

Optical resolution of sulfoxides by inclusion in host dehydrocholic acid

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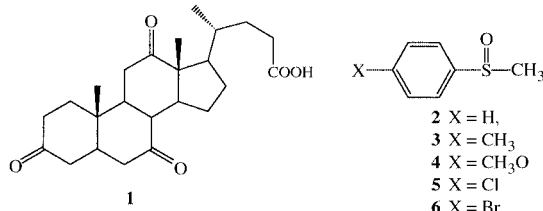
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Dehydrocholic acid serves as an effective chiral host molecule for the optical resolution of aryl alkyl sulfoxides by inclusion.

The optical resolution of different classes of organic substrates by lattice inclusion compounds is receiving significant attention on account of its high efficiency and simplicity.¹ Bile acids have often been used as host molecules both in the direct resolution of a guest racemate^{2,3} and in enantioselective transformation of an inclusion compound.⁴ The resolution of aliphatic alcohols with cholamide (3,7,12-trihydroxy-5-cholan-24-amide)² and that of lactones in the presence of cholic and deoxycholic acid³ are examples of the former case.

Chiral sulfoxides are finding increasing use as auxiliaries in asymmetric synthesis⁵ and as intermediates in the pharmaceutical industry.⁶ Beside the classical resolution methods,⁷ new strategies have been developed mainly based on the oxidation of prochiral sulfides by titanium peroxo species bearing chiral C₂ symmetric diols^{8–10} (e.g. tartaric esters) or C₃ symmetric trialkanolamines.¹¹ However, the limited turnover numbers characterizing most of these oxidation procedures and the kinetic resolution *via* oxidation involving the sulfoxides so produced¹² prompted us to reconsider the resolution method to obtain enantiomerically pure sulfoxides.

Described here is the novel observation that dehydrocholic acid (3,7,12-triketo-5-cholan-24-oic acid) **1**, a bile acid derivative lacking steroidal hydroxy groups can serve as a host molecule to form inclusion compounds with different aryl alkyl sulfoxides **2–6**, leading to the effective optical resolution of this class of compounds.



The inclusion compounds of **1** with sulfoxides were obtained by two different methods based on direct absorption of the melted (method A) or solvent dissolved (method B) sulfoxide. The choice depends on the sulfoxide. In the former case the solid dehydrocholic acid is directly added to the melted sulfoxide in the absence of any solvent, whereas in the latter procedure **2–6** were dissolved in the minimum amount of Et₂O, and poured onto solid **1**. As shown in Table 1, both processes are equally effective, affording sulfoxides in good to high ees in the range 36–99%.

A view of the overall process is given in Scheme 1. On standing at room temperature for 48–72 h, dehydrocholic acid and the selected sulfoxide formed crystals¹³ that were washed with Et₂O. The ethereal layer was separated from the solid phase and evaporated to give the crude sulfoxide in predominant (*S*) configuration. On the other hand, included sulfoxides were easily obtained in quantitative yields in (*R*) for **3–5** and (*S*) configuration for **2**, respectively, by dissolving the crystals with aqueous NaHCO₃ followed by extraction with Et₂O.¹⁴ Furthermore, almost complete recovery of dehydrocholic acid can be obtained upon treatment of the aqueous basic

layer with dilute mineral acid. No significant differences in optical and chemical yields were observed when recycled dehydrocholic acid was used.

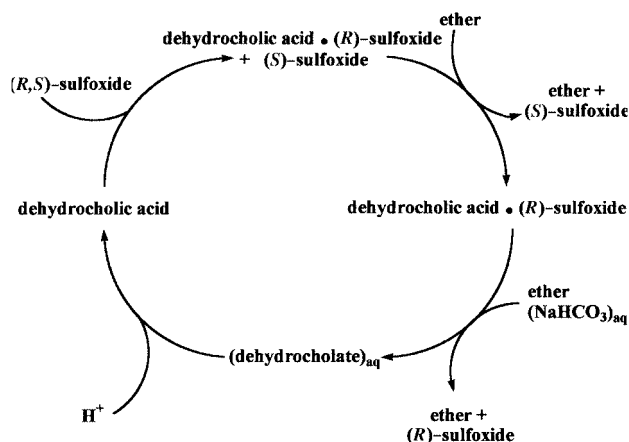
The relative amount of the sulfoxide with respect to **1**, in the inclusion process, was expected to play an important role. Accordingly, a 3-fold excess of **2–6** over the bile acid favored high optical purities of the sulfoxides that are included in **1**, as shown from the data of Table 1, whereas a one-to-one stoichiometry increased the ees of the non-guest sulfoxides obtained from the Et₂O solution. As an example, when **6** is added in equimolar amounts to the bile acid, (*S*)-**6** is recovered from the solution and (*R*)-**6** is obtained from crystals in ees of about 70%. When a 3-fold excess of **6** is used the optical purity of (*R*)-**6** increased to 84% (Table 1).

Compared to **1** the efficiency of the well-known host cholic acid (3,7,12-trihydroxy-5-cholan-24-oic acid) is lower, affording sulfoxides with optical purities in the range 2–47%, depending on the sulfoxide. This is an example of the excellent ability of dehydrocholic acid, a non-naturally occurring steroid lacking hydroxy groups, to recognize sulfoxides according to

Table 1 Optical resolution of *p*-XC₆H₄SCH₃ sulfoxides **2–6** using dehydrocholic acid **1** as host

Sulfoxide	X	Method ^a	<i>t</i> /h	Ee ^c (%)	Predominant configuration ^d
2	H	A	72	74	<i>S</i>
		B	72	36	<i>S</i>
3	CH ₃	A	72	86	<i>R</i>
		B	72	>99	<i>R</i>
4	OCH ₃	A	48	40	<i>R</i>
		B ^b	48	54	<i>R</i>
5	Cl	A	72	82	<i>R</i>
		B	72	77	<i>R</i>
6	Br	A	48	74	<i>R</i>
		B ^b	48	84	<i>R</i>

^a Method A: 1 equiv. of **1** is added to 3 equiv. of melted sulfoxide. Method B: sulfoxide dissolved in Et₂O and added to **1**. ^b A few drops of EtOAc were added to Et₂O. ^c Determined by GC on Megadex DETTBS. ^d Absolute configurations of the material recovered from the crystals were determined by comparison of [α]_D with literature values, see refs. 8–11.



Scheme 1

size, polarity and chirality. Work is in progress to extend this approach to other classes of organic chiral molecules.

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- 13 The inclusion compounds have a host:guest ratio of 1:1 with **3**, **4** and **6** and 2:1 in the other cases. Work is in progress on this specific point.
- 14 For optical purity and absolute configuration, see footnotes of Table 1.

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