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Total synthesis of graphislactone G

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ABSTRACT

We present a total synthesis of the fungal natural product graphislactone G, a chlorinated resorcylic lactone. The key step is a Suzuki coupling used for the construction of the central biaryl bond. Graphislactone G was prepared in 13 steps with 22% yield starting with orcinol and phloroglucinic acid, where the longest linear sequence consists of nine steps.

1. Introduction

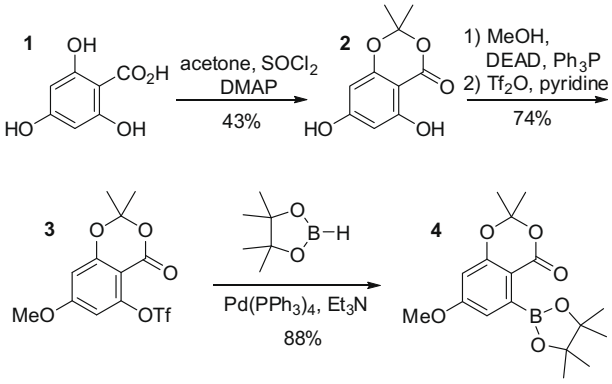
The metabolisms of fungi[1] and lichens[2]—a symbiosis of algae and fungi, where the latter supply the lichens with secondary metabolites—are very similar. Graphislactone A was identified as reduction product of the fungal metabolite botrallin in 1968,[3] but it was first isolated as a natural product from the lichen *Graphis scripta var. pulverulenta*[4] in the late nineties together with graphislactones B–D.[4a–d] Graphislactones E and F have been isolated from *Graphis scripta* and *Graphis prunicola*[4d] and graphislactones G and H have been isolated from the endophytic fungus *Cephalosporium acremonium IFB-E007*.[5] The biosynthesis of the graphislactones is strongly related to that of alternaria metabolites,[4d,6] in fact, 3-desmethylgraphislactone A was identified in the metabolism of alternaria toxins.[7]

A number of biological activities have been reported for graphislactones. Graphislactone A is an antioxidant and a scavenger of free radicals;[8] graphislactones A, G, and H were found to be active against the SW1116 cell line (IC_{50} 8.5, 21, and 12 mg/mL, respectively);[5] and graphislactone A is a moderate inhibitor of AChE.[4e] Total syntheses of graphislactones A–F and H have been published by Abe et al.[9] and by our group,[10] where we were able to supply revised structures of graphislactones E and F. No total synthesis has been published for graphislactones G up to date. Herein we report the first total synthesis of graphislactone G.

2. Results and discussion

Retrosynthesis of the target compound suggested a Suzuki coupling[11] as key step for the construction of the central biaryl bond. Boronate **4** suitable for this transformation could be prepared according to a published procedure[10] starting with commercially available acetal-protected phloroglucinic acid **2** (Scheme 1) or—with one more step necessary—from phloroglucinic acid (**1**).

The other component required for a Suzuki coupling was prepared essentially according to a known protocol[12] starting with commercially available orsellinic acid (**6**), which can be easily prepared in two steps from orcinol (**5**) with 65% yield (Scheme 3).[13] The methyl ester **7** was obtained with methyl iodide and potas-



Scheme 1. Synthesis of boronate **4** suitable for Suzuki coupling.

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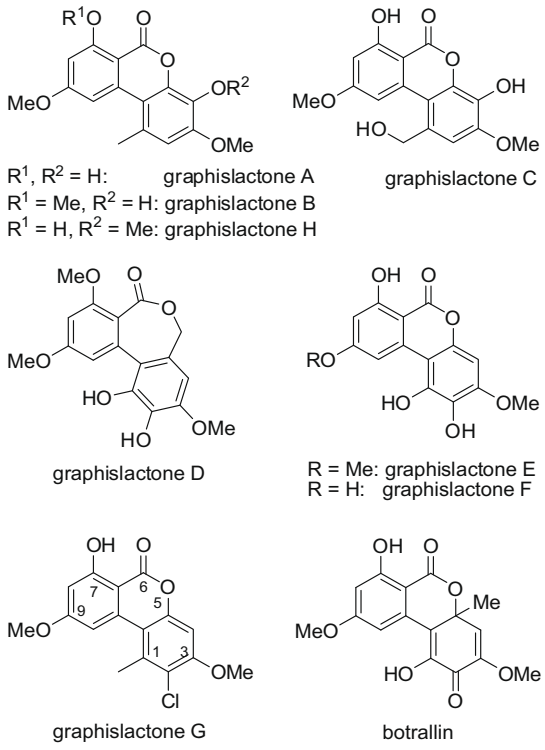
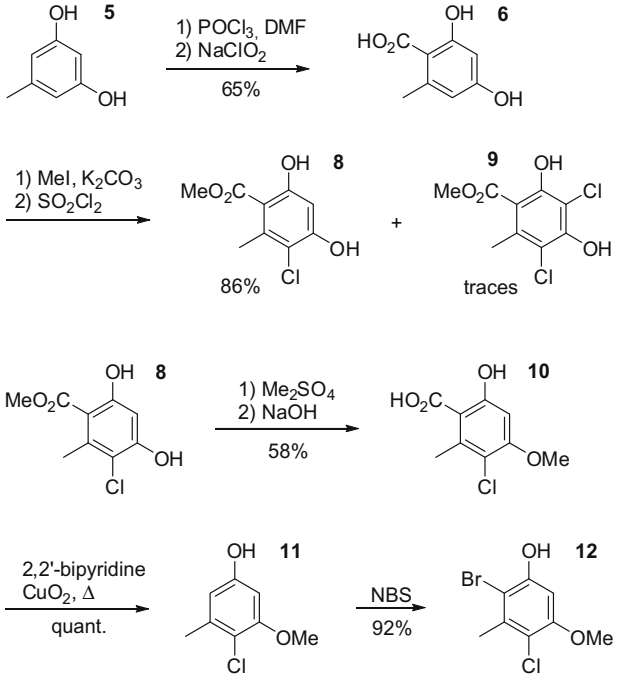


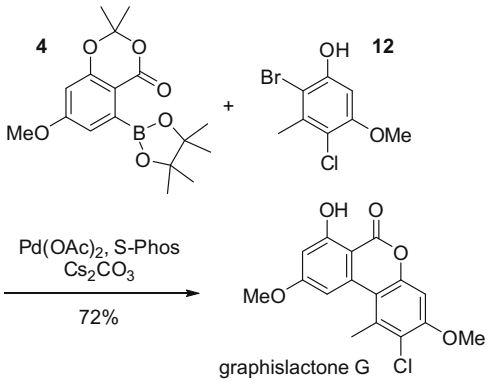
Figure 1. Graphislactones and related compounds.

sium carbonate (91%).[14] Chlorination with freshly distilled sulfuryl chloride afforded chlorinated methyl orsellinate **8** in 95% yield, while the dichlorinated substrate **9** was obtained in traces. Separation was simply achieved by recrystallization (Scheme 2).[15]

Selective methylation of the 4-hydroxyl group with subsequent saponification (→**10**) and decarboxylation using 2,2-bipyridyl in the presence of CuO_2 at elevated temperature (160 °C) furnished the known compound **11** with 58% yield (Scheme 3).[12] The aryl



Scheme 2. Synthesis of aryl bromide **12** suitable for Suzuki coupling.



Scheme 3. Suzuki coupling yielding graphislactone G.

bromide **12** suitable for a Suzuki coupling was obtained by bromination with *N*-bromosuccinimide. The correct constitution of compound **12** was unambiguously proven by analysis of proton NOESY spectra.

Suzuki coupling of aryl bromide **12** and boronate **4** with concomitant lactonization was achieved with a protocol, which previously proved itself suitable for the synthesis of similar compounds,[10,16] thus yielding the natural product graphislactone G in 72% (Scheme 3). The reaction occurred with complete chemoselectivity. No Suzuki coupling of the chloro function was observed.

Comparison of NMR spectra obtained for the synthesized material with published data obtained from the natural product confirmed the identity of both compounds, furthermore giving unambiguous evidence for the proposed structure of the natural product (Table 1).

Table 1
Comparison of NMR data for natural and synthesized graphislactone G

Signal[a]	Natural product[b] δ [ppm] (multiplicity)	Synthesized material δ [ppm] (multiplicity)	Δ
1-CH_3	2.88 (s)	2.89 (s)	0.01
9-OCH_3	3.92 (s)	3.92	0.00
3-OCH_3	3.96 (s)	3.97 (s)	0.01
8-H	6.56 (d, J = 2.1 Hz)	6.57 (d, J = 2.2 Hz)	0.01
H-4	6.8 (s)	6.75 (s)	0.05
H-10	7.19 (d, J = 2.1 Hz)	7.20 (d, J = 2.2 Hz)	0.01
OH	11.78 (br s)	11.79	0.01
	δ [ppm]	δ [ppm]	Δ[c]
1-CH_3	22.0 (q)	21.3	−0.7
9-OCH_3	56.5 (q)	55.8	−0.7
3-OCH_3	57.3 (q)	56.5	−0.8
C-4	99.7 (d)	98.9	−0.8
C-8	100.2 (d)	99.3	−0.9
C-6a	100.5 (s)	99.7	−0.8
C-10	106.3 (d)	105.5	−0.8
C-10b	112.9 (s)	112.1	−0.8
C-2	122.3 (s)	121.6	−0.8
C-1	136.5 (s)	135.7	−0.8
C-10a	137.9 (s)	137.2	−0.7
C-4a	156.1 (s)[d]	150.9 (s)	−5.2[d]
C-3	157.2 (s)[d]	156.0	−1.2[d]
C-7	165.9 (s)	165.2 (s)	−0.7
C-6	165.8 (s)	165.0 (s)	−0.8
C-9	167.2 (s)	166.4 (s)	−0.8

[a] Numbering see Figure 1.
[b] Chemical shifts as published in Ref. 5.
[c] The average deviation of −0.77 ppm (not counting for the deviation at C-4a) suggests a shifted calibration of the spectra which could be confirmed by inspection of the original spectrum ($\Delta\delta$ for $CDCl_3$: +0.8 ppm).
[d] The original ^{13}C NMR spectrum has a low signal-to-noise ratio. Significant spikes are present in the relevant range at δ = 150.3, 151.6, and ~156.8 ppm (with correction[c] at δ = 149.5, 150.8, and ~156.0 ppm).

3. Experimental section

Experimental procedures and detailed spectroscopic data for all compounds are given as Supplementary data.

3.1. 4-Bromo-4-chloro-5-methoxy-3-methylphenol (12)

NBS (0.141 g, 0.791 mmol) was added at 0 °C under an argon atmosphere to phenol **11** (0.130 g, 0.753 mmol) in anhydrous CCl_4 (7 mL) and the yellow mixture was stirred for 30 h at 0 °C. The mixture was filtered and the filtrate was concentrated to yield bromide **12** (0.175 g, 0.696 mmol, 92%) as a yellow solid. R_f = 0.76 (CH_2Cl_2/MeOH, 50:1). mp: 100–103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.51 (s, 3H, Ar*Me*), 3.90 (s, 3H, OMe), 5.63 (br s, 1H, OH), 6.56 (s, 1H, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 19.9 (q), 55.3 (d), 96.6 (q), 103.2 (s), 113.8 (s), 135.5 (s), 150.3 (s), 154.3 (s). Assignment of NMR-spectroscopical data was made according to NOESY spectra. IR (DRIFT): $\tilde{\nu}$ = 3468 cm^{-1} (s), 3171 (s), 3102 (m), 2965 (s), 2942 (s), 2288 (w), 2038 (w), 1590 (s), 1451 (s), 1416 (s), 1344 (s), 1292 (s), 1227 (s), 944.1 (m), 812.9 (s), 696 (s). MS (EI, 140 °C): *m/z* (%) = 254 (22) [$C_8H_8{}^{81}Br^{37}ClO_2$], 252 (100) [$C_8H_8{}^{79}Br^{37}ClO_2$ and $C_8H_8{}^{81}Br^{35}ClO_2$], 250 (76) [$C_8H_8{}^{79}Br^{35}ClO_2$], 209 (22), 207 (16), 171 (2) [$C_8H_8{}^{35}ClO_2{}^+$], 128 (13), 89 (8), 58 (24). HRMS ($C_8H_8{}^{35}Cl^{79}BrO_2$, EI): found 249.9394; calcd 249.9396.

3.2. 2-Chloro-7-hydroxy-3,9-dimethoxy-1-methyl-6*H*-benzo[*c*]chromen-6-one, graphislactone G

A mixture of bromide **12** (0.055 g, 0.22 mmol), boronate **4** (0.095 g, 0.28 mmol), Cs_2CO_3 (0.214 g, 0.656 mmol), $Pd(OAc)_2$ (1.47 mg, 6.56 μmol), and *S*-Phos (purity 97%, 5.6 mg, 0.013 mmol) in degassed solvent (dioxane/H_2O, 7:1, 14 mL) under an argon atmosphere was stirred at 80 °C for 2 h. The mixture was cooled to room temperature, saturated aqueous NH_4Cl-solution (10 mL) was added, and the mixture was extracted with EtOAc (4 × 25 mL). The organic layers were dried (Na_2SO_4), concentrated, and purified by chromatography (silica gel, hexanes/EtOAc, 10:1) yielding graphislactone G (50.3 mg, 0.219 mmol, 72%) as a colourless solid. mp: 243–245 °C (242–244 °C).[5] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.89 (s, 3H, 1-Me), 3.92 (s, 3H, 9-OMe), 3.97 (s, 3H, 3-OMe), 6.57 (d, ^3J = 2.2, 1H, 8-H), 6.75 (s, 1H, 4-H), 7.20 (d, ^3J = 2.2, 1H, 10-H), 11.79 (br s, 1H, OH). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.3 (q, 1-Me), 55.8 (q, 9-OMe), 56.5 (q, 3-OMe), 98.9 (d, C-4), 99.3 (d, C-8), 99.7 (s, C-6a), 105.5 (d, C-10), 112.1 (C-10b), 121.6 (s, C-2), 135.7 (s, C-1), 137.2 (s, C-10b), 150.0 (s, C-4a), 156.0 (s, C-3), 165.0 (s, C-6), 165.2 (s, C-7), 166.4 (s, C-9). IR (DRIFT): $\tilde{\nu}$ = 3417 (w), 2946 (w), 2851 (w), 1670 (m), 1627 (w), 1595 (w), 1460 (w), 1421 (w), 1351 (m), 1281 (m), 1235 (m), 1204 (m), 1162 (w), 836 (w), 823 (w), 771 cm^{-1} (w). UV/VIS: λ^{MeOH} = 343, 302, 291, 256 nm. MS (EI, 140 °C): *m/z* (%) = 322 (35) [$C_{16}H_{13}{}^{37}ClO_5{}^+$], 321 (20) [($C_{16}H_{13}{}^{35}ClO_5$+1)$^+$], 320 (100) [$C_{16}H_{13}{}^{35}ClO_5{}^+$]. 285 (3) [$C_{16}H_{13}O_5{}^+$], 277 (13) [(M−CO−Me)$^+$]. HRMS ($C_{16}H_{13}{}^{35}ClO_5$, EI): found 320.0449; calcd 320.0452. The data are in full agreement with published data for the natural product,[5] except for the ^{13}C NMR signal of C-4a (see Table 1).

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Supplementary data

Supplementary data (Experimental procedures and spectroscopic data for all compounds. Spectra of graphislactone G) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.024.

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