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OPTICAL RESOLUTION OF 2-AZABICYCLO[2.2.1]HEPT-5-EN-3-ONE BY INCLUSION COMPLEXATION WITH BRUCINE

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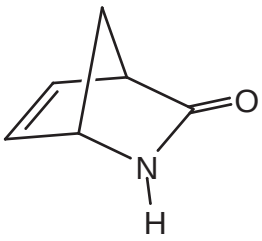
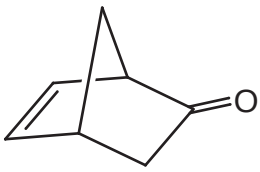
Abstract - A simple optical resolution method of 2-azabicyclo[2.2.1]hept-5-en-3-one by inclusion complexation with brucine was reported. The crystal structure of the inclusion complex was analyzed by X-Ray diffraction in order to elucidate the mechanism of the efficient chiral recognition in the inclusion crystals.

It is not easy to prepare optically pure enantiomers of the title bicyclic lactam (**1**), although this is a useful synthon for the synthesis of (-)-carbovir (**4**) a chemotherapic agent for AIDS.[1-4] Here we report a simple and efficient optical resolution method for **1** by inclusion complexation with brucine (**5**). The crystal structure of the inclusion complex was analyzed by X-Ray diffraction in order to elucidate the mechanism of the efficient chiral recognition in the inclusion crystals.



1



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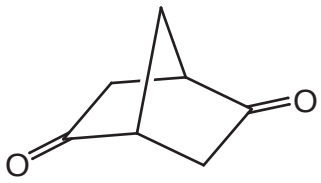

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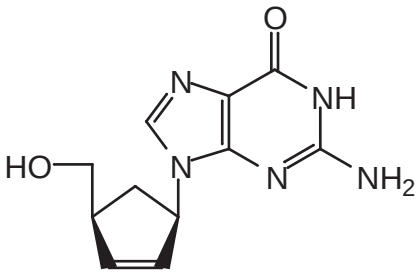

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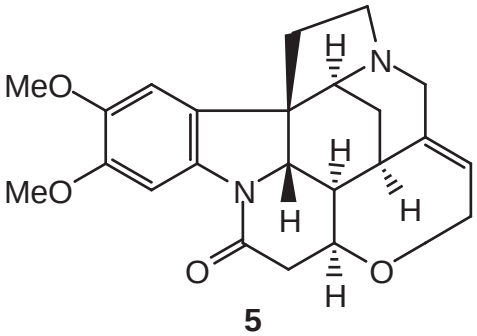

5

When a solution of **5** (36 g, 91 mmol) and (±)-**1** (20 g, 183 mmol) in MeOH (50 mL) was kept at room temperature for 6 h, a 1:1 complex of **5** and (-)-**1** was obtained as colorless prisms (31 g) which upon distillation *in vacuo* gave (-)-**1** of 36% ee. Four recrystallizations of the crude complex from MeOH gave the almost pure complex (6.6 g, mp 173-175 °C) which upon distillation *in vacuo* afforded (-)-**1** of 92% ee (1.3 g, 13%, $[\alpha]_D$-513° (*c* 0.52, $CHCl_3$)). Optical purity of (-)-**1** was determined by HPLC analysis.

Similar optical resolution of **2** by inclusion complexation with **5** was less efficient. For example, when a solution of **5** (1.8 g, 4.6 mmol) and (±)-**2** (1.0 g, 9.3 mmol) in MeOH (5 mL) was kept at room temperature for 6 h, a 1:1 complex of **5** and (+)-**2** was obtained as colorless prisms (1.22 g, mp 138-151 °C) which upon distillation *in vacuo* gave (+)-**2** (0.20 g, 40%, $[\alpha]_D$+274° (*c* 0.55, $CHCl_3$)) of 27% ee.[5] However, the optical purity of (+)-**2** in the inclusion complex was not improved by recrystallization. In the case of bicyclo[2.2.1]heptane-2,5-dione (**3**), **5** could not recognize the chirality of **3** and formed a 1:1 complex with (±)-**3** as colorless prisms (mp 165-168 °C) in 71% yield.

This result suggests that the NH group of **1** plays an important role in the chiral recognition through

NH…N hydrogen bonding between NH of (-)-**1** and N atom of brucine (**5**) in the complex. The IR spectrum of the 1:1 complex of (-)-**1** and **5** showed a broad absorption for the ∩NH of (-)-**1** at lower frequencies, 3300-2700 cm^{-1}. In order to clarify the mechanism of this efficient chiral recognition, the X-Ray crystal structure of the 1:1 inclusion complex of (-)-**1** and brucine (**5**) was analyzed.

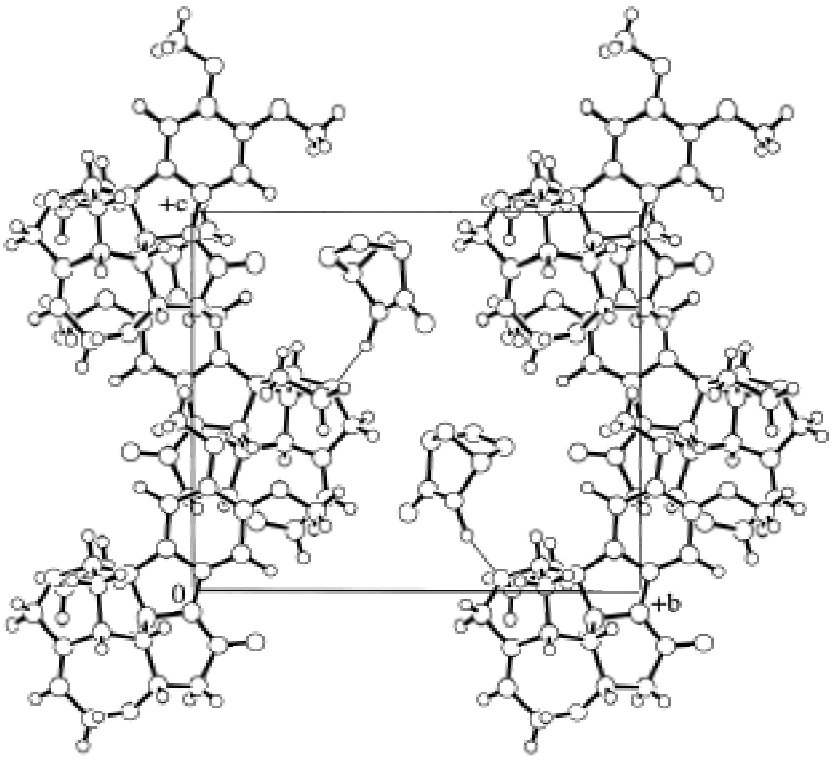

Figure 1. Packing diagram of the 1:1 inclusion complex ((-)-**1**·**5**) viewed down the *a* axis. Thin lines show the hydrogen bonds between N3-H27 in **1** and N2 in **5**.

The packing diagram shows that the guest molecules are located in channel-type cavities formed between the hosts, which extend approximately along the *c* axis of the crystal. (Figure 1). As is expected, the hydrogen bonds between (-)-**1** and brucine (**5**) are confirmed: N3···N2 = 2.98(1) Å, N3-H27···N2 = 1.85 Å, ∠N3-H27···N2 = 159.0˚. (Figure 2) Similar chiral recognition of *tert*-acetylenic alcohol in the inclusion complex with brucine has been reported.[6] The guest molecule (-)-**1** was found to be disordered. (Figure 3) It exhibits a rotational disorder around the NH···N hydrogen bond. However, it is clear that the other enantiomer (+)-**1** cannot fit sterically in this packing structure.

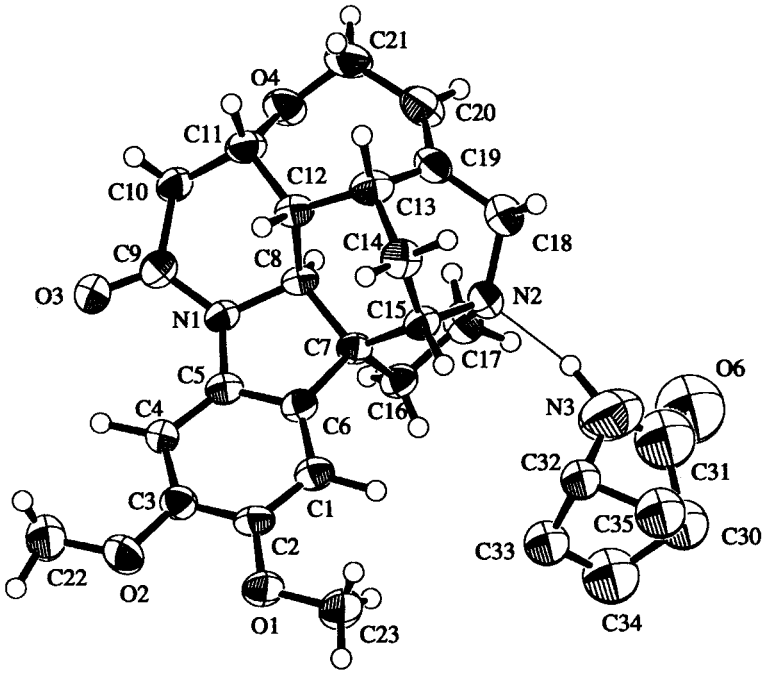

Figure 2. Ortep drawing of the host-guest molecule ((-)-**1**·**5**).

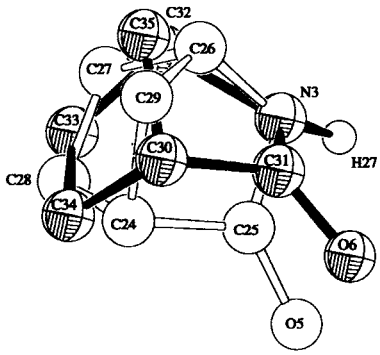

Figure 3. Ortep drawing of the disordered guest molecule (-)-**1**.

EXPERIMENTAL

Optical Resolution of 2-Azabicyclo[2.2.1]hept-5-en-3-one (1) .

When a solution of **5** (36 g, 91 mmol) and (±)-**1** (20 g, 183 mmol) in MeOH (50 mL) was kept at rt for 6 h, a 1:1 complex of **5** and (-)-**1** was obtained as colorless prisms (31 g) which upon distillation *in vacuo* gave (-)-**1** of 36% ee. Four recrystallizations of the crude complex from MeOH gave the almost pure 1:1 complex (6.6 g, mp 173-175 °C): IR (Nujol) 3300~2700 (NH), 1707, 1660 (CO) cm^{-1}; Anal. Calcd for $C_{29}H_{33}N_3O_5$: C, 69.17; H, 6.60; N, 8.34. Found: C, 69.00; H, 6.75; N, 8.29. Upon heating of the 1:1 complex *in vacuo*, (1*R*),(5*S*)-(-)-**1** of 92% ee was obtained as colorless prisms (1.3 g, 13%, mp 89-90 °C, $[\alpha]_D$-513° (*c* 0.52, $CHCl_3$)). Optical purity of (-)-**1** was determined by HPLC analysis using DAICEL CHIRALCEL OD (hexane:2-PrOH 9:1, 0.5 mL/min, 220 nm). The (+)- and (-)-**1** isomers eluted at 19.3 and 28.3 min, respectively.

Optical Resolution of Bicyclo[2.2.1]hept-5-en-2-one (2) .

When a solution of **5** (1.8 g, 4.6 mmol) and (±)-**2** (1.0 g, 9.3 mmol) in MeOH (5 mL) was kept at rt for 6 h, a 1:1 complex of **5** and (+)-**2** was obtained as colorless prisms (1.22 g, mp 138-151 °C): IR (Nujol) 1737, 1655 (CO) cm^{-1}; Anal. Calcd for $C_{30}H_{34}N_2O_5$: C, 71.69; H, 6.82; N, 5.57. Found: C, 71.69; H, 6.96; N, 5.68. Upon heating of the 1:1 complex *in vacuo*, (1*R*),(4*R*)-(+)-**2** of 27% ee was obtained as colorless solid (0.20 g, 40%, $[\alpha]_D$+274° (*c* 0.55, $CHCl_3$)). Optical purity of (-)-**2** was determined by comparison of its measured $[\alpha]_D$ with the literature value.[5]

Optical Resolution of Bicyclo[2.2.1]heptane-2,5-dione (3) .

When a solution of **5** (0.8 g, 2.0 mmol) and (±)-**3** (0.5 g, 4.0 mmol) in MeOH (3 mL) was kept at rt for 6 h, a 1:1 complex of **5** and (±)-**3** was obtained as colorless prisms (0.75 g, mp 138-151 °C): IR (Nujol) 1753, 1655 (CO) cm^{-1}; Anal. Calcd for $C_{30}H_{34}N_2O_6$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.08; H, 6.96; N, 5.42.

X-Ray Crystallography. A colorless prismatic crystal of the inclusion complex of (-)-**1** with **5** having approximate dimensions of 0.54 x 0.20 x 0.16 mm was mounted on a glass fiber. Diffraction data were collected on a Rigaku AFC-7R diffractometer with graphite-monochromated Mo$K\alpha$ radiation (λ = 0.71073 Å) to $2\theta_{\mu\alpha\xi}$ = 55°. Crystal data: orthorhombic, space group $P2_12_12_1$ (No.19), *a* = 14.042(3), *b* = 14.48(1), *c* = 12.27(2) Å, *V* = 2496(4) $Å^3$, *Z* = 4. The structure was solved by direct methods (SIR92) and expanded using Fourier techniques. The guest molecule (**1**) was placed on two disordered positions except for N3 and H27, which are fixed by a hydrogen bond with the host molecule, brucine. The absolute configuration was automatically determined based on the known configuration of brucine. The final cycle of full-matrix least-squares refinement was based on 1880 observed reflections ($I > 2.00\sigma(I)$) and 328 variable parameters and converged with R = 0.057 and R_w = 0.079 ($w = [\sigma^2(F_o) + 0.0009F_o^2]^{-1}$). All calculations were carried out using the teXsan crystallographic software package of Molecular Structure Corporation.

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