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Scalable Synthesis of Enantiomerically Pure *syn*-2,3-Dihydroxybutyrate by Sharpless Asymmetric Dihydroxylation of *p*-Phenylbenzyl Crotonate

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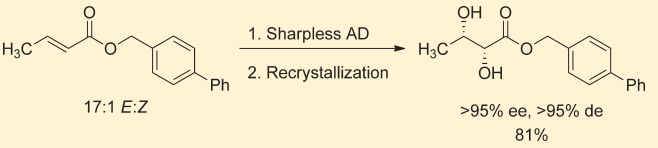
Supporting Information

ABSTRACT: An efficient four-step synthetic route to the useful chiral building block (2*R*,3*S*)-dihydroxybutyric acid acetonide in >95% ee is detailed. The sequence is readily scaled, requires no chromatography, and allows for efficient recycling of *p*-phenylbenzyl alcohol, an expedient for enantio- and diastereoenrichment by recrystallization.



(2*R*,3*S*)-Dihydroxybutyric acid acetonide ((+)-**1**) and its enantiomer serve as valuable building blocks for the construction of complex carbohydrates and other densely oxygenated molecules.[1] Three prior enantioselective routes to *syn*-2,3-dihydroxybutyric acid or its methyl ester are summarized in Scheme 1.[2−4] Only the first of these, involving diazotization−hydrolysis of threonine,[2] has been routinely employed for multigram scale synthesis of **1**, so far as we are aware, and this route is typically used to synthesize the levorotatory form of **1** (from L-threonine), as D-threonine is a less readily available starting material. We required (+)-**1** for a projected route to the rare sugar trioxacarcinose A[5] and so were led to consider alternative routes for its preparation. The Sharpless asymmetric dihydroxylation[6] of crotonic acid esters appeared to be an attractive and general solution, potentially providing access to **1** of either enantiomeric series. As part of their efforts to synthesize natural products of the bengazole family, Ley and co-workers reported that Sharpless asymmetric dihydroxylation of ethyl crotonate with AD-mix-β at 0 °C afforded (−)-**1** ethyl ester[7] in 96% yield (>95% ee, 3-g scale). Relatively large volumes of organic extractant were necessary to isolate the highly water-soluble product, and chromatographic purification was required.[8] In light of this precedent, we began a broader survey of different crotonate esters and reaction conditions in order to develop a procedure optimized toward ease of purification, suitability for large-scale synthesis, and degree of enantiomeric purity of the product.

Methyl, ethyl, and *n*-hexyl crotonate esters are each commercially available in geometrically pure form (reported purity 100% trans). We observed that dihydroxylation of *trans*-methyl crotonate with potassium osmate (0.50 mol %), $(DHQ)_2PHAL$[9] (1.0 mol %), methanesulfonamide (1 equiv), potassium ferricyanide (3 equiv), and potassium carbonate (3 equiv), conditions reported by Sharpless and co-workers,[10] afforded the syn diol in 89% ee[11] and 45% yield (Table 1, entry 1). We attribute the low yield to the poor efficiency of our extraction of the water-soluble product from the aqueous reaction mixture. Dihydroxylation of commercial *trans*-*n*-hexyl crotonate under identical conditions afforded a higher yield of product (88%), but the enantioselectivity of the transformation was too low for our purposes (80% ee, entry 2). The enantioselectivity of the dihydroxylation reaction employing $(DHQ)_2AQN$ as ligand (entry 3) was, as expected, slightly higher than that of the corresponding transformation with $(DHQ)_2$-PHAL.[12] For optimization studies we prepared several esters from a number of different alcohols and commercial crotonoyl chloride, which is inexpensive but impure (∼20:1 mixture of trans and cis isomers, respectively; 90% purity). For example, dihydroxylation of benzyl crotonate prepared in this way and used without purification afforded diol of 92% ee (entry 4).[13] This promising result led us to examine several substituted benzyl crotonate esters (*p*-methoxybenzyl, *p*-nitrobenzyl, benzhydryl, and *p*-phenylbenzyl), all of which were dihydroxylated to form diol products of 87−92% ee. Most encouraging was the dihydroxylation of *p*-phenylbenzyl crotonate (used without purification), which afforded a highly crystalline diol product of 87% ee. A single recrystallization of the product from dichloromethane−hexanes afforded *p*-phenylbenzyl (2*R*,3*S*)-dihydroxybutyrate of >95% ee (entry 5).

Dihydroxylation of *p*-phenylbenzyl crotonate was easily conducted on a multigram scale. For example, in one experiment *p*-phenylbenzyl alcohol (22 g, 119 mmol) was esterified with commercial crotonoyl chloride (∼20:1 *E*:*Z*; 90% purity) in the presence of potassium carbonate (2.0 equiv) and a catalytic quantity of 4-(dimethylamino)pyridine (10 mol %) (Scheme 2). The crude ester, a ∼17:1 mixture of *E* and *Z* isomers, was subjected to conditions for the Sharpless asymmetric dihydroxylation. Complete conversion to the diol was achieved with low catalyst loading (0.25 mol % potassium osmate, 0.50 mol % $(DHQ)_2AQN$), an extended reaction time (∼5 days), and distributed addition of potassium ferricyanide (6 equiv).[14] We found that methanesulfonamide could be removed by a sequence of aqueous washes.[15] The

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Scheme 1. Prior Syntheses of *syn*-2,3-Dihydroxybutyrate and Its Methyl Ester

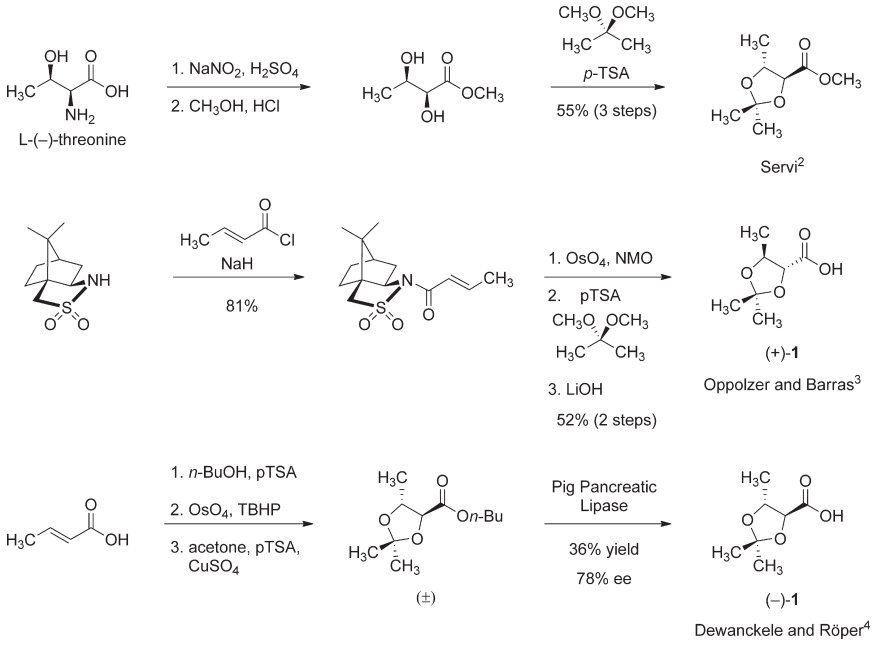
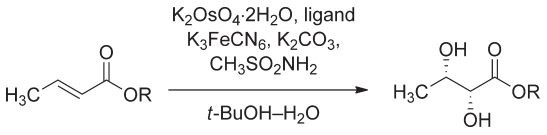


Table 1. Dihydroxylation of *trans*-Crotonate Esters [a]



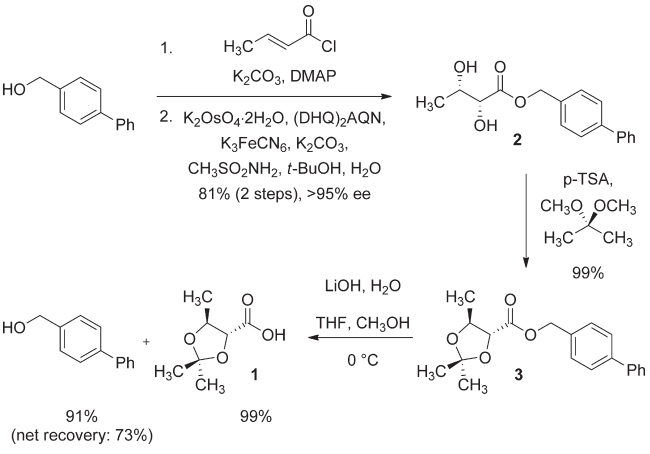
entry	R	ligand	yield (%)	ee (%)[b]
1	CH_3[c]	$(DHQ)_2PHAL$	45	89
2	$(CH_2)_5CH_3$[c]	$(DHQ)_2PHAL$	88	80
3	$(CH_2)_5CH_3$[c]	$(DHQ)_2AQN$	90	85
4	Bn[d]	$(DHQ)_2AQN$	77	92
5	(*p*-Ph)Bn[d,e]	$(DHQ)_2AQN$	81	87[f], >95[g]

[a] Conditions: $K_2OsO_4 \cdot 2H_2O$ (0.50 mol %), ligand (1.0 mol %), $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv), $CH_3SO_2NH_2$ (1 equiv), *t*-BuOH–H_2O, 4 → 23 °C. [b] Determined by integration of the ^1H NMR spectrum of the corresponding bis-Mosher ester. [c] The alkene substrate was 100% trans, from a commercial source. [d] The substrate was prepared from commercial crotonoyl chloride (~20:1 *E*:*Z*; 90% purity) and was used without purification. [e] 0.25 mol % $K_2OsO_4 \cdot 2H_2O$, 0.50 mol % $(DHQ)_2AQN$, and 6 equiv of $K_3Fe(CN)_6$ were used. [f] Before purification. [g] After a single recrystallization of the product from dichloromethane–hexanes.

unpurified diol was found to be of 87% ee by ^1H NMR analysis of the corresponding bis-Mosher ester. A single recrystallization of the solid product from dichloromethane–hexanes furnished pure diol (+)-**2** of >95% ee in 81% yield (from *p*-phenylbenzyl alcohol, 27.8-g batch, $[\alpha]_D = +22.7°$ (*c* 1.04, CH_2Cl_2)).

With an efficient and scalable procedure for the preparation of enantiomerically pure (+)-**2**, we found that a short sequence of standard transformations led efficiently to the desired carboxylic acid (+)-**1**. First, (+)-**2** was transformed into the corresponding acetonide *p*-phenylbenzyl ester **3** in quantitative yield by stirring with 2,2-dimethoxypropane and *p*-toluenesulfonic acid monohydrate (5 mol %). Saponification of the latter product in aqueous lithium hydroxide at 0 °C provided the acid (+)-**1** in 99% yield after extractive isolation (15-g batch, $[\alpha]_D = +34.2°$ (*c* 0.61, $CHCl_3$), lit.[16] $[\alpha]_D = +31.2°$ (*c* 1, $CHCl_3$)). *p*-Phenylbenzyl alcohol, a white solid, was recovered in 91% yield (≥95% purity, 73% net recovery over the three-step sequence).

Scheme 2. Synthesis of Carboxylic Acid 1



The benefits of the optimized Sharpless asymmetric dihydroxylation reaction—excellent yield and enantioselectivity—were somewhat offset by the length of the reaction time in the optimized protocol (~5 days), referred to as "method A" (Table 2, entry 1). We briefly investigated modification of the conditions to shorten the reaction time. More rapid warming of the reaction mixture

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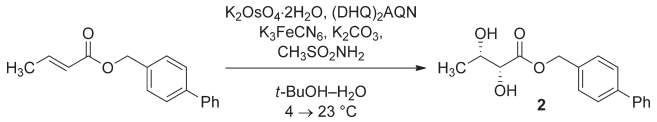
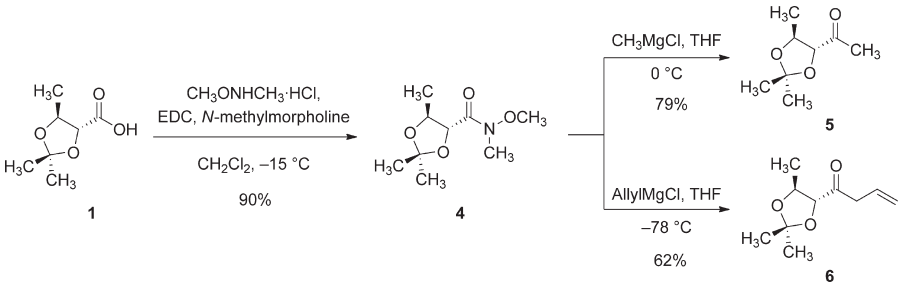
Table 2. Protocols for Large-Scale Dihydroxylation[a]



entry	method	$K_2OsO_4 \cdot 2H_2O$ (mol %)	$(DHQ)_2AQN$ (mol %)	$K_3Fe(CN)_6$ (equiv)	time at 4 °C	time at 23 °C	yield[b] (%)	ee[c] (%)
1	A	0.25	0.50	6	2 d	3 d	81	>95
2	B	1.0	1.0	3	30 min	25 h	60	>95

[a] The starting material, *p*-phenylbenzyl crotonate, was prepared from commercially available crotonoyl chloride (~20:1 *E*:*Z*; 90% purity) and used without purification. Reactions were performed on a scale of at least 0.1 mol. [b] Isolated yield of pure product, after recrystallization. [c] Determined by integration of the ^{1}H NMR spectrum of the corresponding bis-Mosher ester.

Scheme 3. Transformations of Carboxylic Acid 1



during the dihydroxylation under otherwise identical conditions (0.1-mol scale) led to poorer conversion, and *p*-phenylbenzyl alcohol was observed in the crude product mixture. The latter byproduct presumably formed as the result of saponification of the diol product (**2**) or the substrate under the moderately basic conditions of the dihydroxylation reaction.[17] Sharpless and coworkers have noted that for electron-poor olefins turnover can be increased with little or no diminution in enantioselectivity by increasing the loading of osmium.[18] Using increased catalyst loading (1.0 mol % potassium osmate, 1.0 mol % $(DHQ)_2AQN$), and adding sodium bicarbonate (3 equiv) to buffer the aqueous phase, we observed that the large-scale dihydroxylation reaction was complete within 25 h. The crude product mixture contained ≤3% *p*-phenylbenzyl alcohol, as determined by integration of its ^{1}H NMR spectrum. Recrystallization of the product mixture from dichloromethane−hexanes afforded pure diol **2** in 60% yield and >95% ee (Table 2, entry 2, "method B"). We believe that this protocol, with a shorter reaction time and a lower yield, provides a viable alternative to the more lengthy but higher yielding method A.

Finally, we have demonstrated that the acid (+)-**1** can be transformed into a variety of useful enantiopure building blocks. For example, the corresponding Weinreb amide (**4**) was formed in excellent yield by stirring (+)-**1** with *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC) and *N*-methylmorpholine (17.4-g batch, Scheme 3).[19,20] This product in turn provides ready access to ketones such as the methyl ketone **5**[21] and the allyl ketone **6**, for which we provide detail in the Experimental Section.

In summary, we have developed a practical sequence to prepare the useful building block (2*R*,3*S*)-dihydroxybutyric acid acetonide ((+)-**1**) in enantiomerically pure form, using as the key step the Sharpless asymmetric dihydroxylation reaction. *p*-Phenylbenzyl alcohol serves as a useful expedient for enantioenrichment by recrystallization and is readily recycled. Due to its operational ease, we believe this method provides a useful complement to existing methods for the preparation of **1** of either enantiomeric series as well as chiral building blocks derived from these substances.

EXPERIMENTAL SECTION

General Experimental Procedures. Reactions were run in round-bottom flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred by syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation (house vacuum, ca. 25−40 Torr) at ambient temperature, unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using glass plates precoated with silica gel (0.25 mm, 60 Å pore size, 230−400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light and then were stained by submersion in aqueous ceric ammonium molybdate (CAM) or potassium permanganate solutions followed by brief heating on a hot plate. Flash-column chromatography was performed as described by Still et al.,[22] employing silica gel (60 Å, 32−63 μM, standard grade, Dynamic Adsorbents, Inc.). Tetrahydrofuran, dichloromethane, and ether were purified by the method of Pangborn et al.[23] Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 500 MHz at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances), integration, coupling constant (*J*) in Hertz. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 125 MHz at 23 °C. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR

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solvent ($CDCl_3$, δ 77.0). Infrared (IR) spectral data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (vs = very strong, s = strong, m = medium, w = weak, br = broad).

(2*R*,3*S*)-Biphenyl-4-ylmethyl 2,3-Dihydroxybutanoate (2). *Method A.* 4-(Dimethylamino)pyridine (1.46 g, 11.9 mmol, 0.1 equiv) was added to a suspension of crotonoyl chloride (technical grade, 14.0 mL, 146 mmol, 1.22 equiv), *p*-phenylbenzyl alcohol (22.0 g, 119 mmol, 1 equiv), and potassium carbonate (33.0 g, 239 mmol, 2.0 equiv) in dichloromethane (240 mL) at 23 °C. After 7 h, a second portion of crotonoyl chloride (12.7 mL, 133 mmol, 1.11 equiv) was added. After 15 h, water (200 mL) was added. The layers were separated. The aqueous layer was extracted with dichloromethane (200 mL). The organic layers were combined. The combined solution was washed sequentially with saturated aqueous sodium bicarbonate solution (200 mL), 1.0 M aqueous hydrochloric acid solution (200 mL), water (200 mL), and then saturated aqueous sodium chloride solution (200 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was dissolved in a mixture of *tert*-butyl alcohol (240 mL) and water (240 mL). Potassium carbonate (49.5 g, 358 mmol, 3.0 equiv), potassium ferricyanide (118 g, 358 mmol, 3.0 equiv), and $(DHQ)_2AQN$ (511 mg, 0.596 mmol, 0.005 equiv) were added in sequence, and the mixture was cooled to 4 °C. Potassium osmate dihydrate (110 mg, 0.928 mmol, 0.0025 equiv) was added. After 10 min, methanesulfonamide (5.67 g, 59.6 mmol, 0.5 equiv) was added. After 48 h, the cooling bath was removed and the reaction flask was warmed to 23 °C. After 23 h, a second portion of potassium ferricyanide (59.0 g, 179 mmol, 1.5 equiv) was added. After 18 h, a third portion of potassium ferricyanide (59.0 g, 179 mmol, 1.5 equiv) was added. After 25 h, the reaction flask was cooled in an ice bath. Sodium sulfite (150 g, 1.19 mol, 10 equiv) was added slowly. After 1 h, the product mixture was extracted with ethyl acetate (6 × 500 mL). The organic layers were combined. The combined solution was washed sequentially with 1.0 M aqueous sodium hydroxide solution (1.5 L) and then saturated aqueous sodium chloride solution (1.0 L), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was dissolved in a minimal amount of hot dichloromethane (~200 mL, 35 °C). The resulting solution was heated to boiling in an oil bath at 65 °C, and hexanes was added slowly such that boiling was maintained. Upon the first appearance of a white precipitate, an amount of dichloromethane sufficient to dissolve the precipitate was added (~20 mL). The oil bath was removed, and the flask was cooled to 23 °C. The flask was further cooled to −20 °C. After 15 h, a light yellow crystalline solid had precipitated from the yellow supernatant. The mixture was filtered, and the solid was washed with cold hexanes (100 mL, −20 °C) to provide the product, (2*R*,3*S*)-biphenyl-4-ylmethyl 2,3-dihydroxybutanoate (**2**), as light yellow needles (27.8 g, 81% yield based on *p*-phenylbenzyl alcohol): $[\alpha]_D$ = +22.7° (*c* 1.04, CH_2Cl_2); mp 100.0−101.0 °C; TLC (30% ethyl acetate−70% hexanes) R_f 0.11 (CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (t, 4H, *J* = 8.3 Hz), 7.46 (m, 4H), 7.38 (m, 1H), 5.33−5.28 (m, 2H), 4.17 (br, 1H), 4.11 (br, 1H), 3.46 (br, 1H), 2.57 (br, 1H), 1.33 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 141.5, 140.4, 133.9, 128.8, 128.8, 127.5, 127.3, 127, 74.5, 68.7, 67.3, 19.6; FTIR (neat; cm^{-1}) 3335 (br), 1701 (s), 1292 (s), 1138 (m), 1067 (m), 1018 (m), 978 (m), 827 (m); HRMS (ESI) *m*/*z* calcd for $(C_{17}H_{18}O_4 + Na)^+$ 309.1097, found 309.1100.

To determine the enantiomeric excess, (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (6.3 μL, 34 μmol, 2.4 equiv) was added to a solution of (2*R*,3*S*)-biphenyl-4-ylmethyl 2,3-dihydroxybutanoate (**2**; 4 mg, 14 μmol, 1 equiv) and 4-(dimethylamino)pyridine (8.2 mg, 67 μmol, 4.8 equiv) in dichloromethane (280 μL) at 23 °C. After 90 min, the product solution was partitioned between ethyl acetate (20 mL) and water (5 mL). The layers were separated. The organic layer was washed sequentially with 1.0 M aqueous hydrochloric acid solution (5 mL), saturated aqueous sodium bicarbonate solution (5 mL), water (5 mL), and then saturated aqueous sodium chloride solution (5 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. Analysis of the ^{1}H NMR spectrum of the crude product established that complete conversion to the bis-Mosher ester had occurred. The product was determined to be of 49:1 dr (^{1}H NMR analysis (500 MHz, $CDCl_3$) δ 5.76 (qd, 1H, *J* = 6.8, 2.4 Hz (2*S*,3*R*, minor)), 5.70 (qd, 1H, *J* = 6.4, 2.0 Hz (2*R*,3*S*, major))), from which we concluded that the starting diol, (2*R*,3*S*)-biphenyl-4-ylmethyl 2,3-dihydroxybutanoate (**2**), was of >95% ee.

Method B. 4-(Dimethylamino)pyridine (1.46 g, 11.9 mmol, 0.1 equiv) was added to a suspension of crotonoyl chloride (technical grade, 34.3 mL, 358 mmol, 3.0 equiv), *p*-phenylbenzyl alcohol (22.0 g, 119 mmol, 1 equiv), and potassium carbonate (33.0 g, 239 mmol, 2.0 equiv) in dichloromethane (240 mL) at 23 °C. After 12 h, water (200 mL) was added. The layers were separated. The aqueous layer was extracted with dichloromethane (200 mL). The organic layers were combined. The combined solution was washed sequentially with saturated aqueous sodium bicarbonate solution (200 mL), 1.0 M aqueous hydrochloric acid solution (200 mL), water (200 mL), and then saturated aqueous sodium chloride solution (200 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was dissolved in a mixture of *tert*-butyl alcohol (240 mL) and water (240 mL). Potassium carbonate (49.5 g, 358 mmol, 3.0 equiv), sodium bicarbonate (30.1 g, 358 mmol, 3.0 equiv), potassium ferricyanide (118 g, 358 mmol, 3.0 equiv), and $(DHQ)_2AQN$ (1.02 g, 1.19 mmol, 0.01 equiv) were added in sequence, and the mixture was cooled to 4 °C. Potassium osmate dihydrate (440 mg, 1.19 mmol, 0.01 equiv) was added. After 20 min, methanesulfonamide (11.4 g, 119 mmol, 1.0 equiv) was added. After 10 min, the cooling bath was removed and the reaction flask was warmed to 23 °C. After 25 h, the reaction flask was cooled in an ice bath. Sodium sulfite (150 g, 1.19 mol, 10 equiv) was added slowly. After 30 min, the product mixture was extracted with ethyl acetate (6 × 500 mL). The organic layers were combined. The combined solution was washed sequentially with 1.0 M aqueous sodium hydroxide solution (1.5 L), 1.0 M hydrochloric acid (1.0 L), and then saturated aqueous sodium chloride solution (1.0 L), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was recrystallized from dichloromethane−hexanes as in method A to provide the product, (2*R*,3*S*)-biphenyl-4-ylmethyl 2,3-dihydroxybutanoate (**2**), as light yellow needles (20.6 g, 60% based on *p*-phenylbenzyl alcohol). The recrystallized product was of >95% ee by formation of the corresponding bis-Mosher ester as in method A.

(4*R*,5*S*)-Biphenyl-4-ylmethyl 2,2,5-Trimethyl-1,3-dioxolane-4-carboxylate (3). *p*-Toluenesulfonic acid monohydrate (923 mg, 4.85 mmol, 0.05 equiv) was added to a suspension of (2*R*,3*S*)-biphenyl-4-ylmethyl 2,3-dihydroxybutanoate (**2**; 27.8 g, 97.1 mmol, 1 equiv) in 2,2-dimethoxypropane (350 mL) at 23 °C. After 40 min, triethylamine (677 μL, 4.85 mmol, 0.05 equiv) was added. The product solution was filtered through a pad of silica gel (length 8 cm; diameter 8 cm), with ethyl acetate as eluent (2 L). The filtrate was concentrated to provide the product, (4*R*,5*S*)-biphenyl-4-ylmethyl 2,2,5-trimethyl-1,3-dioxolane-4-carboxylate (**3**), as a colorless oil (31.4 g, 99%): TLC (30% ethyl acetate−70% hexanes) R_f = 0.67 (CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (m, 4H), 7.44 (m, 4H), 7.36 (m, 1H), 5.26 (m, 2H), 4.22 (dq, 1H, *J* = 8.2, 6.0 Hz), 4.11 (d, 1H, *J* = 7.8 Hz), 1.48 (s, 3H), 1.45 (s, 3H), 1.44 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 141.3, 140.4, 134.2, 128.7, 128.7, 127.4, 127.3, 127, 110.6, 80.3, 75.1, 66.6, 27.1, 25.6, 18.5; FTIR (neat; cm^{-1}) 2988 (w), 1757 (s), 1184 (s), 1099 (s), 850 (s), 762 (s), 698 (s); HRMS (ESI) *m*/*z* calcd for $(C_{20}H_{22}O_4 + Na)^+$ 349.1410, found 349.1416.

(4*R*,5*S*)-2,2,5-Trimethyl-1,3-dioxolane-4-carboxylic Acid (1). Lithium hydroxide (1.0 M in water, 192 mL, 192 mmol, 2.0 equiv) was

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added over 5 min to an ice-cooled solution of (4*R*,5*S*)-biphenyl-4-ylmethyl 2,2,5-trimethyl-1,3-dioxolane-4-carboxylate (**3**; 31.4 g, 96.0 mmol, 1 equiv) in a mixture of tetrahydrofuran (380 mL) and methanol (190 mL). After 10 min, the product mixture was concentrated to remove organic solvents. The aqueous residue was diluted with ether (1 L). The layers were separated. The aqueous layer was extracted with ether (500 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to provide *p*-phenylbenzyl alcohol as a white solid (16.1 g, 91%). The aqueous layer was acidified to pH ~2 by addition of 1.0 M aqueous hydrochloric acid solution (~100 mL). The acidified solution was extracted with ethyl acetate (500 mL). The pH of the aqueous layer was observed to increase to ~4 after extraction of the acidic product. The aqueous layer was again acidified to pH ~2 by addition of 1.0 M aqueous hydrochloric acid solution (~50 mL). The acidified solution was extracted with ethyl acetate (3 × 500 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to provide the product, (4*R*,5*S*)-2,2,5-trimethyl-1,3-dioxolane-4-carboxylic acid (**1**), as a colorless oil (15.2 g, 99%). ^{1}H and ^{13}C NMR data were in agreement with previously reported values:[16] $[\alpha]_D$ = +34.2° (*c* 0.61, $CHCl_3$), lit.[16] $[\alpha]_D$ = +31.2° (*c* 1, $CHCl_3$); TLC (ethyl acetate) R_f = 0.13 (CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.23 (br, 1H), 4.24 (dq, 1H, *J* = 8.3, 5.9 Hz), 4.09 (d, 1H, *J* = 8.3 Hz), 1.49 (s, 3H), 1.48 (d, 3H, *J* = 5.9 Hz), 1.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 111.0, 79.8, 75.2, 27.1, 25.6, 18.5; FTIR (neat; cm^{-1}) 3158 (br), 2990 (w), 1734 (s), 1383 (m), 1219 (s), 1173 (m), 1099 (s), 853 (m); HRMS (ESI) *m*/*z* calcd for $(C_7H_{12}O_4 + H)^+$ 161.0808, found 161.0816.

(4*R*,5*S*)-*N*-Methoxy-*N*,2,2,5-tetramethyl-1,3-dioxolane-4-carboxamide (4). *N*-(3-(Dimethylamino)propyl)-*N*′-ethylcarbodiimide hydrochloride (20.1 g, 105 mmol, 1.1 equiv) was added over 2 min to a solution of (4*R*,5*S*)-2,2,5-trimethyl-1,3-dioxolane-4-carboxylic acid (**1**; 15.2 g, 95.2 mmol, 1 equiv) and *N*-methylmorpholine (11.5 mL, 105 mmol, 1.1 equiv) in dichloromethane (475 mL) at −20 °C. After 3.5 h, 1.0 M aqueous hydrochloric acid solution (150 mL) was added. The cooling bath was removed, and the reaction flask was warmed to 23 °C. The layers were separated. The aqueous layer was extracted with dichloromethane (400 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium bicarbonate solution (150 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the product, (4*R*,5*S*)-*N*-methoxy-*N*,2,2,5-tetramethyl-1,3-dioxolane-4-carboxamide (**4**), as a pale yellow oil (17.4 g, 90%):[24] TLC (40% ethyl acetate−60% hexanes) R_f = 0.36 (CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.40 (m, 2H), 3.73 (s, 3H), 3.22 (s, 3H), 1.47 (s, 3H), 1.46 (s, 3H), 1.37 (d, 3H, *J* = 5.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 109.9, 78.2, 74.5, 61.3, 32.0, 27.2, 25.8, 17.9; FTIR (neat; cm^{-1}) 2986 (w), 2938 (w), 1670 (s), 1371 (m), 1171 (s), 1055 (m), 854 (m); HRMS (ESI) *m*/*z* calcd for $(C_9H_{17}NO_4 + Na)^+$ 226.1050, found 226.1050.

1-((4*R*,5*S*)-2,2,5-Trimethyl-1,3-dioxolan-4-yl)ethanone (5). Methylmagnesium chloride (3.0 M solution in tetrahydrofuran, 6.25 mL, 18.7 mmol, 3.0 equiv) was added dropwise to an ice-cooled solution of (4*R*,5*S*)-*N*-methoxy-*N*,2,2,5-tetramethyl-1,3-dioxolane-4-carboxamide (**4**; 1.27 g, 6.25 mmol, 1 equiv) in tetrahydrofuran (60 mL). After 35 min, saturated aqueous ammonium chloride solution (30 mL) was added, and the reaction flask was warmed to 23 °C. The product mixture was extracted with ethyl acetate (3 × 70 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to provide the product, 1-((4*R*,5*S*)-2,2,5-trimethyl-1,3-dioxolan-4-yl)ethanone (**5**), as a colorless oil (770 mg, 79%). ^{1}H NMR, ^{13}C NMR, IR, and MS data were in agreement with previously reported values.[25] TLC (30% ethyl acetate−70% hexanes): R_f = 0.70 (CAM).

1-((4*R*,5*S*)-2,2,5-Trimethyl-1,3-dioxolan-4-yl)but-3-en-1-one (6). Allylmagnesium chloride (2.0 M solution in tetrahydrofuran, 1.48 mL, 2.95 mmol, 3.0 equiv) was added dropwise to a solution of (4*R*,5*S*)-*N*-methoxy-*N*,2,2,5-tetramethyl-1,3-dioxolane-4-carboxamide (**4**; 200 mg, 0.984 mmol, 1 equiv) in tetrahydrofuran (10 mL) at −78 °C. After 25 min, saturated aqueous ammonium chloride (5 mL) was added, and the reaction flask was warmed to 23 °C. Water (2 mL) was added, and the product mixture was extracted with ethyl acetate (2 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash-column chromatography (4% ethyl acetate−96% hexanes) to provide the product, 1-((4*R*,5*S*)-2,2,5-trimethyl-1,3-dioxolan-4-yl)but-3-en-1-one (**6**), as a colorless oil (113 mg, 62%): TLC (30% ethyl acetate−70% hexanes) R_f = 0.75 (CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (m, 1H), 5.22−5.14 (m, 2H), 4.05 (dq, 1H, *J* = 8.3, 6.4 Hz), 3.93 (dd, 1H, *J* = 8.3, 1.0 Hz), 3.43 (m, 2H), 1.46 (s, 3H), 1.44 (s, 3H), 1.39 (d, 3H, *J* = 5.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.7, 129.7, 119.1, 110.1, 86.3, 74.3, 43.3, 27.2, 26.3, 18.5; FTIR (neat; cm^{-1}) 2987 (m), 1719 (s), 1382 (s), 1242 (s), 1099 (s), 856 (s); HRMS (ESI) *m*/*z* calcd for $(C_{10}H_{16}O_3 + H)^+$ 185.1172, found 185.1179.

■ ASSOCIATED CONTENT

Supporting Information. Figures giving complete ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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