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Enantioresolution by the chiral phthalic acid method: absolute configurations of (2-methylphenyl)phenylmethanol and related compounds

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Abstract

Racemic (2-hydroxymethylphenyl)phenylmethanol **5** was enantioresolved by the chiral phthalic acid method using acid-amide **2**, and the absolute configurations of (−)-(2-methylphenyl)phenylmethanol **3** and related *o*-substituted diphenylmethanol derivatives were unambiguously determined by X-ray crystallography and chemical correlation.

Recently, much attention has been focused on the asymmetric synthesis of various chiral alcohols using chiral catalysts.[1,2] These catalytic asymmetric syntheses are very powerful for preparing chiral compounds with high enantiomeric excess. However, there are some weak points: (i) although the absolute configuration of products may be estimated by the reaction mechanism and/or by comparison with similar cases, in which the absolute configuration of products is known, such assignments of absolute configurations have remained ambiguous; (ii) the products obtained by asymmetric syntheses are not always enantiopure. As a method for solving these problems, classical enantioresolution using new chiral auxiliaries is of much practical use. For example, we have recently developed new chiral auxiliaries, chiral phthalic acid amides (1*S*,2*R*,4*R*)-(−)-**1** and (1*S*,2*R*,4*R*)-(−)-**2**, which were very useful for the enantioresolution of various alcohols by HPLC on silica gel and also for the X-ray crystallographic determination of their absolute configurations (Fig. 1).[3,4] One group of the authors has intensively studied the catalytic asymmetric reduction of various ketones to chiral alcohols using ruthenium(II) complexes,[1] and has obtained various chiral substituted diphenylmethanols with high enantiopurity.[5] In some cases, however, the absolute configuration of products has remained undetermined or only estimated in an empirical manner. Furthermore, the $[\alpha]_D$ values of some products are very small. Such facts bring much ambiguity to the stereochemical studies of asymmetric synthesis. (2-Methylphenyl)phenylmethanol **3**

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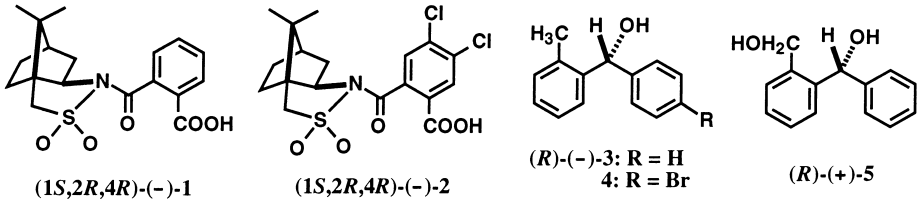


Figure 1. Chiral phthalic acid amides and *o*-substituted diphenylmethanols

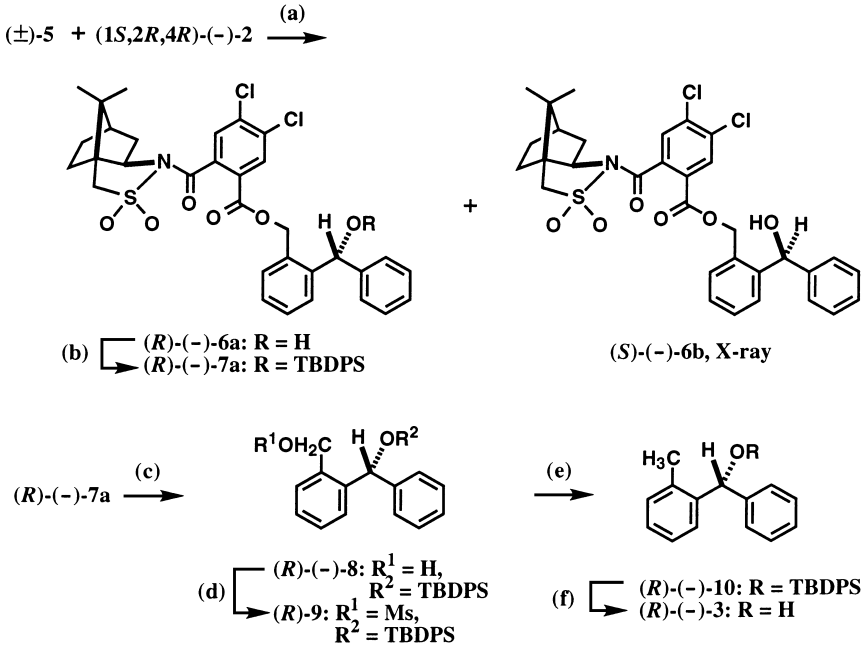
is one such compound (Fig. 1). The absolute configuration of alcohol **3** had been in much confusion; Cervinka et al.[6] reported it to be (*R*)-(−) based upon asymmetric reductions, but Seebach et al.[2] assigned it as (*R*)-(+) by catalytic asymmetric syntheses. In this paper, we report the preparation of enantiopure alcohol **3** and unambiguous determination of its absolute configuration by the chiral phthalic acid method.

To determine the absolute configuration, we first applied the chiral phthalic acid method to **3** itself; however, the diastereomeric mixture of esters formed could not be separated by HPLC on silica gel. Next the method was applied to (4-bromophenyl)-2′-methylphenylmethanol **4**, from which alcohol **3** is obtainable by reduction. In fact, we have previously succeeded in the enantioresolution of (4-bromophenyl)-4′-methylphenylmethanol by this method, and the enantiopure bromo-alcohol obtained was converted into (4-methylphenyl)phenylmethanol.[4f] However, unfortunately the diastereomeric esters formed from (−)-**2** and (±)-**4** were also inseparable by HPLC on silica gel. We therefore took the alternative route to resolve (2-hydroxymethylphenyl)phenylmethanol **5**, which is convertible into alcohol **3**.

Commercially available methyl 2-benzoylbenzoate was reduced with $LiAlH_4$ in diethyl ether to give diol **5**, which was then condensed with chiral dichlorophthalic acid amides (1*S*,2*R*,4*R*)-(−)-**2**; a mixture of diol (±)-**5**, (−)-**2** (1.0 equiv.), 1,3-dicyclohexylcarbodiimide (DCC, 1.2 equiv.), and 4-dimethylaminopyridine (DMAP, 0.2 equiv.) in CH_2Cl_2 was stirred at room temperature for 2 days (Scheme 1). The diastereomeric mixture of esters formed was separated by HPLC on silica gel (hexane:EtOAc, 4:1): separation factor α=1.14; resolution factor *R*s=1.04. The first-eluted ester (−)-**6a** (30%, $[\alpha]_D^{23}$ −8.62 (*c* 2.52, $CHCl_3$)) and the second one (−)-**6b** (32%, $[\alpha]_D^{20}$ −98.4 (*c* 2.36, $CHCl_3$)) were obtained. The less polar ester (−)-**6a** was recrystallized from hexane/EtOAc giving large prisms; however, these were not single crystals when checked by X-ray analysis. On the other hand, single crystals of (−)-**6b** were obtained by recrystallization from EtOH, and subjected to X-ray crystallography: orthorhombic; space group $P2_12_12_1$. The structure was solved as usual: R=0.0324 and R_w=0.0415, while R=0.0470 and R_w=0.0627 for the mirror image structure. The absolute configuration of ester (−)-**6b** was thus determined to be *S* by the heavy atom effect as well as by the internal reference method using the known absolute configuration of the camphor part of auxiliary (−)-**2** (Fig. 2). The *R* absolute configuration was therefore assigned to ester (−)-**6a**.

The secondary hydroxyl group of ester (*R*)-(−)-**6a** was blocked as *tert*-butyldiphenylsilyl (TBDPS) ether as shown in Scheme 1. TBDPS ether (*R*)-(−)-**7a** (97%, $[\alpha]_D^{21}$ −60.6 (*c* 1.36, $CHCl_3$)). Ester (*R*)-(−)-**7a** was hydrolyzed with K_2CO_3 in MeOH to yield alcohol (*R*)-(−)-**8** (81%, $[\alpha]_D^{21}$ −1.31 (*c* 1.87, $CHCl_3$)), which was then converted to mesylate (*R*)-**9** (97%). Reduction of the mesylate group with $LiAlH_4$ afforded compound (*R*)-(−)-**10** (74%, $[\alpha]_D^{23}$ −27.3 (*c* 2.51, $CHCl_3$)), from which the desired enantiopure alcohol (*R*)-(−)-**3** was finally obtained by treatment with tetrabutylammonium fluoride (TBAF) in THF: (*R*)-(−)-**3** (90%, $[\alpha]_D^{23}$ −7.64 (*c* 1.51, $CHCl_3$); $[\alpha]_D^{24}$ −12.9 (*c* 0.570, EtOH)). The absolute configuration of (−)-**3** was thus unambiguously determined as *R*.[7] Reduction of ester (*R*)-(−)-**6a** with $LiAlH_4$ in diethyl ether yielded diol (*R*)-(+)-**5** (87%, $[\alpha]_D^{24}$ +56.9 (*c* 1.39, $CHCl_3$)).

The CD spectrum of alcohol (*R*)-(−)-**3** exhibits characteristic positive Cotton effects with vibrational



Scheme 1. (a) DCC, DMAP/CH_2Cl_2, rt; (b) TBDPSCl, imidazole/DMF, rt; (c) K_2CO_3/MeOH, rt; (d) MsCl, Et_3N/CH_2Cl_2, 0°C; (e) $LiAlH_4/Et_2O$, 0°C; (f) TBAF/THF, rt

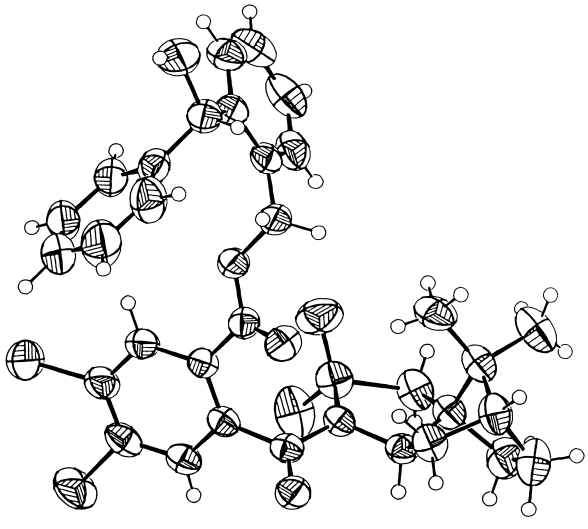


Figure 2. ORTEP drawing of ester (*S*)-(−)-**6b**. The atoms are drawn as 50% probability ellipsoids

structure in the ^1L_b transition region at 240–280 nm (Fig. 3). In addition, it also shows a positive Cotton effect at 225.4 nm. Therefore, the enantiomer **3** is fully specified as (*R*)-[CD(+)225.4]-(−)-**3**.[8]

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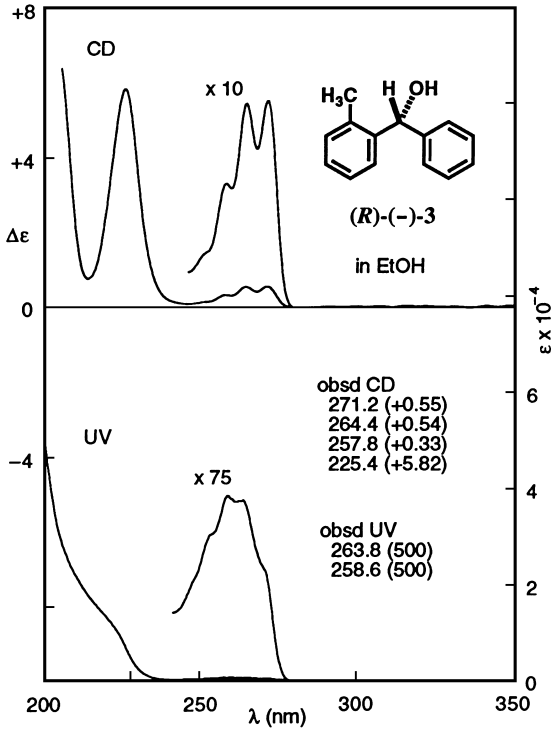

Figure 3. CD and UV spectra of (*R*)-[CD(+)225.4]-(−)-(2-methylphenyl)phenylmethanol **3** in EtOH

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7. The $[\alpha]_D$ values of (*R*)-**3** were previously measured in ethanol, $[\alpha]_D^{20}$ −2.50 (*c* 4.00) (no % ee data),[6] and in benzene, $[\alpha]_D^{25}$ +0.67 (*c* 1.27) (enantiopure),[2] respectively. Since the reported value in benzene is very small, we recommend the use of chloroform or ethanol instead of benzene.
8. When the $[\alpha]_D$ value is small, its measurement necessitates a large amount of sample, and it is hard to obtain a reliable value. In such a case, the designation of enantiomers by CD data is pertinent, because CD measurement generally needs a much smaller amount of sample than $[\alpha]_D$ measurement: Harada, N.; Iwabuchi, J.; Yokota, Y.; Uda, H.; Okamoto, Y.; Yuki, H.; Kawada, Y. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1845. Harada, N. *Enantiomer* **1996**, *1*, 81.