

Experimental Section

Full procedures and characterization data are given in Supporting Information.

Method A: To an oven-dried, septum-capped test tube was added $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ (3.8 mg, 0.01 mmol) and anhydrous TCE (2 mL) under a positive argon pressure vented to a bubbler. To this was added **1** (142.2 mg, 1 mmol) and **2** (127.4 mg, 1.2 mmol). The reaction was stirred at room temperature for 6 h, the dienophile (1.2–1.5 mmol) was then added and the reaction heated to the temperature indicated in Table 1.

Method B: To an oven-dried, septum-capped test tube was added $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ (7.6 mg, 0.02 mmol) and anhydrous TCE (2 mL) under a positive argon pressure vented to a bubbler. To this was added **1** (142.2 mg, 1 mmol), **2** (127.4 mg, 1.2 mmol), and the dienophile (1.5 mmol). The reaction was heated to the temperature indicated in Table 1.

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- [11] **3** was found to decompose with a half life of 30 h at 100 °C, 0.5 M in TCE. $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ accelerated the decomposition. See Supporting Information for additional detail.
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Synthesis of Isotopically Labeled (*E*)- β,γ -Unsaturated Esters with Total or High Diastereoselectivity by Using Samarium Diiodide**

José M. Concellón,* Pablo L. Bernad, and Humberto Rodríguez-Solla

β,γ -Unsaturated esters are generally synthesized by isomerization of α,β -unsaturated esters,^[1] either by selective, conjugate reduction of alkyl alka-2,4-dienoates,^[2] or by carbonylation of allylic compounds,^[3] or from α -bromo- α,β -unsaturated esters.^[4] However, no simple, general, highly diastereoselective preparation of β,γ -unsaturated esters has been described.

Recently, we reported a highly diastereoselective synthesis of (*E*)- α,β -unsaturated esters^[5] and amides^[6] from 2-halo-3-hydroxyesters and amides, respectively, by using SmI_2 . Subsequently, we described a sequential elimination–reduction reaction promoted by SmI_2 , which gave 2,3-dideuterioesters and amides from 2-halo-3-hydroxyesters and amides, respectively, by using D_2O as the deuteration reagent.^[7] Here we report a new method to obtain β,γ -unsaturated esters **2**, with total or high diastereoselectivity by a sequenced elimination–reduction process of the readily available α -halo- β -hydroxy- γ,δ -unsaturated esters **1** by using SmI_2 and H_2O (see Table 1). Taking into account the usefulness of isotopically labeled compounds for establishing the mechanism of organic reactions and the biosynthetic pathways of many natural compounds,^[8] we have also applied this method to obtain α,δ -

[*] Dr. J. M. Concellón, Dr. P. L. Bernad, H. Rodríguez-Solla
Departamento de Química Orgánica e Inorgánica
Facultad de Química, Universidad de Oviedo
33071 Oviedo (Spain)
Fax: (+34) 98-510-34-46
E-mail: jmcg@sauro.chem.uniovi.es

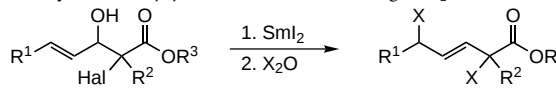
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dideuterio- β,γ -unsaturated esters by using D_2O instead of H_2O .

Treatment of several α -halo- β -hydroxy- γ,δ -unsaturated esters **1** with a solution of SmI_2 (5 equiv) in THF for 30 min at room temperature, followed by reaction with D_2O or H_2O (2 mL) over a period of 30 min afforded the corresponding (*E*)- α,δ -dideuterio- β,γ -unsaturated or (*E*)- β,γ -unsaturated esters **2**, respectively, in high yield (Table 1). No differences

Table 1. Synthesis of β,γ -unsaturated esters using SmI_2 .



Entry	2	R ¹	R ²	R ³	X ^[a]	de ^[b]	Yield [%] ^[c]
1	a	Me	H	Bn	D	60	62
2	b	Me	Me	Et	D	> 98	66
3	c	Me	C ₆ H ₁₃	Et	H ^[d]	> 98	79
4	d	Me	C ₆ H ₁₃	Et	D ^[d]	> 98	82
5	e	Pr	H	Me	D	65	90
6	e	Pr	H	Me	D ^[e]	76	60 ^[f]
7	e	Pr	H	Me	D ^[g]	86	30 ^[f]
8	f	Pr	C ₅ H ₁₁	Et	D ^[d]	> 98	74
9	g	Pr	Ph	iPr	D	> 98	90
10	h	Ph	Me	Et	D	> 98	62
11	i	Ph	C ₆ H ₁₃	Et	D ^[d]	> 98	62

[a] Unless otherwise noted, reactions were carried out using Hal = Cl. See also Experimental Section and Supporting Information. [b] Diastereoisomeric excess (*de*) determined by GC-MS, and 300 MHz ¹H and ¹³C NMR analysis of the crude products **2**. [c] Yield of product isolated after column chromatography based on compound **1**. [d] Reaction was carried out using Hal = Br. [e] Reaction carried out at $-15^{\circ}C$; reaction time = 150 min. [f] Dimerization products at the δ -position were obtained. [g] Reaction carried out at $-40^{\circ}C$; reaction time = 18 h.

were observed in the reaction when D_2O or H_2O was used. In both cases, a C–C double bond was generated with total diastereoselectivity (except for **2a** and **2e**), while the incorporation of deuterium generated a new stereogenic center and consequently the deuterated compounds **2** were isolated as a mixture of diastereoisomers (roughly 1:1).

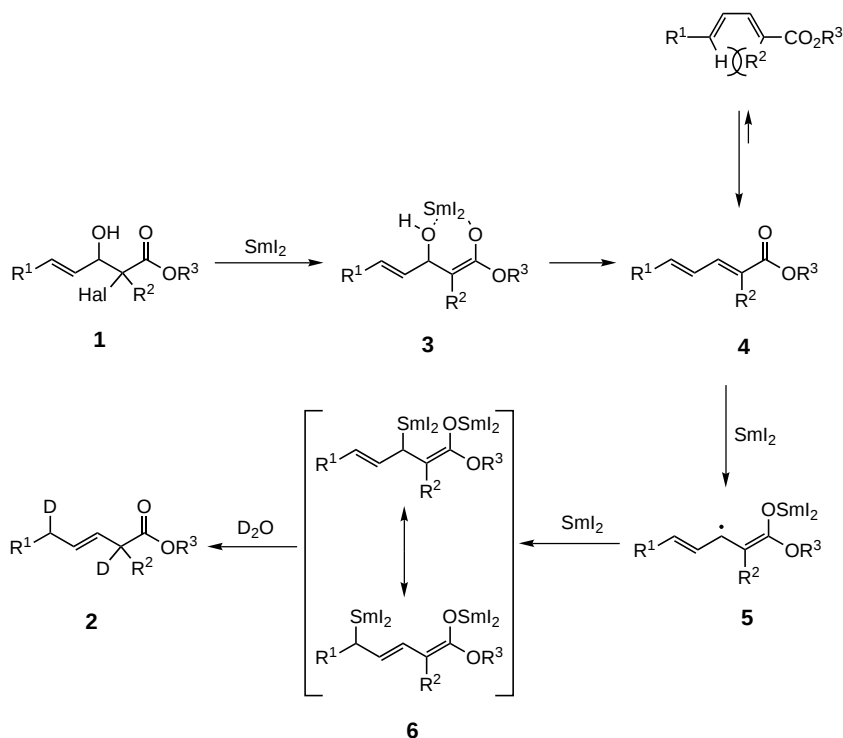
All starting compounds **1** were easily obtained by reaction of the corresponding lithium enolates of α -haloesters (generated by treatment of α -haloesters with lithium diisopropylamide (LDA) at $-78^{\circ}C$) with α,β -unsaturated aldehydes at $-78^{\circ}C$. The diastereoisomeric excess (*de*) in each case was determined on the crude reaction products by ¹H NMR spectroscopy (300 MHz) and GC-MS. The position of the C–C double bond and the deuterium atom was established by ¹H and ¹³C NMR spectroscopy of compounds **2**. The multiplicity of the signals of the olefinic protons was in accordance with the structure shown

in Table 1 (i.e. 1,4-reduction of the conjugated C–C double bond) and in disagreement with a possible reaction to give α,β -dideuterated- γ,δ -unsaturated esters (i.e. by 1,2-reduction). The *E* stereochemistry in the C–C double bond was assigned on the basis of the value of the ¹H NMR coupling constant between the olefinic protons of compound **2**. The complete deuterium incorporation (> 99 %) was confirmed by mass spectrometry.^[9] It is noteworthy that D_2O is the cheapest deuteration reagent available for obtaining organic compounds isotopically labeled with deuterium.

The proposed methodology to prepare (*E*)- α -alkylated- α,δ -dideuterio- β,γ -unsaturated esters **2** is general: R¹, R², and R³ can be varied widely (see Table 1); chloro and bromo hydroxyesters can be used as starting material, and even though mixtures of diastereoisomers of the starting halohydrins **1** were used, the C–C double bond of esters **2b–d** and **2f–i** was obtained with total diastereoselectivity.

When compounds **1** with R² = H were used, the C–C double bond of compounds **2** was obtained with high selectivity, the usual diastereoselectivity/temperature trend was observed by which diastereoselectivity increased as the temperature decreased. However, at low temperature, the previously reported formation of unsaturated diesters by a dimerization of alka-2,4-dienoates (see below) was also observed.^[10]

Synthesis of **2** may be explained by assuming that the metalation of the halogen of **1** with SmI_2 produces an enolate intermediate **3**, in which the chelation of the Sm^{III} center with the oxygen atom of the OH group produces a six-membered ring, which undergoes a β -elimination affording the alkyl (2*E*,4*E*)-alka-2,4-dienoate **4** with total diastereoselection (Scheme 1).^[11] Support for this is provided by isolation of ethyl (2*E*,4*E*)-2-hexylhexa-2,4-dienoate (**4c**) in 90 % yield (starting from ethyl-2-bromo-2-hexyl-3-hydroxyhex-4-enoate



Scheme 1. Proposed mechanism for the conversion of **1** into **2**.

and 2.5 equiv of SmI_2) when, after 30 min, excess SmI_2 was eliminated from the reaction mixture by bubbling a stream of air prior to the hydrolysis.

After formation of the alkyl (2*E*,4*E*)-2-alkylalka-2,4-dienoate **4**, the SmI_2 -promoted 1,4-reduction of the two conjugated C–C double bonds, which is initiated by oxidative addition of SmI_2 , produces an enolate radical **5**,^[12] which could explain the observed dimerization at the δ -position of compounds **4a**, and **4e**. A second electron transfer from SmI_2 affords an allylic dianion **6** and its hydrolysis with H_2O or D_2O produces the corresponding compound **2** (Scheme 1).

The observed lower diastereoselectivity in the formation of the C–C double bond in the synthesis of **2a** and **2e**, neither of which contain α -alkyl substituents, may be explained by assuming that in case of the α -alkylated esters **2b–d** and **2f–i** the *s-cis* conformation of the starting diene is disfavored by steric hindrance produced by the substitution at the α -carbon atom, while the 1,4-reduction of the conjugated C–C double bonds of **2a** and **2e** takes place through both the *s-cis* and *s-trans* conformations. The complete deuteration at C5 instead of at C3 of the dianion **6** could be explained by assuming that in this resonance-stabilized dianion, the 1,4-dianion structure is more stable than the 1,2-dianion structure due to the charge repulsions.

The proposed mechanism is supported by the fact that the synthesis of compounds **2** can be also carried out starting from the corresponding alkyl (2*E*,4*E*)-2-alkylalka-2,4-dienoate **4**. Thus, treatment of ethyl (2*E*,4*E*)-2-hexylhexa-2,4-dienoate (**4d**) with SmI_2 (2.5 equiv) and D_2O (2 mL) for 30 min at room temperature affords **2d** in 84% yield.

The described methodology can be applied to obtain δ -deuterio- β,γ -unsaturated esters. The reaction of **2h** with LDA, followed by treatment with H_2O afforded ethyl (*E*)-5-deuterio-2-methyl-5-phenylpent-3-enoate (**8h**) with total diastereoselectivity (89% yield). Taking into account that the C–C double bond of δ -deuterio- and α,δ -dideuterio- β,γ -unsaturated esters can be easily hydrogenated,^[13] the proposed methodology can be used to prepare saturated δ -deuterio- and α,δ -dideuterioesters, respectively.

In conclusion, in the presence of D_2O , the simple SmI_2 -promoted elimination/reduction sequence provides an efficient method for synthesizing α,δ -dideuterio- β,γ -unsaturated esters **2**, in which the C–C double bond is generated with total or high diastereoselectivity, starting from the readily available α -halo- β -hydroxy- γ,δ -unsaturated esters **1**.

Experimental Section

General procedure: A solution of SmI_2 (2.3 mmol) in THF (24 mL) was slowly added dropwise, under a nitrogen atmosphere, to a stirred solution of **1** (0.4 mmol) in THF (4 mL) at room temperature. After the solution had been stirred for 30 min at the same temperature, H_2O or D_2O (2 mL) were added. The mixture was stirred for 30 min at this temperature and then quenched with aqueous HCl (0.1M, 5 mL). Usual workup afforded crude β,γ -unsaturated esters **2**, which were purified by column flash chromatography over silica gel (10:1 hexane/ethyl acetate). Yields are given in Table 1.

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Allosteric Regulation of an HIV-1 Protease Inhibitor by Zn^{II} Ions**

Simone Valente, Marina Gobbo, Giulia Licini,*
Alessandro Scarso, and Paolo Scrimin*

Allosteric regulation of protein activity by noncovalent modifiers (ions or neutral molecules) is a feature found in many natural systems including enzymes.^[1] The role of these modifiers is to induce conformational changes in the protein that trigger its activity while they are usually not directly involved in the specific function performed by the macromolecule.

[*] Prof. Dr. G. Licini, Prof. Dr. P. Scrimin, Dr. S. Valente, Dr. A. Scarso
Dipartimento di Chimica Organica and CNR-CMRO
Università di Padova
Via Marzolo, 1 35131 Padova (Italy)
Fax: (+39) 049-827-5239
E-mail: giulia.licini@unipd.it, paolo.scrimin@unipd.it
Dr. M. Gobbo
Centro CNR Studio Biopolimeri
Via Marzolo, 1 35131 Padova (Italy)

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