## Electronic supporting information

# Cyclic decapeptide Gramicidin S Derivatives containing phosphines: Novel ligands for asymmetric catalysis

*Gregorio Guisado-Barrios,* [a] *Bianca K. Muñoz,*[a] *Paul C. J. Kamer*[*],[a] *Bas Lastdrager,*[b] *Gijs van der Marel,* [b] *Mark Overhand,*[b] *Marino Vega,*[c] *and Manuel Martin-Pastor*[c]

[a] *School of Chemistry, University of St Andrews, St Andrews, Fife, UK, KY16 9ST, Fax: +44(0) 1334463808; Tel: +44 (0)1334467258; E-mail: pcjk@st-andrews.ac.uk*
[b] *Faculty of Science, Leiden Institute of Science, Eisteinweg55, 2333 CC Leiden ,Netherlands.*
[c] *Laboratorio Integral de Dinámica e Estructura de Biomoléculas José R. Carracido, Unidade de Resonancia Magnética, Edificio CACTUS, RIAIDT, Univesidade de Santiago de Compostela,15706, Santiago de Compostela. Spain*

### General information

Reagent grade solvents were used, dried and distilled before previous use following standard methods. Dichloromethane was distilled over calcium hydride; methanol was distilled over magnesium and iodine, under argon and degassed. Gramicidin S was obtained as reported in literature.[1] *o*–, *m*–, and *p*–Diphenylphosphine benzoic acid (**1a**, **1b** and **1c**), and diphenylphosphine, were purchased from Fluka. Bis(norbornadiene)rhodium(I) tetrafluoro borate, allylpalladium (II) chloride dimer were purchased from Strem Chemicals Inc. Dimethyl-2-methyl succinamate and methyl 2-acetamidoacrylate, were purchased from Aldrich and used without further purification, methyl (Z)-α-acetamidocinnamate was prepared from (Z)-2-acetamido-3-phenylacrylic acid and trimethylsilsyl diazomethane according to a method adapted from literature.[2] Diphenyl allyl acetate was prepared following a reported method[3]. All solid chemicals were used as received without any further purification.

$^{1}H$, $^{31}P$ and $^{13}C$ NMR were recorded in $CDCl_3$ or $CD_2Cl_2$ at room temperature on a Bruker Gemini 400 MHz spectrometer. Chemical shifts were determined relative to solvent residual peaks on $^{1}H$, $^{13}C$ NMR and external $H_3PO_4$ for $^{31}P$ NMR. Maldi TOF spectra were recorded on a Dionex UltiMate 3000 nanoflow HPLC and a Dionex Probot spotting robot. Enantiomeric excesses were determined by capillary GC or HPLC analysis:
GC: Thermo gas chromatograph equipped with a flame ionization detector and two chiral columns: Permabond-L-Chirasyl-Val (Macheray-Nagel), 25 m x 0.25 mm column: He carrier gas: 1.2 bar, inlet injector 280°C, oven (85°C; 10 min, 8°C/min; 135°C; 0 min, 10°C/min; 8 180°C; 35min), FID detector 200 °C; retention time: Methyl *N*-acetylacetamidoacrylate: 6.7 min, Methyl (*R*)-*N*-acetylacetamidoalanine: 11.9 min, Methyl (*S*)-*N*-acetylacetamidoalanine: 13.4 min, Methyl (*R*)-*N*-acetylacetamidophenylalanine: 25.5 min, Methyl (*S*)-*N*-acetylacetamidophenylalanine: 26.2 min, Methyl *N*-acetylacetamidocinnamate: 38.5 min.

Supelco β-DEX 225 column (T=70 °C for 50 min, then ΔT =25 °C $min^{-1}$ (E)-dimethyl 2-methylsuccinate: 58.7 min, (S)-dimethyl 2-methylsuccinate: 41.29 min, (R)-dimethyl 2-methylsuccinate 42.2 min.

HPLC: Diphenyl malonate: AD 60:40, 0.5 mL/min, 254, R (15.4) S (16.8) nm. Phenylmethyl malonate: OD-H 99:1, 1 mL/min, 215 nm. R (15.6) S (14.3)

## Catalysis:

### Synthesis of methyl-Z-α-acetamidocinnamate

This preparative method was adapted from literature.[2] Trimethylsilyl diazomethane in ether (5 mL, 10 mmol) was dissolved in a mixture of toluene (200 mL) and MeOH (40 mL) under argon. The α-acetamidocinnamic acid (2.05 g, 10 mmol) dissolved in 10 mL of MeOH was then added to give a yellowish solution. After stirring for 30 min at room temperature, during which period there was nitrogen evolution. The mixture was extracted with diethyl ether (200 mL), dried over $MgSO_4$ and the solvent was evaporated. The entitled compound was obtained as a colourless solid after recrystalisation with DCM/Pentane, yield (51%). The $^{1}H$ and $^{13}C$ NMR of methyl-2-acetamido cinnamate match with those previously reported using different procedure.[4 5]
$^{1}H$-NMR (400 MHz, $CDCl_3$): δ 7.4 (d, 2 H), 7.3 (m, 4 H), 3.8 (s, 3 H), 1.8 (s, 3H).$^{13}C$-NMR (100 MHz, $CDCl_3$): δ 169.2 (q,-$COCH_3$), 165.8 (q,-$NCOCH_3$), 133.7 (q, Ph), 132.4 (t, Ph), 129.7 (d, Ph), 129.5 (d, C=$CH_2$) 128.6(d, Ph), 124.4 (q, C=$CH_2$), 52.7 (s, -$CH_3$), 23.3 (s,-$CH_3$)

### Hydrogenation protocol

The reactions were carried out in a GC vial, reaction volume (0.5 mL), due to the very small amounts of catalyst required; it was observed that reproducibility of the results critically depends on the care taken in the preparation of the catalytic samples. DCM was distilled over $CaH_2$, and degassed prior use.
Catalytic runs were prepared in GC vials, which were previously purged and flushed with argon three times in a carrousel or a Schlenk vessel under argon.
The metal complex stock solution was obtained by adding 0.1 mL of $[Rh(nbd)_2]BF_4$ (2.21 mg, 5.82 µmol) previously dissolved in 1 mL of DCM to a solution of the appropriate ligand (1 mg, 0.582 µmol) in DCM (0.5 mL). The final volume of the metal complex stock solution was 0.6 mL. The solution was stirred at room temperature for 20 min.
Stock solutions of the different substrates, dimethyl itaconate, methyl acetamidoacrylate, methyl acetamidocinnamate and decane (internal standard) were prepared in Schlenk vessels which were previously purged and flushed with argon three times, 14.6 µmol of substrate were dissolved in 5 mL of DCM, 7.3 µmol of decane in 5 mL of DCM.
The GC vials in the carrousel were filled with 1.46 µmol of substrate, 0.73 µmol of decane, and 58.2 nmol of the metal complex. The GC vial was filled with 0.35 mL of DCM to obtain a final reaction volume of 0.5 mL. All GC vials were placed in a stainless steel insert and introduced in a stainless steel autoclave; under argon, all GC vials were punched with a needle.
The autoclave was flushed 3 times with 5 bar of $H_2$ and finally pressurised with 20 bar of $H_2$ and stirred at room temperature for 18 hours.
After the reaction, 0.5 mL of each run was passed through a silica pad, washed with 1 mL of DCM/MeOH (9:1) solution prior GC analysis.

### Allylic Alkylation protocol

Catalytic runs were prepared on GC vials, which were previously purged and flushed with argon three times in a carrousel or Schlenk vessel under argon containing a catalytic amount of KOAc, and the stirring bar. The GC vials were placed in the carrousel.

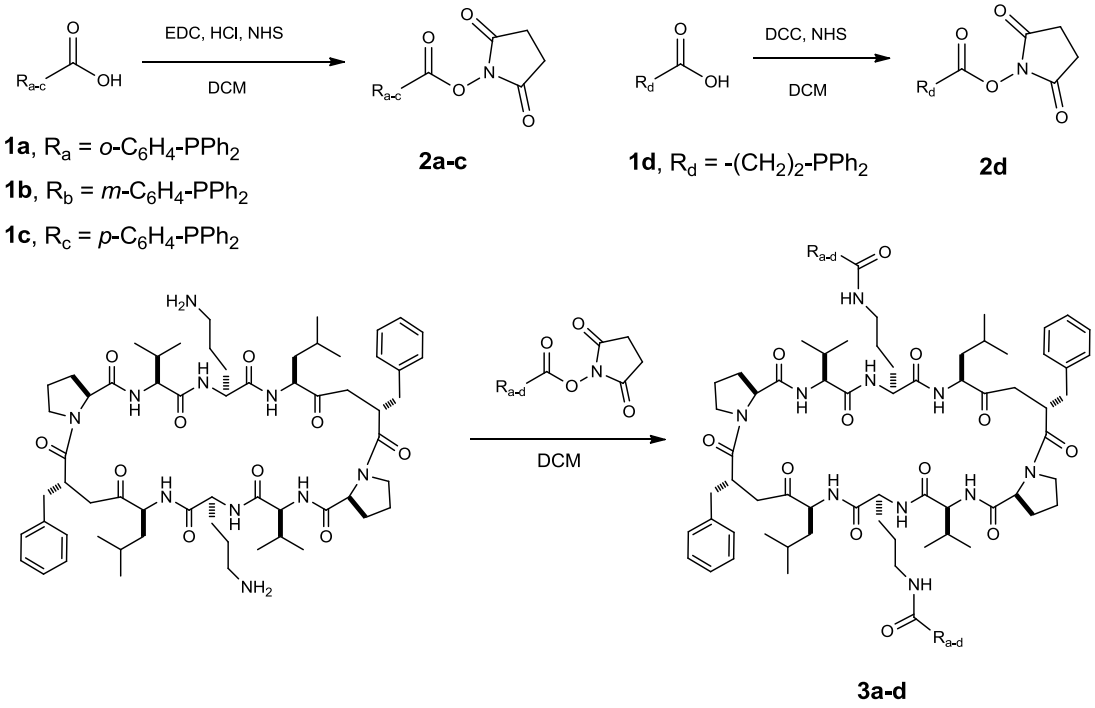
The metal source $[Pd(allyl)Cl]_2$ (1 mg, 2.73 µmol) was dissolved in DCM 1 mL and 0.273 µmol of this solution was added to the stock solution of DCM 0.5 mL of the appropriate ligand (1 mg, 0.582 µmol). The final volume of the stock solution containing the metal complex was 0.6 mL.

Stock solutions of the different substrates, diphenylallyl acetate and phenylmethyl acetate, dimethyl malonate, BSA and diphenyl ether (internal standard) were prepared in Schlenk vessels which were previously purged and flushed with Ar three times.

To the GC vial containing 300 µL, and KOAc, was added 58.2 nmol of the metal complex, 14.6 µmol of substrate, and allowed to stir for 20 min, after this time 6 µmol of dimethyl malonate, 6 µmol of BSA and 7.3 µmol of phenyl ether in DCM 5 mL.

The final reaction volume was 0.5 mL. All GC vials were stirred at room temperature for 18 hours.

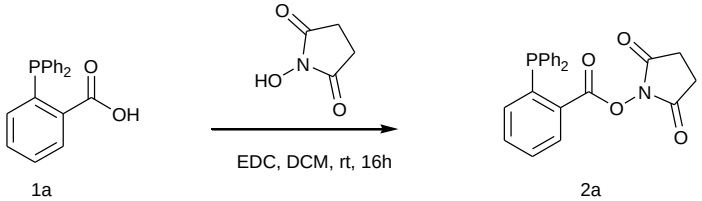
To work up the reactions, the mixture was filtered over silica pad in Pasteur pipette, and washed with 1 mL of DCM. The solvent was evaporated, and hexane HPLC grade was added. The samples were analysed by HPLC.




Phosphine containing GS derivatives, **3a-d**.

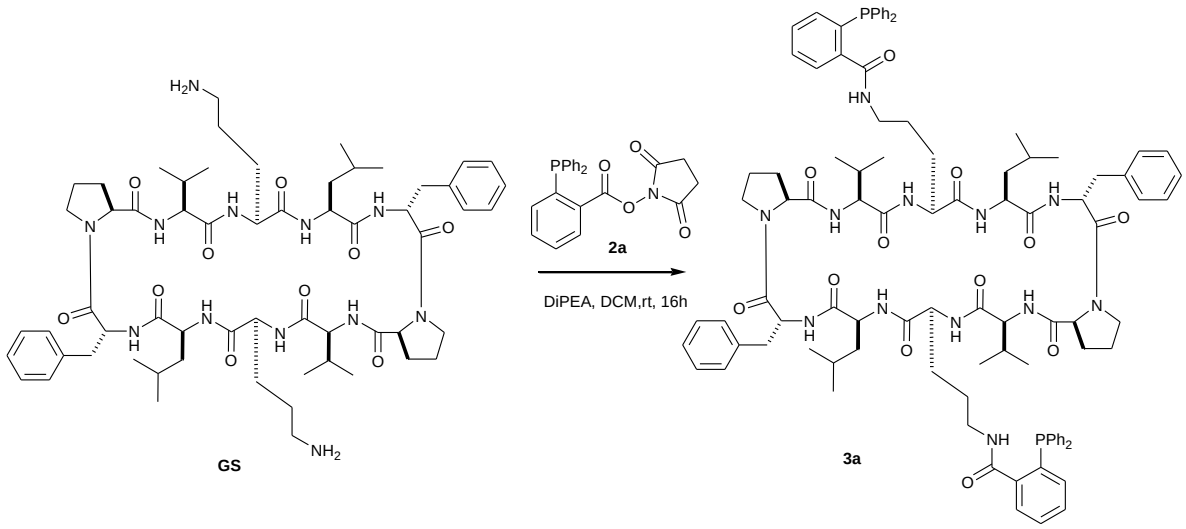
**Synthesis of *N,N'*-(3,3'-((6R,9S,12S,15S,17aS,23R,26S,29S,32S,34aS)-6,23-dibenzyl-9,26-diisobutyl-15,32-diisopropyl-5,8,11,14,17,22,25,28,31,34-decaoxotetratriacontahydrodipyrrolo[1,2-a:1',2'-p][1,4,7,10,13,16,19,22,25,28]decaazacyclotriacontine-12,29-diyl)bis(propane-3,1-diyl))bis(2-(diphenylphosphino)benzamide) (3b).**

**Step 1. Synthesis of 2,5-dioxopyrrolidin-(*ortho*-diphenylphosphino)benzoate (2a).**



Compound **2a** was synthesised following the reported method.[6] *Ortho*-diphenylphosphine benzoic acid (**1a**) (220 mg, 0.72 mmol) was dissolved in dichloromethane (10 mL). EDC·HCl (554 mg, 2.89 mmol) and *N*-hydroxysuccinamide (332 mg, 2.89 mmol) were added to the phosphine solution and the solution was stirred overnight. After 16 hours, the solvent was removed under vacuum and the residue was purified by silica gel column chromatography under argon using petroleum ether and ethylacetate as a mixture of solvents (1:1). The product (**2a**) was obtained pure as a slightly yellow solid (200 mg, 60%). $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.3 (m, 10 H), 2.74 (s, 4H). $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ -4.56 ppm.

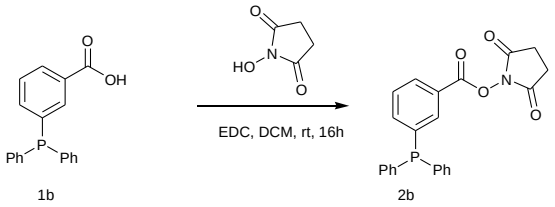
**Step 2. Synthesis of *ortho*-diphenylphosphine Gramicidin S(3a).**




Compound (**3a**) was synthesised following the reported method.[6] A solution of **2a** (17.5 mg, 0.0432 mmol) in dichloromethane (5 mL) was added to a solution of Gramicidin S (15 mg, 0.0108 mmol) and DIPEA (diisopropylethylamine, 5 μL, 0.029 mmol ) in dichloromethane (5 mL). The solution was stirred overnight. After 16 hours the solvent was removed under vacuum and the residue was purified by silica gel column chromatography under argon using dichloromethane and methanol as a mixture of solvents (9:1). The product (**3a**) was obtained pure as a white solid (7 mg, 39%). $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ -9.21 ppm.$^{1}$H NMR (400 MHz, $CD_2Cl_2$): δ = 8.36 (d, 1H, $H_\alpha$ = 9.48 Hz, NH Leu), 7.64 (m, 1H, NH $^{D}$Phe), 7.50 (m, NH Orn), 7.16 (m, 7H, 7x Ar), 7.21-7.07 (m, 5 x Ar), 6.84 (m, 2H, 2 x Ar), 5.40 (m, 1H, $H_\alpha$Orn), 4.74 (m, 1H, $H_\alpha$ Leu), 4.62 (m, 1H, 1$H_\alpha$ $^{D}$Phe), 4.33 (m, 1H, $H_\alpha$Pro), 4.10 (d, 1H, $H_\alpha$Val), 3.57 (m, 1H, $H_\delta$ Pro), 3.21 (m, 3H, m, 2$H_\beta$ $^{D}$Phe, 1$H_\gamma$ Orn), 2.69 (m,1 H, 1$H_\beta$ $^{D}$Phe), 2.60 (m, 2H, $H_\gamma$ Orn), 2.25 (m, 2H, 1$H_\gamma$ Pro, 1$H_\delta$ Pro), 2.09 (m, 1H, $H_\beta$ Val), 1.94 (m, 2H, $H_\beta$ Orn), 1.85 (m,1H, $H_\delta$ Pro), 1.65-1.39 (m, 5 H, 2 $H_\beta$ Pro, 1 $H_\gamma$ Pro), 1.18(m, 2 $H_\gamma$ Orn), 0.79-0.77 (12H, 6x $H_\gamma$ Val, 6x $H_\gamma$ Leu). *m/z* (TOF MS ES+) for $C_{98}H_{118}N_{12}O_{12}P_2$ calculated ($M^{2+}$) =859.43 found 859.57

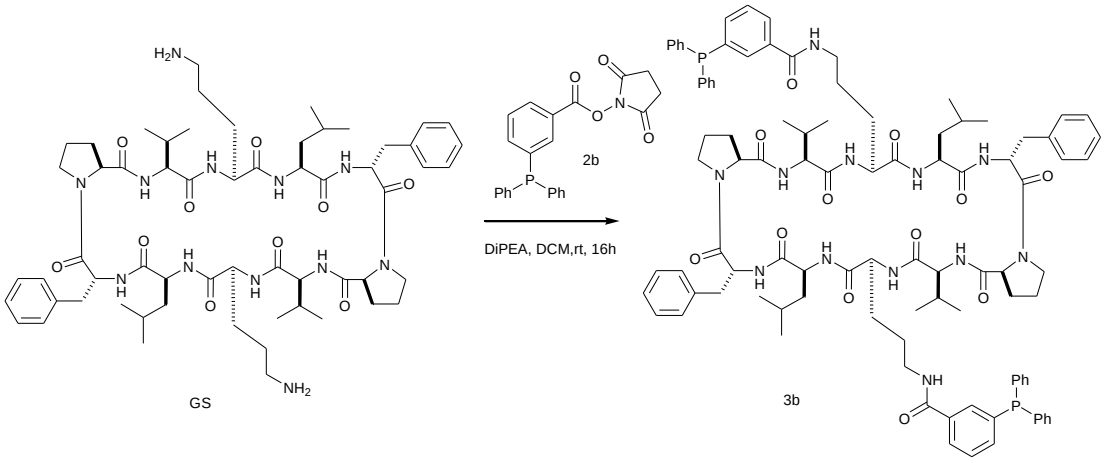
**Synthesis of *N,N'*-(3,3'-((6R, 9S, 12S, 15S, 17aS, 23R, 26S, 29S, 32S, 34aS) -6, 23-dibenzyl-9, 26-diisobutyl-15, 32-diisopropyl 5, 8, 11, 14, 17, 22, 25, 28, 31, 34-decaoxotetratriacontahydrodipyrrolo [1, 2-a :1', 2'-p] [1, 4, 7, 10, 13, 16, 19, 22, 25, 28] decaazacyclotriacontine-12, 29-diyl) bis(propane-3, 1-diyl)) bis(3-(diphenylphosphino) benzamide) (3b).**

**Step 1. Synthesis of 2,5-dioxopyrrolidin-(*meta*-diphenylphosphino)benzoate (2b).**




Compound **2b** was synthesised following a reported method.[6] *Meta*-diphenylphosphine benzoic acid, **1b** (221.5 mg, 0.7 mmol) in dichloromethane (10 mL) was treated with hydroxysuccinimide (333 mg, 2.89 mmol) and EDC·HCl (554.5 mg, 2.89 mmol). The reaction mixture was stirred for 16 h. Afterwards, diluted with dichloromethane (30 mL) and washed with 2 N HCl (5 mL) and water (5 mL). The organic phase was dried ($MgSO_4$), concentrated under reduced pressure and purified using silica gel column chromatography (pure petroleum ether. → 3/7 EtOAc/ petroleum ether). The product **2b** was obtained in high yield as a white solid (211 mg, 83 %, with up to 10 % phosphine oxide).
$^{31}$P NMR (162 MHz, $CDCl_3$): δ -5.10 ppm, 28.4 ppm (10% oxide).

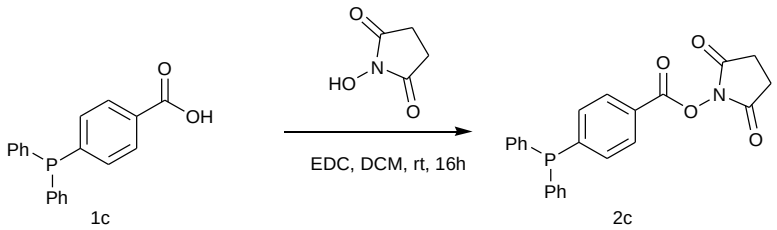
**Step 2. Synthesis of *meta*-diphenylphosphine Gramicidin S (3b).**




Compound **3b** was synthesised following a reported method.[6] A solution of Gramicidin S (208 mg, 0.15 mmol) in dichloromethane (10 mL) was degassed (Argon/vacuum) while stirring. To the reaction mixture was added DiPEA (51 µL, 0.3 mmol) and 2,5-dioxopyrrolidin-(*meta*-diphenylphosphino)benzoate (**2b**) (211 mg, 0.52 mmol) in degassed dichloromethane (5 mL). After stirring for 16 h under an argon atmosphere, the reaction mixture was concentrated under diminished pressure. The residue was purified using silica gel column chromatography (twice!), under nitrogen atmosphere! Using degassed solvents (DCM → 5 % MeOH/DCM). The collected fractions were directly capped to prevent oxidation by air, collected and concentrated. Compound **3b** was obtained pure as a colourless solid (124 mg, 48%). $^{1}$H $^{31}$P NMR (162 MHz, $CDCl_3$): δ -5.76 ppm.$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, 2H, *J* = 8 Hz), 8.13 (m, 2H), 7.92-7.7 (m, 4H), 7.26-6.99 (m, 38H), 4.81 (m, 4H), 4.48-4.24 (m, 6H), 3.73 (m, 2H), 3.46-3.37 (m, 4H), 2.97-2.87 (m, 4H), 2.45-2.43 (m, 2H), 2.15-1.57 (m, 25H), 0.90-0.85 (m, 26H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 172.4, 171.5, 170.8, 170.4, 167.3, 137.8, 137.7, 136.8, 136.8, 136.7, 136.0, 135.7, 135.3, 133.9, 133.7, 133.5, 133.2, 129.2, 128.8, 128.6, 128.5, 128.4, 128.1, 127.8, 127.2, 60.4, 58.6, 54.2, 53.0, 52.8, 50.3, 46.5, 40.4, 36.9, 29.3, 25.3, 24.6, 23.7, 23.2, 22.5, 19.1, 18.9. High resolution MS *m/z* (TOF MS ES+) for $C_{98}H_{119}N_{12}O_{12}P_2$ calculated ($M^{2+}$) = 859.42896 found 859.43207.

**Synthesis of *N,N'*-(3,3'-((6R,9S,12S,15S,17aS,23R,26S,29S,32S,34aS)-6,23-dibenzyl-9,26-diisobutyl-15,32-diisopropyl-5,8,11,14,17,22,25,28,31,34 decaoxotetratriacontahydro dipyrrolo[1,2-a:1',2'-p] [1,4,7,10,13,16,19,22,25,28] decaazacyclotriacontine-12,29-diyl)bis(propane-3,1-diyl))bis(4-(diphenylphosphino)benzamide) (3c).**

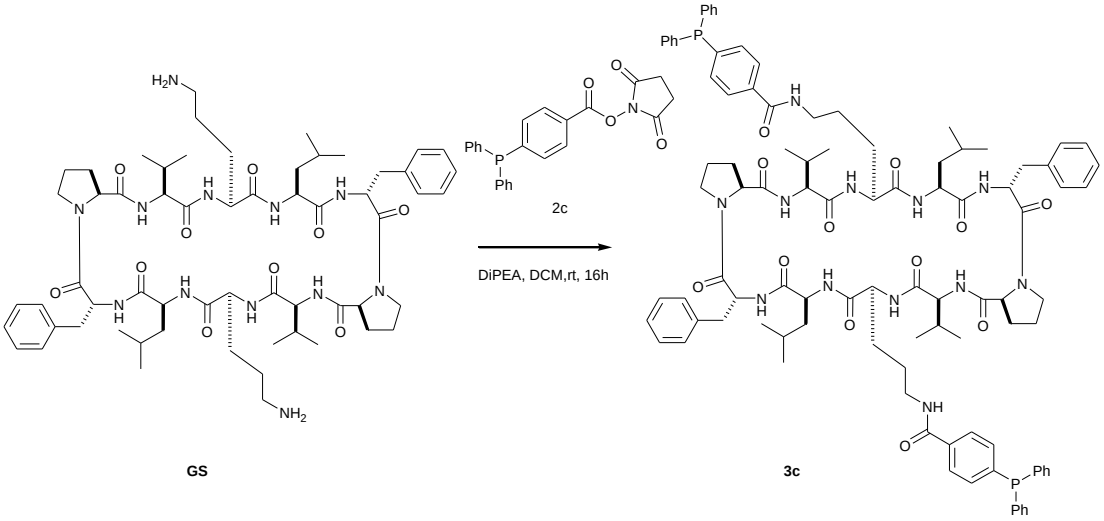
**Step.1 Synthesis of 2,5-dioxopyrrolidin-(*para*-diphenylphosphino)benzoate (2c).**




1c 2c

Compound **2c** was synthesised following a reported method.[6] *Para*-diphenylphosphine benzoic acid (**1c**) (221.5 mg, 0.7 mmol) in dichloromethane (10 mL) was treated with hydroxysuccinimide (333 mg, 2.89 mmol) and EDC·HCl (554.5 mg, 2.89 mmol). The reaction mixture was stirred for 16 h. afterwards, diluted with dichloromethane (30 mL) and washed with 2 N HCl (5 mL) and water (5 mL). The organic phase was dried ($MgSO_4$), concentrated under reduced pressure and purified using silica gel column chromatography (pure petroleum ether. → 3/7 EtOAc/ petroleum ether). The product (**2c**) was obtained as a colourless solid (0.23 g, 80%, with up to 10% phosphine oxide). $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ -3.94.

**Step 2. Synthesis of *para*-diphenylphosphine Gramicidin S (3c).**



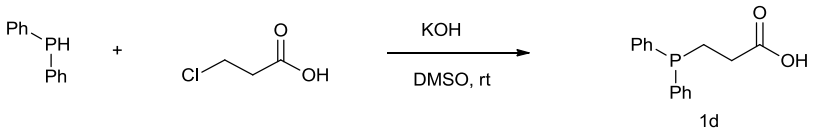

GS 2c 3c

Compound **3c** was synthesised following a reported method.[6] A solution of Gramicidin S (208 mg, 0.15 mmol) in dichloromethane (10 mL) was degassed (Argon/vacuum) while stirring. To the reaction mixture was added DiPEA (51 μL, 0.3 mmol) and 2,5-dioxopyrrolidin-(*para*-diphenylphosphino)benzoate (**2c**) (211 mg, 0.52 mmol) in degassed dichloromethane (5 mL). After stirring for 16 h under an argon atmosphere, the reaction mixture was concentrated under vacuum. The residue was purified using silica gel column chromatography (twice!), under nitrogen atmosphere! Using degassed solvents (DCM → 5 % MeOH/DCM). The collected fractions were directly capped, collected and concentrated. The compound (**3c**) was obtained as a colourless solid (124 mg, 48%) (phosphine oxide :detectable ~ 13.5:1 according to $^{31}P$ NMR.

$^{31}$P NMR (162 MHz, $CDCl_3$): δ -5.68 ppm, $^{1}$H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, 2H, *J* = 9.2 Hz), 7.98 (m, 2H), 7.82-7.80 (m, 4H), 7.39-6.98 (m, 38H), 4.8-4.72 (m, 4H), 4.46 (m, 2H), 4.12 (m, 4H), 3.6-3.43 (m, 4H), 2.96-2.89 (m, 4H), 2.39 (m, 2H), 2.14-1.52 (m, 25H), 0.90-0.84 (m, 26H). MS *m/z* (ES+) for $C_{98}H_{119}N_{12}O_{12}P_2$ calculated ($M^{2+}$) = 858.43 found 859.0.

**Synthesis of (6R,9S,12S,15S,17aS,23R,26S,29S,32S,34aS)-6,23-dibenzyl-12,29-bis(3-(3-(diphenylphosphino)propanoyloxyamino)propyl)-9,26-diisobutyl-15,32-diisopropyl tetra cosahydrodipyrrolo[1,2-a:1',2'-p] [1,4,7,10,13,16,19,22,25,28] decaazacyclotriacontine-5,8,11,14,17,22,25,28,31,34-decaone (3d).**

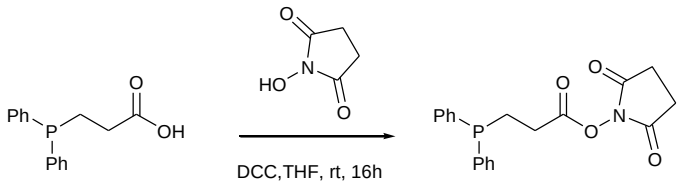
**Step 1. Synthesis of 3-(diphenylphosphino)propanoic acid (1d).**




1d

The 3-(diphenylphosphino)propanoic acid (**1d**) was prepared by combining reported method in literature.[7,8] To a solution of diphenylphosphine (1 g, 5.4 mmol) in dry and degassed DMSO (5 mL) was added grounded KOH (0.76 mg, 13.5 mmol) at once. The solution was stirred during one hour at room temperature. After this time 3-bromopropanoic acid dissolved in DMSO (5 mL) was added dropwise. The reaction mixture was stirred overnight at room temperature. The reaction mixture was acidified with a 2 N aqueous solution of HCl until a colourless precipitated was obtained. The precipitate was filtered, and washed with degassed water. A colourless solid (**1d**) was obtained. (0.62g, 47.2%)
$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.4 (m, 10 H), 2.4 (m, 2 H), 2.3 (m, 2 H), $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 178.3 (d, J = 18 Hz), 137.4 (d, J = 11.1 Hz), 132.7 (d, J = 20 Hz), 128.9, 128.6 (d, J = 6.7 Hz), 30.3 (d, J = 17.6 Hz), 22.7(d, J = 11.8 Hz), $^{31}$P NMR (162 MHz, $CDCl_3$): δ -15.91 ppm, 3.7% oxide.

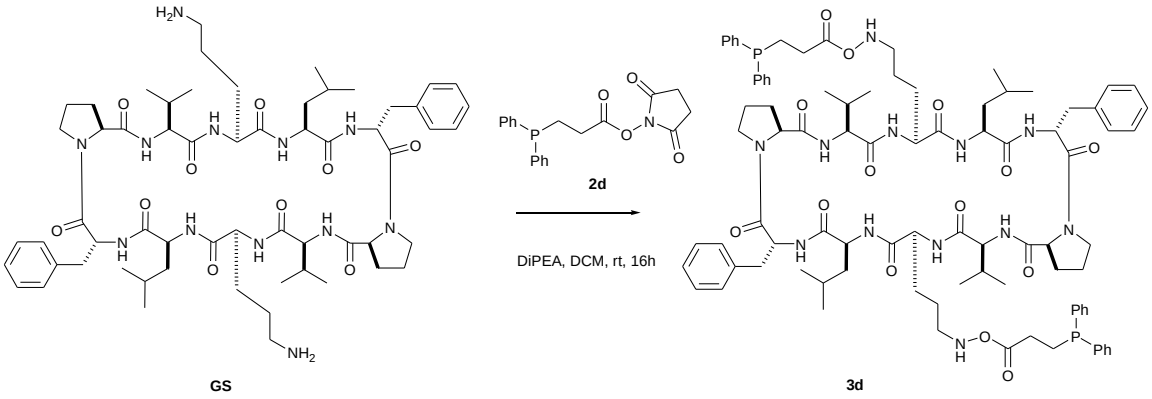
**Step 2. Synthesis of 2,5-dioxopyrrolidin-1-yl 3-(diphenylphosphino)propanoate (2d).**




1d 2d

Compound **2d** was obtained following reported methods.[9,10] To a solution of (**1d**) (200.0 mg, 0.77 mmol) in dry THF (10 mL) was added hydroxysuccinimide (106 mg, 0.93 mmol). After few minutes DCC (190 mg, 0.93 mmol) in THF (5 mL) was added. The reaction mixture was stirred for 16 h. The colourless precipitate corresponding to dicyclohexylurea was removed by filtration via cannula. Concentration of the clear solution under reduced pressure gave a colourless solid, which was washed in dry methanol. The obtained compound (**2d**) was used for the next step without further purification (190 mg, Yield 69%).
$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.3 (m, 10 H), 2.7 (s, 4H), 2.6 (m, 2H), 2.4 (m, 2H), $^{13}$C NMR (100 MHz, $CDCl_3$): δ 169.0, 168.42 (d, J = 16.3 Hz), 137.0 (d, J =12.9 Hz), 132.7 (d, J = 19 Hz), 129.09, 128.7 (d, J = 7.5Hz), 27.57 (d, J = 21.2), 25.58, 22.64 (d, J = 13.85 Hz), $^{31}$P NMR (162 MHz, $CDCl_3$): δ -15.8 ppm (3.6% oxide). $^{31}$P NMR (162 MHz, $CDCl_3$) (decoupled): δ -15.72, -15.77, -15.81, *m/z* (TOF MS ES+) for $C_{19}H_{18}NO_4P$ calculated 394.08 ($M^+$ +O+ Na) found 393.88.

**Step 3. Synthesis of (6R,9S,12S,15S,17aS,23R,26S,29S,32S,34aS) -6,23- dibenzyl-12,29-bis(3-(3-(diphenylphosphino)propanoyloxyamino)propyl)-9,26-diisobutyl-15,32-diisopropyltetracosahydrodipyrrolo [1,2-a:1',2'-p] [1,4,7,10,13,16,19,22,25,28] decaaza cyclotriacontine-5,8,11,14,17,22,25,28,31,34-decaone (3d).**




Compound **3d** was synthesised following similar procedure to the reported method.[6] Compound **2d** (20 mg, 0.0144 mmol) in DCM (5 mL) was degassed while stirring. To the reaction mixture was added DiPEA (51 µL, 0.03 mmol) and compound (**2d**) (17.41 mg, 0.049 mmol) in degassed DCM (5 mL). After stirring for 16 h under an argon atmosphere, the reaction mixture was concentrated under reduced pressure. The crude was purified using silica gel column chromatograph under argon. Solvents were degassed prior use (DCM → 5 % MeOH/DCM). The obtained compound (**3d**) (4 mg, 16.8%) contain 11 % phosphine oxide according to NMR.
$^{31}$P NMR (162 MHz, $CDCl_3$): δ -15.15 ppm, 31.36 ppm (10% oxide). $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, 1H, *J* = 9.48 Hz), 7.68 (m, 1H), 7.41 (m, NH), 7.31 (m, 5H), 7.21-7.17 (m, 9H), 7.05 (m, 2H), 5.27 (m, 1H), 4.64 (m, 2H), 4.40 (m, 1H,), 4.29 (d, 1H, *J* = 7.1), 4.12 (m, 1H), 3.69 (m, 1H), 3.25 (m, 3H), 2.88 (m, 2H), 2.69 (m,1H), 2.56 (m, 2H), 2.48 (m, 2H), 2.29 (m, 2H), 2.14 (m, 1H), 2.02 (m, 2H), 1.95 (m, 1H), 1.68-1.37 (m, 5 H), 0.82-0.76 (12H). *m/z* (TOF MS ES+) for $C_{90}H_{118}N_{12}O_{12}P_2$ calculated (M+$O_2$+Na) = 1675.83 found 1676.63.

**Synthesis of the metal complexes:**

The metal complexes were prepared *in situ* and characterised in solution by $^{1}$H and $^{31}$P NMR and MALDI-TOF.

**Synthesis of (4a): [Rh(nbd)(3a)]$BF_4$**
0.1 mL of a solution of [Rh(nbd)$_2$]BF4 (2.21 mg, 5.86 mmol) in dichloromethane (1 mL) were added to a solution of (**3a**) (1 mg, 58.6 µmol) in dichloromethane (0.5 mL) under argon. The resulting yellow solution was stirred during 5 minutes and the solution was analysed by NMR. $^{31}$P NMR (162 MHz, $CDCl_3$): δ 29.73 ppm, (d, $J_{Rh-P}$ = 170 Hz), *m/z* (TOF MS ES+) $C_{105}H_{126}N_{12}O_{12}P_2Rh$ calculated (M+O-$BF_4$) = 1927.81 found 1927.88.

**Synthesis of (4b): [Rh(nbd)(3b)]$BF_4$**

To a GC vial (previously degassed and purged with argon) containing a solution of (**3b**) (1 mg, 58.6 µmol) in dichloromethane (0.5 mL) was added (0.1 mL) of a solution of [Rh(nbd)$_2$]$BF_4$ (2.21 mg, 5.86 µmol) in dichloromethane (1 mL) under argon. The resulting yellow solution was stirred for five minutes and the solution was analysed by NMR. $^{31}$P NMR

(162 MHz, $CDCl_3$): δ 30.67 ppm, *m/z* (TOF MS ES+) $C_{105}H_{126}N_{12}O_{12}P_2Rh$ calculated ($M^+$ - $BF_4$) = 1912.82 found 1912.71.

**Synthesis of (4c): [Rh(nbd)(3c)]$BF_4$**

To a GC vial (previously degassed and purged with argon) containing a solution of (**3c**) (1 mg, 58.6 μmol) in dichloromethane (0.5 mL) was added 0.1 mL of a solution of [Rh(nbd)$_2$]$BF_4$ ( 2.21 mg, 5.86 μmol) in dichloromethane (1 mL) under argon. The resulting yellow solution was stirred for five minutes and the solution was analysed by NMR. $^{31}$P NMR (162 MHz, $CDCl_3$): δ 31.47, 30.42, 29.57, 28.63 ppm ($J_{Rh-P}$ = 176.8, 161.7 Hz) ppm, *m/z* (TOF MS ES+) for $C_{105}H_{126}N_{12}O_{12}P_2Rh$ calculated ($M^+$) = 1912.82 found 1913.00.

**Synthesis of (4d): [Rh(nbd)(3d)]$BF_4$**

To a NMR tube (previously degassed and purged with argon) containing a solution of (**3d**) (4.36 mg, 2.6 μmol) in $CD_2Cl_2$ (0.37 mL) was added 0.45 mL of a solution of [Rh(nbd)$_2$]$BF_4$ (2.21 mg, 5.82 μmol ) in $CD_2Cl_2$ (1 mL) under argon. The resulting yellow solution was stirred for five minutes and the solution was analysed by NMR. $^{31}$P NMR (162 MHz, $CDCl_3$): 26.01 ppm (d, J = 172.8.Hz), (25.88 ppm (d, J = 175.9 Hz), *m/z* (TOF MS ES+) for $C_{97}H_{126}N_{12}O_{12}P_2Rh$ calculated ($M^+$ +O-$BF_4$) = 1831.91 found 1831.89, ($M^+$-nbd) 1723.73.

**Synthesis of (5b): [Pd(3b)(allyl)]Cl**

To a GC vial (previously degassed and purged with argon) containing a solution of (**3b**) (1 mg, 58.2 μmol) in dichloromethane (0.5 mL) was added 0.1 mL of a solution of [Pd(allyl)Cl]$_2$ (1 mg, 2.73 μmol) in dichloromethane (1 mL) under argon. The resulting yellow solution was stirred for five minutes and the solution was analysed by NMR. $^{31}$P NMR (162 MHz, $CDCl_3$): δ 23.1 ppm, *m/z* (TOF MS ES+) for $C_{101}H_{123}N_{12}O_{12}P_2Pd$ ($M^+$-Cl) = 1863.79 found 1863.56.

**Synthesis of (5c): [Pd(3c)(allyl)]Cl**

To a GC vial (previously degassed and purged with argon) containing a solution of (**3c**) (1 mg, 58.2 μmol) in dichloromethane (0.5 mL) was added 0.1 mL of a solution of [Pd(allyl)Cl]$_2$ (1 mg, 2.73 μmol) in dichloromethane (1 mL) under argon. The resulting yellow solution was stirred for five minutes and the solution was analysed by NMR. $^{31}$P NMR (162 MHz, $CDCl_3$): δ 22.2 ppm, *m/z* (TOF MS ES+) for $C_{101}H_{123}N_{12}O_{12}P_2Pd$ ($M^+$-Cl) = 1863.79 found 1863.76.

**2D and DOSY NMR experiments**
**[Rh(nbd)(3b)]$BF_4$: (4b)**
The $^{31}$P-$^1$H HSQC experiment shows correlations between the $^{31}$P phosphine signal at 26.3 ppm and the two aromatic *ortho* protons located three chemical bonds apart (**fig 20 b**). This observation proves the expected covalent attachment of the phosphine moiety. $^1$H-DOSY experiment shows that all aromatic protons included those signals having $^{31}$P-$^1$H HSQC correlations with the $^{31}$P diffuse with the same diffusion coefficient, confirming the mononuclear chelating structure of the complex. 2D TOCSY (**fig 21 b**) and NOESY experiments show only one set of signals for this sample of [Rh(nbd)(**3b**)]$BF_4$ (**4b**) with the only exception of the side chain of the Leu amino acid, which present a double set of signals. These observations are similar to those found in previous studies of Gramicidin S that showed the existence of a conformational equilibrium that is fast in the NMR time scale. On overall, these observations prove that Gramicidin-S-TPP-Rh is the most abundant component in this sample.

**[Pd(3b)(allyl)]Cl: (5b)**

The $^{31}$P NMR spectrum shows six different signals in the region of the phosphines. The chemical shifts are 30 ppm (very broad, relative intensity 0.17), 26.3 ppm (broad, relative intensity 1.0), 25.9 ppm (broad, relative intensity 0.34), 21 ppm (broad, relative intensity 0.15), 20.5 ppm (very narrow, relative intensity 0.15), 20.02 ppm (narrow, relative intensity 0.38). Interestingly, the very broad signal at 26.3 ppm has the same chemical shift as that previously seen for the Gramicidin S-TPP-Rh complex and according to the information given below was assigned $^{31}$P signal of the TPP moiety of Gramicidin S-TPP-Pd complex.

From the six $^{31}$P signals commented, only three of them showed correlations with aromatic protons in the $^{31}$P-$^{1}$H HSQC spectrum (**fig 20 a**) (26.3, 20.5 and 20.03 ppm). Therefore these signals are the only ones that could possibly correspond to TPP moieties.

The $^{31}$P DOSY only shows the signals at 26.3 and 20.5 ppm and they correspond to species that diffuse with a similar diffusion coefficient. The absence of the other four $^{31}$P signals in the $^{31}$P DOSY spectrum can be due to the experimental conditions used that attenuate the signals corresponding to species with fast diffusion coefficients (very small molecules). The $^{1}$H DOSY experiment shows that all aromatic protons correspond to species that diffuse with the same diffusion coefficient confirming the mononuclear chelating structure of the complex. 2D TOCSY (**fig 21a**) and NOESY experiments show the presence of two set of proton signals for many protons of the amino acid side chains which contrast with the single set of signals obtained during the NMR study of the Gramicidin S-TPP-Rh sample.

On overall these observations point to the conclusion that there is a certain heterogeneity in this sample (i.e. is not pure). There are at least two species of Gramidicin S-TPP. The most abundant ones are the complex Gramidicin S-TPP-Pd (with $^{31}$P signal at 26.3 ppm) and the free Gramicidin S-TPP without the metal (with $^{31}$P signal at 20.5 ppm) with a ratio is 7:1 according to the relative integrals of the respective $^{31}$P signals.

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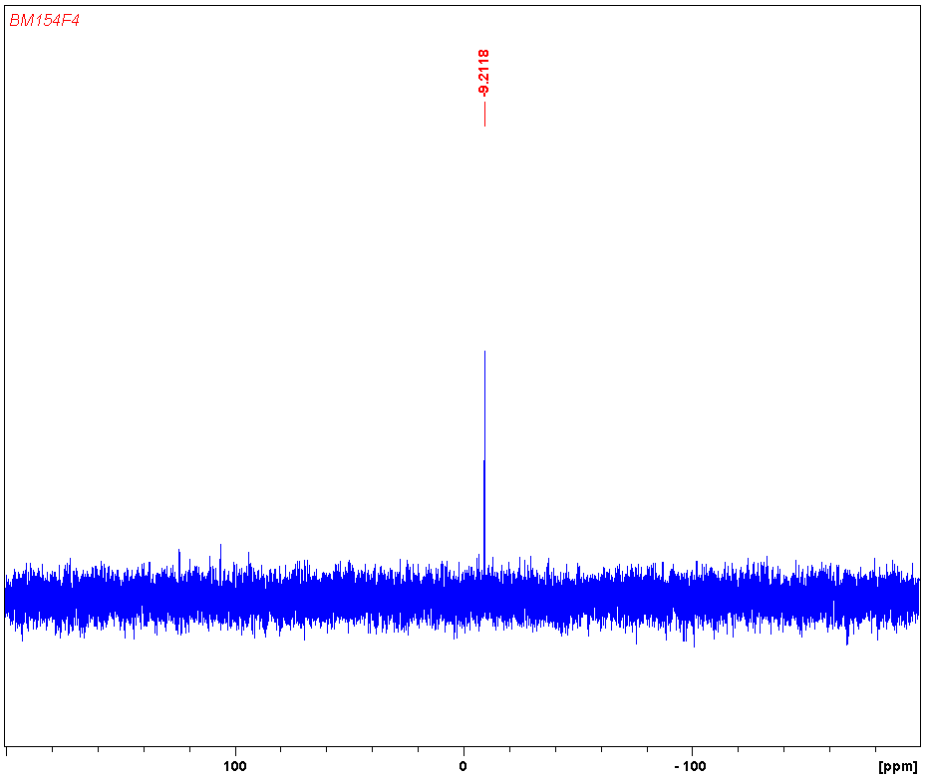


**Fig. S1: $^{31}$P NMR spectrum of (3a).**

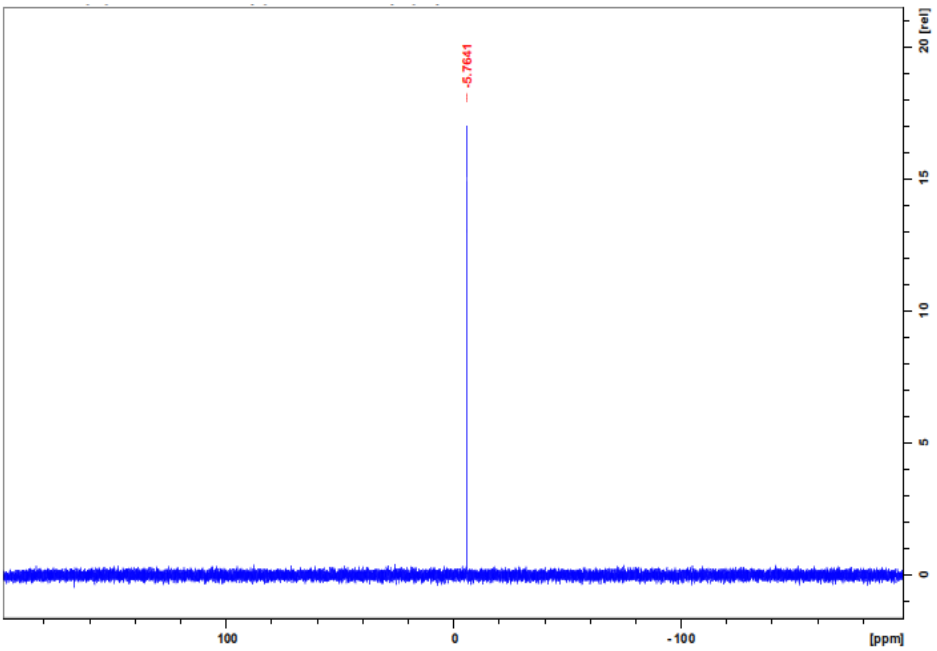


**Fig. S2: $^{31}$P NMR spectrum of (3b).**

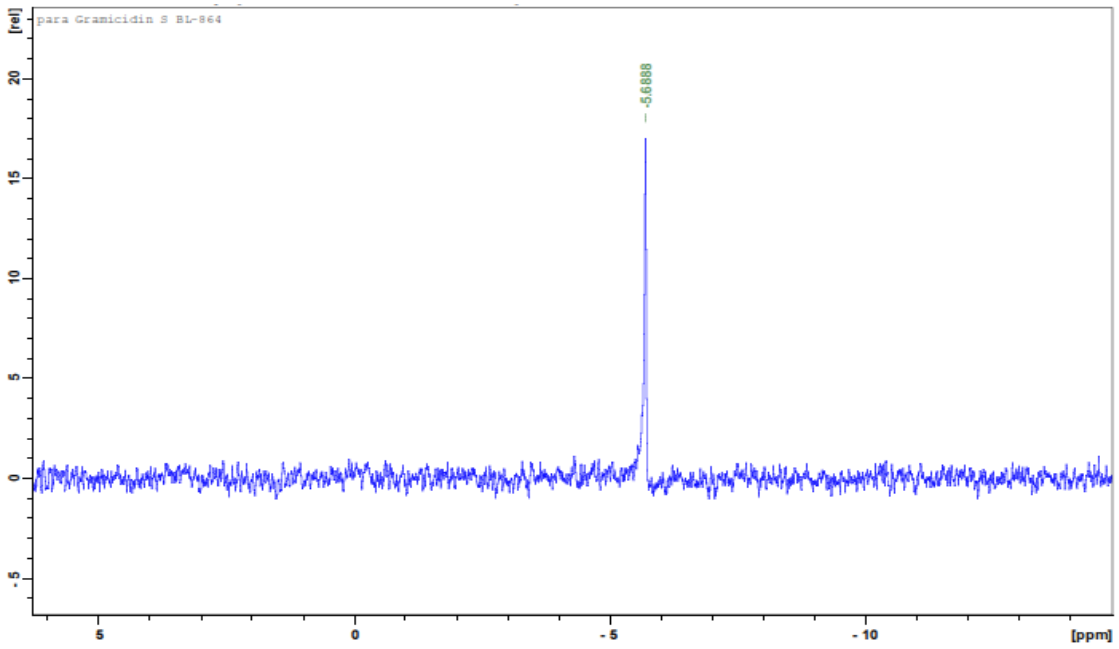


**Fig. S3: $^{31}$P NMR spectrum of (3c).**

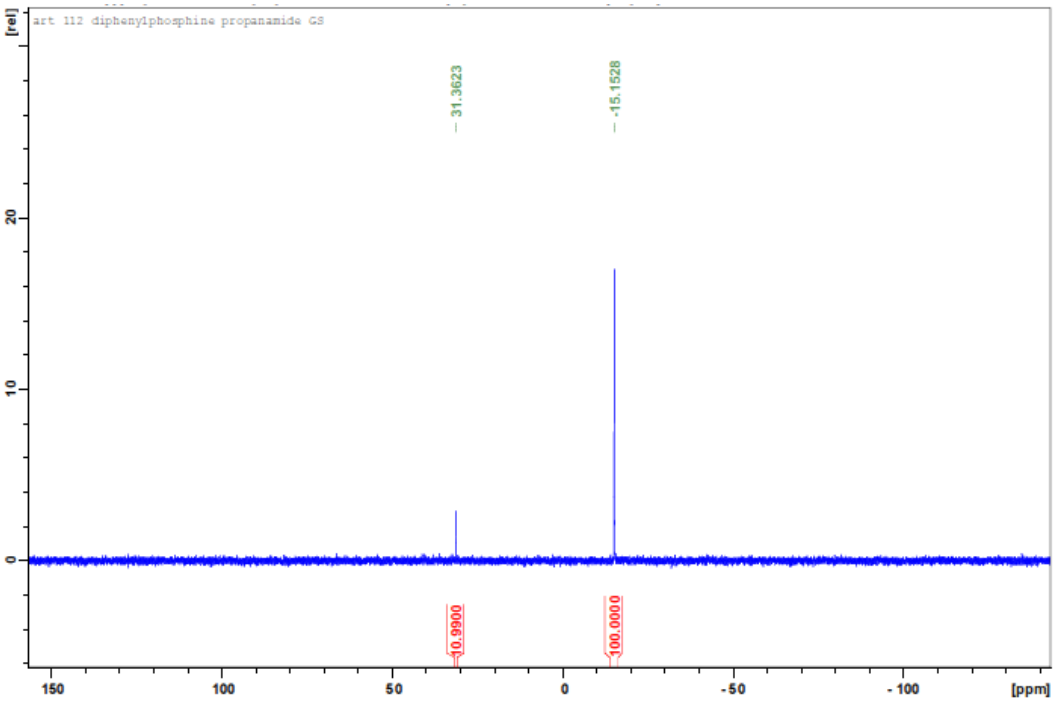


**Fig. S4: $^{31}$P NMR spectrum of (3d).**

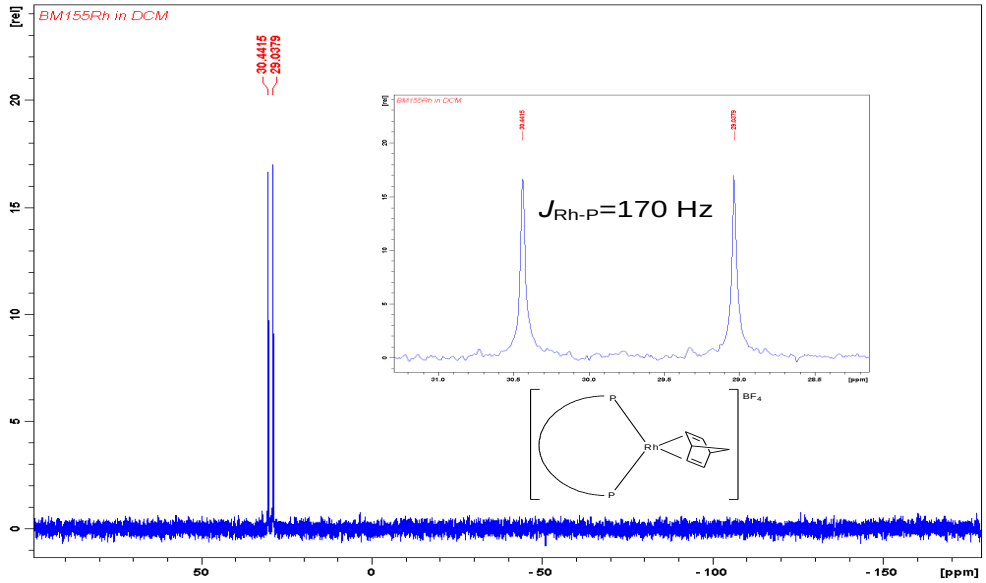


**Fig S5: $^{31}$P NMR spectrum of (4a).**

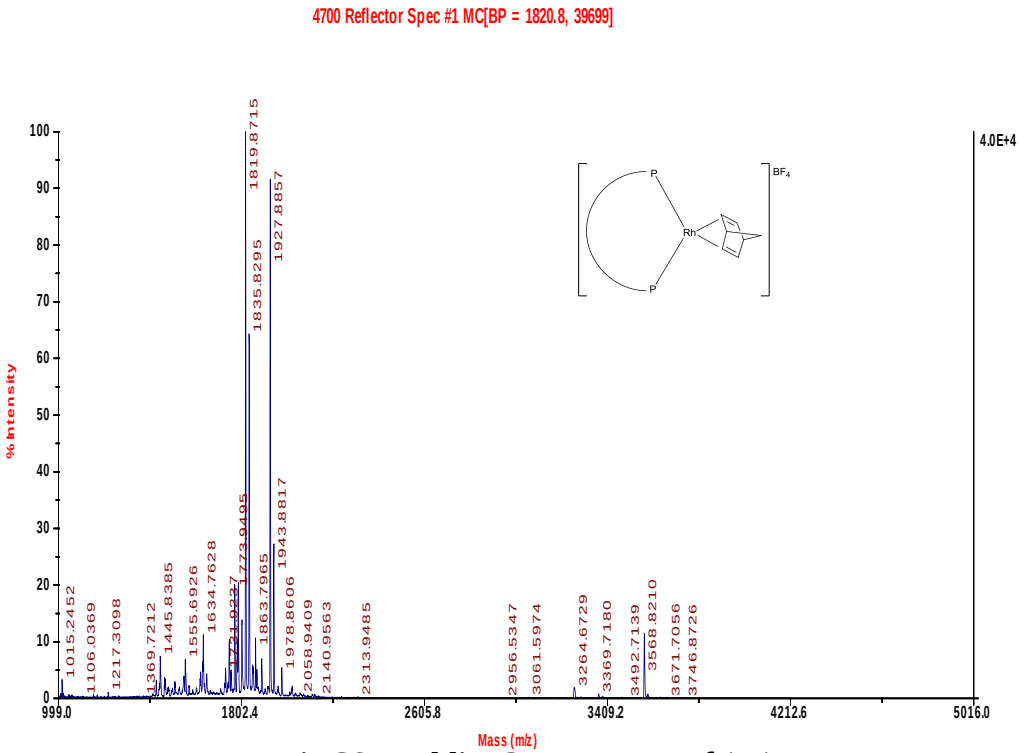


**Fig S6: Maldi-TOF spectrum of (4a).**

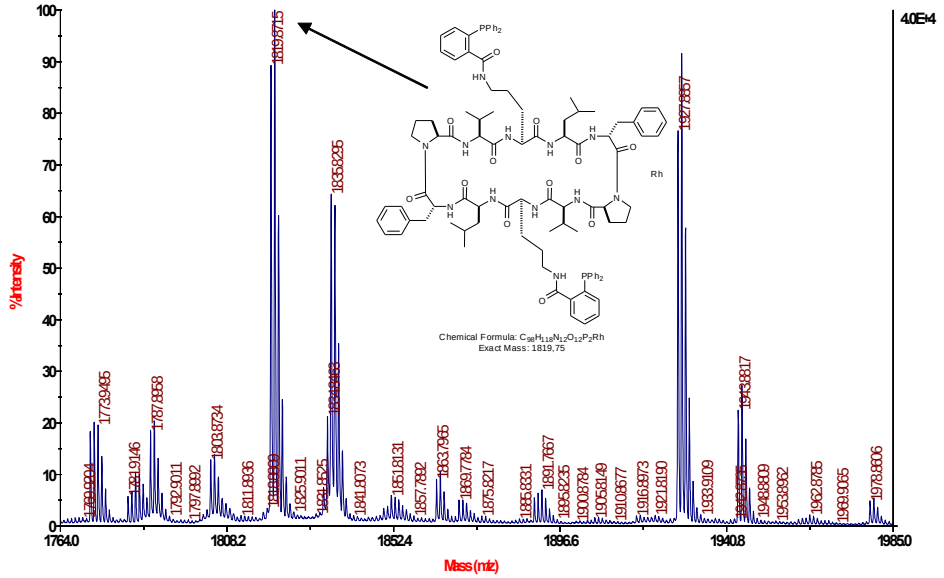


**Fig S7: Maldi-TOF spectrum of (4a).**

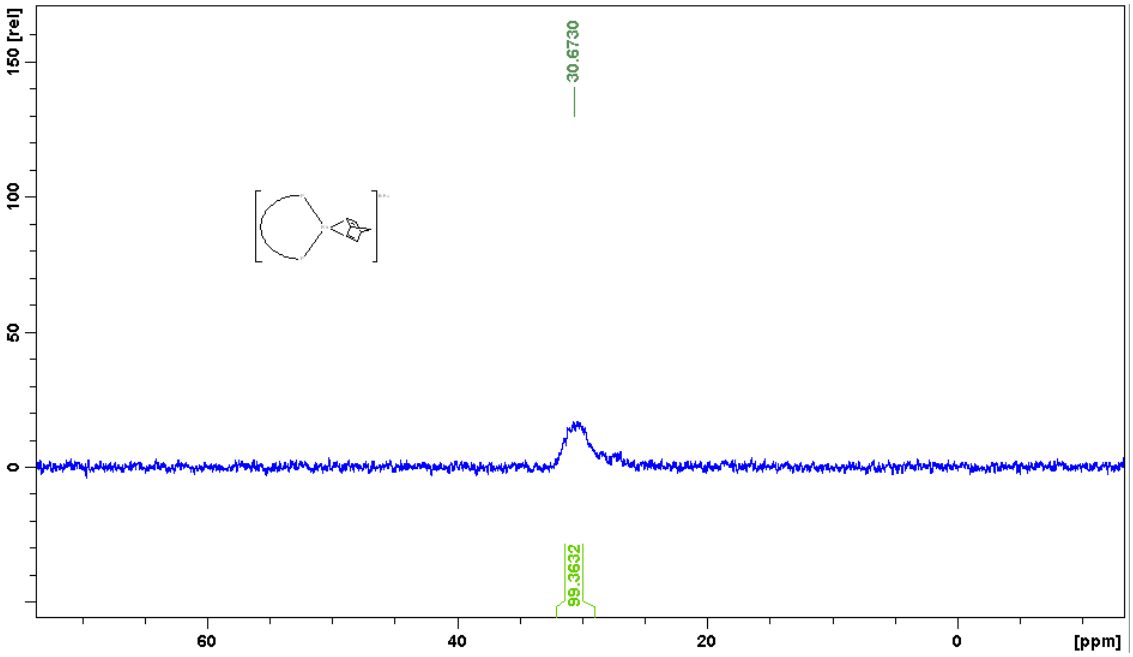


**Fig S8: $^{31}$P NMR spectrum of (4b): [Rh(nbd)(3b)]$BF_4$**

[Rh(nbd)$_2$]BF4 + m-TPP(Gramicidin S):

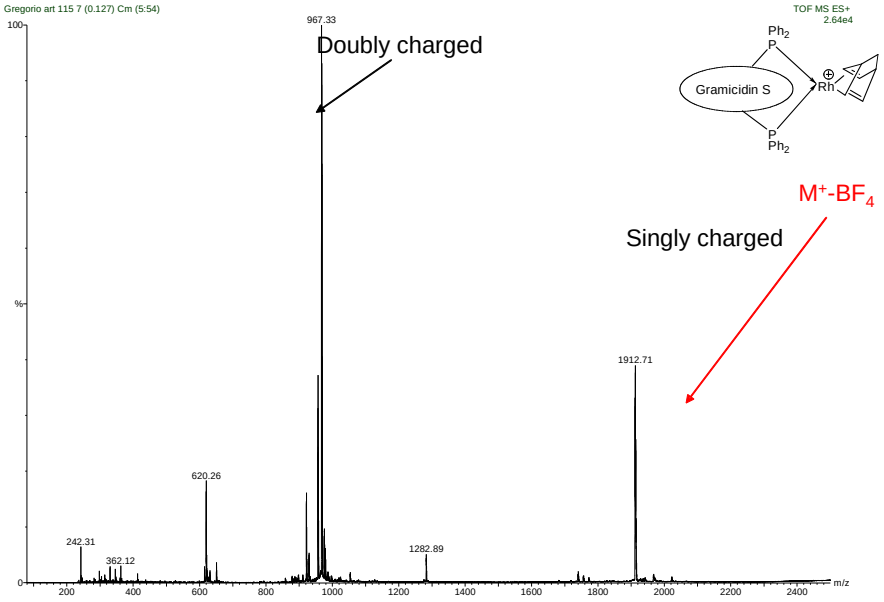


**Fig S9: Maldi-TOF spectrum of (4b): [Rh(nbd)(3b)]BF$_4$**

[Rh(nbd)$_2$]BF4 + m-TPP(Gramicidin S):

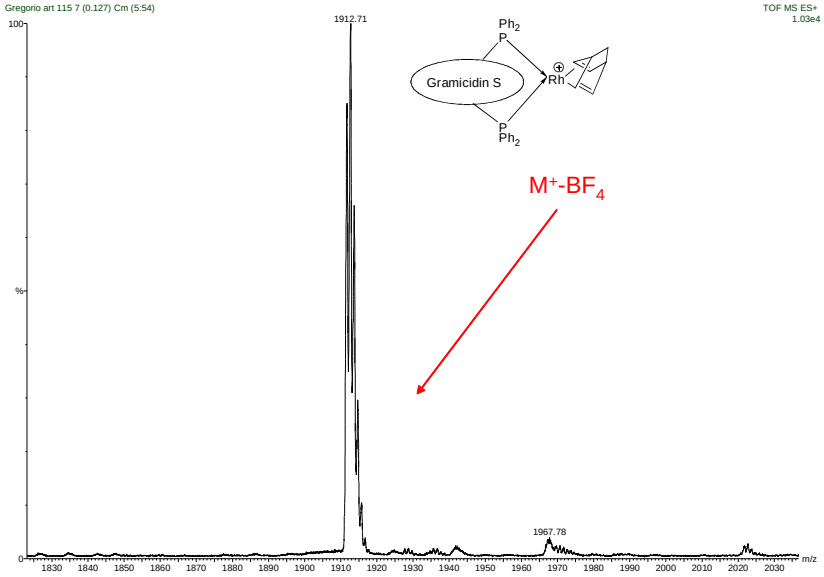


**Fig S10: Maldi-TOF spectrum of (4b): [Rh(nbd)(3b)]BF$_4$**

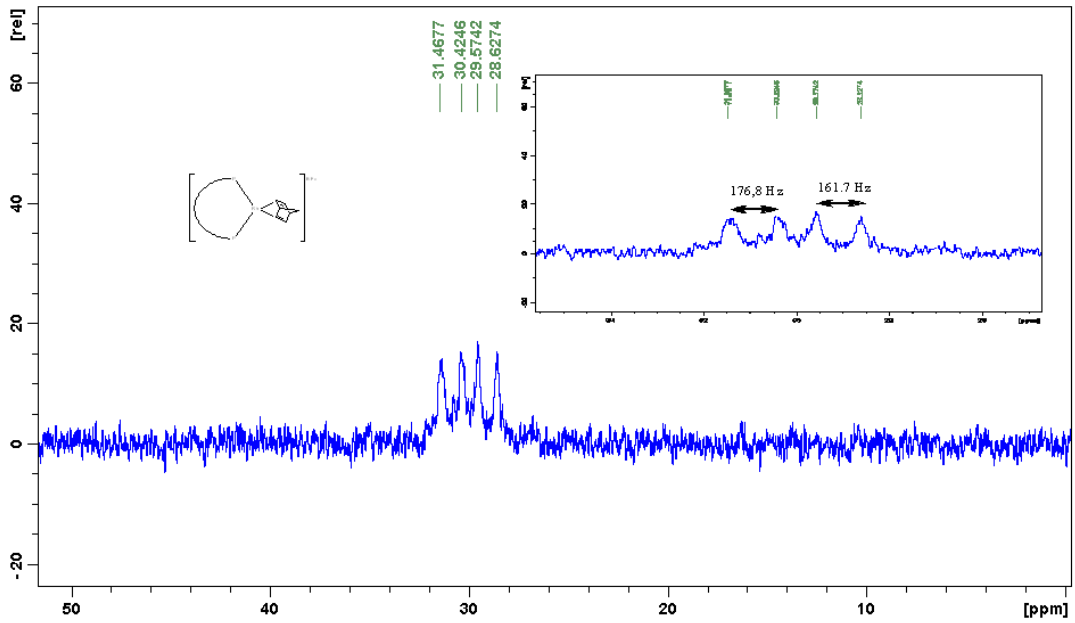


**Fig S11: $^{31}$P NMR spectrum of (4c): [Rh(nbd)(3c)]$BF_4$**

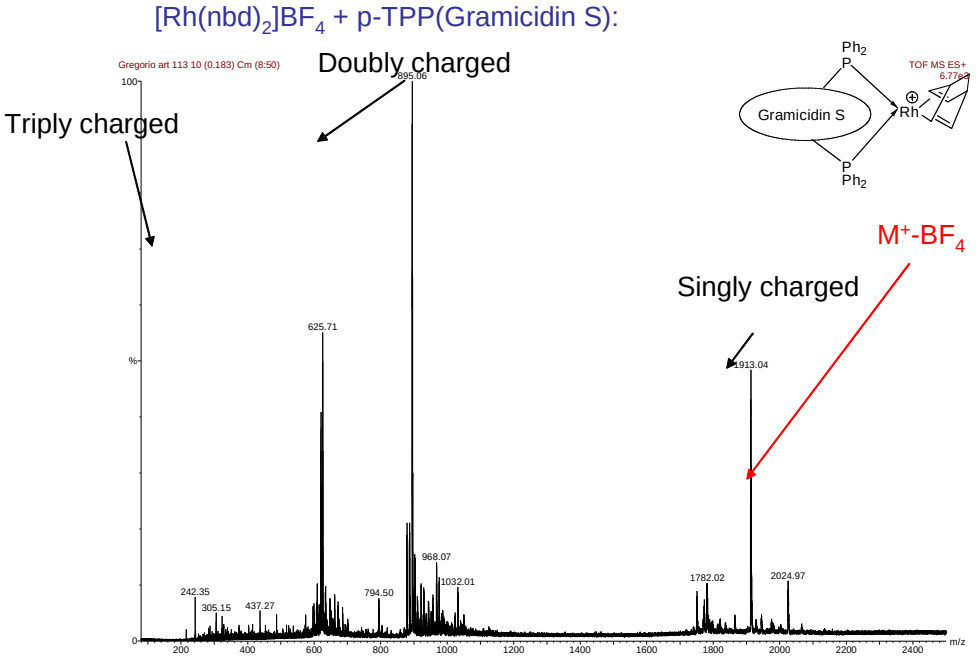


**Fig S12: Maldi-TOF spectrum of (4c): [Rh(nbd)(3c)]$BF_4$**

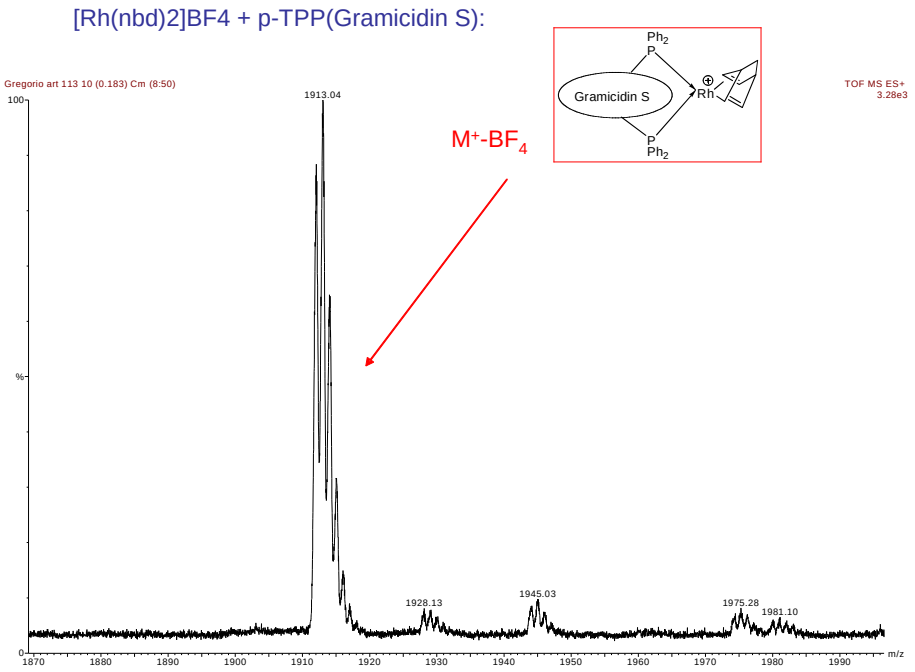


**Fig S13: Maldi-TOF spectrum of (4c): [Rh(nbd)(3c)]$BF_4$**

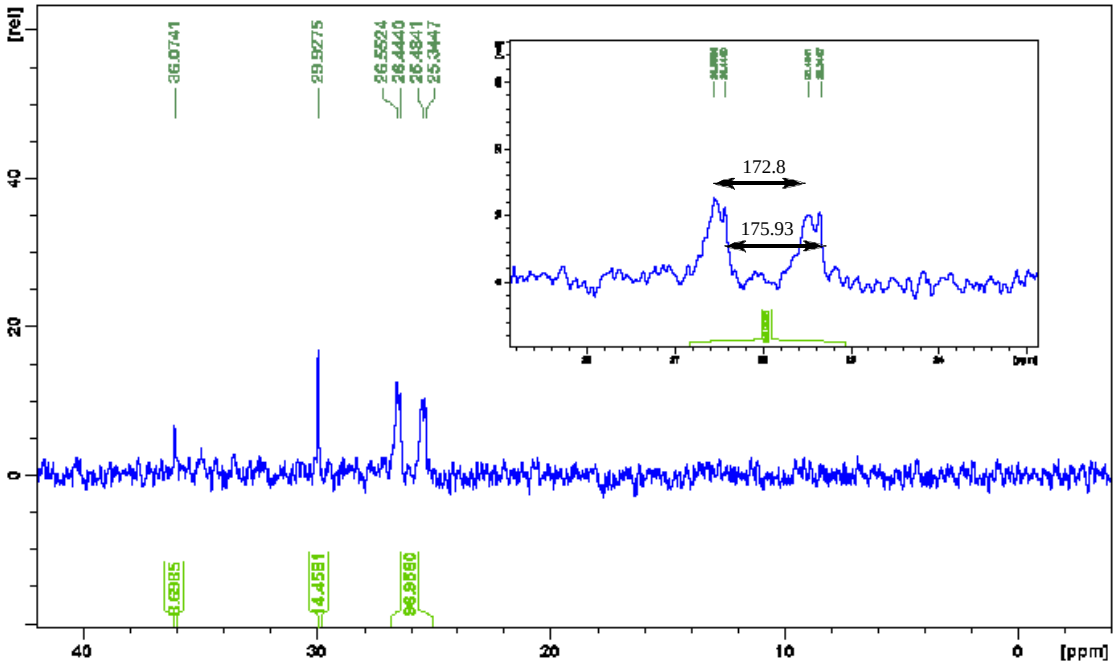


**Fig S14: $^{31}$P NMR spectrum of (4d): [Rh(nbd)(3d)]$BF_4$**

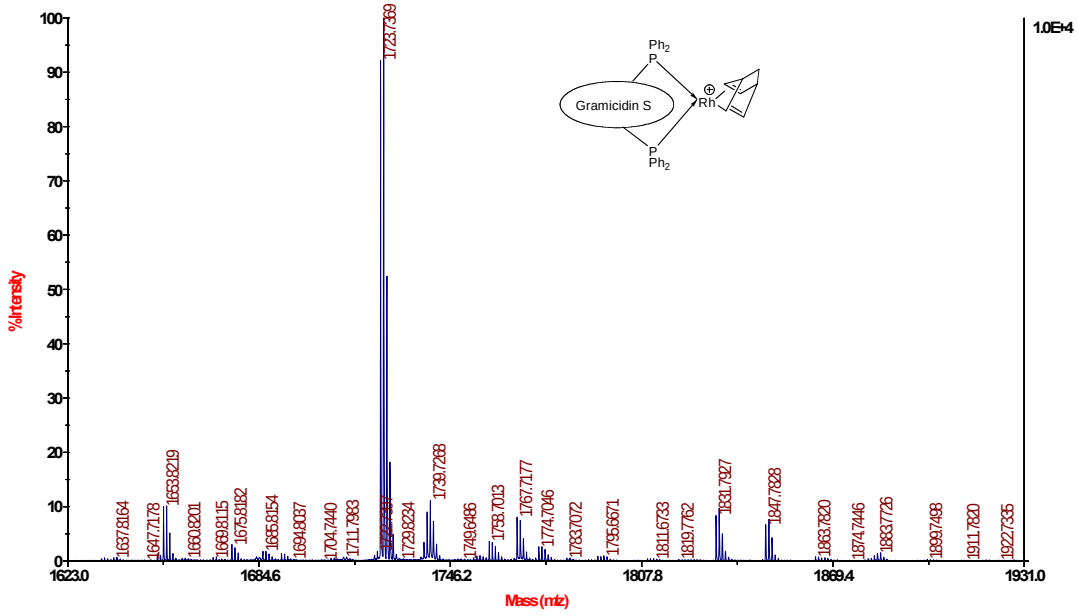


**Fig S15: Maldi-TOF spectrum of (4d): [Rh(nbd)(3d)]$BF_4$**

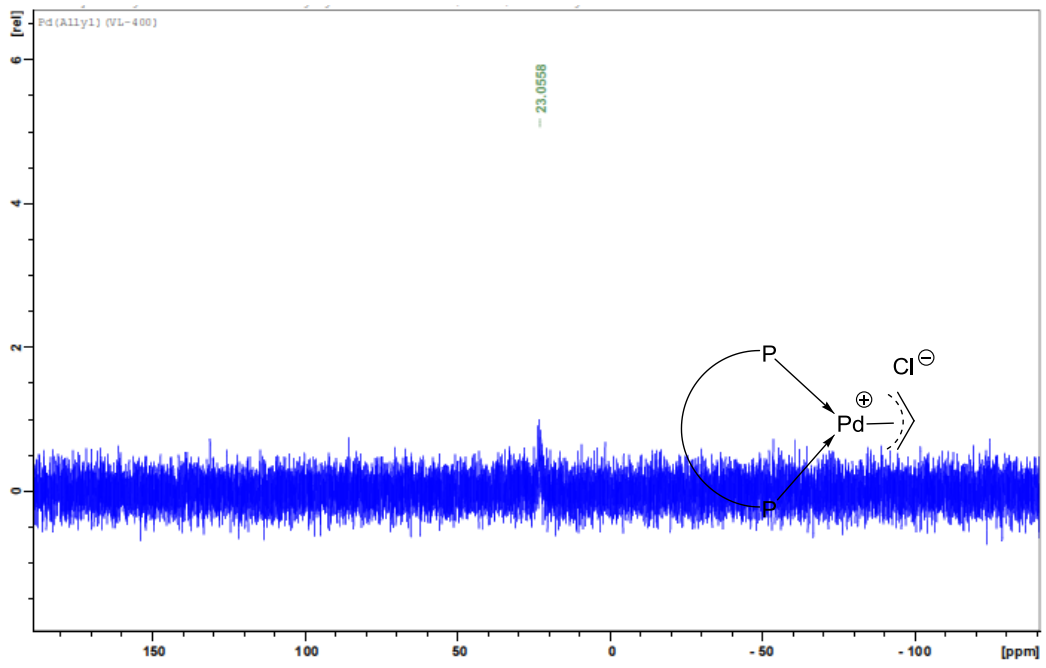

**Fig S16: $^{31}$P NMR spectrum of (5b): [Pd(3b)(allyl)]Cl**

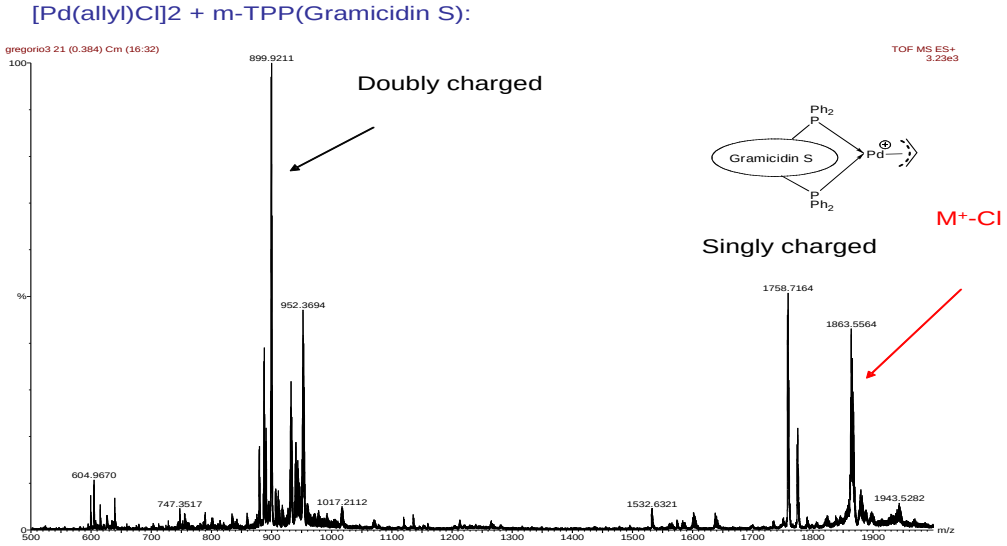


**Fig S17: Maldi-TOF spectrum of (5b): [Pd(3b)(allyl)]Cl**

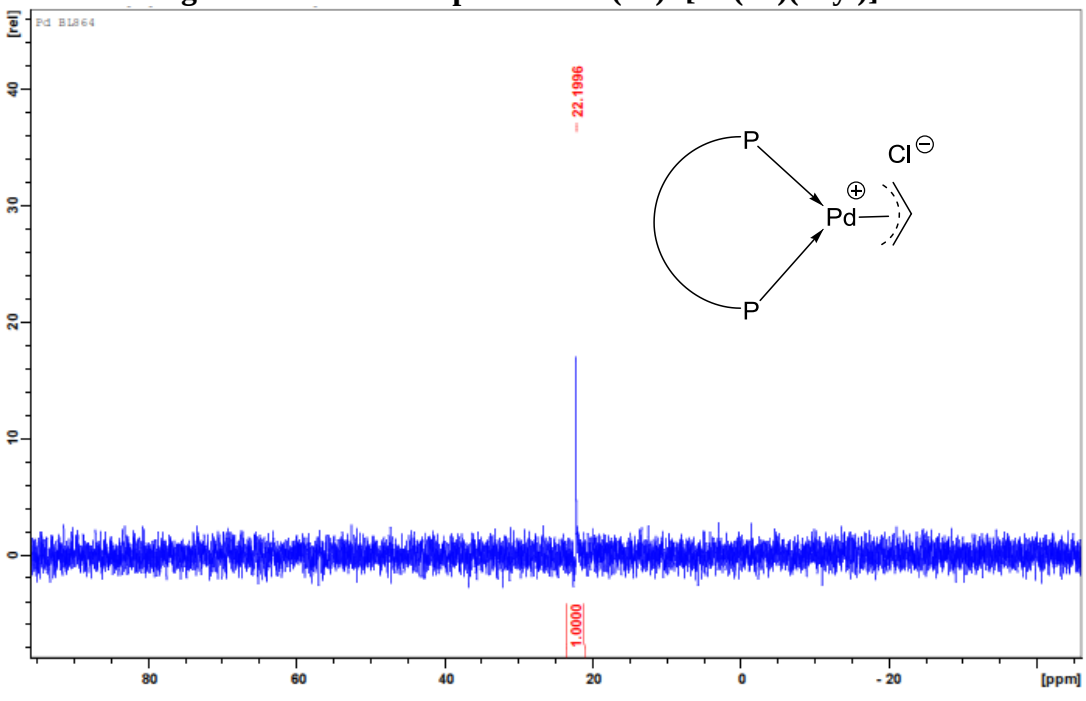

**Fig S18: $^{31}$P NMR spectrum of (5c): [Pd(3c)(allyl)]Cl**

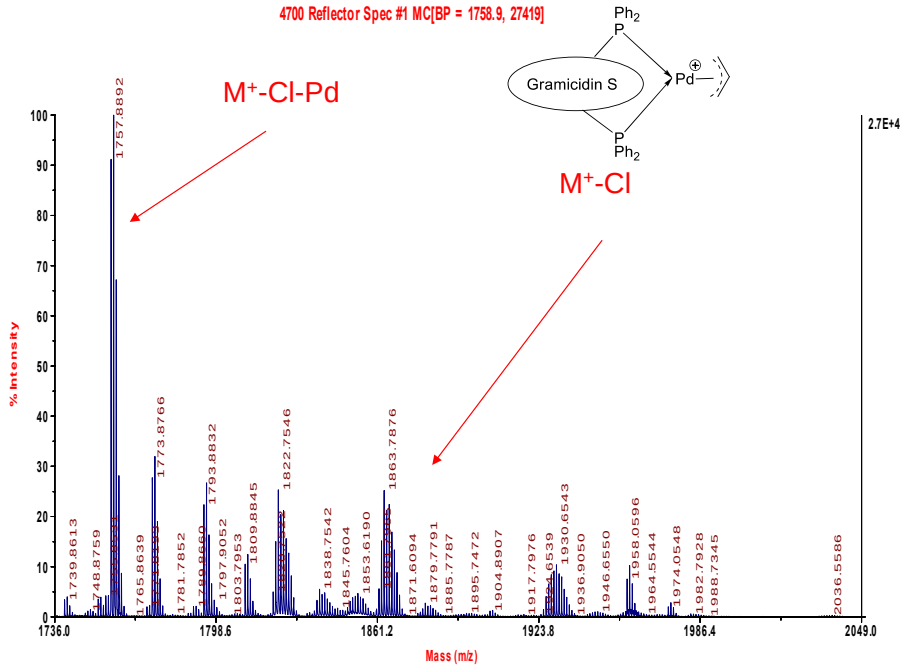


**Fig S19: Maldi-TOF spectrum of (5c): [Pd(3c)(allyl)]Cl**

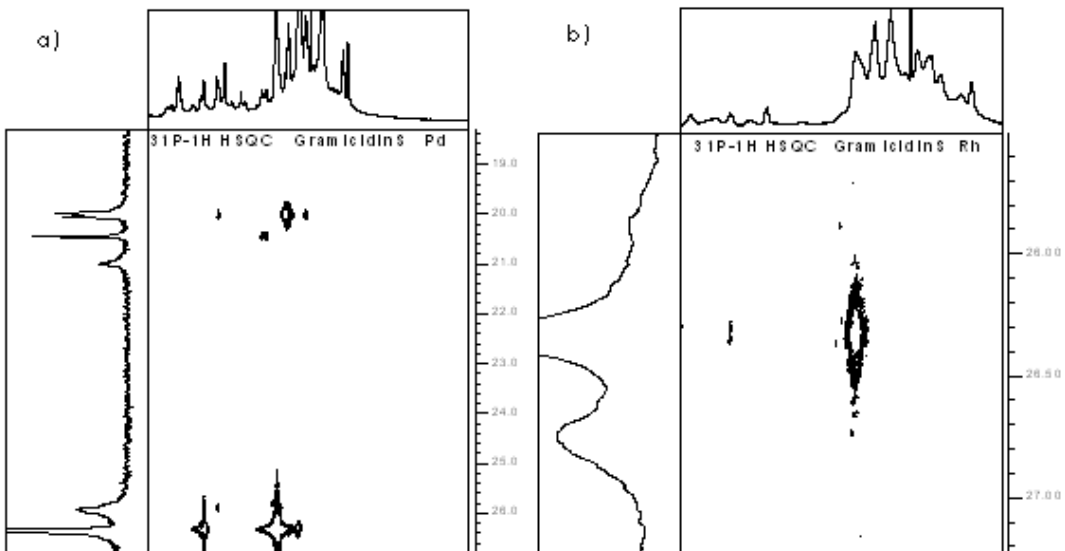

**Fig S20: $^{31}$P-$^{1}$H HSQC spectrum of a) 5b and b) 4b**

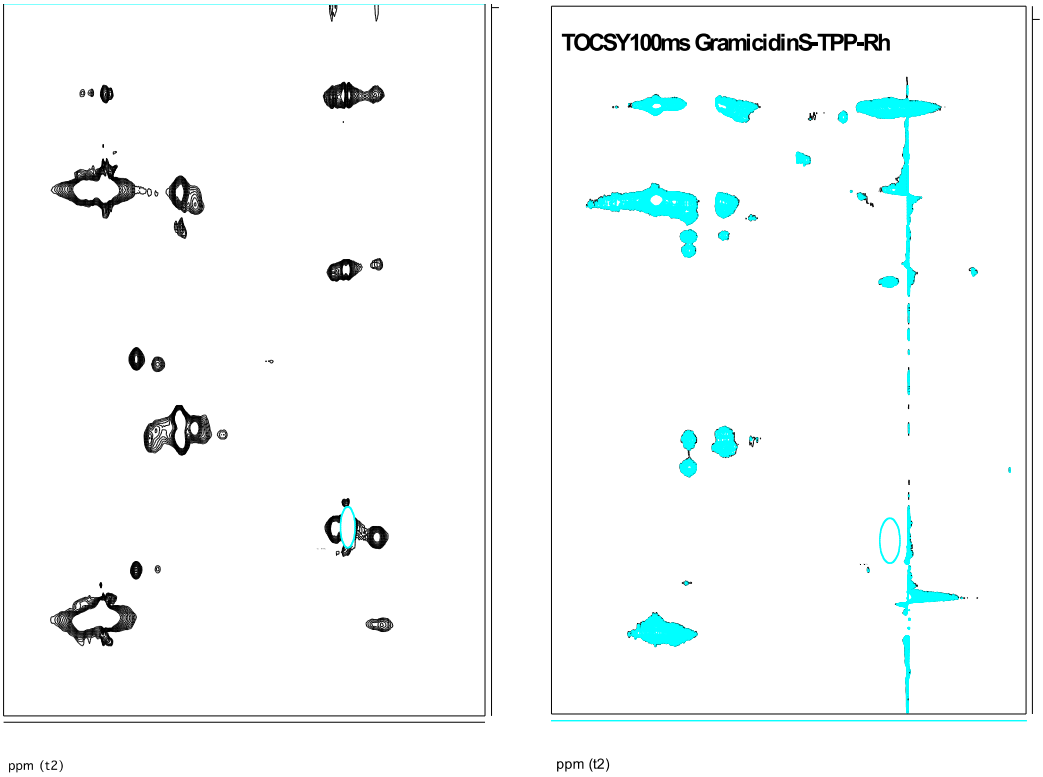


**Fig. 21: a) TOCSY60ms of 5b and b) TOCSY100ms 4b spectrum.**

## Representatives GC and HPLC traces

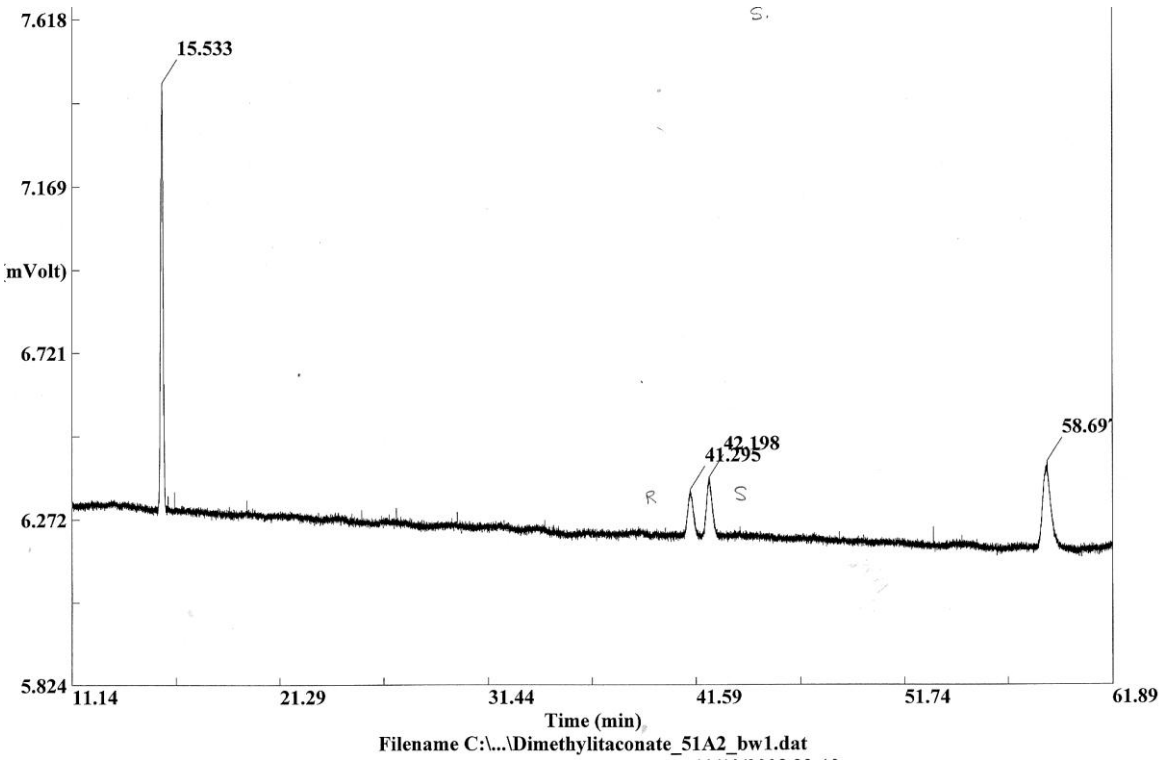


**Fig. 22: GC traces of asymmetric hydrogenation of dimethylitaconate.**

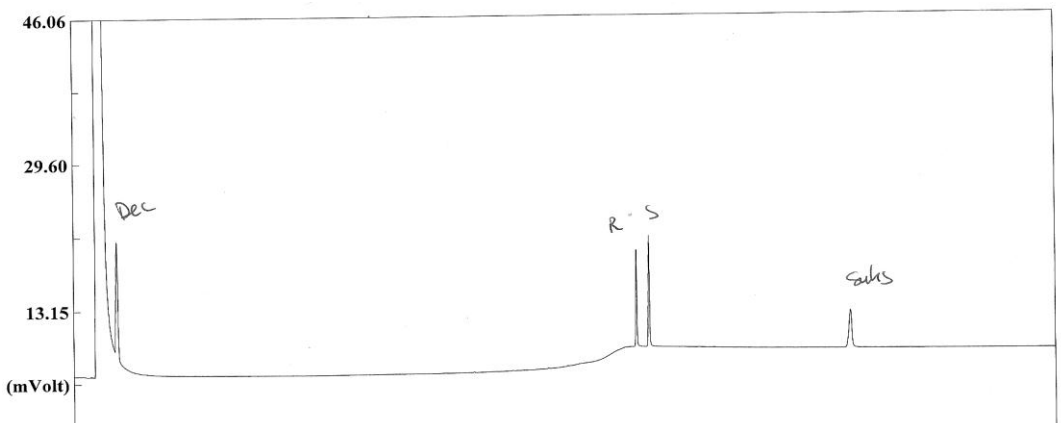

**Fig. 23: GC traces of asymmetric hydrogenation of cinnamate.**

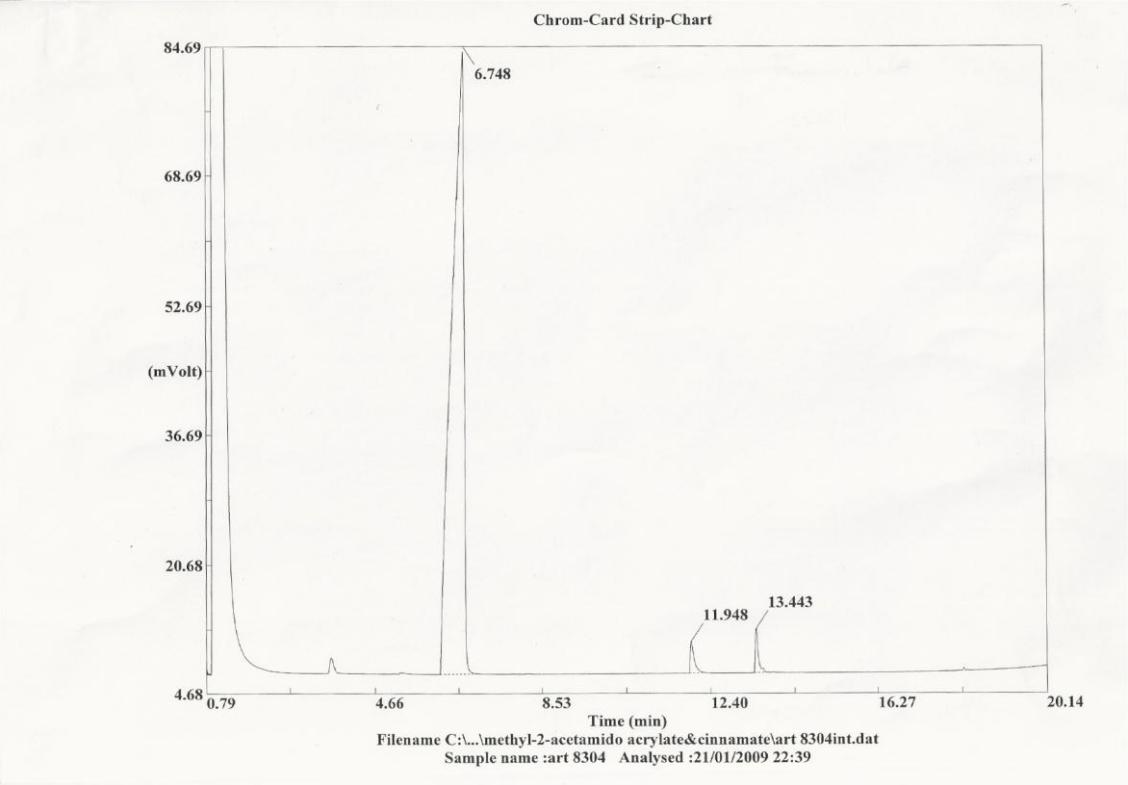


**Fig. 24: GC traces of asymmetric hydrogenation of cinnamate.**

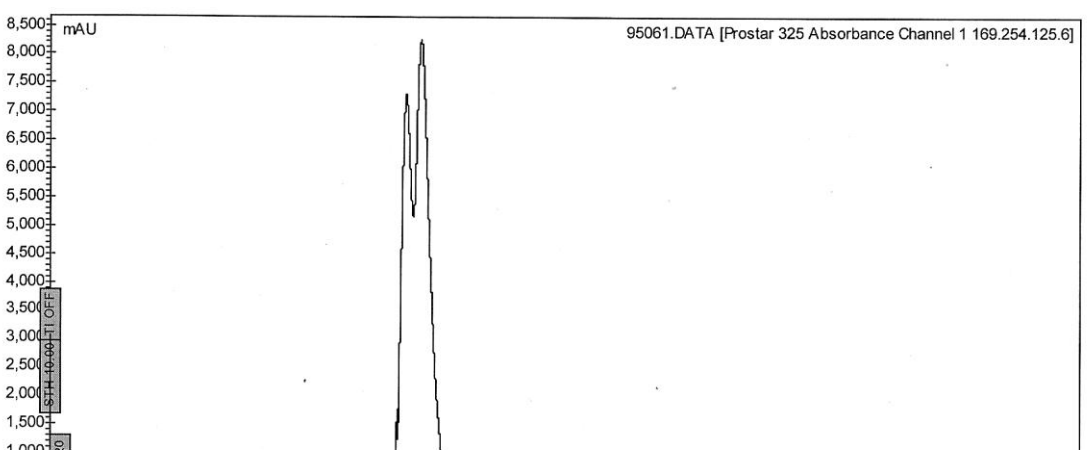

**Fig. 25: HPLC traces of asymmetric allylic alkylation of 1,3-diphenylallyl acetate using 5b.**

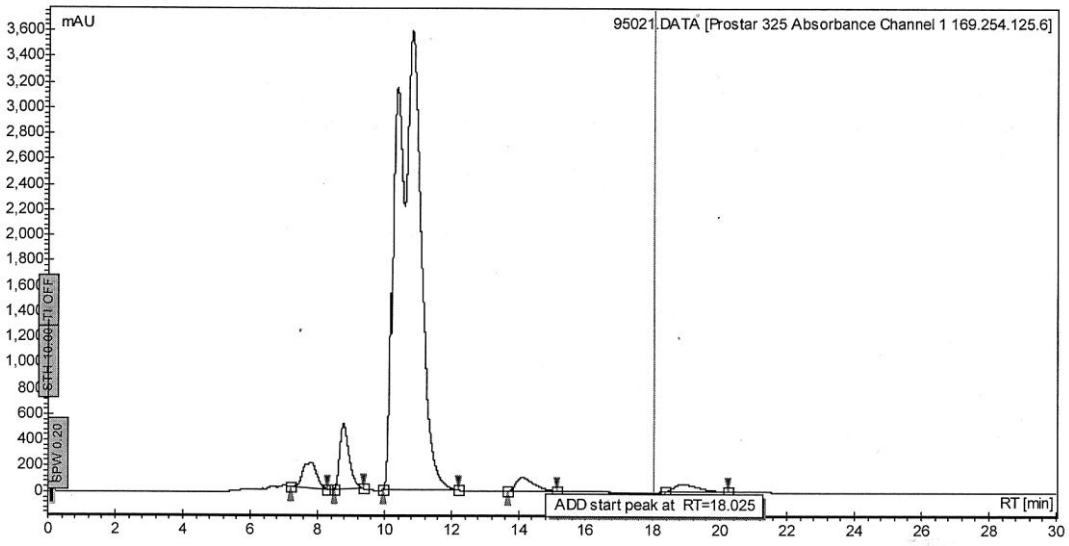


**Fig. 25: HPLC traces of asymmetric allylic alkylation of 1,3-diphenylallyl acetate using 5c.**