Tetrahedron Letters, Vol.31, No.45, pp 6589-6592, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

A GENERAL STEREOSPECIFIC SYNTHESIS OF γ-HYDROXY-α,β-UNSATURATED ESTERS

L. Thijs, F.J. Dommerholt, F.M.C. Leemhuis and B. Zwanenburg*
Department of Organic Chemistry, University of Nijmegen,
Toernooiveld, 6525 ED Nijmegen, The Netherlands

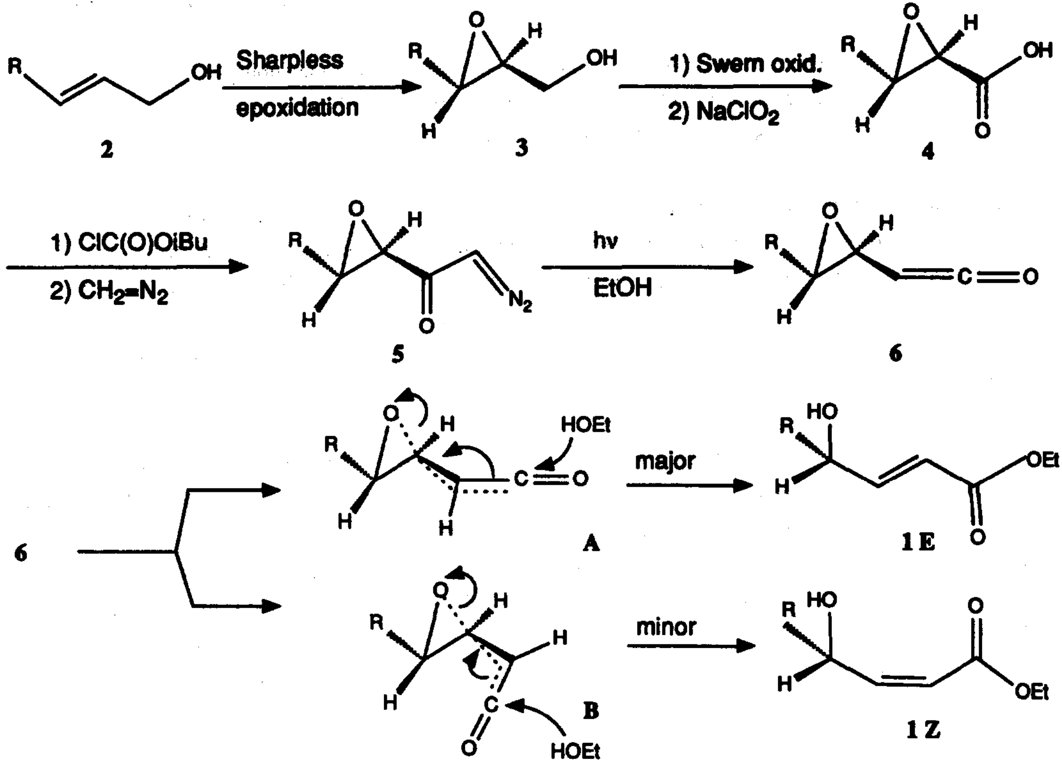
Abstract: *A stereospecific synthesis of optically active γ-hydroxy-α,β-unsaturated esters is achieved, involving successively the Sharpless epoxidation of allylic alcohols, oxidation to glycidic acids, conversion into α,β-epoxy diazomethyl ketones, and irradiation in ethanol at 300 nm. Intermediates in the photo-induced rearrangement are epoxy ketenes, which undergo ethanolysis with simultaneous opening of the epoxide, preferably via a transition state involving the s-trans conformation.*

The γ-hydroxy-α,β-unsaturated ester unit is encountered in several natural products.[1] A general and reliable synthesis of homochiral γ-hydroxy-α,β-unsaturated esters **1** is therefore of interest. The methods described in the literature[2] are lacking general applicability and cannot readily be incorporated in synthetic sequences leading to natural products. In this paper we wish to draw attention to the photo-induced rearrangement of α,β-epoxy diazomethyl ketones[3] **5** in an alcoholic solvent as a good synthetic entry to these γ-hydroxy-α,β-unsaturated esters in an enantiomerically pure form. The substrates required for the preparation of the epoxy diazo ketones **5** are glycidic acids **4**, which are readily obtained, in an almost enantiomerically pure form, by means of the Sharpless epoxidation of allylic alcohols **2** and subsequent oxidation. The total sequence for the synthesis of the target molecules **1** is depicted in the scheme.

By choosing the proper chiral inductor during the Sharpless epoxidation the chirality at Cγ in **1** can be selected at wish. An essential requirement for this route leading to **1** is that there is no loss of chiral integrity during the photo-induced rearrangement or at any other step in the sequence. Both antipodes of epoxy diazo ketones with R is a phenylgroup were prepared from the respective glycidic acids **4** and subsequently converted in the corresponding methyl 4-phenyl-4-hydroxy-but-2-enoates by irradiation in methanol[4]. The resulting esters had the same $[\alpha]_D$ values but with a different sign and more convincingly an ^{1}H-NMR analysis of the corresponding acetate using chiral shift reagents[5] showed the presence of one single enantiomer in both cases.

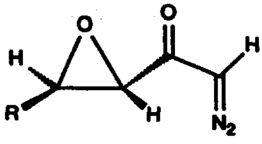
The synthesis of glycidic esters from the epoxy alcohols **3** can be performed by oxidation with ruthenium tetroxide[6] when the R substituents are not functionalized. However, when functional groups are present a two-step oxidation procedure, involving the Swern oxidation to the corresponding epoxy aldehyde followed by oxidation to the carboxylic acid using sodium chlorite, is most appropriate[7]. The Swern oxidation was compared with several other methods and was found superior particularly because the conservation of the optical integrity was the best. The thus obtained glycidic acids were treated, without purification, with isobutyl chloroformate and triethylamine to give mixed anhydrides, which then were added to an excess of ethereal diazomethane. The yields of epoxy diazo ketones **5** are in the range 50-70% based on epoxy alcohol **3** (see table).

Scheme

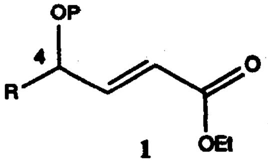


Irradiation of the diazo compounds is conveniently carried out in absolute ethanol at a conc. of 5.10^{-3} Mol/l and at a wavelength of 300 nm. The formation of the hydroxy esters **1** proceeds through the intermediacy of epoxy ketene[3] **6**. Subsequent reaction of ethanol with this ketene occurs with simultaneous opening of the epoxide ring. During the formation of the C_2-C_3 double bond in **1** the π-orbital of the developing carbanionic center at C_2 must be parallel to the C_3-oxygen bond. For this process two transition states, which are probably highly ordered[8], can be envisaged, viz. A(s-trans) and B(s-cis). The former clearly experiences less steric interaction than the latter because of the presence of allylic strain effects herein. Accordingly, the E-alkene esters are the predominant products. Invariably, however, these E-alkene esters are accompanied by a small amount of Z-alkene ester (ca 10%).

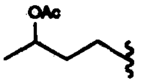
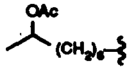
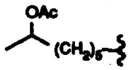
Before purification and use in further syntheses, the alcohol function in compounds **1** was protected with an acetyl or *t*-butyldimethylsilyl group. The optical purity of the protected products **1** obtained, was established by means of a combination of optical shift reagent[5] and 400 Mhz NMR spectroscopy. For this purpose compound **1f** had to be hydrolyzed to the C_7-alcohol, oxidized to the C_7-ketone, hydrolyzed to the C_4-alcohol and acetylated. As can be seen from the Table, the e.e. values are ca. 90%, which is the normal value obtained by Sharpless epoxidation. We may therefore conclude that there is no loss of optical activity during the transformation of an epoxy alcohol to a γ-hydroxy-α,β-unsaturated ester. The synthesis of



5



1

	R	P	config	yield(%)	config	yield(%)	e.e.(%)
a	$C_{10}H_{21}$	Ac	3S,4R	47	4R	50	90
b	$C_{10}H_{21}$	Ac	3R,4S	52	4S	54	80
c	$C_{10}H_{21}$	Ac	rac.	60	4R,S	58	<5
d	C_4H_9	Ac	3R,4S	72	4S	50	92
e	C_5H_{11}	Ac	3R,4S	70	4S	63	91
f		t-BuMe$_2$Si	3S,4R,7R	56	4R,7R	61	91
g		t-BuMe$_2$Si	3R,4S,11R	58	4S,11R	48	*
h		t-BuMe$_2$Si	3R,4S,10R	63	4S,10R	46	**

* Used for the synthesis of natural Patulolide C

** Used for the synthesis of homochiral nor-Patulolide C

compounds **1** presented above is general and very adaptable for the synthesis of natural products as exemplified by the total synthesis of aspicilin[9], patulolide C[10], colletallol[11] and pyrenophorol[11].

Experimental Procedure

Preparation of epoxy diazomethyl ketones **5**. To an ice-cooled and stirred solution of the glycidic acid (10 mmoles) in dry ether (50 ml) was added *i*-butyl chloroformate (10 mmoles) followed by triethylamine (12 mmoles). After stirring for 30 min. the precipitate was filtered off and the filtrate was added to excess of diazomethane solution in ether. The mixture was left overnight. Excess diazomethane was removed by flushing wih nitrogen. After evaporation of the solvent the residue was purified by flash-chromatography (hexane-EtOAc).

Preparation of γ-hydroxy-α,β-unsaturated esters **1**. A nitrogen flushed solution of epoxy diazomethyl ketone **5** (5.10^{-3} mol/l) in ethanol was irradiated with UV-light (300nm)[12]. The rearrangement was monitored by IR-spectroscopy (disappearance of the diazo absorption) and was completed usually after 1.5-2 hrs.

Evaporation of the ethanol gave the crude product that was acetylated or *t*-butyldimethylsilylated. Purification was achieved by flash-chromatography.

REFERENCES

1. Brefeldine: A. E. Harri, W. Loeffler, H. P. Sigg and C. Tamm, Helv. Chim. Acta, 46, 1235 (1963), Cytochalasin B: M. Binder and C. Tamm, Angew. Chemie, 85, 369 (1973), Colletodiol: J. Mac Millan and T. J. Simpson, J. Chem. Soc. Perkin Trans I, 1487 (1973), R. Amstutz, E. Hungerbuehler and D. Seebach, Helv. Chim. Acta 64, 1796 (1981), G. E. Keck, E. P. Boden and M. R. Wiley, J. Org. Chem., 54, 896 (1989).
2. For recent work see: K. Burgess and I. Henderson, Tetrahedron Asymmetry, 1, 57 (1990), Tetrahedron Lett., 30, 4325 (1989), H. J. Gais, Angew. Chemie, 96, 142 (1984).
3. N. F. Woolsey and M. H. Khalil, J. Org. Chem., 40, 3521 (1975), P. M. M. van Haard, L. Thijs and B. Zwanenburg, Tetrahedron Lett., 803 (1975).
4. These epoxy diazo ketones were obtained in homochiral form from the glycidic acids whose resolution has recently been published: L. Thijs, J. J. M. Porskamp, A. A. W. M. van Loon, M. P. W. Derks, R. W. Feenstra, J. Legters and B. Zwanenburg, Tetrahedron, 46, 2611 (1990).
5. Best results were obtained with Eu(hfc)$_3$: Tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]-Europium.
6. H. J. Carlsen, T. Katsuki, V. S. Martin and K. B. Sharpless, J. Org. Chem., 46, 3936 (1981).
7. B. S. Bal, W. E. Childers and H. W. Pinnick, Tetrahedron, 37, 2091 (1981).
8. For stereoselective S_N2' additions to chiral acyclic vinyloxiranes, see J. A. Marshall and J. D. Trometer, Tetrahedron Lett., 28, 4985 (1987).
9. P. P. Waanders, L. Thijs and B. Zwanenburg, Tetrahedron Lett., 28, 2409 (1987).
10. L. Thijs, D. M. Egenberger and B. Zwanenburg, Tetrahedron Lett., 30, 2153 (1989).
11. F. J. Dommerholt, L. Thijs and B. Zwanenburg, to be published.
12. Four Philips TL 20W/12 lamps fitted in a wooden box.

(Received in UK 28 August 1990)