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One-Pot Reactions

A Concise One-Pot Organo- and Biocatalyzed Preparation of Enantiopure Hexahydrofuro[2,3-*b*]furan-3-ol: An Approach to the Synthesis of HIV Protease Inhibitors

Takuya Kanemitsu,[a] Mizuho Inoue,[a] Nono Yoshimura,[a] Kazutoshi Yoneyama,[a] Rie Watarai,[a] Michiko Miyazaki,[a] Yuki Odanaka,[a] Kazuhiro Nagata,[a] and Takashi Itoh*[a]

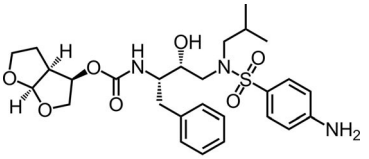
Abstract: A simple and efficient one-pot synthesis of enantiopure hexahydrofuro[2,3-*b*]furan-3-ol, a crucial component of HIV-1 protease inhibitors, was developed. The one-pot process involves an organocatalytic condensation followed by an enzymatic optical resolution. The condensation of 1,2-dihydrofuran and glycolaldehyde was achieved using Schreiner's thiourea catalyst (1 mol-%). A subsequent lipase-catalyzed kinetic resolution gave the target alcohol with >99 % *ee*. To demonstrate the practicality of this method, Darunavir, an HIV-1 protease inhibitor used to treat multi-drug-resistant HIV, was synthesized.

Introduction

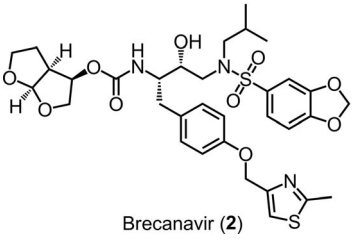
Organocatalysis is an attractive synthetic strategy, because organocatalytic reactions generally proceed under mild conditions without the need for complex preprocessing.[1] In processes involving the use of metal catalysts for the synthesis of pharmaceutical products, complete removal of the catalyst is needed because of catalyst toxicity. Metal-free organocatalytic processes do not require this step. Thus, Brønsted acid and hydrogen-bonding catalytic methods have emerged as powerful tools for organocatalysis. Organic Brønsted acids have been widely investigated as catalysts for carbon–carbon bond-forming reactions.[2] Several classes of Brønsted acids have been reported as metal-free organocatalysts, including thioureas,[3] phosphoric acids,[4] disulfonimides,[5] squaramides,[6] and triflimides.[7]

Enzymatic biocatalysis also has been investigated as an environmentally benign synthetic process in organic chemistry.[8] Biocatalytic kinetic resolution has been shown to be a very efficient stereoselective method for asymmetric synthesis. Lipases and esterases are widely used biocatalysts in this process as a result of their excellent stereoselectivity and broad substrate scope, their potency in organic solvents, and their commercial availability.[9]

(3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-ol (bis-THF alcohol) is a common structural unit in HIV-1 protease inhibitors such as Darunavir (**1**; Figure 1)[10] and Brecanavir (**2**),[11] as well as other drug candidates.[12] Darunavir, which was approved by the US Food and Drug Administration (FDA) in 2006 for the treatment of drug-resistant HIV, was developed by Ghosh and Mitsuya.[13] Darunavir was designed to hydrogen-bond with the backbone of the HIV protease active site. The oxygen atoms of the bis-THF moiety form effective hydrogen bonds with the amide NH groups of Asp29 and Asp30 in the protease backbone, which anchor the protease inhibitor to the S2 subsite. Consequently, several stereoselective procedures for the preparation of the chiral form of the bis-THF alcohol have been reported.[14] Most of these synthetic approaches, however, required multiple steps to obtain the stereoisomer. Therefore, new methods for the large-scale preparation of isomers in a stereoisomerically pure form are needed. Efficient one-step preparations of the bis-THF alcohol have been reported independently by Yu[15] and Xie.[16] The reaction proceeded by condensation of 1,2-dihydrofuran and glycolaldehyde using a transition-metal-based Lewis acid with chiral Evans' pybox ligand complexes. Although the reaction gave high diastereoselectivity, the enantioselectivity was moderate to low. Thus, the authors carried out an enzymatic optical resolution to obtain the chiral bis-THF alcohol.



Darunavir (**1**)



Brecanavir (**2**)

Figure 1. Structures of Darunavir (**1**) and Brecanavir (**2**).

[a] *School of Pharmacy, Showa University*
1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan
E-mail: itoh-t@pharm.showa-u.ac.jp
http://www10.showa-u.ac.jp/~obchem/index.html

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Inspired by these studies and by our own previous work on Brønsted-acid catalysts,[17] we envisioned an efficient and environmentally friendly synthetic route to bis-THF alcohol through the Brønsted-acid-catalyzed condensation of 1,2-dihydrofuran and glycolaldehyde. Based on previous reports, an organocatalyst is expected to promote the formation of the bis-THF alcohol. Thus, a one-pot procedure in which the organocatalytic condensation is followed by an enzyme-catalyzed optical resolution should give the optically pure bis-THF alcohol.

In this paper, we describe an efficient one-pot synthesis using environmentally benign organocatalysis, followed by enzymatic optical resolution to give the optically pure bis-THF alcohol. In addition, the synthesis of Darunavir using the bis-THF alcohol is described to confirm the utility of the procedure.

Results and Discussion

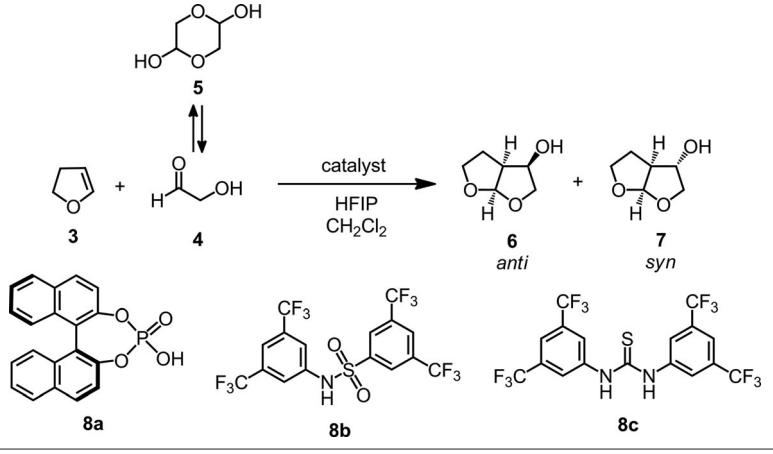
First, the catalytic activity of Brønsted acids was examined for the condensation of 1,2-dihydrofuran (**3**) and glycolaldehyde (**4**). The condensation was carried out using commercially available glycolaldehyde dimer **5**, which is in equilibrium with the monomeric form **4**, in the presence of Brønsted acid (10 mol-%) in CH_2Cl_2. Xie reported that hexafluoroisopropyl alcohol (HFIP) was an effective additive that improved the yield of the condensation reaction.[16] Accordingly, a screening process was carried out in the presence of HFIP to obtain the bis-THF alcohol, including the desired *anti* form (i.e., **6**) accompanied by the *syn* form (i.e., **7**).

Table 1 shows the reactivity of acetic acid, trifluoroacetic acid, 4-toluenesulfonic acid, and phosphoric acid catalyst **8a** (Entries 1–4). Sulfonamide catalyst **8b** did not catalyze the synthesis of bis-THF alcohol (Table 1, Entry 5). However, Schreiner's thiourea catalyst[18] **8c** was more active in the reaction, and a moderate yield of bis-THF alcohols **6** and **7** was achieved (Table 1, Entry 6). The isomers were separated by silica gel chromatography, and the major isomer was the desired *anti* form (i.e., **6**). An evaluation of the catalyst loading was then carried out. Although a decrease in catalyst loading slowed down the condensation process, a longer reaction time solved this problem (Table 1, Entries 7–10). Consequently, 1 mol-% of catalyst **8c** was used in subsequent experiments.

To improve the reactivity and diastereoselectivity, the effect of changing the solvent in the reaction catalyzed by **8c** was investigated, using polar and nonpolar solvents at room temperature. As shown in Table 2, the condensation proceeded effectively with less polar solvents (Table 2, Entries 1–5). In ether solvents and acetonitrile, the products were formed in poor yield (Table 2, Entries 6–8). With more polar solvents, such as DMF or DMSO, little product was obtained (Table 2, Entries 9 and 10). CH_2Cl_2 gave the best result, producing a 32 % yield of **6** and a 5 % yield of **7**, in a diastereomeric ratio of 86:14. Accordingly, CH_2Cl_2 was considered the optimal solvent in terms of the *dr* and the yield of the product.

To further improve the reaction, the amounts of reactants and reagents were optimized (Table 3). For equimolar amounts of 1,2-dihydrofuran (**3**), glycolaldehyde (**4**) (i.e., 0.5 equiv. of **5**),

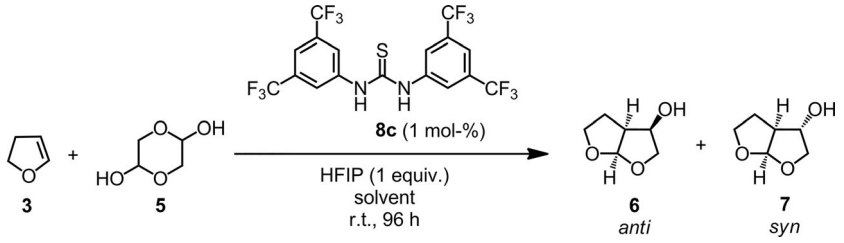
Table 1. Screening of Brønsted-acid catalysts for the preparation of bis-THF alcohol.



Entry[a]	Catalyst (mol-%)	Time [h]	Yield of **6** [%][b]	Yield of **7** [%][b]
1	acetic acid (10)	24	trace	trace
2	trifluoroacetic acid (10)	24	trace	trace
3	4-toluenesulfonic acid (10)	24	5	4
4	**8a** (10)	24	3	2
5	**8b** (10)	24	n.d.[c]	n.d.[c]
6	**8c** (10)	24	30	5
7	**8c** (5)	24	22	4
8	**8c** (1)	24	18	3
9	**8c** (1)	48	27	4
10	**8c** (1)	96	32	5

[a] The reactions were carried out using **3** (1.0 mmol) and **5** (0.5 mmol) with catalyst in CH_2Cl_2 at room temperature. [b] Isolated yields. [c] n.d. = not determined.

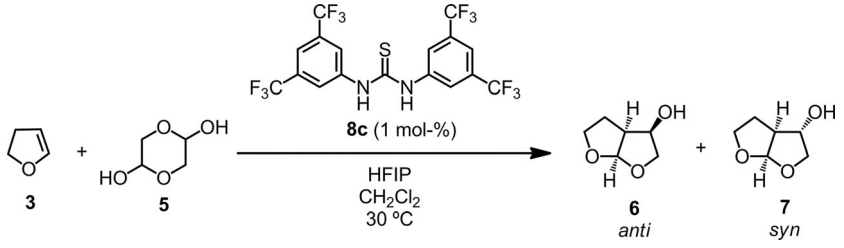
Table 2. Optimization of the reaction conditions.



Entry[a]	Solvent	Yield of **6** [%][b]	Yield of **7** [%][b]	*dr* (*anti*/*syn*)
1	CH_2Cl_2	32	5	86:14
2	$CHCl_3$	30	6	83:17
3	CCl_4	22	11	68:32
4	$ClCH_2CH_2Cl$	29	7	81:19
5	toluene	28	8	77:23
6	Et_2O	4.0	2.7	60:40
7	THF	1.2	0.8	60:40
8	CH_3CN	6	4	63:37
9	DMF	trace	trace	–
10	DMSO	n.d.[c]	n.d.[c]	–

[a] The reactions were carried out using **3** (1.0 mmol) and **5** (0.5 mmol) with catalyst in an appropriate solvent at room temperature. [b] Isolated yields. [c] n.d. = not determined

Table 3. Optimization of the reaction conditions.



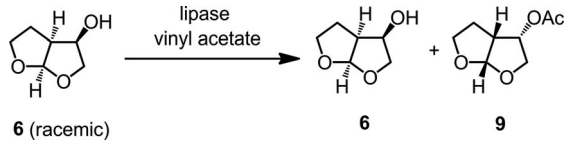
Entry[a]	**3** [equiv.]	HFIP [equiv.]	Time [h]	Yield of **6** [%][b]	Yield of **7** [%][b]	*dr* (*anti*/*syn*)
1	1	1	100	46	11	81:19
2	1	2	100	51	13	80:20
3	2	1	100	53	15	78:22
4	2	2	40	71	19	79:21
5[c]	2	2	100	7	trace	–
6	3	2	30	70	19	78:22
7	4	2	30	70	20	78:22

[a] The reactions were carried out using **3** and **5** with catalyst **8c** (1 mol-%) at 30 °C. [b] Isolated yields. [c] Trifluoroethanol (TFE) was used instead of HFIP.

and HFIP, the condensation proceeded at 30 °C in the presence of thiourea catalyst **8c** to give the desired product (i.e., **6**) in 46 % yield (Table 3, Entry 1). When the reactions were carried out with 2 equiv. of HFIP or **3**, the product was obtained in slightly higher yield (Table 3, Entries 2 and 3). With 2 equiv. of **3** and HFIP, the yield of **6** increased dramatically to 71 %, and the reaction rate also increased (Table 3, Entry 4). This result prompted further investigation of the reaction conditions. When we used 2,2,2-trifluoroethanol (TFE) instead of HFIP, little product was obtained (Table 3, Entry 5). In contrast, the presence of HFIP significantly enhanced the reaction. Presumably, HFIP enhances the formation of monomeric glycolaldehyde (**4**) from the dimeric form **5**. A further increase in the amount of **3** did not affect the yields (Table 3, Entries 6 and 7).

Having established optimal conditions for the condensation reaction, we went on to examine enzymatic optical resolution. The lipase-catalyzed kinetic resolution of *anti*-bis-THF alcohol **6** was attempted by enantioselective esterification with vinyl acetate. The enzymatic activities of several lipases were evaluated in the optical resolution of racemic **6** (Table 4). Treatment of racemic alcohol **6** with vinyl acetate in the presence of lipase AS at 50 °C for 24 h produced enantioenriched alcohol **6** (30 % yield, 28 % *ee*) and acetate **9** (51 % yield; Table 4, Entry 1). When using lipase AK, alcohol **6** was obtained in 30 % yield with 99 % *ee* (Table 4, Entry 2). The optical resolution using lipase PS was very efficient, giving **6** in 37 % yield with excellent *ee* (>99 %). After benzoylation of **6**, the *ee* was determined by chiral HPLC using a Daicel Chiralpak AD-H column. The absolute

Table 4. Screening of lipases for the preparation of (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-ol **6**.



Entry[a]	Lipase	Yield of **6** [%][b]	Yield of **7** [%][b]	*ee* of **6** [%][c]
1	lipase AS	30	51	28
2	lipase AK	30	65	99
3	lipase PS	37	53	>99

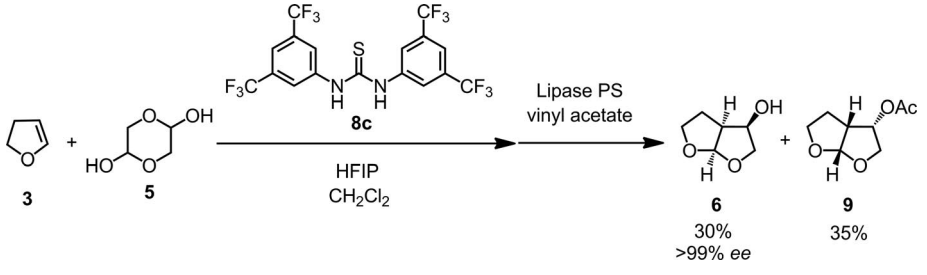
[a] The reactions were carried out using racemic **6** with lipase at 50 °C for 24 h. [b] Isolated yields. [c] Measured by chiral HPLC using a Chiralpak AD-H column after benzoylation.

configuration of chiral product **6** was assigned by optical rotation based on literature data for (–)-**6**.[14b]

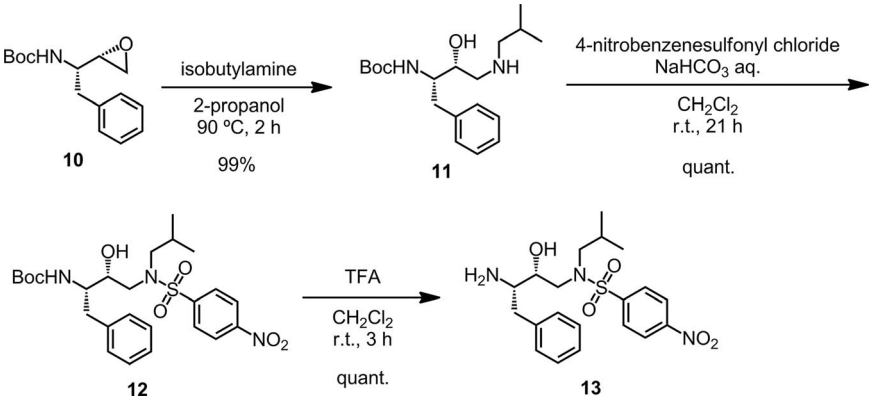
The success of the Schreiner's thiourea-catalyzed condensation of 1,2-dihydrofuran and glycolaldehyde, and of the lipase-catalyzed kinetic resolution, prompted us to develop a one-pot procedure involving both organocatalysis and biocatalysis (Scheme 1). 1,2-Dihydrofuran (**3**) and glycolaldehyde dimer **5** were allowed to react in the presence of Schreiner's thiourea catalyst **8c** in CH_2Cl_2 at 30 °C for 40 h, followed by the addition of lipase PS and vinyl acetate. The enzymatic optical resolution process was carried out at 50 °C for 24 h. The resulting mixture was filtered through a pad of Celite and concentrated in vacuo. The residue was purified by silica gel column chromatography to give **6** in 30 % yield with >99 % *ee*. In addition, a gram-scale (20 mmol) experiment was carried out to show the utility of the one-pot procedure using organocatalyst **8c** and lipase PS (see Supporting Information). The catalytic reaction proceeded smoothly, and the yield (30 %) was maintained to give **6** with a slight decrease in enantioselectivity (97 % *ee*). This result indicates that this one-pot reaction could be practical for the synthesis of the pharmaceuticals.

To demonstrate the utility of the method used for the synthesis of bis-THF alcohol, the synthesis of the HIV-1 protease inhibitor Darunavir was investigated. The synthesis began with the preparation of amino alcohol **13** (Scheme 2). Commercially available epoxide **10** was allowed to react with isobutylamine to give amino alcohol **11** in 99 % yield. This was followed by sulfonylation with 4-nitrobenzenesulfonyl chloride to give **12** in quantitative yield. Removal of the Boc (*tert*-butoxycarbonyl) group from **12** with TFA (trifluoroacetic acid) gave amino alcohol **13** in quantitative yield.

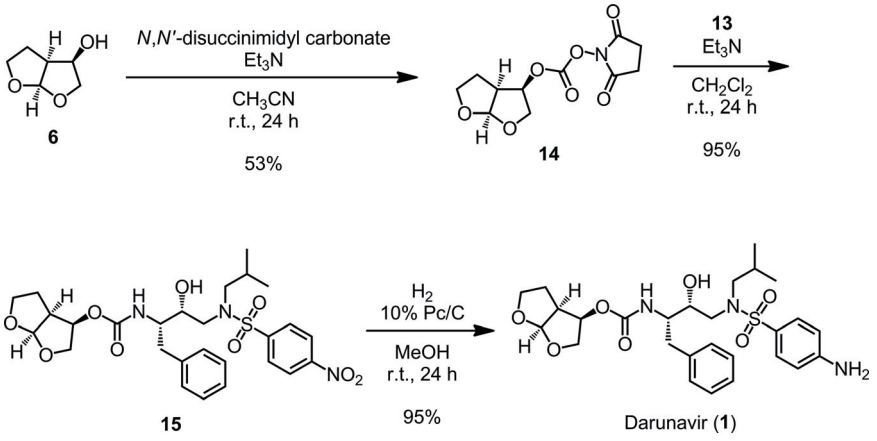
Next, for the synthesis of Darunavir, the corresponding urethane (i.e., **15**) was formed from amino alcohol **13** and bis-THF alcohol **6** (Scheme 3). Then, reaction of alcohol **6** with *N*,*N*′-disuccinimidyl carbonate in the presence of Et_3N in CH_3CN at ambient temperature gave active carbonate **14** in 53 % yield. Treatment of **13** with **14** proceeded smoothly in the presence of Et_3N to give urethane **15** in 95 % yield. Finally, catalytic hydrogenation of the nitro group of **15** was carried out to give Darunavir (**1**) in 95 % yield. The physical and spectroscopic data of the synthetic darunavir are identical to those in the literature.[14e]



Scheme 1. One-pot synthesis of enantiopure bis-THF alcohol **6**.



Scheme 2. Synthesis of amino alcohol **13**.



Scheme 3. Synthesis of Darunavir (**1**).

Conclusions

A one-pot organocatalytic and enzyme-catalyzed preparation of enantiopure bis-THF alcohol **6** was developed. This process involved an organocatalytic condensation of 1,2-dihydrofuran with glycolaldehyde catalyzed by Schreiner's thiourea, followed by an enzymatic optical resolution of the bis-THF alcohol. The condensation was carried out in the presence of Schreiner's thiourea catalyst (1 mol-%) with high diastereoselectivity. Subsequent addition of lipase PS and vinyl acetate to the resulting reaction mixture produced the desired enantiopure bis-THF alcohol. This concise one-pot synthetic method is environmentally friendly and suitable for large-scale production. In addition, the synthesis of the HIV-1 protease inhibitor Darunavir demonstrates the utility of this one-pot procedure. Further investigations into the development of enantioselective condensation reactions with chiral organocatalysts are underway.

Experimental Section

General Information: All materials were purchased from commercial suppliers, and were used without further purification. The progress of reactions was monitored by thin-layer chromatography (TLC), carried out on Merck precoated plates (Kieselgel 60 F_{254}, Art. 5715, 0.25 mm thickness). Plates were visualized with UV light, and with cerium sulfate/ammonium molybdate solution followed by heating. Column chromatography was carried out using a forced flow of the indicated solvent on Sigma H-type silica gel 60N (100–210 μm). ^{1}H and ^{13}C NMR spectra were recorded with a JEOL JNM AL-400 instrument (400 MHz for ^{1}H, and 100 MHz for ^{13}C) in deuterated solvent, using tetramethylsilane (δ = 0.0 ppm in ^{1}H NMR spectra) and $CDCl_3$ (δ = 77.0 ppm in ^{13}C NMR spectra) as internal standards. ^{1}H NMR data are reported as follows: chemical shift (δ in ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, dd = doublet of doublets, m = multiplet), and coupling constant (J in Hz). Optical rotations were measured with a JASCO P1020 polarimeter operating at the sodium D line at room temperature. Concentrations are given in g/100 mL. HPLC analysis was carried out with Shimadzu equipment (254 nm fixed-wavelength absorbance detector) using a Daicel Chemical Industries Ltd. Chiralpak AD-H column with hexane/ethanol solvent systems (composition and flow rate as indicated). HPLC instruments were calibrated with the corresponding racemic mixtures. High-resolution mass spectra (HRMS) were recorded with a JEOL JMS-MS700V instrument using *p*-nitrobenzyl alcohol as a matrix. Known compounds were identified by comparison of their spectroscopic data with those in the literature.

One-Pot Procedure for the Synthesis of (3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-ol (6; bis-THF alcohol): Glycolaldehyde dimer **4** (120 mg, 1.0 mmol), Schreiner's thiourea catalyst **8c** (10 mg, 0.020 mmol), and CH_2Cl_2 (2 mL) were placed in a round-bottomed flask (30 mL) equipped with a magnetic stirrer bar. 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP; 420 μL, 4.0 mmol) and 2,3-dihydrofuran (**3**; 300 μL, 4.0 mmol) were then added to the resulting solution. The reaction mixture was stirred under argon at 30 °C for 72 h. After this time, vinyl acetate (2 mL) and lipase PS (260 mg) were added to the reaction mixture. The resulting suspension was stirred at 50 °C for 2 h, and then the mixture was filtered through a pad of Celite 545. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel with hexane/ethyl acetate (80:20 to 0:100) and ethyl acetate/MeOH (90:10) as eluents to give bis-THF alcohol **6** (78 mg, 30 %) and acetate **9** (120 mg, 35 %). The *ee* value of **6** was determined by chiral-phase HPLC analysis after benzoylation. Data for **6**: Colorless oil. $[\alpha]_D^{27}$ = –12.9 (c = 0.8, CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.69 (d, J = 5.3 Hz, 1 H), 4.44 (dd, J = 7.1, 14.6 Hz, 1 H), 4.01–3.96 (m, 2 H), 3.93–3.87 (m, 1 H), 3.63 (dd, J = 7.1, 9.0 Hz, 1 H), 2.90–2.83 (m, 1 H), 2.44 (br. s, 1 H), 2.35–2.29 (m, 1 H), 1.93–1.82 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 109.5, 73.0, 70.8, 69.8, 46.5, 24.8 ppm. HRMS (FAB): calcd. for $C_6H_{11}O_3$ $[M + H]^+$ 131.0708; found 131.0363. The enantiomeric excess of **6** was determined by chiral HPLC analysis after benzoylation; Daicel Chiralpak AD-H, hexane/EtOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm; major isomer (3*R*,3a*S*,6a*R*): t_R = 11.0 min; minor isomer (3*S*,3a*R*,6a*S*): t_R = 15.4 min. Data for **9**: Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.73 (d, J = 5.1 Hz, 1 H), 5.20 (q, J = 6.6 Hz, 1 H), 4.07 (dd, J = 6.6, 9.8 Hz, 1 H), 4.01–3.96 (m, 1 H), 3.94–3.88 (m, 1 H), 3.77 (dd, J = 6.8, 9.8 Hz, 1 H), 3.10–3.04 (m, 1 H), 2.11 (s, 3 H), 2.04–2.00 (m, 1 H), 1.95–1.85 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 109.0, 72.8, 70.6, 69.4, 44.7, 25.9, 20.7 ppm. HRMS (FAB): calcd. for $C_8H_{13}O_4$ $[M + H]^+$ 173.0814; found 173.0815.

***tert*-Butyl *N*-[(1*S*,2*R*)-2-Hydroxy-3-(2-methylpropylamino)-1-phenylmethylpropyl]carbamate (11):** (2*S*,3*S*)-1,2-Epoxy-3-(Boc-amino)-4-phenylbutane **10** (200 mg, 0.76 mmol) and 2-propanol (6 mL) were placed in a round-bottomed flask (30 mL) equipped with a magnetic stirrer bar. Isobutylamine (340 μL, 4.6 mmol) was added to the resulting solution, and the reaction mixture was

stirred at 90 °C for 72 h. The solvent was then removed under reduced pressure, and the resulting residue was purified by column chromatography with CH_2Cl_2/MeOH (95:5 to 20:80) as eluent to give **11** (252 mg, 99 %) as white crystals; m.p. 106–108 °C. $[\alpha]_D^{18}$ = +7.6 (*c* = 1.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.19 (m, 5 H), 4.70 (d, *J* = 8.8 Hz, 1 H), 3.49–3.44 (m, 1 H), 3.82 (br. s, 1 H), 3.01 (dd, *J* = 4.8, 14.1 Hz, 1 H), 2.89–2.83 (m, 1 H), 2.70 (br. s, 2 H), 2.42 (dd, *J* = 2.2, 6.8 Hz, 2 H), 1.73 (sept, *J* = 6.6 Hz, 1 H), 1.36 (s, 9 H), 0.92 (d, *J* = 6.6 Hz, 3 H), 0.91 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 137.9, 129.5, 128.4, 126.3, 79.4, 70.6, 57.9, 54.1, 51.4, 36.7, 28.33, 28.27, 20.53, 20.51 ppm. HRMS (FAB): calcd. for $C_{19}H_{33}N_2O_3$ $[M + H]^+$ 337.2491; found 337.2509.

***tert*-Butyl *N*-{(1*S*,2*R*)-2-Hydroxy-3-[(2-methylpropyl)-4-nitrophenylsulfonylamino]-1-phenylmethylpropyl}carbamate (12):** Compound **11** (242 mg, 0.72 mmol) and CH_2Cl_2 (10 mL) were placed in a round-bottomed flask (50 mL) equipped with a magnetic stirrer bar. 4-Nitrobenzenesulfonyl chloride (239 mg, 1.1 mmol) and saturated aq. $NaHCO_3$ (10 mL) were added to the resulting solution, and the reaction mixture was stirred at room temperature for 21 h. After this time, H_2O was added, and the mixture was extracted with CH_2Cl_2 (3 ×). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography with CH_2Cl_2/MeOH (98:2) as eluent to give **12** (375 mg, quant.) as a pale yellow solid; m.p. 169–170 °C. $[\alpha]_D^{28}$ = +18.0 (*c* = 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 8.8 Hz, 2 H), 7.96 (d, *J* = 9.0 Hz, 2 H), 7.33–7.22 (m, 5 H), 4.62 (d, *J* = 6.6 Hz, 1 H), 3.83–3.75 (m, 2 H), 3.20 (d, *J* = 5.9 Hz, 2 H), 2.99 (d, *J* = 7.6 Hz, 2 H), 2.96–2.86 (m, 2 H), 1.88 (sept, *J* = 6.6 Hz, 1 H), 1.36 (s, 9 H), 0.89 (d, *J* = 6.3 Hz, 3 H), 0.87 (d, *J* = 6.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4, 150.0, 144.9, 137.4, 129.4, 128.6, 128.5, 126.7, 124.3, 80.2, 72.2, 57.6, 55.2, 52.5, 35.6, 28.2, 26.9, 20.0, 19.8 ppm. HRMS (FAB): calcd. for $C_{25}H_{36}N_3O_7S$ $[M + H]^+$ 522.2274; found 522.2286.

***N*-[(2*R*,3*S*)-3-Amino-2-hydroxy-4-phenylbutyl]-*N*-(2-methylpropyl)-4-nitrobenzenesulfonamide (13):** Compound **12** (337 mg, 0.65 mmol) and CH_2Cl_2 (10 mL) were placed in a round-bottomed flask (50 mL) equipped with a magnetic stirrer bar. Trifluoroacetic acid (1 mL, 13 mmol) was added to the resulting solution at 0 °C, and the reaction mixture was stirred at room temperature for 3 h. The solvent was then removed under reduced pressure, and the resulting residue was purified by column chromatography with CH_2Cl_2/MeOH (90:10) as eluent to give **13** (275 mg, quant.) as white crystals; m.p. 87–89 °C. $[\alpha]_D^{17}$ = +4.6 (*c* = 1.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 8.8 Hz, 2 H), 8.01 (d, *J* = 8.8 Hz, 2 H), 7.34–7.19 (m, 5 H), 3.75 (q, *J* = 5.1 Hz, 1 H), 3.35 (d, *J* = 5.4 Hz, 2 H), 3.18–3.14 (m, 1 H), 3.09–2.99 (m, 2 H), 2.92 (dd, *J* = 4.1, 13.4 Hz, 1 H), 2.53 (dd, *J* = 10.0, 13.7 Hz, 1 H), 1.91 (sept, *J* = 6.8 Hz, 1 H), 0.89 (t, *J* = 6.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.0, 145.1, 138.2, 129.2, 128.7, 128.5, 126.7, 124.3, 72.3, 57.5, 55.5, 51.6, 38.7, 26.8, 20.0, 19.8 ppm. HRMS (FAB): calcd. for $C_{20}H_{28}N_3O_5S$ $[M + H]^+$ 422.1750; found 422.1765.

2,5-Dioxopyrrolidin-1-yl (3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]-furan-3-yl Carbonate (14): Compound **6** (61 mg, 0.47 mmol) and CH_3CN (3 mL) were placed in a round-bottomed flask (30 mL) equipped with a magnetic stirrer bar. *N*,*N*-Disuccinimidyl carbonate (240 mg, 0.94 mmol) and triethylamine (130 µL, 0.94 mmol) were added to the resulting solution, and the reaction mixture was stirred under argon at room temperature for 24 h. The solvent was then removed under reduced pressure, and the resulting residue was purified by column chromatography with hexane/ethyl acetate (60:40 to 0:100) as eluent to give **14** (67 mg, 53 %) as a white solid; m.p. 98–100 °C. $[\alpha]_D^{28}$ = −11.1 (*c* = 1.0, MeOH). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.75 (d, *J* = 5.1 Hz, 1 H), 5.25 (td, *J* = 6.1, 8.0 Hz, 1 H), 4.13 (dd, *J* = 6.1, 10.2 Hz, 1 H), 4.03 (dt, *J* = 2.4, 8.5 Hz, 1 H), 3.95 (dd, *J* = 5.9, 10.2 Hz, 2 H), 3.17–3.10 (m, 1 H), 2.86 (s, 4 H), 2.18–2.12 (m, 1 H), 2.04–1.93 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 151.1, 109.1, 79.6, 70.0, 69.6, 45.0, 25.9, 25.4 ppm. HRMS (FAB): calcd. for $C_{11}H_{14}NO_7$ $[M + H]^+$ 272.0770; found 272.0796.

(3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-yl *N*-{(1*S*,2*R*)-2-Hydroxy-3-[(2-methylpropyl)-4-nitrophenylsulfonylamino]-1-phenylmethylpropyl}carbamate (15): Compound **14** (51 mg, 0.19 mmol), compound **13** (80 mg, 0.19 mmol), and CH_2Cl_2 (10 mL) were placed in a round-bottomed flask (50 mL) equipped with a magnetic stirrer bar. Triethylamine (27 µL, 0.19 mmol) was then added to the resulting solution, and the mixture was stirred under argon at room temperature for 24 h. The solvent was then removed under reduced pressure, and the resulting residue was purified by column chromatography with hexane/ethyl acetate (60:40) as eluent to give **15** (104 mg, 95 %) as a pale yellow solid; m.p. 113–115 °C. $[\alpha]_D^{30}$ = −5.5 (*c* = 1.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.35 (d, *J* = 8.8 Hz, 2 H), 7.97 (d, *J* = 8.8 Hz, 2 H), 7.31–7.20 (m, 5 H), 5.64 (d, *J* = 5.4 Hz, 1 H), 5.10–5.01 (m, 2 H), 3.96–3.81 (m, 4 H), 3.75–3.63 (m, 2 H), 3.48 (br. d, 1 H), 3.27–3.14 (m, 2 H), 3.10–2.88 (m, 4 H), 2.81–2.75 (m, 2 H), 1.89 (sept, *J* = 6.8 Hz, 1 H), 1.78 (s, 1 H), 1.69–1.59 (m, 1 H), 1.46–1.41 (m, 1 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 0.88 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6, 150.0, 144.5, 137.4, 129.2, 128.6, 128.5, 126.7, 124.4, 109.3, 73.6, 72.4, 70.9, 69.5, 57.9, 55.3, 52.8, 45.4, 35.5, 27.0, 25.8, 20.0, 19.8 ppm. HRMS (FAB): calcd. for $C_{27}H_{36}N_3O_9S$ $[M + H]^+$ 578.2172; found 578.2170.

(3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-yl *N*-{(1*S*,2*R*)-3-[4-Aminophenylsulfonyl-(2-methylpropyl)amino]-2-hydroxy-1-phenylmethylpropyl}carbamate (1; Darunavir): Compound **15** (46 mg, 0.079 mmol) and MeOH (5 mL) were placed in a round-bottomed flask (50 mL) equipped with a magnetic stirrer bar. Pd/C (10 %; 8.4 mg) was then added to the resulting solution, and the reaction mixture was stirred under hydrogen at room temperature for 24 h. The mixture was then filtered through a pad of Celite. The solvent was removed under reduced pressure, and the resulting residue was purified by column chromatography with hexane/ethyl acetate (40:60, 20:80, and 0:100) as eluent to give **1** (41 mg, 95 %) as a colorless solid; m.p. 86–88 °C. $[\alpha]_D^{15}$ = +3.8 (*c* = 0.74, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 8.5 Hz, 2 H), 7.29–7.18 (m, 5 H), 6.69 (d, *J* = 8.5 Hz, 2 H), 5.64 (d, *J* = 5.1 Hz, 1 H), 5.06–4.98 (m, 2 H), 3.96–3.82 (m, 4 H), 3.72–3.66 (m, 3 H), 3.17–3.05 (m, 2 H), 3.00–2.86 (m, 3 H), 2.81–2.76 (m, 2 H), 1.83 (sept, *J* = 6.8 Hz, 1 H), 1.67–1.57 (m, 1 H), 1.48–1.44 (m, 1 H), 0.92 (d, *J* = 6.6 Hz, 3 H), 0.88 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.4, 150.7, 137.7, 129.5, 129.4, 128.5, 126.5, 126.1, 114.2, 109.3, 73.4, 72.8, 70.8, 69.6, 58.8, 55.1, 53.7, 45.3, 35.7, 27.3, 25.8, 20.1, 20.0 ppm. HRMS (FAB): calcd. for $C_{27}H_{38}N_3O_7S$ $[M + H]^+$ 548.2430; found 548.2452.

Supporting Information (see footnote on the first page of this article): Characterization data, including ^1H and ^{13}C NMR spectra for selected products, HPLC traces for the result of the one-pot reaction, and experimental procedure for the gram-scale one-pot reaction.

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