Tetrahedron Letters xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Spiroketals of monosaccharides by dye-sensitized photooxygenation of furyl ketoses ☆

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ARTICLE INFO

Article history:
Received 14 October 2013
Revised 27 November 2013
Accepted 4 December 2013
Available online xxxx

Keywords:
Spiroketals
Photooxygenation
Singlet oxygen
Glycosyl furans
Sugars

ABSTRACT

[4+2] Cycloaddition of singlet oxygen to suitably substituted furans followed by reduction of the corresponding endoperoxides afforded functionalized enediones which quickly cyclized into the titled spiroketals. The reported method represents a green synthetic one-pot procedure for novel [6,6]-, [5,6]-, and [5,5]-spiroketals of sugars.

The spiroketal moiety represents a privileged substructure since it can be found in many simple or complex natural products characterized by important and assorted biological properties, from antibiotic to anticancer. Some examples are talaromycins,[1] avermectins,[2] spongistatin 1,[3] and milbemycins.[4] Although a wide array of ring sizes are possible, the most abundant motifs in Nature are [6,6]-, [6,5]-, and [5,5]-spiroketals. Accordingly, extensive investigation on the achievement of spiroketal derivatives is continuously active and, in addition to the classical route based on acid-catalyzed ring closure of oxo diols,[5] many other elegant strategies[6] and asymmetric syntheses[7] have been developed. Some approaches are based on the use of sugars as chiral synthons.[8] However, there are few synthetic strategies for spiroketals oxidized at the 2-position (Fig. 1).

Here, the use of sugar-furan based synthesis for novel spiroketals of monosaccharides is reported.

The strategy is based on the easy oxidability of the furan ring which provides a simple entry to 1,4-dienones. These compounds can be utilized for a large number of structural elaborations. For instance, oxidation of 2-(α-hydroxyalkyl)furans by *m*-CPBA or other oxidizing agents, known as Achmatowicz reaction, leads to the synthetically useful pyran core through an intramolecular cyclization of the corresponding enediones.[9]

1,4-Diketones can also be obtained by reaction of furans with singlet oxygen followed by reduction,[10] which represents a

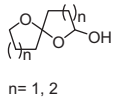
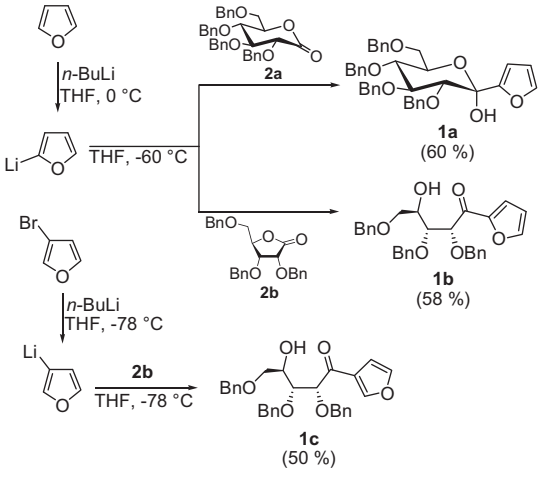


Figure 1. Spiroketals oxidized at C-2.



Scheme 1. Synthesis of furans **1a–c**.

☆ In the memory of Professor Rachele Scarpati (1927–2013).

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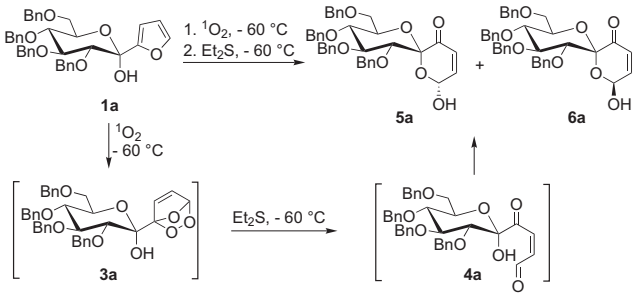
0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.12.009

stereoselective one-pot method for these versatile functionalized compounds.[11] Recently, the use of 1,4-diketones so obtained provided simple procedures for novel pyridazine[12,13] and pyrazoline[13] *C*-nucleosides, spirocyclic *C*-nucleosides,[14] and new functionalized exo-glycals.[13] The procedure has also been used in the synthesis of spiro compounds starting from hydroxyalkylfurans.[6d]

Here, the two-step reaction has been applied to sugar furans **1a**–**c** having a hemiketal function (Scheme 1).

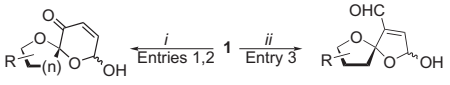
Furans **1a**–**c** were synthetized as shown in Scheme 1. Sugar lactones **2a**,**b** were obtained by Swern oxidation of the corresponding protected hemiacetals,[15] commercially available, and were used as glycosyl donors toward 2-furyllithium, for **1a**,**b** and 3-furyllithium for **1c**. Furan **1a** was obtained as α-anomer of a pyranoside structure,[16] while the novel furyl ketoses **1b**,**c** were found and isolated as open ketone forms.

The dye-sensitized photooxygenation of **1a**, followed by reduction, was carried out at −60 °C[17] and led almost quantitatively to a diasteromeric mixture of the new chiral [6,6]-spiroketals **5a** and **6a**



Scheme 2. Photooxygenation of **1a** and reduction of the endoperoxide **3a**.

Table 1
One-pot procedure for spiroketals



i: 1. $^1O_2$, -60 °C, CH_2Cl_2; 2. Et_2S (1.2 equiv.), -60 °C.
ii: 1. $^1O_2$, -60 °C, CH_2Cl_2; 2. Et_2S (1.2 equiv.), -60 °C; 3. SiO_2, r.t.

Entry	Furyl ketose	Spiroketals	Yield[a] (%)
1	**1a**	**5a** / **6a** 1 : 5 (2 : 1)[b]	80[c]
2	**1b**	**5b** / **6b** 1 : 7 (1.5 : 1)[b]	68[c]
3	**1c**	**5c** / **6c** 1 : 2	25

[a] Chromatographic yields.
[b] Molar ratio at the equilibrium at r.t.
[c] The ^1H NMR spectrum showed only the presence of the diastereoisomeric spiroketals.

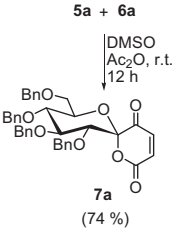
(Scheme 2), in a 1:5 molar ratio (Table 1).[18] They were in equilibrium and, after 48 h in $CDCl_3$ solution, the molar ratio was almost inverted (**5a**:**6a**/2:1). Prompt silica gel chromatography allowed a partial separation of each isomer. The different stereochemistry at the new hemiacetal center was evidenced carrying out a Swern oxidation on a mixture of **5a** and **6a** which quantitatively led to the sole expected spiroketal derivative **7a** (Scheme 3).[19]

Noesy experiments allowed to assign the structure **5a** with the (*R*)-configuration at the new stereocenter (C-2) to the more stable derivative which was the main product at the equilibrium (Fig. 2). These experiments also validated the α-configuration at the sugar-ring of both spiroketals, that is probably ensured by a thermodynamic control since two anomeric effects are in operation in a diaxial arrangement,[20] as previously reported in similar cases.[21]

Theoretical calculations[22] performed on both stereoisomers were in agreement with the experimental data suggesting that spiroketal **5a** is stabilized by an intramolecular hydrogen bond between the OH at C-2 and the sugar-ring oxygen, which is not feasible in isomer **6a**.

Starting from the open structure **1b**, the procedure afforded the new spiroketals **5b** and **6b** (1:7 molar ratio, respectively), probably through a double cyclization of the corresponding enedione **4b** (Scheme 4). Compounds **5b** and **6b** were in equilibrium and after 12 h, in solution at r.t., were present in a 1.5:1 molar ratio. Here, noesy experiments were unsuccessful and the structure of **5b** for the main product at the equilibrium was suggested by theoretical calculations[22a] which found a lower energy for **5b** than for **6b** of 2.3 kcal/mol. As observed for **5a**, the calculated structure for **5b** showed the presence of an intramolecular hydrogen bond between the OH and the sugar-ring oxygen.

Finally, the procedure was applied to furan **1c** and afforded the α,β-unsaturated compound **4c** which had an unsuitable configuration for cyclization. Anyway, silica gel chromatography promoted



Scheme 3. Oxidation of a mixture of **5a** and **6a**; synthesis of **7a**.

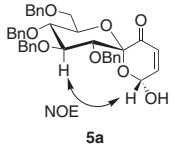
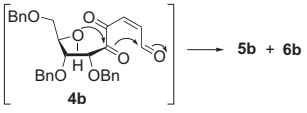
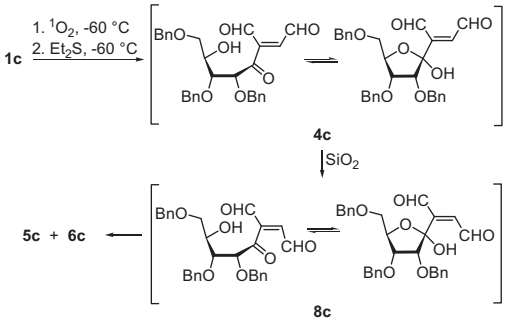


Figure 2. Recorded NOE effect in **5a** (H-2/H-3′).



Scheme 4. Double cyclization of the enedione **4b**.



Scheme 5. Synthesis of the [5,5]-spiroketals **5c** and **6c**.

an acid-catalyzed isomerization into the right enedione **8c** which quickly cyclized into the new spiroketals **5c** and **6c** (Scheme 5).

As suggested by theoretical calculations, to the main product we tentatively assigned the structure (2*S*)-**6c** which was more stable than (2*R*)-**5c** of 2.4 kcal/mol and showed a hydrogen bond between the OH at C-2 and the oxygen at C-2′ of the sugar ring.[22a]

In conclusion, the work reports a methodology based on a one-pot process for the synthesis of new chiral [6,6]-, [5,6]-, and [5,5]-spiroketals of sugars. The aglycone moiety is highly functionalized, and susceptible of further manipulations, as evidenced by the preliminary successful Swern oxidation to the novel spiroketal **7a**. This extends the scope of the reaction highlighting the possibility to construct more complex derivatives containing the spiroketal moiety inside.

Acknowledgments

Financial support from MIUR (PRIN 20109Z2XRJ_007) is gratefully acknowledged. NMR experiments were run at the Centro di Metodologie Chimico-Fisiche, Università di Napoli Federico II.

Supplementary data

Supplementary data (^1H–^1H COSY and NOESY experiments, heteronuclear chemical shift correlations by HMQC pulse sequences, ^1H and ^{13}C NMR for new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.009.

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17. Low temperature was necessary because endoperoxides of furans bearing encumbered groups at 2-position are quite unstable, and rearrange from C–C to C–O derivatives through a Baeyer–Villiger type-mechanism: (a) Cermola, F.; Iesce, M. R.; Montella, S. *Lett. Org. Chem.* **2004**, *1*, 271–275; (b) Cermola, F.; Iesce, M. R.; Astarita, A.; Passananti, M. *Lett. Org. Chem.* **2011**, *8*, 309–314.
18. *General Procedure.* A 0.02 M solution of **1** (0.25 mmol) in dry CH_2Cl_2 was irradiated at −60 °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 ^1H NMR) the disappearance of **1**. When the reaction was complete (ca. 90 min), 1.2 equiv of Et_2S was added to the crude solution, and the resulting mixture was kept at −60 °C for 2 h and then at −25 °C overnight. Thus, the solvent and the unreacted Et_2S were removed under reduced pressure.
19. *Spiroketals **5a** and **6a**.* A 0.02 M solution of **1a** (0.25 mmol) was treated as reported in the general procedure. The ^1H NMR spectrum of the residue showed only the presence of the two diastereisomeric spiroketals **5a** and **6a**. Silica gel chromatography (*n*-hexane/ethyl acetate 7:3 v/v) afforded spiroketal **6a** and successively **5a** in an overall yield of 80% (124 mg). Compound **5a**: IR ($CHCl_3$) ν 3425, 1695, 1640, 1601, 1452, 1273 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.36 (t, J = 9.3 Hz, 1H, H-6$_{A'}$), 3.41 (dd, J = 10.4, 9.3 Hz, 1H, H-4′), 3.71 (dd, J = 9.3, 1.6 Hz, 1H, H-6$_{B'}$), 4.09 (dd, J = 10.4, 9.8 Hz, 1H, H-3′), 4.15 (br s, 1H, OH), 4.27 (d, J = 9.8 Hz, 1H, H-2′), 4.48 (s, 2 H, CH_2 of Bn), 4.50 (d, J = 11.5 Hz, 1H, CH of Bn), 4.55 (m, 1H, H-5′), 4.63 (d, J = 10.9 Hz, 1H, CH of Bn), 4.78 (d, J = 10.9 Hz, 1H, CH of Bn), 4.83 (d, J = 10.9 Hz, 1H, CH of Bn), 4.90 (m, 2 H, CH_2 of Bn), 5.58 (dd, J = 12.7, 3.3 Hz, 1H, H-2), 6.18 (d, J = 10.3 Hz, 1H, H-4), 6.92 (dd, J = 10.3, 3.3 Hz, 1H, H-3), 7.15–7.38 (m, 20 H, 4× Ph); ^{13}C NMR ($CDCl_3$) δ 69.1 (t), 71.9 (d), 73.4 (t), 75.0 (t), 75.5 (t), 75.8 (t), 78.4 (d), 78.5 (d), 83.2 (d), 88.8 (d), 97.7 (s), 124.8 (d), 127.7 (d), 127.8 (d), 127.9 (d), 128.0 (d), 128.2 (d), 128.4 (d), 137.4 (s), 137.7 (s), 138.0 (s), 138.4 (s), 145.7 (d), 188.7 (s). Compound **6a**: IR ($CHCl_3$) ν 3432, 1695, 1643, 1600, 1450, 1276 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.68 (m, 3 H, H-6′$_A$, H-6′$_B$ and H-4), 3.85 (d, J = 10.8 Hz, 1H, OH), 4.04-4.17 (m, 3 H, H-2′, H-3′ and H-5′), 4.47–4.57 (m, 4H, CH_2 of Bn), 4.79 (d, J = 10.4 Hz, 1H, CH of Bn), 4.84 (d, J = 10.9 Hz, 1H, CH of Bn), 4.90 (s, 2H, CH_2 of Bn), 5.65 (br d, J = 10.8 Hz, 1H, H-2), 6.19 (dd, J = 10.4, 1.2 Hz, 1H, H-4), 6.87 (dd, J = 10.4, 1.6 Hz, 1H, H-3), 7.15–7.38 (m, 20 H, 4× Ph); ^{13}C NMR ($CDCl_3$) δ 68.5 (t), 73.4 (t), 74.0 (t), 75.0 (d), 75.7 (t), 75.9 (t), 78.0 (d), 79.5 (d), 82.6 (d), 87.7 (d), 98.3 (s), 127.0 (d), 127.7 (d), 127.8 (d), 128.0 (d), 128.3 (d), 128.4 (d), 137.3 (s), 137.9 (s), 138.1 (s), 138.4 (s), 147.9 (d), 188.6 (s). Anal. Calcd for $C_{38}H_{38}O_8$ on a diastereomeric mixture of **5a** and **6a**: C, 73.29; H, 6.15. Found: C, 73.12; H, 6.01. *Spiroketal **7a**.* A 0.5 mmol of a mixture of spiroketals **5a** and **6a** in ca. 1.3:1 molar ratio was dissolved in dry DMSO (1.4 mL). Then, acetic anhydride (0.8 mL) was added and the resulting solution was stirred at r.t. under argon atmosphere. After *ca* 12 h the reaction was quenched by adding H_2O (ca. 10 mL). The organic layer was extracted with $CHCl_3$, washed with H_2O (5 × 10 mL), dried on $MgSO_4$, and filtered. Then, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate 75:15 v/v) affording spiroketal **7a** as oil in ca. 74% yield (230 mg). IR ($CHCl_3$) ν 1745, 1690, 1600, 1440, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 3.64 (dd, J = 11.3, 1.8 Hz, 1H, H-6′$_A$), 3.77 (dd, J = 11.3 Hz, 3.9, 1H, H-6′$_B$), 3.82 (t, J = 9.4 Hz, 1H, H-4′), 4.08 (d, J = 9.7 Hz, 1H, H-2′), 4.20 (bt, J = 9.4 Hz, 2 H, H-3′ and H-5′), 4.48 (d, J = 12.6 Hz, 1H, CH of Bn), 4.51 (d, J = 11.5 Hz, 1H, CH of Bn), 4.58 (d, J = 12.6 Hz, 1H, CH of Bn), 4.61 (d, J = 10.0 Hz, 1H, CH of Bn), 4.84-4.90 (m, 4 H, 2× CH_2 of Bn), 6.70 (d, J = 10.3 Hz, 1H, H-4), 6.83 (d, J = 10.3 Hz, 1H, H-3), 7.14-7.34 (m, 20 H, 4× Ph); ^{13}C NMR ($CDCl_3$) δ = 67.9 (t), 73.3 (t), 74.7 (d), 75.0 (t), 75.2 (t), 75.8 (t), 77.0 (d), 79.8 (d), 82.1 (d), 101.7 (s), 127.5 (d), 127.6 (d), 127.7 (d), 128.3 (d), 135.0 (d), 136.9 (d), 137.4 (s), 137.9 (s), 138.2 (s), 159.2 (s), 187.5 (s). Anal. Calcd for $C_{38}H_{36}O_8$: C, 73.53; H, 5.85. Found: C, 73.41; H, 5.76.

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22. (a) Theoretical calculations were carried out by SPARTAN '08 Quantum Mechanics Program. The geometric optimizations (method: HF/3-21G) were performed starting from minimized conformers (conformational analysis by MMFF-molecular mechanics). Energies were calculated running single points by B3LYP/6.31G* method.; (b) Calculations found that (2R)-**5a** is more stable than (2S)-**6a** of 3.7 kcal/mol.