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A large-scale asymmetric synthesis of (*S*)-cyclohexylphenyl glycolic acid

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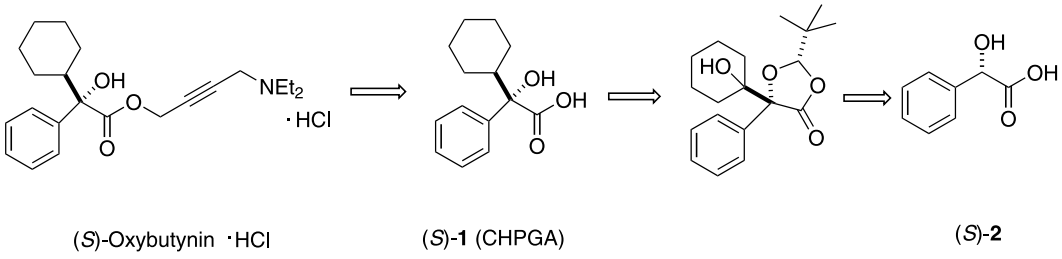
Abstract—A practical asymmetric synthesis of (*S*)-cyclohexylphenyl glycolic acid has been demonstrated at pilot scale. The key step is the asymmetric aldol reaction using the Seebach approach of self-replication of stereochemistry. (*S*)-Mandelic acid was converted into (2*S*,5*S*)-**3** in >99/1 diastereomeric ratio. The dioxolone (2*S*,5*S*)-**3** was then subjected to aldol conditions to give the aldol intermediate (2*S*,5*R*)-**5** in 91% yield with >99.5/0.5 diastereomeric ratio. The aldol product was converted to the desired hydroxy acid, (*S*)-CHPGA, in three steps with only one isolation in high yield (95%) and high purity.

1. Introduction

The incidence of urinary incontinence, the involuntary loss of urine in sufficient quantities to be considered a social or health problem, continues to grow as the geriatric population increases. Urinary incontinence is caused by hyper reactivity of the detrusor muscle and is widely treated by muscarinic receptor antagonists, particularly acting at the M_3 subtype.[1] Racemic oxybutynin (ditropan) is a widely prescribed muscarinic receptor antagonist for the treatment of urinary urgency, frequency and incontinence, but it suffers from side effects such as dry mouth, tachycardia and mydriasis.[2] (*S*)-Oxybutynin is currently being evaluated in phase III clinical trials for the treatment of overactive bladder. As a continuation of our efforts to develop cost-effective syntheses of (*S*)-oxybutynin,[3,4] we have sought to identify an efficient asymmetric synthesis of (*S*)-cyclohexylphenyl glycolic acid, [(*S*)-CHPGA], the key intermediate to (*S*)-oxybutynin (Scheme 1). Herein, we report a successful asymmetric synthesis of (*S*)-CHPGA at pilot scale that is suitable for large-scale manufacturing.



(*S*)-Oxybutynin ·HCl (*S*)-**1** (CHPGA) (*S*)-**2**

Scheme 1.

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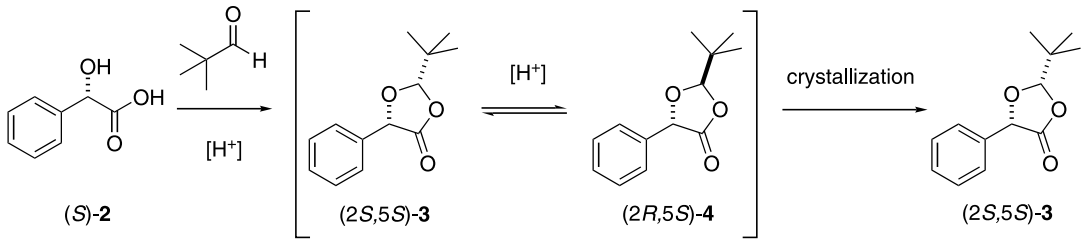


Scheme 2. Synthesis of dioxolone **3**.

2. Results and discussion

2.1. Diastereoselective dioxolone formation

Since the landmark work by Seebach et al.,[5] the concept of self-regeneration of stereocenters has found widespread applications in organic synthesis, especially in the creation of quaternary stereocenters. The requirement of pentane as the reaction solvent, however, severely limited its use in large-scale production. For the practical scale-up of the reaction, the highly volatile and flammable solvent pentane[4b] has to be avoided. It is widely perceived that solvents with higher boiling points such as heptane or hexanes result in rather low diastereoselectivity.[6] The Merck group[7] has used triisopropyl orthoformate in toluene to prepare an orthoester of mandelic acid before the addition of pivaldehyde to achieve high diastereoselectivity of the desired dioxolone, but this approach adds an additional step to the reaction sequence and also requires the use of a relatively expensive reagent, triisopropyl orthoformate. Our goal was to develop a practical method that was both highly selective and economical.

Since the dioxolone **3** is a highly crystalline product, formed from (*S*)-mandelic acid in pentane, we reasoned that the selective formation of the *cis* isomer could be driven by selective crystallization (Scheme 2).[8] If this is the case, under equilibration conditions, crystallization of a mixture of (2*S*,5*S*)-**3** and (2*R*,5*S*)-**4** should result in products that are highly enriched in a single diastereomer, even if the diastereomeric ratio is low in solution.[9] A similar crystallization driven selective formation of imidazolidinones and ketimines has been reported.[10]

Catalytic amounts of methanesulfonic acid were used effectively to catalyze this formation as well as the epimerization of the dioxolones **3** and **4** in hexanes. In a typical experiment, a slurry of (*S*)-mandelic acid in hexanes was allowed to reflux with 1.1 equiv. of pivaldehyde and 0.3 equiv. of methanesulfonic acid. The water generated in the reaction was separated with a Dean–Stark trap. The samples of the slurry were dissolved in THF and the diastereomeric ratios determined by HPLC analysis. At 70°C the diastereomeric ratio was approximately 4/1. When the slurry was allowed to slowly cool, the diastereomeric ratio increased dramatically, and a 51/1 diastereomeric ratio was obtained at 21°C and was increased to 91/1 when the mixture was cooled to 0°C (Fig. 1).

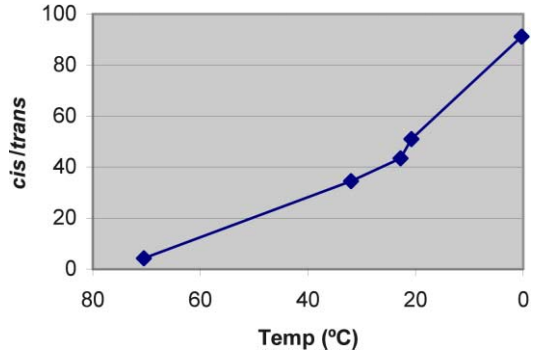


Figure 1. Dependence of diastereomeric ratio on temperature (*cis*/*trans* ratio refers to the diastereomeric ratios of the slurry).

These results are in sharp contrast to the observations made by the Merck group. While the high selectivities achieved by the Merck group seemed to originate from kinetic control, our results appear to favor a thermodynamically controlled formation of the *cis*-diastereomer, presumably due to the highly crystalline nature of *cis*-**3**. In a control experiment, a mixture of the *cis*-**3** and *trans*-**4** isomers was stirred in hexanes at 21°C in the presence of 0.1 equiv. of methanesulfonic acid with the diastereomeric ratio increasing with time (Fig. 2). Starting with a ratio of 1.3/1 *cis*/*trans*, the diastereomeric ratio increased rapidly to 25/1 in 1.3 h at 21°C and approached steady state. Decreasing the temperature to 0°C resulted in a ratio of 42/1. On the other hand, in a toluene solution with 6 mol% of *p*-toluenesulfonic acid monohydrate (similar to the Merck conditions), a mix-

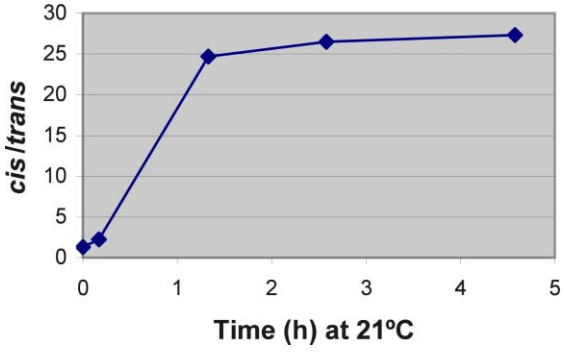


Figure 2. Equilibration of dioxolones **3**/**4** with methanesulfonic acid (*cis*/*trans* ratio refers to the diastereomeric ratios of the slurry).

ture of **3** and **4** (1.3/1 ratio of **3**/**4** by HPLC) did not give any measurable change in ratio at 20–28°C over 18 h.

The increase in the diastereomeric ratio of **3**/**4** at lower temperatures is also closely related to the solubility of **3** in the specific hydrocarbon solvents tested. Figure 3 shows the solubility curve of **3** in heptane.[11] At 69°C, the solubility of **3** is 29.4 mg/mL in heptane while its solubility decreases to <5 mg/mL at 0°C. The isomer *trans*-**4** has not been crystallized, as it is oil at ambient temperature. It is also noteworthy that during the formation of **3** from (*S*)-mandelic acid **2**, the ratio of **3**/**4** remained <2/1 in the solution phase throughout the cooling process from 68 to 0°C. This observation supports the hypothesis that selective formation of **3** is driven by crystallization of **3** from the reaction mixture and is in agreement with LeChatelier's principle.

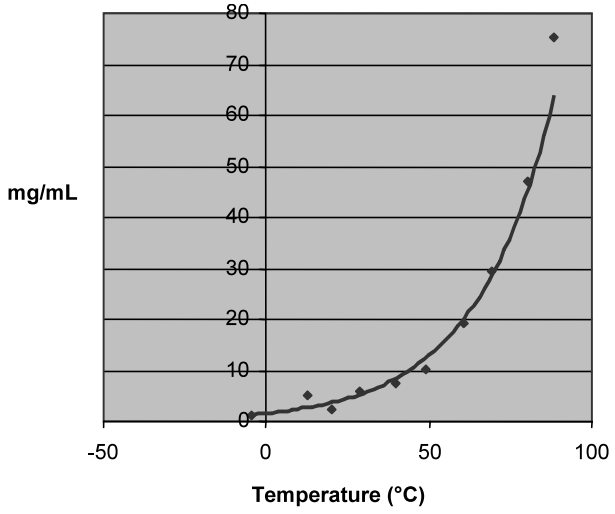


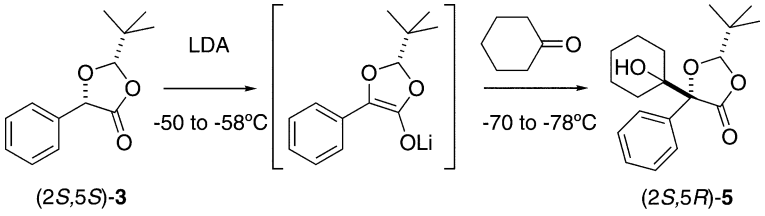
Figure 3. Solubility of **3** in heptane at different temperatures.

Since this process proceeds at a higher temperature compared to previously published conditions in pentane, it is necessary to assess the potential for racemization of dioxolone **3**. A chiral HPLC method was developed to separate each of the four stereoisomers of the dioxolones.[12] Under the reaction conditions above, no detectable racemization occurred. On the other hand, when heptane was used as a reaction solvent, the reflux temperature rose to about 91°C with partial racemization (about 2%/h) occurring. It is possible to lower the reflux temperature of the heptane mixture by applying a vacuum in the system while separating water by a Dean–Stark trap. This method, which was demonstrated at a kilolaboratory scale, eliminated the partial racemization seen at higher temperature and has yielded comparable results as with the hexanes. However, when compared to the hexanes process, this process modification increased the operational difficulty associated with maintaining the system at constant pressure and complicates the efficient scale-up of the process.

2.2. Telescoped process: aldol addition reaction

With a reliable method available for the highly selective synthesis of **3**, we then turned our attention to a telescoped process without isolating dioxolone **3**. In order to solubilize **3** after quenching the reaction, THF was added, and the mixture heated to 60°C. A clear solution formed and the phases were separated. The organic phase was azeotropically dried at reflux with a Dean–Stark trap. This dried solution of **3** was then cooled to about −78°C with dioxolone **3** partially crystallizing to form a slurry in the mixed solvent of THF and hexanes. A solution of LDA was then added to the slurry at −70 to −78°C and the reaction mixture allowed to warm to −50 to −58°C for 1 h to complete the enolate formation. The mixture was then cooled to about −78°C. Cyclohexanone was added between −70 and −78°C and after quenching and aqueous work-up, the desired aldol intermediate **5** was found to be >98% by HPLC analysis (Scheme 3). On the other hand, if the enolate formation was kept below −70°C, the aldol intermediate **5** was found to be contaminated with 10–20% of dioxolone **3**, suggesting that the deprotonation was incomplete at −70 to −78°C. This is not surprising given the fact that both **3** and its lithium enolate were not completely soluble in the reaction solvent system below −40°C. When the enolization was allowed to proceed above −40°C, the reaction yield was decreased and highly variable (50–75%), due to significant side reactions during the enolization reaction at higher temperatures.

The aldol addition reaction proceeded smoothly at −70 to −78°C in 1–2 h. Quenching the reaction at a low temperature proved critical in order to obtain both a high yield and high diastereoselectivity of the aldol intermediate **5**. The reaction could be quenched with either concentrated HCl or an acetic acid solution. When the temperature of the reaction mixture was allowed to rise above −40°C, decomposition of the aldol reaction mixture began to occur and the diastereomeric ratio of **5** was lowered. When the inter-



Scheme 3. Aldol addition reaction.

nal temperature was maintained below −60°C, **5** could be obtained with high diastereoselectivity (>97/3). After quenching the reaction, the organic layer was separated and washed with water and potassium bicarbonate solution. A solvent switch to heptane was performed and the desired product **5** was crystallized and isolated in high yield (91%). This highly efficient process was successfully scaled-up in kilolab and demonstrated at pilot scale with 15 kg input of (*S*)-mandelic acid per batch and the aldol intermediate **5** was isolated in 82–85% yield with high chemical purity and isomeric purity (Table 1).

2.3. Conversion of aldol intermediate 5 to (*S*)-CHPGA 1

During our earlier process research evaluations, we found that the aldol intermediate **5** could be converted to (*S*)-CHPGA **1** via two alternative routes (Scheme 4).[4b] In the first route (Path A), **5** was subjected to an elimination process with thionyl chloride/pyridine followed by hydrolysis under KOH/MeOH/H_2O conditions to yield unsaturated (*S*)-CHPGA **7** that was further converted to (*S*)-CHPGA **1** by hydrogenation with 10% Pd–C. In an alternative route (Path B), the last two steps in Path A were reversed, i.e. hydrogenation was carried out after elimination to afford the saturated dioxolone **8** that was further converted to (*S*)-CHPGA **1** under the hydrolysis conditions described previously. In order to select one of the two routes for further development, both the sequences were carried out on a 25 g scale and compared for the chemical yield, product quality, volumetric productivity, convenience and potential for the development of a telescoped process.

Although both of the routes are very comparable in terms of yields, in general, Path A produced more impurities. In addition, hydrogenation of the potassium salt of **7** did not proceed at a favorable reaction rate, and also generation of the free acid **7** and hydrogenation was very cumbersome and inefficient, which would lead to difficulties in telescoping the two steps. On the other hand, Path B generated less impurities and the crude reaction mixtures were conveniently carried forward in further transformations. Thus, the Path B process was selected for further development.

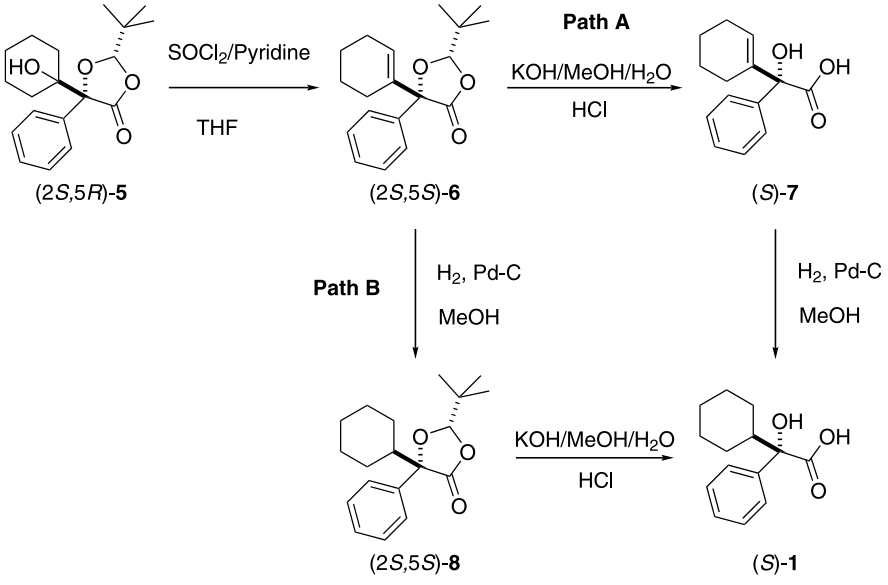
2.4. Elimination reaction of aldol intermediate 5

In our earlier work,[4b] the aldol intermediate **5** was treated with thionyl chloride and pyridine in THF at 0–5°C over about 1 h followed by quenching and washing the reaction with saturated ammonium chloride. Hydrogenation of the resulting reaction mixture was problematic and typically resulted in very low or no conversion most likely due to poisoning of the Pd–C catalyst by sulfurous acid that is formed after hydroly-

Table 1. Data for isolated aldol intermediate **5**

Scale	Yield (%)[a]	Total impurities (%)	SLI[b] (%)	Ee (%)	De (%)
125 g	91	0.1	<0.1	>99.9	>99.9
0.7 kg	87	0.7	0.7	99.8	>99.9
15 kg	**85**	**<0.1**	**<0.1**	**>99.9**	**>99.9**

[a] % yield is the overall yield of the aldol intermediate.
[b] Single largest impurity.



Scheme 4. Synthesis routes of (*S*)-**1** from (2*S*,5*R*)-**5**.

Table 2. Data for elimination reaction

Scale	Conversion (%)	Total Impurities (%)
50 g	>99.9	0.1
100 g	>99.9	0.2

HPLC area %.

sis of excess thionyl chloride. The work-up procedure was modified to remove sulfurous acid, and MTBE, a less expensive and more hydrophobic solvent, was used in place of THF to further improve the process reliability. When the elimination reaction was conducted in MTBE utilizing 1.3–1.4 equiv. of thionyl chloride and 2.1 equiv. of pyridine, the reaction conversion was >99.9% after 1 h at 0–22°C. The by-products in the reaction were identified as the pyridinium salts and sulfurous acid. The pyridinium salts were completely removed by water washes, and aqueous bicarbonate washes were performed to remove the residual sulfurous acid. The elimination process worked very well with these modifications and produced the unsaturated dioxolone **6** in good yields and high quality (Table 2). The elimination process streams with these modifications consistently underwent clean hydrogenation in the next step, indicating that telescoping the elimination and hydrogenation processes was feasible.

2.5. Hydrogenation of unsaturated dioxolone 6

For the development of a telescoped process we first needed to demonstrate that the hydrogenation of unsaturated dioxolone **6** obtained from the process stream would work well at large scale. After an initial screen for the catalyst type and catalyst loading, 10% Pd–C at 0.75 mol% loading was selected for development. An elimination reaction mixture obtained using the work-up conditions described above was hydrogenated at ambient temperature under 50 psi H_2 with 10% Pd–C (50% wet Degussa catalyst). For safety reasons a 50% water wet catalyst was selected and evaluated without pretreatment for batch efficiency. The reaction was judged complete by HPLC after 41 h with >99% conversion and 99.8% purity (Table 3). Further optimization was necessary to achieve the hydrogenation target of 6–8 h reaction time. Increasing the H_2 pressure to 100 psi did not improve the rate of the reaction. However, when the hydrogenation was run at 100 psi H_2, at 50–55°C, the reaction was complete after 16 h. This was an encouraging result, although the time required for the reaction was still longer than desired. In general, hydrogenations proceed faster in polar solvents such as methanol, ethanol, and isopropanol than in non-polar solvents such as MTBE. When 10 vol% of methanol was added to the MTBE solution of the unsaturated dioxolone **6**, and the hydrogenation was conducted at 55°C, 10% Pd–C and 100 psi, H_2, the saturated dioxolone **8** formed with quantitative conversion within 6 h. It was observed that the 50% wet Degussa catalyst does not disperse well in a solution of substrate and MTBE alone. After adding methanol, the catalyst dispersion was markedly improved. The efficient dispersion of the water wet catalyst by reducing the aggregation of the catalyst and increasing the surface area available for the reaction is likely one of the factors for the observed acceleration of the reaction rate.

2.6. Hydrolysis of saturated dioxolone 8 to (*S*)-CHPGA 1

Sodium hydroxide was used for the hydrolysis in place of potassium hydroxide used in the earlier version[4b] of this method due to its lower molecular weight and the higher water solubility of the by-product (NaCl versus KCl), which facilitates the work-up and isolation and affords higher reaction concentrations (increased volumetric productivity). The saturated dioxolone **8** was suspended in a mixture of MeOH/H_2O (1:1) containing 5 equiv. of NaOH and the resulting slurry refluxed at 70–73°C until a clear solution was obtained. After about 2 h, HPLC analysis indicated >99% conversion to CHPGA **1** which could be isolated with 99.96% purity. Since an efficient solvent exchange from MTBE following the hydrogenation was possible, MTBE was removed by distillation after the addition of aq. NaOH and methanol. Each of the three stages could be telescoped into a through process from the aldol intermediate **5** to (*S*)-CHPGA **1**.

The key by-products formed during the hydrolysis reaction and work-up are sodium chloride, pivaldehyde, neopentyl alcohol and pivalic acid. Pivaldehyde, generated during hydrolysis, further undergoes a Cannizzarro reaction to yield neopentyl alcohol and the sodium salt of pivalic acid. The level of NaCl generated during the neutralization of the hydrolysis reaction can have a dramatic effect on the (*S*)-CHPGA **1** crystallization process quality. Therefore, it is desirable to have a minimal amount of NaCl present during the crystallization and a study utilizing <5 equiv. of NaOH was conducted. A portion of the results is summarized in Table 4. As expected, the reaction was slower with fewer equiv. of NaOH, but alternatives are currently

Table 3. Hydrogenation of unsaturated dioxolone **6** with 0.75 mol% of 10% Pd–C catalyst

Conditions	Solvent	Time (h)	Conversion (%)	Total impurities (%)
50 psi/22°C	MTBE	41	>99.9	0.2
100 psi/22°C	MTBE	45	>99.9	0.4
100 psi/55°C	MTBE	16	>99.9	0.3
100 psi/55°C	MTBE/MeOH (10:1)	6	>99.9	0.3

Reaction scale: 25 g.

Table 4. Hydrolysis of saturated dioxolone **8**

Scale	Equiv. of NaOH	Reaction time (h)
25 g	5.0	4.0
25 g	1.5	6.5
25 g	2.0	5.5

under investigation. The hydrolysis reaction was complete after 5.5 and 6.5 h with 2.0 and 1.5 equiv. of NaOH respectively. HPLC analysis of the reaction mixture after completion of the reaction indicated a similar impurity profile for each of these reaction conditions.

2.7. Demonstration of the telescoped process

After successful laboratory execution of each of these reactions to demonstrate both high conversion and purity, the research effort was focused on development of a telescoped process (Scheme 5) first at 150 g and then at pilot plant scale. Since the impurity profile of a telescoped process (no isolated intermediates) would be expected to be different than that of a process with stepwise isolations, it was decided to optimize the robustness of the isolation/crystallization process of (S)-CHPGA **1** in correlation with development of the telescoped reactions.

2.8. Elimination reaction of aldol intermediate 5

When the elimination reaction was scaled up to 150 g using the conditions described earlier, the unsaturated dioxolone **6** was formed with >99.9% conversion and >99.7% purity (HPLC analysis). The elimination reaction worked very well at 1 kg and 10 kg scales (Table 5).

Table 5. Data for elimination reaction

Scale	Conversion (%)	Total impurities (%)
150 g	>99.9	0.24
150 g	>99.9	0.20
1 kg	>99.9	0.18
10 kg	**>99.9**	**0.20**

2.9. Hydrogenation of unsaturated dioxolone 6 reaction stream

The hydrogenation reactions were conducted directly on the reaction mixtures obtained after the work-up of the elimination reaction. Methanol was added to the reaction mixture to make the MTBE/MeOH ratio 10:1, followed by the addition of 0.75 mol% of 10% Pd–C Degussa catalyst (50% water wet). A slow warming of the reaction to 40°C under a controlled feed of hydrogen (<100 psi)[13] was required during the initiation of hydrogenation. The reaction temperature was allowed to rise to 50–55°C. Once the initial exothermic reaction was consumed, the hydrogen feed was adjusted to 100 psi and the reaction temperature maintained at 50–55°C. The reaction was complete after 6 h and the saturated dioxolone **8** produced in high yield and purity. Conversion was nearly quantitative with >99.7% of purity of **8** with <0.3% impurities. Similar results were obtained at 1 kg and 10 kg scales (Table 6).

Table 6. Data for hydrogenation reaction

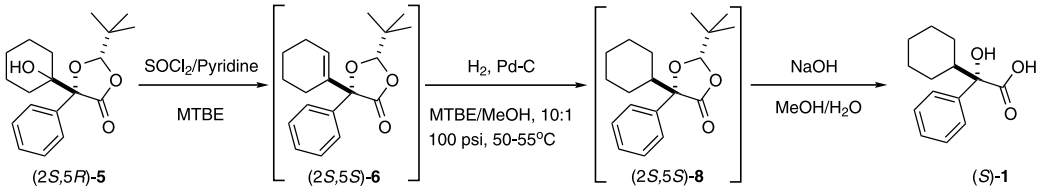
Scale	Conversion (%)	Total impurities (%)
150 g	>99.9	0.20
150 g	>99.9	0.15
1 kg	>99.9	0.20
10 kg	**>99.9**	**0.30**

2.10. Hydrolysis of saturated dioxolone 8

The reaction mixtures obtained after hydrogenation were filtered through celite to remove the catalyst, after which 2 equiv. of aq. NaOH (3 M) were added and MTBE removed by distillation. Methanol was added to the resulting slurry to obtain a 1:1 ratio of methanol/water and the reaction refluxed over approximately 5–6 h to complete the dioxolone hydrolysis. HPLC analysis of the reaction indicated nearly quantitative conversion with formation of <2% in-process impurities and was independent of scale.

2.11. Work-up and isolation of (*S*)-CHPGA 1

During the laboratory investigation phase of this work, it was determined that both pivaldehyde and neopentyl alcohol could not be completely removed by extracting the reaction mixture with heptane. Since the reaction solvent is a 1:1 mixture of methanol/water, and pivaldehyde and neopentyl alcohol are also soluble in methanol, they could not be efficiently extracted with heptane. Using alternative extraction solvents such as MTBE proved to be unsuccessful. MTBE was also found to be partially miscible with the reaction mixture. One solution was to distill methanol and pivaldehyde (bp 74°C/730 mm). Thus, after the completion of the



Scheme 5. Telescope process for the synthesis of (*S*)-**1** from (2*S*,5*R*)-**5**.

reaction, methanol and pivaldehyde were distilled at atmospheric pressure until the reaction temperature reached 95°C. The reaction was then cooled to room temperature and washed with heptane. Methanol and water were added back to the reaction mixture followed by neutralization with about 3 equiv. of 6 M HCl. The resulting slurry was stirred at room temperature, filtered and the wet cake washed twice with water, and then heptane to provide (*S*)-CHPGA after drying in 94–95% yield and >99.9% chemical and enantiomeric purity. The hydrolysis worked very well at kilo and pilot plant scales (Table 7).

In conclusion, a practical and scalable asymmetric synthesis of (*S*)-CHPGA has been developed starting from (*S*)-mandelic acid. This efficient five-step process gives (*S*)-CHPGA in 86% overall yield with only two isolations. This process has been successfully performed at pilot scale (15 kg inputs of mandelic acid) to provide (*S*)-CHPGA **1** with very high chemical and enantiomeric purity.

3. Experimental

3.1. *cis*-(2*S*,5*S*)-2-(*tert*-Butyl)-5-phenyl-1,3-dioxolan-4-one (*S*,*S*)-3

To a suspension of (*S*)-mandelic acid (125 g, 0.822 mol) in hexanes (625 mL) was added pivaldehyde (98.2 mL, 0.904 mol, 1.1 equiv.), followed by the addition of methanesulfonic acid (16.0 mL, 0.25 mol, 0.3 equiv.) under argon with stirring. The internal temperature rose to 26°C from 19°C. The mixture was then heated to reflux with the separation of water by a Dean–Stark trap. When about 11 mL of water was collected, the internal temperature rose to about 71°C. The mixture was then distilled to remove about 125 mL of solvent. The mixture was stirred and cooled to 35°C in about 1 h and HPLC analysis of a sample of the slurry showed about 0.7% (area percent) of (*S*)-mandelic acid and diastereomeric ratio of 30/1. It was then stirred at room temperature for 2 h, cooled to 0°C and stirred for 1 h. The mixture was quenched at 0°C by adding 20% $KHCO_3$ solution (250 g), maintaining the internal temperature below 5°C. After the addition of THF (500 mL), the mixture was heated to 60°C and the solid dissolved. The aqueous layer was removed and HPLC analysis of the organic layer showed 101/1 *syn*/*anti*. The organic solution was refluxed with a Dean–Stark trap to remove water until the organic layer showed <0.1% water by Karl–Fisher titration (internal temperature about 66°C). It was then distilled to remove about 125 mL of solvent and cooled to −78°C with stirring (crystals precipitated from the solution upon cooling).

In a separate flask, LDA was made from diisopropylamine (138 mL, 0.986 mol, 1.2 equiv.) in THF (100) by the addition of *n*-BuLi (2.43 M in hexanes, 372 mL, 0.90 mol, 1.1 equiv.) at 0 to −10°C. The LDA solution was then added to the above slurry maintaining the internal temperature below −70°C. The mixture was then stirred at −70 to −75°C for 2 h, warmed to −55°C and stirred between −50 and −58°C for 2 h to ensure the complete formation of the enolate. The mixture was then cooled to −78°C and a solution of cyclohexanone (93.7 mL, 0.90 mol, 1.1 equiv.) in heptane (95 mL) added slowly to maintain the internal temperature below −70°C. After the addition of cyclohexanone, the mixture was stirred at −70 to −78°C for 2 h. The reaction was quenched by adding concentrated HCl (177 mL, 2.5 equiv.) slowly so that the internal temperature was maintained below −70°C for the first third and below −50°C for the rest of the HCl addition. The mixture was then allowed to warm to 10°C after which water (125 mL) was added. The aqueous layer was removed and the organic layer washed consecutively with water (250 mL), 20% $KHCO_3$ (125 g) and water (125 mL). It was distilled to about 600 mL under reduced pressure, while maintaining the internal temperature <60°C. Heptane (625 mL) was added and distilled to about 600 mL. Another portion of heptane (625 mL) was added and distilled to about 600 mL again. The solvent in the pot contained <1% THF as judged by GC. Heptane (500 mL) was added and the mixture cooled to 0°C and stirred for 2 h. The slurry was then filtered and the cake washed with heptane (125 mL). The solid was dried under high vacuum at 35–45°C for 5 h to give the title compound as a white crystalline product (238.0 g, 91.0%).

3.2. (*S*)-Cyclohexylphenyl glycolic acid 1

To a slurry of (2*S*,5*R*)-2-*tert*-butyl-5-(1-hydroxycyclohexyl)-5-phenyl-[1,3]dioxolan-4-one (150 g, 0.47 mol) in 900 mL MTBE was added thionyl chloride (73.4 g, 0.62 mol) and pyridine (77.34 g, 0.98 mol) sequentially at 0–20°C. The reaction was stirred for 1.5 h. After quenching the reaction with water (600 mL), the aqueous layer and organic layer were separated. The organic layer was washed with water (600 mL), 20% aq. $KHCO_3$ (600 mL) and water (450 mL) successively.

Table 7. Data for isolated (*S*)-CHPGA **1**

Scale	Yield (%)[a]	Assay (%)[b]	Total impurities (%)	SLI[c]	ee (%)
150 g	104 g (94.2)	99.98	0.02	0.02	>99.9
150 g	105 g (95.2)	99.90	0.10	0.03	>99.9
1 kg	0.685 kg (93.1)	99.93	0.07	0.07	>99.9
10 kg	**6.72 kg (92.1)**	**99.90**	**0.10**	**0.05**	**>99.9**

[a] % yield is the overall yield for the three steps.
[b] Purity determined by titration assay.
[c] Single largest impurity.

After adding 90 mL methanol, the organic layer was subjected to hydrogenation for 6 h at 100 psi/55°C using 10% Pd–C (0.75 mol%, 50% wet Degussa type) catalyst. The reaction mixture was filtered through celite to remove the catalyst. A solution of 38 g (0.95 mol) of NaOH in 300 mL of water was added to the MTBE solution and MTBE distilled. 300 mL of methanol was added to the resulting slurry and the heterogeneous reaction heated to reflux for approximately 6 h. After distillation of volatiles, the reaction was washed with heptane (600 mL). Methanol (240 mL) and water (960 mL) were added and the reaction mixture was cooled to 12°C, and 240 mL of 6 M HCl was added while maintaining the temperature below 20°C. The resulting slurry was stirred at room temperature for 1 h. The slurry was then filtered and the cake was washed with water (2×300 mL), heptane (2×300 mL), and dried to yield (*S*)-CHPGA as white solid (104 g, 94.2% yield, >99.9% enantiomeric excess). The ee was determined by HPLC (Chiralpak AS, mobile phase 95% hexane/5% IPA/0.1% TFA). (*S*)-**1** elutes at approximately 9.24 min. (*R*)-**1** elutes at approximately 6.36 min. ^{1}H NMR ($CDCl_3$) δ 1.01–1.76 (m, 10H), 2.17 (m, 1H), 5.20 (bs, 1H), 7.23 (t, $J=7.7$ Hz, 1H), 7.33 (t, $J=7.7$ Hz, 2H), 7.61 (d, $J=7.7$ Hz, 2H). ^{13}C NMR δ 25.57, 26.27, 26.42, 27.52, 81.15, 126.10, 127.85, 128.24, 140.03, 180.97. MS (m/e) 234 (M^+). Anal. calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.86; H, 7.77.

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6. Although both hexane and heptane are classified as flammability 1 solvents (composition of flammable mixture is 1–7 wt% in air), heptane is generally considered to be a better solvent for scale-up because hexane has a higher tendency to build up static charge (conductivity @ 23°C: heptane 200 pS/m; hexane 10 pS/m). See: McConville. F.X. *The Pilot Plant Real Book: A Unique Handbook for the Chemical Process Industry*; FXM Engineering and Design, 2002; Chapter 6.
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11. The solubility curve of dioxolone **3** in hexanes is expected to be similar to that obtained in heptane.
12. HPLC conditions: column: Regis Whelk-O-1(*R*,*R*), 5 μm×25 cm×4.6 mm; mobile phase: hexanes/IPA 97/3, ambient temperature at 1 mL/min; UV detection at 210 nm. Retention times: (2*R*,5*S*)-**4**, 5.95 min; (2*S*,5*R*)-**4**, 8.47 min; of (2*S*,5*S*)-**3**, 9.10 min; of (2*R*,5*R*)-**3**, 12.51 min.
13. Hazard analyses were completed to determine the reaction profile and better define the scale-up conditions.