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The first synthesis of [2-^{13}C]phloroglucinol

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A fast and efficient synthesis of [2-^{13}C]phloroglucinol in six steps from acyclic, non-aromatic precursors is presented, with regioselective placement of a ^{13}C-atom in the aromatic ring. The ^{13}C-label was introduced by reaction of [^{13}C]methyl iodide with methyl 4-chloroformyl butyrate. Cyclization via an intramolecular Claisen condensation, followed by aromatization gave [2-^{13}C]resorcinol. Following subsequent methylation of the hydroxyl groups, the third hydroxyl group was introduced using an iridium-catalysed C–H activation/borylation/oxidation procedure. Demethylation then yielded the desired [2-^{13}C]phloroglucinol.

Keywords: phloroglucinol; resorcinol; C–H activation

Introduction

Many natural products, such as polyketides, coumarins and flavonoids, contain monophenolic or polyphenolic moieties.[1] The 1,3,5-trihydroxybenzene moiety is a common structural motif in these compounds arising via formal cyclization of three acetate units.[1] Phloroglucinol **1** (Figure 1) is a useful intermediate in the synthesis of natural products of this type.[1] New methodology for the preparation of isotopically labelled versions of **1** is potentially valuable. This would allow the synthesis of labelled versions of more complex phenolic compounds for use in metabolic studies or as internal standards for analyses using LC-MS and GC-MS assay techniques. There are only a few examples of the synthesis of isotopically labelled phloroglucinol in the literature.[2,3]

Pateschke *et al.*[2] developed a route to [2,4,6-$^{14}C_3$]phloroglucinol **1a** via the diester **4**, using diethyl [^{14}C]malonate **3** (Scheme 1). After reaction with sodium ethoxide (formed *in situ* from sodium and ethanol) at 135°C for 4 h, phloroglucinol dicarboxylic acid diethyl ester **4** was hydrolysed in refluxing potassium hydroxide solution to yield the tri-labelled phloroglucinol **1a** in 33% yield over the two steps. [2,4,6-$^{14}C_3$]phloroglucinol was also obtained by Birch *et al.*[3] during their biosynthetic studies on the incorporation of ^{14}C-labelled acetic acid into griseofulvin.

We previously developed a synthetic route to [2-^{13}C]resorcinol **2a**, where the phenol was constructed from acyclic precursors, using [^{13}C]methyl iodide as the source of isotopic label.[4,5] Attempts were made to modify this approach for ^{13}C-labelled phloroglucinol by including a suitable oxygen substituent in the precursor, which would become the third hydroxyl group. However, despite considerable investigation, using a variety of precursors and protecting group strategies, it was not possible to retain the oxygen substituent and elimination usually resulted in the synthesis of resorcinol derivatives.

A new synthetic route to [2-^{13}C]phloroglucinol **1b** has been developed, which uses a modification of the iridium catalysed C–H activation/borylation/oxidation procedure recently published by Maleczka *et al.*[6] Using this methodology, a hydroxyl group can be inserted into the 3-position of [2-^{13}C]resorcinol **2a** to give [2-^{13}C]phloroglucinol **1b**, the first single ^{13}C-labelled derivative of phloroglucinol to be reported.

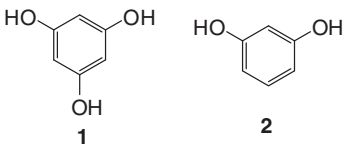
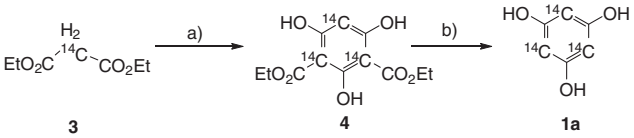


Figure 1. Phloroglucinol 1 and Resorcinol 9.



Scheme 1. Patschke route to [2,4,6-$^{14}C_3$]phloroglucinol 1a[6]. Reagents and conditions: (a) Na, EtOH, 135°C, 4 h (37%); (b) KOH (aq), 130°C (90%).

Results and discussion

The synthesis of [2-^{13}C]phloroglucinol **1b** began with the previously established route[4] to [2-^{13}C]resorcinol **2a**, with some modifications to improve the yields (Scheme 2). The isotopic label was introduced at the first stage of the synthesis by the treatment of methyl 4-chloroformylbutyrate **5** with the lithium dimethylcuprate derived from [^{13}C]methyl iodide. Purification by column chromatography gave methyl 5-oxo-[6-^{13}C]hexanoate **6** in 43% yield.

Cyclization to [2-^{13}C]cyclohexane-1,3-dione **7** was successful in dry tetrahydrofuran, using carefully dried potassium *tert*-butoxide

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as base. Purification by column chromatography yielded the desired product **7** in 69% yield, which was observed to be a mixture of keto and enol tautomers under NMR conditions in deuterated chloroform. It was possible from ^{1}H-^{13}C HSQC and HMBC experiments to distinguish between the two species and determine the ^{1}H and ^{13}C NMR data for each. The final stage in the route to [2-^{13}C]resorcinol **2a** involved the aromatization of [2-^{13}C]cyclohexan-1,3-dione **7** by heating with a palladium on charcoal catalyst in xylene at 138°C. Efforts were made to optimize the yield of this step by varying reaction temperature and time. The best yield was obtained by heating at reflux for 3 h. After purification by column chromatography, [2-^{13}C]resorcinol **2a** was obtained in 88% yield, giving a yield of 26% over the three stages.

Methylation of the hydroxyl groups to give 1,3-dimethoxy-[2-^{13}C]benzene **8** was achieved by the treatment of [2-^{13}C]resorcinol **2a** with methyl iodide in a suspension of caesium carbonate in acetonitrile.[7] The desired product **8** was isolated in a 70% yield after purification.

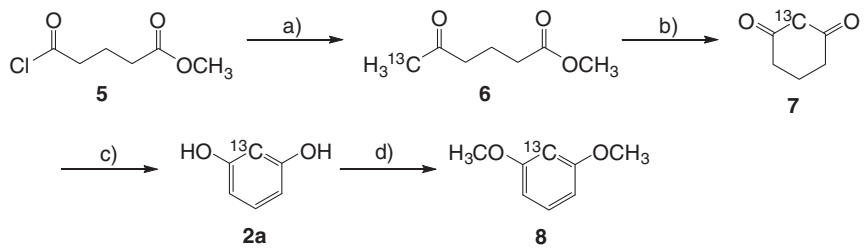
For the introduction of the third hydroxyl group, it was desirable to find a method that gave the desired regioselectivity without polyhydroxylation taking place. This was accomplished by the use of an iridium-catalysed C–H activation/borylation/oxidation procedure reported by Maleczka *et al.*[6] However, the use of such electron-rich arenes had not been previously reported. Optimization studies were therefore undertaken and conditions for the use of 1,3-dimethoxy-[2-^{13}C]benzene **8** were established, where 77% conversion to boronate (**9**) was achieved (Scheme 3).[8] Under the same conditions, 1,3-bis(methoxymethyl)benzene gave 95% conversion to the corresponding boronate. The first stage in this reaction involved the treatment of the substrate with a borylating agent (B_2Pin_2) in the presence of the catalyst [Ir(OMe)(COD)]$_2$, ligand d*t*pby (di-*tert*-butyl-bipyridyl) and *iso*-hexane as the solvent. A reflux temperature of 110°C was found to be optimal for the reaction. Conversions were monitored by using HPLC, and it was found that the largest increase in conversion took place between 0 and 3 h, with a further smaller increase between 3 and 18 h and no significant increase after 18 h. However, to obtain the highest conversion possible, the reaction was allowed to proceed for 18 h. Although the catalyst was found to be relatively air stable as a solid (to the extent that a glove box was not required when handling the catalyst), it was necessary for the reaction to be carried out in degassed solvent under an argon atmosphere. The boronate intermediate **9** was recovered in 77% crude yield and was used in the oxidation step without further purification. It was originally reported that oxidation using Oxone® in a 50:50 solution of acetone and water reaches completion after 5 min at room temperature. However, we found that for our substrates, an oxidation time of 30 min was required to ensure complete oxidation. Formation of poly-hydroxylated species was not observed although some starting material **8** remained. Purification by column chromatography gave the desired 3,5-dimethoxy-[4-^{13}C]phenol **10** in 59% yield.

Finally, demethylation was required to complete the synthesis of [2-^{13}C]phloroglucinol **1b**. A range of conditions was examined, and it was found that treatment of **10** with boron tribromide solution (10 equivalents) in dichloromethane (−78°C to rt) gave the cleanest results and highest yields.[9] After purification by column chromatography, [2-^{13}C]phloroglucinol **1b** was obtained in 81% yield (9% overall yield from **5** over th 6 steps). The ^{13}C-atom was clearly observed as an enhanced singlet at 93.9 ppm in the ^{13}C NMR spectrum. The quaternary carbon atoms were also present in the ^{13}C NMR spectrum (158.8 ppm), with C-1 and C-3 being observed as a doublet with a large *J* value of 66 Hz due to coupling with the adjacent ^{13}C-atom. C-5 was observed as a doublet with a smaller *J* value of 3 Hz. The ^{1}H NMR spectrum was also interesting, with H-2 being observed as a double triplet with a large *J* value of 158 Hz due to coupling with the ^{13}C-atom and a smaller *J* value of 1.8 Hz due to coupling with H-4 and H-6. H-4 and H-6 were observed as a double doublet with *J* values of 4.6 and 1.8 Hz due to coupling with the ^{13}C-atom and H-2 proton, respectively.

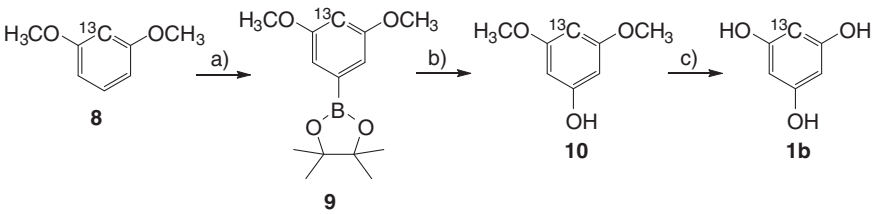
Experimental

General

NMR spectra were recorded on either a Bruker Avance 300 (^{1}H 300 MHz and ^{13}C 75.45 MHz) or a Bruker Avance II 400



Scheme 2. Synthesis of [2-^{13}C]dimethylresorcinol 2a. Reagents and conditions: (a) Et_2O, Li, $^{13}CH_3I$, rt, 1 h, then CuI, 0°C, 30 min, then −20°C, 1 h, then rt, 18 h (43%); (b) THF, KOtBu, reflux, 7 h, then HCl (69%); (c) Xylene, 10% Pd/C, reflux, 3 h, then HCl (88%); (d) Acetonitrile, Cs_2CO_3, CH_3I, reflux, 6 h (70%);



Scheme 3. Synthesis of [2-^{13}C]phlorogluciinol 1b. Reagents and conditions: (a) iso-Hexane, B_2Pin_2, d*t*bpy, [Ir(OMe)(COD)]$_2$, 110°C, 18 h; (b) Acetone, aqueous Oxone®, rt, 30 min (59% over two steps); (c) DCM, BBr_3, −78°C, 1 h, then rt, 18 h (81%).

(^{1}H 400 MHz and ^{13}C 100 MHz) spectrometer in the deuterated solvent stated. ^{13}C NMR spectra were recorded using the PENDANT or DEPTQ sequence and internal deuterium lock. Chemical shifts (δ) in ppm are given relative to tetramethylsilane, coupling constants (*J*) are given in Hz. Low-resolution (LR) and high-resolution (HR) electrospray mass spectral analyses were recorded on a Micromass GC-T spectrometer (time-of-flight). Major fragments are given as percentages of the base peak intensity. Melting points were recorded in open capillaries using an Electrothermal 9100 melting point apparatus and are uncorrected. Analytical TLC was carried out on Merck 5785 Kieselgel 60F_{254} fluorescent plates. The components were observed under ultraviolet light (254 nm). Flash chromatography was performed according to the procedure of Still *et al.*[10] using silica gel of 35–70 μm particle size. Dried solvents were obtained dry using the MBRAUN solvent purification system MB SPS-800. All chemicals and reagents were used as delivered from Sigma-Aldrich, Acros, Strem or Alfa-Aesar unless otherwise indicated. All reactions involving moisture-sensitive reagents were performed in oven-dried glassware under positive pressure of argon. Potassium *tert*-butoxide was dried by heating to 100°C in a vacuum tube for around 2 h and then stored in a dessicator.

Methyl 5-oxo-[6-^{13}C]hexanoate (6)

To dry diethyl ether (300 ml) under an argon atmosphere, lithium pieces were added (2.04 g, 294 mmol). [^{13}C]Methyl iodide (10 g, 70.5 mmol) was added and the reaction mixture stirred at room temperature for 1 h. After this time, the reaction mixture was cooled to 0°C and copper iodide (13.4 g, 70.5 mmol) added. After stirring for 30 min at 0°C, the resulting lithium dimethylcuprate was cooled to −20°C. Pre-cooled methyl 4-chloroformylbutyrate **5** (7 ml, 8.33 g, 50.6 mmol) was then added dropwise with vigorous stirring. The temperature was maintained at −20°C for 1 h, and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated ammonium chloride solution (90 ml) and filtered to remove the copper residue. The filtrate was extracted with diethyl ether (3 × 40 ml), washed with brine (40 ml), and dried ($MgSO_4$). The solvents were removed at reduced pressure to give the crude product. Purification was performed by using column chromatography (silica gel, petroleum ether/ethyl acetate, 9:1) to give **6** as a colourless oil (3.17 g, 43%). *m/z* (ES^+) 168 [$(M+Na)^+$, 45%]; δ_H (400 MHz, $CDCl_3$) 3.63 (3H, s, OCH_3), 1.85 (2H, quintet, *J* 7.2 Hz, CH_2-3), 2.48 (2H, t, *J* 7.2 Hz, CH_2-4), 2.31 (2H, t, *J* 7.2 Hz, CH_2-2), 2.11 (3H, d, *J* 127 Hz, $^{13}CH_3$); δ_C (100 MHz, $CDCl_3$) 207.9 (d, *J* 41.2 Hz, *C*OCH_3), 173.5 (COOMe), 51.5 (OCH_3), 42.4 (CH_2-4), 32.9 (CH_2-2), 29.9 (enhanced, $^{13}CH_3$), 18.8 (CH_2-3).

[2-^{13}C]Cyclohexan-1,3-dione (7)

To a solution of methyl 5-oxo-[6-^{13}C]hexanoate **6** (2.1 g, 14.5 mmol) in dry tetrahydrofuran (280 ml) was added potassium *tert*-butoxide (6.5 g, 57.9 mmol). The mixture was heated at reflux for 7 h, after which time the solvents were removed at reduced pressure. The residue was dissolved in water (120 ml) and acidified to pH 1 with conc. HCl. The aqueous layer was extracted with ethyl acetate (6 × 120 ml). The organic layer was then dried ($MgSO_4$) and the solvents removed at reduced pressure to give an orange solid. Purification was performed by using column chromatography (silica gel, petroleum ether/ethyl acetate, 1:4) to give **7** as a pale yellow solid (1.13 g, 69%). mp 106–106.5°C (Lit (unlabelled)[11] 105°C); *m/z* (CI^+) 114 [$(M+H)^+$, 100%]; Keto and enol tautomers were observed in the ^{1}H NMR spectrum. Data for keto form: δ_H (400 MHz, $CDCl_3$) 3.36 (2H, d, *J* 130.1 Hz, $^{13}CH_2$-2), 2.36 (4H, d*t*, *J* 6.5, 1.8 Hz, CH_2-4,6), 1.88–2.00 (2H, m, CH_2-5); δ_C (100 MHz, $CDCl_3$) 204.0 (d, *J* 36 Hz, C=O), 58.4 (enhanced, $^{13}CH_2$-2), 32.1 (CH_2-4,6), 18.4 (CH_2-5); Data for enol form: δ_H (400 MHz, $CDCl_3$) 8.69 (1H, s, OH), 5.54 (1H, d, J 161.0 Hz, ^{13}CH-2), 2.55 (2H, *t*, *J* 6.5 Hz, CH_2-6), 2.36 (2H, d*t*, *J* 6.5, 1.8 Hz, CH_2-4), 1.88–2.00 (2H, m, CH_2-5); δ_C (100 MHz, $CDCl_3$) 188.2 (C=O), 104.3 (enhanced, ^{13}CH-2), 39.9 (CH_2-6), 32.1 (CH_2-4), 21.0 (CH_2-5).

[2-^{13}C]Resorcinol (2a)

To a flask containing [2-^{13}C]cyclohexane-1,3-dione **7** (0.288 g, 2.55 mmol) and xylene (50 ml), palladium on carbon was added (10%, 1.44 g). The mixture was heated at reflux for 3 h, then the palladium catalyst filtered off through a bed of celite. The reaction mixture was extracted with aqueous sodium hydroxide (20%, 4 × 100 ml). The combined aqueous layers were cooled to 0°C, acidified to pH 2 with concentrated HCl and extracted with diethyl ether (3 × 100 ml) and ethyl acetate (3 × 100 ml). The solvents were then removed at reduced pressure to give an orange oil. Purification was performed by using column chromatography (silica gel, diethyl ether/petroleum ether, 2:1) to give **2a** as a white solid (248 mg, 88%). mp 108–109°C (Lit (unlabelled)[12] 109–111°C); *m/z* (CI^+) 112 [$(M+H)^+$, 100%]; δ_H (400 MHz, acetone-d_6) 8.21 (2H, d, *J* 5.1 Hz, OH), 6.98 (1H, d*t*, *J* 8.1, 1.2 Hz, CH-5), 6.36 (1H, d*t*, *J* 157, 2.3 Hz, ^{13}CH-2), 6.29–6.37 (2H, m, CH-4,6); δ_C (75.45 MHz, acetone-d_6) 159.9 (d, *J* 67 Hz, C-OH), 130.7 (CH-5), 109.0 (CH-4,6), 103.5 (enhanced, ^{13}CH-2).

1,3-Dimethoxy-[2-^{13}C]benzene (8)

To a solution of [2-^{13}C]resorcinol **2a** (0.24 g, 2.16 mmol) and caesium carbonate (1.41 g, 4.32 mmol) in acetonitrile (100 ml), methyl iodide was added (0.68 ml, 1.53 g, 10.8 mmol). The mixture was heated at reflux for 6 h, after which time the solvents were removed at reduced pressure. The residue was dissolved in diethyl ether (2 × 200 ml), washed with water (3 × 60 ml) and the combined organic layers dried ($MgSO_4$). The solvents were removed at reduced pressure to give the crude product. Purification was performed by using column chromatography (silica gel, petroleum ether/ethyl acetate, 4:1) to give **8** as a colourless oil (0.21 g, 70%). *m/z* (CI^+) 140 [$(M+H)^+$, 100%], 139 [$(M)^+$, 15]; HRMS (CI^+) [Found: $(M+H)^+$, 140.0790, $^{13}C^{12}C_7H_{11}O_2$ requires 140.0793]; δ_H (400 MHz, $CDCl_3$) 7.11 (1H, d*t*, *J* 8.2, 1.3 Hz, CH-5), 6.40–6.46 (2H, m, CH-4,6), 6.39 (1H, d*t*, *J* 158.2, 2.4 Hz, ^{13}CH-2), 3.70 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 161.0 (d, *J* 70 Hz, C-1,3), 129.7 (d, *J* 5 Hz, CH-5), 106.1 (d, *J* 3 Hz, CH-4,6), 100.5 (enhanced, ^{13}CH-2), 55.3 (d, *J* 4 Hz, CH_3).

3,5-Dimethoxy-[4-^{13}C]phenol (10) via 3,5-dimethoxy-[4-^{13}C]phenylboronic acid pinacol ester (9)

A solution of degassed 1,3-dimethoxy-[2-^{13}C]benzene **8** (100 mg, 0.72 mmol) in *iso*-hexane (5 ml) was transferred into an air-free flask containing B_2Pin_2 (183 mg, 0.72 mmol), $[Ir(OMe)(COD)]_2$ (4.8 mg, 1 mol%) and d*t*bpy (3.9 mg, 2 mol%). The flask was sealed and the reaction mixture stirred at 100°C for 18 h. The *iso*-hexane was then removed at reduced pressure to give the intermediate borolane **9** (77% conversion) as an orange oil

which was used without further purification. Analysis for crude intermediate: *m/z* (CI^+) 266 [$(M+H)^+$, 100%], 265 [$(M)^+$, 30]; HRMS (CI^+) [Found: $(M+H)^+$, 266.1657, $^{13}C^{12}C_{13}H_{22}O_4B$ requires 266.1645]; δ_H (300 MHz, $CDCl_3$) 6.96 (2H, dd, *J* 6.9, 3.2 Hz, CH-2,6), 6.58 (1H, d*t*, *J* 210, 3.2 Hz, ^{13}CH-4), 3.82 (6H, s, CH_3), 1.35 (12H, s, CH_3); δ_C (100 MHz, $CDCl_3$)[†] 157.1 (C-3,5), 111.3 (CH-2,6), 104.4 (enhanced, ^{13}CH-4), 83.9 ($CO(CH_3)_2$), 55.5 (CH_3), 24.8 (CH_3).[†] Observed by HSQC and/or HMBC, correlates with data from unlabelled compound previously synthesized during optimization studies.

Acetone (2.3 ml) was added to the crude borolane **9** and the mixture stirred to produce a homogeneous solution. An aqueous solution of Oxone® (531 mg, 0.864 mmol, in 2.3 ml of H_2O) was then added dropwise over 2–4 min and the reaction mixture allowed to stir vigorously for 30 min. After this time, the reaction was quenched by the addition of saturated sodium sulphite solution (10 ml). The aqueous phase was extracted with diethyl ether. The organic solvents were removed at reduced pressure and the crude material dissolved in dichloromethane and passed through a plug of silica gel. The solvents were then removed at reduced pressure once more to give the crude product, which contained traces of starting material (77% conversion). Purification was performed by using column chromatography (silica gel, petroleum ether/ethyl acetate, 2:1) to give the desired product **10** as an off-white solid (66 mg, 59%). m.p. 40–40.5°C (Lit (unlabelled)[13] 40°C); *m/z* (CI^+) 156 [$(M+H)^+$, 100%]; HRMS (CI^+) [Found: $(M+H)^+$, 156.0745, $^{13}C^{12}C_7H_{11}O_3$ requires 156.0742]; δ_H (400 MHz, $CDCl_3$) 5.98 (1H, t, *J* 160.0, 2.2 Hz, ^{13}CH-4), 5.97 (2H, d, *J* 4.7, 2.2 Hz, CH-2,6), 3.68 (6H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 161.6 (d, *J* 71 Hz, C-3,5), 157.7 (d, *J* 4 Hz, C-OH), 94.2 (d, *J* 3 Hz, CH-2,6), 92.9 (enhanced, ^{13}CH-4), 55.3 (d, *J* 4 Hz, CH_3).

[2-^{13}C]Phloroglucinol (1b)

To a solution of 3,5-dimethoxy-[4-^{13}C]phenol **10** (66 mg, 0.426 mmol) in dichloromethane (6 ml) at −78°C under an argon atmosphere, boron tribromide solution was added (1 M in dichloromethane, 5 ml, 5 mmol). The reaction mixture was stirred at −78°C for 1 h, then allowed to warm to room temperature. After stirring overnight at room temperature, the solution was cooled to 0°C and water (3 ml) added. The solvents were then removed at reduced pressure and the aqueous phase extracted with ethyl acetate (3 × 15 ml). The organic layers were combined, dried ($MgSO_4$), and the solvents were removed at reduced pressure to give the crude product as a light brown solid. Purification was performed by using column chromatography (silica gel, petroleum ether/ethyl acetate, 1:1) to give **1b** as an off-white solid (44 mg, 81%). m.p. 215–215.5°C (Lit (unlabelled)[14] 216°C); *m/z* (CI^+) 128 [$(M+H)^+$, 100%], 127 [$(M)^+$, 25]; HRMS (CI^+) [Found: $(M+H)^+$, 128.0435, $^{13}C^{12}C_5H_7O_3$ requires 128.0429]; δ_H (300 MHz, DMSO-d_6) 8.93 (3H, t, *J* 2.4 Hz, OH), 5.63 (2H, dd, *J* 4.6, 1.8 Hz, CH-4,6), 5.63 (1H, d*t*, *J* 158.0, 1.8 Hz, ^{13}CH-2); δ_C (100 MHz, DMSO- d_6) 93.9 (enhanced, ^{13}CH-2 and CH-4,6), 158.8 (d, *J* 66 Hz, C-1,3), 158.8 (d, *J* 3 Hz, C-5).

Conclusion

An efficient route for the synthesis of [2-^{13}C]phloroglucinol **1b** via [2-^{13}C]resorcinol **2a** has been developed starting from [^{13}C]methyl iodide. The third hydroxyl group was introduced using an iridium-catalysed C–H activation/borylation/oxidation procedure. This route allows the regioselective placement of one ^{13}C-atom within the aromatic ring, starting from acyclic, non-aromatic precursors.

Acknowledgements

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