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Stereochemical Studies of Odorous 2-Substituted-3(2*H*)-furanones by Vibrational Circular Dichroism

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Chiral naturally occurring aroma compounds often exhibit enantiomeric excesses due to their stereoselective biogenesis. In general, significant organoleptic differences are perceived between these enantiomers. Chiral 2-substituted-3(2*H*)-furanones, featuring a unique keto−enol tautomer, the cause of their racemization, have been known to play an important role in flavor because of their extremely low threshold values and their burnt sugar odor characteristics. Since the discovery of these important aroma chemicals, they have been used in large quantities as raw materials in the flavor and fragrance industry. However, absolute configurations of these furanone derivatives have remained ambiguous for the past 40 years. Here optical resolutions of 2,5-dimethyl-4-hydroxy-3(2*H*)-furanone, 2,5-dimethyl-4-methoxy-3(2*H*)-furanone, and 4-acetoxy-2,5-dimethyl-3(2*H*)-furanone were accomplished using chiral CO_2 supercritical fluid chromatography (SFC). Their absolute configurations were unraveled for the first time using the vibrational circular dichroism (VCD) technique as well as by chemical relay reactions. Odor evaluation of each enantiomer revealed relationships between their configurations and odor activities.

KEYWORDS: Furanone; supercritical fluid chromatography (SFC); chiral; vibrational circular dichroism (VCD); absolute configuration

INTRODUCTION

The naturally occurring 2-substituted-3(2*H*)-furanones, represented by 2,5-dimethyl-4-hydroxy-3(2*H*)-furanone (DMHF, Furaneol, trademark of Firmenich S.A., Switzerland, **1**), 2,5-dimethyl-4-methoxy-3(2*H*)-furanone (DMMF, **2**), 4-acetoxy-2,5-dimethyl-3(2*H*)-furanone (ADMF, **3**), and 2(or 5)-ethyl-4-hydroxy-5(or 2)-methyl-3(2*H*)-furanone (EHMF, **4a** or **4b**), are important flavor compounds contributing to the sensory properties of many natural products and thermally processed foods (*1*−*4*) (**Figure 1**). DMHF (**1**) was initially reported as a product of the Maillard reaction in 1963 (*5*). Following this, **1** was isolated from pineapple, at the same time its methyl ether **2** and acetate derivative **3** were reported in 1965 (*6*, *7*). To date, **1** has been found in various fruits such as pineapple, strawberry, and grape as well as cooked materials such as roasted coffee, bread crust, roasted sesame seeds, roasted beef, beef broth, and stewed beef (*1*−*4*). **2** has been reported in pineapple, raspberry, blackberry, strawberry, mango, and kiwifruit (*1*−*4*), whereas **3** has been reported in yellow passion fruit and ripe wild strawberry (*8*, *9*). 2-Substituted-3(2*H*)-furanones **1**, **2**, **3**, **4a**, and **4b** smell burnt sugar-like, sweet, and fruity and have low odor thresholds [i.e., 60 and 20 ppb for **1** and **4** in water, respectively (*10*)]. Their proprietary intense burnt sugar-like (caramel-like) flavor is associated with a planar keto−enol group of a cyclic compound (*11*) and exceptionally with 3,4-dihydroxy-3-hexene-2,5-dione as an open-chain compound (*12*).

These furanones have been widely used as raw materials in a variety of flavors and fragrances for a long time. For instance, current annual worldwide consumption of **1** arrives at almost 100 tons (*13*).

On the other hand, naturally occurring aroma compounds often exhibit enantiomeric excesses due to stereoselective biogenesis (*14*). Because the respective enantiomers show different odor characters and odor intensities (*15*), many investigations related to enantiomeric ratio and the determination of absolute configuration have been reported (*16*).

These odorous furanones are believed to be biosynthesized in plants via a glycoside from 6-deoxyhexoses (e.g., L-rhamnose) (*1*, *17*, *18*) or via D-fructose-1,6-diphosphate (*19*) as well as to be formed from pentoses in the presence of amines or amino acids in the Maillard reaction (*20*). However, most of these naturally occurring furanones were isolated as optically inactive compounds due to their unique keto−enol tautomeric structures, which cause their rapid racemizations (**Figure 2**).

In past decades, detailed investigations on chirality have revealed that these inherently chiral furanones can be separated by recent chiral chromatographic techniques such as gas chromatography (GC) (*21*−*24*), capillary electrophoresis (CE) (*25*, *26*), and high-performance liquid chromatography (HPLC) (*26*, *27*).

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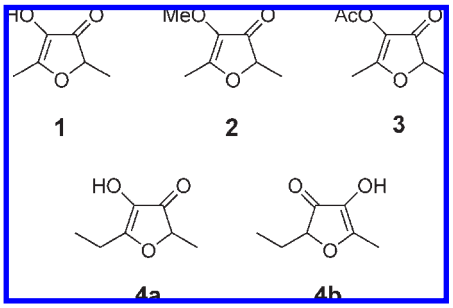

Figure 1. Naturally occurring 2-substituted-3(2*H*)-furanones.

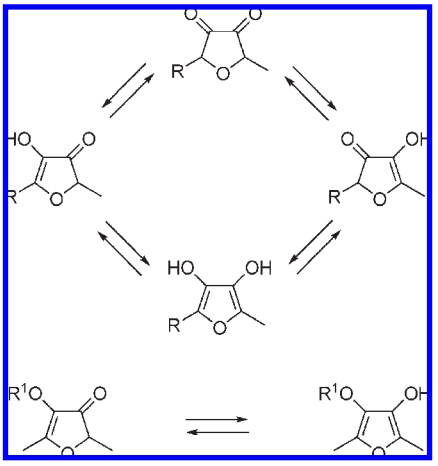

Figure 2. Keto−enol tautomerization of 2-substituted-3(2*H*)-furanones [R = Me (**1**) or Et (**4a**, **4b**), R^1 = Me (**2**) or Ac (**3**)].

To our knowledge, the first chiral gas chromatographic resolution for **1** was performed in 1990 (*21*). The chiral gas chromatography−olfactometry study, which enables odor evaluation of each enantiomer without isolation, afforded the significant difference of odor intensity between enantiomers of **2** to be 1000 times stronger than its antipode (*24*). These results opened the door for many researchers investigating chirality. So far, optical rotations have been reported for **1** and **2** using chiral chromatography (*26*, *27*) or enzyme-catalyzed optical resolution (*28*, *29*). In 2003, Schwab reported that **1** was initially produced as an enantiomerically enriched form that eventually racemized spontaneously into an optically inactive compound. This phenomenon occurred in only a few hours depending on the pH conditions (*26*).

Although it is important to determine their absolute configuration to elucidate their biosynthetic pathway as well as to understand the structural principle included in the unique intense burnt sugar flavor, the absolute configurations remained ambiguous for over 40 years since the discovery of such furanones in 1960s.

It is known that the rapid racemization through the keto−enol tautomerism and extraordinary chemical reactivity of the enol and carbonyl groups obstruct their derivatization toward a generally used X-ray crystallographic study and a standard Mosher method.

CO_2 supercritical fluid chromatographic (SFC) chiral separation is known for the effective preparative-scale optical resolution method in the pharmaceutical field for chemicals that have an aromatic group (*30*, *31*). Lately, we reported the SFC optical resolution for flavor materials (*32*). This method has the advantage of minimizing a thermal procedure, such as an organic solvent evaporation, a potential factor of racemization. Meanwhile, the combination of vibrational circular dichroism (VCD) spectra with density functional theory (DFT) theoretical calculation was recently developed and applied as an emerging reliable technique for stereochemical analyses in the field of life sciences as well as material sciences (*33*−*41*).

Consequently, the aim of this study was to investigate the absolute configuration using the VCD method coupled with chiral SFC optical resolutions.

We reported earlier the preliminary study for **1** and **2** (*42*). In this paper, the detailed stereochemical study of **1**, **2**, and **3** is described.

MATERIALS AND METHODS

Materials. DMHF (**1**) was purchased from Firmenich S.A. (Geneva, Switzerland). DMMF (**2**) and ADMF (**3**) were obtained from Takasago International Corp. (Tokyo, Japan).

Reagents and Solvents. Ethyl acetate, 2-propanol, chloroform, and methanol were purchased from Nacalai Tesque Inc. (Kyoto, Japan). Carbon tetrachloride and trimethylsilyldiazomethane (ca. 10% in hexane, ca. 0.60 mol/L) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan) and Tokyo Chemical Industries, Co., Ltd. (Tokyo, Japan), respectively. Chloroform-*d* 100% D and methylene chloride-d_2 99.6% D were purchased from Euriso-top S.A. (Saint-Aubin, France).

Gas Chromatography. Enantiomeric excess values of isolated optically active compounds were determined by using a 5890 and/or 7890A GC system (Agilent Technologies Inc., Santa Clara, CA) combined with a flame ionization detector (FID) equipped with a CP-Chirasil-DEX CB capillary column (25 m×0.25 mm i.d., 0.25 μm film thickness, Varian, Inc., Palo Alto, CA), at constant 100 kPa pressure with helium as a carrier gas. The initial oven temperature was set at 70 °C and then was raised to 210 °C at 1 °C/min. Injector and detector temperatures were 250 °C.

Gas Chromatography−Mass Spectrometry (GC-MS). The isolated optically active compounds were analyzed by GC-MS-QP2010 (Shimadzu Corp., Kyoto, Japan) equipped with a BC-Wax capillary column (50 m × 0.25 mm i.d., 0.15 μm film thickness) and/or Rxi-5ms (30 m×0.25 mm i.d., 0.25 μm film thickness, Restek Corp., Bellefonte, PA). GC-MS conditions with the BC-Wax column were as follows: Carrier gas flow was set at constant pressure mode (110 kPa) with helium as a carrier gas. The initial oven temperature was set at 70 °C and was raised to 218 °C at 4 °C/min. The temperatures of the injector, mass interface, and ion source were kept at 250, 230, and 200 °C, respectively. Acquisition mass range was m/z 20−650 in the electron ionization (EI) at 27 eV ionization energy. GC-MS conditions with the Rxi-5ms column were as follows: Carrier gas flow was on a constant pressure mode (70 kPa) with helium as carrier gas. The initial oven temperature was set at 50 °C, kept for 1 min, and raised to 250 °C at 4 °C/min. The temperatures of the injector, mass interface, and ion source were kept at 290, 280, and 200 °C, respectively. Acquisition mass range was m/z 20−650 in the EI at 27 eV ionization energy.

Multidimensional Gas Chromatography−Mass Spectrometry (MDGC-MS). The enantioselective MDGC-MS analysis was performed with a MDGC/GCMS-2010 (Shimadzu Corp., Kyoto, Japan) equipped with two capillary columns, a BC-Wax capillary column (30 m×0.25 mm i.d., 0.25 μm film thickness) for the first GC column and a CP-Chirasil-DEX CB capillary column (25 m×0.25 mm i.d., 0.25 μm film thickness) for the second GC column connected via a switching device. GC conditions for the first GC were as follows: Carrier gas flow was on a constant pressure (180 kPa) with helium as carrier gas. The initial oven temperature was set at 70 °C and then was raised to 230 °C at 5 °C/min. The temperatures of the injector, flame ionization detector, and transfer line into the second GC were kept at 250, 250, and 200 °C, respectively. GC conditions of the second GC were as follows: Carrier gas flow was on a constant pressure (switching pressure 130 kPa). The initial oven temperature was set at 70 °C and then was raised to 210 °C at 1 °C/min after heart-cut. The temperatures of the mass interface and ion source were kept at 230 and 200 °C, respectively. Acquisition mass range was m/z 35−350 in the EI at 70 eV ionization energy.

Chiral SFC Analysis. The SFC instrument used for the investigation of enantioselective resolution was an SFC System (Jasco Corp., Tokyo, Japan) equipped with various types of chiral stationary phases; Chiralpak

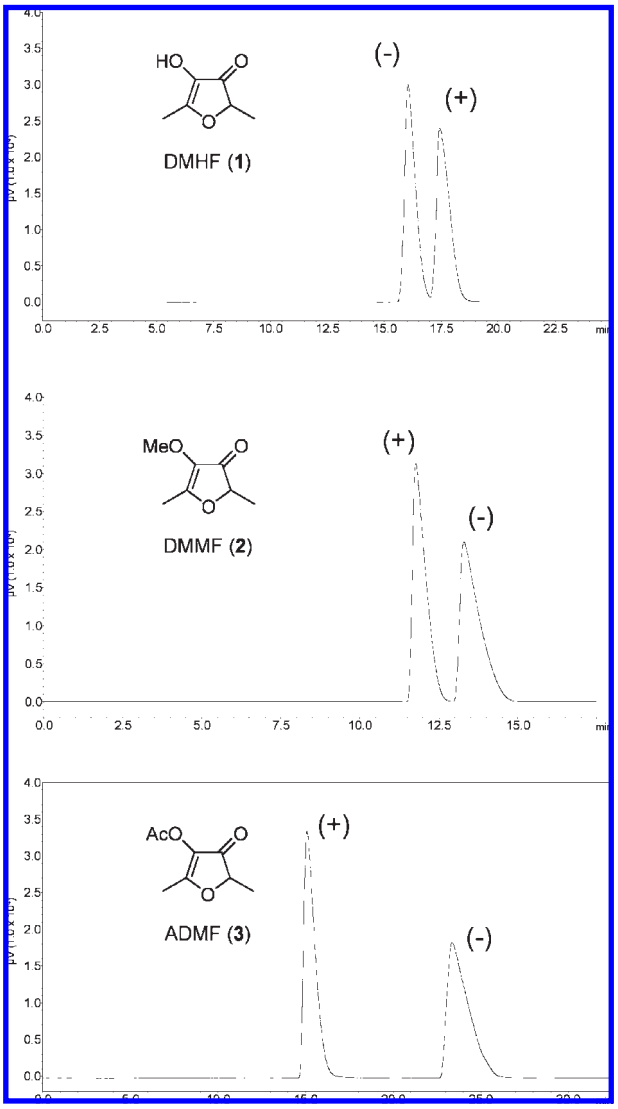

Figure 3. Optical resolution of **1**, **2**, and **3** by enantioselective CO_2 SFC.

IA, IB, and Chiralcel OD-H packed columns (4.6 mm × 250 mm, 5 μm, Daicel Chemical Industries, Ltd., Tokyo, Japan) on 1 mL/min CO_2 flow and 0.005 mL/min 2-propanol flow as an entrainer. The back pressure was kept at 15 MPa. UV signal was recorded at 280 nm. The column oven temperature was kept at 25 °C.

Preparative Chiral SFC. The SFC instrument used for the optical resolution and isolation was an SFC System (Jasco Corp.) equipped with a semipreparative scale Chiralpak IA packed column (20 mm × 250 mm, 5 μm) on 20 mL/min CO_2 flow and 0.08−0.3 mL/min 2-propanol flow as an entrainer. The back pressure was kept at 15 MPa. UV signal was recorded at 280 nm. The column oven temperature was kept at 25 °C.

Optical Rotation. Optical rotation was measured by the digital polarimeter model Jasco P-1020 at 589 nm (sodium D-line) at 20 °C in a 10 mm cell. The values of optical rotation were determined by assuming a standard deviation of < 3%.

VCD Spectroscopy. VCD and IR spectra were measured on a Bomem/BioTools Chiral*ir* spectrometer. All spectra were recorded for 1−3 h at a resolution of 8 cm^{-1} under ambient temperature. Samples were dissolved in CCl_4 and then placed in a 100 μm CaF_2 cell. The concentrations were as follows: (+)-**2**, 0.17 M; (−)-**2**, 0.085 M; (+)-**3**, 0.080 M; and (−)-**3**, 0.080 M. The IR and VCD spectra were corrected by a solvent spectrum obtained at the same experimental conditions and presented in molar absorptivity ε (L/mol·cm).

Sensory Evaluations. The sensory evaluation in this study was performed by expert panels of flavorists. The study was approved by the Institutional Review Board of Takasago International Corp.

Table 1. Specific Optical Rotation Value and Enantiomeric Excess of Isolated Furanones

compound	$[\alpha]_D^{20}$	condition	ee (%)	SFC isolation yield (%)
(+)-**1**	+172	*c* 0.472, CCl_4	80	74
(−)-**1**	−153	*c* 0.526, CCl_4	82	65
(+)-**2**	+148	*c* 0.324, CCl_4	94	46
(−)-**2**	−188	*c* 0.262, CCl_4	91	37
(+)-**3**	+113	*c* 0.784, $CHCl_3$	99	74
(−)-**3**	−128	*c* 0.664, $CHCl_3$	99	76

Optical Resolution and Isolation of 2,5-Dimethyl-4-hydroxy-3(2*H*)-furanone (1). A solution of 208 mg/mL of racemic furanone **1** in ethyl acetate was injected by portion of 50 μL into a preparative SFC system equipped with Chiralpak IA. Flow conditions were 20 mL/min CO_2 with 0.3 mL/min 2-propanol. The optically active compounds were recovered with ethyl acetate as a line-wash solvent. After eight injections, (+)-**1** and (−)-**1** were isolated in 31 mg (74%) and 27 mg (65%) with 80 and 82% ee, respectively.

Optical Resolution and Isolation of 2,5-Dimethyl-4-methoxy-3(2*H*)-furanone (2). A solution of 301 mg/mL of racemic furanone **2** in ethyl acetate was injected by 20 μL portion into a preparative SFC system equipped with Chiralpak IA. Flow conditions were 20 mL/min CO_2 with 0.1 mL/min 2-propanol. The optically active compounds were recovered with ethyl acetate as a line-wash solvent. After 10 injections, (+)-**2** and (−)-**2** were isolated in 14 mg (46%) and 11 mg (37%) with 94 and 91% ee, respectively.

Optical Resolution and Isolation of 4-Acetoxy-2,5-dimethyl-3(2*H*)-furanone (3). A solution of 519 mg/mL of racemic furanone **3** in ethyl acetate was injected by portion of 150 μL into a preparative SFC system equipped with Chiralpak IA. Flow conditions were 20 mL/min CO_2 with 0.1 mL/min 2-propanol. The optically active compounds were recovered with ethyl acetate as a line-wash solvent. After three injections, (+)-**3** and (−)-**3** were isolated in 88 mg (74%) and 89 mg (76%) with 99% ee, respectively.

Derivatization of DMHF to Its Methyl Ether 2. To a 1 mL methanol solution of 5 mg of (−)-**1** was added excess trimethylsilyldiazomethane in hexane at 0 °C, and the mixture was warmed to room temperature. It was stirred at room temperature for an additional 1 h to afford the optically active (−)-**2**. In a similar manner, (+)-**1** gave (+)-**2**.

RESULTS AND DISCUSSION

Chiral Supercritical Fluid Chromatographic Optical Resolution. CO_2 supercritical fluid chromatography (SFC) is known to allow fine resolution even at a high flow rate due to the low viscosity and high diffusivity of CO_2. For separation of the compounds, this method has been considered to be more efficient than HPLC because of a faster run time, inexpensive CO_2, and less waste of the mobile phase liquid. In this case, it is further noteworthy that because CO_2 is vaporized spontaneously at the end of SFC, the minimum thermal workup operation for removing organic solvent as an eluent avoids the risk of racemization. To achieve high-throughput optical resolution affording respective enantiomers of **1**, **2**, and **3**, chiral CO_2 SFC was performed with chiral stationary phase columns. Varieties of columns such as Chiralcel OD-H and Chiralpak IB and IA were screened. After several trials, efficient optical separations of **1**, **2**, and **3** were achieved by Chiralpak IA using 2-propanol as entrainer.

Preparative Supercritical Fluid Chromatographic Optical Resolution. For scaling up high-throughput optical resolution, semipreparative SFC was applied in accordance with the analytical results. As shown in **Figure 3**, respective enantiomers were separated using Chiralpak IA and 2-propanol with excellent separation factors (**1**, $\alpha = 1.12$; **2**, $\alpha = 1.22$; **3**, $\alpha = 1.80$).

Multiple injections under the above-mentioned conditions gave sufficient amounts of each enantiomer with high optical purities applicable for the VCD spectra. These enantiomeric

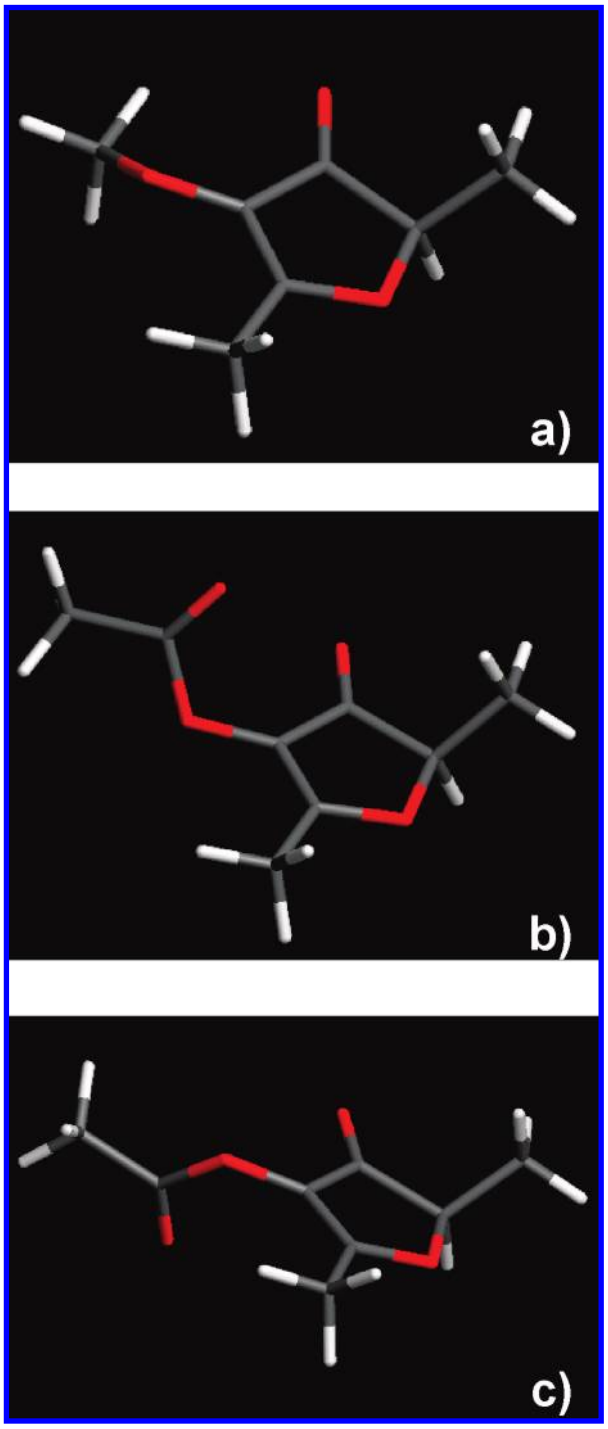

Figure 4. Most stable conformer of (*R*)-**2** (**a**) and two stable conformers of (*R*)-**3** (**b**, **c**).

ratios were determined by chiral GC with a CP-Chirasil-DEX CB column. The afforded enantiomers had specific optical rotation values shown in **Table 1**. To the best of our knowledge, these specific optical rotation values have not yet been reported previously except for (+)-**2** (*29*). No racemization was observed during the collection of fractions and evaporation of solvents. Furthermore, regardless of the rapid racemization rates of these furanones, enantiomeric purities were kept during optical rotation measurements.

IR and VCD Theoretical Calculation. *Conformational Analysis of* (*R*)*-2,5-Dimethyl-4-methoxy-3*(*2H*)*-furanone* [(*R*)-*2*]. The IR and VCD spectra of (*R*)-**2** were theoretically calculated on the

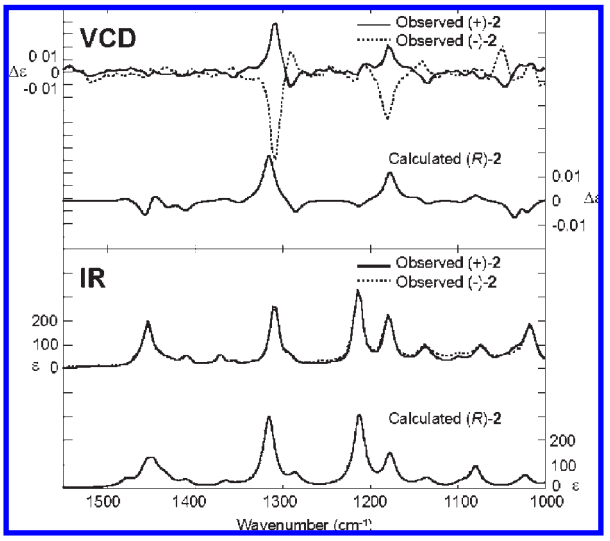

Figure 5. Comparison of IR (lower frame) and VCD (upper frame) spectra observed for (+)-**2** with the one calculated for (*R*)-**2**.

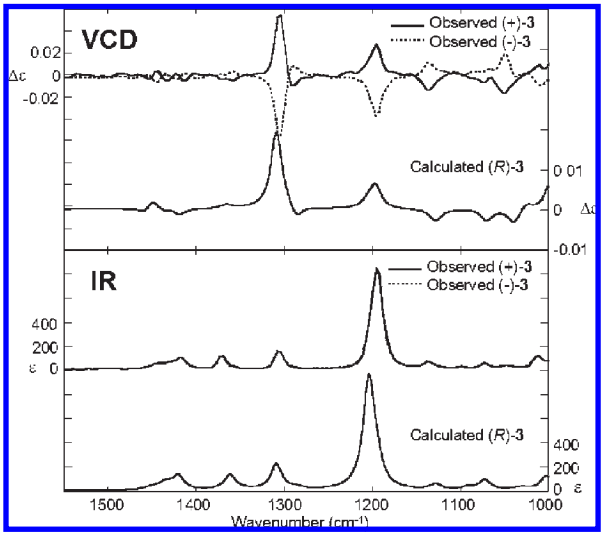

Figure 6. Comparison of IR (lower frame) and VCD (upper frame) spectra observed for (+)-**3** with the one calculated for (*R*)-**3**.

basis of the B3PW91/6-31G(d,p) level density functional theory. Because (*R*)-**2** has only one rotatable bond, there are several starting geometries for conformational analysis with different directions in the methoxy group. As seen in **Figure 4a**, the geometry optimizations gave a sole stable conformer for **2** in which the methoxy group was rotated. 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. The frequency was scaled with 0.97.

Conformational Analysis of (*R*)*-4-Acetoxy-2,5-dimethyl-3*(*2H*)*-furanone* [(*R*)-*3*]. CONFLEX search with MMFF94F force fields was carried out. Geometry optimizations and harmonic vibrational analyses were carried out with the density functional calculation at the B3PW91/6-31G(d,p) level of theory for the four obtained conformers in the CONFLEX search. Geometry optimizations and harmonic vibrational analyses were carried out at the same level of theory. Two low-lying conformations (see **Figure 4b**,**c**) were used to calculate the IR and VCD spectra. The energy difference between these two conformers was 0.06 kcal/mol. This suggests that these two conformers have even contribution

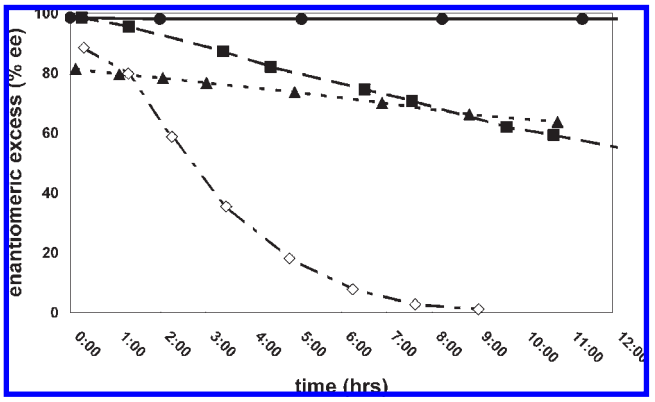

Figure 7. Time course of DMHF racemization in CCl_4 (◇), $CDCl_3$ (■), CD_2Cl_2 (▲), and ethyl acetate (●).

for the IR and VCD spectra. The spectra of these conformers were calculated in the same manner as for (*R*)-**2**. Finally, the spectra were averaged with the Boltzmann weighted population. All calculations were conducted with Gaussian03 program code.

VCD Measurement of Furanones. VCD measures differential absorption of left-versus-right circularly polarized IR radiation by molecular vibrational transitions, which have advantages of both CD and IR features.

As expected, enantiomers of methyl ether **2** showed entirely opposite VCD signals. The enantiomer (+)-**2** showed a strong positive Cotton effect at around 1300 cm^{-1} attributable to C−H bending at the chiral center. As shown in **Figure 5**, the observed VCD spectrum of (+)-**2** was essentially identical to the calculated spectrum of (*R*)-**2**, whereas both IR spectra were almost superimposed. Therefore, (+)-**2** was shown to have the *R* configuration.

Similar to **2**, the observed IR spectra of **3** were almost superimposed to the calculated IR spectra. Meanwhile, the observed VCD spectrum of (+)-**3** closely matched with the calculated spectrum of (*R*)-**3** (**Figure 6**). As a result, the absolute configurations of **3** were confirmed as (*R*)-(+)-**3** and (*S*)-(−)-**3**, respectively.

Racemization of DMHF (1). Tautomeric racemization of **1** in aqueous solution is known to be catalyzed under acidic conditions (pH 2) and especially at pH values >7, whereas it most stable between pH 4 and 5 (*27*).

The solvent dependency for the racemization rates of **1** in various nonpolar organic solvents, which is applicable to measure optical rotation value, IR, and VCD, was investigated. Optically active furanone **1** was dissolved in CCl_4, $CDCl_3$, and CD_2Cl_2 at 0.1 mol/L concentration and then stored in brown glass vials at room temperature, respectively. The time course study of the enantiomeric ratio changes was performed by chiral GC-FID with a CP-Chirasil-DEX CB column. Unfortunately, the racemization of **1** occurred within 2−3 h in CCl_4, $CDCl_3$, and CD_2Cl_2, whereas it was rather stable in ethyl acetate, which is not a suitable solvent for VCD measurement (**Figure 7**). Interestingly, **1** was even stable for >6 days in ethyl acetate.

Absolute Configuration of DMHF (1) Using Chemical Relay Reaction. Toward to this end, to determine the absolute configuration of **1** causing immediate racemization in CCl_4, $CDCl_3$, and CD_2Cl_2, derivatization from **1** to **2** by mild methylation reactions was attempted (**Figure 8**). Careful treatments of (+)-**1** and (−)-**1** with trimethylsilyldiazomethane to prevent racemization successfully afforded the corresponding optically active methyl ether **2**, respectively. The one from (+)-**1** was identified as (*R*)-(+)-**2** by chiral MDGC-MS analysis, whereas (−)-**1** was vice versa. Therefore, the relationship of absolute configuration and optical

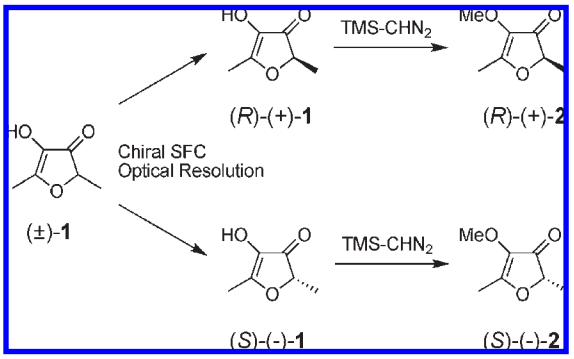

Figure 8. Derivatization of DMHF (**1**) into DMMF (**2**).

Table 2. Odor Evaluation Results of Furanones

compound	odor evaluation
(*R*)-(+)-**1**	obviously strong, sugary, jammy, sweet
(*S*)-(−)-**1**	extremely weak
(*R*)-(+)-**2**	burnt, intense caramel
(*S*)-(−)-**2**	lactone, coumarin-like, no caramelic odor
(*R*)-(+)-**3**	burnt, intense caramel
(*S*)-(−)-**3**	weak caramelic odor

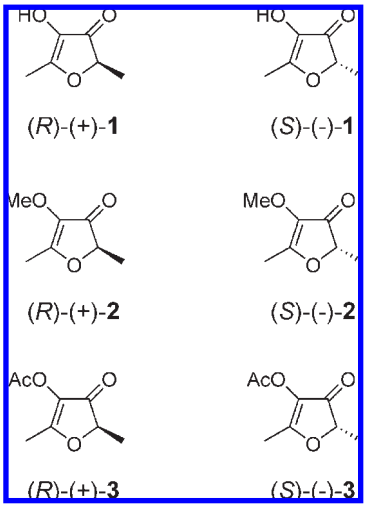

Figure 9. Absolute stereochemistry of 2-substituted-3(2*H*)-furanones.

rotation of **1** was confirmed as (*R*)-(+)-**1** and (*S*)-(−)-**1**, respectively.

Odor Evaluation of DMHF (1), DMMF (2), and ADMF (3). In 1992, Fisher reported that odor threshold values for the enantiomers of **2** differ by about a factor of 1000 and enantiomers of **1** possess similar intensities by sniffing at an outlet port of the chiral gas chromatograph using a gas chromatography−olfactometry aroma extract dilution analysis (AEDA) method (*24*). Meanwhile, Bruche mentioned that (−)-**1** has a more intense caramel-like odor than (+)-**1** by gas chromatography−olfactometry (*23*).

For the first time, both enantiomers of **1**−**3** are prepared with assigned absolute stereochemistry, and odor evaluation of each enantiomer of **1**−**3** was performed under ethyl acetate solution with a smelling strip. As expected, significant organoleptic differences between these enantiomers were perceived as shown in **Table 2**. Contrary to the reported study for **1** (*23*), our result shows that the (*R*)-(+)-isomer exhibits intense odor, whereas the considerable difference of odor intensity between the enantiomers of **2** is agreement with the earlier results. On the other hand, the

(*R*)-(+)-isomer of **3** is revealed to possess a stronger odor than (*S*)-(−)-**3**. Surprisingly, it is found that all (*R*)-(+) isomers of **1**−**3** have an intense burnt caramel note which represents an odor characteristic of 2-substituted-3(2*H*)-furanones.

In conclusion, we succeeded in efficient optical resolutions of **1**, **2**, and **3** by SFC. Moreover, we unveiled for the first time the absolute stereochemistries of (*R*)-(+)-**2**, (*S*)-(−)-**2**, (*R*)-(+)-**3**, (*S*)-(−)-**3**, (*R*)-(+)-**1**, and (*S*)-(−)-**1** by using a state of the art VCD technique and chemical relay reaction (**Figure 9**). In addition, we investigated the structure−activity relationships between absolute configurations and organoleptic characteristics.

Our result shows that the (2*R*)-isomers of furanones are the principal contributors representing the characteristic burnt sugar-like flavor. This result questions how (2*R*)-substituted-3(2*H*)-furanones are perceived in the human olfactory receptors.

Finally, we believe that the VCD method is also useful for the chiroptical characterization of other aroma-active compounds for which absolute chemistries are still unclear.

ABBREVIATIONS USED

CO_2, carbon dioxide; CCl_4, carbon tetrachloride, $CDCl_3$, deuterated chloroform; CD_2Cl_2, deuterated dichloromethane; CE, capillary electrophoresis; DFT, density functional theory; FID, flame ionization detector; GC, gas chromatography; GC-MS, gas chromatography−mass spectrometry; HPLC, high-performance liquid chromatography; IR, infrared absorption; MDGC-MS, multidimensional gas chromatography−mass spectrometry; MS, mass spectrum; ms, mean square; SFC, supercritical fluid chromatography; TMS-CHN_2, trimethylsilyldiazomethane; VCD, vibrational circular dichroism.

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Supporting Information Available: Additional figures. This material is available free of charge via the Internet at http://pubs.acs.org.

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