Organic Syntheses

Enantioselective Preparation of (*S*)-5-Oxo-5,6-dihydro-2H-pyran-2-yl Benzoate

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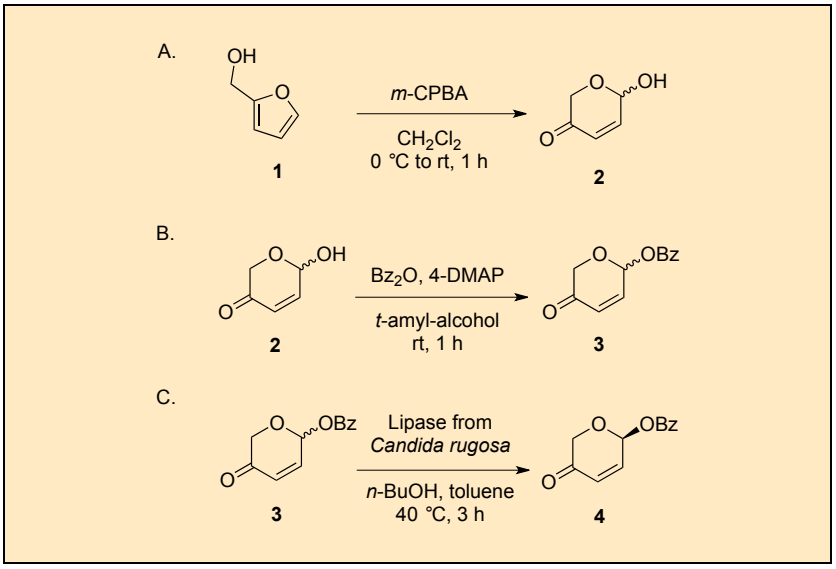

Procedure

Caution! Reactions and subsequent operations involving peracids and peroxy compounds should be run behind a safety shield. For relatively fast reactions, the rate of addition of the peroxy compound should be slow enough so that it reacts rapidly and no significant unreacted excess is allowed to build up. The reaction

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mixture should be stirred efficiently while the peroxy compound is being added, and cooling should generally be provided and maintained since many reactions of peroxy compounds are exothermic. New or unfamiliar reactions, particularly those run at elevated temperatures, should be run first on a small scale. Reaction products should never be recovered from the final reaction mixture by distillation until all residual active oxygen compounds (including unreacted peroxy compounds) have been destroyed. Decomposition of active oxygen compounds may be accomplished by the procedure described in Korach, M.; Nielsen, D. R.; Rideout, W. H. Org. Synth. 1962, 42, 50 (Org. Synth. 1973, Coll. Vol. 5, 414).

A. *5-Oxo-5,6-dihydro-2H-pyran* (**2**). To a clean and dry 3-L four-necked flask equipped with an overhead mechanical stirrer and a PTFE-coated temperature probe, furfuryl alcohol (**1**) (140 g, 1.40 moles, 1.05 equiv) and 1.2 L of dichloromethane are added using medium stirring rate under ambient atmosphere (Note 1). The third neck of the flask is fitted with an inlet adapter with a piece of tubing attached to a bubbler. The fourth neck is sealed with a glass stopper. The flask is cooled to 0–5 °C, then charged with *meta*-chloroperoxybenzoic acid (315 g, 1.36 moles, actual potency 74.7 w%) in five equal portions through the fourth neck, maintaining the internal temperature between 0 and 10 °C (Note 2). Once the addition of oxidant is complete, the heterogeneous mixture is warmed to room temperature by removing the ice bath and stirred at ambient temperature for 1 h (Notes 3 and 4). The reaction is subsequently cooled to 0–5 °C, and the reaction by-product, solid *meta*-chlorobenzoic acid is removed by filtration using a 150 mm Büchner funnel equipped with a Whatman grade 1 filter paper. The solids are washed with pre-cooled (0 °C) dichloromethane (250 mL) (Note 5). The combined filtrate is transferred to a 2 L flask, and one-half of the dichloromethane is removed under reduced pressure (250–350 mmHg) on a rotary evaporator at 30 °C bath temperature. Isopropyl alcohol (450 mL) is added to this solution and the distillation is continued, using vacuum as low as 30 mmHg, until the volume of the solution reached 300 mL (Note 6). After verifying the final volume with a graduated cylinder, the solution is transferred back to the clean 3-L round-bottomed flask. Using an addition funnel heptane (300 mL) is added over 15 min under moderate agitation (Note 7). Once the product crystals appear, the solution is stirred for 30 min, followed by addition of heptane (600 mL) over 15 min. The

slurry is cooled to 0–5 °C, aged for 1 h, and then placed in a 0–5 °C refrigerator overnight (Note 8). The cold slurry is filtered using a 125 mm Büchner funnel equipped with a Whatman grade 1 filter paper, and the solids are subsequently washed with pre-cooled (0 °C) 3:1 heptane:isopropyl alcohol mixture (150 mL), followed by heptane (150 mL). The solid is dried on the filter for 1 h using vacuum, after which 5-oxo-5,6-dihydro-2H-pyran (**2**) 96-98 g, 62-63%) is isolated as a light yellow solid (Note 9).

B. *5-Oxo-5,6-dihydro-2H-pyran-2-yl benzoate (**3**)*. To a clean and dry 3-L four-necked round-bottomed flask equipped with an overhead mechanical stirrer and a PTFE-coated temperature probe, lactol **2** (100 g, 0.876 moles) and *tert*-amyl-alcohol (700 mL) is added using rapid stirring under ambient atmosphere (Note 10). The third neck of the flask is fitted with an inlet

adapter with a piece of tubing attached to a bubbler. The fourth neck is sealed with a glass stopper. The light yellow slurry is heated gently to 20 °C until all lactol dissolves. To this solution is added powdered benzoic anhydride (243 g, 1.05 moles, 1.2 equiv) in one portion, followed by the addition of powdered 4-dimethylaminopyridine (3.3 g, 26.3 mmoles, 0.03 equiv) in one portion (Note 11), through the fourth neck. After addition of the solid reagents, an orange homogeneous solution appears within 15 min, and agitation is continued for 1 h (Note 12). The temperature is maintained between 20–23 °C through the use of a water bath over that time period. Solids begin to precipitate after about 45 min of stirring to form a slurry within 2–3 min. The flask is subsequently cooled to 0–5 °C, which results in a thick white slurry (Note 13). To this slurry is added water (100 mL) in one portion and the suspension is held at 0–5 °C for 1 h (Note 14). The cold slurry is transferred to a 150 mm Büchner funnel equipped with a Whatman grade 1 filter paper, and filtered by applying house vacuum (~100 mmHg). The solids are subsequently washed with pre-cooled (0 °C) 9:1 *tert*-amyl alcohol: water mixture (200 mL), followed in sequence by water (200 mL) and heptane (400 mL). The overall filtration sequence is completed in about 45 min. After drying on the filter for 12 h using house vacuum (~100 mmHg), 5-oxo-5,6-dihydro-2H-pyran-2-yl benzoate (**3**) 142–144 g, 74–75%) is isolated as a light tan solid (Note 15).

C. *(S)-5-Oxo-5,6-dihydro-2H-pyran-2-yl benzoate* (4). To a clean and dry 2-L Erlenmeyer equipped with a PTFE-coated 15 x 80 mm stir bar, benzoate **3** (125 g, 0.573 moles) and toluene (1 L) is charged, and the mixture is heated at 30 °C for 10 min to afford a slightly turbid orange solution. At this point, any remaining red insolubles not dissolved at this temperature are removed by filtration using a 125 mm Büchner funnel equipped with a Whatman grade 1 filter paper, which provides a clear orange solution (Note 16). To a 3-L four-necked, round-bottomed flask equipped with an overhead mechanical stirrer, a 250 mL addition funnel and a PTFE-coated temperature probe, is added lipase from *Candida rugosa* (Lipase MY) (12.5 g, 10 weight%, actual activity 30,000 u/g). The fourth neck is sealed with a glass stopper. The filtered organic layer that contains **3** is added in one portion using rapid stirring under ambient atmosphere (Note 17). The heterogeneous thin suspension is heated carefully to an internal temperature of 40 °C using a heating mantle. The heating is controlled such that the internal temperature of 40 °C is not exceeded. In a separate flask, water (6.25 g) in *n*-butanol (125 mL) is prepared, and this solution is added dropwise to the reaction flask via the 250 mL addition funnel over 30 min

(Note 18). The suspension is agitated for 6.5 h at 40 °C, and then is immediately filtered using a Büchner funnel equipped with a Whatman grade 1 filter paper (Notes 19 and 20). The clear orange filtrate is added to a separatory funnel and then washed with saturated sodium bicarbonate solution (600 mL), followed by water (600 mL). The organic layer is stirred for 20 min with anhydrous sodium sulfate. The suspension is filtered to remove the sodium sulfate and the solution stored in a flask in the refrigerator (4 °C) overnight. The organic layer is concentrated to 250 mL under reduced pressure (<100 mmHg) on a rotary evaporator at 50 °C bath temperature. Upon reaching the desired volume, *tert*-amyl alcohol (500 mL) is added to the flask, and the total volume is reduced under vacuum to 250 mL. The resulting warm solution is transferred to a 500 mL two-necked round-bottomed flask containing a magnetic stirbar and fitted with a thermocouple in one neck and a 250 mL addition funnel in the other. The solution is allowed to cool by stirring at ambient temperature, and crystals begins to precipitate at about 40 °C internal temperature. Once the internal temperature reaches about 30 °C, heptane (125 mL) is added. The suspension is then stirred at ambient temperature for 1 h, cooled to 0–5 °C in an ice/water bath and stirred for 1 h. The cold slurry is filtered on a 125 mm Büchner funnel equipped with a Whatman grade 1 filter paper using house vacuum, and the cake is subsequently washed with 1:1 *tert*-amyl alcohol/n-heptane (125 mL) followed by heptane (125 mL) (Note 21). After drying on the filter for 1 h using house-vacuum, (*S*)-5-oxo-5,6-dihydro-2H-pyran-2-yl benzoate (**4**) (44–46 g, 35–37%, >99%ee) is isolated as a light orange to light brown solid. Purity is determined by normal and chiral phase HPLC as well as NMR (Note 22).

Notes

1. 3-Chloroperoxybenzoic acid, 77%; dichloromethane, Chromasolv for HPLC; 2-propanol, Chromasolv plus for HPLC; *t*-amyl alcohol, ReagentPlus 99%; 4-dimethylamino pyridine, ReagentPlus 99% were purchased from Sigma-Aldrich. Furfuryl alcohol 98%, was purchased from Alfa Aesar; *n*-heptane, Ultra-resi analyzed, and toluene, Baker analyzed for HPLC were purchased from JT Baker; benzoic anhydride, 98% was purchased from Acros. Lipase MY was purchased from Meito–Sangyo Co, Japan. All chemicals were used as received.

2. Detailed safety studies of this reaction have been conducted to show the Achmatowitz rearrangement with *m*CPBA to be a dose-controlled exotherm. To avoid unreacted peroxides in the subsequent distillation, furfuryl alcohol should be used in slight excess. The checkers found that the addition of *m*CPBA takes about 3 h on this scale.
3. The reaction can be monitored by thin layer chromatography (TLC) with EMD 60 F_{254} pre-coated silica gel plates. The plates were eluted with a 1:1 mixture of hexanes and ethyl acetate; furfuryl alcohol (**1)** (R_f = 0.6), lactol **2** (R_f = 0.3) and benzoate **3** (R_f = 0.9) can all be visualized using potassium permanganate stain prepared using 1.5 g of potassium permanganate and 10 g potassium carbonate dissolved in 200 mL water and 1.25 mL of 10 weight% of NaOH solution.
4. Conversion for all three steps can be determined by HPLC on a Imtakt Cadenza CD-C18 3 μM, 4.6 x 75 mm column using 0.05% TFA in CH_3CN:water (5:95) as solvent A and 0.05% TFA in CH_3CN:water (95:5) as solvent B. The 10 min gradient started with B = 0% and became 100% at 8 min. The wavelength of detection was 220 nm and the flow rate was 1 mL/min. Using this method, furfuryl alcohol (**1)** elutes at 3.23 min, lactol **2** elutes at 1.69 min, and benzoate **3** elutes at 6.72 min. Using this HPLC analysis, the oxidation reaction typically achieves 90–93% conversion per furfuryl alcohol.
5. The cake has a tendency to compress and form cracks during the filtration. For an effective cake wash, the solids need to be leveled with a spatula to avoid channeling. The filtration removes about 80% of the 3-chlorobenzoic acid.
6. Low dichloromethane and water contents are critical for good recovery of **2**. The main source of water contamination for this reaction is the wet *m*CPBA that can contain up to 20% water. Both dichloromethane and isopropyl alcohol can azeotrope water. In our experience, adding 450 mL isopropanol per 140 g of furfuryl alcohol has consistently provided a sufficiently dry solution, measured to be less than 1 weight % water based on Karl-Fisher titration.
7. After heptane addition, the product can oil out, but continued stirring leads to crystallization. The addition of seed crystals ensures crystallization. Seed crystals can be generated by transferring a small portion of the reaction solution to a disposable vial, scratching the glass with a metal spatula, then placing the contents under high flow of nitrogen.

8. In general, lactol **2** is the least stable of all compounds produced in this sequence. To ensure good quality **2**, the oxidation and the crystallization should be performed on the same day and the internal temperature should not be allowed to go above 30 °C during evaporation. The checkers found that the isolated yield was only slightly lower (59%) if the filtered dichloromethane solution was stored in the refrigerator overnight before concentration, crystallization and isolation of **2**.
9. Lactol **2** exhibits the following properties: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.14 (d, *J* = 17.0 Hz, 1 H), 4.36 (d, *J* = 5.7 Hz, 1 H), 4.57 (d, *J* = 17.0 Hz, 1 H), 5.63 (dd, *J* = 5.2, 3.0 Hz, 1 H), 6.17 (d, *J* = 10.4 Hz, 1 H), 6.98 (dd, *J* = 10.4, 3.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 66.7, 88.3, 127.9, 146.6, 195.3. IR (film): 3308, 1663, 1624, 1278, 1090, 1008, 980, 847, 686 cm^{-1}. Anal. calcd. for $C_5H_6O_3$: C, 52.63; H, 5.30; found C, 52.66; H, 5.31. HRMS (ESI+): [M+H] calculated: 115.0390, measured: 115.0380. mp 58-60 °C. This product should be stored at or below 5 °C.
10. *tert*-Butanol can also be used as the solvent to give a similar (67–70%) yield of **3**. Once the reagents were added, no freezing of the *tert*-butanol has been observed even after holding the temperature of the reaction mixture at 0 °C.
11. Safety studies have been conducted on this transformation and have revealed that a mild exotherm occurs at the onset of the reaction. This exotherm, however, is offset by the mild endotherm associated with the dissolution of the benzoic anhydride. The internal temperature decreased to 15–16 °C following the benzoic anhydride addition and then rose to 25–26 °C within 10-15 min after the DMAP addition.
12. Using the HPLC method outlined in Note 4 for analysis, >95% conversion of **2** to **3** based on area percent has consistently been observed after 1 h reaction time.
13. Over the course of the reaction, the DMAP also decomposes the final product, turning the solution or slurry to a darker red color. If product crystals do not appear spontaneously within 30 min of the 1 h hold, seeding should be attempted to ensure high product quality. Seed crystals can be generated by the same procedure outlined in Note 7.
14. Water should only be added after the slurry was formed. Even though the slurry is more stable with water, it should still be filtered the same day.

15. Benzoate **3** exhibits the following properties: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.29 (d, *J* = 17.0 Hz, 1 H), 4.61 (d, *J* = 17.0 Hz, 1 H), 6.34 (d, *J* = 10.4 Hz, 1 H), 6.75 (d, *J* = 3.6 Hz, 1 H), 7.06 (dd, *J* = 10.4, 3.6 Hz, 1 H), 7.47 (t, *J* = 7.8, 2 H), 7.61 (t, *J* = 7.5 Hz, 1 H), 8.06 (dd, *J* = 8.0, 1.0 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 67.70, 87.38, 128.80, 129.16, 129.21, 130.13, 134.00, 142.50, 165.22, 193.59. IR (film): 2930, 2856, 1683, 1261, 1089, 1067, 914, 704 cm^{-1}. Anal. calcd. For $C_{12}H_{10}O_4$: C, 66.05; H, 4.61; C, 66.25; H, 4.53; mp 77–79 °C; HRMS (ESI+): [M+H] calculated: 219.065, measured: 219.063. Please store this chemical at or below 5 °C.
16. Polish filtration of the reddish insolubles is critical to avoid premature degradation of the enzyme. If insolubles are still present after the first filtration, the filtration should be repeated until a transparent solution is achieved.
17. Lipases (CAS# 9001-62-1) belong to the hydrolase class of enzymes, acting on ester bonds to catalyze the hydrolysis of fats to fatty acids and glycerol. Lipase MY is a commercial lipase enzyme product obtained from *Candida rugosa* and supplied by Meito-Sangyo Company, Japan. In addition to Lipase MY, we found the reaction to be catalyzed similarly by various *Candida rugosa* lipase products, e.g. *Candida rugosa* lipases L1754 and 62316 from Sigma-Aldrich, Lipase OF from Meito-Sangyo, Lipase AY from Amano. The conditions described here are optimum for Lipase MY with an activity of 30,000 u/g. The optimum conditions are different for other *Candida rugosa* lipase products. The checkers used Lipase MY from Meito-Sangyo Company, Japan with an activity of 30,000 u/g, about 45% of the strength of the submitters batch (66,700 u/g) from the same company. With the same weight amount of lipase, the reaction time had to be approximately doubled to achieve the same outcome as the submitted protocol.
18. The optimal amount of water for this reaction was found to be between 50-100 weight% compared to the enzyme. The amount of water added to the reaction was optimized; less water led to a lower rate and higher water amounts agglomerated the enzyme in toluene, shutting down the reactivity.
19. Enantiomeric excess (ee) was determined on Chiralpak AD-3R 3 μM 4.6 x 150 mm column using 0.05% TFA in CH_3CN:water (5:95) as solvent A and 0.05% TFA in CH_3CN:water (95:5) as solvent B. The 30 min gradient started with B = 10%, became 10% at 5 min, 25% at 10 min, 50% at 15 min and 100% at 20 min. The wavelength of detection was 220 nm and

the flow rate was 1 mL/min. The desired *S*-enantiomer elutes at 18.3 min and the *R*-enantiomer elutes at 20.2 min. At 3 h, chiral HPLC typically indicates >95%ee in the crude solution when Lipase MY with 66,700 u/g is used. By the checkers, the same outcome, >95%ee, was achieved after 6 h with Lipase MY with 30,000 u/g .

20. It is critical to stop the enzyme-catalyzed transesterification reaction immediately after the ee of remaining *S*-enantiomer (**4**) reached the desired level (95%ee) to obtain the highest yield. Lipase MY is very selective, but not absolutely specific and transesterifies the *S*-enantiomer at a much lower rate than *R*-enantiomer. Removal of the enzyme by filtration stops this undesired reaction.
21. In all crystallization procedures examined, the enantioselectivity of product **4** is increased during crystallization. The color of the final crystals can be correlated to step 2 benzoylation; if proper seeding is performed, which results in a lighter color of **2**, the color carried through to step 3 is also less dark.
22. Benzoate **4** exhibits the same properties as benzoate **3** (Note 15). The optical rotation of the final product was determined to be $[\alpha]_D = +252$ (C = 2.0, $CHCl_3$). The product should be stored at or below 5 °C.

Working with Hazardous Chemicals

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.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red “Caution Notes” within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment

should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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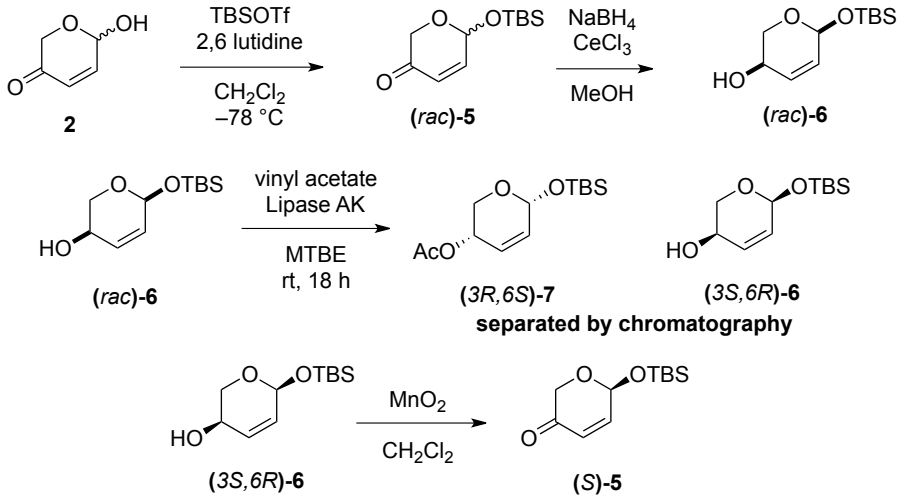
Discussion

Derivatives of lactol **2** contain a rich array of functionalities for elaboration in a diastereoselective fashion,[2,3] and have been shown to be convenient starting materials for natural product synthesis.[4,5] The methods described herein illustrate a chromatography-free synthesis of crystalline benzoate **4** in high enantioselectivity using commercially available chemicals.

Despite the rapid accessibility of **2** from furfurol via the Achmatowitz rearrangement, chiral derivatives such as **4** have been difficult to prepare, especially the *S*-enantiomeric derivatives of **2**.[6] Sugawara and co-workers reported a preparation of non-crystalline TBS ether **5**, but it required over five synthetic operations (Scheme 1).[4]

The Feringa group prepared the analogous acetate of **2**;[2,7] unfortunately, the acetate product required chromatography to isolate, and only in a highly pure form does it appear to be a low-melting solid.[8] The more crystalline benzoate **4** was also prepared by Feringa and co-workers, but racemic **3** had to be separated via chiral chromatography.[2]



Scheme 1. Sugawara synthesis of (*S*)-5

Highlights of our three-step synthetic sequence include isolation of intermediate **2** via crystallization as a white solid, enabling the storage of this otherwise unstable material at 0 °C for extended periods of time. Benzoylation of lactol **2** in a tertiary alcohol solvent[9] allows not only the desired reaction to out-compete the background decomposition, but product **3** also precipitates out of the reaction mixture. Finally, enzymatic transesterification of **3** using a low loading of a commercially available enzyme allows the desired *S*-enantiomer to be accessed without the need for chiral separation. In addition, the enantioselectivity of **4** is further upgraded during the crystallization, ensuring that the desired product is isolated in high quality.

References

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3. Achmatowitz, O. Grynkiewitz, G. *Carb. Res.* **1977**, *54*, 193–198.
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5. For selected examples, see (a) Kolb, H. C.; Hoffmann, H. M. R. *Tetrahedron: Asymm.* **1990**, *1*, 237–250; (b) Fürstner, A.; Feyen, F.; Prinz, H.; Waldmann, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 5361–5364; (c) Sugawara, K. Imanishi, Y.; Hashiyama, T. *Heterocycles* **2007**, 597–607; (d) Jones, R. A.; Krische, M. J. *Org. Lett.* **2009**, *11*, 1849–1851.
6. Treatment of **3** and **4** with either acid or base conditions results in the formation of the oxopyrilium species which can then initiate polymerization of the substrate or 5+2 with a suitable dipolarophile. In addition, lactol **2** undergoes rapid polymerization in presence of base.
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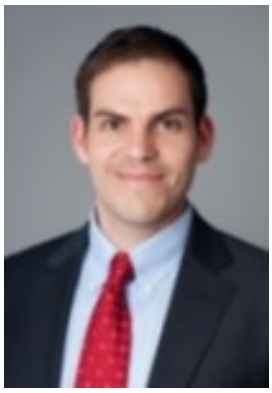
Appendix
Chemical Abstracts Nomenclature (Registry Number)

Furfurol; (98-00-0)
meta-Chloroperbenzoic acid; (937-14-4)
Benzoic anhydride; (93-97-0)
4-Dimethylamino pyridine; (1122-58-3)
Lipases; (9001-62-1)

Tamas Benkovics, a native of Hungary, obtained his B.S. in chemistry from Colorado State University in 2003. After spending two years with the process development group of Amgen in Thousand Oaks, CA, he joined the research group of Professor Tehshik P. Yoon at the University of Wisconsin–Madison. During graduate school, his research was focused on oxaziridine-mediated functionalizations of hydrocarbons. After receiving his Ph.D. in 2010, he joined the process research and development group of Bristol-Myers Squibb.



Adrian Ortiz received his B.S. in chemistry from the University of Arizona in 2004 where he performed research under the guidance of Professor Dominic V. McGrath. He then joined the group of Professor K.C. Nicolaou at the Scripps Research Institute in San Diego, CA where he studied the total synthesis of natural products. Upon completion of his Ph.D. in 2009, he joined the process research and development group at Bristol-Myers Squibb.

Zhiwei Guo obtained his B.S. in chemistry from Beijing University and his Ph.D. in medicinal Chemistry from West China University of Medical Sciences. Following his graduate studies, he has conducted post-doctoral studies at the University of Wisconsin–Madison under the guidance of Professor Charles J. Sih, and at Bristol-Myers Squibb with Ramesh N. Patel. Zhiwei spent the majority of his industrial career at Bristol-Myers Squibb, where he made key contributions using his skills in biocatalysis and knowledge of organic chemistry until his retirement in 2013.
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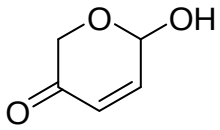
Dr. Animesh Goswami earned his Ph.D. from the University of North Bengal in India and has conducted post-doctoral studies at Arizona State University and University of Iowa in USA. Dr. Goswami has 26 years of industrial experience in the application of biocatalysis for the synthesis of organic compounds. He has joined Bristol-Myers Squibb in 1998, and is currently a research fellow leading the Biocatalysis group of Chemical Development department in Research and Development. Before Bristol-Myers Squibb, he worked in Rhone-Poulenc in USA for 11 years. He is co-author of 45 publications and 15 patents and patent applications.

Dr. Prashant P. Deshpande received his Ph.D. from the State University of New York in 1991 under the supervision of Prof. Olivier R. Martin. After completion of postdoctoral fellowship at the University of Tennessee with Prof. D. C. Baker and at Memorial Sloan Kettering Cancer Center with Prof. S. J. Danishefsky, Prashant joined Bristol Myers Squibb Co. in 1997. Since then he is working as the multi-disciplinary pharmaceutical development & chemical development team leader with 16 years of industrial experience in advancing development of drug candidates from early phase to commercialization. He is co-author of 18 publications and 9 patents and patent applications.

Dr. Magnus Eriksson was born in Stockholm, Sweden. He received his undergraduate degree in Chemical Engineering and his Ph.D. in Organic Chemistry from Chalmers University of Technology in Gothenburg in 1995 under the guidance of Professor Martin Nilsson working on copper-promoted 1,4-additions to carbonyl compounds. After post-doctoral work at Boehringer Ingelheim Pharmaceuticals and at MIT with Professor Stephen Buchwald, he joined Boehringer Ingelheim Pharmaceuticals in 2000 where he is currently a Principal Scientist. His research interests include Process Research, catalytic transformations and synthetic methodology.

Mr. Suresh Kapadia was born in Mumbai, India. He received his B.Sc. in 1972 and M.Sc. in 1974 in organic chemistry from University of Mumbai. He worked as a chemist at New England Nuclear Corporation in Boston from 1977 to 1979. He joined Boehringer Ingelheim Pharmaceuticals in 1979 as Scientist II in medicinal chemistry department. He is currently a senior scientist in chemical development. His research interests include Process Research, Process Development and synthetic methodology.

5-Oxo-5,6-dihydro-2H-pyran (2)



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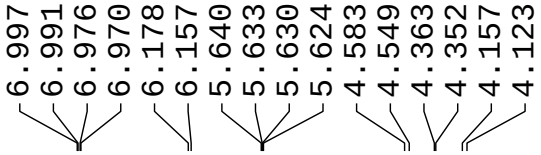
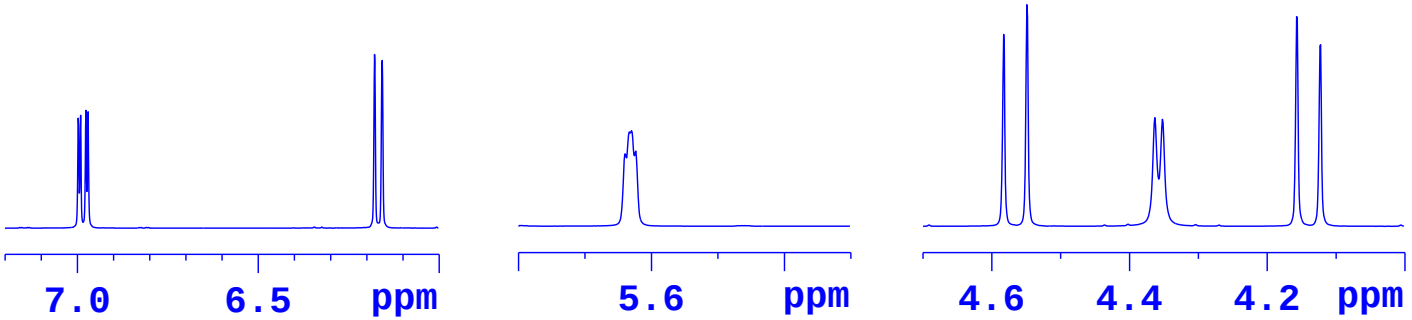
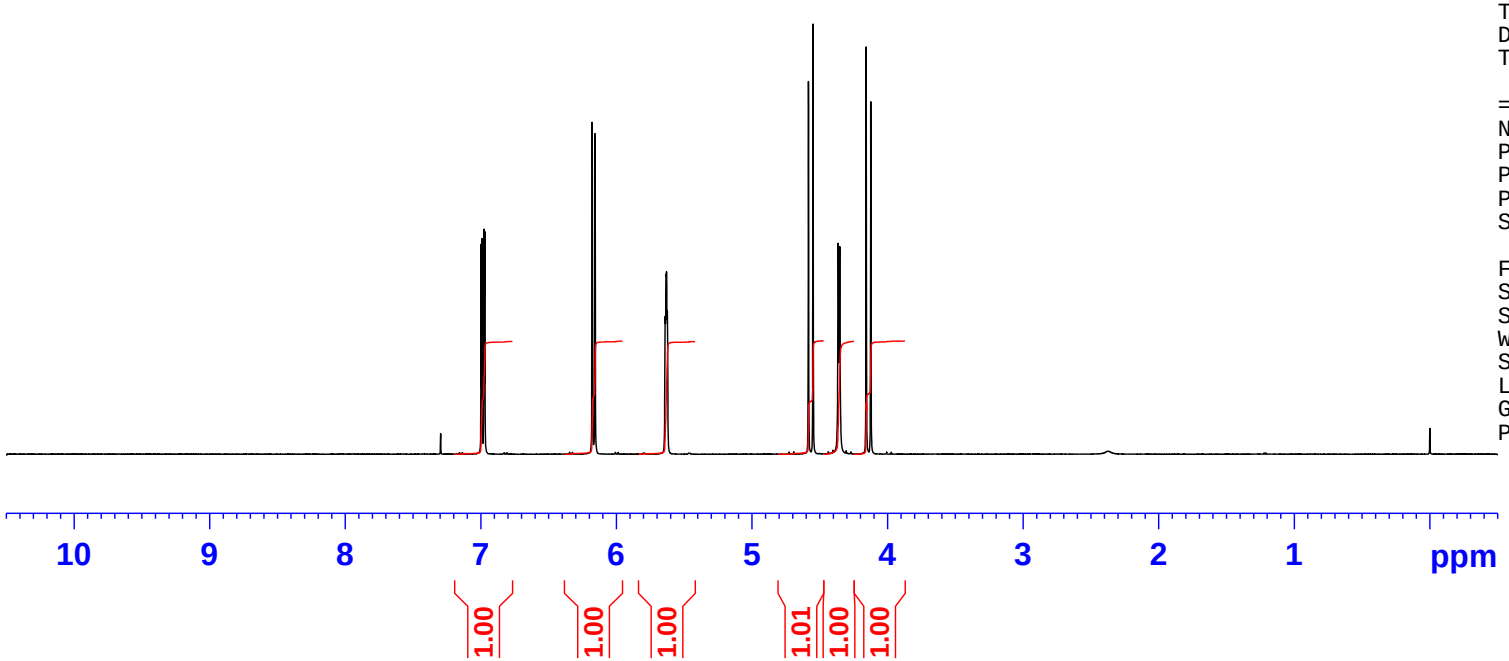
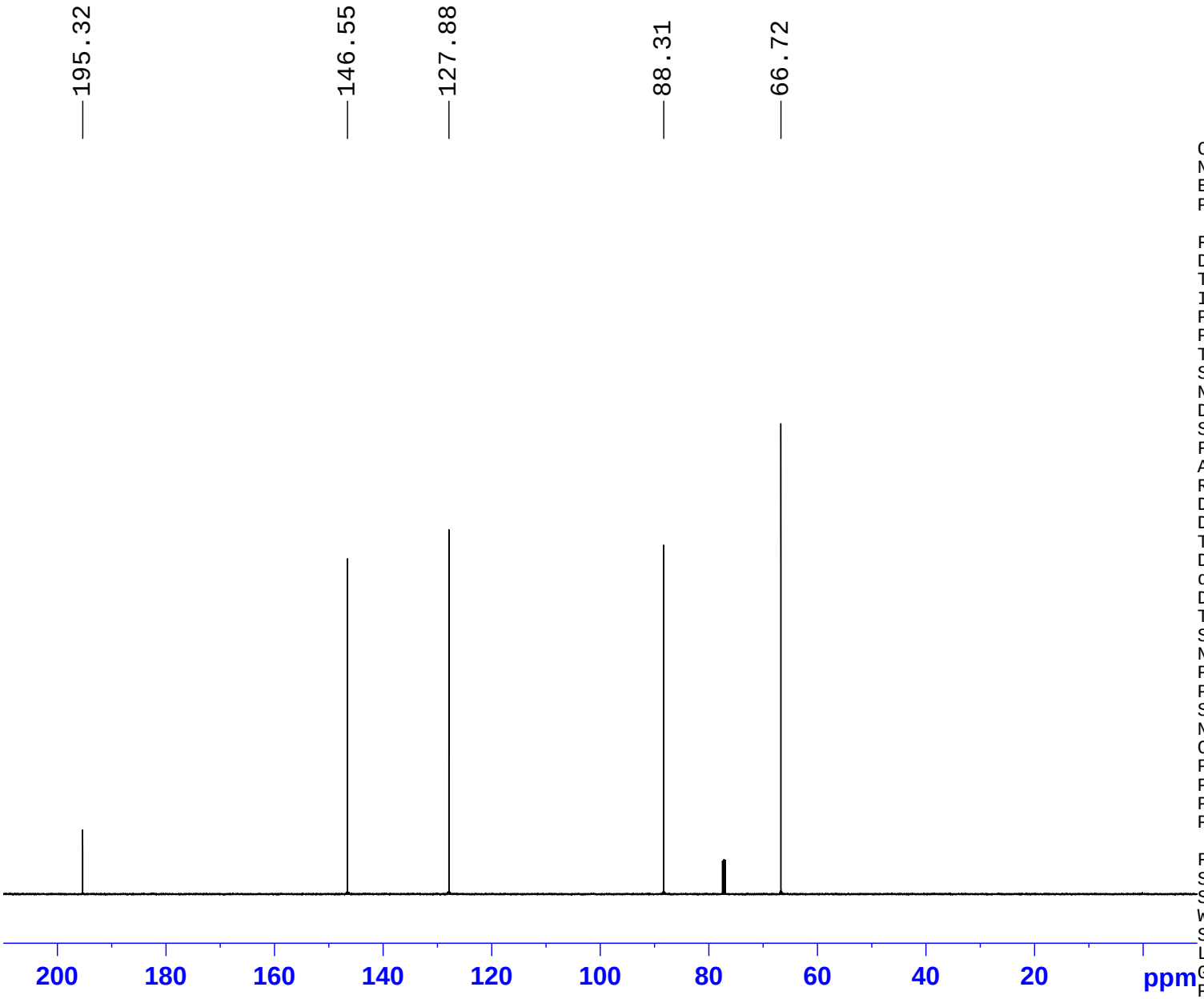


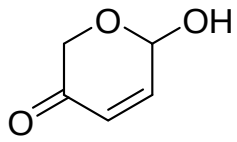





```
Current Data Parameters
NAME       103193-027-5
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20140404
Time              14.09
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                  144
DW                66.667 usec
DE                 6.50 usec
TE                299.0 K
D1             1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                  1H
P1                11.90 usec
PL1                2.10 dB
PL1W        18.43091774 W
SFO1        500.1325007 MHz

F2 - Processing parameters
SI                16384
SF          500.1299946 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

5-Oxo-5,6-dihydro-2H-pyran (2)

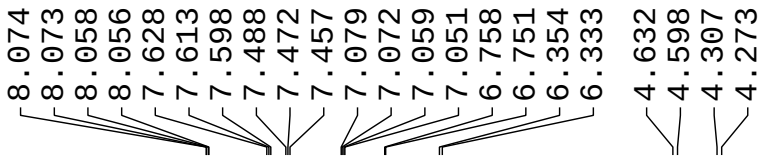


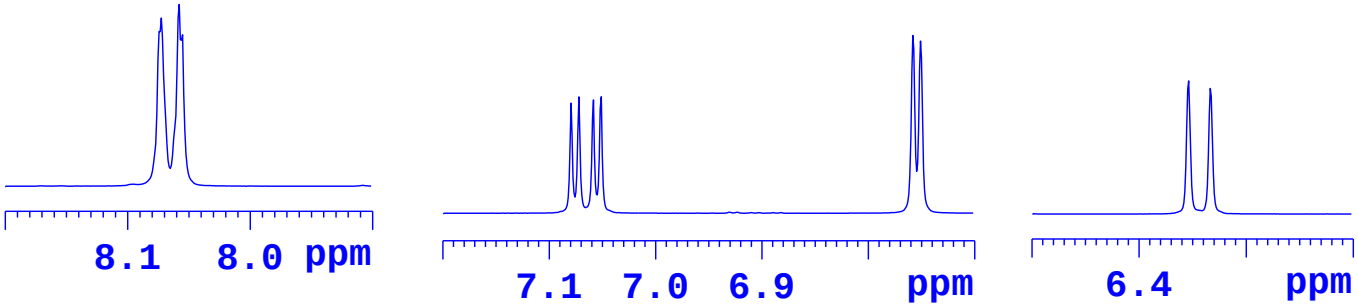


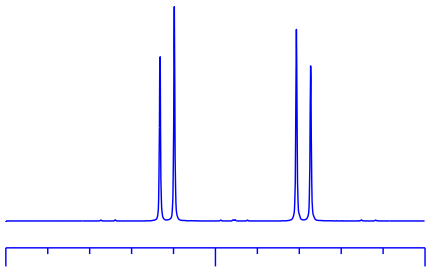
2

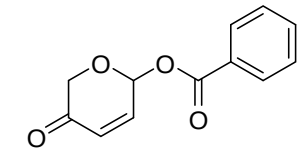
```
Current Data Parameters
NAME       103193-027-5
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20140404
Time              14.27
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG            zgpg
TD               262144
SOLVENT            CDCl3
NS                   200
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                 10.64 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           125.7577720 MHz
WDW                  EM
SSB      0
LB                 0.30 Hz
GB       0
PC                 1.40
```

5-Oxo-5,6-dihydro-2H-pyran-2-yl benzoate (3)







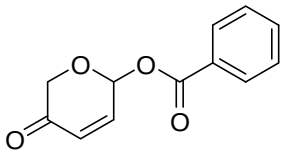


3

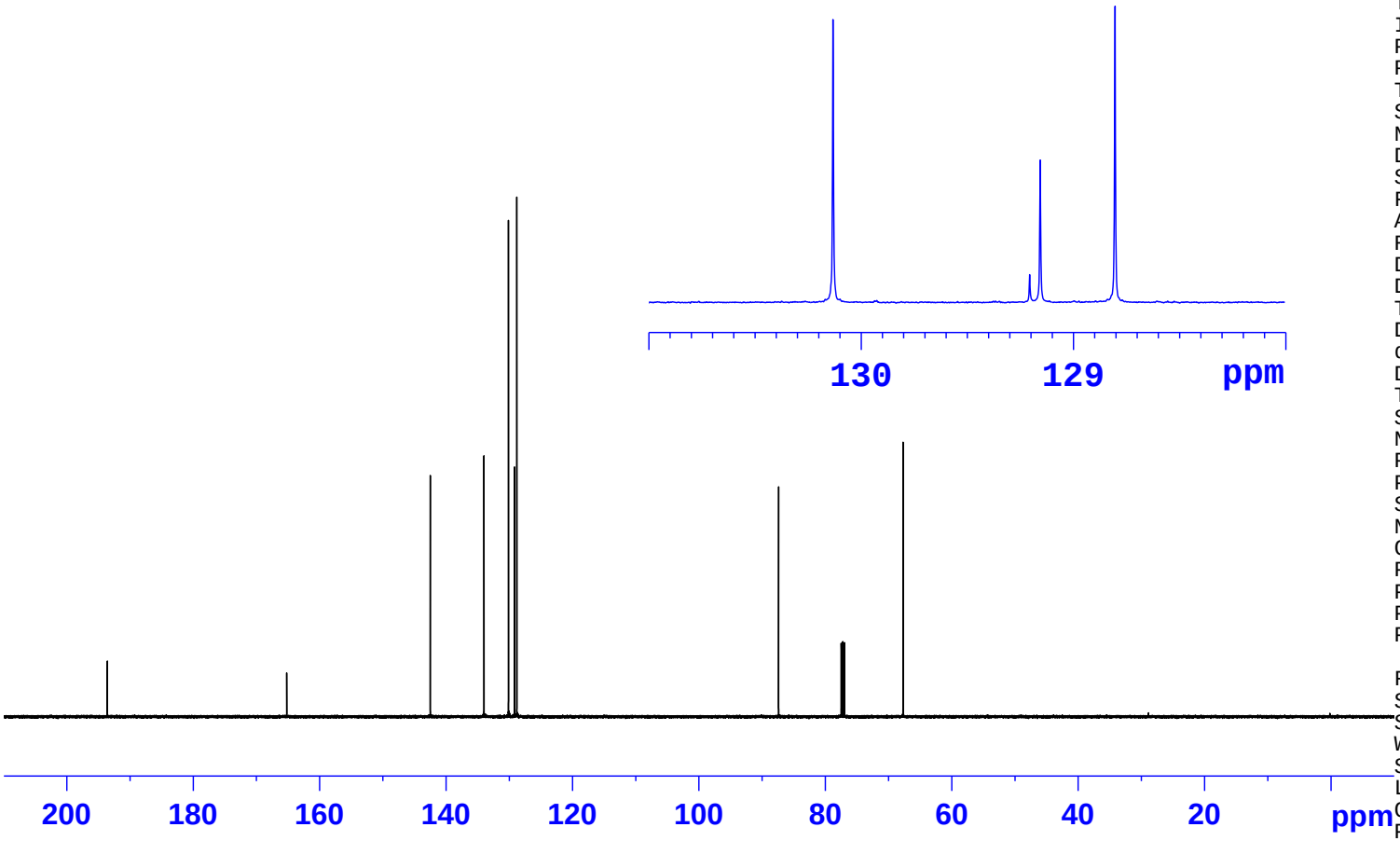
```
Current Data Parameters
NAME       103193-039-3
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20140509
Time              12.43
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                  256
DW                66.667 usec
DE                 6.50 usec
TE                299.0 K
D1           1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                  1H
P1                11.90 usec
PL1                2.10 dB
PL1W        18.43091774 W
SFO1        500.1325007 MHz

F2 - Processing parameters
SI                16384
SF          500.1300094 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

5-Oxo-5,6-dihydro-2H-pyran-2-yl benzoate (3)

193.59
165.22
142.50
134.00
130.13
129.21
129.16
128.80
87.38
67.70



3




```
Current Data Parameters
NAME       103193-039-2
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20140508
Time              15.03
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG            zgpg
TD               262144
SOLVENT            CDCl3
NS                   225
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                 10.64 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           125.7577665 MHz
WDW                  EM
SSB      0
LB                0.30 Hz
GB       0
PC                1.40
```