JOC The Journal of Organic Chemistry

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An Enantioselective Synthesis of an 11-β-HSD-1 Inhibitor via an Asymmetric Methallylation Catalyzed by (*S*)-3,3′-F_2-BINOL

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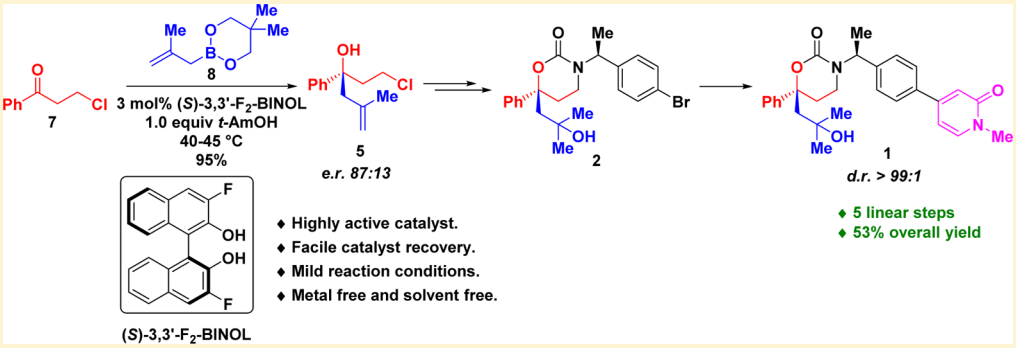
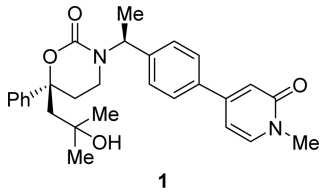
Supporting Information



ABSTRACT: An efficient asymmetric synthesis of 11-β-HSD inhibitor **1** has been accomplished in five linear steps and 53% overall yield, starting from the readily available 3-chloro-1-phenylpropan-1-one. The key feature of the synthesis includes an asymmetric methallylation of 3-chloro-1-phenylpropan-1-one catalyzed by the highly effective organocatalyst (*S*)-3,3′-F_2-BINOL under solvent-free and metal-free conditions.

11-β-Hydroxysteroid dehydrogenase-1 (11-β-HSD-1) is an enzyme that catalyzes the reduction of the inactive glucocorticoid cortisone to active glucocorticoid cortisol.[1] An elevated circulating glucocorticoid level has been correlated to several metabolic comorbidities, including obesity, diabetes, dyslipidemia, and atherosclerosis.[2,3] Compound **1** is a clinical candidate developed as an 11-β-HSD-1 inhibitor for the treatment of type II diabetes (Figure 1). In order to support early development activities, an efficient and economical chemical process amenable to production of multikilogram quantities of **1** was required. Herein, we report a practical and expedient synthesis of the target compound, featuring an asymmetric methallylation catalyzed by (*S*)-3,3′-F_2-BINOL.[4]



1

Figure 1. Structure of 11-β-HSD-1 inhibitor **1**.

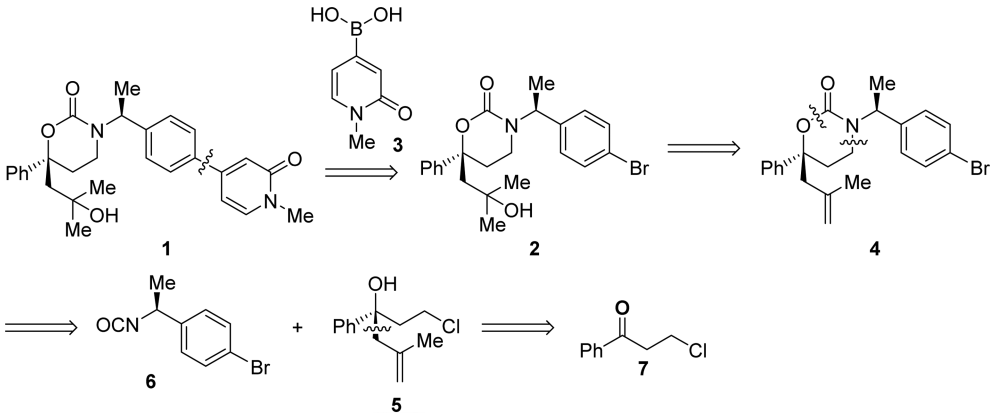
The retrosynthetic analysis of **1** is outlined in Scheme 1. We envisioned that **1** could be accessed from the bromide **2** and the boronic acid **3** via a Suzuki−Miyaura coupling. The tertiary alcohol **2** could be derived from the alkene **4**, which could be accessed by cyclization of tertiary alcohol **5** and chiral isocyanate **6**. It was speculated that **5** could be derived from the readily available ketone **7**. The major synthetic challenge to develop an efficient and cost-effective chemical process for the synthesis of **1** was identifying an efficient method to install the tertiary chiral stereocenter of the tertiary alcohol **5**.

Over the past decade, numerous methodologies have been reported for the asymmetric allylation of ketones,[5,6] but the corresponding asymmetric methylallylation has less precedence. Walsh and co-workers reported the first catalytic asymmetric methallylation of ketones, employing tetramethylallylstannane, in 2006.[7] Shortly thereafter, a chromium-catalyzed enantioselective addition of allyl bromide to ketones was described by the Sigman group,[8] and one example was reported for asymmetric methylallylation.[9] In both cases, toxic metals such as tin and chromium were necessary for the transformation. On the other hand, the direct application of the optimized and well-developed conditions for allylation of ketones was not always feasible for the *meth*allylation process due to the unclear and elusive mechanistic differences between the two processes.[10] For example, no reaction was observed with methallyl pinacolboronate **8** in DMF under the conditions for allylation

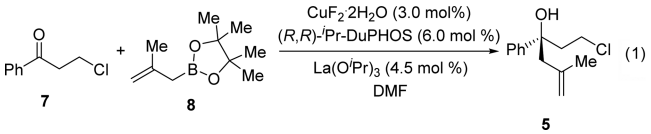
Received: January 27, 2016
Published: February 24, 2016

DOI: 10.1021/acs.joc.6b00189
J. Org. Chem. 2016, 81, 2665−2669

Scheme 1. Retrosynthetic Analysis of 1

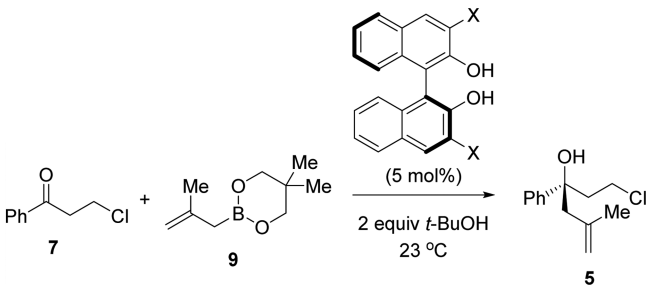


(eq 1).[11] A solvent switch to 2-Me-THF led to 92% conversion. However, low enantioselectivity (62:38) was observed.



In 2006, an efficient organocatalytic asymmetric allylation of ketones catalyzed by (*S*)-3,3′-Br_2-BINOL was reported by Schaus and co-workers.[12] Further mechanistic studies by the same group demonstrated the possibility of lowering the catalyst loadings [2.0 mol % (*S*)-3,3′-Br_2-BINOL].[13] Our investigation revealed that the use of (*S*)-3,3′-Br_2-BINOL for the *methallylation* of ketone **7** with cyclic boronate **9** gave reasonable enantioselectivity (Table 1, entry 1). However, the reactions turned out to be sluggish, giving 61% conversion after 10 h in the presence of 5.0 mol % catalyst. Our results indicated that the use of chiral BINOLs containing CF_3,[14] CO_2Me, or SO_2CF_3[15] at 3,3′-positions gave essentially no enantioselectivity (entries 2−4).

Table 1. Asymmetric Methyallylation of 7



entry[a]	X	*t* (h)	convn (%)	er[b]
1	Br	10	61	89:11
2	CO_2Me	16	84	51:49
3	SO_2CF_3	20	88	50:50
4	CF_3	16	82	52:48
5	Cl	10	70	91:9
6	**F**	**10**	**98**	**87:13**

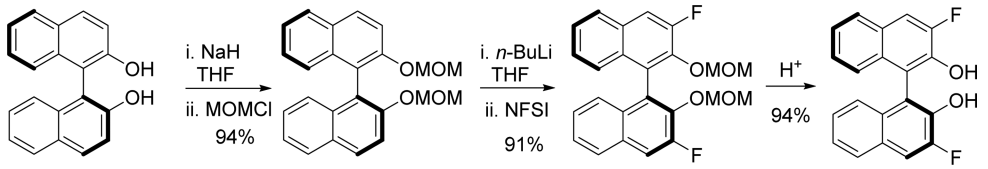
[a]All reactions were performed with ketone **7** (1.0 equiv) and boronate **9** (1.2 equiv) under nitrogen. [b]The er was determined by the chiral HPLC of the reaction mixture.

On the other hand, when Cl substituents were introduced at 3,3′-positions of BINOL, the methallylation with ketone **7** proved to be faster than the reaction with 3,3′-Br_2-BINOL,[16] giving 70% conversion and good enantioselectivity (91:9 er, entry 5). Encouraged by these results, we decided to install a stronger electron-withdrawing halogen, fluorine, at the 3,3′-positions of BINOL. It turned out that (*S*)-3,3′-F_2-BINOL was a highly effective catalyst for the methallylation of **7**. The catalyst (*S*)-3,3′-F_2-BINOL was prepared efficiently in four steps from a widely available chiral BINOL in 85% overall yield (Scheme 2).[4] With a 5.0 mol % catalyst loading, the reaction gave 98% conversion with 87:13 enantioselectivity.

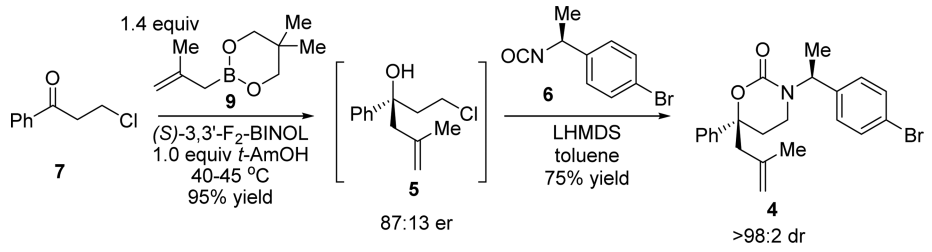
In order to develop an efficient chemical process for the methylallylation of ketone **7**, we set out to optimize the reaction parameters, including the catalyst loading and the reaction temperature (see Supporting Information). With 20 mol % (*S*)-3,3′-F_2-BINOL, the reaction reached completion in less than 4 h at 23 °C, affording the allylation product **5** with 87:13 er. With employment of 3 mol % catalyst, the reaction required 24 h to reach complete conversion, while maintaining the same stereoinduction. To shorten the reaction time, the effect of reaction temperature was investigated. It was found that the reaction became faster at a higher temperature without erosion of the enantioselectivity (30, 40, 50, and 60 °C). Full conversion was observed in all cases after 9 h. When the reaction was performed at 0 °C to investigate the temperature effect on the enantioselectivity, no enantioselectivity improvement was observed, and the reaction became very sluggish and gave 33% conversion after 22 h. When 1.1 equiv of boronate **9** was used, the reaction went to completion with 86:14 er, which indicated that the protodeboronation of **9** in the presence of (*S*)-3,3′-F_2-BINOL was negligible. Current reactions tolerate up to 3.0 equiv of *t*-AmOH in the presence of 2 mol % catalyst at 40 °C. It was observed that the reaction became slightly slower with more *t*-AmOH. To demonstrate the efficiency of the catalyst, the reactions were performed with 1.0 mol % (*S*)-3,3′-F_2-BINOL. The reactions gave full conversion after 24 h with slightly decreased enantioselectivity. Considering the ease of catalyst recovery, 3 mol % (*S*)-3,3′-F_2-BINOL was used for the current chemical process in the presence of 1.4 equiv of boronate **9** and 1.0 equiv of *t*-AmOH. Under our optimized conditions, the methallylation of ketone **7** went to completion in a reasonably short time (9 h) at 40−45 °C. The product **5** was isolated as a solution in toluene with 87:13 er and 95% yield.

DOI: 10.1021/acs.joc.6b00189
J. Org. Chem. 2016, 81, 2665−2669

Scheme 2. Synthesis of (*S*)-3,3′-F_2-BINOL



Scheme 3. Synthesis of 4 via an Asymmetric Methallylation



Scheme 4. Synthesis of 2 via Sequential Epoxidation and Reduction

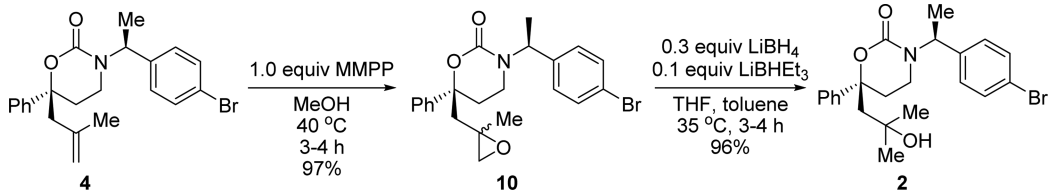
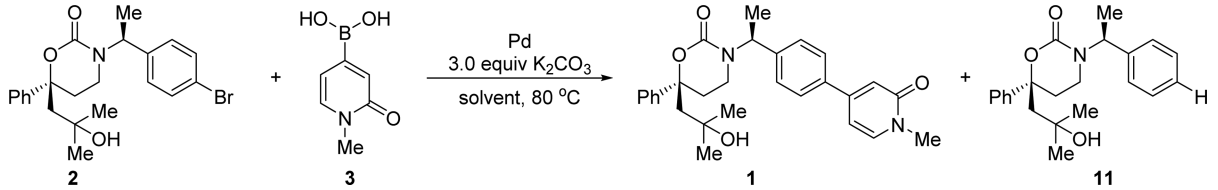


Table 2. Synthesis of 1 via the Suzuki–Miyaura Coupling of 2 and 3[a]



entry	Pd/L	loading (mol %)	solvent	*t* (h)	**1**:**11**[b]
1	1:4 $Pd(OAc)_2/PPh_3$	0.2	IPA	30	83:17
2	$PdCl_2(dppf)\cdot CH_2Cl_2$	0.2	IPA	5	99:1.0
3	$PdCl_2(dppf)\cdot CH_2Cl_2$	0.1	IPA	6	98.5:1.5
4	$PdCl_2(dppf)\cdot CH_2Cl_2$	0.1	EtOH	10	98:2

[a]All of the reactions were conducted with **2** (2.0 g, 4.6 mmol), **3** (0.98 g, 87.0 wt %, 5.5 mmol, 1.2 equiv), K_2CO_3 (1.92 g, 13.88 mmol, 3.0 equiv), and IPA (10 mL) unless noted elsewhere. [b]The ratio of **1** and **11** was determined by HPLC.

With the enantiomerically enriched allyl-tertiary alcohol **5** in hand, the installation of the cyclic carbamate **4** was attempted. In the presence of 4.5 equiv of DBU, the cyclization of **5** and enantiopure isocyanate **6**[17,18] in refluxing THF gave 65% yield and generated multiple impurities. The use of NaHMDS increased the yield to 80%. Further optimization led to the identification of LHMDS as the optimal base for the cyclization, affording the adduct **4** in quantitative yield. After removal of the THF by distillation followed by crystallization in toluene, the product **4** was isolated with 98:2 dr. To simplify the isolation, toluene was used as the single solvent for the cyclization. After the reaction of **5** and isocyanate **6** was complete, the product **4** was isolated with greater than 98:2 dr in 75% yield (Scheme 3).

Direct hydration was first attempted to convert **4** to **2** with $Co(acac)_2$ as the catalyst in 2-propanol.[19,20] However, the reaction stalled with 62% conversion after 4 h at 75 °C, even in the presence of 40 mol % $Co(acac)_3$. At this stage, we focused on conversion of **4** to **2** via a sequential epoxidation and reduction process.[21] Various epoxidation reagents, including MMPP, $NaBO_3$, NIS, urea-hydrogen peroxide (UHP), and Oxzone, were investigated.[22] MMPP (magnesium monoperoxyphthalate hexahydrate)[23] was identified as an economical and mild oxidizing agent, affording the epoxidation product **10** in 97% yield (Scheme 4). To convert the epoxide **10** to tertiary alcohol **2**, a series of reducing reagents, including BH_3-Et_3N,[24] BH_3-THF,[25] and superhydride ($LiBHEt_3$),[26] were tested. Eventually, $LiBHEt_3$ was determined to be optimal to reduce the epoxide **10** to the alcohol **2**. However, the quench of excess $LiBHEt_3$ with hydrogen peroxide was highly exothermic. The slow addition of hydrogen peroxide was required, which made the workup process time-consuming during the scale-up. We speculated that this might be diminished by the use of a catalytic amount of $LiBHEt_3$, which could be regenerated during the reduction in the presence of stoichiometric $LiBH_4$. Indeed, the reaction proceeded with 1.2 equiv of $LiBH_4$ and 0.10 equiv of $LiBHEt_3$, affording greater than 90% yield after 10

DOI: 10.1021/acs.joc.6b00189
J. Org. Chem. 2016, 81, 2665−2669

h at room temperature. When 0.05 equiv of $LiBHEt_3$ was applied, the reaction was slow, giving 84% conversion after 22 h. Meanwhile, some unknown impurities were observed. Further optimization allowed the reaction to achieve completion with 0.3 equiv of $LiBH_4$ and 0.10 equiv of $LiBHEt_3$, producing the tertiary alcohol **2** with 96% yield after 3 h at 35 °C. As such, the alkene **4** was elaborated to the tertiary alcohol **2** in 93% yield and 99.0% dr via a sequential epoxidation and reduction process (Scheme 4).

To convert the bromide **2** to **1**, the installation of the pyridinone ring via a Suzuki−Miyaura coupling was attempted. The catalyst screen indicated that $PdCl_2(dppf)_2{\cdot}CH_2Cl_2$[27] was superior to $Pd(OAc)_2/PPh_3$ (Table 2, entries 1 and 2). The reaction with 0.2 mol % $PdCl_2(dppf)_2{\cdot}CH_2Cl_2$ in IPA provided less of the desbromo byproduct **11** in a shorter reaction time under the same conditions. When the catalyst loading of $PdCl_2(dppf)_2{\cdot}CH_2Cl_2$ was reduced from 0.2 to 0.1 mol %, the reaction still worked well (Table 2, entry 3). A solvent switch from IPA to EtOH slowed the reaction and produced more desbromo product **11** (Table 2, entry 4). Eventually, the Suzuki−Miyaura coupling of **2** and **3** was performed on a multikilogram scale with 0.1 mol % $PdCl_2(dppf)_2{\cdot}CH_2Cl_2$ in IPA at 80 °C, affording the coupling product **1** as a white solid in 95% yield.

In summary, a highly efficient asymmetric synthesis of 11-β-HSD inhibitor **1** has been accomplished in five linear steps with 53% overall yield. The key feature of this synthesis includes an asymmetric methallylation of **7** catalyzed by a highly effective (*S*)-3,3′-F_2-BINOL under solvent-free conditions. The entire process was successfully demonstrated on a multikilogram scale without complication.

EXPERIMENTAL SECTION

General. All reactions were performed in an oven-dried flask under nitrogen. Unless otherwise noted, reagents were commercially available and were used without purification. Chemical shifts are reported in δ (ppm) relative to TMS in $CDCl_3$ as the internal standard (^{1}H NMR) or the residual $CHCl_3$ signal (^{13}C NMR). HPLC conditions for reaction monitoring and quantitation: column Halo C18, 4.6 × 150 mm, 2.7 μm particle size; column temperature at 25 °C; mobile phase A (0.2% H_3PO_4 in water), mobile phase B (acetonitrile), flow rate 1.2 mL min^{-1}, gradient program from 30% B to 70% B over 6 min, and then to 85% B over 1 min, and then to 98% B over 0.5 min, and held at 98% B for 4.5 min; λ = 220 nm. The samples for HPLC were diluted with CH_3CN.

(*R*)-3-((*S*)-1-(4-Bromophenyl)ethyl)-6-(2-methylallyl)-6-phenyl-1,3-oxazinan-2-one 4. To a stirred mixture of the ketone **7** (150.0 g, 98 wt %, 0.87 mol), (*S*)-3,3′-F_2-BINOL (8.49 g, 26.1 mmol), and *t*-amyl alcohol (77.08 g, 0.87 mol, 1.0 equiv) was added the boronate **9** (218.4 g, 94.2 wt %, 1.4 equiv) under nitrogen. The mixture was stirred for 9 h at 35−40 °C. After the mixture was cooled to 20−25 °C, 0.1 M HCl (600 mL) in water was added in one portion. After 0.5 h, toluene (600 mL) was added to extract the product. The organic phase was washed successfully with 1 M NaOH (600 mL) and water (2 × 300 mL). Removal of the solvent gave the product **5** (185.7 g) with 87:13 er and 95% yield.

Chiral HPLC conditions: Chiralcel OJ-RH, 4.6 × 150 mm, 5 μm; mobile phase A (acetonitrile), mobile phase B (0.1% HCO_2H in water, adjusted with NH_4OH to pH 4.0), 40:60 A/B; λ = 220 nm; flow rate 1.3 mL min^{-1}. The samples for HPLC were diluted with MeOH. (*R*)-**5**, *t* = 6.29 min, (*S*)-**5**, *t* = 7.16 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30−7.40 (m, 4H), 7.21−7.26 (m, 1H), 4.92 (s, 1H), 4.77 (s, 1H), 3.53−3.60 (m, 1H), 3.10−3.17 (m, 1H), 2.60−2.49 (dd, 2H, *J* = 13.7, 47.7 Hz), 2.52 (s, 1H), 2.24−2.40 (m, 2H), 1.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.5, 141.7, 128.3, 126.9, 125.1, 116.5, 74.5, 51.5, 46.4, 40.2, 24.3. HRMS (ESI$^+$/TOF): *m*/*z* calcd for $C_{13}H_{21}ClNO_3^+$ (M + NH_4^+) 242.13061, found 242.1297.

A mixture of **5** (13.0 g, 57.85 mmol) and **6** (13.08 g, 57.85 mmol) in toluene (65 mL) was cooled to 10 °C. A solution of LHMDS in toluene (1 M, 63.65 mL, 63.63 mmol) was added below 25 °C. After complete addition, the mixture was stirred at 22 °C for 1.5 h. After the mixture was cooled to 10 °C, 1.5 M hydrochloric acid (42 mL, 63.0 mmol) was added below 25 °C. Then, heptane (9 mL) was added. After a phase cut, the organic layer was washed with water (2 × 24 mL). Most of the solvent in the organic layer was removed by distillation (~26 mL of the solvent remained in the flask). Heptane (130 mL) was added. The solid was collected by filtration and dried to give the product **4** (18.0 g) with 98:2 dr and 75% yield.

HPLC conditions: Halo C8, 4.6 × 150 mm, 2.7 μm; mobile phase A (acetonitrile), mobile phase B (0.2% H_3PO_4) in water, from 30% A to 70% A over 6 min, and then to 85% A over 1 min, and then to 98% A over 0.5 min; λ = 220 nm; flow rate 1.2 mL min^{-1}. The samples for HPLC were diluted with MeOH. (*R*,*S*)-**4**, *t* = 8.51 min, (*S*,*S*)-**4**, *t* = 8.64 min.

Mp: 117−119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.30 (m, 5H), 7.17 (d, 2H, *J* = 8.48 Hz), 6.67 (d, 2H, *J* = 8.24 Hz), 5.60 (dd, 1H, *J* = 6.96, 13.96 Hz), 4.88 (t, 1H, *J* = 1.6 Hz), 4.68 (bs, 1H), 2.91−2.87 (m, 1H), 2.63 (d, 1H, *J* = 13.8 Hz), 2.54 (d, 1H, *J* = 13.8 Hz), 2.36−2.22 (m, 3H), 1.66 (s, 3H), 1.49 (d, 3H, *J* = 7.04 Hz). ^{13}C NMR (100 MHz): δ 153.5, 141.9, 140.4, 138.3, 131.3, 128.7, 128.6, 127.6, 124.9, 121.1, 116.4, 83.1, 52.6, 50.9, 36.1, 30.0, 24.3, 15.2. HRMS (ESI$^+$/TOF): *m*/*z* calcd for $C_{22}H_{24}BrNO_2^+$ (M + H^+) 414.1063, found 414.1059. Optical rotation: $[\alpha]_D^{22}$ = +8.1 (*c* = 0.26, MeOH).

(*S*)-3-((*S*)-1-(4-Bromophenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one 2. To a flask were added the alkene **4** (10.0 g, 24.86 mmol) and MeOH (40 mL) under nitrogen. The mixture was warmed to 35 °C to obtain a solution. MMPP (14.3 g, 86 wt %, 24.86 mmol) was added in four portions at 0.5 h intervals. After 3.5 h, the reaction was complete. The mixture was cooled to 20 °C. Water (80 mL) was added to obtain a suspension. After being stirred at 20 °C for 1 h, the solid was collected by filtration and then rinsed with 1:2 MeOH/water (30 mL). After being dried, 10.4 g of the epoxide product **10** was isolated as a white solid with 97% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.29 (m, 5H), 7.20 (t, 2H, *J* = 7.60 Hz), 7.73 (t, 2H, *J* = 9.20 Hz), 5.62 (m, 1H), 2.81 (m, 1H), 2.59 (m, 0.5H), 2.39 (m, 0.5H), 2.33−1.96 (m, 6H), 1.93−1.49 (m, 4.5 H), 1.01 (s, 1.5H). ^{13}C NMR (100 MHz): δ 153.1, 141.6, 141.3, 138.2, 131.3, 131.3, 128.9, 128.7, 128.0, 127.9, 125.0, 124.6, 121.2, 121.2, 82.8, 82.3, 54.6, 54.2, 54.1, 54.0, 52.8, 52.8, 50.2, 50.1, 36.1, 36.0, 31.8, 31.0, 22.6. HRMS (ESI$^+$/TOF): *m*/*z* calcd for $C_{22}H_{24}BrNO_3^+$ (M + H^+) 430.1012, found 430.1014.

To a stirred solution of **10** (9.7 g, 22.57 mmol) in dry THF (9.7 mL) were added $LiBH_4$ (3.39 mL, 2.0 M, 6.77 mmol, 0.3 equiv) in THF and $LiBEt_3H$ (2.26 mL, 1.0 M, 2.26 mmol, 0.1 equiv) below 30 °C. After being stirred at 35 °C for 3 h, the mixture was cooled to 20 °C. The reaction was quenched with a mixture of acetone (0.5 mL) and MeOH (20 mL). A solution of H_2O_2 (0.55 g, 35%, 5.64 mmol) in 1 mL of water was added. After being stirred at 25−35 °C for 0.5 h, the mixture was cooled to 22 °C, and then 7 mL of water was added. After the mixture was stirred at 22 °C for 15 min to obtain a slurry, up to 56 mL of water was added at 22−25 °C. After 1.5 h at 22 °C, the solid was collected by filtration and then rinsed with 30 mL of MeOH/water (1:2 v/v) and then 20 mL of heptane. After being dried, the solid was slurried in 1:3 EtOAc/heptane (40 mL) to give 9.35 g of **2** as a white solid with 96% yield and >99.0% dr.

Mp: 153−155 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.28 (m, 5H), 7.24−7.22 (m, 2H), 6.81−6.79 (m, 2H), 5.61 (dd, 1H, *J* = 7.04, 13.92 Hz), 2.86−2.81 (m, 1H), 2.46−2.27 (m, 3H), 2.20−2.15 (m, 3H), 1.48 (d, 3H, *J* = 7.0 Hz), 1.17 (bs, 3H), 1.14 (s, 3H). ^{13}C NMR (100 MHz): δ 153.0, 142.4, 138.2, 131.3, 128.8, 128.8, 127.7, 124.9, 121.3, 83.9, 71.0, 53.7, 52.9, 36.1, 33.1, 31.9, 30.4, 15.2. HRMS (ESI$^+$/TOF): *m*/*z* calcd for $C_{22}H_{26}BrNO_3^+$ (M + H^+) 432.1169, found 432.1167. Optical rotation: $[\alpha]_D^{22}$ = +16.1 (*c* = 0.34, MeOH).

DOI: 10.1021/acs.joc.6b00189
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(*S*)-6-(2-Hydroxy-2-methylpropyl)-3-((*S*)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one 1. To a clean flask were added **2** (50.0 g, 115.65 mmol), **3** (19.45, 127.21 mmol, 1.1 equiv), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (94.4 mg, 0.12 mmol, 0.1 mol %), K_2CO_3 (47.95 g, 346.94 mmol, 3 equiv), and IPA (250 mL) under N_2. After the mixture was pumped and refilled with N_2 three times, the mixture was heated to 80 °C for 3−5 h. A solution of *N*-acetyl-L-cysteine (1.89 g, 11.56 mmol, 0.1 equiv) in IPA (50 mL) was added. After 2 h at 80 °C, water (150 mL) was added. The mixture was cooled to 40 °C, and then a small amount of insoluble, off-white solid was filtered off and then washed with 3:1 IPA/water (100 mL). After a phase cut to remove the bottom aqueous layer, distillation of the top layer was performed at 81−83 °C and 760 Torr to reduce the mixture to less than 0.5% water. During the distillation, IPA (1000 mL) was added to maintain the volume of the content (~250 mL). The batch was cooled to 60−65 °C and then seeded with 50 mg of **1**·IPA solvate in 0.5 mL of IPA. After being stirred at 60−65 °C for 0.5 h, the mixture was cooled to 0 °C over 2 h. After 1 h, the solid was collected and then rinsed with chilled IPA (0−5 °C, 100 mL). After being dried at 40 °C under vacuum, 50.6 g of **1** was obtained as a white solid in 95% yield.

Mp: 93−95 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.28 (m, 8H), 7.01 (d, 2H, J = 8.52 Hz), 6.70 (d, 1H, J = 1.64 Hz), 6.35 (dd, 1H, J = 2.04, 7.04 Hz), 5.69 (dd, 1H, J = 7.08, 14.0 Hz), 3.57 (s, 3H), 2.90−2.86 (m, 1H), 2.47−2.39 (m, 2H), 2.32−2.15 (m, 6H), 1.54 (d, 3H, J = 7.0 Hz), 1.17 (s, 3H), 1.14 (s, 3H). ^{13}C NMR (100 MHz): δ 163.2, 153.1, 151.2, 142.4, 140.7, 138.2, 136.3, 128.8, 127.6, 127.6, 126.5, 125.0, 116.7, 105.4, 84.0, 71.1, 53.8, 53.2, 37.4, 36.2, 33.2, 31.9, 30.4, 15.3. HRMS (ESI$^+$/TOF): m/z calcd for $C_{28}H_{32}N_2O_4^+$ (M + H$^+$) 461.2435, found 461.2422. Optical rotation: $[\alpha]_D^{22}$ = +23.0 (c = 0.20, MeOH).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00189.

^{1}H and ^{13}C NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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DOI: 10.1021/acs.joc.6b00189
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