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A Convenient and Chemoselective One-Pot Oxidation/Wittig Reaction for the C_2-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 Francisco Sánchez 2, 38206 La Laguna, Tenerife, Islas Canarias, Spain, and 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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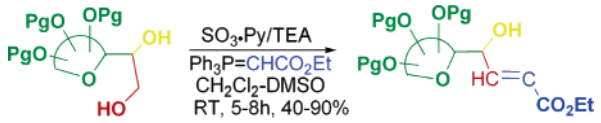
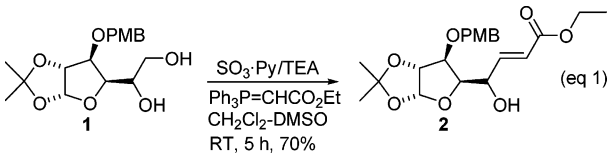


A simple and convenient one-pot protocol for the chemoselective C_2-homologation of carbohydrate-derived glycols is described. The method comprises the chemoselective oxidation of the glycol to the corresponding hydroxyaldehyde and the subsequent Wittig alkenylation. In addition, the method does not need selective protective group manipulation, and it is safe, economical, fast (5 to 6 h), and bench-friendly. Its general utility is discussed.

In a wide research program aimed at the efficient transformation of commercial carbohydrates in high added value synthetic scaffolds[1] and chiral molecular receptors,[2] we were interested in the selective C_2-Wittig homologation[3] 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] $BaMnO_4$,[6] MnO_2,[7] IBX,[8] TPAP,[9] and PCC[10] 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 SO_3·pyridine complex[12] 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 C_2-homologation of carbohydrate-derived glycols **1**, **3**, and **5** and its extension to other systems.



Carbohydrate chain C_2-homologation (eq 1) is a very common synthetic operation that 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 that 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 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. SO_3·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 were pleased to find that the treatment of 1,2-isopropyliden glucose derivative **1** with SO_3·Py (3 equiv) and $Ph_3P{=}CHCO_2Me$ (1.5 equiv) in dichloromethane/dimethyl sulfoxide (2.5:1) cleanly afforded the homologated derivative **2** in 70% overall

* Corresponding authors. (García-Tellado) Phone: +34-922-256847 ext. 248/9. Fax: +34-922-260135. (Martín) Phone: +34-922-318579. Fax: +34-922-318571.
† Universidad de La Laguna.
‡ Consejo Superior de Investigaciones Científicas.

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(11) A general procedure for the one-pot cleavage/Wittig reaction of carbohydrate-derived glycols has been described. Dunlap, N. K.; Mergo, W.; Jones, J. J.; Carrick, J. D. *Tetrahedron Lett.* **2002**, *43*, 3923−3925.
(12) Parick, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.
(13) Collins, P.; Ferrier, R. In *Monosacharides. Their Chemistry and Their Roles in Natural Products*; Wiley: New York, 1996.

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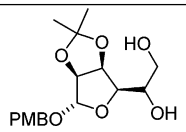
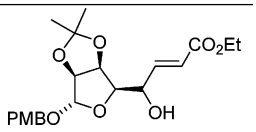
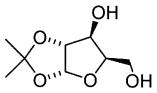
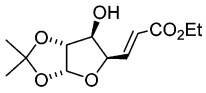
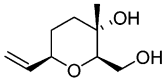
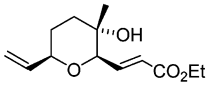
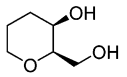
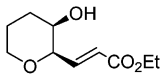
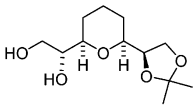
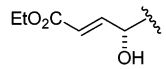
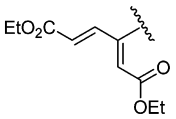
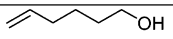
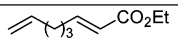
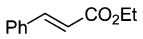
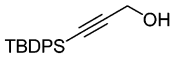
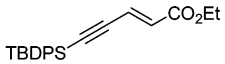
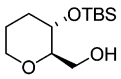
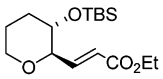
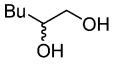
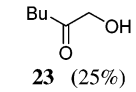
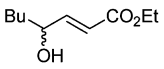
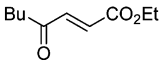
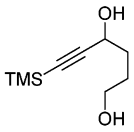
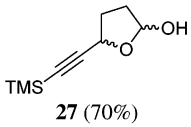
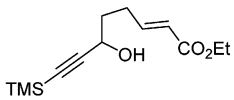
TABLE 1. Chemoselective One-Pot C_2-Homologation of Carbohydrate- and Pyrane-Derived Diols

entry	substrate	t/h	product[a]
1	 **3**	5	 **4** (60%)
2	 **5**	6	 E/Z: 4.5/1 **6** (75%)
3	 **7**	8	 E/Z:1/2 **8** (90%)[b]
4	 **9**	6	 E/Z: 10/1 **10** (30%)
5	 **11**	6	 **12** (40%)  **13** (25%)

[a] The *E*/*Z* ratios were directly determined from the ^{1}HNMR spectra of the isomeric mixtures. [b] Both isomers were separated by silica gel chromatography.

TABLE 2. One-Pot C_2-Homologation of Primary Alcohols

entry	substrate	t/h	product
1	 **14**	3	 **15** (80%)
2	$PhCH_2OH$ **16**	2	 **17** (100%)
3	 **18**	4	 *E*/*Z* : 4.8/1 **19** (70%)
4	 **20**	3	 **21** (75%)
5	 **22**	6	 **23** (25%)  **24** (45%)  **25** (30%)
6	 **26**	1-2	 **27** (70%)
		14	 **28** (55%)

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). Tetrahydropyrane **9** displaying a 1,3-diol system is homologated with modest yield and high stereoselectivity (entry 4). The more elaborated pyrane derivative **11** homologates with modest chemoselectivity: a double oxidation/olefination reaction affords derivative **13** in 25% yield. Although the overall yield of monohomologated product **12** is modest, the stereoselectivity is complete (entry 5).

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 as the homologous reported examples (entries 1-4). 1,2-Hexanediol affords the C_2-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 to 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 C_2-homologation of car-

bohydrate-derived glycols. The method involves the chemoselective oxidation of the glycol to the corresponding hydroxyaldehyde and the subsequent Wittig alkenylation. A mixture of SO_3·pyridine complex and ethyl triphenylphosphoranylidene acetate performs this one-pot C_2-homologation in a very efficient manner. In addition, the method does not need selective protective group manipulation, and it is safe, economical, fast (5 to 6 h), 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, C_2-Homologation of 1,2-Isopropylidenxylofuranose 1 (Representative Example). 1,2-Isopropylidenxylofuranose **1** (100 mg, 0.32 mmol) dissolved in CH_2Cl_2 (1.5 mL), DMSO (0.26 mL), and Et_3N (0.45 mL, 1.9 mmol) was stirred with $Ph_3P{=}CHCO_2Et$ (168 mg, 0.48 mmol) and SO_3·Py (164 mg, 1.58 mmol) for 6 h at room temperature and under a positive N_2 atmosphere. The reaction mixture was poured on 5% HCl and extracted with CH_2Cl_2. The combined organic phases were washed with water and brine, dried over $MgSO_4$, 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**. This material is available free of charge via the Internet at http://pubs.acs.org.

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