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Stereoselective Synthesis of (*Z*)-5-(Trideca-4-enyl)resorcinol and Gibbilimbols A—D

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(*Z*)-5-(Trideca-4-enyl)resorcinol (**1**) and gibbilimbols A—D (**2—5**) were synthesized in 47%—60% yields over 6 steps from commercially available starting materials. The Wittig reaction of various alkyl phosphonium bromides with appropriate aldehydes in the presence of potassium *tert*-butoxide (*t*-BuOK) in anhydrous THF solution at room temperature served as the key step, and the result showed that only (*Z*)-configuration olefins were formed by this procedure. The synthesis of the (*Z*)-5-(trideca-4-enyl)resorcinol (**1**) was reported for the first time.

Keywords (Z)-5-(trideca-4-enyl)resorcinol, gibbilimbol, synthesis, Wittig reaction

Introduction

(*Z*)-5-(Trideca-4-enyl)resorcinol (**1**) was recently isolated from *Lithraea molleoides* and showed strong paralyzing effects on the nematode *Caenorhabditis elegans* at concentrations between 6 and 50 μg/mL *in vitro*.[1] Several similar alkenylphenols were also isolated from the leaves of *Piper gibbilimbum* which identified by spectroscopic methods as (*E*)-4-(4-decenyl)phenol (gibbilimbol A, **2**), (*E*)-4-(3-decenyl)phenol (gibbilimbol B, **3**), (*E*)-4-(4-octenyl)phenol (gibbilimbol C, **4**), (*E*)-4-(3-octenyl)phenol (gibbilimbol D, **5**), respectively (Figure 1). They were found to exhibit cytotoxic activity against KB nasopharyngal carcinoma cells (ED_{50} 2—8 μg/mL) and antibacterial activity against *Staphylococcus epidermidis* and *Bacillus cereus* (MIC 2—4 μg/mL).[2]

The occurrence of the natural alkenylphenols in limited amount in rather inaccessible plant species prompted our interest to search a good synthetic method for them. Perusal of numerous reviews on the chemistry of the alkenylphenols reveals no report of synthesis of (*Z*)-5-(trideca-4-enyl)resorcinol (**1**) and only two general strategies for the assembly of the gibbilimbol skeleton. One approach made use of a coupling of phenolic part with an alkyne, and then reducing the triple bond of the resulting alkynylphenols,[3] the other was a copper-catalyzed coupling reaction of 4-methoxyphenylmagnesium bromide with various unsaturated alkyl bromides.[4] However, both of them involved the expensive starting materials or reagents and rigorous experimental conditions.

Here we report a convenient, high yield and general synthesis of these alkenylphenols, in which a Wittig reaction, affording the (*Z*)-configuration alkenylphenols exclusively, served as the key step. Isomerization of the (*Z*)-intermediates gave gibbilimbols A—D (**2—5**).

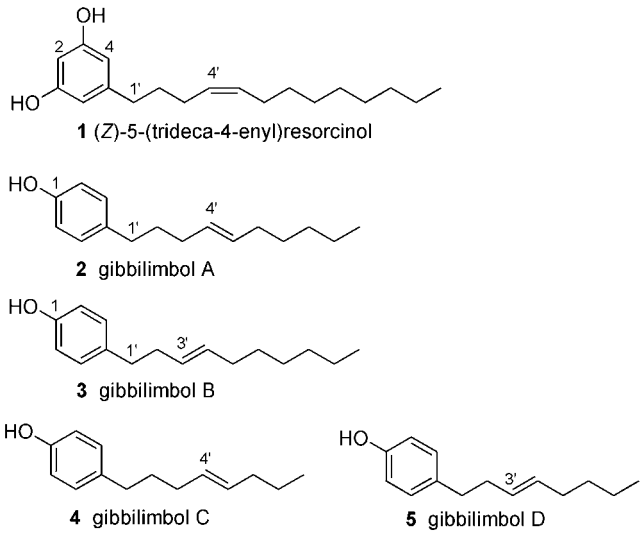

Figure 1 Structures of (*Z*)-5-(trideca-4-enyl)resorcinol (**1**) and gibbilimbols A—D (**2—5**).

Results and discussion

As shown in Scheme 1, 3,5-dihydroxybenzaldehyde (**6**), methyl (4-hydroxyphenyl)acetate (**9**) and 4-hydroxybenzaldehyde (**11**) were chosen as the starting materials. Treatment of **6** with benzyl bromide in the presence of K_2CO_3 in acetone gave the protected aldehyde. This aldehyde was treated with methoxymethyl phosphonium ylide ($Ph_3P{=}CHOMe$)[5] followed by hydrolysis of the resulting vinyl ether in the presence of

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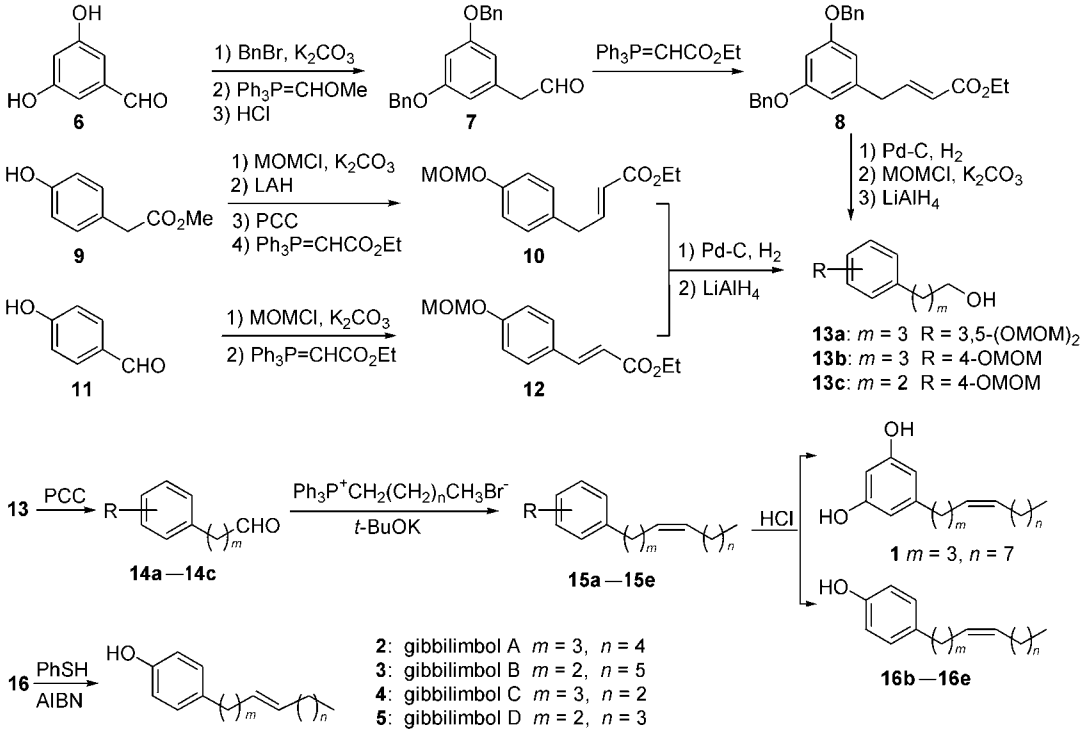
Scheme 1 Synthesis of (*Z*)-5-(trideca-4-enyl)resorcinol (**1**) and gibbilimbols A—D (**2—5**)



hydrochloric acid to afford compound **7**. Wittig reaction of **7** with ethyl (triphenylphosphanylidiene)acetate ($Ph_3P{=}CHCO_2Et$) afforded the α,β-unsaturated ester **8**. Compound **8** was converted to the saturated ester by hydrogenation in the hydrogen atmosphere (Pd/C, 10%). The produced phenol hydroxyls of **8** were then protected by methoxymethyl groups (MOM) by treatment with chloromethyl methyl ether (MOMCl). Subsequent reduction with lithium aluminum hydride ($LiAlH_4$) provided the key intermediate **13a** in over 60% yield. On the other hand, protection of the phenolic group of **9** with MOM, reduction of ester with $LiAlH_4$, and oxidation of the resulting alcohol by pyridinium chlorochromate (PCC) provided the aldehyde, which then reacted with $Ph_3P{=}CHCO_2Et$ to give ester **10**. Compound **10** was reduced to provide the second key intermediate **13b** in 63% yield. Compound **11** underwent a similar reaction sequence as the above description to provide the third key intermediate **13c** in 81% yield.

Alcohols **13a—13c** were oxidized to the corresponding aldehydes **14a—14c** with PCC in dichloromethane at room temperature in high yields. Treatment of aldehydes **14a—14c** with the appropriate alkyl phosphonium bromide[5] in the presence of *t*-BuOK in anhydrous THF at room temperature provided alkenes **15a—15e** in high yields (>90%). In all cases, (*Z*)- configuration was readily diagnosed by examination of NMR, IR spectra and comparison of their spectroscopic properties with those of the analogues reported in the literature.[1,6] Compounds **15a—15e** were refluxed in conc. HCl (5 drops) and methanol (10 mL) for 10 min to provide the corresponding alkenylphenol **1** [(*Z*)-5-(trideca-4-enyl)resorcinol] and **16b—16e** quantitatively. As expected, the double bond formed by Wittig reaction has a (*Z*)-configuration, and this was retained during the deprotection procedure. Examination of the ^{13}C NMR spectra of **1** and **16b—16e** indicated no stereoisomers in each case, and the stereoselectivity of the construction of double bond was over 95% by this procedure. (*Z*)-Alkenylphenols **16b—16e** could be converted to gibbilimbols A—D (**2—5**) by the treatment with thiophenol in refluxing benzene in the presence of azoisobutyronitrile (AIBN).[7]

Conclusion

In summary, we present an efficient and rapid route to the stereoselective synthesis of the natural product (*Z*)-5-(trideca-4-enyl)resorcinol (**1**) and gibbilimbols A—D (**2—5**). The Wittig reaction of various alkyl phosphonium bromides with appropriate aldehydes was an efficient and readily scalable approach to a variety of biologically active phenols carrying with a long hydrocarbon chain. The investigation of their biological activity is in progress.

Experimental

General procedure

IR spectra were recorded on a Nicolet NEXUS 670 FT-IR and a Nicolet AVATAR 360 FT-IR spectrometers. The ^1H and ^{13}C NMR data were recorded on a Brucker AM-400 MHz, a Mercury Plus-300 MHz and an Avance-200 MHz spectrometers. Mass spectra were

recorded on a ZAB−HS spectrometer. HRMS data were obtained on an APEXII47e spectrometer. Flash column chromatography was generally performed on silica gel (200—300 mesh) eluting with petroleum ether ethyl acetate and TLC inspections on silica gel GF_{254} plates with petroleum ether/ethyl acetate, if not noted especially below.

The procedure for the preparation of (3,5-bisbenzyloxyphenyl)acetaldehyde (7)

Treatment of 3,5-dihydroxy benzaldehyde **6** (10 mmol) with BnBr (22 mmol) in the presence of K_2CO_3 gave the corresponding aldehyde, which reacted with Ph_3P=CHOMe (10 mmol) followed by hydrolysis of the resulting vinyl ether in the presence of HCl to afford **7** (7.4 mmol) as colorless oil in 74% yield of 3 steps. ^{1}H NMR (CCl_4, 60 MHz) δ: 3.57 (d, J=3.0 Hz, 2H, 2-CH_2), 5.12 (s, 4H, $PhCH_2O$), 6.45—6.62 (m, 3H, ArH), 7.40—7.52 (m, 10H, PhH), 9.66 (t, J=3.0 Hz, 1H, CHO); IR (KBr) v: 3420, 1648, 1069, 740, 587 cm^{-1}; MS (70 eV) m/z (%): 332 (M^+, 1), 181 (3), 149 (11), 91 (100), 65 (11).

The procedure for the preparation of ethyl (*E*)-4-(3,5-bisbenzyloxyphenyl)but-2-enoate (8)

A solution of **7** (7 mmol) in benzene (5 mL) was added dropwise to a well-stirred solution of Ph_3P=$CHCO_2Et$ (8.4 mmol) in benzene (50 mL). The reaction mixture was refluxed for 4—5 h and then the solvent was evaporated *in vacuo*. Flash chromatography of the residue over silica gel (petroleum ether/ethyl acetate, 8∶1) afforded the (*E*)-α,β-unsaturated ester **8** (6.9 mmol) as colorless oil in 99% yield. ^{1}H NMR (CCl_4, 60 MHz) δ: 1.30 (t, J=7.0 Hz, 3H, CH_3), 3.25 (d, J=6.8 Hz, 2H, 4-CH_2), 4.25 (q, J=7.0 Hz, 2H, OCH_2), 5.12 (s, 4H, $PhCH_2O$), 5.80 (d, J=16.0 Hz, 1H, 2-CH=), 6.40—6.60 (m, 3H, ArH), 6.85—7.16 (m, 1H, 3-CH=), 7.38—7.50 (m, 10H, PhH); IR (KBr) v: 3419, 1715, 1155, 1006 cm^{-1}; MS (70 eV) m/z (%): 402 (M^+, 2), 181 (5), 91 (100), 75 (13), 45 (26); HRMS (EI) calcd for $C_{26}H_{26}O_4$ (M^+): 402.1826, found 402.1835.

The procedure for the preparation of ethyl (*E*)-4-(4-methoxymethoxyphenyl)but-2-enoate (10)

Treatment of methyl (4-hydroxyphenyl)acetate (**9**, 10 mmol) with MOMCl (10.5 mmol) in the presence of K_2CO_3 gave the corresponding ester, which was followed by reduction with LAH (10 mmol), and then oxidation with PCC (12 mmol) to form an aldehyde. The resulting aldehyde reacted with Ph_3P=$CHCO_2Et$ (9 mmol) to give ester **10** (7 mmol) as colorless oil in 70% yield of 4 steps. ^{1}H NMR (CCl_4, 60 MHz) δ: 1.30 (t, J=6.0 Hz, 3H, CH_3), 3.20 (d, J=15.0 Hz, 2H, 4-CH_2), 3.46 (s, 3H, CH_3O), 4.20 (q, J=6.0 Hz, 2H, OCH_2), 5.15 (s, 2H, OCH_2O), 5.76 (d, J=15.0 Hz, 1H, 2-CH=), 6.16—6.35 (m, 1H, 3-CH=), 6.45—6.84 (m, 4H, ArH); IR (KBr) v: 2981, 1718, 1510, 1155, 1005, 923, 831 cm^{-1}; MS (70 eV) m/z (%): 250 (M^+, 7), 189 (4), 173 (5), 131 (6), 45 (100); HRMS (ESI) calcd for $C_{14}H_{19}O_4$ $[M+H]^+$: 251.1278, found 251.1275.

The procedure for the preparation of ethyl (*E*)-3-(4-methoxymethoxyphenyl)acrylate (12)

Treatment of 4-hydroxybenzaldehyde (**11**, 10 mmol) with MOMCl (10.5 mmol) in the presence of K_2CO_3 gave the corresponding aldehyde, which was followed by reaction with Ph_3P=$CHCO_2Et$ (11 mmol) to give ester **12** (9 mmol) as colorless oil in 91% yield of 2 steps. ^{1}H NMR (CCl_4, 60 MHz) δ: 1.30 (t, J=8.0 Hz, 3H, CH_3), 3.40 (s, 3H, CH_3O), 4.10 (q, J=8.0 Hz, 2H, OCH_2), 5.06 (s, 2H, OCH_2O), 5.70 (d, J=16.0 Hz, 1H, 2-CH=), 6.89 (d, J=8.4 Hz, 2H, 2,6-ArH), 6.96 (d, J=8.4 Hz, 2H, 3,5-ArH), 7.04 (d, J=16.0 Hz, 1H, 3-CH=); IR (KBr) v: 2929, 1717, 1510, 1157, 1008 cm^{-1}; MS (70 eV) m/z (%): 236 (M^+, 8), 175 (4), 131 (12), 77 (6), 45 (100); HRMS (ESI) calcd for $C_{13}H_{20}NO_4$ $[M+NH_4]^+$: 254.1387, found 254.1392.

General procedure for the preparation of aldehydes 13a—13c

The ester **8** (6.5 mmol) was hydrogenated under hydrogen atmosphere (10% Pd–C, 10 mg) to give saturated ester. Treatment of this saturated ester with MOMCl (6.5 mmol) in the presence of K_2CO_3 and then reduced by LAH (6 mmol) afforded alcohol **13a** (5.3 mmol) in 82% yield of 3 steps. On the other hand, the individual ester **10** (6.5 mmol) or **12** (6.5 mmol) was hydrogenated as above to give the corresponding saturated ester, which was reduced by LAH (6.5 mmol) to afford the alcohol **13b** (5.8 mmol) or **13c** (5.8 mmol) in 90% yield of 2 steps respectively.

4-(3,5-Bismethoxymethoxyphenyl)butan-1-ol (13a): Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.57—1.73 (m, 4H, 2,3-CH_2), 2.57 (t, J=7.5 Hz, 2H, 4-CH_2), 3.46 (s, 6H, CH_3O), 3.63 (t, J=6.3 Hz, 2H, 1-CH_2), 5.13 (s, 4H, OCH_2O), 6.53—6.56 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz,) δ: 27.2, 32.3, 35.8, 56.0, 62.6, 94.4, 102.2, 109.8, 144.9, 158.2; IR (KBr) v: 3430, 2936, 1606, 1150, 1028, 923 cm^{-1}; MS (70 eV) m/z (%): 270 (M^+, 7), 193 (3), 177 (2), 107(2), 45 (100); HRMS (EI) calcd for $C_{14}H_{22}O_5$ (M^+): 270.1462, found 270.1464.

4-(4-Methoxymethoxyphenyl)butan-1-ol (13b): Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.50—1.80 (m, 4H, 2,3-CH_2), 2.55—2.65 (t, J=7.2 Hz, 2H, 4-CH_2), 3.45 (s, 3H, CH_3O), 3.58—3.62 (m, 2H, 1-CH_2), 5.12 (s, 2H, OCH_2O), 6.94 (d, J=8.4 Hz, 2H, 2,6-ArH), 7.12 (d, J=8.4 Hz, 2H, 3,5-ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 27.6, 32.0, 34.7, 55.7, 62.3, 94.4, 116.1, 129.1, 135.7, 155.1; IR (KBr) v: 3364, 2935, 1510, 1009, 922, 834 cm^{-1}; MS (70 eV) m/z (%): 210 (M^+, 4), 121 (14), 107 (3), 91 (4), 77 (4), 45 (100). HRMS (ESI) calcd for $C_{12}H_{22}NO_3$ $[M+NH_4]^+$: 228.1594, found 228.1587.

3-(4-Methoxymethoxyphenyl)propan-1-ol (13c): Colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.95—2.05 (m, 3H, 2-CH_2, OH), 2.78 (t, J=6.5 Hz, 2H, 3-CH_2), 3.60 (s, 3H, CH_3O), 3.76 (t, J=6.5 Hz, 2H, 1-CH_2), 5.28 (s, 2H, OCH_2O), 7.10 (d, J=8.8 Hz, 2H, 2,6-ArH), 7.16 (d, J=8.8 Hz, 2H, 3,5-ArH); ^{13}C NMR

($CDCl_3$, 50 MHz) δ: 31.1, 34.3, 55.8, 62.0, 94.5, 116.2, 129.3, 135.2, 155.3; IR (KBr) *v*: 3361, 2938, 1077, 1009, 921, 838 cm^{-1}; MS (70 eV) *m/z* (%): 196 (M^+, 4), 121 (9), 77 (4), 45 (100); HRMS (ESI) calcd for $C_{11}H_{20}NO_3$ $[M+NH_4]^+$: 214.1438, found 214.1434.

General procedure for the preparation of aldehydes 14a—14c

A solution of alcohol **13** (3 mmol) in dry dichloromethane (3 mL) was added drop wise to a solution of PCC (0.86 g, 4 mmol) in dry dichloromethane (10 mL) at 0 ℃, and stirring was continued at room temperature for 1—2 h (monitored by TLC). The solvent was removed *in vacuo*. Flash chromatography of the residue over silica gel (petroleum ether/ethyl acetate, 8 ∶ 1) gave **14a—14c**.

4-(3,5-Bismethoxymethoxyphenyl)butyraldehyde (14a): 91% yield. Colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.90—1.95 (m, 2H, 3-CH_2), 2.23—2.25 (m, 2H, 2-CH_2), 2.58 (t, J=8.1 Hz, 2H, 4-CH_2), 3.46 (s, 6H, CH_3O), 5.13 (s, 4H, OCH_2O), 6.52—6.60 (m, 3H, ArH), 9.73 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 23.2, 35.6, 42.9, 55.8, 94.3, 102.4, 109.7, 143.6, 158.2, 202.0; IR (KBr) *v*: 3420, 2935, 1722, 1604, 1147, 1026 cm^{-1}; MS (70 eV) *m/z* (%): 268 (M^+, 1), 250 (15), 115 (8), 45 (100); HRMS (EI) calcd for $C_{14}H_{20}O_5$ (M^+): 268.1305, found 268.1299.

4-(4-Methoxymethoxyphenyl)butyraldehyde (14b): 94% yield. Colorless oil. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.86—1.93 (m, 2H, 3-CH_2), 2.40—2.45 (m, 2H, 2-CH_2), 2.56 (t, J=7.4 Hz, 2H, 4-CH_2), 3.46 (s, 3H, CH_3O), 5.14 (s, 2H, OCH_2O), 6.97 (d, J=8.2 Hz, 2H, 2,6-ArH), 7.13 (d, J=8.2 Hz, 2H, 3,5-ArH), 9.72 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 23.6, 33.9, 42.8, 55.7, 94.3, 116.1, 129.2, 134.4, 155.4, 202.1; IR (KBr) *v*: 2935, 1709, 1079, 1006, 923, 835 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{20}NO_3$ $[M+NH_4]^+$: 226.1438, found 226.1440.

3-(4-Methoxymethoxyphenyl)propionaldehyde (14c): 90% yield. Colorless oil. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.96—2.03 (m, 2H, 2-CH_2), 2.69 (t, J=7.2 Hz, 2H, 3-CH_2), 3.46 (s, 3H, CH_3O), 5.14 (s, 2H, OCH_2O), 6.95 (d, J=8.1 Hz, 2H, 2,6-ArH), 7.10 (d, J=8.1 Hz, 2H, 3,5-ArH), 9.80 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 27.2, 35.7, 55.8, 94.4, 116.2, 129.3, 134.6, 155.4, 201.6; IR (KBr) *v*: 2935, 1709, 1234, 1006, 922, 834 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{18}NO_3$: $[M+NH_4]^+$ 212.1281, found 212.1277.

General procedure for the preparation of 15a—15e

Potassium *tert*-butoxide (0.24 g, 2.1 mmol) was added to a solution of phosphonium bromide (2 mmol) in anhydrous THF (10 mL) at 0 ℃. After stirring at room temperature for 0.5 h a deep red solution appeared, then **14a** or **14b** or **14c** (1.5 mmol) in anhydrous THF (3 mL) was added drop wise to this mixture and stirring was continued for another 0.5 h. The reaction mixture was quenched with water and extracted with ethyl acetate (3×15 mL). The combined organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography of the residue (petroleum ether/ethyl acetate, 10 ∶ 1) gave **15a—15e**.

(*Z*)-3,5-Dimethoxymethoxy-1-(tridec-4-enyl)benzene (15a): 92% yield. Colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.88 (t, J=5.9 Hz, 3H, CH_3), 1.21—1.34 (m, 12H, 7'—12'-CH_2), 1.61—1.71 (m, 2H, 2'-CH_2), 2.00—2.11 (m, 4H, 3',6'-CH_2), 2.55 (t, J=7.8 Hz, 2H, 1'-CH_2), 3.46 (s, 6H, CH_3O), 5.14 (s, 4H, OCH_2O), 5.36—5.40 (m, 2H, 4',5'-CH=), 6.53—6.57 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.0, 22.6, 26.8, 27.2, 29.3, 29.4, 29.5, 29.7, 31.2, 31.9, 35.7, 55.9, 94.4, 102.2, 109.8, 129.1, 130.5, 145.1, 158.2; IR (KBr) *v*: 3412, 2925, 1418, 1026, 833, 339 cm^{-1}; MS (70 eV) *m/z* (%): 378 (M^+, 2), 212 (16), 91 (2), 45 (100); HRMS (EI) calcd for $C_{23}H_{38}O_4$ (M^+): 378.2765, found 378.2758.

(*Z*)-4-(4-Decenyl)-1-methoxymethoxybenzene (15b): 90% yield. Colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.88 (t, J=6.9 Hz, 3H, CH_3), 1.29—1.38 (m, 6H, 7'—9'-CH_2), 1.61—1.69 (m, 2H, 2'-CH_2), 1.96—2.09 (m, 4H, 3',6'-CH_2), 2.57 (t, J=7.8 Hz, 2H, 1'-CH_2), 3.46 (s, 3H, CH_3O), 5.15 (s, 2H, OCH_2O), 5.36—5.40 (m, 2H, 4',5'-CH=), 6.95 (d, J=8.7 HZ, 2H, 2,6-ArH), 7.09 (d, J=8.7 Hz, 2H, 3,5-ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.0, 22.5, 26.7, 27.2, 29.4, 31.5, 31.6, 34.5, 55.8, 94.5, 116.1, 128.6, 129.3, 130.4, 136.0, 155.3; IR (KBr) *v*: 2927, 1510, 1233, 1153, 1079, 923, 835 cm^{-1}; MS (70 eV) *m/z* (%): 276 (M^+, 4), 121 (18), 45 (100); HRMS (ESI) calcd for $C_{18}H_{29}O_2$ $[M+H]^+$: 277.2162, found 277.2152.

(*Z*)-4-(3-Decenyl)-1-methoxymethoxybenzene (15c): 90% yield. Colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.87 (t, J=6.3 Hz, 3H, CH_3), 1.25—1.32 (m, 8H, 6'—9'-CH_2), 1.96—1.98 (m, 2H, 5'-CH_2), 2.28—2.35 (m, 2H, 2'-CH_2), 2.60 (t, J=7.6 Hz, 2H, 1'-CH_2), 3.46 (s, 3H, CH_3O), 5.13 (s, 2H, OCH_2O), 5.36—5.43 (m, 2H, 3',4'-CH=), 6.94 (d, J=8.7 Hz, 2H, 2,6-ArH), 7.10 (d, J=8.7 Hz, 2H, 3,5-ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.0, 22.6, 27.2, 28.9, 29.3, 29.6, 31.7, 35.1, 55.7, 94.5, 116.1, 128.6, 129.3, 130.6, 135.5, 155.4; IR (KBr) *v*: 2925, 1611, 1510, 1233, 923, 827 cm^{-1}; MS (70 eV) *m/z* (%): 276 (M^+, 2), 151 (22), 45 (100); HRMS (ESI) calcd for $C_{18}H_{29}O_2$ $[M+H]^+$: 277.2162, found 277.2152.

(*Z*)-1-Methoxymethoxy-4-(4-octenyl)benzene (15d): 92% yield. Colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.89 (t, J=6.6 Hz, 3H, CH_3), 1.29—1.35 (m, 2H, 7'-CH_2), 1.59—1.69 (m, 2H, 2'-CH_2), 1.95—2.09 (m, 4H, 3',6'-CH_2), 2.57 (t, J=7.2 Hz, 2H, 1'-CH_2), 3.46 (s, 3H, CH_3O), 5.15 (s, 2H, OCH_2O), 5.37—5.40 (m, 2H, 4',5'-CH), 6.95 (d, J=8.4 Hz, 2H, 2,6-ArH), 7.09 (d, J=8.4 Hz, 2H, 3,5-ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.7, 22.8, 26.7, 29.3, 31.6, 34.6, 55.8, 94.5, 116.0, 129.4, 130.1, 130.4, 135.9, 155.3; IR (KBr) *v*: 2927, 1610, 1511, 1233, 1153, 923, 835 cm^{-1}; MS (70 eV) *m/z* (%): 248 (M^+, 3), 121 (20), 45 (100); HRMS (ESI) calcd for $C_{16}H_{25}O_2$ $[M+H]^+$: 249.1849, found 249.1844.

(*Z*)-1-Methoxymethoxy-4-(3-octenyl)benzene (15e): 90% yield. Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.88 (t, J=6.8 Hz, 3H, CH_3), 1.26—1.30 (m, 4H, 6',7'-CH_2), 1.95—2.00 (m, 2H, 5'-CH_2), 2.28—2.34 (m, 2H, 2'-CH_2), 2.59 (t, J=7.2 Hz, 2H, 1'-CH_2), 3.46 (s, 3H, CH_3O), 5.15 (s, 2H, OCH_2O), 5.37—5.40 (m, 2H, 3',4'-CH=), 6.96 (d, J=8.0 Hz, 2H, 2,6-ArH), 7.10 (d, J=8.0 Hz, 2H, 3,5-ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.9, 22.3, 26.9, 29.3, 31.8, 35.2, 55.8, 94.6, 116.2, 128.6, 129.3, 130.6, 135.6, 155.4; IR (KBr) v: 2927, 1510, 1233, 1153, 1079, 923, 834 cm^{-1}; MS (70 eV) *m/z* (%): 248 (M^+, 2), 151 (25), 121 (19), 45 (100); HRMS (ESI) calcd for $C_{16}H_{25}O_2$ $[M+H]^+$: 249.1849, found 249.1844.

General procedure for the preparation of (*Z*)-alkylphenols 1 and 16b—16e

Five drops of conc. HCl was added to a solution of **15** (1 mmol) in methanol (10 mL). The mixture was refluxed for 10 min, then quenched with a piece of ice, extracted with ethyl acetate (3×15 mL). The combined organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography of the residue (petroleum ether/ethyl acetate, 4∶1) gave the desired compounds **1**[1] and **16b—16e**.

(*Z*)-5-(Tridec-4-enyl)resorcinol (1): 95% yield. Colorless oil. ^{1}H NMR (CD_3CN, 300 MHz) δ: 0.87 (t, J=7.0 Hz, 3H, CH_3), 1.23—1.36 (m, 12H, 7'—12'-CH_2), 1.56—1.63 (m, 2H, 2'-CH_2), 1.94—2.06 (m, 4H, 3',6'-CH_2), 2.44 (t, J=8.0 Hz, 2H, 1'-CH_2), 3.18 (br, 2H, OH), 5.36—5.39 (m, 2H, 4',5'-CH=), 6.09 (t, J=2.0 Hz, 1H, 2-ArH), 6.15 (d, J=2.0 Hz, 2H, 4,6-ArH); ^{13}C NMR (CD_3CN, 75 MHz) δ: 14.4, 23.4, 27.5, 27.8, 29.9, 30.0, 30.2, 30.4, 32.1, 32.6, 36.1, 100.7, 107.8, 130.4, 131.2, 146.2, 158.9; IR (KBr) v: 3426, 2924, 1628, 1458, 1155 cm^{-1}; MS (70 eV) *m/z* (%): 290 (M^+, 2), 163 (7), 149 (4), 125 (11), 124 (100), 123 (18), 41 (10); HRMS (SIMS) calcd for $C_{19}H_{31}O_2$ $[M+H]^+$: 291.2319, found 291.2321.

(*Z*)-4-(4-Decenyl)phenol (16b): 93% yield. Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.88 (t, J=7.0Hz, 3H, CH_3), 1.22—1.38 (m, 6H, 7'—9'-CH_2), 1.57—1.67 (m, 2H, 2'-CH_2), 1.93—2.08 (m, 4H, 3',6'-CH_2), 2.55 (t, J=7.5 Hz, 2H, 1'-CH_2), 5.32—5.44 (m, 2H, 4',5'-CH=), 5.57 (br, 1H, OH), 6.75 (d, J=8.1 Hz, 2H, 2,6-ArH), 7.03 (d, J=8.1 Hz, 2H, 3,5-ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.0, 22.5, 26.7, 27.2, 29.3, 31.5, 31.6, 34.5, 115.1, 129.3, 129.4, 130.4, 134.9, 153.1; IR (KBr) v: 3329, 2925, 1609, 1513, 1231, 825 cm^{-1}; MS (70 eV) *m/z* (%): 232 (M^+, 4), 133 (14), 120 (38), 107 (100), 77 (11); HRMS (ESI) calcd for $C_{16}H_{25}O$ $[M+H]^+$: 233.1900, found 233.1902.

(*Z*)-4-(3-Decenyl)phenol (16c): 94% yield. Colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.97 (t, J=6.8 Hz, 3H, CH_3), 1.37—1.42 (m, 8H, 6'—9'-CH_2), 2.00—2.12 (m, 2H, 5'-CH_2), 2.37—2.47 (m, 2H, 2'-CH_2), 2.69 (t, J=7.0 Hz, 2H, 1'-CH_2), 5.43—5.58 (m, 2H, 3',4'-CH=), 6.38 (br, 1H, OH), 6.89 (d, J=8.5 Hz, 2H, 2,6-ArH), 7.10 (d, J=8.5 Hz, 2H, 3,5-ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1, 22.7, 27.3, 29.0, 29.4, 29.6, 31.8, 35.2, 115.3, 128.7, 129.5, 130.7, 134.6, 153.3; IR (KBr) v: 3333, 2925, 2854, 1613, 1232, 826 cm^{-1}; MS (70 eV) *m/z* (%): 232 (M^+, 2), 120 (1), 107 (100), 77 (12); HRMS (ESI) calcd for $C_{16}H_{25}O$ $[M+H]^+$: 233.1900, found 233.1903.

(*Z*)-4-(4-Octenyl)phenol (16d): 99% yield. Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.87 (t, J=6.8 Hz, 3H, CH_3), 1.23—1.31 (m, 2H, 7'-CH_2), 1.56—1.66 (m, 2H, 2'-CH_2), 1.95—2.08 (m, 4H, 3',6'-CH_2), 2.44 (t, J=7.5 Hz, 2H, 1'-CH_2), 5.33—5.44 (m, 2H, 4',5'-CH=), 5.97 (br, 1H, OH), 6.75 (d, J=8.7 Hz, 2H, 2,6-ArH), 7.03 (d, J=8.7 Hz, 2H, 3,5-ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.7, 22.8, 26.7, 29.3, 31.6, 34.5, 115.1, 128.8, 129.4, 130.1, 134.9, 153.1; IR (KBr) v: 3327, 2928, 1611, 1513, 1230, 825 cm^{-1}; MS (70 eV) *m/z* (%): 204 (M^+, 4), 133 (2), 107 (100), 77 (8); HRMS (ESI) calcd for $C_{14}H_{24}NO$ $[M+NH_4]^+$: 222.1852, found 222.1868.

(*Z*)-4-(3-Octenyl)phenol (16e): 96% yield. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.90 (t, J=6.9 Hz, 3H, CH_3), 1.33—1.38 (m, 4H, 6',7'-CH_2), 2.05—2.06 (m, 2H, 5'-CH_2), 2.35—2.40 (m, 2H, 2'-CH_2), 2.65 (t, J=7.8 Hz, 2H, 1'-CH_2), 5.42—5.49 (m, 2H, 3',4'-CH=), 5.79 (br, 1H, OH), 6.82 (d, J=8.4 Hz, 2H, 2,6-ArH), 7.09 (d, J=8.4 Hz, 2H, 3,5-ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.9, 22.3, 26.7, 29.3, 31.8, 35.1, 115.1, 128.6, 129.5, 130.6, 134.5, 153.4; IR (KBr) v: 3332, 2925, 1612, 1513, 1449, 826 cm^{-1}; MS (70 eV) *m/z* (%): 204 (M^+, 2), 133 (1), 120 (1), 107 (100), 77 (9); HRMS (ESI) calcd for $C_{14}H_{24}NO$ $[M+NH_4]^+$: 222.1852, found 222.1868.

General procedure for the isomerization of (*Z*)-alkylphenols 16b—16e to gibbilimbols A—D (2—5)[7]

Azoisobutyronitrile (0.6 mmol, 100 mg) was added to a solution of *Z*-alkylphenols (1.0 mmol) and thiophenol (0.5 mmol) in refluxing benzene (20 mL) in four portions over a period of 8 h. Then the solvent was evaporated *in vacuo*. Flash chromatography of the residue using the same eluting mixture employed for (*Z*)-gibbilimbols gave gibbilimbols A—D (**2—5**).

(*E*)-4-(4-Decenyl)phenol (gibbilimbol A, 2): 2 was obtained as an oil in 96% yield. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.88 (t, J=6.6 Hz, 3H, CH_3), 1.20—1.40 (m, 6H, 7'—9'-CH_2), 1.57—1.67 (m, 2H, 2'-CH_2), 1.90—2.06 (m, 4H, 3',6'-CH_2), 2.55 (t, J=7.2 Hz, 2H, 1'-CH_2), 5.30 (br, 1H, OH), 5.34—5.41 (m, 2H, 4',5'-CH=), 6.74 (d, J=8.1 Hz, 2H, 2,6-ArH), 7.03 (d, J=8.1 Hz, 2H, 3,5-ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.1, 22.5, 29.3, 31.4, 31.7, 32.0, 32.6, 34.4, 115.1, 129.5, 129.8, 130.9, 134.9, 153.3; IR (KBr) v: 3329, 2925, 1609, 1231, 968, 825 cm^{-1}; MS (70 eV) *m/z* (%): 232 (M^+, 2), 120 (37), 107 (100), 77 (24), 41 (43).

(*E*)-4-(3-Decenyl)phenol (gibbilimbol B, 3): 3 was obtained as an oil in 94% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.88 (t, J=6.8 Hz, 3H, CH_3), 1.25—1.29 (m, 8H, 6'—9'-CH_2), 1.85—2.02 (m, 2H, 5'-CH_2), 2.21—

2.34 (m, 2H, 2'-CH_2), 2.58 (t, J=7.2 Hz, 2H, 1'-CH_2), 5.05 (br, 1H, OH), 5.36—5.48 (m, 2H, 3',4'-CH=), 6.74 (d, J=8.4 Hz, 2H, 2,6-ArH), 7.04 (d, J=8.4 Hz, 2H, 3,5-ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.1, 22.6, 28.8, 29.3, 29.5, 31.7, 34.7, 35.2, 115.0, 129.3, 129.5, 131.1, 134.5, 153.3; IR (KBr) v: 3330, 2925, 1609, 1231, 967, 825 cm^{-1}; MS (70 eV) *m/z* (%): 232 (M^+, 2), 133 (12), 107 (100), 77 (25), 55 (19), 41 (47), 39 (23).

(*E*)-4-(4-Octenyl)phenol (gibbilimbol C, 4): 4 was obtained as an oil in 90% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.86 (t, J=6.9 Hz, 3H, CH_3), 1.33—1.40 (m, 2H, 7'-CH_2), 1.60—1.65 (m, 2H, 2'-CH_2), 1.95—2.03 (m, 4H, 3',6'-CH_2), 2.54 (t, J=7.5 Hz, 2H, 1'-CH_2), 5.40 (br, 1H, OH), 5.40—5.42 (m, 2H, 4',5'-CH=), 6.73 (d, J=8.1 Hz, 2H, 2,6-ArH), 7.02 (d, J=8.1 Hz, 2H, 3,5-ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.6, 22.7, 31.6, 32.0, 34.4, 34.7, 115.1, 129.5, 130.0, 130.7, 134.9, 153.2; IR (KBr) v: 3330, 2927, 1609, 1513, 1231, 968, 825 cm^{-1}; MS (70 eV) *m/z* (%): 204 (M^+, 2), 133 (13), 120 (20), 107 (100), 55 (13), 41 (16).

(*E*)-4-(3-Octenyl)phenol (gibbilimbol D, 5): 5 was obtained as an oil in 95% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.88 (t, J=7.0 Hz, 3H, CH_3), 1.26—1.35 (m, 4H, 6',7'-CH_2), 1.97—2.05 (m, 2H, 5'-CH_2), 2.22—2.34 (m, 2H, 2'-CH_2), 2.55 (t, J=7.2 Hz, 2H, 1'-CH_2), 5.00 (br, 1H, OH), 5.36—5.48 (m, 2H, 3',4'-CH=), 6.73 (d, J=8.1 Hz, 2H, 2,6-ArH), 7.05 (d, J=8.1 Hz, 2H, 3,5-ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.9, 22.3, 31.7, 32.2, 34.7, 35.2, 115.0, 129.3, 129.5, 131.1, 134.5, 153.3; IR (KBr) v: 3330, 2925, 1513, 1233, 968, 826 cm^{-1}; MS (70 eV) *m/z* (%): 204 (M^+, 3), 133 (15), 120 (5), 107 (100), 77 (19), 41 (17).

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