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Nickel-Catalyzed Synthesis of Benzocoumarins: Application to the Total Synthesis of Arnottin I

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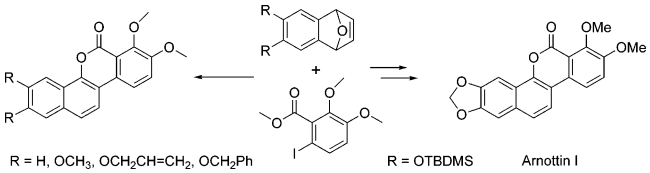

The ring-opening addition of methyl 2,3-dimethoxy-6-iodobenzoate to oxabenzonorbornadienes followed by cyclization in the presence of $NiBr_2$(dppe) and Zn metal powder in acetonitrile at 80 °C to give the corresponding benzocoumarin derivatives is described. This methodology was then applied to the synthesis of natural product arnottin I, first isolated from *Xanthoxylum arnottianum* Maxim, using protecting group chemistry. After deprotection and subsequent ring closure, arnottin I was obtained in 21% overall yield after six steps starting from catechol.

Gilvocarcins[1] and other related compounds, such as ravidomycin[2] and chrysomycins,[3] are metabolites of certain *Streptomyces* species and belong to a class of aryl C-glycoside antibiotics[4] (Figure 1). These molecules, sharing a common tetracyclic aromatic nucleus, 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one to which sugars are attached at the C-4 position, have attracted great attention. Defucogilvocarcins[5] having a similar chromophore have also been extensively studied (Figure 1).

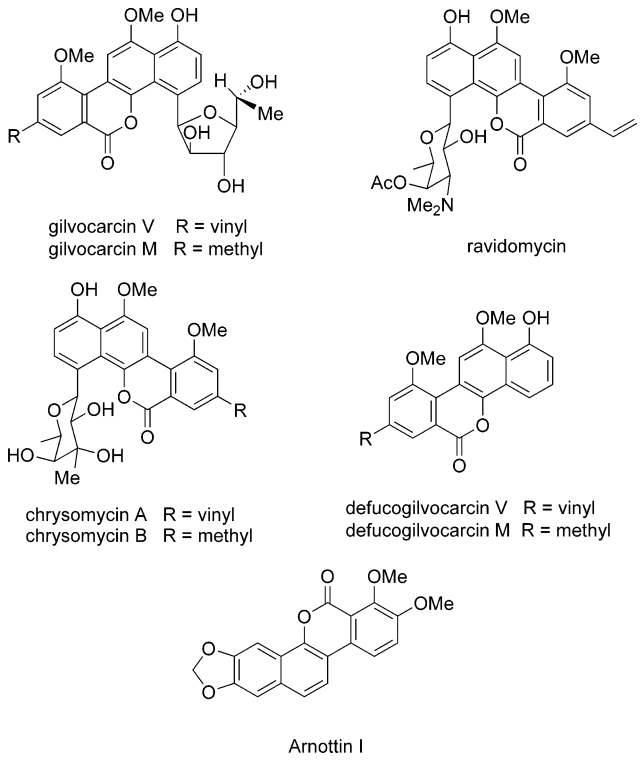

FIGURE 1. Structures of gilvocarcin-class antibiotics.

However, the coumarin-based natural product arnottin I, having a 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one skeleton found in gilvocarcin-type antibiotics, has received less attention.[6] Previously, it has been synthesized utilizing a 2-methylarenofuran as a masked salicylaldehyde[6a] and also via the internal aryl−aryl coupling reaction of aryl *ortho*-halobenzoate catalyzed by palladium complexes.[7]

Our long and continued interest in nickel chemistry[8,9] and the coumarin[10] synthesis encouraged us to investigate a new

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(2) For isolation and structure determination of ravidomycin, see: (a) Findlay, J. A.; Liu, J.-S.; Radics, L.; Rakhit, S. *Can. J. Chem.* **1981**, *59*, 3018. (b) Findlay, J. A.; Liu, J.-S.; Radics, L. *Can. J. Chem.* **1983**, *61*, 323. (c) Narita, T.; Matsumoto, M.; Mogi, K.; Kukita, K.; Kawahara, R.; Nakashima, T. *J. Antibiot.* **1989**, *42*, 347. For the total synthesis of ravidomycin, see: (d) Futagami, S.; Ohashi, Y.; Imura, K.; Ohmori, K.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 1063.

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(4) For an excellent review on aryl C-glycoside antibiotics, see: Hacksell, U.; Daves, G. D., Jr. *Prog. Med. Chem.* **1985**, *22*, 1−65.

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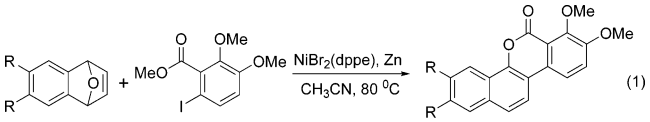
method for the synthesis of arnottin I via a nickel-catalyzed ring-opening addition of substituted *o*-iodobenzoate to oxabenzonorbornadienes. To the best of our knowledge, no nickel-catalyzed synthesis of arnottin I has been reported in the literature. Herein, we report the results of this study.

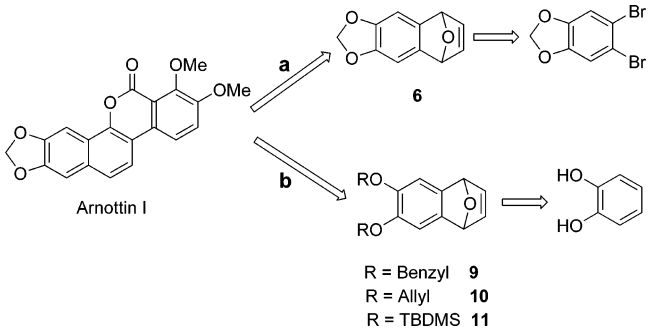
Initially the reaction was tested using commercially available 7-oxabenzonorbornadiene **1** and methyl 2,3-dimethoxy-6-iodobenzoate[11] **2**. Under the standard reaction conditions,[12] that is, $NiBr_2$(dppe) [dppe = 1,2-bis(diphenylphosphino)ethane] and Zn powder in CH_3CN at 80 °C under N_2 atmosphere for 12 h, the desired annulated coumarin **3** was obtained in 75% isolated yield (eq 1). Similarly, treatment of 2,3-dimethoxy-7-oxabenzonorbornadiene **4** with *o*-iodobenzoate **2** gave tetramethoxy-substituted coumarin **5** in 68% isolated yield (eq 1). Starting material **4** was prepared from 4,5-dibromoveratrole and furan in the presence of ^{n}BuLi at −78 °C using Diels−Alder reaction, while **2** was synthesized from 2,3-dimethoxybenzoic acid and thallic trifluoroacetate (prepared in situ by refluxing Tl_2O_3 in CF_3COOH for 2 days).[13]

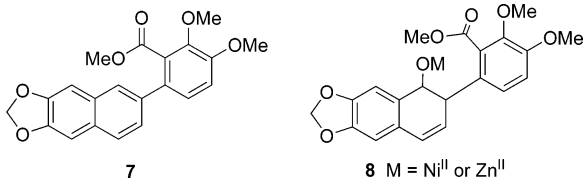


1 R = H, **4** R = OMe; **2**; **3** R = H 75%, **5** R = OMe 68%

The above examples have successfully demonstrated the utility of this nickel-catalyzed reaction in the synthesis of highly functionalized benzocoumarin derivatives. We thus decided to extend this methodology further for preparation of the coumarin-based natural product arnottin I. As shown from retrosynthetic analysis in Scheme 1, two approaches were tested for its synthesis. Path **a** involved the reaction of 1,3-dioxolane-substituted oxabenzonorbornadiene **6** with *o*-iodobenzoate **2**. Compound **6** can be prepared via the Diels−Alder reaction of furan and the benzyne generated from commercially available 1,2-dibromo-4,5-methylenedioxybenzene and ^{n}BuLi. Unfortunately, the reaction of **6** with **2** in the presence of $NiBr_2$(dppe) and Zn powder in CH_3CN failed to give the desired natural product in decent yield even after variation of temperature and change of solvent for the reaction. Different nickel catalyst systems, such as $NiBr_2$(dppe)/dppe/Zn, $NiBr_2$(dppe)/Zn/Et_3N, $NiCl_2$(dppe)/Zn/Et_3N, $NiBr_2$(dppb)/Zn/Et_3N, $NiBr_2$(dppp)/Zn/Et_3N, and Ni(COD)$_2$/PPh_3, gave only a trace amount of the desired product arnottin I. Further, no desired product was observed when nickel complex systems, such as $NiCl_2(PPh_3)_2$/Zn/Et_3N, $NiCl_2(PPh_3)_2$/Zn, and $NiCl_2(PPh_3)_2$/PPh_3/Zn having PPh_3 as the monodentate ligand, were employed. Under these reaction conditions, major product for the reaction of oxabenzonorbornadiene **6** with *o*-iodobenzoate **2** is **7** instead of the expected product arnottin I. Compound **7** is likely from the facile dehydroxylation (−MOH) of reaction intermediate **8** due to the highly electron-rich character of the 1,3-benzodioxolane group that can stabilize an α-carbon cation intermediate or transition state during the elimination of the MOH group in **8** to give **7** (Figure 2).

SCHEME 1. Retrosynthetic Analysis



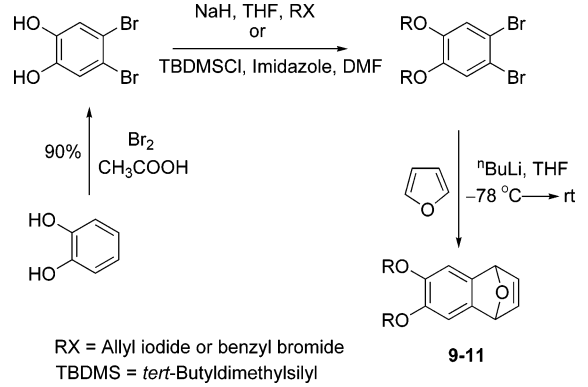


7 **8** M = Ni^{II} or Zn^{II}

FIGURE 2. Structures of **7** and **8**.

We then turned our attention to the alternative route (Scheme 1, path **b**). Using protecting group methodology, benzyl-, allyl-, and silyl-protected oxabenzonorbornadienes **9**−**11** were synthesized in three steps starting from catechol. Treatment of catechol with bromine in acetic acid gave 4,5-dibromocatechol in 90% yield.[14] Protection of the free hydroxyl groups as benzyl-/allyl-substituted derivatives (NaH, THF, RX), followed by the Diels−Alder reaction of the benzynes generated (^{n}BuLi, THF, −78 °C) with furan, gave the corresponding 2,3-dibenzyl- and 2,3-diallyl-7-oxabenzonorbornadienes **9** and **10** in 52 and 46% yields, respectively (Scheme 2). Similarly, *tert*-butyldimethylsilyl was used as the protecting group (TBDMSCl,

SCHEME 2. Preparation of Substituted Oxabenzonorbornadienes 9−11



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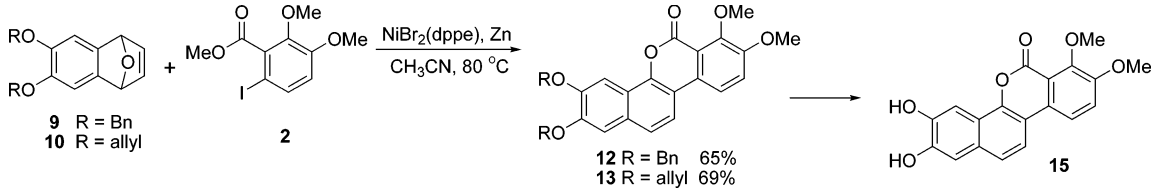
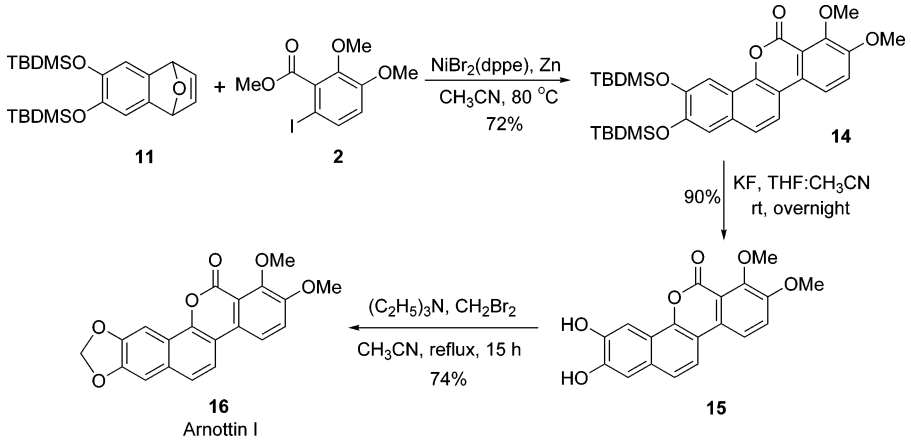
SCHEME 3. Synthesis of Dihydroxy Coumarin 15



SCHEME 4. Total Synthesis of Arnottin I



imidazole, DMF) for the free hydroxyl groups in 4,5-dibromocatechol to prepare 1,2-bis(*tert*-butyldimethylsilyloxy)-4,5-dibromobenzene. The Diels−Alder reaction of the corresponding benzyne generated (^{n}BuLi, THF, −78 °C) with furan then afforded 1,2-bis(*tert*-butyldimethylsilyloxy)-7-oxabenzonorbornadiene **11** in 44% yield over three steps (Scheme 2).

With substituted oxabenzonorbornadienes **9**−**11** in hand, we carried out the nickel-catalyzed coumarin synthesis reaction. Hence, treatment of dibenzyl derivative **9** with *o*-iodobenzoate **2** under our standard reaction conditions furnished dibenzyl coumarin **12** in 65% isolated yield (Scheme 3). Debenzylation using H_2/Pd−C gave the desired dihydroxy compound **15** but only in 25% yield. Next, we used diallyl-substituted oxabenzonorbornadiene **10** as the substrate for reaction with **2** using our standard protocol to furnish diallyl coumarin **13** in 69% yield (Scheme 3). Deallylation with $Pd(PPh_3)_4$/morpholine[15a] in degassed THF gave only a trace amount of dihydroxy derivative **15**. Even Corey's modified Pd-catalyzed conditions[15b] failed to give **15** in decent yield.

Finally, TBDMS-protected oxabenzonorbornadiene **11** was employed as substrate for the reaction with *o*-iodobenzoate **2** to give the corresponding coumarin derivative **14** in 72% isolated yield. The silyl groups were successfully removed by KF (10.0 equiv) in a mixture of THF and CH_3CN (1:1 by volume) to give dihydroxy derivative **15** in 90% yield. Final ring closure was carried out using triethylamine and CH_2Br_2 in CH_3CN under reflux for 15 h to furnish the title compound arnottin I **16** in 74% isolated yield (Scheme 4). The spectroscopic data of this compound are consistent with those reported previously.[6a]

In summary, we have successfully demonstrated the use of the nickel-catalyzed ring-opening addition reaction of methyl 2,3-dimethoxy-6-iodobenzoate **2** to substituted oxabenzonorbornadienes to give highly functionalized benzocoumarin derivatives in good yields. The methodology was further extended to the preparation of natural product arnottin I employing TBDMS-protected oxabenzonorbornadiene **11** as the substrate for reaction with **2**. After removal of the TBDMS group under mild reaction conditions and subsequent ring closure, the desired compound arnottin I **16** was obtained in 21% overall yield after six steps.

Experimental Section

4,5-Dibromocatechol and 1,2-bis(benzyloxy)-4,5-dibromobenzene were prepared according to the methods reported in the literature.[14,16,17]

General Procedure for the Preparation of Benzocoumarins 3 and 5. A round-bottom sidearm flask (25 mL) containing the corresponding bicyclic olefin **1** or **4** (1.5 mmol), methyl *o*-iodobenzoate **2** (1.0 mmol), $NiBr_2$(dppe) (31 mg, 0.05 mmol, 5 mol %), and Zn metal powder (2.75 mmol) was evacuated and purged with nitrogen gas four times. Freshly distilled CH_3CN (3.0 mL) was added to the above mixture, and the reaction mixture was stirred at 80 °C for 12 h. The reaction mixture was then cooled, diluted with methylene chloride (15 mL), and stirred in the air for 15 min. Then it was filtered through a short pad of Celite and silica gel. It was then washed with CH_2Cl_2 several times. The filtrate was concentrated in vacuo, and the crude product was purified by silica gel column using a mixture of ethyl acetate and hexanes as eluent to afford the corresponding benzocoumarin products **3** and **5**.

7,8-Dimethoxy-6*H*-dibenzo[*c*,*h*]chromene-6-one (3): This compound was obtained in 75% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.93 (s, 3H), 3.99 (s, 3H), 7.37 (d, 1H, J = 8.8 Hz), 7.51 (t, 1H,), 7.54 (t, 1H), 7.63 (d, 1H, J = 8.8 Hz), 7.77 (d, 1H, J = 8.0 Hz), 7.83 (d, 1H, J = 8.8 Hz), 7.88 (d, 1H, J = 8.8 Hz), 8.48 (d, 1H, J = 8.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 56.4, 61.6, 112.7, 115.6, 118.0, 119.1, 119.4, 122.1, 123.6, 124.1, 126.9, 127.4, 127.5, 129.3, 133.6, 146.1, 151.6, 153.3, 157.6; HRMS calcd for $C_{19}H_{14}O_4$ 306.0892, found 306.0891.

2,3,7,8-Tetramethoxy-6*H*-dibenzo[*c*,*h*]chromene-6-one (5): This compound was obtained in 68% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.96 (s, 3H), 4.00 (s, 3H), 4.01 (s, 3H), 4.08 (s, 3H), 7.11 (s, 1H), 7.41 (d, 1H, J = 8.8 Hz), 7.53 (d, 1H, J = 8.7 Hz), 7.75

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(s, 1H), 7.81 (d, 1H, $J = 8.7$ Hz), 7.85 (d, 1H, $J = 8.8$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 55.9, 56.4, 56.5, 61.6, 101.0, 106.4, 111.7, 115.3, 117.5, 117.8, 118.8, 119.7, 122.6, 129.8, 129.9, 145.6, 150.2, 150.6, 151.7, 153.0, 157.9; HRMS calcd for $C_{21}H_{18}O_6$ 366.1103, found 366.1105.

General Procedure for the Preparation of Oxabenzonorbornadienes (6, 9−11). To a solution of appropriate dibromo compound (4.0 mmol) and furan (3 mL) in dry THF (25 mL) at −78 °C under N_2 atmosphere was added ^{n}BuLi (4.4 mmol, 2.5 M in hexanes) over a period of 1 h using a syringe pump. After the addition was completed, the reaction mixture was allowed to attain room temperature and was stirred overnight. It was quenched with brine and extracted with diethyl ether (4 × 10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After concentration, the crude product was purified by silica gel chromatography using a mixture of ethyl acetate and hexanes as eluent to afford the corresponding substituted 7-oxabenzonorbornadienes (**6**, **9**−**11**).

2,3-Methylenedioxy-7-oxabenzonorbornadiene (6):[18] This compound was obtained in 45% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.62 (s, 2H), 5.87 (s, 1H), 5.92 (s, 1H), 6.82 (s, 2H), 7.02 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 82.4, 101.1, 103.8, 143.2, 143.3, 144.3; HRMS calcd for $C_{11}H_8O_3$ 188.0473, found 188.0475.

2,3-Bis(benzyloxy)-7-oxabenzonorbornadiene (9): This compound was obtained in 52% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.09 (s, 4H), 5.62 (s, 2H), 6.98 (s, 2H), 6.99 (s, 2H), 7.26−7.42 (m, 10H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 72.3, 82.4, 110.7, 127.8, 128.0, 128.4, 137.4, 142.6, 143.1, 146.0; HRMS calcd for $C_{24}H_{20}O_3$ 356.1412, found 356.1414.

2,3-Bis(allyloxy)-7-oxabenzonorbornadiene (10): This compound was obtained in 46% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53 (d, 4H, $J = 5.0$ Hz), 5.22 (dd, 2H, $J = 1.5$ and 10.5 Hz), 5.36 (dd, 2H, $J = 1.5$ and 17.0 Hz), 5.62 (s, 2H), 6.03 (m, 2H), 6.94 (s, 2H), 6.99 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 70.8, 82.4, 109.9, 117.4, 133.6, 142.1, 143.1, 145.5; HRMS calcd for $C_{16}H_{16}O_3$ 256.1099, found 256.1102.

2,3-Bis(*t*-butyldimethylsilyloxy)-7-oxabenzonorbornadiene (11): This compound was obtained in 57% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.16 (s, 6H), 0.17 (s, 6H), 0.97 (s, 18H), 5.59 (s, 2H), 6.78 (s, 2H), 6.95 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ −4.1 (CH_3−Si), −4.1 (CH_3−Si), 18.3, 25.9, 82.3, 114.9, 141.5, 142.8, 142.9; HRMS calcd for $C_{22}H_{36}O_3Si_2$ 404.2203, found 404.2205.

Methyl 2,3-dimethoxy-6-(naphtho[2,3-*d*][1,3]dioxol-7-yl)benzoate (7). A round-bottom sidearm flask (25 mL) containing **6** (280 mg, 1.5 mmol), *o*-iodobenzoate **2** (320 mg, 1.0 mmol), $NiBr_2$(dppe) (31 mg, 0.05 mmol, 5 mol %), and Zn metal powder (2.75 mmol) was evacuated and purged with nitrogen gas four times. Freshly distilled CH_3CN (3.0 mL) was added to the above mixture, and the reaction mixture was stirred at 80 °C for 12 h. The reaction mixture was then cooled, diluted with methylene chloride (15 mL), and stirred in air for 15 min. Then it was filtered through a short pad of Celite silica gel and washed with CH_2Cl_2 several times. After concentration in vacuo, the crude product was purified by silica gel column (ethyl acetate: hexanes, 1:15) to afford 265 mg of the title compound **7** in 73% yield: ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.63 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 6.02 (s, 2H), 7.01 (d, 1H, $J = 8.5$ Hz), 7.09 (s, 1H), 7.10 (s, 1H), 7.16 (d, 1H, $J = 8.5$ Hz), 7.32 (dd, 1H, $J = 1.8$ and 8.3 Hz), 7.62 (s, 1H), 7.63 (d, 1H, $J = 8.5$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 52.3, 56.0, 61.7, 101.0, 103.6, 104.0, 113.4, 124.8, 125.6, 126.1, 127.0, 128.8, 129.4, 130.3, 132.4, 135.6, 146.0, 147.6, 147.8, 151.7, 168.2; HRMS calcd for $C_{21}H_{18}O_6$ 366.1103, found 366.1104.

General Procedure for the Preparation of Dibenzocoumarins 12−14. These compounds were prepared according to the procedure already reported above for compounds **3** and **5**.

2,3-Bis(benzyloxy)-7,8-dimethoxy-6*H*-dibenzo[*c*,*h*]chromene-6-one (12): This compound was obtained in 65% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.92 (s, 3H), 4.02 (s, 3H), 5.24 (s, 2H), 5.31 (s, 2H), 7.14 (s, 1H), 7.28−7.57 (m, 12H), 7.68−7.73 (m, 2H), 7.85 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 56.6, 61.5, 70.9, 71.0, 103.6, 109.4, 111.7, 115.4, 117.5, 117.6, 119.1, 119.9, 122.6, 126.4, 127.1, 127.2, 127.4, 127.8, 127.8, 128.5, 130.0, 130.0, 136.9, 145.6, 150.0, 150.3, 151.9, 153.0, 157.7; HRMS calcd for $C_{33}H_{26}O_6$ 518.1729, found 518.1730.

2,3-Bis(allyloxy)-7,8-dimethoxy-6*H*-dibenzo[*c*,*h*]chromene-6-one (13): This compound was obtained in 69% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.95 (s, 3H), 4.01 (s, 3H), 4.71 (d, 2H, $J = 5.2$ Hz), 4.78 (d, 2H, $J = 5.2$ Hz), 5.33 (m, 2H), 5.51 (m, 2H), 6.16 (m, 2H), 7.10 (s, 1H), 7.38 (d, 1H, $J = 8.8$ Hz), 7.48 (d, 1H, $J = 8.7$ Hz), 7.75 (s, 1H), 7.76 (d, 1H, $J = 8.8$ Hz), 7.81 (d, 1H, $J = 8.9$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 56.5, 61.5, 69.5, 69.7, 102.5, 108.2, 111.6, 115.2, 117.4, 117.7, 118.0, 118.1, 118.8, 119.6, 122.6, 129.7, 129.9, 132.7, 132.8, 145.5, 149.4, 149.7, 151.6, 152.9, 157.8; HRMS calcd for $C_{25}H_{22}O_6$ 418.1416, found 418.1418.

2,3-Bis(*t*-butyldimethylsilyloxy)-7,8-dimethoxy-6*H*-dibenzo[*c*,*h*]chromene-6-one (14): This compound was obtained in 72% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.28 (s, 6H), 0.30 (s, 6H), 1.02 (s, 9H), 1.03 (s, 2H), 3.91 (s, 3H), 3.99 (s, 3H), 7.16 (s, 1H), 7.33 (d, 1H, $J = 8.8$ Hz), 7.43 (d, 1H, $J = 8.8$ Hz), 7.70 (d, 1H, $J = 8.7$ Hz), 7.76 (d, 1H, $J = 8.7$ Hz), 7.84 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ −4.1 (−CH_3−Si), −4.1 (−CH_3−Si), 18.5, 18.5, 25.9, 26.0, 56.4, 61.4, 110.7, 111.3, 115.3, 116.2, 117.3, 117.6, 119.4, 122.4, 129.8, 130.2, 145.3, 148.4, 148.9, 151.5, 152.8, 157.7; HRMS calcd for $C_{31}H_{42}O_6Si_2$ 566.2520, found 566.2524.

2,3-Dihydroxy-7,8-dimethoxy-6*H*-dibenzo[*c*,*h*]chromene-6-one (15): To a solution of **14** (400 mg, 0.70 mmol) in THF:CH_3CN (1:1, 8 mL) was added KF (406 mg, 7 mmol), and the reaction mixture was stirred at room temperature for 15 h. The solid formed in the reaction mixture was separated and washed several times with diethyl ether. It was then dried under vacuum overnight to furnish 215 mg of **15** (90%): ^{1}H NMR (500 MHz, CD_3CN) δ 3.78 (s, 3H), 3.85 (s, 3H), 6.82 (s, 1H), 7.19 (s, 1H); 7.31 (d, 1H, $J = 8.8$ Hz), 7.59 (d, 1H, $J = 9.0$ Hz), 7.65 (d, 1H, $J = 8.9$ Hz), 7.97 (d, 1H, $J = 9.0$ Hz); ^{13}C NMR (150 MHz, CD_3CN) δ 56.9, 61.5, 100.8, 108.1, 109.1, 114.2, 115.2, 116.9, 118.7, 121.4, 122.6, 130.3, 130.8, 145.0, 150.9, 152.5, 153.8, 155.4, 158.4.

Preparation of Arnottin I (16). A mixture of **15** (200 mg, 0.60 mmol), methylene bromide (156 mg, 0.06 mL, 0.9 mmol), and triethylamine (180 mg, 0.25 mL, 1.8 mmol) in CH_3CN (10 mL) was refluxed for 15 h. After removal of the solvent, the residue was redissolved in CH_2Cl_2 (20 mL), washed with water and brine, and dried over $MgSO_4$. Column chromatographic purification (ethyl acetate:hexanes, 1:5) gave 150 mg of the desired natural product **16** (74%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.97 (s, 3H), 4.01 (s, 3H), 6.08 (s, 2H), 7.11 (s, 1H), 7.42 (d, 1H, $J = 8.4$ Hz), 7.51 (d, 1H, $J = 9.0$ Hz), 7.81 (d, 1H, $J = 9.0$ Hz), 7.83 (s, 1H), 7.87 (d, 1H, $J = 9.0$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 56.6, 61.6, 99.1, 101.5, 104.0, 111.7, 117.7, 117.8, 119.7, 120.0, 123.2, 125.0, 129.8, 131.2, 135.2, 144.0, 145.4, 148.2, 151.8, 153.1, 157.7; HRMS calcd for $C_{20}H_{14}O_6$ 350.0790, found 350.0791.

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Supporting Information Available: Copies of ^{1}H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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