SYNTHESIS OF AN ANTIOXIDANT HAVING A DIBENZ[*b*,*f*]OXEPINE SKELETON

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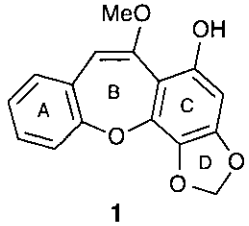
Abstract - Dibenz[*b*,*f*]oxepine derivative (**1**) isolated from a yeast as an antioxidant was synthesized *via* 17 reaction steps starting from methyl gallate. However, the physicochemical data of the synthetic compound (**1**) were different from the previously reported values. Moreover, the antioxidative activity of the synthetic **1** was slightly more active than that of the natural product.

Dibenz[*b*,*f*]oxepines and their analogues, dibenzo[*b*,*f*]thiepines, have been popular synthetic targets for drugs such as antidepressant[1] and antiinflammatory agents.[2] In contrast, except cularine alkaloids[3] few are naturally occurring dibenz[*b*,*f*]oxepines; they were mainly originated from medicinal plants.[4] To our knowledge, little work has been done on total syntheses of natural simple dibenzoxepines.[5]

An antioxidant, 1-hydroxy-3,4-methylendioxy-11-methoxydibenz[*b*,*f*]oxepine (**1**), was isolated from *Saccharomyces cerevisiae*.[6] It was slightly less active than α-tocopherol, a well-known natural antioxidant. This compound has generated our interest, due to its structural features in several functional groups and highly oxygenated C ring, and other biological activities would be also expected from the structure of its dibenz[*b*,*f*]oxepine skeleton. As part of our continuing work on antioxidants, we report herein on a total synthesis of **1** and its antioxidative activity.



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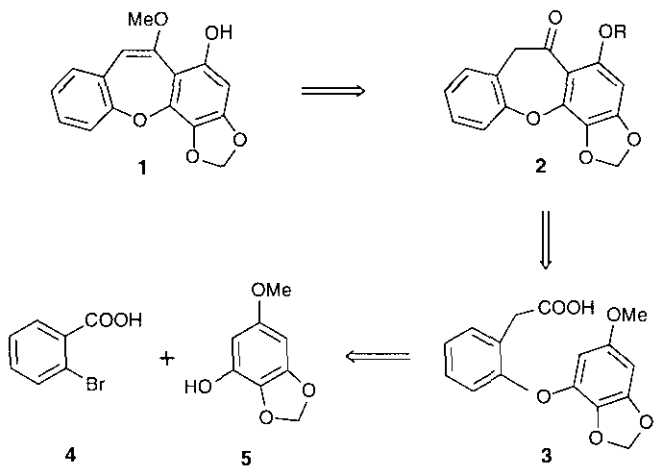
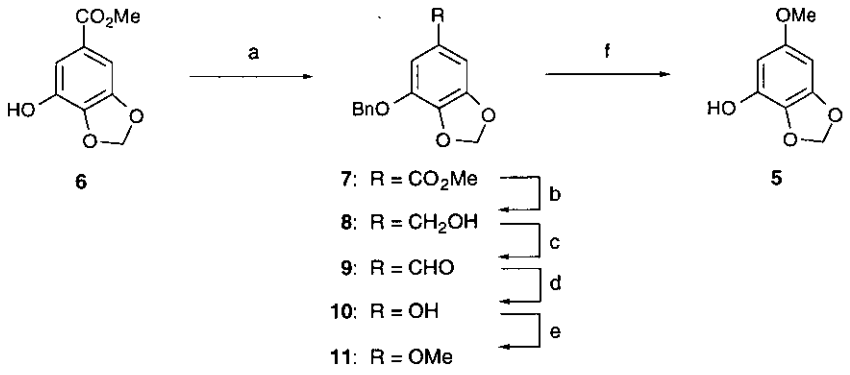
Considerable efforts on the synthesis of dibenzoxepines and dibenzothiepines have been reported.[1,7-8] One of the most common approaches to construction of the seven-membered B ring involves the Ullmann reaction[5,8] and the Friedel-Crafts reaction.[7] In the synthetic studies on cularine and cularimine, Kametani and co-workers observed that the protection of hydroxy groups in dibenz[*b,f*]oxepine derivatives with a methylendioxy group was unsuccessful under alkaline conditions.[9]

Based on these preceding studies, we planned our route for the preparation of **1** as outlined in Scheme 1. We employed the conventional method for the synthesis of key intermediate (**3**) and our synthetic approach began with incorporation of methylendioxy group prior to cyclization. The crucial steps of this synthesis are the annulation to construct a seven-membered B ring (**3**→**2**) and the formation of the enol ether after cleavage of the intramolecular hydrogen-bonding (**2**→**1**).



Scheme 1

Initially, we synthesized phenolic component (**5**), as depicted in Scheme 2. Methylenedioxy derivative (**6**), derived from methyl gallate by the reported procedure,[10] was protected with benzyl group to yield ester (**7**). Reduction of **7** with lithium aluminum hydride ($LiAlH_4$), followed by oxidation with manganese oxide (MnO_2) produced aldehyde (**9**). The Baeyer-Villiger oxidation of **9** gave phenol (**10**). Methylation of **10** with methyl iodide (MeI) in the presence of potassium carbonate (K_2CO_3) in acetone furnished methoxy derivative (**11**), which upon debenzylation with palladium on carbon (Pd-C) afforded the requisite compound (**5**).

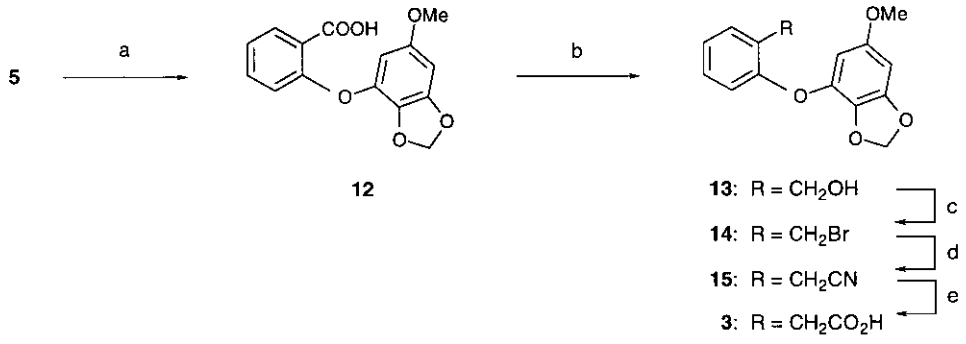


reagents: a. BnBr, NaH, DMF; b. $LiAlH_4$, Et_2O; c. MnO_2, $ClCH_2CH_2Cl$;
d. *m*-CPBA, Na_2HPO_4, CH_2Cl_2; e. MeI, K_2CO_3, acetone; f. H_2, Pd-C

Scheme 2

The Ullmann coupling between **5** and 2-bromobenzoic acid (**4**) using K_2CO_3, a catalytic amount of copper (Cu) and copper(I) iodide (CuI) in 1-methyl-2-pyrrolidinone (NMP) gave benzoic acid (**12**) in a good yield. Conversion of **12** to phenylacetic acid (**3**) requires one carbon homologation, which was achieved by the previously published methods[7] with slight modifications (Scheme 3).

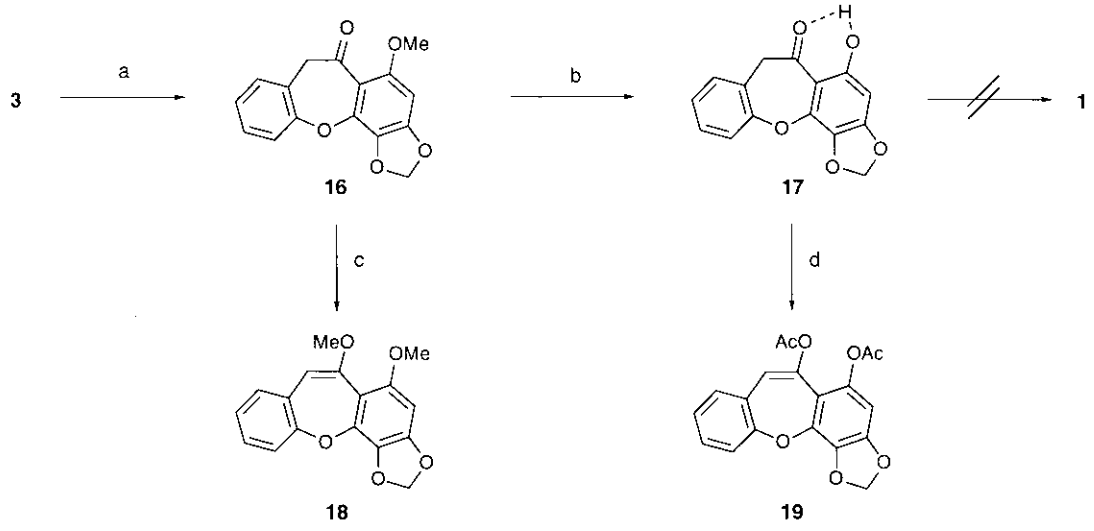
Reduction of **12** with diborane generated *in situ* resulted in a high yield of alcohol (**13**), which was subsequently led to bromide (**14**) by treatment with phosphorus tribromide (PBr_3) in CH_2Cl_2. Reaction of **14** with sodium cyanide (NaCN) in dimethyl sulfoxide (DMSO) gave nitrile (**15**), which underwent alkaline hydrolysis to phenylacetic acid (**3**).



reagents: a. **4**, K_2CO_3, Cu, CuI, NMP; b. $NaBH_4$, $BF_3{\cdot}Et_2O$, THF; c. PBr_3, CH_2Cl_2; d. NaCN, DMSO
e. NaOH (aq), EtOH, THF

Scheme 3

The intramolecular Friedel-Crafts reaction has been achieved by a variety of methods for the construction of various types of cyclic compounds.[1,7,11] In the synthesis of cularicine, however, Noguchi and MacLean reported that since a phenylacetic acid analogue having a methylendioxy moiety was not directly led to the corresponding dibenzoxepine under various Friedel-Crafts conditions, they synthesized the dibenzoxepine in a 13% overall yield from the phenylacetic acid in 4 steps *via* the Bischler-Napieralski type cyclization.[12] Actually, we attempted annulation of **3** by using several acids such as polyphosphoric acid and methanesulfonic acid. In every case the product *via* cyclization by loss of H_2O from acid (**3**) was not detected, but resulted in decomposition of **3**. On the other hand, treatment of **3** with trifluoroacetic anhydride (TFAA) and catalytic $BF_3 \cdot Et_2O$ in CH_2Cl_2 at 25°C for 5 h gave a small amount of **16** and some concomitant oxidation to unidentified yellow materials, which were probably quinones, also occurred. After considerable experimentation, dramatically improved yields were finally achieved through the modification of the reaction conditions described above; when the reaction was carried out with TFAA and 0.5 equiv of $BF_3 \cdot Et_2O$ at 0°C for 15 min, dibenz[*b,f*]oxepin derivative (**16**) was obtained in a satisfactory yield. This methodology will provide a general approach for the intramolecular Friedel-Crafts acylation of unstable compounds under acidic conditions. Exposure of **16** to boron tribromide-methyl sulfide complex ($BBr_3 \cdot (Me)_2S$) in CH_2Cl_2 yielded monohydroxy derivative (**17**).



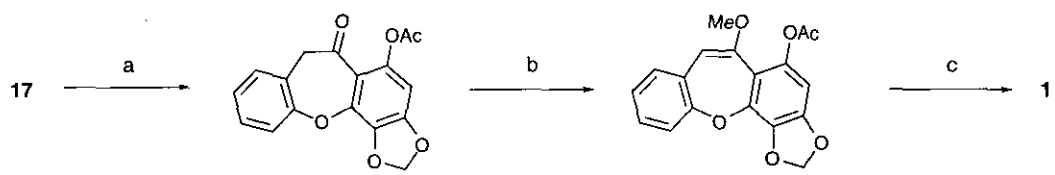
reagents: a. TFAA, $BF_3 \cdot Et_2O$, CH_2Cl_2; b. $BBr_3 \cdot (Me)_2S$, CH_2Cl_2; c. $CH(OMe)_3$, TsOH, MeOH; d. Ac_2O, Et_3N, DMAP, CH_2Cl_2 or Ac_2O, Pyridine

Scheme 4

The enol etherification of tetracycle (**17**) proved to be more difficult than we had expected. Since the carbonyl group at 10-position in compound (**17**) was intramolecularly hydrogen-bonded with the phenolic O-H (δ 13.19) at 9-position, we anticipated that the strong hydrogen-bonding would affect the reactivity of the carbonyl moiety. In order to understand the feature of the hydrogen-bonding, we tried some model experiments as depicted in Scheme 4. On attempting the direct preparation of enol ether (**1**) using trimethyl orthoformate and *p*-toluenesulfonic acid (TsOH) as a catalyst in MeOH under reflux, we observed only the recovery of the starting material. As for methoxy compound (**16**), in contrast, the enol etherification proceeded smoothly at room temperature. Next, to break up the intramolecular hydrogen-bonding, we tried acetylation of hydroxy derivative (**17**) under the conventional conditions, which resulted in diacetyl product (**19**).

These preliminary experiments led us to consider; (i) cleavage of the intramolecular hydrogen-bonding makes it possible to form the enol ether, (ii) selective protection of the phenol of **17** is required for it, and (iii) the protecting group should be tolerate under acidic conditions, but it is preferably labile under basic conditions. Thus an acetyl functionality was chosen as a protective group.

Accordingly, the selective acetylation of the hydroxy group was achieved with the 1.1 equiv of potassium *tert*-butoxide (*tert*-BuOK) and acetyl chloride (AcCl) in THF at -78°C to -20°C in a good yield. As expected, monoacetyl derivative (**20**) was easily enol etherated with trimethyl orthoformate and (+)-10-camphorsulfonic acid (CSA) as a catalyst in MeOH at 80°C to give **21** in a moderate yield together with the target compound (**1**) (31% yield) and the small recovery of **17**. Treatment of **21** with aqueous sodium hydrogencarbonate ($NaHCO_3$) in MeOH afforded **1** in a good yield (Scheme 5).



reagents: a. *tert*-BuOK, AcCl, THF; b. $CH(OMe)_3$, CSA, MeOH; c. $NaHCO_3$ (aq), MeOH

Scheme 5

The structure of the synthetic **1** was determined unambiguously from its analytical and spectral data as shown in EXPERIMENTAL section. The antioxidative activity of the synthetic compound (**1**) was equivalent to that of α-tocopherol, whereas the compound (**17**) having a phenolic hydroxy moiety showed weak antioxidative activity.[13] These results showed that the intramolecular hydrogen-bonding of phenol was also unfavorable for the activity.

The physicochemical data of the synthetic compound (**1**) showed no agreement with the previously reported values about the natural product.[14] To our surprise, the antioxidative activity of the synthetic **1** was more active than that of the natural product. These results indicated that the original structure was incorrect. Studies on the real structure of the natural product are under way in our laboratories.

EXPERIMENTAL

The UV spectra were recorded on a HITACHI U-3210 spectrophotometer. The IR spectra were recorded on a JASCO FT/IR spectrophotometer VALOR III. ^{1}H-NMR spectra were obtained at 400 MHz using a Brucker DPX400. Chemical shifts are given on the δ (ppm) scale downfield from tetramethylsilane as an internal standard. EIMS spectra were taken on a JEOL JMS-AX500. The elemental analysis was carried out with a Perkin-Elmer CHNS/O Analyzer 2400 Series II. Melting points were measured with a Yanaco micro melting point apparatus MP-500D and are uncorrected. Column chromatography was carried out by using Micro Sphere Gel D75-60A (Asahi Glass Co.). Unless otherwise stated, usual workup refers to washing of the organic layer with water and brine, followed by drying over anhydrous magnesium sulfate and removal of the solvents under reduced pressure.

Methyl 3-benzyloxy-4,5-methylendioxybenzoate (7) To a suspension of NaH (60% oil dispersion, 4.94 g, 123.4 mmol) in DMF (20 mL) was added dropwise a solution of **6**[10] (20.17 g, 102.8 mmol) in DMF (7.5 mL) at 0°C and the mixture was stirred at the same temperature for 30 min. Benzyl bromide (14.67 mL, 123.4 mmol) was added to the solution and the resulting mixture was stirred at rt for 1.5 h. The reaction mixture was poured into water and extracted with EtOAc, then worked up as usual to give **7** (20.23 g, 68%) as a crystalline powder, mp 78.2-80.4°C (from benzene, cyclohexane). EIMS *m/z*: 286 (M^+), 91. IR (KBr) ν_{max} (cm^{-1}): 1714, 1634, 1508, 1433, 1365, 1327, 926, 751. ^{1}H-NMR ($CDCl_3$): 3.87 (3H, s), 5.19 (2H, s), 6.05 (2H, s), 7.3-7.5 (7H, m). *Anal.* Calcd for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 67.24; H, 4.83.

3-Benzyloxy-4,5-methylendioxybenzyl alcohol (8) To a suspension of $LiAlH_4$ (3.15 g, 83.1 mmol) in Et_2O (30 mL) was added dropwise a solution of **7** (24.03 g, 83.1 mmol) in THF (50 mL) at 0°C and the mixture was stirred at the same temperature for 1 h. The reaction was quenched with

90% MeOH and saturated NH_4Cl solution. Insoluble materials were removed by filtration and washed with EtOAc, and then the organic layer was worked up as usual. The crude product was purified by column chromatography (*n*-hexane : EtOAc = 2 : 1) to give **8** (23.14 g, 90%) as colorless crystals, mp 61.8-63.2°C (from EtOAc, *n*-hexane). EIMS *m/z*: 258 (M^+), 200, 182. IR (KBr) ν_{max} (cm^{-1}): 3288, 3193, 3031, 1636, 1511, 1438, 1369, 927, 753, 701. ^{1}H-NMR ($CDCl_3$): 1.57 (1H, t, *J* = 5 Hz), 4.55 (2H, d, *J* = 5 Hz), 5.18 (2H, s), 5.97 (2H, s), 6.56 (1H, d, *J* = 2 Hz), 6.60 (1H, d, *J* = 2 Hz), 7.31-7.44 (5H, m). *Anal.* Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.57; H, 5.45.

3-Benzyloxy-4,5-methylendioxybenzaldehyde (9) To a solution of **8** (23.10 g, 89.4 mmol) in 1,2-dichloroethane (15 mL) was added MnO_2 (23.0 g, 102.8 mmol) and the mixture was sonicated for 12 h. Insoluble materials were removed by filtration and washed with EtOAc. The filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography (*n*-hexane : EtOAc = 3 : 1) to give **9** (21.67 g, 95%) as colorless crystals, mp 64.0-65.5°C (from benzene, *n*-hexane). EIMS *m/z*: 256 (M^+), 91. IR (KBr) ν_{max} (cm^{-1}): 1687, 1633, 1597, 1509, 1436, 1330, 926, 844, 748, 734. ^{1}H-NMR ($CDCl_3$): 5.22 (2H, s), 6.10 (2H, s), 7.06 (1H, d, *J* = 1 Hz), 7.17 (1H, d, *J* = 1 Hz), 7.34-7.46 (5H, m), 9.75 (1H, s). *Anal.* Calcd for $C_{15}H_{12}O_4$: C, 70.31; H, 4.72. Found: C, 70.32; H, 4.56.

3-Benzyloxy-4,5-methylendioxyphenol (10) To a suspension of **9** (21.66 g, 84.6 mmol) and sodium hydrogenphosphate (Na_2HPO_4) (21.7 g, 180.9 mmol) in CH_2Cl_2 (90 mL) was added portionwise *m*-CPBA (19.27 g, 111.7 mmol) at 0°C and then the mixture was stirred at rt for 1 h. The resulting mixture was refluxed overnight. The reaction mixture was poured into ice water and extracted with EtOAc, then worked up as usual. The crude product was purified by column chromatography (*n*-hexane : EtOAc = 2 : 1) to give **10** (18.58 g, 90%) as colorless crystals, mp 70.4-71.1°C (from EtOAc, *n*-hexane). EIMS *m/z*: 244 (M^+), 91, 63. IR (KBr) ν_{max} (cm^{-1}): 2951, 1740, 1647, 1508, 1479, 1440, 955, 913, 702. ^{1}H-NMR ($CDCl_3$): 5.15 (2H, s), 5.99 (2H, s), 6.36 (1H, d, *J* = 2 Hz), 6.18 (1H, d, *J* = 2 Hz), 7.32-7.42 (5H, m), 8.21 (1H, s). *Anal.* Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.56; H, 4.55.

1-Benzyloxy-5-methoxy-2,3-methylendioxybenzene (11) A mixture of **10** (12.4 g, 50.8 mmol), MeI (6.20 mL, 141.9 mmol), and K_2CO_3 (12.4 g, 90.1 mmol) in dry acetone (35 mL) was refluxed for 2 d. Insoluble materials were removed by filtration and washed with EtOAc. The filtrate was poured into 1N HCl and extracted with EtOAc, then worked up as usual. The crude product was purified by column chromatography (*n*-hexane : EtOAc = 4 : 1) to give **11** (12.14 g, 93%) as colorless oil. EIMS *m/z*: 258 (M^+), 200, 182, 165, 150. IR (neat) ν_{max} (cm^{-1}): 2890, 1644, 1508, 1446, 928, 804, 740. ^{1}H-NMR ($CDCl_3$): 3.70 (3H, s), 5.17 (2H, s), 5.90 (2H, s), 6.12 (1H, d, *J* = 2 Hz), 6.18 (1H, d, *J* = 2 Hz), 7.31-7.44 (5H, m). *Anal.* Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.72; H,

5.32.

5-Methoxy-2,3-methylendioxyphenol (5) A mixture of **11** (14.2 g, 55.4 mmol) and EtOAc (75 mL) in the presence of 10% Pd-C (715 mg) was stirred overnight under a hydrogen atmosphere. The catalyst was removed by filtration and washed with EtOAc. The filtrate was concentrated *in vacuo* to give **5** (9.03 g, 97%) as a crystalline powder, mp 46.7-48.7°C (from *n*-hexane). EIMS *m/z*: 168 (M^+), 153, 123. IR (KBr) ν_{max} (cm^{-1}): 3370, 1648, 1506, 1445, 942, 831, 797. ^{1}H-NMR ($CDCl_3$): 3.72 (3H, s), 4.81 (1H, s), 5.90 (2H, s), 6.05 (1H, d, J = 2 Hz), 6.14 (1H, d, J = 2 Hz). *Anal.* Calcd for $C_8H_8O_4$: C, 57.14; H, 4.80. Found: C, 56.99; H, 4.70.

2-(5-Methoxy-2,3-methylendioxyphenoxy)benzoic acid (12) A mixture of **5** (5.00 g, 29.7 mmol), vacuum-dried 2-bromobenzoic acid (6.57 g, 32.7 mmol), and K_2CO_3 (7.40 g, 53.5 mmol) in NMP (35 mL) was dried azeotropically. Powdered Cu (472 mg, 7.4 mmol) and CuI (1.42 g, 7.4 mmol) were added to the mixture and then the suspension was stirred at 120°C for 1 h. The reaction mixture was poured into 1N HCl and extracted with EtOAc, then worked up as usual. The crude product was purified by column chromatography (*n*-hexane : EtOAc = 2 : 1) to give **12** (6.42 g, 77%) as colorless crystals, mp 159.7-160.8°C (from EtOAc, *n*-hexane). EIMS *m/z*: 288 (M^+), 243, 168, 121. IR (KBr) ν_{max} (cm^{-1}): 2993, 1695, 1603, 1504, 1460, 933, 845, 769. ^{1}H-NMR ($CDCl_3$): 3.73 (3H, s), 5.92 (2H, s), 6.17 (1H, d, J = 2 Hz), 6.42 (1H, d, J = 2 Hz), 6.95 (1H, dd, J = 8, 1 Hz), 7.21 (1H, ddd, J = 8, 8, 1 Hz), 7.49 (1H, ddd, J = 8, 8, 2 Hz), 8.16 (1H, dd, J = 8, 2 Hz). *Anal.* Calcd for $C_{15}H_{12}O_6$: C, 62.50; H, 4.20. Found: C, 62.28; H, 4.05.

2-(5-Methoxy-2,3-methylendioxyphenoxy)benzyl alcohol (13) To a solution of **12** (6.42 g, 22.3 mmol) in THF (25 mL) was added portionwise $NaBH_4$ (0.93 g, 24.5 mmol) at 0°C over 3 min and then the mixture was stirred at the same temperature for 15 min. To the resulting mixture was then added dropwise $BF_3 \cdot Et_2O$ (3.4 mL, 27.8 mmol) at 0°C over 5 min and further stirred at rt for 1 h. The reaction mixture was poured into 1N HCl and extracted with EtOAc, then worked up as usual. The crude product was purified by column chromatography (*n*-hexane : EtOAc = 2 : 1) to give **13** (5.79 g, 95%) as colorless oil. EIMS *m/z*: 274 (M^+), 226, 198. IR (neat) ν_{max} (cm^{-1}): 3321, 2894, 1636, 1503, 1449, 928, 810, 756. ^{1}H-NMR ($CDCl_3$): 3.70 (3H, s), 4.81 (2H, s), 5.91 (2H, s), 6.09 (1H, d, J = 2 Hz), 6.34 (1H, d, J = 2 Hz), 6.88 (1H, m), 7.11 (1H, m), 7.24 (1H, m), 7.43 (1H, m). *Anal.* Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.14. Found: C, 65.55; H, 5.05.

2-(5-Methoxy-2,3-methylendioxyphenoxy)benzyl bromide (14) To a solution of **13** (5.64 g, 20.6 mmol) in CH_2Cl_2 (30 mL) was added dropwise PBr_3 (0.72 mL, 7.5 mmol) at 0°C over 1 min and then the mixture was stirred at the same temperature for 30 min. The reaction mixture was poured into ice water and extracted with EtOAc, then worked up as usual. The crude product was

purified by column chromatography (*n*-hexane : EtOAc = 5 : 1) to give **14** (5.24 g, 76%) as colorless crystals, mp 108.3-109.8°C (from EtOAc, *n*-hexane). EIMS *m/z*: 336 (M^+), 257, 227. IR (KBr) ν_{max} (cm^{-1}): 2908, 1639, 1504, 1461, 934, 846, 766. ^{1}H-NMR ($CDCl_3$): 3.70 (3H, s), 4.65 (2H, s), 5.92 (2H, s), 6.12(1H, d, J = 2 Hz), 6.35 (1H, d, J = 2 Hz), 6.85 (1H, m), 7.07 (1H, m), 7.24 (1H, m), 7.42 (1H, m). *Anal.* Calcd for $C_{15}H_{13}O_4Br$: C, 53.43; H, 3.89. Found: C, 53.36; H, 3.75.

2-(5-Methoxy-2,3-methylendioxyphenoxy)benzyl cyanide (15) To a solution of **14** (5.10 g, 15.1 mmol) in DMSO (14 mL) was added NaCN (1.11 g, 22.7 mmol) and then the mixture was stirred at 80°C for 1.5 h. The reaction mixture was poured into ice water and extracted with EtOAc, then worked up as usual. The crude product was purified by column chromatography (*n*-hexane : EtOAc = 3 : 1) to give **15** (3.91 g, 91%) as colorless crystals, mp 89.0-90.3°C (from EtOAc, *n*-hexane). EIMS *m/z*: 283 (M^+), 238, 152. IR (KBr) ν_{max} (cm^{-1}): 2892, 2249, 1632, 1490, 1442, 933, 831, 757. ^{1}H-NMR ($CDCl_3$): 3.71 (3H, s), 3.85 (2H, s), 5.90 (2H, s), 6.09 (1H, d, J = 2 Hz), 6.36 (1H, d, J = 2 Hz), 6.87 (1H, m), 7.12 (1H, m), 7.27 (1H, m), 7.47 (1H, m). *Anal.* Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.77: H, 4.41; N, 4.90.

2-(5-Methoxy-2,3-methylendioxyphenoxy)phenylacetic acid (3) To a solution of **15** (3.80 g, 13.4 mmol) in EtOH (11 mL) and THF (5 mL) was added 10N NaOH solution (6.7 mL) and then the mixture was stirred at 110°C for 16 h. The reaction mixture was poured into 1N HCl and extracted with EtOAc, then worked up as usual. The crude product was purified by column chromatography (*n*-hexane : EtOAc = 1 : 1) to give **3** (3.80 g, 94%) as colorless crystals, mp 125.0-126.9°C (from EtOAc, *n*-hexane). EIMS *m/z*: 302 (M^+), 257, 227. IR (KBr) ν_{max} (cm^{-1}): 3002, 2920, 1699, 1632, 1493, 1458, 937, 838, 762. ^{1}H-NMR ($CDCl_3$): 3.66 (3H, s), 3.78 (2H, s), 5.87 (2H, s), 6.05 (1H, d, J = 2 Hz), 6.31 (1H, d, J = 2 Hz), 6.86 (1H, m), 7.06 (1H, m), 7.22 (1H, m), 7.27 (1H, m). *Anal.* Calcd for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67. Found: C, 63.52; H, 4.50.

9-Methoxy-6,7-methylendioxy-10,11-dihydrodibenz[*b,f*]oxepin-10-one (16) To a solution of **3** (2.50 g, 8.27 mmol) in CH_2Cl_2 (25 mL) was added TFAA (1.75 mL, 12.40 mmol) and then stirred at rt for 1 h. After cooling to 0°C, BF_3·Et_2O (0.51 mL, 4.13 mmol) was added dropwise to the solution and then the mixture was stirred at the same temperature for 15 min. The reaction mixture was poured into water, neutralized with saturated $NaHCO_3$ solution, and extracted with EtOAc, then worked up as usual. The crude product was purified by column chromatography (*n*-hexane : EtOAc = 3 : 2) to give **16** (1.82 g, 77%) as a pale yellow crystalline powder, mp 140.8-142.6°C (from EtOAc, *n*-hexane). EIMS *m/z*: 284 (M^+), 269, 239. IR (KBr) ν_{max} (cm^{-1}): 2917, 1673, 1630, 1499, 1468, 935, 809, 755. ^{1}H-NMR ($CDCl_3$): 3.82 (3H, s), 4.02 (2H, s), 6.09 (2H, s), 6.38 (1H, s), 7.19 (1H, m), 7.23-7.30 (3H, m). *Anal.* Calcd for $C_{16}H_{12}O_5$: C, 67.60; H, 4.25. Found: C, 67.34; H, 4.10.

9-Hydroxy-6,7-methylendioxy-10,11-dihydrodibenz[*b,f*]oxepin-10-one (17) To a solution of **16** (2.0 g, 7.04 mmol) in CH_2Cl_2 (20 mL) was added dropwise a solution of $BBr_3 \cdot (Me)_2S$ (3.3 g, 10.55 mmol) in CH_2Cl_2 (10 mL) at 0°C over 5 min and then the mixture was stirred at the same temperature for 10 min. The reaction mixture was poured into water and extracted with EtOAc, then worked up as usual. The crude product was purified by column chromatography (*n*-hexane : EtOAc = 4 : 1) to give **17** (1.64 g, 86%) as yellow crystals, mp 173.1-175.1°C (from EtOAc, *n*-hexane). EIMS *m/z*: 270 (M^+), 253, 241, 225. IR (KBr) ν_{max} (cm^{-1}): 2909, 2805, 1652, 1628, 1476, 938, 835, 758. ^{1}H-NMR ($CDCl_3$): 4.09 (2H, s), 6.06 (2H, s), 6.27 (1H, s), 7.20 (1H, m), 7.26-7.31 (3H, m), 13.19 (1H, s). *Anal.* Calcd for $C_{15}H_{10}O_5$: C, 66.67; H, 3.73. Found: C, 66.50; H, 3.58.

1,11-Dimethoxy-3,4-methylendioxydibenz[*b,f*]oxepine (18) To a solution of **16** (100 mg, 0.35 mmol) in MeOH (5 mL) was added trimethyl orthoformate (770 μL, 7.0 mmol) and TsOH (10 mg), and then the mixture was stirred at rt for 1 h. The reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography (*n*-hexane : EtOAc = 2 : 1) to give **18** (99 mg, 94%) as colorless crystals, mp 127.6-129.3°C (from EtOAc, *n*-hexane). EIMS *m/z*: 298 (M^+), 283, 255, 240. IR (KBr) ν_{max} (cm^{-1}): 2891, 1628, 1482, 1466, 1444, 938, 853, 775. ^{1}H-NMR ($CDCl_3$): 3.76 (3H, s), 3.86 (3H, s), 5.99 (2H, s), 6.02 (1H, s), 6.39 (1H, s), 7.09-7.20 (4H, m). *Anal.* Calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.18; H, 4.50.

1,11-Diacetoxy-3,4-methylendioxydibenz[*b,f*]oxepine (19) To a solution of **17** (65 mg, 0.24 mmol) in CH_2Cl_2 (2 mL) was added Et_3N (100 μL, 0.72 mmol), acetic anhydride (100 μL, 1.06 mmol), and 4-dimethylaminopyridine (3 mg), and then the mixture was stirred at rt for 10 min. The reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography (*n*-hexane : EtOAc = 2 : 1) to give **19** (84 mg, 99%) as colorless crystals, mp 158.3-160.1°C (from EtOAc, *n*-hexane). EIMS *m/z*: 354 (M^+), 312, 270, 241. IR (KBr) ν_{max} (cm^{-1}): 2919, 1763, 1647, 1483, 1197, 932, 863, 754. ^{1}H-NMR ($CDCl_3$): 2.23 (3H, s), 2.29 (3H, s), 6.06 (2H, s), 6.37 (1H, s), 6.54 (1H, s), 7.12-7.29 (4H, m). *Anal.* Calcd for $C_{19}H_{14}O_7$: C, 64.41; H, 3.98. Found: C, 64.52; H, 3.85.

9-Acetoxy-6,7-methylendioxy-10,11-dihydrodibenz[*b,f*]oxepin-10-one (20) To a solution of **17** (500 mg, 1.85 mmol) in THF (10 mL) was added a solution of *tert*- BuOK (218 mg, 1.94 mmol) in THF (10 mL) at 0°C over 5 min and then the mixture was stirred at the same temperature for 30 min. After cooling to -78°C, AcCl (138 μL, 1.94 mmol) was added dropwise to the solution and the resulting solution was stirred at -20°C for 15 min. The reaction mixture was poured into water and extracted with EtOAc, then worked up as usual. The crude product was purified by column chromatography (*n*-hexane : EtOAc = 2 : 1) to give **20** (470 mg, 81%) as colorless crystals, mp 164.8-166.7°C (from EtOAc, *n*-hexane). EIMS *m/z*: 312 (M^+), 270, 253, 241. IR (KBr) ν_{max} (cm^{-1}): 2905,

1761, 1687, 1629, 1484, 935, 878, 750. ^{1}H-NMR ($CDCl_3$): 2.32 (3H, s), 4.00 (2H, s), 6.16 (2H, s), 6.43 (1H, s), 7.18-7.28 (4H, m). *Anal.* Calcd for $C_{17}H_{12}O_6$: C, 65.39; H, 3.87. Found: C, 65.10; H, 3.69.

1-Acetoxy-3,4-methylendioxy-11-methoxydibenz[*b,f*]oxepine (21) To a solution of **20** (400 mg, 1.28 mmol) in MeOH (40 mL) was added trimethyl orthoformate (2.8 mL, 25.62 mmol) and CSA (30 mg, 0.128 mmol), and then the mixture was stirred at 80°C for 2 h. The reaction mixture was poured into water and extracted with EtOAc, then worked up as usual. The crude product was purified by column chromatography (*n*-hexane : EtOAc = 4 : 1) to give **21** (230 mg, 69%) and **1** (93 mg, 31%) as colorless crystals (yield; based on the recovery of **17**). **21**: mp 199.0-201.0°C (from EtOAc, *n*-hexane). EIMS *m/z*: 326 (M^+), 284, 269, 241. IR (KBr) ν_{max} (cm^{-1}): 2911, 1763, 1644, 1630, 1476, 1461, 932, 905, 782. ^{1}H-NMR ($CDCl_3$,): 2.24 (3H, s), 3.82 (3H, s), 5.97 (1H, s), 6.05 (2H, s), 6.41 (1H, s), 7.11-7.21 (4H, m). *Anal.* Calcd for $C_{18}H_{14}O_6$: C, 66.26; H, 4.32. Found: C, 66.28; H, 4.19.

1-Hydroxy-3,4-methylendioxy-11-methoxydibenz[*b,f*]oxepine (1) To a solution of **21** (180 mg, 0.55 mmol) in MeOH (30 mL) was added saturated $NaHCO_3$ solution (2.0 mL) and then the mixture was stirred at rt for 30 min. The reaction mixture was poured into 1N HCl and extracted with EtOAc, then worked up as usual. The crude product was purified by column chromatography (*n*-hexane : EtOAc = 4 : 1) to give **1** (135 mg, 86%) as colorless crystals, mp 149.8-151.1°C (from EtOAc, *n*-hexane). EIMS *m/z* (%): 284 (M^+, 100), 269 (12), 241 (51). IR (KBr) ν_{max} (cm^{-1}): 3338, 2885, 1629, 1472, 1455, 937, 856, 745. UV (EtOH) λ_{max} nm (ε): 321 (12020), 285 (10390). ^{1}H-NMR ($CDCl_3$): 3.96 (3H, s), 5.97 (2H, s), 6.03 (1H, s), 6.30 (1H, s), 7.12-7.24 (4H, m), 8.00 (1H, br s). *Anal.* Calcd for $C_{16}H_{12}O_5$: C, 67.60; H, 4.25. Found: C, 67.59; H, 4.10.

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13. Assayed with guinea pig liver microsomes in MDS Panlabs. Inhibition against lipid peroxidation of compounds (**1**) and (**17**) at 300 μM were 62 and 29%, respectively. In this antioxidant system, the 50% inhibitory concentration of α-tocopherol was 280 μM.
14. Reported physicochemical data of the natural product: EIMS *m/z* (%): 284 (M^+), 269, 213, 185, 155. UV (EtOH) λ_{max} nm (ε): 301 (13800). ^{1}H-NMR (500 MHz, $CDCl_3$): 4.06 (3H, s), 5.93 (2H, s), 6.33 (1H, s), 7.13 (1H, m), 7.27-7.29 (2H, m), 7.50 (1H, m), 7.60 (1H, m) 7.88 (1H, br s).

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