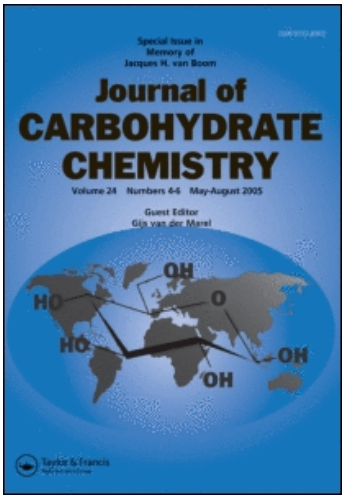


Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

New Stereospecific Rearrangements of Pyranosides

Ralf Miethchen[a]; Daniel Rentsch[a]; Michael Frank[a]
[a] Department of Organic Chemistry, University of Rostock, Rostock, Germany

To cite this Article Miethchen, Ralf , Rentsch, Daniel and Frank, Michael(1996) 'New Stereospecific Rearrangements of Pyranosides', Journal of Carbohydrate Chemistry, 15: 1, 15 — 31
To link to this Article: DOI: 10.1080/07328309608005421
URL: http://dx.doi.org/10.1080/07328309608005421

J. CARBOHYDRATE CHEMISTRY, 15(1), 15-31 (1996)

NEW STEREOSPECIFIC REARRANGEMENTS OF PYRANOSIDES

Ralf Miethchen,* Daniel Rentsch, Michael Frank

University of Rostock, Department of Organic Chemistry,
D-18051 Rostock (Germany)

Received April 5, 1995 - Final Form August 22, 1995

Dedicated to the engaging Hungarian carbohydrate chemist and kind colleague, Prof. Dr. András Lipták, on the occasion of his 60th birthday.

ABSTRACT

Methyl β-D-arabinopyranoside (**1**), phenyl 1-thio-ß-D-galactopyranoside (**3**), methyl α-L-fucopyranoside (**7**), methyl ß-L-fucopyranoside (**9**), 1,6-anhydro-ß-D-galactopyranoside (D-galactosan; **11**), and 1,6-anhydro-ß-D-mannopyranoside (D-mannosan; **14**) were stereospecifically converted in moderate up to good yields into methyl 4-*O*-cyclohexylcarbamoyl-2,3-*O*-(2,2,2-trichloroethylidene)-ß-D-lyxopyranoside (**2**), phenyl 4-*O*-cyclohexylcarbamoyl-6-*O*-formyl-2,3-*O*-(2,2,2-trichloroethylidene)-1-thio-ß-D-gulopyranoside (**4**) / phenyl 4-*O*-cyclohexylcarbamoyl-2,3-*O*-(2,2,2-trichloroethylidene)-1-thio-ß-D-gulopyranoside (**5**), methyl 4-*O*-cyclohexylcarbamoyl-2,3-*O*-(2,2,2-trichloroethylidene)-6-deoxy-α-L-gulopyranoside (**8**), methyl 2,3-*O*-(2,2,2-trichloroethylidene)-4-*O*-cyclohexylcarbamoyl-6-deoxy-ß-L-gulopyranoside (**10**), 1,6-anhydro-4-*O*-cyclohexylcarbamoyl-2,3-*O*-(2,2,2-trichloroethylidene)-ß-D-gulopyranoside (**12**), and 1,6-anhydro-2-*O*-cyclohexylcarbamoyl-3,4-*O*-(2,2,2-trichloroethylidene)-ß-D-altropyranoside (**15**), respectively, using a nonclassic pathway of chloral acetalisation with dicyclohexylcarbodiimide (DCC) as coagent. In the case of **1**, **3**, and **9**, chloral acetalisations yielded

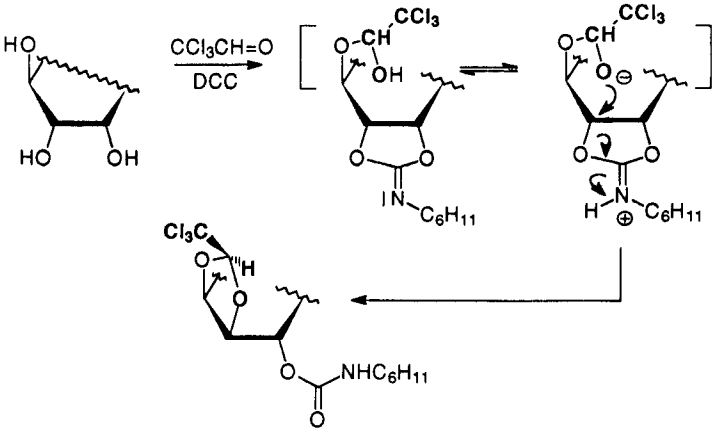
diastereomeric mixtures, e.g., the acetals **2**, **4**, **5**, and **10** consist of *endo*-H/*exo*-H dioxolane type acetals with preference of the *endo*-H form. In contrast to this, the compounds **7**, **11**, and **14** gave exclusively the *endo*-H diastereomers **8**, **12**, and **15**. Additionally, the structure of the anhydro compound **15** was confirmed by intramolecular glycosylation of the 2-*O*-cyclohexylcarbamoyl-3,4-*O*-(2,2,2-trichloroethylidene)-α-D-altropyranosyl fluoride (**17**). Finally, the 6-*O*-formyl-ß-D-gulopyranoside **4** was alternatively deformylated by methanol/triethylamine giving **5** and methanol/sodium methoxide yielding phenyl 6-*O*-cyclohexylcarbamoyl-2,3-*O*-(2,2,2-trichloroethylidene)-1-thio-β-D-gulopyranoside (**6**). The carbamoyl protecting group of **12** was cleaved by refluxing with methanolic sodium methoxide solution giving 1,6-anhydro-2,3-*O*-(2,2,2-trichloroethylidene)-ß-D-gulopyranoside (**13**).

INTRODUCTION

Recently, we reported a new method for stereospecific transformations of monosaccharides in connection with a nonclassic mechanism of acetalisation.[1-3] Thus, high active carbonyl compounds, such as hexafluoroacetone[1] or chloral,[2, 3] reacted in the presence of dicyclohexylcarbodiimide (DCC) as coagent with various methyl pyranosides forming cyclic acetals under nonacidic conditions. In this way, the following transformations were realised by selective inversion at the C-atom 3:

D-*Lyxo*	→	D-*Arabino*
L-*Arabino*	→	L-*Lyxo*
D-*Manno*	→	D-*Altro*
D-*Galacto*	→	D-*Gulo*
L-*Rhamno*	→	6-Deoxy-L-*altro*

The key step of the reaction is the *in situ* formation of a cyclic imidocarbonic ester (or isourea) intermediate,[3, 4] which is intramolecularly attacked by a deprotonated neighbouring hemiacetal moiety in an S_N2-type reaction as shown in Scheme 1. Such a transformation is achievable when the pyranoside (or another *vicinal* cyclic triol) shows a 2,3-*cis* / 3,4-*trans* or 2,3-*trans* / 3,4-*cis* arrangement of the OH groups. In this case the configuration of the chiral central C atom can be inverted (see also reference 5).



Scheme 1

A further favourable aspect of this new method results from the simultaneous introduction of an acid-stable cyclic acetal protecting group and of a carbamoyl function in the carbohydrate molecule. Certainly, the prochiral aldehyde produces two diastereomers (*endo*-H : *exo*-H $\geq$15:1).[2,3] Whereas the previous formation of the chiral hemiacetals is an equilibrium reaction, the following acetalisation step proceeds irreversibly, i.e., it occurs in a kinetically controlled way. From this follows that the *endo*-H/*exo*-H ratio of diastereomeric acetals strongly depends on the latter reaction. On the other hand, it is known that 1,3-dioxolane systems show a strong preference for the *exo*-H (*endo*-alkyl) isomers, when the acetalisation is an equilibrium reaction. This was rationalised by assuming that the 1,3-dioxolane ring adopts a suitable half-chair (or twist) conformation.[6] Consequently, a preference for the *endo*-H form can only take place when the acetalisation step is kinetically controlled (see also reference 7).

If required, the pure *endo*-H derivative can be obtained in some cases by recrystallisation of the *endo*-H/*exo*-H mixture (e.g., from ethanol[8]). In order to remove the acid-stable protecting group, the chloral acetals may be converted into the acid-labile ethylidene acetals by treatment with Raney-Ni[9] or tributylstannane,[7] which are then cleaved in the usual way. A urethane moiety may be quantitatively cleaved by treatment with boiling methanol/sodium methoxide.[2,3]

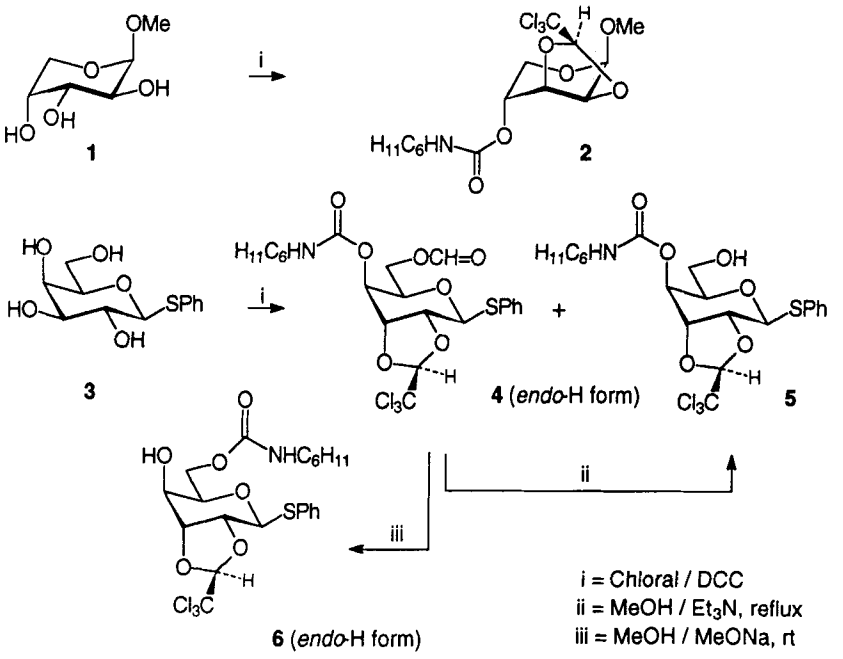
RESULTS AND DISCUSSION

In this paper wider applications of the new method of regio- and stereoselective rearrangements of monosaccharides are reported using a nonclassic pathway of acetalisation. We selected the ß-D-arabinopyranoside **1**, the phenyl 1-thio-ß-D-galactopyranoside **3**, both anomers of L-fucopyranosides **7** and **9**, as well as the 1,6-anhydro sugars D-galactosan (**11**) and D-mannosan (**14**) for the stereospecific transformations via inversion at their 3-position (Scheme 2-4).

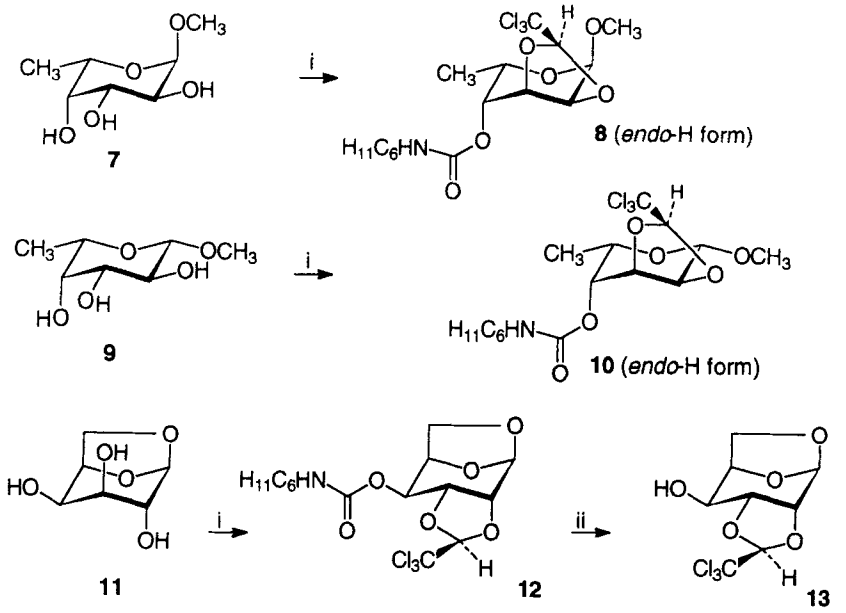
The acetalisations were carried out by refluxing solutions of the sugars with chloral and DCC in 1,2-dichloroethane for about 4.5 h following our previous reports.[1-3] Under these conditions the D-arabinopyranoside **1** was converted into methyl 4-*O*-cyclohexylcarbamoyl-2,3-*O*-(2,2,2-trichloroethylidene)-ß-D-lyxopyranoside (**2**) in a yield of 66%. Because of the prochirality of chloral, an additional chiral centre was generated, so that compound **2** consisted of two diastereomeric cyclic acetals. The *endo*-H isomer predominated over the *exo*-H diastereomer (20:1, determined by ^{1}H NMR spectroscopy). Because both diastereomers do not show differences in their chromatographic behaviour, separation was not possible. On the other hand, such a chromatographic behaviour could be useful when the chloral acetal moiety is only used as a protecting group.

The thiogalactoside **3** reacted with chloral/DCC yielding *endo*-H/*exo*-H diastereomeric acetal mixtures of both the gulopyranosides **4** and **5**. In order to obtain moderate yields (63%) a longer reaction time (8 h) was necessary. Under these conditions phenyl 4-*O*-cyclohexylcarbamoyl-6-*O*-formyl-2,3-*O*-(2,2,2-trichloroethylidene)-1-thio-ß-D-gulopyranoside (**4**) and phenyl 4-*O*-cyclohexylcarbamoyl-2,3-*O*-(2,2,2-trichloroethylidene)-1-thio-ß-D-gulopyranoside (**5**) were formed in a ratio of about 10:1 (detected by NMR); Scheme 2. Generally, longer reaction times favoured the formation of the formyl derivative **4** instead of **5**. The formylation is caused by a haloform reaction of chloral (see also references 2 and 3). It should be noted that the acetalisation of the thiogalactoside **3** to the gulosides **4** and **5** proceeds with a modest *endo*-H-selectivity in regard to the new chiral centre of the acetal grouping. The ratio of the *endo*-H/*exo*-H diastereomers of **4** and **5** is about 6.5:1. (usually $\geq$ 15:1; references 2 and 3).

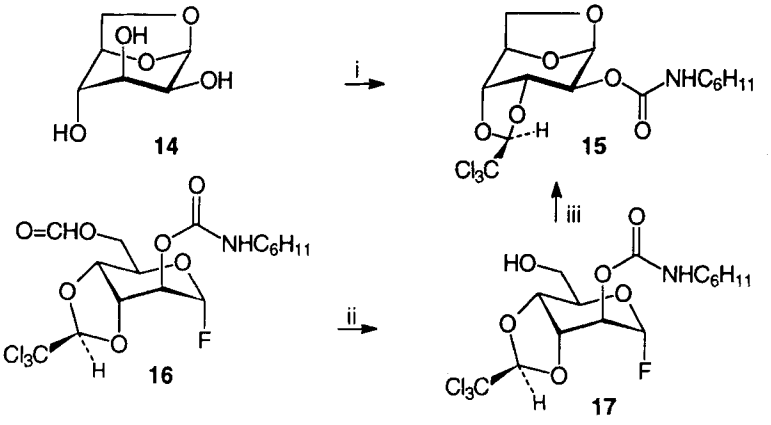
Refluxing the mixture of **4** and **5** with methanol/triethylamine caused deformylation of compound **4** to **5** without intramolecular migration of the carbamoyl group. On the other



Scheme 2



Scheme 3



i = Chloral, DCC ($ClCH_2CH_2Cl$); ii = MeOH, Et_3N; iii = $Et_2O \cdot BF_3$, CH_2Cl_2

Scheme 4

hand, treatment of the same mixture or of the *endo*-H/*exo*-H diastereomeric mixture of **4** alone with methanol/sodium methoxide (Zemplén reagent) gave **6** in good yield, e.g. the deformylation was accompanied by migration of the carbamoyl group from the 4- to the 6-position. This is noticeable, because a 4-*O*- or a 6-*O*-glycosyl acceptor can alternatively be obtained in this simple way. Previously, we had observed such a migration of a carbamoyl group by treatment of methyl 4-*O*-cyclohexylcarbamoyl-6-*O*-formyl-2,3-*O*-(2,2,2-trichloroethylidene)-ß-D-gulopyranoside with the Zemplén reagent.[3] The procedure of the carbamoyl group rearrangement is illustrated in the experimental part by preparation of **6** from **4**. The pure *endo*-H diastereomer of **6** could be separated from the corresponding *endo*-H/*exo*-H diastereomeric mixture by column chromatography in 78% yield.

Furthermore, the methyl L-fucosides **7** and **9** were converted by the chloral/DCC reagent giving the L-gulo derivatives **8** and **10**, respectively, in good yields; Scheme 3. It is noticeable that the α-anomeric fucoside **7** exclusively formed an *endo*-H acetal. The high stereoselectivity of this reaction is probably caused (or powerfully supported) by the strong steric interaction between the methoxy in position 1 and the trichloromethyl group; Scheme 3.

In contrast, the ß-L-fucoside **9** gave as expected both diastereomers of **10** (*endo*-H/*exo*-H = 4:1). Because the proportion of the *exo*-H diastereomer was unexpectedly high, it was

possible to collect more NMR spectroscopic details of the *exo*-H form than usual. The diastereomers were not chromatographically distinguishable under the reported conditions, however, the pure *endo-H* isomer of **10** could be separated by recrystallisation of the diastereomeric mixture from ethanol.

Finally, the 1,6-anhydro sugars **11** and **14** were converted into the corresponding acetals **12** and **15** by treatment with chloral/DCC. The yields of the products **12** (30%) and **15** (44%) were relatively low. However, the reaction mixture obtained from D-galactosan (**11**) contained in relatively large amount a crystalline product of the general composition $C_8H_9Cl_3O_5$ (supported by mass spectroscopy (*m/z* 291; M^+) and C,H,Cl-analysis). The by-product is not identical with 1,6-anhydro-2,3-*O*-(2,2,2-trichloroethylidene)-β-D-gulopyranoside (**13**) obtained from **12** by cleavage of the carbamoyl group using boiling methanol/sodium methoxide (Scheme 3). In spite of H,H-COSY, C,H-COSY, and NOESY experiments, the structure of this by-product can still not be given. Some NMR details were inconsistent with expected structures. Therefore, we will investigate by preparation of some derivatives of the compound and then report its correct structure.

In order to confirm the structure of the anhydro altropyranoside **15**, which was directly prepared from **14**, we carried out an independent synthesis of this compound from 2-*O*-cyclohexylcarbamoyl-6-*O*-formyl-3,4-*O*-(2,2,2-trichloroethylidene)-α-D-altropyranosyl fluoride[2,10] (**16**) according to Scheme 4. The deformylation of **16** to the fluoride **17** was very easily achieved by treating **16** with methanol/triethylamine. The following ring closure to **15** required an activation of **17** by BF_3-etherate (analogously to reference 11). Both the independently synthesised products **15** showed the same physical properties. Furthermore, in the case of the 1,6-anhydro derivative **12**, the ^{1}H NMR coupling constants (J) of the sugar ring protons are very similar to those of the structurally analogous 1,6-anhydro-4-*O*-benzoyl-2,3-*O*-(*R*)-benzylidene-ß-D-gulopyranose.[12] This fact can be regarded as confirmation of the structure. The conformation of the latter compound was reported in the literature as flattened $^1C_4$ (D) caused by the *cis*-fusion of the dioxolane ring.[12]

The structures of all compounds are supported by their ^{1}H and ^{13}C NMR spectral data, which were also compared with data of the previously reported similar derivatives.[3]

Thus, the *endo*-H singlets of the cyclic acetals [δ 5.53 (**2**), 5.47 (**4**), 5.50 (**5**), 5.75 (**10**)] show a characteristic downfield shift in comparison to the signals of the *exo*-H form [5.45 (**2**), 5.32 (**4**), 5.35 (**5**), 5.49 (**10**)]. This phenomena was reported to be typical for diastereomeric chloral acetals.[7,9] Additionally, we checked this result by selected NOESY experiments.[3] Finally, the ratio of the *endo*-H/*exo*-H diastereomers could be determined by integration of these peaks. Various peaks of the *exo*-H acetals were overlapped by those of the corresponding major isomer. Therefore, the spectra of the *endo*-H isomer could completely be evaluated, whereas in the case of the *exo*-H form only the singlet of the acetal-H and doublet of H-1 were always distinguishable. The L-gulose derivative **10** was an exception, because of the relatively large amount (*endo*-H/*exo*-H 4:1) of *exo*-H diastereomer in the mixture (see experimental part).

The significant downfield shifts of the signals of the protons H-2 and H-3 (e.g. in $CDCl_3$ **2**: δ 4.53 and 4.47, respectively; or **12**: δ 4.48 and 4.61, respectively) and likewise of the protons H-3 (δ 4.65) and H-4 (δ 4.54) of **15** (recorded in $CDCl_3$) show that the acetalisation occurred in these positions. Furthermore, the melting point and the ^{1}H NMR data ($CDCl_3$) of the ß-D-lyxopyranoside **2** are identical with the corresponding data of the enantiomeric methyl 4-*O*-cyclohexylcarbamoyl-2,3-*O*-(2,2,2-trichloroethylidene)-β-L-lyxopyranoside discussed in reference 3 in more detail. The ^{1}H NMR chemical shifts of the thiogulosides **4** and **5** (H-2: δ 4.45/4.46 ; H-3: δ 4.70/4.72, and H-4: δ 5.24/5.27) are characteristic for the existing protecting group arrangement, as are the values of their coupling constants. Both series of spectral data are comparable with those of methyl 4-*O*-cyclohexylcarbamoyl-6-*O*-formyl-2,3-*O*-(2,2,2-trichloroethylidene)-ß-D-gulopyranoside reported in reference 3.

In order to distinguish between the 4-carbamoyl and the 6-*O*-carbamoyl derivative the ^{1}H NMR chemical shifts of the protons in 4- and 6-position and the couplings of the free OH group were used.[3] The chemical shifts of **5** (H-4: δ 5.27 and H-6/H6': δ 3.56/3.72) correlate with the corresponding data of the two regioisomeric methyl D-gulosides[3] (4-*O*-carbamoyl H-4: δ 4.94; H-6/H-6': δ 3.52). The 6-*O*-carbamoyl derivative **6** shows a significantly smaller δ-value for H-4 (4.09) and a larger one for H-6/H-6' (δ 4.20 and 4.26, respectively).[3]

EXPERIMENTAL

^{1}H and ^{13}C NMR: Bruker AC 250; internal standard TMS, J values in Hz. TLC: Silica gel foils 60 F_{254} (Merck). Column chromatography: Silica gel 60 (63-200 μm) (Merck). Melting points: Polarising microscope Leitz Laborlux 12 Pol equipped with a hot stage Mettler FP 90. Chemicals: Chloral (Riedel de Haen), dicyclohexylcarbodiimide, methyl ß-D-arabinopyranoside, 1,6-anhydro-ß-D-mannopyranose, and 1,6-anhydro-ß-D-galactopyranose (Aldrich). The TLC detection of all D-gulose derivatives was only satisfactory with a methanol/sulphuric acid mixture containing anhydrous zinc chloride. The *endo/exo* isomers of the prepared chloral acetals were not separated in all cases. Therefore, the $[\alpha]_D$ value was not determined for the *endo*-H/*exo*-H diastereomeric mixture of **2**.

General procedure. 6 mmol of the powdered pyranoside (**1**, **3**,[13] **11**, **7**,[14,15] **9**,[14,15] **14**), 15 mmol of dicyclohexylcarbodiimide (DCC), 21 mmol of chloral and 1,2-dichloroethane (10 mL) were refluxed for 4.5 h, whereby the sugar dissolved. Then the reaction mixture was cooled to room temp and filtered to remove the precipitated *N,N'*-dicyclohexylurea. The filtrate was shaken for 10 min with 0.1 n aq HCl in order to destroy excess DCC. Finally, the organic phase was washed with a saturated aq $NaHCO_3$ solution and water, dried over $MgSO_4$ and concentrated in a rotary evaporator under reduced pressure. The residue was purified by column chromatography (Silica gel 60 /63-200 μm; eluent: toluene/ethyl acetate).

Methyl 4-*O*-cyclohexylcarbamoyl-2,3-*O*-(2,2,2-trichloroethylidene)-β-D-lyxopyranoside (**2**). Powdered methyl β-D-arabinopyranoside (**1**, 1.0 g, 6.1 mmol), dicyclohexylcarbodiimide (3.1 g, 15.2 mmol), chloral (3.1 g, 21.3 mmol) and 1,2-dichloroethane (15 mL) were refluxed for 4.5 h and worked up as described in the general procedure. The yellowish oily residue was purified by column chromatography (eluent: ethyl acetate/toluene 1:6, $R_f = 0.51$) yielding 1.70 g (66 %) of **2** as a mixture of the *endo*-H/*exo*-H diastereomers (20:1); mp 161-163 °C (heptane); ^{1}H NMR ($CDCl_3$), *endo*-H diastereomer: δ 1.23 (m, 5H, cyclohexyl CH_2), 1.63 (m, 3H, cyclohexyl CH_2), 1.93 (m, 2H, cyclohexyl CH_2), 3.41 (s, 3H, OCH_3), 3.45 (m, 1H, cyclohexyl CH), 3.56 (ddd, 1H, $^{4}J_{3,5'}$ = 1.6 Hz, $J_{4,5}$ = 2.0 Hz, $J_{5,5'}$ = 12.9 Hz, H-5), 4.00 (dd, 1H, $J_{4,5'}$ = 2.4 Hz, H-5'), 4.47 (ddd, 1H, $J_{2,3}$ =

5.5 Hz, $J_{3,4}$ = 2.5 Hz, H-3), 4.53 (dd, 1H, $J_{1,2}$ = 4.9 Hz, H-2), 4.68 (d, 1H, $J_{NH,CH}$ = 7.6 Hz, NH), 4.80 (d, 1H, H-1), 5.06 (ddd, 1H, H-4), 5.53 (s, 1H, *endo*-acetal-H); 5.45 *exo*-acetal-H); ^{13}C NMR (DMSO-d6) δ 24.7, 25.3, 32.7 (cyclohexyl CH_2), 49.6 (cyclohexyl CH), 55 ¯ (OCH_3), 57.4 (C-6), 67.1, 73.2, 75.1, 75.1 (C-2, C-3, C-4, C-5), 96.0 (C-1), 99.6 (CCl_3), 107.1 (acetal C), 154.1 (carbamoyl C=O).

Anal. Calcd for $C_{15}H_{22}Cl_3NO_6$ (418.7): C, 43.03; H, 5.29; N, 3.35. Found: C, 43.06; H, 5.30; N, 3.41.

Phenyl 4-*O*-cyclohexylcarbamoyl-6-*O*-formyl-2,3-*O*-(2,2,2-trichloroethylidene)-1-thio-β-D-gulopyranoside (**4**) and **phenyl 4-*O*-cyclohexylcarbamoyl-2,3-*O*-(2,2,2-trichloroethylidene)-1-thio-β-D-gulopyranoside** (**5**). Powdered phenyl 1-thio-β-D-galactopyranoside (**3**) (1.0 g, 3.7 mmol), dicyclohexylcarbodiimide (1.89 g, 9.2 mmol), chloral (1.9 g, 12.9 mmol) and 1,2-dichloroethane (15 mL) were refluxed for 8 h, whereby **3** dissolved. After the reaction mixture was cooled, it was divided into two equal portions. One portion was worked up as described in the general procedure and the crude product was purified by column chromatography (eluent: ethyl acetate/toluene 1:15; **4**: R_f = 0.35, **5**: R_f = 0.12) yielding 0.48 g of **4** (57% related to 1.85 mmol of **3**). The formyl derivative **4** is a noncrystalline solid (*endo*-H/*exo*-H diastereomer 6.3:1); ^{1}H NMR ($CDCl_3$), *endo*-H form: δ 1.24 (m, 5H, cyclohexyl CH_2), 1.65 (m, 3H, cyclohexyl CH_2), 1.92 (m, 2H, cyclohexyl CH_2), 3.46 (m, 1H, cyclohexyl CH), 4.06 (ddd, 1H, $J_{4,5}$= 1.2 Hz, $J_{5,6}$= 4.9 Hz, $J_{5,6'}$= 7.6 Hz, H-5), 4.25 (dd, 1H, $J_{6,6'}$= 12.2 Hz, H-6), 4.36 (dd, 1H, H-6'), 4.45 (dd, 1H, $J_{1,2}$= 9.5 Hz, $J_{2,3}$= 4.9 Hz, H-2), 4.64 (d, 1H, H-1), 4.70 (dd, 1H, $J_{3,4}$= 2.4 Hz, H-3), 4.76 (d, 1H, $J_{NH,CH}$= 8.2 Hz, NH), 5.24 (dd, 1H, H-4), 5.47 (s, 1H, *endo*-acetal H), 7.24-7.60 (5H, phenyl-H), 8.01 (s, 1H, formyl-H); ^{13}C NMR ($CDCl_3$): δ 24.6, 25.4, 33.2 (cyclohexyl CH_2), 50.3 (cyclohexyl CH), 61.7 (C-6), 66.0, 73.4, 75.0, 76.3 (C-2, C-3, C-4, C-5), 84.7 (C-1), 98.7 (CCl_3), 106.6 (acetal C), 128.1-132.9 (phenyl-C), 153.7 (carbamoyl C=O), 160.2 (formyl-C); ^{1}H NMR ($CDCl_3$), *exo*-H diastereomer: δ 5.10 (d, 1H, $J_{1,2}$ = 9.2 Hz, H-1), 5.32 (s, *exo*-acetal-H).

Anal. Calcd for $C_{22}H_{26}Cl_3NO_7S$ (554.88): C, 47.62; H, 4.72; N, 2.52; S, 5.78. Found: C, 47.97; H, 4.99; N, 2.69; S, 5.59.

The second portion of the **4/5** crude product was treated with methanol (10 mL) and Et_3N (0.5 mL), refluxed for 10 min, and then worked up as described for compound **2**. After purification of the residue by column chromatography (eluent: ethyl acetate/toluene: 1:6, R_f = 0.28), 0.61 g (63 % related to 1.85 mmol of **3**) of **5** was obtained as a diastereomeric mixture (*endo*-H/*exo*-H = 6.5:1). The colourless crystals melt at 176.5-178.5 °C (ether/heptane); ^{1}H NMR ($CDCl_3$), *endo*-H diastereomer: δ 1.24 (m, 5H, cyclohexyl CH_2), 1.66 (m, 3H, cyclohexyl CH_2), 1.93 (m, 2H, cyclohexyl CH_2), 3.48 (m, 1H, cyclohexyl CH), 3.56 (dd, 1H, $J_{5,6}$ = 7.6 Hz, $J_{6,6'}$= 11.9 Hz, H-6), 3.72 (dd, 1H, $J_{5,6'}$ = 6.1 Hz, H-6'), 3.88 (ddd, 1H, $J_{4,5}$ = 1.2 Hz, H-5), 4.46 (dd, 1H, $J_{1,2}$ = 9.5 Hz, $J_{2,3}$ = 5.2 Hz, H-2), 4.67 (d, 1H, H-1), 4.72 (dd, 1H, $J_{3,4}$ = 2.8 Hz, H-3), 4.85 (d, 1H, $J_{NH,CH}$ = 8.2 Hz, NH), 5.27 (dd, 1H, H-4), 5.50 (s, 1H, *endo*-acetal H), 7.24-7.60 (5H, phenyl-H); ^{13}C NMR ($CDCl_3$) δ 24.7, 25.4, 33.1 (cyclohexyl CH_2), 50.4 (cyclohexyl CH), 60.1 (C-6), 66.2, 73.5, 75.3, (C-2, C-3, C-4, C-5), 84.8 (C-1), 98.8 (CCl_3), 106.6 (acetal C), 128.0-133.0 (phenyl-C), 154.9 (carbamoyl C=O; ^{1}H NMR ($CDCl_3$), *exo*-H form: δ 4.27 (dd, 1H, $J_{1,2}$ = 9.2 Hz, $J_{2,3}$ = 5.8 Hz, H-2), 4.43 (dd, 1H, $J_{3,4}$ = 2.1 Hz, H-3), 5.14 (d, 1H, H-1), 5.35 (s, *exo*-acetal-H).

Anal. Calcd for $C_{21}H_{26}Cl_3NO_6S$ (526.86): C, 47.87; H, 4.97; N, 2.66; S, 6.09. Found: C, 47.78; H, 5.06; N, 2.93; S, 5.83.

Phenyl 6-*O*-cyclohexylcarbamoyl-2,3-*O*-(2,2,2-trichloroethylidene)-1-thio-β-D-gulopyranoside (6). The 4-*O*-cyclohexylcarbamoyl-D-gulopyranoside **5** (0.20 g, 0.38 mmol) was treated with a solution of sodium methoxide (0.062 g, 1.14 mmol) in anhyd methanol (3 mL) at room temp for 6 h. TLC (eluent: ethyl acetate/chloroform 1:10) showed two spots representing the diastereomers of **6** at R_f = 0.39 (*exo*-H diastereomer) and R_f = 0.48 (*endo*-H form). After neutralisation of the mixture with an acidic ion exchange resin and evaporation of the solvent, the *endo*-H diastereomer of **6** was separated by column chromatography using the same eluent. Yield: 155 mg (78%) of crystalline *endo*-H **6**, mp 159-160 °C (ether/hexane); $[\alpha]^{21}_D$ -8.82 (*c* 0.85, chloroform); ^{1}H NMR ($CDCl_3$), *endo*-H form: δ 1.26 (m, 5H, cyclohexyl CH_2), 1.51 (m, 1H, cyclohexyl CH_2), 1.71 (m, 2H, cyclohexyl CH_2), 1.87 (m, 2H, cyclohexyl CH_2), 3.40 (m, 1H, cyclohexyl

CH), 3.98 (ddd, 1H, $J_{4,5}$ = 1.2 Hz, $J_{5,6}$ = 7.0 Hz, $J_{5,6'}$ = 5.5 Hz, H-5), 4.09 (ddd, 1H, $J_{3,4}$ = 2.4 Hz, $J_{4,OH}$ = 6.7 Hz, H-4), 4.20 (dd, 1H, $J_{6,6'}$ = 11.9 Hz, H-6), 4.29 (dd, 1H, H-6'), 4.51 (dd, 1H, $J_{1,2}$ = 9.8 Hz, $J_{2,3}$ = 5.2 Hz, H-2), 4.62 (d, 1H, OH-4), 4.75 (dd, 1H, H-3), 4.67 (d, 1H, H-1), 5.78 (s, 1H, *endo*-acetal H), 6.12 (d, 1H, $J_{NH,CH}$ = 8.2 Hz, NH), 7.38-7.56 (5H, phenyl-H); ^{13}C NMR ($CDCl_3$) δ 24.7, 25.4, 33.3 (cyclohexyl CH_2), 50.2 (cyclohexyl CH), 61.9 (C-6), 64.6, 74.4, 75.0, 78.3 (C-2, C-3, C-4, C-5), 84.8 (C-1), 99.1 (CCl_3), 106.6 (acetal C), 127.9-132.9 (phenyl-C), 155.8 (carbamoyl C=O).

Anal. Calcd for $C_{21}H_{26}Cl_3NO_6S$ (526.86): C, 47.87; H, 4.97; N, 2.66; S, 6.09. Found: C, 47.88; H, 4.97; N, 2.80; S, 5.98.

Methyl 4-*O*-cyclohexylcarbamoyl-2,3-*O*-(2,2,2-trichloroethylidene)-6-deoxy-α-L-gulopyranoside (8). Powdered methyl-α-L-fucopyranoside (**7**, 1.0 g, 5.62 mmol),[14,15] dicyclohexylcarbodiimide (2.9 g, 14 mmol), chloral (2.9 g, 19.7 mmol), and 1,2-dichloroethane (10 mL) were refluxed for 4.5 h and worked up as described in the general procedure. After purification by column chromatography (eluent: toluene/ethyl acetate = 15:1; R_f = 0.35) 1.41 g of **8** (58%, pure *endo*-H-diastereomer) were obtained; colourless needles, mp 130-132 °C (ethanol or heptane); $[\alpha]^{22}_D$ -39.64 (*c* 1.11, chloroform); ^{1}H NMR (DMSO-d6), *endo*-H form: δ 1.11 (d, 3H, CH_3), 3.34 (s, 3H, OCH_3), 4.11 (dq, 1H, $J_{5,6}$ = 6.7 Hz, H-5), 4.38 (dd, 1H, $J_{3,4}$ = 2.4 Hz, H-3), 4.67 (dd, 1H, $J_{2,3}$ = 5.5 Hz, H-2), 4.84-4.90 (m, 2H, $J_{4,5}$ = 2.1 Hz, H-1, H-4), 5.49 (s, 1H, *endo*-H acetal); ^{13}C NMR (DMSO-d6) δ 15.3 (C-6), 24.7, 25.2, 32.5, 32.7 (cyclohexyl CH_2), 49.9 (cyclohexyl CH), 55.1 (OCH_3), 68.2, 71.1, 74.9, 77.9 (C-2, C-3, C-4, C-5), 96.7 (C-1), 99.5 (CCl_3), 107.3 (acetal-C), 154.7 (carbamoyl C=O).

Anal. Calcd for $C_{16}H_{24}Cl_3NO_6$ (432.73): C, 44.41; H, 5.59; N, 3.24; Cl, 24.58. Found: C, 44.93; H, 5.50; N, 3.23; Cl, 24.50.

Methyl 4-*O*-cyclohexylcarbamoyl-2,3-*O*-(2,2,2-trichloroethylidene)-6-deoxy-ß-L-gulopyranoside (10). Methyl-ß-L-fucopyranoside (**9**, 120 mg, 0.67 mmol)[14,15] dicyclohexylcarbodiimide (236 mg, 1.1 mmol), chloral (236 mg, 1.6 mmol), and 1,2-dichloroethane (15 mL) were refluxed for 4.5 h and worked up as described in the general procedure. After purification by column chromatography (eluent: toluene/ethyl acetate =

30:1; R_f = 0.20) 233 mg (80.2%) of **10** were isolated as a crystalline *endo*-H/*exo*-H diastereomeric mixture of 4:1. Recrystallisation from ethanol yielded 100 mg of the pure *endo*-H form of **10**; mp 139-141 °C (ethanol); $[\alpha]^{22}_D$ +56.13 (*c* 0.93, chloroform); ^{1}H NMR (DMSO-d6), *endo*-H form: δ 1.14 (d, 3H, CH_3), 3.43 (s, 3H, OCH_3), 3.91 (dq, 1H, $J_{5,6}$ = 6.4 Hz, H-5), 4.21 (dd, 1H, $J_{2,3}$ = 5.5 Hz, H-2), 4.48 (dd, 1H, $J_{3,4}$ = 2.1 Hz, H-3), 4.54 (d, 1H, $J_{1,2}$ = 7.0 Hz, H-1), 4.84 (dd, 1H, $J_{4,5}$ = 1.5 Hz, H-4), 5.75 (s, 1H, *endo*-H acetal); ^{1}H NMR (DMSO-d6), *exo*-H form: δ 3.40 (s, 3H, OCH_3), 4.38 (dd, 1H, $J_{3,4}$ = 2.4 Hz, H-3), 4.67 (d, 1H, $J_{1,2}$ = 6.7 Hz, H-1), 4.87 (dd, 1H, $J_{4,5}$ = 1.8 Hz, H-4), 5.49 (s, 1H, *exo*-H acetal); ^{13}C NMR (DMSO-d6) δ 15.4 (C-6), 24.7, 25.2, 32.5, 32.6 (cyclohexyl CH_2), 49.8 (cyclohexyl CH), 56.1 (OCH_3), 67.9, 68.0, 76.3, 77.1 (C-2, C-3, C-4, C-5), 99.4 (C-1), 100.6 (CCl_3), 105.6 (acetal-C), 154.7 (carbamoyl C=O).

Anal. Calcd for $C_{16}H_{24}Cl_3NO_6$ (432.73): C, 44.41; H, 5.59; N, 3.24. Found: C, 44.40; H, 5.44; N, 3.11.

1,6-Anhydro-4-*O*-cyclohexylcarbamoyl-2,3-*O*-(2,2,2-trichloroethylidene)-β-D-gulopyranoside (**12**). Powdered 1,6-anhydro-β-D-galactopyranoside (**11**, 0.75 g, 4.6 mmol), dicyclohexylcarbodiimide (2.4 g, 11.6 mmol), chloral (2.4 g, 16.3 mmol) and 1,2-dichloroethane (15 mL) were refluxed for 4.5 h and worked up as described in the general procedure. The TLC of the crude product (eluent: ethyl acetate/toluene 1:8) showed two major products; **12** (R_f = 0.52) and a unidentified by-product (R_f = 0.21) as well as traces of a few other by-products. Both the main products were separated by column chromatography (eluent: ethyl acetate/toluene 1:20, **12**: R_f = 0.21, by-product: R_f = 0.11). Yield of **12** (0.58 g, 30 %, pure *endo*-H diastereomer); mp 154-156 °C (ether/heptane); $[\alpha]^{22}_D$ +69.71 (*c* 1.03, chloroform); ^{1}H NMR ($CDCl_3$), *endo*-H form: δ 1.23 (m, 5H, cyclohexyl CH_2), 1.63 (m, 3H, cyclohexyl CH_2), 1.91 (m, 2H, cyclohexyl CH_2), 3.45 (m, 1H, cyclohexyl CH), 3.68 (ddd, 1H, $^4J_{4,6}$ = 1.2 Hz, $J_{5,6}$ = 5.3 Hz, $J_{6,6'}$ = 7.9 Hz, H-6), 3.89 (dd, 1H, $J_{5,6'}$ = 1.2 Hz, H-6'), 4.48 (dd, 1H, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 6.4 Hz, H-2), 4.61 (dd, 1H, $J_{3,4}$ = 5.8 Hz, H-3), 4.68 (d, 1H, $J_{NH,CH}$ = 7.6 Hz, NH), 4.72 (ddd, 1H, $J_{4,5}$ = 5.3 Hz, H-5), 4.91 (dd, 1H, H-4), 5.53 (s, 1H, acetal H), 5.61 (d, 1H, H-1); ^{13}C NMR ($CDCl_3$) δ 24.7, 25.4, 33.2

(cyclohexyl CH_2), 50.2 (cyclohexyl CH), 66.3 (C-6), 71.5, 71.8, 77.1, 77.8 (C-2, C-3, C-4, C-5), 98.4 (C-1), 99.3 (CCl_3), 108.0 (acetal C), 153.9 (carbamoyl C=O).

Anal. Calcd for $C_{15}H_{20}C_{13}NO_6$ (416.7): C, 43.23; H, 4.84; N, 3.36. Found: C, 43.36; H, 4.84; N, 3.42.

By-product: (0.36 g, 26.9%); mp 138.5-139.5 °C ($CHCl_3$); $[\alpha]^{21}_D$ -27.22 (*c* 0.97, chloroform); MS (70 eV): *m/z* = 291 (M^+).

Anal. Calcd for $C_8H_9Cl_3O_5$ (291.52): C, 32.96; H, 3.11. Found: C, 33.07 ; H, 2.29.

1,6-Anhydro-2,3-*O*-(2,2,2-trichloroethylidene)-β-D-gulopyranoside (13). A solution of **12** (0.2 g, 0.48 mmol) in abs methanol (3 mL) containing sodium methoxide (0.06 g, 1.4 mmol) was refluxed for 2 h. The reaction mixture was cooled and neutralised with an acidic ion exchange resin. After evaporation of the solvent, **13** was separated from the formed methylurethane by column chromatography (eluent: ethyl acetate/toluene: 1:3, R_f = 0.35). Yield of **13** (0.13 g, 94 %, pure *endo*-H diastereomer); mp 212-212.5 °C (chloroform/heptane); $[\alpha]^{22}_D$ +31.53 (*c* 0.98, chloroform); ^{1}H NMR ($CDCl_3$): 3.63 (ddd, 1H, $^4J_{4,6}$ = 1.2 Hz, $J_{5,6}$ = 4.9 Hz, $J_{6,6'}$ = 7.9 Hz, H-6), 3.96 (ddd, 1H, $J_{3,4}$ = 5.8 Hz, $J_{4,5}$ = 5.5 Hz, $J_{4,OH}$ = 5.5 Hz, H-4), 3.99 (dd, 1H, $J_{5,6'}$ = 1.5 Hz, H-6'), 4.36 (dd, 1H, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 6.4 Hz, H-2), 4.45 (ddd, 1H, H-5), 4.54 (dd, 1H, H-3), 4.96 (d, 1H, OH-4), 5.55 (2H, H-1, *endo*-acetal-H), ^{13}C NMR (acetone-d6), 63.7 (C-6), 70.1, 75.0, 77.9, 82.4 (C-2, C-3, C-4, C-5), 99.1 (C-1), 99.1 (CCl_3), 108.5 (acetal C).

Anal. Calcd for $C_8H_9Cl_3O_5$ (291.52): C, 32.96; H, 3.11. Found C, 33.04; H, 3.13.

1,6-Anhydro-2-*O*-cyclohexylcarbamoyl-3,4-*O*-(2,2,2-trichloroethylidene)-β-D-altropyranoside (15).

Method A: Powdered 1,6-anhydro-β-D-mannopyranoside (**14**, 0.75 g, 4.6 mmol), dicyclohexylcarbodiimide (2.4 g, 11.6 mmol), chloral (2.4 g, 16.3 mmol) and 1,2-dichloroethane (15 mL) were refluxed for 4.5 h and worked up as described in the general procedure. Before chromatographic purification was carried out, the residue was dissolved in methanol (10 mL)/Et_3N (0.5 mL) and the solution was refluxed for 10 min in order to remove formyl groups of by-products. After concentration under reduced pressure, the yellowish oil contained **15** as major product (TLC: eluent: ethyl acetate/toluene 1:8; R_f = 0.44) and traces of few by-products. Compound **15** was separated by column

chromatography (eluent: ethyl acetate/toluene 1:20, R_f = 0.23) yielding colourless crystals (0.84 g, 44 %, pure *endo*-H-diastereomer); mp 212-215 °C (ether / heptane); $[\alpha]^{22.5}_D$ -132.24 (*c* 0.98, chloroform); ^{1}H NMR ($CDCl_3$), *endo*-H form: δ 1.21 (m, 5H, cyclohexyl CH_2), 1.66 (m, 3H, cyclohexyl CH_2), 1.91 (m, 2H, cyclohexyl CH_2), 3.46 (m, 1H, cyclohexyl CH), 3.81 (m, 2H, H-6, H-6'), 4.54 (dd, 1H, $J_{4,5}$ = 1.5 Hz, $J_{3,4}$ = 5.8 Hz, H-4), 4.65 (m, 2H, H-3, H-2), 4.78 (d, 1H, $J_{NH,CH}$ = 7.6 Hz, NH), 4.86 (ddd, 1H, $J_{5,6}$ = 1.5 Hz, $J_{5,6'}$ = 5.2 Hz, H-5), 5.53 (s, 1H, *endo*-acetal H) 5.54 (d, 1H, $J_{1,2}$ = 2.4 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ 24.7, 25.4, 33.2 (cyclohexyl CH_2), 50.1 (cyclohexyl CH), 66.3 (C-6), 73.0, 73.7, 77.8, 77.8 (C-2, C-3, C-4, C-5), 99.0 (CCl_3) 99.3 (C-1), 99.1 (C-1), 107.5 (acetal C), 154.1 (carbamoyl C=O).

Anal. Calcd for $C_{15}H_{20}C_{13}NO_6$ (416.7): C, 43.23; H, 4.84; N, 3.36. Found: C, 43.25; H, 4.81; N, 3.44.

Method B: a) **2-O-cyclohexylcarbamoyl-3,4-O-(2,2,2-trichloroethylidene)-α-D-altropyranosyl fluoride** (**17**). 2-*O*-Cyclohexylcarbamoyl-6-*O*-formyl-3,4-*O*-(2,2,2-trichloroethylidene)-α-D-altropyranosyl fluoride[2] (**16**, 0.2 g, 0.43 mmol) was dissolved in methanol (3 mL) and 0.1 mL Et_3N (0.1 mL) were added. The solution was refluxed for 10 min and concentrated on a rotary evaporator under reduced pressure yielding quantitatively the altropyranosyl fluoride **17** (0.19 g) as a colourless oil. The product **17** was characterised by its NMR data and used for the following synthetic step without any purification; ^{1}H NMR ($CDCl_3$), *endo*-H form: δ 1.21 (m, 5H, cyclohexyl CH_2), 1.66 (m, 3H, cyclohexyl CH_2), 1.91 (m, 2H, cyclohexyl CH_2), 2.68 (broad, 1H, OH-6), 3.47 (m, 1H, cyclohexyl CH), 3.89 (m, 3H, 5-H, H-6, H-6'), 4.64 (dd, 1H, $J_{2,3}$ = 4.3 Hz, $J_{3,4}$ = 6.1 Hz, H-3), 4.73 (dd, 1H, $J_{4,5}$ = 8.9 Hz, H-4), 4.78 (d, 1H, $J_{NH,CH}$ = 7.6 Hz, NH), 5.22 (ddd, 1H, $J_{1,2}$ = 2.8 Hz, $J_{2,F}$ = 7.6 Hz, H-2), 5.49 (s, 1H, *endo*-acetal H), 5.52 (dd, 1H, $J_{1,F}$ = 51.9 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ 24.7, 25.3, 33.1 (cyclohexyl CH_2), 50.3 (cyclohexyl CH), 61.8 (C-6), 67.6 (d, $J_{2,F}$ = 37.7 Hz, C-2), 69.9, 71.5, 75.8 (C-2, C-4, C-5), 99.1 (CCl_3) 105.3 (d, $J_{1,F}$ = 227.2 Hz, C-1), 99.1 (C-1), 107.2 (acetal C), 153.4 (carbamoyl C=O).

b) **1,6-Anhydro-2-*O*-cyclohexylcarbamoyl-3,4-*O*-(2,2,2-trichloroethylidene)-β-D-altropyranoside** (**15**). Compound **17** (0.19 g, 0.43 mmol) was dissolved in dry di-

chloromethane (5 mL) and two drops of distilled $Et_2O \cdot BF_3$ were added. The mixture was allowed to stand for 5 h at rt then the solution was sequentially washed with H_2O (10 mL), saturated aq $NaHCO_3$ solution (10 mL) and H_2O (10 mL), the organic phase was separated, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography to give **15** (0.147 g, 82 %). NMR data and melting point of the compound are identical with the data from **15** prepared by method A.

ACKNOWLEDGEMENT

We are grateful to Dr. Manfred Michalik for his kind cooperation in regard to the NMR spectroscopic investigations. Furthermore, we thank the "Deutsche Forschungsgemeinschaft" and the "Fonds der Chemischen Industrie" for financial support as well as the BOERINGER-Mannheim AG, the BASF and the HOECHST-AG for gifts of various chemicals.

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