View Article Online / Journal Homepage / Table of Contents for this issue

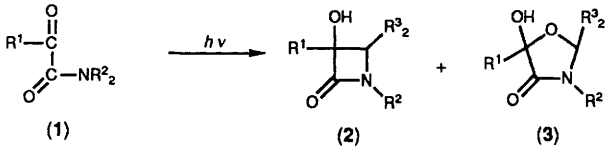
New Preparative and Optical Resolution Method for β-Lactams

Fumio Toda,* Koichi Tanaka, and Minoru Yagi
Department of Industrial Chemistry, Faculty of Engineering, Ehime University, Matsuyama 790, Japan
Zafra Stein and Israel Goldberg *
School of Chemistry, Sackler Faculty of Exact Sciences, Tel-Aviv University, 69978 Ramat-Aviv, Israel

Photoirradiation of a 1:1 inclusion compound of oxoamide and *N,N,N',N'*-tetracyclohexylbiphenyl-2,2'-dicarboxamide in the solid state gave a β-lactam, which was resolved by complexation with optically active 9,9'-biphenanthryl-10,10'-diol. Chiral recognition of the host and guest in the inclusion compound was studied by X-ray crystallographic analysis.

Published on 01 January 1990. Downloaded by Michigan State University on 20/01/2016 15:13:18.

Development of new preparative methods for optically active β-lactams is still an attractive synthetic challenge. We report here such a method, namely, the selective photocyclisation of oxo amides in a host-guest inclusion compound in the solid state and optical resolution of the β-lactam so formed by complexation with an optically active host compound.



(1) (2) (3)

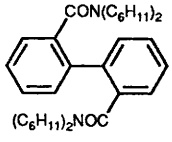
a; R^1 = Me; R^2 = Pr^i
b; R^1 = R^2 = Me

a; R^1 = R^3 = Me; R^2 = Pr^i
b; R^1 = R^2 = Me; R^3 = H

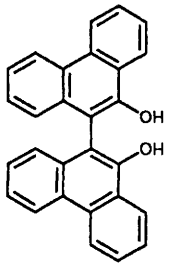
Although photocyclisation of the oxo amides (**1**) to give β-lactams (**2**) has long been known,[1,2] the reaction gives oxazolidinones (**3**) as a by-product. Control of this reaction so as to produce (**2**) exclusively has been achieved by carrying out the reaction in a host-guest inclusion compound.[3] Use of an optically active host gave an enantioselective reaction in which optically active β-lactam was produced.[3,4] However, this control was effective only for (**1**; R^1 = Aryl).[3,4] Here, we report a selective photocyclisation of the corresponding alkyl compounds (**1**; R^1 = Alkyl) to give (**2**) and optical resolution of the latter by complexation with an optically active host.

It has been reported that both the irradiation of (**1a**) in benzene and in neat liquid gives (**3a**) exclusively and the irradiation in the solid state at −78 °C gives (**2a**) and (**3a**) in 31 and 29% yields, respectively.[5] Control of the reaction was attempted by irradiation of an inclusion compound of (**1b**) and deoxycholic acid in the solid state, but this reaction again gave (**3b**) in 10% yield in addition to (**2b**) (40%).[6] On the other hand, irradiation of a 1:1 inclusion compound of (**1a**) and *N,N,N',N'*-tetracyclohexylbiphenyl-2,2'-dicarboxamide (**4**)[7] in the solid state for 40 h gave (**2a**) in 60% yield as the sole isolable product. Similar irradiation of a 1:1 inclusion compound of (**1b**) and (**4**) gave (**2b**) selectively in 56% yield. The steric restrictions of the inclusion compound lead to preferential production of the less bulky (**2**).

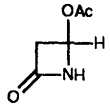
Optically active (**2b**) was easily obtained by complexation with optically active 9,9'-biphenanthryl-10,10'-diol (**5**).[8] For example, when a solution of *rac*-(**2b**) (0.6 g, 5.82 mmol) and (**5**) (1.0 g, 2.59 mmol) in benzene (10 ml) was kept at room temperature for 12 h, a 1:1 inclusion compound of (+)-(**2b**) and (**5**) was obtained as colourless prisms, after one recrystallisation



(4)



(*S*)-(−)-(5)



(6)

from benzene (1.02 g), m.p. 187–190 °C. Chromatography of this on silica gel using THF as a solvent gave (+)-(**2b**) (100% e.e.; 0.23 g, 77%), $[\alpha]_D$ +61.6° (*c* 0.27 in $CHCl_3$). The optical purity was determined by h.p.l.c. on the chiral solid phase, Chiralcel OC.† From the filtrate left after the separation of the 1:1 inclusion compound of (+)-(**2b**) and (**5**), (−)-(**2b**) of 69.8% e.e. was obtained by silica gel chromatography (0.29 g, 97%), $[\alpha]_D$ −43.0° (*c* 0.16 in $CHCl_3$). The resolution method was not applicable to (**2a**). However, a simpler but very important starting material for the synthesis of antibiotics, compound (**6**), was resolved by this method, although optically active (**6**) has not so far been obtained.[9,10] A solution of *rac*-(**6**) (0.67 g, 5.19 mmol) and (**5**) (1.0 g, 2.59 mmol) in benzene–hexane (1:1) (10 ml) when kept at room temperature for 12 h gave a 1:1 inclusion compound of (+)-(**6**) and (**5**) as colourless prisms, after two recrystallisations from benzene (0.87 g), m.p. 147–149 °C. This material when heated at 150 °C/1 mmHg gave (+)-(**6**) (0.21 g, 63%), $[\alpha]_D$ +6.5° (*c* 0.68 in MeOH).

Compound (+)-(**6**) was taken to be optically pure because its $[\alpha]_D$ value did not change by repeating the complexation with (**5**).

In order to understand the mechanism for the efficient chiral recognition between β-lactam and (**5**), an X-ray crystal structural analysis of the 1:1 inclusion compound of (+)-(**6**) and (**5**) was carried out.† The crystal structure consists of continuous chains of hydrogen-bonded entities in which each host donates its hydroxy protons to two different guests and every guest binds to adjacent hosts through its two carbonyl functions (see Figure). The observed hydrogen bonds are

† *Crystal data.* $C_{28}H_{18}O_2 \cdot C_5H_7NO_3$ (1:1), M = 515.56, Orthorhombic, space group $P2_12_12_1$, a = 8.583(1), b = 9.825(1), c = 30.031(4) Å, V = 2 532.45 Å^3, D_c = 1.352 g cm^{-3}, Z = 4, μ = 0.85 cm^{-1}, $F(000)$ = 1 080.

View Article Online

Published on 01 January 1990. Downloaded by Michigan State University on 20/01/2016 15:13:18.

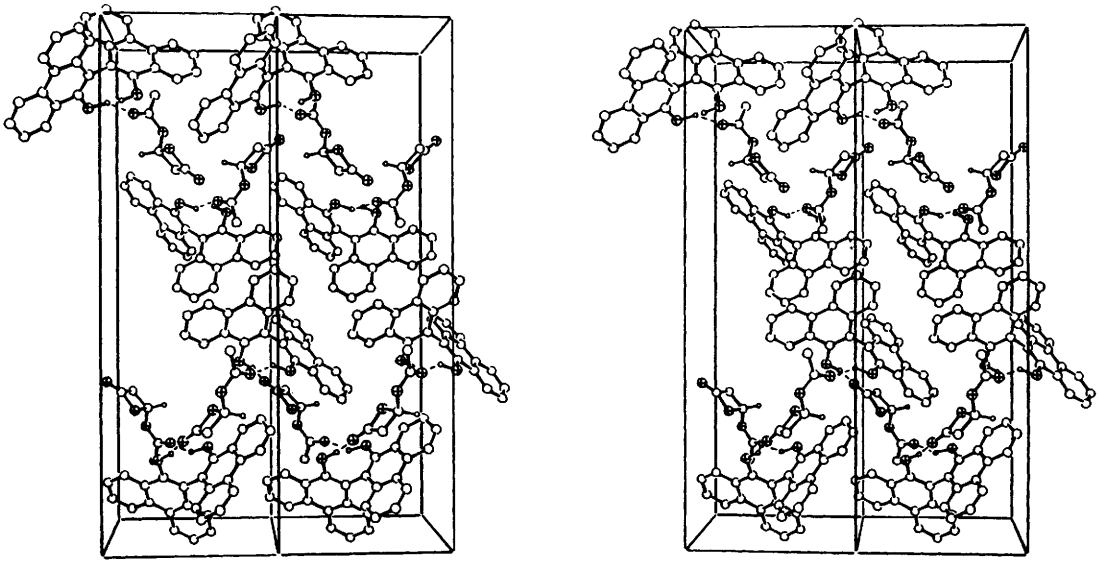


Figure. Stereoview of the crystal structure of the 1:1 inclusion compound of (**5**) and (+)-(**6**) down the *a*-axis (*c* is vertical). Contents of two unit-cells are shown to illustrate better the continuous arrays of co-ordinative interactions between the two components. The crystallographically refined model shown here has an inverted chirality.*

OH · · · O = 2.912(10) and 2.920(11) Å. The upper part of the Figure shows the host-guest-host-guest continuous association; the lower part illustrates the successive arrangement of the neighbouring guest entities along the *b*-axis of the crystal.

Intensity data were measured at room temperature on an automated Huber diffractometer using Mo-K_α (λ = 0.7107 Å) radiation to $2\theta_{max}$ = 50°. No corrections for absorption or secondary extinction effects were applied. The structure was solved by direct methods (SHELX-86).[11] Its refinement by cascade-type least-squares (SHELX-76)[12] converged smoothly at R = 0.057, wR = 0.059, for 1 448 observations above the threshold of $3\sigma(I)$ (out of 2 251 unique data above zero), and 352 refined parameters divided into two blocks. At convergence, the peaks and troughs of the difference density map did not exceed 0.24 and −0.25 e Å^{-3}, respectively. The hydrogen atoms attached to O and N were located directly from difference-Fourier maps; the remaining hydrogens were introduced in calculated positions, the β-lactam methyl being refined as a rigid group. The relatively low data-to-parameters ratio affected the precision of the crystallographic determination. The e.s.d.'s of the atomic co-ordinates x and y (and consequently those of the bond lengths and angles) are particularly high due to a small number of significant reflections from planes near the (h00) and (0k0) zones of the reciprocal space. No attempt was made to confirm the absolute configuration of the inclusion compound from diffraction data; the refined model illustrated in the Figure happens to have an inverted chirality from that of the actual structure. Since the absolute configuration of the host (**5**) is known, that of the included guest (+)-(**6**) is unequivocally determined by the crystallographic analysis.

* Chiralcel OC is available from Daicel Chemical Industries, Ltd., Himeji, Japan.

Acknowledgements

F. T. is grateful to the Ministry of Education, Science and Culture, Japanese Government for the Grant-in-Aid for Science Research on Priority Areas No. 01648006. I. G. is grateful to the Department of Chemistry and Biochemistry at UCLA for the hospitality extended to him while working on this project during a sabbatical stay at UCLA.

References

1 B. Åkermak, N-G. Johansson, and B. Sjöberg, *Tetrahedron Lett.*, 1969, 371.
2 R. Henery-Logan and C. G. Chen, *Tetrahedron Lett.*, 1973, 1103.
3 F. Toda, K. Tanaka, and M. Yagi, *Tetrahedron*, 1987, **43**, 1495.
4 M. Kaftory, M. Yagi, K. Tanaka, and F. Toda, *J. Org. Chem.*, 1988, **53**, 4391.
5 H. Aoyama, T. Hasegawa, and Y. Omote, *J. Am. Chem. Soc.*, 1979, **101**, 5343.
6 H. Aoyama, K. Miyazaki, M. Sakamoto, and Y. Omote, *Tetrahedron*, 1987, **43**, 1513.
7 F. Toda, A. Kai, Y. Tagami, and T. C. W. Mak, *Chem. Lett.*, 1987, 1393.
8 F. Toda and K. Tanaka, *J. Org. Chem.*, 1988, **53**, 3607.
9 E. Arribas, C. Carreiro, and A. M. Valdeolmillos, *Tetrahedron Lett.*, 1988, **29**, 1609.
10 D. Hoppe and T. Hilpert, *Tetrahedron*, 1987, **43**, 2467.
11 G. M. Sheldrick, SHELX-86, in 'Crystallographic Computing 3,' eds. G. M. Sheldrick, C. Kruger, and R. Goddard, Oxford University Press, 1985, pp. 175–189.
12 G. M. Sheldrick, SHELX-76, Program for Crystal Structure Determination, University of Cambridge, England, 1976.

Paper 9/04457D
Received 16*th October* 1989
Accepted 20*th December* 1989