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The first total synthesis of a bioactive metabolite, a spirobenzofuran isolated from the fungi *Acremonium* sp. HKI 0230

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Abstract—The first total synthesis of a bioactive metabolite, isolated from the fungi *Acremonium* sp. HKI 0230, containing a cyclopentaspirobenzofuran carbon framework, employing an Ireland ester Claisen rearrangement and RCM reaction based strategy has been accomplished.
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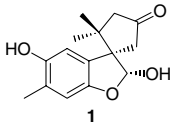
During the screening for bioactive metabolites from fungi, Grafe and co-workers discovered that the strain *Acremonium* sp. HKI 0230 produces several narrow spectrum antibacterial compounds. Bioassay guided fractionation of the mycelium cultures of *Acremonium* sp. HKI 0230 led to the isolation of the sesquiterpene **1**, containing a novel cyclopentane spirofused benzofuran carbon framework incorporating two vicinal quaternary carbon atoms.[1] The spirobenzofuran **1**, biosynthetically related to the *lagopodin* family of fungal metabolites,[2] exhibited antimicrobial activity against a few Gram-positive bacteria such as *Bacilus subtilis* ATCC 6623. The presence of an interesting spirocyclic carbon framework containing two vicinal quaternary carbon atoms, coupled with the biological activity, made the spirobenzofuran **1** an attractive synthetic target. Herein, we describe the first total synthesis of (±)-**1**.[3]



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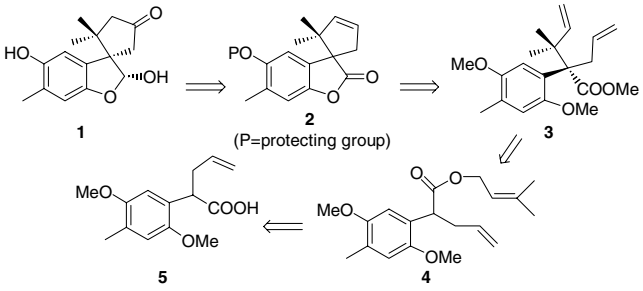
The retrosynthetic analysis is depicted in Scheme 1. It was decided that the spirobenzofuranone **2** containing a cyclopentene moiety and the two quaternary carbon atoms could be elaborated into the target molecule **1**, and ring-closing metathesis (RCM)[4] of the diene ester **3** was considered ideal for the generation of the spirolactone **2**. An Ireland ester Claisen rearrangement[5] was conceived for the generation of the diene ester **3** from the dimethylallyl ester **4**, which could be obtained from 2-arylpentenoic acid **5**.

The synthetic sequence starting from 2,5-dimethoxy-4-methylacetophenone[6] **6** is depicted in Schemes 2 and 3. To begin with, the acetophenone **6** was converted into the known[7] arylacetate **7**. Generation of the lithium enolate of the ester **7** with lithium di-isopropylamide (LDA) and the treatment with allyl bromide furnished the pentenoate **8** in 89% yield. A dicyclohexylcarbodi-imide (DCC) mediated coupling reaction was contemplated for the conversion of the ester **8** into the dimethylallyl ester **4**. Thus, hydrolysis of the ester **8**



Scheme 1.

Keywords: Fungal metabolites; Spirobenzofuran; RCM reaction; Ireland ester Claisen rearrangement.
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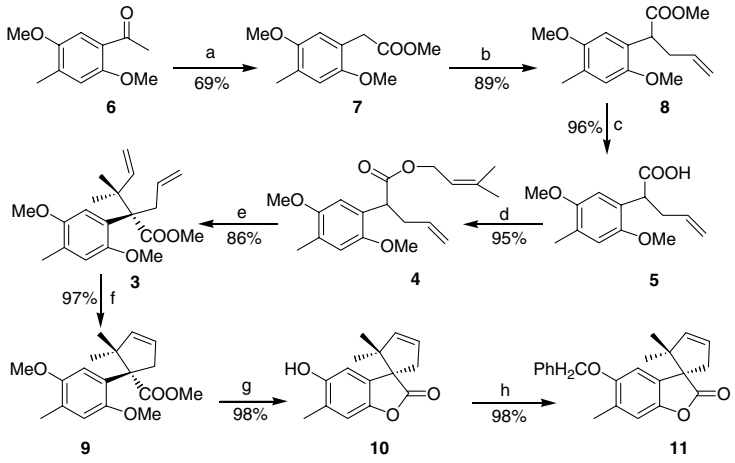
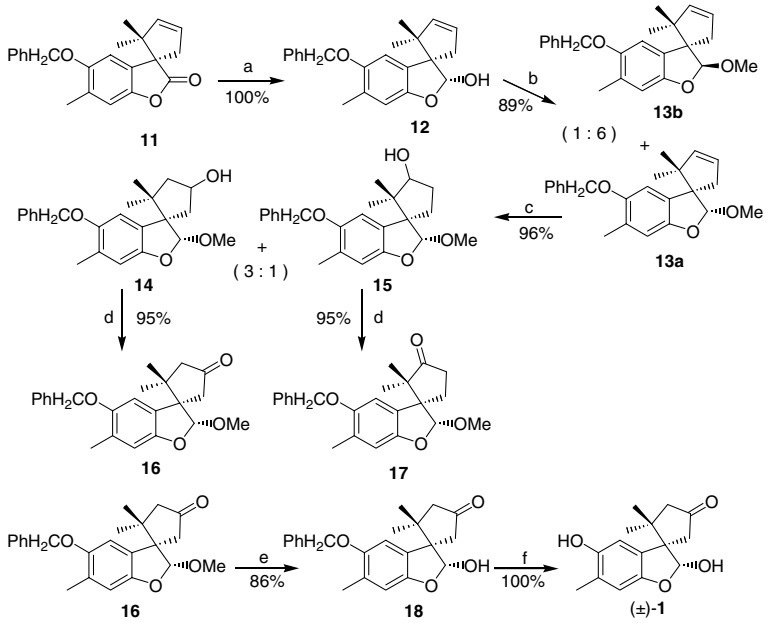
with aqueous sodium hydroxide in methanol furnished the acid **5**. Coupling of the acid **5** with dimethylallyl alcohol employing DCC and 4-*N*,*N*-dimethylaminopyridine (DMAP) generated the key intermediate of the sequence, the ester[†] **4** in 95% yield. The Ireland ester Claisen rearrangement of the ester **4** was then addressed. After exploring a few reaction conditions, it was found that the generation of the TMS enol ether of the ester **4** with LDA, trimethylsilyl chloride and triethylamine in THF at −70 °C, followed by refluxing the reaction mixture for 3 h, resulted in the Ireland ester Claisen rearrangement. Hydrolysis of the reaction mixture with dilute hydrochloric acid followed by esterification with ethereal diazomethane furnished the ester **3** in 86% yield, whose structure was deduced from its spectral data. Treatment of the diene-ester **3** with 5 mol % of Grubbs' first generation catalyst [$Cl_2Ru(PCy_3)_2$=CHPh] in methylene chloride for 5 h at room temperature cleanly furnished the cyclopentene carboxylate[†] **9** in 97% yield. Treatment of the cyclopentene carboxylate **9** with boron tribromide in methylene chloride led to demethylation and concomitant lactonisation to furnish the spirobenzofuranone **10** in 98% yield. The phenolic hydroxy group in **10** was protected as its benzyl ether by treating with potassium carbonate and benzyl bromide in acetone to furnish **11**[†] in 98% yield. To avoid regiochemical problems at a later stage, the lactone group was reduced to a lactol and masked. Thus, controlled reduction of the lactone **11** with di-isobutylaluminium hydride in THF at −70 °C, followed by treatment of the resultant lactol **12** with trimethyl orthoformate and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) in refluxing methanol, furnished a 6:1 epimeric mixture of the methyl acetals **13**. The *anti*-stereochemistry was assigned to the methoxy group in the major isomer **13a** on the basis of kinetic and thermodynamic considerations. A hydroboration–oxidation strategy was explored for the introduction of the ketone group into the cyclopentane ring. Consequently, reaction of the spiroacetal **13a** with freshly prepared diborane in THF followed by oxidation of the alkyl borane with 30% hydrogen peroxide and 3 N aqueous sodium hydroxide furnished a 3:1 regioisomeric mixture of the cyclopentanols **14** and **15**, in 96% yield, in a highly stereoselective manner, which were separated by column chromatography on silica gel. Oxidation of the alcohols **14** and **15** with pyridinium chlorochromate (PCC) and silica gel in methylene chloride furnished the ketones **16**[†] and **17** in excellent yields, whose structures were deduced from their spectral data. Hydrolysis of the acetal group in the spiroketone **16** with 2:1 acetic acid–water and a catalytic amount of trifluoroacetic acid at reflux furnished the lactol **18** in 86% yield. Finally, hydrogenolysis of the benzyl group with 10% palladium on charcoal as the catalyst at one atmospheric pressure of hydrogen (balloon) in ethanol furnished quantitatively the spirobenzofuran[†] (±)-**1**. The synthetic spirobenzofuran **1** exhibited ^1H and ^{13}C NMR spectral data (in DMSO-d_6) identical to those reported for the natural product.

In summary, we have accomplished the first total synthesis of the spirobenzofuran **1** isolated from the mycelial cultures of the fungi *Acremonium* sp. HKI 0230 in an efficient manner, confirming the structure of the natural product. A combination of an Ireland ester Claisen rearrangement and RCM reactions was employed for the creation of two vicinal quaternary carbon atoms. Compound **1** was obtained in 13 steps from the known arylacetate **7** in >30% overall yield.

[†] Yields refer to isolated and chromatographically pure compounds. All the compounds exhibited spectral data (IR, ^1H and ^{13}C NMR and Mass) consistent with their structures. Selected spectral data for dimethylallyl ester **4**: IR (neat): ν_{max}/cm^{-1}: 1731, 1509. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.72 (1H, s), 6.63 (1H, s), 5.72 (1H, ddt, *J* 17.1, 10.2 and 6.9 Hz), 5.26 (1H, m of t, *J* 7.5 Hz), 5.02 (1H, dd, *J* 17.1 and 1.5 Hz), 4.94 (1H, dd, *J* 10.2 and 1.5 Hz), 4.56 (1H, dd, *J* 12.0 and 6.9 Hz), 4.49 (1H, dd, *J* 12.0 and 7.5 Hz), 4.04 (1H, dd, *J* 8.1 and 6.9 Hz), 3.74 (3H, s), 3.72 (3H, s), 2.71 (1H, dt, *J* 14.4 and 7.5 Hz), 2.41 (1H, dt, *J* 14.4 and 6.6 Hz), 2.17 (3H, s), 1.70 (3H, s), 1.65 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 173.4 (C), 151.6 (C), 150.3 (C), 137.9 (C), 135.8 (CH), 125.6 (C), 125.1 (C), 119.1 (CH), 116.2 (CH_2), 114.1 (CH), 110.3 (CH), 61.1 (CH_2), 56.1 (CH_3), 55.5 (CH_3), 43.6 (CH), 37.0 (CH_2), 25.6 (CH_3), 17.8 (CH_3), 16.1 (CH_3). Mass: *m*/*z* 318 (M^+, 74%), 231 (14), 209 (17), 205 (100), 190 (22), 177 (34), 175 (26), 174 (28), 159 (9), 151 (23), 135 (14). HRMS: *m*/*z* Calcd for $C_{19}H_{26}O_4Na$ (M+Na): 341.1729. Found: 341.1713. For the cyclopentene ester **9**: IR (neat): ν_{max}/cm^{-1} 1740, 1504, 1214. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.89 (1H, s), 6.62 (1H, s), 5.62 (1H, dt, *J* 6.0 and 1.8 Hz), 5.56 (1H, dt, *J* 6.0 and 2.1 Hz), 3.74 (3H, s), 3.68 (3H, s), 3.60 (3H, s), 3.14 and 2.68 (2H, 2×d, *J* 16.5 Hz), 2.17 (3H, s), 1.19 (3H, s), 1.02 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 175.0 (C), 150.7 (C), 150.6 (C), 141.8 (CH), 129.1 (C), 125.6 (C), 125.0 (CH), 114.6 (CH), 112.3 (CH), 61.1 (C), 56.0 (CH_3), 55.9 (CH_3), 51.2 (CH_3), 50.2 (C), 42.7 (CH_2), 26.0 (CH_3), 23.9 (CH_3), 16.1 (CH_3). Mass: *m*/*z* 304 (M^+, 69%), 272 (100), 257 (34), 245 (77), 229 (31), 175 (27), 165 (24), 152 (43), 115 (42). HRMS: *m*/*z* Calcd for $C_{18}H_{24}O_4Na$ (M+Na): 327.1572. Found 327.1568. For the spiro lactone **11**: IR (neat): ν_{max}/cm^{-1} 1799. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 7.40–7.25 (5H, m), 6.88 (1H, s), 6.74 (1H, s), 5.78 (1H, dt, *J* 5.7 and 2.1 Hz), 5.60 (1H, dt, *J* 5.7 and 2.1 Hz), 5.03 and 4.98 (2H, 2×d, *J* 12.0 Hz), 3.02 (1H, dt, *J* 16.5 and 2.1 Hz), 2.64 (1H, dt, *J* 16.5 and 2.1 Hz), 2.29 (3H, s), 1.14 (3H, s), 0.83 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 178.6 (C), 153.1 (C), 146.8 (C), 140.3 (CH), 137.2 (C), 128.6 (2C, CH), 128.1 (C), 127.9 (CH), 127.3 (2C, CH), 126.3 (CH), 112.7 (CH), 108.7 (CH), 70.9 (CH_2), 59.2 (C), 52.3 (C), 43.0 (CH_2), 25.1 (CH_3), 24.5 (CH_3), 16.9 (CH_3). Mass: *m*/*z* 334 (M^+, 25%), 243 (20), 215 (22), 91 (100). HRMS: *m*/*z* Calcd for $C_{22}H_{22}O_3Na$ (M+Na): 357.1467. Found: 357.1474. For the spiro ketone **16**: IR (neat): ν_{max}/cm^{-1} 1743. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 7.40–7.20 (5H, m), 6.65 (1H, s), 6.43 (1H, s), 5.34 (1H, s), 4.99 and 4.95 (2H, 2×d, *J* 12.0 Hz), 3.47 (3H, s), 2.96 and 2.42 (2H, 2×d, *J* 19.2 Hz), 2.27 and 2.15 (2H, 2×d, *J* 18.3 Hz), 2.25 (3H, s), 1.08 (3H, s), 0.79 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 215.6 (C), 151.6 (C), 151.4 (C), 137.5 (C), 128.6 (2C, CH), 128.3 (C), 127.8 (CH), 127.3 (2C, CH), 126.8 (C), 112.6 (CH), 109.1 (CH), 109.0 (CH), 71.1 (CH_2), 59.9 (C), 56.0 (CH_3), 52.7 (CH_2), 42.8 (CH_2), 41.7 (C), 24.5 (CH_3), 24.2 (CH_3), 16.9 (CH_3). HRMS: *m*/*z* Calcd for $C_{23}H_{26}O_4Na$ (M+Na): 389.1729. Found: 389.1739. For the spirobenzofuran **1**: IR (neat): ν_{max}/cm^{-1} 3407, 1735, 1172, 1120. ^1H NMR (300 MHz, $CDCl_3$): δ 6.65 (1H, s), 6.47 (1H, s), 5.86 (1H, s), 3.06 and 2.51 (2H, 2×d, *J* 18.9 Hz), 2.45 and 2.26 (2H, 2×d, *J* 18.3 Hz), 2.22 (3H, s), 1.12 (3H, s), 0.90 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 217.0 (C), 151.0 (C), 148.5 (C), 127.0 (C), 124.8 (C), 112.3 (CH), 111.2 (CH), 102.6 (CH), 60.1 (C), 52.7 (CH_2), 42.9 (CH_2), 41.8 (C), 24.3 (CH_3), 24.1 (CH_3), 16.2 (CH_3). HRMS: *m*/*z* Calcd for $C_{15}H_{18}O_4Na$ (M+Na): 285.1103. Found: 285.1105.



Scheme 2. Reagents and conditions: (a) I_2 (2 equiv), $HC(OMe)_3$, rt, 6 h; reflux, 6 h; (b) LDA, THF; $CH_2{=}CHCH_2Br$, −70 °C→rt, 7 h; (c) 10% NaOH, MeOH–H_2O (1:1), reflux, 7 h; (d) DCC, DMAP (catalytic), $Me_2C{=}CHCH_2OH$, CH_2Cl_2, rt, 5 h; (e) (i) LDA, THF; TMSCl, NEt_3, −70 °C, 30 min; rt, 6 h; reflux, 3 h; (ii) dil. HCl, 40 min; (iii) CH_2N_2, Et_2O, 0 °C, 30 min; (f) $Cl_2Ru(PCy_3)_2{=}CHPh$ (5 mol %), CH_2Cl_2, rt, 5 h; (g) BBr_3, CH_2Cl_2, −70 °C, 1.5 h; (h) K_2CO_3, $PhCH_2Br$, acetone, rt, 6 h.



Scheme 3. Reagents and conditions: (a) DIBAL-H, THF, −70 °C, 1.5 h; (b) MeOH, $HC(OMe)_3$, PPTS, reflux, 40 min; (c) (i) $NaBH_4$, $BF_3{\cdot}Et_2O$, THF, 0 °C→rt, 1 h; (ii) 30% aq H_2O_2, 3 N aq NaOH, 0 °C→rt, 7 h; (d) PCC, silica gel, CH_2Cl_2, rt, 1 h; (e) AcOH–H_2O (2:1), CF_3COOH (catalytic), reflux, 14 h; (f) 10% Pd/C, H_2, EtOH, 1 atm, 1.5 h.

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References and notes

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