



[2,3]-Wittig rearrangement of γ -allyloxy- β -ketoesters. A new access to tetronic acids

Isabelle Pévet, Christophe Meyer* and Janine Cossy

Laboratoire de Chimie Organique, associé au CNRS, ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05, France

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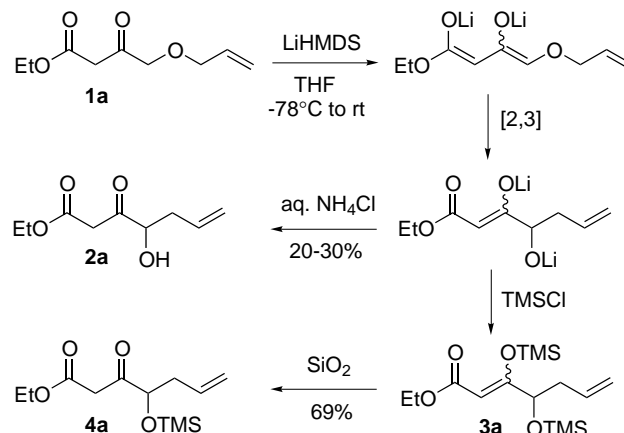
Abstract—Dilithiated γ -allyloxy- β -ketoesters undergo a [2,3]-Wittig rearrangement leading to protected γ -hydroxy- β -ketoesters, which can be converted to tetronic acids. © 2001 Elsevier Science Ltd. All rights reserved.

Tetronic acids and their metabolites are found in many natural products which exhibit a large array of biological properties.¹ They are also valuable intermediates in the synthesis of highly substituted γ -lactones, which also constitute an important class of biologically active compounds.² Conventional methods for the preparation of γ -substituted tetronic acids involve either Dieckmann reactions,³ cyclization of β -ketoesters derivatives bearing a γ -halogen⁴ or γ -oxygenated moiety, the latter being generated by Claisen⁵ or Blaise^{1,6} condensations.⁷ Herein, we report our preliminary results concerning a new method for the elaboration of γ -trimethylsilyloxy- β -ketoesters involving the [2,3]-Wittig rearrangement of γ -allyloxy- β -ketoesters dianions, and their subsequent conversion to tetronic acids.

When ethyl 4-allyloxyacetoacetate **1a**⁸ was treated with lithium hexamethyldisilazide (LiHMDS, 2.5–3.0 equiv., THF, -78°C to rt, 2–5 h), a clean conversion to the γ -hydroxy- β -ketoester **2a** was observed. The formation of this compound was ascribed to a sequence involving dilithiation of the γ -allyloxy- β -ketoester **1a**, followed by a [2,3]-Wittig sigmatropic rearrangement of the corresponding dianion. However, after an aqueous work-up, the isolated yield of **2a** was low (25–30%).⁹ This problem was circumvented by quenching the reaction mixture with chlorotrimethylsilane (TMSCl, 2.5–3.0 equiv.), and subsequent purification of **3a** by chromatography on silica gel resulted in protodesilylation of the sensitive silyl enol ether, which afforded the γ -trimethylsilyloxy- β -ketoester **4a** (69%) (Scheme 1).

This new example of sigmatropic rearrangement is obviously related to enolate [2,3]-Wittig rearrangements.¹⁰ However, unlike simple α -allyloxyester enolates, addition of polar co-solvents^{10,11} or transition metal salts such as Cp_2ZrCl_2 ,^{10,12} are not required in order to obtain decent chemical yields. Furthermore, no competing anionic [3,3]-oxy-Claisen sigmatropic rearrangement occurs as generally observed for α -allyloxyketones.¹³

The [2,3]-Wittig rearrangement of dilithiated γ -allyloxy- β -ketoesters was next applied to a variety of substrates and its stereochemical features (olefinic stereoselection and 1,2-diastereoselectivity) were evaluated. The secondary allylic ether **1b** afforded the rearranged product **4b** as a mixture of geometrical isomers ($E/Z=83/17$). The (*Z*)- and (*E*)- γ -crotyloxy- β -ketoester **1c** afforded



Scheme 1. [2,3]-Wittig rearrangement of dilithiated γ -allyloxy- β -ketoester.

* Corresponding author. Tel.: +33.1.40.79.46.63; fax: +33.1.40.79.46.60; e-mail: christophe.meyer@espci.fr

diastereomeric mixtures of **4c**, in which the *anti* and the *syn* diastereomers were, respectively, formed as the major one.^{14,15} The 1,2-diastereoselection observed in the rearrangement of **1d** bearing a [(*p*-methoxybenzyl)oxy]methyl substituent was assumed to be the same (Table 1). The observed stereochemical outcome is consistent with the general trend observed in the [2,3]-Wittig rearrangement, where the anion is stabilized by a π -acceptor group. The chelated lithioenolate preferen-

tially occupies an *exo* position in the envelope transition state,^{10,17} consequently (*E*)- and (*Z*)- allylic ethers, respectively, afford predominantly *syn* and *anti* rearranged products (Scheme 2). The presence of additional alkyl substituents for R' (R' \neq H) should disfavour the *endo* position of the stabilizing group in the transition state due to 1,3-non-bonding interactions, and therefore the diastereoselectivity of the rearrangement should be increased. When the rearrangement of the dilithiated

Table 1. [2,3]-Wittig rearrangement of substituted γ -allyloxy- β -ketoesters

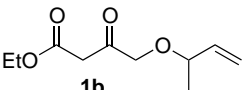
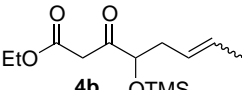
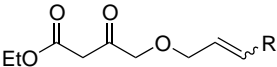
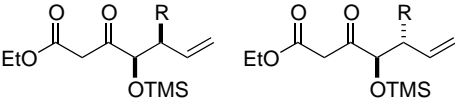
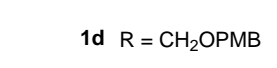
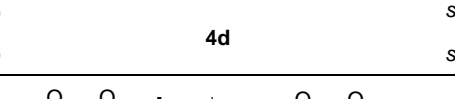
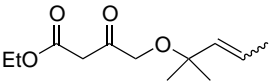
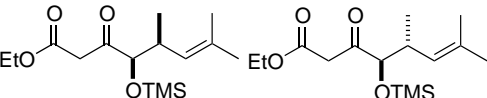
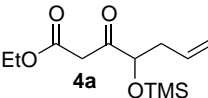
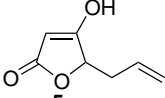
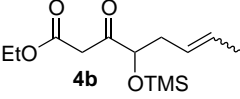
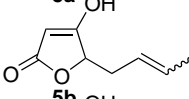
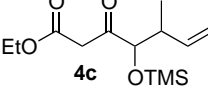
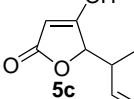
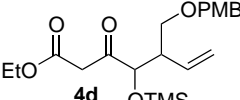
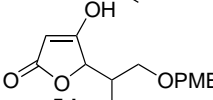
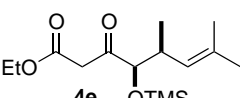
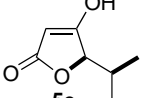
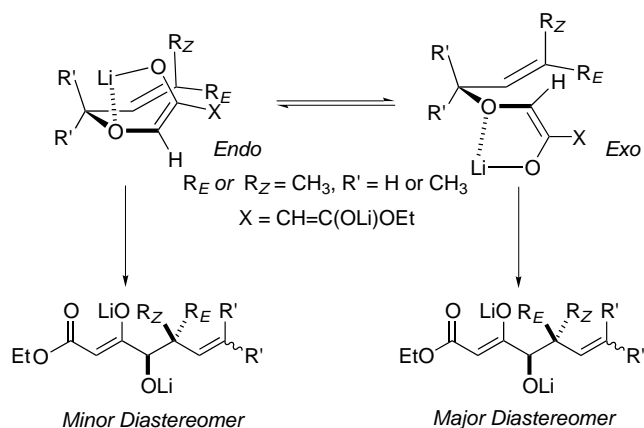
Substrates	Products	Diastereomeric ratio	Yield (%)
 1b	 4b	(<i>E</i>)/(<i>Z</i>) = 83/17	72%
 1c R = CH ₃	 4c	<i>syn/anti</i> = 25/75	62%
		<i>syn/anti</i> = 87/13	64%
 1d R = CH ₂ OPMB	 4d	<i>syn/anti</i> = 20/80	79%
		<i>syn/anti</i> = 94/6	89%
 1e	 4e	<i>syn/anti</i> = 30/70	12%
		<i>syn/anti</i> = 98/2	71%

Table 2. Conversion of γ -trimethylsilyloxy- β -ketoesters to tetronic acids

Substrates	Diastereomeric ratio	Tetronic acid	Yield (method*)
 4a		 5a	87% (A) 90% (B)
 4b	(<i>E</i>)/(<i>Z</i>) = 83/17	 5b	84% (A)
 4c	<i>syn/anti</i> = 25/75 <i>syn/anti</i> = 87/13	 5c	69% (A) 84% (A)
 4d	<i>syn/anti</i> = 20/80 <i>syn/anti</i> = 94/6	 5d	62% (B) 91% (B)
 4e	<i>syn/anti</i> = 98/2	 5e	86% (A)

*A: cat. TsOH, CH₂Cl₂/EtOH, 25–35°C. B: *n*-Bu₄NF, THF, 25°C.



Scheme 2. Proposed transition states for the [2,3]-Wittig rearrangement of dilithiated γ -allyloxy- β -ketoesters.

tertiary ether (*Z*)-**1e** was investigated, an extremely slow reaction was observed, which could not reach completion despite extended reaction times, probably due to the existence of a severe $A^{1,3}$ interaction (between R_Z and $R'=\text{CH}_3$) in the transition state. However, as anticipated, the rearrangement of the tertiary ether (*E*)-**1e** afforded **4e** (71%) in a highly diastereoselective fashion (*syn/anti*=98/2) (Table 1).

The rearranged γ -trimethylsilyloxy- β -ketoesters **4a–e** were then converted to the corresponding tetronic acids (Table 2). This transformation could be carried out in high yields by simple treatment with a catalytic amount of *p*-toluenesulfonic acid in $\text{CH}_2\text{Cl}_2/\text{EtOH}$, 25–35°C (method A). Alternatively, the intermediate γ -trimethylsilyloxy- β -ketoesters could be directly cyclized to the corresponding tetronic acids by treatment of the crude products with tetra-*n*-butylammonium fluoride (*n*-Bu₄NF) in THF at room temperature (method B). In the cases investigated, both methods afforded tetronic acids **5b–e**, without alteration of the diastereomeric purity of the intermediates **4b–e**.^{14a}

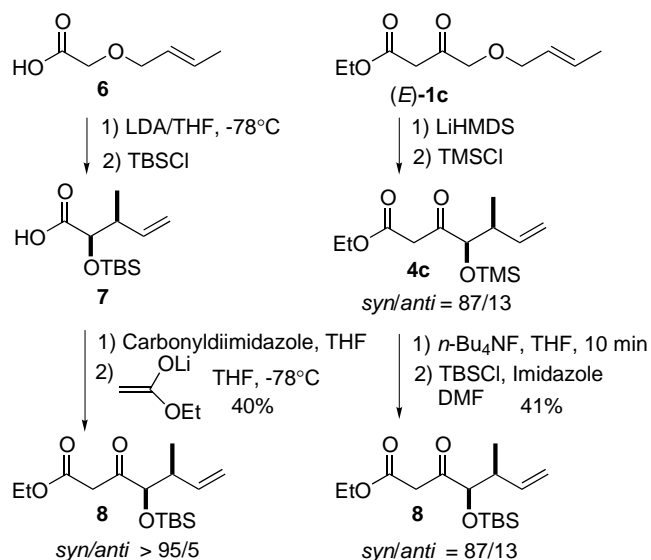
We have shown that dilithiated γ -allyloxy- β -ketoesters can undergo an efficient [2,3]-Wittig rearrangement leading to protected γ -hydroxy- β -ketoesters which can further be converted to the corresponding tetronic acids. Other rearrangements of such type and asymmetric versions are currently being investigated, as well as applications to natural product synthesis.

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14. (a) The diastereomeric ratios were evaluated by careful examination and comparison (due to the presence of keto and enol tautomeric forms for both diastereomers) of the ^1H NMR spectra of the rearranged products **4c–e**, obtained from both geometrical isomers of the starting substituted γ -allyloxy- β -ketoesters **1c–e**. The diastereomeric ratios of the corresponding tetrone acids **5c–e** were easily evaluated by ^1H NMR, since only the enol form was present when the spectra were recorded in CD_3OD . Both calculated values for **4c–e** and **5c–e** were in perfect agreement. (b) Other experimental conditions for the rearrangement of **1c** (variation of enolizing reagent and solvent polarity) resulted in little variations of the diastereomeric ratio.
15. The relative configuration of the *syn/anti* diastereomers of **4c** was established by a chemical correlation. (*E*)- α -Crotyloxy acetic acid **6** was dilithiated and underwent a [2,3]-Wittig rearrangement. After silylation with TBSCl, the rearranged carboxylic acid **7** was assumed to possess a *syn* relative configuration according to previous reports.^{16a,b} The latter was subjected to a Claisen condensation after activation with carbonyldiimidazole,^{16c,d} leading to **8**. Rearrangement of (*E*)-**1c** afforded **4c** (87/13 diastereomeric mixture), in which the protecting group was switched from TMS to TBS to give the same major *syn* diastereomer of **8**.



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