Electronic Supplementary Material (ESI) for ChemComm.

Bioconjugated Arylpalladium Complexes on Solid Supports for Convenient Last-Step Synthesis of ^{11}C-Labelled Tracers for Positron Emission Tomography

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Electronic Supplementary Information

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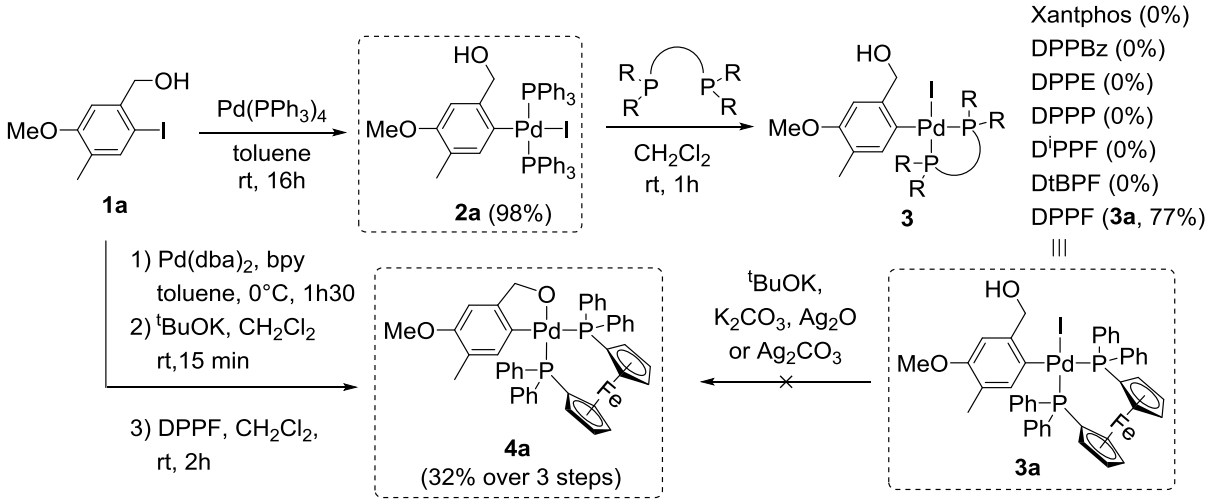
1) General Procedures

All commercial materials were used without further purification, unless indicated. The triphenylphosphine polymer-bound was bought at Sigma-Aldrich® (100-200 mesh, extent of labelling: ~3.0 mmol/g loading, 2 % cross-linked with divinylbenzene, packaging: 5g in glass bottle) and washed with dichloromethane, Et_2O and THF (3 times each) before being dried under vacuum. ^{1}H NMR, ^{13}C NMR and ^{31}P NMR were recorded on a BRUKER AVANCE I 300 MHz spectrometer (^{1}H: 300MHz, ^{13}C: 75.3MHz, ^{31}P: 121.5MHz), Bruker DPX-400 FT (^{1}H: 400MHz, ^{13}C: 100.2 MHz, ^{31}P: 162MHz) and Bruker DPX-600 FT (^{1}H: 600MHz, ^{13}C: 150.6 MHz). The chemical shifts for the NMR spectra are reported in ppm relative to the solvent residual peak. Coupling constants J are reported in hertz (Hz). The following abbreviations are used for the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; qt, quintet; st, sextet; m, multiplet; br, broad; dd, doublet of doublet. Yields refer to isolated material determined to be pure by NMR spectroscopy and thin-layer chromatography (TLC), unless specified in the text. Analytical TLC was performed on Fluka Silica Gel 60 F254. High resolution mass spectra were performed by the CESAMO (Talence, France) and were recorded on Qq-TOF tandem mass spectrometer (API Q-STAR Pulsari, Applied Biosystems). Positive ion mode ESI-MS was used for the analyses. The Inductively Coupled Plasma / Optical Emission Spectrometry (ICP-OES) analyses was performed at the ICMCB (UMR 5026) on a Varian ICP/OES 720 ES apparats. The two-chamber system (S) was bought at SyTracks (http://www.sytracks.com).

2) Screening of arylpalladium complexes

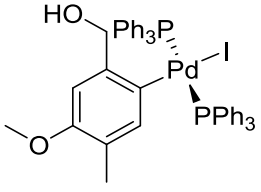
*a. Syntheses of **2a**, **3a** and **4a***

2-Iodobenzylalcohol **1a** could reacted smoothly with tetrakis(triphenylphosphine)-palladium(0) to give **2a** in an almost quantitative yield. As bidentate phosphines proved to be excellent ligands in the catalytic version of the intramolecular alkoxycarbonylation, ligand exchanges from **2a** were attempted with various biphosphines, but bis(diphenylphosphino)ferrocene (DPPF) was the only ligand that provided an isolable complex after oxidative (**3a**, 77% yield). Finally, preparation of the corresponding oxypalladacycle **4a** was unsuccessful from **3a**, but it could be obtained by changing the strategy, i.e. synthesising an aryl-bipyridyl-palladium specie before exchanging its bpy ligand with DPPF.



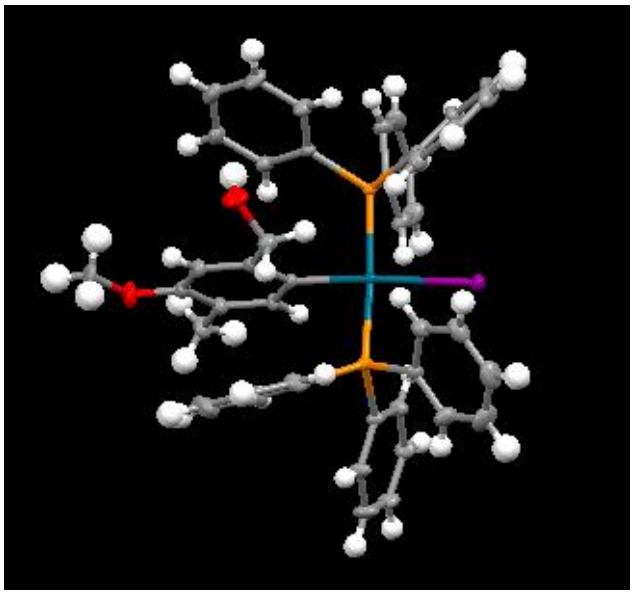
Scheme : Syntheses of model oxidative addition palladium complexes. Xanphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, DPPBz: 1,2-bis(diphenyl-phosphinobenzene), DPPE: 1,2-bis(diphenylphosphinoethane), DPPP: 1,2-bis(diphenylphosphinopropane), D^{i}PPF: 1,1'-bis(di-i-propylphosphino)-ferrocene, D^{t}BPF: 1,1'-bis(di-tert-butylphosphino)ferrocene, DPPF: 1,1'-bis(diphenylphosphino)ferrocene

<u>[(2-Hydroxymethyl-4-methoxy-5-(methyl))phenyl]iodobis(triphenyl-phosphine)palladium 2a:</u>



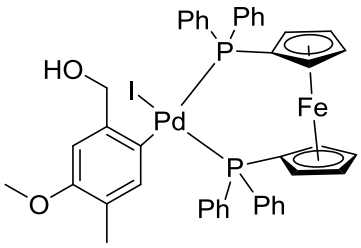
In a tube, were added o-iodobenzylalcohol **1a** (143 mg, 0.51 mmol, 1.0 eq.), $Pd(PPh_3)_4$ (594 mg, 0.51 mmol, 1.0 eq.). The tube was sealed and purged three times. Toluene (3.5 mL) was added and the resulting solution was briefly sonicated, then stirred at room temperature for 16 h. The solid was filtered and washed with cold Et_2O to give **2a** (460 mg, 0.506 mmol, 99 %) as a white yellow solid. **^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm):** 7.51-7.47 (m, 12H), 7,37-7,28 (m, 18H), 6.49-6.47 (m, 1H), 6.07 (s, 1H), 4.25 (d, *J* = 6.5 Hz, 2H), 3.55 (s, 3H), 1.70 (s, 3H), 0.18 (t, *J* = 6.5 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):** 156.0, 145.9, 141.5 (t, J = 4.1 Hz), 138.0, 136.0 (t, J = 4.5 Hz), 134.9 (t, J = 5.9 Hz), 132.2, 131.9, 131.6, 130.3, 130.0, 129.2, 128.7, 128.5, 128.3, 127.8 (t, J = 5.0 Hz), 125.4, 125.2, 111.1, 68.1, 55.8, 16.1. **^{31}P NMR (121.5 MHz, $CDCl_3$) δ (ppm):** 22.7.

Monocrystals of this compound were obtained by slow diffusion of Et_2O in CH_2Cl_2, and X-ray diffraction analysis confirmed a *trans* configuration of the phosphines in this case. Crystallographic data were acquired at CESAMO (UMR 5255) on a Bruker APEX 2 DUO. A single crystal was mounted and immersed in a stream of nitrogen gas [T = 150(2) K]. Data were collected, using a microfocus sealed tube of Mo K_α radiation (k = 0.71073 Å) on a KappaCCD diffractometer. Data collection and cell refinement were performed using APEX2 2013.10-0 (Bruker AXS Inc.), and SAINT v8.34A (Bruker AXS Inc.). Data reduction was performed using SAINT v8.34A (Bruker AXS Inc.). Correction for absorption was performed using multi-scan integration as included in SADABS V2012/1 (Bruker AXS). Structure solutions were found by charge flipping methods (SUPERFLIP (Palatinus & Chapuis, 2007) EDMA (Palatinus et al., 2012)) and refined with (SHELXL).[1] Crystallographic data for this structure has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1897747. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk)



*Mercury drawing of the crystalline structure of **2a** obtained by X-Ray diffraction analysis*

[(2-Hydroxymethyl-4-methoxy-5-(methyl))phenyl]iodo(1,1′-Bis(diphenylphosphino)ferrocene) palladium 3a:

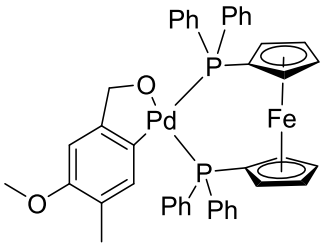


Under inert atmosphere, to a solution of **2a** (272 mg, 0.3 mmol, 1.0 eq.) in CH_2Cl_2 (7,5 mL) was added 1,1'-bis(diphenylphosphino)ferrocene (166 mg, 0.3 mmol, 1.0 eq.) at room temperature for 1 h. The evolution of the reaction was followed by NMR ^{31}P. The solvent was evaporated, and the residue was triturated with cold Et_2O to give **3a** (215 mg, 0.23 mmol, 77%) as an orange solid in mixture with

[1] G. M. Sheldrick *Acta Crystallographica Section A.* **2008**, 64, 112-122.

traces of triphenylphosphine and of the starting complex **2a**. **^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm):** 8.13-7.95 (m, 4H), 7.85-7.72 (m, 2H), 7.54-7.46 (m, 7H), 7.37-7.31 (m, 7H), 6.89-6.84 (m, 1H), 6.23 (s, 1H), 4.99 (br s, 1H), 4.83 (br s, 1H), 4.58 (br s, 1H), 4.87-4.35 (m, 3H), 4.29-4.20 (m, 1H), 4.12 (s, 2H), 4.09-4.01 (m, 1H), 3.57 (s, 3H), 1.90 (s, 3H). **^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm):** 135.7, 135.6, 135.4, 135.3, 135.2, 135.0, 134.7, 134.6, 133.3, 133.2, 132.3, 132.2, 132.1, 132.0, 131.8, 131.7, 131.5, 131.4, 130.1, 128.7, 128.7, 128.6, 128.5, 128.0, 127.9, 112.3, 74.7, 74.2, 73.6, 73.5, 55.3, 16.3. **^{31}P NMR (121.5 MHz, $CDCl_3$) δ (ppm):** 28.2 (d, *J* = 34.4 Hz), 8.2 (d, *J* = 34.4 Hz).

(Oxomethylene-1,2-(4-methoxy-5-methyl)phenylene)-[1,1'-bis(diphenylphosphino)ferrocene)] palladium 4a:



O-iodobenzylalcohol **1a** (163 mg, 0.59 mmol, 1.0 eq.) was added to a suspension of $Pd(dba)_2$ (230 mg, 0.40 mmol, 0.67 eq.) and 2,2'-bipyrydine (84.7 mg, 0.40 mmol, 0.67 eq.) in dry degassed toluene (15 mL) under N_2. The resulting mixture was stirred in an ice bath for 1h30. The solvent was removed and CH_2Cl_2 (15 mL) was added. The solution was filtered over celite, and the orange solution was evaporated to dryness. The residue was triturated with cold Et_2O to give the desired complex (152 mg, 0.28 mmol, 70%) as a yellow solid in mixture with traces of dibenzylideneacetone (ratio 83:17). **^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm):** 9.63-9.58 (m,1H), 8.10-8.06 (m, 2H), 8.05-7.97 (m, 2H), 7.57-7.50 (m, 2H), 7.37-7.32 (m, 1H), 7.21 (s, 1H), 6.83 (s, 1H), 5.15-5.10 (m, 1H), 4.62-4.55 (m, 1H), 3.83 (s, 3H), 2.89-2.85 (m, 1H), 2.15 (s, 3H). **^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm):** 155.9, 155.4, 153.8, 152.8, 150.3, 142.1, 140.2, 138.8, 137.2, 132.6, 127.0, 126.7, 125.3, 122.1, 121.7, 111.3, 68.6, 55.5, 16.3. Then, KOtBu (94 mg, 0.84 mmol, 4.0 eq) was added to a solution of the complex (114 mg, 0.21 mmol, 1.0 eq.) in CH_2Cl_2 (20 mL) under N_2. The mixture was stirred for 15 min at room temperature and then filtered over celite. The resulting yellow solution was evaporated to dryness and triturated with cold Et_2O to give the desired cyclometallated complex (83 mg, 0.20 mmol, 96%) as a yellow solid. **^{1}H NMR (300MHz, $CDCl_3$) δ (ppm):** 9.20 (d, *J* = 5Hz, 1H), 9.04-9.02 (m, 1H), 8.05-8.03 (m, 2H), 8.03-7.96 (m, 2H), 7.61-7.52 (m, 2H), 6.94 (s, 1H), 6.62 (s, 1H), 5.18 (s, 2H), 3.79 (s, 3H), 2.25 (s, 3H). **^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm):** 163.5, 156.5, 155.7, 153.2, 151.9, 149.8, 139.8, 138.6, 137.9, 133.4, 126.6, 126.3, 122.4, 121.2, 121.0, 102.1, 77.4, 55.5, 16.7. Finally, under inert atmosphere, to a solution of the cyclometallated complex (25.9 mg, 0.063 mmol, 1.0 eq.) in CH_2Cl_2 (3.5 mL) was added 1,1'-bis(diphenylphosphino)ferrocene (69.8 mg, 0.126 mmol, 2.0 eq.) at room temperature for 2 h. The evolution of reaction was followed by NMR ^{31}P. The solvent was evaporated, and the residue was triturated with cold Et_2O to give **4a** (32.5 mg, 0.035 mmol, 55%) as an orange solid. **^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm):** 8.09-8.02 (m, 5H), 7.88-7.79 (m, 5H), 7.44-7.35 (m, 10H), 6.67-6.65 (m, 1H), 5.66-5.59 (m, 1H), 5.32 (br s, 2H), 4.57-4.53 (m, 2H), 4.37-4.35 (m, 2H), 4.20-4.18 (m, 2H), 3.69 (s, 3H), 3.57-3.54 (m, 2H), 1.53 (s, 3H). **^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm):** 131.8, 131.5, 131.4,

130.3, 128.5, 128.3, 126.8, 77.4, 74.2, 74.1, 73.7, 73.5, 60.7, 15.4. **^{31}P NMR (121.5 MHz, $CDCl_3$) δ (ppm):** 34.8 (d, *J* = 35.6 Hz), 15.4 (d, *J* = 35.6 Hz).

b. Stability screening

The stabilities of **2a**, **3a** and **4a** towards other functional groups were firstly evaluated. In a NMR tube, complex **2a**, **3a** or **4a** (0.05 mmol) was dissolved in $CDCl_3$ (0.7mL). After a first ^{31}P NMR acquisition, the other compound (water, D-Glucose, L-proline or thymidine, 1.0 eq) was added and the mixture was stirred under ultrasound for 2h at room temperature. Then, a second ^{31}P NMR acquisition was realised to check if the characteristic peaks of the initial complexes could be still detected.

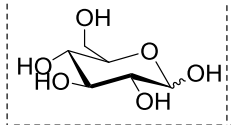
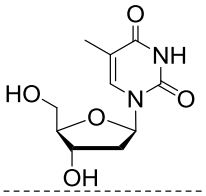
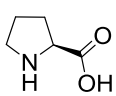
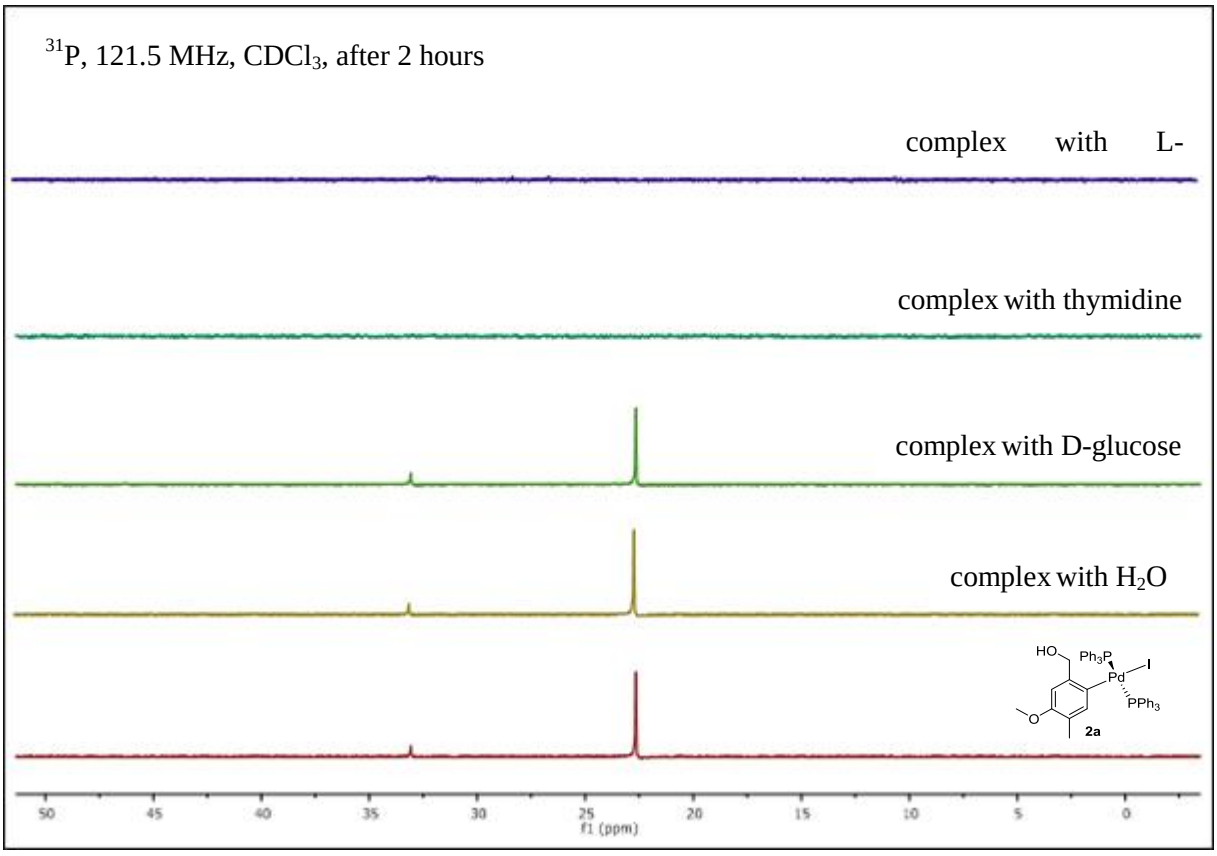
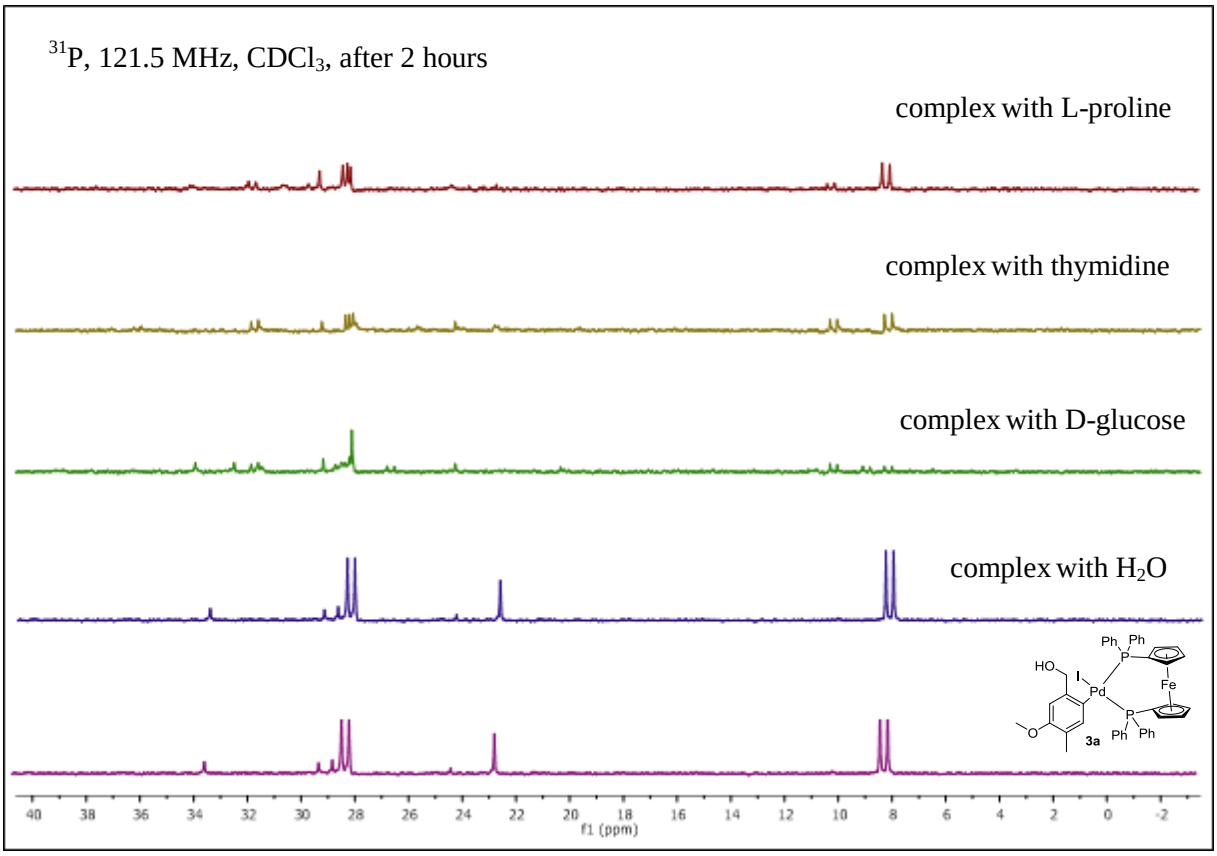
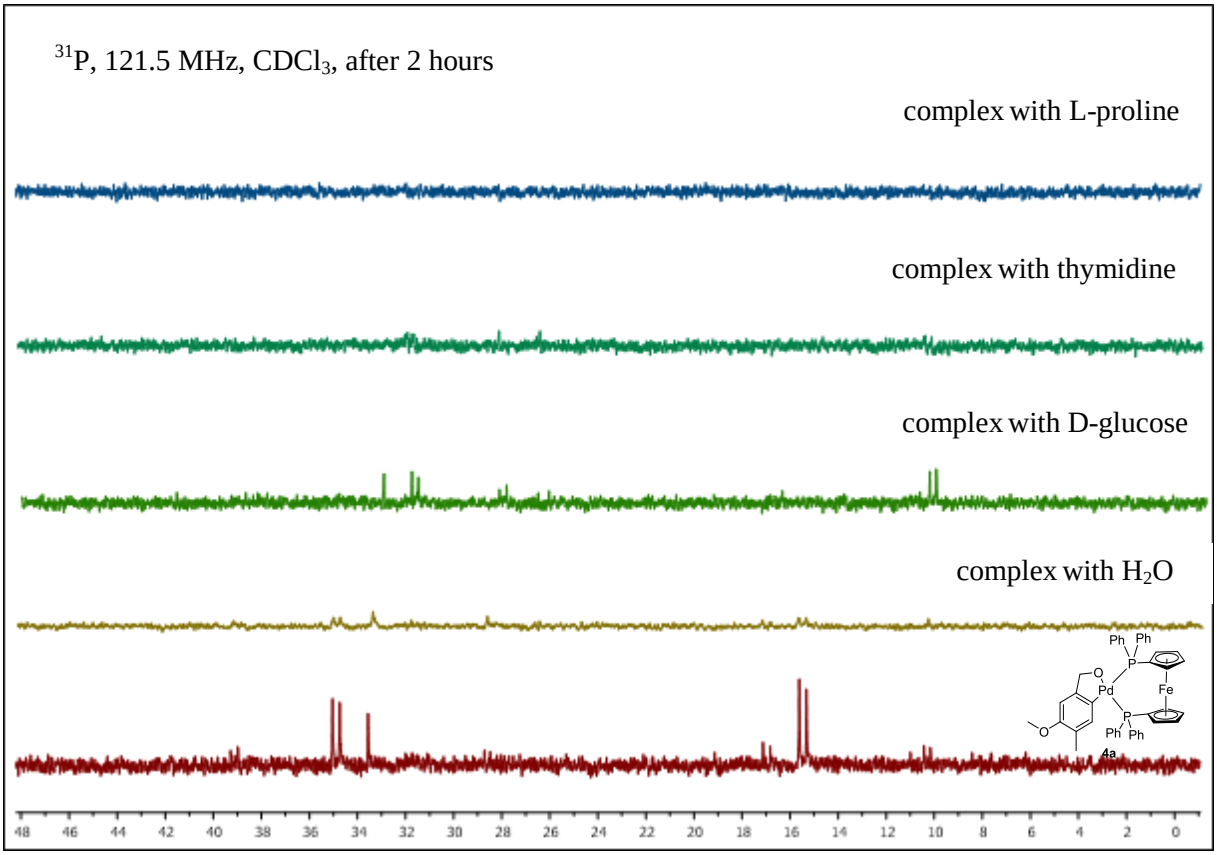
Added molecule	H_2O			
2a				
3a				
4a				

Table : Graphical summary of the stability screening by ^{31}P NMR analysis. Green: ^{31}P NMR peaks of the initial complex still detected after 2h at rt in mixture in $CDCl_3$ with the added molecule; Orange: ^{31}P NMR peaks of the initial complex not detected after 2h.

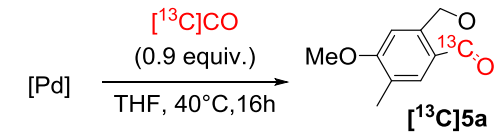



31P, 121.5 MHz, CDCl3, after 2 hours
complex with L-proline
complex with thymidine
complex with D-glucose
complex with H2O
HO
I
Pd
Fe
Ph
P
O
3a
40 38 36 34 32 30 28 26 24 22 20 18 16 14 12 10 8 6 4 2 0 -2
f1 (ppm)


31P, 121.5 MHz, CDCl3, after 2 hours
complex with L-proline
complex with thymidine
complex with D-glucose
complex with H2O
O
Pd
Fe
Ph
P
4a
48 46 44 42 40 38 36 34 32 30 28 26 24 22 20 18 16 14 12 10 8 6 4 2 0

c. Reactivity Screening

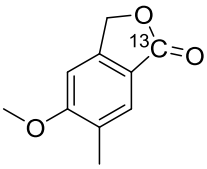
Complexes **2a**, **3a** and **4a** were reacted with 0.9 equivalent of [^{13}C]CO in THF at 40°C for 16h. The results are summarised in the following table.



2a	69% of **[^{13}C]5a**
3a	40% of **[^{13}C]5a**
4a	50% of **[^{13}C]5a**

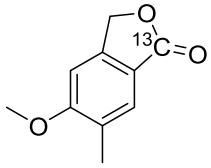
*Table: Carbonylation of complexes **2a**, **3a** and **4a** ([^{13}C]CO was produced from [^{13}C]SilaCOgen in a two-chamber system).*

1-[^{13}C]-5-Methoxy-6-methylisobenzofuran-1(3H)-one [^{13}C]5a (from 2a):



In the chamber 1 of the two-chamber system was added $Ph_2MeSi^{13}COOH$ (24.3 mg, 0.1 mmol, 0.9 eq.). The chamber 1 was sealed with a screwcap fitted with a silicone/PTFE seal. In the chamber 2 of the two-chamber system was added the complex **2a** (100 mg, 0.11 mmol, 1.0 eq.). The chamber 2 was sealed with a screwcap fitted with a silicone/PTFE seal. The atmosphere of the two-chamber system was purged three times with nitrogen. Then, 2 mL of dry THF were added by syringe in each chamber through the silicone/PTFE seal. The loaded two-chamber system was stirred at 40°C, then 16.5 µl of a solution of TBAF (1M in THF, 16.5 μmol, 15 mol%) were added through a silicone/PTFE seal in the chamber 1. The system was stirred at 40°C for 16 hours. After a careful opening, the crude reaction mixture from chamber 2 was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (70/30: cyclohexane/ethyl acetate, R_f = 0.4) affording **[^{13}C]5a** (12.3 mg, 0.068 mmol, 69%) as a white solid. **^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm):** 7.65 (s, 1H), 6.84 (s, 1H), 5.23 (s, 2H), 3.92 (s, 3H), 2.27 (s, 3H). **^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm):** 171.4 (^{13}C-enriched), 163.2, 147.5, 129.1, 127.1, 117.9, 102.5, 69.2, 55.9, 16.8. The spectral data was in accordance with the literature.[2]

1-[^{13}C]-5-Methoxy-6-methylisobenzofuran-1(3H)-one [^{13}C]5a (from 3a):

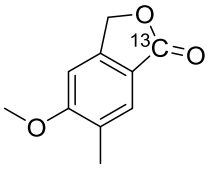


In the chamber 1 of the two-chamber system was added $Ph_2MeSi^{13}COOH$ (6.3 mg, 0.026 mmol, 0.9 eq.). The chamber 1 was sealed with a screwcap fitted with a silicone/PTFE seal. In the chamber 2 of the two-chamber system was added the

[2] T. Cornilleau, H. Audrain, A. Guillemet, P. Hermange, E Fouquet, *Org. Lett.* **2015**, *17*, 354-357.

complex **3a** (29 mg, 0.029 mmol, 1.0 eq.). The chamber 2 was sealed with a screwcap fitted with a silicone/PTFE seal. The atmosphere of the two-chamber system was purged three times with nitrogen. Then, 1 mL of dry THF was added by syringe in each chamber through the silicone/PTFE seal. The loaded two-chamber system was stirred at 40°C, then 4.4 µL of a solution of TBAF (1M in THF, 4.4 μmol, 15 mol%) were added through a silicone/PTFE seal in the chamber 1. The system was stirred at 40°C for 16 hours. After a careful opening, the crude reaction mixture from chamber 2 was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (70/30: cyclohexane/ethyl acetate, R_f = 0.4) affording **[^{13}C]5a** (1.8 mg, 0.010 mmol, 40%) as a white solid.

1-[^{13}C]-5-Methoxy-6-methylisobenzofuran-1(3H)-one [^{13}C]5a (from 4a):

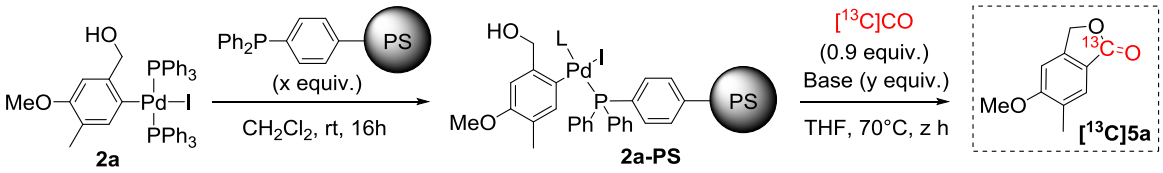


In the chamber 1 of the two-chamber system was added $Ph_2MeSi^{13}COOH$ (8.7 mg, 0.036 mmol, 0.9 eq.). The chamber 1 was sealed with a screwcap fitted with a silicone/PTFE seal. In the chamber 2 of the two-chamber system was added the complex **4a** (32 mg, 0.04 mmol, 1.0 eq.). The chamber 2 was sealed with a screwcap fitted with a silicone/PTFE seal. The atmosphere of the two-chamber system was purged three times with nitrogen. Then, 2 mL of dry THF were added by syringe in each chamber through the silicone/PTFE seal. The loaded two-chamber system was stirred at 40°C, then 6 µL of a solution of TBAF (1M in THF, 6 μmol, 15 mol%) were added through a silicone/PTFE seal in the chamber 1. The system was stirred at 40°C for 16 hours. After a careful opening, the crude reaction mixture from chamber 2 was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (70/30: cyclohexane/ethyl acetate, R_f = 0.4) affording **[^{13}C]5a** (3.2 mg, 0.018 mmol, 50%) as a white solid.

3) Optimisation of the conditions with model complex 2a

The possibility to perform carbonylation reactions with resin-supported arylpalladium complexes was explored by optimising a two-steps sequence model from **2a**, i. e. ligand-exchange with polystyren-bound PPh_3 (PS-*p*C_6H_4-PPh_2), and reaction of the resulting beads with [^{13}C]CO. The first set of conditions used for step 1 (3 equivalents of supported triphenylphosphine in dichloromethane for 16h at rt) produced a resin that gave a promising yield of 38% of **[^{13}C]5a** in step 2 (Table, entry 1). Increasing the amount of the supported ligand likely favoured the ligand exchange step, as **[^{13}C]5a** was isolated in 53% yield when 10 equivalents of PS-*p*C_6H_4-PPh_2 was employed (Table, entry 3). Using this stoichiometry, the effect of the base on the carbonylation step was explored. Employing DABCO instead of K_2CO_3 lead to a similar yield of 53% (Table, entry 4), but the best result was obtained without the addition of any base (60% of **[^{13}C]5a**, Table 1, entry 5). Finally, 1h at 70°C proved to be the optimised reaction time for the carbonylation with [^{13}C]CO. Indeed, only 25% of **[^{13}C]5a** was

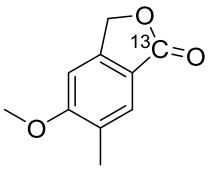
obtained after 30 min of reaction (Table, entry 6), and no yield increased was observed after a prolonged time of 2h (58% yield of **[^{13}C]5a**, Table, entry 7). In all cases, it should be noted that ^{1}H and ^{13}C NMR analyses showed excellent purities for all the resulting samples of **[^{13}C]5a** with a simple filtration and evaporation of the mixture at the end of step 2. (See section 6-c).



Entry	x (equiv.)	Base (y equiv.)	z (h)	Yield[b] (%)
1	3	K_2CO_3 (1.5 equiv)	1	38
2	5	K_2CO_3 (1.5 equiv)	1	40
3	10	K_2CO_3 (1.5 equiv)	1	53
4	10	DABCO[c] (1.5 equiv)	1	53
5	10	-	1	60
6	10	-	0.5	25
7	10	-	2	58

*Table : Optimisation of the conditions for the preparation of lactone **5a** from supported arylpalladium complexes. Step 1: **2a** (0.025 mmol), polymer-bound triphenylphosphine (3 mmol/g, x equiv.) in CH_2Cl_2 (1 mL) at rt for 16h. The resin was filtered, washed with CH_2Cl_2, and dried under vacuum before being engaged in the next step. Step 2: **2a–PS**, [^{13}C]CO from [^{13}C]SilaCOgen (0.9 equiv.), base (y equiv.) in THF (1 mL) at 70 °C for 1 h. [b]Yield of product **[^{13}C]5a** (based on [^{13}C]CO) after filtration through a syringe filter, and confirmed to be pure by ^{1}H NMR analysis of the residue after evaporation. [c]DABCO: 1,4-diazabicyclo[2.2.2]octane.*

1-[^{13}C]-5-Methoxy-6-methylisobenzofuran-1(3*H*)-one [^{13}C]5a :



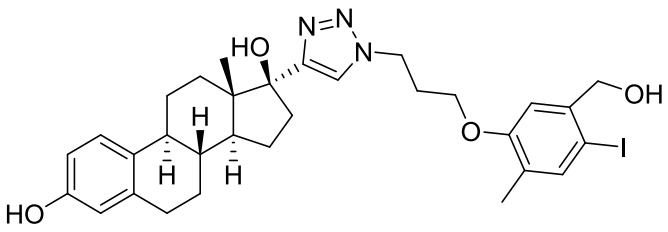
Under inert atmosphere, to a solution of **2a** (136 mg, 0.15 mmol, 1.0 eq.) in CH_2Cl_2 (6 mL) was added triphenylphosphine polymer-bound (100-200 mesh, extent of labelling: ~3 mmol/g) (678 mg, 1.5 mmol, 10.0 eq.) and the reaction mixture was stirred at room temperature for 16 h. The supported complex was filtered, washed with dichloromethane, and dried under vacuum for 4 hours to give **2a–PS**. The filtrate was evaporated and the complex conversion was controlled by ^{31}P NMR analysis of the residue. In the chamber 1 of the two-chamber system was added $Ph_2MeSi^{13}COOH$ (5.5 mg, 0.0225 mmol, 0.9 eq.). The chamber 1 was sealed with a screwcap fitted with a silicone/PTFE seal. In the chamber 2 of the two-chamber system was added the supported complex **2a–PS** (113 mg, 0.0025 mmol, 1.0 eq.). The chamber 2 was sealed with a screwcap fitted with a silicone/PTFE seal. The atmosphere of the two-chamber system was purged three times with nitrogen. Then, 1 mL of dry THF was added by syringe in each chamber through the silicone/PTFE seal. The loaded two-chamber system was stirred at 70°C, then 4 µL of a solution of TBAF (1M in THF, 4 μmol, 15 mol%) were added through a silicone/PTFE seal in the chamber 1. The system was stirred at 70°C for 1 hour. After a careful opening, the crude reaction mixture from chamber 2 was filtered, washed and concentrated under reduced pressure affording without further purification the product **[^{13}C]5a** as a white powder (2.4 mg, 0.013 mmol, 60%). **^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm):** 7.65 (s, 1H), 6.84 (s, 1H), 5.23 (s, 2H), 3.92 (s, 3H),

2.27 (s, 3H). **^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm):** 171.4 (^{13}C-enriched), 163.2, 147.5, 129.1, 127.1, 117.9, 102.5, 69.2, 55.9, 16.8. The spectral data was in accordance with the literature.[2]

4) ^{13}C-carbonylation reactions

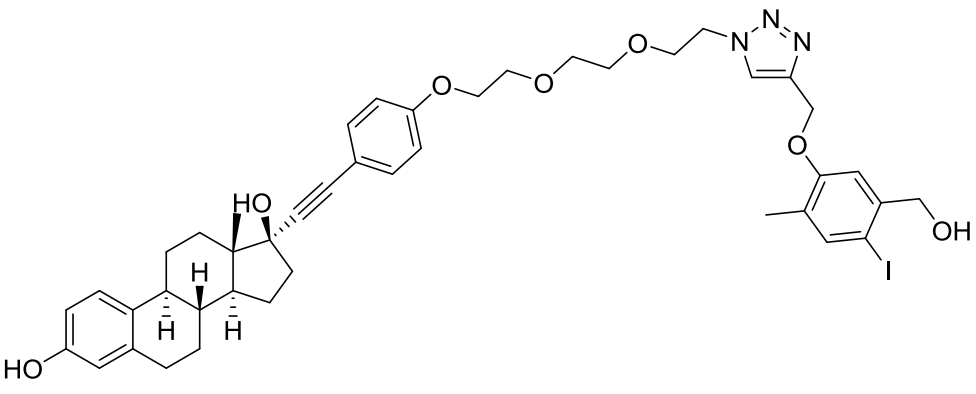
*a. Syntheses of substrates **1b**, **1c** and **1d***

17-(1-(3-(5-(Hydroxymethyl)-4-iodo-2-methylphenoxy)propyl)-1*H*-1,2,3-triazol-4-yl)-estradiol 1b:



Under inert atmosphere, ethynylestradiol (500 mg, 1.7 mmol, 1.0 eq.) was dissolved in 13.6 mL of *t*BuOH/H_2O (3/1). The azido *o*-IBA tag[2] (650 mg, 1.87 mmol, 1.1 eq.), pentahydrate copper sulphate (42 mg, 0.17 mmol, 0.01 eq.) and sodium ascorbate (337 mg, 1.7 mmol, 1.0 eq.) were then added successively. The mixture was stirred at 40°C for 16 hours. The crude reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (80/20: Ethyl Acetate/Cyclohexane, R_f = 0.4) affording **1b** (733.6 mg, 1.14 mmol, 67%) as a white powder. **^{1}H NMR (400 MHz, MeOD) δ (ppm):** 7.77 (s, 1H), 7.52 (s, 1H), 6.98 (s, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 6.52 (dd, *J* = 8.5 Hz, *J* = 2.5 Hz, 1H), 6.45 (d, *J* = 2.5 Hz, 1H), 4.66 (t, *J* = 6.6 Hz, 2H), 4.38 (s, 2H), 3.99-3.89 (m, 2H), 2.76-2.72 (m, 2H), 2.48-2.40 (m, 3H), 2.20 (s, 3H), 2.08-2.05 (m, 1H), 1.97-1.84 (m, 3H), 1.72-1.66 (m, 1H), 1.54-1.44 (m, 3H), 1.38-1.37 (m, 2H), 1.19-1.13 (m, 1H), 1.00 (s, 3H), 0.59-0.52 (m, 1H). **^{13}C NMR (100.2 MHz, MeOD) δ (ppm):** 158.7, 155.9, 155.1, 143.2, 141.3, 138.8, 132.5, 129.0, 127.2, 124.7, 116.1, 113.7, 111.9, 85.8, 83.1, 69.2, 65.4, 49.6, 48.3, 48.1, 44.8, 41.0, 38.3, 34.4, 30.8, 30.7, 28.7, 27.4 24.6, 15.7, 14.8. **HRMS (ESI/TOF+)** $C_{31}H_{38}N_3O_4I$ $[M+H]^+$ calculated 644.1979 found 644.1999.

17-((4-(2-(2-(2-(4-((5-(Hydroxymethyl)-4-iodo-2-methylphenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)phenyl)ethynyl)-estradiol 1c:



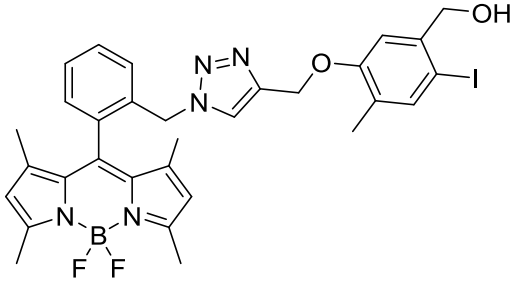
Under an inert atmosphere, 4-iodophenol (215 mg, 1 mmol, 1.0 eq.) was dissolved in 2.5 mL of DMF. 2-(2-(2-azidoethoxy)ethoxy)ethyl 4-

methylbenzenesulfonate[3] (361 mg, 1.1 mmol, 1.1 eq.) and K_2CO_3 (279 mg, 1.8 mmol, 1.8 eq.) were then added to the flask. The mixture was stirred at 70°C for 16 hours. Water was then added and the mixture extracted three times with diethylether. The combined organic layers were washed with water and dried with $MgSO_4$. The solvent was removed under reduced. The residue was purified by silica gel flash chromatography (70/30: cyclohexane/ethyl acetate, R_f = 0.6) affording the desired compound 2-(2-(2-azidoethoxy)ethoxy)ethyl-4-iodophenolate (187 mg, 0.49 mmol, 49%) as a colorless oil. **^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm):** 7.57-7.52 (m, 2H), 6.72-6.67 (m, 2H), 4.11-4.08 (m, 2H), 3.87-3.84 (m, 2H), 3.75-3.72 (m, 2H), 3.70-3.66 (m, 4H), 3.40-3.37 (m, 2H). **^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm):** 158.8, 138.3 (2C), 117.2 (2C), 83.1, 71.1, 70.9, 70.3, 67.9, 50.8. **HRMS (ESI/TOF+)** $C_{12}H_{16}IN_3O_3$ $[M+Na]^+$ calculated 400.0129 found 400.0000. Then, under inert atmosphere, the previous compound (135 mg, 0.36 mmol, 1.0 eq.), ethynylestradiol (93.2 mg, 0.31 mmol, 0.9 eq.), $Pd(PPh_3)_4$ (8.5 mg, 7.4 µmol, 0.02 eq.) and CuI (2.9 mg, 15 µmol, 0.04 eq.) were dissolved in 2.0 mL of THF. Then 2.0 mL of Et_3N was added and the mixture was stirred 16h at rt. The reaction was monitored by TLC (cyclohexane/ethyl: acetate 50/50). The solvent was quenched with a solution of ammonium chloride (5 mL), extracted with ethyl acetate (2x10 mL), washed with brine (10mL) and dried on $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (50/50: cyclohexane/ethyl acetate, R_f = 0.5) affording the Sonogashira coupling compound (145 mg, 0.26 mmol, 85%) as a colorless oil. **^{1}H NMR (300 MHz, MeOD) δ (ppm):** 7.36-7.31 (m, 2H), 7.08 (d, *J* = 8.5 Hz, 1H), 6.90-6.85 (m, 2H), 6.55 (dd, *J* = 8.5 Hz, *J* = 2.5 Hz, 1H), 6.48 (d, *J* = 2.5 Hz, 1H), 4.11-4.08 (m, 2H), 3.83-3.80 (m, 2H), 3.70-3.67 (m, 2H), 3.65-3.62 (m, 4H), 3.34-3.32 (m, 2H), 2.79-2.69 (m, 2H), 2.38-2.29 (m, 2H), 2.16-1.95 (m, 3H), 1.88-1.74 (m, 4H), 1.45-1.26 (m, 4H), 0.90 (s, 3H). **^{13}C NMR (75.3 MHz, MeOD) δ (ppm):** 160.1, 155.9, 138.8, 133.9 (2C), 132.5, 127.3, 116.9,116.0, 115.7 (2C), 113.7, 92.8, 86.2, 80.8, 71.8, 71.5, 71.1, 70.8, 68.6, 51.7, 51.0, 48.8, 45.2, 41.1, 40.0, 34.4, 30.7, 28.6, 27.8, 23.9, 13.6. **HRMS (ESI/TOF-)** $C_{12}H_{16}IN_3O_3$ [M-H]+ calculated 544.3221 found 544.3259. Finally, under inert atmosphere, the previous compound (78 mg, 0.12 mmol, 1.0 eq.) was dissolved in 2 mL of *t*BuOH/H_2O (3/1). The azido *o*-IBA tag[2] (38.7 mg, 0.136 mmol, 1.1 eq.), pentahydrate copper sulphate (3.1 mg, 0.012 mmol, 0.01 eq.) and sodium ascorbate (24.5 mg, 0.124 mmol, 1.0 eq.) were then added successively. The mixture was stirred at 40°C for 16 hours. The crude reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (70/30: Ethyl Acetate/Cyclohexane, R_f = 0.3) affording **1c** (72.5 mg, 86 µmol, 71%) as a white powder. **^{1}H NMR (400 MHz, MeOD) δ (ppm):** 8.10 (s, 1H), 7.50 (s, 1H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.17 (s, 1H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 6.54 (dd, *J* = 8.5 Hz, *J* = 8.5 Hz, 2H), 6.47 (d, *J* = 8.5 Hz, 2H), 5.11 (s, 2H), 4.58-4.56 (m, 2H), 4.51 (s, 2H), 4.06-4.02 (m, 2H), 3.88-3.86 (m, 2H), 3.74-3.72 (m, 2H), 3.61 (s, 4H), 2.80-2.76 (m, 2H), 3.37-2.30 (m, 2H), 2.15-2.13 (m, 1H),

[3] S. Eising, F. Lelivelt, K. Bonger *Angew. Chem. Int. Ed.* **2016**, *55*, 12243-12247.

2.08 (m, 3H), 1.89-1.77 (m, 4H), 1.45-1.29 (m, 5H), 0.91 (s, 3H). **^{13}C NMR (100.2 MHz, MeOD) δ (ppm):** 160.1, 158.3, 155.9, 144.7, 143.1, 141.4, 138.8, 133.9 (2C), 132.5, 129.3, 127.3, 126.2, 116.9, 116.0, 115.6 (2C), 113.7, 112.6, 92.9, 86.3, 86.2, 80.9, 74.8, 71.7, 71.4, 70.7, 70.3, 69.3, 68.6, 62.5, 51.5, 51.1, 45.2, 41.2, 40.0, 34.4, 30.8, 28.7, 27.8, 23.9, 15.7, 13.6. **HRMS (ESI/TOF+)** $C_{43}H_{50}IN_3O_7$ $[M+Na]^+$ calculated 870.2609 found 870.2590.

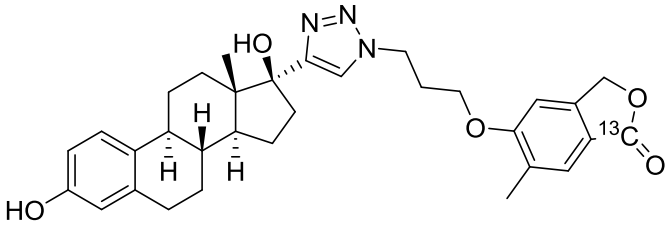
(5-((1-(2-(5,5-difluoro-1,3,7,9-tetramethyl-5H-4l4,5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-10-yl)benzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2-iodo-4-methylphenyl)methanol 1d:



Under inert atmosphere, Azido-BODIPY[4] (91 mg, 0.24 mmol, 1.0 eq.) was dissolved in 4 mL of *t*BuOH/H_2O (3/1). The azido *o*-IBA tag[2] (79 mg, 0.26 mmol, 1.1 eq.), pentahydrate copper sulphate (6.0 mg, 0.024 mmol, 0.01 eq.) and sodium ascorbate (48 mg, 0.24 mmol, 1.0 eq.) were then added successively. The mixture was stirred at 40°C for 16 hours. The crude reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (Gradient: 90/10: Cyclohexane/Ethyl Acetate, R_f = 0 then 50/50: Cyclohexane/Ethyl Acetate, R_f = 0.3) affording **1d** (120 mg, 0.18 mmol, 73%) as an orange powder. **^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm):** 7.53-7.51 (m, 4H), 7.29-7.26 (m, 1H), 7.24 (s, 1H), 7.08 (s, 1H), 5.95 (s, 2H), 5.39 (s, 2H), 5.08 (s, 2H), 4.60 (s, 2H), 2.61 (br s, 1H), 2.55 (s, 6H), 2.12 (s, 3H), 1.23 (s, 6H). **^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm):** 157.0, 156.7, 143.7, 143.1, 141.4, 140.6, 138.2, 135.0, 134.0, 132.5, 130.9, 130.6, 130.3, 129.8, 128.9, 128.8, 123.9, 121.8, 112.0, 86.1, 77.4, 69.2, 61.9, 51.6, 41.1, 15.7, 14.8, 14.0. **HRMS (ESI/TOF+)** $C_{31}H_{31}BF_2IN_5O_2$ $[M+Na]^+$ calculated 704.1475, found 704.1485.

b. ^{13}C-carbonylation reactions

[^{13}C]-17-[1-(3-((6-Methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)oxy)propyl)-1*H*-1,2,3-triazole-4-yl]-estradiol [^{13}C]5b :

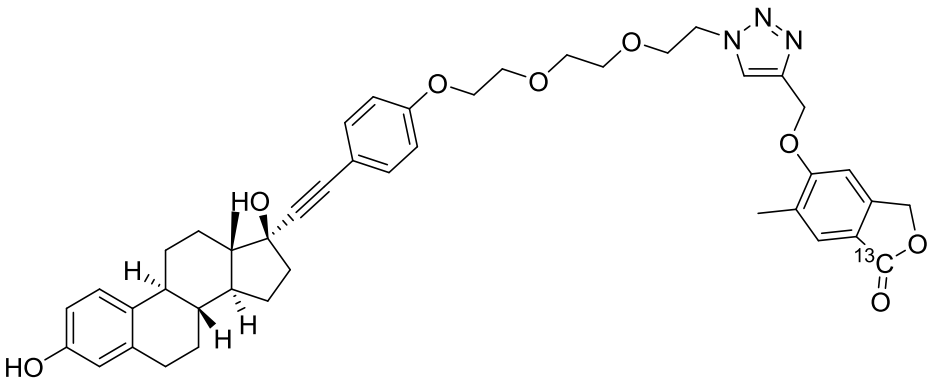


Under inert atmosphere, the bioconjugated substrate **1b** (16.0 mg, 0.025 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (29.0 mg, 0.025 mmol, 1.0 eq.) freshly prepared were dissolved in THF degassed (1 mL). The reaction mixture was stirred 1 hour. The formation of the bioconjugated complex was controlled by ^{31}P NMR. Then the complex in solution was transferred by cannula in a round-bottom flask under nitrogen containing the triphenylphosphine polymer-bound (100-200 mesh, extent of labelling: ~3 mmol/g)

[4] M. del Río, F. Lobo, C. Lopez, A. Oliden, J. Bañuelos, I. Lopez-Arbeloa, I. Garcia-Moreno, A. Gomez *J. Org. Chem.* **2017**, 82, 1240-1247.

(113 mg, 0.25 mmol, 10.0 eq.) and the reaction mixture was stirred at room temperature for 16 h. The supported complex was filtered, washed with dichloromethane and methanol, and dried under vacuum for 4 hours to give **2b–PS**. The filtrate was evaporated and the presence of PPh_3 was controlled by ^{31}P NMR. Finally, in the chamber 1 of the two-chamber system was added $Ph_2MeSi^{13}COOH$ (5.5 mg, 0.0225 mmol, 0.9 eq.). The chamber 1 was sealed with a screwcap fitted with a silicone/PTFE seal. In the chamber 2 of the two-chamber system was added the supported complex **2b–PS** (121 mg, 0.025 mmol, 1.0 eq.). The chamber 2 was sealed with a screwcap fitted with a silicone/PTFE seal. The atmosphere of the two-chamber system was purged three times with nitrogen. Then, 1 mL of dry THF was added by syringe in each chamber through the silicone/PTFE seal. The loaded two-chamber system was stirred at 70°C, then 5 µL of a solution of TBAF (1M in THF, 5 μmol, 15 mol%) were added through a silicone/PTFE seal in the chamber 1. The system was stirred at 70°C for 1 hour. After a careful opening, the crude reaction mixture from chamber 2 was filtered on sintered glass, washed with methanol and concentrated under reduced pressure affording without further purification the desired product **[^{13}C]5b** as a white powder (5.0 mg, 11.8 μmol, 52%). **^{1}H NMR (400MHz, MeOD) δ (ppm):** 7.78 (s, 1H), 7.59-7.58 (m, 1H), 6.99 (s, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.51 (dd, *J* = 8.3 Hz, *J* = 2.7 Hz, 1 H), 6.45 (d, *J* = 2.7 Hz, 1H), 5.10-4.95 (m, 2H), 4.72-4.68 (m, 2H), 4.05-3.96 (m, 2H), 2.68-2.67 (m, 2H), 2.54-2.50 (m, 2H), 2.49-2.48 (m, 1H), 2.34 (s, 3H), 2.10-2.01 (m, 1H), 1.96-1.79 (m, 4H), 1.62-1.47 (m, 3H), 1.45-1.26 (m, 5H), 0.99 (s, 3H), 0.54-0.49 (m, 1H). **^{13}C NMR (100.2 MHz, MeOD) δ (ppm):** 173.6 (^{13}C-enriched), 163.7, 156.0, 155.0, 138.7, 132.2, 130.2, 127.5, 127.4, 126.9, 124.8, 118.7, 116.1, 113.8, 104.9, 83.0, 70.8, 65.9, 48.3, 47.8, 44.9, 40.9, 38.3, 34.4, 30.8, 30.6, 30.5, 28.6, 27.3, 24.5, 16.8, 14.5. **HRMS (ESI/TOF+)** $C_{31}{}^{13}CH_{37}N_5O_6$ $[M+H]^+$ calculated 545.2888, found 545.2881.

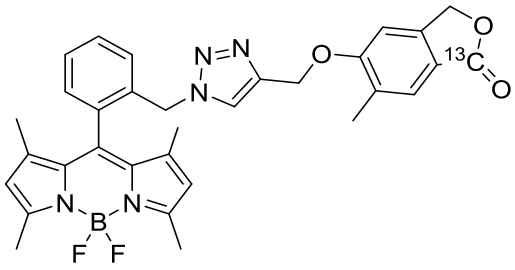
[^{13}C]-17-((4-(2-(2-(2-(4-((6-Methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)phenyl)ethynyl)-estradiol [^{13}C]5c :



Under inert atmosphere, the bioconjugated substrate **1c** (22 mg, 0.025 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (29.0 mg, 0.025 mmol, 1.0 eq.) freshly prepared were dissolved in THF degassed (1 mL). The reaction mixture was stirred 1 hour. The formation of the bioconjugated complex was controlled by ^{31}P NMR. Then the complex in solution was transferred by cannula in a round-bottom flask under nitrogen

containing the triphenylphosphine polymer-bound (100-200 mesh, extent of labelling: ~3 mmol/g) (113 mg, 0.25 mmol, 10.0 eq.) and the reaction mixture was stirred at room temperature for 16 h. The supported complex was filtered, washed with dichloromethane and methanol, and dried under vacuum for 4 hours to give **2c–PS**. The filtrate was evaporated and the presence of PPh_3 was controlled by ^{31}P NMR. Finally, in the chamber 1 of the two-chamber system was added $Ph_2MeSi^{13}COOH$ (5.5 mg, 0.0225 mmol, 0.9 eq.). The chamber 1 was sealed with a screwcap fitted with a silicone/PTFE seal. In the chamber 2 of the two-chamber system was added the supported complex **2c–PS** (121.2 mg, 0.025 mmol, 1.0 eq.). The chamber 2 was sealed with a screwcap fitted with a silicone/PTFE seal. The atmosphere of the two-chamber system was purged three times with nitrogen. Then, 1 mL of dry THF was added by syringe in each chamber through the silicone/PTFE seal. The loaded two-chamber system was stirred at 70°C, then 5 µL of a solution of TBAF (1M in THF, 5 μmol, 15 mol%) were added through a silicone/PTFE seal in the chamber 1. The system was stirred at 70°C for 1 hour. After a careful opening, the crude reaction mixture from chamber 2 was filtered on sintered glass, washed with methanol and concentrated under reduced pressure affording without further purification the desired product **[^{13}C]5c** as a white powder (6.6 mg, 8.8 μmol, 41%). **^{1}H NMR (400MHz, MeOD) δ (ppm):** 8.19 (s, 1H), 7.56 (s, 1H), 7.27-7.25 (m, 2H), 7.11 (s, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 6.81-9.79 (m, 2H), 6.53 (dd, *J* = 8.2 Hz, *J* = 2.7 Hz, 1H), 6.47 (d, *J* = 2.7 Hz, 1H), 5.27 (d, *J* = 1.8 Hz, 2H), 5.18 (s, 2H), 4.60-4.58 (m, 2H), 4.05-4.03 (m, 2H), 3.89-3.87 (m, 2H), 3.75-3.73 (m, 2H), 3.63 (s, 4H), 2.79-2.75 (m, 2H), 2.37-2.33 (m, 2H), 2.20 (s, 3H), 2.12-1.95 (m, 3H), 1.89-1.75 (m, 4H), 1.45-1.29 (m, 5H), 0.91 (s, 3H). **^{13}C NMR (100.2 MHz, MeOD) δ (ppm):** 173.6 (^{13}C-enriched), 163.3, 160.1, 155.9, 149.7, 149.6, 144.0, 138.8, 133.9 (2C), 132.5, 127.6, 127.5, 127.3, 126.5, 117.0, 116.0, 115.7 (2C), 113.8, 105.5, 105.4, 93.0, 86.1, 80.9, 74.0, 71.6, 71.4, 71.0, 70.7, 70.3, 68.7, 63.0, 51.5, 51.1, 45.2, 41.2, 40.0, 34.4, 30.8, 28.7, 27.8, 23.9, 16.9, 13.5. **HRMS (ESI/TOF+)** $C_{43}{}^{13}CH_{49}N_3O_8$ $[M+H]^+$ calculated 749.5825, found 749.5845.

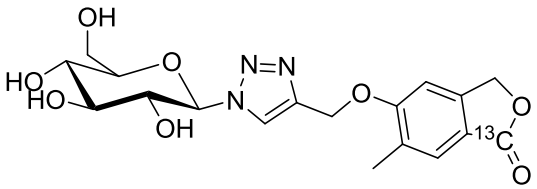
[^{13}C]-5-((1-(2-(5,5-Difluoro-1,3,7,9-tetramethyl-5*H*-4l4,5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]-diaza-borinin-10-yl)benzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-6-methylisobenzofuran-1(3*H*)-one [^{13}C]5d :



Under inert atmosphere, the bioconjugated substrate **1d** (17.0 mg, 0.025 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (29.0 mg, 0.025 mmol, 1.0 eq.) freshly prepared were dissolved in THF degassed (1 mL). The reaction mixture was stirred 1 hour. The formation of the bioconjugated complex was controlled by ^{31}P NMR. Then the complex in solution was transferred by cannula in a round-bottom flask under nitrogen containing the triphenylphosphine polymer-bound (100-200 mesh, extent of labelling: ~3 mmol/g) (113 mg, 0.25 mmol, 10.0 eq.) and the reaction mixture was stirred at room temperature for 16 h. The supported complex was filtered, washed with dichloromethane and methanol, and dried under vacuum for 4 hours to give **2d–PS**. The filtrate was evaporated and the

presence of PPh_3 was controlled by ^{31}P NMR. Finally, in the chamber 1 of the two-chamber system was added $Ph_2MeSi^{13}COOH$ (5.5 mg, 0.0225 mmol, 0.9 eq.). The chamber 1 was sealed with a screwcap fitted with a silicone/PTFE seal. In the chamber 2 of the two-chamber system was added the supported complex **2d–PS** (120.8 mg, 0.025 mmol, 1.0 eq.). The chamber 2 was sealed with a screwcap fitted with a silicone/PTFE seal. The atmosphere of the two-chamber system was purged three times with nitrogen. Then, 1 mL of dry THF was added by syringe in each chamber through the silicone/PTFE seal. The loaded two-chamber system was stirred at 70°C, then 5 µL of a solution of TBAF (1M in THF, 5 μmol, 15 mol%) were added through a silicone/PTFE seal in the chamber 1. The system was stirred at 70°C for 1 hour. After a careful opening, the crude reaction mixture from chamber 2 was filtered on sintered glass, washed with methanol and concentrated under reduced pressure affording without further purification the desired product **[^{13}C]5d** as a white powder (5.3 mg, 9.1 μmol, 41%). **^{1}H NMR (400MHz, $CDCl_3$) δ (ppm):** 7.65 (s, 1H), 7.56-7.49 (m, 3H), 7.30-7.28 (m, 1H), 7.01 (s, 1H), 5.94 (s, 2H), 5.40 (s, 2H), 5.20 (s, 1H), 5.16 (s, 2H), 2.56 (s, 6H), 2.24 (s, 3H), 1.22 (s, 6H). **^{13}C NMR (100.2 MHz, $CDCl_3$) δ (ppm):** 171.3 (^{13}C-enriched), 161.7, 156.6, 147.4, 143.1, 138.2, 134.1, 132.3, 130.9, 130.8, 130.3, 129.9, 129.4, 129.0, 127.3, 124.1, 121.8, 118.2, 117.7, 104.0, 69.3, 62.2, 51.8, 32.1, 29.9, 29.5, 29.3, 22.8, 16.9, 14.8, 14.0, 1.2. **HRMS (ESI/TOF+)** $C_{31}H_{30}BF_2N_5O_3$ $[M+Na]^+$ calculated 605.2339, found 605.2355.

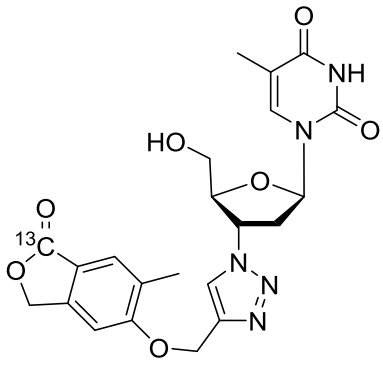
[^{13}C]-α-D-1-Desoxy-1[4-(((6-methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)oxy)methyl)-1*H*-1,2,3-triazole-1-yl]-glucopyranose [^{13}C]5e:



Under inert atmosphere, the bioconjugated substrate **1e** (12.6 mg, 0.025 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (29.0 mg, 0.025 mmol, 1.0 eq.) freshly prepared were dissolved in THF degassed (1 mL). The reaction mixture was stirred 1 hour. The formation of the bioconjugated complex was controlled by ^{31}P NMR. Then the complex in solution was transferred by cannula in a round-bottom flask under nitrogen containing the triphenylphosphine polymer-bound (100-200 mesh, extent of labelling: ~3 mmol/g) (113 mg, 0.25 mmol, 10.0 eq.) and the reaction mixture was stirred at room temperature for 16 h. The supported complex was filtered, washed with dichloromethane and methanol, and dried under vacuum for 4 hours to give **2e–PS**. The filtrate was evaporated and the presence of PPh_3 was controlled by ^{31}P NMR. Finally, in the chamber 1 of the two-chamber system was added $Ph_2MeSi^{13}COOH$ (5.5 mg, 0.0225 mmol, 0.9 eq.). The chamber 1 was sealed with a screwcap fitted with a silicone/PTFE seal. In the chamber 2 of the two-chamber system was added the supported complex **2e–PS** (119 mg, 0.025 mmol, 1.0 eq.). The chamber 2 was sealed with a screwcap fitted with a silicone/PTFE seal. The atmosphere of the two-chamber system was purged three times with nitrogen. Then, 1 mL of dry THF was added by syringe in each chamber through the silicone/PTFE seal. The loaded two-chamber system was stirred at 70°C, then 5 µL of a solution of TBAF (1M in THF, 5 μmol, 15 mol%) were added through a silicone/PTFE seal in the chamber 1. The system was stirred at 70°C for 1 hour. After

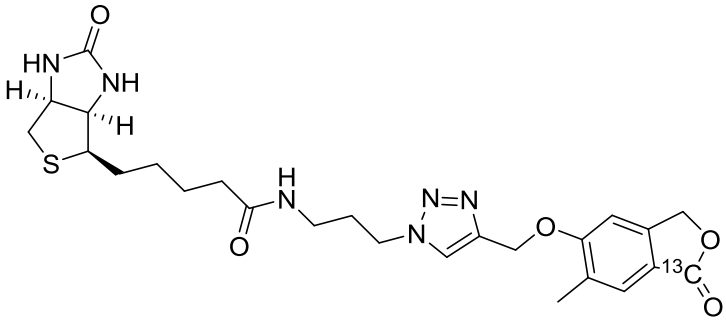
a careful opening, the crude reaction mixture from chamber 2 was filtered on sintered glass, washed with methanol and concentrated under reduced pressure affording without further purification the desired product **[^{13}C]5e** as a white powder (4.1 mg, 10.0 μmol, 45%). **^{1}H NMR (400MHz, $CDCl_3$) δ (ppm):** 8.37 (s, 1H), 7.63-7.62 (m, 1H), 7.32 (s, 1H), 5.64 (d, *J* = 9.2 Hz, 1H), 5.35 (s, 2H), 5.32 (d, *J* = 1.8 Hz, 2H), 3.96-3.86 (m, 2H), 3.74-3.68 (m, 1H), 3.61-6.46 (m, 3H), 2.27 (s, 3H). **^{13}C NMR (100.2 MHz, $CDCl_3$) δ (ppm):** 173.6 (^{13}C-enriched). The spectral data was in accordance with the literature.[2]

[^{13}C]-3'-Desoxy-3'-[4-(((6-methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)oxy)methyl)-1*H*-1,2,3-triazole-1-yl]-thymidine [^{13}C]5f :



Under inert atmosphere, the bioconjugated substrate **1f** (14.2 mg, 0.025 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (29.0 mg, 0.025 mmol, 1.0 eq) freshly prepared were dissolved in THF degassed (1 mL). The reaction mixture was stirred 1 hour. The formation of the bioconjugated complex was controlled by ^{31}P NMR. Then the complex in solution was transferred by cannula in a round-bottom flask under nitrogen containing the triphenylphosphine polymer-bound (100-200 mesh, extent of labelling: ~3 mmol/g) (113 mg, 0.25 mmol, 10.0 eq.) and the reaction mixture was stirred at room temperature for 16 h. The supported complex was filtered, washed with dichloromethane and methanol, and dried under vacuum for 4 hours to give **2f–PS**. The filtrate was evaporated and the presence of PPh_3 was controlled by ^{31}P NMR. Finally, in the chamber 1 of the two-chamber system was added $Ph_2MeSi^{13}COOH$ (5.5 mg, 0.0225 mmol, 0.9 eq.). The chamber 1 was sealed with a screwcap fitted with a silicone/PTFE seal. In the chamber 2 of the two-chamber system was added the supported complex **2f–PS** (121.6 mg, 0.025 mmol, 1.0 eq.). The chamber 2 was sealed with a screwcap fitted with a silicone/PTFE seal. The atmosphere of the two-chamber system was purged three times with nitrogen. Then, 1 mL of dry THF was added by syringe in each chamber through the silicone/PTFE seal. The loaded two-chamber system was stirred at 70°C, then 5 µL of a solution of TBAF (1M in THF, 5 μmol, 15 mol%) were added through a silicone/PTFE seal in the chamber 1. The system was stirred at 70°C for 1 hour. After a careful opening, the crude reaction mixture from chamber 2 was filtered on sintered glass, washed with methanol and concentrated under reduced pressure affording the desired product **[^{13}C]5f** as a white powder (3.2 mg, 6.8 μmol, 30%) in mixture with triphenylphosphine (4.2 mg, 15.9 μmol,). **^{1}H NMR (400MHz, MeOD) δ (ppm):** 8.17 (s, 1H), 7.88 (s, 1H), 7.61 (s, 1H), 7.23 (s, 1H), 6.50-6.47 (m, 1H), 5.44-5.40 (m, 1H), 5.32 (s, 2H), 5.29 (s, 2H), 4.42-4.41 (m, 1H), 3.95-3.91 (m, 1H), 3.79-3.76 (m, 1H), 2.97-2.91 (m, 1H), 2.73-2.65 (m, 1H), 2.27 (s, 3H), 1.91 (s, 3H). **^{13}C NMR (100.2 MHz, MeOD) δ (ppm):** 173.3 (^{13}C-enriched). The spectral data was in accordance with the literature.[2]

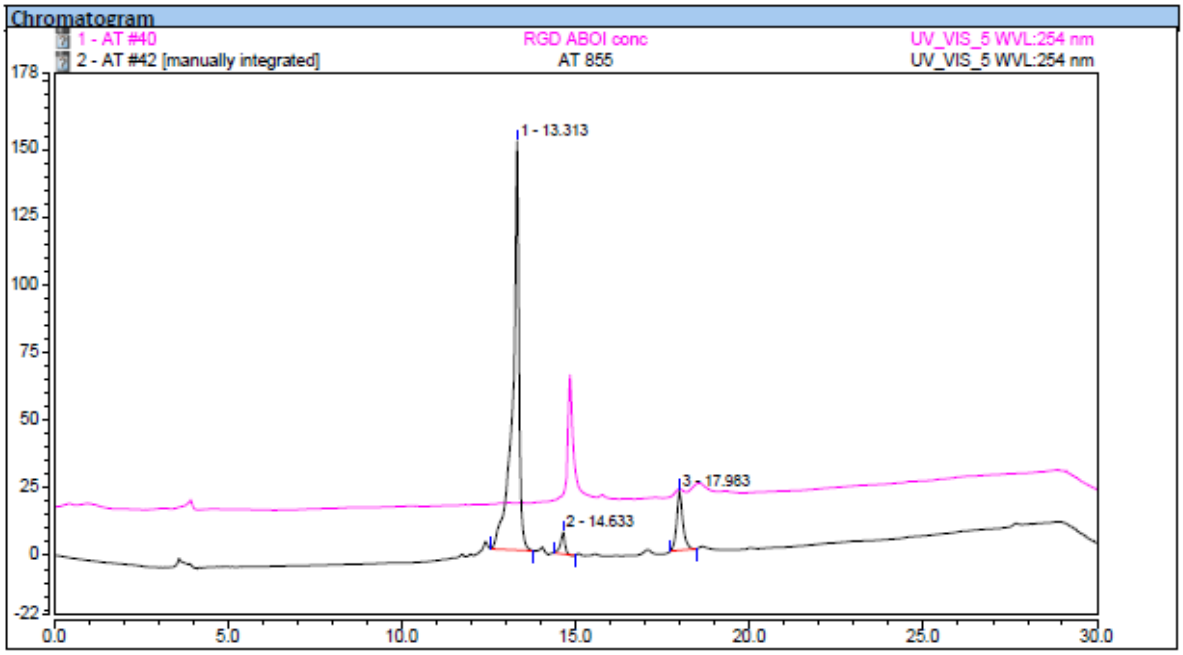
[^{13}C]-*N*-(3-(4-(((6-Methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)propyl)-biotinamide [^{13}C]5g :



Under inert atmosphere, the bioconjugated substrate **1g** (15.7 mg, 0.025 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (29.0 mg, 0.025 mmol, 1.0 eq.) freshly prepared were dissolved in THF degassed (1 mL). The reaction was stirred 1 hour. The formation of the bioconjugated complex was controlled by ^{31}P NMR. Then the complex in solution was transferred by cannula in a round-bottom flask under nitrogen containing the triphenylphosphine polymer-bound (100-200 mesh, extent of labelling: ~3 mmol/g) (113 mg, 0.25 mmol, 10.0 eq.) and the reaction mixture was stirred at room temperature for 16 h. The supported complex was filtered, washed with dichloromethane and methanol, and dried under vacuum for 4 hours to give **2g–PS**. The filtrate was evaporated and presence of PPh_3 was controlled by ^{31}P NMR. Finally, in the chamber 1 of the two-chamber system was added $Ph_2MeSi^{13}COOH$ (5.5 mg, 0.0225 mmol, 0.9 eq.). The chamber 1 was sealed with a screwcap fitted with a silicone/PTFE seal. In the chamber 2 of the two-chamber system was added the supported complex **2g–PS** (119 mg, 0.025 mmol, 1.0 eq.). The chamber 2 was sealed with a screwcap fitted with a silicone/PTFE seal. The atmosphere of the two-chamber system was purged three times with nitrogen. Then, 1 mL of dry THF was added by syringe in each chamber through the silicone/PTFE seal. The loaded two-chamber system was stirred at 70°C, then 5 µL of a solution of TBAF (1M in THF, 5 μmol, 15 mol%) were added through a silicone/PTFE seal in the chamber 1. The system was stirred at 70°C for 1 hour. After a careful opening, the crude reaction mixture from chamber 2 was filtered on sintered glass, washed with methanol and concentrated under reduced pressure affording without further purification the desired product **[^{13}C]5g** as a white powder (3.2 mg, 6.0 μmol, 27%). **^{1}H NMR (400MHz, MeOD) δ (ppm):** 8.17 (s, 1H), 7.62-7.61 (m, 1H), 7.30 (s, 1H), 5.33 (s, 2H), 5.32-5.31 (m, 2H), 4.50-4.45 (m, 3H), 4.32-4.27 (m, 1H), 3.24-3.20 (m, 3H), 2.91 (dd, *J* = 12.9 Hz, *J* = 4.9Hz, 1H), 2.69 (dd, *J* = 12.9 Hz, *J* = 4.9Hz, 1H), 2.27 (s, 3H), 2.21-2.12 (m, 4H), 1.72-1.56 (m, 4H), 1.49-1.39 (m, 2H). **^{13}C NMR (100.2 MHz, MeOD) δ (ppm):** 173.4 (^{13}C-enriched). The spectral data was in accordance with the literature.[2]

[^{13}C]-Cyclo-RGD-[2-(4-(((6-methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)-yl] [^{13}C]5h

Under inert atmosphere, the bioconjugated substrate **1h** (11.6 mg, 0.0125 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol, 1.0 eq.) freshly prepared were dissolved in THF degassed (1 mL) in a NMR tube. The reaction mixture was sonicated 1 hour at 80°C. The formation of the bioconjugated complex was controlled by ^{31}P NMR. Then the complex in solution was transferred by cannula in a round-bottom flask under nitrogen containing the triphenylphosphine polymer-bound (100-200 mesh, extent of labelling: ~3 mmol/g) (56.5 mg, 0.125 mmol, 10.0 eq.) and the reaction mixture was stirred at room temperature for 16 h. The supported complex was filtered, washed with dichloromethane and methanol, and dried under vacuum for 4 hours to give **2h–PS**. The filtrate was evaporated and presence of PPh_3 was controlled by NMR ^{31}P. Finally, in the chamber 1 of the two-chamber system was added $Ph_2MeSi^{13}COOH$ (3.0 mg, 0.012 mmol, 0.9 eq.). The chamber 1 was sealed with a screwcap fitted with a silicone/PTFE seal. In the chamber 2 of the two-chamber system was added the supported complex **2h–PS** (62.9 mg, 0.0125 mmol, 1.0 eq.). The chamber 2 was sealed with a screwcap fitted with a silicone/PTFE seal. The atmosphere of the two-chamber system was purged three times with nitrogen. Then, 1 mL of dry THF was added by syringe in each chamber through the silicone/PTFE seal. The loaded two-chamber system was stirred at 70°C, then 2 µL of a solution of TBAF (1M in THF, 2 μmol, 15 mol%) were added through a silicone/PTFE seal in the chamber 1. The system was stirred at 70°C for 1 hour. After a careful opening, the crude reaction mixture from chamber 2 was filtered on sintered glass, washed with methanol and mixture between acetonitrile and water and concentrated under reduced pressure affording without further purification the desired product **[^{13}C]5h** as a white powder (1.2 mg, 1.4 μmol, 12%). **^{1}H NMR (400MHz, CD_3CN/D_2O) δ (ppm, representative signals):** 7.96 (s, $1H_{triazole}$), 5.26 (s, $2H_{benzylic}$) + others signals. **^{13}C NMR (100.2 MHz, CD_3CN/D_2O) δ (ppm):** 173.6 (^{13}C-enriched). This was in accordance with the literature.[2] The chemical purity was established by analytical UV-HPLC at 254 nm using a reverse phase column (Luna 5µm C18 100Å, 4.6mm*250mm) eluted with acetonitrile (+0.1%TFA) and water (+0.1%TFA) at a flow rate of 1 mL/min (10/90 isocratic for 0-2 min, then gradient to 90/10 for 2-25 min). The retention time of **[^{13}C]5h** was 13.31 min (black chromatogram), whereas the retention time of **[^{13}C]1h** was 14.84 min (pink chromatogram). The chemical purity of **[^{13}C]5h** was measured to 86% (254 nm). It should be noted that the main impurity at 17.98 min is an apolar compound that comes from the starting triphenylphosphine-polymer bound resin despite the thorough washes before use.



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		13.313	32.009	151.038	85.18	83.48	n.a.
2		14.633	1.153	8.097	3.07	4.48	n.a.
3		17.983	4.417	21.784	11.75	12.04	n.a.
Total:			**37.579**	**180.918**	**100.00**	**100.00**	

c. Measurement of the Pd contamination

The Pd contamination was measured for **[^{13}C]5f**. The first sample **(A)** was synthesised using the procedure previously reported with a catalytic amount of Pd-catalyst, and purified by column chromatography.[2] The second sample **(2)** was produced from the supported preformed Pd-complex **2f–PS** and only purified by filtration.

Synthesis of sample **(A)**:

In the chamber 1 of the two-chamber system were added Ph_2MeSi-^{13}COOH (35.6 mg, 0.15 mmol, 1 eq.). The chamber 1 was sealed with a screwcap fitted with a silicone/PTFE seal. In the chamber 2 of the two-chamber system were added successively **1f** (114 mg, 0.2 mmol, 1eq), $Pd(dba)_2$ (11.5 mg, 0.02 mmol, 10 mol%), xantphos (11.5 mg, 0.02 mmol, 10 mol%) and DABCO (44.9 mg, 0.4 mmol, 2 eq.). The chamber 2 was sealed with a screwcap fitted with a silicone/PTFE seal. The atmosphere of the two-chamber system was purged three times with argon. Then, 2 mL of dry THF were added by syringe in each chamber through the silicone/PTFE seal. The loaded two-chamber system was stirred at 70°C, then 15 µL of a solution of TBAF (1M in THF, 0.015 mmol, 10 mol%) were added through the silicone/PTFE seal in the chamber 1. The system was stirred at 70°C for 1 hour. After a careful opening, the crude reaction mixture from chamber 2 was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (97/3: EtOAc/MeOH) affording 76 mg of **[^{13}C]5f** (79% yield, 55.5 mg).

Synthesis of sample **(B)**:

Under an inert atmosphere, the bioconjugated substrate **1f** (14.2 mg, 0.025 mmol, 1.0 eq) and $Pd(PPh_3)_4$ (29.0 mg, 0.025 mmol, 1.0 eq) freshly prepared were dissolved in degassed THF (1 mL). The reaction mixture was stirred 1 hour. The formation of the bioconjugated complex was controlled by ^{31}P NMR. Then the complex in solution was transferred by cannula in round-bottom flask under nitrogen on the triphenylphosphine polymer-bound (100-200 mesh, extent of labelling: ~3 mmol/g) (113 mg, 0.25 mmol, 10.0 eq) and the reaction mixture was stirred at room temperature for 16 h. The supported complex was filtered, washed with dichloromethane and methanol, and dried under vacuum for 4 hours. The filtrate was evaporated and the presence of PPh_3 was controlled by ^{31}P NMR. Finally, in the chamber 1 of the two-chamber system was added Ph_2MeSi^{13}COOH (5.5 mg, 0.0225 mmol, 0.9 eq). The chamber 1 was sealed with a screwcap fitted with a silicone/PTFE seal. In the chamber 2 of the two-chamber system was added the supported complex **2f–PS** (119 mg, 0.025 mmol, 1.0 eq). The chamber 2 was sealed with a screwcap fitted with a silicone/PTFE seal. The atmosphere of the two-chamber system was purged three times with nitrogen. Then, 1 mL of dry THF was added by syringe in each chamber through the silicone/PTFE seal. The loaded two-chamber system was stirred at 110°C, then 5 µL of a solution of TBAF (1M in THF, 5 μmol, 15 mol%) were added through a silicone/PTFE seal in the chamber 1. The system was stirred at 110°C for 1 hour. After a careful

opening, the crude reaction mixture from chamber 2 was filtered on sintered glass, washed with methanol and concentrated under reduced pressure affording **[^{13}C]5f** as a white powder (1.5 mg, 3 μmol, 15%).

Preparation of the samples for ICP-OES analyses:

Each sample (1.6 mg for **(A)** and 1.5 mg for **(B)**) was dissolved in a 1:1 mixture of concentrated hydrochloric acid and nitric acid (1 mL) by stirring at r.t. for 2 hours. Then, each sample was diluted to 10 mL with MilliQ water for the analyses.

Concentrations (mg/L)

Sample	Pd 340.458	Pd 360.955
Blank	0	0
Standard 1		
Standard 2	1	1
Standard 3	2	2
Water	0.029583	0.032313
Water	0.007064	0.006768
(B)	0.232677	0.235901
(B)	0.260242	0.256993
Water	0.008484	0.005082
(A)	0.209048	0.210742
(A)	0.210944	0.207278
Water	0.004302	0.008001
Acid	0.011538	0.009838
Acid	0.006066	0.008944
Water	0.008197	0.005858

Peak Areas

Pd 340.458	Pd 360.955
78.863	82.488
8308.68	5872.28
16994	11896.8
253.141	234.255
62.6859	83.3535
1970.82	1436.88
2203.96	1561.46
74.6976	73.3932
1770.99	1288.26
1787.02	1267.79
39.3265	90.6403
100.523	101.492
54.248	96.207
72.2692	77.9775

Pd contamination was calculated as:

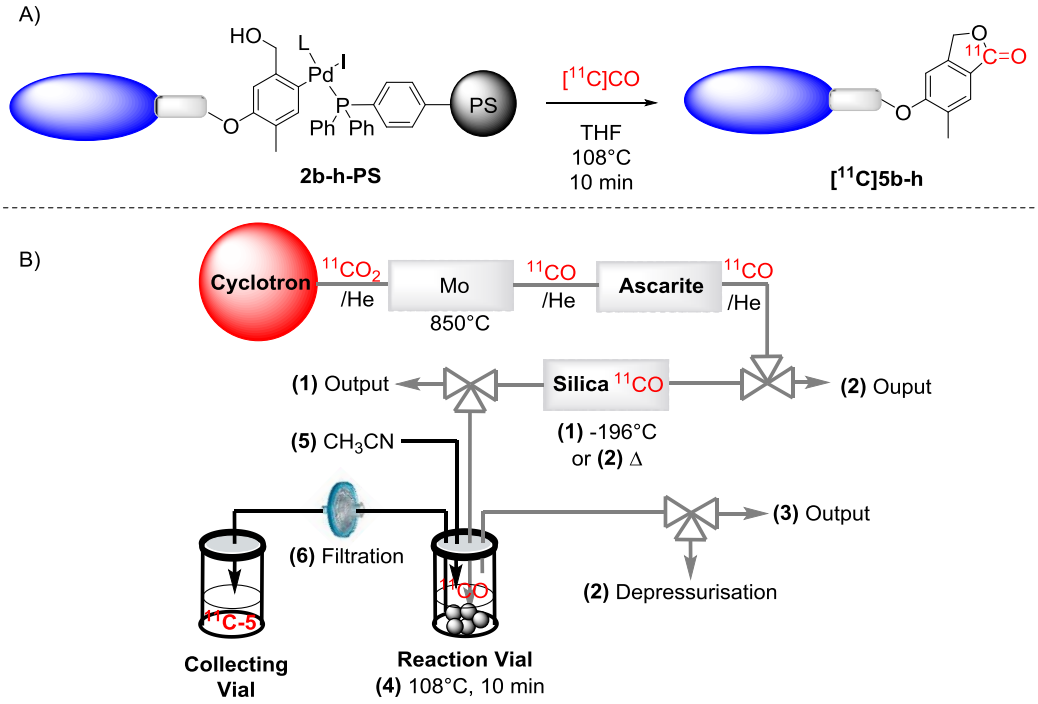
0.246*0.01/1.5=0.16% w/w of Pd for **(B)**

0.21*0.01/1.6=0.13% w/w of Pd for **(A)**

5) ^{11}C-Carbonylation reactions

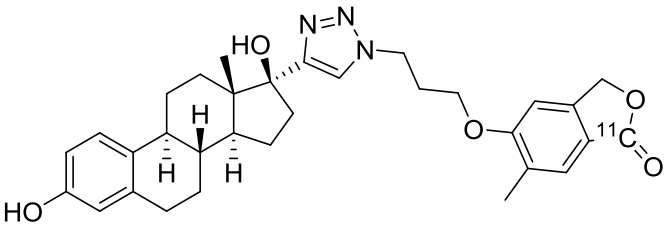
a. General procedure

[^{11}C]Carbon dioxide was produced by the $^{14}N(p,\alpha)^{11}C$ nuclear reaction using a nitrogen gas target (containing 1% oxygen) pressurised to 150 psi and bombarded with 16 MeV protons using the General Electric Medical Systems PETtrace 200 cyclotron. Typically, the irradiation time was ~40 minutes using a 60 μA beam current. After irradiation, [^{11}C]carbon dioxide was trapped and concentrated on 4Å molecular sieves. The trapped [^{11}C]CO_2 was released from molecular sieves in a stream of Helium (30 mL/min) by heating them to 350°C. [^{11}C]CO_2 was reduced on-line to [^{11}C]carbon monoxide after passing through a quartz tube filled with Molybdenum powder heated to 850°C. The produced [^{11}C]carbon monoxide was transferred in the system set-up with a Helium flow (25 mL/min), where it was condensed on a silica gel trap at -196°C. After complete entrapment, the trap was heated in order to release the [^{11}C]CO into the reaction vial (4 mL) previously loaded with the supported complex (45.2 mg, 10 μmol, 1.0 eq.) dissolved in a THF (0.6 mL)], crimped with a microwave cap and depressurised with a syringe (30 mL). The [^{11}C]CO trap was flushed briefly to the reaction vial before disconnection of the Helium low-flow. The vial was stirred for 10 min in an oil bath pre-heated at 108°C. The radioactivity was measured in the reaction vial. Then, the vial was flushed three times with air, and the remaining radioactivity in the vial was measured again. Acetonitrile (5 mL) was added in the vial and the heterogeneous mixture was filtrated through a syringe filter (Acrodisc, 25mm, 1.0 μm glass fiber) in the collecting vial. Trapping efficiency was calculated from the percentage ratio of radioactivity remaining in the reaction vial over the initial radioactivity before the flush. The radiochemical purity (RCP) was established by analytical radio-HPLC using a P680 HPLC pump from Dionex equipped with a 20 μL injection loop connected in series, a variable wavelength UV detector from Dionex (UVD 170U), and a sodium iodide radiodetector of in-house design. Radiochemical conversion (RCC) was obtained by multiplying of the trapping efficiency by the RCP. Radiochemical yield was calculated from the percentage ratio of the decay-corrected radioactivity in the collecting vial over the initial radioactivity in the reaction vial at the end of the reaction (before the air flush). Values are given ± the standard deviation of the n experiments



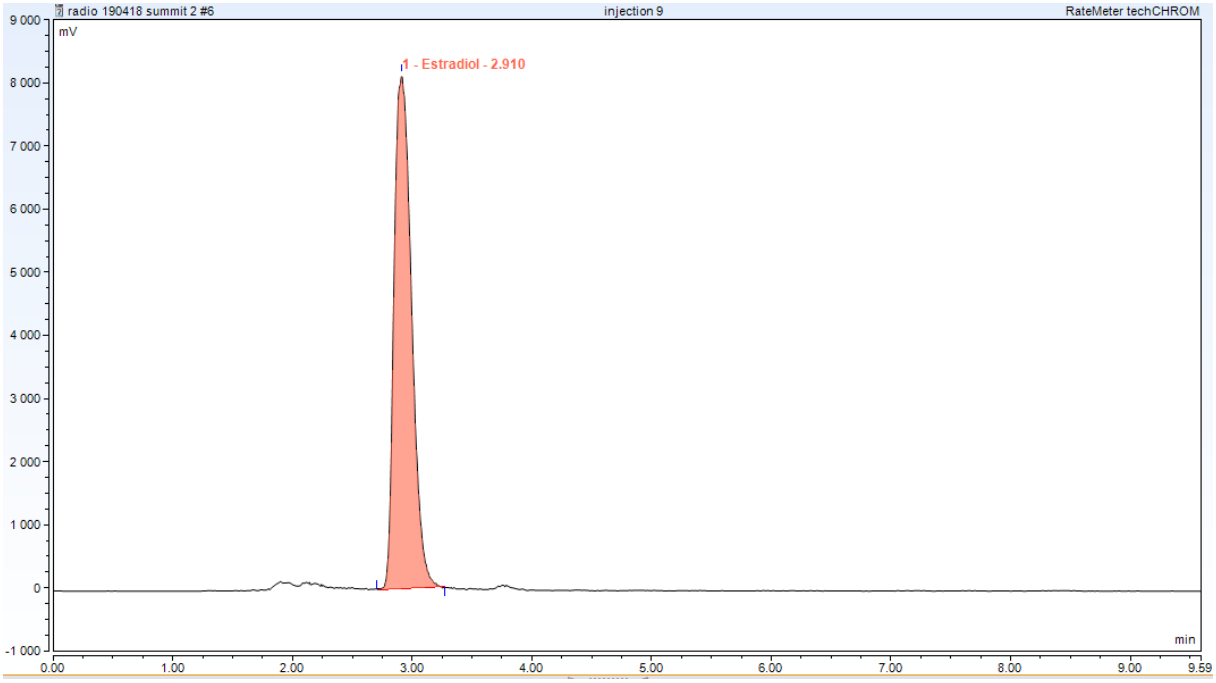
b. [^{11}C]5b

[^{11}C]-17-[1-(3-((6-Methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)oxy)propyl)-1*H*-1,2,3-triazole-4-yl]-estradiol [^{11}C]5b :



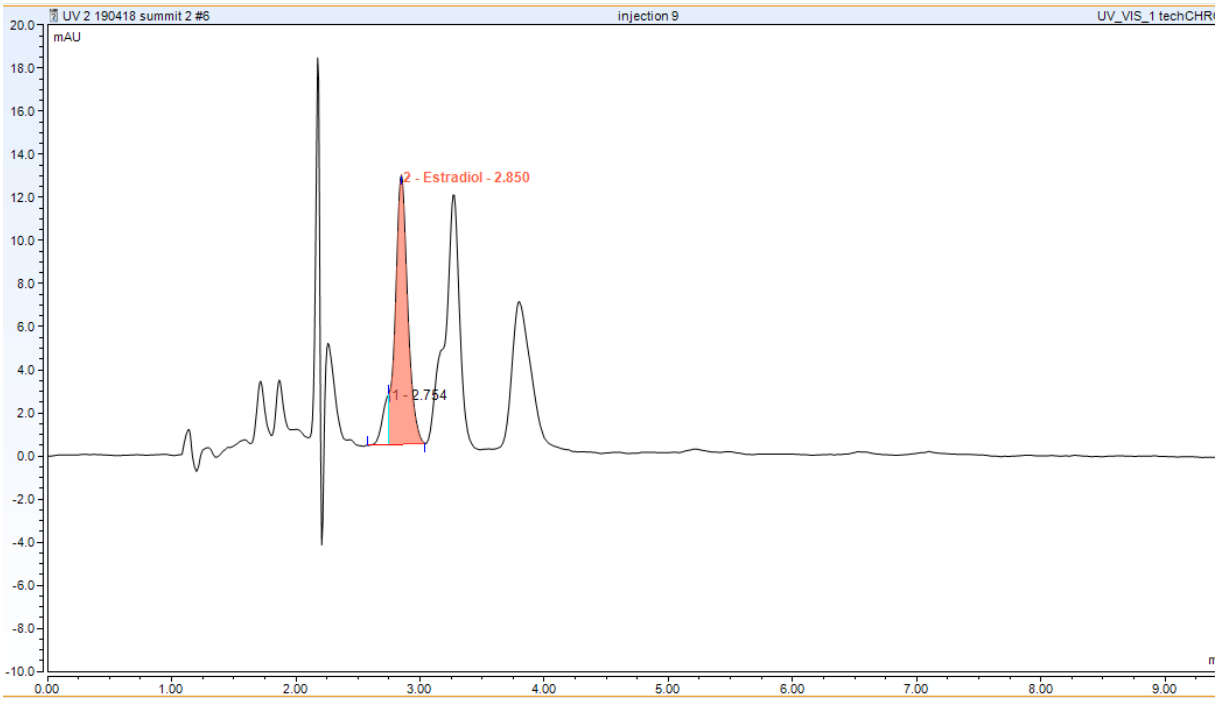
The radiochemical purity (RCP) was established by analytical radio-HPLC using a reverse phase column (Luna 3µ C8 100Å) eluted with acetonitrile and 70mM NaH_2PO_4 (60/40) at a flow rate of 1 mL/min (retention time for radio detection: 2.91 min, retention time for UV detection: 2.85 min). The values for **[^{11}C]5b** were RCP > 98±0%, RCC = 73±11% and RCY = 50±9% (n = 3).

	Exp.	1	2	3
	Bombardment	40 min / 60 µA	53 min / 60 µA	42 min / 60 µA
End of the reaction	**Time (min)**	10	10	10
	Activity in the reaction vial (MBq)	1240.3	1826.0	936.9
After flush of CO	**Time (min)**	11	12	12
	Activity in the reaction vial (MBq)	919.9	1395.2	1040.4
	Trapping efficiency (%)	74	76	57
After filtration	**Time (min)**	14	15	15
	Activity in the collecting vial (MBq)	732.2	912.3	740.8
	Radiochemical purity RCP (%)	>98	>98	>98
	Radiochemical yield RCY (%)	59	50	41



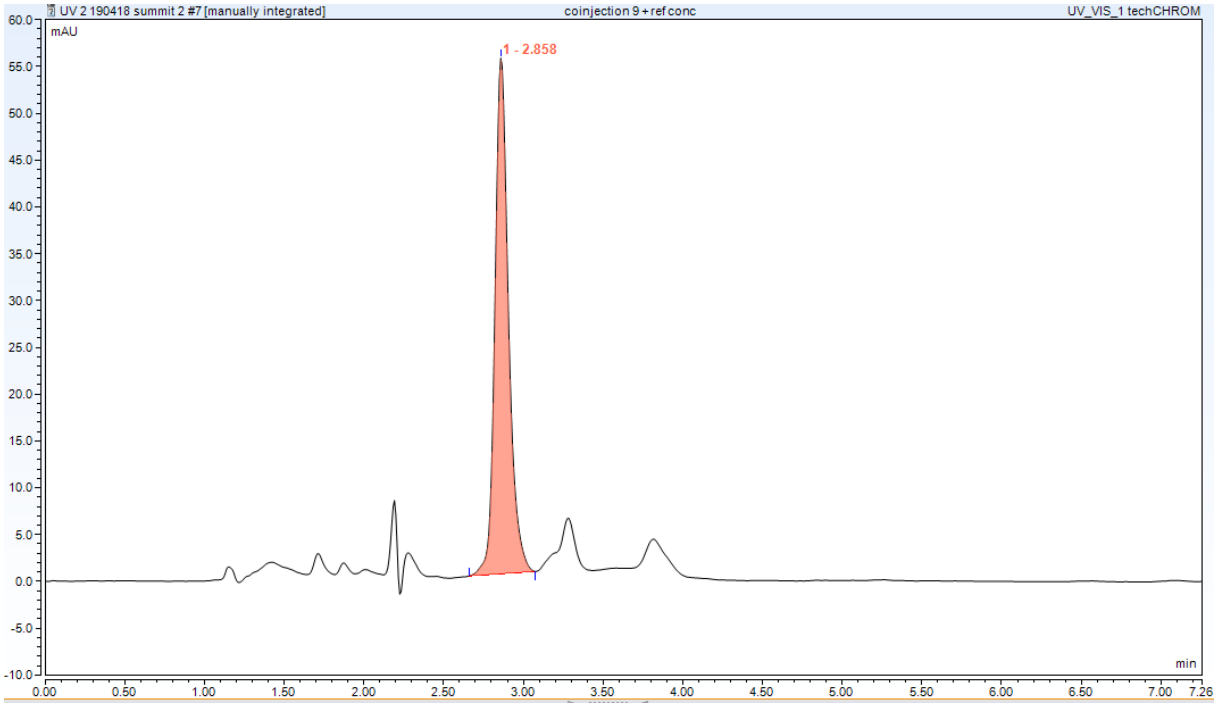
Peak No.	Peak Name	Ret.Time min	Amount	Rel.Area %	Area mV*min	Height mV	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
1	Estradiol	2.910	0.0000	n.a.	1364.9486	8159.90	M	n.a.	n.a.	n.a.	n.a.

Example of radio-chromatogram for the analytical HPLC of **[^{11}C]5b**



Peak No.	Peak Name	Ret.Time min	Amount	Rel.Area %	Area mAU*min	Height mAU	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
1		2.754	0.0000	n.a.	0.1448	2.42	M	n.a.	n.a.	n.a.	n.a.
2	*Estradiol*	*2.850*	*21.2832*	*n.a.*	*1.4135*	*12.52*	*M*	*n.a.*	*n.a.*	*n.a.*	*n.a.*

Example of UV-chromatogram at 220 nm for the analytical HPLC of **[^{11}C]5b**

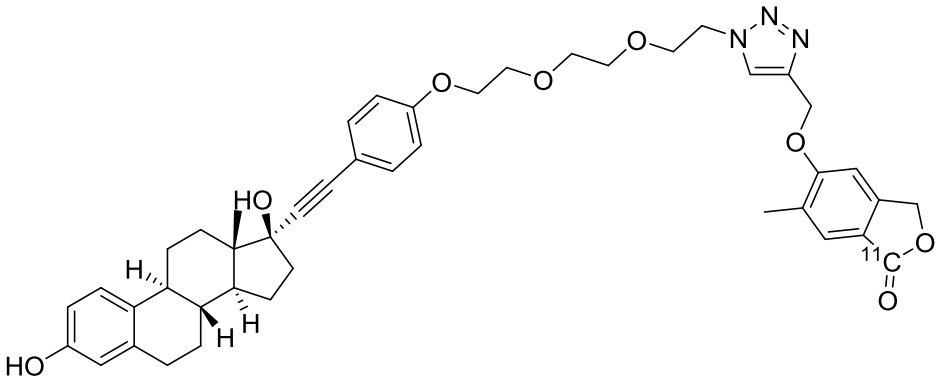


Peak No.	Peak Name	Ret.Time min	Amount n.a.	Rel.Area %	Area mAU*min	Height mAU	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
1		*2.858*	*n.a.*	*100.00*	*5.4068*	*55.11*	*BMB**	*0.086*	*1.28*	*n.a.*	*6156*

Example of UV-chromatogram at 220 nm for the analytical HPLC of **[^{11}C]5b** co-injected with [^{13}**C]5b**

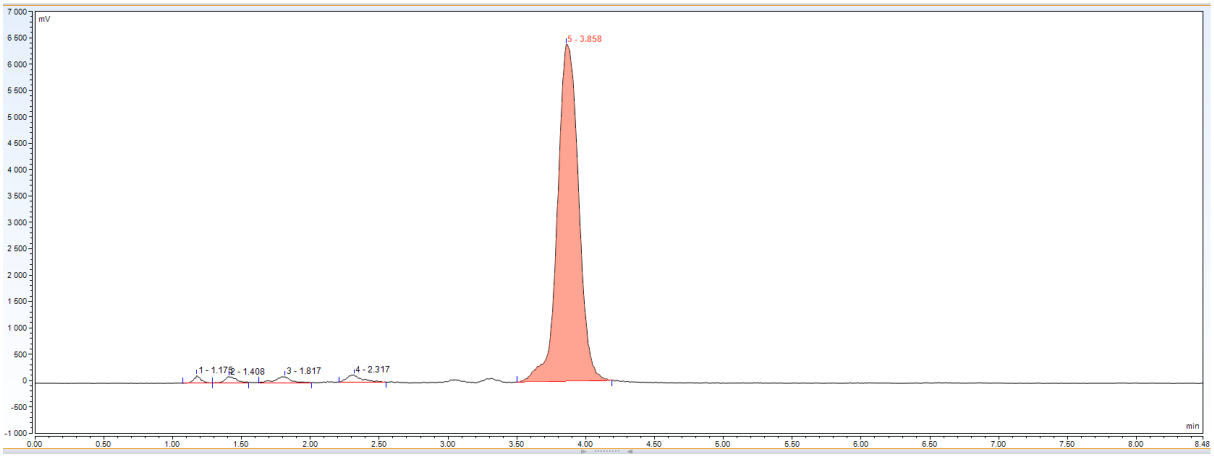
c. [^{11}C]5c

[^{11}C]-17-((4-(2-(2-(2-(4-((6-Methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)phenyl)ethynyl)-estradiol [^{11}C]5c :



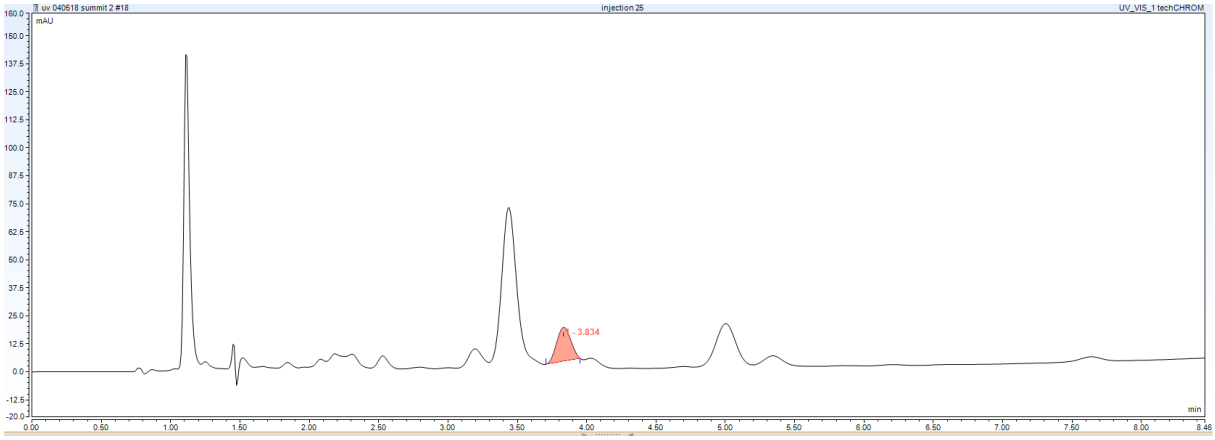
The radiochemical purity (RCP) was established by analytical radio-HPLC using a reverse phase column (Luna 3µ C8 100Å) eluted with acetonitrile and 70mM NaH_2PO_4 (60/40) at a flow rate of 1.5 mL/min (retention time for radio detection: 3.86 min, retention time for UV detection: 3.83 min). The values for **[^{11}C]5c** were RCP = 95±0%, RCC = 86±7% and RCY = 65±5% (n = 2).

	Exp.	1	2	
	Bombardment	52 min / 60 µA	46 min / 60 µA	
End of the reaction	**Time (min)**	10	10	
	Activity in the reaction vial (MBq)	1390.6	1327.4	
After flush of CO	**Time (min)**	13	12	
	Activity in the reaction vial (MBq)	1186.7	1270.4	
	Trapping efficiency (%)	85	96	91 ± 7
After filtration	**Time (min)**	15	14	
	Activity in the collecting vial (MBq)	864.0	910.8	
	Radiochemical purity RCP (%)	95	95	95 ± 0
	Radiochemical yield RCY (%)	62	69	65 ± 5



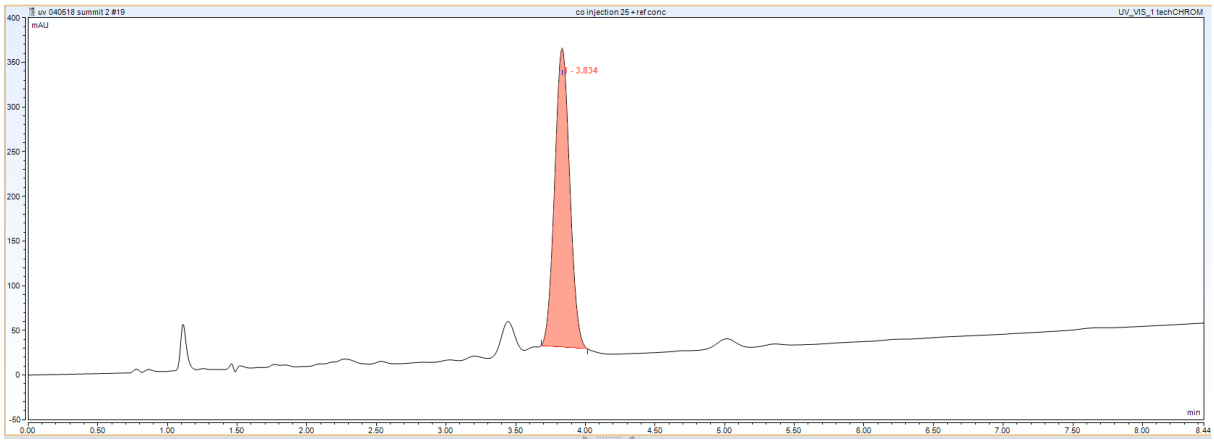
Peak No.	Peak Name	Ret.Time min	Amount n.a.	Rel.Area %	Area mV*min	Height mV	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
1		1.175	n.a.	0.73	8.6852	145.61	BM	0.050	1.26	1.99	3054
2		1.408	n.a.	0.96	11.4397	115.38	MB	0.088	1.38	2.56	1415
3		1.817	n.a.	1.32	15.6349	118.25	BMB	0.100	0.86	2.90	1829
4		2.317	n.a.	1.52	18.0427	142.68	BMB	0.103	1.38	6.84	2796
5		*3.858*	*n.a.*	*95.47*	*1132.6157*	*6388.34*	*BMB**	*0.163*	*1.01*	*n.a.*	*3116*

Example of radio-chromatogram for the analytical HPLC of **[^{11}C]5c**



Peak No.	Peak Name	Ret.Time min	Amount n.a.	Rel.Area %	Area mAU*min	Height mAU	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
1		*3.834*	*0.0000*	*n.a.*	*1.7649*	*15.13*	*M*	*n.a.*	*n.a.*	*n.a.*	*n.a.*

Example of UV-chromatogram at 254 nm for the analytical HPLC of **[^{11}C]5c**

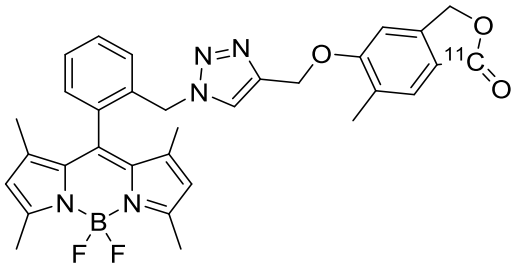


Peak No.	Peak Name	Ret.Time min	Amount n.a.	Rel.Area %	Area mAU*min	Height mAU	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
1		3.834	0.0000	n.a.	41.8568	334.81	M	n.a.	n.a.	n.a.	n.a.

Example of UV-chromatogram at 254 nm for the analytical HPLC of **[^{11}C]5c** co-injected with [^{13}C]**5c**

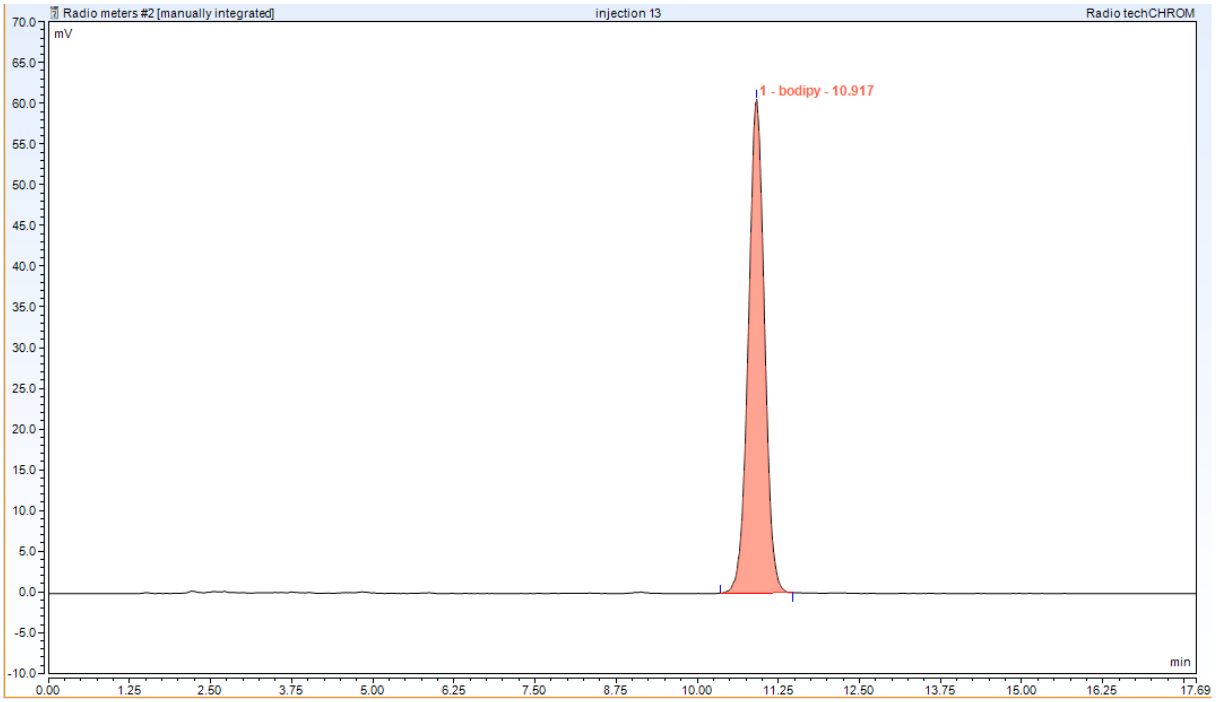
d. [^{11}C]5d

[^{11}C]-5-((1-(2-(5,5-Difluoro-1,3,7,9-tetramethyl-5*H*-4l4,5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diaza-borinin-10-yl)benzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-6-methylisobenzofuran-1(3*H*)-one [^{11}C]5d :



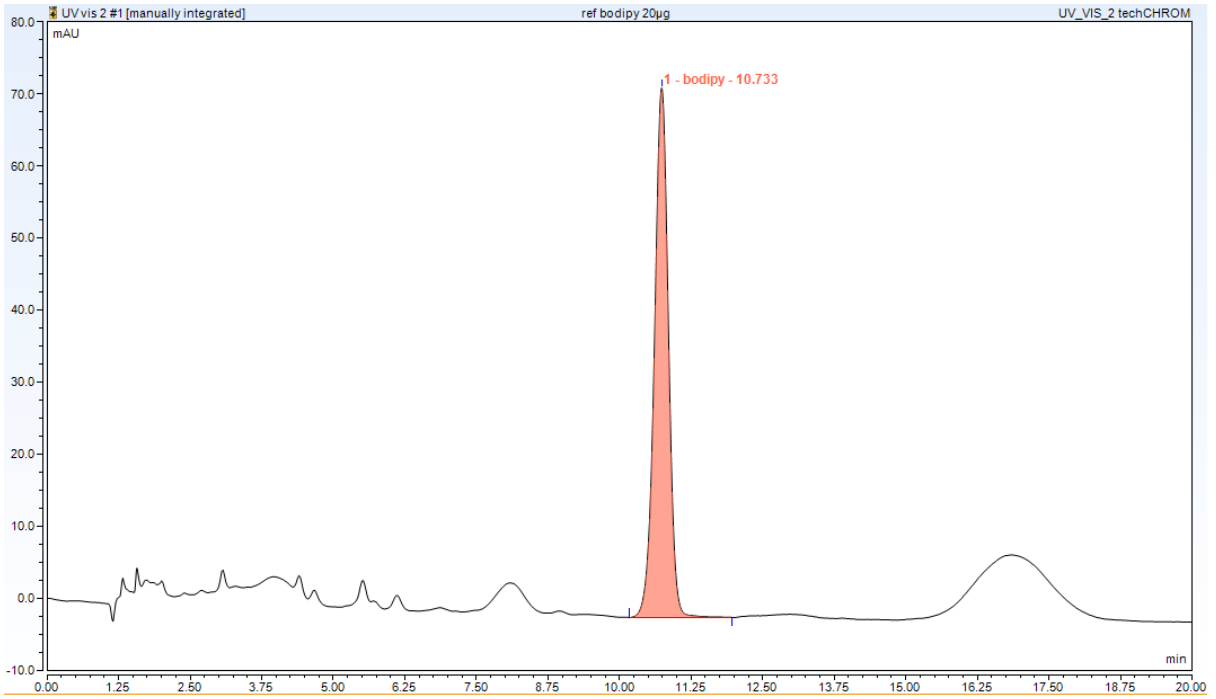
The radiochemical purity (RCP) was established by analytical radio-HPLC using a reverse phase column (Luna 5µ C8 100Å) eluted with acetonitrile and 70mM NaH_2PO_4 (60/40) at a flow rate of 1 mL/min (retention time for radio detection: 10.9 min, retention time for UV detection: 10.7 min). The values for **[^{11}C]5d** were RCP = 98±1%, RCC = 89±4% and RCY = 71±0% (n = 2).

	Exp.	1	2	
	Bombardment	52 min / 60 µA	55 min / 60 µA	
End of the reaction	**Time (min)**	10	10	
	Activity in the reaction vial (MBq)	1545.1	1060.1	
After flush of CO	**Time (min)**	12	14	
	Activity in the reaction vial (MBq)	1338.0	1007.3	
	Trapping efficiency (%)	87	95	91 ± 6
After filtration	**Time (min)**	15	14	
	Activity in the collecting vial (MBq)	1093.7	748.2	
	Radiochemical purity RCP (%)	>98	97	98 ± 1
	Radiochemical yield RCY (%)	71	71	71 ± 0



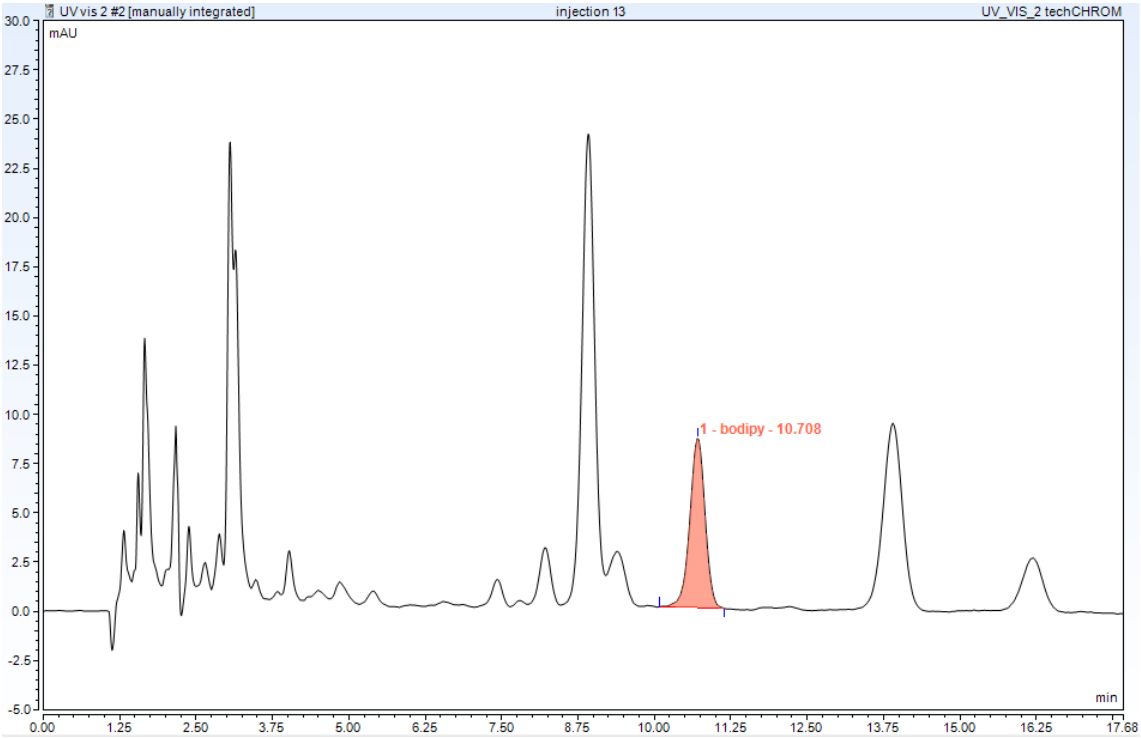
Peak No.	Peak Name	Ret.Time min	Amount	Rel.Area %	Area mV*min	Height mV	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
1	bodipy	10.917	n.a.	100.00	17.3249	60.63	BMB*	0.262	0.99	n.a.	9591

Example of radio-chromatogram for the analytical HPLC of **[^{11}C]5d**



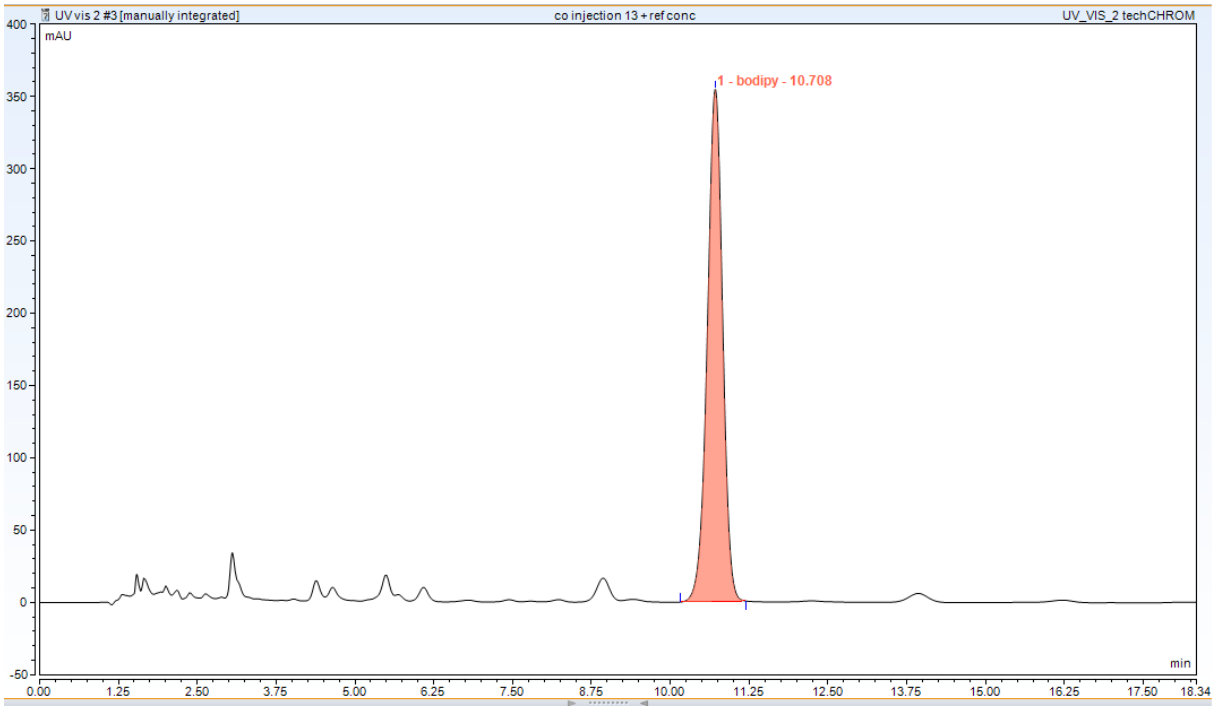
Peak No.	Peak Name	Ret.Time min	Amount	Rel.Area %	Area mAU*min	Height mAU	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
1	bodipy	10.733	n.a.	100.00	20.6242	73.49	BMB	0.255	0.96	n.a.	9818

UV-chromatogram at 254 nm for the analytical HPLC of **[^{13}C]5d** *(20µL from as solution at 20µg/mL)*



Peak No.	Peak Name	Ret.Time min	Amount	Rel.Area %	Area mAU*min	Height mAU	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
1	bodipy	10.708	n.a.	100.00	2.4692	8.61	BMB	0.261	0.94	n.a.	9330

Example of UV-chromatogram at 254 nm for the analytical HPLC of **[^{11}C]5d**



Peak No.	Peak Name	Ret.Time min	Amount	Rel.Area %	Area mAU*min	Height mAU	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
1	bodipy	10.708	n.a.	100.00	99.0410	354.13	BMB*	0.256	0.96	n.a.	9675

Example of UV-chromatogram at 254 nm for the analytical HPLC of **[^{11}C]5d** co-injected with **[^{13}C]5d**

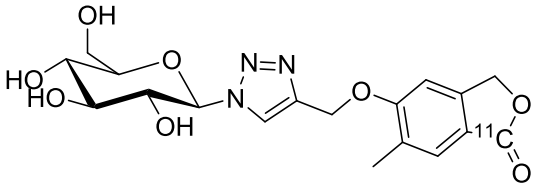
Determination of the molar activity of **[^{11}C]5d**:

1) A standard solution was prepared by dissolving 20µg of **[^{13}C]5d** in 1 mL of CH_3CN, corresponding to 34,5 nmol in 1 mL. Then, 20 µL of this **[^{13}C]5d** standard solution (0.689 nmol of product **[^{13}C]5d**) was injected in the analytical HPLC. The UV-chromatogram showed a peak at 10.7 min with an area of 20.62 mAu.min.

2) After the ^{11}C-carbonylation of **2d-PS** in 0.6 mL of THF, 5 mL of acetonitrile were added in the reaction mixture, and the resulting solution was filtered through a syringe filter and transferred in the collecting vial. The final activity of **[^{11}C]5d** (solubilised in a total of 5.6 mL of a THF/CH_3CN mixture) was measured to 1093.7 MBq. Then, 20 µL of this solution was injected in the analytical HPLC. The radio-chromatogram showed a pic at 10.9 min and the UV-chromatogram showed a peak at 10.7 min with an area of 2.47 mAu.min, thus corresponding to 2.47*0.689/20.62= 0.0825 nmol of product **[^{11}C]5d** in 20 µL, i.e. 0.0825*5600/20 = 23.1 nmol in the overall sample. With this data, a molar activity of 1.0937/0.0231 = **47 GBq/µmol** was calculated for **[^{11}C]5d**.

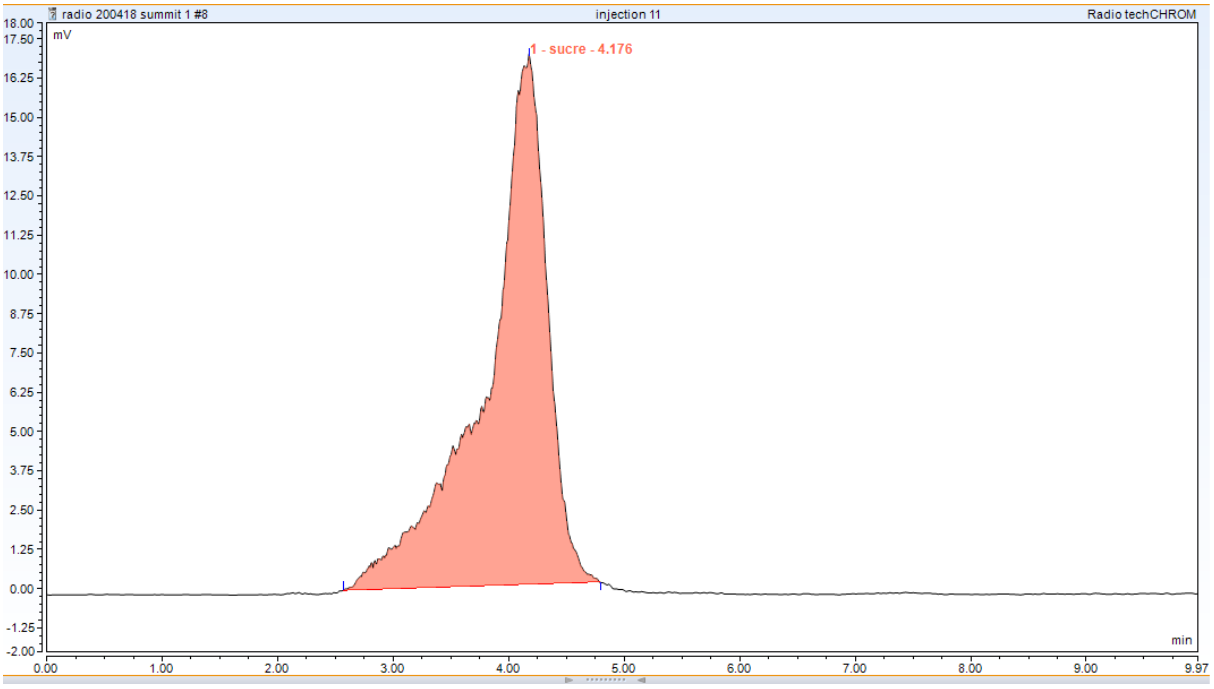
e. [^{11}C]5e

[^{11}C]-α-D-1-Desoxy-1[4-(((6-methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)oxy)methyl)-1*H*-1,2,3-triazole-1-yl]-glucopyranose [^{11}C]5e :



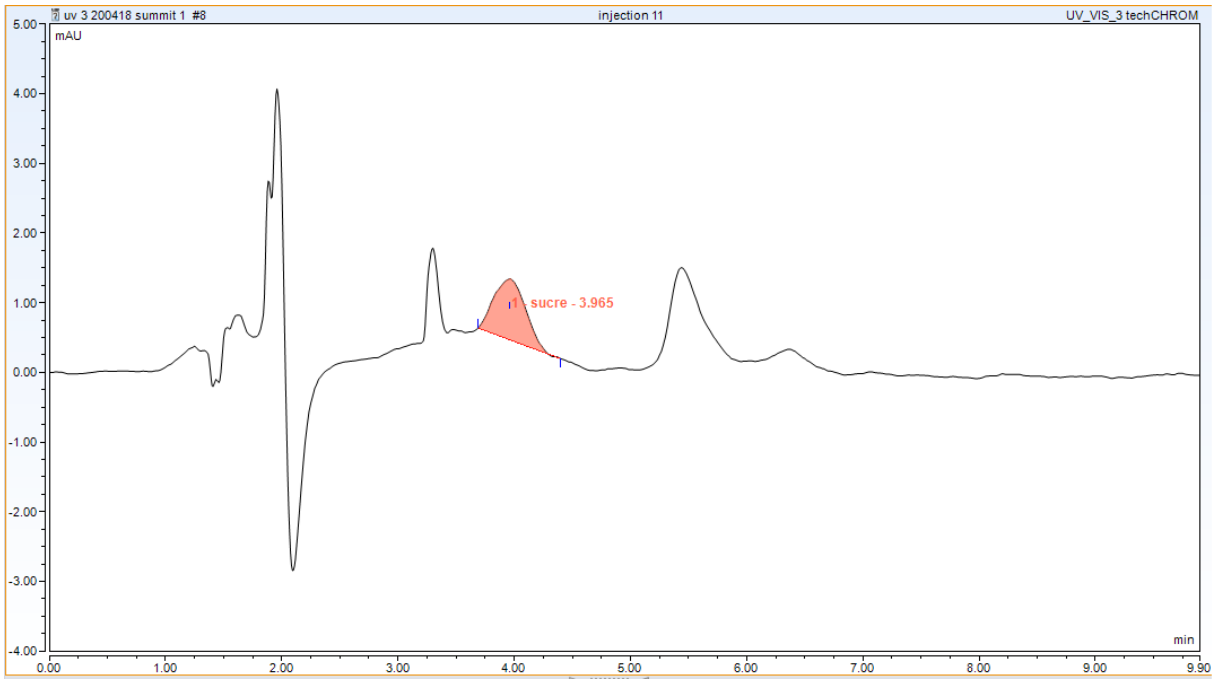
The radiochemical purity (RCP) was established by analytical radio-HPLC using a reverse phase column (Luna 3µ C8 100Å) eluted with acetonitrile and 70mM NaH_2PO_4 (20/80) at a flow rate of 1 mL/min (retention time for radio detection: 4.18 min, retention time for UV detection: 3.97 min). The values for **[^{11}C]5e** were RCP = 88±21%, RCC = 72±11% and RCY = 35±7% (n = 3).

	Exp.	1	2	3	
	Bombardment	40 min / 60 µA	40 min / 60 µA	40 min / 60 µA	
End of the reaction	**Time (min)**	10	10	10	
	Activity in the reaction vial (MBq)	2191.2	178.4	646.1	
After flush of CO	**Time (min)**	12	11	12	
	Activity in the reaction vial (MBq)	1653.7	142.4	601.4	
	Trapping efficiency (%)	75	80	93	83 ± 9
After filtration	**Time (min)**	15	12	15	
	Activity in the collecting vial (MBq)	950.6	60.1	293.0	
	Radiochemical purity RCP (%)	>98	>98	64	88 ± 21
	Radiochemical yield RCY (%)	43	34	45	35 ± 7



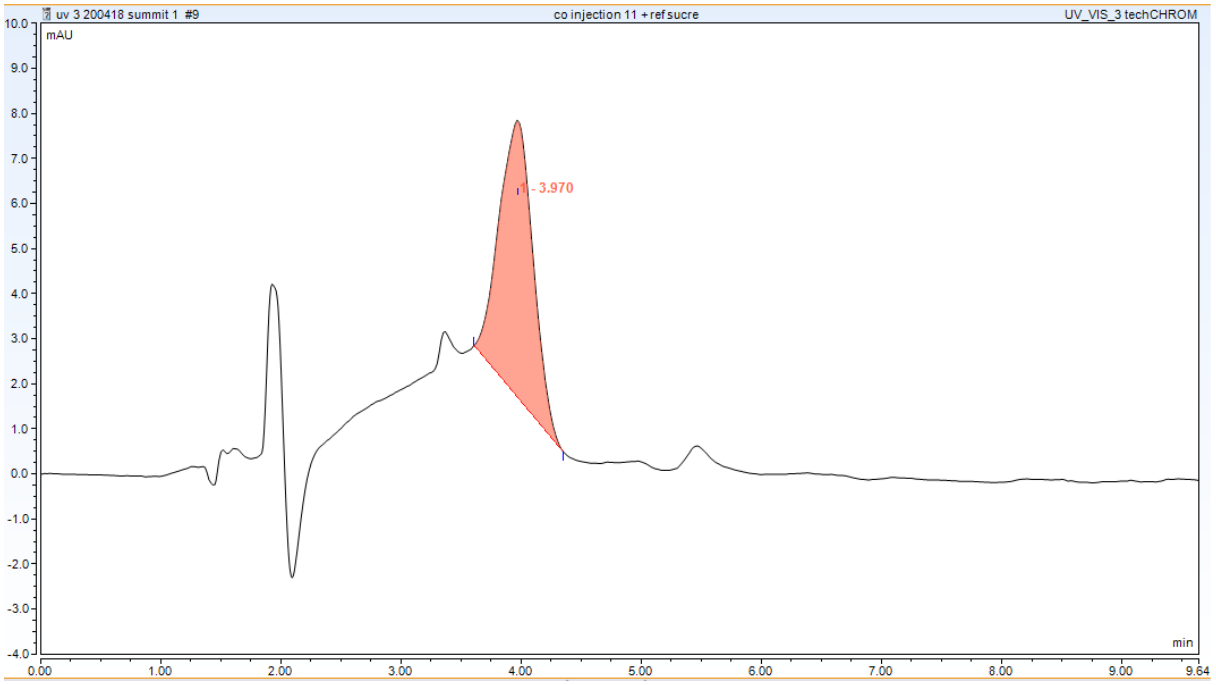
Peak No.	Peak Name	Ret.Time min	Amount	Rel.Area %	Area mV*min	Height mV	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
1	sucre	4.176	0.0000	n.a.	10.3820	16.91	M	n.a.	n.a.	n.a.	n.a.

Example of radio-chromatogram for the analytical HPLC of **[^{11}C]5e**



Peak No.	Peak Name	Ret.Time min	Amount	Rel.Area %	Area mAU*min	Height mAU	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
1	sucre	3.965	0.0000	n.a.	0.2747	0.88	M	n.a.	n.a.	n.a.	n.a.

Example of UV-chromatogram at 254 nm for the analytical HPLC of **[^{11}C]5e**

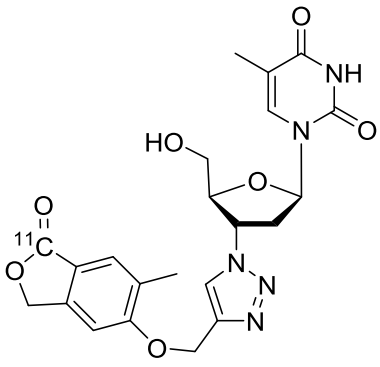


Peak No.	Peak Name	Ret.Time min	Amount n.a.	Rel.Area %	Area mAU*min	Height mAU	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
1		3.970	0.0000	n.a.	1.9831	6.14	M	n.a.	n.a.	n.a.	n.a.

Example of UV-chromatogram at 254 nm for the analytical HPLC of **[^{11}C]5e** co-injected with [^{13}**C]5e**

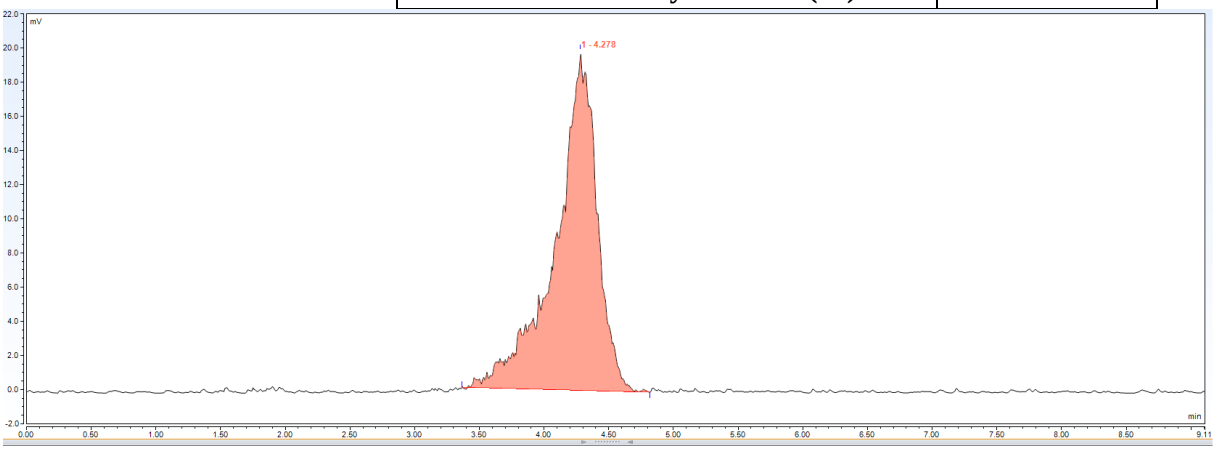
f. [^{11}C]5f

[^{11}C]-3'-Desoxy-3'-[4-(((6-methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)oxy)methyl)-1*H*-1,2,3-triazole-1-yl]-thymidine [^{11}C]5f :



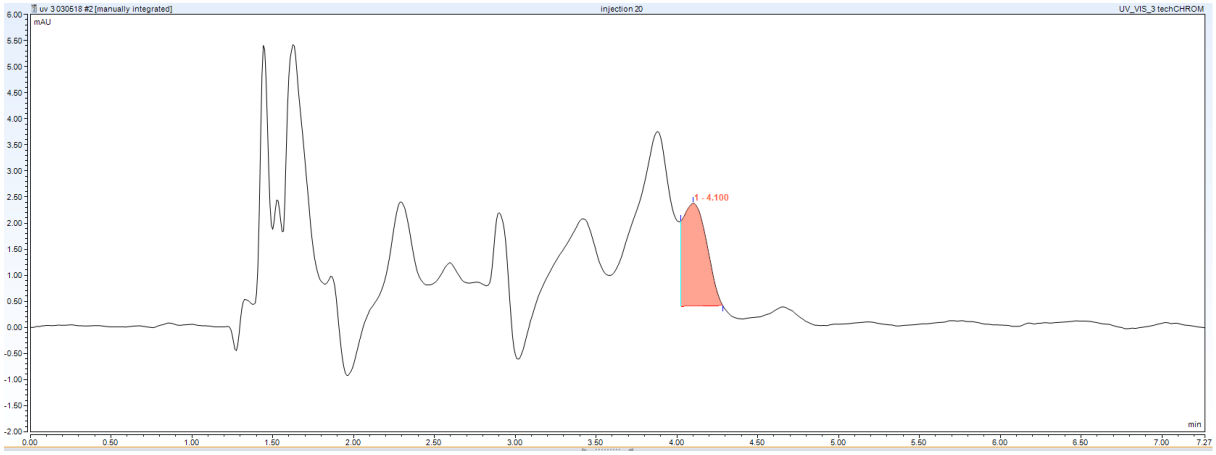
The radiochemical purity (RCP) was established by analytical radio-HPLC using a reverse phase column (Luna 5µ C8 100Å) eluted with acetonitrile and 70mM NaH_2PO_4 (30/70) at a flow rate of 1 mL/min (retention time for radio detection: 4.28 min, retention time for UV detection: 4.1 min). The values for **[^{11}C]5f** were RCP > 98%, RCC = 45% and RCY = 22% (n = 1).

	Exp.	**1**
	Bombardment	46 min / 60 uA
End of the reaction	**Time (min)**	10
	Activity in the reaction vial (MBq)	533.8
After flush of CO	**Time (min)**	12
	Activity in the reaction vial (MBq)	240.5
	Trapping efficiency (%)	45
After filtration	**Time (min)**	15
	Activity in the collecting vial (MBq)	116.5
	Radiochemical purity RCP (%)	>98
	Radiochemical yield RCY (%)	22



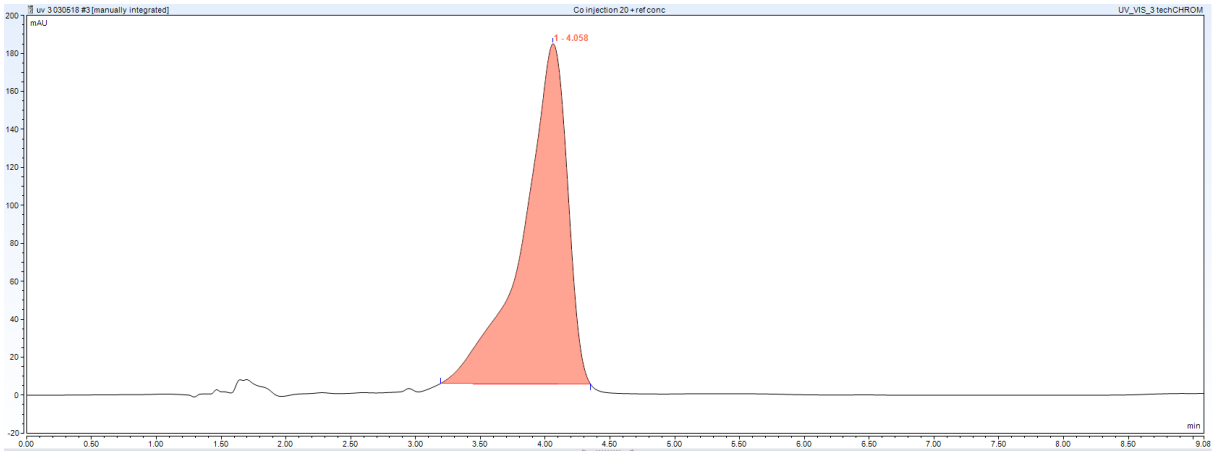
Peak No.	Peak Name	Ret.Time min	Amount n.a.	Rel.Area %	Area mV*min	Height mV	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
1		4.278	0.0000	n.a.	7.3247	19.88	M	n.a.	n.a.	n.a.	n.a.

Radio-chromatogram for the analytical HPLC of **[^{11}C]5f**



Peak No.	Peak Name	Ret.Time min	Amount n.a.	Rel.Area %	Area mAU*min	Height mAU	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
1		4.100	n.a.	100.00	0.3303	1.98	MB*	n.a.	n.a.	n.a.	n.a.

UV-chromatogram at 254 nm for the analytical HPLC of **[^{11}C]5f**

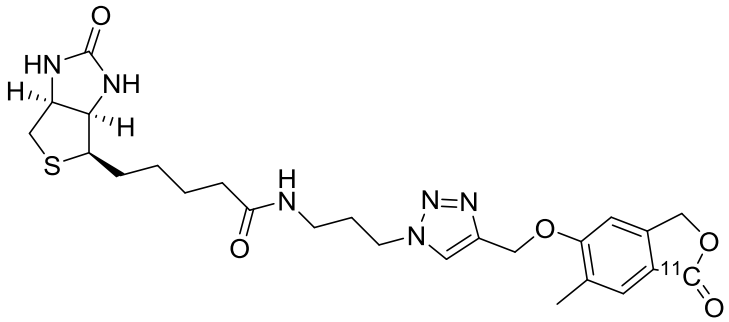


Peak No.	Peak Name	Ret.Time min	Amount n.a.	Rel.Area %	Area mAU*min	Height mAU	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
1		4.058	n.a.	100.00	70.7210	179.25	BMB*	0.329	0.67	n.a.	845

UV-chromatogram at 254 nm for the analytical HPLC of **[^{11}C]5f** co-injected with [^{13}**C]5f**

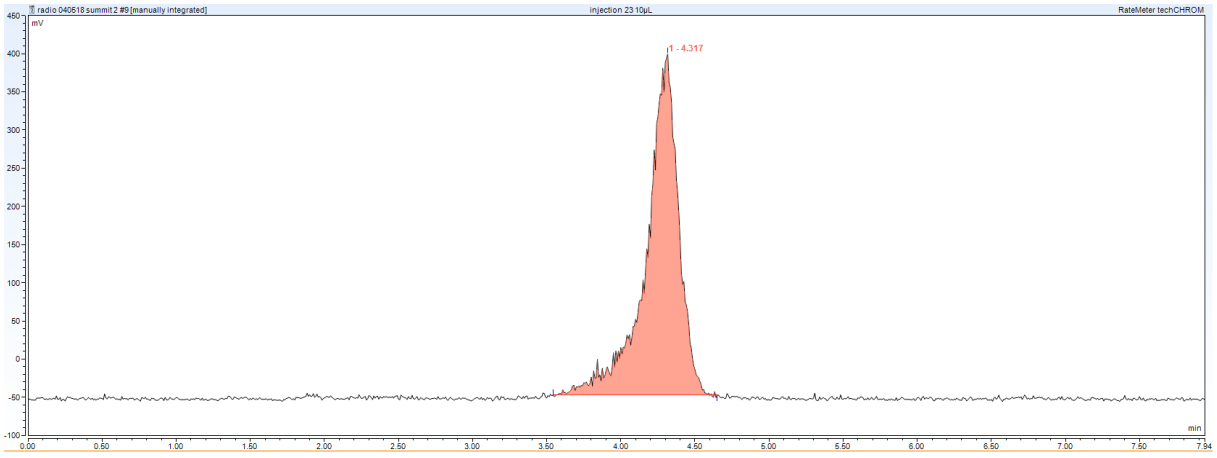
g. [^{11}C]5g

[^{11}C]-*N*-(3-(4-(((6-Methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)propyl)-biotinamide [^{11}C]5g:



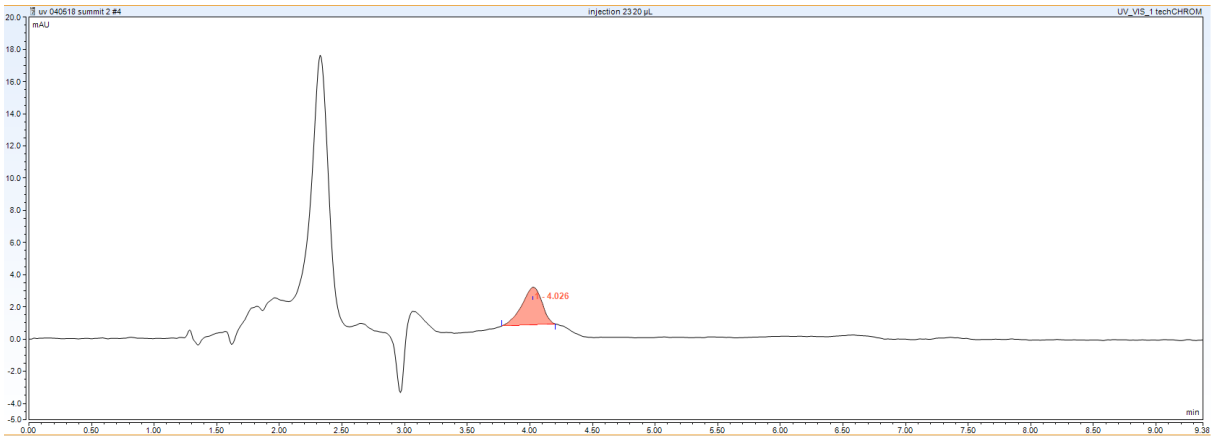
The radiochemical purity (RCP) was established by analytical radio-HPLC using a reverse phase column (Luna 3µ C8 100Å) eluted with acetonitrile and 70mM NaH_2PO_4 (30/70) at a flow rate of 1 mL/min (retention time for radio detection: 4.32 min, retention time for UV detection: 4.03 min). The values for **[^{11}C]5g** were RCP > 98±0%, RCC = 70±3% and RCY = 45±6% (n = 2).

	Exp.	1	2	
	Bombardment	50 min / 60 µA	71 min / 60 µA	
End of the reaction	**Time (min)**	10	10	
	Activity in the reaction vial (MBq)	733.2	894.8	
After flush of CO	**Time (min)**	11	11	
	Activity in the reaction vial (MBq)	540.6	624.9	
	Trapping efficiency (%)	74	70	72 ± 3
After filtration	**Time (min)**	14	15	
	Activity in the collecting vial (MBq)	363.7	362.9	
	Radiochemical purity RCP (%)	>98	>98	>98 ± 0
	Radiochemical yield RCY (%)	50	41	45 ± 6



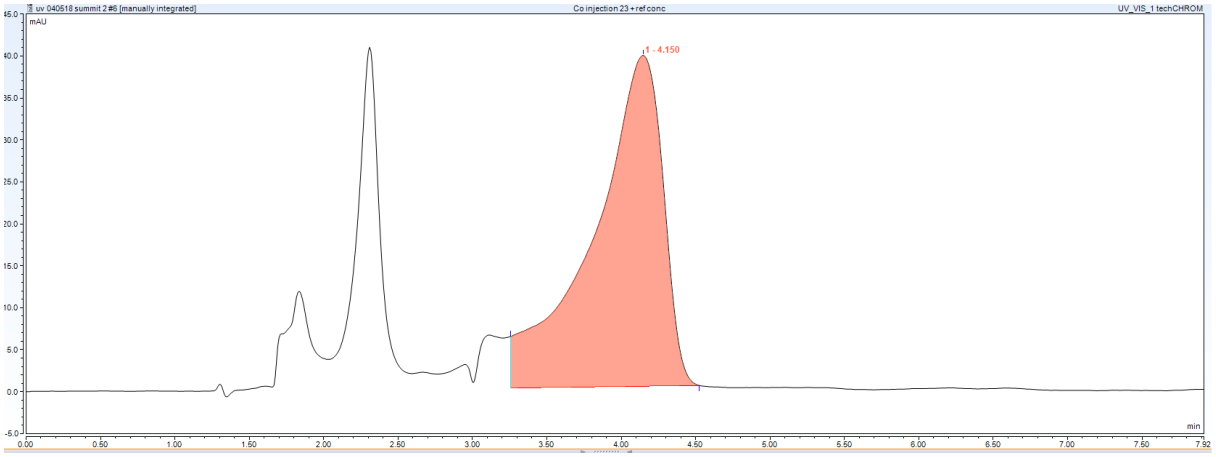
Peak No.	Peak Name	Ret.Time min	Amount n.a.	Rel.Area %	Area mV*min	Height mV	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
1		4.317	n.a.	100.00	112.1653	447.05	BMB*	0.192	0.73	n.a.	2800

Example of radio-chromatogram for the analytical HPLC of **[^{11}C]5g**



Peak No.	Peak Name	Ret.Time min	Amount n.a.	Rel.Area %	Area mAU*min	Height mAU	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
1		4.026	0.0000	n.a.	0.4347	2.34	M	n.a.	n.a.	n.a.	n.a.

Example of UV-chromatogram at 254 nm for the analytical HPLC of **[^{11}C]5g**

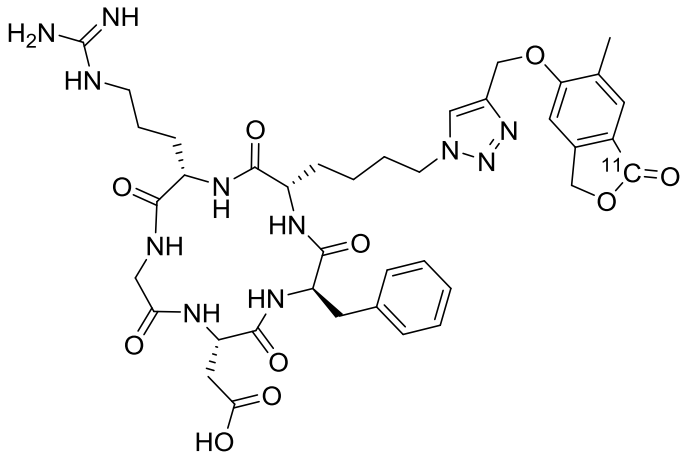


Peak No.	Peak Name	Ret.Time min	Amount n.a.	Rel.Area %	Area mAU*min	Height mAU	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
1		4.150	n.a.	100.00	21.3932	39.42	MB*	0.447	n.a.	n.a.	478

Example of UV-chromatogram at 254 nm for the analytical HPLC of **[^{11}C]5g** co-injected with [^{13}C]**5g**

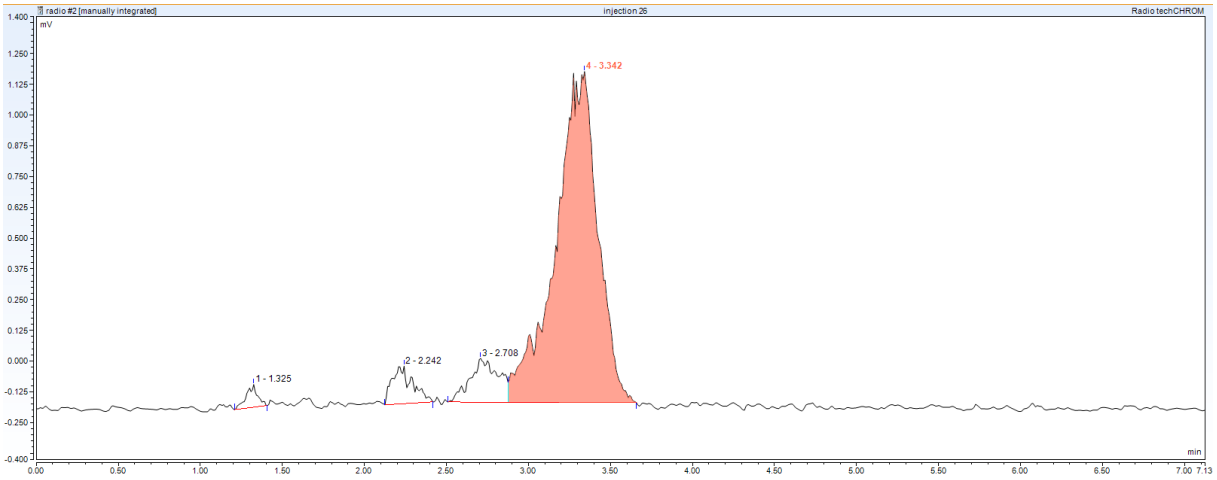
h. [^{11}C]5h

[^{11}C]-Cyclo-RGD-[2-(4-(((6-methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)-yl] [^{11}C]5h:



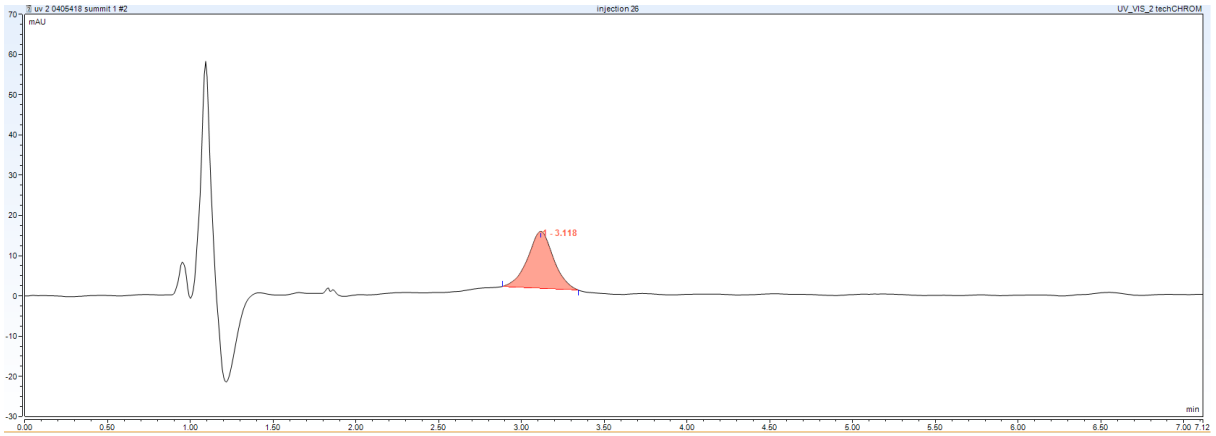
The radiochemical purity (RCP) was established by analytical radio-HPLC using a reverse phase column (Luna 5µ C8 100Å) eluted with CH_3CN and H_2O (30/70) with 1% of TFA at a flow rate of 1.5 mL/min (retention time for radio detection: 3.34 min, retention time for UV detection: 3.12 min). The values for **[^{11}C]5h** were RCP = 86%, RCC = 50% and RCY = 4% (n = 1).

	Exp.	1
	Bombardment	46 min / 60 uA
End of the reaction	**Time (min)**	10
	Activity in the reaction vial (MBq)	952.3
After flush of CO	**Time (min)**	12
	Activity in the reaction vial (MBq)	563.8
	Trapping efficiency (%)	59
After filtration	**Time (min)**	14
	Activity in the collecting vial (MBq)	41.8
	Radiochemical purity RCP (%)	86
	Radiochemical yield RCY (%)	4



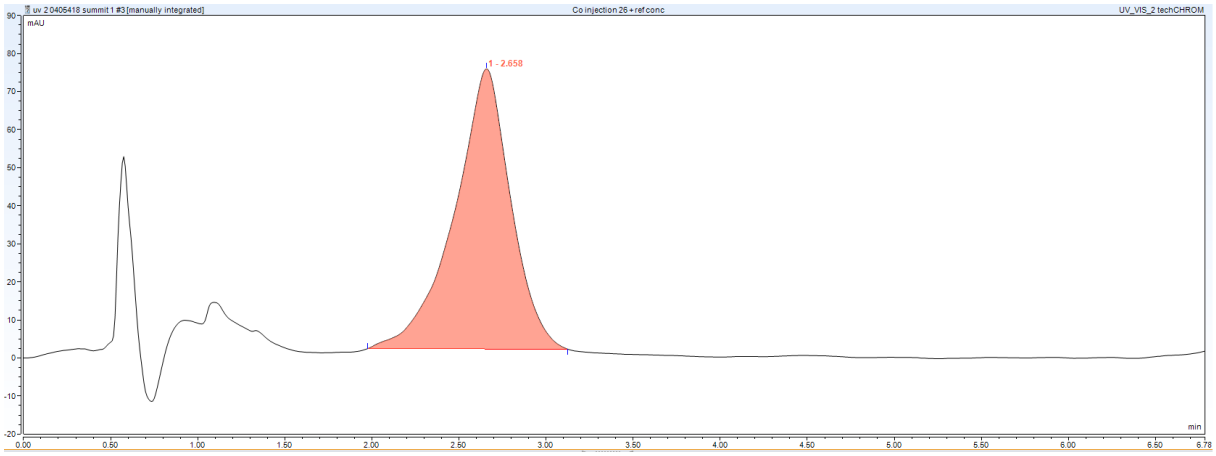
Peak No.	Peak Name	Ret.Time min	Amount n.a.	Rel.Area %	Area mV*min	Height mV	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
1		1.325	n.a.	1.58	0.0074	0.09	BMB	0.066	0.84	6.35	2224
2		2.242	n.a.	4.72	0.0221	0.15	BMB	0.104	1.23	1.59	2560
3		2.708	n.a.	7.53	0.0352	0.18	BM *	0.242	n.a.	1.54	696
4		*3.342*	*n.a.*	*86.17*	*0.4027*	*1.35*	*MB**	*0.245*	*n.a.*	*n.a.*	*1030*

Radio-chromatogram for the analytical HPLC of **[^{11}C]5h**



Peak No.	Peak Name	Ret.Time min	Amount n.a.	Rel.Area %	Area mAU*min	Height mAU	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
1		3.118	0.0000	n.a.	2.5607	14.20	M	n.a.	n.a.	n.a.	n.a.

UV-chromatogram at 254 nm for the analytical HPLC of **[^{11}C]5h**



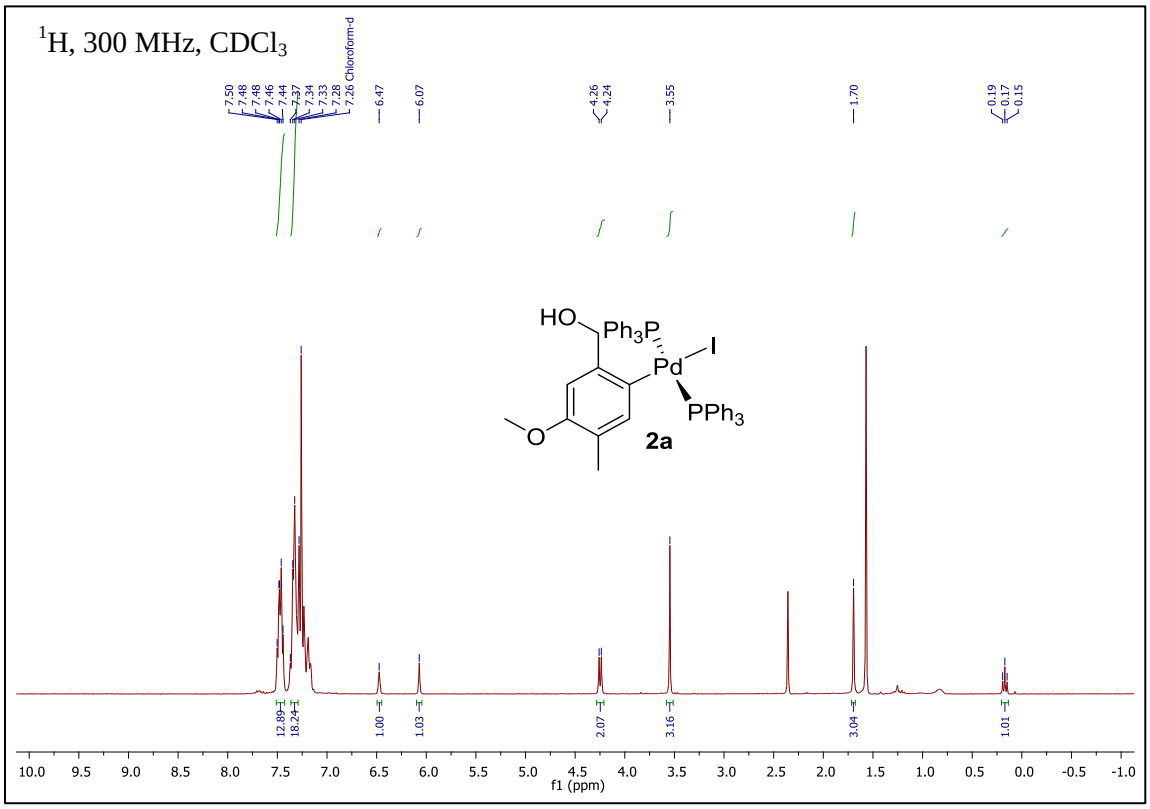
Peak No.	Peak Name	Ret.Time min	Amount n.a.	Rel.Area %	Area mAU*min	Height mAU	Type	Width (50%) min	Asym. EP	Resol. EP	Plates EP
1		2.658	n.a.	100.00	27.7112	73.63	BMB*	0.326	0.85	n.a.	368

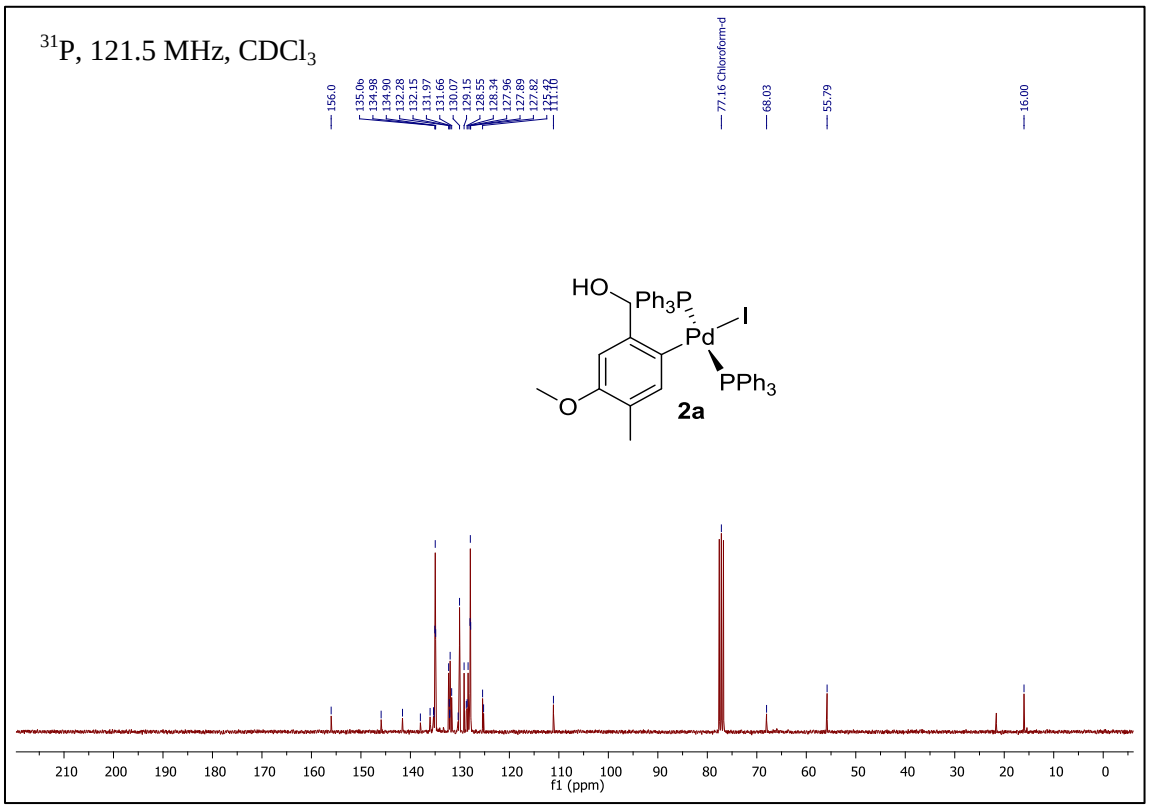
UV-chromatogram at 254 nm for the analytical HPLC of **[^{11}C]5h** co-injected with [^{13}**C]5h**

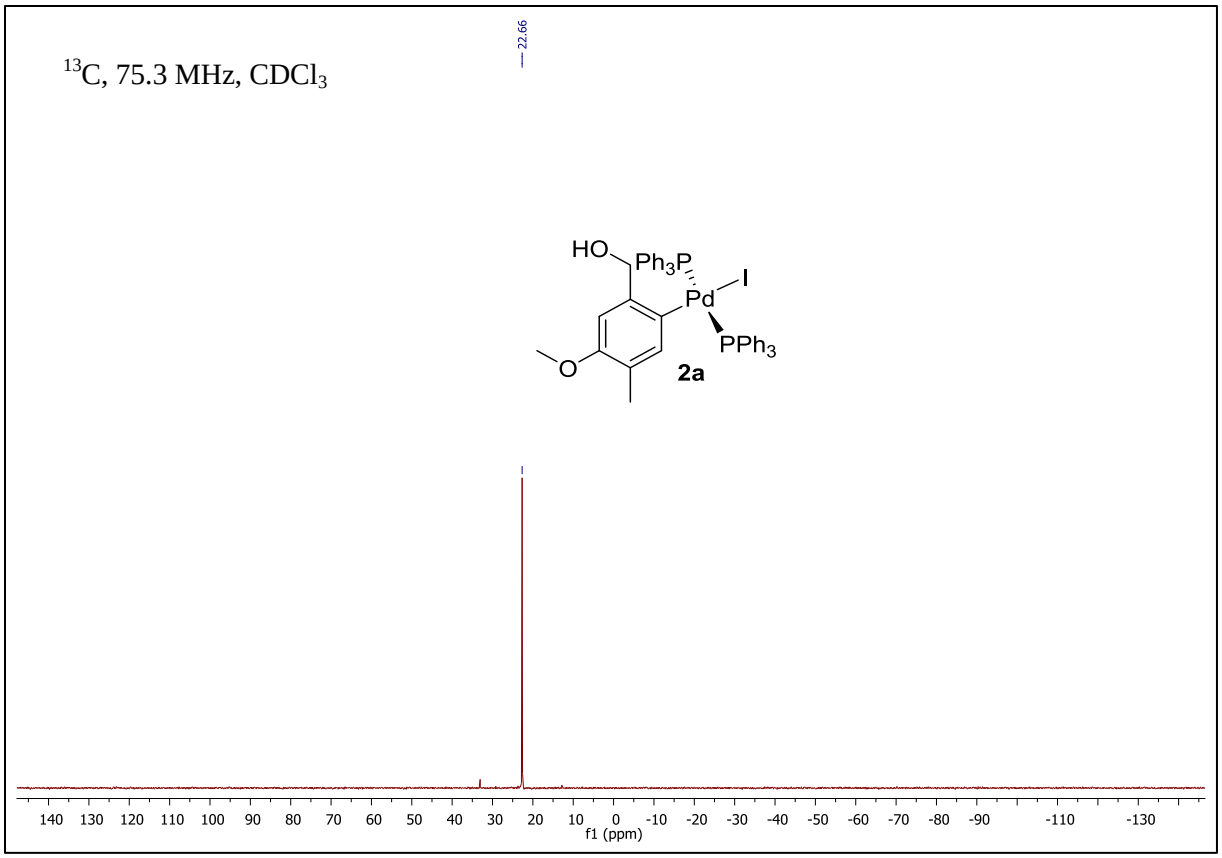
6) NMR Spectra

*a. Arylpalladium complexes **2a**, **3a** and **4a***

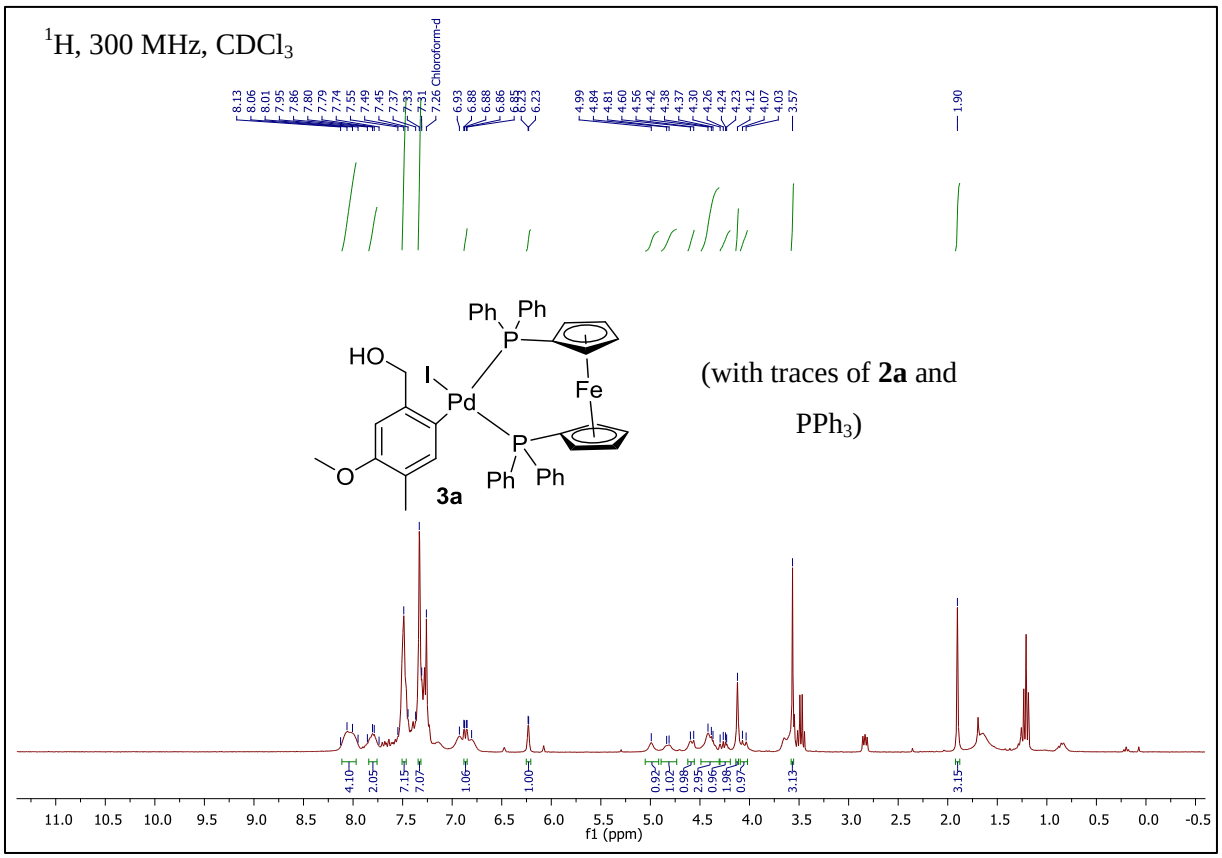
[(2-Hydroxymethyl-4-methoxy-5-(methyl))phenyl]iodobis(triphenyl-phosphine)palladium 2a:



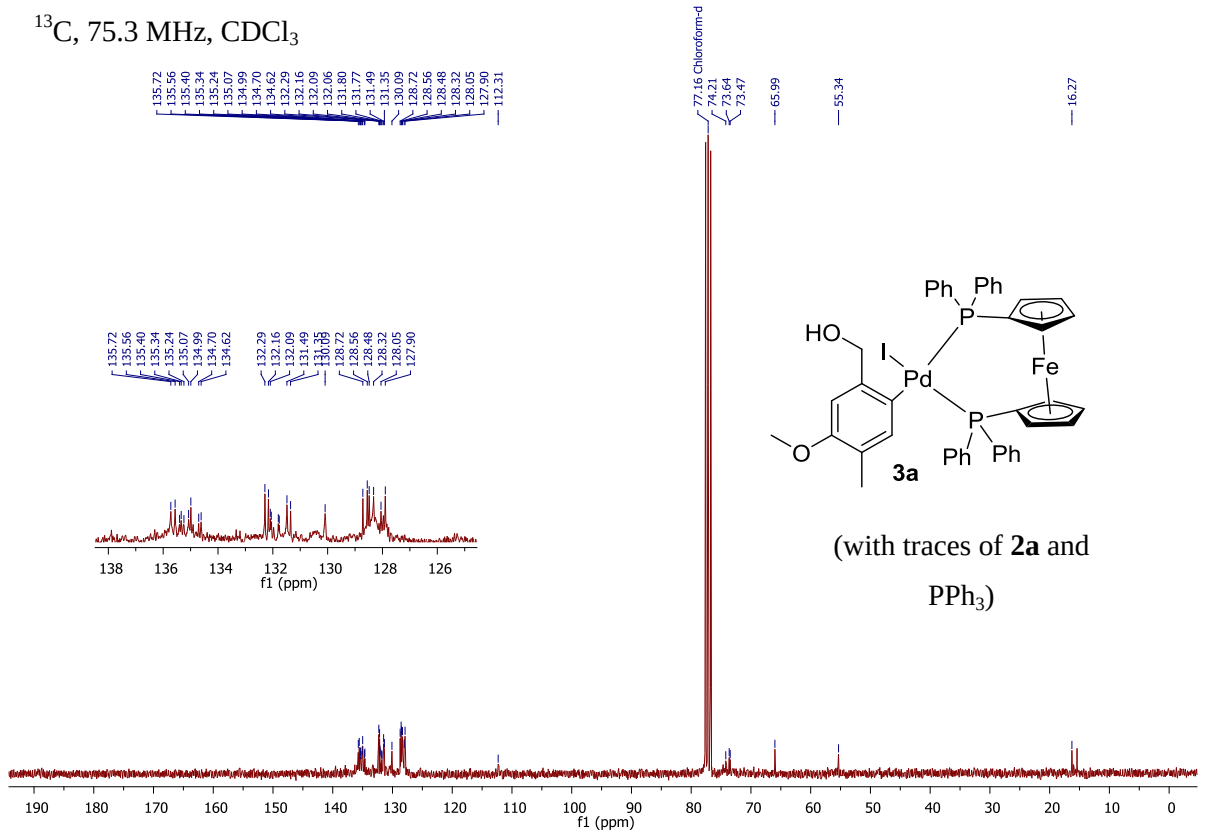




[(2-Hydroxymethyl-4-methoxy-5-(methyl))phenyl]iodo(1,1′-Bis(diphenylphosphino)ferrocene) palladium 3a:

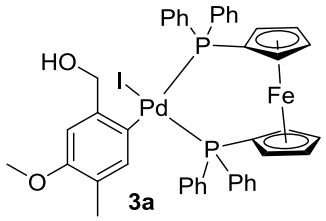


^{13}C, 75.3 MHz, $CDCl_3$

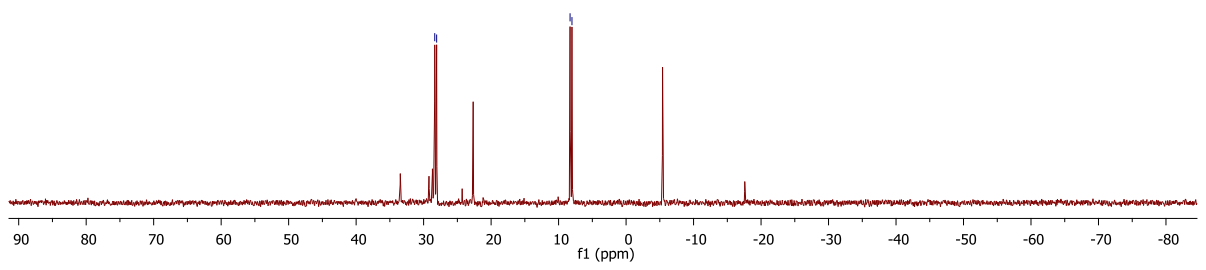


(with traces of **2a** and PPh_3)

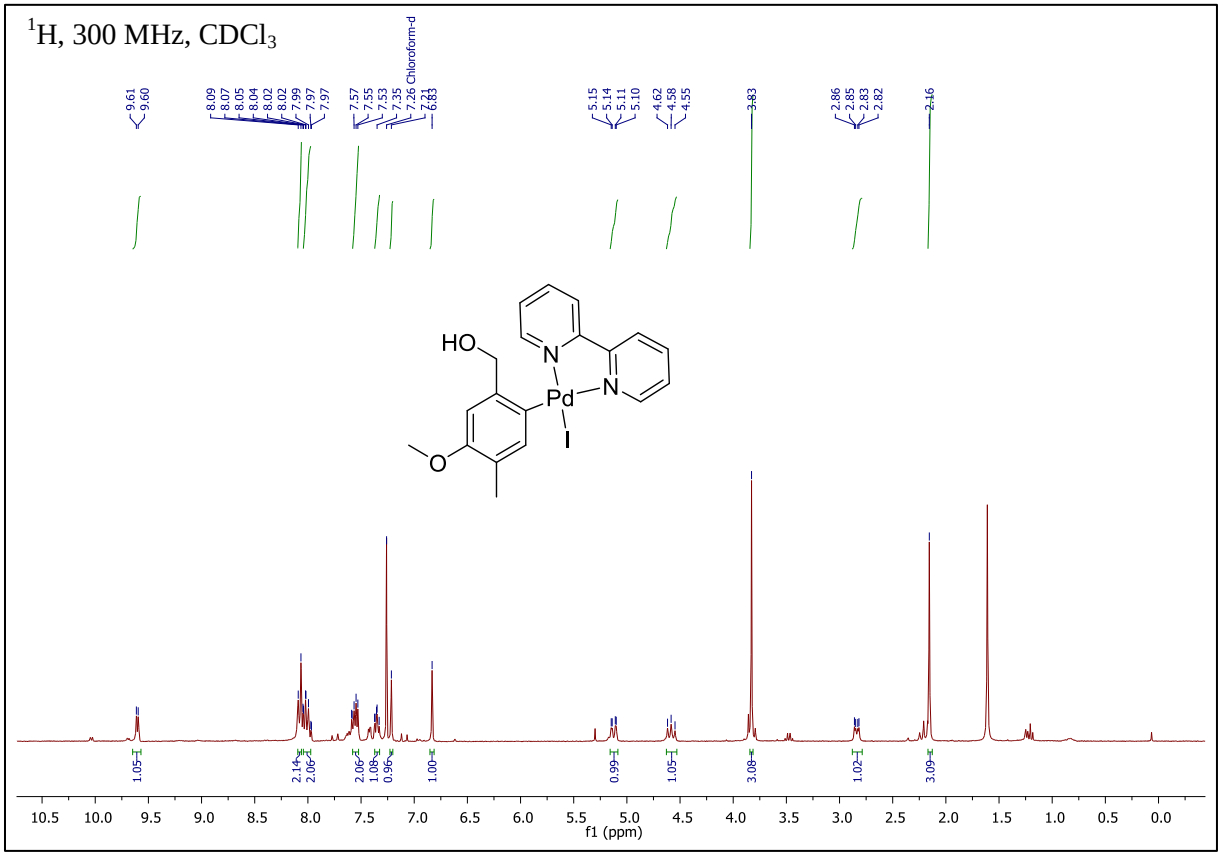
^{31}P, 121.5 MHz, $CDCl_3$

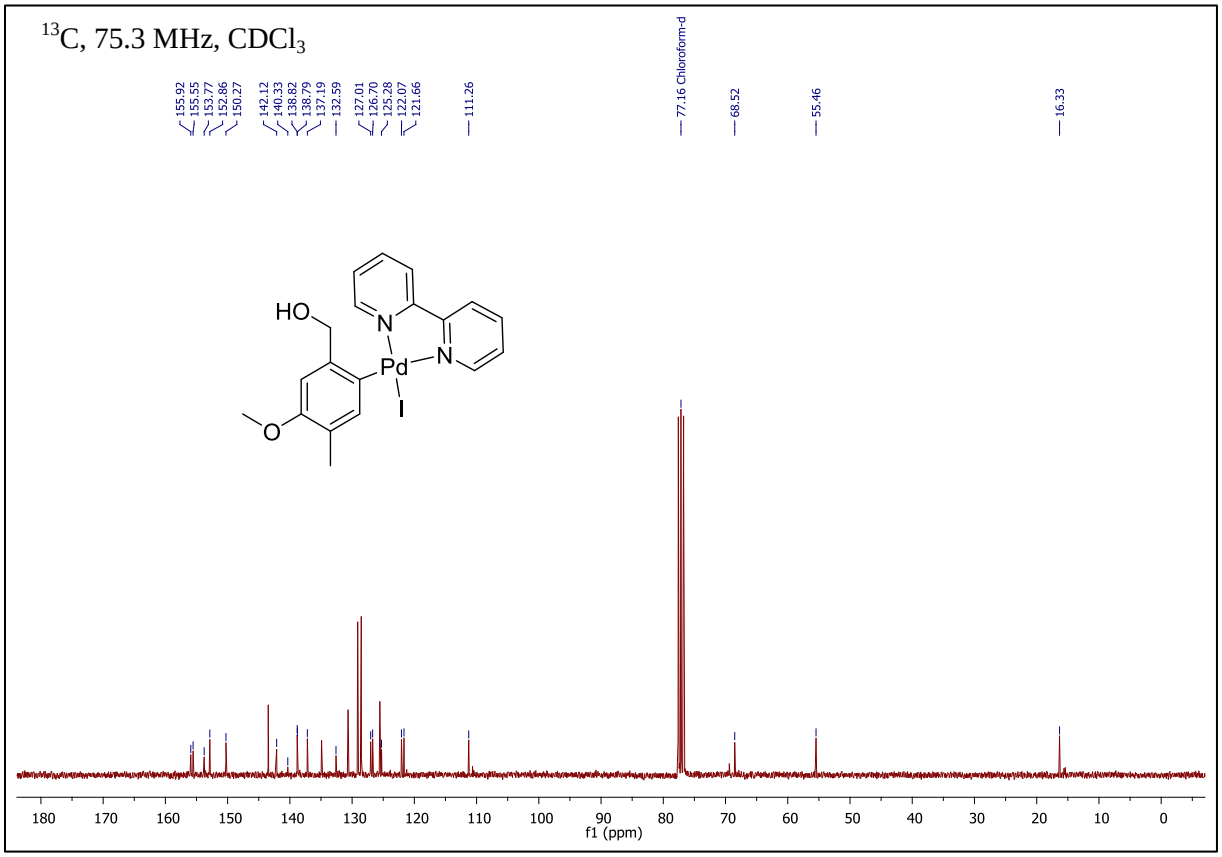


(with traces of **2a** and PPh_3)

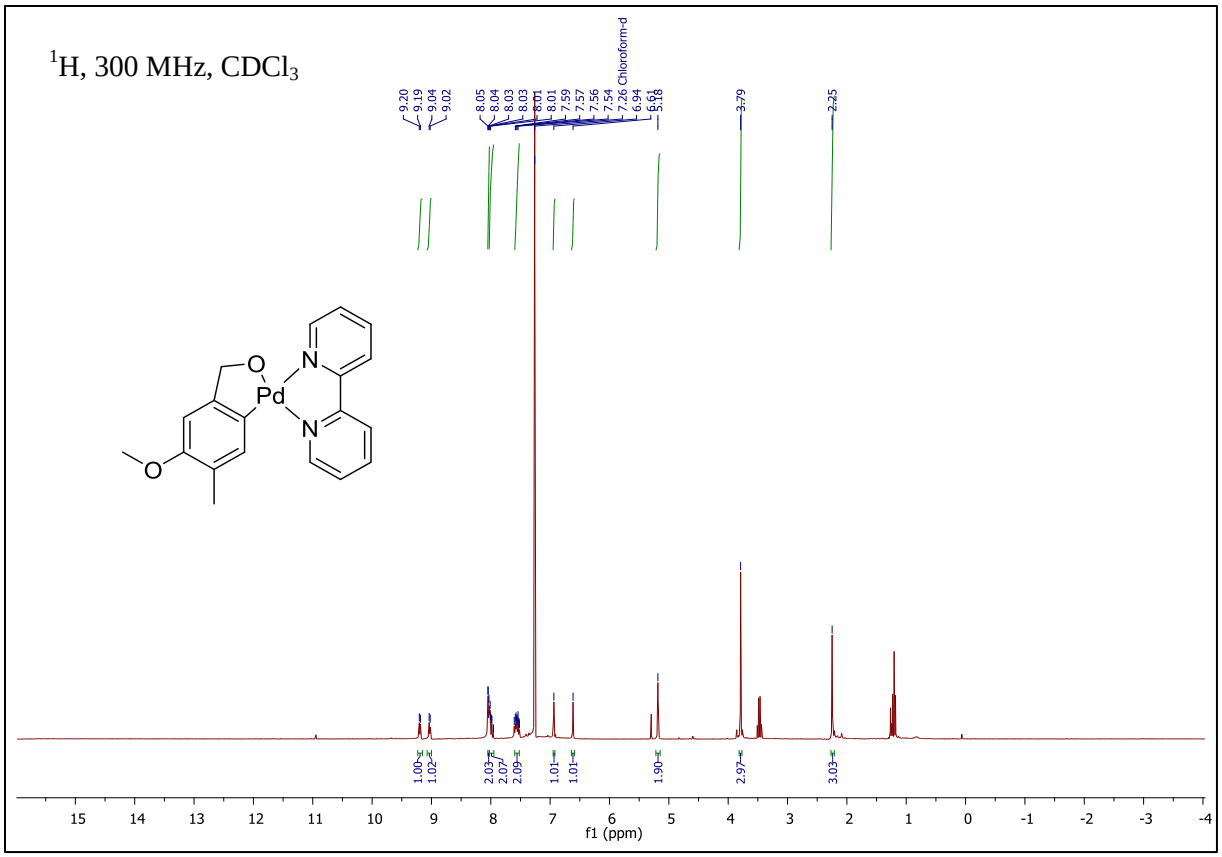


(Oxomethylene-1,2-(4-methoxy-5-methyl)phenylene)-[1,1'-bis(diphenylphosphino)ferrocene)] palladium 4a:

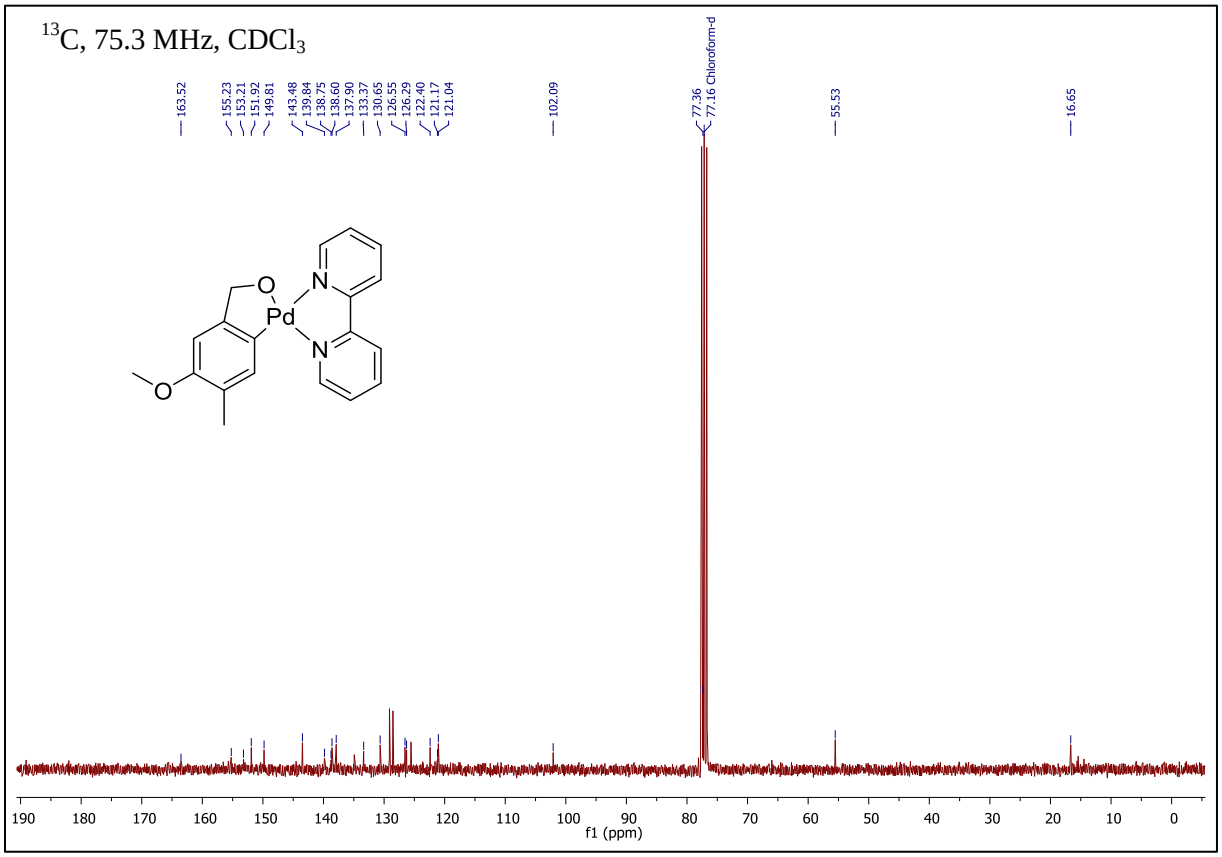




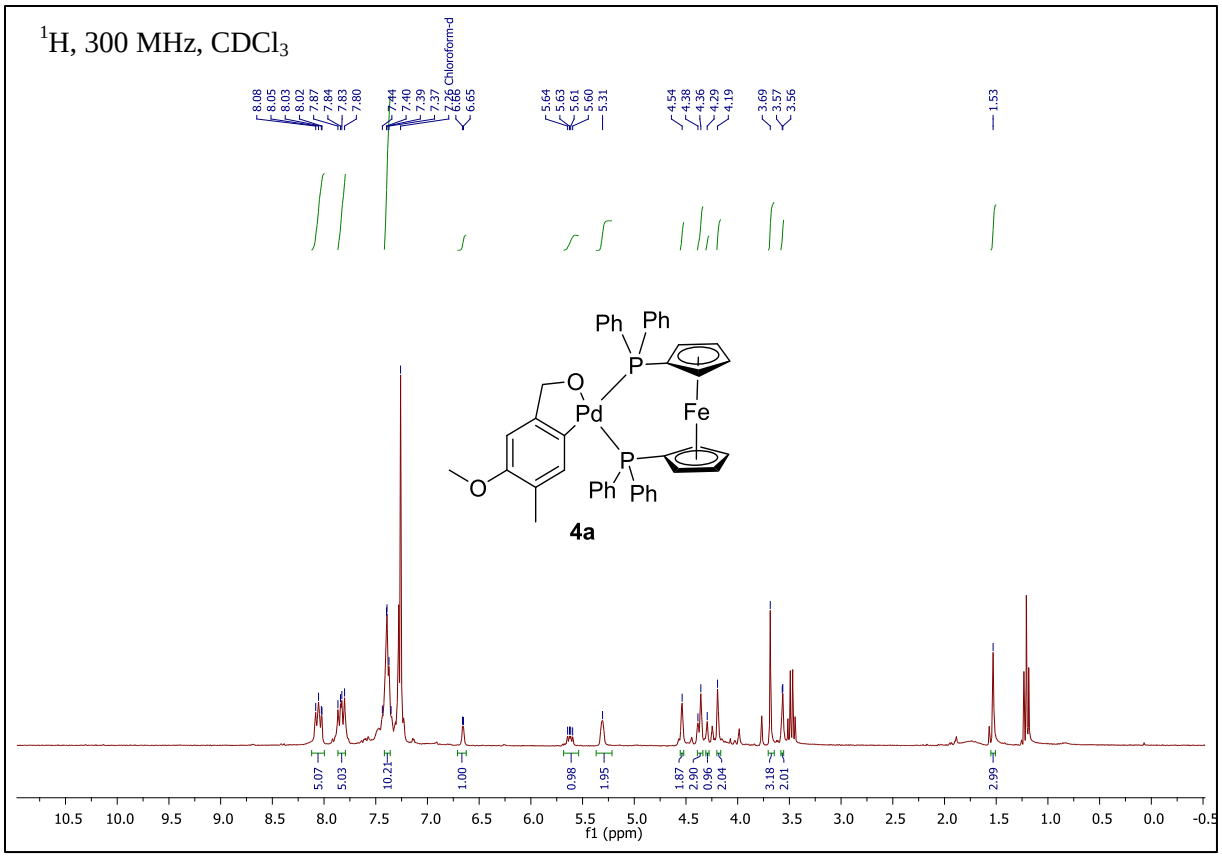
^{1}H, 300 MHz, $CDCl_3$



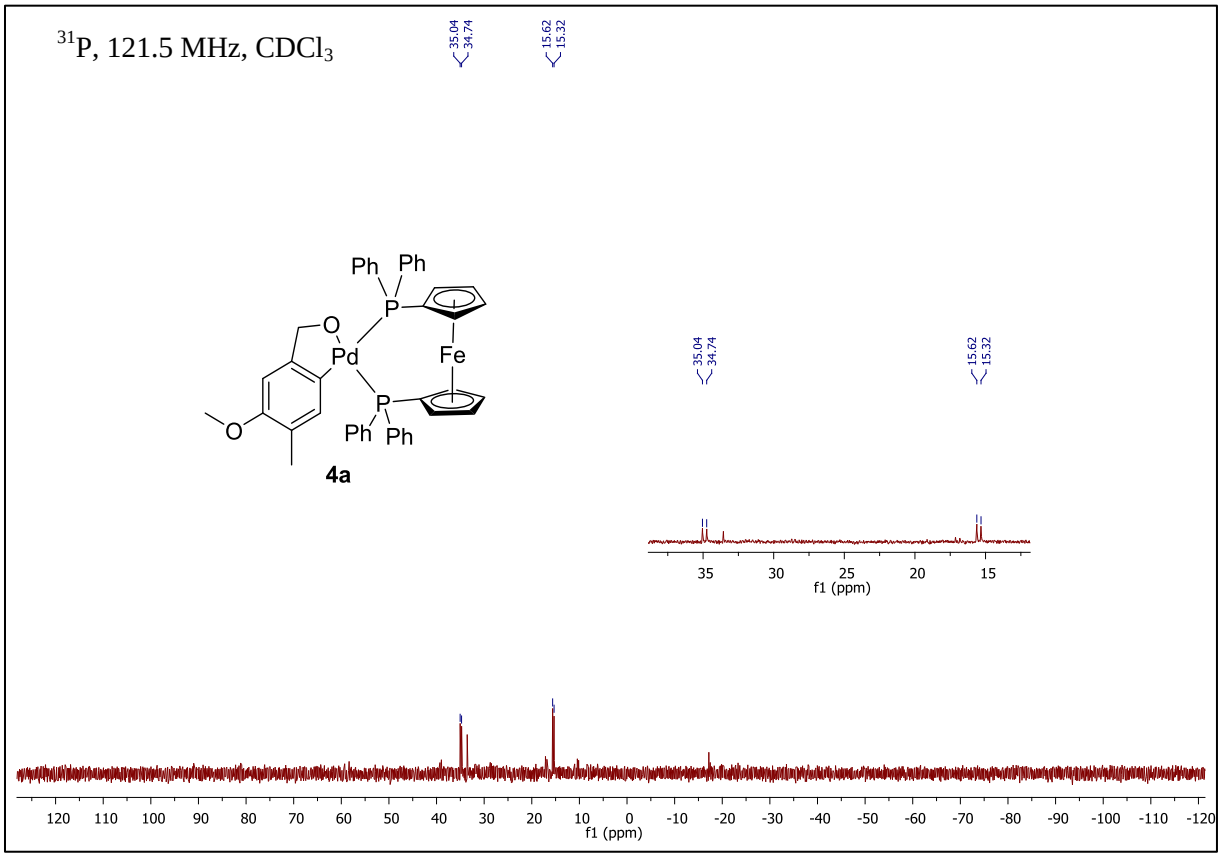
^{13}C, 75.3 MHz, $CDCl_3$



^{1}H, 300 MHz, $CDCl_3$

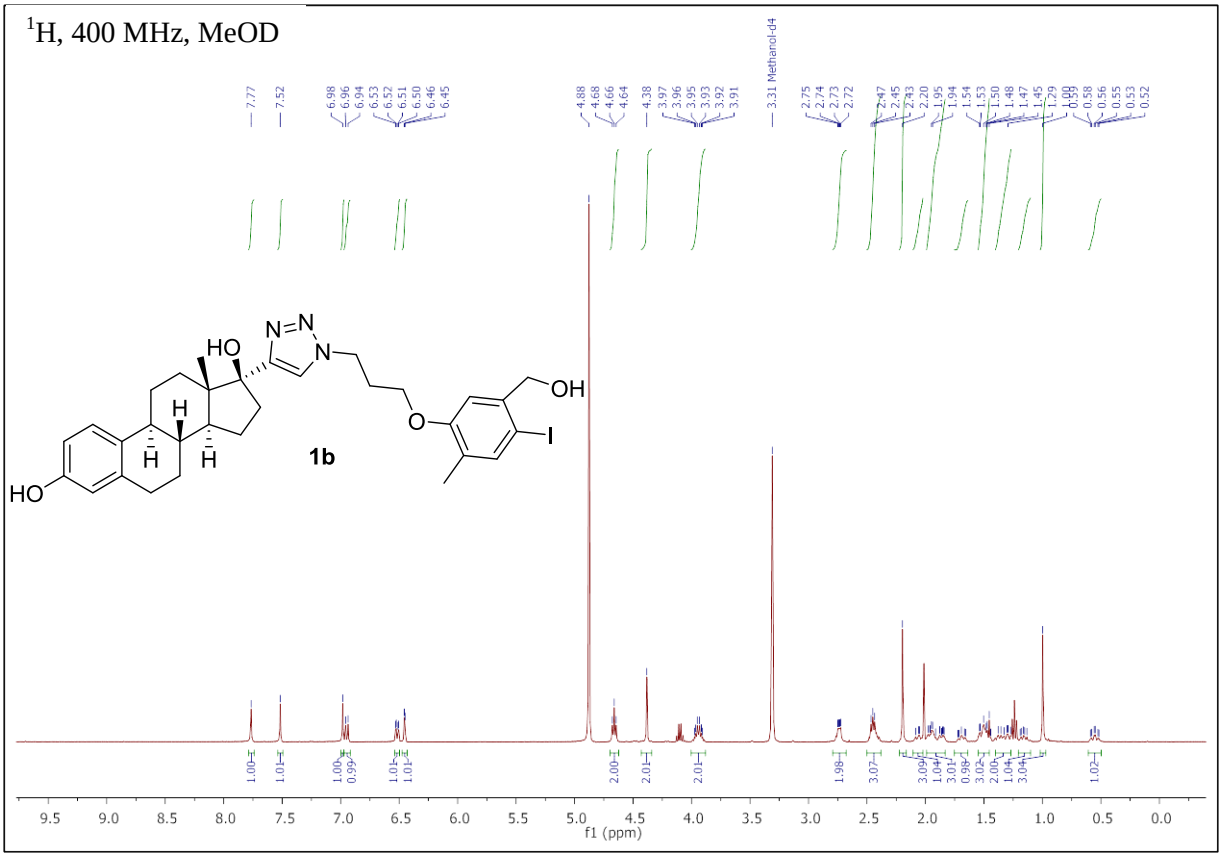


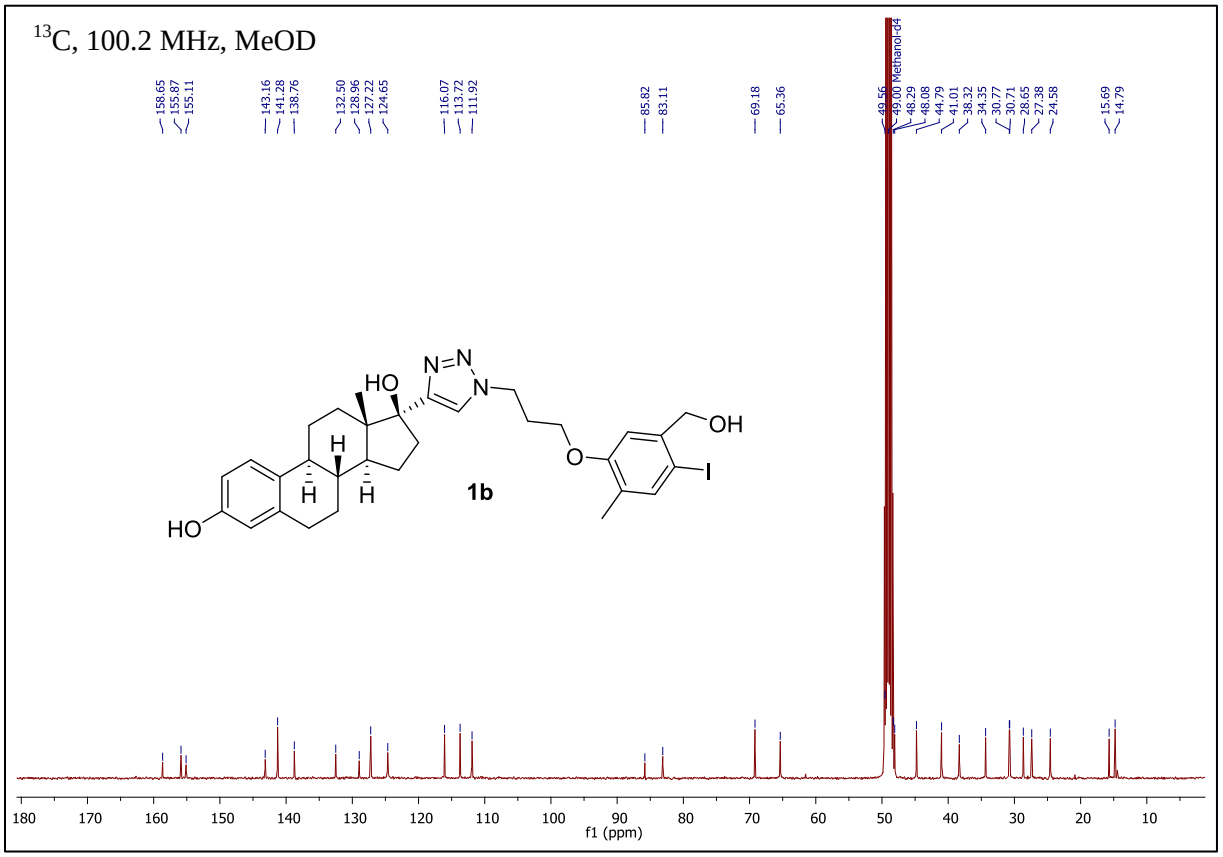
^{31}P, 121.5 MHz, $CDCl_3$



*b. Substrates **1b**, **1c** and **1d***

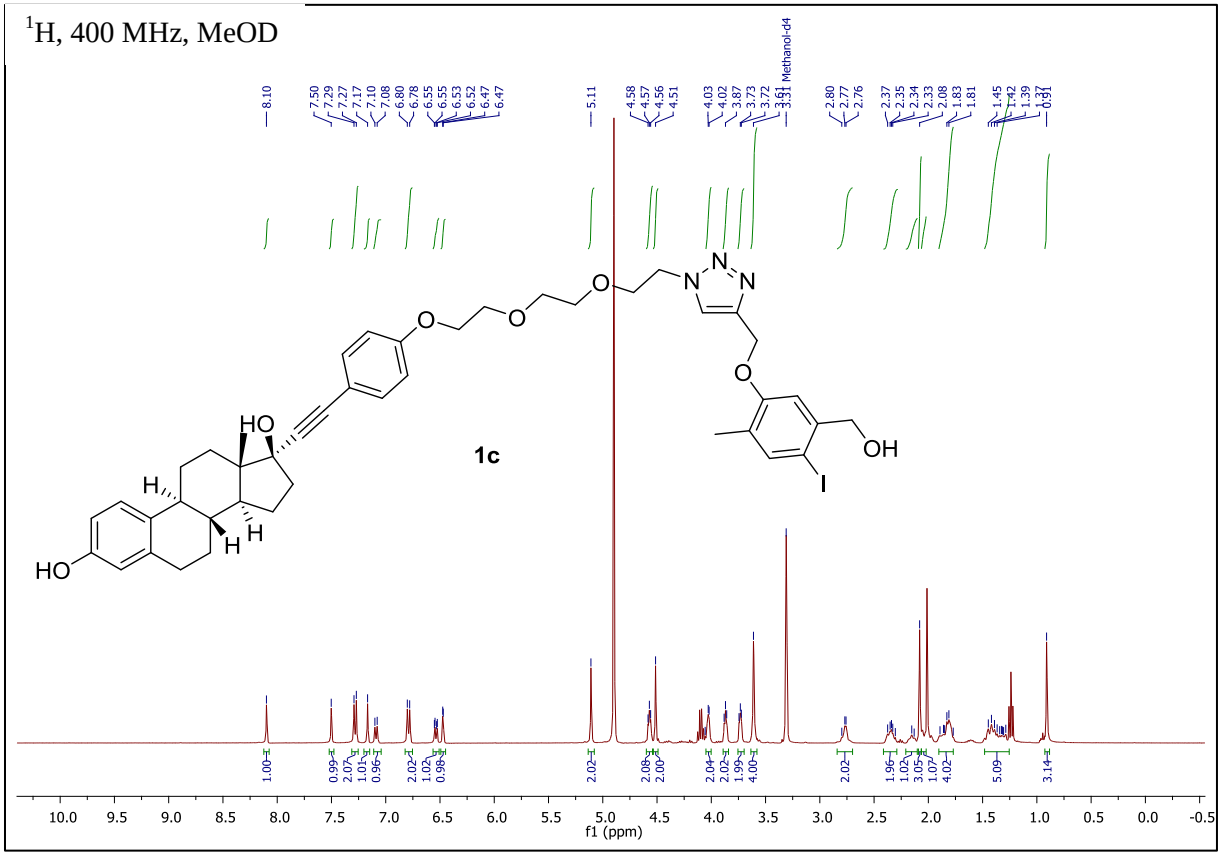
17-(1-(3-(5-(Hydroxymethyl)-4-iodo-2-methylphenoxy)propyl)-1*H*-1,2,3-triazol-4-yl)-estradiol 1b:



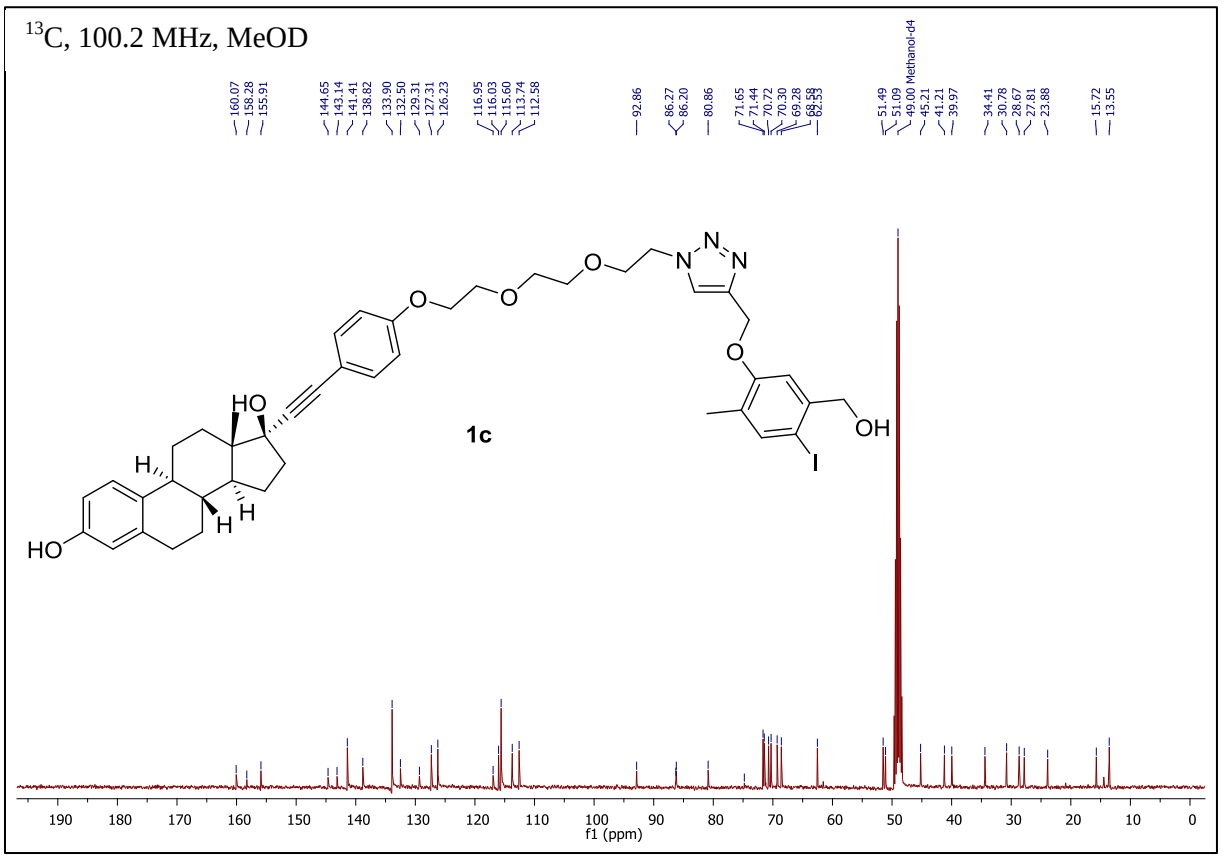


17-((4-(2-(2-(2-(4-((5-(Hydroxymethyl)-4-iodo-2-methylphenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)phenyl)ethynyl)-estradiol 1c:

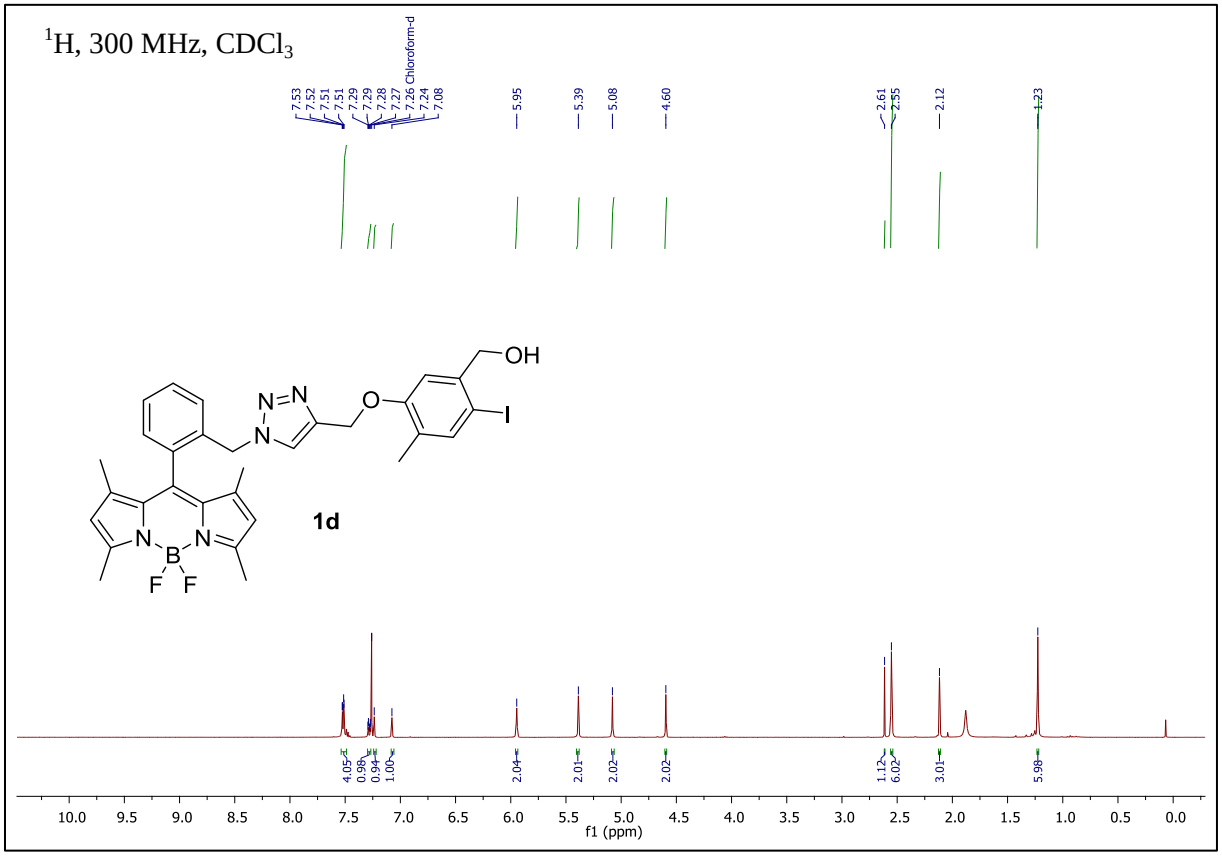
^{1}H, 400 MHz, MeOD

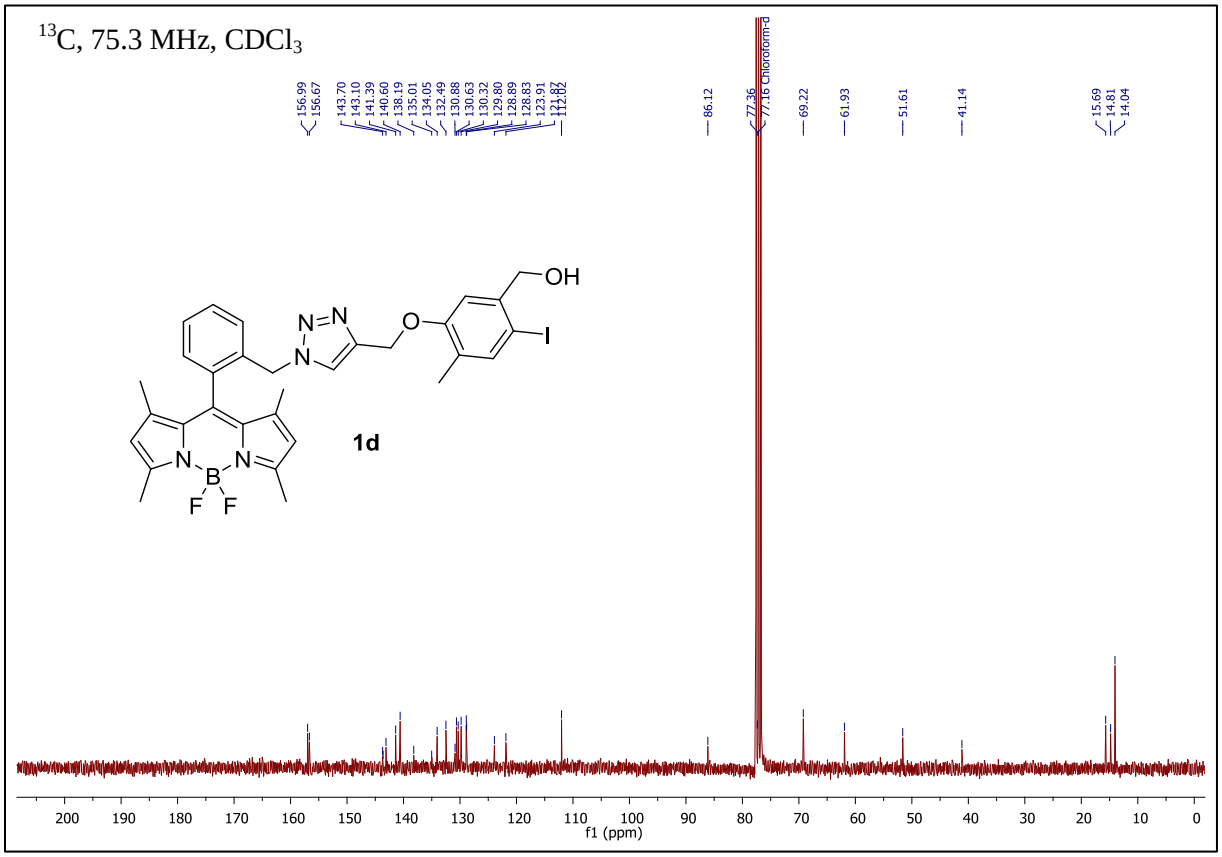


^{13}C, 100.2 MHz, MeOD



(5-((1-(2-(5,5-difluoro-1,3,7,9-tetramethyl-5H-4l4,5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-10-yl)benzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2-iodo-4-methylphenyl)methanol 1d:

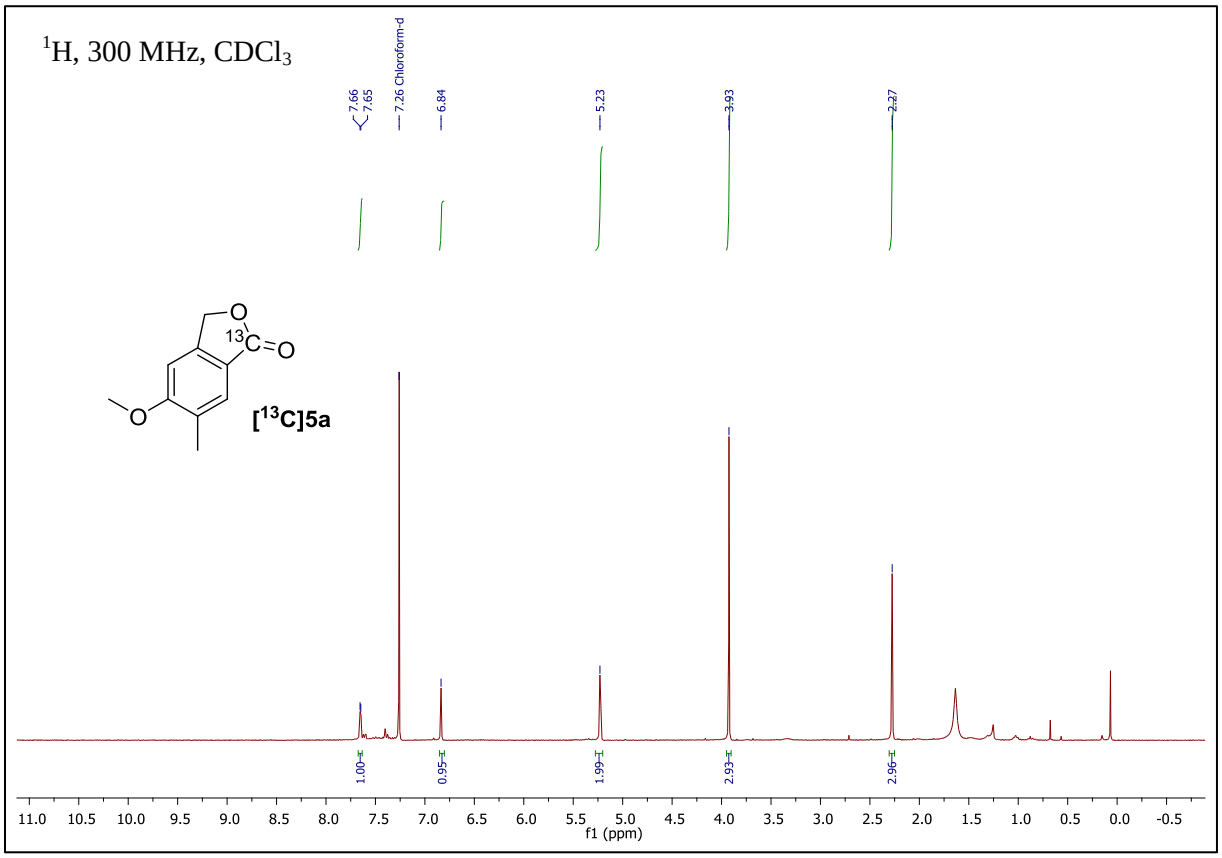


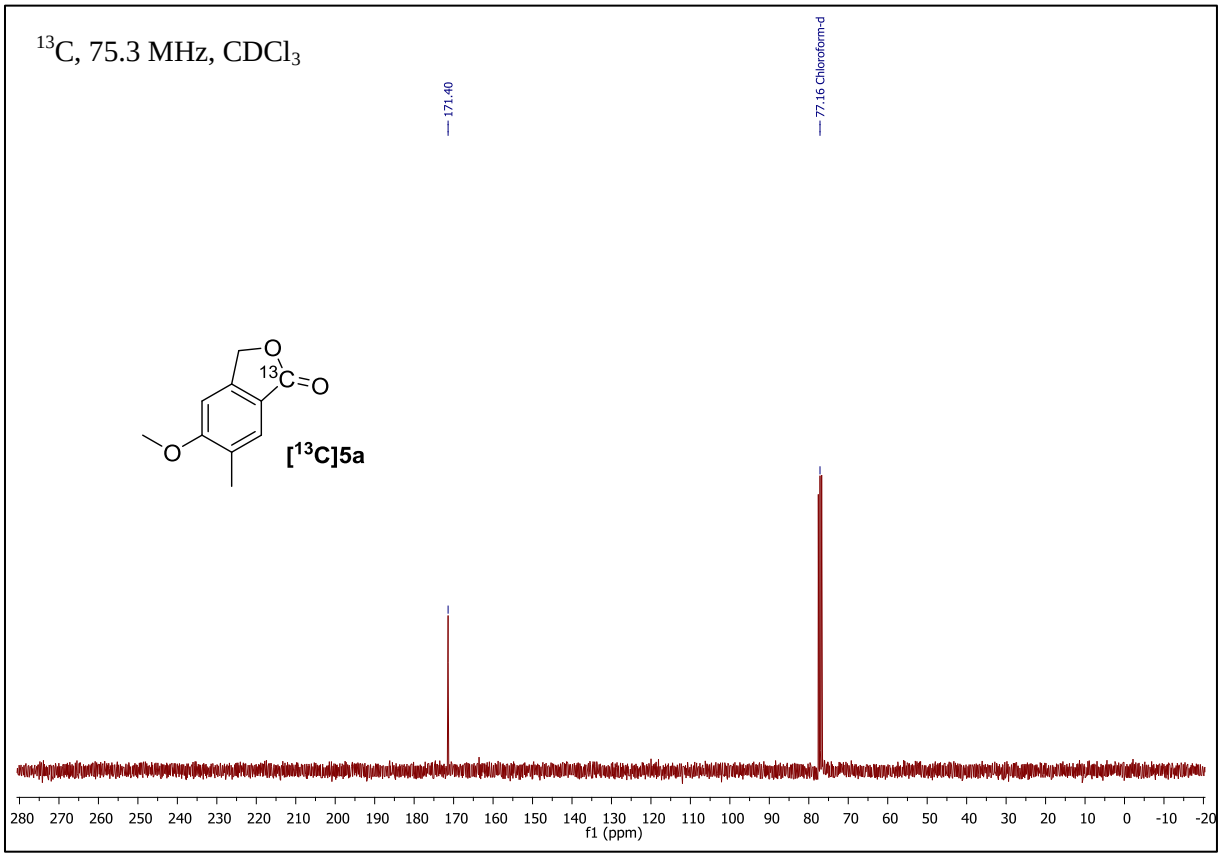


*c. [^{13}C]compounds (**5a-h**)*

5-Methoxy-6-methylisobenzofuran-1(3*H*)-one-1-^{13}C [^{13}C]5a :

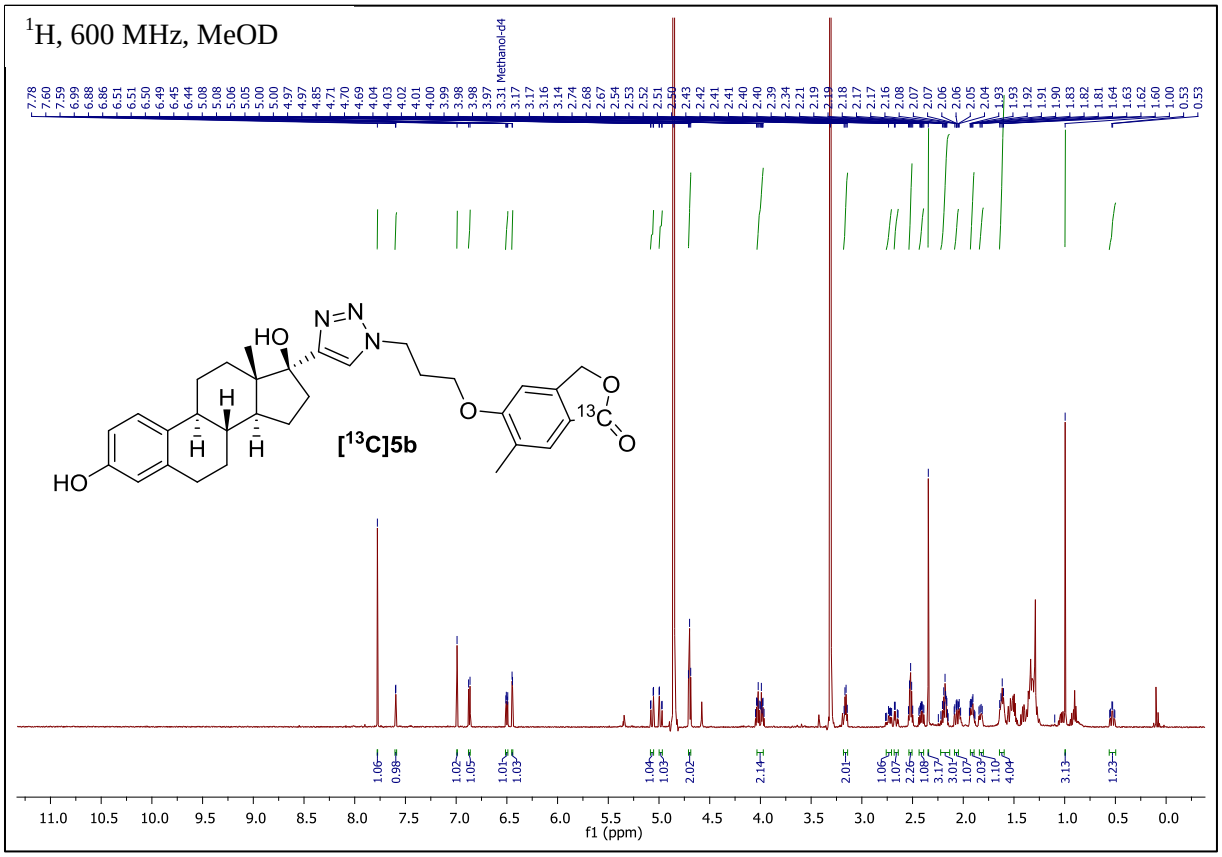
*"From the supported preformed Pd-complex **2-Ps-a**, after filtration on a sintered glass"*

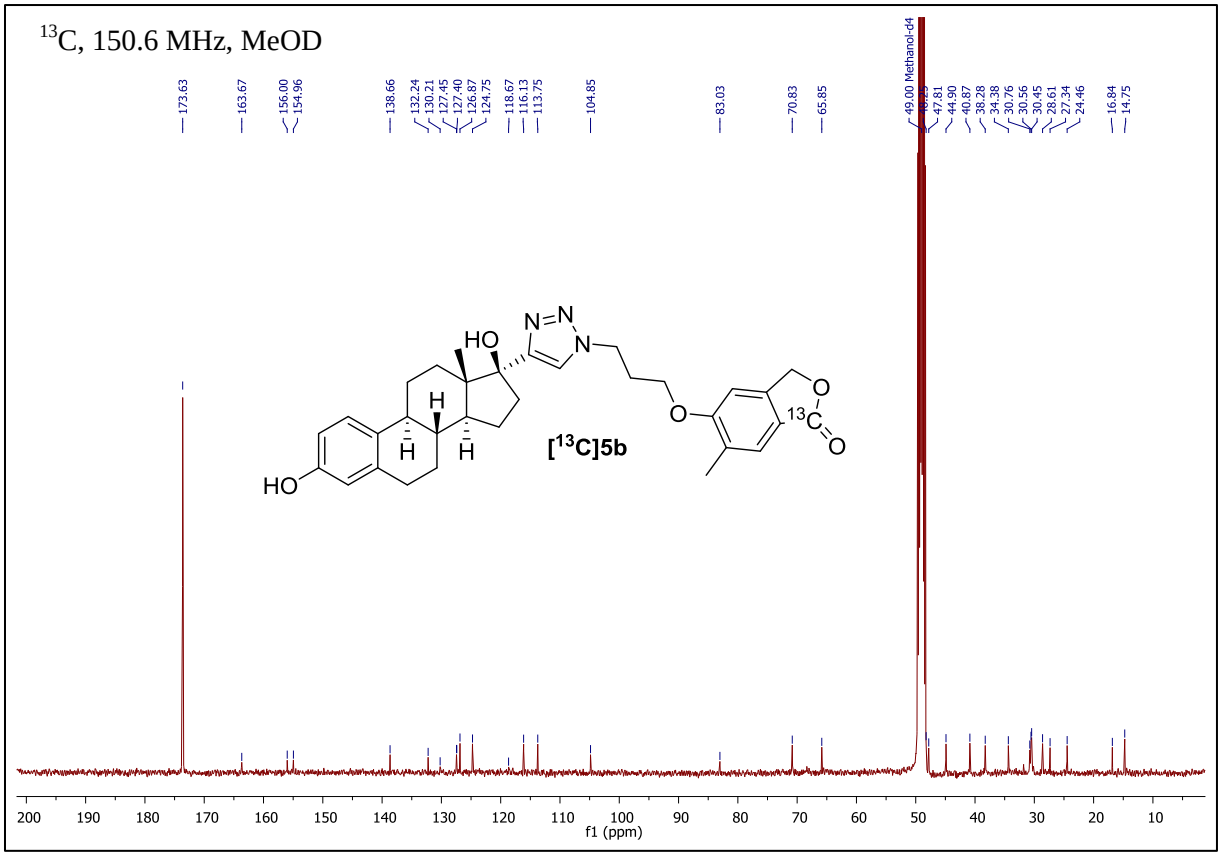




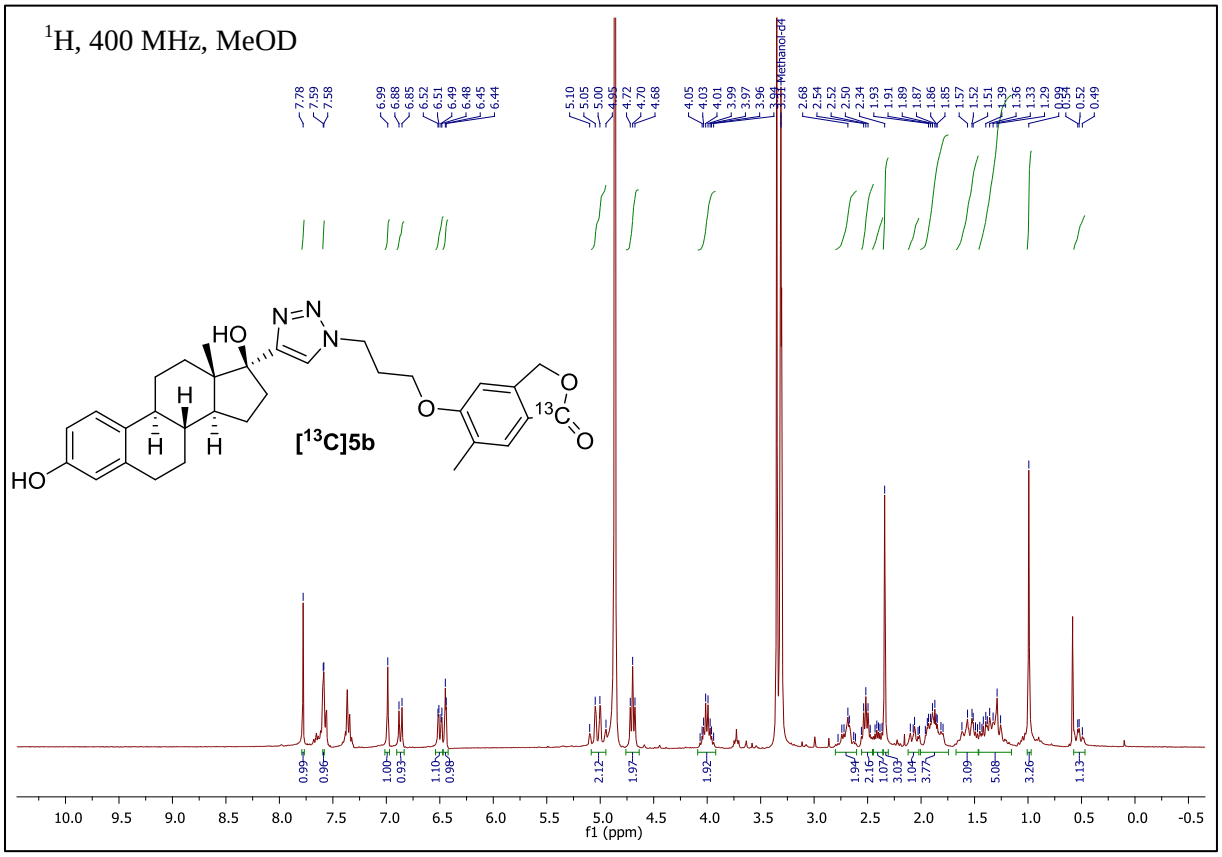
^{13}C-17-[1-(3-((6-Methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)oxy)propyl)-1*H*-1,2,3-triazole-4-yl]-estradiol [^{13}C]5b :

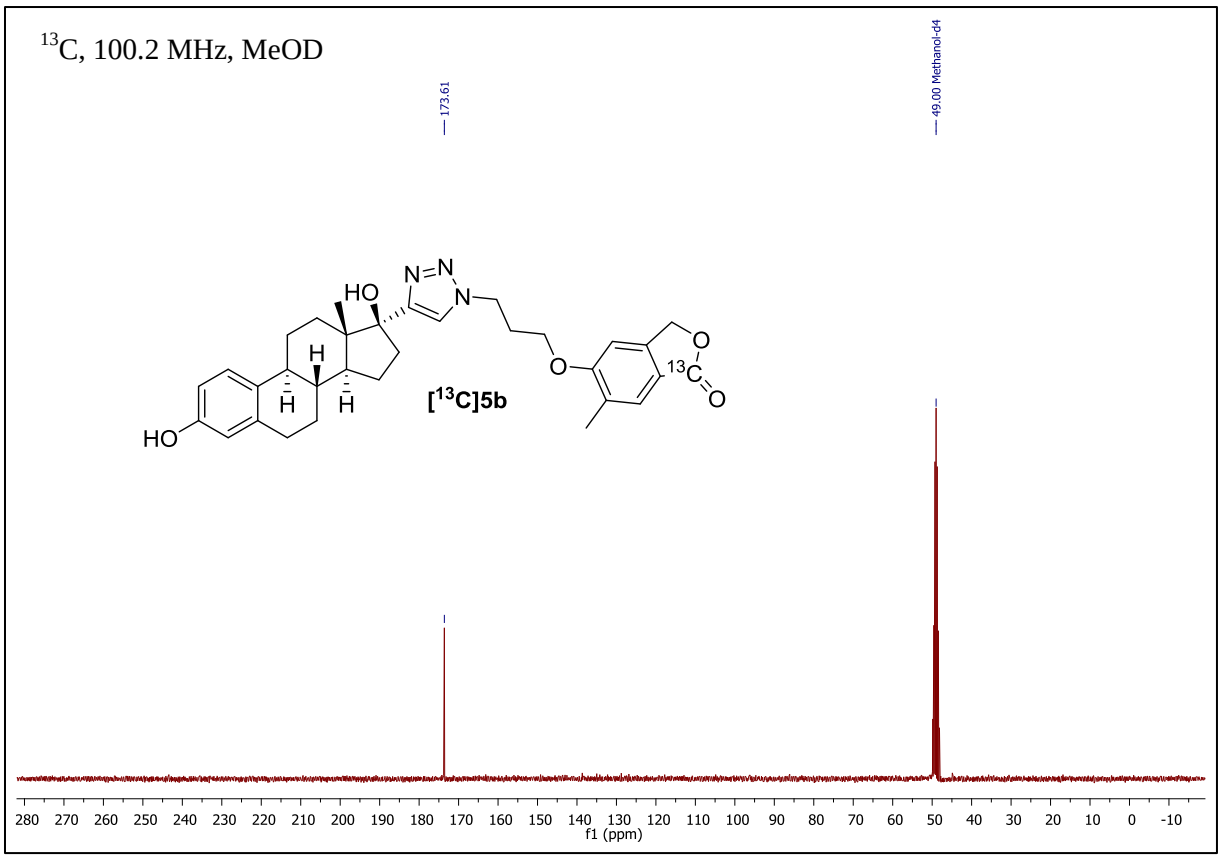
"Using a catalytic amount of Pd-catalyst, after column chromatography on silica gel"





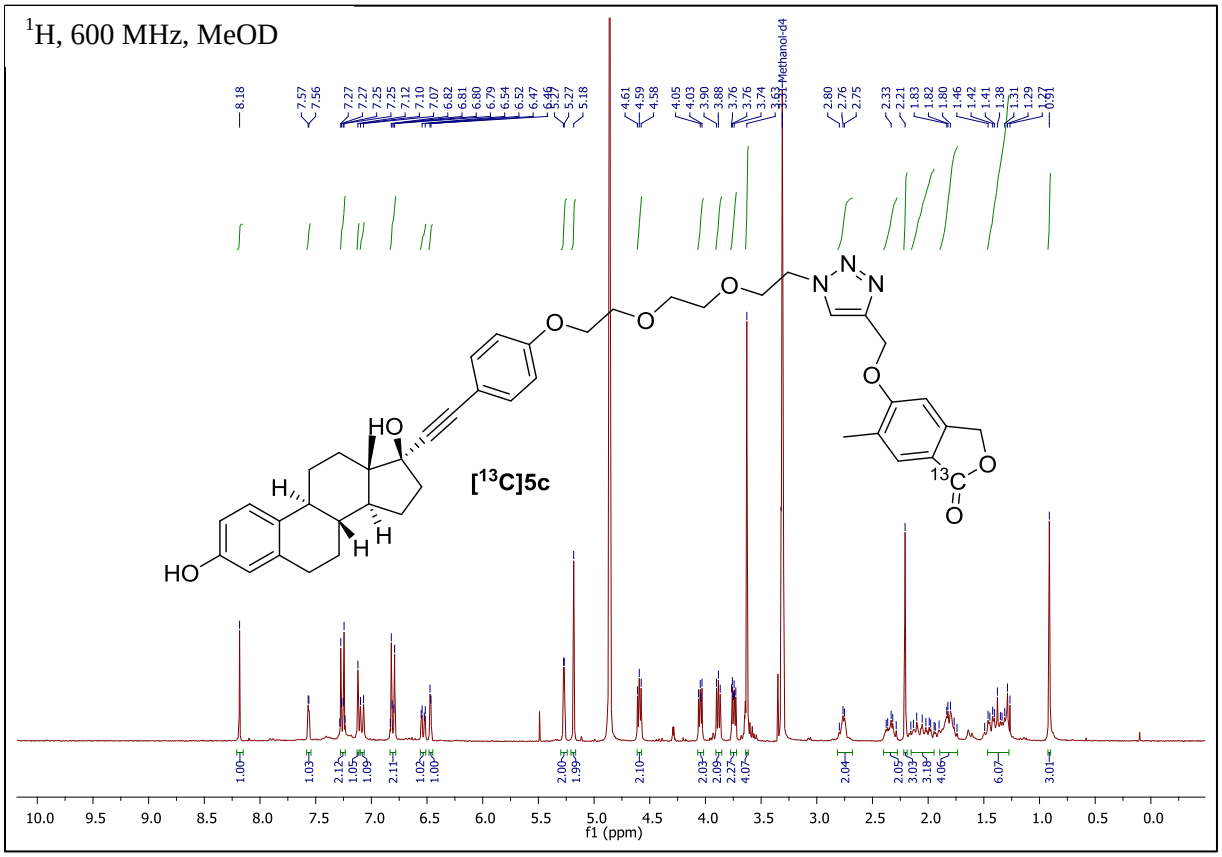
*"From the supported preformed Pd-complex **2b–PS**, after filtration on a sintered glass"*

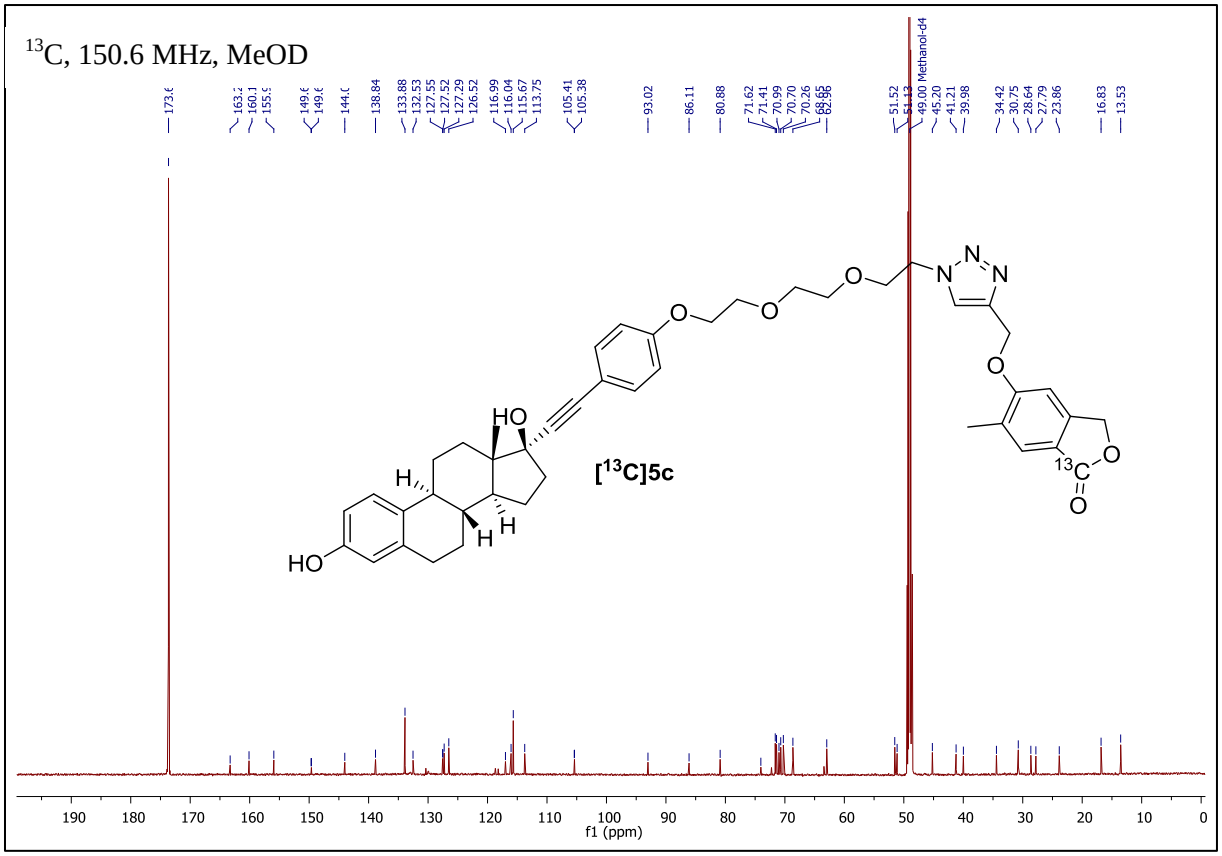




^{13}C-17-((4-(2-(2-(2-(4-((6-Methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)phenyl)ethynyl)-estradiol [^{13}C]5c :

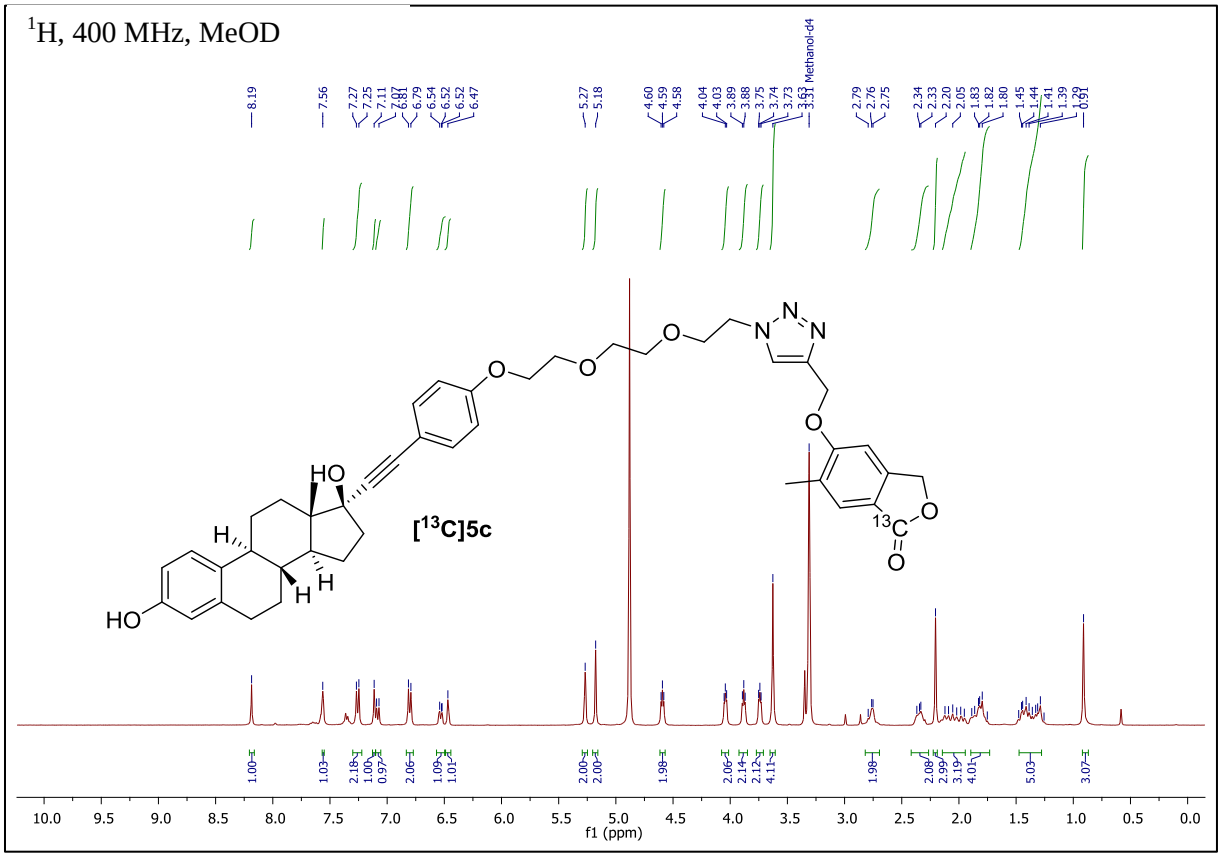
"Using a catalytic amount of Pd-catalyst, after column chromatography on silica gel"



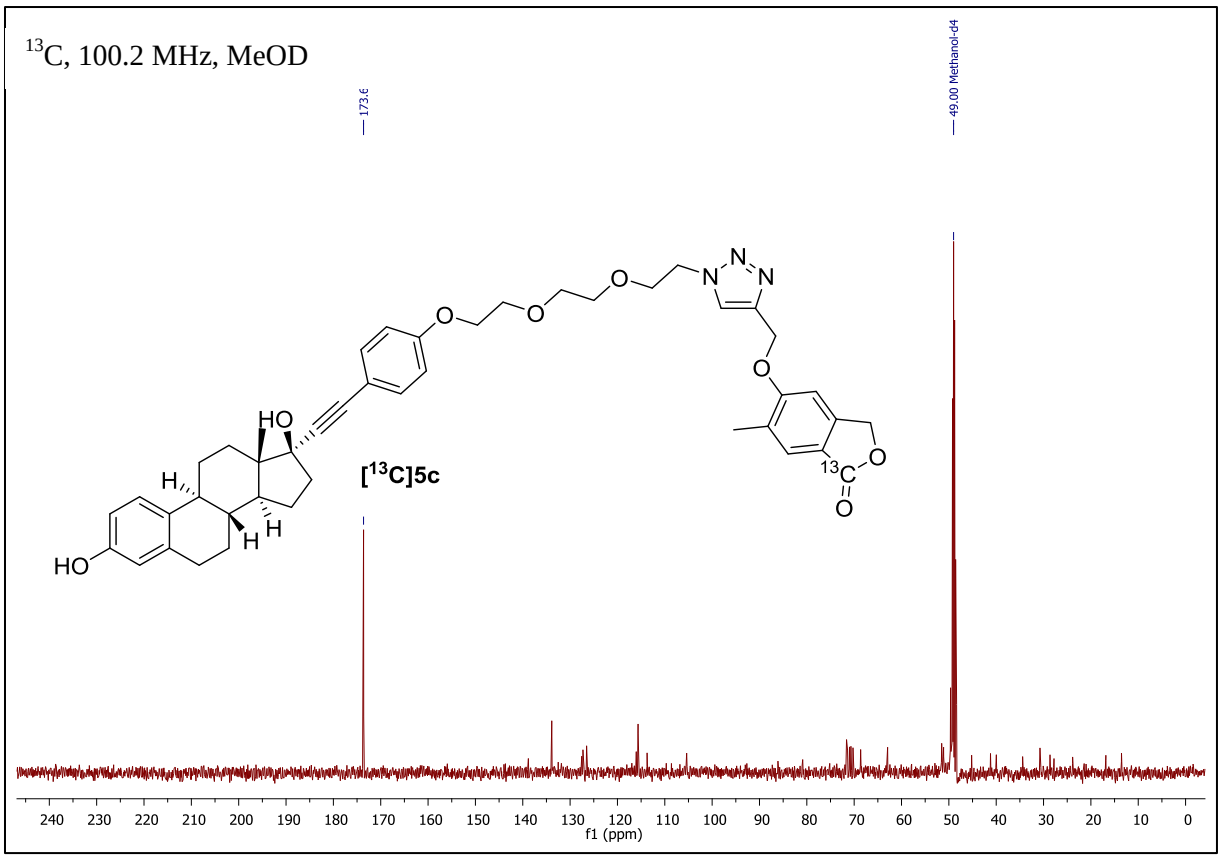


*"From the supported preformed Pd-complex **2c–PS**, after filtration on a sintered glass"*

^{1}H, 400 MHz, MeOD

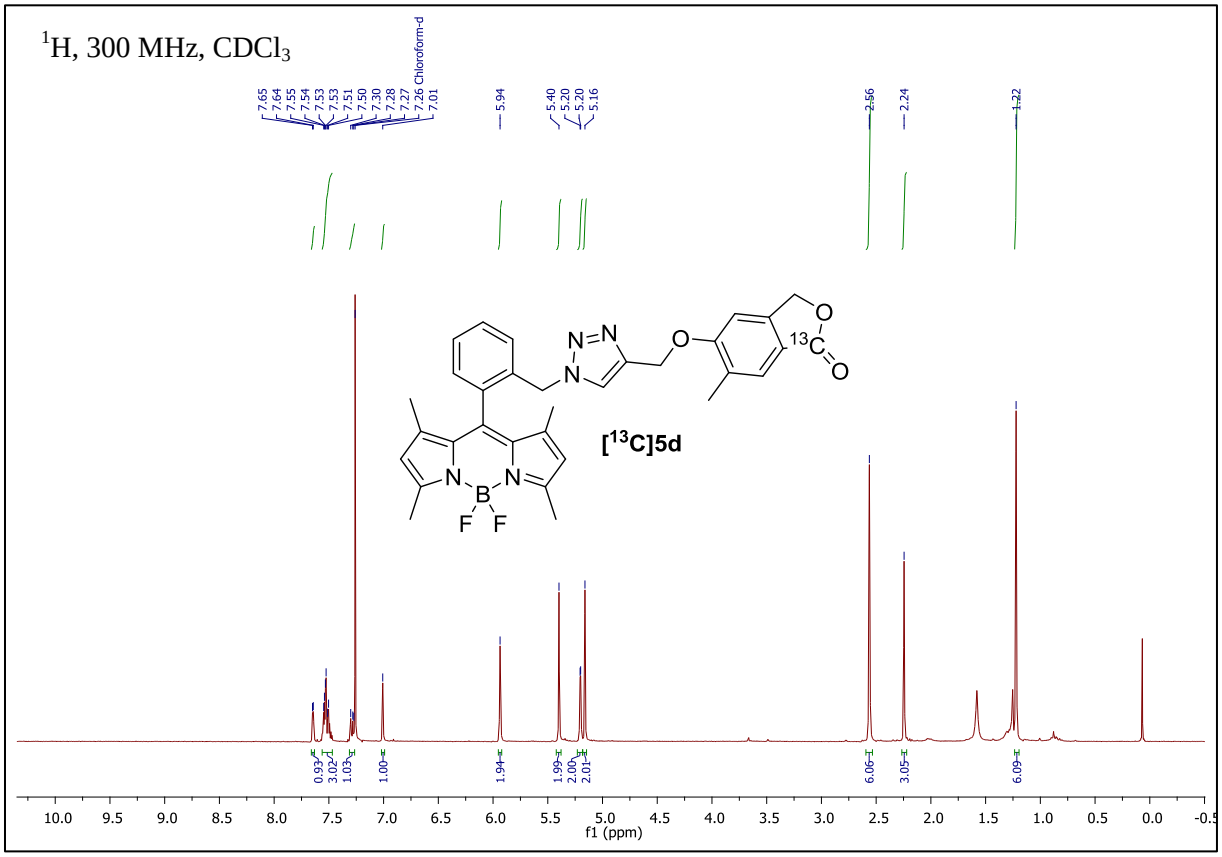


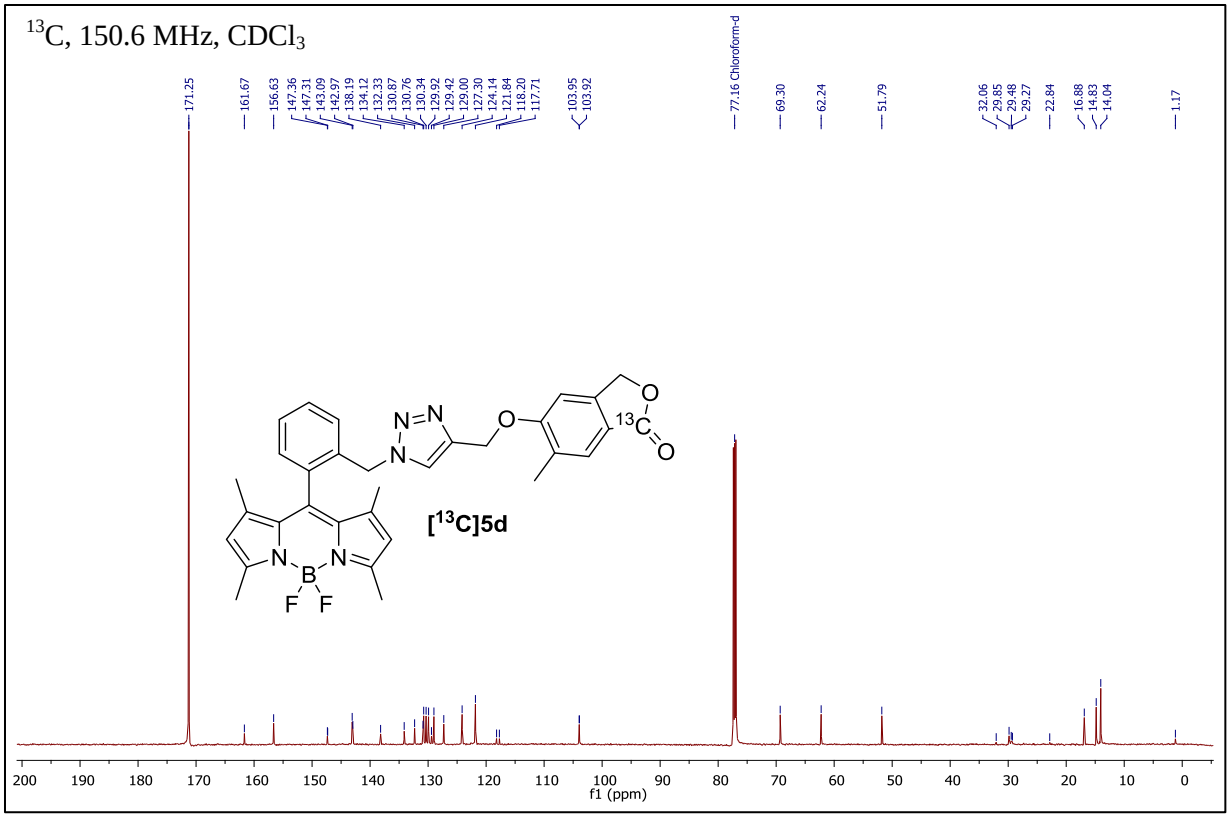
^{13}C, 100.2 MHz, MeOD



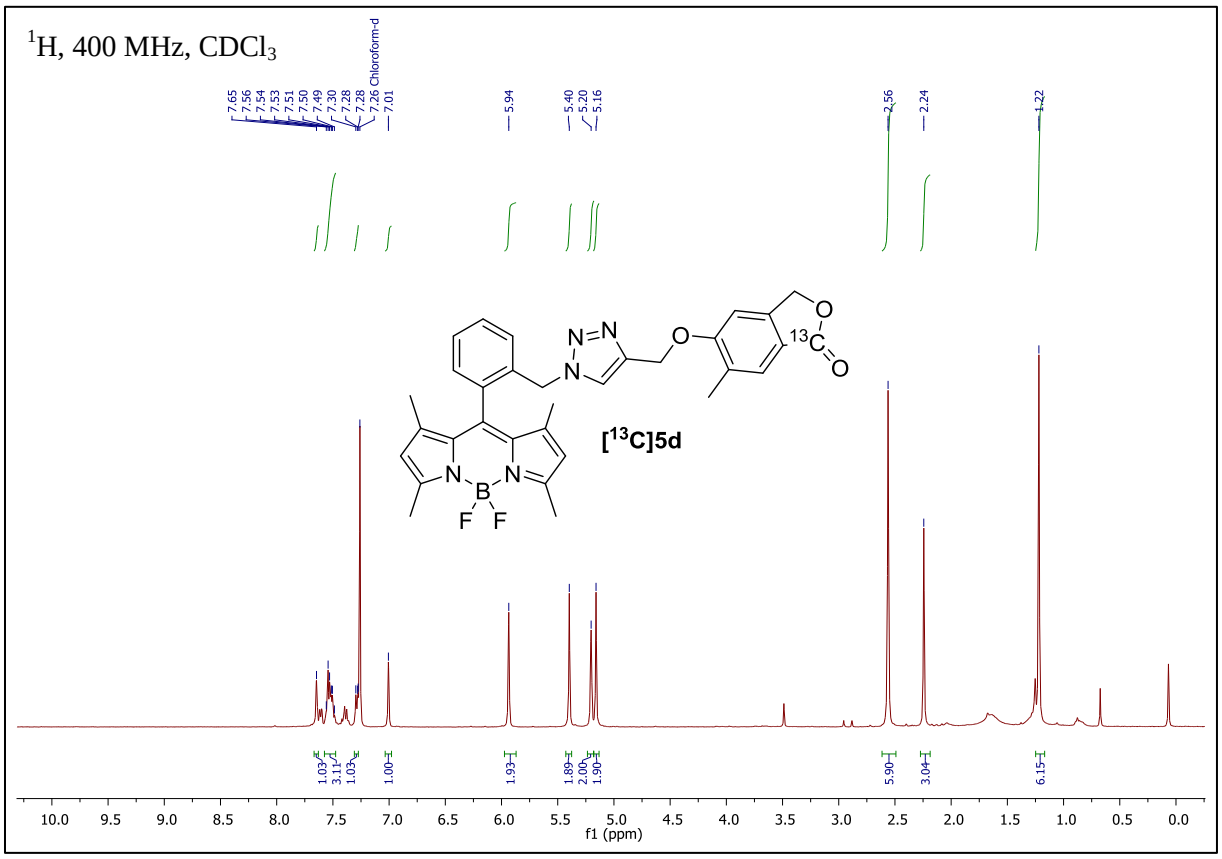
^{13}C-5-((1-(2-(5,5-Difluoro-1,3,7,9-tetramethyl-5*H*-4l4,5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]-diaza-borinin-10-yl)benzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-6-methylisobenzofuran-1(3*H*)-one [^{13}C]5d :

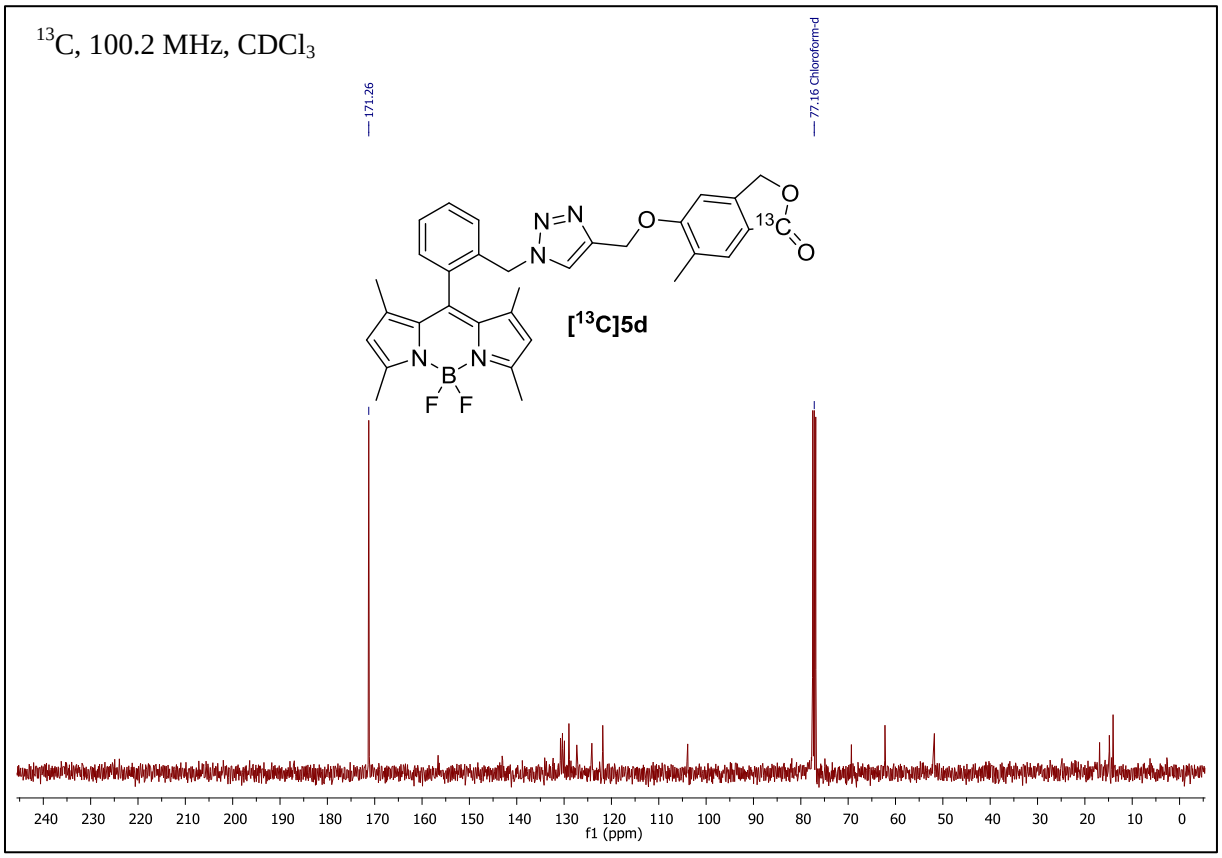
"Using a catalytic amount of Pd-catalyst, after column chromatography on silica gel"





*"From the supported preformed Pd-complex **2d–PS**, after filtration on a sintered glass"*

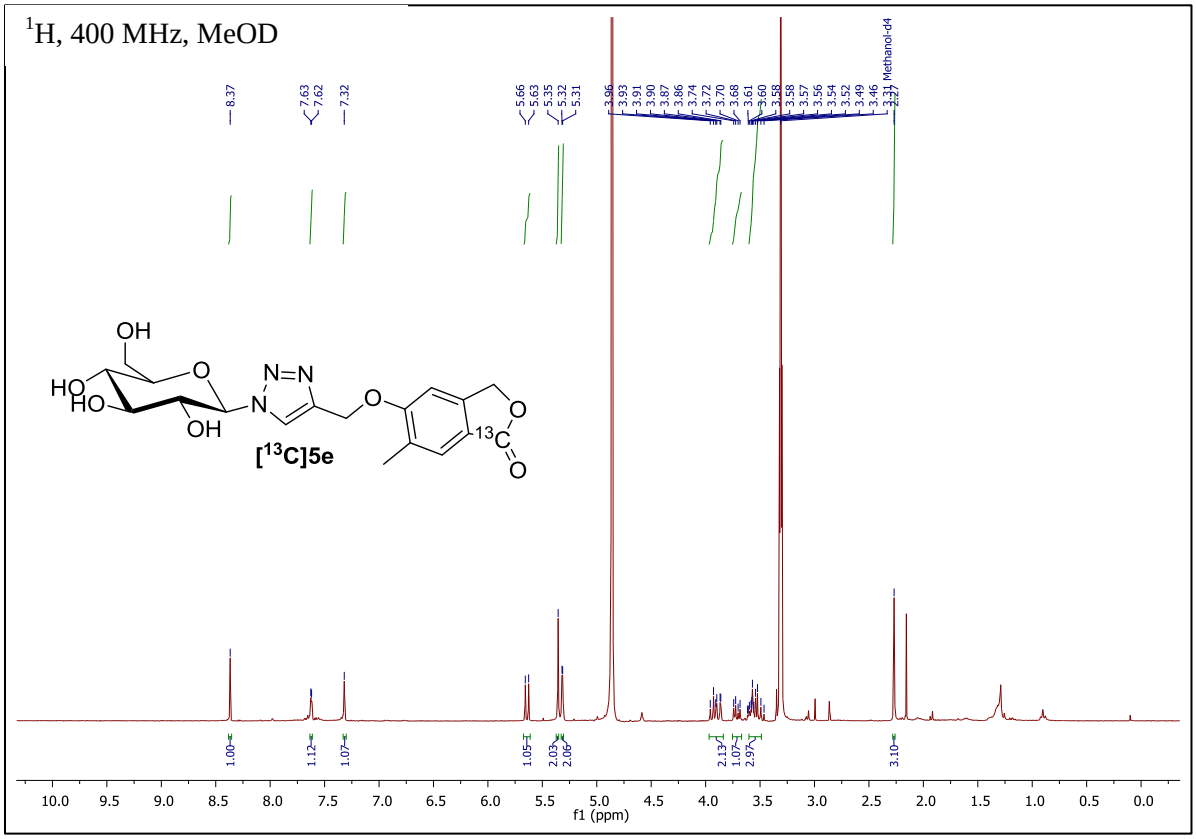




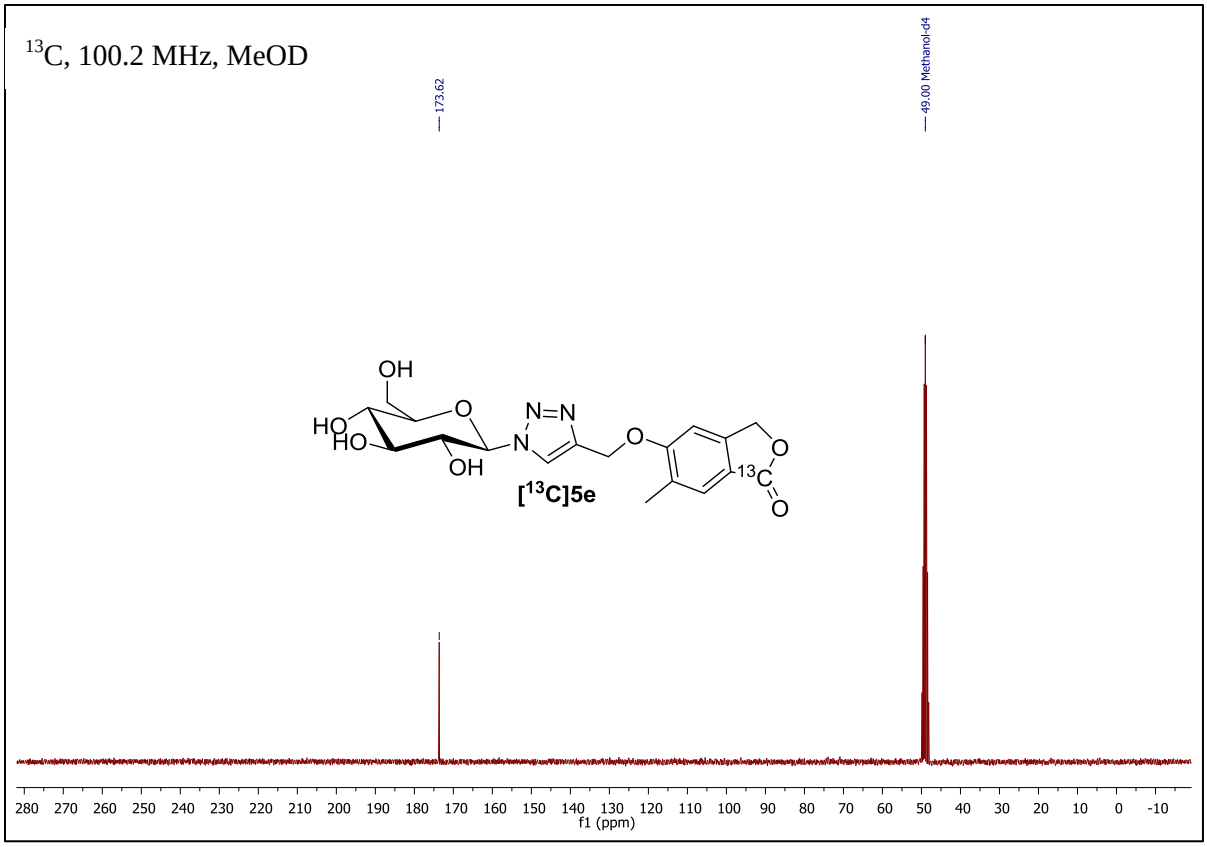
^{13}C-α-D-1-Desoxy-1[4-(((6-methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)oxy)methyl)-1*H*-1,2,3-triazole-1-yl]-glucopyranose [^{13}C]5e:

*"From the supported preformed Pd-complex **2e–PS**, after filtration on a sintered glass"*

^{1}H, 400 MHz, MeOD

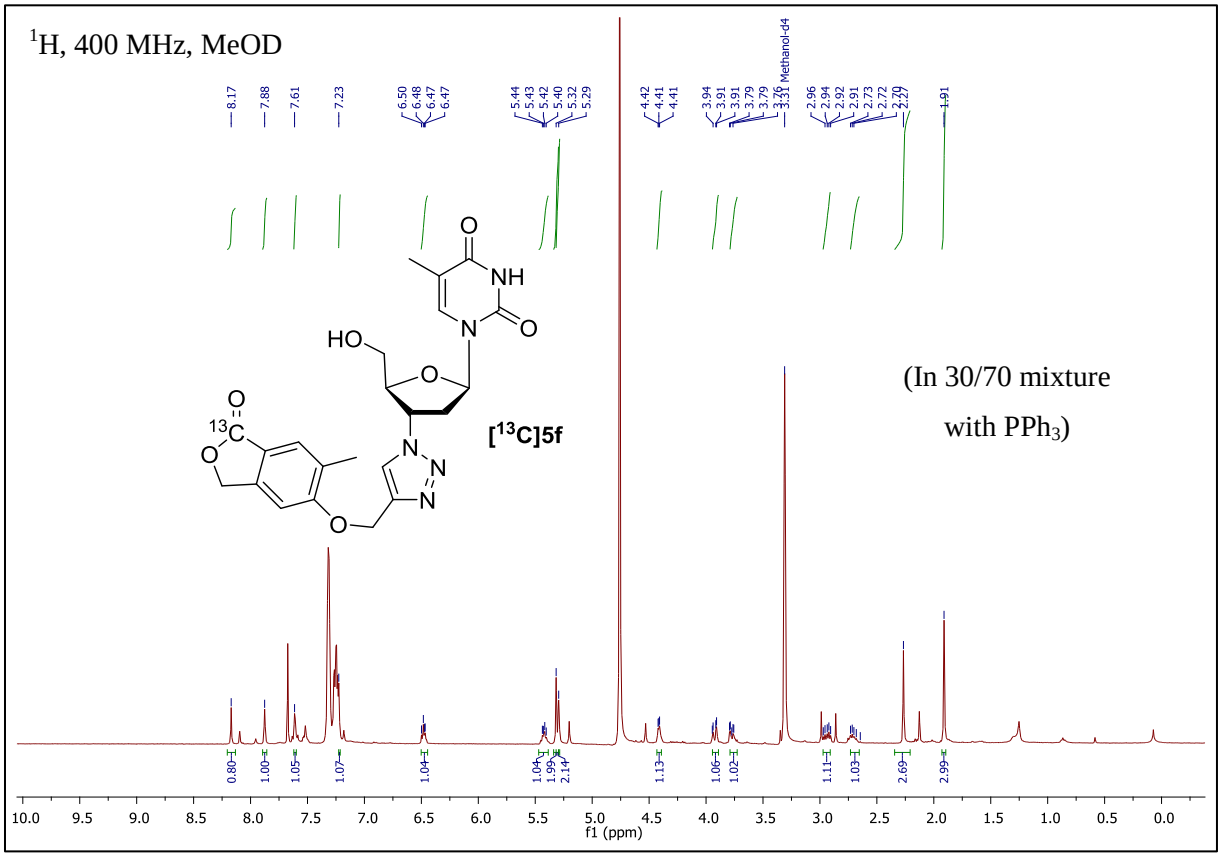


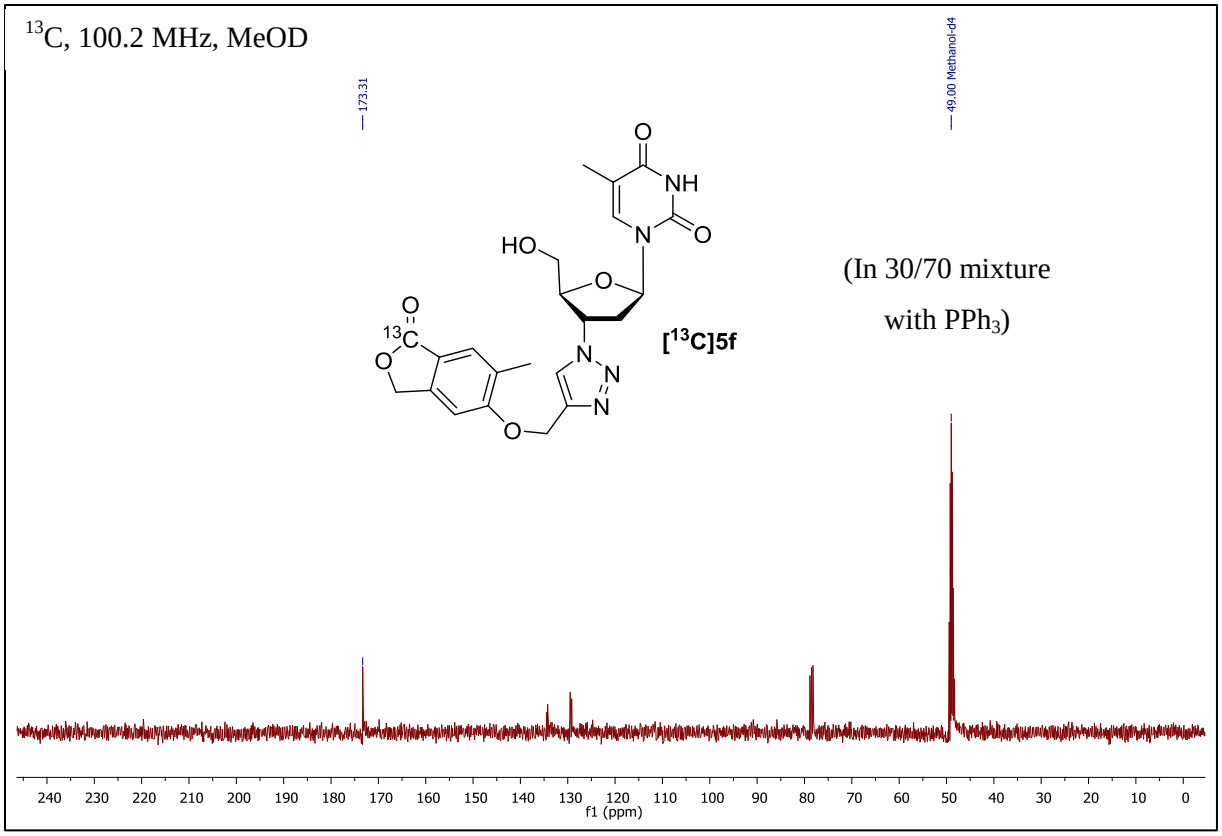
^{13}C, 100.2 MHz, MeOD



^{13}C-3'-Desoxy-3'-[4-(((6-methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)oxy)methyl)-1*H*-1,2,3-triazole-1-yl]-thymidine [^{13}C]5f :

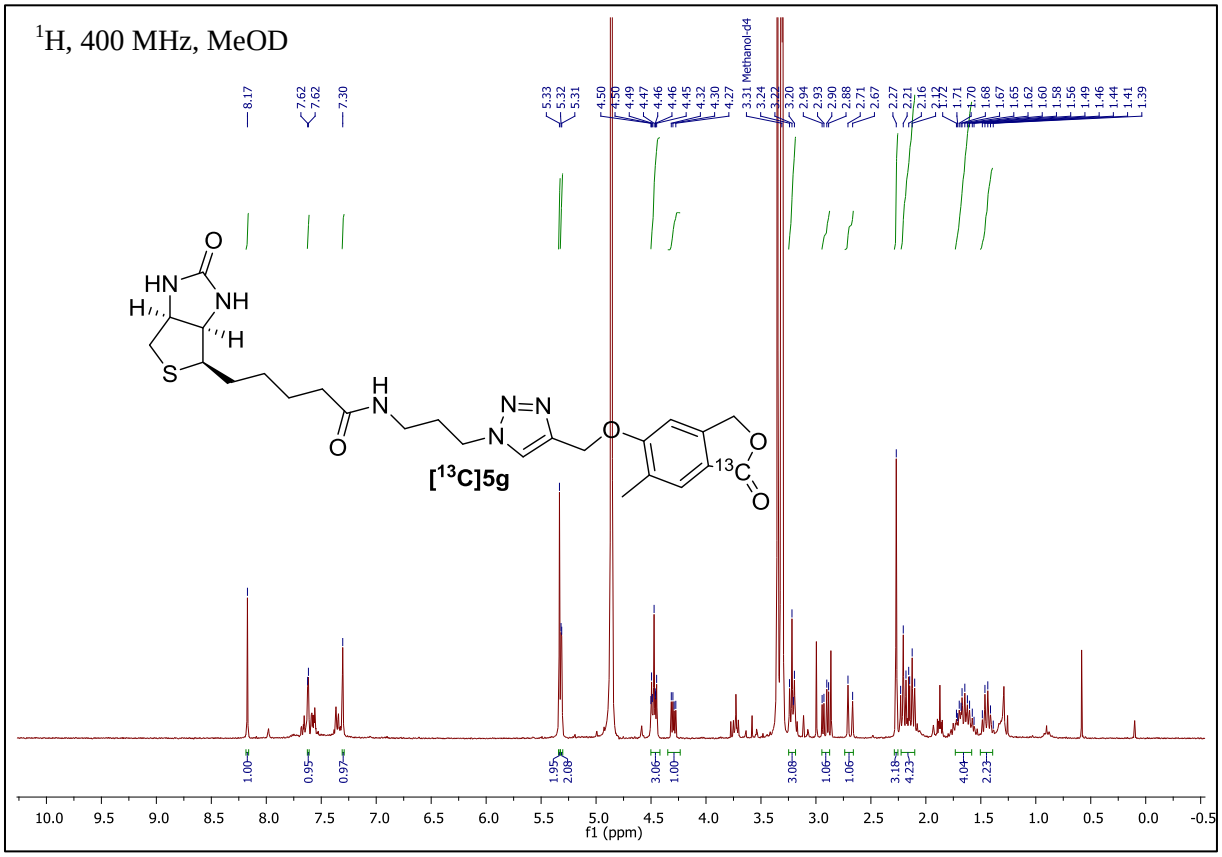
*"From the supported preformed Pd-complex **2f–PS**, after filtration on a sintered glass"*

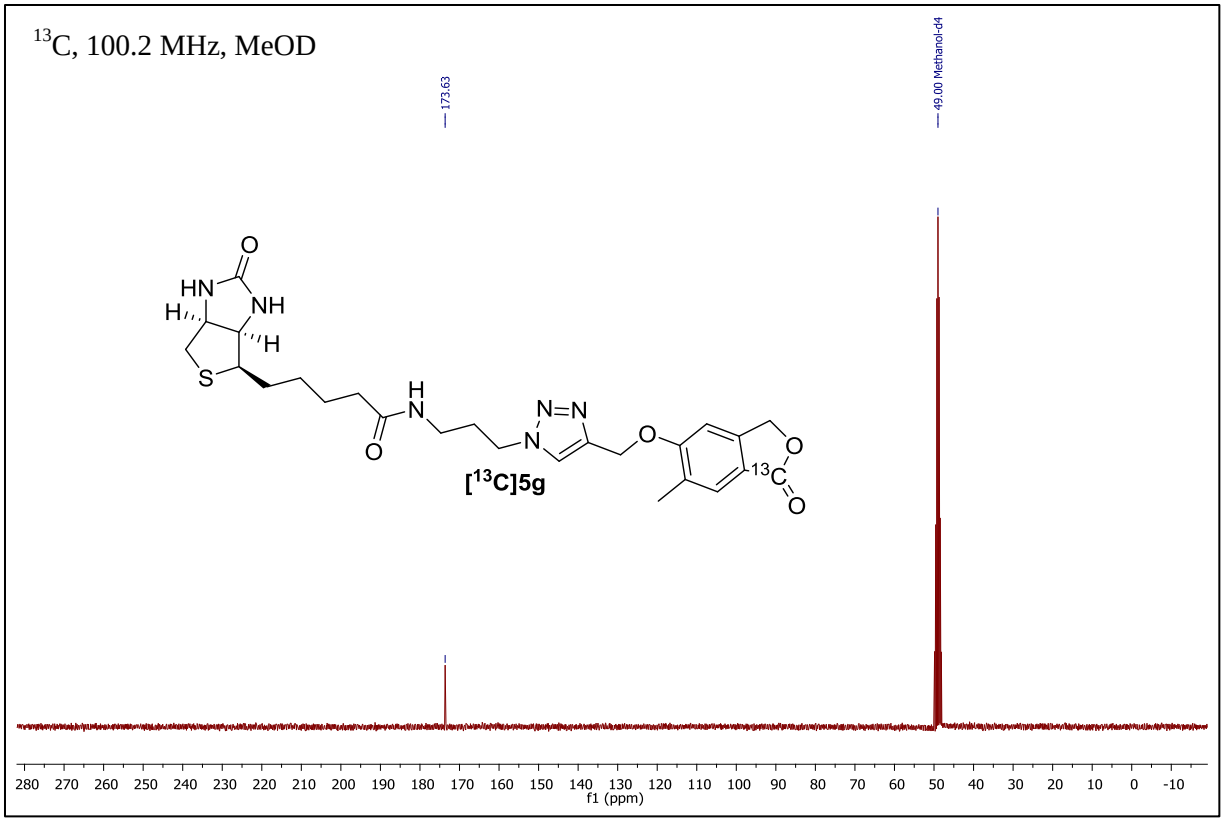




^{13}C-*N*-(3-(4-(((6-Methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)propyl)-biotinamide [^{13}C]5g :

*"From the supported preformed Pd-complex **2g–PS**, after filtration on a sintered glass"*





^{13}C-Cyclo-RGD-[2-(4-(((6-methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)-yl] [^{13}C]5h

*"From the supported preformed Pd-complex **2h–PS**, after filtration on a sintered glass"*