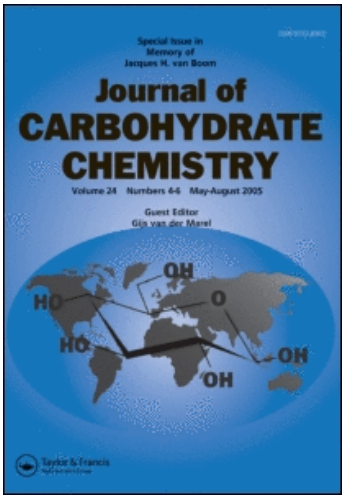

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Epimerization by Non-classical Acetalization—A New Three Component Reaction for Carbohydrates and Inositols

Ralf Miethchen[a]
[a] Department of Chemistry, University of Rostock, Rostock, Germany

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MINI-REVIEW

Epimerization by Non-classical Acetalization—A New Three Component Reaction for Carbohydrates and Inositols[†]

Ralf Miethchen*

Department of Chemistry, University of Rostock, Rostock, Germany

ABSTRACT

This mini-review summarizes the knowledge about the scope and pathway of a novel non-conventional tandem procedure of acetalization which allows a simultaneous epimerization of cyclic polyols with three or four contiguous hydroxyl groups. Such triols and tetrols, e.g., pyranosides or inositols, form acetols on heating with highly active aldehydes or ketones in the presence of a carbodiimide, provided that their OH-groups show a *cis/trans* or *cis/trans/trans* sequence. The inversion of one chiral center (triols) and of one or two chiral centers (tetrols) was achieved. The stepwise removing of the protecting groups is reported.

Key Words: Carbohydrates; Inositols; Cyclitols; Epimerization; Acetalization; Cyclic acetals.

[†]Dedicated to Prof. Dr. Gérard Descotes on the occasion of his 70th birthday.

*Correspondence: Ralf Miethchen, Department of Chemistry, University of Rostock, Albert-Einstein-Strasse 3a, D-18059 Rostock, Germany; E-mail: ralf.miethchen@chemie.uni-rostock.de.

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INTRODUCTION

Several chemical methods are known to invert chiral alcohols, with most being two or more step procedures. A stereoselective displacement of a hydroxyl group first requires activation, i.e., transformation into a good leaving group such as sulfonate esters (tosyl, mesyl, or triflyl). Such ester groups may be displaced with cesium, potassium or tetraalkylammonium carboxylates followed by hydrolysis,[1-12] with potassium superoxide,[13–15] or treatment with nitrite,[16,17] or with nitrate[18,19] followed by reduction. The *Mitsunobu* reaction[20] is special since the alcohol activation and S_N2 displacement reaction take place in a one pot procedure. The method generally produces good yields with high stereoselectivity and is compatible with a wide range of functional groups. Because epimerizations are important tools in synthesizing less available diastereomers from reasonable common precursors, the above mentioned methods have been also established in synthetic carbohydrate and inositol chemistry.[20–29] However, a more or less lavish protecting group chemistry is indispensable in order to achieve regioselectivity with such highly functionalised substrates. By contrast, the subsequently described new three components method allows the use of unprotected triols or tetrols for regio- and stereoselective epimerization of carbohydrates and inositols, respectively.

In 1994, we reported about a non-conventional acetalization of methyl α-L-rhamnopyranoside (**1**) which was accompanied by a highly stereoselective epimerization of the sugar, Scheme 1.[30,31] In a one pot procedure, the L-altrose derivatives **2** and **3**[a] were formed on heating of **1** with hexafluoroacetone (HFA) and dicyclohexylcarbodiimide (DCC) in dichloromethane. Under analogous conditions, methyl α-D-mannopyranoside (**4**) could be converted into the α-D-altrose derivative **5**, likewise epimerized at C-atom 3, Scheme 1.[30,32] The surprising result initiated investigations with further highly carbonyl active reagents, such as perfluoroalkanals and trichloroacetaldehyde (chloral), which were very successful.

An advantage of the introduced acetal moieties is their stability to strong acids. In contrast to acid-catalyzed ethylidenations of carbohydrates, which predominantly generate *exo*-H diastereomers[33–36] the cyclic acetals synthesized by the new three components method with chloral or perfluoroalkanals, are predominantly *endo*-H diastereomers.

The acetalization is non-conventional, because the reaction is not catalyzed by acids and because the oxygen atom of the carbonyl compound (but not that of the alcoholic component) is inserted into the acetal moiety, Scheme 2.

SCOPE AND PATHWAY OF THE REACTION

The acetalization/epimerization method, described in various original papers and in the book ''*Essentials of Carbohydrate Chemistry and Biochemistry*,''[27] is a three component reaction which requires the following prerequisites:

- *Substrates*: Cyclic triols (or tetrols) with contiguous hydroxyl groups in a *cis–trans* sequence. The reaction always proceeds with clean inversion of the configuration at the middle C-atom of the *cis–trans* triol unit.

[a]Initially, the correct structure of L-altropyranoside **3** was not identified.[32]

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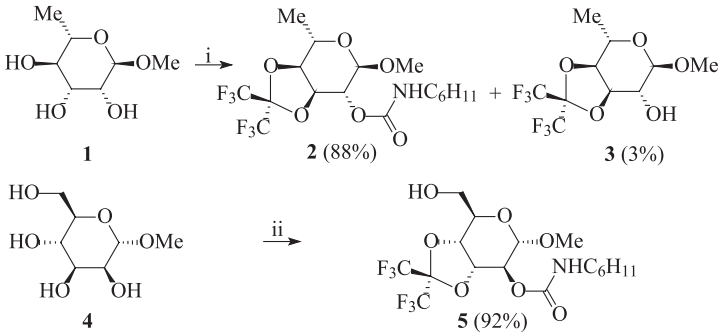
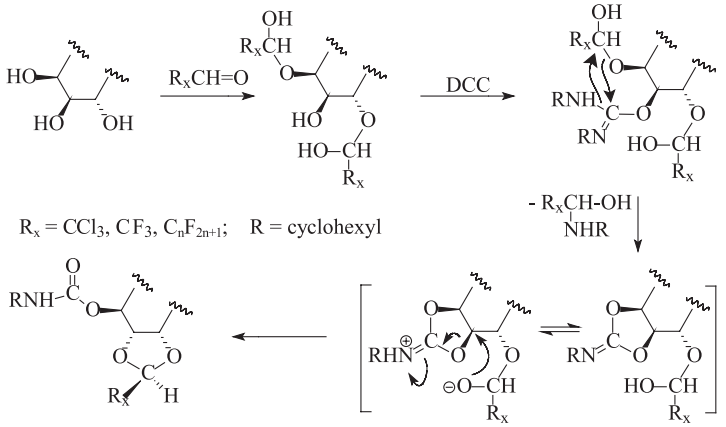


Scheme 1. i = HFA, DCC, CH_2Cl_2, 50°C, 6 h (from Refs. [30,32].), ii = HFA, DCC, CH_2Cl_2, 50°C (2 h) → rt (2 h). (From Ref. [30].)

- *Reagents*: Only highly active carbonyl reagents such as trichloroacetaldehyde (chloral), hexafluoroacetone or perfluoroalkanals.
- *Co-reagents*: Carbodiimides like dicyclohexyl- or diisopropylcarbodiimide.

The following information threw additional light on the reaction sequence

1. The carbamoyl group is always introduced on the *cis*-side of the triol unit.
2. The highly active carbonyl reagent forms hemiacetals in a reversible reaction with the polyol.[37]
3. These hemiacetals cause solubilization of the corresponding polyol in the solvents dichloromethane or 1,2-dichloroethane, and acidification of neighboring hydroxyl groups as a result of their electron withdrawing ability.
4. Adequately acidic OH groups add to carbodiimides generating a corresponding isourea. The middle OH group of an all *vicinal* triol unit is the most acidic, should the occasion arise for formation of two neighboring hemiacetals.



Scheme 2. Pathway of the non-classical acetalization of cyclic *cis-trans*-triols.

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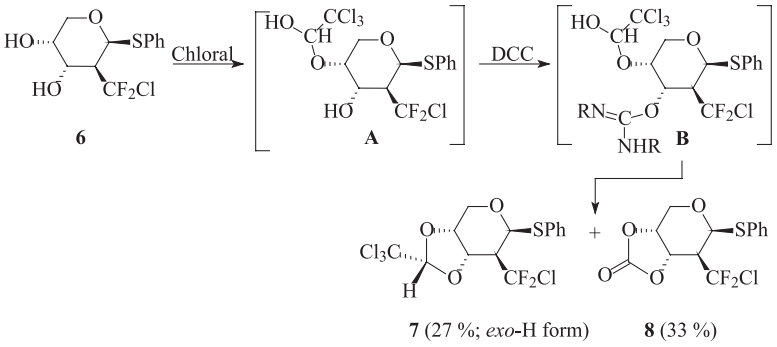
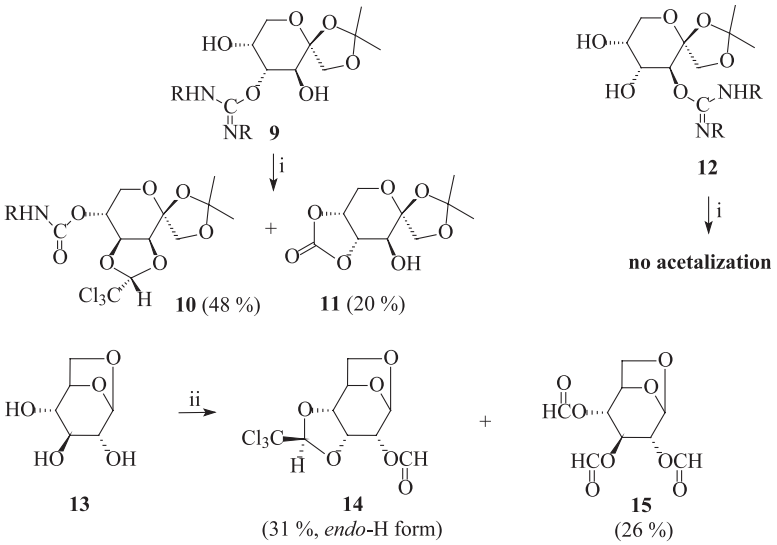


Scheme 3. R = cyclohexyl.

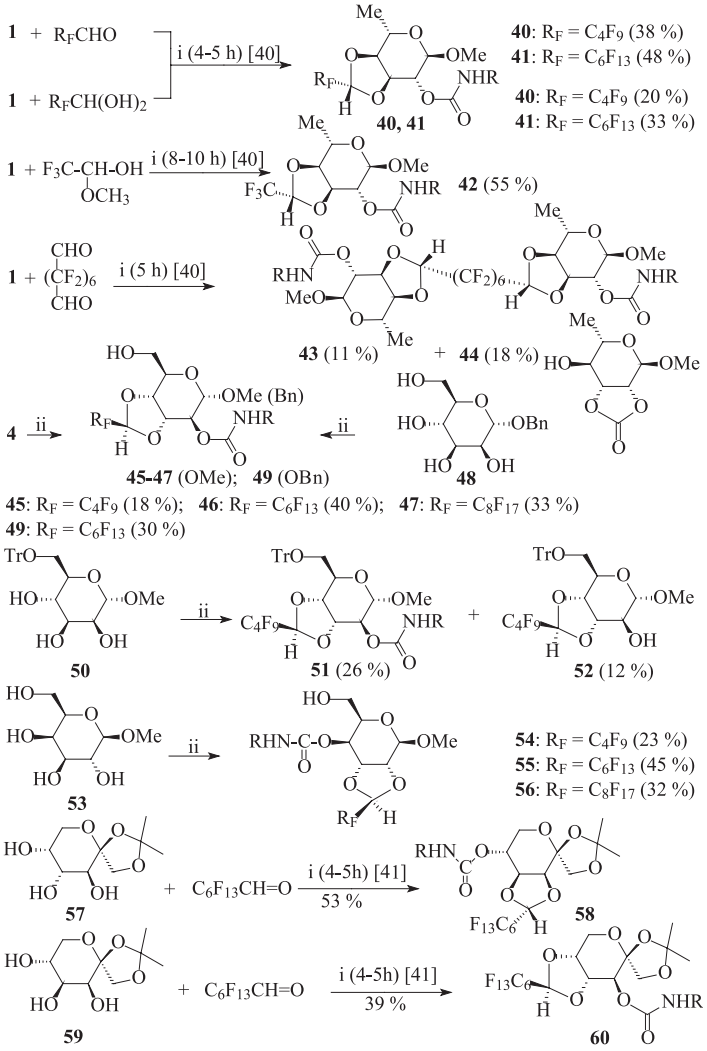
When an OH group becames more acidic only by one neighboring acceptor group, the formation of isourea takes place much slower. The latter could be confirmed by the model experiment shown in Scheme 3. Phenyl 2-chlorodifluoromethyl-2-deoxy-1-thio-D-arabinopyranoside (**6**) and DCC were refluxed in 1,2-dichloroethane. After 30 h, only about 70% of the starting material had been converted into a complex mixture of products, which was not investigated further. In a second experiment, 0.5 equivalents of chloral were added to the starting mixture. After refluxing of this mixture for 3 h, two major products were detected and isolated, the acetal **7** (27%) and cyclic carbonic acid ester **8** (33%).[38,39] In this case, the OH group in the 3-position was acidified by the



Scheme 4. i = chloral, $(CH_2Cl)_2$, reflux, 6 h; ii = chloral, DCC, $(CH_2Cl)_2$, reflux, 8 h; R = cyclohexyl.

chlorodifluoromethyl group as well as by a hemiacetal moiety in the 4-position (intermediate **A**) stimulating the formation of intermediate **B**, Scheme 3.

5. Isoureas evidently react fast to give cyclic imidocarbonic acid esters in the presence of a *cis*-arranged hemiacetal group. The subsequent acetalization step (irreversible intramolecular S_N2—reaction) also proceeds fast, since that is the only interpretation for the high regio- and the stereoselectivity of the acetalization reaction (for the competing pathway see paragraph 6). Cyclic carbonates, the hydrolysis products of the imidocarbonic acid ester intermediates, could be isolated in some cases.[40,41] (Schemes 3, 4 and 5)



Scheme 5. R = cyclohexyl; i = DCC, $(CH_2Cl)_2$, reflux; ii = R_FCH=O, DCC, $(CH_2Cl)_2$, reflux, 5–6 h. (From Ref. [65].)

6. Finally, the nitrogen atom of the cyclic imidocarbonic acid ester intermediate is protonated by the neighboring hemiacetal function followed by a fast intramolecular S_N2 attack of the hemiacetal anion as shown in Scheme 2. Thus, the cyclic acetal and the carbamoyl group are formed. The acetalization 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 step. Normally, the *endo*-H form is predominant; acetal **7** is an exception, Scheme 3.[38]
7. The configuration of acetal **7** indicates a divergent pathway for acetal formation from intermediate **B**, Scheme 3. The hypothesis is that, after protonation of the isourea moiety by the *cis*-arranged hemiacetal, dicyclohexylurea leaves the molecule in an S_N1-type reaction. Consequently, this reaction step certainly competes with the formation of an iminodioxolane ring, but the generation of a carbenium ion proceeds slower, as described in the paragraphs 4 and 5. The final ring closure step proceeds with retention, because a *cis*-arrangement of the acetal is favoured.

Comparative experiments with the regioisomers 1,2-*O*-isopropylidene-4-*O*-(*N,N′*-dicyclohexylisoureido)-*β*-D-fructopyranose (**9**) and 1,2-*O*-isopropylidene-3-*O*-(*N,N′*-dicyclohexylisoureido)-*β*-D-fructopyranose (**12**) had shown that only the 4-*O*-isoureido derivative **9** forms a cyclic acetal on heating with chloral in 1,2-dichloroethane, whereas the 3-*O*-isoureido isomer did not give isolable amounts of any trichloroethylidene product, Scheme 4.[42] This allows the conclusion that direct replacements of the isoureido group by intramolecular attack of a *trans*-arranged neighboring hemiacetal are not favoured in competition with the formation of imidocarbonic acid ester intermediates. However, the successful acetalization of 1,6-anhydro-D-glucose (**13**) indicates that a direct replacement of isoureido groups by a *trans*-arranged hemiacetal is possible under the reaction conditions, Scheme 4.[39]

EPIMERIZATION OF CARBOHYDRATES

Reactions with Chloral

Cyclic acetals are generally important protecting groups in carbohydrate chemistry. They are commonly prepared by acid-catalyzed equilibrium reactions[43–47] and therefore, only temporary protecting groups in the presence of aqueous acids. Acid-catalyzed acetalizations of carbohydrates with chloral require more drastic reaction conditions and produce only modest regioselectivities.[48–50] Thus, the sulfuric acid catalyzed acetalization of D-glucose with chloral or chloral hydrate results in two diastereomeric monoacetals and four stereoisomeric diacetals of α-D-glucofuranose.[48] From these compounds the so-called α-chloralose (1,2-*O*-trichloroethylidene-α-D-glucofuranose) was occasionally used as a sedative. In 1993 Jacobsen and Sløk[51] reported the synthesis of carbohydrate trichloroethylidene derivatives via epoxide opening procedures. In addition, the authors described a convenient two step procedure for the removal of these acid-stable protecting groups, see also Ref. [52].

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A particular advantage of the one-pot acetalization/epimerization method reported here is the easy access of rare natural or non-natural sugars from reasonable, common monosaccharides, e.g., gulose from galactose, altrose from mannose, and tagatose from fructose. The following survey gives an overview of sugar epimerizations realized *via* acetalization with chloral/DCC:

D-Arabinose → *D-Lyxose*[53–55]

L-Arabinose → *L-Lyxose*[56]

D-Lyxose → *D-Arabinose*[56]

D-Galactose → *D-Gulose*[53,55–57]

L-Fucose → *6-Deoxy-L-gulose*[53,55]

D-Mannose → *D-Altrose*[30,32,53,55,57,58]

L-Rhamnose → *6-Deoxy-L-altrose*[30,32,58]

D-Fructose → *D-Tagatose*[59]

Various protecting groups are tolerated under the reaction conditions. Thus, methyl glycosides, benzyl glycosides, phenyl 1-thioglycosides, glycosyl azides, isopropylidene and benzylidene acetals can be used as starting materials as outlined in Table 1. α- and β-Glycosides of the same sugar produce different yields of epimerization products, when the acetal function is introduced in the 2,3-position of the sugar. Thus, β-D-galactopyranosides and β-L-fucopyranosides, respectively, give significantly higher yields of epimerization products (63%, 80%) than the corresponding α-anomers (16%, 58%),[53,56] Table 1.

Two Important Annotations

1. Chloral produces formylated side products, for some examples see Schemes 6 and 8. The formyl group results from a haloform cleavage of chloral (see also Ref. [60]). Therefore, the yield of chloral acetals can be decreased, because formylation also occurs within the triol unit. Generally, longer reaction times increase the percentage of formyl derivatives. The rigid 1,6-anhydrosugars D-glucosan, D-galactosan, and D-mannosan, which are only slowly acetalized, give therefore relatively high amounts of formyl products and reduced yields of acetals[39]
2. The prochiral chloral reagent produces stereoisomeric acetals, i.e., *endo*-H and *exo*-H diastereomers. These diastereomers show very similar chromatographic properties, i.e., separation of the pure major isomer is rarely successful in this way. However, it is not essential when the trichloroethylidene group is only used as a temporary acid-stable protecting group. Generally, the *endo*-H form is predominant (5:1 to 30:1) and can be purified in many cases by fractional crystallization. The singlet of the acetal proton is a good marker to distinguish between the two diastereomeric forms, because the *endo*-H proton is always

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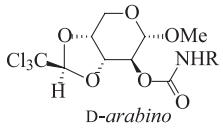
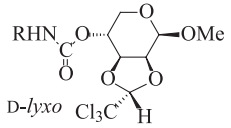
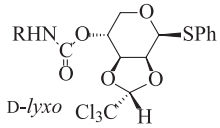
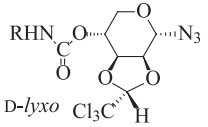
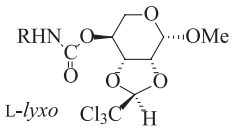
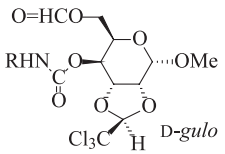
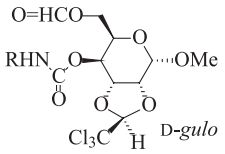
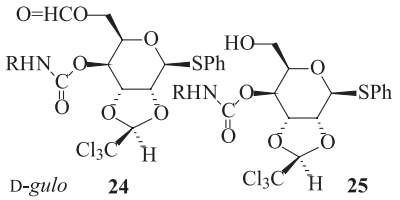
Table 1. Epimerization of carbohydrates with trichloroacetaldehyde and dicyclohexylcarbodiimide in $(CH_2Cl)_2$ (R = cyclohexyl).

	Starting material	Conditions	Products	Ref.
1	Methyl α-D-lyxopyranoside	reflux, 4.5 h	 D-*arabino* **16** (63%) mp 137-141 °C	[56]
2	Methyl β-D-arabinopyranoside	reflux, 4.5 h	 D-*lyxo* **17** (66%) mp 161-163 °C	[53]
3	Phenyl 1-thio-β-D-arabinopyranoside	reflux, 4.5 h	 D-*lyxo* **18** (60%) mp 140-141 °C	[54]
4	α-D-Arabinopyranosyl azide	reflux, 7–8 h	 D-*lyxo* **19** (52%) amorphous solid	[55]

5	Methyl β-L-arabinopyranoside	reflux, 4.5 h	 L-*lyxo* **20** (67%) mp 160-162.5 °C	[56]
6	Methyl α-D-galactopyranoside	reflux, 4.5 h	 D-*gulo* **21** (16%) mp 132-134 °C	[56]
7	Methyl β-D-galactopyranoside	reflux, 4.5 h	 D-*gulo* **21** (16%) mp 132-134 °C	[56]
8	Phenyl 1-thio-β-D-galactopyranoside	reflux, 8 h	 D-*gulo* **24** **25** **24** (57%) amorphous solid and 6-OH-derivative **25** (6%); mp 177.5-178.5 °C	[53]

(*continued*)

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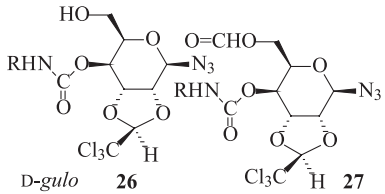
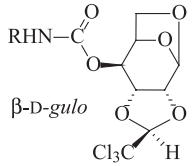
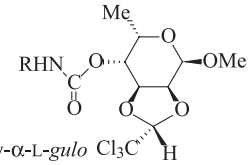
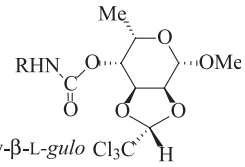
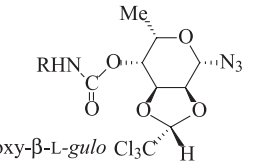
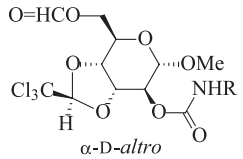
Table 1. Continued

9	β-D-Galactopyranosyl azide	reflux, 8 h	 D-*gulo* **26** **27** **26** (58%) mp 138-140 °C and 13% of the 6-*O*-formylated derivative **27**	[55]
10	1,6-Anhydro-β-D-galactopyranoside	reflux, 4.5 h	 β-D-*gulo* **28** (30%) mp 154-156 °C and formylated by-products	[53]
11	Methyl α-L-fucopyranoside	reflux, 4.5 h	 6-Deoxy-α-L-*gulo* **29** (58%) mp 130-132 °C	[53]

12	Methyl β-L-fucopyranoside	reflux, 4.5 h	 6-Deoxy-β-L-*gulo* **30** (80%) mp 139-141 °C	[53]
13	β-L-Fucopyranosyl azide	reflux, 8 h	 6-Deoxy-β-L-*gulo* **31** (70%) mp 128-130 °C	[55]
14	Methyl α-D-mannopyranoside	reflux, 4.5 h	 α-D-*altro* **32** (66%) mp 138-147 °C [a)]	[58]

(*continued*)

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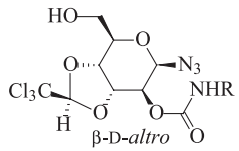
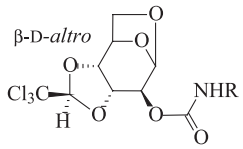
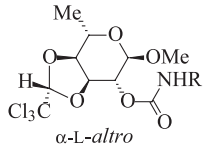
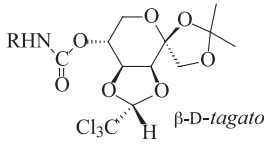
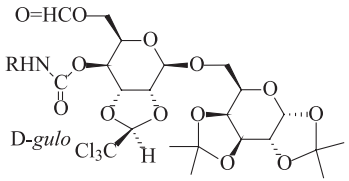
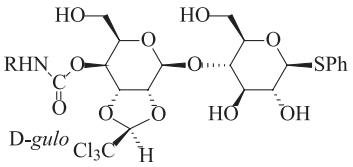
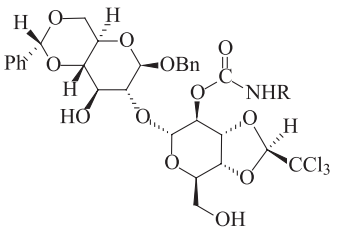
Table 1. Continued

15	β-D-Mannopyranosyl azide	reflux, 12 h	 β-D-*altro* **33** (69%) amorphous solid mp 68-70 °C	[55]
16	1,6-Anhydro-β-D-mannopyranoside	reflux, 4.5 h	 β-D-*altro* **34** (44%) mp 212-215 °C and formylated by-products	[53]
17	Methyl α-L-rhamnopyranoside	reflux, 4.5 h	 α-L-*altro*	[58]
18	1,2-*O*-Isopropylideneβ-D-fructopyranose	reflux, 4.5 h	 β-D-*tagato* **36** (51%) mp 198.5-201 °C	[59]

19	6-*O*-(*β*-D-Galactopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose	reflux, 8 h	 **37** (40%) mp 183-185 °C and 6% non-formylated product mp 226-228 °C	[57]
20	Phenyl 4-*O*-(*β*-D-galactopyranosyl)-1-thio-*β*-D-glucopyranoside	reflux, 8 h		[57]
21	Benzyl 4,6-*O*-benzylidene-2-*O*-(α-D-mannopyranosyl)-*β*-D-glucopyranoside	reflux, 6 h		[57]

a) Diastereomeric mixture of the *endo*-H and the *exo*-H form (14:1).

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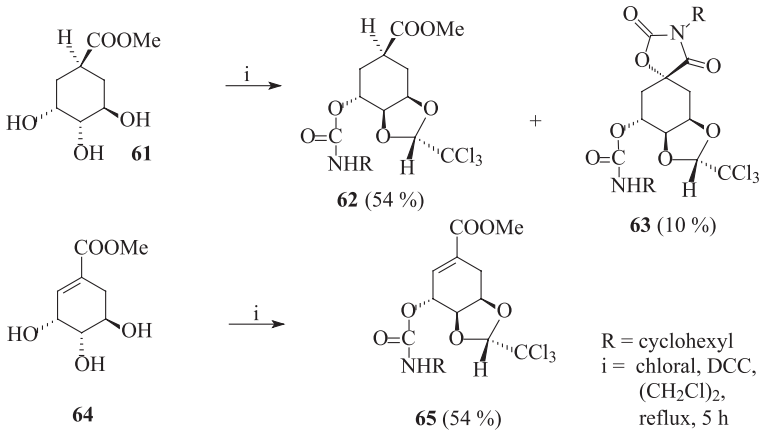


Scheme 6. Epimerization of methyl quinate and methyl shikimate.

downfield shifted (0.1–0.25 ppm.[53]) compared to the corresponding *exo*-H signal. Integration of the acetal-H singlets allows the estimation of the *endo*-H/*exo*-H ratio in the crude product mixture.

Reactions with Hexafluoroacetone, Perfluoroaldehydes, and Perfluorodialdehydes

Amphiphiles with perfluoroalkyl chains are effective surfactants and tend to form ordered supramolecular assemblies of higher stability than their hydrocarbon counterparts. Fluorocarbon chains are not only more hydrophobic but also stiffer than hydrocarbon chains and therefore have less conformational freedom.[61,62] Representatives of this group of surfactants were tested as emulsifiers for artificial oxygen carriers (fluorocarbon emulsions), as components in drug delivery systems or contrast agents based on fluorocarbons.[63,64] Perfluoroalkylated carbohydrates have neutral and non-toxic head groups which even may represent binding sites for bio-receptors. Our one-pot acetalization method allows the production of the precursors of a new type of perfluoroalkyl substituted carbohydrate surfactants and liquid crystals, respectively.[41,64-66]

Scheme 5 summarizes epimerizations of monosaccharides with perfluoroalkanals in the presence of DCC. Thus, methyl α-L-rhamnopyranoside (**1**) was acetalized with nonafluoropentanal and tridecafluoroheptanal, respectively, generating the corresponding methyl 2-*O*-cyclohexylcarbamoyl-6-deoxy-3,4-*O*-polyfluoroalkylidene-α-L-altropyranosides **40** and **41** in isolated yields of 38–48%.[40] It is noteworthy, that perfluoroalkanals tend to polymerise, therefore, making the use of the corresponding methyl hemiacetals more favourable. In the case of trifluoroethanal (fluoral), acetalization of rhamnoside **1** was only successful when the latter was treated with the methyl hemiacetal of fluoral and DCC. In this way, altrose derivative **42** was obtained in 55% yield.[40] Hydrates of perfluoroalkanals were also suitable acetalization reagents; however, the yields of the acetals decreased significantly, Scheme 5.

In a further experiment, methyl L-rhamnoside (**1**) was reacted with the α,ω-dialdehyde dodecafluorooctane-1,8-dial in the presence of DCC. The corresponding bis-

L-altroside derivative **43** was formed in a yield of 11%, Scheme 5.[40] Further acetalization/epimerization reactions were reported for methyl α-D-mannopyranoside (**4**), benzyl α-D-mannopyranoside (**48**), methyl 6-*O*-trityl-α-D-mannopyranoside (**50**), and methyl β-d-galactopyranoside (**53**) using C5-, C7-, and C9-perfluoroaldehydes, respectively, Scheme 5.[65]

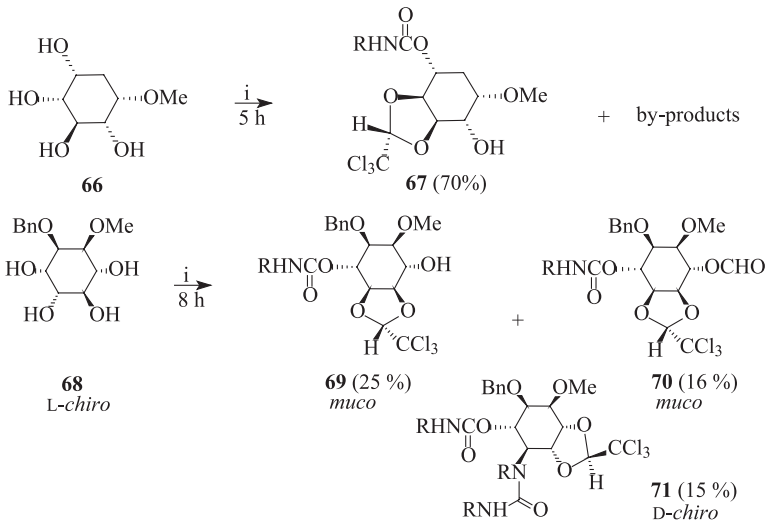
The *endo*-H/*exo*-H diastereomeric mixtures accumulate in a ratio of about 5:1. Column chromatographic separation of the diastereomers failed; however, the pure *endo*-H form was obtained by fractional crystallization. The altrose derivatives **45–47**, **49**, **51**, **52** and the gulose derivatives **54–56** are precursors for the synthesis of perfluoroalkyl substituted amphiphilic mesogens.[64,66]

EPIMERIZATION OF CYCLITOLS

Cyclitols with three or four contiguous OH groups are potential candidates for epimerizations by non-conventional acetalization. The biological relevance of cyclitols is well known, although, the separation of inositol derivatives from natural sources is limited to a few representatives, requiring chemical syntheses of various compounds of this type.[67–71] (−)—Quinic acid is commercially available and its abundance in the chiral pool has made it an attractive starting material for asymmetric multistep syntheses of naturally occurring substances and related compounds.[72] The structurally related shikimic acid can be used as a chiral template in a similar manner. Both quinic acid and shikimic acid have to show a *cis–trans* triol unit.

Methyl quinate (**61**) and methyl shikimate (**64**) were converted into the corresponding 4-*epi*-derivatives **62**,[73] **63**[73] and **65**[73] as shown in Scheme 6. The pure *endo*-H diastereomers were obtained by fractional crystallization from ethyl acetate.

In a study with a cyclitol containing four contiguous OH groups with *cis–trans–trans* sequence of the tetrol unit, (1*S*, 2*S*, 3*S*, 4*R*, 5*R*)-1-methoxy-2,3,4,5-tetrahydroxy-



Scheme 7. i = chloral, DCC, $(CH_2Cl)_2$, reflux; R = cyclohexyl.

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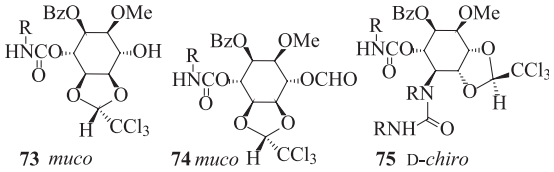
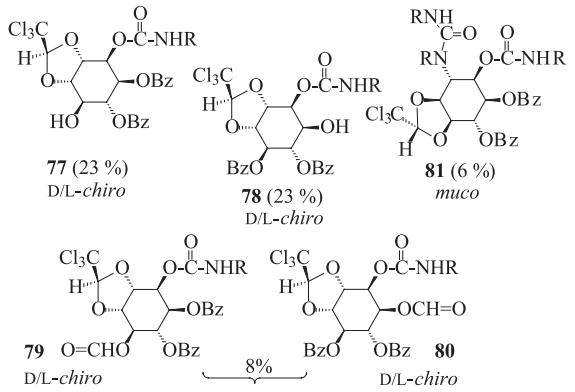
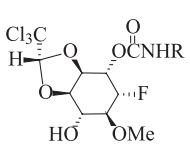
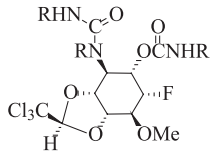
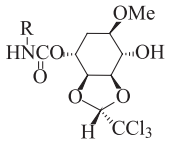
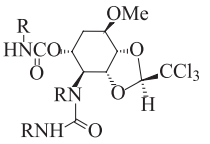
Table 2. Epimerization of cyclitols with trichloroacetaldehyde and dicyclohexyl-carbodiimide in 1,2-dichloroethane (Reflux, 8 h; R = Cyclohexyl).

	Starting material	Products
1	1-*O*-Benzoyl-2-*O*-methyl-(−)-*chiro*-inositol (**72**)	 **73** *muco* **74** *muco* **75** D-*chiro* **73** (53%) amorphous solid; **74** (2%) syrup; **75** (12%) mp 110-112 °C
2	3,4-Di-*O*-benzoyl-*myo*-inositol (**76**)	 **77** (23 %) D/L-*chiro* **78** (23 %) D/L-*chiro* **81** (6 %) *muco* **79** D/L-*chiro* 8% **80** D/L-*chiro* **77** mp 196 °C; **78** mp 175-176 °C; **79** mp 210-215 °C; **80** [a], **81** mp 141-148 °C

3	(1*S*,2*S*,3*R*,4*S*,5*S*, 6*S*)-1-Fluoro-2-methoxy-3,4,5,6-tetra-hydroxy-cyclohexane (**82**)	 **83** (18 %)  **84** (1 %) **83** mp 145-146 °C; **84** mp 236-237 °C
4	(1*R*, 2*R*, 3*S*, 4*R*, 5*R*)-1-Methoxy-2,3,4,5-tetra-hydroxy-cyclohexane (**85**)	 **86** (61%)  **87** (19%) **86** mp 176-177 °C; **87** mp 126-128 °C

[a] **80** was not obtained in pure form; contaminated with **79**.
(Adapted from Refs. [54,78].)

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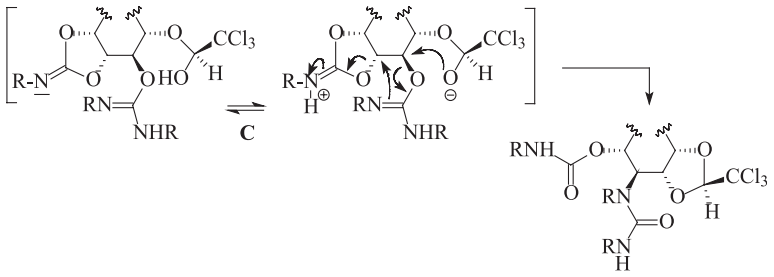


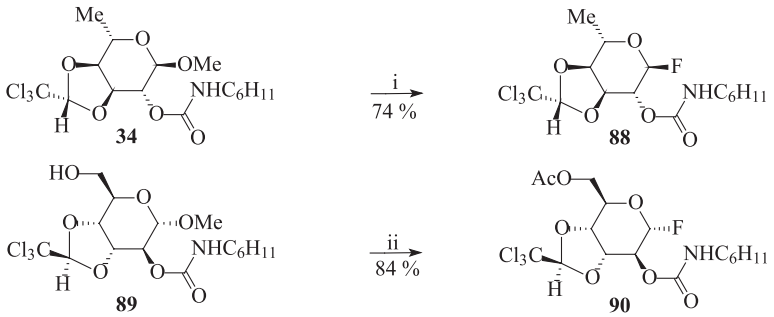
Scheme 8. Competing pathway of a non-classical acetalization using cyclic *cis-trans-trans*-tetrols.

cyclohexane (**66**) treatment with chloral/DCC yielded a syrupy mixture which predominantly contained the amorphous solid **67**, Scheme 7.[74] A by-product also containing a trichloroethylidene group was also detected but not identified.

When L-1-*O*-benzyl-2-*O*-methyl-*chiro*-inositol (**68**) was treated with chloral/DCC, a competing pathway of epimerization was recognized that generated the D-*chiro*-configured by-product **71** (15% yield) besides the major products **69** and **70** with a *muco*-configuration, Scheme 7.[75,76]

The formation of *muco*-inositol derivatives is in conformity with the reaction pathway described for acetalizations/epimerizations of *cis–trans* triols (single inversion at one chiral C-atom), Scheme 2. By contrast, D-*chiro*-inositol **71** showed inversion of configuration at two chiral C-atoms related to the starting material. The course of the reaction could be a tandem-sequence via key intermediate C as marked by arrows in Scheme 8. It explains the regioselective introduction of the carbamoyl group into the 6-position of **71** as well as the C–N-coupling at C-5 of **71**. The latter corresponds to isourea experiments of Vowinkel and Gleichenhagen.[77]

Additional epimerization experiments were carried out with L-1-*O*-benzoyl-2-*O*-methyl-*chiro*-inositol (**72**), D/L-3,4-di-*O*-benzoyl-*myo*-inositol (**76**), (1*S*, 2*S*, 3*R*, 4*S*, 5*S*, 6*S*)-1-fluoro-2-methoxy-3,4,5,6-tetrahydroxycyclohexane (**82**), and (1*R*, 2*R*, 3*S*, 4*R*, 5*R*)-1-methoxy-2,3,4,5-tetrahydroxycyclohexane (**85**). In all cases, the expected



Scheme 9. i = HF, Ac_2O, $MeNO_2$ (10 : 1 : 35 v/v/v), rt, 4 h; (from Ref. [58].); ii = HF, Ac_2O, $MeNO_2$ (1 : 0.23 : 1.07 v/v/v), rt, 4 h. (From Ref. [79].)

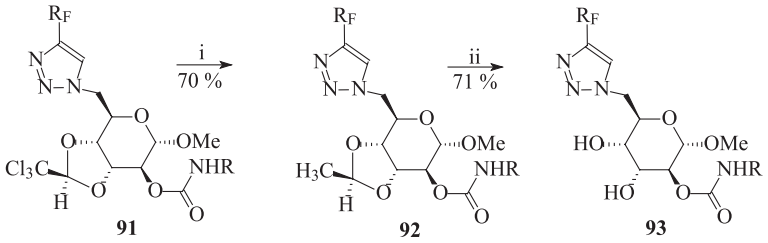
products of the two competing pathways were found, Table 2.[54,78] The resulting ratio of single inversion products (*muco*-inositols **73**, **74,** D/L-*chiro*-inositols **77–80**, fluoroinositol **83**, and cyclitol derivative **86**, respectively) to the double inverted products (D-*chiro*-inositol **75**, *muco*-product **81**, fluoroinositol **84**, and cyclitol derivative **87**, respectively) indicates that electron withdrawing groups suppress the tandem-course with two inversions, Scheme 8. The acetalization of D/L-3,4-di-*O*-benzoyl-*myo*-inositol was partly accompanied by benzoyl group migration, Table 2.[54,78]

DEPROTECTION

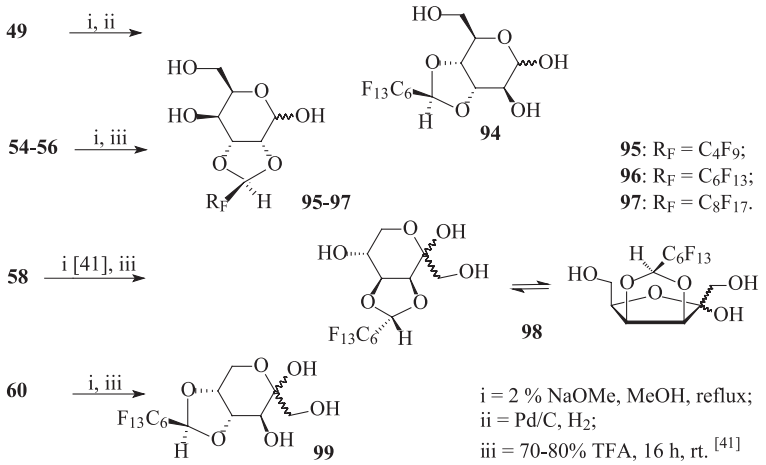
The products formed by acetalization of carbohydrates and inositols with chloral/DCC contain a useful protecting group pattern which is suitable for stepwise deprotection reactions. Thus, a selective deformylation of the carbohydrate derivatives **24**,[53]**32**,[79] and the inositol derivatives **70**,[75,76]**74**[78] was possible by heating in 10% methanolic triethylamine (10–15 min), whereas the inositols **77–80** were simultaneously debenzoylated under these reaction conditions, see also Refs. [52,55].

Carbamoyl groups are stable toward methanolic triethylamine in each case. However, carbamoyl groups located at the 4-position of hexopyranosides migrate to the 6-position on treatment of the compound with methanolic sodium methoxide at room temperature. That was demonstrated with the 4-*O*-cyclohexylcarbamoyl-2,3-*O*-trichloroethylidene-D-gulosides **22**, **23**, and **25** generating the corresponding 6-*O*-cyclohexylcarbamoyl-2,3-*O*-trichloroethylidene-D-gulosides.[53,56] Carbamoyl migration was not observed, when the 2-*O*-cyclohexylcarbamoyl-D-altroside **32** was deformylated with methanolic sodium methoxide at room temperature.[58] On refluxing of carbamoylated carbohydrates or inositols in 1–2% methanolic sodium methoxide, this protecting group was selectively removed. The decarbamoylation of compounds **2**,[30,32]**5**,[30,32]**16**,[56]**20**,[56]**22**,[56]**23**,[56]**26**,[55]**28**,[53]**32**[58]**35**,[58]**45–47**,[65]**49**,[65]**54–56**,[65]**62**,[73]**67**,[74]**69**,[76]**71**[76] was described, see also Refs. [52,80,81].

As expected, the trichloroethylidene group or a perfluoroalkylidene group is not attacked by triethylamine or dilute methanolic solutions of sodium methoxide. These acetals are also stable towards strong acids such as anhydrous HF or HF-containing systems, Scheme 9.[58,79] However, trichloroethylidene groups can be removed in a two step procedure. First, the chloral acetal is converted into an ethylidene acetal by



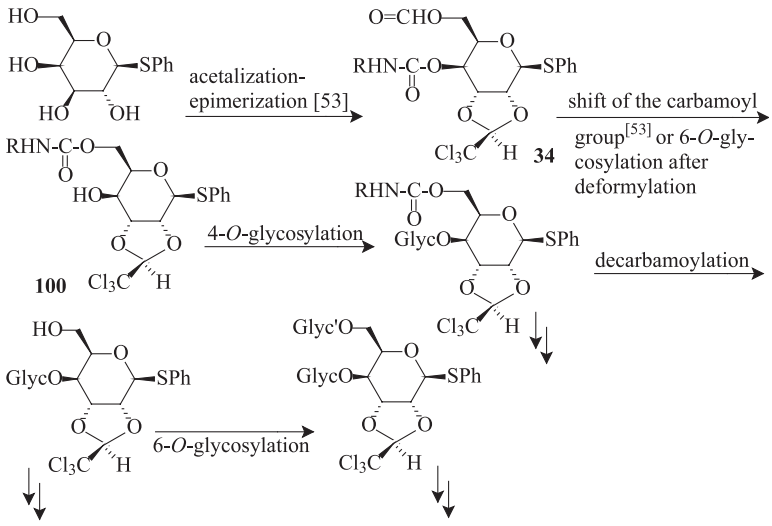
Scheme 10. i = Bu_3SnH, AIBN, toluene, 75°C; ii = 60% TFA, 50°C; R=C_6H_{11}; R_F=C_6F_{13}.



Scheme 11. Perfluoralkyl substituted amphiphilic acetals.

reduction with Raney-Ni[48] or tributylstannane/AIBN.[51] The latter reagent turned out to be particularly favorable and was therefore exclusively used by us for the reductive dechlorination step.[52,55,74,80,81] The ethylidene acetals were cleaved without a problem by acid catalyzed hydrolysis.[52,74,76,80,81] Scheme 10 gives an example of this reaction sequence.[81]

No method is known to selectively remove perfluoroalkylidene groups. Because perfluoroalkyl and perfluoroalkylidene substituted carbohydrates are of interest as emulsifiers in blood substitutes (see review Ref. [63]) and as liquid crystals (see review



Scheme 12. D-Gulopyranosyl donors from phenyl 1-thio-β-D-galactopyranoside.

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Ref. [64]), the amphiphilic D-altrose **94**,[65,66] D-guloses **95–97**,[65,66] D-tagatose **98**,[41] and D-fructose **99**[41] were synthesized, Scheme 11.

CONCLUSIONS

1. Monosaccharides, oligosaccharides, and cyclitols containing three contiguous hydroxyl groups with a *cis–trans* sequence may be selectively epimerized by a very simple one-pot procedure, the glycosidic position of sugars being protected.
2. Formaldehyde or carbonyl active imides such as $ClCH_2CCl_2CH{=}N{-}C(O)CH_3$[82] do not result in the hoped for epimerization. The latter only formed several open-chain products on heating (30 h) with methyl α-L-rhamnoside in the presence of DCC.[39]
3. Inositol derivatives containing four contiguous hydroxyl groups with a *cis–trans–trans* sequence turn out to be precursors for two competing epimerization reactions realized in a one-pot procedure.
4. The three component acetalization/epimerization method opened various opportunities for subsequent synthetic steps, because of the diversity of the protecting group pattern. A practicable example is given in Scheme 12 for D-gulose derivatives starting with phenyl 1-thio-β-D-galactopyranoside.

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