ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D



Communication

# Development of a Robust and Highly-Selective Ru(II)-Catalyzed Dynamic Kinetic Resolution Used to Manufacture AMG 232

Austin Gerald Smith, Matthew Michael Bio, John T Colyer, Khalid DIKER, Gilles Gorins, Sian Jones, Maria V. Silva Elipe, Jason S. Tedrow, Shawn D. Walker, and Seb Caille

*Org. Process Res. Dev.*, **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.9b00427 • Publication Date (Web): 27 Mar 2020





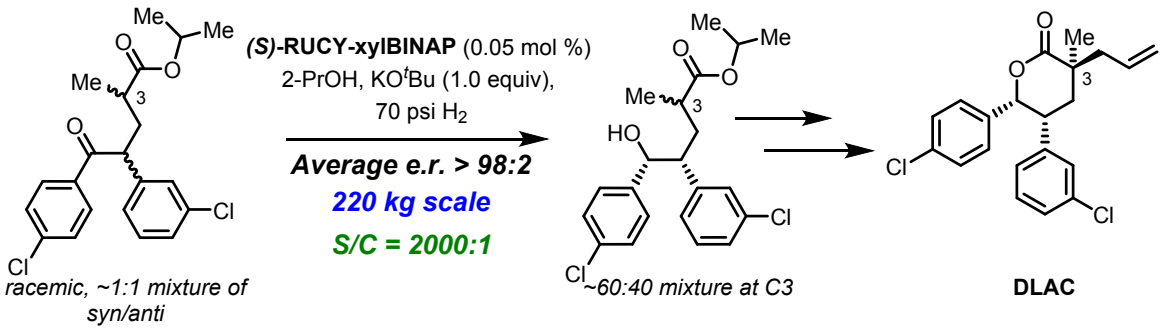
is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

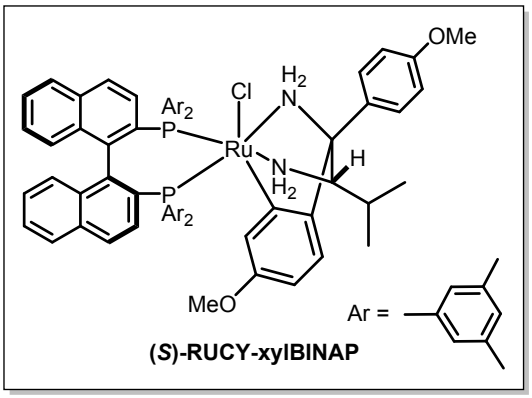
# Development of a Robust and Highly-Selective Ru(II)-Catalyzed Dynamic Kinetic Resolution Used to Manufacture AMG 232

*Austin G. Smith,* Matthew M. Bio,† John Colyer, Khalid Diker,‡ Gilles Gorins,‡ Sian C. Jones, Maria Silva Elipe, Jason S. Tedrow, Shawn D. Walker,¥ and Seb Caille*

Drug Substance Technologies, Process Development, Amgen, Inc., 1 Amgen Center Drive, Thousand Oaks, CA, 91320, United States

TOC graphic


(S)-RUCY-xylBINAP (0.05 mol %)
2-PrOH, KO$^t$Bu (1.0 equiv),
70 psi $H_2$
Average e.r. > 98:2
220 kg scale
S/C = 2000:1
racemic, ~1:1 mixture of syn/anti
~60:40 mixture at C3
DLAC


(S)-RUCY-xylBINAP
Ar =

**Abstract**

We describe herein the development of a scalable, Noyori reductive dynamic kinetic resolution (DKR) to manufacture **DLAC**, a Δ-lactone precursor to the active pharmaceutical ingredient AMG 232. Central to this work was the identification of the ruthenabicyclic complex RuCl[(*S*)-diapena][(*S*)-xylBINAP] ((*S*)-RUCY-xylBINAP), which afforded product in > 98:2 enantiomeric ratio at substrate to catalyst loadings (S/C) of 2000:1. By transesterifying to a more sterically hindered isopropyl ester prior to the hydrogenation, we were able to curb unexpected ester reduction. Optimization of base equivalents in the final alkylation step to form **DLAC** prevented product degradation. The optimized process was scaled to > 200 kg, providing 147 kg of **DLAC** in 56% overall yield and 99.9% optical purity.

**Keywords:** DKR, ketone hydrogenation, ruthenium, Noyori, catalytic, sustainable

**Introduction:** The MDM2-p53 protein-protein interaction is a hallmark of several different types of cancer.[1] Disrupting this interaction by molecularly binding to MDM2 has been shown to lead to increased cellular p53 concentration and tumor growth inhibition.[2] Amgen's discovery research group has previously reported that the densely functionalized piperidinone AMG 232 functions as an inhibitor of the MDM2-p53 interaction (**Figure 1,** structure **1**).[3] The discovery route to AMG 232 identified highly substituted Δ-lactone **2 (Figure 1, DLAC,** structure **2)** as a versatile and crystalline synthetic intermediate that could be elaborated to the final active pharmaceutical ingredient (API).[4]

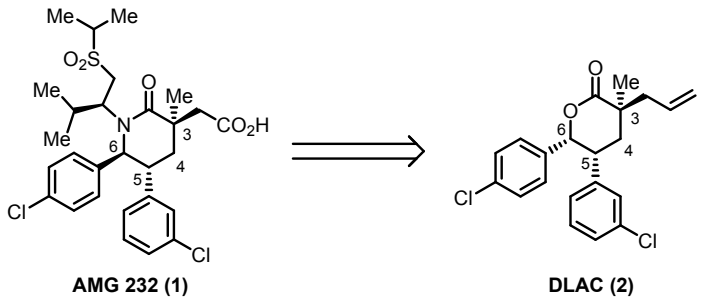



**Figure 1: Structure of MDM2-p53 inhibitor AMG 232 (1) derived from intermediate DLAC 2**

This manuscript details process development toward a scalable asymmetric synthesis of **DLAC 2** via development of a robust and highly-selective Ru(II)-catalyzed dynamic kinetic resolution (DKR). Key features of this work include the identification of ruthenabicyclic complex RuCl[(*S*)-diapena][(*S*)-xylBINAP] ((*S*)-RUCY-xylBINAP) as a highly effective catalyst for ketone hydrogenation with respect to conversion, yield, selectivity, catalyst loading, and cycle time. This report discusses an important transesterification event to prepare a more sterically hindered isopropyl ester prior to hydrogenation and thus curb unexpected byproduct formation during the reaction. We also detail process control of a deleterious carboxylic acid impurity in the starting material to optimize DKR catalyst performance. Lastly, by controlling the amount of

lithium hexamethyldisilazide (LiHMDS) used during the final alkylation to form **DLAC**, we were able to control product isomerization that was hindering yield. Comprehensive process improvements led to a 56% overall yield of **DLAC 2** on production scale. Desired product was isolated in > 90 kg as part of three separate production campaigns, including 147 kg of **DLAC** in the most recent manufacturing campaign.[5]

The discovery synthesis of **DLAC** is described in **Scheme 1**. Starting from 4-chloroacetophenone **3**, Pd-catalyzed α-arylation with *m*-bromochlorobenzene provided ketone **4** in 94% yield. After silica gel purification and crystallization, **4** was treated with 10 mol % potassium tert-butoxide (KO$^t$Bu) and methyl methacrylate in THF to provide **5** in 97% yield as a mixture of diastereomers. The diastereomeric mixture **5** was then taken into a Noyori reductive dynamic kinetic resolution using 0.3 mol% of $RuCl_2$[(*S*-xylBINAP)-(*S*-DIAPEN)] catalyst **(*S*)-6a (Figure 2)**.[3a] Product was obtained as a complex mixture of carboxyl functionality; the major product, isopropyl ester **7**, was measured to be in 96:4 er (approximately 60:40 mixture of epimers at the C3 position).[6] The ester was hydrolyzed using lithium hydroxide (LiOH), followed by treatment with pyridinium p-toluenesulfonate (PPTS) at refluxing temperature in toluene. After purification by silica gel chromatography, methyl lactone **9** was isolated in 84% yield from **5** as a 3:1 mixture of epimers at C3. Lactone **9** then underwent a highly diastereoselective alkylation using LiHMDS and allyl bromide to provide desired lactone **2** in 93% yield and 96:4 er.[7] The enantiopurity of **2** was further upgraded to 99.2:0.8 er by recrystallization from heptane.

**Scheme 1. Discovery Route to DLAC**

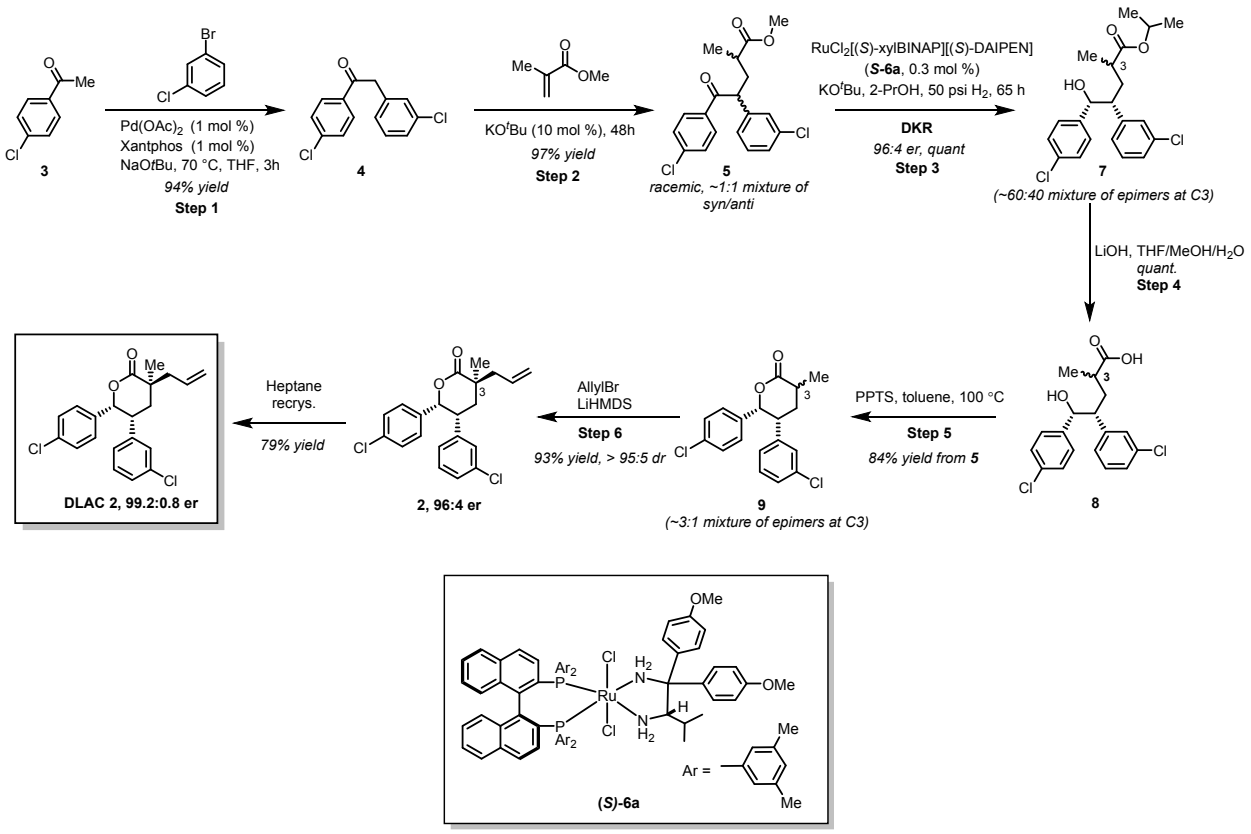
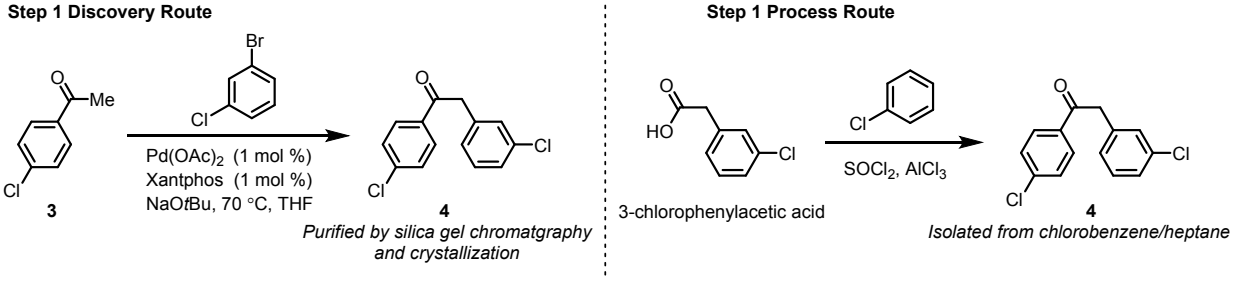



**Figure 2. Structure of catalyst $RuCl_2$[(S)-xylBINAP][(S)-DAIPEN] ((*S*)-6a).**

The discovery route shown in Scheme 1 was effective in producing multigram scale quantities of **DLAC**; however, the route suffered from high catalyst loadings, long cycle times, and issues of robustness in the DKR step. While 96:4 er was an acceptable level of enantiopurity for early phase development work, and a chiral purity upgrade of **DLAC** was possible via downstream recrystallization, an efficient process route demanded higher selectivity to minimize the mass loss observed in the final step and meet the chiral purity requirements for the API starting material. In addition, the discovery synthesis of **DLAC** required multiple chromatographic purifications, which impeded scalability and throughput. To meet the multi-kilogram clinical demands for the final API, we required a high-yielding, highly selective, scalable manufacturing route to **DLAC**.

**Process Improvements to diaryl ketone 4.** The first step in the discovery route to **DLAC** featured a $Pd(OAc)_2$/Xantphos catalyzed α-arylation of 4-chloroacetophenone to form **4**. Upon scaling, this chemistry proved to be air and water sensitive and required rigorous drying and nitrogen-sparging to avoid incomplete conversion. In addition, a silica gel purification was required prior to crystallization from diethyl ether/hexanes to remove palladium metal. To establish process robustness and enable cost reduction, we explored an alternative approach to **4** that would obviate the need for a transition-metal catalyst (**Scheme 2**). Starting from commercially available 3-chlorophenylacetic acid, Friedel-Crafts alkylation with $SOCl_2$ and $AlCl_3$ in chlorobenzene resulted in a highly selective *para*-alkylation to provide the desired diaryl ketone. The desired product was crystallized by charging 10 volumes of heptane to the concentrated chlorobenzene/ethanol/water solution containing **4**. Desired product was isolated as a white solid via filtration in 92% yield and high purity; residual chlorobenzene proved to be well tolerated in the subsequent Michael addition step.

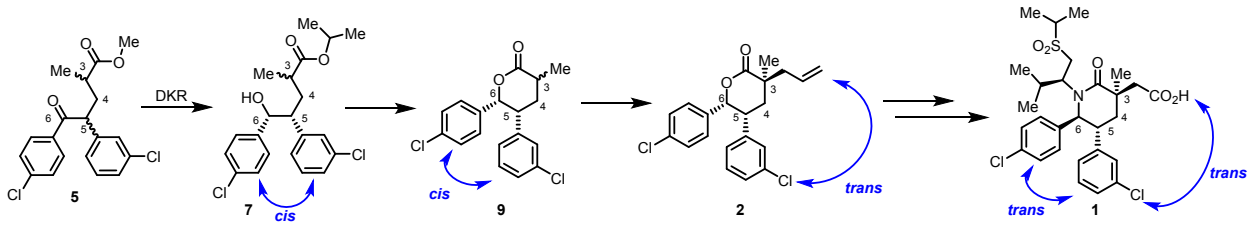
**Scheme 2. Discovery Route and Process Route to Ketone 4**




**Process Development of the DKR:** The Noyori reductive dynamic kinetic resolution from **5** to **7** described previously in Scheme 1 established both the relative and absolute stereochemical relationship of the *cis*-5,6-diaryl functionality found in **DLAC**. Additionally, the *cis*-relationship between carbon atoms C5 and C6 illustrated in methyl lactone **9** directed the highly diastereoselective alkylation used to establish the C3-quaternary center found in **DLAC**. As

previously reported, **DLAC** was further elaborated to the final API via a lactone ring-opening reaction followed by a stereospecific ring closure that proceeded with inversion of stereochemical configuration at the C6-center.[4] Thus, high selectivity in the upstream DKR step was paramount in order to control the stereochemical identity of the final API (**Scheme 3**).

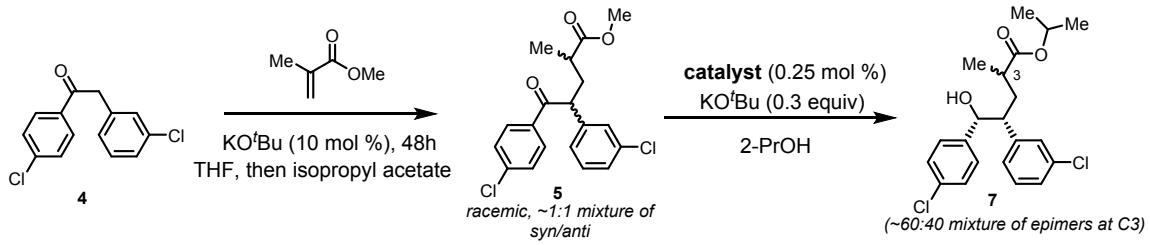
**Scheme 3. Stereochemical Relationship Established in DKR Controls the Stereochemistry of 1**




With the criticality of a reliable and highly selective Noyori ketone hydrogenation established, our attention turned to optimization of the DKR. A summary of our early DKR efforts is described in **Table 1**. Preliminary experiments with ketone **5** and catalyst **(*S*)-6a** afforded product in 92:8 er (~60:40 mixture of C3 epimers),[8] but routinely led to incomplete conversion (**Table 1**, entry 1). Elevated temperatures resulted in incomplete conversion and an erosion of enantiopurity (entry 2). The use of the less sterically encumbered Ru (II) catalyst **(*S*)-6b** (**Figure 3**) gave complete conversion, but at the cost of a lower enantiomeric ratio (85:15 er, entry 3). Okhuma and coworkers have previously reported a novel ruthenabicyclic complex, RuCl[(*S*)-diapena][(*S*)-xylBINAP] **((*S*)-RUCY-xylBINAP, (*S*)-6c),** that showed enhanced efficiency and selectivity in hydrogenation studies with a variety of ketone substrates.[9] The authors speculate that the notable difference in reactivity between the ruthenabicyclic catalyst and the benchmark $RuCl_2$(diphosphine)(1,2-diamine) catalyst systems such as **6a** and **6b** may be in part due to the *trans*-influence of the arene carbon and the Ru—H bond in the active catalytic species, a byproduct of the unique ruthenabicyclic structure.[10] In our system, catalyst **(*S*)-6c** significantly outperformed **(*S*)-6a** and **(*S*)-6b**, providing **7** in 97:3 er with complete conversion of starting material in less than 2 hours

(Table 1, entry 4). Consistent with the results using catalyst **(*S*)-6a**, higher temperatures led to an erosion in enantiomeric ratio (entries 5 and 6). The superior enantiomeric ratios and reactions times observed during optimization led us to continue our development work with **(*S*)-6c** as the catalyst.

**Table 1. Summary of DKR Catalyst Studies in the Reaction of 5 to 7**




| Entry | Catalyst[a] | Temp (°C) | Base (equiv) | $H_2$ (psi) | Time (hrs) | Conversion | e.r. |
|---|---|---|---|---|---|---|---|
| **1** | **(*S*)-6a** | 21 | 0.3 | 70 | 48 | 34 | 92:8 |
| **2** | **(*S*)-6a** | 60 | 0.3 | 70 | 48 | 50 | 84:16 |
| **3** | **(*S*)-6b** | 21 | 0.3 | 70 | 48 | 100 | 85:15 |
| **4** | **(S)-6c** | 21 | 0.3 | 70 | 2 | 100 | 97:3 |
| **5** | **(*S*)-6c** | 60 | 0.3 | 70 | 2 | 80 | 94:6 |
| **6** | **(*S*)-6c** | 40 | 0.3 | 70 | 2 | 95 | 96:4 |

[a] Experiments performed at 0.25 mol % catalyst loading.

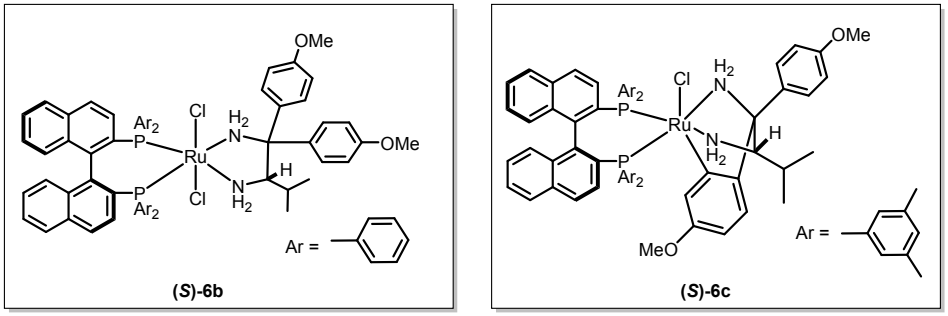
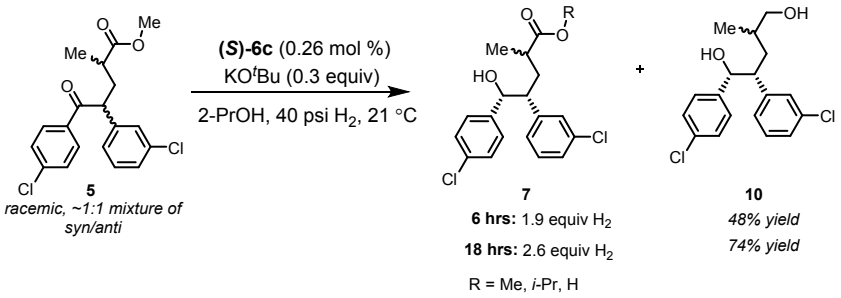


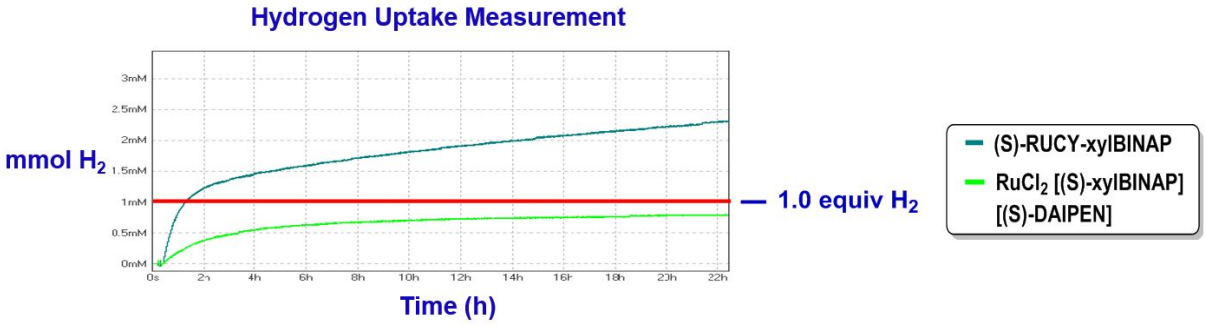

**Figure3. Structure of catalysts $RuCl_2$[(*S*-BINAP)-(*S*-DIAPEN)] ((*S*)-6b) and RuCl[(*S*)-diapena][(*S*)-xylBINAP] ((*S*)-6c)**

During our studies using catalyst **(*S*)-6c** in the hydrogenation of racemic ketone **5**, we observed higher than expected levels of $H_2$ consumption at extended reaction times. The data is summarized in **Figure 4**. After 1 hour, the reaction reached complete conversion with respect to expected $H_2$

uptake. This observation was confirmed by HPLC analysis of the reaction mixture, which showed the reaction to be in 98% conversion (< 2% of **5** remaining). However, after 6 hours, 1.9 equivalents of $H_2$ had been consumed. At the 18-hour mark, 2.6 equivalents of $H_2$ had been consumed. These values corresponded to a 48% and 74% yield, respectively, of a newly formed impurity as measured by HPLC assay. The impurity was identified as the diol **10**, a byproduct of the reduction of the pendant carboxyl functionality.[11] Carboxyl group reduction was not observed with either **(*S*)-6a** or **(*S*)-6b** as the catalyst under otherwise identical reaction conditions.

**Scheme 4. Reaction of methyl ester 5 under hydrogenation conditions leads to alcohol 7 and diol 10**



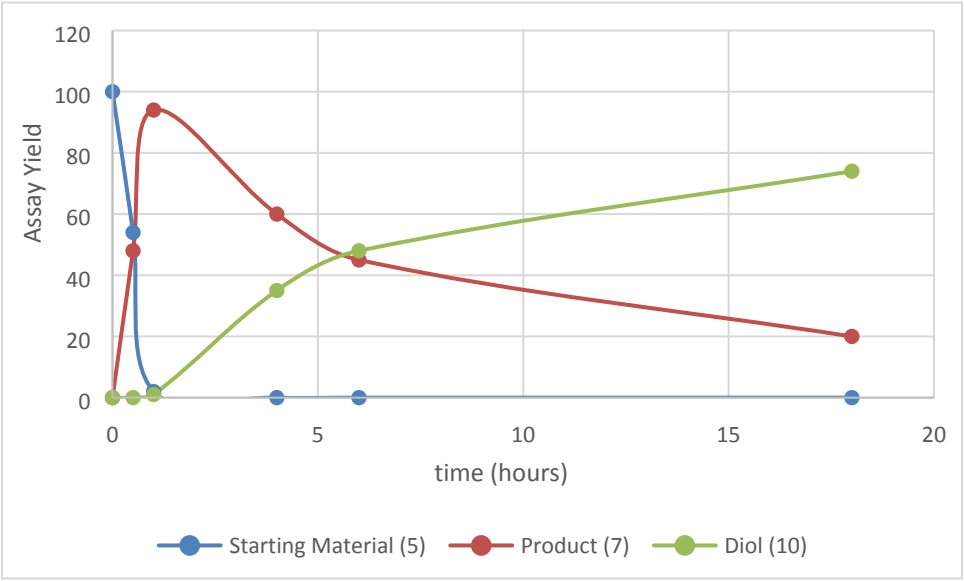
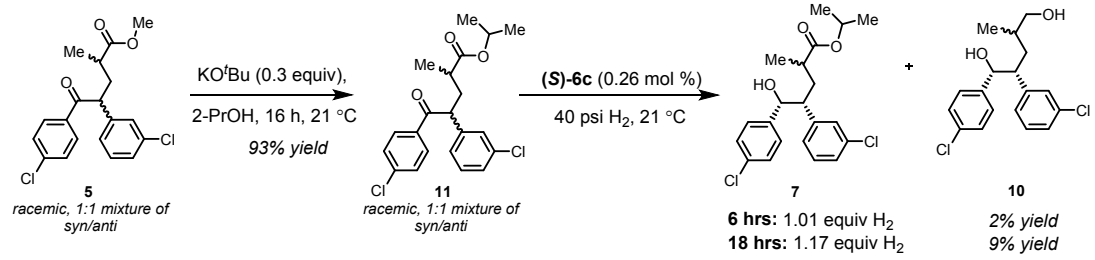



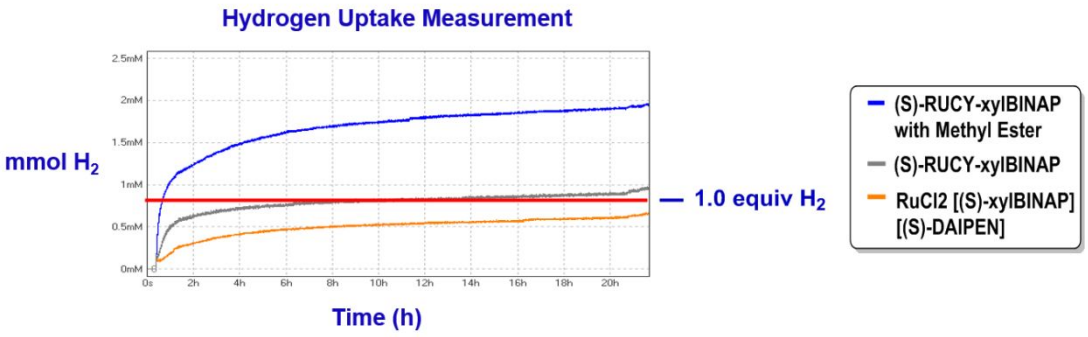

**Figure 4, Top: A plot of $H_2$ update data vs time with catalysts (*S*)-6c (blue) and (*S*)-6b (green) in the DKR of 5 to 7. Red bar corresponds to 1.0 equivalent of $H_2$. Bottom: A plot of conversion of 5 to product 7 and diol 10 as measured by HPLC.**

Upon observing the diol shown in Figure 4, we postulated that allowing for transesterification from the methyl ester to the more sterically hindered isopropyl ester prior to

ketone hydrogenation could curb the undesired reduction of the ester functionality. To test this hypothesis, we converted methyl ester **5** to its corresponding isopropyl ester **11** using base esterification in 2-PrOH. Catalyst **(*S*)-6c** was then added, and the system was pressurized to 40 psi $H_2$. After 6 hours, the reaction reached complete conversion as measured by HPLC analysis. This data corresponded well with $H_2$ uptake data; approximately 1.0 equivalent of $H_2$ had been consumed at this time point (**Scheme 5** and **Figure 5**). Extended reaction times resulted in a slower $H_2$ uptake and slower reduction of the more sterically hindered carboxyl group as compared to the methyl ester series. At 18 hours, 1.17 equivalents of $H_2$ had been consumed during the reaction. This data corresponded well with data obtained by HPLC analysis, which showed **10** to be in 9% yield (**Figure 5**). The transesterification to **11** prior to hydrogenation did not affect the stereoselectivity of the DKR; alcohol **7** was obtained in 97.5:2.5 er as measured by chiral HPLC analysis.

**Scheme 5. Isopropyl ester 11 under hydrogenation conditions leads to slower ester reduction compared to methyl ester 5**



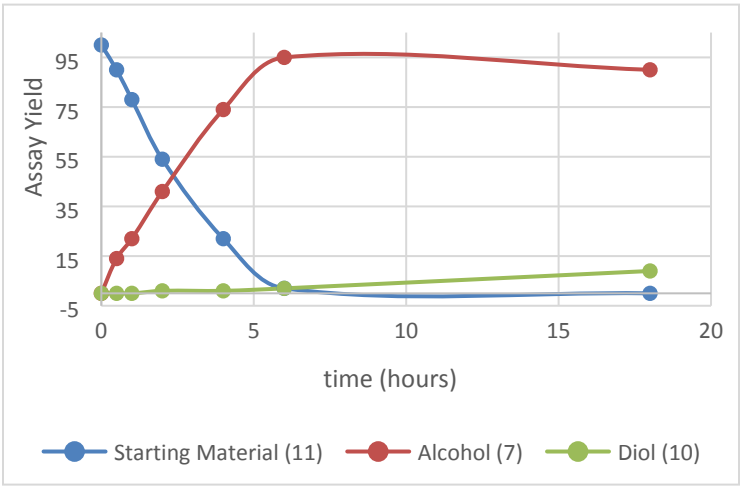



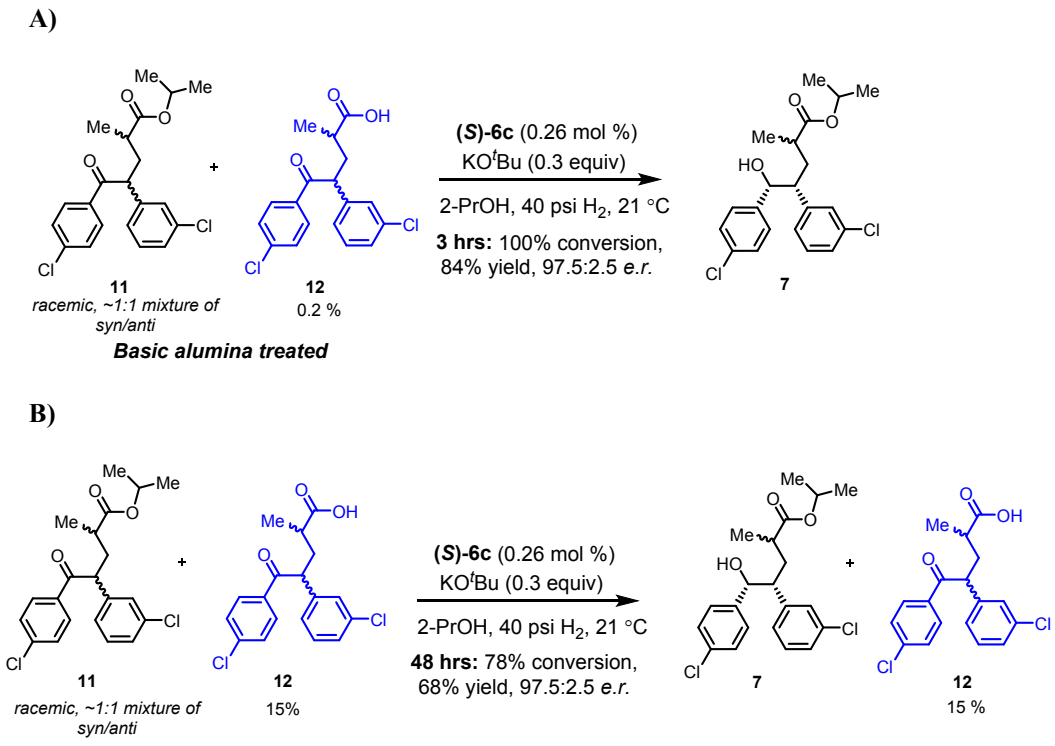

**Figure 5, Top: A plot of $H_2$ update data vs time in the reaction of 11 to 7 (gray) with catalyst (*S*)-6c. Blue curve depicts control experiment with starting material 5 using (*S*)-6c under identical reaction conditions. Orange curve depicts control experiment with starting material 11 and catalyst (*S*)-6b under identical reaction conditions. Red bar corresponds to 1 equivalent of $H_2$. Bottom: Plot of the conversion of 11 to desired product 7 and diol 10 over time as measured by HPLC.**

In early process development work on the DKR, we observed batch to batch variability and stalling in the conversion **5** to **7**, an effect that was attributed to the presence of low levels of carboxylic acid impurity **12**, a byproduct of the hydrolysis of ester **5**. To control the quality of the

incoming starting material stream, we treated **5** with basic alumina prior to hydrogenation to remove **12**. While suitable for early phase manufacturing, we aspired to simplify the process by installing procedural controls to minimize the introduction of **12**.

First, we explicitly demonstrated through a series of control experiments that the presence of **12** had the same detrimental impact on the hydrogenation using newly identified catalyst **(*S*)-6c** and isopropyl ester starting material **11**. As indicated in **Scheme 6**, spiking 15% of **12** into a mixture containing **11** led to incomplete conversion in the DKR after 48 hours, with product obtained in only 68% yield.

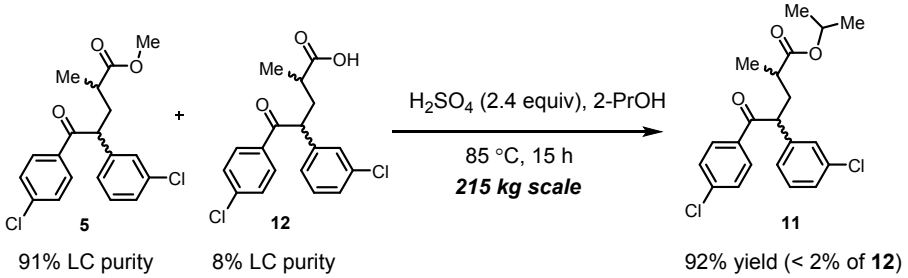
**Scheme 6. Control Experiments in the DKR with Acid Impurity 12**



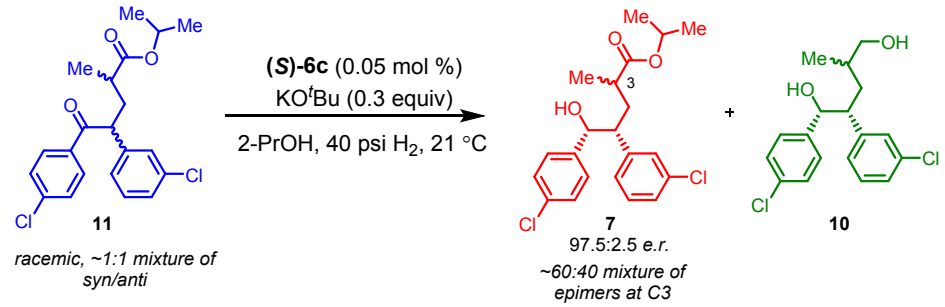

Acid **12** did not undergo ketone reduction under the hydrogenation conditions described and was recovered from the reaction mixture. In addition, desired product **7** was determined to be in 97.5:2.5 *e.r.* in both experiments described in Scheme 6A and 6B, despite the significantly slower reaction rates observed in the control experiment with **12**. Laboratory experiments revealed no

significant impact to the reaction rate when levels of acid **12** were kept below 5 mol %. Thus, as a solution to both the need for transesterification and appropriate process control of impurity **12**, the chemical process was modified to include an acid-promoted Fisher esterification step prior to the DKR. After Michael addition to methyl methacrylate, aqueous workup, and solvent exchange to 2-PrOH, methyl ester **5** was determined to be in 91% purity, with 8% of the undesired carboxylic acid **12**. The mixture was treated with sulfuric acid and heated to reflux to convert both **5** and **12** to the desired isopropyl ester **11**; after aqueous workup, **11** was obtained in 92% yield. HPLC analysis of the crude solution revealed approximately 5% of the unreacted methyl ester **5** and less than 2% of acid **12** in the product stream (**Scheme 7**). This protocol experimentally simplifies the DKR process by obviating the need for a basic alumina treatment of **5** prior to the hydrogenation.

**Scheme 7. Fischer Esterification Converts 5 and 12 to Isopropyl Ester 11**




To demonstrate the DKR process, we performed the ketone hydrogenation on 250 grams of **11** in a 5-liter Buchi pressure reactor at 40 psi. Lowering the catalyst loading to 0.05 mol% led to complete conversion after 8 hours of stirring; product was measured to be in 97% yield by HPLC solution assay, with diol **10** in only 3% yield. Stressing the reaction mixture by allowing it to stir overnight resulted in a slight erosion in the yield of **7**. **10** was determined to be in 7% yield at the 22-hour reaction time point (**Figure 6**), which was easily purged from the reaction mixture during the downstream isolation. Thus, lowering the catalyst loading provides the additional benefit of process robustness, in addition to a reduced cost of goods.



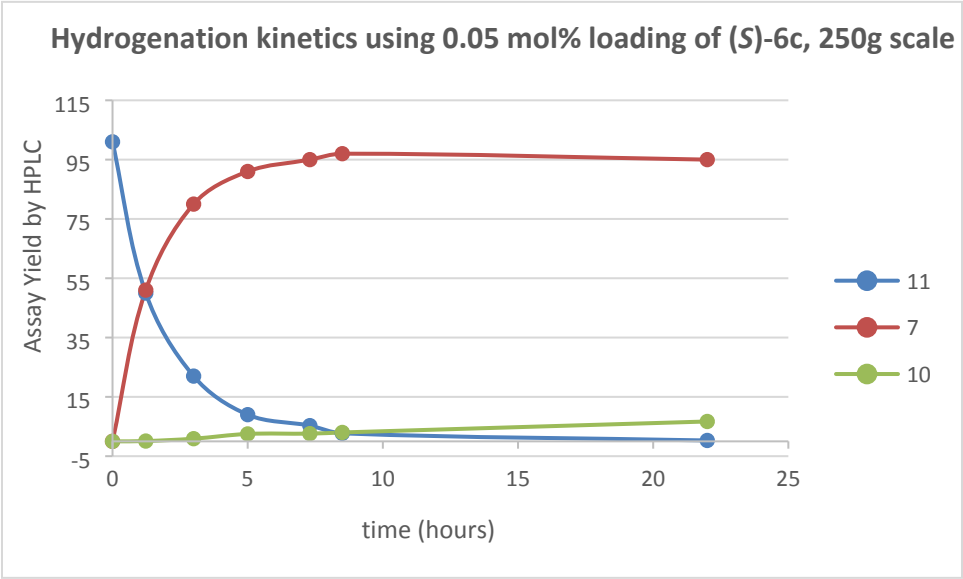




**Figure 6. 250-gram scale DKR reaction progression over time of 11 to 7 and 10 at 0.05 mol % catalyst loading using (*S*)-6c.**

With the optimal catalyst loading identified, we studied the impact of $H_2$ pressure on reaction rate and product quality. Performing the hydrogenation at various $H_2$ pressures revealed a faster reaction at 70 psi, with no detrimental impact on purity profile and enantiopurity (**Figure 7**). Reactions above 70 psi led to increased levels of diol **10.**

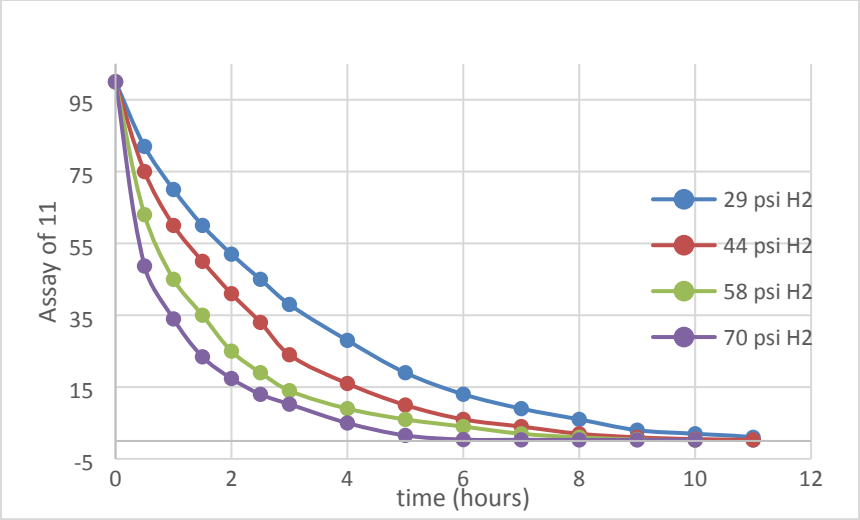
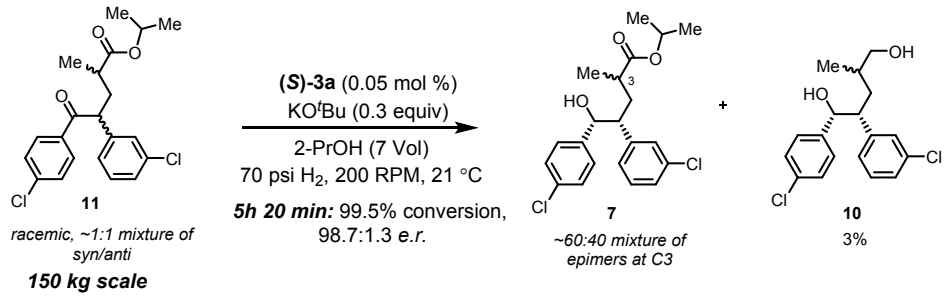
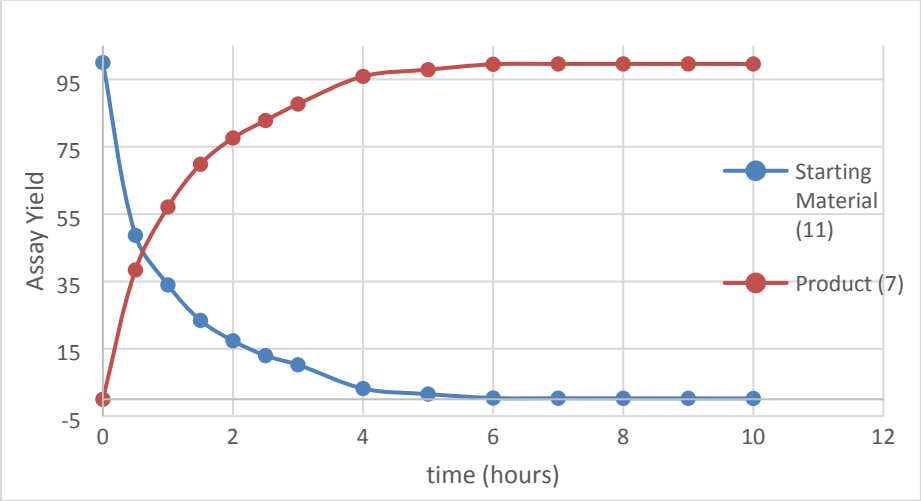



**Figure 7. Hydrogenation kinetics using 0.05 mol % catalyst loading of (*S*)-6c at various pressures.**

The DKR process was scaled to 150 kg as part of a production campaign toward lactone **2.** The vessel was pressurized to 70 psi $H_2$ and allowed to stir at 21 °C. At 5 hours and 20 minutes, the reaction reached 99.5% conversion; **7** was obtained in 98.7:1.3 *e.r.*, with only 3% yield of impurity **10** observed (**Scheme 8**). The yield was assumed quantitative, and the mixture was telescoped directly into the next step.

**Scheme 8. DKR Results on 150 kg Scale with 0.05 mol% of Catalyst (*S*)-6c**

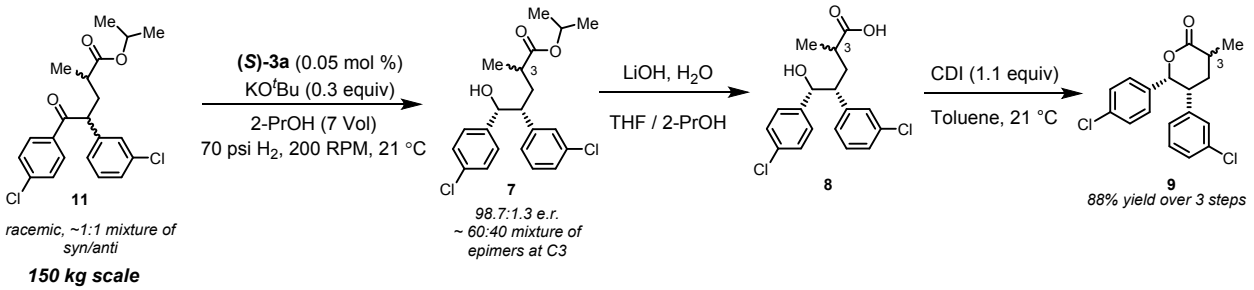



**Hydrolysis of 7 and lactonization to 9.** The hydrolysis of **7** was easily accomplished using aqueous lithium hydroxide (LiOH) and gave > 99.6% conversion to the desired acid on production scale. The product was isolated as a solution in toluene and telescoped directly into the lactonization step.

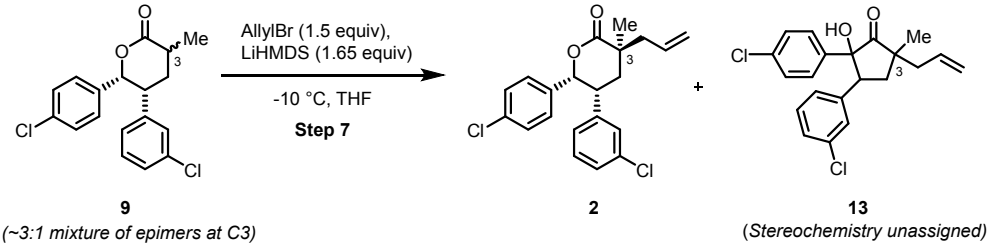
The initial discovery route utilized 3 mol % of PPTS in refluxing toluene to afford lactone **9** in 84% yield over 3 steps from methyl ester **5**. During process optimization it was found that using 1.1 equivalents of 1,1'-carbonyldiimidazole (CDI) at ambient temperature allowed for a much cleaner reaction profile with fewer side products. These conditions were successfully applied on > 200 kg scale, resulting in 88% overall yield of lactone **9** over 3 steps from ketone **11** (**Scheme 9)**.

**Scheme 9. DKR, Hydrolysis and Lactonization to Furnish Lactone 9**




**Alkylation of Lactone 9 to DLAC.** The alkylation of **9** was originally performed on discovery scale using 3 equivalents of allyl bromide and 1.3 equivalents of LiHMDS at -35 °C. The product was isolated in 93% yield and 96:4 *e.r.,* with recrystallization from a heptane/toluene solution affording an increase in chiral purity to 99.2:0.8 *e.r.* **(**see **Scheme 1)**. The process used 1.5 equivalents of allyl bromide and 1.1 equivalents of LiHMDS. Conversion stalled at 85%; an additional 0.50 equivalents of LiHMDS was added in two portions to reach full conversion. Compound **2** was crystallized from a diisopropyl ether/isopropanol/water mixture in 55% yield. A careful inspection of the mother liquors revealed a major impurity that was cleared in the crystallization but was difficult to visualize over the course of the reaction due to poor peak separation by HPLC. The impurity was isolated by chromatography from the mother liquors and identified as cyclopentanone **13** (**Scheme 10**).

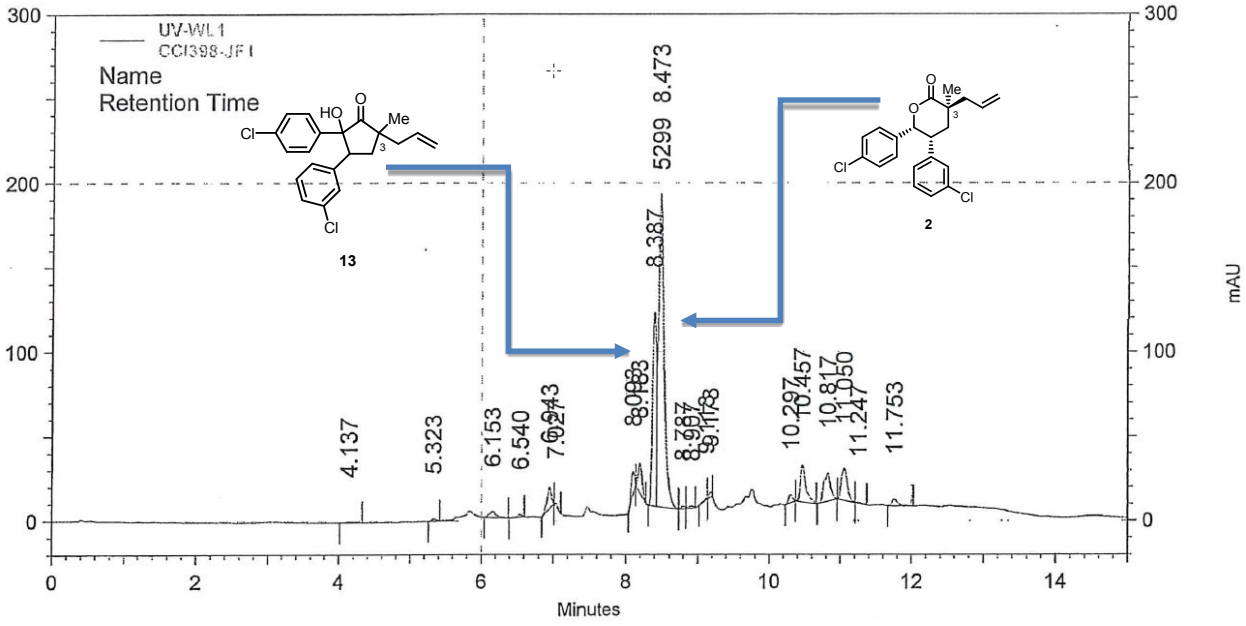
**Scheme 10. Alkylation of 9 to Produce 2 and LC chromatogram of Mother Liquors Showing Overlap of 2 and 13**




**9**
*(~3:1 mixture of epimers at C3)*

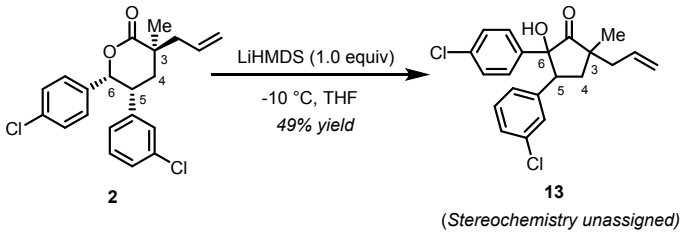
**2**

**13**
*(Stereochemistry unassigned)*




We discovered that excess LiHMDS added to force the conversion to 100% led to the unexpected formation of cyclopentanone **13** with extended reaction times**.** A control experiment treating **2** with LiHMDS led to the formation of **13** in 49% yield, suggesting a mechanism by which **9** is initially alkylated to form **2**, followed by base-promoted ring contraction and 1,2-Wittig rearrangement/acyl transfer to yield **13** (**Scheme 11**).[12]

**Scheme 11. Base-Induced Rearrangement of DLAC 2 yields Cyclopentanone 13**




Based on the demonstrated instability of **DLAC 2** to base while attempting to push the reaction to full conversion, we optimized the Step 7 chemistry and isolation to instead reject unreacted **9**. A crystallization study using spiked levels of **9** demonstrated that up to 5% of **9** could be cleared by doubling the crystallization volume from the FIH process conditions (**Table 2**).

**Table 2. Clearance of Impurity 9 in the DLAC Crystallization**

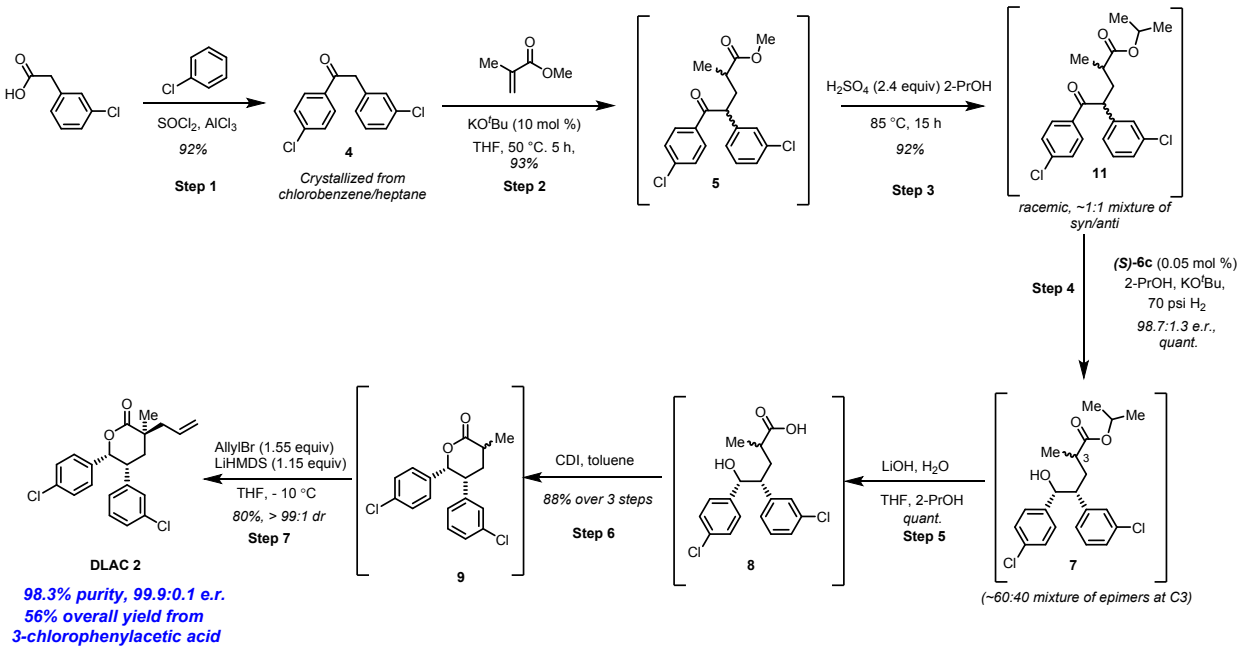
| Total Solvent | Amount of 9 charged | Amount of 9 in product |
|---|---|---|
| **1.4 vol (1x)** | 5% | 2% |
| **1.4 vol (1x)** | 10% | 5.5% |
| **2.8 vol (2x)** | 2.5% | undetected |
| **2.8 vol (2x)** | 5% | undetected |
| **2.8 vol (2x)** | 10% | 4.1% |

The final optimized reaction conditions for the alkylation of **9** utilized 1.55 equivalents of allyl bromide, 1.15 equivalents of LHMDS in 7.5 volumes of THF at -10 °C. Implementation of the revised reaction and crystallization protocols led to an increase in yield of **2** from 68% in the first-generation process to 80% on 165 kg scale. Product was isolated and determined to be in >98% purity by achiral HPLC and 99.9:0.1 *e.r.* by chiral HPLC.

**Conclusion:** A series of process improvements led to the efficient and scalable production of **DLAC**, a key intermediate in the production of AMG 232, on approximately 150 kg scale (**Scheme 12**). Two significant yield bottlenecks were removed during process development: *1)* a scalable, robust, and stereoselective dynamic kinetic resolution of racemic aryl ketone **11** was achieved

through the identification of a highly active ruthenabicyclic complex, **(*S*)-6c**, and *2)* product erosion during the final alkylation step was curbed by stopping the reaction at 95% conversion. The overall yield of the 7-step sequence was 56%, nearly doubling the original 28% yield observed in the FIH process. In addition, we eliminated three chromatography operations from the original discovery route, thus streamlining the overall scalability of the new process.

**Scheme 12. Manufacturing Process Route to DLAC**




## Experimental Section.

**2-(3-chlorophenyl)-1-(4-chlorophenyl)ethan-1-one (4).** To a 1600 L enameled reactor fitted with an NaOH scrubber was charged chlorobenzene (120 L, 1 vol), 3-chlorophenylacetic acid (120.0 kg, 1.0 equiv.), and *N,N*-dimethylformamide (1.6 L, 0.03 equiv.). The mixture was cooled to -5 ˚C, and thionyl chloride (110.5kg, 1.3 equiv.) was added. The mixture was warmed and stirred for 2 hours at 15-20 ˚C. The mixture was then cooled to -5 ˚C, and to the reactor was charged aluminum chloride (103.2 kg, 1.1 equiv.). The mixture was slowly warmed to 15-20 ˚C and stirred for 16 hours. The mixture was cooled to 0 – 5 ˚C, then ethanol (100 L, 0.83 vol) was added, followed by a mixture of deionized water (504 L, 4.2 vol) and ice (100 kg). Heptane (1200 L, 10 vol) was added, and the mixture was held at 0 – 5 ˚C and stirred for 16 hours. After aging, the mixture was filtered on a 1200 mm polypropylene filter. The reactor vessel was washed twice with heptane (2 x 240 L, 2 x 2 vol), and the washings were used to rinse the solid on the filter. To the reactor vessel was charged deionized water (480 L, 4 vol) and ethylenediaminetetraacetic acid sodium salt hydrate (14.4 kg, 0.05 equiv.). The filtered solid was added into the reactor and the

mixture was stirred at 15-25 ˚C for 2 hours. The solid was filtered and rinsed with deionized water (3 x 480 L, 3 x 4 vol). The wet solid was dried under vacuum at 50 ˚C overnight. **4** (181.9 kg) was obtained as white solid in 91.8% yield, 97.1% purity by HPLC and 94.2 w/w% purity. **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.87 - 7.92 (m, 2H), 7.36 - 7.43 (m, 2H), 7.18 - 7.26 (m, 3H), 7.07 - 7.13 (m, 1H), 4.19 (s, 2H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 195.4, 139.7, 135.9, 134.5, 134.2, 129.7, 129.4, 128.9, 127.6, 127.1, 44.6; **MS (ESI+):** *m/z* 265.0 (M + 1).

**(±)-methyl 4-(3-chlorophenyl)-5-(4-chlorophenyl)-2-methyl-5-oxopentanoate (5)**. To a 2500 L enameled reactor was charged THF (850 L, 5 vol), **4** (179.9 kg, 94.2 wt%, l.0 equiv.), and methyl methacrylate (67.9 kg, 1.06 equiv.). The mixture was warmed to 35 ˚C, and a solution of potassium tert-butoxide solution in THF (36.2 kg, 0.1 equiv., 1.7 M solution in THF) was added over 25 minutes, keeping the internal temp below 50 ˚C. The mixture was stirred at 45 ˚C for 4 hours, then cooled to 25 ˚C and quenched with aqueous hydrochloric acid (0.13 equiv., 84 L, 1.0 M aqueous solution). Isopropyl acetate (1020 L, 6 vol) was added, followed by aqueous sodium chloride (856 L, 5 wt% NaCl solution), and the biphasic mixture was stirred for 5 minutes at 15-20 ˚C. The phases were split, and the organic layer was concentrated under vacuum at 45 ˚C to an oil. Isopropanol (860 L, 5 vol) was added and the mixture concentrated under vacuum until total volume reached 720 L. Compound **5** (666.6 kg, 32 w/w%) was obtained as a yellow solution in 92.9% yield based on HPLC assay (mixture of diastereomers) and telescoped directly into the next step. A sample of the product solution was distilled to dryness and purified through a pad of silica gel, eluting with 20% EtOAc/Heptane, to obtain a purified sample for characterization purposes. **Spectral data for 5 (mixture of isomers)**: **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.84 - 7.91 (m, 4 H), 7.33 - 7.38 (m, 4 H), 7.26 - 7.31 (m, 2 H), 4.62 (td, *J*=9.07, 5.49 Hz, 2 H), 3.67 (s, 3 H), 3.59 (s, 3 H), 2.42 - 2.51 (m, 2 H), 2.29 - 2.38 (m, 2 H), 2.05 - 2.12 (m, 1 H), 1.96 (ddd, *J* = 13.79, 9.02, 4.56 Hz, 1 H), 1.21 (d, *J* = 7.05 Hz, 3 H), 1.15 (d, *J*=7.05 Hz, 3 H); **$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 197.3, 197.3, 176.3, 176.3, 140.8, 140.4, 139.5, 139.5, 134.8, 134.7, 134.4, 130.2, 130.0, 128.8, 128.3, 127.6, 127.5, 126.5, 126.1, 51.6, 51.4, 50.8, 50.7, 37.3, 17.8, 17.6; **MS (ESI+):** *m/z* 365.1 (M + 1).

**(±)-isopropyl 4-(3-chlorophenyl)-5-(4-chlorophenyl)-2-methyl-5-oxopentanoate (11).** To a 2500 L enameled reactor equipped with an NaOH scrubber was charged a solution of **5** in isopropanol from the previous step (666.6 kg solution, 32 w/w%, l.0 equiv. based on HPLC assay) and isopropanol (860 L, 3.6 vol). Sulfuric acid (159.3 kg, 2.4 equiv., 86 wt% solution) was added over 15 minutes, and the mixture was heated to 80-84 ˚C for 15 hours. Isopropanol was distilled at 85 ˚C and atmospheric pressure over 9 hours and replaced with fresh isopropanol (800 L, 3.4 vol). After conversion to the isopropyl ester, the mixture was concentrated by distillation at atmospheric pressure over 9.5 hours until total volume reached 640 L. Deionized water (396 L, 1.7 vol) was added over 1 hour, keeping the internal temperature below 25 ˚C, followed by isopropyl acetate (600 L, 2.5 vol). The mixture was stirred for 15 minutes at 15-20 ˚C and the layers were separated. The aqueous layer was removed, and the organic layer was washed three times with deionized water (3 x 470 L, 3 x 2 vol), followed by two washes with sat. aqueous $NaHCO_3$ (2 x 470 L) and a final wash with aqueous sodium chloride (470 L, 25 wt% aqueous solution). The resultant organic layer was filtered on a cartridge and transferred into a 1000 L enameled reactor. The original 2500 L reactor was washed with 200 L of isopropanol and transferred to the 1000 L reactor. The mixture was concentrated until total volume reached 546 L. Distillation was resumed with the addition of fresh isopropanol (1760 L, 7.4 vol) and continued until total volume reached 650 L. Compound **11** (654 kg solution) was obtained in 92% molar yield based on HPLC assay

and 33.7 w/w% solution as a mixture of diastereomers and telescoped directly into the next step. A sample of the product solution was distilled to dryness and purified through a pad of silica gel, eluting with 20% EtOAc/Heptane, to obtain a purified sample for characterization purposes. **Spectral data for 11 (mixture of isomers)**: **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.82 - 7.91 (m, 4H), 7.30 - 7.35 (m, 4 H), 7.25 - 7.29 (m, 2 H), 7.11 - 7.23 (m, 6 H), 5.00 - 5.10 (m, 1 H), 4.90 - 5.00 (m, 1 H), 4.60 - 4.68 (m, 2 H), 2.16 - 2.45 (m, 4 H), 1.92 - 2.08 (m, 2 H), 1.25 - 1.28 (m, 3 H), 1.21 - 1.23 (m, 3 H), 1.09 - 1.19 (m, 12 H); **$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 197.3, 197.3, 175.3, 141.0, 140.3, 139.5, 139.4, 134.7, 134.7, 134.4, 130.2, 130.1, 130.0, 129.9, 129.9, 128.8, 128.4, 127.9, 127.5, 127.4, 126.5, 126.0, 67.5, 67.5, 50.8, 50.6, 37.9, 37.8, 36.9, 36.8, 31.7, 28.8, 22.5, 21.8, 21.6, 21.6, 18.0, 17.7, 13.9. **MS (ESI+):** *m/z* 393.1 (M + 1).

**isopropyl (*4R,5R*)-4-(3-chlorophenyl)-5-(4-chlorophenyl)-5-hydroxy-2-methylpentanoate (7)**. To a 1600 L enameled reactor was charged isopropanol (700 kg, 875 L, 4 vol). The reactor was then purged with nitrogen (4 x 1.5 bar). Potassium *tert*-butoxide (59.25 kg, 0.94 equiv. based on molar assay of **11**) was added under nitrogen flow, and the reactor was purged again with nitrogen (3 x 1.5 bar). A solution of **11** was added (653.8 kg, 33.7 w/w%, 1.0 molar equiv based on HPLC assay), and the equipment transfer lines were rinsed with degassed isopropanol and charged to the reactor vessel. To a separate, 60 L enameled pressure reactor was charged isopropanol (29 kg), followed by purging with nitrogen (3 x 1.5 bar). To the pressure reactor was charged RuCl[(*S*)-diapena][(*S*)-xylBINAP] ((***S*)-6c**) catalyst (332 g, 0.0005 equiv. based on molar assay of **11**). The resultant catalyst solution was transferred into the 1600 L reactor, and the pressure reactor was rinsed with degassed isopropanol (19 kg) and then transferred to the 1600 L enameled reactor vessel. The reactor vessel was purged again with nitrogen (4 x 1.5 bar), followed by purging with hydrogen (4 x 2 bar). The vessel was then pressurized to 5 bar of hydrogen, and stirring was initiated. The mixture was agitated under 5 bar of hydrogen at 15-25 ˚C for 3.5 hours. The reactor vessel was decompressed and purged with nitrogen (3 x 1.5 bar). Product **7** (1411 kg solution mass**)** was kept as a brown isopropanol solution in 15.7 w/w% and assumed quantitative yield and telescoped directly into the next step. **Chiral HPLC analysis:** Column: CHIRALPACK AD-H, 4.6 x 250 mm, 5 µM, Eluent: 2% EtOH in n-Hexane 1.5mL/min, Column temperature: 20 °C, Wavelength: 220 nm, Diluent 50% 2-PrOH/50% n-Hexane**;** Isomer 1 (major), 9.158 min = 55.26, Isomer 2 (major), 10.776 min = 39.87, Isomer 2 (minor), 15.75 min = 0.77, Isomer 1 (minor), 21.692 min = 0.91. Isomer 1 e.r. = 98.4 : 1.6; Isomer 2 e.r. = 98.1 : 1.9; average e.r. = 98.3 : 1.7. A sample of the product solution in isopropanol was distilled to dryness to obtain material for characterization purposes. **Spectral data for 7 (mixture of isomers)**: **$^1$H NMR (400 MHz, $CDCl_3$)**: δ 7.31 (m, 2H), 7.25 (m, 2H), 7.19 (m, 3H), 7.04 (m, 1H), 4.96 (septet, J = 6.1 Hz, 0.6H), 4.86 (septet, J = 6.3 Hz, 0.4 H), 4.75 (d, J = 7.0Hz, 0.4H), 4.71 (d, J = 7.6 Hz, 0.6H), 2.90 (m, 1H), 2.06 (m, 1.4H), 1.80 (br s, 1H), 1.79 (ddd, J = 13.9, 11.2, 4.1 Hz, 0.6H), 1.60 (m, 0.6H), 1.55 (m, 0.4H), 1.21 (d, J = 6.4 Hz, 1.8H), 1.17 (m, 4.2H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 175.5, 142.4, 141.9, 140.7, 140.5, 134.5, 133.6, 129.8, 129.0, 128.9, 128.5, 128.1, 128.0, 127.4, 127.4, 127.3, 127.2, 77.6, 77.4, 67.6, 67.5, 51.7, 51.3, 37.4, 37.1, 36.3, 34.9, 21.8, 21.7, 18.6, 16.3; **MS (ESI+):** *m/z* 395.1 (M + 1).

**(*4R,5R*)-4-(3-chlorophenyl)-5-(4-chlorophenyl)-5-hydroxy-2-methylpentanoic acid (8)**. To a 2500 L enameled reactor was charged a solution of **7** in isopropanol from the previous step (1411 kg crude solution, 15.7 w/w%, 1.0 molar equiv.) and THF (775 L, 3.5 vol). A solution of lithium hydroxide monohydrate (40.8 kg, 1.7 equiv. based on molar assay of **7**) in deionized water (510

L, 2.3 vol, 1.9 M solution) was added over 1 hour, keeping the internal temperature between 15 – 25 ˚C. After 24 hours of stirring at this temperature, HPLC analysis showed 100% conversion. The mixture was drained from the reactor and divided into 2 batches (2 x 1320 kg). The first batch of the reaction mixture was charged into the 2500 L reactor, followed an aqueous solution of 1M HCl (320 L). Toluene (485 L, 2.2 vol) was added, the mixture was stirred for 30 minutes, and the phases separated. The aqueous layer was back extracted with toluene (630 L, 2.8 vol). The second batch of the reaction mixture was treated the same way as the first batch. The organic layers were combined, and then washed with a solution of sat. aq. sodium chloride (886 L, 4 vol), followed by phase separation. The organic layer was concentrated at 95 ˚C until a total volume of 1000 L, followed by the addition of 1100 L of toluene and further concentration to reach 1000 L. Product **8** was kept in the reactor as a solution in toluene and telescoped directly into the next step with an assumed quantitative yield. A sample of the product solution was distilled to dryness and purified through a pad of silica gel, eluting with 50% EtOAc/Heptane, to obtain a purified sample for characterization purposes. **Spectral data for 8 (mixture of isomers)**: **$^1$H NMR (400 MHz, $CDCl_3$)**: δ 7.17 – 7.30 (m, 10H), 7.09-7.13 (m, 2H), 7.01-7.06 (m, 3H), 6.89 – 6.95 (m, 1H), 4.72 (d, *J* = 7.8 Hz, 2H), 2.94-3.03 (m, 1H), 2.85 – 2.94 (m, 1 H), 2.05 – 2.25 (m, 3H), 2.02 (s, 1H), 1.91 – 2.01 (m, 1H), 1.47 – 1.62 (m, 2H), 1.07 (d, *J* = 8 Hz, 3H), 1.02 (d, *J* = 8 Hz, 3H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 182.6, 182.4, 142.2, 141.7, 140.5, 134.4, 134.3, 133.6, 129.8, 129.6, 129.0, 128.9, 128.5, 128.3, 128.2, 128.0, 127.5, 127.3, 127.3, 77.5, 77.0, 51.3, 50.9, 37.7, 36.9, 35.0, 34.7; **MS (ESI+):** *m/z* 353.1 (M + 1).

**(*5R,6R*)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyltetrahydro-2H-pyran-2-one (9).** To a 2500 L enameled reactor containing **8** as a solution in toluene was charged 1,1'-carbonyldiimidazole (94.9 kg, 1.1 equiv. based on molar assay of **8**) over 50 minutes, keeping the temperature less than 25 ˚C. After 3 hours of stirring at 15 – 25 ˚C, analysis by HPLC showed 76.4% conversion. Additional 1,1'-carbonyldiimidazole (4.3 kg, 0.05 equiv.) was added, and the mixture was stirred for 2 more hours. HPLC analysis showed 99.4% conversion. After cooling to 10 ˚C, a solution of phosphoric acid (111.1 kg, 1.6 equiv.) in deionized water (638 L, 3.4 vol, 1.4 M solution) was added over 2 hours, keeping the internal temp < 15 ˚C. After 30 minutes of stirring, the mixture was phase separated, and the aqueous layer was removed. The organic layer was washed with a solution of sat. aq. sodium chloride (560L), stirred for 15 minutes, and the layers separated. The organic layer was then concentrated at 95 ˚C to reach a residual oil. THF (1000 L, 5.3 vol) was added and the mixture was concentrated at atmospheric pressure until the total volume reached 713 L. Compound **9** was obtained as a 612 kg brown solution in 88% yield over 3 steps based on HPLC assay (27 w/w%, 3:1 mixture of epimers at C3). The solution was telescoped directly into the next step. A sample of the product solution was distilled to dryness and purified through a pad of silica gel, eluting with 20% DCM/MeOH, to obtain a purified sample for characterization purposes. **Spectral data for 9 (mixture of isomers)**:**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.22-6.98 (m, 5H), 6.91 (dt, J = 7.4, 1.2 Hz, 0.3H), 6.81 (m, 2H), 6.73 (dt, J = 7.6, 1.4 Hz, 0.7H), 5.76 (d, J = 4.1 Hz, 0.3 H), 5.69 (d, J = 4.7 Hz, 0.7H), 3.67 (dt, J = 6.6, 4.3 Hz, 0.3H), 3.55 (td, J = 7.8, 4.7 Hz, 0.7 H), 2.96 (d of quintets, J = 13.5, 6.7 Hz, 0.7 H), 2.81 (m, 0.3 H), 2.56 (dt, J = 14.3, 8.0 Hz, 0.7 H), 2.32 (dt, J = 13.69, 7.0 Hz, 0.3 H), 2.06 (ddd, J = 13.7, 8.4, 4.1, 0.3 H), 1.85 (ddd, J = 14.1, 12.5, 7.4, 0.7 H), 1.42 (d, J = 7.0 Hz, 0.9 H), 1.41 (d, J = 6.7 Hz, 2.1H); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 174.8, 173.6, 141.6, 140.0, 135.2, 134.6, 134.4, 134.1, 133.7, 129.7, 129.6, 128.9, 128.7, 128.3, 128.1, 127.5, 127.4, 127.2, 126.7, 126.7, 82.8, 81.0, 44.8, 41.8, 34.6, 33.1, 32.8, 32.6, 18.3, 16.0; **MS (ESI+):** *m/z* 335.1 (M + 1).

**(*3S,5R,6R*)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyltetrahydro-2H-pyran-2-one (DLAC, 2).** To a 1600 L reactor was charged a 612 kg solution containing **9** from the previous step (27 w/w%, l.0 equiv based on HPLC assay) and THF (203 L, 1.2 vol). The mixture was cooled to -10 ˚C, and allyl bromide (93 kg, 1.55 equiv. based on HPLC assay of **9**) was added. Lithium bis(trimethylsilyl)amide solution (388 kg, 1.15 equiv. 25 wt% solution in THF) was added to the mixture over 6 hours, keeping the internal temp below -5 ˚C. The mixture was stirred for 1 hour at 5 ˚C, followed by addition of a solution of phosphoric acid (219.5 kg, 4.0 equiv. 77 wt%) in deionized water (340 L, 2.1 vol, 5 M solution) over 3 hours, keeping the internal temperature below 5 ˚C. The mixture was allowed to warm to 15-20 ˚C overnight. After phase separation, deionized water (170 L, 1 vol) and MTBE (470 L, 2.85 vol) were added, the mixture was stirred at 15-20 ˚C for 15 minutes, and the phases separated. Deionized water was added (170 L, 0.9 vol) and the mixture stirred again at 15-20 ˚C for 15 minutes. After phase separation, the organic layer was washed twice with a solution of sat. aq. sodium chloride. The organic layer was transferred through a cartridge filter and transferred into a 1000 L enameled reactor. The filtrate was concentrated at atmospheric pressure until total volume reached 282 L. Isopropanol (1460 L, 9.4 vol) was added and distillation was continued for 6 hours until total volume reached 282 L. Diisopropyl ether (130 L, 0.8 vol) was added, followed by a mixture of deionized water (38 L, 0.25 vol) and isopropanol (55 L, 0.35 vol) at 60-70 ˚C over 25 minutes. The mixture was seeded with **DLAC** and stirred at 60-70 ˚C, and a white slurry was observed. Another seed batch of **2** (7.8 kg) was added to the suspension and the mixture was allowed to slowly cool to 15-25 ˚C over 14 hours. The suspension was filtered on a 1200 mm polypropylene filter, and the solid was washed with heptane (2 x 113 L, 2 x 0.7 vol). The wet solid was dried under vacuum at 45 ˚C for 63 hours and grinded on 2 mm mesh to give 147.7 kg of **DLAC 2** as a white powder in 80% yield and 98.3% HPLC purity. **Chiral HPLC analysis:** Column: CHIRALPACK AD-H, 4.6 x 250 mm, 5 µM, Eluent: 3% EtOH in n-heptane, 1.5mL/min, Column temperature: 30 °C, Wavelength: 220 nm, Diluent: 100% 2-PrOH**;** 6.10 min = 99.91 (major), 9.01 min = = 0.09 (minor), e.r. = 99.9 : 0.1. **$^{1}$H NMR** (600 MHz, DMSO-*d*6): δ 7.29 (d, *J* = 8.5 Hz, 2H), 7.25 (ddd, *J* = 7.7, 2.0, 1.5 Hz, 1H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.05 (t, *J* = 2.0 Hz, 1H), 6.88 (dt, *J* = 7.7, 1.5 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 2H), 5.92 (d, *J* = 4.7 Hz, 1H), 5.83 (dddd, *J* = 17.0, 10.1, 7.8, 7.1 Hz, 1H), 5.16 (dd, *J* = 17.0, 2.2 Hz, 1H), 5.13 (dd, *J* = 10.1, 2.2 Hz, 1H), 4.03 (dt, *J* = 11.7, 4.7 Hz, 1H), 2.58 (ddt, *J* = 13.8, 7.8, 1.2 Hz, 1H), 2.48 (ddt, *J* = 13.8, 7.1, 1.2 Hz, 1H), 1.98 (dd, *J* = 14.1, 11.7 Hz, 1H), 1.90 (ddd, *J* = 14.1, 4.7, 1.2 Hz, 1H), 1.30 (s, 3H); **$^{13}$C NMR** (151 MHz, DMSO-*d6*): δ 175.1, 141.2, 135.5, 133.0, 132.8, 132.3, 129.9, 128.4, 128.3, 127.7, 127.0, 126.8, 119.4, 82.7, 43.2, 41.5, 39.0, 31.7, 25.2; **MS (ESI+)** *m/z* 375.1 (M + 1).

**Author Information.**
Corresponding Author
*****Email: ausmith@amgen.com.

**Present Addresses.**
[†]Snapdragon Chemistry, Inc., 00 2nd Ave, Waltham, MA 02451.

[‡]Norchim SAS, 33 quai d'Amont, 60340 Saint Leu D'Esserent, France.

[¥]Johnson Matthey, 25 Patton Road, Devens, Massachusetts 01434, United States.

**Acknowledgements.**
The authors wish to thank Anil Guram and Simon Hedley for helpful discussions and support with hydrogenation experiments in the catalysis laboratory.

---

**Supporting Information.** Copies of $^{1}H$ and $^{13}C$ spectra for compounds **2**, **4**, **5**, **7-13**, 2D NMR spectra for compounds **2** and **13**, and chiral HPLC chromatograms for compounds **2** and **7** can be found in the supporting information section.

**References.**

[1]For reviews, see (a) Sanz, G.; Singh, M.; Peuget, S.; Selivanova, G. Inhibition of p53 Inhibitors: Progress, Challenges and Perspectives, *Journal of Molecular Cell Biology,* **2019,** *11*, 586-599. (b) Karni-Schmidt, O.; Lokshin, M.; Prives, C. The Roles of MDM2 and MDMX in Cancer, *Annual Review of Pathology: Mechanisms of Disease,* **2016**, *11*, 617-644. (c) Joerger, A. C.; Fersht, A. R. The p53 Pathway: Origins, Inactivation in Cancer, and Emerging Therapeutic Approaches, *Annual Review of Biochemistry*, **2016**, *85*, 375-404. (d) Kamal, A.; Mohammed A. A.; Shaik, T. B. p53-Mdm2 Inhibitors: Patent Review (2009-2010). *Expert Opin. Ther. Patients*, **2012**, *22*, 95-105.

[2] Vassilev, L. T.; Vu, B. T.; Graves, B.; Carvajal, D.; Podlaski, F.; Filipovij, Z.; Kong, N.; Kammlott, U.; Lukacs, C.; Klein, C.; Fothoui, N.; Liu, E. A. In vivo Activation of the p53 Pathway by Small-Molecule Antagonists of MDM2, *Science* **2004**, *303,* 844-848.

[3] (a) Lucas, B. S.; Fisher, B.; McGee, L. R.; Olson, S. H.; Medina, J. C.; Cheung, E. An Expeditious Synthesis of the MDM2-p53 Inhibitor AM-8553, *J. Am. Chem. Soc.* **2012**. *134*, 12855. (b) Sun, D.; Li, Z.; Rew, Y.; Gribble, M.; Bartberger, M. D.; Beck, H. P.; Canon, J.; Chen, A.; Chen, X.; Chow, D.; Deignan, J.; Duquette, J.; Eksterowicz, J.; Fisher, B.; Fox, B. M.; Fu, J.; Gonzalez, A. Z.; Gonzalez-Lopez De Turiso, F.; Houze, J. B.; Huang, X.; Jiang, M.; Jin, L.; Kayser, F.; Liu, J. J.; Lo, M.-C.; Long, A. M.; Lucas, B.; McGee, L. R.; McIntosh, J.; Mihalic, J.; Oliner, J. D.; Osgood, T.; Peterson, M. L.; Roveto, P.; Saiki, A. Y.; Shaffer, P.; Toteva, M.; Wang, Y.; Wang, Y. C.; Wortman, S.; Yakowec, P.; Yan, X.; Ye, Q.; Yu, D.; Yu, M.; Zhao, X.; Zhou, J.; Zhu, J.; Olson, S. H.; Medina, J. C. Discovery of AMG 232, a Potent, Selective, and Orally Bioavailable MDM2-p53 Inhibitor in Clinical Development, *J. Med. Chem.* **2014**, *57*, 1454-1472.

[4] The ring carbon atoms are labeled C3-C6 in the **DLAC** structure shown in **Figure 1**. We use this notation throughout the manuscript in order to maintain clarity and consistency when referring to specific carbon atoms in the starting material and product.

[5] The commercial process development to convert **DLAC (2)** to **AMG 232 (1**) has been previously described. See: Cochran, B. M.; Corbett, M. T.; Correll, T. L.; Fang, Y-Q.; Flick, T. G.; Jones, S. C.; Silva Elipe, M. V.; Smith, A. G.; Tucker, J. L.; Vounatsos, F.; Wells, G.; Yeung, D.; Walker, S. D.; Bio, M. M.; Caille, S. Development of a Commercial Process to Prepare AMG 232 Using a Green Ozonolysis–Pinnick Tandem Transformation, *J. Org. Chem.* **2019**, *84*, 4763-4779.

[6] Both epimers at the C3 position are enantioenriched. The average er is 96:4. See ref 3a and supporting information therein for specific data.

[7] For a mechanistic hypothesis on the high diastereoselectivity in the alkylation of **9**, see ref 3a. For a literature example of high-*trans* alkylation of cis-5,6-disubstituted δ-lactones, see: Grieco, P. A.; Williams, E.; Tanaka, H.; Gilman, S. Elaboration of the C(3)-C(12) Carbon Fragment of Calcimycin (A-23187). Formal Total Synthesis of Calcimycin, *J. Org. Chem*. **1980**, *45*, 3537-3539.

[8] The enantiomeric ratios reported in Table 1 and throughout the manuscript refers to the average e.r. of the two epimeric compounds at C3. Both epimers are enantioenriched in roughly the same ratio. For specific data, see Supporting Information.

[9] Matsumura, K.; Arai, N.; Hori, K.; Saito, T.; Sayo, N.; Ohkuma, T. Chiral Ruthenabicyclic Complexes: Precatalysts for Rapid, Enantioselective, and Wide-Scope Hydrogenation of Ketones, *J. Am. Chem. Soc.* **2011**, *133*, 10696-10699.

[10] The corresponding $RuCl_2$(diphosphine)(1,2-diamine) catalyst systems display a *trans*-$RuH_2$ as the expected catalytic species. See: Hamilton, R. J.; Leong, C. G.; Bigam, G.; Miskolzie, M.; Bergens, S. H. A Ruthenium-Dihydrogen Putative Intermediate in Ketone Hydrogenation, *J. Am. Chem. Soc*. **2005**, *127,* 4152–4153.

[11] For examples of ester reductions using Noyori-type Ru catalysts and $H_2$, see: Werkmeister, S.; Junge, K.; Beller, M. Catalytic Hydrogenation of Carboxylic Acid Esters, Amides, and Nitriles with Homogeneous Catalysts, *Org. Process Res. Dev.* **2014**, *18*, 289 and references therein.

[12] Organolithium-induced rearrangements of this type are precedented in the literature. For examples, see (a) Lansbury, P.T. and Pattison, V. A. The Wittig Rearrangement of the Benzyl Ethers of Cyclobutanol and Cyclopropylcarbinol, *J. Am. Chem. Soc.,* **1962**, *84*, 4295-4298. (b) Govindan, M. and Pinnick, H. W. Benzaldehyde plus Potassium Hydride – Benzoyl Anion? *J. Org. Chem.* **1981**, *46*, 5011-5014. (c) Dua, S., Chia, B., Bowie, J. H. Formation of two deprotonated forms of benzyl acetate and higher homologues: some unusual fragmentations, International Journal of Mass Spectrometry, **1998**, *179/180,* 61-66.