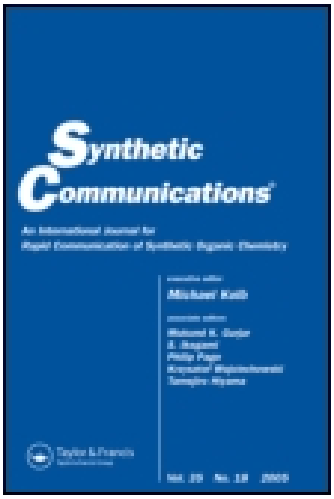

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Synthetic Approach to 4a-Methyltetrahydrofluorene-Type Diterpenoids via an Aromatic Oxidation of Phenol Derivatives

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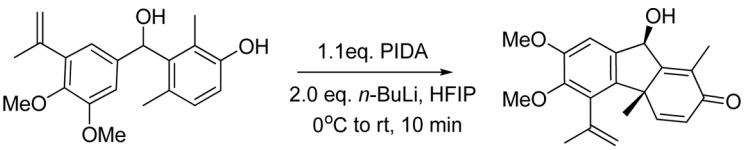
GRAPHICAL ABSTRACT



Abstract *An intramolecular aromatic oxidation of a phenolic compound with a hypervalent iodine reagent afforded the coupling product, in which the coupling took place at the* para-*position of the methoxy goup of the starting material instead of the desired* para-*position of the isopropenyl group, unfortunately.*

Keywords Aromatic oxidation; dichroanone; diterpenoid; hypervalent iodine reagent; 4a-methyltetrahydrofluorene skeleton

INTRODUCTION

Recently, several diterpenoids possessing structurally scarce 4a-methyltetra-(and hexa-) hydrofluorene skeletons, such as taiwaniaquinol A (**1**), B (**2**),[1] and C (**3**);[2] taiwaniaquinone A (**4**),[1] D (**5**),[3] and H (**6**);[4] dichroanone (**7**);[5] dichroanal B (**8**); and standishinal (**9**);[6] have been isolated from *Taiwania cryptomerioides*,[1–4] *Salvia dichroantha*,[5] *Thuja standishii*,[6] and other related plants (Fig. 1).

Some of them exhibit attractive biological activities. For example, taiwaniaquinone D (**5**) is known to show antitumor activity, and standishinal (**9**) with aromatase-inhibitory activity is recognized as a promising candidate for the treatment of breast cancer.[7] Because of their significant biological activities and intriguing structural features, these diterpenoids have received special attention, and several synthetic methods have been developed to date.[8]

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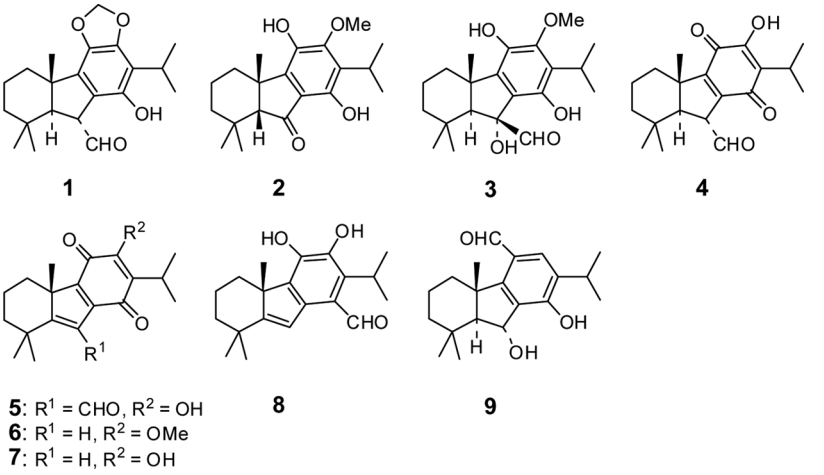


Figure 1. Structures of 4a-methyltetra- (and hexa-) hydrofluorene-type diterpenes.

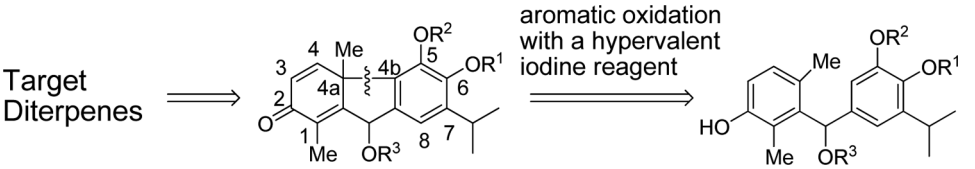
As part of our continuing exploitation of an aromatic oxidation strategy with a hypervalent iodine reagent in the synthesis of bioactive natural products,[9] we are also interested in developing a general synthetic procedure for these diterpenes.

For the synthesis of these diterpenenes, we focused our attention on the bond formation between the 4a and 4b positions of the basic skeleton by using an aromatic oxidation of a phenolic compound with a hypervalent iodine reagent as depicted in Scheme 1, although there have been several strategies to achieve such a bond formation.[8]

RESULTS AND DISCUSSION

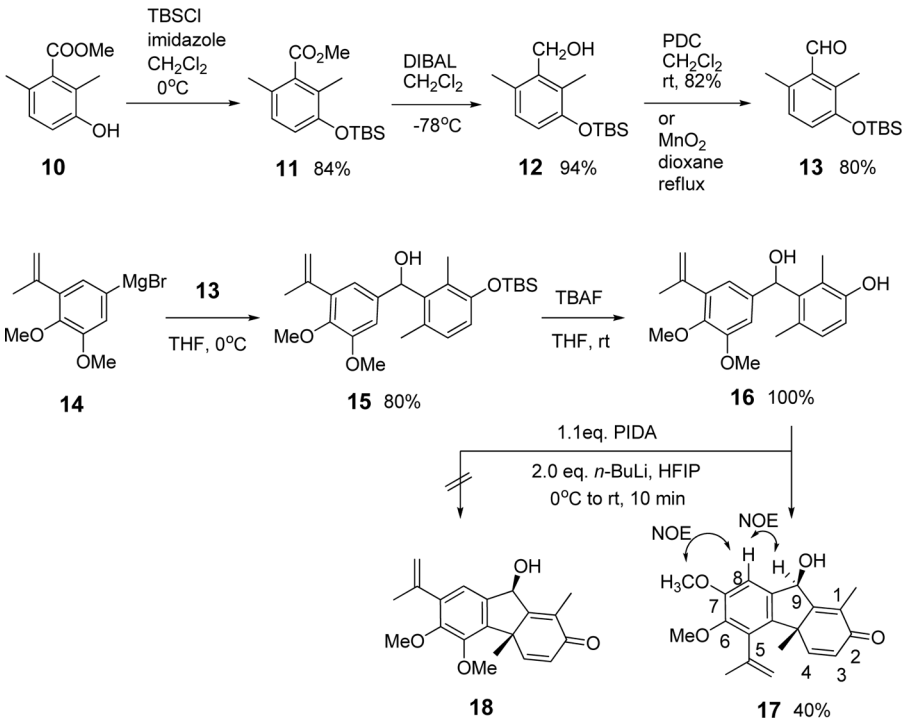
The starting phenolic compound as a precursor for an aromatic oxidation was prepared as follows.

The known phenolic ester (**10**),[10] readily prepared from 2,6-dimethylbenzoic acid, was protected as its silyl ether (**11**). Reduction of **11** with diisobutylaluminum hydride (DIBAL), followed by oxidation of the resulting alcohol (**12**) with pyridinium dichromate (PDC) or manganese dioxide, afforded the corresponding aldehyde (**13**) in 63% overall yield from **10**. A coupling reaction of **13** with the Grignard reagent (**14**), derived from the known 5-bromo-1-isopropenyl-2,3-dimethoxybenzene,[11] was successfully carried out in tetrahydrofuran (THF) at 0 °C to give the alcohol



Scheme 1. Retrosynthetic analysis of the target diterpenes.

(**15**) in 80% yield. Deprotection of the silyl group of **15** by treatment with tetrabutylammonium fluoride (TBAF) in THF gave the resulting phenolic compound (**16**), which was then subjected to the key aromatic oxidation. We note in advance that an aromatic oxidation of a phenolic compound with a hypervalent iodine reagent in the presence of 2.0 equivalents of base sometimes gives the desired product in better yield than in the absence of the base.[9d] Therefore, we adopted such reaction conditions for the oxidation of **10** as follows. Treatment of **16** with 1.1 equivalents of iodobenzene diacetate (PIDA) in hexafluoroisopropanol (HFIP) in the presence of 2.0 equivalents of *n*-BuLi at 0 °C to room temperature for 10 min provided the oxidation product (**17**) in 40% yield (Scheme 2). Based on the examination of the molecular models for the possible two products, we first assumed that the aromatic oxidation might occur at the *para*-position of isopropenyl group, providing the desired compound (**18**), because the steric hindrance between the isopropenyl group and the angular methyl group was observed in **17**. However, the aromatic oxidation took place at the *para*-position of the methoxy group to furnish **17** as the sole coupling product, whose structure was determined by analysis of its NMR spectra. In our analysis of the nuclear Overhauser effect (NOE) experiment, NOEs between 8-H and 9-H, and also 8-H and the methyl group of the 7-methoxy function, were observed, unambiguously supporting the structure of **17**. The relative stereochemistry of the hydroxy group and an angular methyl group of **17** were assumed to be *cis* on the basis



Scheme 2. Aromatic oxidation of the phenolic compound (**16**) with PIDA.

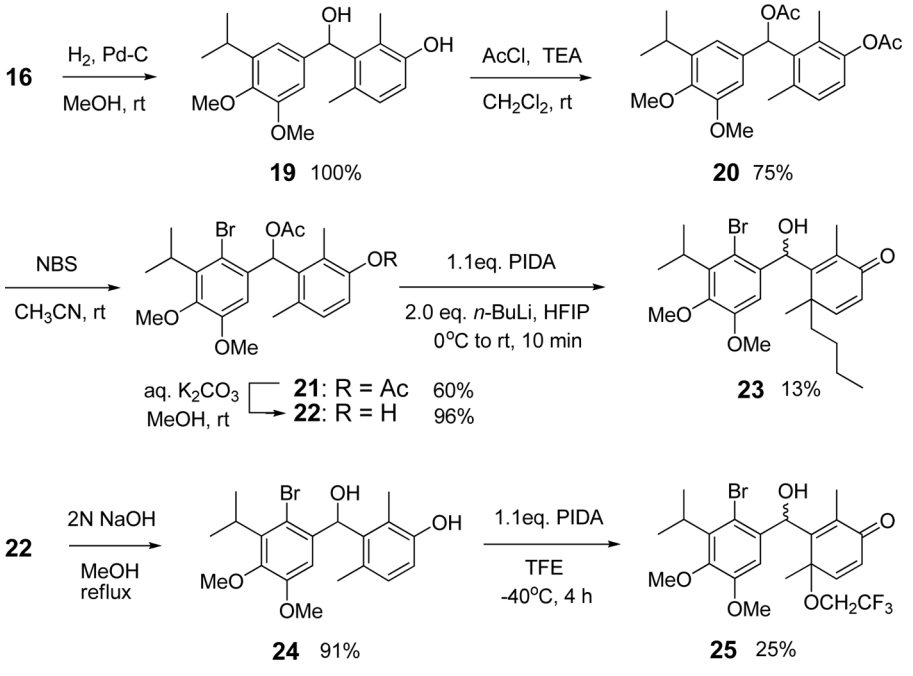
of the NOE experiment, where no NOE was observed between the proton underneath the hydroxy and the methyl groups.

Similar cyclization was also observed in the synthesis of dichroanone and taiwaniaquinol B.[8i] To obtain the desired coupling compound, we decided to prepare the bromide (**24**), in which the *para*-position of the methoxy group was blocked with a bromine atom and hence the coupling would be expected to occur at the *para*-position of the isopropenyl group.

Thus, the isopropenyl group of **16** was hydrogenated over palladium on carbon to give the isopropyl derivative (**19**). After protection of both hydroxy groups by acetylation in the usual manner, the resulting diacetate (**20**) was brominated with *N*-bromosuccimide (NBS) in acetonitrile to provide the bromide (**21**). Partial hydrolysis of **21** with aqueous potassium carbonate in MeOH afforded a phenolic compound (**22**). However, oxidation of **22** with PIDA in HFIP, as described previously, gave none of the coupling product, unfortunately. Interestingly, an addition of an *n*-butyl moiety to **22**, leading to the formation of the dienone (**23**) in poor yield, was observed under these reaction conditions (Scheme 3).

By changing the solvent from TFIP to 2,2,2-trifluoroethanol (TFE) in the absence of base, an addition of the trifluoroethoxy group to **24** took place at the *para*-position of the phenolic hydroxy group to generate the dienone (**25**) as a mixture of diastereoisomers in 25% yield.[12]

We thought that the introduction of a bromine atom might decrease the reactivity of the benzene ring, providing **23** or **25** instead of the desired cyclization



Scheme 3. Aromatic oxidation of the phenolic compounds (**22** and **24**) with PIDA.

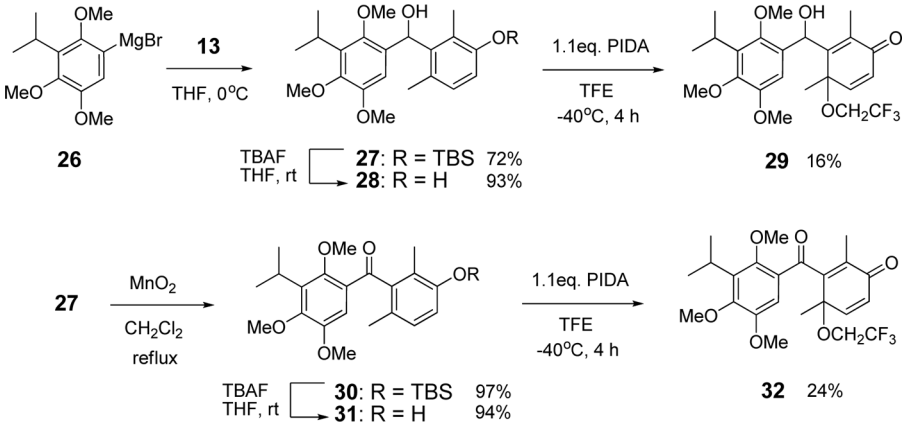
product; therefore, the preparation of the precursor having an electron-donating group at the same position as the bromide (**22**) was investigated next.

Addition of the Grignard reagent (**26**), derived from the known 1-bromo-3-isopropyl-2,4,5-trimethoxybenzene,[13] to the aldehyde (**13**) gave the alcohol (**27**), which, on treatment with TBAF in THF, afforded the desired phenolic compound (**28**). Again, the oxidation of **28** using PIDA as the oxidant in TFE afforded the adduct (**29**) in 16% yield, and none of the coupling product could be isolated under these reaction conditions (Scheme 4).

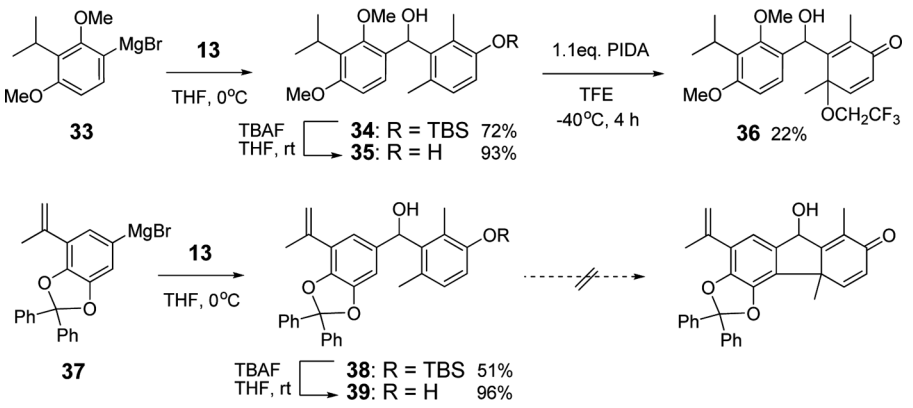
The aromatic oxidation was also applied to the acetate of **28**; however, decomposition of the starting material was always observed under a variety of reaction conditions. Again, the oxidation of the ketone (**31**) produced the adduct (**32**) as the sole isolable product in 24% yield. Although the trimethoxybenzene derivative is superior to the corresponding dimethoxybenzene derivative for the desired aromatic oxidation in terms of electron density, we speculate that a trimethoxybenzene ring is unfavorable for the coupling in terms of steric hindrance. Thus, the dimethoxy derivative was synthesized for further investigation of the oxidation. The precursor (**35**) was prepared starting from 1-bromo-3-isopropyl-2,4-dimethoxybenzene[14] using the same procedure as described for the synthesis of the trimethoxy derivative (**28**). Attempted oxidation of **35**, however, afforded the dienone (**36**) in 22% yield as the sole isolable product (Scheme 5).

In 1998, Kita and coworkers reported that the acetal is an effective protecting group to give the coupling product, regioselectively, in an intramolecular oxidative coupling with a hypervalent iodine reagent.[15] Thus, we synthesized the acetal derivative (**39**) from the Grignard reagent, prepared from the corresponding bromide,[16] as the precursor for the oxidation. However, attempted oxidations for **39** under a variety of reaction conditions all failed to obtain the desired coupling product.

For the synthesis of a core skeleton of the target compounds, we focused on the bond formation between the 4a- and 4b- positions of the basic structures by using an aromatic oxidation of a phenolic compound with a hypervalent iodine reagent; however, none of attempts gave the desired product, unfortunately. Thus, we decided to

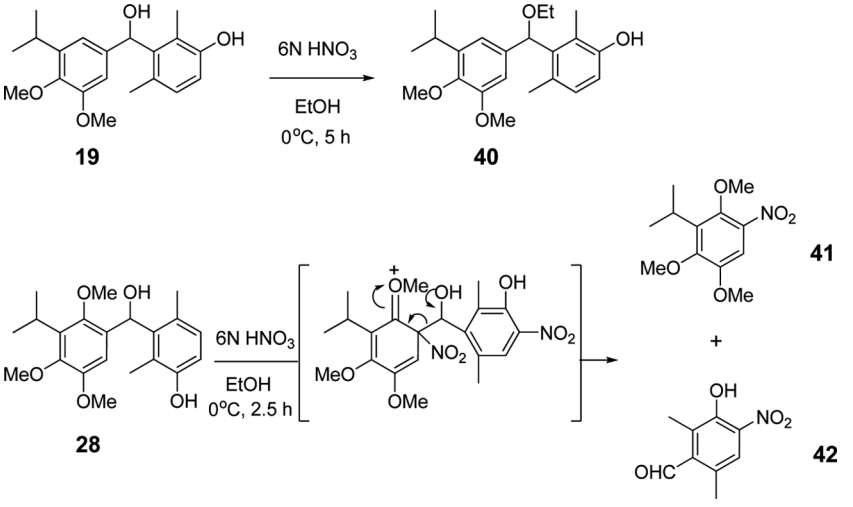


Scheme 4. Attempted aromatic oxidation of **28** and **31** with PIDA.



Scheme 5. Attempted aromatic oxidation of **35** and **39** with PIDA.

change the synthetic strategy, in which a benzoquinone derivative derived by oxidation of the isopropyl-substituted benzene ring would be involved as a key intermediate. Oxidation of **19**, a reduction product of **16**, with 6 N nitric acid in ethanol at 0 °C gave the ethoxy-substituted compound (**40**) in 68% yield (Scheme 6). When **28** was treated with 6 N nitric acid in EtOH at 0 °C for 2.5 h, the fragmentation products, 3-isopropyl-1,2,4-trimethoxy-5-nitrobenzene (**41**) and 3-hydroxy-2,6-dimethyl-4-nitrobenzaldehyde (**42**), were obtained, respectively. The structure of **41** was determined based on the analyses of its spectroscopic data and comparison with those of the structurally related compounds.[17] The structure of **42** also was unambiguously confirmed based on its spectroscopic data. An alternative oxidation of **19, 28**, or **31** with silver(II) oxide and 6 N nitric acid[18] in an appropriate solvent, such as dioxane, ethanol, and acetone, under various reaction conditions gave a complex mixture of structurally unidentified compounds.



Scheme 6. Attempted oxidation of **19** and **28** with HNO_3.

CONCLUSION

In summary, we disclose the preparation of the basic skeleton of 4a-methyltetrahydrofluorene diterpenes by exploitation of an aromatic oxidation of a phenolic compound with a hypervalent iodine reagent.

Although it is very hard to rationalize the relationship between the reactivity and the substitution patterns of the phenolic compounds for the aromatic oxidation at present, it is worthy of note that the addition of a trifluoroethoxy group to the phenolic compounds takes place under the aromatic oxidation conditions using 1.1 equivalents of PIDA in TFE. With the suitable substitution pattern of substrate, the strategy developed here can be applied to the synthesis of this class of diterpenes.

EXPERIMENTAL

Melting points were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-200 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained on Bruker AV 400 (^{1}H-NMR: 400 MHz, ^{13}C-NMR: 100 MHz), or JEOL LA-500 (^{1}H-NMR: 500 MHz, ^{13}C-NMR: 125 MHz) instrument for solutions in $CDCl_3$ unless otherwise noted, and chemical shifts are reported on the δ scale from internal TMS. MS spectra were measured with a JEOL JMS-D 300 spectrometer. Elemental analyses were performed on a Yanaco-MT5.

Methyl 3-(*tert*-Butyldimethylsilyloxy)-2,6-dimethylbenzoate (11)

To a stirred solution of **10** (8.3 g, 46 mmol) and imidazole (6.3 g, 92 mmol) in dry CH_2Cl_2 (100 mL) was added TBSCl (10.4 g, 69 mmol) in one portion at 0 °C. The resulting mixture was stirred at room temperature for 3 h, and then poured into ice water. The whole mixture was extracted with dichloromethane, and the extract was dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography eluting with hexane-Et_2O (20/1, v/v) to afford **11** (11.0 g, 80%) as a colorless oil. IR: ν_{max} 2954, 2931, 1733, 1287 and 837 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.19 (s, 6H), 1.00 (s, 9H), 2.13 (s, 3H), 2.21 (s, 3H), 3.90 (s, 3H), 6.71 (d, $J = 8.0$ Hz, 1H), 6.88 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.2, 13.8, 18.3, 18.9, 25.8, 51.9, 119.5, 125.6, 126.9, 128.0, 135.4, 151.7, 170.4. MS (CI): m/z 295 ($M^+ + 1$). HRMS (CI) calcd. for $C_{16}H_{27}O_3Si$: 295.1729; found: 295.1702.

3-(*tert*-Butyldimethylsilyloxy)-2,6-dimethylbenzyl Alcohol (12)

DIBAL-H (80 mL, 81 mmol, 1.02 mol/L in hexane) was added to a stirred solution of **11** (11.0 g, 36.8 mmol) in dry CH_2Cl_2 (150 mL) dropwise at −78 °C, and the resulting mixture was stirred at the same temperature for 1 h. HCl (1 mol/L) and water were successively added to the mixture. The mixture was extracted with ethyl acetate, and the extract was dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography, eluting with hexane–Et_2O (5/1, v/v), to afford the desired product **12** (9.2 g, 94%) as a white solid. IR ν_{max}: 3305, 2957, 2929, 1482 and 1273 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.20 (s, 6H),

1.01 (s, 9H), 2.29 (s, 3H), 2.35 (s, 3H), 4.71 (s, 2H), 6.67 (d, $J = 8.0$ Hz, 1H), 6.89 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.2, 12.3, 18.3, 19.0, 25.9, 59.6, 118.3, 128.0, 128.5, 129.7, 137.9, 152.1. MS (CI): m/z 277 ($M^+ + 1$). HRMS (CI) calcd. for $C_{15}H_{27}O_2Si$: 267.1780; found: 267.1788.

3-(*tert*-Butyldimethylsilyloxy)-2,6-dimethylbenzaldehyde (13)

Pyridinium dichromate (2.1 g, 5.6 mmol) was added to a solution of **12** (1.0 g, 3.7 mmol) in CH_2Cl_2 (15 mL) at room temperature, and the resulting mixture was stirred at the same temperature for 3 h. Ethyl acetate and celite were added to this mixture, and the whole mixture was filtered to remove insoluble materials. The filtrate was concentrated and purified by flash column chromatography, eluting with hexane–Et_2O (1/10, v/v), to afford **13** (810 mg, 82%) a colorless oil. IR ν_{max}: 2957, 2930, 1743 and 1277 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.20 (s, 6H), 1.02 (s, 9H), 2.45 (s, 3H), 2.51 (s, 3H), 6.88 (d, $J = 8.0$ Hz, 1H), 6.93 (d, $J = 8.0$ Hz, 1H), 10.58 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.3, −4.2, 12.3, 18.3, 19.9, 25.8, 123.4, 129.4, 131.5, 133.3, 133.8, 152.4, 194.2. MS (CI): m/z 264 (M^+). HRMS (CI) calcd. for $C_{15}H_{24}O_2Si$: 264.1546; found: 264.1527.

General Procedure for the Grignard Reaction

A solution of the bromide (1.2 eq.) in dry THF was added to a stirred suspension of magnesium turnings (1.3 eq.) in dry THF in the presence of a small crystal of iodine at room temperature under argon. The mixture started to reflux during the addition. After addition of all the bromide, the reaction mixture was refluxed for 30 min. The Grignard solution thus prepared was added to a solution of the aldehyde (1.0 eq.) in dry THF at 0 °C, and the resulting mixture was stirred at ambient temperature for 2 h. The mixture was treated with saturated aqueous ammonium chloride solution and extracted with Et_2O. The ethereal layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–Et_2O afforded the desired product.

(3-[*tert*-Butyldimethylsilyloxy]-2,6-dimethylphenyl)(3-isopropenyl-4,5-dimethyl)methanol (15)

IR ν_{max}: 3480, 2956, 2930, 1479 and 1260 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.18 (s, 3H), 0.19 (s, 3H), 0.99 (s, 9H), 2.07 (s, 3H), 2.12 (s, 3H), 2.20 (s, br, 1H), 2.25 (s, 3H), 3.76 (s, 3H), 3.80 (s, 3H), 4.97 (s, 1H), 5.07 (s, 1H), 6.25 (d, $J = 4.0$ Hz, 1H), 6.59 (s, 1H), 6.70 (d, $J = 8.0$ Hz, 1H), 6.85 (s, 1H), 6.89 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.2, −4.1, 13.5, 18.3, 20.2, 23.5, 25.9, 55.8, 60.7, 71.5, 108.9, 115.2, 118.3, 118.3, 128.3, 128.9, 129.5, 137.4, 138.7, 140.4, 143.7, 152.6, 152.6. MS (CI): m/z 442 (M+). HRMS (EI) calcd. for $C_{26}H_{38}O_4Si$: 442.2539; found: 442.2559.

General Procedure for Removal of Silyl Group with TBAF

To a stirred solution of the silyl ether (1.0 eq.) in dry THF, a solution of TBAF (1 mol/L in THF, 1.1 eq.) was added at 0 °C, and the resulting mixture was stirred

for 30 min at room temperature. The reaction was treated with water and extracted with Et_2O. The ethereal layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica. Elution with hexane–Et_2O afforded the desired product.

3-[Hydroxyl(3-isopropenyl-4,5-dimethoxyphenyl)methyl]-2,4-dimethylphenol (16)

IR ν_{max}: 3420, 2934, 1456, 1261 and 1070 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.07 (s, 3H), 2.14 (s, 3H), 2.22 (d, $J = 4.4$ Hz, 1H), 2.26 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 4.75 (s, 1H), 4.98 (s, br, 1H), 5.08 (s, br, 1H), 6.26 (d, $J = 4.4$ Hz, 1H), 6.59 (s, 1H), 6.69 (d, $J = 8.0$ Hz, 1H), 6.87 (s, 1H), 6.91 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4, 20.2, 23.4, 55.9, 60.7, 71.3, 109.0, 114.5, 115.2, 118.3, 123.5, 128.5, 129.0, 137.4, 138.6, 140.3, 143.7, 144.8, 152.5, 153.1. MS (CI): m/z 328 (M+). HRMS (EI) calcd. for $C_{20}H_{24}O_4$: 328.1674; found: 328.1682.

(4a*R**,9*R**)-9-Hydroxy-5-isopropenyl-6,7-dimethoxy-1,4a-dimethyl-4a,9-dihydro-2*H*-fluoren-2-one (17)

n-BuLi (0.32 mL, 1.59 mol/L in hexane, 0.52 mmol) was gradually added to HFIP (2 mL) over 3 min at 0 °C. A solution of **16** (100 mg, 0.26 mmol) in HFIP was added to that solution at the same temperature, and the resulting mixture was treated with PIDA (83 mg, 0.26 mmol). After being stirred for a further 10 min at ambient temperature, the mixture was directly purified by silica-gel column chromatography. Elution with hexane–Et_2O (1/1, v/v) gave **17** (40 mg, 40%) as a yellow powder. IR ν_{max}: 3422, 2930, 1635, 1464 and 1023 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.75 (s, 3H), 2.04 (s, 3H), 2.06 (s, 3H), 3.77 (s, 1H), 3.81 (s, 3H), 3.90 (s, 3H), 5.05 (s, 1H), 5.42 (s, 1H), 5.57 (d, $J = 4.4$ Hz, 1H), 6.26 (d, $J = 8.0$ Hz, 1H), 7.02 (s, 1H), 7.60 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.1, 25.8, 35.2, 50.8, 55.9, 61.4, 72.6, 108.5, 116.5, 117.8, 127.7, 130.1, 133.1, 134.8, 137.3, 141.5, 150.9, 152.9, 162.4, 187.1. MS (CI): m/z 326 (M^+), 308. HRMS (EI) calcd. for $C_{20}H_{22}O_4$: 326.1518; found: 326.1545.

3-[Hydroxy(3-isopropyl-4,5-dimethoxyphenyl)methyl]-2,4-dimethylphenol (19)

A mixture of **16** (50 mg, 0.15 mmol), 10% Pd/C (10 mg), and MeOH (5 mL) was stirred at room temperature under an atmospheric pressure of hydrogen for 16 h. The reaction mixture was filtrated through a pad of celite, and the filtrate was concentrated under reduced pressure to give the desired product **19** (50 mg, 100%) as a white crystal. IR ν_{max}: 3393, 2962, 1488 and 1457 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, $J = 6.8$ Hz, 3H), 1.15 (d, $J = 6.8$ Hz, 3H), 2.13 (s, 3H), 2.18 (d, $J = 4.4$ Hz, 1H), 2.26 (s, 3H), 3.24–3.34 (m, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 4.68 (s, 1H), 6.27 (d, $J = 4.4$ Hz, 1H), 6.70 (d, $J = 8.0$ Hz, 3H), 6.92 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4, 20.1, 23.5, 26.9, 55.7, 60.9, 71.5, 107.4, 114.4, 115.4, 123.5, 128.5, 128.9, 138.8, 140.5, 141.9, 144.8, 152.4, 153.1. MS (EI): m/z 330 (M^+). HRMS (EI) calcd. for $C_{20}H_{26}O_4$: 330.1831; found: 330.1839.

[3-(Acetoxy)-2,6-dimethylphenyl](3-isopropyl-4,5-dimethoxyphenyl)-methyl Acetate (20)

Acetyl chloride (1.72 mL, 24 mmol) was added to a stirred solution of **19** (1.6 g, 4.8 mmol) and triethylamine (6.7 mL, 48 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C, and the resulting mixture was stirred at ambient temperature for 14 h. The mixture was treated with water and extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by silica-gel column chromatography. Elution with hexane–Et_2O (2/1, v/v) gave **20** (1.5 g, 75%) as a white foam. IR ν_{max}: 2341, 2359, 1761, 1741 and 1219 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, $J = 6.8$ Hz, 3H), 1.14 (d, $J = 6.8$ Hz, 3H), 2.08 (s, 3H), 2.17 (s, 3H), 2.30 (s, 3H), 2.36 (s, 3H), 3.25–3.33 (m, 1H), 3.73 (s, 3H), 3.79 (s, 3H), 6.44 (s, 1H), 6.58 (s, 1H), 6.92 (d, $J = 8.0$ Hz, 1H), 7.06 (d, $J = 8.0$ Hz, 1H), 7.32 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.2, 20.4, 20.7, 20.8, 21.1, 23.4, 27.0, 55.7, 60.9, 72.9, 107.8, 116.0, 121.8, 129.2, 130.1, 134.3, 135.5, 137.1, 142.2, 145.6, 148.2, 152.6, 169.3, 170.3. MS (EI): m/z 414 (M^+). HRMS (EI) calcd. for $C_{24}H_{30}O_6$: 414.2042; found: 414.2062.

3-[(Acetoxy)-(2-bromo-3-isopropyl-4,5-dimethoxyphenyl)methyl]-2,4-dimethylphenyl Acetate (21)

NBS (0.47 g, 2.65 mmol) was added to a stirred solution of **20** (1.5 g, 2.4 mmol) in dry acetonitrile (25 mL) at room temperature. The mixture was stirred at the same temperature for 4 days, and the solvent was removed under reduced pressure to leave a residue, which was purified by silica-gel column chromatography, eluting with hexane–Et_2O (2/1, v/v) to give **21** (1.1 g, 61%) as a white foam. IR ν_{max}: 1760, 1743, 1229 and 1194 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, $J = 6.8$ Hz, 3H), 1.37 (d, $J = 6.8$ Hz, 3H), 2.10 (s, 3H), 2.17 (s, 3H), 2.31 (s, 3H), 2.35 (s, 3H), 3.25–3.33 (m, 1H), 3.59 (s, 3H), 3.84 (s, 3H), 6.46 (s, 1H), 6.92 (d, $J = 8.0$ Hz, 1H), 7.07 (d, $J = 8.0$ Hz, 1H), 7.32 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 20.7, 20.9, 21.0, 23.4, 55.6, 55.7, 60.8, 75.1, 112.8, 121.7, 121.8, 129.5, 129.6, 135.0, 136.1, 141.4, 148.5, 151.77, 169.4, 169.8. MS (EI): m/z 492 ($M^+ - 1$). HRMS (EI) calcd. for $C_{24}H_{29}O_6$ ^{81}Br: 492.1147; found: 492.1120.

(2-Bromo-3-isopropyl-4,5-dimethoxyphenyl)(3-hydroxy-2,6-dimethylphenyl)methyl Acetate (22)

A mixture of **21** (228 mg, 0.46 mmol), K_2CO_3 (0.19 g, 1.38 mmol), H_2O (5 mL), and MeOH (5 mL) was stirred at room temperature for 2 h, and then the solvent was removed under reduced pressure. The residue was extracted with Et_2O, and the extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave **22** (200 mg, 96%) as a white foam. IR ν_{max}: 3414, 1740, 1273 and 1233 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (d, $J = 6.8$ Hz, 3H), 1.38 (d, $J = 6.8$ Hz, 3H), 2.11 (s, 3H), 2.26 (s, 3H), 2.28 (s, 3H), 3.59 (s, 3H), 3.71–3.80 (m, 1H), 3.84 (s, 3H), 4.63 (s, 1H), 6.49 (s, 1H), 6.70 (d, $J = 8.0$ Hz, 1H), 6.93 (d, $J = 8.0$ Hz, 1H), 7.30 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.1, 20.6, 20.8, 21.0, 55.6, 60.8, 75.7, 112.9,

114.8, 123.2, 129.0, 129.2, 135.8, 141.3, 151.7, 152.5, 170.1. MS (EI): m/z 451 (M^+). HRMS (EI) calcd. For $C_{22}H_{27}O_5$ ^{81}Br: 451.1120; found: 451.1140.

(2-Bromo-3-isopropyl-4,5-dimethoxyphenyl)(6-butyl-2,6-dimethylphenyl-3-oxocyclohexa-1,4-dien-1-yl)methyl Acetate (23)

n-BuLi (0.27 mL, 1.59 mol/L in hexane, 0.44 mmol) was gradually added to HFIP (2 mL) over 3 min at 0 °C. A solution of **22** (100 mg, 0.22 mmol) in HFIP (3 mL) was added to this solution at 0 °C, and the resulting mixture was treated with PIDA (78 mg, 0.24 mmol). After being stirred for 10 min at ambient temperature, the mixture was directly purified by flash silica-gel column chromatography, eluting with hexane–Et_2O (2/1, v/v) to give **23** (15 mg, 13%) as a yellow foam. IR ν_{max}: 1748, 1667 and 1227 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.86–0.89 (m, 2H), 1.24–1.40 (m, 13H), 1.77 (s, 3H), 2.10 (s, 3H), 2.18 (s, 3H), 3.74 (s, 3H), 3.77–3.80 (m, 1H), 3.86 (s, 3H), 6.23 (d, $J = 8.0$ Hz, 1H), 6.77 (s, 1H), 6.88 (d, $J = 8.0$ Hz, 1H), 6.99 (s, 1H). MS (EI): m/z $C_{26}H_{35}O_5$ ^{81}Br 507 ($M^+ - 1$).

3-[(2-Bromo-3-isopropyl-4,5-dimethoxyphenyl)(hydroxyl)methyl]-2,4-dimethylphenol (24)

A mixture of **22** (500 mg, 1.1 mmol), 2 N NaOH (1.1 mL), and MeOH (5 mL) was refluxed for 1 h. After removal of the solvent under reduced pressure, the residue was acidified with 2 N HCl, and the mixture was extracted with Et_2O. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by silica-gel column chromatography, eluting with hexane–Et_2O (1/1, v/v), to give **24** (410 mg, 91%) as a white foam. IR ν_{max}: 3380, 2961, 2872, 1462 and 771 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (d, $J = 6.8$ Hz, 6H), 2.23 (s, 3H), 2.24 (s, 3H), 2.69 (s, 1H), 3.66 (s, 3H), 3.71–3.80 (m, 1H), 3.84 (s, 3H), 4.63 (s, 1H), 6.37 (s, 1H), 6.69 (d, $J = 8.0$ Hz, 1H), 6.76 (s, 1H), 6.90 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.8, 20.8, 21.0, 55.6, 60.9, 73.7, 111.6, 114.4, 123.4, 128.9, 129.2, 138.5, 140.8, 151.8, 152.5. MS (EI): m/z 409 ($M^+ + 1$). HRMS (EI) calcd. for $C_{20}H_{26}O_4$ ^{79}Br: 409.1014; found: 409.1043.

3-[(2-Bromo-3-isopropyl-4,5-dimethoxyphenyl)(hydroxyl)methyl]-2,4-dimethyl-4-(2,2,2-trifluoroethoxy)cyclohexa-2,5-dien-1-one (25)

A solution of PIDA (50 mg, 0.15 mmol) in TFE (2 mL) was added to a solution of **24** (57.5 mg, 0.14 mmol) in TFE (2 mL) at −40 °C, and the mixture was stirred for 4 h at the same temperature. The solvent was removed under reduced pressure, and the residue was purified by column chromatography, eluting with hexane–Et_2O (1/1, v/v), to give **25** (18 mg, 25%) as a yellow foam. IR ν_{max}: 1670, 1639 and 1160 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.19 (s, 3H), 1.37 (d, $J = 6.8$ Hz, 6H), 2.20 (s, 3H), 3.17 (d, $J = 4.0$ Hz, 1H), 3.70 (s, 3H), 3.65–3.71 (m, 1H), 3.86 (s, 3H), 6.14 (d, $J = 4.0$ Hz, 1H), 6.45 (d, $J = 8.0$ Hz, 1H), 6.69 (s, 1H), 6.75 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.7, 21.0, 21.2, 25.8, 29.7, 55.9, 61.0, 63.0 (q), 71.1, 75.0, 111.0, 123.7 (q), 130.0, 139.6, 141.9, 149.0, 151.5, 152.0, 185.7. MS (EI): m/z 506 (M^+). HRMS (EI) calcd. for $C_{22}H_{26}O_5F_{37}$ ^{79}Br: 506.0915; found: 506.0914.

(3-[*tert*-Butyldimethylsilyloxy]-2,6-dimethylphenyl)(3-isopropyl-2,4,5-trimethyl)methanol (27)

The alcohol **27** was prepared from **26** and **13** by the same procedure as described for the synthesis of **15**, in 72% yield. IR ν_{max}: 3470, 2956, 2933, 1479 and 1268 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.18 (s, 3H), 0.19 (s, 3H), 1.00 (s, 9H), 1.34 (d, $J = 6.8$ Hz, 3H), 1.38 (d, $J = 6.8$ Hz, 3H), 2.19 (s, 3H), 2.27 (s, 3H), 3.34–3.37 (m, 1H), 3.61 (s, 6H), 3.84 (s, 3H), 6.41 (s, 1H), 6.43 (s, 1H), 6.69 (d, $J = 8.0$ Hz, 1H), 6.89 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.2, −4.1, 13.8, 18.3, 20.7, 21.9, 21.9, 25.9, 26.0, 55.8, 60.6, 61.7, 69.9, 109.9, 118.1, 128.5, 128.9, 129.9, 130.1, 135.0, 138.8, 148.5, 149.2, 149.7, 152.4. MS (EI): m/z 474 (M^+). HRMS (EI) calcd. for $C_{27}H_{42}O_5Si$: 474.2801; found: 474.2825.

3-[Hydroxyl(3-isopropyl-2,4,5-trimethoxyphenyl)methyl]-2,4-dimethylphenol (28)

The phenol **28** was derived from **27** by the same procedure as described for the preparation of **16**, in 93% yield. IR ν_{max}: 3401, 2958, 1480, 1218 and 772 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, $J = 6.8$ Hz, 3H), 1.38 (d, $J = 6.8$ Hz, 3H), 2.23 (s, 3H), 2.27 (s, 3H), 3.34–3.38 (m, 1H), 3.47 (s, 1H), 3.62 (s, 3H), 3.64 (s, 3H), 3.85 (s, 3H), 4.69 (s,1H), 6.40 (s, 1H), 6.44 (s, 1H), 6.68 (d, $J = 8.0$ Hz, 1H), 6.91 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.8, 20.5, 21.8, 21.9, 25.9, 55.8, 60.5, 61.7, 69.6, 110.0, 114.2, 123.9, 128.6, 128.9, 130.2, 134.9, 138.8, 149.2, 149.6, 153.1. MS (EI): m/z 360 (M^+). HRMS (EI) calcd. for $C_{21}H_{28}O_5$: 360.1937; found: 360.1936.

3-[(2-Bromo-3-isopropyl-4,5-dimethoxyphenyl)(hydroxyl)methyl]-2,4-dimethyl-4-(2,2,2-trifluoroethoxy)cyclohexa-2,5-dien-1-one (29)

A solution of PIDA (98 mg, 0.30 mmol) in TFE (3 mL) was added to a solution of **28** (100 mg, 0.28 mmol) in TFE (3 mL) at −40 °C, and the mixture was stirred for 15 h at the same temperature. The solvent was removed under reduced pressure, and the residue was purified by column chromatography, eluting with hexane–Et_2O (1/1, v/v), to give **29** (20 mg, 16%) as a yellow foam. IR ν_{max}: 3499, 2988, 2938, 1671, 1641 and 1279 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.35 (d, $J = 6.8$ Hz, 3H), 1.40 (d, $J = 6.8$ Hz, 3H), 2.04 (s, 3H), 3.37–3.41 (m, 1H), 3.65–3.71 (m, 1H), 3.68 (s, 3H), 3.75 (s, 1H), 3.84 (s, 3H), 3.87 (s, 3H), 3.99–4.06 (m,1H), 6.04 (s, 1H), 6.39 (s, 1H), 6.45 (d, $J = 8.0$ Hz, 1H), 6.79 (d, $J = 8$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 21.8, 21.8, 26.0, 26.2, 29.7, 56.2, 60.7, 61.9, 63.2 (q), 67.0, 75.1, 109.6, 123.8 (q), 127.6, 130.1, 136.0, 140.1, 149.1, 149.4, 149.5, 150.6, 151.6, 185.7. MS (EI): m/z 458 (M^+). HRMS (EI) calcd. for $C_{23}H_{29}O_6F_3$: 458.1916; found: 458.1890.

(3-[*tert*-Butyldimethylsilyloxy]-2,6-dimethylphenyl)(3-isopropenyl-2,4,5-trimethylphenyl)methanone (30)

Manganese dioxide (1.19 g, 13.5 mmol) was added to a solution of **27** (0.64 g, 1.35 mmol) in CH_2Cl_2 (30 mL), and the resulting mixture was heated at reflux for 12 h. The mixture was filtered to remove insoluble materials, and the filtrate was

concentrated under reduced pressure to leave a residue, which was purified by flash silica-gel column chromatography, eluting with hexane–Et_2O (5/1, v/v), to give the ketone **30** (620 mg, 97%) as a colorless oil. IR ν_{max}: 2957, 2932, 1476, 1328 and 1275 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.19 (s, 6H), 1.00 (s, 9H), 1.32 (s, 3H), 1.33 (s, 3H), 2.03 (s, 3H), 2.09 (s, 3H), 3.40–3.47 (m, 1H), 3.48 (s, 3H), 3.73 (s, 3H), 3.92 (s, 3H), 6.72 (d, $J = 8.0$ Hz, 1H), 6.89 (d, $J = 8.0$ Hz, 1H), 7.04 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.2, 13.8, 19.0, 21.7, 25.6, 25.8, 55.9, 60.8, 62.4, 112.8, 118.8, 125.0, 126.4, 126.5, 128.0, 136.3, 142.2, 149.2, 151.7, 153.7, 153.9. MS (EI): m/z 472 (M^+). HRMS (EI) calcd. for $C_{27}H_{40}O_5Si$: 472.2645; found: 472.2643.

(3-Hydroxy-2,6-dimethylphenyl)(3-isopropenyl-2,4,5-trimethylphenyl)methanone (31)

Deprotection of the silyl group of **30** was carried out by the same procedure as described for the preparation of **16** to give **32** in 94% yield. IR ν_{max}: 3398, 2958, 2937, 1649, 1479 and 1329 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.33 (s, 3H), 2.07 (s, 3H), 2.09 (s, 3H), 3.38–3.45 (m, 1H), 3.46 (s, 3H), 3.75 (s, 3H), 3.92 (s, 3H), 4.68 (s, 1H), 6.72 (d, $J = 8.0$ Hz, 1H), 6.91 (d, $J = 8.0$ Hz, 1H), 7.09 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.7, 18.9, 21.5, 25.6, 55.8, 60.7, 62.4, 112.9, 115.3, 120.5, 125.5, 126.1, 128.1, 136.3, 142.7, 149.2, 152.0, 153.7, 154.1. MS (EI): m/z 359 ($M^+ + 1$), HRMS (EI) calcd. for $C_{21}H_{27}O_5$: 359.1858; found: 359.1886.

3-(3-Isopropyl-2,4,5-trimethoxybenzoyl)-2,4-dimethyl-4-(2,2,2-trifluoroethoxy)cyclohexa-2,5-dien-1-one (32)

A solution of PIDA (130 mg, 0.40 mmol) in TFE (3 mL) was added to a solution of **31** (132 mg, 0.37 mmol) in TFE (3 mL) at −40 °C, and the mixture was stirred for 4 h at the same temperature. The solvent was removed under reduced pressure, and the residue was purified by column chromatography, eluting with hexane–Et_2O (1/1, v/v), to give **32** (40 mg, 24%) as a yellow foam. IR ν_{max}: 2958, 2933, 1642, 1479 and 1332 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.31 (d, $J = 6.8$ Hz, 3H), 1.35 (d, $J = 6.8$ Hz, 3H), 1.47 (s, 3H), 1.91 (s, 3H), 3.42–3.49 (m, 1H), 3.51–3.59 (m, 1H), 3.71 (s, 3H), 3.79 (s, 3H), 3.93 (s, 3H), 4.08–4.16 (m,1H), 6.43 (d, $J = 8.0$ Hz, 1H), 6.72 (d, $J = 8.0$ Hz, 1H), 6.99 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 21.5, 21.6, 25.7, 26.8, 29.7, 56.1, 60.9, 63.0, 63.1 (q), 74.6, 112.6, 123.7 (q), 125.0, 129.9, 133.7, 136.9, 149.2, 153.2, 154.1, 154.5, 185.2, 193.8. MS (EI): m/z 456 (M^+). HRMS (EI) calcd. for $C_{23}H_{27}O_6F_3$: 456.1759; found: 456.1774.

(3-[*tert*-Butyldimethylsilyloxy]-2,6-dimethylphenyl)(3-isopropenyl-2,4-dimethyl)methanol (34)

The alcohol **34** was synthesized from the Grignard reagent **33** and **13** by the same procedure as described for the preparation of **15** in 80% yield. IR ν_{max}: 3503, 2956, 2932, 1593, 1263 and 1106 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.19 (s, 6H), 1.00 (s, 9H), 1.32 (d, $J = 6.8$ Hz, 3H), 1.37 (d, $J = 6.8$ Hz, 3H), 2.17 (s, 3H), 2.24 (s, 3H), 3.40–3.44 (m, 2H), 3.74 (s, 3H), 3.76 (s, 3H), 6.41 (s, 1H), 6.48 (d, $J = 8.0$ Hz, 1H), 6.64 (d, $J = 8.0$ Hz, 1H), 6.69 (d, $J = 8.0$ Hz, 1H), 6.88 (d,

$J = 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.2, −4.1, 13.9, 18.3, 20.8, 20.89, 20.93, 25.6, 25.9, 55.2, 61.8, 70.0, 106.8, 117.8, 125.9, 127.3, 128.6, 128.7, 129.5, 129.8, 138.8, 152.4, 156.8, 159.5. MS (EI): m/z 444 (M^+-1); HRMS (CI) calcd. for $C_{26}H_{41}O_4Si$: 445.2774; found: 445.2770.

(3-Hydroxy-2,6-dimethylphenyl)(3-isopropenyl-2,4-dimethyl)-methanol (35)

Deprotection of the silyl group of **34** was carried out by the same procedure as described for the preparation of **16** to give **35** in 93% yield. IR ν_{max}: 3391, 2957, 1593, 1263 and 1106 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (d, $J = 6.8$ Hz, 3H), 1.38 (d, $J = 6.8$ Hz, 3H), 2.21 (s, 3H), 2.24 (s, 3H), 3.40–3.49 (m, 2H), 3.55 (s, 1H), 3.77 (s, 6H), 6.42 (s, 1H), 6.48 (d, $J = 8.0$ Hz, 1H), 6.62 (d, $J = 8.0$ Hz, 1H), 6.69 (d, $J = 8.0$ Hz, 1H), 6.91 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.0, 20.6, 20.87, 20.90, 25.6, 55.2, 61.8, 69.9, 106.9, 114.3, 124.0, 125.9, 127.0, 128.87, 128.91, 129.5, 138.4, 152.8, 156.7, 159.6. MS (EI): m/z 330 (M^+). HRMS (CI) calcd. for $C_{20}H_{27}O_4$ ($M^+ + 1$): 331.1909; found: 331.1887.

3-[3-Isopropyl-2,4-dimethoxyphenyl)(hydroxyl)methyl]-2,4-dimethyl-4-(2,2,2-trifluoroethoxy)cyclohexa-2,5-dien-1-one (36)

The oxidation of **35** was carried out by the same procedure as described for the preparation of **29** to give **36** in 22% yield. IR ν_{max}: 3514, 2958, 1641, 1483 and 1218 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (s, 3H), 1.33 (d, $J = 6.8$ Hz, 3H), 1.40 (d, $J = 6.8$ Hz, 3H), 2.02 (s, 3H), 3.43–3.50 (m, 1H), 3.63–3.69 (m, 1H), 3.80 (s, 3H), 3.88 (s, 3H), 4.01–4.05 (m, 1H), 6.00 (s, 1H), 6.44 (d, $J = 8.0$ Hz, 1H), 6.54 (d, $J = 8.0$ Hz, 1H), 6.76 (d, $J = 8.0$ Hz, 1H), 6.77 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 20.7, 20.8, 25.7, 25.8, 29.7, 55.3, 61.8, 63.2 (q), 66.9, 75.1, 106.9, 123.7 (q), 125.3, 129.9, 130.4, 140.1, 149.5, 151.5, 157.2, 160.2, 185.8. MS (EI): m/z 429 ($M^+ + 1$). HRMS (CI) calcd. for $C_{22}H_{28}O_5F_3$: 429.1889; found: 429.1859.

(3-[*tert*-Butyldimethylsilyloxy]-2,6-dimethylphenyl)(7-isopropenyl-2,2-diphenyl-1,3-benzodioxol-5-yl)methanol (38)

The alcohol **38** was synthesized from the Grignard reagent **37** and **13** by the same procedure as described for the preparation of **15** in 51% yield. IR ν_{max}−: 2955, 2929, 2361, 1480 and 1255 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.19 (s, 6H), 0.99 (s, 9H), 2.11 (s, 3H), 2.13 (s, 1H), 2.14 (s, 3H), 2.22 (s, 3H), 5.24 (s, 1H), 5.68 (s, 1H), 6.18 (s, 1H), 6.64 (s, 1H), 6.68 (d, $J = 8.0$ Hz, 1H), 6.86 (s, 1H), 6.87 (d, $J = 8.0$ Hz, 1H), 7.33–7.35 (m, 6H), 7.55–7.58 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.2, 13.5, 18.3, 20.3, 22.5, 25.9, 71.8, 105.6, 116.0, 117.4, 118.2, 122.9, 126.2, 127.9, 128.2, 128.3, 128.9, 129.0, 129.4, 136.5, 139.3, 140.4, 140.6, 140.7, 143.1, 147.4, 152.6. MS (EI): m/z 578 (M^+); HRMS (EI) calcd. for $C_{37}H_{42}O_4Si$: 578.2852; found: 578.2882.

3-[Hydroxy(7-isopropenyl-2,2diphenyl-1,3-benzodioxol-5-yl)methyl-2,4-dimethylphenol (39)

Deprotection of the silyl group of **38** was carried out by the same procedure as described for the preparation of **16** to give **39** in 96% yield. IR ν_{max}: 3393, 2360, 2341, and 1217 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.12 (s, 3H), 2.15 (s, 3H), 2.17 (d, $J = 4.4$ Hz, 1H), 2.24 (s, 3H), 4.59 (s, 1H), 5.25 (s, 1H), 5.69 (s, 1H), 6.20 (d, $J = 4.4$ Hz, 1H), 6.63 (s, 1H), 6.68 (d, $J = 8.0$ Hz, 1H), 6.88 (s, 1H), 6.90 (d, $J = 8.0$ Hz, 1H), 7.32–7.38 (m, 6H), 7.54–7.59 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.5, 20.2, 22.5, 71.6, 105.6, 114.5, 116.1, 117.5, 123.0, 123.3, 126.2, 128.3, 128.9, 129.0, 129.1, 136.3, 139.3, 140.3, 140.55, 140.63, 147.4, 152.7. MS (EI): m/z 464 (M^+). HRMS (EI) calcd. for $C_{31}H_{28}O_4$: 464.1987; found: 464.2011.

3-[Ethoxy(3-isopropyl-4,5-dimethoxyphenyl)methyl]-2,4-dimethylphenol (40)

To a stirred solution of **19** (50 mg, 0.15 mmol) in EtOH (2 mL) 6 N HNO_3 (1 mL), was added at 0 °C, and the resulting mixture was stirred at the same temperature for 5 h. The mixture was treated with saturated $NaHCO_3$ solution, and the whole was extracted with EtOAc. The organic layer was dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography, eluting with hexane–EtOAc (10/1, v/v), to afford **40** (37.0 mg, 68%) as a colorless oil. IR ν_{max}: 3407, 2964, 1589 and 1487 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): **5** 1.11 (d, $J = 7.0$ Hz, 3H), 1.13 (d, $J = 7.0$ Hz, 3H), 1.26 (t, $J = 7.0$, 3H), 2.14 (s, 3H), 2.24 (s, 3H), 3.22–3.33 (m, 1H), 3.42–3.60 (m, 2H), 3.77 (s, 3H), 3.79 (s, 3H), 5.14 (br s, 1H), 5.85 (s, 1H), 6.66 (d, $J = 8.0$ Hz, 1H), 6.67 (s, 1H), 6.71 (s, 1H), 6.87 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) **5** 12.1, 15.5, 20.2, 23.4, 26.9, 55.6, 60.9, 64.2, 78.7, 108.0, 114.2, 116.1, 123.8, 128.6, 129.5, 137.5, 138.4, 141.6, 144.8, 152.2, 152.5. MS (CI): m/z 358 (M^+). HRMS (CI) calcd. for $C_{22}H_{30}O_4$: 358.2144; found: 358.2155.

3-Isopropyl-L,2,4-trimethoxy-5-nitrobenzene (41) and 3-Hydroxy-2, 6-dimethyl-4-nitrobenzaldehyde (42)

To a stirred solution of **28** (50 mg, 0.14 mmol) in EtOH (2 mL) 6 N HNO3 (1 mL) was added at 0 °C, and the resulting mixture was stirred at the same temperature for 2.5 h. The mixture was treated with saturated $NaHCO_3$ solution, and the whole was extracted with EtOAc. The organic layer was dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography, eluting with hexane–EtOAc (10/1, v/v), to afford **41** (25.9 mg, 73%) as a pale yellow oil. IR ν_{max}: 1522 and 296 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, $J = 7.1$ Hz, 6H), 3.47–3.54 (m, 1H), 3.82 (s, 3H) 3.88 (s, 3H), 3.92 (s, 3H), 7.33 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 25.9, 56.1, 61.0, 63.0, 106.6, 137.3, 139.9, 146.9, 148.8, 153.3. MS (CI): m/z 256 (M^+). HRMS (CI) calcd. for $C_{12}H_{18}NO_5$: 256.1173; found: 256.1185. Further elution with the same solvent system gave **42** (19.2 mg, 71%) as a pale yellow oil. IR ν_{max}: 3235, 1703, and 1524 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.53 (s, 3H), 2.54 (s, 3H), 7.86 (s, 1H),

10.61 (s, 1H), 10.85 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 19.5, 124.0, 129.7, 130.9, 131.8, 139.9, 151.9, 193.3. MS (CI): m/z 196 (M^+). HRMS (CI) calcd. for $C_9H_{10}NO_4$: 196.0594; found: 196.0610.

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