OPTICAL RESOLUTION BY INCLUSION COMPLEX FORMATION

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ABSTRACT.   Novel optical resolutions of guest compounds by
inclusion complex formation with optically active host com-
pound are reviewed. Tertiary acetylenic alcohols, cyano-
hydrins, and secondary alcohols were resolved by complexation
with alkaloids such as brucine or sparteine. Cycloalkanones,
2,3-epoxycyclohexanones, and some other neutral compounds
were resolved by complex formation with optically active
diacetylenic diol. Mutual optical resolution of bis-β-
naphthol and sulfoxides by complex formation was also
reviewed.

1.   INTRODUCTION

The preparation of an optically active compound is not easy.
Two methods, optical resolution and enantioselective reaction
are available for the preparation of an optically active com-
pound. However, the preparation of an optically active com-
pound by enantioselective reaction is not always successful.
In particular, it is very difficult to prepare an optically
pure compound, because enantioselectivity is not perfect in
most cases. On the other hand, optical resolution can be
repeated until the optical purity of the compound becomes
100%, even though the optical resolution by the diastereomeric
method is difficult to apply to a neutral compound.
    The application of host-guest inclusion complex formation
to optical resolution is ideal. When an optically active host
molecule includes one enantiomer of a racemic guest compound
selectively, this inclusion phenomena can be used as a simple
optical resolution method. Furthermore, this method might be
applied to various neutral guest compounds. According to this
idea, we tried to develop new optical resolution methods and
established some new ones.

2.   OPTICAL RESOLUTION BY COMPLEX FORMATION WITH ALKALOID

2.1.   Optical Resolution of Tertiary Acetylenic Alcohols by Complex Formation with Brucine

An optically active acetylenic alcohol is an useful starting material to prepare various chiral compounds, because it has two functional groups. However, the optical resolution of an acetylenic alcohol by the diastereomeric method for its phthalic acid half-ester is complicated and successful only in a few cases.[1] Recently, the preparation of optically active secondary acetylenic alcohol by the enantioselective reduction of ethynyl ketone[2] or by the enantioselective addition of lithium acetylide to aldehyde[3] has been reported. However, these methods are not applicable to the preparation of optically active tertiary acetylenic alcohols.

    We found that some tertiary acetylenic alcohols form a 1:1 complex with brucine, and that the acetylenic alcohols were easily resolved by utilizing the complexation.[4,5] As an example, the experimental detail of the resolution of 1,1-dimethyl-2-phenyl-3-pentyn-2-ol (1f) is described. A solution of 1f (8.12 g, 43.2 mmol) and brucine (17.0 g, 43.2 mmol) in acetone (260 ml) was kept at room temperature for 12 h, and the 1:1 brucine complex of (+)-1f (12.1 g) formed was decomposed with dil HCl and extracted with ether. The ether solution was evaporated to give 71% ee (+)-1f (3.9 g, 96%, $[\alpha]_D$ +8.8°). When a solution of the 71% ee (+)-1f (3.9 g, 20.7 mmol) and brucine (8.2 g, 20.7 mmol) in acetone (100 ml) was kept for 12 h, the brucine complex was obtained which upon treatment with the same procedure as above gave 100% ee (+)-1f (3.16 g, 78%, $[\alpha]_D$ +12.4°). The acetone solution left after separation of the brucine complex of 71% ee (+)-1f was treated as above to give 66% ee (-)-1f (4.06 g, 100%). By the same method, 1a-e and 1g-m were also resolved quite easily (Table 1).

    Although 2a-g were also easily resolved, 3a and 3b did not form complexes with brucine.[5] These results show that an aromatic or heteroaromatic group is essential for the brucine complex formation. In order to know how both components recognize the chirality of each other in the complex, an X-ray structural analysis of the brucine complex of (-)-1a was carried out.[4,5]
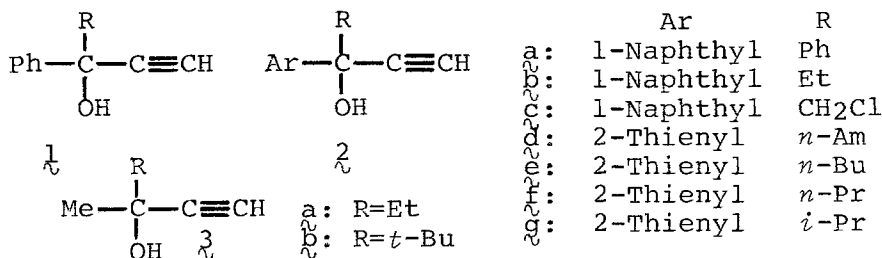

	Ar	R
a:	1-Naphthyl	Ph
b:	1-Naphthyl	Et
c:	1-Naphthyl	CH_2Cl
d:	2-Thienyl	n-Am
e:	2-Thienyl	n-Bu
f:	2-Thienyl	n-Pr
g:	2-Thienyl	i-Pr

a: R=Et
b: R=t-Bu

TABLE 1. Yields and $[\alpha]_D$ Values of 100% ee 1a-m Obtained by Optical Resolution by Complexation with Brucine

1	R	Complexation Time	$[\alpha]_D$ (°)	Yield (%)
a	o-Br-C_6H_4-	3	-134	63
b	o-Cl-C_6H_4-	8	-135	10
c	o-F-C_6H_4-	3	-59.1	14
d	o-Me-C_6H_4-	6	-53.7	21
e	t-Am	1	+10.5	84
f	t-Bu	2	+12.4	77
g	n-Bu	1	+7.9	47
h	n-Pr	2	+4.5	29
i	i-Pr	3	+1.1	19
j	Et	2	+7.2	36
k	CCl_3	4	+13.8	33
l	$CHCl_2$	2	-3.4	70
m	CH_2Cl	3	+11.1	39

2.2. Mutual Optical Resolution of Tertiary Acetylenic Alcohols and Sparteine by Complex Formation

We also found that optically active sparteine can be used instead of brucine for the optical resolution of tertiary acetylenic alcohols (1 and 2), and that sparteine can also be resolved by complexation with optically active acetylenic alcohols.[5,6] Efficiency of the optical resolution of acetylenic alcohols with sparteine was compared to that with brucine (Table 2). In some cases, optical resolution by complexation with sparteine is more efficient than that with brucine, and the use of the much less poisonous sparteine also has advantages over the use of the poisonous brucine.

In order to investigate how both components recognizes so efficiently the chirality of each other in the complex, an X-ray analysis of the structure of the (-)-sparteine complex of (-)-1a was carried out.[5,6]

TABLE 2. Optical Resolution of 1a-c and 1f by One Complexation with (-)-Sparteine and Brucine

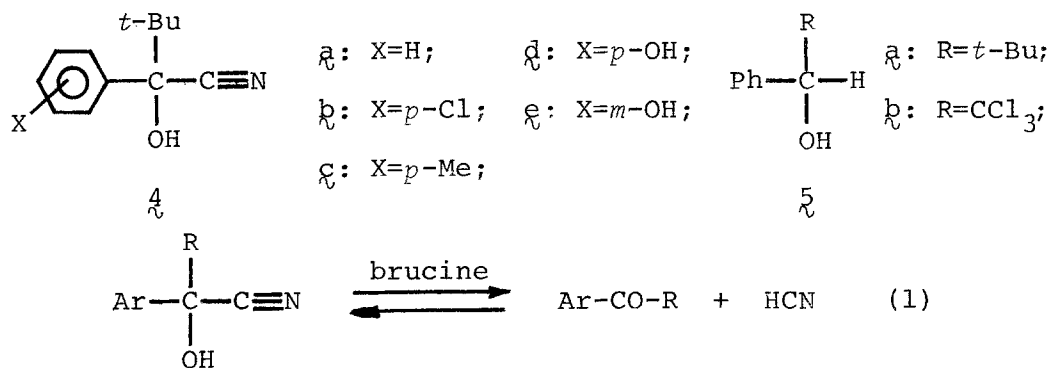| Enantiomer	With (-)-Sparteine		With Brucine	
	Yield (%)	%ee	Yield (%)	%ee
(-)-1a	61	50	65	39
(+)-1a	37	81	35	81
(-)-1b	51	55	60	15
(+)-1b	44	60	38	22
(-)-1c	36	34	45	60
(+)-1c	61	23	52	53
(-)-1f	49	59	50	66
(+)-1f	51	57	48	71

2.3. Optical Resolution of Cyanohydrins and Secondary Alcohols by Complex Formation with Brucine

The method used for the optical resolution of acetylenic alcohols by complexation with brucine was found to be applicable to cyanohydrins (4)[7] and some secondary alcohols (5). Surprisingly, it was also found that racemic cyanohydrins are converted into one optically active isomer in yields of more than 50% in the presence of brucine. For example, When a solution of racemic 4a (1.0 g) and an equimolar amount of brucine (2.1 g) in MeOH (2 ml) was kept in an uncapped flask at room temperature for 24 h, a brucine complex of (+)-4a crystallized out. Decomposition of the complex gave 100% ee (+)-4a in almost quantitative yield. This is not a simple optical resolution method but a novel preparation method of optically active cyanohydrins. This eantiomerization method can be applied to 4b-e.[7]

The process of the enantiomerization probably consists of racemization of cyanohydrin through the equilibrium shown in Equation (1) and the selective inclusion of one enantiomer in brucine.

By the complexation method with brucine, usual secondary alcohols (5a and 5b) were also resolved efficiently and 100% ee enantiomers were obtained easily.

However, 4 and 5 which have sterically less hindered alkyl group do not form complex with brucine.

a: X=H; d: X=p-OH; a: R=t-Bu;
b: X=p-Cl; e: X=m-OH; b: R=CCl$_3$;
c: X=p-Me;

4   5

$$Ar-\overset{\underset{OH}{|}}{\underset{}{C}}-C{\equiv}N \; \underset{\xleftarrow{\hspace{1.5cm}}}{\xrightarrow{\text{brucine}}} \; Ar-CO-R \; + \; HCN \qquad (1)$$

3. OPTICAL RESOLUTION BY COMPLEX FORMATION WITH OPTICALLY ACTIVE 1,6-BIS(o-HALOPHENYL)-1,6-DIPHENYLHEXA-2,4-DIYNE-1,6-DIOL

Previously, we have reported a high ability of 1,1,6,6-tetra-phenylhexa-2,4-diyne-1,6-diol (6a) to include various guest compounds.[8] When this diacetylenic diol is optically active, it can be used for an optical resolution of the guest compound. Optically active diacetylenic diol can easily be

obtained by an oxidative coupling of the optically active
acetylenic alcohol (1 and 2) prepared by resolution with
brucine. By this method, 100% ee 6b ([α]$_D$ 47.7°), 6c ([α]$_D$
122°), and 6d ([α]$_D$ 129°) were prepared.[9]

3.1. Optical Resolution of 3-Methylcycloalkanones and 5-Methyl-γ-butyrolactone by Complexation with Optically Active 1,6-Bis(o-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol

When a solution of (−)-6c (19.2 g, 39.8 mmol) and racemic 3-
methylcyclohexanone (7, 17.8 g, 159 mmol) in ether-petroleum
ether (1:1, 100 ml) was kept at room temperature for 6 h, a
1:2 complex of (−)-6c and (+)-7 (25.5 g, 91%) was obtained
as colorless prisms. Upon heating the complex, 28% ee (+)-7
(8.0 g, 90%) was obtained by distillation. Two recrystalli-
zations of the 1:2 complex of (−)-6c and 28% ee (+)-7 from
ether-petroleum ether (1:1) gave the complex that, on distil-
lation, gave 66% ee (+)-7 (3.5 g, 39.3%). When the same re-
crystallization was repeated twice for the complex prepared
from (−)-6c and the 66% ee (+)-7 (3.7 g), the 1:2 complex of
(−)-6c and 100% ee (+)-7 (4.1 g, 15%, mp 78-79 °C, [α]$_D$ −71.7°).
Upon heating the complex, 100% ee (+)-7 (1.16 g, 13%, [α]$_D$
+14.4°) was obtained after distillation.[9]
    By the same method, 3-methylcyclopentanone (8) and 5-
methyl-γ-butyrolactone (9) were also resolved to give 100% ee
(−)-8 and (+)-9 in 6 and 4.5% yields, respectively.[9]
    When (+)-6c was used instead of (−)-6c for the resolution
of 7, 8, and 9, the other enantiomers (−)-7, (+)-8, and (−)-
9 were obtained, respectively, in almost the same yields as
those by (−)-6c. Although 6d showed almost the same effici-
ency as did 6c for the resolution, 6b was much less effective.

a: X=H,   c: X=Cl
b: X=F,   d: X=Br

6   7   8   9
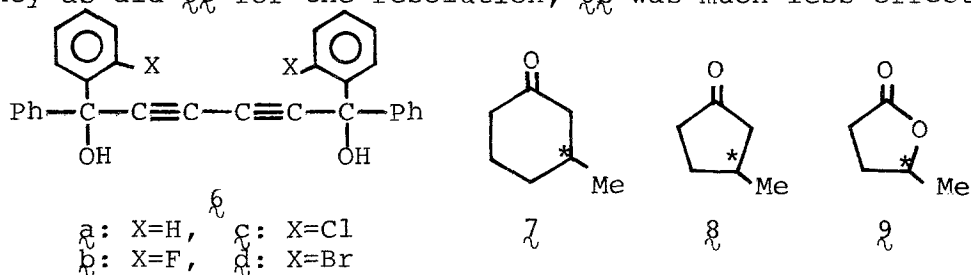
3.2. Optical Resolution of 2,3-Epoxycyclohexanones by Complexation with Optically Active 1,6-Bis(o-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol

The resolution method by complexation with optically active
diacetylenic diol (6) was found to be very effective for the
resolution of 2,3-epoxycyclohexanones (10-12).[10] For example,
when a solution of (−)-6c (5.10 g, 10.6 mmol) and 10 (5.94 g,
42.4 mmol) in 1:1 diethyl ether-light petroleum (20 ml) was
kept at room temperature for 6 h, a 1:1 complex of (−)-6c

and (−)-10 (4.68 g, 58%) was obtained as colorless prisms, which upon Kugelrohr distillation in vacuo gave 90% ee (−)-10 (51%, $[α]_D$ −122°). Two recrystallizations of the 1:2 complex of (−)-6c and 90% ee (−)-10 (4.68 g) from 1:1 ethyl ether-light petroleum (50 ml each) gave the complex of (−)-6c and 100% ee (−)-10 (2.74 g, 34%, mp 117-118 °C), which upon Kugelrohr distillation in vacuo gave 100% ee (−)-10 (0.9 g, 30%, $[α]_D$ −136°).[10]

The other two 2,3-epoxycyclohexanones (11 and 12) were also easily resolved by the same manner, and 100% ee (+)-11 (31%, $[α]_D$ +13.5°) and 100% ee (+)-12 (18%, $[α]_D$ +58.3°) were obtained.[10]

10   11   12
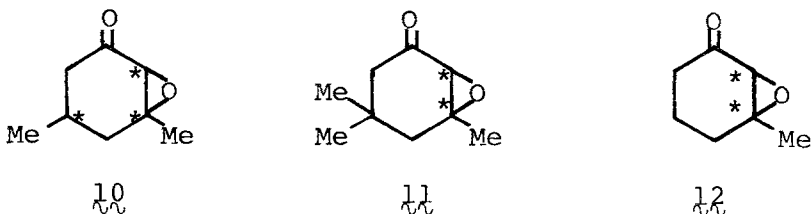
We also found that this resolution method is useful for resolutions of bicyclic ketones and bicyclic lactones. For example, some important synthones, 13-16, were easily resolved by complexation with 6c, and their 100% ee enantiomers were obtained.[11]

13   14   15   16
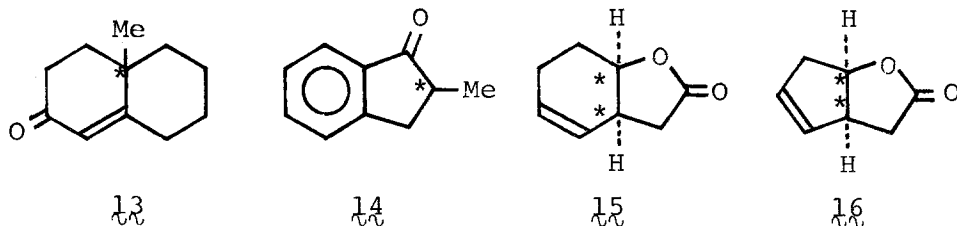
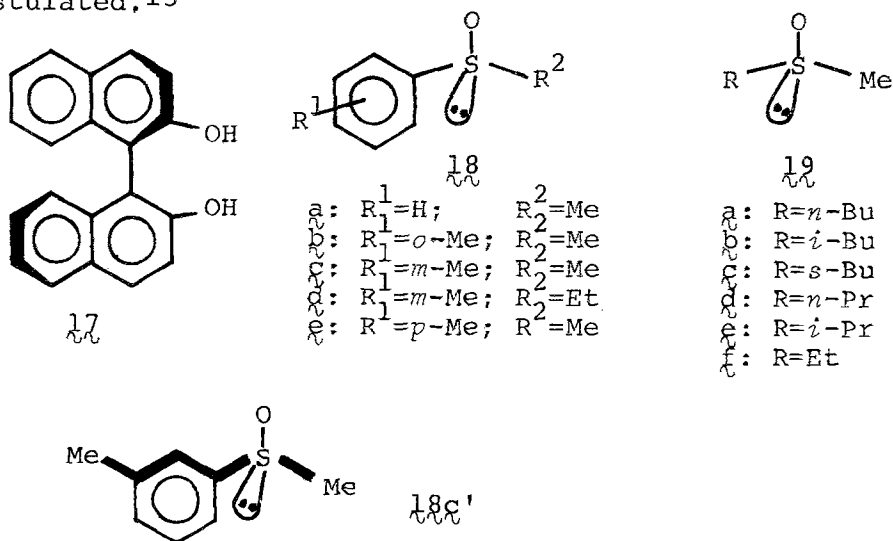## 4.   MUTUAL OPTICAL RESOLUTION OF BIS-β-NAPHTHOL AND ALKYL ARYL OR DIALKYL SULFOXIDES BY COMPLEX FORMATION

Recently, we found that bis-β-naphthol (17) and alkyl aryl (18) or dialkyl sulfoxides (19) form a crystalline complex in which each component recognizes the chirality of the other very efficiently and that optical resolution can be done very easily by using the complex formation.[12]   For example, when a solution of 100% ee (R)-(+)-17 (3.0 g, 10.5 mmol) and racemic methyl m-methylphenyl sulfoxide (18c, 3.23 g, 21.0 mmol) in benzene-n-hexane (1:1, 20 ml) was kept at room temperature for 12 h, a 1:1 complex of (R)-(+)-17 and (+)-18c (4.10 g, 89%) was obatined as colorless prisms. Decomposition of the complex after one recrystallization from benzene gave 100% ee (+)-18c (1.24 g, 77%, $[α]_D$ +140°). The mothor liquor left from the initial complexation reaction was evaporated to

dryness and the residue was chromatographed to give 62% ee
(-)-18c (1.30 g, 80%). When a solution of the 62% ee (-)-18c
(1.30 g, 8.44 mmol) and 100% ee (S)-(-)-17 (2.41 g, 8.44 mmol)
in benzene (10 ml) was kept at room temperature for 12 h, a
1:1 complex (2.39 g, 52%) was obtained. Decomposition of the
complex after one recrystallization from benzene gave 100% ee
(S)-(-)-18c (1.16 g, 48%, [α]$_D$ -37.7°).[12]

By the same procedure, ethyl m-methylphenyl sulfoxide
(18d) was also easily resolved to give 100% ee (+)- and (-)-
enantiomers ([α]$_D$ 199°) in good yields. However, methyl
phenyl sulfoxide (18a) was poorly resolved and methyl o-methyl
(18b) and methyl p-methylphenyl sulfoxide (18e) did not form
complex with 17. Molecular shape of 18 would be important
for complexation and efficient chiral recognition in the com-
plex. As depicted in 18c , straight chain part of m-methyl-
phenyl moiety would be important for these. It was found
to be true by studying optical resolution of dialkyl sulf-
oxides (19) with 17. n-Butyl methyl (19a) and methyl
n-propyl sulfoxide (19d) were easily resolved by the comp-
lexation with optically active 17 to give 100% ee (+)- and
(-)-enantiomers of 19a ([α]$_D$ 111°) and of 19d ([α]$_D$ 123°),
respectively in good yields. However, optical resolution of
i-butyl methyl (19b) and ethyl methyl sulfoxide (19f) was not
effective and approximately 25% ee enantiomer of 19b and 19f
were obtained by one complexation with optically active 17.
s-Butyl methyl (19c) and methyl i-propyl sulfoxide (19e) did
not form complex with 17.[12]

X-Ray structural study of the complex of (R)-(+)-17 and
(R)-(+)-18c showed that the straight chain part of m-methyl-
phenyl group is important for the formation of complex and
efficient chiral recognition in the complex, as it has been
postulated.[13]

17

18

a: R^1=H;   R^2=Me
b: R^1=o-Me;   R^2=Me
c: R^1=m-Me;   R^2=Me
d: R^1=m-Me;   R^2=Et
e: R^1=p-Me;   R^2=Me

19

a: R=n-Bu
b: R=i-Bu
c: R=s-Bu
d: R=n-Pr
e: R=i-Pr
f: R=Et

18c'

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