ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D
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pubs.acs.org/OPRD

Research and Development of an Efficient Synthesis of a Key Building Block for Anti-AIDS Drugs by Diphenylprolinol-Catalyzed Enantio- and Diastereoselective Direct Cross Aldol Reaction

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Supporting Information

ABSTRACT: An efficient method for synthesizing 1-({[(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yloxy]carbonyl}oxy)-pyrrolidine-2,5-dione (**1**), a key building block for HIV protease inhibitors, has been developed. A diphenylprolinol-catalyzed highly enantio- and diastereoselective cross aldol reaction of polymeric ethyl glyoxylate with an aldehyde was used as the key step. Acetalized aldol adduct was reduced with $NaBH_4$ to give the diol intermediate in quantitative yield. The acetal exchange reaction followed by hydrogenation with Pd/C catalyst afforded **1′** in 95% yield over 2 steps. The condensation of **1′** with a carbonate gave crystalline **1** (>99/1 dr, > 99% ee) after single crystallization. This is a highly practical synthetic method since environmentally benign organocatalysis is utilized, the amount of catalyst is reduced to 3 mol %, and all of the intermediates before **1′** can be used without any purification.

INTRODUCTION

A bis-tetrahydrofuranyl (bis-THF) moiety has been utilized in the design of a number of potent HIV protease inhibitors.[1] Much effort has been devoted to the synthesis of (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-ol (**1′**) or 1-({[(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yloxy]carbonyl}oxy)pyrrolidine-2,5-dione (**1**). One approach involves the synthesis of racemic form of bis-THF alcohol **1′** followed by enzymatic optical resolution.[2] Although this synthetic approach has been demonstrated to be highly practical, half of bis-THF alcohol should be discarded, and in some cases a toxic tin compound is needed. A second approach by Uchiyama et al. utilizes asymmetric oxyselenenylation of 2,3-dihydrofuran.[3] This looks interesting but is not likely to be benign as a toxic selenium compound is needed. A third approach utilizes substrate-controlled synthesis starting from a chiral pool material such as D-glyceraldehyde derivatives.[4,5] Quaedflieg et al. reported a notable synthesis along this approach, which starts from (*S*)-2,3-*O*-isopropylideneglyceraldehyde, involving diastereoselective Michael addition of nitromethane.[5] The synthesis seems efficient; however, it still requires multiple steps. Ghosh et al. also reported an asymmetric synthesis of bis-THF alcohol **1′** based on anti-aldol reaction of an ester-derived titanium enolate.[6] In this method, a stoichiometric amount of a chiral indanol is needed, and the diastereoselectivity is moderate even at low temperature (−78 °C). Research groups of Gilead Sciences and GlaxoSmithKline independently reported short syntheses based on chiral Lewis acid catalyzed cycloaddition of glycolaldehyde and 2,3-dihydrofuran.[7] While syntheses of both groups are relatively efficient due to the overall short synthetic sequences, enzymatic enhancements are still required to obtain bis-THF alcohol **1′** with sufficient enantiomeric purity. Few examples of highly enantio- and diastereoselective syntheses of bis-THF alcohol **1′** through chiral catalysis including our own works have been reported.[8,9]

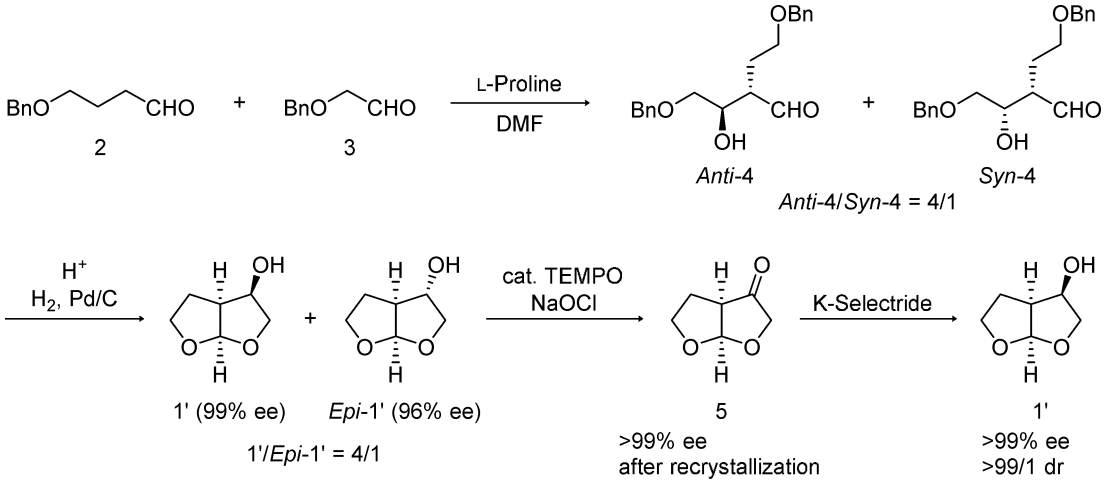
In our previous study, a practical method for the synthesis of bis-THF alcohol **1′** through chiral enamine catalysis was developed (Scheme 1, our first generation).[9] The route is based on an enantioselective proline catalyzed direct cross aldol reaction between aldehydes[10] to give predominantly *Anti*-**4** followed by cyclization and TEMPO oxidation to afford ketone **5**, which is reduced diastereoselectively to give bis-THF alcohol **1′** in an optically pure form. This method was successfully scaled up and proven to be environmentally benign; however, there was still room for improvement. Benzyloxyacetaldehyde **3** is rather expensive because of its synthetic difficulty. More problematic is the moderate diastereoselectivity in the proline catalyzed aldol reaction, necessitating an additional redox process to obtain a single diastereomer.

In 2010, a highly enantio- and diastereoselective direct cross aldol reaction of polymeric ethyl glyoxylate with aldehydes using diarylprolinol catalyst was reported.[11] Ethyl glyoxylate is commercially available in its polymeric form as a toluene solution and relatively inexpensive. In addition, it could be directly used without pyrolysis; thus, we regarded this highly stereoselective reaction as a promising candidate for a practical synthesis of **1′** or **1**. Herein, we report a new and efficient method for the synthesis of **1** utilizing the above-mentioned asymmetric cross aldol reaction as the key step (Scheme 2, our second generation). This practical synthetic route has been developed based on the findings from our detailed investigation on the mechanism of the key step.

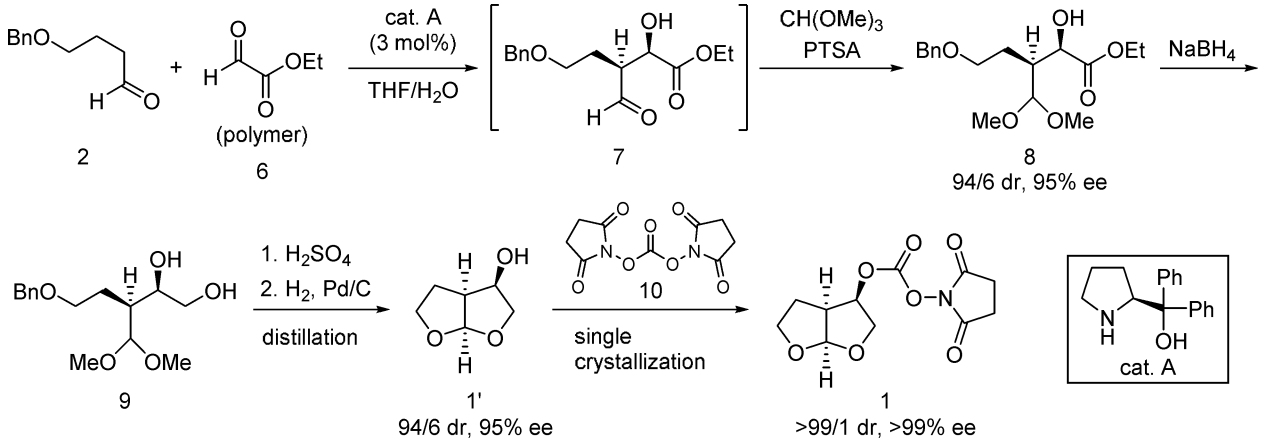
Received: May 20, 2016

DOI: 10.1021/acs.oprd.6b00178
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Scheme 1. Our First-Generation Synthesis of 1′



Scheme 2. Our Second-Generation Synthesis of 1



RESULTS AND DISCUSSION

We applied the stereoselective aldol reaction in the report[11] to our synthesis of bis-THF alcohol **1′** starting from aldehyde **2**. Fortunately, the aldol adduct **7** was obtained with high enantio- and diastereoselectivity (around 85% yield, >95% ee, and >10/1 dr) under the conditions described there (10 mol % of (*S*)-diphenylprolinol catalyst **cat. A** loading).[11]

Reducing the amount of catalyst would have a great impact for cost saving in practical synthesis. However, when the amount of **cat. A** was reduced to 3 mol %, the reaction rate strangely varied depending on manufacturers of ethyl glyoxylate and sometimes became much lower (Table 1, entries 1, 2). Changing the solvents, temperature, or concentration did not improve the results of this aldol reaction.[12a,b] In this aldol reaction, rapid monomerization of polymeric ethyl glyoxylate in situ was assumed to be important because only monomeric form of ethyl glyoxylate could react with aldehyde **2**. We guessed the rate of monomerization of polymeric ethyl glyoxylate differed from manufacturers or lots and was sometimes much lower because of differences of the degree of polymerization. Unexpectedly, however, the aldol reaction using freshly distilled monomeric ethyl glyoxylate was much slower, which implied the presence of another factor (Table 1, entry 3). Investigating the reactivity of ethyl glyoxylate in detail by the analyses of byproducts in the reaction mixture, we found there were two significant factors for those decreasing rate and low reproducibility of the aldol reaction. The first is deactivation of catalyst by the formation of **16**, a cyclic hemiaminal of ethyl glyoxylate and **cat. A**, which accounts for the lower reaction rate of entry 3 in which a larger amount of monomeric ethyl glyoxylate was present in the initial stage of the aldol reaction. The second is, as indicated by the detection of aldehydic acid **15** in the reaction mixture, the presence of a varying amount of glyoxylic acid **14** in commercial polymeric ethyl glyoxylate, which would affect the rates of polymer degradation and catalytic cycle. After various studies, we found a very simple additional operation to solve these problems. Stirring polymeric ethyl glyoxylate in toluene solution with water before aldol reaction for an appropriate period until the ratio of ethyl glyoxylate **6**/glyoxylic acid **14** became between 97:3 and 95:5 was very effective to accelerate the reaction when using 3 mol % of **cat. A** (Table 1, entries 2, 4, 5).[12c] This method also ensured great reproducibility for the aldol reaction even when polymeric ethyl glyoxylate from another manufacturer or lot was utilized (Table 1, entries 6, 7). By ^{1}H NMR and HPLC analyses of the mixture of ethyl glyoxylate with water, it turned out that the polymeric form of ethyl glyoxylate was degraded to monomeric "hydrated form" **13** by water, and a small portion of ethyl glyoxylate was hydrolyzed to glyoxylic acid **14**. The formation of "hydrated form" **13** is likely to inhibit the production of **16** and retains catalyst activity. Monomeric "aldehyde form" **6** seems to be gradually generated from **13** by the elimination of H_2O and rapidly react with enamine **11**. A small amount of glyoxylic acid **14** could accelerate polymer

DOI: 10.1021/acs.oprd.6b00178
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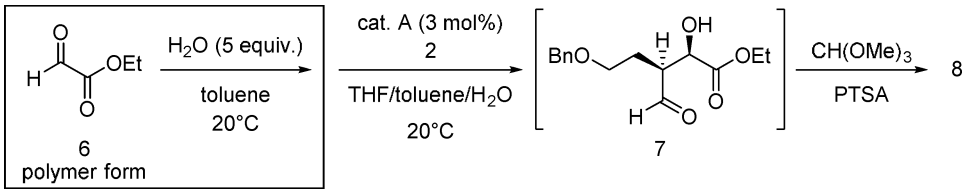
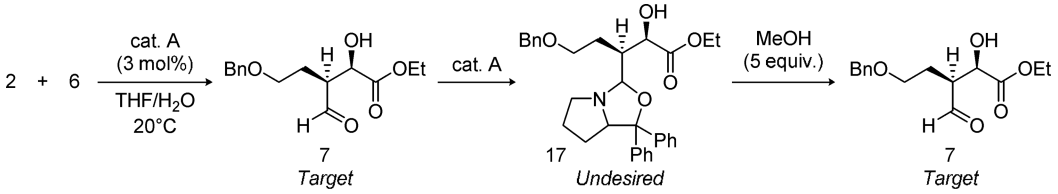
Table 1. Treatment of Ethyl Glyoxylate with Water before the Aldol Reaction



					aldol reaction			
entry	**6** manufacturer[a]	**6** lot no.	stirring time of **6** with water	**6**:**14**	time	yield[d]	dr[e]	ee[e]
1	TCI	FZ6DM	0 h	N/A	21 h	84%	92/8	95%
2	JJC	1430901	0 h	99/1	72 h	81%	92/8	95%
3[b]	Clariant	FRBBDJ1981	0 h	N/A	24 h	<5%	N/A	N/A
4	JJC	1430901	7 h	97/3	17 h	85%	94/6	95%
5	JJC	1430901	24 h	93/7	17 h	82%[c]	94/6	95%
6	JJC	13100701	1 h	96/4	17 h	86%	94/6	95%
7	TCI	FZ6DM	5 h	97/3	19 h	84%	94/6	96%

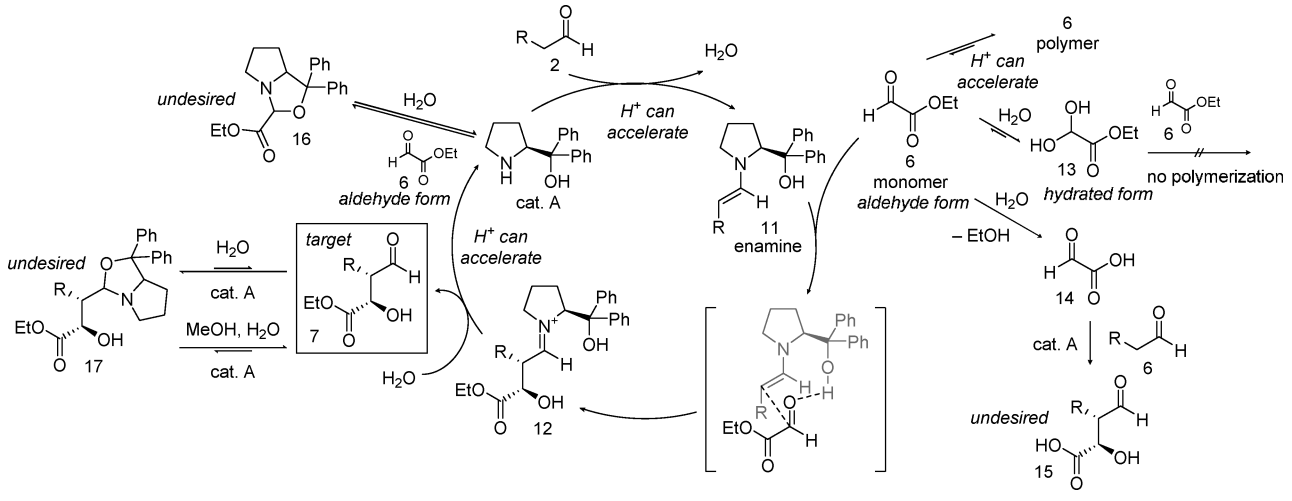
[a]TCI = Tokyo Kasei Inc. JJC = Jiaxing Jlight Chemicals. [b]Freshly distilled **6** was used. **6** manufactured by Clariant was used because its content was 100% (it was not toluene solution). [c]**15** was formed in 6.5 area % (HPLC). [d]Determined by HPLC analysis with an internal standard (acetanilide) after the acetalization. [e]Determined by HPLC analysis after the acetalization by $CH(OMe)_3$ and catalytic PTSA.

Table 2. Addition of MeOH after the Aldol Reaction



	HPLC area %	
after aldol reaction	target **7**	undesired **17**
before adding MeOH	67.4%	3.5%
6 h after adding MeOH	73.2%	0.3%

Scheme 3. Detailed Proposed Reaction Mechanism of the Cross Aldol Reaction



degradation and the catalytic cycle while a large amount of it decreased the yield of aldol reaction due to the formation of aldol adduct **15** by reacting with aldehyde **2** (Table 1, entry 5).

Moreover, we found the desired product **7** reacted with **cat. A** to give the corresponding adduct **17**, which was inactive for the following acetalization. Intensive studies revealed that **7** could be recovered from this adduct by adding methanol to the reaction mixture (Table 2).

The proposed detailed mechanism of the present aldol reaction is summarized in Scheme 3.

Under the above-mentioned optimized conditions, the desired product **8** could be surely obtained in around 85% yield from **2**, with 94/6 dr and 95% ee. Acetalized **8** was successfully transformed to the final product **1** in a fairly practical way, as shown in Scheme 2. Reduction of **8** with $NaBH_4$ afforded diol **9** in quantitative yield. Acetal exchange reaction by catalytic H_2SO_4

DOI: 10.1021/acs.oprd.6b00178
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

followed by hydrogenation with Pd/C catalyst afforded crude **1′** in quantitative yield over two steps. No purification was needed before the distillation of crude **1′**.

The condensation reaction of **1′** with **10** proceeded in quantitative yield. However, purification other than chromatographic method was difficult because both **1** and the byproduct *N*-hydroxysuccinimide were not so soluble in organic solvents, and **1** was easily hydrolyzed by the addition of water to the reaction mixture although *N*-hydroxysuccinimide was quite soluble in water. Investigating the stability of **1**, we found that pure crystalline **1** was appreciably stable even in the presence of water below 5 °C; however, **1** was still easily hydrolyzed when water was added to the reaction mixture below 5 °C. Pyridine, which was used as a base in the condensation reaction, was found to accelerate the hydrolysis. Thus, we thought that the use of acidic aqueous solution could suppress this decomposition, and after all, **1** was found to be stable against water even in the presence of pyridine in the reaction mixture by using excess amount of diluted hydrochloric acid below 5 °C. Finally, crystalline **1** with high purity (>99% assay, >99/1 dr, >99% ee) was obtained in around 80% yield only by adding the reaction mixture to cooled diluted hydrochloric acid and filtering the precipitated crystals.

CONCLUSION

We have developed an efficient synthetic method of **1** using diphenylprolinol catalyzed enantio and diastereoselective cross aldol reaction of polymeric ethyl glyoxylate with an aldehyde as the key reaction. This method is highly practical due to (1) the use of environmentally benign organocatalysis and inexpensive reagents, (2) low catalyst loading and great reproducibility by the simple pretreatment, and (3) the achievement of quite high purity with only single crystallization.

EXPERIMENTAL SECTION

General Remarks. Chemicals and solvents were purchased from commercial suppliers. ^{1}H NMR spectra were measured on a JEOL JMN400 FT-NMR (400 MHz) spectrometer. Chemical shifts were reported in ppm from tetramethylsilane as an internal standard. Data were reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quintet, m = multiplet, br = broad, app = apparent), coupling constants (Hz). ^{13}C NMR spectra were recorded on a JEOL JMN400 FT-NMR (100 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. HPLC was performed on Shimadzu LC-10AT and Shimadzu LC-20AD instruments equipped with UV detectors. GC was carried out using Shimadzu GC-17A, Shimadzu GC-2010, and Agilent Technologies 6890N instruments equipped with FID detectors. The HRMS were performed on Thermo Fisher Scientific Q-Exactive spectrometer. Optical rotations were measured on a JASCO P-1030 polarimeter.

Synthesis of Ethyl (2*R*,3*S*)-2-Hydroxy-3-dimethoxymethyl-5-benzyloxypentanoate (8). A mixture of water (126.4 g, 7.01 mol) and ethyl glyoxylate **6** in toluene solution (50.8% assay, 338.3 g, 1.68 mol) was stirred at 20 °C for 5 h (ratio of **6**/**14** = 95:5). After (*S*)-diphenylprolinol **cat. A** (99.3% assay, 10.7 g, 0.042 mol, 3 mol %) and THF (312.5 g) were added to the reaction mixture, aldehyde **2** (93.1% assay, 268.6 g, 1.40 mol) was added slowly dropwise to the reaction mixture over 2 h at 20 °C. After stirring for an additional 17 h at 20 °C, the reaction mixture was then poured into 20% NaCl aqueous solution (500.0 g) and separated at 20 °C. To the organic layer was then added methanol (224.7 g, 7.01 mol). After stirring for 6 h, this mixture was added slowly dropwise to a mixture of trimethyl orthoformate (99.6% assay, 373.5 g, 3.51 mol) and *p*-toluenesulfonic acid monohydrate (98.5% assay, 13.5 g, 0.070 mol) at 20 °C. After stirring for 3 h at the same temperature, solid $NaHCO_3$ (23.6 g, 0.28 mol) was added to quench *p*-toluenesulfonic acid, and the mixture was concentrated in vacuo. To this residue was added toluene (219.2 g), and the mixture was then poured into a mixture of 4% $NaHCO_3$ and 4% NaCl aqueous solution (325.0 g) and separated. The organic layer was washed with 5% $NaHCO_3$ and 5% NaCl aqueous solution (250.0 g) and concentrated in vacuo to afford the crude product 8 (pale-yellow oil, 671.0 g, 58.9% assay, 86% yield, 94/6 dr, 95% ee), which was utilized in the next step without purification.

HPLC analysis (ratio of ethyl glyoxylate **6**/glyoxylic acid **14**): Scherzo SS-C18 (4.6 mm × 150 mm, 3 μm), mobile phase A; 10 mM aqueous solution of K_2HPO_4 (pH 7 with H_3PO_4), mobile phase B; acetonitrile, flow rate = 1.0 mL/min, detector; UV 215 nm, gradient program (B conc.); 0 min (10%) → 5 min (10%) → 15 min (80%) → 25 min (80%) → 25.01 min (10%) → 50 min (stop), retention time; 2.0 min (glyoxylic acid **14**) and 2.7 min (ethyl glyoxylate **6**).

HPLC analysis (assay of **8**, acetanilide as an internal standard): CAPCELL PAK C18 MGIII (4.6 mm × 150 mm, 5 μm), mobile phase A; 0.05% aqueous solution of trifluoroacetic acid (hereinafter referred to as TFA), mobile phase B; 0.05% acetonitrile solution of TFA, flow rate = 1.0 mL/min, detector; UV 215 nm, gradient program (B conc.); 0 min (20%) → 35 min (50%) → 50 min (80%) → 65 min (80%) → 65.5 min (20%) → 80 min (stop), retention time; 7.2 min (acetanilide), 30.8 min (major diastereomer of **8**), 31.6 min (minor diastereomer of **8**).

HPLC analysis (enantiomeric excess): CHIRALPAK AS-RH (4.6 mm × 150 mm, 5 μm) and L-column ODS (4.6 mm × 15 mm, 5 μm), water/acetonitrile = 7:3, flow rate = 1.0 mL/min, detector; UV 220 nm, retention time; 50.4 min (minor), 53.5 min (major).

Crude **8** was partially purified by column chromatography on silica gel 60, spherical, neutrality (Nacalai Tesque) for ^{1}H NMR spectrum, ^{13}C NMR spectrum, and HRMS measurements. ^{1}H NMR (400 MHz, $CDCl_3$, major diastereomer) δ 7.34−7.27 (5H, m), δ 4.56 (1H, d, J = 12.4 Hz), δ 4.50 (1H, d, J = 12.4 Hz), δ 4.36 (1H, d, J = 7.2 Hz), δ 4.23 (2H, q, J = 7.2 Hz), δ 4.21−4.19 (1H, m), δ 3.62−3.58 (2H, m), δ 3.32 (3H, s), δ 3.31 (3H, s), δ 2.51−2.46 (1H, m), δ 1.96−1.78 (2H, m), δ 1.31 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereomer) δ 174.7, 138.3, 128.3, 127.55, 127.51, 105.5, 72.8, 70.2, 67.9, 61.2, 56.0, 53.2, 41.6, 26.9, 14.1; HRMS (ESI-HESI$^+$) calcd for $C_{17}H_{26}NaO_6$: 349.1622 ($[M + Na]^+$), found: 349.1621 ($[M + Na]^+$).

Synthesis of (2*R*,3*S*)-3-Dimethoxymethyl-5-benzyloxy-1,2-pentanediol (9). To a solution of crude **8** (544.4 g, 0.926 mol as 8) in methanol (63.0 g) and toluene (396.9 g) was added $NaBH_4$ (99.6% assay, 52.8 g, 1.39 mol) with nine portions at 35 °C. After stirring at the same temperature for 15 h, the reaction mixture and additional toluene (300.0 g) for washing the reaction vessel were slowly poured into a mixture of 10% NaCl aqueous solution (300.0 g), acetic acid (75.0 g), and water (150.0 g) at 0 °C. The mixture was heated to 25 °C, stirred for 30 min, and separated. The organic layer was washed with water (300.0 g), and the resulted organic layer including **9** (1161.7 g,

DOI: 10.1021/acs.oprd.6b00178
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

22.4% assay, 99% yield) was used in the next step without concentration and purification.

HPLC analysis (assay of **9**, heptylbenzene as an internal standard): L-column2 (4.6 mm × 250 mm, 5 μm), mobile phase A; 10 mM aqueous solution of K_2HPO_4 (pH 7 with H_3PO_4), mobile phase B; acetonitrile, flow rate = 1.0 mL/min, detector; UV 215 nm, gradient program (B conc.); 0 min (24%) → 40 min (24%) → 70 min (80%) → 90 min (80%) → 90.1 min (24%) → 110 min (stop), retention time; 26.3 min [**9** (diastereomers are not separated)], 88.2 min (heptylbenzene).

Crude **9** was partially purified by column chromatography on silica gel 60, spherical, neutrality (Nacalai Tesque) for ^{1}H NMR spectrum, ^{13}C NMR spectrum, and HRMS measurements. ^{1}H NMR (400 MHz, $CDCl_3$, major diastereomer) δ 7.37−7.27 (5H, m), δ 4.51 (2H, s), δ 4.42 (1H, d, J = 5.2 Hz), δ 3.76 (1H, br s), δ 3.65 (1H, app d, J = 4.8 Hz), δ 3.61−3.50 (2H, m), δ 3.40 (3H, s), δ 3.38 (3H, s), δ 2.73 (1H, br s), δ 2.08−2.03 (1H, m), δ 1.82−1.67 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereomer) δ 137.9, 128.4, 127.71, 127.67, 107.7, 73.0, 72.1, 68.6, 64.7, 56.0, 54.9, 40.8, 26.6; HRMS (ESI-HESI$^+$) calcd for $C_{15}H_{24}NaO_5$: 307.1516 ($[M + Na]^+$), found: 307.1515 ($[M + Na]^+$).

Synthesis of Crude (3*R*,3*aS*,6*aR*)-Hexahydrofuro[2,3-*b*]furan-3-ol (1′). To a solution of toluene (12.1 g), 2-propanol (168.8 g), and the organic layer including **9** (359.4 g, 0.263 mol as **9**) was slowly added 98% sulfuric acid (1.85 g, 0.018 mol, 7 mol %) at 25 °C. After stirring for 2 h at the same temperature, to this reaction mixture were added 98% sulfuric acid (2.90 g, 0.029 mol, 11 mol %) and wet 10% Pd/C (1.88 g as dry) to undergo the reaction at a hydrogen pressure of 0.5 MPa at 25 °C for 4 h. After completion of the hydrogenation, Pd/C was filtered out. To the filtrate was added 28% NaOMe/MeOH (20.3 g, 0.105 mol, 0.40 equiv) to quench sulfuric acid, and the obtained mixture was concentrated in vacuo to afford the crude product **1′** (brown oil, 74.0 g, 45.8% assay, 99% yield, 94:6 dr).

GC analysis (assay of **1′**, *n*-hexadecane as an internal standard): HP-5 (0.25 mmφ × 30 m, 0.25 μm), flow rate = 1.69 mL/min, injection mode; split (1/20), injection temperature; 260 °C, column temperature; 60 °C (5 min) → 5 °C/min → 250 °C (10 min), detection temperature; 260 °C (FID), retention time; 16.0 min (minor diastereomer of **1′**), 16.7 min (major diastereomer of **1′**), 26.0 min (*n*-hexadecane).

Purification of Crude 1′ by Distillation. To the crude **1′** (129.5 g, 0.448 mol as **1′**) was added PEG #400 (58.7 g) and distilled under reduced pressure (0.132−0.120 kPa, 72−197 °C) to give **1′** (pale-brown oil, 63.6 g, 88.4% assay, 96% yield, 94/6 dr).

The distilled **1′** was partially purified by column chromatography on silica gel 60, spherical, neutrality (Nacalai Tesque) for optical rotation, ^{1}H NMR spectrum, and ^{13}C NMR spectrum measurements. $[\alpha]^{25}_D$ = −14.4 (c 1.31, methanol); ^{1}H NMR (400 MHz, $CDCl_3$, major diastereomer) δ 5.68 (1H, d, J = 5.2 Hz), δ 4.47−4.40 (1H, m), δ 4.00−3.87 (3H, m), δ 3.61 (1H, dd, J = 8.8, 7.2 Hz), δ 3.03 (1H, d, J = 4.8 Hz), δ 2.89−2.83 (1H, m), δ 2.35−2.29 (1H, m), δ 1.92−1.82 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereomer) δ 109.4, 72.9, 70.5, 69.8, 46.4, 24.7.[13]

Synthesis of 1-({[(3*R*,3*aS*,6*aR*)-Hexahydrofuro[2,3-*b*]-furan-3-yloxy]carbonyl}oxy)pyrrolidine-2,5-dione (1). To a mixture of **1′** (50.0 g, 0.351 mol as 1′) and *N*,*N*′-disuccinimidyl carbonate **10** (98.3% assay, 109.9 g, 0.42 mol) in toluene (228.7 g) was added dropwise pyridine (99.5% assay, 37.3 g, 0.47 mol) at 25 °C. The reaction mixture was heated to 40 °C and stirred for 9 h. The resulting mixture and additional toluene (228.7 g) were slowly added to cooled 4% HCl aqueous solution (414.9 g) below 5 °C. The precipitated crystals were filtered below 5 °C and washed with cooled water (91.5 g) twice, cooled 2-propanol (91.5 g) twice, and cooled toluene (91.5 g). The wet crystals were dried in vacuo below 40 °C to furnish **1** (71.9 g, 100% assay, 76% yield, >99/1 dr, >99% ee).

GC analysis (assay of **1**, heptylbenzene as an internal standard): DB-17 (0.25 mmφ × 30 m, 0.25 μm), flow rate = 2.4 mL/min, injection mode; split (1/50), injection temperature; 180 °C, column temperature; 110 °C (15 min) → 10 °C/min → 280 °C (8 min), detection temperature; 280 °C (FID), retention time; 8.5 min (heptylbenzene), 31.9 min (major diastereomer of **1**), 32.0 min (minor diastereomer of **1**).

HPLC analysis (optical purity): CHIRALPAK IA-3 (4.6 mm*250 mm, 3 μm), hexane/0.01% THF solution of TFA = 45:55, flow rate = 0.5 mL/min, detector; UV 254 nm, retention time; 9.3 min (minor), 11.9 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (1H, d, J = 4.8 Hz), δ 5.25 (1H, dt, J = 8.4, 6.0 Hz), δ 4.11 (1H, dd, J = 10.4, 6.4 Hz), δ 4.03 (1H, td, J = 8.8, 2.4 Hz), δ 3.97−3.91 (2H, m), δ 3.17−3.10 (1H, m), δ 2.86 (4H, s), δ 2.17−2.12 (1H, m), δ 2.04−1.93 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 151.1, 109.1, 79.6, 69.9, 69.6, 45.0, 25.9, 25.4; HRMS (ESI-HESI$^+$) calcd for $C_{11}H_{17}N_2O_7$: 289.1030 ($[M + NH_4]^+$), found: 289.1028 ($[M + NH_4]^+$).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.6b00178.

^{1}H NMR and ^{13}C NMR spectra for compound **8**, **9**, **1′**, **1**, and HPLC and GC data of the syntheses of compound **8**, **9**, **1′**, and **1** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully thank Prof. Yujiro Hayashi (Department of Chemistry, Graduate School of Science, Tohoku University) for valuable discussions.

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DOI: 10.1021/acs.oprd.6b00178
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(12) (a) When employing (*S*)-2-[bis(3,5-bis-trifluoromethylphenyl) hydroxymethyl] pyrrolidine as catalyst instead of **cat. A**, the diastereoselectivity of the aldol reaction became lower while the enantioselectivity was slightly higher (under the same conditions as entry 1 in Table 1: reaction time; 45 h, 87% yield, 89:11 dr, 97% ee). (b) We did not try to use diphenylprolinol TMS ether as a catalyst because the hydroxyl group of **cat. A** is considered to play an important role in enantioselectivity as shown in Scheme 3. In fact, Hayashi's report (ref 11) shows that both enantio and diastereoselectivities became much lower when using diphenylprolinol TMS ether. (c) Unfortunately, when the amount of **cat. A** was reduced to 1 mol%, the aldol reaction became much slower and did not complete.

(13) The optical rotation, ^{1}H NMR spectrum, and ^{13}C NMR spectrum matched those reported in the literature.[2b,3,4c]

DOI: 10.1021/acs.oprd.6b00178
Org. Process Res. Dev. XXXX, XXX, XXX−XXX