Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 2216–2219

# Resolution of 4-oxoazetidin-2-yl benzoate by inclusion crystallization with an optically active host compound

Koichi Tanaka,[a,*] Hiroko Takenaka[a] and Mino R. Caira[b,*]

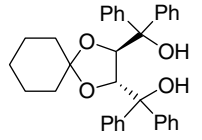
[a]*Department of Applied Chemistry, Faculty of Engineering and HighTechnology Research Center, Kansai University, Suita, Osaka 564-8680, Japan*
[b]*Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa*

Received 13 June 2006; revised 7 August 2006; accepted 8 August 2006
Available online 8 September 2006

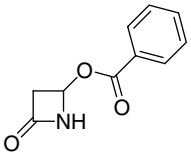
**Abstract**—4-Oxoazetidin-2-yl benzoate was resolved efficiently by an inclusion complexation with a chiral host compound, (*R*,*R*)-(−)-*trans*-4,5-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.5]decane. The phenyl substituent on the β-lactam ring was found to play an important role in an efficient chiral recognition in the inclusion crystals.


## 1. Introduction

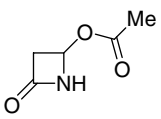
Optically active β-lactams have attracted much attention in the recent years, since the β-lactam functionality is a key structural element in many biological compounds, such as penicillins, cephalosporins, and carbapenems. 4-Oxoazetidine-2-yl benzoate is an important synthon for some antibacterial compounds.[1]



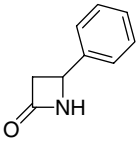

**1**




**2**




**3**




**4**

However, the preparation of optically active β-lactams is not easy, although some enzymatic enantioselective reactions have been reported.[2] Herein, we report the efficient resolution of β-lactams **2** and **4** by inclusion crystallization with an optically active host compound **1**[3] derived from tartaric acid. The X-ray crystal structure of the 1:1 inclusion complex of (*R*,*R*)-(−)-**1** and (*S*)-(−)-**2** is also discussed.

## 2. Results and discussion

A solution of (*R*,*R*)-(−)-**1** (0.51 g, 1.0 mmol) and (±)-**2** (0.38 g, 2.0 mmol) in $CH_2Cl_2$–hexane (1:1, 20 ml) was kept at room temperature for several days, during which time colorless prisms of the 1:1 inclusion complex of (*R*,*R*)-(−)-**1** with (*S*)-(−)-**2** (0.56 g) and colorless needles of (*R*)-(+)-**2** (0.17 g, 90% yield, 93% ee) were formed. From the 1:1 inclusion complex of (*R*,*R*)-(−)-**1** with (*S*)-(−)-**2**, (*S*)-(−)-**2** was obtained in 98% ee and 74% yield by silica gel column chromatographic separation. The enantiomeric excess was determined by means of a HPLC column (Chiralpak AS). In the infrared spectrum of the 1:1 inclusion complex of (*R*,*R*)-(−)-**1** with (*S*)-(−)-**2**, the *ν*OH peak appeared at 3137 $cm^{-1}$ relative to 3530 and 3340 $cm^{-1}$ in the free host molecule. The *ν*C=O peak of (±)-**2** appearing at 1788 $cm^{-1}$ in the free guest was also shifted to lower frequency and split into two peaks at 1762 and 1727 $cm^{-1}$. In contrast, when a solution of (*R*,*R*)-(−)-**1** (1.0 g, 2.0 mmol) and (±)-**3** (0.40 g, 3.0 mmol) in toluene–hexane (3:1, 15 ml) was kept at room temperature for several days, a 2:1 inclusion complex of (*R*,*R*)-(−)-**1** and **3** was obtained as colorless prisms (0.75 g), which upon heating at 200 °C in vacuo afforded (−)-**3** in only 8% ee. These data suggested that the phenyl substituent of the β-lactam plays an important role in chiral recognition in inclusion crystals. We next

* Corresponding authors. Tel./fax: +81 6 6368 0861 (K.T.); e-mail: ktanaka@ipcku.kansai-u.ac.jp

0957-4166/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2006.08.004

examined the resolution of 4-phenylazetidin-2-one **3**, in which the phenyl group is directly linked to the β-lactam ring. When a solution of (*R*,*R*)-(−)-**1** (1.0 g, 2.0 mmol) and (±)-**4** (0.30 g, 2.0 mmol) in *n*-butylether–hexane (5:1, 30 ml) was kept at room temperature for several days, a mixture of the 1:1 inclusion complex of (*R*,*R*)-(−)-**1** and (−)-**4** (colorless prisms, 0.39 g, 60% yield, 47% ee) and the 2:1:1 complex of (*R*,*R*)-(−)-**1**, (−)-**4**, and *n*-butylether (colorless needles, 0.18 g, 16% yield, 60% ee) was obtained. These two inclusion crystals were separated by manual sorting and were recrystallized from *n*-butylether to afford the 2:1:1 complex of (*R*,*R*)-(−)-**1**, (−)-**4**, and *n*-butylether in 80% ee and 96% ee, respectively (Table 1).

**Table 1.** Resolution of β-lactams **2**–**4** by inclusion complexation with optically active host **1**

| β-Lactam | h:g ratio[a] | Mp (°C) | ee[b] (%) |
|---|---|---|---|
| **2** | 1:1 | 153–155 | 98 |
| **3** | 2:1 | 197–198 | 8 |
| **4** | 2:1:1 (*n*-$Bu_2O$) | 197 (dec) | 60 |
| | 1:1 | 122–125 | 47 |

[a] Host–guest ratio was determined by $^1$H NMR.
[b] Enantiomeric excess was determined by HPLC.

### 2.1. X-ray analysis

The asymmetric unit of the 1:1 inclusion complex between host molecule (*R*,*R*)-(−)-**1** and (*S*)-(−)-**2** is shown in Figure 1. Table 2 lists the crystal data, data-collection, and refinement parameters. In the host molecule, the five-membered ring adopts an envelope conformation (flap at C15) resulting in a dihedral angle C2–C15–C16–C25 of −91.0(2)°, the negative value being consistent with the stated chiralities (*R*) at the C15 and C16 centers. A strong O1–H···O26 intramolecular hydrogen bond (Table 3) stabilizes the molecular conformation. The same hydrogen bond was invariably observed in inclusion complexes of this host.[4] The orientations of the four host phenyl groups are determined by intramolecular C–H···O hydrogen bonds, one for each ring, and each involving one of the four host oxygen atoms as an acceptor. Thus, as regards possible interaction with guest molecules, the fairly rigid host molecule presents a hydrogen bond acceptor (O1) and a donor (O26). Figure 1 shows only the H-bonds in the asymmetric unit. The complete arrangement in the crystal is described below.

The absolute configuration of guest atom C48 (*S*) was established from the known chirality of the host used in crystal preparation, while the Flack parameter (Table 2) is consistent with this assignment. The four atoms comprising the β-lactam ring display small deviations (0.013(2)–0.016(1) Å) from their least-squares plane and the conformation of the guest molecule is defined by the dihedral angles N49–C48–O47–C45 −76.3(2)°, C48–O47–C45–C39 −177.9(1)°, and O47–C45–C39–C34 171.7(1)°, the last indicating that the phenyl ring is twisted by ∼8° with respect to the $–CO_2$-residue.

As inferred from IR data, there is extensive hydrogen bonding in the crystal of (*R*,*R*)-(−)-**1**·(*S*)-(−)-**2**. The N–H and C=O groups of the β-lactam ring, respectively, act as donor and acceptor in hydrogen bonds with the –OH functions of two $2_1$-related host molecules (Table 3) giving rise to infinite spirals of hydrogen bonded host and guest molecules parallel to the crystal *b*-axis (Fig. 2).

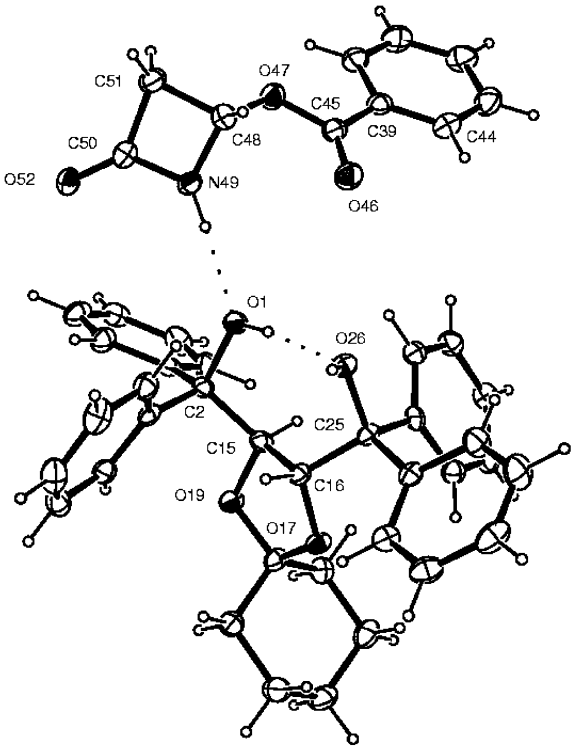



**Figure 1.** ORTEP figure of the asymmetric unit in (*R*,*R*)-(−)-**1**·(*S*)-(−)-**2**. Thermal ellipsoids are drawn at the 50% probability level.

**Table 2.** Crystallographic data for (*R*,*R*)-(−)-**1**·(*S*)-(−)-**2**

| | |
|---|---|
| Formula | $C_{34}H_{34}O_4{\cdot}C_{10}H_9NO_3$ |
| Formula weight | 697.79 |
| Crystal system | Orthorhombic |
| Space group | $P2_12_12_1$ |
| *a* (Å) | 12.4477(2) |
| *b* (Å) | 13.1325(2) |
| *c* (Å) | 22.3530(3) |
| *V* (Å$^3$) | 3654.03(9) |
| *Z* | 4 |
| λ (Å) | 0.71073 ($MoK_\alpha$) |
| Reflections with $I > 2\sigma(I)$ | 5695 |
| $R_1$ | 0.0345 |
| $wR_2$ | 0.0708 |
| Goodness of fit | 1.049 |
| Flack parameter | −0.2(6) |

**Table 3.** Principal hydrogen bonds in (*R*,*R*)-(−)-**1**·(*S*)-(−)-**2**

| D–H···A | H···A (Å) | D···A (Å) | D–H···A (°) |
|---|---|---|---|
| O1–H1···O26 | 1.834(1) | 2.665(2) | 170.0(1) |
| N49–H49···O1 | 2.022(1) | 2.847(2) | 155.8(1) |
| O26–H26···O52$^i$ | 1.839(1) | 2.659(2) | 164.9(1) |

Symmetry codes: (i) 1 − x, −1/2 + y, 1/2 − z.

Given the experimental observation that the presence of a phenyl group in the β-lactam seems to be important for chiral discrimination by the host, a detailed examination of the interactions involving the phenyl group of the guest (*S*)-(−)-**2** in the inclusion crystal above was performed. This phenyl residue is surrounded primarily by host phenyl and cyclohexyl residues. A search for intermolecular C–H···O/C–H···N, π–π, and X–H···π interactions revealed no such hydrogen bonds, no π–π interactions with ring centroids (Cg) separated by less than 4.5 Å, and only two C–H···π interactions involving the guest phenyl group, with C–H···Cg 2.68 (guest as donor) and 3.00 Å (guest as acceptor). It is also noteworthy that the H atom attached to the stereogenic carbon C(48) does not likewise engage in any significant intermolecular interactions. Thus, it must be concluded that while host–guest molecular recognition is driven by strong hydrogen bond formation (N–H···O, O–H···O), enantioselectivity in this case is based primarily on shape selection, inclusion of the (*S*)-(−)-**2** guest exclusively by host (*R*,*R*)-(−)-**1** molecules resulting in a close-packed crystal.

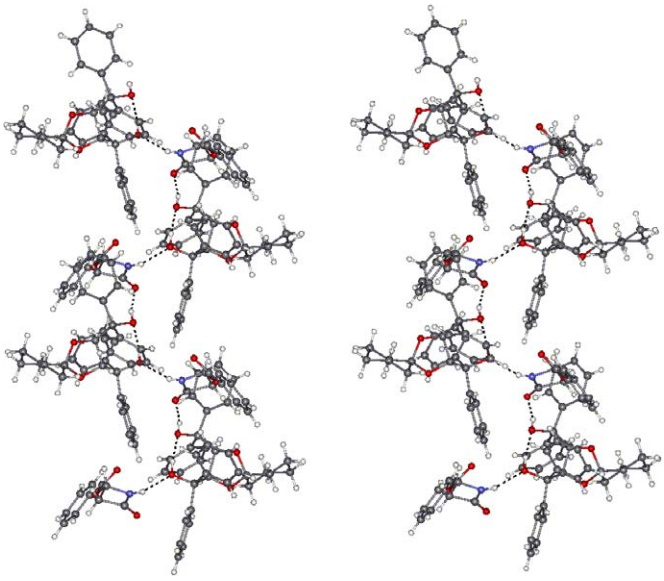


**Figure 2.** Stereoview of the spiral hydrogen bonding motif in (*R*,*R*)-(−)-**1**·(*S*)-(−)-**2**.

## 3. Experimental

Melting points were measured by Stanford Research Systems MPA-100. $^1$H NMR spectra were obtained with a JEOL EX-270. IR spectra were recorded on a JASCO FT/IR 4100 spectrometer. Optical rotations were measured on a ATAGO AP-100 polarimeter and enantiomeric excesses were determined by HPLC on Chiralpak AS (Daisel).

### 3.1. Resolution of 4-oxoazetidin-2-yl benzoate 2 by inclusion complexation with (*R*,*R*)-(−)-*trans*-4,5-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.5]decane 1

When a solution of (*R*,*R*)-(−)-**1** (0.51 g, 1.0 mmol) and (±)-**2** (0.38 g, 2.0 mmol) in $CH_2Cl_2$–hexane (1:1, 20 ml) was kept at room temperature for several days, a mixture of colorless prisms of the 1:1 inclusion complex of (*R*,*R*)-(−)-**1** with (*S*)-(−)-**2** (0.56 g, mp 150–154 °C) and colorless needles of (*R*)-(+)-**2** (0.17 g, 90% yield, 98% ee) were formed. These two crystals were separated by manual sorting and were analyzed by $^1$H NMR spectra to determine the host–guest ratios. From the 1:1 inclusion complex of (*R*,*R*)-(−)-**1** with (*S*)-(−)-**2**, (*S*)-(−)-**2** (0.14 g, 74% yield, 98% ee) was obtained by silica gel column chromatographic separation. The enantiomeric excess was determined by HPLC analysis with Chiralpak AS (Daicel Chemical Industries, Ltd.); eluent, hexane/EtOH = 80/20; flow rate, 1.0 ml/min; detection, UV 254 nm; retention time, 13 min (*S*-enantiomer) and 17 min (*R*-enantiomer).

### 3.2. X-ray diffraction

Preliminary unit cell determination indicated the orthorhombic system and from the systematic absences, the space group $P2_12_12_1$ was deduced. Crystal intensity data were collected on a Nonius Kappa CCD diffractometer using $MoK_\alpha$ radiation and $\phi$- and $\omega$-scans of 1.0° and 1.5°, respectively, using the strategy recommended by the program COLLECT.[5] A single crystal of equant shape (0.30 × 0.25 × 0.25 mm) was prepared, coated in Paratone N oil (Exxon) and cooled in a stream of nitrogen vapor to 113 K. Unit cell dimensions before and after cooling were comparable, indicating that no phase change occurred when altering the crystal temperature. The program DENZO-SMN[6] was used for unit cell refinement and data reduction. The structure was solved by direct methods using the program SHELXS86[7] and refined by full-matrix least-squares against $F^2$ with the program SHELX-97.[8] Molecular parameters were calculated with PLATON.[9] The programs ORTEP[10] and WebLab ViewerPro 3.7[11] were used for illustrations. Crystal data for the structure have been deposited with the Cambridge Crystallographic Data Centre (Deposition Number 606025).

## Acknowledgements

K.T. acknowledges the financial support from 'High-Tech Research Center' Project for Private Universities: mating fund subsidy from MEXT (Ministry of Education, Culture, Sports, Science and Technology), 2005–2009. M.R.C. thanks the University of Cape Town and the NRF (Pretoria) for research support.

## References

1. For example, see: (a) Pfaendler, H. R.; Medicus, C. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 623; (b) Basak, A.; Khamarai, U. *Synth. Commun.* **1994**, *24*, 131.
2. (a) Forro, E.; Fulop, F. *Tetrahedron: Asymmetry* **2001**, *12*, 2351; (b) Gyarmati, Z. C.; Liljeblad, A.; Rintola, M.; Bernath, G.; Kanerva, L. T. *Tetrahedron: Asymmetry* **2003**, *14*, 3805; (c) Yang, Y.; Drolet, M.; Kayser, M. M. *Tetrahedron: Asymmetry* **2005**, *16*, 2748.
3. (a) Seebach, D.; Beck, A. K.; Imwinkeiried, R.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954; (b) Toda, F.;

Sato, A.; Tanaka, K.; Mak, T. C. W. *Chem. Lett.* **1989**, *5*, 873; (c) Tanaka, K.; Fujiwara, T. *Org. Lett.* **2005**, *7*, 1501.
4. Tanaka, K.; Kuchiki, D.; Caira, M. R. *Tetrahedron: Asymmetry* **2006**, *17*, 1678.
5. Hooft, R. *COLLECT*; Nonius B.V.: Delft, The Netherlands, 1998.
6. Otwinowski, Z.; Minor, W. *Meth. Enzymol.* **1997**, *276*, 307.
7. Egert, E.; Sheldrick, G. M. *Acta Crystallogr.* **1985**, *A41*, 262.
8. Sheldrick, G. M.; University of Göttingen: Germany, 1997.
9. Spek, A. L. *Acta Crystallogr.* **1990**, *A46*, C34.
10. Farrugia, L. J. *J. Appl. Crystallogr.* **2000**, *30*, 565.
11. WebLab ViewerPro 3.7. 2000. San Diego, CA: Molecular Simulations, Inc.