

4.11. Preparation of compounds 11, 11a, 24, 24a, and 25

To a stirred solution of the corresponding 1,4-anhydro-compounds **6**,**23** and **18** (0.527 mmol) in dry CH_2Cl_2

(10.0 mL) over 3 Å molecular sieves at rt, ethanethiol (21.6 mmol), and PTSA (catalytic amount) were added. The reaction was stirred for 15 min, controlled by TLC (CH_2Cl_2/MeOH), and then neutralized with satd aq $NaHCO_3$, washed with water, and dried ($MgSO_4$) for **25** and **11**. The mixture was treated with basic resin Amberlite IRA-400(OH^-) for **24**. In all cases, the mixture was filtered and evaporated to dryness. Column chromatography (CH_2Cl_2, CH_2Cl_2/MeOH 100:1) of the residue gave in the case of **6** a mixture of **5*R*** and **5*S*** diastereoisomers **11** and **11a** (98%, **11/11a** ratio 4:1), whereas in the cases of **23** and **18** gave the corresponding thioglycosides **24** and **24a**, or **25** and **25a** as isolated products.

4.11.1. (1*S*,3*S*,5*S*,6*R*,7*S*,7a*S*)-6,7-Dibenzoyloxy-3-diethoxycarbonylmethyl-5-ethylthio-1-*p*-methoxybenzyloxymethyl-2-oxapyrrolizidine, 11 and (1*S*,3*S*,5*R*,6*R*,7*S*,7a*S*)-6,7-dibenzoyloxy-3-diethoxycarbonylmethyl-5-ethylthio-1-*p*-methoxybenzyloxymethyl-2-oxapyrrolizidine, 11a. Compound **11** was an amorphous solid. FABMS *m/z* 744 [(M+Na)$^+$]; IR, 2980, 2932, 2870, 1734, 1609, 1514, 1370, 1252, 831, 719 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09–6.77 (m, 14H, Ar), 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), 4.53, 4.48 (each d, each, 2H, $J_{H,H} = 11.7$, H_2COPMB), 4.35 (d, 1H, H-5), 4.33 (m, 1H, H-1), 4.25–4.14 (m, 4H, OCH_2CH$_3$), 3.80 (dd, 1H, $J_{1,7a} = 8.0$, H-7a), 3.78 [(d, 1H, *H*C(CO$_2$Et)$_2$], 3.77–3.70 (m, 2H, H-8a, H-8b), 3.75 (s, 3H, OCH$_3$), 2.74, 2.68 (each dq, each 1H, $^2J_{H,H} = 11.5$, $^3J_{H,H} = 7.5$, SCH_2CH$_3$), 1.28–1.24 (m, 9 H, 2OCH$_2$CH_3, SCH$_2$CH_3). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 166.7 (CO), 166.0 (2CO), 165.2 (CO), 159.2–113.7 (Ar), 95.2 (C-3), 80.8 (C-1), 80.4 (C-6), 79.0 (C-7), 73.2 (OCH$_2$MP), 72.4 (C-5), 69.6 (H$_2$*C*OPMB), 69.0 (C-7a), 61.5 (2O*C*H$_2$CH$_3$), 58.5 [CH(CO$_2$Et)$_2$], 55.3 (OCH$_3$), 22.3 (SCH$_2$CH$_3$), 14.2, 14.1 (each OCH$_2$*C*H$_3$), 14.2 (S*C*H$_2$CH$_3$). HRCIMS *m/z* obsd 722.2608, calcd for $C_{38}H_{44}NO_{11}S$ 722.2635.

Compound **11a** had, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09–6.71 (m, 14H, Ar), 5.86 (dd, 1H, $J_{5,6} = 5.5$, $J_{6,7=} = 8.2$, H-6), 5.82 (d, 1H, $J_{3,CH} = 8.8$, H-3), 5.51 (dd, 1H, $J_{7,7a} = 4.3$, H-7), 4.92 (d, 1H, H-5), 4.49, 4.38 (each d, each 1H, $J_{H,H} = 11.7$, H_2COMBn), 4.25–4.14 (m, 4 H, OCH$_2$CH$_3$), 4.17 (m, 1H, H-1), 3.74 (s, 3H, OCH$_3$), 3.73 [(d, 1H, *H*C(CO$_2$Et)$_2$], 3.69 (m, 2H, H-8a, H-8b), 3.62 (dd, 1H, $J_{1,7a} = 8.4$, H-7a), 2.63–2.56 (m, 2H, SCH_2CH$_3$), 1.31–1.24 (m, 6H, 2OCH$_2$CH_3), 1.19 (t, 3H, $^3J_{H,H} = 7.4$, SCH$_2$CH_3). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 166.8–165.2 (4CO), 159.2–113.6 (Ar), 91.5 (C-3), 82.6 (C-1), 78.4 (C-6), 76.7 (C-7), 73.1 (OCH$_2$MP), 72.1 (C-5), 69.2 (H$_2$*C*OPMB), 65.8 (C-7a), 61.5 (2O*C*H$_2$CH$_3$), 58.1 [CH(CO$_2$Et)$_2$], 55.3 (OCH$_3$), 28.1 (S*C*H$_2$CH$_3$), 15.7 (SCH$_2$*C*H$_3$), 14.5, 14.4 (each OCH$_2$*C*H$_3$).

4.11.2. (1*R*,3*R*,5*S*,6*R*,7*R*,7a*R*)-3-diethoxycarbonylmethyl-5-ethylthio-6,7-dihydroxy-1-methyl-2-oxapyrrolizidine, 24. Amorphous solid; IR, 3444, 2983, 2935, 1720, 1593, 1386, 1243 cm^{-1}; CIMS *m/z* 378 [M$^+$]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56 (d, 1H, $J_{3,CH} = 7.5$, H-3), 4.31 (br s, 1H, H-6), 4.29 (s, 1H, H-5), 4.42–4.13 (m, 5H, H-7, 2CH_2CH$_3$), 3.67 (dq, 1H, $J_{1,7a} = 8.5$, $J_{1,CH_3} = 6.0$, H-1), 3.52 (d, 1H, CH(CO$_2$Et)$_2$), 3.09 (dd, 1H, $J_{7,7a} = 4.5$, H-7a), 2.90 (br s, 2H, OH-6, OH-7), 2.67 (m, 2H, SCH$_2$*C*H$_3$), 1.27 (m, 12H, 1 CH$_3$, 2OCH$_2$CH_3, 1 SCH$_2$*C*H$_3$). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 167.2, 166.8 (2CO), 90.3 (C-3), 81.6 (C-6), 79.1 (C-1), 74.9 (C-5), 74.4 (C-7a), 72.6 (C-7), 61.6, 61.5 (2O*C*H$_2$CH$_3$), 58.6 [*C*H(CO$_2$Et)$_2$], 27.7 (S*C*H$_2$CH$_3$), 18.7 (CH$_3$), 15.5 (SCH$_2$*C*H$_3$), 14.2, 14.1 (2OCH$_2$*C*H$_3$). HREIMS *m/z* obsd 377.1510, calcd for $C_{16}H_{27}NO_7S$ 377.1508.

4.11.3. (1*R*,3*R*,5*R*,6*R*,7*R*,7a*R*)-3-diethoxycarbonylmethyl-5-ethylthio-6,7-dihydroxy-1-methyl-2-oxapyrrolizidine, 24a. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.26 (d, 1H, $J_{3,CH} = 8.5$, H-3), 4.43 (d, 1H, $J_{5,6} = 6.0$, H-5), 4.29–4.18 (m, 5H, H-6, 2CH_2CH$_3$), 3.98 (br s, 1H, H-7), 3.65 (dq, 1H, $J_{1,7a} = 8.5$, $J_{1,CH_3} = 6.0$, H-1), 3.47 [d, 1H, CH(CO$_2$Et)$_2$], 3.33 (d, 1H, $J_{6,OH-6} = 5.5$, OH-6), 3.27 (dd, 1H, $J_{7a,7} = 2.5$, H-7a), 2.81 (d, 1H, $J_{7,OH-7} = 7.5$, OH-7), 2.58, 2.57 (each q, each, 1H, $J_{H,H} = 7.5$, SCH_2CH$_3$), 1.33 (d, 3H, CH$_3$), 1.30–1.23 (m, 6 H, 2CH$_2$CH_3). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 166.4, 166.2 (2CO), 96.4 (C-3), 77.4 (C-1), 76.2 (C-5), 75.0 (C-7a), 73.7 (C-7), 70.4 (C-6), 61.7, 61.6 (2O*C*H$_2$CH$_3$), 58.7 [*C*H(CO$_2$Et)$_2$], 25.1 (S*C*H$_2$CH$_3$), 19.5 (SCH$_2$*C*H$_3$), 15.0 (CH$_3$), 14.1 (2OCH$_2$CH_3).

4.11.4. (1*S*,3*R*,5*S*,6*R*,7*R*,7a*R*)-6,7-dibenzoyloxy-3-diethoxycarbonylmethyl-5-ethylthio-1-methyl-2-oxapyrrolizidine, 25. Amorphous solid. $[\alpha]_D^{26} = +37$ (*c* 0.9, CH_2Cl_2); CIMS *m/z* 586 [(M+H)$^+$]; IR, 3071, 2991, 2928, 1736, 1649, 1545, 1371, 1116, 719 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04–7.31 (m, 10 H, Ar), 5.92 (d, 1H, $J_{6,7} = 4.5$, H-6), 5.68 (d, 1H, $J_{3,CH} = 8.0$, H-3), 5.63 (dd, 1H, $J_{7,7a} = 5.0$, H-7), 4.51 (s, 1H, H-5), 4.20, 4.08 (each m, each 2H, OCH_2CH_3), 3.98 (dq, 1H, $J_{1,7a} = 8.0$, $J_{1,CH_3} = 6.0$, H-1), 3.54 [(d, 1H, *H*C(CO$_2$Et)$_2$], 3.48 (dd, 1H, H-7a), 2.78, (q, 2H, $^3J_{H,H} = 7.5$, SCH_2CH$_3$), 1.37 (t, 3H, SCH$_2$CH_3). 1.33 (d, 3H, CH$_3$), 1.25, 1.13 (each t, each 3H, $J_{H,H=} = 7.5$, OCH$_2$CH_3). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 166.7 (2CO), 165.9 (CO), 165.7 (CO), 133.5–128.5 (Ar), 90.5 (C-3), 82.0 (C-6), 79.6 (C-1), 73.4 (C-7), 72.6 (2C, C-5, C-7a), 61.6, 61.4 (2O*C*H$_2$CH$_3$), 59.1 [*C*H(CO$_2$Et)$_2$], 27.5 (S*C*H$_2$CH$_3$), 19.3 (CH$_3$), 15.5 (SCH$_2$*C*H$_3$), 14.2 (2OCH$_2$*C*H$_3$). HRCIMS *m/z* obsd 586.2093, calcd for $C_{30}H_{36}NO_9S$ 586.2111. Conventional benzoylation of **24** (see Section 4.3) gave **25**.

4.11.5. (1*S*,3*R*,5*R*,6*R*,7*R*,7a*R*)-6,7-dibenzoyloxy-3-diethoxycarbonylmethyl-5-ethylthio-1-methyl-2-oxapyrrolizidine, 25a. Amorphous solid. FABMS *m/z* 744 [(M+Na)$^+$]; IR, 2980, 2932, 2870, 1734, 1609, 1514, 1370, 1252, 831, 719 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04–7.33 (m, 10 H, Ar), 5.75 (dd, 1H, $J_{5,6} = 6.1$, $J_{6,7} = 5.4$, H-6), 5.48 (dd, 1H, $J_{7,7a} = 2.4$, H-7), 5.35 (d, 1H, $J_{3,CH} = 7.71$, H-3), 4.72 (d, 1H, H-5), 4.24-4.18 (m,

4H, OCH_2CH_3), 3.97 (m, 1H, H-1), 3.58 [(d, 1H, $HC(CO_2Et)_2$], 3.53 (dd, 1H, $J_{1,7a} = 7.7$, H-7a), 2.61, (q, 2H, $^3J_{H,H} = 7.5$, SCH_2CH_3), 1.37 (t, 3H, SCH_2CH_3). 1.33 (d, 3H, $J_{1,CH_3} = 6.1$, CH_3), 1.27 (m, 6H, $2OCH_2CH_3$). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 166.3 (2CO), 165.9 (CO), 165.6 (CO), 133.4–128.4 (Ar), 96.2 (C-3), 78.2 (C-1), 74.0 (C-7), 73.5 (C-6), 72.8 (C-7a), 72.5 (C-5), 61.7, 61.6 ($2OCH_2CH_3$), 59.5 [$CH(CO_2Et)_2$], 25.2 (SCH_2CH_3), 19.8 (CH_3), 14.8 (SCH_2CH_3), 14.2, 14.1 ($2OCH_2CH_3$). HRCIMS m/z obsd 586.2120, calcd for $C_{30}H_{36}NO_9S$ 586.2111.

4.12. (*S*,3*S*,5*S*,6*R*,7*S*,7a*S*)-3-Diethoxycarbonylmethyl-5-ethylthio-6,7-dihydroxy-1-*p*-methoxybenzyloxymethyl-2-oxapyrrolizidine, 12

To a solution of **11** (0.036 mmol) in anhydrous methanol (6.8 mL) at rt, 1 M NaOMe in methanol (17.2 μL) was added. The process was controlled by TLC (CH_2Cl_2/MeOH, 15:1) until total deacylation of the starting material was achieved. After 4 h, the reaction mixture was neutralized with CO_2, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2, CH_2Cl_2/MeOH, 15:1). Compound **12** (70%) was an amorphous solid. CIMS m/z 514 [$(M+H)^+$]; ^1H 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), 3.78 (s, 3H, OCH_3), 3.73 [d, 1H, $CH(CO_2Et)_2$], 2.65–2.55 (m, 2H, SCH_2CH_3). ^{13}C NMR (125.7 MHz, MeOD) δ 169.5 (CO), 169.3 (CO), 160.8–114.7 (Ar), 95.8 (C-3), 79.8 (C-1), 77.5 (C-6), 74.1 (C-7), 74.0 (OCH_2MP), 72.0 (C-5), 71.0 (C-7a), 70.9 (CH_2OPMB), 61.3 (2C, OCH_2CH_3), 59.5 [$CH(CO_2Et)_2$], 55.7 (OCH_3), 22.0 (SCH_2CH_3), 19.3 (CH_3), 14.8, 14.5 ($2OCH_2CH_3$), 14.4 (SCH_2CH_3). HRCIMS m/z obsd 514.2112, calcd for $C_{24}H_{36}NO_9S$ 514.2111.

Acknowledgements

We thank the Dirección General de Enseñanza Superior e Investigación Científica of Spain and the Junta de Andalucia for financial support (grant numbers BQU2001-3740 and FQM-134), and the Ministerio de Educación, Cultura y Deporte, and the Fundación Cámara of the University of Seville, for the award of fellowships to F.J.S., and J.M.I., respectively. This work is part of the European Programme COST D13, action number D13/0001/98.

References and notes

1. Nubbemeyer, U. *Synthesis* **2003**, 961–1008.
2. See as examples (a) Hoces, M. *Eur. J. Org. Chem.* **2003**, 235–239; (b) Kunz, H.; Rück, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *105*, 336–358.
3. Fuentes, J.; Olano, D.; Pradera, M. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3443–3456.
4. Fuentes, J.; Gasch, C.; Olano, D.; Pradera, M. A.; Repetto, G.; Sayago, F. J. *Tetrahedron: Asymmetry* **2002**, *13*, 1743–1753.
5. For a recent review see Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515–553.
6. Hartmann, T.; Witte, L. Chemistry, Biology, and Chemoecology of the pyrrolizidine Alkaloids. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, 1995; Vol. 9, pp 155–233.
7. See as examples: (a) Driguez, H. In *Thiooligosaccharides in Glycobiology*; Driguez, H.; Thiem, J. Eds.; Top. Curr. Chem.; 1997; Vol. 187, p 85; (b) Bertozzi, C.; Bednasski, M. In *Modern Methods in Carbohydrate Synthesis*; Khan, S. H., O'Neil, R. A., Eds.; Harwood Academic: Amsterdam, 1996; pp 316–351.
8. Defaye, J.; Gelas, J. In *Studies in Natural Products Chemistry*; Attaur-Rahman Ed.; Elsevier Science: Amsterdam; 1991; Vol. 8.
9. For thioglycosides see as examples (a) Witczak, Z. J.; Boryczewski, D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3265–3268; (b) Fitz, W.; Rosenthal, P.; Wong, C. H. *Bioorg. Med. Chem. Lett.* **1996**, *4*, 1349–1353.
10. For iminocyclitols see as examples (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; (b) Deshpande, P. P.; Danishefsky, S. J. *Nature* **1997**, *387*, 164; (c) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199–215; (d) Papandreou, G.; Tong, M. K.; Ganem, B. *J. Am. Chem. Soc.* **1993**, *115*, 11682–11690; (e) Stutz, A. E. *Iminosugars as Glycosidase Inhibitors. Nojirimycin and Beyond*; Wiley VCH: Weinheim, 1999.
11. (a) Berges, D. A.; Fan, J.; Devinck, S.; Liu, N.; Dalley, N. K. *Tetrahedron* **1999**, *55*, 6759–6770; (b) Marek, D.; Wadouachi, A.; Uzau, R.; Beaupere, D.; Nowogrocki, G.; Laplace, G. *Tetrahedron Lett.* **1996**, *37*, 49–52; (c) Siriwardena, A. H.; Chiaroni, A.; Riche, C.; Grierson, D. S. *J. Org. Chem.* **1992**, *57*, 5661–5666.
12. Lee, R. E.; Smith, M. D.; Nash, R. J.; Griffiths, R. C.; McNeil, M.; Grewal, R. K.; Yan, W.; Besra, G. S.; Brenan, P. J.; Fleet, G. W. G. *Tetrahedron Lett.* **1997**, *38*, 6733–6736.
13. Paulsen, H.; Steinert, K.; Heyns, K. *Chem. Ber.* **1970**, *103*, 1599–1620.
14. Bernotas, C. R. *Tetrahedron Lett.* **1990**, *31*, 469–473.
15. Lombardo, M.; Fabbroni, S.; Trombini, C. *J. Org. Chem.* **2001**, *66*, 1264–1268.
16. Pham-Huu, D.-Ph.; Gizaw, Y.; Be-Miller, J. N.; Petrus, L. *Tetrahedron Lett.* **2002**, *43*, 383–385.
17. Dudot, B.; Micouin, L.; Bausanne, I.; Royer, J. *Synthesis* **1999**, 688–694.
18. (a) Pradera, M. A.; Sayago, F. J.; Illangua, J. M.; Gasch, C.; Fuentes, J. *Tetrahedron Lett.* **2003**, *44*, 6605–6608; (b) Sayago, F. J.; Fuentes, J.; Illangua, J. M.; Gasch, C.; Pradera, M. A. *Book of Abstracts*, Presented at the 12th European Carbohydrate Symposium Grenoble, France, July 6–11, 2003; p 229.
19. Gómez Sánchez, A.; Gómez Guillén, M.; Cert Ventulá, A.; Scheiddeger, V. *An. Real Soc. Españ. Fis. Quim.* **1968**, *64B*, 579–590.
20. Pretsch, E.; Bühlmann, P.; Affolter, C.; Herrera, A.; Martinez, R. *Determinación Estructural de Compuestos Orgánicos*; Springer Ibérica: Barcelona, 2001; pp 140–141.
21. Pretsch, E.; Bühlmann, P.; Affolter, C.; Herrera, A.; Martinez, R. *Determinación Estructural de Compuestos Orgánicos*; Springer Ibérica: Barcelona, 2001; p 120.

22. Nicolaou, K. C.; Veale, C. A.; Hwang, C. K.; Hutchinson, J.; Prasad, C. N. C.; Ogilvie, W. W. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 299.
23. Wüthrich, K.; Billeter, M.; Braun, W. *J. Mol. Biol.* **1983**, *169*, 949–961.
24. Boudot, D.; Canet, D.; Brondeau, J.; Boubel, J. C. *J. Magn. Reson.* **1989**, *83*, 428–433.
25. Boudot, D.; Roumestand, C.; To, F.; Canet, D. *J. Magn. Reson.* **1990**, *90*, 221–227.
26. Mairon, D.; Ikura, M.; Tschudin, R.; Bax, A. *J. Magn. Reson.* **1989**, *85*, 393–399.
27. Neuhaus, D.; Williamson, M. P. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH: New York, 1989.