ORGANIC
LETTERS

2002
Vol. 4, No. 2
189−191

Synthesis of (*E*)-α,*β*-Unsaturated Esters with Total or High Diastereoselectivity from α,*β*-Epoxyesters

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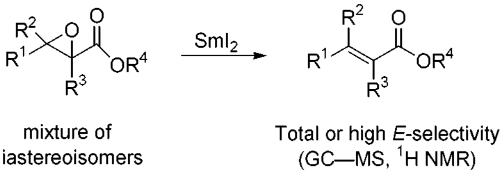
Received October 11, 2001

ABSTRACT



High stereoselective *β*-elimination in 2,3-epoxyesters 1 was achieved using samarium diiodide, yielding α,*β*-unsaturated esters 2, in which the C═C bond is di-, tri- or tetrasubstituted. The starting compounds 1 are easily prepared by reaction of the corresponding lithium enolates of α-chloroesters with aldehydes or ketones at −78 °C. The influence of the reaction conditions and the structure of the starting compounds in the stereoselectivity of the *β*-elimination reaction is also discussed.

Although deoxygenation reactions of epoxides promoted by SmI_2 to afford alkenes with very poor diastereoselection are well-known, no application of this methodology to α,*β*-epoxyesters has been published. Moreover, to the best of our knowledge, no selective, general methodology has been developed to deoxygenate noncyclic α,*β*-epoxyesters to obtain α,*β*-unsaturated esters with high diastereoselectivity.[1] Several papers have described the transformation of cyclic α,*β*-epoxyesters into cyclic α,*β*-unsaturated esters,[2] in which no mixture of *Z*/*E* diastereoisomers can be obtained. However, the scarce examples reported starting from noncyclic α,*β*-epoxyesters afford noncyclic α,*β*-unsaturated esters in low yield[3] or lead to a mixture of diastereoisomers[4] or compounds,[5] while in other papers no information of the diastereoselection is available.[6] Moreover, taking into account that α,*β*-unsaturated esters can be easily transformed into α,*β*-epoxyesters,[7] the sequence α,*β*-unsaturated ester → α,*β*-epoxyester → α,*β*-unsaturated ester can be used as a protection−deprotection methodology of the C═C double bond of α,*β*-unsaturated esters. For this reason a new general and easy transformation of α,*β*-epoxyesters into α,*β*-unsaturated esters with high diastereoselection would be desirable.

Recently we developed a new, easy, and simple highly diatereoselective *β*-elimination reaction promoted by samarium diiodide and starting from different functionalized

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[1] In the best of our knowledge, the scarce papers published contain only one example of this transformation, and only the synthesis of (*E*)-ethyl cinnamate from the corresponding α,*β*-epoxyester has been described in high yield and with total diastereoselection: Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468−4475.

[2] By using Zn/AcOH: (a) Trost, B. M.; Krische, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 6131−6141. By using WCl_6 + BuLi: (b) Krische, M. J.; Trost, B. M. *Tetrahedron* **1998**, *54*, 7109−7120. By using $CrCl_2$: (c) Emmer, G.; Graf, W. *Helv. Chim. Acta* **1981**, *64*, 1398−1406. (d) Kehrli, A. R. H.; Taylor, D. A. H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2067−2070. (e) Ekong, D. E. U.; Olagbemi, E. O. *J. Chem. Soc. C* **1966**, 944−946. (f) Nozaki, H.; Hiroi, M.; Takaoka, D.; Nakayama, M. *J. Chem. Soc., Chem. Commun.* **1983**, 1107−1108. (g) Banerji, J.; Chatterjee, A.; Ghoshal, N.; Das, A.; Sarkar, S. *J. Indian Chem. Soc.* **1982**, *59*, 145−149. (h) Bennett, R. D.; Hasegawa, S. *Phytochemistry* **1982**, *21*, 2349−2354.

[3] (a) Ameer, F.; Drewes, S. E.; Hoole, R.; Kaye, P. T.; Pitchford, A. T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2713−2717. (b) Kobayashi, T.; Nitta, M. *Chem. Lett.* **1982**, 325−328. (c) Vedejs, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1973**, *95*, 822−825.

[4] (a) Rosenblum, M.; Saidi, M. R.; Madhavarao, M. *Tetrahedron Lett.* **1975**, *16*, 4009−4011. (b) Bissing, D. E.; Speziale, A. J. *J. Am. Chem. Soc.* **1965**, *87*, 2683−2690.

[5] Mawson, S. D.; Weavers, R. T. *Tetrahedron* **1995**, *51*, 11257−11270.

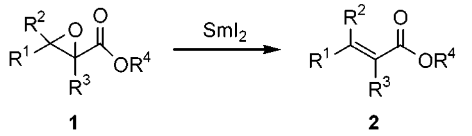
[6] (a) Frazier, J. W.; Staszak, M. A.; Weigel, L. O. *Tetrahedron Lett.* **1992**, *33*, 857−860. (b) Alper, H.; Des Roches, D. *Tetrahedron Lett.* **1977**, *18*, 4155−4158.

[7] (a) Meth-Cohn, O.; Moore, C.; Taljaard, H. T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2663−2674. (b) Kehrli, A. R. H.; Taylor, D. A. H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2067−2070.

10.1021/ol016894p CCC: $22.00

halohydrins. This is the first general stereoselective β-elimination reaction promoted by SmI_2. In this respect, we have described the diastereoselective synthesis of (*Z*)-vinyl halides from *O*-acetylated 1,1-dihaloalkan-2-ols,[8] the preparation of (*E*)-α,β-unsaturated esters[9] or amides[10] from 2-halo-3-hydroxyesters or amides, respectively, and the obtention of (*Z*)-vinylsilanes from 1-chloro-1-trialkylsilylalkan-2-ols.[11] Here, we describe a new methodology to obtain (*E*)-α,β-unsaturated esters with total or high *E*-selectivity by deoxygenation of α,β-epoxyesters using samarium diiodide (Scheme 1).

Scheme 1. Synthesis of (*E*)-α,β-Unsaturated Esters



Our first attempts were carried out to establish the reaction conditions of the β-elimination process to obtain α,β-unsaturated esters **2**. Thus, the α,β-epoxyester **1d** was treated with a solution of SmI_2 in THF, at several temperatures (−50 °C, room temperature and reflux of THF). The yield and diastereoisomeric excess (de) of the elimination reaction of **1d** were similar at room temperature and at reflux, whereas **2d** was isolated in lower yield at −50 °C (Table 1, entries 4−6). Taking into account these results, the remaining reactions were performed at room temperature or at reflux of THF. In general, the yield and degree of purity of **2** was higher at reflux than at room temperature; for this reason when the elimination reaction afforded other side products at room temperature, the reaction was carried out at reflux. Hence, the reaction of different α,β-epoxyesters **1** with a solution of SmI_2 in THF at room temperature or reflux gave the corresponding di- or trisubstituted (*E*)-α,β-unsaturated esters **2** in high yield and with total or very high stereoselectivity (Table 1, entries 1−13).[12]

Table 1. Synthesis of (*E*)-α,β-Unsaturated Esters **2**

entry	2^a	R^1	R^2	R^3	R^4	de	yield^b
1	**2a**	*p*-$MeOC_6H_4$	H	H	Me	>98	79%
2	**2b**^{c}	MeCH(Ph)	H	H	Me	>98	81%
3	**2c**	*n*-Bu	H	Ph	*i*-Pr	93	68%
4	**2d**^{c}	C_7H_{15}	H	Me	Et	92	80%
5	**2d**	C_7H_{15}	H	Me	Et	93	77%
6	**2d**^{d}	C_7H_{15}	H	Me	Et	>98	62%
7	**2e**^{c}	cyclohexyl	H	Me	Et	>98	84%
8	**2e**	cyclohexyl	H	Me	Et	>98	72%
9	**2f**	Ph	H	Bu	Et	>98	83%
10	**2g**	*p*-$MeOC_6H_4$	H	Me	Et	>98	90%
11	**2h**	*p*-CNC_6H_4	H	Me	Et	>98	82%
12	**2i**	MeCH(Ph)	H	C_6H_{13}	Et	>98	85%
13	**2j**^{c}	$C_9H_{17}{}^e$	H	Me	Et	>98	59%
14	**2k**	-$(CH_2)_5$-		Me	Et		70%
15	**2l**	Ph	Me	Me	Et	61	85%
16	**2m**	Ph	Et	Me	Et	71	75%
17	**2n**	Bn	Me	Me	Et	70	66%

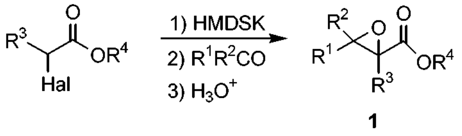
[a] Unless otherwise noted, reactions were carried out at room temperature. [b] Isolated yield after column chromatography based on compound **1**. [c] The reaction was carried out at reflux of THF. [d] The reaction was carried out at −50 °C. [e] C_9H_{17}: $Me_2C{=}CH(CH_2)_2CH(Me)CH_2$.

The proposed deoxygenation reaction is general for the preparation of di- or trisubstituted α,β-unsaturated esters. Thus, R^1 can be aliphatic (linear, branched, or cyclic) unsaturated or aromatic (electron-rich or -deficient), R^3 has been also changed (aliphatic and aromatic), and in addition the selectivity and yield were unaffected by the presence of bulky groups R^4 on the carbonyl ester (Table 1, entry 4), in contrast to other elimination reactions.[13]

This methodology can be also used to obtain α,β-unsaturated esters **2**, in which the C═C bond is tetrasubstituted. In this case, all reactions were carried out at reflux, the α,β-unsaturated esters **2** were isolated in high yield, and logically, a decrease of the diastereoselectivity was observed (Table 1, entries 15−17).[14]

The starting compounds **1** were easily obtained by reaction of aldehydes or ketones with the potassium enolate of α-chloroesters (generated by treatment of α-chloroesters with potassium hexamethyldisilazide at −78 °C) at temperatures ranging from −78 to 25 °C.

Scheme 2. Synthesis of Starting Compounds



The de was calculated on the crude reaction products by ^1H NMR spectroscopy (300 MHZ) and GC−MS.[15]

The *E* stereochemistry in the double bond C═C of the obtained α,β-unsaturated esters **2**, in which the C═C is di-

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[9] Concellón, J. M.; Pérez-Andrés, J. A.; Rodríguez-Solla, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2773−2775.

[10] Concellón, J. M.; Pérez-Andrés, J. A.; Rodríguez-Solla, H. *Chem. Eur. J.* **2001**, *7*, 3062−3068.

[11] Concellón, J. M.; Bernad, P. L.; Bardales, E. *Org. Lett.* **2001**, *3*, 937−939.

[12] **Representative Experimental Procedure.** A solution of SmI_2 (1.6 mmol) in THF (19 mL) was added, under nitrogen atmosphere, dropwise to a stirred solution of the corresponding epoxyester **1** (0.4 mmol) in THF (4 mL) at room temperature or at reflux. The reaction mixture was stirred for 90 min (rt) or 2 h (reflux), and then the reaction was quenched with aqueous HCl (20 mL of a 0.1 M solution). Usual workup afforded crude α,β-unsaturated ester **2**, which was purified by column flash chromatography over silica gel (10:1 hexane/ethyl acetate).

[13] By example, the diastereoselectivity of the Wittig reaction, to obtain α,β-unsaturated esters, decreases with bulky alcoholic groups: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927.

[14] To the best of our knowledge, no diastereoselective synthesis of tetrasubstituted α,β-unsaturated esters from α,β-epoxiesters has been described.

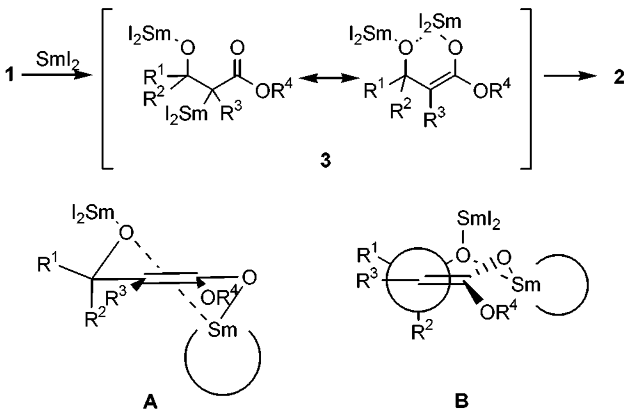
[15] The ^1H NMR determination was in agreement with the de obtained by GC−MS.

or trisubstituted, was established by comparison of their ^{1}H and ^{13}C spectra with authentic samples, as has been previously described in the literature.[9] The *E* stereochemistry of the C═C double bond of the tetrasubstituted α,*β*-unsaturated esters **2** was assigned by NOESY experiments (compound **2m**).

It is noteworthy that although the starting α,*β*-epoxyesters were used as mixtures of *cis* and *trans* diastereoisomers, the corresponding α,*β*-unsaturated esters were obtained with total or very high *E*-selectivity.

The mechanism and stereochemistry may be explained based on the ability of SmI_2 to reduce α-heterosubstituted esters to esters (Scheme 3). Thus, the SmI_2-promoted reduction of the C_α−O bond of **1** affords an intermediate enolate **3**. Chelation of the oxophilic Sm^{III} center of the enolate **3** with the second oxygen atom produces a six-membered ring.[16] Tentatively we propose a transition state model **A**. If $R^1 > R^2$, the largest group R^1 occupies an equatorial position and the smallest group R^2 an axial position (to avoid interactions with the samarium coordination sphere). This transition state could also explain the total or very high diastereoselectivity observed in the elimination reaction from a mixture of diastereoisomers of **1**. As depicted in **B** (another projection of the same transition state), R^1 and R^3 show a *cis* relationship. Consequently, elimination from **A** affords (*E*)-α,*β*-unsaturated esters.

Scheme 3. Proposed Mechanism



In conclusion, an easy, general methodology has been developed to synthesized α,*β*-unsaturated esters, in which the double bond C═C is di-, tri-, or tetrasubstituted with total or high *E*-diastereoselectity from easily available α,*β*-epoxyesters, the reaction being promoted by samarium diiodide.

Acknowledgment. We thank Ministerio de Educación y Cultura (PB-EX01-11) and Principado de Asturias (BQU2001-3807) for financial support. J.M.C. thanks Carmen Fernández for her time. E.B. thanks the Universidad de Oviedo and the Principado de Asturias for a predoctoral fellowship. Our thanks to Robin Walker for his final revision of the manuscript.

Supporting Information Available: Experimental procedure of **1**, spectroscopic data of **1** and **2**, ^{13}C NMR spectra of **2**, and GC of compounds **2l**, **2m** and **2n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Similar six-membered ring transition state models have been proposed to explain the selectivity in other reactions of SmI_2: (a) Urban, D.; Skrydstrup, T.; Beau, J. M. *J. Org. Chem.* **1998**, *63*, 2507−2516. (b) Molander, G. A.; Etter, J. B.; Zinke, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 453−463.