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Diastereoselective synthesis of 1,2-*O*-isopropylidene-1,6-dioxaspiro[4,4]nonane applying the methodology of generation of radical cations under non-oxidizing conditions

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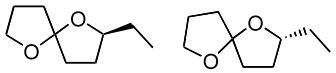
This manuscript is dedicated to the memory of our friend, Adelina González

Abstract—We report the stereoselective synthesis of an optically pure spiroketal via an intramolecular tandem hydrogen abstraction reaction promoted by an alkoxy radical. Expanding the use of alkene radical cation under non-oxidizing conditions in the synthetic scenario. © 2003 Elsevier Science Ltd. All rights reserved.

The generation of radical cations from β-(phosphatoxy)alkyl and β-(acetoxy)alkyl radicals under non-oxidizing conditions has been widely studied.[1] The importance of this finding not only has enormous implications on the understanding of the DNA degradation by anti-cancer agents such as bleomycin and enedyine agents,[2] but, on the synthesis of various heterocycles.[3] In this regard, Crich et al., have developed new access for the construction of tetrahydrofuran,[3a,b] pyrrolizidine,[3c] indolizidine[3d,e] and spiroacetal nucleus.[3f] Although, spiroacetal nucleus[3f] were synthesized for mechanistic purposes, yields were very low after purification. Thus, we decided to apply this methodology for the construction of a spiroketal nucleus. These nucleus are present in many molecular structures, and some exhibit pheromonal activity (Scheme 1).[4]

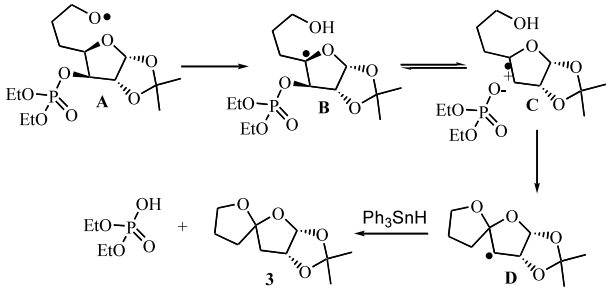
Our strategy was based on the tandem hydrogen abstraction cyclization sequence, promoted by an alkoxy radical (**A**).[3a] Radical (**A**) abstracted the hydrogen atom at C′4 position, and the alkyl radical formed (**B**) rapidly expelled the phosphate group affording (**C**). Then, the enol ether radical cation (**C**) was trapped by the hydroxy group, and finally, the reduction reaction afforded the expected spiroketal **3** (Scheme 2).

A convenient alkoxy radical precursor was the *N*-alkoxyphthalimide **4**. So, the synthesis of compound **4**, was started with a 'one pot' hydrolysis–oxidation and Wittig olefination of the 1:2,5:6-di-*O*-isopropylidene-α-D-glucose **5a** to give the corresponding α,β-unsaturated ester **6a** followed by a reduction reaction to afford **7**. The reduction of the double bond and carbonyl group of **6a** was performed first, with $H_2/Pd(OH)_2$, then with



1 **2**

Scheme 1. 2-Ethyl-1,6-dioxaspiro[4,4]nonane (**1** and **2**). Principal aggregation pheromone of *Pityogenes chalcographus*.



Scheme 2. Tandem hydrogen abstraction cyclization sequence.

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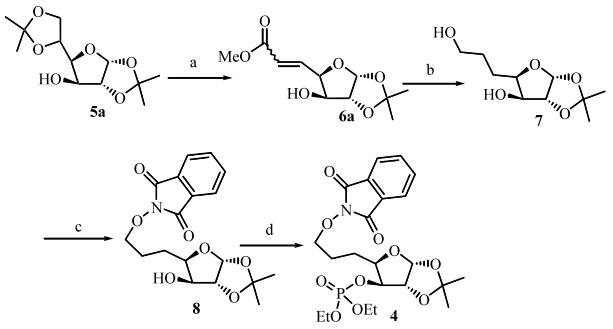
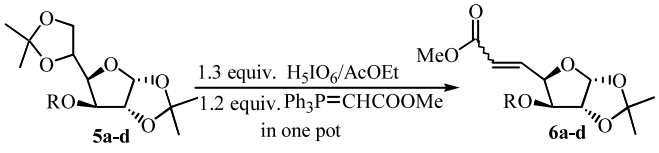
$LiAlH_4$.[5] Diol **7** was converted regioselectively to the primary *N*-alkoxyphthalimide **8** in good yield using the Mitsunobu protocol.[6] Finally, **8** was phosphorylated with diethylchlorophosphate in the presence of DMAP yielding the alkoxy radical precursor **4** (see Scheme 3).

The accessibility of the sequential hydrolysis–oxidation and Wittig olefination transformation of **5a** to the corresponding α,β-unsaturated ester **6a** in one pot prompted us to test this protocol to other 1:2,5:6-di-*O*-isopropylidene-α-D-glucose derivatives **5b–d**.[7] The selectivity of the double bond formation was modest and low, as previously some authors have reported when stabilized ylides and protected or unprotected α-alkoxyaldehydes are used[8] (see Table 1).



Scheme 3. *Reagents and conditions*: (a) i. 1.3 equiv. H_5IO_6/AcOEt; ii. 2.3 equiv. Ph_3P=CHCOOMe/THF (one pot) (86%); (b) i. H_2/$Pd(OH)_2$/AcOEt; ii. $LiAlH_4$/THF/rt (one pot) (88%); (c) *N*-hydroxyphthalimide/Ph_3P/DEAD/THF/rt/15 h (76%); (d) EtO_2POCl/DMAP/CH_2Cl_2/rt/24 h (72%).

Table 1. Sequential hydrolysis–oxidation–Wittig olefination (SHOWO)[a]



Entry	Compound	R	Product	*E*/*Z*	Yield
1[b]	**5a**	H-	**6a**	4/1.0[c]	86
2	**5b**	Me-	**6b**	1/1.4	83
3	**5c**	Bn-	**6c**	1/1.5	81
4	**5d**	MsO-	**6d**	1/3.0	80

[a] Yields were obtained after purification in column chromatographic and *E*/*Z* ratios were determined by ^1H NMR.
[b] 2.5 equivalents of ylide were added.
[c] *Z* olefin was obtained as an α,β-lactone.

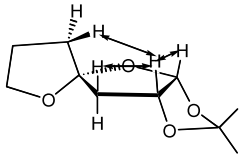
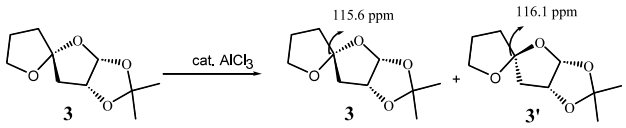


Figure 1. Representative NOESY interactions observed for the spiroketal **3**.



Scheme 4. $AlCl_3$-catalyzed spiroisomerization of **3**.

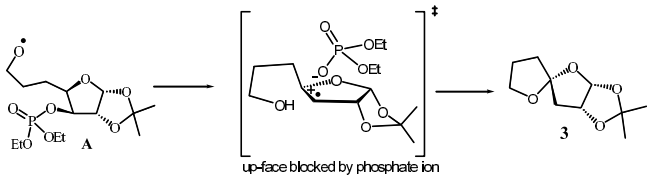


Figure 2. Intermediate ion pair model for the nucleophilic addition of the alkoxy radical **A** to the radical cation.

Tin hydride-mediated cleavage of the *N*-alkoxyphthalimide **4** was carried out using the Kim's[3a,9] protocol. Compound **4** was refluxed in benzene. Then, a solution of Ph_3SnH, and a catalytic amount of AIBN in benzene were added dropwise. The analysis of the reaction mixture by ^1H NMR showed the presence of only two products in a ratio 10:1 (based on the anomeric hydrogen), ^{13}C NMR spectrum showed only one ketalic carbon at 115.6 ppm. The major product corresponded to the expected spiroketal **3**[10] (in a 75% yield).

The stereochemistry of the spiroketal **3** was deducted by 2D NOESY experiments. The main cross-peak interactions are shown in Figure 1.

Unfortunately, after several attempts, we could not isolate the minor product. Nevertheless, we looked forward to prove that the minor product was not the diastereoisomeric spiroketal **3′**. So, we prepared **3′** adding a catalytic amount of $AlCl_3$ into the NMR tube containing spiroketal **3** in $CDCl_3$. The mixture was analyzed by ^{13}C NMR, and the ^{13}C NMR spectrum showed two ketalic carbons at 115.6 and 116.1 ppm (Scheme 4).

Thus, the regioselectivity and stereoselectivity outcome depend on two important factors. First, the remarkable favored [1,5] hydrogen abstraction over [1,6] hydrogen abstraction, due to the well-known entropic factors. Second, the contact ion pair and memory effects recently introduced by Crich and Ranganathan (see Fig. 2).[3e]

In conclusion, a novel protocol for dehomologation and transformation of 1:2,5:6-di-*O*-isopropylidene-α-D-glucose and some derivatives to the corresponding α,β-unsaturated esters (in one pot) was described. Besides, the introduction of a new way of generation of C′4 β-(phosphatoxy)alkyl radical was discussed. Finally, a novel method for the synthesis of spiroketals is described. In this regard, the applications of this methodology for the synthesis of optically pure spiroketals with pheromonal activity are currently underway and will be reported in due course.

Acknowledgements

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5. Protocol for the double bond and carbonyl groups reduction of the **5a** 'in one pot': A solution of **5a** (803 mg, 3.28 mmol) and palladium hydroxide, 20% wt (100 mg) in 20 mL of dry ethyl acetate was allowed to stir for 4 h under an hydrogen atmosphere. Then, solid catalyst was filtered and the organic phase was evaporated under reduced pressure. The colorless syrup obtained was dissolved in 20 mL of dry THF, LAH was added (377 mg, 9.9 mmol) at 0°C and the reaction mixture was allowed to stir for 2 h. The reaction was quenched by the slow addition of a mixture of H_2O and THF (1:1). Finally, the reaction mixture was dried with Na_2SO_4 and evaporated under reduced pressure to give **6a** (0.63 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.49 (s, 3H), 1.52–1.8 (m, 4H), 3.66 (m, 2H), 4.0 (s, 1H), 4.14 (t, 1H, $J=6.6$ Hz), 4.16 (a, 1H), 4.5 (d, 1H, $J=3.6$ Hz), 5.8 (d, 1H, $J=3.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 26.1, 26.6, 28.5, 62.3, 75.0, 80.7, 82.2, 85.3, 104.2, 111.4.
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7. General protocol for the SHOWO: A solution of **5a–d** (0.8 mmol) and periodic acid (0.9 mmol) in 15 mL of dry ethyl acetate was allowed to stir for 3 h, then filtration, and evaporation under reduce pressure afforded a colorless syrup which immediately was dissolved in 5 mL of dry THF and added to the freshly prepared ylide (1.9 mmol of phosphonium salt and 1.2 mL of *n*-BuLi, 1.6 M (1.9 mmol) dissolved in 30 mL of dry THF at 0°C were stirred for 30 min). The reaction mixture was allowed to react overnight, quenched with H_2O and extracted with ethyl acetate and the residue was purified by flash chromatography.
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10. To a solution of **4** (100 mg, 0.2 mmol) in 40 mL of dried and degased benzene at 80°C was added dropwise Ph_3SnH (91 g, 2.6 mmol) and AIBN (8 mg) dissolved in 40 mL of dried and degased benzene. The reaction mixture was allowed to stir for 2 h before evaporating under reduced pressure. The residue was purified by column chromatography through silica gel (petroleum ether–ethyl acetate–triethylamine, 80:10:1) giving **3** as colorless oil (30 mg, 75%). $[\alpha]_D=+32.2$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.54 (s, 3H), 1.94 (m, 2H), 2.17 (m, 2H), 2.31 (m, 1H), 2.38 (dd, 1H, $J=14.4$, 5.8 Hz), 3.86 (m, 1H), 3.97 (m, 1H), 4.78 (ddd, 1H, $J=5.8$, 4.0, 1.8 Hz), 5.81 (d, 1H, $J=4.0$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 26.7, 27.5, 37.2, 41.3, 67.8, 80.1, 104.6, 112.2, 115.8. Anal calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found C, 60.23; H, 8.21%.