catalysts

Supporting Materials: Application of Heterogeneous Catalysts in the First Steps of the Oseltamivir Synthesis

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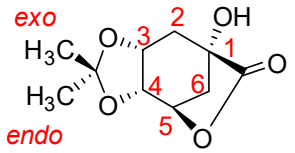
Materials and Methods

Amberlyst IR-15 (sulfonated polystyrene macroreticular resin, 20% divinylbenzene, 4.7 mmol S/g) was purchased from Alfa Aesar. Deloxan ASP I/9 (polysiloxane supported alkyl sulfonic acid 0.1-0.4 mm particle size, 0.80 mmol S/g) was a gift from Degussa (currently not commercially available). SAC-13 (nafion-silica composite, 13% wt nafion content, 0.17 mmol S/g) was a gift from Dupont (currently not commercially available).

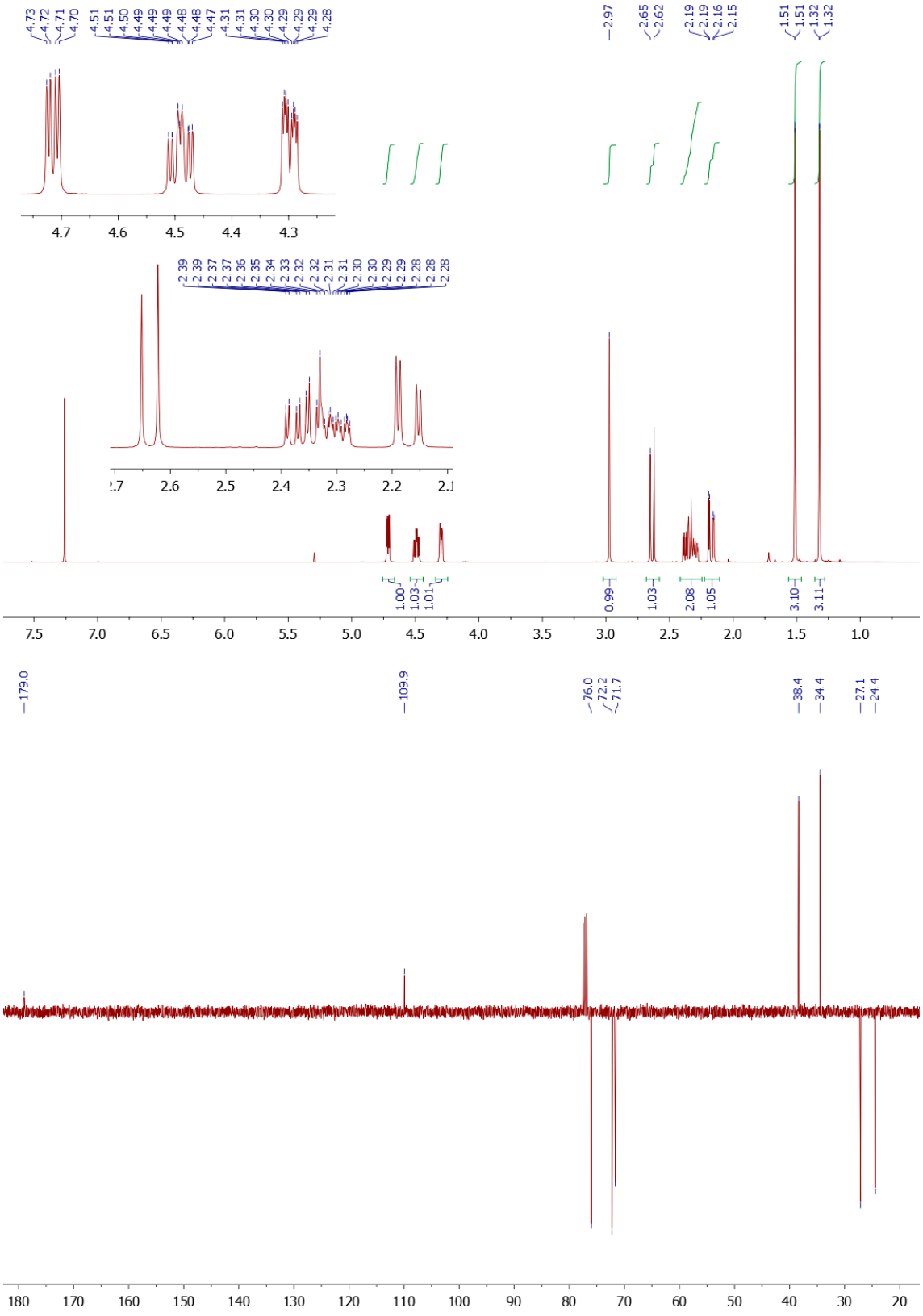
Sulfonated hydrothermal carbon (SHTC, 0.80 mmol S/g) was prepared in two steps from D-glucose, first a hydrothermal synthesis at 195°C and then sulfonation with concentrated sulfuric acid at 150°C, as previously described [1]. Amberlite IRA-400 (trimethylbenzylammonium substituted gel type polystyrene resin, 8% divinylbenzene, basic form, 3.8 mmol/g) was purchased from Carlo Erba. TBD-PS (1,5,7-triazabicyclo[4.4.0]dec-5-ene supported on gel type polystyrene, 1% divinylbenzene, 3.0 mmol/g) and TBD-SiO_2 (1,5,7-triazabicyclo[4.4.0]dec-5-ene supported on silica gel, 0.7 mmol/g) were purchased from Aldrich. All the catalysts were dried at 100ºC under vacuum overnight prior to use.

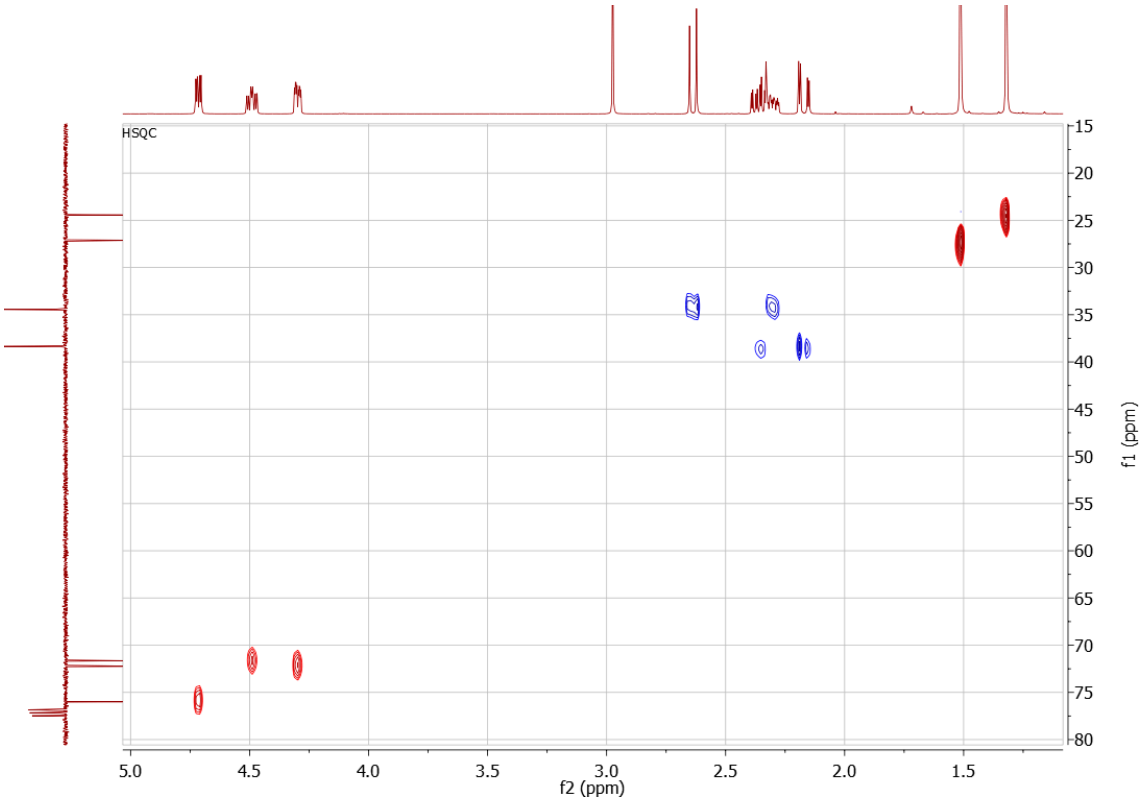
Solvents were dried following standard procedures and all the reactions were carried out under argon atmosphere.



2a

3,4-*O*-Isopropylidenequinic acid 1,5-lactone (2a) [2,3]**.** To a solution of quinic acid (192 mg, 1 mmol) in acetone (4 mL) was added SHTC (13 mg, 0.01 mmol) and 2,2-dimethoxypropane (364 mg, 430 μL, 3.5 mmol). The mixture was stirred at 56 ºC for 3h, then the acid catalyst was removed by filtration, the filtrate was concentrated under vacuum and purified by column chromatography on silica gel (hexanes/EtOAc = 6:4, Rf 0.3), affording the compound **2a** (179 mg, 84 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.32 (3H, s, CH_{3exo}), 1.51 (3H, s, CH_{3endo}), 2.17 (1H, dd, J = 14.7, 2.9 Hz, $H2_{ax}$), 2.30 (1H, dddd, J = 11.7, 6.2, 2.3, 1.4 Hz, $H6_{eq}$), 2.36 (1H, ddd, J = 14.7, 7.1, 2.3 Hz, $H2_{eq}$), 2.64 (1H, d, J = 11.7 Hz, $H6_{ax}$), 2.97 (1H, br s, OH), 4.30 (1H, ddd, J = 6.5, 2.5, 1.4 Hz, H4), 4.49 (1H, ddd, J = 7.2, 7.0, 3.2 Hz, H3), 4.71 (1H, dd, J = 6.2, 2.5 Hz, H5). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 24.4 (CH_{3exo}), 27.1 (CH_{3endo}), 34.4 (C6), 38.4 (C2), 71.7 (C3), 71.7 (C1), 72.2 (C4), 76.0 (C5), 109.9 ($C_{isoprop.}$), 179.0 (C=O). HRMS (ESI) Calcd for $C_{10}H_{14}NaO_5$: 237.0733. Found: 237.0731.

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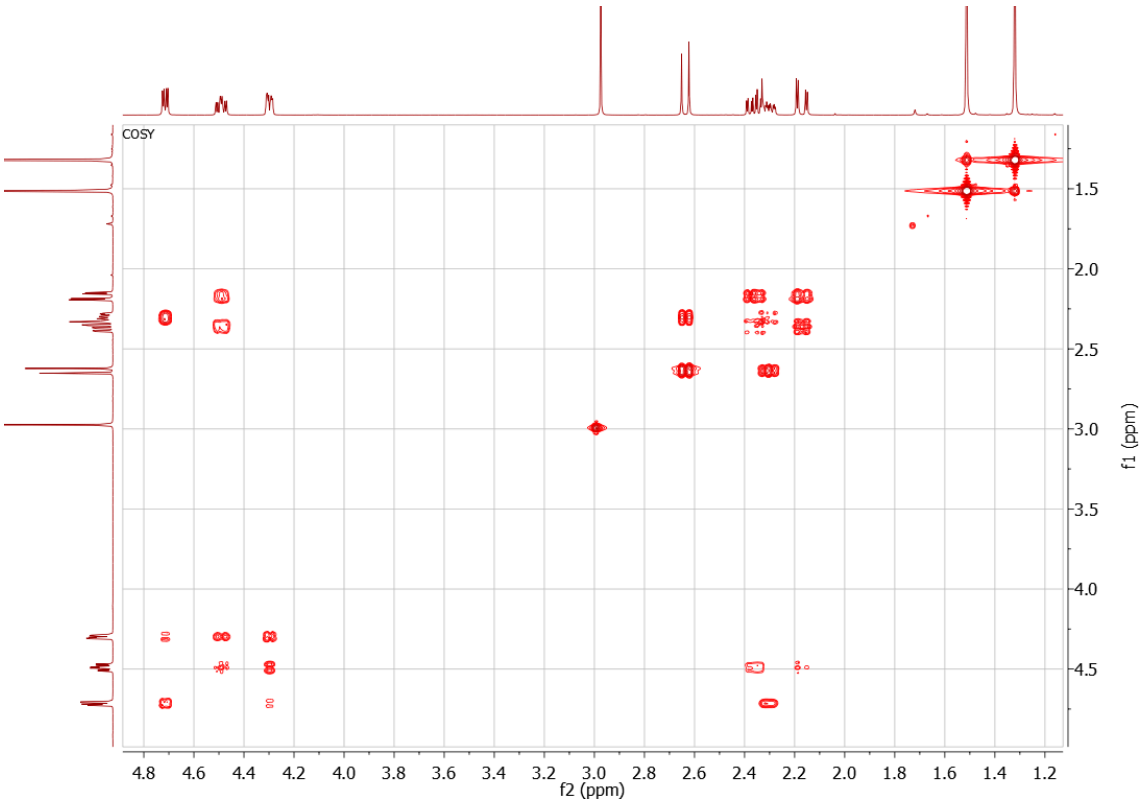
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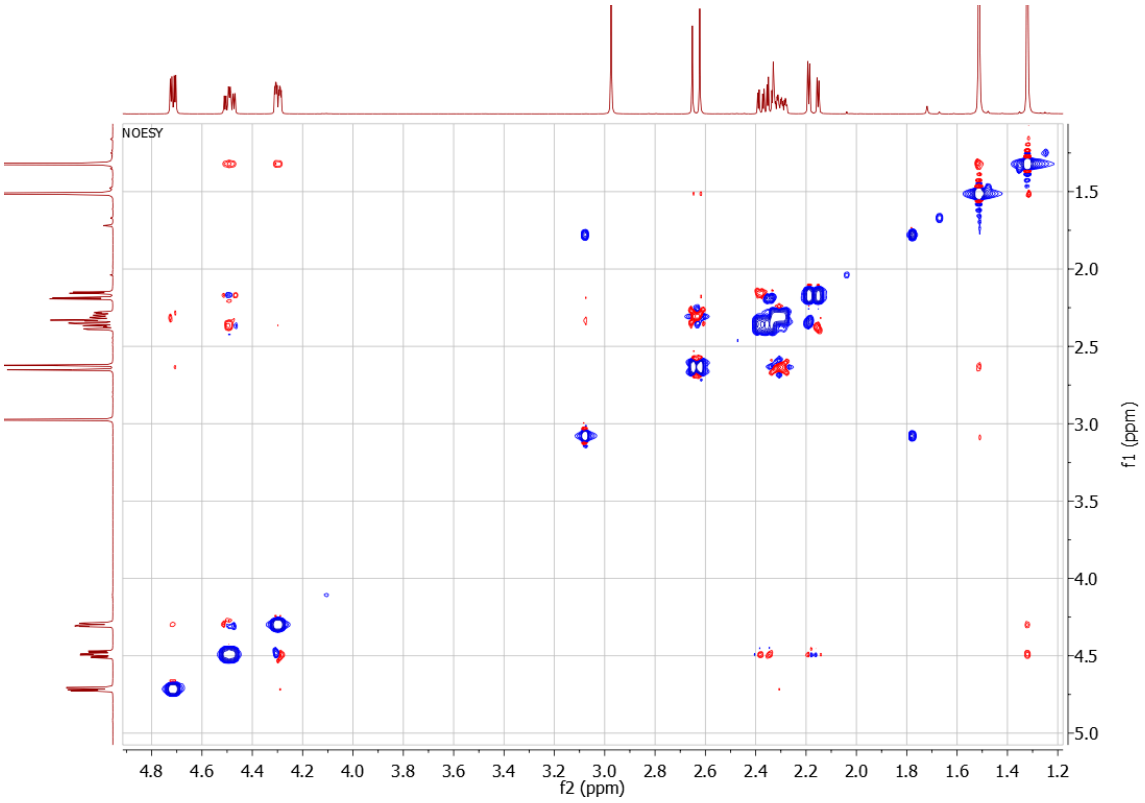
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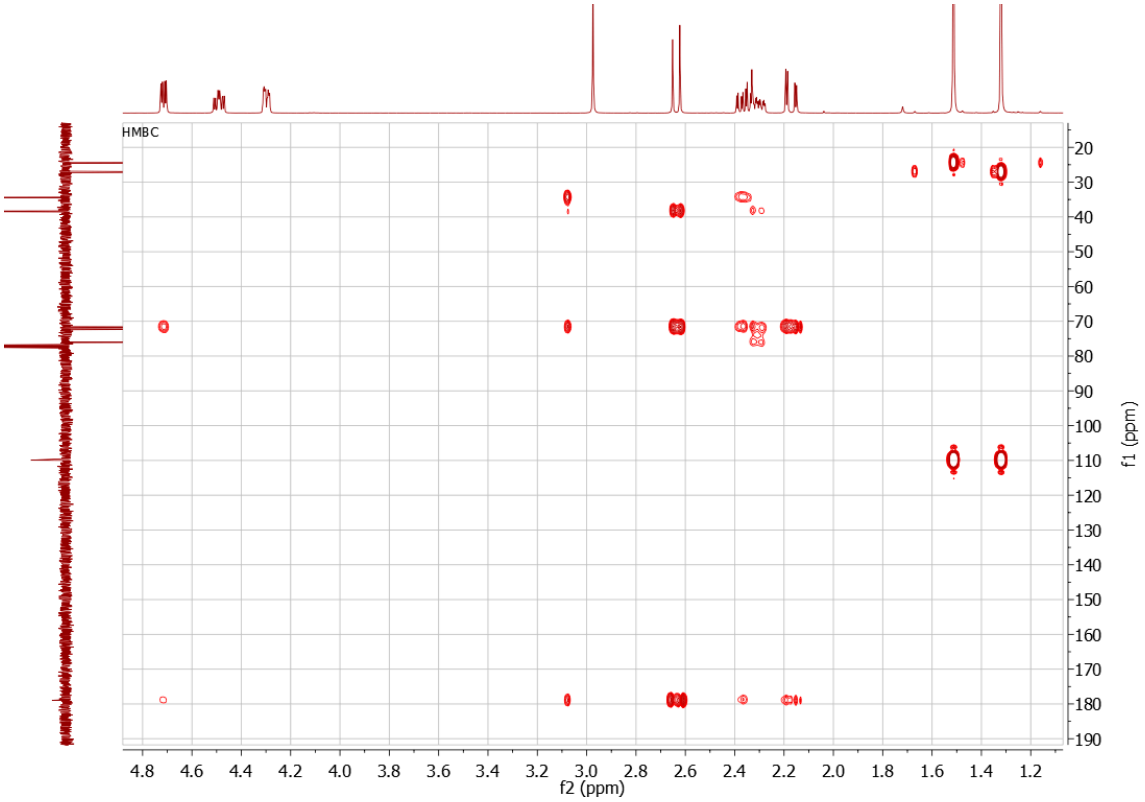
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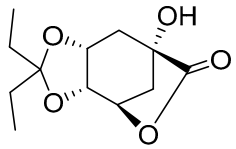
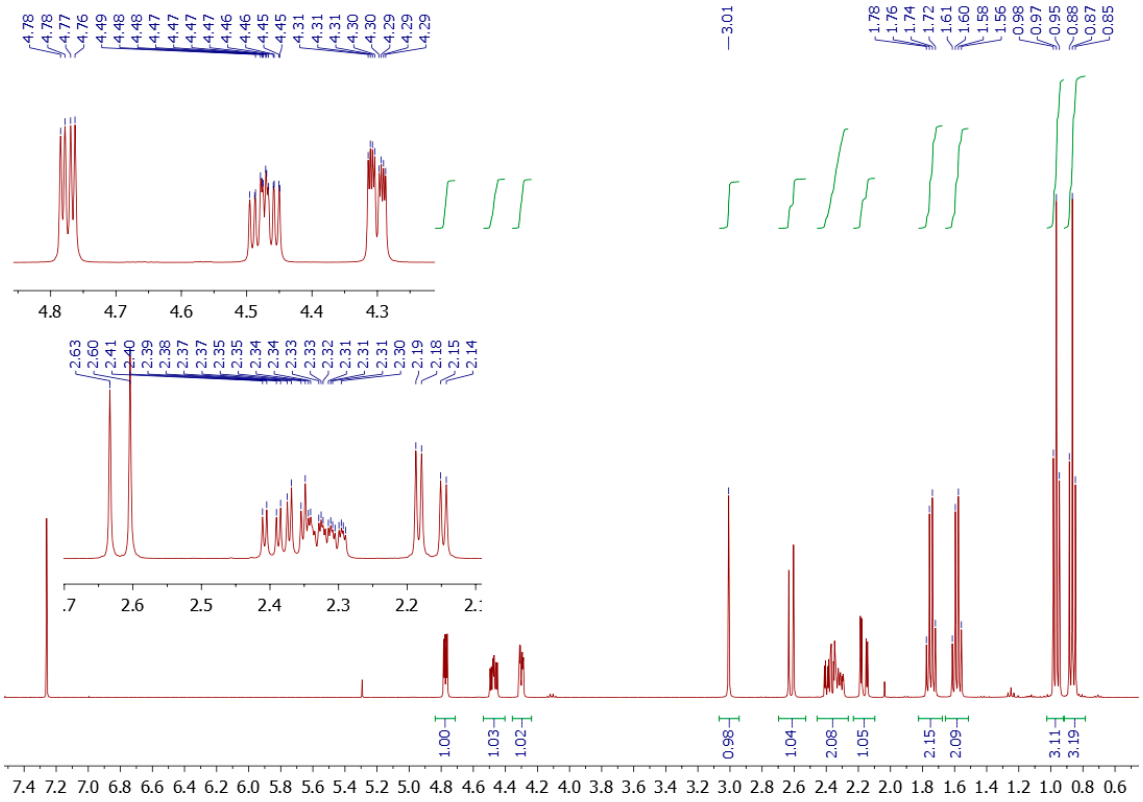
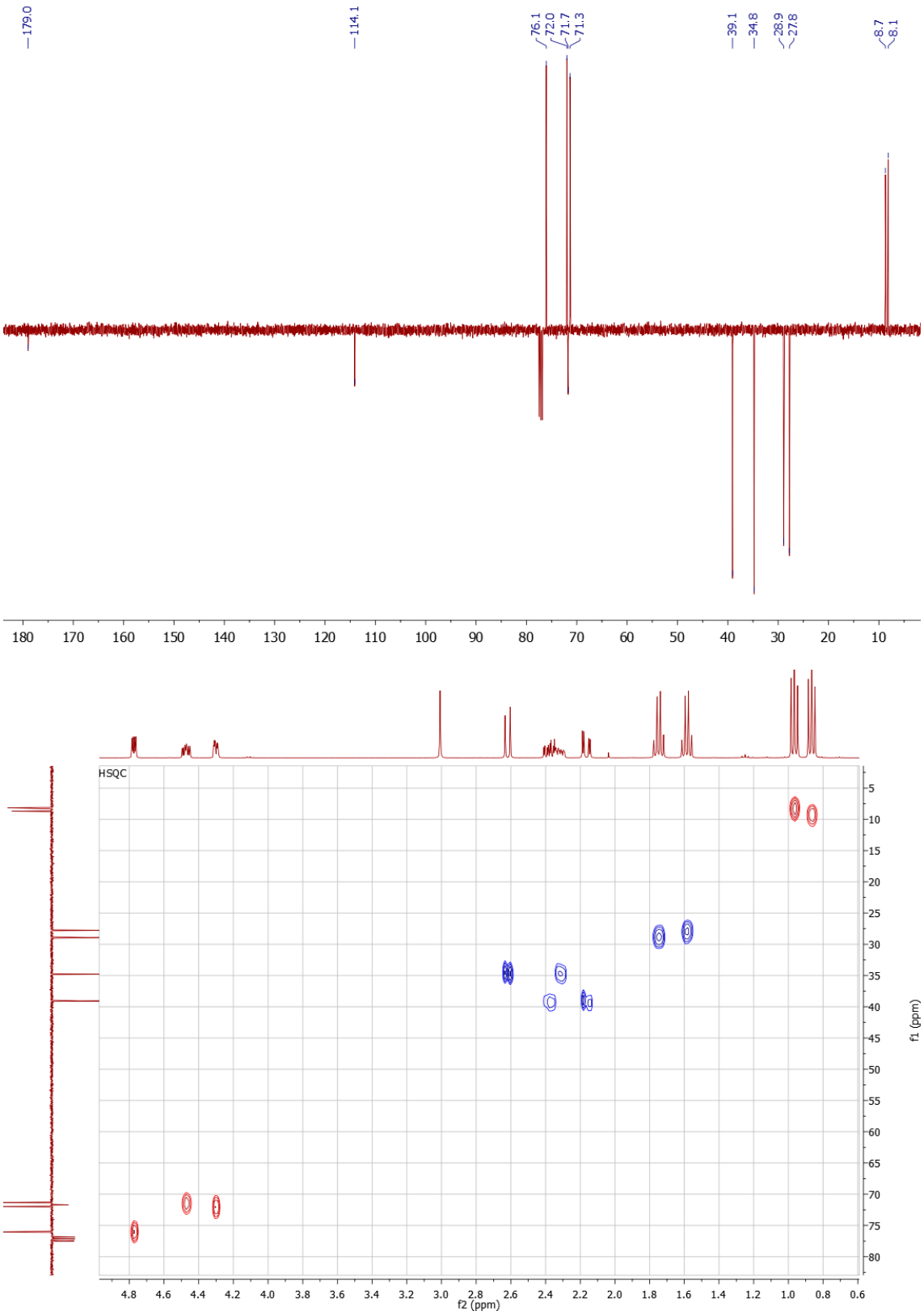


2b

3,4-*O*-Pent-2-ylidenequinic acid 1,5-lactone (2b) [4]**.** To a solution of quinic acid (192 mg, 1 mmol) in pentan-3-one (4 mL) was added deloxan (13 mg, 0.01 mmol). The mixture was stirred at 101 ºC for 24 h, then the acid catalyst was removed by filtration, the filtrate was concentrated under vacuum and purified by column chromatography on silica gel (hexanes/EtOAc = 6:4, Rf 0.3), affording the compound **2b** (230 mg, 95 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.87 (3H, t, J = 7.5 Hz, CH_{3exo}), 0.97 (3H, t, J = 7.5 Hz, CH_{3endo}), 1.59 (2H, q, J = 7.5 Hz, OCH_2CH_{3exo}), 1.75 (2H, q, J = 7.5 Hz, OCH_2CH_{3endo}), 2.17 (1H, dd, J = 14.4, 3.3 Hz, $H2_{ax}$), 2.32 (1H, dddd, J = 11.8, 6.2, 2.7, 1.3 Hz, $H6_{eq}$), 2.38 (1H, ddd, J = 14.4, 8.1, 2.7 Hz, $H2_{eq}$), 2.62 (1H, d, J = 11.8 Hz, $H6_{ax}$), 3.01 (1H, br s, OH), 4.30 (1H, ddd, J = 6.5, 2.7, 1.3 Hz, H4), 4.47 (1H, ddd, J = 8.1, 6.5, 2.7 Hz, H3), 4.77 (1H, dd, J = 6.2, 2.7 Hz, H5). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 8.1 (CH_{3endo}), 8.7 (CH_{3exo}), 27.8 (CCH_2CH_{3exo}), 28.9 (CCH_2CH_{3endo}), 34.8 (C6), 39.1 (C2), 71.3 (C3), 71.7 (C1), 72.0 (C4), 76.1 (C5), 114.1 ($C_{pentylid.}$), 179.0 (C=O). HRMS (ESI) Calcd for $C_{12}H_{18}NaO_5$: 265.1046. Found: 265.1040.

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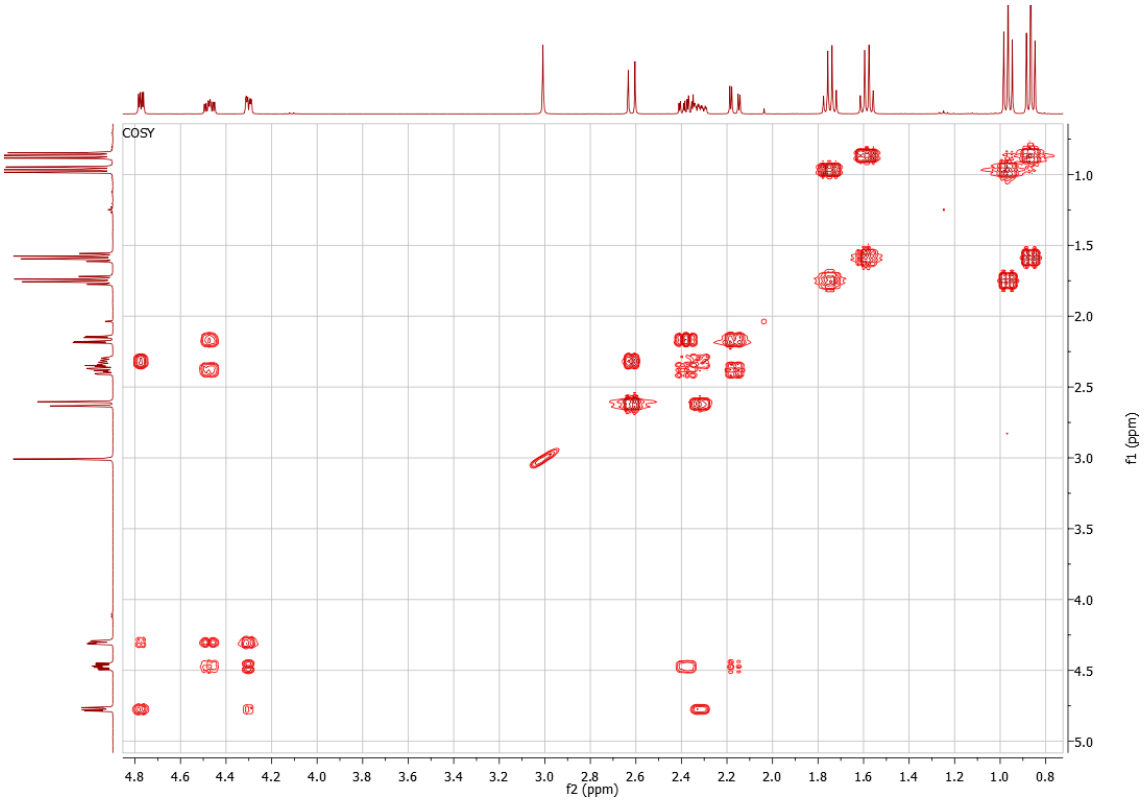
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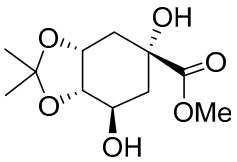
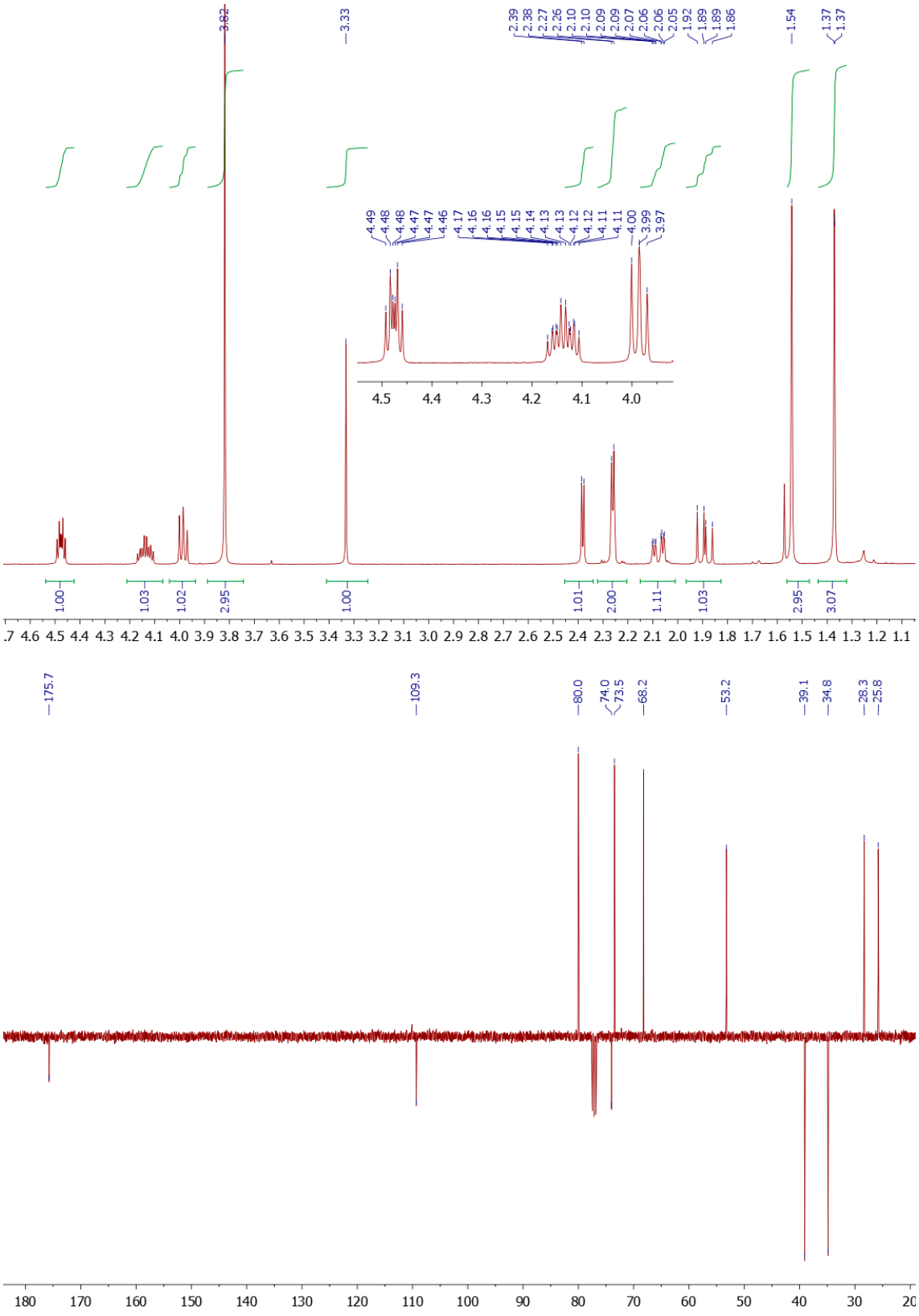


3aa

Methyl 3,4-*O*-isopropylidenequinate (3aa) [2]**.** To a solution of 3,4-*O*-isopropylidenequinic acid 1,5-lactone **(2a)** (214 mg, 1 mmol) in methanol (4 mL) was added TBD-PS (33 mg, 0.1 mmol). The mixture was stirred at 0 ºC for 48 h, then the catalyst was removed by filtration, the filtrate was concentrated under vacuum and purified by column chromatography on silica gel (hexanes/EtOAc = 4:6, Rf 0.3), affording the compound **3aa** (226 mg, 92 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.37 (3H, s, CH_{3endo}), 1.54 (3H, s, CH_{3exo}), 1.89 (1H, dd, J = 13.7, 10.7 Hz, $H2_{ax}$), 2.08 (1H, dd, J = 13.7, 4.2 Hz, $H2_{eq}$), 2.26 (2H, m, H6), 2.39 (1H, d, J = 3.6 Hz, CHO*H*), 3.33 (1H, br s, OH), 3.82 (3H, s, OCH_3), 3.99 (1H, dd, J = 6.4, 5.7 Hz, H4), 4.14 (1H, dddd, J = 10.7, 6.4, 4.2, 3.7 Hz, H3), 4.48 (1H, dt, J = 5.7, 3.7 Hz, H5). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 25.8 (CH_{3endo}), 28.3 (CH_{3exo}), 34.8 (C6), 39.1 (C2), 53.2 (OCH_3), 68.2 (C3), 73.5 (C5), 74.0 (C1), 80.0 (C4), 109.3 ($C_{isoprop.}$), 175.7 (C=O). HRMS (ESI) Calcd for $C_{11}H_{18}NaO_6$: 269.0996. Found: 269.1009.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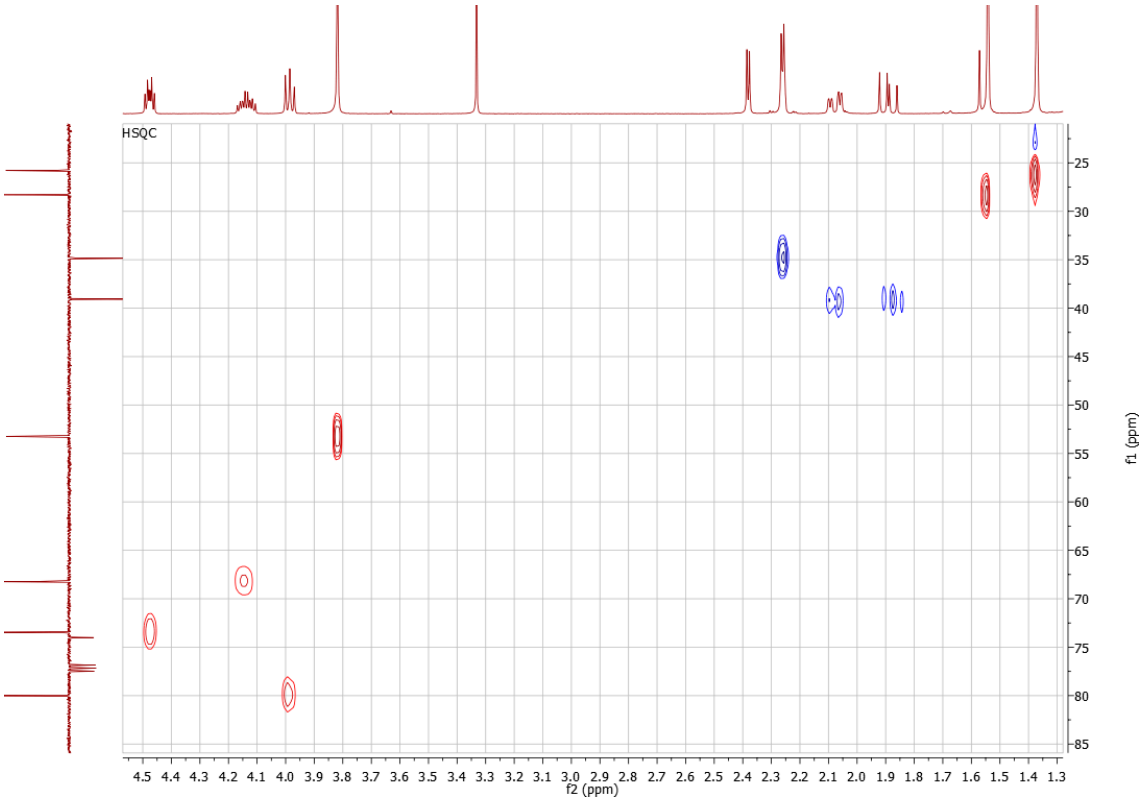
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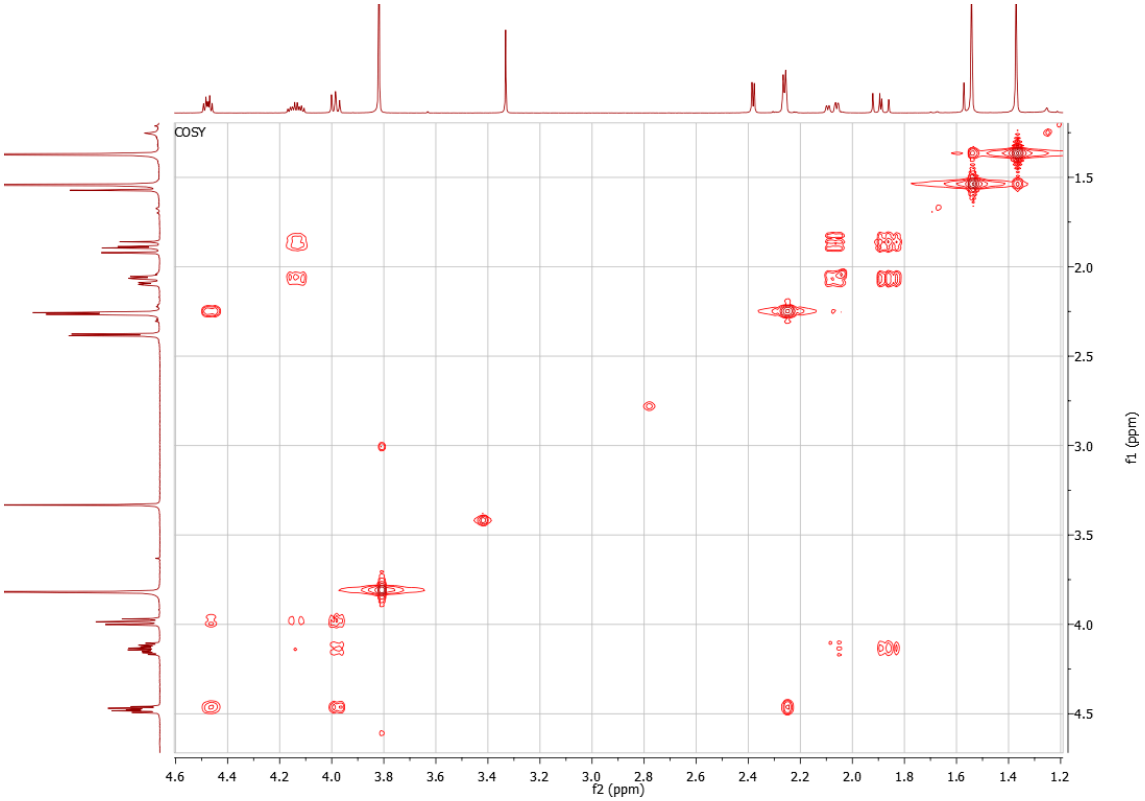
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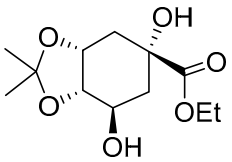
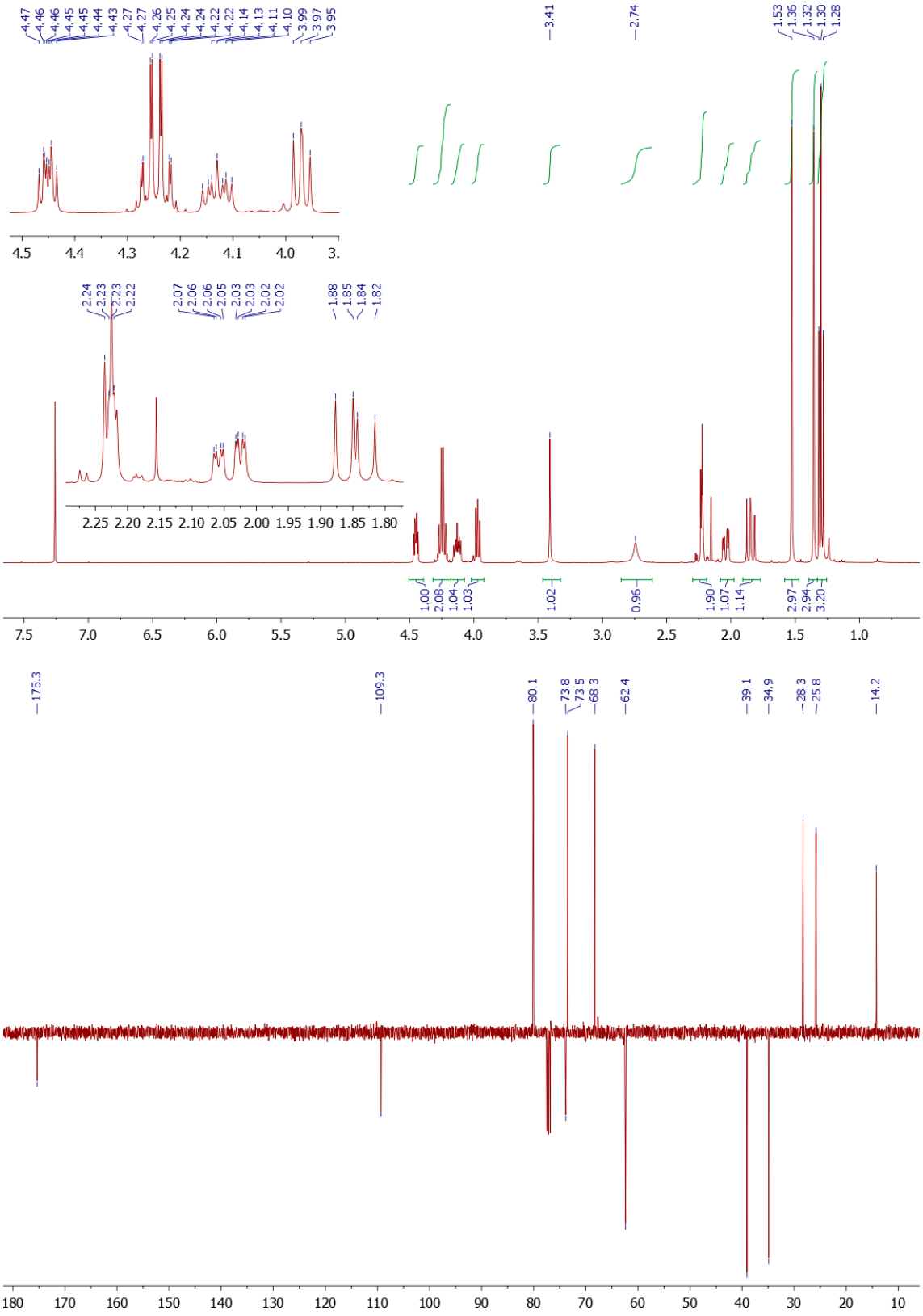


3ab

Ethyl 3,4-*O*-isopropylidenequinate (3ab). To a solution of 3,4-*O*-isopropylidenequinic acid 1,5-lactone **(2a)** (214 mg, 1 mmol) in ethanol (4 mL) was added TBD-PS (33 mg, 0.1 mmol). The mixture was stirred at 0 ºC for 48 h, then the catalyst was removed by filtration, the filtrate was concentrated under vacuum and purified by column chromatography on silica gel (hexanes/EtOAc = 4:6, Rf 0.3), affording the compound **3ab** (215 mg, 83 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.30 (3H, t, J = 7.1 Hz, OCH_2CH_3), 1.36 (3H, s, CH_{3endo}), 1.53 (3H, s, CH_{3exo}), 1.85 (1H, dd, J = 13.6, 11.0 Hz, $H2_{ax}$), 2.04 (1H, ddd, J = 13.6, 4.3, 1.5 Hz, $H2_{eq}$), 2.16–2.27 (2H, m, H6), 2.74 (1H, br s, OH), 3.41 (1H, br s, OH), 3.97 (1H, dd, J = 6.4, 5.7 Hz, H4), 4.13 (1H, ddd, J = 11.0, 6.4, 4.0 Hz, H3), 4.24 (1H, dq, J = 10.6, 7.1 Hz, $OCHHCH_3$), 4.25 (1H, dq, J = 10.6, 7.1 Hz, $OCHHCH_3$), 4.45 (1H, ddd, J = 5.7, 4.2, 3.6 Hz, H5). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 14.2 (OCH_2CH_3), 25.8 (CH_{3endo}), 28.3 (CH_{3exo}), 34.9 (C6), 39.1 (C2), 62.4 (OCH_2CH_3), 68.3 (C3), 73.5 (C5), 73.8 (C1), 80.1 (C4), 109.3 ($C_{isoprop.}$), 175.3 (C=O). HRMS (ESI) Calcd for $C_{12}H_{20}NaO_6$: 283.1152. Found: 283.1154.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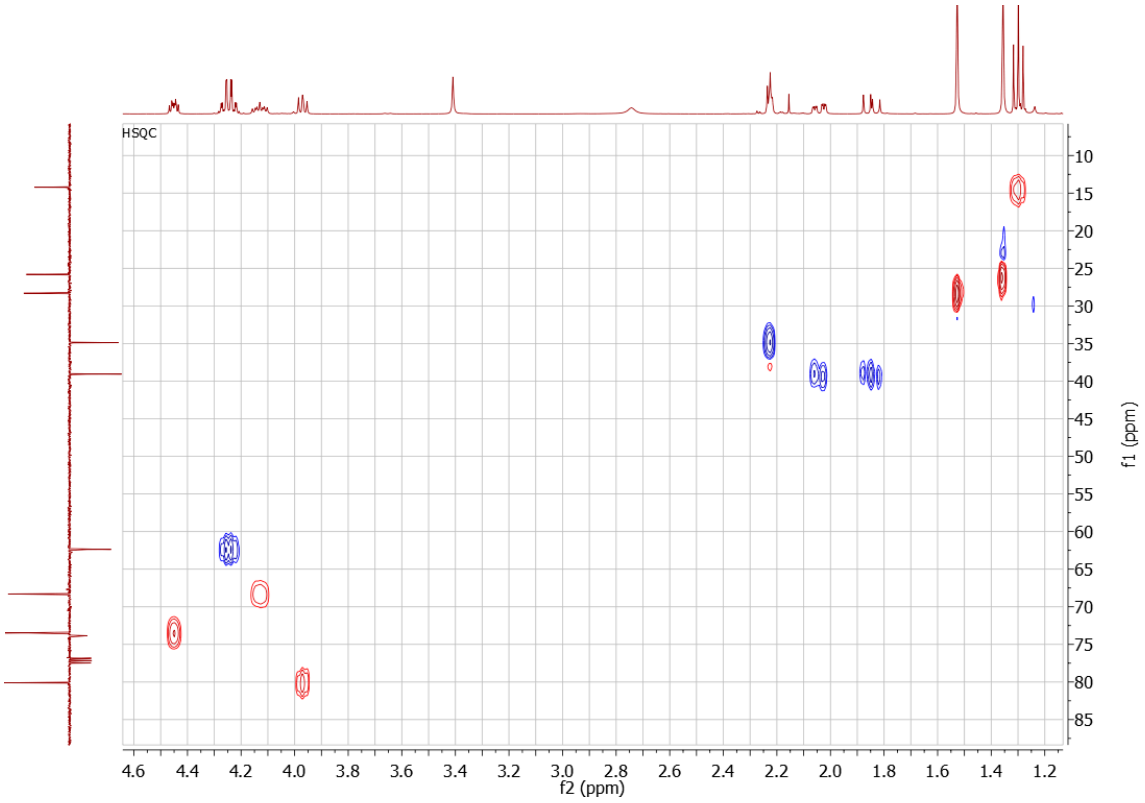
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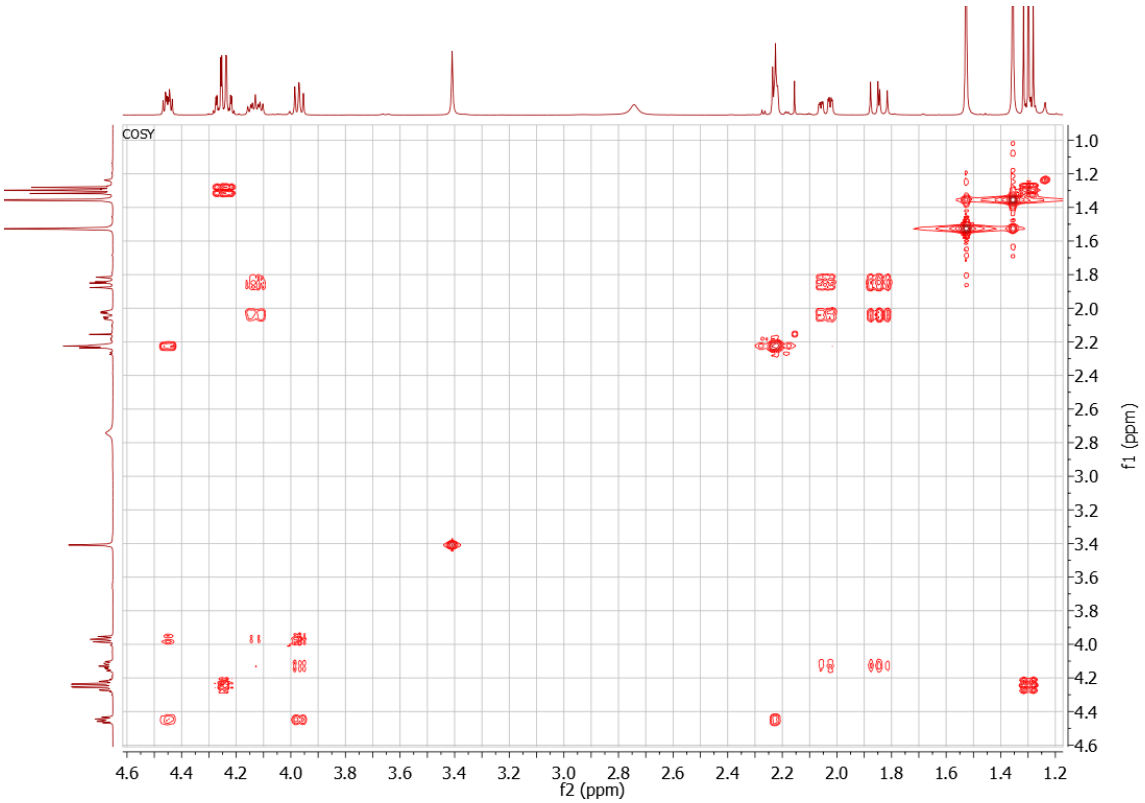
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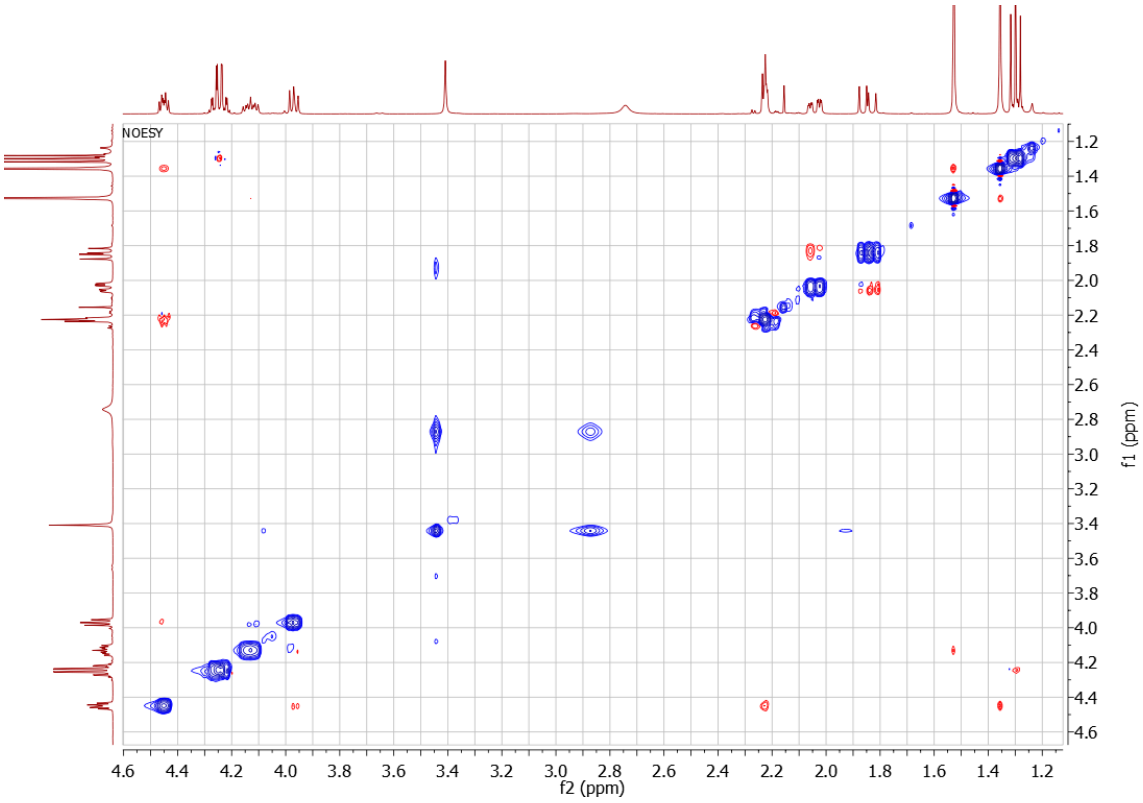
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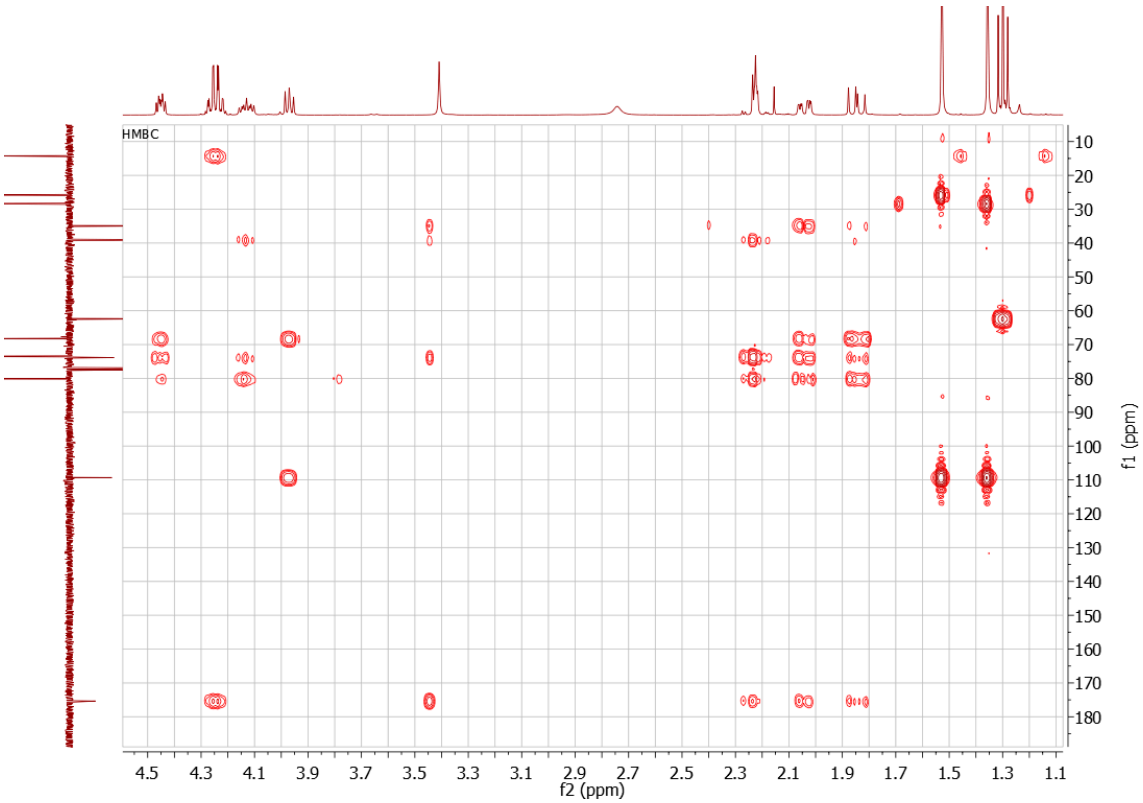
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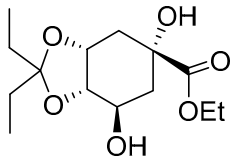
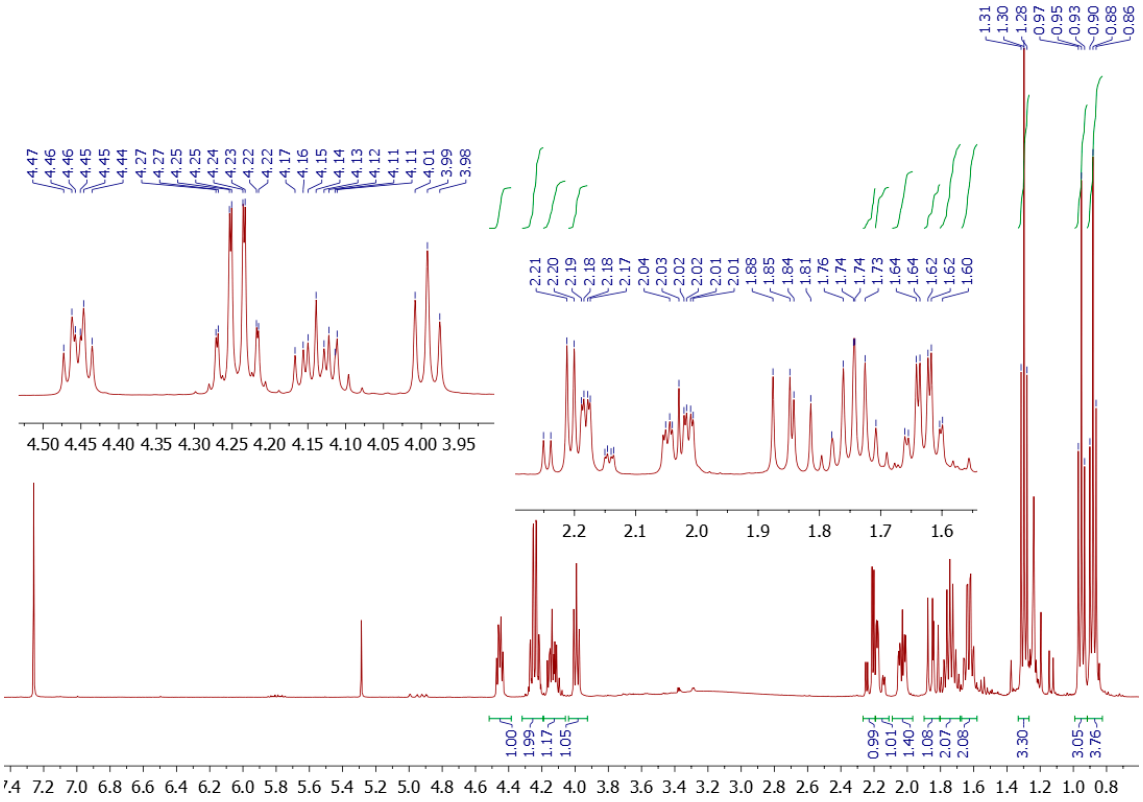
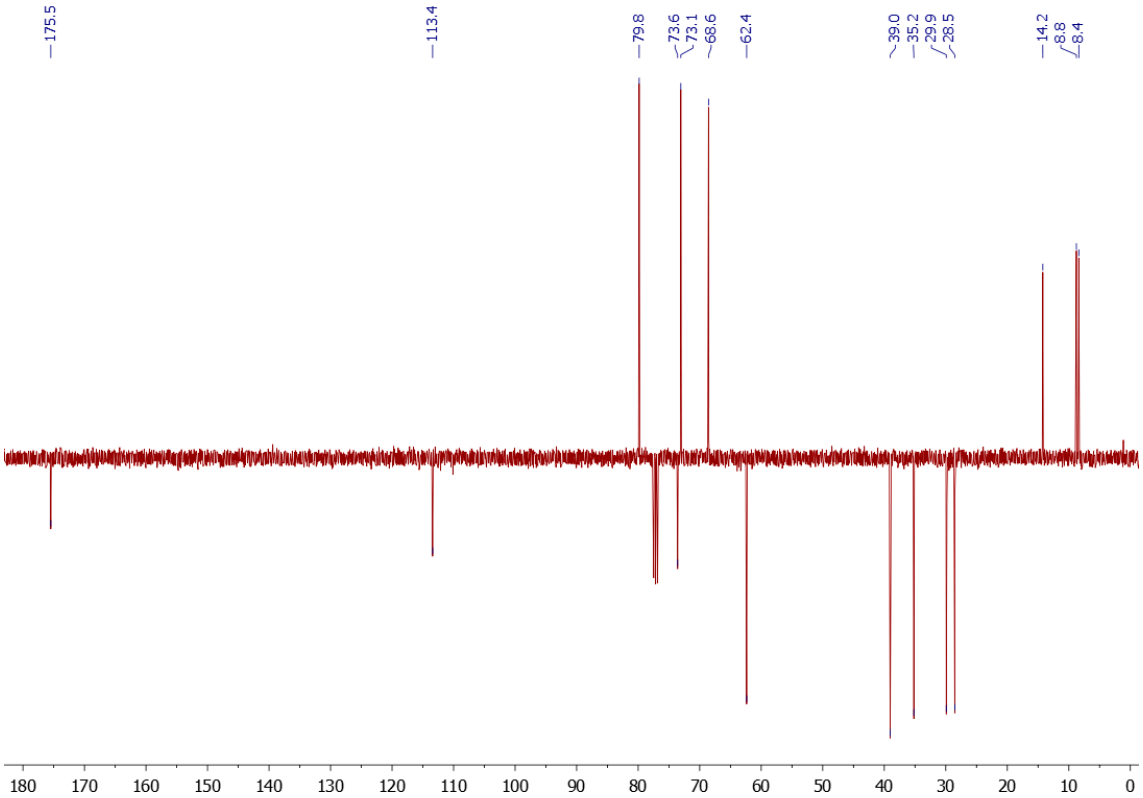


3bb

Ethyl 3,4-*O*-pent-3-ylidenequinate (3bb). To a solution of 3,4-*O*-pent-2-ylidenequinic acid 1,5-lactone **(2b)** (242 mg, 1 mmol) in ethanol (4 mL) was added TBD-PS (33 mg, 0.1 mmol). The mixture was stirred at 0 ºC for 48 h, then the catalyst was removed by filtration, the filtrate was concentrated under vacuum and purified by column chromatography on silica gel (hexanes/EtOAc = 3:7, Rf 0.3), affording the compound **3bb** (239 mg, 83 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.88 (3H, t, J = 7.5 Hz, CCH_2CH_{3endo}), 0.95 (3H, t, J = 7.5 Hz, CCH_2CH_{3exo}), 1.30 (3H, t, J = 7.1 Hz, OCH_2CH_3), 1.62 (1H, dq, J = 13.5, 7.5 Hz, $CCHHCH_{3endo}$), 1.64 (1H, dq, J = 13.5, 7.5 Hz, $CCHHCH_{3endo}$), 1.72 (1H, dq, J = 14.1, 7.5 Hz, $CCHHCH_{3exo}$), 1.76 (1H, dq, J = 14.1, 7.5 Hz, $CCHHCH_{3exo}$), 1.85 (1H, dd, J = 13.7, 11.0 Hz, $H2_{ax}$), 2.03 (1H, ddd, J = 13.7, 4.3, 1.7 Hz, $H2_{eq}$), 2.16 (1H, ddd, J = 15.3, 4.1, 1.7 Hz, $H6_{eq}$), 2.23 (1H, dd, J = 15.3, 4.8 Hz, $H6_{ax}$), 3.99 (1H, t, J = 6.5 Hz, H4), 4.14 (1H, ddd, J = 11.0, 6.3, 4.3 Hz, H3), 4.24 (1H, dq, J = 10.6, 7.1 Hz, $OCHHCH_3$), 4.25 (1H, dq, J = 10.6, 7.1 Hz, $OCHHCH_3$), 4.45 (1H, dt, J = 6.3, 4.4 Hz, H5). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 8.4 (CCH_2CH_{3exo}), 8.8 (CCH_2CH_{3endo}), 14.2 (OCH_2CH_3), 28.5 (CCH_2CH_{3endo}), 29.9 (CCH_2CH_{3exo}), 35.2 (C6), 39.0 (C2), 62.4 (OCH_2CH_3), 68.6 (C3), 73.1 (C5), 73.6 (C1), 79.8 (C4), 113.4 ($C_{pentylid}$), 175.5 (C=O). HRMS (ESI) Calcd for $C_{14}H_{24}NaO_6$: 311.1465. Found: 311.1457.

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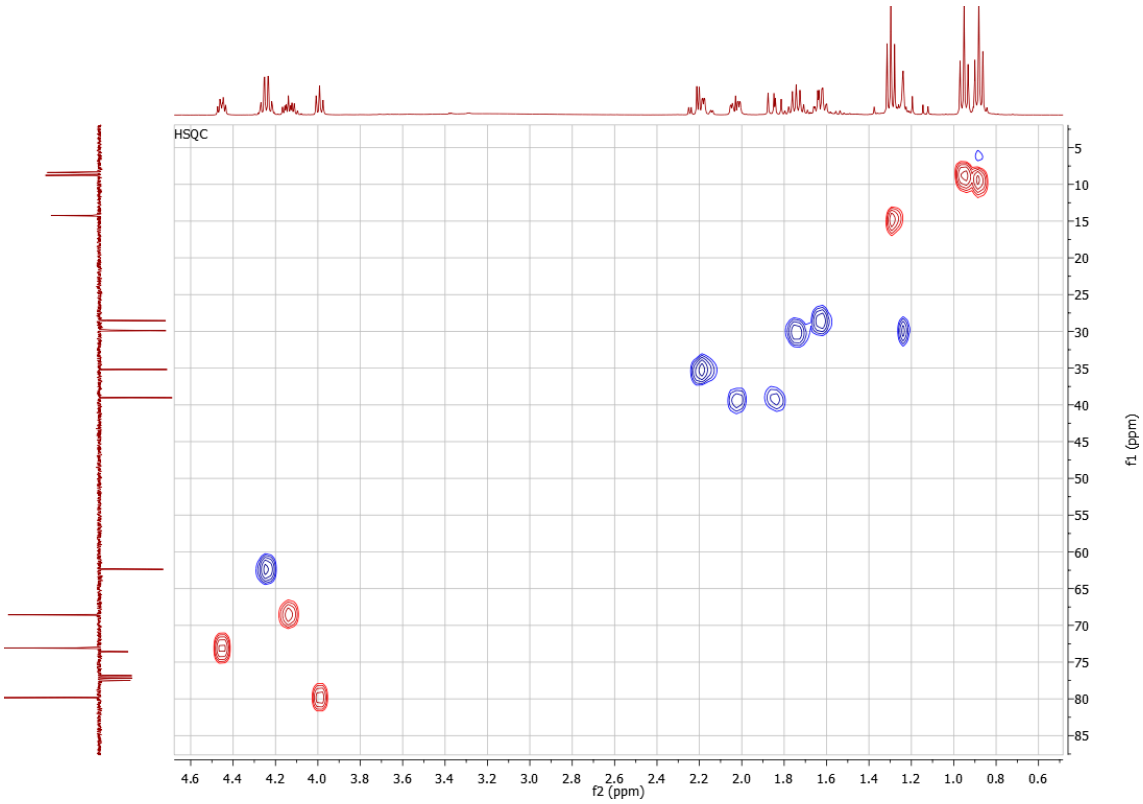
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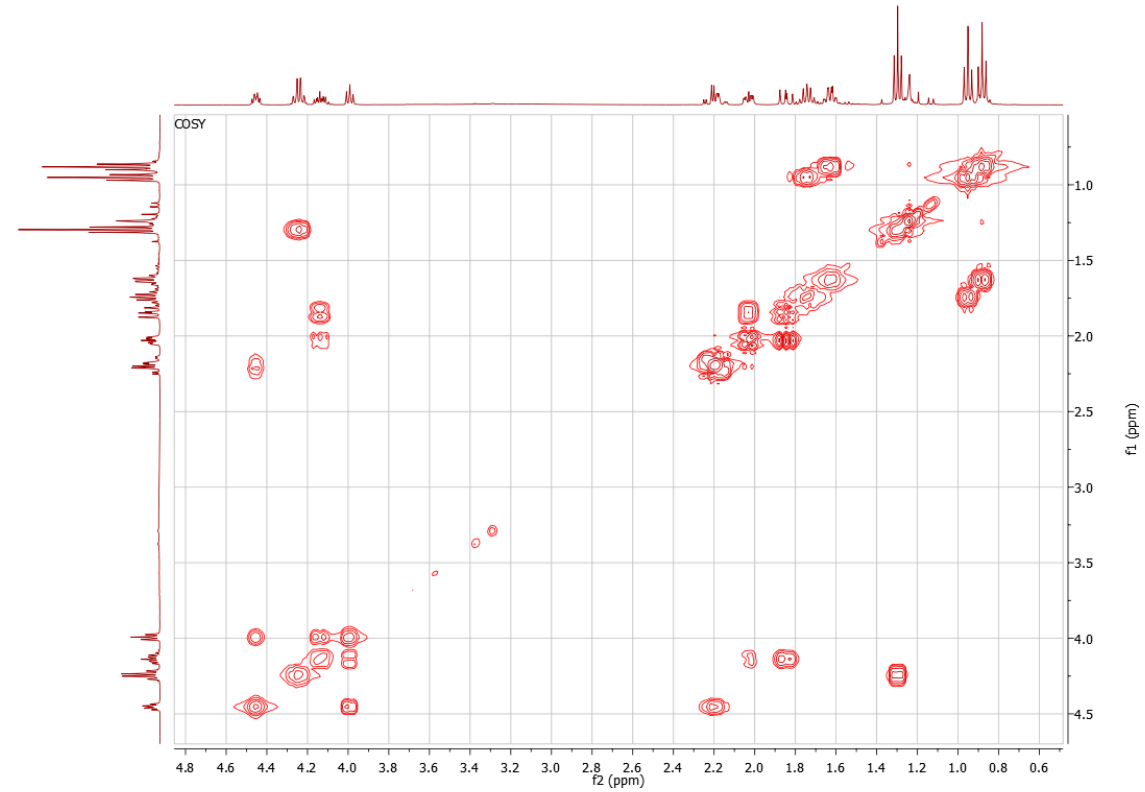
f1 (ppm)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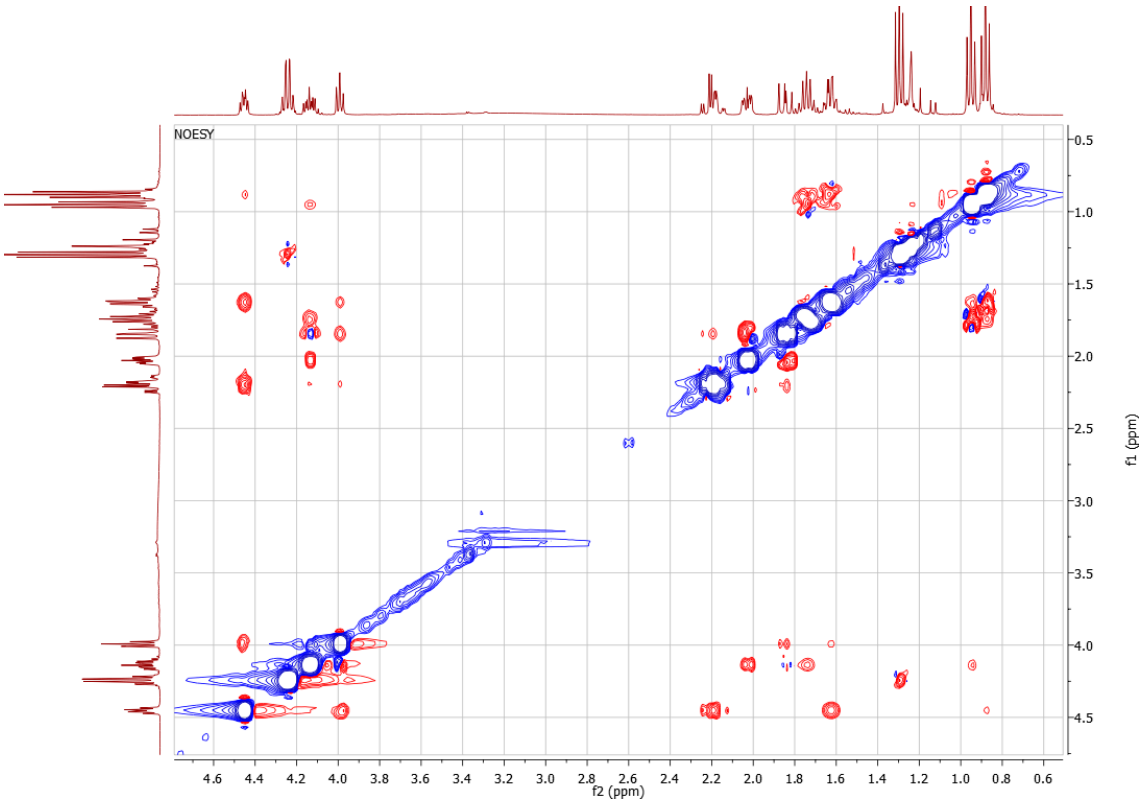
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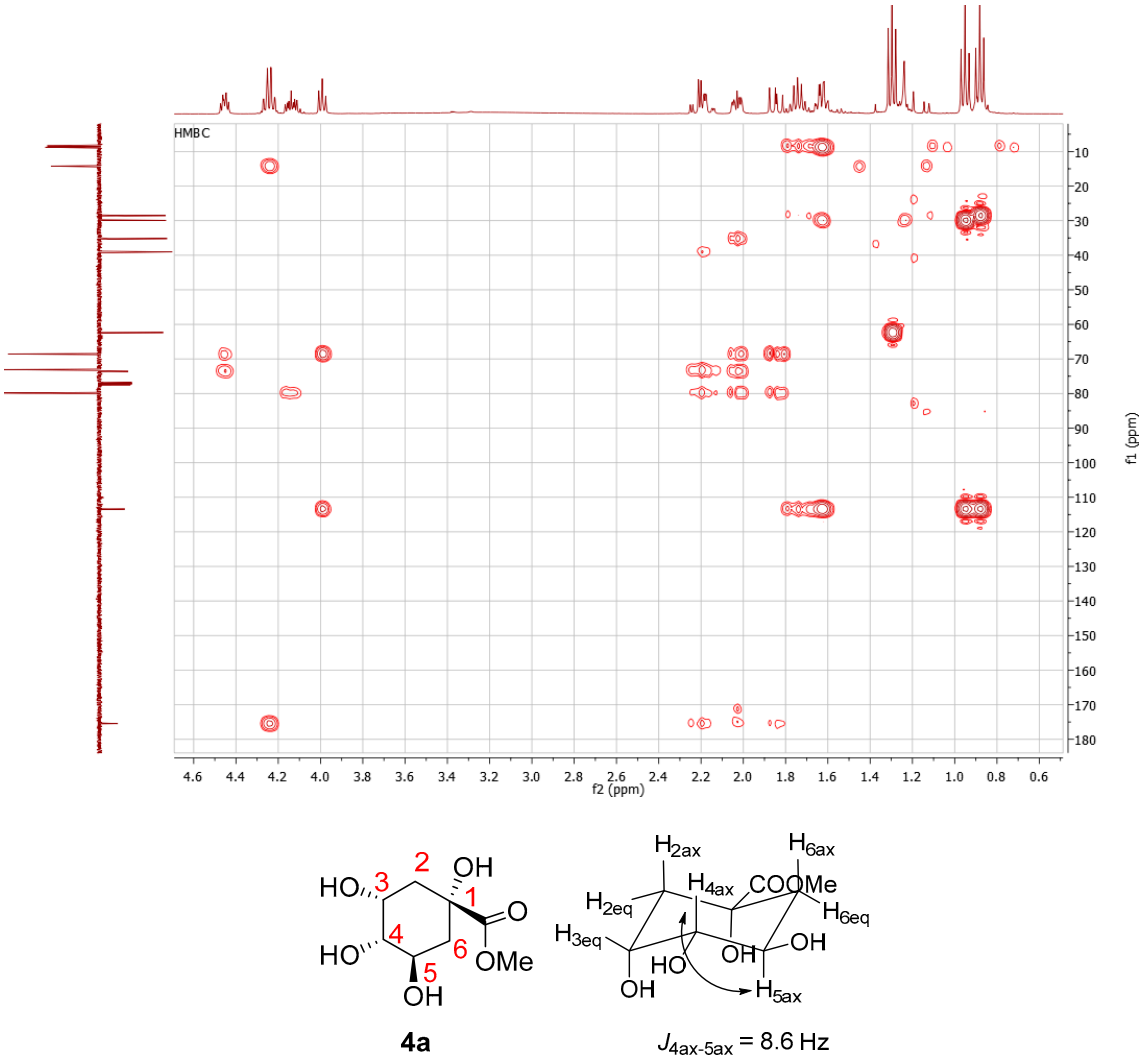
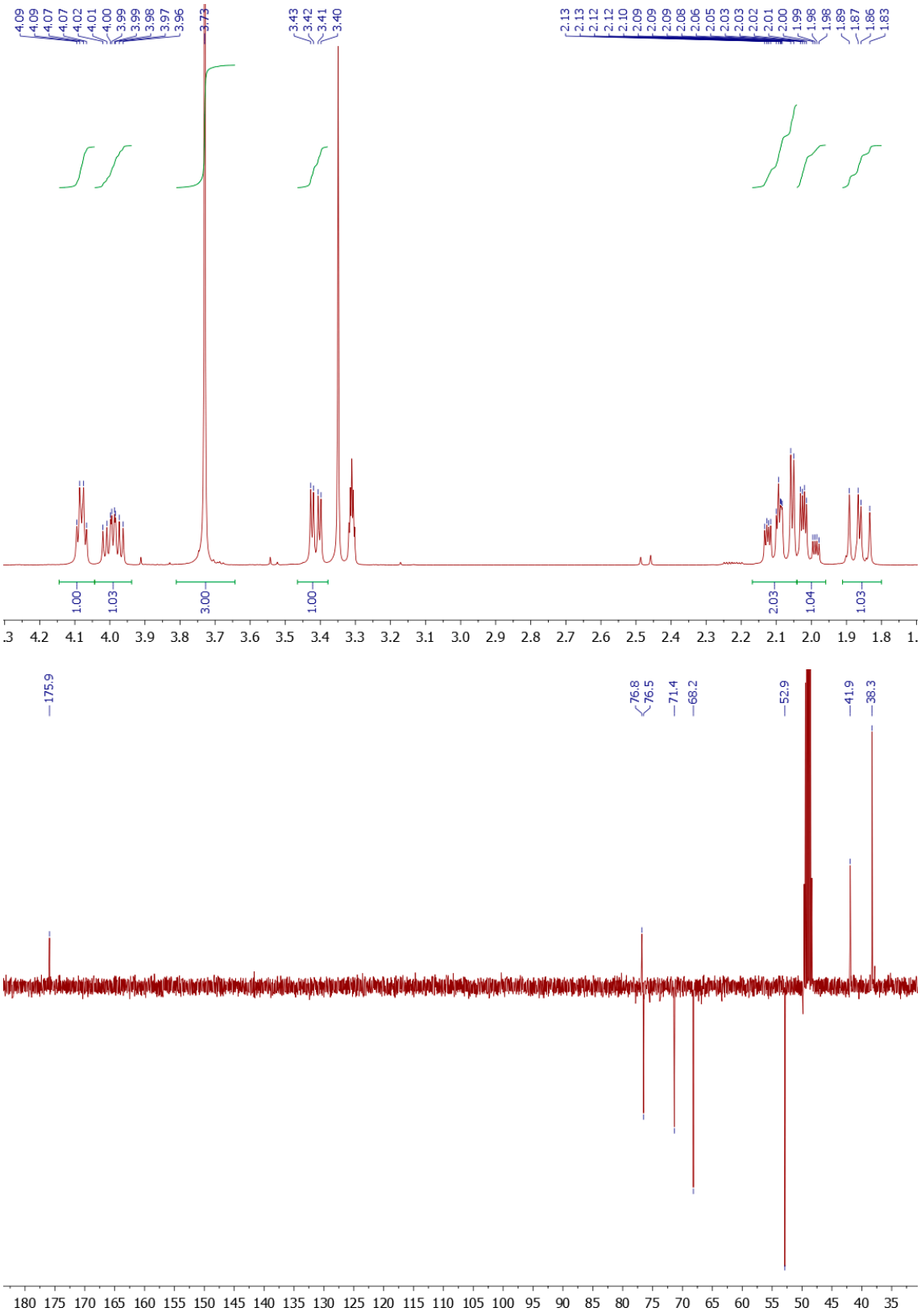
f2 (ppm)
f1 (ppm)



Methyl quinate (4a) [5-7]**.** To a solution of quinic acid (192 mg, 1 mmol) in methanol (4 mL) was added deloxan (13 mg, 0.01 mmol). The mixture was stirred at 65 ºC for 48 h, then the acid catalyst was removed by filtration and the filtrate was concentrated under vaccum. The product was crystallized from dichloromethane/methanol affording the compound **4a** (165 mg, 80 %). ^{1}H NMR (400 MHz, CD_3OD) δ_H 1.86 (1H, dd, J = 13.2, 10.1 Hz, $H6_{ax}$), 2.00 (1H, ddd, J = 14.2, 4.7, 2.3 Hz, $H2_{ax}$), 2.07 (1H, dd, J = 14.2, 3.4 Hz, $H2_{eq}$), 2.11 (1H, ddd, J = 13.2, 4.5, 2.3 Hz, $H6_{eq}$), 3.41 (1H, dd, J = 8.6, 3.2 Hz, H4), 3.73 (3H, s, OCH_3), 3.99 (1H, ddd, J = 10.1, 8.6, 4.5 Hz, H5), 4.08 (1H, ddd, J = 4.7, 3.4, 3.2 Hz, H3). ^{13}C NMR (100.6 MHz, CD_3OD) δ_C 38.3 (C2), 41.9 (C6), 52.9 (OCH_3), 68.2 (C5), 71.4 (C3), 76.5 (C4), 76.8 (C1), 175.9 (C=O). HRMS (ESI) Calcd for $C_8H_{14}NaO_6$: 229.0683. Found: 229.0687.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4.07
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4.01
4.00
3.99
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3.98
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3.43
3.42
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2.05
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2.03
2.02
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1.83
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1.03
3.00
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2.03
1.04
1.03
.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.
175.9
76.8
76.5
71.4
68.2
52.9
41.9
38.3
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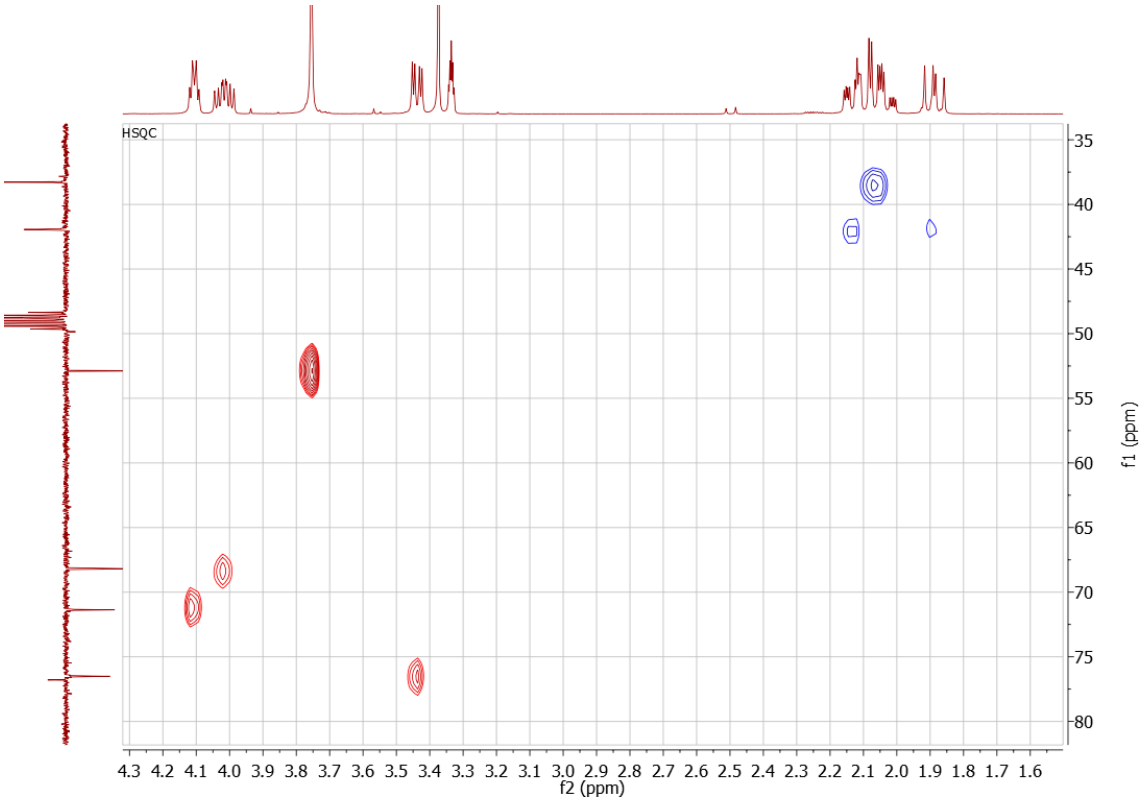
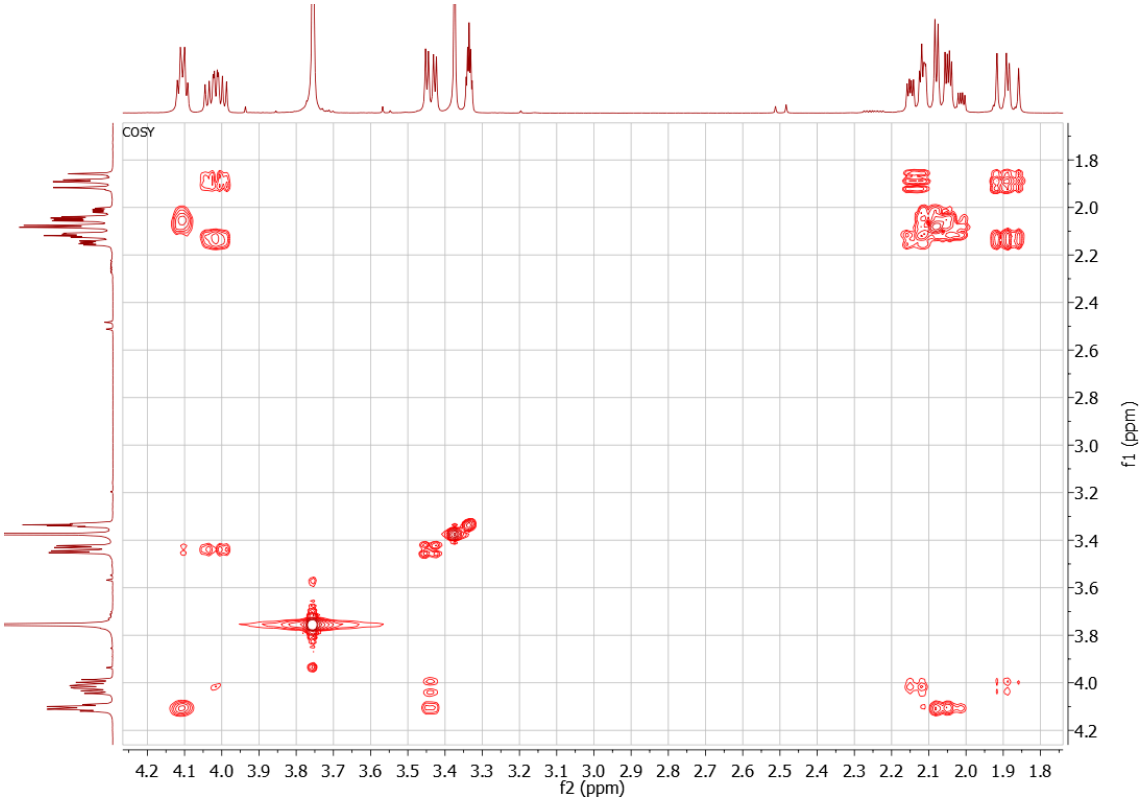

HSQC
35
40
45
50
55
60
65
70
75
80
f1 (ppm)
4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6
f2 (ppm)


COSY
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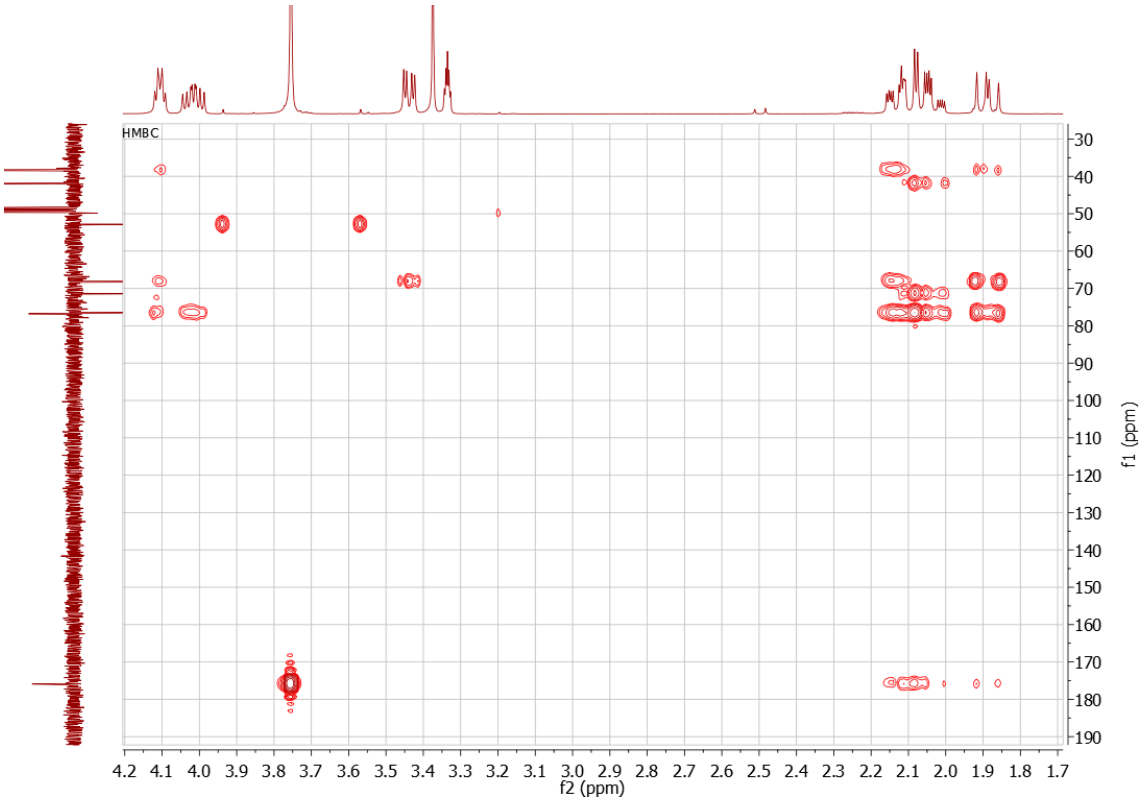
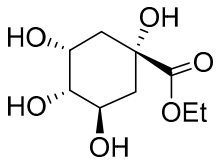
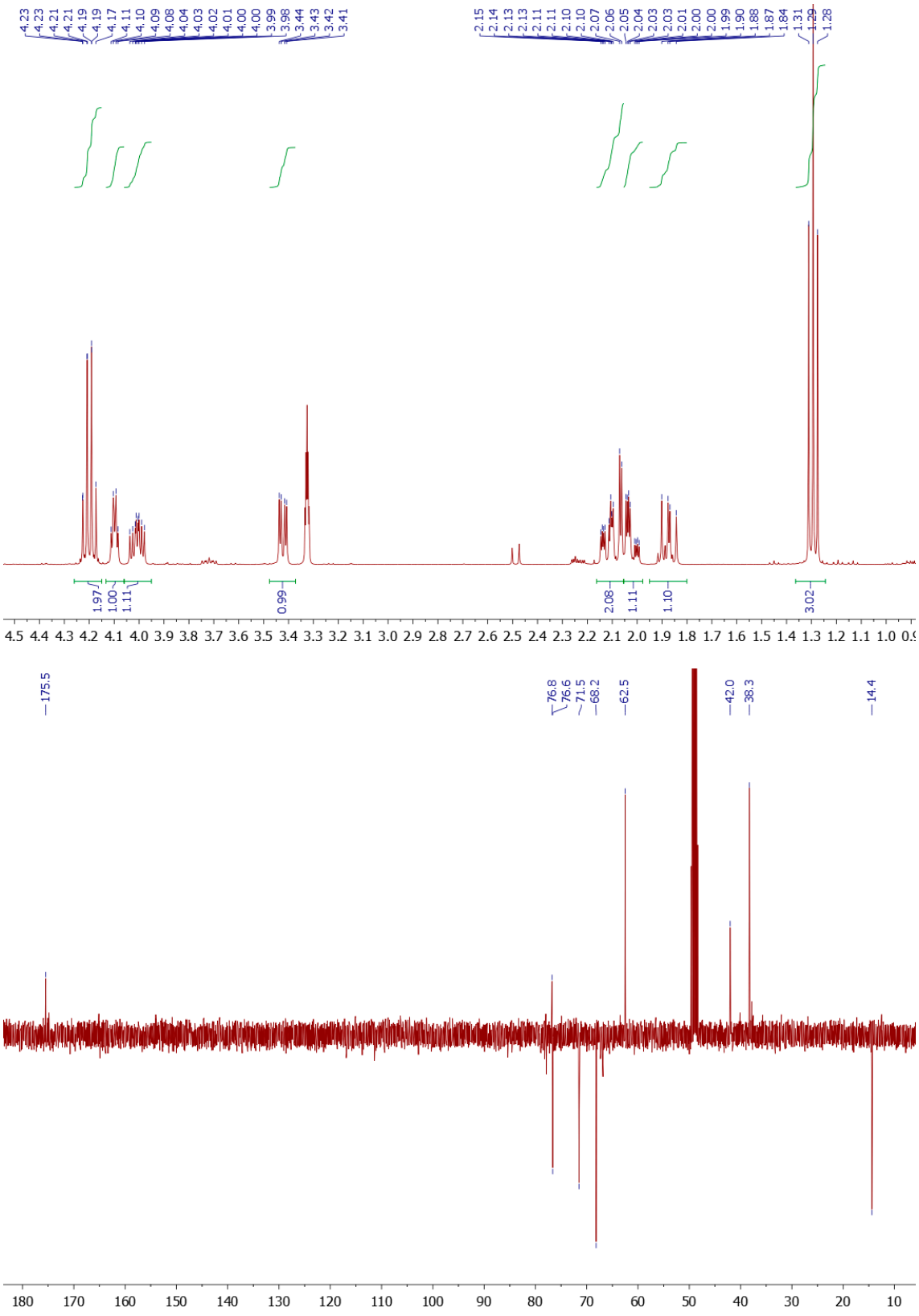
3.2
3.4
3.6
3.8
4.0
4.2
f1 (ppm)
4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8
f2 (ppm)





4b

Ethyl quinate (4b). To a solution of quinic acid (192 mg, 1 mmol) in ethanol (4 mL) was added SHTC (13 mg, 0.01 mmol). The mixture was stirred at 78 ºC for 72 h, then the acid catalyst was removed by filtration and the filtrate was concentrated under vacuum. The product was crystallized from dichloromethane/methanol affording the compound **4b** (172 mg, 78 %). ^{1}H NMR (400 MHz, CD_3OD) δ_H 1.29 (3H, t, J = 7.1, Hz, CH_3), 1.87 (1H, dd, J = 13.2, 10.2 Hz, $H6_{ax}$), 2.02 (1H, ddd, J = 14.3, 4.5, 2.5 Hz, $H2_{ax}$), 2.09 (1H, dd, J = 14.3, 3.4 Hz, $H2_{eq}$), 2.12 (1H, ddd, J = 13.2, 4.3, 2.3 Hz, $H6_{eq}$), 3.42 (1H, dd, J = 8.7, 3.2 Hz, H4), 4.01 (1H, ddd, J = 10.2, 8.7, 4.3 Hz, H5), 4.10 (1H, ddd, J = 4.5, 3.4, 3.2 Hz, H3), 4.19 (2H, q, J = 7.1 Hz, OCH_2CH_3). ^{13}C NMR (100.6 MHz, CD_3OD) δ_C 14.4 (CH_3), 38.3 (C2), 42.0 (C6), 62.5 (OCH_2CH_3), 68.2 (C5), 71.5 (C3), 76.6 (C4), 76.8 (C1), 175.5 (C=O). HRMS (ESI) Calcd for $C_9H_{16}NaO_6$: 243.0839. Found: 243.0847.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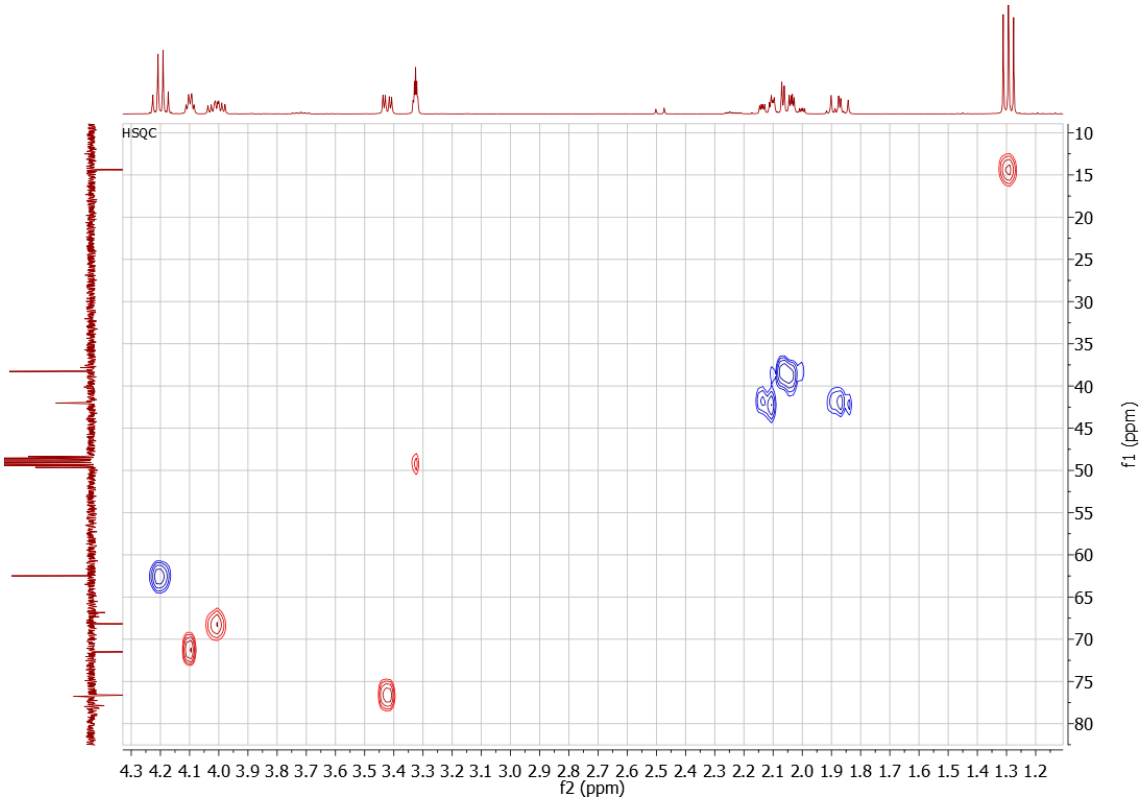
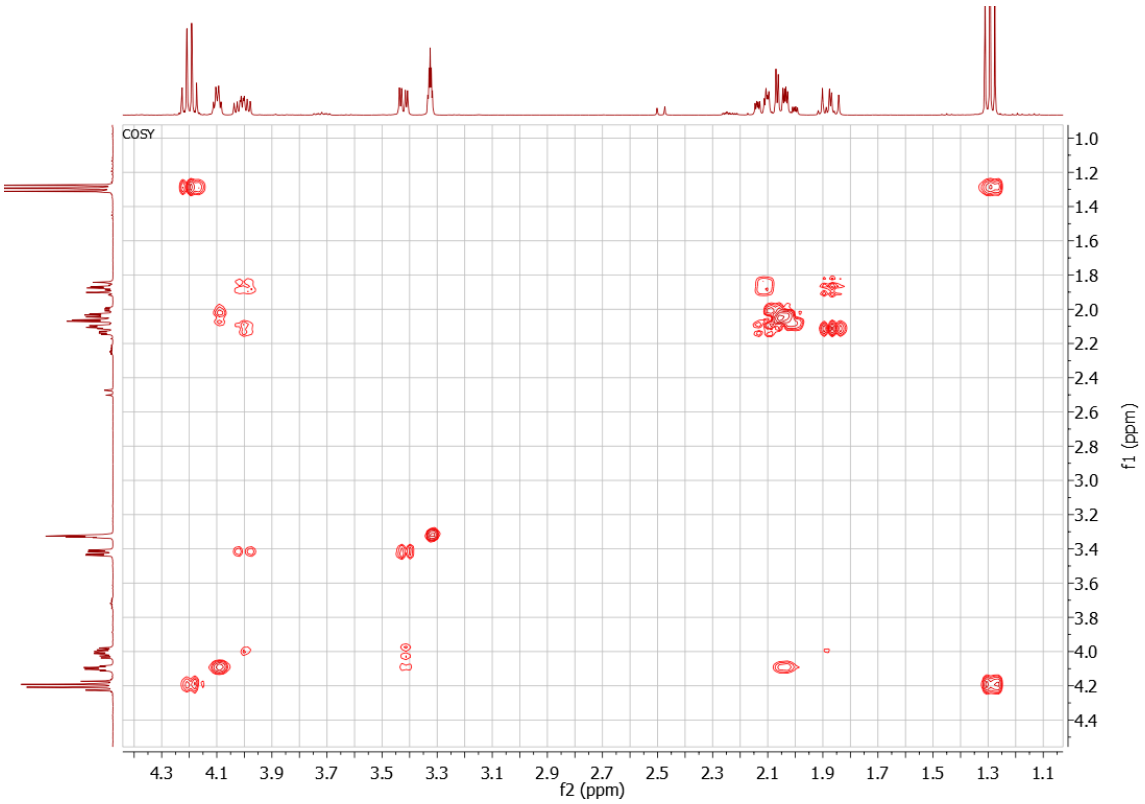
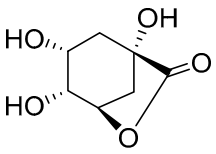
2.00
1.99
1.90
1.88
1.87
1.84
1.31
1.29
1.28
1.97
1.00
1.11
0.99
2.08
1.11
1.10
3.02
4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0
175.5
76.8
76.6
71.5
68.2
62.5
42.0
38.3
14.4
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

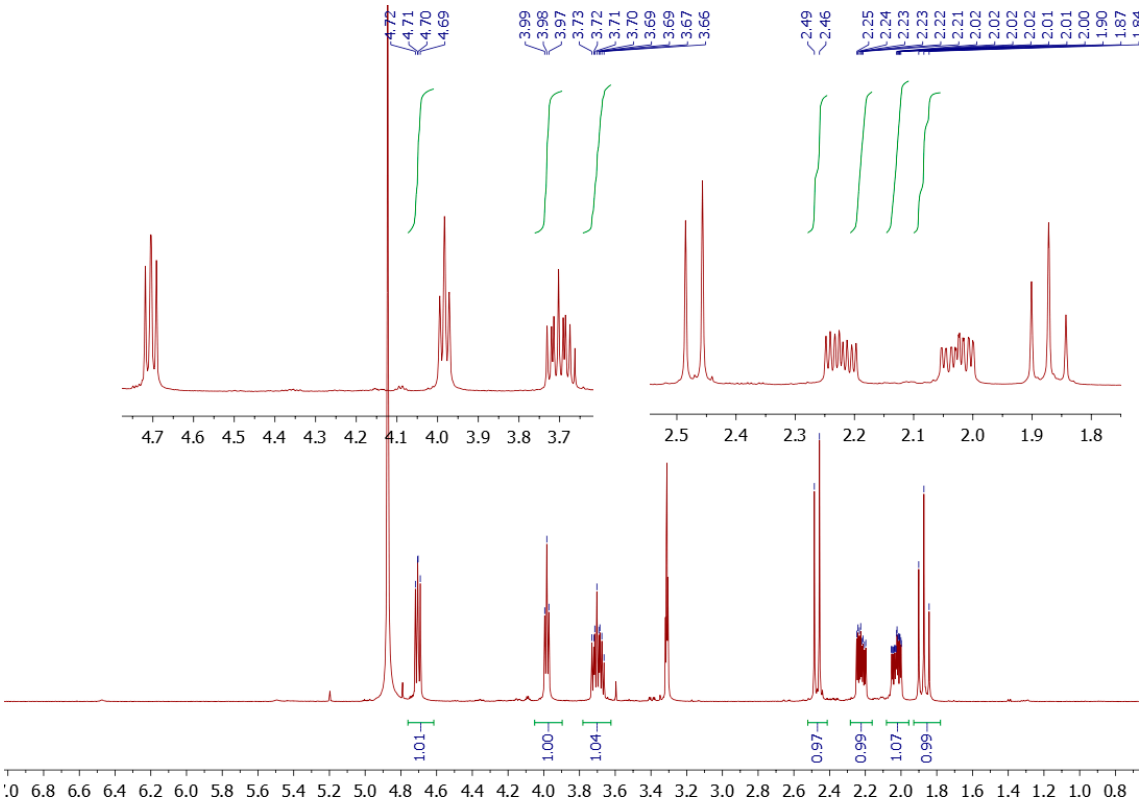

HSQC
f1 (ppm)
f2 (ppm)

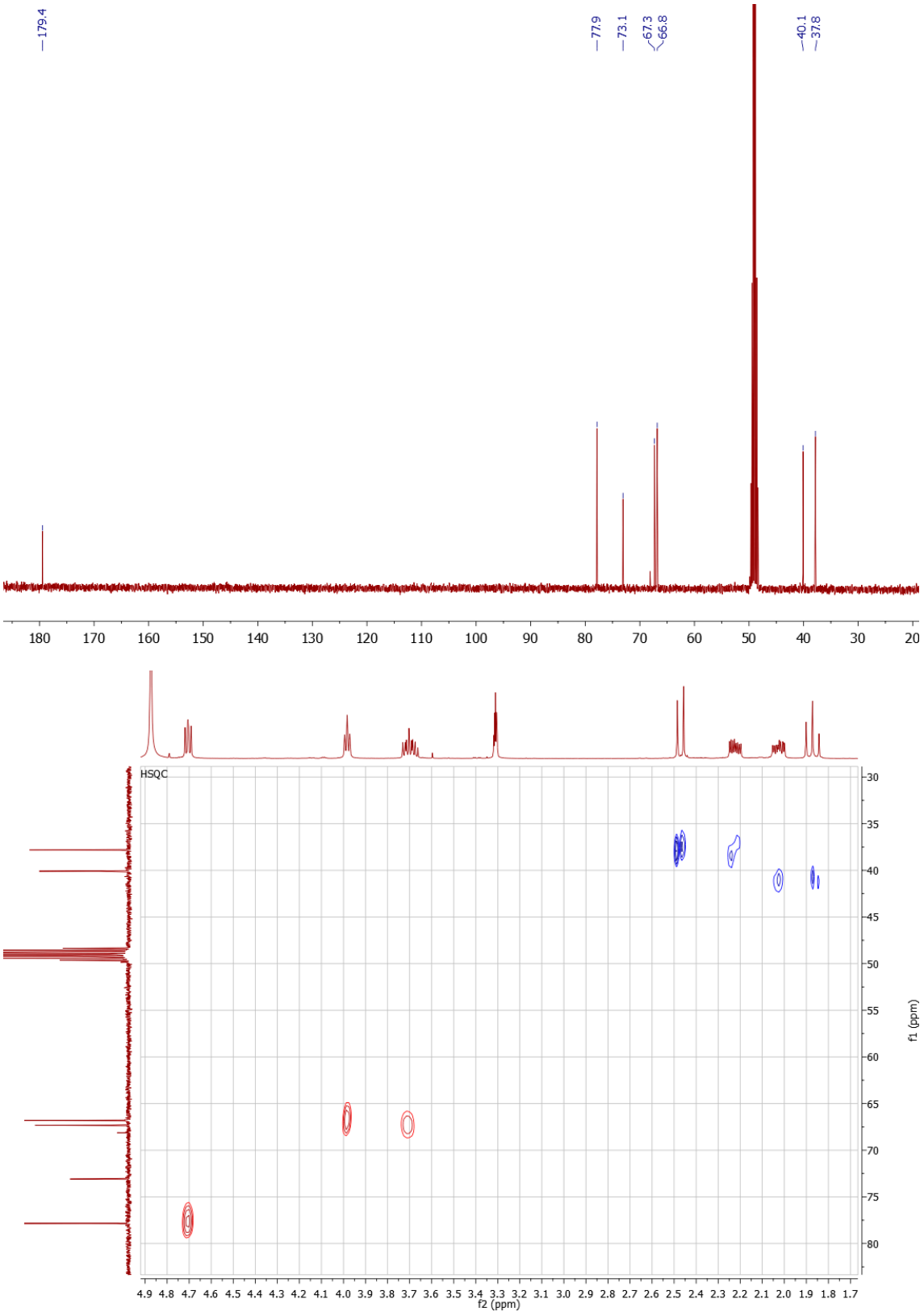

COSY
f1 (ppm)
f2 (ppm)

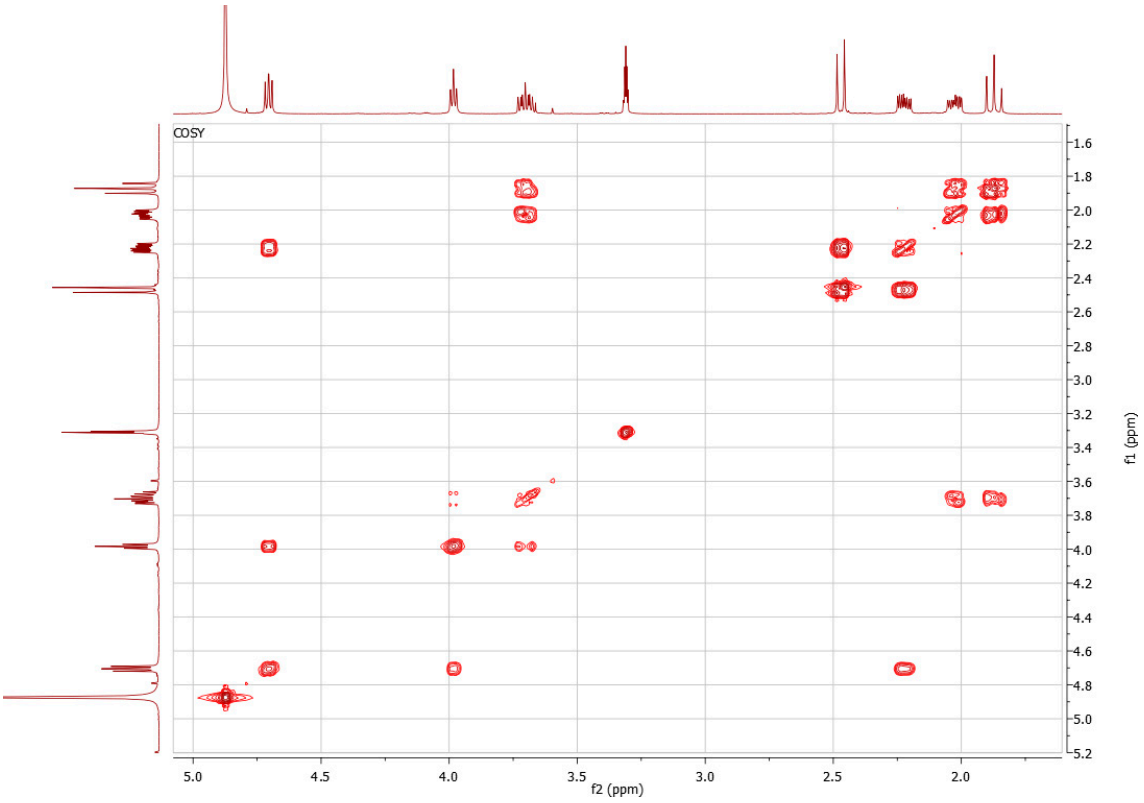


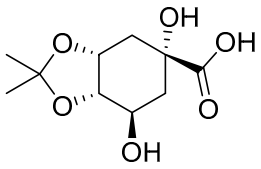
5

Quinic acid 1,5-lactone (5) [8]. To a solution of quinic acid (192 mg, 1 mmol) in ethanol (4 mL) was added deloxan (13 mg, 0.01 mmol). The mixture was stirred at 78 ºC for 24h then the acid catalyst was removed by filtration, the filtrate was concentrated under vacuum and purified by column chromatography on silica gel (diclorometha ne/MeOH = 9:1, Rf 0.4), affording the compound **5** (33 mg, 19 %). ^{1}H NMR (400 MHz, CD_3OD) δ_H 1.87 (1H, t, J = 11.6 Hz, $H2_{ax}$), 2.03 (1H, dddd, J = 11.6, 6.6, 2.9, 0.8 Hz, $H2_{eq}$), 2.22 (1H, ddd, J = 11.4, 6.0, 2.9, Hz, $H6_{eq}$), 2.47 (1H, d, J = 11.4 Hz, $H6_{ax}$), 3.70 (1H, ddd, J = 11.2, 6.6, 4.4 Hz, H3), 3.98 (1H, ddd, J = 4.9, 4.4, 0.8 Hz, H4), 4.71 (1H, dd, J = 6.0, 4.9 Hz, H5). ^{13}C NMR (100.6 MHz, CD_3OD) δ_C 37.8 (C6), 40.1 (C2), 66.8 (C4), 67.3 (C3), 73.1 (C1), 77.9 (C5), 179.4 (C=O). HRMS (ESI) Calcd for $C_7H_{10}NaO_5$: 197.0420. Found: 197.0412.



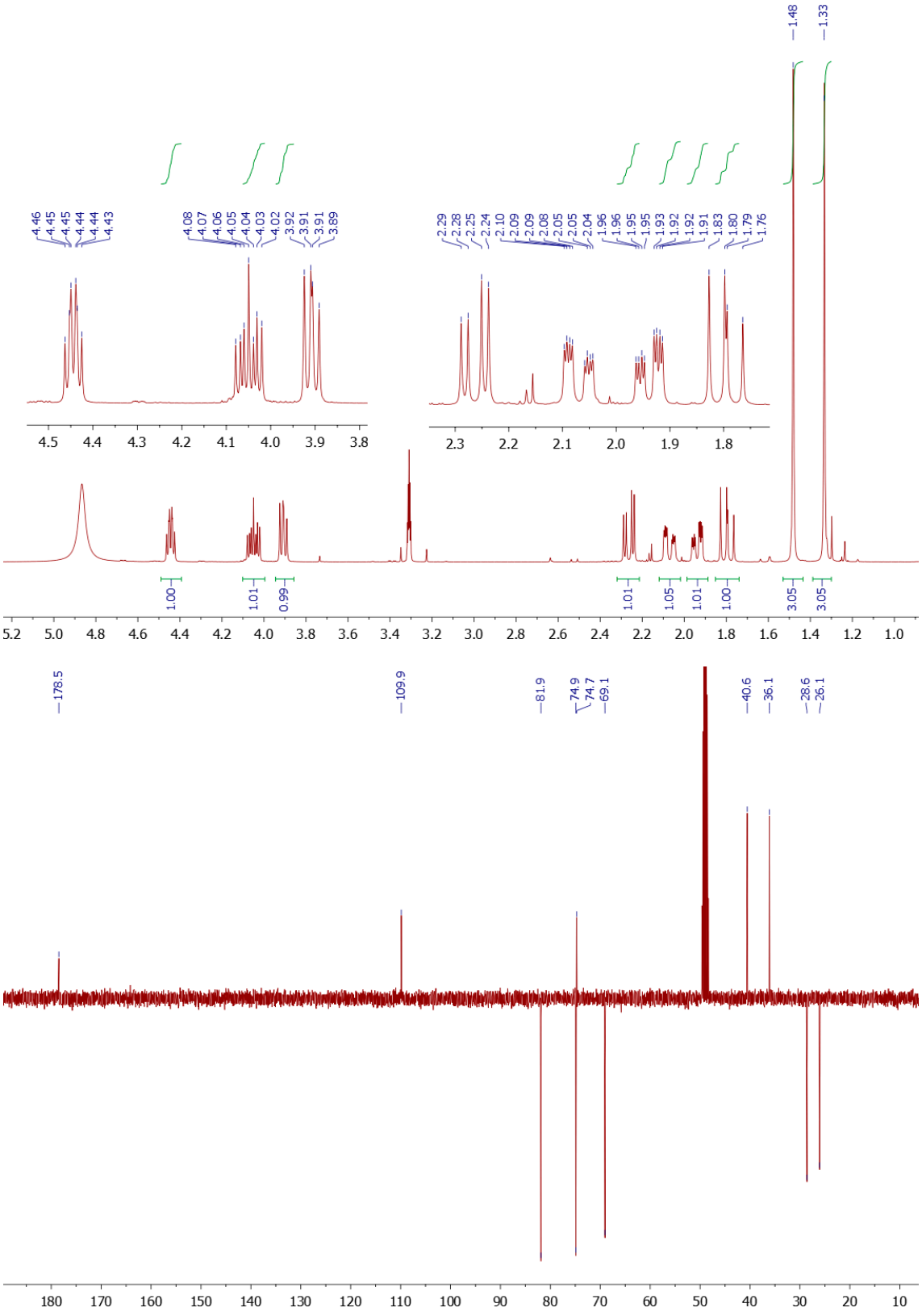

179.4
77.9
73.1
67.3
66.8
40.1
37.8
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
HSQC
f1 (ppm)
f2 (ppm)





6

3,4-*O*-Isopropylidenequinic acid (6). To a solution of quinic acid (192 mg, 1 mmol) in acetone/ethanol 1:1 (4 mL) was added deloxan (13 mg, 0.01 mmol) and 2,2-dimethoxypropane (364 mg, 430 µL, 3.5 mmol). The mixture was stirred at 78 ºC for 24 h, then the acid catalyst was removed by filtration and the filtrate was concentrated under vacuum. The solid residue was washed with dichloromethane affording the compound **6** (37 mg, 16 %). ^{1}H NMR (400 MHz, CD_3OD) δ_H 1.33 (3H, s, CH_{3endo}), 1.48 (3H, s, CH_{3exo}), 1.80 (1H, dd, J = 13.5, 11.7 Hz, $H2_{ax}$), 1.94 (1H, ddd, J = 13.5, 4.4, 2.0 Hz, $H2_{eq}$), 2.07 (1H, ddd, J = 15.3, 4.1, 1.9 Hz, $H6_{eq}$), 2.26 (1H, dd, J = 15.3, 5.2, Hz, $H6_{ax}$), 3.91 (1H, dd, J = 7.5, 5.8 Hz, H4), 4.05 (1H, ddd, J = 11.7, 7.5, 4.3 Hz, H3), 4.44 (1H, dt, J = 5.4, 4.0 Hz, H5). ^{13}C NMR (100.6 MHz, CD_3OD) δ_C 26.1 (CH_{3endo}), 28.6 (CH_{3exo}), 36.1 (C6), 40.6 (C2), 69.1 (C3), 74.7 (C1), 74.9 (C5), 81.9 (C4), 109.9 ($C_{isoprop.}$), 178.5 (C=O). HRMS (ESI) Calcd for $C_{10}H_{16}NaO_6$: 255,0839. Found: 255,0849.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1.92
1.91
1.83
1.80
1.79
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1.01
0.99
1.01
1.05
1.01
1.00
3.05
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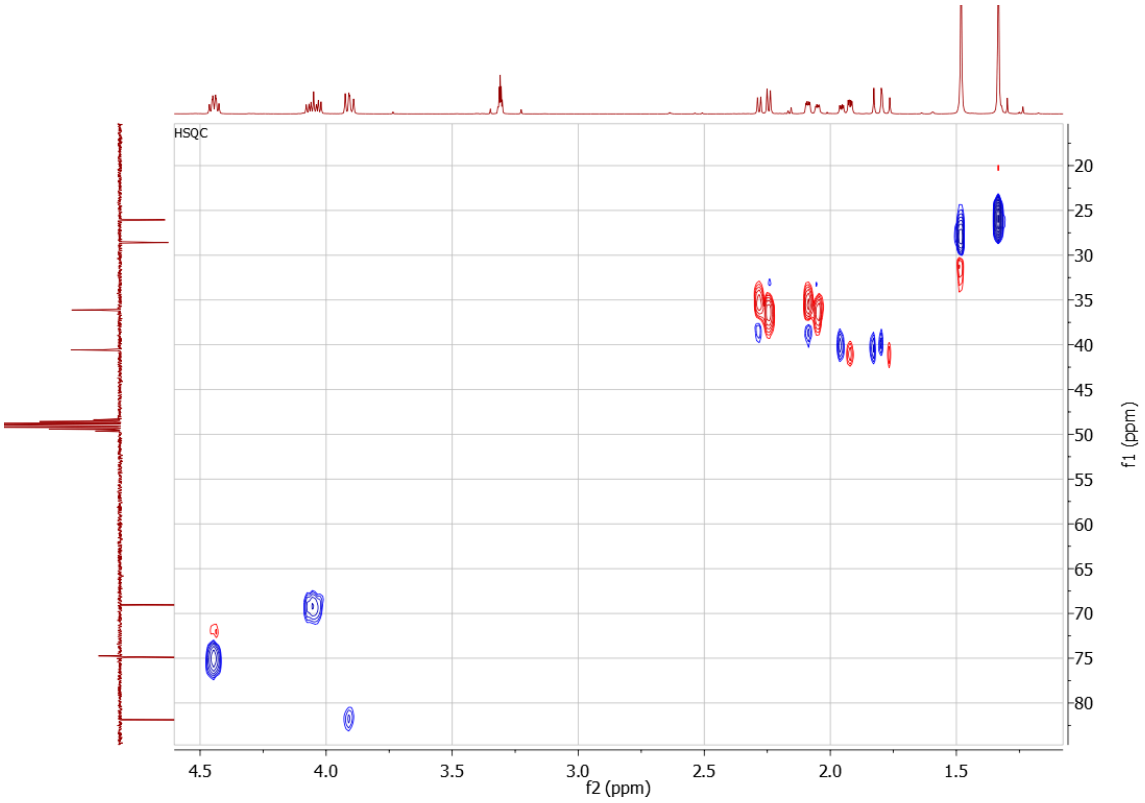
28.6
26.1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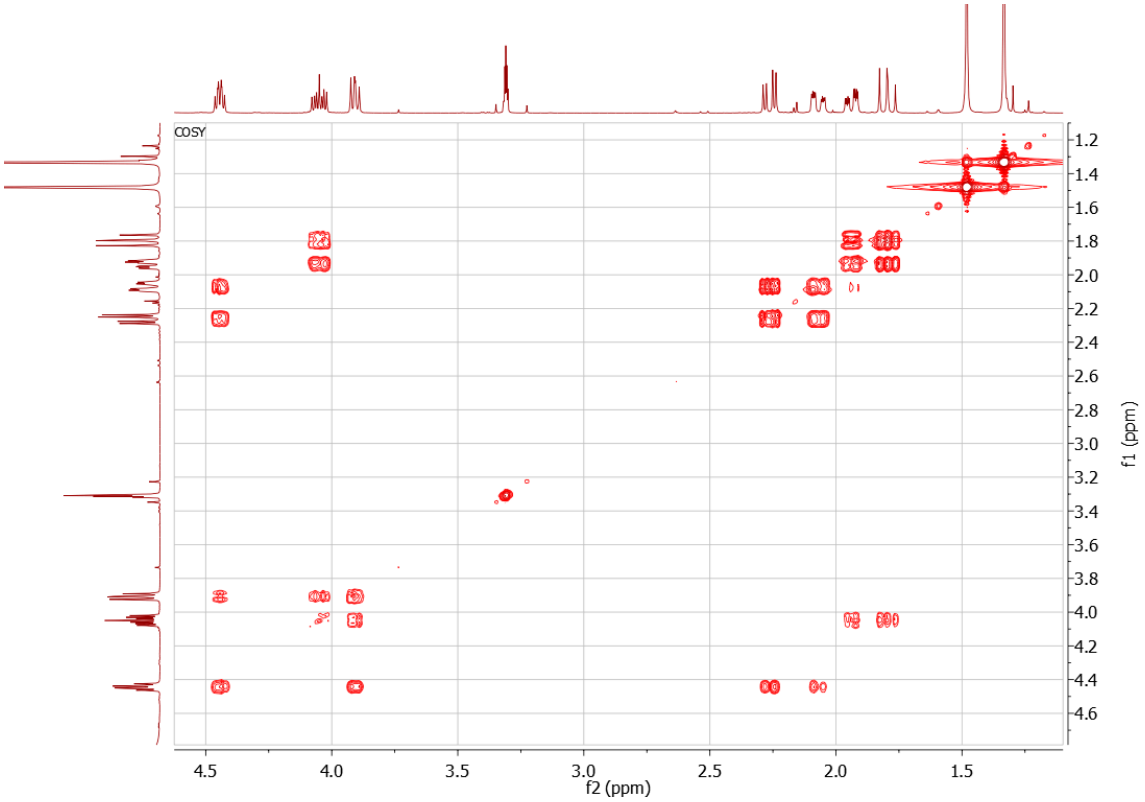
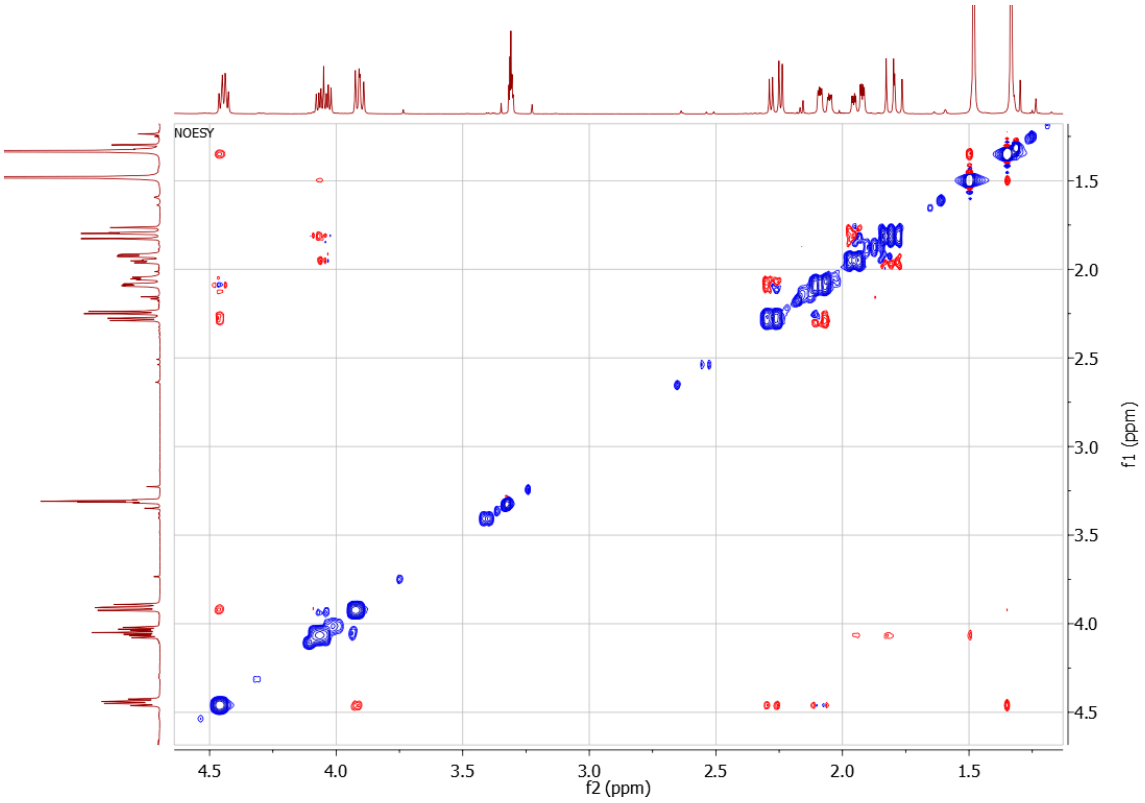
f2 (ppm)
f1 (ppm)


COSY
f2 (ppm)
f1 (ppm)


NOESY
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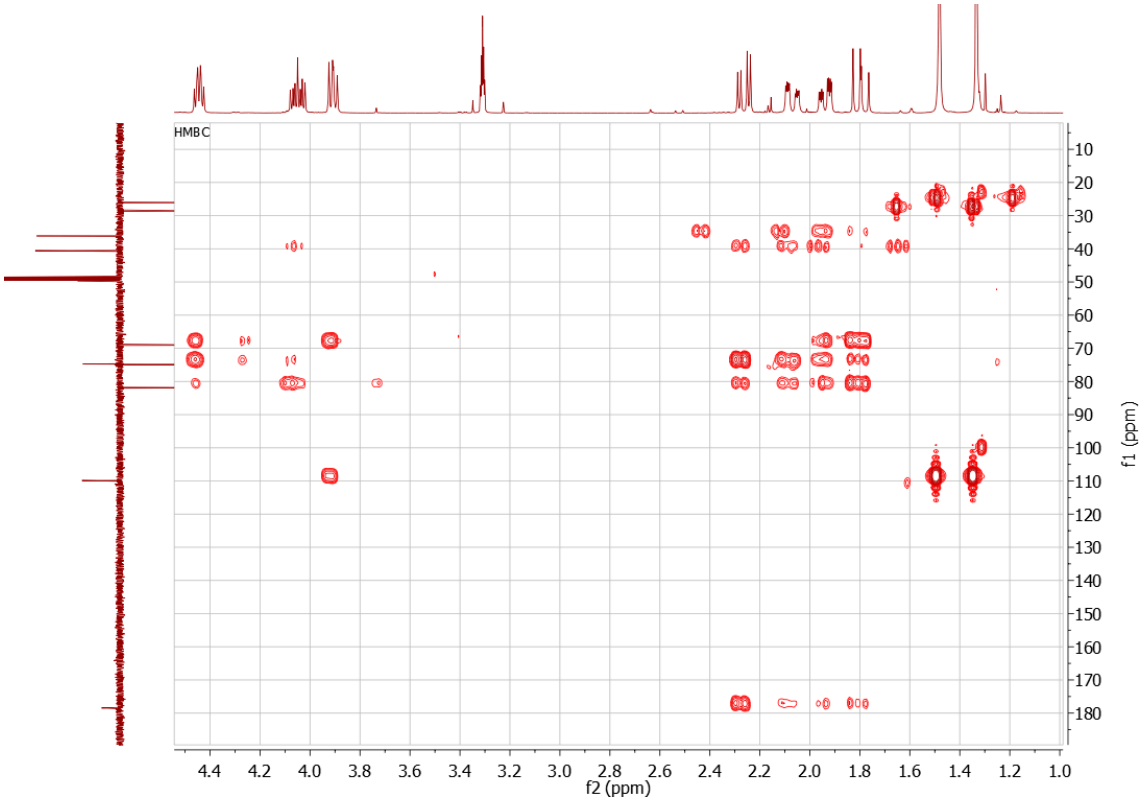
f1 (ppm)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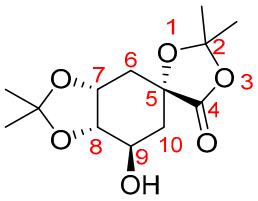
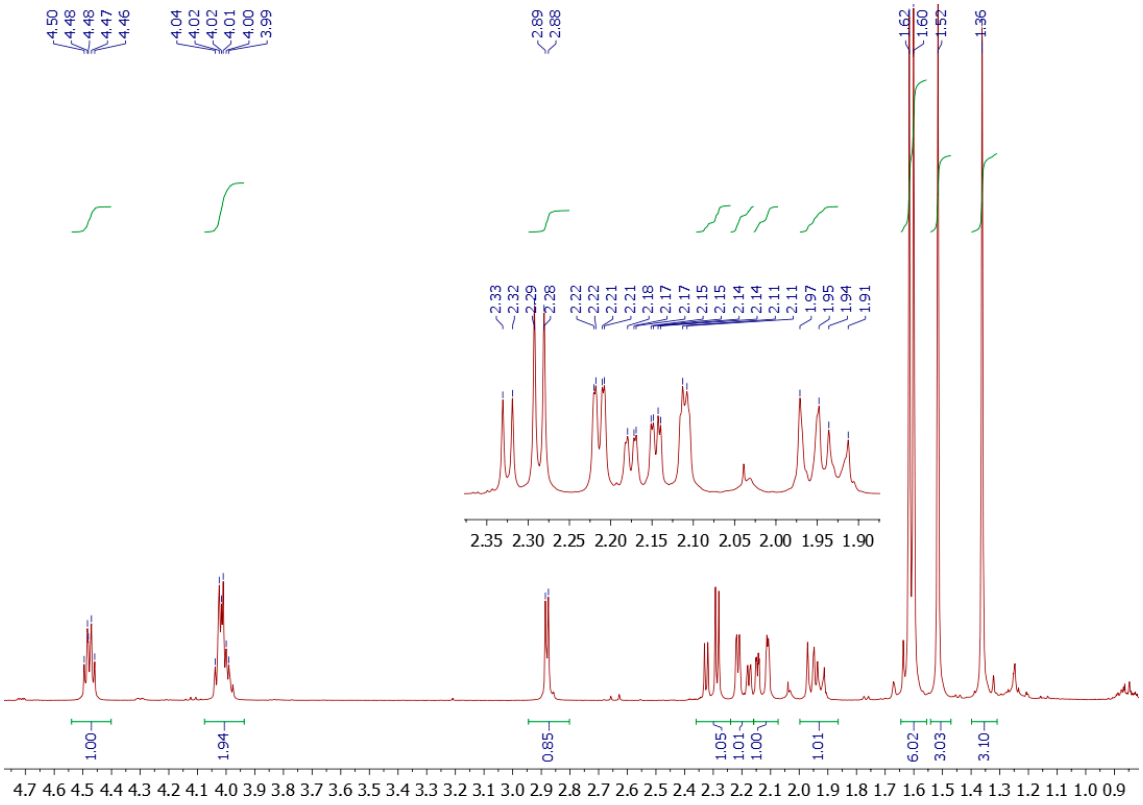
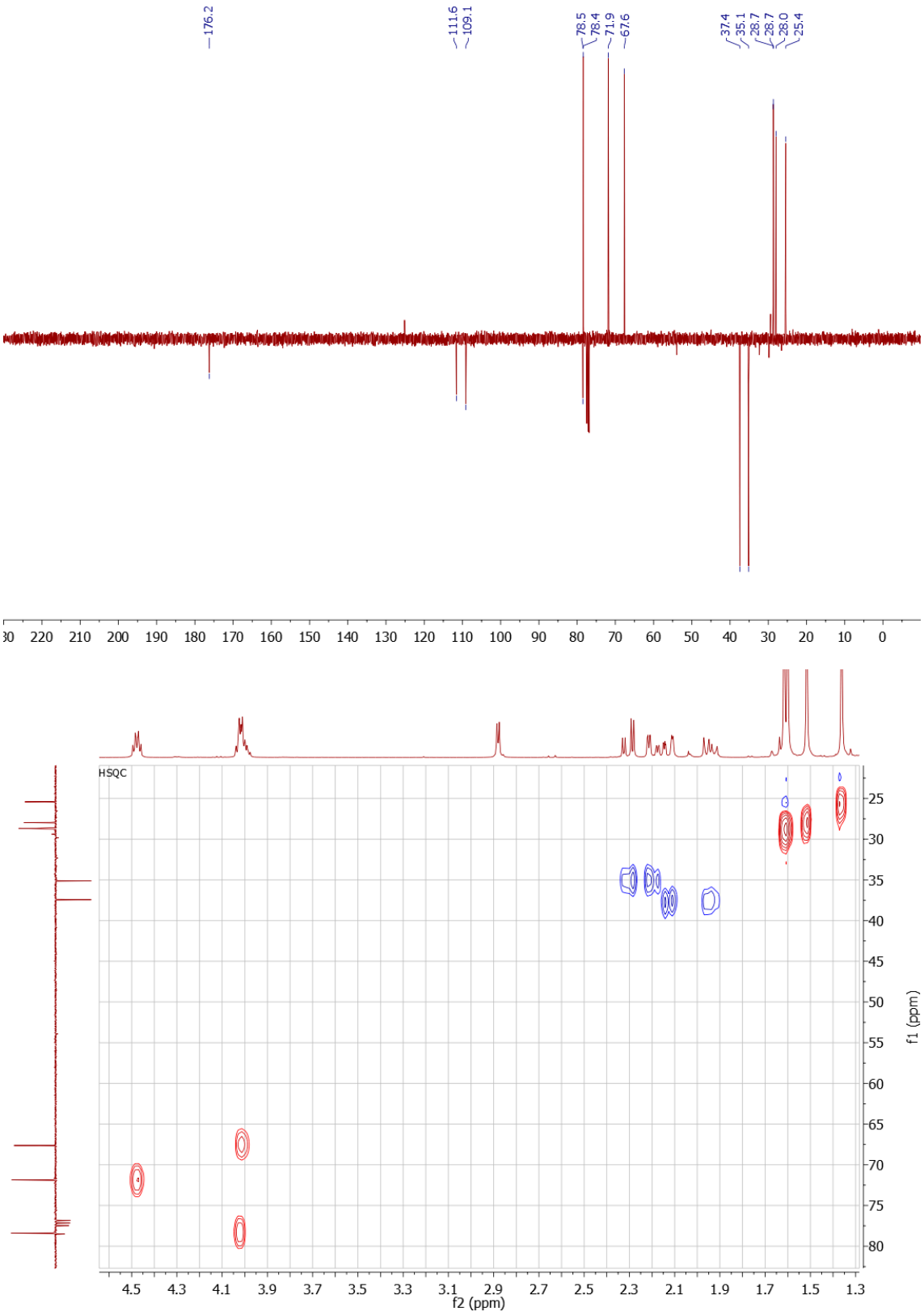
f2 (ppm)
f1 (ppm)



7

7,8-*O*-Isopropylidene (5*S*,7*R*,8*S*,9*R*)-7,8,9-trihydroxy-2,2-dimethyl-1,3-dioxaspiro [4.5]decan-4-one (7). To a solution of quinic acid (192 mg, 1 mmol) in acetone (4 mL) was added deloxan (13 mg, 0.01 mmol) and 2,2-dimethoxypropane (364 mg, 430 µL, 3.5 mmol). The mixture was stirred at 56 ºC for 4 h, then TBD-PS (33 mg, 0.1 mmol) and ethanol (4 mL) were added. The mixture was stirred at 0 ºC for 24 h, then the catalysts were removed by filtration, the filtrate was concentrated under vacuum and purified by column chromatography on silica gel (hexanes/EtOAc = 6:4, Rf 0.3), affording the compound **7** (73 mg, 27 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.36 (3H, s, CH_{3endo}), 1.52 (3H, s, CH_{3exo}), 1.60 (3H, s, CH_3), 1.62 (3H, s, CH_3), 1.94 (1H, dd, J = 14.1, 9.3 Hz, $H6_{ax}$), 2.13 (1H, ddd, J = 14.1, 4.0, 1.2 Hz, $H6_{eq}$), 2.20 (1H, ddd, J = 15.4, 4.5, 1.2 Hz, $H10_{eq}$), 2.30 (1H, dd, J = 15.4, 4.7 Hz, $H10_{ax}$), 2.88 (1H, d, J = 4.2 Hz, OH), 3.98–4.30 (2H, m, H7+H8), 4.48 (1H, dt, J = 5.8, 4.5 Hz, H9). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 25.4 (CH_{3endo}), 28.0 (CH_{3exo}), 28.7 (2×CH_3), 35.1 (C10), 37.4 (C6), 67.6 (C7), 71.9 (C9), 78.4 (C8), 78.5 (C5), 109.1 (C2), 111.6 ($C_{isoprop.}$), 176.2 (C=O). HRMS (ESI) Calcd for $C_{13}H_{20}NaO_5$: 295.1152. Found: 295.1154.




176.2
111.6
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78.5
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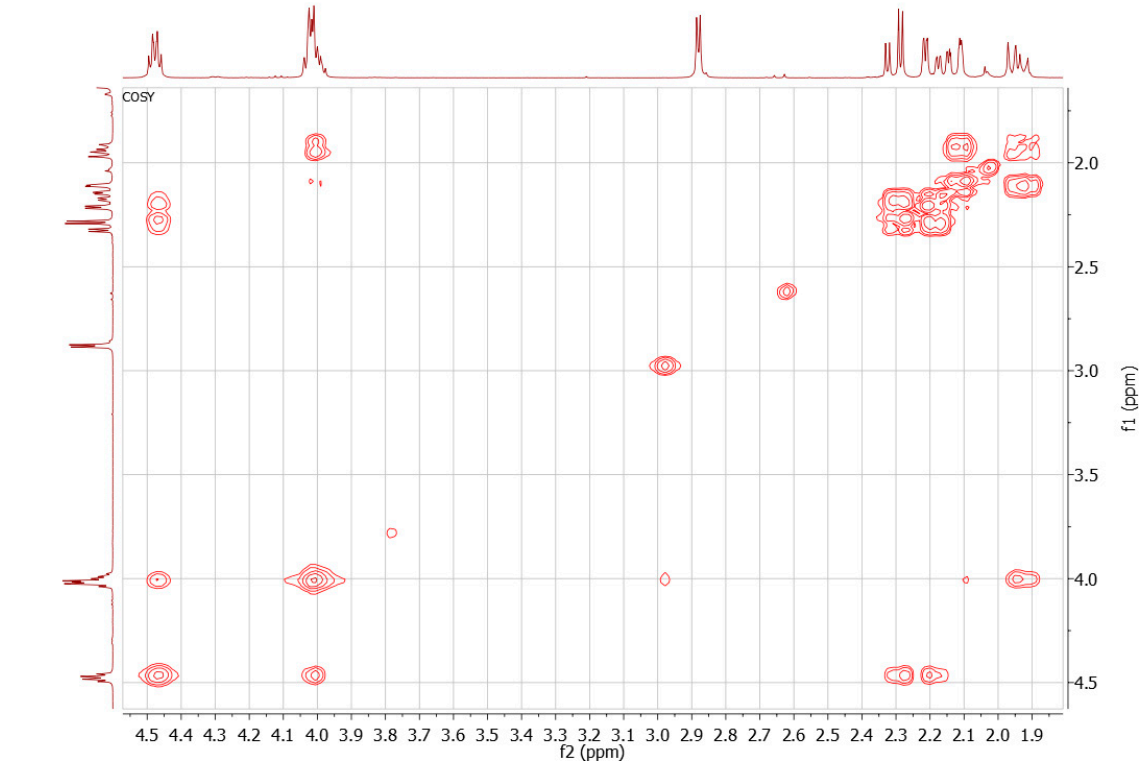
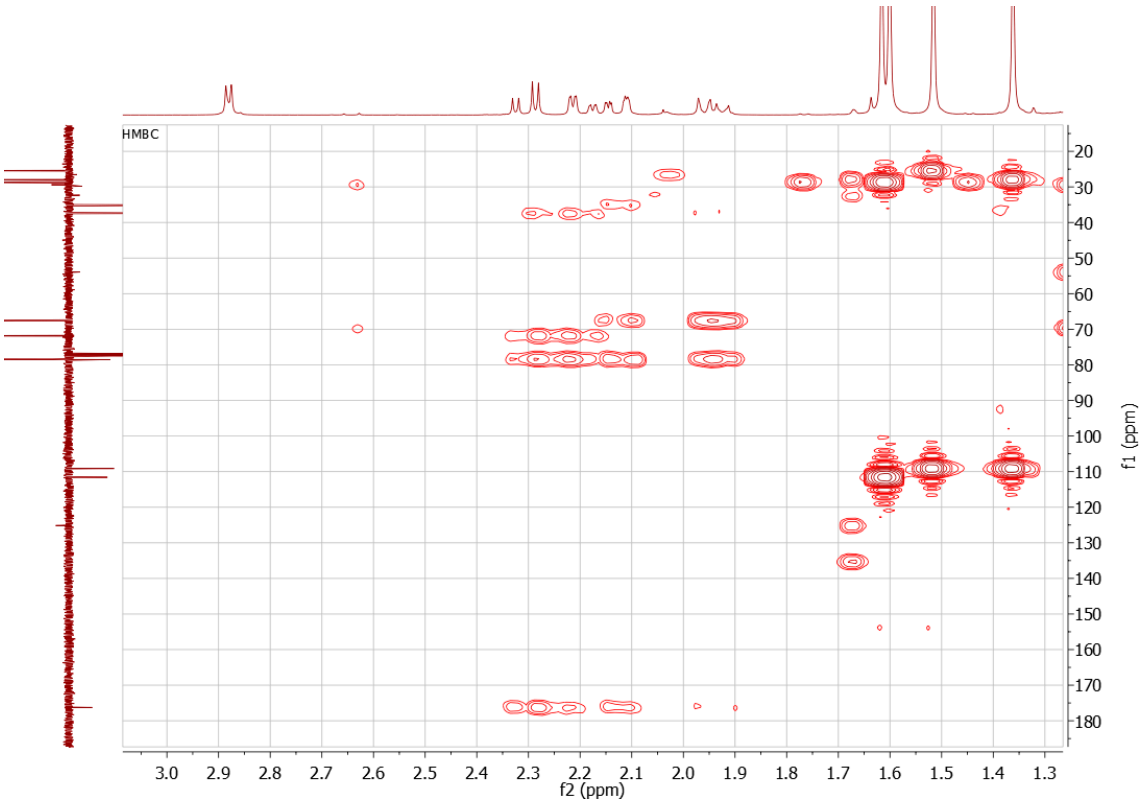
37.4
35.1
28.7
28.7
28.0
25.4
HSQC
f2 (ppm)
f1 (ppm)





References and Notes

1. Fraile, J.M.; García-Bordejé, E.; Pires, E.; Roldán, L. New insights into the strength and accessibility of acid sites of sulfonated hydrothermal carbon. *Carbon* **2014**, *77*, 1157–1167, doi:10.1016/j.carbon.2014.06.059.
2. The assignment is based on COSY, NOESY, HSQC and HMBC experiments. It differs from that reported in: Sánchez-Abella, L.; Férnandez, S.; Armesto, N.; Ferrero, M.; Gotor, V. Novel and efficient syntheses of

(−)-methyl 4-epi-shikimate and 4,5-epoxy-quinic and -shikimic acid derivatives as key precursors to prepare new analogues. *J. Org. Chem.* **2006**, *71*, 5396–5399, doi:10.1021/jo0606249.

3. Our assignment is identical for ^{1}H NMR and slightly different for ^{13}C NMR from that reported in: Baptistella, L.H.B.; Cerchiaro, G. Studies for the transformation of carbocycles into carbohydrates: Approach toward the synthesis of higher sugar derivatives. *Carbohydr. Res*. **2004**, *339*, 665–671, doi:10.1016/j.carres.2003.10.026.
4. This assignment is also slightly different from that described in: Lange, G.L.; Humber, C.C.; Manthorpe, J.M. [2+2] Photoadditions with chiral 2,5-cyclohexadienone synthons. *Tetrahedron Asymmetry* **2002**, *13*, 1355–1362, doi:10.1016/S0957-4166(02)00339-7.
5. This assignment has been reached taking into account the only possible axial-axial arrangement of H4 with H3 or H5, present in the conformation represented in the figure, that explains the J = 8.6 Hz detected between H4 and one of the vicinal protons. This value is in agreement with those found for $J_{ax\text{-}ax}$ in polyhydroxylated cyclohexanes: Aucktor, J.; Brückner, R. Total Synthesis of quercitols: (+)-allo-, (−)-proto-, (+)-talo-, (−)-gala-, (+)-gala-, neo-, and (−)-epi-quercitol. *Synlett* **2015**, *26*, 250–258, doi:10.1055/s-0034-1379603.
6. This assignment is different from that described in: Banwell, M.G.; Hungerford, N.L.; Jolliffe, K.A. Synthesis of the sialic acid (−)-KDN and certain epimers from (−)-3-dehydroshikimic acid or (−)-quinic acid. *Org. Lett.* **2004**, *6*, 2737–2740, doi:10.1021/ol049048y.
7. This assignment is different from that described in: Zhang, W.; Zhu, X.-L.; Ding, W.; Shi, X.-X. A novel stereoselective synthesis of (−)-quinic acid starting from the naturally abundant (−)-shikimic acid. *Tetrahedron Asymmetry* **2015**, *26*, 1375–1381, doi:10.1016/j.tetasy.2015.10.008.
8. Same assignment as in: Sinisi, V.; Boronov, K.; Colomban, S.; Navarini, L.; Berti, F.; Forzato, C. Synthesis of mono-, di-, and tri-3,4-dimethoxycinnamoyl-1,5-γ-quinides. *Eur. J. Org. Chem.* **2014**, 1321–1326, doi:10.1002/ejoc.201301657.