

AN EFFICIENT ASYMMETRIC SYNTHESIS OF SUBSTITUTED PHENYL GLYCIDIC ESTERS

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SUMMARY: Chiral substituted glycidic esters have been prepared from their corresponding chalcones *via* a two step procedure consisting of an asymmetric epoxidation mediated by a poly-L-leucine polymer, followed by a previously unreported Baeyer-Villiger oxidation. The regioselectivity of this latter procedure was found to depend on the aryl substituent.

The chiral phenyl-substituted glycidic ester is an important synthetic intermediate in organic synthesis. From this key intermediate a variety of other chiral compounds (eg. acids, amides, etc.) can be easily prepared.¹ During a recent investigation on the preparation of another important chiral synthon, the epoxyketone, it became apparent that the glycidic esters can be prepared from this precursor in a direct fashion.

Asymmetric epoxidation of chalcones have been reported using a triphasic system of H₂O₂/NaOH, an organic solvent, and a polyamino acid² or *via* asymmetric catalysis.³ The yields and optical purity of the resulting epoxides have varied from poor to excellent, depending on the conditions and method used.

We herein report an extension of the Julia method that affords chiral epoxyketones in good yields and optical purity. Epoxidation of substituted chalcones⁴ (1a-e) with a poly-L-leucine polymer⁵ and H₂O₂/NaOH in CCl₄ for 42 hours at ambient temperature affords the desired chiral epoxyketones (2a-e).⁶ The optical purity of the epoxyketones were determined using chiral HPLC⁷ by comparison with their racemates⁸ (Table 1).

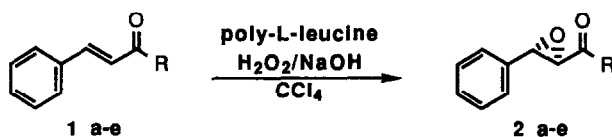
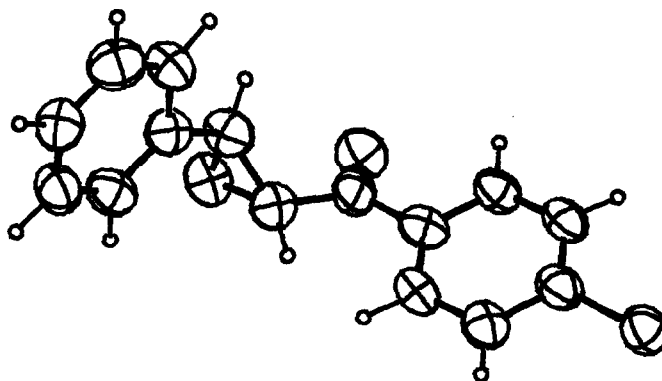


TABLE 1. ASYMMETRIC EPOXIDATION OF SUBSTITUTED CHALCONES

ENTRY	R	YIELD(%) ^a	ee(%) ^b	ee(%) ^c	MP(°C)	[α] _D ^d ₅₈₉
2a	Phenyl	76	68	88	57-58	-195.0 ° (c, 2.73)
2b	<i>p</i> -Cl-Phenyl	79	88	86	92-93	-162.4 ° (c, 1.44)
2c	<i>p</i> -OMe-Phenyl	77	90	92	62-63	-154.8 ° (c, 1.27)
2d	<i>p</i> -Me-Phenyl	87	92	94	59-60	-200.9 ° (c, 1.03)
2e	2-Naphthyl	83	92	>98	110-112	-137.2 ° (c, 1.45)

- a) Yields based on recrystallized material. b) % ee of crude product. c) % ee of recrystallized material.
d) All optical rotations taken in THF.

The absolute configuration of the epoxyketones (**2a-e**) were assigned to be 2R, 3S. This was determined by an X-ray crystal structure determination of **2b**.⁹ The R configuration is assigned to the carbon α to the ketone and the S configuration to the carbon β to the ketone functionality.



X-ray structure of **2b**

It is seen from the table that the resultant asymmetric induction in the epoxidation depends on the ketone substituent. The *p*-methoxy, tolyl and naphthyl groups offering especially high enantiopurities.

Conversion to the glycidic ester was achieved via a previously unreported Baeyer-Villiger¹² oxidation of the epoxyketones. The epoxyketones (**2a-e**) were treated with 2.8 equivalents of *m*-chloroperoxybenzoic acid in refluxing methylene chloride under N₂ for 16 h. The solution was then concentrated to approximately one-half its original volume and cooled to 0 °C for 2 h. The *m*-chlorobenzoic acid was filtered off and washed with a small amount of methylene chloride. The filtrate was concentrated to dryness and the residue recrystallized with ethyl acetate/hexane to afford the glycidic esters (**3a-e**) in good yield. The optical purity was determined via chiral HPLC¹³ in comparison with the racemates¹⁴ (Table 2).

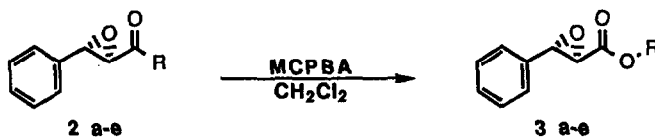


TABLE 2. BAEYER VILLIGER OXIDATION OF CHIRAL EPOXY KETONES

ENTRY	R	YIELD(%) ^a	ee(%) ^b	MP(°C)	$[\alpha]_{589}^d$
3a	Phenyl	74	>99	89-90	-184.7 ° (c, 1.18)
3b	<i>p</i> -Cl-Phenyl	63	88	135-136	-176.3 ° (c, 1.14)
3c	<i>p</i> -OMe-Phenyl	57	90	86-87	-163.6 ° (c, 1.06)
3d	<i>p</i> -Me-Phenyl	80	>99	84-85	-189.7 ° (c, 1.09)
3e	2-Naphthyl	59	>99	118-119	-202.2 ° (c, 1.36)

a) Yields based on recrystallized material. b) % ee of recrystallized material.

c) All optical rotations taken in THF.

Again, the substituent plays an important role in the regioselectivity of the reaction since we found that with **3b** the reaction lacked regioselectivity. This resulted in the formation of a byproduct (ca. 20%) where the epoxide moiety had migrated.¹⁵ We have demonstrated that one can prepare optically active epoxyketones and glycidic esters in good yields and on a multihundred gram scale if needed, from their corresponding chalcones. Presumably the opposite enantiomer can be prepared in the same fashion by using the poly-D-leucine polymer. It should also be pointed out that the poly-L-leucine polymer can be recovered, dried and reused without any decrease in yield or optical purity. Thus a variety of important optically active building blocks can be assembled in a quick and accessible fashion.

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- Chalcone (**1a**) and *p*-methoxychalcone (**1c**) were from Aldrich Chemical Company. *p*-Chlorochalcone (**1b**) was obtained from Lancaster Synthesis. *p*-Methylchalcone (**1d**) and 2-naphthylchalcone (**1e**) were synthesized according to the following literature procedure: *Org. Synth.* **1947**, *Collect. Vol. I*, 78. NOTE: NaOEt was substituted for NaOH.
- Poly-L-leucine polymer, molecular weight 3,000-15,000, was obtained from Sigma Chemical Company, St. Louis, MO.
- All compounds has satisfactory elemental analyses, ¹H NMR, ¹³C NMR, optical rotations and melting points.
- The optical purities of the chiral epoxyketones (**2a-e**) were determined using the following columns (4.6 mm I.D. x 25 cm) and conditions at a wavelength of 211 nm: (**2a**) Daicel OP (+) with a methanol mobile phase at a flowrate of 1.5 mL/min. (**2b**) Daicel OC with a hexane/2-propanol (1:1) mobile phase at a flowrate of 1.0 mL/min. (**2c-d**) Daicel OC with a hexane/2-propanol mobile phase at a flowrate of 0.5 mL/min. (**2e**) Daicel OA with a hexane/2-propanol mobile phase at a flowrate of 2.0 mL/min.
- The racemic epoxyketones were prepared by epoxidation of the chalcones (**1a-e**) with H₂O₂ in toluene using a phase transfer catalyst (Aliquot 336). Both enantiomers of the racemates were resolved using chiral HPLC with the conditions cited in note 7.

9. Crystals of **2b** were grown by slow evaporation from isopropanol; specimen: 0.50 x 0.45 x 0.05 mm needle. Crystal data: $C_{15}H_{11}ClO_2$, $M_r = 258.71$, monoclinic, $P2_1$, $a = 5.559(4)$, $b = 9.914(6)$, $c = 11.319(8)\text{\AA}$, $\beta = 94.92(8)^\circ$, $V = 621.6(12)\text{\AA}^3$, $Z = 2$, $T = 173\text{K}$, $F(000) = 268$, $\mu = 26.657\text{ cm}^{-1}$, $\rho_{\text{calc}} = 1.382\text{ g}\cdot\text{cm}^{-3}$ for graphite monochromatized copper radiation ($\lambda = 1.5406\text{\AA}$). A quadrant of data and the Friedel mates of these were collected on an Enraf-Nonius CAD-4 diffractometer in an ω - 2θ mode with variable scan speeds. A total of 2086 reflections were measured ($-6 \leq h \leq 0$; $0 \leq k \leq 11$; $-13 \leq l \leq 13$). The structure was solved by direct methods and refined by full-matrix least-squares methods where the function minimized was $\sum w(|F_o| - |F_c|)^2$. Weights (w) were assigned as $1/s^2(F_o)$ with $s^2(F_o) = [\sigma^2(I_o) + (0.06F_o)^2]$. Nonhydrogen atoms were refined with anisotropic thermal parameters. H-atom positions were assigned based on geometrical considerations with isotropic temperature factors fixed as $1.3 \times U_C$. Enantiomer assignment was based on analysis of Friedel mates and an R-factor ratio test. For the 1815 unaveraged data, corrected empirically for absorption (max., min. and ave. correction factors 1.513, 0.519, and 0.970), the residual values were R (0.085), wR (0.111) for the (2R,3S) isomer; for the enantiomer, R (0.095), wR (0.126). The difference is significant at the 99.995% confidence level.¹⁰ Of the 28 Friedel pairs which showed F_c differences of 12% or more, 25 of the signs of the intensity ratios pointed to the (2R,3S) isomer as the correct enantiomer. Refinement was completed with averaged data; 861 observations with $I \geq 3\sigma(I)$, residuals R (0.074), wR (0.099), GOF (1.718) for 162 variables. Maximum excursions in a final difference Fourier map were $\pm 0.509\text{ e}\text{\AA}^{-3}$. Neutral atom scattering factors, including values of $\Delta f'$ and $\Delta f''$ for nonhydrogen atoms, were used in computations with a locally modified SDP¹¹ program system. Additional details have been deposited with the Cambridge Crystallographic Database.
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13. The optical purity of the chiral glycidic esters (**3a-e**) were determined using a Daicel OC column (4.6 mm I.D. x 25 cm) with the following mobile phase and wavelengths: (**3a**) Hexane/2-propanol (1:1) at a flowrate of 0.5 mL/min at 211 nm. (**3b,d**) Hexane/2-propanol (1:1) at a flowrate of 0.5 mL/min at 211 nm. (**3c**) Hexane/2-propanol (1:1) at a flowrate of 1.5 mL/min at 223 nm. (**3e**) Hexane/2-propanol (19:1) at a flowrate of 2.0 mL/min at 219 nm.
14. The racemic glycidic esters were prepared using identical Baeyer-Villiger conditions on the racemic epoxyketones. These were resolved using the chiral HPLC conditions cited in note 13.
15. The byproduct was isolated and fully characterized by mass spec, ^1H and ^{13}C NMR and assigned the following structure:

