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Total Syntheses of Balsacone B and Balsacone C

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Abstract: The first total syntheses of Balsacone C (**16**) and Balsacone B (**17**), mainly based on a convergent strategy, were described. The crucial step of this strategy was the alkylation of trihydroxydihydrochalcone derivatives **7** and **8** with cinnamyl bromide derivative **13**. For this, compounds **7** and **8** were prepared starting from trihydroxyacetophenone (**1**) in four steps. Then compound **13** was prepared starting from coumaric acid (**9**) in four steps.

Keywords: Synthesis; natural product; Balsacone B; Balsacone C.

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INTRODUCTION

Due to the increasing antibiotic resistance among bacterial species, there is an increasing demand to discover new antibacterial compounds (1). Although microbial secondary metabolites, to date, are the major source of new antibiotics, only two novel antibiotic classes have led to the development of alternative strategies within the last 50 years (2). Natural products originating from plants are considered as the source of new compounds with potential antibiotic properties (3). The use of herbal sources for the treatment of bacterial infections has been a very common practice in traditional medicine worldwide (4-7).

Populus balsamifera L. belonging to the *Salicaceae* family is a tree growing in almost all regions in North America. There are many studies reporting the use of *P. balsamifera* L. buds by native Canadians in traditional medicine. For example, these plant species have been used for treating dermatological and gastrointestinal conditions (8). Moreover, the Canadian native population has prepared ointment from the buds of this plant, used it for treating wounds, and reported that this ointment has protective effects against infections (8). Phytochemical studies that were previously conducted on the buds of this plant have led to the identification of alkanes (9), fatty acids (10), terpenes (10), phenols (11), flavonoids (11-12), chalcones (11-12), carbohydrates (13), and prostaglandins (13).

Balsacones B and C, the total syntheses of which were performed within the scope of this study, were first isolated as antibacterial compounds from *P. balsemifera* L. by Lavoie *et al.* in 2013 (8). Each of these natural products was tested against *Escherichia coli* (gram negative) and *Staphylococcus aureus* (gram positive), and both were reported to exert significant activity against *S. aureus* (Table 1) (8).

Table 1. Antibacterial and cytotoxic activities of compounds **16** and **17** (8).

Compounds	MIC[a] (μM)		IC_{50} (μM)
	E. coli	*S. aureus*	WS1
16	>200	3.1	23.6 ± 0.8
17	>200	6.3	>200
Gentamicin[c]	0.04	0.02	NT[b]

[a] Minimum inhibitory concentration.

[b] Not tested.

[c] Positive control.

In recent studies, the extracts of *Populus* species have been reported to have antimicrobial, antioxidant, and cytotoxic activities (14-16). The structures of natural products for which total syntheses were performed are shown in Figure 1.

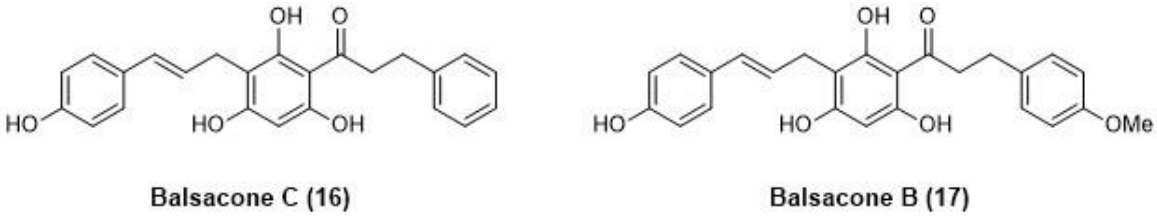


Figure 1: Structures of synthesized compounds.

EXPERIMENTAL

Chemicals and Instrumentation

Chemicals and reagents were purchased from Sigma Aldrich and used without further purification. THF was purified and distilled over Na. All other solvents and reagents were used as received. The progress of the reaction was monitored via TLC, using TLC Merck silica gel 60 F254. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded over 400 (100) MHz Varian spectrometer using $CDCl_3$, CD_3OD and Acetone-d_6. Column chromatography was performed on silica gel 60 (70–230 mesh ASTM). Infrared (IR) spectra were obtained from solutions in 0.1-mm cells with a Perkin-Elmer spectrometer (Waltham, MA).

2,4-Bis(methoxymethoxy)-6-hydroxyacetophenone (2)

To a solution of trihydroxyacetophenone (**1**) (4.8 g, 28.5 mmol) in DCM (20 mL, dry) was added DIPEA (13 mL, 82.5 mmol) dropwise at 0 ˚C under N_2. The resulting mixture was stirred for 20 min, then MOMCl (5 mL, 82.5 mmol) was added to the mixture at the same temp. After being stirred for additional 20 min at 0 ˚C, the reaction mixture was diluted with EtOAc (200 mL), washed with water (50 mL), dried (Na_2SO_4) and concentrated. Purification of the crude product by silica gel chromatography using EtOAc/Hexane as eluent (25%) afforded the known compound **2** as a colorless liquid (5.15 g, 71%). R_f = 0.53 (40%, EtOAc/Hexanes). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 13.72 (s, 1H), 6.27 (d, 1H, *J* = 2.4 Hz), 6.25 (d, 1H, *J* = 2.4 Hz), 5.26 (s, 2H), 5.17 (s, 2H), 3.52 (s, 3H), 3.47 (s, 3H), 2.65 (s, 3H). ^{1}H-NMR spectrum of compound **2** was in agreement with the data given in the literature (17).

(2E)-1-[2-Hydroxy-4,6-bis(methoxymethoxy)phenyl]-3-phenyl-2-propen-1-one (3)

To a solution of **2** (645 mg, 2.52 mmol) in MeOH (10 mL) was added sequentially 50% KOH solution (8 mL) and benzaldehyde (0.26 mL, 2.52 mmol) and stirred for 18 h at room

temperature. After 18 h, the reaction mixture was diluted with EtOAc (60 mL), washed with 2M HCl solution (5 mL), dried (Na_2SO_4) and concentrated. Purification of the remaining residue by column chromatography over silica gel using gradient elution with EtOAc and hexanes afforded the known compound **3** as a yellow solid (830 mg, 95%). Rf = 0.5 (40%, EtOAc/Hexanes). M.P. = 97-98 ^oC. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 13.82 (s, 1H), 7.93 (d, 1H, *J* = 15.6 Hz), 7.79 (d, 1H, *J* = 15.6 Hz), 7.60 (dd, 2H, *J* = 7.4, *J* = 2.1 Hz), 7.46 – 7.33 (m, 3H), 6.32 (d, 1H, *J* = 2.3 Hz), 6.25 (d, 1H, *J* = 2.3 Hz), 5.29 (s, 2H), 5.19 (s, 2H), 3.54 (s, 3H), 3.49 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 193.2, 167.6, 163.7, 160.1, 142.7, 135.7, 130.4, 129.2, 128.5, 127.6, 97.7, 95.4, 94.9, 94.3, 57.1, 56.7. IR (neat cm^{-1}) 2924, 1629, 1209.

(2E)-1-[2-Hydroxy-4,6-bis(methoxymethoxy)phenyl]-3-(4-methoxyphenyl)-2-propen-1-one (4)

To a solution of **2** (200 mg, 0.78 mmol) in MeOH (5 mL) was added sequentially 50% KOH solution (1.25 mL) and p-methoxybenzaldehyde (0.2 mL, 1.56 mmol) and stirred for 18 h at room temp. After 18 h, the reaction mixture was diluted with EtOAc (100 mL), washed with 2M HCl solution (5 mL), dried (Na_2SO_4) and concentrated. Purification of the remaining residue by column chromatography over silica gel using gradient elution with EtOAc and hexanes afforded the known compound **4** as a yellow solid (247 mg, 84%). Rf = 0.5 (40%, EtOAc/Hexanes). M.P. = 100-101 $^{\circ}C$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 13.92 (s, 1H), 7.88 – 7.73 (m, 2H), 7.56 (d, 2H, *J* = 8.8 Hz), 6.93 (d, 2H, *J* = 8.8 Hz), 6.32 (d, 1H, *J* = 2.4 Hz), 6.24 (d, 1H, *J* = 2.4 Hz), 5.29 (s, 2H), 5.19 (s, 2H), 3.85 (s, 3H), 3.54 (s, 3H), 3.48 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 193.1, 167.5, 163.5, 161.7, 160.0, 142.9, 130.3, 128.4, 125.2, 114.6, 107.8, 97.7, 95.4, 94.9, 94.23, 57.1, 56.7, 55.6. IR (neat cm^{-1}) 2957, 2836, 1625.

2',4',6'-Trihydroxychalcone (5)

To a solution of **3** (738 mg, 2.14 mmol) in MeOH (10 mL) was added 12 M HCl solution (0.27 mL) drop by drop at room temp. Reaction mixture was stirred for 23 h. After 23 h, the reaction mixture was diluted with EtOAc (100 mL), washed with H_2O (10 mL), dried (Na_2SO_4) and concentrated. Purification of the remaining residue by column chromatography over silica gel using gradient elution with EtOAc and hexanes (40% EtOAc/Hexanes) afforded compound **5** as a yellow solid (438.3 mg, 80%). R_f = 0.2 (40%, EtOAc/Hexanes). ^{1}H-NMR (400 MHz, CD_3OD) 8.23 (d, 1H, *J* = 15.8 Hz), 7.74 (d, 1H, *J* = 15.8 Hz), 7.38–7.62 (m, 5H), 5.85 (s, 2H). ^{1}H-NMR spectrum of compound **5** was in agreement with the data given in the literature (18).

2',4',6'-Trihydroxy-4-methoxychalcone (6)

To a solution of **4** (1.5 g, 4.00 mmol) in MeOH (20 mL) was added 12 M HCl solution (0.3 mL) drop by drop at room temp. Reaction mixture stirred for 23 h. After 23 h reaction mixture was diluted with EtOAc (100 mL), washed with H_2O (10 mL), dried (Na_2SO_4) and concentrated. Purification of the remaining residue by column chromatography over silica gel using gradient elution with EtOAc and hexanes (40% EtOAc/Hexanes) afforded compound **6** as a yellow solid (938 mg, 82%). R_f = 0.16 (40%, EtOAc/Hexanes). ^{1}H-NMR (400 MHz, CD_3OD) δ 8.12 (d, 1H, *J* = 15.6 Hz), 7.72 (d, 1H, *J* = 15.6 Hz), 7.58 (d, 2H, *J* = 8.6 Hz), 6.97 (d, 2H, *J* = 8.6 Hz), 5.87 (s, 2H), 3.84 (s, 3H). ^{1}H-NMR spectrum of compound **6** was in agreement with the data given in the literature (19).

2',4',6'-Trihydroxydihydrochalcone (7)

To a solution of trihydroxychalcone **5** (435 mg, 1.69 mmol) in MeOH (15 mL), Pd/C (10%) was added. The reaction flask was purged with hydrogen gas three times before being allowed to stir under a hydrogen balloon for 4 h at room temp. Then, the reaction mixture was filtered and concentrated *in vacuo* to yield compound **7** as a pale yellow solid (337 mg, 77%). R_f = 0.36 (60%, EtOAc/Hexanes). ^{1}H-NMR (400 MHz, Acetone) δ 11.73 (s, 2H), 9.23 (s, 1H), 7.43 – 7.13 (m, 5H), 5.95 (s, 2H), 3.45 – 3.37 (m, 2H), 3.03 – 2.96 (m, 2H). ^{1}H-NMR spectrum of compound **7** was in agreement with the data given in the literature (20).

2',4',6'-Trihydroxy-4-methoxydihydrochalcone (8)

To a solution of trihydroxychalcone **6** (938 mg, 3.27 mmol) in MeOH (15 mL), Pd/C (10%) was added. The reaction flask was purged with hydrogen gas three times before being allowed to stir under a hydrogen balloon for 4 h at room temp. Then, the reaction mixture was filtered and concentrated *in vacuo* to yield compound **8** as a white solid (862 mg, 61%). R_f = 0.2 (40%, EtOAc/Hexanes). ^{1}H-NMR (400 MHz, CD_3OD) δ 7.11 (d, 2H, *J* = 8.7 Hz), 6.79 (d, 2H, *J* = 8.7 Hz), 5.82 (s, 2H), 3.72 (s, 3H), 3.29 – 3.24 (m, 2H), 2.94 – 2.83 (m, 2H). ^{13}C-NMR (100 MHz, CD_3OD) δ 205.1, 164.9, 164.6, 158.1, 133.9, 129.1, 113.6, 104.2, 94.6, 54.5, 45.9, 30.2. ^{1}H-NMR and ^{13}C-NMR spectra of compound **8** were in agreement with the data given in the literature (21).

Methyl 4-hydroxycinnamate (10)

A solution of **9** (1 g, 6.1 mmol) in MeOH (20 mL) was treated with *p*-TSA (cat. amount) and refluxed for 17 h. The reaction mixture was quenched by the addition of $NaHCO_3$ (30 mL) and extracted with EtOAc (3 x 50 mL). The combined extracts were dried (Na_2SO_4) and the solvent concentrated *in vacuo* to give the known compound **10** as a white solid (1 g, 92%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.64 (d, 1H, *J* = 16.0 Hz), 7.44 (d, 2H, *J* = 8.6 Hz),

6.85 (d, 2H, *J* = 8.6 Hz), 6.31 (d, 1H, *J* = 16.0 Hz), 5.22 (s, 1H), 3.80 (s, 3H). ^{1}H-NMR spectrum of compound **10** was in agreement with the data given in the literature (22).

(E)-Methyl 3-(4-(tert-butyldimethylsilyloxy)phenyl)acrylate (11)

To a solution of **10** (500 mg, 2.8 mmol) and TBDMSCl (634 mg, 4.21 mmol) in DCM (5 mL, dry), stirred at 0 ˚C, added TEA (0.6 mL, 4.21 mmol) in dropwise under N_2. The reaction mixture was slowly warmed up to ambient temp. After the completion of reaction monitored by TLC analysis, the reaction mixture was diluted with DCM (150 mL), washed with of NH_4Cl (20 mL, saturated aqueous solution) and brine, dried (Na_2SO_4), and concentrated. After filtration, the known compound **11** was obtained as a colorless liquid (766.3 mg, 99%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42 (d, 1H, *J* = 16.0 Hz), 7.20 (d, 2H, *J* = 8.6 Hz), 6.62 (d, 2H, *J* = 8.6 Hz), 6.08 (d, 1H, *J* = 16.0 Hz), 3.57 (s, 3H), 0.77 (s, 9H), 0.00 (s, 6H). ^{1}H-NMR spectrum of compound **11** was in agreement with the data given in the literature (23).

(E)-3-(4-(tert-Butyldimethylsilyloxy)phenyl)prop-2-en-1-ol (12)

To a solution of **11** (408 mg, 1.39 mmol) in DCM (10 mL), stirred at -78 °C, was added a DIBAL-H solution (3 mL of 1.5 M toluene solution) in dropwise through 30 min. After 30 min stirring at –78 ˚C, the reaction mixture was quenched by the dropwise addition of MeOH and slowly warmed up to ambient temp. Then, NaCl (10 mL, saturated aqueous solution) was added to the reaction mixture and the resulted emulsion was stirred at ambient temperature until the emulsion was clear-up. The organic material was extracted with DCM (3 x 50 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give known compound **12** as a colorless liquid (365 mg, 99% yield). R_f = 0.53 (40%, EtOAc/Hexanes). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.06 (d, 2H, *J* = 8.4 Hz), 6.59 (d, 2H, *J* = 8.4 Hz), 6.35 (d, 1H, *J* = 15.9 Hz), 6.04 (dt, 1H, *J* = 15.9, *J* = 5.9 Hz), 4.10 (t, 2H, *J* = 5.9 Hz), 0.78 (s, 9H), 0.00 (s, 6H). ^{1}H-NMR spectrum of compound **12** was in agreement with the data given in the literature (23).

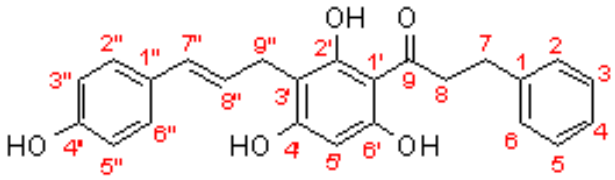
4-(tert-Butyldimethylsiloxy)cinnamyl bromide (13)

A solution of alcohol **12** (320 mg, 1.21 mmol) in Et_2O (10 mL) was cooled to 0 ˚C, and PBr_3 (0.04 mL, 0.38 mmol) was added with a syringe. This mixture was stirred for half an hour. After monitoring with TLC, NaCl (15 mL, saturated aqueous solution) was added to the mixture. The organic layer was then separated and concentrated. The crude product was dissolved in DCM (50 mL), dried ($MgSO_4$) and concentrated to afford known compound **13** as a white solid (120 mg, 96%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.07 (d, 2H, *J* = 8.5 Hz), 6.60 (d, 2H, *J* = 8.5 Hz), 6.38 (d, 1H, *J* = 15.6 Hz), 6.06 (dt, 1H, *J* = 15.5, 7.8 Hz), 3.97

(dd, 2H, *J* = 12.0, 4.5 Hz), 0.78 (s, 9H), 0.00 (s, 6H). ^{1}H-NMR spectrum of compound **13** was in agreement with the data given in the literature (24).

Balsacone C (16)

To a solution of **7** (211 mg, 0.82 mmol) in THF (5 mL) was added NaH (41 mg, 1.02 mmol) under N_2 at room temp. After stirring 5 min, compound **13** (335 mg, 1.02 mmol) was added to the mixture and the reaction was stirred at room temp. for 2 days. After monitoring with TLC, the reaction was stopped and the solvent was removed. The crude product was diluted with EtOAc (150 mL) and 2 M HCl solution was added until pH 1-2. The organic layer was dried (Na_2SO_4) and the solvent was concentrated to afford compound **14**. Compound **14** was used for the next step without further purification. For this, compound **14** was dissolved in THF (3 mL) and TBAF (0.38 mL, 0.38 mmol) was added to the mixture under N_2 at 0 °C. The reaction mixture was stirred for 30 min. at the same temperature. After monitoring with TLC, the reaction was stopped and the solvent was removed. 2 M HCl solution was added until pH 1-2 and then the mixture was extracted with EtOAc (3 x 50 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was concentrated. Purification of the crude product by column chromatography (silica gel, DCM/MeOH 19:1) afforded Balsacone C (**16**) as a white solid (89.58 mg, 28% for two steps). R_f = 0.33 (5%, MeOH/DCM).

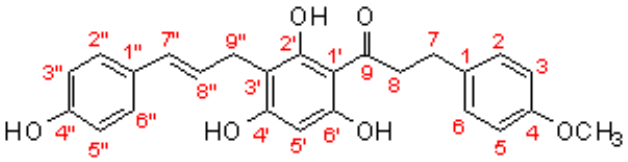


^{1}H-NMR (400 MHz, CD_3OD) δ 7.28 – 7.19 (m, 5H), 7.12 (d, 2H, *J* = 8.6 Hz), 6.66 (d, 2H, *J* = 8.6 Hz), 6.26 (d, 1H, *J* = 15.8 Hz), 6.10 (dt, 1H, *J* = 15.8, *J* = 6.4 Hz), 5.94 (s, 1H), 3.38 – 3.28 (m, 4H), 2.97 – 2.92 (m, 2H). ^{13}C-NMR (100 MHz, CD_3OD) δ 204.9 (C-9), 163.9 (C-4'), 162.7 (C-2'), 160.6 (C-6'), 156.1 (C-4''), 142.1 (C-1), 130.1 (C-1''), 128.9 (C-7''), 128.3 (C-2 and C-6), 128.2 (C-3 and C-5), 126.9 (C-2'' and C6'')), 125.6 (C-4), 125.6 (C-8'') , 114.9 (C-3'' and C-5''), 105.5 (C-3'), 104.0 (C-1'), 93.7 (C-5'), 45.9 (C-8), 31.2 (C-7), 25.2 (C-9''). IR (neat cm^{-1}) 3322.63, 2924.36, 1609.71, 1512.30, 1435.43, 1218.47, 833.16.

Balsacone B (17)

To a solution of **8** (320 mg, 1.11 mmol) in THF (5 mL) was added NaH (55 mg, 1.39 mmol) under N_2 at room temperature. After stirring 5 min., compound **13** (456 mg, 1.39 mmol) was added to the mixture and the reaction was stirred at room temperature for 22 h. After monitoring with TLC, the reaction was stopped and the solvent was removed. The crude product was diluted with EtOAc (150 mL) and 2 M HCl solution was added until pH becomes

1-2. The organic phase was dried (Na_2SO_4) and the solvent was concentrated to afford compound **15**. Compound **15** was used for the next step without further purification. For this, compound **15** was dissolved in THF (6 mL) and TBAF (0.28 mL, 0.28 mmol) was added to the mixture under N_2 at 0 °C. The reaction mixture was stirred for 30 min. at the same temp. After monitoring with TLC, the reaction was stopped and the solvent was removed. 2 M HCl solution was added until pH 1-2 and then the mixture was extracted with EtOAc (3 x 50 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was concentrated. Purification of the crude product by column chromatography (silica gel, DCM/MeOH 19:1) afforded Balsacone B (**17**) as a white solid (109.24 mg, 23% for two steps). R_f = 0.33 (5%, MeOH/DCM).

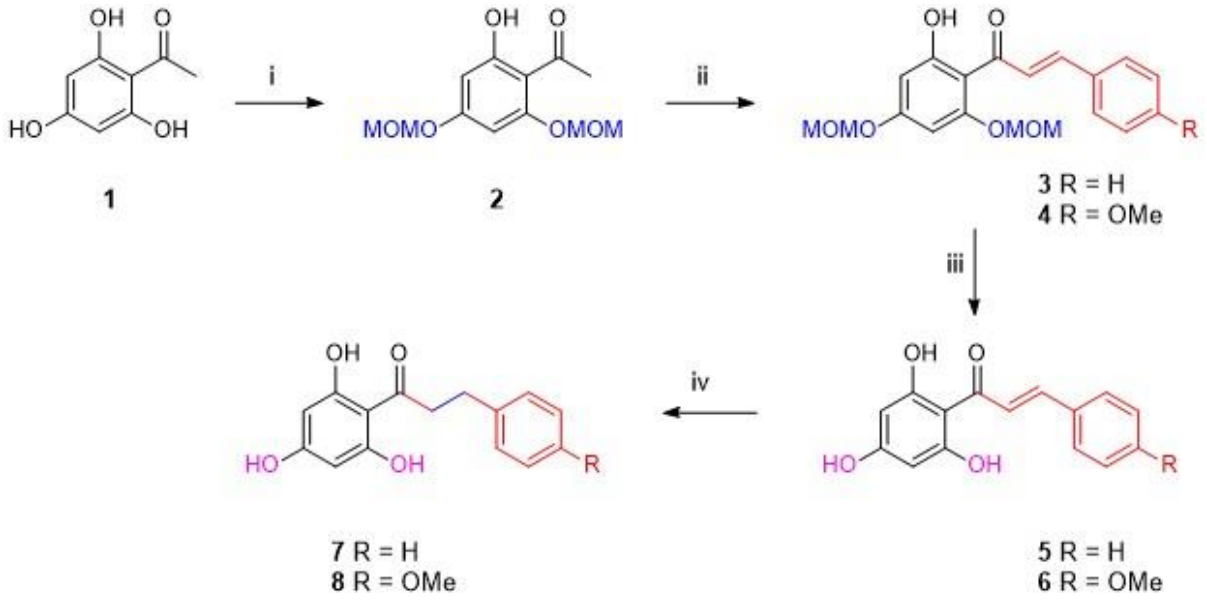


^{1}H-NMR (400 MHz, CD_3OD) δ 7.12 (d, 4H, *J* = 8.4 Hz), 6.79 (d, 2H, *J* = 8.6 Hz), 6.66 (d, 2H, *J* = 8.6 Hz), 6.25 (d, 1H, *J* = 15.8 Hz), 6.10 (dt, 1H, *J* = 15.7, *J* = 6.4 Hz), 5.94 (s, 1H), 3.73 (s, 3H), 3.35 (d, 2H, *J* = 5.7 Hz), 3.32 – 3.25 (m, 2H), 2.90 – 2.86 (m, 2H). ^{13}C-NMR (100 MHz, CD_3OD) δ 205.2 (C-9), 163.9 (C-4'), 162.7 (C-2'), 160.7 (C-6'), 158.1 (C-4), 156.1 (C-4''), 134.1 (C-1), 130.2 (C-1''), 129.4 (C-2 and C-6), 128.3 (C-7''), 128.2 (C-2'' and 6''), 126.9 (C-8''), 114.9 (C-3'' and 5''), 113.6 (C-3 and C-5), 105.5 (C-3'), 104.5 (C-1'), 93.4 (C-5'), 54.4 (OMe), 46.4 (C-8), 30.4 (C-7), 25.4 (C-9''). IR (neat cm^{-1}) 3321.50, 2929.97, 1609.40, 1512.59, 1245.92, 826.36.

RESULTS AND DISCUSSION

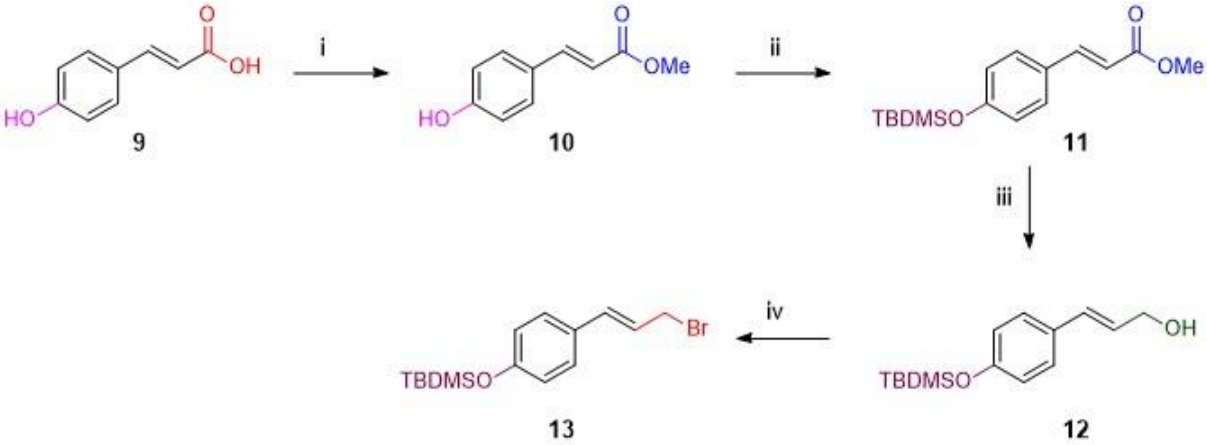
The natural products, Balsacone B (**17**) and Balsacone C (**16**), contain key fragments in which simple disconnection approaches can be pursued to achieve a possible synthetic pathway. In analyzing the structures of these products we devised a strategy to first access the core trihydroxy-dihydrochalcone unit. Our synthesis is based on a convergent strategy in which the related trihydroxy- dihydrochalcone derivatives **7** and **8** were first prepared and further alkylated to yield the Balsacone structure. To the best of our knowledge, there are no reports on the total synthesis of Balsacone B (**17**) and Balsacone C (**16**). The preparation of the related dihydrochalcone derivatives is shown in Scheme 1. For this, methoxymethyl (MOM)-protected trihydroxy-acetophenone (**2**) was condensed with the related benzaldehydes to give MOM-protected chalcone derivatives **3** and **4**. After

deprotection, trihydroxy-dihydrochalcone derivatives **7** and **8** were prepared by Pd-C catalyzed hydrogenation.

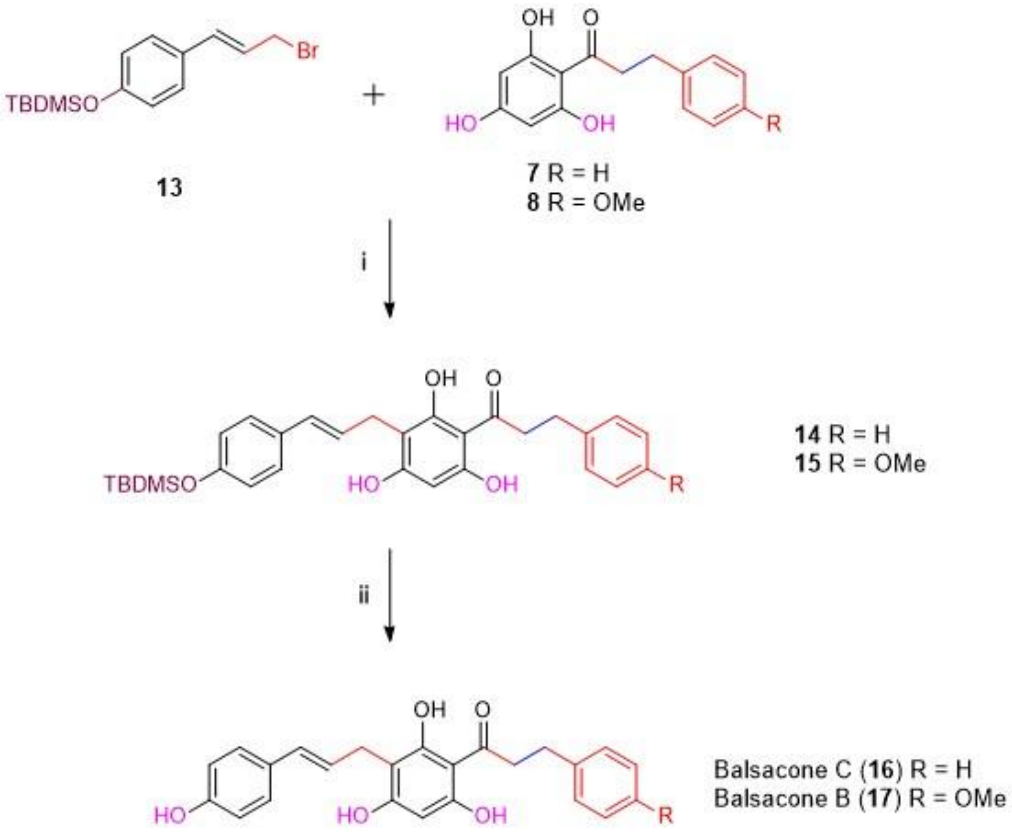


Scheme 1. (i) MOMCl, DIPEA, DCM, 0-25 ˚C, 6 h, 71%; (ii) a) benzaldehyde, KOH, MeOH, 25 ˚C, 18 h, 95%; b) p-methoxybenzaldehyde, KOH, MeOH, 25 ˚C, 18 h, 84%; (iii) a) conc. HCl, MeOH, 25 ˚C, 23 h, 80%; b) conc. HCl, MeOH, 25 ˚C, 23 h, 82%; (iv) a) H_2 (gas), Pd-C (cat.), MeOH, 25 ˚C, 4 h, 77%; b) H_2 (gas), Pd-C (cat.), MeOH, 25 ˚C, 4 h, 61%.

tert-Butyldimethylsilyl (TBDMS)-protected cinnamyl bromide (**13**) was synthesized in four steps starting from *p*-hydroxycinnamic acid (**9**). Acid-catalyzed esterification of the *p*-hydroxycinnamic acid (**9**) with MeOH gave the ester derivative **10**. TBDMS-protection of ester **10** gave compound **11**. The reduction of the TBDMS-protected cinnamic ester **11** with DIBAL-H afforded cinnamyl alcohol **12**, which was converted to cinnamyl bromide **13** via treatment with PBr_3 (Scheme 2).



Scheme 2. (i) p-TSA, MeOH, reflux, 17 h, 92%; (ii) TBDMSCl, TEA, dry DCM, 0 ˚C, 1,5 h 99%; (iii) DIBAL-H, dry DCM, -78 ˚C, 0,5 h, 99%; (iv) PBr_3, diethylether, 0 ˚C, 0,5 h, 96%.



Scheme 3. (i) NaH, THF, rt, 24 h, 50% (for compound **14**); NaH, THF, rt, 22 h, 45% (for compound **15**); (ii) TBAF, TFA, 0 ˚C, 0,5 h, 55% (for compound **16**); TBAF, TFA, 0 ˚C, 0,5 h, 50% (for compound **17**).

The final step of our synthetic strategy was the alkylation of trihydroxy-dihydrochalcone derivatives **7** and **8** with compound **13**. For this, alkylation of compound **7** and **8** with compound **13** in the presence of NaH gave compounds **14** and **15**. After deprotection in the presence of TBAF, the target compounds Balsacone C (**16**) and Balsacone B (**17**) were obtained in a yield of 55% and 50% respectively (Scheme 3).

CONCLUSION

In summary, the first ever syntheses of natural products Balsacone B (**17**) and Balsacone C (**16**) were realized within this work. The key factor in synthesizing these natural products rested on harnessing the Friedel-Crafts alkylation reaction between cinnamylbromide **13** and dihydrochalcone derivatives **7** and **8**. A straightforward alkylation in the presence of base afforded a clean product without any by-products allowing for a relatively facile approach. We envision that this method can be used to access a variety of compounds with a similar backbone and allows for simple preparation of antibacterial property containing natural products.

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