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Resolution of Aliphatic Alcohols by Hydrogen Bond "Double Hooks" of Cholanamide Inclusion Compounds

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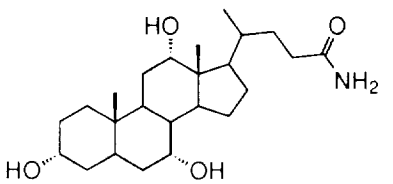
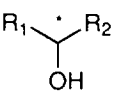
Abstract : Resolution of aliphatic alcohols by an inclusion method with cholanamide (3α, 7α, 12α-trihydroxy-5β-cholan-24-amide) is studied.

The resolution of neutral organic substances by lattice inclusion compounds has recently received much attention because of highly efficient and easy procedure.[1] However, the use of the compounds for optical resolution of aliphatic alcohols have been limited and their enantioselectivities are relatively low.[2] This is because steric differences between the alkyl substituents are too small for the large cavities of the inclusion compounds. During the course of our studies on the inclusion compounds of steroidal bile acids and their derivatives, we found that cholanamide (3α, 7α, 12α-trihydroxy-5β-cholan-24-amide, **1**) includes a wide range of alcohols in the crystalline lattice.[3] Optically active host **1** led us to investigate the chiral recognition of aliphatic alcohols. We report here the resolution of aliphatic secondary alcohols by an inclusion method using **1** as a host molecule.



1 : Cholanamide



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The host **1** was recrystallized from various neat alcohols, and the solutions were kept at room temperature for 24 hours. The resulting crystals were filtered and air-dried for several hours on a filter paper. Included guests were recovered by a micro-distillation from the crystals. Enantiomeric excesses and configurations of the guest molecules were determined as the corresponding phenylcarbamate derivatives by HPLC analysis or polarimetry. Table I shows results of the resolution of aliphatic alcohols by the inclusion method of **1**. After one cycle of the recrystallization, racemic **7** and **10** yielded 56% and 59% e.e., respectively. When the above *R*-enriched-**7** was reused for the second recrystallization, the e.e. of the recovered alcohol rose to 86% e.e.. It is in good agreement with the calculated value from the result of the first run, suggesting that e.e. will become higher than 90% after a few cycles of the recrystallization. The alcohols having other polar functional groups (**11** and **12**) gave 21% and 48% e.e., respectively. Consequently, the weak hydrogen bond donors such as esters or amino groups do not interfere in the chiral recognition of **1**. As reported earlier, the hydroxy groups of the guest molecules are fixed by the hydrogen bond 'double hooks' on the walls of deformed pentagonal channels.[3] The facile chiral recognition of aliphatic alcohols may be caused by the amide 'hooks' as a binding site and the asymmetric steric environment of the host cavity.

Predominant configurations of the included alcohols are all R-isomers except 2-butanol. This difference is caused by polymorphism of the host lattice. The compound with 2-butanol has a powder X-ray diffraction

Table 1. Resolution of the aliphatic alcohols by inclusion method of **1**.

Guest	R_1	R_2	e.e.%[a]	Predominant Configuration[b]
2	-Me	-Et	17	*S* - (+)
3	-Me	-^{n}Pr	30	*R* - (-)
4	-Me	-^{i}Pr	20	*R* - (-)
5	-Me	-^{n}Bu	13	*R* - (-)
6	-Me	-^{t}Bu	18	*R* - (-)
7	-Me	-^{i}Bu	56 (86)[c]	*R* - (-)
8	-Me	-^{n}Pentyl	26	*R* - (-)
9	-Me	-^{n}Hexyl	7	*R* - (-)
10	-Me	-Ph	59	*R* - (+)
11	-Me	-CH_2COOEt	21	*R* - (-)
12	-Me	-$CH_2CH_2N(Me)_2$	48	*R* - (-)
13	-Et	-^{n}Pr	19	*R* - (-)
14	-Et	-C≡CH	12	*R* - (-)

a) Determined by HPLC on Daicel Chiralcel OD column.

b) Determined by HPLC on Daicel Chiralcel OD column and polarimetry.

c) Result after second recrystallization shown in parenthesis.

pattern similar to those reported previously.[3] However, the other alcohols listed in Table 1 give different powder patterns, indicating that the cystal structure of **1** with 2-butanol is different from those with the other alcohols. Therefore, the different predominant configuration, (S) in the case of 2-butanol is explained by the structural change of host arrangements of **1**. Geometries around the amide 'hooks' in former crystal structure are suitable for S-isomer of 2-butanol.

In conclusion, **1** recognizes the chirality of aliphatic secondary alcohols, and has versatility in their resolution. **1** is superior to other host compounds in enantioselectivity as well as in versatility for the simple aliphatic alcohols.[2] The subsequent structural investigation of the inclusion compounds of **1** will provide us some indications for the mechanism of the chiral recognition.

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References and Notes

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1 Reviews: (a) Worsh, D. ; Vögtle, F., *Top. Curr. Chem.* **1987**, *140*, 21; (b) Toda, F., *Top. Curr. Chem.* **1987**, *140*, 43; (c) Toda, F. In *Inclusion Compounds, Vol. 4*, Atwoods, J. L.; Davies, J. E. D.; MacNicol, D.D.; Eds.; Oxford Press, Oxford, **1991**, p126.

2 (a) Allemand, J.; Gerdil, R. *Cryst. Struct. Commun.* **1981**, *10*, 33. (b) Worsch, D.; Vögtle, F. *Naturwissenschaften* **1984**, *71* 423; (c) Anderson K. V.; Buchardt, O.; Hansen, H. F.; Jensen, R.B.; Larsen, S., *J. Chem. Soc., Perkin Trans. 2* **1990**, 1871; (d) Gnaim, J.M.; Green, B.S.; Arad-Yellin, R.; Vyas, K.; Levy, T.; Frolow, F.; Keehn P.M. *J.Am.Chem.Soc.* **1992**, *114*, 1915.

3 Sada, K.; Kondo T.; Miyata, M.; Tamada, T.; Miki, K. *J. Chem. Soc., Chem. Commun.* **1993**, 753 ; (b) Sada, K.; Kondo T.; Miyata, M.; Miki, K. *Chem. Mater.* **1994**, *6*, 1103.

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