Tetrahedron 68 (2012) 9592–9597

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Unified route to asymmetrically substituted butenolide, maleic anhydride, and maleimide constituents of *Antrodia camphorata*

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ARTICLE INFO

Article history:
Received 12 August 2012
Received in revised form 7 September 2012
Accepted 11 September 2012
Available online 18 September 2012

Keywords:
Cross-coupling
Dimethyldioxirane
Furan
γ-Hydroxybutenolide
Oxidation

ABSTRACT

The first synthesis of antrocinnamomin D and a new synthesis of antrodins A and B have been achieved in 6–8 steps and high overall efficiency (51, 46, and 43%, respectively) from commercially available methyl 4-hydroxyphenylacetate. Key steps include Fürstner–Kochi iron-catalyzed sp^2–sp^3 cross-coupling and 2-silyloxyfuran oxyfunctionalization.

1. Introduction

Antrodia camphorata is a renown parasitic fungus used in traditional Chinese medicine for the treatment of liver cancer, drug intoxication, hypertension, and a host of other conditions.[1] The fungus can only be found in Taiwan where it grows slowly in the wild on the inner heartwood of the endangered native tree *Cinnamomun kanehirai*. Because the fungus is difficult to cultivate for commercial purposes and its fruiting body is hardly noticeable unless the host tree has fallen down, fruiting bodies are extremely rare and precious retailing at €10,000–28,000/kg.[2]

Extensive investigation of *A. camphorata* over the past decade has led to the isolation and characterization of an impressive array of natural products.[1] Of these, a small family of maleic anhydrides and relatives,[3–5] represented by antrodins A–C **1**–**3**[3,6] and antrocinnamomin D **4**[4] (Fig. 1), have garnered particular attention on account of their diverse pharmacological effects including antitumor,[3,7] antiviral,[8] and anti-inflammatory activities.[4,5,9] For example, anhydride **1** is a noncytotoxic, potent, and selective inhibitor of hepatitis C virus (HCV) protease (IC_{50}=0.9 μg/mL),[8] whereas its maleimide counterpart **2** is devoid of anti-HCV activity but displays strong cytotoxicity against Lewis lung carcinoma (LLC) cells.[4,10] Furthermore, recent studies have revealed that **2** suppresses the growth of estrogen-independent, highly invasive MDA-MB-231 breast cancer cells in nude mice at a dose of 3 mg/kg (×3/week, ip) without side-effects.[11] Newer members of this family, such as **4**, have been shown to inhibit the production of pro-inflammatory mediators in macrophages (e.g., NO and IL-6),[4,5] although their limited availability has prevented more comprehensive screening.[9]

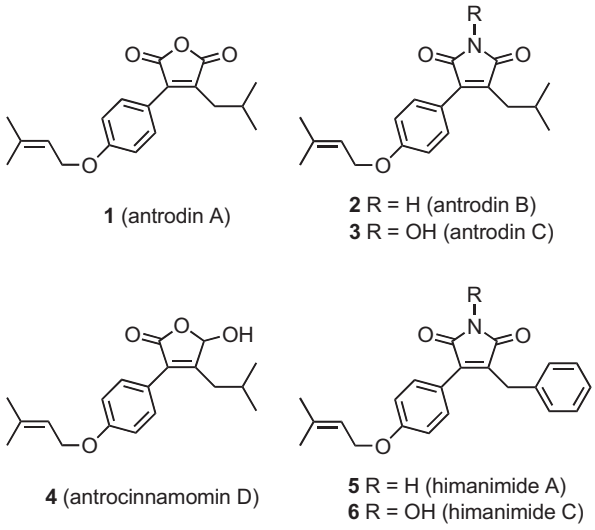

Fig. 1. Antrodins and related natural products.

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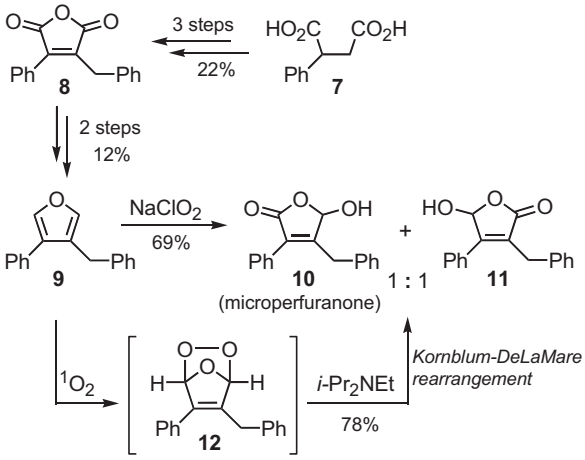
http://dx.doi.org/10.1016/j.tet.2012.09.064

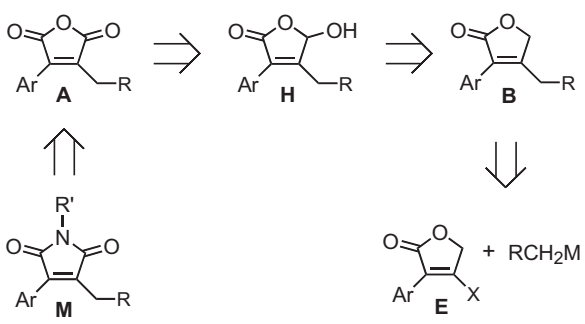
Understandably, the therapeutic potential and scarcity of these compounds have stimulated considerable interest in their synthesis. Antrodins A–C have been synthesized by the groups of Argade, Stewart, and Lee.[12–14] A number of antrodin analogues have also been prepared.[13b] Included in this group are the antimicrobial/fungicidal himanimides (e.g., **5**–**6**, Fig. 1), obtained from the Chilean fungus *Serpula himantoides*, and their unnatural analogues.[14,15]

Whereas all of the previous syntheses have targeted the anhydrides and maleimides, we were interested in a de novo synthetic approach that would also provide the γ-hydroxybutenolide antrocinnamomin D (**4**). The difficulties associated with the latter target are illustrated by Clive's synthesis of a related natural product, namely, microperfuranone **10** (Scheme 1).[16,17] Besides the low-yielding preparation of anhydride **8** from phenylsuccinic acid **7**, earlier described by Momose and Muraoka,[18,19] and the equally low-yielding transformation of **8** to furan **9**, eventual oxidation of the latter using either sodium chlorite or the Faulkner method afforded **10** as a 1:1 mixture with its regiomer **11** (Scheme 1).[16] Evidently, the lack of regioselectivity in the all-important oxidation step reflects the absence of significant steric/electronic bias in both furan **9** and its endoperoxide **12** from which **10** and **11** derive via Kornblum–DeLaMare rearrangement[20] under the Faulkner conditions.[21]



Scheme 1. Clive's synthesis of microperfuranone.[16]

As indicated in Scheme 2, our approach to such γ-hydroxybutenolides (cf. **H**) completely eliminates this challenge. Regiospecific access to **H** would be gained by installing the hydroxyl group onto butenolide **B**, which would in turn arise from **E** by cross-coupling with the appropriate nucleophile. Subsequent conversion of **H** to anhydride (**A**) and then to maleimides (**M**) would swiftly extend the route to the full gamut of fungal metabolites. Reported herein is the successful implementation of this strategy to the first synthesis of antrocinnamomin D and a new synthesis of antrodins A and B.



Scheme 2. Unified synthetic strategy.

2. Results and discussion

Our synthetic study commenced with the preparation of ester **14** from commercially available methyl 4-hydroxyphenylacetate **13** (Scheme 3). Crafting **14** into tetronic acid **15** was conveniently accomplished in a single operation by adaptation of a recently conveyed method by Le Gall.[22] Thus, treatment of **14** with methyl glycolate and *t*-BuOK in DMF for 50 h at rt cleanly effected tandem transesterification/Dieckmann condensation to furnish after a simple work-up crystalline **15** in essentially quantitative yield. The next task entailed activation of **15** for the ensuing cross-coupling reaction. Although both β-tetronic acid bromides[23] and triflates[24] generally perform well as electrophiles, the bromides are usually preferred since they are more robust and often highly crystalline. Unfortunately, however, they are also notoriously difficult to prepare from the corresponding tetronic acids.[25–27] Accordingly we opted for triflate **16**, whose preparation from **15** proved uneventful when carried out using Tf_2O/*i*-Pr_2NEt.[28]

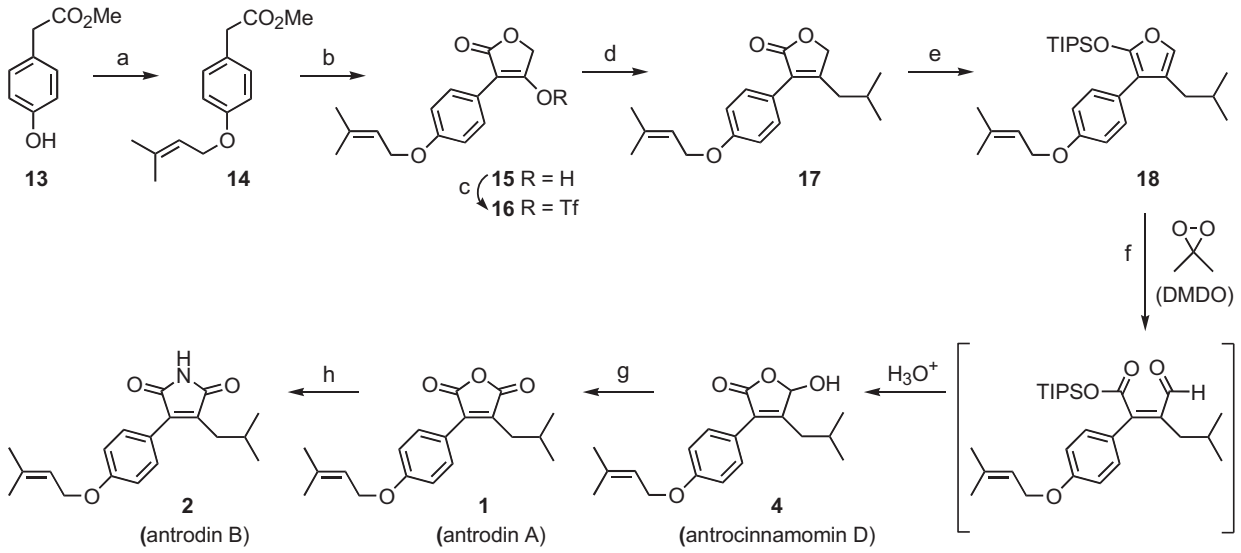
Among the plethora of cross-coupling regimens extant, that reported by Fürstner and co-workers[29] appeared best suited to our needs. Notwithstanding the steric bulk of the aryl substituent positioned adjacent to the triflate group in **16**, iron-catalyzed[29,30] coupling with *i*-BuMgBr proceeded smoothly at −30 °C in 15 min to provide butenolide **17** in a reproducible yield of 67% after flash chromatography. For the sake of comparison, we also tried the somewhat delicate Suzuki–Miyaura coupling of **16** with commercial isobutylboronic acid.[31,32] The best yield of **17** (55%) was realized under Falck's conditions[33] necessitating the use of a 2.5-fold excess of Ag_2O in addition to the Pd-catalyst and a strong base (Scheme 3).

With a viable route to the antrodin skeleton, we turned our attention to the conversion of **17** into the initial synthetic target, antrocinnamomin D **4**. Prompted by a literature report describing an ostensibly simple and efficient autoxidation of the α,β-diarylbutenolide rofecoxib (Vioxx™) to γ-hydroxyrofecoxib (O_2/charcoal/EtOAc, 92% yield),[34] we set out to explore the possibility of directly converting **17** to **4** under similar conditions. However, exposure of an ethyl acetate solution of **17** to oxygen in the presence of activated charcoal at rt for several days failed to give **4** in any detectable amounts. Inclusion of DBU, known to facilitate such reactions,[35] was to no avail. Clearly, the capacity of butenolides to undergo autoxidation is dictated to a considerable degree by the nature of their substitution.

At this point, we decided to deploy our two-step oxyfunctionalization method,[36] which has displayed remarkable generality and scope.[37,38] Thus, silylation of **17** with TIPSOTf/Et_3N, followed by sequential treatment of the resulting 2-silyloxyfuran **18** with dimethyldioxirane (DMDO) and a few drops of water/Amberlyst 15, led uniquely to antrocinnamomin D **4** (84%, two steps) whose spectral properties were in good agreement with those reported for the natural product.[4,39] Subsequent oxidation of **4** with Dess–Martin periodinane[40] cleanly provided antrodin A **1** (90%), thereby setting the stage for easy access to maleimides (cf. antrodins B and C **2** and **3**, Fig. 1). Even though the latter have been synthesized from **1** on several occasions,[12–14] the reported procedures for preparing **2** were deemed overly harsh (urea/135–140 °C or $AcONH_4$/AcOH/120 °C, 60–88%).[12–14] Pleasingly, we were able to convert **1** to antrodin B **2** in excellent yield (93%) by rt reaction with hexamethyldisilazane (HMDS) in MeOH/DMF[41] (Scheme 3).

3. Conclusion

The first synthesis of antrocinnamomin D and a new synthesis of antrodins A and B have been achieved from methyl 4-hydroxyphenylacetate in 6–8 steps and overall yields of 51, 46, and 43%, respectively. Besides establishing a unified, modular, and efficient pathway to this family of fungal metabolites, the foregoing



Scheme 3. Reagents and conditions: (a) $Me_2C{=}CHCH_2Br$, K_2CO_3, acetone, reflux, 17 h (97%); (b) $HOCH_2CO_2Me$, *t*-BuOK, DMF, rt, 50 h; (c) Tf_2O, *i*-Pr_2NEt, CH_2Cl_2, −40 °C, 40 min (93%, two steps); (d) *method A*: *i*-BuMgBr, $Fe(acac)_3$ (5 mol %), NMP, THF, −30 °C, 15 min (67%), *method B*: *i*-$BuB(OH)_2$, $Pd(dppf)Cl_2$ (10 mol %), Ag_2O (2.5 equiv), K_2CO_3 (3.0 equiv), THF, 80 °C, 16 h (55%); (e) TIPSOTf/Et_3N, CH_2Cl_2, 0 °C→rt, 1 h (86%); (f) DMDO in acetone, CH_2Cl_2, −78→−20 °C; ca. 1 h, then Amberlyst 15/water, rt, 30 min (98%, one-pot procedure); (g) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h (90%); (h) HMDS, MeOH/DMF, rt, 14 h (93%).

work highlights: (i) the value of Fürstner's iron-catalyzed cross-coupling protocol as a practical, greener alternative to the more mainstream Pd-catalyzed cross-coupling reactions, and (ii) the serviceability of our oxyfunctionalization method for constructing γ-hydroxybutenolides of predetermined substitution.

4. Experimental

4.1. General methods

Unless otherwise indicated, all air- and/or moisture-sensitive reactions were carried out under an argon or nitrogen atmosphere in glassware that had been flame-dried under a stream of the same inert gases. Glass syringes and stainless steel needles or cannulae were used to transfer air- and moisture-sensitive liquids/solutions. Sealed tube reactions were performed in Kimble Kimax® thick-walled screw-cap tubes measuring 13×100 mm. Prior to use, DMF was left to stand at rt for 24 h over 4 Å molecular sieves that had previously been oven-dried at 200–300 °C for 3–4 days; dichloromethane and methanol were distilled from calcium hydride, acetone from calcium sulfate, and THF from sodium/acetophenone. Commercial reagents were used as received except for Hünig's base that was distilled from KOH pellets. Reactions were monitored by thin layer chromatography (TLC) carried out using Merck 0.2 mm silica gel 60 F_{254} aluminum-backed plates. These plates were visualized by UV light and either cerium ammonium molybdate (CAM) or a potassium permanganate solution was used as developing agent. Flash column chromatography was performed using Silicycle® silica gel 60 (230–400 mesh). The term 'neutralized silica gel' is used to describe silica gel that has been flushed three times in the chromatography column with a mixture of hexanes/triethylamine (95:5) before use. NMR spectra were recorded on either an Agilent DDR spectrometer operating at 500 MHz for ^1H and 125 MHz for ^{13}C nuclei, or a Varian Inova spectrometer operating at 400 MHz for ^1H and 100 MHz for ^{13}C nuclei; ^1H and ^{13}C spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard (^1H NMR: δ_H 7.260 in $CDCl_3$, 2.050 in acetone-d_6; ^{13}C NMR: δ_C 77.00 in $CDCl_3$, 39.52 in acetone-d_6). Melting points were recorded on a Barnstead/Thermolyne MelTemp® Electrothermal Apparatus, electrospray ionization (ESI) high-resolution mass spectra were recorded on an Agilent 6210 TOF LC/MS instrument. Infra-red spectra were recorded on a Bomem Arid Zone MB-series FTIR instrument, with samples prepared on single NaCl plates, as either a pure film if in liquid form, or a neat layer if solid.

4.2. Methyl 4-prenyloxyphenylacetate (14)

A mixture of methyl 4-hydroxyphenylacetate **13** (6.83 g, 41.1 mmol, 1.0 equiv) and potassium carbonate (8.86 g, 64.1 mmol, 1.6 equiv) was stirred in freshly distilled acetone (62 mL) for 5 min, and prenyl bromide (7.96 g, 6.17 mL, 53.8 mmol, 1.3 equiv) was added dropwise over the course of 10 min. The resulting mixture was refluxed for 17 h. Once TLC had indicated complete disappearance of starting material, the solvent was removed under reduced pressure. The residue was dissolved in water and extracted with ethyl acetate (3×100 mL). The organic layer was dried with sodium sulfate, filtered, and concentrated in vacuo to leave a brown oil, which was purified by flash column chromatography (15% EtOAc/hexanes) to yield **14** as a colorless oil (9.37 g, 97% yield). R_f=0.40 (20% EtOAc/hexanes); IR (NaCl, film): ν 2975, 2952, 2873, 1733, 1612, 1512, 1435, 1239, 1157, 1004, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, J=8.5 Hz, 2H), 6.88 (d, J=8.5 Hz, 2H), 5.50 (t, J=6.6 Hz, 1H), 4.49 (d, J=6.6 Hz, 2H), 3.67 (s, 3H), 3.56 (s, 2H), 1.80 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 157.9, 137.8, 130.1, 125.8, 119.7, 114.6, 64.6, 51.8, 40.1, 25.7, 18.0; HRMS (ESI): m/z calcd for $C_{14}H_{18}O_3$: 234.1256; found: 234.1268.

4.3. 4-Hydroxy-3-(4-prenyloxyphenyl)-furan-2(5*H*)-one (15)

To a solution of ester **14** (4.00 g, 17.1 mmol, 1.0 equiv) and methyl glycolate (1.60 mL, 1.87 g, 20.7 mmol, 1.2 equiv) in 80 mL of anhydrous DMF was slowly added 40 mL of a THF solution of potassium *tert*-butoxide (1 M, 40.0 mmol, 2.3 equiv). The resulting light yellow suspension was stirred under argon at rt for 50 h. The reaction mixture was then poured in one portion into 200 mL of ice cold aq 1 M HCl. The resulting suspension was subsequently kept in an ice bath for 20 min, filtered, and the filter cake washed with ice cold aq 1 M HCl. The filter cake was then dissolved in ethyl acetate and washed with water then brine, dried over sodium sulfate, filtered,

and concentrated in vacuo. The resulting beige crystals of tetronic acid **15** (4.44 g, 99% yield) were pure enough for utilization in the next step. Mp 121–122.5 °C; R_f=0.38 (10% MeOH/CH_2Cl_2+0.2% AcOH); IR (NaCl, film): ν 2925, 2871, 2696, 1695, 1652, 1608, 1425, 1394, 1293, 1253, 1172, 1052, 1003, 834, 738 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6): δ 7.90 (d, J=9.2 Hz, 2H), 6.92 (d, J=9.0 Hz, 2H), 5.44 (t, J=7.2 Hz, 1H) 4.73 (s, 2H), 4.54 (d, J=6.8 Hz, 2H), 1.74 (s, 3H), 1.72 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 172.8, 171.4, 158.0, 137.0, 128.4, 123.0, 120.5, 114.3, 99.5, 65.9, 64.6, 25.1, 17.5; HRMS (ESI): m/z calcd for $C_{15}H_{16}O_4$: 260.1049; found: 260.1059.

4.4. 3-(4-Prenyloxyphenyl)-4-trifluoromethanesulfonyl-furan-2(5*H*)-one (16)

Tetronic acid **15** (30.7 mg, 0.118 mmol, 1.0 equiv) was dissolved in 2 mL of anhydrous dichloromethane and cooled to −40 °C, at which point 41.1 μL of Hünig's base (30.5 mg, 0.236 mmol, 2.0 equiv) was added, followed by a slow dropwise addition of 25.9 μL of trifluoromethanesulfonic anhydride (43.4 mg, 0.154 mmol, 1.3 equiv). After 40 min at this same temperature, TLC indicated complete disappearance of starting material, at which point 5 mL of water was added and the temperature allowed to rise to rt. Once the water had melted the organic layer was separated and the aqueous layer extracted with dichloromethane (3×10 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated in vacuo to yield a brown oil. Purification by flash column chromatography (10% EtOAc/hexanes) yielded triflate **16** as a bright orange oil, which solidified when stored in the freezer (43.8 mg, 94% yield). Mp 44 °C; R_f=0.35 (5% EtOAc/hexanes); IR (NaCl, film): ν 3356, 2975, 2918, 1780, 1609, 1513, 1436, 1248, 1224, 1142, 1002, 951, 836, 810, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J=9.0 Hz, 2H), 6.99 (d, J=9.2 Hz, 2H), 5.49 (t, J=6.8 Hz, 1H), 5.06 (s, 2H), 4.56 (d, J=6.8 Hz, 2H), 1.81 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 160.5, 157.6, 139.0, 130.0, 119.3, 118.5 (q, J_{C-F}=319.7 Hz), 117.9, 117.2, 115.3, 66.1, 65.1, 26.1, 18.5; HRMS (ESI): m/z calcd for $C_{16}H_{15}O_6SF_3$: 392.0541; found: 392.0546.

4.5. 4-Isobutyl-3-(4-prenyloxyphenyl)-furan-2(5*H*)-one (17)

Method A: A solution of isobutylmagnesium bromide (2 M in THF, 300 μL, 0.154 mmol, 1.2 equiv) was rapidly added to a solution of triflate **16** (50 mg, 0.128 mmol, 1.0 equiv) and $Fe(acac)_3$ (2.1 mg, 0.0064 mmol, 0.05 equiv) in THF (2 mL) and 1-methyl-2-pyrrolidinone (NMP, 0.1 mL) at −30 °C. There was an immediate color change from orange-red to brown/black. The mixture was left stirring for 15 min at that temperature before it was quenched with aq saturated ammonium chloride (1 mL). The mixture was partitioned between water (15 mL) and diethyl ether (15 mL) and was repeatedly extracted with diethyl ether (3×15 mL). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo to give a brown residue. Purification by flash column chromatography on silica gel (25% EtOAc/hexanes) gave butenolide **17** as a yellow oil (25.5 mg, 67% yield). R_f=0.30 (15% EtOAc/hexanes); IR (NaCl, film): ν 2958, 2927, 2870, 1752, 1608, 1511, 1465, 1385, 1290, 1242, 1178, 1127, 1037, 986, 955, 834, 780, 628 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J=8.8 Hz, 2H), 6.97 (d, J=9.0 Hz, 2H), 5.51 (t, J=6.8 Hz, 1H), 4.80 (s, 2H), 4.54 (d, J=6.8 Hz, 2H), 2.49 (d, J=7.6 Hz, 2H), 1.91–184 (m, 1H), 1.81 (s, 3H), 1.76 (s, 3H), 0.93 (d, J=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 160.3, 159.2, 138.7, 130.5, 127.4, 122.5, 119.7, 114.9, 71.6, 65.0, 36.9, 27.8, 26.1, 22.9, 18.5. HRMS (ESI): m/z calcd for $C_{19}H_{24}O_3$: 300.1725; found: 300.1727.

Method B: In a screw-cap sealed tube, a suspension of isobutylboronic acid (78.0 mg, 0.765 mmol, 1.5 equiv), triflate **16** (200 mg, 0.510 mmol, 1.0 equiv), $Pd(dppf)Cl_2$ (41.7 mg, 0.051 mmol, 0.1 equiv), powdered potassium carbonate (211.5 mg, 1.530 mmol, 3.0 equiv), and Ag_2O (295.5 mg, 1.275 mmol, 2.5 equiv) in THF (8 mL) was degassed with a flow of bubbling argon, sealed, and then stirred under argon at 80 °C. After 16 h, the mixture was cooled to rt, then concentrated in vacuo and purified by flash column chromatography (10% EtOAc/hexanes) to afford **17** as a yellow oil (84.8 mg, 55% yield), whose ^1H and ^{13}C NMR data were identical to those just described (*method A*).

4.6. 4-Isobutyl-3-(4-prenyloxyphenyl)-2-triisopropylsilyloxyfuran (18)

To a solution of butenolide **17** (61.9 mg, 0.206 mmol, 1.0 equiv) in anhydrous dichloromethane (4 mL) that had been cooled to 0 °C, were added sequentially triethylamine (37.3 μL, 27.1 mg, 0.268 mmol, 1.3 equiv) and triisopropylsilyl trifluoromethanesulfonate (66.5 μL, 75.7 mg, 0.247 mmol, 1.2 equiv). After 1 h, the mixture was poured into aq 10% sodium bicarbonate (10 mL). The aqueous layer was extracted twice using dichloromethane (2×15 mL) and the combined organic layers were dried with magnesium sulfate. The mixture was concentrated in vacuo and purified by flash column chromatography on neutralized silica gel (100% hexanes), furnishing **18** as a colorless oil (80.5 mg, 86% yield). R_f=0.65 (100% hexanes); IR (NaCl, film): ν 2946, 2868, 1651, 1609, 1575, 1516, 1464, 1404, 1289, 1238, 1174, 1035, 991, 883, 831, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, J=9.0 Hz, 2H), 6.90 (d, J=8.8 Hz, 2H), 6.65 (s, 1H), 5.52 (t, J=6.8 Hz, 1H), 4.52 (d, J=7.0 Hz, 2H), 2.31 (d, J=6.8 Hz, 2H), 1.81 (s, 3H), 1.76 (s, 3H), 1.69–1.62 (m, 1H), 1.23–1.14 (m, 3H), 1.02 (d, J=8.0 Hz, 18H), 0.84 (d, J=6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0, 153.1, 138.2, 129.9, 128.3, 126.1, 125.0, 120.1, 114.5, 99.1, 64.9, 34.6, 27.8, 26.1, 22.8, 18.4, 17.8, 12.5; HRMS (ESI): m/z calcd for $C_{28}H_{44}O_3Si$: 456.3060; found: 456.3063.

4.7. Antrocinnamomin D (4)

Furan **18** (80.5 mg, 0.176 mmol, 1.0 equiv) was dissolved in anhydrous dichloromethane (1 mL) and cooled to −78 °C, whereupon dimethyldioxirane in acetone (6.5 mL, ca. 0.05–0.07 M)[42] was added dropwise. After 30 min, the mixture was allowed to warm to ca. −20 °C, at which point TLC (on silica plates pre-neutralized with 10% triethylamine in hexanes, elution with hexanes) showed that all starting material was consumed. The volatiles were removed under reduced pressure at ca. −20 °C and the residue was dissolved in acetone (3 mL), to which 10 drops of water were added along with 15 mg of Amberlyst 15. After stirring for 30 min at rt, the solution was concentrated under reduced pressure and diethyl ether (25 mL) was added. After drying with $MgSO_4$, filtration and removal of the volatiles under reduced pressure, purification by flash chromatography (30% EtOAc/hexanes) gave **4** as a white solid (54.4 mg, 98% yield). Mp 66–68 °C; R_f=0.25 (30% EtOAc/hexanes); IR (NaCl, film): ν 3393, 2958, 2870, 1761, 1733, 1608, 1512, 1464, 1291, 1243, 1178, 1115, 994, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, J=8.8 Hz, 2H), 6.96 (d, J=9.2 Hz, 2H), 6.08 (s, 1H), 5.50 (t, J=6.4 Hz, 1H), 4.54 (d, J=6.8 Hz, 2H), 4.33 (br s, 1H), 2.49 (d, J=7.6 Hz, 2H), 2.03–1.96 (m, 1H), 1.81 (s, 3H), 1.76 (s, 3H), 0.97 (d, J=6.8 Hz, 3H), 0.86 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 159.5, 159.1, 138.8, 130.6, 129.7, 121.7, 119.6, 114.9, 97.3, 65.0, 35.6, 27.3, 26.1, 23.6, 22.5, 18.5. HRMS (ESI): m/z calcd for $C_{19}H_{24}O_4$: 316.1675; found: 316.1694.

4.8. Antrodin A (1)

Antrocinnamomin D **4** (37.3 mg, 0.118 mmol, 1.0 equiv) was stirred in a glass screw-cap vial in dichloromethane (1.5 mL) at rt. Dess–Martin periodinane (0.3 M in THF, 0.472 mL, 0.142 mmol, 1.2 equiv) was added and the reaction was monitored by TLC. After

1 h, the mixture was partitioned between a saturated solution of sodium sulfite (15 mL) and dichloromethane (20 mL). The organic layer was then washed successively with aq saturated sodium bicarbonate (15 mL), then brine (15 mL) and was dried with magnesium sulfate. The mixture was concentrated in vacuo and the residue subjected to flash column chromatography (8% EtOAc/hexanes) to give **1** as a fluorescent yellow oil (33.2 mg, 90% yield). R_f=0.50 (20% EtOAc/hexanes); IR (NaCl, film): ν 2959, 2917, 2872, 1838, 1764, 1605, 1506, 1422, 1350, 1233, 1170, 994, 926, 901, 838, 824, 752, 616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J=8.8 Hz, 2H), 7.02 (d, J=9.2 Hz, 2H), 5.50 (t, J=6.8 Hz, 1H), 4.56 (d, J=7.0 Hz, 2H), 2.60 (d, J=7.2 Hz, 2H), 2.18–2.08 (m, 1H), 1.82 (s, 3H), 1.77 (s, 3H), 0.95 (d, J=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 165.7, 161.2, 140.4, 140.0, 139.3, 131.3, 120.1, 119.1, 115.4, 65.2, 33.8, 28.2, 26.1, 22.9, 18.5; HRMS (ESI): m/z calcd for $C_{19}H_{22}O_4$: 314.1518; found: 314.1527.

4.9. Antrodin B (2)

A solution of antrodin A **1** (23.6 mg, 0.075 mmol, 1.0 equiv) in DMF (0.6 mL) was treated with methanol (16 μL, 12.7 mg, 0.395 mmol, 5.3 equiv) and hexamethyldisilazane (158 μL, 122.3 mg, 0.758 mmol, 10.1 equiv). After 16 h at rt, the mixture was poured into water (50 mL) and extracted with ethyl acetate (2×30 mL). The combined extracts were washed with water (25 mL) and dried with magnesium sulfate. After filtration and concentration in vacuo, the residue was purified by flash column chromatography (15% EtOAc/hexanes), to furnish **2** as bright yellow crystals (21.9 mg, 93% yield) that fluoresced under a UV lamp. Mp 104–105 °C (lit.[3] 110–111 °C, lit.[14] 104.5–105 °C). R_f=0.21 (15% EtOAc/hexanes); IR (NaCl, film): ν 3287 (br), 2959, 2926, 1770, 1709, 1605, 1511, 1349, 1247, 1176, 988, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J=8.7 Hz, 2H), 7.37 (br s, 1H), 7.00 (d, J=8.7 Hz, 2H), 5.51 (t, J=6.6 Hz, 1H), 4.56 (d, J=6.6 Hz, 2H), 2.53 (d, J=7.3 Hz, 2H), 2.02–2.10 (m, 1H), 1.82 (s, 3H), 1.77 (s, 3H), 0.91 (d, J=6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.9, 171.2, 160.2, 139.3, 138.9, 138.8, 131.1, 121.3, 119.3, 115.0, 65.0, 33.0, 29.9, 28.2, 26.0, 22.9, 18.4; HRMS (ESI): m/z calcd for $C_{19}H_{23}NO_3$: 313.1678; found: 313.1689.

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) and the FQRNT/Quebec Centre in Green Chemistry and Catalysis (CGCC) for financial support. We also thank NSERC and FQRNT for doctoral scholarships to R.P.L. and V.A. respectively.

Supplementary data

^1H NMR and ^{13}C NMR spectra for all compounds synthesized (**1**, **2**, **4**, **13**–**18**). Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.09.064.

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