Optical Resolution of Cyclic Amides by Inclusion in Dehydrocholic Acid

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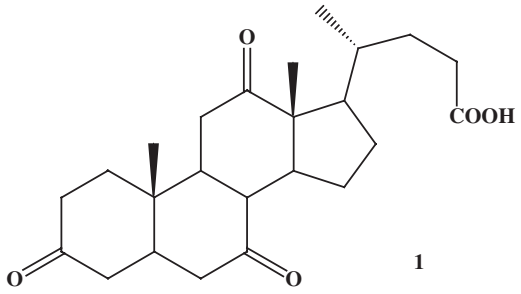
Dehydrocholic acid serves as an effective chiral host for the resolution of several five-, six-, and seven-membered cyclic amides by inclusion.

Bile acids represent a cheap and readily available class of chiral host molecules for the direct resolution of guest racemates.[1] The procedure is based on the ability of the bile acids, in particular of cholic and deoxycholic acids, to incorporate enantioselectively within their molecular structure one of the two forms of the racemic guest, thus allowing separation and recovery of both enantiomers. Examples include the resolution of organic substrates such as lactones,[2] alcohols,[3] epoxides[4] and cyclic ketones.[5] In addition, we have recently described[6] the first report on the use of dehydrocholic acid **1** (3,7,12-trioxo-5β-cholan-24-oic acid) a bile acid lacking hydroxyl groups, for the resolution of alkyl aryl sulfoxides with enantiomeric excesses up to 99%.

This approach has been extended to the resolution of several five-, six- and seven-membered cyclic amides **2**–**10**, owing to the fact that the obtainment of these derivatives in high optical yield is limited to few selected cases like 4-amino-p-chlorobutyric acid lactam[7] and 4-acetoxy-2-azetidinone.[8] Lactams,[9] in fact, are important structural frameworks of biologically active compounds as alkaloids,[10] β-lactam antibiotics[11] or GABA analogues.[12]

The resolution procedure is simple and straightforward, exemplified for amide **2** in milligram and multigram scale as follows, in agreement with Scheme 1. One equivalent (100 mg) of dehydrocholic acid, commercially available bile acid used without further purification, is added to a solution containing 5 equivalents of the racemic amide **2**, dissolved in 1 mL of ethyl acetate–ether (1:1). After 24 h at room temperature the crystals



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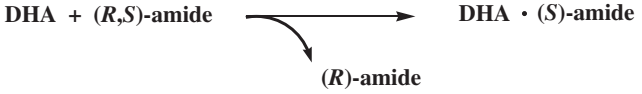
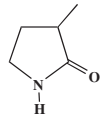
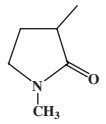
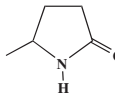
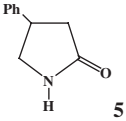
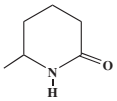
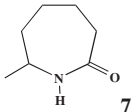
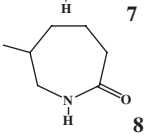
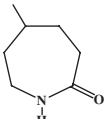
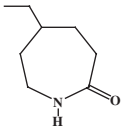


DHA = dehydrocholic acid

Scheme 1.

Table 1. Resolution of cyclic amides using dehydrocholic acid **1** as chiral host

Cyclic amide	**1**:amide ratio[a]	ee %[b] 1st cycle	ee %[b] 2nd cycle	Config.[c]
 **2**	1:1	42	80	(-)-(S)[13]
 **3**	1:1	0	---	---
 **4**	1:1	64	92	(+)-(R)[14]
 **5**	1:1	30	62	(+)-(R)[15]
 **6**	1:1	17	32	(+)-(S)[18]
 **7**	1.4:1	50	87	(+)
 **8**	1.3:1	11	23	(+)-(S)[16]
 **9**	1:1	75	94	(+)-(R)[17]
 **10**	1:1	13	30	(+)-(R)[17]

[a] Determined by ^{1}H NMR on the formed crystals. [b] determined by GC on Megadex DETTBS. [c] the absolute configurations were established by comparison of $[\alpha]_D$ with literature values, see references from 13 to18.

were filtered, washed with ethyl acetate–ether (1:1), analyzed by ^{1}H NMR to obtain the host:guest ratio, treated with aqueous $NaHCO_3$ and extracted with ethyl acetate. The extracts were analyzed by GC for the ee determination and by polarimetry to assign the absolute configuration, see Table 1. For resolution on multigram scale, 5 g of dehydrocholic acid were added to a solution of **2** (5 g) dissolved in 50 mL of ethyl acetate–ether (1:1). The crystals were collected by filtration, washed several times with ethyl acetate–ether and (−)-**2** was recovered, 1 g ca. 42% ee, upon distillation using a Kugelrohr apparatus (150 °C, 1 mm Hg). When the same procedure was repeated on the partially resolved racemate, (−)-**2** was obtained with an optical yield of 80%. As expected although not reported in the Table, depending on the number of cycles, the complete resolution of the substrates is obtained in all cases except for the *N*-methyl derivative **3**. The complete set of results, including the two-cycle procedure, is shown in Table 1.

As reported in the second row of the Table the bile acid-to-amide inclusion ratio is generally 1:1, however some noticeable differences demonstrate the independence of the steric dimensions of the cyclic amide with respect to the inclusion stoichiometry, see for example **2** and **9**. The host-guest relationship of the included molecules is well evident in a comparison between the FT-IR spectra of the ''free'' and included amides in KBr. As an example **2** gives rise to a broad signal, centered at 3201 cm^{-1}, ascribable to an intermolecular N–H stretching. The same signal resolved in a sharp band at 3354 cm^{-1} upon inclusion in the host.

Worthy of note are the results obtained with the five-membered amide **2** if compared with the *N*-methyl homologue **3**. Both derivatives include within the dehydrocholic acid in a one-to-one ratio, however only **2** showed enantioselective incorporation in the host, thus suggesting a possible role played by the N–H function on the enantiodiscrimination.

We are currently extending this readily accessible and low cost methodology to the resolution of other classes of ''neutral'' organic molecules.

References and Notes

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