scale, there are the following difficulties and problems:

- On each synthesis stage, complicated protective group transformations and in each case a chromatographic purification have to be carried out.
- The use of liquid ammonia and elemental lithium at very low temperatures (step B2).
- Introduction and removal of a particular silyl protective group which has a high molar mass and is difficult to obtain commercially (steps B3 and B5).
- Use of DAST as fluorinating agent. In addition to the fact that DAST is difficult to obtain, safety concerns (handling temperature, decomposition of DAST in an exothermal reaction with formation of gas) play an important role in the scale-up of this reaction (step 4).
- The use of ozone at very low temperatures (B7).
- High temperatures (110°C) during the Pummerer rearrangement and the formation of about 20% of by-product B8 [J.K. Watts et al, *J. Org. Chem.* 2006, *71*, 921-925].

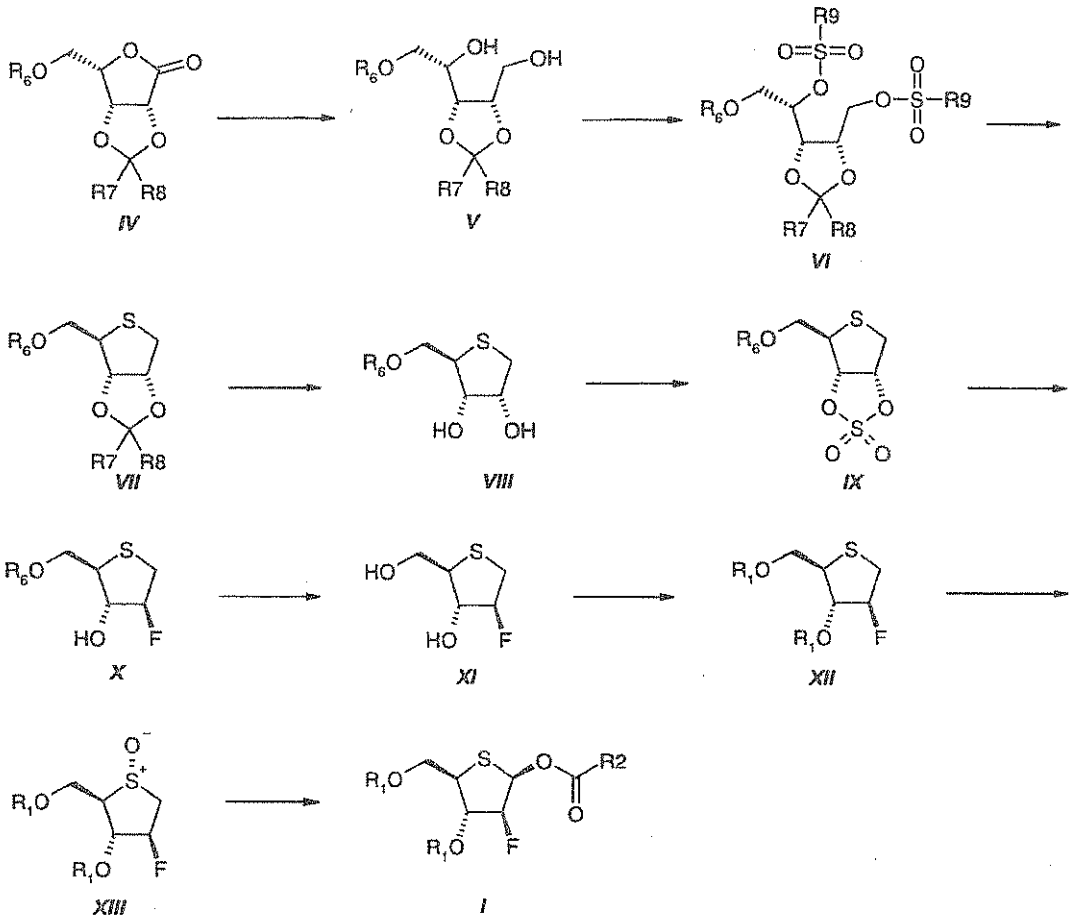
[0019] Owing to the difficulties, described here, in the individual steps of the synthesis, which render scale-up difficult or impossible, and owing to the limited availability of the starting material, the process shown in Scheme 2 is likewise not very suitable for the industrial commercial preparation of the compound II.

Summary ~~of Invention~~

[0020] Against this background, it was the object of the embodiments disclosed herein~~present invention~~ to provide an alternative process allowing the industrial preparation of compounds of formula I.

[0021] According to the ~~invention~~disclosure, this object was achieved by a process which affords compounds of formula I in high yields in 10 chemical steps starting with commercially readily available compounds of formula IV via the key steps "introduction of the fluorine atom via targeted opening of a cyclic sulphate" and "Pummerer rearrangement of a sulphoxide using a special catalyst" (Scheme 3).

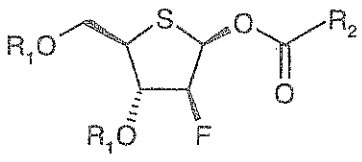
[0022] [Scheme 3]



[0023] Compounds of formula IV, used as starting materials for the process according to the ~~inventiondisclosure~~, can be synthesized in 4 chemical steps from natural and thus readily available D-ribose. Both D-ribose and compounds of the type IV (for example 5-O-benzyl-2,3-O-isopropylidene-L-lyxono-1,4-lactone) are commercially available (U.S. Patent No. 6,448,415 B1).

[0024] Furthermore, the process according to the ~~inventiondisclosure~~ uses exclusively reagents which are readily available even in kg amounts.

[0024a] In a first aspect, there is provided a process for preparing a compound of formula I



I

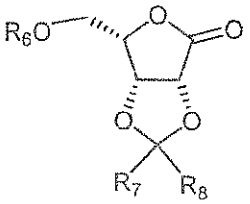
wherein

R1 represents -C(O)-C_1-C_6-alkyl or -C(O)-aryl; and

R_2 represents C_1-C_6-alkyl, C_1-C_4-perfluoroalkyl or aryl,

which comprises the following steps:

(1) reduction of a lyxonolactone of formula IV



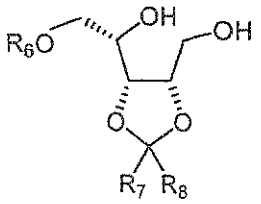
IV

wherein

R_6 represents C_1-C_6-alkyl or arylmethylene; and

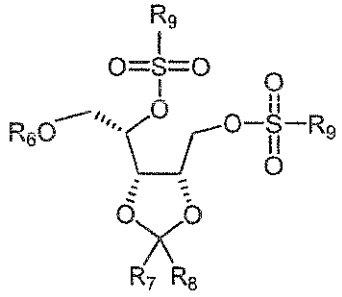
R_7 and R_8 independently represent hydrogen, C_1-C_6-alkyl, C_1-C_4-perfluoroalkyl or aryl;

in the presence of 0.5-10 molar equivalents of hydride donors of the formula $A(AlH_4)$ or $A(BH_4)$, wherein A is an alkali metal, to give the diol of the formula V:



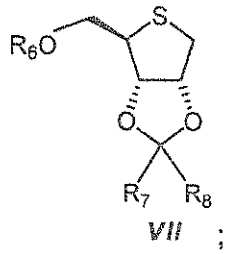
V ;

(2) reaction of the diol of formula V with at least 2 molar equivalents of sulphonyl chloride R_9-SO_2Cl or sulphonic anhydride R_9-SO_2-O-SO_2-R_9, wherein R_9 represents C_1-C_6-alkyl, C_1-C_4-perfluoroalkyl or aryl, in the presence of at least 2 molar equivalents of a tertiary amine or a pyridine, to give the compound of formula VI:



VI ;

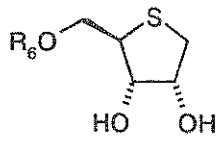
(3) reaction of the bissulphonate of formula VI with at least 1 molar equivalent of sodium sulphide (Na_2S) in a polar aprotic solvent, at a temperature of more than 50°C, to give the thiofuranose of formula VII:



VII ;

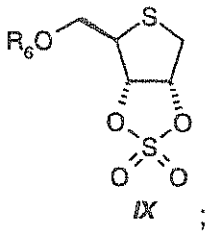
(4) conversion of the thiofuranose of formula VII in a solvent mixture of water and an organic solvent selected from the group of the ethers, alcohols, and aromatic

hydrocarbons, with 0.01-5 molar equivalents of an acid selected from the group of the mineral acids, alkanesulphonic acids, arylsulphonic acids, perfluorosulphonic acids and perfluoroalkanecarboxylic acids, into the diol of formula VIII:



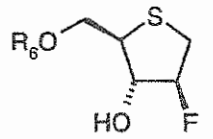
VIII ;

(5) reaction of the diol of formula VIII in the presence of at least 0.2 molar equivalents of a base of the formula AH, A_2CO_3 or A(OtBu), wherein A represents an alkali metal; with 1-2 molar equivalents of a diol-activating reagent of the formula X_1-SO_2-X_2, wherein X_1 and X_2 independently represent Cl or imidazoyl, to give the cyclic sulphate ester of formula IX:



IX ;

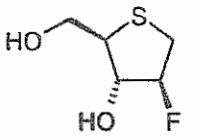
(6) the cyclic sulphate ester of formula IX is initially reacted with 1-3 molar equivalents of an ammonium fluoride of the formula $N(R_{11})_4F$, wherein R_{11} represents C_1-C_6-alkyl, at a temperature between 0°C and 30°C, and the reaction mixture obtained in this manner is reacted with an acid selected from the group of the mineral acids, alkylsulphonic acids, arylsulphonic acids, perfluorosulphonic acids and perfluoroalkanecarboxylic acids to give the ether of formula X:



X ;

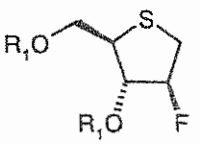
(7) the ether of formula X is

in partial step a) reacted in the presence of at least 1 molar equivalent of a boron halide BY_3, wherein Y represents F, Cl or Br, at a temperature between 0°C and -80°C;
in partial step b), the reaction mixture obtained in partial step a) is reacted with a mixture of an alcohol component selected from the group consisting of a C_1-C_6-alkanol, an aryl alkanol and phenols; and a base selected from the group of the aliphatic tertiary amines and pyridines; to give the diol of formula XI:



XI ;

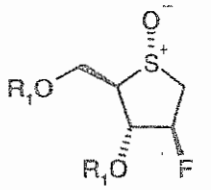
(8) the diol of formula XI is in the presence of at least 2 molar equivalents of a base selected from the group of aliphatic tertiary amines and pyridines, reacted with at least 2 molar equivalents of an acid chloride R_1-C_l or an acid anhydride R_1-O-R_1, wherein R_1 represents -C(O)-C_1-C_6-alkyl or -C(O)-aryl; to give the compound of formula XII:



XII ;

(9) the sulphide of formula XII is oxidized in a solvent mixture of water and a

ketone of the formula R_9-C(O)-R_9', wherein R_9 and R_9' independently represents C_1-C_6-alkyl, C_1-C_4-perfluoroalkyl or aryl, with 0.5-1 molar equivalent of an alkali metal persulphate of the formula $AHSO_5$, wherein A^+ represents an alkali metal, at a temperature between 0°C and 50°C to give the sulphoxide of formula XIII:



XIII ;

(10) the sulphoxide of formula XIII is reacted with at least 1 molar equivalent of an acid anhydride R_2–C(O)–O–C(O)–R_2, wherein R_2 represents C_1-C_6-alkyl, C_1-C_4-perfluoroalkyl or aryl; in the presence of 0.01-2 molar equivalents of a protic acid selected from mineral acids, alkanesulphonic acids, arylsulphonic acids, perfluorosulphonic acids and perfluoroalkanecarboxylic acids

or

in the presence of 0.01-2 molar equivalents of a Lewis acid or arylmethylene; at a temperature between 30°C and 100°C.

[0025] The intermediates V, VI and VII are isolated only as crude products and in each case employed directly for the next step. Finally, the compound VIII is crystallized in

high purity (> 97%). Thus, time- and resource-intensive purifications (for example preparative chromatography) can be dispensed with.

[0026] Steps IX, XI and XII are likewise not isolated and directly used as crude materials for the subsequent step.

[0027] According to the ~~invention~~disclosure, over the entire synthesis sequence, only 3 intermediates (VIII, X and XIII) have to be isolated, and only a single preparative chromatography is required (X). The intermediates VIII, XII and the product I (II) are isolated in high yields and high purities (> 93%) by crystallization.

[0028] The process according to the ~~invention~~disclosure does not require any complicated protective group transformations.

[0029] The oxidation of the sulphide XII can be carried out in a targeted manner at room temperature using OXONE (potassium monopersulphate triple salt, 2 $KHSO_5$ * $KHSO_4$ * K_2SO_4), overoxidation can be excluded without any problems by using equimolar amounts (cf. Scheme 2, reaction yielding B7).

[0030] According to the ~~invention~~disclosure, the Pummerer rearrangement (XIII→ I) is carried out in the presence of catalytic amounts of potassium bisulphate. By using this catalyst, it is possible to achieve high yields (> 80%) and at the same time very little side-product formation (< 5%) at low reaction temperatures (< 90°C) [cf. Scheme 2, reaction yielding II]. The crude product I obtained comprises so few impurities and also only very small proportions of the α-anomer that a simple crystallization is sufficient for purification.

[0031] The process according to the ~~invention~~disclosure does make use of general chemical transformations, known to the person skilled in the art, for constructing a thiofuranose via formation of a diol, its activation via a bissulphonate and cyclization with sodium sulphide; for protective group techniques and for oxidizing a sulphide with OXONE. However, a particular aspect of the present ~~invention~~disclosure is the targeted and highly efficient

construction of the individual stereocentres of the thiofuranoses.

[0032] A further ~~aspect~~embodiment of the present ~~invention~~disclosure is the stereospecific introduction of the fluorine atom at the C3 atom of compound X via stereoselective opening of the cyclic sulphate IX.

[0032a] In a second aspect, there is provided a compound which is selected from

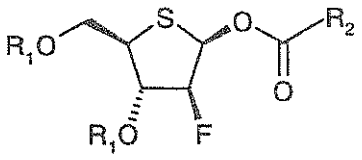
1,4-anhydro-5-O-benzyl-2,3-O-isopropylidene-4-thio-D-ribitol;

1,4-anhydro-5-O-benzyl-2,3-O-sulphonyl-4-thio-D-ribitol; and

1,4-anhydro-5-O-benzyl-2-deoxy-2-fluoro-4-thio-D-arabinitol.

Description of Embodiments

[0033] In the first step of the process according to the invention for preparing a compound of formula I:



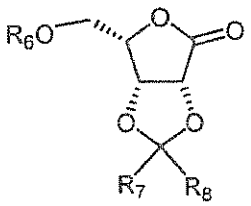
I

in which

R_1 represents -C(O)-C_1-C_6-alkyl or -C(O)-aryl; and

R_2 represents C_1-C_6-alkyl, C_1-C_4-perfluoroalkyl or aryl,

a lyxonolactone of formula IV



IV

in which

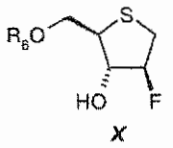
R_6 represents C_1-C_6-alkyl or arylmethylene; and

R_7 and R_8 independently of one another represent hydrogen, C_1-C_6-alkyl, C_1-C_4-perfluoroalkyl or aryl;

5 molar equivalents of acetic anhydride.

[Claims 22] The process according to Claim 1, wherein the product IIβ is isolated by crystallization from ethanol.

[Claims 23] The process for preparing a compound of formula X

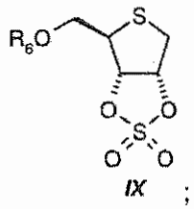


X

wherein R_6 represents C_1-C_6-alkyl, arylmethylene,

which comprises the following steps:

(a) the cyclic sulphate ester of formula IX



IX ;

is initially reacted with 1-3 molar equivalents of an ammonium fluoride of the formula $N(R_{11})_4F$, wherein R_{11} represents C_1-C_6-alkyl, at a temperature between 0°C and 30°C, and

(b) the reaction mixture obtained in this manner is reacted with an acid selected from the group of mineral acids, alkylsulphonic~~afkylsulphonic~~ acids, arylsulphonic acids, perfluorosulphonic acids and perfluoroalkanecarboxylic acids.

[Claims 24] The process according to Claim 23, wherein 1-3 molar equivalents of tetrabutylammonium fluoride are used.

[Claims 25] The process according to Claim 23, wherein the reaction mixture