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A NEW CHIRAL HOST COMPOUND 10,10'-DIHYDROXY-9,9'-BIPHENANTHRYL. OPTICAL RESOLUTION OF PROPIONIC ACID DERIVATIVES, BUTYRIC ACID DERIVATIVES, AND 4-HYDROXYCYCLOPENT-2-EN-1-ONE DERIVATIVES BY COMPLEXATION

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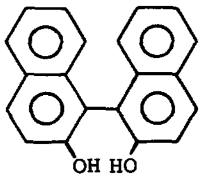
Summary - Optically active 10,10'-dihydroxy-9,9'-biphenanthryl was designed as a new chiral host compound for optical resolution of guest compounds, and was found to be very effective for resolution of the title guest compounds.

Previously we reported that optically active 2,2'-dihydroxy-1,1'-binaphthyl (**1**) is useful for the resolution of sulphoxides,1-3) selenoxides,1,4) phosphine oxides,5) phosphinates,5) and arsine oxides,6) through complexation of these with **1**. However, the resolution with **1** is not applicable to the compounds which have chiral carbon. We designed dibenzo-derivatives of **1**, 10,10'-dihydroxy-9,9'-biphenanthryl (**2**), and found that optically active **2** is very effective for resolution of propionic acid derivatives (**4**-**5**), butyric acid derivatives (**6**, **8**-**10**), and 4-hydroxycyclopent-2-en-1-one derivatives (**12**-**15**).

Although preparation of optically active **2** has been reported,7,8) its use for resolution has not been known. The best preparative method of the optically active **2** in bulk is a resolution of racemic **2** by complexation with (+)-N,N,N',N'-tetramethyl-1,3-dioxolane-*trans*-4,5-dicarboxamide which can easily be derived from naturally occurring (-)-tartaric acid.8)

Optical resolutions were carried out as follows: for example, when a suspension of **2a** (1.0 g, 2.59 mmol) and ethyl 4-chloro-3-hydroxybutyrate (**8**) (0.79 g, 5.18 mmol) in hexane (2 ml) was kept at room temperature for 12 h, a 1:1 complex of **2a** and (-)-**8** was obtained as colorless prisms (0.81 g, 58% yield, mp 94-97 °C), which upon heating in vacuo gave (-)-**8** of 95.3% ee by distillation (0.23 g, 57% yield, $[\alpha]_D$ -22.4° (*c* 1.6, $CHCl_3$)). Evaporation of the filtrate left after the separation of the above complex gave (+)-**8** of 40.2% ee (0.53 g), which upon treatment with **2b** as above resulted in (+)-**8** of 97.8% ee (0.27 g, 68% yield, $[\alpha]_D$ -22.4° (*c* 1.5, $CHCl_3$)).



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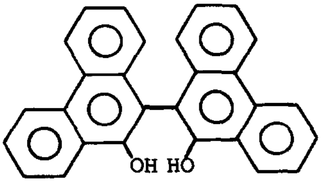

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a: (-)-form
b: (+)-form

When the complexation of (−)-**8** of 95.3% ee with **2a** and of (+)-**8** of 97.9% ee with **2b** is repeated again, (−)-**8** and (+)-**8** of 100% ee were obtained, respectively. Optical purity of **8** was determined by comparing its $[\alpha]_D$ value with that reported.[9] Some other derivatives of propionic and butyric acids were treated by the same complexation method, and yields, $[\alpha]_D$ values, and optical purities of the optical isomers obtained by one complexation with **2a** are summarized in Table 1. Although **3** and **7** did not form complex with **2a**, other esters were resolved efficiently by the complexation with **2a**. Resolution of **5** was very efficient and gave optically pure (−)-**5** by one complexation. Optically pure (−)-**4**, (+)-**6**, and (+)-**9** were easily obtained by repeating the complexation with **2a** again. The complex of (−)-**10** and **2a** is stable enough for a purification by recrystallization, and (−)-**10** of 100% ee was easily obtained by this method. From the filtrate left after the separation of the complex of **2a** and the enantiomers shown in Table **1**, the other enantiomers of 100% ee were obtained by the complexation with **2b** in the yields of more than 70%. Optical purity of **4**,[10] **5**,[11] **6**,[12] **9**, and **10** was determined by comparing their $[\alpha]_D$ values with those reported. Optical purity of **10** was also determined by measuring ^{1}H NMR spectrum of its 1:1 complex with **2**, because optically active **2** works as a chiral shift reagent as does **1**.[13]

Table 1. Yields, $[\alpha]_D$ values, and Optical Purities of Optically Active Propionic and Butyric Acid Derivatives Obtained by One Complexation with **2a**.

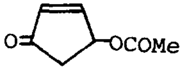
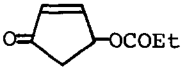
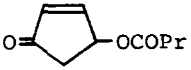
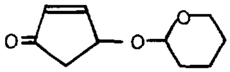
Guest Compound	Yield (%)	$[\alpha]_D$ Value (°)	(c,Solvent)	Optical Purity (% ee)
Me-CH(OH)-COOMe (**3**)[a]	---	---	---	---
Me-CHCl-COOMe (**4**)	75	−19.3	(1.0, $CHCl_3$)	69.4
Me-CH(OPh)-COOMe (**5**)	86	−43.5	(1.1, $CHCl_3$)	100
Me-CH(OH)-CH_2-COOEt (**6**)	86	+39.2	(0.85, $CHCl_3$)	92.7
Me-CHCl-CH_2-COOMe (**7**)[a]	---	---	---	---
$ClCH_2$-CH(OH)-CH_2-COOMe (**8**)	57	−22.4	(1.6, $CHCl_3$)	95.3
MeOOC-CH(OH)-CH_2-COOMe (**9**)	81	+1.8	(1.1, $CHCl_3$)	60.0
Me-CH(NH_2)-CH_2-COOEt (**10**)	85	−17.3	(0.39, MeOH)	58.0

a) No complexation occurred.

Optically active **4**, **5**, **6**, **8**, **9**, and **10** are all important starting materials of the synthesis of biologically active compounds. For example, **4** and **5** are important for synthesis of agricultural chemicals, **6** and **8** are important for synthesis of β-lactam[14] and carnitin,[15] respectively, and **9** and **10** are derivatives of malic acid and β-amino acid, respectively. However, synthesis of optically pure enantiomers of these is not easy. Biological preparative method of **4**,[10] **6**,[12] and **8**[9] does not give optically pure enantiomers. Preparation of optically pure 5 by a diastereomeric resolution method has been reported, but the process is not simple.[11] Only an elegant preparation method of optically pure 6 by enantioselective reduction of ethyl 3-oxobutyrate using BINAP-Rh complex has been reported.[16]

The resolution method by the complexation with 2 was found to be applicable to derivatives (12-15) of 4-hydroxycyclopent-2-en-1-one (11) which is very important starting material of the synthesis of prostaglandins.[17] For example, when a solution of 2a (0.8 g, 2.07 mmol) and 12 (0.58 g, 4.14 mmol) in MeOH (5 ml) was kept at room temperature for 12 h, a 1:1 complex of 2a and (-)-12 (0.88 g) was obtained as colorless prisms. Recrystallization of the complex from MeOH gave pure complex (0.51 g, 47% yield, mp 154-156 °C, $[\alpha]_D$ -69.9° (*c* 0.3, MeOH)), which upon heating in vacuo gave (-)-12 of 100% ee (0.13 g, 45% yield, $[\alpha]_D$ +99.3° (*c* 0.25, MeOH)). From the filtrate left after the separation of a crude 1:1 complex of 2a and (-)-12, (+)-12 of 100% ee (0.16 g, 55% yield, $[\alpha]_D$ +99.3° (*c* 0.25, MeOH)) was obtained by treatment with 2b. By the same method, 13 and 14 were also resolved efficiently. Yields and $[\alpha]_D$ values of (-)-enantiomers of 100% ee obtained by complexation with 2a were summarized in Table 2.

Table 2. Yields and $[\alpha]_D$ Values of 12-15 of 100% ee Obtained by Complexation with 2a.

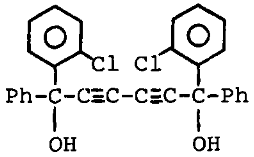
Guest Compound	Yield (%)	$[\alpha]_D$ Value (°)	(*c*, Solvent)
 (11)[a]	---	---	---
 (12)	45	-99.3	(0.51, MeOH)
 (13)	28	-86.8	(0.16, MeOH)
 (14)	51	-107	(0.71, MeOH)
 (15)	51	-111	(0.92, $CHCl_3$)

[a] By one complexation with 2a followed by decomplexation, (-)-11 of only 2.2% ee was obtained.

Unfortunately, 11 was not efficiently resolved with 2, although it forms a 1:1 complex with 2a (Table 2). Furthermore, it is difficult to hydrolyze 12-14 into 11 without racemization. Since tetrahydropyranyl ether of 11 (15) is easily hydrolyzed without racemization under mild conditions, resolution of 15 has an advantage. The resolution of 15 with 2 was very successful (Table 2). Hydrolysis of (-)-15 with dil HCl gave (-)-11[18] without any racemization in almost quantitative yield.

We also found that optically active 1,6-diphenyl-1,6-di(*o*-chlorophenyl)-hexa-2,4-diyne-1,6-diol (**16**)[1,13] is useful for resolution of **14**. For example, when a solution of **16a** (4.83 g, 10 mmol) and **14** (3.36 g, 20 mmol) in ether-petrol ether (1:1) (20 ml) was kept at room temperature for 12 h, a 1:1 complex of **16a** and (-)-**14** (4.69 g) was obtained as colorless prisms. Recrystallization of the complex from ether-petrol ether (1:1) gave pure complex (3.48 g), which upon heating in vacuo gave (-)-**14** of 100% ee (0.94 g, 56% yield). Treatment with **16b** of the filtrate left after the separation of a crude complex of **16a** and (-)-**14**, finally gave (+)-**14** of 100% ee (0.01 g, 60% yield). However, **16** was not effective for resolution of **11**-**13** and **15**, and **16** does not include **3**-**10**.

The high chiral recognition ability of **2** for **4**-**10** and **12**-**15** is interesting. This will be clarified in future by X-ray crystal structural study of the complex of **2**.



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a: (-)-form

b: (+)-form

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