New preparative method for optically active 2,2′- and 4,4′-dihydroxybiphenyl derivatives. A new chiral host compound 4,4′-dihydroxy-2,2′,3,3′,6,6′-hexamethylbiphenyl

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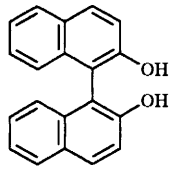
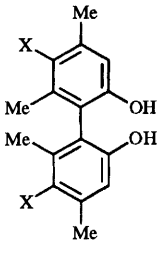
The title 2,2′- and 4,4′-dihydroxybiphenyl derivatives were efficiently resolved by complexation with an optically active host compound. Other kinds of guest compound were also complexed by the host compounds.

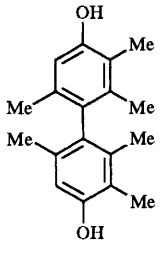
Optically active 2,2′-dihydroxy-1,1′-binaphthyl **1** is important not only as a key compound to prepare chiral catalysts for asymmetric synthesis [1] but also as a chiral shift reagent [2] and a chiral host compound for optical resolution of various guest compounds.[3] Similar, axially-chiral 2,2′-dihydroxybiphenyl derivatives are also expected to behave in a similar fashion to **1**. To our knowledge, two methods for the preparation of optically active 2,2′-dihydroxybiphenyl are known. (−)-3,3′,5,5′-Tetrachloro-2,2′-dihydroxy-4,4′,6,6′-tetramethylbiphenyl **2b** has been prepared by resolution *via* salt formation with (1*R*,2*R*)-pseudoephedrine.[4] Although titanium salts of (−)-**2b** have been synthesized,[4] their use in asymmetric synthesis has not been reported and fully substituted biphenyl derivatives like **2b** may have disadvantages as chiral catalysts in asymmetric synthesis. Preparation of less substituted optically active 2,2′-dihydroxybiphenyl derivatives through acetal formation with menthone has also been reported.[5] However, this synthesis is rather complicated and consists of many steps.



1

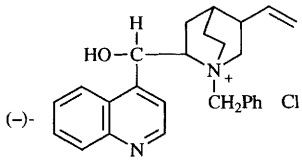


2
a X = H
b X = Cl



3

We have found that 2,2′-dihydroxy-4,4′,6,6′-tetramethylbiphenyl **2a** can easily be resolved by inclusion complexation with *N*-benzylcinchonidium chloride **4**. We also found that the 4,4′-dihydroxybiphenyl derivative can also be resolved by a similar inclusion complexation method. For example, 4,4′-dihydroxy-2,2′,3,3′,6,6′-hexamethylbiphenyl **3** was easily resolved by complexation with (*R*,*R*)-(−)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.4]nonane **5**. This is the first example of the preparation of an optically active 4,4′-dihydroxybiphenyl derivative.



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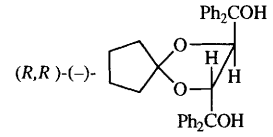

5

When a solution of *rac*-**2a** [6] (2 g, 8.26 mmol) and **4** (1.74 g, 4.13 mmol) in EtOH (10 cm^3) was kept at room temperature for 12 h, a 1 : 1 inclusion complex of (+)-**2a** and **4** was formed. Two recrystallizations of the complex from EtOH gave the pure complex (1.1 g, mp 138–140 °C), which upon mixing with AcOEt (20 cm^3)–water (20 cm^3) decomposed into the components. From the AcOEt solution, (+)-**2a** of >99.9% ee was obtained as colourless needles {0.53 g, 53%, mp 187–189 °C, $[\alpha]_D$ +59.5 (*c* 0.22, MeOH)†}. The optical purity was determined by HPLC using a column which contained Chiralcel OJ‡ as a chiral solid phase. From the aqueous solution, **4** was recovered. Treatment with AcOEt–water of the crude inclusion complex initially formed by the recrystallization of *rac*-**2a** and **4** from EtOH gave (+)-**2a** with 88% ee in 87% yield. This simple resolution method would be available to various derivatives of 2,2′-dihydroxybiphenyl.

Previously, we have reported that *rac*-**1** is easily resolved by inclusion complexation with **4** since **4** includes (+)-**1** selectively and forms a 1 : 1 inclusion complex.[7] X-Ray structure analysis of the complex showed that a hydrogen bond between Cl^- of **4** and the OH group of the (+)-**1** is formed.[8] On formation of the 1 : 1 inclusion complex, two sharp absorptions in the IR spectrum attributed to *ν*(OH) of (+)-**1** at 3510 and 3430 cm^{-1} (in Nujol mull) were shifted to a broad hydrogen bonded OH absorption at 3180 cm^{-1}.[7,8] Since two sharp absorptions attributed to *ν*(OH) of **2a** at 3450 and 3400 cm^{-1} were also shifted to a broad hydrogen bonded OH absorption at 3180 cm^{-1} on complexation with **4**, a similar hydrogen bond between Cl^- of **4** and the OH group of **2a** is probably formed in the complex.

When a solution of *rac*-**3** (5 g, 18.5 mmol) and **5** [9] (4.56 g, 9.27 mmol) in dibutyl ether (20 cm^3)–hexane (10 cm^3) was kept at room temperature for 12 h, a 1 : 1 inclusion complex of (+)-**3** and **5** was obtained (3.9 g), which upon recrystallization from dibutyl ether–hexane (2 : 1) gave the pure complex (2.43 g, 34%, mp 135–137 °C). The pure complex was dissolved in aqueous NaOH (10%). From the aqueous NaOH solution, (+)-**3** of >99.9% ee was obtained by acidification with dilute HCl

† $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}.
‡ Available from Daicel Chemical Industries, Ltd., Himeji, Japan.

Table 1 Melting point and ν(OH) absorption of the 1:1 inclusion complexes of (+)-**3** and guest compounds

Guest compound	Mp (T/°C)	ν(OH)/cm^{-1} (in Nujol mull)
MeOH	180–182	3420, 3220, 3150
EtOH	174–176	3430, 3270, 3150
Cyclopentanone	97–103	3500, 3400
THF	nc[a]	3350, 3150
Dioxane	nc[a]	3330, 3200
CCl_4	178–179	3270
DMF	113–115	3220
DMSO	115–117	3270
Pyridine	182–184	3220
Benzene	nc[a]	3320

[a] Did not show clear melting point.

followed by recrystallization as colourless prisms {0.76 g, 30%, mp 167–168 °C, $[\alpha]_D$ +1.5 (*c* 0.34, MeOH)}. The optical purity of the (+)-**3** was determined by HPLC using a column containing Chiralpak As‡ as a chiral solid phase. Compound **5** which was insoluble in aqueous NaOH, was recovered unchanged in quantitative yield by extraction with ether. The 1:1 complex of (+)-**3** and **5** was also decomposed to the components on treatment with dioxane. Recrystallization of the pure complex from dioxane (10 cm^3)–hexane (50 cm^3) gave a mixture of two kinds of crystals, relatively large colourless prisms of a 1:1 dioxane complex of (+)-**3** and relatively small colourless prisms of a 1:1 dioxane complex of **5**. These two complex crysals of (+)-**3** and **5** with dioxane were separated mechanically, and evaporation of the dioxane by heating under reduced pressure gave pure (+)-**3** and **5**, respectively.

In the IR spectra of the components, (+)-**3** shows a broad ν(OH) at 3280 cm^{-1} and **5** shows two sharp ν(OH) at 3590 and 3400 cm^{-1}; however, their 1:1 inclusion complex shows two hydrogen bonded ν(OH) at 3320 and 3270 cm^{-1}. The result clearly shows that the inclusion complex is constructed by the formation of hydrogen bonds.

Although **1**,[3] **4**[7,8] and **5**[9] include various kinds of guest compounds and form inclusion complex crystals, (+)-**2a** did not show any inclusion ability for the guest compounds tested. However, (+)-**3** showed a very high inclusion ability for a large variety of guest compounds. For example, all the typical guest compounds shown in Table 1 were included with (+)-**3** and formed 1:1 inclusion complexes which show clear melting points in most cases. On formation of the inclusion complexes, the ν(OH) of (+)-**3** at 3280 cm^{-1} in Nujol mull shifted to lower or higher frequencies as indicated in Table 1.

Furthermore, (+)-**3** showed a very efficient chiral-recognition ability for the chiral guest compounds. Using this chiral recognition ability, racemic guest compounds were easily resolved through complexation with (+)-**3**. For example, when a solution of (+)-**3** (0.5 g, 1.85 mmol) and *rac*-methyl phenyl sulfoxide **6** (0.52 g, 3.7 mmol) in toluene (5 cm^3) was kept at room temperature for 3 h, a 1:1 inclusion complex of (+)-**3** and (+)-**6** was obtained as colourless prisms (0.49 g), which upon heating under reduced pressure gave (+)-**6** of 86% ee upon distillation. One recrystallization of the crude 1:1 inclusion complex of (+)-**3** and (+)-**6** of 86% ee (0.49 g) from toluene gave the pure complex as crystals (0.39 g, 51%), mp 140–142 °C), which upon heating under reduced pressure gave (+)-**6** of >99.9% ee {0.12 g, 46%, $[\alpha]_D$ +134 (*c* 0.15, MeOH)} upon distillation. The optical purity of (+)-**6** was determined by HPLC using a column containing Chiralcel OD‡ as the chiral solid phase.

Although optically active **6** is an important synthon for various chiral compounds,[10] no efficient synthesis of optically active **6** in bulk is known, except one recently reported resolution method.[11] The efficient resolution of *rac*-**6** by complexation with the simple host compound (+)-**3** is therefore useful.

Experimental

Preparation of *rac*-3

A mixture of powdered 2,3,5-trimethylphenol (50 g, 0.37 mol) and $FeCl_3 \cdot 6H_2O$ (198.3 g, 0.73 mol) was irradiated by ultrasound (28 KHz) at room temperature for 30 h according to the reported procedure of phenol coupling in the solid state.[12] The reaction mixture was added to dilute HCl and extracted with toluene. The crude product obtained from the toluene solution was chromatographed on silica gel using hexane–AcOEt (8:2) as an eluent to give, after recrystallization from toluene, *rac*-**3** (7.3 g, 15% yield, mp 174–176 °C).

Acknowledgements

We thank the Ministry of Education, Science and Culture, Japan, for a Grant-in-Aid for Scientific Research on Priority Areas, No. 0624101.

References

1 R. Noyori, I. Tomio, Y. Tanimoto and M. Nishizawa, *J. Am. Chem. Soc.*, 1984, **106**, 6709; D. Seebach, A. K. Beck, A. Roggo and A. Wonnacott, *Chem. Ber.*, 1985, **118**, 3673; B. M. Trost and D. J. Murphy, *Organometallics*, 1985, **4**, 1143.

2 F. Toda, K. Mori and J. Okada, *Chem. Lett.*, 1988, 131; F. Toda, K. Mori and A. Sato, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 4167.

3 F. Toda, K. Mori, Z. Stein and I. Goldberg, *Tetrahedron Lett.*, 1989, **30**, 1841; K. Mori and F. Toda, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 2127; F. Toda and K. Mori, *J. Chem. Soc., Chem. Commun.*, 1986, 1059; F. Toda and K. Mori, *J. Chem. Soc., Chem. Commun.*, 1986, 1357; F. Toda, K. Mori, Z. Stein and I. Goldberg, *J. Org. Chem.*, 1988, **53**, 308.

4 E. J. Corey, M. A. Letavic, M. C. Noe and S. Sharshar, *Tetrahedron Lett.*, 1994, **35**, 7553.

5 T. Harada, S. Ueda, T. Yoshida, A. Inoue, M. Takeuchi, N. Ogawa and A. Oku, *J. Org. Chem.*, 1994, **59**, 5775; T. Harada, T. Yoshida, A. Inoue, M. Takeuchi and A. Oku, *Synlett.*, 1995, 283.

6 D. R. Armstrong, C. Cameron, D. C. Nonhebel and P. G. Perkins, *J. Chem. Soc., Perkin Trans. 2*, 1983, 563.

7 K. Tanaka, T. Okada and F. Toda, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1147.

8 F. Toda, K. Tanaka, Z. Stein and I. Goldberg, *J. Org. Chem.*, 1994, **59**, 5748.

9 F. Toda, A. Sato, L. R. Nassimbeni and M. L. Niven, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1971.

10 T. Koizumi, *Yukigousei, Kagaku Kyoukaishi*, 1986, **44**, 576; G. Solladie, *Pure Appl. Chem.*, 1988, **60**, 1699.

11 F. Toda, K. Tanaka and T. Okada, *J. Chem. Soc., Chem. Commun.*, 1995, 639.

12 F. Toda, K. Tanaka and S. Iwata, *J. Org. Chem.*, 1989, **54**, 3009.

Paper 5/05857K
Received 5th *September* 1995
Accepted 8th *February* 1996