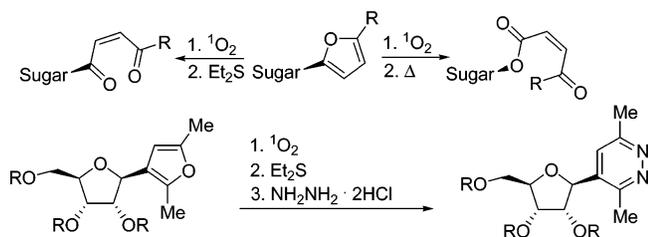# JOC*Note*

Dye-Sensitized Photooxygenation of Furanosyl Furans: Synthesis of a New Pyridazine *C*-Nucleoside

Flavio Cermola,* M. Rosaria Iesce, and
Gianluca Buonerba

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

cermola@unina.it

Received March 4, 2005

The dye-sensitized photooxygenation of furanosyl furans easily affords *C*- or *O*-glycosides with cis-α,β-unsaturated 1,4-dioxo aglycones. The reaction, performed on a ribofuranosyl furan, provides a useful new entry to a novel pyridazine *C*-nucleoside that can be achieved through a simple one-pot procedure.

C-Nucleosides are compounds of great interest owing to their potential biological activity together with their higher stability than nucleosides.[1–5] The research of new synthetic procedures for this compound class is a field of organic chemistry continuously explored. Generally, the synthetic approach is based on coupling reactions between a glycosyl-donor and a heterocycle as well as on the elaboration of a preexistent residue that is selectively converted into the desired aglycone.[6] In the framework of the latter strategy,[6a] the use of furan is well-known.[7,8]

Recently, we have tested the use of the dye-sensitized photooxygenation on some glucopyranosyl furans with the aim to introduce this procedure as additional methodology toward new and functionalized glycosides.[9]

SCHEME 1[a]

a; R= H
b; R= Me

[a] Conditions: (i) furan (6 equiv), SnCl₄ (1.6 equiv), CH₂Cl₂, 4 h (for **1a**); 2-methylfuran (1 equiv), SnCl₄ (1.6 equiv), CH₂Cl₂, 2 h (for **1b**); (ii) 2,5-dimethylfuran (1 equiv), SnCl₄ (1.6 equiv), CH₂Cl₂, 1 h.

Here, we extend the procedure to five-ring sugar furans to provide a new synthetic entry for novel *C*-nucleosides. First, we verify the chemical behavior of furanosyl furans **1a,b** under photooxygenation conditions and, finally, we report a one-pot procedure for a novel pyridazine *C*-nucleoside.

The furanosyl furans **1**, previously unknown, were prepared starting from the 2,3,5-tri-*O*-benzyl-1-*O*-(4-nitrobenzoyl)-D-arabinofuranose (for **1a,b**), and from the 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose (for **1c**), all commercially available (Scheme 1).[10,11] The reactions afforded a mixture of the α and β-anomers of **1** (α: β/1:3, 1:2 and 1:8 molar ratio for **1a**, **1b** and **1c**, respectively)[12] so showing a different stereochemical trend from that observed in the synthesis of glucosyl furans[9] which were obtained in α-configuration.

Thus, we start with the methylene blue-sensitized photooxygenation in dichloromethane at −20 °C of the arabinofuranosyl furan **1a** as an α- and β-anomeric mixture in a 1:6 molar ratio. When the reaction was

(1) (a) Suhadolnik, R. J. *Nucleoside as Biological Probes;* John Wiley & Sons: New York, 1979; (b) Suhadolnik, R. J. *Nucleoside Antibiotics*; Wiley-Interscience: New York, 1979.
(2) Simons, C. *Nucleoside Mimetics Their Chemistry and Biological Properties;* Gordon and Breach Science Publisher: Australia, Canada, 2001.
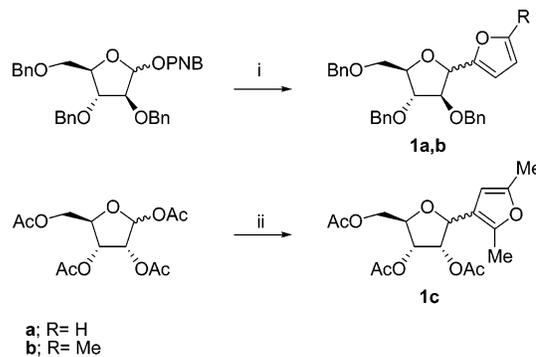(3) Peasley, K, *Med. Hypotheses* **2000**, *55*, 408.
(4) Townsend, L. B. *Chemistry of Nucleosides and Nucleotides*; Plenum Press: New York, 1994; pp 421–535.
(5) Miller, P. S. Antisense/Antigene Oligonucleotides. In *Bioorganic Chemistry-Nucleic Acids*; Hecht, S. M., Ed.; Oxford Univerisity Press: New York, 1996; pp 347–274.
(6) (a) Postema, H. D. M. *C-Glycoside Synthesis*; CRC Press: London, 1995. (b) Du, Y.; Linhardt, R. J. *Tetrahedron* **1998**, *54*, 9913. (c) Wu, Q.; Simons, C. *Synthesis* **2004**, 1533.
(7) (a) Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.* **1989**, *111*, 2193 and references therein. (b) Dondoni, A.; Junquera, F.; Merchán, F. L.; Merino, P.; Scherrmann, M.-C.; Tejero, T. *J. Org. Chem.* **1997**, *62*, 5484.

(8) (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.
(9) Cermola, F.; Iesce, M. R.; Montella, S. *Lett. Org. Chem.* **2004**, *1*, 271.
(10) *C*-Glycosides **1** were synthesized using 6 equiv (for **1a,c**) and 1 equiv (for **1a**) of the related furan. The use of a large amount of 2-methylfuran for **1b** has to be avoided. Indeed, when 6 equiv of the 2-methylfuran was used, the reaction afforded only an open-chain product deriving from a further furan addition to the furanoside ring (unpublished results).
(11) NMR data for all new compounds are consistent with the assigned structures. Spectra were recorded at 500 MHz for [¹H] and 125 MHz for [¹³C]. The carbon multiplicity was determined by DEPT and the proton coupling by ¹H−¹H COSY experiments. The heteronuclear chemical shift correlations were determined by HMQC and HMBC pulse sequences.
(12) Stereochemistry was assigned on the basis of both the ³J_{H1−H2} and the ¹H and ¹³C chemical shifts of the anomeric-H1 and C1 and by comparison with the data reported in the literature for α- and β-glycoside derivatives: (a) Mizutani, K.; Kasai, R.; Nakamura, M.; Tanak, O. *Carbohydr. Res.* **1989**, *185*, 27. (b) Agrawal, P. K. *Phytochemistry* **1992**, *31*, 3307.

SCHEME 2

a; R= H
b; R= Me
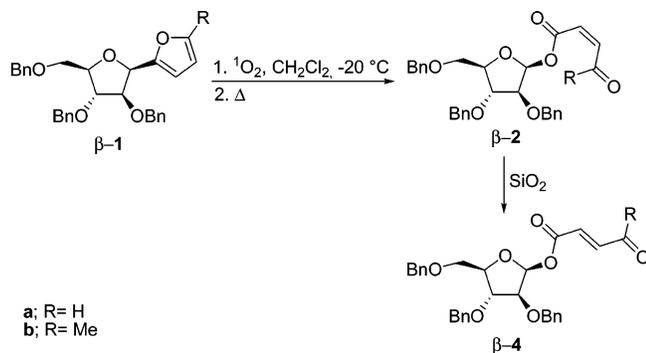
SCHEME 3
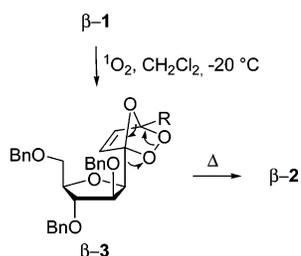
complete (90 min, TLC), the solution was warmed to rt. The ^{1}H NMR showed the presence of the only *cis-O*-furanoside **2a** (>90%) as an α,β-anomeric mixture in the same molar ratio as the starting **1a**. When the photooxygenation was performed under the same conditions starting from the only β-**1a**, only the β-**2a** was obtained (Scheme 2). These results showed that the intermediate endoperoxides **3** deriving from the cycloaddition of singlet oxygen to furanosyl furans undergo a selective thermal rearrangement to the corresponding O-derivatives as observed for the glucopyranosyl analogues (Scheme 3). Moreover, the stereochemical trend confirmed that the Baeyer−Villiger type-rearrangement occurs with complete retention of the configuration, as previously suggested.[9] On contact with chromatographic adsorbents, compound **2a** isomerized into *trans*-**4a**, and the extent of the isomerization strictly depended on the time employed for the analysis. Similar results were obtained starting from the 2,5-disubstitued furan β-**1b** (Scheme 2).

The new *C*-glycosides **5a,b** were obtained by carrying out the photooxygenation of β-**1a,b** in methanol[13] at −20 °C and, when each reaction was complete, by adding Et$_2$S to the crude mixture, kept at this temperature.

(13) Methanol as a solvent is particularly attractive for α,α′-disubstituted furans, for example **1b**, since it adds to the corresponding endoperoxides leading to 5-hydroperoxy-2,5-dihydrofurans (below), which are more stable than the parent peroxides. Moreover, these hydroperoxides are readily deoxygenated by alkyl sulfides to the cis-α,β-unsaturated 1,4-dicarbonyl compounds, and the reduction can be carried out on the crude methanolic solution.
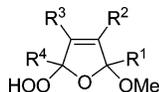
In the other cases, when alcohol addition fails, e.g., with endoperoxides of α,α′- or α-unsubstituted furans as **1a**, methanol can also be used while maintaining the temperature at low values to avoid thermal rearrangement of the endoperoxide intermediate (Iesce, M. R.; Cermola, F.; Temussi, F *Curr. Org. Chem.* **2005**, *9*, 109−139).

SCHEME 4

a; R= H
b; R= Me
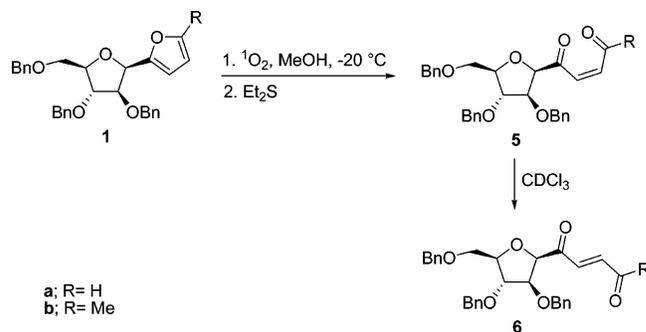
Compound **5** was configurationally unstable and in CDCl$_3$ rapidly isomerized into the corresponding *trans*-**6**, which could not be isolated by silica gel chromatography (Scheme 4).[14]

With the aim to achieve configurationally stable and more manageable *cis*-1,4-diketones as aglyconic residues, we carried out the photooxygenation of β-**1c** in dichloromethane at −20 °C, which was complete after 30 min (TLC). The ^{1}H NMR of an aliquot warmed to rt showed the presence of two compounds to which we tentatively assigned the structure of the diastereomeric endoperoxides β-**3c**.[15] The ^{1}H NMR spectrum in fact showed a complex pattern of signals among which were two singlets at δ 6.19 and 6.26 ppm in a 1:6 ca. molar ratio. The peroxidic nature was revealed by Et$_2$S addition, which quantitatively afforded the *C*-ribofuranoside **5c** (Scheme 5).[16]

As expected, the diketone **5c** was configurationally stable, and since it decomposed slightly on contact with chromatographic adsorbents, it was characterized by one- and two-dimensional NMR spectroscopy recorded on the crude mixture. Thus, after removal of the solvent, to a dry methanol solution of the crude β-**5c** was added hydrazine hydrochloride, and the resulting solution was kept at rt under stirring. After 3 days, the workup afforded the new pyridazine *C*-nucleoside β-**7c**, which was isolated by silica gel chromatography (Scheme 5). The MB-sensitized photooxygenation in methanol[13] followed by addition of Et$_2$S and, successively, of hydrazine hydrochloride to the crude reaction mixture provided a simple one-pot procedure for the access to the nucleoside **7** (70% from furan **1c**).

In conclusion, in this work we extended the dye-sensitized photooxygenation to five-membered-ring sugar-

(14) Rapid isomerization in CDCl$_3$ was also observed in the glucoside series.[9] It is reasonable that it occurs for unsubstituted unsaturated 1,4-dicarbonyl derivatives.

(15) Thermal stability of endoperoxides of 2,5-dialkylfurans has been reported: Graziano, M. L.; Iesce, M. R.; Scarpati, R. *J. Chem. Soc., Chem. Commun.* **1981**, 720. On the other hand, the lack of the *O*-glycoside starting from **1c** was expected; indeed the Baeyer−Villiger-type rearrangement is reported not to occur for endoperoxides of 2,5-dialkylfurans. It has been demonstrated only for monosubstituted endoperoxides with an acyl group at C1 (Bloodworth, A. J.; Eggelte, H. J. In *Singlet Oxygen*; Frimer, A. A., Ed.; CRC Press: Boca Raton, FL, 1985; Vol. II, p 165) or with −CH$_2$OCOR groups (Kuo, Y.-H.; Shih, K.-S.; Lee, S.-M. *J. Photochem. Photobiol., A: Chem.* **1988**, 97). Thus, as for the *C*-glucoside analogues, the formation of **2** is probably due to the electrophilicity of the anomeric carbon of the sugar, which promotes this pathway also for both mono- and disubstitued **1a,b**.

(16) When Et$_2$S was added to an aliquot in CDCl$_3$, the ^{1}H NMR spectrum showed the disappearance of these two signals together with the appearance of the signals of **5c**. The cis relationship of the carbonyl groups in **5c** was unambiguously related to the bicyclic structure of the parent endoperoxides **3c**.

SCHEME 5
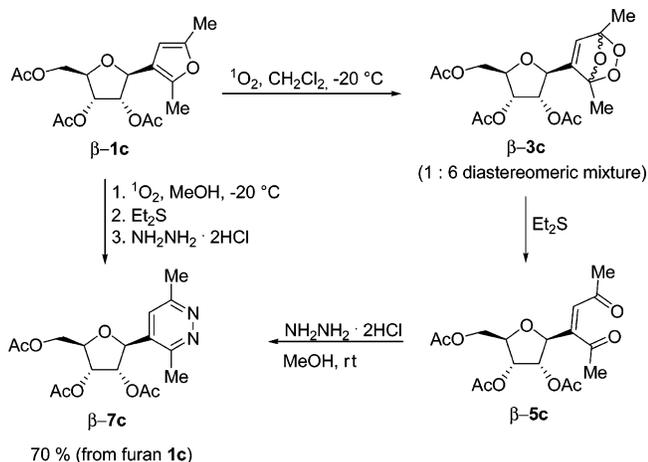
furans. The results confirm both the high diastereo-selectivity of the reaction, affording only the cis-unsaturated aglycones, and the stereospecificity of the sugar moiety migration in obtaining *O*-glycosides. Moreover, a simple one-pot procedure for a new pyridazine *C*-nucleoside is reported. Compound **7c** is structurally related to pharmacologically active analogues,[17] and only a few synthetic approaches to this compound class are reported in the literature. Hence, this work demonstrates the use of dye-sensitized photooxygenation of a glycosyl furan moiety as an additional methodology in the field of glycoside organic synthesis. Work is under progress to extend the procedure to a variety of *C*-nucleoside derivatives.

Experimental Section

The ^{1}H and ^{13}C NMR spectra, DEPT experiments, ^{1}H–^{1}H COSY experiments, and heteronuclear chemical shift correlations (HMQC and HMBC pulse sequences) were run on a 500 NMR spectrometer in CDCl$_3$.

General Procedure of Dye-Sensitized Photooxygenation. A 0.02 M solution of **1** (0.25 mmol) in dry CH$_2$Cl$_2$ 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 (TLC, or ^{1}H NMR) the disappearance of **1**. When the reactions were complete (ca. 60–90 min), the solutions were heated to rt (entry **a**) or 40 °C (entry **b**). Then, after removal of the solvent, each residue was taken up in Et$_2$O; the suspension was filtered to remove the insoluble sensitizer (MB), and the filtrate was evaporated to give *cis*-**2** (yields > 90%). The addition of silica gel to the crude photooxygenated mixtures and, after 60 min, the removal of silica gel and MB by filtration afforded trans compound **4** in ca. 70% yields.

cis-*β*-**2a:** ^{1}H NMR $\delta = 3.61$ (dd, $J = 10.3, 5.1$ Hz, 1 H, H-5$_A$), 3.64 (dd, $J = 10.3, 5.1$ Hz, 1 H, H-5$_B$), 4.03 (m, 1 H, H-3), 4.13 (s, 1 H, H-2), 4.40 (q, $J = 5.1$ Hz, 1 H, H-4), 4.50 (s, 2 H, PhC*H*$_2$), 4.54 (d, $J = 11.6$ Hz, 1 H, PhC*H*$_2$), 4.57 (s, 2 H, PhC*H*$_2$), 4.63 (d, $J = 11.6$ Hz, 1 H, PhC*H*$_2$), 6.35 and 6.36 (s + dd, $J = 11.4, 7.3$ Hz, 2 H, H-1 and H-2′), 6.59 (d, $J = 11.4$, 1 H, H-3′), 7.23–7.38 (m, 15 H, 3 x Ph), 10.53 (d, $J = 7.3$ Hz, 1 H, H-1′); ^{13}C NMR $\delta = 69.5$ (t, C-5), 72.10 (t, PhCH$_2$), 72.2 (t, PhCH$_2$), 73.4 (t, PhCH$_2$), 83.3 (d, C-3), 84.2 (d, C-4), 86.7 (d, C-2), 101.5 (d, C-1), 127.8, 127.9, 128.1, 128.3, 128.4 and 128.5 (d, CH of Ph), 133.0 (d, C-3′), 137.0, 137.3, 137.8 (s, C$_q$ of Ph), 141.0 (d, C-2′), 163.1 (s, CO$_2$), 192.2 (d, C-1′).

trans-*β*-**4a:** ^{1}H NMR (CDCl$_3$) $\delta = 3.62$ (m, 1 H, H-5$_A$ and 5$_B$), 4.00 (d, $J = 5.1$ Hz, H-3), 4.11 (s, 1 H, H-2), 4.40 (q, $J = 5.1$ Hz, 1 H, H-4), 4.49 (s, 2 H, CH of Ph), 4.52 (d, $J = 12.2$ Hz, 1 H, CH of Ph), 4.54 (s, 2 H, PhC*H*$_2$), 4.63 (d, $J = 12.2$ Hz, 1 H, CH of Ph), 6.35 (s, 1 H, H-1), 6.68 (d, $J = 16.5$ Hz, 1 H, H-3′), 6.97 (dd, $J = 16.5, 7.2$ Hz, 1 H, H-2′), 7.20–7.40 (m, 15 H, 3 x Ph), 9.76 (d, $J = 7.2$ Hz, H-1′); ^{13}C NMR (CDCl$_3$) $\delta = 69.5$ (t, C-5), 72.1 (t, PhCH$_2$), 72.2 (t, PhCH$_2$), 73.4 (t, PhCH$_2$), 83.4 (d, C-3), 84.1 (d, C-4), 86.7 (d, C-2), 101.6 (d, C-1), 127.7, 127.8, 127.9, 128.1, 128.3, 128.4, 128.5 (d, CH of Ph), 137.0, 137.4, and 137.8 (s, C$_q$ of Ph), 138.6 (d, C-3′), 141.0 (d, C-2′), 163.8 (s, CO$_2$), 192.1 (d, C-1′).

One-Pot Synthesis of 7c. A 0.02 M solution of **1c** (1 mmol) in dry MeOH was photooxygenated as reported in the general procedure. When the reaction was complete (30 min), 1.2 equiv of Et$_2$S was added to the crude methanol solution, and the resulting mixture was kept at rt under stirring for 60 min. Then, 1.2 equiv of hydrazine hydrochloride was added. After 3 days, the solvent was removed under reduced pressure, and the residue, dissolved in ethyl acetate, was extracted with a HCl solution 1 M (3×30 mL). The aqueous solution was neutralized with a NaOH solution until a basic condition was achieved and extracted with ethyl acetate (3×30 mL). The organic layer was washed with brine, dried with MgSO$_4$, and filtered. Silica gel chromatography (CHCl$_3$/MeOH 95:5 v/v) afforded the pyridazine *C*-**7c**: yield 70%; oil; ^{1}H NMR[18] $\delta = 2.10$ (s, 3 H, C*H*$_3$CO), 2.11 (s, 3 H, C*H*$_3$CO), 2.14 (s, 3 H, C*H*$_3$CO), 2.67 (s, 3 H, Me-3′), 2.69 (s, 3 H, Me-6′), 4.36 (m, 2 H, H-4 and H-5$_A$), 4.45 (dd, $J = 9.8, 3.8$ Hz, 1 H, H-5$_B$), 5.11 (m, 2 H, H-1 and H-2), 5.25 (t, $J = 5.2$ Hz, 1 H, H-3), 7.41 (s, 1 H, H-5′); ^{13}C NMR $\delta = 19.7$ (q, Me-3′), 20.4 (q, *C*H$_3$CO), 20.5 (q, *C*H$_3$CO), 20.8 (q, *C*H$_3$-CO), 22.1 (q, Me-6′), 63.0 (t, C-5), 70.8 (d, C-3), 75.7 (d, C-2), 77.6 (d, C-1), 79.7 (d, C-4), 123.0 (d, C-5′), 136.5 (s, C-4′), 155.2 (s, C-3′), 158.7 (s, C-6′), 169.2 (s, CO$_2$), 167.6 (s, CO$_2$), 170.4 (s, CO$_2$).

Supporting Information Available: General procedures, spectral and/or physical data for new compounds, ^{1}H and ^{13}C NMR spectra, DEPT experiments, ^{1}H−^{1}H COSY experiments, and heteronuclear chemical shift correlations by HMQC and HMBC pulse sequences for the pyridazine **7c**, together with mass spectra (EI) of compounds **1c**, **5c**, and **7c**. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) (a) Borowski, P.; Lang, M.; Haag, A.; Schmitz, H.; Choe, J.; Chen, H.-M.; Hosmane, R. S. *Antimicrob. Agents Chemother.* **2002**, *46*, 1231. (b) Cook, P. D.; Dea, P.; Robins, R. K. *J. Heterocycl. Chem.* **1978**, *15*, 1. (c) Joshi, U.; Josse, S.; Pipelier, M.; Chevallier, F.; Pradere, J.-P.; Hazard, R.; Legoupy, S.; Huet, F.; Dubreuil, D. *Tetrahedron Lett.* **2004**, *45*, 1031.

(18) ^{1}H NMR signals of the pyridazine **7c** undergo large shifts when the concentration of the CDCl$_3$ solution is changed. This is probably due to strong nonbonded intermolecular interactions between one of the heterocyclic nitrogens with the sufficiently acidic hydrogen at C5′ ($\delta = 7.41$ ppm).