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Cascade Wittig reaction-double Claisen and Cope rearrangements: one-pot synthesis of diprenylated coumarins gravelliferone, balsamiferone, and 6,8-diprenylumbelliferone

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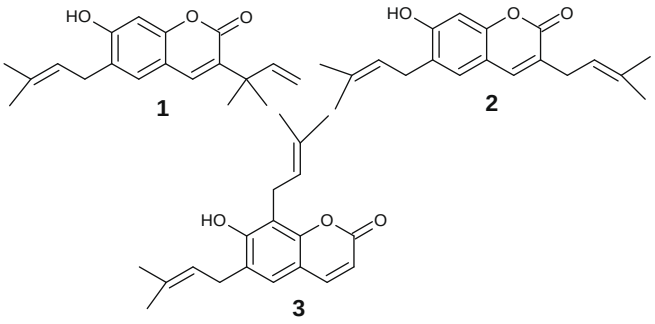
ABSTRACT

A cascade Wittig reaction-double Claisen and Cope rearrangements has been employed for a one-pot synthesis of diprenylated coumarins gravelliferone, balsamiferone, and 6,8-diprenylumbelliferone from a common precursor 2,4-diprenyloxybenzaldehyde.

Cascade,[1] domino[2] or tandem[3] reactions play an important role in the construction of complex molecular framework in fewer steps leading to saving time, cost, and energy. In 2002, Schobert and Gordon reviewed domino Wittig and pericyclic reactions for bioactive heterocycles.[4a] Taylor and Quesada reported a tandem Horner–Wadsworth–Emmons olefination/Claisen rearrangement/hydrolysis sequence.[4b] In continuation of our interest in such reactions, we explored a Wittig reaction in combination with ene,[5a] Diels–Alder,[5b] electrocyclic,[5c] oxidation,[5d] and reduction[5e] reactions. Herein, we report one-pot synthesis of naturally occurring gravelliferone **1**, balsamiferone **2**, and 6,8 diprenylumbelliferone **3** from 2,4-diprenyloxybenzaldehyde **4**, employing a cascade Wittig reaction, double Claisen and Cope rearrangements.



Coumarins are a group of an important class of abundant natural oxygen heterocycles having a wide range of biological activities[6] such as *anti*-HIV, *anti*-tumor, *anti*-hypertension, *anti*-arrhythmia, *anti*-osteoporosis, pain relief, antisepsis as well as prevention of asthma. Several of these coumarins have prenyl side chains in their skeleton either intact or in a modified form as a furan or pyran ring.[7] Gravelliferone **1** [3-(1,1′-dimethylallyl)-6-(3,3′-dimethylallyl)-7-hydroxy coumarin] isolated[8] from *R. graveolens*, balsamiferone **2** [3,6-di-(3,3′-dimethylallyl)-7-hydroxy coumarin] isolated[9] from *Amyris balsamifera*, and 6,8-diprenylumbelliferone **3** isolated[10] from *Citrus species* are three typical diprenylated coumarins.

All the known synthetic routes[11] for the gravelliferone **1** employ single Claisen–Cope rearrangement for the introduction of a prenyl group in the pyran ring. Realizing the presence of two such prenyl groups in the skeleton, we speculated that if two consecutive Claisen–Cope rearrangements can occur, a concise route for **1** could be unfolded. Thus, 2′-prenyloxy group of the ethyl cinnamate **6** could undergo preferential Claisen–Cope rearrangement over 4′-prenyloxy group due to steric crowding during the formation of **1** via 7-prenyloxy-6-prenyl coumarin **8**, a well known intermediate[11] for the synthesis of gravelliferone (Scheme 1). Recently, Nicolaou et al. demonstrated two such consecutive Claisen rearrangements for the total synthesis of artochamins.[12]

To check the above hypothesis, the required 2,4-diprenyloxybenzaldeyde **4** was prepared from 2,4-dihydroxybenzaldehyde in a straight forward manner.[13a] Initially, the Wittig reaction was carried out in refluxing diphenyl ether for 20 min. To our satisfaction, we could isolate **8** (30%) along with **6** (50%). After confirming the formation of **8**, we proceeded to the planned synthesis of **1** by extending the refluxing time in diphenyl ether for 4 h. Purification of reaction products by flash chromatography, provided 7-prenyloxy-3-prenyl coumarin **9** (2.5%), 8,9,9-trimethyl-6-(3-methylbut-2-enyl)-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one **10** (15%), 6,8-diprenylumbelliferone **3** (15%), balsamiferone **2** (5%),[11c,14] gravelliferone **1** (10%), and demethylsuberosin **11** (20%) (Scheme 2).[13b]

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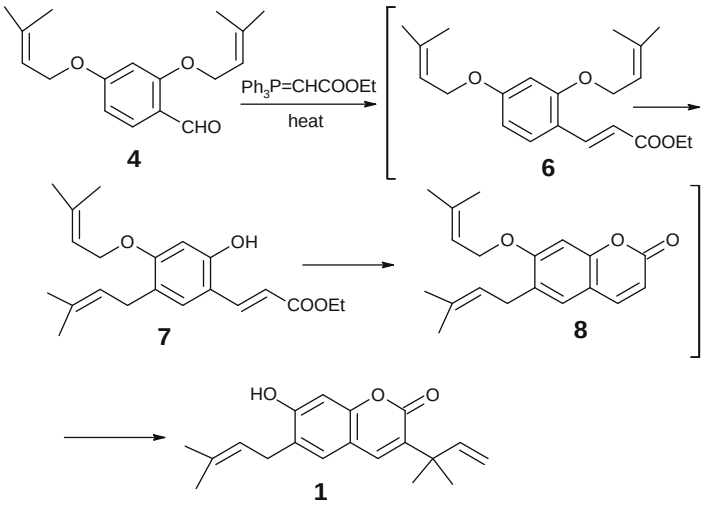
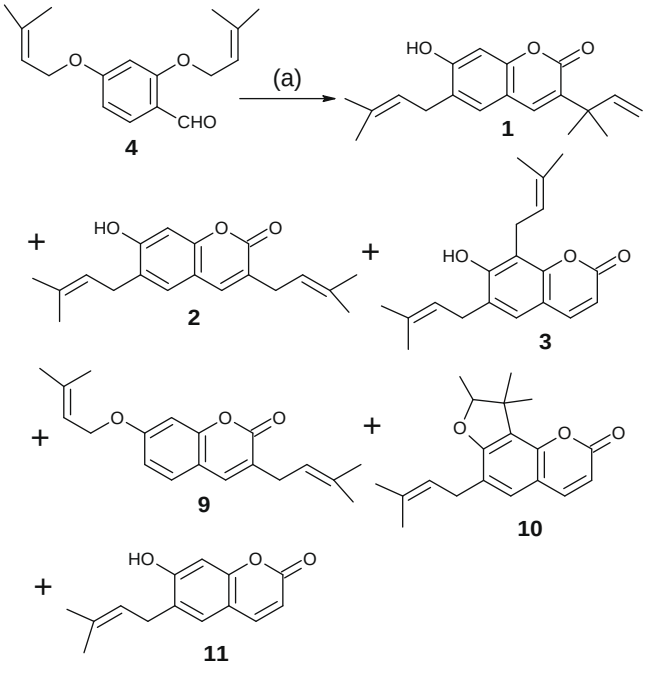


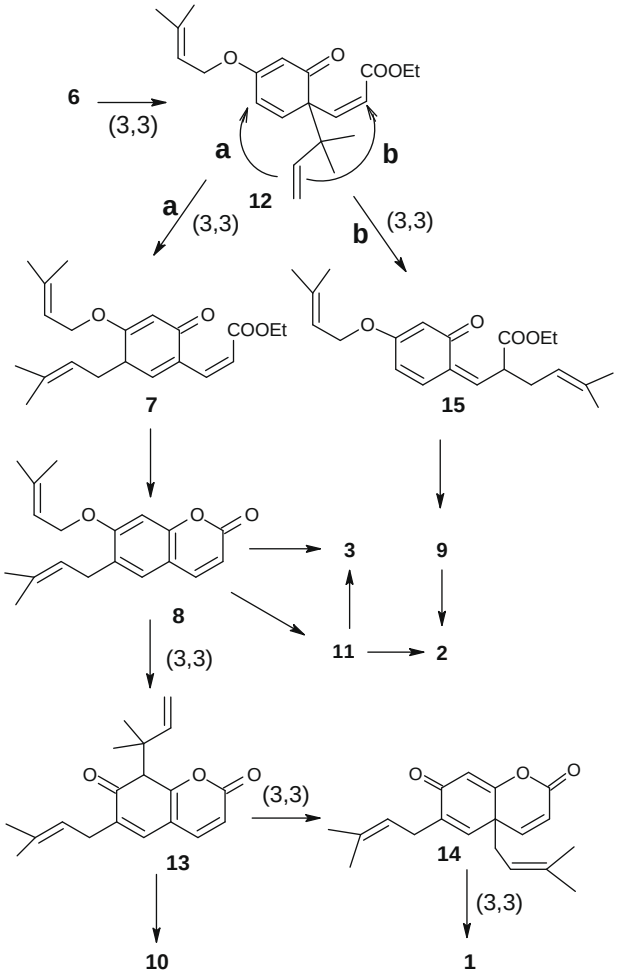
Scheme 1. Synthetic plan for gravelliferone.

The formation of gravelliferone **1** is rationalized by a postulated sequential Wittig reaction, the first Claisen rearrangement of 2′-prenyloxy group leading to **12** followed by 3,3-sigmatropic rearrangement (Cope rearrangement) via route **a** (Scheme 3) to form intermediate **7**, which on cyclization forms pyran ring **8**. The second Claisen rearrangement of the 7′-prenyloxycoumarin **8** to form **13**, followed by two consecutive Cope rearrangements gives **1** via **14**. While **10** is formed by annulation of intermediate **13**, 3-prenyl-7-prenyloxy coumarin **9** may have arisen by Cope rearrangement product **15** (from **12**) getting cyclized (Scheme 3, route **b**). The balsamiferone[14] **2** may have formed by prenylation of the deprenylated product demethylsuberosin **11** or from **9** via an intra/intermolecular pathway. Similarly, the natural product 6,8-diprenylumbelliferone **3** may have formed from direct prenylation of **11** or by intramolecular prenylation of **8** (Scheme 3).

In conclusion, the present work successfully demonstrates utility of the cascade Wittig reaction, double Claisen, and Cope rearrangements for the synthesis of naturally occurring coumarins gravelliferone **1**, balsamiferone **2**, and 6,8-diprenylumbelliferone **3** in a single step. This is the shortest route for the synthesis of gravelliferone **1** and balsamiferone **2** and the first report on the total synthesis of 6,8-diprenylumbelliferone **3**. Further studies to see the effect of introduction of group at 3-position of coumarin by



Scheme 2. Reagents and conditions: (a) Ph_3P=CHCOOEt **5**, PhOPh, reflux.



Scheme 3. Postulated mechanism for the formation of **1**, **2**, **3,** and **9**.

using appropriate Wittig reagent on this double Claisen–Cope rearrangements and the possibility of cascade Wittig multiple Claisen–Cope rearrangements will be undertaken.

Acknowledgments

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13. (a) *Procedure for the synthesis of 2,4-diprenyloxybenzaldehyde* (**4**):To the mixture of resorcylaldehyde (2.00 g, 14.50 mmol) and potassium carbonate (5.00 g, 36.23 mmol) in acetone (40 mL), prenylbromide (5.20 g, 36.23 mmol) was added slowly in portions. The reaction mixture was refluxed for 12 h. It was then cooled, filtered, and acetone was removed under vacuum. To this, water (20 mL) was added and extracted with diethyl ether (3 × 20 mL). The combined organic layer was washed with 2 N sodium hydroxide (2 × 15 mL) and then with water (2 × 15 mL). The organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave a viscous liquid, which was purified over silica gel column chromatography (EtOAc/hexanes = 1:99) to afford 3.30 g (82.50%) of 2,4-diprenyloxybenzaldehyde **4** as a yellow oil; IR (KBr) 1675 (CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.77 (6H, s), 1.81 (6H, s), 4.59 (4H, m), 5.50 (2H, m), 6.48 (1H, s), 6.55 (1H, d, J = 8.7 Hz), 7.81 (1H, d, J = 8.7 Hz), 10.30 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.19, 18.23, 25.70, 25.75, 65.14, 65.43, 99.65, 106.43, 118.81, 118.90, 119.23, 130.18, 138.81, 139.01, 163.04, 165.33, 188.39. HRMS m/z $[M+Na]^+$ 297.1460 (calcd for $C_{17}H_{22}O_3Na$, 297.1467).
(b) *Cascade Wittig reaction, double Claisen, Cope rearrangements of 2,4-diprenyloxybenzaldehyde* **4**. A solution of 2,4-diprenyloxybenzaldehyde **4** (0.20 g, 0.73 mmol) and phosphorane **5** (0.38 g, 1.1 mmol) and diphenyl ether (10 mL) was refluxed for 4 h. The reaction mixture was loaded over silica gel column. Using hexanes, diphenyl ether was removed, followed by elution with ethyl acetate and hexanes (1:1) separated triphenylphosphine oxide from the mixture of coumarins. The mixture of coumarins was then further purified by flash chromatography using ethyl acetate and hexanes (1:9) as eluent. First fraction gave 3-(3-methylbut-2-enyl)-7-(3-methylbut-2-enyloxy) coumarin (**9**), second fraction gave 8,9,9-trimethyl-6-(3-methylbut-2-enyl)-8,9-dihydro-2H-furo[2,3-h]chromen-2-one (**10**), third fraction gave 6,8-diprenylumbelliferone (**3**), fourth fraction gave balsamiferone (**2**), fifth fraction gave gravelliferone (**1**), and the last fraction gave demethylsuberosin (**11**).
3-(3-Methylbut-2-enyl)-7-(3-methylbut-2-enyloxy) coumarin (**9**): Yield: 5.4 mg (2.5%); gummy mass; IR (KBr) 1725 (CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70 (3H, s), 1.78 (3H, s), 1.82 (6H, s), 3.24 (2H, d, J = 6.9 Hz), 4.57 (2H, d, J = 6.9 Hz), 5.32 (1 H, m), 5.49 (1H, m), 6.85 (2H, m), 7.33 (1H, d, J = 9.0 Hz), 7.40 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.82, 18.27, 25.80, 28.67, 65.33, 100.00, 101.20, 112.93, 113.19, 118.83, 119.48, 120.00, 125.22, 128.00, 135.36, 138.14, 139.00, 162.90; HRMS m/z $[M+H]^+$ 299.1637 (calcd for $C_{19}H_{23}O_3$, 299.1647).
8,9,9-Trimethyl-6-(3-methylbut-2-enyl)-8,9-dihydro-2H-furo[2,3-h]chromen-2-one (**10**): Yield: 33 mg (15%); white solid; mp 136–137 °C: Lit.[11] 136–139 °C; IR (KBr) 1725 (CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (3H, d, J = 6.6 Hz), 1.57 (3H, s), 1.58 (3H, s), 1.71 (3H, s), 1.77 (3H, s), 3.29 (2H, d, J = 7.2 Hz), 5.29 (1H, m), 4.50 (1H, q, J = 6.6 Hz), 6.17 (1H, d, J = 9.3 Hz), 7.00 (1H, s), 7.60 (1H, d, J = 9.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.16, 17.71, 20.97, 25.33, 25.68, 27.16, 44.38, 111.66, 113.09, 120.99, 121.25, 121.80, 127.33, 133.58, 144.27, 150.04, 160.32; HRMS m/z $[M+H]^+$ 299.1645 (calcd for $C_{19}H_{23}O_3$, 299.1647).
6,8-Diprenylumbelliferone (**3**): Yield: 33 mg (15%); white solid; mp 134–136 °C; IR (KBr) 3420 (OH) and 1725 (CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.78 (6H, s), 1.81 (3H, s), 1.88 (3H, s), 3.37 (2H, d, J = 6.9 Hz), 3.63 (2 H, d, J = 6.9 Hz), 5.30 (2H, m), 6.11 (1H, s), 6.24 (1H, d, J = 9.3 Hz), 7.09 (1 H, s), 7.61 (1H, d, J = 9.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.87, 22.26, 25.81, 28.88, 112.32, 112.54, 114.49, 120.46, 121.06, 124.81, 125.92, 135.16, 135.89, 144.02, 151.06, 156.57, 161.55. HRMS m/z $[M+Na]^+$ 321.1457 (calcd for $C_{19}H_{22}O_3Na$, 321.1467).
Balsamiferone (**2**): Yield: 11 mg, (5%); white solid; mp 135–136 °C: Lit[11] 134–136 °C; IR (KBr) 3420 (OH) and 1725 (CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.71 (3H, s), 1.76 (3H, s), δ 1.80 (3H, s), 1.81 (3H, s), 3.23 (2H, d, J = 6.9 Hz), 3.39 (2H, d, J = 6.9 Hz), 5.30 (2H, m), 6.99 (1H, s), 7.16 (1H, s), 7.41 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$); δ 17.62, 25.82, 28.46, 102.75, 112.97, 119.53, 121.00, 124.55, 125.39, 127.63, 134.70, 135.33, 139.00, 155.82, 157.28, 163.22; HRMS m/z $[M+Na]^+$ 321.1459 (calcd for $C_{19}H_{22}O_3Na$, 321.1467).
Gravelliferone (**1**): Yield: 22 mg (10%); white solid; mp 165–166 °C: Lit[11] mp 166–167 °C; IR (KBr) 3480 (OH) and 1725 (CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (6H, s), 1.78 (3H, s), 1.81 (3H, s), 3.39 (2H, d, J = 7.2 Hz), 5.08 (2H, m), 5.32 (1H, t), 6.18 (1H, dd, J = 10.8 and 16.8 Hz), 6.54 (1H, brs,), 6.94 (1H, s), 7.19 (1H, s), 7.54 (1H, s). HRMS m/z $[M+Na]^+$ 321.1461 (calcd for $C_{19}H_{22}O_3Na$, 321.1467).
Demethylsuberosin (**11**): Yield: 33 mg (20%); white solid; mp 134–136 °C: Lit[11] 133–135 °C; IR (KBr) 3420 (OH) and 1725 (CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.75 (3H, s), 1.79 (3H, s), 3.38 (2H, d, J = 7.2 Hz), 5.31 (1H, t, J = 7.2 Hz), 6.24 (1H, d, J = 9.3 Hz), 7.00 (1H, s), 7.21 (1H, s), 7.67 (1H, d, J = 9.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$); δ 17.83, 25.80, 28.03, 102.77, 111.98, 112.00, 121.25, 126.39, 128.14, 134.27, 144.72, 154.02, 158.88, 162.95. HRMS m/z $[M+H]^+$ 231.1022 (calcd for $C_{14}H_{15}O_3$, 231.1021).
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