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Efficient Synthesis of Chiral α,β-Epoxyesters via a Cyclic Sulfate Intermediate

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Abstract: An efficient synthesis of chiral α,β-epoxyester **1** from chiral 2,3-dihydroxyester **2** has been developed. Ester **2** is converted to the corresponding cyclic sulfate **3**, which is opened with either LiBr in THF or Bu_4NBr in acetone at rt to furnish 2-bromo-3-hydroxyester **4**. Treatment of **4** with K_2CO_3 in methanol at low temperature gives α,β-epoxyester **1** in excellent overall yield and in the same ee as in the starting diol.

Epoxyesters are important chiral building blocks for the preparation of a wide variety of natural products with potential pharmaceutical applications. For example, α,β-epoxyesters **1** have been opened regioselectively: (1) with MgI_2 followed by reduction with Bu_3SnH to provide α-hydroxyesters;[1] (2) with $TMSN_3$ followed by reduction to furnish 2-amino-3-hydroxyesters;[2] (3) with $MgBr_2$ followed by azide substitution and reduction to afford 3-amino-2-hydroxyesters.[3] Although cyclic sulfate **3** tends to be more reactive than the epoxyester **1** toward nucleophiles, the regioselectivities of **1** and **3** could be completely different.[4]

Darzens glycidic ester condensation is one of the earliest methods to prepare non-chiral α,β-epoxyesters.[5] A modified aldol-type condensation of chiral 3-(haloacyl)-2-oxazolidinones with aldehydes followed by cyclization mediated by $PhCH_2OLi$ provides chiral epoxyesters.[6] However, this method requires the use of an expensive chiral auxiliary, and the yield of the halohydrin-making step was only 50-60%. A general method to prepare chiral epoxyester **1** from an allylic alcohol is the following three-step sequence of reactions: (i) Sharpless asymmetric epoxidation of an allylic alcohol; (ii) oxidation of the epoxy alcohol; (iii) esterification of the epoxyacid. However, asymmetric epoxidation of *trans* allylic alcohols often results in unsatisfying enantiomeric excess (< 90% ee) and chemical yield,[7] even though the method has been refined after it was first developed. The oxidation also gives only moderate chemical yield although the conversion is facile.[8] In contrast, the Sharpless asymmetric dihydroxylation (AD) of *trans*-α,β-olefinic esters (easily accessed through the Wittig reaction) generally results in high chiral purity (> 95% ee) and excellent chemical yield of diol **2**.[9] We took advantage of this unique merit, together with the ease in handling of the subsequent reactions, to develop a high yield route toward the preparation of **1**, as shown in Scheme 1.

The vicinal diol **2** is first converted to the cyclic sulfate **3** using a modification of the procedures developed by Sharpless et al.[10] The conversion can be completed in one pot; use of an acid scavenger (pyridine, Et_3N) makes the method compatible with acid-sensitive functionalities, such as TBDPS as shown in Table 1 (entry 9). Another advantage of using an acid scavenger is that it greatly shortens the reaction time. Typically the reaction

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Scheme 1. Synthesis of Epoxyester 1 from 2,3-Diol Ester 2

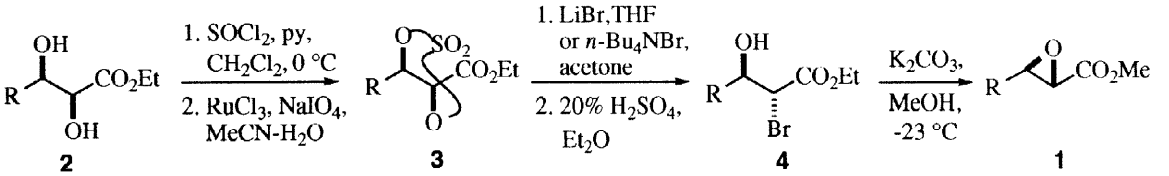
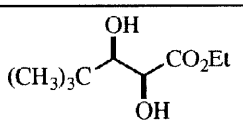
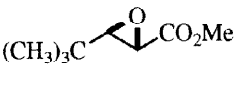
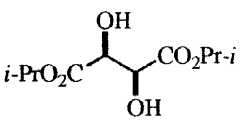
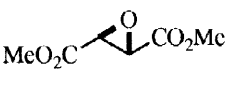
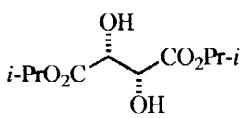
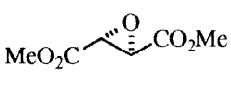
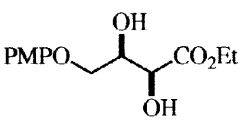
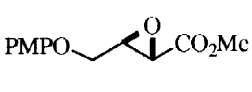
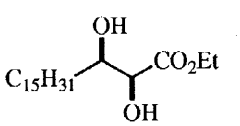
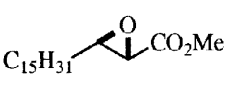
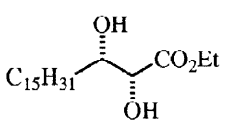
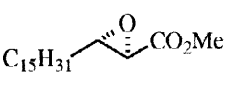
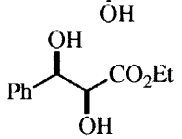
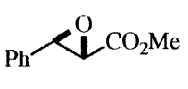
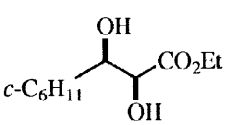
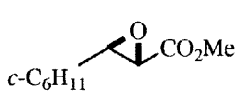
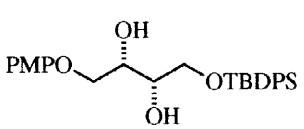
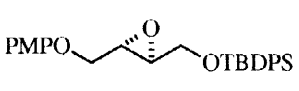


Table 1. Yields and ee of Epoxides Synthesized from Diols

Entry	Vicinal Diol[a]	Epoxyester	Product (1)		
	2	1	% Yield[b]	% ee[c]	$[\alpha]_D^{25}$ [d]
1			91		+7.8°
2			86	97	+137.6°[e] [lit.[11a] +136.7°][e]
3			86	98	-137.3°[e]
4			94		+44.5°
5			93	98	+16.8°
6			94	97	-17.6°
7			80		+179.4° [lit.[11b] +179.7°]
8			95		+24.4°
9			88		-15.0°

[a] All diols except those in entries 2 and 3 were prepared from the corresponding *E*-olefins using procedures in ref. 9b. The diols in entries 2 and 3 were obtained from Aldrich. [b] Isolated yields based on diols. [c] The ee was calculated by 400-MHz ^{1}H-NMR in the presence of Eu(hfc)$_3$. [d] Optical rotations were measured in $CHCl_3$ (*c* 1-2), unless noted otherwise. [e] (*c* 1.26, MeOH).

of diol **2** with $SOCl_2$ is complete in 10 min. Cyclic sulfate **3** is obtained by oxidation of the cyclic sulfite with RuO_4 ($NaIO_4$/cat. $RuCl_3$) in McCN-H_2O.

Ring opening of cyclic sulfate **3** with Br^- is generally carried out for 2 h at rt, but for substrates with high steric hindrance (Table 1, entries 1 and 9), higher temperature (50-60 °C) and longer reaction times are required. Even though there are two regiochemical possibilities for opening of the cyclic sulfate with Br^-, both regioisomers lead to the same chiral product, since bromide ion serves as a leaving group in the subsequent step, and a double inversion of the reaction center is involved. Because the C=O group of the ester activates the α position,[4,10] ring opening with Br^- occurs almost exclusively ($\alpha/\beta > 20$) at the 2 position of ester **3**. Hence in entries 1-8, only one isomer of bromohydrin **4** was observed by NMR, whereas when no ester functionality was present as in entry 9, both isomers were isolated in a ratio of 4:1 and characterized by ^{1}H- and ^{13}C-NMR. The major isomer was formed by attack of Br^- at the OPMP side of cyclic sulfate **3**. This regioselectivity may be due in part to the steric effect of the TBDPS group. The high chiral purity of several products was demonstrated by ^{1}H-NMR in the presence of Eu(hfc)$_3$ and by comparison of the specific rotations of the products in entries 2 and 7 with the literature data.[11]

To minimize the decomposition of epoxyester **1** in basic media during cyclization, low temperature (-23 °C) was employed.[12] However, in all entries studied except entry 9, epoxidation could still be completed within 30 min, but a mixture of methyl and ethyl/isopropyl epoxyesters was observed if the reaction was quenched at this stage. Therefore, epoxide formation was allowed to proceed for a period of 3.5-4 h at -23 °C in order to complete the ester exchange from ethyl or isopropyl to methyl. In entry 9, cyclization at 0 °C proceeded only very slowly, apparently because of the deactivating effect of the aryloxy and silyloxy groups as well as the steric hindrance of the TBDPS group. However, at rt the reaction was completed within 1.5 h.

The reaction sequence shown in Scheme 1 is simple to carry out. Generally no column separation of intermediates **3** and **4** is required since in each step the conversion is almost quantitative and the by-products are salts, which are easily removed by filtration through a pad of silica gel.[13] To isolate the epoxide from the reaction mixture, one could either choose to quench the reaction by adding aqueous NH_4Cl followed by extracting with CH_2Cl_2, or simply adding Et_2O and passing the mixture through a pad of silica gel, then concentrating, dissolving the residue in CH_2Cl_2, and passing the solution through a pad of silica gel again. Both isolation procedures provided almost pure epoxyester **1** based on TLC and NMR. Because the cyclic sulfate of the cinnamate derivative (entry 7) was extremely unstable, isolation gave only decomposed by-products. However, the problem was overcome by filtering the mixture quickly through a short column containing silica gel and Celite (~1:1) into a THF solution containing a large excess of LiBr as soon as the oxidation was completed (about 4-5 min).

In conclusion, a simple enantioselective synthetic route to the important epoxyesters **1** with excellent chemical yield and chiral purity has been developed. This method also tolerates acid-sensitive functional groups, and is applicable to diether vicinal diols (entry 9).

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References and Notes

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12. When epoxide formation in entry 1 was attempted at rt, the product was obtained in only 40% yield. Since we did not use dry MeOH, the low yield obtained at rt may result from ring opening and/or saponification.
13. General procedure (entry 5): To a solution of ethyl (2*R*,3*R*)-2,3-dihydroxyoctadecanoate (345 mg, 1.0 mmol) and pyridine (242 mg, 3.0 mmol) in 15 mL of dry CH_2Cl_2 was added $SOCl_2$ (102 μL, 1.4 mmol) at 0 °C. After 10 min, the reaction mixture was filtered through a pad of silica gel, which was rinsed with 4:1 hexane-EtOAc. The filtrate was concentrated to give a cyclic sulfite. To a solution of the sulfite in CH_3CN (10 mL) were added $NaIO_4$ (321 mg, 1.5 mmol) and then a solution of $RuCl_3 \cdot H_2O$ (2.5 mg, 0.01 mmol) in H_2O (2 mL). After the mixture was stirred for 10 min, Et_2O (20 mL) was added to precipitate the salts. The clear solution was separated and the slurry was washed twice with Et_2O (20 mL each), and dried (Na_2SO_4). The combined Et_2O solution was passed through a pad of silica gel to remove the salts. Concentration of the filtrate gave 385 mg (95%) of cyclic sulfate **3** as a pure product (TLC and NMR). To a solution of **3** in dry THF (15 mL) was added anhydrous LiBr (347 mg, 4.0 mmol). Alternatively, to a solution of **3** in 15 mL of acetone was added *n*-Bu_4NBr (1.29 g, 4 mmol). The mixture was stirred under nitrogen until the disappearance of **3**. After solvent was removed in vacuo, Et_2O (30 mL) and 20% aqueous H_2SO_4 (20 mL) were added to the residue. The mixture was stirred vigorously for 4 h, then the layers were separated, and the aqueous layer was extracted with Et_2O (2 x 30 mL). The combined ether layer was dried over Na_2SO_4 with $NaHCO_3$ and concentrated. To a solution of crude bromohydrin **4** in 8 mL of MeOH was added anhydrous K_2CO_3 (552 mg, 4.0 mmol). After the heterogeneous mixture was stirred at -23 °C under nitrogen for 3.5-4 h, saturated aqueous NH_4Cl solution (15 mL) and H_2O (5 mL) were added to quench the reaction. Extraction with CH_2Cl_2 provided 304 mg (93% yield, 97% ee) of epoxyester **1** as a pure product (by TLC and NMR).