Supplementary Information

An Isomerisation Approach to Tesirine and Pyrrolobenzodiazepines

Andrew D. Campbell[†], Simone Tomasi[†], Arnaud C. Tiberghien[‡], and Jeremy S. Parker[§]*

[†]Chemical Development, Pharmaceutical Technology & Development, AstraZeneca, Macclesfield, SK10 2NA, United Kingdom

[‡]Spirogen, QMB Innovation Centre, 42 New Road, E1 2AX London, United Kingdom

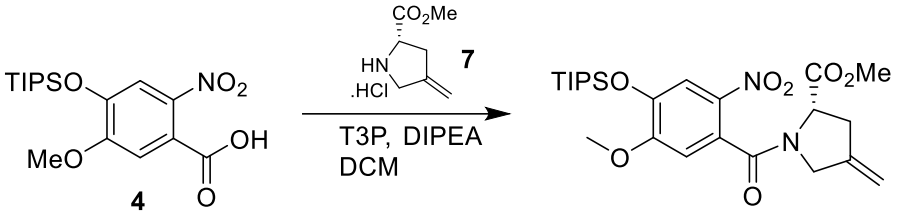
[§]Early Chemical Development, Pharmaceutical Sciences, R&D, AstraZeneca, Macclesfield, United Kingdom

jeremy.parker@astrazeneca.com

Contents

Large scale conversion of 5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)benzoic acid (4) to (*S*)-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-methylenepyrrolidin-1-yl)(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)phenyl)methanone (8)

Preparation of methyl (S)-1-(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)benzoyl)-4-methylenepyrrolidine-2-carboxylate



Propanephosphonic acid anhydride (T3P, 1.91kg, 6.00mol, 2.0eq), followed by DIPEA (3.14L, 18.0mol, 6.0eq) were added dropwise at -15°C to a mixture of 5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)benzoic acid (**4**, 1.11kg, 3.00mol, 1.0eq) and methyl (*S*)-4-methylenepyrrolidine-2-carboxylate hydrochloride (**7**, 640g, 3.60mol, 1.2eq) in dichloromethane (12L, 10.8vol). The reaction mixture was allowed to stir at -15 °C for 1h. Reaction completion was observed by HPLC. The reaction was quenched with water (12L, 10.8vol) at 5 °C. The organic phase was washed with 10% (w/w) aqueous citric acid (12L, 10.8vol), brine (12L, 10.8vol), and dried over sodium sulfate. The volatiles were removed under reduced pressure and the residue was purified by chromatography (heptane/ethyl acetate gradient from 90/10 to 75/25) to give methyl (*S*)-1-(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)benzoyl)-4-methylenepyrrolidine-2-carboxylate (1.1kg, 74%, LC purity 99.8%) as light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, two atropisomers in a 1/1.74 ratio) 7.75 – 7.62 (m, 1H), 6.89 – 6.74 (m, 1H), 5.19 – 4.54 (m, 3H), 4.29 – 3.50 (m, 8H), 3.15 – 2.95 (m, 1H), 2.79 – 2.57 (m, 1H), 1.37 – 1.19 (m, 3H), 1.17 – 1.01 (m, 18H).

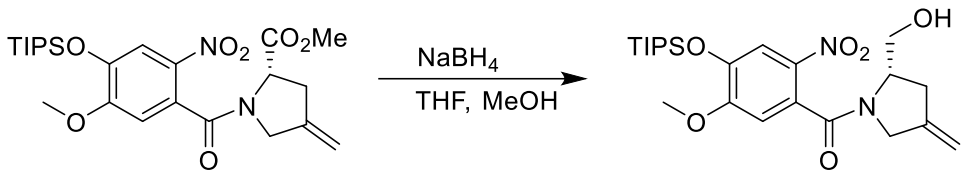
^{13}C NMR (101 MHz, $CDCl_3$) 172.10, 171.97, 166.90, 166.67, 156.62, 156.21, 146.19, 146.14, 142.01, 141.54, 137.38, 127.34, 126.88, 116.21, 116.11, 110.67, 109.93, 109.16, 109.06, 60.76, 58.32, 56.33, 56.21, 52.63, 52.51, 52.22, 50.44, 37.32, 35.71, 17.93, 17.90, 12.93, 12.90.

IR (cm^{-1}): 2946, 2868, 1745, 1652, 1570, 1522, 1421, 1334, 1290, 1223, 1063, 884, 841, 684.

$[\alpha]^{21}_{D}$ = -12°.

HRMS (ESI) m/z: Calcd for $C_{24}H_{36}N_2O_7Si$ 493.23645; Measured 493.23657.

*Preparation of (*S*)-(2-(hydroxymethyl)-4-methylenepyrrolidin-1-yl)(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)phenyl)methanone*



Sodium borohydride (180g, 4.75mol, 2.5eq), was added at 0°C to a solution of (*S*)-1-(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)benzoyl)-4-methylenepyrrolidine-2-carboxylate (935g, 1.90mol, 1.0eq) in tetrahydrofuran (5.6L, 6vol). Methanol (1.9L, 2vol) was then added at 0°C and the reaction mixture was allowed to stir at 0°C for 2h. Reaction completion was observed by HPLC. The reaction was diluted with cold DCM (6.5L, 7vol) and quenched with 10% (w/w) aqueous citric acid (6.2L, 6.6vol) at 5°C, followed by water (5.6L, 6vol). The aqueous layer was extracted with DCM 2 x (5.6L, 6vol). The organics were washed with saturated aqueous sodium bicarbonate (5.6L, 6vol), brine (5.6L, 6vol), and dried over sodium sulfate. The volatiles were removed under reduced pressure and the residue was purified by chromatography (heptane/ethyl acetate gradient from 80/20 to 50/50) to give (*S*)-(2-(hydroxymethyl)-4-methylenepyrrolidin-1-yl)(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)phenyl) methanone (0.83kg, 94%, LC purity 97.5%) as light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, Atropisomers in 0.14/1 ratio) 7.76 – 7.61 (m, 1H), 6.94 – 6.69 (m, 1H), 5.05 – 4.80 (m, 2H), 4.68 – 4.53 (m, 1H), 3.98 – 3.48 (m, 8H), 2.94 – 2.75 (m, 1H), 2.60 – 2.40 (m, 1H), 1.37 – 1.19 (m, 3H), 1.17 – 1.01 (m, 18H).

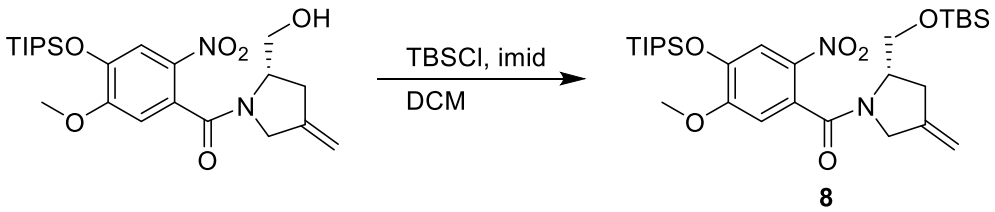
^{13}C NMR (101 MHz, $CDCl_3$) 156.79, 146.19, 142.79, 137.26, 127.65, 116.20, 109.50, 108.36, 60.47, 56.35, 53.08, 34.50, 17.91, 12.92.

IR (cm^{-1}) 2945, 2867, 1622, 1570, 1522, 1431, 1334, 1291, 1225, 1060, 884, 842, 684.

$[\alpha]^{21}_{D}$ = -34°.

HRMS (ESI) m/z: Calcd for $C_{23}H_{36}N_2O_6Si$ 465.24154; Measured 465.24176

*Preparation of (*S*)-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-methylenepyrrolidin-1-yl)(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)phenyl)methanone (**8**)*



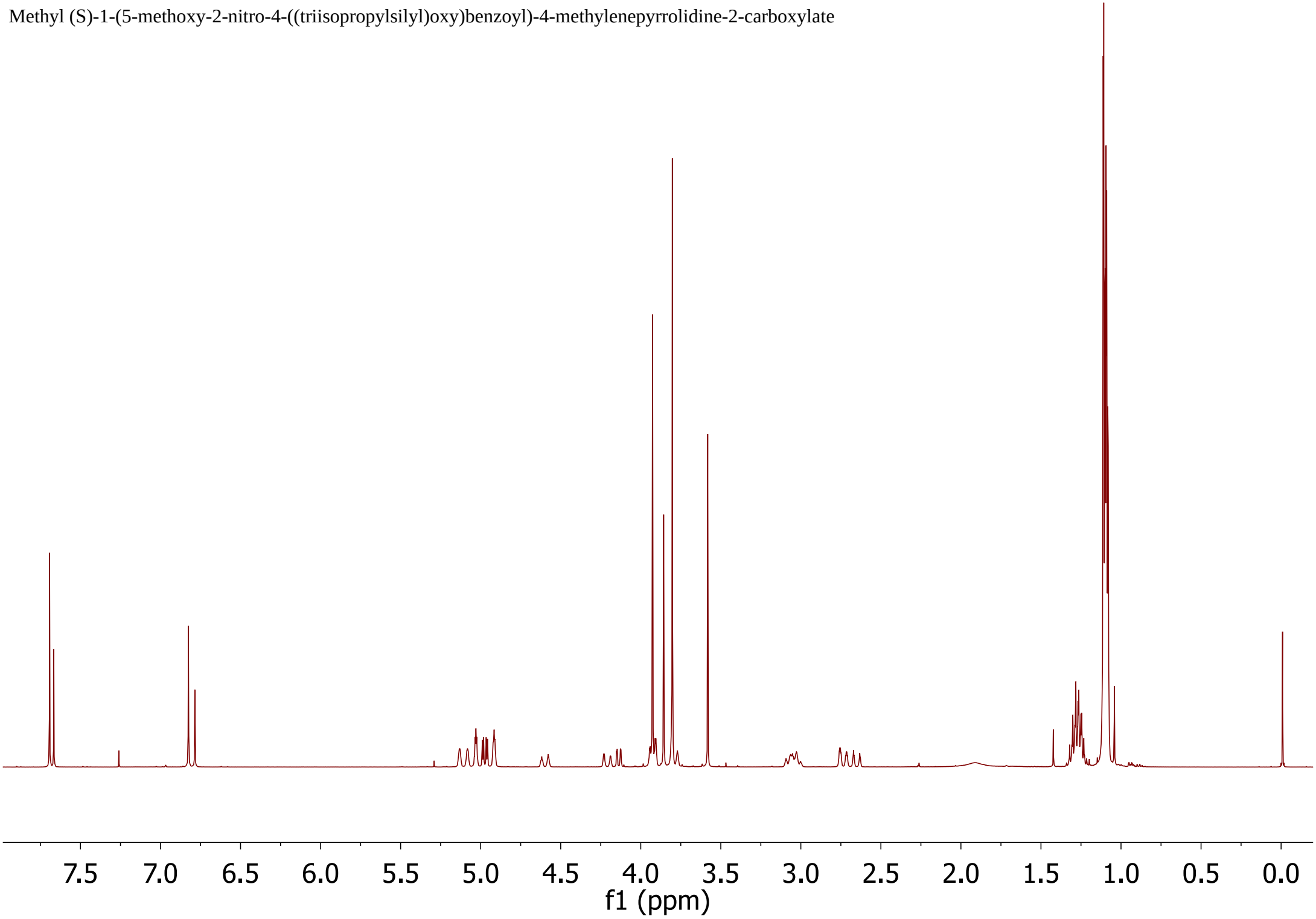
8

(*S*)-(2-(hydroxymethyl)-4-methylenepyrrolidin-1-yl)(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy) phenyl)methanone (837g, 1.79mol) and imidazole (244g, 3.59mol, 2.0eq) were dissolved in dichloromethane (5.0L, 6vol) at room temperature. TBSCl (404g, 2.68mol, 1.5eq) was added portionwise whilst keeping the temperature below 30°C. The reaction mixture was stirred at 25°C for 1h. Reaction completion was observed by HPLC. The solids were removed by filtration and washed with dichloromethane (1.7L, 2vol). The solution was washed with water (4.2L, 5vol), then brine (4.2L, 5vol), and dried over sodium sulfate. The volatiles were removed under vacuum and the residue was purified by filtration through a short pad of silica gel (heptane/ethyl acetate) to give (*S*)-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-methylenepyrrolidin-1-yl)(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)phenyl)methanone (**8**, 1010g, 1.74mol, 97% yield, LC purity 99%) as a yellow oil.

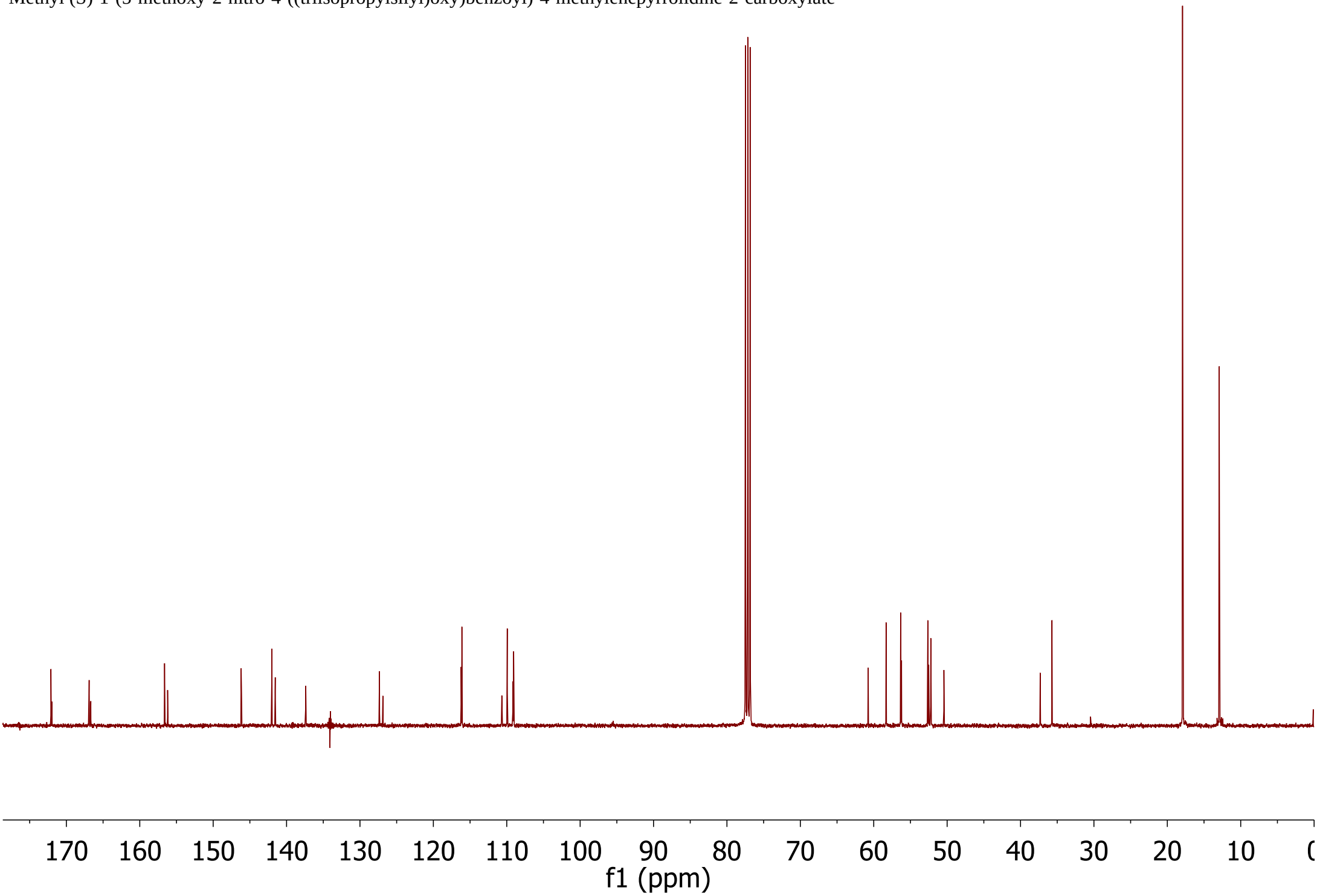
^{1}H NMR (400 MHz, $CDCl_3$, Atropisomers in 2/1 ratio) 7.78 – 7.57 (m, 1H), 6.84 – 6.64 (m, 1H), 5.19 – 4.45 (m, 3H), 4.07 – 3.64 (m, 6H), 3.62 – 3.18 (m, 1H), 2.90 – 2.41 (m, 2H), 1.38 – 1.18 (m, 3H), 1.15 – 1.03 (m, 18H), 0.96 – 0.72 (m, 9H), 0.15 – -0.20 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) 166.69, 166.43, 156.40, 156.12, 145.99, 145.78, 144.20, 143.36, 137.39, 137.31, 128.07, 127.25, 116.04, 110.42, 109.51, 108.28, 107.42, 63.73, 62.58, 60.21, 58.14, 56.09, 56.07, 52.76, 50.57, 35.00, 33.97, 25.85, 25.76, 25.67, 18.20, 17.99, 17.81, 17.72, 17.65, 13.10, 12.82, 12.80, 12.51, -3.57, -5.41, -5.43, -5.58.

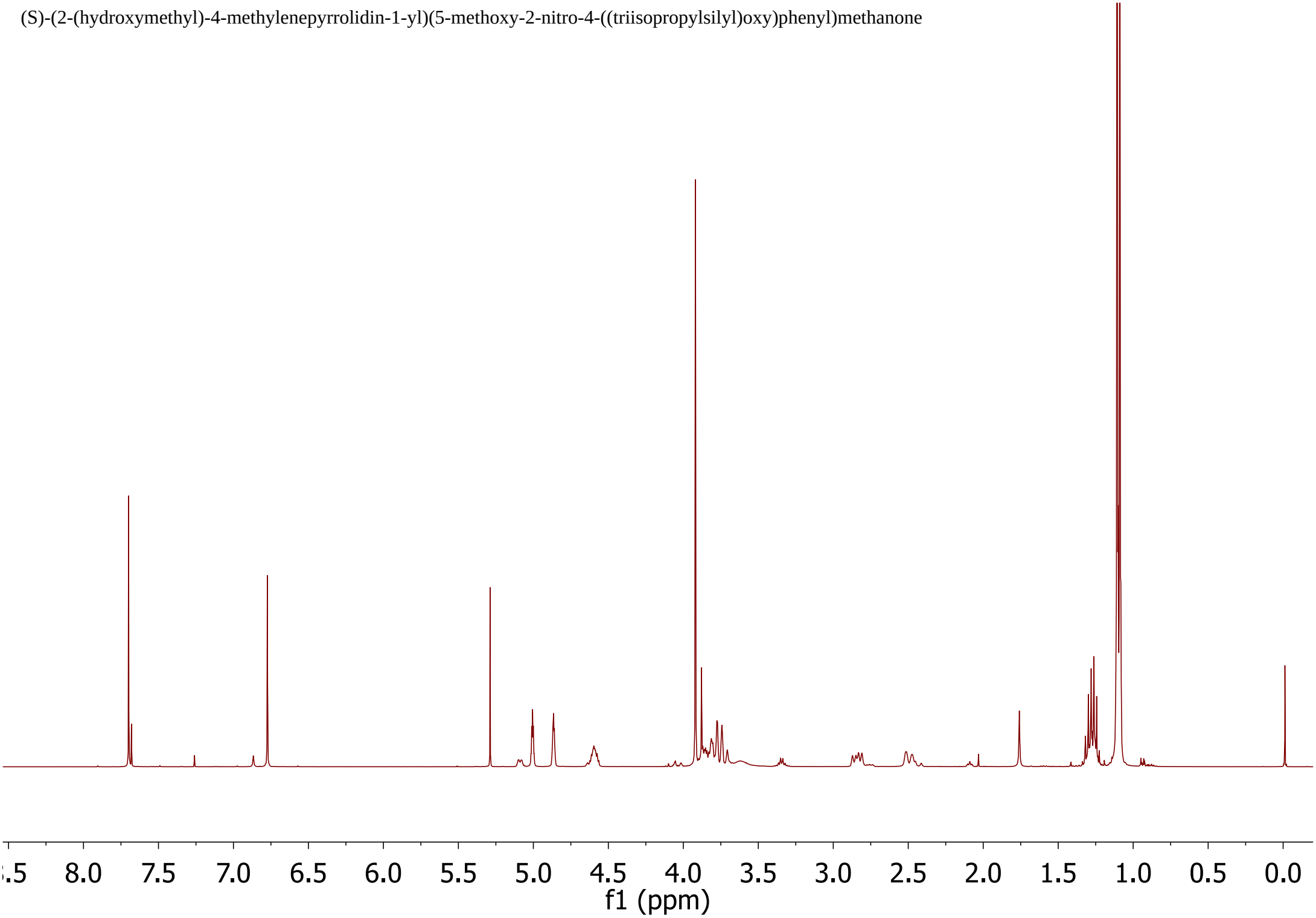
Methyl (S)-1-(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)benzoyl)-4-methylenepyrrolidine-2-carboxylate



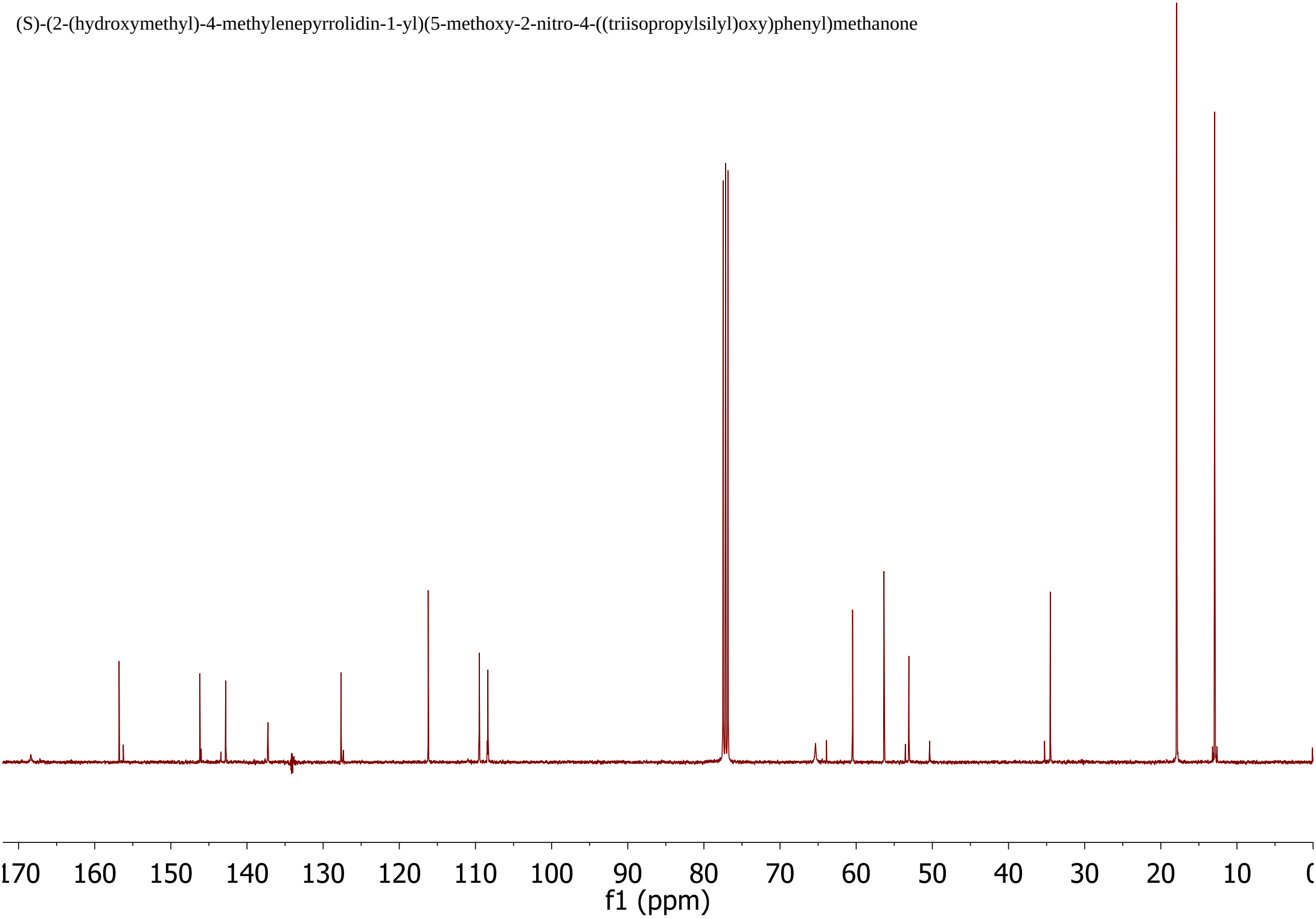
Methyl (S)-1-(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)benzoyl)-4-methylenepyrrolidine-2-carboxylate



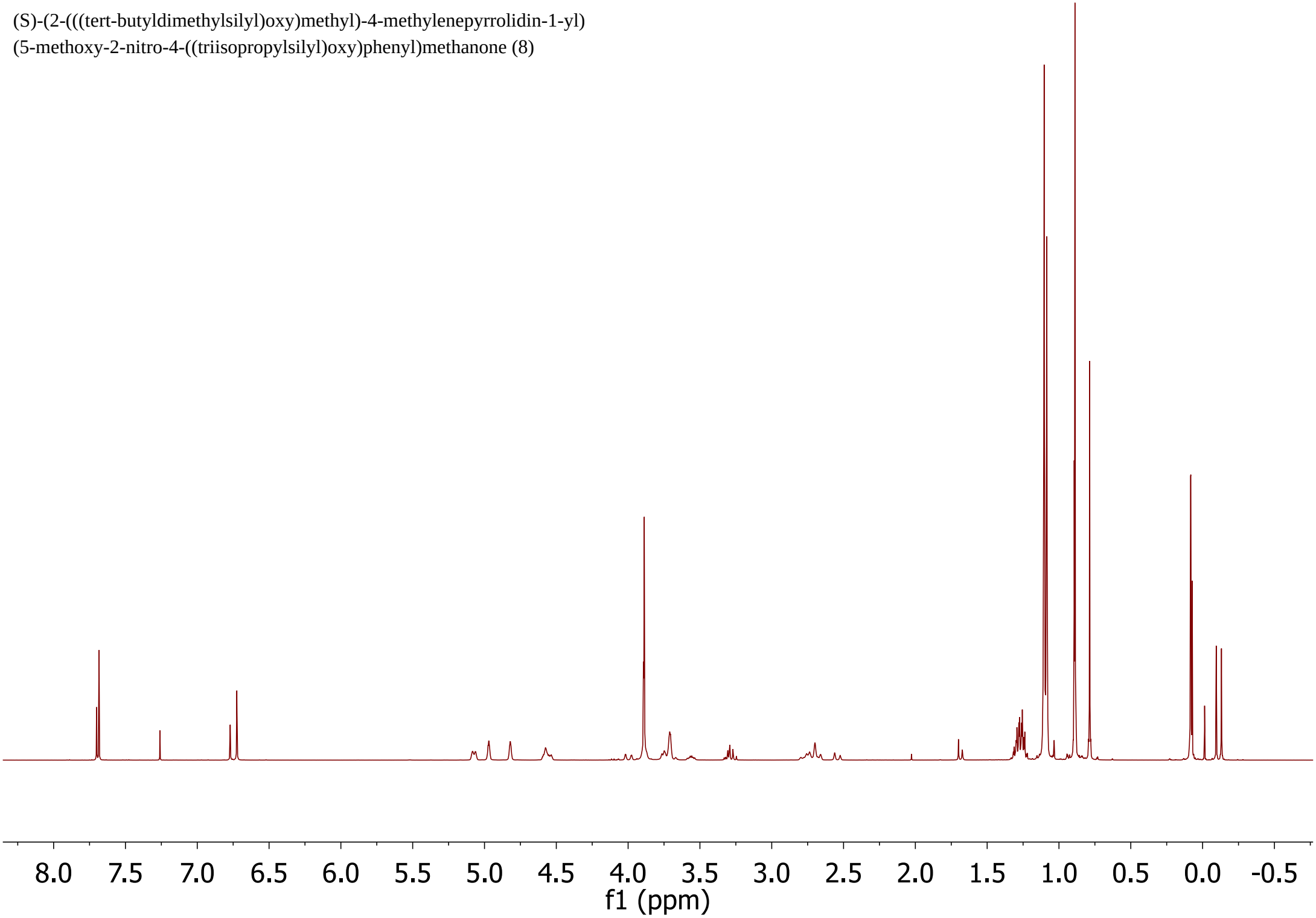
(S)-(2-(hydroxymethyl)-4-methylenepyrrolidin-1-yl)(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)phenyl)methanone



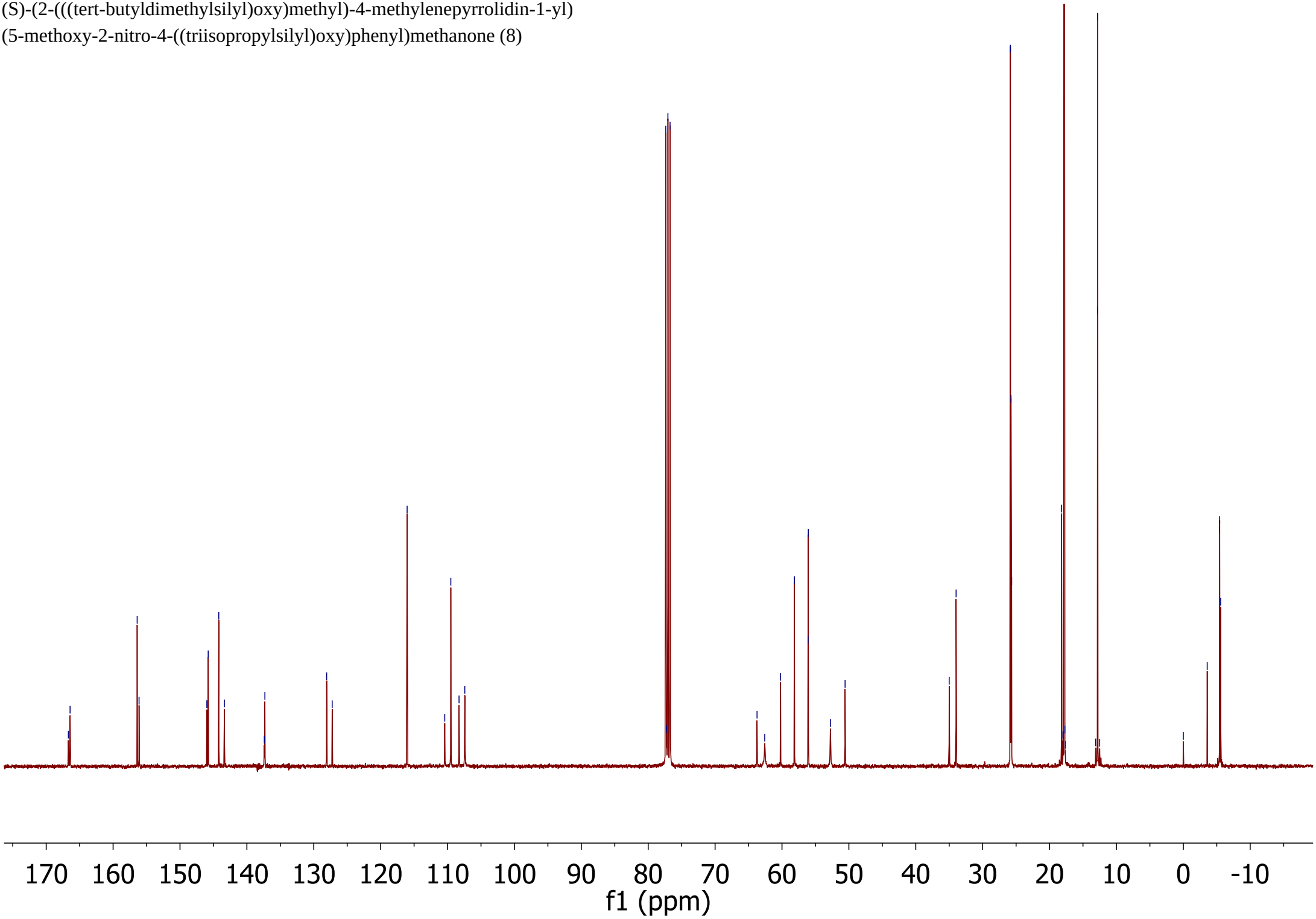
(S)-(2-(hydroxymethyl)-4-methylenepyrrolidin-1-yl)(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)phenyl)methanone



(S)-(2-(((tert-butyldimethylsilyl)oxy)methyl)-4-methylenepyrrolidin-1-yl)
(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)phenyl)methanone (8)

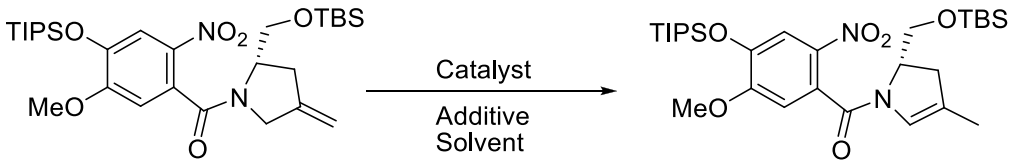


(S)-(2-(((tert-butyldimethylsilyl)oxy)methyl)-4-methylenepyrrolidin-1-yl)
(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)phenyl)methanone (8)



Catalyst Screening

*Screening work completed on conversion of (S)-(2-((tert-butyldimethylsilyloxy) methyl)-4-methylenepyrrolidin-1-yl)(5-methoxy-2-nitro-4-(triisopropylsilyloxy) phenyl)methanone (**8**) to (S)-(2-((tert-butyldimethylsilyloxy)methyl)-4-methyl-2,3-dihydro-1H-pyrrol-1-yl)(5-methoxy-2-nitro-4-(triisopropylsilyloxy)phenyl)methanone (**6**)*



Screen 1

Initial isomerisation screen to asses a wide range of methods

Catalyst selection made by literature review and in-house knowledge.

Experimental Set-Up

- On a 100mg scale of alkene, reactions were performed in 4mL vials in a 24-well plate format, situated in an inerted glovebox (<10ppm O_2 and <1ppm H_2O)
- Metal sources were weighed by hand (if air insensitive) or were dispensed as solids using a Quantos weighing robot situated inside the glovebox
- Stir discs were added to each vial
- Starting material (2g) was dissolved in dry degassed toluene (10mL total) and 500µL was dispensed to each vial (100mg/reaction)
- Each vial was then made up to 2mL with the solvent stated in the reaction plan
- Liquid additives (reactions 2, 5 and 16) were then added
- The reactions were sealed and heated at 60°C for 4h then at 100°C for a further 18h for all reactions except reaction 4 (in MeOH, kept at 60°C)
- Samples for UPLC/MS analysis were prepared at 1h and 22h.

UPLC Analysis:

Column: Phenomenex Kinetex 2.6u C18 100A 75mm x 3mm
Mobile phase A: 0.03% TFA in water
Mobile phase B: 0.025% TFA in acetonitrile

Gradient:

Time	%A	%B
0.00	30	70
8.00	15	85
8.50	5	95

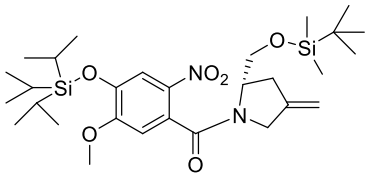
Flow rate: 1.2mL/min
Detection: UV @ 220nm
Temperature: 40°C

Reaction Plan and Results

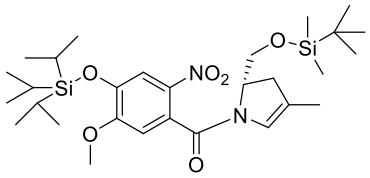
												Area% at 220nM at 22h			
Reaction Number	Catalyst	Catalyst (mol%)	Additive	Additive eq.	Alkene (SM)	Temp. °C	Solvent (20vols)	Conversion at 1h	Product/ Isomer ratio	Conversion at 22h	Product/ Isomer ratio	Product	isomeric product	SM	Other peaks
1	Grubbs I	5	none		1.0eq.	60-100	Toluene	0.0	0.0	20.6	0.6	7.7	12.4	77.9	2.0
2	Grubbs I	5	Et3SiH	1	1.0eq.	60-100	Toluene	0.0	0.0	32.1	1.1	12.3	11.0	49.1	27.7
3	Grubbs II	5	none		1.0eq.	60-100	Toluene	0.0	0.0	19.5	5.3	14.5	2.7	71.1	11.7
4	Grubbs II	5	none		1.0eq.	60	MeOH	19.5	1.2	100.0	0.9	46.2	52.4	0.0	1.4
5	none		Fe(CO)5	3	1.0eq.	60-100	CPME	0.0	0.0	0.0	0.0	0.0	0.0	70.1	29.9
6	Crabtrees Cat.	5	none		1.0eq.	60-100	Toluene	0.0	0.0	13.8	22.1	12.1	0.5	78.8	8.6
7	Crabtrees Cat.	5	none		1.0eq.	60-100	IPA/Toluene	0.0	0.0	100.0	0.8	29.2	36.9	0.0	33.9
8	Ru(H2)(PPh3)4	5	none		1.0eq.	60-100	Toluene	0.0	0.0	0.0	0.0	0.0	0.0	95.2	4.8
9	RuHCl(CO)PPh3	5	none		1.0eq.	60-100	Toluene	18.5	0.1	100.0	0.4	26.4	68.6	0.0	5.0
10	cationic CpRu(Pr3) (strem)	5	none		1.0eq.	60-100	Toluene	83.5	0.3	100.0	0.4	25.2	71.4	0.0	3.3
11	RhH(CO)PPh3	5	none		1.0eq.	60-100	Toluene	21.2	0.0	47.2	0.2	6.3	38.6	50.3	4.8
12	RhCl3.H20	5	none		1.0eq.	60-100	nBuOH	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0
13	Rh(COD)2BF4	5	Binap	0.05	1.0eq.	60-100	Toluene	0.0	0.0	100.0	0.4	25.1	56.6	0.0	18.3
14	Pd/C	5	none		1.0eq.	60-100	Toluene	0.0	0.0	0.0	0.0	0.0	0.0	99.7	0.3
15	Pd-113	5	none		1.0eq.	60-100	Toluene	100.0	2.4	100.0	15.7	89.5	5.7	0.0	4.8
16	Pd-118	5	Et3SiH	0.1	1.0eq.	60-100	Toluene	97.0	0.3	100	0.3	20.5	64.4	0.0	15.2
17	Pd(MeCN)2Cl2	5	none		1.0eq.	60-100	Toluene	0.0	0.0	0	0	0.0	0.0	91.4	8.6
18	Pd(OAc)2/PhS(O)(CH2)2S(O)Ph	5	none		1.0eq.	60-100	Toluene	0.0	0.0	0	0	0.0	0.0	93.5	6.5

$$\textbf{Conversion}(\%) = \frac{100 * (\text{Product Area\%} + \text{Isomeric product Area\%})}{(\text{SM Area\%}) + (\text{Product Area\%}) + (\text{Isomeric product Area\%})}$$

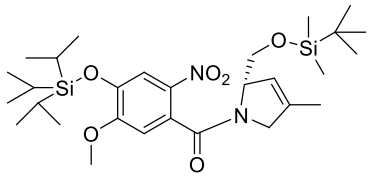
Reaction Products and Impurities



Starting material, Rt=7.9mins
Molecular Weight: 578.89

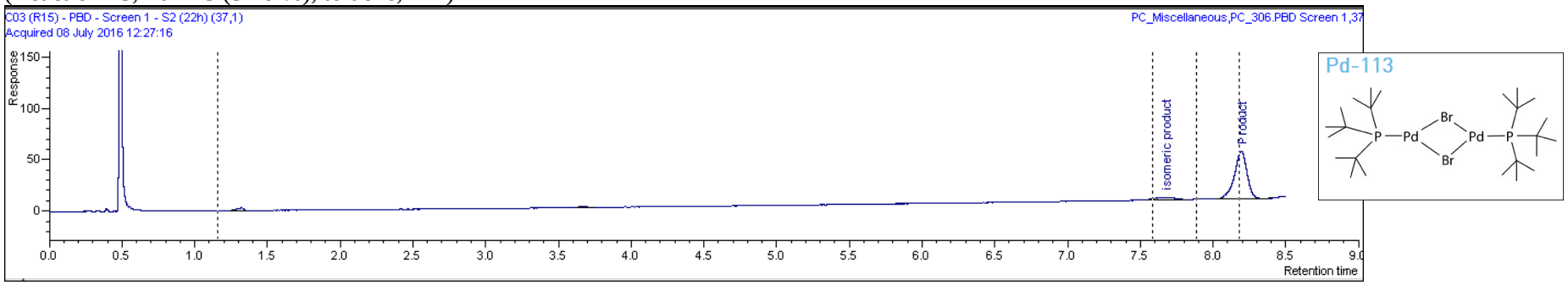


Product, Rt=8.2mins
Molecular Weight: 578.89

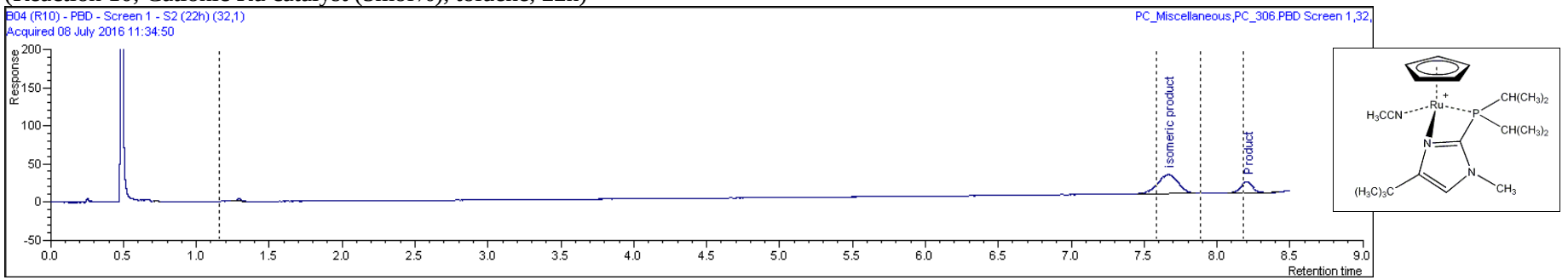


Isomeric product, Rt=7.6mins
Molecular Weight: 578.89

Typical HPLCs (toluene peak at 0.5mins)
(Reaction 15, Pd-113 (5mol%), toluene, 22h)



(Reaction 10, Cationic Ru catalyst (5mol%), toluene, 22h)



Conclusions

- Product is formed in a number of reactions
- The best reaction uses Pd-113 which provides relatively clean product (~89% by HPLC) with small amounts of isomeric product
    - For Pd-113, the isomeric product appears to be an intermediate which progresses on to the desired product (data from 1h and 22h HPLC samples)
    - 5mol% of Pd-113 is actually 10mol% of Pd as the structure is dimeric
    - A Pd-mirror is formed in this reaction
- A number of metal hydride type catalysts do give product although the selectivity for product appears to be poor
    - There is no evidence that the isomeric product isomer is turning over to the desired product in these systems

Screen 2

Assess a wide range of palladium catalysts (32) with 3 methods to form palladium hydride species:

Method 1 (no additive) – In-house knowledge.
Method 2 (Et_3SiH) – see Noonan, G. M.; Hayter, B. R.; Campbell, A. D.; Gorman, T. W.; Partridge, B. E.; Lamont, G. M. *Tetrahedron Lett.* **2013**, *54*, 4518–4521.
Method 3 (iPrCOCl) – see Gauthier, D.; Lindhardt, A. T.; Olsen, E. P. K.; Overgaard, J.; Skrydstrup, T. *J. Am Chem. Soc.* **2010**, *132*, 7998-8009.

Experimental Set-Up

- Reactions were performed in 1mL vials in a 96-well plate format, situated in an inerted glovebox (<10ppm O_2 and <1ppm H_2O)
- Ligands (12mol% for bidentate and 20mol% for monodentate) and Pd-113 were preweighed as solids using a Quantos weighing robot inside an inerted glovebox
- Pd sources (10mol%), Internal Standard (IS, 4-4'-Di-tert-butyl biphenyl, 10mol%) were dispensed as 0.01M stock solutions ($CHCl_3$) in the 96-well vials according to reaction plan
- The carrier solvents were evaporated using a Genevac EZ-2 situated inside a glovebox
- Stir discs were added to each vial
- Three separate solutions of Alkene starting material (3 x 998mg in 20mL toluene) were prepared:
    - Vial 1 contained alkene in toluene
    - Vial 2 contained alkene and Et_3SiH (27.7µL) was added to give 100mol% alkene and 10mol% Et_3SiH in each reaction
    - Vial 3 contained alkene and iPrCOCl (18.3µL) was added to give 100mol% alkene and 10mol% iPrCOCl in each reaction
- 579µL of each solution was added in each vial to provide 28.9mg of alkene per reaction.
- Et_3N (1.4µL, 20mol%) was added to each vial that contained a ligand as its HBF_4 salt (D4, D8 D12 ,E4, E8, E12, F4, F8, F12, G4, G8, G12)
- The reactions were sealed and heated at the 80°C for 20h
- Samples for UPLC/MS analysis were prepared at 2h and 20h

Reaction Plan

	10 mol% Pd(OAc)2				10 mol% Pd(OAc)2/Et3SiH (10mol%)				10mol% Pd(dba)2/iPrCOCl (10mol%)			
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
A	PPh3	P(o-tol)3	dppb	dppp	PPh3	P(o-tol)3	dppb	dppp	PPh3	P(o-tol)3	dppb	dppp
B	P(m-(MeO)-Ph)3	(Cy2-naphOPO)PNMe2	dppm	Xantphos	P(m-(MeO)-Ph)3	(Cy2-naphOPO)PNMe2	dppm	Xantphos	P(m-(MeO)-Ph)3	(Cy2-naphOPO)PNMe2	dppm	Xantphos
C	P(C6F5)3	P(OH)(t-Bu)2	Phanephos	dpephos	P(C6F5)3	P(OH)(t-Bu)2	Phanephos	dpephos	P(C6F5)3	P(OH)(t-Bu)2	Phanephos	dpephos
D	P(O-(2,4-t-Bu)-Ph)3	$P(Adam)_2(n\text{-}Bu)$	Biphephos	P(t-Bu)3.HBF4	P(O-(2,4-t-Bu)-Ph)3	$P(Adam)_2(n\text{-}Bu)$	Biphephos	P(t-Bu)3.HBF4	P(O-(2,4-t-Bu)-Ph)3	$P(Adam)_2(n\text{-}Bu)$	Biphephos	P(t-Bu)3.HBF4
E	Ru-phos	$P(CH_2CH_2CN)_3$	$1,3\text{-}(Di\text{-}tBu)_2PCH_2Ph$	$P(t\text{-}Bu)_2(Me).HBF_4$	Ru-phos	$P(CH_2CH_2CN)_3$	$1,3\text{-}(Di\text{-}tBu)_2PCH_2Ph$	$P(t\text{-}Bu)_2(Me).HBF_4$	Ru-phos	$P(CH_2CH_2CN)_3$	$1,3\text{-}(Di\text{-}tBu)_2PCH_2Ph$	$P(t\text{-}Bu)_2(Me).HBF_4$
F	P(2-furyl)3	$P(Ph)_2(c\text{-}Hexyl)$	BINAP	$PCy_3.HBF4$	P(2-furyl)3	$P(Ph)_2(c\text{-}Hexyl)$	BINAP	$PCy_3.HBF4$	P(2-furyl)3	$P(Ph)_2(c\text{-}Hexyl)$	BINAP	$PCy_3.HBF4$
G	P(3,5-CF3Ph)3	X-Phos	dppe	$Cy_2P(CH_2)_3PCy_2.HBF4$	P(3,5-CF3Ph)3	X-Phos	dppe	$Cy_2P(CH_2)_3PCy_2.HBF4$	P(3,5-CF3Ph)3	X-Phos	dppe	$Cy_2P(CH_2)_3PCy_2.HBF4$
H	t-Bu-Xphos	dppf	DtBPF	Pd-113	t-Bu-Xphos	dppf	DtBPF	Pd-113	t-Bu-Xphos	dppf	DtBPF	Pd-113

Results

Overview of results at 2h (Product/Internal Standard values, higher values are higher yields)

	10 mol% Pd(OAc)2				10 mol% Pd(OAc)2/Et3SiH (10mol%)				10mol% Pd(dba)2/iPrCOCl (10mol%)			
	1	2	3	4	5	6	7	8	9	10	11	12
A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.6	0.0	0.0
B	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.4	0.0	0.0	0.0	0.0
C	0.0	0.5	0.0	0.0	0.0	0.9	0.9	0.0	0.0	0.6	0.0	0.0
D	0.0	0.0	0.0	0.0	0.0	0.0	0.5	2.2	1.9	0.0	0.0	1.8
E	0.0	0.0	0.0	1.2	0.9	0.0	0.0	1.6	0.3	0.0	0.0	0.0
F	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.2	0.3	0.0	0.0	0.0
G	0.0	0.0	0.0	0.0	0.5	0.4	0.0	0.0	0.0	0.6	0.0	0.0
H	0.0	0.0	0.0	10.2	0.9	0.0	0.5	9.7	0.4	0.0	0.0	2.6

Overview of results at 20h (Product/Internal Standard values, higher values are higher yields)

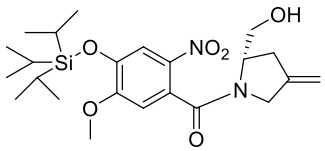
	10 mol% Pd(OAc)2				10 mol% Pd(OAc)2/Et3SiH (10mol%)				10mol% Pd(dba)2/iPrCOCl (10mol%)			
	1	2	3	4	5	6	7	8	9	10	11	12
A	0.0	0.0	0.0	0.0	0.1	0.3	0.0	0.0	0.2	0.9	0.0	0.0
B	0.0	0.0	0.0	0.9	0.0	0.0	0.0	1.3	0.2	0.0	0.0	0.0
C	0.2	4.2	0.0	0.0	0.2	3.9	1.1	0.0	0.0	0.6	0.0	0.0
D	0.0	0.0	0.4	0.6	0.4	0.0	0.7	1.3	1.5	0.0	0.0	2.1
E	0.0	0.0	0.0	1.6	1.1	0.2	0.0	1.2	0.6	0.3	0.0	0.0
F	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.3	0.0	0.0	0.0
G	0.2	0.2	0.0	0.0	1.2	0.5	0.0	0.0	0.0	1.5	0.0	0.0
H	0.0	0.0	0.0	8.8	1.5	0.0	0.4	9.1	0.4	0.1	0.0	3.4

Results (sorted by product area%)

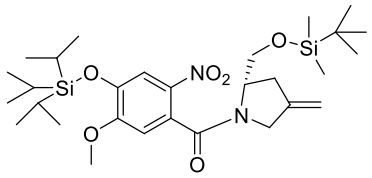
Row	Col	Pd loading (mol%)	Metal Source (10mol%)	Ligand	Ligand charge (mol%)	Additive (10mol%)	Et3N (mol%)	Alkene (SM)	Temp. (°C)	Solvent	Reaction Conc. (vols)	Conv. (2h)	P/IS (2h)	Conv (20h)	P/IS (20h)	Product	Alkene SM	isomeric product	SM - TBS	Other peaks
H	8	1.5	Pd-113	none	0	Et3SiH	0	1 eq.	80	Toluene	20	98.3	9.7	93.5	9.1	85.3	0.0	5.9	0.4	8.4
H	4	1.5	Pd-113	none	0	none	0	1 eq.	80	Toluene	20	94.0	10.2	98.8	8.8	76.4	0.0	1.0	0.4	22.3
C	6	1.5	Pd(OAc)2	P(OH)(t-Bu)2	20	Et3SiH	0	1 eq.	80	Toluene	20	8.4	0.9	44.6	3.9	41.6	0.0	51.6	1.6	5.2
C	2	1.5	Pd(OAc)2	P(OH)(t-Bu)2	20	none	0	1 eq.	80	Toluene	20	5.1	0.5	40.2	4.2	38.4	52.2	4.9	0.0	4.5
H	12	1.5	Pd-113	none	0	iPrCOCl	0	1 eq.	80	Toluene	20	96.1	2.6	97.3	3.4	34.4	0.0	1.0	1.4	63.3
D	12	1.5	Pd(dba)2	P(t-Bu)3.HBF4	20	iPrCOCl	20	1 eq.	80	Toluene	20	23.4	1.8	26.1	2.1	25.3	0.0	71.6	1.2	1.8
D	8	1.5	Pd(OAc)2	P(t-Bu)3.HBF4	20	Et3SiH	20	1 eq.	80	Toluene	20	23.1	2.2	25.0	1.3	24.5	0.0	73.5	0.0	2.0
F	8	1.5	Pd(OAc)2	PCy_3.HBF4	20	Et3SiH	20	1 eq.	80	Toluene	20	26.3	2.2	26.5	1.0	23.5	0.0	65.1	2.5	9.0
E	8	1.5	Pd(OAc)2	$P(t\text{-}Bu)_2(Me).HBF_4$	20	Et3SiH	20	1 eq.	80	Toluene	20	17.0	1.6	21.3	1.2	20.0	0.7	73.1	0.0	6.2
E	4	1.5	Pd(OAc)2	$P(t\text{-}Bu)_2(Me).HBF_4$	20	none	20	1 eq.	80	Toluene	20	11.4	1.2	17.9	1.6	17.7	21.3	60.2	0.0	0.8
D	9	1.5	Pd(dba)2	P(O-(2,4-t-Bu)-Ph)3	20	iPrCOCl	0	1 eq.	80	Toluene	20	25.9	1.9	27.1	1.5	14.3	0.0	38.3	6.1	41.3
H	5	1.5	Pd(OAc)2	t-Bu-Xphos	20	Et3SiH	0	1 eq.	80	Toluene	20	9.1	0.9	15.5	1.5	13.5	6.9	66.9	0.0	12.6
B	8	1.5	Pd(OAc)2	Xantphos	12	Et3SiH	0	1 eq.	80	Toluene	20	16.9	1.4	20.4	1.3	13.2	24.2	27.5	7.9	27.1
G	10	1.5	Pd(dba)2	X-Phos	20	iPrCOCl	0	1 eq.	80	Toluene	20	6.0	0.6	13.8	1.5	12.2	36.6	39.3	0.0	12.0
C	7	1.5	Pd(OAc)2	Phanephos	12	Et3SiH	0	1 eq.	80	Toluene	20	11.1	0.9	13.4	1.1	10.1	1.3	63.7	3.5	21.4
E	5	1.5	Pd(OAc)2	Ru-phos	20	Et3SiH	0	1 eq.	80	Toluene	20	9.0	0.9	11.9	1.1	9.9	25.1	48.8	6.4	9.8
G	5	1.5	Pd(OAc)2	P(3,5-CF3Ph)3	20	Et3SiH	0	1 eq.	80	Toluene	20	4.5	0.5	12.3	1.2	9.7	69.3	0.1	7.1	13.8
B	4	1.5	Pd(OAc)2	Xantphos	12	none	0	1 eq.	80	Toluene	20	0.0	0.0	10.3	0.9	8.5	59.6	14.2	6.6	11.2
A	10	1.5	Pd(dba)2	P(o-tol)3	20	iPrCOCl	0	1 eq.	80	Toluene	20	8.5	0.6	12.8	0.9	7.7	15.1	37.7	5.6	33.8
E	9	1.5	Pd(dba)2	Ru-phos	20	iPrCOCl	0	1 eq.	80	Toluene	20	3.5	0.3	7.2	0.6	6.7	54.9	32.1	0.0	6.3
D	7	1.5	Pd(OAc)2	Biphephos	12	Et3SiH	0	1 eq.	80	Toluene	20	5.8	0.5	10.9	0.7	5.7	39.5	6.7	12.4	35.8
D	4	1.5	Pd(OAc)2	P(t-Bu)3.HBF4	20	none	20	1 eq.	80	Toluene	20	0.0	0.0	5.4	0.6	5.2	76.4	14.3	1.6	2.5

$$\textbf{Conversion}(\%) = \frac{100 * (\text{Product Area\%} + \text{Isomeric product Area\%})}{(\text{SM Area\%}) + (\text{Product Area\%}) + (\text{Isomeric product Area\%})}$$

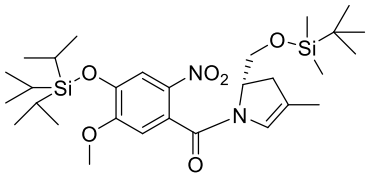
Reaction Products and Impurities



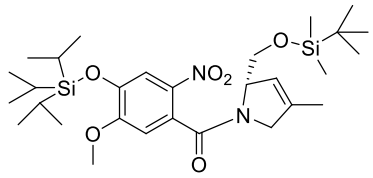
SM - TBS, Rt=1.09mins
Molecular Weight: 464.63



Starting material, Rt=7.9mins
Molecular Weight: 578.89

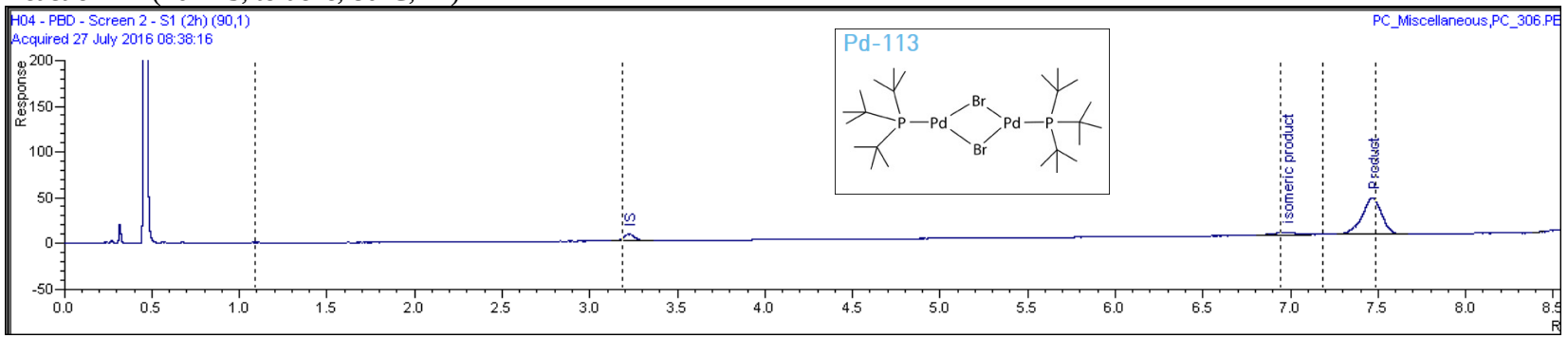


Product, Rt=8.2mins
Molecular Weight: 578.89

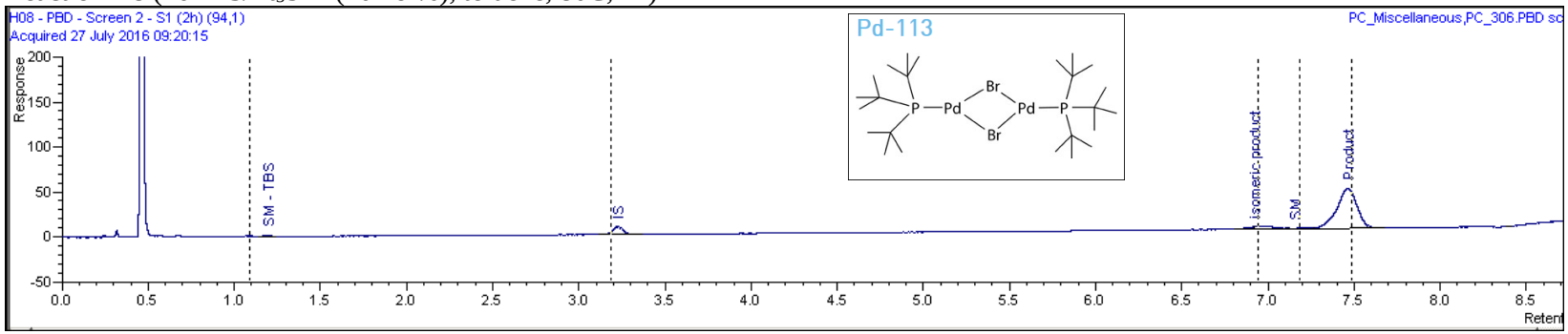


Isomeric product, Rt=7.6mins
Molecular Weight: 578.89

Typical HPLCs (toluene peak at 0.5mins)
Reaction H4 (Pd-113, toluene, 80°C, 2h)



Reaction H8 (Pd-113/Et_3SiH (10mol%), toluene, 80C, 2h)



Conclusions

- No other catalyst other than Pd-113 appears to work well to give clean conversion to product
- The addition of Et_3SiH appears to avoid a Pd-mirror on the reaction vial

Screen 3

Isomerisation screen focussing on understanding the mechanism and potential for scale up utilising P^tBu_3 as a ligand in various different palladium combinations

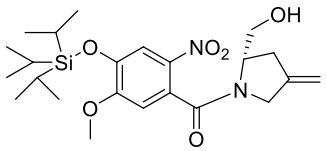
Experimental Set-Up

- On a 100mg scale of alkene, reactions were performed in 4mL vials in a 24-well plate format, situated in an inerted glovebox (<10ppm O_2 and <1ppm H_2O).
- Grubbs II, benzoquinone and product and internal standard (for reaction 14 only) were weighed by hand and the vials then placed into the glovebox environment.
- All other solids were dispensed as solids using a Quantos weighing robot situated inside the glovebox.
- Stir discs were added to each vial.
- Starting material (1.4g) and internal standard (64.4mg) was dissolved in dry degassed toluene (14mL total) and 1mL was dispensed to each vial. (100mg/reaction and 10mol% internal standard)
- Reaction 14 contained product (100mg), internal standard (4.6mg, 10mol%) and 1mL of toluene was added.
- Liquid additives for reactions 5, 6, 10 and 11 were then added.
- The reactions were sealed and heated at the 70°C for 18h for all reactions.
- Samples for UPLC/MS analysis were prepared at 1h and 22h.

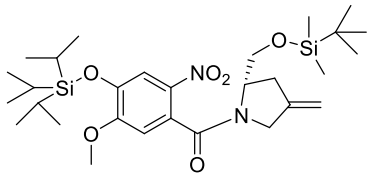
Reaction Plan and Results

														Area% at 220nM at 18h				
Reaction Number	Catalyst	Catalyst (mol%)	Additive	Additive (mol%)	Alkene (SM)	Temp. °C	Solvent (10vols)	Product (Area%) at 0.5h	SM (Area%) at 0.5h	Product isomer (Area%) at 0.5h	Product (Area%) at 2h	SM (Area%) at 2h	Product isomer (Area%) at 2h	Product /IS at 18h	Product (Area%) at 18h	SM (Area%) at 18h	Product isomer (Area%) at 18h	Other peaks
1	Grubbs II	5	n-BuOH	1000uL	1.0eq. SM	70	Toluene	23.3	53.8	20.7	45.3	6.9	47.1	5.5	54.2	0.0	44.1	1.7
2	Pd-113	5	none	none	1.0eq. SM	70	Toluene	89.4	0.0	7.5	92.4	0.0	7.6	12.9	89.1	0.0	6.3	4.5
3	Pd-113	2.5	none	none	1.0eq. SM	70	Toluene	82.5	0.0	16.1	90.3	0.0	8.9	13.0	89.2	0.0	8.2	2.6
4	Pd-113	1.25	none	none	1.0eq. SM	70	Toluene	64.0	0.0	35.8	82.9	0.0	16.8	11.7	82.8	0.0	16.0	1.2
5	Pd-113	2.5	Et3SiH	10	1.0eq. SM	70	Toluene	68.0	0.0	25.4	88.3	0.0	10.7	11.7	87.2	0.0	5.5	7.3
6	Pd-113	2.5	Et3N	20	1.0eq. SM	70	Toluene	21.0	0.0	78.4	20.7	0.0	78.8	2.7	20.6	0.0	78.8	0.6
7	Pd-113	2.5	PPh3	10	1.0eq. SM	70	Toluene	15.0	41.1	43.6	15.7	37.7	46.2	2.3	17.1	32.9	49.7	0.3
8	Pd-113	2.5	Benzoquinone	10	1.0eq. SM	70	Toluene	0.0	98.7	0.2	1.7	97.2	0.3	0.2	1.6	95.9	1.8	0.7
9	Pd-113	2.5	Phenanthroline	5	1.0eq. SM	70	Toluene	0.0	99.4	0.2	0.0	99.5	0.1	0.0	0.0	99.7	0.2	0.2
10	Pd(OAc)2	5	tBu3P/Et3SiH	5, 10	1.0eq. SM	70	Toluene	0.0	98.0	0.1	2.5	92.9	0.2	0.6	4.4	79.9	10.3	5.5
11	Pd(OAc)2	5	tBu3P/Et3SiH	10, 10	1.0eq. SM	70	Toluene	0.0	99.6	0.2	0.0	98.7	0.1	0.0	0.0	98.3	0.2	1.6
12	(tBu3P)2Pd(HCl)	5	none	none	1.0eq. SM	70	Toluene	37.2	0.0	62.0	47.1	0.0	52.5	7.8	59.5	0.0	40.0	0.5
13	(tBu3P)2Pd(HCl)	2.5	none	none	1.0eq. SM	70	Toluene	45.6	0.0	53.6	57.5	0.0	42.1	10.0	75.0	0.0	24.7	0.3
14	Pd-113	5	none	none	1.0eq product	70	Toluene	94.5	0.0	5.5	92.4	0.0	7.6	13.1	90.5	0.0	7.5	2.1

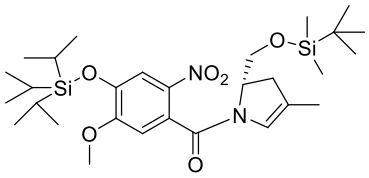
Reaction products and impurities



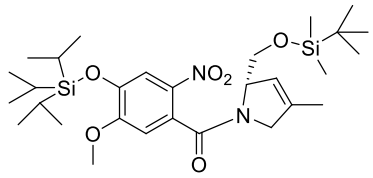
SM - TBS, Rt=1.09mins
Molecular Weight: 464.63



Starting material, Rt=7.9mins
Molecular Weight: 578.89

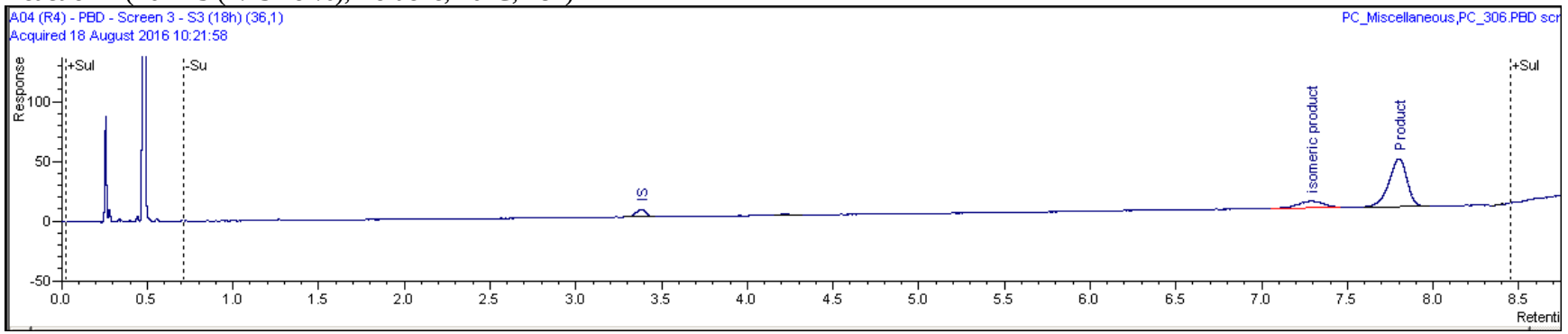


Product, Rt=8.2mins
Molecular Weight: 578.89

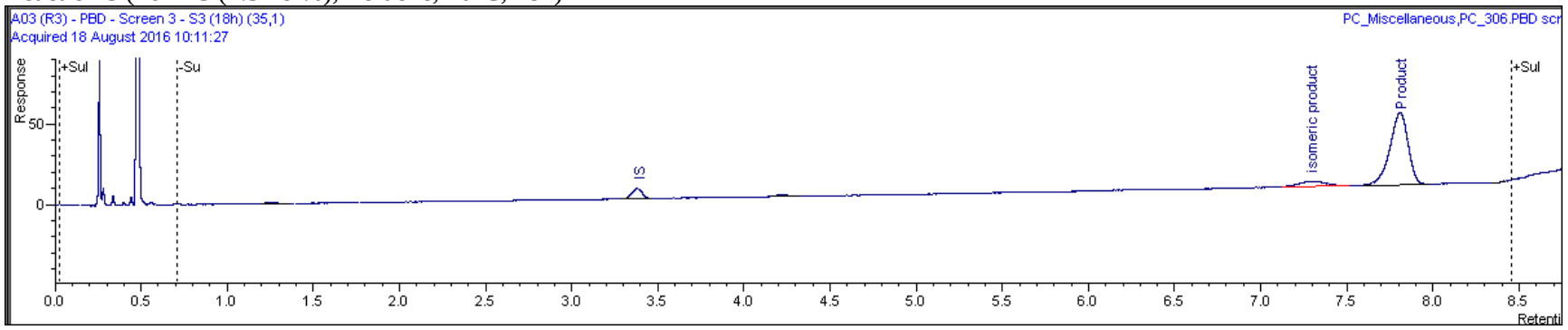


Isomeric product, Rt=7.6mins
Molecular Weight: 578.89

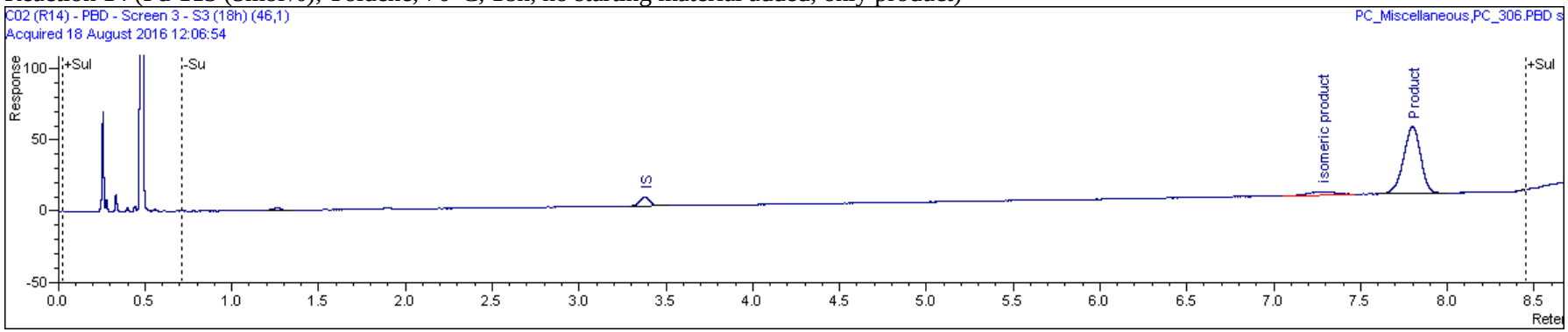
Typical HPLCs (toluene peak at 0.5mins)
Reaction 4 (Pd-113 (1.25mol%), Toluene, 70°C, 18h)



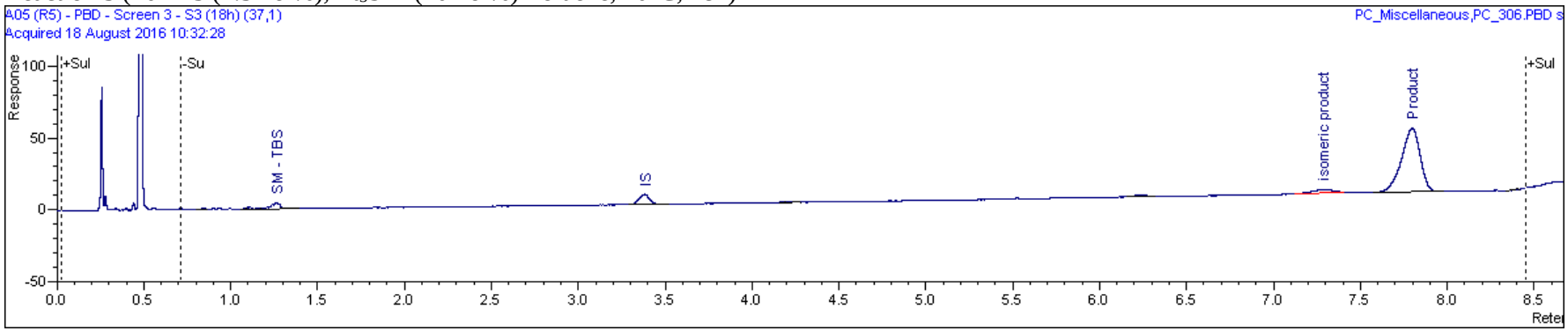
Reaction 3 (Pd-113 (2.5mol%), Toluene, 70°C, 18h)



Reaction 14 (Pd-113 (5mol%), Toluene, 70°C, 18h, no starting material added, only product)



Reaction 5 (Pd-113 (2.5mol%), Et_3SiH (10mol%) Toluene, 70°C, 18h)

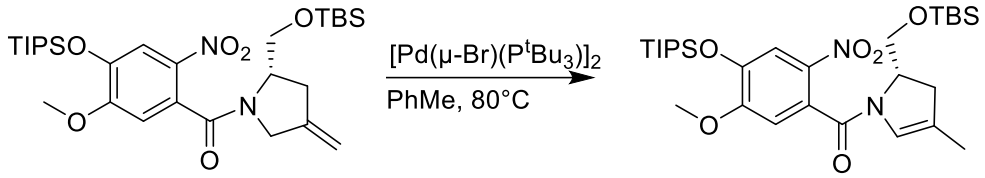


Conclusions

- Alternative methods to generate $tBu_3PPd(HX)$ do not work as well as Pd-113 e.g. reactions 10,11
- Grubbs catalyst derived Ru-H catalysts do not reach full conversion. (Reaction 1)
- Co-ligand addition (Reactions 6-9) prevent mirroring but also stall the reaction.
- Use of isolated palladium complex $(tBu_3P)_2PdHCl$ (see Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.*, **2004**, *126*, 13178-13179 for method of preparation) is less effective than Pd-113.
- The reaction proceeds smoothly with Pd-113 even with loading as low as 1.25mol% to afford 80% product (area%)
- Addition of Et_3SiH (10mol%) appears to avoid Pd-mirroring (Reaction 5)
- If the product is submitted to the reaction conditions (Reaction 14) the reaction again ends up with the equilibrium ratio of products.

Reaction Profiling

*Preparation of (*S*)-(2-amino-5-methoxy-4-((triisopropylsilyl)oxy)phenyl)(2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-methyl-2,3-dihydro-1H-pyrrol-1-yl)methanone (**6**)*



To an inerted solution of (*S*)-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-methylenepyrrolidin-1-yl)(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)phenyl)methanone (**8**, 50mg, 100.0% w/w, 861μmol) in toluene (1mL) was added di-μ-bromobis(tri-tert-butylphosphine)dipalladium(I) (3.34mg, 4.32μmol, 0.05eq). The reaction was heated to 80ºC and sampled regularly.

UPLC Analysis:

Column: Phenomenex Kinetex 2.6u C18 100A 75mm x 3mm
Mobile phase A: 0.03% TFA in water
Mobile phase B: 0.025% TFA in acetonitrile

Gradient:

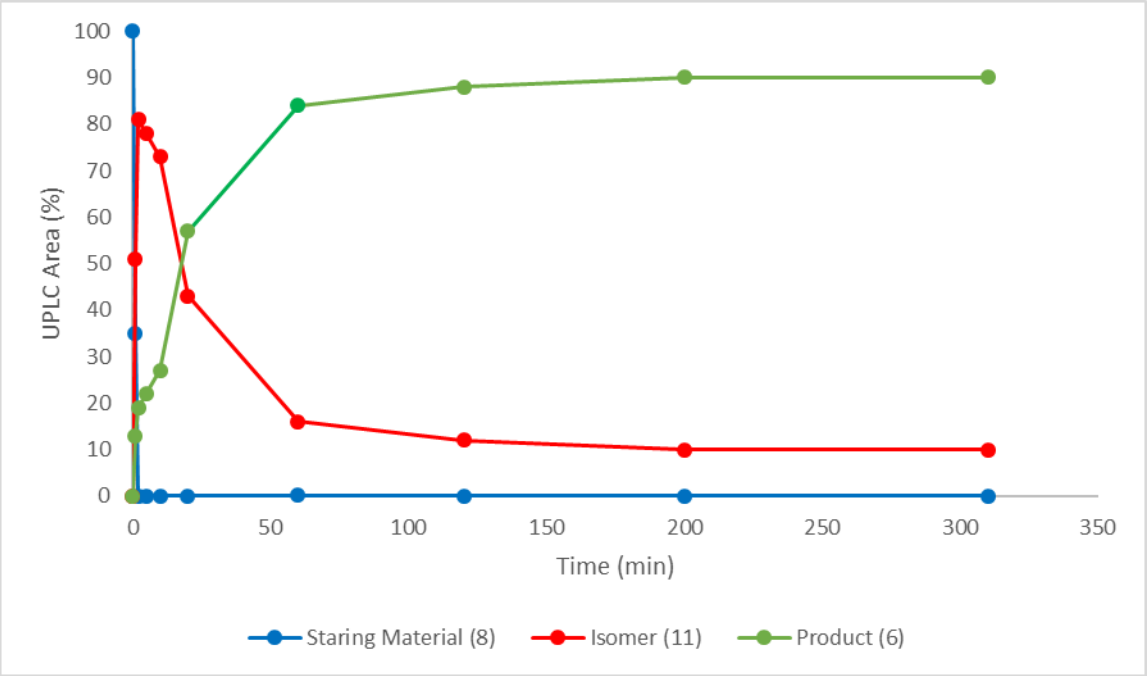
Time	%A	%B
0.00	30	70
8.00	15	85
8.50	5	95

Flow rate: 1.2mL/min
Detection: UV @ 220nm
Temperature: 40°C

Profile Table

Time	Starting Material (**8**)	Isomer (**11**)	Product (**6**)
Minutes	Area %	Area %	Area %
0	100	0	0
1	35	51	13
2	0	81	19
5	0	78	22
10	0	73	27
20	0	43	57
60	0	16	84
120	0	12	88
200	0	10	90
310	0	10	90
1320	0	9	91

Profile Graph

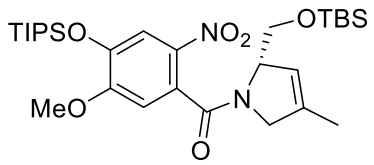


4-Methyl-2,5-dihydropyrrole (11**) and 2-Methylene-4-methylpyrrolidine (**12**) Isomers**

*Isomerisation of (*S*)-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-methylenepyrrolidin-1-yl)(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)phenyl)methanone (**8**)*

To an inerted solution of (*S*)-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-methylenepyrrolidin-1-yl)(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)phenyl)methanone (**8**, 296mg, 100.0% w/w, 0.551mmol) in toluene (3mL) was added di-μ-bromobis(tri-tert-butylphosphine)dipalladium(I) (9.94μg, 12.4μmol, 0.025eq). The reaction was heated to 70ºC and after 2 hours in-process analysis indicated the isomerisation had stalled at 73% isomer and 26% product. The reaction mixture was cooled, filtered and solvent removed in vacuo affording a yellow oil. The mixture was purified using flash column chromatography (25g of silica gel, gradient of 0% to 100% MTBE in heptane) affording:

*(*S*)-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-methyl-2,5-dihydro-1H-pyrrol-1-yl)(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)phenyl)methanone (**11**)*



Pale yellow oil

Major Rotamer (75%):

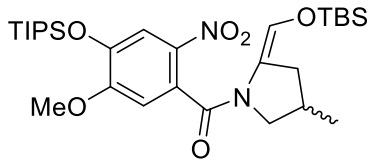
^{1}H NMR (500 MHz, $CDCl_3$) 0.08 (d, J = 6.6 Hz, 6H), 0.90 (s, 9H), 1.11 (dt, J = 7.5, 1.3 Hz, 18H), 1.28 (ddd, J = 14.8, 7.4, 2.6 Hz, 3H), 1.69 (t, J = 1.6 Hz, 3H), 3.64 – 3.83 (m, 2H), 3.90 (s, 3H), 3.92 – 4.09 (m, 2H), 4.96 (s, 1H), 5.54 (s, 1H), 6.77 (s, 1H), 7.70 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) 166.00, 156.10, 145.44, 137.00, 134.45, 127.89, 122.77, 115.77, 109.33, 65.81, 62.47, 58.29, 55.75, 25.53, 17.85, 17.51, 13.79, 12.49, -5.64.

Minor Rotamer (25%):

^{1}H NMR (500 MHz, $CDCl_3$) 0.08 (d, J = 6.6 Hz, 6H), 0.90 (s, 9H), 1.11 (dt, J = 7.5, 1.3 Hz, 18H), 1.28 (ddd, J = 14.8, 7.4, 2.6 Hz, 3H), 1.69 (t, J = 1.6 Hz, 3H), 3.64 – 3.83 (m, 2H), 3.90 (s, 3H), 3.92 – 4.09 (m, 2H), 4.54 (d, J = 15.2 Hz, 1H), 5.38 (s, 1H), 6.82 (s, 1H), 7.71 (s, 1H).

*(*E*)-(2-(((*tert*-butyldimethylsilyl)oxy)methylene)-4-methylpyrrolidin-1-yl)(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)phenyl)methanone (**12**)*



Pale yellow oil

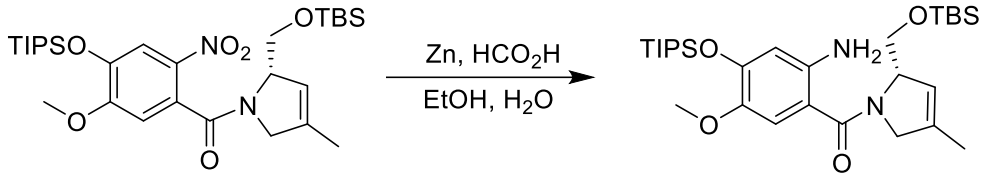
^{1}H NMR (500 MHz, $CDCl_3$) 0.18 (d, J = 0.7 Hz, 6H), 0.96 (s, 9H), 1.00 (d, J = 6.5 Hz, 3H), 1.11 (d, J = 7.4 Hz, 18H), 1.22 – 1.35 (m, 3H), 2.21 – 2.34 (m, 2H), 2.88 – 2.98 (m, 2H), 3.37 (dd, J = 10.0, 6.5 Hz, 1H), 3.91 (s, 3H), 6.76 (s, 1H), 7.70 (s, 1H), 7.83 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) 163.65, 156.12, 145.38, 136.68, 129.99, 128.35, 127.35, 115.66, 109.21,

57.64, 55.81, 34.52, 30.19, 25.44, 17.93, 17.53, 17.50, 12.48, -5.49.

NMR assignment of **11** was complicated by the presence of rotamers, thus reduction of the nitro group was completed to afford the aniline:

*Preparation of (*S*)-(2-amino-5-methoxy-4-((triisopropylsilyl)oxy)phenyl)(2-(((*tert-*butyldimethylsilyl)oxy)methyl)-4-methyl-2,5-dihydro-1H-pyrrol-1-yl)methanone*

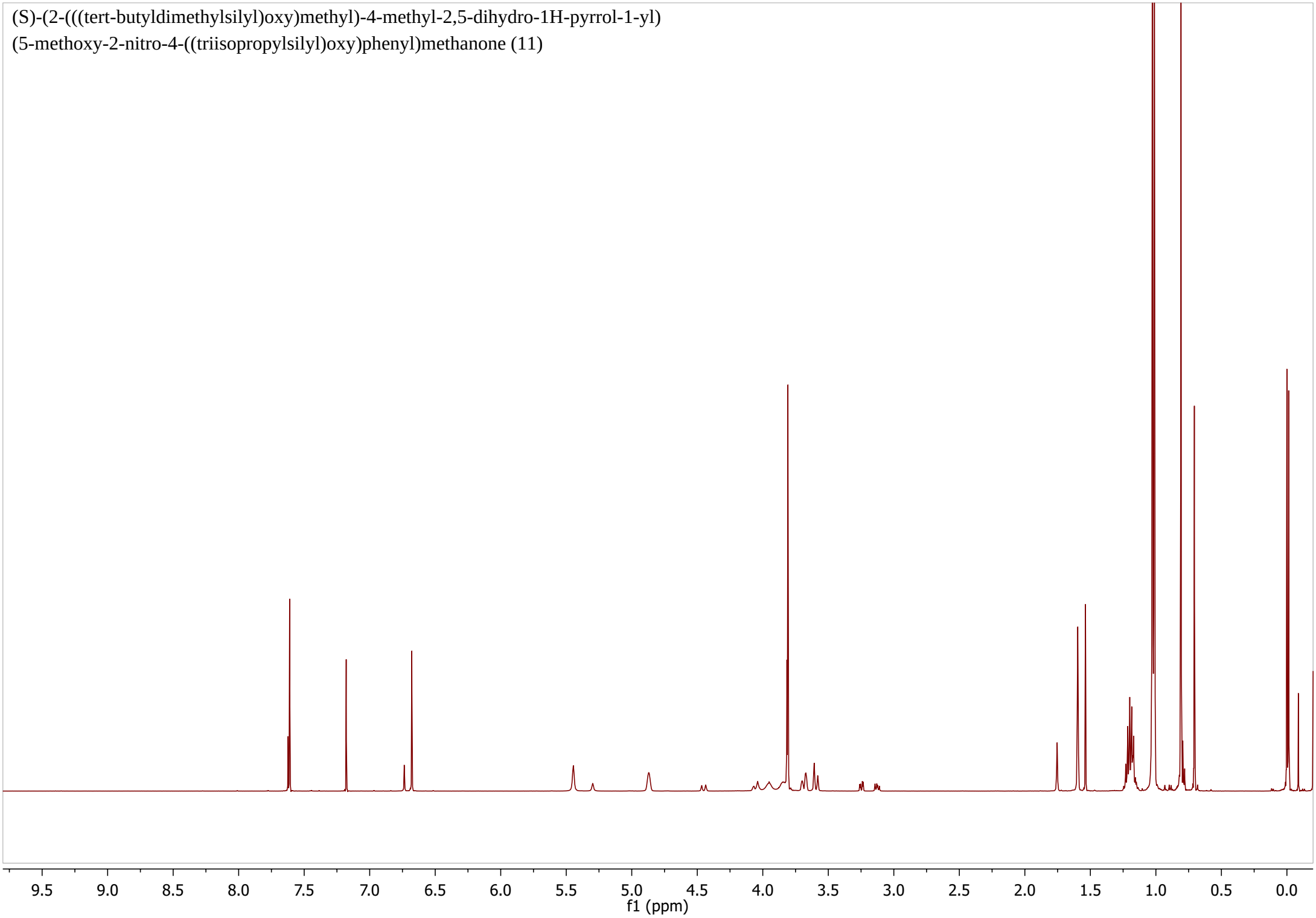


Zinc (170mg, 2.60mmol) was added to a mixture of ethanol (0.32mL), water (0.020mL) and formic acid (0.020mL, 0.53mmol) at ambient temperature and stirred vigorously. To this mixture, a solution (*S*)-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-methyl-2,5-dihydro-1H-pyrrol-1-yl)(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)phenyl)methanone (**11**, 20 mg, 0.0345mmol) in ethanol (0.080mL) was added dropwise with a pipette. The reaction was stirred for 30 min at room temperature at which time in-process analysis indicated the reaction was complete. The mixture was diluted with ethyl acetate (3mL), the solids removed by filtration through a plug of cotton wool and the filtrate was washed with saturated sodium bicarbonate solution (5mL). The volatiles were removed by evaporation to give the product (17 mg, 0.0310mmol, 90%) as a colourless gummy solid.

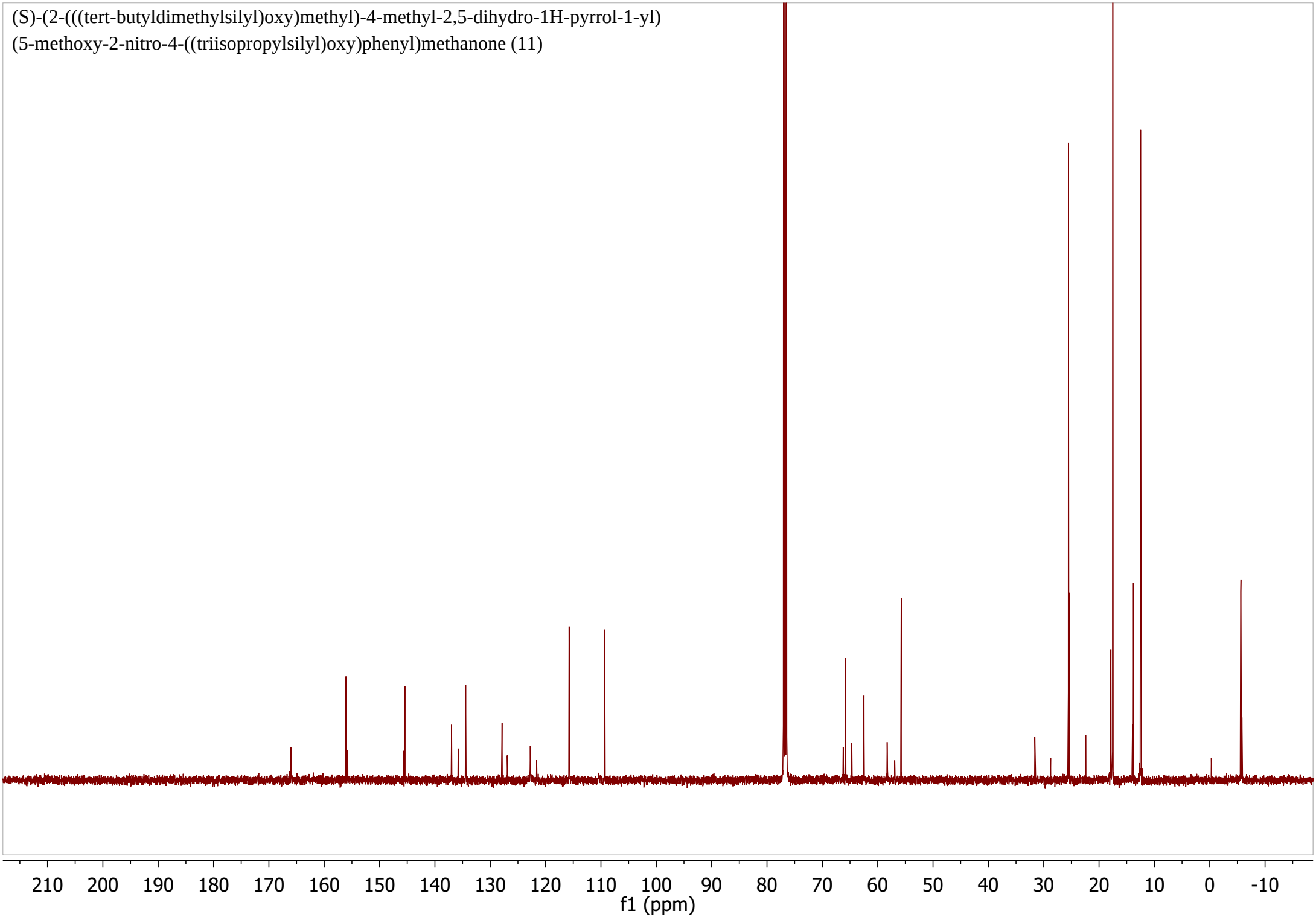
^{1}H NMR (500 MHz, $CDCl_3$) -0.04 – 0.1 (m, 6H), 0.87 (s, 9H), 1.07 – 1.12 (m, 18H), 1.19 – 1.31 (m, 3H), 1.73 (s, 3H), 3.71 (s, 3H), 3.78 (s, 1H), 3.81 – 4.05 (m, 2H), 4.23 – 4.32 (m, 2H), 5.37 – 5.45 (m, 1H), 6.26 (s, 1H), 6.77 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) 169.25, 148.10, 142.74, 140.19, 135.46, 121.85, 113.05, 112.83, 108.94, 65.55, 62.82, 59.46, 56.28, 25.50, 17.86, 17.63, 13.83, 12.60, -5.69.

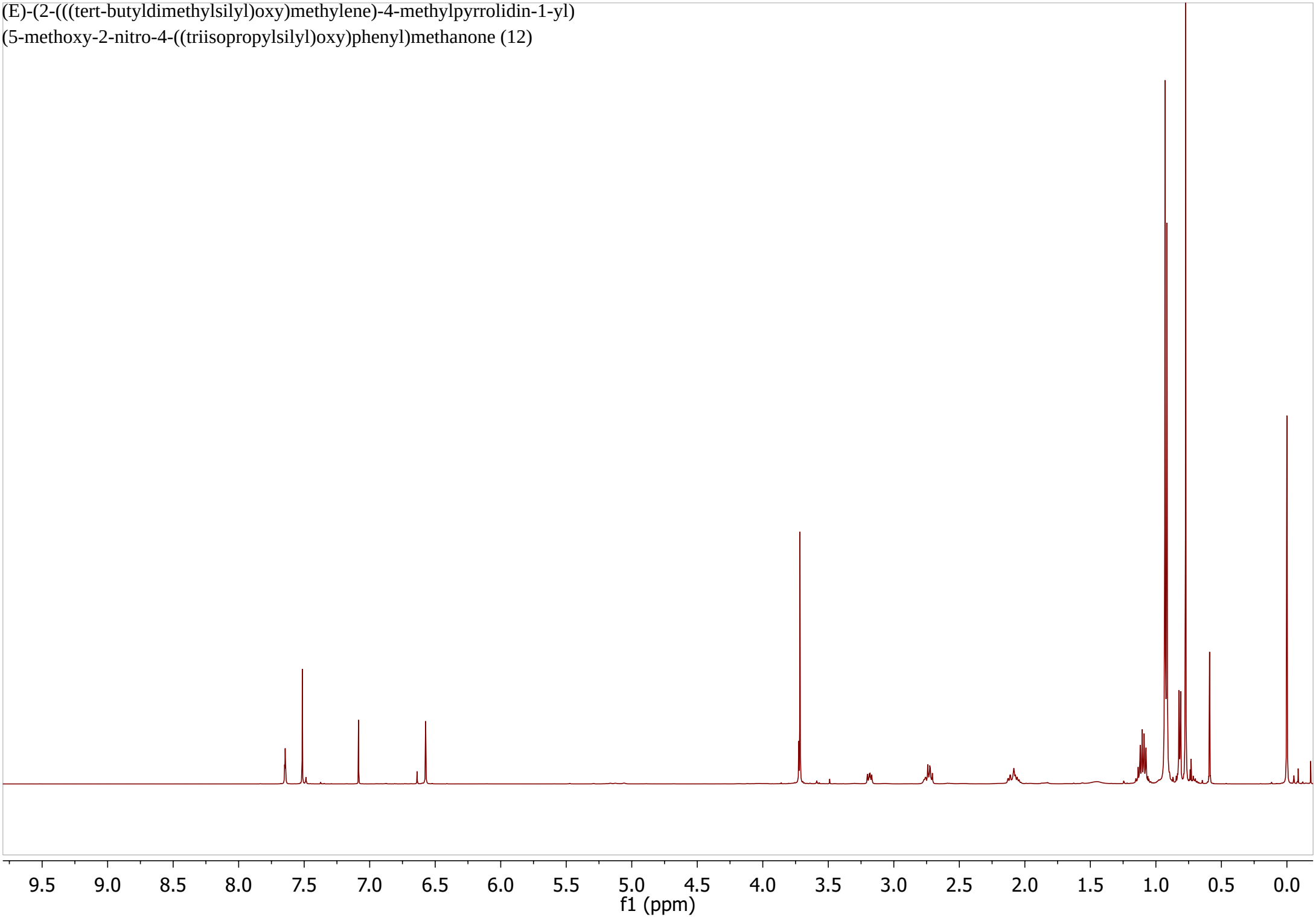
(S)-(2-(((tert-butyldimethylsilyl)oxy)methyl)-4-methyl-2,5-dihydro-1H-pyrrol-1-yl)
(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)phenyl)methanone (11)



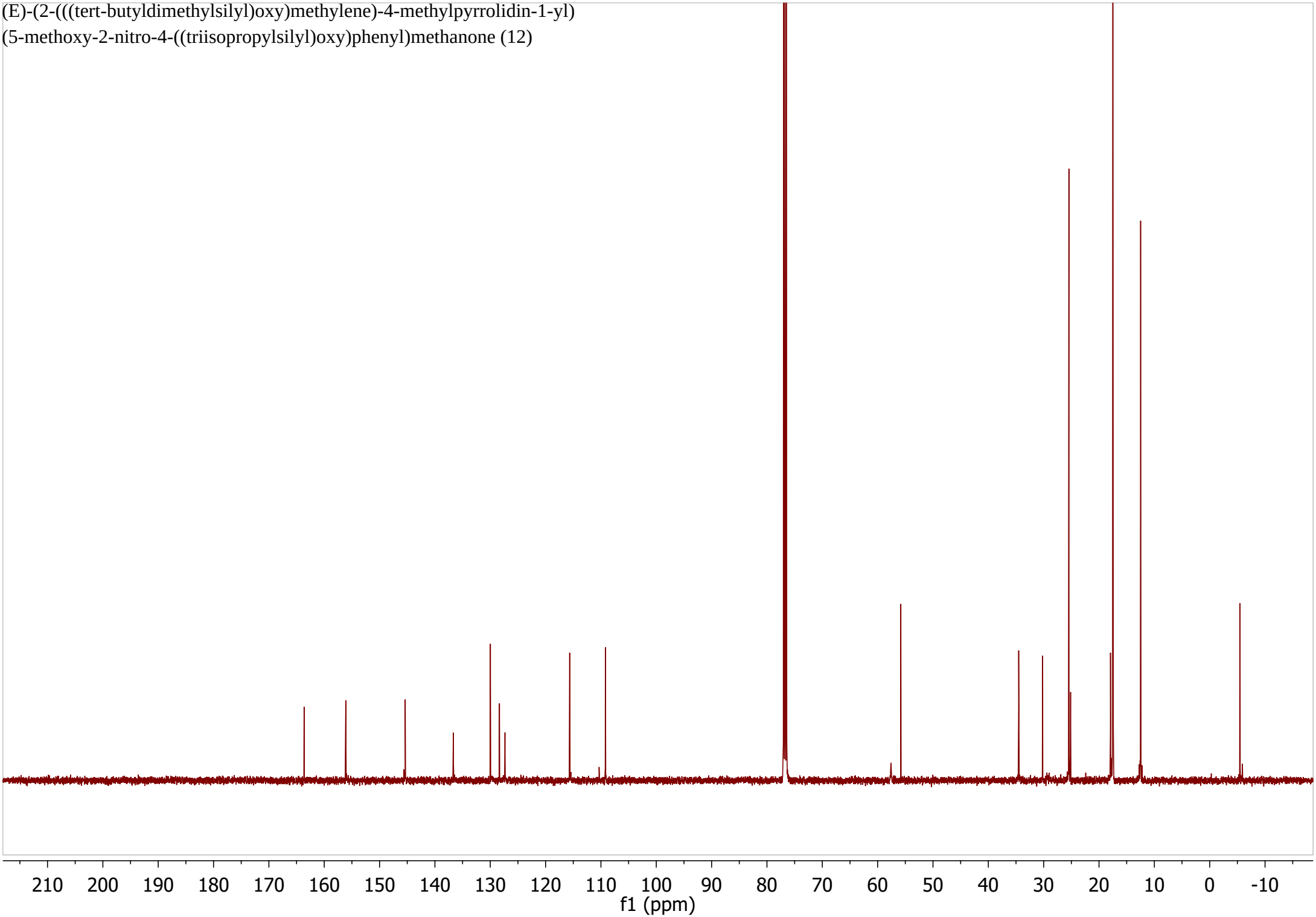
(S)-(2-(((tert-butyldimethylsilyl)oxy)methyl)-4-methyl-2,5-dihydro-1H-pyrrol-1-yl)
(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)phenyl)methanone (11)



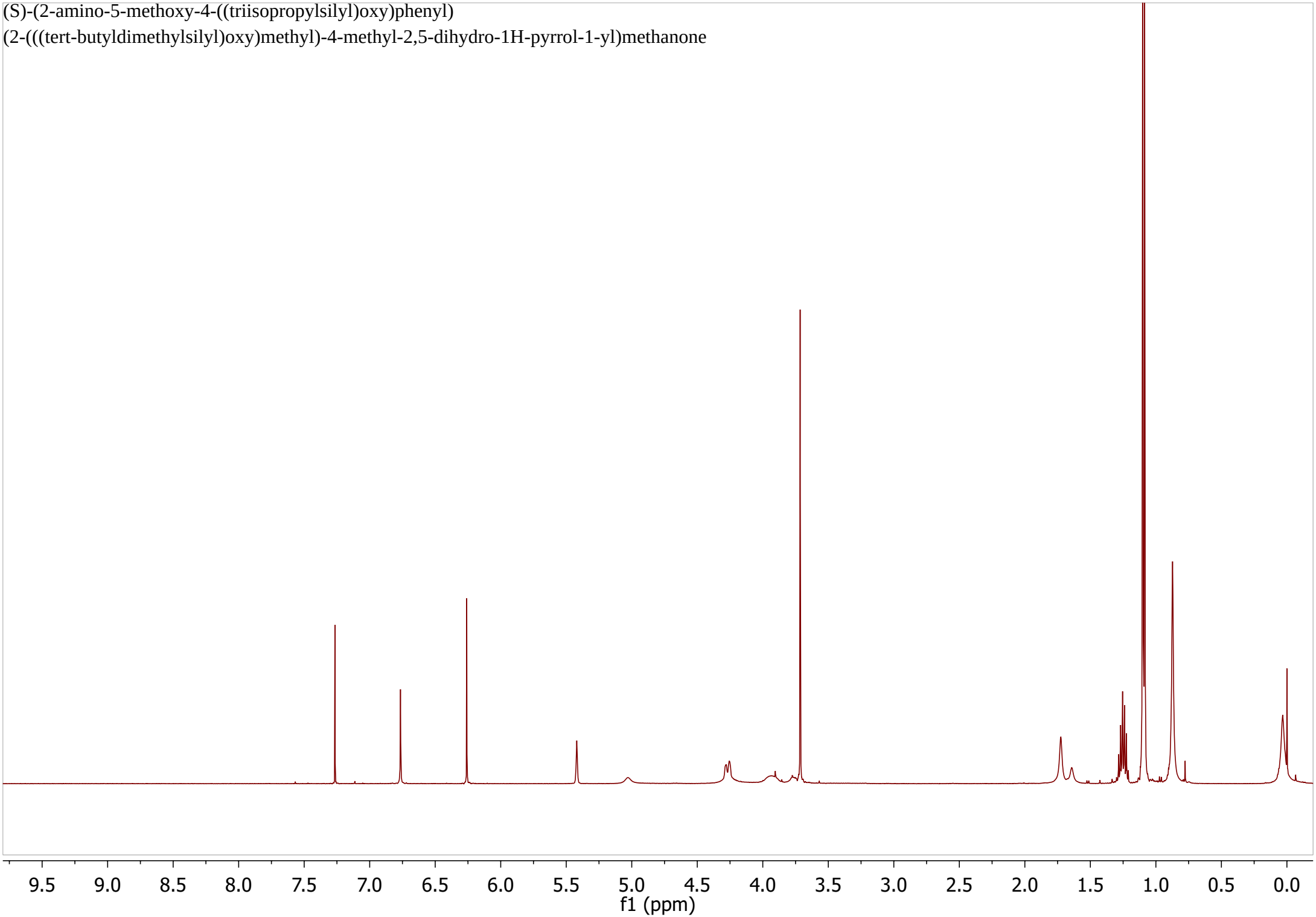
(E)-(2-(((tert-butyldimethylsilyl)oxy)methylene)-4-methylpyrrolidin-1-yl)
(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)phenyl)methanone (12)



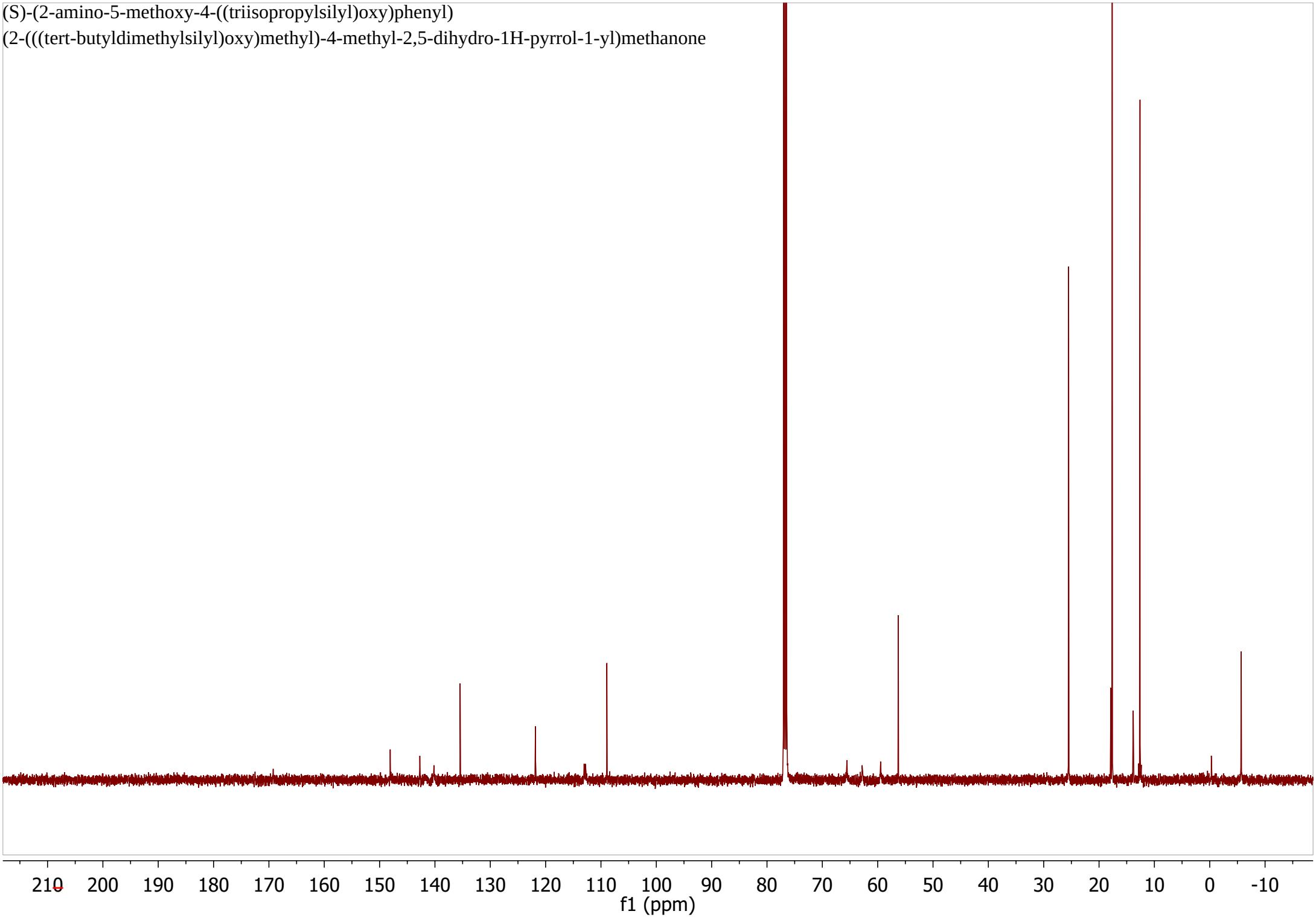
(E)-(2-(((tert-butyldimethylsilyl)oxy)methylene)-4-methylpyrrolidin-1-yl)
(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)phenyl)methanone (12)



(S)-(2-amino-5-methoxy-4-((triisopropylsilyl)oxy)phenyl)
(2-(((tert-butyldimethylsilyl)oxy)methyl)-4-methyl-2,5-dihydro-1H-pyrrol-1-yl)methanone



(S)-(2-amino-5-methoxy-4-((triisopropylsilyl)oxy)phenyl)
(2-(((tert-butyldimethylsilyl)oxy)methyl)-4-methyl-2,5-dihydro-1H-pyrrol-1-yl)methanone



Computational Estimates for the Thermodynamics of the Isomerisation Reactions

The thermodynamics of double bond migration were studied with quantum chemistry.

All calculations were carried out with the Gaussian 16 (Rev C.01) software. All optimized structures were confirmed as being local minima from the absence of negative vibrational frequencies.

The work used computational approaches reported by Yu and Karton in their comprehensive computational study of the thermodynamics of conjugated to non-conjugate double bond isomerisation reactions.[1] Three levels of theory were used for the study:

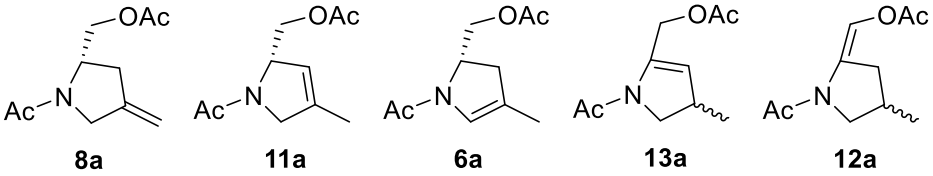
1. Accurate composite method CBS-QB3
2. B3LYP-D3BJ/cc-pVTZ
3. B3LYP-D3BJ/cc-pVTZ//M06-2X-D3/aug-cc-pVTZ

Calculations at the M06-2X-D3/aug-cc-pVTZ level have also ranked very well also in another comprehensive evaluation of computational benchmarks by Goerigk and Grimme.[2]

Double bond migration in compounds **6**, **8**, **11**, **12** and **13** was studied using two model systems:

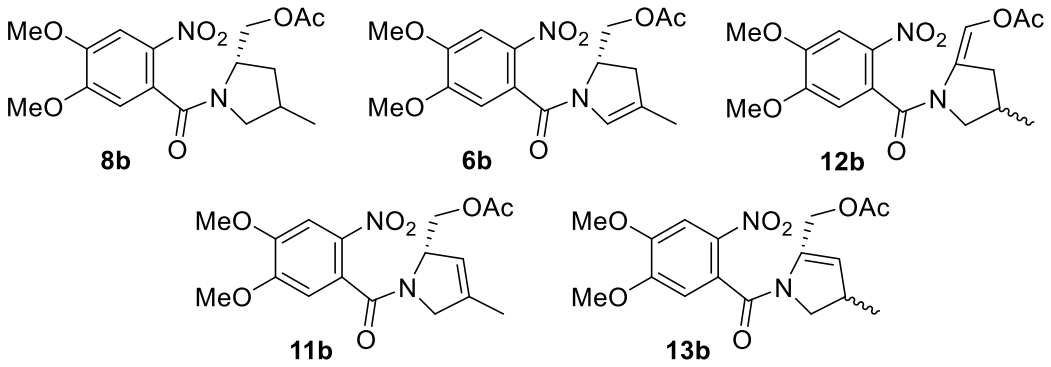
Model 1

A pared-down set of models, containing a minimal set of structural features (**6a**, **8a**, **11a**, **12a** and **13a**), were studied at levels 1, 2 and 3.



Model 2

A realistic set of models, containing all major structural features of the original compounds, but with different protecting groups (**6b**, **8b**, **11b**, **12b** and **13b**), were studied at levels 2 and 3.



For all structures a preliminary conformation search was carried out the OPLS3 forcefield implemented in Schrodinger's Macromodel (Release 2019-2) and up to ten conformers of each structure taken into the quantum chemical studies. The relative enthalpies and free energies reported below refer to the most stable conformation found for each structure.

		Relative enthalpies (kJ/mol) of models for structures			Relative free energies (kJ/mol) of models for structures		
		CBS-QB3	B3LYP-D3BJ/cc-pVTZ	B3LYP-D3BJ/cc-pVTZ//M06-2X-D3/aug-cc-pVTZ	CBS-QB3	B3LYP-D3BJ/cc-pVTZ	B3LYP-D3BJ/cc-pVTZ//M06-2X-D3/aug-cc-pVTZ
Model 1	**8a**	0	0	0	0	0	0
	11a	-17.3	-16.5	-15.6	-20.5	-19.7	-18.8
	6a	-22.7	-22.8	-22.2	-22.8	-24.7	-22.7
	13a	1.2	-0.4	1.5	-3.0	-6.3	-4.2
	12a	0.2	-5.0	-0.8	-1.3	-8.6	-4.4
Model 2	**8b**	0	0	0	0	0	0
	11b	N/A	-16.7	-16.5	N/A	-19.2	-17.2
	6b	N/A	-22.7	-20.7	N/A	-27.3	-23.6
	13b	N/A	8.4	N/A	N/A	9.9	1.5
	12b	N/A	-1.5	2.2	N/A	-5.9	-2.3

Comparison of the numerical results between models and levels of theory reveals that the thermodynamics of double bond migration are consistent across models and levels of theory, lending credibility to the statement that **6** is the thermodynamic sink for the double bond migration. Values in the shaded boxes are reported in Scheme 2 of the paper.

References

1. Yu, L-J.; Karton, A. Assessment of theoretical procedures for a diverse set of isomerization reactions involving double-bond migration in conjugated dienes *Chem. Phys.* **2014**, *441*, 166–177.
2. Goerigk, L.; Grimme, S. A thorough benchmark of density functional methods for general main group thermochemistry, kinetics, and noncovalent interactions *Phys. Chem. Chem. Phys.* **2011**, *13*, 6670-6688.

Chiral Analysis of 4-Methyl-2,3-dihydropyrrole (6**)**

To demonstrate that the chiral centre was not racemised during the isomerisation, single enantiomers of (*S*)-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-methylenepyrrolidin-1-yl)(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)phenyl)methanone (**6**) and (*R*)-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-methylenepyrrolidin-1-yl)(5-methoxy-2-nitro-4-((triisopropylsilyl)oxy)phenyl)methanone were prepared using previously described methodology.

These were used to identify a chiral SFC method for separation of the enantiomers.

SFC Analysis:

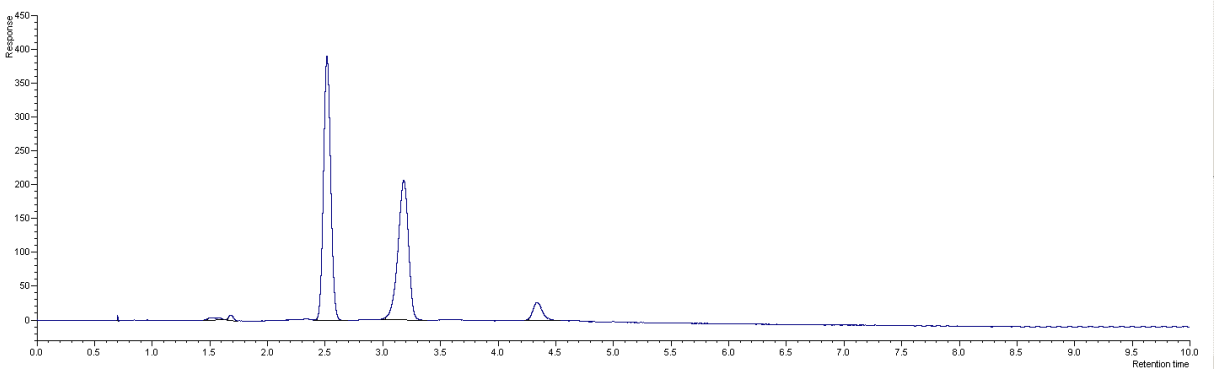
Column: Lux Cellulose 2 3µm (150mm x 4.6mm)
Mobile phase A: CO_2
Mobile phase B: EtOH/MeOH/isopropylamine 50/50/0.1 v/v

Gradient:

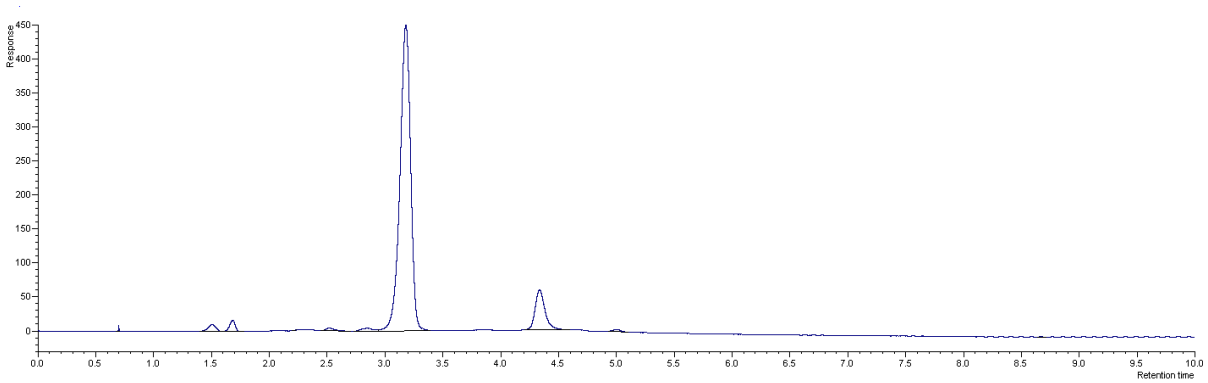
Time	%A	%B
0.00	95	5
8.00	50	50
10.00	50	50

Flow rate: 2.5mL/min
Detection: UV @ 254nm
Temperature: 35°C
BPR: 150bar

Pseudoracemate

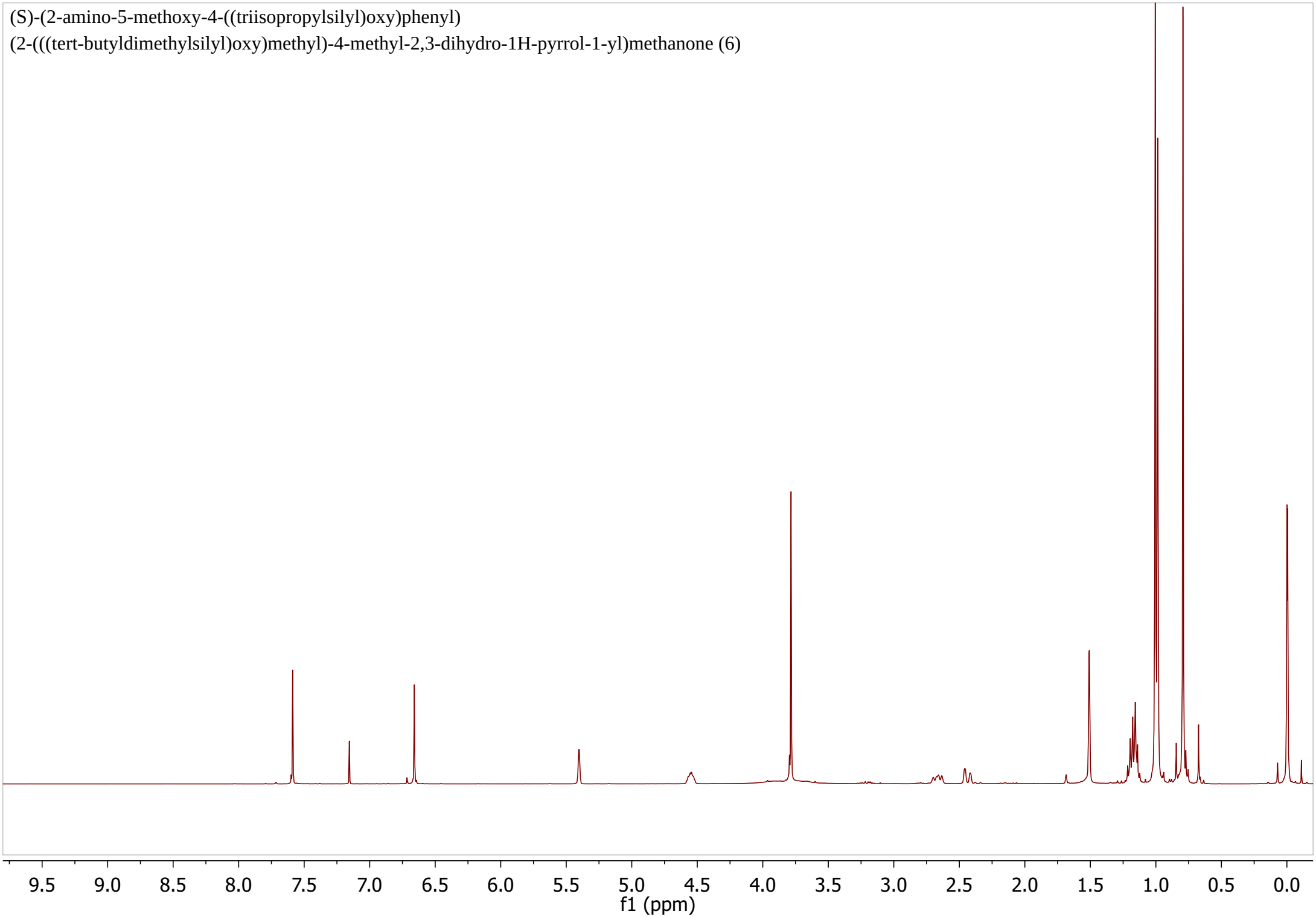


Sample of (*S*)-(2-amino-5-methoxy-4-((triisopropylsilyl)oxy)phenyl)(2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-methyl-2,3-dihydro-1H-pyrrol-1-yl)methanone (**6**) prepared using isomerisation



(*S*)-Isomer: 99.6%
(*R*)-Isomer: 0.4%

(S)-(2-amino-5-methoxy-4-((triisopropylsilyl)oxy)phenyl)
(2-(((tert-butyldimethylsilyl)oxy)methyl)-4-methyl-2,3-dihydro-1H-pyrrol-1-yl)methanone (6)



(S)-(2-amino-5-methoxy-4-((triisopropylsilyl)oxy)phenyl)
(2-(((tert-butyldimethylsilyl)oxy)methyl)-4-methyl-2,3-dihydro-1H-pyrrol-1-yl)methanone (6)