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# A Scalable Synthesis of (*R*,*R*)-2,6-Dimethyldihydro-2*H*-pyran-4(3*H*)-one

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Supporting Information

**ABSTRACT:** A scalable synthesis of (*R*,*R*)-2,6-dimethyldihydro-2*H*-pyran-4(3*H*)-one is reported. Key to this strategy is the Ti(O*i*Pr)$_4$-catalyzed Kulinkovich cyclopropanation of silyl protected (*R*)-ethyl 3-hydroxybutanoate, and subsequent oxidative fragmentation of the cyclopropanol. The resulting vinyl ketone intermediate was then subjected to oxidative Heck cyclization to form the enone substrate required for conjugate addition. A diastereoselective copper-catalyzed Grignard addition procedure was implemented to install the requisite methyl group, with the inclusion of 1,3-bis(diphenylphosphino)propane and trimethylsilyl chloride greatly increasing the robustness of this process.

## INTRODUCTION

Dimethyl pyranone **1** was a key intermediate required for the synthesis of an asset within our portfolio. The chosen strategy to access **1** relied upon the addition of methyl cuprate to enone **2** (Figure 1). Previous reports of this transformation utilizing

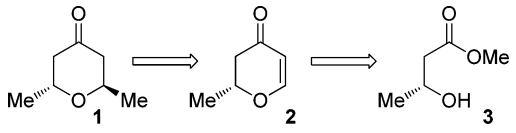
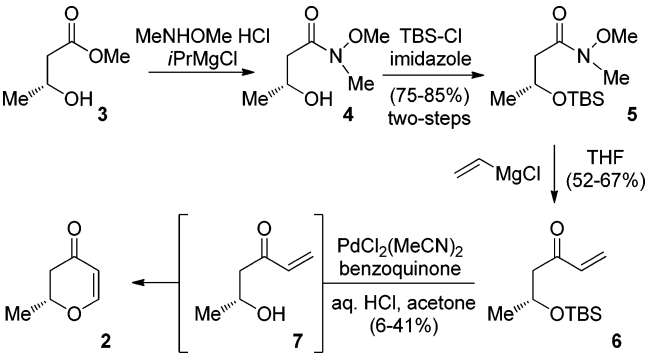



**Figure 1.** Retrosynthesis of dimethylpyranone **1**.

*rac*-**2** proceeded in 87% isolated yield, indicating a high degree of *trans*-diastereoselectivity.[1] To utilize this strategy for our needs, an efficient, chiral synthesis of enone **2** was required. In 2010, Astra Zeneca (AZ) published their efforts toward a scalable synthesis of the antipode of **2**.[2] Guided by their in-depth investigations, we originally utilized their route to enone **2** to produce material for initial development work. On the basis of the previously reported success of the cuprate addition, it was anticipated that the conversion of **2** to **1** would be straightforward.

Initially we repeated the AZ sequence (Scheme 1) to deliver approximately 10 kg of **2**. The reaction sequence was slightly modified to serve our purpose, with the enantiomeric ester **3** serving as the starting material, and the Weinreb amide of **4**/**5** being utilized as the substrate for vinyl Grignard addition instead of the dimethylamide. Overall, similar yields to those reported by AZ were achieved (four-step yield was 14%, 11% at AZ). Areas for improvement were noted during this campaign, with the vinyl Grignard addition causing significant challenges. We found that the outcome of this step was highly dependent on the quality of the vinyl Grignard, and in addition, cryogenic temperatures (−20 °C) were necessary. As a result, an alternative route to vinyl ketone intermediate **6** that did not require vinyl Grignard could help streamline the large-scale production of **2**. We also hoped to improve the robustness of

**Scheme 1. Route to enone 2 based on Astra Zeneca publication**




the oxidative Heck cyclization where the poor stability of both intermediate **7** and product **2** led to modest yields. These stability issues were compounded on scale where degradation occurred during prolonged reaction holds under acidic conditions or during the basic workup.

## RESULTS AND DISCUSSION

**Development of Kulinkovich Cyclopropanation Process.** We set out to evaluate alternative routes towards **2**, with the ultimate goal of identifying a more streamlined synthesis of vinyl ketone **6**. The AZ paper did a thorough job in laying the groundwork for this endeavor, as many of the logical routes to **6** had already been investigated and could be excluded. In 2005, Singh utilized **6** to prepare all the stereoisomers of tarchonanthuslactone.[3] Singh's strategy to **6** was based on Kulinkovich cyclopropanation and subsequent oxidative fragmentation of an appropriately protected 3-hydroxybutanoate ester (Scheme 2). The reported yields for these

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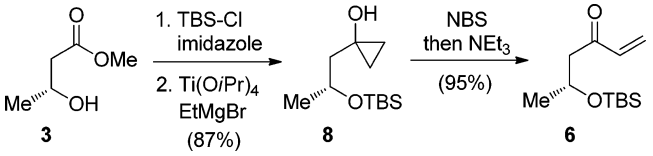
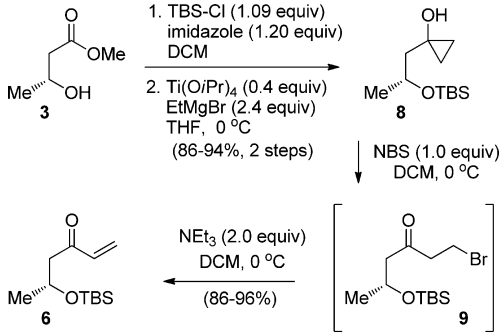
**Scheme 2. Literature route to vinyl ketone 6 based on Kulinkovich cyclopropanation/oxidative fragmentation**




transformations were very high (87% and 95% respectively), although no procedures were reported. Intrigued by this result, we began to evaluate this strategy with regards to scalability and reproducibility. If this approach could be used on scale, it would have the advantage of obviating the requirement for the vinyl Grignard reagent, the inconsistent quality of which caused significant problems during the previous scale-up campaign.

During initial lab-scale investigations (<250 g), alcohol **3**[4] was protected as the TBS-silyl ether, and then a 2-MeTHF solution of this compound was treated with stoichiometric titanium(IV) isopropoxide (1.1 equiv) and ethyl magnesium bromide (3.0 equiv). After complete consumption of the starting material, quench of the reaction with aqueous ammonium chloride led to a large amount of black precipitate which was removed by filtration. This reaction performed as reported, and after workup the product was isolated in very high purity and yield (>90%) without further purification. To lessen the burden of the filtration on scale, a catalytic version of this transformation was developed (0.4 equiv $Ti(OiPr)_4$, 2.40 equiv of EtMgBr) to minimize titanium-derived salt formation[5] (Scheme 3). This procedure was scaled to produce 73.7 kg of **8**

**Scheme 3. Kilogram-scale conditions for conversion of ester 3 to vinyl ketone 6 on scale**



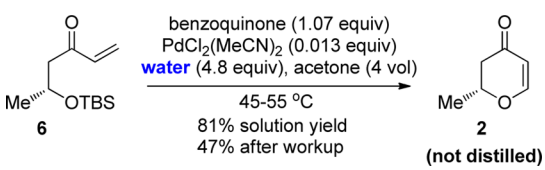

(94.3% yield) without issue. While successful, we realized that it would be optimal to remove the filtration of the titanium-derived salts entirely. For the subsequent delivery, the process was simplified through the introduction of a 20% aqueous citric acid wash to adjust the pH to 2−3 which solubilized the solids. This led to easily separable layers, with minimal impact on yield (506 kg of **8** produced, 85.9−90.7% yield).

**Development of Oxidative Fragmentation Process.** With a viable process to cyclopropanol **8** in hand, we began to examine the oxidative fragmentation to produce vinyl ketone **6**. Again, the reaction performed as described in the initial communication, and high-quality product could be isolated without purification in >90% yield on lab scales (up to 250 g). In practice the reaction is performed as a two-stage process. First, cyclopropanol **8** is treated with NBS (1.0 equiv), added in multiple portions to control the reaction exotherm; then the intermediate $\beta$-bromoketone **9** is converted to vinyl ketone **6** upon addition of triethylamine (2.0 equiv). This process was scaled to produce high-quality **6** (>450 kg, yield 86−96%), with aqueous extractions being the only means of purification during the three-step process. This was a welcome outcome, as further purification would require reduced-pressure distillation as all of the intermediates in this sequence are oils. The overall three-step yield (89% lab scale, 82% multikg scale) to vinyl ketone **6** from ester **3** compares favorably to the yields obtained using the AZ route (27−48%), and has the additional advantages of not requiring cryogenic (−20 °C) temperatures or vinyl-magnesium bromide.

With a scalable route to **6** in place, we set out to further optimize the oxidative cyclization. The reported yield for this transformation in the AZ communication was 40%, but this was a combined yield obtained in two separate operations: (1) the initial product distillation, and (2) recovery of additional product by back extraction of the aqueous followed by a second distillation. This modest yield not only is a testament to the difficulty of the transformation but is also due to the inherent properties of **2** (volatility, water solubility, acid/base instability) complicating the isolation. The sensitivity of **2** towards acid/base led us to develop a process that did not require additional acid for the removal of the TBS-group.

A 1985 report by Lipshutz includes the serendipitous result that $PdCl_2(MeCN)_2$ can remove TBS-groups from alcohols.[6] A follow up report by Keay suggested that the effectiveness of this deprotection is enhanced by the inclusion of a few equivalents of water.[7] Since this is the same catalyst utilized in our oxidative cyclization, we were curious to see how the transformation would proceed without additional acid. Performing the reaction via a modified AZ procedure (5 equiv of water were used instead of aq HCl) led to rapid removal of the TBS-group to liberate the free-alcohol. This compound then efficiently cyclized to form compound **2**. In-process yields as high as 81% have been achieved for this acid-free transformation on kilogram scale, but the yield for the product after workup was only slightly improved (47%, Scheme 4). The discrepancy

**Scheme 4. "Acid-free" oxidative Heck cyclization**




between the in-process and workup yields is a direct result of the physical properties of **2** and their impact during processing. Significant loss (20−30%) was realized upon solvent swaps due to the volatility of **2**, and 10% was lost to the aqueous washes due to water solubility. No attempt was made in this campaign to recover this material as the improvement in yield brought on by the Kulinkovich/oxidative fragmentation pathway to **6** allowed us to satisfy our delivery requirement even with this loss. Performing the solvent swap with better vacuum control, and recovery of the material lost to the aqueous stream would likely increase the yield in subsequent campaigns. Running the reaction on lab scales has led to isolation of **2** in yields ranging from 65 to 72%. It should be noted that the modified oxidative Heck procedure (no additional acid), produced high-quality material after workup. The THF stream resulting from solvent swap could be directly utilized in the methyl cuprate addition without further purification.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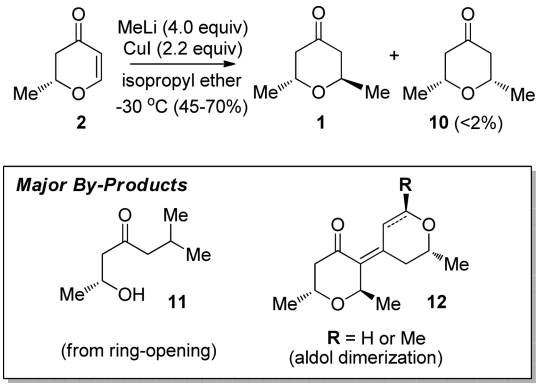
Although the acid-free oxidative Heck process offered the potential for significant yield increase, separation of the product from the benzoquinone/hydroquinone (BQ/HQ) by methods other than product distillation remained a challenge. This was hoped to be avoided, due to timeline constraints and the volatile nature of the product leading to additional losses during distillation. Lab-scale experiments demonstrated that BQ/HQ could be effectively precipitated from DCM and removed by filtration. Upon further evaluation of this protocol, reproducibility issues were encountered, and in some cases >10 mol % of BQ/HQ was present in the THF stream of **2** after workup. As an alternative, the kilogram-scale batches utilized the non-optimal process of washing the DCM stream of **2** with aq LiOH (1.5 equiv with respect to HQ quantitation). Although minimal degradation was encountered during the <2 h necessary to perform this operation, we were aware of potential problems imposed by the base sensitivity of enone **2**. Despite the risk, the LiOH protocol produced material (15.3 kg) of sufficiently high quality which could be used in the next transformation without additional purification.

**Methyl Cuprate Process Development.** With a more robust process to prepare **2**, we next turned our attention to the final transformation (methyl cuprate addition) which presented significant challenges. The procedure utilized for the first campaign is displayed in Scheme 5, and consisted of addition of a solution of enone **2** to a slurry of methyl cuprate reagent. This process presented many technical complications on scale, such as extremely thick and difficult to stir slurries, poor mass balance, variable yields, and the issues arising from the required removal of 6.2 equiv of metal salts (4 equiv Li, 2.2 equiv Cu). The major byproducts detected were the *cis*-diastereomer (**10**), the compound resulting from ring-opening after initial cuprate addition and subsequent addition of a second cuprate to generate **11**, and a mixture of aldol dimerization products (**12**) (at least two visible by GC). The levels of the dimerization products could be as high as 15% and thus were a major source of yield loss. Performing the reaction at −30 °C controlled the level of ring-opening product **11** (<5%) and the *cis*-diastereomer (<2%). Due to the poor mass balance, variable yields (45−70% before purification), and the equipment limitations set forth by the requirement of a −30 °C reaction temperature, this procedure was performed on a maximum scale of 500 g. As a result, 18 batches were necessary to provide the desired 5.0 kg of dimethyl pyranone **1**.

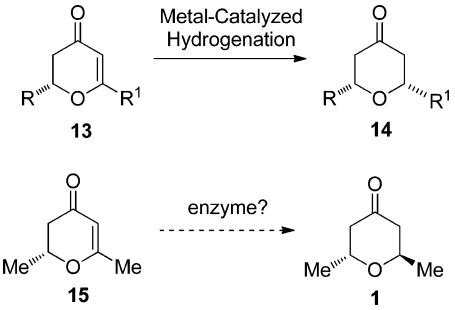
**Scheme 5. Initial procedure used to produce 1, and major byproducts that are generated in the process**




To better understand the variability of the conjugate addition process, we utilized in-process IR to monitor the consumption of the enone on laboratory scale. A reverse addition protocol, where the cuprate slurry was slowly added to a solution of the enone at −20 °C, clearly suggested that the reaction was dose controlled.[8] This finding indicated that efficient mixing during this process is essential, a requirement difficult to achieve even on 500 g scale due to the density of the cuprate slurry. It should be noted that, although process modifications such as the inclusion of a stoichiometric equivalent of lithium bromide with respect to copper could be used to produce a near-homogeneous cuprate slurry,[9] this protocol was found to be extremely sensitive to moisture (during charging) and was not robust. As our quantity requirements for **1** were increasing, we knew the limitations associated with this process would hinder throughput moving forward. We began simultaneously evaluating the following two options: modification of the cuprate addition protocol to arrive at a more robust and scalable process, and an alternative strategy where an enzyme-mediated reduction would allow for the methyl group to be installed by methods that do not rely on conjugate addition.

**Search for an Enzymatic Solution To Set Relative Configuration of Methyl Groups.** The literature is replete with examples of metal-catalyzed hydrogenation of enone substrates such as **13** producing the 2,6-*cis*-substituted product (**14**).[10] It was postulated that an enzymatic reduction might override the inherent facial bias induced by the existing chiral center, allowing us to access the *trans*-pyranone **1**. Examples of asymmetric enzymatic reductions of *β*-substituted cyclohexenones are known,[11] but to the best of our knowledge, no examples have been reported where the ring contains the additional oxygen found in the pyranone structure (Scheme 6).

**Scheme 6. Proposed biocatalytic generation of 1**




The synthesis of the proposed enzymatic reduction substrate **15**, has already been reported by Xian,[12] but due to the amounts that we would potentially require, we began evaluating alternative syntheses.

Gouverneur has reported the gold-(I)-catalyzed oxy-Michael cyclizations of *β*-hydroxy ynones,[13] providing support that this strategy could be a viable option to access enzymatic substrate **15**. Although the yield for this reported transformation was low (34%), unreacted starting material accounted for the remainder of the material balance, so we were optimistic that we could further improve the yields of this process with our substrate. Addition of propynyl Grignard to TES-protected Weinreb amide **17** (prepared from ethyl ester **16**) led to cyclization substrate **18** (Scheme 7). Initial Au(I)-catalyzed cyclization attempts in DCM and $CDCl_3$ provided inconsistent yields. It was found that the presence of water (2 equiv) assisted in silyl protecting group removal (similar to the oxidative Heck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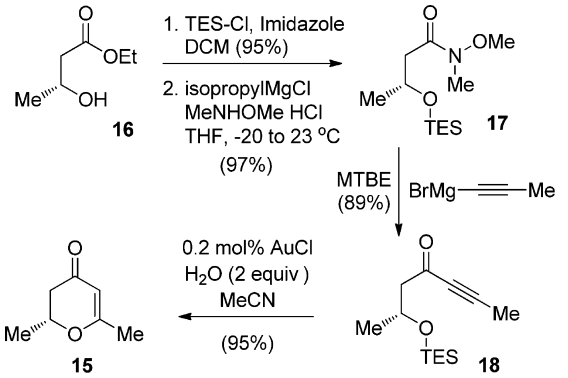
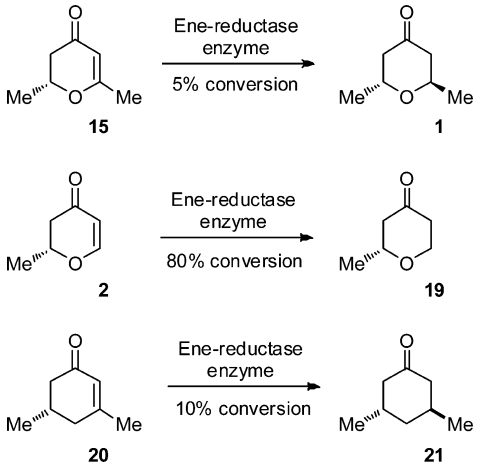
**Scheme 7. Synthesis of enzymatic reduction substrate 15**




reaction, **6** to **2**) which greatly increased the rate and yield of this reaction. Using a solvent that is miscible with water (acetonitrile) produced more consistent reaction rates, and catalyst loadings as low as 0.2 mol % produced enone **15** in 95% yield. In addition to the excellent yield for this transformation, this mode of closure has the advantage of not requiring a co-oxidant such as benzoquinone, the removal of which greatly complicated product isolation in the oxidative Heck reaction to form **2**.

With a route that would provide gram quantities of enone **15** in hand, we needed to evaluate the plausibility of the enzymatic reduction before investing additional effort into developing a scalable synthesis of this intermediate.[14] After extensive screening of commercially available ene-reductase enzymes, the enzymatic reduction of the double bond would not proceed further than 5% conversion (Scheme 8). Although this result

**Scheme 8. Effect of $\beta$-methyl group on enzymatic reduction**




was disappointing, it is noteworthy that the product that formed was the desired 2,6-*trans*-dimethylpyranone (**1**), with no indication of the 2,6-*cis* compound **10**. To determine the cause of the poor conversion, ene-reductase-catalyzed reduction of substrate analogues was investigated. Pyrenone **2** showed up to 80% conversion, indicating that oxygen could be tolerated adjacent to the olefin. To the best of our knowledge, this is the first report of ene-reductase-catalyzed reduction of a pyrenone. No available ene-reductases were found to reduce 2,6-dimethyl-4-pyrone, while 4-pyrone was reduced by many ene-reductase enzymes. Also, while cyclohex-2-enone showed complete reduction, reduction of 3,5-dimethyl cyclohex-2-enone (**20**) only proceeded to ~10% conversion. Taken together, these results implicate the presence of the methyl group on the olefin as the primary reason for the poor reactivity of **15**. Initial efforts to improve the reduction of **15** through directed evolution of the relevant enzyme resulted in a ~3-fold increase in conversion without impacting the diastereoselectivity, which could potentially be further improved with additional optimization of the enzyme. This evolved enzyme also gave 100% reduction of 3,5-dimethyl cyclohex-2-enone (**20**).

**Process Change to a Copper-Catalyzed Grignard Addition.** On the basis of the difficulties with increasing the conversion of the enzymatic transformation, and the delivery timelines associated with the need of intermediate **1**, we fully invested our efforts into making the cuprate addition to enone **2** more robust. In an attempt to enhance the reproducibility and yield of the cuprate addition for the upcoming campaigns, we needed to address the issues encountered with the original process; (1) difficult to stir reaction slurry, (2) cryogenic (−30 °C) conditions, (3) dimerization and ring-opening byproducts, (4) 6 equiv of metal in the reaction, and (5) poorly reproducible yields (45−70%). Changing the process to a copper-catalyzed Grignard addition could, in theory, overcome the problems encountered with the thick cuprate slurry and the need to remove 6 equiv of metals from the reaction stream. Inclusion of TMS-Cl in the reaction should also prevent the aldol dimerization product as well as the byproduct from double addition. A deprotection strategy, either as part of the workup or as a second independent step, would have to be included to remove the fairly labile trimethylsilyl group.

Evaluation of the copper-catalyzed Grignard addition in the absence of TMS-Cl determined that CuCl (vs CuBr or CuI) was the optimum Cu(I) source and could be used in levels as low as 2%. Addition of MeMgCl (1.2 equiv) over 20−30 min to a thin slurry of CuCl (2−5%) and enone **2** at −20 °C led to results comparable to the stoichiometric cuprate process. Less than 2% of the 1,2-addition product was observed; however, the double addition product **11** and dimerization products **12** and the *cis*-diastereomer **10** were still present at similar levels.

Performing the copper-catalyzed process in the presence of TMS-Cl (1.5 equiv), led to a vast improvement with respect to impurities **11** and **12**, as trapping of the enolate as the silyl enol ether prevented ring-opening and dimerization. It is known that the inclusion of TMS-Cl in cuprate conjugate addition reactions produces a more reactive cuprate reagent[15] and can also alter the diastereoselectivity[16] (vs the non-TMS-Cl process). Unfortunately, TMS-Cl had a detrimental impact on the *trans*/*cis* ratio of our process (Scheme 9),[17] which could be offset by running the reaction at −40 °C to ensure the level of the *cis*-diastereomer was below 2%. Running the reaction at −5 °C produced the *cis*-diastereomer **10** in levels as high as 11%. The distillation of **1** is not an effective process for the removal of **10**, and as a result, the limit of the *cis*-diastereomer was set at 2% based on the ability to remove this impurity in the downstream chemistry. One of the goals of the redesigned process was to allow the reaction to be run at the more manageable temperature of −20 °C or above (vs −30 °C in the previous campaign). The impact of TMS-Cl was counter-productive with our desire to increase the reaction temperature, but TMS-Cl was necessary to control the level of the other impurities (**11** and **12**). We reasoned that if we could temper the reactivity of the active copper species, it could be possible to return to the high level of *trans*-selectivity previously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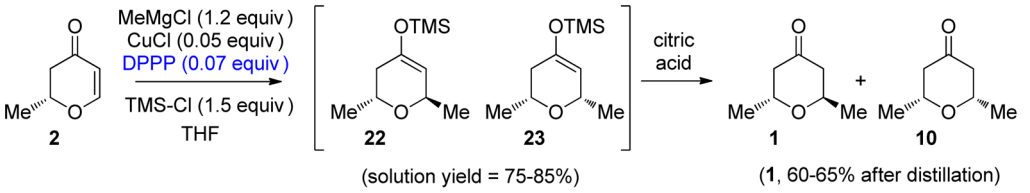
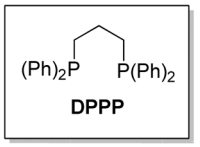
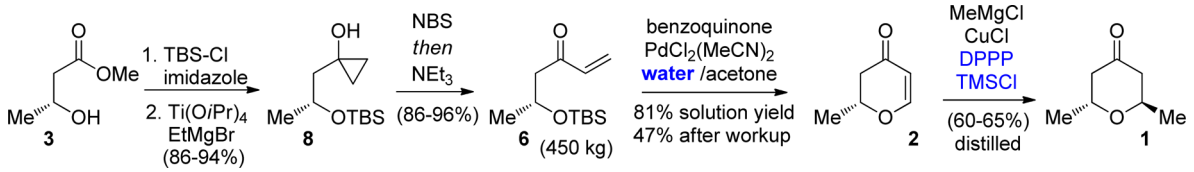
**Scheme 9. Copper-catalyzed Grignard addition, and the effect of DPPP on diastereoselectivity**




| Temperature (°C) | Level of 10 (%) | |
|---|---|---|
| | Without DPPP | With DPPP |
| +4 | -- | 2.7 |
| -5 | 9-11 | -- |
| -10 | 6.0 | -- |
| -15 | -- | 1.7 |
| -20 | 3-4 | 1.5 |
| -30 | 2.2-2.7 | 1.4 |
| -40 | 2 | -- |

**Scheme 10. Overall process to prepare dimethylpyranone 1; only distillation of the final product was required for purification**




observed, and consequently allow operation at a higher reaction temperature.

Chiral phosphine ligands have been extensively studied for the enantioselective conjugate addition of carbon nucleophiles to enones.[18] Guided by an account by Feringa[19] which reports the copper-catalyzed asymmetric conjugate addition of Grignard reagents to cyclic enones (>95% ee), we wondered if we could use a bulky phosphine ligand to return the level of facial selectivity we observed prior to TMS-Cl inclusion. We assumed that the use of more exotic/expensive chiral phosphine ligands would not be required, as the stereocenter already present in the molecule should direct the addition. Inclusion of the readily available bidentate ligand 1,3-bis(diphenylphosphino)propane (DPPP) (7 mol % for 5 mol % CuCl), had a significant impact on the diastereoselectivity of the addition (Scheme 9). The reaction could now be run at temperatures as high as −15 °C while maintaining *cis*-diastereomer **10** below the required limit (<2%). Remarkably, reactions conducted at 4 °C in the presence of DPPP produced only 2.7% of **10**. Removal of the DPPP from the product was facilitated by its low solubility in MTBE, the workup solvent for the reaction. The majority of the ligand was removed by filtration prior to TMS−enol ether hydrolysis. Catalyst loadings as low as 1 mol % CuCl and 2 mol % DPPP produced 1.9% of the *cis* compound at −20 °C. The more economical triphenyl phosphine (0.15 equiv for 0.05 equiv of CuCl) was also examined. While the diastereomer **10** was formed in an acceptable level of 1.9% at −20 °C, the reaction profile was not as clean, and ligand removal proved to be more difficult. These challenges led us to proceed with the DPPP reaction conditions.

Hydrolysis of the intermediate TMS-enol ether (**22**/**23**) was straightforward. Washing the organic workup stream with 1 M aqueous citric acid led to rapid conversion to **1**/**10**. Purification via careful distillation yielded dimethylpyranone **1** as a colorless oil on lab scale (62%, 1.8% **10**). Although there was little reduction in the level of *cis*-diastereomer **10** during distillation, the level in the isolated product was <2.0% and was adequate for the project needs. Although the program that utilized this intermediate was terminated prior to demonstration of this new process on kilogram scale, our development experience and lab results suggested this would have been a scalable process capable of delivering kilogram quantities of **1** in good yield and quality.

## CONCLUSION

The Ti(O*i*Pr)$_4$ Kulinkovich cyclopropanation/oxidative fragmentation strategy to **6** increased the overall yield to this intermediate from 27%−48% to 82%. This alternative route offered the additional benefits wherein purification, cryogenic conditions, and vinyl magnesium bromide were no longer required. The oxidative Heck conversion of **6** to **2** was made more robust by developing an acid-free cyclization process. Although the demonstrated yield was only slightly improved (47 vs 40%), the in-process yield was high (81%), and areas for yield improvements were identified: (1) more controlled concentrations (20−30% loss during solvent distillation) and (2) additional back extractions to minimize loss to the aqueous stream (10%). A copper-catalyzed Grignard conjugate addition in the presence of trimethylsilyl chloride was demonstrated to overcome the issues that were encountered with the previous standard cuprate addition process. To obtain a sufficient level of diastereoselectivity during the conjugate addition it was necessary to increase the steric bulk of the active species via the addition of DPPP. This led to the *cis*/*trans* selectivity being less susceptible to temperature effects and allowed us to effectively control the level of the undesired diastereomer and impurities to produce high quality *trans*-dimethylpyranone (see Scheme 10 for overall process).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## EXPERIMENTAL SECTION

**General.** Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica plates (60F-254), using basic potassium permanganate stain and heat as the visualizing agent. For reactions monitored by GC, a Hewlett-Packard HP6890 with an auto injector was utilized (ZB-1701 Column, 30 m × 0.32 mm × 1.0 $\mu$m; carrier = helium at 2.0 mL/min; oven temp 65 °C for 1 min, 5 °C/min to 220 °C, hold 1 min, 33 min run time; inlet (front) 200 °C, split 20:1, gas saver 15 mL/min at 2 min; detection FID (rear) 280 °C, 30 mL/min hydrogen + 300 mL/min air). Reported yields are for isolated materials or calculated solution yields and are corrected for potency.

**(*R*)-1-(2-((*tert*-Butyldimethylsilyl)oxy)propyl)-cyclopropanol (8).** DCM (164.4 kg) was added to a reactor, followed by methyl (*R*)-3-hydroxybutyrate (**3**) (43.1 kg, 364.8 mol, 1.0 equiv) and imidazole (29.7 kg, 436.3 mol, 1.2 equiv). Once the solid dissolved, the solution was cooled to 0−10 °C, and a solution of TBS-Cl (60.2 kg, 399.4 mol, 1.09 equiv) in DCM (65.0 kg) was added at a rate of 60−90 kg/h. Once the addition was complete, the reactor contents were warmed to 20−25 °C over 90 min and stirred for 5 h. The reaction was complete by GC (<3% SM vs silylated **3**), and water (215.1 kg) was added. After mixing for 30 min, the layers were separated, and the aqueous was extracted with DCM (200.5 kg). The combined organics were washed with water (129 kg), and the DCM solution of silylated **3** was dried with activated molecular sieves (20.2 kg) for 3 h to a KF < 0.05%. The molecular sieves were removed by filtration, and the cake was washed with DCM (2 × 50 kg). The filtrate and rinses were combined. The organic stream was concentrated under reduced pressure (<50 °C) until 100−150 L remained. THF (221.0 kg) was added, and the mixture was concentrated under reduced pressure until <0.5% DCM remained. THF (430 kg) was added, leading to a 16.6 wt % solution of silylated **3** in THF. The mixture was cooled to 16 °C, and titanium(IV) isopropoxide (41.3 kg, 145.0 mol, 0.40 equiv) was added. After cooling to 0 °C, a THF solution (889.1 kg) of 13.1 wt % ethyl magnesium bromide (116.5 kg, 874.2 mol, 2.40 equiv) was added at a rate of 60−150 kg/h (11 h total). After stirring an additional 2 h, GC indicated reaction completion (<1% of silylated **3** vs **8**). The reaction was cooled to 0 °C, and a 20 wt % aqueous $NH_4Cl$ solution (300.0 kg) was added slowly as an initial exotherm and gas evolution was observed. After this portion was added, an additional 20 wt % aqueous $NH_4Cl$ (544.4 kg) was added at a rate (200−300 kg/h) to maintain the temperature below 20 °C (2 h 20 min). The resulting slurry was stirred for 30 min and then filtered with a centrifuge. The cake was washed with MTBE (161.6 + 160.8 kg), with the cake being soaked for 1 h before solvent removal. The filtrate and the rinses were combined, stirred for 30 min, held for 30 min, and then separated. The aqueous phase was extracted with MTBE (96.2 kg) and this wash combined with the other organic stream. This produced 1524.4 kg of a 5.2 wt % solution of cyclopropanol **8** (79.3 kg, 344.1 mol, 94.3%). The stream was then solvent swapped to DCM (<0.5% MTBE) for use in the next step, as subsequent purification was not required. A small portion of this material was isolated via flash column chromatography on silica gel (5% ethyl acetate in hexanes as eluent) for characterization purposes. Colorless oil, $R_f$ = 0.40 (10% ethyl acetate in hexanes); **$^1$H NMR** ($CDCl_3$, 400 MHz) 4.29−4.21 (m, 1 H), 3.93 (br. s, 1 H), 1.82 (ddd, $J$ = 14.4, 7.4, 1.3 Hz, 1 H), 1.63 (ddd, $J$ = 14.4, 3.8, 1.2 Hz, 1 H), 1.26 (d, $J$ = 6.3 Hz, 3 H), 0.92 (s, 9 H), 0.84−0.78 (m, 1 H), 0.72−0.66 (m, 1 H), 0.47 (ddd, $J$ = 10.8, 6.3, 5.2 Hz, 1 H), 0.38 (ddd, $J$ = 10.8, 6.0, 4.6 Hz, 1 H), 0.14 (s, 3 H), 0.13 (s, 3 H) ppm; **$^{13}$C NMR** ($CDCl_3$, 100 MHz) 69.8, 54.9, 45.3, 25.7, 23.7, 17.8, 13.6, 11.6, −4.3, −4.9 ppm; $[\alpha]^{25}_D$ = −33.4 ($c$ = 1.0, $CHCl_3$); **HRMS** calcd for [M + H] $C_{12}H_{27}O_2Si$ = 231.1775, found = 231.1781.

**Alternative Procedure for 8 That Avoids Filtration of the Mg/Ti Salts.** A THF solution (298.24 kg of 51.3 wt %) of silylated **3** (153 kg, 623.8 mol, 1.0 equiv) and THF (1200 L) were placed in a reactor and the contents cooled to between −5 and 0 °C. Titanium(IV) isopropoxide (86.87 kg, 305.6 mol, 0.49 equiv) was added, and the reactor contents were stirred for 10−20 min. Ethyl magnesium bromide (2.0 mol/L in 2-MeTHF, 873.3 L, 1747 mol, 2.8 equiv) was added over ∼1 h, keeping the temperature between −5 and 10 °C. The reaction was then stirred at 0 to 5 °C until GC showed less than 1% of silylated **3** with respect to **8** (2 h). $NH_4Cl$ (25 wt % aqueous, 900.1 kg) was added at a rate that maintained the temperature between −5 and 10 °C (pH 8−9 after addition) and minimized initial off-gassing. 20 wt % aqueous citric acid (1002 kg) was added at a rate to maintain the temperature between −5 and 10 °C (pH 2−3 after addition), and the layers were mixed for 20 min. MTBE (291.5 kg) was added, and the reactor contents were warmed to 10−15 °C. After mixing for 30 min, the layers were separated. The aqueous was extracted with MTBE (590.1 kg) and the combined organics were washed with 7 wt % aqueous $NaHCO_3$ (610 kg, pH 7−8 after addition), and brine (2 × 650 kg). The organic layer was then concentrated to ∼600 L under reduced pressure (temp = 25 °C). DCM (1501 kg) was added, and the volume was reduced to 750 L under reduced pressure (25 °C). This distillation was repeated two more times, after which DCM (2800 kg) was added. The stream was dried with anhydrous $MgSO_4$ (22 kg), and after removal of the solid by filtration, the solution was concentrated to yield 886.8 kg of a 14.6 wt % solution of **8** (129.5 kg, 561.9 mol, 90.1% yield) in DCM. This stream could be used without purification in the subsequent step.

**(*R*)-5-((*tert*-Butyldimethylsilyl)oxy)hex-1-en-3-one (6).** DCM (983.7 kg) and a DCM stream (178.9 kg) containing 41.2 wt % cyclopropanol **8** (73.7 kg, 319.93 mol, 1.0 equiv) were placed in a reactor. The solution was cooled to between −5 and 5 °C, and *N*-bromosuccinimide (56.7 kg, 318.6 mol 1.0 equiv) was added in 5−10 kg portions in 15 min intervals (each addition is slightly exothermic). After the final addition, the reaction was stirred at −5 to 5 °C until complete by GC (<1% of **8** vs **9**), 1 h. Triethylamine (64.8 kg, 640.4 mol, 2.0 equiv) was added at a rate of 40−60 kg/h to maintain the temperature between −5 and 5 °C. The reaction was stirred at this temperature for 2 h, and was complete by GC (<1.0% **9** vs **6**). The 0 °C reaction was washed with 16.3 wt % aqueous citric acid (275.2 and 317.6 kg), and 7.9 wt % aqueous $NaHCO_3$ (217.1 kg). Hydroquinone (7.4 g, 0.067 mol, 0.0002 equiv) was added to increase product stability during solvent exchange. The solvent was removed under reduced pressure until 250−300 L remained. The concentrated stream was filtered through a nutsche filter preloaded with silica gel (16.0 kg), and the cake was washed with DCM (49.4 kg × 2). The filtrate and rinses were combined, and hydroquinone was added (7.4 g, 0.067 mol, 0.0002 equiv). The stream was concentrated under atmospheric pressure until 90−150 L remained, and then under reduced pressure (∼100 Torr, <50 °C) for 2−3 h. This yielded a stream (82.2 kg, 82.4 wt %) of **6** (67.73 kg, 296.7 mol, 92.3%)


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that could be used in the next step without further purification. **Caution**: Vinyl ketone **6** was identified as a skin sensitizer in a LLNA assay (EC3 <1%). A small portion of this material was isolated via distillation for characterization purposes. Colorless oil, **BP** = 89−91 °C at 4−5 mmHg; **$^1$H NMR** ($CDCl_3$, 400 MHz) 6.36 (dd, $J$ = 17.5, 10.5 Hz, 1 H), 6.22 (d, $J$ = 17.5 Hz, 1 H), 5.85 (d, $J$ = 10.5 Hz, 1 H), 4.38−4.30 (ddd, $J$ = 7.2, 6.0, 5.2 Hz, 1 H), 2.85 (dd, $J$ = 14.8, 7.2 Hz, 1 H), 2.54 (dd, $J$ = 14.8, 5.2 Hz, 1 H), 1.20 (d, $J$ = 6.0 Hz, 3 H), 0.85 (s, 9 H), 0.06 (s, 3 H), 0.02 (s, 3 H) ppm; **$^{13}$C NMR** ($CDCl_3$, 100 MHz) 199.6, 137.5, 128.5, 65.8, 49.1, 25.8, 24.2, 18.0, −4.6, −5.0 ppm; $[\alpha]^{25}_D$ = −33.3 ($c$ = 1.0, $CHCl_3$); **HRMS** calcd for [M + H] $C_{12}H_{25}O_2Si$ = 229.1618, found = 229.1623.

**(*R*)-2-Methyl-2*H*-pyran-4(3*H*)-one (2).** Acetone (213.6 kg), purified water (26.0 kg, 1443 mol, 4.8 equiv), benzoquinone (34.4 kg, 318.3 mol, 1.07 equiv), and bis-(acetonitrile)dichloropalladium (0.99 kg, 3.82 mol, 0.013 equiv) were charged to a reactor. The reactor contents were heated to 45−50 °C, and compound **6** (80 kg of 82.5 wt % from above, 68.0 kg, 297.7 mol, 1.0 equiv) was added at a constant rate over 2 h. The reaction was held at this temperature until complete (<1.5% of **6** vs **2** by GC), typically 3−4 h. The reaction was cooled to 20 °C, and the mixture was concentrated under reduced pressure (>160 Torr, 14−28 °C) until 120−150 L remained. Water (266 kg) was added, the reactor contents were cooled to 0−10 °C, and stirred at this temperature for 2 h. The resulting slurry was filtered and the cake washed with water (3 × 67 kg). The filtrate and all rinses were combined. *n*-Hexane (44.0 kg) was added to the combined filtrates, and the mixture was stirred at 15−25 °C for 40 min. The layers were separated, and the aqueous was washed further with *n*-hexane (44.0 + 43.9 kg). The combined *n*-hexane washes were washed with water (2 × 33.3 kg), and aqueous fractions were combined. Dichloromethane (267.1 kg) and sodium chloride (96.2 kg) were added to the aqueous, and the layers were mixed for 40 min, before being allowed to stand for 40 min. The layers were separated, and the aqueous was extracted with DCM (400.2 kg). Analysis of the organic layer determined the level of hydroquinone (26.2 kg, 237.9 mol) present. The organic was washed with a solution of lithium hydroxide (14.9 kg, 355.1 mol, 1.5 equiv vs hydroquinone) in water (297.9 kg) for 15 min, before separating the layers. The organic was washed with a solution of sodium dihydrogen phosphate (0.9 kg) and disodium hydrogen phosphate (2.5 kg) in water (50 kg) to adjust the pH. The aqueous layer from this wash was back extracted with DCM (198.9 kg), and this organic wash was combined with the previous. The organic phase was dried with 4 Å molecular sieve powder (10.0 kg) for 3−4 h, after which an additional 5 kg of molecular sieves was added and stirring continued for 1−2 h (this was repeated one additional time). At this point the KF of the solution was <0.05%. The molecular sieves were removed by filtration. The cake was washed with THF (2 × 66.5 kg), and these washes were initially kept separate. The DCM filtrate was concentrated at atmospheric pressure (<50 °C) until 50−90 L remained, and then the pressure was reduced to 300 Torr until 30−60 L remained. The THF from the cake washes was added, and the distillation continued to a volume of 30 L. THF (99.8 kg) was added, and the concentration continued until the level of DCM and acetone were <0.5 vol %. This resulted in a 95.4 kg stream containing 16.0 wt % of **2** (15.4 kg, 137.4 mol, 46% yield). This material was of sufficient purity to be used in the next step without further purification. A small portion of this material was isolated via distillation for characterization purposes. Colorless oil, **BP** = 63−65 °C at 15 mmHg; **$^1$H NMR** ($CDCl_3$, 400 MHz) 7.33 (d, $J$ = 6.0 Hz, 1 H), 5.38 (dd, $J$ = 6.0, 1.0 Hz, 1 H), 4.59−4.49 (m, 1 H), 2.45 (dd, $J$ = 16.6, 12.6 Hz, 1 H), 2.42 (ddd, $J$ = 16.6, 4.6, 1.0 Hz, 1 H), 1.44 (d, $J$ = 6.6 Hz, 3 H) ppm; **$^{13}$C NMR** ($CDCl_3$, 100 MHz) 192.4, 163.1, 106.6, 75.8, 43.2, 20.1 ppm; $[\alpha]^{25}_D$ = +205.7 ($c$ = 1.0, $CHCl_3$); **HRMS** calcd for [M + H] $C_6H_9O_2$ = 113.0597, found =113.0602.

**(2*R*,6*R*)-2,6-Dimethyldihydro-2*H*-pyran-4(3*H*)-one (1) via Stoichiometric Cuprate on 500 g Scale.** Copper(I) iodide (1.87 kg, 9.81 mol, 2.2 equiv) was slurried in dry isopropyl ether (5.0 L) and cooled to 0 °C. A solution of methyl lithium (3.0 M in diethoxymethane, 5.94 L, 17.83 mol, 4.0 equiv) was added to the CuI slurry, and the mixture was stirred for 30 min at 0 °C. The bright-yellow slurry was cooled to −20 to −30 °C, and crude **2** (500 g, 4.46 mol, 1.0 equiv) in isopropyl ether (7.5 L) was added over 10 min. The reaction was then stirred at −20 to −30 °C for 30 min, and then added to 1.0 M aqueous HCl (3 L) that was previously cooled to 0 °C. After stirring for 20 min, the gray suspension was filtered, and the filtrate was extracted with MTBE (2 × 3 L). The combined organics were dried with $MgSO_4$, filtered, and then concentrated to yield crude **1** (394.4 g, 3.08 mol, 69% yield). This material could be further purified by distillation. For distillation conditions and characterization data, see copper-catalyzed Grignard addition procedure that follows. As mentioned in the text, this procedure produced variable yields before distillation, ranging from 45 to 70%.

**Ethyl (*R*)-3-((Triethylsilyl)oxy)butanoate Silylated 16.** Ethyl (*R*)-(−)-3-hydroxybutyrate (**16**) (70.0 g, 0.520 mol, 1.0 equiv) was dissolved in dichloromethane (840 mL) and cooled to 0 °C. Imidazole (70.0 g, 1.03 mol, 2.0 equiv) was added and stirred until completely dissolved. Chlorotriethylsilane (93.7 mL, 0.556 mol, 1.05 equiv) was slowly added to the mixture which was then allowed to warm to 20 °C and stirred for 18 h. Water (700 mL) was added, and the phases were separated. The aqueous layer was washed with dichloromethane (300 mL). The combined organics were then washed with water (200 mL) and brine (200 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford ethyl (*R*)-3-((triethylsilyl)oxy)butanoate (silylated **16**, 123.0 g, 499.2 mmol, 96% yield) as a clear, colorless oil. This material could be used in the subsequent step without additional purification. $R_f$ = 0.62 (20% ethyl acetate in hexanes); **$^1$H NMR** ($CDCl_3$, 500 MHz) 4.33−4.23 (m, 1 H), 4.17−4.06 (m, 2 H), 2.48 (dd, $J$ = 14.6, 7.3 Hz, 1 H), 2.36 (dd, $J$ = 14.6, 5.6 Hz, 1H), 1.25 (t, $J$ = 7.2 Hz, 3 H), 1.21 (d, $J$ = 6.1 Hz, 3 H), 0.94 (t, $J$ = 8.0 Hz, 9 H), 0.59 (q, $J$ = 7.9 Hz, 6 H) ppm; **$^{13}$C NMR** ($CDCl_3$, 126 MHz) 171.6, 65.6, 60.2, 44.9, 23.9, 14.2, 6.7, 4.8 ppm; $[\alpha]^{25}_D$ = −21.3 ($c$ = 1.38, $CHCl_3$); **HRMS** calcd for [M + H] $C_{12}H_{27}O_3Si$ = 247.1724, found = 247.1734.

**(*R*)-*N*-Methoxy-*N*-methyl-3-((triethylsilyl)oxy)-butanamide (17).** Silylated **16** (60.0 g, 244 mmol, 1.0 equiv) was dissolved in tetrahydrofuran (0.60 L). *N*,*O*-dimethylhydroxylamine hydrochloride (36.8 g, 337 mmol, 1.55 equiv), was added, and after complete dissolution the solution was cooled to −31 °C. To this mixture was added isopropylmagnesium chloride (2.0 mol/L in THF, 360 mL, 720 mmol, 2.96 equiv) over 25 min to maintain the temperature below −15 °C. Once addition was complete, the reaction was maintained at −20 °C for 2 h followed by quenching with saturated aqueous $NH_4Cl$ (400 mL). The solution was allowed to warm to 20 °C and stirred overnight. The phases were separated, and the aqueous


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layer was extracted with MTBE (2 × 100 mL). The combined organics were dried over $MgSO_4$. Removal of solvent under reduced pressure afforded Weinreb amide **17** (60.0 g, 230 mmol, 94% yield) as a light-brown oil, which could be used directly in the subsequent step. A small portion of this material was purified by flash column chromatography on silica gel. $R_f$ = 0.28 (20% ethyl acetate in hexanes); **$^1$H NMR** ($CDCl_3$, 500 MHz) 4.41−4.32 (m, 1 H), 3.70 (s, 3 H), 3.18 (s, 3 H), 2.78 (dd, $J$ = 14.2, 6.3 Hz, 1 H), 2.40 (dd, $J$ = 14.8, 5.7 Hz, 1 H), 1.24 (d, $J$ = 6.0 Hz, 3 H), 0.95 (t, $J$ = 8.0 Hz, 9 H), 0.61 (q, $J$ = 8.1 Hz, 6 H) ppm; **$^{13}$C NMR** ($CDCl_3$, 126 MHz) 172.2, 65.6, 61.1, 41.7, 31.8, 24.1, 6.6, 4.6 ppm; $[\alpha]^{25}_D$ = −14.3 ($c$ = 0.86, $CHCl_3$); **HRMS** calcd for [M + H] $C_{12}H_{28}O_3NSi$ = 262.1833, found = 262.1839.

**(*R*)-6-((Triethylsilyl)oxy)hept-2-yn-4-one (18).** Weinreb amide **17** (20.0 g, 76.5 mmol, 1.0 equiv) was dissolved in MTBE (200 mL) and cooled to −40 °C. 1-Propynylmagnesium bromide (0.5 mol/L in THF, 306 mL, 153 mmol, 2.0 equiv) was added slowly to maintain the temperature below −10 °C. The reaction mixture was then allowed to warm to −2 °C over 2.5 h and then was quenched with saturated aqueous $NH_4Cl$ (300 mL). The phases were separated, and the aqueous layer was extracted with MTBE (3 × 100 mL). The combined organics were dried over $MgSO_4$, and solvent was removed under reduced pressure. The crude oil was then purified via silica gel column chromatography (300 g column, 0−20% EtOAc in hexanes gradient) to afford ynone **18** (18.4 g, 68.2 mmol, 89.2% yield) as a pale-yellow oil. $R_f$ = 0.52 (20% ethyl acetate in hexanes); **$^1$H NMR** ($CDCl_3$, 500 MHz) 4.44−4.37 (m, 1 H), 2.77 (dd, $J$ = 15.0, 7.1 Hz, 1 H), 2.58 (dd, $J$ = 15.1, 5.7 Hz, 1 H), 2.03 (s, 3H), 1.22 (d, $J$ = 6.3 Hz, 3 H), 0.96 (t, $J$ = 7.9 Hz, 9 H), 0.61 (q, $J$ = 7.9 Hz, 6 H) ppm; **$^{13}$C NMR** ($CDCl_3$, 126 MHz) 186.1, 90.1, 80.6, 65.0, 55.2, 23.9, 6.7, 4.7, 3.9 ppm; $[\alpha]^{25}_D$ = −19.5 ($c$ = 1.50, $CHCl_3$); **HRMS** calcd for [M + H] $C_{13}H_{25}O_2Si$ = 241.1618, found = 241.1624.

**(*R*)-2,6-Dimethyl-2*H*-pyran-4(3*H*)-one (15).** Ynone **18** (5.0 g, 20.8 mmol, 1 equiv) was dissolved in MeCN (50 mL), then AuCl (51 mg, 0.21 mmol, 0.01 equiv) and water (0.75 mL, 41.6 mmol, 2.0 equiv) were added. The reaction mixture was stirred at 20 °C for 18 h and then transferred to a separatory funnel and washed with hexanes (2 × 25 mL). The MeCN layer was concentrated under reduced pressure. The resulting oil contained solids and was diluted with a minimal amount of dichloromethane, filtered through a plug of silica gel eluting with dichloromethane, and concentrated to afford cyclic enone **15** (2.62 g, 20.0 mmol, 96% yield) as a light-yellow oil. This compound has been reported previously (Bianchi, G.; Tava, A. *Agric. Biol. Chem.* **1987**, *51*, 2001), and all spectroscopic data was in agreement.

**Procedure for Ene-Reductase-Mediated Reduction.** Ene-reductase (5 mg), glucose (12 mg), NADP (1 mg), glucose dehydrogenase (0.1 mg, 7.65 U from Amano), and enone (2 μL) in 1 mL 0.1 M potassium phosphate buffer pH 7 were incubated in microfuge tubes at 30 °C. Samples (0.5 mL) were extracted with 1 mL ethyl acetate and centrifuged for 5 min, and the extract (1 μL injection) was analyzed by GC. The chiral column was a BGB-174 30 m × 0.25 mm × 0.25 μm, carrier was helium 1.4 mL/min, inlet 220 °C, split 20:1. For screening for reductions the oven program was 40 °C for 2 min, 15 °C/min to 200 °C, hold for 2 min (run time = 14.67 min), and the retention times for **10** and **1** were 11.3 and 9.5 min, respectively. The oven program for separation of product enantiomers was 85 °C for 2 min, 0.5 °C/min to 96 °C, hold for 2 min, 15 °C/min to 200 °C, hold for 2 min (run time = 33 min). Detection was by FID, 270 °C 30:300 hydrogen:air mL/min. Retention times with the enantiomer separation oven program were 18.3 min for **1**, 19.2 min for *ent*-**1**, 11.8 min for the *cis* isomer **10**.

**(2*R*,6*R*)-2,6-Dimethyldihydro-2*H*-pyran-4(3*H*)-one (1) via Copper-Catalyzed Grignard Addition.** 1,3-Bis-(diphenylphosphino)propane (DPPP, 1.96 g, 4.61 mmol, 0.07 equiv), copper(I) chloride (0.33 g, 3.3 mmol, 0.05 equiv), and THF (110 mL) were added to a reactor. After stirring for 30 min, the inorganics had almost completely dissolved. Compound **2** (7.39 g, 65.9 mmol, 1.0 equiv) dissolved in THF (37 mL) was added to the Cu/ligand slurry. After stirring for 1 h, the reaction was cooled to between −15 and −20 °C, and chlorotrimethylsilane (12.9 mL, 99.0 mmol, 1.5 equiv) was added over 5 min (slight exotherm of 2 °C). Methylmagnesium chloride (26.4 mL of 3.0 M in THF, 79.2 mmol, 1.20 equiv) was added over 1 h. Once the addition was complete, the reaction was stirred for 10 min, and then transferred over 5 min to a 5 °C mixture of MTBE (100 mL) and saturated aqueous $NaHCO_3$ (100 mL) with stirring. The mixture was allowed to warm to 23 °C, and then stirred for 10 min. The layers were separated, and the aqueous was washed with MTBE (25 mL). The combined organics were washed with saturated aqueous $NH_4Cl$ (50 mL) and then brine (50 mL). At this point there was a significant amount of DPPP ligand precipitate. The mixture was then stirred overnight to precipitate more ligand and then filtered. The solution was concentrated to ∼80 mL (25 °C, 160 Torr). Quantitation at this stage showed 9.49 g of silylenol ether **22** (72%) and 0.675 g of compound **1**, for a combined solution yield of 80%. This stream was added to 1 M aqueous citric acid (100 mL) and mixed for 1 h. The layers were separated, saturated aqueous brine (5 mL) was added to the aqueous layer, and it was back extracted with MTBE (2 × 25 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (2 × 25 mL) and brine (25 mL). The MTBE product stream was passed through a short plug of silica (washing with MTBE). The solvent was removed under reduced pressure (175 Torr), and then distillation (40 Torr, 89 °C) yielded compound **1** (5.12 g, 40.57 mmol, 62% yield) as a colorless oil. The level of *cis*-diastereomer **10** was 1.8% (identical to that before distillation). Colorless oil, **bp** = 89 °C at 40 mmHg; $R_t$ (GC) = 11.83 min, (10.52 min for *cis*-compound **10**); **$^1$H NMR** ($CDCl_3$, 400 MHz) 4.36−4.29 (m, 2 H), 2.55 (ddd, $J$ = 14.2, 4.8, 1.5 Hz, 2 H), 2.24 (ddd, $J$ = 14.2, 6.6, 1.5 Hz, 2 H), 1.27 (d, $J$ = 6.6 Hz, 6 H) ppm; **$^{13}$C NMR** ($CDCl_3$, 100 MHz) 207.6, 68.2, 48.3, 20.6 ppm; $[\alpha]^{25}_D$ = +24.7 ($c$ = 1.0, $CHCl_3$); **HRMS** calcd for [M + H] $C_7H_{13}O_2$ = 129.0910, found = 129.0914.

## ■ ASSOCIATED CONTENT

### Supporting Information

$^1$H- and $^{13}$C NMR for compounds **1**, **2**, **6**, **8**, **17**, **18**, and silylated **16** (listed as **SI-2**), as well as the in situ IR cuprate addition studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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