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EASY AND GENERAL METHOD TO SYNTHESIZE CHIRAL 2-HYDROXYACID BENZOATES

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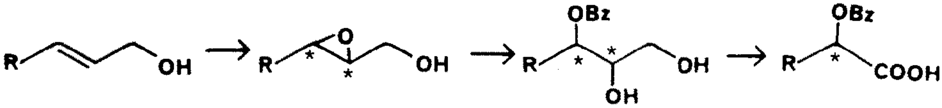
Abstract: The synthesis of 2-hydroxyacid benzoates, with high yields and excellent enantioselectivity, by regioselective opening of chiral 2,3-epoxyalcohols and ruthenium dioxide oxidation, is described.

Chiral 2-hydroxyacids are one of the most important kinds of compounds used in asymmetric synthesis either as building blocks or as chiral auxiliaries.1) Unfortunately only a few of them are available from natural sources as a single enantiomer. The other enantiomer or the remainder 2-hydroxyacids are available by resolution of the racemic mixture or by preparation through a series of steps from commercially available related compounds.1)

In this communication we describe an easy procedure to synthesize 2-hydroxyacid benzoates 4 which make use of the chiral 2,3-epoxyalcohols 2, readily prepared by the asymmetric epoxidation2) of an adequate E-allylic alcohol 1 (Scheme I).

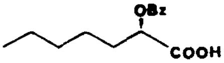
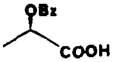
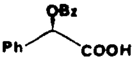
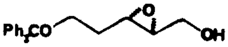
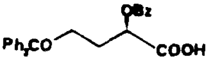
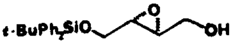
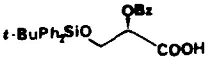
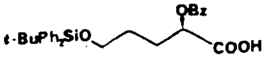


Scheme I

In Table I we describe the results obtained from a series of chiral 2,3-epoxyalcohols with a wide variation of functionality and protecting groups. The regioselective opening of chiral 2,3-epoxyalcohols 2 assisted by titanium (IV) isopropoxide (CH_2Cl_2, PhCOOH, $Ti(OPr^i)_4$, R.T., 0.5 hr.)3) yielded the diolbenzoates 3, which without purification were submitted to ruthenium dioxide oxidation (CH_3CN, CCl_4, H_2O, $NaIO_4$, R.T., 2 hr.)4) to give the 2-hydroxyacid benzoates 4 according to the isolated yields reported in Table I.

The procedure works with clean inversion of the 3-carbon configuration of the epoxyalcohol, and oxidation with the ruthenium dioxide occurs without any epimerization of the chiral centre, as proven by the optical purities checked by NMR analysis of the methyl esters, which are totally similar to those observed in the precursory 2,3-epoxyalcohols (Table I).

Table I

Entry	2,3-Epoxyalcohol$^{a)}$	$\lvert\alpha\rvert_D$$^{b)}$	2-Hydroxyacid benzoate$^{c)}$	Yield$^{d)}$	$\lvert\alpha\rvert_D$$^{b)}$
1.		-34.6° (5.7)		88%	+3.3° (1.1)
2.		-35.8° (2.1)		78%	-23.4° (2.2)
3.		-49.2° (2.1)		86%	-103.3° (2.4)
4.		-23.8° (0.9)		60%	+12.9° (4.3)
5.		-9.6° (1.2)		65%	+17.6° (0.6)
6.		-11.0° (2.6)		61%	+3.4°$^{e)}$ (1.8)

a) The 2,3-epoxyalcohols were prepared by asymmetric epoxidation of the suitable E-allylic alcohol (stoichiometric$^{2a,2b)}$ (Entries 1, 4, 5, 6) or catalitic$^{2c)}$ (Entries 2, 3); b) The optical rotations presented in this work were measured at 25°C, in $CHCl_3$, at the concentration shown in parentheses in gr/100 mL; c) Optical purities, checked by NMR over the corresponding methyl esters (CH_2N_2, Et_2O) using $Eu(hfbc)_3$ as chiral shift reagent, were in all cases above 95% ee, except in entry 2 which was 91% ee, similar to that obtained por the precursory 2,3-epoxyalcohol; d) Isolated yields from 2,3-epoxyalcohols; e) Optical rotation measured in ether (in $CHCl_3$ it is close to zero).

With this procedure we can extend even further the wide application of asymmetric epoxidation to asymmetric synthesis. Use of this methodology in synthesis of natural products is being applied and will be published shortly.

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c) Gao,Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B.; **J.Am.Chem.Soc.**, 1987, **109**, 5780.

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4) Carlsen, P.H.J.; Katsuki, T.; Martín, V.S.; Sharpless, K.B.; **J.Org. Chem.**, 1981, **46**, 3936. In all cases the same ratio of solvent/oxidable material (2(CH_3CN) : 2(CCl_4) : 3(H_2O) mL/mmol. of diolbenzoate) and 4.2 equiv. of $NaIO_4$ and 2% of $RuCl_3.5H_2O$ were used.

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