Organic Syntheses

Asymmetric Synthesis of All-Carbon Benzylic Quaternary Stereocenters via Conjugate Addition to Alkylidene Meldrum's Acids

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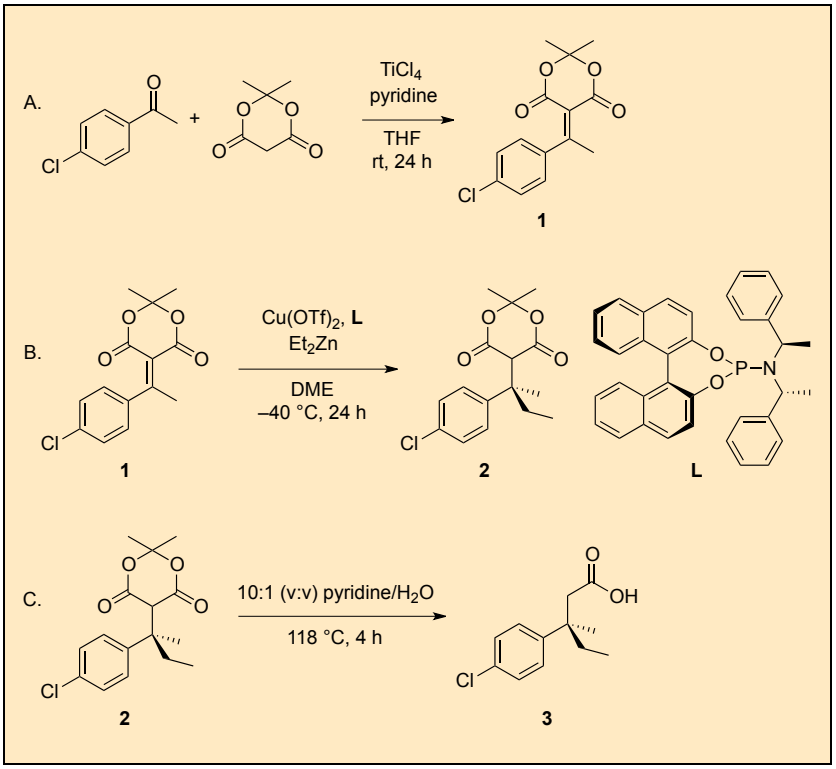
Checked by Li Zhang and Chris Senanayake



Org. Synth. **2015**, *92*, 182-194
DOI: 10.15227/orgsyn092.0182

Published on the Web 6/18/2015

Procedure

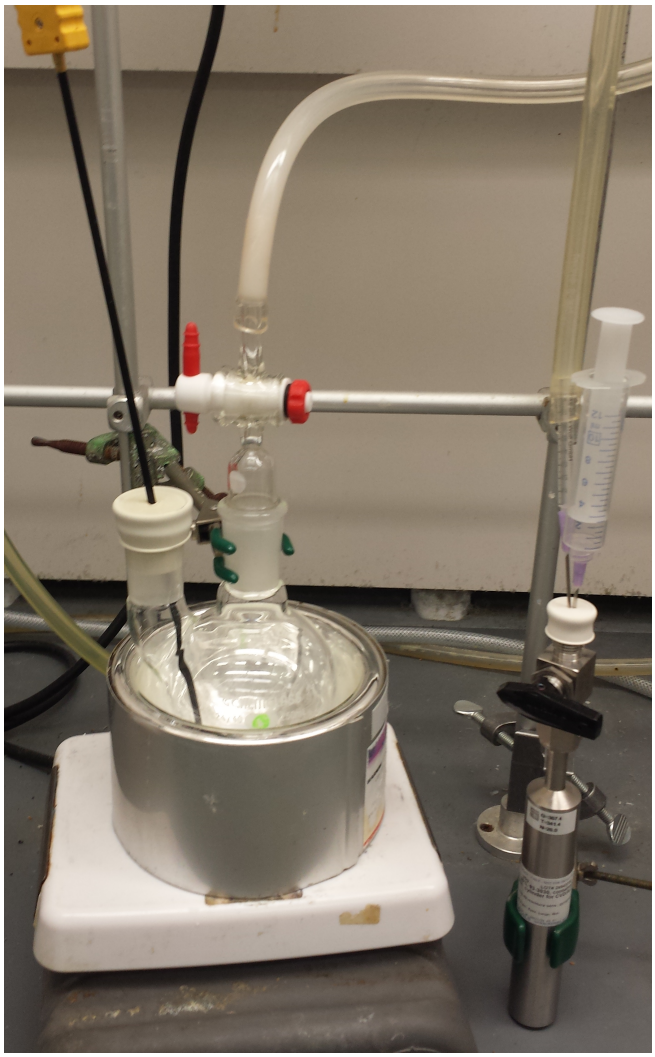
Caution! Neat diethylzinc is extremely pyrophoric and moisture sensitive. Handle under argon or nitrogen at all times. Fires should be extinguished using a dry powder extinguisher.

A. *5-(1-(4-Chlorophenyl)ethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione* (**1**).[2,3] An oven-dried 1000 mL, single-necked, round-bottomed flask, equipped with a 3 cm oval Teflon®-coated magnetic stirring bar and a rubber septum, is purged with nitrogen. The flask is charged with THF (300 mL) and cooled to 0 °C (bath temp) in an ice bath (Note 1). An oven-dried 100 mL, single-necked, round-bottomed flask equipped with a rubber septum is charged with dichloromethane (50 mL), and then titanium (IV) chloride (18.0 mL, 31.1 g, 164 mmol, 2.13 equiv) is added and the flask is swirled for 10 s (Notes 2 and 3). The $TiCl_4$ solution is added to the flask containing THF in four portions via a 20 mL Norm-ject plastic syringe at a rate of 4.3 mL/min with stirring (Note 4). During this addition smoke forms inside the reaction flask and the mixture becomes a cloudy yellow suspension. An oven-dried 250 mL, single-necked, round-bottomed flask is charged with 2,2-dimethyl-1,3-dioxane-4,6-dione (11.1 g, 77.0 mmol, 1.00 equiv) and THF (80 mL). The flask is sealed with a rubber septum and purged with nitrogen before 4′-chloroacetophenone (10.1 mL, 12.0 g, 77.8 mol, 1.01 equiv) is added via syringe. The flask is swirled until the solid has dissolved (<2 min) (Notes 5 and 6). The Meldrum's acid/4′-chloroacetophenone solution is added to the reaction flask containing $TiCl_4$ via cannula over a period of 10 min. During the addition, the mixture changes color from bright yellow to dark yellow/brown. The 250 mL flask is rinsed with 5 mL of THF, which is rapidly transferred to the reaction via cannula. Pyridine (31.5 mL, 30.7 g, 388 mmol, 5.04 equiv) is then added via a 20 mL syringe in 2 portions at a rate of 4.3 mL/min (Note 7). During this addition, a red color is observed initially and the mixture becomes a muddy brown suspension by the end of the addition. The vigorously stirred reaction is kept at 0 °C for 1 h and then allowed to stir at room temperature for 24 h. The mixture is cooled to 0 °C using an ice-water bath and 150 mL of deionized water is added. The stir bar is removed and the reaction is transferred to a 1000 mL separatory funnel with the assistance of 50 mL of deionized water and 50 mL of ethyl acetate. The layers are partitioned and the aqueous layer is extracted with

ethyl acetate (3 x 150 mL). The combined organic layers are dried over $MgSO_4$ (14 g, <2 min), filtered through a 7 cm diameter filter funnel packed with cotton into a 2 L round-bottomed flask, and concentrated by rotary evaporation (30 °C, 20 mmHg). The resulting dark yellow oil is dissolved in ethyl acetate (200 mL), which is washed sequentially with saturated $NaHCO_3$, (2 x 100 mL) and brine (150 mL) and then dried over $MgSO_4$ (6 g, <2 min) (Note 8). The mixture is filtered through a 7 cm diameter filter funnel packed with cotton and concentrated by rotary evaporation (30 °C, 20 mmHg) to obtain a bright yellow solid (Note 9). The solid is dissolved in ethyl acetate (50 mL) and transferred, with rinsing, to a 250 mL, single-necked round-bottomed flask. The solvent is removed by rotary evaporation (30 °C, 20 mmHg) (Note 9). Methanol (60 mL) and a 1 cm rod-shaped magnetic stirring bar are added and the mixture is placed in an oil bath heated to 50 °C with stirring until the solid dissolves (20 min) (Note 10). The flask is removed from the oil bath and swirled gently to dissolve any solid on the walls of the flask, and then the solution is allowed to cool to room temperature (1 h) before being placed in an ice-water bath for 1 h. The solid is collected by suction filtration (room temperature, ~20 mmHg) through a Büchner funnel equipped with a filter paper and is washed with 30 mL of methanol that has been cooled to –25 °C. The nearly colorless needles are pulverized using a mortar and pestle before being dried under reduced pressure (1 mmHg, 1 h, room temperature) to afford 13.2–13.8 g (61–64%) of 5-(1-(4-chlorophenyl)ethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione [**1**] as an off-white powder (Notes 11, 12, 13, and 14).

B. *(R)-5-(2-(4-Chlorophenyl)butan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione* (**2**).[3] An oven-dried 250 mL, two-necked round-bottomed flask equipped with a 2 cm rod-shaped Teflon®-coated magnetic stirring bar and a thermocouple is charged with copper (II) trifluoromethanesulfonate (322 mg, 0.890 mmol, 2.5 mol %) then connected to a vacuum line and placed under reduced pressure (0.5 mmHg) before being placed in an oil bath heated to 100 °C (Note 15). The flask is held at this temperature for 3 h before the flask is removed from the oil bath and allowed to cool to room temperature (30 min) while still under reduced pressure. The flask is opened to air and (*S*)-2,2´-binaphthoyl-(*R*,*R*)-di(1-phenylethyl)aminoyl-phosphine[4] (961 mg, 1.78 mmol, 5.0 mol%) is quickly added before the flask is sealed with a rubber septum and purged with argon (Note 16). 1,2-Dimethoxyethane (45 mL) is then added via syringe and the mixture is stirred at room temperature for 30 min before being placed in an isopropanol bath maintained at -40 °C using an immersion cooler

(Notes 17 and 18). Diethylzinc (7.3 mL, 8.8 g, 71 mmol, 2.0 equiv) is added via a 10 mL gas-tight syringe under argon over 10 min and the reaction is allowed to stir for 15 min (Note 19). An oven-dried 100 mL, single-necked



Set-up for Step B

round-bottomed flask equipped with a rubber septum is purged with argon and charged with 5-(1-(4-chlorophenyl)ethylidene)-2,2-dimethyl-1,3-

dioxane-4,6-dione (**1**) (10.0 g, 35.6 mmol, 1.00 equiv) and 1,2-dimethoxyethane (35 mL). The flask is swirled to dissolve the solid (1 min) before being transferred to the reaction by cannula over a period of 10 min. 1,2-Dimethoxyethane (5 mL) is used to rinse the 100 mL flask, which is transferred to the reaction by cannula in 30 s and the reaction is allowed to stir for 24 h. While still at –40 °C, hydrochloric acid (100 mL, 2 M) is added to the reaction over 2 min (Note 20). Then ethyl acetate (50 mL) is added. The cooling bath is removed and the reaction is allowed to stir for 10 min in a room temperature water bath. The mixture is transferred to a 500 mL separatory funnel with the assistance of deionized water (50 mL) and ethyl acetate (50 mL). The layers are partitioned and the aqueous layer is extracted with ethyl acetate (3 x 50 mL). The combined organic layers are washed once with 100 mL of brine and dried over $MgSO_4$ (6 g, <2 min), filtered through a 7 cm diameter filter funnel packed with cotton and concentrated by rotary evaporation (35 °C, 20 mmHg). The resulting white solid is mixed with dichloromethane (30 mL) to form a suspension, then subjected to flash chromatography (350 g silica, 60 cm x 5 cm inner diameter, 200 mL fractions) using 6 L of 9:1 hexanes/ethyl acetate as the eluent (Notes 21 and 22). The product is found in fractions 11-24, which are concentrated by rotary evaporation (35 °C, 20 mmHg) followed by removal of residual ethyl acetate under reduced pressure (23 °C, 5 mmHg, 30 min) to obtain 8.8–8.9 g (79–80% yield, 97:3–98:2 er) of (*R*)-5-(2-(4-chlorophenyl)butan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione as a white solid (Notes 23, 24, and 25).

C. *(R)-3-(4-Chlorophenyl)-3-methylpentanoic acid* (**3**).[3] A 100 mL, single-necked round-bottomed flask equipped with a 1 cm oval Teflon®-coated magnetic stirring bar and a reflux condenser is charged with (*R*)-5-(2-(4-chlorophenyl)butan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (8.00 g, 25.7 mmol, 1.00 equiv), pyridine (47.0 mL, 45.8 g, 579 mmol, 22.5 equiv) and deionized water (4.7 mL, 4.7 g, 0.26 mol, 10 equiv) then the condenser is equipped with a rubber septum and the apparatus is purged with nitrogen (Note 7). The apparatus is placed in an oil bath preheated to 118 °C and the brownish yellow solution is allowed to stir for 4 h under nitrogen. The reaction is removed from the oil bath and allowed to cool for 10 min before being concentrated by rotary evaporation (50 °C, 20 mmHg) to obtain a brownish yellow oil. The residue is cooled to 0 °C in an ice-water bath before being treated with 3M hydrochloric acid (40 mL) and allowed to stir for 5 min (Note 20). The resulting biphasic solution is diluted with methyl *t*-butyl ether (40 mL) and transferred to a 125 mL separatory funnel. The

layers are partitioned and the aqueous layer is extracted with methyl *t*-butyl ether (3 x 40 mL). The combined organic layers are dried over $MgSO_4$ (6 g, <2 min) and filtered through a 4 cm diameter filter funnel packed with cotton before being concentrated by rotary evaporation (25 °C, 20 mmHg). The resulting oil is subjected to flash chromatography (100 g silica, 60 cm x 5 cm inner diameter, 200 mL fractions) using 2 L of hexanes:ethyl acetate (7:1) as the eluent (Note 22). The product is collected from fractions 6-15, which are concentrated by rotary evaporation (35 °C, 20 mmHg) followed by removal of residual ethyl acetate under reduced pressure (23 °C, 5 mmHg, 30 min) to obtain 5.5–5.7 g (94–98%) of (*R*)-3-(4-chlorophenyl)-3-methylpentanoic acid [**3**] as a pale yellow oil (Notes 26, 27 and 28).

Notes

1. ACS Reagent tetrahydrofuran (99.0%, contains 250 ppm BHT) was obtained from Sigma-Aldrich Company and distilled from sodium-benzophenone ketyl immediately prior to use.
2. Titanium (IV) chloride, ReagentPlus®, 99.9%, was obtained from Sigma-Aldrich Company and used without further purification.
3. Dichloromethane (99.9%, HPLC grade, contains 15-200 ppm amylene) was dried by percolation through two columns packed with neutral alumina under a positive pressure of nitrogen.
4. In some cases the $TiCl_4$ solution causes corrosion of the plastic syringe during one of the additions. If this occurs, the current addition is allowed to complete and a new syringe is used for the remaining additions.
5. 4′-Chloroacetophenone, 98%, was obtained from Oakwood Products, Inc. and used without further purification.
6. 2,2-Dimethyl-1,3-dioxane-4,6-dione, 99%, was obtained from Oakwood Products, Inc. and used without further purification.
7. Pyridine, 99%, was obtained from Caledon Laboratories Ltd. and used without further purification. In step C, an excess of pyridine is used because it is the solvent for the reaction.
8. A large amount of CO_2 gas evolves when the $NaHCO_3$ is added.
9. If the resulting residue is an oil, methanol (10 mL) is added and the flask is swirled for <2 min to precipitate the solid.

10. Methanol (99.8%, HPLC grade) was obtained from Caledon Laboratories Ltd. and used without further purification.
11. Whatman® 70 mm filter papers are used.
12. 5-(1-(4-Chlorophenyl)ethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione is stable in excess of six months when stored in the freezer.
13. The product displayed the following physiochemical properties: mp 72–74 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.83 (s, 6 H), 2.70 (s, 3 H), 7.12 (d, J = 8.5 Hz, 2 H), 7.38 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 26.3, 27.4, 104.0, 117.2, 127.4, 128.8, 135.6, 140.0, 160.2, 161.0, 171.7; IR (thin film, CH_2Cl_2) ν_{max} (cm^{-1}) 1765, 1726; HRMS (DART) m/z calcd. for $C_{14}H_{13}{}^{35}ClO_4 \bullet Na^+$: 303.0400, found: 303.0386. The purity of product (97–99%) is determined by quantitative HPLC (Halo-C18 0.46 cm × 15 cm column) using acetonitrile (A) and water (B, contains 0.2% H_3PO_4 and 60 mM NH_4PF_6) as eluent (1.3 mL/min, percentage of A starts from 35%, changes to 45% in 4 min, increases to 98% in another 3 min and keeps at 98% for another 2 min). t_R = 7.00 min. Purity of the quantification standard is determined by NMR assay using dimethyl fumarate as internal standard.
14. Sometimes it is possible to obtain a second crop from the filtrate. The filtrate is transferred to a 100 mL single-necked round-bottomed flask and concentrated by rotary evaporation (30 °C, 20 mmHg). Methanol (5 mL) is added to the resulting dark orange oil and the flask is swirled for 1 min to form a uniform solution. The flask is placed in a –25 °C freezer for 18 h. The solid is collected by suction filtration (room temperature, ~20 mmHg) through a Büchner funnel equipped with a filter paper and are washed with 10 mL of methanol at –25 °C to obtain an additional 0.98 g (5%) of **1** as a pale yellow solid contaminated with traces of Meldrum's acid and 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione.
15. Copper (II) trifluoromethanesulfonate, 98%, was purchased from Strem Chemicals, Inc. and used without further purification. It was stored in a desiccator containing Drierite® under nitrogen.
16. (*S*)-2,2′-Binaphthoyl-(*R*,*R*)-di(1-phenylethyl)aminoyl-phosphine was prepared following literature procedure.[4]
17. 1,2-Dimethoxyethane (99.0%) was obtained from TCI America, Inc., purified by distillation from sodium-benzophenone ketyl, and degassed using the freeze-pump-thaw method (3 cycles).
18. A Kinetics Flexi-Cool 100 immersion cooler was used.

19. Diethylzinc, 95%, was purchased from Strem Chemicals, Inc. and used without further purification.
20. Hydrochloric acid, 37%, was obtained from Sigma-Aldrich Co. and used as received. The 2 M solution was prepared by diluting 82 mL of concentrate in deionized water to a 500 mL solution. The 3 M solution was prepared by diluting 10 mL of concentrate in 30 mL of deionized water.
21. The crude white solid starts to turn yellow if allowed to stand overnight.
22. SiliaFlash® F60 (40-63 μm, 230-400 mesh) silica gel was used.
23. Occasionally, fractions 8-10 contained some product that was contaminated with an unknown compound that is UV active (R_f = 0.28 in 9:1 hexanes/ethyl acetate). These fractions can be purified via flash chromatography as follows. After concentration by rotary evaporation (35 °C, ~20 mmHg), the mixed fractions were dissolved in dichloromethane (3 mL) and loaded onto a 40 cm x 3 cm inner diameter column containing 60 g of silica gel. The product was eluted with 750 mL of hexanes/ethyl acetate (9:1) and collected in 30 mL fractions. Fractions 11-24 were concentrated using rotary evaporation (35 °C, ~20 mmHg) before drying under reduced pressure (23 °C, 0.5 mmHg, 0.5 h) to obtain 0.5–1.0 g of **2** (5–9% yield).
24. (*R*)-5-(2-(4-Chlorophenyl)butan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione is stable in excess of six months when stored in the freezer.
25. The product displayed the following physiochemical properties: mp 89–92 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.73 (t, *J* = 7.6 Hz, 3 H), 1.36 (s, 3 H), 1.60 (s, 3 H), 1.65 (s, 3 H), 2.11 (q, *J* = 7.5 Hz, 2 H), 3.62 (s, 1 H), 7.22–7.24 (m, 2 H), 7.29-7.32 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 8.6, 21.4, 27.5, 29.0, 32.7, 45.7, 57.0, 105.1, 128.3, 128.4, 128.7, 132.8, 141.3, 163.8, 164.3; IR (thin film, CH_2Cl_2) ν_{max} (cm^{-1}) 2982, 1742; HRMS (DART) *m*/*z* calcd. for $C_{16}H_{20}{}^{35}ClO_4{}^+$: 311.1050, found: 311.1038. $[\alpha]^{20}_D$ = +16.1 (*c* 0.57, MeOH) (er 97 (*R*) : 3 (*S*)). Enantiomeric ratio (er) (97:3–98:2 (*R*:*S*)) determined by HPLC (Chiralcel OD-H 0.46 cm × 25 cm column) using 1% 2-propanol and 0.1% trifluoroacetic acid in hexanes as eluent (1 mL/min, prepared by diluting 2-propanol (5 mL) and trifluoroacetic acid (0.5 mL) with hexanes to make a 500 mL solution). t_{R1} = 11.1 min, t_{R2} = 14.3 min. The purity of product (97–99%) is determined by quantitative HPLC (Halo-C18 0.46 cm × 15 cm column) using acetonitrile (A) and water (B, contains 0.2% H_3PO_4 and 60 mM NH_4PF_6) as eluent (1.3 mL/min, percentage of A starts from 35%, changes to 45%

in 4 min, increases to 98% in another 3 min and keeps at 98% for another 2 min). t_R = 7.94 min. Purity of the quantification standard is determined by NMR assay using dimethyl fumarate as internal standard.

26. The submitters report that under vacuum the pale yellow oil slowly (>24 h) crystallizes to a white solid (mp = 39-41 °C); however, the checkers did not observe crystallization.
27. (*R*)-3-(4-Chlorophenyl)-3-methylpentanoic acid is stable in excess of six months when stored in the freezer.
28. The product displayed the following physiochemical properties: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.66 (t, *J* = 7.6 Hz, 3 H), 1.45 (s, 3 H), 1.64–1.73 (m, 1 H), 1.75–1.83 (m, 1 H), 2.55 (d, *J* = 14.4 Hz, 1 H), 2.69 (d, *J* = 14.4 Hz, 1 H), 7.21 (d, *J* = 8.8 Hz, 2 H), 7.26 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.5, 23.8, 35.4, 40.2, 46.3, 127.6, 128.2, 131.7, 144.5, 176.5; IR (thin film, neat) ν_{max} (cm^{-1}) 2968 (br), 1701; HRMS (DART) *m*/*z* calcd. for $C_{12}H_{15}{}^{35}ClO_2 \bullet Na^+$: 249.0658, found: 249.0649. $[\alpha]^{20}_D$ = –11.8 (*c* 0.67, MeOH) (er 97 (*R*):3 (*S*)). Enantiomeric ratio (er) (97:3–98:2 (*R*:*S*)) determined by HPLC (Chiralcel AD-H 0.46 cm × 25 cm column) using 1% 2-propanol and 0.1% trifluoroacetic acid in hexanes as eluent (1 mL/min, prepared by diluting 2-propanol (5 mL) and trifluoroacetic acid (0.5 mL) with hexanes to make a 500 mL solution). t_{R1} = 28.8 min, t_{R2} = 30.2 min. The purity of product (96–98%) is determined by quantitative HPLC (Halo-C18 0.46cm × 15 cm column) using acetonitrile (A) and water (B, contains 0.2% H_3PO_4 and 60 mM NH_4PF_6) as eluent (1.3 mL/min, percentage of A starts from 35%, changes to 45% in 4 min, increases to 98% in another 3 min and keeps at 98% for another 2 min). t_R = 7.01 min. Purity of the quantification standard is determined by NMR assay using dimethyl fumarate as internal standard.

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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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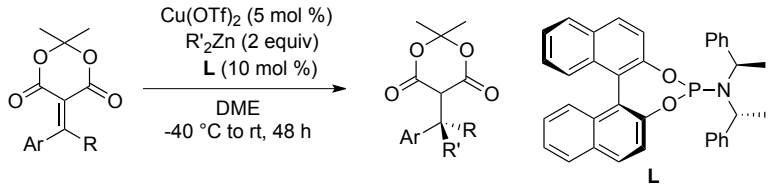
Discussion

The catalytic asymmetric formation of all carbon benzylic quaternary centres is an important goal in organic chemistry as these moieties are ubiquitous in natural products and pharmaceuticals. Conjugate addition of organometallic reagents to tri- and tetrasubstituted alkenes activated by carbonyl, nitro or sulfone groups is an efficient method that can be used to synthesize these motifs. The conjugate addition of dialkylzinc reagents to 5-ylidene Meldrum's acid derivatives presented herein is a flexible and convenient method to perform this transformation because the substrates are readily prepared by Knoevenagel condensation[2] of various commercially available aryl ketones and the conjugate addition products may undergo a wide variety of transformations. In addition, the substrate scope is broad as the reaction tolerates numerous functional groups.[3,5-8]

Table 1. Asymmetric Conjugate Addition Reactions to Alkylidene Meldrum's Acids[3,7]



entry	Ar	R	R′	yield (%)	er (*R*:*S*)
1	C_6H_5	Me	Et	95	92:8
2	2-naphthyl	Me	Et	66	97.5:2.5
3	2-furyl	Me	Et	97	95.5:4.5
4	4-MeC_6H_4	Me	Et	82	94.5:5.5
5	4-PhC_6H_4	Me	Et	76	97.5:2.5
6	4-ClC_6H_4	Me	Et	88	97.5:2.5
7	4-BrC_6H_4	Me	Et	84	96:4
8	4-FC_6H_4	Me	Et	83	96:4
9	4-(F_3C)C_6H_4	Me	Et	87	96:4
10	4-(BnO)C_6H_4	Me	Et	75	96.5:3.5
11	3-MeC_6H_4	Me	Et	93	89:11
12	3-ClC_6H_4	Me	Et	96	87:13
13	3-(BnO)C_6H_4	Me	Et	97	89.5:10.5
14	3,4-$Cl_2C_6H_3$	Me	Et	98	92.5:7.5
15	2-MeC_6H_4	Me	Et	NR	N/A
16	2-ClC_6H_4	Me	Et	NR	N/A
17	2-(BnO)C_6H_4	Me	Et	NR	N/A
18	4-ClC_6H_4	*n*-Bu	Et	78	97:3
19	C_6H_5	*i*-Pr	Et	NR	N/A
20	4-ClC_6H_4	Et	Me	N/A	N/A
21	4-ClC_6H_4	Me	*n*-Bu	87	93.5:6.5

As shown in Table 1, asymmetric conjugate addition reactions of 5-(1-arylalk-1-ylidene) Meldrum's acid derivatives occur in good to excellent yield and excellent enantiomeric excess for 3- and 4-substituted aryl groups, although no reaction is obtained for 2-substituted aryl groups due to steric reasons.[3,7] The reaction is successful when R is a primary alkyl group but no addition occurs for secondary alkyl groups; however, both primary and secondary alkyls are tolerated as the nucleophile, although poor results

have been obtained for dimethylzinc under these conditions (it has been shown that dimethylzinc adds effectively under modified conditions).[6]

References

1. Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada, N2L 3G1, efillion@uwaterloo.ca. This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC) and the University of Waterloo. E. B. thanks NSERC for USRA scholarship (2012) and CGS-M scholarship (2014) and the Government of Ontario for OGS scholarship (2013).
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Appendix
Chemical Abstracts Nomenclature (Registry Number)

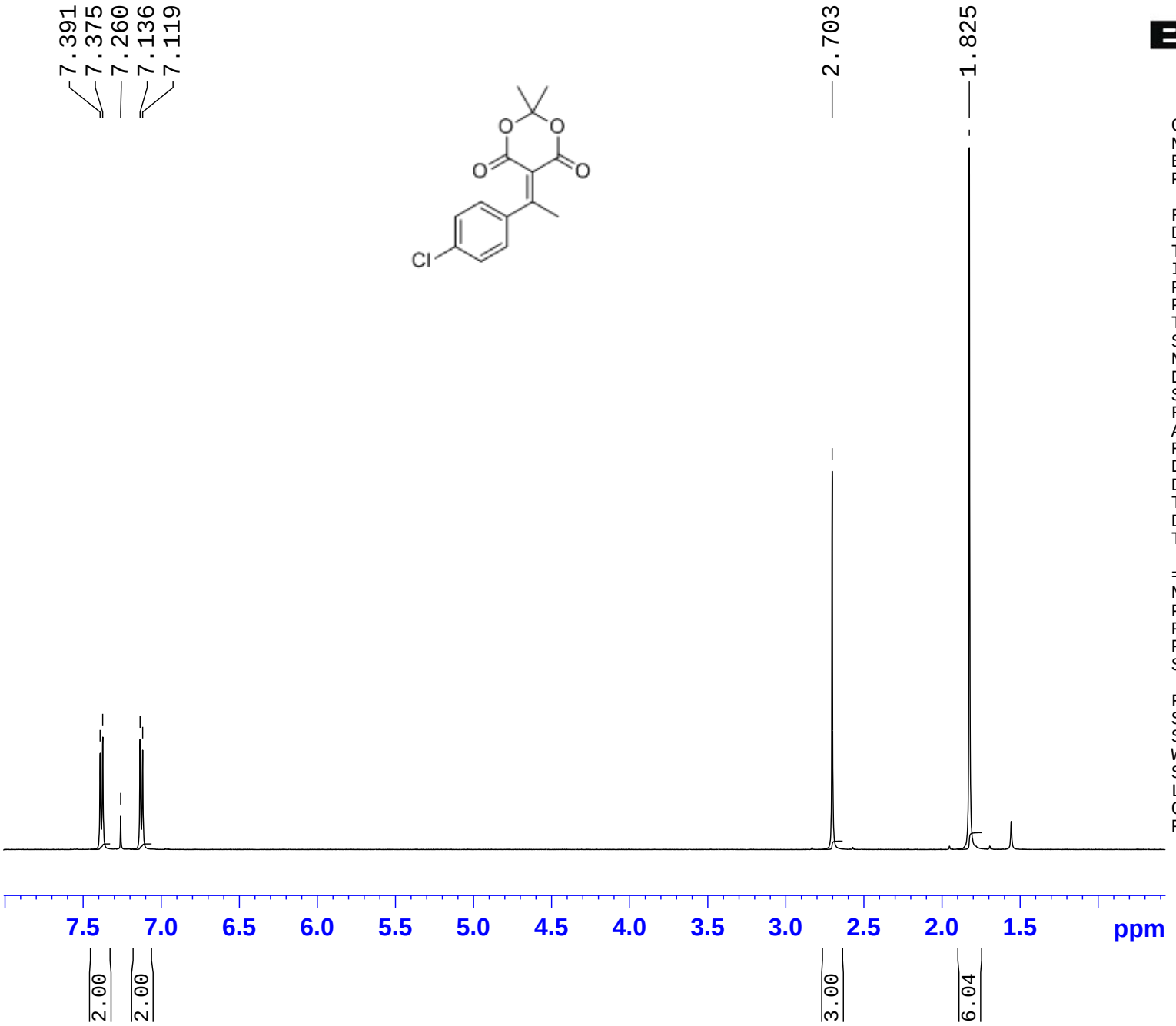
1-(4-Chlorophenyl)ethanone: 4′-chloroacetophenone; (99-91-2)
2,2-Dimethyl-1,3-dioxane-4,6-dione: Meldrum's acid; (2033-24-1)
Titanium (IV) chloride; (7550-45-0)
Pyridine; (110-86-1)
5-(1-(4-Chlorophenyl)ethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione; (882161-49-1)
Copper (II) trifluoromethanesulfonate; (34946-82-2)
Diethylzinc; (557-20-0)
(*S*)-2,2´-Binapthoyl-(*R*,*R*)-di(1-phenylethyl)aminoyl-phosphine; (712352-08-4)
1,2-dimethoxyethane; (110-71-4)
(*R*)-5-(2-(4-Chlorophenyl)butan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione; (882161-62-8)
(*R*)-3-(4-Chlorophenyl)-3-methylpentanoic acid; (number not yet assigned)

Eric Beaton was born in 1988 in Kitchener, ON, Canada. He graduated with a B.Sc. in Chemical Physics in 2012 from the University of Waterloo where his honors thesis was done under the supervision of Professor Eric Fillion. In 2013, he started his M. Sc. studies under the direction of Eric Fillion where he is studying Lewis acid-promoted substitution reactions of benzyl Meldrum's acid derivatives.

Eric Fillion received his undergraduate degree in biochemistry at the Université de Sherbrooke. After completing his M. Sc. in medicinal chemistry at the Université de Montreal with Professor Denis Gravel, he began his doctoral studies at the University of Toronto under the direction of Professor Mark Lautens. From 1998-2000, he was an NSERC post-doctoral fellow in the laboratories of Professor Larry E. Overman at the University of California, Irvine. In August 2000, he joined the Department of Chemistry at the University of Waterloo, where he is currently a Professor of Chemistry.

Li Zhang received his undergraduate degree in chemistry at the Nanjing University in 1994. After completing his M. Sc. in organic chemistry at the Iowa State University with Professor Richard C. Larock in 1999, he joined Chemical Development at Boehringer Ingelheim Pharmaceuticals, Inc., where he is currently a senior scientist. He is the co-author of more than 30 papers and patents in synthetic organic chemistry and pharmaceutical industry.

103415-099



Current Data Parameters
NAME 103415-099
EXPNO 1
PROCNO 1

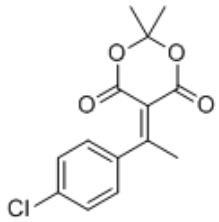
F2 - Acquisition Parameters
Date_ 20141204
Time 11.47
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg10
TD 32768
SOLVENT CDCl3
NS 16
DS 0
SWH 7500.000 Hz
FIDRES 0.228882 Hz
AQ 2.1845334 sec
RG 362
DW 66.667 usec
DE 6.50 usec
TE 299.0 K
D1 1.00000000 sec
TD0 1

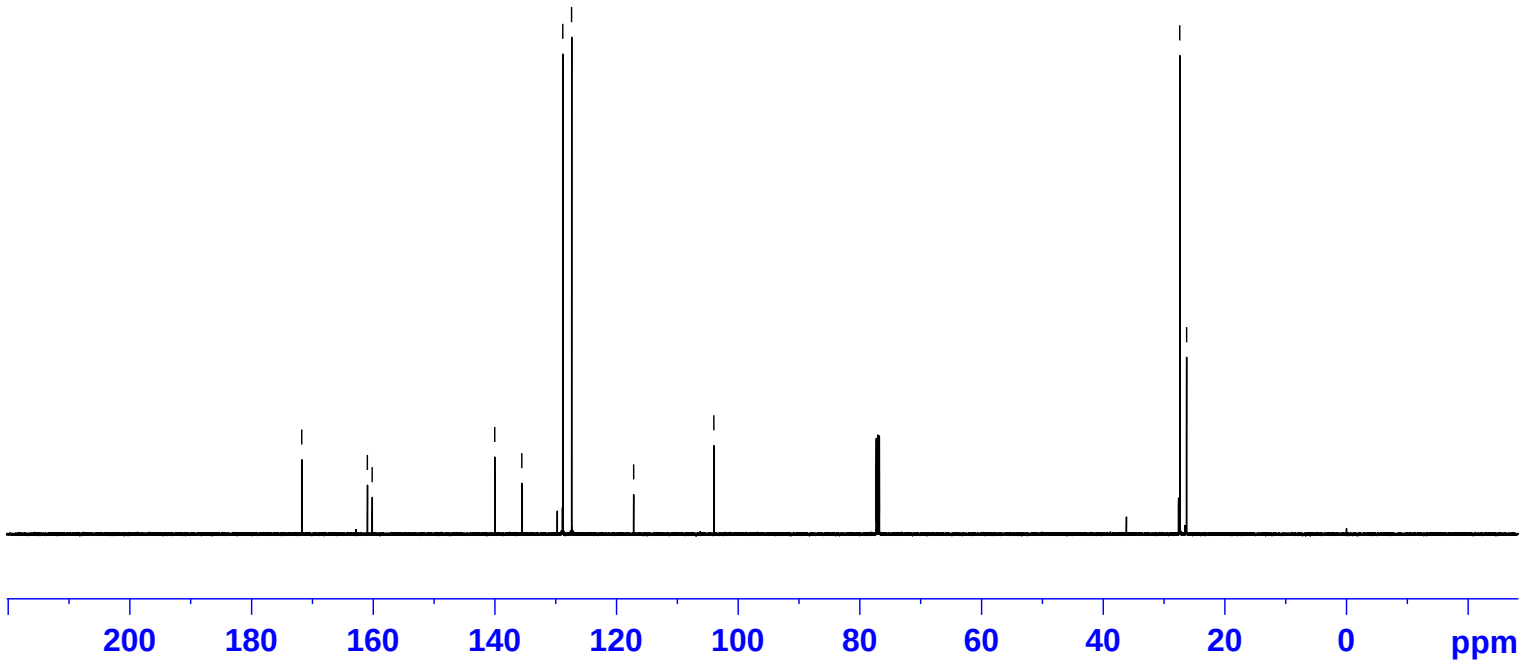
======== CHANNEL f1 ========
NUC1 1H
P1 11.95 usec
PL1 2.10 dB
PL1W 18.43091774 W
SFO1 500.1325007 MHz

F2 - Processing parameters
SI 16384
SF 500.1300130 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

103415-099

171.740
160.959
160.173
140.032
135.576
128.847
127.383
117.196
104.010
27.413
26.295



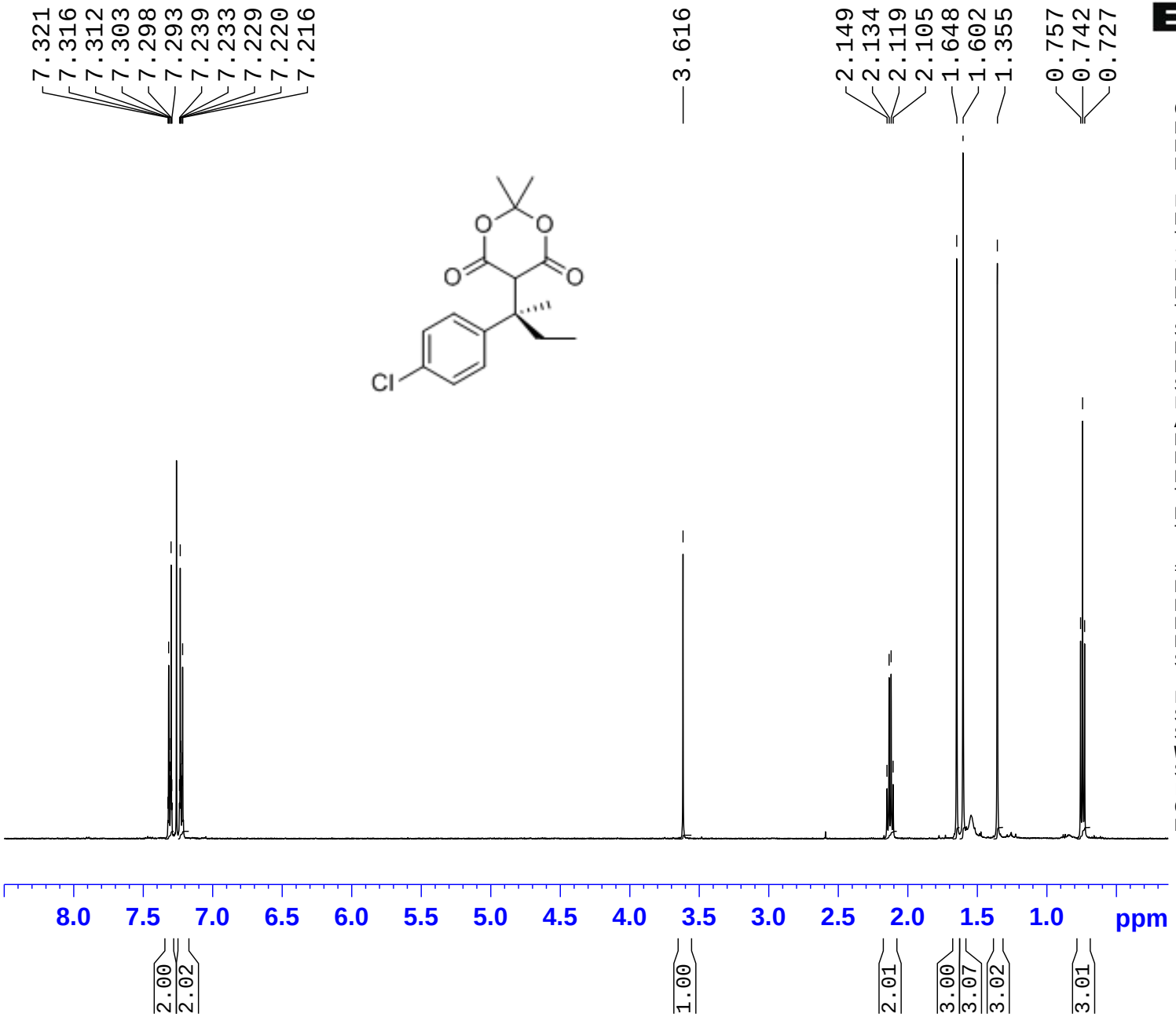


Current Data Parameters
NAME 103415-099
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20150219
Time 10.32
INSTRUM spect
PROBHD 5 mm PABBO BB-
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 9.75 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

103485-014



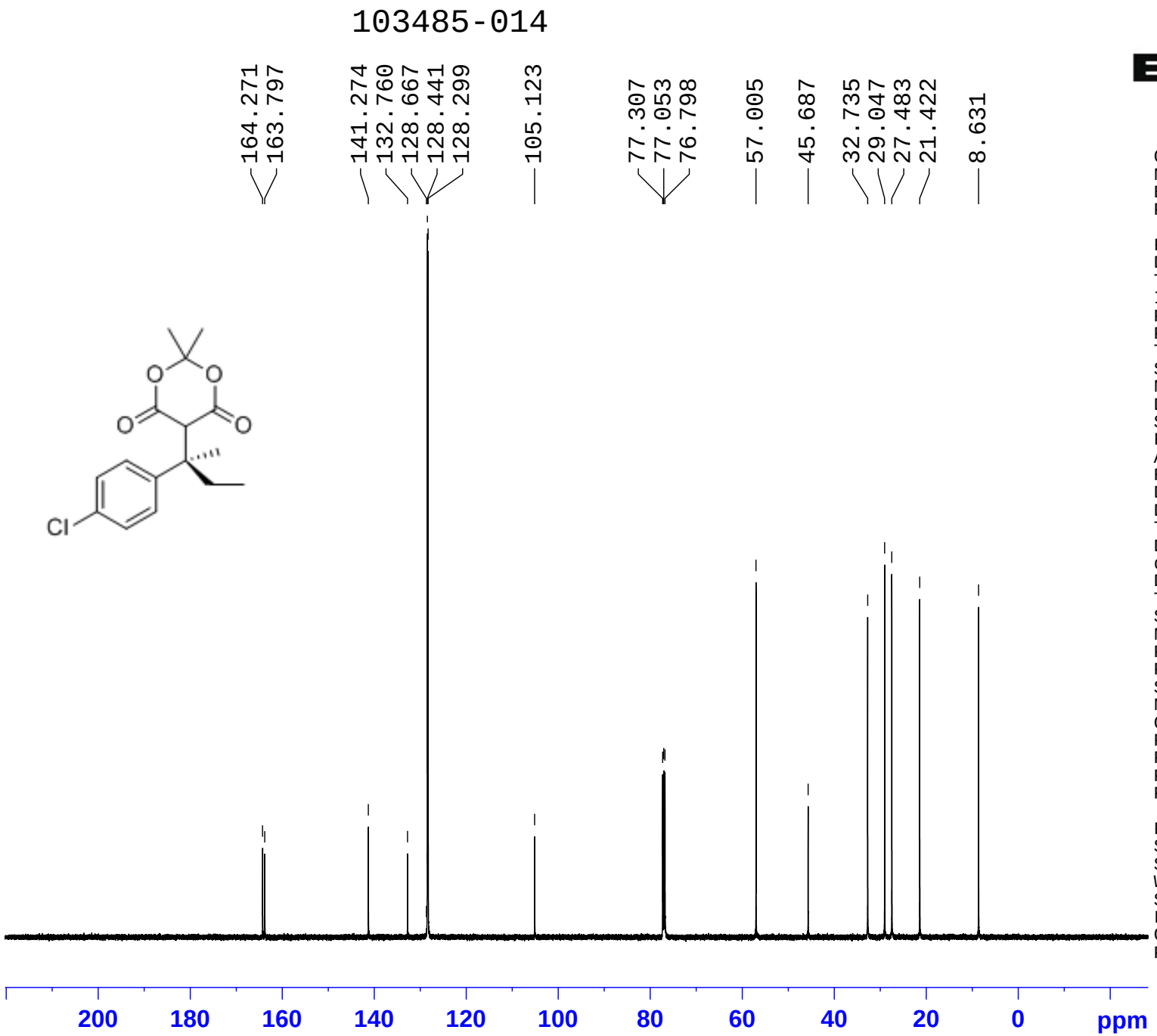
Current Data Parameters
NAME 103485-014
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20150219
Time 10.36
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg10
TD 32768
SOLVENT CDCl3
NS 16
DS 0
SWH 7500.000 Hz
FIDRES 0.228882 Hz
AQ 2.1845334 sec
RG 512
DW 66.667 usec
DE 6.50 usec
TE 299.0 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 11.95 usec
PL1 2.10 dB
PL1W 18.43091774 W
SFO1 500.1325007 MHz

F2 - Processing parameters
SI 16384
SF 500.1300131 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

103485-014



Current Data Parameters

NAME	103485-014
EXPNO	2
PROCNO	1

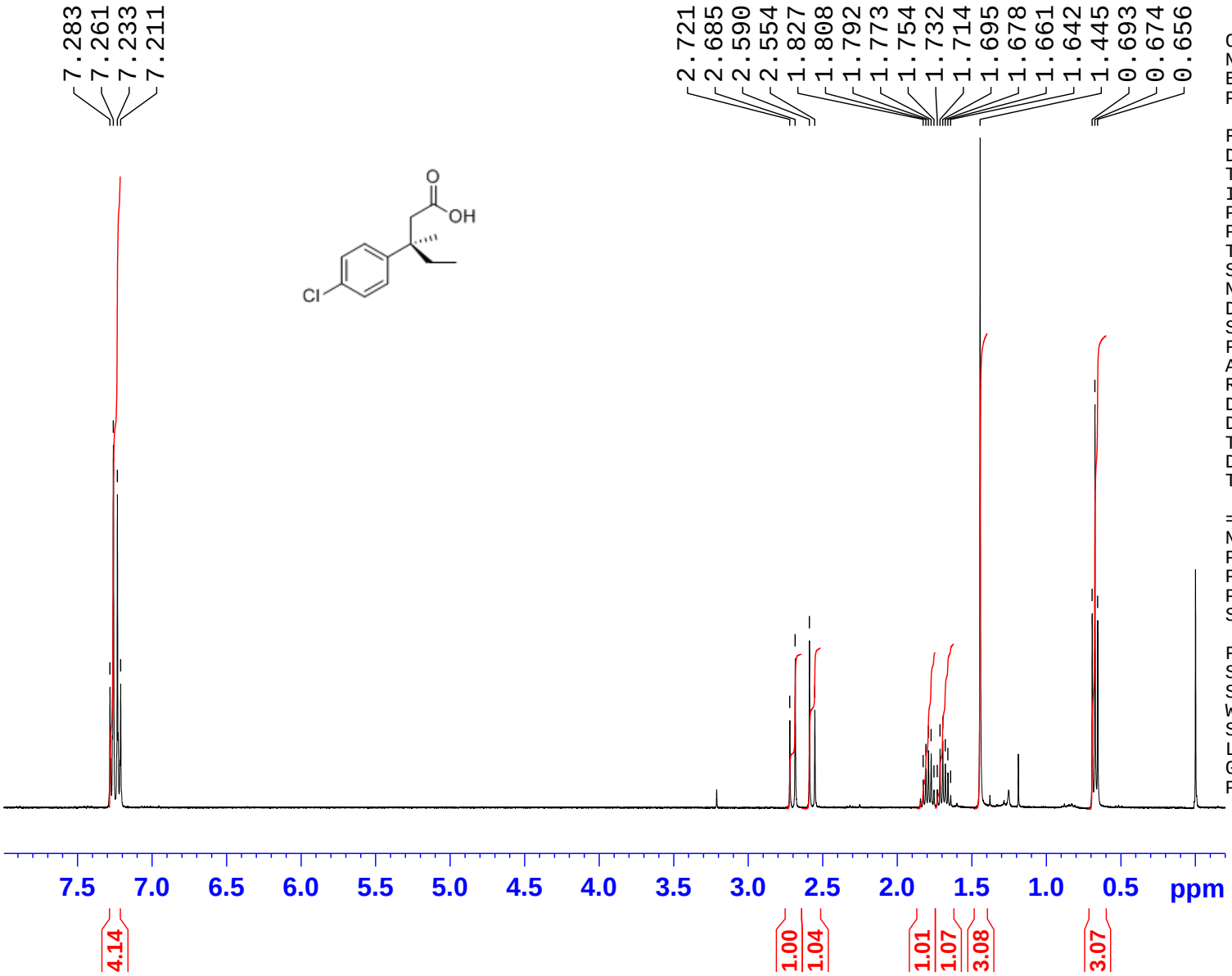
F2 - Acquisition Parameters

Date_	20150114
Time	23.54
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg
TD	262144
SOLVENT	CDCl3
NS	1024
DS	0
SWH	31250.000 Hz
FIDRES	0.119209 Hz
AQ	4.1943040 sec
RG	1820
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	9.75 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

103485-039 product



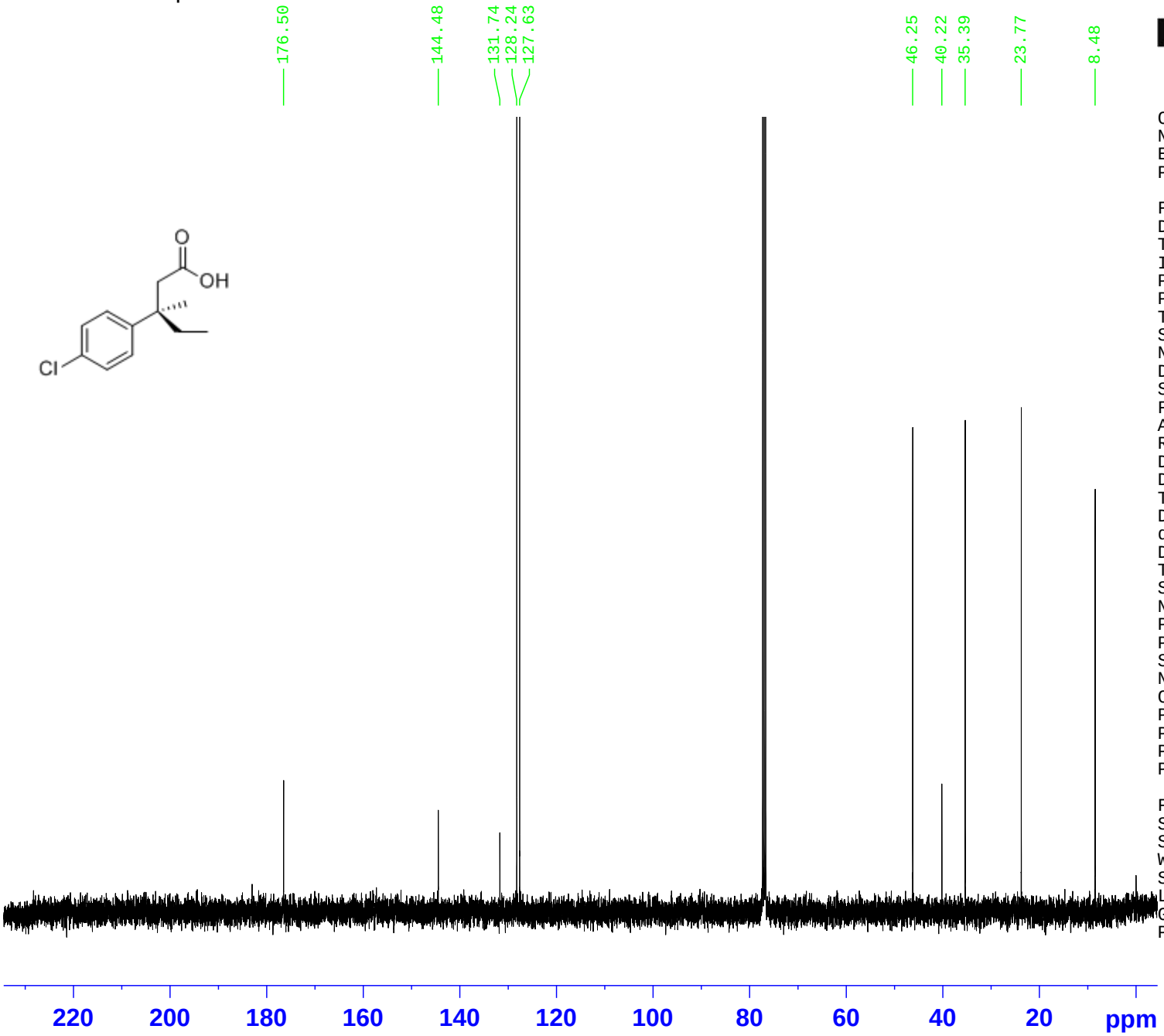
Current Data Parameters
NAME 103485-039
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20150218
Time 9.31
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg10
TD 32768
SOLVENT CDCl3
NS 32
DS 4
SWH 5896.227 Hz
FIDRES 0.179939 Hz
AQ 2.7787263 sec
RG 724
DW 84.800 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 15.00 usec
PL1 0 dB
PL1W 10.49968529 W
SFO1 400.1327209 MHz

F2 - Processing parameters
SI 65536
SF 400.1300104 MHz
WDW EM
SSB 0
LB 0.05 Hz
GB 0
PC 1.00

103485-039 product



Current Data Parameters
NAME 103485-039
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20150218
Time 9.56
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
DELTA 1.89999998 sec
TD0 1
SFO1 100.6243395 MHz
NUC1 13C
P1 10.10 usec
PLW1 -1.00000000 W
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 -1.00000000 W
PLW12 -1.00000000 W
PLW13 -1.00000000 W

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