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(54) Title: 1,5 AND 1,4-ANHYDROKETOSES, METHODS FOR THE PREPARATION OF 1,5-AND 1,4-ANHYDROKETOSES, INTERMEDIATES, AND USES OF 1,5-AND 1,4-ANHYDROKETOSES

(57) Abstract: The present invention relates to 1,4- and 1,5-anhydro-D-ketoses (monosaccharides, oligosaccharides and various glycoconjugates), e.g. 1,5-anhydro-D-fructose. Moreover, the invention provides synthetic methods and novel intermediates and precursors suitable for their preparation. The methods include catalytic- and/or pyrolytic sulfenic acid elimination of corresponding B-hydroxy sulfoxides, N-deprotection of N-substituted-aminoglycals, O-deprotection of carbohydrate enoethers and/or O-acyl-substituted carbohydrate enols, and regio- and stereoselective modification and subsequent chemical transformation of bicyclic and/or tricyclic 1,4- and 1,5-anhydro-glycoderivatives. Furthermore, the present invention provides novel applications of 1,4- and 1,5-anhydroketoses within pharmaceutical, food and cosmetic industries.



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1,5- AND 1,4-ANHYDROKETOSES, METHODS FOR THE PREPARATION OF 1,5- AND 1,4-ANHYDROKETOSES, INTERMEDIATES, AND USES OF 1,5- AND 1,4-ANHYDROKETOSES

FIELD OF INVENTION

The present invention relates to 1,4- and 1,5-anhydroketoses, i.e. derivatised and underivatised 1,4- and 1,5-anhydroketoses (e.g. anhydroketopyranoses, anhydroketo-furanoses, anhydroketopyranosides, anhydroketofuranosides, anhydroketopyranose ketals, anhydroketofuranose ketals of diverse glycoderivatives including derivatised and underivatised monosaccharides, oligosaccharides and various glycoconjugates). Moreover, the invention provides 1,4- and 1,5-anhydroketoses-related novel synthetic methodologies and novel intermediates suitable/required for their preparation. The invention also provides several novel methods suitable for the preparation of novel as well as known 1,4- and 1,5-anhydro-D-ketoses (e.g. 1,5-anhydro-D-fructose) and their derivatives and analogues including regio- and stereoisomers thereof. Furthermore, the present invention provides novel applications of 1,4- and 1,5-anhydroketoses within pharmaceutical, food and cosmetic industries.

BACKGROUND OF THE INVENTION

1,4- and 1,5-anhydroketoses belong to a unique group of cyclic ether-type carbohydrates displaying numerous important chemical/biological/physiological properties. One of the most characteristic members of anhydroketoses is 1,5-anhydro-D-fructose (AF) (**1**) (Figure 1).

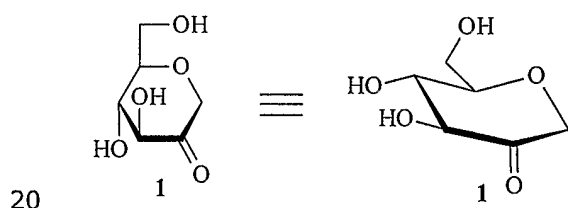
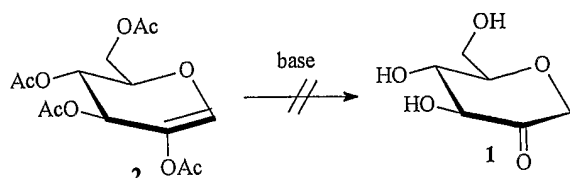


Figure 1. 1,5-Anhydro-D-Fructose.

In recent years, 1,5-anhydro-D-fructose itself and a few derivatives and analogues thereof have been considered as the most potential carbohydrate product candidates for pharmaceutical, food and cosmetic applications. However, the preparation of anhydroketoses is still a challenging task preventing long term commercialization efforts.

25

1,5-Anhydro-D-fructose (**1**) has not been known for a long time despite of the fact that its protected precursors/derivatives such as 2-acyloxyglycals **2** have been synthesized (Figure 2).¹



5 Figure 2. Unsuccessful liberation of 1,5-Anhydro-D-fructose by base- catalyzed hydrolysis.

Attempts to prepare 1,5-anhydro-D-fructose by base-catalyzed deacylation of per-acylated 2-hydroxyglycal derivatives **2** (Figure 2)^{2,3,4} have given complex mixtures of products. This fact is due to the liberation of the carbonyl group which triggers a 3,4-elimination, followed by an aldol condensation and/or benzilic acid rearrangements of the 2,3-diuloses formed, resulting in a multi-component mixture of carbohydrates and degradation products.

1,5-Anhydro-D-fructose (**1**) was finally synthesized in 1980 by Lichtenthaler et al. from 1,5-anhydro-2,3,4,6-tetra-*O*-benzoyl-D-*arabino*-hex-1-enitol **3** (Figure 3).¹ Per-*O*-benzoylated 2-hydroxyglucal⁷ **3** was reacted with hydroxylamine to form the oxime **4** which was subsequently successfully debenzoylated under Zemplén conditions to give the unprotected oxime **5**. Transoximation of compound **5** using acetaldehyde resulted in 1,5-anhydro-D-fructose **1** in low overall yield.

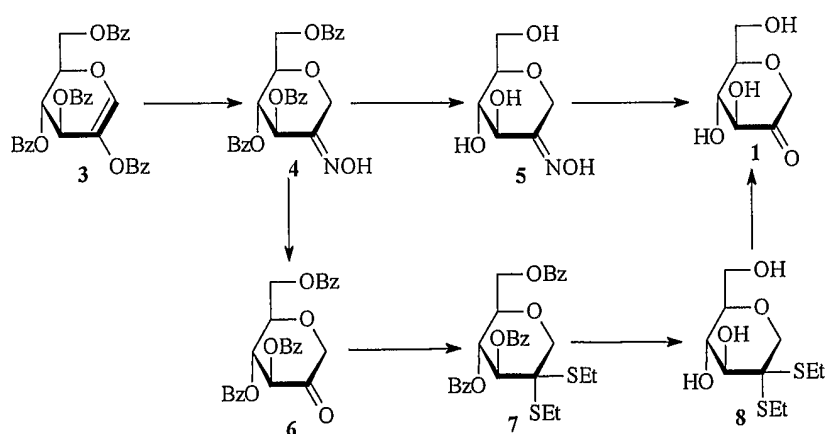


Figure 3. The first successful preparation of 1,5-anhydro-D-fructose.

To avoid base induced degradation of intermediates, oxime **4** was also transformed to a base stable dithioketal **7** by transoximation of **4** followed by treatment of intermediate **6** with ethanethiol. Zemplén deprotection of tribenzoate **7** using sodium methoxide gave the unprotected thioketal **8**. Mercury ion catalyzed hydrolysis of thioketal **8** afforded 1,5-anhydro-D-fructose in a very moderate yield. No direct structural proof of the obtained product has been given, but dimeric forms were mentioned.

In 1988, a different synthetic route to 1,5-anhydro-D-fructose was published, based upon the oxidation of C-2 hydroxyl function of a 1,5-anhydroglucitol derivative (Figure 4).⁸

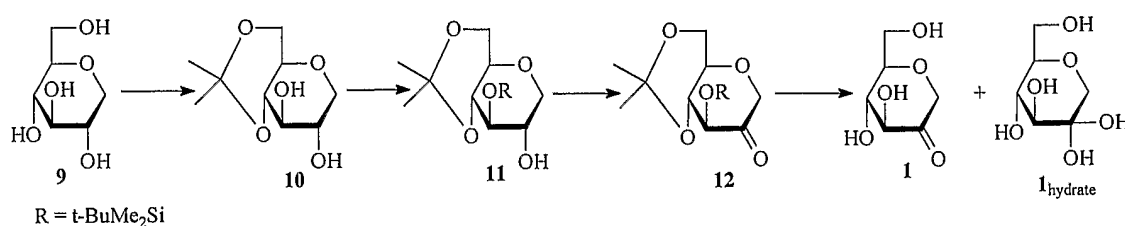


Figure 4. Preparation of 1,5-anhydro-D-fructose by O-2 oxidation.

Thus, 1,5-anhydro-glucitol **9** was partially protected as cyclic 4,6-O-isopropylidene acetal **10**. Poor regioselectivity and low yield has been achieved in the selective silylation of diol **10** affording compound **11**. Oxidation of 1,5-anhydro-alditol derivative **11** by pyridinium dichromate provided compound **12**, which was deprotected under acidic conditions giving 1,5-anhydro-D-fructose **1** in admixture with the hydrated form **1_{hydrate}** in an overall poor yield.

In 1988 a glucan lyase, which degrades starch and related oligosaccharides from the non-reducing end giving 1,5-anhydro-D-fructose **1** was identified.⁹ Later more than ten similar lyases have been isolated from different sources and used in enzymatic studies for the preparation of 1,5-anhydro-D-fructose.¹⁰

In 1993, an methodology for the preparation of 1,5-anhydro-D-fructose based upon pyranose 2-oxidase enzyme-catalyzed oxidation of 1,5-anhydro-glucitol **9** was reported.¹¹ In 1998, a preparative scale biocatalyzed process providing 1,5-anhydro-D-fructose **1** was developed (Figure 5).¹²

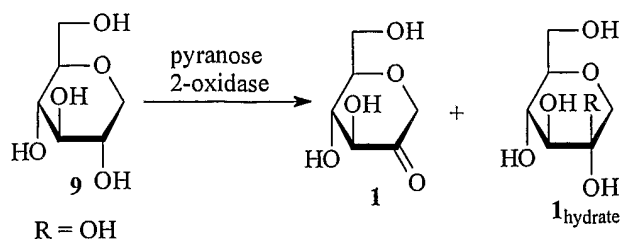


Figure 5. Enzymatic oxidation of 1,5-anhydro-glucitol.

According to Baute's enzymatic methodology, 1,5-anhydro-D-fructose has been prepared from starch in 40–50% yield. The process has attracted significant commercial interest for enzymatic production of 1,5-anhydro-D-fructose.^{13, 14, 15} The 1,5-anhydro-D-fructose-producing enzyme has also been cloned and expressed in *Aspergillus niger*^{16, 17}, outlining a more rational and industrially favored production strategy.

1,5-Anhydro-D-fructose has never been isolated in a pure monomeric form due to its hygroscopic nature and its high tendency for dimerization. 1,5-anhydro-D-fructose has been isolated as mixtures consisting of monomeric and dimeric forms^{18, 19} or the monomeric and the hydrated form (Figure 6).

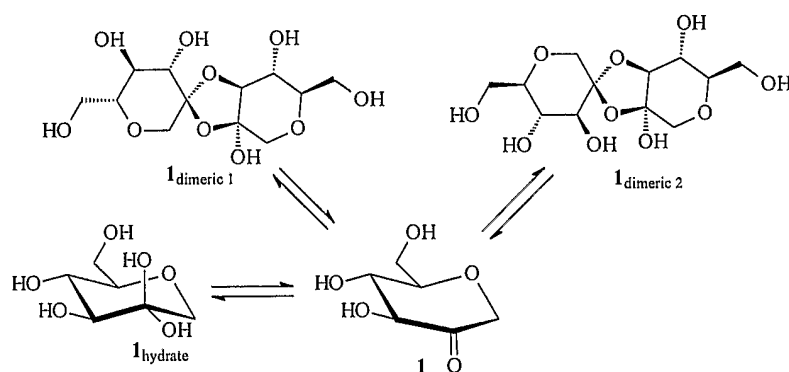


Figure 6. Monomeric-, dimeric- and hydrated forms of 1,5-Anhydro-D-Fructose.

Powerful antioxidant and antimicrobial agent character of 1,5-anhydro-D-fructose have been discovered/demonstrated.^{20, 21} Moreover aqueous solutions of 1,5-anhydro-D-fructose has outstanding stabilities in numerous conditions. Quite contrary, aqueous solutions of L-ascorbic acid expressing a similar antioxidant potential becomes easily oxidized by molecular oxygen.²² The present inventors envisage that 1,5-anhydro-D-fructose and other 1,4- and 1,5-anhydroketoses could have equivalent and/or superior properties than L-ascorbic acid itself in several food/cosmetic/therapeutic products.

Novel 1,4- and 1,5-anhydroketoses have the potentials to find wide applications in food industry²³⁻²⁵ - preventing pigment discoloration, enzymic browning, protecting flavour, aroma and nutrient content, extending shelf life -, in cosmetics industry²⁶ - replacing the unstable and ionic L-ascorbic acid - and in pharmaceutical industry - increasing hormone secretion of insulin via stimulating glucagon-like peptide 1 (GLP 1) expression.^{27,28}

It has also been proven that in mammals and humans, glycogen degrades by α -(1 $\rightarrow$ 4)-glucan lyase to 1,5-anhydro-D-fructose^{29,30} which subsequently is reduced to 1,5-anhydro-D-glucitol by a NADPH-dependent 1,5-anhydro-D-fructose specific reductas.³¹ This constitutes a third glycogenolytic pathway, in addition to the phosphorolytic and hydrolytic degradation sequences

The non-toxic character of 1,5-anhydro-D-fructose towards important fungi and yeasts used in food industry has also been proven.

1,5-Anhydro-D-fructose and its derivatives are important carbohydrates attracting industrial interest. Only a few substituted/derivatised 1,5-anhydro-D-fructose derivatives and other anhydroketoses have been synthesized due to the high base sensitivity of anhydroketose products and intermediates. Furthermore, structural analysis of anhydroketoses has greatly suffered from the strong dimer formation tendency of anhydroketoses, including unprotected 1,5-anhydro-D-fructose (Figure 6). It was not until recently that the correct structure of 1,5-anhydro-D-fructose has been elucidated.

In spite of the outstanding product potentials of 1,5-anhydro-D-fructose, derivatives thereof and other 1,4- and 1,5-anhydroketoses, the preparation of these important carbohydrates remained unsolved. Though, the progress made in enzymatic preparation of 1,5-anhydro-D-fructose, 1,5-anhydro-D-fructose is still not commercialized due to lack of efficient and cost-efficient manufacturing technologies.

To date, no chemical methodology has been published, which could provide bulk access to 1,5-anhydro-D-fructose, novel 1,5-anhydro-D-fructose derivatives and other important 1,4- and 1,5-anhydroketoses.

Thus, there is a need for convenient synthetic routes for the preparation of 1,4- and 1,5-anhydroketoses, in particular 1,4-anhydro-D-fructose.

SUMMARY OF THE INVENTION

The present invention represent a characteristic breakthrough in the field by providing a number of simple chemical methods suitable for the preparation of diverse 1,4- and 1,5-anhydroketoses. The present invention also gives the very first synthetic methodologies
5 suitable for bulk production of 1,5-anhydro-D-fructose itself and its numerous derivatives and analogues. The present invention has the power to initiate commercialization of 1,5-anhydro-D-fructose, derivatives and analogues thereof and chemical/biological/physiological exploration of numerous novel 1,4- and 1,5-anhydroketoses.

10 The present invention, thus, relates to novel, simple, chemical methods for the synthesis of 1,4- and 1,5-anhydroketoses, in particular 1,5-anhydro-D-fructose, and derivatives and stereoisomers hereof, the hydrated forms, the dimeric forms or any mixture of said forms, from accessible starting materials, which typically are easily prepared from inexpensive and easily available starting materials following literature procedures.

15 The first aspect of the present invention provides novel 1,4- and 1,5-anhydroketoses of a wide variety derivatised/underderivatised carbohydrates including mono- and oligosaccharides, iminosugars, carbasugars, thiosugars and C-glycosides characterised by either five- or six-membered ring structures.

20 The second aspect of the present invention provides synthetic methodologies for the preparation of derivatised/underderivatised 1,4- and 1,5-anhydroketoses - including 1,5-anhydro-D-fructose and its analogues/derivatives - via any of the following chemical procedures:

- 25 - Catalytic- and/or pyrolytic sulfenic acid elimination of derivatised/underderivatised β -hydroxy sulfoxides of carbohydrates derived from monosaccharides, oligosaccharides, iminosugars, thiosugars, carbocycles, C-glycosides and glycoconjugates of thereof.
- N-Deprotection of N-substituted-aminoglycals derived from monosaccharides, oligosaccharides, iminosugars, thiosugars, carbocycles, C-glycosides and glycoconjugates of thereof.
- 30 - O-Deprotection of carbohydrate enolethers and/or O-acyl-substituted carbohydrate enols derived from monosaccharides, oligosaccharides, iminosugars, thiosugars, carbocycles, C-glycosides and glycoconjugates of thereof.

- Regio- and stereoselective modification and subsequent chemical transformation of bicyclic and/or tricyclic 1,4- and 1,5-anhydro-glycoderivatives such as bicyclic 1,4- and/or 1,5-anhydro-glycosides, bicyclic 1,4- and/or 1,5-anhydro-thioglycosides, bicyclic 1,4- and/or 1,5-anhydro-glycosylamines, tricyclic cyclic-acetals of 1,4- and/or 1,5-anhydro-carbohydrates, tricyclic cyclic-ketals of 1,4- and/or 1,5-anhydro-carbohydrates, tricyclic cyclic-orthoesters of 1,4- and/or 1,5-anhydro-carbohydrates, bicyclic open chain acetals of 1,4- and/or 1,5-anhydro-carbohydrates and bicyclic open chain ketals of 1,4- and/or 1,5-anhydro-carbohydrates into 1,4- and 1,5-anhydroketoses.

- 10 The third aspect of the present invention provides utilities for 1,4- and 1,5-anhydroketoses such as anti-oxidants, sweeteners, non-caloric sweeteners, taste enhancing agents, taste improving agents, emulsifiers, water solubility enhancing agents, antimicrobial agents, food preserving agents, feed preserving agents, chelating agents, starch deterioration inhibiting agents, food colour retaining or stabilising agents, water retaining agents, moisturisers, 15 water-storing agents, fragrance stabilisers, taste stabilisers, protein stabilisers, moisture-releasing agents, bilayer forming agents, micelle forming agents, detergents, bulking agents, tensides, surfactants, functional foods, non-caloric functional foods.

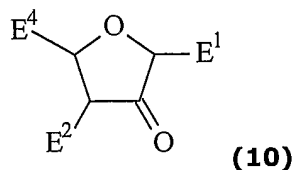
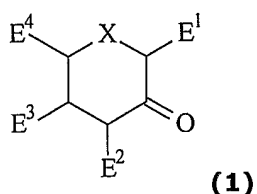
- 20 The fourth aspect of the present invention provides novel carbohydrate intermediates suitable for the synthesis of numerous glycoderivatives including but not limiting to preparation of 1,4- and 1,5-anhydroketoses and their derivatives/analogues.

The sixth aspect of the present invention provides novel uses of 1,5-anhydro-D-fructose within food-, cosmetic- and pharmaceutical industries.

DETAILED DESCRIPTION OF THE INVENTION

- 25 As mentioned above, the present invention i.a. relates to preparation methodologies for 1,4- and 1,5-anhydroketoses and to novel compounds within the class of 1,4- and 1,5-anhydroketoses, as well as novel intermediates.

The novel methodologies of the invention relate to the preparation of compounds of General Formula **1** and General Formula **10**, namely



wherein

X is selected from the group consisting of O, S, NH, NHR^1 , CH_2 , CHOH , CHOR^1 , CHNH_2 , CHNHR^1 , CHSH , CHSR^1 , C=O , S=O and SO_2 , in particular O;

- 5 E^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-20} -alkyl, optionally substituted heteroalkyl, optionally substituted C_{2-20} -alkenyl, optionally substituted C_{2-20} -alkynyl, optionally substituted C_{3-10} -cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted C_{2-20} -acyl; with the proviso that if X is selected from the group consisting of CH_2 , CHOH , CHOR^1 , CHNH_2 , CHNHR^1 , CHSH , CHSR^1 , C=O , S=O and SO_2 , then E^1 may also be selected from the group consisting of OH, $=\text{O}$, NH_2 , NHR^1 , NH_3^+A^- , NHR^1 , NR^1R^2 , SH, S^-M^+ , SR^1 , S=O , N_3 and halogen, in particular hydrogen;
- 10

E^2 and E^3 are independently selected from the group consisting of OH, O^-M^+ , OR^1 , $=\text{O}$, $=\text{S}$, SH, S^-M^+ , SR^1 , N_3 , NH_2 , NH_3^+A^- , NHR^1 , NR^1R^2 , and halogen, in particular OH and OR^1 ;

- 15 E^4 is selected from the group consisting of hydrogen, CH_3 , $-\text{CH}_2\text{OH}$, $-\text{CH}(\text{OH})\text{CH}_2\text{OH}$, $\text{CH}(\text{OH})\text{CH}(\text{OH})\text{CH}_2\text{OH}$, $-\text{CH}(\text{OH})\text{CH}_2\text{OR}^1$, $-\text{CH}(\text{OR}^1)\text{CH}_2\text{OH}$, $-\text{CH}(\text{OR}^1)\text{CH}_2\text{OR}^1$, $-\text{CH}_2\text{OR}^1$, $-\text{CH}(\text{OH})\text{CH}(\text{OH})\text{CH}_2\text{OR}^1$, $-\text{CH}(\text{OR}^1)\text{CH}(\text{OH})\text{CH}_2\text{OH}$, $-\text{CH}(\text{OH})\text{CH}(\text{OR}^1)\text{CH}_2\text{OH}$, $-\text{CH}(\text{OR}^1)\text{CH}(\text{OR}^1)\text{CH}_2\text{OH}$, $-\text{CH}(\text{OR}^1)\text{CH}(\text{OH})\text{CH}_2\text{OR}^1$, $-\text{CH}(\text{OR}^1)\text{CH}(\text{OR}^1)\text{CH}_2\text{OR}^1$, $-\text{CH}=\text{O}$; $-\text{CH}_2\text{SH}$, $-\text{CH}_2\text{S}^-\text{M}^+$, $-\text{CH}_2\text{SR}^1$, $-\text{CH}_2\text{N}_3$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{NH}_3^+\text{A}^-$, $-\text{CH}_2\text{NHR}^1$, $-\text{CH}_2\text{NR}^1\text{R}^2$, $-\text{COOH}$, $-\text{COO}^-\text{M}^+$, and $-\text{COOR}^1$; with the proviso that if X is selected from the group consisting of CH_2 , CHOH , CHOR^1 , CHNH_2 , CHNHR^1 , CHSH , CHSR^1 , C=O , S=O and SO_2 , then E^4 may also be selected from the group consisting of $-\text{OH}$, O^-M^+ , OR^1 , SH, S^-M^+ , N_3 , NH_2 , NH_3^+A^- , NHR^1 , NR^1R^2 , $=\text{O}$, $=\text{S}$, and halogen; in particular E^4 is selected from the group consisting of CH_3 , $-\text{CH}_2\text{OH}$, $-\text{CH}(\text{OH})\text{CH}_2\text{OH}$, $\text{CH}(\text{OH})\text{CH}(\text{OH})\text{CH}_2\text{OH}$, $-\text{CH}(\text{OH})\text{CH}_2\text{OR}^1$, $-\text{CH}(\text{OR}^1)\text{CH}_2\text{OH}$, $-\text{CH}(\text{OR}^1)\text{CH}_2\text{OR}^1$, $-\text{CH}_2\text{OR}^1$;
- 20
- 25

R^1 is selected from the group consisting of optionally substituted C_{1-20} -alkyl, optionally substituted heteroalkyl, optionally substituted C_{2-20} -alkenyl, optionally substituted C_{2-20} -alkynyl, optionally substituted C_{3-10} -cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C_{2-20} -acyl, $\text{C}(\text{O})\text{R}^2$,

SO₃H, SO₃⁻M⁺, SO₂R², C(O)NHR², P(O)(OH)₂, an acetal or ketal, and a carbohydrate structural motif, in particular R¹ is selected from the group consisting of optionally substituted C₁₋₆-alkyl, optionally substituted heteroalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted C₂₋₆-acyl, C(O)R², C(O)NHR², and a carbohydrate structural motif;

R² is selected from the group consisting of optionally substituted C₁₋₂₀-alkyl, optionally substituted heteroalkyl, optionally substituted C₂₋₂₀-alkenyl, optionally substituted C₂₋₂₀-alkynyl, optionally substituted C₃₋₁₀-cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl; in particular R² is selected from the group consisting of optionally substituted C₁₋₆-alkyl, optionally substituted heteroalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

two of R¹ and/or R² may further be covalently linked so as to provide a cyclic structure;

M⁺ is any inorganic or organic cation; and A⁻ is any inorganic or organic anion.

It is evident from the following that the methods of the present invention are particularly useful for the preparation of 1,5-anhydro-D-fructose and 1,5-anhydro-D-tagatose as well as compounds of the General Formulas **1a**, **2**, **3**, **4**, **5**, **6**, **7**, **10** and **11** defined herein.

Definitions

In the present context, the term "C₁₋₂₀-alkyl" is intended to mean a linear or branched hydrocarbon group having 1 to 20 carbon atoms, such as methyl, ethyl, propyl, *iso*-propyl, butyl, *tert*-butyl, *iso*-butyl, pentyl, hexyl, octyl, nonyl, decyl, undecyl, dodecyl, etc. Analogously, the term "C₁₋₆-alkyl" is intended to mean a linear or branched hydrocarbon group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, *iso*-propyl, pentyl, and hexyl, and the term "C₁₋₄-alkyl" is intended to cover linear or branched hydrocarbon groups having 1 to 4 carbon atoms, e.g. methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, and *tert*-butyl.

Whenever the term "C₁₋₂₀-alkyl" is used herein, it should be understood that a particularly interesting embodiments thereof are "C₁₋₆-alkyl" and "C₈₋₂₀-alkyl".

The term "alkoxy" means "alkyl-oxy".

The term "C₂₋₂₀-acyl" means "C₁₋₁₉-C(=O)-".

Similarly, the term "C₂₋₂₀-alkenyl" is intended to cover linear or branched hydrocarbon groups having 2 to 20 carbon atoms and comprising one or more unsaturated bonds. Examples of alkenyl groups are vinyl, allyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, heptadecaenyl, butadienyl, pentadienyl, hexadienyl, heptadienyl, heptadecadienyl, hexatrienyl, heptatrienyl, octatrienyl, and heptadecatrienyl.

Similarly, the term "C₂₋₂₀-alkynyl" is intended to mean a linear or branched hydrocarbon group having 2 to 20 carbon atoms and comprising a triple bond. Examples hereof are ethynyl, propynyl, butynyl, octynyl, and dodecaynyl.

When used herein, the term "heteroalkyl" is intended to mean a hydrocarbon chain interrupted by one or more heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur. The chain may have a total length of in the range of 4-500 atoms, such as 10-100 atoms. Illustrative examples of heteroalkyl substituent are polyethylene glycols, polyethylene imines, etc.

The term "C₃₋₁₀-cycloalkyl" is intended to mean a cyclic hydrocarbon group having 3 to 10 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

"Halogen" includes fluoro, chloro, bromo, and iodo.

In the present context, the term "aryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system, such as phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, anthracyl, phenanthracyl, pyrenyl, benzopyrenyl, fluorenyl and xanthenyl, among which phenyl is a preferred example.

The term "heteroaryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e.g. nitrogen (=N- or -NH-), sulphur, and/or oxygen atoms. Examples of such heteroaryl groups are oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, coumaryl, furyl, thienyl, quinolyl, benzothiazolyl, benzotriazolyl, benzodiazolyl, benzooxazolyl, phthalazinyl, phthalanyl, triazolyl, tetrazolyl, isoquinolyl, acridinyl, carbazolyl, dibenzazepinyl, indolyl, benzopyrazolyl, phenoxazonyl. Particularly interesting heteroaryl groups are oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl, thienyl, quinolyl, triazolyl, tetrazolyl, isoquinolyl, indolyl in particular pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, thienyl, quinolyl, tetrazolyl, and isoquinolyl.

The term "heterocyclyl" is intended to mean a non-aromatic carbocyclic ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e.g. nitrogen (=N- or -NH-), sulphur, and/or oxygen atoms. Examples of such heterocyclyl groups are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, aziridine, azirine, azetidine, pyroline, tropane, oxazinane (morpholine), azepine, dihydroazepine, tetrahydroazepine, and hexahydroazepine, oxazolane, oxazepane, oxazocane, thiazolane, thiazinane, thiazepane, thiazocane, oxazetane, diazetane, thiazetane, tetrahydrofuran, tetrahydropyran, oxepane, tetrahydrothiophene, tetrahydrothiopyrane, thiepane, dithiane, dithiepane, dioxane, dioxepane, oxathiane, oxathiepane. The most interesting examples are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, azetidine, tropane, oxazinane (morpholine), oxazolane, oxazepane, thiazolane, thiazinane, and thiazepane, in particular imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, pyrrolidine, piperidine, azepane, oxazinane (morpholine), and thiazinane.

For the purpose of this specification the term "substituted" in the definitions of R₁ and R₂, and in definitions of other substituents within this specification, means that the substituent is itself substituted with a group which modifies the general chemical characteristics of the chain. Preferred substituents include but are not limited to halogen, nitro, amino, azido, oxo, hydroxyl, thiol, carboxy, carboxy ester, carboxamide, alkylamino, alkylidithio, alkylthio, alkoxy, acylamido, acyloxy, or acylthio, each of 1 to 3 carbon atoms. Such substituents can be used to modify characteristics of the molecule as a whole, such as stability, solubility, and ability to form crystals. The person skilled in the art will be aware of other suitable substituents of a similar size and charge characteristics, which could be used as alternatives in a given situation.

More generally in connection with the terms "alkyl", "alkenyl", "alkynyl" and "cycloalkyl", the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-3 times, with group(s) selected from the group consisting of hydroxy (which when bound to an unsaturated carbon atom may be present in the tautomeric keto form), C₁₋₆-alkoxy (i.e. C₁₋₆-alkyl-oxy), C₂₋₆-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality), C₁₋₆-alkoxycarbonyl, C₁₋₆-alkylcarbonyl, formyl, aryl, aryloxycarbonyl, aryloxy, arylamino, arylcarbonyl, heteroaryl, heteroarylamino, heteroaryloxycarbonyl, heteroaryloxy, heteroarylcarbonyl, amino, mono- and di(C₁₋₆-alkyl)amino, carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkylcarbonylamino, cyano, guanidino, carbamido, C₁₋₆-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C₁₋₆-alkanoyloxy, C₁₋₆-alkyl-sulphonyl, C₁₋₆-alkyl-sulphinyl, C₁₋₆-

alkylsulphonyloxy, nitro, C₁₋₆-alkylthio, halogen, where any aryl and heteroaryl may be substituted as specifically described below for "optionally substituted aryl and heteroaryl", and any alkyl, alkoxy, and the like representing substituents may be substituted with hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbamoylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, or guanidino.

Preferably, the substituents are selected from the group consisting of hydroxy (which when bound to an unsaturated carbon atom may be present in the tautomeric keto form), C₁₋₆-alkoxy (i.e. C₁₋₆-alkyl-oxy), C₂₋₆-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality), C₁₋₆-alkylcarbonyl, formyl, aryl, aryloxy, arylamino, arylcarbonyl, heteroaryl, heteroarylamino, heteroaryloxy, heteroarylcarbonyl, amino, mono- and di(C₁₋₆-alkyl)amino; carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkylcarbamoylamino, guanidino, carbamido, C₁₋₆-alkyl-sulphonyl-amino, C₁₋₆-alkyl-sulphonyl, C₁₋₆-alkyl-sulphinyl, C₁₋₆-alkylthio, halogen, where any aryl and heteroaryl may be substituted as specifically described below for "optionally substituted aryl and heteroaryl".

Especially preferred examples are hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbamoylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, and guanidino.

Moreover, in connection with the terms "aryl", "heteroaryl", "heteroalkyl" and "heterocyclyl", the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-5 times, in particular 1-3 times) with group(s) selected from the group consisting of hydroxy (which when present in an enol system may be represented in the tautomeric keto form), C₁₋₆-alkyl, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, oxo (which may be represented in the tautomeric enol form), carboxy, C₁₋₆-alkoxycarbonyl, C₁₋₆-alkylcarbonyl, formyl, aryl, aryloxy, arylamino, aryloxycarbonyl, arylcarbonyl, heteroaryl, heteroarylamino, amino, mono- and di(C₁₋₆-alkyl)amino; carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkylcarbamoylamino, cyano, guanidino, carbamido, C₁₋₆-alkanoyloxy, C₁₋₆-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C₁₋₆-alkyl-sulphonyl, C₁₋₆-alkyl-sulphinyl, C₁₋₆-alkylsulphonyloxy, nitro, sulphonyl, amino, amino-sulfonyl, mono- and di(C₁₋₆-alkyl)amino-sulfonyl, dihalogen-C₁₋₄-alkyl, trihalogen-C₁₋₄-alkyl, halogen, where aryl and heteroaryl representing substituents may be substituted 1-3 times with C₁₋₄-alkyl, C₁₋₄-alkoxy, nitro, cyano, amino or halogen, and any alkyl, alkoxy, and the like representing substituents may be substituted with hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbamoylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, or guanidino.

Preferably, the substituents are selected from the group consisting of hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, oxo (which may be represented in the tautomeric enol form), carboxy, C₁₋₆-alkylcarbonyl, formyl, amino, mono- and di(C₁₋₆-alkyl)amino; carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkylcarbonylamino, guanidino, carbamido, C₁₋₆-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C₁₋₆-alkyl-sulphonyl, C₁₋₆-alkyl-sulphinyl, C₁₋₆-alkylsulphonyloxy, sulphonyl, amino, amino-sulfonyl, mono- and di(C₁₋₆-alkyl)amino-sulfonyl or halogen, where any alkyl, alkoxy and the like representing substituents may be substituted with hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbonylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, or guanidino. Especially preferred examples are C₁₋₆-alkyl, C₁₋₆-alkoxy, amino, mono- and di(C₁₋₆-alkyl)amino, sulphonyl, carboxy or halogen, where any alkyl, alkoxy and the like representing substituents may be substituted with hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbonylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, or guanidino.

When used herein, the expression "carbohydrate structural motif" is intended to encompass (but not being limited to) derivatised and underivatised mono- and oligosaccharides, iminosugars, thiosugars, C-glycosides, and carbocycles. The carbohydrate structural motif is directly- and/or indirectly linked via covalent linkages including but not limited to ether, acyl or glycosidic bonds to heteroatoms of which the carbohydrate structural motif is said to be a substituent (R¹).

The term "a cyclic structure" as a possible meaning for two of R¹ and/or R² is in particular referring to cyclic ketals and acetals, and cyclic structures as referred to in General Formulas **94, 95, 96, 97** and **98** (see Figure 22), namely acetals, ketals, carbonates, orthoesters, lactones, etc.

This being said, it should furthermore be understood that the compounds defined herein include other salts (salts other than the quaternary amino salts having Q as the counter-ion) thereof, of which pharmaceutically acceptable salts are of course especially relevant for the therapeutic applications. Salts include acid addition salts and basic salts. Examples of acid addition salts are hydrochloride salts, fumarate, oxalate, etc. Examples of basic salts are salts where the (remaining) counter ion is selected from the group consisting of alkali metals, such as sodium and potassium, alkaline earth metals, such as calcium salts, potassium salts, and ammonium ions (⁺N(R')₄), where the R's independently designate optionally substituted C₁₋₆-alkyl, optionally substituted C₂₋₆-alkenyl, optionally substituted aryl, or optionally substituted heteroaryl). Pharmaceutically acceptable salts are, e.g., those described in Remington's - The Science and Practice of Pharmacy, 20th Ed. Alfonso R. Gennaro (Ed.), Lippincott, Williams & Wilkins; ISBN: 0683306472, 2000, and in Encyclopedia of Pharmaceutical Technology.

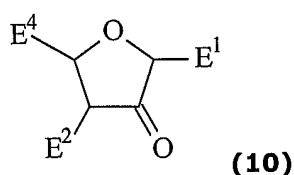
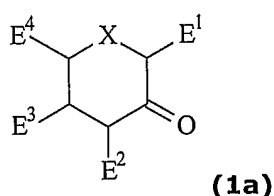
M^+ is any inorganic or organic cation. The metal ion can be mono- or multivalent, and may form a complex salt. Examples of cations are sodium, potassium, calcium, magnesium, zinc, ammonium, quaternary ammonium, etc.

A^- is any inorganic or organic anion known in the art. The anion can be mono- or multivalent, and may form a complex salt. Examples of anions are halides, anions of organic acids, anions of mineral acids, etc. Examples hereof are chloride (Cl^-), bromide (Br^-), iodide (I^-), acetate, lactate, maleate, fumarate, oxalate, sulphate, nitrate, etc.

It will be appreciated by the person skilled in the art that the compounds defined herein as final products, intermediates and precursors, etc. may exist in different tautomeric, hydrated and dimeric forms. It will also be evident that from the formulae defined herein and the definitions associated therewith, that the compounds of the present invention typically are chiral. Moreover, the presence of the cyclic fragments and multiple stereogenic atoms provides for the existence of diastereomeric forms of the compounds. The invention is intended to include all stereoisomers, including optical isomers, and mixtures thereof, as well as pure, partially enriched, or, where relevant, racemic forms. Thus, the above-mentioned carbohydrate compounds may be in the D- or L-form, or mixtures of such forms.

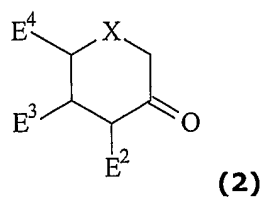
1,4- and 1,5-anhydroketoses

It is believed that the majority of the above-defined 1,4- and 1,5-anhydroketoses are novel *per se*, and the present invention therefore in particular relates to such novel compounds, i.e. compounds of General Formula **1a** and General Formula **10**



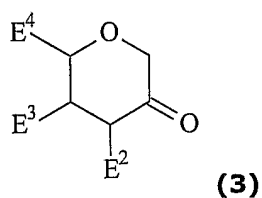
wherein E^1 , E^2 , E^3 , E^4 and X are as defined for General Formulas **1** and **10**, with the proviso that the compound is not selected from the group consisting of 1,5-anhydro-D-fructose (X = O; E^2 = equatorial OH; E^3 = equatorial OH; E^4 = CH_2OH in equatorial configuration) and 1,5-anhydro-D-tagatose (X = O; E^2 = equatorial OH; E^3 = axial OH; E^4 = CH_2OH in equatorial configuration).

In a preferred embodiment, the anhydroketose is characterized by General Formula **2**.



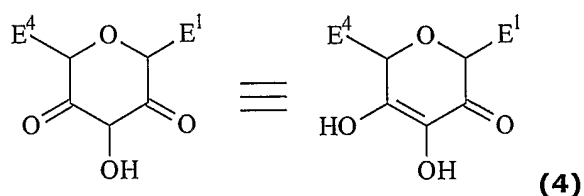
wherein X, E², E³ and E⁴ are as defined for General Formula **1a**, with the proviso that the compound is not selected from the group consisting of 1,5-anhydro-D-fructose and 1,5-anhydro-D-tagatose.

- 5 In a more preferred embodiment, the anhydroketose is characterized by General Formula **3**.



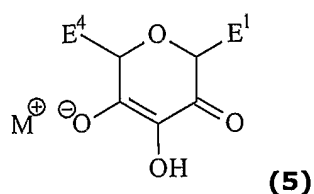
wherein E², E³ and E⁴ are as defined for General Formula **1a**, with the proviso that the compound is not selected from the group consisting of 1,5-anhydro-D-fructose and 1,5-anhydro-D-tagatose.

- 10 In another preferred embodiment, the anhydroketose is characterized by General Formula **4**.



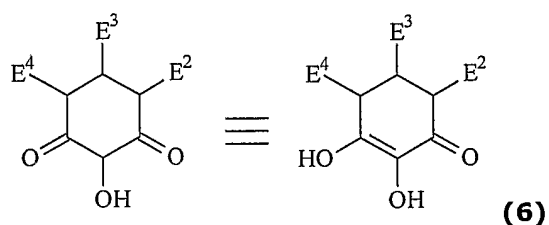
wherein E¹ and E⁴ are as defined for General Formula **1a**.

In a still further preferred embodiment, the anhydroketose is characterized by General Formula **5**.



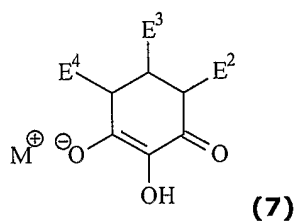
wherein M^+ , E^1 and E^4 are as defined for General Formula **1a**.

In a further preferred embodiment, the anhydroketoses is characterized by General Formula **6**.



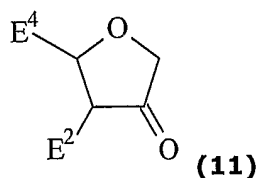
5 wherein E^2 , E^3 and E^4 are as defined for General Formula **1a**.

In a further preferred embodiment, the anhydroketose is characterized by General Formula **7**.



wherein M^+ , E^2 , E^3 and E^4 are as defined for General Formula **1a**.

10 In an further preferred embodiment, the compound is characterized by General Formula **11**.



wherein E^2 and E^4 are as defined for General Formula **10**.

Use of 1,4- and 1,5-anhydroketoses

15 A further aspect of the present invention relates to various utilities for the 1,4- and 1,5-anhydroketoses characterized by General Formulas **1a**, **2-7**, **10** and **11**. It is belived that

individual compounds or mixtures of such compounds will be useful as an antioxidant, a radical scavenger, a sweetener, a non-caloric sweetener, a taste enhancing agent, a taste improving agent, an emulsifier, a water solubility enhancing agent, an antimicrobial agent, an antidiabetic agent, a glycosidase inhibitor, a food preserving agent, a feed preserving agent, a chelating agent, a starch deterioration inhibiting agent, a food colour retaining or stabilising agent, a water retaining agent, a moisturiser, a water-storing agent, a fragrance stabiliser, a taste stabiliser, a protein stabiliser, a moisture-releasing agent, a bilayer forming agent, a micelle forming agent, a detergents, a bulking agent, a tenside, a surfactant, a functional food, and/or a non-caloric functional food additive, applied either alone or in compositions with other compounds in food-, cosmetic- and pharmaceutical products.

In a preferred embodiment, the 1,4- and 1,5-anhydroketoses characterized by General Formulas **1a**, **2-7**, **10** and **11** are used as antioxidant agents applied either alone or in composition with other compounds in food-, cosmetic-, and pharmaceutical products.

In a further preferred embodiment, compounds characterized by General Formulas **1a**, **2-7**, **10** and **11** are used as antimicrobial agents applied either alone or in compositions with other compounds in food-, cosmetic- and pharmaceutical products.

In a still further preferred embodiment, compounds characterized by General Formulas **1a**, **2-7**, **10** and **11** are used as non-caloric sweeteners applied either alone or in compositions with other compounds in food- and pharmaceutical products.

In a still further preferred embodiment, compounds characterized by General Formulas **1a**, **2-7**, **10** and **11** are used as moisturizing agents applied either alone or in compositions with other compounds in cosmetic- and pharmaceutical products.

In a still further preferred embodiment, compounds characterized by General Formulas **1a**, **2-7**, **10** and **11** are used as emulsifier or non-ionic surfactant agents applied either alone or in compositions with other compounds in food-, cosmetic- and pharmaceutical products.

In an even further preferred embodiment, compounds characterized by General Formulas **1a**, **2-7**, **10** and **11** are used as non-caloric functional food additives applied either alone or in compositions with other compounds in food-, cosmetic- and pharmaceutical products.

Some of the above-mentioned uses may also be relevant for 1,5-anhydro-D-tagatose.

Uses of 1,5-anhydro-D-fructose

A number of uses are already known for 1,5-anhydro-D-fructose. However, the present inventors believe that hitherto unrealized utilities of 1,5-anhydro-D-fructose are possible, e.g. as a non-caloric sweetener, a non-caloric functional food additive, a functional food, an antidiabetic functional food, a functional food for elderly, a moustering agent, a moisture-releasing agent, and/or a protein-stability enhancing agent.

Methods for the preparation of 1,4- and 1,5-anhydroketoses

As mentioned further above, the present inventors have developed a series of methods for the preparation of compounds of the above-mentioned class, and this will be described in detail in the following.

Sulfenic acid elimination of β -hydroxyl sulfoxides of carbohydrates

Sulfenic acid elimination of derivatised/underderivatised β -hydroxy sulfoxides of carbohydrates derived from monosaccharides, oligosaccharides, iminosugars, thiosugars, carbocycles, C-glycosides and glycoconjugates of thereof is one of the key features of this aspect of the invention.

The most general variant of this aspect provides a method for the preparation of a 1,4- or 1,5-anhydroketose of General Formula **1** or General Formula **10**, said method comprising the step of subjecting a corresponding β -hydroxy-sulfoxide to pyrolysis.

The preparation of 1,4- and 1,5-anhydroketoses characterized by General Formulas **1-7**, **10** and **11** by using pyrolysis of the corresponding β -hydroxy-sulfoxides is typically carried out in either organic or aqueous solutions at temperatures ranges 60–120°C in acidic, neutral or slightly basic reaction conditions. Solvents including but not limited to toluene, benzene, 1,4-dioxane, DMF, N-methylpyrrolidine, water, pyridine and the mixtures of thereof can be used for such chemical transformation. Acidic- and/or basic substances such as inorganic/organic acids, inorganic/organic bases and salts of thereof might be preferred during the pyrolysis in order to control pH and catalytic procedures. The reaction time for the pyrolysis typically varies from 3-48 hours depending on the structures of substrates and the set temperature and the 1,4- or 1,5-anhydroketose is typically obtained in yields ranging from 60 to 95%.

In one embodiment hereof, the invention provides a method for the preparation of a 1,5-anhydroketose of the General Formula **18** or a 1,4-anhydroketose of the General Formula **30**, wherein E^2 , E^3 and E^4 are as defined for General Formula **1**, said method comprising the steps of subjecting a sulfenic acid of the General Formula **17** or General Formula **29**, wherein
5 E^2 , E^3 and E^4 are as defined above for General Formulas **18** and **29**, and R is selected from the group consisting of C_{1-8} -alkyl and aryl, to pyrolysis

In one variant, the sulfenic acid of the General Formula **17** is

- a) prepared from the corresponding sulphide of the General Formula **16** wherein E^2 , E^3 , E^4 and R are as defined for General Formula **17**, by oxidation of the sulphide; or
- 10 b) prepared from the corresponding protected sulfenic acid of the General Formula **15** wherein E^2 , E^3 , E^4 and R are as defined above for General Formula **16**, and P is a hydroxy group protecting group, by deprotection of the hydroxy group (removal of the group P).

Furthermore, the protected sulfenic acid of the General Formula **15** may be prepared from the corresponding protected sulphide of the General Formula **14** wherein E^2 , E^3 , E^4 , R and P
15 are as defined for General Formula **15**, by oxidation.

Alternatively, the sulphide of the General Formula **16** may be prepared from the corresponding protected sulphide of the General Formula **14** wherein E^2 , E^3 , E^4 , R and P are as defined for General Formula **15**, by deprotection of the hydroxy group (removal of the group P).

- 20 Typically, the protected sulphide of the General Formula **14** is prepared from the precursor of the General Formula **13** wherein E^4 and R are as defined for General Formula **14**, by derivatisation or protection. Unprotected thioglycosides **13** are general building blocks of carbohydrate chemistry. Thioglycosides support selective/unselective acylation, alkylation, glycosylation, cyclic- and acyclic acetal formation, nucleophilic displacement of sulfonates,
25 wide range of nucleophili, electrophilic/acid- and base treatments described in numerous textbooks such as Bertram O. Fraser-Reid, Kuniaki Tatsua, Joachim Thiem, "Glycoscience: Chemistry and Chemical Biology I-III" , Springer, 2001

Alternatively, the sulphide of the General Formula **16** is prepared from the precursor of the General Formula **13** wherein E^4 and R are as defined for General Formula **16**, by
30 derivatisation or protection.

Illustrative examples of the method of this aspect are given below.

β -Hydroxy carbohydrate sulfoxides have never been used as precursors for the preparation of 1,4- and 1,5-anhydroketoses. The present invention provides the very first examples, in which 2-hydroxy-glycosyl sulfoxides are used for the synthesis of 1,4- and 1,5-anhydroketoses in catalytic- and/or neutral pyrolytic sulfenic acid elimination reactions (Figure 7).

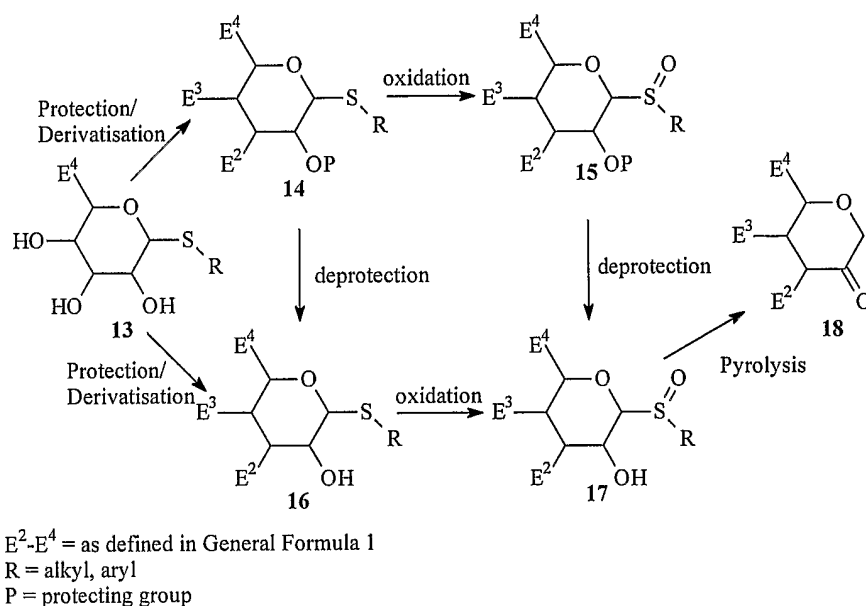


Figure 7. Synthesis of complex 1,5-anhydroketoses via sulfenic acid elimination of carbohydrate sulfoxides.

The synthesis of highly functionalized 1,5-anhydroketoses **18** is based upon a flexible thioglycoside derivation and/or protecting group manipulation strategy. For example, unprotected thioglycoside **13** can be modified via regioselective manipulations to produce either intermediate **14** or compound **16**. Subsequent selective oxidation of partially protected thioglycosides **14** and **16** into sulfoxide derivatives affords **15** and **17**. Intermediate **15** can easily be transformed into compound **17** via removal of the protecting group at O-2 position. Compound **17** carries the β -hydroxy-sulfoxide moiety required for subsequent sulfenic acid elimination initiated via pyrolysis providing derivatised 1,5-anhydroketoses **18**. The simplicity of the overall process and the structural diversity of products accessible by the approach are valuable features of the present invention. Thioglycosides are extremely stable during structural modifications allowing facile syntheses of wide arrays of anhydroketoses in a final pyrolysis step of the inventive process.

Another important feature of the present invention is characterized by the use of unprotected glycosyl sulfoxides such as **22** as precursors for the preparation of unprotected/unmodified 1,5-anhydroketoses **23** (Figure 8).

- 5 1,5-Anhydro-D-fructose could also be prepared via this approach in a neutral pyrolytic process providing the most straightforward procedure for the preparation of 1,5-anhydro-D-fructose and unsubstituted and derivatised analogues thereof. This represents a very important embodiment of the invention.

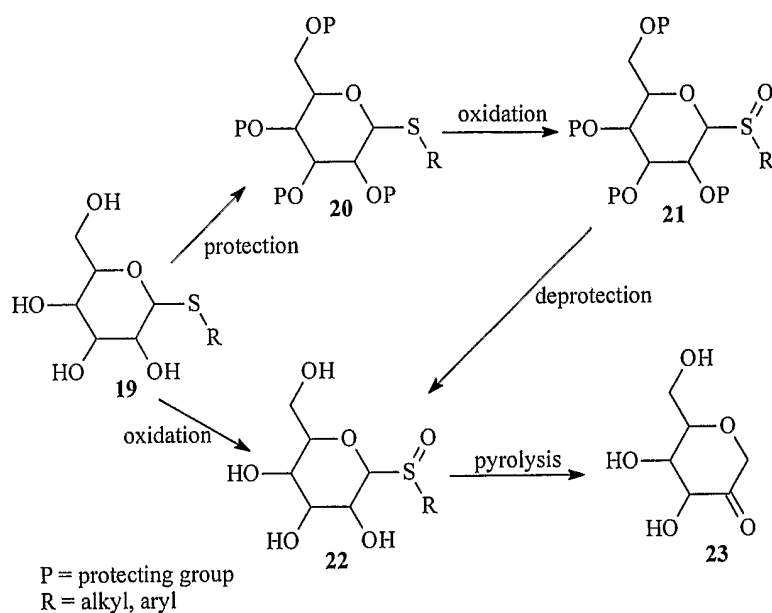


Figure 8. Synthesis of unprotected 1,5-anhydroketoses.

- 10 Another unique feature of the present invention is characterized by the general use of β -hydroxy sulfoxides of oligosaccharides or β -hydroxy sulfoxides of other complex glycoderivatives in sulfenic acid elimination reactions affording novel 1,5-anhydroketoses of oligosaccharides (Figure 9).

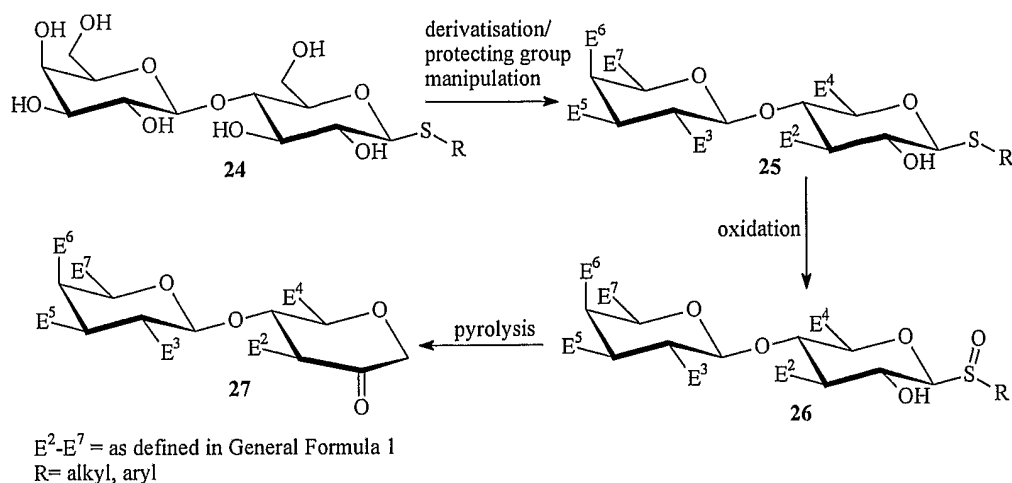


Figure 9. Preparation of 1,5-anhydroketoses of oligosaccharides via sulfenic acid elimination of β-hydroxy-glycosyl sulfoxides.

Substituents E⁵ and E⁶ are independently selected among groups defined for E² and E³ in General Formula 1. E⁷ is freely selected among groups defined for E⁴ in General Formula 1.

For example, lactose thioglycoside **24** could extensively be modified by different chemical procedures providing highly functionalized oligosaccharide derivative **25**. Oxidation of thioglycoside **25** provided β-hydroxy-glycosyl sulfoxide **26** suitable for sulfenic acid elimination. Thus, pyrolysis of **26** gave access to highly functionalized oligosaccharide-type 1,5-anhydroketoses such as **27**.

A further important feature of the present invention provides simple and economical methodologies for direct pyrolysis of unprotected β-hydroxy-sulfoxides of oligosaccharides such as **24** affording unsubstituted 1,5-anhydroketoses of oligomeric glycomolecules such as 1,5-anhydro-D-lactulose **28** (Figure 10). The formation of anhydroketoses occurs in completely neutral conditions during pyrolysis without any use of additional catalysts/reagents.

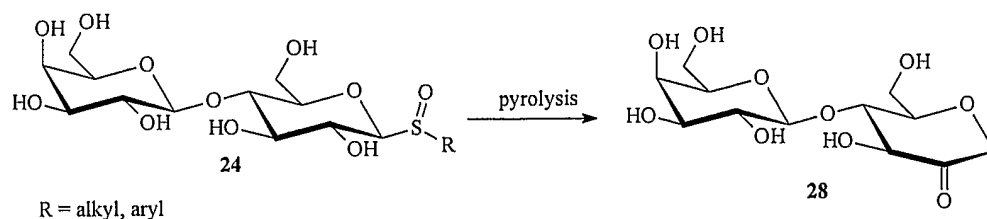
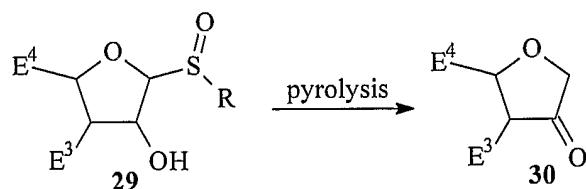


Figure 10. Preparation of unprotected 1,5-anhydroketoses of oligosaccharides.

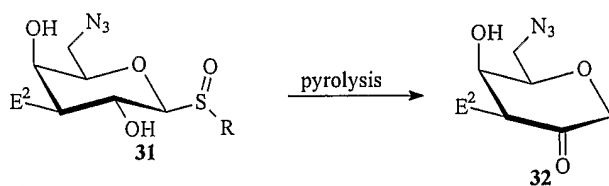
The synthetic methodologies provided by the present invention could also be used for the pyrolysis of derivatised/un-derivatised β -hydroxy sulfoxides of furanoses **29** providing access to 1,4-anhydroketofuranoses **30** characterized by five-membered ring structures (Figure 11).



E^3, E^4 = as defined in General Formula 1
R = alkyl, aryl

5 Figure 11. Preparation of 1,4-anhydroketoses.

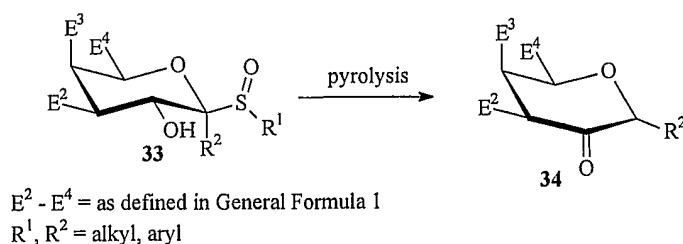
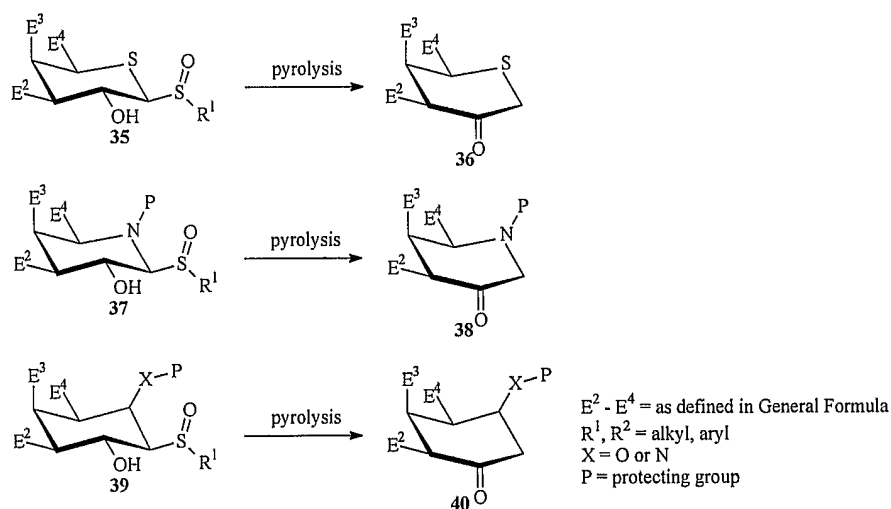
The unique nature of pyrolytic sulfenic acid elimination of both furanosyl- and pyranosyl-type β -hydroxy sulfoxides of carbohydrates provided by the present invention makes the method compatible with the presence of a wide range of functional groups - including but not limited to hydroxyl, amino, azido, acylamido, acyloxy, carboxyl etc. - assisting the syntheses of structurally diverse 1,4- and 1,5-anhydroketoses of monosaccharides and oligosaccharides (Figure 12). For example, several unprotected functional groups present in the structure of **31** could not have any influence on the intramolecular sulfenic acid elimination initiated by pyrolysis affording compound **32**.



E^2 = as defined in General Formula 1
R = alkyl, aryl

15 Figure 12. Demonstration of functional group compatibility during sulfenic acid elimination.

An additional object of the present invention provides access to C-derivatised anhydroketoses. For example, β -hydroxy sulfoxides of C-glycosides such as **33** give C-derivatives of anhydroketoses **34** in pyrolytic sulfenic acid elimination reactions. Thus, the present invention gives the methodologies for the preparation of both C-substituted 1,4-anhydro-glycofuranoses and 1,5-anhydro-glycopyranoses.

Figure 13. Preparation of anhydroketoses from β -hydroxyl sulfoxides of C-glycosides.Figure 14. Preparation of *S*-, *N*- and *C*-analogues of 1,4- and 1,5-anhydroketoses.

- 5 A further object of the present invention provides methodologies for the preparation of *S*-, *N*- and *C*-analogues of 1,4- and 1,5-anhydroketoses by pyrolysis of iminosugar- and carbosugar-type β -hydroxy sulfoxides (Figure 14; E^2 - E^4 are as defined for General Formula 1). For example, β -hydroxy sulfoxides of thiosugars **35**, iminosugars **37** and carbocycles **39** could serve as precursors for the synthesis of anhydroketoses **36**, **38** and **40** in pyrolytic reaction
- 10 conditions.

N-Deprotection of *N*-substituted-amino-glycals of carbohydrates

- N*-deprotection of *N*-substituted-amino-glycals of carbohydrates is a key feature of this aspect of the invention, preferably *N*-deprotection is obtained via the removal of acyclic vinylogous amide functionalities in acidic, neutral or slightly basic reaction conditions, e.g. of
- 15 compounds of General Formulas **8**, **9** and **12**.

Thus, the invention provides method for the preparation of a 1,4- or 1,5-anhydroketose of General Formula **1** or General Formula **10**, said method comprising the step of deprotecting a corresponding N-protected aminoglycal, preferably a compound of General Formulas **8**, **9** or **12**.

- 5 A wide range of reagents including but not limited to Cl_2 , Br_2 , ammonia, ammonia/boric acid, ethylene diamine, basic ion exchange resin, hydrazine, hydrazine acetate etc. known by a person skilled in the art are suitable for the indicated chemical transformation of aminoglycals into 1,4- and 1,5-anhydroketoses. A wide range of solvents including but not limited to dichloromethane, chloroform, ethers, alcohols, acetone, acetonitrile, acetic acid, DMF, water and the mixtures of thereof could be used for the indicated reaction. Room temperature is preferred but lower or higher temperatures could also be suitable depending on solubilities of precursors/reagents. Yields related to 1,4- and 1,5-anhydrocarbohydrate formation using acyclic vinylogous deprotection of aminoglycals range from 60% to 95% depending on the presence of sensitive/robust functionalities and applied reaction conditions.
- 15 Derivatised/underderivatised *N*-substituted aminoglycals of monosaccharides **41** and derivatised/underderivatised *N*-substituted aminoglycals of oligosaccharides **44** (exemplified in Figure 13. (Substituents E^5 and E^6 are independently selected among groups defined for E^2 and E^3 in General Formula **1**. E^7 is freely selected among groups defined for E^4 in General Formula **1**)) are ideal building blocks for the preparation of diverse 1,4- and 1,5-anhydroketoses via the procedures of the present invention characterized by selective removal of the N-protecting group of aminoglycals followed by aqueous work-up.
- 20

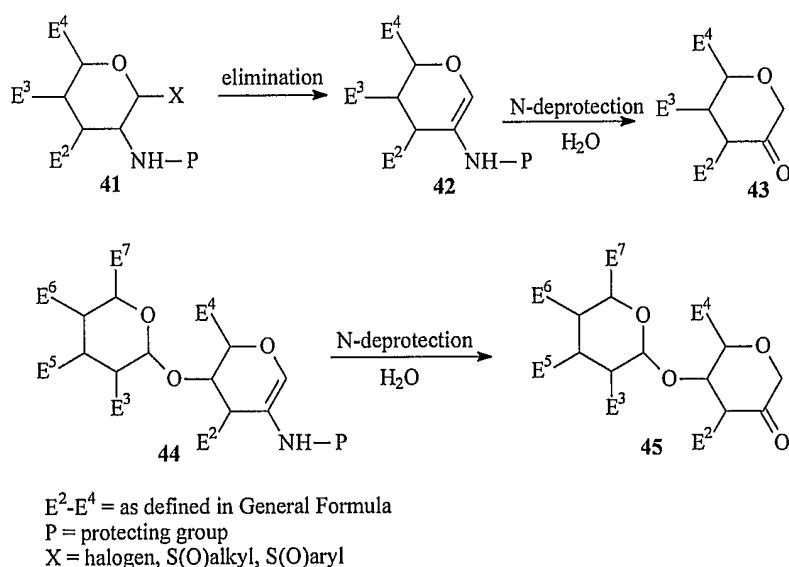


Figure 15. Preparation of anhydroketoses from N-protected aminoglycals.

The general reaction scheme above also shows some of the most convenient preparations of precursors **42** from glycosyl halides **41** (X = halogen) by base (NaH, DBU) induced- or from glycosyl sulfoxides **41** (X = S(O)alkyl or S(O)aryl) by thermal treatment initiated

5 derivatisation/protecting group manipulations become possible in the N-protected aminoglycal stage of the synthesis. Thus, compounds **42** and **44** could stand numerous reaction conditions suitable for the derivatisation of N-protected aminoglycals **43** and **45** providing access to diverse 1,4- and 1,5-anhydroketoses.

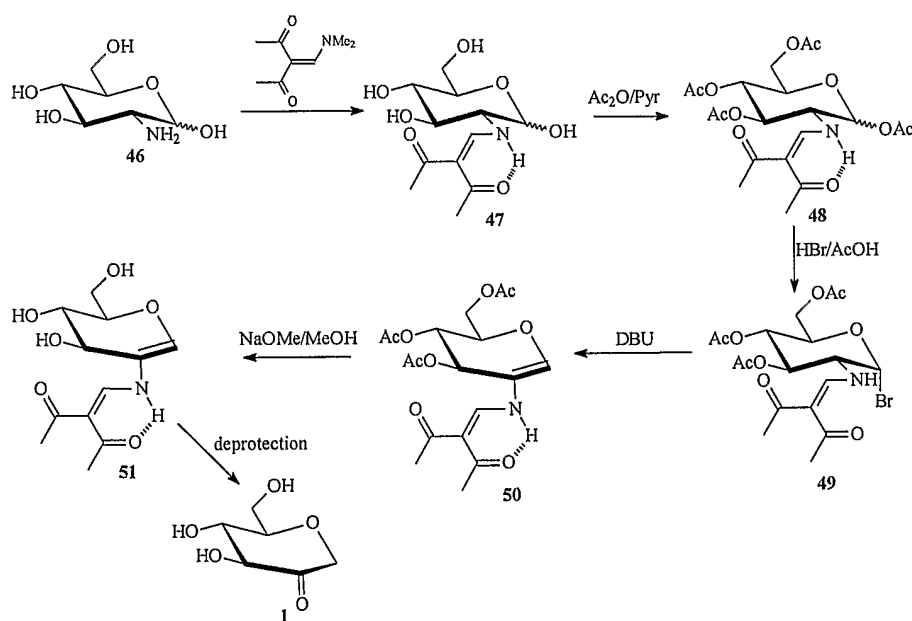
The applied P-protecting group could be widely selected among blocking groups (carbamates, amides, vinylogous amides, etc.) known in the art, see, e.g. "Protective Groups in Organic

10 Chemistry" by Wuts and Greene, Wiley-Interscience; ISBN: 0471160199; 3rd edition (May 15, 1999).

Acyclic vinylogous amides are especially suitable for the synthesis of diverse arrays of anhydroketoses as acyclic vinylogous amide intermediates stand numerous reaction

15 conditions but could easily be removed in acidic, basic or neutral reaction conditions.

The present invention related to the preparation of diverse anhydroketoses via N-protected aminoglycals could also be applied for the direct synthesis of 1,5-anhydro-D-fructose using commercially available cheap glucosamine precursor (Figure 16).



20 Figure 16. Preparation of 1,5-anhydro-D-fructose via deprotection of N-protected aminoglycals.

Thus, acyclic vinylogous amide protection of glucosamine **46** could be achieved in nearly quantitative yield using vinylogous reagents giving N-protected glucosamine derivatives such as **47**. Per-O-acetylation of N-protected glucosamines could be achieved by acetic anhydride treatment of the precursors affording peracetates such as **48**. Preparation of glycosyl bromides such as **49** was completed by HBr/AcOH treatment of peracetates. Subsequent base induced elimination was initiated by DBU affording N-protected aminoglucals such as **50**. Removal of O-acetyl groups by Zemplen deprotection gave the final aminoglycal intermediates such as **51**. Several deprotection strategies of acyclic vinylogous amides known in the art could be used in the final deprotection step of 1,5-anhydro-D-fructose preparation. Thus, hydrazine, diethylamine, ammonia/boric acid and chlorine treatment of final intermediates such as **51** could afford 1,5-anhydro-D-fructose.

The above described methodology for producing 1,5-anhydro-D-fructose based upon N-deprotection of cheap substituted 2-aminoglucals represents a highly economical synthetic approach for potential manufacturing of 1,5-anhydro-D-fructose.

The aminoglycal approach of the present invention is equivalent in most of the cases with the β -hydroxy sulfoxide approach described previously for the preparation of 1,4- and 1,5-anhydroketoses. However, the aminoglycal approach could be superior for the preparation of specific 4-thio-, 5-thio-analogues of anhydroketoses - exemplified in the preparation of **55-57** -, than the β -hydroxy sulfoxide method, which shows limitations in regioselective manipulations of multiple thioether/sulfoxide/sulfone moieties in this specific area (Figure 17).

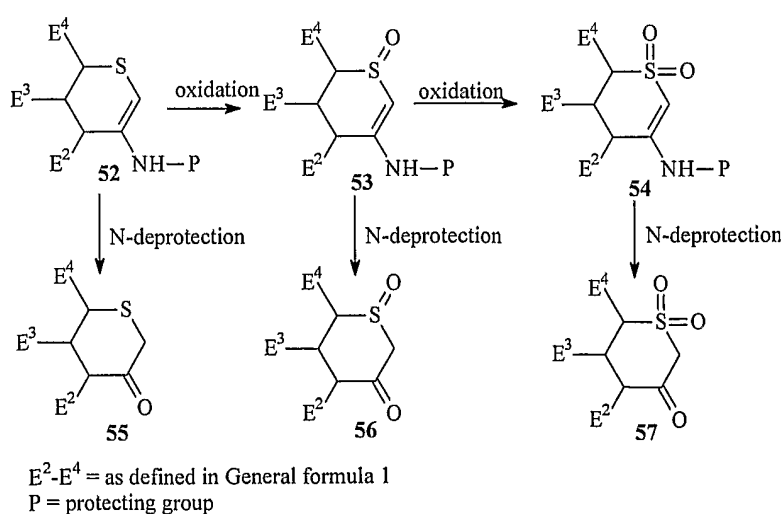


Figure 17. Preparation of 5-thio-1,5-anhydroketoses and their oxidised derivatives.

For example, stepwise oxidation of thiosugar **52** could lead to the formation of cyclic sulfoxide **53** and cyclic sulfone **54**. Subsequent N-deprotection of protected aminoglycal precursors **52-54** could afford the required anhydroketoses **55-57**.

- Methodologies related to the aminoglycal approach of the present invention are also suitable for the preparation of wide range of anhydroketoses of iminosugars, C-glycosides, carbocycles and glycoconjugates thereof (Figure 18; E²-E⁴ are as defined for General Formula **1**).

Thus, the general procedure of N-deprotection of aminoglycals of different carbohydrates **58**, **60** and **62** provides the desired anhydroketoses **59**, **61** and **63**.

- Furthermore, selective chemical modifications - such as N- or O-derivation of N-substituted aminoglycals - always give extra options for the constructions of numerous different 1,4- and 1,5-anhydroketoses.

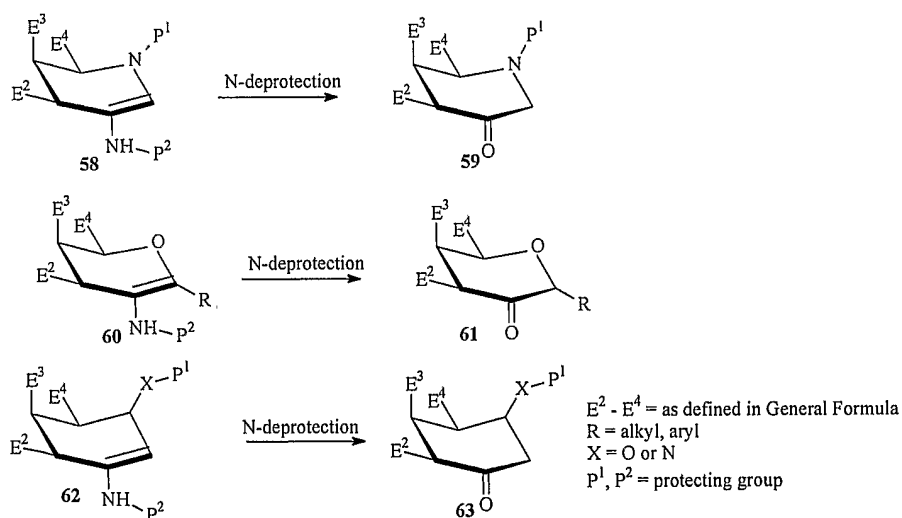
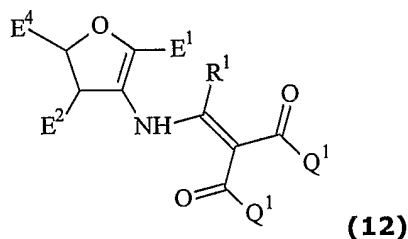
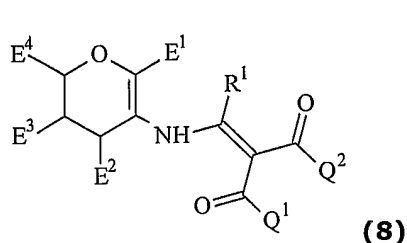


Figure 18. Preparation of anhydroketoses of iminosugars, C-glycosides and carbocycles.

15 *N*-substituted-amino-glycals of carbohydrates

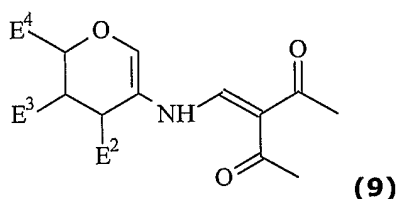
Amino-glycals having an acyclic vinylogous amide N-substituent, e.g., as defined above in Figure 16, are believed to represent novel, important intermediates for the above-mentioned method.

Thus, another aspect of the present invention provides compounds characterized by General Formula **8** and General Formula **12**



wherein R^1 , E^1 , E^2 , E^3 and E^4 are as defined for General Formula **1**, and

- 5 Q^1 and Q^2 are independently selected from the group consisting of optionally substituted C_{1-20} -alkyl, optionally substituted heteroalkyl, optionally substituted C_{2-20} -alkenyl, optionally substituted C_{2-20} -alkynyl, optionally substituted C_{3-10} -cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C_{1-20} -alkyloxy, and optionally substituted aryloxy.
- 10 In one preferred embodiment, the glycals is characterized by General Formula 9



wherein E^2 , E^3 and E^4 are as defined for General Formula **1**.

- A further aspect of the invention relates to the preparation of such compounds of General Formulas **8-9** and **12**. Thus, the invention also provides methodologies for the preparation of
- 15 the *endo*-glycals characterized by General Formulas **8**, **9** and **12** by using either pyrolysis of β -*N*-acyclic vinylogous amide protected sulfoxides of carbohydrates in reaction conditions described or base induced elimination of *N*-acyclic vinylogous amide protected glycosyl halide precursors. Pyrolysis of *N*-acyclic vinylogous amide protected sulfoxides requires temperatures of 60-120°C using a wide variety of solvents known by a person skilled in the
- 20 art. Base induced elimination of acyclic vinylogous amides of glycosyl halides such as glycosyl chlorides, glycosyl bromides and glycosyl iodides require inorganic/organic bases including but not limited to sodium hydride, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,8-bis(dimethylamino)naphthalene (proton sponge), potassium *t*-butoxide, potassium fluoride or

any other fluoride ion source, etc. Applied temperatures of base induced elimination reactions of glycosyl halides vary from -20°C to 40°C depending on the selection of base catalysts providing the desired protected aminoglycals with yields ranging from 60% to 90%.

O-Deprotection of carbohydrate enolethers and/or O-acyl-substituted carbohydrate enols

5 O-Deprotection of carbohydrate enolethers and/or O-acyl-substituted carbohydrate enols is a key feature of the method according to this aspect of the invention. Thus, the present invention provides methodologies for the preparation of compounds characterized by General Formulas **1-7**, **10** and **11** by O-deprotection of carbohydrate enolethers and/or O-acyl-substituted carbohydrate enols in suitable reaction conditions.

10 More specifically, the invention also relates to a method for the preparation of a 1,4- or 1,5-anhydroketose of the General Formula **1** or General Formula **10**, said method comprising the step of deprotecting a corresponding carbohydrate enolether or an O-acyl-substituted carbohydrate enol.

Carbohydrate enolethers include, but are not limited to, O-alkyl-enolethers, O-substituted-alkyl-enolethers, O-acyclic/cyclic acetal-type enolethers, O-glycosyl-type enolethers, etc. undergo deprotection in acidic reaction conditions using inorganic/organic acid catalysts, acidic ion-exchange resin, etc known by a person skilled in the art. Application of neutral and slightly basic reaction conditions known in the art for the cleavage of enolethers is also covered by the present invention. O-Acyl carbohydrate enols including but not limited to O-acetyl-, O-benzoyl-, O-chloroacetyl-, O-trifluoroacetyl, O-phenoxyacetyl, O-pivaloyl etc. are also included in the procedure provided by the present invention. Reagents including but not limited to inorganic/organic acids, acidic or basic ion-exchange resins, metal alkoxides, acidic and basic inorganic/organic salts, organic bases are equally suitable for the preparation of anhydroketoses from O-acyl-substituted enols. Organic and aqueous solutions containing alcohols, DMF, dioxane, and many other solvents known by a person skilled in the art could be used. Reaction temperature can vary between -40°C to 50°C according to the chosen catalyst and solvent applied. Yields of 60-95% could be achieved depending on the nature of precursors.

30 This special aspect of the present invention is especially suited for the preparation of 1,5-anhydro-D-fructose, the hydrated form, the dimeric form or any mixture of said forms, including derivatives and stereoisomers, characterised by deacylation of a 2-O-acyl-glycals.

In one embodiment according to the invention precursor acyloxyglycal may carry several other O-acyl groups or may be any glyco-motif. By the term "glyco-motif" is meant any group comprising mono-, oligo- or polysaccharides including glycans, which is a generic term for any sugar or assembly of sugars, in free form or attached to another molecule, used interchangeably with carbohydrate or "sugar".

In a highly preferred embodiment, the configuration of the precursor carbohydrate is *gluco-* and all the substituents are O-acetylated. This particular embodiment results in the preparation of 1,5-anhydro-D-fructose.

The deacylation of per-O-acetylated 2-hydroxy-glycals is performed by means of a base preferably of the formula M^+OR^2 , wherein M is an alkali or alkaline earth metal cation or a quaternary ammonium group and R^2 is as defined for General Formula **1**, preferably R^2 is a C_1 - C_6 alkyl group. In a preferred embodiment, said base is sodium methoxide.

In order to avoid side reactions such as elimination and rearrangement reactions the deacylation method according to the invention is performed at a reaction temperature in the range of -50°C to -30°C , most preferably about -40°C .

The deacylation method according to the invention preferably takes place in a solvent wherein said solvent is selected from the group consisting of protic, polar aprotic solvents or mixtures thereof, optionally in combination with a minor proportion of an inert, non-polar solvent.

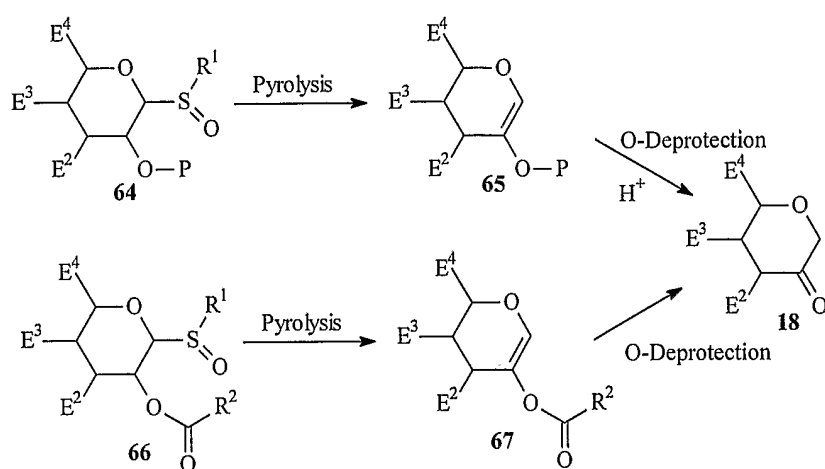
Such solvents are well known to the skilled person and examples of use in the method according to the invention are DMF, DMSO, dioxane, C_1 - C_6 alcohols or mixtures thereof, particularly a lower alcohol such as methanol.

Preparation of carbohydrate enolethers via traditional methods could lead to severe synthetic problems, which have prevented the preparation of such carbohydrate derivatives. However, as it has been described in the present invention, pyrolysis of carbohydrate sulfoxides **64** provides the gentlest method for the preparation of diverse carbohydrate enolether such as **65** (Figure 19). Thus, the present invention provides access to 1,4- and 1,5-anhydroketoses from enolether precursors **65** by selective deprotection of the enolether functions.

One of the methodologies of the present invention is based upon acid treatments of acid sensitive carbohydrate enolethers **65** providing 1,4- and 1,5-anhydroketoses **18** of monosaccharides, oligosaccharides, thiosugars, iminosugars, C-glycosides, carbocycles, etc. and glycoconjugates thereof.

This method provides a general procedure for the preparation of anhydroketoses independently from the nature of enolether moiety used for the acid catalyzed removal of P protecting group. Any alkyl, substituted alkyl, aryl, substituted aryl, acyclic acetal, cyclic acetal, glycosyl moieties and numerous other groups known in the art could be part of the carbohydrate enolether moiety in General Formula **65**.

It is important to emphasize that 1,4-anhydroketoses could also be prepared by the methodology described in the present invention based upon acid hydrolysis of carbohydrate enolethers.



E^2-E^4 = as defined in General Formula 1

R^1, R^2 = alkyl, aryl

P = ether or acetal type protecting group

Figure 19. Preparation of anhydroketoses via carbohydrate enolethers and O-acyl-substituted enols

An additional methodology of the present invention belongs to selective deprotection of O-acylated/carbamoylated carbohydrate enolethers such as **67** affording 1,4- and 1,5-anhydroketoses **18**. Several methodologies known in the art have been developed for removal of different O-acyl groups in acidic, neutral and basic reaction conditions from general carbohydrate scaffolds. Acidic/neutral O-acyl deprotection methods applied to acyloxyglycals are directly suitable for the preparation of anhydroketoses by the removal of O-acylated enolethers of carbohydrate precursors. Basic methodologies require extra attention and considerations of tuning deprotection conditions due to base sensitivity of many anhydroketoses.

However, the present invention describes several reaction conditions, in which selectivity could be found and unwanted base-induced elimination could be avoided. Thus, methodologies based upon the removal of acyl moieties from O-acylated enol ethers of carbohydrates – including but not limited to acyloxyglycals - have the advantage of an easy access to cheap carbohydrate precursors such as O-acylated carbohydrate enols. Both methodologies - O-deprotection of carbohydrate enoethers and O-deprotection of O-acyl-substituted carbohydrate enols - provided by the present invention could be directly used for the preparation of anhydro-D-fructose and related derivatives/analogues.

The preferred acetoxyglycal for the preparation of anhydro-D-fructose according to the present invention is tetra-O-acetyl-2-hydroxy-D-glucal. Tetra-O-acetyl-2-hydroxy-D-glucal is readily available by methods known *per se*. Thus, tetra-O-acetyl-2-hydroxy-D-glucal may be prepared from D-glucose by acetylation and direct conversion to acetylated glucosyl bromide by treatment with hydrogen bromide. Elimination of HBr by an organic base, such as an amine, e.g. diethylamine or DBU (1,5-diazabicyclo[5.4.0]undec-5-ene) gives the acetylated hydroxyglucal.

Tetra-O-acetyl-2-hydroxy-D-glucal may be prepared from acetobromoglucose in a yield of 60-80% by treatment with diethylamine and sodium iodide in acetone as it is known by a person skilled in the art. Alternatively, said process may be carried out in a yield of 83% by treatment glycosyl bromide with DBU in DMF.

Another practical synthetic plan uses underivatised sulfoxides **22** as a universal precursor of both approaches characterized by O-deprotection of O-substituted carbohydrate enols (Figure 20). O-Acylation and O-alkylation could provide intermediates **68** and **69** supporting the formation of O-acylated enols **70** and carbohydrate enoethers **71** in subsequent pyrolytic sulfenic acid elimination reactions. Final removal of protecting groups from intermediates **70** and **71** could provide the desired anhydroketoses.

It is crucial to emphasize the importance of the nature of protecting functions employed. Chloroacetyl, phenoxyacetyl, trifluoroacetyl groups are especially suitable for the removal of blocking functions from O-acylated carbohydrate enols via gentle base treatment. Application of optimal reaction time and furthermore conducting the deprotection step at low temperatures are also tools to avoid unwanted degradation processes. Application of properly selected protecting groups such as tetrahydropyranyl (THP), tetrahydrofuranyl, methoxybenzyl, etc. known in the art for derivatisation of sulfoxide **22** could also provide benefits at the final removal synthetic step.

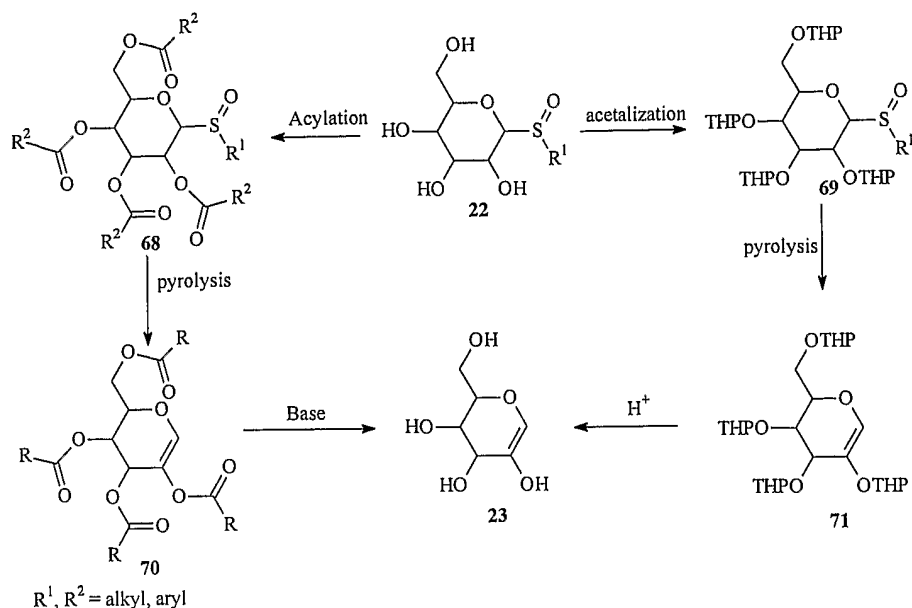
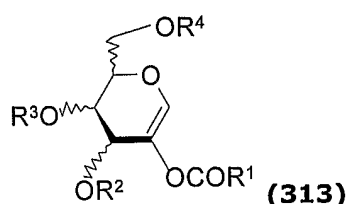


Figure 20. Preparation of unsubstituted anhydroketoses via alkylated/acylated carbohydrate enols

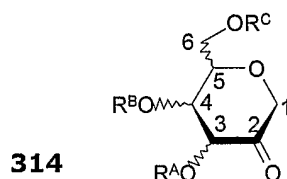
Both methodologies using O-deprotection of carbohydrate enoethers and O-deprotection of O-acyl-substituted carbohydrate enols are also highly suitable for the preparation of anhydroketoses of thiosugars, iminosugars, C-glycosides, carbocycles and glycoconjugates thereof.

A particular variant of the above, relates to a method for the preparation of 1,5-anhydro-D-fructose, the hydrated form, the dimeric form or any mixture of said forms, including derivatives and stereoisomers, characterised by deacylation of a 2-O-acyl-glycal of the General Formula **313**



wherein R^1, R^2, R^3 and R^4 , which may be identical or different, are selected independently from the group consisting of hydrogen, optionally substituted, linear, branched or, if applicable, cyclic C_1 - C_6 alkyl, optionally substituted aryl, optionally substituted Ar- $(C_1$ - C_6 alkyl), optionally substituted Ar- $(C_1$ - C_6 alkoxy), wherein said substituents are selected among halogen, such as fluoro, chloro, bromo, iodo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, or wherein R^2, R^3 and

R^4 , which may be identical or different, are selected independently from any glyco-motif, or wherein any one, two or three of R^2 , R^3 and R^4 may be COR^1 , where R^1 has any of the meanings of above, at a reaction temperature below $0^\circ C$ with a base to obtain 1,5-anhydro-D-fructose or derivatives and stereoisomers hereof of the General Formula **314**



- 10 wherein R^A , R^B , R^C has the meaning of R^2 , R^3 , R^4 above for this variant with the proviso that R^A , R^B , R^C can not be COR^1 .

In one embodiment according to this variant, R^2 , R^3 and R^4 , of which the exact identity may or may not be known or defined, may be any glyco-motif, while R^1 is selected from the group consisting of hydrogen, methyl, chloromethyl, ethyl, t-butyl, phenyl, chlorophenyl or methoxy phenyl. By the term "glyco-motif" is meant any group comprising mono-, oligo- or polysaccharides including glycans, which is a generic term for any sugar or assembly of sugars, in free form or attached to another molecule, used interchangeably with carbohydrate or "sugar".

20 In a preferred embodiment of this variant, R^2 , R^3 and R^4 are identical while R^1 is selected from the group consisting of hydrogen, methyl, chloromethyl, ethyl, t-butyl, phenyl, chlorophenyl or methoxy phenyl.

In a particularly preferred embodiment of this variant, R^2 , R^3 and R^4 are each COR^1 , where R^1 has the meaning of above.

In a further embodiment, R^2 , R^3 , R^4 and COR^1 are identical.

25 R^1 is preferably a methyl group.

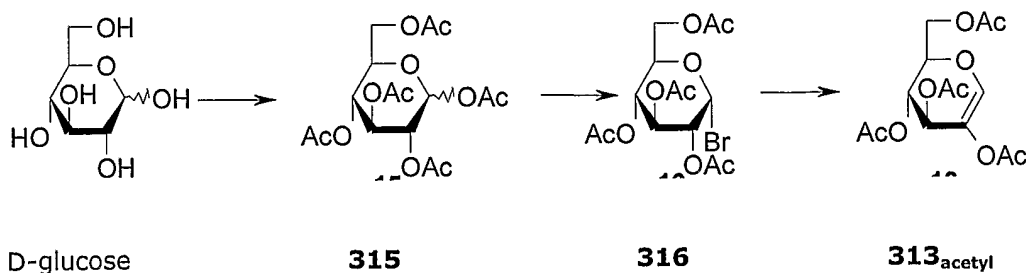
In a most preferred embodiment of this variant, R^2 , R^3 and R^4 are each COR^1 , and R^1 is a methyl group. This particular embodiment results in the preparation of 1,5-anhydro-D-Fructose which can be viewed as a compound of the General Formula **314** wherein R^A , R^B , and R^C are hydrogen.

The deacylation of a 2-*O*-acyl-glycal of the General Formula **313** is performed by means of a base preferably of the formula M^+OR^5 , wherein M is an alkali or alkaline earth metal cation or a quaternary ammonium group of the formula $(R^6)_4N^+$, wherein R^5 and R^6 are each C_1 - C_6 alkyl group. In a preferred embodiment, said base is sodium methoxide.

- 5 In order to avoid side reactions such as elimination and rearrangement reactions the deacylation method is performed at a reaction temperature in the range -100°C to 0°C . More particularly said reaction temperature is in the range -80°C to -20°C depending on the respective acyl groups to be displaced. In an even more preferred embodiment, said reaction temperature is in the range -50°C to -30°C , most preferably about -40°C .
- 10 The deacylation method according to this variant preferably takes place in a solvent. Said solvent is typically selected from the group consisting of protic, polar aprotic solvents or mixtures thereof, optionally in combination with a minor proportion of an inert, non-polar solvent. Such solvents are well known to the skilled person and examples of use in the method according to the invention are DMF, DMSO, dioxane, C_1 - C_6 alcohols or mixtures thereof, particularly a lower alcohol such as methanol.

- The preferred starting material for the method, tetra-*O*-acetyl-2-hydroxy-D-glucal, **313_{acetyl}** (a compound of the General Formula **313** where, $R^1 = \text{CH}_3$, R^2 - $R^4 = \text{COR}^1$) is readily available by methods known *per se*. Thus, tetra-*O*-acetyl-2-hydroxy-D-glucal may be prepared from D-glucose by acetylation and direct conversion to acetylated glucosyl bromide by treatment
- 20 with hydrogen bromide generated *in situ* ($P + \text{Br}_2$) in a two steps-one pot reaction, followed by crystallisation. Elimination of HBr by an organic base, such as an amine, e.g. diethylamine or DBU (1,5-diazabicyclo[5.4.0]undec-5-ene) gives the acetylated hydroxyglucal.

- As a further example a crystalline compound of the General Formula **313_{acetyl}** can be prepared according to the following reaction scheme as disclosed by R. U. Lemieux (R. U. Lemieux, Methods in Carbohydrate Chemistry, Vol. II, 221-222- Eds. R. L. Whistler, M. L. Wolfrom and J. N. BeMiller, Academic Press, 1963, New York).



As an alternative starting material for the synthesis of **313_{acetyl}**, the compound **315**, commercially available as D-glucose-pentaacetate, may be treated with a solution of HBr/acetic acid to give acetobromoglucose (**316**), a reaction which is general for carbohydrates having an acyl group at C-1. Acetobromoglucose (**316**) is also commercially available from e.g. Sigma-Aldrich or Fluka.

Tetra-O-acetyl-2-hydroxy-D-glucal, **13_{acetyl}**, may be prepared from acetobromoglucose in a yield of 60-80% by treatment with diethylamine and sodium iodide in acetone as disclosed by R.J. Ferrier (R.J. Ferrier, Methods in Carbohydrate Chemistry, Vol. VI, 307-311.- Eds. R. L. Whistler, J. N. BeMiller, Academic Press, 1972, New York).

Alternatively, said process may be carried out in a yield of 83% by treatment with DBU in DMF as disclosed by Varela et al (O.Varela, G. M, DE Fina, R. M. Lederkremer, Carbohydr. Res. 167, 1987, 187-196).

Regio- and stereoselective modification and subsequent chemical transformation of bicyclic and/or tricyclic 1,4- and 1,5-anhydro-glycoderivatives

A further aspect of the present invention provides methodologies for the preparation of 1,5-anhydroketoses, in particular 1,5-anhydro-D-fructose, by chemical modifications based upon the liberation of the hemiketal functionalities of bicyclic- and tricyclic anhydrocarbohydrate precursors characterized by General Formulas **13-15** and **17-24** using either acid catalyzed hydrolysis of glycosides, cyclic ketals, cyclic acetals, cyclic orthoesters and cyclic carbonates or by any other method known by a person skilled in the art such as reductive ring opening of acetals/ketals, activation of thioglycosides, hydrolysis of glycosyl amines, glycosyl amides etc. Preferably, aqueous acetic acid at 20-80°C, alkyl/arylsulfonic acids in methanol at 40-65°C or acidic ion exchange resin in water and/or alcohols at 20-60°C are used affording anhydroketoses in 80-98% yield.

One preferred embodiment hereof provides methodologies for the preparation of 1,5-anhydro-D-fructose by chemical modifications based upon the liberation of the hemiketal functionalities of tricyclic anhydrocarbohydrate precursors characterized by General Formulas **19** using either acid catalyzed hydrolysis of cyclic ketals or any other method known by a person skilled in the art suitable for the ring opening/removal of the cyclic ketal function. Preferably, aqueous acetic acid at 20-80°C, alkyl/arylsulfonic acids in methanol at 40-65°C or acidic ion exchange resin in water and/or alcohols at 20-60°C are used affording anhydroketoses in 90-98% yield.

Another preferred embodiment hereof provides methodologies for the preparation of 1,5-anhydro-D-fructose by acid catalyzed hydrolysis of the precursor cyclic ketal of tricyclic anhydrocarbohydrate precursor characterized by General Formulas **19** in which R⁴ is hydrogen. Preferably, aqueous acetic acid at 20-80°C, alkyl/arylsulfonic acids in methanol at 40-65°C or acidic ion exchange resin in water and/or alcohols at 20-60°C are used affording anhydroketoses in 90-98% yield.

Several ketoses such as fructose, lactulose are cheap chiral building blocks for organic syntheses. Utilisation of such common renewable resources is an important industrial aim. Synthesis of anhydroketoses from naturally occurring ketoses themselves is an absolutely novel approach of the present invention initiating industrial use of such valuable resources.

Thus, the present invention provides the preparation of 1,4- and 1,5-anhydroketoses from simple ketose precursors such as **72** (fructose) via either bicyclic- or tricyclic-anhydrocarbohydrate intermediates (Figure 21).

Generation of bicyclic anhydrocarbohydrate intermediates belongs to the preparation of glycosides-, thioglycosides-, glycosylamines-, and glycosyl halides of anhydroglycopyranosides and anhydroglycofuranosides. Furthermore, anomeric O-acyl-anhydropyranoses, anomeric O-acyl-anhydrofuranoses, anomeric S-acyl-anhydropyranoses and S-acyl-anhydrofuranoses are also suitable intermediates of anhydroketose syntheses. The present invention provides the very first methodologies suitable for the preparation of these novel bicyclic anhydrocarbohydrates. One of the most important objects of the present invention provides 6-hydroxy-1,5-anhydroketoses **83** using the above discussed bicyclic anhydrocarbohydrates such as **79-82** via selective ring-opening reactions triggered by chemical modifications taking place at the glycosidic position of intermediates.

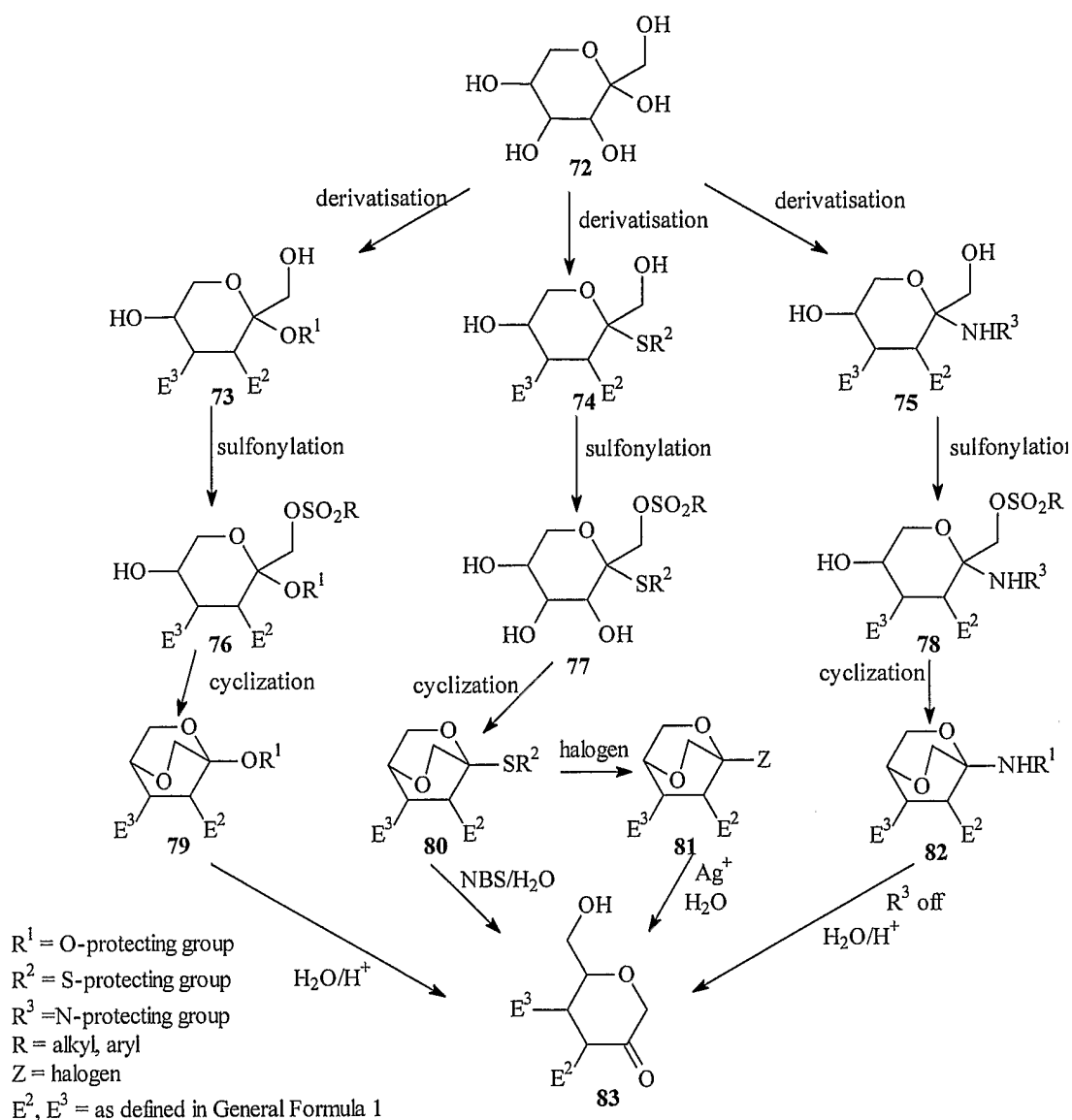


Figure 21. Preparation of anhydroketoses via ring-opening reactions of bicyclic anhydrocarbohydrates.

Thus, the removal of R^1 from bicyclic anhydroglycosides **79**, activation of bicyclic thioglycosides **80**, R^3 deprotection of bicyclic anhydroglycosyl amines **82** and activation of bicyclic anhydroglycosyl halides **81** initiate selective ring-opening processes providing 6-hydroxy-1,5-anhydroketoses **83**.

Thus, in one embodiment, the invention relates to the preparation of a 6-hydroxy-1,5-anhydroketose of General Formula **83**, said method comprising the step of

(a) O-deprotecting a corresponding bicyclic anhydroglycoside of General Formula **79** by removal of the R¹ group by hydrolysis under acidic conditions;

(b) activating a corresponding bicyclic thioglycoside of General Formula **80** so as to remove the S-R² group (e.g. NBS/H₂O);

5 (c) activating a corresponding bicyclic anhydroglycosyl halide **81** so as to remove the halogen atom; or

(d) N-deprotecting a corresponding bicyclic anhydroglycosyl amine **82** by removal of the R³ (R¹) group by hydrolysis under acidic conditions.

10 The access to bicyclic anhydrocarbohydrates could occur via derivatisation and/or protecting group manipulation known in the art of common ketoses affording intermediates **73–75**. Selective 1-O-sulfonylation of intermediates **73–75** and subsequent cyclization of sulfonates **79–82** could result in the formation of bicyclic anhydrocarbohydrates **79**, **80** and **82**. Thioglycosides of bicyclic anhydrocarbohydrates such as **80** are ideal precursors for the preparation of diverse bicyclic anhydrocarbohydrates such as glycosyl halides **81**.

15 A different aspect of the present invention provides novel tricyclic anhydrocarbohydrates and related methodologies suitable/required for the preparation of 1,4- and 1,5-anhydroketoses via ring-opening processes.

For example, tricyclic acetals **94** and tricyclic ketals **95** could be efficiently transformed into 1,5-anhydroketoses by the removal/ring opening of the cyclic acetal/cyclic ketal functions.
20 Both acid catalysed hydrolysis of cyclic acetal/ketal functions and reductive ring opening of the same functionalities assist the formation of the desired 1,5-anhydroketoses **99** (Figure 22). Similarly, tricyclic orthoesters such as **97** are also highly suitable for anhydroketose **99** formation via selective ring opening or acid catalysed hydrolysis of the cyclic orthoester functionality. Selective hydrolysis of tricyclic glycosides **98** also provides valuable 1,5-
25 anhydroketoses. Hydrolysis of tricyclic carbohydrate esters such as cyclic carbonate **96** could also be used as precursors for 1,5-anhydroketose formations.

Thus, the present invention also provides a method for the preparation of a 1,5-anhydroketose of the General Formula **99**, said method comprising the steps of subjecting a compound of General Formula **94** or **95** or **96** or **97** or **98** to ring opening conditions, e.g. acidic or basic
30 conditions, so as to liberate the corresponding 1,5-anhydroketose (**99**).

The present invention also provides facile methodologies for the preparation of novel tricyclic anhydrocarbohydrate precursors. Common ketoses such as fructose **72** could be derivatised/protected using methodologies known in the art affording intermediates **84-88**. Selective O-sulfonylation of the primary alcohol position leads to the formation of bicyclic sulfonates **89-93**. Subsequent intramolecular ether formation by displacement of bicyclic O-sulfonates **89-93** via intramolecular nucleophilic attack of O-5 hydroxyl groups provides the tricyclic anhydrocarbohydrates **94-98** suitable for anhydroketose synthesis. The invention is based upon simple general methodologies, which could provide easy access to diverse intermediates and products. To date, no similar methodologies have been described.

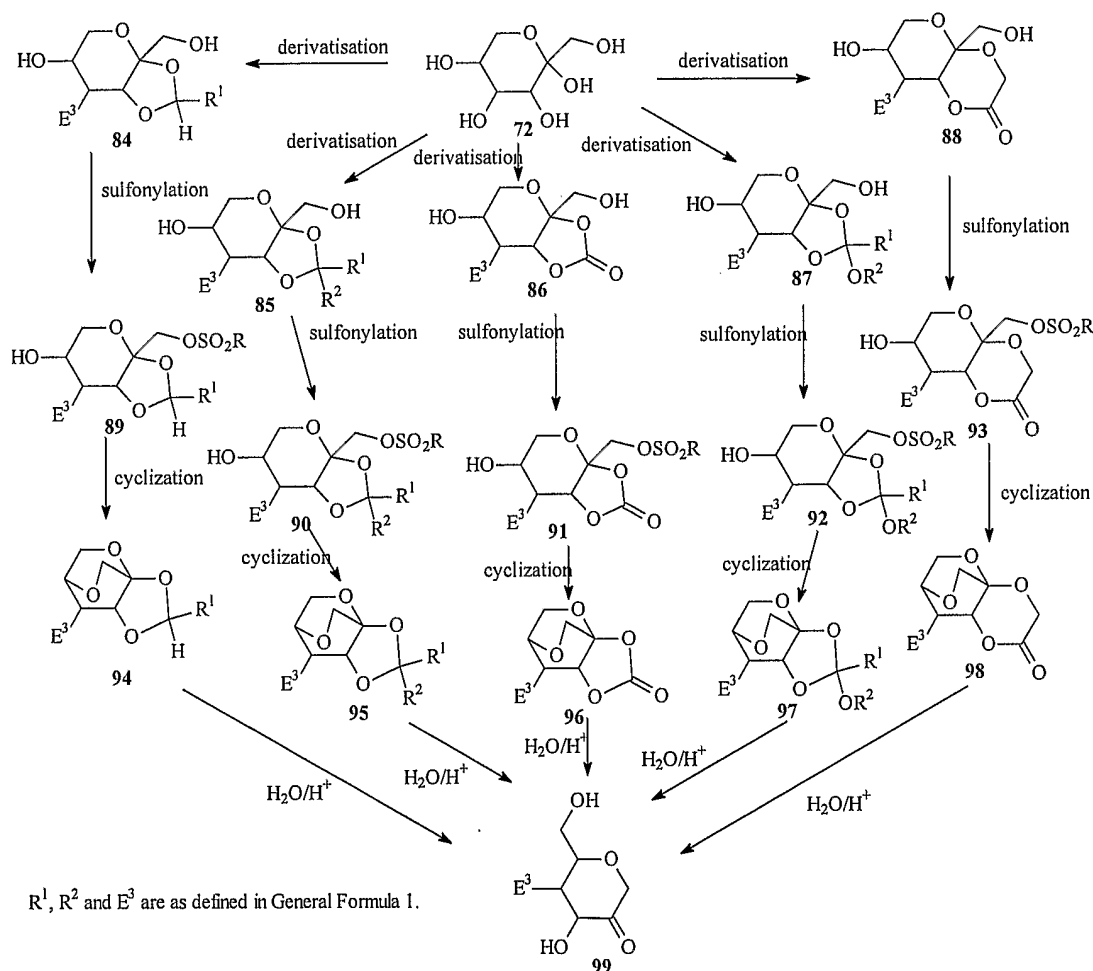


Figure 22. Preparation of anhydroketoses via tricyclic anhydrocarbohydrate intermediates.

Synthetic strategies provided by the present invention and characterized by the use of bicyclic- and tricyclic-anhydrocarbohydrate intermediates (Figure 21 and Figure 22) are also suitable for the preparation of 1,5-anhydroketoses of thiosugars, iminosugars, carbasugars

and C-glycosides using ring-opening reactions, in which the glycosidic carbon atom is directly involved (Figure 23).

For example, hydrolysis of bicyclic anhydrothiosugar **100** and tricyclic anhydrothiosugar **102** precursors result in the formation of the desired 1,5-anhydroketoses of thiosugars **101** and **103**.

Similarly, hydrolysis of bicyclic anhydroiminosugar **104** and tricyclic anhydroiminosugar **106** derivatives gives anhydroketoses of iminosugars such as **105** and **107** respectively.

The described general method is also suitable to provide 1,5-anhydroketoses of carbasugar derivatives. Thus, ring-opening chemical modifications at the glycosidic center such as acid catalysed hydrolysis or any other suitable modification known in the art provide 1,5-anhydroketoses of carbasugars **109** and **110** using the corresponding bicyclic anhydrocarbasugar **108** or tricyclic anhydrocarbasugar **111** precursors.

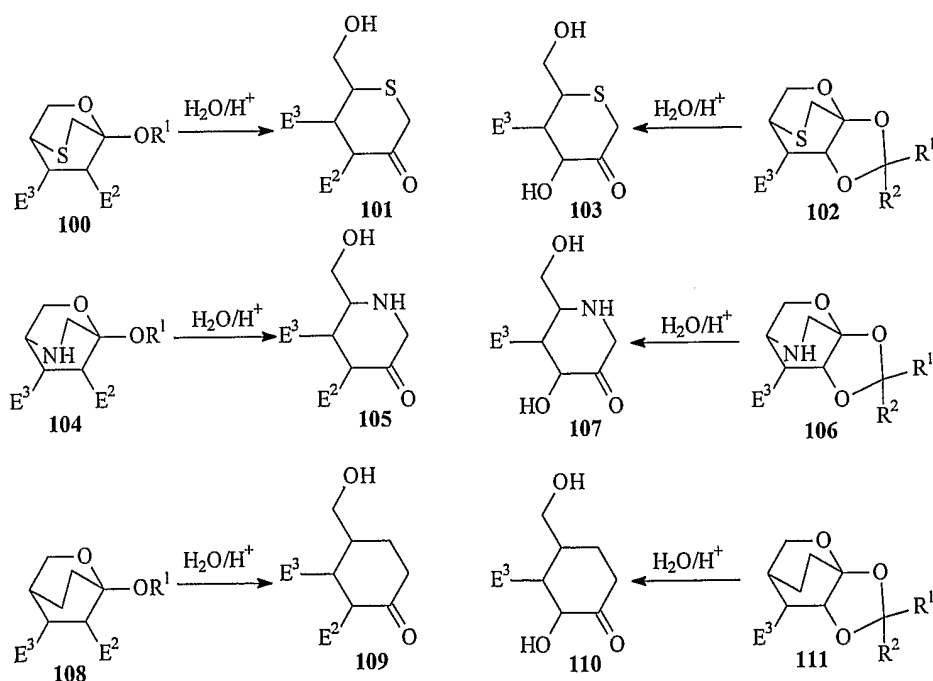


Figure 23. Preparation of 1,5-anhydroketoses of thiosugars, iminosugars and carbasugars using bicyclic- and tricyclic anhydrocarbohydrate derivatives.

Methodologies of the present invention characterized by selective cyclic acetal/ketal/-orthoester/carbonate/lactone- and glycopyranose-ring-opening of anhydrocarbohydrates

affording 1,5-anhydroketose derivatives are also highly suitable for the preparation of 1,5-anhydrofructose.

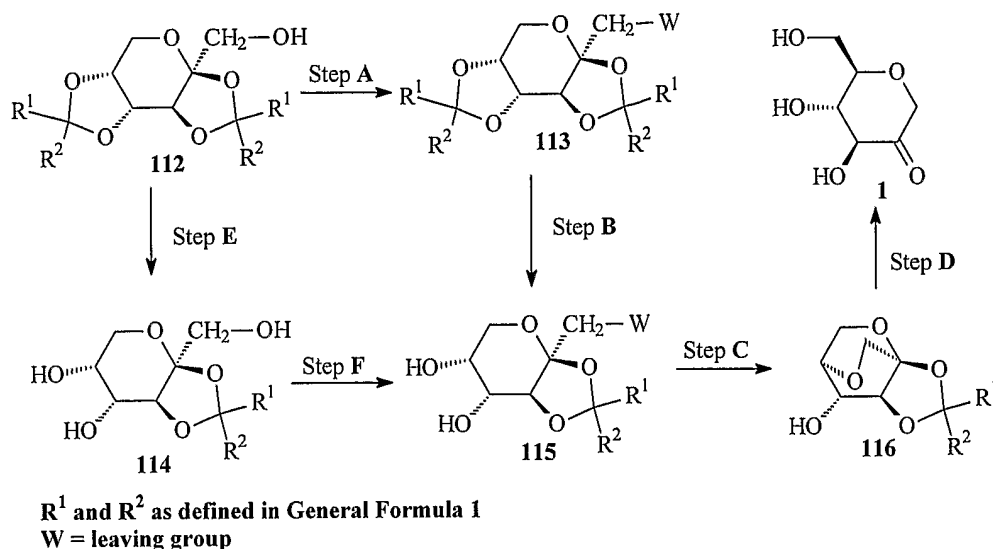
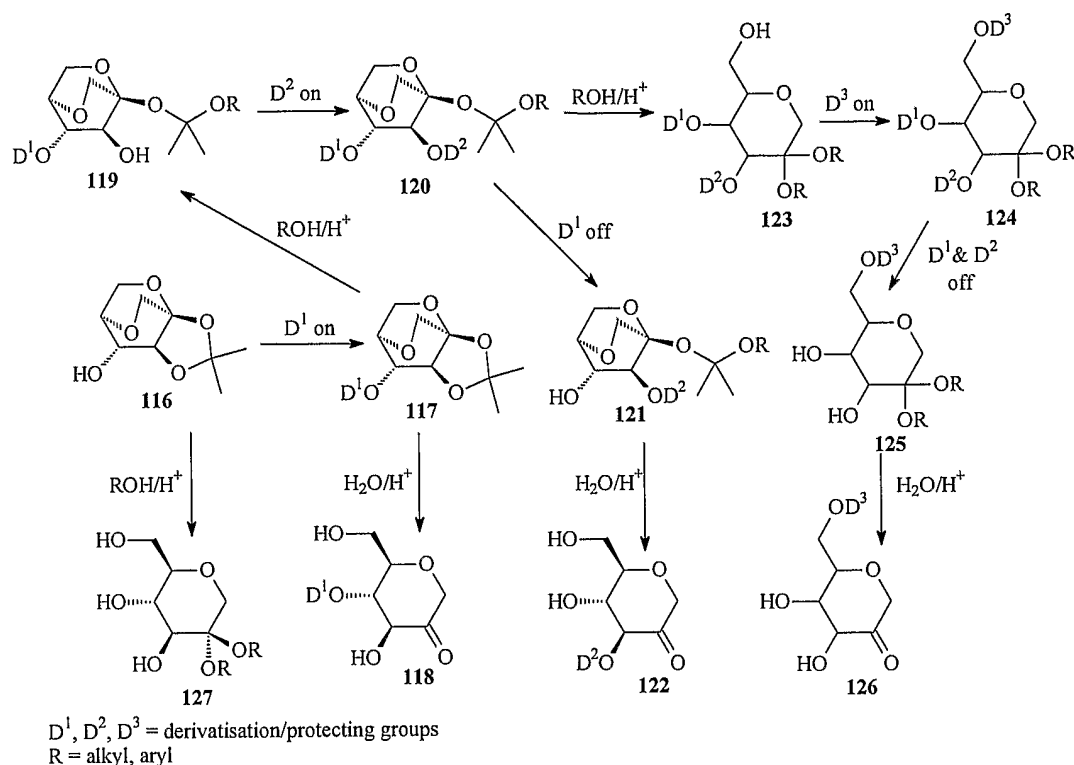


Figure 24. Preparation of 1,5-anhydrofructose using selective ring-opening of tricyclic anhydrocarbohydrates.

One of the typical approaches of the present invention uses bis-acetal/ketal protected carbohydrates characterized by General Formula **112**. Optionally, reaction step **A** halogenation, O-sulfate-, O-chlorosulfate, O-alkyl/arylsulfonate etc. formation affording carbohydrates **113** suitable for nucleophilic displacement reactions (W = halogen, alkyl/arylsulfonates, sulfate, phosphate, etc). Step **B** is a selective removal of one of the cyclic acetal/ketal functions giving intermediate **115** suitable for intramolecular nucleophilic displacement reactions with one of the liberated hydroxyl groups. Alternatively, the same intermediate can also be prepared via selective substitution of the primary hydroxyl function of **114** (Step **F**) accessible via acid catalyzed hydrolysis (Step **E**) of compound **112**. Reaction step **C** is a selective intramolecular nucleophilic displacement reaction affording the required tricyclic anhydrocarbohydrate intermediate **116**. Step **D** indicates a method, which removes the cyclic acetal/ketal substituent from the glycosidic position of **116** via ether acid catalyzed hydrolysis or any other suitable methodology affording 1,5-anhydro-D-fructose **1** (Figure 24).

The present invention provides access to site-selectively monosubstituted/derivatised anhydroketoses via regioselective derivatisation of bicyclic and/or tricyclic anhydrocarbohydrate intermediates. This unique opportunity becomes possible by inventing three new chemical transformations of anhydroketoses.

Thus, the present invention provides the very first examples of selective ring opening of cyclic isopropylidene rings of anhydroketoses such as **117** with alcohols in acidic conditions affording acyclic ketal derivatives of anhydrocarbohydrates such as **119–121** (Figure 25).



5 Figure 25. Regioselective derivatisation of tricyclic anhydrocarbohydrates providing monosubstituted 1,5-anhydrofructose derivatives.

Acyclic ketals of ketoses have never been synthesized.

A second chemical transformation of the present invention belongs to aqueous acid treatment of acyclic ketals of anhydrocarbohydrates such as **121** triggering a ring opening reaction by the hydrolysis of the acyclic ketal moiety leading to the formation of anhydroketoses such as **122**. No similar reactions have been published in carbohydrate chemistry.

The third reaction of the present invention provides diketals of anhydroketoses such as **127** from tricyclic anhydrocarbohydrate precursors such as **116** using alcohol nucleophiles in acidic conditions. Such a unique chemical reaction has never been described.

15 The combination of these three methods in specific synthetic plans could be used for the preparation of regioselectively derivatised anhydroketoses.

For example, treatment of tricyclic anhydrocarbohydrate **116** with different alcohols (methanol, ethanol, propanol, etc) in anhydrous conditions in the presence of acid catalysts (dry HCl) could give diketals of anhydroketoses **127** (R = methyl, ethyl, propyl, etc) in practically quantitative yields. This methodology of diketal formation of anhydroketoses opens new opportunities for derivatisation chemistries. Diketals of anhydroketoses are extremely stable in basic conditions allowing extended derivatisation chemistries at any position of the carbohydrate. Nucleophilic substitution reactions including but not limited to alkylation, acylation, halogenation, glycosylation; redox reactions such as oxidation, reduction; nucleophilic displacement reactions such as displacement of sulfonates became possible on the unique scaffold of diketals of anhydroketoses.

Direct derivatisation of tricyclic anhydrocarbohydrate **116** via reactions including but not limited to acylation, alkylation, glycosylation reactions at the only available O-4 position provided O-4-modified tricyclic anhydrocarbohydrates **117**. Subsequent aqueous acid treatment including but not limited to the use of organic- and inorganic acids, acidic ion-exchange resins, etc. known in the art provided O-4 derivatised anhydroketoses. Thus, the present invention gives facile methodologies for the synthesis of O-4 substituted anhydroketoses. The synthesis of similar compounds using traditional approaches would require rather tedious and sophisticated protecting group manipulations.

Selective isopropylidene ring-opening reaction of **117** with alcohols in the presence of acid catalyst including but not limited to p-toluenesulfonic acid, camphorsulfonic acid, etc afforded acyclic ketals of anhydroketoses **119**. Subsequent derivatisation –including but not limited to alkylation, acylation, glycosylation, etc known by a person skilled in the art- of the free hydroxyl group at C-3 position becomes possible characterized by the formation of intermediate **120**. Removal of D¹ protecting/derivatisation group gave intermediate **121**. A final aqueous acid treatment of **121** provided selectively O-3-derivatised anhydroketoses **122**. It is important to emphasize that similar compounds have never been synthesized due to the difficult derivatisation chemistries of base-labile anhydroketoses.

The present invention also provides methodologies for the preparation of O-6 modified anhydroketoses from intermediate **120** using diketal formation and subsequent derivatisation of compound **123** using diverse derivatisation chemistries including but not limited to alkylation, acylation, glycosylation, etc. Selective removal of D¹ and D² protecting functions from **124** gave intermediate **125**. Aqueous acid catalyzed treatment of **125** provides examples for the formation of O-6 selectively derivatised anhydroketoses **126**.

A person skilled in the art can similarly make all the di-O-substituted and tri-O-substituted anhydroketose derivatives using the above-demonstrated derivatisation synthetic system of the present invention.

The present invention also gives procedures for the preparation of anhydroketose derivatives/analogues altered at a selected position. Configuration exchange at certain position is the key chemistry needed for the synthesis of analogues of anhydroketoses. Regioselective oxidation of selected hydroxyl groups of anhydroketoses and subsequent stereoselective reduction of the resulted uloses found to be the best methodology for the synthesis of analogues of anhydroketoses (Figure 26).

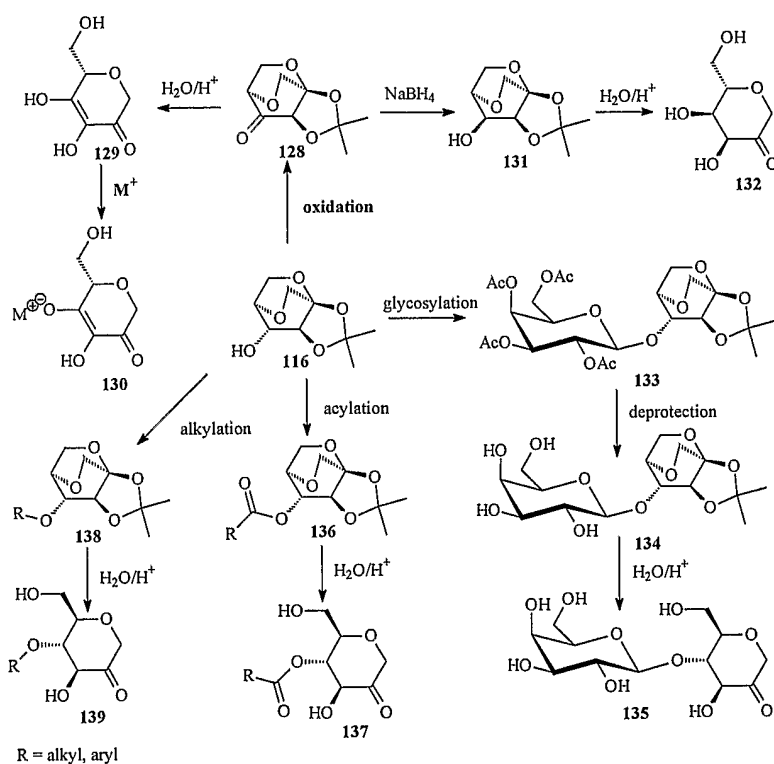


Figure 26. Derivatisation of a tricyclic anhydrocarbohydrate at O-4 position.

The diversity of anhydroketoses produced by the present invention and related methodologies suitable for chemical modifications at a selected site of a chosen anhydroketose is demonstrated in Figure 26. Tricyclic anhydrocarbohydrate **116** is a key intermediate for all the structural modifications taking place at C-4 position of anhydroketoses. Thus, oxidation of the O-4 hydroxy function at C-4 using general oxidation protocols afforded ulose **128**. Aqueous acid treatment provided diulose **129**, which exist entirely in enediol tautomeric form. Enediol **129** provided salt **130** with metal ions due to the acidic character of the hydroxyl group of at C-4 position.

Stereoselective reduction of ulose **128** using sodium borohydride afforded tagato-compound **131** with 100% stereoselectivity. Subsequent aqueous hydrolysis provided 1,5-anhydro-D-tagatose **132**.

5 Glycosylation at O-4 position of key intermediate **116** became also possible using different glycosylating methodologies known in the art providing **133**. Orthogonal deprotection strategy gave intermediate **134** and glycosylated unprotected anhydroketose **135**.

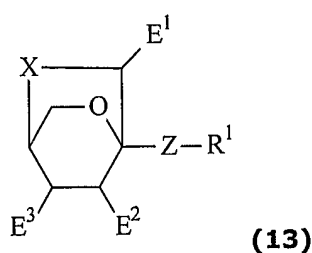
Alkylation of tricyclic anhydrocarbohydrate **116** with several different alkylating agents provided protected O-alkylated intermediates **138**. Subsequent aqueous acid treatment resulted in the formation of several important O-alkylated anhydroketoses **139**.

10 In a similar fashion, tricyclic anhydrocarbohydrate **116** was also O-acylated using several different acylating agents affording intermediates **136**. A final isopropylidene deprotection of **136** gave unprotected O-acylated anhydroketoses **137**.

Intermediates

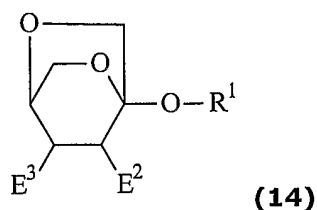
15 It is believed that some of the above-mentioned intermediates are novel *per se*, and the invention therefore also provides such novel intermediates.

Hence, a further aspect of the present invention relates to novel bicyclic anhydrocarbohydrates as precursors of 1,5-anhydroketose preparation characterized by General Formula **13**.



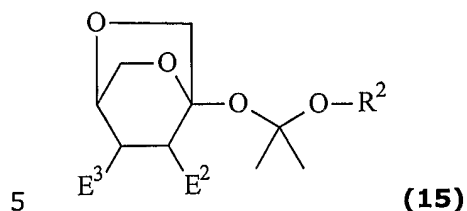
20 wherein X, E¹, E², E³ and R¹ are as defined for General Formula **1**, and Z is O, S, NH, NR² where R² is as defined for General Formula **1**.

In one preferred embodiment hereof relates to bicyclic anhydroglycosides suitable for the preparation of 1,5-anhydroketoses, characterized by General Formula **14**.



wherein E^2 , E^3 and R^1 are as defined for General Formula **1**.

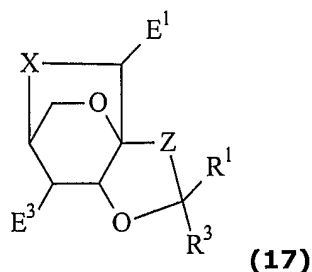
Another embodiment relates to bicyclic anhydroglycosides suitable for the preparation of 1,5-anhydroketoses, characterized by General Formula **15**.



wherein E^2 , E^3 and R^2 are as defined for General Formula **1**.

A further interesting group of intermediates are those corresponding to General Formula **14** wherein E^2 and R^1 are joined and where E^2 is of the type $O-R^1$, and where the joined R^1 groups are cleavable under acidic or basic conditions.

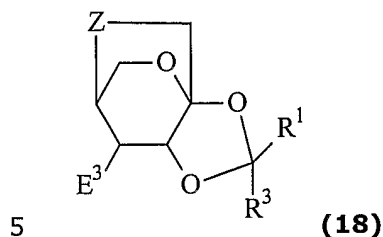
- 10 Thus, in one embodiment hereof, the present invention provides tricyclic anhydrocarbohydrates characterized by General Formula **17** suitable as precursors for the preparation of 1,5-anhydroketoses



- 15 wherein X, E^1 , E^3 and R^1 are as defined for General Formula **1**, R^3 is selected from the group consisting of hydrogen, optionally substituted C_{1-20} -alkyl, optionally substituted heteroalkyl, optionally substituted C_{2-20} -alkenyl, optionally substituted C_{2-20} -alkynyl, optionally substituted C_{3-10} -cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally

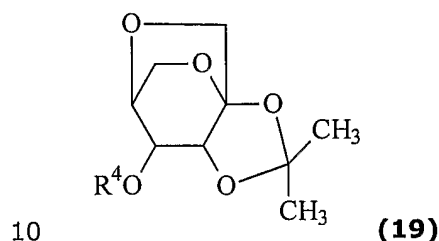
substituted heteroaryl and substituted heteroaryl, and Z is selected from the group consisting of O, S, NH, NR², where R² is as defined for General Formula **1**.

In another embodiment, the invention provides novel tricyclic anhydrocarbohydrates suitable for the preparation of 1,5-anhydroketoses, characterized by General Formula **18**



wherein E³ and R¹ are as defined for General Formula **1**, and R³ and Z are as defined for General Formula **17**.

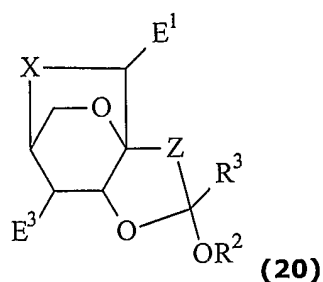
A still further embodiment novel tricyclic anhydrocarbohydrates characterized by General Formula **19** suitable for the preparation of 1,5-anhydroketoses



wherein R⁴ is selected from the group consisting of hydrogen, optionally substituted C₁₋₂₀-alkyl, optionally substituted heteroalkyl, optionally substituted C₂₋₂₀-alkenyl, optionally substituted C₂₋₂₀-alkynyl, optionally substituted C₃₋₁₀-cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C₂₋₂₀-acyl, CH₂OR², any substituted/unsubstituted carbohydrate moiety including mono- and oligo- and polysaccharides, a polymeric moiety (including, but not limited to, any poly(ethyleneglycol)-containing moiety), and an insoluble solid support.

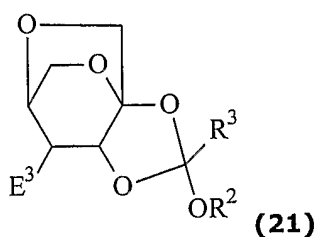
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An even still further embodiment provides tricyclic anhydrocarbohydrates characterized by General Formula **20** suitable as precursors for the preparation of 1,5-anhydroketoses



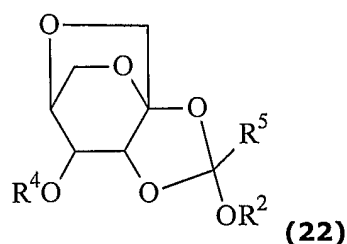
wherein X, E¹, E³ and R² are as defined for General Formula **1**, and Z and R³ are as defined for General Formula **17**.

A still further embodiment provides novel tricyclic anhydrocarbohydrates characterized by General Formula **21** suitable for the preparation of 1,5-anhydroketoses



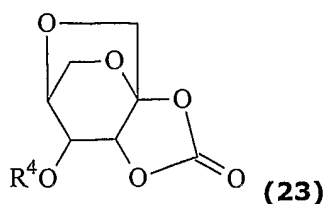
wherein E³ and R² are as defined for General Formula **1**, and R³ is as defined for General Formula **17**.

A still further embodiment provides novel tricyclic anhydrocarbohydrate orthoesters characterized by General Formula **22** suitable for the preparation of 1,5-anhydroketoses



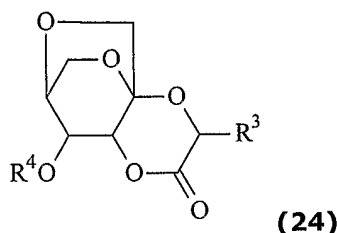
wherein R¹ and R² are as defined for General Formula **1**, R⁴ is as defined for General Formula **19**, and R⁵ is selected from the group consisting of hydrogen, methyl, ethyl, and phenyl.

A still further embodiment provides novel tricyclic anhydrocarbohydrates characterized by General Formula **23** suitable as precursors for the preparation of 1,5-anhydroketoses



wherein R⁴ is as defined for General Formula **19**.

An even still further embodiment provides novel tricyclic anhydrocarbohydrates characterized by General Formula 24 suitable as precursors for the preparation of 1,5-anhydroketoses

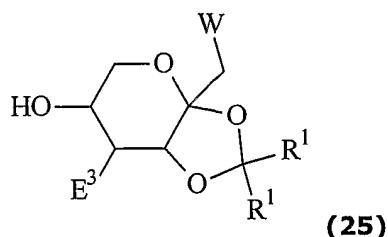


wherein R⁴ is as defined for General Formula **19**, and R³ is as defined for General Formula **17**.

The present invention also provides novel methodologies for the preparation of specific carbohydrate intermediates characterized by General Formula **18** suitable for the preparation of 1,5-anhydroketoses by base catalyzed intramolecular cyclization of molecules described by General Formulas **25** and **26**. Inorganic and organic bases including but not limited to sodiumhydride, sodium hydroxide, potassiumhydroxide, potassium carbonate, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), etc or any other base known by a person skilled in the art could be used for intramolecular cyclization in DMF, water, alcohols, acetonitrile, etc. Temperature of the cyclization can take place in the range of 20–100°C depending on the chosen base. Room temperature is preferred in the case of sodium hydride reaction carried out in DMF. Temperature of 100°C is preferred in cases in which water is used as a solvent. Reaction time varies from 5 minutes to 2 hours depending on the selected reaction conditions. Yield of cyclized anhydrocarbohydrates varies from 80-95% depending on the nature of substituents of the precursor molecules.

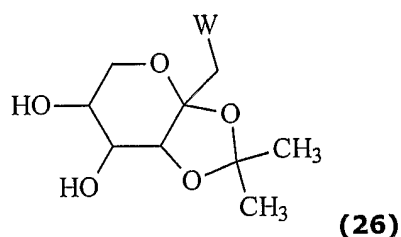
Precursors for intermediates and the preparation thereof

A further aspect of the present invention provides novel bicyclic carbohydrate intermediates characterized by General Formula **25** suitable for the preparation of 1,5-anhydroketoses



wherein R^1 and E^3 are as defined for General Formula **1**, and W is selected from the group consisting of halogen, OSO_2R^2 , OSO_2Cl , $OSO_2NR^1R^2$; where R^1 and R^2 are as defined for General Formula **1**.

- 5 A still further preferred embodiment of the present invention provides bicyclic carbohydrate intermediates characterized by General Formula **26** suitable for the preparation of 1,5-anhydroketoses



wherein W is as defined for General Formula **25**.

- 10 A further aspect provides novel methodologies for the preparation of novel bicyclic carbohydrate intermediates characterized by General Formulas 25 and 26 supporting the synthesis of novel 1,5-anhydrocarbohydrates characterized by General Formulas **17-24**. These methodologies are based upon the derivatisation of known bicyclic carbohydrates including but not limited to either regioselective O-1 alkyl/arylsulfonylation or C-1
- 15 halogenation. One of the preferred embodiments relates to methodologies using methylsulfonyl chloride, tosyl chloride, triflic anhydride, imidazoysulfonate etc. or any other similar reagent known by a person skilled in the art. Organic solvents including but not limited to dichloromethane, piridine, DMF, ethers are suitable for the transformation. Organic and/or inorganic base could be preferred to catalyze the reaction such as triethylamine, N,N-dimethylaminopyridine, potassium carbonate etc. The temperature range of the transformation
- 20 is $-20^{\circ}C$ to $80^{\circ}C$. The preferred reaction temperature is $0^{\circ}C$ at the beginning of the reaction and room temperature in the later stages of the O-sulfonylation. The selective sulfonylation/halogenation could be characterized by average yields of 75-95%.

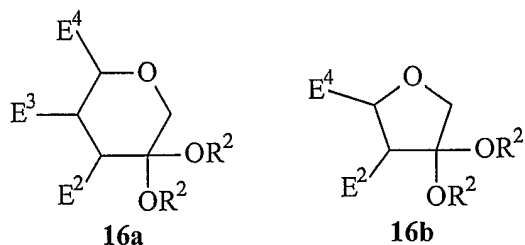
Preparation of diketals of anhydroketoses

A further aspect of the present invention provides novel methodologies for the preparation of diketals of 1,4- and 1,5-anhydroketoses characterized by General Formulas **16a**, **16b** and **16c** from bicyclic- and tricyclic-anhydroketoses defined for General Formulas **17–24** via acid catalyzed trans-ketalization processes in the presence of appropriate alcohols.

Transketalization of bicyclic- and tricyclic-anhydrocarbohydrates could be catalyzed by any inorganic/organic acid including but not limited to dry HCl, HBr, acidic ion-exchange resins, p-toluenesulfonic acid, camphor sulfonic acid, trifluoroacetic acid etc known by a person skilled in the art. Appropriate alcohols could also be used acting as both solvents and reagents. Numerous dry organic solvents such as dichloromethane, ethers, acetonitrile, DMF could also act as proper solvents assisting the required trans-ketalization processes. The reaction could be carried out at a wide range of temperatures such as 0°C to 120 °C. Preferably the reaction is carried out at room temperature in alcohols using dry HCl as a catalyst. HCl could be used directly or generated in situ from acetyl chloride in alcohols as it is known by a person skilled in the art. The yields of the trans-ketalization may vary between 75-95%.

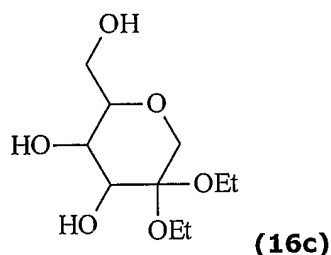
Thus, more specifically, the present invention also provides a method for the preparation of diketals of 1,4- and 1,5-anhydroketoses characterized by General Formulas **16a**, **16b** and **16c**, said method comprising the step of subjecting a compound selected from the group consisting of bicyclic- and tricyclic-anhydroketoses of General Formulas **17–24** to an acid catalyzed trans-ketalization process in the presence of an alcohol of formula R²-OH, in particular EtOH, and in particular not MeOH.

A further preferred embodiment of the present invention, thus, provides novel diketals of anhydroglycosides characterized by General Formulas **16a** and **16b** suitable for the preparation of 1,5-anhydroketoses



wherein E², E³, E⁴ and R² are as defined for General Formula **1**, with the proviso that R² is not a methyl group.

A preferred embodiment of the above, provides novel diethyl ketals of anhydroglycosides characterized by General Formula **16c**. Such diketals are able to release 1,5-anhydroketoses and ethanol in physiological conditions acting as a non-toxic antioxidant alcoholic food additive.



Use of novel diketals of anhydroketoses

A further aspect of the present invention provides utilities of diethylketals of anhydro-D-fructose and other novel diethylketals of 1,4- and 1,5-anhydrocarbohydrates characterized by General Formulas **16a**, **16b** and **16c** as novel food additives *in situ* producing
 10 anhydroketoses - including but not limited to anhydro-D-fructose - and ethanol in physiological conditions which are characteristic to digestion conditions in stomach.

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EXPERIMENTALS

25 General

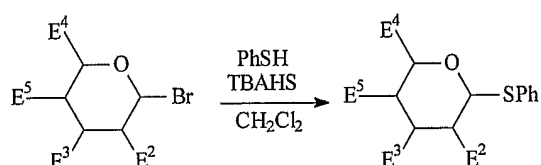
Melting points were recorded on a Tottoli apparatus and are uncorrected. Optical rotations were measured on a JASCO Digital Polarimeter or with a Perkin Elmer 341 with a path length of 10 cm. NMR spectra were recorded at 200 as well as 500 MHz (^1H), and at 50 and 125 MHz (^{13}C). Chemical shifts are listed in delta employing residual, not deuterated, solvent as the internal standard. The signals of aromatic substituents as well as of the protecting groups were found in the expected regions and are not listed explicitly. Structures of crucial intermediates were unambiguously assigned by 1D-TOCSY and HSQC experiments. TLC was performed on precoated aluminum sheets (E. Merck 5554). Compounds were detected by staining with concd H_2SO_4 containing 5% vanillin. For column chromatography Silica Gel 60 (E. Merck) was used.

General Procedures

Sulfenic acid elimination of β -hydroxyl sulfoxides of carbohydrates

General Procedure for the preparation of thioglycosides

Method A:



$\text{E}^2 - \text{E}^4$ = as defined in General Formula 1

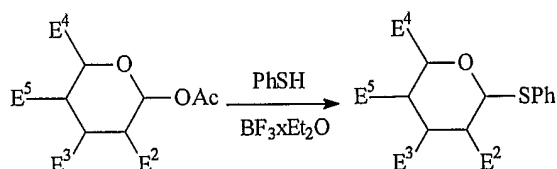
E^5 = is defined as E^2 or E^3

5

To a solution of appropriate glycosyl bromide (1 equiv), tetrabutylammonium hydrogen sulphate (TBAHS) (1 equiv) in CH_2Cl_2 (10 mL / 1 g of bromide) was added 1 M Na_2CO_3 solution (10 mL / 1 g of bromide) and thiophenol (3 eq). The two phase reaction mixture was vigorously stirred for 30 minutes at room temperature. The reaction mixture was diluted with CH_2Cl_2 (3 times of the volume of the reaction mixture) and the phases were separated. The organic phase was washed with 1 M NaOH solution, twice with water, brine, dried over MgSO_4 and evaporated. The residu was crystallized from EtOH or purified by chromatography affording thioglycosides in yields of 85–95%.

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Method B:



$\text{E}^2 - \text{E}^4$ = as defined in General Formula 1

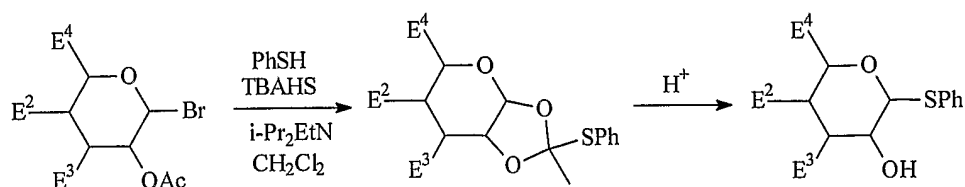
E^5 = is defined as E^2 or E^3

15

Anomeric O-acetates of carbohydrates (1 equiv) in dry CH_2Cl_2 (4 mL / 1 g anomeric O-acetate) at 0°C was added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (40%, 0.75 mL / g anomeric O-acetate) and thiophenol (1.5 equiv). After 25 minutes at 0°C the reaction mixture was neutralized by 5% NaHCO_3 solution. The organic layer was washed with water (three times with the volume of the

organic phase), dried (MgSO_4) and concentrated. The residue was crystallized from either ether or purified by chromatography giving the desired thioglycoside in 80-85% yield.

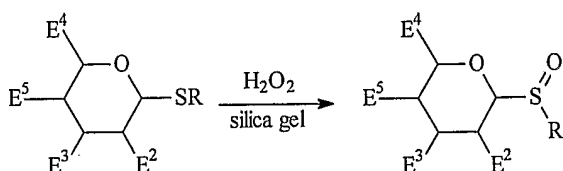
General Procedure for the preparation of 2-hydroxy-thioglycosides



$\text{E}^2 - \text{E}^4$ = as defined in General Formula 1

- 5 A mixture of glycosyl bromide (1 equiv), molecular sieves (1 g / 1 g of glycosyl bromide) in anhydrous CH_2Cl_2 (15 mL / 1 g glycosyl bromide) was stirred at room temperature and
- terabutylammonium bromide (0.6 g / 1 g of glycosyl bromide), $i\text{-Pr}_2\text{EtN}$ (0.1 mL / g glycosyl
- 10 bromide) and thiophenol (2 equiv) were added. The reaction mixture was stirred at room temperature for 5 hours and filtered. The filtrate was concentrated in vacuum and the
- resulted residue was purified by chromatography giving phenylthio orthoester in 72-80% yield. Subsequently, phenylthio orthoester was dissolved in 1,2-dichloroethane and refluxed
- in the presence of catalytic amount of camphorsulfonic acid for 3-5 hours. The reaction mixture was neutralized by addition of triethylamine and concentrated in vacuum. The
- 15 residue was taken up in abs. MeOH and treated with catalytic amount of sodium methoxide.
- The reaction mixture was neutralized by Amberlite IR 120 (H^+) ion-exchange resin and concentrated. The residue was purified by chromatography giving 2-hydroxy-thioglycoside in
- 80-85% yield.

General Procedure for the preparation of derivatised/underderivatised glycosyl sulfoxides - including β -hydroxy glycosyl sulfoxides - from thioglycosides



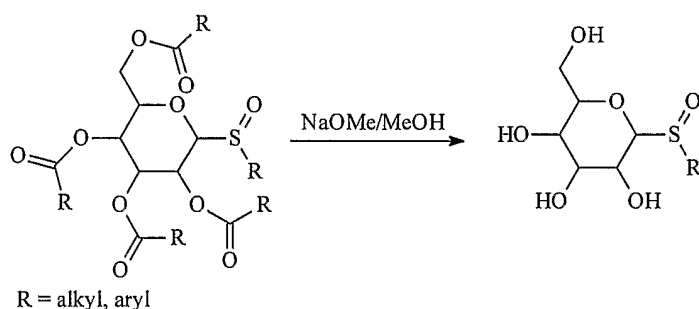
$\text{E}^2 - \text{E}^4$ = as defined in General Formula 1

E^5 = is as E^2 or E^3

R = alkyl, aryl

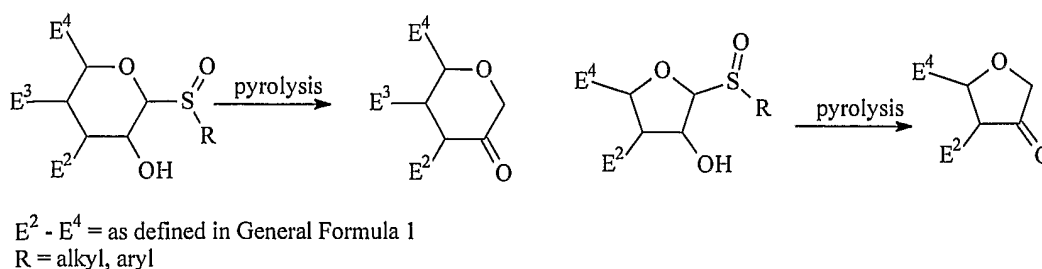
To a stirred mixture of appropriate thioglycoside (1 mmol), Ac₂O (1.1 mmol), and silica gel (200 mg, 230-400 mesh) in CH₂Cl₂ (5 mL) was added aqueous 30% H₂O₂ solution (1.2 mmol). After being stirred at room temperature between 2 and 24 h (reaction progress is monitored by TLC), the reaction mixture was filtered and the filtrate washed with saturated solutions of NaHSO₃ (50 mL), NaHCO₃ (50 mL), and brine (50 mL). The organic layer was separated, dried (anhydrous Na₂SO₄), and concentrated to furnish a mixture of *R* and *S* sulfoxides. The resulted sulfoxides were further purified via either crystallization or by chromatography.

General procedure for the preparation of unprotected glycosyl sulfoxides from O-acylated derivatives



O-Acylated sulfoxide (1 equiv) was dissolved in dry methanol (20 mL / 1 g sulfoxide) and catalytic amount of sodium methoxide (0.01 equiv) was added. The resulting solution was stirred at room temperature for 2-4 hours (monitoring the reaction by TLC). The reaction mixture was neutralized by the addition of Amberlite IR 120 (H⁺) and filtered. The filtrate was concentrated giving the desired unprotected sulfoxides in 94-97% yield.

General procedure for the preparation of anhydroketoses via pyrolysis of β -hydroxy glycosyl sulfoxides

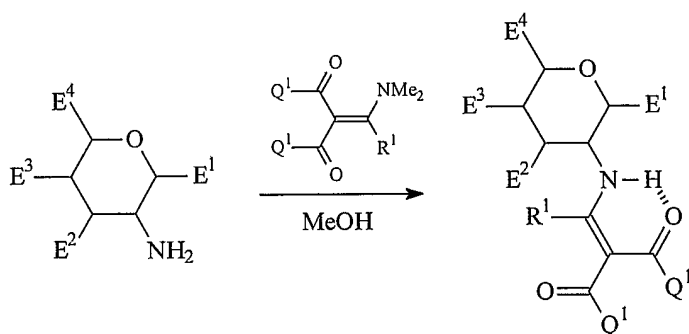


Method A: An appropriate glycosyl sulfoxide (1 equiv) was dissolved in toluene/dioxane 1:1 mixture and refluxed for 2-8 hours while monitoring the reaction with TLC. After full conversion of sulfoxides, the reaction mixture was concentrated in vacuum. The resulting residue was purified by chromatography affording anhydroketoses in 60–90% yield.

- 5 Method B: Water-soluble sulfoxide was dissolved in water or a mixture of i-PrOH /H₂O. The reaction mixture was refluxed for 2-8 hours keeping the pH neutral by the addition of aqueous NaHCO₃ solution (5%) while the reaction was monitored by TLC. After completion, the reaction mixture was concentrated in vacuum and the resulted residue was purified by chromatography giving anhydroketoses in 60–90% yield.

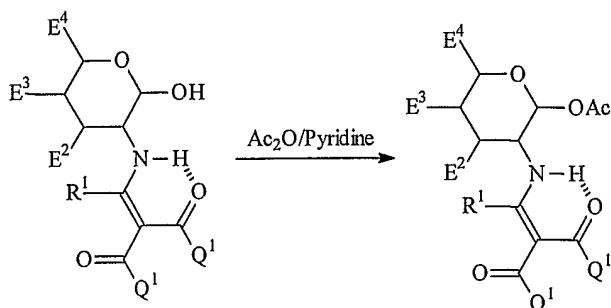
10 *N-Deprotection of novel N-substituted-amino-glycals of carbohydrates*

General procedure for the preparation of acyclic vinylogous amide-protected 2-amino-2-deoxy-carbohydrates



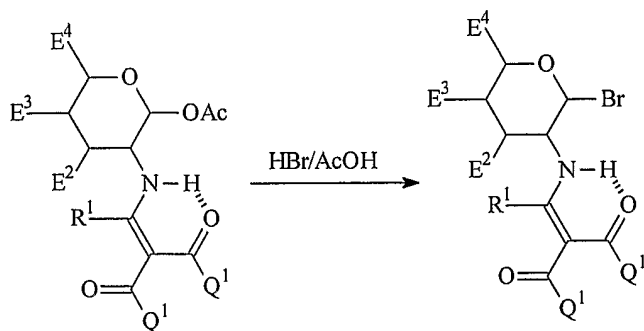
- 15 A mixture of carbohydrate amine (1 equiv) and dimethylaminoalkylene vinylogous reagent (1.5–2.0 equiv) in MeOH (20 mL / g carbohydrate amine) was stirred at 40°C overnight. In most of the cases, the resulting precipitate was filtered out giving acyclic vinylogous amide derivatives of carbohydrates in 75–85% yield. In other cases, the reaction mixture was evaporated. The resulting residue was crystallized from EtOH or purified by chromatography giving the desired products in 75–85% yield.

General procedure for the preparation of anomeric O-acetylated acyclic vinylogous amide-protected 2-amino-2-deoxy-carbohydrates



- 5 A mixture of acyclic vinylogous amide lactol (1 equiv), pyridine (10 mL / 1 g of acyclic vinylogous amide lactol) and acetic anhydride (5 mL / 1 g of acyclic vinylogous amide lactol) was stirred at room temperature overnight. The reaction mixture was concentrated in vacuum and purified by chromatography to give Per-O-acetylated product in 90–95% yield.

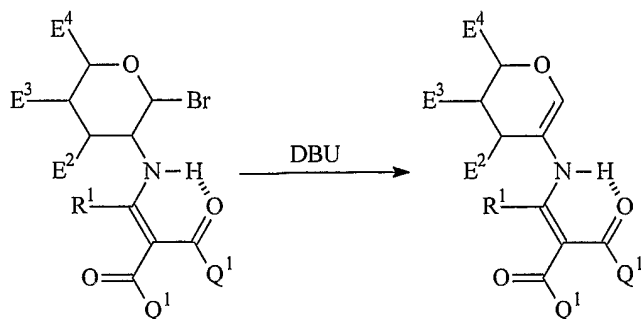
General procedure for the preparation of glycosyl bromides of acyclic vinylogous amide derivatives of carbohydrates



10

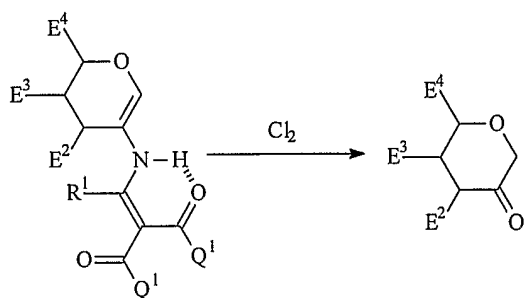
- 15 Anomeric O-acetate of acyclic vinylogous amide (1equiv) was dissolved in CH_2Cl_2 (10 mL / 1 g of anomeric O-acetate) and cooled to 0°C . Hydrogen bromide in acetic acid (30%) was added and the reaction mixture was allowed to warm to room temperature. The yellowish solution was stirred at room temperature for 3 hours and diluted with cold CH_2Cl_2 (20 mL / 1 g of anomeric O-acetate). The resulting solution was washed twice with H_2O (50 mL / 1 g of anomeric O-acetate), saturated NaHCO_3 solution (50 mL / 1 g of anomeric O-acetate), dried over MgSO_4 and concentrated giving glycosyl bromides of acyclic vinylogous amides in 85–90% yield.

General procedure for the preparation of acyclic vinylogous amide protected aminoglycals

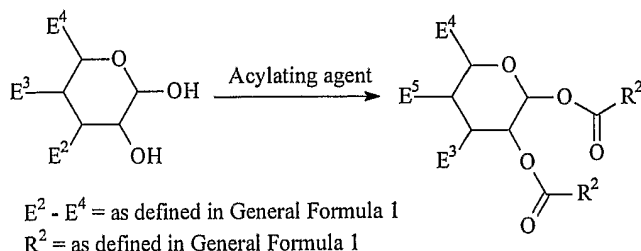


Acyclic vinylogous amide-type glycosyl bromide (1 equiv) was dissolved in THF (10 mL / 1 g of glycosyl bromide/ and cooled to 0°C. Subsequently, 1,8-diazabicyclo[5.4.0]undec-7-ene
 5 was added dropwise to the cold solution. The reaction mixture was stirred for 3 hours and evaporated. The residue was dissolved in CH₂Cl₂ (20 mL / 1 g of glycosyl bromide) and washed with water (10 mL / 1 g of glycosyl bromide), dried and concentrated. The residue was purified by chromatography giving the desired acyclic vinylogous amide-protected aminoglycal in 75–85% yield.

10 General procedure for the preparation of anhydroketoses from acyclic vinylogous amide protected aminoglycals



Acyclic vinylogous amide protected aminoglycal (1 equiv) was dissolved in CHCl₃ (10 mL / 1 g aminoglycan) and a saturated solution of Cl₂ in CHCl₃ was added dropwise until slight yellow
 15 color appeared. The reaction mixture was stirred at room temperature for 15 minutes and evaporated. The residue was titrated with Et₂O. The resulting solid was filtered and dissolved in water and treated with sodium borate (0.2 N) adjusting pH 7.6-8. The solution was evaporated then the residue was purified by chromatography giving the desired anhydroketose in 85–90% yield.

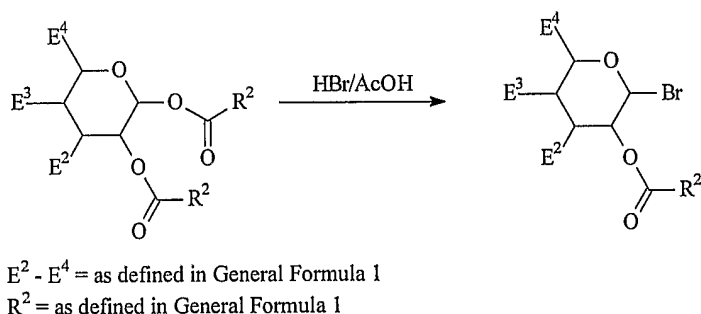
*O-Deprotection of carbohydrate enolethers and/or O-acyl-substituted carbohydrate enols*General procedure for the preparation of 1,2-di-O-acylated carbohydrates

To a 5% solution of the respective precursor carbohydrate lactol in dry pyridine, 1.2

- 5 equivalents of the required amount of the respective acylating agent (e. g., acetic anhydride, benzoyl chloride, ethoxycarbonyl chloride, or the like) as well as a catalytic amount of N,N-dimethylaminopyridine were added and the mixture was stirred until all starting material had been consumed. Water or methanol was added to destroy excess of reagent and the mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane or tert butyl methyl ether were added and the solution was consecutively washed with 3-5% aqueous HCl and saturated aqueous sodium bicarbonate, dried (sodium sulfate), filtered and concentrated under reduced pressure.
- 10

The remaining residue was either immediately used in the next step or purified by (re-) crystallisation or chromatography. Yields ranged between 75 and 90%.

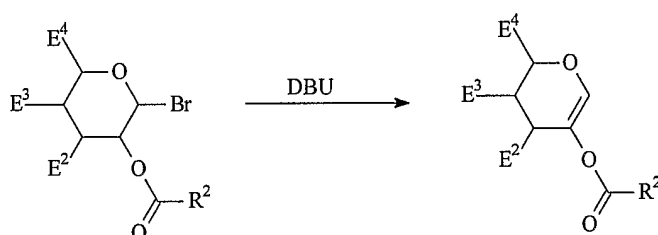
- 15 General procedure for the preparation of 2-O-acylated glycosyl bromides



1,2-Di-O-acyl-derivative of carbohydrates (1 equiv.) was dissolved in CH_2Cl_2 (10 mL / 1 g of 1,2-di-O-acyl-carbohydrate) and cooled to 0°C . Hydrogen bromide in acetic acid (30%) (1 mL / 1 g of 1,2-di-O-acyl-carbohydrate) was added and the reaction mixture was allowed to

- warm to room temperature. The yellowish solution was stirred at room temperature for 3 hours and diluted with cold CH_2Cl_2 (20 mL / 1 g of 1,2-di-O-acyl-carbohydrate). The resulting solution was washed twice with H_2O (50 mL / 1 g of 1,2-di-O-acyl-carbohydrate), saturated NaHCO_3 solution (50 mL / 1 g of 1,2-di-O-acyl-carbohydrate), dried over MgSO_4 and concentrated giving 2-acyl-glycosyl bromides in 85–90% yield.

General procedure for the preparation of 2-O-acylated glyals from 2-O-acyl glycosyl bromides

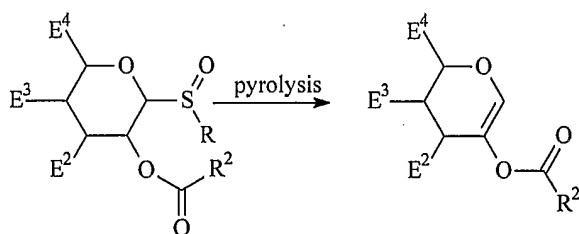


$\text{E}^2 - \text{E}^4$ = as defined in General Formula 1

R^2 = as defined in General Formula 1

- 2-O-Acyl-glycosyl bromide (1 equiv) was dissolved in THF (10 mL / 1 g of glycosyl bromide/ and cooled to 0°C . Subsequently, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added dropwise to the cold solution. The reaction mixture was stirred for 3 hours at room temperature and evaporated. The residue was dissolved in CH_2Cl_2 (20 mL / 1 g of glycosyl bromide), washed with water (10 mL / 1 g of glycosyl bromide), dried and concentrated in reduced pressure. The residue was purified by either crystallization or chromatography giving the desired acyloxy-glycal in 75–85% yield.

- General procedure for the preparation of 2-O-acylated glyals from 2-O-acyl glycosyl sulfoxides



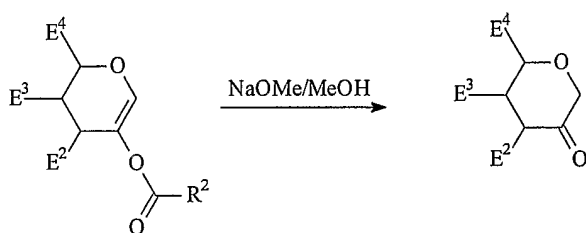
$\text{E}^2 - \text{E}^4$ = as defined in General Formula 1

R^2 = as defined in General Formula 1

R = alkyl, aryl

An appropriate glycosyl sulfoxide (1 equiv) was dissolved in toluene (50 mL / 1 g of 2-O-acyl glycosyl sulfoxide) and refluxed for 2-8 hours while monitoring the reaction with TLC. After full conversion of sulfoxides, the reaction mixture was concentrated in reduced pressure. The resulting residue was purified by chromatography affording acyloxyglycals in 60–90% yield.

5 General procedure for the preparation of anhydroketoses from 2-O-acylated glyals



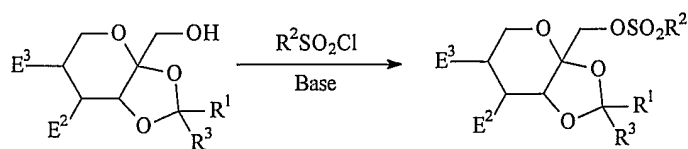
$E^2 - E^4$ = as defined in General Formula 1

R^2 = as defined in General Formula 1

10 An appropriate acyloxy-glycal (1 equiv) was dissolved in MeOH (60 mL / 1 g of acyloxy-glycal) at room temperature and subsequently the solution was cooled to -40°C . Sodium methoxide (1-1.5 equiv) in dry MeOH was added and the reaction mixture was stirred at -40°C for 3-4 hours while the reaction conversion was monitored with TLC. Subsequently, the cold reaction mixture was neutralized with Amberlite IR 120 (H^+). The reaction mixture was filtered and concentrated in reduced pressure giving the desired anhydroketose in 93–97% yield.

15 *Regio- and stereoselective modification and subsequent chemical transformation of novel bicyclic and/or tricyclic 1,4- and 1,5-anhydro-glycoderivatives*

General procedure for the preparation of 1-O-alkyl/arylsulfonates of ketopyranoses

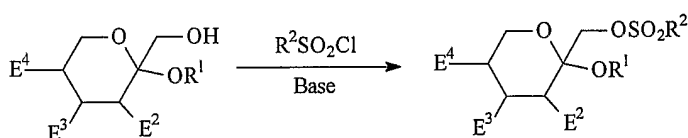


R^1, R^2, E^2, E^3 = as defined in General Formula 1

R^3 = as defined in General Formula 17

A mixture of an appropriate bicyclic ketopyranose (1 equiv), triethylamine (1.1 equiv) in dichloromethane (10 mL / 1 g of bicyclic ketopyranose) was cooled to 0°C. Alkyl/arylsulfonyl chloride (1.1 equiv) in dichloromethane (5 mL / 1 g of bicyclic ketopyranose) was added dropwise to the stirred ketopyranose solution. The addition was completed within 30 minutes and the reaction mixture was let to warm to room temperature. The progress of the reaction was followed by TLC. After completion of conversion, the reaction mixture was diluted with CH₂Cl₂ (5 mL / 1 g bicyclic ketopyranose) and washed with water, 5% HCl solution, water and a 1:1 v/v mixture of saturated NaCl and saturated NaHCO₃ solution. The organic phase was dried over Na₂SO₄ and evaporated. The desired product was purified by either crystallization or chromatography giving 1-O-sulfonates of bicyclic ketopyranoses in 93–97% yield.

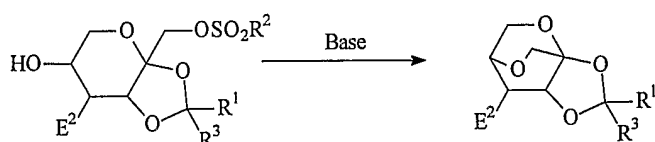
General procedure for the preparation of 1-O-alkyl/arylsulfonates of β -ketopyranosides



R^1, R^2, E^2, E^3 = as defined in General Formula 1

An appropriate β -ketopyranoside (1 equiv) was dissolved in dry pyridine and cooled to 0°C. Alkyl/arylsulfonyl chlorides (1,2 equiv) in CH₂Cl₂ was added dropwise within 30 minutes. The reaction mixture was let to warm to room temperature and stirred for 5 -12 hours. Subsequently, the reaction mixture was evaporated at 45°C under reduced pressure. The residue was dissolved in CH₂Cl₂ (15 mL / 1 g of β -ketopyranoside), washed with 5% HCl solution, water, saturated NaHCO₃ solution, dried and concentrated. The residue was purified by chromatography giving 1-O-alkyl/arylsulfonylated β -ketopyranoside in 60–75% yield.

General procedure for the preparation of tricyclic 1,5-anhydro-carbohydrates from 5-hydroxy-1-O-alkyl/arylsulfonates of β -ketopyranoses

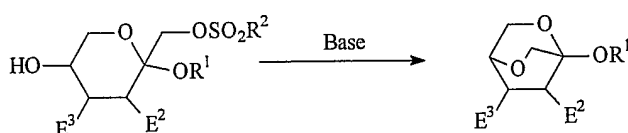


R^1, R^2, E^2, E^3 = as defined in General Formula 1
 R^3 = as defined in General Formula 17

Method A: An appropriate 5-hydroxy-1-O-alkyl/aryldulfonyl-ketopyranose (1 equiv) was dissolved in aqueous sodium hydroxide solution (containing 1.3–1.5 equivalent sodium hydroxide). The reaction mixture was refluxed for 10–30 minutes, then concentrated under reduced pressure. The resulting residue was titrated with CH_2Cl_2 (20 mL / 1 g of 5-hydroxy-1-O-alkyl/aryldulfonyl-ketopyranose) and filtered. The filtrate was concentrated and the product was purified by crystallization giving the desired crude tricyclic 1,5-anhydro-carbohydrate in 85–95% yield.

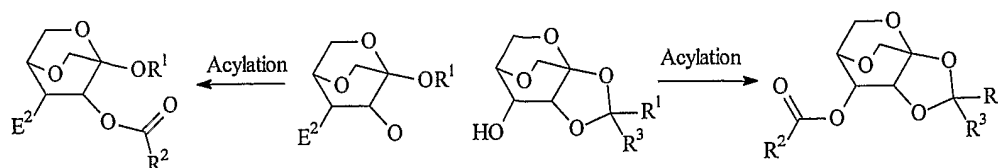
Method B: An appropriate 5-hydroxy-1-O-alkyl/aryldulfonyl-ketopyranose (1 equiv) was dissolved in anhydrous DMF and sodium hydride (1.5 equiv) (60%) was added at 0°C . The reaction mixture was let to warm to room temperature and stirred for 3 hours. Subsequently the solvent was removed by evaporation under reduced pressure. The resulting residue was titrated with CH_2Cl_2 (20 mL / 1 g of 5-hydroxy-1-O-alkyl/aryldulfonyl-ketopyranose) and filtered. The filtrate was concentrated and the product was purified by crystallization giving the desired crude tricyclic 1,5-anhydro-carbohydrate in 85–95% yield.

General procedure for the preparation of bicyclic 1,5-anhydro-carbohydrates from 5-hydroxy-1-O-alkyl/arylsulfonates of β -ketopyranosides



$\text{R}^1, \text{R}^2, \text{E}^2, \text{E}^3$ = as defined in General Formula 1

An appropriate 5-hydroxy-1-O-alkyl/aryldulfonyl-ketopyranoside (1 equiv) was dissolved in anhydrous DMF (10 mL / 1 g of 5-hydroxy-1-O-alkyl/aryldulfonyl-ketopyranoside) and sodium hydride (1.5 equiv) (60%) was added at 0°C . The reaction mixture was let to warm to room temperature and stirred for 3 hours. Subsequently the solvent was removed by evaporation under reduced pressure. The resulting residue was titrated with CH_2Cl_2 (20 mL / 1 g of 5-hydroxy-1-O-alkyl/aryldulfonyl-ketopyranose) and filtered. The filtrate was concentrated and the product was purified by chromatography giving the desired crude tricyclic 1,5-anhydro-carbohydrate in 75–85% yield.

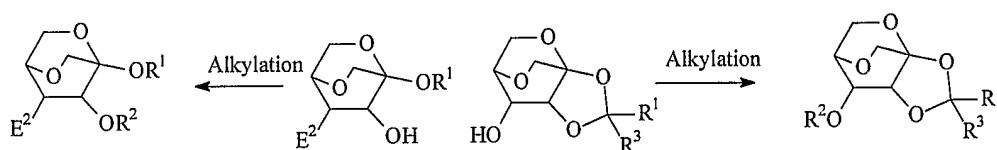
General procedure for O-acylation of bicyclic- and tricyclic-1,5-anhydro-carbohydrates

R^1, R^2, E^2 = as defined in General Formula 1

R^3 = as defined in General Formula 17

To a 5% solution of the respective starting material in dry pyridine, 1.2 equivalents of the required amount of the respective acylating agent (e. g., acetic anhydride, benzoyl chloride, ethoxycarbonyl chloride, or the like) as well as a catalytic amount of *N,N*-dimethylaminopyridine were added and the mixture was stirred until all starting material had been consumed. Water or methanol was added to destroy excess of reagent and the mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane or tert butyl methyl ether were added and the solution was consecutively washed with 3-5% aqueous HCl and saturated aqueous sodium bicarbonate, dried (sodium sulfate), filtered and concentrated under reduced pressure.

The remaining residue was either immediately used in the next step or purified by (re-) crystallisation or chromatography. Yields ranged between 75 and 90%.

General procedure for O-alkylation of bicyclic- and tricyclic-1,5-anhydro-carbohydrates

R^1, R^2, E^2 = as defined in General Formula 1

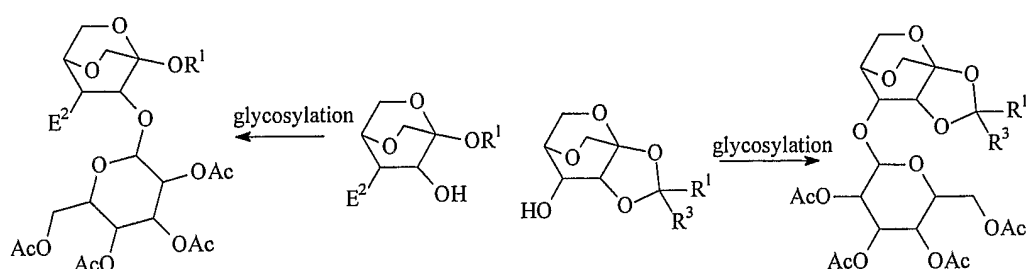
R^3 = as defined in General Formula 17

To a 5% solution of the respective starting material (1 equiv) in *N,N*-dimethylformamide sodium hydride (1.5 equiv) was added at 0°C. The reaction mixture was stirred at 0°C for 30 minutes then the desired alkyl halide (e. g., benzyl bromide) or sulfonate (e. g., palmityl tosylate), was added (1.5 equivalent) and the mixture was stirred at room temperature overnight. The reaction mixture was cooled and the excess of sodium hydride was reacted with MeOH. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane. The organic layer was consecutively washed with 5% aqueous HCl and

saturated aqueous sodium bicarbonate, dried (sodium sulfate), filtered and concentrated under reduced pressure. The material obtained was used immediately for the next step or was further purified by crystallization or chromatography.

General procedure for the O-glycosylation of bicyclic- and tricyclic-1,5-anhydro-carbohydrates

5

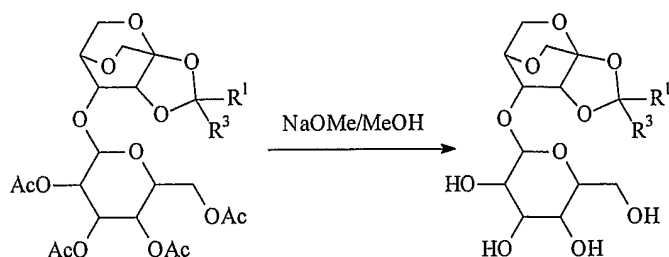


R^1, E^2 = as defined in General Formula 1
 R^3 = as defined in General Formula 17

To a 5% solution of the respective glycosyl acceptor (bicyclic- and tricyclic-1,5-anhydro-carbohydrates) in dry dichloromethane containing molecular sieves 4 A, (1.7 g / 1 g of acceptor (bicyclic- and tricyclic-1,5-anhydro-carbohydrates), the respective 2,3,4,6-tetra-O-acetyl-glycopyranosyl trichloroacetimidate (1.2 equivalents) are added and the mixture was cooled to a suitable temperature between 0 and -60°C . A catalytic amount of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in dry dichloromethane was added and the mixture was stirred for another hour at -20°C . The acid catalyst was quenched with pyridine and ethyl acetate was added. The mixture was filtered and the filtrate was washed with aqueous sodium bicarbonate and dried (sodium sulfate).

After filtration, the solvent was removed under reduced pressure and the residue was either immediately used in the next step or further purified by (re-)crystallisation or chromatography. Yields ranged between 60 – 75%.

General procedure for Zemplen deprotection of O-glycosylated bicyclic- and tricyclic-1,5-anhydro-carbohydrates

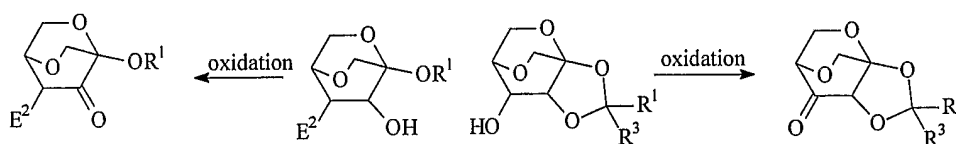


R¹ = as defined in General Formula 1

R³ = as defined in General Formula 17

- 5 An appropriate per-O-acetylated glycoside of tricyclic 1,5-anhydrocarbohydrate (1 equiv) was dissolved in dry MeOH (10 mL / 1 g of per-O-acetylated glycosides of tricyclic 1,5-anhydrocarbohydrate) and NaOMe (catalytic amount) was added. The reaction mixture was stirred for 2–3 hours, neutralized by Amberlite IR 120 (H+) ion-exchange resin and evaporated to give the desired deprotected glycosides of 1,5-anhydrocarbohydrates in quantitative yield.

10 General procedure for the oxidation of bicyclic- and tricyclic-anhydrocarbohydrates

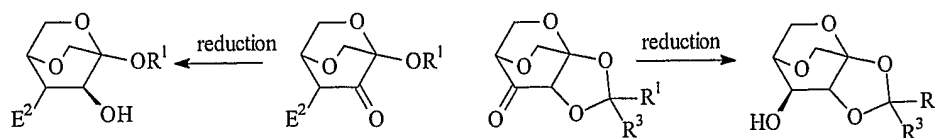


R¹, R², E² = as defined in General Formula 1

R³ = as defined in General Formula 17

- 15 To a 3% dichloromethane solution of the respective bicyclic- or tricyclic-anhydrocarbohydrate (1 equiv), Dess-Martin reagent (1.2 equivalents) was added and the mixture was stirred at ambient temperature until all alcohol had been consumed. Ethyl acetate was added and the solution was washed with aqueous sodium bicarbonate, dried (sodium sulfate), filtered and concentrated under reduced pressure. The remaining material was taken into the next step or further purified by (re-)crystallisation or chromatography. Yields ranged between 66 and 78%.

General procedure for stereoselective reduction of oxidized bicyclic- and tricyclic-anhydrocarbohydrates /preparation of analogues of 1,5-anhydrocarbohydrates via configuration exchange of specific carbon atoms/



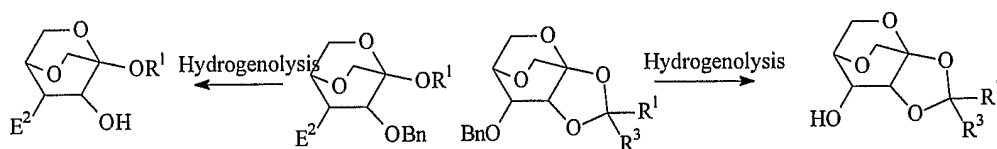
R^1, R^2, E^2 = as defined in General Formula 1

R^3 = as defined in General Formula 17

- 5 To a 5% methanolic solution of the respective carbonyl compound, NaBH_4 (1.5 to 3 equivalents) was added and the mixture was stirred at ambient temperature until all starting material had been consumed. Amberlite IR 120 (H^+) ion-exchange resin was added and the mixture was stirred until neutral. After filtration, the solution was concentrated under reduced pressure and the residue dissolved in methanol. Concentration under reduced
- 10 pressure gave the crude product, which could either be immediately employed in the next step or was purified by crystallisation or chromatography.

Alternatively, the reaction mixture could be concentrated under reduced pressure and either extracted with a suitable solvent or chromatographed to obtain purified product. Yields ranged between 65 and 95%.

- 15 General procedure for the removal of benzyl ethers of bicyclic- and tricyclic-1,5-anhydrocarbohydrates via hydrogenolysis



R^1, R^2, E^2 = as defined in General Formula 1

R^3 = as defined in General Formula 17

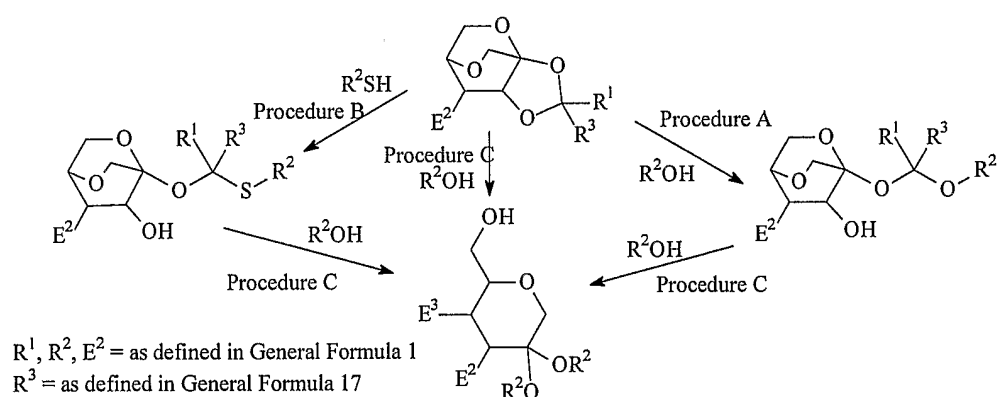
To a 5% alcoholic solution of the O-benzylated bicyclic- or tricyclic-1,5-anhydrocarbohydrate, a catalytic amount of Perlman's catalyst, $\text{Pd}(\text{OH})_2$ on charcoal, 20%, was added.

- 20 Method A: The mixture was stirred under an atmosphere of hydrogen at ambient pressure and ambient temperature until all starting material had been converted to a final more polar product. The catalyst was removed by filtration and the filtrate was concentrated under

reduced pressure. The remaining material was either immediately employed in the next step or further purified by (re-) crystallisation or chromatography. Yields ranged between 81 and 95%.

- Method B: Excess ammonium formate was added and the mixture was stirred at ambient temperature until all starting material had been converted to a final more polar product. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The remaining material was further purified by (re-) crystallisation or chromatography. Yields ranged between 45 and 78%.

10 General Procedure for Trans-Acetalation Reactions of bicyclic- and tricyclic-1,5-anhydrocarbohydrates



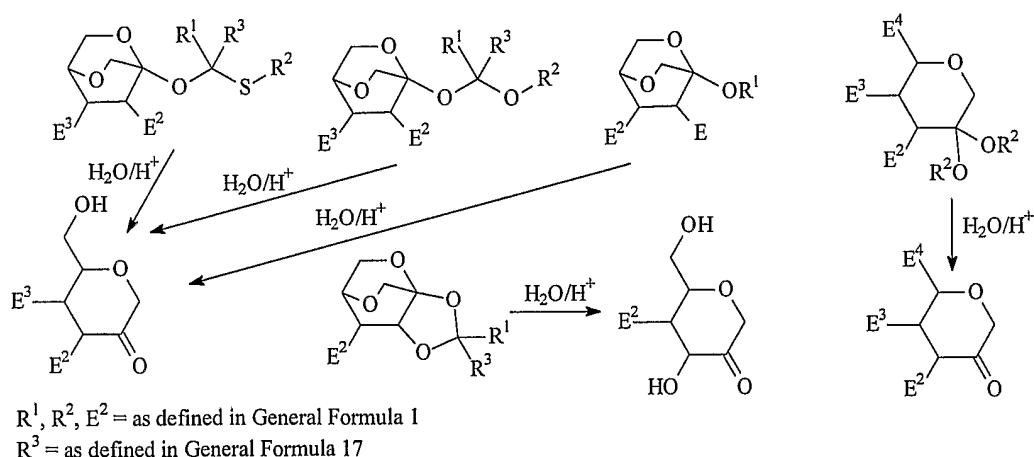
- Procedure A: The dry alcohol was used as the solvent: To a 5% solution of the respective tricyclic-1,5-anhydrocarbohydrate in the desired alcohol, a catalytic amount of a suitable acid (e. g., camphor sulfonic acid or 4-toluenesulfonic acid) was added to adjust to a suitable pH value between 1 and 3. The reaction mixture was kept at ambient or suitable elevated temperature until all starting acetal had been converted. Solid sodium bicarbonate (excess) was added and the mixture was stirred for 30 minutes. After filtration, the solution was concentrated under reduced pressure and the product was immediately used in the next step or further purified by (re-)crystallisation or chromatography. Yields ranged between 35 and 87%.

- Procedure B. An inert solvent was employed: To a 5% solution of the respective tricyclic-1,5-anhydrocarbohydrate in dry dichloromethane, the respective thiol (2-5 equivalents) was added and the mixture was adjusted to pH 1-3 by addition of appropriate amounts of 4-toluenesulfonic or camphor sulphonic acid or other suitable acidic catalysts. When all starting material had been converted, the reaction mixture was washed with aqueous sodium

bicarbonate until neutral, the organic layer was dried (sodium sulfate) and the solvent was removed under reduced pressure. The product obtained was immediately used in the next step or further purified by (re-)crystallisation or chromatography. Yields ranged between 35 and 82%.

- 5 Procedure C: The respective bicyclic- or tricyclic-1,5-anhydrocarbohydrate (1 equiv) was added to a mixture of the desired dry alcohol – acetyl chloride (10:1) (30 mL / 1 g of bicyclic- or tricyclic-1,5-anhydrocarbohydrate) at 0°C. The reaction mixture was kept at ambient temperature overnight. The reaction mixture was neutralized by basic ion-exchange resin and filtered. The filtrate was concentrated under reduced pressure. The crude product
- 10 was immediately used in the next step or further purified by (re-)crystallisation or chromatography. Yields ranged between 85 and 90%.

General procedure for acid catalyzed hydrolysis of acyclic-ketal/cyclic-ketal and diketals of anhydrocarbohydrates



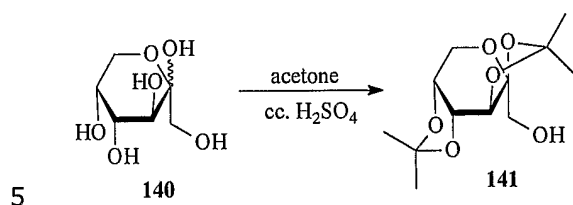
- 15 Method A: To a 5% solution of the starting material in acetonitrile/water 1:1 (v/v), acidic ion exchange resin (e. g., Amberlite IR 120) was added and the mixture was stirred at a suitable temperature between ambient temperature and 75°C until all starting material had reacted. The resin was removed by filtration and washed with water, the filtrate and washings were concentrated under reduced pressure and the remaining residue was purified by
- 20 (re-)crystallisation or chromatography. Yields ranged between 75 and 90%.

Method B: A 5% solution of the starting material in 80% aqueous acetic acid was stirred at a suitable temperature between ambient temperature and 80°C until all starting material had formed a more polar main product. The reaction mixture was concentrated at ambient temperature followed by co-concentration of the residue with toluene. The remaining material

was dissolved in water and lyophilised or (re-)crystallised or chromatographed to obtain pure deprotected product. Yields ranged between 85 and 92%.

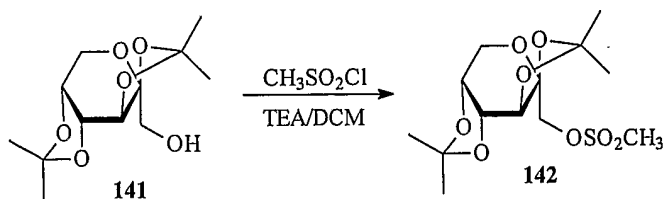
Specific Procedures

2,3:4,5-Di-O-isopropylidene-β-D-fructopyranose (141)



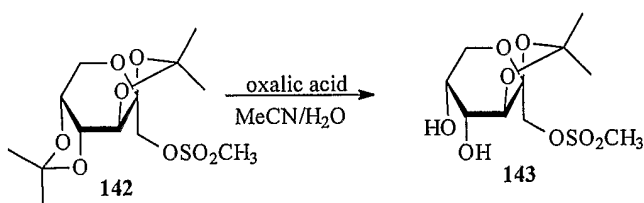
Acetone (460 mL) was stirred at room temperature and cc. H₂SO₄ (20 mL) was slowly added. The resulting solution was vigorously stirred and D-fructose **140** (47.6 g, 264 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 2 hours and subsequently cooled to 10°C. Concentrated NaOH solution (15.8 g NaOH in 60 mL water) was slowly added to the vigorously stirred reaction mixture. Basic pH was reached by the addition of triethylamine (40 mL). The reaction mixture was evaporated under vacuum at 70°C. The resulting residue was taken up in a mixture of water (400 mL) and dichloromethane (200 mL) and the two phases were intensively mixed. The phases were separated. The aqueous phase was further extracted with dichloromethane (2 x 200 mL). The combined organic phase (approx. 600 mL) was washed with water (300 mL) and saturated NaCl solution (300 mL). The dichloromethane solution was dried over anhydrous Na₂SO₄ and evaporated to dryness. The warm residue was taken up in petroleum ether (50–70°C) using intensive stirring. The resulting suspension was refluxed for 5 minutes. The suspension was let to cool to room temperature. The crystallization is completed by reducing the crystallization temperature to 0°C. The white crystalline product was filtered and dried to give 2,3:4,5-Di-O-isopropylidene-β-D-fructopyranose (**141**) (58.4 g, 85%).

2,3:4,5-Di-O-isopropylidene-1-O-methanesulfonyl-β-D-fructopyranose (142)



A mixture of 2,3:4,5-Di-O-isopropylidene- β -D-fructopyranose (**141**) (40 g, 153 mmol) and triethylamine (43 mL) in dichloromethane (160 mL) was stirred in ice-bath. Mesyl chloride (13 mL, 169 mmol) in dichloromethane (60 mL) was added dropwise to the stirred fructopyranose solution. The addition has been completed within 45 minutes and the reaction mixture was let to warm to room temperature. The reaction mixture was diluted with CH₂Cl₂ (250 mL) and washed with water (150 mL), 5% HCl solution (150 mL), water (150 mL) and a 1:1 v/v mixture of saturated NaCl and saturated NaHCO₃ solution (150 mL). The organic solution was dried over Na₂SO₄ and evaporated. The crude product crystallizes at the end of the evaporation. Petroleum ether (50–70°C) (150 mL) was added to the residue and the suspension was refluxed for 5 minutes. The suspension was cooled in ice-bath for 1 hour and the white crystalline solid was filtered to give 2,3:4,5-Di-O-isopropylidene-1-O-methanesulfonyl- β -D-fructopyranose (**142**) (49.8 g, 96%).

2,3-O-Isopropylidene-1-O-methanesulfonyl- β -D-fructopyranose (**143**)

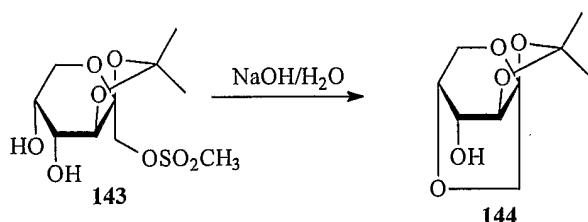


A mixture of 2,3:4,5-Di-O-isopropylidene-1-O-methanesulfonyl- β -D-fructopyranose (**142**) (40 g, 118 mmol) and oxalic acid (8.5 g, 94 mmol) in a mixture of MeCN–H₂O 5:1 v/v (600 mL) was gently refluxed (oil-bath temperature: 95°C) for 28 hours. The reaction mixture was cooled in ice-bath and aqueous ammonia solution (25%) (16 mL) was added slowly within 5 minutes. The resulting suspension was stirred in ice-bath for 30 minutes and filtered. The precipitate was washed with MeCN (100 mL) on the funnel. The filtrate and the MeCN washing were combined and evaporated to dryness under reduced pressure. The residue was taken up in CH₂Cl₂ (200 mL) and the resulting solution was separated from the insoluble part of the residue. The CH₂Cl₂ solution was washed with distilled water (20 mL). The organic phase was kept for further work-up and the aqueous phase was extracted with CH₂Cl₂ (3 x 100 mL). Petroleum ether (50–70°C) (100 mL) was added to the combined organic phases (approx. 500 mL) and the resulting solution was extracted with distilled water (3 x 200 mL). The combined aqueous solution was evaporated under reduced pressure to give the crude product as a slow moving oil. The residue was taken up in EtOAc–Petroleum ether (50 –70°C) 1-1 mixture (100 mL) and was vigorously stirred at room temperature. The resulting suspension was cooled to 0°C, stirred for 2 hours and filtered to give 2,3-O-Isopropylidene-1-O-methanesulfonyl- β -D-fructopyranose (**143**) (19 g, 71%). The mother liquor was

evaporated and the residue was crystallized from EtOAc–Petroleum ether 1:1 v/v (10 mL) to give further 0.7 g (2.6%) of pure product.

The CH_2Cl_2 phase of the extraction step was evaporated to give un-reacted 2,3:4,5-Di-O-isopropylidene-1-O-methanesulfonyl- β -D-fructopyranose (**142**) (10g, 25%).

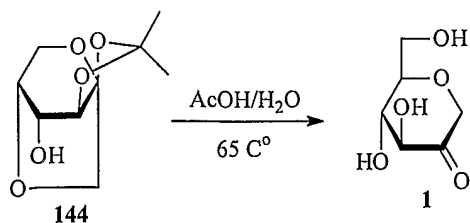
5 2,3-O-Isopropylidene-1,5-anhydro- β -D-fructopyranose (**144**)



2,3-O-Isopropylidene-1-O-methanesulfonyl- β -D-fructopyranose (**143**) (30 g, 100 mmol) was dissolved in aqueous sodium hydroxide solution made from NaOH (7.24 g) and water (83 mL). The reaction mixture was stirred under gentle reflux for 15 minutes.

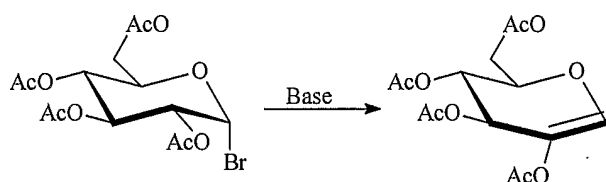
- 10 The reaction mixture was cooled in ice-bath and slightly acidified with 10% HCl solution to pH = 6. Aqueous ammonia solution (25%) (2 mL) was added to make the pH of the reaction mixture basic. The reaction mixture was evaporated to dryness under reduced pressure. The residue was taken up in CHCl_3 (500 mL) during vigorous stirring at room temperature and filtered. The solid was intensively washed with CHCl_3 (300 mL) on the funnel. The combined
- 15 CHCl_3 solution was evaporated. The resulting solid residue was refluxed in toluene (150 mL) and the solution was let to cool to room temperature. The crystallization was finalized by stirring the crystalline suspension at 0°C for two hours. The crystalline product was collected by filtration and dried to give 2,3-O-Isopropylidene-1,5-anhydro- β -D-fructopyranose (**144**) (18 g, 90%).

20 1,5-Anhydro-D-fructose (**1**)



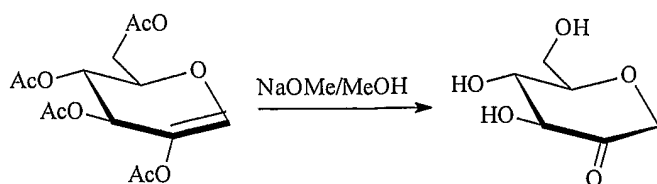
2,3-O-Isopropylidene-1,5-anhydro- β -D-fructopyranose (**144**) (10g, 49.5 mmol) was dissolved in 80% aqueous acetic acid solution (30 mL). The reaction mixture was stirred for 15 minutes at 65°C and evaporated under reduced pressure. The warm oily residue was taken up in abs. MeOH (50 mL) and let to cool to room temperature. The methanolic solution was added dropwise to vigorously stirred cold ether (1000 mL) at 0°C. The resulting suspension was stirred at 0°C for two hours and filtered. The solid was washed with ether (300 mL) on the funnel. The still ether-wet precipitate was dried in vacuum to give 1,5-Anhydro-D-fructose (**1**) (8 g, 94%) as a fluffy white powder.

Tetra-O-acetyl-2-hydroxy-D-glucal



Method A: Acetobromoglucose (80 g, 194.7 mmol) was dissolved in dry acetone (150 mL) containing sodium iodide (40 g) and after 15 min dry diethylamine (80 ml, 777 mmol) was added. After stirring for 1 h at room temperature the mixture was diluted with dichloromethane (300 mL) followed by water (500 mL). The organic phase was washed with aqueous hydrochloric acid (5%) and water, dried (MgSO₄), filtered and concentrated to give a residue, which was crystallized from ethanol. Yield 41 g (65%), m.p. 59-61 oC (lit. m.p.: 61-62 oC).

Method B: Acetobromoglucose (50 g, 121.7 mmol) was dissolved in dry tetrahydrofuran (THF) (300 mL) in a 3-necked bottle and cooled to 0 oC after which 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (20 ml, 134 mmol) was slowly added. The cooling bath was removed and the mixture was stirred for 2 hours, or until TLC (ethyl acetate-hexane, 1:2) indicated that the starting material had disappeared. Filtration and concentration left a residue, which was dissolved in dichloromethane (300 mL). This solution was washed with water and aq. HCl (5%). The aqueous phases were again extracted with dichloromethane, and the combined organic phases were washed with brine, and dried (MgSO₄). After concentration the product could be crystallized from ethanol to give 34.4 g (85.7%) of the tetra-O-acetyl-2-hydroxy-D-glucal. M.P. 59-60°C.

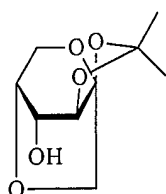
1,5-Anhydro-D-fructose (**1**)

2,3,4,6-Tetra-O-acetyl-2-hydroxy-D-glucal (1.00 g, 3.03 mmol) was dissolved in MeOH (60 ml) at room temperature and the solution was cooled to $-40\text{ }^{\circ}\text{C}$. The appropriate amount of sodium methoxide (150 mg, 2.8 mmol) was added (as a solid or in a methanolic solution) and the mixture was stirred at $-40\text{ }^{\circ}\text{C}$ for approximately 3 hours after which time the solution was allowed to return to $0\text{ }^{\circ}\text{C}$. Acidic ion exchange resin (Amberlite IR-120, H^{+}) was added and the mixture was stirred for five minutes (to neutral pH), filtered and concentrated to a light yellow foam (0.48 g, 98%). A ^{13}C -NMR spectrum in D_2O immediately after dissolution shows the presence of both the hydrate and the two different dimeric forms, but after 2-5 hours all compounds were converted into the hydrated form of 1,5-anhydro-D-fructose showing 6 peaks in the ^{13}C -NMR spectrum.

^{13}C -NMR: 72.6 (C-1), 93.5 (C-2), 77.7 (C-3), 69.8 (C-4), 81.5 (C-5) and 62.0 (C-6). ^1H -NMR: 3.33 (d, H-1a/b), 3.65 (d, H-1b/a), 3.45 (d, H-3), 3.30 (t, H-4), 3.66 (mp, H-5), 3.78 (dd, H6a/b), 3.56 (dd, H6b/a). ^{13}C - and ^1H NMR spectra were identical with those reported.

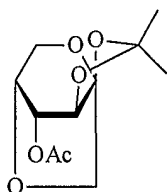
1,5-anhydro-D-fructose could be isolated and handled as a freeze dried product, consisting of the monomer **1**, the dimeric forms **1_{dimer1}**, **1_{dimer2}**, and some of the hydrated 1,5-anhydro-D-fructose **1_{hydrate}**.

Characterisation of novel compounds prepared:

20 1,5-Anhydro-2,3-O-isopropylidene- β -D-fructopyranose

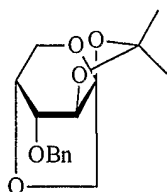
- 5 $[\alpha]_D^{20} +18.0$ (c 0.8, MeOH), mp 110-113°C. $^1\text{H-NMR}$ (MeOH- d_4): δ 4.28 (d, 1 H, $J_{1a,1b}$ 9.0 Hz, H-1a), 4.19 (dd, 1 H, $J_{5,6a}$ 1.5 Hz, $J_{6a,6b}$ 10.2 Hz, H-6a), 4.16 (d, 1 H, $J_{3,4}$ 3.6 Hz, H-3), 3.99 (d, 1 H, H-4), 3.97 (dd, 1 H, $J_{5,6b}$ 1.5 Hz, H-6b), 3.86 (d, 1 H, H-1b), 3.85 (m, 1 H, H-5). $^{13}\text{C-NMR}$ (CDCl_3): 115.6 (C-1'), 99.4 (C-2), 87.8, 77.0, 74.6, 73.9, 71.2, 66.9 (C-1, C-3, C-4, C-5, C-6), 28.0 (C-2'a), 25.8 (C-2'b).

4-O-Acetyl-1,5-anhydro-2,3-O-isopropylidene- β -D-fructopyranose

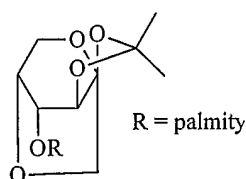


- 10 $[\alpha]_D^{20} +5.3$ (c 0.85, CH_2Cl_2), mp 98-102°C. $^1\text{H-NMR}$ (CDCl_3): δ 5.16 (d, 1 H, $J_{3,4}$ 4.2 Hz, H-4), 4.36 (d, 1 H, $J_{1a,1b}$ 9.0 Hz, H-1a), 4.27 (dd, 1 H, $J_{5,6a}$ 1.5 Hz, $J_{6a,6b}$ 10.2 Hz, H-6a), 4.22 (d, 1 H, H-3), 4.13 (dd, 1 H, $J_{5,6b}$ 1.5 Hz, H-6b), 4.05 (bs, 1 H, H-5), 3.95 (d, 1 H, H-1b). $^{13}\text{C-NMR}$: δ 170.6 (C=O), 99.2 (C-2), 83.7, 77.0, 71.3, 71.1, 66.9 (C-1, C-3, C-4, C-5, C-6), 21.2 (COMe).

1,5-Anhydro-4-O-benzyl-2,3-O-isopropylidene- β -D-fructopyranose

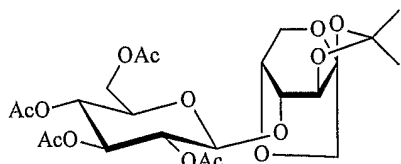


- 15 $[\alpha]_D^{20} +35$ (c 0.82, MeOH), mp 59-60°C. $^1\text{H-NMR}$ (CDCl_3): δ 4.73 (d, 1 H, J_{gem} 10.8 Hz, benzyl-H), 4.59 (d, 1 H, benzyl-H), 4.33 (d, 1 H, $J_{1a,1b}$ 9.0 Hz, H-1a), 4.23 (dd, 1 H, $J_{5,6a}$ 1.7 Hz, $J_{6a,6b}$ 10.2 Hz, H-6a), 4.19 (d, 1 H, $J_{3,4}$ 3.8 Hz, H-3), 4.02 (bs, 1 H, H-5), 4.00 (d, 1 H, H-4), 3.96 (dd, 1 H, $J_{5,6b}$ 1.8 Hz, H-6b), 3.95 (d, 1 H, H-1b). $^{13}\text{C-NMR}$: δ 99.7 (C-2), 85.9, 81.2, 71.4, 71.1 (2 C), 67.3 (C-1, C-3, C-4, C-5, C-6, benzyl- CH_2).

1,5-Anhydro-2,3-O-isopropylidene-4-O-palmityl-β-D-fructopyranose

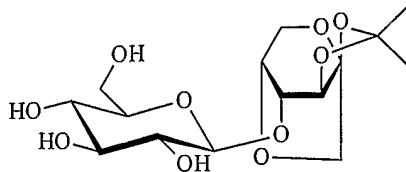
$[\alpha]_D^{20} +17.0$ (c 1.4, MeOH), mp 36-37°C). $^1\text{H-NMR}$ (CDCl_3): δ 4.32 (d, 1 H, $J_{1a,1b}$ 9.9 Hz, H-1a), 4.25 (dd, 1 H, $J_{5,6a}$ 2 Hz, $J_{6a,6b}$ 10.6 Hz, H-6a), 4.07 (d, 1 H, $J_{3,4}$ 3.9 Hz, H-3), 4.01 (dd, 1 H, $J_{5,6b}$ 1.7 Hz, H-6b), 4.00 (bs, 1 H, H-5), 3.92 (d, 1 H, H-1b), 3.85 (d, 1 H, H-4), 3.58 (m, H-1'a), 3.48 (m, 1 H, H-1'b), 1.63 (m, 2 H, H-2'), 1.38-1.22 (m, 26 H), 0.85 (t, 3 H). $^{13}\text{C-NMR}$: δ 99.6 (C-2), 85.9, 81.8, 71.4, 71.0, 69.5, 67.3 (C-1, C-3, C-4, C-5, C-6, C-1'), 32.2 (C-2'), 29.95, 29.9, 29.85, 29.8, 29.7, 29.6, 28.0, 22.9 (C-3' - C-15'), 14.4 (C-16').

10 4-O-(2',3',4',6'-Tetra-O-acetyl-β-D-glucopyranosyl)-1,5-anhydro-2,3-O-isopropylidene-β-D-fructopyranose [2',3',4',6'-Tetra-O-acetyl-1,5-anhydro-2,3-O-isopropylidene-β-D-cellobiulose]



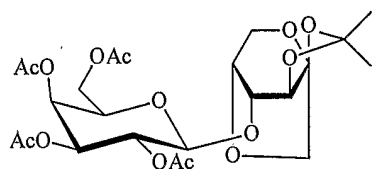
$^1\text{H-NMR}$ (DMSO-d_6): δ 5.24 (dd, 1 H, $J_{2',3'}$ 9.7 Hz, $J_{3',4'}$ 9.7 Hz, H-3'), 5.00 (d, 1 H, $J_{1',2'}$ 8.1 Hz, H-1'), 4.95 (dd, 1 H, $J_{4',5'}$ 9.7 Hz, H-4'), 4.79 (dd, 1 H, H-2'), 4.21 (dd, 1 H, $J_{5'6'a}$ 4.4 Hz, $J_{6'a,6'b}$ 12.3 Hz, H-6'a), 4.19 (m, 1 H, H-4), 4.13 (1 H, d, $J_{1a,1b}$ 8.5 Hz, H-1a), 4.08 (m, 1 H, H-6a), 4.07 (d, 1 H, $J_{3,4}$ 3.8 Hz, H-3), 4.03 (dd, 1 H, $J_{5',6b'}$ 2.2 Hz, H-6'b), 3.97 (m, 1 H, H-6b), 3.97 (m, 1 H, H-5), 3.93 (m, 1 H, H-5'), 3.87 (d, 1 H, H-1b). $^{13}\text{C-NMR}$: δ 97.8 (C-1'), 83.9 (C-3), 80.2 (C-4), 71.7 (C-3'), 70.5 (C-5'), 70.4 (C-2'), 70.2 (C-5), 69.3 (C-1), 67.7 (C-4'), 65.8 (C-6), 61.3 (C-6').

4-O-(β -D-glucopyranosyl)-1,5-anhydro-2,3-O-isopropylidene- β -D-fructopyranose [1,5-anhydro-2,3-O-isopropylidene- β -D-cellobiulose]



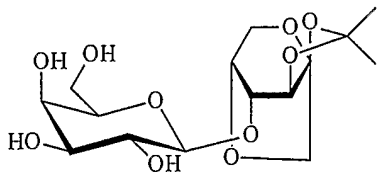
$^1\text{H-NMR}$ (DMSO- d_6): δ 5.08 (d, 1 H, $J_{2',\text{OH}}$ 5.1 Hz, 2'-OH), 4.99 (d, 1 H, $J_{3',\text{OH}}$ 4.8 Hz, 3'-OH), 4.94 (d, 1 H, $J_{4',\text{OH}}$ 5.3 Hz, 4'-OH), 4.34 (d, 1 H, $J_{1',2'}$ 7.9 Hz, H-1'), 4.29 (dd, 1 H, $J_{6'a,\text{OH}}$ 4.8 Hz, $J_{6'b,\text{OH}}$ 7.6 Hz, 6'-OH), 4.20 (m, 1 H, H-4), 4.18 (d, 1 H, H-3), 4.14 (d, $J_{1a,1b}$ 8.5 Hz, H-1a), 4.07 (m, 1 H, H-6a), 4.06 (m, 1 H, H-5), 3.94 (m, 1 H, H-6b), 3.86 (d, 1 H, H-1b), 3.66 (m, 1 H, H-6'a), 3.44 (m, 1 H, H-6'b), 3.13 (m, 2 H, H-3', H-5'), 3.06 (m, 1 H, H-4'), 3.02 (m, 1 H, H-2'). $^{13}\text{C-NMR}$: δ 101.6 (C-1'), 84.8 (C-3), 79.8 (C-4), 76.5 (2 C, C-3', C-5'), 73.2 (C-2'), 70.0 (C-5), 69.95 (C-4'), 69.4 (C-1), 66.1 (C-6), 61.0 (C-6').

4-O-(2',3',4',6'-Tetra-O-acetyl- β -D-galactopyranosyl)-1,5-anhydro-2,3-O-isopropylidene- β -D-fructopyranose [2',3',4',6'-Tetra-O-acetyl-1,5-anhydro-2,3-O-isopropylidene- β -D-lactulose]



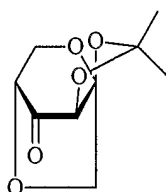
$^1\text{H-NMR}$ (DMSO- d_6): δ 5.27 (dd, 1 H, $J_{3',4'}$ 3.6 Hz, $J_{4',5'}$ <1 Hz, H-4'), 5.14 (dd, 1 H, $J_{2',3'}$ 10.2 Hz, H-3'), 4.96 (dd, 1 H, $J_{1',2'}$ 7.9 Hz, H-2'), 4.90 (d, 1 H, H-1'), 4.19 (m, 1 H, H-4), 4.16 (m, 1 H, H-5'), 4.13 (d, 1 H, $J_{1a,1b}$ 8.8 Hz, H-1a), 3.87 (d, H-1b), 4.09 (m, 1 H, H-6a), and 3.99 (m, 1 H, H-6b), 4.06 (d, 1 H, H-3), 4.05 (m, 2 H, H-6'a, H-6'b), 3.95 (m, 1 H, H-5). $^{13}\text{C-NMR}$: δ 98.4 (C-1'), 84.0 (C-3), 80.3 (C-4), 70.1 (C-5), 69.7 (C-5'), 70.0 (C-3'), 69.6 (C-1), 68.5 (C-2'), 66.8 (C-4'), 65.8 (C-6), 60.7 (C-6').

4-O-(β -D-galactopyranosyl)-1,5-anhydro-2,3-O-isopropylidene- β -D-fructopyranose [1,5-anhydro-2,3-O-isopropylidene- β -D-lactulose]



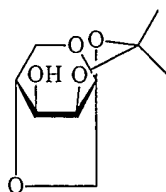
- $^1\text{H-NMR}$ (DMSO- d_6): δ 4.90 (d, 1 H, $J_{2',\text{OH}}$ 4.7 Hz, 2'-OH), 4.73 (d, 1 H, $J_{3',\text{OH}}$ 5.7 Hz, 3'-OH), 4.38 (m, 2 H, 4'-OH, 6'-OH), 4.28 (d, 1 H, $J_{1',2'}$ 7.6 Hz, H-1'), 4.18 (m, 2 H, H-3, H-4), 4.15 (d, 1 H, H-1a) 3.86 (d, 1 H, H-1b), 4.08 (m, 1 H, H-6a), 4.05 (m, 1 H, H-5), 3.98 (m, 1 H, H-6b), 3.64 (m, 1 H, H-4'), 3.51 (m, 2 H, H-6'), 3.36 (m, 1 H, H-5'), 3.34 (m, 1 H, H-2'), 3.28 (m, 1 H, H-3'). $^{13}\text{C-NMR}$: δ 103.5 (C-1'), 85.9 (C-3), 80.9 (C-4), 76.2 (C-5'), 74.7 (C-3'), 71.5 (C-2'), 71.2 (C-5), 70.7 (C-1), 69.2 (C-4'), 67.5 (C-6), 61.4 (C-6').

10 1,5-Anhydro-2,3-O-isopropylidene- β -D-threo-hexo-2,4-diulopyranose



- $^1\text{H-NMR}$ (DMSO- d_6): δ 4.83 (1, 1 H, H-3), 4.55 (d, 1 H, $J_{1a,1b}$ 9.1 Hz, H-1a), 4.13 (d, 1 H, H-1b), 4.39 (m, 1 H, H-6a), 4.16 (m, 1 H, H-6b), 4.15 (m, 1 H, H-5). $^{13}\text{C-NMR}$: δ 86.8 (C-3), 76.4 (C-5), 70.8 (C-1), 68.4 (C-6). mp 97-102°C.

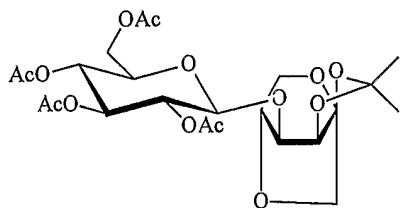
15 1,5-Anhydro-2,3-O-isopropylidene- β -D-tagatopyranose



- $^1\text{H-NMR}$ (DMSO- d_6): δ 5.14 (d, 1 H, $J_{4,\text{OH}}$ 5.3 Hz, 4-OH), 4.24 (m, 1 H, H-4), 4.20 (dd, 1 H, $J_{5,6}$ 1.8 Hz, $J_{6,6'}$ 9.9 Hz, H-6), 4.13 (d, 1 H, $J_{1,1'}$ 8.4 Hz, H-1), 4.02 (d, 1 H, $J_{3,4}$ 8.1 Hz, H-3) 3.97 (dd, 1 H, $J_{5,6'}$ 1 Hz, H-6'), 3.80 (m, 1 H, H-5), 3.72 (d, 1 H, H-1'). $^{13}\text{C-NMR}$ (DMSO-

d6): δ 98.9 (C-2), 77.8 (C-3), 69.6 (C-5), 69.55 (C-1), 65.0 (C-4), 64.0 (C-6). ^{13}C -NMR (MeOH- d_4): δ 98.3 (C-2), 77.7 (C-3), 70.1, 69.7 (C-1, C-5), 65.3, 64.1 (C-4, C-6).

4-O-(2',3',4',6'-Tetra-O-acetyl- β -D-glucopyranosyl)-1,5-anhydro-2,3-O-isopropylidene- β -D-tagatopyranose

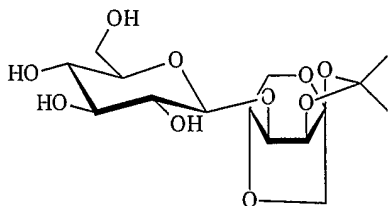


5

^1H -NMR (DMSO- d_6): δ 5.24 (dd, 1 H, $J_{2',3'}$ 9.8 Hz, $J_{3',4'}$ 9.8 Hz, H-3'), 4.92 (dd, 1 H, $J_{4',5'}$ 9.8 Hz, H-4'), 4.86 (d, 1 H, $J_{1',2'}$ 7.9 Hz, H-1'), 4.77 (dd, 1 H, H-2'), 4.53 (d, 1 H, $J_{3,4}$ 6.3 Hz, H-3), 4.47 (dd, 1 H, $J_{4,5}$ 1.6 Hz, H-4), 4.18 (dd, 1 H, $J_{6'a,6'b}$ 12.3 Hz, H-6'a), 4.09 (m, 2 H, H-1), 4.05 (m, 1 H, H-5), 4.04 (dd, 1 H, H-6'b), 3.99 (m, 1 H, H-5'), 3.92 (dd, 1 H, $J_{5,6a}$ 3.5 Hz, $J_{6a,6b}$ 11.4 Hz, H-6a), 3.64 (dd, 1 H, $J_{5,6b}$ 8.2 Hz, H-6b). ^{13}C -NMR: δ 99.8 (C-1'), 75.5 (C-4), 75.3 (C-3), 74.6 (C-5), 72.3 (C-1), 71.7 (C-3'), 70.4 (C-2'), 70.1 (C-5'), 68.7 (C-6), 68.0 (C-4'), 61.2 (C-6').

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4-O-(β -D-glucopyranosyl)-1,5-anhydro-2,3-O-isopropylidene- β -D-tagatopyranose

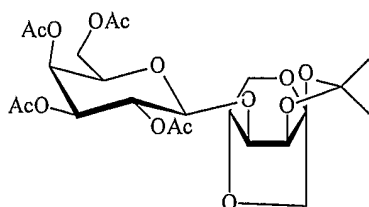


15

^1H -NMR (DMSO- d_6): δ 5.00 (d, 1 H, $J_{2',\text{OH}}$ 5.0 Hz, 2'-OH), 4.95 (d, 1 H, $J_{3',\text{OH}}$ 4.7 Hz, 3'-OH), 4.89 (d, 1 H, $J_{4',\text{OH}}$ 5.4 Hz, 4'-OH), 4.55 (dd, 1 H, $J_{3,4}$ 6.3 Hz, $J_{4,5}$ 1.6 Hz, H-4), 4.53 (d, 1 H, H-3), 4.50 (dd, 1 H, $J_{6'a,\text{OH}}$ 5.7 Hz, $J_{6'b,\text{OH}}$ 6.0 Hz, 6'-OH), 4.20 (d, 1 H, $J_{1',2'}$ 7.6 Hz, H-1'), 4.11 (m, 1 H, H-5), 4.09 (m, 2 H, H-1a, H-1b), 3.93 (dd, 1 H, $J_{5,6a}$ 4.1 Hz, $J_{6a,6b}$ 11.4 Hz, H-6a), 3.68 (m, 1 H, H-6'a), 3.63 (dd, 1 H, $J_{5,6b}$ 7.6 Hz, H-6b), 3.42 (m, 1 H, H-6'b), 3.12 (m, 2 H, H-3' and H-5'), 3.02 (m, 1 H, H-4'), 2.96 (m, 1 H, H-2'). ^{13}C -NMR: δ 102.9 (C-1'), 76.5 (C-3', C-5'), 75.7 (C-5), 75.7 (C-3, C-4), 73.1 (C-2'), 72.3 (C-1), 69.9 (C-4'), 67.9 (C-6), 60.7 (C-6').

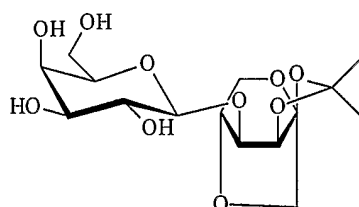
20

4-O-(2',3',4',6'-Tetra-O-acetyl-β-d-galactopyranosyl)-1,5-anhydro-2,3-O-isopropylidene-β-d-tagatopyranose



¹H-NMR (DMSO-d₆): δ 5.26 (dd, 1 H, J_{3',4'} 3.5 Hz, J_{4',5'} <1 Hz, H-4'), 5.14 (dd, 1 H, J_{2',3'} 10.4 Hz, H-3'), 4.94 (dd, 1 H, J_{1',2'} 7.9 Hz, H-2'), 4.78 (d, 1 H, H-1'), 4.53 (d, 1 H, J_{3,4} 6.3 Hz, H-3), 4.47 (dd, 1 H, J_{4,5} 1.3 Hz, H-4), 4.19 (m, 1 H, H-5'), 4.08 (m, 2 H, H-1a, H-1b), 4.05 (m, 2 H, H-6'a, H-6'b), 4.04 (m, 1 H, H-5), 3.92 (dd, 1 H, J_{5,6a} 3.8 Hz, J_{6a,6b} 11.4 Hz, H-6a), 3.64 (dd, 1 H, J_{5,6b} 7.9 Hz, H-6b). ¹³C-NMR: δ 100.2 (C-1'), 75.6 (C-4), 75.4 (C-3), 74.8 (C-5), 72.2 (C-1), 70.0 (C-3'), 69.8 (C-5'), 68.7 (C-6), 68.4 (C-2'), 67.0 (C-4'), 61.0 (C-6').

4-O-(β-d-galactopyranosyl)-1,5-anhydro-2,3-O-isopropylidene-β-d-tagatopyranose



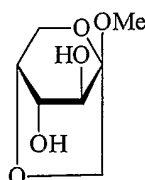
¹H-NMR (DMSO-d₆): δ 4.83 (d, 1 H, J_{2',OH} 4.7 Hz, 2'-OH), 4.70 (d, 1 H, J_{3',OH} 5.4 Hz, 3'-OH), 4.55 (m, 3 H, 4'-OH, H-3, H-4), 4.33 (dd, 1 H, J_{6'a,OH} 4.4 Hz, J_{6'b,OH} 10.1 Hz, 6'-OH), 4.15 (d, 1 H, J_{1',2'} 7.3 Hz, H-1'), 4.09 (m, 3 H, H-1a, H-1b, H-5), 3.90 (m, 1 H, H-6a), 3.61 (m, 1 H, H-4'), 3.50 (m, 2 H, H-6'a, H-6'b), 3.46 (m, 1 H, H-6b), 3.32 (m, 1 H, H-5'), 3.28 (m, 1 H, H-2'), 3.25 (m, 1 H, H-3'). ¹³C-NMR: δ 103.2 (C-1'), 75.4 (C-3, C-4), 74.8 (C-5'), 74.6 (C-5), 73.1 (C-3'), 72.1 (C-1), 69.9 (C-2'), 67.9 (C-4'), 67.5 (C-6), 60.21 (C-6').

2,3-O-Isopropylidene-1-O-methanesulfonyl-d-fructopyranose

¹H NMR. (DMSO d₆) δ: 5.33 (d, 1 H, J_{OH,4} 3.72 Hz, 4-OH), 4.87 (d, 1 H, J_{OH,5} 6.13 Hz, 5-OH), 4.30 (ABq, 2 H, J_{gem} 10.96 Hz, H-1), 4.00 (m, 2 H, H-3 and H-4), 3.80 (m, 1 H, H-5),

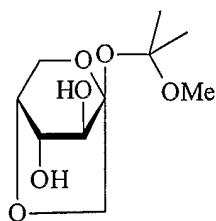
3.58 and 3.51 (2 × dd, each 1 H, J_{gem} 11.09 Hz, H-6), 3.19 (s, 3 H, OMe), 1.43 and 1.30 (2 × s, each 3 H, 2 × -CH₃).

Methyl 1,5-anhydro-β-D-fructopyranoside



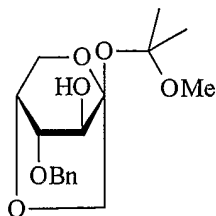
- 5 Syrup. $[\alpha]_{\text{D}}^{20} +5.3$ (c 1.1, MeOH). $^1\text{H-NMR}$ (MeOH- d_4): δ 4.16 (d, 1 H, $J_{1a,1b}$ 9.3 Hz, H-1a), 4.12 (m, 2 H, H-3, H-4), 4.05 (dd, 1 H, $J_{5,6a}$ 6.9 Hz, $J_{6a,6b}$ 10.8 Hz, H-6a), 3.79 (d, 1 H, H-1b), 3.62 (dd, 1 H, $J_{5,6b}$ 9.1 Hz, H-6b), 3.41 (s, 3 H, OMe). $^{13}\text{C-NMR}$: δ 102.7 (C-2), 81.0, 71.9, 69.6, 65.3, 63.8 (C-1, C-3, C-4, C-5, C-6), 52.2 (OMe).

(1'-Methoxy-1'-methyl)ethyl 1,5-anhydro-β-D-fructopyranoside

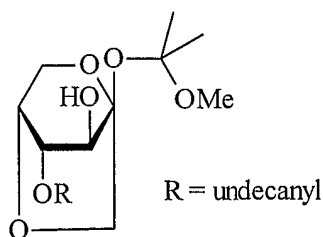


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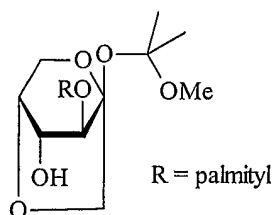
- 15 Syrup. $[\alpha]_{\text{D}}^{20} -57$ (c 0.37, MeOH). $^1\text{H-NMR}$ (MeOH- d_4): δ 4.20 (d, 1 H, $J_{1a,1b}$ 12.2 Hz, H-1a), 3.96 (d, 1 H, $J_{3,4}$ 6.3 Hz, H-3), 3.81 (dd, 1 H, $J_{5,6a}$ 2.5 Hz, $J_{6a,6b}$ 11.8 Hz, H-6a), 3.61 (dd, 1 H, $J_{5,6b}$ 1 Hz, H-6b), 3.60 (d, 1 H, H-1b), 3.54 (dd, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 3.27 (s, 3 H, OMe), 3.20 (ddd, 1 H, H-5). $^{13}\text{C-NMR}$: δ 111.5 (C-1'), 103.7 (C-2), 86.4, 79.7, 70.3, 68.4 (C-1, C-3, C-4, C-5), 61.9 (C-6), 48.0 (OMe), 27.8, 27.4 (C-2', C-3').

(1'-Methoxy-1'-methyl)ethyl 1,5-anhydro-4-O-benzyl-β-D-fructopyranoside

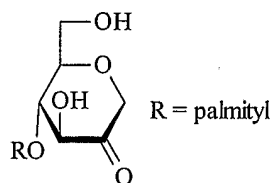
Syrup, $[\alpha]_{\text{D}}^{20}$ -30 (c 1.6, MeOH). $^1\text{H-NMR}$ (MeOH- d_4): δ 4.80 (d, 1 H, benzyl-CHa), 4.58 (d, 1 H, benzyl-CHb), 4.20 (d, 1 H, $J_{1a,1b}$ 12.2 Hz, H-1a), 4.19 (d, 1 H, $J_{3,4}$ 5.9 Hz, H-3), 3.78 (dd, 1 H, $J_{5,6a}$ 2.8 Hz, $J_{6a,6b}$ 11.7 Hz, H-6a), 3.60 (d, 1 H, H-1b), 3.57 (dd, 1 H, $J_{5,6b}$ 5.8 Hz, H-6b), 3.51 (dd, 1 H, $J_{4,5}$ 8.9 Hz, H-4), 3.30 (m, 1 H, H-5), 3.29 (s, 3 H, OMe), 1.46 (s, 3 H), 1.44 (s, 3 H).

(1'-Methoxy-1'-methyl)ethyl 1,5-anhydro-4-O-benzyl-3-O-undecanyl-β-D-fructopyranoside

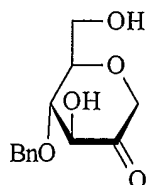
$[\alpha]_{\text{D}}^{20}$ -26 (c 2.0, MeOH), mp 42-43°C. $^1\text{H-NMR}$ (MeOH- d_4): δ 4.80 (d, 1 H, benzyl-CHa), 4.58 (d, 1 H, benzyl-CHb), 4.18 (d, 1 H, $J_{3,4}$ 6.5 Hz, H-3), 4.17 (d, 1 H, $J_{1a,1b}$ 12.1 Hz, H-1a), 3.62 (dd, 1 H, $J_{5,6a}$ 2.8 Hz, $J_{6a,6b}$ 10.8 Hz, H-6a), 3.59 (d, 1 H, H-1b), 3.58 (m, 1 H, H-4), 3.53 (dd, 1 H, $J_{5,6b}$ 4.9 Hz, H-6b), 3.47 (m, 1 H, H-1'a), 3.39 (m, 2 H, H-5, H-1'b), 3.29 (s, 3 H, OMe), 1.47 (m, 18 H, H-2' - H-10'), 0.90 (t, 3 H, H-11'). $^{13}\text{C-NMR}$: δ 111.6 (C-1'), 103.8 (C-2), 85.6, 77.5, 76.6, 72.2, 71.5, 70.1, 68.5 (C-1, C-3, C-4, C-5, C-6, CH₂Ph, C-1''), 60.3 (OMe), 31.9 (C-2''), 29.6, 29.55, 29.5, 29.4, 29.3, 26.8, 26.1, 22.6 (C-3'' - C-10''), 27.7, 27.2 (C-2', C-3'), 14.4 (C-16'').

(1'-Methoxy-1'-methyl)ethyl 1,5-anhydro-3-O-palmityl-β-D-fructopyranoside

¹H-NMR (MeOH-d₄): δ 4.17 (d, 1 H, *J*_{1a,1b} 12.2 Hz, H-1a), 3.95 (d, 1 H, *J*_{3,4} 6.6 Hz, H-3), 3.68 (dd, 1 H, *J*_{5,6a} 2.5 Hz, *J*_{6a,6b} 10.9 Hz, H-6a), 3.60 (d, 1 H, H-1b), 3.58–3.46 (m, 4 H, H-4, H-6b, H-1'a, H-1'b), 3.30 (m, 1 H, H-5), 3.28 (s, 3 H, OMe), 1.58 (m, 2 H, H-2'), 1.49 (s, 3 H), 1.47 (s, 3 H), 1.35–1.27 (m, 26 H), 0.90 (t, 3 H, H-16'). ¹³C-NMR: δ 103.7 (C-2), 86.3, 78.6, 71.6, 70.4, 70.3, 68.3 (C-1, C-3, C-4, C-5, C-6, C-1'), 31.9 (C-2'), 29.6, 29.55, 29.5, 29.4, 26.1, 22.6 (C-3' – C-15'), 13.4 (C-16').

1,5-Anhydro-4-O-palmityl-D-fructopyranose

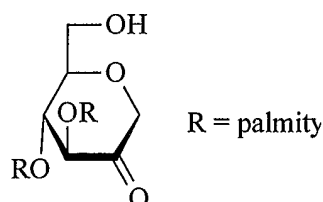
Mixture of ketose and hydrate. ¹³C-NMR (CDCl₃): δ 209.9, 99.7 (C-2), 85.7, 81.7, 81.6, 80.2, 79.1, 73.2, 72.0, 71.5, 71.0, 69.7, 67.2, 62.3 (C-1, C-3, C-4, C-5, C-6, O-CH₂-C15), 32.1, 31.2, 30.3, 30.0, 29.9, 29.85, 29.8, 29.75, 29.7, 29.6, 29.55, 28.0, 26.3, 26.2, 25.8, 22.9, 14.3 (C-2' – C-16').

1,5-Anhydro-4-O-benzyl-D-fructopyranose

¹H NMR. (DMSO d₆) δ: 7.42–7.20 (m, 5 H, Ph), 4.90–4.51 (m, 2 H, -CH₂Ph), 4.18–3.88 (m, 2 H, H-1), 3.70–3.15 (m, 5 H, H-3, H-4, H-5 and H-6). ¹³C-NMR (DMSO d₆) δ: 139.57, 128.87,

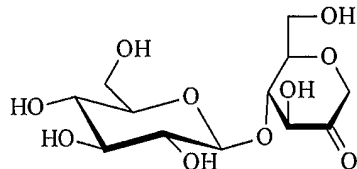
128.75, 128.74, 128.53 and 128.39 (aromatic), 108.85 (C-2), 80.12, 79.14, 77.57, 71.47 and 71.06 (C-1, C-3, C-4, C-5, -CH₂Ph).

1,5-Anhydro-3,4-di-O-palmityl-D-fructopyranose



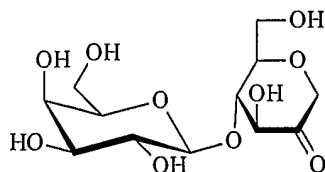
- 5 Mixture of ketose and hydrate. ¹³C-NMR (CDCl₃): δ 213.3 (C-2, ketose). Main component: 98.7, 87.5, 80.2, 74.3, 73.9, 62.4 (C-1 – C-6), 58.3, 57.7 (2 O-CH₂-C₁₅), 30.6, 29.95, 29.9, 29.7, 26.3, 22.9, 16.0, 15.8 (2 O-CH₂-C₁₅).

1,5-Anhydro-4-O-(β-D-glucopyranosyl)-D-fructopyranose



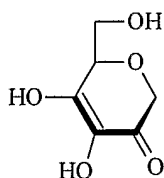
- 10 ¹H-NMR (D₂O): δ 4.44 (d, 1 H, J_{1',2'} 7.9 Hz, H-1'), 3.88 (m, 2 H, H-6a, H-6'a), 3.69 (m, 2 H, H-6b, H-6'b), 3.68 (m, 1 H, H-1a), 3.62 (m, 1 H, H-3), 3.59 (m, 1 H, H-4), 3.47 (m, 1 H, H-5), 3.45 (m, 2 H, H-3', H-5'), 3.40 (m, 1 H, H-1b), 3.35 (m, 1 H, H-4'), 3.25 (m, 1 H, H-2').
¹³C-NMR: δ 103.0 (C-1'), 92.9 (C-2), 79.7 (C-5), 79.3 (C-4), 76.0 (2 C, C-3', C-5'), 75.8 (C-3), 73.7 (C-2'), 72.0 (C-1), 70.1 (C-4'), 61.0 (2 C, C-6 and C-6').

- 15 1,5-Anhydro-4-O-(β-D-galactopyranosyl)-D-fructopyranose



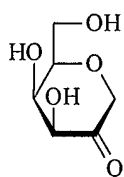
- 1H-NMR (D₂O): δ 4.28 (d, 1 H, *J*_{1',2'} 7.9 Hz, H-1'), 3.79 (dd, 1 H, *J*_{6'a,6'b} 12.3 Hz, H-6'a), 3.76 (m, 1 H, H-5'), 3.60 (dd, 1 H, H-6'b), 3.60 (m, 2 H, H-6a, H-6b), 3.59 (m, 1 H, H-5), 3.57 (d, 1 H, *J*_{1a,1b} 12.0 Hz, H-1a), 3.54 (m, 1 H, H-4'), 3.50 (m, 1 H, H-3'), 3.49 (m, 1 H, H-3), 3.38 (m, 1 H, H-2'), 3.37 (m, 1 H, H-4), 3.29 (d, 1 H, H-1b). ¹³C-NMR: δ 103.4 (C-1'), 93.0 (C-2), 79.7 (C-4), 79.2 (C-3), 75.9 (C-4' and C-5), 72.9 (C-3'), 71.9 (C-1), 71.1 (C-2'), 69.2 (C-5'), 61.5 (C-6), 60.9 (C-6').

1,5-Anhydro-D-threo-hexo-2,4-diulopyranose [(R)-4,5-dihydroxy-6-hydroxymethyl-2H-pyran-3(6H)-one]

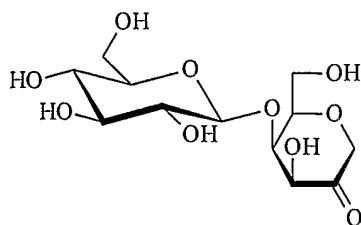


- 10 Mp 97-102°C. $[\alpha]_{\text{D}}^{20}$ -59.7 (c 1.0, MeOH). ¹H-NMR (D₂O): δ 4.35 (m, 3 H, H-1, H-1', H-5), 3.92 (dd, 1 H, *J*_{5,6} 2.5 Hz, *J*_{6,6'} 12.6 Hz, H-6), 3.78 (dd, *J*_{5,6'} 5.4 Hz, H-6'). ¹³C-NMR: δ 178.1 (C-4), 173.9 (C-2), 130.0 (C-3), 79.0 (C-5), 66.7 (C-5), 61.0 (C-6).

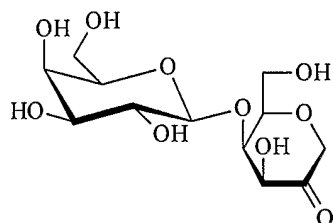
1,5-Anhydro-D-tagatopyranose



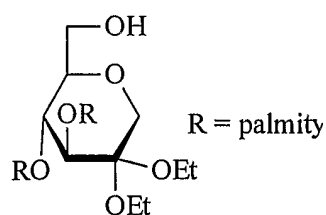
- 15 Syrup, mixture of free ketose and hydrate. ¹³C-NMR (Acetone-d₆): δ 215.4 (C-2, ketose), 92.3 (C-2, hydrate), 79.8, 78.6, 75.9, 72.6, 72.5, 72.4, 71.7, 69.3.6, 61.3, 61.1.

1,5-Anhydro-4-O-(β -D-glucopyranosyl)-D-tagatopyranose

- ¹H-NMR (D₂O): δ 4.44 (d, 1 H, $J_{1',2'}$ 7.9 Hz, H-1'), 3.89 (m, 1 H, H-4), 3.85 (m, 2 H, H-6a, H-6'a), 3.76 (m, 1 H, H-3), 3.73 (m, 1 H, H-1a), 3.69 (m, 1 H, H-5), 3.65 (m, 2 H, H-6b, H-6'b), 3.41 (m, 2 H, H-3' and H-5'), 3.38 (m, 1 H, H-1b), 3.32 (m, 1 H, H-4'), 3.23 (m, 1 H, H-2'). ¹³C-NMR: δ 102.9 (C-1'), 92.5 (C-2), 78.8 (C-3), 76.2 (C-3', C-5'), 73.6 (C-2'), 72.9 (C-1), 72.0 (C-5), 71.2 (C-4'), 70.0 (C-4), 61.2 (C-6, C-6').

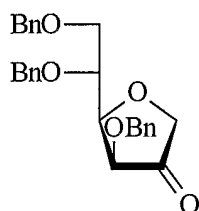
1,5-Anhydro-4-O-(β -D-galactopyranosyl)-D-tagatopyranose

- ¹H-NMR (D₂O): δ 4.38 (d, 1 H, $J_{1',2'}$ 7.9 Hz, H-1'), 3.91 (m, 1 H, H-4), 3.86 (m, 1 H, H-4'), 3.77 (m, 1 H, H-3), 3.74 (d, 1 H, $J_{1a,1b}$ 12.0 Hz, H-1a), 3.70 (m, 4 H, H-6a, H-6b, H-6'a, H-6'b), 3.69 (m, 1 H, H-5), 3.63 (m, 1 H, H-5'), 3.58 (m, 1 H, H-3'), 3.47 (m, 1 H, H-2'), 3.39 (d, 1 H, H-1b). ¹³C-NMR: δ 103.7 (C-1'), 92.4 (C-2), 78.9 (C-3), 75.6 (C-5'), 73.2 (C-3'), 73.0 (C-1), 72.0 (C-5), 71.3 (C-2'), 70.0 (C-4), 69.2 (C-4'), 61.6 (C-6, C-6').

15 1,5-Anhydro-3,4-di-O-palmityl-D-fructopyranose diethylacetal

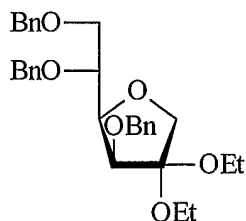
Colourless wax, $[\alpha]_D^{20} -3.5$ (c 1.9, CH₂Cl₂). ¹H-NMR (CDCl₃): δ 3.87 (d, 1 H, *J*_{1a,1b} 12.0 Hz, H-1a), 3.82 (dd, 1 H, *J*_{5,6a} 2.7 Hz, *J*_{6a,6b} 11.7 Hz, H-6a), 3.80–3.30 (m, 11 H, H-3, H-4, H-6b, 2 H-1', 2 H-1'', 2 OCH₂Me), 3.22 (ddd, 1 H, *J*_{4,5} 9.2 Hz, *J*_{5,6b} 5.2 Hz, H-5), 3.16 (d, 1 H, H-1b), 1.35–1.20 (m, 56 H, H-2' – H-15''), 1.21, 1.16 (t each, 3 H each, OCH₂Me), 0.87 (t, 6 H, 3 H-16', 3 H-16''), ¹³C-NMR: δ 98.6 (C-2), 87.7, 79.8, 77.8, 74.2, 73.7, 70.1, 62.8, 58.1, 57.5 (C-1, C-3, C-4, C-5, C-6, C-1', C-1'', 2 OCH₂Me), 32.6, 29.9, 29.8, 29.6, 22.9 (C-2' – C-15'', 2 OCH₂Me), 14.3 (2 C₁₅H₃₀Me).

1,4-Anhydro-3,5,6-tri-O-benzylfructose



- 10 Syrup, $[\alpha]_D^{20} -54.6$ (c 1.6, CH₂Cl₂), ¹H-NMR (CHCl₃): δ 4.90–4.56 (m, 6 H, 3 O-CH₂Ph), 4.33 (dd, 1 H, *J*_{3,4} 5.3 Hz, *J*_{4,5} 7.3 Hz, H-4), 4.24 (d, 1 H, *J*_{1a,1b} 17.5 Hz, H-1a), 4.17 (ddd, 1 H, *J*_{5,6a} 3.4 Hz, *J*_{5,6b} 4.8 Hz, H-5), 4.01 (d, 1 H, H-3), 3.86 (dd, 1 H, *J*_{6a,6b} 10.7 Hz, H-6a), 3.73 (dd, 1 H, H-6b). ¹³C-NMR: δ 211.7 (C-2), 79.6, 77.0, 76.2, 73.7, 73.0, 72.3, 70.2, 69.7 (C-1, C-3, C-4, C-5, C-6, 3 O-CH₂Ph).

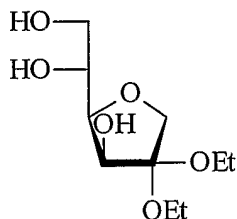
- 15 1,4-Anhydro-3,5,6-tri-O-benzylfructose diethylacetal



- Syrup, $[\alpha]_D^{20} -20.6$ (c 2.7, CH₂Cl₂), ¹H-NMR (CHCl₃): δ 5.00–4.50 (m, 6 H, 3 O-CH₂Ph), 4.32 (dd, 1 H, *J*_{3,4} 3 Hz, *J*_{4,5} 9.5 Hz, H-4), 4.09 (ddd, 1 H, *J*_{5,6a} 2 Hz, *J*_{5,6b} 5.3 Hz, H-5), 4.08 (d, 1 H, H-3), 4.05 (d, 1 H, *J*_{1a,1b} 8.8 Hz, H-1a), 3.96 (dd, 1 H, *J*_{6a,6b} 10.5 Hz, H-6a), 3.92 (d, 1 H, H-1b), 3.75 (dd, 1 H, H-6b), 3.72–3.50 (m, 4 H, 2 O-CH₂Me), 1.30–1.24 (m, 6

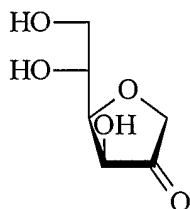
H, 2 O-CH₂Me). ¹³C-NMR: δ 109.8 (C-2), 80.3, 79.1, 76.8, 73.9, 73.7, 72.4, 71.4, 70.9 (C-1, C-3, C-4, C-5, C-6, 3 O-CH₂Ph), 59.6, 57.3 (2 O-CH₂Me), 15.8, 15.7 (2 O-CH₂Me).

1,4-Anhydrofructose diethylacetal

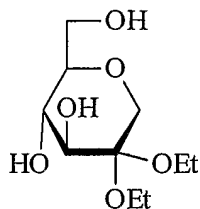


- 5 Mp 92-93°C, $[\alpha]_D^{20}$ -0.6 (c 2.1 MeOH), ¹H-NMR (MeOH-d₄): δ 4.06 (d, 1 H, J_{3,4} 3 Hz, H-3), 3.93 (dd, 1 H, J_{4,5} 8.5 Hz, H-4), 3.87 (m, 1 H, H-5), 3.86 (d, 1 H, J_{1a,1b} 8.8 Hz, H-1a), 3.73 (d, 1 H, H-1b), 3.73 (dd, 1 H, J_{5,6a} 5 Hz, J_{6a,6b} 11.7 Hz, H-6a), 3.70-3.50 (m, 5 H, H-6b, 1.21, 1.18 (2 t, 3 H each, 2 O-CH₂Me). ¹³C-NMR: δ 109.1 (C-2), 81.6, 72.4, 70.0, 69.4, 63.8 (C-1, C-3, C-4, C-5, C-6). 58.6, 56.8 (2 O-CH₂Me), 14.6, 14.3 (2 O-CH₂Me).

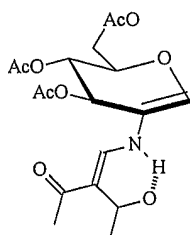
10 1,4-Anhydro-D-fructose



Mixture of ketose and hydrate/dimers. Main component: ¹³C-NMR (MeOH-d₄): δ 105.5 (C-2), 81.3, 73.9, 73.4, 71.6, 70.1, 63.7 (C-1, C-3, C-4, C-5, C-6). Ketose: δ 214.1, 82.0, 73.9, 71.7, 70.0, 63.8. Minor component: 105.45, 79.8, 73.4, 72.2, 68.9, 63.0.

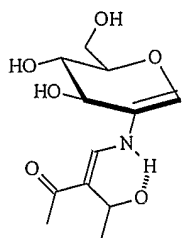
1,5-Anhydrofructose diethylacetal

- 1H NMR. (DMSO d6) δ : 4.82 (d, 1 H, $J_{OH,3}$ 5.57 Hz, 3-OH), 4.66 (d, 1 H, $J_{OH,4}$ 7.03 Hz, 4-OH), 4.52 (dd, 1 H, $J_{OH,6}$ 5.93 Hz, 6-OH), 3.79 and 3.48 (2 $\times$ q, each 2 H, $-\text{CH}_2\text{CH}_3$), 3.77 and 2.96 (2 $\times$ d, each 1 H, J_{gem} 12.47 Hz, H-1), 3.64 and 3.34 (2 $\times$ m, each 1 H, H-6), 3.34 (m, 1 H, H-4), 3.192 (m, 1 H, H-3), 3.04 (m, 1 H, H-5), 1.10 (t, 3 H, J 7.05 Hz, $-\text{CH}_3$), 1.05 (t, 3 H, J 7.07 Hz, $-\text{CH}_3$).

3,4,6-Tri-O-Acetyl-2-(2,2-Diacetylvinyl)amino-D-glucal

- 10 1H NMR. (CDCl_3) δ : 12.01 (d, 1 H, $J_{\text{NH},\text{HC}=\text{}}$ 12.30 Hz, NH), 7.70 (d, 1 H, $-\text{CH}=\text{}$), 7.64 (s, 1 H, H-1), 5.60 (d, 1 H, $J_{3,4}$ 4.66 Hz, H-3), 5.24 (dd, 1 H, $J_{4,5}$ 5.93 Hz, H-4), 4.45 and 4.18 (2 $\times$ dd, 2 H, J_{gem} 11.81 Hz, H-6), 4.37 (ddd, 1 H, $J_{5,6}$ 6.52 Hz and 3.13 Hz, H-5), 2.48 and 2.26 (2 $\times$ s, each 3 H, $-\text{CH}_3$), 2.12, 2.10 and 2.10 (3 $\times$ s, each 3 H, OAc).

- 15 ^{13}C -NMR (CDCl_3) δ : 201.27, 194.83, 169.58, 170.49 and 170.61 (5 $\times$ CO), 154.72 ($-\text{HN}-\text{CH}=\text{}$), 139.25 (C-1), 116.34 (C-2), 74.38 (C-5), 67.07 (C-4), 66.15 (C-3), 60.91 (C-6), 32.11, 27.54, 20.99, 20.95 and 20.94 (5 $\times$ CH_3).

2-(2,2-Diacetylvinyl)amino-D-glucal

1H NMR. (DMSO d6) δ : 11.89 (d, 1 H, $J_{\text{NH,HC}} = 13.1$ Hz, NH), 7.97 (d, 1 H, -CH=), 6.95 (s, 1 H, H-1), 5.74 (bs, 1 H, OH), 5.41 (bs, 1 H, OH), 4.71 (bs, 1 H, OH), 4.05 (m, 1 H, H-3),
 5 3.70-3.48 (m, 4 H, H-4, H-5 and H-6), 2.31 and 2.22 (2 $\times$ s, each 3 H, -CH₃).

¹³C-NMR (DMSO d6) δ : 199.22 and 195.00 (2 $\times$ CO), 155.23 (-HN-CH=), 136.73 (C-1), 120.08 (C-2), 111.71 (=C-(CO)₂), 80.66 (C-5), 69.30 and 69.09 (C-4 and C-3), 60.55 (C-6), 32.20 and 28.03 (2 $\times$ CH₃).

O-deprotection of O-protected hydroxyglycals

- 10 Preparation of a preferred starting material tetra-*O*-acetyl-2-hydroxy-D-glucal (compound of the General Formula **313** where, R¹, = CH₃, R²-R⁴ = COR¹) of use according to the invention.

Method I:

- 15 Acetobromoglucose (**316**) (80 g, 194.7 mmol) was dissolved in dry acetone (150 ml) containing sodium iodide (40 g) and after 15 min dry diethylamine (80 ml, 777 mmol) was added. After stirring for 1 h at room temperature the mixture was diluted with dichloromethane (300 ml) followed by water (500 ml). The organic phase was washed with aqueous hydrochloric acid and water, dried (MgSO₄), filtered and concentrated to give a residue, which was crystallized from ethanol. Yield 41 g (65%), m.p. 59-61°C (lit. Ferrier: m.p. 61-62°C).

- 20 Method II:

The procedure is an improvement (change of solvent) from the one described by Varela et. al. (O.Varela, G. M, DE Fina, R. M. Lederkremer, Carbohydr. Res. 167, 1987, 187-196).

Acetobromoglucose (**316**) (50 g, 121.7 mmol) was dissolved in dry tetrahydrofuran (THF) (300 ml) in a 3-necked bottle and cooled to 0 °C after which DBU (20 ml, 134 mmol) was slowly added. The cooling bath was removed and the mixture was stirred for 2 hour, or until TLC (ethyl acetate-hexane, 1:2) shows that the starting material had disappeared. Filtration and concentration left a residue which was dissolved in dichloromethane (300 ml). This solution was washed with water and aq. HCl. The aqueous phases were again extracted with dichloromethane, and the combined organic phases were washed with brine, and dried (MgSO₄). After concentration the product could be crystallized from ethanol to give 34.4 g (85.7%) of the tetra-*O*-acetyl-2-hydroxy-D-glucal. mp 59-60°C.

10 Example 1

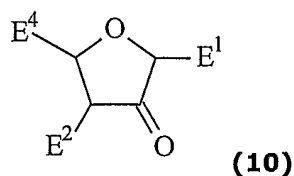
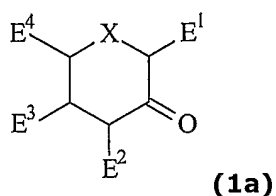
2,3,4,6-Tetra-*O*-acetyl-2-hydroxy-D-glucal (compound of the General Formula **313** where, R²-R⁴ = COR¹ and R¹, = CH₃) (1.00 g, 3.03 mmol) was dissolved in MeOH (60 ml) at room temperature and the solution was cooled to -40°C. The appropriate amount of sodium methoxide (150 mg, 2.8 mmol) was added (as a solid or in a methanolic solution) and the mixture was stirred at -40°C for approximately 3 hours after which time the solution was allowed to return to 0°C. Acidic ion exchange resin (Amberlite IR-120, H⁺) was added and the mixture was stirred for five minutes (to neutral pH), filtered and concentrated to a light yellow foam (0.48 g, 98%). A ¹³C-NMR spectrum in D₂O immediately after dissolution shows the presence of both the hydrate and the two different dimeric forms, but after 2-5 hours all compounds were converted into the hydrated form of 1,5-anhydro-D-fructose showing 6 peaks in the ¹³C-NMR spectrum.

¹³C-NMR: 72.6 (C-1), 93.5 (C-2), 77.7 (C-3), 69.8 (C-4), 81.5 (C-5) and 62.0 (C-6). ¹H-NMR: 3.33 (d, H-1a/b), 3.65 (d, H-1b/a), 3.45 (d, H-3), 3.30 (t, H-4), 3.66 (mp, H-5), 3.78 (dd, H6a/b), 3.56 (dd, H6b/a). ¹³C and ¹H NMR spectra were identical with those reported.

25 1,5-anhydro-D-fructose can be isolated and handled as a freeze dried product, consisting of the monomer 1,5-anhydro-D-fructose (**1**), the dimeric forms **1_{dimer1}**, **1_{dimer 2}**, and some of the hydrated 1,5-anhydro-D-fructose **1_{hydrate}**.

CLAIMS

1. A compound of the General Formula **1a** or General Formula **10**



wherein

- 5 X is selected from the group consisting of O, S, NH, NHR¹, CH₂, CHOH, CHOR¹, CHNH₂, CHNHR¹, CHSH, CHSR¹, C=O, S=O and SO₂;

- E¹ is selected from the group consisting of hydrogen, optionally substituted C₁₋₂₀-alkyl, optionally substituted heteroalkyl, optionally substituted C₂₋₂₀-alkenyl, optionally substituted C₂₋₂₀-alkynyl, optionally substituted C₃₋₁₀-cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted C₂₋₂₀-acyl; with the proviso that if X is selected from the group consisting of CH₂, CHOH, CHOR¹, CHNH₂, CHNHR¹, CHSH, CHSR¹, C=O, S=O and SO₂, then E¹ may also be selected from the group consisting of OH, =O, NH₂, NHR¹, NH₃⁺A⁻, NHR¹, NR¹R², SH, S⁻M⁺, SR¹, S=O, N₃ and halogen;

- 15 E² and E³ are independently selected from the group consisting of OH, O⁻M⁺, OR¹, =O, =S, SH, S⁻M⁺, SR¹, N₃, NH₂, NH₃⁺A⁻, NHR¹, NR¹R², and halogen;

- E⁴ is selected from the group consisting of hydrogen, CH₃, -CH₂OH, -CH(OH)CH₂OH, CH(OH)CH(OH)CH₂OH, -CH(OH)CH₂OR¹, -CH(OR¹)CH₂OH, -CH(OR¹)CH₂OR¹, -CH₂OR¹, -CH(OH)CH(OH)CH₂OR¹, -CH(OR¹)CH(OH)CH₂OH, -CH(OH)CH(OR¹)CH₂OH, -CH(OR¹)CH(OR¹)CH₂OH, -CH(OR¹)CH(OH)CH₂OR¹, -CH(OR¹)CH(OR¹)CH₂OR¹, -CH=O; -CH₂SH, -CH₂S⁻M⁺, -CH₂SR¹, -CH₂N₃, -CH₂NH₂, -CH₂NH₃⁺A⁻, -CH₂NHR¹, -CH₂NR¹R², -COOH, -COO⁻M⁺, and -COOR¹; with the proviso that if X is selected from the group consisting of CH₂, CHOH, CHOR¹, CHNH₂, CHNHR¹, CHSH, CHSR¹, C=O, S=O and SO₂, then E⁴ may also be selected from the group consisting of -OH, O⁻M⁺, OR¹, SH, S⁻M⁺, N₃, NH₂, NH₃⁺A⁻, NHR¹, NR¹R², =O, =S, and halogen;

R¹ is selected from the group consisting of optionally substituted C₁₋₂₀-alkyl, optionally substituted heteroalkyl, optionally substituted C₂₋₂₀-alkenyl, optionally substituted C₂₋₂₀-

alkynyl, optionally substituted C₃₋₁₀-cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C₂₋₂₀-acyl, C(O)R², SO₃H, SO₃⁻M⁺, SO₂R², C(O)NHR², P(O)(OH)₂, an acetal or ketal, and a carbohydrate structural motif;

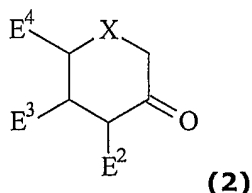
- 5 R² is selected from the group consisting of optionally substituted C₁₋₂₀-alkyl, optionally substituted heteroalkyl, optionally substituted C₂₋₂₀-alkenyl, optionally substituted C₂₋₂₀-alkynyl, optionally substituted C₃₋₁₀-cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

two of R¹ and/or R² may further be covalently linked so as to provide a cyclic structure;

- 10 M⁺ is any inorganic or organic cation; and A⁻ is any inorganic or organic anion,

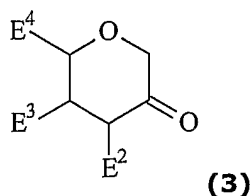
with the proviso that the compound is not selected from the group consisting of 1,5-anhydro-D-fructose and 1,5-anhydro-D-tagatose.

2. The compound according to claim 1, which is characterized by General Formula **2**



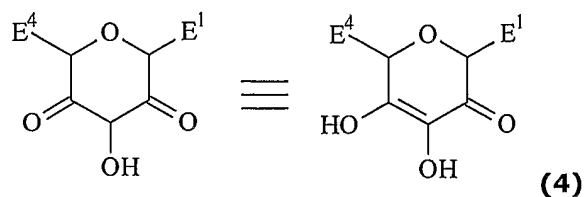
- 15 wherein X, E², E³ and E⁴ are as defined for General Formula **1a**.

3. The compound according to claim 2, which is characterized by General Formula **3**



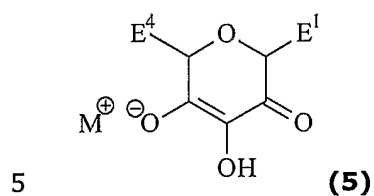
wherein E², E³ and E⁴ are as defined for General Formula **1a**.

4. The compound according to any one of the claims 1-3, which is characterized by General Formula **4**



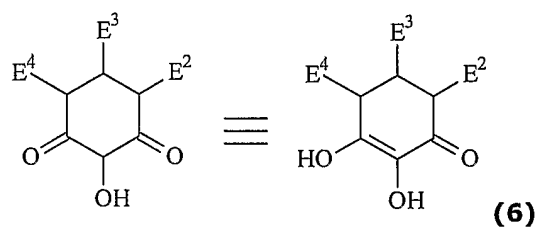
wherein E^1 and E^4 are as defined for General Formula **1a**.

5. The compound according to any one of the claims 1-3, which is characterized by General Formula **5**



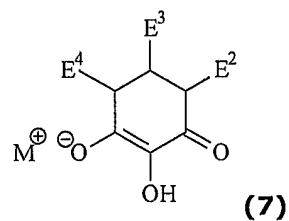
wherein M^+ , E^1 and E^4 are as defined for General Formula **1a**.

6. The compound according to claim 1, which is characterized by General Formula **6**.



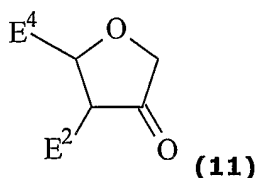
wherein E^2 , E^3 and E^4 are as defined for General Formula **1a**.

10 7. The compound according to claim 1, which is characterized by General Formula **7**.



wherein M^+ , E^2 , E^3 and E^4 are as defined for General Formula **1a**.

8. The compound according to claim 1, which is characterized by General Formula **11**



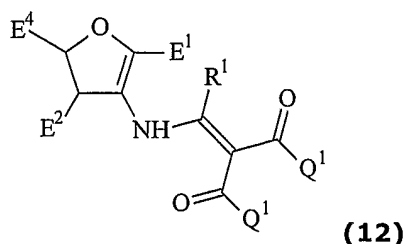
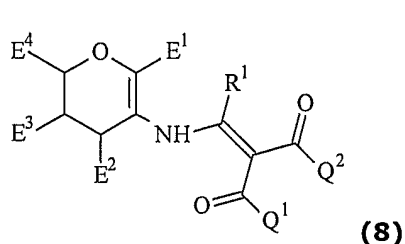
wherein E² and E⁴ are as defined for General Formula **10**.

9. A method for the preparation of a 1,4- or 1,5-anhydroketose of General Formula **1** or General Formula **10**, said method comprising the step of subjecting a corresponding β-hydroxy-sulfoxides acid to pyrolysis.

10. The method according to claim 9 for the preparation of a 1,5-anhydroketose of the General Formula **18** or a 1,4-anhydroketose of the General Formula **30**, wherein E², E³ and E⁴ are as defined for General Formula **1**, said method comprising the steps of subjecting a sulfenic acid of the General Formula **17** or General Formula **29**, wherein E², E³ and E⁴ are as defined above for General Formulas **18** and **29**, and R is selected from the group consisting of C₁₋₈-alkyl and aryl, to pyrolysis.

11. A method for the preparation of a 1,4- or 1,5-anhydroketose of General Formula **1** or General Formula **10**, said method comprising the step of deprotecting a corresponding N-protected aminoglycal.

12. A compound characterized by General Formula **8** or General Formula **12**



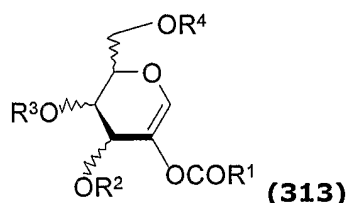
wherein R¹, E¹, E², E³ and E⁴ are as defined for General Formula **1**, and

Q¹ and Q² are independently selected from the group consisting of optionally substituted C₁₋₂₀-alkyl, optionally substituted heteroalkyl, optionally substituted C₂₋₂₀-alkenyl, optionally substituted C₂₋₂₀-alkynyl, optionally substituted C₃₋₁₀-cycloalkyl, optionally substituted

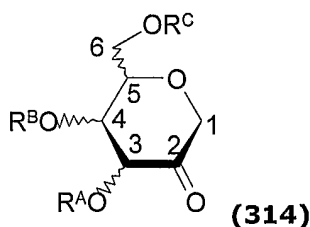
heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C₁₋₂₀-alkyloxy, and optionally substituted aryloxy.

13. A method for the preparation of a 1,4- or 1,5-anhydroketose of the General Formula **1** or General Formula **10**, said method comprising the step of deprotecting a corresponding carbohydrate enolether or an O-acyl-substituted carbohydrate enol.

14. A method for the preparation of 1,5-anhydro-D-fructose as well as derivatives and stereoisomers hereof, the hydrated forms, the dimeric forms or any mixture of said forms, characterised by deacylation of a 2-O-acyl-glycal of the General Formula **313**



- 10 wherein R¹, R², R³ and R⁴, which may be identical or different, are selected independently from the group consisting of hydrogen, optionally substituted, linear, branched or, if applicable, cyclic C₁-C₆ alkyl, optionally substituted aryl, optionally substituted Ar-(C₁-C₆ alkyl), optionally substituted Ar-(C₁-C₆ alkoxy), wherein said substituents are selected among halogen, such as fluoro, chloro, bromo, iodo, C₁-C₆ alkyl, C₁-C₆ alkoxy, or wherein R², R³ and
- 15 R⁴, which may be identical or different, are selected independently from any glyco-motif, or wherein any one, two or three of R², R³ and R⁴ may be COR¹, where R¹ has any of the meanings of above, at a reaction temperature below 0°C with a base to obtain 1,5-anhydro-D-fructose or derivatives and stereoisomers hereof of the General Formula **314**



- 20 wherein R^A, R^B, R^C have the meaning of R², R³, R⁴ above with the proviso that R^A, R^B, R^C can not be COR¹.

15. A method for the preparation of a 6-hydroxy-1,5-anhydroketose of General Formula **83**, said method comprising the step of

(a) O-deprotecting a corresponding bicyclic anhydroglycoside of General Formula **79** by removal of the R^1 group by hydrolysis under acidic conditions;

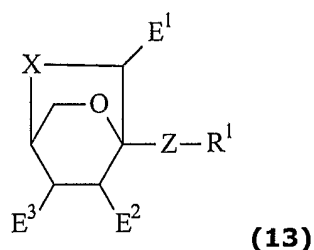
(b) activating a corresponding bicyclic thioglycoside of General Formula **80** so as to remove the $S-R^2$ group (e.g. NBS/ H_2O);

5 (c) activating a corresponding bicyclic anhydroglycosyl halide **81** so as to remove the halogen atom; or

(d) N-deprotecting a corresponding bicyclic anhydroglycosyl amine **82** by removal of the R^3 (R^1) group by hydrolysis under acidic conditions.

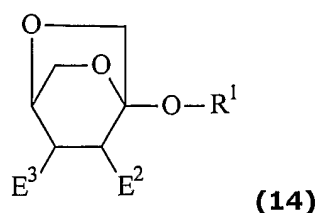
10 16. A method for the preparation of a 1,5-anhydroketos of the General Formula **99**, said method comprising the steps of subjecting a compound of General Formula **94** or **95** or **96** or **97** or **98** to ring opening conditions so as to liberate the corresponding 1,5-anhydroketose (**99**).

17. A bicyclic anhydrocarbohydrate of General Formula **13**.



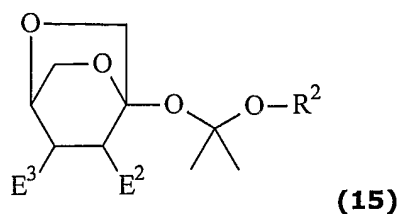
15 wherein X, E^1 , E^2 , E^3 and R^1 are as defined for General Formula **1**, and Z is O, S, NH, NR^2 where R^2 is as defined for General Formula **1**.

18. A bicyclic anhydroglycoside of General Formula **14**.



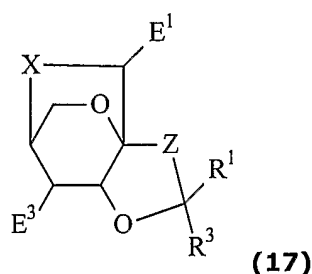
wherein E^2 , E^3 and R^1 are as defined for General Formula **1**.

19. A bicyclic anhydroglycoside of General Formula **15**.



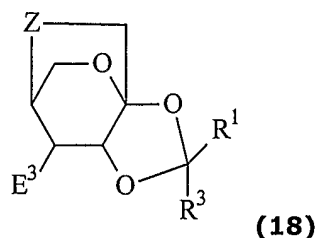
wherein E², E³ and R² are as defined for General Formula **1**.

20. A tricyclic anhydrocarbohydrate of General Formula **17**



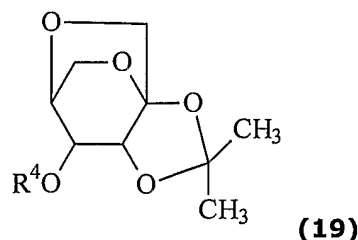
wherein X, E¹, E³ and R¹ are as defined for General Formula **1**, R³ is selected from the group consisting of the group consisting of hydrogen, optionally substituted C₁₋₂₀-alkyl, optionally substituted heteroalkyl, optionally substituted C₂₋₂₀-alkenyl, optionally substituted C₂₋₂₀-alkynyl, optionally substituted C₃₋₁₀-cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl and substituted heteroaryl, and Z is selected from the group consisting of O, S, NH, NR², where R² is as defined for General Formula **1**.

21. A tricyclic anhydrocarbohydrate of General Formula **18**



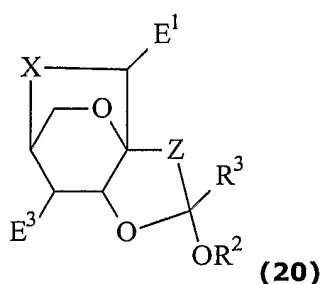
wherein E³ and R¹ are as defined for General Formula **1**, and R³ and Z are as defined for General Formula **17**.

22. A tricyclic anhydrocarbohydrate of General Formula **19**



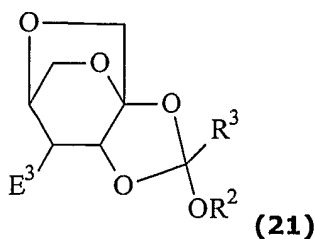
wherein R^4 is selected from the group consisting of hydrogen, optionally substituted C_{1-20} -alkyl, optionally substituted heteroalkyl, optionally substituted C_{2-20} -alkenyl, optionally substituted C_{2-20} -alkynyl, optionally substituted C_{3-10} -cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C_{2-20} -acyl, CH_2OR^2 , any substituted/unsubstituted carbohydrate moiety including mono- and oligo- and polysaccharides, a polymeric moiety, and an insoluble solid support.

23. A tricyclic anhydrocarbohydrate of General Formula **20**



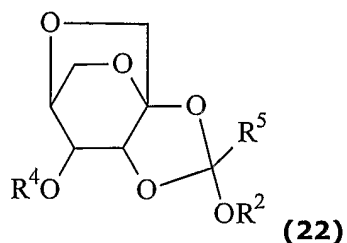
wherein X, E^1 , E^3 and R^2 are as defined for General Formula **1**, and Z and R^3 are as defined for General Formula **17**.

24. A tricyclic anhydrocarbohydrate of General Formula **21**



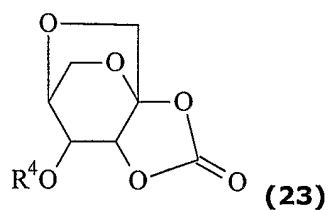
wherein E^3 and R^2 are as defined for General Formula **1**, and R^3 is as defined for General Formula **17**.

25. A tricyclic anhydrocarbohydrate orthoester of General Formula **22**



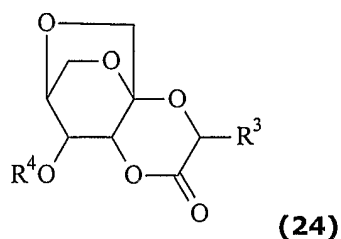
wherein R^1 and R^2 are as defined for General Formula **1**, R^4 is as defined for General Formula **19**, and R^5 is selected from the group consisting of hydrogen, methyl, ethyl, and phenyl.

5 26. A tricyclic anhydrocarbohydrate of General Formula 23



wherein R^4 is as defined for General Formula **19**.

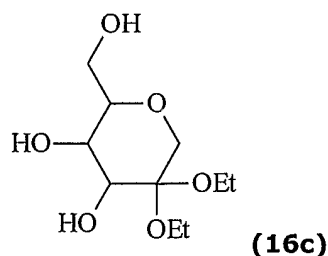
27. A tricyclic anhydrocarbohydrate of General Formula 24



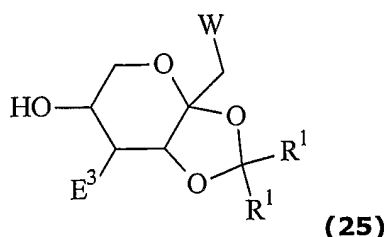
10 wherein R^4 is as defined for General Formula **19**, and R^3 is as defined for General Formula **17**.

28. A bicyclic carbohydrate intermediate of General Formula **25**

32. A diethyl ketal of an anhydroglycoside of General Formula **16c**

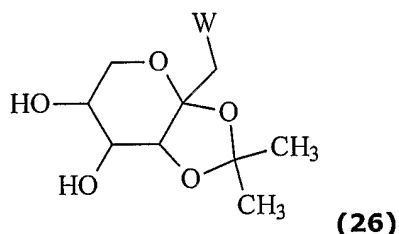


33. Use of a compound of General Formulas **1a**, **2-7**, **10** and **11** as defined in any one of claims 1-8 as an antioxidant, a radical scavenger, a sweetener, a non-caloric sweetener, a taste enhancing agent, a taste improving agent, an emulsifier, a water solubility enhancing agent, an antimicrobial agent, an antidiabetic agent, a glycosidase inhibitor, a food preserving agent, a feed preserving agent, a chelating agent, a starch deterioration inhibiting agent, a food colour retaining or stabilising agent, a water retaining agent, a moisturiser, a water-storing agent, a fragrance stabiliser, a taste stabiliser, a protein stabiliser, a moisture-releasing agent, a bilayer forming agent, a micelle forming agent, a detergents, a bulking agent, a tenside, a surfactant, a functional food, and/or a non-caloric functional food additive.
34. Use of 1,5-anhydro-D-fructose as a non-caloric sweetener, a non-caloric functional food additive, a functional food, an antidiabetic functional food, a functional food for elderly, a moustering agent, a moisture-releasing agent, and/or a protein-stability enhancing agent.
35. Use of a diketals of any one of the General Formulas **16a**, **16b** and **16c** as defined in any one of claims 31-32 as a food additive *in situ* producing anhydroketoses.



wherein R^1 and E^3 are as defined for General Formula **1**, and W is selected from the group consisting of halogen, OSO_2R^2 , OSO_2Cl , $OSO_2NR^1R^2$; where R^1 and R^2 are as defined for General Formula **1**.

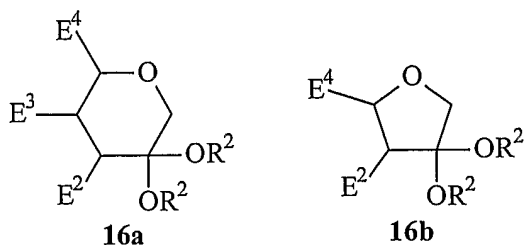
- 5 29. A bicyclic carbohydrate intermediate of General Formula **26**



wherein W is as defined for General Formula **25**.

30. A method for the preparation of diketals of 1,4- and 1,5-anhydroketoses characterized by General Formulas **16a**, **16b** and **16c**, said method comprising the step of subjecting a
 10 compound selected from the group consisting of bicyclic- and tricyclic-anhydroketoses of General Formulas **17-24** to an acid catalyzed trans-ketalization process in the presence of an alcohol of formula R^2-OH , in particular EtOH.

31. A diketal of an anhydroglycoside of General Formulas **16a** and **16b**



- 15 wherein E^2 , E^3 , E^4 and R^2 are as defined for General Formula **1**, with the proviso that R^2 is not a methyl group.