Tetrahedron: Asymmetry Vol. 4, No. 8, pp. 1755-1758, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

A Chiral Probe Useful for Optical Resolution and X-Ray Crystallographic Determination of the Absolute Stereochemistry of Carboxylic Acids

Nobuyuki Harada,* Tomomi Soutome, Shinji Murai, and Hisashi Uda

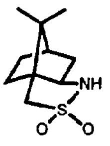
Institute for Chemical Reaction Science, Tohoku University, 2-1-1 Katahira, Aoba, Sendai 980, Japan

(*Received in UK* 26 *April* 1993)

This paper is dedicated to the memory of Professor Gunther Snatzke (1928-1992)

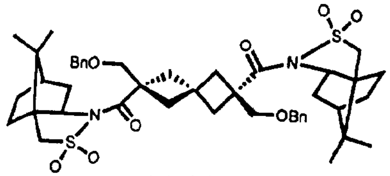
Abstract: (1*S*,2*R*,4*R*)-(−)-2,10-Camphorsultam is a very useful chiral probe for optical resolution by HPLC and X-ray crystallographic determination of the absolute stereochemistry of carboxylic acids. The absolute configurations of 2,6-dimethylspiro[3.3]heptane-2,6-dicarboxylic acid and [2.2]paracyclophane-4-carboxylic acid are determined.

In addition to the CD exciton chirality method,[1] the X-ray crystallographic Bijvoet method[2] which is based on the anomalous dispersion effect of heavy atoms is one of the most reliable nonempirical methods for determination of the absolute stereochemistry of chiral compounds. We report here that (1*S*,2*R*,4*R*)-(−)-2,10-camphorsultam (1)[3] is very useful as a chiral probe for optical resolution and X-ray crystallographic determination of the absolute stereochemistry of carboxylic acids having the following advantages; i) in general, a diastereomeric mixture of amides synthesized from racemic acid with camphorsultam **1** is more easily separable by HPLC on silica gel than the case of usual diastereomeric esters because of the polarity of amide and sulfone moieties; ii) camphorsultam amide generally crystallizes as large prismatic crystals and has a higher melting point, which imply the strong crystal packing force due to the polar groups; iii) the camphorsultam probe has a sulfur atom as a heavy atom, which enables one to earn more X-ray diffraction intensity, and hence a small crystal can be used; iv) when solving the crystal structure from the diffraction data, it is easy to find a heavy atom, which is also effective for the successive Fourier syntheses; v) the sulfur atom of the probe is enough for determination of the absolute stereochemistry by the Bijvoet method, if a copper radiation source is used in the X-ray diffraction; vi) since the absolute configuration of the camphor part is known, it can be used as an internal reference of the absolute configuration. Therefore, the absolute stereochemistry of carboxylic part is doubly determinable; vii) finally, unlike the case of common amides, the camphorsultam amide group is easily cleaved.[3b]



(1*S*,2*R*,4*R*)-(−)-1

(±)-2



(*S*)-(−)-3a

The followings are the examples of this method. A new compound, (±)-2,6-bis(benzyloxymethyl)-

spiro[3.3]heptane-2,6-dicarboxylic acid (**2**), was converted to acid chloride, which was allowed to react with the anion of (1*S*,2*R*,4*R*)-(–)-2,10-camphorsultam **1** generated with sodium hydride. The diastereomeric bisamides formed appear as clearly separated two spots even on a 5 cm TLC plate of silica gel. The diastereomeric mixture was easily separated by HPLC on silica gel on a 100 mg scale (benzene/EtOAc = 20:1): resolution factor, Rs = 2.9. The crystalline material of the first-eluted fraction was recrystallized from EtOAc to give prisms, which were subjected to X-ray crystallographic structure analysis: (–)-**3a**, mp 210-212 °C; $[\alpha]_D$ –2.4 (c 1.149, $CHCl_3$). The crystal structure was solved in a usual way; absorption correction was made by use of the data of face indices and the size of the crystal. All hydrogens were placed at idealized positions. Block diagonal least-squares refinement of positional and thermal parameters, including anomalous scattering factors, led to the final convergence with the *R* value listed in Table 1. Since the *R* value for the (*S*) absolute configuration is definitely smaller than that of the mirror image structure, the absolute stereochemistry of the spiro center of bisamide (–)-**3a** was determined to be (*S*) as illustrated in Figure 1. Since the absolute configuration of the camphorsultam part is known to be (1*S*,2*R*,4*R*), the determination of the relative configuration of **3a** simultaneously led to the conclusion that the absolute stereochemistry of the spiro center was (*S*). The absolute stereochemistry of this spiro compound was thus doubly determined by the X-ray methods. Bisamide (*S*)-(–)-**3a** was then converted, via several reactions, to (*S*)-(+)-2,6-dimethylspiro[3.3]heptane-2,6-dicarboxylic acid **4**; $[\alpha]_D$ +9.07 (c 1.67, acetone).

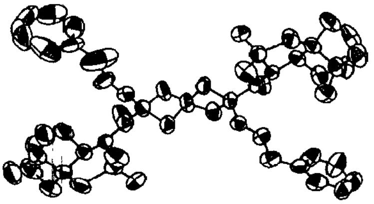
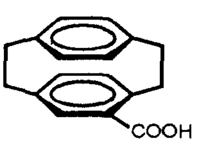
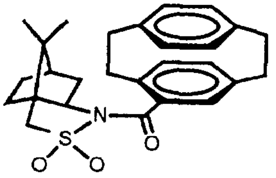


Figure 1. ORTEP drawing of (*S*)-(–)-3a

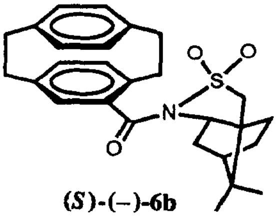
(*S*)-(+)-4



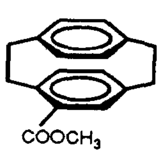
(±)-5



(*R*)-(–)-6a



(*S*)-(–)-6b



(*R*)-(–)-7

The camphorsultam method was next applied to [2.2]paracyclophane-4-carboxylic acid (**5**), the absolute configuration of which was once in a controversy in relation with other paracyclophane carboxylic acids.[4,6] Acid chloride of (±)-[2.2]paracyclophane-4-carboxylic acid **5** was allowed to react with the anion of (1*S*,2*R*,4*R*)-(–)-sultam **1**, and the diastereomeric mixture of amides formed was separated by HPLC on silica gel (hexane/EtOAc 5:1): Rs = 1.6. The syrup of the first-eluted fraction was crystallized from methanol to give sultamamide **6a** as prisms, which were subjected to the X-ray structure analysis: mp 243-244 °C; $[\alpha]_D$ –179 (c 1.013, $CHCl_3$). It was found that in the crystal, two molecules were contained in one asymmetric unit. The crystal structure was solved in a usual manner, and no hydrogen atoms were included.

Full matrix least-squares refinement led to the final convergence as shown in Table 1, where the final *R* value remained large. Although the difference between the *R* values of (*R*) configuration and its mirror image structure is relatively small, the data imply that the absolute configuration of (–)-**6a** is (*R*). In addition, the absolute stereochemistry of (–)-**6a** was definitely determined on the basis of its relative configuration and the absolute configuration of the chiral probe **1** (Figure 2). The camphorsultam method is thus powerful even in such a case where direct application of the Bijvoet method does not lead to a reliable determination.

The solid material of the second-eluted fraction was recrystallized from EtOAc to afford amide **6b** as prisms: mp 280-282 °C; $[\alpha]_D$ –15.7 (c 0.3304, $CHCl_3$). The crystal structure was similarly solved, and all hydrogen atoms were found by the difference Fourier syntheses. Absorption correction was made by use of

Table 1. Physical and X-ray crystallographic data of camphorsultam amides (–)-**3a**, (–)-**6a**, and (–)-**6b**.[a]

Compound	(–)-3a	(–)-6a	(–)-6b
mp (°C)	210-212	243-244	280-282
$[\alpha]_D$ in $CHCl_3$	–2.4 (c 1.149)	–179 (c 1.013)	–15.7 (c 0.3304)
crystal dimension (mm)	0.30 × 0.26 × 0.21	0.40 × 0.25 × 0.20	0.41 × 0.25 × 0.25
No. of molecule in one asymmetrical unit	1	2	1
formula	$C_{45}H_{58}N_2O_8S_2$	$C_{27}H_{31}NO_3S$	$C_{27}H_{31}NO_3S$
formula weight	819.10	449.61	449.61
crystal system	triclinic	monoclinic	monoclinic
space group	P1	$P2_1$	$P2_1$
a (Å)	11.671 (2)	23.535 (6)	8.1149 (9)
b (Å)	12.623 (2)	8.118 (2)	17.503 (3)
c (Å)	7.864 (1)	11.840 (4)	8.0945 (9)
α (°)	101.59 (1)	–	–
β (°)	100.32 (1)	90.16 (2)	97.242 (9)
γ (°)	91.74 (1)	–	–
vol (Å^3)	1113.9 (3)	2262 (1)	1140.5 (3)
Z	1	4	2
ρ(calcd) (g/cm^3)	1.221	1.321	1.309
ρ(obsd) (g/cm^3)[b]	1.218	1.315	1.307
linear absorption coefficient (cm^{-1})	14.683	14.01	13.90
independent reflections $F_o > 3.0\ \sigma(F_o)$	3326	3759	1851
hydrogen and position	all and idealized	no	all and difference Fourier
absorption correction	face indices and size	no	statistical
least squares refinement	block diagonal	full matrix	full matrix
no. of variables	747	577	391
absolute configuration	(*S*)	(*R*)	(*S*)
final *R* and (R_w)	0.0660	0.1226 (0.1371)	0.0299 (0.0339)[c]
final *R* and (R_w) for the mirror image	0.0691	0.1239 (0.1387)	0.0348 (0.0398)[c]

[a] A Rigaku AFC-6B automated four circle diffractometer; Cu K_α (1.541 78 Å); monochromator, graphite crystal; temperature 20 °C; θ–2θ scan; 2θ scan limits, 2-130°; no indication of standard reflection decay during data collection. [b] By flotation using a CCl_4/hexane solution. [c] Without absorption correction, R = 0.0378 and R_w = 0.0421 for the (*S*) configuration, while R = 0.0420 and R_w = 0.0468 for the mirror image.

the statistical method developed by C. Katayama, et al.[5] Full matrix least-squares refinement shown in Table 1 led to the unambiguous determination of the absolute stereochemistry of (–)-**6b** as shown in Figure 3. Furthermore, the (*S*) absolute configuration of the [2.2]paracyclophane-4-carboxylic acid part was also obtained on the basis of the relative configuration of (–)-**6b** and the absolute configuration of the camphorsultam probe.

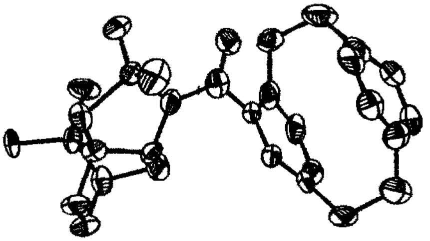


Figure 2. ORTEP drawing of (*R*)-(–)-6a

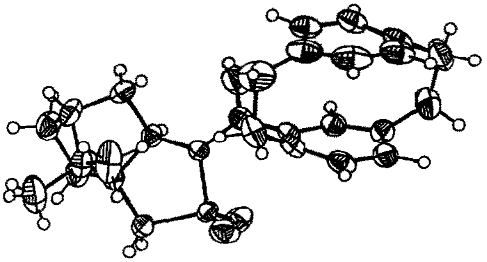


Figure 3. ORTEP drawing of (*S*)-(–)-6b

Amide (*R*)-(–)-**6a** was reduced with $LiAlH_4$ to give alcohol, which was treated with Jones reagent, and then with CH_2N_2 to yield methyl [2.2]paracyclophane-4-carboxylate (*R*)-(–)-**7**: $[\alpha]_D$ –149 (c 0.3738, $CHCl_3$). Amide (*S*)-(–)-**6b** of the second fraction was similarly converted to methyl ester (*S*)-(+)-**7**: $[\alpha]_D$ +140 (c 0.1581, $CHCl_3$). The absolute stereochemistry of methyl [2.2]paracyclophane-4-carboxylate **7** was thus established by the X-ray structure analysis of camphorsultam amides **6a** and **6b**. This conclusion is consistent with the determination of the absolute configurations of [2.2]paracyclophane-4-methanol derivatives reported by Tochtermann, et al.[6]

Acknowledgment. This work was supported in part by grants from the Ministry of Education, Science, and Culture, Japan (General (A) No. 59430005, General (B) No. 01470026, Priority Areas Nos. 01648501, 02230201, 03214107, 02250103, 03236101, and 04220101, and International Joint Research No. 02044014 to N.H.).

References and Notes

1. Harada, N.; Nakanishi, K. "Circular Dichroic Spectroscopy - Exciton Coupling in Organic Stereochemistry -", University Science Books, Mill Valley, Calif. and Oxford University Press, Oxford, 1983.
2. Bijvoet, J. M.; Peerdman, A. F.; Bommel, A. J. *Nature*, **1951**, *168*, 271. See also, Ibers, J.; Hamilton, W. C. *Acta Crystallogr.* **1964**, *17*, 781.
3. (a) Shriner, R. L.; Shotton, J. A.; Sutherland, H. *J. Am. Chem. Soc.*, **1938**, *60*, 2794. (b) Oppolzer, W.; Lienard, P. *Helv. Chim. Acta*, **1992**, *75*, 2572. (c) Weismiller, M. C.; Towson, J. C.; Davis, F. A. *Organic Syntheses*, **1990**, *69*, 154.
4. The absolute configuration of [8]paracyclophane-10-carboxylic acid was previously determined by the chemical correlation with [2.2]paracyclophane-4-carboxylic acid. However, we recently found that the absolute stereochemistry of [8]paracyclophane-10-carboxylic acid should be revised: Harada, N.; Soutome, T.; Nehira, T.; Uda, H. *Abstract of the Annual Meeting of Chem. Soc. Jpn.* 2 A7 16, Tokyo, March 1993.
5. Katayama, C.; Sakabe, N.; Sakabe, K. *Acta Cryst.* **1972**, *A28*, 293.
6. Tochtermann, W.; Olsson, G.; Vogt, C.; Peters, E.-M.; Peters, K.; von Schnering, H. G. *Chem. Ber.* **1987**, *120*, 1523, and references cited therein.