Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 45 (2004) 5359–5361

Tetrahedron Letters

Diastereoselectivity in the epoxidation of γ-hydroxy α,β-unsaturated esters: temperature and solvent effect☆

Santiago Rodríguez, Alberto Vidal, Juan J. Monroig and Florenci V. González*

Departament de Química Inorgànica i Orgànica, Universitat Jaume I, E-12071 Castelló, Spain

Received 27 April 2004; revised 17 May 2004; accepted 17 May 2004

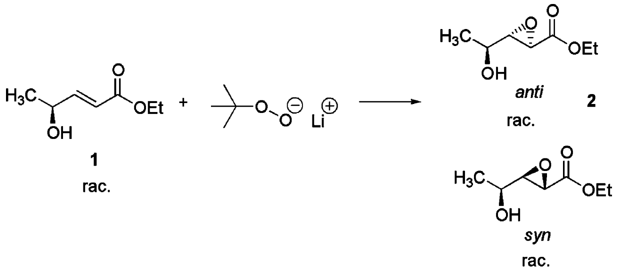
Abstract—The diastereoselectivity in the nucleophilic epoxidation of γ-hydroxy α,β-unsaturated compounds using lithium-*tert*-butylperoxide is highly dependent on the reaction solvent but not influenced by the temperature. The free hydroxyl is key for stereoselection.

Asymmetric epoxidation of γ-chiral α,β-unsaturated esters provides chiral α,β-epoxyesters that can be converted into useful chiral building blocks.[1] Although some reports have been published about the asymmetric epoxidation of γ-hydroxy α,β-unsaturated sulfoxides[2] and sulfones,[3] there are no reports of diastereoselective epoxidation of γ-hydroxy α,β-unsaturated esters.

The most convenient method for the epoxidation of unsaturated esters is using a hydroperoxide in the presence of a base.[4] The diastereoselectivity of this reaction must be interpretated as a conjugate addition to an unsaturated ester modulated by a stereocentre in γ-position.[5]

We now wish to report a study of the diastereoselectivity in the epoxidation of γ-chiral γ-hydroxy-α,β-unsaturated esters and particularly the influence of the temperature and solvent effect on the process.

We chose ethyl *trans*-4-hydroxy-2-pentenoate **1** as a model system and lithium-*tert*-butylperoxide (TBPLi) as oxidative reagent. The stereoselectivity was measured as the ratio between racemic mixtures of *anti*/*syn* diastereomers **2** (Scheme 1).



Scheme 1. General epoxidation reaction of compound **1**.

The model compound **1** was obtained through treatment of ethyl (*E*)-4-oxo-2-butenoate **5** with a grignard (Scheme 2).

Fumaraldehydic ester **5** was obtained[6] starting from 2-furoic acid, which was converted into butenolide **3** through a photooxygenation reaction according to J. D. White's procedure.[7] Compound **3** was then submitted to ketalisation–esterification[8] reaction followed by potassium bisulfate[9] treatment and the resulting compound **4** was then hydrolysed[10] to afford aldehyde **5**, which upon treatment with methyl magnesium chloride gave hydroxyester **1** (Scheme 2).

Table 1 documents the influence of the solvent. The diastereoselectivity of the epoxidation of compound **1** proved to be highly dependent on the reaction solvent.

We carried out the reactions using ethyllithium[11] as base at −20 °C for 20 h in different solvents. The results show the more polar the media was, the better selectivity was

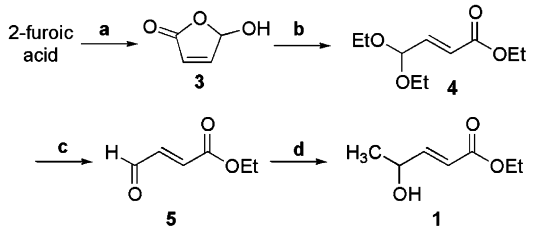
---

Keywords: Diastereoselective epoxidation; Unsaturated esters; Solvent effect; Temperature influence.

☆ Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tetlet.2004.05.080

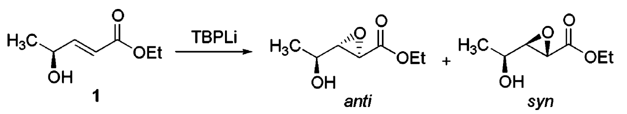
* Corresponding author. Tel.: +34-964728241; fax: +34-964728214; e-mail: fgonzale@qio.uji.es

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.05.080



Scheme 2. Synthesis of ethyl *trans*-4-hydroxy-2-pentenoate **1**. Reagents and conditions: (a) *hv*, Rose Bengal, CH_3OH; (b) (i) EtOH, $BF_3{\cdot}Et_2O$, (ii) $KHSO_4$; (c) Amberlyst-15, H_2O, acetone, (39%, three steps); (d) CH_3MgCl, THF, −78 °C, 72%.

Table 1. Diastereoselectivity in the epoxidation of **1** in different solvents



Entry	Solvent	*T* (°C)/*t* (h)	*anti*/*syn*[a]	Yield (%)
1	THF/HMPA	−20/20	88/12	42
2	THF/DMF	−20/20	85/15	51
3	THF	−20/20	75/25	40
4	Hexanes	−20/20	54/46	25
5	Toluene	−20/20	32/68	53

[a] Ratio measured over ^{13}C NMR in reaction crude.

reached in favour of the *anti* diastereomer. If DMF or HMPA are used as co-solvents in the presence of THF the selectivity was better than in THF itself.

The poorest selectivity was obtained using hexanes, toluene gave the *syn* isomer as the major one, opposite to selectivity reached using more polar solvents.

The solvent effect can be rationalised in terms of the solvation of lithium cation by the solvent: the better the solvent coordinates to lithium (THF, DMF and HMPA[12]), the better selectivity is observed furnishing *anti* isomer as the major one.

Table 2. Diastereoselectivity in the epoxidation of **1** at different temperatures

Entry	Solvent	*T* (°C)/*t* (h)	*anti*/*syn*[a]	Yield (%)
1	THF	−80/72	73/27	30
2	THF	−60/46	78/22	55
3	THF	−40/24	77/23	54
4	THF	−20/20	75/25	60
5	THF	0/14	74/26	55
6	THF	25/3	78/22	52
7	THF	50/5	76/24	45

[a] Ratio measured over ^{13}C NMR in reaction crude.

The selectivity was also studied at different temperatures, all the assays were done using ethyllithium as base and THF as solvent but differing on the temperature and time (Table 2).

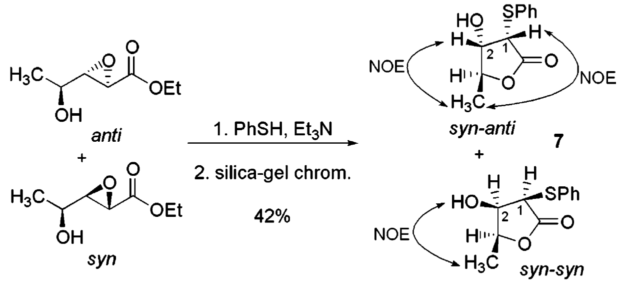
Table 2 shows there is no temperature dependence since the diastereomeric ratios at different temperatures in a range between −80 and 50 °C are same within experimental error.

On the other hand, compound **1** was protected as *O-tert*-butyldiphenylsilyl ether and the protected compound **6** was epoxidised under the same conditions as **1** (in this case room temperature was needed for reaction go to completion). The epoxidation of compound **6** was nonselective (*dr* 55:45), this result shows that the free hydroxyl is key for stereoselection (Scheme 3).

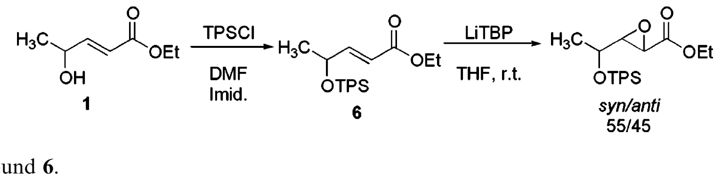
The stereochemistry of epoxides was assigned by transforming the mixtures of epoxides through treatment with thiophenol, which opened the oxirane ring through attack of the more reactive position followed by cyclisation of the resulting diol to afford the corresponding diastereomeric γ-butyrolactones **7**, separable by silica-gel chromatography (Scheme 4).

The stereochemical assignment was performed by NOE experiments over the γ-butyrolactones: major γ-butyrolactone gave NOE between the methyl and H-1 and between the methyl and H-2 whilst the minor γ-butyrolactone gave NOE between the methyl and OH but not between the methyl and H-1.[13]

In summary, we report a study of the influence of the temperature and solvent over the stereoselectivity in the epoxidation of γ-hydroxy α,β-unsaturated esters employing lithium *tert*-butyl peroxide. The results described herein show that the reaction is dependent on the nature of the solvent and is not influenced by the temperature when THF is used. Studies of the influence of protecting groups and substituents in the epoxidation of these compounds is currently underway in our laboratory.



Scheme 4. Opening of epoxyalcohols.



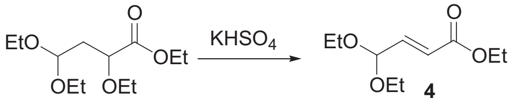
Scheme 3. Epoxidation of compound **6**.

Acknowledgements

This work was financed by Conselleria d'Educació, Cultura i Ciència de la Generalitat Valenciana (CTIDIA/2002/124) and Bancaixa-UJI foundation (PI-1B2002-06). We thank Serveis Centrals d'Instrumentació Científica de la Universitat Jaume I for technical support and especially Prof. William R. Roush for helpful discussions.

References and notes

1. (i) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 4435–4436; (ii) Saito, S.; Takahashi, N.; Ishikawa, T.; Moriwake, T. *Tetrahedron Lett.* **1991**, *32*, 667–670; (iii) Lanier, M.; Pastor, R. *Tetrahedron Lett.* **1995**, *36*, 2491–2492; (iv) Righi, G.; Rumboldt, G. *J. Org. Chem.* **1996**, *61*, 3557–3560; (v) Concellón, J. M.; Bardales, E. *Org. Lett.* **2002**, *4*, 189–191; (vi) Tosaki, S.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 495–498; (vii) Concellón, J. M.; Bardales, E.; Llavona, R. *J. Org. Chem.* **2003**, *68*, 1585–1588.
2. Fernández de la Pradilla, R.; María Victoria Buergo, M. V.; Manzano, P.; Montero, C.; Priego, J.; Viso, A.; Cano, F. H.; Martínez-Alcázar, M. P. *J. Org. Chem.* **2003**, *61*, 4797–4805.
3. (i) Jackson, R. F. W.; Standen, S. P.; Clegg, W.; McCamley, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 149–156; (ii) Jackson, R. F. W.; Standen, S. P.; Clegg, W. *J. Chem. Soc., Perkin Trans. 1* **1995**, 141–148.
4. (i) Meth-Cohn, O.; Moore, C.; Taljaard, H. C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2663–2674; (ii) Yang, N. C.; Finnegan, R. B. *J. Am. Chem. Soc.* **1958**, *5*, 5845–5848.
5. For stereoselective Michael reactions of γ-alkoxy α,β-unsaturated esters see: (i) Yamamoto, Y.; Chounan, Y.; Nishii, S.; Ibuka, T.; Kitahara, H. *J. Am. Chem. Soc.* **1992**, *114*, 7652–7660; (ii) Asao, N.; Shimada, T.; Sudo, T.; Tsukada, N.; Yazawa, K.; Gyoung, Y. S.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 6274–6282.
6. Although the reactions in Scheme 2 appear in the literature, they have been optimised so as to provide an efficient way of making aldehyde **5**.
7. White, J. D.; Carter, J. P.; Kezar, H. S., III. *J. Org. Chem.* **1982**, *47*, 929–932.
8. Meyers, A. I.; Nolen, R. L.; Collington, E. W.; Narwid, T. A.; Strickland, R. C. *J. Org. Chem.* **1973**, *38*, 1974–1982.
9. Distillation over potassium bisulfate of the crude is necessary to convert a nondesired product resulting from ethanol incorporation into the desired alkene **4**:



See: Fariña, F.; Victory, P. *Tetrahedron Lett.* **1969**, *38*, 3219–3222.
10. Coppola, G. M. *Synthesis* **1984**, 1021–1023.
11. When we used *n*-BuLi partial transesterification of the epoxy ethyl ester was observed, this must be due to the formation of *n*-BuOLi from oxidation of *n*-BuLi by TBPLi (see: Boche, G.; Mbus, K.; Harms, K.; Lohrenz, J. C. W.; Marsch, M. *Chem. Eur. J.* **1996**, *2*, 604–607) or probably already present in the *n*-BuLi. If EtLi is used, the ester is not affected.
12. Reich, H. J.; Sikorski, W. H. *J. Org. Chem.* **1999**, *64*, 14–15.
13. Modelling of the lactones give as the closest distance between the methyl and H-1: 3 Å for *syn–anti* lactone (possible NOE) and 4.2 Å for the *syn–syn* one (no possible NOE).