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Scalable Preparation of Both Enantiomers of 2-(1-Hydroxy-2-oxocyclohexyl)acetic Acid

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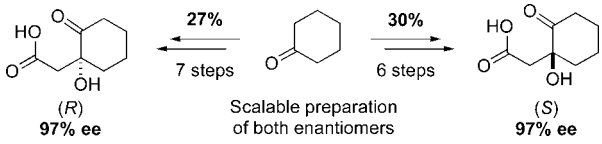
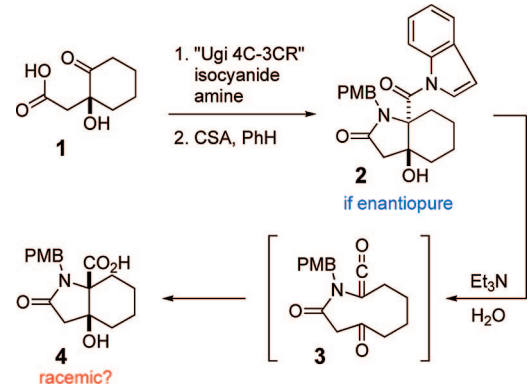


The efficient, scalable preparation of both enantiomers of 2-(1-hydroxy-2-oxocyclohexyl)acetic acid in enantiomerically pure form is reported using environmentally benign conditions in 30% overall yield (6 steps) for the (*S*)-isomer, in 27% (7 steps) for the (*R*)-isomer, from cyclohexanone.

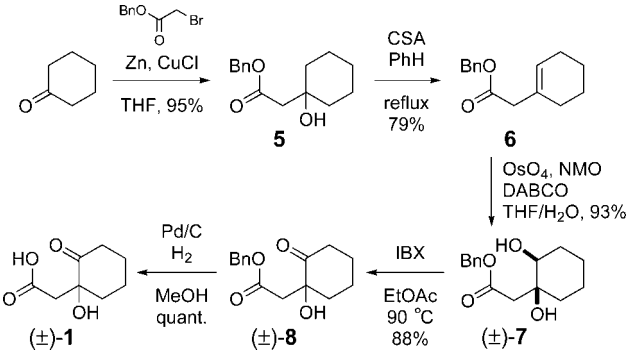
Chiral α-hydroxyketone-containing compounds are important synthons for natural products synthesis.[1] 2-(1-Hydroxy-2-oxocyclohexyl)acetic acid (**1**) is an especially attractive target owing to its potential application in the Passerini and Ugi multicomponent reactions which can construct a complex heterobicyclic framework in a single step.[2] This compound can be useful not only in the synthesis of a particular natural product target but also in the construction of a library of bicyclic γ-lactams (Ugi product) or γ-lactones (Passerini product). In the course of our studies on the diastereoselective synthesis of pyroglutamic acid derivative **2**, we needed a straightforward entry to the optically active γ-keto acid **1** for use in the Ugi four-center three-component (4C-3C) reaction (Scheme 1). γ-Ketoacid **1** is an especially attractive and challenging chiral synthon because it contains four different oxidation levels in four contiguous carbon atoms. Although its racemic synthesis was reported in 1963,[3] an efficient procedure to prepare both enantiomers of γ-ketoacid **1** has never been reported. Herein, we report the first scalable preparation of both enantiomers of 2-(1-hydroxy-2-oxocyclohexyl)acetic acid (**1**).

Recently, we reported a unique stereoisomerization at the angular position of the racemic bicyclic *anti*-pyroglutamic acid derivative **2** during basic hydrolysis of the *N*-acylindole moiety (Scheme 1).[4]We proposed a Grob-type fragmentation of the anti isomer **2** to give an achiral ketene intermediate **3**, which then

SCHEME 1. Unique Stereoisomerization at the Angular Position of *N*-Acylindole 2 To Give *syn*-Pyroglutamic Acid 4



SCHEME 2. Racemic Synthesis of 2-(1-Hydroxy-2-oxocyclohexyl)acetic Acid (±)-(1)



underwent formal aldol condensation to give only *syn*-pyroglutamic acid **4**. In order to test this mechanism, we needed enantioselective access to the γ-keto acid **1**. Based on our hypothesis, we would expect to see racemization of bicyclic pyroglutamic acid **4** upon hydrolysis of *N*-acylindole **2** (via achiral ketene **3**).[5]

Our racemic synthesis of 2-(1-hydroxy-2-oxocyclohexyl)acetic acid (±)-(**1**) began with the Reformatsky reaction of cyclohexanone and benzyl bromoacetate to give benzyl β-hydroxy ester **5** in 95% yield (Scheme 2).[6] It was important to use the benzyl ester in this step for a clean conversion of the ester to the carboxylic acid in a later step (vide infra). Dehydration of the tertiary alcohol led to the regiocontrolled formation of β,γ-olefin **6** in 79% yield (as an 11:1 regioisomeric mixture with the α,β-olefin).[7] Dihydroxylation of **6** with osmium tetraoxide gave the racemic *syn*-diol (±)-**7** in 93% yield (as an 11:1 isomeric mixture with the α,β-diol) without γ-lactone formation, a known side reaction from γ-hydroxy esters.[8] Oxidation of the secondary alcohol of (±)-**7** (11:1 isomeric ratio) with 2-iodoxybenzoic acid (IBX) gave γ-ketoester (±)-**8** in 87%

(1) Hanessian, S. In *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon: New York, 1983; Chapter 2.

(2) For a recent review of isocyanide-based multi-component reactions, see: Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89.

(3) Mondon, A.; Menz, H.; Zander, J. Racemic 2-(1-hydroxy-2-oxocyclohexyl)acetic acid (±)-(**1**) has been synthesized by a different strategy. *Chem. Ber.* **1963**, *96*, 826–839.

(4) Vamos, M.; Ozboya, K.; Kobayashi, Y. *Synlett* **2007**, 1595–1599.

(5) However, we can still not rule out the possibility that the stereochemical information contained in **2** could be retained in the ketene intermediate **3** due to rotational barriers associated with the putative nine-membered ring.

(6) Fürstner, A. In *Organozinc Reagents: A Practical Approach*; Knochel, P., Jones, P., Eds.; Oxford University Press: New York, 1999; p 287.

(7) For a discussion of ring size and endo/exo selectivity, see: Screttas, C. G.; Smonou, I. C. *J. Org. Chem.* **1998**, *53*, 893–894.

(8) Kapferer, T.; Brückner, R. *Eur. J. Org. Chem.* **2006**, 2119–2133.

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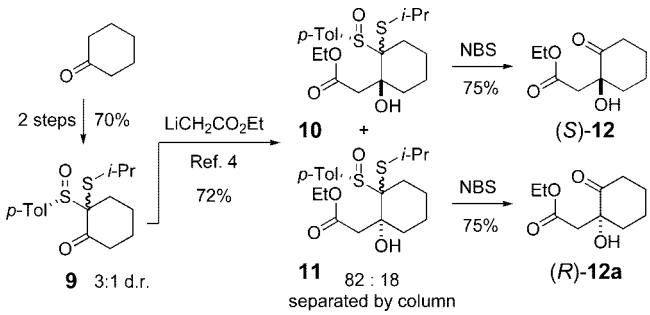
SCHEME 3. Maestro's Synthesis of Optically Active γ-Keto Esters 12 and 12a



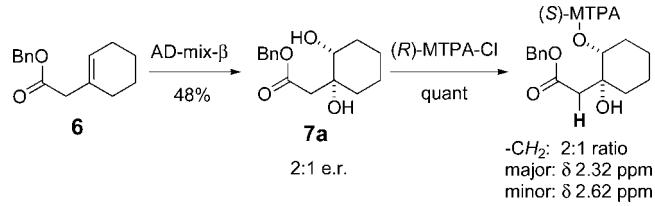
yield (isolated as a single isomer after SiO_2 chromatography).[9] Mild oxidation conditions were important here based on the propensity of the tertiary alcohol to eliminate under acidic and basic conditions and also to avoid oxidative cleavage of the 1,2-diol during the oxidation of (±)-**7**. Alkaline hydrolysis of the ester caused elimination of the hydroxyl group to give an α,β-unsaturated acid, indicating the necessity of the benzyl ester to avoid this side reaction in the final deprotection. Hydrogenation of the benzyl ester (±)-**8** cleanly furnished the racemic γ-keto acid (±)-**1** in quantitative yield and in 61% overall yield over five steps from cyclohexanone.

There is one report for the enantioselective preparation of the ethyl ester **12**, a possible precursor to 2-(1-hydroxy-2-oxocyclohexyl)acetic acid (**1**). In 1998, Maestro introduced methodology which gives asymmetric access to the ethyl ester **12** in four steps and 31% overall yield from cyclohexanone to **12**.[10] Ketone **9** was prepared as a 3:1 diastereomixture from cyclohexanone with the chiral menthyl *p*-toluenesulfinate in 70% yield (two steps). The key step in the synthesis was a diastereoselective aldol reaction (82:18 dr) to the chiral ketone **9** shown in Scheme 3. Following the diastereoselective aldol reaction and separation of the resulting diastereomixture **10** and **11** by chromatography, a deprotection of the *S,S*-ketal afforded enantiomerically pure ethyl esters **12** and **12a**. Our attempted base-promoted hydrolysis of γ-keto ester **12** failed to give a good conversion to the γ-keto acid **1**; instead, the α,β-unsaturated acid was formed by elimination of β-hydroxyl group. Thus, **12** is not a suitable precursor to 2-(1-hydroxy-2-oxocyclohexyl)acetic acid (**1**).

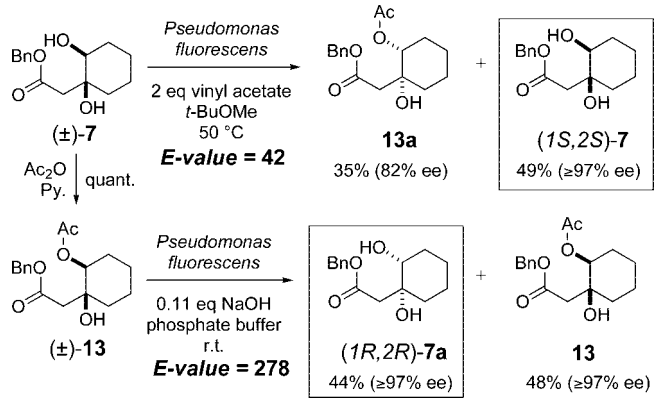
As shown in the racemic synthesis above (Scheme 2), diol (±)-**7** is a key precursor to the γ-keto acid (±)-**1**. Therefore, an enantioselective synthesis of **1** can be accomplished through enantioselective preparation of diol **7**. Sharpless asymmetric dihydroxylation[11] of β,γ-unsaturated ester **6**[8] was the first choice; however, as shown in Scheme 4, the yield and enantioselectivity for this reaction were both poor (48% yield and 2:1 er).[12] Although this reaction is generally useful for a broad range of substrates, there still remains a number of specific alkene substrates that deliver poor enantioselectivity.[13]

In order to obtain the enantiomerically pure diol **7**, we turned our attention to the possible biocatalytic transformations involving

SCHEME 4. Attempted Sharpless Asymmetric Dihydroxylation of Olefin 6

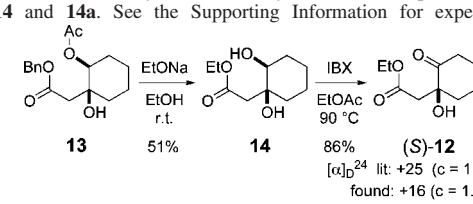


SCHEME 5. Enzymatic Resolution of Racemic Diol (±)-7 and Acetate (±)-13



lipase enzymes.[14,15] We performed an enzymatic resolution of the racemic diol (±)-**7** by transesterification with vinyl acetate to give acetate **13a** and the remaining enantioenriched diol **7**. Based on its broad application in the resolution of secondary alcohols, the Amano lipase AK derived from *Pseudomonas fluorescens* was chosen.[15] Shown in Scheme 5 are the results of the resolution. Heating diol (±)-**7** to 50 °C with 2 equiv of vinyl acetate in *t*-BuOMe in the presence of the lipase gave 47% of the acetate **13a** (82% ee)[16] and 49% of the recovered diol **7** (≥97% ee) after filtration through Celite and column chromatography (SiO_2). The secondary alcohol of **7** was then converted to the Mosher ester and the enantiomeric excess was determined from its ^1H NMR spectrum (≥97% ee).[17] The calculated *E* value[18] for the lipase in this resolution is 42.

To access the free diol **7a** from acetate **13a** (taken from the enzymatic acetylation in Scheme 5), we performed the deacety-



(9) (a) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001–3003. (b) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538.

(10) García Ruano, J. L.; Barros, D.; Maestro, M. C.; Alcudia, A.; Fernández, I. *Tetrahedron: Asymmetry* **1998**, *9*, 3445–3453.

(11) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771.

(12) See the Supporting Information for the reaction conditions and details.

(13) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

(14) Zhao, Y.; Rodrigo, H.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67–70.

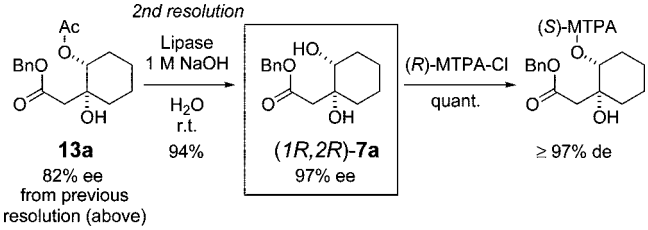
(15) For reviews, see:(a) Faber, K.; Riva, S. *Synthesis* **1992**, 895–910. (b) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071–1140. (c) Otera, J. *Chem. Rev.* **1993**, *93*, 1449–1470.

(16) Although the absolute stereochemistry of the hydrolyzed secondary alcohol can be assumed from the empirical rule for enzymatic resolutions (Xie, Z.-F.; Suemune, H.; Sakai, K. *Tetrahedron: Asymmetry* **1990**, *1*, 395–402),. the absolute stereochemistry of acetates **13** and **13a** was confirmed by conversion to the known compounds (*S*)-**12** and (*R*)-**12a** and comparison of the sign of specific optical rotation from ref 10. Also, the enantiopurity of acetates **13** and **13a** was determined by ^1H NMR analysis of the corresponding Mosher esters of **14** and **14a**. See the Supporting Information for experimental details

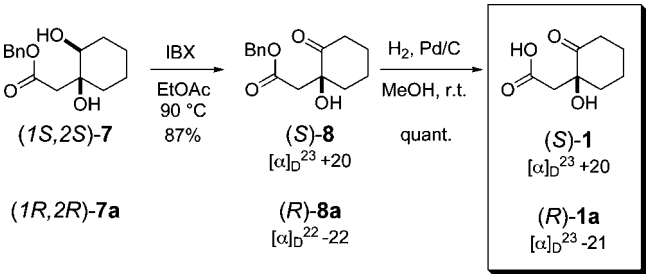
(17) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096, For the ^1H NMR spectrum of the Mosher ester of both the racemic and enantiopure diols **7**, see the Supporting Information.

(18) Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C.-J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.

SCHEME 6. Lipase-Catalyzed Conversion of Acetate 13a to Diol 7a and Determination of Enantiopurity



SCHEME 7. Conversion of Diol 7 to 2-(1-Hydroxy-2-oxocyclohexyl)acetic Acid (1)



lation using the same lipase as for the previous resolution (Scheme 6). This, as before, allows for selective hydrolysis of the acetate in the presence of the benzyl ester, a transformation we found to be nontrivial using other methods.[19] An added benefit of this lipase-catalyzed hydrolysis is the further enantiomeric enrichment of the diol **7a** (starting from 82% ee with acetate **13a** to ≥97% ee with diol **7a**). When acetate **13a** was treated with lipase AK and 0.875 equiv of 1 M NaOH under conditions identical to the enzymatic hydrolysis shown above the diol, **7a** was recovered in 94% yield. This two-step process involving two enzymatic resolutions to access diol **7a** is not as efficient as the two-step procedure involving racemic formation of the acetate (±)-**13** followed by enzymatic deacetylation (as shown in Scheme 5 and described below). Important to note is the selective hydrolysis of the acetate ester and not the benzyl ester, presumably due to the greater steric hindrance of the benzyl ester. This chemoselective hydrolysis was not possible without the use of the lipase. The secondary alcohol of **7a** was then converted to the MTPA ester and the enantiomeric excess was determined from its ^{1}H NMR spectrum (≥97% ee).

To access the *syn*-diol enantiomer **7a** using a single enzymatic resolution, we performed an enzymatic deacetylation with racemic *syn*-diol monoacetate (±)-**13** as shown in Scheme 5. Treatment of the substrate (±)-**13** with the lipase and 0.11 equiv (total over two additions) of 1 M aqueous NaOH in a phosphate buffer at room temperature yielded 44% of the diol **7a** (≥97% ee) resulting from acetate hydrolysis along with a 48% recovery of the remaining acetate **13** (≥97% ee).[16] The calculated *E*-value for the lipase in this resolution is 278.

The desired (*S*)-2-(1-hydroxy-2-oxocyclohexyl)acetic acid (**1**) could easily be obtained from the diol (*1S*,*2S*)-**7** as shown in Scheme 7. IBX oxidation of diol **7** followed by hydrogenation of benzyl ester (*S*)-**8** afforded the precursor to the Ugi 4C-3C reaction, γ-keto acid (*S*)-**1**.[20] The importance of carrying through the benzyl (as opposed to a simple alkyl) ester in **8**, thus allowing for mild access to the carboxylic acid **1**, was apparent upon attempted base-promoted hydrolysis; a major competing reaction involving elimination of the tertiary alcohol of **8** could not be avoided.

The scalable preparation of both enantiomers of 2-(1-hydroxy-2-oxocyclohexyl)acetic acid (**1**) (in six steps and 32% overall yield for (*S*)-**1**, 7 steps and 27% overall yield for (*R*)-**1a**, from cyclohexanone) has been demonstrated through an enzymatic resolution using a common enzyme and simply varying the reaction conditions. The enantioselective preparation of the acid was reported for the first time in the literature. The ease of operation and fewer numbers of synthetic manipulations, as well as the use of environmentally benign reagents make this method more attractive than the previous preparation. This methodology allows for access to optically active vicinal diol **7** and also β-hydroxy-γ-ketoacid **1** which can be valuable synthons for natural product synthesis. An important aspect of this strategy is minimal loss of material by elimination of the tertiary alcohol or γ-lactone formation. The application of 2-(1-hydroxy-2-oxocyclohexyl)acetic acid (**1**) in the stereocontrolled Ugi reaction for the synthesis of proteasome inhibitor salinosporamide A derivatives and investigation of the reaction mechanism of the angular stereoisomerization with the enantiomerically pure bicyclic pyroglutamic acid derivative will be reported in due course.

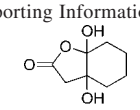
Experimental Section

Benzyl 2-(1-Hydroxycyclohexyl)acetate (5). A suspension of zinc dust (13.32 g, 203 mmol, 4.0 equiv) and copper(I) chloride (2.02 g, 20.3 mmol, 0.4 equiv) in THF (125 mL) was stirred under reflux for 30 min under an N_2 atmosphere. The flask was removed from heating, and benzyl 2-bromoacetate (7.99 mL, 50.9 mmol, 1.0 equiv) in THF (30 mL) was added via addition funnel at a rate to maintain reflux. After 1 h and allowing the solution cool to 23 °C, cyclohexanone (5.28 mL, 50.9 mmol, 1.0 equiv) in THF (50 mL) was added via addition funnel over 5 min. The mixture was stirred for 3 h and then filtered through Celite and the cake rinsed with ether (100 mL). Water (200 mL) was added, and the mixture again filtered through Celite, and the cake rinsed with ether (50 mL). The filtrate was then washed with saturated aqueous sodium chloride (150 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The resultant oil was purified by flash chromatography on silica gel (4:1 → 3:1 hexanes/ethyl acetate) to yield the product **5** (11.99 g, 48.3 mmol, 95%). R_f = 0.33 (3:1 hexanes/ethyl acetate) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33−7.39 (m, 5H), 5.15 (s, 2H), 3.33 (bs, 1H), 2.53 (s, 2H), 1.60−1.72 (m, 4H), 1.48−1.48 (m, 2H), 1.38−1.48 (m, 2H), 1.25−1.32 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.0, 135.8, 128.9 (2C), 128.6, 128.5 (2C), 70.3, 66.6, 45.5, 37.7 (2C), 25.8, 22.2 (2C). HRMS: calcd for $C_{15}H_{20}O_3$ 248.1407, found 248.1406.

Benzyl 2-Cyclohexenylacetate (6). To a solution of benzyl 2-(1-hydroxycyclohexyl)acetate **5** (7.95 g, 32.0 mmol, 1.0 equiv) in benzene (300 mL) was added DL-camphorsulfonic acid (11.16 g, 48.0 mmol, 1.5 equiv). A Dean−Stark apparatus was attached, and the mixture was refluxed at 100 °C for 26 h. Periodically during that time, an additional 3 equiv of CSA (22.2 g, 96.0 mmol, 3 equiv) was added in

(19) Standard acetate deprotection conditions involving potassium carbonate in methanol cleaved the acetyl group but also converted the benzyl ester to the methyl ester. As mentioned later in the text, base-promoted hydrolysis of this particular ester did not give the desired γ-keto acid **1**.

(20) 2-(1-Hydroxy-2-oxocyclohexyl)acetic acid (**1**) can also exist in the hemiketal form **15** as reported previously in its racemic synthesis (ref 3). The ^{1}H NMR chemical shifts of the α-C H_2 of the cyclohexanone moiety observed in CD_3OD, D_2O, and acetone-d_6 indicated the keto form rather than hemiketal form (see the Supporting Information for the ^{1}H NMR spectrum).



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three installments. The mixture was partitioned between saturated aqueous sodium bicarbonate (300 mL) and EtOAc (350 mL) and then washed with saturated aqueous sodium chloride (100 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The resultant oil was purified by flash chromatography on silica gel (15:1 → 13:1 → 11:1 hexanes/ethyl acetate) to yield **6** (5.83 g, 25.3 mmol, 79%, 11:1 mixture of β,γ- to α,β-olefin isomers) as a colorless oil as an 11:1 mixture of β,γ to α,β olefin regioisomers. $R_f = 0.57$ (3:1 hexanes/ethyl acetate). Data for major, desired isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (m, 5H), 5.58 (s, 2H), 3.00 (s, 2H), 1.96−2.06 (m, 4H), 1.52−1.66 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.6, 135.8, 130.8, 128.4 (2C), 127.99, 127.96 (2C), 125.8, 66.2, 43.6, 28.5, 25.4, 22.8, 22.1. HRMS: calcd for $C_{15}H_{18}O_2$ 230.1301, found 230.1304.

Benzyl 2-(*cis*-1,2-Dihydroxycyclohexyl)acetate (±)-(7). To a solution of **6** (5.70 g, 24.8 mmol, 1.0 equiv, 11:1 mixture of β,γ- to α,β-olefin isomers) in 10:1 THF/H_2O (150 mL) were added 4% OsO_4 in H_2O (4.55 mL, 0.743 mmol, 0.03 equiv), 4-methylmorpholine *N*-oxide (8.70 g, 74.3 mmol, 3.0 equiv), and 1,4-diazabicyclo[2.2.2]octane (139 mg, 1.24 mmol, 0.05 equiv). After the mixture was stirred for 14 h, saturated aqueous sodium bisulfite (100 mL) was added, and the mixture was extracted with ethyl acetate (3 × 200 mL). The organics were washed with brine (150 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The resultant solid was purified by flash chromatography on silica gel (3:1 → 1:1 hexanes/ethyl acetate) to yield (±)-**7** (6.08 g, 23.0 mmol, 93%, 11:1 mixture of β,γ to α,β diol isomers) as an off-white powder. Use of the 11:1 mixture poses no problem in the following steps, and the minor isomer was removed after IBX oxidation. This 11:1 diol mixture was recrystallized two times (5:1 hexanes/EtOAc) to give a nearly pure β,γ-diol for collection of physical data (see the Supporting Information for NMR of the mixture and purified material). $R_f = 0.13$ (3:1 hexanes/ethyl acetate). Data for major, desired isomer. Mp = 71−73 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.30−7.40 (m, 5H), 5.15 (s, 2H), 3.66 (s, 1H), 3.33, (dd, 1H, J = 10.5, 4.5 Hz), 2.90 (d, 1H, J = 15.3 Hz), 2.43 (d, 1H, J = 15.3 Hz), 2.18 (d, 1H, J = 7.5 Hz), 1.84 (dt, 1H, J = 13.5, 4.0 Hz), 1.65−1.74 (m, 2H), 1.50−1.65 (m, 2H), 1.38−1.42 (m, 1H), 1.20−1.32 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.5, 135.7, 128.9 (2C), 128.7, 128.5 (2C), 77.0, 74.2, 66.9, 43.1, 35.7, 30.5, 23.9, 21.1. HRMS: calcd for $C_{15}H_{20}O_4$ 264.1356, found 264.1354.

Benzyl 2-((1*S*,2*S*)-2-Acetoxy-1-hydroxycyclohexyl)acetate (±)-(13). To a solution of (±)-**7** (5.2 g, 19.7 mmol, 1.0 equiv, 11:1 mixture of β,γ- to α,β-diol isomers) in pyridine (40 mL, 0.491 mol, 25 equiv) was added acetic anhydride (20 mL, 0.212 mol, 11 equiv). After being stirredfor 20 h, the mixture was diluted with ethyl acetate (200 mL) and washed with 1 M HCl (3 × 100 mL). The organics were further washed with saturated aqueous $NaHCO_3$ (2 × 100 mL), dried over sodium sulfate, and concentrated in vacuo to yield (±)-**13** (6.03 g, 19.7 mmol, 100%, 11:1 mixture of isomers). $R_f = 0.24$ (3:1 hexanes/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30−7.40 (m, 5H), 5.12 (s, 2H), 4.64 (dd, 1H, J = 4.4, 10.4 Hz), 3.45 (bs, 1H), 2.64 (d, 1H, J = 15.6 Hz), 2.41 (d, 1H, J = 15.2 Hz), 2.01 (s, 3H), 1.87 (apparent d, 1H, J = 14.0 Hz), 1.70−1.80 (m, 3H), 1.60−1.68 (m, 1H), 1.30−1.48 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.0, 170.5, 135.4, 128.7 (2C), 128.5, 128.3 (2C), 77.4, 71.5, 66.6, 43.1, 36.3, 26.8, 23.9, 21.2, 20.4. HRMS: calcd for $C_{17}H_{22}O_5$ 306.1462, found 306.1460.

Preparation of Benzyl 2-((1*S*,2*S*)-1,2-Dihydroxycyclohexyl)-acetate (7) by Enzymatic Acetylation. A solution of diol (±)-**7** (4.97 g, 18.8 mmol, 1.0 equiv, 11:1 mixture of β,γ- to α,β-diol isomers), vinyl acetate (0.890 g, 10.3 mmol, 0.55 equiv), and Amano lipase AK (0.498 g, 176 units lipase/mmol diol, 3 equiv based on 20000 units/g of lipase) in *t*-BuOMe (50 mL) was heated to 50 °C. It was heated for a total of 72 h with addition of additional vinyl acetate (1.0 mL) after 30 h. Reaction progress was checked by integration of peaks (diol: 2.89 ppm, acetate: 2.64 ppm) in the ^{1}H NMR spectrum of a crude aliquot (see the Supporting Information for ^{1}H NMR spectrum). At the 50% completion point, the mixture was filtered through Celite and concentrated in vacuo. The resultant oil was purified by flash chromatography on silica gel (4:1 → 3:1 hexanes/ethyl acetate) to yield acetate **13a** (2.74 g, 8.94 mmol, 47%, 82% ee (by derivatization to the Mosher esters), $[\alpha]^{23}_D$ +5 (*c* 1.0, $CHCl_3$), 11:1 mixture of isomers) and the remaining diol (−)-**7** (2.47 g, 9.34 mmol, 49%, ≥ 97% ee (by derivatization to the Mosher esters), $[\alpha]^{23}_D$ −4 (*c* 1.0, $CHCl_3$), 11:1 mixture of isomers). Included in the Supporting Information are the NMRs of the crude aliquot mentioned above and the MTPA ester of the diol showing its enantiopurity.

Preparation of Benzyl 2-((1*R*,2*R*)-1,2-Dihydroxycyclohexyl) acetate (7a) by Enzymatic Hydrolysis. To a solution of acetate (±)-**13** (157 mg, 0.512 mmol, 1.0 equiv, 11:1 mixture of β,γ- to α,β-diol isomers) and Amano lipase AK (30 mg, 176 units lipase/mmol diol, 6 equiv based on 20000 units/g of lipase) in 1 mL of pH = 7 phosphate buffer was added 1 M NaOH (35 μL, 0.068 equiv). The mixture was stirred at rt for 16 h, and then more 1 M NaOH (20 mL, 0.039 equiv) was added and the mixture stirred for another 27 h. Reaction progress was checked as above and indicated nearly 50% conversion. The mixture was extracted with dichloromethane (3 × 15 mL), and the organics were washed with brine (15 mL), dried over sodium sulfate, and concentrated in vacuo. The resultant oil was purified by flash chromatography on silica gel (5:1 hexanes/ethyl acetate) to yield the remaining acetate **13** (74 mg, 0.241 mmol, 48%, ≥97% ee (by derivatization to the Mosher esters), $[\alpha]^{23}_D$ −8 (*c* 1.0, $CHCl_3$), 5:1 mixture of isomers) and diol **7a** (52 mg, 0.197 mmol, 44%, ≥97% ee (by derivatization to the Mosher esters), $[\alpha]^{23}_D$ +3 (*c* 1.0, $CHCl_3$), 14:1 mixture of isomers).

(S)-Benzyl 2-(1-Hydroxy-2-oxocyclohexyl)acetate (8). To a solution of **7** (4.10 g, 15.5 mmol, 1.0 equiv, 11:1 mixture of β,γ- to α,β-diol isomers) in ethyl acetate (300 mL) was added IBX (6.52 g, 23.3 mmol, 1.5 equiv). After being heated at reflux for 6 h, the mixture was filtered through Celite and concentrated in vacuo. The resultant oil was purified by flash chromatography on silica gel (5:1 hexanes/ethyl acetate) to yield **8** (3.60 g, 13.7 mmol, 87%), $R_f = 0.23$ (3:1 hexanes/ethyl acetate), as a single isomer. For the *S*-enantiomer **8**: $[\alpha]^{23}_D$ +20 (*c* 1.1, $CHCl_3$). For the *R*-enantiomer **8a**: $[\alpha]^{22}_D$ −22 (*c* 1.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32−7.40 (m, 5H), 5.12 (s, 2H), 4.58 (s, 1H), 3.00 (d, 1H, J = 15.2 Hz), 2.72−2.80 (m, 1H), 2.60 (d, 1H, J = 15.6 Hz), 2.44−2.52 (m, 1H), 1.88−2.00 (m, 3H), 1.78−1.86 (m, 2H), 1.56−1.70 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.3, 170.9, 135.1, 128.2 (2C), 128.0, 127.9 (2C), 77.1, 66.5, 41.5, 41.3, 37.8, 28.3, 21.7. HRMS: calcd for $C_{15}H_{18}O_4$ 262.1200, found 262.1202.

(*S*)-2-(1-Hydroxy-2-oxocyclohexyl)acetic Acid (1). To a solution of **8** (422 mg, 1.61 mmol, 1.0 equiv) in methanol (35 mL) was added 10 wt % Pd/C (150 mg). A balloon of H_2 was applied for 16 h, and then the mixture was filtered through Celite and concentrated in vacuo to yield **1** (283 mg, 1.61 mmol, 100%). For the *S*-enantiomer **1**: $[\alpha]^{23}_D$ +20 (*c* 0.8, DMSO). For the *R*-enantiomer **1a**: $[\alpha]^{23}_D$ −21 (*c* 0.8, DMSO). ^{1}H NMR (400 MHz, CD_3OD) δ: 2.80 (d, 1H, J = 16.0 Hz), 2.58 (d, 1H, J = 15.6 Hz), 2.28 (bs, 1H), 2.16 (bs, 1H), 1.68 (m, 6H). ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ: 208.0, 175.3, 77.7, 43.4, 38.8, 37.4, 26.6, 23.2. HRMS: calcd for $C_8H_{12}O_4$ 172.0730, found 172.0733.

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **1**,**5**−**8**, and **12**−**14**, as well as partial ^{1}H NMR spectra of the Mosher esters of **7** and **7a**. Additional experimental procedures for Sharpless asymmetric dihydroxylation of **6** and ref 16 (**13** → **14** → **12**). This material is available free of charge via the Internet at http://pubs.acs.org.

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