Efficient resolution of (±)-α-cyclopropylethanol by crystallization of its inclusion complex with chiral diols

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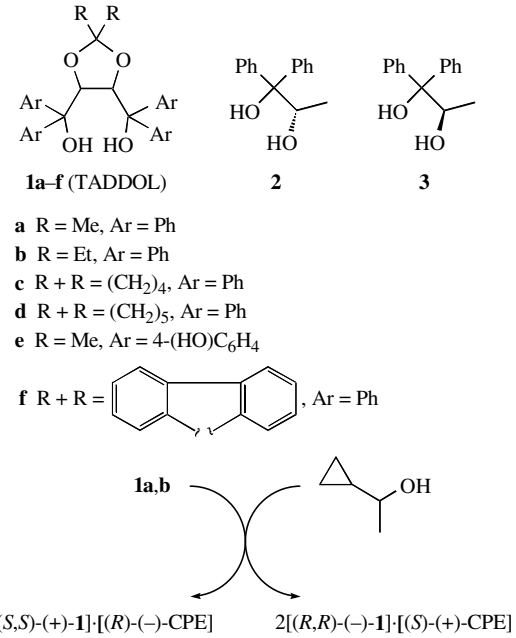
The two-step inclusion crystallization of the chiral diol TADDOL with α-cyclopropylethanol has been found to allow resolving the racemic alcohol to yield (*R*)- or (*S*)-enantiomer (> 98% *ee*).

α-Cyclopropylethanol (CPE) and its derivatives, first of all esters, belong to compounds that exhibit the enhanced biological activity. Thus, the CPE fragment is contained in a dehydrogenase inhibitor,[1] β-blockers[2] and substances showing insecticide[3] or herbicide[4] activity. Over the past decades, the catalytic synthesis of optically active CPE by reduction of cyclopropyl methyl ketone in the presence of chiral metal complexes[5] or alcohol dehydrogenase[6,7] has been elaborated. However, the former variant is complicated by technological requirements (H_2 gas pressure), and in the latter case the reaction proceeds with moderate enantioselectivity (44% *ee*) or inadequate ketone conversion (46%).[7] The latter applies to reduction of cyclopropyl methyl ketone with chiral organoborane[8] and alumohydride[9] reagents as well.

Here we describe a method of straightforward resolution of (±)-CPE *via* crystallization of its inclusion complexes (IC) with chiral diols TADDOL† **1**.‡ The method is convenient for preparative use because it requires only two crystallization steps for complete resolution of the racemate to give pure (*R*)- or (*S*)-CPE (> 98% *ee*). A number of molecular complexes of TADDOL with alcohols have been described earlier;[10–14] however, there were no published data regarding CPE-containing IC and their use for resolution of CPE enantiomers.

To obtain CPE-containing IC, crystallization of chiral diols **1**–**3** in the presence of CPE has been attempted. Table 1 demonstrates that only three host compounds **1a**, **1b** and **1e** proved to form IC with CPE, the **1**/CPE ratio being 2:1 in each case. Note that the resolution degree for (±)-CPE depends on both the diol structure and the solvent nature. Thus, the one-step crystallization of the complex 2(**1a**)·(CPE) from diethyl ether–hexane gave an enantiomeric enrichment (*ee*) of 75%, whereas no resolution was observed after crystallization of the same IC from benzene–hexane. The degree of (±)-CPE resolution by complexation with diol **1b** from diethyl ether–hexane was considerably higher than that from THF–hexane. On the other hand, inclusion crystallization of diol **1e** with CPE from ether–hexane and other solvents proceeded nonstereoselectively.



Scheme 1

Table 1 Crystallization of TADDOL in the presence of (±)-CPE.[a]

TADDOL	Crystalline product	*ee* (%)
(*S*,*S*)-(+)-**1a**	IC[b]	75 (> 98) (*R*)[c]
(*S*,*S*)-(+)-**1a**	IC[b]	0[d]
(*R*,*R*)-(–)-**1b**	IC[b]	78 (97) (*S*)[c]
(*R*,*R*)-(–)-**1b**	IC[b]	46 (*S*)[e]
(*R*,*R*)-(–)-**1c**	**1c**	—
(*R*,*R*)-(–)-**1d**	**1d**	—
(*R*,*R*)-(–)-**1e**	IC[b]	0
(*R*,*R*)-(–)-**1f**	**1f**	—
(*S*)-(–)-**2**	**2**	—
(*R*)-(+)-**3**	**3**	—

[a]Unless otherwise noted, crystallization was carried out from a solution of 2.5 mmol of chiral diol **1**–**3** and 10 mmol of (±)-CPE in diethyl ether (10 ml)–hexane (50 ml) at –15 °C for 24 h; *ee* refers to CPE included into crystalline IC. [b]Molar ratio TADDOL:CPE = 2:1. [c]The *ee* values for CPE isolated after the first and the second (in parentheses) crystallization of IC carried out according to the procedure described. [d]Crystallization was performed from benzene (10 ml)–hexane (50 ml). [e]Crystallization was performed from THF (10 ml)–hexane (50 ml).

† α,α,α′,α′-Tetraaryl-1,3-dioxolane-4,5-dimethanols.

‡ *(±)-CPE resolution procedure*. (*S*,*S*)-(+)-**1a** (2.5 g, 5.25 mmol) and (±)-CPE (0.452 g, 5.25 mmol) were dissolved in diethyl ether (8 ml), and hexane (80 ml) was added dropwise with stirring. The mixture was left to crystallise first at room temperature, then at 0 °C and finally at –25 °C (for 24 h at each temperature above). The precipitated crystals of the complex 2[(*S*,*S*)-(+)-**1a**]·[(*R*)-(–)-CPE] (2.6 g, 96% yield, 75% *ee* for CPE included into IC) were crystallised repeatedly from diethyl ether (5 ml)–hexane (50 ml) at –25 °C for 24 h. The complex obtained (1.2 g) was heated *in vacuo* (5 Torr) at gradually increased temperature from 60 to 90 °C for 1 h, CPE elevated being collected at the dry ice cooled trap. 0.1 g of (*R*)-(–)-CPE has been obtained [45% with respect to (*R*)-(–)-CPE in the starting racemate], *ee* > 98%. Absolute configuration was assigned on the basis of the optical rotation sign for the (*R*)-enantiomer of CPE {$[\alpha]_D$ –7.55 ($CHCl_3$), 44% *ee*}.[6] The residue after the thermal decomposition of IC was pure diol **1a**. Enantiomeric analysis of CPE was carried out by GLC (after acetylation of the alcohol by Ac_2O in the presence of pyridine) on a Biokhrom-21 instrument using 30 m × × 0.25 mm × 0.25 μm β-DEX™ capillary column (Supelco). The carrier gas (He) flow rate was 1 ml min^{-1}. The retention times of the compounds were as follows (50 °C, min): CH_4 (nonretainable gas), 1.5; (*S*)-CPE acetate, 15.3; (*R*)-CPE acetate, 18.7. Mother liquors obtained after the first and second crystallization steps were combined and evaporated. The residue was heated at 100 °C for 1 h to give pure chiral diol **1a**. Totally, 2.4 g (96%) of pure resolving reagent (*S*,*S*)-(+)-**1a** was returned back.

Following the above procedure, analogous results were obtained for the resolution of (±)-CPE with chiral diol **1b**. The thermal decomposition of the isolated complex 2[(*R*,*R*)-(–)-**1b**]·[(*S*)-(+)-CPE] gave (*S*)-(+)-CPE (97% *ee*) in 43% yield with respect to (*S*)-CPE in the starting racemate, 95% of pure (*R*,*R*)-(–)-**1b** being returned back.

On the basis of the results obtained (Table 1), chiral diols **1a** and **1b** were taken for preparative resolution of (±)-CPE *via* IC formation. Two-step inclusion crystallization of these diols with (±)-CPE from diethyl ether–hexane followed by thermal dissociation of the IC at 60–90 °C afforded optically pure CPE (97 and > 98% *ee* using diols **1a** and **1b**, respectively). After evaporation of mother liquors and the subseqent heating of the residue, 95–96% of the starting diol was returned back. In the course of isolation of optically active CPE and diols **1** no racemization was observed. Resolution of (±)-CPE using starting and regenerated **1** gave identical results.

References

1 I. Macinnes, D. C. Nonhebel, S. T. Orszulik, C. J. Suckling and R. Wrigglesworth, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2771.

2 M. Bouzoubaa, G. Leclerc, N. Decker, J. Schwartz and G. Andermann, *J. Med. Chem.*, 1984, **27**, 1291.

3 J. F. Carroll, *J. Econ. Entomol.*, 1984, **77**, 980.

4 M. Los, *USA Patent 4,188,487*, 1980 (*Chem. Abstr.*, 1980, **92**, 180836h).

5 T. Ohkuma, M. Koizumi, H. Doucet, T. Pham, M. Kozawa, K. Murata, E. Katayama, T. Yokozawa, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1998, **120**, 13529.

6 E. Keinan, E. K. Hafeli, K. K. Seth and R. Lamed, *J. Am. Chem. Soc.*, 1986, **108**, 162.

7 C. W. Bradshaw, W. Hummel and C.-H. Wong, *J. Org. Chem.*, 1992, **57**, 1532.

8 M. M. Midland, J. I. McLoughlin and J. Gabriel, *J. Org. Chem.*, 1989, **54**, 159.

9 M. G. Vinogradov, L. S. Gorshkova, G. V. Chel'tsova, V. A. Pavlov, I. V. Razmanov, V. A. Ferapontov, O. R. Malyshev and G. L. Heise, *Izv. Akad. Nauk, Ser. Khim.*, 2003, 450 (*Russ. Chem. Bull., Int. Ed.*, 2003, **52**, 471).

10 F. Toda, S. Matsuda and K. Tanaka, *Tetrahedron: Asymmetry*, 1991, **2**, 983.

11 F. Toda and Y. Tohi, *J. Chem. Soc., Chem. Commun.*, 1993, 1238.

12 F. Toda and H. Takumi, *Enantiomer*, 1996, **1**, 29.

13 M. G. Vinogradov, L. S. Gorshkova, G. V. Chel'tsova, D. V. Kurilov, V. A. Ferapontov, O. V. Shishkin and G. L. Heise, *Izv. Akad. Nauk, Ser. Khim.*, 2003, in press.

14 D. Seebach, A. K. Beck and A. Heckel, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 92.

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