Resolution of Unfunctionalized Epoxides by Cholic Acid Inclusion Compounds

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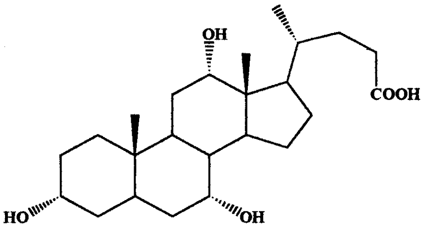
A simple method for the optical resolution of several unfunctionalized epoxides by inclusion in cholic acid is presented. (ee values up to 95%).

The inclusion of racemic chiral substrates in homochiral crystalline multimolecular cavities[1,2] for the optical resolution[3] or enantioselective transformation[4] of guest compounds proved to be an alternative and powerful method to obtain chiral compounds. Steroids, in particular bile acids, are one of the best sources of host compounds for the inclusion of a wide variety of organic molecules and biologically important derivatives.[3b]

In a previous study[3d] we reported that dehydrocholic acid (3,7,12-triketo-5β-cholan-24-oic acid) serves as effective chiral host for the optical resolution of several alkyl aryl sulfoxides by inclusion. We have now extended this approach to the resolution of unfuctionalized epoxides, owing to the fact that the obtainment of these derivatives in high enantiomeric yields is limited to selected cases.[5] Different natural and unnatural bile acids were investigated for this purpose and cholic acid (3α,7α,12α-trihydroxy-5β-cholan-24-oic acid) **1** offered the best results.



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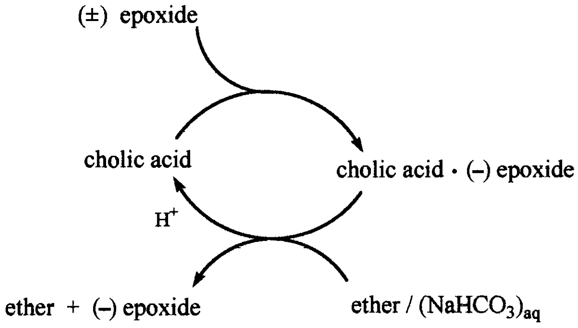
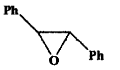
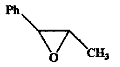
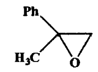
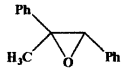
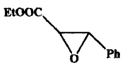
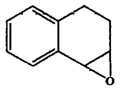
The procedure is relatively simple and its view is given in the Scheme 1, for a generic (–)-epoxide.



Scheme 1.

The inclusion compounds of **1** with epoxides were obtained by adsorption methods. Depending on the physical status of the guests, in fact, host crystals were directly added to the epoxide, liquid or melted if solid. The results are shown in Table 1.

Table 1. Optical resolution of epoxides using cholic acid **1** as host

Guest substrate	Meth.[a]	ee %[b]	Confign[c]	Ratio host:guest[d]
 **2**	A	50	(-)-S,S	2:1
	B*	95	(-)-S,S	2:1
 **3**	C	64	(-)-1S,2S	2:1
 **4**	B□	16	(+)-R	
	C	9		2:1
 **5**	B°	67.	(+)-1R,2R	
	C	41	(+)-1R,2R	2.5:1
 **6**	C	16	(+)-2S,3R	---
 **7**	C	40	(+)-1R,2S	2.4:1

[a] Method A: 1 equiv. of **1** is added to 3 equiv. of melted epoxide; Method B: 1 equiv. of **1** (100 mg) is added to 3 equiv. of the epoxide dissolved in 0.5 mL of 2-butanol (*), benzene (□) or toluene (°); Method C: 1 equiv. of **1** is added to 3 equiv. of the liquid epoxide; [b] Determined by GC on Megadex DETTBS; [c] Absolute configuration of the material recovered from the crystals were determined by comparison of $[\alpha]_D$ with literature values, see refs. 5b,7,8,11b; [d] Determined by ^1H NMR ($CDCl_3$).

A good alternative for solid epoxides is their dissolution in specific solvents. Accordingly, a significant increase in the optical resolution of **2** is obtained in the presence of 2-butanol, reluctant toward inclusion in bile acids.[6] In some cases, inclusion competition between the epoxide and the solvent i.e., benzene or toluene, increases the chiral recognition, likely via formation of epoxide : solvent : cholic acid complexes, as suggested by preliminary NMR data.

The optical resolution described for **3** is typical: 1 equivalent (100 mg) of cholic acid **1**, commercially available purified by recrystallization from methanol and dried in vacuo at 110 °C for 6 h, is added to 3 equiv of the epoxide **3** and the crystals were kept at room temperature for 48 h. The crystals were washed with hexane–ether (80:20), filtered, analyzed by ^1H NMR to obtain the host–guest ratio, treated with aqueous $NaHCO_3$ and extracted with Et_2O. (1*S*,2*S*)-(–)-1,2-Epoxy-1-phenylpropane was obtained in enantiomeric excess of 64%.

All the other epoxides listed in the Table 1 were prepared by epoxidation of the corresponding commercially available olefins with *m*-chloroperoxybenzoic acid (MCPBA),[9] by oxidation with MCPBA-KF complex,[10] or via the Darzens reaction.[11a] These epoxides were resolved according to this simple procedure.

Attempts to extend the proposed method to unfunctionalized aliphatic epoxides like 1,2-epoxyoctane or 1,2-3,4-diepoxy butane were unsuccessful, suggesting a possible role played by the aromatic ring(s) present in the substrate for specific interactions within the host cavities.

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References and Notes

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