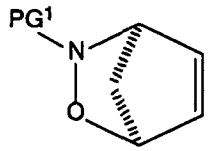
ORIGINAL

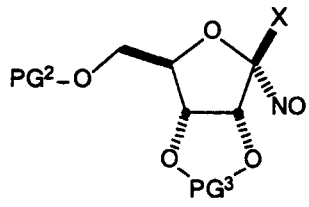
PROCESS FOR THE PREPARATION OF (1S,4R)-2-OXA-3-AZABICYCLO[2,2.1]HEPT-5-ENES

Abstract of the Invention

Enantiomerically enriched (1 S,4R)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene of formula wherein PG^1 is an amino-protective group, are prepared from cyclopentadiene via hetero-Diels-Alder cycloaddition with protected 1-*C*-nitroso-β-D-ribofuranosyl halides of formula wherein X is a halogen atom selected from fluorine, chlorine, bromine and iodine, PG^2 is a hydroxyl-protective group and PG^3 is a 1,2-diol-protective group.



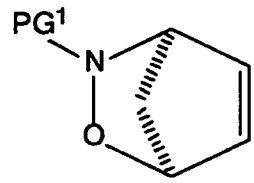
(I)



(II)

We Claim:

1. A process for the preparation of an enantiomerically enriched (1*S*,4*R*)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene of formula

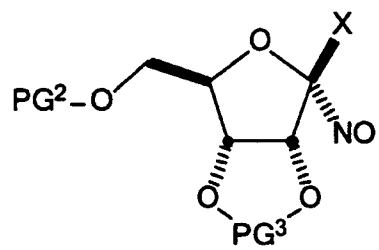


(I)

wherein PG^1 is an amino-protective group,

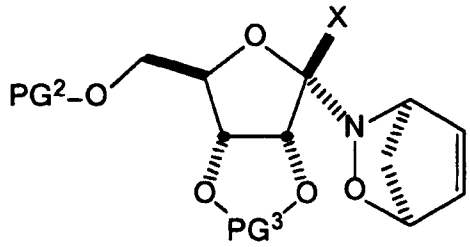
comprising the steps of

(i) reacting a protected 1-*C*-nitroso-β-D-ribofuranosyl halide of formula



(II)

wherein X is a halogen atom selected from fluorine, chlorine, bromine and iodine, PG^2 is a hydroxyl-protective group and PG^3 is a 1,2-diol-protective group, with cyclopentadiene to obtain a (1*S*,4*R*)-3-(1-*C*-halo-α-D-ribo-furanosyl)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene of formula



(III)

wherein X, PG^2 and PG^3 are as defined above;

(ii) hydrolyzing the compound obtained in step (i) to obtain free (1*S*,4*R*)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene (I; PG^1 = H) or the corresponding hydrohalide and the corresponding 5-*O*-protected D-ribonolactone; and

(iii) introducing the amino-protective group PG^1.

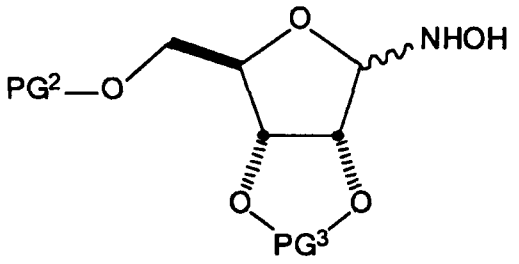
2. The process of claim 1 wherein the amino-protective group PG^1 is a benzyloxy-carbonyl group and is introduced by reacting the (1*S*,4*R*)-2-oxa-3-azabicyclo-[2.2.1]hept-5-ene with benzyl chloroformate.

3. The process of claim 1 or 2 wherein X is chlorine.

4. The process of any of claims 1 to 4 wherein the 1,2-diol-protective group PG^3 is an isopropylidene group.

5. The process of any of claims 1 to 5 wherein the steps (i) to (iii) are carried out without isolating the intermediate of formula III or the free (1*S*,4*R*)-2-oxa-3-aza-bicyclo[2.2.1]hept-5-ene (I; PG^1 = H) or its hydrohalide.

6. The process of any of claims 1 to 6 wherein the protected 1-*C*-nitroso-β-D-ribo-furanosyl halide of formula II has been prepared by reacting the corresponding protected D-ribofuranose oxime of formula



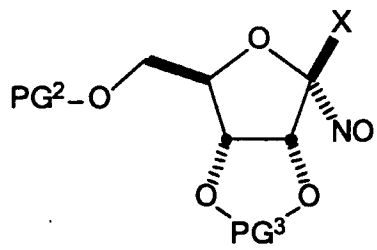
(IV)

wherein PG^2 is a hydroxyl-protective group and PG^3 is a 1,2-diol-protective group, with two equivalents of a hypohalite of formula

$$M^{n+}(OX)_n^-$$

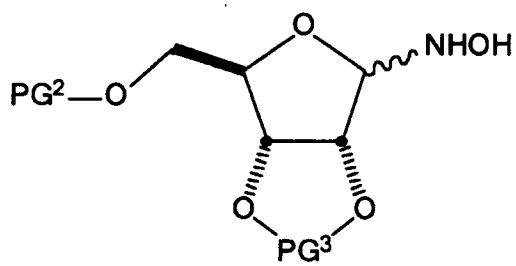
wherein X is chlorine, bromine or iodine, n is 1 or 2 and M is selected from the group consisting of alkali metals and alkaline earth metals.

7. A process for the preparation of a protected 1-*C*-nitroso-β-D-ribofuranosyl halide of formula



(II)

wherein X is a halogen atom selected from chlorine, bromine and iodine, PG^2 is a hydroxyl-protective group and PG^3 is a 1,2-diol-protective group,
wherein a protected D-ribofuranose oxime of formula



(IV)

wherein PG^2 and PG^3 are as defined above,
is reacted with two equivalents of a hypohalite of formula

$$M^{n+}(OX)_n^-$$

wherein X is as defined above, n is 1 or 2 and M is selected from the group consisting of alkali metals and alkaline earth metals.

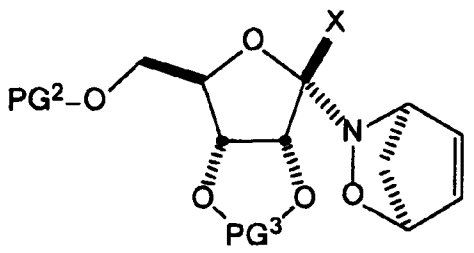
8. The process of claim 6 or 7 wherein the hypohalite is sodium hypochlorite.

9. The process of any of claims 1 to 8 wherein the protected D-ribonolactone obtained in step (ii) is recovered and reconverted into the protected 1-*C*-nitroso-β-D-ribofuranosyl halide (II).

10. The process of any of claims 1 to 9 wherein the hydroxyl-protective group PG^2 is an optionally substituted triphenylmethyl group.

11. The process of any of claims 1 to 10 wherein the 1,2-diol-protective group PG^3 is an isopropylidene group.

12. A (1*S*,4*R*)-3-(1-*C*-halo-α-D-ribofuranosyl)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene of formula



(III)

wherein
X is a halogen atom selected from fluorine, chlorine, bromine and iodine,
PG^2 is a hydroxyl-protective group, and
PG^3 is a 1,2-diol-protective group.

13. The (1*S*,4*R*)-3-(1-*C*-halo-α-D-ribofuranosyl)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene of claim 12 wherein X is chlorine.

14. The (1*S*,4*R*)-3-(1-*C*-halo-α-D-ribofuranosyl)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene of claim 12 or 13 wherein PG^2 is a triphenylmethyl group.

15. The (1*S*,4*R*)-3-(1-*C*-halo-α-D-ribofuranosyl)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene of any of claims 12 to 14 wherein PG^3 is an isopropylidene group.

Dated this the 1st Day of March, 2012

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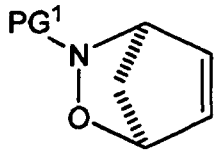
LEX ORBIS IP PRACTICE

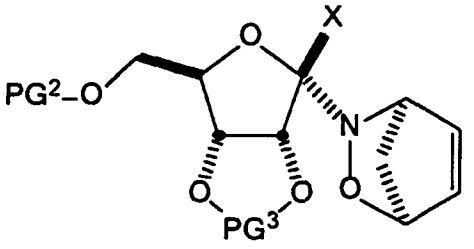
The invention relates to a process for the preparation of enantiomerically enriched (1*S*,4*R*)-2-oxa-3-azabicyclo[2.2.1]hept-5-enes of formula



(I)

wherein PG^1 is an amino-protective group.

It further relates to novel 5-*O*-protected (1*S*,4*R*)-3-(1-*C*-halo-α-D-ribofuranosyl)-2-oxa-3-azabicyclo[2.2.1]hept-5-enes of formula



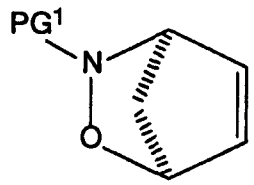
(III)

wherein X is a halogen atom selected from fluorine, chlorine, bromine and iodine, PG^2 is a hydroxyl-protective group and PG^3 is a 1,2-diol-protective group.

N-Protected 2-oxa-3-azabicyclo[2.2.1]hept-5-enes are valuable intermediates in the synthesis of various pharmaceutically active ingredients. See e.g. EP-A-0 322 242 and EP-A-0 658 539 for the N-benzyloxycarbonyl derivative. While some racemic compounds are relatively easily obtainable by hetero-Diels–Alder cycloaddition of nitroso compounds such as benzyl nitrosoformate (obtainable from benzyl *N*-hydroxycarbamate by oxidation, e.g. with periodate) with cyclopentadiene, a commercially feasible method for the production of the enantiopure or enantiomerically enriched compounds with a wide variety of possible protective groups has not been available.

It is therefore an objective of the present invention to provide a method for the production of enantiomerically enriched N-protected (1*S*,4*R*)-2-oxa-3-azabicyclo[2.2.1]-hept-5-enes that uses commercially available or at least easily accessible starting materials and allows the synthesis of compounds with various protective groups.

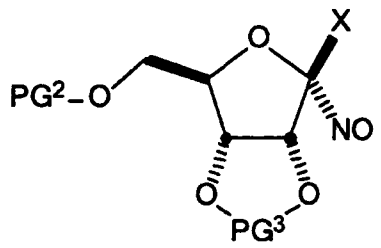
It has been found that enantiomerically enriched (1*S*,4*R*)-2-oxa-3-azabicyclo[2.2.1]-hept-5-enes of formula



(I)

wherein PG^1 is an amino-protective group, can be prepared by a method comprising the steps of

(i) reacting a protected 1-*C*-nitroso-β-D-ribofuranosyl halide of formula



(II)

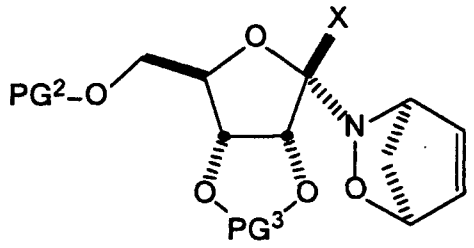
wherein

X is a halogen atom selected from fluorine, chlorine, bromine and iodine,

PG^2 is a hydroxyl-protective group, and

PG^3 is a 1,2-diol-protective group,

with cyclopentadiene to obtain a (1*S*,4*R*)-3-(1-*C*-halo-α-D-ribofuranosyl)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene of formula



(III)

wherein X, PG^2 and PG^3 are as defined above;

(ii) hydrolyzing the compound obtained in step (i) to obtain free (1*S*,4*R*)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene (I; PG^1 = H) or the corresponding hydrohalide and the corresponding protected D-ribonolactone; and

(iii) introducing the amino-protective group PG^1.

This finding is quite surprising since it had been found that a structurally related xylose-derived α-chloronitroso compound underwent hetero-Diels–Alder cycloadditions with both 1,3-cyclohexadiene and 1,3-cycloheptadiene, but failed to give any cycloaddition product with cyclopentadiene (A. Hall et al., *Chem. Commun.* 1998, 2251–2252).

Suitable amino-protective groups PG^1 are in particular groups forming a carbamate moiety with the amino nitrogen, such as simple alkoxycarbonyl groups, in particular methoxy-, ethoxy- or *tert*-butoxycarbonyl groups, or substituted methoxycarbonyl groups such as benzyloxycarbonyl (phenylmethoxycarbonyl) or (9-fluorenylmethoxy)-carbonyl groups, wherein the phenyl or fluorenyl part may optionally be substituted with one or more alkyl groups or halogen atoms. Such carbamate-forming protective groups are easily introduced by reacting the unprotected amino compound with the respective chloroformate. Other possible amino-protective groups are acyl groups such as acetyl or benzoyl groups which can be introduced by reacting the unprotected amino compound with the respective acyl chloride or anhydride, or benzyl groups which can be introduced by reacting the unprotected amino compound with benzyl chloride or bromide. Acetyl groups may also be introduced by reacting the unprotected amino compound with ketene.

The most preferred amino protective group PG^1 is the benzyloxycarbonyl group which can be introduced by reacting the unprotected amino compound with benzyl chloroformate.

The hydroxyl-protective group PG^2 may be any group that is not cleaved under the conditions of the process of the invention or during the synthesis of the nitrosoribofuranosyl halide (II). Since the process of the invention does not comprise the cleavage of PG^2, it is not necessary that PG^2 can be cleaved easily and/or selectively. Suitable hydroxyl-protective groups are those forming an ether (including silyl ether) or ester (including esters of carboxylic acids, carbonic acid, sulfonic acids and alkyl- or aryl-carbamic acids) moiety with the hydroxy group at C-5 of the ribose molecule. Ethers may be alkyl ethers, such as methyl or substituted methyl (e.g., methoxymethyl, benzyloxymethyl or triphenylmethyl) ethers, or silyl ethers, such as trialkylsilyl (e.g. trimethylsilyl, triethylsilyl or triisopropylsilyl) ethers. Esters may, for example, be those

of simple alkanoic or arenecarboxylic acids, such as acetate or benzoate, of alkane- or arenesulfonic acids, such as methanesulfonate (mesylate) or *p*-toluenesulfonate (tosylate), or of *N*-arylcarbamic acids, such as *N*-phenylcarbamate. These and other protective groups and suitable methods for their introduction are either known to a skilled person or can be found in well-known textbooks and monographs, such as *Greene's Protective Groups in Organic Synthesis* by Peter G. M. Wuts and Theodora W. Greene, John Wiley & Sons, Hoboken, NJ.

A particularly preferred hydroxyl-protective group PG^2 is the triphenylmethyl (trityl) group which may have one or more substituents such as C_{1-4} alkyl groups or halogen atoms at its phenyl groups.

Suitable 1,2-diol-protective groups include aldehyde- and ketone-derived groups which, together with the oxygen atoms (O-2 and O-3) and the adjacent carbon atoms (C-2 and C-3) form a cyclic acetal or ketal. Such protective groups can be introduced by either directly reacting the unprotected diol with an aliphatic or aromatic aldehyde or an aliphatic, cycloaliphatic or aromatic ketone, or via trans-acetalization or trans-ketalization using a suitable open-chain acetal or ketal, such as dimethoxymethane or 2,2-dimethoxypropane. These (trans-) acetalization or ketalization reactions are usually acid-catalyzed. Examples of acetal- and ketal-forming 1,2-diol-protective groups are methylene (introduced by reacting with formaldehyde or a formaldehyde acetal), ethylidene (by reacting with acetaldehyde or an acetal thereof), benzylidene (by reacting with benzaldehyde or an acetal thereof), isopropylidene (by reacting with acetone or 2,2-dimethoxypropane), cyclopentylidene (by reacting with cyclopentanone or 1,1-dimethoxycyclopentane) and cyclohexylidene (by reacting with cyclohexanone or 1,1-dimethoxycyclohexane).
Other suitable 1,2-diol-protective groups are those forming a cyclic orthoester or cyclic carbonate. Examples of cyclic orthoester-forming protective groups are methoxy- and ethoxymethylene (by reacting with trimethyl and triethyl orthoformate, respectively) or 1-methoxyethylidene (by reacting with trimethyl orthoacetate or 1,1-dimethoxyethene). A cyclic carbonate group may be introduced by reacting the 1,2-diol with phosgene, diphosgene (trichloromethyl chloroformate) or triphosgene (bis(trichloromethyl) carbonate).

In a particularly preferred embodiment the 1,2-diol-protective group PG^3 is isopropylidene ($=C(CH_3)_2$).

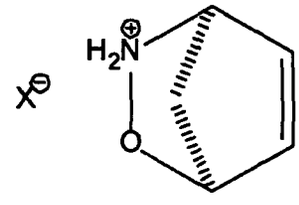
In a preferred embodiment, the substituent X is chlorine.

The cycloaddition step (i) is advantageously carried out in an inert solvent such as an aliphatic or aromatic hydrocarbon, a halogenated hydrocarbon, or an open-chain or cyclic ether. Non-limiting examples for such classes of solvents are hexanes, toluene, dichloromethane, tetrahydrofuran, methyl *tert*-butyl ether, and the like.

The cycloaddition step (i) is advantageously carried out at a temperature between −100 and +40 °C, preferably between −80 and 0 °C and most preferably at about −78 °C.

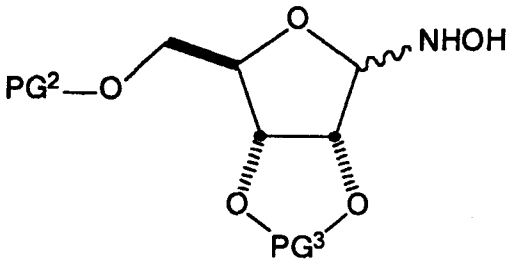
The reaction time of the cycloaddition step (i) is typically in the range of a few minutes to about one hour.

In a preferred embodiment the three steps (steps (i) to (iii)) of the process of the invention are carried out without isolating the intermediates (1*S*,4*R*)-3-(1-*C*-halo-α-D-ribofuranosyl)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene of formula III, and/or the unprotected (1*S*,4*R*)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene (formula I; PG^1 = H) or its hydrohalide of formula



wherein X is as defined above.

In a preferred embodiment the the 5-*O*-protected 1-*C*-nitroso-β-D-ribofuranosyl halide of formula II used in step (i) has been prepared by reacting the corresponding 5-*O*-protected D-ribofuranose oxime of formula



(IV)

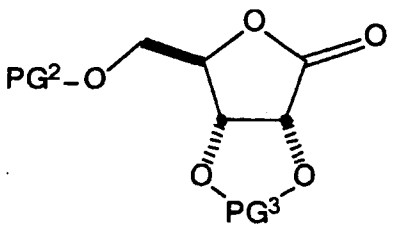
wherein PG^2 and PG^3 are as defined above, with two equivalents of a hypohalite of formula

$$M^{n+}(OX)_n^-$$

wherein X is chlorine, bromine or iodine, n is 1 or 2 and M is selected from the group consisting of alkali metals and alkaline earth metals, i.e., with a hypohalite selected from the group consisting of alkali metal hypohalites and alkaline earth metal hypohalites. The 5-*O*-protected D-ribofuranose oxime (IV) may also be present in the open-chain aldoxime form or as a mixture of the open-chain and the depicted furanose form. While the prior art syntheses of 5-*O*-protected 1-*C*-nitroso-β-D-ribofuranosyl halides and related compounds from the corresponding oximes comprise two steps, namely an oxidation step (e.g. with periodate) to the corresponding oximinolactone and an oxidative halogenation (e.g. with *tert*-butyl hypochlorite) to the nitrosoribofuranosyl halide, it has been found that the transformation can be achieved in one process step using two equivalents of an inexpensive alkali or alkaline earth metal hypohalite which serves as oxidant and halogenating agent.

Most preferably, the transformation is carried out with sodium hypochlorite as hypohalite.

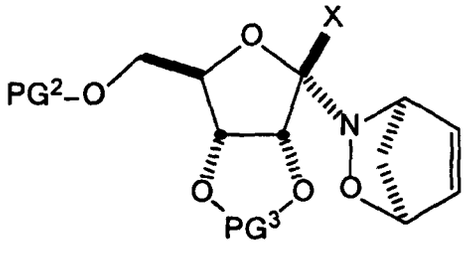
In another preferred embodiment the 5-*O*-protected D-ribonolactone of formula



(V)

wherein PG^2 and PG^3 are as defined above, which is formed in the hydrolysis of the intermediate of formula III, is recovered and reconverted via the oximinolactone into the protected 1-*C*-nitroso-β-D-ribofuranosyl halide of formula II, e.g. by reducing it to the corresponding protected D-ribofuranose which is then reacted with hydroxylamine to obtain the corresponding oxime of formula IV, which in turn is reacted with hypohalite as described above. When this recycling method is used, the consumption of the chiral auxiliary is minimized and — theoretically — only cyclopentadiene, hydroxylamine, sodium hypochlorite, a suitable reducing agent for the reduction of the lactone, and a source of the amino-protective group PG^1 are required in stoichiometric amounts.

The protected (1*S*,4*R*)-3-(1-*C*-halo-α-D-ribofuranosyl)-2-oxa-3-azabicyclo[2.2.1]hept-5-enes of formula



(III)

wherein X, PG^2 and PG^3 are as defined above are novel and also an object of the invention.

In a preferred embodiment of the (1*S*,4*R*)-3-(1-*C*-halo-α-D-ribofuranosyl)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene of formula III, X is chlorine.

In another preferred embodiment of the (1*S*,4*R*)-3-(1-*C*-halo-α-D-ribofuranosyl)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene of formula III, PG^2 is a triphenylmethyl group.

In still another preferred embodiment of the (1*S*,4*R*)-3-(1-*C*-halo-α-D-ribofuranosyl)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene of formula III, PG^3 is an isopropylidene group

According to the process of the invention it is possible to obtain the desired enantiomerically enriched (1*S*,4*R*)-2-oxa-3-azabicyclo[2.2.1]hept-5-enes (I) in an enantiomeric

excess (ee) of 80% or more, preferably 90% or more and particularly preferably 95% or more.

The following non-limiting examples will illustrate the process of the invention and the preparation of the novel intermediates.

Example 1

2,3-*O*-Isopropylidene-D-ribofuranose

Concentrated sulfuric acid (0.3 mL) was added to a suspension of D-ribose (12.5 g, 83 mmol) in acetone (125 mL). The reaction mixture was stirred at room temperature for 90 min to obtain a clear solution which was then neutralized with saturated aqueous sodium carbonate. The mixture was filtered over Celite® and concentrated *in vacuo*.
Yield: 15.7 g (≈100%)

Example 2

2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribofuranose

2,3-*O*-Isopropylidene-D-ribofuranose (15.7 g, 83.1 mmol) was dissolved in pyridine (100 mL) and trityl chloride (27.8 g, 0.1 mol) was added. The mixture was stirred at room temperature for 24 h. The solvent was evaporated and the residue purified by column chromatography on silicagel using hexanes/ethyl acetate (*v:v* = 4:1) as eluant.
Yield: 32.3 g (90%)

Example 3

2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribofuranose

2,3-*O*-Isopropylidene-D-ribofuranose (20 g, 105.2 mmol) was dissolved in dichloromethane (200 mL) at 0 °C. Triethylamine (10.9 g, 107.5 mmol) and a catalytic. amount of pyridine were added to the reaction mixture, followed by the addition of trityl chloride

(27.8 g, 0.1 mol). The mixture was stirred at 0 °C for 3 h and further 12 h at room temperature. To the reaction mixture was added saturated aqueous sodium bicarbonate (80 mL) and the phases were separated. The organic phase was dried over anhydrous sodium sulfate, filtered, and the solvents were removed *in vacuo*. The crude product was used without further purification in the next step.
Yield: 38.5 g (85%)

Example 4

2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribofuranose oxime (IV; PG^2 = trityl, PG^3 = $=C(CH_3)_2$)

Hydroxylamine hydrochloride (58 g, 0.83 mol) was added to a solution of 2,3-O-isopropylidene-5-*O*-trityl-D-ribofuranose (30 g, 0.69 mol) in pyridine (200 mL). The mixture was stirred at room temperature for 3 h and then water (250 mL) and dichloromethane (250 mL) were added and the phases were separated. The organic phase was dried over anhydrous sodium sulfate and filtered and the solvent was evaporated. The residue was purified by column chromatography on silicagel using hexanes/ethyl acetate (*v:v* = 7:3) as eluant.
Yield: 25.5 g (82%)

Example 5

2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribofuranose oxime (IV; PG^2 = trityl, PG^3 = $=C(CH_3)_2$)

To hydroxylamine hydrochloride (10.9 g, 0.16 mol) in ethanol (150 mL) was added sodium bicarbonate (13.11 g, 0.16 mol). The reaction mixture was stirred at room temperature until the evolution of carbon dioxide ceased. Then 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranose (15 g, 0.34 mol), dissolved in ethanol (50 mL), was added and stirring was continued for 2 h. The reaction mixture was then filtered over a plug of silica and ethyl acetate (200 mL) and water (200 mL) were added. The organic phase was dried over anhydrous sodium sulfate and filtered and the solvent was evaporated. The crude product was used without further purification in the next step.
Yield: 13.4 g (86%).

Example 6

2,3-*O*-Isopropylidene-1-*C*-nitroso-5-*O*-trityl-β-D-ribofuranosyl chloride (II, X = Cl, PG^2 = triphenylmethyl, PG3 = $=C(CH_3)_2$)

Sodium hypochlorite (5 wt.% aqueous solution, 140 mL, 0.92 mol) was added dropwise at 0 °C under stirring to a solution of 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranose oxime (25.5 g, 0.57 mol) in dichloromethane (150 mL). After 30 min at 0 °C the reaction mixture was allowed to warm to room temperature and stirred for another 30 min. Water (50 mL) was added and the phases were separated. The organic phase was dried over anhydrous sodium sulfate and filtered. The product was isolated by evaporating the solvent.

Yield: 25 g (88%)

Example 7

(1*S*,4*R*)-3-Benzyloxycarbonyl-2-oxa-3-azabicyclo[2.2.1]hept-5-ene

(I, PG^1 = $-COOCH_2C_6H_5$)

2,3-*O*-Isopropylidene-1-*C*-nitroso-5-*O*-trityl-β-D-ribofuranosyl chloride (1 g, 1.96 mmol) was dissolved in toluene or dichloromethane (10 mL). The solution was cooled to −78 °C and cyclopentadiene (1 g, 14.6 mmol) was added within 30 min under stirring. The reaction mixture was stirred at −78 °C for 1h and the warmed to 0 °C. Water (25 mL) was added at 0 °C and the phases were separated. Methyl *tert*-butyl ether (5 mL), benzyl chloroformate (350 mg, 2.0 mmol) and sodium hydroxide (25 wt.% aqueous solution, 800 mg, 5 mmol) were added and the resulting mixture stirred at room temperature for 30 min. The phases were separated, the organic phase was washed with brine (5 mL), dried over anhydrous sodium sulfate and filtered. The product was isolated by evaporating the solvent.

Yield: 89%

ee: 96%

When the reaction with cyclopentadiene was repeated at −20 °C and 0 °C, the ee of the product was 88% and 82%, respectively.