# Total Synthesis of Bulbophylol-B

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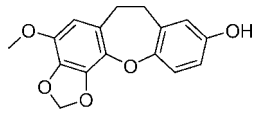
The first total synthesis of bulbophylol-B (**1**) has been achieved with the longest linear sequence of 12 steps and an overall yield of 17.9% via a new and practical approach to construct the dihydrodibenz[*b*,*f*]oxepin skeleton employing Wittig, selective reduction, and intramolecular Ullmann reactions as key steps.

Dihydrodibenz[*b*,*f*]oxepins are a set of rare natural products present in plants such as *Bauhinia purpurea* Linn, *Bauhinia variegata* Linn, and *Juncus effusus* Linn, most of which exhibit interesting and useful biological activities.[1−3] Bulbophylol-B (**1**), a natural polyoxygenated dihydrodibenz[*b*,*f*]oxepin isolated from *Bulbophyllum kwangtungense* Schltr (Orchidaceae) by Wu and co-workers, demonstrated significant cytotoxicity against human epithelial carcinoma (HeLa) and human erythromyeloblastoid leukemia (K562) cell lines.[4] Kitanaka et al. indicated that bulbophylol-B exhibited a potent inhibitory effect on nitric oxide (NO) production and radical-scavenging activity.[5] In our laboratory, **1** was also obtained from *Bulbophyllum odoratissimum* Lindl, a folk herb used for the treatment of phthisis and rheumatism in the southern part of China.[6] Although several methods for construction of the dihydrodibenz[*b*,*f*]oxepin skeleton have been reported,[7,8] to the best of our knowledge, total synthesis of dihydrodibenz[*b*,*f*]oxepin natural products, including **1**, has never been documented. Our continued interest in searching for new antitumor agents and understanding their structure−activity relationships prompted us to develop a reliable and efficient synthetic route to bulbophylol-B.




Bulbophylol-B (1)

The strategy for the synthesis of bulbophylol-B (**1**) involved the Wittig reaction, selective reduction of a carbon−carbon double bond, and intramolecular Ullmann diaryl ether forming reaction as the key steps for construction of the dihydrodibenz[*b*,*f*]oxepin skeleton, while the retro-synthetic analysis of the target molecule led to substituted benzaldehyde **2** and benzyltriphenyl-phosphonium salt **3** (Scheme 1).

Synthesis of **2** commenced with the commercially available benzene-1,2,3-triol **4**, which was converted to ketone **5**.[9] Monomethylation of *p*-OH was achieved by treating **5** with $(CH_3O)_2SO_2$ under basic conditions to give compound **6**. Treatment of **6** with $CH_2Cl_2$ and $K_2CO_3$ in DMF afforded **7**. Baeyer−Villiger oxidation of **7** with *m*-CPBA in the presence of $Na_2HPO_4$ gave the corresponding ester (**8**), which was hydrolyzed to furnish phenol **9**. Vilsmeier reaction of **9** by treatment with dimethylformamide (DMF) and phosphorus oxychloride gave the corresponding salicylaldehyde **10**, which was then protected with the triisopropyllsilyl (TIPS) group by the usual method to give the intermediate **2** (Scheme 2).

Conversion of 3-hydroxybenzaldehyde to the benzyltriphenyl-phosphonium salt (**3**) was achieved in a five-step reaction sequence. Bromination of 3-hydroxybenzaldehyde (**11**) provided **12**,[10] which was protected with a benzyl group to give **13**. Reduction of **13** with $NaBH_4$ in THF/MeOH (1:1) at 0 °C gave the corresponding phenylmethanol (**14**), which was treated with phosphorus tribromide to furnish benzyl bromide **15**. Treatment of **15** with triphenylphosphine in toluene under reflux provided **3**, which was used directly in the next step (Scheme 3).

Having prepared intermediates **2** and **3**, we focused our attention on synthesis of the target molecule (**1**). Wittig reaction of aldehyde **2** with benzyltriphenylphosphonium salt **3** (1.1 equiv) by treating with *n*-BuLi (1.1 equiv) in THF at −78 °C afforded a mixture of *trans*- and *cis*-stilbene **16** in an approximate 6:4 ratio, in 78% yield. Then deprotection of **16** with tetrabutylammonium fluoride (1.1 equiv) gave **17** in near quantitative yield (Scheme 4).

Since catalytic hydrogenation had been proved to be an efficient and convenient process for the conversion of stilbenes to dihydrostilbenes,[11] we treated stilbene **17** under $H_2$ using Pd/C or Raney Ni as catalyst in solvents such as EtOAc and MeOH. However, the main product was 5-(3-hydroxyphenethyl)-7-methoxybenzo-[*d*][1,3]dioxol-4-ol, a natural dihydrostilbene reported previously,[12] and no **18** was found in the reaction mixture. This result illustrated that the carbon−bromine bond of **17** was sensitive under these conditions and had been cleaved via catalytic hydrogenolysis. Therefore, other reduction systems, such as Zn/HCl,[13] $NaBH_4$/$NiCl_2$,[14] and $TsNHNH_2$/NaOAc[15] were tested, and the latter was found to be the most efficient agent. The solution of stilbene **17**, 4-methylbenzenesulfonohydrazide (5.0 equiv), and anhydrous sodium acetate (2.0 equiv) in EtOH was refluxed under $N_2$ for 2 h to provide the desired dihydrostilbene **18** in 95% yield. Under these conditions, the double bond of **17** was reduced with a high degree of selectivity, while the aromatic benzyl ether and aromatic halide bonds remained unaffected.

Compared with palladium-catalyzed O-arylations[16] or $S_NAr$-based reactions on aryl fluorides,[17] the Ullmann reaction is a more common method for forming biaryl-ether linkages. Attempted synthesis of **19** was carried out in pyridine at 130−140 °C by employing Cu, $Cu_2O$, CuCl, or CuBr as a catalyst, in the presence of $K_2CO_3$ or NaH as a base, but the reaction did not go to completion and/or a complex mixture was obtained. In 2002, Olivera[18] and co-workers reported that a soluble copper(I) complex, CuBr·DMS, promoted intramolecular Ullmann biaryl-ether coupling in good yields (74−87%).

Following the procedure described above, the premixed solution of dihydrostilbene **18**, CuBr·DMS (2.0 equiv), and NaH (1.1 equiv) in anhydrous pyridine was heated under $N_2$ at 120 °C for 6 h to give dihydrodibenzoxepin **19** in 89% yield. The excellent yield obtained was due probably to the high catalytic efficiency of the copper(I) bromide−dimethylsulfide complex and the stability of the dihydrostilbene substrate under Ullmann reaction conditions.

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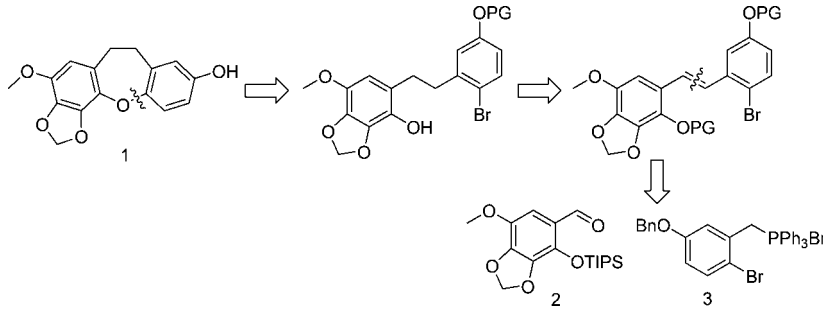
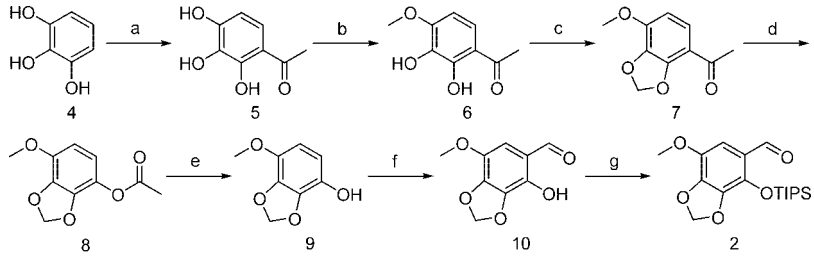
**Scheme 1**

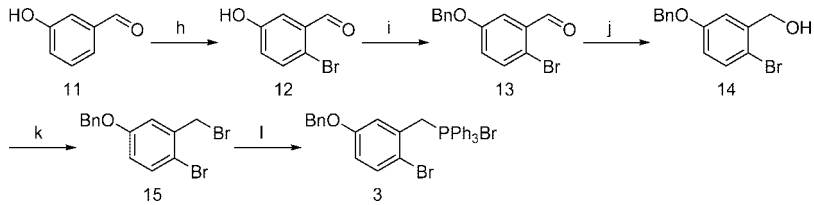


**Scheme 2**[a]



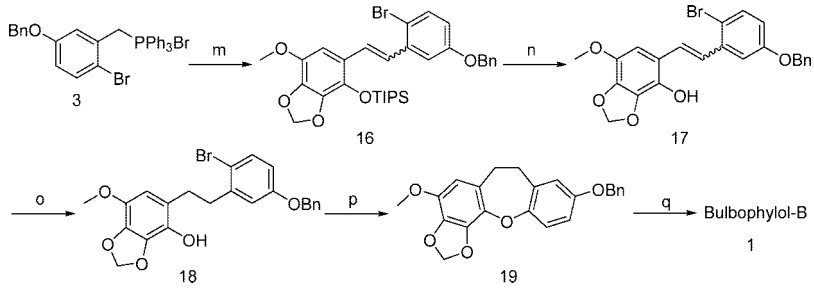
[a] Reagents and conditions: (a) $(CH_3CO)_2O$ (1.1 equiv), $H_2SO_4$, reflux (90%); (b) $(CH_3O)_2SO_2$ (0.6 equiv), $K_2CO_3$ (1.2 equiv), $CH_3COCH_3$, reflux; (c) $CH_2Cl_2$ (2 equiv), $K_2CO_3$ (1.5 equiv), DMF, 90 °C (59% from **5**); (d) *m*-CPBA (5.0 equiv), $Na_2HPO_4$, (1.3 equiv), $CH_2Cl_2$, 0 °C, then reflux; (e) KOH (1.1 equiv), $H_2O$, RT (78%) (from **7**); (f) $POCl_3$ (4.0 equiv), DMF (8.7 equiv), 0 °C, then 75 °C (79%); (g) TIPS-Cl (1.0 equiv), imidazole (2.5 equiv), THF, reflux (89%).

**Scheme 3**[a]



[a] Reagents and conditions: (h) $Br_2$ (1.0 equiv) $CCl_4$, 0 °C (76%); (i) BnCl (1.1 equiv), $K_2CO_3$ (1.5 equiv) DMF, 80 °C (98%); (j) $NaBH_4$ (0.5 equiv), THF/MeOH, 0 °C (98%); (k) $PBr_3$ (0.4 equiv), THF, 0 °C to reflux (95%); (l) $PPh_3$ (1.0 equiv), toluene, reflux (90%).

**Scheme 4**[a]



[a] Reagents and conditions: (m) *n*-BuLi (1.1 equiv), THF, then **2** (1.0 equiv), −78 °C (78%); (n) TBAF (1.1 equiv), THF, RT (98%); (o) Ts-$NHNH_2$ (5.0 equiv), NaOAc (2.0 equiv), EtOH, reflux (95%); (p) CuBr·DMS (2.0 equiv), NaH (1.1 equiv), Py, 120 °C (89%); (q) $H_2$, 10% Pd/C, EtOH, RT (95%).

Cleavage of the benzyl protecting group of **19** via hydrogenolysis in the presence of Pd/C gave **1** in near quantitative yield. Synthetic **1** was identical in all respects ($^1$H NMR, $^{13}$C NMR, MS) with natural bulbophylol-B (Scheme 4).

In summary, we have completed an efficient total synthesis of bulbophylol-B (**1**) from commercially available benzene-1,2,3-triol and 3-hydroxybenzaldehyde with the longest linear sequence of 12 steps and an overall yield of 17.9%. This is the first example of the total synthesis of a dihydrodibenz[*b*,*f*]oxepin natural product. Further, we have developed a new and practical approach to construct the dihydrodibenz[*b*,*f*]oxepin skeleton employing Wittig, selective reduction, and intramolecular Ullmann reactions as key steps. Compared with reported methods, the main advantages of the present procedure are higher yields and milder conditions.

## Experimental Section

**General Experimental Procedures.** Melting points were determined using a hot-stage microscope and are uncorrected. $^1$H and $^{13}$C NMR spectra were taken in $CDCl_3$ solution on Bruker ARX-300 or Bruker ARX-600 spectrometers with TMS as the internal reference (Bruker BioSciences). Mass spectra were obtained using a Micromass Quattro micro API mass spectrometer (Waters Corp, Milford, MA). Elemental analyses (C and H) were performed at Jilin University (Changchun, China). Thin-layer chromatography was performed on GF254 silica gel plates (0.25 mm layer, Qingdao Ocean Chemicals), and the plates

were examined under UV light at 254 nm. Column chromatography was run on silica gel (200−300 mesh) from Qingdao Ocean Chemicals (Qingdao, China). Unless otherwise noted, all materials were obtained from commercially available sources and were used without further purification.

**2,3,4-Trihydroxyacetophenone (5).** Equimolar quantities of pyrogallol (**4**) (2.5 g, 19.8 mmol) and $Ac_2O$ (1.9 mL, 19.8 mmol) were refluxed with a drop of concentrated $H_2SO_4$ for 1 h. The mixture was cooled and poured into 10 mL of $H_2O$ containing 2 mL of EtOH. Two drops of concentrated HCl was added, and the solution was refluxed for 45 min to decompose excess $Ac_2O$. The reaction mixture was concentrated *in vacuo* and the residue crystallized from *n*-hexane/EtOAc, yielding **5** as a yellow, crystalline solid (3.0 g, 90%): mp 171−173 °C. (lit.[9] mp 169−172 °C); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 12.73 (1H, s, OH), 7.30 (1H, d, $J$ = 8.9 Hz, Ar-H6), 6.53 (1H, d, $J$ = 8.9 Hz, Ar-H5), 5.84 (1H, s, OH), 5.44 (1H, s, OH), 2.57 (3H, s, $COCH_3$).

**2,3-Dihydroxy-4-methoxyacetophenone (6).** A solution of **5** (5.0 g, 29.8 mmol) and $K_2CO_3$ (4.9 g, 35.5 mol) in 200 mL of acetone was stirred at room temperature for 45 min. Then $(CH_3O)_2SO_2$ (1.6 mL, 16.4 mmol) was added dropwise over 1.5 h. The reaction mixture was refluxed for 6 h and then cooled to room temperature. After filtration and concentration, the resulting residue was used directly in the next step.

**4-Methoxy-2,3-methylenedioxyacetophenone (7).** To a solution of **6** (5.4 g, 29.8 mmol) in DMF (30 mL) were added $CH_2Cl_2$ (9.5 mL, 59.5 mmol) and $K_2CO_3$ (6.2 g, 44.6 mmol). The reaction mixture was stirred under reflux for 6 h at 90 °C. After filtration, the solvent was removed *in vacuo* to afford a black solid, which was subjected to flash column chromatography (*n*-hexane/EtOAc, 5:1) to yield **7** as a white solid (4.7 g, two steps total yield 59%): mp 99−100 °C (lit.[19] mp 100−101 °C); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.44 (1H, d, $J$ = 9.1 Hz, Ar-H6), 6.59 (1H, d, $J$ = 9.1 Hz, Ar-H5), 6.11 (2H, s, $OCH_2O$), 3.96 (1H, s, $OCH_3$), 2.56 (3H, s, $COCH_3$).

**4-Methoxy-2,3-methylenedioxyphenyl Acetate (8).** To a suspension of **7** (5.0 g, 25.5 mmol) and anhydrous $Na_2HPO_4$ (4.7 g, 33.2 mmol) in $CH_2Cl_2$ (50 mL) was added *m*-CPBA (85%, 23.4 g, 127.5 mmol), in portions and in an ice−water bath, and the mixture was stirred at room temperature for 1 h. The resulting mixture was refluxed overnight, then cooled and filtered. The filter cake was washed with $CH_2Cl_2$ (3 × 30 mL). Evaporation of the solvent *in vacuo* gave a residue, which was directly used in the next reaction.

**4-Methoxy-2,3-methylenedioxyphenol (9).** KOH (1.4 g, 25 mmol) in $H_2O$ (10 mL) was added to the crude **8** (5.5 g, 25.8 mmol) in MeOH (20 mL), and the mixture was stirred for 2 h at room temperature. The mixture was concentrated to 10 mL and acidified with 2 M HCl (5 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 20 mL), washed with $H_2O$ (2 × 20 mL) and brine (20 mL), dried over anhydrous $Na_2SO_4$, and concentrated. The residue was purified by column chromatography (CC) (*n*-hexane/EtOAc, 3:1) to give **9** (4.38 g; two steps total yield 78%) as a white solid: mp 103−105 °C (lit.[12] mp 100−101 °C); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.43 (1H, s, H-6), 6.42 (1H, s, H-5), 5.99 (2H, s, $OCH_2O$), 4.48 (1H, s, O*H*), 3.85 (1H, s, $OCH_3$).

**2-Hydroxy-3,4-methylenedioxy-5-methoxybenzaldehyde (10).** $POCl_3$ (5.5 mL, 59.5 mmol) was added dropwise to DMF (10 mL, 129.4 mmol) over 15 min at 5 °C, then stirred at room temperature for 20 min followed by addition of **9** (2.5 g, 14.9 mmol) in portions. The mixture was slowly heated to 75 °C and then stirred at this temperature for 2 h. The resulting mixture was cooled to 5 °C and poured into $H_2O$ (50 mL). After filtration, the filter cake was purified by CC (*n*-hexane/$CHCl_3$, 1:1) to give **10** (2.3 g, 79%) as a white solid: mp 181−182 °C (lit.[12] mp 179−180 °C); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.83 (1H, C*H*O), 9.73 (1H, s, O*H*), 6.75 (1H, s, Ar-H), 6.18 (2H, s, $OCH_2O$), 3.93 (3H, s, $OCH_3$).

**2-Triisopropylsilyoxy-3,4-methylenedioxy-5-methoxybenzaldehyde (2).** Imidazole (1.9 g, 28.4 mmol) was added to a solution of **10** (2.0 g, 11.4 mmol) and triisopropylchlorosilane (2.4 mL, 11.4 mmol) in anhydrous THF (20 mL). The mixture was stirred for 4 h, diluted with 5% $NaHCO_3$ (10 mL), extracted with EtOAc (3 × 20 mL), dried, and concentrated *in vacuo*. The residue was purified by CC (*n*-hexane/EtOAc, 10:1) to give **2** (3.4 g, 89%) as a white solid: mp 28−30 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.33 (1H, s, C*H*O), 7.07 (1H, s, Ar-H6), 6.05 (2H, s, $OCH_2O$), 3.88 (3H, s, $OCH_3$), 1.29−1.37 (3H, m, 3 × C*H*), 1.11 (18H, s, 6 × $CH_3$); EIMS *m*/*z* $[M]^+$ 309 (11), 174 (11), 131 (100), 103 (63).

**2-Bromo-5-hydroxybenzaldehyde (12).** $Br_2$ (4.2 mL, 82 mmol) was added dropwise over 15 min to a solution of 3-hydroxbenzaldehyde **11** (10.0 g, 82 mmol) in $CCl_4$ (250 mL) kept at 25 °C. The reaction mixture was stirred for 2 h at room temperature, after which $H_2O$ (350 mL) and $CH_2Cl_2$ (350 mL) were added. The organic layer was separated and dried, and the solvent was removed *in vacuo* to afford **12** (6.26 g, 76%) as a white solid: mp 134−136 °C (lit.[20] mp 135−136 °C); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.29 (1H, s, ArC*H*O), 7.53 (1H, d, $J$ = 9.0 Hz, Ar-H2), 7.40 (1H, d, $J$ = 3.0 Hz, Ar-H5), 7.01 (1H, dd, $J$ = 9.0 Hz, 3.0 Hz, Ar-H3). Anal. Calcd for $C_7H_5BrO_2$: C, 41.82; H, 2.51. Found: C, 41.66; H, 2.46.

**2-Bromo-5-benzyloxybenzaldehyde (13).** A mixture of **12** (8.0 g, 39.9 mmol), 1-(chloromethyl)benzene (4.9 mL, 41.9 mmol), and anhydrous $K_2CO_3$ (8.3 g, 59.9 mmol) in DMF (50 mL) was stirred at 80 °C for 2 h, cooled to room temperature, and then poured into $H_2O$ (200 mL). The solid was filtered and washed, and the filtrate was extracted with EtOAc, brined, dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo* to give **13** (11.3 g, 98%) as a pale yellow solid: mp 44−46 °C (lit.[21] mp 43−45 °C); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.30 (1H, s, ArC*H*O), 7.50−7.55 (2H, m, Ar-H2/H5), 7.34−7.44 (5H, m, 5 × Ar-H), 7.10 (1H, dd, $J$ = 9.0 Hz, 3.0 Hz, Ar-H3), 5.09 (2H, s, $ArOCH_2Ph$). Anal. Calcd for $C_{14}H_{11}BrO_2$: C, 57.36; H, 3.81. Found: C, 57.39; H, 3.85.

**2-Bromo-5-benzyloxybenzyl Alcohol (14).** $NaBH_4$ (65.0 mg, 1.7 mmol) was added, in portions, to **13** (1.0 g, 3.5 mmol) in 10 mL of $CH_3OH$/THF (1:1) in an ice−water bath for 30 min. The solvent was evaporated. Then 1 M HCl was poured into the mixture, which was then extracted with $CH_2Cl_2$, brined, dried ($Na_2SO_4$), and concentrated *in vacuo* to afford **14** (1.0 g, 98%) as white solid: mp 88−90 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.33−7.43 (6H, m, 5 × Ar-H, Ar-H6), 7.15 (1H, d, $J$ = 3.0 Hz, Ar-H2), 6.79 (1H, dd, $J$ = 8.7 Hz, 3.0 Hz, Ar-H3), 5.07 (2H, s, $ArOCH_2Ph$), 4.71 (2H, s, $CH_2OH$); EIMS *m*/*z* $[M]^+$ 292 (3), 293 (3), 91 (100), 89 (6), 77 (5), 66 (5). Anal. Calcd for $C_{14}H_{13}BrO_2$: C, 57.36; H, 4.47. Found: C, 57.26; H, 4.43.

**2-Bromo-5-benzyloxybenzyl Bromide (15).** To a solution of **14** (2.0 g, 6.8 mmol) in 20 mL of anhydrous THF was added $PBr_3$ (0.7 g, 2.7 mmol) in anhydrous THF (3.0 mL) at a rate maintaining reflux. After heating and stirring for an additional 4 h under $N_2$, the mixture was cooled and poured into $H_2O$ and extracted with EtOAc. The organic layer was washed successively with a saturated $NaHCO_3$ solution, $H_2O$, and brine, then dried over anhydrous $Na_2SO_4$. The solvent was removed *in vacuo* to give **15** (2.3 g, 95%) as a white solid: mp 64−65 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.37−7.46 (6H, m, 5 × Ar-H, Ar-H6), 7.08 (1H, d, $J$ = 3.0 Hz, Ar-H2), 6.80 (1H, dd, $J$ = 8.7 Hz, 3.0 Hz, Ar-H3), 5.04 (2H, s, $ArOCH_2Ph$), 4.55 (2H, s, $CH_2Br$); EIMS *m*/*z* $[M]^+$ 358 (2), 356 (4), 275 (3), 156 (3), 91 (100), 77 (10). Anal. Calcd for $C_{14}H_{12}Br_2O$: C, 47.23; H, 3.40. Found: C, 47.20; H, 3.45.

**Benzyltriphenyphosphonium Salt (3).** The mixture of **15** (10.0 g, 36.4 mmol) and triphenylphosphine (9.5 g, 36.4 mmol) in anhydrous toluene was refluxed for 8 h, then cooled and filtered. The filter cake was washed with toluene and dried to afford **3** (17.6 g, 90%) as a white solid.

**1-(2-Triisopropylsilaneoxy-3,4-methylenedioxy-5-methoxyphenyl)-2-(2-bromo-5-benzyloxy)ethene (16).** To a suspension of **3** (2.0 g, 3.7 mmol) in anhydrous THF (15 mL) at −78 °C was added *n*-BuLi (1.6 mL of a 2.5 M solution in hexane; 4.1 mmol). The resulting red solution was stirred under $N_2$ for 1 h. Then a solution of **2** (1.2 g, 3.7 mmol) in anhydrous THF (5 mL) was added dropwise over 30 min. The reaction mixture was stirred for an additional 2 h under $N_2$, then stirred for 2 h at room temperature. The reaction was quenched with saturated aqueous $NH_4Cl$. Then the mixture was extracted with $CH_2Cl_2$, and the combined organic layer was washed with brine and dried ($Na_2SO_4$). The solvent was removed *in vacuo* to afford a crude product, which was separated by flash chromatography (*n*-hexane/EtOAc, 20:1) to yield **16** (1.7 g, 78%, mixture of *Z*/*E* isomers) as a clear oil: $^1$H NMR (300 MHz, $CDCl_3$) *Z*/*E* $\delta$ 7.30−7.46 (6H, m, 5 × Ar-H, Ar-H3′), 6.87/6.90 (1H, d, $J$ = 3.0 Hz, Ar-H4′), 6.82/6.77 (1H, d, $J$ = 12 Hz, C*H*═), 6.72 (1H, d, $J$ = 3.0 Hz, Ar-H6′), 6.54/6.77 (1H, d, $J$ = 12 Hz, C*H*═), 6.18/6.80 (1H, s, Ar-H6), 5.91/5.96 (2H, s, $OCH_2O$), 4.80/5.04 (2H, s, $ArOCH_2Ph$), 3.42/3.93 (3H, s, $OCH_3$), 1.26−1.36 (3H, m, 3 × C*H*),1.22 (18H, s, 6 × $CH_3$); EIMS *m*/*z* $[M]^+$ 287 (2), 174 (10), 133 (99), 103 (75), 89 (16), 75 (100).

**1-(2-Hydroxy-3,4-methylenedioxy-5-methoxyphenyl)-2-(2-bromo-5-benzyloxy)ethene (17).** To a stirred solution of **16** (1.0 g, 1.7 mmol) in THF (5 mL) was added TBAF (46.2 mg, 1.8 mmol). The reaction mixture was stirred for 30 min at room temperature, then diluted with EtOAc and washed with 0.5 M HCl, and the organic layer was extracted with EtOAc. The combined organic layer was washed with $H_2O$ and brine, then dried ($Na_2SO_4$) and concentrated *in vacuo* to give **17** (0.8 g, 98%) as a clear oil: $^1$H NMR (300 MHz, $CDCl_3$) *Z*/*E* $\delta$ 7.29−7.46 (6H, m, 5 × Ar-H, Ar-H3′), 6.82/7.14 (1H, d, $J$ = 3.0 Hz, Ar-H6′), 6.74/6.77 (1H, d, $J$ = 3.0 Hz, Ar-H4′), 6.69/6.70 (H, br s, C*H*═C*H*), 6.21 (1H, s, Ar-H6), 5.97/6.02 (2H, s, OC$H_2$O), 4.57/4.82 (2H, s, ArOC$H_2$Ph), 3.57/3.91 (3H, s, OC$H_3$); EIMS *m*/*z* $[M]^+$ 378 (2), 376 (20), 285 (23), 181 (17), 111 (16), 97 (28). 91(100). Anal. Calcd for $C_{23}H_{19}BrO_5$: C, 60.67; H, 4.21. Found: C, 60.57; H, 4.15.

**1-(2-Hydroxy-3,4-methylenedioxy-5-methoxyphenyl)-2-(2-bromo-5-benzyloxy)ethane (18).** NaOAc (0.9 g, 11 mmol) and *p*-tolysulfonylhydrazide (0.9 g, 4.4 mmol) were added to a solution of **17** (1.0 g, 2.2 mmol) in EtOH (10 mL), and the mixture was refluxed for 2 h under $N_2$. Then the solution was worked up using $Et_2O$, saturated aqueous $NaHCO_3$, and brine and dried over $MgSO_4$, and the solvent was removed *in vacuo*. The residue was purified by CC (*n*-hexane/EtOAc, 4:1) to give **18** (1.0 g, 95%) as a white solid: mp 139−142 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.34−7.55 (6H, m, 5 × Ar-H, Ar-H3′), 6.83 (1H, d, $J$ = 3.0 Hz, Ar-H6′), 6.68 (1H, dd, $J$ = 8.7, 3.0 Hz, Ar-H4′), 6.24 (1H, s, Ar-H6), 5.93 (2H, s, OC$H_2$O), 4.99 (2H, s, ArOC$H_2$Ph), 3.80 (3H, s, OC$H_3$), 2.93 (2H, d, $J$ = 8.1 Hz, C$H_2$), 2.84 (2H, d, $J$ = 8.1 Hz, C$H_2$); EIMS *m*/*z* $[M]^+$ 358 (2), 356 (4), 354 (2), 156 (3), 91 (100), 77 (10). Anal. Calcd for $C_{23}H_{21}BrO_5$: C, 60.41; H, 4.63. Found: C, 60.35; H, 4.60.

**2-Methoxy-3,4-methylenedioxy-8-benzyloxy-10,11-dihydrodibenz-[*b*,*f*]oxepin (19).** NaH (95% in oil dispersion, 64.0 mg, 2.4 mmol) was added to a stirred solution of **18** (1.0 g, 2.2 mmol) and CuBr·$Me_2S$ (99%, 0.8 g, 4.4 mmol) in anhydrous pyridine (10 mL) under $N_2$ at ambient temperature. After stirring for 15 min, the reaction mixture was heated at 120 °C for 5.5 h. The mixture was allowed to cool, poured into 1.37 M HCl (10 mL), and extracted with $CH_2Cl_2$ (5 × 10 mL). The organic layer was washed with 0.31 M $CuSO_4$ (1 × 5 mL) and dried ($Na_2SO_4$), and the solvent removed *in vacuo*. The residue was purified by CC (*n*-hexane/EtOAc, 8:1) to give **19** (0.7 g, 89%) as a white solid: mp 148−150 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.37−7.42 (5H, m, 5 × Ar-H), 7.26 (1H, d, $J$ = 3.0 Hz, Ar-H9), 6.83 (1H, d, $J$ = 8.7 Hz, Ar-H6), 6.70 (1H, dd, $J$ = 8.7, 3.0 Hz, Ar-H7), 6.24 (1H, s, Ar-H1), 5.95 (2H, s, OC$H_2$O), 4.99 (2H, s, ArOC$H_2$Ph), 3.80 (3H, s, OC$H_3$), 2.92−2.95 (2H, m, C$H_2$), 2.81−2.85 (2H, m, C$H_2$); EIMS *m*/*z* $[M]^+$ 377 (6), 347 (2), 283 (8), 271 (11), 181 (24), 91 (100). Anal. Calcd for $C_{23}H_{20}O_5$: C, 73.39; H, 5.36. Found: C, 73.32; H, 5.40.

**2-Methoxy-3,4-methylenedioxy-8-hydroxy-10,11-dihydrodibenz-[*b*,*f*]oxepin (1, bulbophylol-B).** A solution of **19** (1.0 g, 2.7 mmol) in EtOAc (20 mL) was stirred in the presence of 10% Pd−C (50 mg) under $H_2$ at room temperature for 12 h. The catalyst was removed by filtration and washed with EtOAc. The filtrate was concentrated *in vacuo* to give **1** (0.7 g, 95%) as a light yellow power: mp 106−108 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.06 (1H, d, $J$ = 4.8 Hz, Ar-H9), 6.61 (2H, br s, Ar-H6, H7), 6.25 (1H, s, Ar-H1), 6.0 (2H, s, OC$H_2$O), 3.84 (3H, s, OC$H_3$), 3.05 (4H, br s, C$H_2$C$H_2$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 151.8 (C, C-8), 151.0 (C, C-5a), 139.7 (C, C-2), 139.2 (C, C-4), 136.1 (C, C-4a), 134.6 (C, C-3), 133.0 (C, C-9), 126.7 (C, C-11a), 121.9 (C, C-7), 116.5 (C, C-9a), 113.7 (C, C-6), 107.7 (C, C-1), 102.1 (C, OC$H_2$O), 56.9 (C, OC$H_3$), 30.6 (C, C-11), 29.7 (C, C-10); EIMS *m*/*z* $[M]^+$ 286 (100), 265 (10), 228 (16), 213 (13), 185 (11), 128 (10), 77 (11). Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 67.05; H, 4.98.

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**Supporting Information Available:** Copies of proton and carbon NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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