

## SUPPORTING INFORMATION

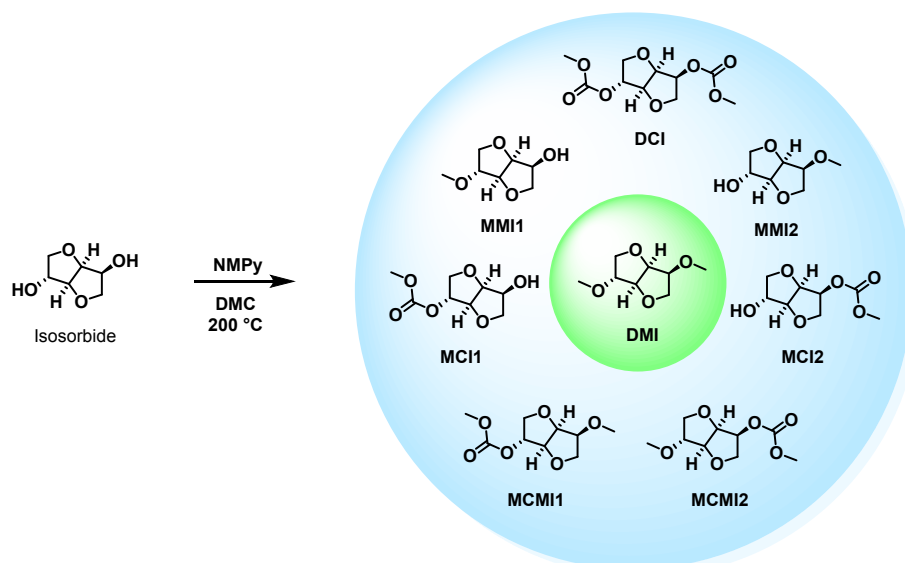
# Dimethyl isosorbide via organocatalyst N-methyl pyrrolidine: scaling up, purification and concurrent reaction pathways

Mattia Annatelli, Davide Dalla Torre, Manuele Musolino and Fabio Aricò\*

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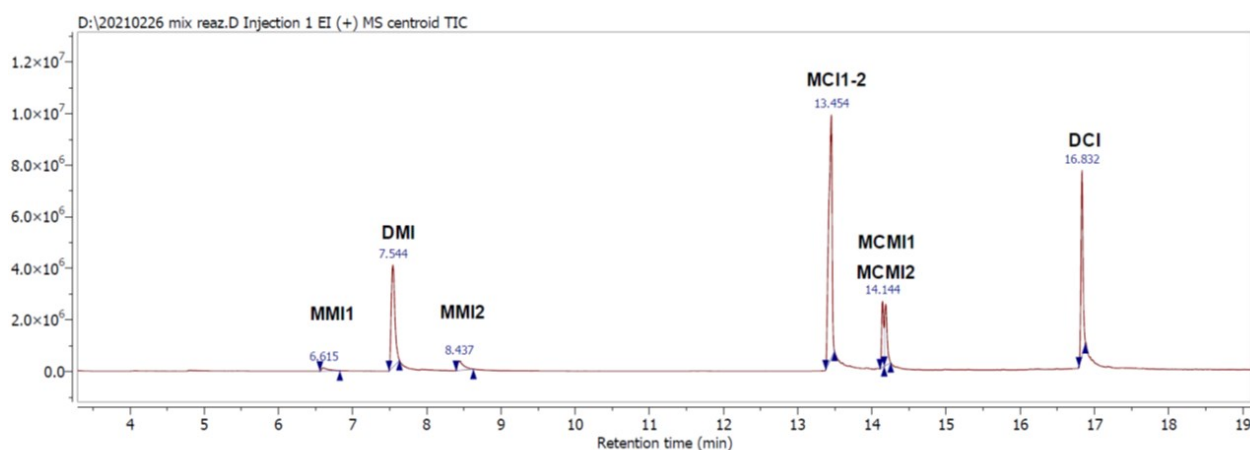
## GC-MS method used for the analysis of isosorbide conversion into DMI



**Scheme S1.** Synthesis of dimethyl isosorbide (DMI) and its reaction intermediates.

**Table S1.** GC System 6890N parameters.

| Temperature ramp rate        |             |                           |
|------------------------------|-------------|---------------------------|
| Rate (°C*min <sup>-1</sup> ) | Temperature | Hold (min)                |
| ---                          | 110 °C      | 2.00                      |
| 5                            | 130 °C      | 5                         |
| 20                           | 250 °C      | 5                         |
| Pressure                     |             | 8.8 psi                   |
| Flow                         |             | 13.7 mL*min <sup>-1</sup> |
| Column model                 |             | Agilent 19091S-433        |



**Figure S1.** GC System 6890N analysis.

## pKa Table of nitrogen organocatalyst<sup>1</sup>

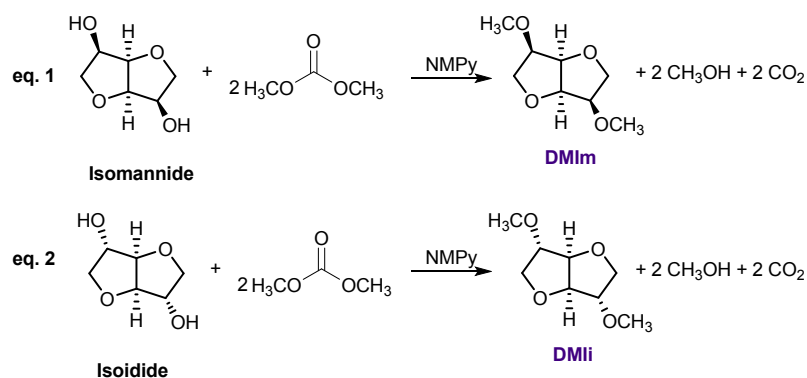
**Table S2.** Pka Table of nitrogen organocatalyst

| # | <i>Base</i>       | <i>pKa value</i> |
|---|-------------------|------------------|
| 1 | TBD               | 26.02            |
| 2 | DBU               | 24.31            |
| 3 | Et <sub>3</sub> N | 18.83            |
| 4 | NMPy              | 18.42            |
| 5 | DABCO             | 18.29            |
| 6 | DMAP              | 17.96            |
| 7 | Pyridine          | 5.2              |

<sup>1</sup> J. R. Ochoa-Gómez, L. Lorenzo-Ibarreta, C. Diñeiro-García and O. Gómez-Jiménez-Aberasturi, *RSC Adv.*, 2020, **10**, 18728-18739.

## Dimethyl isomannide and dimethyl isoidide via DMC chemistry

**Table S3.** Methylation of isomannide and isoidide<sup>a</sup>



| # | Substrate  | Amount | P<br>bar | Conv<br>% | Selectivity %   |                 |                 |
|---|------------|--------|----------|-----------|-----------------|-----------------|-----------------|
|   |            | (g)    |          |           | MM <sup>b</sup> | DM <sup>c</sup> | Other compounds |
| 1 | Isoidide   | 1      | 14       | 100       | ---             | DMli 100        | 0               |
| 2 | Isoidide   | 5      | 20       | 100       | ---             | DMli 100        | 0               |
| 3 | Isomannide | 1      | 14       | 100       | 6               | DMIm 94         | 0               |
| 4 | Isomannide | 5      | 16       | 100       | 5               | DMIm 95         | 0               |

<sup>a</sup> Reaction conditions: NMPy: 0.5 eq.mol, Temperature: 200°C, time: 12 h, <sup>b</sup>Monomethyl derivatives, <sup>c</sup>Dimethyl derivatives

## Methylation of isosorbide over time

**Table S4.** Methylation of isosorbide over time<sup>a</sup>

| T   | Time   | P   | Conv | Selectivity % |     |      |        |         |     |
|-----|--------|-----|------|---------------|-----|------|--------|---------|-----|
| °C  | h      | bar | %    | MMI1          | DMI | MMI2 | MCI1-2 | MCMI1-2 | DCI |
| 140 | - 0.5  | 0   | 70   | 20            | 1   | 3    | 38     | 20      | 16  |
| 160 | - 0.33 | 5   | 97   | 22            | 3   | 42   | 7      | 15      | 11  |
| 180 | - 0.16 | 10  | 97   | 26            | 6   | 51   | 0      | 17      | 0   |
| 200 | 0      | 16  | 100  | 33            | 15  | 35   | 0      | 17      | 0   |
| 200 | 0.33   | 16  | 100  | 28            | 28  | 17   | 0      | 27      | 0   |
| 200 | 0.66   | 16  | 100  | 24            | 39  | 8    | 0      | 29      | 0   |
| 200 | 1      | 16  | 100  | 25            | 38  | 13   | 0      | 24      | 0   |
| 200 | 2      | 16  | 100  | 22            | 46  | 10   | 0      | 22      | 0   |
| 200 | 4      | 16  | 100  | 14            | 68  | 5    | 0      | 13      | 0   |
| 200 | 6      | 16  | 100  | 11            | 75  | 2    | 0      | 12      | 0   |
| 200 | 8      | 16  | 100  | 6             | 94  | 0    | 0      | 0       | 0   |
| 200 | 10     | 16  | 100  | 6             | 94  | 0    | 0      | 0       | 0   |
| 200 | 12     | 15  | 100  | 2             | 98  | 0    | 0      | 0       | 0   |

<sup>a</sup> Reaction conditions: Isosorbide (1 g), DMC (50 eq. mol), NMPy (0.5 eq. mol)

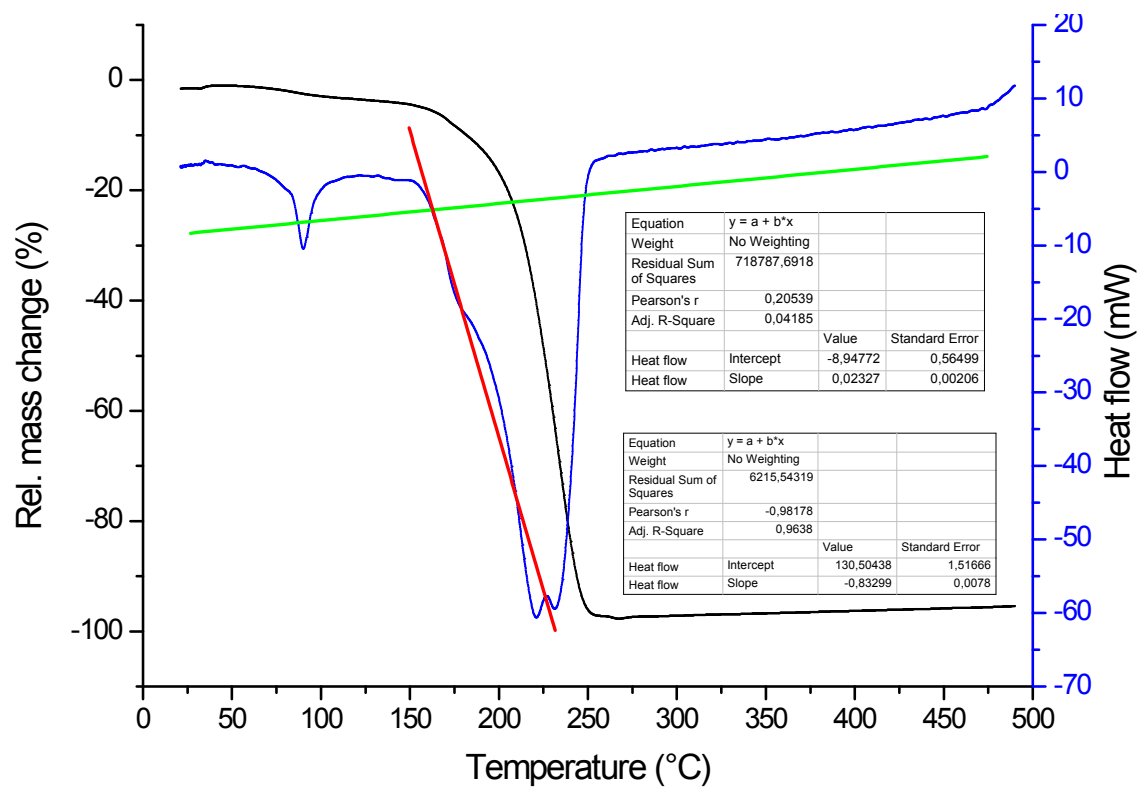
## DCI decarboxylation reaction over time

**Table S5.** DCI decarboxylation over time<sup>a</sup>

| T   | time   | P   | Conv | Selectivity % |     |      |        |         |
|-----|--------|-----|------|---------------|-----|------|--------|---------|
| °C  | h      | bar | %    | MMI1          | DMI | MMI2 | MCI1-2 | MCMI1-2 |
| 140 | - 0.5  | 0   | 24   | 0             | 0   | 0    | 81     | 19      |
| 160 | - 0.33 | 5   | 30   | 0             | 0   | 0    | 85     | 15      |
| 180 | - 0.16 | 8   | 35   | 3             | 1   | 2    | 64     | 30      |
| 200 | 0      | 10  | 50   | 6             | 2   | 2    | 58     | 32      |
| 200 | 0.33   | 15  | 65   | 8             | 6   | 2    | 38     | 46      |
| 200 | 0.66   | 15  | 65   | 7             | 10  | 5    | 18     | 60      |
| 200 | 1      | 12  | 85   | 10            | 15  | 7    | 11     | 57      |
| 200 | 2      | 15  | 100  | 16            | 24  | 7    | 3      | 50      |
| 200 | 4      | 15  | 100  | 17            | 27  | 7    | 2      | 47      |
| 200 | 6      | 15  | 100  | 10            | 36  | 4    | 2      | 48      |
| 200 | 8      | 15  | 100  | 9             | 52  | 3    | 2      | 34      |
| 200 | 10     | 15  | 100  | 8             | 71  | 2    | 0      | 19      |
| 200 | 12     | 15  | 100  | 6             | 84  | 2    | 0      | 8       |

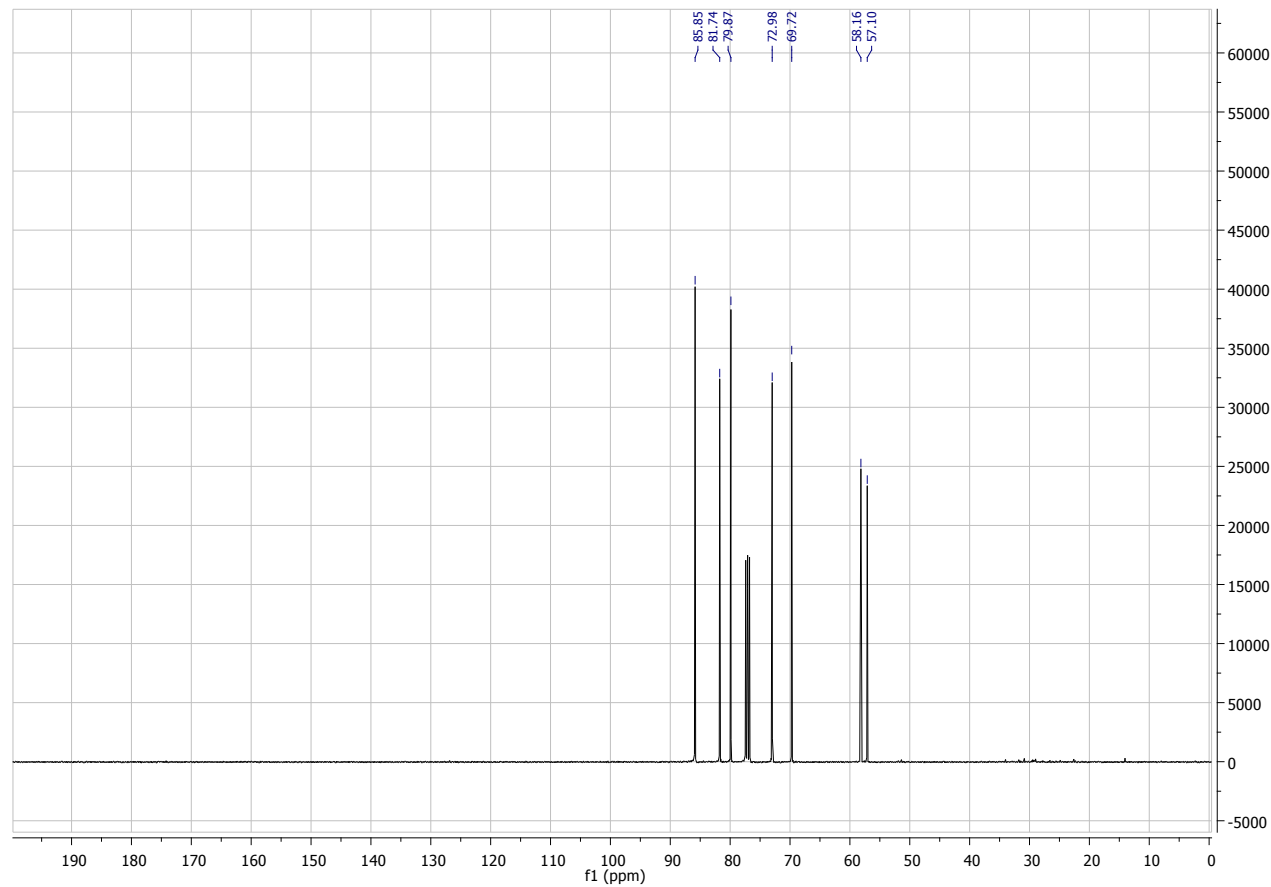
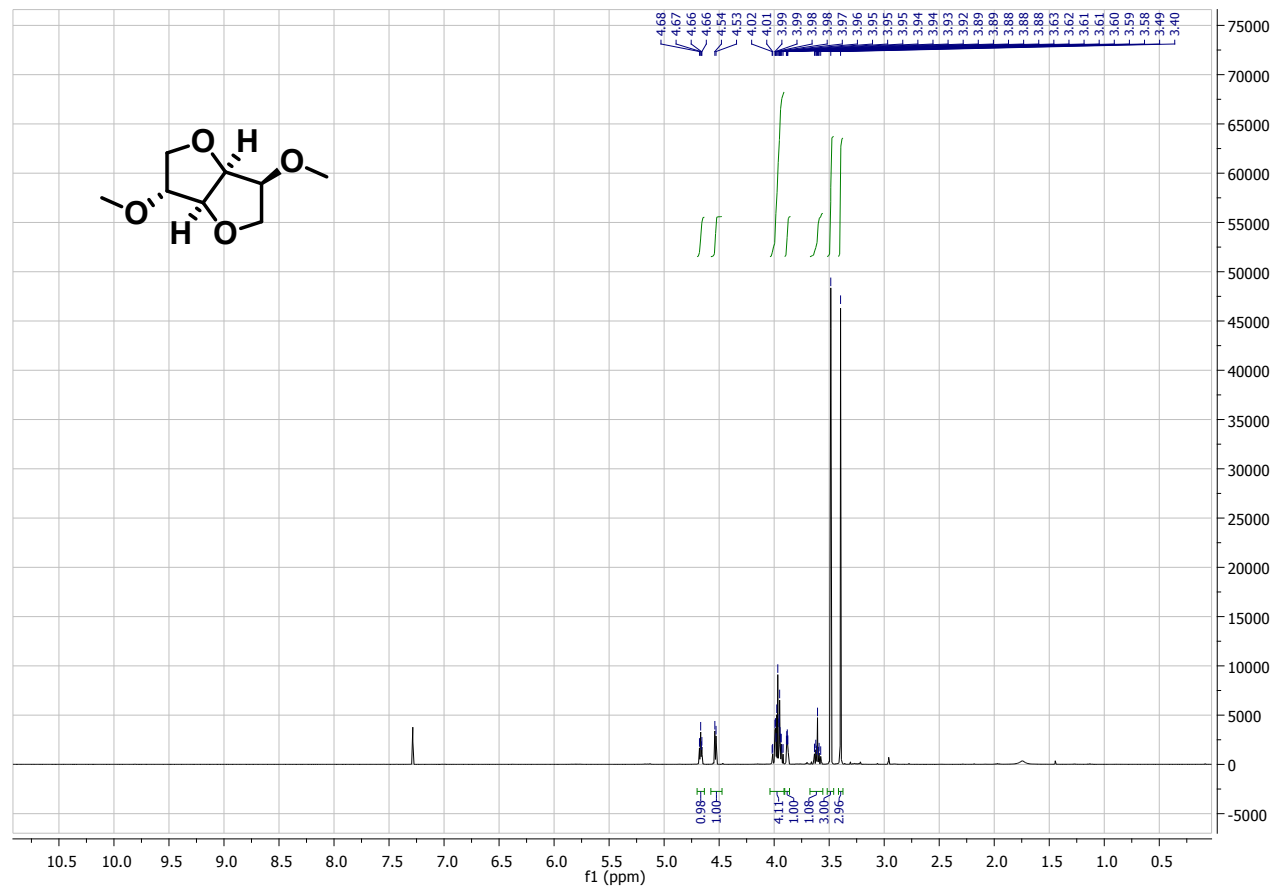
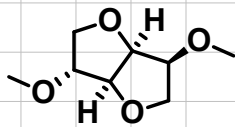
<sup>a</sup> Reaction conditions: DCI (0.5 g), DMC (50 eq. mol), NMPy (0.5 eq. mol)

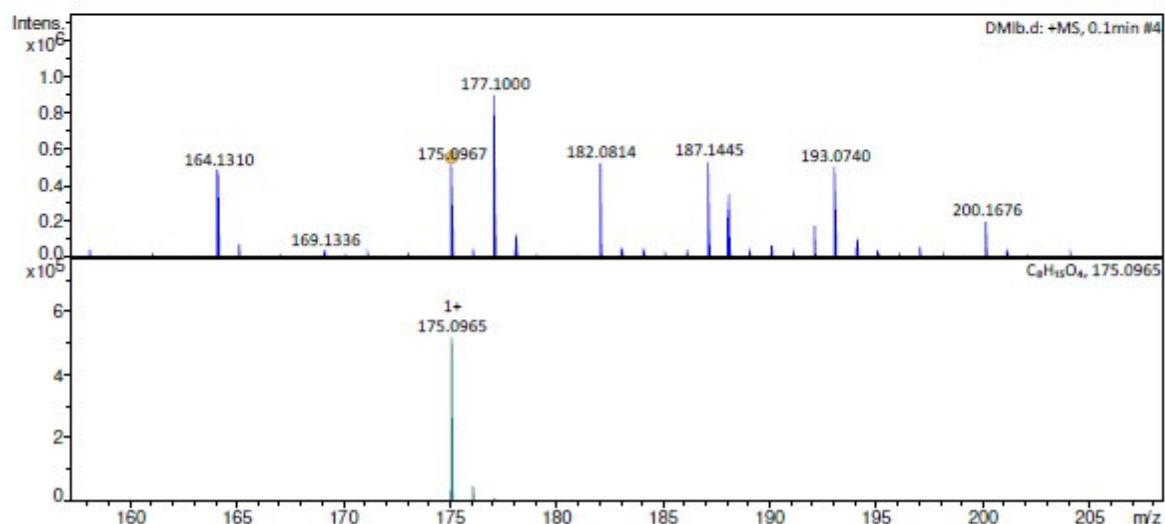
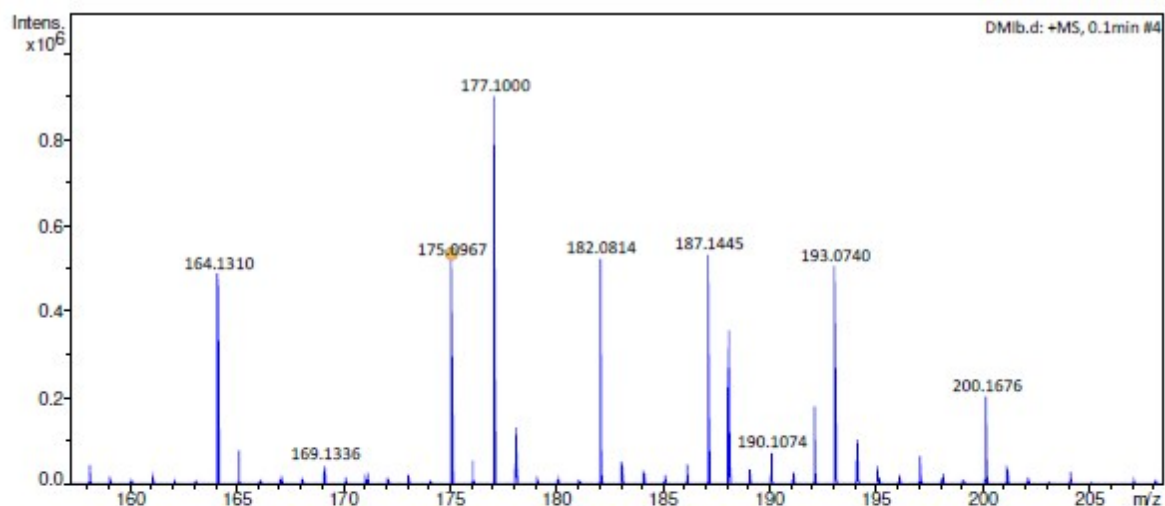
Thermogravimetric analysis of DMPyC



## **$^1\text{H}$ -NMR, $^{13}\text{C}$ -NMR & Mass – Spectra**

Dimethyl Isosorbide (DMI)





| Meas. m/z | # | Ion Formula | m/z      | err [ppm] | mSigma | # mSigma | Score  | rdB | e <sup>-</sup> | Conf | N-Rule |
|-----------|---|-------------|----------|-----------|--------|----------|--------|-----|----------------|------|--------|
| 175.0967  | 1 | C8H15O4     | 175.0965 | -1.4      | 620.9  | 1        | 100.00 | 2.0 | even           |      | ok     |
|           | 2 | C4H11N6O2   | 175.0938 | -16.7     | 623.7  | 2        | 7.88   | 3.0 | even           |      | ok     |
|           | 3 | C9H11N4     | 175.0978 | 6.3       | 624.5  | 3        | 25.71  | 7.0 | even           |      | ok     |

#### Analysis Info

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 Sample Name DMib  
 Comment

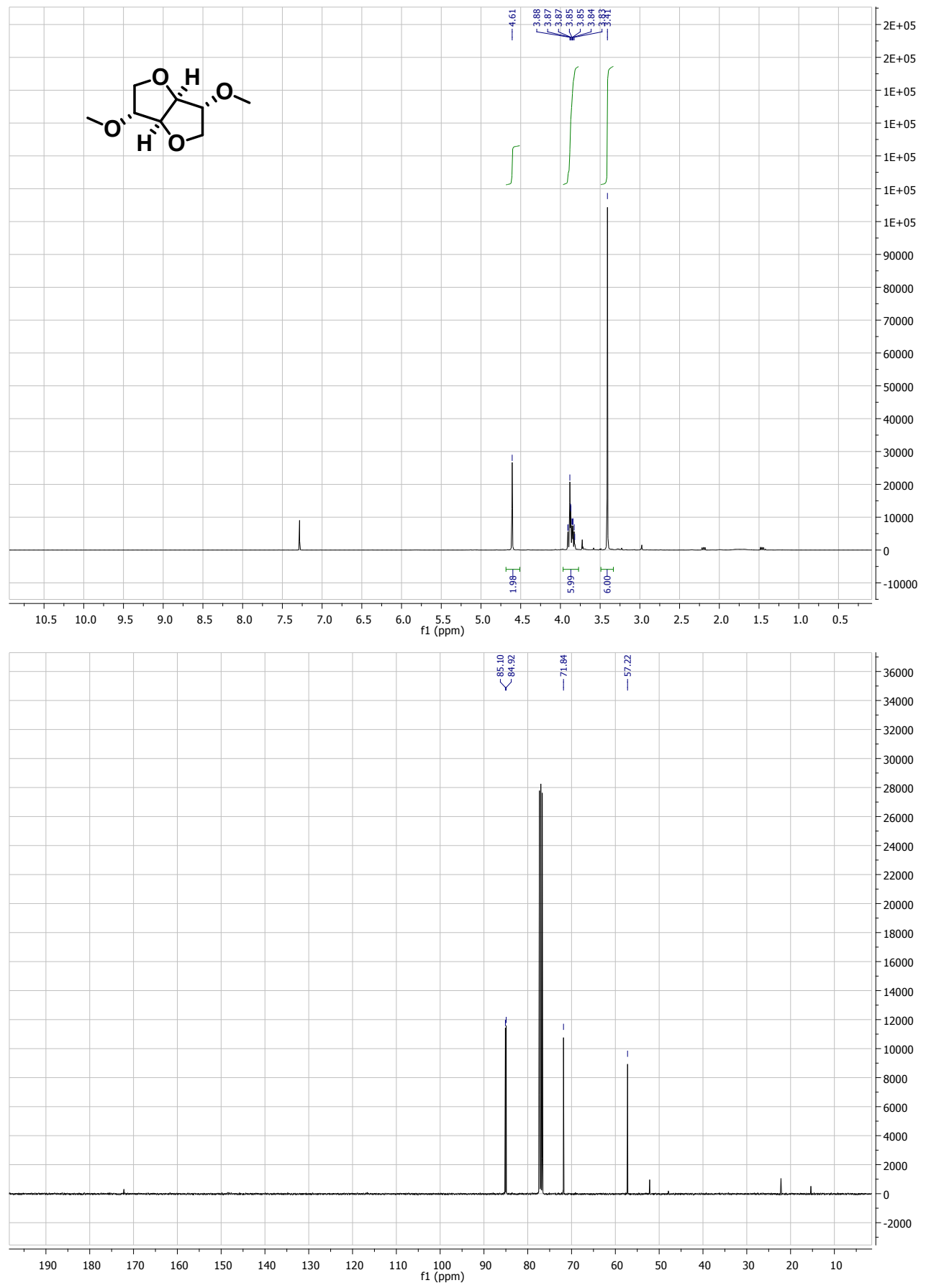
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Operator Demo User  
 Instrument compact 8255754.20209

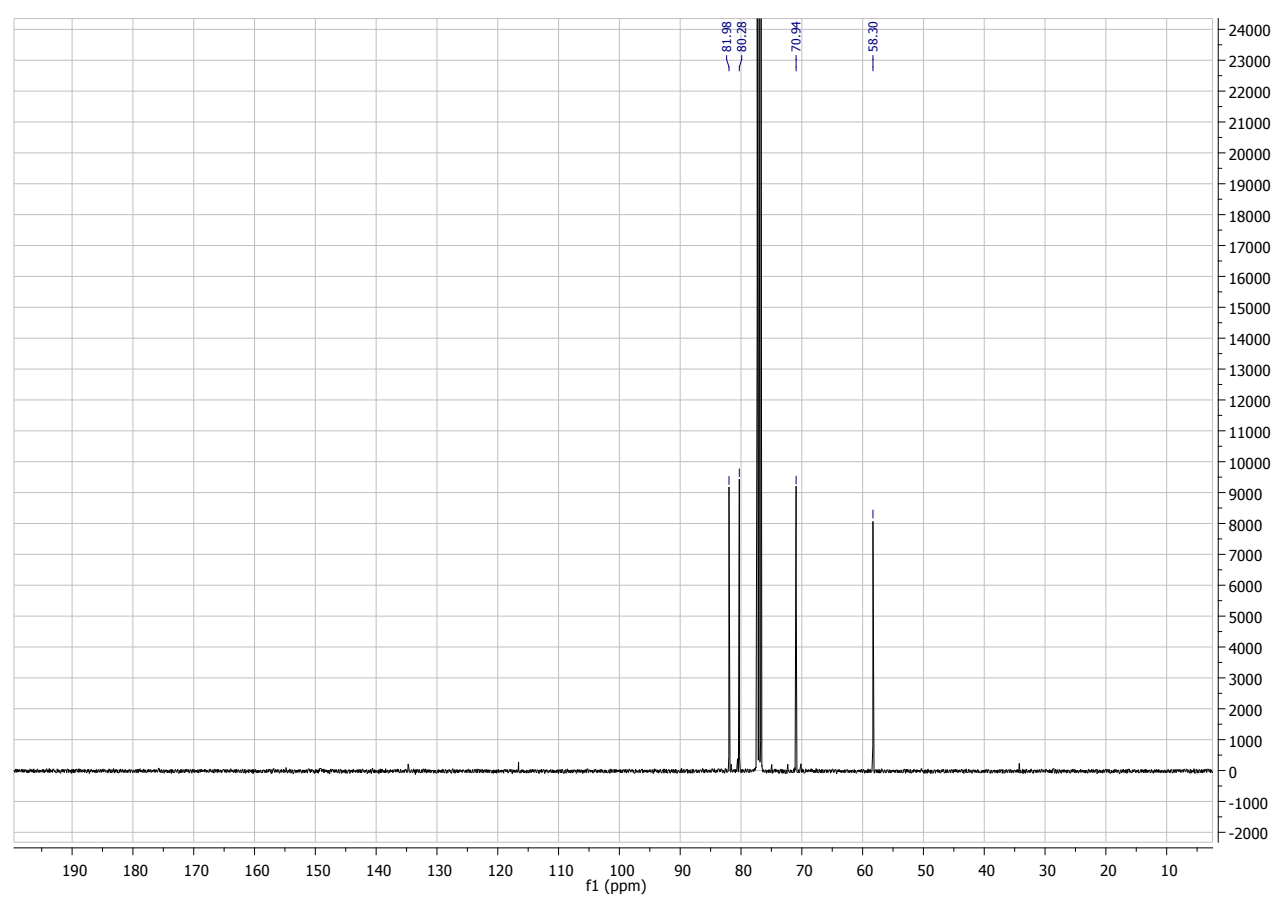
#### Acquisition Parameter

|             |            |                       |           |                  |           |
|-------------|------------|-----------------------|-----------|------------------|-----------|
| Source Type | ESI        | Ion Polarity          | Positive  | Set Nebulizer    | 0.4 Bar   |
| Focus       | Not active | Set Capillary         | 4500 V    | Set Dry Heater   | 180 °C    |
| Scan Begin  | 100 m/z    | Set End Plate Offset  | -500 V    | Set Dry Gas      | 4.0 l/min |
| Scan End    | 600 m/z    | Set Collision Cell RF | 650.0 Vpp | Set Divert Valve | Source    |

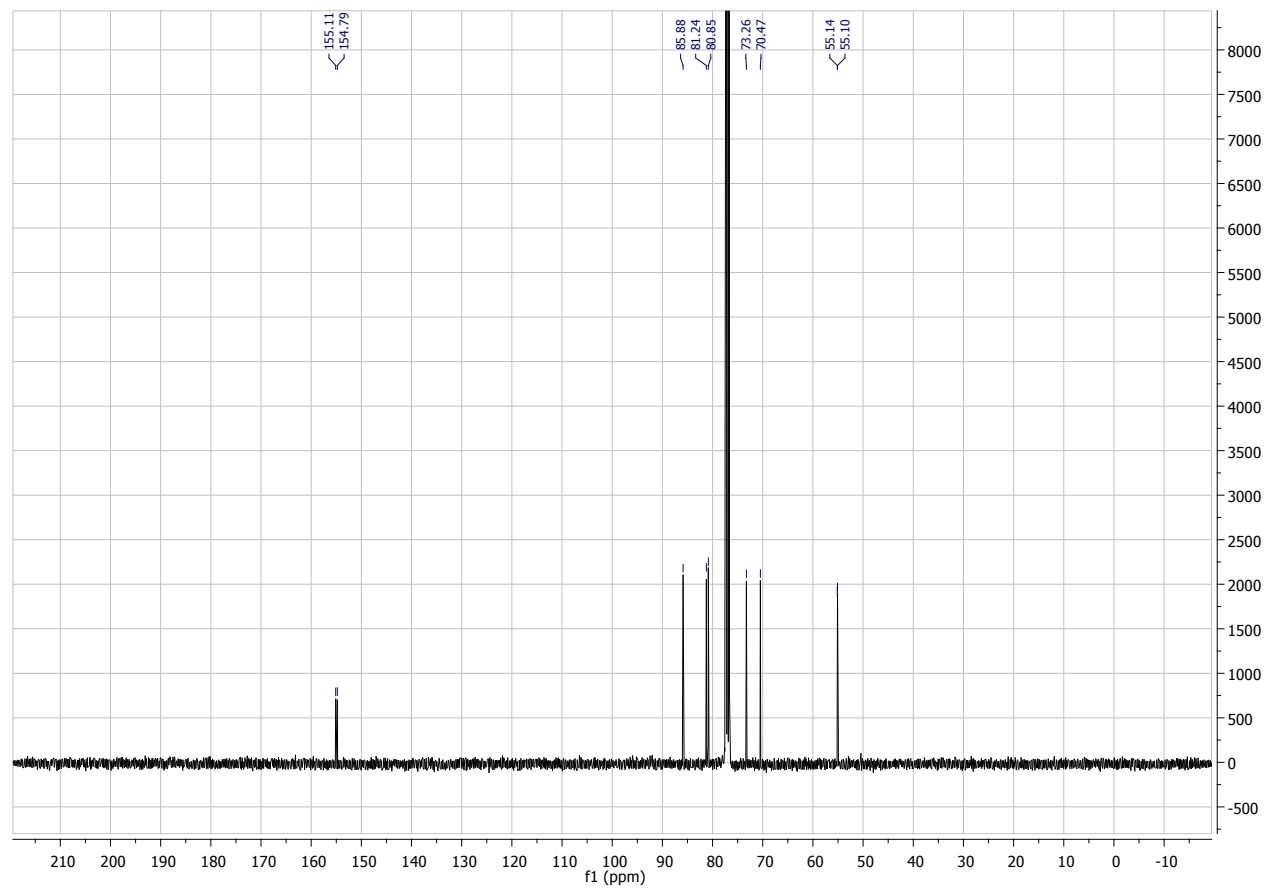
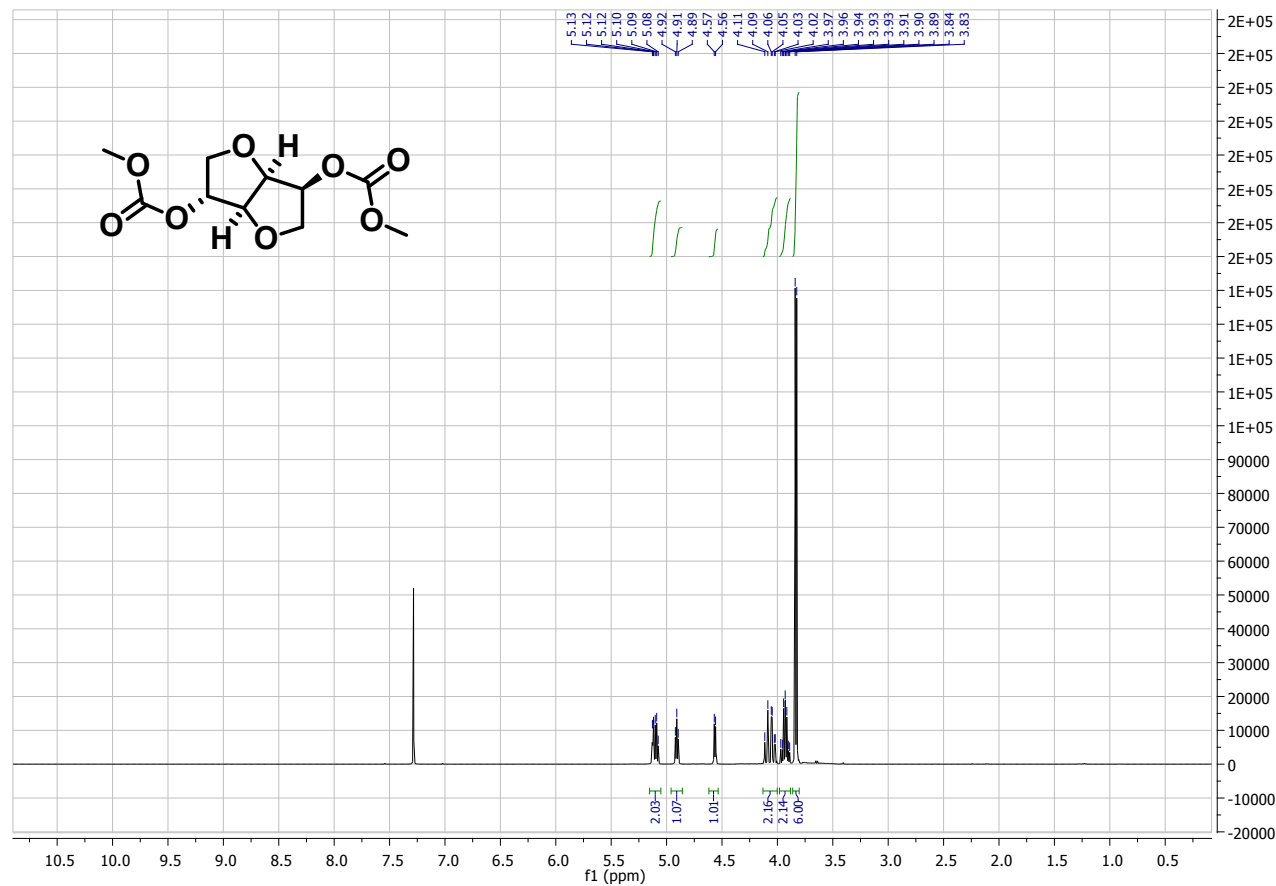
Dimethyl Isoidide (DMli)

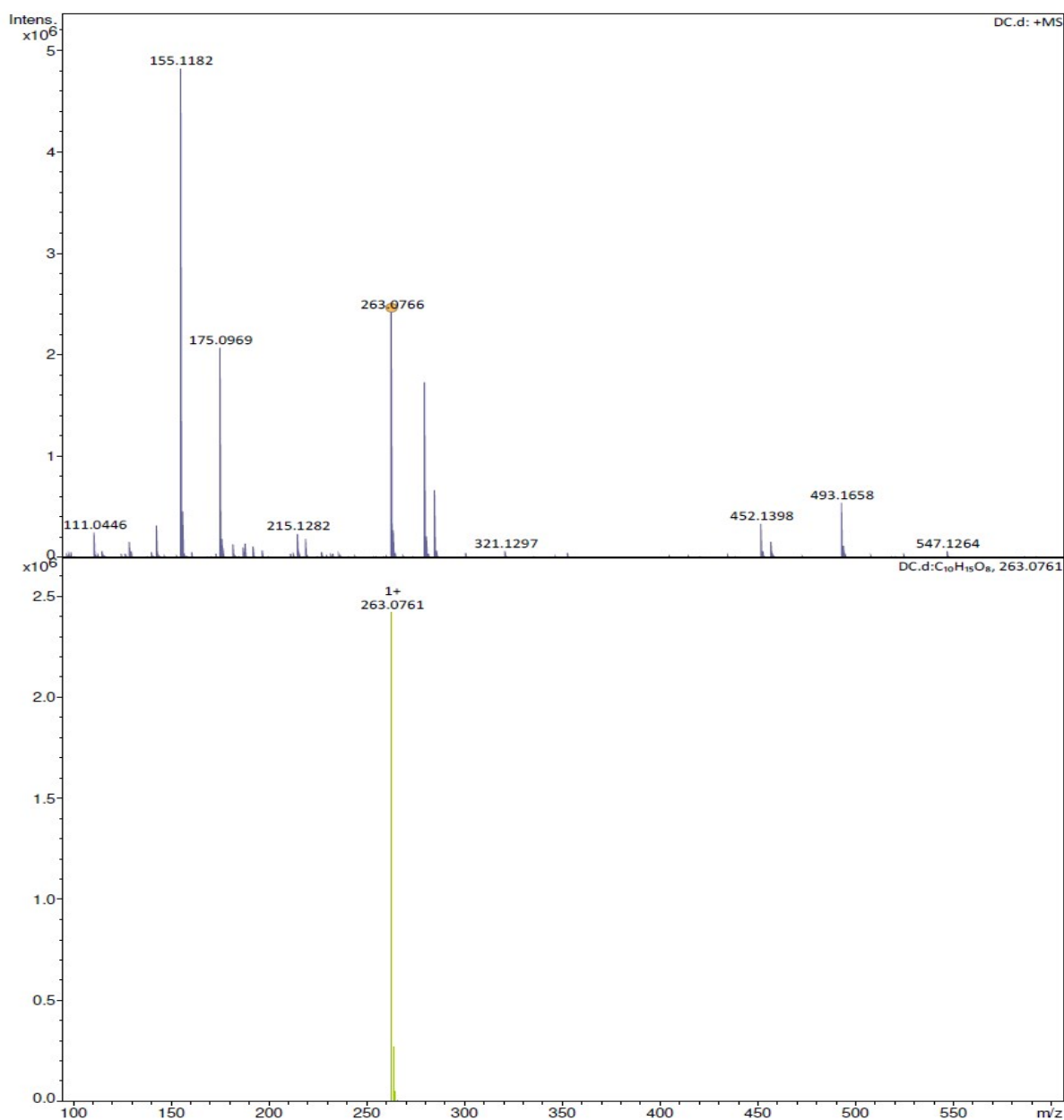


Dimethyl Isomannide (DMIIm)



Dicarboxymethyl Isosorbide – DCI





| Meas. m/z | # | Ion Formula | m/z      | err [ppm] | mSigma | # mSigma | Score  | rdb  | e <sup>-</sup> Conf | N-Rule |
|-----------|---|-------------|----------|-----------|--------|----------|--------|------|---------------------|--------|
| 263.0766  | 1 | C10H15O8    | 263.0761 | -1.7      | 0.1    | 1        | 100.00 | 4.0  | even                | ok     |
|           | 2 | C7H7N10O2   | 263.0748 | -6.9      | 7.0    | 2        | 39.86  | 10.0 | even                | ok     |
|           | 3 | C6H11N6O6   | 263.0735 | -11.9     | 13.4   | 3        | 11.20  | 5.0  | even                | ok     |
|           | 4 | C11H11N4O4  | 263.0775 | 3.4       | 14.0   | 4        | 62.77  | 9.0  | even                | ok     |
|           | 5 | C12H7N8     | 263.0788 | 8.4       | 27.8   | 5        | 18.86  | 14.0 | even                | ok     |

#### Analysis Info

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Sample Name DC  
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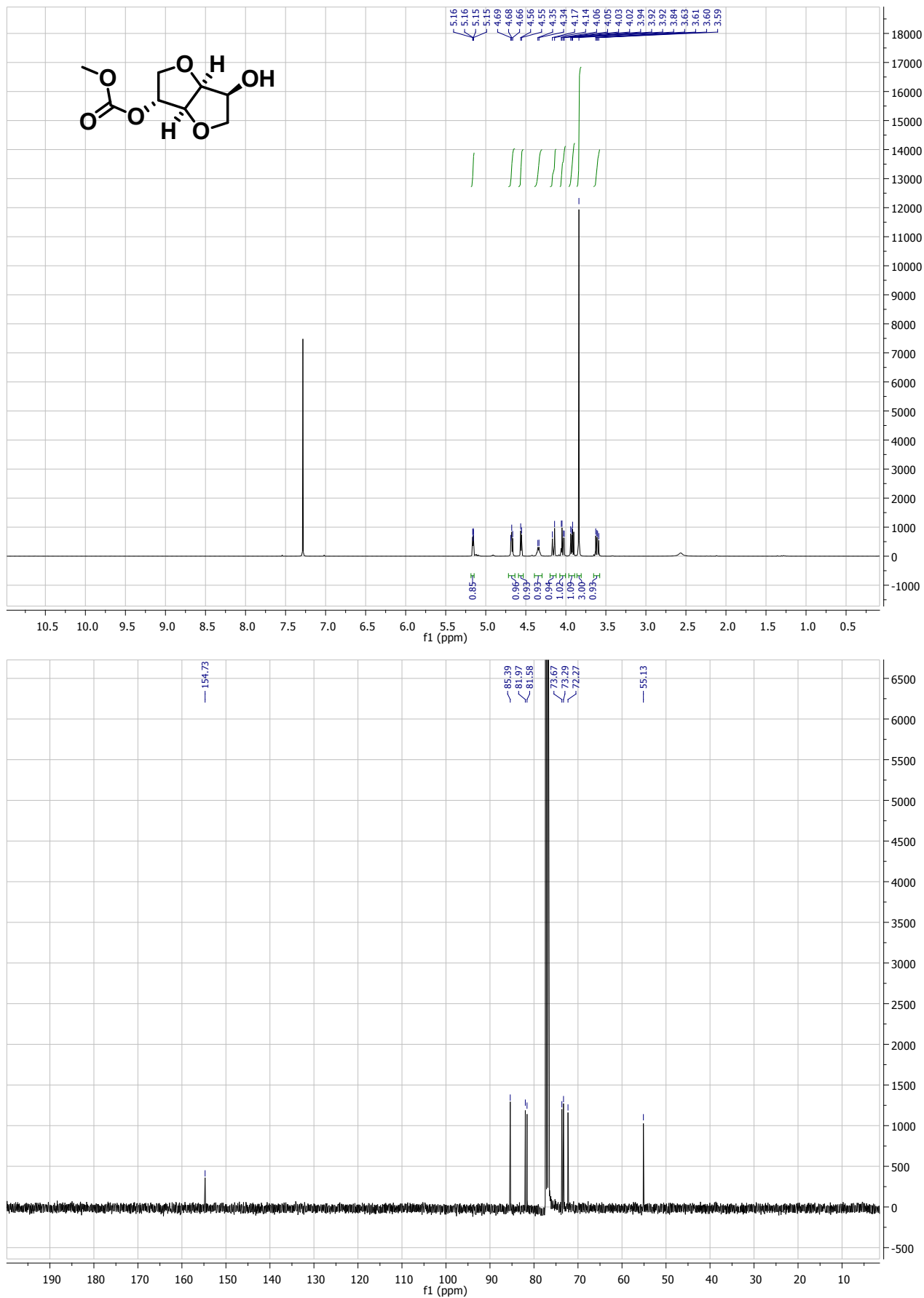
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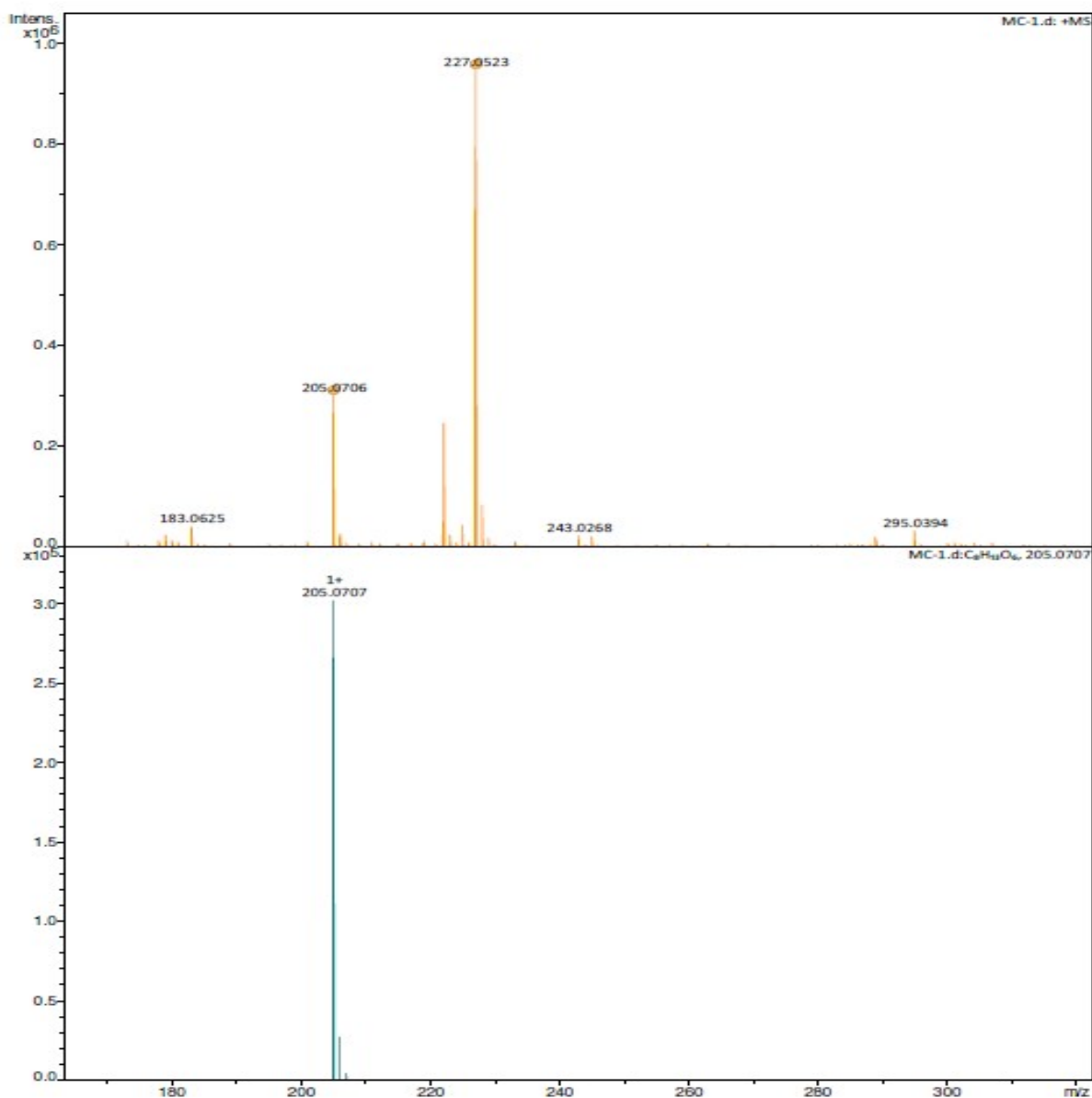
Operator Demo User  
Instrument compact 8255754.20209

#### Acquisition Parameter

|             |            |                       |           |                  |           |
|-------------|------------|-----------------------|-----------|------------------|-----------|
| Source Type | ESI        | Ion Polarity          | Positive  | Set Nebulizer    | 0.4 Bar   |
| Focus       | Not active | Set Capillary         | 4500 V    | Set Dry Heater   | 180 °C    |
| Scan Begin  | 100 m/z    | Set End Plate Offset  | -500 V    | Set Dry Gas      | 4.0 l/min |
| Scan End    | 600 m/z    | Set Collision Cell RF | 650.0 Vpp | Set Divert Valve | Source    |

Monocarboxymethyl Isosorbide - MCI1





| Meas. m/z | # | Ion Formula | m/z      | err [ppm] | mSigma | # mSigma | Score  | rdB | e <sup>-</sup> Conf | N-Rule |
|-----------|---|-------------|----------|-----------|--------|----------|--------|-----|---------------------|--------|
| 205.0706  | 1 | C8H13O6     | 205.0707 | 0.4       | 0.1    | 1        | 100.00 | 3.0 | even                | ok     |
|           | 2 | C5H5N10     | 205.0693 | -6.2      | 6.9    | 2        | 48.09  | 9.0 | even                | ok     |
|           | 3 | C4H9N8O4    | 205.0680 | -12.7     | 13.4   | 3        | 15.56  | 4.0 | even                | ok     |
|           | 4 | C9H9N4O2    | 205.0720 | 6.9       | 13.9   | 4        | 38.75  | 8.0 | even                | ok     |
| 227.0523  | 1 | C8H12NaO6   | 227.0526 | 1.2       | 1.6    | 1        | 100.00 | 3.0 | even                | ok     |
|           | 2 | C5H4N10Na   | 227.0513 | -4.7      | 7.8    | 2        | 60.24  | 9.0 | even                | ok     |
|           | 3 | C4H8N6NaO4  | 227.0499 | -10.6     | 12.1   | 3        | 21.48  | 4.0 | even                | ok     |
|           | 4 | C9H8N4NaO2  | 227.0539 | 7.1       | 15.6   | 4        | 36.51  | 8.0 | even                | ok     |

#### Analysis Info

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Sample Name MC-1  
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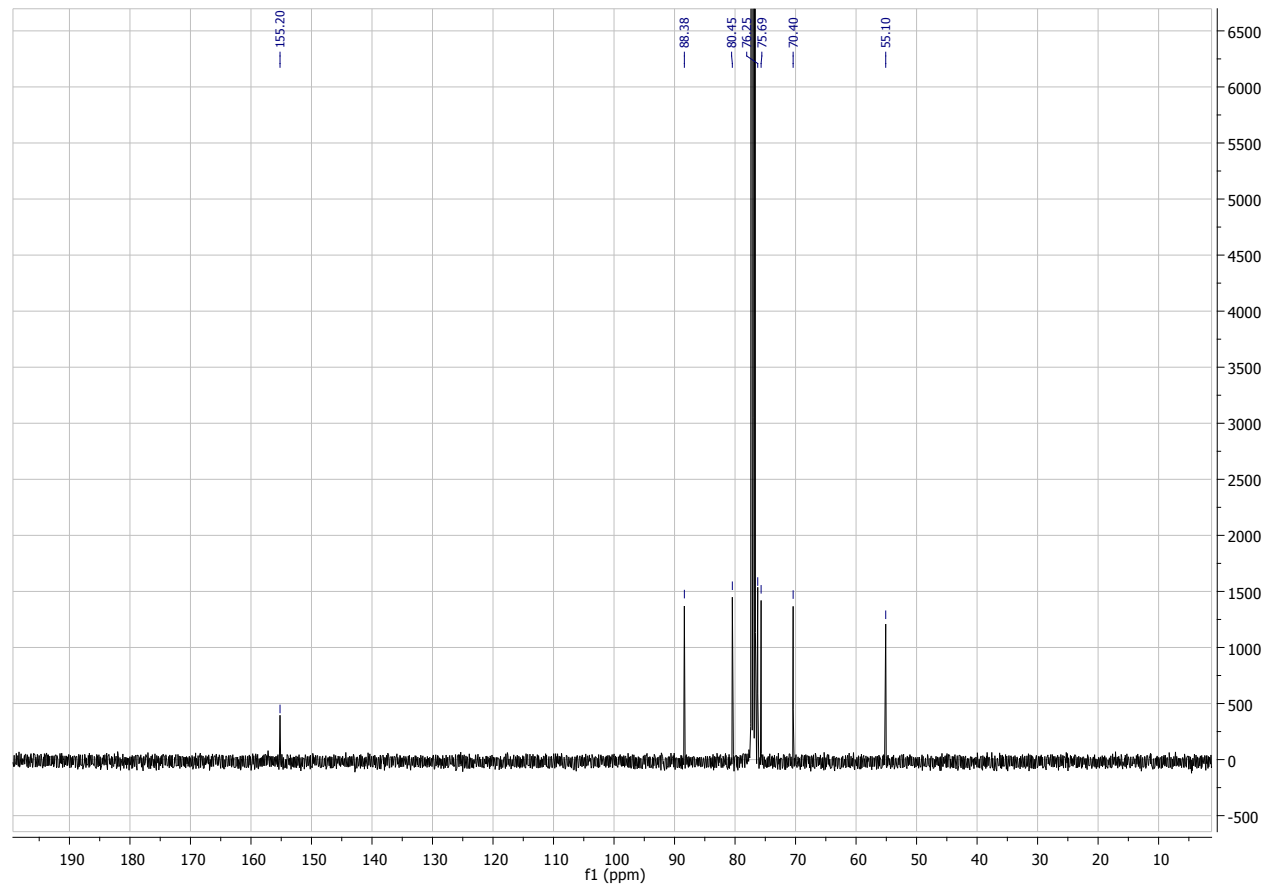
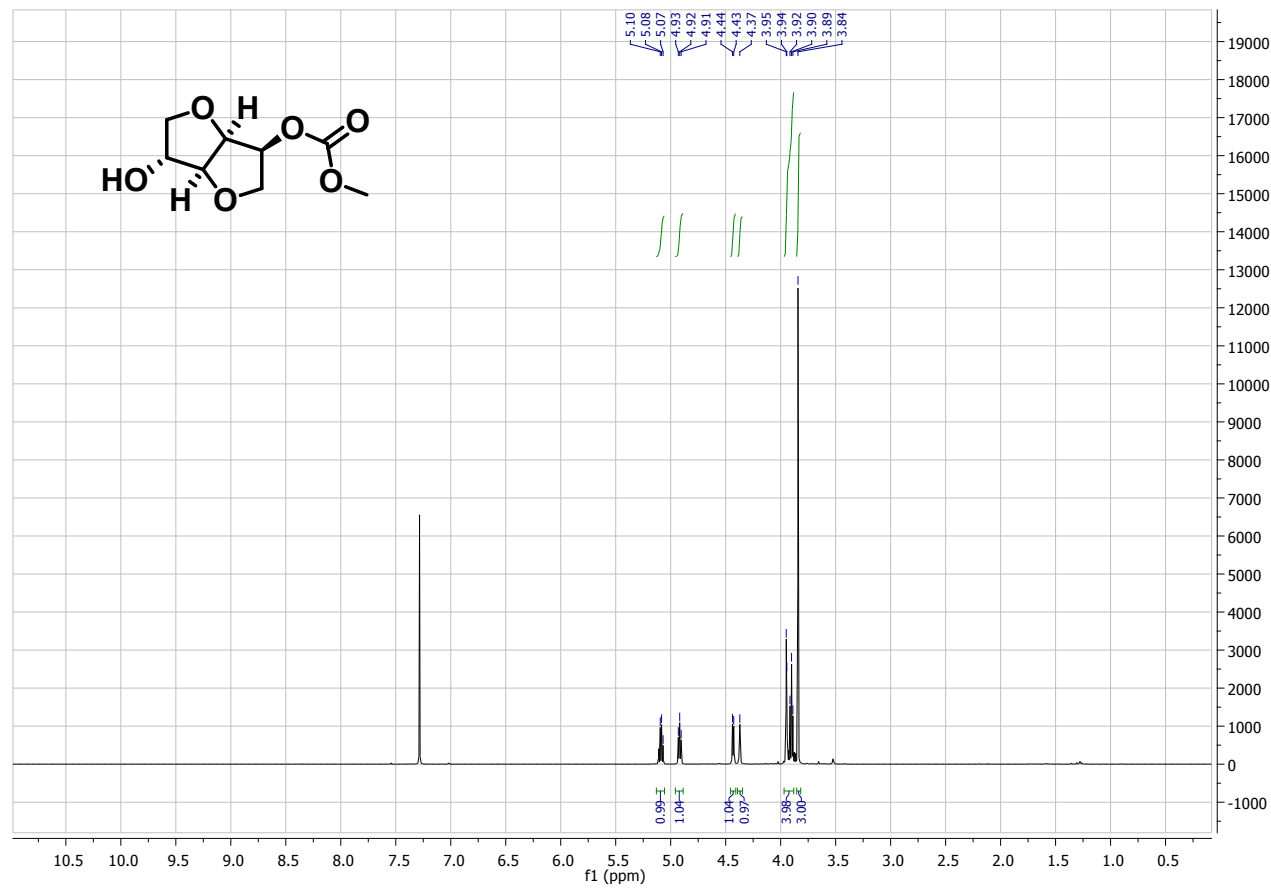
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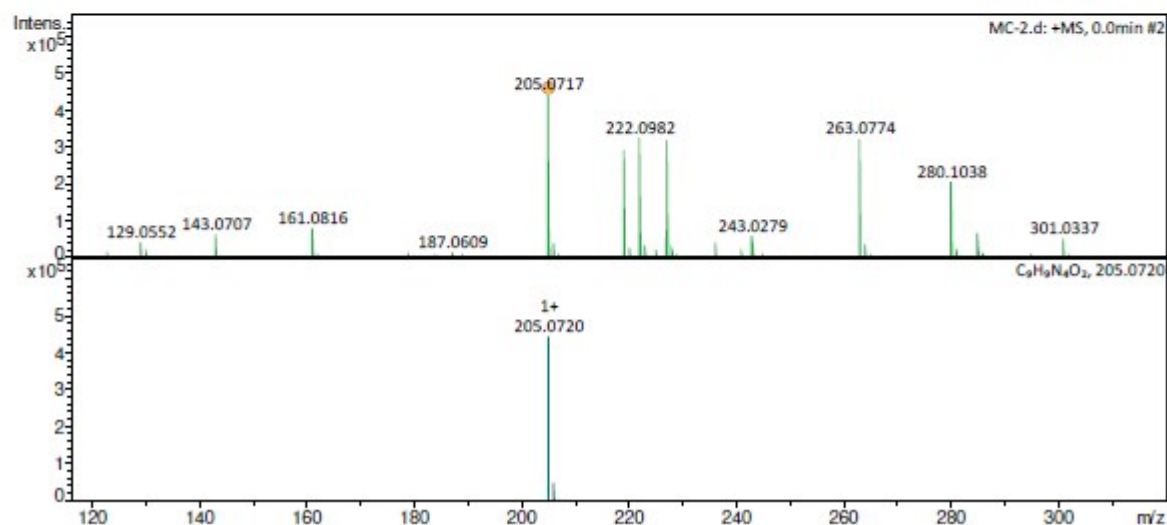
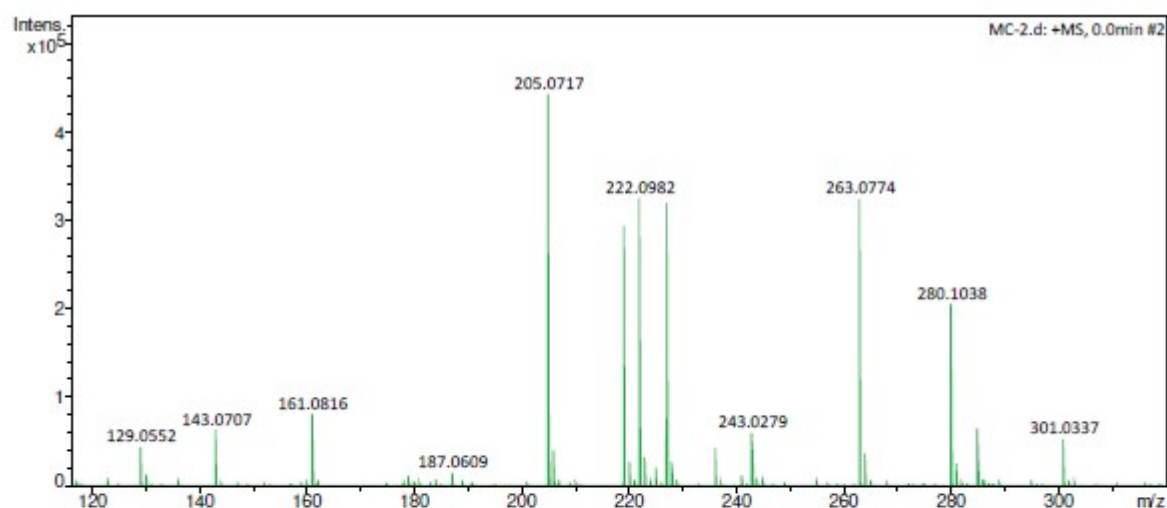
Operator Demo User  
Instrument compact 8255754.20209

#### Acquisition Parameter

|             |            |                       |           |                    |           |
|-------------|------------|-----------------------|-----------|--------------------|-----------|
| Source Type | ESI        | Ion Polarity          | Positive  | Set Nebulizer      | 0.4 Bar   |
| Focus       | Not active | Set Capillary         | 4500 V    | Set Dry Heater     | 180 °C    |
| Scan Begin  | 100 m/z    | Set End Plate Offset  | -500 V    | Set Dry Gas        | 4.0 l/min |
| Scan End    | 600 m/z    | Set Collision Cell RF | 650.0 Vpp | Set Diverter Valve | Source    |

Monocarboxymethyl Isosorbide - MCI2





| Meas. m/z | # | Ion Formula | m/z      | err [ppm] | mSigma | # mSigma | Score  | rdb | e <sup>-</sup> | Conf | N-Rule |
|-----------|---|-------------|----------|-----------|--------|----------|--------|-----|----------------|------|--------|
| 205.0717  | 1 | C8H13O6     | 205.0707 | -5.2      | 0.4    | 1        | 84.50  | 3.0 | even           |      | ok     |
|           | 2 | C5H5N10     | 205.0693 | -11.8     | 7.1    | 2        | 28.92  | 9.0 | even           |      | ok     |
|           | 3 | C9H9N4O2    | 205.0720 | 1.3       | 13.6   | 3        | 100.00 | 8.0 | even           |      | ok     |
|           | 4 | C4H9N6O4    | 205.0680 | -18.3     | 13.8   | 4        | 6.81   | 4.0 | even           |      | ok     |

#### Analysis Info

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 Sample Name MC-2  
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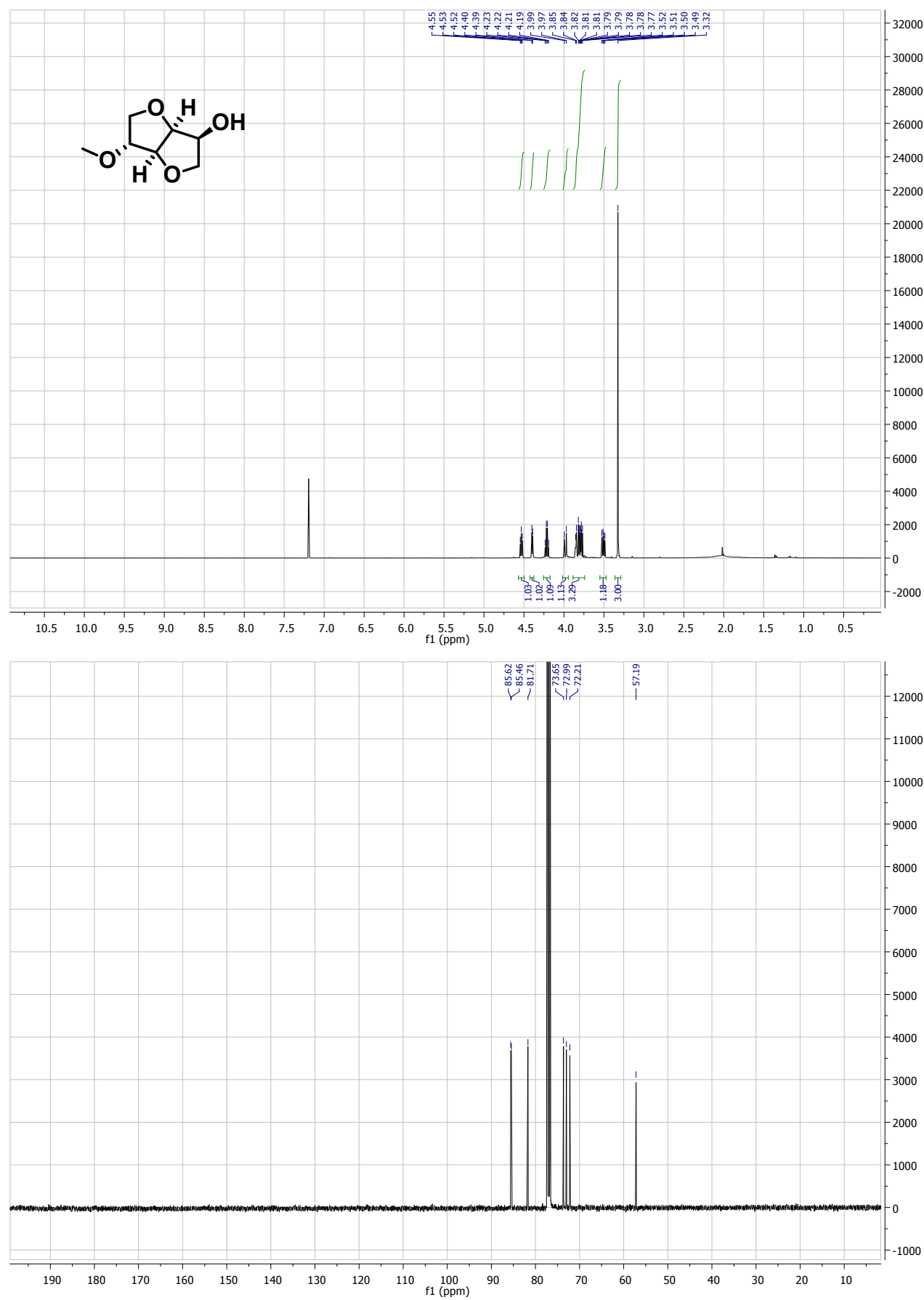
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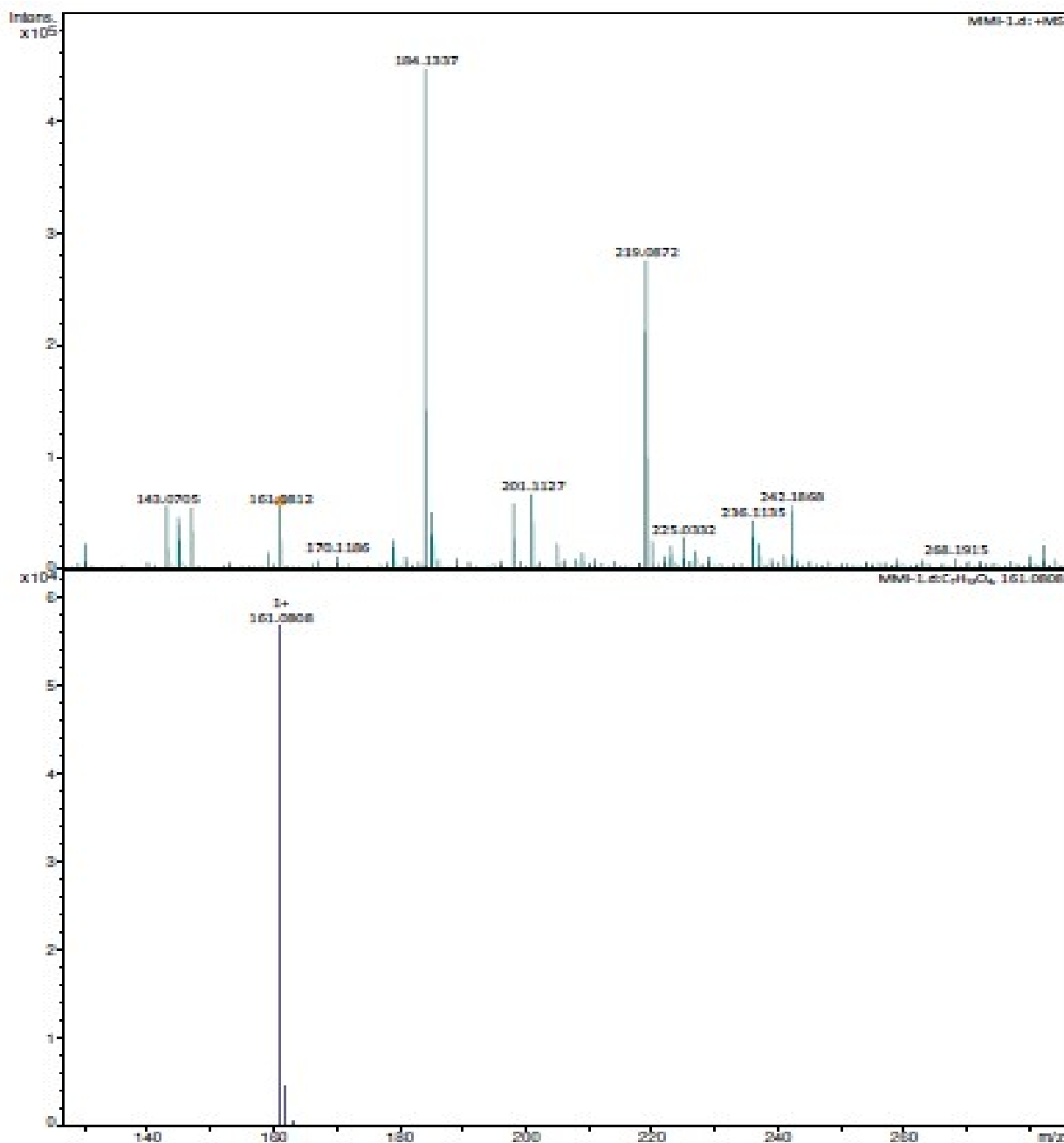
Operator Demo User  
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#### Acquisition Parameter

|             |            |                       |           |                  |           |
|-------------|------------|-----------------------|-----------|------------------|-----------|
| Source Type | ESI        | Ion Polarity          | Positive  | Set Nebulizer    | 0.4 Bar   |
| Focus       | Not active | Set Capillary         | 4500 V    | Set Dry Heater   | 180 °C    |
| Scan Begin  | 100 m/z    | Set End Plate Offset  | -500 V    | Set Dry Gas      | 4.0 l/min |
| Scan End    | 600 m/z    | Set Collision Cell RF | 650.0 Vpp | Set Divert Valve | Source    |

Monomethyl Isosorbide - MMI1





| Meas. m/z | # | Ion Formula | m/z      | err [ppm] | mSigma | # mSigma | Score  | rdb | e <sup>-</sup> | Conf | N-Rule |
|-----------|---|-------------|----------|-----------|--------|----------|--------|-----|----------------|------|--------|
| 161.0812  | 1 | C7H13O4     | 161.0808 | -2.4      | 8.3    | 1        | 100.00 | 2.0 | even           |      | ok     |
|           | 2 | C3H9N6O2    | 161.0781 | -19.1     | 11.8   | 2        | 13.79  | 3.0 | even           |      | ok     |
|           | 3 | C8H9N4      | 161.0822 | 5.9       | 21.5   | 3        | 57.73  | 7.0 | even           |      | ok     |

#### Analysis Info

Analysis Name D:\Data\Jack\Arico\281220\MMI-1.d  
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 Sample Name MMI-1  
 Comment

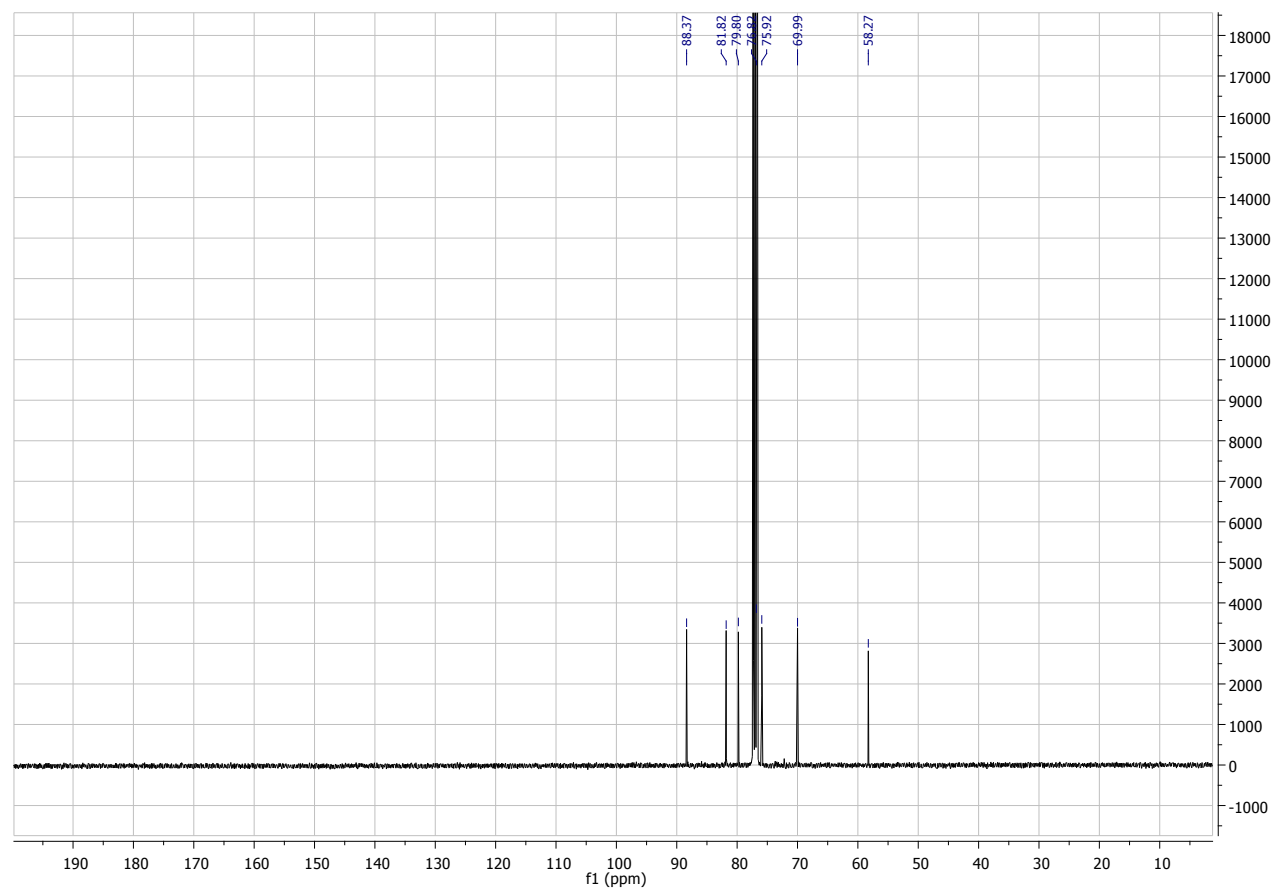
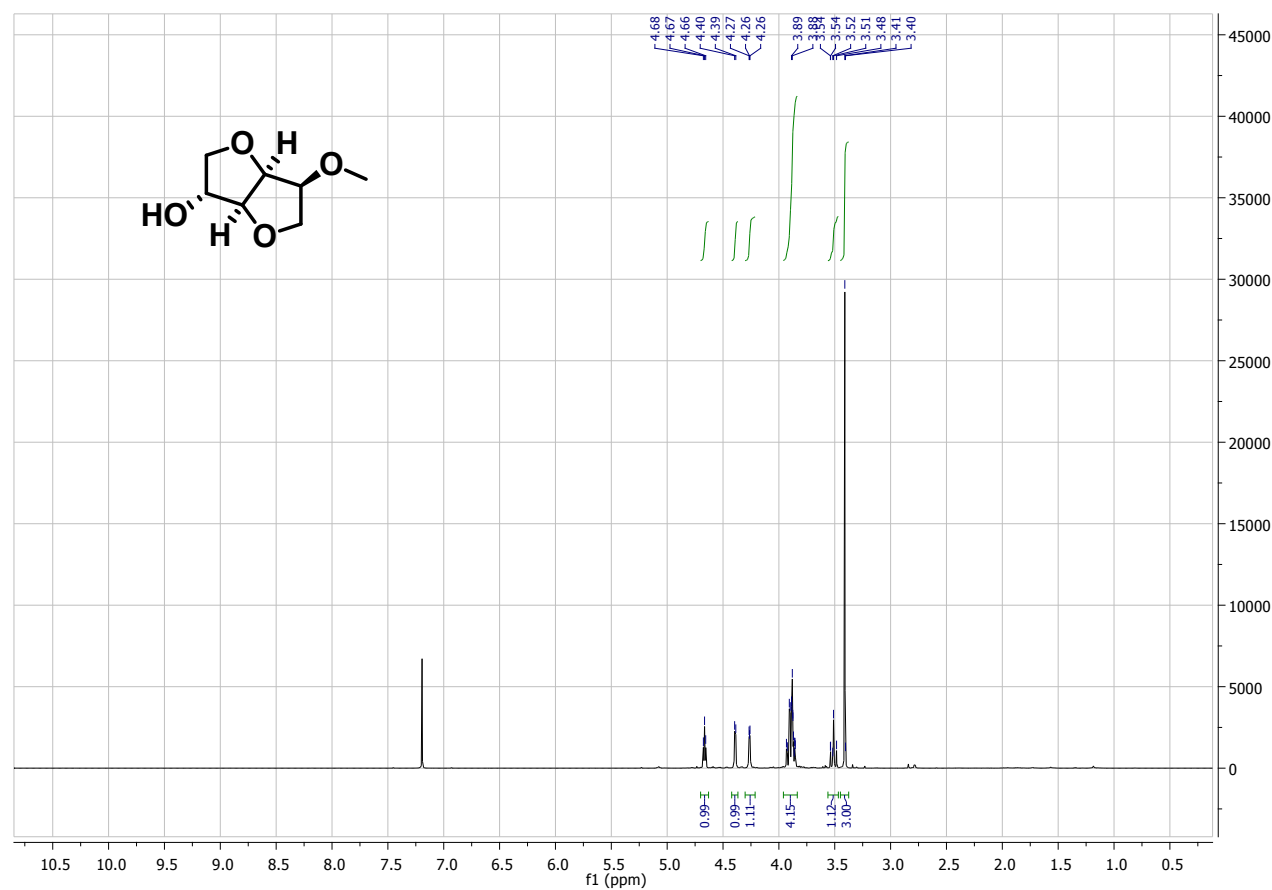
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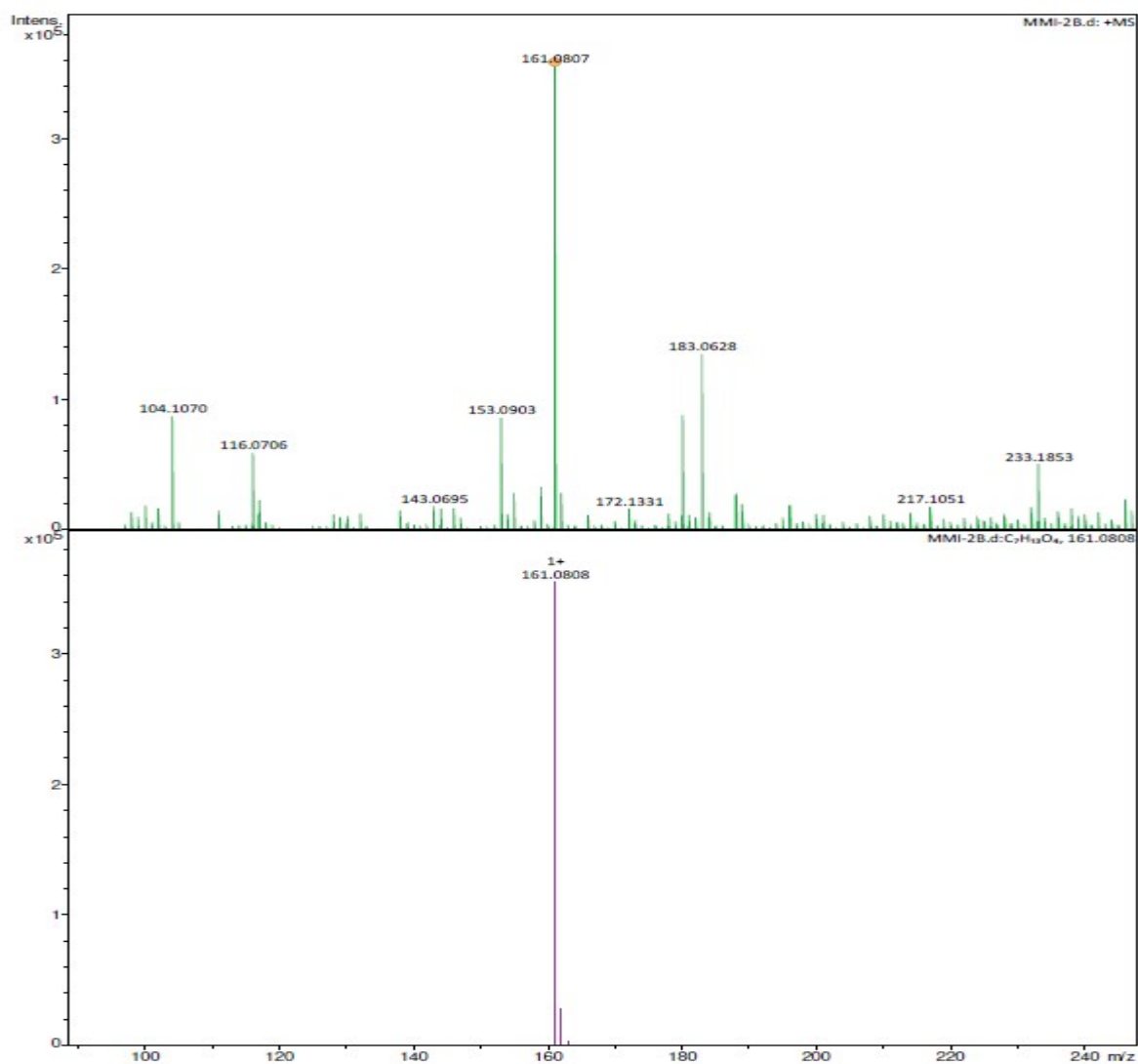
Operator Demo User  
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#### Acquisition Parameter

|             |            |                       |           |                  |           |
|-------------|------------|-----------------------|-----------|------------------|-----------|
| Source Type | ESI        | Ion Polarity          | Positive  | Set Nebulizer    | 0.4 Bar   |
| Focus       | Not active | Set Capillary         | 4500 V    | Set Dry Heater   | 180 °C    |
| Scan Begin  | 100 m/z    | Set End Plate Offset  | -500 V    | Set Dry Gas      | 4.0 l/min |
| Scan End    | 600 m/z    | Set Collision Cell RF | 650.0 Vpp | Set Divert Valve | Source    |

Monomethyl Isosorbide - MMI2





| Meas. m/z | # | Ion Formula | m/z      | err [ppm] | mSigma | # mSigma | Score  | rdb | e <sup>-</sup> | Conf | N-Rule |
|-----------|---|-------------|----------|-----------|--------|----------|--------|-----|----------------|------|--------|
| 161.0807  | 1 | C7H13O4     | 161.0808 | 0.6       | 1.6    | 1        | 100.00 | 2.0 | even           |      | ok     |
|           | 2 | C8H9N4      | 161.0822 | 9.0       | 12.6   | 2        | 40.33  | 7.0 | even           |      | ok     |
|           | 3 | C3H9N6O2    | 161.0781 | -16.0     | 15.0   | 3        | 16.11  | 3.0 | even           |      | ok     |

#### Analysis Info

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Sample Name MMI-2B  
Comment

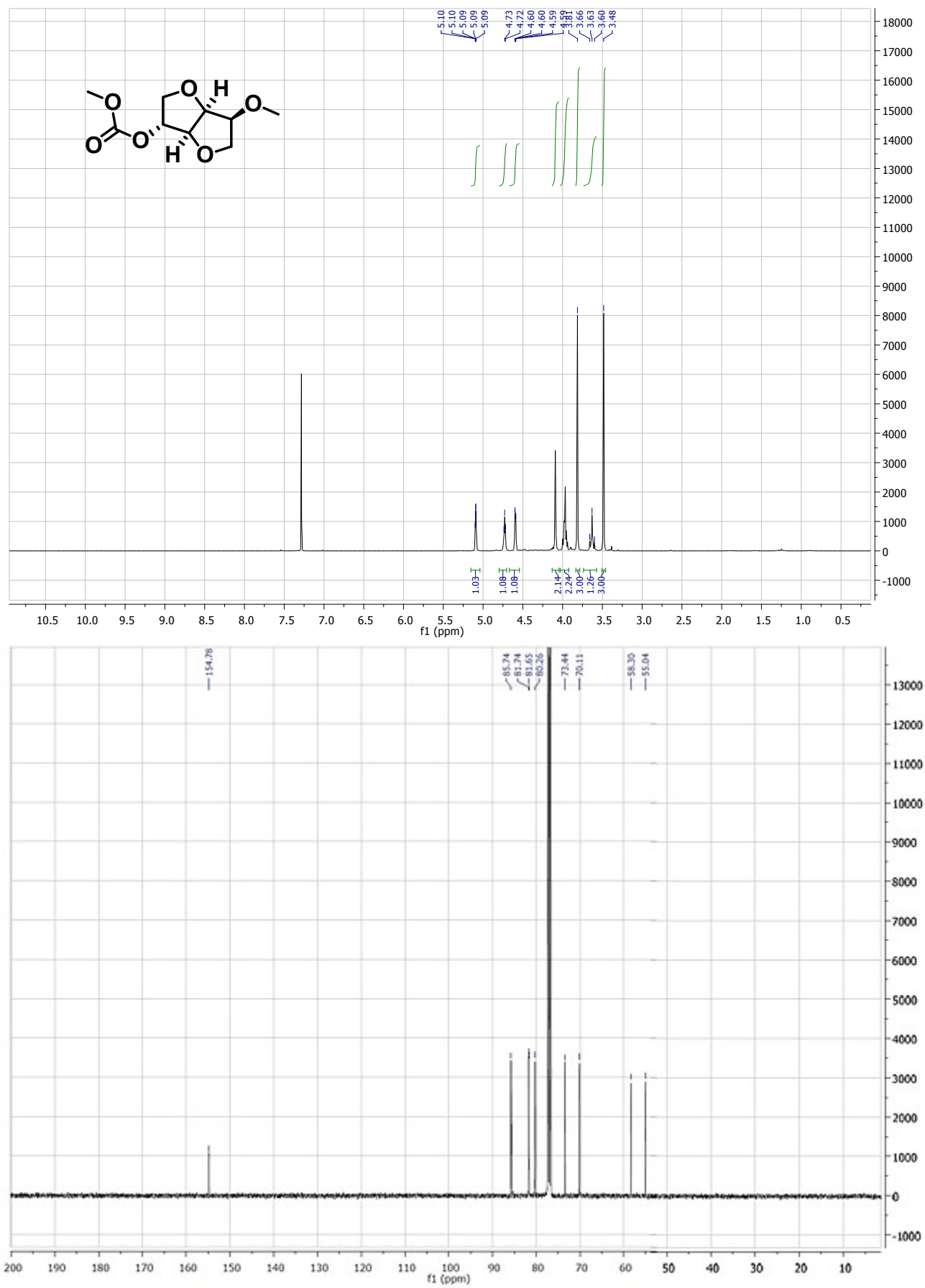
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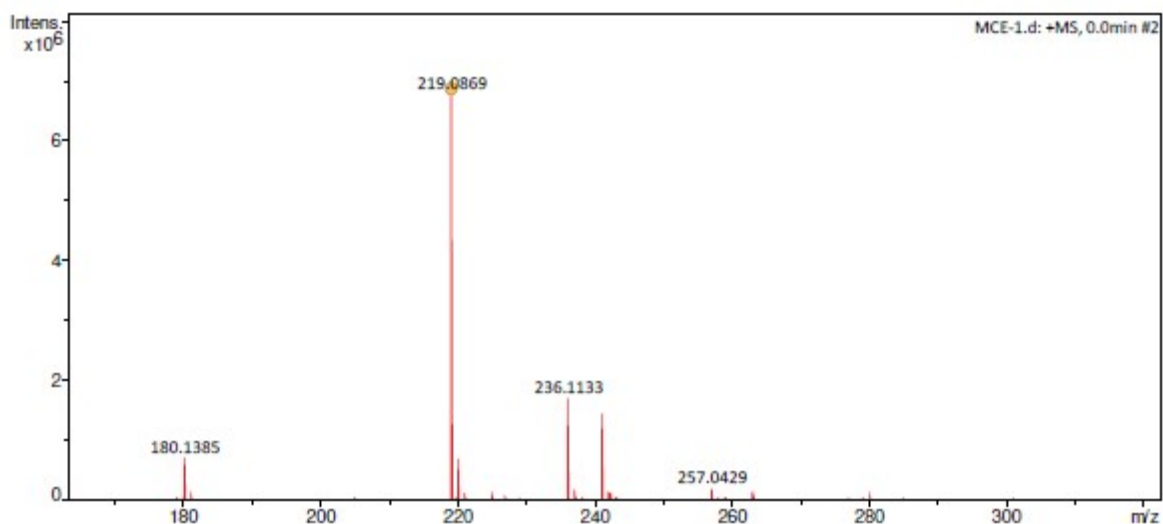
Operator Demo User  
Instrument compact 8255754.20209

#### Acquisition Parameter

|             |            |                       |           |                  |           |
|-------------|------------|-----------------------|-----------|------------------|-----------|
| Source Type | ESI        | Ion Polarity          | Positive  | Set Nebulizer    | 0.4 Bar   |
| Focus       | Not active | Set Capillary         | 4500 V    | Set Dry Heater   | 180 °C    |
| Scan Begin  | 100 m/z    | Set End Plate Offset  | -500 V    | Set Dry Gas      | 4.0 l/min |
| Scan End    | 600 m/z    | Set Collision Cell RF | 650.0 Vpp | Set Divert Valve | Source    |

Monomethylcarboxy Methyl Isosorbide - MCM11





| Meas. m/z | # | Ion Formula | m/z      | err [ppm] | mSigma | # mSigma | Score  | rdB | e <sup>-</sup> Conf | N-Rule |
|-----------|---|-------------|----------|-----------|--------|----------|--------|-----|---------------------|--------|
| 219.0869  | 1 | C9H15O6     | 219.0863 | -2.6      | 0.2    | 1        | 100.00 | 3.0 | even                | ok     |
|           | 2 | C6H7N10     | 219.0850 | -8.7      | 6.8    | 2        | 38.98  | 9.0 | even                | ok     |
|           | 3 | C5H11N6O4   | 219.0836 | -14.9     | 13.5   | 3        | 10.57  | 4.0 | even                | ok     |
|           | 4 | C10H11N4O2  | 219.0877 | 3.5       | 13.8   | 4        | 70.82  | 8.0 | even                | ok     |

#### Analysis Info

Analysis Name D:\Data\Jack\Arico\281220\MCE-1.d  
 Method DirectInfusion - MS - positive.m  
 Sample Name MCE-1  
 Comment

Acquisition Date 12/28/2020 12:53:26 PM

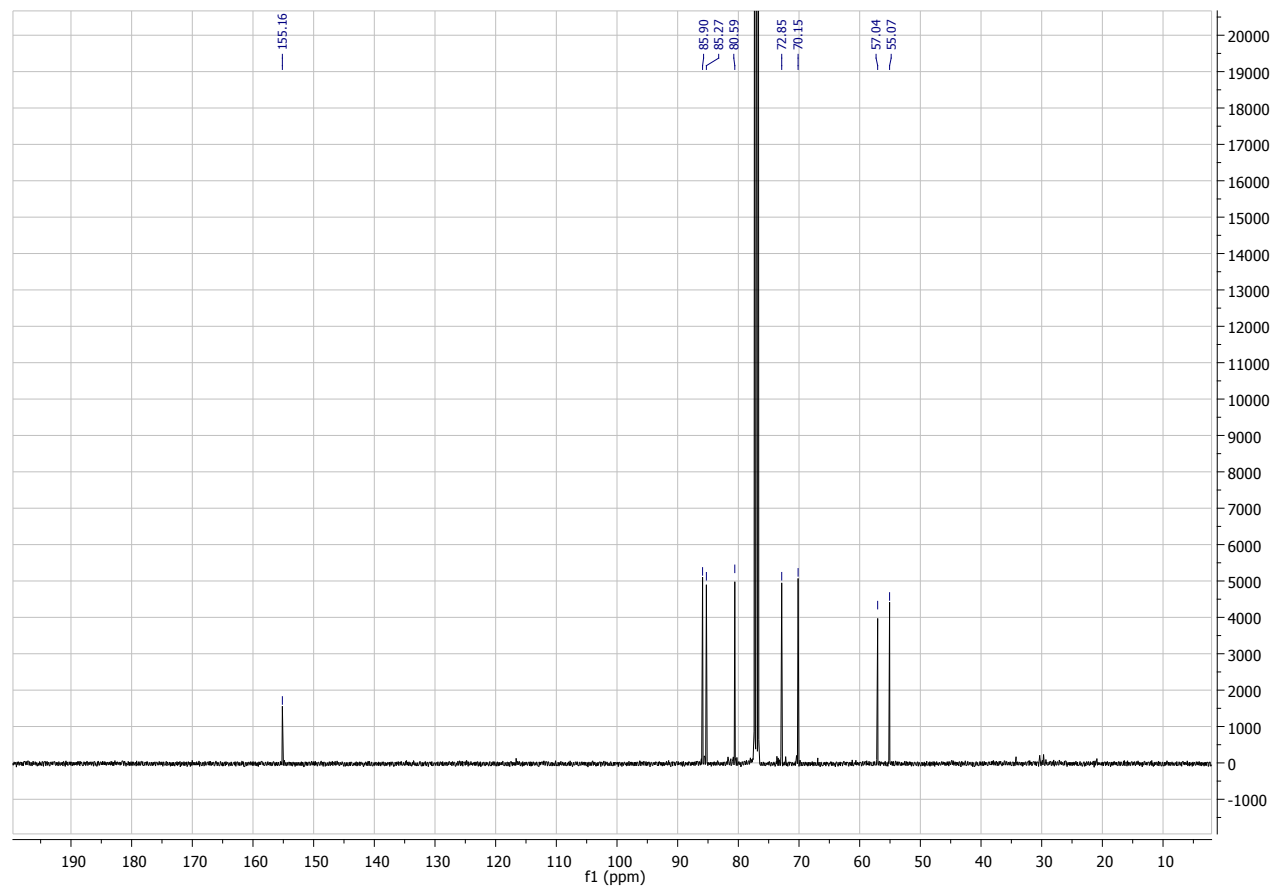
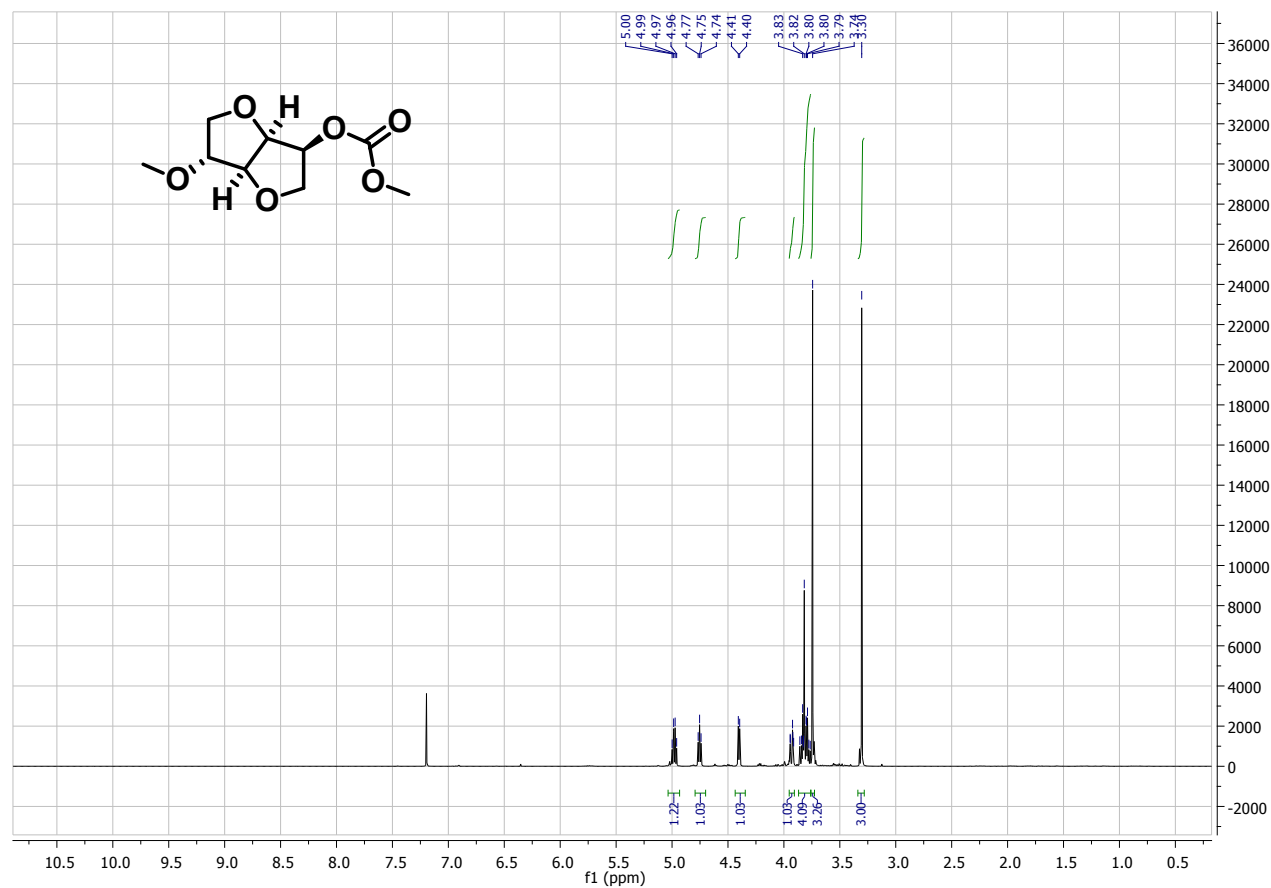
Operator Demo User

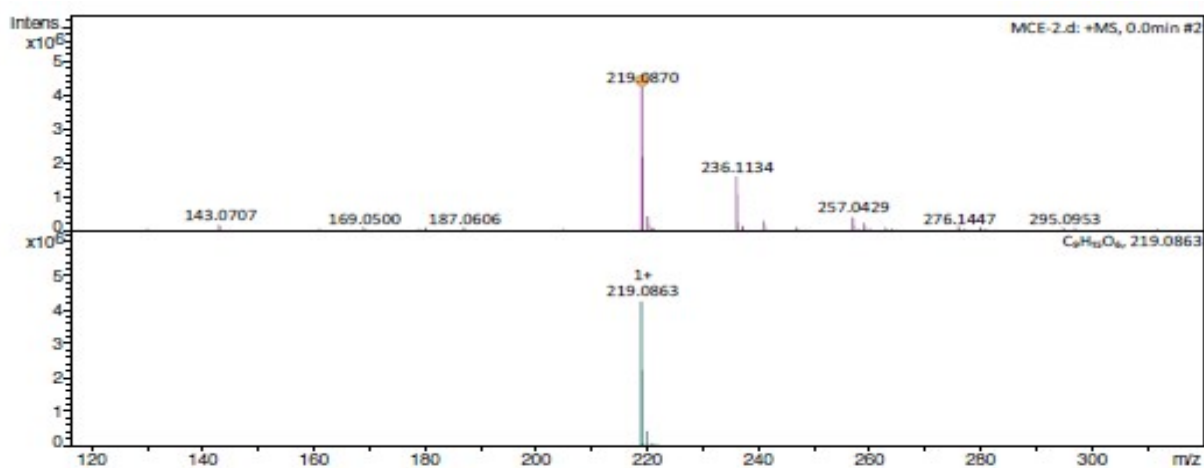
Instrument compact 8255754.20209

#### Acquisition Parameter

|             |            |                       |           |                  |           |
|-------------|------------|-----------------------|-----------|------------------|-----------|
| Source Type | ESI        | Ion Polarity          | Positive  | Set Nebulizer    | 0.4 Bar   |
| Focus       | Not active | Set Capillary         | 4500 V    | Set Dry Heater   | 180 °C    |
| Scan Begin  | 100 m/z    | Set End Plate Offset  | -500 V    | Set Dry Gas      | 4.0 l/min |
| Scan End    | 600 m/z    | Set Collision Cell RF | 650.0 Vpp | Set Divert Valve | Source    |

Monomethylcarboxy Methyl Isosorbide - MCM12





| Meas. m/z | # | Ion Formula                                                   | m/z      | err [ppm] | mSigma | # mSigma | Score  | rdB | e <sup>-</sup> Conf | N-Rule |
|-----------|---|---------------------------------------------------------------|----------|-----------|--------|----------|--------|-----|---------------------|--------|
| 219.0870  | 1 | C <sub>9</sub> H <sub>15</sub> O <sub>6</sub>                 | 219.0863 | -3.0      | 0.2    | 1        | 100.00 | 3.0 | even                | ok     |
|           | 2 | C <sub>8</sub> H <sub>7</sub> N <sub>10</sub>                 | 219.0850 | -9.1      | 6.8    | 2        | 38.18  | 9.0 | even                | ok     |
|           | 3 | C <sub>5</sub> H <sub>11</sub> N <sub>6</sub> O <sub>4</sub>  | 219.0836 | -15.2     | 13.4   | 3        | 10.13  | 4.0 | even                | ok     |
|           | 4 | C <sub>10</sub> H <sub>11</sub> N <sub>4</sub> O <sub>2</sub> | 219.0877 | 3.1       | 13.9   | 4        | 77.04  | 8.0 | even                | ok     |

#### Analysis Info

Analysis Name D:\Data\Jack\Arico\281220\MCE-2.d  
 Method DirectInfusion - MS - positive.m  
 Sample Name MCE-2  
 Comment

Acquisition Date 12/28/2020 1:10:21 PM

Operator Demo User  
 Instrument compact 82557 54.20209

#### Acquisition Parameter

|             |            |                       |           |                  |           |
|-------------|------------|-----------------------|-----------|------------------|-----------|
| Source Type | ESI        | Ion Polarity          | Positive  | Set Nebulizer    | 0.4 Bar   |
| Focus       | Not active | Set Capillary         | 4500 V    | Set Dry Heater   | 180 °C    |
| Scan Begin  | 100 m/z    | Set End Plate Offset  | -500 V    | Set Dry Gas      | 4.0 l/min |
| Scan End    | 600 m/z    | Set Collision Cell RF | 650.0 Vpp | Set Divert Valve | Source    |

Catalyst - DMPyC

