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Intramolecular 9-membered hydrogen bonding of 2-arylmethylphenols having carbonyl groups at 2′-position

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Abstract—Thermodynamic parameters of nine-membered intramolecular hydrogen bonding between carbonyl groups and phenolic hydroxyl groups of 2-arylmethylphenols having methoxycarbonyl, dimethylcarbamoyl, and formyl groups were determined by variable temperature ^{1}H NMR studies and van't Hoff analysis. The enthalpy of the hydrogen bonding was related to the electron-withdrawing ability of the substituents on the phenol and the basicity of the carbonyl group. The entropy loss of the hydrogen bonding was dependent on the rotation freedom of the phenol group.

1. Introduction

Intramolecular hydrogen bonding plays an important role in the conformation of biomolecules and biochemical reactions. Recently, much attention has been paid to the intramolecular hydrogen bonding of unnatural polymers such as β,γ,δ-peptides,[1] oligoanthranilamides,[2] and oligocarbohydrate amino acids.[3] Despite the fact that phenolic compounds are well known as antioxidants in the biological system and are used as additives in food, polymers, paints to prevent oxidation of these materials, the intramolecular hydrogen bonding of these compounds has been less discussed except the chemical behavior of salicylic ester and its related compounds which form the typical 6-membered hydrogen bonding.[4] The intramolecular hydrogen bonding of these phenolic compounds substantially changes their chemical and physical properties. In particular, the ability of an antioxidant in ubiquinol is dependent on the formation of intramolecular hydrogen bonding of the phenolic hydroxyl group.[5] Interestingly, the phenolic hydrogen atom which forms the intramolecular hydrogen bonding is more easily abstracted by the radical than the one which forms intermolecular hydrogen bonding.

We have recently reported a novel 9-membered intramolecular hydrogen bonding between ester carbonyl and phenolic hydroxyl groups both in the solid state and in $CDCl_3$ solution.[6] This is a rare example of medium-ring size hydrogen bonding[7] in phenolic compounds, and it was found that the variable temperature ^{1}H NMR chemical shifts of phenolic protons showed the equilibrium of the intramolecular hydrogen bonding. In this paper, we now report that 2-arylmethylphenols having ester, amide, and aldehyde at the 2′-position could form an intramolecular 9-membered hydrogen bonding between aromatic carbonyl and phenolic hydroxyl groups in $CDCl_3$ solution, and the substituent effects of these compounds indicated that the intramolecular hydrogen bonding depended on the acidity of the phenol and the basicity of the carbonyl group. The phenolic proton chemical shifts with variable temperature gave the thermodynamic parameters, which could reveal the details of the intramolecular 9-membered hydrogen bonding.

2. Results and discussion

2.1. Preparation of 2-arylmethylphenol derivatives

2-(1-Methoxycarbonyl-2-naphthyl)methylphenol and its derivatives **1a–f** have been prepared by photo-Claisen type rearrangement as reported before (Scheme 1).[8] The preparation of 2-(1-methoxycarbonyl-2-phenyl)methylphenol derivatives **2a–e** from 1-bromo-2-methylbenzene is

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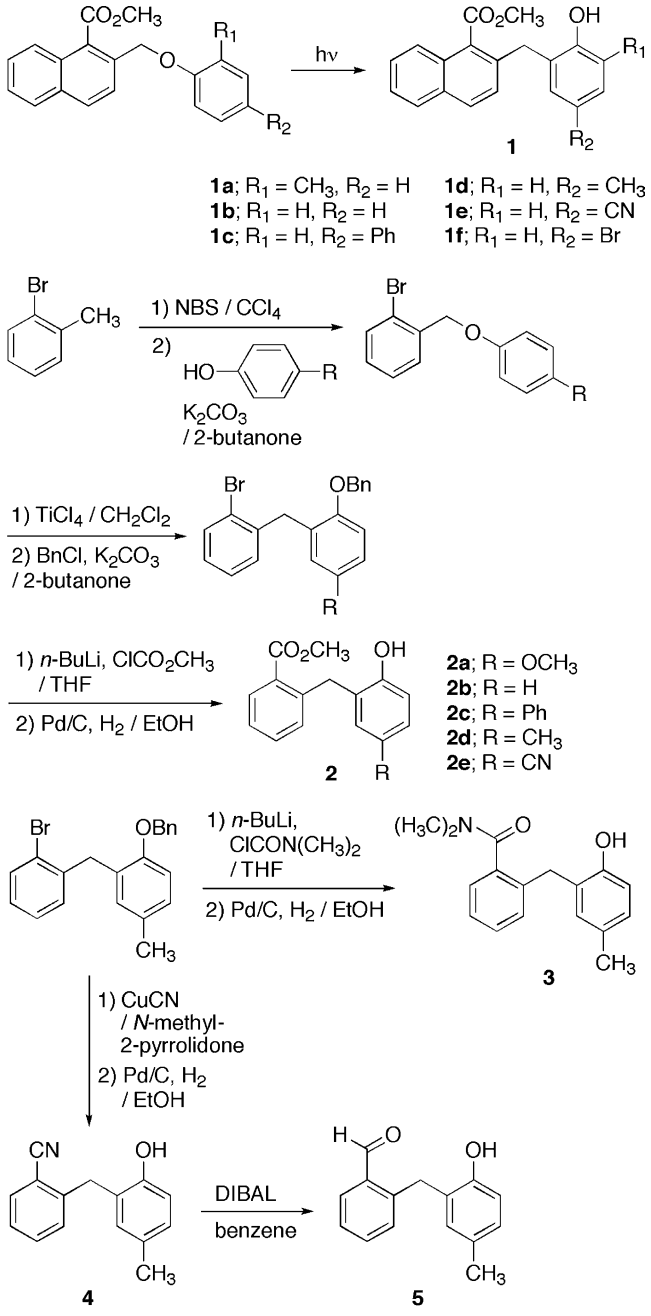
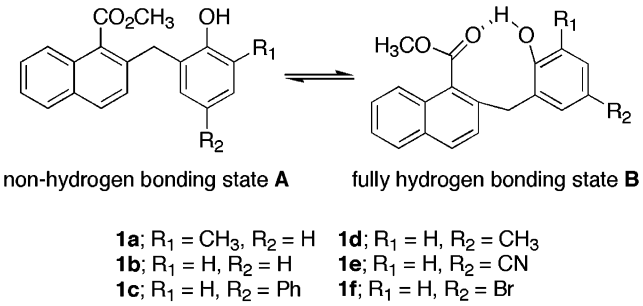


Scheme 1.

shown in Scheme 1. The 2-bromobenzyl phenyl ethers were synthesized by bromination and etherification of 1-bromo-2-methylbenzene. Then, the ethers were rearranged to the *ortho*-position by $TiCl_4$, and were protected by the benzyl group. **2a–e** were given by the esterification, followed by deprotection with Pd/C and H_2. The amide derivative **3** was obtained by a similar method. DIBAL reduction of **4**, which was prepared by cyanation and deprotection from the corresponding bromo derivative, gave the aldehyde **5**.

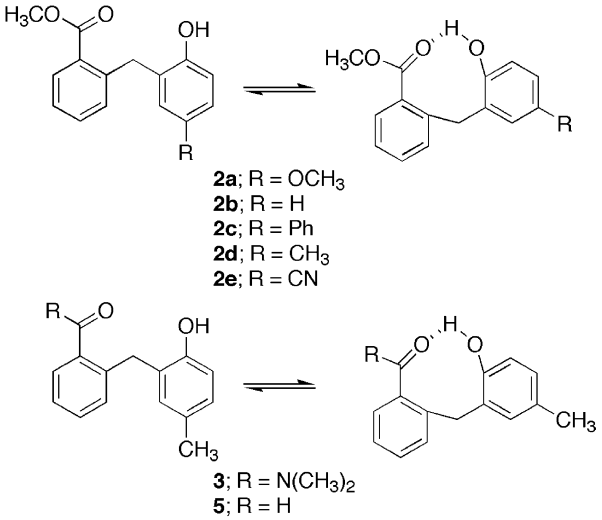
2.2. Intramolecular 9-membered hydrogen bonding between aromatic carbonyl and phenolic hydroxyl groups in $CDCl_3$ solution

The X-ray crystallographic analysis of **1a** showed the possibility of the intramolecular 9-membered hydrogen bonding in crystalline state.[5] The ^1H NMR studies of **1a–f** (5 mM) in $CDCl_3$ at 20 °C indicated a significant downfield shift of the phenolic hydrogen (7.36, 7.49, 7.25, 6.93, 7.65, 8.91 ppm) compared to those of the reference compounds, such as 2-methylphenol (5 mM, 4.63 ppm), phenol (5 mM, 4.70 ppm), 4-phenylphenol (5 mM, 4.78 ppm), 4-methylphenol (5 mM, 4.52 ppm), 4-bromophenol (5 mM, 4.80 ppm), and 4-cyanophenol (5 mM, 5.52 ppm), respectively. The ^1H NMR chemical shifts of **1a–f** at 20 °C were independent of those concentrations (1–50 mM). These results suggested that **1a–f** formed the intramolecular hydrogen bonding in $CDCl_3$ solution. In addition, the FT-IR spectrum of **1a** in $CHCl_3$ (5 mM) at room temperature showed two carbonyl absorptions at 1721 (weak) and 1702 (strong) cm^{-1}. The former absorption indicated the existence of a free ester carbonyl group, and the latter one was assigned to the hydrogen-bonded ester carbonyl group. These results suggest the existence of equilibrium between the non-hydrogen bonding state A and the fully hydrogen bonding state B (Scheme 2).



Scheme 2.

The ^1H NMR studies of the corresponding benzoyl derivatives **2a–e**, **3**, **5** also gave results similar to those of **1a–f**, which clearly indicated that they formed the intramolecular 9-membered hydrogen bonding in $CDCl_3$ (Scheme 3). On the other hand, the cyano derivative **4** having no carbonyl group did not form the intramolecular hydrogen bonding, since the phenolic proton chemical shifts



Scheme 3.

of **4** with variable temperature showed the same chemical shifts of 4-methylphenol.

2.3. Substituent effects of intramolecular hydrogen bonding

Figure 1 shows the temperature dependence of the phenolic proton chemical shifts of **1a–f** in $CDCl_3$, and its $\Delta\delta/\Delta T$ is shown in Table 1. The chemical shifts of phenolic protons of **1a–f** linearly moved to downfield with lowered temperature, and were shifted to upfield with elevated temperature. Proton exchange of the intramolecular hydrogen bonding was rapid in the NMR time scale, and the observed chemical shifts were averaged. The downfield chemical shift of the phenolic proton indicated that the proportion of the intramolecular hydrogen bonding state **B** is larger than that of the non-hydrogen bonding state **A**. The amount of the intramolecular hydrogen bonding state at the equilibrium was increased with the decrease of temperature. The intramolecular hydrogen bonding of **1e** having an electron-withdrawing group (cyano group) was much stronger than that of **1d** having an electron-donating group (methyl group), because the phenolic proton chemical shifts of **1e** were shifted to further downfield than that of **1d** compared to the reference phenols.

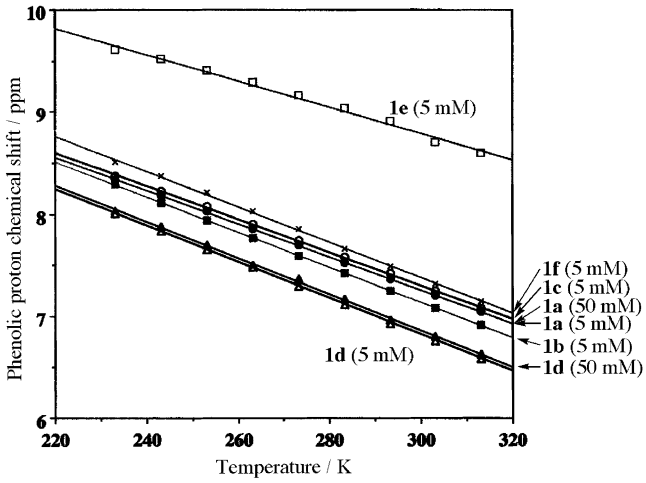


Figure 1. Temperature dependence of the phenolic proton chemical shifts of **1a–f** (5, 50 mM) in $CDCl_3$.

Table 1. $\Delta\delta/\Delta T$ of the intramolecular hydrogen bonding of **1a–f**

1[a]	R_1	R_2	$\Delta\delta/\Delta T$ ($\times 10^{-2}$)
1a	CH_3	H	−1.63
1a[b]	CH_3	H	−1.63
1b	H	H	−1.73
1c	H	Ph	−1.74
1d	H	CH_3	−1.78
1d[b]	H	CH_3	−1.78
1e	H	CN	−1.28
1f	H	Br	−1.60

[a] [**1**]=5 mM.
[b] [**1**]=50 mM.

The temperature dependence of the phenolic proton chemical shifts of **2a–e** in $CDCl_3$ and its $\Delta\delta/\Delta T$ are shown in Figure 2 and Table 2, respectively. Similarly, the substituent effect of **2a–e** revealed that the hydrogen

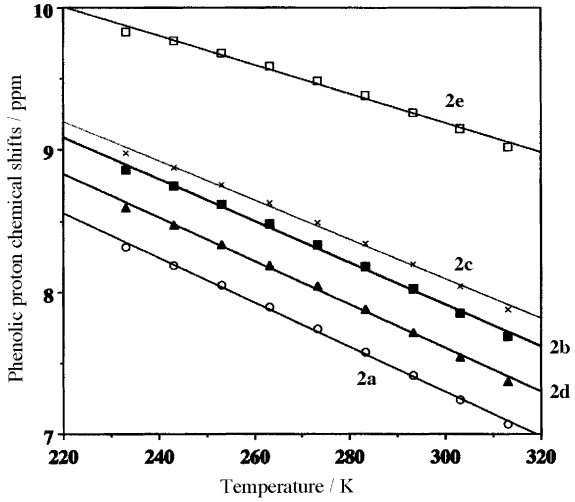


Figure 2. Temperature dependence of the phenolic proton chemical shifts of **2a–e** (5 mM) in $CDCl_3$.

Table 2. $\Delta\delta/\Delta T$ of the intramolecular hydrogen bonding of **2a–e**

2[a]	R	$\Delta\delta/\Delta T$ ($\times 10^{-2}$)
2a	OCH_3	−1.57
2b	H	−1.48
2c	Ph	−1.38
2d	CH_3	−1.53
2e	CN	−1.02

[a] [**2**]=5 mM.

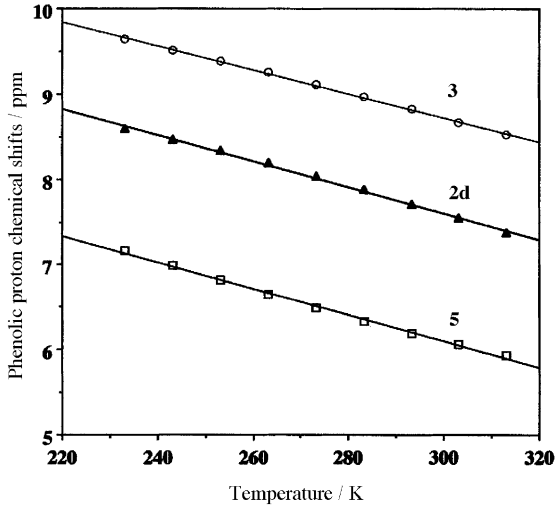


Figure 3. Temperature dependence of the phenolic proton chemical shifts of **2d**, **3**, **5** (5 mM) in $CDCl_3$.

Table 3. $\Delta\delta/\Delta T$ of the intramolecular hydrogen bonding of **2d**, **3**, **5**

Compound[a]	R	$\Delta\delta/\Delta T$ ($\times 10^{-2}$)
2d	OCH_3	−1.53
3	$N(CH_3)_2$	−1.41
5	H	−1.54

[a] [**2d**, **3**, **5**]=5 mM.

bonding of **2e** was much stronger than that of **2a**. These results indicated that the intramolecular hydrogen bonding depended on the acidity of the phenol.

Figure 3 shows the temperature dependence of the chemical shifts of phenolic protons of **2d**, **3**, and **5** in $CDCl_3$, and its $\Delta\delta/\Delta T$ is shown in Table 3. The substituent effect on the carbonyl group showed that the hydrogen bonding of **3**, having a more electron-donating group on the carbonyl group, was much stronger than that of **5**. This means that the intramolecular hydrogen bonding depends on the basicity of the carbonyl group.

2.4. Thermodynamic parameter of intramolecular hydrogen bonding

According to Eq. 1 (van't Hoff analysis), it is possible to determine the thermodynamic parameters (ΔH and ΔS) of a hydrogen bonding by ^{1}H NMR chemical shifts.[9]

$$\ln K = -\frac{\Delta H}{R}\frac{1}{T} + \frac{\Delta S}{R},\quad K = \frac{\delta_{obs} - \delta_n}{\delta_b - \delta_{obs}}$$

δ_{obs} : observed chemical shift

δ_n : chemical shift of non − hydrogen bond state

δ_b : chemical shift of full − hydrogen bond state

(1)

Although the value of δ_b was not directly obtained, the value of δ_n was given by the phenolic proton chemical shifts of the corresponding *para*-substituted phenols under the same conditions. Since **1d**,**e**,**f** had roughly the same-size substitution at the *para*-position, we estimated that the entropy loss (ΔS) of the intramolecular hydrogen bonding of **1d**,**e**,**f** was equal. Calculation of unknown constants ΔH and δ_b to let ΔS values of **1d**,**e**,**f** become a same value gave δ_b= 10.15 ppm. Figure 4 shows the van't Hoff plot of these compounds **1a**–**f** using δ_b=10.15 ppm.

The van't Hoff plot gave enthalpy and entropy values of the intramolecular 9-membered hydrogen bonding of **1a**–**f** as shown in Table 4. The thermodynamic parameters of

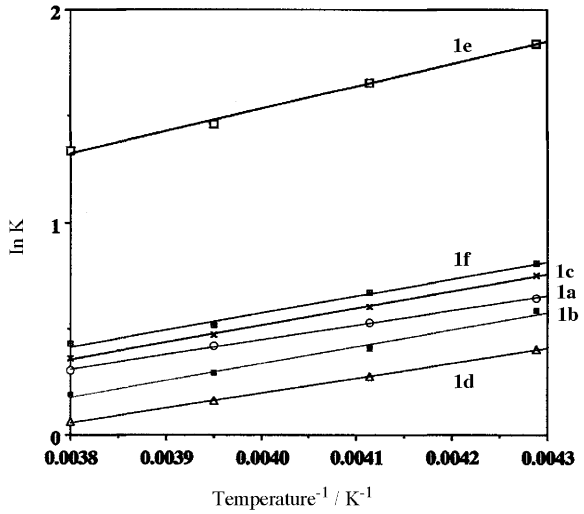


Figure 4. van't Hoff plot in ranging from 233 to 263 K.

Table 4. Thermodynamic parameters of the intramolecular hydrogen bonding of **1a**–**f** and **2a**–**e**

Compound	Hammett constant (σ^-)	ΔH (kcal mol^{-1})	ΔS (e.u.)
1a (*ortho*-CH_3)	—	−1.374	−4.61
1b (H)	0	−1.578	−5.64
1c (*para*-Ph)	0.20	−1.584	−5.31
1d (*para*-CH_3)	−0.17	−1.595	−5.17
1e (*para*-CN)	0.96	−2.079	−5.27
1f (*para*-Br)	0.23	−1.374	−5.24
2a (*para*-OCH_3)	−0.27	−1.117	−3.54
2b (H)	0	−1.363	−3.67
2c (*para*-Ph)	0.20	−1.372	−3.50
2d (*para*-CH_3)	−0.17	−1.226	−3.48
2e (*para*-CN)	0.96	−1.925	−3.52

compounds **2a**–**e** were also obtained by the same method using the value of δ_b=10.15 ppm. From these results, the enthalpy of the hydrogen bonding was related to electron-withdrawing ability of the substituents on the phenol. Since the acidity of the phenol group was dependent on the electron-withdrawing ability of the substituent, the gain of enthalpy of the intramolecular hydrogen bonding increased with increase of the electron-withdrawing ability of the substituent, in other words, with increase of the Hammett constant (σ^-).

Table 4 also shows that the entropy loss of the intramolecular hydrogen bonding of **1b** having a non-substituent on the phenol group was the largest value, and that of **1a** having a methyl group at the *ortho*-position was the smallest value, and those of other compounds **1c**–**f** having a substituent at the *para*-position were roughly the same value. These results suggested that the entropy loss of the hydrogen bonding was dependent on the rotation freedom of the phenol group. Since the *ortho*-methyl group of **1a** strongly prevented the rotation of the phenol group when it was the non-hydrogen bonding state **A**, the entropy loss caused by the hydrogen bonding was smaller. On the other hand, the rotation of **1b** was less prevented, and the entropy loss was larger. The intramolecular hydrogen bonding of 2-(1-methoxycarbonyl-2-phenyl)methylphenol derivatives **2a**–**e** showed similar results as shown in Table 4. The intramolecular hydrogen bonding of **1** was enthalpically favored relative to that of **2**, because the naphthyl group can act as a more electron-donating group to get more basicity of the carbonyl group. The hydrogen bonding of **1** was entropically disfavored relative to that of **2**, because the *peri*-hydrogen gave a more rigid intramolecular hydrogen bonding structure.

Figure 5 shows that the Hammett constant versus Gibbs free energy ΔG obtained by ΔH and ΔS at 253 K is a good linear relationship. The linear free energy relationship clarified that the assumption (δ_b=10.15 ppm) was correct.

3. Conclusion

It was found that the phenol derivatives **1**–**3**, **5** having two chromophores formed a novel intramolecular 9-membered hydrogen bonding between aromatic carbonyl and phenolic hydroxyl groups in $CDCl_3$ solution. The chemical shifts of the phenolic protons with variable temperature could give

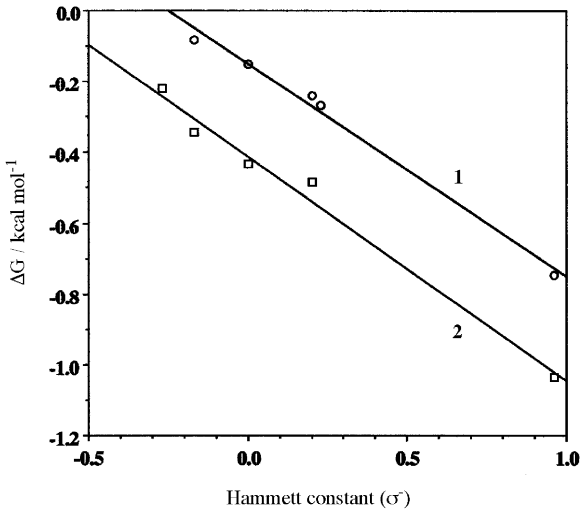


Figure 5. Hammett constant versus ΔG at 253 K.

the thermodynamic parameters of the intramolecular hydrogen bonding. These thermodynamic parameters revealed that the intramolecular hydrogen bonding depended on the acidity of the phenols and the basicity of the carbonyl groups. They also indicated that the intramolecular hydrogen bonding of **1** having a naphthalene ring was enthalpically favored, but entropically disfavored relative to that of **2**. In addition, the intramolecular hydrogen bonding was entropically dependent on the position of the substituent on the phenol group.

4. Experimental

4.1. General

Melting points were taken on a hot stage and were uncorrected. ^{1}H NMR and variable temperature ^{1}H NMR spectra were recorded on Varian Mercury (300 MHz) spectrometer and for solutions in $CDCl_3$ containing tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on a Varian Mercury (75 MHz) spectrometer in $CDCl_3$ with chloroform (77.05 ppm) as an internal standard. IR spectra were obtained on JASCO FT/IR-230, mass spectra on a JMS-AX 500 mass spectrometer. Elemental analyses were carried out on a Yanaco MT-3 elemental analyzer. The light source was Eiko-sha PIH 300 W high-pressure mercury arc. High resolution mass spectra were obtained on a JEOL MStation (MS700).

4.2. Materials

$CDCl_3$ and $CHCl_3$ were freshly distilled before use from CaH_2 under N_2, and were stored in the presence of molecular sieves 4 Å. 1-Bromo-2-methylbenzene, NBS, $TiCl_4$, $ClCON(CH_3)_2$, CuCN, 10% Pd/C, and DIBAL were purchased.

4.3. General procedure for the photo-Claisen rearrangement

A solution of 2-(1-methoxycarbonylnaphthyl)methyl aryl ethers (10 mM) in benzene was purged with argon for 15 min and irradiation of the solution through Pyrex filter with a 300 W high-pressure mercury lamp (>280 nm) afforded *ortho*-rearranged products as main products accompanying 1-methoxycarbonyl-2-methylnaphthalene, 1,2-bis(1-methoxycarbonyl-2-naphthyl)ethane, and phenols.[8] The progress of the reaction was monitored by GLC (Silicone OV-17 5%), HPLC, and TLC. These products were isolated by column chromatography on silica gel using hexane and ethyl acetate as eluents.

4.3.1. 2-Methyl-6-[(1-methoxycarbonyl-2-naphthyl)-methyl]phenol (1a). Colorless crystals; mp 111 °C; ^{1}H NMR ($CDCl_3$): δ 7.87 (d, 1H, J=8.1 Hz), 7.81–7.75 (m, 2H), 7.56–7.45 (m, 2H), 7.36 (d, 1H, J=8.5 Hz), 7.30 (s, 1H), 7.16 (d, 1H, J=6.7 Hz), 7.05 (d, 1H, J=6.9 Hz), 6.82 (t, 1H), 4.14 (s, 3H), 4.08 (s, 2H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 171.8, 153.3, 136.2, 131.9, 130.8, 129.9, 129.8, 129.0, 128.2, 128.1, 127.2, 127.1, 126.0, 125.3, 124.8, 124.3, 119.4, 53.1, 35.3, 16.3; IR (KBr) 3353, 1698 cm^{-1}; Ms m/z 306 (M^+). Anal. Calcd for $C_{20}H_{18}O_3$: C 78.41, H 5.92, O 15.67. Found: C 78.51, H 5.92, O 15.39.

4.3.2. 2-(1-Methoxycarbonyl-2-naphthyl)methylphenol (1b). Colorless crystals; mp 91 °C; ^{1}H NMR ($CDCl_3$): δ 7.87 (d, 1H, J=8.2 Hz), 7.79 (d, 2H, J=8.4 Hz), 7.57–7.46 (m, 2H), 7.35 (d, 1H, J=8.8 Hz), 7.29 (s, 1H), 7.09–7.13 (m, 2H), 6.89 (t, 1H), 6.81 (d, 1H, J=8.2 Hz), 4.13 (s, 3H), 4.11 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 171.7, 155.0, 136.1, 132.0, 131.4, 130.8, 129.8, 128.6, 128.5, 128.2, 127.3, 127.2, 126.1, 125.0, 120.1, 116.6, 53.1, 35.1; IR (KBr) 3385, 1726 cm^{-1}; Ms m/z 292 (M^+). Anal. Calcd for $C_{18}H_{16}O_3$: C 78.07, H 5.52, O 16.41. Found: C 78.07, H 5.36, O 16.57.

4.3.3. 4-Phenyl-2-[(1-methoxycarbonyl-2-naphthyl)-methyl]phenol (1c). Colorless crystals; mp 146–147 °C; ^{1}H NMR ($CDCl_3$): δ 7.88 (d, 1H, J=8.4 Hz), 7.80 (d, 2H, J=8.4 Hz), 7.61–7.25 (m, 12H), 6.88 (d, 1H, J=8.2 Hz), 4.17 (s, 2H), 4.15 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 171.8, 154.8, 140.8, 136.0, 132.0, 130.9, 130.1, 129.9, 128.7, 128.4, 128.2, 127.3, 127.3, 127.2, 126.7, 126.5, 126.1, 125.2, 124.9, 117.1, 53.2, 35.5; IR (KBr) 3427, 1692 cm^{-1}; Ms m/z 368 (M^+). Anal. Calcd for $C_{25}H_{20}O_3$: C 81.50, H 5.47, O 13.03. Found: C 81.39, H 5.43, O 13.18.

4.3.4. 4-Methyl-2-[(1-methoxycarbonyl-2-naphthyl)-methyl]phenol (1d). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.86 (d, 1H, J=8.6 Hz), 7.79 (d, 2H, J=8.2 Hz), 7.57–7.45 (m, 2H), 7.36 (d, 1H, J=8.6 Hz), 7.01 (s, 1H), 6.95 (d, 1H, J=8.1 Hz), 6.91 (s, 1H), 6.72 (d, 1H, J=8.1 Hz), 4.12 (s, 3H), 4.08 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 171.5, 152.6, 136.2, 131.9, 131.8, 130.6, 129.8, 129.1, 128.9, 128.6, 128.1, 127.3, 127.2, 126.0, 124.9, 124.8, 116.3, 53.0, 35.0, 20.6; IR (neat) 3423, 1719 cm^{-1}; Ms m/z 306 (M^+). Anal. Calcd for $C_{20}H_{18}O_3$: C 78.41, H 5.92, O 15.67. Found: C 78.60, H 5.93, O 15.47.

4.3.5. 4-Cyano-2-[(1-methoxycarbonyl-2-naphthyl)-methyl]phenol (1e). Colorless crystals; mp 91 °C; ^{1}H NMR ($CDCl_3$): δ 8.81 (s, 1H), 7.92–7.81 (m, 3H), 7.65–7.44 (m, 4H), 7.29 (d, 1H, J=8.5 Hz), 6.85 (d, 1H, J=8.5 Hz), 4.18 (s, 3H), 4.10 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 163.1, 159.7, 141.5, 138.7, 135.6, 135.1, 132.4, 131.7,

128.5, 128.3, 127.9, 127.1, 126.7, 126.4, 125.2, 118.2, 105.8, 53.7, 35.3; IR (KBr) 3244, 2239, 1715 cm^{-1}; Ms *m/z* 317 (M^+). Anal. Calcd for $C_{20}H_{15}NO_3$: C 75.70, H 4.76, N 4.41, O 15.12. Found: C 75.68, H 4.93, N 4.40, O 14.99.

4.3.6. 4-Bromo-2-[(1-methoxycarbonyl-2-naphthyl)-methyl]phenol (1f). Colorless oil; ^1H NMR ($CDCl_3$): δ 7.89–7.79 (m, 3H), 7.58–7.41 (m, 3H), 7.41 (s, 1H), 7.43 (d, 1H, $J=8.6$ Hz), 7.24 (d, 1H, $J=8.4$ Hz), 6.68 (d, 1H, $J=8.4$ Hz), 4.14 (s, 3H), 4.05 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 171.9, 154.4, 135.4, 133.6, 132.1, 131.3, 131.1, 129.8, 128.4, 128.2, 127.4, 127.1, 126.3, 124.9, 118.5, 111.7, 53.2, 35.0; IR (neat) 3371, 1700 cm^{-1}; Ms *m/z* 372 (M^+). Anal. Calcd for $C_{19}H_{15}O_3Br$: C 66.88, H 4.43. Found: C 67.04, H 4.31.

4.4. General procedure for the preparation of 2

1-Bromo-2-methylbenzene was added to a solution of NBS in CCl_4 containing BPO, and the mixture was refluxed for 5 h. The mixture is filtrated, concentrated, and recrystallized to give 1-bromo-2-bromomethylbenzene (94%). 1-Bromo-2-bromomethylbenzene was etherified by the 4-substituted phenols with K_2CO_3. Then the ethers in CH_2Cl_2 were added by $TiCl_4$ under argon atmosphere. The mixture was stirred at room temperature, and quenched by water. The products were extracted, dried (Na_2SO_4), concentrated, and purified by column chromatography on silica gel (eluent: hexane and ethyl acetate) to give *ortho*-rearranged phenols. The amount of $TiCl_4$, reaction time, and product yields were dependent on the substituent at 4-position. In the case of **1e** having an electron-withdrawing group (cyano group), the CH_2Cl_2 solution (200 ml) containing 1-bromo-2-[(4-cyanophenoxy)methyl]benzene (4.5 g, 15.7 mmol) and 5 equiv of $TiCl_4$ (8.6 ml, 78.5 mmol) was stirred for 24 h at room temperature under argon atmosphere, quenched by water, and purified to give **1e** in very low yield (2%). On the other hand, the CH_2Cl_2 solution (50 ml) containing the other ethers (10 mmol) and 1 equiv of $TiCl_4$ (10 mmol) was stirred for 3 h at room temperature, quenched by water, and purified to give **1a–d** in moderate yields (ca. 20–40%).

These phenols (4 mmol) were protected by benzyl chloride (5 mmol) in the presence of K_2CO_3 (4 g) to give the ethers (>90%). *n*-BuLi (15 wt% in *n*-hexane solution, 14.6 ml, 22.8 mmol) was added drop-wise to the ethers (19 mmol) in THF (100 ml) at −60 °C. The mixture was stirred for 2 h at −60 °C under argon atmosphere, and $ClCO_2CH_3$ (1.8 ml, 23 mmol) in THF (15 ml) was added. Then the mixture was stirred for 1 h at room temperature, and 3 N HCl was added. The product was extracted with ether, washed with H_2O, dried (Na_2SO_4), and concentrated. Purification by column chromatography on silica gel (eluent: hexane and ethyl acetate) gave the corresponding ester derivatives in moderate yields (ca. 60%). Then, the esters (3.5 mmol) in ethanol (150 ml) were stirred for 8 h with 10% Pd/C (140 mg) under hydrogen atmosphere to afford **2a–e**, respectively (90%).

4.4.1. 4-Methoxy-2-[(1-methoxycarbonyl-2-phenyl)-methyl]phenol (2a). Colorless oil; ^1H NMR ($CDCl_3$): δ 7.85 (d, 1H, $J=7.9$ Hz), 7.46–7.36 (m, 3H), 7.28–7.23 (m, 1H), 6.80–6.77 (m, 2H), 6.71–6.67 (m, 1H), 4.22 (s, 2H), 3.95 (s, 3H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.1, 153.0, 148.7, 141.2, 132.5, 131.5, 130.4, 128.5, 127.0, 126.3, 117.0, 116.8, 112.8, 55.8, 52.9, 34.0; IR (neat) 3384, 1719 cm^{-1}; Ms *m/z* 272 (M^+); HRMS (EI) Calcd for $C_{16}H_{16}O_4$: 272.1049. Found: 272.1061.

4.4.2. 2-(1-Methoxycarbonyl-2-phenyl)methylphenol (2b). Colorless oil; ^1H NMR ($CDCl_3$): δ 7.93 (s, 1H), 7.83 (d, 1H, $J=7.4$ Hz), 7.45–7.36 (m, 2H), 7.28–7.22 (m, 2H), 7.17–7.11 (m, 1H), 6.89–6.83 (m, 2H), 4.24 (s, 2H), 3.98 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.5, 154.9, 141.3, 132.5, 131.5, 131.0, 128.4, 128.2, 126.3, 126.0, 119.9, 116.6, 53.0, 33.8; IR (neat) 3368, 1698 cm^{-1}; Ms *m/z* 242 (M^+). Anal. Calcd for $C_{15}H_{14}O_3$: C 74.36, H 5.83. Found: C 74.70, H 5.84.

4.4.3. 4-Phenyl-2-[(1-methoxycarbonyl-2-phenyl)-methyl]phenol (2c). Colorless crystals; mp 103 °C; ^1H NMR ($CDCl_3$): δ 8.14 (s, 1H), 7.85 (d, 1H, $J=7.7$ Hz), 7.61–7.24 (m, 10H), 6.94 (d, 1H, $J=8.2$ Hz), 4.32 (s, 2H), 4.00 (s, 3H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.1, 152.4, 141.1, 133.0, 132.6, 130.3, 129.8, 128.6, 128.4, 127.0, 126.7, 126.5, 126.4, 126.2, 117.0, 53.2, 34.1; IR (KBr) 3324, 1696 cm^{-1}; Ms *m/z* 318 (M^+). Anal. Calcd for $C_{21}H_{18}O_3$: C 79.22, H 5.70. Found: C 78.92, H 5.54.

4.4.4. 4-Methyl-2-[(1-methoxycarbonyl-2-phenyl)-methyl]phenol (2d). Colorless oil; ^1H NMR ($CDCl_3$): δ 7.83 (d, 1H, $J=7.7$ Hz), 7.71 (s, 1H), 7.46–7.27 (m, 2H), 7.28–7.22 (m, 1H), 7.06 (s, 1H), 6.94 (d, 1H, $J=8.2$ Hz), 6.74 (d, 1H, $J=8.2$ Hz), 4.21 (s, 2H), 3.97 (s, 3H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.3, 152.6, 141.4, 132.4, 131.5, 131.4, 130.2, 128.9, 128.7, 128.4, 126.2, 125.7, 116.4, 53.0, 33.8, 20.6; IR (neat) 3371, 1700 cm^{-1}; Ms *m/z* 256 (M^+); HRMS (EI) Calcd for $C_{16}H_{16}O_3$: 256.1099. Found: 256.1074.

4.4.5. 4-Cyano-2-[(1-methoxycarbonyl-2-phenyl)-methyl]phenol (2e). Colorless oil; ^1H NMR ($CDCl_3$): δ 9.20 (s, 1H), 7.85 (d, 1H, $J=7.5$ Hz), 7.60 (s, 1H), 7.51–7.42 (m, 2H), 7.36–7.26 (m, 2H), 6.88 (d, 1H, $J=8.4$ Hz), 4.21 (s, 2H), 4.01 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 171.0, 159.3, 140.0, 135.1, 133.6, 132.9, 132.7, 131.5, 130.4, 128.3, 127.2, 126.9, 119.5, 117.8, 53.4, 33.5; IR (neat) 3315, 2225, 1718 cm^{-1}; Ms *m/z* 267 (M^+); HRMS (EI) Calcd for $C_{16}H_{13}O_3N$: 267.0895. Found: 267.0858.

4.5. General procedure for the preparation of 3–5

The amide derivative **3** was synthesized by the amidation of the corresponding bromo derivative according to a similar method of esterification (by $ClCON(CH_3)_2$, 30% yield).

The cyano derivative **4** was also obtained by the cyanation according to the method described in the literature, followed by deprotection. A mixture of the bromo derivatives (1.1 mmol), CuCN (5.5 mmol), and *N*-methyl-2-pyrrolidone (10 ml) was heated at 180 °C for 20 min under argon. After cooling to room temperature, 10% aqueous ammonia solution (50 ml) and dichloromethane (50 ml) were added to the solution and filtered. The filtrate was combined with Et_2O, washed with H_2O, and dried (Na_2SO_4). After removal of *N*-methyl-2-pyrrolidone in vacuo, column chromatography on silica gel (eluent: hexane and ethyl acetate)

afforded the cyano derivative (95%), and then similarly deprotection by Pd/C and H_2 gave **4** (78%).

DIBAL solution (0.2 ml, 0.2 mmol) was added drop-wise to the benzene solution of cyano derivative **4** (40 mg, 0.18 mmol) under argon atmosphere at 0 °C. The mixture was stirred for 1 h at 0 °C, and quenched by 5% H_2SO_4. The product was extracted, washed with H_2O, dried (Na_2SO_4), and concentrated. Purification by column chromatography on silica gel (eluent: hexane and ethyl acetate) gave the aldehyde derivative **5** (95%).

4.5.1. 4-Methyl-2-[(2-*N*,*N*-dimethylcarbamoylphenyl)-methyl]phenol (3). Colorless crystals; mp 112 °C; ^{1}H NMR ($CDCl_3$) δ 10.18 (s, 1H), 7.80 (d, 1H, J=7.7 Hz), 7.57–7.52 (m, 1H), 7.44–7.29 (m, 2H), 6.93–6.91 (m, 2H), 6.73 (d, 1H, J=8.6 Hz), 6.20 (s, 1H), 4.33 (s, 2H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 194.7, 151.4, 142.2, 134.1, 133.5, 133.4, 131.6, 131.1, 129.7, 128.4, 126.8, 125.7, 116.0, 32.3, 20.6; IR (KBr) 3057, 1663 cm^{-1}; MS *m*/*z* 226 (M^+); HRMS (EI) Calcd for $C_{17}H_{19}O_2N$: 269.1416. Found: 269.1440.

4.5.2. 4-Methyl-2-[(2-cyanophenyl)methyl]phenol (4). Colorless crystals; mp 128–129 °C; ^{1}H NMR (300 MHz) δ 7.65–7.62 (m, 1H), 7.49–7.44 (m, 1H), 7.30–7.25 (m, 2H), 6.95–6.92 (m, 2H), 6.67 (d, 1H, J=7.7 Hz), 4.67 (s, 1H), 4.18 (s, 2H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 151.1, 144.6, 132.7, 132.6, 131.6, 130.3, 129.7, 128.5, 126.4, 125.0, 118.3, 115.4, 112.5, 34.4, 20.6; IR (KBr) 3398, 2228 cm^{-1}; MS *m*/*z* 223 (M^+); HRMS (EI) Calcd for $C_{15}H_{13}ON$: 223.0997. Found: 223.0925.

4.5.3. 4-Methyl-2-[(2-formylphenyl)methyl]phenol (5). Colorless crystals; mp 38 °C; ^{1}H NMR (300 MHz) δ 8.82 (s, 1H), 7.34–7.15 (m, 4H), 7.01 (s, 1H), 6.92 (d, 1H, J=8.1 Hz), 6.72 (d, 1H, J=8.1 Hz), 3.87 (s, 2H), 3.16 (s, 3H), 2.92 (s, 3H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.6, 153.3, 138.3, 133.8, 131.6, 130.7, 129.6, 128.6, 128.1, 126.2, 125.6, 125.7, 117.1, 39.5, 35.2, 34.5, 20.5; IR (KBr) 3316, 1622 cm^{-1}; MS *m*/*z* 269 (M^+); HRMS (EI) Calcd for $C_{15}H_{14}O_2$: 226.0994. Found: 226.0929.

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Supplementary data

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