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Stereochemical Study of Chiral Tautomeric Flavorous Furanones by Vibrational Circular Dichroism

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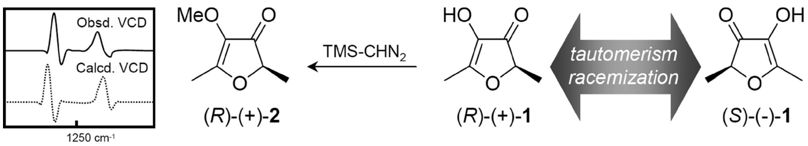
ABSTRACT



2-Substituted-3(2*H*)-furanone derivatives are industrially significant aroma compounds possessing a unique keto−enol tautomeric feature causing their racemization. Absolute configurations of two flavorous furanones, which have remained unclear for the past 40 years since their discovery, were clarified by the vibrational circular dichroism technique as well as chemical relay reactions. Odor evaluation of each enantiomer revealed relationships between their configurations and their odor activities.

The naturally occurring furanones represented by 2,5-dimethyl-4-hydroxy-3(2*H*)-furanone (DMHF, **1**), 2,5-dimethyl-4-methoxy-3(2*H*)-furanone (DMMF, **2**), and 2(or 5)-ethyl-4-hydroxy-5(or 2)-methyl-3(2*H*)-furanone (EMHF, **3a** or **3b**) are major flavor components in numerous fruits such as pineapples and strawberries.[1] (Compounds **1** and **2** have frequently been called “Furaneol” as a commodity name and “mesifuran”, respectively. “Furaneol” is a registered trademark of Firmenich SA, Switzerland.) They have also been found in a range of highly cooked foodstuffs as pleasant odor components that are formed mainly via Maillard reactions between sugars and amino acids during heating.[1] These furanones are known to play an important role in flavor because of their extremely low threshold values and their burnt sugar odor characteristics. For instance, odor threshold values in water for **1**, **2**, and **3** are 60, 0.4, and 20 ppb, respectively.[2] Therefore, these compounds have been investigated extensively as significant flavor chemicals. Since the discovery of these important aroma chemicals, large quantities have been utilized as raw materials in the flavor and fragrance industry, with worldwide annual consumption of up to almost 100 t.[3]

These flavor-related furanones are believed to be biosynthesized via a glycoside from 6-deoxy-L-mannose in plants.[1a,4] However, most of the naturally occurring ones were isolated as optically inactive compounds[1a,5] due to their unique keto−enol tautomeric structures causing racemization.

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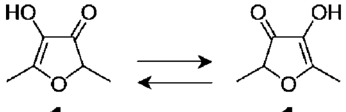
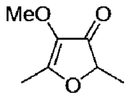
Detailed examination of the chirality of these compounds over the past decade has revealed that these inherently chiral furanones can be separable by recent chiral GC,[5,6a−c] CE,[6d,7] and HPLC[6e] techniques. Moreover, it has been shown that enzymatic reaction can produce enantiomerically enriched **1** followed by spontaneous racemization in only a few hours depending on their pH conditions.[7]

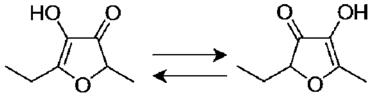
However, attempts to determine absolute configurations of the compounds have not been successful due to rapid racemization through the keto−enol tautomerism and extraordinary chemical reactivity of the enol and carbonyl groups obstructing their derivatization toward an X-ray crystallographic study and a standard Mosher method. Consequently, we applied the vibrational circular dichroism (VCD) technique to more stable methyl ether **2** (DMMF). VCD measures differential absorption of left-versus-right circularly polarized IR radiation by molecular vibrational transitions, which have both advantages of CD and IR features.[8] VCD is an emerging reliable technique for stereochemical analyses in the field of life sciences as well as material sciences in combination with DFT theoretical calculation. Herein, we report the absolute configurations of these unique molecules, which have remained unclear for the past 40 years since their isolation.[9]



1 **1**



2



3a **3b**

Table 1. Specific Optical Rotation Value, Enantiomeric Excess, and Odor Evaluation of Each Enantiomer

	$[\alpha]_D^{20}$ [a]	ee[b] [%]	odor evaluation
(+)-**1**	+172	80	obviously strong, sugary, jammy, sweet
(−)-**1**	−153	82	extremely weak
(+)-**2**	+148	94	burnt, intensive caramel
(−)-**2**	−188	91	lactone, coumarin like, no caramelic odor

[a] (+)-**1**: (*c* 0.472, CCl_4), (−)-**1**: (*c* 0.526, CCl_4), (+)-**2**: (*c* 0.324, CCl_4), (−)-**2**: (*c* 0.262, CCl_4). [b] Determined by the chiral GC.

Optical resolution of **1** and **2** was efficiently performed by an environmental friendly CO_2 supercritical fluid chromatography (SFC) chiral separation technique with normal-phase HPLC.[10] After several trials, efficient optical separation of **1** and **2** was achieved by the use of CHIRALPAK IA with chiral stationary phase using 2-propanol (**1**: $\alpha = 1.12$, **2**: $\alpha = 1.22$).[11] Semipreparative scale chromatography with multiple injections gave approximately 30 mg of each enantiomer. The afforded enantiomers had specific optical rotation values shown in Table 1. The enantiomeric ratio was determined by chiral GC with a Chirasildex CB column.[11] No racemization was observed during the workup such as collection of fractions and evaporation of solvent.

The IR and VCD spectra of each enantiomer were measured on a commercial Fourier transform VCD spectrometer as CCl_4 solution through a 100-μm path length cell with CaF_2 windows.[11] Unfortunately, **1** was decomposed during measurement because of its low stability in $CDCl_3$ and CCl_4, whereas enantiomers of its methyl ether (**2**) showed entirely opposite VCD signals. An enantiomer (+)-**2** showed a strong positive Cotton effect at around 1300 cm^{-1} attributable to C−H bending at the chiral center.

The IR and VCD spectra of **2** were theoretically calculated based on the density functional theory at the B3PW91/6−31G(d,p) level of theory. Conformational analysis offered a sole stable conformer for **2** in which the methoxy group was rotated (Figure 1).

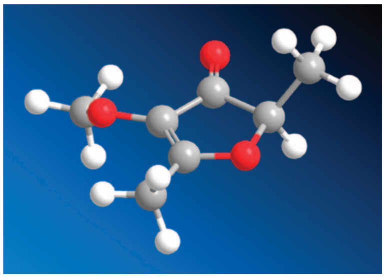


Figure 1. Most stable conformer of (*R*)-**2**.

After harmonic vibrational analysis, simulated absorption and VCD spectra were obtained by using convolution with Lorentzian functions with 8 cm^{-1} full width at half-height.

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(11) See Supporting Information.

The frequency was scaled with 0.97. All of the calculations were conducted with Gaussian03 program code. The observed VCD spectrum of (+)-**2** was essentially identical to the calculated spectrum of (*R*)-**2** (Figure 2), while IR spectra of them were almost superimposed. Therefore, (+)-**2** was shown to have an *R* configuration.

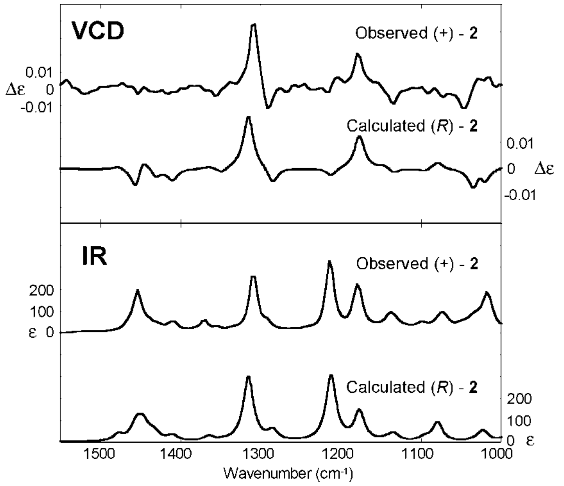


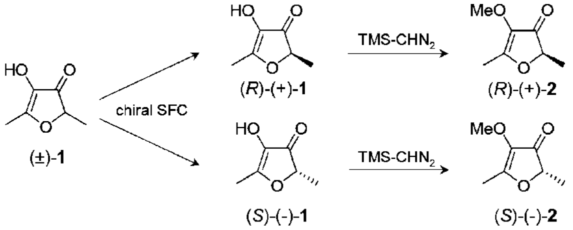
Figure 2. Comparison of IR (lower frame) and VCD (upper frame) spectra observed (CCl_4, $c = 0.17$ M, $l = 100$ μm) for (+)-**2** with one calculated for (*R*)-**2**.

To determine the absolute configuration of the tautomeric compound **1**, derivatization from **1** to **2** by mild methylation reactions was attempted. Careful treatments of (+) and (−)-**1** with trimethylsilyl-diazomethane to prevent racemization successfully afforded the corresponding optically active **2**.[11] The methyl ether derivative from (+)-**1** was identified as (*R*)-(+)-**2** by chiral GC/MS analysis,[11] whereas (−)-**1** was *vice versa*. Therefore, the relationship of absolute configuration and optical rotation of **1** was confirmed as (*R*)-(+)-**1** and (*S*)-(−)-**1**, respectively.

Odor evaluation of each enantiomer of **1** and **2** was carried out. As expected, these enantiomers exhibited different odor characteristics, dramatically as shown in Table 1. The *R* isomers were found as a burnt caramel note, which represents an odor characteristic of 2-substituted-3(2*H*)-furanones.

Thus, we succeeded in efficient chiral separation by the SFC technique and in determination of the absolute configurations of (*R*)-(+)-**2**, (*S*)-(−)-**2**, (*R*)-(+)-**1**, and (*S*)-(−)-**1** by using the recent VCD technique. We also investigated the structure−activity relationships between absolute configurations and odor characteristics. We believe that the VCD method is also useful chiroptical characterization of other aroma active compounds which absolute chemistry has been unclear.

Scheme 1



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Supporting Information Available: Details of VCD spectroscopy measurements, the optical resolutions of **1** and **2** by the chiral SFC system, derivatization reactions, and chiral GC analyses of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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