Chiral Mandelic Acid Template Provides a Highly Practical Solution for (*S*)-Oxybutynin Synthesis

Paul T. Grover, Nandkumar N. Bhongle, Stephen A. Wald, and Chris H. Senanayake*

Chemical Research and Development, Sepracor Inc., 111 Locke Drive, Marlborough, Massachusetts 01752

csenanay@sepracor.com

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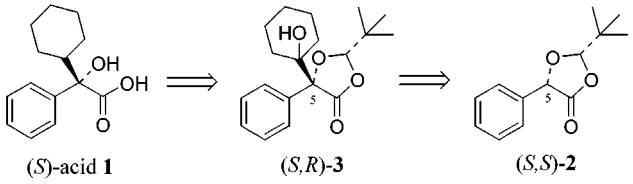
Introduction

The abundant occurrence and biological significance of compounds containing a tertiary α-hydroxy acid has stimulated considerable interest in their synthesis.[1] Tertiary hydroxy acids are highly important intermediates in the asymmetric synthesis of a variety of medicinal agents[2] and natural products.[3] For example, racemic oxybutynin (Ditropan) is a widely prescribed muscaronic receptor antagonist for the treatment of urinary frequency, urgency, and urge incontinence. Unfortunately, it exhibits classical antimuscarine side effects, such as dry mouth.[4] However, preliminary biological results suggest that (*S*)-oxybutynin displays an improved therapeutic profile compared to its racemic counterpart, and it is currently in phase III clinical trials. Like a majority of the muscarinic receptor antagonists, oxybutynin is composed of a tertiary α-hydroxy acid as a key component.[2] Recently, we disclosed an attractive process for the production of enantiopure (*S*)-acid **1** utilizing the addition of cyclohexyl Grignard to aminoindanol-derived ketoesters.[5] Although the diastereoselective Grignard addition process is appealing for the large-scale synthesis of (*S*)-oxybutynin, a more economic route was sought. Several approaches can be devised for the synthesis of enantiopure (*S*)-acid **1** by analysis of various asymmetric synthetic protocols. However, for the development of a highly practical and cost-effective process the following criteria must be met: (a) starting materials should be inexpensive and available on a commercial scale; (b) the overall process should be highly diastereo- or enantioselective with excellent yields, and (c) the overall process should be practical and amenable to scale-up. Herein, we disclose a cost-effective and operationally simple practical technology for (*S*)-**1** of oxybutynin by utilizing the readily available and inexpensive starting materials (*S*)-mandelic acid and cyclohexanone.

Scheme 1. Synthetic Plan for the Generation of Enantipure α-Tertiary Acid 1



Seebach and co-workers have described alkylation and aldol reactions of chiral lithium enolate acetal derivatives that react with self-reproduction of chirality.[6] This self-generation of stereocenter concept has been applied in numerous occasions in natural product and medicinally important target synthesis.[7] As outlined in Scheme 1, our strategy was to use mandelic acid derivative **2** as a chiral controller for the diastereoselective C−C bond forming process at the C-5 carbon of dioxolone **2** with cyclohexanone,[8] to provide enantiopure strategic lactone **3**. The lactone **3** then effectively transfers to (*S*)-acid **1** by simple and practical chemistry.

Results and Discussion

First, we focused on the development of a practical process for diastereomerically pure (*S,R*)-lactone **3**. To develop an economical and scalable process for (*S,R*)-**3**, the following diastereoselective processes needed to be highly controlled: (a) (*S*)-mandelic acid acetalization with pivaldehyde needs to be high yielding and highly selective; and (b) the aldol process of (*S,S*)-**2** with cyclohexanone needs to be highly diastereoselective, high yielding, and amenable to scale-up. Preparation of (*S,S*)-**2** has been reported on multiple occasions in the literature; however, no systematic optimization has been disclosed.[9] Therefore, we reexamined this important acetalization process.

* Ph: (508) 357-7459. Fax: (508) 357-7808.

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(8) (a) Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, 40. (b) We found the dioxolone prepared from pivaldehyde to be the dioxolone of choice. Other dioxolones prepared from $(CH_3)_2CHCHO$, $(Ph)_2CHCHO$, $(Me)_2PhCHCHO$, and $MePh_2CCHO$ were also examined. However, the diastereoselectivity in the preparation of these dioxolones was poor.

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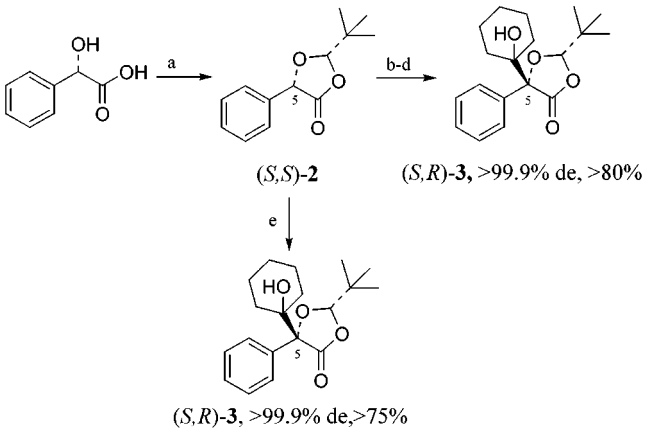
A variety of acid catalysts, such as MsOH, TsOH, H_2SO_4, P_2O_5, H_3PO_4, Amberlyst, clay-10, TfOH, H_2SO_4–MsOH, etc., with various solvents, such as pentane, hexane, heptane, toluene and ethers, for acetalization of pivaldehyde with (*S*)-mandelic acid were examined.[10]

Interestingly, reaction conditions employing catalytic TfOH (3–5 mol %) as the most effective catalyst with pentane as the solvent at reflux were used to obtain the highest *cis*-selectivity (dr, 97:3). The process was conducted as follows. Simply mix 1.1 equiv of pivaldehyde[11] and 1.0 equiv of (*S*)-mandelic acid in pentane with catalytic TfOH (1–5 mol %), followed by azeotropic removal of water. Once the acetalization is complete (reaction is monitored by HPLC), the reaction mixture is washed with aqueous $NaHCO_3$, followed by a solvent switch to water, which resulted in a 96% yield of pure white solid (*S*,*S*)-**2** with >97% *cis*-selectivity. It is important to note that the compound (*S*,*S*)-**2** (dr, 97:3) could be readily enriched to its diastereomeric purity by simple crystallization with heptane/EtOAc (20:1) affording excellent recovery (>95%). This process was routinely conducted on a greater than 100-g scale in our laboratory without complications. Our attention was then focused on the examination of a stereocontrolled aldol reaction between the enolate of (*S*,*S*)-**2** with cyclohexanone (Scheme 2). Deprotonation of diastereomerically pure (*S*,*S*)-**2** with LHMDS in THF at −78 °C, followed by the addition of cyclohexanone at −78 °C, and aging for a minimum of 15 min affords the aldolate in excellent diastereoselectivity (98:2) with an 85% yield.[12] Crystallization of crude aldol adduct (*S*,*R*)-**3** (dr, 98:2) in heptane provided diastereomerically pure (*S*,*R*)-**3** in >90% recovered yield. From a process simplicity point of view, the following aldol process was designed for generation of diastereomerically pure (*S*,*R*)-**3**. The (*S*,*S*)-**2** (dr, 97:3) was subjected to newly developed aldol conditions in THF at −78 °C to provide (*S*,*R*)-**3** with ~95% diastereoselectivity. The reaction mixture was then quenched with 10% NH_4Cl solution at −78 °C. The organic layer was separated, and the solvent was switched to heptane to induce crystallization, which yielded diastereopure (*S*,*R*)-**3** in 76%. This process was consistently performed on a 100-g scale without complications.

Scheme 2



Reagents and conditions: (a) pivaldehyde, cat. TfOH, pentane, >97% dr; (b) crystallization in heptane, >95%, >99.5% de; (c) LHMDS, THF, −78 °C, 1 h then cyclohexanone, 85%, 98:2 dr; (d) crystallization in heptane, >90%; (e) LHMDS, THF, −78 °C, 1 h then cyclohexanone at −78 °C, >1 h, 10% NH_4Cl, then solvent switch to heptane, >99.9% de, >75%.

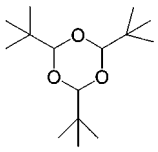
Table 1. Influence of Temperature on the Diastereoselective Aldol Process

entry	temperature (°C)	dr of (*S*,*R*)-**3**:(*S*,*S*)-**3**
1	−78	98:2
2	−40	1.1:1
3	0	18:82

The salient feature of the aldol reaction is the temperature dependence of the diastereoselectivity (Scheme 3). At −78 °C, the aldol addition occurs to the face opposite the sterically encumbered *tert*-butyl group. As depicted in Table 1, the aldol addition of (*S*,*S*)-**2** with cyclohexanone at −78 °C favors *anti*-adduct (*S*,*R*)-**3** with 98:2 diastereoselectivity (Table 1, entry 1).[13] It is interesting to note that at higher temperatures, such as 0 °C, the aldol addition provides the thermodynamically preferred *syn*-adduct (*S*,*S*)-**3** with a dr of 82:18.[14] At −40 °C, very low selectivity was observed (Table 1, entry 2).

After development of a highly selective aldol process for (*S*,*R*)-**3**, our attention was focused on the removal of the hindered tertiary hydroxy group in the most effective fashion for the production of (*S*)-acid **1**. Literature indicates that there are several interesting methods to remove hydroxy groups; however, limited practical technologies are available.[15] Our approach to produce (*S*)-acid **1** uses the following protocol (Scheme 4): (a) elimination of tertiary alcohol using simple reagents such as $SOCl_2$/pyridine to give lactone (*S*,*S*)-**4**, and (b) either hydrolysis of lactone (*S*,*S*)-**4** and then hydrogenation of (*S*)-**5** (Scheme 4, path a) or hydrogenation of a double bond of (*S*,*S*)-**4** and then hydrolysis of (*S*,*S*)-**6** (Scheme 4, path b).

(10) (a) The optimal reaction temperature is between 35 and 40 °C. Higher temperatures provide decomposition and byproduct formation. The major byproduct formation process is trimerization of pivaldehyde, which was characterized as **10**.[11] Using 1.1 equiv of pivaldehyde and controlling the temperature to ~35 °C can totally minimize the trimerization process. (b) The optimal solvent for this process is pentane (bp = 35–36 °C). Other solvents such as hexanes, heptane, and toluene provided low selectivity after isolation, even at 35–40 °C. Higher reaction temperatures (>40 °C) and ethereal solvents also provided low selectivity. The optimal acid catalyst was found to be TfOH. Other acids, including MsOH, TsOH, and H_2SO_4 provided reasonable selectivities from 90:10 to 94:6.



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(11) Using 1.1 equiv of pivaldehyde is ideal for the reaction. Using more equivalents of aldehyde results in formation of the trimer byproduct **10**; see Denmark, S. E.; Wilson, T.; Willson, T. M. *J. Am. Chem. Soc.* **1998**, *120*, 984.

(12) (a) React IR experiments indicated that after addition of cyclohexanone at −78 °C, the reaction was complete within 5 min. However, the reaction was aged for an additional 30 min. (b) The absolute stereochemistry at C-2 was established by conversion of (*S*,*R*)-**3** to known (*S*)-**1** (lit. $[\alpha]^{22}_D$ = +22.6° (EtOH))[5] according to Scheme 3, path a.

(13) The reaction was performed at −100 °C; however the rate of reaction was greatly reduced and the selectivity was not improved.

(14) Heating to higher temperatures (>0 °C) results in some decomposition.

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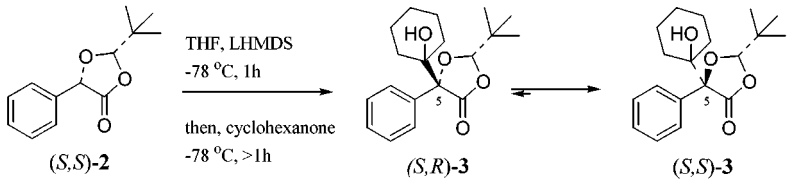
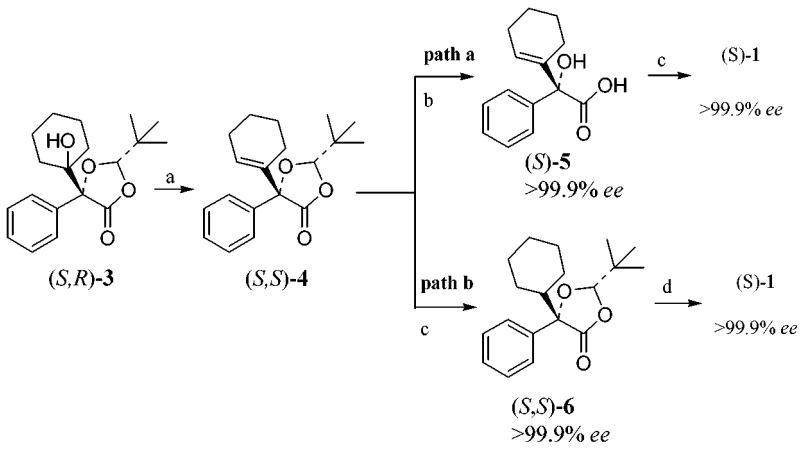
Scheme 3

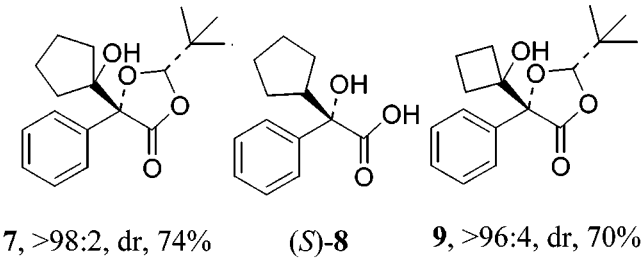


Scheme 4. Conversion of (*S*,*R*)-3 to Optically Pure (*S*)-Acid 1[a]



[a] Reagents and conditions: (a) $SOCl_2$, pyridine, THF, >98%; (b) KOH, MeOH, then HCl, 96%; (c) H_2, Pd/C, MeOH, 95% (d) KOH, MeOH, then HCl, 95%.

Scheme 5



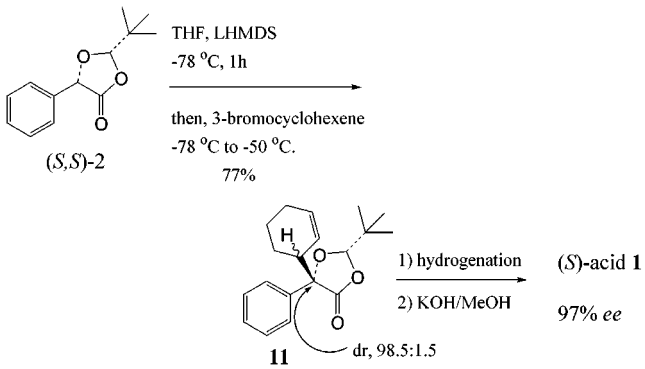
The preparation of (*S*)-**1** is depicted in Scheme 4. In this event, treatment of (*S*,*R*)-**3** with thionyl chloride in THF, followed by pyridine at 0 °C for 3−4 h, and then a mild acidic wash provided crude (*S*,*S*)-**4** in THF.[16] Crude (*S*,*S*)-**4** was not isolated but was directly converted to (*S*)-**5** via basic hydrolysis (KOH/MeOH/H_2O), to give the potassium salt of (*S*)-**5**. Treatment of the potassium salt solution of (*S*)-**5** with 6 N HCl directly precipitated (*S*)-**5** in 96% overall yield with >99.9% ee. The synthesis concludes with the hydrogenation of (*S*)-**5** with hydrogen over Pd/C (3 mol %) in MeOH. (*S*)-**1** was directly isolated from the reaction after a solvent switch to toluene in 95% yield with a >99.9% ee. Alternatively, as shown in Scheme 4, path b, treatment of (*S*,*S*)-**4** with 3 mol % Pd/H_2 in MeOH and then KOH followed by neutralization with 6 N HCl provided (*S*)-acid **1** in >90% yield with >99.9% ee. The process described in Scheme 4 provided an extremely practical entry for the preparation of the key subunit (*S*)-**1**, of (*S*)-oxybutynin. The overall yield of optically pure (*S*)-**1** is >65% from inexpensive mandelic acid.[17]

Encouraged by the outstanding efficiency of this asymmetric synthesis, related aldols derived from cyclopentanone and cyclobutanone were also prepared by this route (Scheme 5). In both cases, the diastereoselectivities of the aldol processes are excellent (dr, >96:4). However, the elimination of the hydroxy group of compound **9** using $SOCl_2$/Py at 0 °C was unsuccessful. Aldol product **7** was converted to the corresponding (*S*)-acid **8** in excellent yield, in a similar manner as the conversion of (*S*,*R*)-**3** to (*S*)-**1**, as shown in Scheme 4.[18]

In conclusion, we have shown a novel and practical solution for the synthesis of the optically active tertiary α-hydroxy acid component of (*S*)-oxybutynin. This new methodology should be applicable for large-scale preparations, owing to the crystalline intermediates formed, its

(16) (a) To obtain a clean reaction product, the order of addition of thionyl chloride and pyridine is essential. Thionyl chloride is added first, followed by pyridine. (b) A mild wash with aqueous ammonium chloride is necessary to remove sulfur impurities, which can poison Pd/C and render the hydrogenation to (*S*)-**1** ineffective.

(17) Alkylation of (*S*,*S*)-**2** with cyclohexyl iodide was unsuccessful. The more expensive 3-bromocyclohexene undergoes smooth alkylation to provide the alkylated adduct in 77% yield with >98:2 selectivity, which after hydrogenation followed by hydrolysis provides (*S*)-**1** in 97% ee in high yields. This alkylation chemistry is a facile entry to (*S*)-**1**. However, the availability of the bromocyclohexenyl in large scale limits practicality.



(18) The stereochemical assignments of **7**, **8**, and **9,** respectively, were predicated in an analogus manner to the (*S*)-**1** as discussed in ref 12b.

inexpensiveness, and the simplicity of the procedure. The scope and limitation of generating tertiary alcohol centers of medicinally valuable targets, with dioxolone derivatives, are being explored.

Experimental Section

General. Flash chromatography was performed on EM Science silica gel 60. Thin-layer chromatography was performed using silica gel 60 F_{254} plates, and compound visualization was effected with 10% H_2SO_4 containing 5% ammonium molybdate and 0.2% ceric sulfate. All reactions were carried out in oven-dried glassware under an argon atmosphere. KOH, (*S*)-(+)-mandelic acid, pentane, trifluoromethanesulfonic acid, 10% Pd/C, and lithium bis(trimethylsilyl)-amide were purchased from Aldrich chemical Company. Pivaldehyde was purchased from Lancaster chemical company.

***cis*-(2*S*,5*S*)-2-(*tert*-Butyl)-5-phenyl-1,3-dioxolan-4-one ((*S*,*S*)-2).** To a suspension of (*S*)-(+)-mandelic acid (50.0 g, 328 mmol) in pentane (500 mL) was added pivaldehyde (42.7 mL, 396 mmol), followed by addition of trifluoromethanesulfonic acid (1.23 mL, 14 mmol) at 22 °C. To the reaction flask was added a Dean-Stark trap. The mixture was warmed to 36 °C and allowed to reflux for 5.5 h. The reaction mixture was allowed to cool to room temperature, 8 wt % aqueous $NaHCO_3$ was added. and the reaction was concentrated in vacuo to remove volatiles (pentane). The slurry was filtered and dried to give 68.4 g (96%) of product with 97:3 diastereoselectivity. The formation of dioxolone is followed by HPLC (Zorbax RX C-8, mobile phase 0.05 M NaH_2PO_4 (pH 2.5)/methanol (40:60, v/v)) by observing the appearance of the dioxolone peak at approximately 8.85 min. ^{1}H NMR ($CDCl_3$) δ 1.11 (s, 9H), 5.27 (s, 1H), 5.35 (s, 1H), 7.46 (m, 5H). ^{13}C NMR δ 23.82, 34.68, 109.52, 127.26, 128.94, 129.39, 133.70, 172.07. Mass spectrum (*m*/*e*) 220 (M^+). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.88; H, 7.34.

***cis*-(2*S*,5*R*)-2-(*tert*-Butyl)-5-phenyl-5-(cyclohexyl-1-ol)-1,3-dioxolan-4-one ((2*S*,5*R*)-3).** To a −78 °C solution of lithium bis(trimethylsilyl)-amide (59.05 mL, 59.05 mmol, 1.0 M in hexanes) was added crude *cis*-(2*S*,5*S*)-2-(*tert*-butyl)-5-phenyl-1,3-dioxolan-4-one (10.0 g, 45.42 mmol, (dr 97:3), dissolved in 68 mL THF). The reaction mixture was allowed to stir for 1 h at −78 °C, followed by the addition of neat cyclohexanone (6.59 mL, 63.59 mmol). The reaction was aged for 15 min. With stirring, a solution of 10% NH_4Cl (10.0 mL) was slowly added. The reaction mixture was poured into a separatory funnel containing 10% NH_4Cl (131 mL). The aqueous layer was discarded. The organic layers solvent was switched to heptane, and the slurry was then filtered to provide 10.99 g of crude aldol product (76%) as a white solid. The formation of (2*S*,5*R*)-**3** is followed by HPLC (Zorbax RX C-8, mobile phase 0.05 M NaH_2PO_4 (pH 2.5)/methanol (40:60, v/v)) by observing the appearance of the (2*S*,5*R*)-**3** peak at approximately 12.93 min. The minor diastereomer (2*S*,5*S*)-**3** peak is observed at 13.27 min. The diastereomeric ratio is >99.5%. ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 9H), 1.38−1.98 (m, 10H), 5.53 (s, 1H), 7.39 (m, 3H), 7.76 (m, 2H). ^{13}C NMR δ 21.14, 21.23, 23.59, 25.32, 30.99, 31.22, 35.69, 86.68, 111.10, 126.98, 127.66, 128.13, 135.42, 172.54. Mass spectrum (*m*/*e*) 301 ($M^+ - H_2O$). Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.79; H, 8.15.

(*S*)-Cyclohex-1-enyl-hydroxy-phenyl-acetic Acid ((*S*)-5). To a 0 °C solution of *cis*-(2*S*,5*R*)-2-(*tert*-butyl)-5-phenyl-5-(cyclohexyl-1-ol)-1,3-dioxolan-4-one (72.7 g, 223 mmol) in THF (727 mL) was added thionyl chloride (46.5 mL, 637 mmol), followed by pyridine (82.8 mL, 1.02 mol). The reaction mixture was allowed to stir for 1 h at 0 °C, followed by the addition of saturated NH_4Cl solution (543 mL). The layers were separated, and the aqueous layer was discarded. The organic layer was charged with 274 g of water and 128 g of KOH. The reaction mixture was concentrated to remove volatiles, after which 136 mL of MeOH was added. The reaction mixture was then heated to reflux for 3 h and then cooled to 22 °C. Heptane (208 g) was charged. The layers were separated and the heptane layer was discarded. Next, 255 mL of 6 N HCl was added, in which white solids precipitated. The slurry was filtered to provide 51.0 g of product (96%). The ee is determined by HPLC (Chiralpak AS, mobile phase 95% hexane/5% IPA/0.1% TFA) by observing the (*R*)- and (*S*)-cyclohexenyl phenyl glycoxilic acid. (*S*)-**5** elutes at approximately 17.73 min. (*R*)-**5** elutes at approximately 13.43 min. The optical purity is >99.9% ee. ^{1}H NMR (DMSO-D_6) δ 1.50 (m, 4H), 1.85 (m, 2H), 2.00 (m, 2H), 5.70 (d, J = 3.4 Hz, 1H), 7.23 (t, J = 7.3 Hz, 1H), 7.31 (t, J = 7.2 Hz, 2H), 7.46 (d, J = 7.2 Hz, 2H). ^{13}C NMR δ 21.84, 22.43, 24.50, 24.72, 81.44, 123.75, 123.75, 126.99, 127.48, 134.31, 139.44, 141.59, 179.76. Mass spectrum (*m*/*e*) 232 (M^+), found M^+ (*m*/*z* + Na) 261.1323; $C_{14}H_{16}NaO_3$ requires 261.1314. IR 695.7, 1056.7, 1129.8, 1723.5, 2918.9, 3408.7 cm^{-1}.

(*S*)-Cyclohexenyl Phenyl Glycoxilic Acid ((*S*)-1). To a solution of (*S*)-cyclohex-1-enyl-hydroxy-phenyl-acetic acid (50.7 g, 218 mmol) in methanol (288 mL) was added 10% Pd/C (2.53 g). The reaction was subjected to 1 ATM of hydrogen and was allowed to stir for 18 h. The reaction mixture was filtered through a plug of Celite and washed with 150 mL of MeOH. The solution solvent was switched to heptane. The solution was distilled to a volume of 50 wt %. The slurry was filtered to provide 47.2 g of (*S*)-CHPGA in 94% yield and >99.9% ee. The ee is determined by HPLC (Chiralpak AS, mobile phase 95% hexane/5% IPA/0.1% TFA) by observing the (*R*)- and (*S*)-**1**. (*S*)-**1** elutes at approximately 9.24 min. (*R*)-**1** elutes at approximately 6.36 min. ^{1}H NMR (DMSO-D_6) 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. Mass spectrum (*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.

***cis*-(2*S*,5*S*)-2-(*tert*-Butyl)-5-phenyl-5-(cyclohexyl)-1,3-dioxolan-4-one ((*S*,*S*)-6).** To a solution of *cis*-(2*S*,5*S*)-2-(*tert*-butyl)-5-phenyl-5-(cyclohex-1-ene)-1,3-dioxolan-4-one ((*S*,*S*)-**4**) (2.34 g, 7.8 mmol, dr > 99.9%) in methanol (35 mL) was added 10% Pd/C (0.23 g). The reaction was subjected to 1 atm of hydrogen and was allowed to stir for 6 h. The reaction mixture was filtered through a plug of Celite and concentrated in vacuo to provide 2.21 g of crude product (95%). ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 9H), 1.04−1.80 (m, 11H), 5.42 (s, 1H), 7.31 (m, 1H), 7.38 (tt, J = 1.6, 7.0 Hz, 2H), 7.67 (dt, J = 1.6, 7.0 Hz, 2H). ^{13}C NMR δ 23.81, 26.21, 26.36, 28.31, 35.86, 48.68, 85.45, 110.93, 125.63, 127.82, 128.12, 138.12, 173.99 Mass spectrum (*m*/*e*) 302 (M^+). Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.40; H, 8.41.

(*S*)-Cyclohexenyl Phenyl Glycoxilic Acid ((*S*)-1). To a solution of *cis*-(2*S*,5*S*)-2-(*tert*-butyl)-5-phenyl-5-(cyclohexyl)-1,3-dioxolan-4-one (1.0 g, 3.31 mmol) in MeOH (10 mL) was added a 1.8 M solution of KOH (10 mL, 5 equiv). The reaction was allowed to reflux for 3.0 h. After cooling to 22 °C, the volatiles (MeOH) were removed in vacuo, and the aqueous reaction mixture was extracted with ethyl acetate (50 mL). The aqueous layer was acidified to pH 1 with 1 N HCl, and the resulting mixture was washed with ethyl acetate (2 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to provide 0.735 g (95%, 99.9% ee) of (*S*)-**1**. The ee is determined by HPLC (Chiralpak AS, mobile phase 95% hexane/5% IPA/0.1% TFA) by observing the (*R*)- and (*S*)-**1**. (*S*)-**1** elutes at approximately 9.24 min. (*R*)-**1** elutes at approximately 6.36 min. ^{1}H NMR (DMSO-D_6) 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. Mass spectrum (*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.

***cis*-(2*S*,5*R*)-2-(*tert*-Butyl)-5-phenyl-5-(cyclopentyl-1-ol)-1,3-dioxolan-4-one ((*S*,*R*)-7).** To a −78 °C solution of lithium bis(trimethylsilyl)-amide (11.8 mL, 11.8 mmol, 1.0 M in hexanes) in THF (13.7 mL) was added *cis*-(2*S*,5*S*)-2-(*tert*-butyl)-5-phenyl-1,3-dioxolan-4-one (2.0 g, 9.08 mmol, dissolved in 13.7 mL of THF). The reaction mixture was allowed to stir for 30 min at −78 °C, followed by the addition of neat cyclopentanone (1.12 mL, 12.7 mmol). After stirring for 2 h at −78 °C, saturated $NaHPO_4$ solution (2.0 mL) was added. The reaction mixture was poured into a separatory funnel containing saturated NH_4Cl solution (20 mL). The aqueous layer was separated and extracted with ethyl acetate (2 × 300 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to provide 2.4 g of crude aldol product (dr 98:2). The crude aldol product was recrystallized from heptane to provide 2.01 g (74%)

of pure product as a white solid (>99.5% de). ^{1}H NMR ($CDCl_3$) δ 0.89 (s, 9H), 1.53−2.05 (m, 8H), 5.54 (s, 1H), 7.34 (m, 3H), 7.79 (dd, J = 1.5, 8.3 Hz, 2H). ^{13}C NMR δ 23.01, 23.40, 23.70, 35.18, 35.28, 35.80, 85.60, 87.54, 111.19, 126.80, 127.91, 128.31, 136.12, 172.85. Mass spectrum (*m*/*e*) 304 (M^+). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 71.09; H, 7.94.

(*S*)-Cyclopent-1-enyl-hydroxy-phenyl-acetic Acid. A 0 °C solution of *cis*-(2*S*,5*R*)-2-(*tert*-butyl)-5-phenyl-5-(cyclopentyl-1-ol)-1,3-dioxolan-4-one ((*S*,*R*)-7) (1.47 g, 4.83 mmol) in THF (14.7 mL) was charged with thionyl chloride (0.98 mL, 13.5 mmol), followed by pyridine (1.76 mL, 21.73 mmol). The reaction mixture was allowed to stir for 1 h at 0 °C, followed by the addition of saturated NH_4Cl solution (30 mL). The layers were separated, and the aqueous layer was washed with ethyl acetate (2 × 200 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to provide 1.6 g of crude product (100%). ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9H), 1.90−2.52 (m, 6H), 5.23 (s, 1H), 6.01 (m, 1H), 7.29 (m, 4H), 7.57 (m, 1H). To a solution of crude *cis*-(2*S*,5*S*)-2-(*tert*-butyl)-5-phenyl-5-(cyclopentyl-1-ene)-1,3-dioxolan-4-one (1.17 g, 4.09 mmol) in MeOH (2.27 mL) and water (4.52 mL) was added solid KOH (2.29 g, 40.9 mmol). The reaction was allowed to reflux for 3 h. After cooling to room temperature, the reaction mixture was extracted with heptane (25 mL × 2). The aqueous layer was acidified to pH 1 with 1 N HCl, and the resulting mixture was washed with ethyl acetate (2 × 200 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to provide 0.82 g of crude product (92%). ^{1}H NMR ($CDCl_3$) δ 1.81 (m, 2H), 2.29 (m, 4H), 5.59 (s, 1H), 7.24 (t, J = 6.8 Hz, 1H), 7.32 (t, J = 7.1 Hz, 2H), 7.48 (d, J = 7.8 Hz, 1H). ^{13}C NMR δ 23.71, 32.54, 32.66, 39.55, 78.67, 127.08, 127.82, 127.91, 128.28, 142.39, 146.57, 175.08. Mass spectrum (*m*/*e*) 218 (M^+). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.22; H, 6.44.

(*S*)-Cyclopentyl Phenyl Glycoxilic Acid ((*S*)-8). To a solution of (*S*)-cyclopent-1-enyl-hydroxy-phenyl-acetic acid (0.58 g, 2.66 mmol) in methanol (5 mL) was added 10% Pd/C (0.058 g). The reaction was subjected to 1 atm of hydrogen and was allowed to stir for 18 h. The reaction mixture was filtered through a plug of Celite and concentrated in vacuo to provide 0.544 g of product (93%). The ee is determined by HPLC (Chiralpak AS, mobile phase 95% hexane/5% IPA/0.1% TFA) by observing the (*R*)- and (*S*)-**8**. (*S*)-**8** elutes at approximately 7.60 min. (*R*)-**8** elutes at approximately 6.25 min. ^{1}H NMR ($CDCl_3$) δ 1.33−1.80 (m, 8H), 2.88 (m, 1H), 7.24 (td, J = 1.2, 6.6 Hz, 1H), 7.34 (td, 1.2, 6.6 Hz, 2H), 7.62 (d, J = 7.2 Hz, 1H). ^{13}C NMR δ 25.60, 25.90, 26.06, 26.72, 46.83, 78.54, 125.77, 126.84, 127.72, 143.19, 176.08. Mass spectrum (*m*/*e*) 220 (M^+). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.70; H, 7.39.

***cis*-(2*S*,5*R*)-2-(*tert*-Butyl)-5-phenyl-5-(cyclobutyl-1-ol)-1,3-dioxolan-4-one ((*R*,*S*)-9).** To a −78 °C solution of lithium bis(trimethylsilyl)-amide (66.0 mL, 66.0 mmol, 1.0 M in hexanes) was added *cis*-(2*S*,5*S*)-2-(*tert*-butyl)-5-phenyl-1,3-dioxolan-4-one (11.2 g, 50.88 mmol, dissolved in 76 mL THF). The reaction mixture was allowed to stir for 30 min at −78 °C, followed by the addition of neat cyclobutanone (5.33 mL, 71.34 mmol). After stirring for 2 h at −78 °C, saturated NaH_2PO_4 solution (60.0 mL) was added. The reaction mixture was poured into a separatory funnel containing saturated NH_4Cl solution (60 mL). The aqueous layer was separated and extracted with ethyl acetate (2 × 500 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to provide 15.5 g of crude aldol product. The crude aldol product was chromatographed using 20% EtOAc/hexane as eluent to provide a 70% yield of pure product as a white solid. ^{1}H NMR ($CDCl_3$) δ 0.87 (s, 9H), 1.07 (m, 1H), 1.76 (m, 1H), 1.97 (m, 2H), 2.51 (m, 2H), 5.50 (s, 2H), 7.35 (m, 3H), 7.80 (dd, J = 2.0, 7.8 Hz, 2H). ^{13}C NMR δ 13.0, 23.6, 31.9, 35.7, 80.1, 84.5, 111.1, 126.3, 128.1, 128.4, 135.1, 172.4. Mass spectrum (*m*/*e*) 290 (M^+). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.09; H, 7.57.

CAS numbers (provided by author): (*S*)-(+)-mandelic acid (17199-29-0), trifluoromethanesulfonic acid (1493-13-6), trimethylacetaldehyde (630-19-3), lithium bis(trimethylsilyl)amide (4039-32-1), potassium hydroxide (1310-58-3).

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