# Rapid Access to Enantiopure Protected (R)-Paraconyl Alcohol

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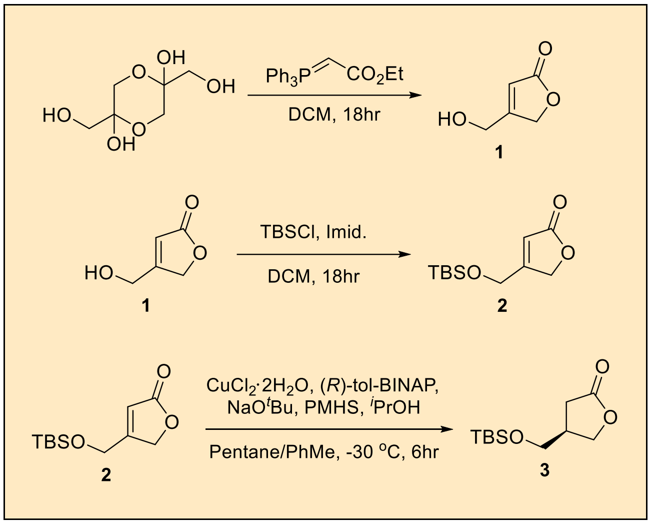


## **Procedure** (Note 1)

A: *4-(hydroxymethyl)furan-2(5H)-one* (**1**): In a flame-dried, 500 mL round bottom flask equipped with a football shaped stir-bar, 1,3-dihydroxyacetone dimer (Note 2) (10.00 g, 55.5 mmol, 1.00 eq) was dissolved in anhydrous dichloromethane (Note 3) (150 mL, *c* = 0.37M). The (carbethoxymethylene)triphenylphosphorane (Note 4) (46.41 g, 133.21 mmol, 2.4 eq) was then added to the solution portion-wise, resulting in a cloudy pale-orange color (Figure 1a). The reaction was allowed to stir under nitrogen for 18 hours at room temperature (Note 5), as monitored by TLC, (Note 6); wherein, it became amber in color (Figure 1b). After which, the dichloromethane was removed first by rotary evaporator (21 mmHg, 30 ˚C) to afford an opaque orange oil (Figure 1c). The crude material was further concentrated under high vacuum (9 mmHg, rt) while stirring for a minimum of 12 hours (Note 7). The triphenylphosphine oxide (TPPO) byproduct was precipitated by adding 100 mL of deionized water to the viscous oil. The oil on the sides of the flask was scraped to the bottom with a spatula, stirred to break up the chunks, and the dispersion was sonicated in a Fisher Brand sonicator for 15 min. The sides of the flask were scraped again and sonicated for an additional 15 min (Figure 1d). The resulting pale-yellow solids were then vacuum filtered (9 mmHg) and washed twice with 50 mL deionized water (room temperature), and the yellow filtrate was collected into a round bottom flask (Figure 1e). The filtrate was concentrated (3.1 mmHg, 45 ˚C) to afford a yellow oil. This oil was dissolved in 70 mL of warm ethyl acetate (35 ˚C) (Note 8), then decanted into a 250 mL Erlenmeyer flask containing a cylindrical stirbar. A white precipitate began to form, and the flask was cooled to 0 ˚C in an ice bath and stirred for 1.5hrs. The resulting crystals were then quickly vacuum filtered (9 mmHg) to afford *4-(hydroxymethyl)furan-2(5H)-one* **1** as an off-white powder (7.36g, 53%, 96.3% pure) (Note 9) (Figure 1f).

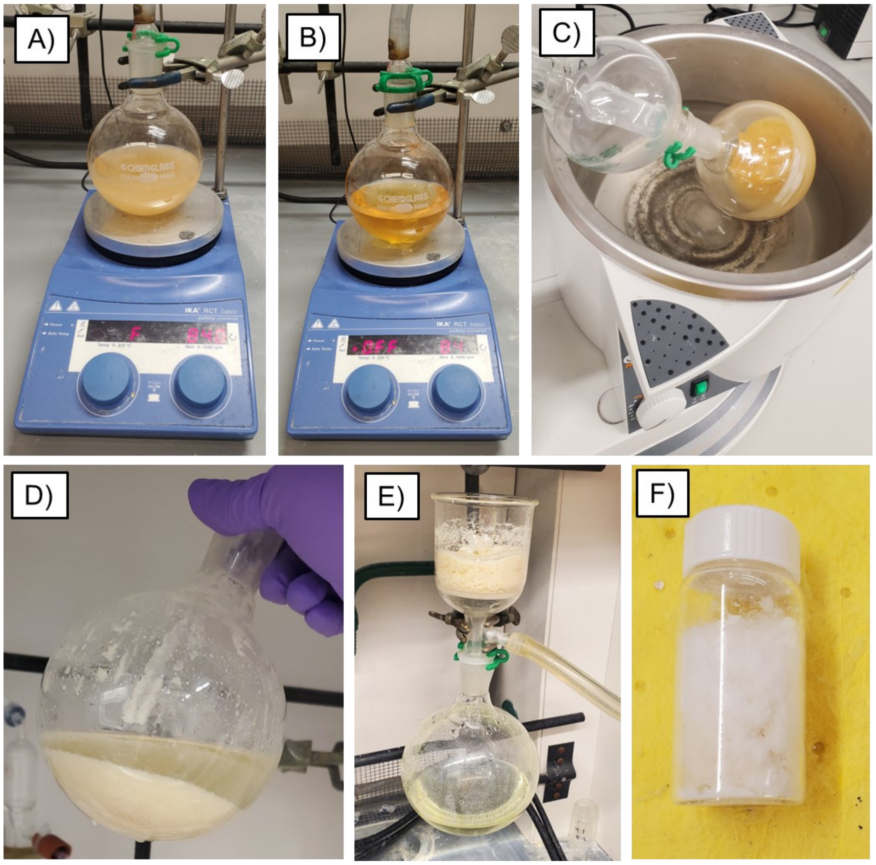


**Figure 1: A) The reaction color and turbidity at the beginning of the reaction. B) The reaction color and transparency at the end of the reaction. C) The color and consistency of the concentrated reaction. D) The precipitated TPPO byproduct after sonication. E) The filtration of the TPPO byproduct and pale-yellow aqueous filtrate. F) The final product obtained as an off-white powder.**

B: *4-(((tert-butyldimethylsily)oxy)methyl)furan-2(5H)-one* (**2**): In a flame-dried, 500 mL round bottom flask equipped with a football shaped stir bar, was dissolved *4-(hydroxymethyl)furan-2(5H)-one* (**1**) (7.25 g, 63.54 mmol, 1 eq) in anhydrous dichloromethane (65 mL, *c* = 0.98M). Imidazole (Note 10) (8.64 g, 127.08 mmol, 2 eq) was then added in one portion and the reaction was allowed to stir for 5 minutes under nitrogen. During this time, the pale-yellow solution became slightly cloudy (Figure 2a). *Tert*-butyldimethylchlorosilane (Note 11) (10.54 g, 69.89 mmol, 1.1 eq) was then added to the solution, which then turned opaque white (Figure 2b). The reaction was allowed to stir at room temperature, under nitrogen for 18hr. Upon completion of the reaction by TLC analysis (Note 12), 96 mL of 1M hydrochloric acid (Note 13) was added to the stirring solution. The mixture was poured into a 250 mL separatory funnel (Figure 2c), and the organic layer was removed. The aqueous phase was further extracted with dichloromethane (80 mL, 2x). The organic layers were combined in a 500 mL separatory funnel, washed with brine (100mL), dried with magnesium sulfate (5.5 g) (Note 14), filtered, and concentrated under reduced pressure (21 mmHg, 28 °C). The resulting pale-yellow oil (Figure 2d) was suspended in 110 mL pentane (Note 15). The mixture was transferred to a 250 mL Erlenmeyer flask containing a long stir bar and vigorously stirred in a -20 °C freezer to recrystallize for 1.5 hours. The resulting white crystals were vacuum filtered (9 mmHg) and washed with 20 mL cold (stored in -20 °C freezer) pentane to afford *4-(((tert-butyldimethylsily)oxy)methyl)furan-2(5H)-one* (**2**) (10.83g, 75%, 96.1% pure) (Note 16) (Figure 2e).

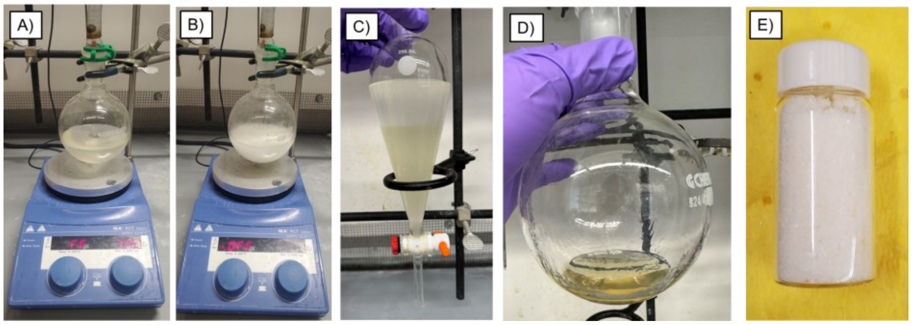


**Figure 2: A) The reaction color after the addition of imidazole. B) The reaction cloudiness after the addition of TBSCl. C) The aqueous and organic phases in the separatory funnel. D) The crude yellow oil after concentration. E) The final product obtained as a white solid after recrystallization.**

C: *(S)-4-(((tert-butyldimethylsily)oxy)methyl)dihydrofuran-2(3H)-one* (**3**): A 250mL 3-neck flask, equipped with a stir-bar and an addition funnel was flame dried and charged with copper (II) chloride dihydrate (Note 17) (0.19 g, 1.09 mmol, 0.05 eq), (*R*)-tol-BINAP (Note 18) (0.74 g, 1.09 mmol, 0.05 eq), and sodium *tert*-butoxide (Note 19) (0.42 g, 4.38 mmol, 0.20 eq). The vessel was fitted with a thermometer then evacuated and re-filled with nitrogen gas twice before adding anhydrous pentane (Note 20) (29 mL, *c* = 0.75M). The dispersion was stirred and polymethylhydrosiloxane (PMHS, note 21) (3.90 mL, 3.94 g, 65.70 mmol, 3 eq) was added dropwise via addition funnel over 5 minutes. The reaction was allowed to stir at room temperature for 2 hours. Over this period, the solution went from white to dark yellow (Figure 3a,b). After 2 hours at room temperature, the vessel was brought to -30 °C using a Neslab CC100 immersion cooler with an isopropanol bath (Note 22), and 20 mL of anhydrous toluene (Note 23) was added to the reaction flask, followed by a solution of *4-(((tert-butyldimethylsily)oxy)methyl)furan-2(5H)-1-one* (**2**) (5.00 g, 21.90 mmol, 1 eq), isopropanol (5.02 mL, 3.95 g, 65.70 mmol, 3 eq), and toluene (10 mL, *c* = 0.75M) via addition funnel over 10 minutes. During the addition of the solution, the reaction changed from a dark yellow to orange-red (Figure 3c). The reaction was stirred under nitrogen at -30 ˚C for 4 hours. After consumption of starting material, as observed by NMR (Note 24), the reaction was quenched with 96 mL of 1 M HCl at -30 ˚C, then transferred to a 250 mL separatory funnel (Figure 3d). The phases were mixed, and the organic layer was removed. The aqueous phase was extracted with ethyl acetate (80 mL, 2x). The organic layers were combined in a 500 mL separatory funnel, washed with brine (100 mL), dried with magnesium sulfate (8.0 g), and vacuum filtered (9.6 mmHg) with a fritted vacuum funnel (Note 25). The magnesium sulfate was washed with 50 mL of ethyl acetate and the filtrate was concentrated to afford an opaque yellow oil (Figure 3e). The crude sample was loaded onto a pre-equilibrated (12% EtOAc in hexanes) (Note 26) short plug of silica (Note 27) (3in, d = 90 mm, flow rate = 2in/min) in 5 mL of hexanes. The sample was purified with 3L of 12% EtOAc in hexanes. Collection began after the yellow band started eluting (approximately 250 mL) and fractions 21-99 (25 mL each) were combined (Figure 3f,g) and concentrated to afford a yellow oil (3.59g) (Figure 3h). The resulting yellow oil was transferred to a 10 mL round bottom flask in 2 mL of chloroform (Note 28) and equipped with a half-inch stir bar, and a short-path distillation apparatus (110 mm width x 115mm height), which was connected to vacuum and a pre-weighed 10 mL conical receiving flask. Vacuum was slowly introduced until vigorous bubbling ceased (approx. 15min, 150 mmHg). The flask containing the oil was then brought to 150 ˚C in a silicone oil bath and full vacuum (9.6 mmHg) was introduced. The neck of the distillation apparatus was heated with a heat gun to assist in evaporation. After a clear condensate began to form at the top of the apparatus (approx. 15 min), the temperature was increased to 160 ˚C. After another 15 min the temperature was increased again to 170 ˚C and remained until no more condensate was present and the heated flask contained a thick yellow slurry (Figure 3i). *(S)-4-(((tert-butyldimethylsily)oxy)methyl)dihydrofuran-2(3H)-one* (**3**) was collected as a clear oil (2.73 g, 53%, 95%ee, 99.0% pure) (Note 29) (Figure 3j).

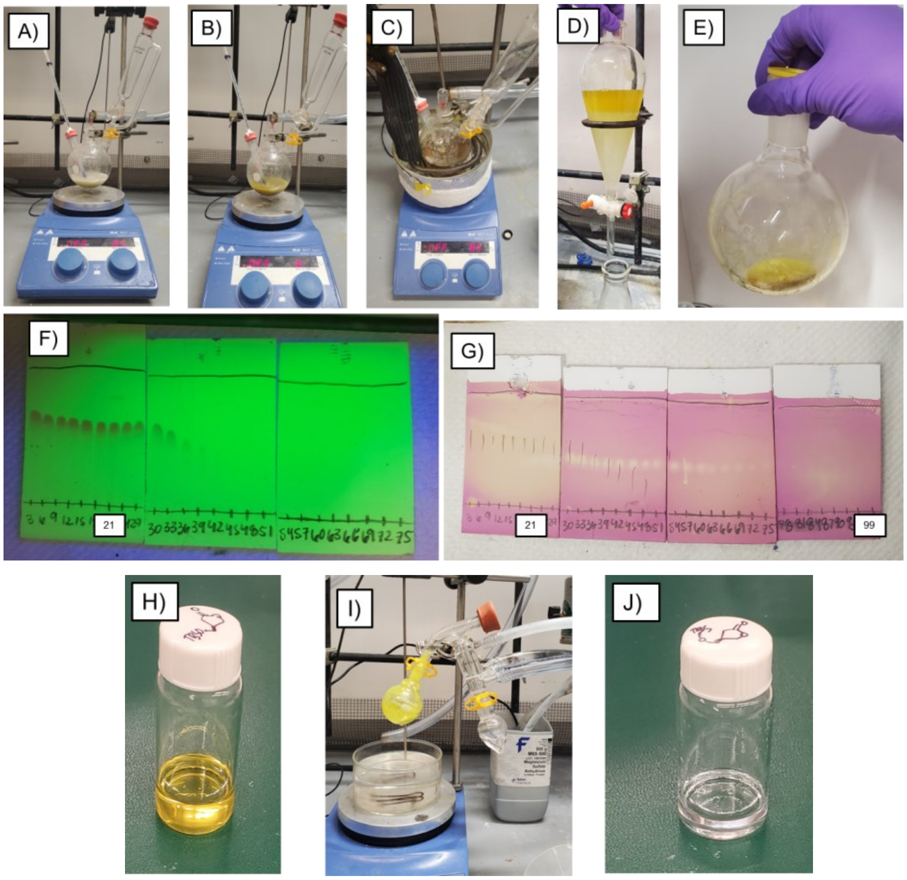


**Figure 3: A) The reaction color at the start of the reaction. B) The reaction color after 2 hr. C) The color of the reaction after the addition of the butenolide 2. D) The aqueous and organic phases in the separatory funnel. E) The crude yellow oil. F) TLCs from column chromatography visualized using UV (254 nm). Fractions 21-99 were combined (Rf = 0.4, 4:1 Hexanes:EtOAc). G) TLC of the fractions stained with $KMnO_4$ stain. H) Resulting yellow oil of the combined fractions. I) The distillation set up after completion of the distillation. J) The pure material as a clear oil.**

## Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/about/governance/committees/chemical-safety.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with 1,3-dihydroxy acetone dimer, dichloromethane, imidazole, *tert*-butyldimethylchlorosilane, hydrochloric acid, sodium *tert*-butoxide, (*R*)-tol-BINAP, hexanes, as well as the proper procedures for vacuum distillations.
2. 1,3-Dihydroxyacetone dimer (97%) was purchased from Thermo Scientific and used as received.
3. Dichloromethane (≥99.9), unstablized and HPLC grade was purchased from Fisher and dried using a solvent purifying system from Inert.
4. (Carbethoxymethylene)triphenylphosphorane (90%) was purchased from Oakwood Chemical and used as received.
5. Room temperature was monitored at a range from 20-24 °C.
6. TLC plates, Silica gel 60 $F_{254}$ (20 cm x 20 cm), were purchased from Supelco. The reaction was monitored in 1:4 Hexanes:EtOAc and visualized under UV and in $KMnO_4$ stain (Rf = 0.30). Consumption of the dihydroxyacetone dimer was used to assess reaction completion (Figure 4a,b). $KMnO_4$ stain was prepared by dissolving 1.5g of potassium permanganate (Oakwood, 97%), 10g of $K_2CO_3$ (Thermo Fisher, 99%), and 1.25 mL of 10% NaOH (Thermo Fisher, 99%) in 200 mL of water and stored in a glass jar, with the sides covered in aluminum foil.

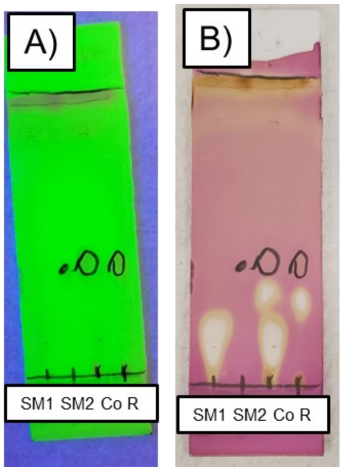


**Figure 4: A) The reaction progress at 18hrs under UV (254 nm). To TLC 1, a drop of the reaction solution was removed and diluted with 0.5 mL of DCM. SM1 = 1,3-dihydroxyacetone, SM2 = (carbethoxymethylene)triphenyphosphorane. The circles in pencil correspond to UV active spots. B) The reaction progress at 18hrs in $KMnO_4$ stain.**

7. Excess DCM in the crude oil will solubilize the TPPO in water and can result in more impurities going into the recrystallization.
8. Ethyl acetate (≥99.5) was purchased from Fisher and used without further purification.
9. *4-(hydroxymethyl)furan-2(5H)-one* (**1**) has the following chemical properties: mp: 43-46 ˚C; $^1H$ NMR (500 MHz, $CDCl_3$ (Cambridge Isotope, 99%)) δ 6.03 (s, 1H), 4.86 (s, 2H), 4.60 (s, 2H), 2.88 (s (*br*), 1H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 173.80, 169.51, 115.04, 71.31, 58.99; FTIR (neat), 3395.70 cm $^{-1}$, 1724.43 cm$^{-1}$; HRSM (acpi+): *m/z* $[M+H]^+$ calcd for $C_5H_6O_3H$: 115.0389, found: 115.0386. It was found to be 96.3% pure by qNMR using dimethylsulfone as a standard (Note 30). The product could be stored neat in a -20 °C freezer for at least 6 months.
10. Imidazole (ACS grade, 99%) was purchased from Oakwood Chemical and used as received. It is used in slight excess (2 eq) to neutralize any HCl that may have been liberated from the TBSCl reagent.
11. Tert-butyldimethylchlorosilane (99%) was purchased from Oakwood and used without further purification.

12. Reaction progress was monitored in 1:1 Hexanes:EtOAc and visualized in $KMnO_4$ stain (Rf = 0.8) (Figure 5).

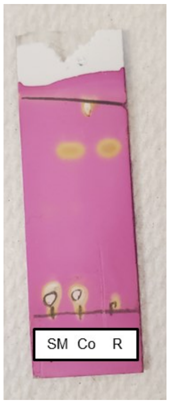


**Figure 5: A) The reaction progress at 18hrs in $KMnO_4$ stain. To TLC 2, a drop of the reaction solution was removed and diluted with 0.5 mL of DCM. SM = 1.**

13. Hydrochloric acid (ACS grade) was purchased from Fisher Chemical and used without further purification. It was diluted with deionized water to achieve 1M concentration.
14. Magnesium sulfate anhydrous (powder/certified) was purchased from Fisher Chemical and used as received.
15. Pentane was purchased from Fisher Chemical and used as received.
16. *4-(((tert-butyldimethylsily)oxy)methyl)furan-2(5H)-1-one* (**2**) has the following chemical properties: mp = 28-31 ˚C; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 5.98 (s, 1H), 4.81 (s, 2H), 4.56 (s, 2H), 0.91 (s, 11H), 0.10 (s, 7H), $^{13}$C NMR (126 MHz, $CDCl_3$) δ 173.57, 169.70, 114.73, 71.13, 59.61, 25.71, 18.23, -5.52.; FTIR (neat): 1731.80 cm$^{-1}$; HRMS (ACPI+): *m/z* $[M+H]^+$ calcd for $C_{11}H_{20}O_3SiH$: 229.1260, found: 229.1257. It was found to be 96.1% pure by qNMR using dimethylsulfone as a standard. The product could be stored neat in a -20 °C freezer for at least 6 months.
17. Copper (II) chloride dihydrate (99%) was purchased from Sigma Aldrich and used as received. In our hands, bottles that had been open for 6 months or longer were found to have diminished reactivity, likely due to the hygroscopic nature of the reagent.

18. (*R*)-tol-BINAP (98.0%),was purchased from Tokyo Chemical Industry and used as received. It is imperative to handle under an inert atmosphere.
19. Sodium *tert*-butoxide (99%) was purchased from Thermo Fisher and used as received.
20. Pentane anhydrous (>99%) in a SureSeal bottle was purchased from Sigma Aldrich and used without further purification.
21. Polymethylhydrosiloxane was purchased from Thermo Scientific and used as received. After being open for a period of time, white solids appeared at the bottom of the reagent, likely from further polymerization. The reagent could still be used but resulted in variable yields (38-59%). Excess PMHS was used to ensure efficient formation of the active copper-hydride catalyst.
22. Isopropanol certified ACS Plus (99%) was purchased from Fisher and used as received. Excess reagent was used to ensure efficient turnover of the copper catalyst.
23. Toluene, HPLC grade (≥99.7), was purchased from Fisher and dried with a solvent purifying system from Inert.
24. A 0.1mL aliquot was removed via syringe from the reaction and dispensed into a vial containing 0.5 mL 1M HCl and 0.5 mL EtOAc. The vial was shaken, and the top layer was removed, concentrated, and taken up in 0.4 mL $CDCl_3$ for $^1H$ NMR analysis. The reaction was considered complete when the peak at 5.98 ppm (corresponding to the $\alpha$ proton of the starting material, **2**) had disappeared. TLC analysis can be performed (4:1 Hex:EtOAc, visualized in UV and KMnO4 (Rf = 0.4)); however, the starting material and the product are copolar. Upon treatment of the TLC plate with KMnO4, the starting material spot appears almost immediately and is darker in color; whereas the product takes longer to appear and is lighter in color (Figure 6a,b,c).

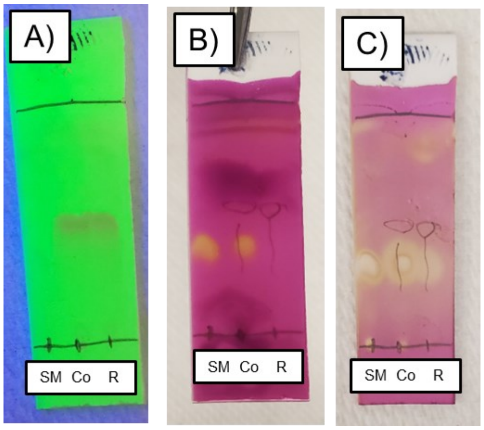
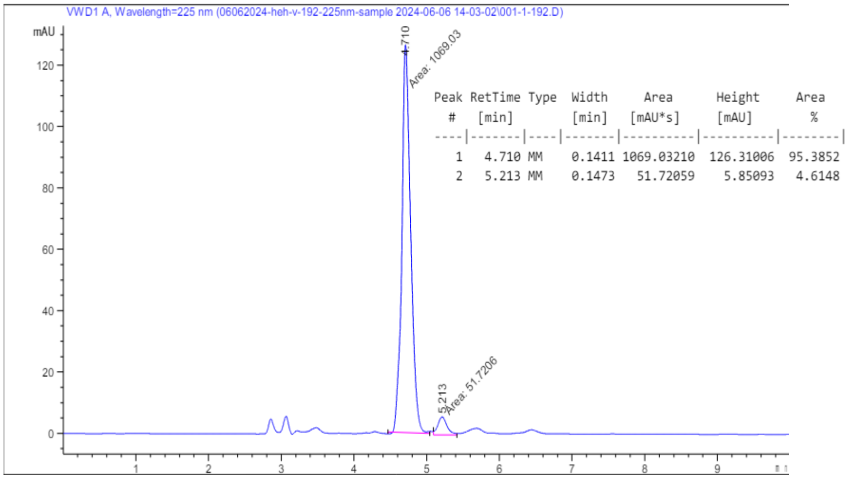


**Figure 6: A) The reaction progress at 3hrs in under UV (254 nm). The crude 3hr NMR sample was used as a TLC sample for 3. SM = 2. The circles in pencil correspond to UV active spots. B) The TLC after immediate exposure to KMnO₄ stain. C) The TLC after development of the KMnO₄ stain.**

25. PMHS and the isopropoxysilane byproducts can clog filter papers and cotton causing a very slow filtration that will ultimately halt.[2]
26. Hexanes (≥98.5) was purchased from Fisher and used as received.
27. SiliaFlash Irregular Silica Gel GE60, 60-200 μm, 60 Å was purchased from SiliCycle and used as purchased.
28. Chloroform was purchased from Fisher and used as received.
29. *(S)-4-(((tert-butyldimethylsily)oxy)methyl)dihydrofuran-2(3H)-one* (**3**) has the following properties: $[\alpha]_D^{23}$ = -20.59 (*c*1.00, $CHCl_3$), lit[3] $[\alpha]_D^{25}$ = -19.8 (*c*2.4, $CHCl_3$, for 95%ee); bp = 249- 253 ˚C; $^1H$ NMR (500 MHz, $CDCl_3$) δ 4.36 (dd, *J* = 9.5, 3.6 Hz, 1H), 4.17 (dt, *J* = 9.1, 5.2 Hz, 1H), 3.66 – 3.57 (m, 2H), 2.76 – 2.66 (m, 1H), 2.54 (ddd, *J* = 17.6, 9.1, 2.9 Hz, 1H), 2.38 (dd, *J* = 17.3, 6.2 Hz, 1H), 0.88 (s, 10H), 0.05 (s, 6H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 177.11, 70.51, 63.28, 37.30, 30.69, 25.77, 18.20, -5.52; FTIR (neat) = 1774.01 $cm^{-1}$; HRMS (ACPI+) *m/z* $[M+H]^+$ calcd for $C_{11}H_{22}O_3SiH$ 231.1416, found 231.143. Enantiomeric excess was determined by HPLC using a Chiralpak AD-H column in 5% isopropanol in hexanes at 1.0 mL/min at 30˚C with detection at 225 nm, $t_R$ (major) = 4.71 min and $t_R$ (minor) = 5.21 min (Figure 7). It was found to be 99.0% pure by qNMR using dimethylsulfone as a standard. The product could be stored neat in a -20 °C freezer for at least 6 months.



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Peak RetTime Type  Width     Area      Height     Area
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   1   4.710 MM    0.1411 1069.03210  126.31006  95.3852
   2   5.213 MM    0.1473   51.72059    5.85093   4.6148
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**Figure 7) Chiral HPLC data of 3 using the aforementioned purification conditions. The peaks at t=2.0 and t=3.1 are artifacts of the column and appear in the blank.**

30. Dimethylsulfone (99%) was purchased from Tokyo Chemical Industry and used as received.

## Working with Hazardous Chemicals

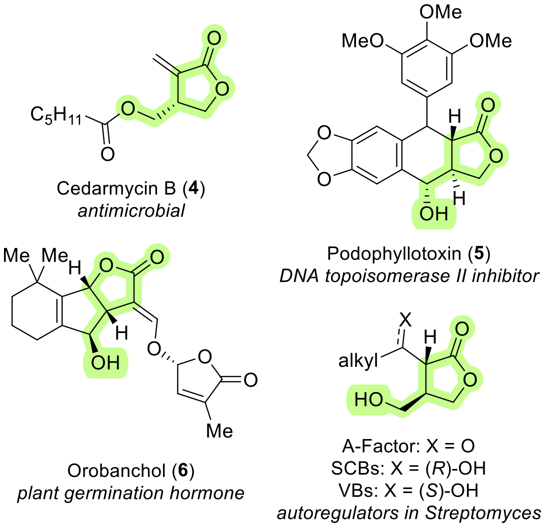
The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The 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.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

## Discussion

Chiral $\gamma$-butyrolactones (GBLs) are common motifs in natural products and have been found to have a variety of bioactivities including anticancer, antimicrobial, and antifungal (Figure 8).[4–6] Additionally, many species of *Streptomyces* utilize highly substituted, epimeric GBLs to regulate natural product production.[7] Some of these autoregulators include A-Factor from *Streptomyces griseus*, the *Streptomyces coelicolor* butanolides (SCBs), and the *Streptomyces virginiae* butanolides (VBs), which all contain the same *anti* $\alpha$,$\beta$-substituted lactone motif with variation in oxidation or stereochemistry at the C1′ position (Figure 8). These densely substituted, highly stereogenic, and labile lactones have inspired our synthetic endeavors.



Cedarmycin B (**4**)
*antimicrobial*

Podophyllotoxin (**5**)
*DNA topoisomerase II inhibitor*

Orobanchol (**6**)
*plant germination hormone*

A-Factor: X = O
SCBs: X = (*R*)-OH
VBs: X = (*S*)-OH
*autoregulators in Streptomyces*

**Figure 8: Select GBL containing natural products and metabolites.**

Historically, these hormones have been synthesized through an aldol or acylation reaction with protected (R)-paraconyl alcohol. There has been interest in accessing this enantiopure core, as evidenced by investigations into methods ranging from kinetic resolution to chiral auxiliary and organocatalytic approaches (Figure 9). One of the first reported approaches was from Mori and Yamane which involved performing a kinetic resolution of (+/-) paraconic acid with (*R*)-(+)-a-phenethylamine; however, multiple recrystallizations were necessary to obtain enantiopure material, resulting in a low yield of 3%.[8] Complete reduction of the carboxylic acid followed by protection of the alcohol to a trimethylsilyl (TMS) ether afforded a protected common intermediate; however, they obtained low overall yields. The use of the labile TMS protecting group resulted in epimerization of the hydroxymethyl substituent at the beta position through transesterification. Mori and Chiba later applied commercially available lipase M to selectively desymmetrize allyl diacetate **7** in 83%ee.[9] The resulting alcohol was doubly oxidized and cyclized under acidic conditions to afford (R)-paraconic acid in 15% overall yield. Rawlings and coworkers successfully circumvented the issues of low yield and epimerization through the use of the Evans' oxazolidinone chiral auxiliary and a bulkier, less labile 1,1,2-trimethylpropylsilyl ether protecting group. They successfully installed a benzyl-protected hydroxymethyl group alpha to the *N*-acyloxazolidinone **8** in 94% yield and >99:1 d:r and in seven steps, successfully obtaining a silyl protected (R)-paraconyl alcohol in 11% overall yield.[10] Most recently, Appayee et al, reported a short route to the tert-butyldimethylsilyl (TBS) protected (*R*)-paraconyl alcohol through an organocatalytic hydroxymethylation approach. Starting from expensive methyl 4-oxobutanoate ($510/g from Sigma Aldrich), **9**, hydroxymethylation alpha to the methyl ester via a biaryl prolinol catalyst was afforded in 95% ee in 6 days. Subsequent Pinnick oxidation, cyclization, reduction, and deprotection afforded the protected (*R*) paraconyl alcohol in 35% overall yield and 95%ee.[3] Although this route efficiently produces **2** in high enantiopurity, the route is hindered by long reaction times and expensive starting materials.

The approach reported herein utilizes affordable commercially available starting materials and can be performed on multi-gram scale to afford enantio-enriched TBS-protected (*R*)-paraconyl alcohol in under a week.[11] The route commences via Wittig olefination between dihydroxyacetone ($0.30/g) (carbethoxymethylene)triphenyl phosphorane ($0.47/g) and spontaneous cyclization to form the butenolide **1**. This has been previously described by Zutter and coworkers as a potential scalable route to (*S*)-3-fluoromethyl-y-butyrolactone; however, they were unsuccessful in isolating the butenolide on kilogram scale due to triphenylphosphine oxide (TPPO) impurities and

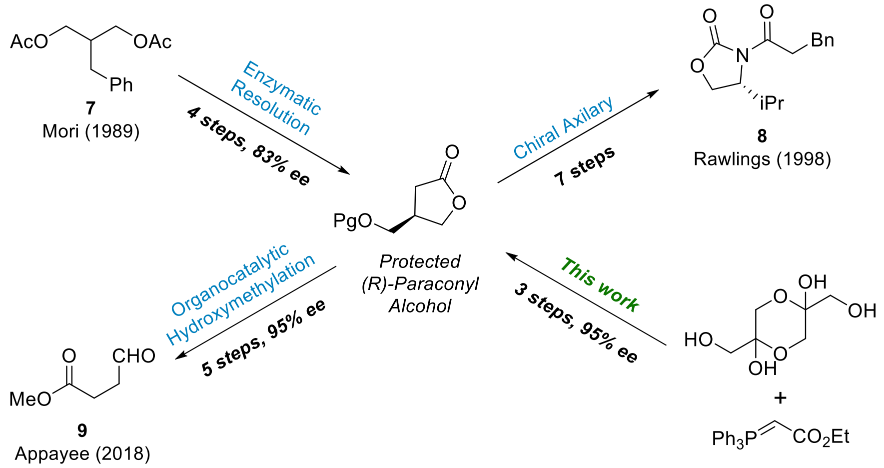


**Figure 9: An overview of previous methods to access protected (R)-paraconyl alcohol.**

abandoned this route.[12] We utilized the water-soluble nature of **1** and were successfully able to precipitate out the TPPO. Following recrystallization, butenolide **2** was obtained in modest yield and high purity (96%). With **2** in hand, the alcohol moiety was protected as a TBS-ether in 75% yield and 96% purity after recrystallization in cold pentane. To obtain saturated butenolides, the Donate group previously reported a ruthenium catalyzed hydrogenation of 4-hydroxymethyl furanones, where they successfully hydrogenated both mono- and disubstituted butenolides but with a broad range of enantiomeric excesses (8-100%ee) and conversions (28-100%).[13] This method suffers from long reaction times (a minimum of 72 h) and requires elevated pressure (80 atm). To circumvent the long reaction times and need for high pressures, we were inspired by the copper catalyzed conjugate hydride addition methodology utilizing polymethylhydrosiloxane (PMHS) as a hydride source developed by Buchwald.[14,] Through slight modifications in the equivalences of PMHS and isopropanol used, butenolide **2** was successfully reduced to lactone **3** in 53% yield with 95%ee. This three-step route provides access to the synthetically useful building block **3** from readily available starting materials in 21% overall yield and 95%ee.

## References

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2. Lavis, J. M.; Maleczka, R. E.; Chandrasekaran, V.; Collier, S. J. Polymethylhyrdosiloxane. *Wiley* **2016**.
3. Sarkale, A. M.; Kumar, A.; Appayee, C. Organocatalytic Approach for Short Asymmetric Synthesis of (R)-Parconyl Alcohol: Application to the Total Syntheses of IM-2, SCB2, and A-Factor Gamma-Butyrolactone Autoregulators. *J. Org. Chem.* **2018**, *83* (7), 4167–4172. https://doi.org/10.1021/acs.joc.8b00122.

4. Mazur, M.; Maslowiec, D. Antimicrobial Activity of Lactones. *Antibiotics* **2022**, *11*, 1327. https://doi.org/10.3390/antibiotics11101327.
5. Hur, J.; Jang, J.; Sim, J. A Review of the Recent Pharmacological Activities and Recent Synthetic Advances of Gamma-Butyrolactones. *Int J Mol Sci* **2021**, *22* (5), 2769. https://doi.org/10.3390/ijms22052769.
6. Sartori, S. K.; Noguiera Diaz, M. A.; Diaz-Munoz, G. Lactones: Classification, Synthesis, Biologica l Activites, and Industrial Applications. *Tetrahedron* **2021**, *84*, 132001. https://doi.org/10.1016/j.tet.2021.132001.
7. Niu.; Charter, K. F.; Tian, Y. Specialised Metabolites Regulating Antibiotic Biosynthesis in Streptomyces Spp. *FEMS Microbiol Rev* **2016**, *40* (4), 554–573. https://doi.org/10.1093/femsre/fuw012.
8. Mori, K. Revision of the Absolute Configuration of A-Factor. *Tetrahedron* **1983**, *39* (19), 3107–3109. https://doi.org/10.1016/S0040-4020(01)91552-2.
9. Mori, K.; Chiba, N. Preparative Bioorganic Chemistry, XI Preparation of the Enantiomers of Paraconic Acid Employing Lipase-Mediated Asymmetric Hydrolysis of Prochiral Diacetates as the Key Step. *Liebigs Ann Chem.* **1989**, *1989* (10), 957–962. https://doi.org/10.1002/jlac.198919890251.
10. Crawforth, J. M.; Fawcett, J.; Rawlings, B. J. Asymmetric Synthesis of A-Factor. *J Chem Soc Perkin Trans 1* **1998**, *1998* (10), 1721–1726. https://doi.org/DOI https://doi.org/10.1039/A708638E.
11. Wilbanks, L. E.; Hennigan, H. E.; Martinez-Brokaw, C. D.; Lakkis, H.; Thormann, S.; Eggly, A. S.; Buechel, G.; Parkinson, E. I. Synthesis of Gamma-Butyrolactone Hormones Enables Understanding of Natural Product Induction. *ACS Chem. Biol.* **2023**, *18* (7), 1624–1631. https://doi.org/10.1021/acschembio.3c00241.
12. Adam, J.-M.; Foricher, J.; Hanlon, S.; Lohri, B.; Moine, G.; Schmid, R.; Stahr, H.; Weber, M.; Wirz, B.; Zutter, U. Development of a Scalable Synthesis of (S)-3-Fluoromethyl-γ-Butyrolactone, Building Block for Carmegliptin's Lactam Moiety. *Org. Process Res. Dev.* **2011**, *15* (3), 515–526. https://doi.org/10.1021/op200019k.
13. Bronze-Uhle, E. S.; de Sairre, M. I.; Donate, P. M.; Frederico, D. Enantioselective Hydrogenation of 4-(Hydroxymethyl)Furan-2(5*H*)-One Derivatives. *J. Mol. Catal. Chem.* **2006**, *259* (1), 103–107. https://doi.org/10.1016/j.molcata.2006.05.066.

14. Hughes, G.; Kimura, M.; Buchwald, S. L. Catalytic Enantioselective Conjugate Reduction of Lactones and Lactams. *J. Am. Chem. Soc.* **2003**, *125* (37), 11253–11258. https://doi.org/10.1021/ja0351692.

## Appendix
## Chemistry Abstracts Nomenclature (Registry Number)

| | |
|---|---|
| 1,3-Dihydroxyacetone Dimer | (26776-70-5) |
| (Carbethoxymethylene)triphenylphosphorane | (1099-45-2) |
| Dichloromethane | (75-09-2) |
| *tert*-Butyldimethylchlorosilane | (18162-48-6) |
| Imidazole | (288-32-4) |
| Copper (II) Chloride Dihydrate | (10125-13-0) |
| (*R*)-tol-BINAP | (99646-28-3) |
| Sodium *tert*-Butoxide | (865-48-5) |
| Isopropanol | (67-63-0) |
| Polymethylhydrosiloxane | (63148-57-2) |
| Pentane | (109-66-0) |
| Toluene | (108-88-3) |

Insert photograph of each author here, and submit as a separate JPG file. A head-and-torso photo (4 cm x 5 cm) is preferred.

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Insert photograph of each author here, and submit as a separate JPG file. A head-and-torso photo (4 cm x 5 cm) is preferred.

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Insert photograph of each author here, and submit as a separate JPG file. A head-and-torso photo (4 cm x 5 cm) is preferred.

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