Tetrahedron 64 (2008) 6744–6748

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Dye-sensitized photooxygenation of sugar furans: novel bis-epoxide and spirocyclic C-nucleosides

Anna Astarita, Flavio Cermola *, M. Rosaria Iesce, Lucio Previtera

Dipartimento di Chimica Organica e Biochimica, Università di Napoli Federico II, Complesso Universitario di M. Sant'Angelo, Via Cinthia 4, 80126 Napoli, Italy

ARTICLE INFO

Article history:
Received 4 February 2008
Received in revised form 15 April 2008
Accepted 1 May 2008
Available online 3 May 2008

Keywords:
C-nucleosides
Photooxygenation
Singlet oxygen
Glycosyl furans

ABSTRACT

Dye-sensitized photooxygenation of 2-methyl 5-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)furoate leads to (1*S*,4*R*)-*endo*-peroxide, highlighting a high facial diastereoselectivity. This *endo*-peroxide rearranges into *syn*-(1*R*,2*R*:3*S*,4*R*)-diepoxide C-nucleoside, while by Et_2S-reduction followed by NEt_3 catalysis affords a spirocyclic C-nucleoside.

1. Introduction

Over the years, many synthetic approaches for C-glycosides have been developed, due to the biological activity, which often characterizes these molecules.[1] The interest is enhanced by their high stability towards both enzymatic and chemical hydrolysis due to the presence of the carbon–carbon bond at the anomeric centre.[2]

Among the most used methodologies, many approaches for natural or novel glycosides of biological interest employ the furan system as building block.[3,4] In this context, on the basis of our numerous investigations on the [4+2] cycloaddition of singlet oxygen to aromatic heterocycles,[5] we have undertaken research aimed at using the furan skeleton as a pre-existent aglycone of sugars and the dye-sensitized photooxygenation as convenient methodology for the construction of the desired target.

Previous results on the dye-sensitized photooxygenation of polyhydroxyalkyl- and anhydro sugar furans showed that the steric hindrance of the substituents at the furan ring does not avoid singlet oxygen addition.[6] We examined 2-glycosyl and 2-ribofuranosylfurans and found that the cycloaddition products, named *endo*-peroxides, underwent a migration of the sugar moiety from carbon to the peroxidic oxygen (Bayer–Villiger type rearrangement) with retention of the configuration at the anomeric carbon.[7] Similar rearrangements have been observed starting from 2-alkyl- or 2-aryl-monosubstituted furans,[8a] or from 2-polyhydroxyalkyl furans,[6] but they were not observed for 2,5-disubstitued ones.[8b] Thus, the reaction showed straight electronic control by the sugar moiety on the fate of the bicyclic peroxides. In addition to O-glycosides, new functionalized C-glycosides could be obtained selectively, with very high yield and controlled stereochemistry.[6,7,9] More recently, the research on the dye-sensitized photooxygenation of 2,5-dimethyl-3-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)furan has provided a straightforward one-pot synthesis for new pyridazine[9] and pyrazoline[10] C-nucleosides, as well as for new *exo*-glycals,[10] all compounds of pharmacological and synthetic interest.

2. Results and discussion

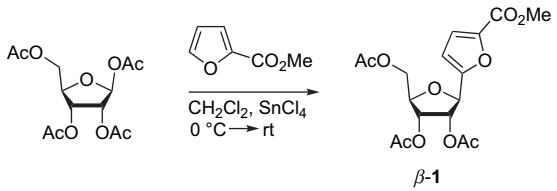
Here, we synthesized a novel 2-sugar furan bearing a methoxycarbonyl function at the 5-position, selected as representative of electron-withdrawing substituents. Previous data highlighted how the fate (thermal stability, rearrangement type) of the *endo*-peroxide depends on the nature, number and position of the substituent on the furan ring.[5]

The aim was to examine the influence of an electron-withdrawing α-substituent on the reactivity of sugar *endo*-peroxides, and hence extend the synthetic application of the [4+2] cycloaddition of $^1O_2$ for modified nucleosides.

The synthesis of methyl 5-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-2-furoate is reported in Scheme 1. The procedure afforded only the β-anomer of **1**, which was isolated by silica gel chromatography in a 60% yield. The high observed β-stereoselectivity could

* Corresponding author. Tel.: +39 (0) 81674331; fax: +39 (0) 81674393.
E-mail address: cermola@unina.it (F. Cermola).

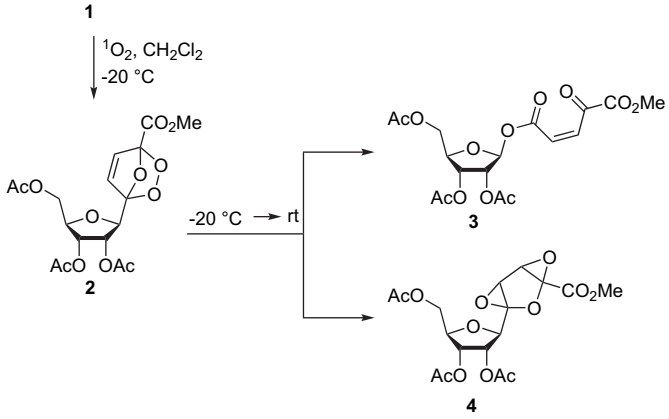
0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.05.002



Scheme 1.

be probably due to the neighbouring participation of the acetyl at C-2′ during the departure of the leaving group at the C-1.[†]

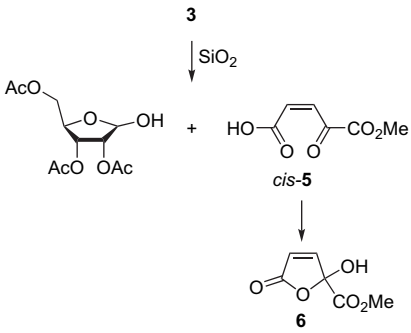
The dye-sensitized photooxygenation of **1** was carried out in dry dichloromethane at −20 °C and was complete after 90 min (TLC). To the two products, which were present in ca. 1:1 molar ratio, were assigned structures **3** and **4** on the basis of 1D and 2D NMR spectroscopic data (Scheme 2).



Scheme 2.

Nucleoside **4** was isolated by silica gel chromatography.[‡] In addition to the sugar signals, it exhibited two doublets at δ_C 52.7 and 55.5, correlated to two doublets at δ_H 3.90 and 4.09, respectively, and two singlets at δ_C 92.4 and 98.9 indicative of a saturated structure and typical of a diepoxidic function. Chromatography caused the complete hydrolysis of the O-glycoside **3** and, hence, its spectral data were collected on the crude photooxygenation mixture of **1**, rejecting the signals of isolated **4**. The ^{1}H NMR spectrum of this mixture showed two doublets of unsaturated protons at δ_H 6.73 (H-2) and 6.40 (H-3) correlated to doublets at δ_C 139.3 and 128.5, respectively, and a signal at δ_H 6.44 (H-1′), correlated to a doublet at δ_C 95.5, typical for anomeric O-glycoside hydrogens. A signal at δ_C 185.6 representative of the unsaturated ketone carbon was also present in the ^{13}C NMR spectrum. Chromatography led to the isolation, besides **4**, of furanone **6** formed by cyclization of hydrolysis product *cis*-**5** (Scheme 3).

The sugar-migration from C-4 to O-3 giving the new O-glycoside **3** was, almost in part, expected[6,7,9] while it is likely that the electronic effect of the carbomethoxy group influenced the reaction course promoting the rearrangement, which leads to the bis-epoxide C-glycoside **4** (Scheme 2).



Scheme 3.

It is noteworthy here that only one bis-epoxide was found either by NMR analysis or by TLC.

Similar rearrangements have been previously observed starting from methyl 2-polyhydroxyalkyl-3-furan carboxylates and from the 3-acetyl-5-(2′,3′-di-*O*-acetyl-β-D-threofuranosyl)furan, having a sugar-ring structure, which led to a diastereomeric mixture of the two *syn*-isomers.[6b,c] These results evidence both a concerted mechanism pathway, which accounts for the absence of trans-isomers, and a complete lack of facial diastereoselectivity in the [4+2] cycloaddition of singlet oxygen, which consequently leads to the diastereoisomeric mixture of *endo*-peroxides.[6b,c]

The same stereochemical trend has been observed starting from racemic mixtures of *endo*-peroxides, which occur in a stereospecific fashion affording only *syn*-diepoxides.[12,13]

On contrast, the dye-sensitized photooxygenation followed by thermal rearrangement of the peroxidic cycloadducts has been applied in the enantiospecific synthesis of (+)-crotepoxide and other natural biologically active epoxides.[14,15] In those cases, the presence of a chiral substituent on the diene provided a very high facial diastereoselectivity in the oxygen addition affording the less hindered *syn*-derivative.[14]

Thus, the concerted mechanism invoked in this rearrangement and the presence here of only one diepoxide **4** suggest the formation of the only *endo*-peroxide **2** and, hence, a very high facial diastereoselectivity in the [4+2] cycloaddition of singlet oxygen to the furan ring likely due to the concomitant presence of the sugar and a crowded COOMe at 2,5-positions of the starting heterocycle.

On the basis of these remarks, and the ^{1}H NMR spectrum recorded immediately after the sample was warmed to rt,[§] we assigned the *syn*-configuration[¶] to the two epoxide groups in **4**. In addition, since the cycloaddition is an endothermic process, we tentatively assigned the (1*R*,2*R*:3*S*,4*R*) configuration to *syn*-diepoxide **4**,[‖] which is accessible from the (1*S*,4*R*)-*endo*-peroxide **2**, through a concerted mechanism (Fig. 1).

Indeed, geometry optimization by the HF/6.31G* method performed on the two diastereoisomeric cycloadducts **2** showed that (1*S*,4*R*)-*endo*-peroxide **2** is more stable than the (1*R*,4*S*)-**2** of 8.40 kcal/mol (Fig. 2).[††]

[†] The $^3J_{1,2}$ of 4.7 Hz was measured by recording the ^{1}H NMR in C_6D_6, the signal of H-1′ in $CDCl_3$ overlapping with that of H-3′. The value fits in with the other reported β-structures, as for example, showdomycin[11] ($^3J_{1,2}$=4.9 and 3.9 Hz for β and α-anomers, respectively), bearing electron-withdrawing residues at the anomeric carbon.

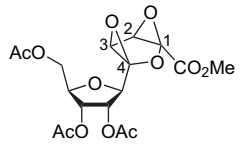
[‡] The yield of isolated **4** was found to be lower than that observed by ^{1}H NMR spectroscopy in the crude mixture owing to a partial decomposition during the chromatography.

[§] The ^{1}H NMR at rt of a freshly prepared sample of a photooxygenated mixture of **1** showed the signals of one transient species together with those of **3** and **4**, which over 30 min were the only present compounds.

[¶] Unfortunately, the value of 1 Hz for the observed H-2/H-3 proton coupling in **4** does not allow to establish positively the cis-configuration, owing to the presence of many heteroatoms as well as the electron-withdrawing methyl ester at the C-1, which decrease the spin–spin coupling magnitude.

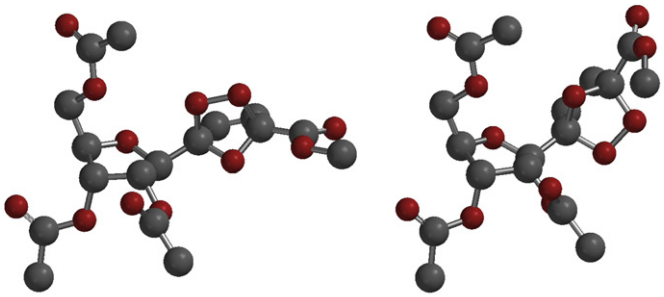
[‖] The numbering showed was used to expedite the stereochemical correlations between **2** and **4** structures.

[††] Theoretical calculation was performed by SPARTAN '06 Quantum Mechanics Program. The optimizations (method: RHF—Basis set: 6-31G*) performed starting from a minimized conformer (conformational analysis by MMFF-molecular mechanics) assigned a SCF total energy of −974,742.85 kcal/mol and of −974,751.25 kcal/mol to (1*R*,4*S*)-**2** and (1*S*,4*R*)-**2**, respectively.



(1R,2R:3S,4R)-**4**

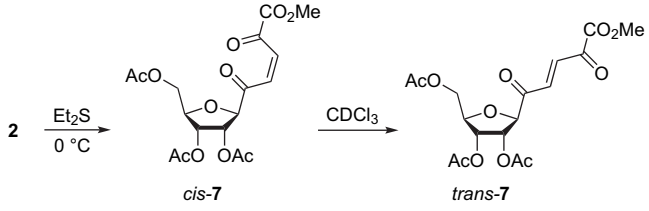
Figure 1. *syn*-Diepoxide C-nucleoside **4**.



(1S,4R)-**2** (1R,4S)-**2**

Figure 2. Optimized geometries for the diastereoisomeric ribofuranosyl *endo*-peroxides **2** by HF/6.31G* method.

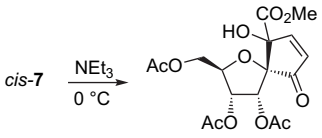
When precooled Et_2S was added at 0 °C to the crude photooxygenated mixture, NMR spectroscopic analysis of a sample in $CDCl_3$ showed the presence of (*E*)-methyl 5-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-2,5-dioxopent-3-enoate **7**. It was formed by isomerization in $CDCl_3$ of *cis*-**7**, which was unstable, as previously observed for other similar unsaturated system.[6,7,9] Indeed, the ^1H NMR spectrum of the same reaction mixture recorded in C_6D_6, showed both *cis*-**7** and *trans*-**7** in ca.4:1 molar ratio (Scheme 4).[‡‡] After 12 h at rt, the *trans*-**7** amount was slightly increased to the expense of cis-isomer. The isomerization of *cis*-**7** was therefore due to both the mild acidity of deuterated chloroform and, in a minor extent, to the temperature.



Scheme 4.

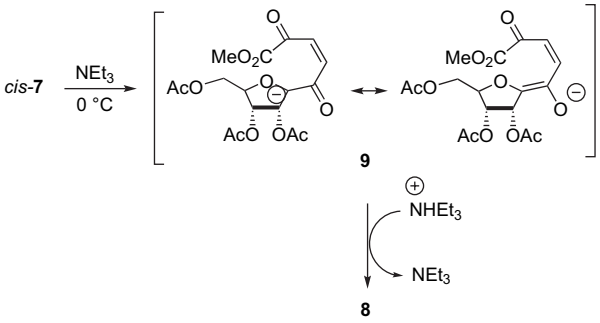
We wished to use the highly functionalized α,β-unsaturated **7** as starting compound for modified nucleosides, as previously described.[8,10] The (*Z*) to (*E*)-isomerization avoided the possibility of synthesizing the corresponding pyridazine C-nucleoside by addition of hydrazine hydrochloride. Moreover, the [3+2] cycloaddition with diazomethane failed affording only polymeric material, probably due to the high reactivity of the α keto ester function.

A peculiar result was obtained when a catalytic amount of NEt_3 was added to a crude sample of *cis*-**7** at 0 °C. After 30 min, the ^1H NMR spectrum showed the presence of a new product, which was isolated by silica gel chromatography. The structure of spirocyclic C-nucleoside **8** was assigned on the basis of 1D and 2D NMR data (Scheme 5).[§§] In particular, in the ^1H NMR spectrum the signal of the anomeric proton was absent. The cyclopentenonic structure was deduced by the presence, in the proton spectrum, of two characteristic doublets at δ_H 6.48 and 7.16 (J=6.6 Hz) and in the ^{13}C NMR spectrum of the corresponding two doublets δ_C 136.8 and 154.7, respectively, and of three quaternary carbons at δ_C 82.8, 94.5 and 197.4 for the oxygenated C-1, C-5 and ketone carbon, respectively.[¶¶]



Scheme 5.

As reported for other ribofuranosides analogous to **7**, it is likely that the base promotes the formation of a stabilized enolate anion at the anomeric carbon.[10] The intermediate **9** then undergoes a nucleophilic intramolecular attack of the C-1 to the high electrophilic carbonyl group leading to the novel spirocyclic C-nucleoside **8** (Scheme 6).



Scheme 6.

Only one isomer of **8** was found. Attempts to assign the stereochemistry of both C-1 and newly formed chiral carbon by NOESY experiments failed. The high diastereoselectivity could be due to steric reasons, which should favour the isomer with the methoxycarbonyl group opposite to the 2-acetyl group. Moreover, the chemical shift of the OH group in the ^1H NMR spectrum is not affected by $CDCl_3$ dilution. This suggests an intramolecular hydrogen-bond between the O–H donor and the ribofuranose oxygen affording a five-membered stable ring. This interaction occurs when the hydroxy group at C-5 is placed in the back at the same side of the sugar-ring oxygen. These two arguments suggest the *R*,*R*-configurations at C-1 and C-5 of **8** as shown in Figure 3.

A control experiment performed by adding catalytic amounts of NEt_3 to the *trans*-**7** showed that this isomer did not react, the ^1H NMR spectrum showing the presence of the unchanged trans-isomer **7**.

3. Conclusion

In conclusion, the work reports results on the dye-sensitized photooxygenation of the novel sugar furan **1**, which evidence a strong influence from the nature of furan substituents. Indeed, the presence of a methoxycarbonyl group promotes a thermal rearrangement of the corresponding *endo*-peroxide affording the bis-epoxide C-nucleoside **4**, whose aglycone is structurally related to

[‡‡] Spectral data for *cis*-**7** were recorded in C_6D_6 solution on the crude reduction mixture subtracting the signals of trans-isomer **7**.

[§§] The numbering showed for structure **8** in Figure 3 was used to facilitate the reading of spectral data (see Section 4).

[¶¶] The ^1H and ^{13}C NMR signals of the aglycone in **8** appeared to be very similar to furanone **6** obtained by silica gel hydrolysis of the O-glycoside **3**.

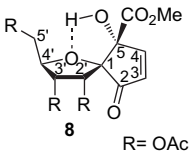


Figure 3.

the antitumoral (+)-crotepoxide.[14,15] Moreover, the work confirms the synthetic potential of glycosides such as **7**, which by base catalysis quantitatively leads to the novel stable spirocyclic nucleoside **8**. Work is in progress to deprotect the C-nucleoside **4** and screening for potential biological activities.

4. Experimental

4.1. General

Low-resolution electron impact mass spectra were obtained operating at 70 eV on a GCMS-QP5050A (Shimadzu). IR spectra were recorded on Nicolet Magna 750 FT-IR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, on a Fourier Transform NMR Varian 500 Unity Inova spectrometer. The carbon multiplicity was evidenced by DEPT experiments. The proton couplings were evidenced by HH-COSY experiments. The heteronuclear chemical shift correlations were determined by HMQC (optimized for $^1J_{HC}$, 140 Hz) and HMBC (optimized for $^1J_{HC}$, 8 Hz) pulse sequences. Analytical TLC was performed on precoated silica gel plates (Macherey-Nagel) with 0.2 mm film thickness. Spots were visualized by UV light and by spraying with EtOH/H_2SO_4 (95:5) followed by heating for 5 min at 110 °C. Column chromatography was performed on silica gel (0.063–0.2 mm) (Macherey-Nagel). Reagent-grade commercially available reagents and solvents were used.

4.2. General procedure of dye-sensitized photooxygenation

A 0.02 M solution of **1** (0.25 mmol) in dry CH_2Cl_2 was irradiated at −20 °C with a halogen lamp (650 W) in the presence of methylene blue (MB, 1×10^{-3} mmol), while dry oxygen was bubbled through the solution. The progress of each reaction was checked by periodically monitoring the disappearance of **1** by TLC, or by ^{1}H NMR spectroscopy.

*4.2.1. Methyl 5-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl)-2-furoate (**1**)*

To a stirred solution of 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose (2.00 g, 6.25 mmol) in dry CH_2Cl_2 (40 mL) under argon and in the presence of molecular sieves, methyl furan-2-carboxylate (4.730 g, 37.50 mmol) and a dichloromethane solution of $SnCl_4$ (1 M, 10 mL) were added at rt. After 4 h the reaction was quenched by the addition of $NaHCO_3$ solution (20 mL, satd aq) and the resulting mixture stirred for 5 min. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3×30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent evaporated in vacuo. Silica gel chromatography (50% EtOAc/hexane) gave the pure *title compound* **1** (1.44 g, 60%) as an oil. [Found: C, 52.75; H, 5.10. $C_{17}H_{20}O_{10}$ requires: C, 53.13; H, 5.25.] R_f (50% EtOAc/hexane) 0.50; IR (neat, ZnSe) ν 2918, 2847, 1744, 1219 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.11 (d, J=3.8 Hz, 1H, H-3), 6.48 (d, J=3.8 Hz, 1H, H-4), 5.62 (t, J=4.9 Hz, 1H, H-2′), 5.36 (m, 2H, H-1′ and H-3′), 4.46 (m, 1H, H-4′), 4.37 (dd, J=12.6, 2.7 Hz, 1H, H-5′$_B$), 4.18 (dd, J=12.6, 4.9 Hz, 1H, H-5′$_A$), 3.87 (s, 3H, OCH_3), 2.11 (s, 3H, CH_3CO), 2.06 (s, 3H, CH_3CO), 1.99 (s, 3H, CH_3CO) [selected signals: ^{1}H NMR (C_6D_6) δ_H 6.92 (d, J=3.4 Hz, 1H, H-3), 6.15 (d, J=3.4 Hz, 1H, H-4), 5.54 (t, J=4.7 Hz, 1H, H-2′), 5.20 (dd, J=5.8, 4.7 Hz, 1H, H-3′), 4.83 (dd, J=4.7, 1.5 Hz, 1H, H-1′), 4.35 (m, 1H, H-4′), 4.26 (s, 3H, OCH_3), 4.20 (dd, J=12.6, 3.4 Hz, 1H, H-5′$_B$), 4.00 (dd, J=12.6, 4.4 Hz, 1H, H-5′$_A$)]; ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 170.5 (s, CH_3CO), 169.7 (s, CH_3CO), 169.4 (s, CH_3CO), 158.8 (s, CO_2CH_3), 153.8 (s, C-5), 144.4 (s, C-2), 118.5 (d, C-3), 111.1 (d, C-4), 78.1 (d, C-4′), 75.2 (d, C-1′), 71.9 (d, C-2′), 71.8 (d, C-3′), 63.4 (t, C-5′), 51.8 (q, OCH_3), 20.3, 20.4 and 20.7 (3×q, 3×CH_3CO); MS m/z (%) 353 [M^+−31] (13), 352 [M^+−32] (18), 324 (42), 292 (50), 205 (73), 85 (100), 43 (87).

4.3. Thermal rearrangement of the 1,4-*endo*-peroxide 2: synthesis of C-nucleoside 4

When the photooxygenation reaction was complete (ca. 90 min), the solution was heated to rt. The ^{1}H NMR spectrum of an aliquot showed **3** and **4** in ca. 1:1 molar ratio (total yields >90%). After removal of the solvent, chromatography of the residue on silica gel afforded successively methyl 2-hydroxy-5-oxo-2,5-dihydrofuran-2-carboxylate (**6**) (20% EtOAc/hexane), 2′,3′,5′-tri-*O*-acetyl-D-ribofuranose (40% EtOAc/hexane) and the bis-epoxide **4** (70% EtOAc/hexane).

*4.3.1. (Z)-1-(2′,3′,5′-Tri-O-acetyl-β-D-ribofuranosyl) 5-methyl 4-oxopent-2-enedioate (**3**)*

Selected signals from the crude mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.73 (d, J=11.5 Hz, 1H, H-2), 6.44 (t, J=3.0 Hz, 1H, H-1′), 6.40 (d, J=11.5 Hz, 1H, H-3), 5.25 (d, J=3.0 Hz, 1H, H-2′), 3.89 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 185.6 (s, CO), 139.3 (d, C-2), 128.5 (d, C-3), 95.5 (d, C-1′), 82.4 (d, C-4′), 69.9 (d, C-2′), 63.2 (t, C-5′), 53.2 (q, OCH_3).

*4.3.2. Methyl 2-hydroxy-5-oxo-2,5-dihydrofuran-2-carboxylate (**6**)*

Yield 30%; oil; R_f (50% EtOAc/hexane) 0.40; IR (neat, ZnSe) ν 3402, 2925, 1736, 1218 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.19 (d, J=5.4 Hz, 1H, H-4), 6.33 (d, J=5.4 Hz, 1H, H-3), 4.98 (br s, 1H, OH), 3.88 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 169.3 (s, CO_2), 167.5 (s, CO_2CH_3), 149.9 (d, C-4), 125.2 (d, C-3), 100.5 (s, C-5), 53.4 (q, OCH_3).

*4.3.3. Methyl 6-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl)-3,5,7-trioxatricyclo[4.1.0.0.^{2,4}]heptane-4-carboxylate (**4**)*

Yield 40%; oil. [Found: C, 48.56; H, 4.62. $C_{17}H_{20}O_{12}$ requires: C, 49.04; H, 4.84.] R_f (50% EtOAc/hexane) 0.18; IR (neat, ZnSe) ν 2952, 1746, 1231 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.72 (dd, J=5.3, 4.9 Hz, 1H, H-2′), 5.30 (dd, J=8.6, 5.3 Hz, 1H, H-3′), 4.59 (d, J=4.9 Hz, 1H, H-1′), 4.32 (m, 2H, H-4′ and H-5′$_B$), 4.12 (dd, J=11.9, 4.2 Hz, 1H, H-5′$_A$), 4.09 (d, J=1.0 Hz, 1H, H-2), 3.90 (d, J=1.0 Hz, 1H, H-3), 3.83 (s, 3H, OCH_3), 2.09 (s, 3H, CH_3CO), 2.07 (s, 3H, CH_3CO), 2.06 (s, 3H, CH_3CO); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 170.5 (s, CH_3CO), 169.6 (s, CH_3CO), 168.9 (s, CH_3CO), 162.4 (s, CO_2CH_3), 98.9 (s, C-4), 92.4 (s, C-1), 78.5 (d, C-4′), 74.6 (d, C-1′), 71.2 (d, C-2′), 71.0 (d, C-3′), 62.9 (t, C-5′), 55.5 (d, C-2), 53.4 (q, OCH_3), 52.7 (d, C-3), 20.8 (q, CH_3CO), 20.4 (q, CH_3CO), 20.3 (q, CH_3CO); MS m/z (%) 416 [M^+] (3), 357 (3), 329 (7), 259 (38), 187 (32), 167 (49), 43 (100).

4.4. Methyl 5-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-2,5-dioxopent-3-enoate (7)

To a crude photooxygenated mixture of **1** at −20 °C, after the completion of the reaction, a precooled dichloromethane solution of Et_2S (2 equiv) was added, and the resulting mixture was kept at −20 °C overnight. Then, the solution was heated to rt and the

solvent and the unreacted Et_2S were removed under reduced pressure. Two different treatments of the residue were performed to characterize each isomer.

trans-**7**: The residue was taken-up with Et_2O and filtered to remove the sensitizer (MB). The ^1H NMR spectrum of the residue in $CDCl_3$, showed the presence, in addition to Et_2SO, of the only *trans*-**7** (yields >90%), which was isolated by silica gel chromatography (90% Et_2O/hexane) in 68% yield; oil. [Found: C, 50.65; H, 4.91. $C_{17}H_{20}O_{11}$ requires: C, 51.00; H, 5.04.] R_f (90% Et_2O/hexane) 0.20; IR (neat, ZnSe) ν 3031, 1735, 1627, 1233 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.56 (s, 2H, H-3 and H-4), 5.77 (t, J=4.9 Hz, 1H, H-2′), 5.33 (dd, J=7.12, 4.9 Hz, 1H, H-3′), 5.47 (d, J=5.5 Hz, 1H, H-1′), 4.97 (m, 1H, H-4′), 4.39 (dd, J=12.6, 3.3 Hz, 1H, H-5′$_B$), 4.18 (dd, J=12.6, 4.4 Hz, 1H, H-5′$_A$), 3.95 (s, 3H, OCH_3), 2.12 (s, 3H, CH_3CO), 2.03 (s, 3H, CH_3CO), 2.00 (s, 3H, CH_3CO); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 195.6 (s, CO), 182.6 (s, *C*OCO_2Me), 170.5 (s, CH_3CO), 169.4 (s, CH_3CO), 169.0 (s, CH_3CO), 160.9 (s, CO_2Me), 136.5 (d, C-4 or C-3), 131.7 (d, C-3 or C-4), 83.1 (d, C-1′), 79.1 (d, C-4′), 72.6 (d, C-2′), 71.4 (d, C-3′), 62.9 (t, C-5′), 53.4 (q, OCH_3), 20.7 (q, *C*H_3CO), 20.3 (q, 2×*C*H_3CO); MS *m*/*z* (%) 400 [M^+] (2), 341 [M^+-59] (6), 259 (30), 197 (10), 179 (60), 141 (3), 112 (22), 43 (100).

cis-**7**: The residue was taken-up with C_6D_6. The ^1H NMR spectrum at rt showed both the isomers (*cis*-**7**/*trans*-**7**=4:1 molar ratio; total yields >90%); *cis*-**7** (selected signals): ^1H NMR (500 MHz, C_6D_6) δ_H 6.43 (d, J=11.7 Hz, 1H, H-3 or H-4), 6.02 (d, J=11.7 Hz, 1H, H-3 or H-4), 5.62 (t, J=4.9 Hz, 1H, H-2′), 5.10 (dd, J=7.3, 4.4 Hz, 1H, H-3′), 4.18 (d+m, J=4.9 Hz, 2H, H-1′+H-4′), 4.13 (dd, J=11.7, 3.4 Hz, 1H, H-5′$_B$), 3.94 (dd, J=11.7, 4.4 Hz, 1H, H-5′$_A$), 3.30 (s, 3H, OCH_3), 1.76 (s, 3H, *C*H_3CO), 1.64 (s, 3H, *C*H_3CO), 1.60 (s, 3H, *C*H_3CO).

4.5. Methyl 3,4-bis(acetyloxy)-2-[(acetyloxy)methyl]-6-hydroxy-9-oxo-1-oxaspiro[4.4]non-7-ene-6-carboxylate (8)

A photooxygenated mixture of **1** was treated as above reported with Et_2S. When the reduction was complete, the crude mixture was heated to 0 °C. Then, 50 μL of NEt_3 was added to the mixture, which was kept at this temperature. After 1 h the reaction was complete (TLC), the solvent was removed under reduced pressure and the residue chromatographed on silica gel (70% EtOAc/hexane), affording the spirocyclic nucleoside **8**; yield 50%; oil. [Found: C, 50.60; H, 4.88. $C_{17}H_{20}O_{11}$ requires: C, 51.00; H, 5.04.] R_f (70% EtOAc/hexane) 0.64; IR (neat, ZnSe) ν 3490, 1735, 1219 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.16 (d, J=6.6 Hz, 1H, H-4), 6.48 (d, J=6.6 Hz, 1H, H-3), 5.72 (d, J=4.9 Hz, 1H, H-2′), 5.35 (dd, J=8.2, 4.9 Hz, 1H, H-3′), 4.48 (m, 2H, H-4 and H-5′$_B$), 4.30 (br s, 1H, OH), 3.98 (dd, J=12.6, 3.8 Hz, 1H, H-5′$_A$), 3.75 (s, 3H, OCH_3), 2.12 (s, 3H, *C*H_3CO), 2.06 (s, 3H, *C*H_3CO), 2.05 (s, 3H, *C*H_3CO); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 197.4 (s, *C*O), 170.9 (s, *C*O_2CH_3), 170.7 (s, CH_3CO), 169.5 (s, CH_3CO), 169.3 (s, CH_3CO), 154.7 (d, C-4), 136.8 (d, C-3), 94.5 (s, C-5), 82.8 (s, C-1), 79.2 (d, C-4′), 73.9 (d, C-2′), 69.9 (d, C-3′), 61.6 (t, C-5′), 54.4 (q, OCH_3), 20.7 (q, *C*H_3CO), 20.5 (q, *C*H_3CO), 20.4 (q, *C*H_3CO); MS *m*/*z* (%) 400 [M^+] (8), 341 [M^+-59] (13), 281 (10), 280 (8), 238 (35), 179 (67), 43 (100).

Acknowledgements

Financial support from MIUR (PRIN 2005–2007) is gratefully acknowledged. NMR experiments were run at the Centro di Metodologie Chimico-Fisiche, Università di Napoli Federico II.

Supplementary data

MS (EI) spectra, DEPT experiments, ^1H–^1H COSY experiments and heteronuclear chemical shift correlations by HMQC and HMBC pulse sequences for compounds **1**, *trans*-**7**, **4** and **8** and ^1H NMR spectrum of furanone **6**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.05.002.

References and notes

1. See for example: Specker, D.; Wittmann, V. *Top. Curr. Chem.* **2007**, *267*, 65; Krishna, P. R.; Reddy, V. V. R.; Srinivas, R. *Tetrahedron* **2007**, *63*, 9871; Franck, R. W.; Tsuji, M. *Acc. Chem. Res.* **2006**, *39*, 692; Gustafsson, T.; Hedenstroem, M.; Kihlberg, J. *J. Org. Chem.* **2006**, *71*, 1911; Wellington, K. W.; Benner, S. A. *Nucleosides Nucleotides Nucleic Acids* **2006**, *25*, 1309; Elgemeie, G. H.; Zaghary, W. A.; Amin, K. M.; Nasr, T. M. *Nucleosides Nucleotides Nucleic Acids* **2005**, *24*, 1227; Postema, M. H. D.; Piper, J. L.; Betts, R. L. *Synlett* **2005**, 1345; Lee, D. Y. W.; He, M. *Curr. Top. Med. Chem.* **2005**, *5*, 1333; Wu, Q.; Simons, C. *Synthesis* **2004**, *10*, 1533; Gumina, G.; Olgen, S.; Chu, C. K. *Antiviral Nucleosides* **2003**, 77; Ferrier, R. *J. Carbohydr. Chem.* **2003**, *34*, 248; Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913; Togo, H.; He, W.; Waki, Y.; Yokohama, M. *Synlett* **1998**, 700; Hacksell, U.; Daves, G. D., Jr. *Prog. Med. Chem.* **1985**, *22*, 1.
2. Postema, M. H. D. *C-Glycoside Synthesis*; CRC: London, 1995; Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: Oxford, 1995.
3. (a) Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.* **1989**, *111*, 2193 and references therein; (b) Dondoni, A.; Junquera, F.; Mercha'n, F. L.; Merino, P.; Scherrmann, M.-C.; Tejero, T. *J. Org. Chem.* **1997**, *62*, 5484; (c) Dondoni, A.; Marra, A.; Schermann, M. C. *Tetrahedron Lett.* **1993**, *34*, 7323.
4. (a) Maeba, I.; Iijima, T.; Matsuda, Y.; Ito, C. *J. Chem. Soc., Perkin Trans. 1* **1990**, 73; (b) Maeba, I.; Takeuchi, T.; Iijima, T.; Kitaori, K.; Muramatsu, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 649; (c) Maeba, I.; Kitaori, K.; Ito, C. *J. Org. Chem.* **1989**, *54*, 3927; (d) Maeba, I.; Takeuchi, T.; Iijima, T.; Furukawa, H. *J. Org. Chem.* **1988**, *53*, 1401; (e) Maeba, I.; Hara, O.; Suzuki, M.; Furukawa, H. *J. Org. Chem.* **1987**, *52*, 2368; (f) Maeba, I.; Iwata, K.; Usami, F.; Furukawa, H. *J. Org. Chem.* **1983**, *48*, 2998.
5. (a) Iesce, M. R.; Cermola, F.; Temussi, F. *Curr. Org. Chem.* **2005**, *9*, 109; (b) Iesce, M. R. *Synthetic Organic Photochemistry*; Griesbeck, A. G., Mattay, J., Eds.; Marcel Dekker: New York, NY, 2005; Vol. 12, p 299; (c) Scarpati, R.; Iesce, M. R.; Cermola, F.; Guitto, A. *Synlett* **1998**, 17.
6. (a) Lopez Aparicio, F. J.; Plaza Lopez-Espinosa, M. T.; Robles Diaz, R. *An. Quim., Ser. C* **1984**, *80*, 156; (b) Lopez Aparicio, F. J.; Robles Diaz, R.; Isac Garcia, J.; Calvo-Flores, F. G. *Carbohydr. Res.* **1986**, *148*, 235; (c) Robles Diaz, R.; Calvo-Flores, F. G.; Guardia, L. A.; Aparicio, F. J. L. *Carbohydr. Res.* **1989**, *191*, 209.
7. Cermola, F.; Iesce, M. R.; Montella, S. *Lett. Org. Chem.* **2004**, *1*, 271.
8. (a) Bloodworth, A. J.; Eggelte, H. J. *Singlet Oxygen*; Frimer, A. A., Ed.; CRC: Boca Raton, FL, 1985; Vol. II, p 165; (b) Graziano, M. L.; Iesce, M. R.; Scarpati, R. *J. Chem. Soc., Chem. Commun.* **1981**, 720.
9. Cermola, F.; Iesce, M. R.; Buonerba, G. *J. Org. Chem.* **2005**, *70*, 6503.
10. Cermola, F.; Iesce, M. R. *Tetrahedron* **2006**, *62*, 10694.
11. (a) Barrett, A. G. M.; Broughton, H. B. *J. Org. Chem.* **1986**, *51*, 495; (b) Hungerford, N. L.; Armitt, D. J.; Banwell, M. G. *Synthesis* **2003**, 1837.
12. Boyd, J. D.; Foote, C. S.; Imagawa, D. K. *J. Am. Chem. Soc.* **1980**, *110*, 3641.
13. (a) Graziano, M. L.; Iesce, M. R.; Scarpati, R. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2007; (b) Graziano, M. L.; Iesce, M. R.; Cinotti, A.; Scarpati, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1883; (c) Giordano, F.; Graziano, M. L.; Iesce, M. R. *J. Chem. Soc., Perkin Trans. 2* **1988**, 773.
14. Shing, T. K. M.; Tam, E. K. W. *Tetrahedron: Asymmetry* **1996**, *7*, 353.
15. Shing, T. K. M.; Tam, E. K. W. *J. Org. Chem.* **1998**, *63*, 1547.