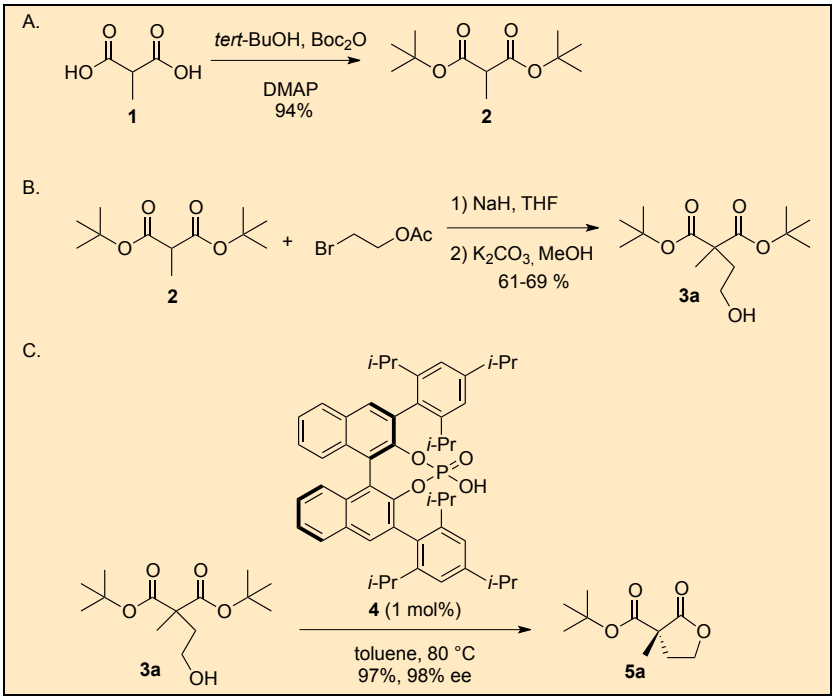
Organic Syntheses

Enantioselective Synthesis of α,α-Disubstituted Lactones via a Chiral Brønsted Acid Catalyzed Intramolecular Cyclization

Jennifer E. Wilent, Ghassan Qabaja, and Kimberly S. Petersen[1]*

Department of Chemistry and Biochemistry, University of North Carolina at Greensboro, Greensboro, NC 27412

Checked by Bo Qu and Chris H. Senanayake



Procedure

A. *Di-tert-butyl-2-methylmalonate (**2**).* An oven-dried 500-mL three-necked round-bottomed flask equipped with an egg-shaped stirring bar

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(30 mm x 15 mm) is fitted with two rubber septa and placed under an Ar atmosphere through a gas inlet. After cooling to 23 °C, methyl malonic acid (**1**) (12.0 g, 97.6 mmol, 1.0 equiv) (Note 1) is added followed by addition of diethyl ether (50 mL) (Note 2), 4-(dimethylamino)pyridine (1.2 g, 9.8 mmol, 0.1 equiv) (Note 3), *tert*-butyl alcohol (150 mL) (Note 4), and solid di-*tert*-butyl dicarbonate (48.3 g, 214.6 mmol, 2.2 equiv) (Note 5). The heterogeneous slurry is stirred (500 rpm) at room temperature (23 °C) for 48 h, after which time the reaction mixture became a clear pale yellow mixture (Figure 1). The reaction mixture is then diluted by addition of diethyl ether (150 mL), transferred to a 1000-mL separatory funnel and washed with water (2 x 50 mL) and HCl (1.0 M, 2 x 50 mL). The organic layer is dried over $MgSO_4$, gravity filtered using coarse filter paper, rinsed with diethyl ether (2 x 20 mL), and concentrated *in vacuo* using a rotary

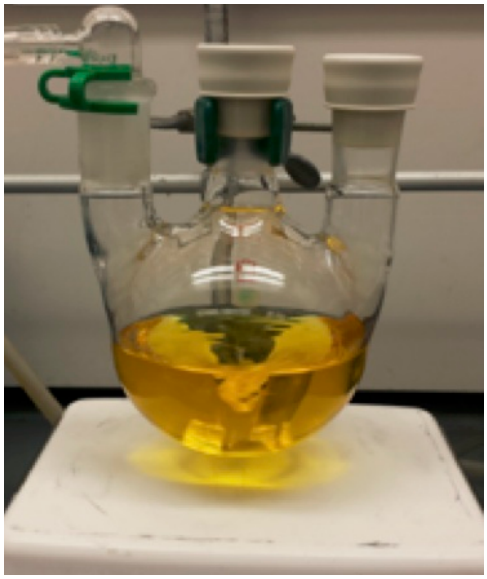

Figure 1. Reaction Mixture in Step A after 48 h

evaporator (27 °C, 7.5 mmHg) to give an oil, which is dissolved in 200 mL of hexanes and ethyl acetate (10:1) and passed through a plug of silica gel (3 x 5.2 cm) (Note 6) using a 60-mL medium fritted filter funnel. The colorless filtrate is received into a 500-mL round-bottomed flask and concentrated *in vacuo* using a rotary evaporator (27 °C, 7.5 mmHg), the colorless oil is put

under high vacuum (23 °C, 0.4 mmHg) for 30 min to yield 21.1 g of the product **2** as a colorless oil at >99% purity (94% yield) (Notes 7 and 8).

B. *Di-tert-butyl-2-(2-hydroxyethyl)-2-methylmalonate (**3a**).* An oven-dried 500-mL three-necked round-bottomed flask equipped with an egg-shaped stirring bar (30 mm x 15 mm) is fitted with two rubber septa and placed under an Ar atmosphere through a gas inlet. After cooling to 23 °C, tetrahydrofuran (100 mL) (Note 9) is added via a syringe and the reaction flask is cooled with an ice-water bath. After stirring for 15 min, NaH (3.13 g, 78.2 mmol, 1.2 equiv) (Note 10) is added in one portion and the slurry is stirred for an additional 15 min. Di-*tert*-butyl-2-methylmalonate (**2**) (15.0 g, 65.1 mmol, 1.0 equiv) is dissolved in tetrahydrofuran (30 mL) in a 100-mL oven dried pear-shaped flask and this solution is transferred by cannula into the sodium hydride slurry in portions over 15 min. After 30 min 2-bromoethyl acetate (8.9 mL, 78.2 mmol, 1.2 equiv) (Note 11) is added drop wise via a syringe over a period of 5 min. The reaction mixture is allowed to slowly warm to room temperature (23 °C). The progress of the reaction is monitored by TLC analysis (Note 12). TLC analysis indicated consumption of the di-*tert*-butyl-2-methylmalonate (**2**) after 16 h. The reaction flask is cooled in an ice-water bath for 15 min, and a solution of saturated NH_4Cl solution (10 mL) is added drop wise via syringe. The mixture is diluted with diethyl ether (300 mL) and transferred to a 1000-mL separatory funnel. The ether layer is washed with water (2 x 50 mL) and saturated NaCl solution (50 mL), dried over $MgSO_4$, gravity filtered using coarse filter paper, rinsed with diethyl ether (2 x 20 mL), and concentrated *in vacuo* using a rotary evaporator (27 °C, 7.5 mmHg) to give a pale yellow oil which is dissolved in methanol (50 mL) (Note 13). The solution is transferred to an oven dried 500-mL three-necked round-bottomed flask equipped with an egg-shaped stir bar (30 mm x 15 mm) and two septa. A temperature probe is placed through the septum in the side neck to monitor the internal temperature of the reaction (Figure 2). The reaction flask is filled with argon and held under an atmosphere of Ar. The reaction flask is cooled to −20 to −10 °C using acetonitrile/dry ice bath (Note 14) and K_2CO_3 (9.0 g, 65.1 mmol) (Note 15) is added in five portions such that the internal temperature stays below −5 °C. After 2 h, the reaction mixture is diluted with diethyl ether (200 mL) and deionized water (50 mL) is added drop wise such that the internal temperature stays below −5 °C. The contents of the flask are transferred to a 1000-mL separatory funnel and hexanes (100 mL) are added. The organic layer is washed with water (3 x 50 mL)

and saturated NaCl solution (50 mL), dried over $MgSO_4$, gravity filtered using coarse filter paper, rinsed with diethyl ether (2 x 20 mL), and concentrated *in vacuo* using a rotary evaporator (27 °C, 7.5 mmHg) to give a

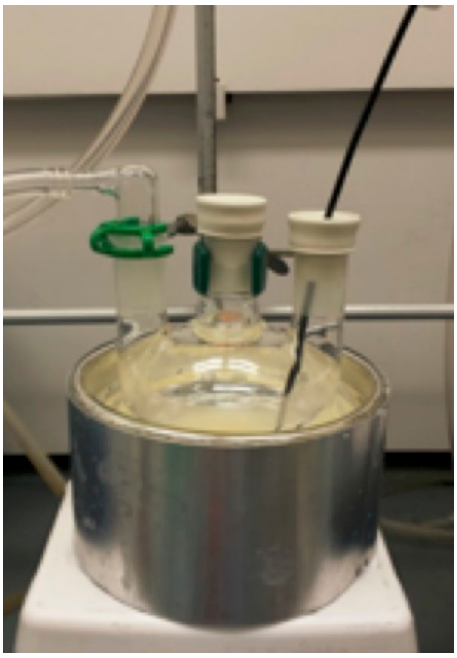

Figure 2. Step B Assembly with Temperature Probe Inserted

light yellow oil. The oil is dissolved into hexanes (100 mL) and the flask is cooled with an ice-water bath for 1 h to yield a layer of white solids. The solids are broken via a spatula and collected via vacuum filtration into a 100 mL ceramic Buchner funnel equipped with filter paper of moderate porosity and washed with ice-cold hexanes (25 mL). A second crop of solids are obtained after the filtrate is concentrated under vacuum and the residue is dissolved in hexanes (20 mL), cooled with an ice water bath for 2 h and filtered as before. The two batches are combined to yield 10.9 g of product **3a** as a white crystalline solid (61% yield) (Notes 16 and 17).

C. (*S*)-*tert*-Butyl-3-methyl-2-oxotetrahydrofuran-3-carboxylate (***5a***). A 500-mL two-necked, round-bottomed flask equipped with an egg-shaped magnetic stir bar (38 x 16 mm) is flame-dried under vacuum. After cooling to 23 °C, di-*tert*-butyl 2-(2-hydroxyethyl)-2-methylmalonate (**3a**) (8.5 g, 31 mmol) is added to the round-bottomed flask, a rubber septum is fitted,

the reaction flask is put under an atmosphere of Ar, and toluene (310 mL) (Note 18) is added via syringe. A thermometer probe is placed through the septum in the side neck to monitor internal temperature of the reaction. To this clear colorless solution, (*R*)-3, 3′-bis(2,4,6-triisopropylphenyl)-1,1′-binapthyl-2,2′-diylhydrogenphosphate (**4**, TRIP) (0.23 g, 0.31 mmol, 0.01 equiv) (Note 19) is added as a solid and an oven-dried reflux condenser is attached. Using an oil bath, the reaction mixture is heated to 80 °C (internal reaction temperature 76–80 °C) with stirring. The reaction is stirred at 500 rpm. The progress of the reaction is monitored by TLC analysis (Note 20). TLC analysis indicated consumption of the di-*tert*-butyl 2-(2-hydroxyethyl)-2-methylmalonate after 48 h. The round-bottomed flask is allowed to cool slowly in the oil bath to 23 °C. The reflux condenser is removed and EtOAc (50 mL) is added. After stirring for 5 min, the reaction mixture is transferred to a 500-mL separatory funnel and washed with deionized water (250 mL). After the layers separate, the lower, clear water layer is drained and the upper, cloudy EtOAc layer is collected in a 500 mL Erlenmeyer flask. The water layer is returned to the separatory funnel and reextracted with EtOAc (200 mL). The combined EtOAc layers are dried over $MgSO_4$, gravity filtered through coarse filter paper into a 1000 mL round bottomed flask and the $MgSO_4$ is rinsed with EtOAc (50 mL). The 1000 mL flask is concentrated *in vacuo* using a rotary evaporator (28 °C, 7.5 mmHg) and the crude reaction mixture is purified via flash chromatography (Note 21) resulting in the isolation of 6.02 g (97% yield) of product **5a** as a white crystalline solid (98% ee) (Notes 22, 23, and 24).

Notes

1. Methyl malonic acid (96%) was purchased from Acros and used as received.
2. Diethyl ether was purchased from Pharmaco-AAper (Reagent Grade ACS Anhydrous) and used without purification.
3. DMAP (4-(Dimethylamino)pyridine, ReagentPlus®, ≥99%) was purchased from Aldrich and used as received.
4. *tert*-Butyl alcohol (99.5%, extra pure) was purchased from Acros and used as received.
5. Di-*tert*-butyl dicarbonate (97%) was purchased from Acros and used as received.

6. Silica gel was purchased from Silicylce, Inc. (SiliaFlash P60 (230-400 mesh)) and used as received.
7. Physical characteristics of di-*tert*-butyl-2-methylmalonate (**2**): colorless liquid with >99% purity as determined by quantitative ^{1}H NMR using dimethyl fumarate as the internal standard; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.32 (d, *J* = 7.4 Hz, 3H), 1.46 (s, 18H), 3.24 (q, *J* = 7.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 13.4, 27.9, 48.1, 81.1, 169.6; IR (neat) cm^{-1} 2978, 1725, 1136, 848; HRMS ($C_{12}H_{22}O_4$, ESI): calculated 253.1415 $[M+Na]^{+1}$, found 253.1423;
8. A second run produced 21.3 g of the product **2** as colorless oil, 95% yield, >99% purity.
9. THF (tetrahydrofuran, minimum 99%, inhibited with <0.025% butlylated hydroxytoluene) was purchased from Acros and distilled under Ar over benzophenone and sodium.
10. Sodium hydride (60% dispersion in mineral oil in soluble bags, in resealable cans) was purchased from Acros and used as received.
11. 2-Bromoethyl acetate (97%) was purchased from Acros and used without further purification.
12. TLC analysis was performed on silica gel with 10:1 hexanes-EtOAc as eluent and visualization with *p*-anisaldehyde. The starting material has R_f = 0.38 (blue) and the product has R_f = 0.22 (blue). TLC plates were purchased from Silicycle, Inc. (Glass Backed TLC Extra Hard Layer, 60Å).
13. Anhydrous methanol (anhydrous, 99.8%, AcroSeal (TM)) was purchased from Acros and used received.
14. Saturated NaCl solution/ice bath was used by the submitting authors. The checkers observed that temperature is difficult to be kept under –5 °C using this cooling bath at this scale after addition of base K_2CO_3.
15. Anhydrous potassium carbonate (Certified ACS Granular Powder) was purchased from Fisher and used as received.
16. NMR spectra and purity of the first batch and second batch of di-*tert*-butyl 2-(2-hydroxyethyl)-2-methylmalonate (**3a**) are the same: white crystalline solid with 98% purity as determined by quantitative ^{1}H NMR using dimethyl fumarate as an internal standard; mp = 38–39 °C; ^{1}H NMR (500 MHz $CDCl_3$) δ: 1.40 (s, 3H), 1.48 (s, 18H), 2.09 (t, *J* = 6.3 Hz, 2H), 2.13 (br s, 1H), 3.75 (t, *J* = 6.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 20.2, 27.8, 38.2, 53.7, 59.0, 81.5, 172.0; IR (neat) cm^{-1} 3446, 2977, 1710,

1367, 1154, 1112, 1019, 844 ; HRMS ($C_{14}H_{26}O_5$, ESI): calculated 297.1672 $[M+Na]^{+1}$, found 297.1665;

17. A second run produced 12.4 g of product **3a**, 69% yield, 98% purity.
18. Toluene was purchased from Innovative Technology and passed through a Pure Solv MD 5 Solvent Purification System. The checkers used toluene purchased from Aldrich and distilled over CaH_2.
19. (*R*)-3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binapthyl-2,2′-diyl hydrogen phosphate (**4**) was purchased from Corvinus Chemicals (currently Ark Chemicals) and used as received.
20. TLC analysis was performed on silica gel with 30% EtOAc-hexanes as eluent and visualization with *p*-anisaldehyde. The starting material has R_f = 0.37 (blue) and the product has R_f = 0.58 (blue). TLC plates were purchased from Silicycle, Inc. (Glass Backed TLC Extra Hard Layer, 60Å).
21. Column diameter: 3.8 cm, silica: 84.0 g (Silicycle Inc., silica 60 (230-400 mesh), eluant: 500 mL 4:1 EtOAc:hexane), fraction size: 20 mL (16 x 150 mm test tubes), product typically found in factions 6-20.
22. Physical characteristics of (*S*)-*tert*-butyl 3-methyl-2-oxotetrahydrofuran-3-carboxylate (**5a**): white solid with 99% purity, as determined by quantitative ^{1}H NMR using dimethyl fumarate as an internal standard; mp = 49–50 °C; $[\alpha]_D^{24.5}$ = +7.08° (c = 1.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.49 (s, 12 H), 2.18 (m, 1H), 2.71 (m, 1H), 4.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) : 20.1, 27.8, 35.1, 50.5, 65.8, 82.8, 169.4, 176.3; IR (neat) cm^{-1} 2980, 1763, 1730, 1426, 1370, 1227, 1132, 1025, 845; HRMS ($C_{10}H_{20}NO_4$, ESI): calculated 218.13868 $[M+NH_4]^{+1}$, found 218.1385;
23. Enantiomeric purity was assessed at 98% ee by chiral HPLC: Chiralcel OJ-3, 4.6 x 150 mm, 3 micro; isocratic: 1% of IPA in heptane; eluent Rate: 1.3 mL/ min; Temperature 5 °C; UV detector 220 nm; RT_{major} = 10.2 min, RT_{minor} = 11.2 min.
24. A second run produced 5.97 g of product **5a**, 96% yield, 99% purity, 98% ee.

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The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for

work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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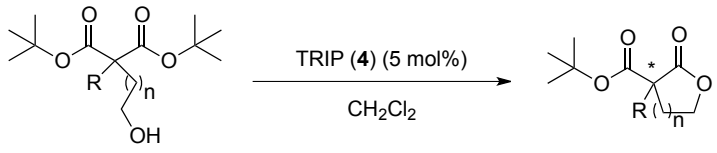
Discussion

The development of single-enantiomer chiral compounds has been a trend in the drug industry due to the potentially diverse pharmacology and toxicology of different stereoisomers of a molecule. The field of asymmetric methodology development has thus gained importance over the past several decades.[2] Often the key to an enantioselective synthesis is the availability of small chiral building blocks. Enantioenriched α-substituted lactones are common structural motifs and/or key intermediates in the synthesis of many biologically active compounds.[3] Organocatalysis and specifically chiral Brønsted acid and hydrogen bonding catalysts as a strategy to generate single enantiomer compounds through asymmetric synthesis has become a widely explored field.[4]

Recently, we have developed an enantioselective desymmetrization of prochiral diesters through a Brønsted acid catalyzed intramolecular cyclization to yield lactones containing an α-quaternary center.[5] Disubstituted hydroxy *tert*-butyl malonates **3a–3g** were readily prepared in 3 steps and in the presence of Binol based chiral Brønsted acid, (*R*)- or (*S*)-TRIP (**4**), enantioenriched lactones **5a–5g** were formed (Table 1). Coordination of the chiral phosphoric acid through one or more hydrogen bonds to the substrate likely leads to a rigid transition state which allows for discrimination of the enantiotopic ester groups.

Table 1. Substrate Scope



3a–3g **5a–5g**

entry	R	n	catalyst	time (h)	temp (°C)	yield (%)[a]	ee (%)[b]
1	Me (**5a**)	1	*S*	120	25	95	98
2	**Me** (**5a**)	**1**	***R* (1 mol%)**	**48**	**80[c]**	**96**	**98**
3	H (**5b**)	1	*S*	72	5	93	91
4	Et (**5c**)	1	*S*	120	25	93	95
5	*i*-Pr (**5d**)	1	*R*	192	35	89	90
6	allyl (**5e**)	1	*R*	168	35	96	97
7	benzyl (**5f**)	1	*S*	155	35	67	94
8	Me (**5g**)	2	*S*	144	25	84	86

[a] isolated yield; [b] determined by GC or HPLC analysis with a chiral support column; [c] toluene used as solvent.

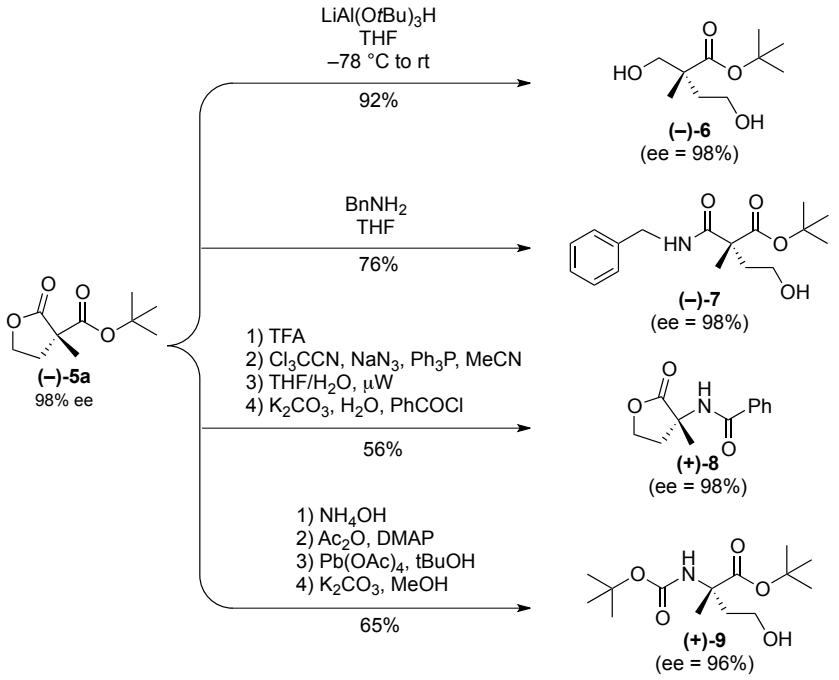
A bulky ester is necessary for the process, however the R group can vary in length and branching. Small alkyl groups such as methyl (**5a**, entry 1), ethyl (**5c**, entry 4), and allyl (**5e**, entry 6) as well as larger groups such as isopropyl (**5d**, entry 5) and benzyl (**5f**, entry 7) all generate γ-lactones in good to excellent yields (67–96%) and enantioselectivities (90–98%). A one

carbon homologation of the hydroxy chain led to the formation of δ-lactone with minimal loss in enantioselectivity (**5ge**, entry 8).

The cyclization was originally performed at room temperature using 5 mol% of catalyst (entry 1). The process has now been optimized such that catalyst loading can be lowered to 1 mol% with heating at 80 °C in toluene with no loss in ee or yield (entry 2). Additionally, the improved reaction conditions vastly lowered the reaction time from 120 to 48 hours.

Absolute configuration of lactones **5a–5g** was determined by comparison of the reduced diol of lactone **5f** to known values.[6]

Lactones such as **5a** where shown to be versatile intermediates through transformation into highly functionalized small building blocks (Scheme 1). Each transformation exhibited good yields while maintaining excellent enantioselectivity. Selective reduction of lactone (–)-**5a** with lithium tri-*tert*-butoxyaluminum hydride yielded diol (–)-**6** in 92% yield and without loss



Scheme 1. Transformations of the γ-Lactones

of enantiopurity (ee = 98%).[7] Treatment of lactone **5a** with the benzyl amine gave amide ester (–)-**7** in 76% yield and 98% ee.[8] Curtius rearrangement of intermediate acyl azide yielded amido lactone (+)-**8** in 56% overall yield and no loss of enantiopurity.[9] Treatment of lactone **5a** with aqueous ammonium hydroxide followed by acetylation of the resulting alcohol yielded an amide ester that then underwent a Hofmann rearrangement with lead (IV) acetate and hydrolysis with potassium carbonate to give α-amino ester (+)-**9** in 65% overall yield and 96% ee.[10]

In conclusion, we have developed a highly efficient and generalized procedure for the synthesis of enantioenriched lactones containing a quaternary center through a Brønsted acid catalyzed desymmetrization of hydroxy diesters. The process has been improved to utilize only 1 mol% of Binol based phosphoric acid and proceed in under 48 hours.

References

1. Department of Chemistry and Biochemistry, University of North Carolina, Greensboro, NC 27412, kspeters@uncg.edu. Financial support is gratefully acknowledged from the National Institutes of Health (GM116041) and the American Chemical Society Petroleum Research Fund (53916-DNI).
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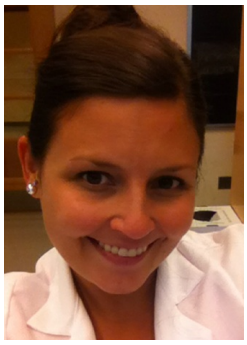
Appendix
Chemical Abstracts Nomenclature (Registry Number)

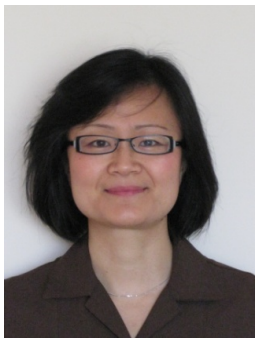
Methyl malonic acid: Propanedioic acid, methyl-; (516-05-2)
4-(Dimethylamino)pyridine: 4-Pyridinamine, *N*,*N*-dimethyl-; (1122-58-3)
tert-butanol: 2-Propanol, 2-methyl-; (75-65-0)
Di-*tert*-butyl dicarbonate: Dicarbonic acid, bis(1,1-dimethylethyl) ester (24424-99-5)
Sodium hydride; (7646-69-7)
2-Bromoethyl acetate; (927-68-4)
(*R*)-3, 3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binapthyl-2,2′-diylhydrogenphosphate; (791616-63-2)

Kimberly S. Petersen received her B.S. in chemistry from the University of Wisconsin, Madison. She then earned her Ph.D. at Johns Hopkins University under the supervision of Professor Gary Posner followed by postdoctoral research at the California Institute of Technology with Professor Brian Stoltz. In 2011, she began her independent career at the University of North Carolina at Greensboro.

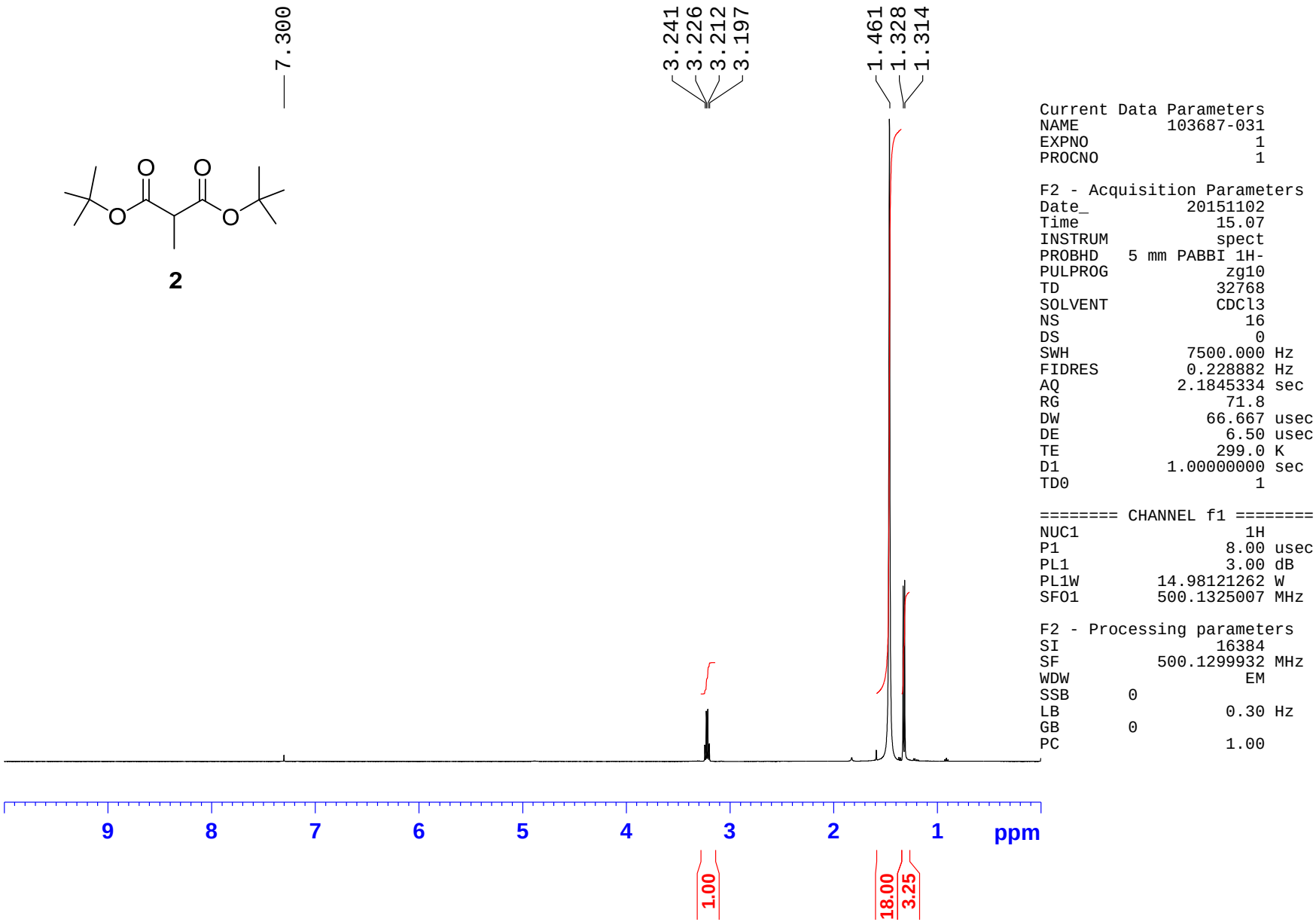


Jennifer E. Wilent received her B.S. and M.S. in chemistry from the University of North Carolina at Wilmington. In 2011, she began her doctoral studies under the supervision of Dr. Kimberly S. Petersen. Her Ph.D. studies focus on asymmetric enantioselective syntheses of novel heterocycles.

Dr. Ghassan Qabaja was born and raised in West Bank, Palestine. He received his undergraduate degree from Yarmouk University in Jordan. In 2000, he received his Ph.D. from Northeastern University under the supervision of Graham Jones. His graduate studies focused on multistep synthesis of complex natural products and designed compounds. He worked as a medicinal chemistry in the biotechnology sector prior to his work at the University of North Carolina at Greensboro. He began as a research scientist for Dr. Kimberly S. Petersen in 2011.



Dr. Bo Qu received her Ph.D. with Professor Richard Adams at the University of South Carolina in 2002 followed by postdoctoral fellow with Professor David Collum at Cornell University. In 2006 she joined Chemical Development at Boehringer Ingelheim Pharmaceuticals in Ridgefield, CT, where she is currently a Principal Scientist. Dr. Qu's research interests focus on development of new catalytic transformations for efficient chemical processes. She has authored more than 80 papers and patents.

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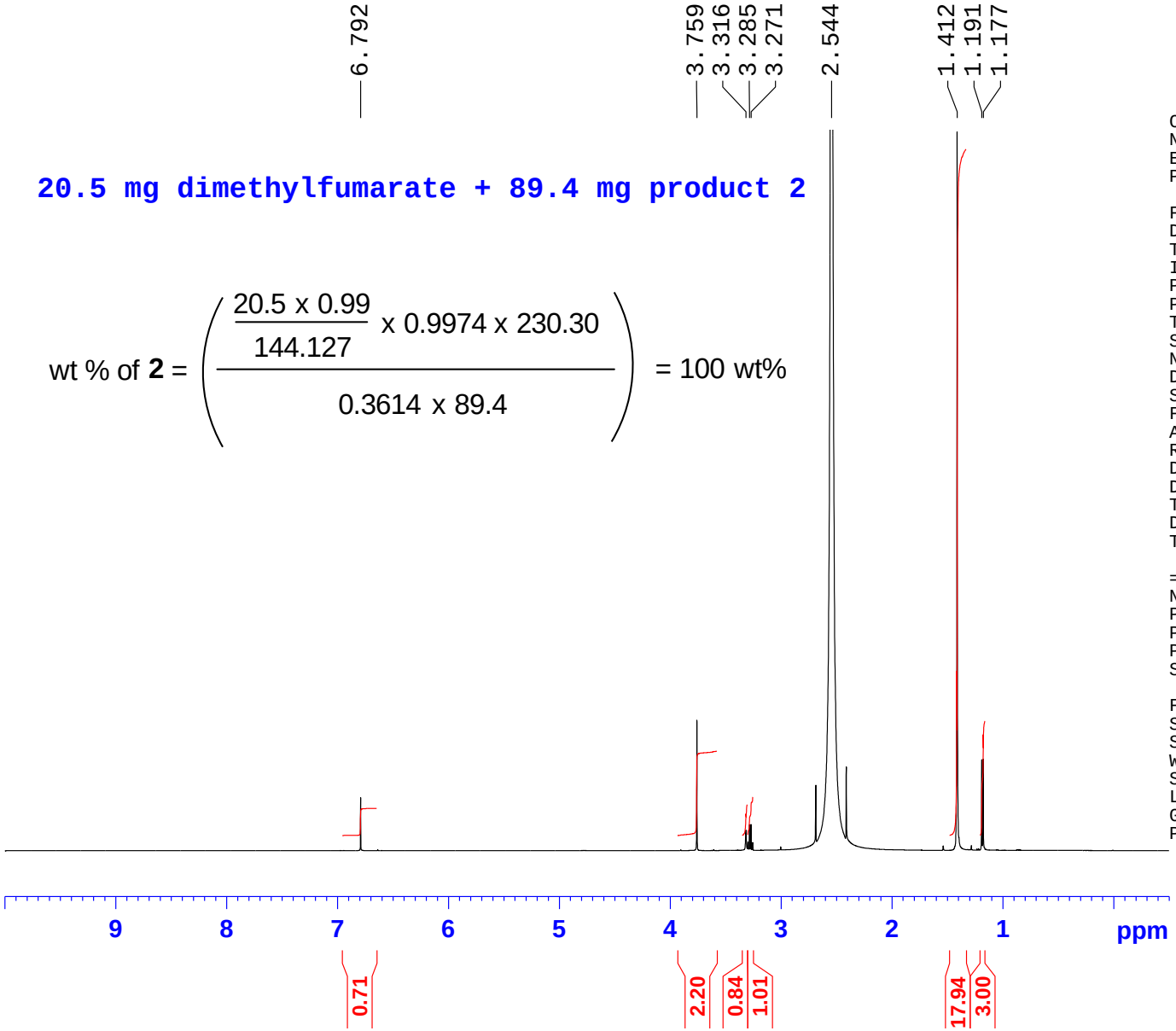
```

Quantitative 1H NMR assay of the product **2** in DMSO-D6 using 99% of dimethylfumarate as internal standard

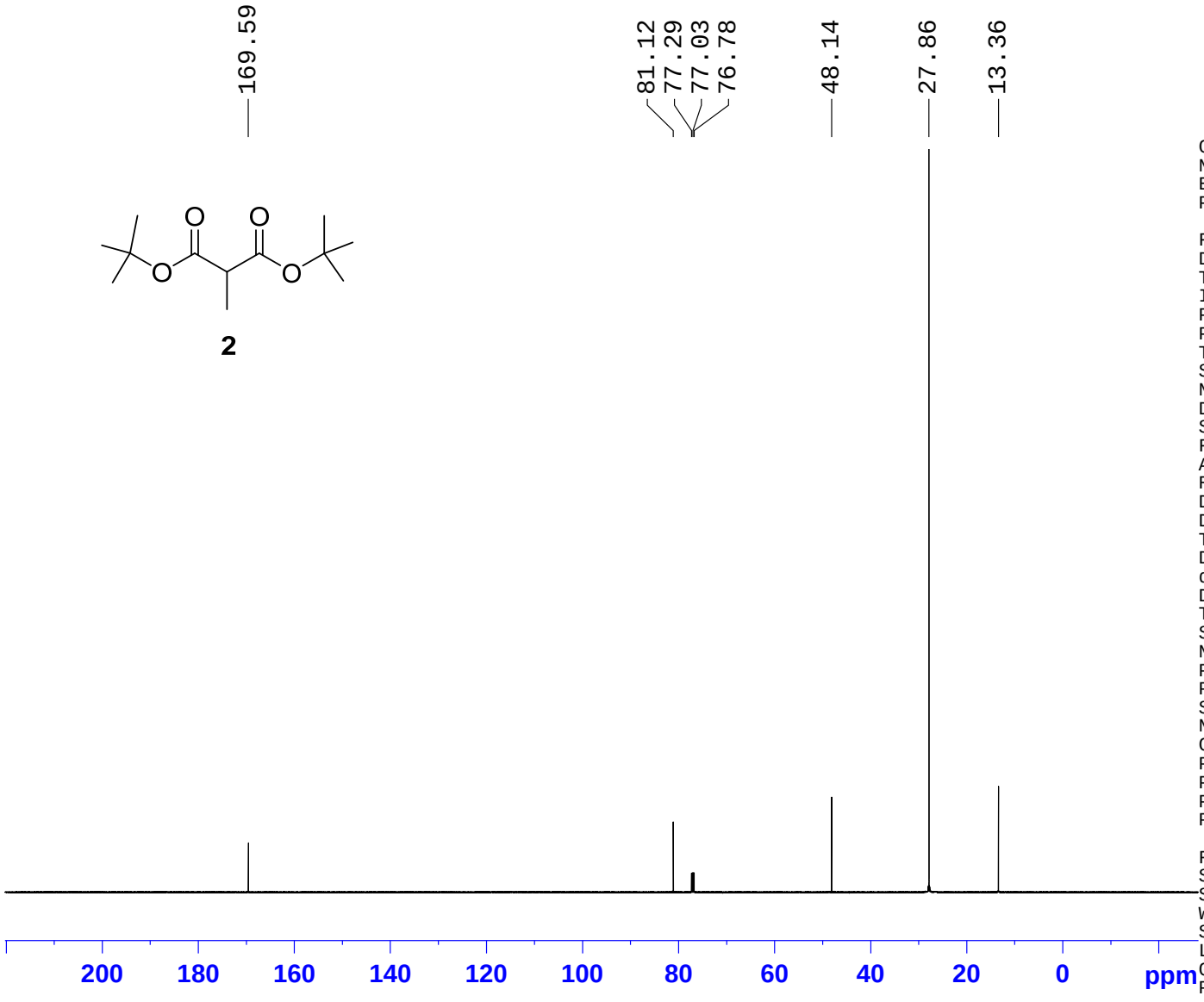



```
Current Data Parameters
NAME      103687-031-assay
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_           20151103
Time               11.11
INSTRUM            spect
PROBHD   5 mm PABBI 1H-
PULPROG           q_zg10
TD                 32768
SOLVENT             DMSO
NS                   128
DS                     0
SWH             9014.423 Hz
FIDRES          0.275098 Hz
AQ             1.8175317 sec
RG                    18
DW                55.467 usec
DE                 6.50 usec
TE                299.0 K
D1           2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 8.00 usec
PL1                3.00 dB
PL1W        14.98121262 W
SFO1        500.1334009 MHz

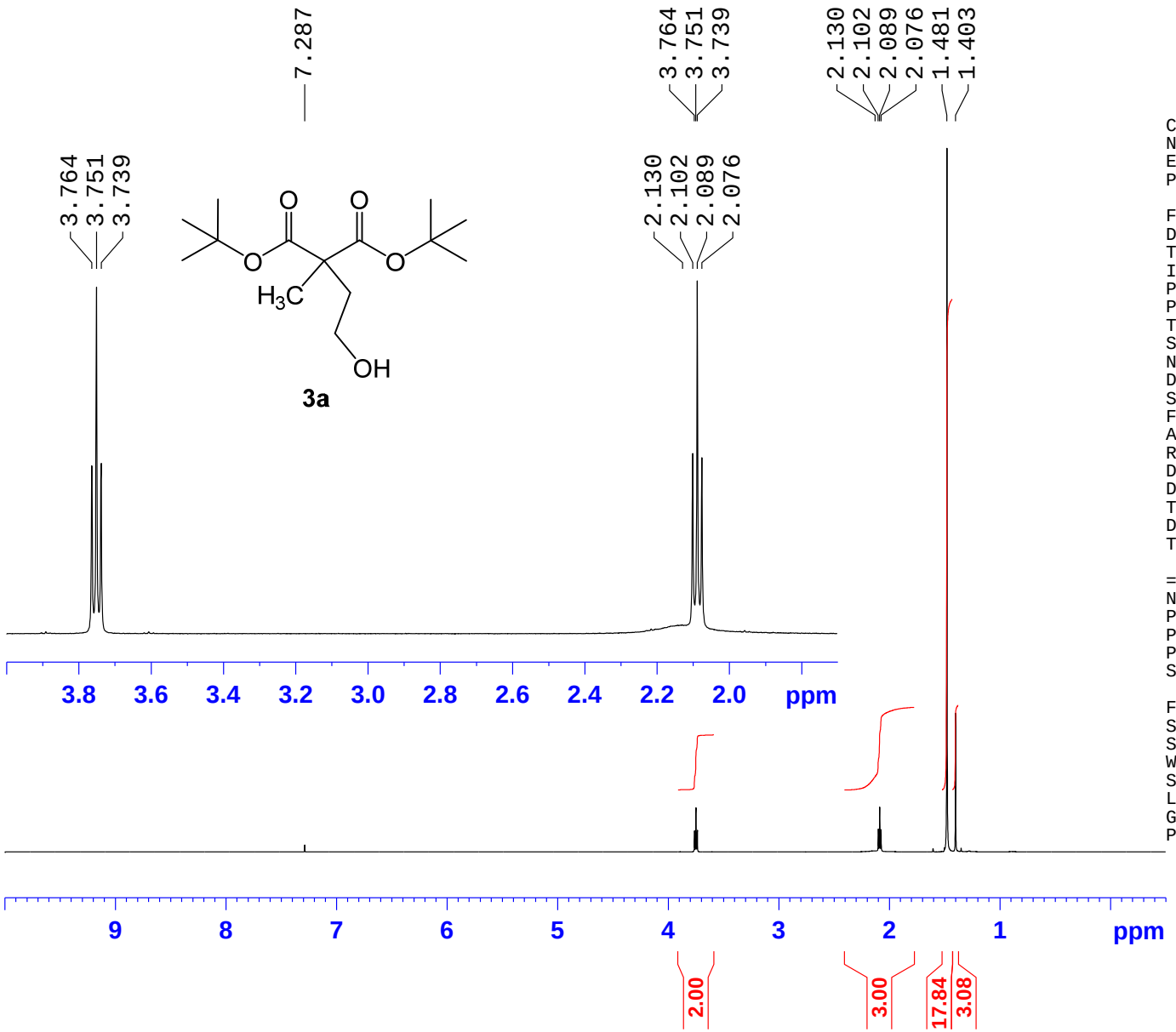
F2 - Processing parameters
SI                 16384
SF          500.1300000 MHz
WDW                   EM
SSB      0
LB                 0.30 Hz
GB       0
PC                 1.00
```




```
Current Data Parameters
NAME          103687-031
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20151102
Time               15.31
INSTRUM            spect
PROBHD   5 mm PABBI 1H-
PULPROG            zgpg
TD                262144
SOLVENT            CDCl3
NS                   256
DS                     0
SWH            31250.000 Hz
FIDRES          0.119209 Hz
AQ             4.1943040 sec
RG                  2050
DW                16.000 usec
DE                 6.50 usec
TE                299.0 K
D1             1.00000000 sec
d11            0.03000000 sec
DELTA          0.89999998 sec
TD0                    1
SFO1         125.7698617 MHz
NUC1                 13C
P1                15.75 usec
PLW1         -1.00000000 W
SFO2         500.1325007 MHz
NUC2                 1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         -1.00000000 W
PLW12        -1.00000000 W
PLW13        -1.00000000 W

F2 - Processing parameters
SI                131072
SF           125.7577890 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.40
```



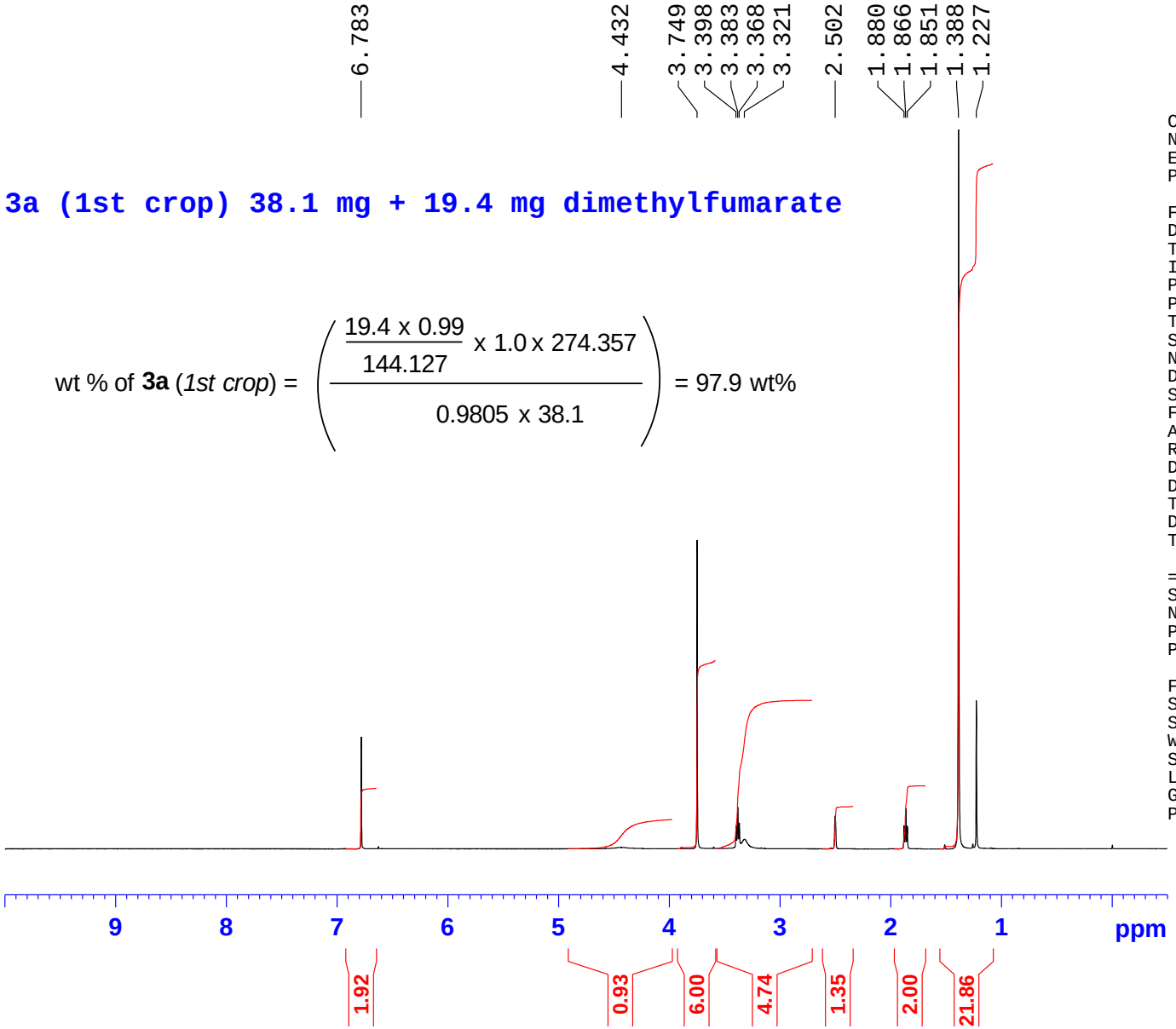

```
Current Data Parameters
NAME        103687-032a
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20151103
Time               8.54
INSTRUM           spect
PROBHD   5 mm PABBI 1H-
PULPROG            zg10
TD                32768
SOLVENT           CDCl3
NS                   16
DS                    0
SWH            7500.000 Hz
FIDRES         0.228882 Hz
AQ            2.1845334 sec
RG                  575
DW               66.667 usec
DE                6.50 usec
TE                299.0 K
D1           1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 1H
P1                8.00 usec
PL1               3.00 dB
PL1W        14.98121262 W
SFO1        500.1325007 MHz

F2 - Processing parameters
SI                16384
SF          500.1300000 MHz
WDW                  EM
SSB      0
LB                0.30 Hz
GB       0
PC                1.00
```

Quantitative 1H NMR assay of the products **3a** in DMSO-D6 using 99% of dimethylfumarate as internal standard

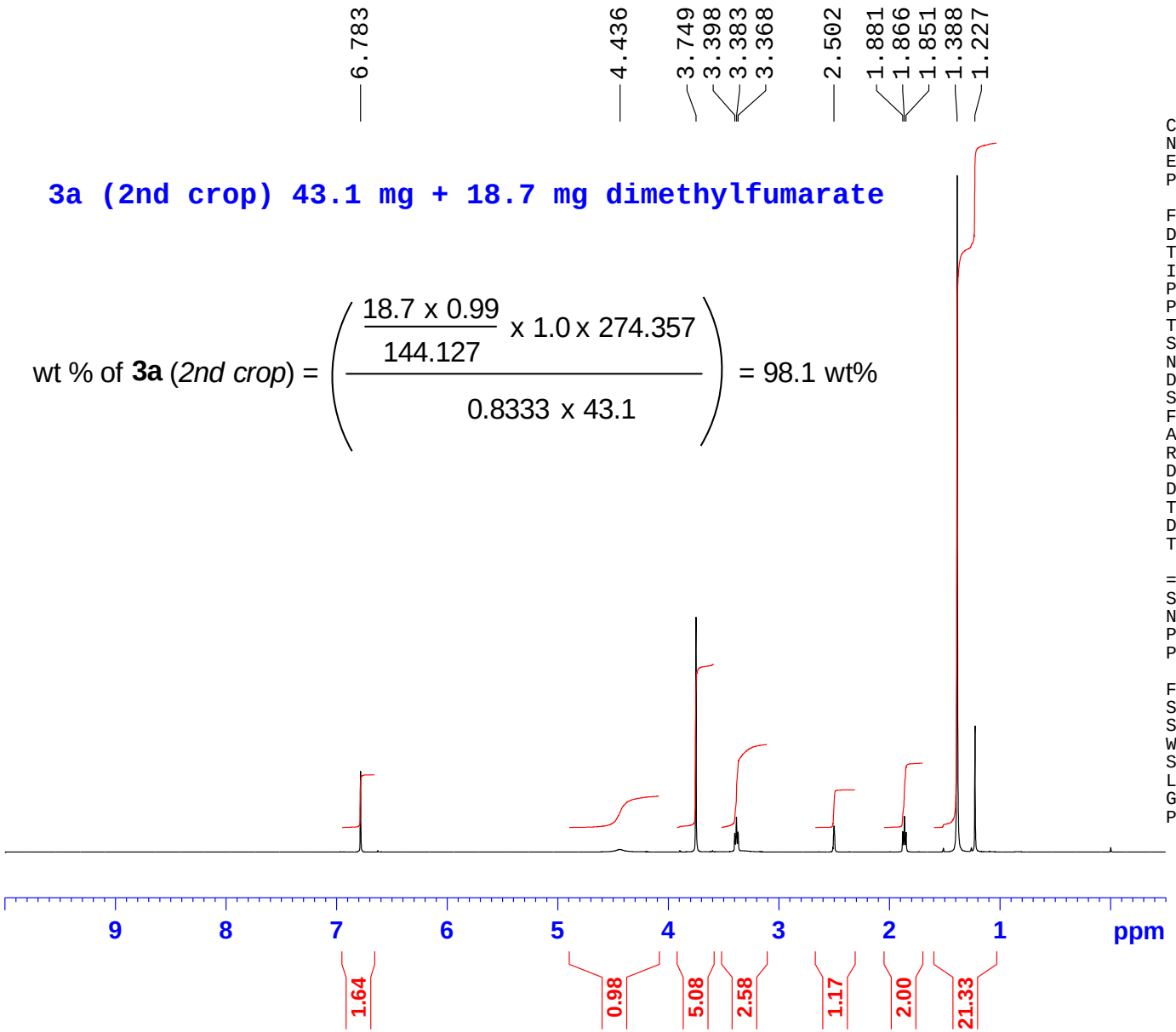



```
Current Data Parameters
NAME      103687-035-1st
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160204
Time               19.11
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG           q_zg10
TD                 32768
SOLVENT             DMSO
NS                   128
DS                     0
SWH             9014.423 Hz
FIDRES          0.275098 Hz
AQ             1.8175317 sec
RG                   228
DW                55.467 usec
DE                 6.50 usec
TE                299.0 K
D1           2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1334009 MHz
NUC1                1H
P1                11.75 usec
PLW1         18.39999962 W

F2 - Processing parameters
SI                 16384
SF           500.1300029 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

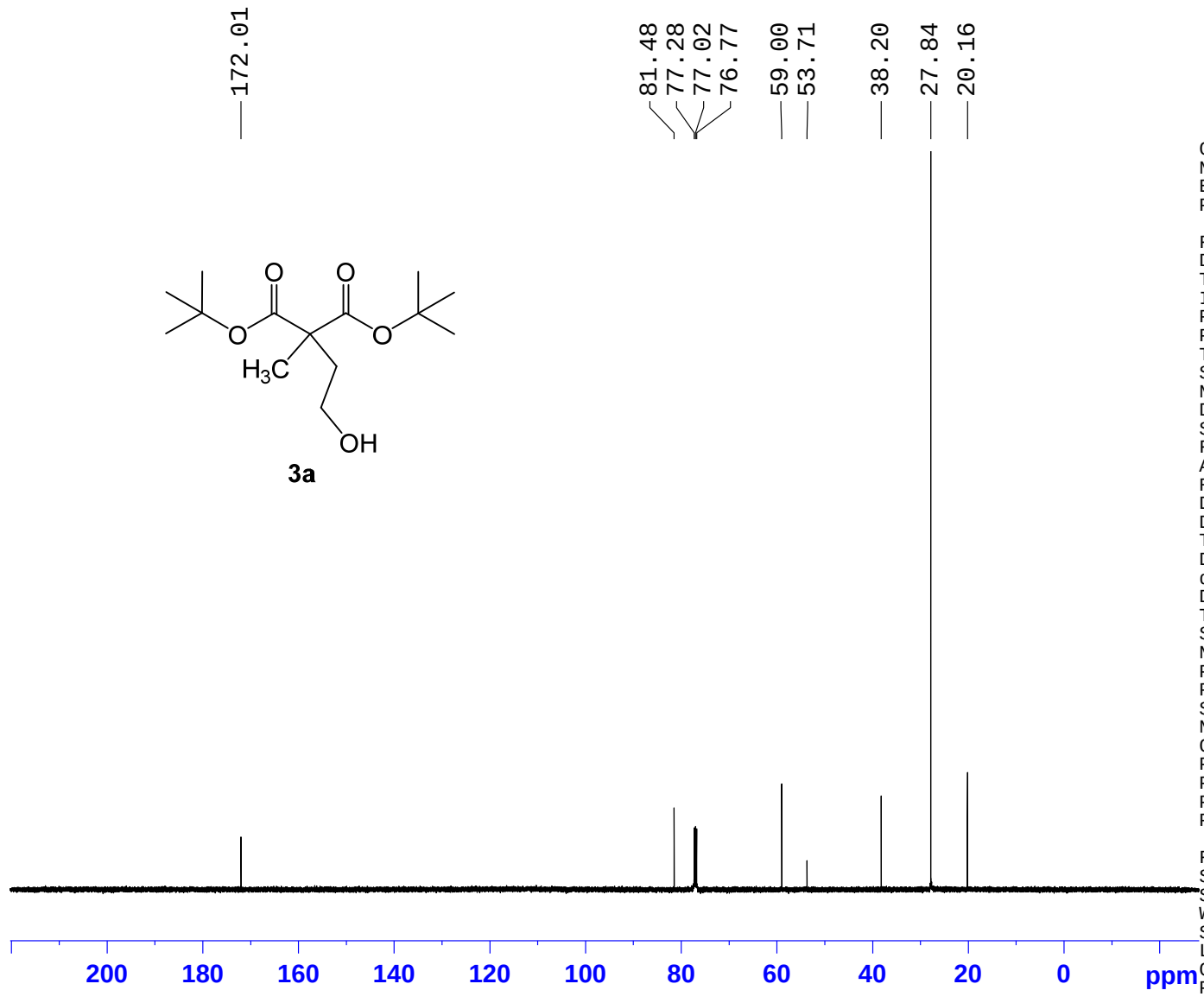



```
Current Data Parameters
NAME      103687-035-2nd
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160204
Time               19.23
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG          q_zg10
TD                32768
SOLVENT            DMSO
NS                   128
DS                     0
SWH             9014.423 Hz
FIDRES          0.275098 Hz
AQ             1.8175317 sec
RG                   203
DW                55.467 usec
DE                 6.50 usec
TE                299.0 K
D1            2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1334009 MHz
NUC1                   1H
P1                 11.75 usec
PLW1         18.39999962 W

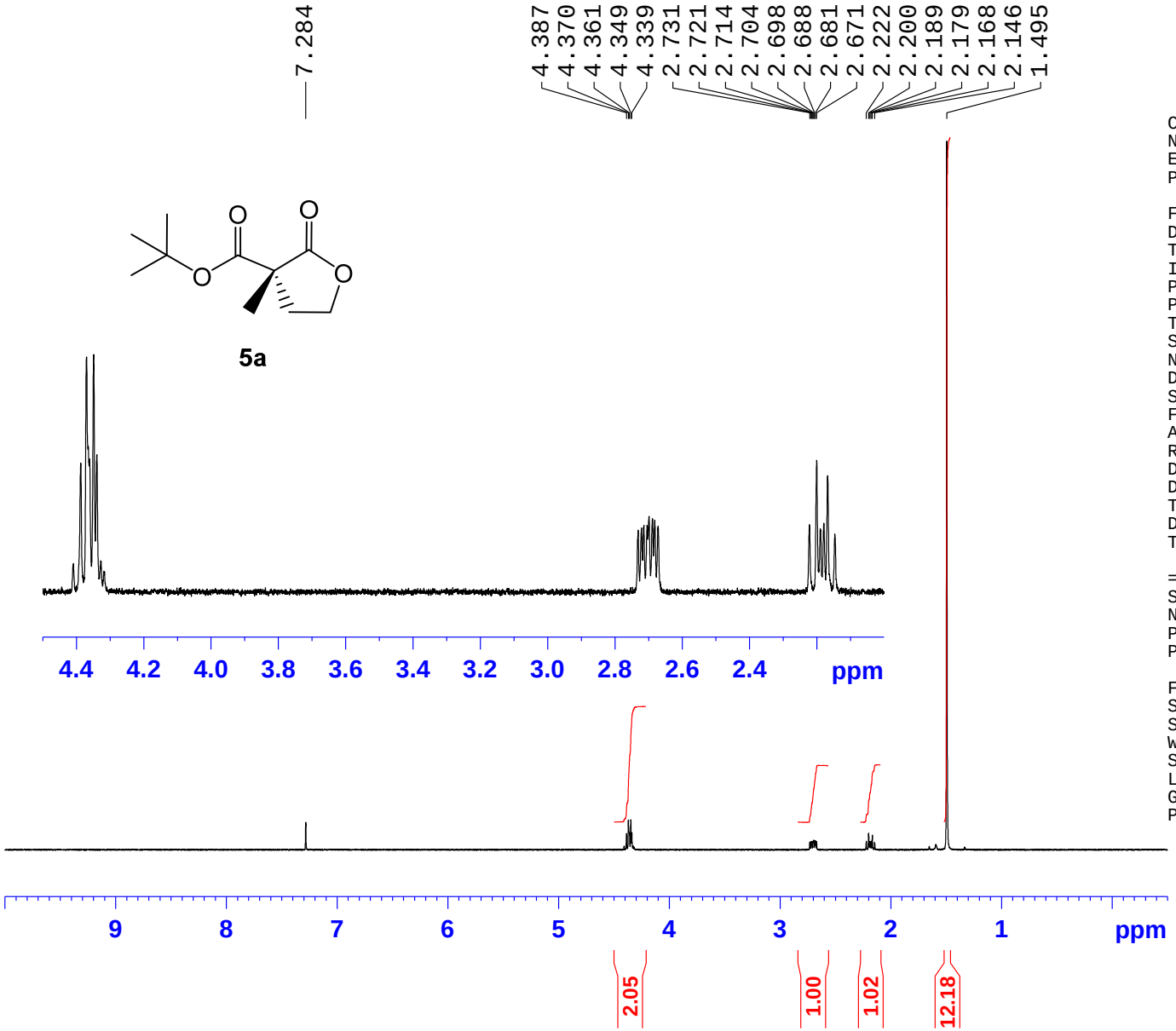
F2 - Processing parameters
SI                 16384
SF           500.1300030 MHz
WDW                   EM
SSB      0
LB                 0.30 Hz
GB       0
PC                 1.00
```




```
Current Data Parameters
NAME         103687-032b
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20151103
Time                9.20
INSTRUM            spect
PROBHD   5 mm PABBI 1H-
PULPROG             zgpg
TD                262144
SOLVENT            CDCl3
NS                   256
DS                     0
SWH            31250.000 Hz
FIDRES          0.119209 Hz
AQ              4.1943040 sec
RG                  2050
DW                16.000 usec
DE                 6.50 usec
TE                299.0 K
D1             1.00000000 sec
d11            0.03000000 sec
DELTA          0.89999998 sec
TD0                    1
SFO1          125.7698617 MHz
NUC1                 13C
P1                15.75 usec
PLW1          -1.00000000 W
SFO2          500.1325007 MHz
NUC2                 1H
CPDPRG[2         waltz16
PCPD2              80.00 usec
PLW2          -1.00000000 W
PLW12         -1.00000000 W
PLW13         -1.00000000 W

F2 - Processing parameters
SI                 131072
SF            125.7577890 MHz
WDW                    EM
SSB      0
LB                 0.30 Hz
GB       0
PC                 1.40
```



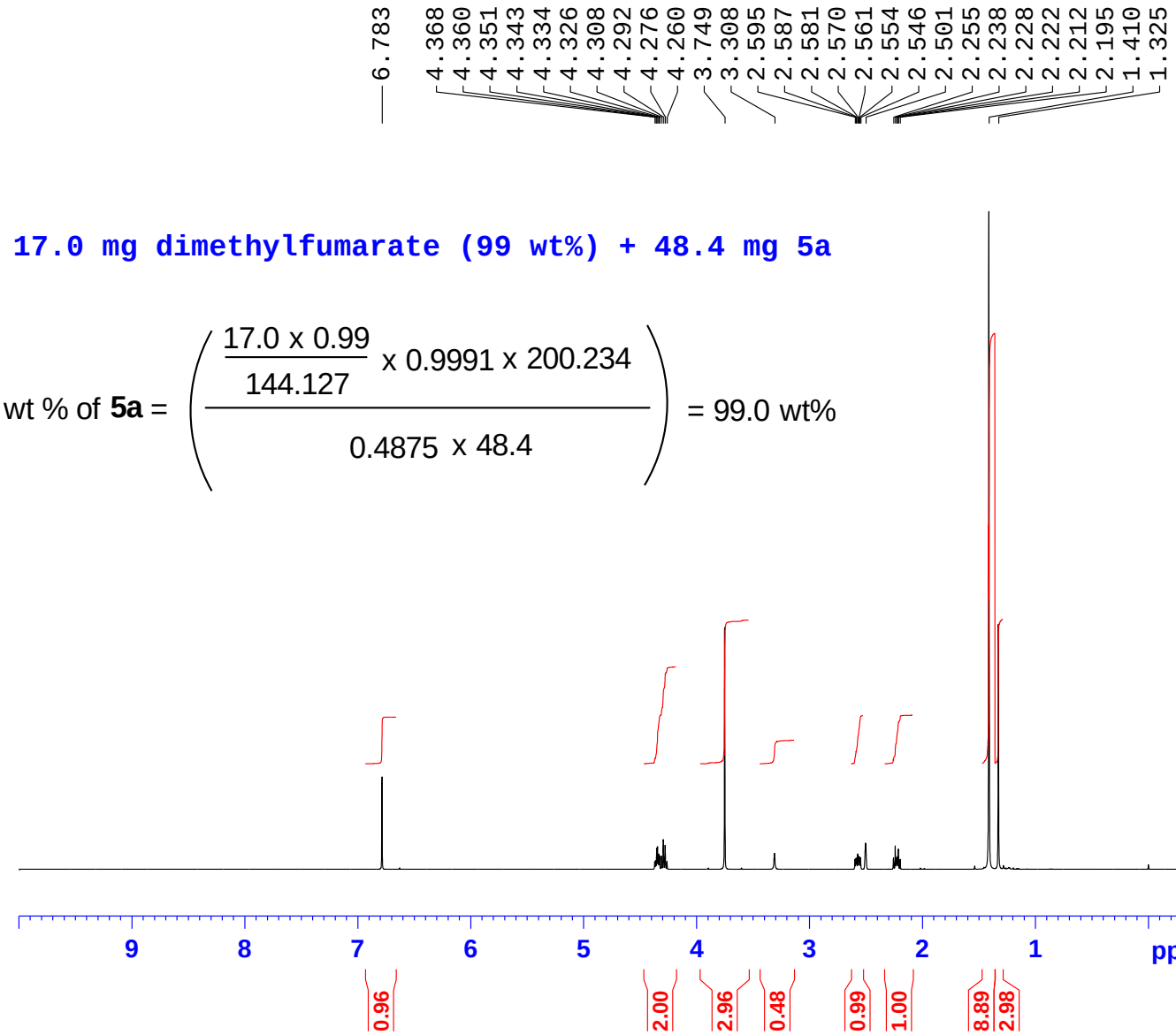

```
Current Data Parameters
NAME        103687-054p
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20151224
Time               9.21
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG            zg10
TD                32768
SOLVENT           CDCl3
NS                    4
DS                    4
SWH            5896.227 Hz
FIDRES         0.179939 Hz
AQ            2.7787263 sec
RG                  812
DW               84.800 usec
DE                6.50 usec
TE                298.0 K
D1           2.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        400.1327209 MHz
NUC1                1H
P1                15.00 usec
PLW1        10.50000000 W

F2 - Processing parameters
SI                65536
SF          400.1300000 MHz
WDW                 EM
SSB      0
LB                0.05 Hz
GB       0
PC                1.00
```

Quantitative 1H NMR assay of the product **5a** in DMSO-D6 using 99% of dimethylfumarate as internal standard

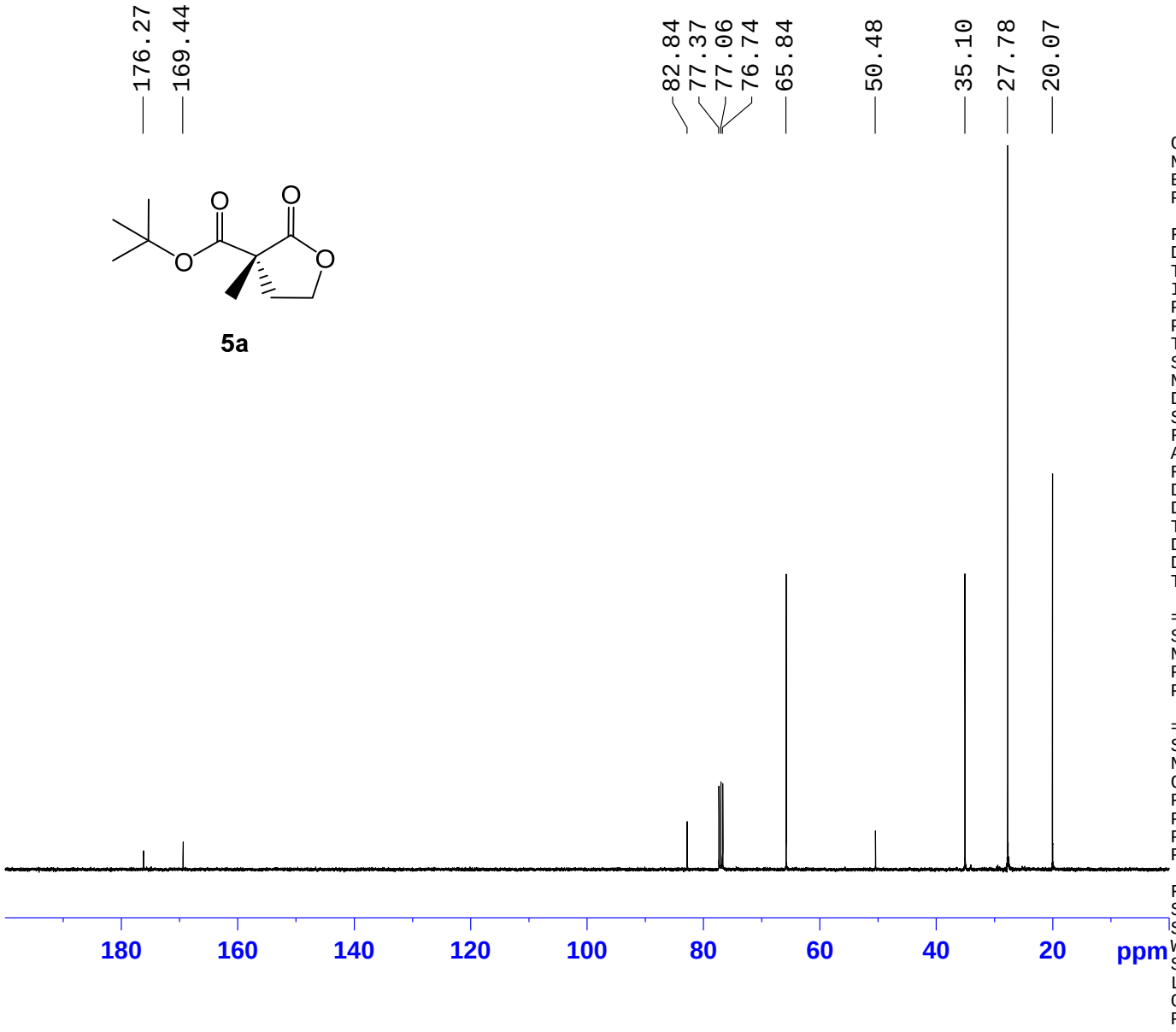



```
Current Data Parameters
NAME         103687-054
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20160204
Time              19.34
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG         q_zg10
TD                32768
SOLVENT            DMSO
NS                   128
DS                     0
SWH           9014.423 Hz
FIDRES        0.275098 Hz
AQ            1.8175317 sec
RG                   203
DW               55.467 usec
DE                6.50 usec
TE               299.0 K
D1            2.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        500.1334009 MHz
NUC1                1H
P1                11.75 usec
PLW1        18.39999962 W

F2 - Processing parameters
SI                16384
SF          500.1300034 MHz
WDW                  EM
SSB      0
LB                0.30 Hz
GB       0
PC                1.00
```




```
Current Data Parameters
NAME        103687-054b
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20151222
Time              17.13
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG            zgpg
TD                32768
SOLVENT           CDCl3
NS                  512
DS                    4
SWH           24038.461 Hz
FIDRES         0.733596 Hz
AQ            0.6815744 sec
RG                 2050
DW               20.800 usec
DE                6.50 usec
TE                298.0 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        100.6243395 MHz
NUC1                13C
P1                10.90 usec
PLW1        43.00000000 W

======== CHANNEL f2 ========
SFO2        400.1316005 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2        10.50000000 W
PLW12        0.29166999 W
PLW13        0.14670999 W

F2 - Processing parameters
SI                 65536
SF          100.6127690 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```