JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

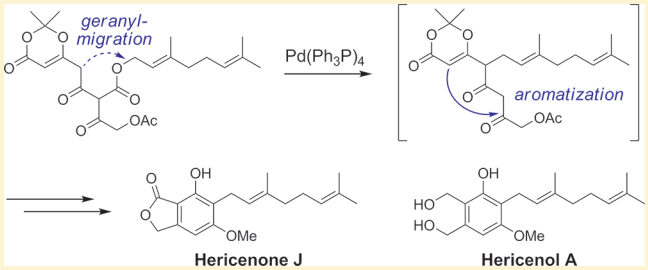
Total Syntheses of Angelicoin A, Hericenone J, and Hericenol A via Migratory Prenyl- and Geranylation−Aromatization Sequences

Jens Cordes, Frederick Calo, Katie Anderson, Toni Pfaffeneder, Sylvain Laclef, Andrew J. P. White, and Anthony G. M. Barrett*

Department of Chemistry, Imperial College, London, SW7 2AZ, England

Supporting Information

ABSTRACT: A five-step synthesis of the natural product angelicoin A using a late stage highly regioselective palladium(0)-catalyzed decarboxylative prenyl migration and aromatization sequence as the key step is reported. The method was extended with geranyl migration in eight-step total syntheses of hericenone J and hericenol A from geraniol.



INTRODUCTION

Molecules containing prenyl, geranyl, and other terpenoid functionalized arenes occur widely in natural products from plants,[1−5] algae,[6] fungi,[7,8] bacteria,[9] and ascidia.[10] Their biological effects include cytotoxic,[1,8−10] antibiotic,[2,9] antifungal,[3] antioxidant,[4] and anti-inflammatory[5] activities. Among these substances are angelicoin A (**1**),[11] hericenone J (**2**),[12] and the antimicrobial hericenol A (**3**)[13] (Figure 1), which were

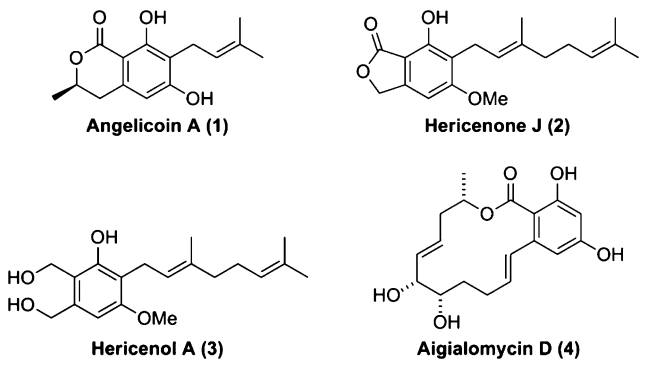


Figure 1. Angelicoin A, hericenone J, hericenol A, and aigialomycin D.

respectively isolated by Baba et al. from the roots of *Pleurospermum angelicoides* collected in Lijiang, China,[11] by Kawagishi and co-workers from the fruiting body of the edible mushroom *Hericium erinaceum* collected in Nagano, Japan,[12] and by Sterner and colleagues from a fungus of *Stereum* species collected in Kenya.[13]

Previous synthetic approaches to such aryl terpenes include arene metalation and subsequent nucleophilic substitution[14,15] or cross coupling[16,17] with a prenyl or geranyl derivative, direct prenylation or geranylation of an electron-rich phenol with a prenyl or geranyl halide or related electrophile in the presence of a base[18] or a Lewis acid,[15] or in two steps via formation of a prenyl or geranyl aryl ether and subsequent Claisen rearrangement.[19] Such syntheses invariably require the use of protection groups, and the phenolate alkylations and Claisen rearrangements tend to be low-yielding. Herein, we report full descriptions and full experimental details on a flexible new strategy for the total synthesis of terpene-resorcylates, which should be of considerable general utility.

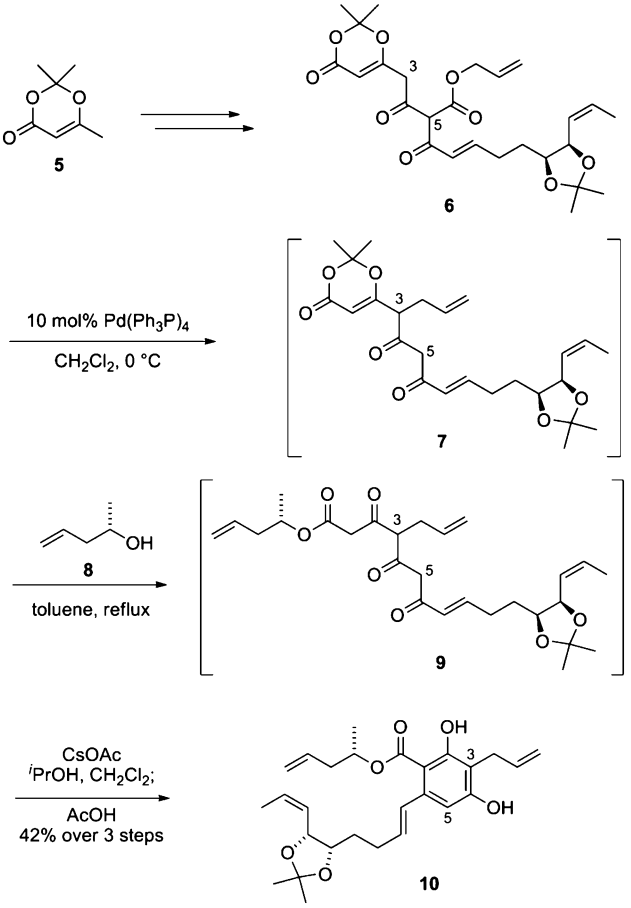
RESULTS AND DISCUSSION

Since hericenone J (**2**) and hericenol A (**3**) share the same carbon skeleton and are derivatives of resorcylic acid, we considered that they and the related prenyl-resorcylate angelicoin A (**1**) should be easily synthesized by a combination of our biomimetic synthesis of resorcylates using dioxinone chemistry[20] with a palladium(0)-catalyzed migratory decarboxylation−alkylation.[21] This variation of our general approach to resorcylates, which was inspired by the earlier work of Harris,[22] Hyatt,[23] and Boeckman,[24,25] was originally discovered during our total synthesis of aigialomycin D (**4**).[26] In this synthesis, dioxinone **5** was converted to diketo-ester **6** in two steps (Scheme 1).[27] The ester functionality was used to facilitate a selective mild Claisen condensation to introduce the side chain at C-5. Studies toward the optimization of the subsequent palladium(0)-catalyzed decarboxylative deprotection of the allyl ester **6** led us to the serendipitous discovery that, in the absence of morpholine as a palladium π-allyl cation scavenger,[28] a modified Carroll rearrangement[29] occurred, giving keto-dioxinone **7**. Reaction of **7** with alcohol **8** via one-pot dioxinone fragmentation, ketene trapping, and aromatization of ester **9** gave the resorcylate **10** (42%) with regiospecific allyl substitution at C-3.[21]

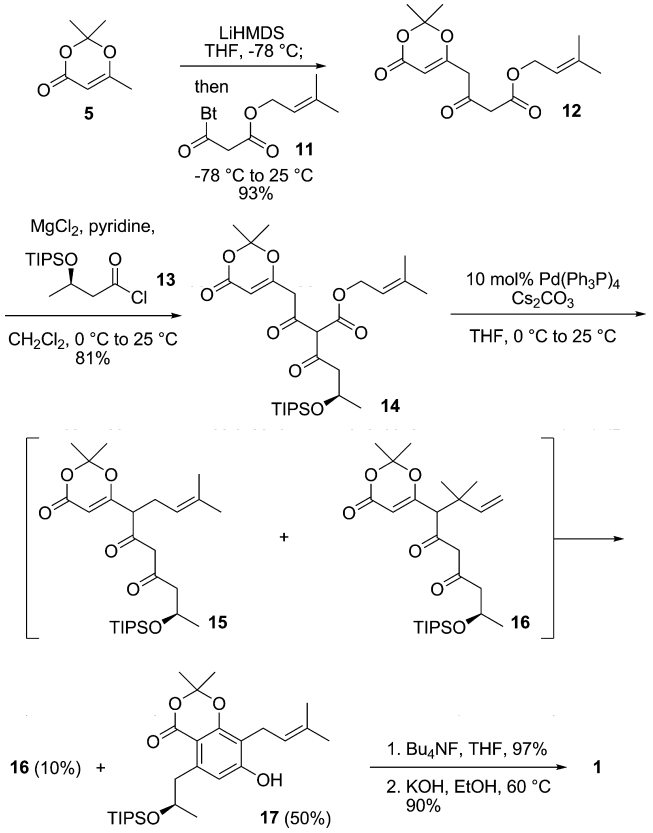
Received: November 15, 2011
Published: November 22, 2011

   dx.doi.org/10.1021/jo202354j | J. Org. Chem. 2012, 77, 652−657

Scheme 1. Unexpected Migratory Allylation−Aromatization Sequence in the Synthesis of Arene (10)[21,26]



Scheme 2. Migratory Prenylation−Aromatization Sequence in the Total Synthesis of Angelicoin A (1)[21]



Since the migration of the allyl moiety proceeded in remarkable yield and excellent C-3 regioselectivity with no substitution at C-5 being observed, we sought to apply this reaction in prenyl-[21] and geranyl-resorcylate natural product syntheses. Sequential acylation of dioxinone **5** with acyl benzotriazole **11**[30] and Claisen condensation with acyl chloride **13**,[21] in the presence of magnesium chloride and pyridine,[20] gave diketoester **14** (75% overall). $Pd(Ph_3P)_4$ (10 mol %) catalyzed decarboxylation of diketoester **14** gave a separable mixture of dioxinone **16** and resorcylate **17** in a combined yield of 60% (Scheme 2). It is noteworthy in these transformations that the linear terpene **15** underwent aromatization faster than its branched isomer **16**. Deprotection of the silyl ether **17**, followed by lactonization under basic conditions, provided angelicoin A (**1**) in an overall yield of 33% over five linear steps from dioxinone **5**.[21]

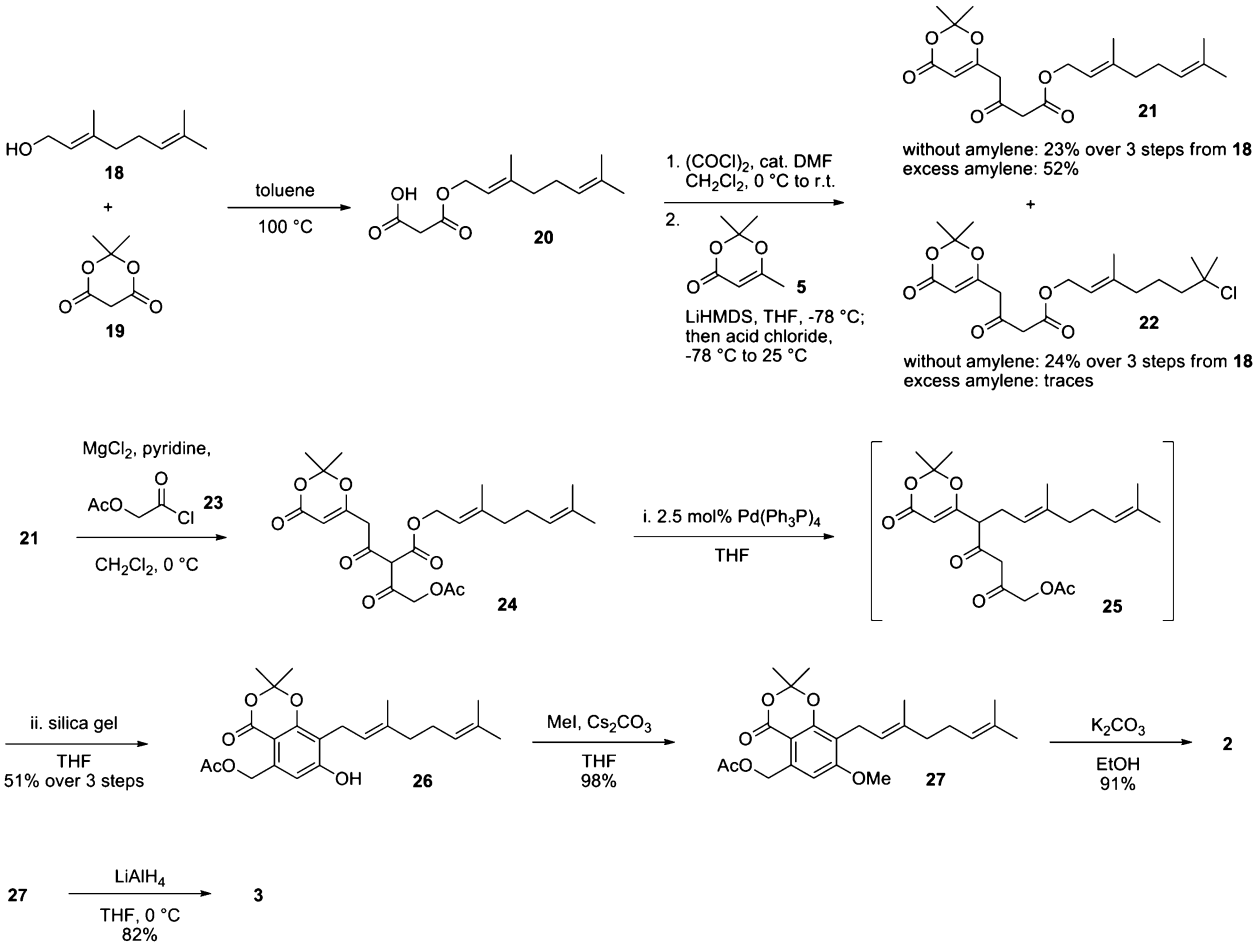
Encouraged by the results for simple allyl and prenyl moieties, we next applied the method for the synthesis of the geranyl resorcylates **2** and **3**. Reaction of geraniol (**18**) with Meldrum's acid (**19**) gave the malonic acid monoester **20**, which was converted to the corresponding acid chloride in the presence of excess amylene and alkylated with the enolate derived from dioxinone **5** to produce the β-keto-ester **21** in 52% over three steps (Scheme 3). Reaction in the absence of amylene resulted in a reduced yield (23%) and the formation of chloride **22** (24%). The β-keto-ester **21** was converted into diketo-ester **24** by a Claisen condensation reaction with acetoxyacetyl chloride (**23**) in presence of magnesium chloride and pyridine.[20] Subsequent reaction with $Pd(Ph_3P)_4$ resulted in a decarboxylative geranyl migration to form intermediate **25**, which was directly cyclized to the resorcylate **26** (51%) in the presence of silica gel. Although it is known that palladium-catalyzed geranylation reactions may result in the formation of *E*/*Z*-mixtures,[16] arene **26** was obtained as only the *E*-isomer and without the formation of branched addition products. Although this reaction appears to be very similar to the conversion of **14** to **17**, the conditions needed to be changed significantly. Since the prenyl transfer from **14** to **15** and **16** is complete within a few minutes at 0 °C, Cs_2CO_3 was added at the beginning of the reaction. In the case of geranyl ester **24**, this led only to the decomposition of the starting material. The palladium(0)-catalyzed geranyl migration seems to be significantly slower than the corresponding reaction with the simpler prenyl moiety and required several hours at room temperature. Additionally, the reaction proceeded regiospecifically at C-3 and without the formation of the branched isomer.

Methylation of phenol **26** gave ether **27** (98%), which was respectively deprotected and lactonized using potassium carbonate in ethanol to provide hericenone J (**2**) (91%) and reduced with lithium aluminum hydride to give hericenol A (**3**) (82%).

The analytical data of both compounds **2** and **3** were in full agreement with reported values of the isolated natural products. Furthermore, the molecular structure of hericenone J (**2**) was confirmed unambiguously by single crystal X-ray structure determination.[31] This also confirmed the regioselectivity of the palladium(0)-catalyzed geranyl transfer reaction.

dx.doi.org/10.1021/jo202354j | J. Org. Chem. 2012, 77, 652−657

Scheme 3. Total Syntheses of Hericenone J (2) and Hericenol A (3)



CONCLUSION

Biomimetic total syntheses of angelicoin A (**1**), hericenone J (**2**), and hericenol A (**3**) were respectively completed in five, eight, and eight steps using a common strategy with overall yield of 33% (for **1**), 24% (for **2**), and 21% (for **3**), respectively. We have shown the efficiency of palladium(0)-catalyzed prenyl and geranyl migration and a biomimetic approach to the total synthesis of terpenoid-resorcylate natural products. Further studies on related resorcylate natural products and mechanistic studies on the decarboxylation and allyl migration reactions will be reported in due course.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out in oven-dried glassware under N_2, using commercially supplied solvents and reagents unless otherwise stated. THF, toluene, and CH_2Cl_2 were redistilled from Na-Ph_2CO, Na, and CaH_2, respectively. Flash chromatography was carried out on silica (eluents are given in parentheses). Analytical TLC was performed on precoated silica gel F_{254} aluminum plates with visualization under UV light or by staining with acidic vanillin, anisaldehyde, or ninhydrin spray reagents. ^1H and ^{13}C NMR spectra were respectively recorded at 400 and 100 MHz with chemical shifts (δ) quoted in ppm. Data are reported as follows: s = singlet, d = duplet, t = triplet, q = quartet, m_c = symmetric multiplet (center is given), m = unsymmetric multiplet (shift range is given). Full experimental details for the syntheses of **6** and **14** and for the conversion of the resorcylate **17** into angelicoin A (**1**) are given in the Supporting Information sections of references 21 and 26.

(*S*)-Pent-4-en-2-yl 3-Allyl-6-((*E*)-4-((4*S*,5*S*)-2,2-dimethyl-5-((*Z*)-prop-1-enyl)-1,3-dioxolan-4-yl)but-1-enyl)-2,4-dihydroxybenzoate (10).[21] $Pd(Ph_3P)_4$ (9.2 mg, 16 μmol) in CH_2Cl_2 (1 mL) was added with stirring to dioxinone **6**[26] (80 mg, 0.16 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After 30 min, the reaction was quenched with brine (30 mL), and the aqueous layer was extracted with Et_2O (50 mL); the extract was dried ($MgSO_4$), filtered, and rotary evaporated to give diketo-dioxinone **7** as a pale yellow oil. PhMe (5 mL) and alcohol **8** (100 mg, 1.16 mmol) were added, and the mixture heated at reflux for 1 h. After rotary evaporation, the residue was dissolved in CH_2Cl_2 and ^{i}PrOH (1:1; 16 mL), and CsOAc (500 mg, 2.6 mmol) was added with stirring at room temperature. After 3 h, AcOH (1 mL, 15.9 mmol) was added; after a further 18 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (15 mL), and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (hexanes/Et_2O 2:1) to give resorcylate **10** (30 mg, 66 μmol, 42%) as a pale yellow oil: R_f 0.60 (Et_2O/hexanes 1:1); $[\alpha]_D^{25}$ = −29.4 (*c* 1.0, CH_2Cl_2); IR ν_{max} 3338, 1639, 1613, 1590, 1315, 1266, 1216, 1120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.05 (s, 1H), 6.96 (d, *J* = 15.5 Hz, 1H), 6.40 (s, 1H), 5.99 (ddt, *J* = 16.1, 10.1, 6.1 Hz, 1H), 5.98−5.69 (m, 3H), 5.48 (m_c, 1H), 5.42 (s, 1H), 5.24 (app. sextet, *J* = 6.2 Hz, 1H), 5.19 (dq, *J* = 9.1, 1.6 Hz, 1H), 5.14−5.09 (m, 3H), 4.95 (dd, *J* = 9.2, 6.0 Hz, 1H), 4.18 (ddd, *J* = 9.6, 6.0, 4.5 Hz, 1H), 3.47 (d, *J* = 6.0 Hz, 2H), 2.53−2.32 (m, 3H), 2.27−2.16 (m, 1H), 1.70 (dd, *J* = 7.0, 1.8 Hz, 3H), 1.58−1.52 (m, 2H), 1.49 (s, 3H), 1.39 (s, 3H), 1.36 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 162.3, 158.9, 141.7, 135.8, 133.3, 131.6, 131.2, 128.7, 126.4, 118.2, 115.8, 111.2, 108.2, 108.0, 104.1, 77.6, 73.6, 71.9, 40.2, 30.2, 29.6, 28.5, 27.2, 25.8, 19.6, 13.3; HRMS

dx.doi.org/10.1021/jo202354j | J. Org. Chem. 2012, 77, 652−657

(CI) m/z calcd for $C_{27}H_{36}NaO_6$ (M + Na^+) 479.2410, found 479.2422.

(*R*)-7-Hydroxy-2,2-dimethyl-8-(3-methylbut-2-enyl)-5-(2-(triisopropylsilyloxy)propyl)-4*H*-benzo[*d*][1,3]dioxin-4-one (17) and (2*R*)-7-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-8,8-dimethyl-2-(tri-isopropylsilyloxy)dec-9-ene-4,6-dione (16).[21] $Pd(PPh_3)_4$ (32 mg, 28 μmol) and Cs_2CO_3 (91 mg, 0.28 mmol) were stirred in THF (1 mL) for 10 min at 0 °C. Diketoester-dioxinone **14**[21] (150 mg, 0.28 mmol) in THF (1 mL) was added dropwise with stirring. After 18 h at room temperature, the reaction was quenched with brine (20 mL), the aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic layers were dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (CH_2Cl_2/EtOAc/hexanes 1:1:12) to give resorcylate **17** as a white solid (67 mg, 0.14 mmol, 50%) and diketo-dioxinone **16** as a colorless oil (14 mg, 28 μmol, 10%). Resorcylate **17**: mp 79−81 °C (PhH); R_f 0.60 (CH_2Cl_2/EtOAc/hexanes 1:1:6); $[\alpha]_D^{25}$ = −31.3 (c 1.0, $CHCl_3$); IR ν_{max} 1725, 1702, 1608, 1279, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.49 (s, 1H), 6.45 (s, 1H), 5.15 (t, J = 7.2 Hz, 1H), 4.26 (app. sextet, J = 6.0 Hz, 1H), 3.30 (d, J = 7.2 Hz, 2H), 3.23 (dd, J = 12.4, 5.2 Hz, 1H), 3.05 (dd, J = 12.5, 7.1 Hz, 1H), 1.78 (s, 3H), 1.71 (s, 3H), 1.67 (s, 6H), 1.17 (d, J = 6.0 Hz, 3H), 0.99−0.96 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 159.6, 156.1, 143.8, 134.2, 121.0, 115.4, 113.6, 105.1, 104.6, 69.0, 44.7, 25.7 (2C), 25.6, 24.1, 21.9, 18.1 (6C), 17.9, 12.5 (3C); HR-MS (ESI) m/z calcd for $C_{27}H_{45}O_5Si$ (M + H^+) 477.3028, found 477.3036. Anal. Calc. for $C_{27}H_{44}O_5Si$: C, 68.02, H, 9.30. Found: C, 67.95, H, 9.17. Diketo-dioxinone **16**: ca. 1:1 mixture of diastereomers, R_f 0.55 (CH_2Cl_2/EtOAc/hexanes 1:1:6); $[\alpha]_D^{25}$ = −85.7 (c 0.35, $CHCl_3$); IR ν_{max} 1731, 1612, 1463, 1376, 1250, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, sum of diastereomers) δ 15.41 (brs, 2H), 5.99 (dd, J = 17.3, 10.9 Hz, 1H), 5.97 (dd, J = 17.2, 10.9 Hz, 1H), 5.56 (s, 1H), 5.55 (s, 1H), 5.50 (s, 1H), 5.49 (s, 1H), 5.02 (d, J = 10.6 Hz, 2H), 5.00 (d, J = 17.7 Hz, 2H), 4.40 (app. septet, J = 6.0 Hz, 2H), 2.90 (s, 2H), 2.49 (dd, J = 13.7, 6.6 Hz, 2H), 2.35 (dd, J = 13.8, 6.0 Hz, 1H), 2.34 (dd, J = 13.7, 5.9 Hz, 1H), 1.67 (s, 6H), 1.66 (s, 6H), 1.22 (d, J = 6.1 Hz, 6H), 1.19−1.17 (m, 12H), 1.05−1.02 (m, 42H); ^{13}C NMR (100 MHz, $CDCl_3$, sum of diastereomers) δ 191.6 (2C), 189.4, 189.3, 166.9, 166.8, 160.8, 160.7, 144.5 (2C), 112.7 (2C), 106.6 (2C), 103.0, 102.7, 96.6 (2C), 66.3, 66.2, 62.7, 62.6, 48.2 (2C), 40.6, 40.5, 25.9, 25.8, 25.7 (2C), 25.6 (2C), 24.7, 24.6, 24.1 (2C), 18.0 (12C), 12.4 (6C); HR-MS (ESI) m/z calcd for $C_{27}H_{47}O_6Si$ (M + H^+) 495.3146, found 495.3155.

(*E*)-3-(3,7-Dimethyl-2,6-octadienyl-1-oxy)-3-oxopropanoic acid (20). Meldrum's acid (**19**, 10.0 g, 69.4 mmol), PhMe (20 mL), and geraniol (**18**, 10.7 g, 69.4 mmol) were heated at 100 °C for 6 h. After cooling, rotary evaporation gave acid **20** (16.8 g) as a yellow oil, sufficiently pure for the next step. An analytically pure sample (86%) was obtained by chromatography (hexanes/Et_2O 9:1; EtOAc/MeOH 9:1) as a colorless oil: R_f 0.07 (hexanes/Et_2O 1:1); IR ν_{max} 1718, 1151, 977, 904, 829, 756 cm^{-1}; ^1H NMR ($CHCl_3$, 400 MHz) δ 9.62 (brs, 1H), 5.34 (t, 1H, J = 7.3 Hz), 5.07 (t, 1H, J = 6.1 Hz), 4.69 (d, 2H, J = 7.2 Hz), 3.43 (s, 2H), 2.13−2.03 (m, 4H), 1.71 (s, 3H), 1.67 (s, 3H), 1.59 (s, 3H); ^{13}C NMR ($CHCl_3$, 100 MHz) δ 171.1, 167.1, 143.5, 131.9, 123.6, 117.3, 62.8, 40.7, 39.5, 26.2, 25.6, 17.6, 16.5; HRMS (CI) m/z calcd for $C_{13}H_{24}NO_4$ (M + NH_4^+) 258.1705, found 258.1710.

(*E*)-3,7-Dimethyl-2,6-octadien-1-yl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (21). 2-Methyl-2-butene (22 mL, 208 mmol) followed by oxalyl chloride (2.0 mL, 22.9 mmol) and a drop of DMF were added sequentially with stirring to acid **20** (5.00 g, 20.8 mmol) in CH_2Cl_2 (21 mL) at 0 °C. After 30 min at 0 °C and 3 h at room temperature, the mixture was rotary evaporated, and the residue was dried under vacuum to obtain the crude acid chloride as a brown oil. *n*-BuLi in hexanes (2.5 M; 28.3 mL, 70.8 mmol) was added dropwise with stirring under Ar to hexamethyldisilazane (13.9 mL, 66.6 mmol) in THF (100 mL) at 0 °C. After 1 h, the solution was cooled to −78 °C, and dioxinone **5** (8.9 mL, 62.5 mmol) was added dropwise with stirring. After 3.5 h, the crude acyl chloride in THF (7 mL) was added dropwise at −78 °C. After 2 h, saturated aqueous NH_4Cl (10 mL) was added, and the mixture was allowed to warm to room temperature; then, it was diluted with Et_2O (100 mL), and HCl (1 M) was added to pH ∼ 2. The phases were separated, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), rotary evaporated, and chromatographed (hexanes/Et_2O 3:1 to 1:1) to obtain β-keto ester **21** (3.93 g, 10.8 mmol, 52% over three steps from alcohol **18**) as a yellow oil: R_f 0.32 (hexanes/Et_2O 1:1); IR ν_{max} 1721, 1375, 1272, 1201, 1015 cm^{-1}; ^1H NMR ($CHCl_3$, 400 MHz) δ 5.34 (s, 1H), 5.31 (m_c, 1H), 5.05 (m_c, 1H), 4.65 (d, 2H, J = 7.2 Hz), 3.50 (s, 2H), 3.49 (s, 2H), 2.08−2.01 (m, 4H), 1.69 (s, 9H), 1.65 (s, 3H), 1.58 (s, 3H); ^{13}C NMR ($CHCl_3$, 100 MHz) δ 195.6, 166.4, 163.5, 160.5, 143.6, 132.0, 123.5, 117.3, 107.3, 97.1, 62.6, 49.1, 46.9, 39.5, 26.2, 25.6, 25.0, 17.7, 16.5; HRMS (ESI) m/z calcd for $C_{20}H_{29}O_6$ (M + H^+) 365.1964, found 365.1951.

(*E*)-7-Chloro-3,7-dimethyloct-2-enyl 4-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (22). When the synthesis of **21** was carried out as described above but without the addition of amylene (using instead twice the amount of CH_2Cl_2), starting from 2.00 g (8.33 mmol) of **18**, **21** (708 mg, 1.94 mmol, 23% over three steps from alcohol **18**) was isolated along with **22** (793 mg, 1.98 mmol, 24% over three steps from alcohol **18**) as a yellow oil: R_f 0.24 (hexanes/Et_2O 1:1); IR ν_{max} 1721, 1374, 1272, 1201, 1015 cm^{-1}; ^1H NMR ($CHCl_3$, 400 MHz) δ 5.40−5.33 (m, 2H), 4.67 (d, 2H, J = 7.2 Hz), 3.51 (s, 2H), 3.50 (s, 2H), 2.06 (t, 2H, J = 7.0 Hz), 1.71−1.59 (m, 13H), 1.56 (s, 6H); ^{13}C NMR ($CHCl_3$, 100 MHz) δ 195.6, 166.3, 163.5, 160.4, 143.2, 117.7, 107.3, 97.1, 70.9, 62.5, 49.1, 47.0, 45.3, 39.3, 32.4 (2C), 25.0 (2C), 22.9, 16.3; HRMS (ESI) m/z calcd for $C_{20}H_{30}ClO_6$ (M + H^+) 401.1731, found 401.1746.

(*E*)-3,7-Dimethylocta-2,6-dienyl 4-Acetoxy-2-(2-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)acetyl)-3-oxobutanoate (24). Pyridine (1.55 mL, 19.2 mmol) and $MgCl_2$ (914 mg, 9.60 mmol) were added with stirring to β-keto ester **21** (3.5 g, 9.60 mmol) in CH_2Cl_2 (40 mL) at 0 °C. After 15 min, acetoxyacetyl chloride (**23**) (1.25 mL, 12.0 mmol) was added dropwise, and the resulting mixture was stirred at 0 °C for 1.5 h. Saturated aqueous NH_4Cl (5 mL) was added, followed by HCl (1 M) to pH ∼ 2. The phases were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and rotary evaporated to obtain diketo-ester **24** (4.29 g) as a yellow oil of sufficient purity for the next step. An analytically pure sample (86%) was obtained by chromatography (hexanes/Et_2O 1:3 to Et_2O) as a colorless oil: R_f 0.34 (hexanes/Et_2O 1:3); IR ν_{max} 1726, 1390, 1375, 1272, 1224, 1203, 1059, 1015, 754 cm^{-1}; ^1H NMR ($CHCl_3$, 400 MHz) δ 5.38 (t, 1H, J = 7.3 Hz), 5.34 (s, 1H), 5.13 (s, 2H), 5.06 (m_c, 1H), 4.73 (d, 2H, J = 7.2 Hz), 3.81 (s, 2H), 2.17 (s, 3H), 2.10−2.03 (m, 4H), 1.73 (s, 3H), 1.68 (s, 6H), 1.66 (s, 3H), 1.59 (s, 3H); ^{13}C NMR ($CHCl_3$, 100 MHz) δ 196.0, 190.9, 170.4, 164.9, 164.7, 160.6, 143.9, 132.0, 123.4, 117.3, 107.2, 106.2, 96.4, 65.5, 62.0, 41.7, 39.5, 26.2, 25.6, 24.9 (2C), 20.4, 17.7, 16.5; HRMS (ESI) m/z calcd for $C_{24}H_{33}O_9$ (M + H^+) 465.2125, found 465.2117.

(*E*)-(8-(3,7-Dimethylocta-2,6-dienyl)-7-hydroxy-2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-5-yl)-methyl acetate (26). Crude allyl ester **24** (1.50 g) in THF (16 mL) was degassed by purging with Ar for 15 min, when $(Ph_3P)_4Pd$ (112 mg, 0.03 mmol) was then added with stirring. After 15 h, silica (1.5 g) was added, and the solvent was evaporated. The crude product was chromatographed (hexanes/Et_2O 1:1) to provide phenol **26** (660 mg, 1.64 mmol, 51% over three steps from β-keto ester **21**) as a colorless oil: R_f 0.29 (hexanes/Et_2O 1:1); IR ν_{max} 1720, 1696, 1597, 1297, 1274, 1207, 1166, 1107, 1029, 753 cm^{-1}; ^1H NMR ($CHCl_3$, 400 MHz) δ 7.42 (s, 1H), 6.67 (s, 1H), 5.52 (s, 2H), 5.16 (t, 1H, J = 7.1 Hz), 5.03 (t, 1H, J = 7.1 Hz), 3.31 (d, 2H, J = 7.1 Hz), 2.13 (s, 3H), 2.08−1.97 (m, 4H), 1.76 (s, 3H), 1.68 (s, 6H), 1.64 (s, 3H), 1.56 (s, 3H); ^{13}C NMR ($CHCl_3$, 100 MHz) δ 171.1, 161.0, 160.9, 156.3, 139.4, 137.5, 131.7, 123.8, 120.6, 115.1, 110.0, 105.3, 103.2, 64.2, 39.6, 26.4, 25.6 (3C), 21.8, 20.9, 17.6, 16.1; HRMS (ESI) m/z calcd for $C_{23}H_{31}O_6$ (M + H^+) 403.2121, found 403.2123.

(*E*)-(8-(3,7-Dimethylocta-2,6-dienyl)-7-methoxy-2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-5-yl)-methyl acetate (27). Cs_2CO_3 (1.08 g, 3.32 mmol) and MeI (0.21 mL, 3.32 mmol) were added with stirring to phenol **26** (445 mg, 1.11 mmol) in THF (11 mL) under Ar. After 3 h, saturated aqueous NH_4Cl (50 mL) and Et_2O

dx.doi.org/10.1021/jo202354j | J. Org. Chem. 2012, 77, 652−657

(50 mL) were added. The separated aqueous layer was extracted with Et_2O (2 × 50 mL), and the combined organic layers were dried ($MgSO_4$), rotary evaporated, and chromatographed (hexanes/Et_2O 2:1) to obtain methyl ether **27** (453 mg, 1.09 mmol, 98%) as a colorless oil: R_f 0.64 (hexanes/Et_2O 1:1); IR ν_{max} 1725, 1607, 1580, 1295, 1207, 1168, 1120, 1029 cm^{-1}; ^1H NMR ($CHCl_3$, 400 MHz) δ 6.70 (s, 1H), 5.56 (s, 2H), 5.10−5.02 (m, 2H), 3.90 (s, 3H), 3.27 (d, 2H, J = 7.3 Hz), 2.16 (s, 3H), 2.06−2.00 (m, 2H), 1.96−1.92 (m, 2H), 1.74 (s, 3H), 1.68 (s, 6H), 1.63 (s, 3H), 1.56 (s, 3H); ^{13}C NMR ($CHCl_3$, 100 MHz) δ 170.4, 162.5, 160.3, 155.6, 139.7, 135.6, 131.4, 124.1, 121.1, 117.6, 105.2, 104.6, 104.4, 64.3, 55.7, 39.7, 26.6, 25.7 (2C), 25.6, 21.7, 21.0, 17.6, 16.0; HRMS (ESI) m/z calcd for $C_{24}H_{33}O_6$ ($M + H^+$) 417.2277, found 417.2271.

Hericenone J ((*E*)-6-(3,7-Dimethylocta-2,6-dienyl)-7-hydroxy-5-methoxyisobenzofuran-1(3*H*)-one, 2). K_2CO_3 (218 mg, 1.58 mmol) was added with stirring to ester **27** (219 mg, 0.53 mmol) in EtOH (26 mL). After 18 h, Et_2O (50 mL) was added, followed by HCl (1 M) to pH ∼ 2. The separated aqueous layer was extracted with Et_2O (2 × 50 mL), and the combined organic layers were dried ($MgSO_4$) and rotary evaporated to obtain hericenone J (**2**, 151 mg, 0.48 mmol, 91%) as colorless tablets: R_f 0.26 (hexanes/Et_2O 1:1); mp 86−88 °C ($CHCl_3$); IR ν_{max} 1723, 1342, 1251, 1085, 1072, 1053 cm^{-1}; ^1H NMR ($CHCl_3$, 400 MHz) δ 7.72 (s, 1H), 6.48 (s, 1H), 5.23 (s, 2H), 5.17 (t, 1H, J = 7.2 Hz), 5.06 (t, 1H, J = 6.9 Hz), 3.89 (s, 3H), 3.36 (d, 2H, J = 7.2 Hz), 2.08−2.02 (m, 2H), 1.98−1.94 (m, 2H), 1.77 (s, 3H), 1.64 (s, 3H), 1.57 (s, 3H); ^{13}C NMR ($CHCl_3$, 100 MHz) δ 172.7, 164.7, 154.3, 145.9, 135.7, 131.1, 124.2, 121.2, 116.8, 104.1, 96.0, 70.3, 56.0, 39.7, 26.6, 25.6, 21.5, 17.6, 16.0; HRMS (ESI) m/z calcd for $C_{19}H_{25}O_4$ ($M + H^+$) 317.1753, found 317.1747. The analytical data were in full agreement with literature values.[12]

Hericenol A ((*E*)-(4-(3,7-Dimethylocta-2,6-dienyl)-3-hydroxy-5-methoxy-1,2-phenylene)-dimethanol, 3). $LiAlH_4$ in Et_2O (2.0 M, 1.6 mL, 3.15 mmol) was added dropwise with stirring to ester **27** (657 mg, 1.58 mmol) in THF (25 mL) under Ar at 0 °C. After 1 h, H_2O (0.12 mL) was carefully added dropwise with stirring to destroy the excess of $LiAlH_4$, followed by NaOH (1 M, 0.6 mL). After 30 min, solid NH_4Cl was added, and the solids were filtered off through silica using Et_2O as an eluent. Rotary evaporation and chromatography (hexanes/Et_2O 1:3) gave hericenol A (**3**, 415 mg, 1.50 mmol, 82%) as a colorless oil that turned slowly into a waxy white solid: R_f 0.30 (hexanes/Et_2O 1:3); IR ν_{max} 1583, 1448, 1423, 1376, 1319, 1217, 1166, 1111, 1043, 996, 828 cm^{-1}; ^1H NMR ($CHCl_3$, 400 MHz) δ 7.15 (s, 1H), 6.39 (s, 1H), 5.19 (t, 1H, J = 7.0 Hz), 5.05 (t, 1H, J = 6.9 Hz), 4.68 (s, 2H), 4.46 (s, 2H), 3.78 (brs, 4H), 3.57 (brs, 1H), 3.37 (d, 2H), 2.09−2.04 (m, 2H), 2.00−1.94 (m, 2H), 1.78 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H); ^{13}C NMR ($CHCl_3$, 100 MHz) δ 157.3, 155.1, 137.0 (2C), 131.5, 124.1, 121.9, 117.5, 116.4, 103.9, 63.6, 57.8, 55.6, 39.7, 26.5, 25.6, 22.2, 17.6, 16.0; HRMS (ESI) m/z calcd for $C_{19}H_{28}NaO_4$ ($M + Na^+$) 343.1885, found 343.1902. The analytical data were in full agreement with literature values.[13]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra for hericenone J (**2**), hericenol A (**3**), and compounds **10**, **16**, **17**, **20**−**22**, **24**, **26**, and **27** and X-ray structural data for **2**. Spectra for all other compounds are available from the Supporting Information sections of references 21 and 26. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: agm.barrett@imperial.ac.uk.

■ ACKNOWLEDGMENTS

We thank the European Research Council (ERC) and the Engineering and Physical Sciences Research Council (EPSRC) for grant support, GlaxoSmithKline for the generous Glaxo endownment, P. R. Haycock and R. N. Sheppard (Imperial College London) for high-resolution NMR spectroscopy, and Professor Kimiye Baba (Osaka University of Pharmaceutical Sciences) for providing NMR spectra of authentic angelicoin A (**1**).

■ REFERENCES

(1) (a) Yoder, B. J.; Cao, S.; Norris, A.; Miller, J. S.; Ratovoson, F.; Razafitsalama, J.; Andriantsiferana, R.; Rasamison, V. E.; Kingston, D. G. I. *J. Nat. Prod.* **2007**, *70*, 342. (b) Beutler, J. A.; Shoemaker, R. H.; Johnson, T.; Boyd, M. R. *J. Nat. Prod.* **1998**, *61*, 1509.

(2) (a) Šmejkal, K.; Chudík, S.; Klouček, P.; Marek, R.; Cvačka, J.; Urbanová, M.; Julínek, O.; Kokoška, L.; Šlapetová, T.; Holubová, P.; Zima, A.; Dvorská, M. *J. Nat. Prod.* **2008**, *71*, 706. (b) Venkata Rao, E.; Sridhar, P.; Narasimha Rao, B. V. L; Ellaiah, P. *Phytochemistry* **1999**, No. 50, 1417.

(3) (a) Jayasinghe, L.; Balasooriya, B. A. I. S.; Padmini, W. C.; Hara, N.; Fujimoto, Y. *Phytochemistry* **2004**, *65*, 1287. (b) ElSohly, H. N.; Joshi, A. S.; Nimrod, A. C.; Walker, L. A.; Clark, A. M. *Planta Med.* **2001**, *67*, 87.

(4) (a) Kumazawa, S.; Ueda., R.; Hamasaka, T.; Fukumoto, S.; Fujimoto, T.; Nakayama, T. *J. Agric. Food Chem.* **2007**, *55*, 7722. (b) Hayashi, K.; Komura, S.; Isaji, N.; Ohishi, N.; Yagi, K. *Chem. Pharm. Bull.* **1999**, *47*, 1521.

(5) (a) Chen, C.-C.; Tsai, P.-C.; Wei, B.-L.; Chiou, W.-F. *Eur. J. Pharmacol.* **2008**, *590*, 430. (b) Makabe, H.; Miyazaki, S.; Kamo, T.; Hirota, M. *Biosci., Biotechnol., Biochem.* **2003**, *67*, 2038.

(6) (a) Roussis, V.; King, R. L.; Fenical, W. *Phytochemistry* **1993**, *34*, 107. (b) Capon, R. J.; Ghisalberti, E. L.; Jefferies, P. R. *Phytochemistry* **1981**, *20*, 2598. (c) Högberg, H.-E.; Thomson, R. H.; King, T. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1696.

(7) (a) Kawagishi, H.; Sato, H.; Sakamura, S.; Kobayashi, K.; Ui, T. *Agric. Biol. Chem.* **1984**, *48*, 1903. (b) Kosuge, Y.; Suzuki, A.; Tamura, S. *Agric. Biol. Chem.* **1974**, *38*, 1265.

(8) Cai, S.; Sun, S.; Zhou, H.; Kong, X.; Zhu, T.; Li, D.; Gu, Q. *J. Nat. Prod.* **2011**, *74*, 1106.

(9) Tsuda, M.; Nemoto, A.; Komaki, H.; Tanaka, Y.; Yazawa, K.; Mikami, Y.; Kobayashi, J. *J. Nat. Prod.* **1999**, *62*, 1640.

(10) Aiello, A.; Fattorusso, E.; Luciano, P.; Macho, A.; Menna, M.; Muñoz, E. *J. Med. Chem.* **2005**, *48*, 3410.

(11) Shibano, M.; Naito, H.; Taniguchi, M.; Wang, N.-H.; Baba, K. *Chem. Pharm. Bull.* **2006**, *54*, 717.

(12) Ueda, K.; Tsujimori, M.; Kodani, S.; Chiba, A.; Kubo, M.; Masuno, K.; Sekiya, A.; Nagai, K.; Kawagishi, H. *Bioorg. Med. Chem.* **2008**, *16*, 9467.

(13) Omolo, J. O.; Anke, H.; Sterner, O. *Phytochemistry* **2002**, *60*, 431.

(14) (a) Mente, N. R.; Wiemer, A. J.; Neighbors, J. D.; Beutler, J. A.; Hohl, R. J.; Wiemer, D. F. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 911. (b) Iikubo, K.; Ishikawa, Y.; Ando, N.; Umezawa, K.; Nishiyama, S. *Tetrahedron Lett.* **2002**, *43*, 291. (c) Treadwell, E. M.; Cermark, S. C.; Wiemer, D. F. *J. Org. Chem.* **1999**, *64*, 8718. (d) Mann, I. S.; Widdowson, D. A.; Clough, J. M. *Tetrahedron* **1991**, *47*, 7991. (e) Saimoto, H.; Hiyama, T. *Tetrahedron Lett.* **1986**, *27*, 597. (f) Trost, B. M.; Saulnier, M. G. *Tetrahedron Lett.* **1985**, *26*, 123.

(15) Neighbors, J. D.; Buller, M. J.; Boss, K. D.; Wiemer, D. F. *J. Nat. Prod.* **2008**, *71*, 1949.

(16) Takaoka, S.; Nakade, K.; Fukuyama, Y. *Tetrahedron Lett.* **2002**, *43*, 6919.

(17) (a) Takaoka, S.; Takaoka, N.; Minoshima, Y.; Huang, J.-M.; Kubo, M.; Harada, K.; Hioki, H.; Fukuyama, Y. *Tetrahedron* **2009**, *65*, 8354. (b) Knölker, H.-J.; Baum, E.; Reddy, K. R. *Tetrahedron Lett.* **2000**, *41*, 1171.

(18) (a) Lee, Y. R.; Li, X.; Kim, J. H. *J. Org. Chem.* **2008**, *73*, 4313. (b) Basabe, P.; de Román, M.; Diez, D.; Marcos, I. S.; Bodero, O.; Blanco, A.; Mollinedo, F.; Urones, J. G. *Synlett* **2008**, 1149. (c) Suh, H.; Lee, S.; Kim, N.; Han, J.; Kim, J. *Bioorg. Med. Chem. Lett.* **1999**, *9*,

1433. (d) Crombie, L.; Jones, R. C. F.; Palmer, C. J. *Tetrahedron Lett.* **1985**, *26*, 2933.
(19) (a) Sugamoto, K.; Matsusita, Y.; Matsui, K.; Kurogi, C.; Matsui, T. *Tetrahedron* **2011**, *67*, 5346. (b) Vogel, S.; Heilmann, J. *J. Nat. Prod.* **2008**, *71*, 1237. (c) Romano, J. J.; Casillas, E. *Tetrahedron Lett.* **2005**, *46*, 2323. (d) Al-Maharik, N.; Botting, N. P. *Tetrahedron* **2003**, *59*, 4177.
(20) Navarro, I.; Basset, J.-F.; Hebbe, S.; Major, S. M.; Werner, T.; Howsham, C.; Bräckow, J.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2008**, *130*, 10293.
(21) For a preliminary account on the synthesis of angelicoin A see: Anderson, K.; Calo, F.; Pfaffeneder, T.; White, A. J. P.; Barrett, A. G. M. *Org. Lett.* **2011**, *13*, 5748. Full experimental details on the synthesis of compounds **10** to **17** and **1** are provided in the Supporting Information of this paper
(22) Harris, T. M.; Harris, C. M. *Tetrahedron* **1977**, *33*, 2159.
(23) Hyatt, J. A.; Feldman, P. L.; Clemens, R. J. *J. Org. Chem.* **1984**, *49*, 5105.
(24) (a) Boeckman, R. K. Jr.; Shao, P.; Wrobleski, S. T.; Boehmler, D. J.; Heintzelman, G. R.; Barbosa, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 10572. (b) Boeckman, R. K. Jr.; Perni, R. B. *J. Org. Chem.* **1986**, *51*, 5486. (c) Boeckman, R. K. Jr.; Starrett, J. E. Jr.; Nickell, D. G.; Sum, P.-E. *J. Am. Chem. Soc.* **1986**, *108*, 5549.
(25) For further information see: (a) Barrett, A. G. M.; Morris, T. M.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2272. (b) Birch, A. J. *Fortschr. Chem. Org. Naturst.* **1957**, *14*, 186. (c) Birch, A. J.; Donovan, F. W. *Aust. J. Chem.* **1953**, *6*, 360.
(26) Calo, F.; Richardson, J.; Barrett, A. G. M. *Org. Lett.* **2009**, *11*, 4910. Full experimental details on the synthesis of compound **6** are provided in the Supporting Information of this paper.
(27) The diketo-dioxinones and triketo-compounds exist as mixtures of keto−enol tautomers. For simplicity, all are drawn in the all-keto form.
(28) (a) Kunz, H.; Waldmann, H. *Angew. Chem., Int. Ed.* **1984**, *23*, 71. (b) Kunz, H.; Waldmann, H. *Angew. Chem.* **1984**, *96*, 49.
(29) (a) Tsuda, T.; Chujo, Y.; Nishi, S.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381. (b) Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199. (c) Carroll, M. F. *J. Chem. Soc.* **1941**, 507. (d) Carroll, M. F. *J. Chem. Soc.* **1940**, 1266. (e) Carroll, M. F. *J. Chem. Soc.* **1940**, 704.
(30) Katritzky, A. R.; Wang, Z.; Wang, M.; Hall, C. D.; Suzuki, K. *J. Org. Chem.* **2005**, *70*, 4854.
(31) CCDC 850168, see associated Supporting Information.