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# Total Syntheses of Multicaulins via Oxidative Photocyclization of Stilbenes

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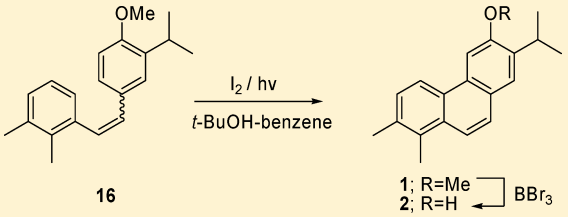
Supporting Information

**ABSTRACT:** The Wittig reaction of 3-isopropyl-4-methoxybenzaldehyde and 2,3-dimethylbenzylphosphonium bromide afforded the corresponding stilbene mixture **16**. Oxidative photocyclization of stilbene **16** with iodine facilitated the first total synthesis of 7-isopropyl-6-methoxy-1,2-dimethylphenanthrene, multicaulin (**1**). The *O*-demethylation of **1** with $BBr_3$ afforded the 7-isopropyl-1,2-dimethylphenanthren-6-ol, *O*-demethylmulticaulin (**2**).




*Salvia* is a common genus among medicinal plants. More than 700 secondary metabolites from *Salvia* species include various terpenoids, steroids, and polyphenols, and their biological activities have recently been reviewed.[1] These metabolites possess acetylcholinesterase (AChE) inhibitory, antitumor, antifeedant, antihypertensive, cardiovascular, antileishmanial, antimicrobial, antioxidant, cytotoxic, and anti-HIV activities. In 1997, Ulubelen and co-workers[2] isolated four new aromatic norditerpenoids (**1**−**4**), two new abiatene diterpenoids (**5**, **6**), and a new pimarene diterpenoid (**7**) along with a series of known compounds from *Salvia multicaulis*. Compounds **1**−**7** were tested against the *Mycobacterium tuberculosis* strain H37Rv and exhibited strong antituberculous activity, with MIC values ranging from 0.46 to 7.3 μg/mL. Among these compounds, *O*-demethylmulticaulin (**2**) exhibited the strongest antituberculous activity, with an MIC value of 0.46 μg/mL. Sairafianpour and co-workers[3] isolated compound **2** and its dihydro derivative **8** from *Salvia hydrangea* as new 20-norabiatenes. Only two reports describing the isolation of multicaulins from nature are known. To date, synthesis pathways toward the formation of either **1** or **2** have not been described. The synthesis of **1** and **2** was attempted due to their high antituberculosis activities.

Our synthesis is based on a convergent method in which the relevant stilbene **16**, which possesses all of the required functionalities, was first prepared. Therefore, 2-isopropylphenol (**9**) was *O*-methylated with $Me_2SO_4$ to yield 2-isopropylanisole (**10**) (93% yield). Bromination of electron-rich aromatic compound **10** using molecular $Br_2$ afforded bromoanisole **11** in low yield along with several side products. However, the bromination of 2-isopropylanisole (**10**) with LiBr/$(NH_4)_2Ce(NO_3)_6$[4] selectively yielded 4-bromo-2-isopropylanisole (**11**) in 97% yield. Subsequent lithiation of **11** with *n*-BuLi followed by formylation with *N*-formylpiperidine instead of conventionally used DMF[5] afforded 3-isopropyl-4-methoxybenzaldehyde (**12**) in 90% yield (Scheme 1).

2,3-Dimethylbenzyl bromide (**15**) was synthesized in two steps starting from 2,3-dimethylbenzaldehyde (**13**). Reduction

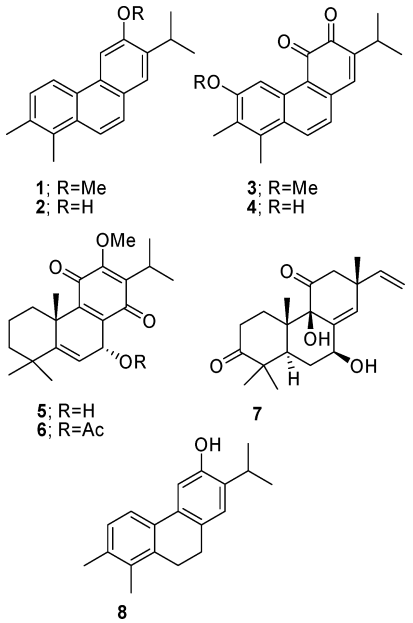



**Figure 1.** Structures of natural compounds **1**−**8**.

of benzaldehyde **13** with $LiAlH_4$ afforded 2,3-dimethybenzyl alcohol (**14**) (89% yield), which was converted to 2,3-dimethylbenzyl bromide (**15**) in 93% yield via treatment with $PBr_3$ (Scheme 2).

2,3-Dimethylbenzyl bromide (**15**) was converted to the corresponding phosphonium salt, which was used in the next step without further purification. The Wittig reaction between the phosphonium salt and 3-isopropyl-4-methoxybenzaldehyde (**12**) resulted in (*E*/*Z*)-stilbene mixture **16** in a yield of 90%. Kaliakoudas and co-workers[6] developed a successful $I_2$-oxidative photocyclization of stilbenes to afford substituted

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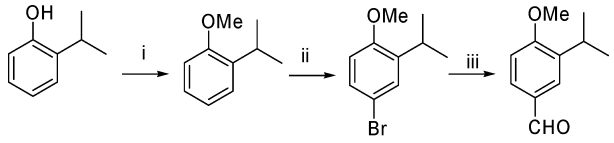
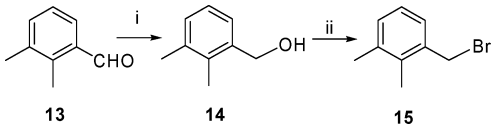
**Scheme 1. Synthesis of Compound 12**[a]



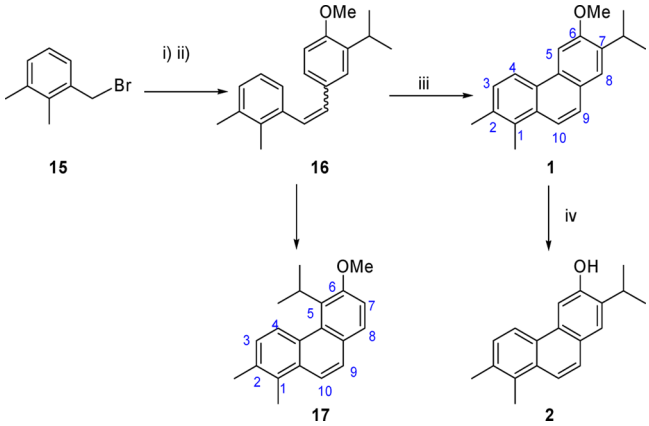

[a]Reaction conditions and reagents: (i) $Me_2SO_4$, NaOH(aq), 90 °C, 4 h, 93%; (ii) LiBr/$(NH_4)_2Ce(NO_3)_6$, $CH_3CN$, 20 °C, 2 h, 97%; (iii) *n*-BuLi, −78 °C, *N*-formylpiperidine, THF; then rt, 12 h, 90%.

**Scheme 2. Synthesis of 2,3-Dimethylbenzyl Bromide (15)**[a]




[a]Reaction conditions and reagents: (i) $LiAlH_4$, THF, 0 °C → rt, 4 h, 89%; (ii) $PBr_3$, $CH_2Cl_2$, 0 °C → rt, 12 h, 93%.

**Scheme 3. Synthesis of Multicaulins 1 and 2**[a]




[a]Reaction conditions and reagents: (i) $PPh_3$, $CH_3CN$, $N_2$ atm, reflux, 24 h; (ii) NaH, 0 °C, $N_2$ atm, 1 h; then benzaldehyde **12**, rt, 48 h, 90%; (iii) $I_2$, *t*-BuOH/benzene (9:1), 25 °C, *hν*, 120 h, 41%; (iv) $BBr_3$, $CH_2Cl_2$, $N_2$ atm, 0 °C → rt, 12 h, 93%.

phenanthrenes. By applying this methodology, the (*E*/*Z*)-stilbene mixture **16** was converted to multicaulin (**1**) in a yield of 41%. The $^1$H NMR spectrum of **1** displayed two singlets for H-8 ($\delta$ 7.66) and H-5 ($\delta$ 7.95) and two AB systems for H-4/H-3 ($\delta$ 8.38 and $\delta$ 7.42) and H-10/H-9 ($\delta$ 7.86 and 7.69), which are in agreement with the data reported by Ulubelen and co-workers.[2] However, the $^{13}$C NMR spectrum of the synthetic multicaulin (**1**) was quite different from that reported by Ulubelen and co-workers for the natural product.[2] In this context, both spectra exhibit eight quaternary and six tertiary olefinic carbons. However, the spectrum of the natural product **1** contains three carbons above 140 ppm (140.0, 147.8, 151.4), while the spectrum of our synthetic compound **1** contains only one carbon (156.9) in that region. Compound **17**, a regioisomer of compound **1**, was not observed in the oxidative cyclization most likely due to the steric effect of the isopropyl group. *O*-Demethylation of multicaulin (**1**) by treatment with $BBr_3$ yielded *O*-demethylmulticaulin (**2**) in 93% yield. The $^1$H NMR spectrum of *O*-demethylmulticaulin (**2**) was in good agreement with the spectra reported by the Ulubelen[2] and Sairafianpour[3] groups. Although the $^{13}$C NMR spectrum was different from that reported by the Ulubelen group, the $^{13}$C NMR spectrum of synthetic **2** was in perfect agreement with that reported by the Sairafianpour group.[3] The latter authors properly discussed the conflicting $^{13}$C NMR data and predicted that the alternative structural isomer for *O*-demethylmulticaulin (**2**) reported from *S. multicaulis* by Ulubelen and co-workers[2] may be 7-isopropyl-1,2-dimethylphenanthren-5-ol.[3] Our results confirm the results reported by Sairafianpour and co-workers[3] and provide confirmation of the structures of **1** and **2**.

In conclusion, we report the first total synthesis of multicaulin (**1**) in seven steps with 30% overall yield. *O*-Demethylmulticaulin (**2**) was also obtained via simple *O*-demethylation of **1** (93% yield). In addition, our synthesis resolves the dispute between the Ulubelen[2] and Sairafianpour[3] groups regarding the structure elucidation of **1** and **2**. Our methodology may find application in the syntheses of more potent multicaulin derivatives to combat the tuberculosis epidemic.

## EXPERIMENTAL SECTION

**General Experimental Procedures.** Solvents were purified and dried by standard methods. Reactions were monitored via TLC. The $^1$H NMR and $^{13}$C NMR spectra were recorded on a 400(100) MHz Varian spectrometer. Column chromatography was performed on silica gel 60 (70−230) mesh ASTM, and thin-layer chromatography was carried out on silica gel (254−366 mesh ASTM).

**Syntheses.** *2-Isopropylanisole (**10**).* A solution of NaOH (9.18 g, 229 mmol) in $H_2O$ (47 mL) was added to a solution of 2-isopropylphenol (**9**) (10.0 g, 73.4 mmol) in $H_2O$ (30 mL), and the mixture was heated to 90 °C. $Me_2SO_4$ (10.65 g, 7.7 mL, 84.4 mmol) was added, and the resulting mixture was stirred for 4 h at the same temperature. The reaction mixture was allowed to cool to rt, and the solution was extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to yield 2-isopropylanisole (**10**) as a pale yellow liquid (10.19 g, 93%): $R_f$ 0.86 (1:4 EtOAc−hexanes). The $^1$H NMR and $^{13}$C NMR spectra are in agreement with reported data.[7]

*4-Bromo-2-isopropylanisole (**11**).* Ammonium cerium(IV) nitrate (18.96 g, 34.6 mmol) and LiBr (3.00 g, 34.5 mmol) were placed in a 250 mL flask, and $CH_3CN$ (50 mL) was added under $N_2$. 2-Isopropylanisole (**10**) (4.71 g, 31.4 mmol) was dissolved in $CH_3CN$ (50 mL) and added dropwise to the reaction mixture under $N_2$. The mixture was stirred for 2 h at rt, and the solvent was removed under reduced pressure. The crude product was dissolved in EtOAc (50 mL), washed with $H_2O$ (2 × 25 mL) and a solution of saturated aqueous $NaHCO_3$ (50 mL), and dried over $Na_2SO_4$. The solvent was removed under reduced pressure to afford 4-bromo-2-isopropylanisole (**11**) as a yellow liquid (7.02 g, 97%): $R_f$ 0.85 (1:9 EtOAc−hexanes). The $^1$H NMR and $^{13}$C NMR spectra are in agreement with reported data.[8]

*3-Isopropyl-4-methoxybenzaldehyde (**12**).* A solution of 4-bromo-2-methoxyanisole (**11**) (6.78 g, 29.6 mmol) in THF (30 mL) was cooled to −78 °C under $N_2$. Then, *n*-BuLi (2.5 M, 14.1 mL, 35.2 mmol) was added dropwise at the same temperature. After stirring for 1 h at −78 °C, *N*-formylpiperidine (6.1 mL, 6.63 g, 55.6 mmol) was added. The reaction mixture was allowed to reach rt and then stirred for 12 h. After monitoring with TLC, the mixture was quenched by a saturated solution of $NH_4Cl$ (10 mL), and the solvent was removed under reduced pressure. The crude mixture was extracted with EtOAc (3 × 75 mL). The combined organic layers were dried over $Na_2SO_4$. After removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (1:20 EtOAc−hexanes) to yield 3-isopropyl-4-methoxybenzaldehyde (**12**) as a pale yellow liquid (4.75 g, 90%): $R_f$ 0.41 (1:9 EtOAc−hexanes). The $^1$H NMR and $^{13}$C NMR spectra are in agreement with reported data.[9]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*2,3-Dimethylbenzyl Alcohol (**14**).* To a suspension of $LiAlH_4$ (281 mg, 7.45 mmol) in THF (15 mL) was added dropwise a solution of 2,3-dimethylbenzaldehyde (**13**) (1.00 g, 7.5 mmol) in THF (20 mL) at 0 °C under $N_2$, and the mixture was allowed to reach rt and then stirred for 4 h. After monitoring with TLC, the reaction mixture was cooled to 0 °C, and a saturated solution of $NH_4Cl$ (10 mL) was added, followed by the addition of EtOAc (20 mL). The precipitate was filtered, and the organic phase was washed with $H_2O$ (2 × 20 mL) and dried over $Na_2SO_4$. The solvent was removed under reduced pressure to yield 2,3-dimethylbenzyl alcohol (**14**) as a yellow crystalline solid (913 mg, 89%): mp 62−64 °C; lit.[6] 63−65 °C; $R_f$ 0.51 (1:4 EtOAc−hexanes). The $^1$H NMR and $^{13}$C NMR spectra are in agreement with reported data.[10]

*2,3-Dimethylbenzyl Bromide (**15**).* To a solution of 2,3-dimethylbenzyl alcohol (**14**) (950 mg, 6.98 mmol) in $CH_2Cl_2$ (50 mL) was added dropwise $PBr_3$ (2.07 g, 0.72 mL, 7.67 mmol) at 0 °C. The reaction mixture was stirred for 12 h at rt. After monitoring with TLC, $H_2O$ (50 mL) was added, the organic layer was separated and dried over $Na_2SO_4$, and the solvent was removed under reduced pressure to afford 2,3-dimethylbenzyl bromide (**15**) as a yellow liquid (1.28 g, 93%): $R_f$ 0.66 (1:9 EtOAc−hexanes); the $^1$H NMR spectrum is in agreement with reported data;[6] $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 137.9; 136.1; 135.9; 130.9; 128.1; 126.0; 33.6 ($CH_2Br$); 20.7 ($CH_3$); 15.1 ($CH_3$).

*(2,3-Dimethylbenzyl)triphenylphosphonium Bromide.* To a solution of 2,3-dimethylbenzyl bromide (**15**) (2.52 g, 12.72 mmol) in $CH_3CN$ (100 mL) was added $PPh_3$ (3.67 g, 14.0 mmol), and the reaction mixture was refluxed for 24 h under $N_2$. After monitoring with TLC, the solvent was removed under reduced pressure to afford (2,3-dimethylbenzyl)triphenylphosphonium bromide as a white solid (6.19 g). The salt was used for the next step without further purification.

*(E/Z)-1-(3-Isopropyl-4-methoxyphenyl)-2-(2,3-dimethylphenyl)-ethane (**16**).* To a suspension of NaH (366 mg, 15 mmol) in $CH_2Cl_2$ (20 mL) was added (2,3-dimethylbenzyl)triphenylphosphonium bromide (700 mg, 1.51 mmol) in $CH_2Cl_2$ (40 mL) at 0 °C, and the mixture was stirred for 1 h at the same temperature under $N_2$. After 1 h, 3-isopropyl-4-methoxybenzaldehyde (**12**) (272 mg, 1.53 mmol) in $CH_2Cl_2$ (40 mL) was added, and the reaction mixture was stirred for 48 h at rt. After monitoring with TLC, a saturated solution of $NH_4Cl$ (20 mL) was added dropwise to the mixture to quench the excess NaH. The organic layer was separated and dried over $Na_2SO_4$. The solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography (1:4 EtOAc−hexanes) to yield an isomeric mixture of stilbene (*E*/*Z*)-**16** (385 mg, 90%) as a yellow-colored liquid. This mixture was used for the next step without further purification. A small amount of the *E*-isomer of stilbene **16** was separated by thin-layer silica gel chromatography.

*E-Isomer of stilbene **16**:* $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.41 (bd, 1 H, H-6″, $J_{5'',6''}$ = 7.0 Hz); 7.36−7.32 (m, 2 H, H-2′, H-5″); 7.26 (d, 1 H, H-2, $J_{1,2}$ = 16.1 Hz); 7.11 (d, 1 H, H-5′, $J_{5',6'}$ = 7.3 Hz); 7.07 (bd, 1 H, H-6′); 6.89 (d, 1 H, H-1, $J_{1,2}$ = 16.1 Hz); 6.85 (d, 1 H, H-4″, $J_{4'',5''}$ = 8.1 Hz); 3.86 (s, 3 H, $OCH_3$); 3.33 (septet, 1 H, C<u>H</u>$Me_2$, *J* = 7.0 Hz); 2.33 (s, 3 H, $CH_3$); 2.32 (s, 3 H, $CH_3$); 1.25 (d, 6 H, CH<u>Me</u>$_2$, *J* = 7.0 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.9 (C-4′); 137.5 (s); 137.4 (s); 136.9 (s); 134.3 (s); 130.8 (d); 130.6 (s); 129.0 (d); 125.8 (d); 125.5 (d); 125.0 (d); 124.8 (d) 123.9 (d); 110.9 (d); 55.7 ($OCH_3$); 27.1 (C<u>H</u>$Me_2$); 22.8 (CH<u>Me</u>$_2$); 20.9 ($CH_3$); 15.7 ($CH_3$).

*7-Isopropyl-6-methoxy-1,2-dimethylphenanthrene (**1**).* The *E*/*Z* mixture of stilbene **16** (112 mg, 0.40 mmol) was dissolved in 150 mL of *t*-BuOH−benzene (9:1), and $I_2$ (101.4 mg, 0.39 mmol) was added. The reaction mixture was irradiated for 120 h using a 400 W mercury arc lamp. The solvent was removed under reduced pressure, and the crude product purified by TLC to afford 7-isopropyl-6-methoxy-1,2-dimethylphenanthrene (**1**) as a yellow gum (45 mg, 41%): $R_f$ 0.74 (1:4 EtOAc−hexanes); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.38 (d, 1 H, H-4, *J* = 8.8 Hz); 7.95 (s, 1 H, H-5); 7.86 (d, 1 H, H-10, *J* = 9.2 Hz); 7.69 (d, 1 H, H-9, *J* = 9.2 Hz); 7.66 (s, 1 H, H-8); 7.42 (d, 1 H, H-3, *J* = 8.8 Hz); 4.06 (s, 3 H, $OCH_3$); 3.46 (septet, 1 H, C<u>H</u>$Me_2$, *J* = 7.0 Hz); 2.65 (s, 3 H, $CH_3$); 2.53 (s, 3 H, $CH_3$); 1.33 (d, 6 H, CH<u>Me</u>$_2$, *J* = 7.0 Hz); the $^1$H NMR spectrum is in agreement with reported data;[2] $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.8 (C-6); 138.0 (s); 134.0 (s); 132.4 (s); 131.1 (s); 130.2 (s); 128.7 (d); 128.4 (s); 126.5 (d); 126.0 (s); 125.6 (d); 120.5 (d); 120.2 (d); 102.0 (d); 55.6 ($OCH_3$); 27.3 (C<u>H</u>$Me_2$); 23.0 (CH<u>Me</u>$_2$); 21.1 ($CH_3$); 15.3 ($CH_3$).

*7-Isopropyl-1,2-dimethylphenanthren-6-ol (**2**).* To a solution of multicaulin (**1**) (100 mg, 0.36 mmol) in $CH_2Cl_2$ (30 mL) was added dropwise $BBr_3$ (110 mg, 0.04 mL, 0.44 mmol) under $N_2$ at 0 °C, and the mixture stirred for 12 h at room temperature. After monitoring with TLC, 10 mL of MeOH was added, the solvent removed under reduced pressure, and the crude product dissolved in EtOAc (90 mL), washed with $H_2O$ (2 × 30 mL), and dried over $Na_2SO_4$. The removal of the solvent under reduced pressure yielded 7-isopropyl-1,2-dimethylphenanthrene-6-ol (**2**) as a yellow, viscous oil (88 mg, 93%): $R_f$ 0.55 (1:4 EtOAc−hexanes); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.28 (d, 1 H, H-4, *J* = 8.4 Hz); 7.91 (s, 1 H, H-5); 7.84 (d, 1 H, H-10, *J* = 9.1 Hz); 7.68 (d, 1 H, H-9, *J* = 9.1 Hz); 7.67 (s, 1 H, H-8); 7.40 (d, 1 H, H-3, *J* = 8.4 Hz); 3.38 (septet, 1 H, C<u>H</u>$Me_2$, *J* = 7.0 Hz); 2.64 (s, 3 H, $CH_3$); 2.52 (s, 3 H, $CH_3$); 1.39 (d, 6 H, CH<u>Me</u>$_2$, *J* = 7.0 Hz); the $^1$H NMR spectrum is in agreement with reported data;[2,3] $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 152.6 (s); 135.6 (s); 134.2 (s); 132.4 (s); 131.1 (s); 130.4 (s); 128.8 (d); 128.0 (s); 126.5 (d); 126.5 (s); 126.2 (d); 120.6 (d); 120.2 (d); 107.1 (d); 27.7 (C<u>H</u>$Me_2$); 22.7 (CH<u>Me</u>$_2$); 21.1 ($CH_3$); 15.2 ($CH_3$); the $^{13}$C NMR spectrum is in agreement with reported data.[3]

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

$^1$H and $^{13}$C NMR spectra of all new compounds are available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION


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### Notes

The authors declare no competing financial interest.

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## ■ DEDICATION

Dedicated to Prof. Dr. Ayhan Ulubelen on the occasion of her 83rd birthday.

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