DOI: 10.1002/ejoc.200900427

Coupling Radical and Ionic Processes: An Unusual Rearrangement Affords Sugar and *C*-Glycoside Derivatives

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Keywords: Radical reactions / Rearrangement / Carbohydrates / Sequential processes / Photochemistry

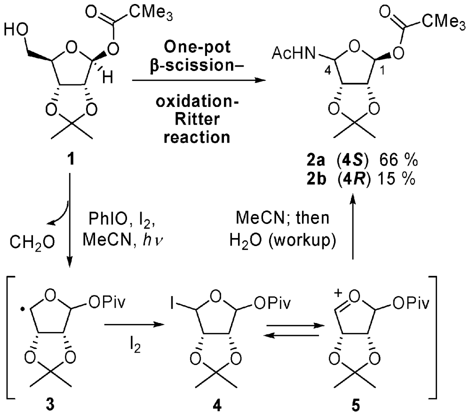
An unusual scission–rearrangement process, which couples radical and ionic reactions, was observed with galactofuranose derivatives. This one-pot procedure afforded, in good yields, highly functionalized 1,4-dioxanes, which could be considered as six-membered-ring sugar analogues. The synthesis of *C*-glycoside analogues is also possible with this methodology.

Introduction

The development of sequential processes,[1] which reduce the number of steps, avoid the isolation of intermediates and reduce waste, is a hot research area in sustainable chemistry. The application of such processes to the preparation of high-profit products from relatively inexpensive substrates is particularly interesting.

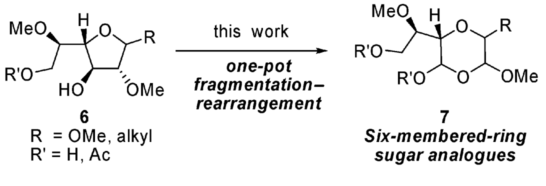
In this line, we have been studying sequential processes[2] (which combine radical with ionic reactions[3] and take place in mild conditions) that are compatible with most functional groups. These processes are very versatile and allow the conversion of carbohydrates, amino alcohols or α-amino acid derivatives into a variety of products (substituted cyclic ethers, unusual sugars, nucleoside analogues, alkaloid precursors, unnatural amino acids and modified peptides).

For instance, the ribose derivative **1** (Scheme 1) was converted into the 2,4-diacetals **2a** and **2b**, by using a one-pot fragmentation–oxidation-Ritter process.[4] Thus, when substrate **1** was treated with iodosylbenzene and iodine under visible light, a primary 5-alkoxyl radical was formed, which underwent β-scission to give the intermediate **3**. The latter reacted with iodine to yield an α-iodoacetal **4**.[5] Extrusion of iodine generated an oxycarbenium intermediate **5**, which was trapped by the solvent to afford compounds **2a**/**2b** (81% global yield) after aqueous workup.[4]



Scheme 1. Sequential processes that combine radical and ionic processes.

When *secondary* alkoxyl radicals are generated, both α,β-C–C bonds could be cleaved. To study the regioselectivity of the scission, we prepared different substrates with secondary hydroxy groups. In this preliminary communication, we report that galactofuranose derivatives **6** (Scheme 2) undergo a regioselective C^2–C^3 scission, followed by a rearrangement process, to give new sugar or *C*-glycoside analogues **7**.



Scheme 2. Unusual scission–rearrangement process yielding six-membered-ring sugar analogues.

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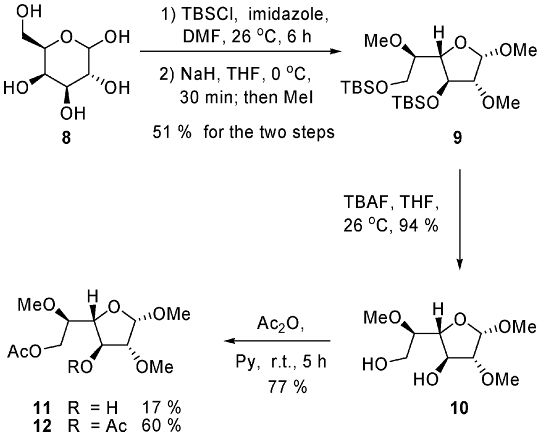
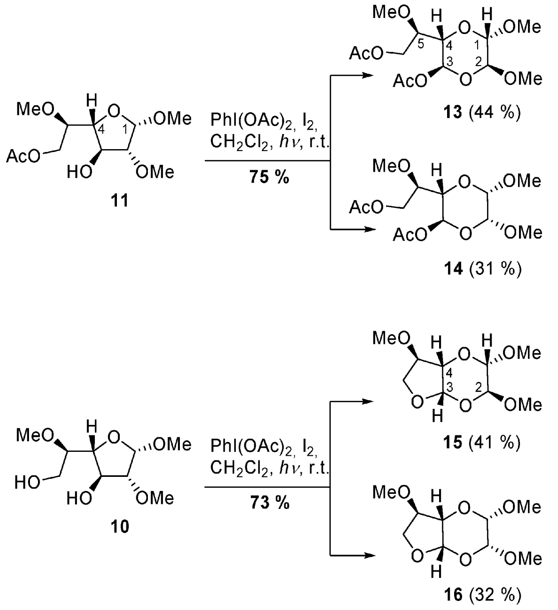
Results and Discussion

The galactofuranose substrates were prepared from commercial D-galactopyranose **8** (Scheme 3). Silylation with TBSCl, followed by methylation with NaH and MeI, afforded the galactofuranose **9**. This synthetic intermediate was desilylated to give diol **10**. The primary hydroxy group was protected by acetylation to yield compound **11**, as well as the diacetylated compound **12**.



Scheme 3. Preparation of galactofuranose substrates.

When compound **11** (Scheme 4) was treated with (diacetoxyiodo)benzene (DIB) and iodine in dichloromethane, under irradiation with visible light, two unexpected scission–rearrangement products were obtained, which were assigned the structures **13** and **14**. On the other hand, when the dihydroxy substrate **10** was subjected to the same conditions, two related rearrangement products **15** and **16** were obtained.



Scheme 4. Scission–rearrangement processes.

The stereochemistry of compounds **13**–**16** was determined with the use of the experimental ^{1}H NMR coupling constants (Table 1) and NOESY experiments (Figure 1). Further, X-ray analysis of product **15** (Figure 2) confirmed the proposed structure and configuration.

Table 1. Experimental ^{1}H NMR coupling constants [Hz].

J	13	14	15	16
$J_{1,2}$	4.3	1.6	3.7	1.4
$J_{3,4}$	7.0	8.3	3.7	3.5
$J_{4,5}$	3.0	3.0	2.1	1.5

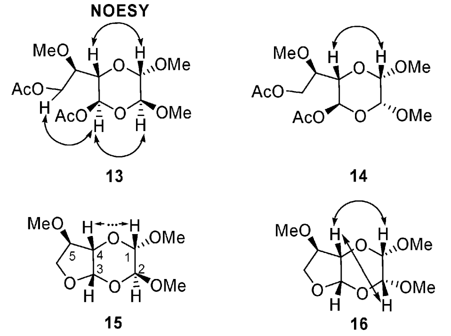


Figure 1. NOESY experiments of products **13**–**16** (weak interaction for **15**).

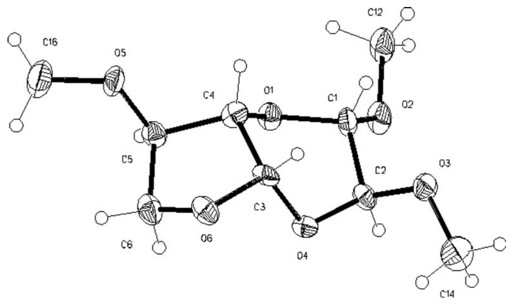
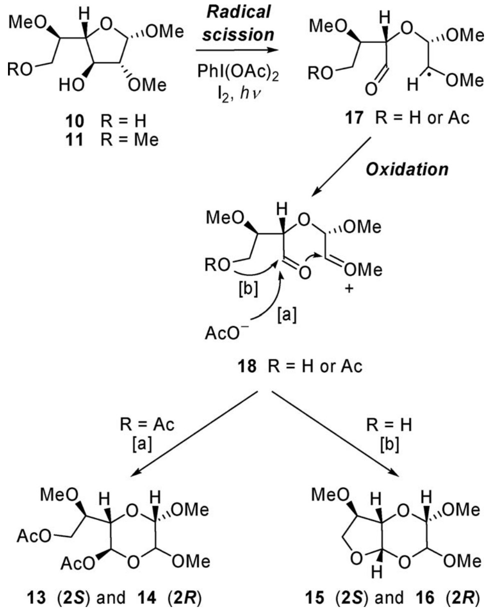


Figure 2. ORTEP representation of **15** with thermal displacement ellipsoids drawn at the 50% probability level.

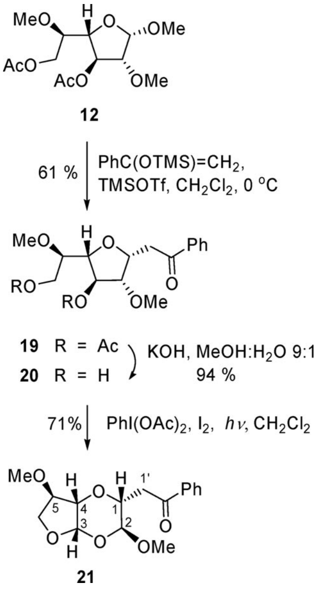
These results can be explained according to the mechanism shown in Scheme 5. Thus, the radical scission of substrates **10** or **11** generated *C*-radical **17**,[6] which underwent oxidation to an oxycarbenium ion **18**.[7] The oxygen atom from the carbonyl group at C3 acts as a nucleophile, and the resulting ion was trapped either by acetate from DIB (route [a]) or by the hydroxyl group on C6 (route [b]).[8] Route [a] affords compounds **13** and **14**, while route [b] yields the bicyclic products **15** and **16**. It should be noted that in the scission of the dihydroxylated substrate **10**, fragmentation of the secondary *O*-radical (which generates **15** and **16**) is much faster than the scission of the primary radical (no products derived from C^5–C^6 fragmentation were detected).[9] The formation of (2*S*) and (2*R*) derivatives in almost 1:1 ratio implies that the rotation of the C^1–C^2 bond in intermediates **17** or **18** is also fast.



Scheme 5. Possible mechanisms for the scission–rearrangement process.

Finally, the addition of acetate to C3 (route [a]) occurs on the face opposite the alkyl chain on C4 to give the 3,4-*trans* products **13** and **14**. On the contrary, when the hydroxyl group on C6 acts as the nucleophile (route [b]), the 3,4-*cis* products **15** and **16** were formed.

Products **13**–**16** are analogues of six-membered-ring sugars. In order to assess if this process could also afford analogues of *C*-glycosides,[10] 2-alkyl galactofuranose **20** (Scheme 6) was prepared from the diacetate **12** by alkylation of the anomeric position (to afford phenone **19**), followed by hydrolysis of the acetate groups (to yield alcohol **20**).[11] Substrate **20** was treated with DIB and iodine and irradiated with visible light. The scission–rearrangement process generated, in good yield, *C*-glycoside analogue **21**, whose configuration was assigned as (1*R*, 2*S*) (Table 2).



Scheme 6. Formation of a *C*-glycoside analogue.

Table 2. Experimental and theoretical[12] ^{1}H NMR coupling constants [Hz] for the possible isomers.

J	**21**	(1*R*,2*R*)	(1*R*,2*S*)	(1*S*,2*R*)	(1*S*,2*S*)
$J_{1,2}$	7.5	1.5	7.3	1.0	3.1
$J_{3,4}$	2.8	3.0	2.6	3.4	2.8
$J_{4,5}$	0.0	1.1	1.2	1.1	1.2

The formation of product **21** is remarkable, since several side reactions (such as the abstraction of 1′-H) could have taken place. However, the reaction was clean and no side-products were isolated. Therefore, this methodology would allow the efficient preparation of analogues of *C*-glycosides. The synthesis of other rigid *C*-glycoside analogues (as potential antiviral or cytotoxic compounds) is currently under way and will be reported in due time.

Conclusions

An unusual scission–rearrangement process, which couples radical and ionic reactions, was observed with galactofuranose derivatives. This one-pot procedure afforded six-membered-ring sugar analogues in good yields, which were characterized by spectroscopic methods and X-ray analysis. A possible mechanism for the process is discussed. The method can also be applied to prepare *C*-glycoside analogues.

Experimental Section

General Procedure for the Scission–Rearrangement Process: To a solution of the carbohydrate substrate (0.1 mmol) in dry dichloromethane (2 mL) was added iodine (25 mg, 0.1 mmol) and DIB (39 mg, 0.12 mmol). The resulting mixture was stirred for 2 h at 26 °C, under irradiation with visible light (80 W tungsten-filament lamp, available in DIY shops). The mixture was poured into 10% aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was dried on sodium sulfate and filtered, and the solvents evaporated under vacuum. The residue was purified by column chromatography on silica gel (hexanes/EtOAc).

13: isolated (44%) as a syrup. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 2.09 (s, 3 H), 2.12 (s, 3 H), 3.45 (s, 3 H), 3.46 (s, 3 H), 3.51 (s, 3 H), 3.52 (ddd, J = 2.9, 5.8, 5.9 Hz, 1 H, 5-H), 3.73 (dd, J = 3.0, 7.0 Hz, 1 H, 4-H), 4.28 (d, J = 5.9 Hz, 2 H, 6-H$_a$, 6-H$_b$), 4.40 (d, J = 4.3 Hz, 1 H, 1-H), 4.51 (d, J = 4.3 Hz, 1 H, 2-H), 6.11 (d, J = 7.0 Hz, 1 H, 3-H) ppm. ^{13}C NMR (125.7 MHz, CDCl$_3$): δ = 20.8 (CH$_3$, Ac), 20.9 (CH$_3$, Ac), 56.3 (CH$_3$, OMe), 56.6 (CH$_3$, OMe), 59.4 (CH$_3$, OMe), 62.4 (CH$_2$, C6), 72.9 (CH, C4), 76.5 (CH, C5), 88.0 (CH, C3), 99.6 (CH, C2), 100.6 (CH, C1), 169.1 (C, CO), 170.7 (C, CO) ppm. HMRS (EI): calcd. for $C_{12}H_{19}O_8$ [M$^+$ – OMe] 291.1080; found 291.1102.

14: isolated (31%) as a syrup. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 2.09 (s, 3 H), 2.13 (s, 3 H), 3.43 (s, 3 H), 3.54 (s, 3 H), 3.56 (m, 1 H, 5-H), 3.57 (s, 3 H), 3.74 (dd, J = 3.0, 8.4 Hz, 1 H, 4-H), 4.27 (dd, J = 6.0, 11.5 Hz, 1 H, 6-H$_a$), 4.31 (dd, J = 6.0, 11.5 Hz, 1 H, 6-H$_b$),4.57 (d, J = 1.7 Hz, 1 H, 1-H), 4.62 (d, J = 1.6 Hz, 1 H, 2-

H), 6.16 (d, J = 8.3 Hz, 1 H, 3-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 20.9 (2×CH_3, Ac), 55.7 (CH_3, OMe), 57.1 (CH_3, OMe), 59.1 (CH_3, OMe), 62.2 (CH_2, C6), 75.5 (CH, C4), 76.3 (CH, C5), 84.7 (CH, C3), 97.3 (CH, C2), 99.0 (CH, C1), 168.7 (C, CO), 170.7 (C, CO) ppm. HMRS (EI): calcd. for $C_{12}H_{19}O_8$ [M^+ – OMe] 291.1080; found 291.1081.

15: isolated (41%) as a crystalline solid. M.p. 72–73 °C (from EtOAc/*n*-hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.40 (s, 3 H), 3.50 (s, 3 H), 3.53 (s, 3 H), 3.93 (dd, J = 1.7, 9.9 Hz, 1 H, 6-H_a), 4.04 (ddd, J = 1.9, 1.9, 4.9 Hz, 1 H, 5-H), 4.10 (dd, J = 2.1, 3.6 Hz, 1 H, 4-H), 4.24 (d, J = 3.7 Hz, 1 H, 1-H), 4.29 (dd, J = 4.9, 9.9 Hz, 1 H, 6-H_b), 4.58 (d, J = 3.7 Hz, 1 H, 2-H), 5.39 (d, J = 3.7 Hz, 1 H, 3-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 56.0 (CH_3, OMe), 56.5 (CH_3, OMe), 57.1 (CH_3, OMe), 70.9 (CH_2, C6), 77.7 (CH, C4), 83.9 (CH, C5), 95.3 (CH, C3), 97.9 (CH, C2), 98.2 (CH, C1) ppm. HMRS (EI): calcd. for $C_8H_{13}O_5$ [M^+ – OMe] 189.0763; found 189.0753.

X-Ray Analysis of 15: $C_9H_{16}O_6$, M_r = 220.22, colourless needle crystal (0.50×0.21×0.06 mm) from EtOAc/*n*-hexane, monoclinic, space group *C*2 (no. 5), a = 14.892(8) Å, b = 4.395(2) Å, c = 16.651(9) Å, V = 1063.6(9) Å^3, Z = 4, $\rho_{calcd.}$ = 1.375 g cm^{-3}, F(000) = 472, μ = 0.116 mm^{-1}. 3841 measured reflections, of which 1251 were unique (R_{int} = 0.0866). The asymmetric unit of the structure is formed by one molecule of **15**. Because of a large su on the Flack parameter, the Friedel pairs were averaged in the refinement (MERG 4 command). Thereby, the absolute configuration of new chiral centres has been assigned by reference to other unchanging chiral centres of known absolute configuration in the synthetic procedure. Refined parameters: 139, final R_1 = 0.0588, for reflections with $I > 2\sigma(I)$, wR_2 = 0.1351 (all data), GOF = 1.019. The max/min residual electron density: +0.263/–0.262 e Å^{-3}. CCDC-725226 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

16: isolated (32%) as a syrup. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.39 (s, 3 H), 3.54 (s, 3 H), 3.56 (s, 3 H), 3.83 (d, J = 9.6 Hz, 1 H, 6-H_a), 4.00 (dd, J = 1.0, 3.9 Hz, 1 H, 5-H), 4.21 (dd, J = 1.4, 3.1 Hz, 1 H, 4-H), 4.35 (dd, J = 4.0, 9.6 Hz, 1 H, 6-H_b), 4.48 (d, J = 1.3 Hz, 1 H, 1-H), 4.52 (d, J = 1.4 Hz, 1 H, 2-H), 5.27 (d, J = 3.5 Hz, 1 H, 3-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 55.9 (CH_3, OMe), 56.8 (CH_3, OMe), 57.1 (CH_3, OMe), 70.1 (CH_2, C6), 77.0 (CH, C4), 84.4 (CH, C5), 94.6 (CH, C2), 96.6 (2×CH, C1 + C3) ppm. HMRS (EI): calcd. for $C_8H_{13}O_5$ [M^+ – OMe] 189.0763; found 189.0770.

21: isolated (71%) as a syrup. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.22 (d, J = 7.5 Hz, 1′-H_a), 3.23 (d, J = 4.5 Hz, 1′-H_a), 3.33 (s, 3 H), 3.49 (s, 3 H), 3.73 (d, J = 4.1 Hz, 1 H, 5-H), 3.84 (d, J = 9.8 Hz, 1 H, 6-H_a), 3.96 (ddd, J = 4.5, 7.4, 7.5 Hz, 1 H, 1-H), 4.08 (d, J = 2.8 Hz, 1 H, 4-H), 4.26 (dd, J = 4.2, 9.7 Hz, 6-H_a), 4.70 (d, J = 7.5 Hz, 1 H, 2-H), 5.47 (d, J = 2.8 Hz, 1 H, 3-H), 7.47 (dd, J = 7.6, 7.9 Hz, 2 H, Ph), 7.58 (dd, J = 7.4, 7.4 Hz, 1 H, Ph), 7.95 (d, J = 7.39 Hz, 2 H, Ph) ppm. ^{1}H NMR (500 MHz, C_6D_6): δ = 2.76 (s, 3 H), 2.95 (d, J = 4.5 Hz, 1′-H_a), 2.96 (d, J = 7.5 Hz, 1′-H_b), 3.26 (s, 3 H), 3.44 (d, J = 4.6 Hz, 1 H, 5-H), 3.75 (d, J = 9.6 Hz, 1 H, 6-H_a), 3.80 (d, J = 2.7 Hz, 4-H), 4.14 (dd, J = 4.3, 9.6 Hz, 6-H_a), 4.20 (ddd, J = 4.4, 7.4, 7.6 Hz, 1 H, 1-H), 4.78 (d, J = 7.5 Hz, 1 H, 2-H), 5.58 (d, J = 2.7 Hz, 1 H, 3-H), 7.01 (dd, J = 7.3, 7.8 Hz, 2 H, Ph), 7.09 (dd, J = 7.4, 7.4 Hz, 1 H, Ph), 7.79 (d, J = 7.1 Hz, 2 H, Ph) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 40.3 (CH_2, C1′), 56.3 (CH_3, OMe), 57.1 (CH_3, OMe), 71.0 (CH_2, C6), 72.0 (CH, C1), 76.2 (CH, C4), 83.9 (CH, C5), 98.0 (CH, C2), 98.8 (CH, C3), 128.2 (2×CH, Ph), 128.6 (2×CH, Ph), 133.3 (CH, Ph), 137.0 (C, Ph), 196.5 (C, CO) ppm. HMRS (EI): calcd. for $C_{15}H_{17}O_5$ [M^+ – OMe] 277.1076; found 277.1053.

Acknowledgments

This work was supported by the Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica, and Ministerio de Educación y Ciencia, Spain (Research Program CTQ2006-14260/PPQ). We also acknowledge financial support from FEDER funds. D. H. thanks the Gobierno de Canarias (Consejería de Industria) – CSIC for a research contract.

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[6] Only products derived from scission of the C^2–C^3 bond were isolated. The cleavage of the C^3–C^4 bond was not detected. Since both scissions would give radical intermediates of similar stability (secondary *C* radicals stabilized by alkoxy groups) and aldehyde derivatives as products, the causes for the regioselectivity are not clear. A possible explanation would be a better stabilization of the developing radical on C^2 by the 2-alkoxy group, since good orbital overlapping is possible. In contrast, the developing radical on C^4 would be less stabilized by the

nonbonding orbitals of the ring oxygen atom, since proper orbital alignment is not possible until bond cleavage is complete.

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[11] The phenone **19** was obtained as an optically pure product. However, an isomerization process took place with time (observable by NMR spectroscopy) to afford a mixture of epimers at C1. The same happened with the phenone **20**. Thus, to preserve the optical purity, product **19** was hydrolyzed and then immediately treated under the scission–rearrangement conditions to afford compound **21**, which was quite resistant to epimerization.

[12] Calculations were made using an AMBER force field model implanted in the Macromodel 7.0 program. The calculations were also performed with an MMFF force field, by using high-quality parameters. Similar results were obtained in both cases. The theoretical coupling constants were calculated over the minimized structures for all possible isomers, by using the Karplus–Altone equation implemented in Macromodel.

Received: April 17, 2009