A Versatile Palladium-Mediated Three-Component Reaction for The One-Pot Synthesis of Stereodefined 3-Arylidene-(or 3-Alkenylidene-) Tetrahydrofurans.

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Supplementary Material

Characterization of compounds 4 b-f, i, j, l-n, q, r, t, u.

General methods: All reactions were carried out under a nitrogen atmosphere using standard syringe, cannula, and septa techniques. Commercial reagents were used as purchased. Tetrahydrofuran and dimethylsulfoxide were distilled over calcium hydride. Thin-layer chromatography was carried out on Merck silica 60/F-254 aluminium-backed plates. Flash chromatography was performed using Merck silica gel 60 (40-63 μm). Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$. Chemical shifts (δ) are quoted in parts per million. *J* values are given in Hz.

Ethyl 4-(3-trifluoromethane)benzylidene-2-phenyl-tetrahydrofuran-3,3-dicarboxylate (4b): oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58-7.24 (M, 9H), 6.91 (s, 1H), 5.79 (s, 1H), 5.08 (d, *J*=14.0 and 2.6, 1H), 4.79 (d, *J*=14.0 and 2.9, 1H), 4.32 (m, 2H), 3.81 (m, 1H), 3.51 (m, 1H), 1.33 (t, *J*=7.0, 3H), 0.80 (t, *J*=7.0, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.1, 167.7, 142.2, 140.3, 137.2, 137.0, 131.5, 131.0 (q, $^2J_{(C,H)}$=33), 130.6,

129.5, 128.4, 128.0, 126.8, 125.4 (q, $^{3}J_{(C,H)}$=4), 124.8, 124.2 (q, $^{3}J_{(C,H)}$=4), 124.1 (q, $^{1}J_{(C,H)}$=275), 84.8, 70.1, 69.6, 62.2, 61.5, 14.1, 13.4.

Ethyl 4-(4-methoxycarbonyl)benzylidene-2-phenyl-tetrahydrofuran-3,3-dicarboxylate (4c): solid; mp 120-122°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.04 (d, *J*=7.7, 2H), 7.46 (d, *J*=7.7, 2H), 7.32-7.27 (M, 5H), 6.90 (s, 1H), 5.78 (s, 1H), 5.10 (d, *J*=14.0, 1H), 4.80 (d, *J*=14.0, 1H), 4.36 (m, 2H), 3.93 (s, 3H), 3.82 (m, 1H), 3.49 (m, 1H), 1.34 (t, *J*=7.0, 3H), 0.79 (t, *J*=7.0, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.4, 168.1, 167.1, 141.2, 141.1, 137.3, 130.3, 129.4, 128.9, 128.7, 128.4, 127.2, 125.6, 85.2, 70.7, 70.1, 62.6, 61.9, 52.6, 14.5, 13.8.

Ethyl 4-(4-methyl)benzylidene-2-phenyl-tetrahydrofuran-3,3-dicarboxylate (4d): solid; mp 76-78°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50-7.26 (M, 5H), 7.20 (d, *J*=8.1, 2H), 7.11 (d, *J*=8.1, 2H), 6.83 (s, 1H), 5.77 (s, 1H), 5.09 (dd, *J*=13.6 and 2.2, 1H), 4.80 (dd, *J*=13.6 and 2.6, 1H), 4.35 (q, *J*=7.3, 2H), 3.81 (m, 1H), 3.51 (m, 1H), 2.37 (s, 3H), 1.33 (t, *J*=7.3, 3H), 0.80 (t, *J*=7.3, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.8, 168.4, 137.9, 137.7, 137.3, 134.0, 129.7, 129.0, 128.6, 128.3, 127.2, 126.3, 85.2, 70.8, 70.0, 62.4, 61.7, 21.7, 14.5, 13.8. Anal. Calcd for $C_{24}H_{26}O_5$: C, 73.08; H, 6.64. Found C, 73.03; H, 6.71.

Ethyl 4-(4-methoxy)benzylidene-2-phenyl-tetrahydrofuran-3,3-dicarboxylate (4e): solid; mp 91-93°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51-7.27 (M, 5H), 7.18 (d, *J*=8.7, 2H), 6.93 (d, *J*=8.7, 2H), 6.83 (s, 1H), 5.79 (s, 1H), 5.11 (dd, *J*=13.4 and 2.2, 1H), 4.80 (dd, *J*=13.4 and 2.6, 1H), 4.36 (q, *J*=7.1, 2H), 3.82 (s, 3H), 3.81 (m, 1H), 3.54 (m, 1H), 1.35 (t, *J*=7.1, 3H), 0.81 (t, *J*=7.1, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.5, 167.7, 159.1, 137.4, 135.7, 130.1, 129.3, 128.2, 128.0, 126.9, 125.5, 114.1, 84.8, 70.4, 69.6, 62.0, 61.3, 55.3, 14.1, 13.5. Anal. Calcd for $C_{24}H_{26}O_6$: C, 70.23; H, 6.38. Found C, 70.11; H, 6.39.

Ethyl 4-(2-methoxy)benzylidene-2-phenyl-tetrahydrofuran-3,3-dicarboxylate (4f): oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55-6.80 (M, 10H), 5.78 (s, 1H), 5.15 (dd, *J*=13.6 and 2.2, 1H), 4.80 (dd, *J*=13.6 and 2.6, 1H), 4.35 (m, 2H), 3.83 (s, 3H), 3.82 (m, 1H),

3.55 (m, 1H), 1.34 (t, *J*=7.4, 3H), 0.81 (t, *J*=7.4, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.5, 168.1, 157.1, 137.6, 137.5, 129.1, 128.8, 128.2, 127.9, 126.9, 125.5, 120.9, 120.4, 110.9, 84.8, 70.4, 69.7, 61.9, 61.3, 55.6, 14.1, 13.4.

Ethyl 4-benzylidene-2-(3,4-dioxymethylene)phenyl-tetrahydrofuran-3,3-dicarboxylate (4i): solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45-7.18 (M, 5H), 6.96 (m, 2H), 6.88 (s, 1H), 6.77 (d, *J*=8.5, 1H), 5.92 (s, 2H), 5.68 (s, 1H), 5.10 (dd, *J*=13.7 and 2.2, 1H), 4.79 (dd, *J*=13.6 and 2.7, 1H), 4.35 (q, *J*=7.1, 2H), 3.92 (m, 1H), 3.71 (m, 1H), 1.34 (t, *J*=7.1, 3H), 0.95 (t, *J*=7.1, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.3, 167.9, 147.5, 147.4, 138.0, 136.4, 131.0, 128.6, 127.7, 126.0, 120.5, 107.9, 107.6, 101.0, 84.6, 70.3, 69.5, 62.1, 61.5, 14.1, 13.7.

Ethyl 4-(3,4-dioxymethylene)benzylidene-2-(3,4-dioxymethylene)phenyl-tetrahydrofuran-3,3-dicarboxylate (4j): solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.95-6.62 (M, 6H), 5.97 (s, 2H), 5.92 (s, 2H), 5.65 (s, 1H), 5.02 (dd, *J*=13.6 and 2.2, 1H), 4.72 (dd, *J*=13.6 and 2.9, 1H), 4.32 (q, *J*=7.0, 2H), 3.89 (m, 1H), 3.68 (m, 1H), 1.32 (t, *J*=7.0, 3H), 0.92 (t, *J*=7.0, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.3, 168.0, 148.0, 147.4, 147.3, 147.1, 136.2, 131.0, 130.7, 125.6, 123.0, 120.4, 107.8, 107.6, 101.0, 84.6, 70.3, 69.4, 62.0, 61.4, 14.1, 13.6.

Ethyl 4-(4-methoxy)benzylidene-2-(3,4-dioxymethylene)phenyl-tetrahydrofuran-3,3-dicarboxylate (4l): solid; mp 115-117°C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.14 (d, *J*=8.0, 2H), 7.00-6.73 (M, 6H), 5.92 (s, 2H), 5.67 (s, 1H), 5.06 (d, *J*=13.4, 1H), 4.75 (d, *J*=13.7, 1H), 4.33 (q, *J*=7.1, 2H), 3.91 (m, 1H), 3.82 (s, 3H), 3.70 (m, 1H), 1.34 (t, *J*=7.1, 3H), 0.94 (t, *J*=7.1, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.4, 168.1, 159.1, 147.5, 147.3, 135.6, 131.1, 130.0, 129.2, 125.4, 120.5, 114.1, 107.8, 107.6, 101.0, 84.6, 70.3, 69.5, 62.0, 61.4, 55.3, 14.1, 13.7. Anal. Calcd for $C_{25}H_{26}O_8$: C, 66.07; H, 5.77. Found C, 65.82; H, 6.00.

Ethyl 4-(3,4,5-trimethoxy)benzylidene-2-(4-fluoro)phenyl-tetrahydrofuran-3,3-dicarboxylate (4m): oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 (m, 2H), 6.96 (m, 2H),

6.78 (s, 1H), 6.42 (s, 2H), 5.70 (s, 1H), 5.08 (d, J=13.4, 1H), 4.78 (dd, J=13.4 and 2.3, 1H), 4.32 (m, 2H), 3.84 (s, 6H), 3.83 (m, 1H), 3.82 (s, 3H), 3.49 (m, 1H), 1.31 (t, J=7.1, 3H), 0.84 (t, J=7.1, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.2, 167.9, 162.7 (d, $^1J_{(C,F)}$= 245), 153.6, 153.5, 153.3, 137.9, 137.1, 133.0, 132.1, 128.6 (d, $^3J_{(C,F)}$= 8), 126.4, 114.8 (d, $^2J_{(C,F)}$= 21), 106.0, 84.2, 70.2, 69.4, 62.1, 61.5, 60.9, 56.2, 56.1, 14.1, 13.5.

Ethyl 4-benzylidene-2-(2,3,4-trimethoxy)phenyl-tetrahydrofuran-3,3-dicarboxylate (4n): solid; mp 68-70°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38-7.21 (m, 5H), 7.02 (d, J=8.8, 1H), 6.80 (s, 1H), 6.58 (d, J=8.8, 1H), 6.10 (s, 1H), 5.03 (dd, J=13.6 and 2.2, 1H), 4.78 (dd, J=13.6 and 2.6, 1H), 4.30 (m, 2H), 3.90 (s, 3H), 3.89 (m, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.64 (m, 1H), 1.29 (t, J=7.0, 3H), 0.89 (t, J=7.0, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.6, 167.9, 153.7, 151.9, 141.6, 138.7, 136.6, 128.6, 127.6, 126.5, 124.2, 122.0, 106.8, 80.1, 69.7, 68.9, 62.0, 61.2, 60.8, 60.7, 56.0, 14.1, 13.6. Anal. Calcd for $C_{26}H_{30}O_8$: C, 66.37; H, 6.43. Found C, 66.23; H, 6.58.

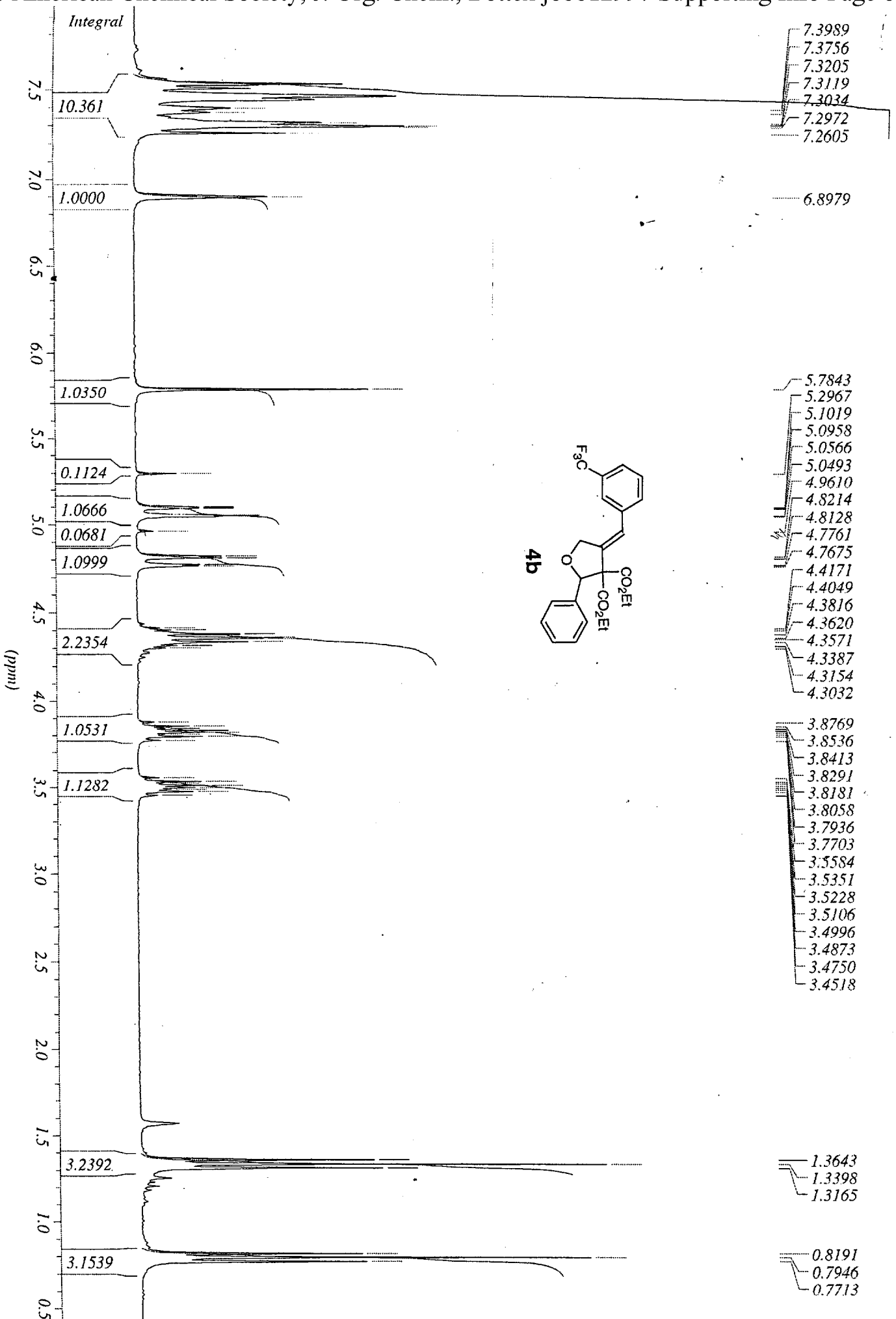
Ethyl 4-(3-methoxy)benzylidene-5-methyl-2-phenyl-tetrahydrofuran-3,3-dicarboxylate (4q): An oil containing a 1.5:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55-6.80 (M, 20H), 5.96 (s, 1H), 5.75 (s, 1H), 5.57 (dq, J=6.6 and 2.2, 1H), 5.28 (dq, J=6.2 and 2.9, 1H), 4.32 (m, 4H), 3.84 (m, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.73 (m, 2H), 1.42 (d, J=6.2, 3H), 1.36 (d, J=6.6, 3H), 1.33 (t, J=7.0, 3H), 1.32 (t, J=7.0, 3H), 0.81 (t, J=7.0, 3H), 0.80 (t, J=7.0, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.7, 168.4, 168.1, 168.0, 159.7, 159.6, 143.9, 142.9, 137.6, 137.5, 137.2, 129.5, 129.4, 128.8, 128.2, 128.0, 127.9, 127.0, 126.7, 126.3, 125.4, 121.2, 121.1, 114.4, 114.3, 113.5, 113.0, 83.6, 81.7, 76.5, 76.0, 70.4, 69.9, 62.0, 61.9, 61.4, 61.3, 55.3, 55.2, 18.8, 18.1, 14.2, 14.1, 13.4.

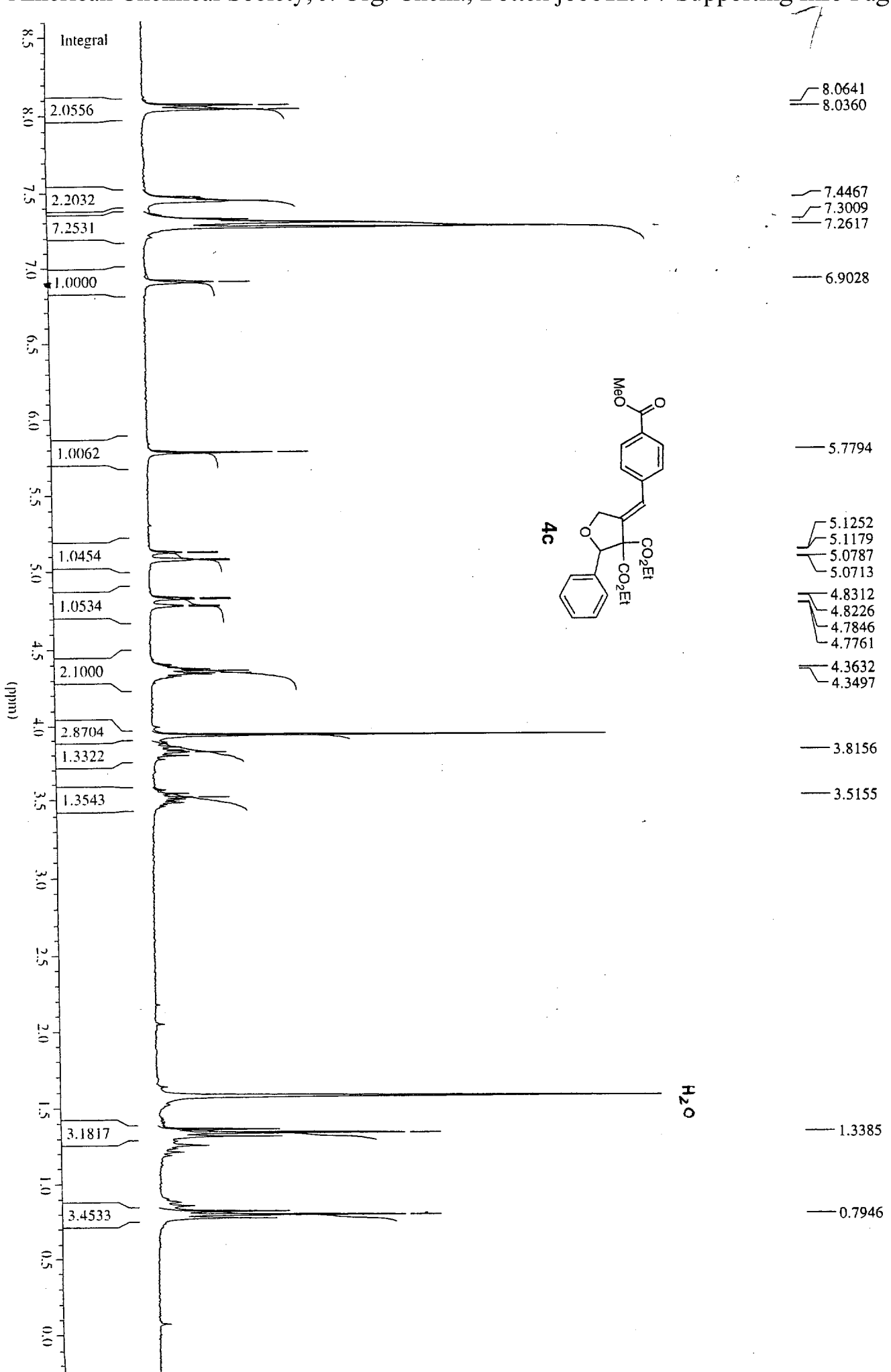
Ethyl 4-benzylidene-5,5-dimethyl-2-phenyl-tetrahydrofuran-3,3-dicarboxylate (4r): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48-7.15 (M, 10H), 6.98 (s, 1H), 5.95 (s, 1H), 4.41-4.25 (m, 2H), 3.78 (m, 1H), 3.48 (m, 1H), 1.45 (s, 3H), 1.34 (s, 3H), 1.30 (t, J=7.0, 3H), 0.82 (t, J=7.0, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.8, 168.4, 146.9, 137.6, 136.7,

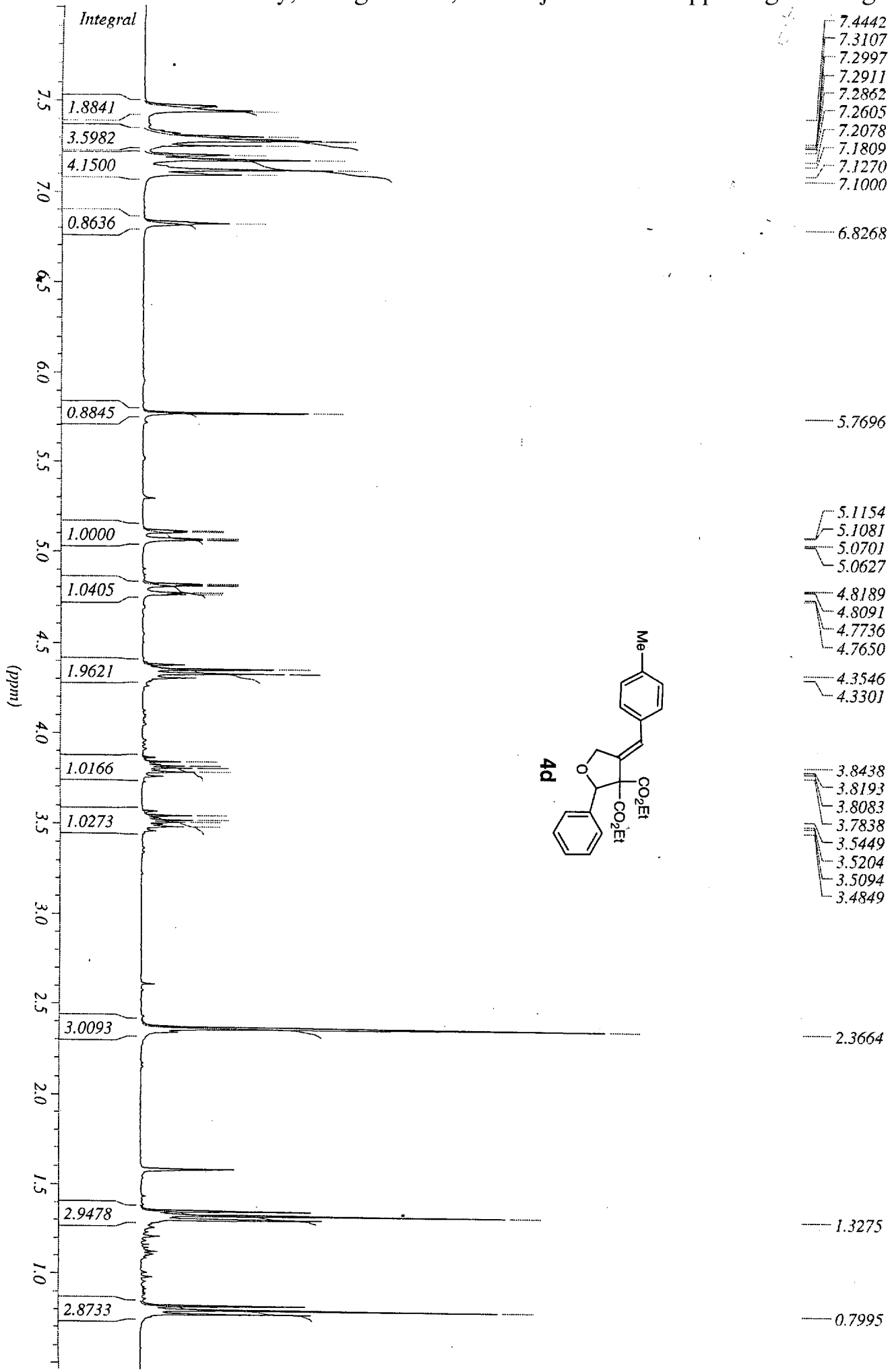
128.6, 128.1, 128.0, 127.9, 127.1, 126.8, 126.3, 82.4, 80.7, 71.2, 61.9, 61.2, 27.9, 27.1, 14.0, 13.4.

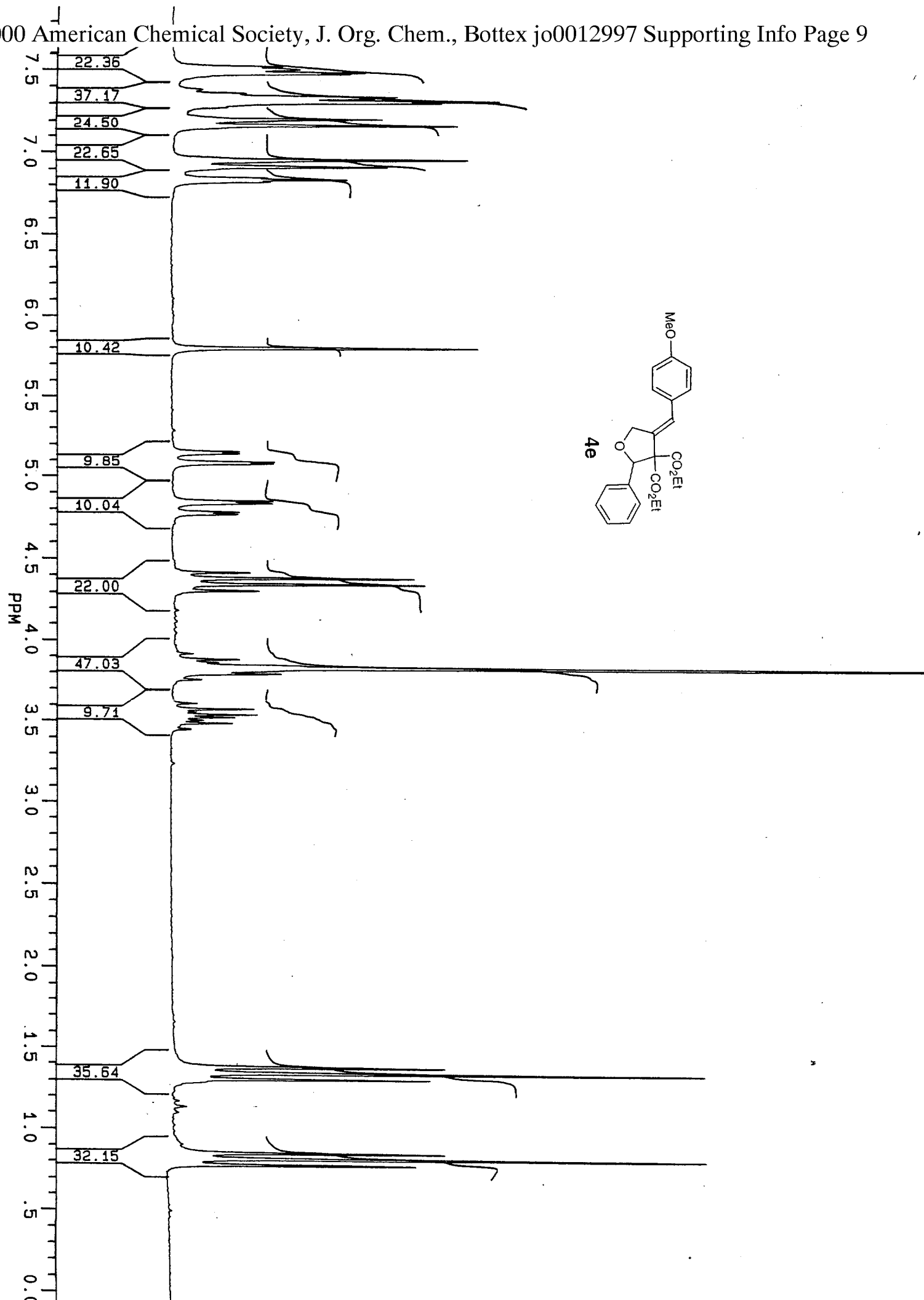
Ethyl 4-benzylidene-2-phenyl-5-(3,4-dioxymethylene)phenyl-tetrahydrofuran-3,3-dicarboxylate (4t): An oil containing a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55-6.80 (M, 26H), 6.75 (d, *J*=8.0, 1H), 6.56 (d, *J*=8.0, 1H), 6.14 (s, 1H), 5.95 (m, 3H), 5.83 (m, 3H), 4.35 (m, 4H), 3.86 (m, 1H), 3.77 (m, 1H), 3.49 (m, 2H), 1.35 (m, 6H), 0.79 (m, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.7, 168.6, 168.4, 148.2, 147.8, 147.3, 141.6, 138.2, 137.1, 137.0, 135.9, 135.4, 132.2, 131.4, 130.0, 129.1, 129.0, 128.8, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.6, 126.9, 124.2, 121.7, 110.0, 108.5, 108.1, 107.4, 101.2, 100.8, 83.8, 83.1, 81.3, 81.2, 70.7, 70.6, 62.1, 62.0, 61.5, 61.4, 14.2, 14.1, 13.5, 13.4.

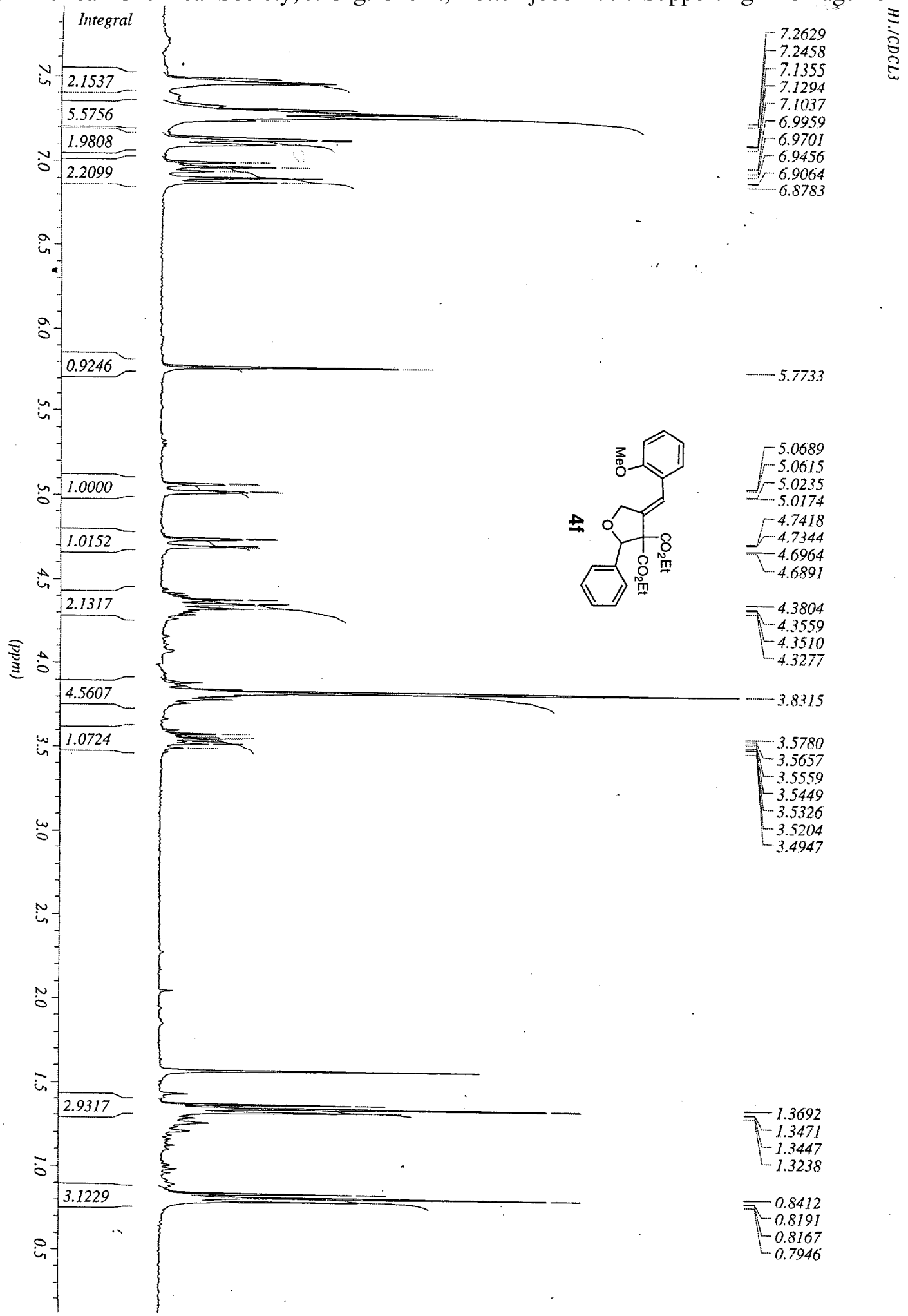
Ethyl 4-benzylidene-2-(4-fluoro)phenyl-5-(3,4-dioxymethylene)phenyl-tetrahydrofuran-3,3-dicarboxylate (4u): An oil containing a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55-6.83 (M, 26H), 6.75 (d, *J*=8.0, 1H), 6.56 (d, *J*=8.0, 1H), 6.12 (s, 1H), 5.97 (br s, 2H), 5.89 (s, 1H), 5.83 (br s, 2H), 5.78 (s, 1H), 5.67 (s, 1H), 4.35 (m, 4H), 3.86 (m, 2H), 3.58 (m, 2H), 3.49 (m, 2H), 1.36 (m, 6H), 0.86 (m, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.7, 168.5, 168.4, 168.3, 164.0 (d, $^{1}J_{(C,F)}$= 246), 162.6 (d, $^{1}J_{(C,F)}$= 246), 148.2, 147.8, 147.4, 147.3, 141.2, 140.8, 138.0, 135.8, 135.3, 133.0, 132.1, 131.6 (d, $^{3}J_{(C,F)}$= 9), 130.1, 129.1 (d, $^{3}J_{(C,F)}$= 9), 129.0, 128.8, 128.7, 128.6, 127.9, 127.6, 127.2, 124.2, 121.7, 116.0 (d, $^{2}J_{(C,F)}$= 21), 114.9 (d, $^{2}J_{(C,F)}$= 21), 109.9, 108.4, 108.1, 107.3, 101.3, 100.8, 83.1, 81.4, 80.6, 70.5, 65.8, 62.2, 62.1, 61.8, 61.7, 61.6, 61.5, 14.1, 14.0, 13.6, 13.5.

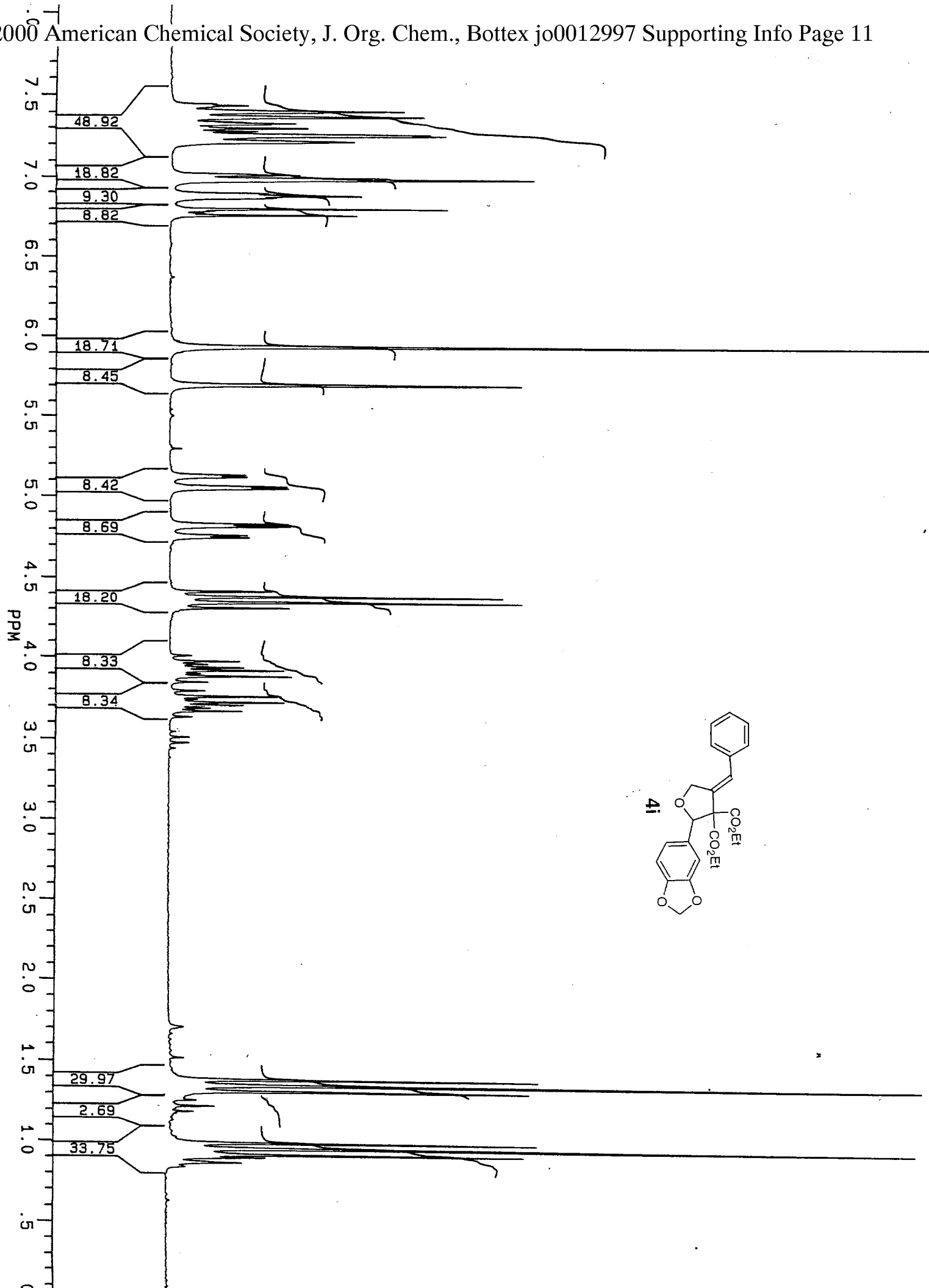




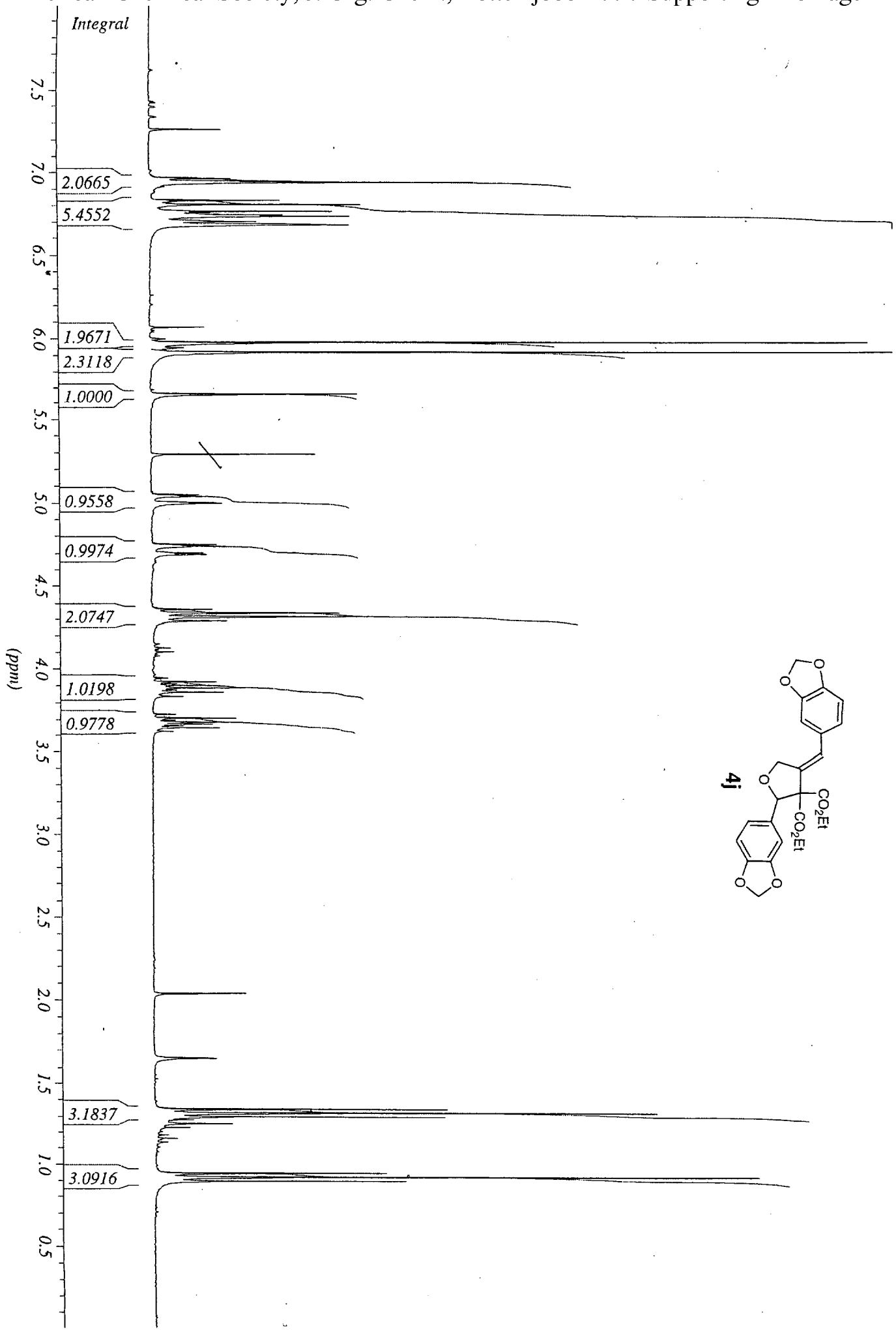








4i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3.0916
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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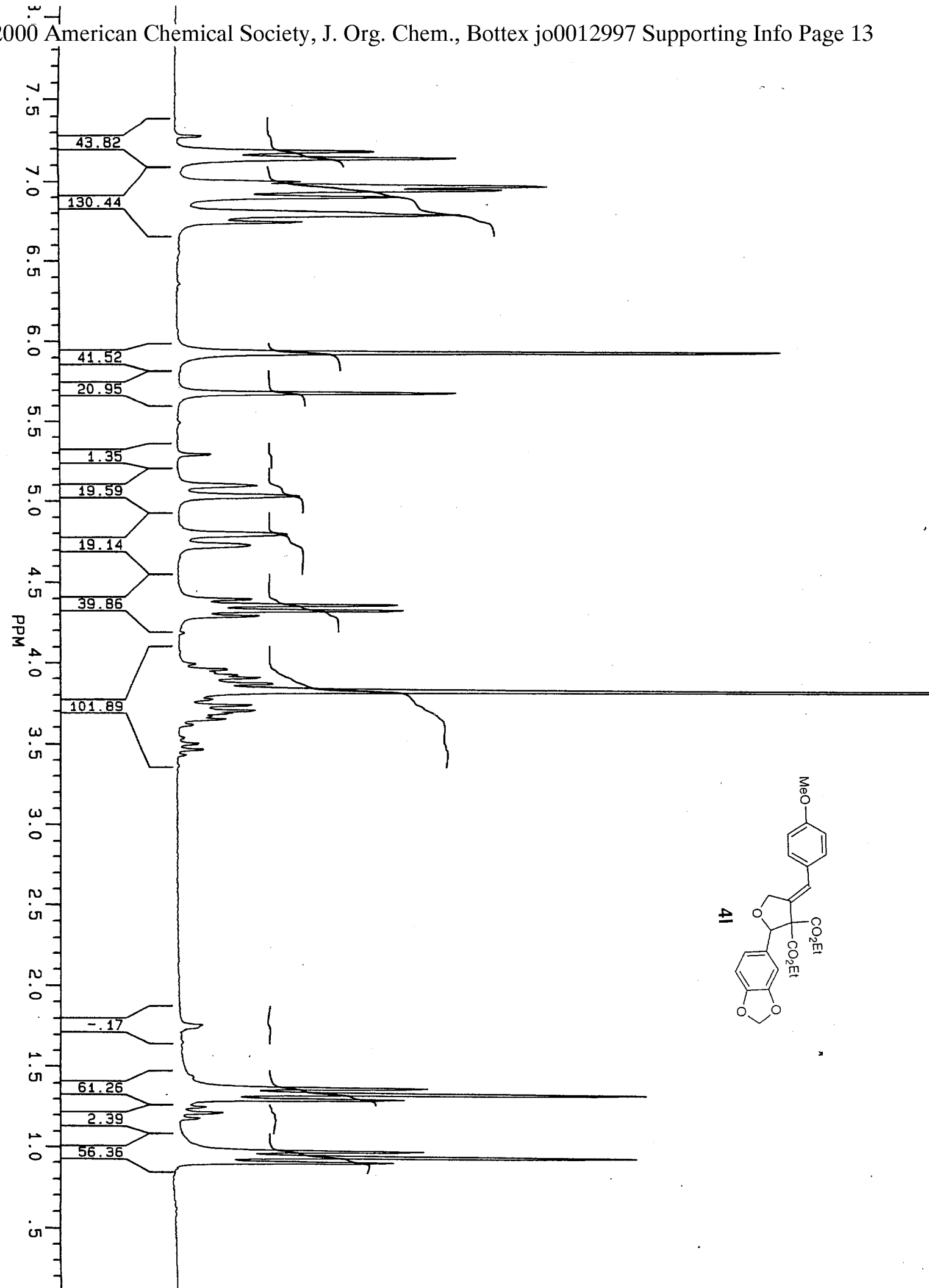
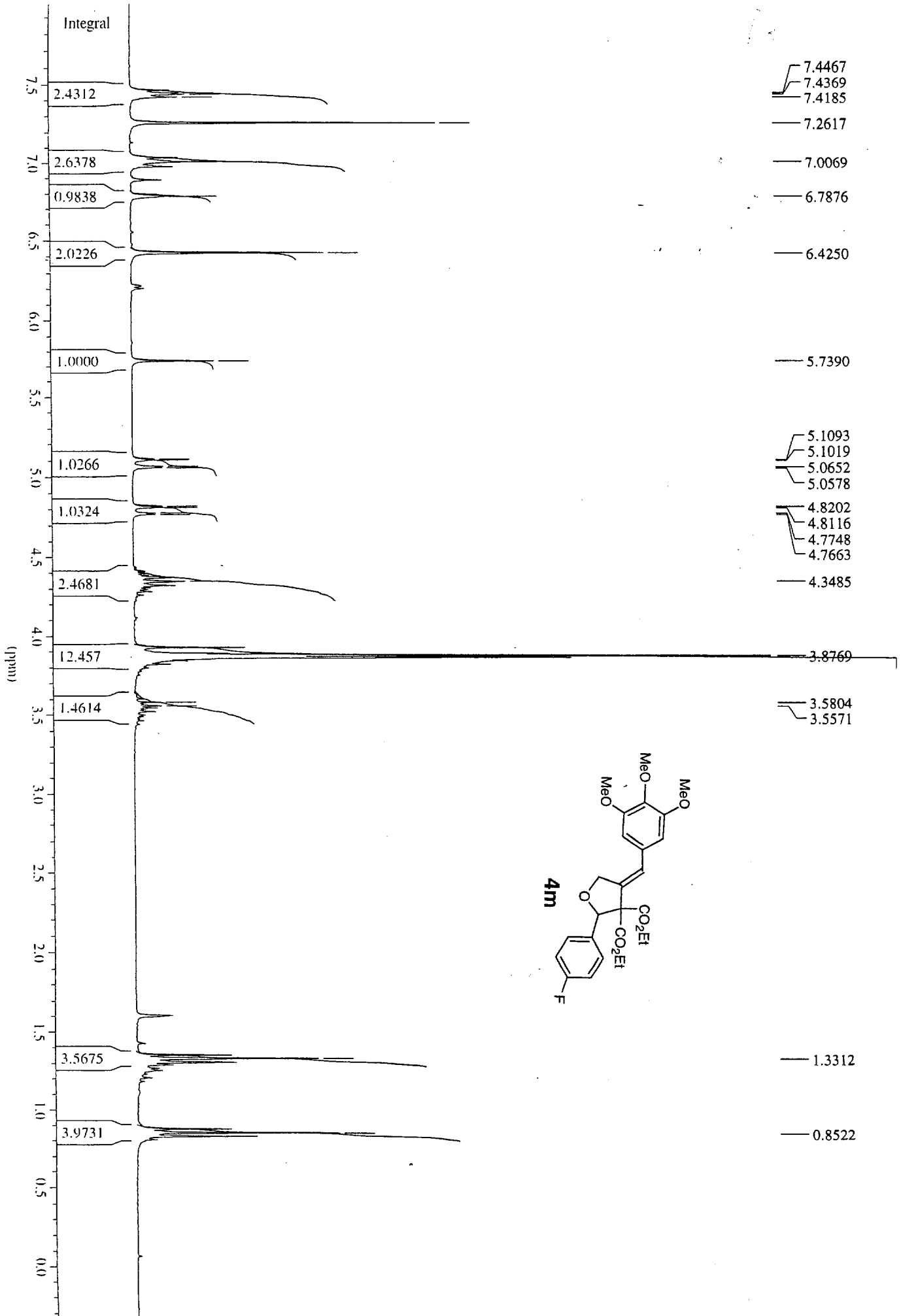
(ppm)

CO2Et
CO2Et

4j



41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5.0578
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4.8116
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(ppm)
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CO2Et
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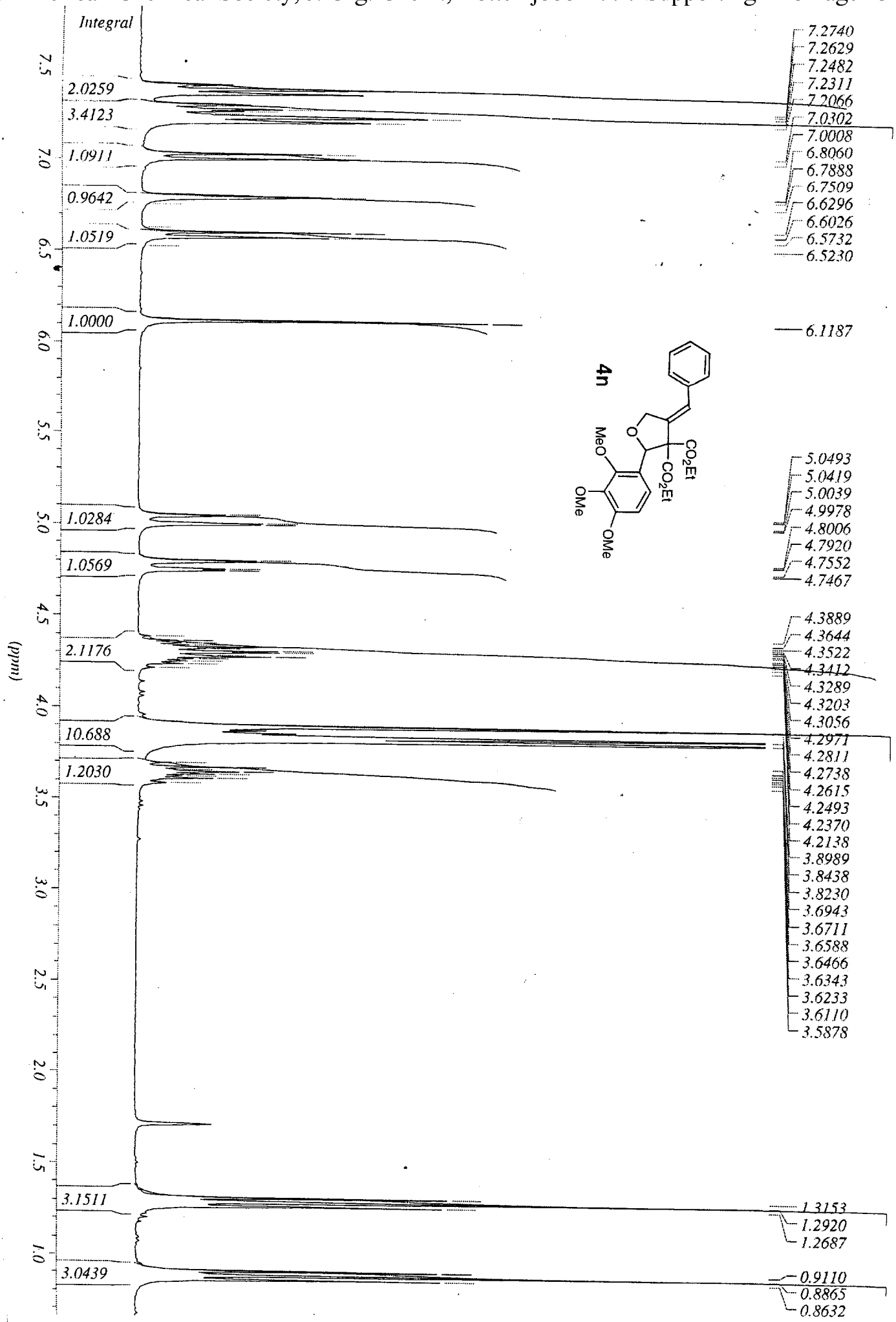

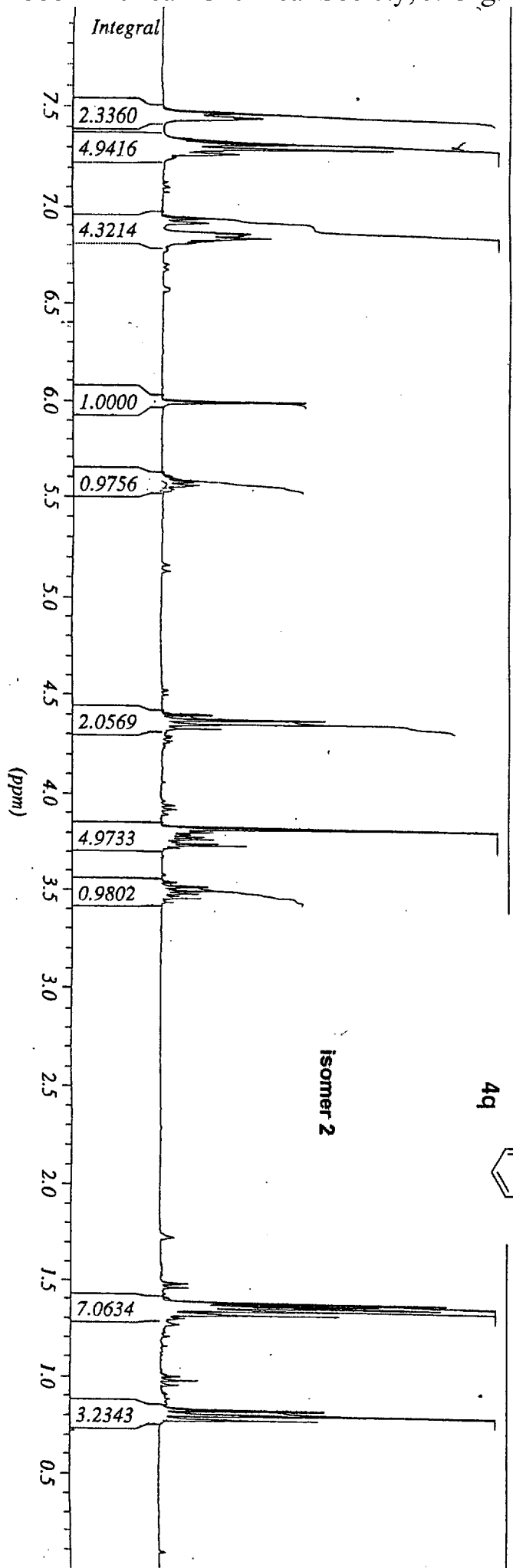
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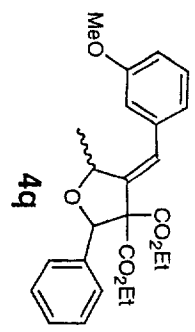
(ppm)
isomer 2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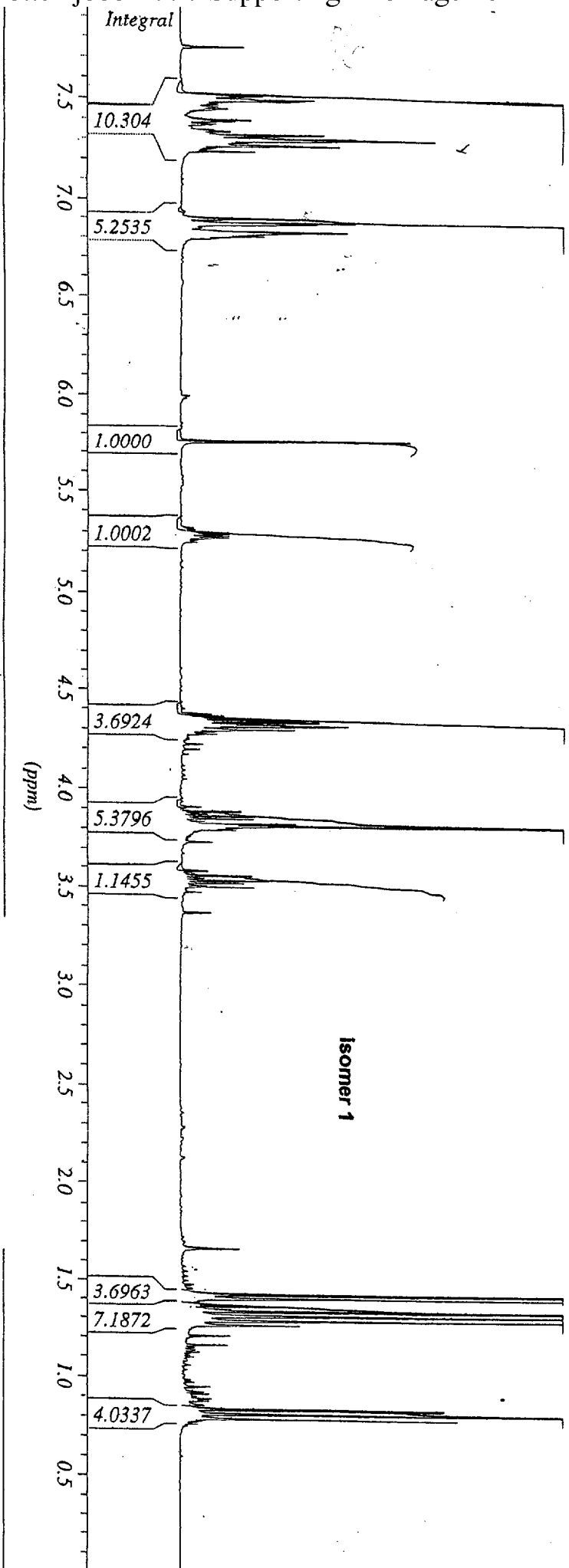
CO2Et

4q


Integral
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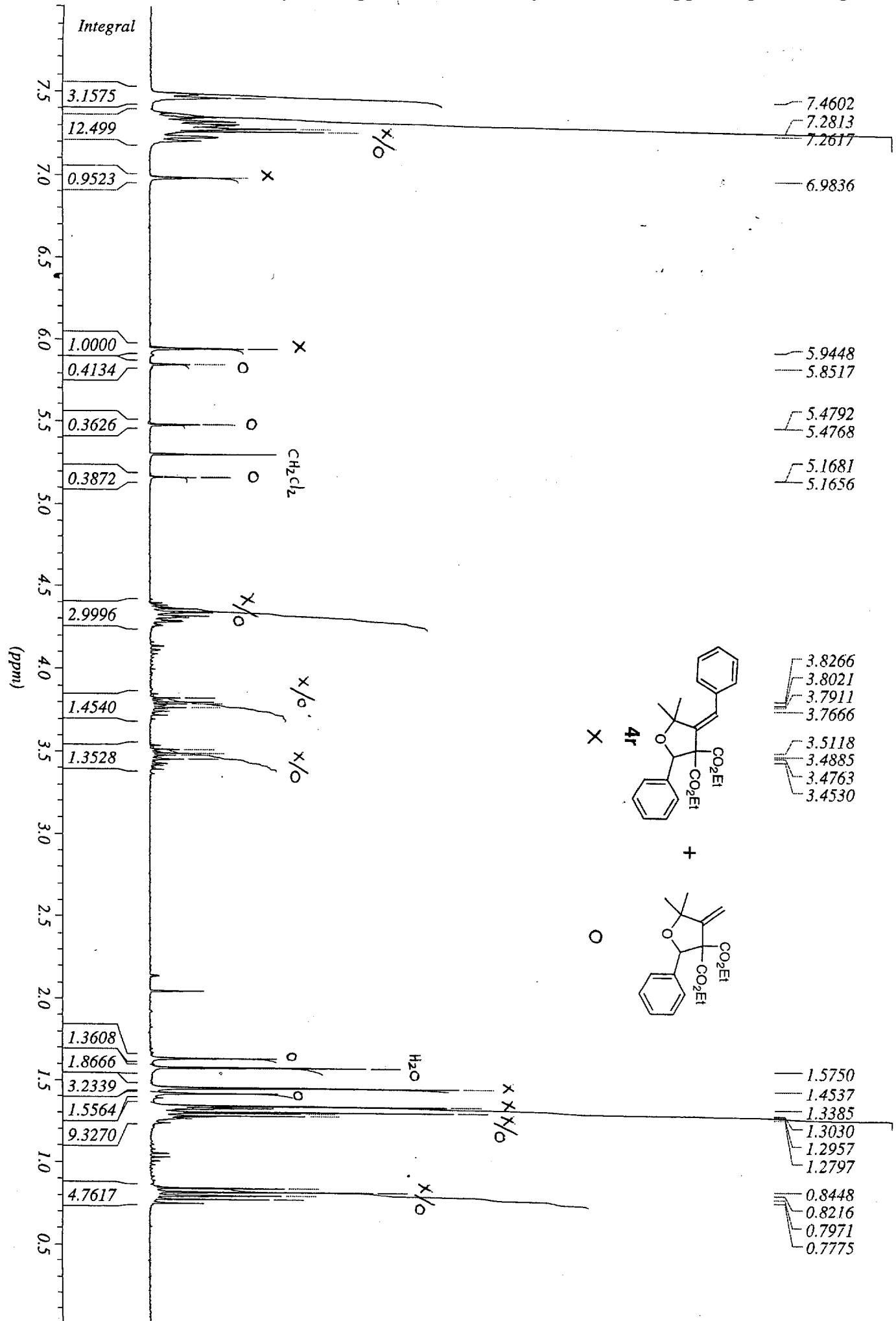
(ppm)
isomer 1


Integral
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3.2339
1.5564
9.3270
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5.4768
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5.1656
3.8266
3.8021
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3.7666
3.5118
3.4885
3.4763
3.4530
1.5750
1.4537
1.3385
1.3030
1.2957
1.2797
0.8448
0.8216
0.7971
0.7775
CH2Cl2
H2O
4r
CO2Et
CO2Et
(ppm)