Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 7, pp. 1495-1498, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00181-6

Enantiomer Resolution by Crystallization with Chiral Hosts: Application to Monoterpenes, Verbenone and Apoverbenone

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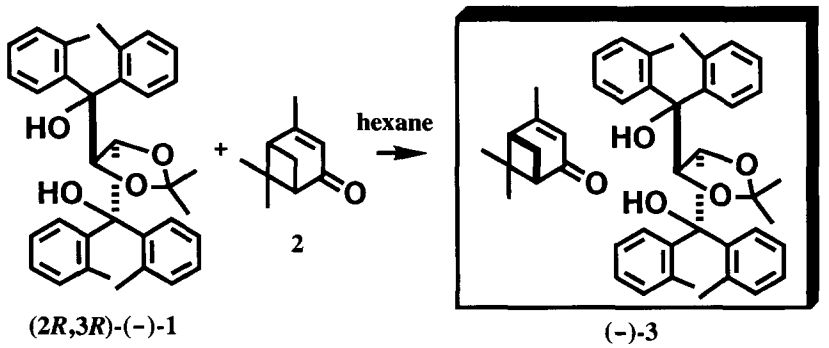
Abstract: Chiral hosts, (2*R*,3*R*)-(-)-2,3-*O*-isopropylidene-1,1,4,4-tetrakis(2-methylphenyl)-1,2,3,4-butanetetrol (**1**) and (2*R*,3*R*)-(-)-2,3-*O*-isopropylidene-1,1,4,4-tetraphenyl-1,2,3,4-butanetetrol (**5**), enantioselectively form crystalline 1:1 inclusion complexes with (1*S*,5*S*)-(-)-verbenone (**2**) and (1*R*, 5*R*)-(+)-apoverbenone (**6**), respectively, and by applying this chiral discrimination in crystallization, enantiopure verbenone and apoverbenone are obtained.

Monoterpenes have been used as chiral building blocks for the total syntheses of various biologically active natural products.[1] However, some naturally occurring monoterpenes, *e.g.*, α-pinene and β-pinene, exist as a mixture of both enantiomers with variable enantiomeric excess. Therefore, it is difficult to obtain enantiopure monoterpenes and their derivatives from natural resources. One group of the authors has developed a novel method for enantiomer resolution of various compounds using the principle of chiral discrimination in crystallization.[2,3] We report here a practical procedure of enantiomer resolution of monoterpene ketones, verbenone and apoverbenone, by application of the method of enantioselective crystallization with chiral hosts.

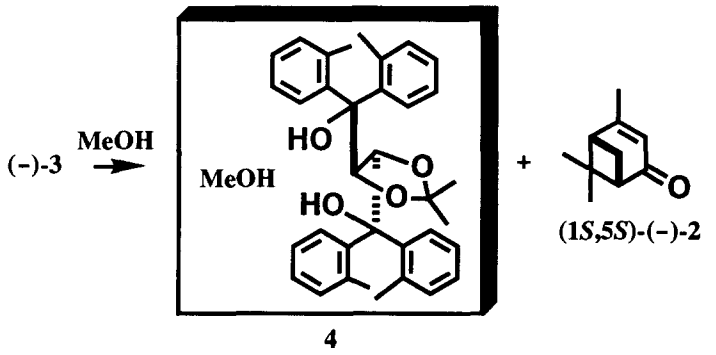


(2*R*,3*R*)-(-)-1 (-)-3

Scheme 1. Enantioselective crystallization of verbenone **2** with chiral host (-)-**1**.

A solution of (2*R*,3*R*)-(-)-2,3-*O*-isopropylidene-1,1,4,4-tetrakis(2-methylphenyl)-1,2,3,4-butanetetrol **1** (22 g, 42 mmol) and (-)-verbenone **2** (78 % ee, 7.5 g, 50 mmol) in hexane (125 ml) was kept at room temperature for 12 h, during which time crystals deposited. Three recrystallizations of the crystals from hexane gave colorless prisms of inclusion complex (-)-**3** composed of (-)-**1**/(-)-**2** (1:1 molar ratio, 13.5

g, 48 % based on **1**: mp 111-112 °C, $[\alpha]_D^{20}$ -86.6 (*c* 1.75, $CHCl_3$)).[4] The general method for recovering guests is to heat inclusion complexes, and guests are distilled *in vacuo*.[2] However, we found another efficient method; since methanol interacts more strongly with (-)-**1**, the guest (-)-**2** can be replaced with methanol. Treatment of the crystals of (-)-**3** (9.1 g) with methanol (10 ml) yielded crystals of (-)-**1**/methanol complex (**4**), which were collected by filtration. From the filtrate, enantiopure verbenone (-)-**2** (2.01 g, 99 %) was recovered: $[\alpha]_D^{20}$ -274 (*c* 0.4, $CHCl_3$), 99 % ee checked by using a HPLC column of Chiralpak AS.[5] The enantioselectivity in this crystallization is very strong; we tried to make inclusion crystals using chiral host (-)-**1** and (+)-verbenone **2**, but no inclusion crystals were obtained.



Scheme 2. Recovery of enantiopure verbenone (1*S*,5*S*)-(-)-**2** from the inclusion complex (-)-**3**.

The major force of the complexation in a crystalline state seems a hydrogen bonding, because the IR spectrum of the inclusion complex (-)-**3** exhibits the carbonyl absorption band at 1658.5 cm^{-1}, while that of enone (-)-**2** shows the corresponding band at 1679.7 cm^{-1}; the hydrogen bonding thus causes a lower wavenumber shift of 21.2 cm^{-1}. Intermolecular hydrogen bonding is also suggested by a change in the O-H

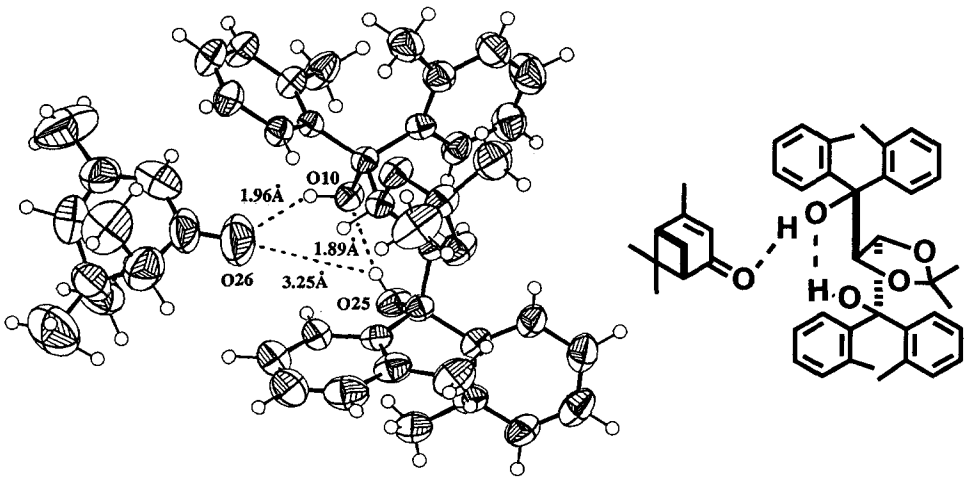
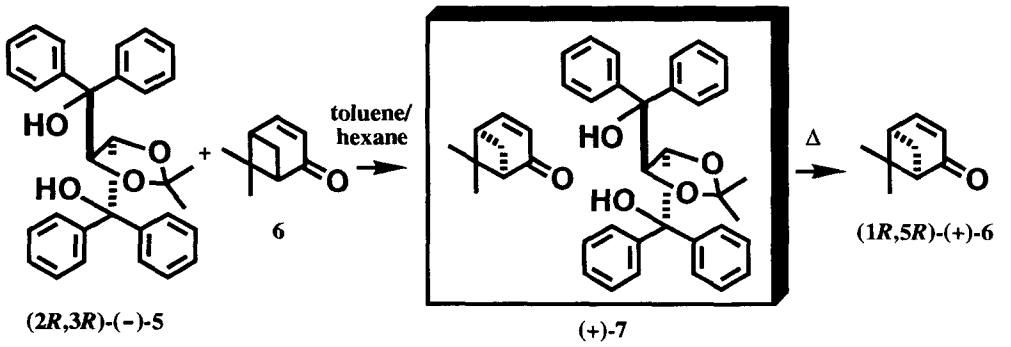


Figure 1. X-ray ORTEP drawing and structure of inclusion complex (-)-**3**.
The atoms are drawn as 50% probability ellipsoids.

stretching vibrational region around 3500-3200 cm^{-1}; chiral host (-)-**1** exhibits sharp and strong bands at 3531.1 cm^{-1} (intramolecular hydrogen bonding) and at 3328.6 cm^{-1} (intermolecular hydrogen bonding), while complex (-)-**3** does a broad and intense band around 3270 cm^{-1} (intermolecular hydrogen bonding).

To clarify the complexation mechanism more clearly, the X-ray crystallographic structure analysis of the complex (-)-**3** was performed.[6] The crystals of (-)-**3** were found to be orthorhombic and the space group to be $P2_12_12_1$. As illustrated in the ORTEP drawing of Figure 1, it is evident that the major force of complexation is a hydrogen bonding between one hydroxyl group of the host and carbonyl oxygen of the guest: distance between O(26) and H(O10), 1.96 Å. The other remaining hydroxyl group (O25) of host **1** makes an intramolecular hydrogen bonding with the hydroxyl group of O10: distance between O10 and H of O25, 1.89 Å. This is the reason why 1:1 complex of (-)-**1** and (-)-**2** was formed in crystallization. The absolute configuration of (-)-verbenone was confirmed to be (1*S*,5*S*) by the X-ray analysis.



Scheme 3. Enantiomer resolution of apoverbenone **6**.

A solution of (2*R*,3*R*)-(-)-2,3-*O*-isopropylidene-1,1,4,4-tetraphenyl-1,2,3,4-butanetetrol **5** (2.0 g, 4.0 mmol) and (+)-apoverbenone **6** (91 % ee, 1.2 g, 8.8 mmol) in toluene (5 ml) and hexane (10 ml) was kept at room temperature for 12 h, during which time crystals of 1:1 inclusion complex (**7**) composed of (-)-**5** and (+)-**6** of 94 % ee deposited as colorless prisms (2.4 g, 95 % based on **5**). Three recrystallizations of the crystals from toluene afforded prisms of enantiopure inclusion complex **7** (1.2 g, 47 % on **5**: mp 111-112 °C, $[\alpha]_D^{20}$ +6.6 (*c* 1.07, $CHCl_3$)). By heating the crystals obtained (1.2 g) *in vacuo* (ca 133 Pa) at 200 °C in a Kugelrohr distillation apparatus, enantiopure apoverbenone (+)-**6** (0.22 g, 81 %) was recovered: $[\alpha]_D^{20}$ +268 (*c* 0.1, $CHCl_3$), 98 % ee (Chiralpak AS).

It is noteworthy that in the case of apoverbenone **6**, the (+)-enantiomer was enantioselectively incorporated in host-guest crystals, while (-)-enantiomer was selected in the case of verbenone **2**. Namely, stereoisomers (-)-**2** and (+)-**6**, which are almost enantiomorphic each other, were selected by the similar chiral hosts (-)-**1** and (-)-**5** with the same absolute configuration, respectively. The difference between the two cases is the fact that host **1** has 2-methylphenyl groups and guest **2** has an olefinic methyl group, while host **5** and guest **6** lack such methyl groups. The enantioselectivity in host-guest crystallization is thus very sensitive to a small difference in structure.

Acknowledgment. This work is supported in part by grants from the Ministry of Education, Science, and Culture, Japan (Priority Areas No. 06242105 to F. T. and K. T.; Developmental Research No. 05554017 and Priority Areas No. 06240204 to N. H.).

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4 Inclusion complex (-)-**3**: IR (crystalline powder, diffuse reflection) ν_{max} 3304, 3236, 3070, 2983, 1659, 1614, 1487, 1452, 1381, 1373, 1340, 1298, 1284, 1238, 1173, 1088, 1009, 891, 860, 762, 741, 663, 636, 511 cm^{-1}. Anal. Calcd for $C_{45}H_{52}O_5$: C, 80.32; H, 7.79. Found: C, 80.12; H, 7.44.

5 All enantiomeric excesses were determined by HPLC using the Chiralpak AS column (available from Daicel Chemical Industries Ltd., Japan) and hexane-EtOH (95:5).

6 *Crystal data* for inclusion complex of (-)-**3**: $C_{45}H_{52}O_5$; M_r = 672.90; colorless prism (0.42 × 0.40 × 0.33 mm); orthorhombic; space group $P2_12_12_1$; a = 17.202(1), b = 20.467(2), c = 11.242(1) Å; V = 3957.9(6) $Å^3$; Z = 4; D_C = 1.129 g cm^{-3}; D_O = 1.135 g cm^{-3} by flotation using a CCl_4-hexane solution; $F(000)$ = 1448; μ(Cu-Kα) = 4.95 cm^{-1}; Rigaku AFC-6B diffractometer; Cu-Kα radiation (1.541 78 Å); graphite crystal monochromator; T = 291 K; scan type, 2θ-θ; scan speed, 2°.min^{-1}; scan range, $\Delta\omega$ = 1.3 + 0.3 tanθ; scan limits, 2° < 2θ < 130°; standard reflections, 3 per 50 reflections; indices, (2,3,0), (0,2,2), (2,0,1); crystal stability, no indication of standard reflection decay during data collection; total independent reflections scanned, 3787; unique data $F_O > 3\sigma(F_O)$, 3509. The skeletal structure was solved by the direct method and successive Fourier syntheses. All hydrogens were found by the difference Fourier syntheses. Full matrix least-squares refinement of positional and thermal parameters, including anomalous scattering factors of oxygen and carbon atoms, led to the final convergence with R = 0.0600 and R_W = 0.0553. The absolute configuration was assigned as shown by using the (2*R*,3*R*) absolute configuration of the host part **1** as an internal reference. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

7 Inclusion complex (+)-**7**, Anal. Calcd for $C_{40}H_{42}O_5$: C, 79.70; H, 7.02. Found: C, 79.90; H, 6.84.

(*Received in Japan* 12 *April* 1995; *accepted* 31 *May* 1995)