A Convenient and Chemoselective One-Pot Oxidation/Wittig Reaction for the C₂-Homologation of Carbohydrate-Derived Glycols

Fernando R. Pinacho Crisóstomo,[†] Romen Carrillo,[†] Tomás Martín,^{†‡} Fernando García-Tellado^{‡}
and Víctor S. Martín^{*†}*

Instituto Universitario de Bioorgánica “Antonio González”, Universidad de La Laguna, Astrofísico
Astrofísico Francisco Sánchez 2, 38206 La Laguna, Tenerife, Islas Canarias, Spain

Instituto de Productos Naturales y Agrobiología, Consejo Superior de Investigaciones Científicas,
Astrofísico Francisco Sánchez 3, 38206 La Laguna, Tenerife, Islas Canarias, Spain

fgarcia@ipna.csic.es

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^{*‡} Address correspondence to this author. Phone number: +34-922-256847 ext. 248/9. Fax: +34-922-260135.

^{*†} Address correspondence to this author. Phone number: +34-922-318579. Fax: +34-922-318571.

[†] Universidad de La Laguna

[‡] Consejo Superior de Investigaciones Científicas

Abstract. A simple and convenient one-pot protocol for the chemoselective C₂-homologation of carbohydrate-derived glycols is described. The method comprises the chemoselective oxidation of the glycol to the corresponding hydroxy-aldehyde and the subsequent Wittig alkenylation. In addition, the method does not need selective protective group manipulation and it is safe, economical, fast (5-6 hours) and bench-friendly. Its general utility is discussed.

Keywords. Oxidation, aldehydes, hydroxyl aldehydes, SO₃·pyridine, one-pot, C₂-homologation, chemoselective, Wittig homologation, carbohydrates, chain homologation, diols, protecting group economy.

In a wide research program aimed at the efficient transformation of commercial carbohydrates in high added value synthetic scaffolds¹ and chiral molecular receptors,² we were interested in the selective C₂-Wittig homologation³ shown in eq 1. The transformation requires the selective oxidation of the primary hydroxyl group to the corresponding aldehyde and the subsequent Wittig olefination. One-pot oxidation/Wittig sequences including Swern,⁴ Dess-Martin,⁵ BaMnO₄,⁶ MnO₂,⁷ IBX,⁸ TPAP⁹ and PCC¹⁰ oxidants have been developed. Although these methods work well for simple primary alcohols, the chemoselective homologation of a primary alcohol in the presence of a free secondary or tertiary alcohol has not been reported.¹¹ We decided to explore the SO₃·Pyridine complex¹² as a mild, selective, cheap, safe and easily-handled oxidant to achieve this chemoselective transformation. We report herein on our results utilizing this complex and ethyl triphenylphosphoranylidene acetate as the stabilized ylide for the chemoselective one-pot C₂-homologation of carbohydrate-derived glycols **1**, **3** and **5** and its extension to other systems.

Carbohydrate chain C₂-homologation (eq 1) is a very common synthetic operation which normally requires the selective protection of the secondary alcohol in the presence of the primary hydroxyl group.¹³ This selective transformation requires a tedious protecting group manipulation chemistry which involves at least three synthetic steps: selective primary hydroxyl group protection, secondary hydroxyl group protection and finally, selective primary hydroxyl group cleavage. Once the primary hydroxyl group is liberated, then oxidation to the corresponding aldehyde and Wittig olefination introduce the homologation chain. Cleavage of the protecting group at the secondary alcohol prepares the molecule for further transformation on this center. In terms of chemical efficiency and synthetic step economy it would be desirable to reduce reduce this methodology to a simple, one-pot protocol without protecting groups. The protocol should be facile, using widely available, cheap, stable, easily-handled and safe reagents. SO₃·Pyridine complex fulfills all of these requirements and it appeared to us to be the ideal candidate to achieve the chemoselective oxidation of the primary alcohol group.

After some experimental work, we pleasantly found that the treatment of 1,2-isopropyliden-glucose derivative **1** with SO₃·Py (3 eq) and Ph₃P=CHCO₂Me (1.5 eq) in dichloromethane/dimethylsulfoxide (2.5 : 1) cleanly afforded the homologated derivative **2** in 70% overall yield (30% of starting material recovered) and total control on the conjugated double bond geometry (100% of *E*-isomer) (eq 1). Once the protocol was standardized, we carried out this transformation with other carbohydrate-derived glycols and heterocyclic diols (Table 1). Mannose-derivative **3** affords homologated derivative **4** in both excellent yield and stereoselectivity (30% of starting material is recovered) (entry 1). In a similar manner, the xylose-derivative **5** is homologated to the derivative **6** with good yield and good stereoselectivity (entry 2). The diol **7** carrying a tertiary free hydroxyl group is also homologated with high efficiency but modest stereoselectivity (entry 3). Tetrahydropyran **9** displaying a 1,3-diol system is homologated with modest yield and high stereoselectivity (entry 4). The more elaborated pyran derivative **11** homologates with modest chemoselectivity: a double oxidation/olefination reaction affords derivative **13** in 25% yield. Although the overall yield of mono-homologated product **12** is modest, the stereoselectivity is complete (entry 5).

TABLE 1. Chemoselective One-Pot C₂-Homologation of Carbohydrate- and Pyrane-derived Diols

entry	substrate	t/h	product ^a
1		5	4 (60%)
2		6	E/Z: 4.5/1 6 (75%)
3		8	E/Z: 1/2 8 (90%) ^b
4		6	E/Z: 10/1 10 (30%)
5		6	12 (40%)
			13 (25%)

^a The E/Z ratios were directly determined from the ¹HNMR spectra of the isomeric mixtures. ^bBoth isomers were separated by silica gel chromatography.

TABLE 2. One-pot C₂-Homologation of Primary Alcohols

entry	substrate	t/h	product
1	14	3	15 (80%)
2	PhCH ₂ OH 16	2	17 (100%)
3	18	4	<i>E/Z</i> : 4.8/1 19 (70%)
4	20	3	21 (75%)
5	22	6	23 (25%) 24 (45%) 25 (30%)
6	26	1-2 14	27 (70%) 28 (55%)

In order to compare this protocol with those described for the homologation of primary alcohols,⁴⁻¹⁰ we performed the homologation of the alcohols shown in Table 2. Simple activated and unactivated

primary alcohols homologate with similar efficiency and stereoselectivity that the homologous reported examples (entries 1-4). 1,2-Hexanediol affords the C₂-homologated derivative **24** in modest yield because of competing oxidation at the secondary position (**23** and **25**) (Entry 5). Remarkably, no homologation through the secondary position is observed, in sharp opposition to the double homologation observed with diol **11**. Diol **26** was chemoselectively oxidized in a few hours (1-2) to the corresponding lactol **27** in good yield (70%) with traces of the hydroxyester **28**. However, when the reaction was prolonged to 14 h, only the *E*-ester **28** was obtained with 55% overall yield after purification. Interestingly we did not observe oxidation at the secondary alcohol, avoiding the expensive and tedious protection-deprotection protocol.

In summary, we have described a convenient one-pot protocol for the chemoselective C₂-homologation of carbohydrate-derived glycols. The method involves the chemoselective oxidation of the glycol to the corresponding hydroxy-aldehyde and the subsequent Wittig alkenylation. A mixture of SO₃·Pyridine complex and ethyl triphenylphosphoranylidene acetate performs this one-pot C₂-homologation in a very efficient manner. In addition, the method does not need selective protective group manipulation and it is safe, economical, fast (5-6 hours) and bench-friendly. *At least five synthetic steps are reduced to one in an overall yield of 60-75%.* When applied to other diolic systems, the efficiency is reduced but still remains within a valuable synthetic range. Simple primary alcohols are homologated with similar efficiency to the previously reported one-pot transformations.⁴⁻¹⁰

Experimental Section

One-pot, C₂-homologation of 1,2-Isopropyliden-xylofuranose **1 (representative example):** 1,2-Isopropyliden-xylofuranose **1** (100 mg, 0.32 mmol) dissolved in CH₂Cl₂ (1.5 mL), DMSO (0.26 mL) and Et₃N (0.45 mL, 1.9 mmol) was stirred with Ph₃P=CHCO₂Et (168 mg, 0.48 mmol) and SO₃·Py (164 mg, 1.58 mmol) for 6 h at room temperature and under a positive N₂ atmosphere. The reaction mixture was poured on 5% HCl and extracted with CH₂Cl₂. The combined organic phases were washed with water and brine, dried over MgSO₄, filtered and concentrated. Dry flash chromatography yielded 93 mg of pure derivative **2**¹¹ (70 %).

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Supporting Information Available: Spectroscopic and analytical data for compounds **2**, **4**, **8E**, **8Z**, **10**, **12**, **13**, **15**, **17**, **19**, **21**, **24**, **25**, **27** and **28** (PDF). This material is available free of charge via internet at <http://pubs.acs.org>.

Referentes and notes

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