Supplementary Material (ESI) for Green Chemistry

Highly recyclable, imidazolium derived ionic liquids of low antimicrobial and antifungal toxicity: A new strategy for acid catalysis

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1.0 General

Proton Nuclear Magnetic Resonance spectra were recorded on a 400 MHz spectrometer in $CDCl_3$ referenced relative to residual $CHCl_3$ (δ = 7.26 ppm) unless otherwise stated. Chemical shifts are reported in ppm and coupling constants in Hertz. Carbon NMR spectra were recorded on the same instrument (100 MHz) with total proton decoupling. All melting points are uncorrected. Infrared spectra were obtained on a Perkin Elmer spectrophotometer. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated $60F_{254}$ slides, and visualised by UV irradiation, $KMnO_4$ or anisaldehdye staining. All aldehydes were sourced commercially and either distilled under vacuum (if liquid) or dissolved in CH_2Cl_2 and washed with NaOH(if solid) prior to use. Methanol and THF were distilled over sodium and stored under argon-best results were obtained using freshly distilled methanol. All reactions were carried out under protective argon atmospheres. Careful drying of all catalysts/ionic liquids is essential for best results - a convenient procedure for this follows: the catalysts/ionic liquids were dissolved in dry toluene under argon. The solvent was removed in vacuo and the procedure was repeated twice, taking care that the compound was not exposed to air. The catalysts/ionic liquids were then dried under high vacuum for 2 h and used in the reaction.

2.0 Toxicology

Antifungal activity

In vitro antifungal activities of the compounds were evaluated on a panel of four ATCC strains (*Candida albicans* ATCC 44859, *Candida albicans* ATCC 90028, *Candida parapsilosis* ATCC 22019, *Candida krusei* ATCC 6258) and eight clinical isolates of yeasts (*Candida krusei* E28, *Candida tropicalis* 156, *Candida glabrata* 20/I, *Candida lusitaniae* 2446/I, *Trichosporon beigelii* 1188) and filamentous fungi (*Aspergillus fumigatus* 231, *Absidia corymbifera* 272, *Trichophyton mentagrophytes* 445) from the collection of fungal strains deposited at the Department of Biological and Medical Sciences, Faculty of Pharmacy, Charles University, Hradec Králové, Czech Republic. Three of the above ATCC strains (*Candida albicans* ATCC 90028, *Candida parapsilosis* ATCC 22019, *Candida krusei* ATCC 6258) also served as the quality control strains. All the isolates were maintained on Sabouraud dextrose agar prior to being tested.

Minimum inhibitory concentrations (MICs) were determined by the microdilution format of the NCCLS M27-A guidelines.[12] Dimethyl sulfoxide (100 %) served as a diluent for all compounds; the final concentration did not exceed 2 %. RPMI 1640 (Sevapharma, Prague) medium supplemented with L-glutamine and buffered with 0.165 M morpholinepropanesulfonic acid (Serva) to pH 7.0 by 10 N NaOH was used as the test medium. The wells of the microdilution tray contained 100 µl of the RPMI 1640 medium with 2-fold serial dilutions of the compounds (2000 or 1000 to 0.48 µmol/l) and 100 µl of inoculum suspension. Fungal inoculum in RPMI 1640 was prepared to give a final concentration of $5 \times 10^3 \pm 0.2$ cfu.ml^{-1}. The trays were incubated at 35°C and MICs were read visually for filamentous fungi and photometrically for yeasts as an absorbance at 540 nm after 24 h and 48 h. The MIC values for the dermatophytic strain (*T. mentagrophytes*) were determined after 72 h and 120 h. The MICs were defined as 80 % inhibition of the growth of control. MICs were determined twice and in duplicate. The deviations from the usually obtained values were no higher than the nearest concentration value up and down the dilution scale.

Antibacterial activity

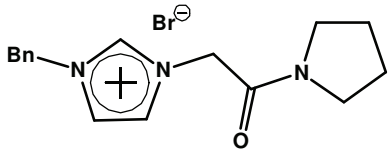
In vitro antibacterial activities[13] of the compounds were evaluated on a panel of three ATCC strains (*Staphylococcus aureus* ATCC 6538, *Escherichia coli* ATCC 8739, *Pseudomonas aeruginosa* ATCC 9027) and five clinical isolates (*Staphylococcus aureus* MRSA HK5996/08, *Staphylococcus epidermidis* HK6966/08, *Enterococcus* sp. HK14365/08, *Klebsiella pneumoniae* HK11750/08, *Klebsiella pneumoniae* ESBL HK14368/08) from the collection of fungal strains deposited at the Department of Biological and Medical Sciences, Faculty of Pharmacy, Charles University, Hradec Králové, Czech Republic. The above-mentioned ATCC strains also served as the quality control strains. All the isolates were maintained on Mueller-Hinton dextrose agar prior to being tested.

Dimethyl sulfoxide (100 %) served as a diluent for all compounds; the final concentration did not exceed 2 %. Mueller-Hinton agar (MH, HiMedia, Čadersky-Envitek, Czech Republic) buffered to pH 7.4 (±0.2) was used as the test medium. The wells of the microdilution tray contained 200 µl of the Mueller-Hinton medium with 2-fold serial dilutions of the compounds (2000 or 1000 to 0.48 µmol/l) and 10 µl of inoculum suspension. Inoculum in MH medium was prepared to give a final concentration of 0.5 McFarland scale (1.5×10^8 cfu.ml^{-1}). The trays were incubated at 36°C and MICs were read visually after 24 h and 48 h. The MICs were defined as 80 % inhibition of the growth of control. MICs were determined twice and in duplicate. The deviations from the usually obtained values were no higher than the nearest concentration value up and down the dilution scale.

3.0 Synthesis of IL catalysts:

3-Methyl-1-(methoxycarbonylmethyl)imidazolium bromide (**11**), 3-methyl-1-(methoxycarbonylmethyl)imidazolium NTf_2 (**13**), 3-methyl-1-(pyrrolidinecarbonylmethyl)imidazolium bromide (**15**) and 2,3-dimethyl-1-(pyrrolidinecarbonylmethyl)imidazolium bromide (**19**) were prepared according to literature methods.[11] All ILs synthesized have been analysed on NMR, LC-MS, and Karl Fischer (showing values range between 0.5 to 4.4 wt% water) for purity. ILs **10**, **12**, **13**, **14**, **16**, **18**, and **20** gave a negative result for bromide in the silver test.

Preparation of 3-Benzyl-1-(pyrrolidinecarbonylmethyl)imidazolium bromide (17):



To a stirred solution of pyrrolidine bromoacetate (2.00 g, 10.41 mmol) in diethyl ether (100 mL) at 0 ºC under Nitrogen atmosphere was added dropwise 1-benzylimidazole (1.65 g, 10.41 mmol). The reaction mixture was stirred vigorously at 0 ºC for 1 h, then at RT overnight. The upper diethyl ether phase was decanted and the IL washed with diethyl ether (5 x 50 mL), then residual solvent was removed on the rotary evaporator. The product was dried *in vacuo* for 1 day to give a white solid at RT in 76 % yield (2.78 g, 7.94 mmol).

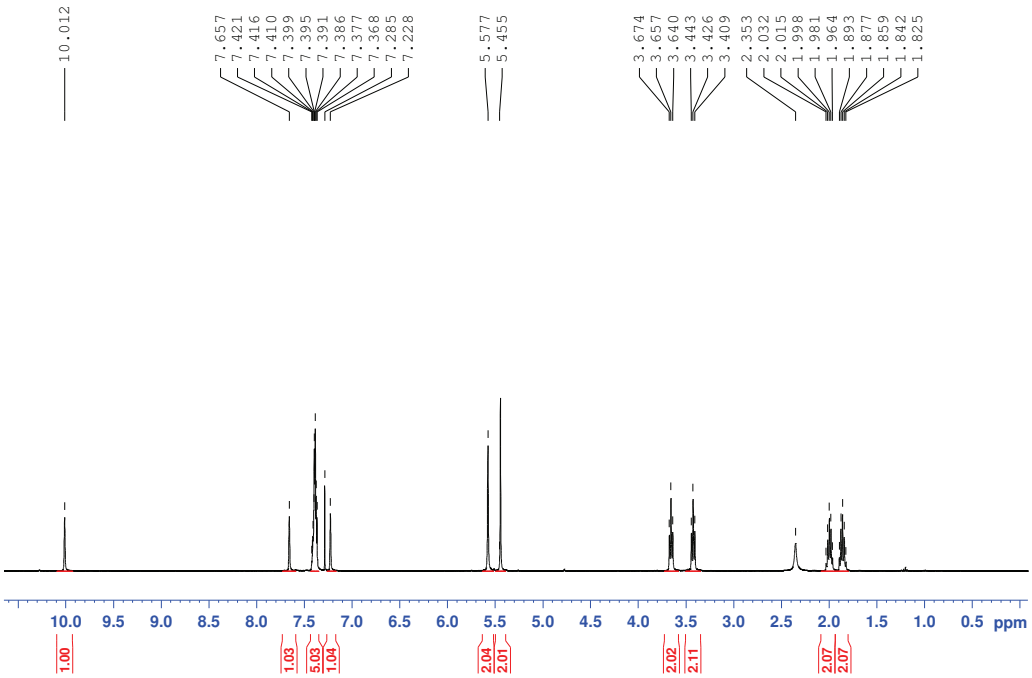
^{1}H NMR (400 MHz, $CDCl_3$): 10.01 (s, 1H), 7.65 (s, 1H), 7.42-7.36 (m, 5H), 7.22 (s, 1H) 5.57 (s, 2H), 5.45 (s, 2H) 3.65 (t, 2H, J 6.8), 3.42 (t, 2H, J 6.8), 2.03-1.96 (m, 2H), 1.89-1.82 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): 162.61, 137.69, 132.61, 129.57, 129.52, 128.84, 124.61, 120.69, 53.52, 51.21, 46.53, 46.20, 25.97, 24.03.

Melting point: 150-152 ºC.

ES-MS (+ve): m/z 270.1602

Karl Fischer Analysis: 4.12 wt% water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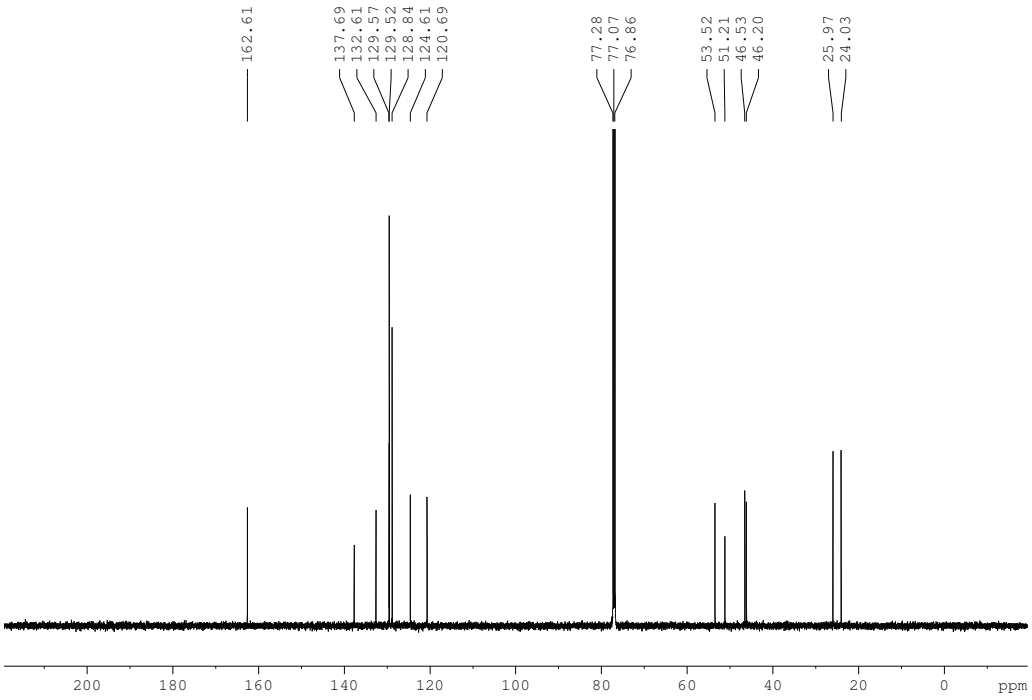
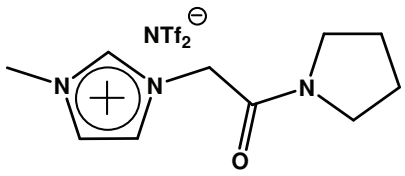
7.416
7.410
7.399
7.395
7.391
7.386
7.377
7.368
7.285
7.228
5.577
5.455
3.674
3.657
3.640
3.443
3.426
3.409
2.353
2.032
2.015
1.998
1.981
1.964
1.893
1.877
1.859
1.842
1.825
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.03
5.03
1.04
2.04
2.01
2.02
2.11
2.07
2.07


162.61
137.69
132.61
129.57
129.52
128.84
124.61
120.69
77.28
77.07
76.86
53.52
51.21
46.53
46.20
25.97
24.03
200 180 160 140 120 100 80 60 40 20 0 ppm

Preparation of 3-methyl-1-(pyrrolidinecarbonylmethyl)imidazolium NTf_2 (16):



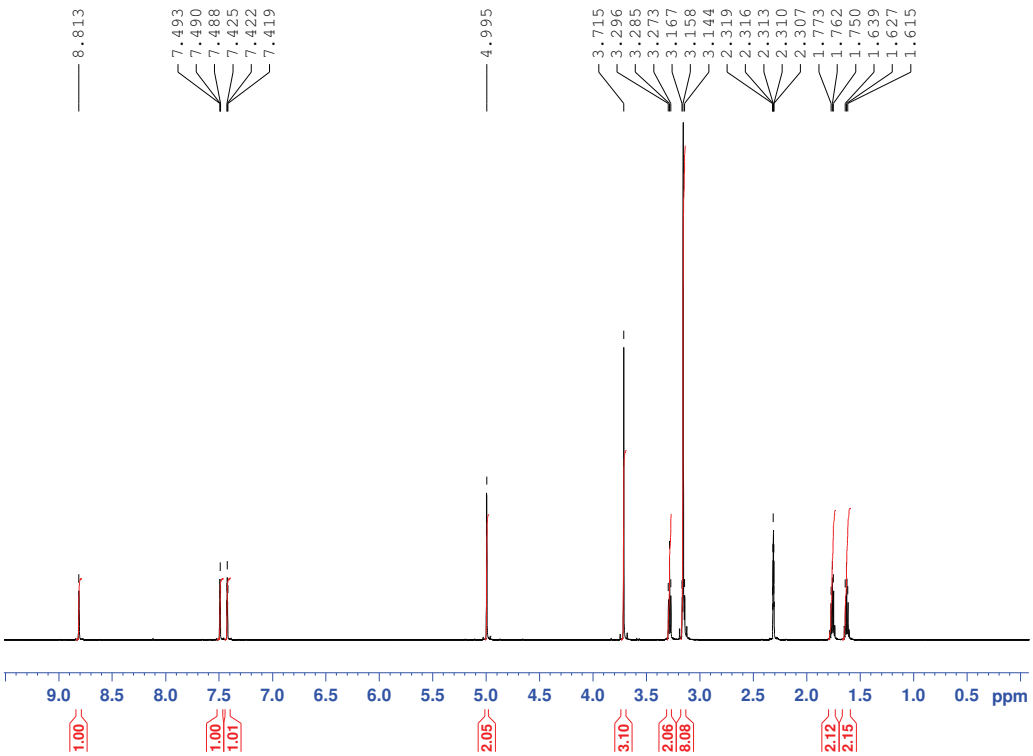
A flask was charged with 3-methyl-1-(pyrrolidinecarbonylmethyl)imidazolium bromide (11.00 g, 40.14 mmol) and distilled water (40 mL). $LiNTf_2$ (11.52 g, 40.14 mmol) in distilled water (40 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The top aqueous layer was removed, the IL washed with water (3 x 40 mL) then the solvent removed on the rotary evaporator. The product was dried *in vacuo* for 72 h to give a colourless liquid at RT in 69 % yield (13.15 g, 27.72 mmol).

^{1}H NMR (600 MHz, DMSO-d6): 8.82 (s, 1H), 7.49 (t, J 1.6, 1H), 7.42 (t,1H, J 1.6), 4.99 (s, 2H), 3.74 (s, 3H), 3.28 (t, 2H, J 6.8), 3.16 (t, 2H, J 6.8), 1.77-1.75 (m, 2H), 1.63-1.61 (m, 2H).

^{13}C NMR (150 MHz, DMSO-d6): 163.01, 137.70, 123.85, 122.90, 119.47 (q), 50.36, 45.93, 45.04, 35.80, 25.47, 23.66.

ES-MS (+ve): m/z 194.1297

Karl Fischer Analysis: 1.63 wt% water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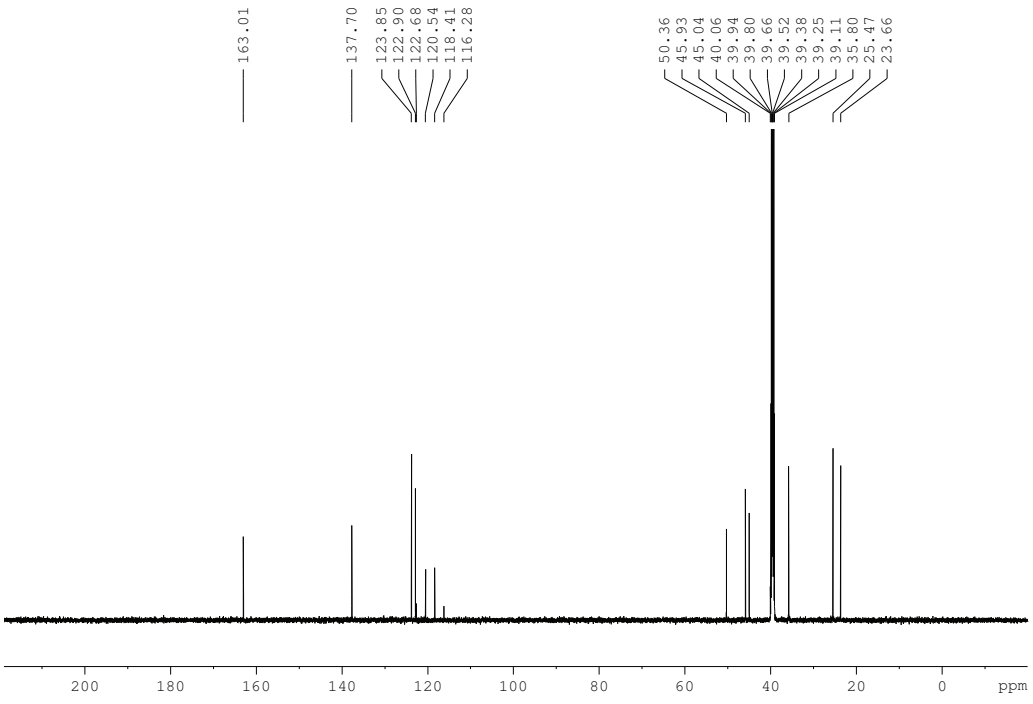
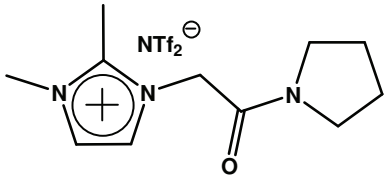
7.490
7.488
7.425
7.422
7.419
4.995
3.715
3.296
3.285
3.273
3.167
3.158
3.144
2.319
2.316
2.313
2.310
2.307
1.773
1.762
1.750
1.639
1.627
1.615
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.00
1.01
2.05
3.10
2.06
8.08
2.12
2.15


163.01
137.70
123.85
122.90
122.68
120.54
118.41
116.28
50.36
45.93
45.04
40.06
39.94
39.80
39.66
39.52
39.38
39.25
39.11
35.80
25.47
23.66
200 180 160 140 120 100 80 60 40 20 0 ppm

Preparation of 2,3-dimethyl-1-(pyrrolidinecarbonylmethyl)imidazolium bromide (20):



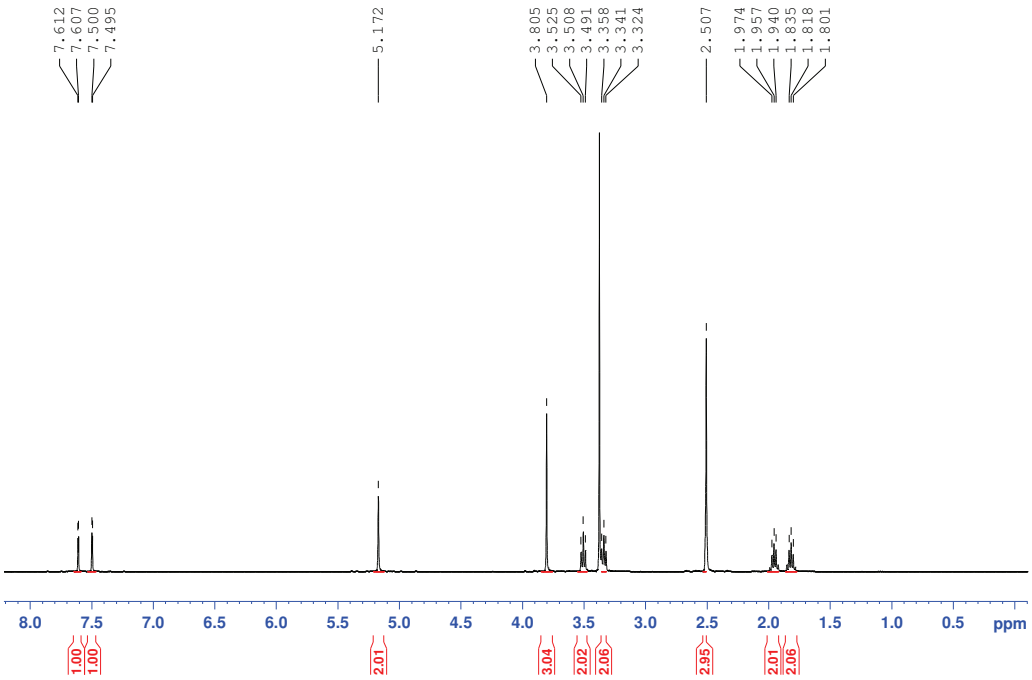
A flask was charged with 2,3-dimethyl-1-(pyrrolidinecarbonylmethyl)imidazolium bromide (11.00 g, 38.19 mmol) and distilled water (40 mL). $LiNTf_2$ (10.96 g, 38.19 mmol) in distilled water (40 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The top aqueous layer was removed, the IL washed with water (3 x 50 mL) then the solvent removed on the rotary evaporator. The product was dried *in vacuo* for 72 h to give a colourless liquid at RT in 75 % yield (14.13 g, 28.92 mmol).

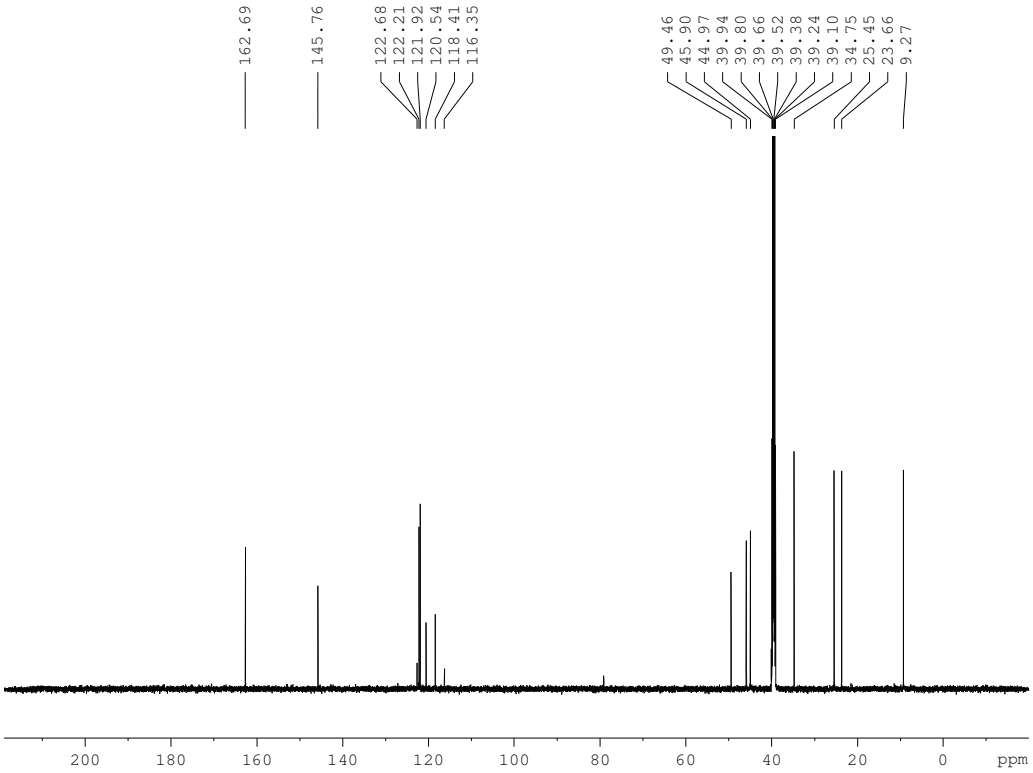
^{1}H NMR (400 MHz, DMSO-d6): 7.61 (d, J 2.0, 1H), 7.50 (d, 1H, J 2.0) 5.17 (s, 2H), 3.80 (s, 3H), 3.50 (t, 2H, J 6.8,), 3.34 (t, 2H, J 6.8), 2.51 (s, 3H), 1.97-1.94 (m, 2H), 1.83-1.80 (m, 2H)

^{13}C NMR (150 MHz, DMSO-d6): 162.69, 145.76, 122.21, 121.92, 119.47 (q, J = 309 Hz, 2 CF_3), 49.46, 45.90, 44.97, 34.75, 25.45, 23.66, 9.27.

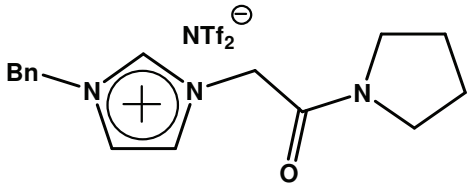
ES-MS (+ve): m/z 208.1447

Karl Fischer Analysis: 2.27 wt% water





Preparation of 3-benzyl-1-(pyrrolidinecarbonylmethyl)imidazolium NTf_2 (18):



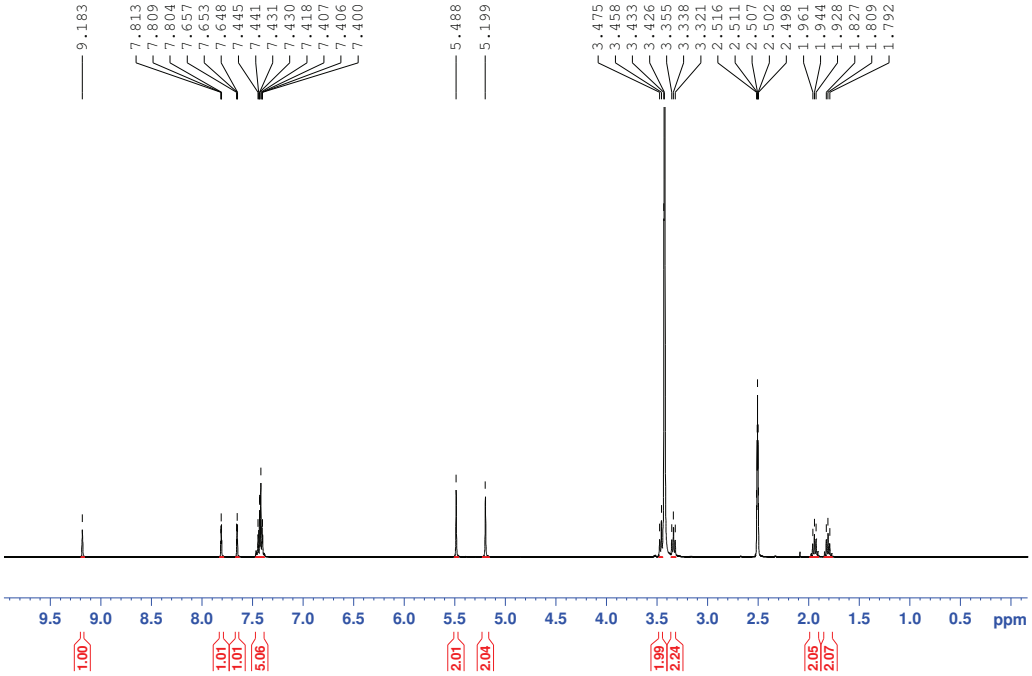
A flask was charged with 3-benzyl-1-(pyrrolidinecarbonylmethyl)imidazolium bromide (200 mg, 0.57 mmol) and distilled water (2 mL). $LiNTf_2$ (163 mg, 0.57 mmol) in distilled water (2 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The top aqueous layer was removed, the IL washed with water (3 x 4 mL) then the solvent removed on the rotary evaporator. The product was dried *in vacuo* for 72 h to give a colourless liquid at RT in 86 % yield (271 mg, 0.49 mmol).

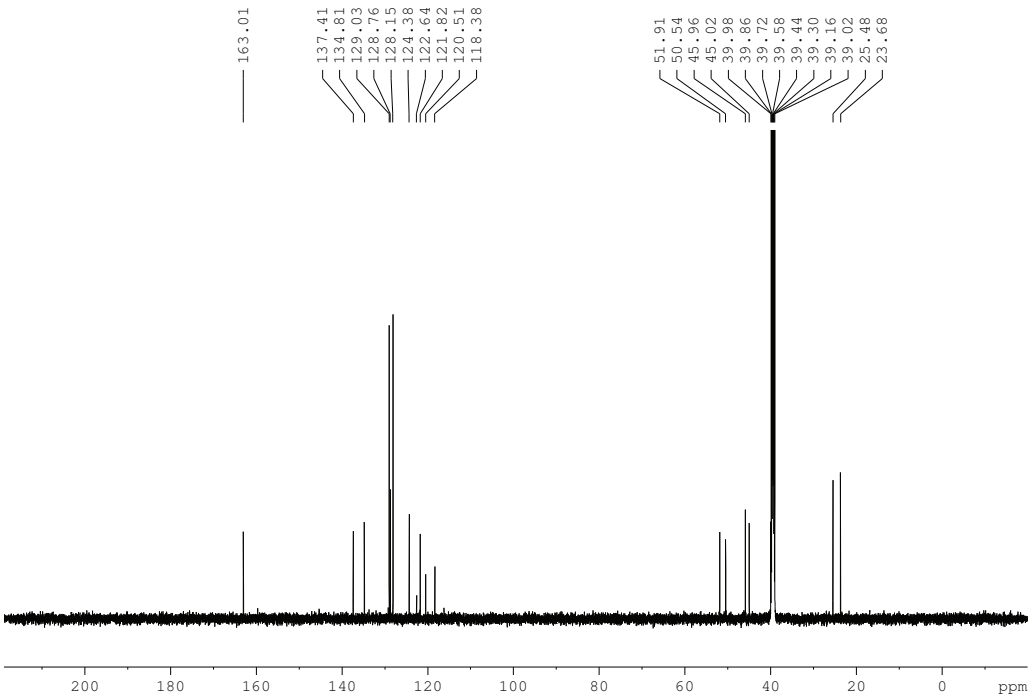
^{1}H NMR (400 MHz, DMSO-d6): 9.18 (s, 1H), 7.80 (t, 1H, J 1.6), 7.65 (t, 1H, J 1.6), 7.44-7.40 (m, 5H), 5.88 (s, 2H), 5.19 (s, 2H), 3.45 (t, 2H J 6.8,), 3.29 (t, 2H, J 6.8) 1.96-1.92 (m, 2H), 1.82-1.79 (m, 2H).

^{13}C NMR (150 MHz, DMSO-d6) 163.01, 137.41, 134.81, 129.03, 128.76, 128.15, 124.38, 121.82, 119.44 (q, J = 319 Hz, 2 CF_3), 51.91, 50.54, 45.96, 45.02, 25.48, 23.68.

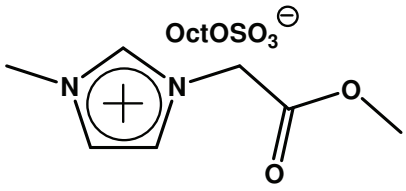
ES-MS (+ve): m/z 270.1606

Karl Fischer Analysis: 4.99 wt% water





Preparation of 3-methyl-1-(methoxycarbonylmethyl)imidazolium Octylsulfate (14):



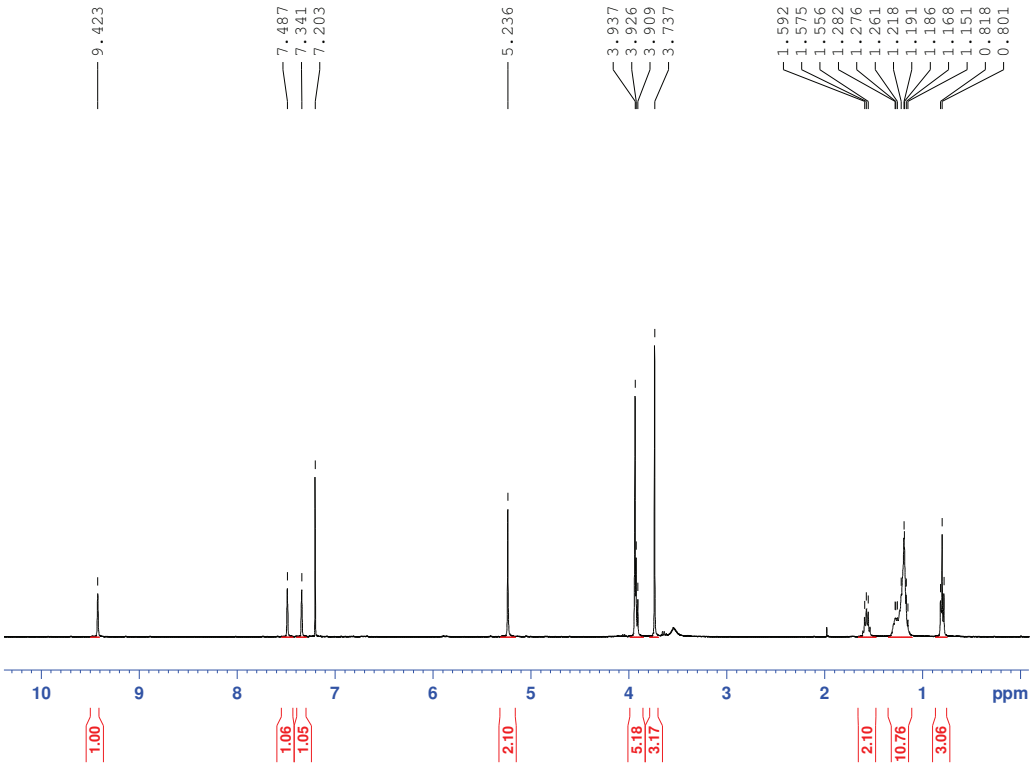
A flask was charged with 3-methyl-1-(methoxycarbonylmethyl)imidazolium bromide (2.00 g, 8.51 mmol) and distilled water (7.5 mL). Sodium octylsulfate (1.97 g, 8.51 mmol) in distilled water (7.5 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The water was removed on the rotary evaporator and residue was dissolved in dichloromethane (15 mL) and washed with water. Organic layer was dried over anhydrous magnesium sulphate, filtered and filtrate was evaporatorated. The product was dried *in vacuo* for 72 h to give a colourless viscous liquid in 64 % yield (1.91 g, 5.24 mmol).

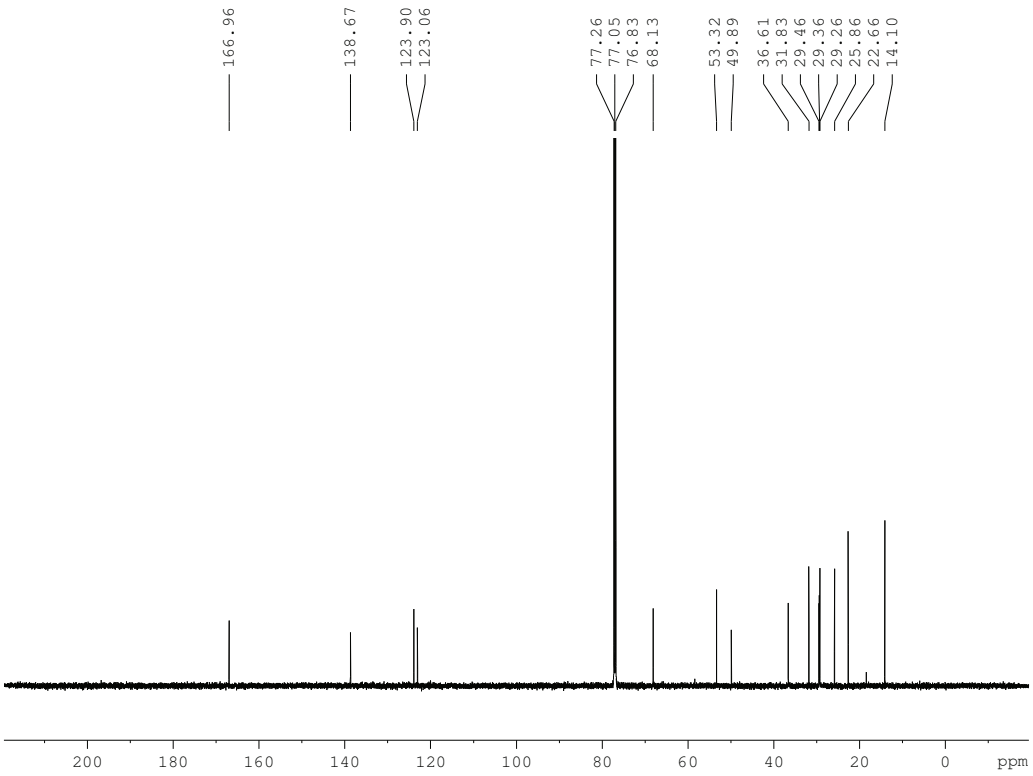
^{1}H NMR (400 MHz, DMSO-d6): 9.42 (s, 1H), 7.48 (s, 1H), 7.34 (s, 1H), 5.23 (s, 2H), 3.93-3.90 (m, 5H), 3.73 (s, 3H), 1.59-1.55 (m, 2H), 1.28-1.15 (m, 10H), 0.81 (t, 3H, J 6.8)

^{13}C NMR (150 MHz, DMSO-d6): 166.96, 138.67, 123.90, 123.06, 68.13, 53.32, 49.89, 36.61, 31.83, 29.46, 29.36, 29.26, 25.86, 22.66, 14.10.

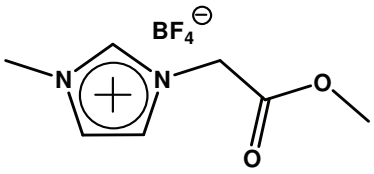
ES-MS (+ve): m/z 155.0820

Karl Fischer Analysis: 2.82 wt% water





Preparation of 3-methyl-1-(methoxycarbonylmethyl)imidazolium tetrafluoroborate (10):



A flask was charged with 3-methyl-1-(methoxycarbonylmethyl)imidazolium bromide (500 mg, 2.31 mmol) and acetone (4 mL) under a Nitrogen atmosphere. $NaBF_4$ (31 mg, 2.31 mmol) was added in one portion and the suspension was stirred vigorously for 4 days at RT. The fine white precipitate was filtered quickly in air and washed with dry acetone (2 x 4 mL). The filtrate and washings were combined and solvent removed by rotary evaporation, then *in vacuo* for 2 days to give a white solid in 95 % yield (492 mg, 2.03 mmol).

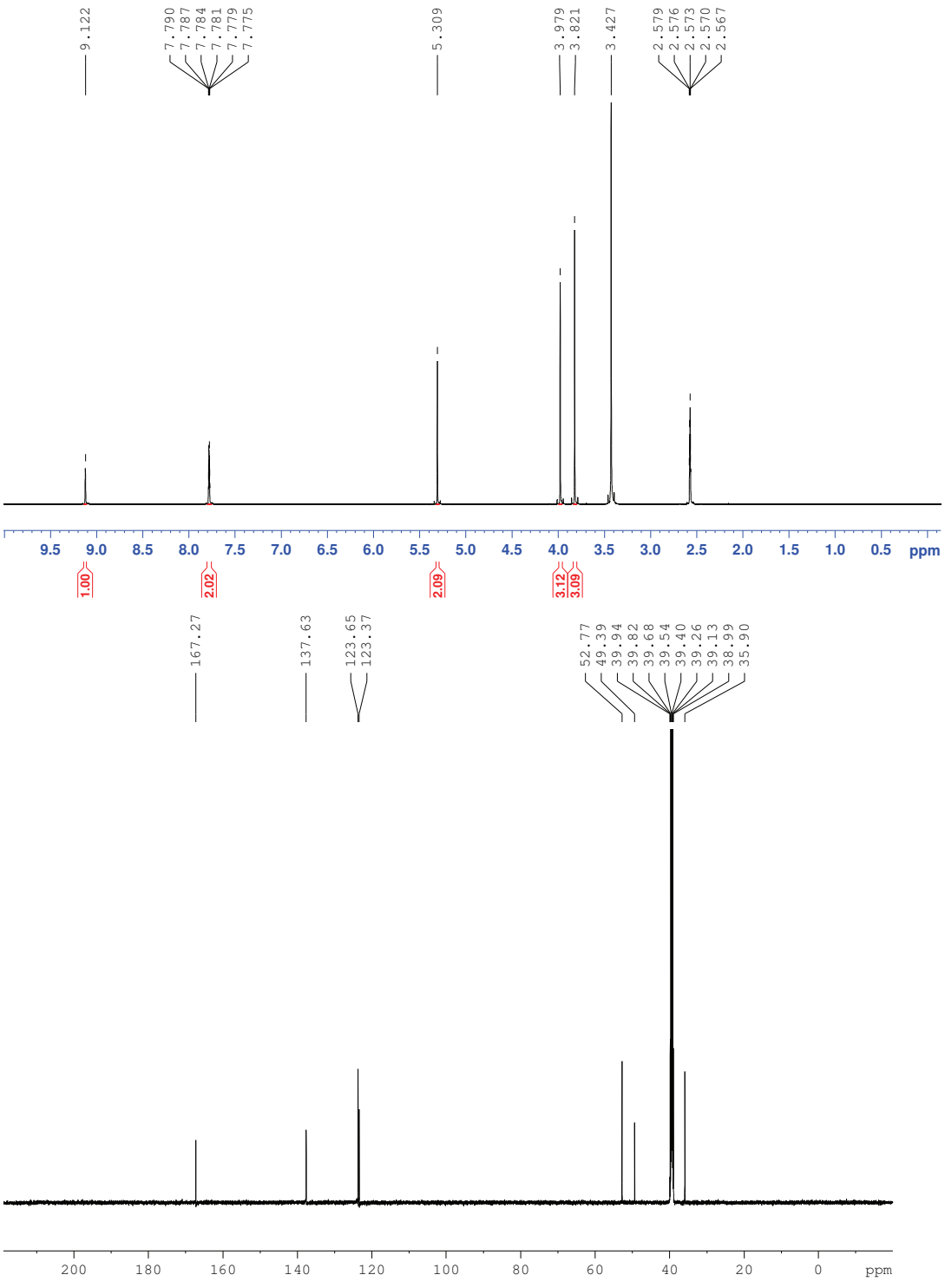
^{1}H NMR (600 MHz, DMSO-d6) 9.12 (s, 1H), 7.79-7.77 (m, 2H), 5. 31 (s, 2H), 3.97 (s, 3H), 3.82 (s, 3H).

^{13}C NMR (150 MHz, DMSO-d6) 167.27, 137.63, 123.65, 123.37, 52.77, 49.39, 35.90.

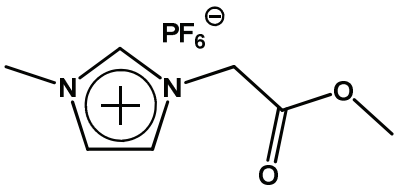
Melting point: 45-47 ºC.

ES-MS (+ve): m/z 155.0821

Karl Fischer Analysis: 1.22 wt% water



Preparation of 3-methyl-1-(methoxycarbonylmethyl)imidazolium hexafluorophosphate (12):



A flask was charged with 3-methyl-1-(ethoxycarbonylmethyl)imidazolium bromide (500 mg, 2.13 mmol), and acetone (2 mL). KPF_6 (600 mg, 3.49 mmol) in acetone (2 mL) was added in one portion and the suspension was stirred vigorously for 4 days under reflux. After 4 days the fine white precipitate was filtered quickly in air and washed with dry acetone (2 x 4 mL). The filtrate and washings were combined, solvent removed by rotary evaporation, then *in vacuo* for 2 days to yield a white solid at RT in 95 % yield (605 mg, 2.01 mmol).

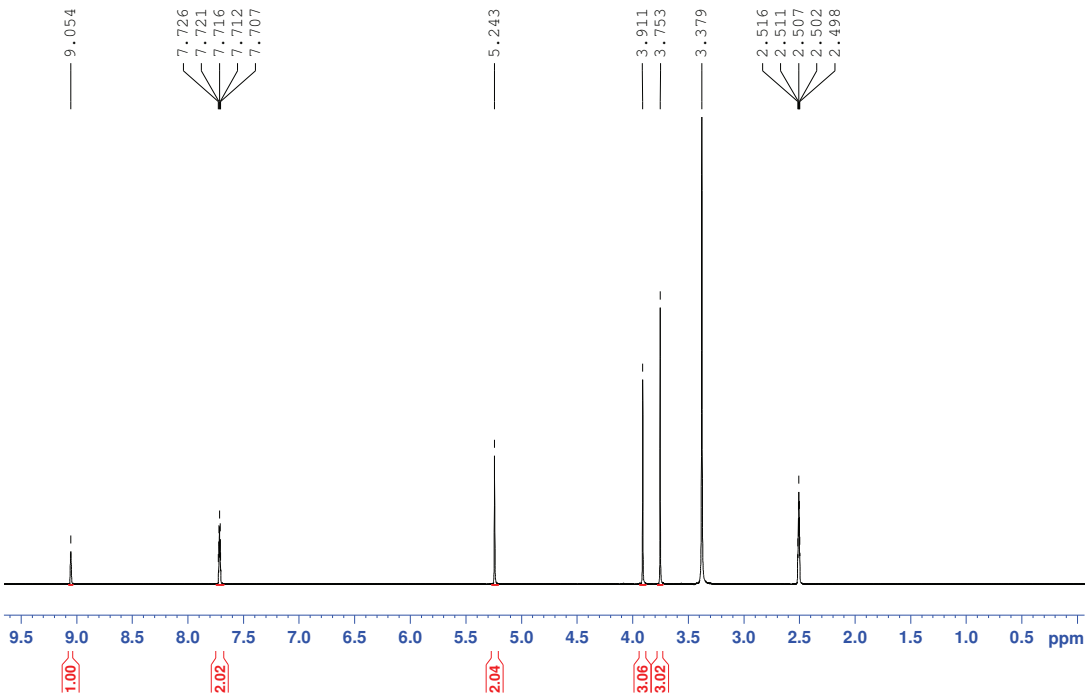
^{1}H NMR (400 MHz, DMSO-d6): 9.05 (s, 1H), 7.72-7.70 (m, 2H), 5.24 (s, 2H), 3.91 (s, 3H), 3.75 (s, 3H)

^{13}C NMR (150 MHz, DMSO-d6): 167.28, 137.66, 123.67, 123.40, 52.76, 49.41, 35.92.

Melting point: 84-86 ºC.

ES-MS (+ve): m/z 155.0820

Karl Fischer Analysis: 0.56 wt% water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7.712
7.707
5.243
3.911
3.753
3.379
2.516
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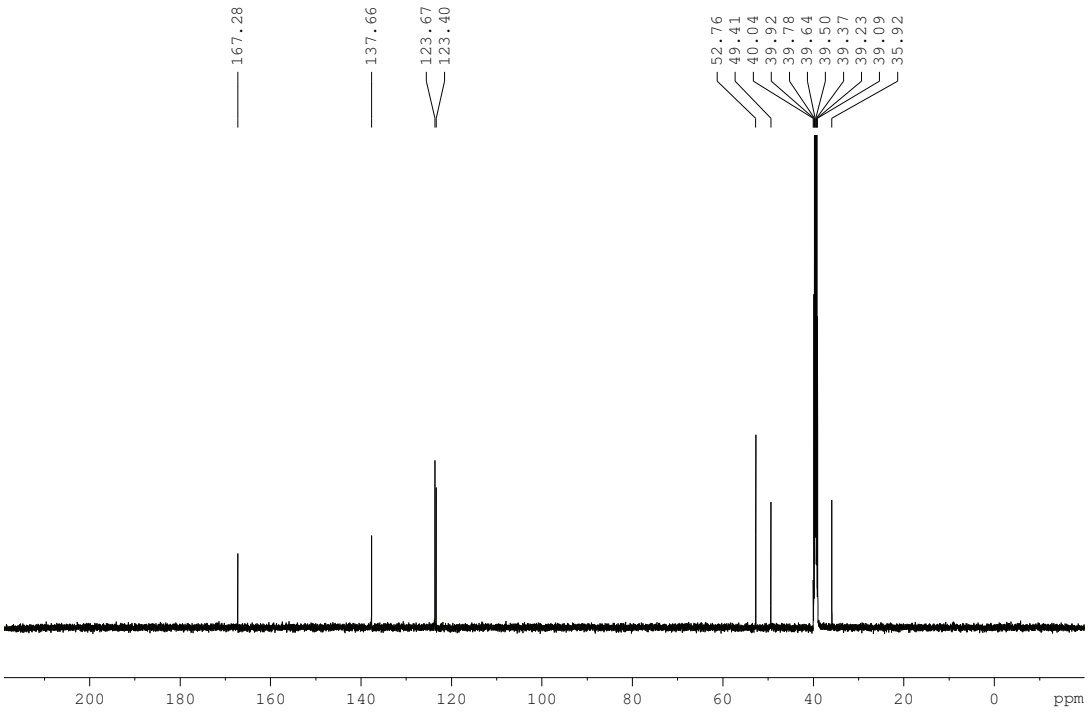
2.507
2.502
2.498
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
2.02
2.04
3.06
3.02

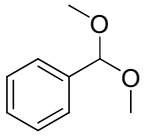

167.28
137.66
123.67
123.40
52.76
49.41
40.04
39.92
39.78
39.64
39.50
39.37
39.23
39.09
35.92
200 180 160 140 120 100 80 60 40 20 0 ppm

5.0 General Procedure- Acetalisation of aldehydes

An 20 mL reaction flask was fitted with a magnetic stirring bar, charged with catalyst (0.08 mmol), fitted with a septum and flushed with argon. Benzaldehyde (170 µL, 1.67 mmol) was added followed by dry methanol (3.4 mL) *via* syringe. The solution was then stirred under argon at room temperature for 24 h. When conversion was judged to be either complete or >95% (by ^{1}H NMR spectroscopic analysis) the reaction was quenched with $PhNHNH_2$ and the solvent was removed *in vacuo*. The crude product was then purified by flash-chromatography or yield was calculated by ^{1}H NMR spectroscopy using an internal standard.

6.0 Characterisation data- Acetalisation of aldehydes

Benzaldehyde dimethyl acetal (8)

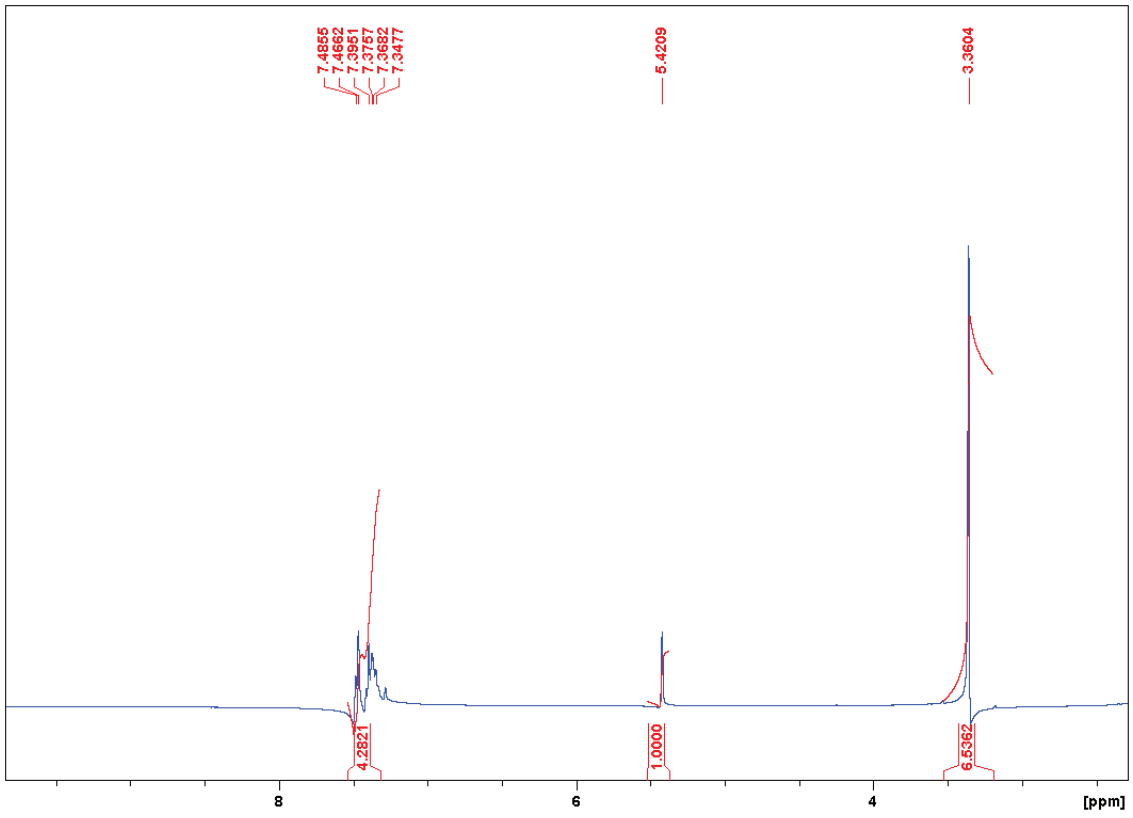


The dimethyl acetal was obtained following the general procedure using catalyst **10** (20.5 mg, 0.08mmol), methanol (3.4 mL) and benzaldehyde (170 µL, 1.67 mmol). After purification of the crude material by flash chromatography (3:1 Hexane: EtOAc) the product **8** was obtained as a pale yellow liquid (216 mg, 86%).

The NMR spectra of **8** were consistent with those previously reported.[1]

^{1}H NMR (400 MHz, $CDCl_3$):3.36 (s, 6H,), 5.42 (s, 1H), 7.34-7.39 (m, 3H), 7.47-7.49 (m,2H).

^{13}C NMR (100 MHz, $CDCl_3$): 52.2, 102.7, 126.2, 127.7, 128.0, 137.5 (q)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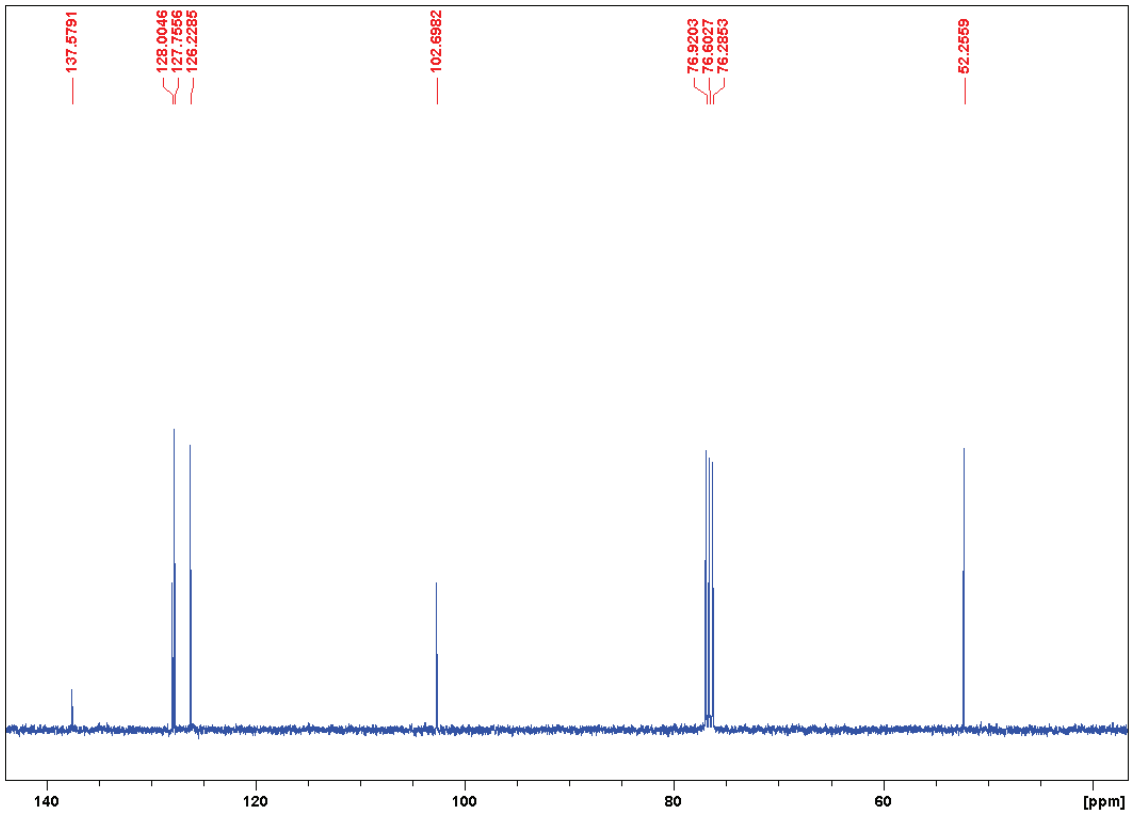
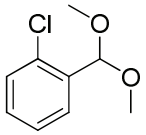
7.4662
7.3951
7.3757
7.3682
7.3477
5.4209
3.3604
4.2821
1.0000
6.5362
8
6
4
[ppm]


137.5791
128.0046
127.7556
126.2285
102.6982
76.9203
76.6027
76.2853
52.2559
140
120
100
80
60
[ppm]

2-Chlorobenzaldehyde dimethyl acetal (21)

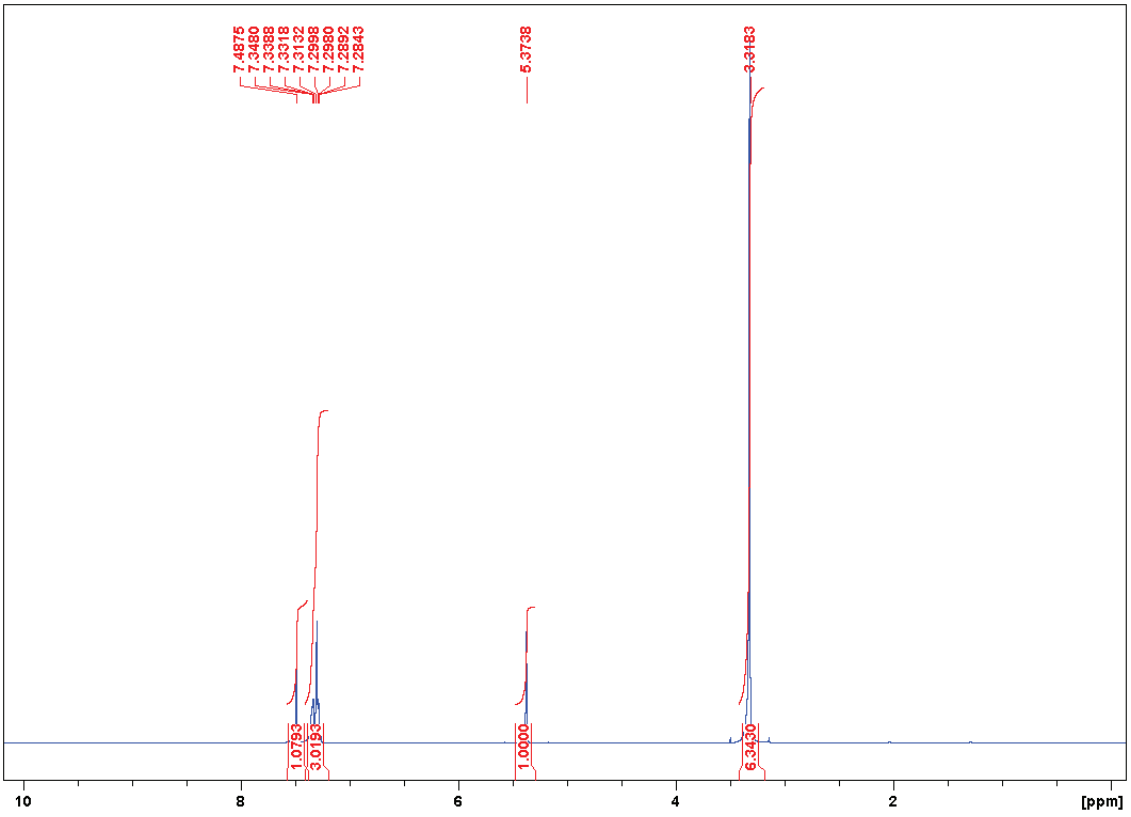


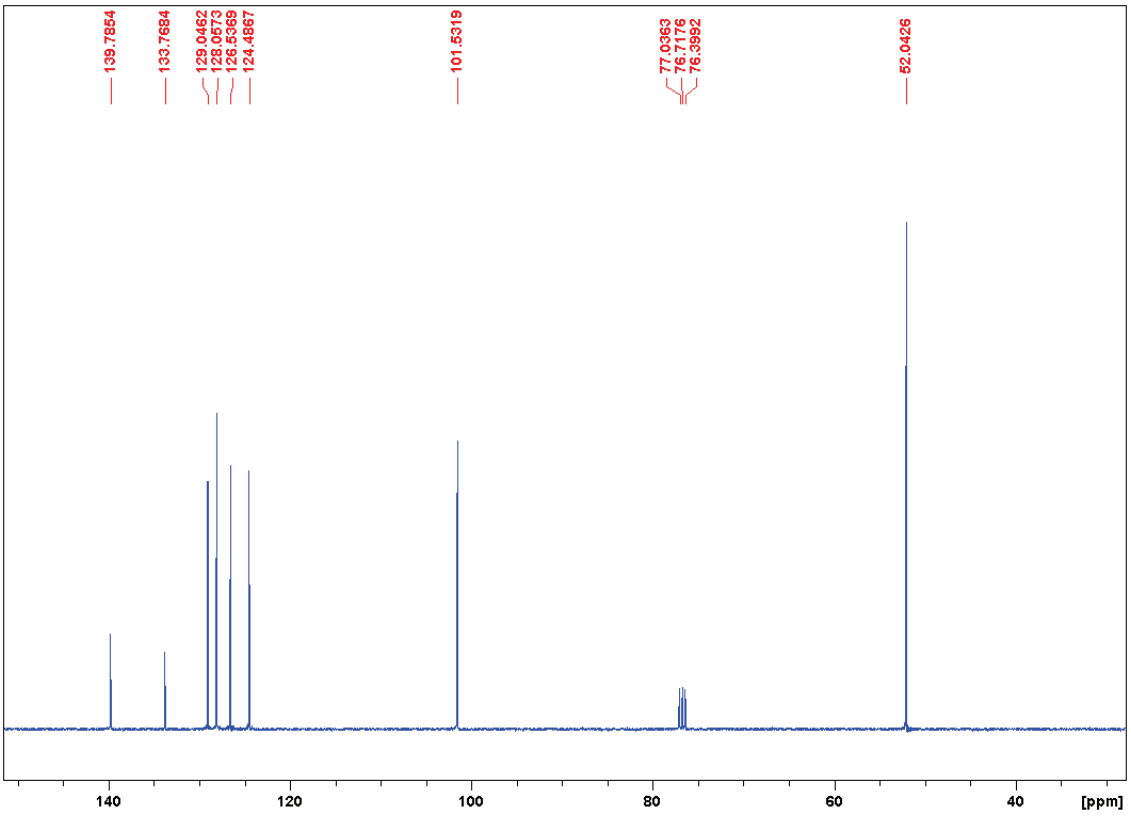
The dimethyl acetal was obtained following the general procedure using catalyst **10** (22.7 mg, 0.09 mmol), methanol (3.4 mL) and 2-chlorobenzaldehyde (200 µL, 1.78 mmol). After purification of the crude material by flash chromatography (5:1 Hexane: EtOAc) the product **21** was obtained as a pale yellow liquid (318 mg, 96%).

The NMR spectra of **21** were consistent with those previously reported.[2]

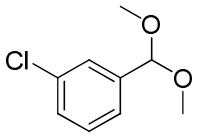
^{1}H NMR (400 MHz, $CDCl_3$):3.32 (s, 6H), 5.39 (s, 1H), 7.28-7.35 (m, 3H), 7.48 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): 52.2, 101.6, 124.4, 126.5, 128.1, 129.1, 133.8 (q), 139.8 (q).





3-Chlorobenzaldehyde dimethyl acetal (22)

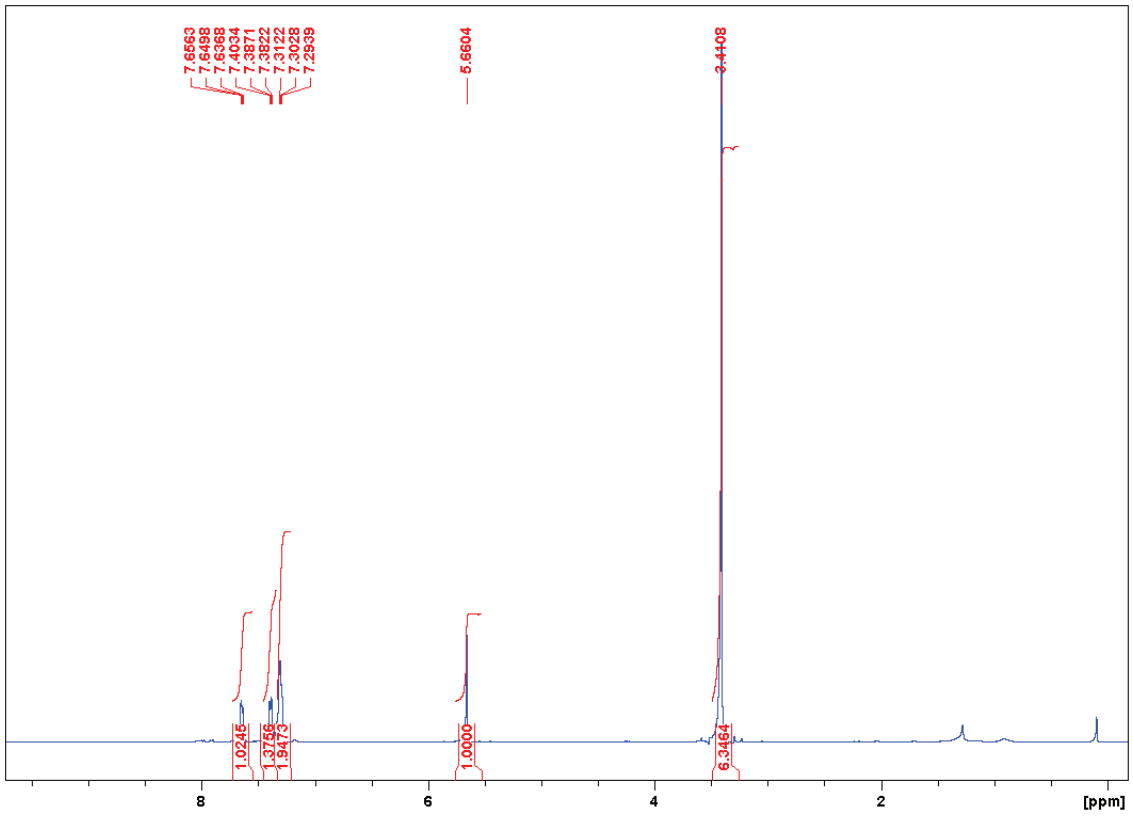


The dimethyl acetal was obtained following the general procedure using catalyst **10** (22.7 mg, 0.09 mmol), methanol (3.4 mL) and 3-chlorobenzaldehyde (200 µL, 1.78 mmol). After purification of the crude material by flash chromatography (5:1 Hexane: EtOAc) the product **22** was obtained as a pale yellow liquid (307 mg, 93%).

The NMR spectra of **22** were consistent with those previously reported.[2]

^{1}H NMR (400 MHz, $CDCl_3$): 3.41 (s, 6H), 5.66 (s, 1H), 7.29-7.31 (m, 2H), 7.38-7.40 (m,1H,), 7.63-7.65 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): 53.4, 100.5, 126.1, 127.6, 129.1, 129.3, 132.7 (q), 134.8 (q)


7.6563
7.6498
7.6368
7.4034
7.3871
7.3822
7.3122
7.3028
7.2939
5.6604
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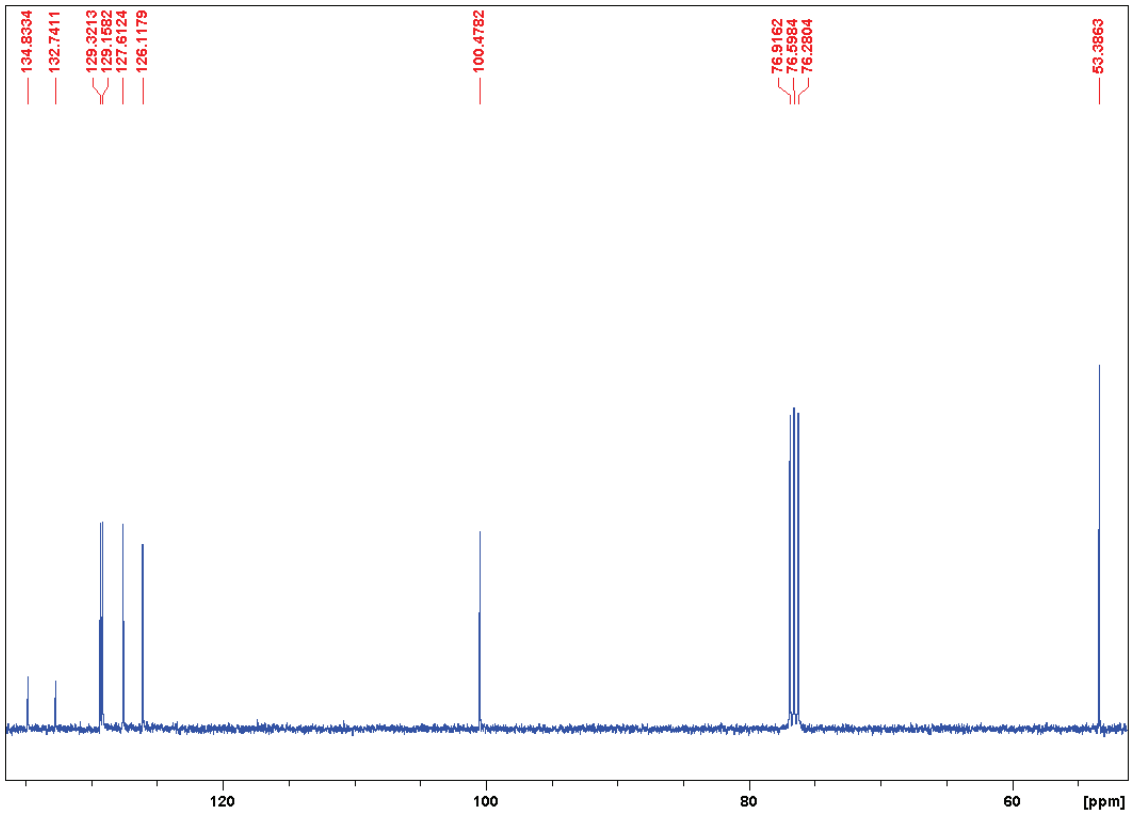
1.0245
1.3756
1.9473
1.0000
6.3464
8
6
4
2
[ppm]


134.8334
132.7411
129.3213
129.1682
127.6124
126.1179
100.4782
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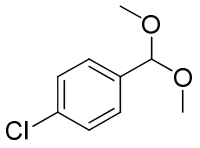
76.5984
76.2804
53.3863
120
100
80
60
[ppm]

4-Chlorobenzaldehyde dimethyl acetal (23)

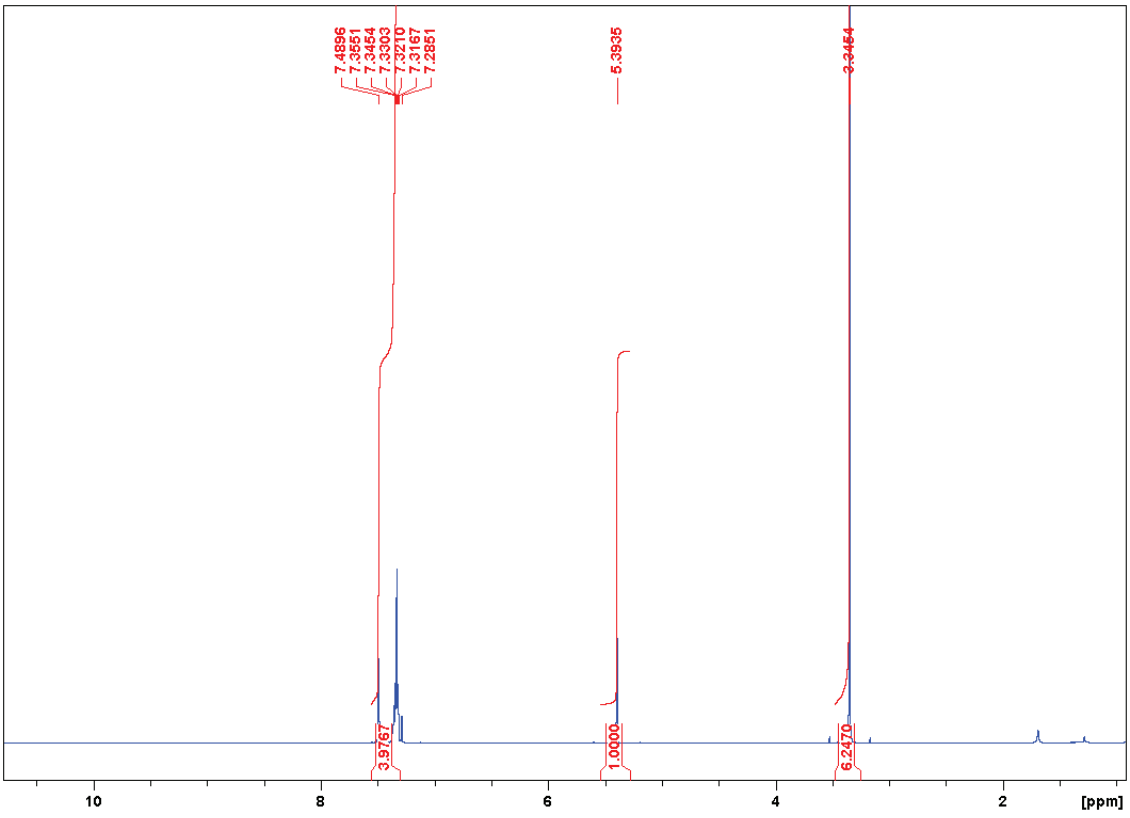


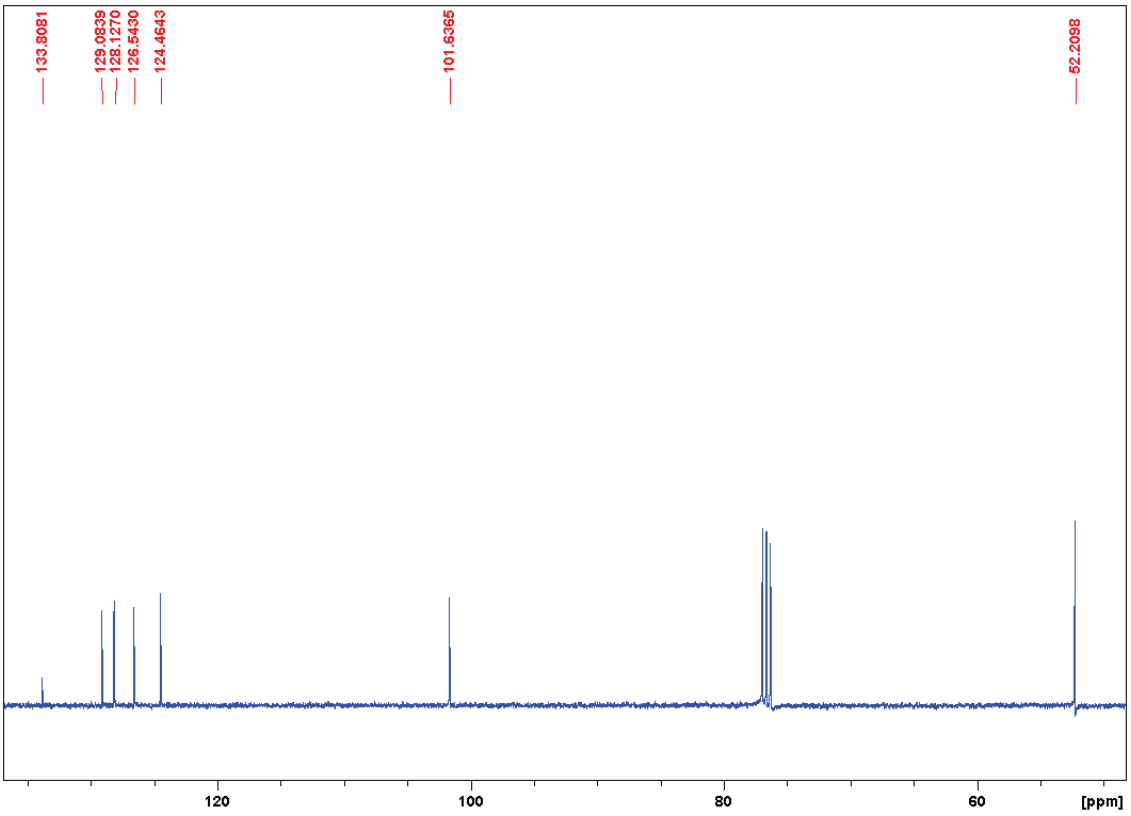
The dimethyl acetal was obtained following general procedure using catalyst **10** (22.7 mg, 0.09 mmol), methanol (3.6 mL) and 4-chlorobenzaldehyde (250 mg, 1.78 mmol). After purification of the crude material by flash chromatography (5:1 Hexane: EtOAc) the product **23** was obtained as a pale yellow liquid (314 mg, 95%).

The NMR spectra of **23** were consistent with those previously reported.[1]

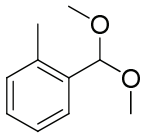
^{1}H NMR (400 MHz, $CDCl_3$): 3.34 (s, 6H,), 5.39 (s, 1H), 7.32 (d, 2H, J 8.5), 7.48 (d, 2H, J 8.5).

^{13}C NMR (100 MHz, $CDCl_3$): 52.2, 101.6, 124.6, 126.4, 128.4, 133.8 (q)





2-Methylbenzaldehyde dimethyl acetal (24)

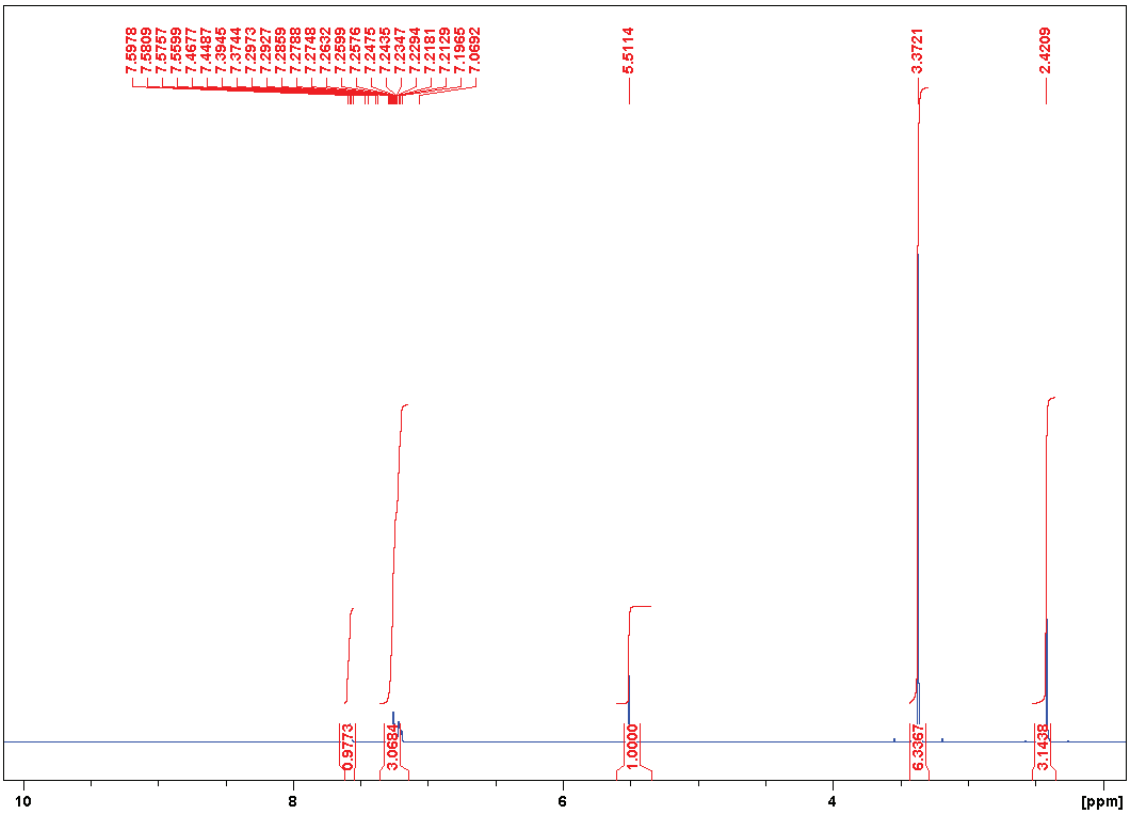


The dimethyl acetal was synthesised was synthesised following general procedure using catalyst **10** (22.7 mg, 0.09 mmol), methanol (2.3 mL) and 2-methylbenzaldehyde (100 µL, 0.86 mmol). After purification of the crude material by flash chromatography the product **24** was obtained as a pale yellow liquid (125 mg, 87%).

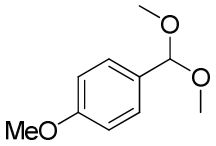
The NMR spectra of **24** were consistent with that previously reported.[3]

^{1}H NMR (400 MHz, $CDCl_3$): 2.42 (s, 3H,), 3.37 (s, 6H), 5.51(s, 1H) 7.06-7.25(m, 3H), 7.57-7.59 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): 18.4, 52.5, 101.3, 124.9, 126.1, 127.9, 130.1, 135.2 (q), 135.8 (q)



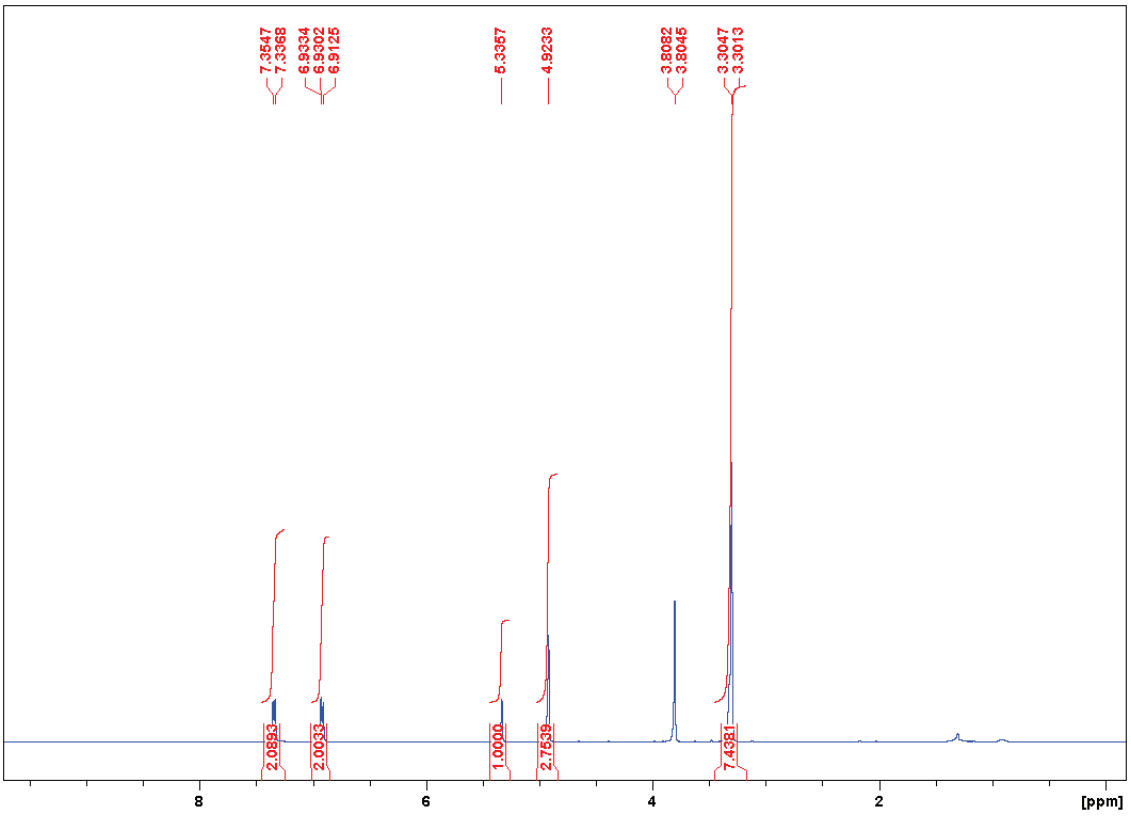
4-Methoxybenzaldehyde dimethyl acetal (25)



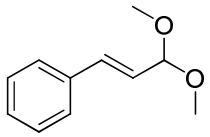
The dimethyl acetal was obtained following the general procedure using catalyst **10** (20.2 mg, 0.08 mmol), methanol (2.2 mL) and 4-methoxybenzaldehyde (100 µL, 0.82 mmol). The reaction mixture was then heated at 35 ^{O}C for 24 h. After purification of the crude material by flash chromatography (15:1 Hexane:EtOAc) the product **25** was obtained as a pale yellow liquid (130 mg, 87%). **Note:** the use of $PhNHNH_2$ was not required.

The NMR spectra of **25** were consistent with those previously reported.[1]

^{1}H NMR (400 MHz, CD_3OD): 3.30 (s, 6H), 3.81 (s, 3H), 5.34 (s, 1H), 6.92 (d, 2H, J 8.9), 7.32 (d, 2H, J 8.9)



3,3-Dimethoxypropenyl benzene (27)

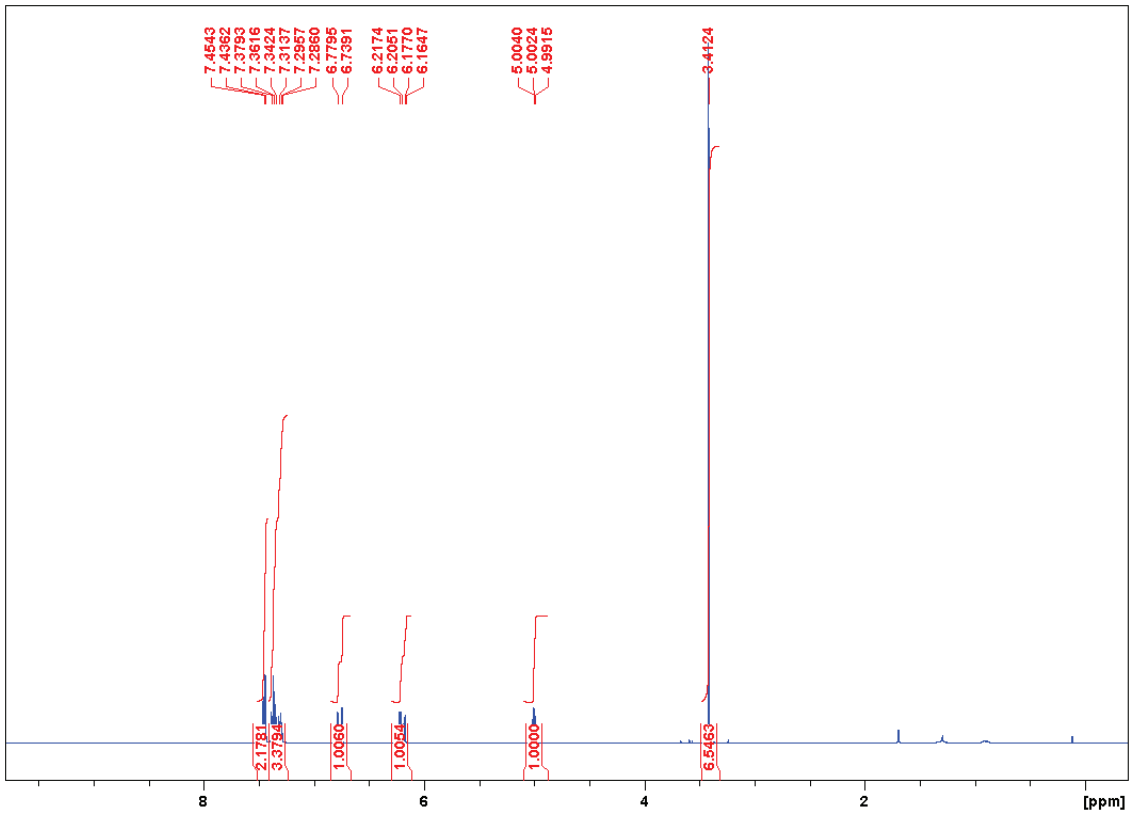


The desired dimethyl acetal was obtained following the general procedure using the catalyst **10** (20.2 mg, 0.08 mmol), methanol (2.1 mL) and cinnamaldehyde (100 µL, 0.79 mmol). After purification of the crude material by flash chromatography (3:1 Hexane: EtOAc) the product **27** was obtained as a pale yellow liquid (116 mg, 83%). **Note:** the use of $PhNHNH_2$ was not required.

The NMR spectra of **27** were consistent with those previously reported.[5]

^{1}H NMR (400 MHz, $CDCl_3$):3.41 (s, 6H), 5.00 (dd, 1H, J 5.1), 6.18 (dd, 1H, J 16.4, 5.1), 6.69 (d, 1H, J 16.4), 7.29-7.38 (m, 3H), 7.44-7.45 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 52.3, 102.5, 125.2, 126.3, 127.6, 128.2, 133.2, 135.6 (q)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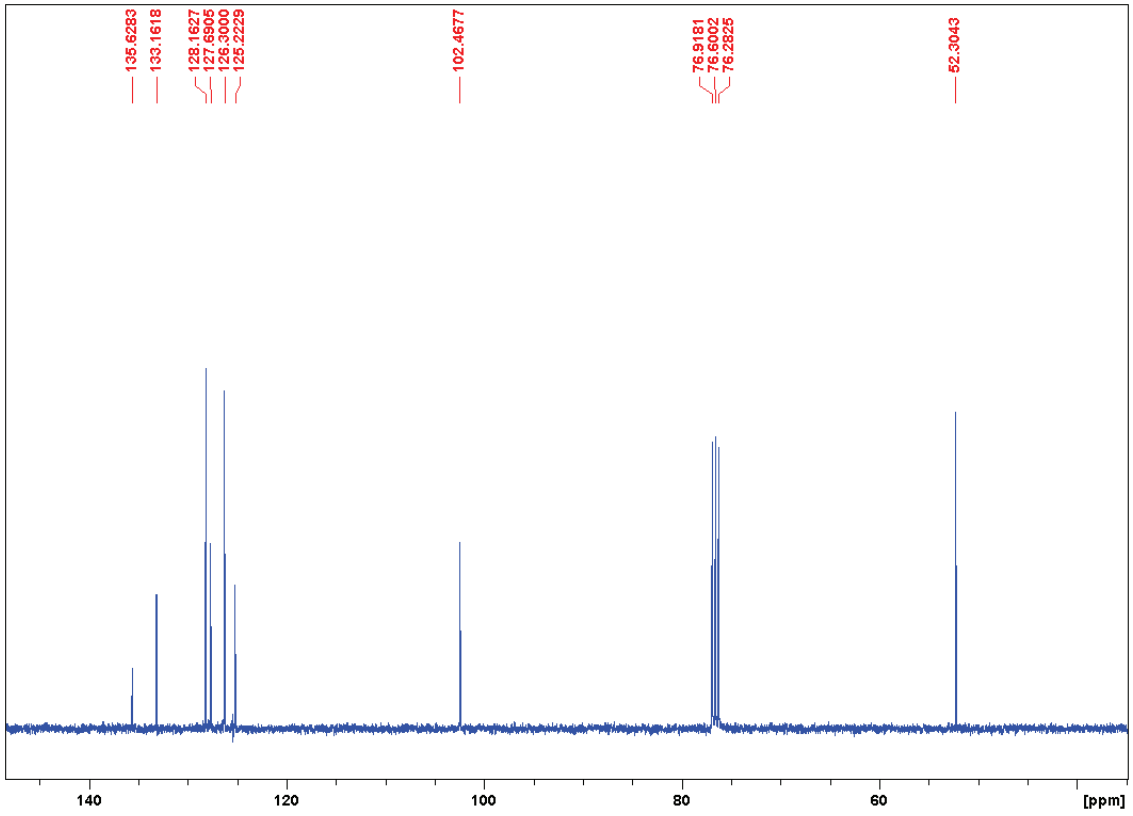
7.4362
7.3793
7.3616
7.3424
7.3137
7.2957
7.2860
6.7795
6.7391
6.2174
6.2051
6.1770
6.1647
5.0040
5.0024
4.9915
3.4424
2.1781
3.3794
1.0060
1.0054
1.0000
6.5463
8
6
4
2
[ppm]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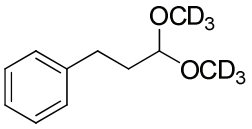
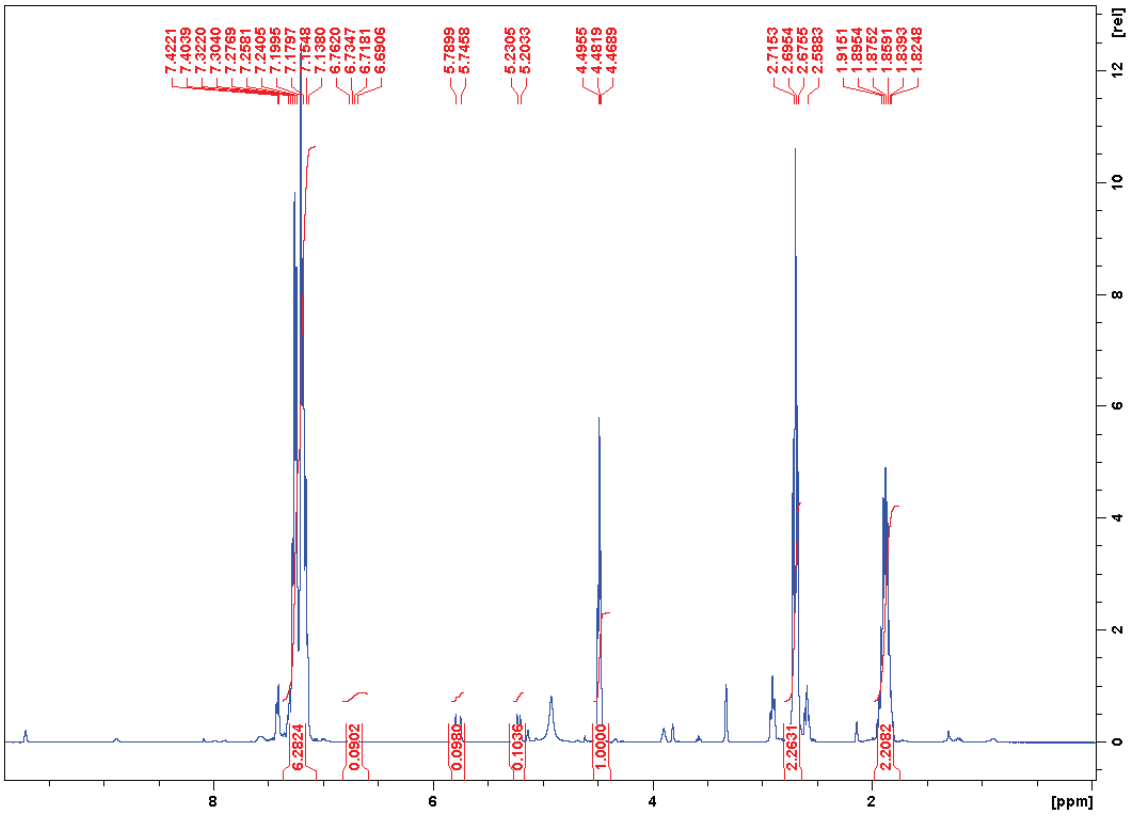
128.1627
127.6905
126.3000
125.2229
102.4677
76.9181
76.6002
76.2825
52.3043
140
120
100
80
60
[ppm]

3,3-Dimethoxypropyl benzene (28)

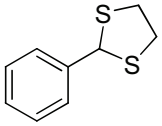


The desired dimethyl acetal was obtained following the general procedure using catalyst **10** (1.01 mg, 0.004 mmol), deuterated methanol (1 mL) and 3-pheylpropanal (50 µL, 0.38 mmol). The reaction mixture was stirred for 1 minute then styrene (43 µL, 0.038 mmol) was added *via* syringe. The yield of **28** was determined using ^{1}H NMR spectroscopy (97%).[6]

^{1}H NMR (400 MHz, $CDCl_3$):1.82-1.91 (m, 2H), 2.69 (t, 2H, J 8.1), 4.48 (t, 1H, J 5.6,), 7.13-7.42 (m, 5H)



Phenyl-1,3-dithiolane (32)

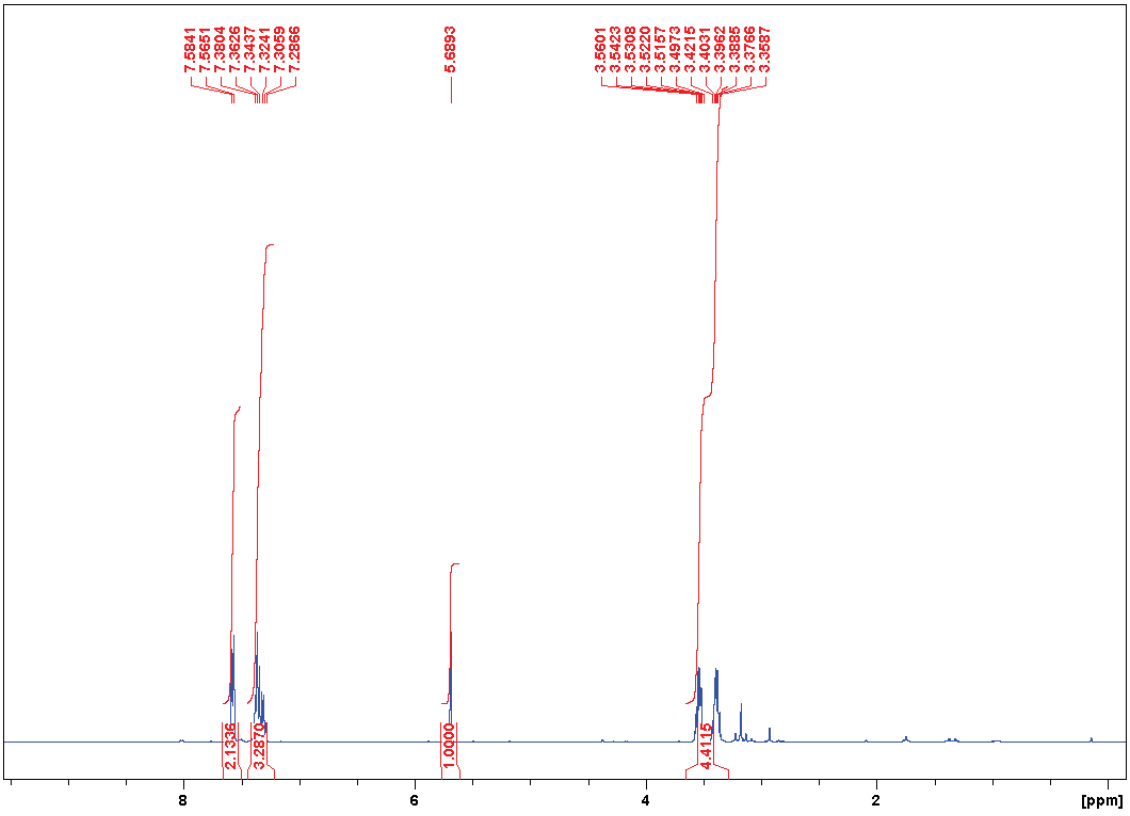


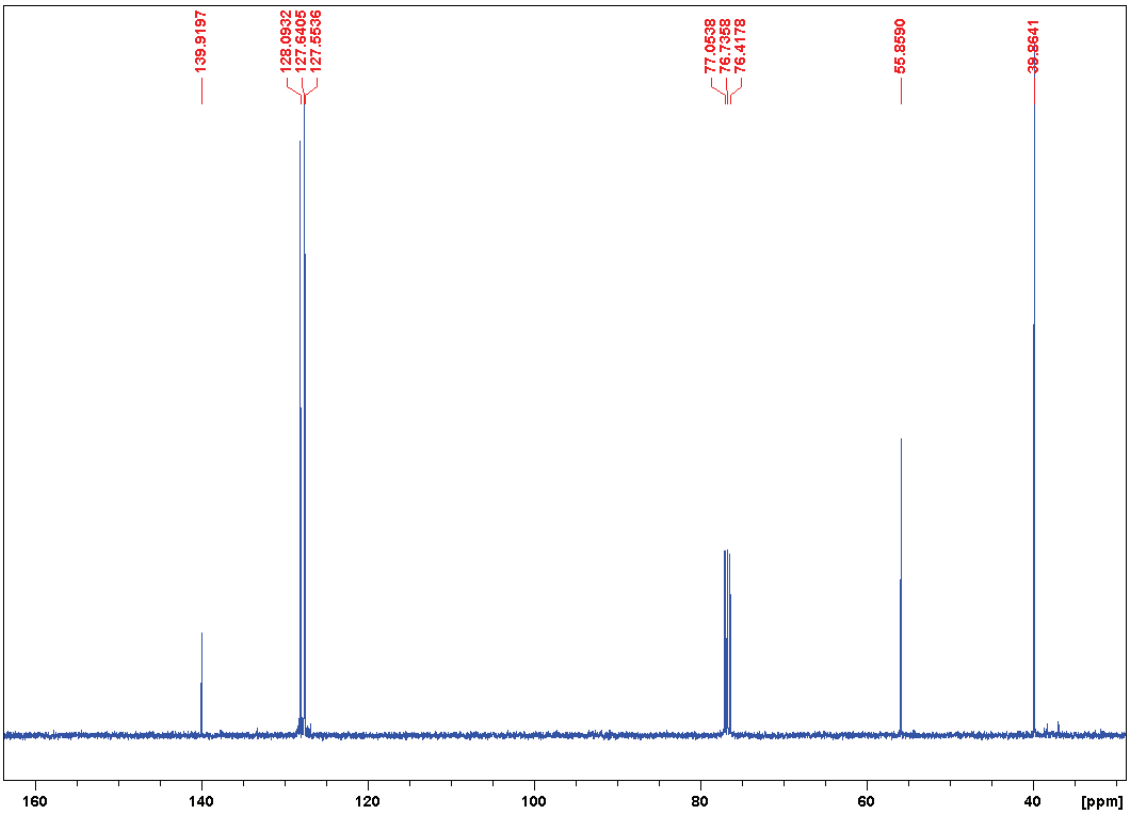
The dithiolane was obtained following the general procedure using catalyst **10** (27.8 mg, 0.11 mmol), 1,2-ethanedithiol (100 µL, 1.19 mmol), THF (200 µL) and benzaldehyde (110 µL, 1.08 mmol). After completion of the reaction, the reaction mixture was added to a saturated $NaHCO_3$ solution (5 mL) and the product was extracted with ethyl acetate (2 x 10 mL). The organic layer was separated, dried over $MgSO_4$ and the solvent was removed under reduced pressure. After purification by flash chromatography the product **32** was obtained as a colourless liquid (180 mg, 92 %).

The NMR spectra of **32** were consistent with those previously reported.[7]

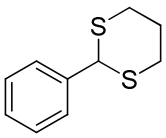
^{1}H NMR (400 MHz, $CDCl_3$):3.34-3.40 (m, 2H), 3.48-3.54 (m, 2H), 5.66 (s, 1H), ^{13}C NMR (100 MHz, $CDCl_3$):39.8, 55.8, 127.5, 127.6, 128.1, 139.9 (q)

^{13}C NMR (100 MHz, $CDCl_3$):39.8, 55.8, 127.5, 127.6, 128.1, 139.9 (q)





Phenyl-1,3-dithiane (33)



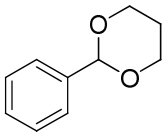
The dithiane was obtained following the general procedure using catalyst **10** (68.3 mg, 0.27 mmol), 1,3-propanedithiol (300 µL, 2.98 mmol), anhydrous THF (9.1 mL) and benzaldehyde (276 µL, 2.71 mmol). After completion of the reaction, the reaction mixture was added to a saturated solution of $NaHCO_3$ (5 mL) and the product was extracted with EtOAc (2 x 10 mL). The organic layer was separated, dried over $MgSO_4$ and the solvent was removed under reduced pressure. After purification by flash chromatography the product **33** was obtained as a white solid (344 mg, 65%).

The NMR spectra of **33** were consistent with those previously reported.

^{1}H NMR (400 MHz, $CDCl_3$):1.93-1.98 (m, 1H) 2.19-2.23 (m, 1H), 2.91-2.95 (m, 2H,), 5.16 (s, 1H, H-4), 2.96-3.13(m, 2H) 7.28-7.36 (m, 3H), 7.46-7.48 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$):24.6, 31.6, 51.0, 127.3, 128.0, 128.3, 139.9 (q)

Phenyl-1,3-dioxane (34)

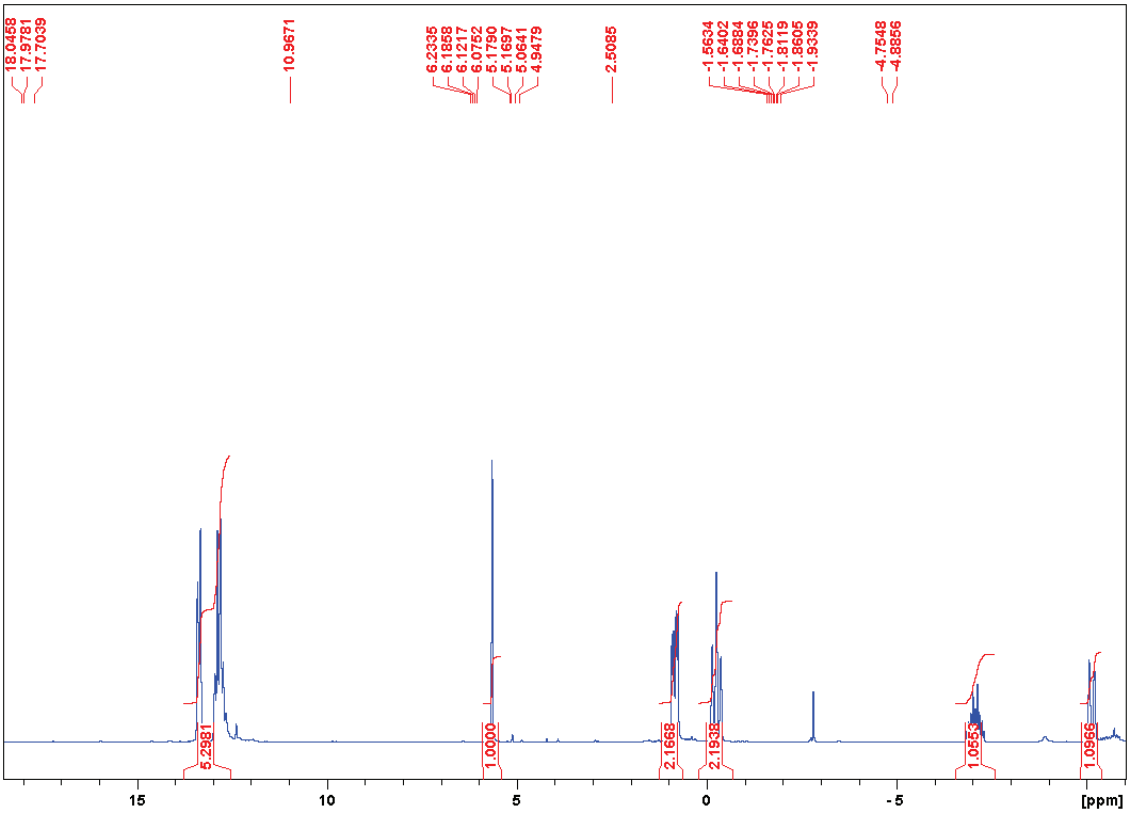


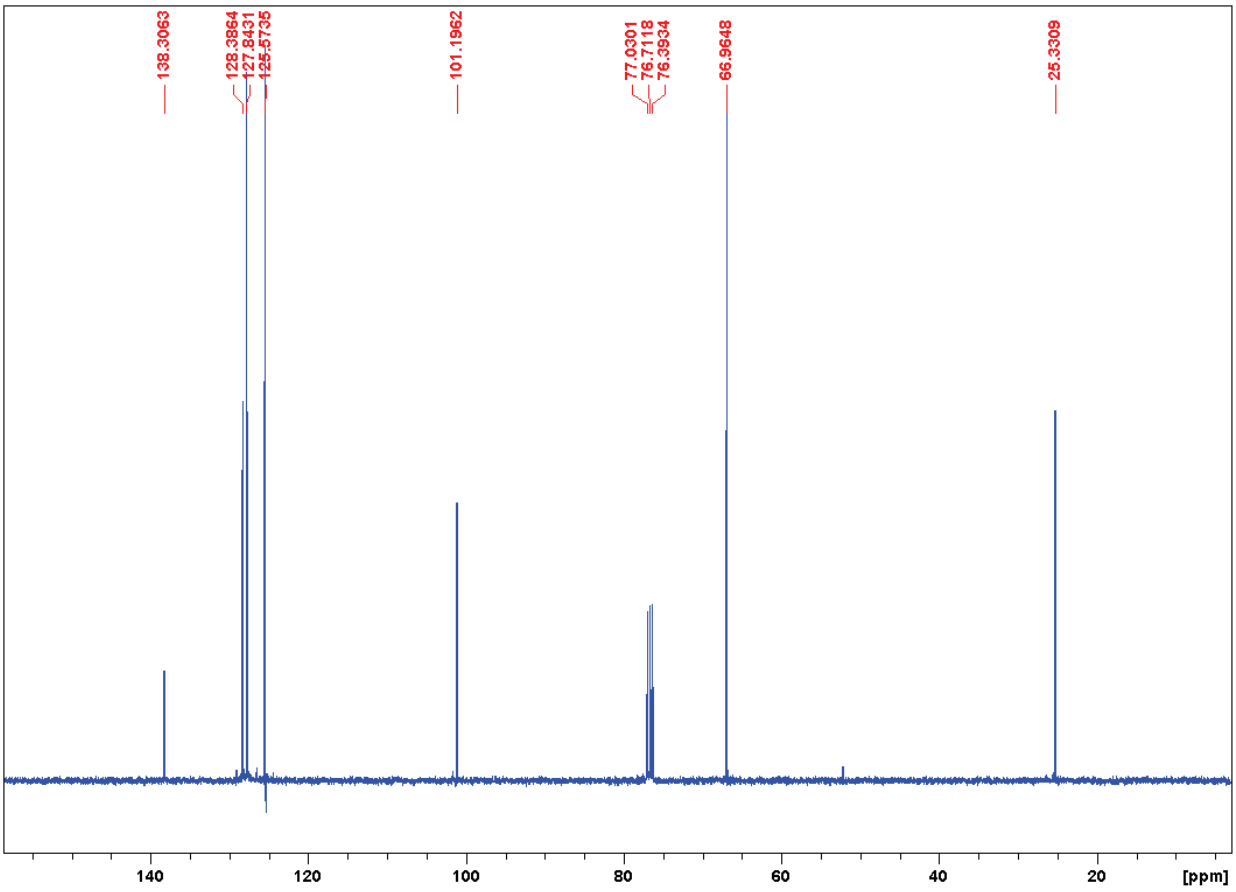
The dioxane was obtained following the general procedure using catalyst **10** (32.9 mg, 0.13 mmol), 1,3-propanediol (100 µL, 1.38 mmol) and benzaldehyde (128 µL, 1.26 mmol). After purification of the crude material by flash chromatography the product **34** was obtained as a pale yellow liquid (177 mg, 86%).

The NMR spectra of **34** were consistent with those previously recorded.[10]

^{1}H NMR (400 MHz, $CDCl_3$):1.40-1.51 (m, 1H,), 2.15-2.28 (m, 1H,), 4.04 (ddd, 2H, J 14.0, 12.3, 1.7), 4.32 (ddd, 2H, J 11.7, 5.3, 1.2), 5.51 (s, 1H) 7.32-7.39 (m, 3H), 7.48-7.50 (m, 2H)

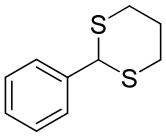
^{13}C NMR (100 MHz, $CDCl_3$): 25.3, 66.9, 101.2, 125.6, 127.9, 128.4, 138.3





7.0 Recyclability study

Phenyl-1,3-dithiane (33)



The dithiane was obtained following the general procedure using catalyst **10** (68.3 mg, 0.27 mmol), 1,3-propanedithiol (300 µL, 2.98 mmol), anhydrous THF (9.1 mL) and benzaldehyde (276 µL, 2.71 mmol). (*E*)-stilbene (2.71mmol) was added as an internal standard. After 24h, the yield of product 33 was obtained by ^{1}H NMR spectroscopy with the internal standard. The catalyst was extracted using hexane, dried in vacuo and reused in subsequent reaction.

8.0 References

1. B. Hatano, k. Nagahashi, S. Habaue, *Chem. Lett.,* 2007, **36**, 1418.
2. U. Azzena, G. Dettori, G. Sforazzini, M. Yus, F. Foubelo, *Tetrahedron*, 2006, **62**, 1557 - 1563
3. J. Tateiwa, H. Horiuchi, S. Uemura, *J. Org. Chem*., 1995, **60**, 4039.
4. A. Clerici, N. Pastori, O. Porta, *Tetrahedron*, 1998, **62** ,15679 – 15690.
5. P.J. Baldry, *J. Chem. Soc. Perkin Trans., I* 1975, 1913.
6. Y.S. Hon, C.F. Lee, R.J. Chen, Y.F. Huang, *Syn. Comm.,* 2003, **33**, 2829.
7. A. Hashmat, M.G.Gomes, *Synthesis,* 2005, **8**, 1326.
8. G. M Drew, W . Kitchin,. *J. Org. Chem.,* 1981, **46**, 558.
9. a) B. Bartels, R.J. Hunter,. *Org. Chem,.* 1993, **58**, 6756. b) K. Pihlaja, H. Nummelin, K.D. Klika, J. Czombos, *Magn. Reson. Chem,.* 2001, **39**, 657.
10. (a) N. Gathergood and P. J. Scammells *Aus. J. Chem.*, 2002, **55**, 557. (b) M. T. Garcia, N. Gathergood and P. J. Scammells, *Green Chem*., 2004, **7**, 9. (c) S. Morrissey, B. Pegot, D. Coleman, M. T. Garcia, D. Ferguson, B. Quilty and N. Gathergood, *Green Chem.*, 2009, **11**, 475.
11. National Committee for Clinical Laboratory Standards. Reference method for broth dilution antifungal susceptibility testing of yeasts: Approved Standard, NCCLS document M27-A, 771 E. Lancaster Avenue, Villanova, PA, 19085, **1997**.
12. Clinical and Laboratory Standards Institute. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically: Approved Standard – Seventh Edition, CSLI document M07-A7, 940 West Valley Road, Suite 1400, Wayne, PA, 19087-1898, **2006.**

```
==========================================================================
Acq. Operator    : Wioleta
Acq. Instrument  : Instrument 1                    Location : Vial 1
Injection Date   : 3/30/2010 2:11:18 AM                 Inj :   1
                                                 Inj Volume : 10 µl
Acq. Method      : D:\METHODS\WIOLA.M
Last changed     : 3/30/2010 2:09:55 AM by Wioleta
                   (modified after loading)
Analysis Method  : D:\DATA\WIOLETA\BLANK000024.D\DA.M (WIOLA.M)
Last changed     : 3/30/2010 10:34:27 PM by Wioleta
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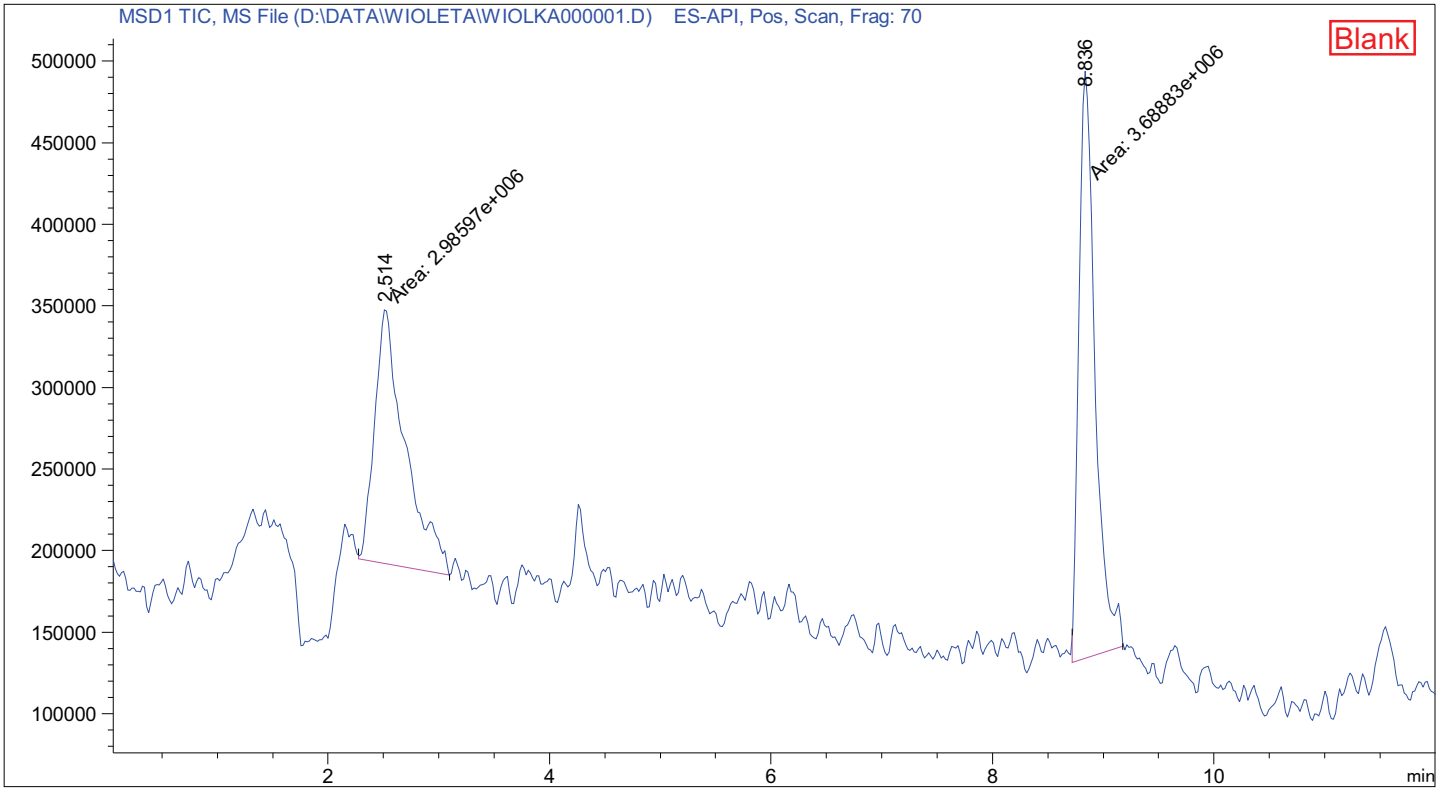


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Fraction collection off
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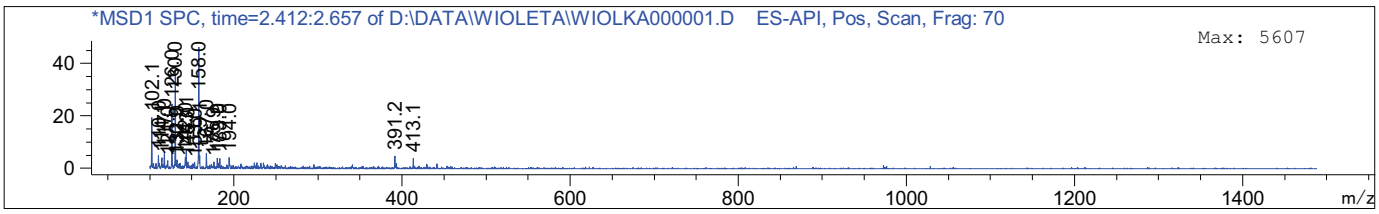
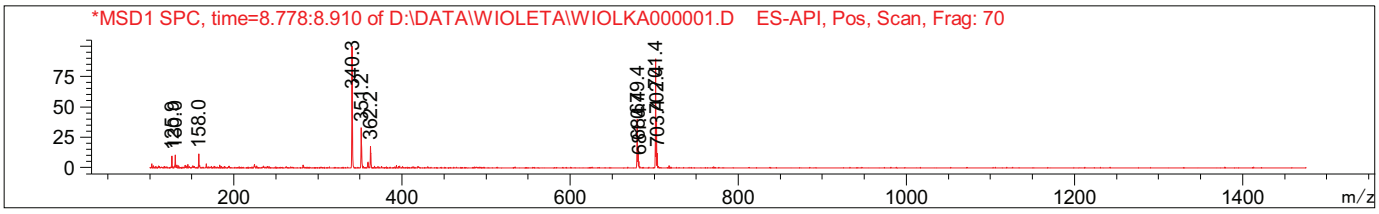
No Fractions found.
==========================================================================================
```

MS Signal: MSD1 TIC, MS File, ES-API, Pos, Scan, Frag: 70
Spectra averaged over upper half of peaks.
Noise Cutoff: 1000 counts.
Reportable Ion Abundance: > 10%.

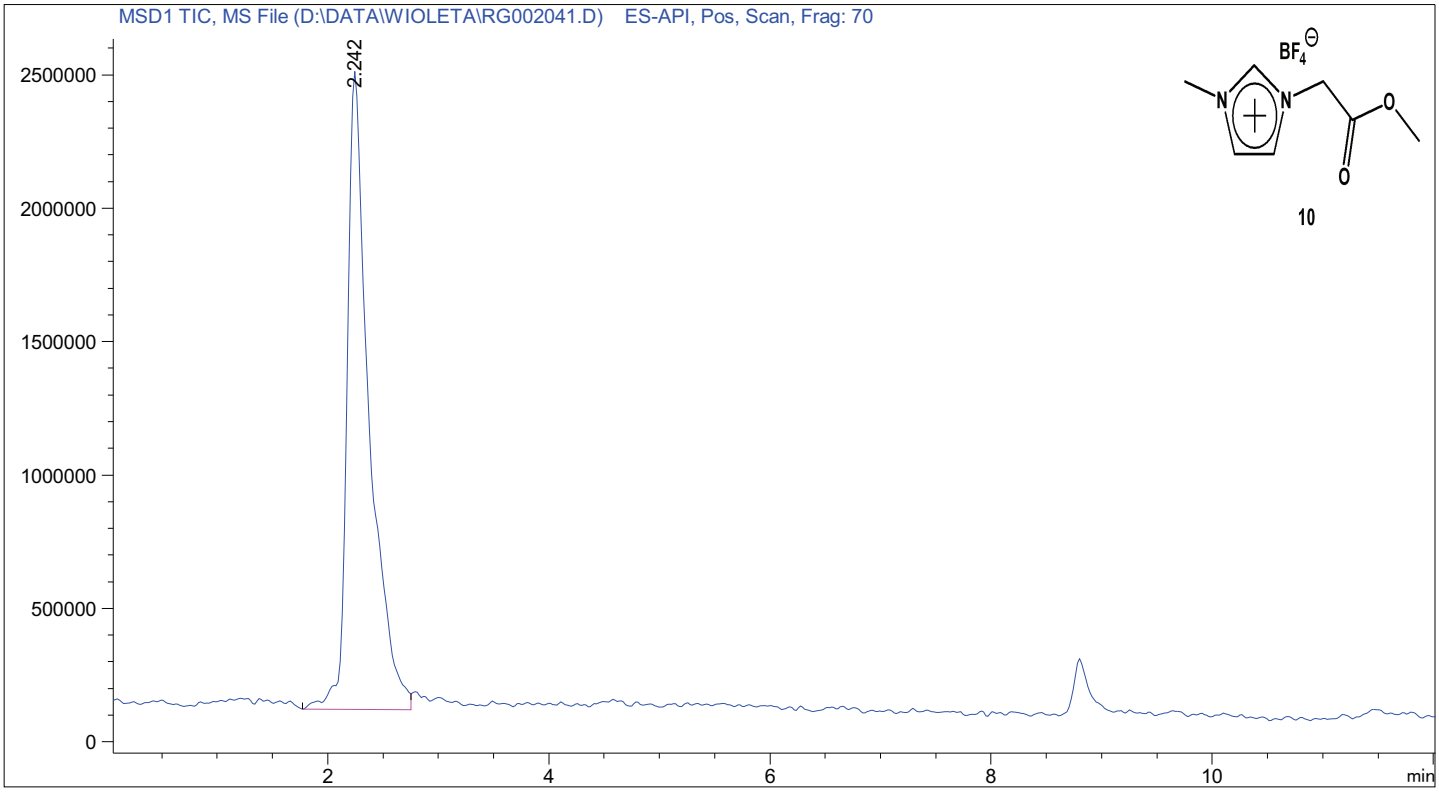
Retention Time (MS)	MS Area	Mol. Weight or Ion	
2.514	2985975	158.00	I
		130.00	I
		126.00	I
		102.10	I
8.836	3688831	703.40	I
		702.40	I
		701.40	I
		680.40	I
		679.40	I
		362.20	I
		351.20	I
		340.30	I
		158.00	I
		130.00	I





*** End of Report ***

```
==========================================================================
Acq. Operator    : Wioleta
Acq. Instrument : Instrument 1                    Location : Vial 7
Injection Date  : 3/30/2010 9:28:52 AM                 Inj :   1
                                                 Inj Volume : 10 µl
Acq. Method      : D:\METHODS\WIOLA.M
Last changed     : 3/30/2010 12:36:38 AM by Wioleta
Analysis Method : D:\DATA\EWA\EWA 070509 2009-11-16 16-51-09\007-1202.D\DA.M (METHOD1F70.M)
Last changed     : 10/15/2009 6:00:58 PM by Ewa
```

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==========================================================================
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No Fractions found.
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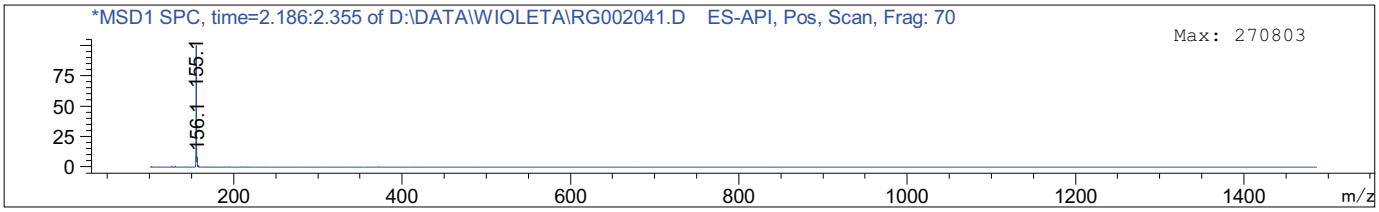
MS Signal: MSD1 TIC, MS File, ES-API, Pos, Scan, Frag: 70
Spectra averaged over upper half of peaks.
Noise Cutoff: 1000 counts.
Reportable Ion Abundance: > 10%.

Retention Time (MS)	MS Area	Mol. Weight or Ion	
2.242	33501210	155.10	I



*** End of Report ***

```
==========================================================================
Acq. Operator    : Wioleta
Acq. Instrument : Instrument 1                    Location : Vial 8
Injection Date  : 3/30/2010 10:29:47 AM               Inj :   1
                                                 Inj Volume : 10 µl
Acq. Method      : D:\METHODS\WIOLA.M
Last changed     : 3/30/2010 10:28:42 AM by Wioleta
Analysis Method : D:\DATA\EWA\EWA 070509 2009-11-16 16-51-09\007-1202.D\DA.M (METHOD1F70.M)
Last changed     : 10/15/2009 6:00:58 PM by Ewa
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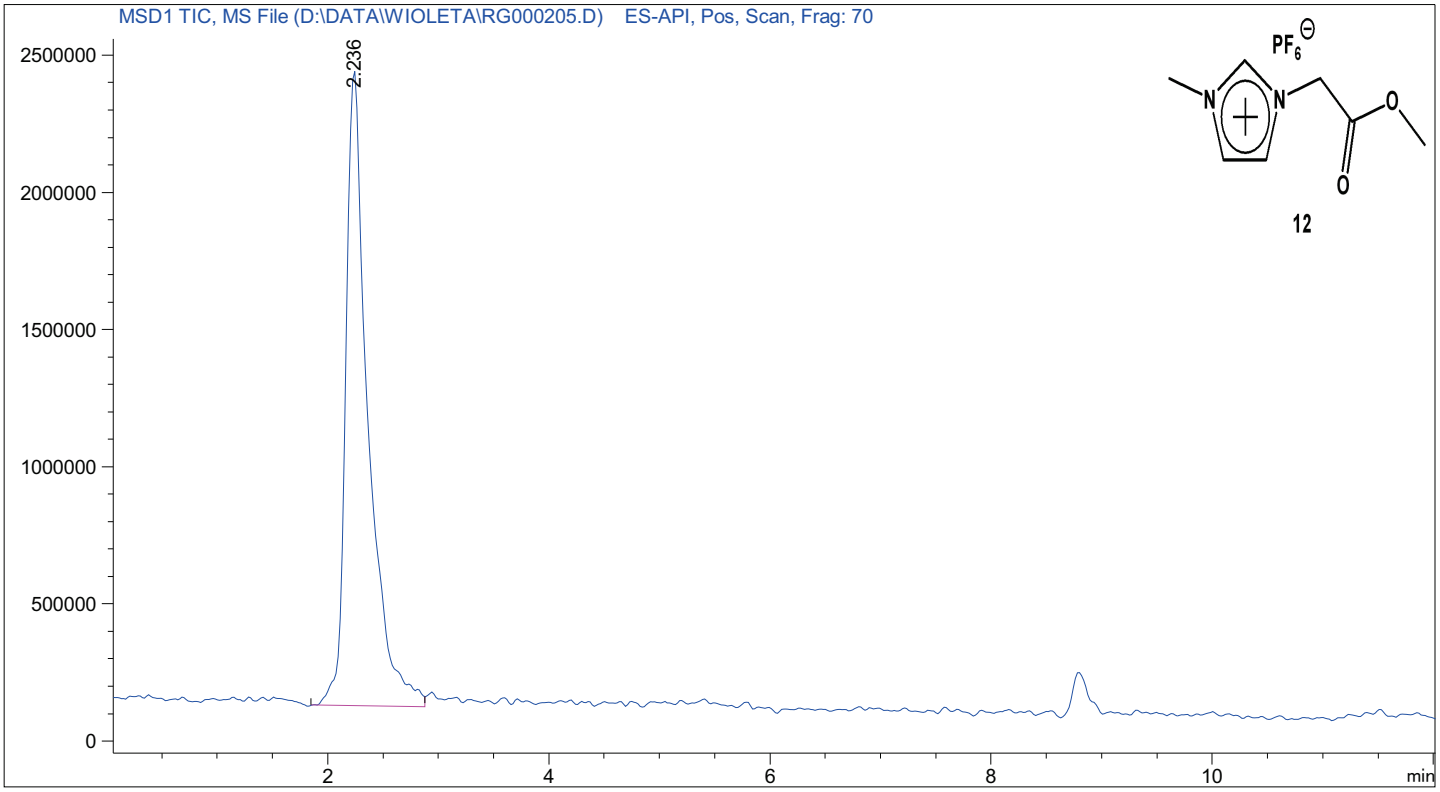


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==========================================================================
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Fraction collection off
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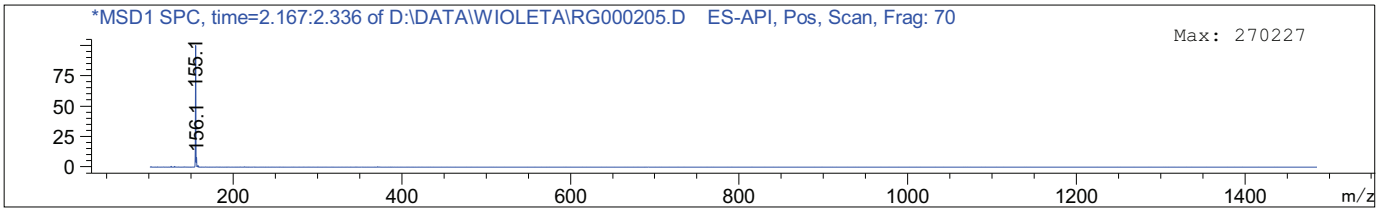
No Fractions found.
==========================================================================
```

MS Signal: MSD1 TIC, MS File, ES-API, Pos, Scan, Frag: 70
Spectra averaged over upper half of peaks.
Noise Cutoff: 1000 counts.
Reportable Ion Abundance: > 10%.

Retention Time (MS)	MS Area	Mol. Weight or Ion
2.236	32691932	155.10 I



*** End of Report ***

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==========================================================================
Acq. Operator    : Wioleta
Acq. Instrument : Instrument 1                    Location : P1-B-01
Injection Date  : 3/30/2010 11:04:48 PM               Inj :   1
                                                 Inj Volume : 10 µl
Acq. Method      : D:\METHODS\WIOLA.M
Last changed     : 3/30/2010 11:03:20 PM by Wioleta
Analysis Method : D:\DATA\WIOLETA\BLANK000024.D\DA.M (WIOLA.M)
Last changed     : 3/30/2010 10:34:27 PM by Wioleta
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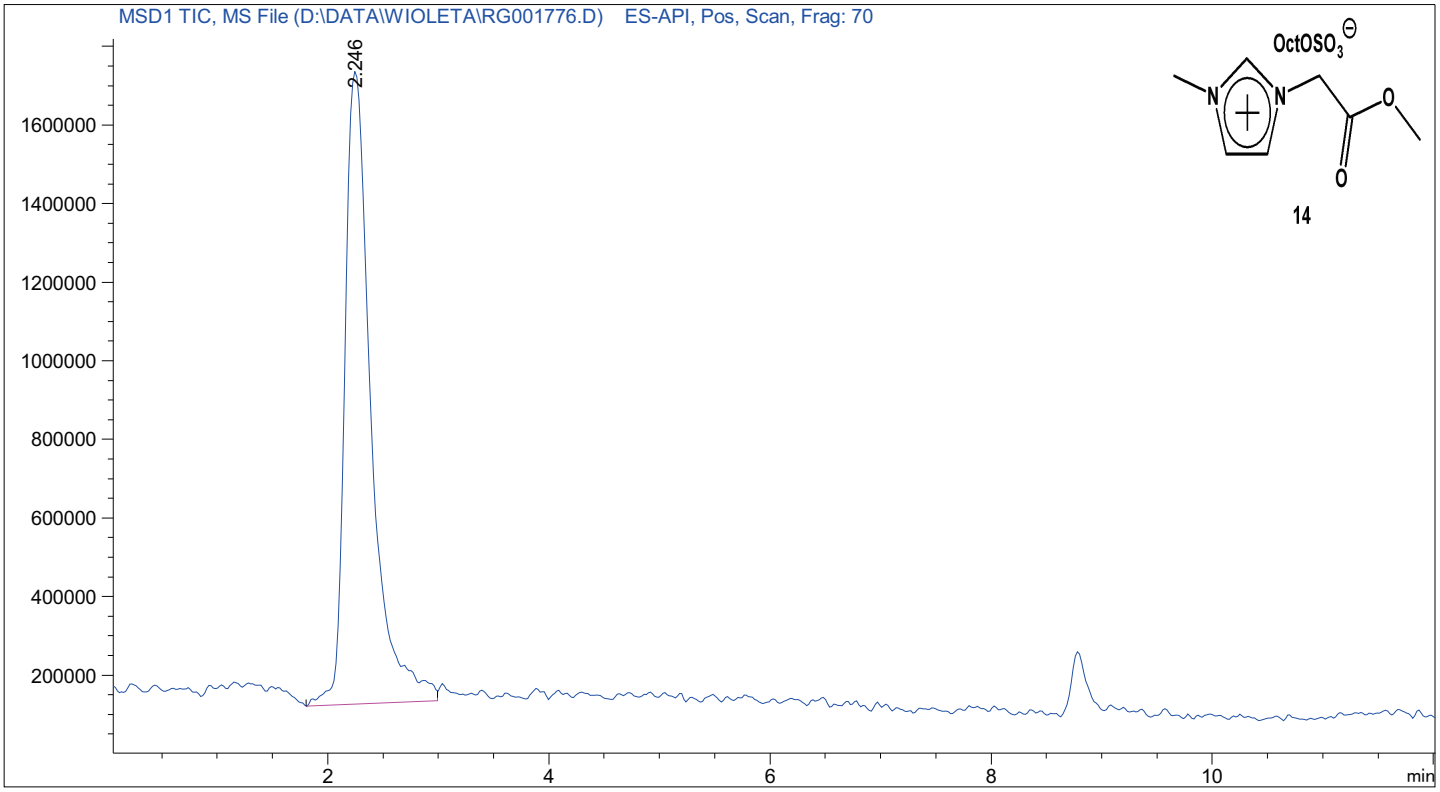


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==========================================================================
                        Fraction Information
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Fraction collection off
==========================================================================
No Fractions found.
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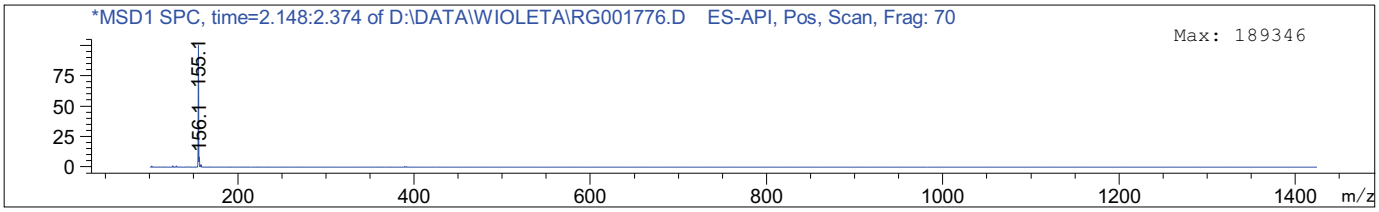
MS Signal: MSD1 TIC, MS File, ES-API, Pos, Scan, Frag: 70
Spectra averaged over upper half of peaks.
Noise Cutoff: 1000 counts.
Reportable Ion Abundance: > 10%.

Retention Time (MS)	MS Area	Mol. Weight or Ion
2.246	26704926	155.10 I



*** End of Report ***

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==========================================================================
Acq. Operator   : Wioleta
Acq. Instrument : Instrument 1                    Location : P1-C-01
Injection Date  : 3/30/2010 6:59:07 AM                 Inj :   1
                                                 Inj Volume : 10 µl
Acq. Method     : D:\METHODS\WIOLA.M
Last changed    : 3/30/2010 6:57:47 AM by Wioleta
                  (modified after loading)
Analysis Method : D:\DATA\EWA\EWA 070509 2009-11-16 16-51-09\007-1202.D\DA.M (METHOD1F70.M)
Last changed    : 10/15/2009 6:00:58 PM by Ewa
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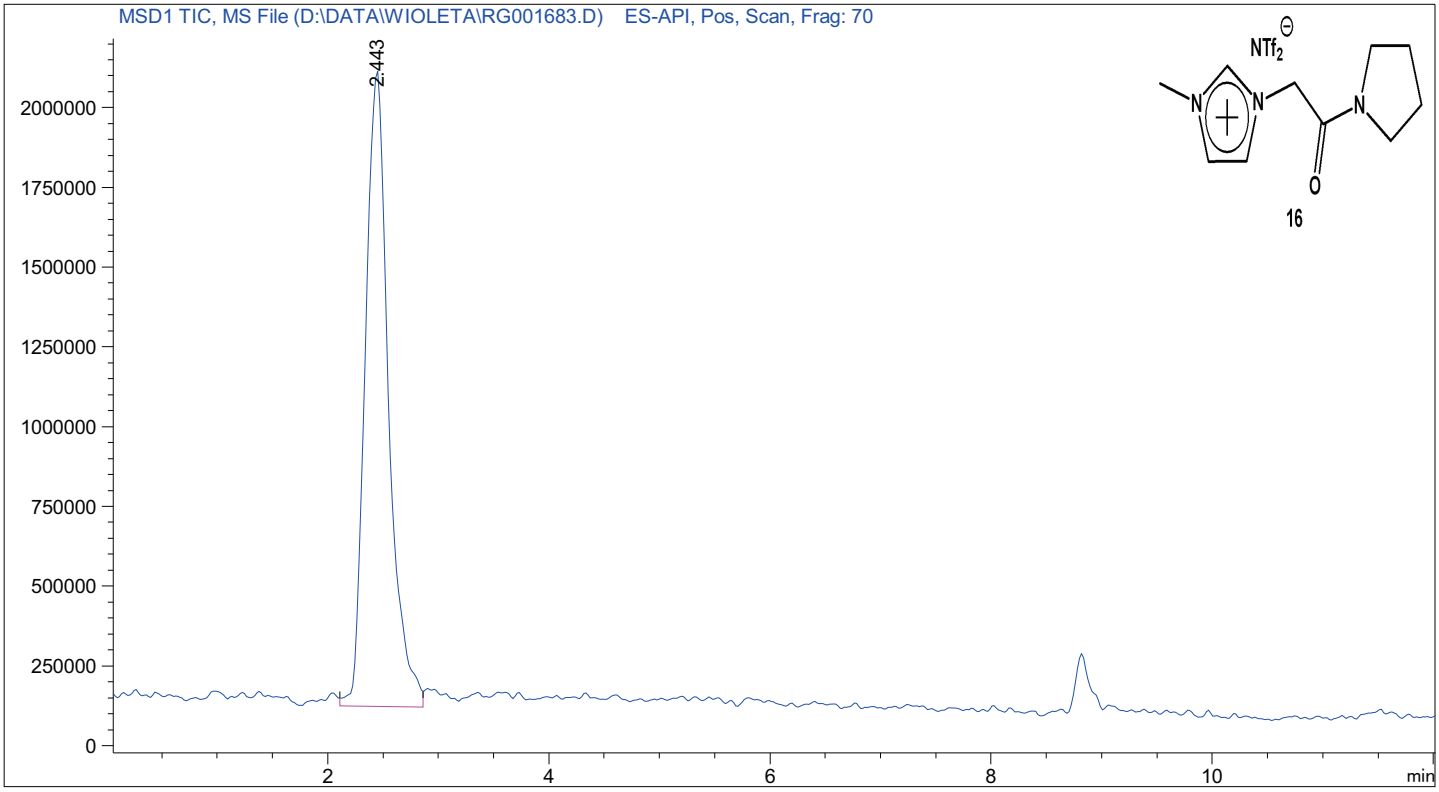


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==========================================================================
                        Fraction Information
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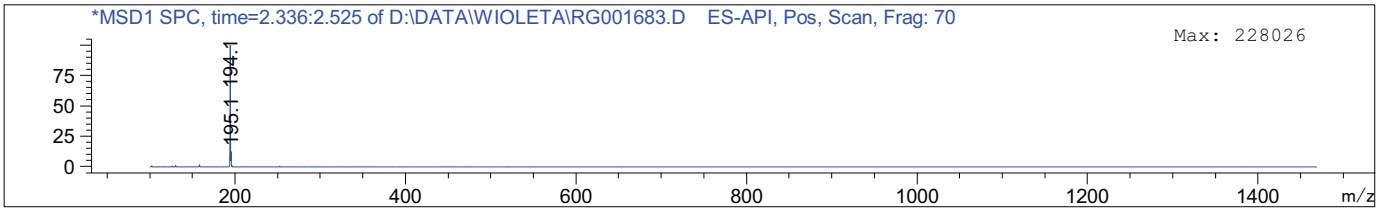
Fraction collection off
==========================================================================
No Fractions found.
==========================================================================
```

MS Signal: MSD1 TIC, MS File, ES-API, Pos, Scan, Frag: 70
Spectra averaged over upper half of peaks.
Noise Cutoff: 1000 counts.
Reportable Ion Abundance: > 10%.

Retention Time (MS)	MS Area	Mol. Weight or Ion
2.443	29307798	195.10 I
		194.10 I



*** End of Report ***

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==========================================================================
Acq. Operator    : Wioleta
Acq. Instrument : Instrument 1                    Location : Vial 2
Injection Date  : 3/30/2010 2:33:09 AM                 Inj :   1
                                                 Inj Volume : 10 µl
Acq. Method      : D:\METHODS\WIOLA.M
Last changed     : 3/30/2010 2:30:43 AM by Wioleta
                   (modified after loading)
Analysis Method : D:\DATA\WIOLETA\WIOLETA1  2010-03-30 00-45-14\001-0103.D\DA.M (WIOLA.M)
Last changed     : 3/30/2010 2:08:22 AM by Wioleta
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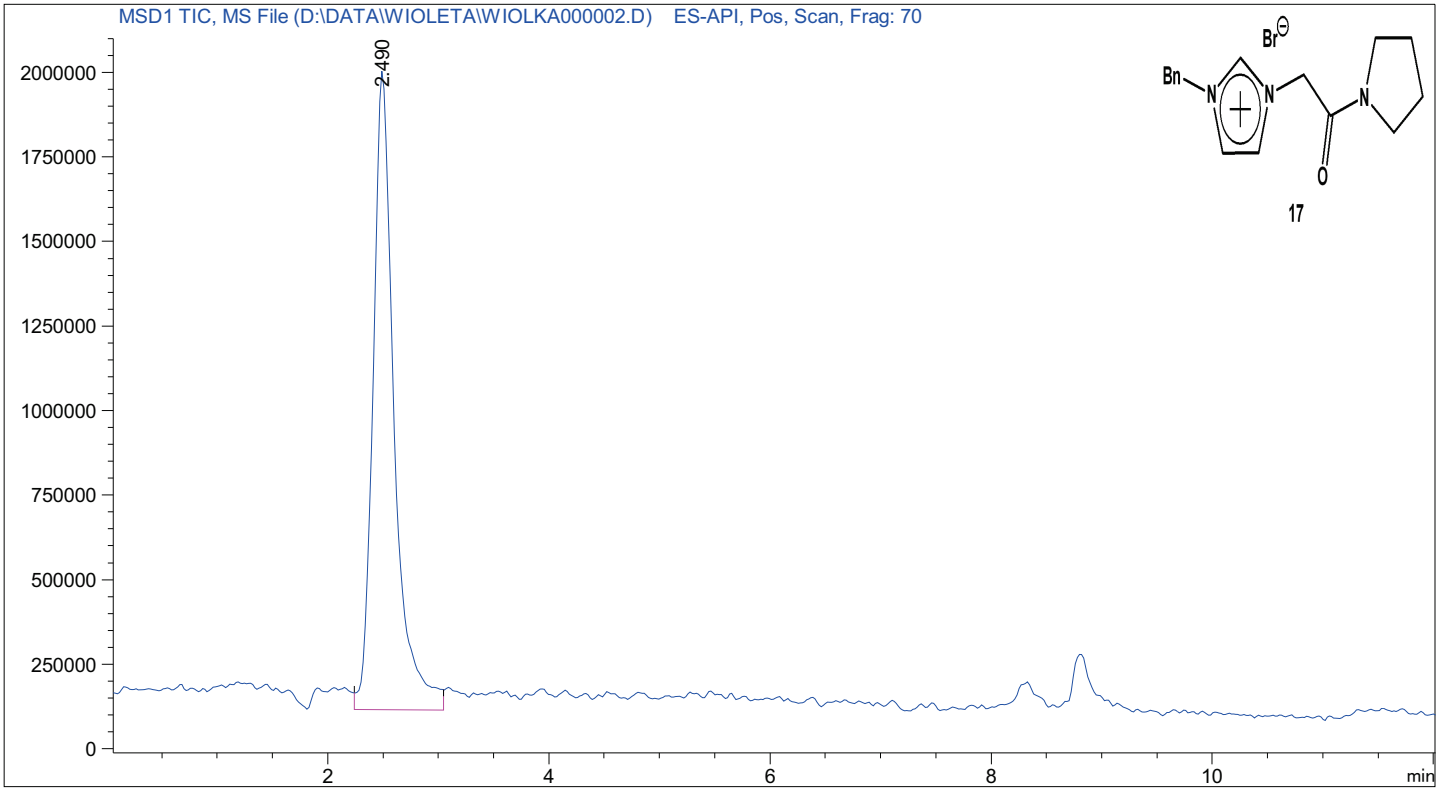


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==========================================================================================
                              Fraction Information
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Fraction collection off
==========================================================================================
No Fractions found.
==========================================================================================
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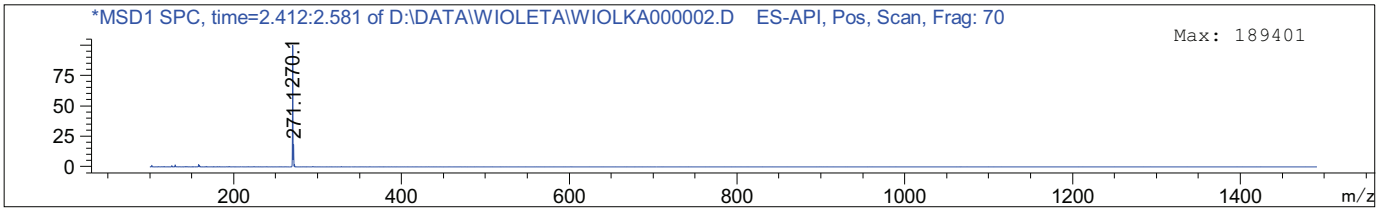
MS Signal: MSD1 TIC, MS File, ES-API, Pos, Scan, Frag: 70
Spectra averaged over upper half of peaks.
Noise Cutoff: 1000 counts.
Reportable Ion Abundance: > 10%.

Retention Time (MS)	MS Area	Mol. Weight or Ion
2.490	25102350	271.10 I
		270.10 I



*** End of Report ***

Data File D:\DATA\WIOLETA\BLANK000023.D
Sample Name: rg206

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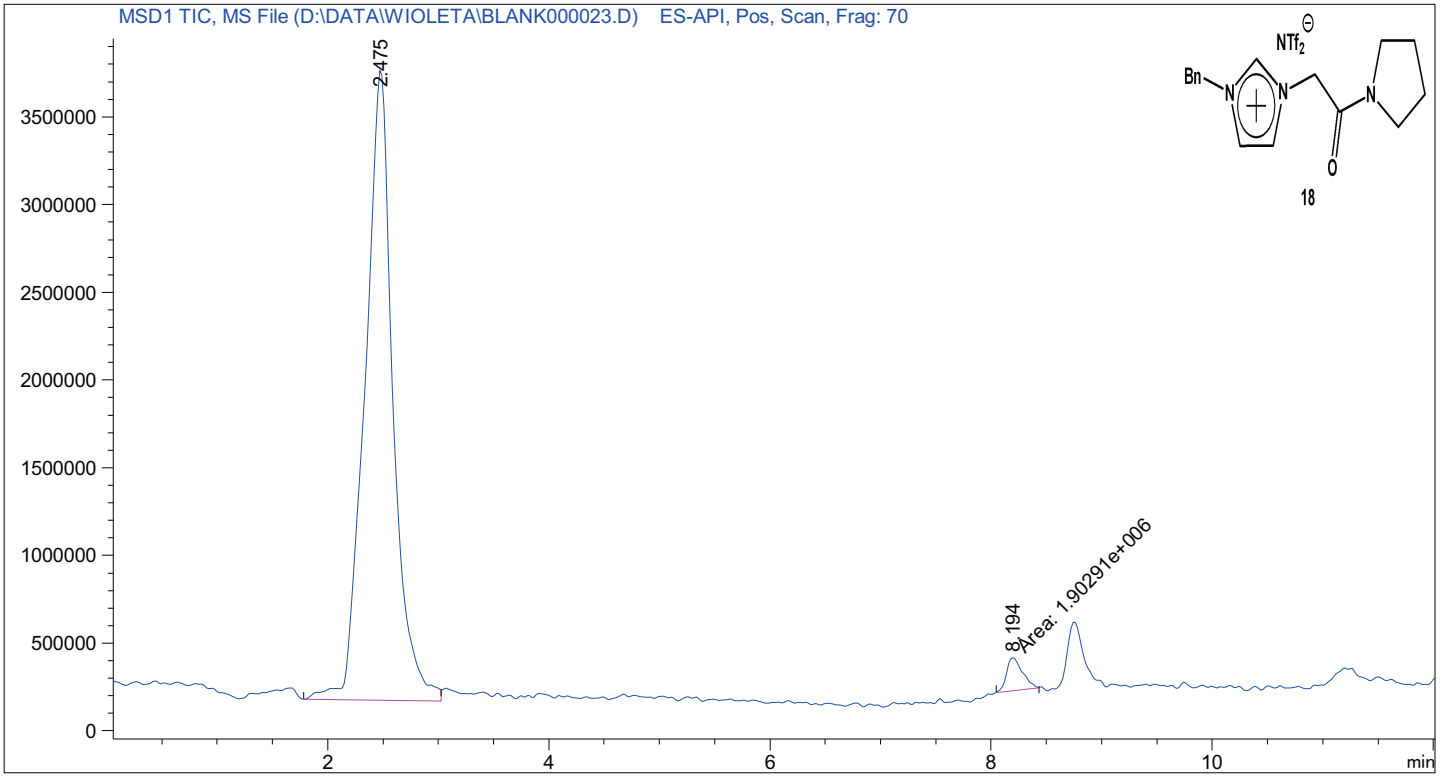
Acq. Operator : Wioleta
Acq. Instrument : Instrument 1 Location : Vial 5
Injection Date : 3/30/2010 9:14:57 PM Inj : 1
Inj Volume : 10 µl
Acq. Method : D:\METHODS\WIOLA.M
Last changed : 3/30/2010 12:31:13 PM by Wioleta
Analysis Method : D:\DATA\WIOLETA\BLANK000024.D\DA.M (WIOLA.M)
Last changed : 3/30/2010 10:34:27 PM by Wioleta



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Fraction Information

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Fraction collection off

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No Fractions found.

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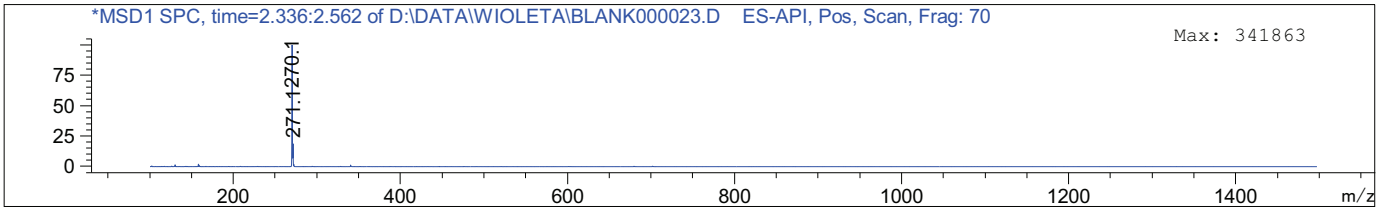
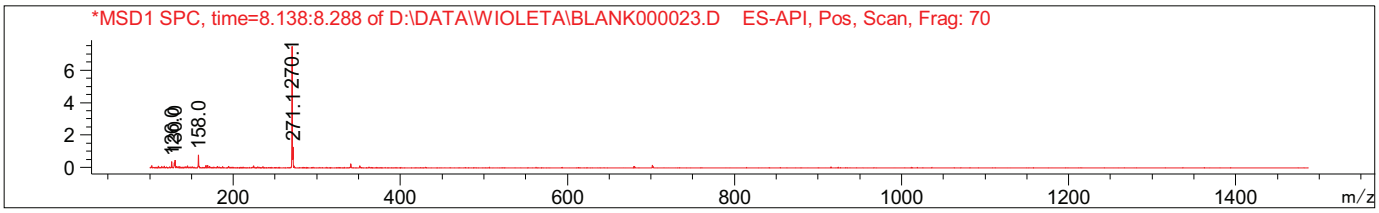
Data File D:\DATA\WIOLETA\BLANK000023.D
Sample Name: rg206

MS Signal: MSD1 TIC, MS File, ES-API, Pos, Scan, Frag: 70
Spectra averaged over upper half of peaks.
Noise Cutoff: 1000 counts.
Reportable Ion Abundance: > 10%.

Retention Time (MS)	MS Area	Mol. Weight or Ion
2.475	63339640	271.10 I
		270.10 I
8.194	1902914	271.10 I
		270.10 I
		158.00 I





*** End of Report ***

Data File D:\DATA\WIOLETA\WIOLETA1 2010-03-30 08-05-34\1CB-0101.D
Sample Name: RG169

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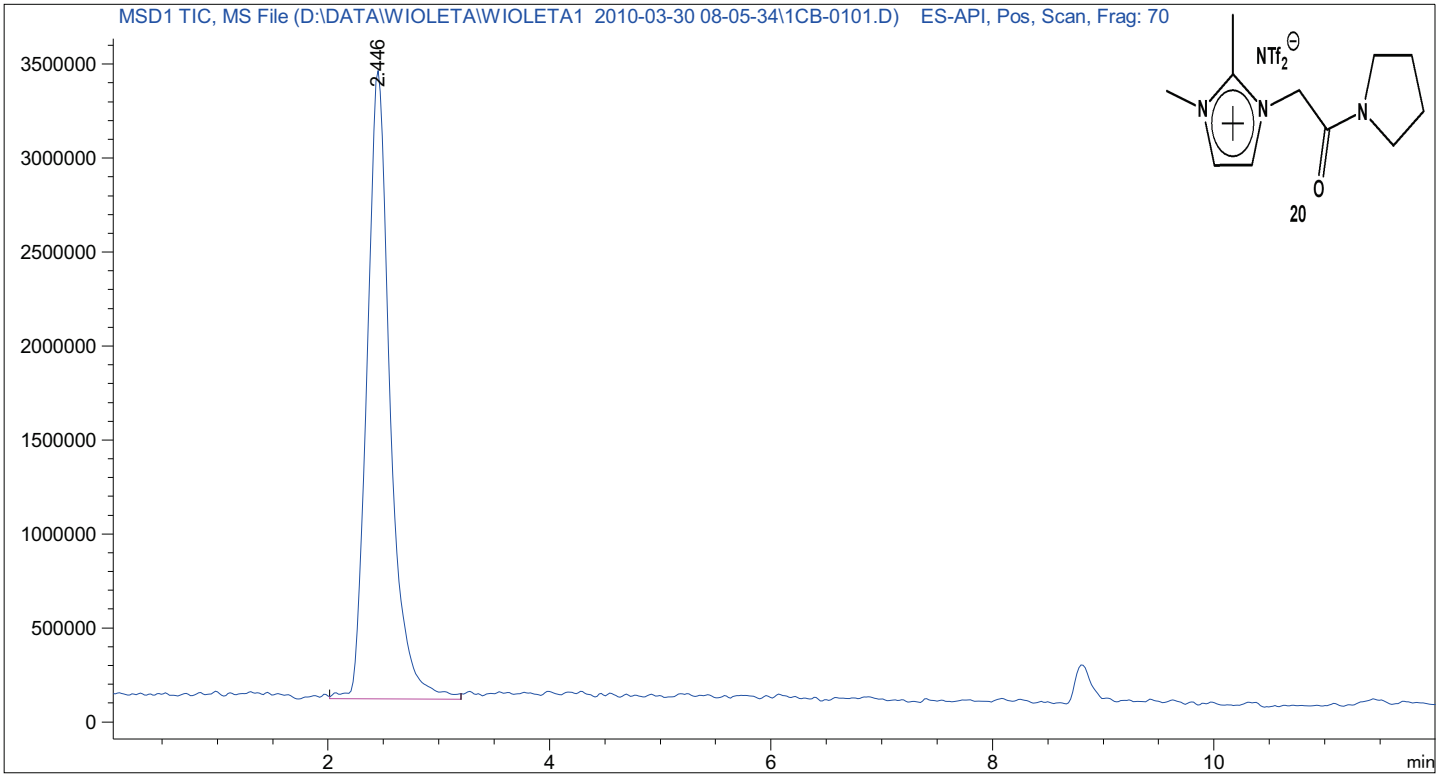
Acq. Operator : Wioleta Seq. Line : 1
Acq. Instrument : Instrument 1 Location : P1-C-02
Injection Date : 3/30/2010 8:06:04 AM Inj : 1
Inj Volume : 10 µl
Acq. Method : D:\DATA\WIOLETA\WIOLETA1 2010-03-30 08-05-34\WIOLA.M
Last changed : 3/30/2010 12:36:38 AM by Wioleta
Analysis Method : D:\DATA\EWA\EWA 070509 2009-11-16 16-51-09\007-1202.D\DA.M (METHOD1F70.M)
Last changed : 10/15/2009 6:00:58 PM by Ewa



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Fraction Information

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Fraction collection off

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No Fractions found.

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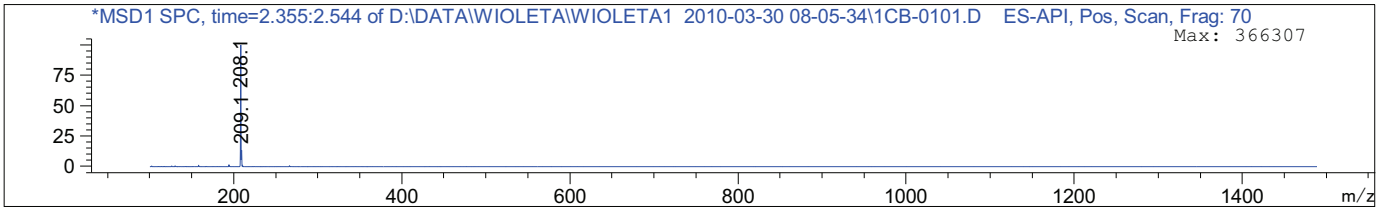
Data File D:\DATA\WIOLETA\WIOLETA1 2010-03-30 08-05-34\1CB-0101.D
Sample Name: RG169

MS Signal: MSD1 TIC, MS File, ES-API, Pos, Scan, Frag: 70
Spectra averaged over upper half of peaks.
Noise Cutoff: 1000 counts.
Reportable Ion Abundance: > 10%.

Retention Time (MS)	MS Area	Mol. Weight or Ion
2.446	48814408	209.10 I
		208.10 I



*** End of Report ***