

Short Communication

Molecular chirality by isotopic substitution. Synthesis, absolute configuration and circular dichroism spectra of ^{13}C -substituted chiral diphenylmethanol

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ABSTRACT: ^{13}C -Substituted chiral diphenylmethanol, α -phenylbenzene[1,2,3,4,5,6- $^{13}\text{C}_6$]methanol, [CD(–)270]-(*S*)-3, was synthesized from 4-bromo- α -(phenyl[1,2,3,4,5,6- $^{13}\text{C}_6$])benzenemethanol (4), which was enantioresolved by the chiral phthalic acid method. The *S* absolute configuration of [CD(–)270]-3 was unambiguously determined by x-ray crystallography of camphanic acid ester of (–)-4. Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: molecular chirality by isotopic substitution; ^{13}C -substituted chiral diphenylmethanol; α -phenylbenzene[1,2,3,4,5,6- $^{13}\text{C}_6$]methanol; 4-bromo- α -(phenyl[1,2,3,4,5,6- $^{13}\text{C}_6$])benzenemethanol; circular dichroism spectra; absolute configuration; chiral phthalic acid method; x-ray crystallography

INTRODUCTION

Chiroptical activity is attributable to the dissymmetric molecular structure, which is not superimposable with its mirror image. As a unique case of molecular asymmetry, there is the category of chirality generated by isotopic substitution. For example, recently we reported the synthesis of ^2H -substituted chiral diphenylmethanols, α -phenylbenzene[2,3,4,5,6- $^2\text{H}_5$]methanol, [CD(–)270.4]-(*S*)-1 and α -phenylbenzene[4- ^2H]methanol, [CD(+270.6)]-(*R*)-2 (Fig. 1), which exhibited very weak circular dichroism (CD) Cotton effects characteristic to the vibronic structure of the $^1\text{L}_b$ transition of a benzene chromophore around 250–280 nm.¹ The $^1\text{L}_b$ transition of benzene, which appears as eight or nine weak UV peaks around 220–280 nm, is essentially forbidden, but it becomes slightly allowed by coupling with the vibration of the benzene skeleton. The major vibration mode responsible for the $^1\text{L}_b$ transition has been assigned to the totally symmetrical vibration of a benzene ring; peak interval of progression, 923 cm^{-1} .² Therefore,

the CD Cotton effects of the $^1\text{L}_b$ transition also acquire their intensities from the coupling with the totally symmetrical vibration, showing the corresponding vibrational structure.¹

The vibrational frequency depends on the mass of an oscillator, i.e. carbon and hydrogen atoms in a benzene ring in the case of alcohols 1 and 2. Therefore, the CD spectra of isotopically substituted compounds 1 and 2 reflect the mass difference between oscillators. In the case of 1 and 2, the mass difference, $\Delta m = 1$, between ^{12}C - ^1H ($m = 13$) and ^{12}C - ^2H ($m = 14$) is essential for generating the CD activity. Chiral alcohols 1 and 2 show very weak but distinct Cotton effects with vibrational structure.¹ There is another class of isotopic chirality in diphenylmethanol. As shown in formula 3 (Fig. 1), ^{13}C

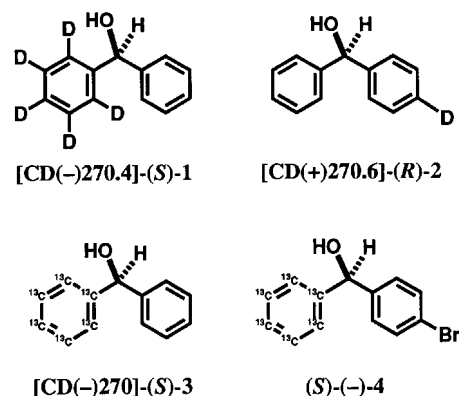


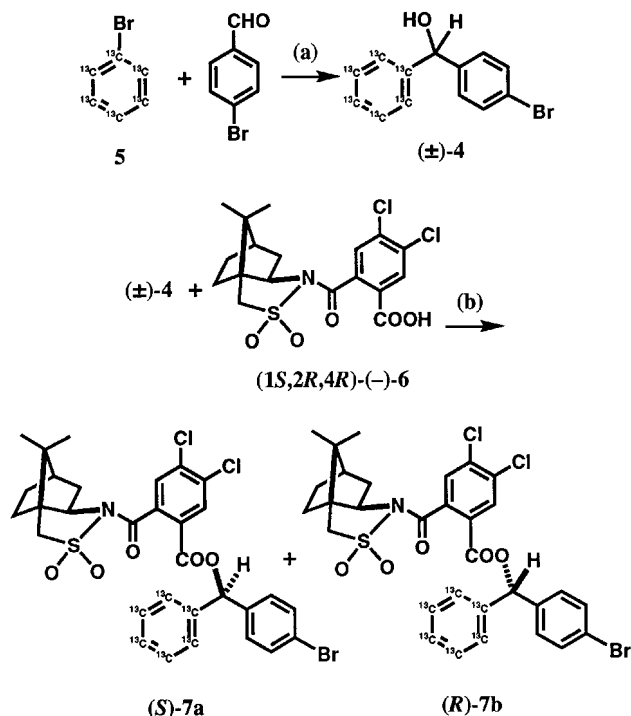
Figure 1. ^2H - and ^{13}C -substituted chiral diphenylmethanols and derivative

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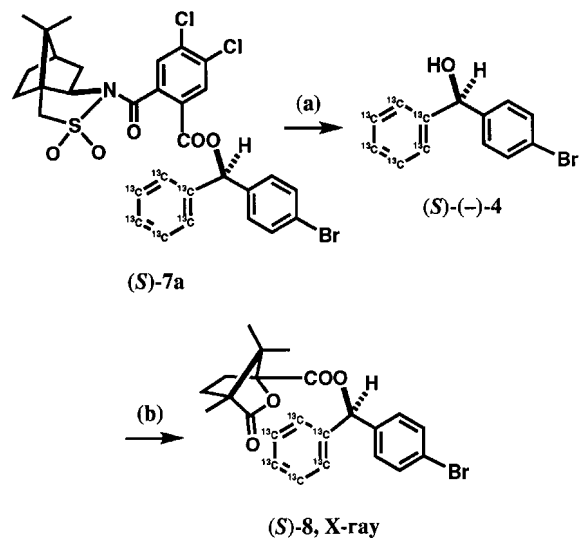
Scheme 1. (a) Mg -THF; (b) DCC, DMAP- CH_2Cl_2

substitution also forms molecular chirality. In this case, the mass difference, $\Delta m = 1$, between ^{12}C - ^1H ($m = 13$) and ^{13}C - ^1H ($m = 14$) is intrinsic to chiroptical activity, and it is similar to the cases of **1** and **2**. Therefore, it is intriguing to compare the CD spectrum of **3** with those of **1** and **2**. In this paper we report the enantioresolution, synthesis and absolute configurations of new ^{13}C -substituted chiral diphenylmethanol **3** and related compounds.

EXPERIMENTAL AND RESULTS

4-Bromo- α -(phenyl[1,2,3,4,5,6- $^{13}\text{C}_6$])benzenemethanol (**4**) was prepared from bromobenzene[$^{13}\text{C}_6$] (**5**, >99 atom% ^{13}C , purchased from Isotec) and 4-bromobenzaldehyde by the Grignard reaction: 90% yield from **5** (Scheme 1). Racemic alcohol (±)-**4** was enantioresolved by the chiral phthalic acid method:^{3–5} a mixture of alcohol (±)-**4**, chiral dichlorophthalic acid (–)-**6**, 4-dimethylaminopyridine (DMAP) and 1,3-dicyclohexylcarbodiimide (DCC) in CH_2Cl_2 was stirred at room temperature overnight, yielding a diastereomeric mixture of esters **7a** and **7b**. The mixture was easily separated by HPLC on silica gel [hexane–EtOAc (8:1)], separation factor $\alpha = 1.1$; resolution factor $R_s = 1.5$. The first-eluted ester **7a** (48%) and the second one **7b** (48%) were obtained.

In the application of the chiral phthalic acid method, large single crystals of esters suitable for x-ray diffraction have been obtained in most cases. However, esters **7a** and



Scheme 2. (a) LiAlH_4 -THF; (b) (1S)-(-)-camphanic acid, DCC, DMAP- CH_2Cl_2

7b crystallized as fine needles. From our previous experience with the ^2H -substituted analogues, we had expected that (–)-camphanic acid esters would form good single crystals, the x-ray analysis of which would lead to the unambiguous determination of absolute configuration.¹ Therefore, to synthesize camphanate esters, **7a** was treated with LiAlH_4 in THF affording the enantiopure alcohol (–)-**4** (84%): $[\alpha]_D^{25} -15.9^\circ$ (c 0.73, CHCl_3) (Scheme 2). Esterification with camphanic acid was carried out as usual; a mixture of alcohol (–)-**4**, (–)-camphanic acid, DCC and DMAP in CH_2Cl_2 was stirred at room temperature overnight yielding ester **8** (96%).

When recrystallized from MeOH, ester **8** appeared as colorless prisms suitable for x-ray diffraction. A single crystal of **8** was subjected to x-ray analysis: crystal data for ester (S)-**8**, $^{13}\text{C}_6^{12}\text{C}_{17}\text{H}_{23}\text{BrO}_4$; $M_r = 449.10$; colorless prism ($0.44 \times 0.41 \times 0.30$ mm); monoclinic; space group $P2_1$ (#4); $a = 12.520(3)$, $b = 6.685(2)$, $c = 12.514(2)$ Å, $\beta = 93.04(2)^\circ$; $V = 1045.9(4)$ Å³; $Z = 2$; $D_x = 1.426$ g cm^{–3}; $D_m = 1.420$ g cm^{–3} by flotation using a CCl_4 –hexane solution; radiation, Cu K α (1.54178 Å); unique data $F_o > 3\sigma(F_o)$, 1952. The skeletal structure was solved by the direct method and successive Fourier syntheses. Absorption correction and full matrix least-squares refinement of positional and thermal parameters, including anomalous scattering factors of bromine, oxygen and carbon atoms, led to the final convergence with $R = 0.0288$ and $R_w = 0.0494$, while $R = 0.0338$ and $R_w = 0.0565$ for the mirror image structure. The absolute stereochemistry of ester **8** was thus determined as *S* by the heavy atom effect as shown in Fig. 2. The *S* configuration of **8** was confirmed by the internal reference method using the known absolute configuration of the camphanate part. The *S* absolute configuration of alcohol (–)-**4** was thus established.

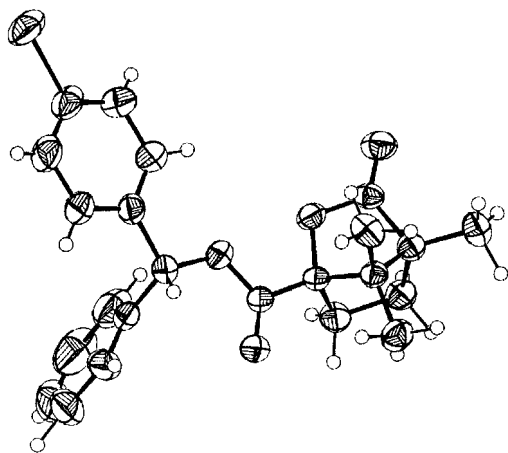
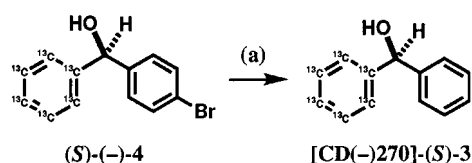


Figure 2. ORTEP drawing of ester (S)-8. The atoms are drawn as 50% probability ellipsoids

Alcohol (S)-(-)-4 was reduced with $\text{H}_2\text{NNH}_2\text{-H}_2\text{O}$ and Pd-C in EtOH yielding enantiopure α -phenylbenzene[1,2,3,4,5,6- $^{13}\text{C}_6$]methanol, (S)-3, in 98% yield (Scheme 3). The CD spectrum of (S)-3 showed weak and complex, but distinct, Cotton effects around 250–270 nm due to the molecular chirality by the ^{13}C isotopic substitution (Fig. 3). These Cotton effects are assigned to the vibronic $^1\text{L}_b$ transition of the benzene chromophore. Since ^{13}C -substituted alcohol (S)-3 shows a negative Cotton effect at 270 nm, the chiroptical property and absolute configuration of α -phenylbenzene[1,2,3,4,5,6- $^{13}\text{C}_6$]methanol were designated as [CD(-)270]-(S)-3 (see the definition of enantiomers by CD data⁶).

As discussed above, we have succeeded in the synthesis and unequivocal determination of the absolute configurations of ^{13}C -substituted chiral diphenylmethanol, the CD spectrum of which correlates with the absolute configuration as follows. When the molecule (S)-3 is placed as shown in Fig. 1, i.e. the hydroxyl group is oriented top and front, the ^{13}C -substituted phenyl group is located at the left side and the regular phenyl group at the right side. This arrangement, i.e. a heavier phenyl group at the left side and a lighter one at the right side, leads to a negative CD Cotton effect at 270 nm (Fig. 3). The present correlation holds for the cases of deuterium-substituted chiral diphenylmethanols 1 and 2. Alcohol



Scheme 3. (a) $\text{H}_2\text{NNH}_2\text{-H}_2\text{O}$, Pd-C, EtOH, reflux

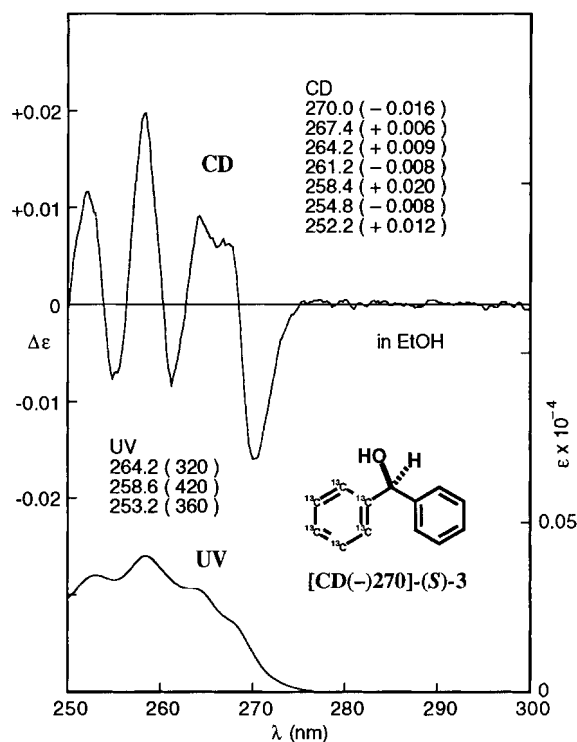


Figure 3. CD and UV spectra of α -phenylbenzene[1,2,3,4,5,6- $^{13}\text{C}_6$]methanol, [CD(-)270]-(S)-3, in EtOH

[CD(-)270.4]-(S)-1, having a heavier ^2H -substituted phenyl group at the left side and a lighter regular phenyl group at the right side, shows a negative CD Cotton effect at 270 nm (Fig. 1).¹ On the other hand, in the case of monodeuterated alcohol [CD(+270.6)]-(R)-2, a heavier group at the right side and a lighter one at the left side brings a positive CD at 270 nm. The correlation between the CD in the $^1\text{L}_b$ transition region and the absolute configuration of chiral diphenylmethanol is thus rationalized.

The CD Cotton effects of [CD(-)270]-(S)-3 are much weaker than those of [CD(-)270.4]-(S)-1: CD of (S)-3, λ_{ext} 270.0 nm, $\Delta\epsilon$ -0.016; CD of (S)-1, λ_{ext} 270.4 nm, $\Delta\epsilon$ -0.073. The CD intensity of ^{13}C -substituted diphenylmethanol (S)-3 is ca one fifth of that of the ^2H -substituted (S)-1, and almost comparable to that of [CD(+270.6)]-(R)-2: CD of (R)-2, λ_{ext} 270.6 nm, $\Delta\epsilon$ +0.011.¹ As discussed in the Introduction, the mass difference in [CD(-)270]-(S)-3 is the same as that in [CD(-)270.4]-(S)-1, and therefore we had expected a similar CD intensity for them. However, the observed CD intensities are very different. This observation indicates that hydrogen atoms in the totally symmetrical vibration of the benzene skeleton contribute much more to the CD intensity than do carbon atoms. The CD intensity is sensitive to the vibration of the C—H part rather than the C—C part. Further studies of the molecular chirality generated by isotopic substitution are in progress.

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